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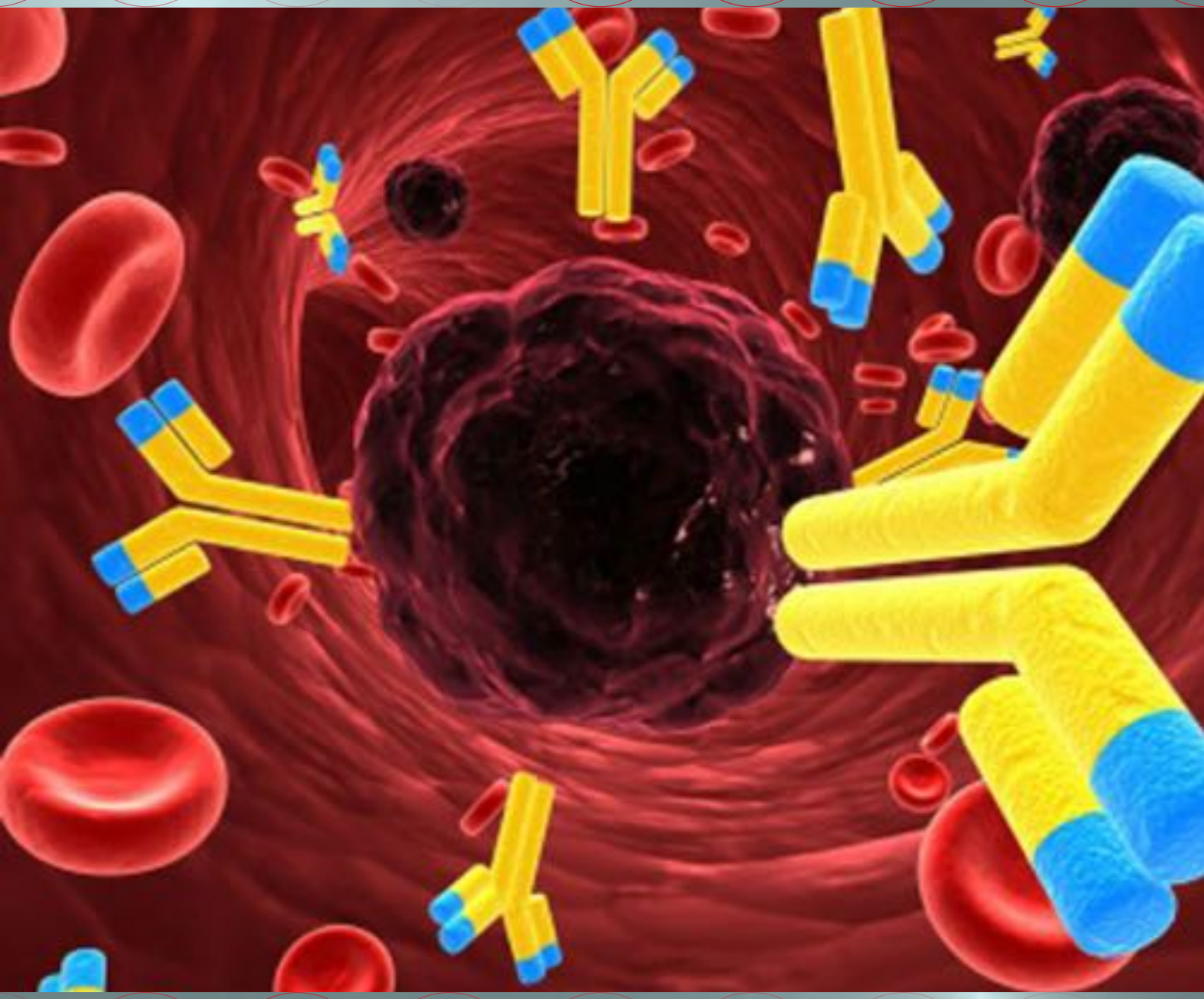
Hematological ONCOLOGY



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Hematological Oncology

17th International Conference on Malignant Lymphoma
Palazzo dei Congressi, Lugano, Switzerland
13 - 17 June, 2023

organized by the Foundation for the Institute of Oncology Research (IOR)
in cooperation with the American Association for Cancer Research (AACR),
the European School of Oncology (ESO)
and the European Society for Medical Oncology (ESMO).

The event has been accredited **25 ESMO-MORA category 1 points.**

Hematological ONCOLOGY

Aims and Scope

Hematological Oncology considers for publication articles dealing with experimental and clinical aspects of neoplastic diseases of the hemopoietic and lymphoid systems and relevant related matters. Translational studies applying basic science to clinical issues are particularly welcomed. Manuscripts dealing with the following areas are encouraged:

- Clinical practice and management of hematological neoplasia, including
  - Acute and chronic leukemias
  - Malignant lymphomas
  - Myeloproliferative disorders
- Diagnostic investigations, including imaging and laboratory assays
- Epidemiology, pathology and pathobiology of hematological neoplasia
- Therapeutic issues including Phase 1, 2 or 3 trials as well as allogeneic and autologous stem cell transplantation studies
- Aspects of the cell biology, molecular biology, molecular genetics and cytogenetics of normal or diseased hematopoeisis and lymphopoiesis, including stem cells and cytokines and other regulatory systems.

Concise, topical review material is welcomed, especially if it makes new concepts and ideas accessible to a wider community. Proposals for review material may be discussed with the Editor-in-Chief. Collections of case material and case reports will be considered only if they have broader scientific or clinical relevance. The Journal may be viewed and manuscripts submitted online at http://wileyonlinelibrary.com/journal/hon

Hematological Oncology

Vol. 41 Suppl. 2 June 2023
17th International Conference on Malignant Lymphoma

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SUPPLEMENT ARTICLE

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The Organizers would like to express their sincere gratitude to the Industry Partners who continue to support the Conference. Their unrestricted support is essential to the dissemination of the Scientific and Industry programs to the worldwide community engaged in the study and treatment of lymphoid neoplasms:
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(updated on April 2023)

The Organizers would like to express their sincere gratitude to the following Partners for their precious support, essential to the organization of our Conference and to the achievement of its objectives:
Agenzia Turistica Ticinese SA
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(updated on April 2023)

SAVE THE DATE: 18-ICML—18th International Conference on Malignant Lymphoma
Lugano, Switzerland
June 17–21, 2025

17-ICML REVIEWERS' LIST

The 17-ICML Organizing Committee wishes to thank the following colleagues and friends for their professional help:
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SUPPLEMENT ARTICLE

SCIENTIFIC PROGRAM (as of May 15, 2023) CONFIDENTIAL

Tuesday, June 13, 2023		
09:00–17:00		**CLOSED WORKSHOP**
Polivalente Room		Lugano Classification: Looking toward the future
East Campus USI		Organizing Committee: Sally Barrington, London, GB, Bruce D. Cheson, Bethesda, MD, USA, Andrew T. Lister, London, GB, Emanuele Zucca, Bellinzona, CH *organized with the support of the American Association for Cancer Research—AACR, the European School of Oncology—ESO and the European Society for Medical Oncology—ESMO (by invitation only)*
15:00–17:30		**LYMPHOMA RADIOTHERAPY WORKSHOP**
Cinema Corso		Radiation therapy as an immunogenic cell death mechanism in the environment of immunotherapy and adoptive cell therapy Moderators: Bouthaina S. Dabaja, Houston, TX, USA and Joachim Yahalom, New York, NY, USA *organized in collaboration with the International Lymphoma Radiation Oncology Group—ILROG (open to all 17-ICML attendees)*
15:05		Past, present and future (hematology perspective)
		Stephen Ansell, Rochester, MN, USA
15:25		Experimental basis for the contribution of radiation therapy to CAR-T cell therapy
		Carl DeSelm, St Louis, MO, USA
15:40		Review of current RT/ CAR-T programs data
		Brandon Imber, New York, NY, USA
16:00		Break
16:20		Is there a role for consolidation RT post-CAR-T? Patient selection and technical considerations
		George Mikhaeel, London, UK
16:40		Spectrum of CAR-T and future directions
		Bouthaina S. Dabaja, Houston, TX, USA
16:55		Case presentation and discussion
		Bouthaina S. Dabaja, Houston, TX, USA and Timothy Robinson, New Haven, CT, USA
17:15		Summary and Conclusions
		Joachim Yahalom, New York, NY, USA
Wednesday, June 14, 2023		
08:30–09:15	Article nr.	**"MEET THE PROFESSOR" SESSIONS**
		5 parallel sessions

(Continued)

Wednesday, June 14, 2023		
Room A	EB05	Update on Follicular Lymphoma
		Jonathan W. Friedberg, Rochester, NY, USA
		repeated on Friday, June 16, in Polivalente room
Room B	EB08	Germinal center in the genesis of lymphomas
		Laura Pasqualucci, New York, NY, USA
		repeated on Friday, June 16, in Auditorium
Cinema Corso	EB07	Are we reaching the maximum cure rate for Hodgkin lymphoma?
		Peter W.M. Johnson, London, GB
		repeated on Thursday, June 15, in Room A
Auditorium	EB10	Reappraisal of role of radiation therapy in lymphoma treatment
West Campus USI		Lena Specht, Copenhagen, DK
		offered only once
Polivalente room	EB01	Advances in PET and radiomics
East Campus USI		Sally Barrington, London, GB
		repeated Friday, June 16, in Room B
09:30–10:15		**"MEET THE PROFESSOR" SESSIONS**
		5 parallel sessions
Room A	EB11	Peripheral T-cell lymphomas
		Pier Luigi Zinzani, Bologna, IT
		repeated on Thursday, June 15, in Room B
Room B	EB12	Marginal zone lymphomas
		Emanuele Zucca, Bellinzona, CH
		repeated on Thursday, June 15, in Cinema Corso
Cinema Corso	EB09	Lymphoma in pregnancy
		Fedro A. Peccatori, Milan, IT
		offered only once
Auditorium	EB03	Management of Primary and Secondary CNS Lymphoma
West Campus USI		Kate Cwynarski, London, GB
		repeated on Thursday, June 15, in Polivalente room
Polivalente room	EB04	Mantle Cell lymphoma—Update on molecular biology, prognostication and treatment approaches
East Campus USI		Martin Dreyling, Munich, DE
		repeated on Friday, June 16, in Room A
10:00–12:00		POSTER SESSION set—up
Marquee		
10:35–12:00		**EDUCATIONAL SYMPOSIA**
		2 parallel sessions
Room A broadcast in Cinema Corso		**Diffuse Large B-Cell Lymphomas**
		Chair: Gilles Salles, New York, NY, USA

(Continues)

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Wednesday, June 14, 2023		
10:35	EB15	CAR T-cell Therapy in Large B Cell Lymphoma
		Gilles Salles, New York, NY, USA
11:00	EB14	The evolving therapy of DLBCL: Bispecific antibodies
		Martin Hutchings, Copenhagen, DK
11:25	EB13	Novel Agents in Relapsed/Refractory Diffuse Large B-cell Lymphoma
		Ranjana H. Advani, Stanford, CA, USA
11:50		Discussion
Room B broadcast in Marquee and Polivalente room, East Campus USI		**Chronic Lymphocytic Leukemia**
		Chair: Michael Hallek, Cologne, DE
10:35	EB16	Functional consequences of inhibition of Bruton's Tyrosine kinase by ibrutinib in chronic lymphocytic leukemia
		Nicholas Chiorazzi, Manhasset, NY, USA
11:00	EB17	First line therapy of CLL
		Michael Hallek, Cologne, DE
11:25	EB18	Therapy of relapsed disease and Richter's Syndrome
		John F. Seymour, Melbourne, AU
11:50		Discussion
12:00–18:00		**POSTER SESSION**
Marquee	Abstract nr.	
	157	EPIDEMIOLOGY
	158–171	BIOLOGY
	172–198	MICROENVIRONMENT
	199–216	TRANSLATIONAL STUDIES, B-CELL LYMPHOMAS
	217–226	TRANSLATIONAL STUDIES, PCTL AND cHL
	227–241	TRANSLATIONAL STUDIES, LIQUID BIOPSY
	242–251	IMAGING
	252–267	HODGKIN LYMPHOMA
	268–290	INDOLENT LYMPHOMAS
	291–303	EXTRANODAL LYMPHOMAS NON MZL
	304–337	DLBCL
	338–345	CLL
	346–359	MCL
	360–378	PTCL
	379–380	PLASMA CELL NEOPLASMS AND AMYLOIDOSIS
	381–402	CAR-T (CELLULAR THERAPIES)
	403 -419	PRECLINICAL NEW DRUGS
	420–451	PHASE I-II
	452–455	PEDIATRIC / YOUNG ADULTS
	456–458	INFECTIONS

(Continued)

Wednesday, June 14, 2023		
13:00–13:55		**OPENING OF THE CONFERENCE**
Room A broadcast in all rooms		WELCOME AND INTRODUCTORY REMARKS
		F. Cavalli, Bellinzona, CH
		HENRY KAPLAN MEMORIAL LECTURE AND SAN SALVATORE FOUNDATION PRIZE
		Introduction to San Salvatore Foundation: Stefano Coduri, Lugano, CH
		Laudatio: Rolf Stahel, Zurich, CH
	001	Lessons Learned from the Genetic Heterogeneity of Lymphoid Malignancies
		Margaret A. Shipp, Boston, MA, USA
14:00–15:15		**PLENARY SESSION**
		Chairs: Franco Cavalli, Bellinzona, CH and Catherine Thieblemont, Paris, FR
	004	Frontline intensified ABVD demonstrates superior efficacy than PET-adapted ABVD in advanced Hodgkin Lymphoma: the FIL-Rouge Phase 3 Trial by the Fondazione Italiana Linfomi
		Antonio Pinto, Naples, IT
	005	Nivolumab(N)-AVD Improves Progression-Free Survival Compared to Brentuximab Vedotin(BV)-AVD in Advanced Stage (AS) Classic Hodgkin Lymphoma (HL): Results of SWOG S1826
		Alex F. Herrera, Duarte, CA, USA
		Discussant
		Peter Borchmann, Cologne, DE
	006	Fourth generation huCART19-IL18 produces durable responses in lymphoma patients previously relapsed/refractory to anti-CD19 CAR T-cell therapy
		Jakub Svoboda, Philadelphia, PA, USA
		Discussant
		Gilles Salles, New York, NY, USA
15:45–16:45		**AACR—ICML JOINT SESSION**
Room A broadcast in all rooms		Technology that will change lymphoma understanding and care
		Chairs: Francesco Bertoni, Bellinzona, CH and Margaret Foti, Philadelphia, PA, USA
15:45	007	Single cell omics in the study of B cell lymphoma
		Katia Basso, New York, NY, USA
16:05	008	Circulating tumor DNA (liquid biopsy)
		Davide Rossi, Bellinzona, CH
16:25	009	Organoids
		Arianna Baggiolini, Bellinzona, CH
17:00–18:00		**"FOCUS ON..." SESSIONS**
		5 parallel sessions
Room A		**Mantle Cell Lymphoma**
		Chairs: Martin Dreyling, Munich, DE and John P. Leonard, New York, NY, USA

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Wednesday, June 14, 2023		
17:00	098	Five-year update of the first-line IMCL-2015 GELTAMO study. Prolonged molecular and clinical responses were observed after MRD-driven ibrutinib discontinuation
		Eva Giné, Barcelona, ES
17:10	099	Acalabrutinib with rituximab as first-line therapy for older patients with mantle cell lymphoma—a phase II clinical trial
		Preetesh Jain, Houston, TX, USA
17:20	100	Very Long-term follow-up of rituximab maintenance in young patients with mantle cell lymphoma included in the LYMA trial, a LYSA study.
		Clémentine Sarkozy, Saint Cloud, FR
17:30	101	Ibrutinib-rituximab and venetoclax (IRV) followed by risk-stratified R-HyperCVAD/MTX in young patients with untreated mantle cell lymphoma—phase-II WINDOW-2 trial
		Michael L. Wang, Houston, TX, USA
17:40	102	Pirtobrutinib in covalent BTK-inhibitor pre-treated mantle cell lymphoma: updated results, subgroup analysis from BRUIN with >3 years follow-up from start of enrollment
		Chan Y. Cheah, Perth, AU
17:50	103	Outcomes of autologous transplant, allogeneic transplant, and CAR T cell therapy in TP53 altered mantle cell lymphoma: a multi-institution retrospective analysis
		Marcus Messmer, Philadelphia, PA, USA
Room B broadcast in Marquee		**Hodgkin Lymphoma**
		Chairs: Ranjana H. Advani, Stanford, CA, USA and Peter Borchmann, Cologne, DE
17:00	104	Correlation between progression-free and overall survival in patients with classical Hodgkin lymphoma: a comprehensive analysis of individual patient data from GHSG trials
		Paul J. Bröckelmann, Cologne, DE
17:10	105	Early FDG-PET adapted treatment of limited stage Hodgkin lymphoma (HL): 10y long term follow-up analysis of the randomized Intergroup EORTC/LYSA/FIL H10 trial
		Massimo Federico, Modena, IT
17:20	106	Pembrolizumab as first therapy for Hodgkin lymphoma is deliverable in older or ABVD-ineligible patients, allows subsequent therapy, and gives adequate survival
		Michael J. Dickinson, Melbourne, AU
17:30	107	Phase 2 trial of Nivolumab plus Adriamycin, Vinblastine, Dacarbazine (N-AVD) as Frontline Therapy in Older Adults with Hodgkin Lymphoma
		Pallawi Torka, New York, NY, USA
17:40	108	Avelumab monotherapy followed by a PET adapted chemotherapy approach in the first line treatment of classical Hodgkin Lymphoma: Initial results from the AVENuE window study
		Graham P. Collins, Oxford, GB
17:50	109	Favezelimab plus pembrolizumab in anti–PD-1–refractory classical Hodgkin lymphoma (cHL): Estimating the relative efficacy of favezelimab
		Philippe Armand, Boston, MA, USA

(Continued)

Wednesday, June 14, 2023		
Cinema Corso		**Ongoing trials**
		Chairs: John Kuruvilla, Toronto, ON, CA and Grzegorz S. Nowakowski, Rochester, NJ, USA
17:00	OT1	SAKK 38/19: Assessing a ctDNA and PET-oriented therapy in patients with DLBCL. A multicenter, open-label, phase II trial.
		Anastasios Stathis, Bellinzona, CH
17:10	OT2	REMoDL-A: A Randomised Phase II Evaluation of Molecular Guided Therapy for Diffuse Large B-cell Lymphoma (DLBCL) with Acalabrutinib
		Vivek S. Radhakrishnan, Southampton, GB
17:20	OT3	Brentuximab Vedotin-Nivolumab alone and then with Rituximab-Cyclophosphamide-Doxorubicin-Prednisone as Frontline Therapy of Primary Mediastinal Large B-cell Lymphoma
		Raphael E. Steiner, Houston, TX, USA
17:30	OT4	MAHOGANY: A phase 3 trial of zanubrutinib plus anti-CD20 versus lenalidomide plus rituximab in patients with relapsed/refractory follicular or marginal zone lymphoma
		Laurie H. Sehn, Vancouver, BC, CA
17:40	OT5	SUNMO: Phase III trial of mosunetuzumab plus polatuzumab vedotin vs. rituximab plus gemcitabine and oxaliplatin in relapsed/refractory aggressive non-Hodgkin lymphoma
		Astrid Pavlovsky, Buenos Aires, AR
17:50	OT6	ZUMA-23: A Global, Phase 3, Randomized Controlled Study of Axicabtagene Ciloleucel vs. Standard of Care as First-Line Therapy in Patients with High-Risk Large B-Cell Lymphoma
		Jason R. Westin, Houston, TX, USA
Auditorium		**Liquid Biopsy and Minimal Residual Disease**
West Campus USI		Chairs: Christiane Pott, Kiel, DE and Davide Rossi, Bellinzona, CH
17:00	110	Molecular clustering on ctDNA improves the prognostic stratification of DLBCL patients compared to ctDNA levels
		Riccardo Moia, Novara, IT
17:10	111	Circulating tumor DNA (ctDNA) status and clinical outcomes in patients (pts) with previously untreated diffuse large B-cell lymphoma (DLBCL) in the POLARIX study
		Alex F. Herrera, Duarte, CA, USA
17:20	112	MRD-Negativity After Frontline DLBCL Therapy: Pooled Analysis of 6 Clinical Trials
		Mark Roschewski, Bethesda, MD, USA
17:30	113	Early ctDNA clearance after CAR T-cell infusion predicts outcome in patients with Large B-cell lymphoma: results from ALYCANTE, a phase 2 LYSA study
		Marie-Hélène Delfau-Larue, Creteil, FR
17:40	114	Cell-free DNA kinetics decipher potential mechanisms of action of Ibrutinib combination therapy in mantle cell lymphoma (MCL)
		Mouhamad Khouja, Kiel, DE
17:50	115	Combined use of minimal residual disease monitoring and FDG-PET for outcome prediction in follicular lymphoma: results from the Fondazione Italiana Linfomi (FIL) FOLL12 trial
		Simone Ferrero, Turin, IT

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Wednesday, June 14, 2023		
Polivalente room		**Mechanisms of treatment resistance**
East Campus USI		Chairs: Vincent Ribrag, Villejuif, FR and Patrizia Mondello, Rochester, MN, USA
17:00	116	Genomic evolution and resistance to pirtobrutinib in covalent BTK-inhibitor pre-treated chronic lymphocytic leukemia patients: results from the phase I/II BRUIN study
		Krish Patel, Seattle, WA, USA
17:10	117	Single-cell RNA-Seq of classic hairy cell leukemia reveals disease drivers linked to intrinsic treatment resistance and identifies DUSP1 as potential new therapeutic target
		Jan-Paul Bohn, Innsbruck, AT
17:20	118	IL16 production is a mechanism of resistance to BTK inhibitors and to R-CHOP
		Alberto Arribas, Bellinzona, CH
17:30	119	Enhancer RNAs (eRNAs) play a role in the response to small molecules and in the development of acquired resistance in marginal zone lymphoma (MZL).
		Sara Napoli, Bellinzona, CH
17:40	120	Harnessing BTKi therapy by CDK4/6i control of T cell surveillance
		Selina Chen-Kiang, New York, NY, USA
17:50	121	Immune-depleted tumor microenvironment is associated with poor outcomes and BTK inhibitor resistance in mantle cell lymphoma
		Preetesh Jain, Houston, TX, USA
Thursday, June 15, 2023		
08:15–09:00	Article nr.	**"MEET THE PROFESSOR" SESSIONS**
		5 parallel sessions
Room A	EB07	Are we reaching the maximum cure rate for Hodgkin lymphoma?
		Peter W.M. Johnson, London, GB
		repetition
Room B	EB11	Peripheral T-cell lymphomas
		Pier Luigi Zinzani, Bologna, IT
		repetition
Cinema Corso	EB12	Marginal zone lymphomas
		Emanuele Zucca, Bellinzona, CH
		repetition
Auditorium	EB06	Post-Transplant Lymphoproliferative Disease (PTLD) in Children, Adolescents, and Young Adults
West Campus USI		Thomas Gross, Aurora, CO, USA
		offered only once
Polivalente room	EB03	Management of Primary and Secondary CNS Lymphoma
East Campus USI		Kate Cwynarski, London, GB
		repetition
09:15–10:30		**"CLINICAL CASES DISCUSSION" SESSIONS**
		3 parallel sessions

(Continued)

Thursday, June 15, 2023		
Room A		HODGKIN AND T-CELL LYMPHOMAS
		Chair: Andrew T. Lister, London, UK
		Presenter: Alden Moccia, Bellinzona, CH
		Discussants: Richard Hoppe, Stanford, CA, USA, Andrew T. Lister, London, UK and Astrid Pavlovsky, Buenos Aires, AR
Cinema Corso		INDOLENT NHLs AND CLL
		Chair: Jonathan Friedberg, Rochester, NY, USA
		Presenter: Adalgisa Condoluci, Bellinzona, CH
		Discussants: Jonathan Friedberg, Rochester, NY, USA, Mary Gospodarowicz, Toronto, ON, CA and Michael Hallek, Cologne, DE
Auditorium		PEDIATRIC LYMPHOMAS
West Campus USI		Chair: Wilhelm Wössmann, Hamburg, DE
		Presenter: Francesco Ceppi, Lausanne, CH
		Discussant: Thomas Gross, Aurora, CO, US
09:15–10:30		**SESSION 1—DISSECTING LYMPHOMAS AT THE SINGLE CELL LEVEL**
Room B broadcast in Marquee		Chair: Elias Campo, Barcelona, ES and Leticia Quintanilla—Martinez, Tuebingen, DE
09:15	010	The tumor microenvironment of Hodgkin lymphoma at single cell resolution
		Christian Steidl, Vancouver, B.D., CA
09:35	011	Trajectories of lymphomagenesis
		Bertrand Nadel, Marseille, FR
09:55	012	Subclonal heterogeneity driving progression and transformation in chronic lymphocytic leukemia
		Elias Campo, Barcelona, ES
10:15	013	Diversity of intratumoral regulatory T cells in B-cell non-Hodgkin lymphoma
		Ivana Spasevska, Olso, NO
09:15–10:30		**SESSION 2—LYMPHOMAS AFFECTING THE CNS**
Polivalente room		Chairs: Kate Cwynarski, London, GB and Andrés J. Ferreri, Milan, IT
East Campus USI		
09:15	014	Identification of Genomic Biomarkers of Disease Progression and Survival in Newly-Diagnosed Primary CNS Lymphoma
		James Rubenstein, San Francisco, CA, USA
09:30	015	Consolidative HCT-ASCT is superior to non-myeloablative chemo-immunotherapy in newly-diagnosed PCNSL—Updated results of the randomized phase III MATRix/IELSG43 trial
		Gerard Illerhaus, Stuttgart, DE
09:45	016	CAR-T cells radically modify the management of relapsed/refractory primary cerebral lymphomas. Real life results of the French LOC network
		Sylvain Choquet, Paris, FR
10:00	017	Phase 2 study of ibrutinib with temozolomide, etoposide, liposomal doxorubicin, dexamethasone, rituximab (TEDDi-R) for secondary CNS lymphoma

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(Continued)

Thursday, June 15, 2023		
		Mark Roschewski, Bethesda, MD, USA
10:15	018	Five-year results of a phase 2 study of CNS-oriented therapy with R-CHOP for untreated intravascular large B-cell lymphoma: Final analysis of the PRIMEUR-IVL study
		Kazuyuki Shimada, Nagoya, JP
11:00–12:00		**SESSION 3—TREATMENT OF AGGRESSIVE LYMPHOMAS**
Room A broadcast in all rooms		Chair: Franck Morschhauser, Lille, FR and Laurie H. Sehn, Vancouver, BC, CA
11:00	019	A randomized trial of observation versus radiotherapy in primary mediastinal B-cell lymphoma patients with complete metabolic response after standard immunochemotherapy.
		Andrew J. Davies, Southampton, GB
11:15	020	R-CODOX-M/R-IVAC versus DA-EPOCH-R in Patients with newly diagnosed high-risk Burkitt lymphoma: FINal results of a multi-center randomized HOVON/SAKK trial.
		Martine Chamuleau, Amsterdam, NL
11:30	021	Biomarker-driven treatment strategy in high-risk large B-cell lymphoma (NLG-LBC-06 phase II trial): Impact of ctDNA and TP53 aberrations on clinical outcome
		Sirpa Leppa, Helsinki, FI
11:45	022	Primary overall survival analysis of the Phase 3 randomized ZUMA-7 study of axicabtagene ciloleucel versus standard of care in relapsed/refractory large B cell lymphoma
		Jason R. Westin, Houston, TX, USA
12:00–18:00		POSTER SESSION
Marquee		
13:00–13:45		**GIANNI BONADONNA MEMORIAL LECTURE**
Room A broadcast in all rooms		Supported by the European School of Oncology—ESO
		Laudatio: Riccardo Dalla-Favera, New York, NY, USA
	002	Elucidating the enigmatic pathobiology of Hodgkin lymphoma
		Ralf Küppers, Essen, DE
13:45–15:15		**SESSION 4—CLL AND RICHTER SYNDROME**
Room A broadcast in room B, Marquee, Cinema Corso and Polivalente room, East Campus USI		Chairs: Michael J. Hallek, Cologne, DE and Thorsten Zenz, Zurich, CH
13:45	023	FoxO1-Rictor axis induces Akt phosphorylation during CLL cell adaptation to BCR inhibitors: implications for combinatorial therapy
		Laura Ondrisova, Brno, CZ
14:00	024	Ibrutinib versus placebo in patients with asymptomatic, treatment-naïve early stage chronic lymphocytic leukemia (CLL): Final results of the CLL12 trial
		Petra Langerbeins, Cologne, DE
14:15	025	Venetoclax-Obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized CLL14 study
		Othman Al-Sawaf, Cologne, DE

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Thursday, June 15, 2023		
14:30	026	Lisocabtagene maraleucel (liso-cel) in R/R chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): primary analysis of TRANSCEND CLL 004
		Tanya Siddiqi, Duarte, CA, USA
14:45	027	Efficacy and safety of MOLTO, a multicenter, open label, phase II clinical trial evaluating venetoclax, atezolizumab and obinutuzumab combination in Richter Syndrome
		Anna M. Frustaci, Milan, IT
15:00	028	Glofitamab monotherapy induces durable complete remissions and has a manageable safety profile in patients with Richter's transformation
		Carmelo Carlo-Stella, Milan, IT
13:45–16:45		**SESSION 5—PEDIATRIC LYMPHOMAS**
Auditorium		Chair: Francesco Ceppi, Lausanne, CH
West Campus USI		
13:45	029	Primary mediastinal B cell lymphoma in children, adolescents and young adults
		Lisa Giulino Roth, New York, NY, USA
14:10	030	Minimal disseminated and residual disease in pediatric NHL
		Wilhelm Wössmann, Hamburg, DE
14:35	031	Phase 2 KEYNOTE-667: Pembrolizumab in children and young adults with classical Hodgkin lymphoma (cHL) with slow early response to front-line chemotherapy
		Luciana Vinti, Rome, IT
14:50	032	Analysis treatment outcome of 46 refractory/relapsed pediatric mature B cell lymphoma patients-multi-center experience from China
		Yonghong Zhang, Beijing, CN
15:05	033	Allogeneic hematopoietic stem cell transplantation with reduced-toxicity conditioning for pediatric relapsed or refractory ALK-positive anaplastic large cell lymphoma
		Fabian Knörr, Hamburg, DE
15:20	034	Patterns of presentation and outcomes in Stage IV Hodgkin lymphoma: A report from the Children's Oncology Group (COG) AHOD1331 trial
		Dana Casey, Chapel Hill, NC, USA
15:35		Break
15:45	035	Landscape of driver mutations and their clinical impacts in Chinese pediatric patients with mature B-cell non-Hodgkin's lymphoma and T-cell lymphoblastic lymphoma
		Qinlong Zheng and Yang Liu, Beijing, CN
15:57	036	ALK-positive anaplastic large cell lymphoma with variant ALK-fusion partner: a population-based analyses of the NHL-BFM study group
		Christine Damm-Welk, Hamburg, DE
16:09	037	Lung staging in pediatric Hodgkin Lymphoma: Staging Evaluation & Response Criteria Harmonization for Childhood, Adolescent & Young Adult HL (SEARCH for CAYAHL) consensus (432)
		Jennifer Seelisch, London, CA
16:21	038	Quality of Life in Pediatric High-Risk Hodgkin Lymphoma Treated with Brentuximab-Based Intensive Chemotherapy—Comparison to Historical Treatment Cohort and Healthy Peers

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Thursday, June 15, 2023		
		Angela M. Feraco, Boston, MA, USA
16:33	039	Quantitative whole-body MRI for predicting treatment outcome in pediatric patients with aggressive non-Hodgkin lymphoma undergoing chimeric antigen receptor T cell therapy
		Yu Xia Li, Weihui, CN
15:30–16 :45		**SESSION 6—PERIPHERAL T-CELL LYMPHOMAS**
Room A broadcast in Cinema Corso		Chairs : Julie Vose, Omaha, NE, USA and Pier Luigi Zinzani, Bologna, IT
15:30	040	The genetic subtypes and the tumor microenvironment signatures are associated with distinct outcomes in peripheral T-cell lymphoma
		Yasuhito Suehara, Tsukuba, JP
15:45	041	Romidepsin plus CHOP versus CHOP in Patients with Previously Untreated Peripheral T-Cell Lymphoma: final analysis of the Ro-CHOP trial
		Vincent Camus, Rouen, FR
16:00	042	Targeted agents combined with CHOP compared with CHOP as the first-line therapy for peripheral T-cell lymphoma: preliminary results from a phase 2 GUIDANCE-03 Trial
		Weili Zhao, Shanghai, CN
16:15	043	Golidocitinib in Treating Refractory or Relapsed Peripheral T- Cell Lymphoma: Primary Analysis of the Multinational Pivotal Study Results (JACKPOT8)
		Won Seog Kim, Seoul, KR
16:30	044	First in human study of AUTO4, a TRBC1-tragetting CART T cell therapy in Relapsed/Refractory TRBC1-Positive Peripheral T-cell Lymphoma
		Kate Cwynarski, London, GB
15:30–16 :45		**SESSION 7—NEW CAR-T CELL APPROACHES**
Room B broadcast in Marquee and Polivalente room, East Campus USI		Chairs: Elise A. Chong, Philadelphia, PA, USA and Anna Sureda, Barcelona, ES
15:30	045	Phase 2 Study of Anbal-cel, Novel Anti-CD19 CAR-T therapy with Dual Silencing of PD-1 and TIGIT in Relapsed or Refractory Large B Cell Lymphoma—Interim Analysis Result
		Won Seog Kim, Seoul, KR
15:45	046	Point-of-care anti-BCMA CAR T-cell therapy induces encouraging response rates in high-risk relapsed/refractory multiple myeloma
		Hila Magen, Tel Hashomer, IL
16:00	047	Off-the-shelf CD30.CAR-modified Epstein-Barr Virus-specific T cells (CD30.CAR EBVSTs) provide a safe and effective therapy for patients with Hodgkin lymphoma (HL)
		Carlos A. Ramos, Houston, TX, USA
16:15	048	Durables responses with anti-CD19 allogeneic CAR T ALLO-501/501A in phase 1 trials of relapsed/refractory large B-cell lymphoma (r/r LBCL)
		Frederick L. Locke, Tampa, FL, USA
16:30	049	High efficacy and favorable safety of 3rd generation CD20 CAR-T (MB-106) for outpatient treatment of follicular lymphoma (FL)—results of a single-institution trial
		Mazyar Shadman, Seattle, WA, USA

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Thursday, June 15, 2023		
17:00–18:00		**"FOCUS ON…" SESSIONS**
		5 parallel sessions
Room A		**T- Cell Lymphomas**
		Chairs : Stefano Luminari, Reggio Emilia, IT and Won Seog Kim, Seoul, KR
17 :00	122	Lack of SMARCB1 expression characterizes a subset of peripheral T-cell lymphomas enriched in children and young adults
		Anja Fischer, Ulm, DE
17:10	123	Chromatin Accessibility Profiling to Increase Diagnostic Accuracy and Refine Cell-of-Origin Classification of Mature T-Cell Lymphomas
		Edith Julia, Lyon, FR
17:20	124	BRCA1/2 mutations impact on the development of breast implant-associated lymphoma (BIA-ALCL) in women with breast cancer reconstructed with textured breast implants.
		Paola Ghione, New York, NY, USA
17:30	125	A phase 2 trial of CHOP with anti-CCR4 antibody mogamulizumab for elderly patients with CCR4-positive adult T-cell leukemia/lymphoma.
		Atae Utsunomiya, Kagoshima, JP
17:40	126	AFM13 in patients with CD30-positive relapsed or refractory (R/R) peripheral T cell lymphoma (PTCL): Results from the Phase 2 REDIRECT study
		Won Seog Kim, Seoul, KR
17:50	127	Lacutamab in patients with advanced mycosis fungoides (MF): efficacy results according to updated lymph node (LN) classification in the TELLOMAK study
		Pierluigi Porcu, Philadelphia, PA, USA
Room B broadcast in Marquee		**CAR-T Cell**
		Chairs: Tanya Siddiqi, Duarte, CA, USA and Jason R. Westin, Houston, TX, USA
17:00	128	Proteomic profiling identifies granzyme B inhibitor Serpin B9 as mediator of resistance to CAR T-cell and bispecific antibody treatment in nodal B-cell lymphoma
		Berit J. Brinkmann, Heildelberg, DE
17:10	129	CART-SIE real life study: primary mediastinal B-cell lymphoma (PMBCL) have a superior outcome compared to large B-cell lymphoma (LBCL) treated with axicabtagene ciloleucel
		Annalisa Chiappella, Milan, IT
17:20	130	Impact of response to systemic bridging therapy on clinical outcomes and cytokine profile in patients receiving CAR T-cell therapy for aggressive B-cell lymphoma
		Beatriz Wills, New York, NY, USA
17:30	131	Bendamustine lymphodepletion triggers reduced inflammatory cytokines and decreased toxicities after both 4-1BB- and CD28-costimulated CART19 for non-Hodgkin lymphoma
		Guido Ghilardi, Philadelphia, PA, USA
17:40	132	Prognostic scoring systems for severe CRS and ICANS after autologous anti-CD19 CAR T cells in large B-cell lymphoma: a DESCAR-T registry study form the LYSA

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Thursday, June 15, 2023		
		Pierre Sesques, Pierre Benite, FR
17:50	133	Severe hematological toxicity following CD19 CAR-T for relapsed/refractory LBCL is associated with suppressive immune dysregulation and limited CAR-T expansion
		Kai Rejeski, Munich, DE
Cinema Corso		**Large B-Cell and Double Hit Lymphomas**
		Chairs: Andrew J. Davies, Southampton, GB and Brad Kahl, Saint Louis, MO, USA
17:00	134	MYC/BCL6 double hit lymphoma negative for t(3;8) BCL6::MYC fusion is associated with inferior survival, in contrast with t(3;8) positive pseudo-double hit lymphoma
		Bernard D. Maybury, Birmingham, GB
17:10	135	High complete metabolic response rates with epcoritamab + R-CHOP in previously untreated (1L) high-risk DLBCL, including double-hit/triple-hit: EPCORE NHL-2 update
		Lorenzo Falchi, New York, NY, USA
17:20	136	waveLINE-004: open-label, phase 2 study of zilovertamab vedotin (MK-2140) in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)
		Alexander Fosså, Olso, NO
17:30	137	Long-term responses with loncastuximab tesirine: updated results from LOTIS-2, the pivotal phase 2 study in patients with relapsed/refractory diffuse large b-cell lymphoma
		Paolo F. Caimi, Cleveland, OH, USA
17:40	138	Lisocabtagene maraleucel (liso-cel) vs. standard of care (SOC) as second-line therapy in large B-cell lymphoma (TRANSFORM study): Subgroup analyses by prior therapy response
		Loretta J. Nastoupil, Houston, TX, USA
17:50	139	Comparative accuracy of alternative early measures of residual disease after CAR19 therapy of relapsed/refractory LBCL
		Brian J. Sworder, Palo Alto, CA, USA
Auditorium		**Radiotherapy**
West Campus USI		Chairs: Bouthaina S. Dabaja, Houston, TX, USA and Lena Specht, Copenhagen, DK
17:00	140	Rituximab-Containing Combined Modality Therapy in Limited Stage Follicular Lymphoma: Mature follow up and derivation of a novel prognostic score from the TROG99.03 Trial
		Michael MacManus, Brisbane, AU
17:10	141	Radiotherapy bridging in large B-cell lymphoma patients receiving CD19 CAR-T—The UK experience
		Andrea Kuhnl, London, GB
17:20	142	High rate of metabolic complete response after low dose radiotherapy and Obinutuzumab in early stage follicular lymphoma: Initial results of the GAZAI study (GLA 2018-3)
		Klaus Herfarth, Heidelberg, DE
17:30	143	Very low dose Radiation therapy for Indolent lymphoma: Comparing "Big Boom" (4 Gy × 1) versus "Boom Boom" (2 Gy × 2)
		Joachim Yahalom, New York, NY, USA

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Thursday, June 15, 2023		
17:40	144	Salvage Radiotherapy in Relapsed/Refractory Large B-Cell Lymphoma After CAR T-Cell Therapy Failure
		Chirayu Patel, Boston, MA, USA
17:50	145	Bone marrow volume irradiated and risk of cytopenias in aggressive B-cell lymphoma patients bridged with radiation therapy for CART cell therapy
		Bouthaina S. Dabaja, Houston, TX, USA
Polivalente room		**Lymphoma microenvironment**
East Campus USI		Chairs: Nicholas Chiorazzi, Manhasset, NY, USA and Laurence L. de Leval, Lausanne, CH
17:00	146	Immune contexture analysis in POLARIX suggests response to Pola-R-CHP treatment reduces tumor microenvironment dependency
		Franck Morschhauser, Lille, FR
17:10	147	Spatially-resolved transcriptomics define clinically relevant subsets of macrophages in diffuse large B-cell lymphoma
		Anand D. Jeyasekharan, Singapore, SG
17:20	148	Coordinated changes in the tumor microenvironment (TME) are associated with increased risk of therapeutic failure in newly diagnosed diffuse large B-cell lymphoma (DLBCL)
		José C. Villasboas, Rochester, MN, USA
17:30	149	EZH2 inhibition enhances CAR T antitumor effect by inducing lymphoma immunogenicity and enhancing T cell function
		Wendy Béguelin, New York, NY, USA
17:40	150	Single cell analysis reveals immune dysfunction in large B cell Lymphoma (LBCL) pts with hypomagnesemia receiving Axi-cel: results from ZUMA-1 trial and Mayo Clinic cohort
		Patrizia Mondello, Rochester, MN, USA
17:50	151	Follicular lymphoma patient-derived organoids for bispecific T-cell engager immunotherapy
		Joseph G. Schroers-Martin, Stanford, CA, USA
Friday, June 16, 2023		
08:15–09 :00		**"MEET THE PROFESSOR" SESSION**
Room A	EB04	Mantle Cell lymphoma—Update on molecular biology, prognostication and treatment approaches
		Martin Dreyling, Munich, DE
		repetition
Room B	EB01	Advances in PET and radiomics
		Sally Barrington, London, GB
		repetition
Cinema Corso	EB02	Cutaneous T-cell lymphomas—focus on some problems and some solutions
		Helmut Beltraminelli, Locarno, CH
		offered only once
Auditorium	EB08	Germinal center in the genesis of lymphomas
West Campus USI		Laura Pasqualucci, New York, NY, USA
		repetition
Polivalente room	EB05	Update on Follicular Lymphoma

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Friday, June 16, 2023		
East Campus USI		Jonathan W. Friedberg, Rochester, NY, USA
		repetition
09:00–12:00		**LYMPHOMA RADIOTHERAPY WORKSHOP**
Auditorium West Campus USI		Opportunities in Lymphoma Radiation Therapy Today: Lower Doses, Fewer Fractions, and Real World "Big Data" Analyses using Machine Learning and Artificial Intelligence Moderators: Lena Specht, Copenhagen, DK and Mary Gospodarowicz, Toronto, ON, CA *organized in collaboration with the International Lymphoma Radiation Oncology Group—ILROG (open to all 17-ICML attendees)*
09:00		Background for lower and ultra-low radiation doses for lymphoma
		Andrea Ng, Boston, Massachusetts, USA
09:30		Clinical Experience with ultra-low dose regimens in indolent lymphomas—lessons from the COVID experience
		Joanna Yang, St. Louis, MO, USA
09:50		Background for fewer but larger fractions (hypofractionation)
		Umberto Ricardi, Turin, IT
10:20		Clinical experience with hypfractionation—lessons from the COVID experience
		Joanna Yang, St. Louis, MO, USA
10:40		Real world "Big Data" analyses to discover what really works
		Lena Specht, Copenhagen, DK
09:15–10:30		**"CLINICAL CASES DISCUSSION" SESSIONS**
		2 parallel sessions
Room A		AGGRESSIVE NHLs
		Chair: John P. Leonard, New York, NY, USA
		Presenter: Maria Cristina Pirosa, Bellinzona, CH
		Discussants: Brad Kahl, Saint Louis, MO, USA and John P. Leonard, New York, NY, USA
Cinema Corso		DIFFICULT PATHOLOGICAL CASES
		Chair: Luca Mazzucchelli, Locarno, CH
		Presenters: Luca Mazzucchelli, Locarno, CH and Emanuele Zucca, Bellinzona, CH
		Discussants: Stephan Dirnhofer, Basel, CH and Leticia Quintanilla—Martinez, Tuebingen, DE
09:15–10 :30		**SESSION 8—EPIGENETIC MECHANISMS AND TARGETED THERAPIES IN B- AND T-CELL LYMPHOMAS**
Room B broadcast in Marquee		Chairs: Ari M. Melnick, New York, NY, USA and Margaret A. Shipp, Boston, MA, USA
09:15	050	Epigenetic basis and therapy of DLBCL
		Ari M. Melnick, New York, NY, USA
09:35	051	Epigenetic regulation of immune microenvironment interactions in lymphoma
		Michael R. Green, Houston, TX, USA

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Friday, June 16, 2023		
09:55	052	Epigenetic basis and therapy of follicular helper T-cell lymphomas
		François Lemonnier, Créteil, FR
10:15	053	Super-enhancer hypermutation in DLBCL: role of alterations in the glucocorticoid receptor pathway
		Elodie Bal, New York, NY, USA
09:15–10 :30		**SESSION 9—LYMPHOMA IMAGING**
Polivalente room East Campus USI		Chairs: Sally F. Barrington, London, GB and Bruce D. Cheson, Bethesda, MD, USA
09:15	054	Baseline PET Radiomics Outperforms Clinical Risk Scores in Predicting Primary Mediastinal B-Cell Lymphoma Outcome: Insights from the IELSG37 Study
		Luca Ceriani, Bellinzona, CH
09:30	055	Risk stratification of DLBCL with MVED2 score using integrative host adipose density and metabolic tumor characteristics compared to other indexes
		Catherine Thieblemont, Paris, FR
09:45	056	Baseline SUV and early response, but not MTV, are associated with outcome in relapsed/refractory Hodgkin lymphoma patients treated with nivolumab in the CHECKMATE 205 trial
		Sally F. Barrington, London, GB
10:00	057	Dynamics of radiomic features following bridging therapy determine CD19 chimeric antigen receptor (CAR) T-cell therapy outcome
		Brandon S. Imber, New York, NY, USA
10:15	058	Radiomics reflecting both tumor and host features improves outcome prediction in follicular lymphoma
		Louis Rebaud, Paris, FR
10:00–18:00		POSTER SESSION
Marquee		
11:00–12:00		**SESSION 10—HODGKIN LYMPHOMA**
Room A broadcast in Room B, Marquee, Cinema Corso and Polivalente room, East Campus USI		Chairs: Andrew T. Lister, London, GB and Astrid Pavlovsky, Buenos Aires, AR
11:00	059	Genetically Distinct Pathogenesis of Epstein-Barr Virus (EBV)-positive Versus EBV-negative Classical Hodgkin (cHL) Lymphoma
		Enrico Tiacci, Perugia, IT
11:15	060	Distinct Hodgkin lymphoma subtypes identified by noninvasive genomic profiling
		Stefan K. Alig, Stanford, CA, USA
11:30	061	Dual targeting of Hodgkin's Lymphoma by anti-CD30 CAR-T cells co-transduced with an anti-PDL1 costimulatory receptor to overcome the immunosuppressive microenvironment
		Brunangelo Falini, Perugia, IT
11:45	062	The prognostic impact of clinical factors and immunoarchitectural patterns for nodular lymphocyte-predominant Hodgkin lymphoma: an international study by GLOW
		Michael S. Binkley, Stanford, CA, USA

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Friday, June 16, 2023		
13:00–13:45		**JOHN ULTMANN MEMORIAL LECTURE**
Room A broadcast in all rooms		Supported by the American Association for Cancer Research—AACR
		Laudatio: Jonathan W. Friedberg, Rochester, NY, USA
	003	25 years of antibody treatments for lymphoma
		Peter W.M. Johnson, Southampton, GB
13:45–15:00		**SESSION 11—MARGINAL ZONE LYMPHOMA**
Room A broadcast in Cinema Corso		Chairs: Izidore S. Lossos, Miami, FL, USA and Grzegorz S. Nowakowski, Rochester, NJ, USA
13:45	063	Marginal Zone Lymphoma International Prognostic Index (MZL-IPI): a prognostic score for the entire spectrum of marginal zone lymphomas. A FIL and SPORE-MER study
		Stefano Luminari, Reggio Emilia, IT
14:00	064	Staging FDG-avidity in extranodal marginal zone lymphoma (EMZL) by disease location
		Juan P. Alderuccio, Miami, FL, USA
14:15	065	Rituximab and Ibrutinib Combination Is Safe and Effective in Untreated Splenic and Nodal Marginal Zone Lymphomas: Planned Subset Analysis of the IELSG47/MALIBU Phase II Study
		Catherine Thieblemont, Paris, FR
14:30	066	The IELSG39 Trial: Efficacy of First-Line Chlamydia psittaci Eradication with a Six-Month Regimen of Doxycycline in Patients with Stage-I MALT Lymphoma of the Ocular Adnexae
		Andrés J. M. Ferreri, Milan, IT
14:45	067	Immunotherapy alone versus chemoimmunotherapy as first-line treatment of marginal zone lymphoma (MZL): a real-world analysis
		Adam J. Olszewski, Providence, RI, USA
13:45–15:00		**SESSION 12—LYMPHOMA BIOLOGY**
Room B broadcast in Marquee		Chairs: Riccardo Dalla-Favera, New York, NY, USA and Gianluca Gaidano, Novara, IT
13:45	068	BTG2 super-enhancer mutations disrupt TFAP4 binding and dysregulate BTG2 expression in Diffuse Large B-cell Lymphoma
		Elodie Bal, New York, NY, USA
14:00	069	Clonal architecture of relapsed or refractory follicular helper T-cell lymphoma: an ancillary study of the ORACLE trial, a LYSA study
		François Lemonnier, Creteil, FR
14:15	070	Molecular characterization contributes to diagnosis and predicts outcome in primary mediastinal large B-cell lymphomas: a LYSA study
		Vincent Camus, Rouen, FR
14:30	071	Gene expression profiling of t(14;18)-negative CD23+ follicle center lymphoma demonstrates activation of the IL4/JAK/STAT6 pathway and a role in its pathogenesis
		Tim-Colin Schade, Tuebingen, DE
14:45	072	Immunoglobulin class dictates transformation trajectory and BCR status of MYC/BCL2 double-hit lymphoma: biology and clinical implications
		Stefano Casola, Milan, IT

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Friday, June 16, 2023		
14:30–16:30		**IBSA FOUNDATION SPECIAL FORUM**
Auditorium		Personalized therapy in oncology
West Campus USI		Moderator: Andrea Alimonti, Bellinzona, CH
		Organized by IBSA Foundation for scientific research
14:30		Institutional greetings and introduction
14:40		Organoids model human disease
		Hans Clevers, Basel, CH
15:20		Unconventional approaches to cancer therapy
		René Bernards, Amsterdam, NL
16:00		Patient-specific models of multicellular oncogenic competence in metastasis
		Arianna Baggiolini, Bellinzona, CH
16:15		Q&A
14:30–17:30		**UCLI—ICML JOINT SESSION**
Polivalente room		LYMPHOMA RESEARCH: NEWS FROM CHINA AND EUROPE
East Campus USI		In collaboration with Union for China Lymphoma Investigators—UCLI
		Honorary co-chairs: Jun Ma, Harbin, CN, Jun Zhu, Beijing, CN, Franco Cavalli, Bellinzona, CH and Julie Vose, Omaha, NE, USA
		Executive co-chairs: Yuqin Song, Beijing, CN, Junning Cao, Shanghai, CN, Emanuele Zucca, Bellinzona, CH and Laurence L. de Leval, Lausanne, CH
14:30		Welcome by the co-chairs
14:40	073	Introduction of Lymphoma Database of National Health Commission of the People's Republic of China
		Weiping Liu, Beijing, CN
15:05	074	1998-2023 Twenty-five years of commitment to improving our understanding of lymphoma
		Emanuele Zucca, Bellinzona, CH
15:30	075	Smart Start with Tislelizumab as the Front-line Treatment in Patients with High-risk Stage IIB and Advanced-stage Classical Hodgkin Lymphoma
		Zhiming Li, Guangzhou, CN
15:55		Break
16:10	076	Role of checkpoint inhibitor in Germany
		Peter Borchmann, Cologne, DE
16:35	077	New Drug Development in Lymphoma of China Is Going Global
		Keshu Zhou, Zhengzhou, CN
17:00	078	New trends in lymphoma treatment in Western Countries
		Pier Luigi Zinzani, Bologna, IT
17:25		Conclusions remarks by the co-chairs
15:15–15:30		**Report of the 17-ICML Closed Workshop**
Room A broadcast in room B, Marquee and Cinema Corso		Bruce D. Cheson, Bethesda, MD, USA
15:30–17:00		**SESSION 13—FOLLICULAR LYMPHOMA**

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Friday, June 16, 2023		
Room A broadcast in room B, Marquee and Cinema Corso		Chairs: Jonathan W. Friedberg, Rochester, NY, USA and Eva Kimby, Stockholm, SE
15:30	079	A "Functional Cure" May be Achievable in a Subset of Patients with Follicular Lymphoma treated with chemoimmunotherapy: 15-Year Follow-Up of Phase III SWOG-S0016
		Mazyar Shadman, Seattle, WA, USA
15:45	080	SAKK 35/14 randomized trial of rituximab with or without ibrutinib for untreated patients with advanced follicular lymphoma in need of therapy
		Emanuele Zucca, Bellinzona, CH
16:00	081	Zanubrutinib plus obinutuzumab versus obinutuzumab in patients with relapsed/refractory follicular lymphoma: Updated analysis of the ROSEWOOD study
		Pier Luigi Zinzani, Bologna, IT
16:15	082	Odronextamab in patients with relapsed/refractory follicular lymphoma (FL) grade 1–3a: Results from a prespecified analysis of the pivotal Phase II study ELM-2
		Silvana Novelli, Barcelona, ES
16:30	083	Mosunetuzumab demonstrates durable responses in patients with relapsed/refractory follicular lymphoma and ≥2 prior therapies: updated analysis of a pivotal Phase II study
		Laurie H. Sehn, Vancouver, BC, CA
16 :45	084	Epcoritamab with rituximab + lenalidomide (R2) provides durable responses in high-risk follicular lymphoma, regardless of POD24 status
		David Belada, Hradec Králové, CZ
17:00–17:30		**ESMO—ICML Special Lecture**
Room A broadcast in room B, Marquee and Cinema Corso	085	Does it matter how we name lymphomas?
		James O. Armitage, Omaha, NE, USA
18:00–19:00		**THE BIG DEBATE**
Room A		MOVING TARGETS IN LYMPHOMA TREATMENT
		Chair: Emanuele Zucca, Bellinzona, CH
		Satellite symposium organized by the Foundation for the Institute of Oncology Research (IOR). Supported by sponsorship from Gilead Sciences Europe Ltd. Gilead has had no input into the agenda, speaker selection or content of the presentations used at this event.
		DEBATE 1.
		Best therapy in aggressive mantle cell lymphoma: Time for frontline chemotherapy-free regimens?
		YES Michael L. Wang, Houston, TX, USA
		NO Martin Dreyling, Munich, DE
		DEBATE 2.
		Towards a cure for relapsing/refractory diffuse large B cell lymphoma: Bispecific antibodies better than CAR-T cells?
		YES Laurie H. Sehn, Vancouver, BC, CA
		NO Gloria Iacoboni, Barcelona, ES

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Friday, June 16, 2023		
		DEBATE 3.
		Frontline treatment of advanced Hodgkin lymphoma: Should A+AVD replace PET-driven strategies?
		YES Stephen M. Ansell, Rochester, MN, USA
		NO Peter Borchmann, Cologne, DE
Saturday, June 17, 2023		
08:45–10:15		**SESSION 14—NOVEL AGENTS**
Room A		Chairs: M. Lia Palomba, New York, NY, USA and Anastasios Stathis, Bellinzona, CH
08:45	086	High Complete Response Rate With TNB-486, a Novel CD19xCD3 T-Cell Engager, in Relapsed/Refractory Follicular Lymphoma: Interim Results from an Ongoing Phase 1 Study
		Ranjit Nair, Houston, TX, USA
09:00	087	Phase 1b/2a study of AZD4573 (CDK9i) and acalabrutinib in patients (pts) with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL)
		Alexey Danilov, Duarte, CA, USA
09:15	088	Phase 1 Study Of JNJ-67856633, A First-In-Human MALT1 Inhibitor, In Relapsed/Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL) And Chronic Lymphocytic Leukemia (CLL)
		Mark Hertzberg, Randwick, NSW, AU
09:30	089	Enhancer of zeste homolog 2 (EZH2) inhibitor SHR2554 in relapsed or refractory (r/r) peripheral T-cell lymphoma (PTCL): updated outcomes from the first-in-human phase 1 study
		Yuqin Song, Beijing, CN
09:45	090	Open-label phase 1/2 study of CC-99282, a cereblon E3 ligase modulator (CELMoD) agent ± rituximab, in patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL)
		Jean M. Michot, Villejuif, FR
10:00	091	Combining CD19-4-1BBL (RO7227166) with glofitamab is safe and shows early efficacy in patients suffering from relapsed or refractory B-cell Non-Hodgkin Lymphoma
		Michael Dickinson, Melbourne, AU
08:45–10:15		**SESSION 15—IMMUNOTHERAPY FOR AGGRESSIVE LYMPHOMAS**
Room B		Chairs: Urban Novak, Bern, CH and Catherine Thieblemont, Paris, FR
08:45	092	Glofitamab plus polatuzumab vedotin demonstrates durable responses and a manageable safety profile in patients with relapsed/refractory diffuse large B-cell lymphoma
		Martin Hutchings, Copenhagen, DK
09:00	093	Odronextamab in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL): Results from a prespecified analysis of the pivotal Phase II study ELM-2
		Michelle Poon, Singapore, Singapore, SG
09:15	094	Subcutaneous epcoritamab induces deep, durable complete remissions in relapsed/refractory large B-cell lymphoma: longer follow-up from the pivotal EPCORE NHL-1 trial
		Catherine Thieblemont, Paris, FR

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Saturday, June 17, 2023		
09:30	095	Glofitamab monotherapy in patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL): extended follow-up and landmark analyses from a pivotal Phase II study
		Michael Dickinson, Melbourne, AU
09:45	096	Bispecific anti-CD20/19 CAR-T—Zamtocabatagene Autoleucel for relapsed/refractory DLBCL—Interim analysis results of DALY-II-USA Study
		Matthew Ulrickson, Gilbert, AZ, USA
10:00	097	Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma in Transplant-Ineligible Patients: Final Analysis of ALYCANTE, a Phase 2 LYSA Study
		Roch Houot, Rennes, FR
10:15–11:30		**SESSION 16 – LATE BREAKING ABSTRACTS**
Room A		Chairs: Franco Cavalli, Bellinzona, CH and Martin Dreyling, Munich, DE
10:15	LBA1	Genome-wide association study of childhood Burkitt Lymphoma in East Africa identifies a novel germline susceptibility locus on chromosome 21
		Sam M. Mbulaiteye, Rockville, MD, USA
10:30	LBA2	Ibrutinib plus BR or R-CHOP in previously treated patients with Follicular or Marginal Zone Lymphoma: the phase 3 SELENE Study
		Loretta J. Nastoupil, Houston, TX, USA
10:45	LBA3	Lisocabtagene maraleucel (liso-cel) in R/R MCL: primary analysis results from the MCL cohort of the single-arm, multicenter, seamless design TRANSCEND NHL 001 study
		Michael L. Wang, Houston, TX, USA
11:00	LBA4	TRANSCEND FL: Phase 2 study results of lisocabtagene maraleucel (liso-cel) in patients (pts) with relapsed/refractory (R/R) follicular lymphoma (FL)
		Franck Morschhauser, Lille, FR
11:15	LBA5	BrECADD is non-inferior to eBEACOPP in patients with advanced stage classical Hodgkin Lymphoma: efficacy results of the GHSG phase III HD21 trial
		Peter Borchmann, Cologne, DE
10:15–11:05		**"FOCUS ON…" SESSION**
Room B		Long term results of CLL trials Chairs: Barbara F. Eichhorst, Cologne, DE and John Seymour, Melbourne, AU
10:15	152	5-Year (Y) Follow-up of a Phase 2 Study of Ibrutinib Plus Fludarabine, Cyclophosphamide, Rituximab (iFCR) as Initial Therapy for Younger CLL Patients (Pts)
		Inhye E. Ahn, Boston, MA, USA
10:25	153	Long-term follow-up of multicenter phase II trial of zanubrutinib, obinutuzumab, and venetoclax (BOVen) in previously untreated patients with CLL/SLL
		Jacob D. Soumerai, Boston, MA, USA
10:35	154	Zanubrutinib (zanu) vs. bendamustine + rituximab (BR) in patients (pts) with treatment-naïve (TN) CLL/SLL: Extended follow-up of the SEQUOIA study
		Mazyar Shadman, Seattle, WA, USA

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Saturday, June 17, 2023		
10:45	155	Fixed-duration ibrutinib + venetoclax in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 4-y follow-up from the FD cohort of the phase 2 CAPTIVATE study
		Paolo Ghia, Milan, IT
10:55	156	MURANO: Final 7 year follow up and retreatment analysis in venetoclax-rituximab (VenR)-treated patients with relapsed/refractory chronic lymphocytic leukemia (R/R CLL)
		John F. Seymour, Melbourne, AU
11:30–11:50		**17-ICML HIGHLIGHTS** "Take Home Messages"
Room A		Martin Dreyling, Munich, DE
11:50–12:00		**CLOSURE AND FAREWELL**
Room A		Franco Cavalli, Bellinzona, CH
13:30–18:00		**VI INTERNATIONAL WORKSHOP ON CANINE LYMPHOMA**
Room B		*organized by the European Canine Lymphoma Network*
		open to all 17-ICML attendees
		Co-chairs: Luca Aresu, Turin, IT, Stefano Comazzi, Milan, IT, Fausto Guscetti, Zurich, CH and Laura Marconato, Bologna, IT

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ORAL PRESENTATIONS

KEYNOTE LECTURES

001 | LESSONS LEARNED FROM THE GENETIC HETEROGENEITY OF LYMPHOID MALIGNANCIES

M. A. Shipp

Dana-Farber Cancer Institute, Division of Hematologic Neoplasia, Boston, Massachusetts, USA

Genetic signatures of lymphoid malignancies identify key signaling and survival pathways and associated therapeutic vulnerabilities. Specific lymphoid malignancies also utilize genetic bases of immune evasion to limit recognition and avoid attack. The most common lymphoma in adults, diffuse large B-cell lymphoma (DLBCL), includes genetically defined subsets with distinct coordinate signatures, pathogenetic mechanisms and outcomes following standard therapy. Certain extranodal large B-cell lymphoma subtypes, including primary central nervous system lymphoma and primary testicular lymphoma, share genetic features, treatment targets and extranodal tropism with specific systemic DLBCLs (Cluster 5/MCD tumors). In contrast, primary mediastinal large B-cell lymphomas (PMBLs) more closely resemble classical Hodgkin lymphomas (cHLs) with respect to genetic signatures, associated mechanisms of immune evasion and defining tumor microenvironmental features. In both PMBL and cHL, genetic bases of increased PD-1 ligand expression prompted trials of PD-1 blockade and the incorporation of this modality into the treatment of relapsed and newly diagnosed disease.

Keywords: diagnostic and prognostic biomarkers, molecular targeted therapies, pathology and classification of lymphomas, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

002 | ELUCIDATING THE ENIGMATIC PATHOBIOLOGY OF HODGKIN LYMPHOMA

R. Küppers

University of Duisburg-Essen, Essen, Germany

Classical Hodgkin lymphoma (HL) is a unique type of lymphoma and its pathobiology has long remained enigmatic. Several key features of HL account for this. First, the Hodgkin and Reed-Sternberg (HRS) tumor cells usually represent less than a few percent of cells among a complex immunological microenvironment. Second, HRS cells originate from mature B cells, likely pre-apoptotic germinal center (GC) B cells, but have lost most of the B-cell typical gene expression program. Third, the lymphoma clone is consistently composed of mononuclear Hodgkin and bi- or multinucleated Reed-Sternberg cells. Fourth, HRS cells seem hyperactivated with constitutive activation of numerous signaling pathways.

Several of the key features of HRS cells and classical HL has been at least partly elucidated in recent years: HRS cells attract various types of immune cells and thereby actively orchestrate their complex microenvironment. This supports their survival and proliferation, and creates an immunosuppressive environment. Hodgkin cells give rise to Reed-Sternberg cells through incomplete cytokinesis and refusion of Hodgkin cells. Recurrent genetic lesions in members of the NF-kB and JAK/STAT pathways and of factors of immune evasion are major factors in the molecular pathogenesis of classical HL, but so far, no genetic lesions were identified that explain the unique characteristics of HRS cells and their lost B-cell phenotype. HRS cells are in their gene expression profile relatively similar to the rare normal CD30+ B cells, and we recently obtained evidence that CD30 expression is a survival factor for HRS cells.

Also in nodular lymphocyte predominant HL, the LP lymphoma cells derive from GC B cells, but in this form of HL from functional GC B cells that have retained their typical GC B-cell expression program and follicular microenvironment. Recent studies indicate a role of bacterial antigen triggering of the B-cell receptor of LP cells in early stages of its pathogenesis.

Keywords: genomics, epigenomics, and other -omics, Hodgkin lymphoma, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

003 | 25 YEARS OF ANTIBODY TREATMENTS FOR LYMPHOMA

P. M. W. Johnson

Medical Oncology, School of Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

Starting from the invention of technology to produce monoclonal antibodies in 1978, and the subsequent immunophenotypic characterisation of the molecules expressed on the surface of lymphoid cells, the idea of targeting the malignant cells of lymphoma using specific antibodies held an intuitive appeal. Fully murine antibodies were initially used for in vitro purging of bone marrow harvests and in limited ways for therapy in vivo, but it was the development of molecular techniques to replace mouse constant domains with human sequences which allowed the expansion of systemic treatments. By chimerising and later humanising antibodies in this way, their half-life was extended from hours to weeks, and toxic and neutralising human anti-mouse antibody responses were abolished. The licencing of rituximab in 1997 was a turning point in lymphoma treatment, which is now visible as a point of inflexion on population-based mortality figures for lymphoma in many countries.

In addition to studies of the clinical benefits from anti-CD20 antibody therapy across the spectrum B-cell lymphomas, their mechanisms of action have been extensively investigated, yielding important biological insights into the relationship between structure and function. The relative contributions of complement fixation, antibody-directed cellular cytotoxicity and direct induction of apoptosis have been determined, highlighting the various effects of target ligation. The definition of two different types of antibody, one predominantly acting through recruitment of immune effectors and susceptible to induction of inhibitory immunoglobuin constant region (Fc) receptor expression on the target cells; the other more capable of inducing apoptosis, has underpinned the development of a new generation of reagents with higher potency.

Other antibodies have been used to block survival signals in lymphoid malignancies, with the most prominent example being the immune checkpoint-blocking antibodies targeting the interaction of programmed-death ligands (PDLs) on Hodgkin Reed-Sternberg cells and macrophages with adjacent T-cells expressing the PD1 receptor. These have demonstrated remarkable results both singly and in combination with chemotherapy for Hodgkin lymphoma, holding out the prospect that this disease may be about to see a similar antibody-based transformation in outcomes.

Whilst endogenous antibody effector mechanisms have been behind the largest improvements in clinical results, the use of antibodies to convey radionuclide or cytotoxic payloads has also been an important area of clinical investigation. The anti-CD20 radioimmunoconjugates demonstrated high potency but have not been widely adopted owing to the logistic difficulties of their administration and concerns about potential bone marrow damage in the longer term. Antibody-drug conjugates however have been more successful, particularly the anti-CD30 conjugate targeting the microtubule disrupting agent monomethyl auristatin-E for Hodgkin lymphoma, and the anti-CD79b conjugate targeting the same agent for diffuse large B-cell lymphoma, both of which have shown modest but definite improvements in outcomes in combination with conventional cytotoxics, as well as having useful activity as single agents.

Taken as a whole, the use of antibodies to target lymphoma has been a good example of forward and reverse translation: the application of novel biology has improved the outlook for patients with many different types of lymphoma, and the observations made in the clinic have in turn led to new insights into how antibodies and their targets on the cell surface interact, and how we can use this knowledge to further improve their efficacy for the future.

Keywords: antibody-drug conjugate, antibody therapy, checkpoint-blocking antibody, immunotherapy, lymphoma

No conflicts of interests pertinent to the abstract.

PLENARY SESSION

004 | FRONTLINE INTENSIFIED ABVD DEMONSTRATES SUPERIOR EFFICACY THAN PET-ADAPTED ABVD IN ADVANCED HODGKIN LYMPHOMA: THE FIL-ROUGE PHASE 3 TRIAL BY THE FONDAZIONE ITALIANA LINFOMI

A. Pinto[1], G. Corazzelli[1], A. Evangelista[2], C. Patti[3], S. De Lorenzo[4], A. Re[5], F. Merli[6], B. Botto[7], G. Tarantini[8], A. Guarini[9], G. Leonardi[10], S. Hohaus[11], F. Cavallo[12], A. Pulsoni[13], M. Gotti[14], M. Celli[15], F. Gaudio[16], F. Ricci[17], A. M. Liberati[18], V. Pavone[19], D. Rota-Scalabrini[20], L. Flenghi[21], A. Arcari[22], M. Cimminiello[23], V. R. Zilioli[24], E. Morelli[1], A. Mulè[3], M. Arcamone[1], C. Pagani[5], L. Arletti[6], M. Levis[25], R. De Filippi[26], A. Cuccaro[1], M. Cesaretti[27], E. Borgo[27], P. Musto[16], U. Vitolo[20], S. Chauvie[28], U. Ricardi[25], G. Ciccone[2], A. Santoro[17]

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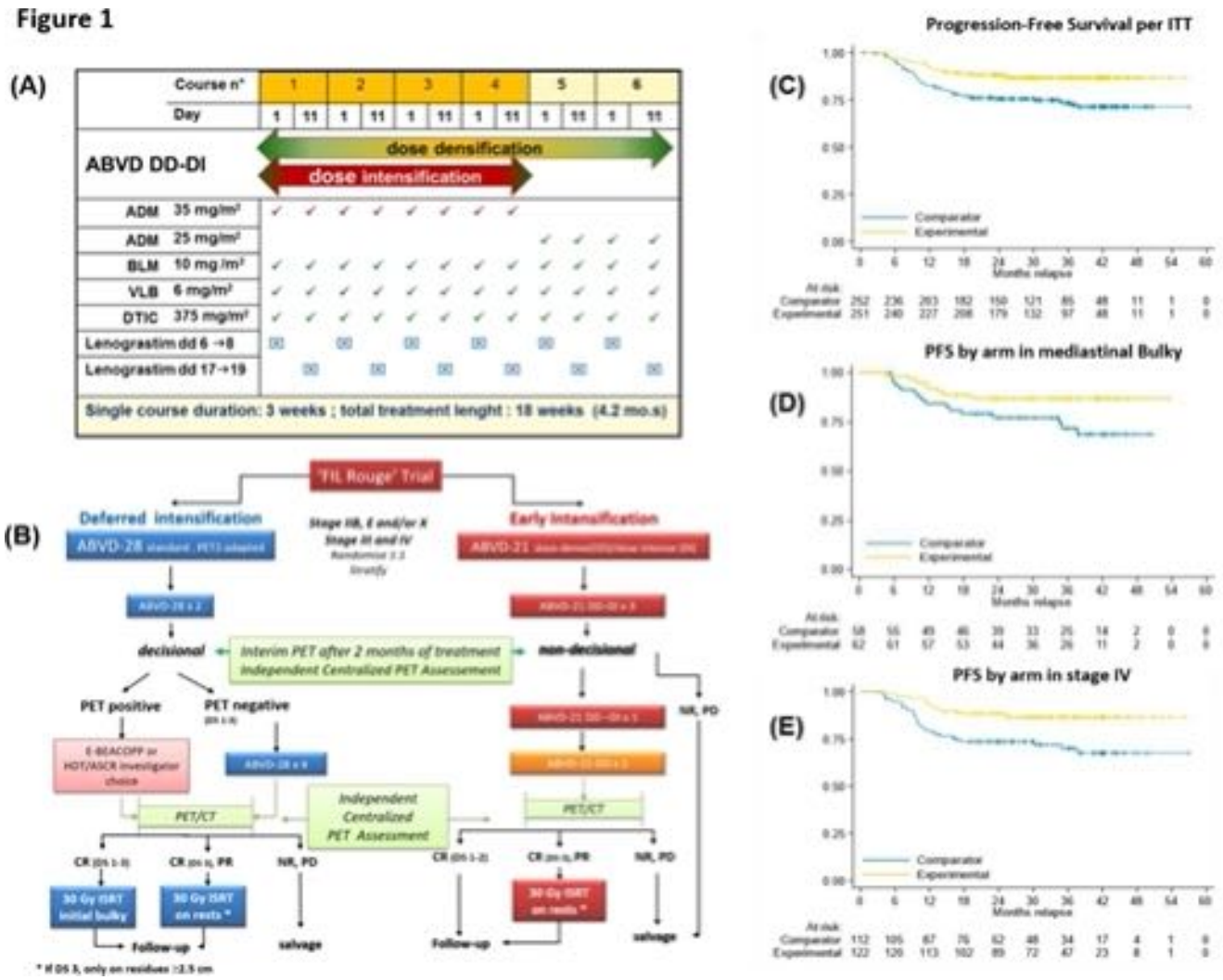
Introduction: PET-adapted ABVD with deferred intensification is the favored therapy for most patients with advanced Hodgkin Lymphoma (HL), while upfront intensification ('first hit') with escBEACOPP remains an option in the high-risk disease. These strategies are challenged by the brentuximab vedotin (BV)-based AVD regimen due to superior outcomes versus ABVD. The FIL-Rouge trial (NCT03159897) was designed to implement the 'first-hit' principle into the ABVD platform by demonstrating the superiority of a dose-dense/dose-intense regimen ($ABVD_{DD\text{-}DI}$; Russo et al. 2014, Figure 1A), without BV and PET-adaptation, versus a PET2-adapted ABVD program.

Methods: This open-label, phase 3 trial, with blinded centralized PET assessment, accrued untreated pts aged 18–60 with advanced-stage HL (IIB extranodal and/or bulky, III, IV) at 46 FIL Centers. Pts were randomized 1:1 and stratified for stage (IIB/III, IV), age (<45/≥45), bulky (Yes/No), and IPS (0–2/≥3). In the comparator arm, pts received two ABVD (d1, d14; q28 days); PET2−ve (DS 1–3) pts continued with four ABVD, while those PET2+ve (DS 4–5) diverted to escBEACOPP or ASCT. In the experimental arm, pts received four cycles of $ABVD_{DD\text{-}DI}$ (d1, d11; q21 days; doxorubicin 70 mg/m^2/cycle) followed by two $ABVD_{DD}$ (Figure 1B). ISRT (30 Gy) was planned for PET−ve (DS 3) rests (≥2.5 cm) and PET+ve pts (DS 4–5). Pts given ABVD had to receive RT (30 Gy) at bulky sites if in CR (DS 1–3). The primary endpoint was a minimum expected absolute improvement of 10% in 3-y PFS.

Results: From July 2017 to March 2021, 503 pts were enrolled (males 54%; median age 33.6 [IQR 26.2–43.0] with stage IIB (20%), III (33%), IV (47%) and IPS score 0–2 (58%), 3 (25%) and 4–7 (17%). Nodal (≥10 cm) and mediastinal (MT > 0.35) bulky were present in



13% and 24% of pts, respectively. At interim PET, CRs (DS ≤ 3) were 85.5% for the $ABVD_{DD\text{-}DI}$ and 80.5% for ABVD ($p = 0.15$). At a median FU of 35 mo.s, 97 pts had a PFS event ($ABVD_{DD\text{-}DI}$ $n = 32$; ABVD $n = 65$). The 3-y PFS per ITT was 86.7% (95% CI: 81.7–90.4) for $ABVD_{DD\text{-}DI}$ and 73.2% (95% CI: 66.9–78.5) for ABVD (Δ: 13.46%; $p = 0.0001$) [HR 0.44 (95% CI 0.28–0.67; $p = 0.0002$)] (Figure 3C). A superior 3-y PFS was also achieved in pts with mediastinal bulky ($ABVD_{DD\text{-}DI}$ 87.0% vs. ABVD 71.9%) and stage IV disease ($ABVD_{DD\text{-}DI}$ 86.4% vs. ABVD 70%) (Figure 3D, E). RT was delivered to 10% of pts in $ABVD_{DD\text{-}DI}$ and 32% in ABVD. Nine pts died ($ABVD_{DD\text{-}DI}$: 3 PD, 1 COVID; ABVD: 4 PD, 1 H_1N_1). Neutropenia ≥G3 (40.8% vs. 30.4%; $p = 0.016$) and mucositis ≥G3 (3.2% vs. 0%; $p = 0.005$) occurred more frequently in $ABVD_{DD\text{-}DI}$ versus ABVD. No excess of cardiotoxicity (G2: 0.8%, G3: 0.8%) nor respiratory events (G2: 6%, G3: 2.4%, G4: 0.4%) were recorded for $ABVD_{DD\text{-}DI}$ versus ABVD (cardiac, G2: 0.4%, G3: 0.4%; respiratory, G2: 4.4%, G3: 1.2%, G4: 0.4%).

Conclusions: The study met its primary objective. $ABVD_{DD\text{-}DI}$ improved 3-year PFS by >10%, with a reduced need for RT, no PET-adaptation, and no alarming acute safety signals. It was also more active in pts with mediastinal bulk and stage IV disease.

The research was funded by: Bando AIFA (Agenzia Italiana del Farmaco)-2016-02364973.

Keywords: chemotherapy, Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

005 | NIVOLUMAB(N)-AVD IMPROVES PROGRESSION-FREE SURVIVAL COMPARED TO BRENTUXIMAB VEDOTIN(BV)-AVD IN ADVANCED STAGE (AS) CLASSIC HODGKIN LYMPHOMA (HL): RESULTS OF SWOG S1826

A. F. Herrera[1], M. LeBlanc[2], S. M. Castellino[3], H. Li[2], S. C. Rutherford[4], A. M. Evens[5], K. Davison[6], A. Punnett[7], D. Hodgson[8], S. K. Parsons[9], S. Ahmed[10], C. Casulo[11], N. L. Bartlett[12], J. M. Tuscano[13], M. G. Mei[1], B. T. Hess[14], R. Jacobs[15], H. Saeed[16], P. Torka[17], B. Hu[18], C. Moskowitz[19], S. Kaur[20], G. Goyal[21], C. Forlenza[22], A. Doan[23], A. Lamble[24], P. Kumar[25], S. Chowdhury[26], B. Brinker[27], N. Sharma[28], A. Singh[29], K. Blum[30], A. M. Perry[31], A. Kovach[23], L. S. Constine[11], L. Kostakoglu Shields[32], A. Prica[8], R. F. Little[33], M. A. Shipp[34], M. Crump[8], B. Kahl[12], J. P. Leonard[4], S. M. Smith[35], J. Y. Song[1], K. M. Kelly[36], J. W. Friedberg[11]

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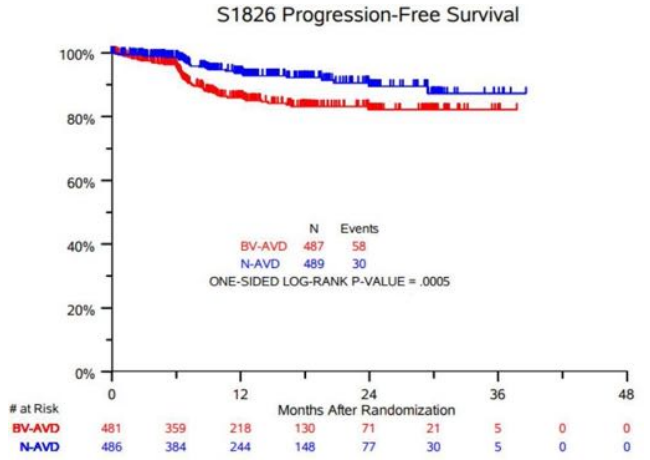
Background: The addition of BV to initial chemotherapy improves outcomes in adult and pediatric patients (pts) with AS HL. However, frontline BV adds toxicity, most pediatric pts receive radiation therapy (RT), and 7%–20% of pts still develop relapsed/refractory (RR) HL. The PD-1 pathway is central to the pathogenesis of HL and PD-1 blockade is effective in RR HL. The adult and pediatric cooperative groups of the National Clinical Trials Network (NCTN) conducted the randomized, phase 3 S1826 trial to evaluate N-AVD versus BV-AVD in pts with newly diagnosed AS HL.

Methods: Eligible pts were ≥12 years (y) with stage 3–4 HL. Pts were randomized 1:1 to either 6 cycles of N-AVD or BV-AVD. G-CSF neutropenia prophylaxis was required with BV-AVD versus optional with N-AVD. Pre-specified pts could receive RT to residually metabolically active lesions on end of treatment PET. Pts were stratified by age, international prognostic score (IPS), and intent to use RT. Response and disease progression were assessed by investigators using 2014 Lugano Classification. The primary endpoint was progression-free survival (PFS); secondary endpoints included



overall survival (OS), event-free survival, patient-reported outcomes (PROs), and safety.

Results: 994 pts were enrolled from 7/9/19 to 10/5/22; 976 were eligible and randomized to N-AVD (n = 489) or BV-AVD (n = 487). Median age was 27y (range 12–83y), 56% of pts were male, 76% were white, 12% were black, and 13% were Hispanic. 24% of pts were <18y, 10% were > 60y, and 32% had IPS 4–7. To date, <1% of pts received RT. At the planned 2nd interim analysis (50% of total PFS events) the SWOG Data and Safety Monitoring Committee recommended to report the primary results because the primary PFS endpoint crossed the protocol-specified conservative statistical boundary. 30 PFS events occurred after N-AVD versus 58 events after BV-AVD. With a median follow-up of 12.1 months, PFS was superior in the N-AVD arm (HR 0.48, 99% CI 0.27–0.87, one-sided p = 0.0005); 1y PFS: N-AVD, 94%, BV-AVD, 86% (Figure). 11 deaths (7 due to adverse events, AE) were observed after BV-AVD compared to 4 after N-AVD (3 due to AE). The rate of grade (gr) ≥3 hematologic AE was 48.4% (45.1% gr ≥3 neutropenia) after N-AVD compared to 30.5% (23.9% gr ≥3 neutropenia) after BV-AVD. Rates (any gr) of febrile neutropenia (5.6% N vs. 6.4% BV), pneumonitis (2.0% N vs. 3.2% BV), ALT elevation (30.7% N vs. 39.8% BV), and colitis (1% N vs. 1.3% BV) were similar. Hypo/hyperthyroidism was more frequent after N-AVD (7%/3% N vs. <1% BV) while peripheral neuropathy was more common after BV-AVD (sensory: 28.1%, 1.2% gr ≥ 3 N vs. 54.2%,7.8% gr ≥ 3 BV; motor: 4% N vs. 6.8% BV).

Conclusions: N-AVD improved PFS versus BV-AVD in pts with AS HL. Few immune AEs were observed and < 1% of pts received RT. Longer follow-up is needed to assess OS and PROs. S1826, the largest HL study in NCTN history, is an important step towards advancing and harmonizing the pediatric and adult treatment of AS HL.

Encore Abstract—previously submitted to ASCO 2023

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Keywords: Hodgkin lymphoma, immunotherapy, targeting the tumor microenvironment

Conflicts of interests pertinent to the abstract

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Research funding: Bristol-Myers Squib, Genentech, Merck, SeaGen, KITE Pharma/Gilead Sciences, AstraZeneca, ADC Therapeutics

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006 | FOURTH GENERATION HUCART19-IL18 PRODUCES DURABLE RESPONSES IN LYMPHOMA PATIENTS PREVIOUSLY RELAPSED/REFRACTORY TO ANTI-CD19 CAR T-CELL THERAPY

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Introduction: Lymphoma (NHL) patients (pts) relapsing/refractory (R/R) to anti-CD19 chimeric antigen receptor T-cells (CART) represent a challenging group in need of effective therapies. HuCART19-IL18 is a 4th generation 4-1BB CART product designed to express humanized anti-CD19 CAR and secrete interleukin 18, a pro-inflammatory cytokine shown to enhance CART efficacy in pre-clinical models. Its humanized scFv may allow for better persistence, and the additional use of a novel expedited 3-day manufacturing protocol may improve the product's potency.

Methods: We are conducting a first-in-human trial of huCART19-IL18 in pts ≥18 years old with CD19+ R/R B-cell NHL or CLL, who have had at least 2 prior lines of therapy including failure of prior CART. Using a modified Bayesian optimal interval dose titration design, we are exploring doses between 3 and 300 million huCART19-IL18+ cells. The product is administered as a single IV infusion following lymphodepleting (LD) chemotherapy. Bridging therapy is optional and huCART19-IL18 re-treatment is permitted for pts not achieving complete response (CR). Responses are assessed at 3, 6, 9, and 12 months (mo) using Lugano criteria for NHL and revised iwCLL criteria for CLL.

Results: As of 3 March 2023, 16 pts have enrolled. 15 pts had huCART19-IL18 manufactured and all achieved a minimum protocol-defined dose. The 13 pts infused to date include 5 DLBCL, 4 FL, 2 MCL, 1 HGBCL, 1 THRBCL pts. The median age is 65 years (53–74), 77% male, 92% had prior anti-CD19 CART (axi-cel 6, tisa-cel 4, brex-cel 1, tisa-cel+liso-cel 1) with 67% relapsed and 33% refractory to prior CART. The median number of prior therapies was 8 (4–14); 11 (85%) pts received bridging therapy. LD

chemotherapy was used in 12 (92%) pts. Three were treated at DL1 (3×10^6 CART+ cells), 2 at DL2 (7×10^6), 1 at dose between DL2-3 (2.8×10^7), 6 at DL3 (3×10^7) and 1 at DL4 (7×10^7). Two pts underwent re-treatment (at DL1 and DL3). Twelve pts are evaluable for safety. There were no study related deaths. Most common possibly related non-hematologic G3/4 toxicities included infection (17%), CRS-related hypoxia (17%) and hypotension (17%). CRS was seen in 7 (58%) pts (G1 in 4, G2 in 2, G3 in 1) and ICANS in 2 (17%) pts (G1 in 1, G2 in 2), which were transient/reversible with 3 (25%) pts requiring tocilizumab. 11 pts are evaluable for efficacy with 3-month overall response rate 82% (90% CI: 53–97) and CR rate 55% (90% CI: 27–80). 1 pt with PR at 3 mo achieved sustained CR after huCART-IL18 re-treatment. At median follow-up 12 mo (3–20) for evaluable pts, responses are durable (median not reached) and all pts are alive as shown in Figure 1. Correlative analyses of CART expansion/persistence and cytokine levels are ongoing.

Conclusions: HuCART19-IL18 therapy results in durable responses in pts with CD19+ NHL who are R/R to prior 2nd generation anti-CD19 CART. Enrollment continues at DL4 with protocol amendment to include CD19+ B-ALL pts.

The research was funded by: Institutional funds from the University of Pennsylvania

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies

Conflicts of interests pertinent to the abstract

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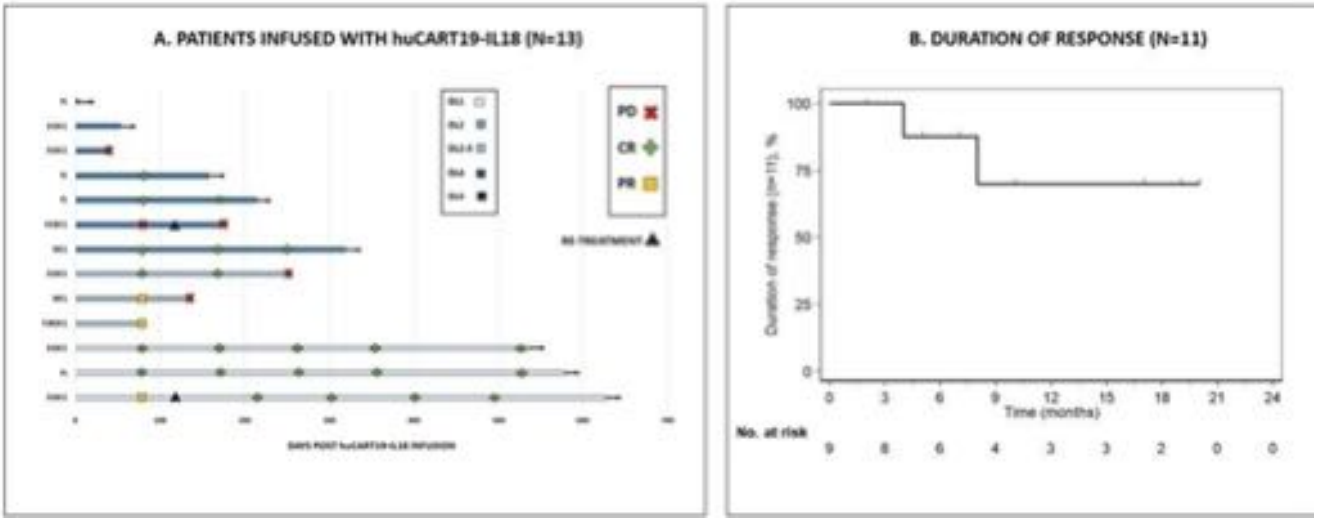
FIGURE 1



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Research funding: Capstan Therapeutics

AACR-ICML JOINT SESSION

007 | SINGLE CELL OMICS IN THE STUDY OF B CELL LYMPHOMA

K. Basso
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Analysis of the genomic and transcriptomic landscape of tumors has contributed extensively to dissect the mechanisms of malignant transformation and to stratify patients based on genetic and molecular features. In the context of germinal center (GC)-derived B cell lymphomas, these studies have identified key genetic and epigenetic drivers of malignant transformation and informed on disease heterogeneity. In particular, transcriptomic studies led to the identification of the prognostically distinct GCB and ABC subtypes of diffuse large B cell lymphomas (DLBCL), that are now recognized by the WHO classification. In addition, extensive genetic characterization has pinpointed to the major players in the pathogenesis of DLBCL subtypes and more recently led to the development of genetic classifiers.

Nonetheless, tumor heterogeneity is not only a feature observed across individual patients, rather a characteristic of each tumor itself. The genetic spectrum of intra-tumor heterogeneity has been long appreciated and inferred, for example, from the variant-allele frequencies of somatic mutations identified in bulk sequencing studies. Single-cell (sc)-transcriptomic technologies have provided the tools to dissect the heterogeneity of both tumor cells and normal infiltrating components. Several studies have explored follicular lymphoma and DLBCL by sc-transcriptomic analysis, highlighting the presence of diverse subpopulations and the contribution of the normal infiltrating cells to the tumor development and response to therapy.
Recently, we have investigated Burkitt lymphoma (BL), the most common pediatric GC-derived lymphoma, using sc-transcriptomic and immunoglobulin repertoire analysis. The transcriptomic analysis restricted to the tumor cells showed, as expected, patient-specific features. Nonetheless, the large majority of specimens were characterized by the presence of distinct subpopulations that were recurrently detected across patients. This intra-tumor transcriptional heterogeneity was associated with multiple distinct features including cell cycle, activation markers and cell-of-origin signatures. Overall, we identified transcriptional intra-tumor heterogeneity that is retained across BL patients suggesting the presence of distinct programs in BL cells.

Keywords: genomics, epigenomics, and other -omics, microenvironment, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

008 | CIRCULATING TUMOR DNA (LIQUID BIOPSY)

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Circulating tumor DNA (ctDNA) is DNA released by cancer cells into body fluids. The collection of body fluids that contains ctDNA, also known as lliquid biopsy, allows to access tumor DNA through a minimally invasive procedure. ctDNA has been proposed alternative source of tumor DNA for genotyping purposes and for longitudinal genetic monitoring. Also, ctDNA is radiation-free tool that allows the early identification of chemorefractory patients. We will discuss clinical applications of the liquid biopsy in lymphomas and the controversies around this biomarker.

Keywords: liquid biopsy, minimal residual disease

No conflicts of interests pertinent to the abstract.

009 | ABSTRACT INCLUDED IN THE LBA SECTION

SESSION 1 - DISSECTING LYMPHOMAS AT THE SINGLE CELL LEVEL

010 | THE TUMOR MICROENVIRONMENT OF HODGKIN LYMPHOMA AT SINGLE CELL RESOLUTION

C. G. Steidl
British Columbia Cancer, Vancouver, Canada

Single cell technologies mark a paradigm shift in cancer research and various technology implementations have enabled studies to describe cellular heterogeneity, identify cell populations that were previously hard to detect and define, and to make inferences about cell-to-cell interactions at single cell resolution. In particular, single cell RNA sequencing has broadened opportunities to describe the composition and cellular subsets in the ecosystem of the tumor microenvironment (TME). Synergistic to advances in single cell sequencing, multiplexed imaging techniques have added a new dimension to describing cellular crosstalk in the context of the histology architecture of lymphomas. Classic Hodgkin lymphoma (CHL) can serve as a study paradigm due to its unique TME, featuring infrequent tumor cells among numerous non-malignant immune cells with significant inter- and intra-patient variability. From TME single cell studies, multiple rational treatment targets have been identified, including PD-1, CTLA-4 and LAG3 on T cells, and refined classification might enable classification-driven treatment choices. There is also increasing evidence that TME composition and function is significantly shaped by the predominance of certain cytokines and chemokines produced by HRS cells and surrounding immune cells to form immunosuppressive niches. Most recent correlative and studies indeed reinforced a strong link between cytokine and chemokine expression and the abundance of specific cellular subsets, with prominent examples being the importance of IL-6 for induction of LAG3+ Tregs and IL-10 and TGFβ for CXCL13+ helper T cell subsets. In aggregate, these insights hold the promise to accelerate biomarker discovery for novel immunotherapeutic approaches, and to serve as future assay platforms for biomarker-informed treatment selection including immunotherapies.

Keyword: microenvironment

No conflicts of interests pertinent to the abstract.

011 | TRAJECTORIES OF LYMPHOMAGENESIS

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In the last 10 years, we have dramatically increased our knowledge on the (epi)genetics, the etiology, and the dynamics of Follicular lymphoma (FL). In that period, it has become widely accepted that the preclinical and subclinical development phases of FL, taking years from the emergence of a unique *t*(14;18)+ B cell in the BM to the detection of symptomatic LN full of its descendants aggregated in FL follicles, involves multiple transits of Mem-like *t*(14;18)+ B cells through sequential GC. The remarkable plasticity and longevity of normal Mem B cells, coupled with the mutation-prone and proliferative states of GC B cells, provide fertile grounds for transformation of B cells into malignant neoplasia. But until very recently, the common view was that the GC-Mem dynamic cycle would stop at one stage when the cells would 'freeze' in their final overt FL state. Among others, single-cell analyses are challenging that concept, and portraying a model of FL where GC<->Mem dynamics continue to fuel FL progression, and likely relapses, in the overt disease stage. In that revised model, FL B cells are not 'frozen,' but are likely as functionally plastic as their pre-malignant *t*(14;18)+ B cell counterparts, circulating as Mem-like cells from one follicle to the next, to another LN or to the BM. With recent advances in single-cell methods and spatial single-cell genomics, many unresolved questions on FL physiopathology are now within reach. What drives the state transitions of FL B cells? How do genetics affect FL B cell states? How do FL B cells integrate signals from their microenvironment with their genetically rewired signaling networks and perturbed epigenetics? How will we translate those new biological concepts into clinical advances? Can we rewire FL B cells to respond differently to their microenvironment? Can we purge FL B cells from all the organs where they may home? The upcoming drawing of a comprehensive functional picture of FL within its ecosystem holds great promise to address the unmet medical needs of this complex lymphoma.

Keywords: genomics, epigenomics, and other -omics, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

012 | SUBCLONAL HETEROGENEITY DRIVING PROGRESSION AND TRANSFORMATION IN CHRONIC LYMPHOCYTIC LEUKEMIA

E. Campo
Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain

The evolution of lymphoid neoplasms may be driven by their heterogeneous subclonal composition and competition, selection, and expansion of the different tumor cell subpopulations. The evolution of chronic lymphocytic leukemia (CLL) varies from stable to very aggressive disease with some patients transforming to a diffuse large B cell lymphoma (Richter transformation, RT). Novel single cell technologies allow the analysis of the transcriptome and (epi)genomic features of tumors and their evolution with an

unprecedented resolution. Single cell RNA sequencing of CLL has revealed three major clusters characterized by different expression of *CXCR4*, *CD27* and *MIR155HG*, respectively, which may represent the recirculation of CLL cells between peripheral blood and lymph node. The expression profile of CLL changes dramatically in the RT samples in which the subclones are dominated by the expression of proliferation related genes. The transcriptional and mutational analysis of longitudinal sequential samples from diagnosis, relapses after therapy and RT has identified that the subclones expanding at these different time points are already present as very small subpopulations in samples obtained at diagnosis and different time points years before their clinical expansion. The early seeding of these subclones identified by single cell analysis is concordant with the in silico prediction by bulk whole genome sequence of multiple longitudinal samples. The transcriptional program of RT cells converges into activation of the OXPHOS pathway and downregulation of BCR signaling that could be detected in samples at diagnosis and before treatment with BCR inhibitors. Pharmacological inhibition of OXPHOS reduces the proliferation of RT cells in vitro. All these observations highlight the power of single cell analysis to reveal the dynamic evolution of tumors and discover new diagnostic and therapeutic opportunities.

Keywords: genomics, epigenomics, and other -omics, microenvironment, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

013 | DIVERSITY OF INTRATUMORAL REGULATORY T CELLS IN B-CELL NON-HODGKIN LYMPHOMA

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Introduction: Tumor-infiltrating regulatory T cells (Tregs) contribute to an immunosuppressive tumor microenvironment. Despite extensive studies, the prognostic impact of tumor infiltrating Tregs in non-Hodgkin lymphomas (NHL) remains unclear. Emerging studies suggest substantial heterogeneity in the phenotypes and suppressive capacity of Tregs, emphasizing the importance of understanding Treg diversity and the need for markers to identify highly suppressive Tregs.

Methods: Live $CD4^+$ T cells were obtained by FACS sorting from NHL malignant lymph nodes (diffuse large B cell lymphoma (DLBCL, $n = 3$), follicular lymphoma (FL, $n = 3$)), and healthy donor tonsils ($n = 3$) and subjected to single-cell RNA sequencing (scRNAseq), CITE-seq and scTCR-seq by the 10X Genomics platform. The computational framework of CIBERSORTx was used to generate a unique signature matrix for the Treg subsets identified by scRNAseq, to facilitate validation in separate scRNAseq cohorts (King, Sci Immunol 2021; Roider, Nat Cell Biol 2020; Steen, Cancer Cell 2021), and to impute frequencies of the Treg subsets and correlate with survival in cohorts with bulk RNAseq data (Steen, Haematologica 2019; Pastore, Lancet Oncol 2015). High-dimensional cytometry and functional immunosuppression assays were applied to characterize Treg subsets in single-cell suspensions from DLBCL, FLand healthy donors peripheral blood and tonsils. Spatial and neighborhood analysis were performed by Imaging Mass Cytometry on FL tissue.

Results: We identified three distinct transcriptional states of Tregs; resting, activated and $LAG3^+FOXP3^-$ Tregs. Activated Tregs were enriched in NHL tumors and had higher expression of checkpoint receptors (TNFRSF4, TNFRSF18, TIGIT), NF-κB pathway (NFKBIA, NFKBIZ, REL), chemokine receptors (CXCR4) and transcription factors (JUN, JUNB, BATF) compared to resting Tregs. Phenotypical characterization showed that activated Tregs co-expressed several checkpoint receptors (PD-1, TIGIT, CTLA4, ICOS, OX40) and had stronger immunosuppressive activity compared to resting Tregs. In FL tumor microenvironment, activated Tregs were found in closer proximity to $CD4^+$ and $CD8^+$ T cells than other cell types. Using a unique gene signature matrix for each Treg subset, we confirmed that activated Tregs were the major subset in FL, and high abundance was associated with adverse outcome in two independent FL cohorts.

Conclusion: This study demonstrates that Tregs infiltrating NHL tumors are transcriptionally and functionally diverse and include highly immunosuppressive activated Tregs co-expressing several checkpoint receptors, which distinguish them from resting Tregs. Activated intratumoral Tregs could limit clinical responses to immunotherapy and identifying and targeting their vulnerabilities has the potential to improve anti-tumor immune responses.

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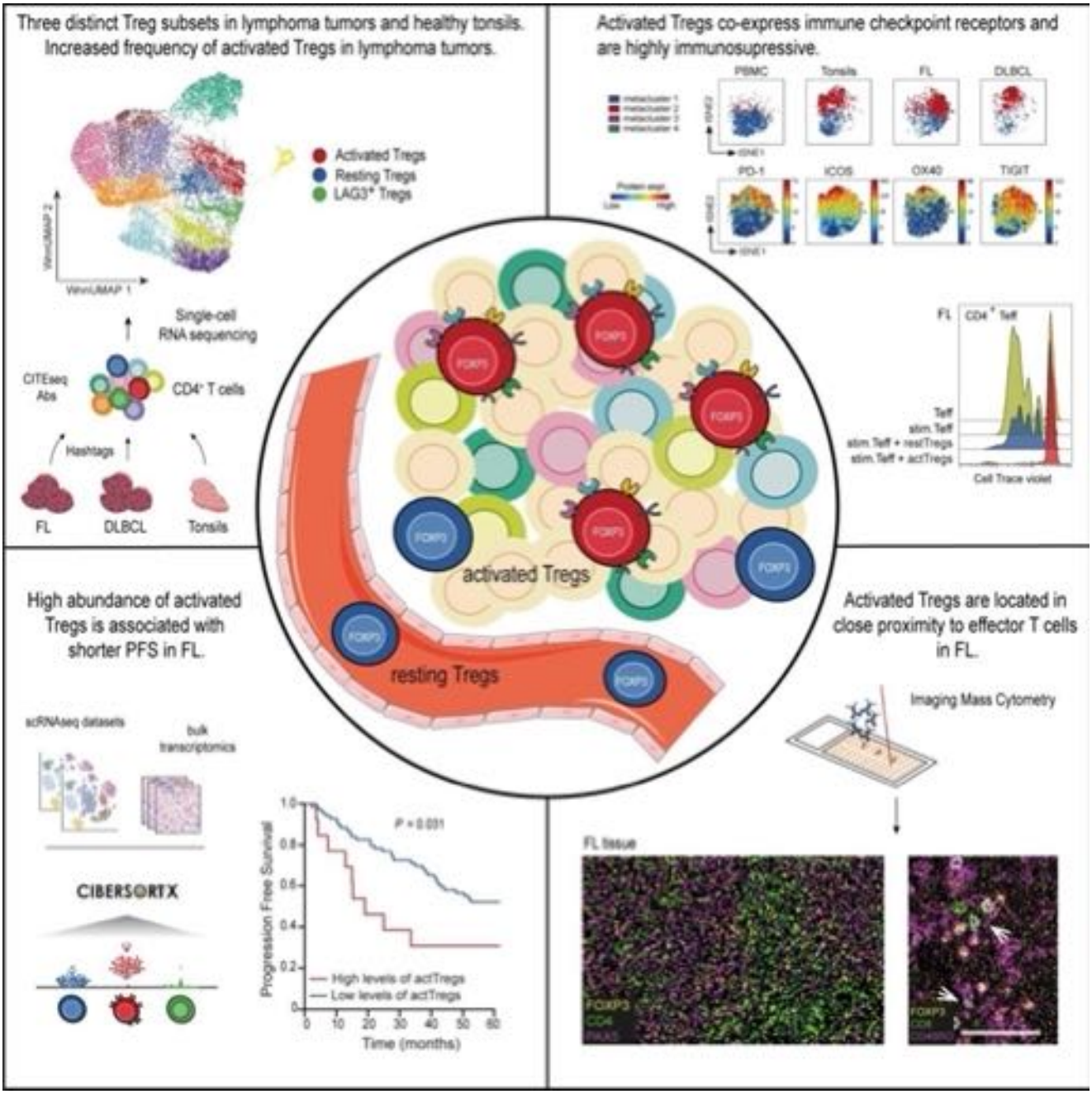
Keywords: aggressive B-cell non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, microenvironment

No conflicts of interests pertinent to the abstract.



SESSION 2 - LYMPHOMAS AFFECTING THE CNS

014 | IDENTIFICATION OF GENOMIC BIOMARKERS OF DISEASE PROGRESSION AND SURVIVAL IN NEWLY-DIAGNOSED PRIMARY CNS LYMPHOMA

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Introduction: There is a significant unmet need for robust genomic biomarkers that identify patients with newly-diagnosed primary CNS lymphoma (PCNSL) at high risk of progression, both during standard methotrexate-based induction as well as after dose-intensive consolidation.

Methods: We performed targeted next-generation sequencing of 529 cancer genes of formalin-fixed, paraffin-embedded tumors from 74 patients with newly diagnosed primary CNS diffuse large B-cell lymphoma using the UCSF500 Cancer Panel and the Institute for Human Genetics CLIA Laboratory. The assay detects structural variants including single nucleotide variants, small insertions and deletions, and copy-number alterations (CNAs). Sixty-four EBV-negative PCNSL patients treated with a standard methotrexate,

temozolomide, rituximab (MTR) induction were available for complete analysis.

Results: We identified frequent mutations involving MYD88 (77%), CD79B (41.9%), ETV6 (27%) and BTG1 (25.7%) as well as frequent CNA involving 6q loss (62.5%), 9p loss (34.4%) and 12 gain (31.3%). Three genomic alterations were most significantly associated with early disease progression in PCNSL: (1) Alterations at 6p21.3, predominantly copy neutral loss of heterozygosity (CN-LOH) at the HLA Class I (HLA-A, B, C) and Class II loci (HLA-DR, DP, DQ, TAP1) as well as homozygous deletion of HLA Class II; (2) Mutations of tumor suppressor genes BTG1 and ETV6. Overall, these genomic alterations were detected in 28 out of 31 progression events in the cohort. The subgroup with either CN-LOH or homozygous deletion at 6p had the earliest progression, followed by the subgroup with mutations at either BTG1/ETV6 and no 6p CN-LOH or homozygous deletion, compared to no alterations at these 3 loci. 10 of 18 tumors with these alterations at 6p also contained BTG1 and/or ETV6 mutations. Survival analysis demonstrates that the subgroup with 6p CN-LOH or homozygous deletion had the earliest progression, followed by the subgroup with BTG1/ETV6 mutations compared to no alterations at these 3 loci (PFS $p = 3.7e\text{-}5$, OS $p = 0.0017$, logrank test, Figure 1). Multivariate Cox proportional hazard analysis demonstrated a significant 3.24-fold increased risk of progression with 6p CN-LOH/homozygous deletion or BTG1/ETV6 mutations (p = 3.5e-5, adjusted by Age, KPS, IELSG, MSKCC, IOL, Maintenance, and Consolidation).

Conclusions: We identify CN-LOH and homozygous deletions involving the HLA region at 6p21 as well as BTG1 and ETV6 mutations as candidate genomic biomarkers that correlate with accelerated disease progression with MTR-based chemotherapy in PCNSL. These genomic alterations may be applied in risk stratification in future clinical trials.

The research was funded by: National Cancer Institute NIH R01CA139-83-01A1

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, genomics, epigenomics, and other-omics

No conflicts of interests pertinent to the abstract.

015 | CONSOLIDATIVE HCT-ASCT IS SUPERIOR TO NON-MYELOABLATIVE CHEMO-IMMUNOTHERAPY IN NEWLY-DIAGNOSED PCNSL - UPDATED RESULTS OF THE RANDOMIZED PHASE III MATRIX/IELSG43 TRIAL

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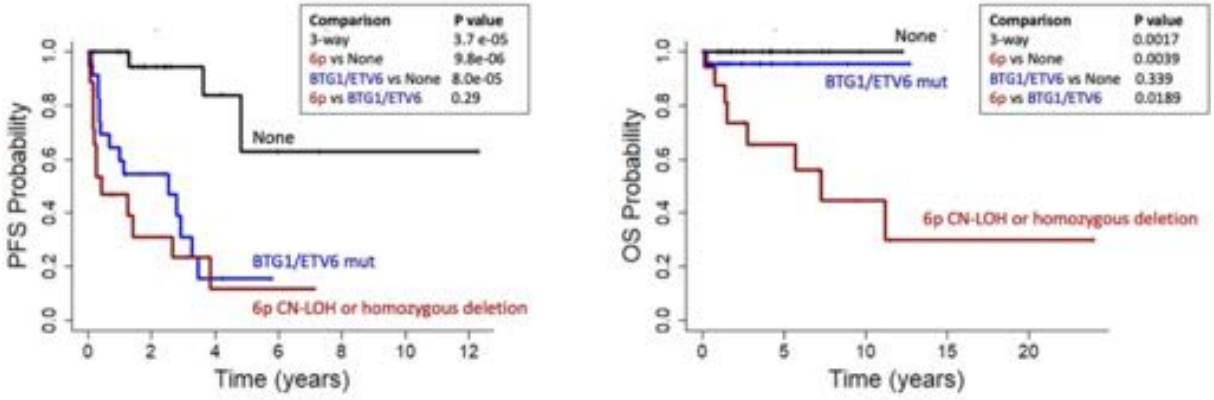
Figure 1. Progression-free survival and Overall survival in newly-diagnosed PCNSL treated with MTR



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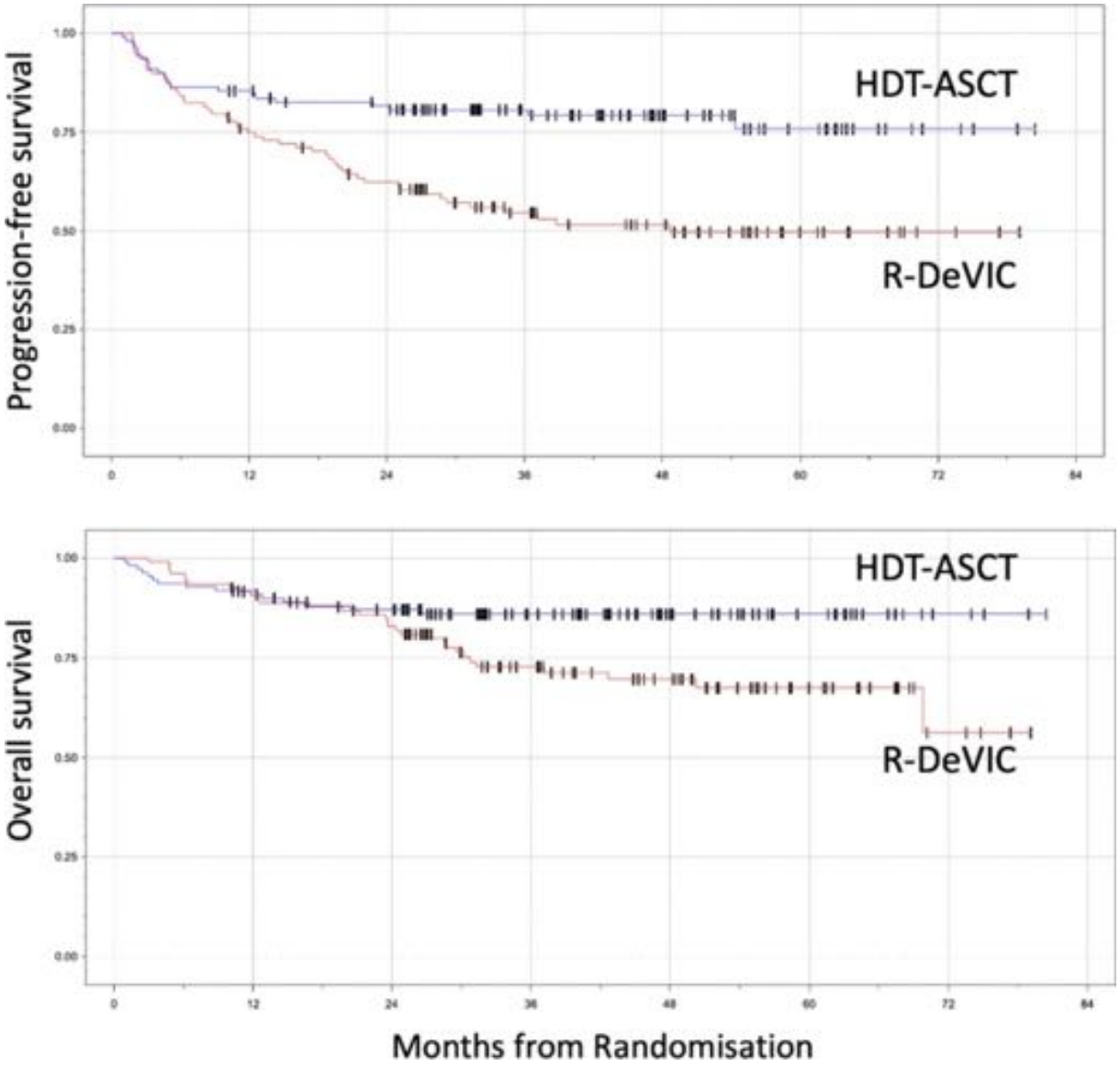

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Background: Current treatment options for patients with primary central nervous system lymphoma (PCNSL) eligible for intensive treatment approaches comprise high-dose methotrexate (HD-MTX) based immuno-chemotherapy (IT) followed by consolidating high-dose chemotherapy and ASCT (HDC-ASCT). To clarify, whether minimal residual disease may also be eliminated by non-myeloablative IT, comprising non-cross resistant cytotoxic agents, the MATRix/IELSG43 trial, an international randomised phase III trial comparing HDC-ASCT with non-myeloablative consolidation in patients with newly diagnosed PCNSL (NCT02531841) was conducted. This is an updated report on the main study endpoints.

Methods: This randomized phase III trial was conducted in 79 centers in five countries. Immuno-competent patients with untreated PCNSL, aged 18–65 years irrespective of ECOG PS or 66–70 years with ECOG PS $\leq$ 2 were considered eligible. Induction comprised four cycles MATRix (rituximab 375 mg/m^2/d days(d) 0,5; methotrexate 3.5 g/m^2 d1; cytarabine 2 $\times$ 2 g/m^2/d d2,3; thiotepa 30 mg/m^2 d4, every three weeks. Stem cell harvest following cycle 2. Randomization was performed for patients achieving at least partial response (PR) following induction therapy. Arm A consisted of two cycles R-DeVIC (375 mg/m^2 d0; dexamethasone 40 mg/d d1–3; etoposide 100 mg/m^2/d d1–3; ifosfamide 1500 mg/m^2/d d1–3; carboplatin 300 mg/m^2 d1); Arm B, consisted of HDC-ASCT (BCNU 400 mg/m^2 (d-6) and thiotepa 2 $\times$ 5 mg/kg/d d-5,-4)). The primary endpoint progression-free survival (PFS) was analyzed with a Cox proportional hazards model.

Results: 368 pts were registered between July 2014 and August 2019, 230/346 pts (67%) were randomly assigned to arm A and arm B, respectively. 116 patients discontinued induction treatment, mainly due to toxicity (15%) or progressive disease (12%). Median age of the randomized pts was 59 years (range 21–70) with 22% being ≥65 years. Overall response rate (ORR) following induction treatment was 69% (52% PR, 27% CR). Thirteen pts died due to treatment-related toxicity, comprising mainly infectious complications. Following consolidation CR rate increased substantially to 65% in arm A and 68% in arm B. Six patients died of toxicity during consolidation treatment (2 in arm A and 4 in arm B), Median follow-up was 45 months (range 0.2–86). The 3-year PFS and OS rates were 79% (95% CI 71–86) and 86% (95% CI 78–91) following HDC-ASCT and 53% (95% CI 44–62%) and 71% (95% CI 61–78) after R-DeVIC (HR 0.41; p = 0.0002). The evaluation of neurocognitive functions showed no difference between arms.

Discussion: This is the largest randomized phase III study comparing consolidating HDT-ASCT and non-myeloablative immuno-chemotherapy for newly diagnosed PCNSL patients. HDT-ASCT was significantly associated with improved PFS and OS despite similar ORR following consolidation. Most recent results will be presented.

The research was funded by: Riemser, Roche

Keywords: aggressive B-cell non-Hodgkin lymphoma, stem cell transplant

Conflicts of interests pertinent to the abstract

G. Illerhaus
Consultant or advisory role: Roche, Gilead, Incyte
Educational grants: Roche, Gilead

016 | CAR-T CELLS RADICALLY MODIFY THE MANAGEMENT OF RELAPSED/REFRACTORY PRIMARY CEREBRAL LYMPHOMAS. REAL LIFE RESULTS OF THE FRENCH LOC NETWORK

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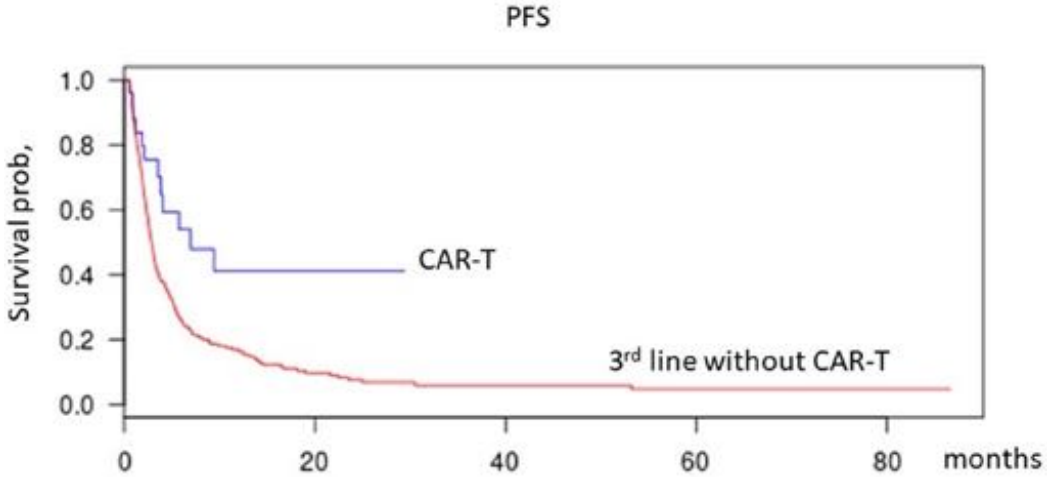
Introduction: Primary central nervous system lymphoma (PCNSL) have recently benefited from therapeutic progress but after the 2nd line the prognosis is particularly poor, with a survival of less than 6 months. CAR-T cells are of major contribution for systemic lymphomas, but the indication in PCNSL is prohibited in the United



States, in Europe the prohibition is not specified. Since 2020, French centers, within the French national LOC network, have treated PCNSL in 3rd line and above. We present here the real-life results of the use of commercial CAR-T cells in PCNSL with a prolonged follow up and compare them to the results of patients in the LOC network who did not benefit from them.

Methods: We retrospectively selected from the French LOC network database the PCNSL patients treated with CAR-T cells from the 3rd line of treatment. As control, we studied PCNSL patients from the LOC database treated with any treatment, at least in 3rd line and considered not eligible for an autologous stem cell transplantation (ASCT) or in relapse after ASCT.

Results: 25 PCNSL patients (median age: 68, ECOG 3–4 for 20%, 12 women, 13 men) were treated with CAR-T cells (tisa-cel : $N = 16$, axi-cel : $N = 9$) between May 2020 and December 2022. They had previously received a median of three lines of treatment, including ASCT in 14/25 cases. 20 had a cerebral involvement (±eye and CSF) 4 an isolated CSF involvement, 1 CSF + eye. All but one patient received a bridging therapy before CAR-T cells, resulting in complete response (CR) or partial response (PR) in 13 cases. The median follow-up after CAR-T cells is 14.2 months. Best response after CAR-T is CR in 14 patients (56%), PR in 6 patients and PD in 5 patients (overall response rate (ORR) of 80%), in case of response after bridging therapy, the CR rate is 64% after CAR-T. Patients enter CR in 44% of cases after Tisa-cel, 78% after axi-cel. Median progression-free survival (PFS) is 7 months, PFS at 1 year is 41%, with a clear plateau, median overall survival (OS) is 19.87 months. 23/25 (92%) patients experienced a CRS, including 2 grade III-IV, 14/25 (56%) an ICANS, including 6 grade III-IV, and 9/25 grade III-IV cytopenia lasting more than 28 days. In the control group ($N = 247$), median age was 68 and median KPS 60. The efficacy endpoints were significantly worse in the control group compared to the CAR-T group: ORR of 41% ($p = 0.004$), median PFS of 2.9 months ($p = 0.04$) (cf figure) and median OS of 4.8 months ($p = 0.02$).

Conclusions: CAR-T cells are clearly effective in PCNSL, with results clearly superior to those usually known in third line and over. In comparison with LOC network data, this processing significantly improves PFS and OS. First data on ICANS seems to see a greater toxicity than in systemic NHL, requiring multidisciplinary care between hematologists, neurologists, ICU, radiologists. Data on a larger number of patients will make it possible to define prognostic factors for response and refine the indications.

Encore Abstract—previously submitted to EHA 2023

Keyword: extranodal non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

S. Choquet
Consultant or advisory role: Kite/Gilead, Novartis

017 | PHASE 2 STUDY OF IBRUTINIB WITH TEMOZOLOMIDE, ETOPOSIDE, LIPOSOMAL DOXORUBICIN, DEXAMETHASONE, RITUXIMAB (TEDDI-R) FOR SECONDARY CNS LYMPHOMA

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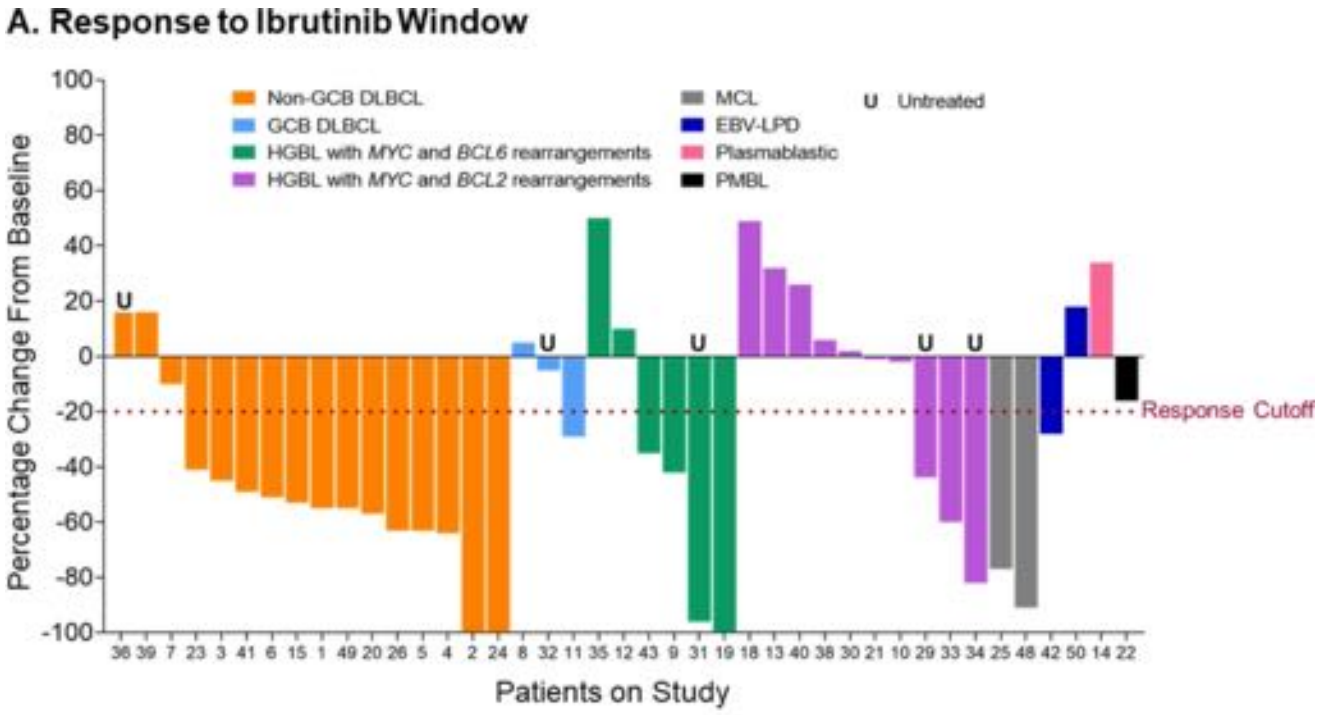
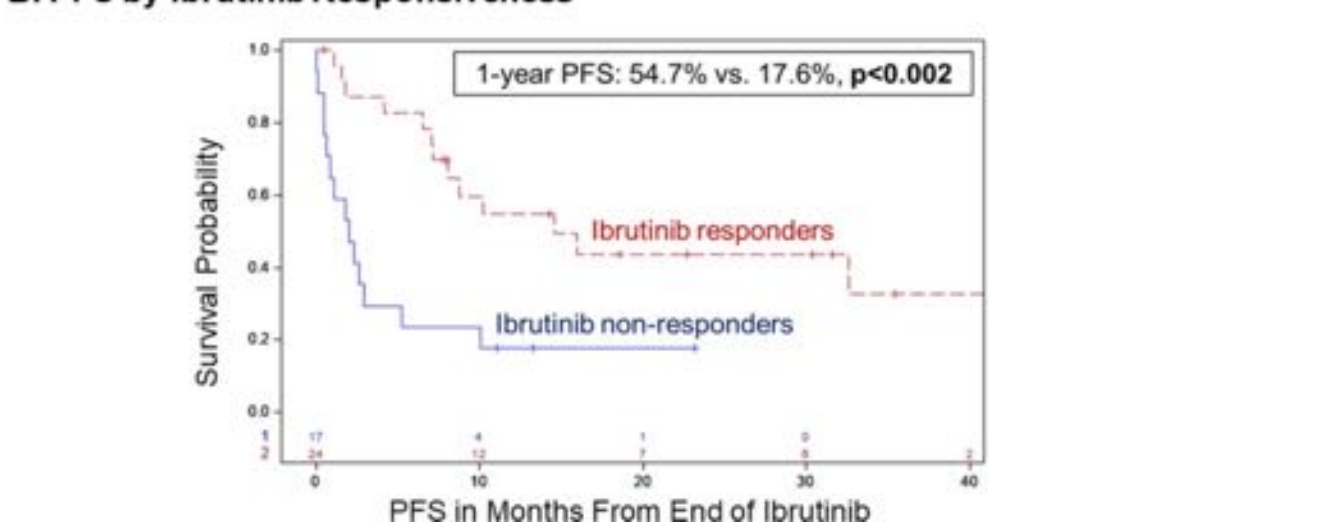
Introduction: PCNSL has BCR signaling that responds to BTKi but the molecular profile of SCNSL is heterogeneous. TEDDi-R was developed to achieve therapeutic CNS levels of potentially curative agents. We present results of ibrutinib with TEDD-R in SCNSL to characterize the molecular correlates of BTKi response and overall treatment efficacy (NCT03964090).

Methods: Pts with untreated or recurrent B-cell lymphoma with CNS ± systemic involvement were eligible. Pts first received ibrutinib 560 mg × 14d in a window. Pts with ≥20% reduction after ibrutinib received TEDDi-R; those with <20% reduction received TEDD-R. Therapy was 4 cycles × 21d with IT therapy (no maintenance) and mostly outpatient. All pts received isavuconazole. Response was assessed after cycles[2], 4. CR was confirmed with PET brain/body and CSF.

Results: 49 pts enrolled; 17 (35%) were female with median age 62 (range 26–89) and 15 (31%) aged ≥70. 27 (55%) had DLBCL including 20 (41%) non-GCB, 5 (10%) GCB, 1 (2%) PMBL, and 1 (2%) unknown. 16 (33%) had HGBL including 10 (20%) with *MYC*-R and *BCL2*-R and





6 (12%) with *MYC*-R and *BCL6*-R. 2 (4%) pts each had MCL and EBV-LPD, while 1 pt each had plasmablastic (2%) and BL (2%). 28 (57%) had synchronous CNS/peripheral dz while 21 (43%) had isolated CNS. 5 (10%) were untreated while 44 (90%) had a median of 2 (range 1–4) prior therapies. Of rel/ref pts, 44 (100%) had anthracycline, 28 (64%) had HD-MTX, 19 (43%) had CNS prophylaxis, and 8 (18%) had CAR-T. Of 42 pts who completed the ibrutinib window, 24 (57%) were ibrutinib-responsive and 17 (43%) were ibrutinib-resistant (Figure A). After TEDDi-R ($N = 26$), the ORR was 92% and CR rate was 77%. After TEDD-R ($N = 18$), the ORR was 45% and CR rate was 28%. G3/G4 neutropenia occurred in 29% and 40% of cycles, while FN occurred in 10%. G3/G4 thrombocytopenia occurred in 30% and 12% of cycles. 30 (63%) pts received blood and 18 (38%) received platelet transfusion. Other G3 AEs included UTI (21%), hypokalemia (21%), sepsis (15%), diarrhea (15%), hypotension (11%), anorexia (11%), and adrenal insufficiency (11%). No opportunistic infections were observed. 14 (30%) pts had hand-foot syndrome and 4 (9%) had G3 afib. After a median follow-up of 23m, the 1-year PFS and OS was 36.7% and 60.8%. 15 (83%) deaths were due to progression while 1 (2%) was related to treatment. A landmark analysis after the window showed the 1-year PFS and OS for pts with ibrutinib-responsive versus ibrutinib-resistant tumors was 54.7% versus 17.6% ($p < 0.002$) (Figure B) and 76.7% versus 47.1% ($p = 0.08$). 88% of ibrutinib-responsive tumors were CD10 neg. Pts with CD10 neg tumors had an ORR of 83%, and a 70% rate of CR. The 1-year PFS and OS for pts with CD10 neg tumors was 48.0% and 64.7%
Conclusions: Ibrutinib-responsive SCNSL achieves high rates of CR to TEDDi-R that can be durable. TEDDi-R is safely delivered as outpatient to all ages. Ibrutinib-responsive tumors are mostly CD10 negative and TEDDi-R may improve the outcomes of this subgroup.

The research was funded by: The Intramural Research Program of the National Institutes of Health

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, molecular targeted therapies

Conflicts of interests pertinent to the abstract

K. Dunleavy
Consultant or advisory role: Astra Zeneca, Amgen, Beigene, Kite, ADC Therapeutics, Cellectar
Research funding: ONO Pharmaceuticals, Genentech, Kymera

018 | FIVE-YEAR RESULTS OF A PHASE 2 STUDY OF CNS-ORIENTED THERAPY WITH R-CHOP FOR UNTREATED INTRAVASCULAR LARGE B-CELL LYMPHOMA: FINAL ANALYSIS OF THE PRIMEUR-IVL STUDY

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Introduction: Intravascular large B-cell lymphoma (IVLBCL) is a rare disease entity of extranodal large B-cell lymphoma characterized by selective growth of lymphoma cells in the lumina of small vessels. The prognosis of IVLBCL is typically poor without timely diagnosis. Based on the promising efficacy of rituximab-containing chemotherapy and a high incidence of secondary central nervous system (CNS) involvement after rituximab-chemotherapy, we conducted the PRIMEUR-IVL study to explore the efficacy of CNS-oriented therapy with rituximab-chemotherapy whose primary analysis demonstrated

2-year progression-free survival (PFS) of 76% and 2-year overall survival (OS) of 92% with a low incidence of secondary CNS involvement of 3%.

Patients and Methods: The PRIMEUR-IVL study is a multicenter, single-arm, phase 2 trial at 22 hospitals in Japan for untreated histologically confirmed IVLBCL patients without apparent CNS involvement at diagnosis. The treatment regimen includes three cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) followed by two cycles of rituximab with high-dose methotrexate and additional three cycles of R-CHOP. Intrathecal chemotherapy including methotrexate, cytarabine, and prednisolone was administered four times during the R-CHOP phase. We present a preplanned final analysis of the PRIMEUR-IVL study including 5-year PFS, OS and secondary CNS involvement.

Results: A total of 38 patients were enrolled, of whom 37 patients were eligible. One patient with a history of testicular lymphoma was excluded. As of July 2021, with a median follow-up of 7.1 years (interquartile range 5.6–8.7), 5-year PFS in all eligible patients was 68% (95% confidence interval [CI] 50%–80%) and OS was 78% (95% CI 61%–89%). Median PFS and OS were not reached. No additional secondary CNS involvement was observed after primary analysis with 3% of cumulative incidence. Severe adverse events after the primary analysis were grade 4 neutropenia ($n = 1$) and grade 4 myelodysplastic syndrome that did not require specific treatment ($n = 1$). During the observation period after enrollment, there were a total of eight deaths due to following reasons: primary disease ($n = 6$), sepsis ($n = 1$), and unknown sudden death ($n = 1$).

Conclusions: In this 5-year, long-term follow-up analysis of the PRIMEUR-IVL study, frontline treatment of CNS-oriented therapy with standard R-CHOP for untreated IVLBCL patients without apparent CNS involvement provided durable response and clinically meaningful results for PFS, OS, and low incidence of secondary CNS involvement with manageable toxicity. Our result provides one of active treatment for untreated IVLBCL patients.

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Keyword: chemotherapy

Conflicts of interests pertinent to the abstract

K. Shimada
Honoraria: AstraZeneca, Chugai, Eisai, Kyowa Kirin, Symbio

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Research funding: Kyowa Kirin, Takeda, Chugai, Bristol Myers Squibb, Janssen, AstraZeneca, Ono, AbbVie, Nippon Shinyaku, Daiichi-Sankyo, Zenyaku Kogyo, Solasia

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SESSION 3 - TREATMENT OF AGGRESSIVE LYMPHOMAS

019 | A RANDOMIZED TRIAL OF OBSERVATION VERSUS RADIOTHERAPY IN PRIMARY MEDIASTINAL B-CELL LYMPHOMA PATIENTS WITH COMPLETE METABOLIC RESPONSE AFTER STANDARD IMMUNOCHEMOTHERAPY

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Introduction: Primary mediastinal B-cell lymphoma (PMBCL) has a poor prognosis if remission is not rapidly achieved, or the disease recurs. Mediastinal radiotherapy (RT) may consolidate responses to dose-intensive immunochemotherapy; however, it increases the risk of second malignancies and coronary or valvular heart disease. The IELSG37 (NCT01599559) randomized trial was planned with a non-inferiority design to test whether RT can be omitted in PMBCL patients who achieve a complete metabolic response (CMR) after immunochemotherapy.

Methods: Patients with newly diagnosed PMBCL were eligible. The initial rituximab and anthracyclines-based immunochemotherapy regimen was chosen according to local practice. Based on the Lugano classification, CMR was defined as Deauville score 1–3, upon central review of positron emission computed tomography (PET/CT) scans. Responding patients were randomized to observation (OBS) or consolidation RT (30 Gy). Randomization was stratified on gender, chemotherapy regimen, country, and PET/CT score. The primary endpoint was progression-free survival (PFS) after randomization. The sample size (540 patients to enroll, and 376 to randomize) was calculated assuming a 30-month PFS probability of 0.85 in both arms, with alpha at 0.05, 80% power, and a hazard ratio (HR) of 1.77 as a non-inferiority margin.

Results: Although the number of observed events at a median follow-up of 30 months was considerably lower than expected, the Independent Data Monitoring Committee (IDMC) recommended completing the planned total accrual without increasing the study size or duration. According to the IDMC recommendation, the primary endpoint analysis was performed with ≥80% of patients having a minimum follow-up of 30 months. 545 patients (209 men, 336 women) were enrolled. Induction immunochemotherapy was completed and response assessed in 530 patients, 268 of them (50.6%) achieved a CMR and were randomly allocated to OBS (N = 132) or RT (N = 136). At a median follow-up of 5 years, the 30-month PFS was 98.5% (95% CI, 94.3–99.6) in the RT arm and 96.2% (95% CI, 91.1–98.4) in the OBS arm (p = 0.278). The estimated relative effect of radiotherapy versus observation in terms of hazard ratio (HR) was 0.47 (0.12–1.88) without adjustments and 0.68 (0.16–2.91) after stratification for the variables used for randomization. At 30 months the absolute risk reduction from RT was 2.3% (−1.5 to 6.2) unadjusted, and 1.2% (−3.2 to 7.0) with stratified HR. The number needed to treat is high (43 patients, unadjusted, and 126 after stratification).

Overall survival at 5 years was 99% in both arms. Longer follow-up is needed to evaluate late toxicity.

Conclusions: This is the largest prospective trial of PMBCL ever conducted. Although the event rate did not reach the anticipated level, the study evidence strongly supports the omission of RT in patients with CMR after immunochemotherapy.

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Keywords: aggressive B-cell non-Hodgkin lymphoma, PET-CT, radiation therapy

Conflicts of interests pertinent to the abstract

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Educational grants: Roche
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020 | R-CODOX-M/R-IVAC VERSUS DA-EPOCH-R IN PATIENTS WITH NEWLY DIAGNOSED HIGH-RISK BURKITT LYMPHOMA: FINAL RESULTS OF A MULTI-CENTER RANDOMIZED HOVON/SAKK TRIAL

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Background: Optimal first-line treatment for patients with high-risk Burkitt lymphoma (BL) remains to be defined. Treatment with high-dose multi-agent regimens such as R-CODOX-M/R-IVAC is effective at the cost of significant toxicity. In single arm phase II studies, DA-EPOCH-R has demonstrated favorable progression free survival (PFS) and overall survival (OS) and less toxicity. Until now, no formal comparison between the regimens has been performed.

Methods: This investigator initiated study (EudraCT2013-004394-27) is an international randomized phase III trial designed to demonstrate 2 year PFS (primary endpoint) improvement from 70% with R-CODOX-M/R-IVAC to 85% with DA-EPOCH-R in patients with (sporadic and HIV-associated) BL.

Patients (18–75 year) with newly diagnosed high-risk BL (defined as any of: elevated LDH, WHO PS ≥2, stage III/IV, mass ≥10 cm) were eligible. Patients with central nervous system (CNS) involvement were excluded.

Patients were randomly assigned to treatment with 2 cycles of R-CODOX-M/R-IVAC or 6 cycles of DA-EPOCH-R. All patients received intrathecal CNS prophylaxis. Due to slow accrual rate, the trial was closed prematurely.

Results: From 2014 to 2021, 89 patients were enrolled. Five patients were excluded, 84 patients were randomized (43 to R-CODOX-M/R-IVAC, 41 to DA-EPOCH-R).

In the R-CODOX-M/R-IVAC arm, 23% discontinued treatment versus 10% in the DA-EPOCH-R arm. In the R-CODOX-M/R-IVAC arm 65% achieved complete metabolic remission (CMR) versus 66% in the DA-EPOCH-R arm.

With a median FU of 28.5 (0.03–88) months and at least 12 months for all patients that completed treatment, survival rates were comparable. Two year PFS in the R-CODOX-M/R-IVAC arm was 76% (95% CI: 60%–86%) versus 70% (95% CI: 54%–82%) in the DA-EPOCH-R arm. Two year OS rates were 76% (95% CI 60%–86%) in the R-CODOX-M/R-IVAC arm versus 75% (95% CI 59%–86%) in the DA-EPOCH-R arm.

Patients treated with R-CODOX-M/R-IVAC experienced significantly more infectious adverse events (AE): 56% had ≥one infectious grade 3–5 AE versus 34% of patients treated with DA-EPOCH-R ($p = 0.047$).

Patients treated with R-CODOX-M/R-IVAC arm received significantly more transfusions (platelets and red blood cells, $p < 0.01$ both), and were significantly more hospitalized (46 (mean, 1–99) versus 25 (4–78) days ($p < 0.01$)) then DA-EPOCH-R treated patients. Hospitalization days for AE did not differ between the arms.

Conclusion: This is the first multi-center randomized trial comparing two different chemotherapy regimens in BL. The trial was closed after enrollment of 89 patients. Treatment with DA-EPOCH-R did not result in superior CMR and survival rates compared to R-CODOX-M/R-IVAC, but was associated with significantly less infectious complications, transfusions and hospitalization days. Besides R-CODOX-M/R-IVAC, treatment with DA-EPOCH-R is a valid and less toxic therapeutic option for high-risk BL patients without CNS localization.

The research was funded by: Dutch Cancer Foundation, Schumacher-Kramer Foundation

Keywords: aggressive B-cell non-Hodgkin lymphoma, chemotherapy

No conflicts of interests pertinent to the abstract.

021 | BIOMARKER-DRIVEN TREATMENT STRATEGY IN HIGH-RISK LARGE B-CELL LYMPHOMA (NLG-LBC-06 PHASE II TRIAL): IMPACT OF CTDNA AND TP53 ABERRATIONS ON CLINICAL OUTCOME

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Introduction: Intensified immunochemotherapy combined with early systemic high-dose methotrexate (HD-Mtx) has been shown to be effective, and stratification according to biological risk factors feasible in young patients with high-risk large B-cell lymphoma (LBCL). However, existing clinical and biological features suboptimally capture risk of treatment failure. Here we aimed to dissect molecular determinants in the circulating tumor DNA (ctDNA) to resolve heterogeneity and characterize the patients with poor outcome.

Methods: This biomarker-driven Nordic Lymphoma Group phase II trial (NLG-LBC-06) included patients aged <65 years with high-risk aggressive B-cell lymphoma. All patients received two cycles of R-CHOP-21 with HD-Mtx on day 15 and depending on the biological risk factors (*C-MYC* translocation, *C-MYC* and *BCL2* translocation (double hit), *17p/TP53* deletion, co-expression of MYC and BCL2, P53+ and/or CD5+) either four additional courses of R-CHOEP-14 (no biological risk factors) or four courses of dose-adjusted EPOCH-R (biological risk factors). In addition, one course of R-HD-cytarabine was given to all patients. Plasma samples were collected at multiple time points, and ctDNA was analyzed as an exploratory noninvasive biomarker using custom capture-based gene panel with in-house adapted duplex strategy and sequencing.

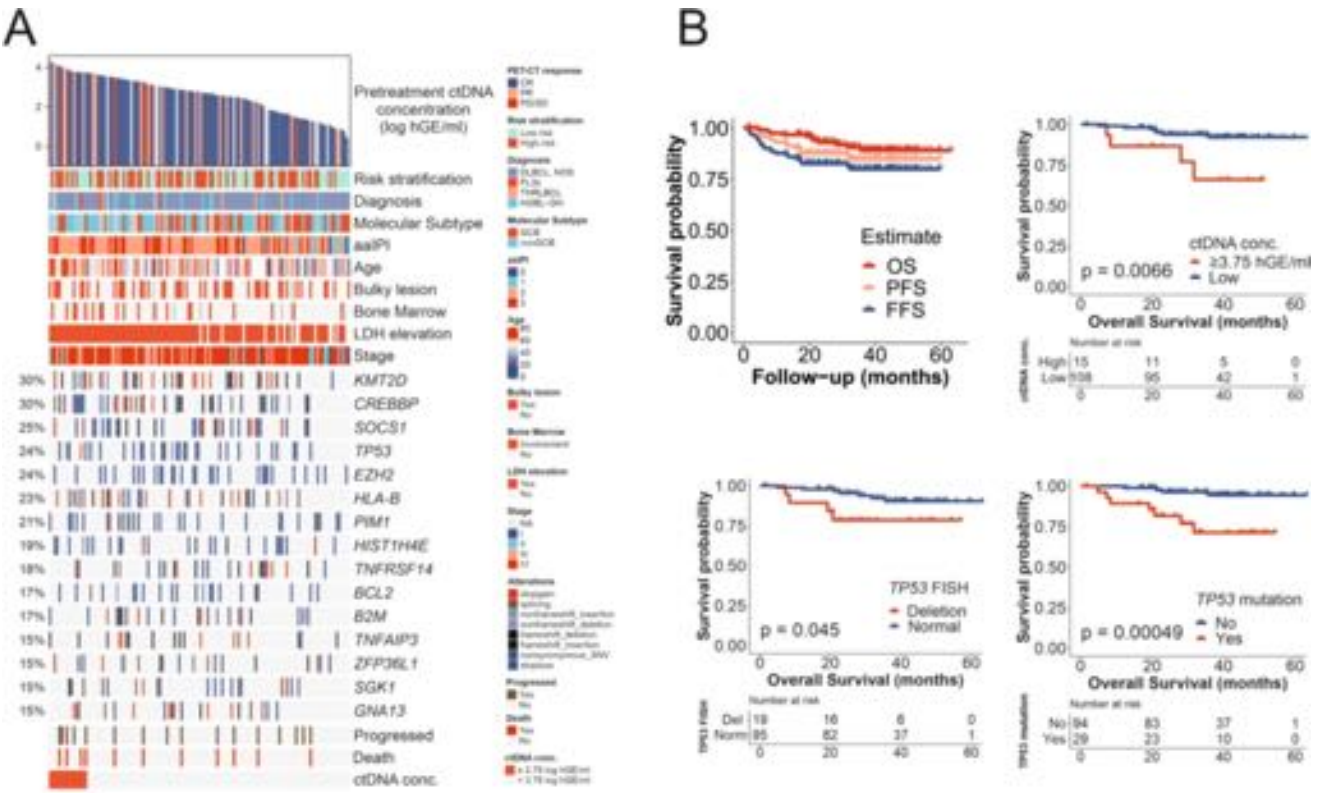

Figure 1. A. Oncoprint of the mutation landscape according to pretreatment ctDNA concentration. **B.** Kaplan-Meier survival estimates for FFS, PFS and OS in the entire trial cohort, and for OS according to high pretreatment ctDNA burden, 17p/TP53 deletion and TP53 mutations.

Results: Of the 123 patients who were eligible, 61 were stratified to biological high-risk and 62 to the low-risk group. After a median follow up of 37 months (1–63), 3-year failure free survival (FFS), progression free survival (PFS) and overall survival (OS) rates for the entire study population were 79%, 84% and 90%, respectively (Figure 1). Survival was comparable in biologically high- and low-risk patients. In a multivariable analysis with age and aaIPI, *17p/TP53* deletion remained the only significant predefined biological risk factor for progression and death. While pretreatment ctDNA levels and mutational content varied substantially between the patients (Figure 1), and also within the aaIPI risk groups, there was no difference in the ctDNA burden between low and high biological risk groups. Yet high pretreatment ctDNA levels and *TP53* mutations, which were detected in both low and high biological risk patients, translated to inferior survival (Figure 1). ctDNA profiling of the mid- and end-of-therapy samples is ongoing and the results will be presented.

Conclusion: Intensified immunochemotherapy results in a favorable outcome in patients with high-risk LBCL apart from those with *17p/TP53* deletion, *TP53* mutations and/or high ctDNA burden. Our findings highlight the role of ctDNA as a noninvasive biomarker with a potential to improve risk stratification beyond biological and clinical factors and to guide treatment decisions in patients with high-risk LBCL.

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Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, diagnostic and prognostic biomarkers

Conflicts of interests pertinent to the abstract

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Research funding: Bayer, Celgene, Genmab, HutchMed, Novartis, Roche (to the Institution)

022 | PRIMARY OVERALL SURVIVAL ANALYSIS OF THE PHASE 3 RANDOMIZED ZUMA-7 STUDY OF AXICABTAGENE CILOLEUCEL VERSUS STANDARD OF CARE IN RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA

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Introduction: In ZUMA-7 (NCT03391466), axicabtagene ciloleucel (axi-cel) was superior to a chemotherapy-based standard of care (SOC; hazard ratio [HR]: 0.398; $p < 0.0001$) in the primary analysis of event-free survival (EFS) as second-line therapy in patients with early relapsed or refractory large B-cell lymphoma (LBCL; Locke et al. *NEJM.* 2022). In a preplanned interim analysis, median overall survival (OS) was numerically prolonged in the axi-cel arm (Locke et al. TCT 2022. Abstract 1). We now report the primary analysis of OS from ZUMA-7.

Methods: Study procedures and eligibility were previously reported. The intention-to-treat (ITT) primary OS analysis occurred 5 years after the first patient was randomized (01/25/2018) per protocol. A log-rank test stratified by randomization stratification factors compared OS between the 2 arms. In addition to the ITT analysis, prespecified OS sensitivity analyses were conducted to adjust for confounding due to subsequent cellular immunotherapy in the SOC arm. Other endpoints included progression-free survival (PFS) per investigator assessment, OS in key subgroups, and safety. Exploratory analyses were conducted to determine the association between OS and axi-cel pharmacokinetics and product features.

Results: In total, 359 patients were randomized, 180 to axi-cel and 179 to SOC. As of 01/25/2023, at a median follow-up of 47.2 mo, axi-cel demonstrated a statistically significant improvement in OS over SOC (HR: 0.726, 95% CI: 0.540–0.977; stratified log-rank 1-sided $p = 0.0168$ [efficacy boundary, 0.0249]). Median OS was prolonged with axi-cel versus SOC (not reached vs. 31.1 mo, respectively); 48-mo OS estimates were higher with axi-cel (54.6% vs. 46.0%, respectively). OS benefit with axi-cel versus SOC was consistent in prespecified key subgroups, including age ≥65 years, primary refractory, early relapse, high-grade B-cell lymphoma, and high second-line age-adjusted IPI. In the SOC arm, 102 (57%) patients received subsequent cellular immunotherapy off protocol. Prespecified OS sensitivity analyses

showed an even greater OS benefit with axi-cel versus SOC, with stratified HR of 0.608 (95% CI: 0.449–0.824) by Rank-Preserving Structural Failure Time model. PFS by investigator confirmed benefit of axi-cel over SOC (HR: 0.506, 95% CI: 0.383–0.669), with 48-mo PFS estimates of 41.8% versus 24.4%, respectively. No new cytokine release syndrome or neurologic events and no new treatment-related deaths occurred since the primary EFS analysis. The safety profile of axi-cel remained consistent with prior studies. Improved OS was associated with an increased proportion of a naive T-cell phenotype (CCR7+CD45RA+ T cells, descriptive $p < 0.05$) in the infused product.

Conclusions: Axi-cel as second-line therapy demonstrated a significant improvement in overall survival over chemotherapy-based SOC in patients with early relapsed/refractory LBCL.

Keyword: aggressive B-cell non-Hodgkin lymphoma

Encore Abstract—previously submitted to ASCO 2023

Conflicts of interests pertinent to the abstract

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SESSION 4 - CLL AND RICHTER SYNDROME

023 | FOXO1-RICTOR AXIS INDUCES AKT PHOSPHORYLATION DURING CLL CELL ADAPTATION TO BCR INHIBITORS: IMPLICATIONS FOR COMBINATORIAL THERAPY

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Introduction: Although genetic mechanisms of resistance to BCR inhibitors in CLL are well-known, it remains elusive whether non-genetic adaptation mechanisms might exist. We focused on the possible role of Akt pathway as PI3K-Akt activation is the only known factor that rescues the apoptosis induced by BCR deletion in mature B cells in mouse models (Srinivasan *et al.* Cell, 2009).

Methods: We performed transcriptome profiling (Illumina) and analyzed samples obtained from CLL patients before and during ibrutinib or idelalisib therapy (1–12 weeks of therapy, $n = 70$ patients with 194 samples) and performed gene editing in MEC1 cells to reveal the functional role of FoxO1/Rictor.

Results: We observed that during ibrutinib therapy *in vivo* Akt activity ($pAkt^{S473}$) increases above pre-therapy levels in ~80% of CLL cases within first 12 weeks of therapy ($n = 43$; $p < 0.005$; Figure A). RNA profiling of paired CLL samples obtained before and during ibrutinib ($n = 22$) or idelalisib therapy ($n = 18$) revealed that during BCR inhibitor treatment the levels of transcription factor FoxO1 are increased in CLL cells (no *BTK* or *PLCG2* mutations detected during early weeks of therapy). FoxO1 subsequently induces transcription of *RICTOR*, an essential assembly protein for mTORC2 complex which directly phosphorylates Akt on S473. Knock-out of *FoxO1* or *Rictor* in the MEC1 cell line led to a 70% decrease in pAkt levels ($p < 0.0001$) and resulted in a growth disadvantage in a competitive growth assay in the presence of ibrutinib (Figure B; $p < 0.05$). Similar results were obtained with idelalisib, suggesting that the FoxO1-Rictor-pAkt axis does not require BTK or PI3Kδ activity.

FoxO1 inhibitor (AS1842856) decreased basal and ibrutinib-induced pAkt levels and blocked anti-IgM-induced pAkt and cMYC ($p < 0.01$). It also induced primary CLL cells' apoptosis alone (~40% apoptosis) or more potently in combination with ibrutinib or idelalisib (~60% apoptosis; Figure C, $n = 7$). The apoptosis induced by FoxO1 inhibition could not be rescued by CLL cells coculture with HS5 cells or HS5 engineered to produce CD40L+IL21+IL4, and FoxO1 inhibitor blocked proliferation of primary CLL cells induced by these T-cell factors (Figure D).

Conclusions: We describe for the first time that CLL cells activate the FoxO1-Rictor-pAkt axis to adapt to BCR inhibitors (Figure E) and suggest that FoxO1 is a potential novel therapeutic target since its inhibition decreases CLL cell viability and reduces CLL proliferation induced by T-cell signals.

Keywords: chronic lymphocytic leukemia (CLL), tumor biology and heterogeneity

Encore Abstract - previously submitted to EHA 2023

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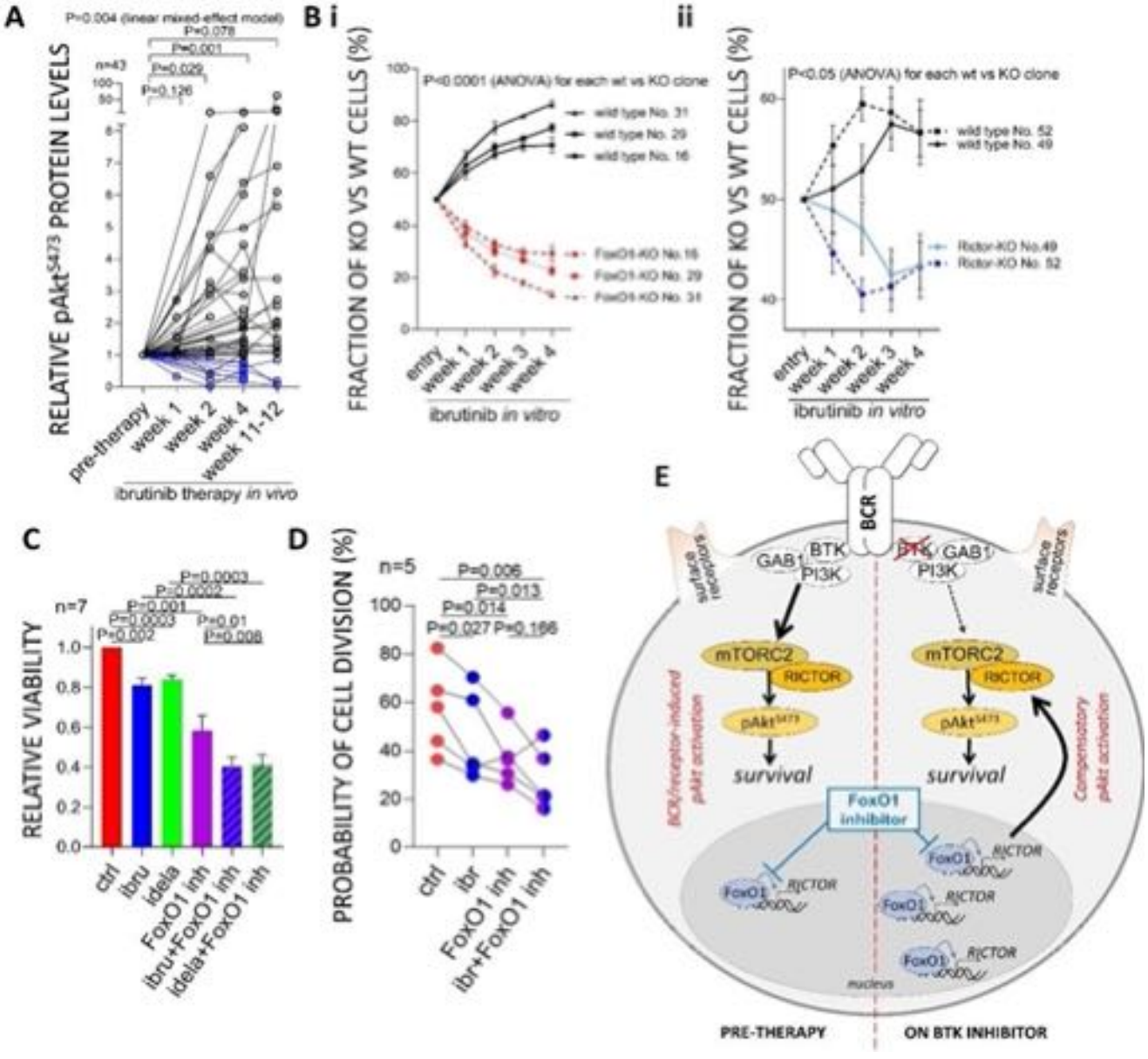
Conflicts of interests pertinent to the abstract



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024 | IBRUTINIB VERSUS PLACEBO IN PATIENTS WITH ASYMPTOMATIC, TREATMENT-NAïVE EARLY STAGE CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): FINAL RESULTS OF THE CLL12 TRIAL

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Introduction: We present the final analysis of the phase 3, double-blind, placebo-controlled CLL12 trial evaluating ibrutinib in patients with early stage CLL at increased risk of progression defined by a comprehensive score (NCT02863718).

Methods: We randomly assigned patients with asymptomatic, treatment-naïve Binet stage A CLL at increased risk of progression in a 1:1 ratio to receive ibrutinib (n = 182) or placebo (n = 181) at a dose of 420 mg daily. Patients with low risk CLL were allocated to the watch and wait group (W&W; n = 152). The final analysis evaluated event-free survival (EFS; defined as time to *symptomatic* progression, CLL treatment or death), progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS).

Results: At a median observation time of 69.3 months the overall response rate was 72.5% in the ibrutinib group. PFS, EFS and TTNT were not reached in the ibrutinib group as compared to 14 months ($p < 0.001$; HR 0.174, 95% CI 0.122–0.246), 51.6 months ($p < 0.001$; HR 0.276, 95% CI 0.188–0.407), and 68.5 months ($p < 0.001$; HR 0.244, 95% CI 0.156–0.380) in the placebo group.

A total of 29 (15.9%), 79 (43.6%), and 25 (16.4%) subsequent treatment lines were administered in the ibrutinib, placebo and W&W group, respectively.

The median overall survival was not reached in neither treatment group (p = 0.562, HR 0.791, 95% CI 0.358–1.748) with 12 (6.6%) deaths in the ibrutinib and 14 (7.7%) deaths in the placebo group. The estimated survival rate at 5 years for patients treated with ibrutinib and placebo was 93.3% and 93.6%, respectively.

A total of 6 (3.9%) deaths occurred in the W&W group with median survival from CLL diagnosis not reached, as compared to 258 months for the placebo and not reached for the ibrutinib group.

Causes of death were progressive disease (1x ibrutinib), Richter Transformation (3x placebo), treatment-related adverse event (1x ibrutinib, subdural hematoma), infection (2x ibrutinib, 1x placebo, 1x W&W), concomitant disease (4x ibrutinib, 5x placebo, 4x W&W), and other (4x ibrutinib, 5x placebo, 1x W&W).

Adverse events were documented in 99.4% of ibrutinib and placebo treated patients, with 71.8% and 66.1% of patients experiencing CTC grade 3–5 events, respectively.

More bleeding events (36.5% vs. 14.9%), cardiac arrhythmias (22.4% vs. 9.5%), other cardiac events (17.6% vs. 15.5%), diarrhoea (40.6% vs. 28.6%), and hypertensive disorders (19.4% vs. 8.3%) occurred in ibrutinib as compared to placebo-treated patients.

Conclusions: Early ibrutinib-treatment of patients with asymptomatic Binet stage A CLL at high risk of progression failed to demonstrate an overall survival benefit when compared to placebo. Based

on these results, watch and wait should remain the standard of care of patients with early stage CLL with inactive disease - regardless of genetic, laboratory or clinical risk factors.

Encore Abstract - previously submitted to EHA 2023

The research was funded by: Janssen

Keyword: molecular targeted therapies

Conflicts of interests pertinent to the abstract

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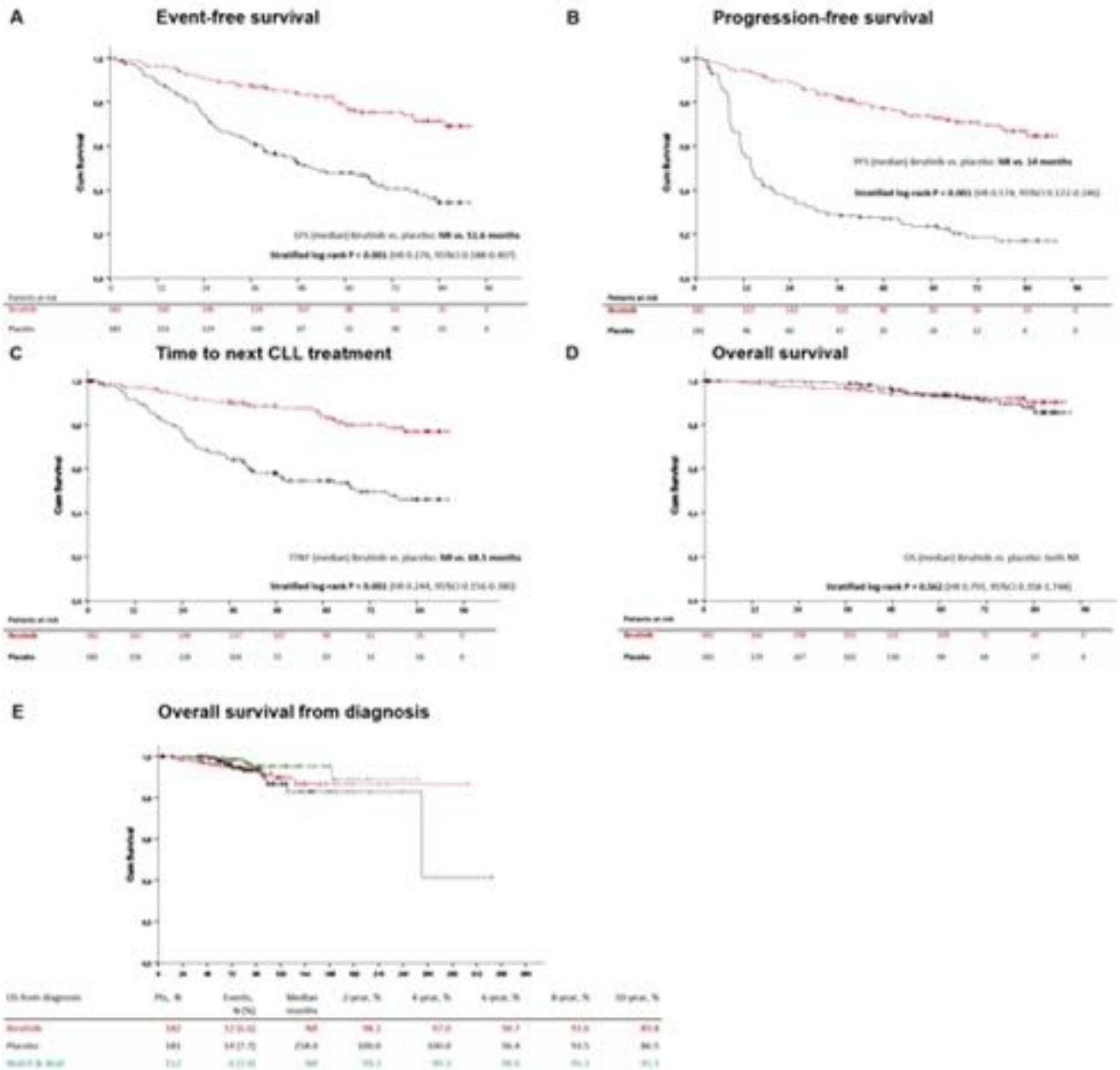
Figure 1. Primary and secondary endpoints of the CLL12 trial. Endpoints are shown for all patients by therapy received for EFS (A), PFS (B), TTNT (C) and overall survival. Overall survival from diagnosis (E) is shown for all patients by therapy received and for low-risk patients of the watch & wait group.



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025 | VENETOCLAX-OBINUTUZUMAB FOR PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA: 6-YEAR RESULTS OF THE RANDOMIZED CLL14 STUDY

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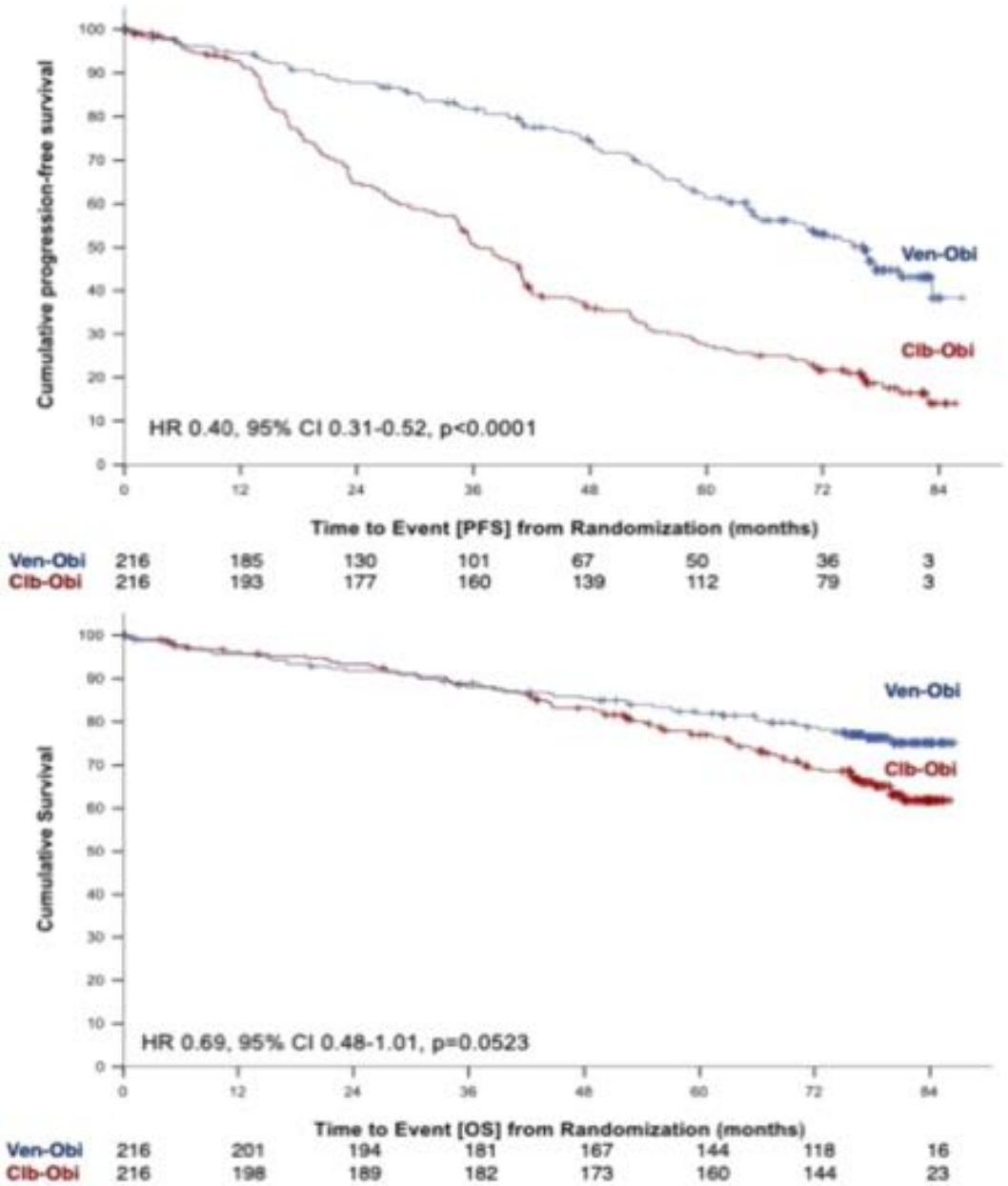
Background: One-year fixed-duration venetoclax-obinutuzumab (Ven-Obi) is a standard-of-care for patients (pts) with previously untreated chronic lymphocytic leukemia (CLL). Due to its ongoing follow-up, the CLL14 study provides unique insights into long-term outcomes of pts after Ven-Obi therapy.

Methods: Pts with previously untreated CLL and coexisting conditions were randomized 1:1 to Ven-Obi or chlorambucil-obinutuzumab (Clb-Obi). Primary endpoint was investigator-assessed progression-free survival (PFS). Secondary endpoints included safety, rates of minimal residual disease (MRD), time to next treatment (TTNT) and overall survival (OS).

Results: Of 432 enrolled pts, 216 were randomly assigned to Ven-Obi, 216 to Clb-Obi. At a median follow-up of 76.4 months (interquartile range 52.5–80.5), PFS remained superior for Ven-Obi compared to Clb-Obi (median 76.2 vs. 36.4 months; HR 0.40 [95% CI 0.31–0.52], $p < 0.0001$). Progressive disease (PD) occurred in 67 cases in the Ven-Obi arm with 39 second-line treatments, and in 141 cases in the Clb-Obi arm (with 103 second-line treatments). TTNT was significantly longer after Ven-Obi (6-year TTNT 65.2% vs. 37.1%; HR 0.44, 95% CI 0.33–0.58, $p < 0.0001$). In both arms, the most frequent second-line treatments were BTK inhibitors (61.5% in the Ven-Obi arm, 55.4% in the Clb-Obi arm).



The PFS and TTNT difference between the two arms was maintained across all risk groups, including pts with *TP53* mutation/deletion (median PFS 51.9 vs. 20.8 months; median TTNT 57.3 vs. 29.0 months) and unmutated IGHV status (median PFS 64.8 vs. 26.9 months; median TTNT 85.4 vs. 40.6 months). Multivariate analysis identified *TP53* deletion/mutation, unmutated IGHV and lymph node size ≥5 cm as independent negative prognostic factors for PFS in pts treated with Ven-Obi.

Five years after treatment completion, 17 (7.9% of the intention-to-treat population) pts in the Ven-Obi arm still had uMRD ($<10^{-4}$ by NGS in peripheral blood), 22 (10.2%) had low (L)-MRD ($\geq 10^{-4}$ and $<10^{-2}$) and 23 (10.6%) high (H)-MRD ($\geq 10^{-2}$), compared to 4 (1.9%) uMRD, 9 (4.2%) L-MRD and 18 (8.3%) H-MRD in the Clb-Obi arm.

Overall, 48 deaths were reported in the Ven-Obi arm (9 PD related) and 70 in the Clb-Obi arm (26 PD related); 6-year-OS rate was 78.7% in the Ven-Obi and 69.2% in the Clb-Obi arm (HR 0.69 [0.48–1.01], $p = 0.052$). Second primary malignancies were reported in 30 pts in the Ven-Obi and 18 in the Clb-Obi arm; cumulative incidences 6 years after randomization were 14.2% and 8.5%, respectively ($p = 0.071$). No new safety signals were observed.

Conclusion: These data confirm a long-term PFS benefit of fixed-duration Ven-Obi treatment compared to Clb-Obi, including pts with high-risk CLL. Five years after completing Ven-Obi, over half of pts remained in remission, and over 60% had not required second-line treatment. The 1-year Ven-Obi regimen is an effective fixed-duration option for pts with CLL and coexisting conditions.

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Keywords: chronic lymphocytic leukemia (CLL), combination therapies

Conflicts of interests pertinent to the abstract

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026 | LISOCABTAGENE MARALEUCEL (LISO-CEL) IN R/R CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)/SMALL LYMPHOCYTIC LYMPHOMA (SLL): PRIMARY ANALYSIS OF TRANSCEND CLL 004

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Introduction: Achieving durable CR with current treatment is uncommon in patients (pts) with R/R CLL/SLL that progressed on BTKi and failed venetoclax (ven)-based treatment. New therapies that achieve deep and durable responses are needed. We report the primary analysis of the phase 1/2, single-arm, multicenter TRANSCEND CLL 004 (NCT03331198) study evaluating liso-cel in pts with R/R CLL/SLL.

Methods: Pts must have received at least two prior lines of therapy, including a BTKi. Eligible pts received liso-cel at a target dose of either 50 (DL1) or 100 (DL2) $\times$ 10^6 CAR^+ T cells. The primary endpoint was rate of CR and CR with incomplete marrow recovery (CRi) by IRC per 2018 iwCLL criteria in the prespecified subset of efficacy-evaluable pts with disease progression on BTKi and ven failure (primary efficacy analysis set [PEAS]) at DL2 (null hypothesis [H_0]: ≤5%). Key secondary endpoints were ORR (H_0: ≤40%) and rate of undetectable minimal residual disease (uMRD; 10^{-4}) in blood (H_0: ≤5%).

Results: Of 137 leukapheresed pts, 117 received liso-cel (safety set), 96 (DL1 = 9; DL2 = 87) were efficacy evaluable, and 53 (DL1 = 4; DL2 = 49) were in the PEAS. In the safety set, median (range) age was 65 y (49–82), 83% had high-risk features, median (range) lines of prior therapy was 5 (2–12), and all pts had prior BTKi. Median (range) on-study follow-up was 21.1 mo (0.4–55.6) for the safety set. In the PEAS at DL2, the primary endpoint of CR/CRi rate was met at 18.4% (95% CI, 8.8–32.0; 1-sided $p = 0.0006$; **Table**). ORR was 42.9% and was not statistically significant (95% CI, 28.8–57.8; 1-sided $p = 0.3931$). The uMRD rate was 63.3% in blood and 59.2% in marrow. Median (95% CI) DOR was 35.3 mo (11.01–not reached [NR]) with a median follow-up of 19.7 mo. Median duration of CR/CRi was NR. In the safety set, rate of any-grade CRS was 84.6% (gr 3, 8.5%; no gr 4/5) and neurological events (NE) was 45.3% (gr 3, 17.9%; gr 4, 0.9%; no

Table

Efficacy	PEAS at DL2 (n = 49)	Full efficacy set at DL2 (n = 87)
CR/CRi rate[a]	9 (18.4) [8.8–32.0]; ***P* = 0.0006**	16 (18.4) [10.9–28.1]
ORR[a]	21 (42.9) [28.8–57.8]; ***P* = 0.3931**	41 (47.1) [36.3–58.1]
uMRD in blood[a]	31 (63.3) [48.3–76.6]	56 (64.4) [53.4–74.4]
uMRD in marrow[a]	29 (59.2) [44.2–73.0]	51 (58.6) [47.6–69.1]
DOR[b]	35.3 (11.01–NR)	35.3 (19.78–NR)
Duration of CR/CRi[b]	NR (NR–NR)	NR (12.22–NR)
PFS[b]	11.9 (5.72–26.18)	18.0 (9.43–30.13)

[a]n (%) [95% CI]; [b]Median (95% CI), mo.

gr 5); 69.2% received tocilizumab and/or corticosteroids for CRS/NEs. Rate of gr ≥3 infections, hypogammaglobulinemia, and prolonged cytopenia was 17.1%, 15.4%, and 53.8%, respectively. One death related to liso-cel was due to hemophagocytic lymphohistiocytosis. Liso-cel exhibited rapid in vivo expansion and was detected by qPCR in blood up to 36 mo after infusion.

Conclusions: Liso-cel demonstrated durable CR/CRi, high uMRD rates, and a manageable safety profile in pts with heavily pretreated, high-risk R/R CLL/SLL and high unmet need.

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Keyword: cellular therapies

Conflicts of interests pertinent to the abstract

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027 | EFFICACY AND SAFETY OF MOLTO, A MULTICENTER, OPEN LABEL, PHASE II CLINICAL TRIAL EVALUATING VENETOCLAX, ATEZOLIZUMAB AND OBINUTUZUMAB COMBINATION IN RICHTER SYNDROME

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Introduction: Chemoimmunotherapy is the standard first line treatment of diffuse large B-cell lymphoma (DLBCL) variant of Richter syndrome (RS). However, response rate and duration are unsatisfactory. The biology of RS (high rate of DNA damage response pathway defects, high tumor mutation burden coupled with the expression of the PD1/PDL1 axis) prompts investigation of non-chemo combinations leveraging agents that circumvent TP53 abnormalities and trigger anti-tumor immune response. MOLTO is a multicenter international phase 2 study (NCT04082897) evaluating activity and safety of atezolizumab (humanized monoclonal antibody blocking PD-L1), venetoclax (BCL2 inhibitor) and obinutuzumab (anti-CD20 MoAb) combination in untreated DLBCL-RS.

Methods: Treatment consisted of 35 q21 cycles with obinutuzumab (1000 mg C1–8), atezolizumab (1200 mg C1–18) and venetoclax (400 mg/d C1–35). Primary endpoint was ORR ≥67% at C6. RS diagnosis was centrally revised. RS mutation profile was tested on pre-treatment cell free DNA. Minimal residual disease (MRD) was tested by 8 colors flow cytometry and NGS on peripheral blood mononuclear cells and plasma.

Results: Overall 28 planned pts were enrolled from October 2019 to October 2022 (Table 1). Three were not evaluable for primary endpoint due to G5 infection ($n = 1$) or early withdrawn ($n = 2$). As per intention-to-treatment ORR was 67.9% (19/28) thus meeting primary endpoint. CR rate was 28.6% (8/28). No clinical characteristics influenced ORR at C6. After a median follow-up of 11.6 months, 11/19 pts (57.9%) are in continuous remission (8 on active therapy, 2 received allogenic transplant, 1 discontinued due to MDS), among them 6 for ≥24 months. Of the remaining 8 pts, 7 progressed after a median of 14 cycles, 1 died from sepsis at C9 in remission. Median duration of response was 11.7 months, median PFS was 16.2 months and median OS 31.6 months. Out of the 13 pts who progressed, 4 received a salvage therapy and are alive at a median follow-up of 24.3 months. Bulky disease and ECOG PS >1 affected PFS. Rate of unmeasurable MRD and impact of mutations and chronic lymphocytic leukemia-RS clonal relation on outcomes will be presented at the meeting. A total of 43 G3–4 adverse events (AE) occurred in 17 pts (60.7%), mostly hematological (51.2%). Any grade immune-related AEs was reported in 6 pts (G3–4 in 2), none led to discontinuation. No tumor lysis was observed. Infections ≥G3 occurred in 6 pts, including 2 G5. One pt developed MDS.

Conclusions: Atezolizumab, obinutuzumab and venetoclax combination is active in pts with untreated DLBCL-RS. This regimen led to durable remissions, longer than 2 years in one third of responders.

Table 1. Patients' characteristics

	N (%)
Median age (range)	70 y (32-81)
Age ≥65 y	22 (78.6)
ECOG 1-2	16 (57.1)
Previously treated for CLL	20 (71.4)
median N of prior CLL treatments (range)	1 (0-3)
Prior BTKi/CIT	11 (39.3)/9 (32.1)
Bulky disease	16 (57.1)
del17p/*TP53mut*	11 (42.9)
Ann Arbor stage III-IV	22 (78.6)

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Conflicts of interests pertinent to the abstract

A. M. Frustaci
Other remuneration: Abbvie, AstraZeneca, Janssen, Beigene; advisory boards, travel grants, speaker invitations

028 | GLOFITAMAB MONOTHERAPY INDUCES DURABLE COMPLETE REMISSIONS AND HAS A MANAGEABLE SAFETY PROFILE IN PATIENTS WITH RICHTER'S TRANSFORMATION

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Introduction: Richter's transformation (RT) is characterized by transformation of chronic lymphocytic leukemia to an aggressive lymphoma, most commonly CD20+ large B-cell lymphoma (LBCL). Prognosis for patients (pts) with RT is poor and no standard of care

exists; there remains a major unmet medical need. Glofitamab is a T-cell engaging bispecific antibody (Ab) with a novel 2:1 (CD20:CD3) format. In a Phase I/II study (NCT03075696), fixed-duration glofitamab monotherapy demonstrated durable responses and a manageable safety profile in pts with relapsed/refractory LBCL (Dickinson et al. 2022). We report the efficacy and safety of glofitamab monotherapy in pts with RT after a median follow-up of 40.6 months (range: 0.3–53.9).

Methods: All pts had RT and had received ≥1 prior regimen including ≥1 anti-(a) CD20 Ab. Pts received obinutuzumab pretreatment (1000 or 2000mg) 7 days before the first glofitamab dose and intravenous glofitamab at a fixed dose (0.6, 16, or 25mg) or with step-up dosing (SUD) in Cycle 1 (target dose 16 or 30mg) every 3 weeks for up to 12 cycles. Responses were assessed using Lugano 2014 criteria. Cytokine release syndrome (CRS) events were graded by ASTCT criteria.

Results: As of 10 October 2022, 11 pts had received glofitamab at a fixed dose (0.6–25 mg, $n = 5$) or with SUD (2.5/10/16 mg, $n = 3$; 2.5/10/30 mg, $n = 3$). Median age was 71 years (range: 48–76); six pts were aged >70 years. Overall, 91.0% of pts had Ann Arbor stage III–IV disease and 45.5% had an IPI score ≥3. Median number of prior therapies was 3 (range: 1–4) and 54.6% of pts had ≥3 prior therapies. Most pts were refractory to a prior aCD20 Ab-containing regimen (90.9%) and all to their most recent regimen (100%); 54.5% of pts were refractory to their initial therapy. Investigator-assessed overall response rate and complete response (CR) rate were 63.6% and 45.5%, respectively. Median time to CR was 3 months (95% CI: 2.5–not estimable [NE]). Complete responses were durable and most (4/5; 80%) had been ongoing for ≥24.9 months at data cut (**Figure**). CRS occurred in 72.7% of pts, was primarily associated with the initial doses, and was mostly Grade (Gr) 1 (27.3%) or Gr 2 (27.3%); Gr 3 (9.1%, $n = 1$) or Gr 4 (9.1%, $n = 1$) events were uncommon. Glofitamab-related neurologic adverse events (AEs) potentially consistent with immune effector cell-associated neurotoxicity syndrome occurred in 5 pts (Gr 3, $n = 1$ [syncope]; Gr 1, $n = 4$). No glofitamab-related Gr 5 (fatal) AEs or glofitamab-related AEs leading to discontinuation were reported.

Conclusions: Fixed-duration glofitamab monotherapy induces durable complete remissions and has a manageable safety profile in pts with RT. Glofitamab represents a potential therapy for pts with RT who have a high unmet need. Longer-term follow-up data will be presented.

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Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy, ongoing trials

Conflicts of interests pertinent to the abstract

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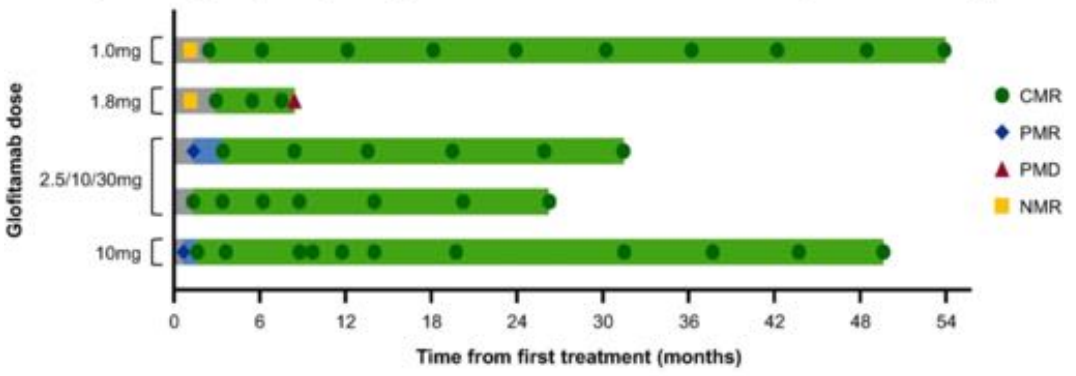
Other remuneration: Travel, accommodation, expenses - F. Hoffmann-La Roche

Figure: Durability of complete response in patients with Richter's transformation who received glofitamab monotherapy.



CMR, complete metabolic response; NMR, no metabolic response; PMD, progressive metabolic disease; PMR, partial metabolic response.

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SESSION 5 - PEDIATRIC LYMPHOMAS

029 | PRIMARY MEDIASTINAL B-CELL LYMPHOMA IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

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Although previously characterized as a subtype of diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL) is a now recognized as a distinct subtype of NHL with unique clinical and biologic features, many of which overlap with classic Hodgkin lymphoma. PMBCL has a peak incidence in the adolescent and young adult (AYA) population and, unlike other subtypes of NHL, a higher incidence among females. Recent studies into the molecular biology of PMBCL have revealed frequent amplifications in 9p24.1 which includes the locus for PD-L1 and genomic alterations in *CIITA*, *CD58*, *B2M*, which likely further contribute to tumor immune evasion.

Treatment for PMBCL varies across centers with no single standard of care. When treated on historic pediatric protocols designed for mature B-NHL, children and AYAs with PMBCL have inferior outcomes compared to patients with DLBCL treated on the same protocol. Recent clinical trials have sought to improve outcomes in PMBCL with the addition of rituximab with and modifications to pediatric regimens and/or the adoption of the dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) chemotherapy regimen. Despite this, outcomes in prospective multicenter trials remain suboptimal.

There is strong rationale for immune checkpoint blockade in PMBCL including the key molecular features outlined above as well as data from phase II trials in adults showing efficacy of pembrolizumab and nivolumab in the relapsed setting. As such, we are now conducting a phase III trial evaluating the role of nivolumab in addition to chemotherapy for children and adults with previously untreated PMCBL. In this session we will review the current state of the science in PMBCL and provide an update on our ongoing phase III trial.

Keywords: extranodal non-Hodgkin lymphoma, non-Hodgkin (pediatric, adolescent, and young adult)

No conflicts of interests pertinent to the abstract.

030 | MINIMAL DISSEMINATED AND MINIMAL RESIDUAL DISEASE IN CHILDHOOD AND ADOLESCENT NON-HODGKIN LYMPHOMA

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Introduction: Minimal disease determination might serve for risk stratification, response evaluation and follow-up disease monitoring in childhood Non-Hodgkin lymphomas. Besides helping to judge minimal residual disease (MRD) during therapy, detection of minimal disseminated disease (MDD) at diagnosis may be of prognostic value itself. However, different subtypes, high cure rates, low patient numbers, limited initial tumour material and early progression pose challenges.
Methods: Pubmed literature search on MDD and MRD in pediatric lymphomas.
Results: Current clinical applications of minimal disease determination differ between the subtypes. For lymphoblastic lymphomas, both flow-cytometry detecting aberrant immunophenotypes and PCR-based assays for TCR- or Ig-rearrangements have been used for minimal disease measurement. A prognostic value of MDD could not be clearly established yet. MRD has not been analysed in larger patient cohorts so far. In Burkitt-lymphoma and -leukemia, *MYC-Ig*-fusion sequences or *Ig*-rearrangements enable minimal disease detection. While conflicting data on the role of MDD as risk factor for Burkitt lymphoma have been published, the prognostic value of early MRD in Burkitt leukaemia treated by risk-adapted chemotherapy has been described by two study groups. However, its role in the rituximab-era needs to be confirmed. In ALK-positive anaplastic large cell lymphoma (ALCL), MDD and MRD determined by qualitative or quantitative PCR for *ALK*-fusion transcripts are validated independent prognostic parameters. They are standard of care parameters assessed in routine clinically practice and used for patient stratification in clinical studies. Early MRD might even serve as endpoint for clinical trials and for guiding individual therapy.

Conclusions and future outlook: Validation of MDD and MRD as prognostic parameters is required for all subtypes but ALCL. Next-generation sequencing based methods and the use of circulating cell-free tumour DNA as medium may provide new options and applications for minimal disease evaluation in childhood lymphomas.

Keywords: diagnostic and prognostic biomarkers, minimal residual disease, non-Hodgkin (pediatric, adolescent, and young adult)

No conflicts of interests pertinent to the abstract.

031 | PHASE 2 KEYNOTE-667: PEMBROLIZUMAB IN CHILDREN AND YOUNG ADULTS WITH CLASSICAL HODGKIN LYMPHOMA (CHL) WITH SLOW EARLY RESPONSE TO FRONT-LINE CHEMOTHERAPY

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Introduction: Patients (pts) with cHL with slow early response (SER) to initial chemotherapy (chemo) have a high risk of relapse. Current treatments such as chemo dose intensification and radiotherapy (RT) can increase the risk of secondary malignancies and cause long-term toxicity. KEYNOTE-667 (NCT03407144) is an open-label, phase 2 study being conducted to evaluate pembrolizumab (pembro) plus chemo in pts with cHL and SER to front-line chemo. We present results of an interim analysis of pts with high-risk cHL and SER (group 2).

Methods: Pts eligible for group 2 were aged 3–17 (children) or 18–25 y (young adults) with newly diagnosed high-risk (stage IIEB, IIIEA, IIIEB, IIIB, IVA, or IVB) cHL. Pts in group 2 received induction therapy with 2 cycles of vincristine, etoposide, prednisone/prednisolone, and doxorubicin (OEPA). Response was then assessed by PET/MRI/CT. Pts with rapid early response to OEPA received nonstudy therapy and pts with SER to OEPA (Deauville score, 4/5) received consolidation with 4 cycles of cyclophosphamide, vincristine, prednisone/prednisolone, dacarbazine (COPDAC-28) plus pembro 2 mg/kg up to 200 mg IV Q3W (3–17 y) or 200 mg IV Q3W (18–25 y). After consolidation, pts with PET positivity (Deauville score, 4/5 at late response assessment [LRA]) received involved-site RT (28.8 Gy) to late PET-positive residua. RT was omitted in pts with PET negativity. All pts with SER continued to receive pembro Q3W for 17 doses. The primary end point was ORR in pts with SER by blinded independent central review (BICR) per Cheson 2007 International Working Group criteria. Secondary end points included PET negativity at LRA and safety.

Results: 49 pts with high-risk cHL with SER to OEPA were included in group 2. The median age was 15 y (range, 6–22), 24 pts (49%) had bulky disease, and 31 (63%) had Ann Arbor stage IV disease. At data cutoff (2 September 2022), the median follow-up was 15.3 mo (range, 3.2–30.5); 22 pts (45%) had completed treatment and 24 (49%) were ongoing on consolidation/maintenance. Median time on pembrolizumab was 10.4 mo (range, 0.5–11.8). 42 pts (86%) had an LRA, of whom 27 (64%) were PET negative by BICR (30 pts [71%] were PET negative by investigator review). Adverse events (AEs) occurred in 42 pts (86%), with grade 3/4 AEs in 13 pts (27%). Serious AEs were reported in 7 pts (14%). No pts died because of an AE. Treatment-related AEs occurred in 30 pts (61%), with grade 3/4 treatment-related AEs in 6 pts (12%). 4 pts (8%) had immune-mediated AEs: 2 grade 1 hypothyroidism and 2 grade 2 hypothyroidism.

Conclusions: The results showed that pembro plus COPDAC-28 consolidation had manageable safety and promising efficacy in children and young adults with high-risk cHL and SER to front-line chemo. 64% of pts with a LRA had a PET-negative response and were spared RT. These findings suggest that adding pembro to COPDAC-28 consolidation may augment responses in this high-risk cHL population.

Encore Abstract - previously submitted to ASCO 2023 and EHA 2023

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Keywords: Hodgkin lymphoma, immunotherapy

Conflicts of interests pertinent to the abstract

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032 | ANALYSIS TREATMENT OUTCOME OF 46 REFRACTORY/RELAPSED PEDIATRIC MATURE B CELL LYMPHOMA PATIENTS-MULTI-CENTER EXPERIENCE FROM CHINA

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Introduction: Aim to find the efficacy treatment strategy for refractory/relapsed(r/r) patients with pediatric mature B-cell lymphoma (MBL) by summarizing the treatment outcome of 46 patients from Chinese Children's Lymphoma Multi-center Cooperation Group (CNCL).

Methods: The MBL children treated from 1 May 2017 to 31 December 2022 were enrolled. The modified LMB89/96 protocol was adopted for the initial treatment. Clinical characteristics and risk factors were analyzed with r/r patients. Two treatment groups after r/r: salvage chemotherapy (ICE protocol), chimeric antigen receptor T-cell (CAR-T) group. OS and EFS were both analyzed.

Results: Total of 861 newly diagnosed children with MBL $\leq$ 18 years old were enrolled in this study, of which 46(5.3%) cases were relapsed or refractory(R/R).

Baseline characteristics of 46 patients: the median age was9 (1~16) years old, 38/46 males, 8/46 females. Stage I-II was 0/46, Stage III–IV was 19/46 and 27/46 according to St. Jude's stage, of which 11/46 (23%) had a leukemia stage, and 14 (30.4%) had CNS invasion. Risk grouping: group B: 3 cases (%), group C1: 28/46 cases group C2: 14/46 cases. Pathological types: 34/46 cases of Burkitt's lymphoma, 5/46 cases of diffuse large B-cell lymphoma, 5/46 cases of high grade B-cell lymphoma, and 2/46 cases of other types. There were 17/46 with bulky disease, 26/46 cases with LDH > 1000 U/L. Univariate analysis showed that LDH > 1000, Bulky disease, leukemia stage and CNS invasion before initial chemotherapy was significantly related to poor survival.

Treatment result: the median follow-up time was 12.49 months (95% CI: 12.86, 23.99), (0.3~59.6) months, 46 patients with r/r. Salvage treatment: 24 patients received second-line chemotherapy: 6 patients got a CR2, 6 patients quit to treatment due to SD/PD, 4 patients got a treatment related death, 8 patients died of PD/SD. The median survival time was 4.3 months (0.3~45.9), 2-year OS was 33.33 $\pm$ 15.90%. 22 patients received CAR-T therapy: 15 cases got a CR2, 4 cases got a PR (combined with targeted treatment sequentially), 2 cases died of PD and 1 case died of grade IV CRS with infection. ORR was 85.9%, the median survival time was 28.5 months (0.9~59.7), and the 2-year event-free survival rate (EFS) after CR2 was (55.04 $\pm$ 7.56)% (Figure 2). The 2-year OS of the 2 treatment group were (35.56 $\pm$ 9.66)% versus (79.59 $\pm$ 9.22)% respectively (Figure 1). The survival rate of CAR-T group was significantly better (HR = 0.228 95% CI: 0.076, 0.684, $p = 0.0084$).

Discussion and conclusion: The outcomes with r/r patients treated with salvage chemotherapy is poor, CART therapy can significantly improve the outcomes of r/r patients, and is expected to be an effective treatment strategy for children with r/r MBL.

Figure 1. Treatment outcomes in r/r patients (CAR-Tvs. Non-CAR-T)

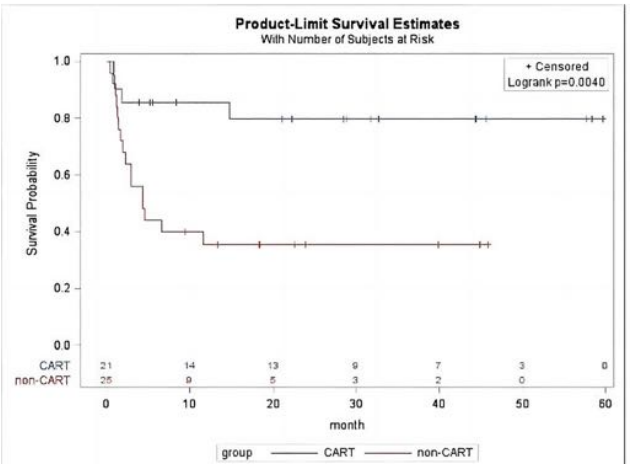
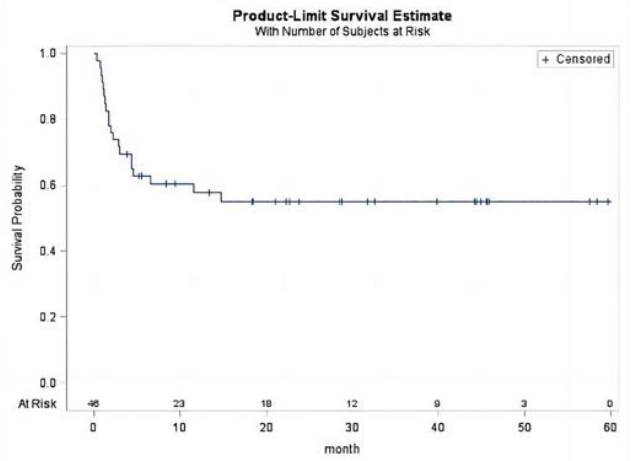


Figure 2. 2 years EFS of r/r patients in CAR-T group



Keywords: chemotherapy, immunotherapy, non-Hodgkin (pediatric, adolescent, and young adult)

No conflicts of interests pertinent to the abstract.

033 | ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH REDUCED-TOXICITY CONDITIONING FOR PEDIATRIC RELAPSED OR REFRACTORY ALK-POSITIVE ANAPLASTIC LARGE CELL LYMPHOMA

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Introduction: For children and adolescents with refractory or relapsed (r/r) anaplastic large cell lymphoma (ALCL), consolidation by allogeneic hematopoietic stem cell transplantation (SCT) after re-induction chemotherapy offers long-time cure. In CNS-negative patients, total body irradiation (TBI)-based conditioning regimens were increasingly replaced by Treosulfan-based regimens without irradiation over the last decade. To describe the efficacy of the different conditioning regimens, we performed a population-based analysis of pediatric patients with r/r ALCL consolidated by allogeneic SCT in Germany between 2013 and 2021.

Methods: Patients with r/r ALK-positive ALCL enrolled in the NHL-BFM registry 2012 consolidated by an allogeneic SCT were analyzed. Data was extracted from the NHL-BFM registry 2012 and the German pediatric registry for SCT (PRST). Three-year progression-free survival (PFS) and overall survival (OS) were calculated from SCT. Four patients with CNS involvement at relapse were excluded from this analysis.

Results: Twenty-five CNS-negative patients with a median age of 8 years (range, 0.9–17.6) at SCT were included. All patients had received ALCL99 front-line chemotherapy. Indications for SCT were progression during front-line treatment in 5 (20%), persisting minimal residual disease (MRD) positivity by in 4 (16%), relapse within one year of diagnosis in 15 (60%), and late (>1 year) relapses in one (4%) patient. Two patients received the SCT for a second relapse or progression. Re-induction therapy before SCT was heterogeneous, including ALK-inhibitors, brentuximab vedotin, vinblastine, and chemotherapy. From 21 patients with available data, MRD was positive in 5, and negative in 16 patients before SCT. The conditioning regimen was Treosulfan/Fludarabin/Thiotepa in 21 and TBI-based in 4 patients. Seventeen patients were transplanted from a matched unrelated donor (MUD), 7 from a matched sibling donor (MSD), and one from a haploidentical related donor. Median follow-up after SCT was 2.9 years (range, 1.0–9.2).

PFS was 80% ± 8% and OS was 96% ± 4%. One patient died of complications of chronic graft-versus host disease. There was no difference in PFS between patients receiving TBI- or Treosulfan-based conditioning. We observed a non-significantly higher PFS after SCT in 20 patients older than 4 years (85% ± 8%) compared to five younger patients (60% ± 22%, $p = .23$), and a higher PFS in patients transplanted from a MUD (94% ± 6%, $n = 17$) compared to an MSD (57% ± 18%, $n = 7$; $p = .023$).

Conclusion: The outcomes after allogeneic SCT were comparable with previous reports with mainly TBI-based conditioning, indicating that TBI can be replaced by reduced-toxicity conditioning in CNS-negative relapse patients. The observations of possibly inferior outcomes in younger patients after SCT and of improved outcomes for children transplanted from unrelated donors warrant further investigation.

Keywords: non-Hodgkin (pediatric, adolescent, and young adult), stem cell transplant

No conflicts of interests pertinent to the abstract.

034 | PATTERNS OF PRESENTATION AND OUTCOMES IN STAGE IV HODGKIN LYMPHOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG) AHOD1331 TRIAL

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Introduction: Outcomes for high-risk pediatric and adolescent and young adult (AYA) classic Hodgkin lymphoma (cHL) improved substantially with the addition of brentuximab vedotin (Bv) to AVEPC (adriamycin, vincristine, etoposide, prednisone, cyclophosphamide) chemotherapy. As patients with stage IV disease have poor outcomes, we evaluated the prognostic implications of sites contributing to stage IV disease.

Methods: On AHOD1331 (NCT02166463), patients age 2–21 years with high-risk cHL (stage IIB with bulk, IIIB, IVA, and IVB) were randomized to 5 cycles of AB (bleomycin)VE-PC versus Bv-AVE-PC, and consolidative radiotherapy based on interim response and large mediastinal adenopathy at diagnosis. Patients with stage IV disease, as determined by protocol defined and centrally reviewed PET-CT, were identified. Stage IV was defined as disseminated involvement of ≥1 extralymphatic organ or tissues (with or without lymph node involvement) or isolated extralymphatic organ involvement with distant nodal involvement. E-lesions were distinguished from sites of stage IV involvement in the lung, but any liver and/or bone marrow involvement, regardless of contiguity, was considered stage IV. Central review was performed to confirm institutional classification of stage, upstaging 33 patients to stage IV and downstaging 17 among the 353 enrolled and stratified as Stage IV by the institution. Baseline characteristics and progression-free survival (PFS) were compared by pattern of metastatic involvement (lung only, bone only, bone marrow only, or multi-site, defined as >1 site of involvement).

Results: 369 patients (median age 15 years, range 3–22) with stage IV disease treated on AHOD1331 were included, of which 183 (50%) were treated with ABVE-PC and 186 (50%) with Bv-AVE-PC. Patterns of disease included: isolated involvement of lung (185; 50%); bone marrow (5; 1%); or bone (8; 2%), and 171 (46%) had multi-site involvement. B symptoms were present in 80% and 88% with bone marrow or bone involvement respectively, 50% of those with lung, and 57% with multi-site disease. The 3 year-PFS (95% CI) by site of involvement was: 88.0% (82.3, 91.9) for lung, 100% for isolated bone marrow or bone, and 82.5% (75.8, 87.5) for multi-site ($p = 0.21$). Bv-AVE-PC significantly improved PFS among stage IV patients compared to ABVE-PC (3-year PFS 90.2% vs. 81.5%, $p = 0.01$). Among those with isolated lung involvement, there was a non-significant increased PFS with Bv (3-year PFS 91.2% vs. 84.7%, $p = 0.16$), while those with multi-site metastatic disease experienced significantly improved PFS with Bv (3 year-PFS 88.1% vs. 77.1%, $p = 0.05$).

Conclusions: Among pediatric and AYA patients with stage IV cHL, PFS was notably improved with Bv among patients with multi-site metastatic involvement. These results will help guide future efforts to understand strategies to improve outcomes among children with stage IV disease.

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Keywords: Hodgkin lymphoma, molecular targeted therapies, Lymphoid Cancers - Other

No conflicts of interests pertinent to the abstract.

035 | LANDSCAPE OF DRIVER MUTATIONS AND THEIR CLINICAL IMPACTS IN CHINESE PEDIATRIC PATIENTS WITH MATURE B-CELL NON-HODGKIN'S LYMPHOMA AND T-CELL LYMPHOBLASTIC LYMPHOMA

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Introduction: Mature B-cell non-Hodgkin's lymphoma (MB-NHL) and T-cell lymphoblastic lymphoma (T-LBL) account for ~50% and ~20%,

respectively, among the different pediatric NHL entities. Our understanding of the genetic lesions and profiling of these patients may help to improve the clinical management of patients with these lymphomas. The aim of this study is to analyze the mutational status and the associations between genetic features and treatment outcomes in the Chinese pediatric lymphoma cohort.

Methods: A total of 207 patients treated at multiple clinical centers of the Chinese Children's Lymphoma Collaborative Group (CNCL) from 2017 to 2023 were included in this retrospective study. Targeted next-generation sequencing (*t*-NGS) with a panel of lymphoma-related genes was performed on tumor samples collected at the time of initial diagnosis and at tumor of refractory or relapse (r/r), and the correlations of somatic mutations with survival rates as well as with relapse and other clinical factors were analyzed.

Results: A total of 136 driver genes with somatic mutations were detected in the entire cohort. In 133 pediatric MB-NHL patients, the most frequently mutated genes from 77 initially diagnostic samples were *ID3* (52%), *TP53* (47%), *CCND3* (30%), *ARID1A* (29%), and *DDX3X* (27%) (Figure 1a). In 56 *r/r* samples, the most commonly mutated genes were *TP53* (84%), followed by *ID3* (59%), *ARID1A* (41%), *CCND3* (32%), and *DDX3X* (25%) (Figure 1b). *TP53* mutation was significantly more frequent in *r/r* samples than that in initially diagnostic samples ($p < 0.001$) and patients with *TP53* mutations had poor survival (log-rank $p = 0.0013$, Figure 1c). Among patients treated with chimeric antigen receptor T-cell (CAR-T) therapy, those with *ARID1A* mutations exhibited poorer response to CAR-T treatment and shorter overall survival compared with the patients without such mutations (mOS = 180 days, log-rank $p = 0.00081$, Figure 1d).

In 74 pediatric T-LBL patients,the most commonly mutated genes were *NOTCH1* (50%), followed by *FBXW7* (26%), *JAK1* (16%), *NRAS* (16%), and *JAK3* (11%) (Figure 1e). Genes in the JAK signaling pathway were more frequently mutated in Chinese patients than the corresponding western patients, such as *JAK1* (16% vs. 2%) and *JAK3* (11% vs. 5%). Further analysis showed that the incidence of *NOTCH1* (68% vs. 27%) and *FBXW7* (37% vs. 12%) mutations in patient group with initial remission ($n = 41$) was significantly higher than that in patient group with *r/r* T-LBL ($n = 33$) ($p = 0.005$, $p = 0.036$, respectively, Figure 1f), indicating that *NOTCH1* and *FBXW7*mutations were associated with good prognosis.

Conclusion: *TP53* mutations were more common in Chinese pediatric patients with *r/r* MB-NHL than those without *r/r* and were associated with poor outcome. *ARID1A* alteration is a potential prognostic marker that may predict poor treatment outcome of CAR-T therapy in *r/r* MB-NHL. The presence of *NOTHC1* or *FBXW7* alterations signals favorable outcomes. These results may help clinicians to tailor treatments for their patients with these high-risk genetic alterations.

Keywords: diagnostic and prognostic biomarkers, immunotherapy, non-Hodgkin (pediatric, adolescent, and young adult)

No conflicts of interests pertinent to the abstract.

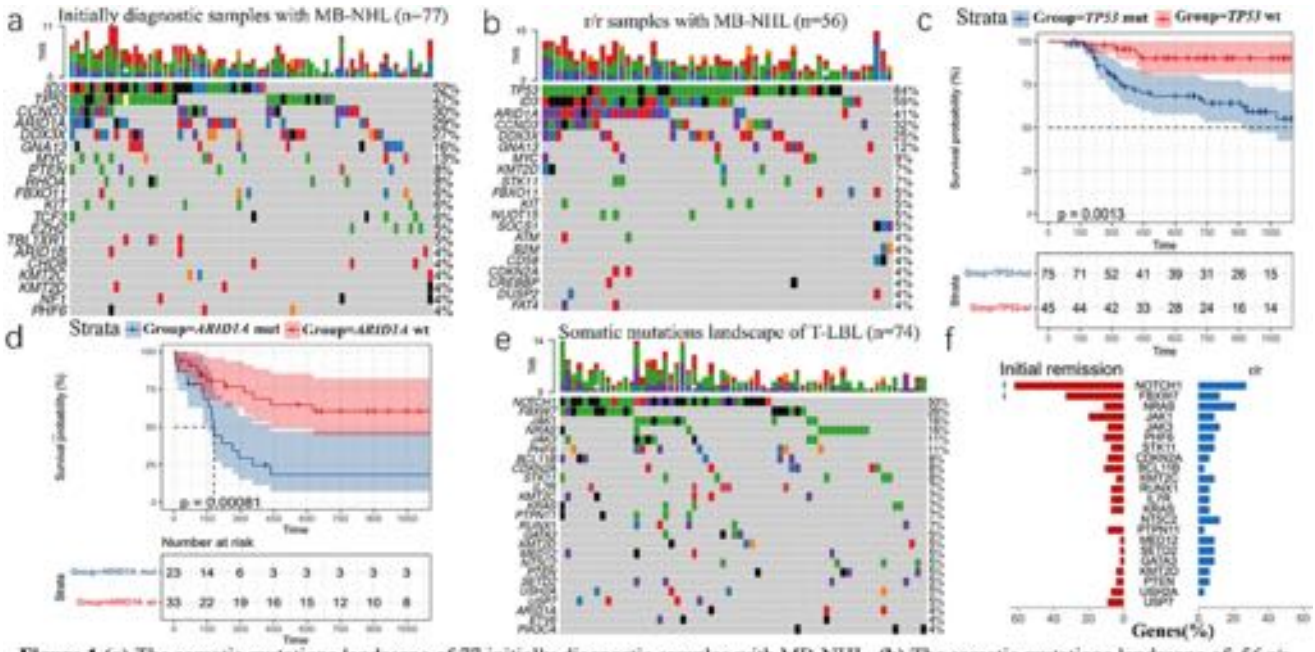

Figure 1.(a) The somatic mutations landscape of 77 initially diagnostic samples with MB-NHL. **(b)** The somatic mutations landscape of 56 r/r samples with MB-NHL. **(c)** Overall survival (OS) by *TP53* status in MB-NHL pediatric patients.**(d)** The somatic mutations landscape of T-LBL (n=74). **(e)** OS by *ARID1A* status in patients treated with CAR-T cell therapies. **(f)** Comparison of mutations profiling between initial remission patients with T-LBL (left, red) and r/r T-LBL (right, blue).

036 | ALK-POSITIVE ANAPLASTIC LARGE CELL LYMPHOMA WITH VARIANT ALK-FUSION PARTNER: A POPULATION-BASED ANALYSES OF THE NHL-BFM STUDY GROUP

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Introduction: ALK-positive anaplastic large cell lymphomas (ALCL) are characterized by rearrangements involving the *ALK* gene on chromosome 2. The translocation *t*(2;5) (p23;q35) resulting in the *NPM1::ALK* gene fusion is detected in the majority of ALCL. In 10%–20% of ALCL, *ALK* is fused to various other partner genes. Compared to NPM1::ALK, variant ALK-fusion proteins are not expressed in the nucleus. The frequency, distribution, and possible prognostic significance of the different variant *ALK* partner genes have not been analyzed in population-based studies so far. We investigated all patients with ALK-positive ALCL with exclusive cytoplasmic ALK-expression diagnosed in a uniformly treated cohort of ALCL patients in the NHL-BFM study group.

Patients and Methods: Between 2000 and 2017, 312 children and adolescents were diagnosed with an ALK-positive ALCL in Austria, Germany, Switzerland and the Czech Republic, and included in the ALCL 99 trial or the NHL-BFM registry 2012. Reference pathology demonstrated exclusive cytoplasmic ALK-staining in 49 tumors. Formalin-fixed-paraffin-embedded or frozen tumors of 43/49 patients were available for molecular analyses. Tumor-DNA was analyzed by an ALK-specific genomic capture high throughput sequencing assay. *ALK*-partner gene-specific RT-PCR assays were used to identify the respective partner genes when tumor cDNA was available.

Results: 41 of 43 available tumors with exclusive cytoplasmic ALK-staining could be analyzed. 13 were *NPM1::ALK* positive and 28 tumors had a variant ALK partner. *TPM3::ALK* ($n = 9$, 32%) and *ATIC::ALK* ($n = 8$, 29%) were the most common variant partner genes. *XPOI* could be identified as a novel ALK fusion partner. The patients´ characteristics of ALCL expressing Variant::ALK were comparable to those with NPM1::ALK fusions. The five-year event-free survival (EFS) and overall survival were comparable between the 284 NPM1::ALK and the group of 28 different Variant::ALK-expressing patients. However, none of the 9 patients with TPM3::ALK positive ALCL relapsed, compared to 5 relapses among 8 patients with ATIC::ALK positive ALCL.

Conclusions: In our population-based cohort of ALK-positive ALCL-patients, less than 10% carried variant ALK-fusion partners, 60% of which were TPM3 or ATIC. In patients with exclusive cytoplasmic ALK staining patterns, NPM1::ALK positivity should be excluded by molecular analysis. The tendency of a different relapse risk between ATIC::ALK and TPM3::ALK -positive ALCL-patients suggests that the fusion partner might confer tumor aggressiveness or drug resistance.

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Keyword: diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

037 | LUNG STAGING IN PEDIATRIC HODGKIN LYMPHOMA: STAGING EVALUATION & RESPONSE CRITERIA HARMONIZATION FOR CHILDHOOD, ADOLESCENT & YOUNG ADULT HL (SEARCH FOR CAYAHL) CONSENSUS

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Figure 1: Expert Consensus Statements for the Staging of Lung Lesions in Pediatric Hodgkin Lymphoma

	STATEMENT
1	Lung biopsy is invasive, and therefore is not routinely recommended for lung lesions.
2	In rare circumstances in which there remains ambiguity in determining whether lesions may be infectious nodules versus disease, if accessible, biopsy may be warranted if the outcome will result in a change to therapy.
3	Whenever the possibility of lung involvement is present, careful evaluation for respiratory symptoms, or known infectious history (eg. Histoplasmosis) is important to take into consideration.
4	When the presence of lung involvement is unclear, early response assessment after 2 cycles of therapy should be taken into consideration.
5	The current definition of an E-lesion is outdated given advances in radiation technology and imaging quality. This definition should no longer be used and requires updating. Current definition: 'encompassing of the lesion within an irradiation field appropriate for nodal disease of the same anatomic extent treated to a tumoricidal dose'
6	The concept of contiguous disease is subjective and creates confusion. Therefore, this requires improvement to a more refined definition.
7	We recommend the use of 'contiguous' to indicate a lesion which is in contact with adjacent lymph nodes with no separation (E-lesion). Lesions not in immediate contact with the adjacent lymph nodes should be considered Stage IV disease.
8	For scenarios in which there remains uncertainty as to whether a lesion is contiguous or not, consultation with a center with expertise is suggested if this will result in any change to therapy.
9	Where available, FDG-PET-CT should be used to evaluate lung lesions.
10	All PET avid (Deauville 4 or 5) intraparenchymal lung lesions should be considered involved (Stage IV), regardless of size, provided they are not contiguous with hilar lymph nodes, and not otherwise explained (eg. By known respiratory illness).
11	Non-PET avid intraparenchymal lung lesions should not be considered lung involvement if size is greater than 1cm (provided that other areas of disease are PET-avid). Other potential etiologies should be investigated.
12	Non-PET avid intraparenchymal lung lesions should be considered lung involvement if 3 or more lesions are present measuring between >/5-10mm, and not otherwise explained (eg. By known respiratory illness)

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Introduction: Staging of lung lesions in pediatric Hodgkin lymphoma (HL) is a long standing, controversial issue. Consortium groups define lung involvement and its distinction from E-lesions differently. Application of these criteria to individual patients are technically challenging and require expertise. The SEARCH group, working to create harmonization across consortia for the staging of pediatric HL, has completed this task for lung lesions.

Methods: A survey of 7 case vignettes was distributed to 26 world experts in pediatric HL, replicating the previously published survey by Connors et al in 1984. Experts were asked to stage each case as lung involvement, or an E-lesion. Similar to Connors findings, our results demonstrated that experts were greatly divided on several cases, indicating ongoing differences in interpretation. Accordingly, the SEARCH group performed a harmonization initiative for the contemporary staging criteria for lung lesions.

Representatives from each major consortium group (Pediatric Hodgkin Consortium, EuroNet PHL, Children's Oncology Group) provided their current definitions for lung involvement, and rationale for staging decisions for the lung cases presented. Based on these discussions, a Delphi survey was drafted containing 12 statements pertaining to the staging criteria for lung lesions and distributed electronically to members of the SEARCH committee representing each consortium. Consensus was defined as a score of 3.75 or greater on a 5-point Likert scale (strongly disagree [1] to strongly agree [5]). Delphi rounds continued until consensus was achieved for all statements, or until a decision was made to remove a statement. Responses were collected anonymously and scores were pooled and reviewed after each round. Extreme scores and all comments were reviewed on committee calls before proceeding to the next round.

Results: 21 experts responded to the first Delphi round, including pediatric oncologists, nuclear medicine radiologists, and radiation oncologists. 8 of 12 statements met consensus in Round 1. Several statements were edited to improve clarity and 1 statement was added. A second Delphi round was completed with 20 responses. All statements met consensus with the exception of one which was ultimately removed for group consensus that further investigation was required. Final consensus statements are available in Figure 1.

Conclusions: Staging and response criteria for lung lesions in pediatric HL remain controversial. We present an initial survey highlighting ongoing discrepancies among current world experts. Additionally, the SEARCH for CAYAHL group has completed a harmonization project for the staging of lung lesions. We present our results as expert consensus statements to promote more consistent practices. An update to the Cotswold-modified Ann Arbor Criteria is needed to better represent modern staging of pediatric patients.

Keywords: Hodgkin lymphoma, non-Hodgkin (pediatric, adolescent, and young adult)

No conflicts of interests pertinent to the abstract.

038 | QUALITY OF LIFE IN PEDIATRIC HIGH-RISK HODGKIN LYMPHOMA TREATED WITH BRENTUXIMAB-BASED INTENSIVE CHEMOTHERAPY—COMPARISON TO HISTORICAL TREATMENT COHORT AND HEALTHY PEERS

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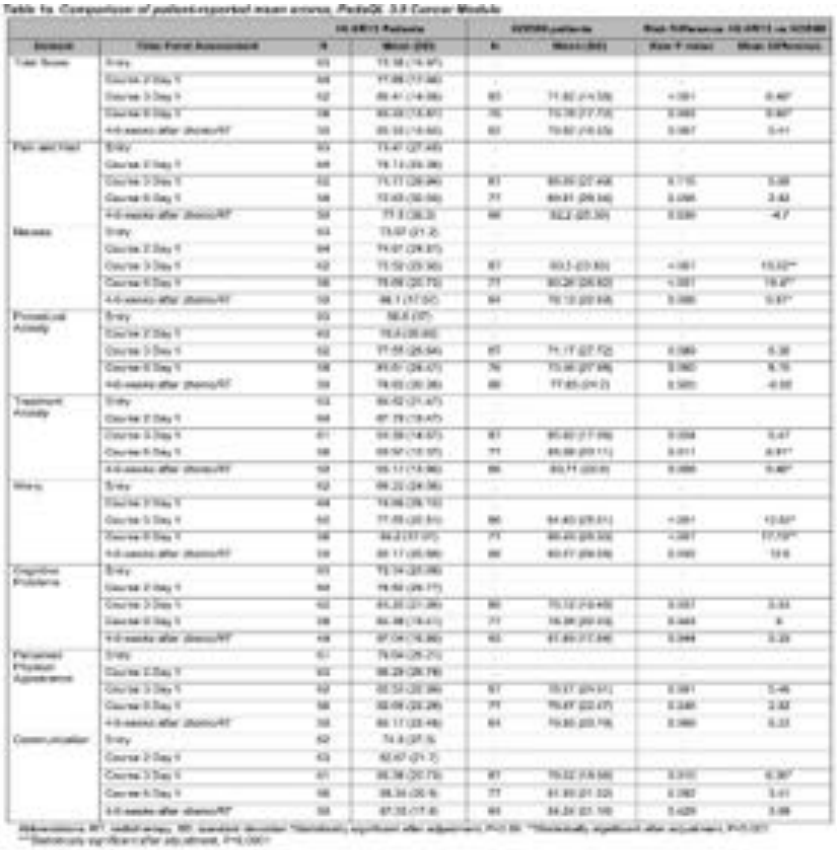
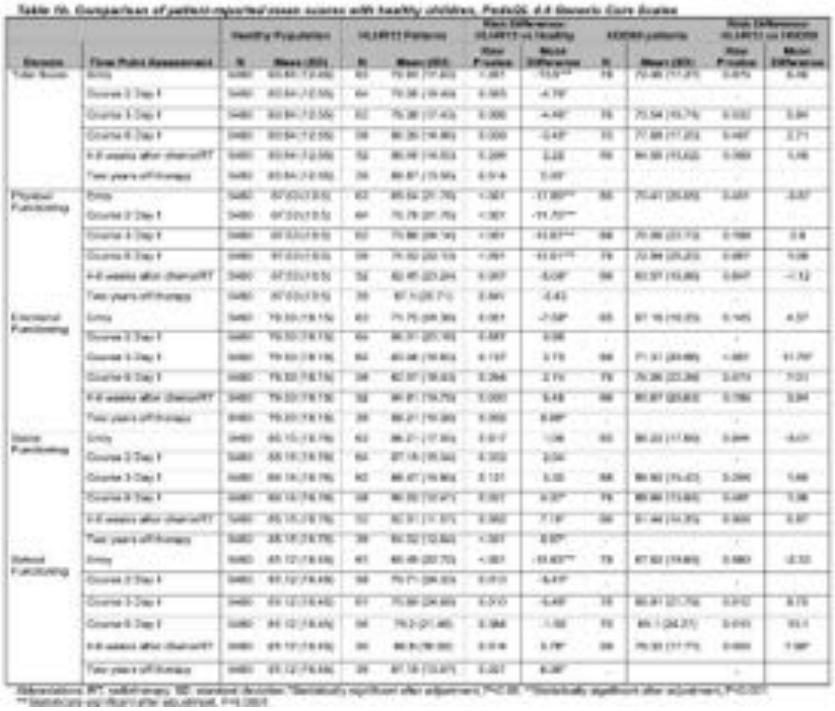
Introduction: Hodgkin lymphoma (HL) in children, adolescents, and young adults (CAYA) is highly curable. Patient experiences during cancer treatment vary substantially and may influence later quality of life (QOL). We sought to: (1) describe patient-reported QOL during treatment for high-risk classical HL in CAYA with HLHR13, a brentuximab-incorporating chemotherapy regimen with response-adapted radiotherapy (r-aRT); (2) compare QOL among patients treated on HLHR13, high-risk HL patients treated with Stanford V chemotherapy and r-aRT (HOD99), and healthy CAYA.

Methods: Eligible patients were ≤18 (HLHR13) or ≤21 years old (HOD99) upon diagnosis of Stage IIB, IIIB, or IV HL. For HLHR13 and HOD99, QOL was assessed with PedsQL 4.0 Generic Core Scales and PedsQL 3.0 Cancer Module. HLHR13 consisted of 2 "AEPA" cycles (brentuximab, etoposide, prednisone, and doxorubicin) and 4 "CAP-Dac" cycles (cyclophosphamide, brentuximab, prednisone, and dacarbazine) with r-aRT (25.5 vs. 0 Gy). HLHR13 chemotherapy lasted 20 weeks including 6 rest weeks. HOD99 consisted of 12 weeks of Stanford V (bleomycin, doxorubicin, mechlorethamine, prednisone, vinblastine, and vincristine) with r-aRT (25.5 vs. 15 Gy). Despite differing regimen durations, QOL assessments were compared at timepoints considered equivalent. HLHR13 incorporated 2-year off-therapy long-term follow up QOL assessments. Patient demographics and QOL scores were summarized by descriptive statistics. We used Wilcoxon rank-sum tests to compare PedsQL 3.0 scores in HLHR13 patients vs. HOD99 patients and pooled two sample t-tests to compare patient and healthy CAYA PedsQL 4.0 scores. Raw p-values were corrected for multiple comparisons.





Results: At study entry, HLHR13 patients' ($n = 63$) QOL was significantly worse than healthy CAYA and consistent with HOD99 patients' ($n = 78$) QOL as measured by PedsQL 4.0 Generic Core Scales. HLHR13 patients' QOL gradually improved. Compared to HOD99 patients, HLHR13 patients had better cancer-specific QOL scores (PedsQL 3.0 Cancer Module) during treatment, particularly for nausea, worry, cognitive problems and treatment anxiety. Two years off therapy, HLHR13 patients ($n = 39$) reported better QOL in social and emotional domains than did healthy CAYA.

Conclusions: Among similar groups of CAYA with HL, HLHR13 treatment was associated with higher patient-reported cancer-specific QOL than was HOD99 despite longer treatment duration

and more intensive administration schedule. PedsQL 3.0 Cancer Module distinguished cancer-specific experience differences between HLHR13 and HOD99. Mechlorethamine in HOD99 may have produced excess nausea. Two years after treatment, HLHR13-treated CAYA reported better social and emotional QOL than healthy peers. Observed excellent QOL could reflect positive psychosocial impacts of living beyond lymphoma or a biased group of CAYA continuing in survivorship care.

Keywords: chemotherapy, late effects in lymphoma survivors, Hodgkin lymphoma

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M. P. Link
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J. E. Flerlage
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039 | QUANTITATIVE WHOLE-BODY MRI FOR PREDICTING TREATMENT OUTCOME IN PEDIATRIC PATIENTS WITH AGGRESSIVE NON-HODGKIN LYMPHOMA UNDERGOING CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY

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Introduction: Chimeric antigen receptor (CAR) T cell therapy has shown great promise in treating pediatric patients with aggressive non-Hodgkin lymphoma (NHL), but its effectiveness can vary greatly among individuals. Accurate prediction of treatment response can aid in patient selection and treatment planning. Quantitative whole-body diffusion-weighted MRI (WB-DW MRI) has emerged as a potential tool for predicting treatment response in various types of cancer, but its predictive value for CAR-T cell therapy in pediatric patients with aggressive NHL has not been fully explored. This prospective multicenter study aimed to investigate the predictive value of quantitative whole-body diffusion-weighted MRI in this patient population.

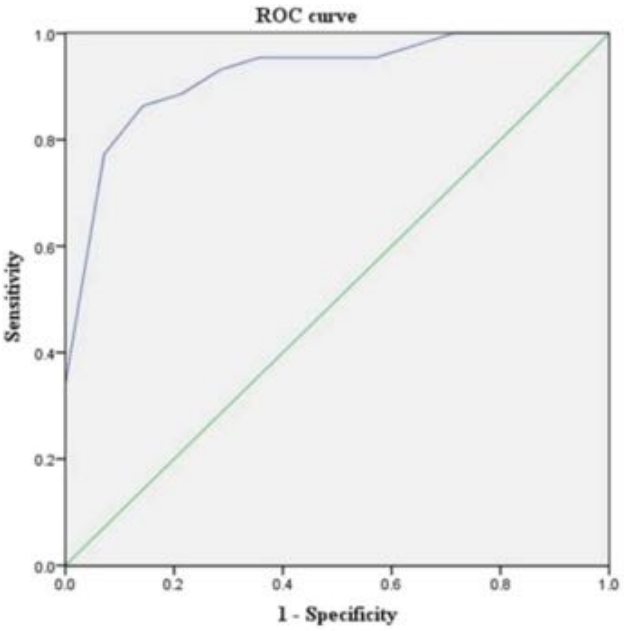
Methods: Thirty-six pediatric patients with aggressive NHL who underwent CAR T cell therapy were enrolled from three participating centers. All patients underwent WB-DW MRI before and after CAR T cell therapy. T2 values, apparent diffusion coefficient (ADC) values, and the ADC change between baseline and within 15 days after infusion were calculated. Patients were categorized into good outcome (complete remission) and poor outcome (progressive or recurrent disease) groups based on their treatment response. Receiver operating characteristic (ROC) curve analysis was used to evaluate the correlation between ADC values and treatment outcome.

Results: The mean age of patients was 11 years, with 31 males. The mean change in ADC value between baseline and within 15 days after infusion was significantly higher in the good outcome group compared to the poor outcome group ($p < 0.01$). The change in ADC value was an independent predictor of treatment outcome on logistic regression analysis after adjusting for age, gender, and disease stage (odds ratio: 1.017; 95% confidence interval: 1.003–1.030; $p < 0.01$). The area under the ROC curve for ADC change was 0.794 (95% confidence interval: 0.649–0.939).

Conclusions: This study suggests that quantitative whole-body MRI may serve as a useful tool for predicting treatment outcome in pediatric patients with aggressive NHL undergoing CAR-T cell therapy. The ADC value, a noninvasive biomarker, could be utilized for identifying patients who are more likely to benefit from CAR T cell therapy. These findings have important implications for patient selection and treatment planning.

Keywords: cellular therapies, immunotherapy, Imaging and Early Detection - Other

No conflicts of interests pertinent to the abstract.



	OR	95% C.I.		P
ADC value change	1.02	1.00	1.04	<0.01
Gender	0.00	0.00		1.00
Baseline size	1.49	0.97	2.27	0.07
Baseline T2 value	0.99	0.99	1.00	0.16

Figure : Receiver operating characteristic curves for the performance of multivariable model in the prediction of good outcome

SESSION 6 - PERIPHERAL T-CELL LYMPHOMAS

040 | THE GENETIC SUBTYPES AND THE TUMOR MICROENVIRONMENT SIGNATURES ARE ASSOCIATED WITH DISTINCT OUTCOMES IN PERIPHERAL T-CELL LYMPHOMA

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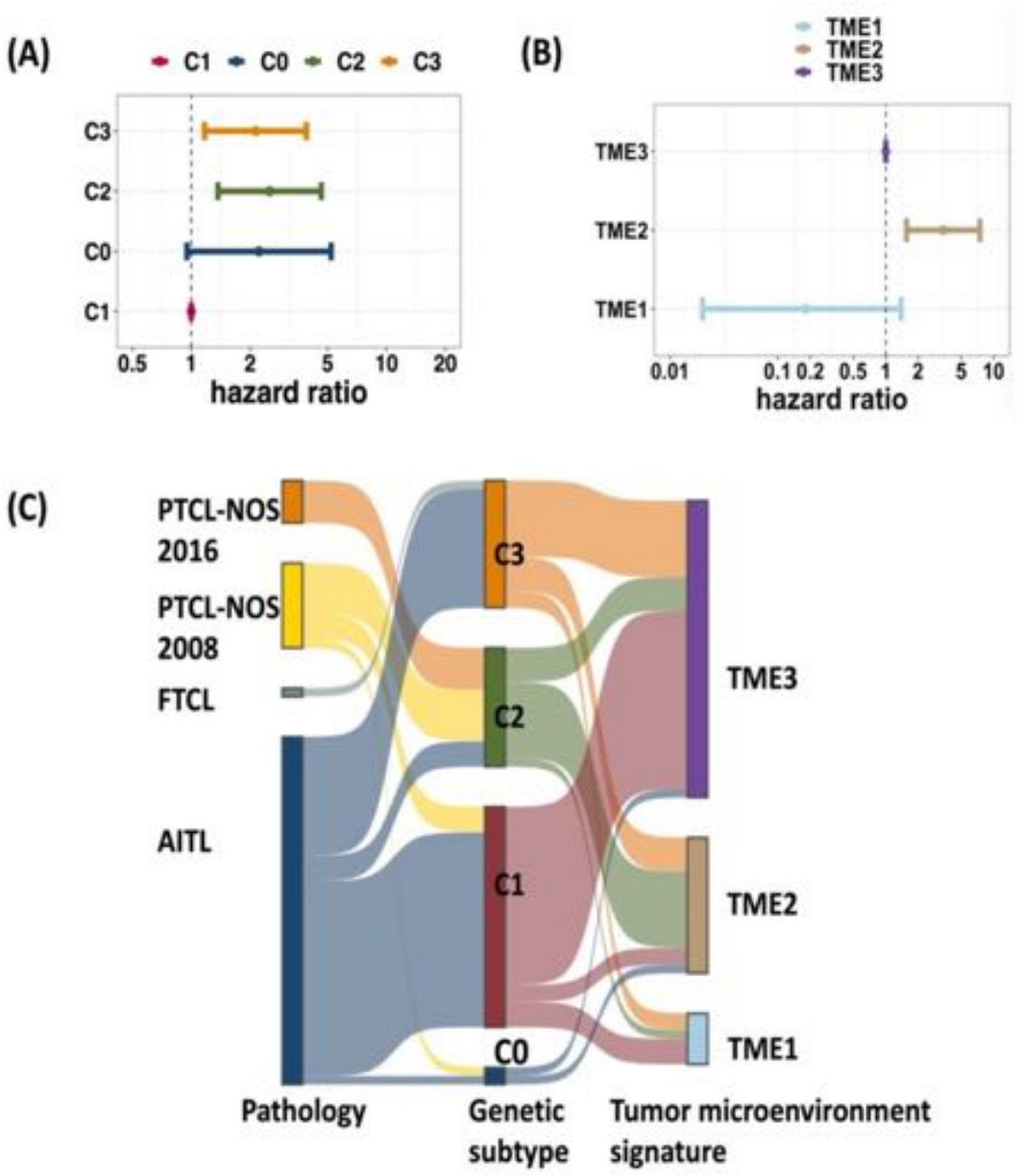
Background: Emerging evidence suggests the prognostic impact of the tumor microenvironment (TME) in peripheral T-cell lymphomas (PTCLs). To better understand PTCL pathobiology, we performed an integrative multi-omics study to explore the genetic subtypes and the



TME signatures of PTCLs, especially nodal T-follicular helper T-cell lymphomas (nTFHLs) and PTCL, not otherwise specified (PTCL-NOS).
Method: We performed whole-exome sequencing of 92 nTFHLs and 37 PTCL-NOSs, a total of 129 cases. Ninety-two nTFHLs included 85 angioimmunoblastic T-cell lymphomas (AITLs), four nPTCL with TFH phenotypes, two follicular T-cell lymphomas, and one unclassifiable nTFHL. Genetic drivers were integrated using non-negative matrix factorization consensus clustering (NMF). We estimated the proportion of immune cell fractions from bulk RNA sequencing data (n = 57) using CIBERSORTx and classified the TME signatures using hierarchical clustering.
Results: NMF clustering analysis revealed three genetic subtypes within our cohort, except for 10 cases lacking recurrent genetic abnormalities (denoted as cluster 0). C2 was characterized by *TP53* mutation, *CDKN2A* loss, *PTEN* loss, and chromosomal instability, corresponding to the previously described GATA3-PTCL subtype. C1 and C3 shared TFH-related genomic alterations, but C3 had significantly higher frequencies of chromosome (Chr) 5 gain, Chr 21 gain, *RHOA*, *IDH2*, and *CD28* mutations. A higher frequency of rash and higher C-reactive protein levels than the other AITLs characterized C3-AITL. Pairwise association analysis of genomic alterations revealed that multiple *TET2* mutations, rather than a single *TET2* mutation, significantly co-occurred with *IDH2* and *RHOA* mutations. A Bradley-Terry model estimated that the first *TET2* and *DNMT3A* mutations occurred earlier, and the second or later *TET2*, *RHOA*, and *IDH2* mutations occurred later. Compared to C1, significantly inferior survival was observed in C2 (hazard ratio (HR), 2.52; 95% CI, 1.37–4.63) and C3(HR, 2.14; 95% CI, 1.17–3.89; Figure A). The TME signatures were divided into TME1 (B-cells and follicular helper T-cells), TME2 (activated memory CD4 T-cells, M2 macrophages, and CD8 T-cells), and TME3 (naïve CD4 T-cells and activated mast cells). mTORC1 signaling was enriched in the TME2 signature compared to TME1 and TME3 signatures. The TME2 signature was significantly associated with shorter survival than the TME3 signature (HR: 3.4, 95% CI 1.6–7.5; Figure B). C2 had significantly more TME2 signature than C1 (64.3% vs. 7.7%), while C1 had significantly more TME3 signature than C2 (80.8% vs. 28.6%, p = 0.006; Figure C).
Conclusion: The genetic subtypes and the TME signatures were associated with distinct outcomes in PTCLs.

Keywords: genomics, epigenomics, and other -omics, microenvironment

Encore Abstract—previously submitted to EHA 2023

The research was funded by: Japan Society for the Promotion of Science KAKENHI grants (grant numbers: 19K23879, 22K19451, and 21H02945) and Japan Agency for Medical Research and Development (AMED) grants (20ck0106544 and 21ck0106644)

041 | ROMIDEPSIN PLUS CHOP VERSUS CHOP IN PATIENTS WITH PREVIOUSLY UNTREATED PERIPHERAL T-CELL LYMPHOMA: FINAL ANALYSIS OF THE RO-CHOP TRIAL

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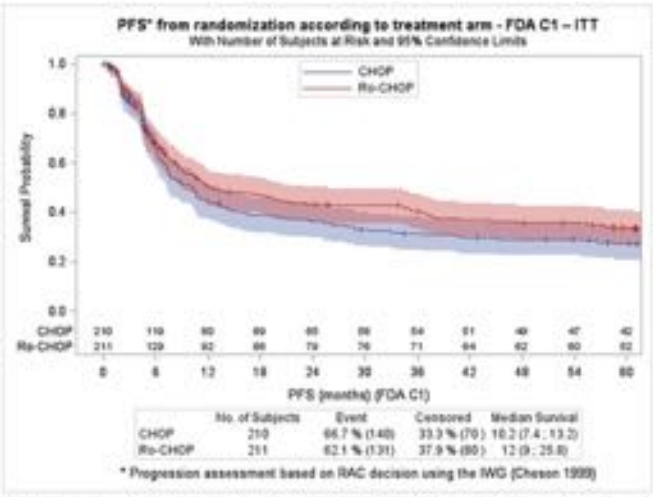
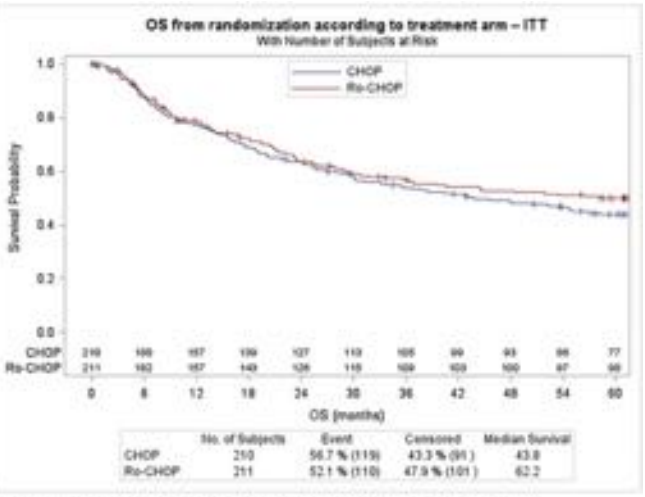
Introduction: The primary analysis of the Ro-CHOP trial (*NCT01796002*) demonstrated that romidepsine (Ro) plus CHOP did not provide an increased efficacy compared with CHOP alone in patients with previously untreated peripheral T-cell lymphoma (PTCL). We report here the final analysis of the Ro-CHOP trial.



Progression-free survival based on RAC decision using the IWG (Cheson 1999) in the intention-to-treat population according to treatment arm



Overall survival in the intention-to-treat population according to treatment arm.

Methods: The study was an open-label multicenter randomized (1:1) phase III study of Ro-CHOP versus CHOP as frontline treatment of patients 18–80 years with PTCL. The primary endpoint was progression-free survival (PFS) according to IWG 1999 criteria. Overall survival (OS) was a secondary endpoint, relapse patterns and PFS/OS after the first progression (PFS2/OS2) were analyzed post-hoc. The cut-off date was set to 2022/12/13, that is, five years after the last patient was enrolled.

Results: 211 and 210 patients were assigned to receive 6 cycles of Ro-CHOP or CHOP in 3-week cycles, respectively. Median age was 65 (25–81) years. With a median follow-up of 71.8 months, 271 patients (64.4%) presented a PFS event by independent RAC assessment. Median PFS was 12 months (95% CI = [9; 25.8]) and 10.2 months ([7.4; 13.2]) for Ro-CHOP and CHOP, respectively (HR = 0.79 [0.62; 1.005], $p = 0.054$, 2-sided p-value). Based on 229 deaths, median OS was 62.2 months and 43.8 months for Ro-CHOP and CHOP, respectively. The causes of death were the following: lymphoma ($n = 165$, 72.4%), concurrent illness ($n = 30$, 13.2%), other reasons ($n = 12$, 5.3%), toxicity of salvage treatment ($n = 8$, 3.5%), toxicity of study treatment ($n = 4$, 1.8%), unknown ($n = 9$, 3.9%). No new safety signal was observed.

A significantly prolonged PFS in the follicular helper T-cell (TFH) lymphoma subgroup (centrally reviewed) was still observed with this longer follow-up. The median PFS was 19.5 months ([11.5; 44.4]) in the Ro-CHOP arm and 10.6 months ([7.4; 14.9) the CHOP arm with a HR of 0.703 ([0.502; 0.985], $p = 0.0395$).

Additional treatment was given to 251 patients after progression (Ro-CHOP = 115, and CHOP = 136), leading to an overall response rate of 35.7% (CR/CRu: 21.7%) and 31.6% (CR/CRu: 22.1%) in the Ro-CHOP and CHOP groups, respectively. Overall, 191 of the 251 patients (76.1%) progressed after second-line therapy, and 20 patients died without a second progression (8.0%). The median PFS2 and OS2 were 3.3 months (95% CI, [2.7; 4.5]) and 11.5 months ([9.6; 15.9]), respectively. Twenty-three patients (9.2%) received an allogeneic stem cell transplantation (median age 51 [29–70] years) and displayed 1-year PFS2 and OS2 rates estimated at 59.7% and 81.8%, respectively. Detailed outcome according to salvage treatment at progression will be presented at the meeting.

Conclusion: Five years after randomization of the last patient, outcome of patients treated for PTCL was confirmed to be not significantly different between the Ro-CHOP and CHOP arms, except for PTCL from TFH origin. Second-line treatments led to poor results after disease progression/relapse.

The study was sponsored by the LYSARC, with funding provided by Celgene/BMS

Keyword: aggressive T-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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Consultant or advisory role: Roche, BMS, Novartis, Kite-Gilead, Janssen, Abbvie, Sanofi, Octapharma, Kyowa Kirin Pharma
Research funding: Iqone Healthcare, BMS
Educational grants: Pfizer, Roche, BMS, Novartis, Kite-Gilead

M. Delfau-Larue
Honoraria: Takeda, Amgen, Roche, Gilead, Abbvie
Research Funding: Celgene, BMS, Roche

042 | TARGETED AGENTS COMBINED WITH CHOP COMPARED WITH CHOP AS THE FIRST-LINE THERAPY FOR PERIPHERAL T-CELL LYMPHOMA: PRELIMINARY RESULTS FROM A PHASE 2 GUIDANCE-03 TRIAL

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Introduction: Peripheral T-cell lymphoma (PTCL) is a heterogeneous disease with dismal outcomes. Standard CHOP (Cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy is still the most widely used regimen for front-line management. To explore new targeted drugs in PTCL, we conducted a phase 2, multi-center, non-randomized clinical trial, comparing the efficacy and safety of targeted agents combined with CHOP (CHOPX) with CHOP in newly diagnosed patients with PTCL.

Methods: The primary outcome was complete response rate (CRR) at the end of treatment (EOT). Patients with newly diagnosed PTCL had enough tumor tissue for next generation sequencing (NGS) and were assigned to CHOPX and CHOP group based on investigators' discretion. Patients in CHOPX group received intravenous cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (up to a maximum of 2 mg) on day 1, and oral prednisone 60 mg/m^2 (up to a maximum of 100 mg) on day 1–5 every 21 days at the first cycle. X (i.e., targeted agent) was added from the second to sixth cycles as following, intravenous decitabine 10 mg/m^2 on day -5 to -1 if with *TP53* mutation. Subcutaneous azacytidine 100 mg on day −7 to −1 if with *TET2/KMT2D* mutation. Oral chidamide 20 mg on day1, 4, 8, 11 if with *CREBBP/EP300* mutation. Oral lenalidomide 25 mg on day 1–10 if without above mutations. Patients in control group received standard CHOP regimen for 6 cycles. Analysis of efficacy and safety was of the intent-to-treat population. The study was registered with ClinicalTrials.gov, number NCT04480099.

Results: Between 20 June 2020 and 22 September 2022, 108 patients were assessed for eligibility in the study. Ten patients met exclusion criteria and 2 patients withdrew informed consent before treatment. Forty-eight patients in the CHOPX group and 48 patients in the CHOP group were included into intent-to-treatment population. Baseline patient characteristics like age, gender, Ann Arbor stage, performance status, prognostic risk group was comparable between CHOPX and CHOP groups. The most common pathological subtypes were angioimmunoblastic T-cell lymphoma (67% vs. 60%), PTCL-not otherwise specified (17% vs. 21%), anaplastic T-cell lymphoma (6% vs. 8%) in the CHOPX and CHOP groups. As of 1 February 2023, 91 patients completed response evaluation at EOT. CRR in the CHOPX group was higher than the CHOP group (58% [25/43] vs. 33% [16/48]). The most common grade 3–4 hematological adverse events in CHOPX group were neutropenia (61%) and febrile neutropenia (27%).

Conclusions: Preliminary analysis showed targeted agents combined with CHOP was effective and safe compared with standard CHOP in PTCL. Therapeutic strategy specifically towards molecular features may change current PTCL management in front-line setting.

Keywords: combination therapies, molecular targeted therapies

No conflicts of interests pertinent to the abstract.

043 | GOLIDOCITINIB IN TREATING REFRACTORY OR RELAPSED PERIPHERAL T-CELL LYMPHOMA: PRIMARY ANALYSIS OF THE MULTINATIONAL PIVOTAL STUDY RESULTS (JACKPOT8)

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Introduction: Currently there is no consensus on the treatment of relapsed/refractory (r/r) PTCL, and patient prognosis was poor. Golidocitinib is an orally available, JAK1-selective inhibitor currently being evaluated in a multinational, pivotal study in r/r PTCL (JACKPOT8 Part B, NCT04105010). Here we reported the primary analysis of efficacy and safety results of this study.

Methods: PTCL patients who had relapsed from or had been refractory/intolerant to ≥1 (but ≤3) prior systemic therapy(ies) were enrolled to receive golidocitinib at 150 mg once daily until disease progression or pre-defined discontinuation criteria were met. The primary endpoint was CT-based objective response rate (ORR) assessed by an independent review committee (IRC) according to Lugano 2014 classification. The efficacy analysis set included patients whose pathological diagnosis of PTCL had been retrospectively confirmed by a central laboratory and who had at least one measurable lesions at baseline. The safety analysis set included all dosed patients.

Results: As of 30 November 2022, a total of 104 patients with r/r PTCL were enrolled and dosed with golidocitinib. Baseline characteristics: median age was 58 yrs; 64.4% were male; 20.2% had baseline bone marrow involvement. Major subtypes included NOS (46.2%), AITL (15.4%) and ALCL (9.6%). The median prior lines of therapies were two. All of the patients had been treated with chemotherapies, and 48.1% had been treated with histone deacetylase inhibitors.

By the data cut-off (DCO) date, a total of 80 patients had both IRC assessment and central pathology review results available, and thus were included in the efficacy analysis. Among them, 35 patients achieved tumor response (ORR = 43.8%), including 20 patients (25.0%) achieved complete responses. Tumor response was observed in various subtypes, including AITL (56.3%), NOS (45.7%), ALCL (11.1%) and others (44.4%). In patients who relapsed from HDAC inhibitor treatment, 54.8% achieved tumor response. With a median follow-up of 5.5 months for responders, the median duration of response (DoR) has not been reached.

Golidocitinib was tolerated in patients with r/r PTCL. By the DCO date, the longest duration on treatment was 15.7 months (still responding). The most common ≥ grade 3 treatment-related adverse events (TRAEs) were hematological in nature, including neutrophil count decreased (26.0%), white blood cell count decreased (25.0%), platelet count decreased (16.3%) and lymphocyte count decreased (16.3%). TRAEs leading to dose interruption, reduction, and discontinuation were 37.5%, 5.8%, and 7.7%, respectively. The majority of TRAEs were reversible or clinically manageable.

Conclusions: Golidocitinib demonstrated its potential as a novel targeted therapy for the treatment of r/r PTCL. The updated data will be presented at the conference.

Encore Abstract—previously submitted to ASCO 2023

Keywords: aggressive T-cell non-Hodgkin lymphoma, molecular targeted therapies

Conflicts of interests pertinent to the abstract

W. Yu

Employment or leadership position: Employed by Dizal Pharmaceutical

044 | FIRST IN HUMAN STUDY OF AUTO4, A TRBC1-TRAGETTING CART T CELL THERAPY IN RELAPSED/REFRACTORY TRBC1-POSITIVE PERIPHERAL T-CELL LYMPHOMA

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Introduction: Relapsed/refractory (r/r) peripheral T cell lymphomas (PTCL) are highly aggressive tumors associated with very poor prognosis. We recently described a new targeting strategy based on the mutually exclusive expression of T cell receptor beta-chain constant domains 1 and 2 (TRBC1 and TRBC2) (Maciocia, PM. et al. Nat Med, 2017) which can spare a proportion of the normal T cell compartment. Here we describe first in human clinical findings of AUTO4, a TRBC1 directed autologous CAR T cell therapy for patients with TRBC1-positive PTCL.

Methods: NCT03590574 is an ongoing, multi-centre, single-arm phase 1/2 study of AUTO4 in r/r TRBC1-positive PTCL. Here we report the findings of the dose escalation. Four dose levels were explored: 25×10^6, 75×10^6, 225×10^6, and 450×10^6 CAR T cells were administered as a single dose. CAR T-cell products were generated using a semi-automated closed process. The initial AUTO4 manufacturing process A was optimized and is now being used in process B to define the recommended phase 2 dose. Primary endpoints in phase 1 are incidence of ≥Grade 3 toxicity occurring within 60 days of AUTO4 infusion and the frequency of dose limiting toxicities (DLT) within 28 days of AUTO4 infusion. Overall response (CR + PR) rate by Lugano PET-CT criteria is a secondary endpoint.

Results: As of 8 February 2023, 12 patients (10 process A, 2 process B) have been treated with AUTO4. The median age was 57 years (range 34–72) with a median prior lines of 2 (range 1–5). 7 patients were diagnosed with PTCL-NOS, 4 with AITL (Angioimmunoblastic T-cell lymphoma) and 1 with ALCL (Anaplastic large cell lymphoma). Chemotherapy bridging was given to 70% of patients and 4/8 CD30+ patients recieved brentuximab as bridging or as prior line therapy. 3/12 patients had prior autoSCT. The most common treatment adverse events were transient Grade1–4 neutropenia, thrombocytopenia. Lymphopenia was observed with CD3 + lymphocytes recovering to baseline levels after pre-conditioning. No ≥Grade 3 infections were observed. Any grade CRS was observed in 6/12 patients (5 at 450×10^6, 1 at 250×10^6) and one

patient developed Grade 3 CRS which resolved within 3 days. No ICANS or DLTs were observed. Response at month 1 was evaluable in 9/10 patients using process A. Five patients were in complete metabolic response (CMR) (1/5 was in CMR at the time of lymphodepletion), 1 patient achieved a partial response (PR) and 3 patients had no response. At the $450x10^6$ dose level, 3/4 patients achieved CMR at month 1, and 2 of them are in ongoing remission at 12 and 15 months, respectively. The efficacy non-evaluable patient at month 1, due to COVID19 infection, showed no response at month 3 but achieved a delayed PR by month 9 without any further treatment.

Conclusions: AUTO4 was well tolerated with no DLT. Ongoing CMR at months 12 and 15 are encouraging. Updated data and longer follow up using the improved manufacturing process B will be presented.

The research was funded by: Autolus Ltd

Keywords: aggressive T-cell non-Hodgkin lymphoma, cellular therapies, ongoing trials

Conflicts of interests pertinent to the abstract

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SESSION 7 - NEW CAR-T CELL APPROACHES

045 | PHASE 2 STUDY OF ANBAL-CEL, NOVEL ANTI-CD19 CAR-T THERAPY WITH DUAL SILENCING OF PD-1 AND TIGIT IN RELAPSED OR REFRACTORY LARGE B CELL LYMPHOMA - INTERIM ANALYSIS RESULT

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Introduction: Anbal-cel is a novel autologous anti-CD19 CAR-T cell therapy which has been knocked-down for PD-1 and TIGIT expression using OVIS platform. It demonstrated superior T-cell functionality compared to other marketed CD19 CAR-T cells at preclinical studies. Phase 1 dose escalation study confirmed anbal-cel is safe and potentially effective.

Methods: Patients with relapsed or refractory LBCL were enrolled from six Korean investigator sites to receive anbal-cel at a dose of 2×10^6 CAR-T cells/kg. Primary endpoint is objective response rate (ORR) assessed by Independent Review Committee (IRC). Secondary endpoints are progression-free survival (PFS), duration of response (DOR), pharmacokinetics (PK) and safety profiles.

Results: As of 28 February 2023, a total of 41 patients were infused and 34 patients completed at least one tumor response evaluation at day 28. With the median age of 63 (range 37–82), 66% of the patients (27/41) were double expressor. Non-GCB type was 76% (31/41) and 42% (17/41) were primary refractory patients. Median follow-up period was 4.6 months.

ORR (CR/PR) assessed by investigators was 85.3% and CR rate at day 28 & month 3 were 73.5% (25/34) and 71.4% (22/31) respectively. IRC assessment result was similar and will be presented at the meeting.

Among the 41 patients, grade 3 CRS and ICANS were reported from 6 patients (14.6%) and 2 patients (4.9%) respectively. No grade 4 CRS and ICANS was observed. Prolonged neutropenia was observed in 11 patients (26.8%) and thrombocytopenia was observed in 12 patients (29.3%). Three (7.3%) serious infections (1 bacteria and 2 COVID-19 infections) were reported during primary follow-up period.

Responder group (CR) reported higher incidence and severity of CRS compared to non-responder group (Non-CR), but it was insignificant. Incidence rate, severity of ICANS and prolonged cytopenia were comparable between the two groups.

Among CAR+ T-cells in the anbal-cel product, median CD4:CD8 ratio was 3.6 and CCR7+ memory phenotype CAR T-cells account for

65.8% of CAR-T cells. Median knock-down rates of PD-1 and TIGIT were 65% and 96% respectively.

The responder group showed a significantly increased level of CCR7+ memory phenotype (68.6% vs. 44.9%) and PD-1 knock-down rate (71.8% vs. 59.3%) compared to the non-responder group, which showed correlation with increased levels of $AUC_{0\text{-}28days}$ and C_{max}. Anbal-cel expansion was not correlated to tumor volume measured by SPD and TMTV.

In addition, the responder group had notable changes in cytokine levels of IL-2, IL-10, IFN-γ, granzyme, GM-CSF and peak levels of various cytokines were proportional to severity of CRS. Patients with higher levels of IL-15 and MCP-1 at baseline had tendency to experience ICANS.

Conclusions: Anbal-cel demonstrated unique characteristics in product profile which demonstrated potential to correlate with treatment outcomes and warrant to confirm with more data.

The research was funded by: Curocell Inc.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, immunotherapy

No conflicts of interests pertinent to the abstract.

046 | POINT-OF-CARE ANTI-BCMA CAR T-CELL THERAPY INDUCES ENCOURAGING RESPONSE RATES IN HIGH-RISK RELAPSED/REFRACTORY MULTIPLE MYELOMA

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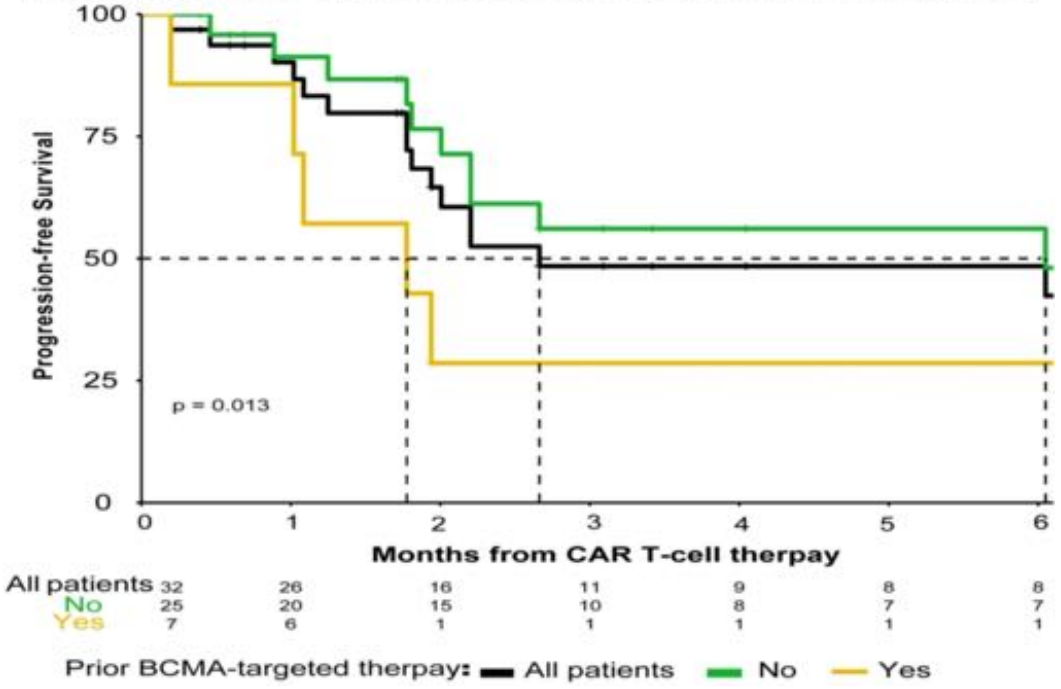
Table 1. Best response rate following CAR T-cell therapy

Overall response rate (PR at least)	19 (59%)
Stringent complete response	5 (16%)
Complete response	4 (12%)
Near complete response	2 (6%)
Very good partial response	2 (6%)
Partial response	6 (19)
Minimal response	1 (3%)
Stable disease	11 (34%)
Progressive disease	1 (3%)

Figue 1. PFS by prior exposure to BCMA-targeted therapy



Introduction: Anti-BCMA chimeric antigen receptor (CAR) T-cell therapy showed excellent efficacy in patients with relapsed/refractory multiple myeloma (R/R MM). Point-of-care (POC) CAR manufacturing abrogates the need for cryopreservation and shipment of cells, thus shortening the manufacturing process and reducing the necessity of bridging therapy. We report outcomes of phase 1b/2 single-center clinical trial of autologous POC anti-BCMA CAR T-cell therapy in patients (pts) with R/R MM treated with ≥3 prior therapies (NCT05243212).

Methods: Pts underwent a single peripheral blood leukapheresis. Fresh T-cells were transduced with retroviral vector encoding the anti-BCMA CAR (based on 11D5-3 ScFv, CD28 costimulatory domain, and CD3-ζ signaling domain). Cell dose was 6×10^6/kg (dose level I [$n = 3$]) or 9×10^6/kg (dose level II [$n = 29$]) CAR T-cells. Response was defined per IMWG criteria. Last follow-up was as of 02/2023.

Results: All 32 pts (median age 60, IQR 54–67) enrolled received CAR T-cell infusion in a median of 11 days (IQR 11–11) after leukapheresis. Only 2 pts received bridging chemotherapy. The median number of prior therapies was 4 (IQR 3–5), with 59% and 34% of the pts being penta- and quad-refractory, respectively. 7 (22%) pts had prior exposure to BCMA-targeted therapy (belantamab mafodotin, $n = 5$ [16%]; talqeutamab, $n = 2$ [6%]). At enrollment, 10 (34%) pts had high-risk cytogenetics, 7 (22%) had double-hit myeloma, and 17 (57%) had extramedullary involvement. Only 17 (53%) and 2 (16%) pts were eligible to enroll in the KarMMa (NEJM, 2021) and CARTITUDE-1 (Lancet, 2021) studies, respectively.

One patient (3%) developed grade 3 cytokine release syndrome. Immune effector cell-associated neurotoxicity syndrome was not noted. Grade 3–4 neutropenia and thrombocytopenia occurred in 31 (97%) and 16 (50%), respectively. Anemia requiring transfusion occurred in 14 (44%) pts. Cellular therapy-related death was not observed.

The median follow-up was 3.9 months (IQR 2.6–7.3). Best Overall response rate (PR at least) was 59% (VGPR at least, 40%). Median time to first response was 31 days (95% CI: 26–33). Estimated 6-months OS, PFS and duration of response were 89% (95% CI: 75–100), 48% (95% CI: 33–72), and 63% (95% CI: 41–97), respectively. Patients with prior exposure to BCMA-targeted therapies had an inferior PFS (HR 3.4 [95% CI: 1.2–9.7] $p = 0.03$; Figure 1).

Conclusion: POC anti-BCMA CAR T-cells induced high response rates with an excellent safety profile in high-risk MM patients mostly not eligible to be enrolled in the pivotal trials. The rapid CAR-T production time obviated the need for bridging therapy in most patients. It is noteworthy that prior exposure to BCMA-targeted therapies is associated with dismal PFS, hence those therapies should be carefully considered when CAR T-cell therapy might be intended.

Encore Abstract—previously submitted to EHA 2023

Keywords: cellular therapies, multiple myeloma

No conflicts of interests pertinent to the abstract.

* H. Magen, E. Shkury and A. Avigdor contributed equally to the abstract.

047 | OFF-THE-SHELF CD30.CAR-MODIFIED EPSTEIN-BARR VIRUS-SPECIFIC T CELLS (CD30.CAR EBVSTS) PROVIDE A SAFE AND EFFECTIVE THERAPY FOR PATIENTS WITH HODGKIN LYMPHOMA (HL)

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Off-the-shelf allogeneic T-cell therapies face the major challenges of graft-versus-host disease (GVHD) and graft rejection mediated by host and recipient alloreactive T cells, respectively. To address GVHD, we are using Epstein-Barr Virus-specific T cells (EBVST), which are virus specific rather than allo-specific and have not produced GVHD in over 300 allogeneic recipients. To prevent graft rejection, we modified the EBVST with a chimeric antigen receptor (CAR) targeting CD30, an antigen that is upregulated on allo-activated T-cells, which will consequently become targets for CD30.CAR EBVST. Hence, CD30.CAR EBVST can kill both CD30+ lymphoma cells and alloreactive T cells through their CAR, and may be boosted *in vivo* in EBV+ recipients via their native TCR. We are evaluating this approach in a phase 1 trial (NCT04288726) in patients with CD30+ lymphoma.

We generated a bank of 7 CD30.CAR EBVST products by stimulating PBMC from healthy donors with overlapping EBV peptide mixtures followed by retroviral transduction with a 2nd generation, CD28-containing CD30.CAR. We have treated 16 patients (median age 36, range 22–53) with relapsed or refractory HL. Patients had undergone a median of 5 (range 3–7) prior lines of treatment. Escalating doses of $4 \times 107 - 8 \times 108$ (DL1–4) CD30.CAR EBVST were infused after lymphodepletion. The frequency of CD30.CAR EBVST was measured by real time qPCR for the transgene in blood. Changes in the frequency of T-cells responding to EBV or tumor-associated antigens (epitope spreading) were measured by IFNɣ ELISpots. Clinical responses were assessed per Lugano criteria by PET/CT scans performed 4–8 wks post infusion.

CD30.CAR EBVST were well tolerated, with no GVHD and only two patients having reversible grade 4 cytopenia. Five patients at DL3–4 had grade 1 cytokine release syndrome (CRS), but all resolved without treatment. Of the 16 patients treated, 6 had partial responses (PR) and 6/13 patients at DL2–4 had complete responses (CR), giving an overall objective response rate (ORR) of 75%. Despite these remarkable responses, qPCR for the CD30.CAR transgene showed near background levels by wk 1 post infusion. Although this could mean that CAR-T are quickly eliminated by alloreactive T-cells, additional infusions from the same donor product into the same patient can be associated with response (Figure 1); an alloreactive response would be anticipated to be amplified after each infusion and preclude additional responses. We are therefore analyzing tumor

biopsy samples to determine the presence of CD30.CAR EBVST at tumor sites and characterize their phenotype for functionality.
Thus, we have shown CD30.CAR EBVST can be a safe and effective treatment for HL, and may avert GVHD and immediate rejection even after multiple infusions. We now seek to improve the durability of responses and test whether CD30.CAR EBVST can be used as a platform for other off-the-shelf CAR-T therapies.

The research was funded by: Leukemia and Lymphoma Society SCOR (Heslop) and Tessa Therapeutics (Rooney/Ramos) through a grant to Baylor College of Medicine.

Keywords: cellular therapies, Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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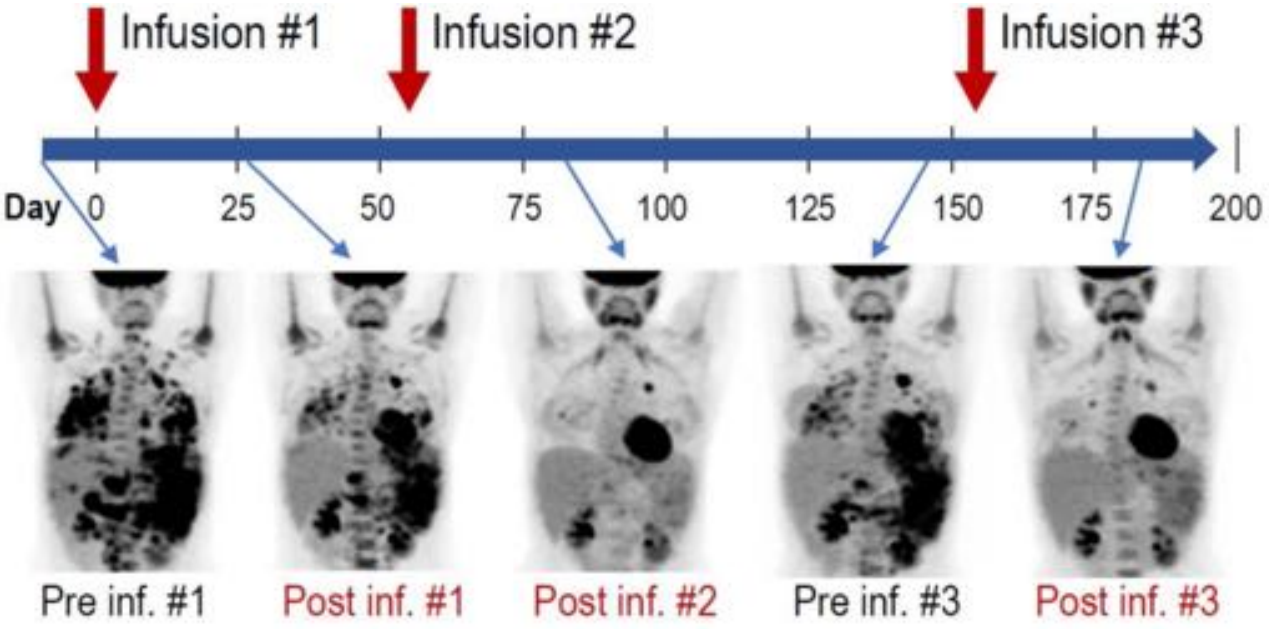

Figure 1. Clinical responses in patient who had high tumor burden and received 3 CD30.CAR-EBVST infusions at DL3. The timeline shows timing of infusions and diagnostic PET/CT scans, evidencing PR after each infusion.

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048 | DURABLES RESPONSES WITH ANTI-CD19 ALLOGENEIC CAR T ALLO-501/501A IN PHASE 1 TRIALS OF RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA (*R/R* LBCL)

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Introduction: Despite progress in treating LBCL, approximately 50% to 60% of pts will either not achieve a complete response (CR) or will relapse after current first- or second-line therapy. Autologous anti-CD19 chimeric antigen receptor (CAR) T cells have revolutionized the care of pts with *r/r* LBCL; however, patient-specific manufacturing processes and long wait times prevent their broad use and many pts who would be eligible are unable to receive therapy due to lack of accessibility. Derived from healthy donor T cells, allogeneic CAR T cells may address this bottleneck by providing pts with rapid access to a one-dose treatment, prescribed with curative intent. Phase 1 data for anti-CD19 ALLO-501 (NCT03939026) and successor, ALLO-501A (NCT04416984), which use Cellectis' technologies, demonstrated a manageable safety profile with no dose-limiting toxicities (DLTs) and efficacy outcomes comparable to published results for autologous CAR T therapy in pts with *r/r* LBCL. New data document the durability of responses achieved with ALLO-501/501A following conditioning with fludarabine (F), cyclophosphamide (C), and ALLO-647 (A).

Methods: In two multicenter, single-arm, open-label, phase 1 trials, autologous CAR T-naïve pts with *r/r* LBCL in single-dose cohorts received conditioning with F (30 mg/m^2/day) and C (300 mg/m^2/day) over 3 days, and A (13 mg/day over 3 days or 30 mg/day over 2 or 3 days, for total doses of 39 mg, 60 mg, or 90 mg) followed by a single dose of ALLO-501/501A (range: 40 M cells to 360 M cells). Pts in consolidation cohorts received the same conditioning over 3 days followed by a single dose of ALLO-501/501A (120 M cells). Pts without progression at Day 28 received consolidation with additional A (30 mg on Day 29) and a second cell infusion (120 M cells on Day 30).

Results: As of 26 January 2023, 33 pts were treated with Alloy-manufactured product; median times from enrollment to initiation of conditioning were 2–6 days across dosing cohorts and all (100%) pts received ALLO-501/501A per specifications. Through follow-up of up to 42.7 months, no DLTs, Gr3+ cytokine-release syndrome events, or graft versus host disease occurred; Gr3+ neurologic toxicity occurred in 6.1% of patients. Overall, CR was achieved in 14 (42.4%) pts and partial response occurred in 5 (15.2%; ORR: 57.6%) pts. Of the 14 pts who achieved CR, 9 (64.3%) remained in CR at the cutoff date, with median duration of response not reached and longest response ongoing at 29.6 months; median follow-up was 17.7 months.

Conclusions: ALLO-501/501A following FCA conditioning provided durable responses with a manageable safety profile in autologous CAR T-naïve pts with *r/r* LBCL. Durable complete remissions continue in 9 pts with the longest ongoing response at 29.6 months. These findings support broader evaluation of ALLO-501A/ALLO-647 in the ongoing, first, potentially pivotal phase 2 trial (ALPHA2) of allogeneic CAR T therapy.

The research was funded by: Allogene Therapeutics

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, immunotherapy

Conflicts of interests pertinent to the abstract

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Research funding: Kite Pharma (Institutional), Allogene (Institutional), CERo Therapeutics (Institutional), Novartis (Institutional), BlueBird Bio (Institutional), BMS (Institutional), National Cancer Institute, Leukemia and Lymphoma Society, Allogene
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049 | HIGH EFFICACY AND FAVORABLE SAFETY OF 3RD GENERATION CD20 CAR-T (MB-106) FOR OUTPATIENT TREATMENT OF FOLLICULAR LYMPHOMA (FL)—RESULTS OF A SINGLE-INSTITUTION TRIAL

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Background: Immunotherapy is an effective treatment strategy for FL, and CD19 CAR-Ts and a CD20 bispecific antibody are standard of care for relapsed FL. Toxicities like CRS and ICANS for CAR-T and the need for continuous therapy for bispecifics may limit their use. MB-106 is a fully human 3rd-generation CD20 CAR-T product with both 4-1BB and CD28 costimulatory domains. We present the final results of the FL cohort from a single-institution phase I/II clinical trial investigating MB-106 for B-cell lymphoma/CLL.

Methods: Patients (Pts) with relapsed CD20-positive FL were eligible. Prior treatment with CD19 CAR-T was allowed. Lymphodepletion consisted of Cy/Flu. Dose levels (DL) included: DL1: 3.3×10^5, DL2: 1×10^6, DL3: 3.3×10^6, DL4: 1×10^7 CAR T cells/kg. A continual reassessment method dose escalation design was used to find the maximally tolerated dose. CAR-T was infused in the outpatient setting except for the first pt of each dose cohort (overnight observation). Best responses are reported here. CRS and ICANS are graded per ASTCT.

Results: Between Dec 2019 and Nov 2022, 20 pts with FL were treated. Median age was 63 yrs (range: 44–81), 9 pts (45%) were > 65 and 3 pts (20%) were >80 yrs. High-risk features included POD24 ($n = 15$; 75%), history of histologic transformation ($n = 4$; 20%), prior treatment with a CD19 CAR-T ($n = 1$; 5%). Median prior lines of treatment was 4 (range 1–12). Median time between leukapheresis and lymphodepletion was 15 days (range: 10–28), and 5 pts received bridging therapy. All DLs were reached (DL0 = 1, DL1 = 3, DL2 = 5, DL3 = 8, DL4 = 3), with no DLTs. All CRS events were grade 1 ($n = 5$; 25%) or grade 2 ($n = 1$; 5%), with no grade ≥3 CRS events. There was no occurrence of ICANS of any grade. No pts had tumor lysis syndrome or Gr 3–4 infections. In the first 28 days, thrombocytopenia (Gr 3–4: 20%) and neutropenia (Gr 3–4: 95%) were common but there were no bleeding complications, and the rate of febrile neutropenia was 15%. Two pts developed CMV reactivation, and 1 pt developed grade 3 maculopapular rash. Overall response (ORR) rate was 95% (19/20) and complete response (CR) rate was 80% (16/20). Pts who received DL3 or DL4 had an ORR 100% and CR rate of 91%. Nine and 6 pts remain alive and in remission >1 yr and >2 yrs, respectively. The patient with a prior CD19 CAR-T achieved a CR and remains in remission after 15 months. With median follow-up of 15 months, 3 patients died (1 MDS, 1 COVID-19, 1 unknown). Robust CAR T cell expansion was seen regardless of cell dose, with a median peak of 154 cells/mcl (range 4–2368) and persistence beyond 1 year in all pts with adequate follow-up.

Conclusion: Treatment with MB-106, a 3rd-generation CD20 targeting CAR-T, resulted in high ORR and CR rates and CAR-T persistence in FL pts and was associated with a favorable safety profile with no occurrence of Gr 3 or Gr 4 CRS and no ICANS of any grade. A multicenter trial for treatment of B-cell malignancies including FL is ongoing in the US.

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Keywords: cellular therapies, immunotherapy, indolent non-Hodgkin lymphoma`

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Stock ownership: • A2 Biotherapeutics • Navan Technologies
Research funding: Kite Pharma, Juno Therapeutics, Celgene, Legend Biotech, BMS
Other remuneration: • Dr. Maloney has the rights to royalties from Fred Hutch for patents licensed to Juno Therapeutics/BMS

B. G. Till
Consultant or advisory role: Mustang Bio and Proteios Technology
Research funding: Mustang Bio and Juno Therapeutics, a Bristol-Myers Squibb company
Other remuneration: Inventor on a patent held by Fred Hutchinson Cancer Center directed towards the CD20 CAR construct, which is licensed to Mustang Bio

SESSION 8 - EPIGENETIC MECHANISMS AND TARGETED THERAPIES IN B- AND T-CELL LYMPHOMAS

050 | EPIGENETIC BASIS AND THERAPY OF DLBCL

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Somatic mutations of transcription factors and chromatin modifiers are a genetic hallmark of DLBCLs regardless of subtype. Most DLBCLs arise from B cells transiting the germinal center reaction during the humoral immune response. During this process B cells undergo a series of rapid phenotypic changes, induce through the immune synapse they form with specialized T follicular helper (THF cells). During their proliferative burst, germinal center B-cells downregulate many immune synapse genes which allows them to undergo somatic hypermutation without interruption. Somatic mutations that impair expression of subsets of immune synapse genes lead to development of GCB-DLBCLs, whereas mutations that hijack and enhance immune synapse genes lead to ABC-DLBCLs. In GCB-DLBCLs impaired expression of immune synapse genes is often due to mutations in chromatin modifiers EZH2, CREBBP, KMT2D, ARID1A, etc. Each of these genes have specific and distinct biochemical functions and caused somewhat different phenotypes that cause immune evasion and shape the lymphoma immune microenvironment in different ways. Novel selective therapeutic agents now exist to counteract each of these four classes of chromatin modifiers, enable the immune system to re-engage and kill these lymphomas and potently enhance the activity of immunotherapies, which if properly sequenced and dosed may have profound anti-lymphoma activity. Although chromatin modifiers are not often mutated in ABC-DLBCL, the effect of canonical mutations in signaling genes such as $MYD88^{L256P}$ ultimately mediate their effects by reprogramming the epigenome of B cells, favoring emergence of aberrant transcriptional programs, such as the TBET autoimmune B cell program. These mechanisms also provide opportunities for novel epigenetic therapeutic interventions. Here, we will review these concepts with a view towards how lymphomas may be eradicated by

re-establishing proper control of immune surveillance genes and other functions.

Keywords: genomics, epigenomics, and other -omics, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

051 | EPIGENETIC REGULATION OF IMMUNE MICROENVIRONMENT INTERACTIONS IN LYMPHOMA

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The majority of lymphomas are derived from B-cells in the germinal center (GC) reaction, a dynamic and tightly-regulated process that has evolved to promote the affinity maturation of antibodies. Transit through the GC reaction involves cell state transitions required for entry into the GC dark zone as centroblasts, transition into the light zone as centrocytes, and either recycling back to the dark zone or exit from the GC and terminal differentiation into memory B-cells or plasma cells. These cell state transitions involve remarkable changes at the epigenetic and transcriptional level that support functions associated with each state, such as proliferation and somatic hypermutation in the dark zone, and antigen uptake from follicular dendritic cells and presentation to T follicular helper cells in the light zone. These normal cell state transitions are perturbed in lymphomas via a range of somatic mutations, including those targeting chromatin modifying genes such as CREBBP and EZH2. In turn, the failure to install epigenetic and transcriptional programs required for immune synapse formation has significant effects on the composition and functional states within the immune microenvironment. Modulating these programs with epigenetically-targeted agents therefore has the potential to elicit both tumor-intrinsic and immune-mediated responses in GC-derived lymphomas. Here, I will review the mechanistic basis for epigenetic regulation of immune microenvironment interactions, its deregulation by chromatin modifying gene mutations, and the potential for driving anti-tumor immunity using epigenetically-targeted agents.

Keywords: genomics, epigenomics, and other -omics, microenvironment, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

052 | EPIGENETIC BASIS AND THERAPY OF FOLLICULAR HELPER T-CELL LYMPHOMAS

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Peripheral T-cell lymphomas are a group of heterogeneous diseases that encompass around 30 entities. Follicular helper T-cell lymphoma (TFHL) is the most frequent entity, representing around 45% of non-cutaneous T-cell lymphomas. They are characterized by a prominent microenvironment and by frequent mutations in *TET2*, *DNMT3A*, and *IDH2*, which are associated with impaired cytosine methylation and hydroxymethylation. *TET2* and *DNMT3A* mutations can occur in hematopoietic progenitor cells, resulting in clonal hematopoiesis that can be detected in more than half of TFHL patients. This clonal hematopoiesis is likely the first step in the TFHL lymphomagenesis and could result in epigenetically abnormal neoplastic cells as well as microenvironment cells. In addition, others mutations such as $IDH2^{R172}$ can synergize with *TET2* alterations in malignant cells to drive the oncogenesis, and contribute to remodel the microenvironment. At the therapeutic level, TFHL appears to have an elective sensitivity to epigenetic drugs. They have a better sensitivity to histone deacetylase inhibitors, such as romidepsin, used as a single agent or in combination with chemotherapy or other agents. They also have a better sensitivity to 5-azacytidine, which was associated with prolonged survival in TFHL patients compared to investigator choice. 5-azacytidine-based combination therapy appears to be promising and warrants development to overcome the poor prognosis of this disease.

Keywords: genomics, epigenomics, and other -omics, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

053 | SUPER-ENHANCER HYPERMUTATION IN DLBCL: ROLE OF ALTERATIONS IN THE GLUCOCORTICOID RECEPTOR PATHWAY

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Introduction: Subclassifications of Diffuse large B-cell lymphoma (DLBCL) based on genetic alterations has led to the identification of affected genes/pathways, as well as subtypes with prognostic and therapeutic significance. However, these efforts have been largely based on coding genes, while we have recently reported that functionally relevant non-coding regulatory elements of the DLBCL genome, that is, super-enhancers (SEs) are highly and specifically hypermutated in >90% of DLBCL samples (Bal et al. *Nature* 2022). Hypermutated SEs display signatures of AID activity and are linked to genes encoding B-cell developmental regulators and oncogenes. Of oncogenic relevance, hypermutated SEs linked to several proto-oncogenes, including *BCL6*, *BCL2* and *CXCR4*, prevent the binding and transcriptional downregulation by their specific transcriptional repressors. Genetic correction of selected mutations restores repressor DNA-binding, downregulates target gene expression, and lead to the counter-selection of cells harboring corrected alleles, indicating oncogenic dependency on the SE mutations and the important and pervasive pathogenetic role of SE hypermutation. We have now extended these studies toward the comprehensive identification

of commonly involved SEs and the analysis of the most involved pathways.

Methods: Genomic analysis including SE hypermutation analysis was performed on a panel of 93 DLBCL cases. Mutational profiles were integrated with NR3C1 ChIP-seq and Cut&Run, and single cell and bulk RNA-seq data generated from normal human germinal center (GC) B cells and/or DLBCL cell lines to identify programs modulated by NR3C1 and disrupted in lymphoma.

Results: We observed that ~80 distinct SEs can be found hypermutated in a panel of 93 DLBCL cases analyzed, with an average of 18 hypermutated SEs/case (range 3–71). Of particular relevance in terms of potential pathogenetic and clinical implications is the involvement of clusters of SE mutations affecting targets of the NR3C1 glucocorticoid receptor. The *NR3C1* gene encodes a glucocorticoid-activated transcription factor/receptor which we found expressed and active in the nucleus of normal GC B cells. DNA binding profiles in normal GC B cells showed that NR3C1 binds to hundreds of key genes relevant to GC development, including *BCL2* and *CXCR4*, as well as genes regulated by the GC master regulator BCL6. A number of these genes escape NR3C1-mediated regulation via mutation of its target sequences within hypermutated SEs.

Conclusions: These results, together with the direct genetic inactivation of NR3C1, indicate a pervasive role for the alteration of the glucocorticoid pathway in DLBCL, with physiologic, pathogenetic and clinical implications.

The research was funded by: NCI and AstraZeneca

Keywords: aggressive B-cell non-Hodgkin lymphoma, genomics, epigenomics, and other-omics

No conflicts of interests pertinent to the abstract.

SESSION 9 - LYMPHOMA IMAGING

054 | BASELINE PET RADIOMICS OUTPERFORMS CLINICAL RISK SCORES IN PREDICTING PRIMARY MEDIASTINAL B-CELL LYMPHOMA OUTCOME: INSIGHTS FROM THE IELSG37 STUDY

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Introduction: A major challenge in treating primary mediastinal B-cell lymphoma (PMBCL) is the early identification of patients who are likely to fail first-line therapy. To address this issue, the present analysis explored the potential of using PET radiomics, a new technique for extracting quantitative parameters from PET images, to predict treatment outcomes in PMBCL patients.

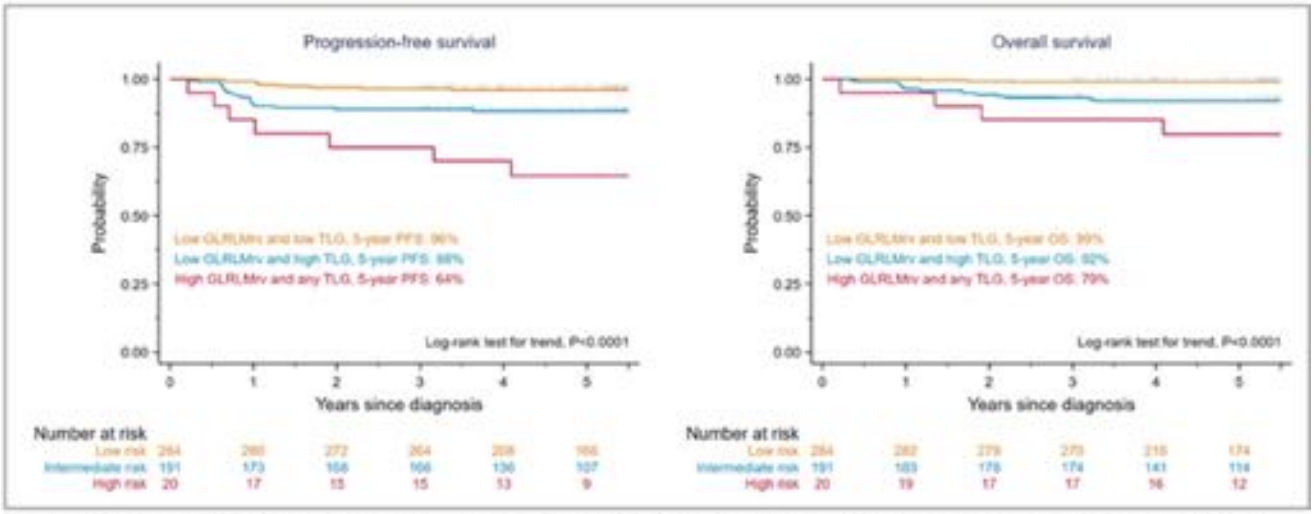
Methods: The study examined baseline PET/CT scans from 501 PMBCL patients treated with rituximab and doxorubicin-based immunochemotherapy regimens, with 342 of them receiving consolidation radiotherapy. Functional PET parameters indicating tumor burden (metabolic tumor volume, MTV), glucose consumption (total lesion glycolysis, TLG), and heterogeneity (area under curve of cumulative SUV-volume histogram, AUC-CSH) were calculated for each patient using a segmentation algorithm with a 25%-SUVmax threshold. In addition, 107 radiomics features (RF) were extracted from the baseline scans of 495 patients using the PyRadiomics package. 74 RFs uncorrelated with SUVmax and MTV were selected and then explored with a machine-learning approach based on the recursive-partitioning classification tree (CTree) method. Statistical analysis was performed using either Stata-17 or R software packages, as appropriate.

Results: The CTree analysis identified a single RF with significant prognostic impact: the Grey-Level-Run- Length-Matrix run variance (GLRLMrv), which is a marker of metabolic heterogeneity (MH). Patients with low MH (GLRLMrv <0.137) had a 93% progression-free survival (PFS) rate at 5 years, while those with high MH had a 65% PFS rate (log-rank test, $p < 0.0001$). Overall survival (OS) rates were 96% and 80%, respectively (log-rank test, $p < 0.0001$).

A subsequent CTree analysis was conducted, including GLRLMrv, as well as other dichotomized clinical variables and PET metrics that had a significant association with PFS ($p < 0.05$) at univariable analysis (TLG, MTV, SUVmax, SUVpeak, maximal lesion diameter stage, sex, LDH, and number of extra-nodal localizations). The CTree selection generated a new prognostic model based on the combination of GLRLMrv and TLG, which discriminated patients with different PFS and OS ($p < 0.0001$ for both). Concordance probability estimate showed a higher predictive accuracy (highest Harrell's C value) of this radiomic model in comparison with the main international prognostic indices, namely IPI, revised-IPI and age-adjusted IPI. The better discriminatory power was also confirmed by its lowest Akaike's information criterion.

Conclusions: A radiomic prognostic model based on TLG and MH identifies patients at high risk of disease progression more accurately than the standard clinical indices. The results of this study could have important implications for identifying patients who may benefit from different treatments, and for improving overall outcomes for PMBCL patients.

The research was funded in part by grants from the Swiss National Science Foundation (SNSF) – Project 32003B_146931,



Outcome of 495 primary mediastinal B cell lymphoma patients enrolled in the IELSG37 study and treated with rituximab and doxorubicine-containing regimens (with or without radiotherapy) according to a PET-derived prognostic model that integrates the total tumor glycolysis (TLG) and a radomic feature of metabolic heterogeneity (GLRLMrv). Median follow up, 64 months.

Krebsforschung Schweiz – Project KFS-2852-08-2011 and Cancer Research UK (C30423/A16247) The enrolment of Swiss patients was supported by the Swiss Group for Clinical Cancer Research (SAKK). This analysis was funded by a grant from the Swiss Cancer League KLS-5406-08-2021.

Keywords: diagnostic and prognostic biomarkers, PET-CT

No conflicts of interests pertinent to the abstract.

055 | RISK STRATIFICATION OF DLBCL WITH MVED2 SCORE USING INTEGRATIVE HOST ADIPOSE DENSITY AND METABOLIC TUMOR CHARACTERISTICS COMPARED TO OTHER INDEXES

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Introduction: The prognosis of diffuse large B-cell lymphoma (DLBCL) is assessed by the International Prognostic Index (IPI). Since 1993 developments in diagnosis and therapy have improved the prognosis of DLBCL, especially for high-risk groups. Although IPI remains prognostic, its ability to estimate treatment failure has reduced. FDG-PET-CT has been routinely implemented to evaluate the lymphoma extent at baseline and the metabolic response during treatment. At baseline, FDG-PET-CT also quantifies more accurately the tumor burden by two metabolic measures, the total metabolic tumor volume (TMTV) and the distance between 2 lesions (SDmax), and a host parameter, the lumbar subcutaneous adipose density (LSAD). We recently demonstrated that the MVED2 score (**TMTV**, **E**COG PS, **SD**Max, LSA**D**) allowed to discriminate the very high-risk DLBCL pts. The aim of this analysis was to compare the performance of **MVED^2 score** to the IPI and other prognostic scores for DLBCL, NCCN IPI, international metabolic prognostic index (IMPI), and the ECOG/TMTV score.

Methods: Pts were included in the REMARC study (NCT01122472), DLBCL >60–80 years old, responder to R-CHOP randomized between lenalidomide or placebo maintenance. The discriminatory power measured by C-index was compared between the **MVED^2 score** (0.59 (if **TMTV** > 220**)** + 0.57 (if **E**COG PS ≥ 2) + 0.76 (if **SD**Max > 32) + 0.70 (if LSA**D** > −90)) and the other scores.

Results: 273 patients were analyzed. According to the **MVED^2 score**, 10% of the patients were classified into the high-risk category, compared to 38% into the high-risk (4–5) IPI, 14% high-risk NCCN IPI, 10% into the IMPI, and 10% into the high-risk ECOG-PS score. The **MVED^2 score** had a significant impact on PFS ($p < 0.001$) and OS ($p < 0.001$). The MVED2 score allowed better identification of pts with shorter PFS and OS than did the IPI, the NCCN IPI, the IMPI, and the ECOG-PS score. The MVED2 score displayed higher model performance than IPI and the other scores, showing a higher C-index for both PFS and OS (Table 1).

Conclusion: The **MVED^2 score** outperforms IPI, NCCN IPI, IMPI, and TMTV/ECOG score, and enables individualized estimates of pts outcome.

Keyword: risk models

No conflicts of interests pertinent to the abstract.

	Score MVED[2]	IPI	NCCN IPI	Score IMPI	Score ECOG PS/TMTV
Low	177 (65%)	76 (28%)	70 (27%)	161 (59%)	109 (40%)
Inter	68 (25%)	92 (34%)	155 (59%)	84 (31%)	136 (50%)
High	28 (10%)	103 (38%)	36 (14%)	28 (10%)	28 (10%)
PFS					
VPP*	68%	37%	38%	50%	54%
VPN**	75%	76%	72%	73%	73%
C-Index/AIC	0.668/734	0.615/757	0.582/782	0.638/751	0.650/750
Median PFS for High risk (months)***	15.6 (9.6-26.2)	60.9 (36.3-NR)	NR (24.7-NR)	30.1 (10.1-NR)	30.1 (11.7-NR)
OS					
VPP*	50%	25%	28%	39%	43%
VPN**	85%	86%	83%	84%	84%
C-Index	0.689	0.622	0.609	0.644	0.682

*H risk pts with event/total—** L and I risk pts without PFS/total—*** 95% CI

056 | BASELINE SUV AND EARLY RESPONSE, BUT NOT MTV, ARE ASSOCIATED WITH OUTCOME IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA PATIENTS TREATED WITH NIVOLUMAB IN THE CHECKMATE 205 TRIAL

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Introduction: PD-1 blockade is effective in relapsed/refractory classical Hodgkin lymphoma (R/R cHL). To date, early metabolic response has been the best predictor of outcome in this setting. In this study, we explored additional baseline and early FDG PET-CT parameters as potential prognosticators in patients with R/R cHL treated with single agent nivolumab in the CHECKMATE 205 trial.

Methods: Available PET-CT scans from patients without progression (by IRC Lugano 2007 criteria) by week (wk) 17 were retrospectively reviewed by 2 readers blinded to outcome. Baseline and wk17 metabolic parameters in tumour and healthy tissues uninvolved by lymphoma were examined for their association with PFS using Cox regression.

Results: Baseline scans have been reviewed to date for 57 patients, and 49 patients at wk17 from 19 centres, with median follow up 60.7 months. There was a significant association between baseline maximum standardised uptake value (SUV) and PFS [HR 1.48 (95% CI 1.09–2.02) $p = 0.012$], wk17 Deauville score (DS) [Log-rank trend $p = 0.0008$] and Lugano response [HR 4.83 PMR vs. CMR (1.37–17.03) $p = 0.014$]. There was possible but non-significant association between the maximum distance between lesions at baseline and PFS ($p = 0.07$), but not for baseline metabolic tumour volume (MTV), wk17 MTV, change in MTV or change in SUVmax. Interestingly, baseline bone marrow and splenic uptake in *uninvolved* organs were associated with PFS, but not uptake in other uninvolved organs (liver, mediastinal blood pool, bowel, skeletal muscle and adipose tissue). The effect of baseline SUVmax remained very similar even in Lugano responders (CMR/PMR, $n = 33$) at wk17 HR 1.45 (95% CI 0.90—2.33) 1.45 (95% CI 0.90–2.33), though with the reduced sample size ($n = 33$) did not reach significance $p = 0.13$.

Conclusion: Baseline SUVmax and week 17 PET-CT response in this prospectively acquired clinical trial dataset, but not MTV, were significantly associated with PFS in patients with R/R HL treated with nivolumab. The lack of an apparent prognostic impact of MTV contrasts with its prognostic value in chemotherapy-based treatments, and lends caution for trial designs using checkpoint-based treatment that stratify patients based on MTV. Baseline uptake in uninvolved bone marrow and spleen, which may reflect immune activation state, may be potential biomarkers of immunological response with checkpoint inhibitors. This phenomenon, and the underlying immunologic mechanism, warrant further exploration.

Keywords: diagnostic and prognostic biomarkers, Hodgkin lymphoma, PET-CT

Conflicts of interests pertinent to the abstract

D. Grootendorst

Employment or leadership position: Director of Global Oncology Imaging Bristol Myers Squibb

A. Akyol

Employment or leadership position: Employee Bristol Myers Squibb
Stock ownership: Bristol Myers Squibb

057 | DYNAMICS OF RADIOMIC FEATURES FOLLOWING BRIDGING THERAPY DETERMINE CD19 CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY OUTCOME

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Introduction: Higher disease burden is associated with poor chimeric antigen receptor T-cell (CAR T) outcomes. Bridging therapy (BT) is widely used to debulk or palliate between apheresis and CAR T infusion. We studied whether the dynamics of radiomic cytoreduction during bridging are prognostic.

Methods: Large B-cell lymphoma (LBCL) patients (pts) treated with anti-CD19 CAR T cells were stratified into 4 BT groups: (1) no BT (2) systemic therapy (ST) (including steroids) (3) radiotherapy (RT) and (4) combined ST/RT. To better assess the impact of BT, we created an MTV analysis cohort of pts who received BT and had repeat PET post-BT but pre-CAR T infusion. Max SUV and total metabolic tumor volume (MTV) using an automated method and SUV4 threshold were calculated for all pts off the pre-apheresis PET and for the analysis cohort on the post-BT PET. Pts in the analysis cohort were ordered into equal sized tertiles by absolute MTV amount first pre-apheresis and then again post-BT. To quantify impact of BT cytoreduction, we created 5 risk groups from the analysis cohort per degree of MTV change during BT: (a) High MTV (highest MTV tertile both pre and post BT) (b) Mid MTV (middle tertile pre and post BT) (c) Low MTV (lowest tertile pre and post BT) (d) Improved MTV (tertile decreased post BT) and (e) Progressing MTV (tertile increased post BT). Overall survival (OS) post-CAR T was estimated by Kaplan Meier.

Results: 198 pts with LBCL (80%), high grade BCL (17%) or primary mediastinal BCL (3%) received CAR T (49% axicabtagene, 32% tisagenlecleucel, 19% lisocabtagene). Max SUV at apheresis was 18.5 (interquartile range, IQR 9.8 – 25.3) and MTV was 45.7 (IQR 5.7–167). 51 (26%) received no BT, 116 (59%) had ST, 20 (10%) had RT, 11 (6%) had ST/RT. Median OS was 13.9 mo overall, and 20.6 mo, 12.1 mo, 26.4 mo and 5.5 mo for the no BT, ST, RT and ST/RT groups, respectively.

The MTV analysis cohort included 112/147 BT (76%) pts ($n = 88$ ST, $n = 16$ RT, $n = 8$ CMT). Median baseline max SUV was 20.0 (IQR 13.7—26.1), which was reduced 28% to 14.4 (IQR 5.5—22.1) post-BT. Median baseline MTV was 67.2cc (IQR 15.0—218.7) which was reduced 42% to 39.0cc (IQR 2.1—235.2) post-BT. Roughly half (53%) had any degree of quantitative cytoreduction post-BT (Figure A). The MTV burden both pre-apheresis and post-BT was significantly associated with post-CAR T OS (Figure B, C, $p = 0.004$, $p < 0.0001$, respectively). Median OS for the High MTV ($n = 22$), Mid MTV ($n = 17$) and Low MTV ($n = 22$), Improved MTV ($n = 24$) and Progressing MTV ($n = 27$) risk groups was 4.1, 15.5, 21.6, 13.6 and 10.1 mo, respectively (Figure D).

Conclusion: In our real-world experience, while most had BT, many did not have successful disease cytoreduction prior to CAR T cells. While disease extent both pre-apheresis and post-BT are prognostic, the quantitative dynamics of BT cytoreduction may further refine prognostic ability. BT responders have better outcomes while stably high or rising MTV through BT is associated with poor prognosis.

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Keywords: cellular therapies, PET-CT, radiation therapy

Conflicts of interests pertinent to the abstract

G. L. Shah

Consultant or advisory role: DSMB for ArcellX
Research funding: Research funding to the institution from Janssen, Amgen, Beyond Spring, and BMS

P. B. Dahi

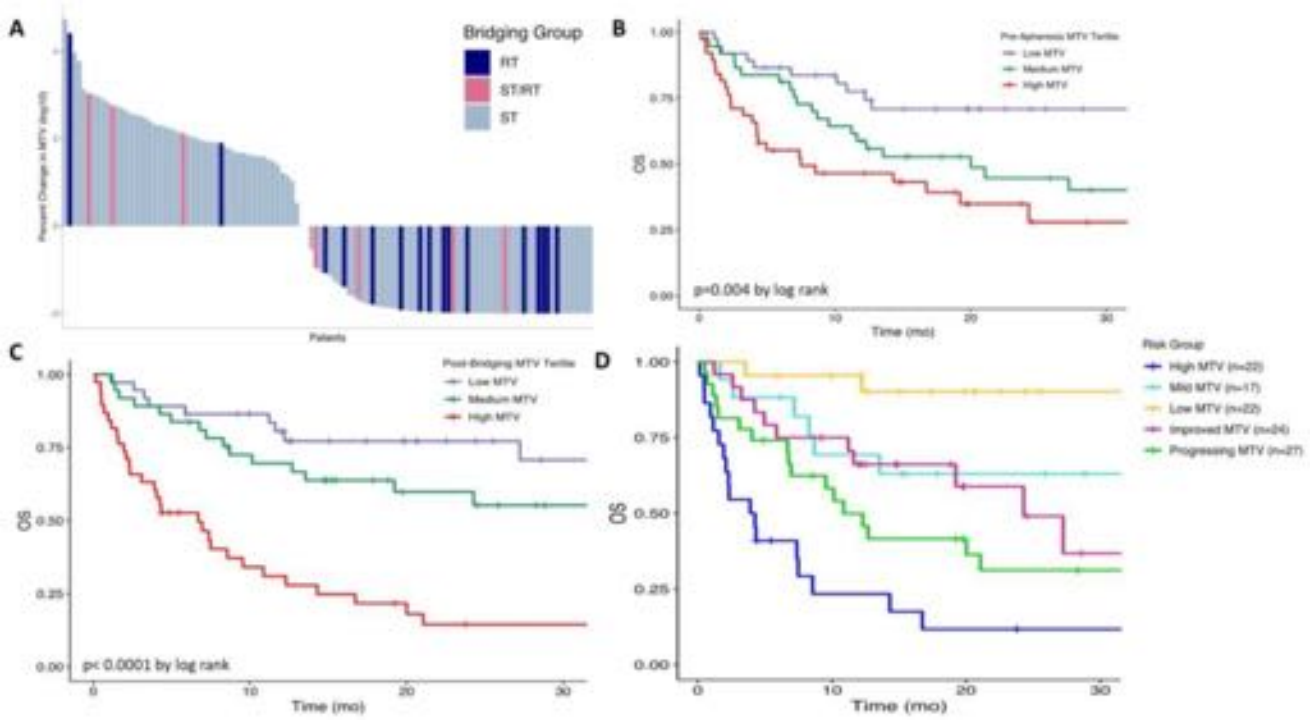
Consultant or advisory role: Curio Science LLC, Kite Pharmaceuticals, OncLive, Targeted Oncology

S. Giralt

Consultant or advisory role: Amgen, Actinuum, Celgene, Johnson & Johnson, Janssen, JAZZ Pharmaceuticals, Takeda, Novartis, Kite, Spectrum Pharma
Research funding: Amgen, Actinuum, Celgene, Johnson & Johnson, Miltenyi, Takeda, Omeros

M. Scordo

Consultant or advisory role: McKinsey & Company, Angiocrine Bioscience, Inc., and Omeros Corporation, Kite – A Gilead Company
Honoraria: i3Health and Medscape for CME-related activity
Research funding: Angiocrine Bioscience, Inc., and Omeros Corporation



G. Salles
Consultant or advisory role: Abbvie, Atbtherapeutics, Bayer, Beigene, BMS/Celgene, Debiopharm, Epizyme, Genentech/Roche, Genmab, Incyte, Ipsen, Janssen, Kite/Gilead, Loxo/Lilly, Molecular Partners, Morphosys, Nordic Nanovector, Novartis, Regeneron, Takeda
Stock ownership: Owkin

M. L. Palomba
Consultant or advisory role: Synthekine, Cellectar, Beigene, Kite, BMS

M. Perales
Consultant or advisory role: on DSMBs for Cidara Therapeutics, Medigene, and Sellas Life Sciences, and the scientific advisory board of NexImmune
Stock ownership: NexImmune, Omeros and OrcaBio
Honoraria: Adicet, Allovir, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equilium, Exevir, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Syncopation, VectivBio AG, and Vor Biopharma
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058 | RADIOMICS REFLECTING BOTH TUMOR AND HOST FEATURES IMPROVES OUTCOME PREDICTION IN FOLLICULAR LYMPHOMA

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Introduction: To date, several indices widely based on simple clinical or biologic parameters have been proposed to refine prognosis of follicular lymphoma (FL). The prognostic value of 18F-FDG PET/CT parameters such as Total Metabolic Tumor Volume (TMTV) remains

controversial. Here, we explored the prognostic impact of additional features obtained from 18F-FDG PET/CT images in patients included in the phase III RELEVANCE trial (Morschhauser, NEJM 2018, JCO 2022), which compared rituximab-chemotherapy (R-chemo) with rituximab-lenalidomide (R2) in patients with previously untreated, high tumor burden FL.

Methods: Baseline 18F-FDG PET/CT scans and clinical information (ECOG, age, Ann Arbor stage, and FLIPI) were available for 351 follicular lymphoma patients. Lesions were segmented semi-automatically by expert physicians on the PET/CT scans. Deep learning tools (TotalSegmentator and MOOSE) were used to automatically segment organs from PET-registered CT scans. A total of 7437 PET and CT features were calculated, including tumor radiomics from segmented lesions and host radiomics from segmented organs and correlated to PFS and OS. To select predictive features, a permutation test was used to ensure that less than one false positive was selected. Highly correlated features were dropped to reduce feature redundancy and only features significantly predictive of both PFS and OS were selected. Finally, a Cox model was trained and evaluated in a 10x10 nested cross-validation with feature selection and hyperparameters tuning performed in the inner loop. Averaged time-dependent ROC-AUC (tAUC) was used to assess the prognostic value of the different features and models. Three models with different feature sets were built: basic (clinical features and TMTV), tumor (clinical features, TMTV, and tumor radiomics), and global (clinical features, TMTV, tumor radiomics, and host radiomics).

Results: Median number of selected tumor features was 5, reflecting tumor metabolic activity, and tissue densities measured on CT in lesion surroundings. They had an average univariate tAUC of 0.56 $\pm$ 0.03 for PFS and 0.59 $\pm$ 0.01 for OS. Median number of selected organ features was 2 with an averaged tAUC of 0.56 $\pm$ 0.04 for PFS and 0.60$\pm$0.06 for OS. Selected features reflected FDG uptake magnitude in liver, lung and kidney density. The basic model reached a tAUC of 0.58$\pm$0.04 for PFS and 0.65$\pm$0.05 for OS. The tumor model led to tAUC of 0.59 $\pm$ 0.04 for PFS and 0.67 $\pm$ 0.06 for OS. The global model yielded to a tAUC of 0.63 $\pm$ 0.04 for PFS and 0.72 $\pm$ 0.05 for OS. Global model was significantly better than clinical on both PFS and OS ($p < 0.01$) while tumor model was significantly better than basic model on PFS ($p < 0.01$) but not on OS ($p < 0.27$).

Conclusions: Our study suggests that radiomics features complementary to TMTV derived from baseline 18F-FDG PET/CT scans can improve outcome prediction for follicular lymphoma patients.

Keywords: diagnostic and prognostic biomarkers, indolent non-Hodgkin lymphoma, PET-CT

Conflicts of interests pertinent to the abstract

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Employment or leadership position: PhD student employee of Siemens Healthineers

SESSION 10 - HODGKIN LYMPHOMA

059 | GENETICALLY DISTINCT PATHOGENESIS OF EPSTEIN-BARR VIRUS (EBV)-POSITIVE VERSUS EBV-NEGATIVE CLASSICAL HODGKIN (CHL) LYMPHOMA

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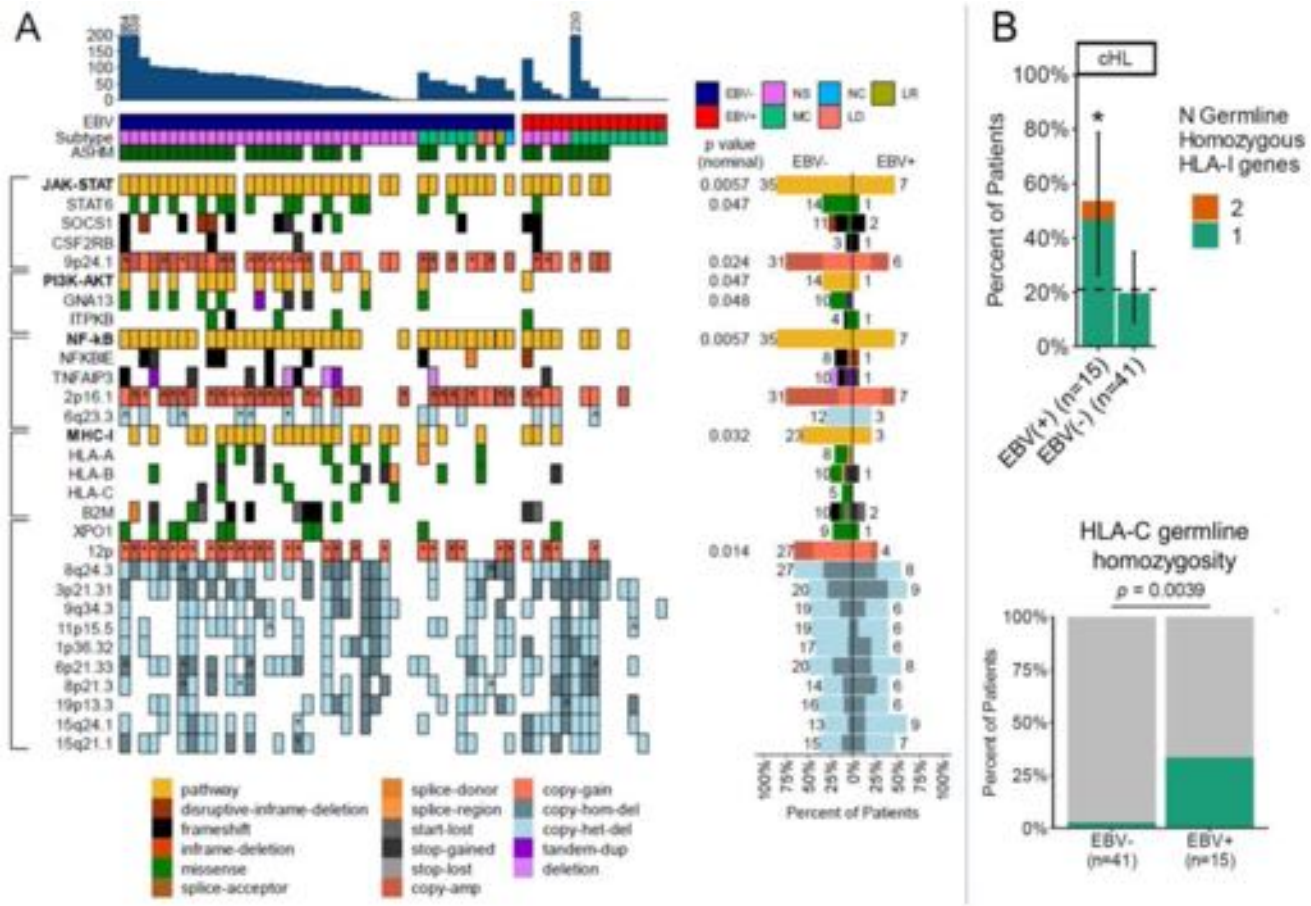
Introduction: Latent EBV infection of the cHL clone is more frequent in the mixed-cellularity (MC) histological subtype, in early childhood and older adulthood, and in developing countries. Based on these and other epidemiologic features, EBV+ cHL has been hypothesized to have distinct etiology and pathogenesis compared to EBV− cHL. However, the landscape of genetic lesions in the EBV+ cHL genome is incompletely defined.

Methods: We studied 57 cHL cases (10–83 year-old; 41 EBV−, 16 EBV+) by whole-exome sequencing/WES ($n = 56$ cases; 34 from Tiacci et al. Blood 2018; 18 from Wienand et al. Blood Adv 2019; and 4 cases newly added) and/or whole-genome sequencing/WGS (32 cases newly processed, including 31 also subjected to WES). Tumor and normal cells were purified from frozen samples by microdissection ($n = 39$; 9 EBV+, 30 EBV−) or flow cytometry ($n = 18$; 7 EBV+, 11 EBV−). EBV+ and EBV- cases were sequenced at identical median depths (WGS 44X; WES 146X) and subjected to the same bioinformatics pipelines.

Results: Clonal nonsynonymous somatic mutations were much fewer in EBV+ versus EBV− cHL (median 4.5 vs. 57; $p = 0.0013$), and the same was observed for total mutations genome-wide (median 112 vs. 6826; $p < 0.0001$). In contrast, within EBV− cHL, MC ($n = 6$) and non-MC ($n = 33$) cases had similar mutation load ($p = 0.56$), indicating a link with viral status rather than histological subtype. AID-associated mutational signatures were stronger in EBV− versus EBV+ cHL, both genome-wide (SBS9, $q = 0.069$; SBS85, $q = 0.023$) and in the target region of 126 genes known to undergo AID-driven aberrant somatic hypermutation (median of 4 vs. 0 mutations/Mb; $p = 0.045$).

Compared to EBV− cHL, EBV+ cHL had fewer mutations or copy number alterations in ≥1 genes of multiple pathways that drive cHL pathogenesis and can be activated by EBV latent proteins (possibly surrogating cellular genetic lesions). In particular (Figure A): (i) JAK-STAT signaling genes STAT6, SOCS1, CSF2RB and JAK2 were mutated in 85% EBV− versus 47% EBV+ cases ($p = 0.0057$); (ii) PI3K-AKT signaling genes GNA13 and ITPKB were mutated in 34% EBV−



versus 7% EBV+ cases ($p = 0.047$); and (iii) NF-κB signaling genes TNFAIP3, NFKBIE and REL were mutated in 85% EBV− versus 47% EBV+ cases ($p = 0.0057$).

EBV− cHL had also more frequent mutations of the MHC-I genes B2M and HLA-A/B/C (56% vs. 20% in EBV+ cHL, $p = 0.0032$; Figure A), possibly to prevent presentation of tumor neo-antigens generated by the much higher mutation burden. In contrast (Figure B), EBV+ cases showed germline homozygosity of ≥1 HLA-I genes more often than EBV− cases (53% vs. 19%; $p < 0.05$), particularly for HLA-C (33% vs. 2%; $p = 0.0039$), which may predispose to development of EBV+ cHL through a reduced diversity of HLA-I alleles available for viral antigen presentation.

Conclusions: In the largest series characterized genome-wide to date, EBV+ and EBV− cHL genetically diverged in their germline and somatic routes to lymphoma development.

Encore Abstract - previously submitted to EHA 2023

Keywords: genomics, epigenomics, and other-omics, Hodgkin lymphoma, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

* K. Gomez and G. Schiavoni are co-first authors.

^ R. Rabadan and Tiacci are co-last authors.

060 | DISTINCT HODGKIN LYMPHOMA SUBTYPES IDENTIFIED BY NONINVASIVE GENOMIC PROFILING

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Introduction: The scarcity of malignant Reed-Sternberg cells has hampered comprehensive genomic profiling of classic Hodgkin lymphoma (cHL) as might inform personalized therapeutic strategies. Since profiling of circulating tumor DNA (ctDNA) has shown utility in non-Hodgkin lymphoma genotyping and risk stratification, we employed a noninvasive approach in cHL to overcome challenges imposed by low tumor fractions.

Methods: We profiled baseline plasma samples from 366 patients diagnosed with cHL, 99% of whom were enrolled prior to anti-lymphoma therapy. Median age was 32 (range 4–88), 48% had advanced stage (III/IV) disease, and among the subset with early stage (I/II) disease (52%), 91% had unfavorable GHSG risk. We applied CAPP-Seq and Whole Exome Sequencing (WES) to explore noninvasive genotypes. Whole exome genotypes were generated using a novel gradient boosting model from mutation and cfDNA fragmentomic features. Distinct cHL genetic subtypes were identified by lexical clustering through Latent Dirichlet Allocation.

Results: We first profiled all pretreatment samples using a 576-kb capture panel targeting genes recurrently mutated in cHL and other B-cell lymphomas. 293 patients (80% of cases) were evaluable for noninvasive genotyping and clustering analyses. We additionally used WES to profile a subset of patients ($n = 119$; 41%) enriched for samples with higher plasma allelic fractions. We then integrated somatic copy-number aberrations (SCNAs) with non-silent somatic mutation calls as weighted features to discover 2 dominant genetic subtypes. Cluster H1 comprised ~68% of cases and was dominated by somatic mutations in genes canonically involved in NFκB, JAK/STAT, and PI3K signaling. Conversely, cluster H2 (~32% of cases) was characterized by a variety of SCNA events as well as mutations in *TP53*, *KMT2D*, and *BCL2* (Figure A). H1 tumors had a significantly higher somatic mutational burden, while H2 tumors had a larger fraction of their genome affected by SCNAs (both $p < 0.001$, Figure B, C). Patients with H2 subtype demonstrated the known bimodal age distribution of cHL with an early peak in the 20s and a second peak at >60 years. In contrast, H1 tumors predominantly occurred in younger patients ($p = 0.02$, Figure D). Patients with an H2 genotype were predominantly male ($p = 0.007$), enriched for EBV positive tumors ($p < 0.0001$, Figure **E**) and mixed cellularity subtype ($p = 0.01$, Figure F). Importantly, patients with the H2 subtype had inferior clinical outcomes ($p < 0.01$, Figure G) independent of high ctDNA levels (Hazard ratio 2.0, $p < 0.05$). Exploration of transcriptional differences between genetic subtypes using invasive and noninvasive methods are under way and will be presented at the meeting.

Conclusions: With our novel non-invasive approach, we overcome known challenges in cHL profiling and delineate molecularly distinct cHL subtypes with clinical and prognostic correlates.

The research was funded by: National Cancer Institute (R01CA257655 and R01CA233975).

Keywords: genomics, epigenomics, and other-omics, Hodgkin lymphoma, liquid biopsy

Conflicts of interests pertinent to the abstract

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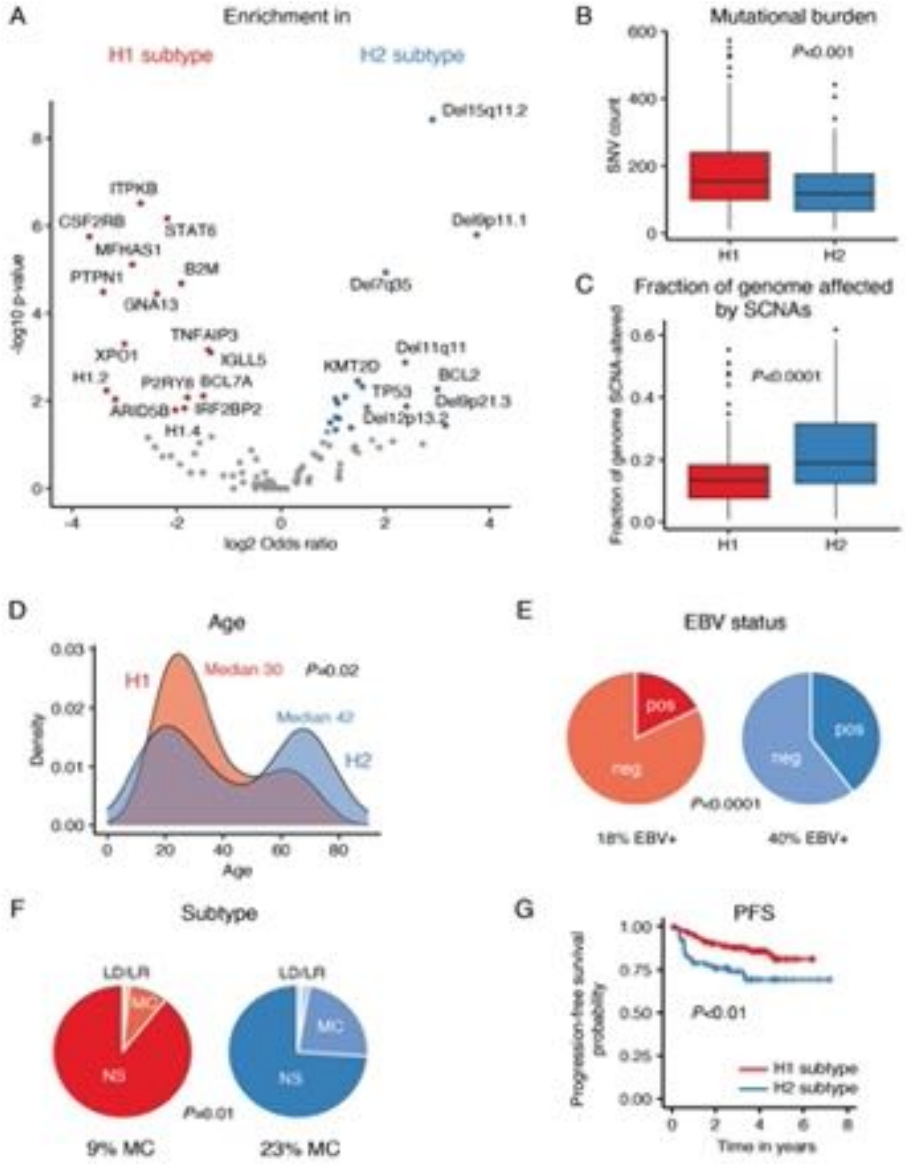

Genetic subtypes in Classic Hodgkin Lymphoma identified from noninvasive profiling. (A) Volcano plot summarizing differentially altered genetic features between cluster H1 (red, left) and cluster H2 (blue, right). Genetic features with significant p-values ($P<0.05$) are highlighted in red and blue, respectively. **(B)** Single nucleotide variant mutational burden, **(C)** Fraction of genome affected by somatic copy number aberrations (SCNA), **(D)** Age distribution, **(E)** EBV status, **(F)** Histological subtype (NS: nodular sclerosis, MC: mixed cellularity, LR/LD: lymphocyte rich/depleted), and **(G)** Progression-free survival (PFS) stratified by genetic subtype.

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Stock ownership: Syncopation, Foresight Diagnostics, Gilead, Cibermed

Research funding: BMS

061 | DUAL TARGETING OF HODGKIN'S LYMPHOMA BY ANTI-CD30 CAR-T CELLS CO-TRANSDUCED WITH AN ANTI-PDL1 COSTIMULATORY RECEPTOR TO OVERCOME THE IMMUNOSUPPRESSIVE MICROENVIRONMENT

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Background: Classic Hodgkin's lymphoma (cHL) has generally a good prognosis, but patients primary refractory or relapsed after auto-transplant have a poor outcome. Clinical trials of CD30 CAR-T cells in relapsed/refractory (r/r) cHL showed inferior results compared to CD19 CAR-T cells in non-Hodgkin lymphomas. CD30 CAR-T cell failure in r/r cHL may be related to PDL1 overexpression by tumor cells and/or the tumor microenvironment causing T cell anergy, exhaustion and apoptosis. To overcome this issue, we propose (Figure 1A) to engineer T cells to coexpress 2nd-generation anti-CD30 CAR (CD28-based) and anti-PDL1 costimulatory chimeric receptor (CCR, 4.1BB-based) devoid of signaling domain. The CD30 CAR would preserve the MHC-independent tumor cytotoxicity while the non-cytotoxic PDL1 CCR would avoid exhaustion signals, competing with the endogenous PD-1 receptor for PD-L1 engagement on tumor and/or immunosuppressive cells, mimicking an anti-PD1 immune checkpoint inhibitor effect.

Methods: Single chain fragment variable (scFv) sequences from 5 newly generated anti-CD30 mAbs were selected by surface plasmon resonance to identify the one with the highest affinity. Anti-PDL1 scFv was developed to specifically recognize the extracellular portion which interacts functionally with the cognate PD-1. Single (controls) and double targeting CAR transgenes were cloned in lentiviral vectors.

Results: CD30 and PDL1 target recognition was initially optimized exploring the in vitro activity of several CD30 (CD28) and PD-L1 (4.1BB) CARs differing for spacer length (Figure 1B). Untransduced T cells were included as controls together with single-targeting PDL1 CCR to confirm the inability of the PDL1 CCR to induce T cell effector functions per se. We next generated a bicistronic dual-targeting construct with the best spacers (CH3 for CD30 CAR and CD8 for PDL1 CCR) to be compared (Figure 1C) with single-targeting CD30 CAR in long term assays at unfavourable E:T ratio (0.25:1). After 96 h of coculture with the CD30+/PDL1+ HD-LM2 cHL cell line, dual CD30.CAR/PDL1.CCR T cells showed higher cytotoxicity (mean 85.5% vs. 60.2%), enhanced T cell proliferation (mean 66.8% vs. 43%), reduced differentiated T cell memory phenotype (mean central memory population 29.2% vs. 19.1%) and less PD1 expression (mean 22.2% vs. 30,3%), as compared to single CD30.CAR T cells.

Conclusions: A self-replicating and constitutive biological treatment that continuously target the PD1/PDL1 immunosuppressive pathway in situ could be a new strategy to boost immune attack in the immunosuppressive microenvironment of cHL, matching T cell activity and PD-1/PD-L1 blockade at the same time. Further investigations are required to confirm early findings and explore if this approach could also enhance T cell persistence in vivo through the 4.1BB stimulation triggered by PDL1+ cells.

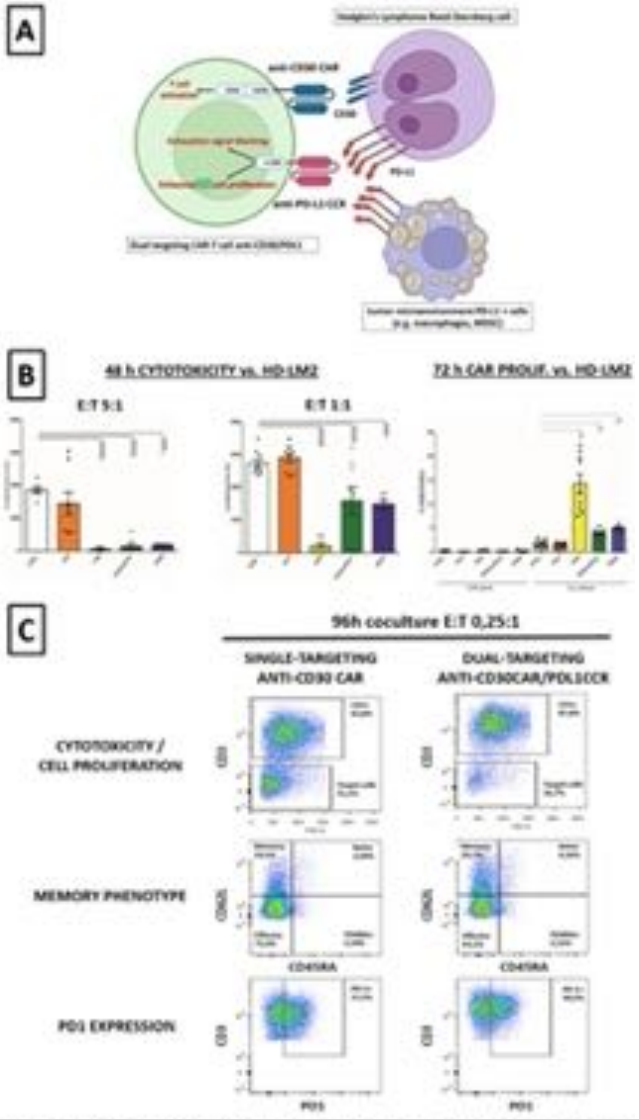

Figure 1. A) Anti-CD30/PD-L1 dual strategy. The anti-CD30 CAR would retain MHC-independent cytotoxicity against CD30+ HRS cells, overcoming MHC downregulation. The anti-PDL1 CCR could avoid cell exhaustion signals, competing with endogenous PD-1 for PD-L1 engagement on HRS tumor and PD-L1+ microenvironmental cells (macrophages and myeloid-derived suppressor cells, MDSC). **B) Example of spacer optimization on anti-PD-L1 CAR-T cells.** CD8 spacer anti-PDL1 CARs display the highest in vitro activity among other constructs, differing for spacer length, against PD-L1+ HDLM-2 cHL cell line (n=3 donors). The same approach has been used also for anti-CD30 CAR spacer optimization. **C) Representative long-term (96h) coculture assay upon challenging single or dual targeting CARs with HD-LM2 HL cell line.** Dual anti-CD30.CAR/PDL1.CCR showed higher T cell proliferation and enhance killing against cHL cells as compared to single targeting CD30.CAR with equal spacer (CH3). Of note, dual CD123 anti-CD30.CAR/PDL1.CCR have more central memory T cells and less PD1 expression as compared to single CD30.CARs.

* E. Tiacci and B. Falini are co-last authors

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Keywords: cellular therapies, Hodgkin lymphoma, targeting the tumor microenvironment

No conflicts of interests pertinent to the abstract.

062 | THE PROGNOSTIC IMPACT OF CLINICAL FACTORS AND IMMUNOARCHITECTURAL PATTERNS FOR NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA: AN INTERNATIONAL STUDY BY GLOW

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Introduction: Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare entity. Studies evaluating outcomes for patients of all ages with scoring of immunoarchitectural patterns (IAPs) are needed to inform optimal management. We sought to perform an international multicenter study of pediatric and adult patients with all stages of NLPHL to develop a prognostic model and assess the impact of IAP.

Methods: Thirty-seven centers participated in the **G**lobal n**L**PHL **O**ne **W**orking Group (GLOW) to retrospectively identify cases of NLPHL diagnosed from 1992 to 2021. Pathology was reviewed at individual centers with scoring of IAPs when available. For analysis, the presence of any variant IAP pattern (C-F) in biopsies were scored as variant cases. We measured progression-free survival (PFS), overall survival (OS), transformation rate, and lymphoma-specific death rate. We performed uni- and multivariable (MVA) Cox regression stratified by management type to select factors for inclusion in the lymphocyte-predominant international prognostic score (LP-IPS). Time-dependent ROC modeling was used to test model performance with bootstrapping for internal validation. Analyses were two-tailed and significant with $p < 0.05$ (R version 4.2.2).

Results: We identified 2193 patients with a median age of 37 years (quartiles: 2–23, >23–37, >37–51, >51). Median follow up was 6.3 years (IQR = 3.5–10.8). Most patients were male (74.8%) and had stage I-II (73.3%) disease. A minority had B-symptoms (9.9%) or splenic involvement (5.1%) at presentation. IAP data was available for 916 patients (41%), of which 73.8% were pattern A/B, 8.5% C, 9.0% D, 7.3% E, and 1.4% F. Upfront management included: chemotherapy alone (32.0%), combined modality therapy (30.9%), radiotherapy alone (24.0%), observation after excision (4.6%), rituximab alone (4.0%), active surveillance (3.4%), and rituximab and radiotherapy (1.1%). PFS, OS, transformation, and lymphoma-specific death rates at 10 years

were 71.1%, 91.7%, 4.9%, and 3.2% respectively. Individual IAPs were not significantly associated with PFS or OS on MVA, but pattern E was significantly associated with higher risk of transformation on MVA (HR = 1.81, p = 9.2e-3). Based on our MVA, model AUC statistics, and similar HR sizes, we developed the LP-IPS which assigns 1 point each for age ≥45, stage III–IV, Hb < 10.5 g/dL, or splenic involvement. Increasing LP-IPS was significantly associated with worse PFS (HR = 1.53), OS (HR = 2.34), lymphoma specific death (HR = 2.67), and higher rates of transformation (HR = 1.53) per risk point ($p < 0.05$).

Conclusions: In the largest cohort of patients with NLPHL of all ages and stages to date, we developed a prognostic model to identify patients at highest risk of progression, transformation, and death. Outcomes for the different management groups will be reported, and our findings will inform design of prospective clinical trials through GLOW.

Keywords: diagnostic and prognostic biomarkers, Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

K. J. Savage
Employment or leadership position: Beigene
Consultant or advisory role: Celgene, Seagen, BMS, Merck, Gilead, Astra Zeneca, Janssen, Abbvie
Honoraria: BMS, Merck, Gilead, Astra Zeneca, Janssen, Abbvie
Other remuneration: DSMC: Regeneron

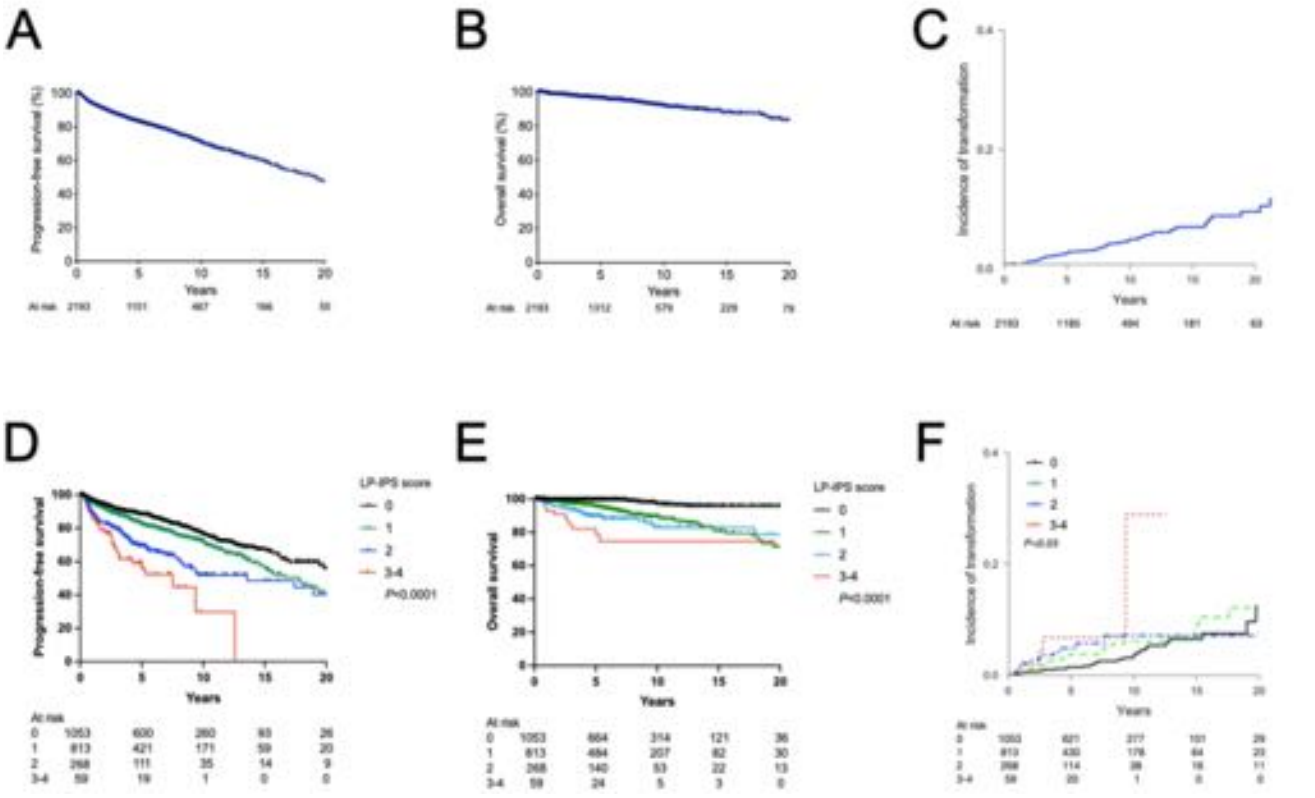
F. Vega
Research funding: CRISP Therapeutics, Allogene, and Geron corporation
Other remuneration: supported by a R01CA222918 from the National Cancer Institute

A. Prica
Honoraria: Astra-Zeneca, Abbvie, Kite Gilead

D. Talaulikar
Honoraria: Roche, Janssen, Beigene, MSL, EUSA, CSL, Amgen
Research funding: Roche, Janssen, Beigene, MSL, EUSA, CSL, Amgen

D. A. Eichenauer
Honoraria: Takeda and Sanofi-Genzyme

Figure 1. Outcomes for the entire cohort. Panels A, B, and C, demonstrate progression-free survival, overall survival, and incidence of transformation, respectively. Panels D, E, and F demonstrate the progression-free survival, overall survival, and incidence of transformation stratified by the lymphocyte-predominant international prognostic score (LP-IPS).



SESSION 11 - MARGINAL ZONE LYMPHOMA

063 | MARGINAL ZONE LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (MZL-IPI): A PROGNOSTIC SCORE FOR THE ENTIRE SPECTRUM OF MARGINAL ZONE LYMPHOMAS. A FIL AND SPORE-MER STUDY

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Background: Marginal zone lymphomas (MZL) include extranodal (ENMZL), nodal (NMZL), and splenic (SMZL) subtypes. While MZL subtypes have largely been studied as separate entities, most clinical trials evaluate MZL as a single entity. In this setting, a prognostic score for all MZL would be very useful.

Methods: We analyzed patients that were prospectively enrolled in the NF10 observational study with the aim to define a prognostic score for all MZL. We included adult patients with MZL who started a systemic therapy. For the purposes of this study, patients were classified as SMZL, ENMZL and NMZL according to pathologic diagnosis. Patients without a clear pattern of organ involvement were categorized as disseminated MZL (dissMZL). The primary study endpoint was progression-free survival (PFS) which was calculated from the date of treatment start. For validation, we applied the same inclusion criteria and model used for the NF10 study to an independent cohort of patients from the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE) Molecular Epidemiology Resource (MER).

Results: Starting from the NF10 study, we identified 501 eligible patients: 166 SMZL (33%), 197 ENMZL (39%), 60 NMZL (12%) and 78 dissMZL (16%). At presentation, 40% of the patients were >70 years old, 80% were stage III-IV, 31% had elevated LDH, 41% had Hb <12 g/dl, 20% had lymphopenia (absolute lymphocyte count $<1 \times 10^{9/L}$), and 14% had platelets $<100 \times 10^{9/L}$. After a median follow-up of 61 months, 5-year(y) PFS was 72% (95% CI 68%–76%). In the final multivariate model, elevated LDH, anemia, lymphopenia, thrombocytopenia, and subtype (NMZL or dissMZL) were independently associated with a worse PFS. A prognostic model was then built with those 5 factors, and patients were classified into low (LRG, 0 factors, 27%), intermediate (IRG, 1–2 factors, 57%) and high (HRG, 3+ factors, 16%) risk groups. 5y PFS was 85% for the LRG, 66% for IRG, and 37% for HRG (Figure), with c-Harrell = 0.64 and robust internal validation and calibration. Compared to the LRG, the IRG (Hazard Ratio [HR] = 2.30, 95% CI 1.39–3.80) and HRG (HR = 5.41, 95% CI 3.12–9.38) had inferior PFS. In the validation using the MER cohort of 192 MZL patients, 5y PFS was 57% (95% CI 51–64). Applying the MZL-IPI to the MER, 41(21%), 113 (59%), and 38 (20%) patients were classified as LRG, IRG, and HRG, respectively. The MZL-IPI was associated with PFS (log-rank test $p = 0.043$; c-Harrell = 0.60, 95% CI 0.55–0.66); compared to the LRG, the IRG (HR = 1.57, 95% CI 0.97–2.54) and HRG (HR = 2.04, 95% CI 1.15–3.62) had inferior PFS. In both the training and the validation studies, MZL-IPI was associated with the best prediction and discrimination performance, as compared to the IPI, FLIPI and MALT-IPI, and was also prognostic for overall survival.

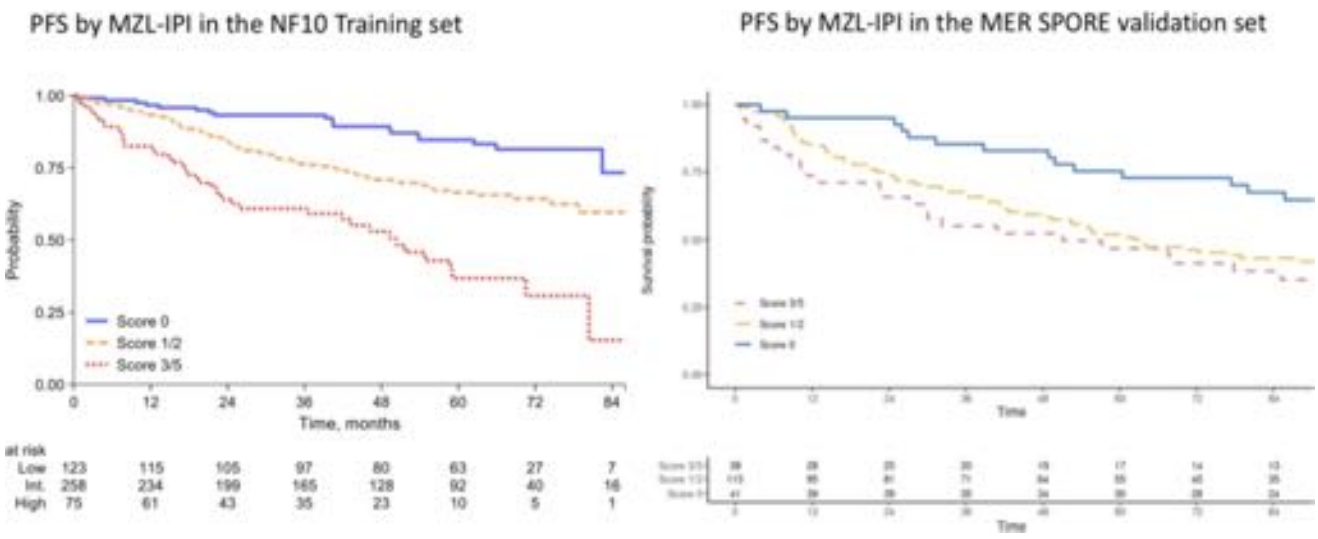
Conclusions: MZL-IPI is a new validated prognostic score for all patients with MZL who are considered for systemic treatment.

Keywords: indolent non-Hodgkin lymphoma, risk models

Conflicts of interests pertinent to the abstract

S. Luminari

Consultant or advisory role: Roche, Jannsen, Incyte, Gilead, Beigene, BMS, Regeneron



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Consultant or advisory role: Janssen, EUSA Pharma, Incyte, Clinigen, Italfarmaco

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Research funding: Janssen, Gilead, Morphosys, Beigene

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Honoraria: EUSA Pharma, Novartis

Research funding: Gilead Sciences

064 | STAGING FDG-AVIDITY IN EXTRANODAL MARGINAL ZONE LYMPHOMA (EMZL) BY DISEASE LOCATION

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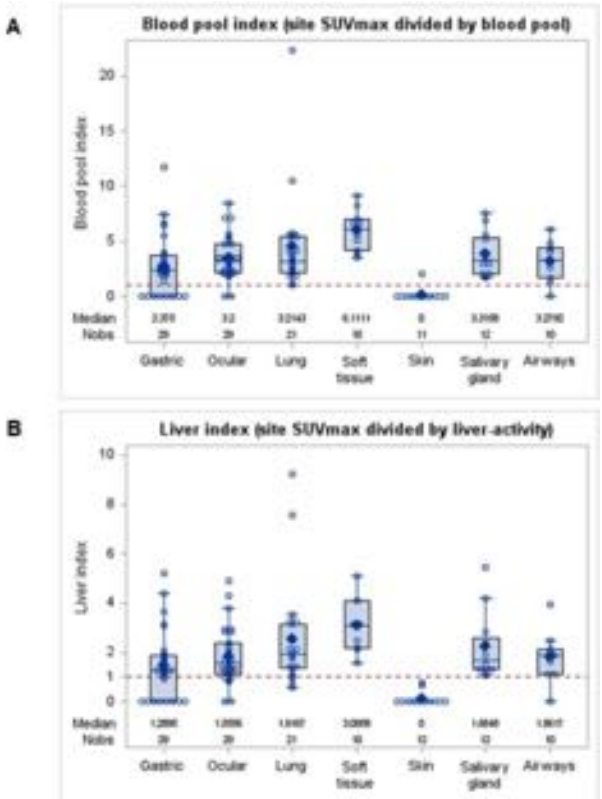
Introduction: Fluorodeoxyglucose (FDG)-PET/CT is the standard imaging modality to assess initial tumor burden and response to therapy in lymphoma. FDG-avidity in EMZL remains unclear with variability by extranodal locations. Thus, the current Lugano staging suggested to use CT scans in EMZL. Recent data is challenging this suggestion. Thus, we evaluated FDG-avidity in EMZL using a large MZL database.

Methods: We assessed the University of Miami MZL database searching for patients with staging PET/CT. Currently, this database includes 715 patients with 578 (80.8%) patients with EMZL; 152 (26.3%) have staging PET/CT and were analyzed. Patients with high-grade transformation at diagnosis were excluded. In patients with >1 extranodal site, each location was counted independently providing a total of 187 locations. PET/CTs were reviewed by expert radiologists to ascertain tumor and not surrounding tissue avidity, with specific attention to ocular and GI locations; if scans were not available (n = 15), we retrieved data from reports. GI involvement was defined as focal uptake above normal physiologic GI activity. We considered FDG-avid disease if SUVmax was ≥2 and calculated ratios between lymphoma SUVmax with mediastinal blood pool (BP index) and liver background (Liver index).

Results: This cohort includes 152 patients (2/2016–1/2023) with EMZL. Most patients were women (n = 88, 58%), median age 62 years (range 33–83), and Hispanics (n = 77, 51%). LDH was largely normal (n = 126, 83%) with most patients having early-stage disease (n = 98, 64%). Among 187 EMZL locations, most common were gastric (n = 33,17.6%), ocular (n = 31, 16.6%), lung (n = 30, 16%), skin and soft tissue (n = 16, 8.6%, each), salivary gland (n = 13, 7%), airways (n = 11, 5.9%), and breast (n = 9, 4.8%). Most common FDG-avid locations (SUVmax ≥2) were salivary gland (100%), soft tissue (93.8%), lung (93.3%), ocular (93.5%, with conjunctiva FDG-avid in 75%), airways (90.9%), bone (83.3%), GI-nongastric (80%), gastric (72.7%), and breast (44.4%). Skin (93.8%) was a largely non-FDG avid location (Table 1). Median size of FDG-avid lesions was 2.4cm (range, 0.7–17.4). All 22 patients with multiple mucosal sites demonstrated FDG-avidity in at least one site, and 17 across all sites. In patients with data about background FDG avidity (n = 150), a BP index and Liver index ≥1 detected lymphoma in 79.3% and 71.5%, respectively. Both indexes failed to identify skin and breast EMZL (Figure 1A,B).

Location by SUVmax (n=187 locations in 152 patients)						
	Total		SUVmax ≥2		SUVmax <2	
	N	%	N	%	N	%
Total	187	100.0	146	78.1	41	21.9
Location						
Gastric	33	17.6	24	72.7	9	27.3
Ocular	31	16.6	29	93.5	2	6.5
Lung	30	16.0	28	93.3	2	6.7
Skin	16	8.6	1	6.3	15	93.8
Soft tissue	16	8.6	15	93.8	1	6.3
Salivary gland	13	7.0	13	100.0	-	-
Airways	11	5.9	10	90.9	1	9.1
Breast	9	4.8	4	44.4	5	55.6
Bone	6	3.2	5	83.3	1	16.7
Colon	6	3.2	3	50.0	3	50.0
GI-non gastric	5	2.7	4	80.0	1	20.0
Liver	4	2.1	4	100.0	-	-
Tongue	2	1.1	2	100.0	-	-
Thyroid	2	1.1	2	100.0	-	-
Pancreas	1	0.5	-	-	1	100.0
GU	1	0.5	1	100.0	-	-
Adrenal gland	1	0.5	1	100.0	-	-



Conclusions: In this large study we showed that EMZL is largely an FDG-avid disease and PET/CT should be included in the staging of these patients. Furthermore, we observed that patients with multiple mucosal disease uniformly possess FDG-avidity across most extranodal sites providing insight into the biology of this entity. A lower SUV threshold for diagnosis and modification of current response assessment by Lugano classification may be needed in EMZL.

The research was funded by: Sylvester Comprehensive Cancer Center National Cancer Institute (NCI) core grant P30CA240139

Keywords: extranodal non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, PET-CT

No conflicts of interests pertinent to the abstract.

065 | RITUXIMAB AND IBRUTINIB COMBINATION IS SAFE AND EFFECTIVE IN UNTREATED SPLENIC AND NODAL MARGINAL ZONE LYMPHOMAS: PLANNED SUBSET ANALYSIS OF THE IELSG47/MALIBU PHASE II STUDY

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Introduction: Although in a phase III trial of extranodal MZL (EMZL) patients (pts) the combination of rituximab and chlorambucil had superior progression-free and event-free survival (PFS, EFS)

compared to either drug given alone (Zucca et al. JCO 2016), there is no standard front-line therapy for MZL pts requiring systemic treatment, and no randomized trial specifically addressed initial treatment for the splenic (SMZL) and nodal (NMZL) MZL subtypes. BTK inhibitors have shown durable responses with a favorable benefit-risk profile for all MZL subtypes in the relapsed setting. The ongoing IELSG47/MALIBU phase II trial is exploring efficacy and safety of rituximab plus ibrutinib in untreated MZL, with a focus on EMZL. We report here a planned preliminary analysis of the response and toxicity in the exploratory cohort of SMZL and NMZL pts.

Methods: Treatment was comprised of 8 rituximab doses (the first 4 weekly and the subsequent 4 monthly, all but the first given subcutaneously) in combination with ibrutinib (560 mg once daily) for 2 years. Response evaluation was planned at 6, 24 weeks, and 12, 18, and 24 months after treatment start and was performed using Matutes criteria in SMZL and Lugano Classification in NMZL.

Results: Between October 2019 and June 2021, 45 pts (30 with SMZL and 15 with NMZL) were enrolled from 16 centers in France, Italy, and Switzerland. Median age was 68 years (range: 44–81), 17 pts were male (38%), 41 pts had stage IV (91%), and 17 had elevated LDH (38%). All SMZL and 9 (60%) NMZL pts had bone marrow involvement. The best objective response reached in the entire cohort at any time was complete response (CR) in 22 pts (49%) and partial response (PR) in 19 pts (42%). Of the 36 pts currently evaluable for response at 12 months, 18 (50%) had a CR and 15 (42%) had a PR, while 3 (8%) had disease progression. The median time to best response was 2 months (range: 1–20). At a median follow-up of 23 months, 7 pts relapsed (1 SMZL and 6 NMZL) with a median duration of response of 18 months (range: 1–28 +); 3 pts died (due to SARS-CoV2 infection, ischemic stroke, and car accident, respectively). The 2-year overall survival (OS) rate was 92% (95% CI: 75–97), with no significant difference between SMZL and NMZL. Median PFS was 24 months in the NMZL subset and was not reached among SMZL pts ($p = 0.0133$). The 2-year PFS was 77% (95% CI: 59–88) in the whole cohort, 86% (95% CI: 62%–95%) in SMZL, and 59% (95% CI: 27–81) in NMZL. Treatment was generally well-tolerated, with the most frequent grade 3–4 adverse events being neutropenia (reported in nine pts [20%]) and cutaneous rash (reported in four pts [9%]). Grade 3 atrial fibrillation or hypertension were reported in one (2%) and two (4%) pts, respectively. Treatment was discontinued in 15 pts (33%) after a median of 8 months (range: 2–23): 3 due to progressive disease, 6 due to toxicities, 4 due to unrelated events (1 second primary tumor, 1 stroke, 1 car accident, 1 cold agglutinine disease) and 2 due to consent withdrawal.

Conclusions: The combination of rituximab and ibrutinib shows promising activity, especially in SMZL, with an acceptable toxicity profile.

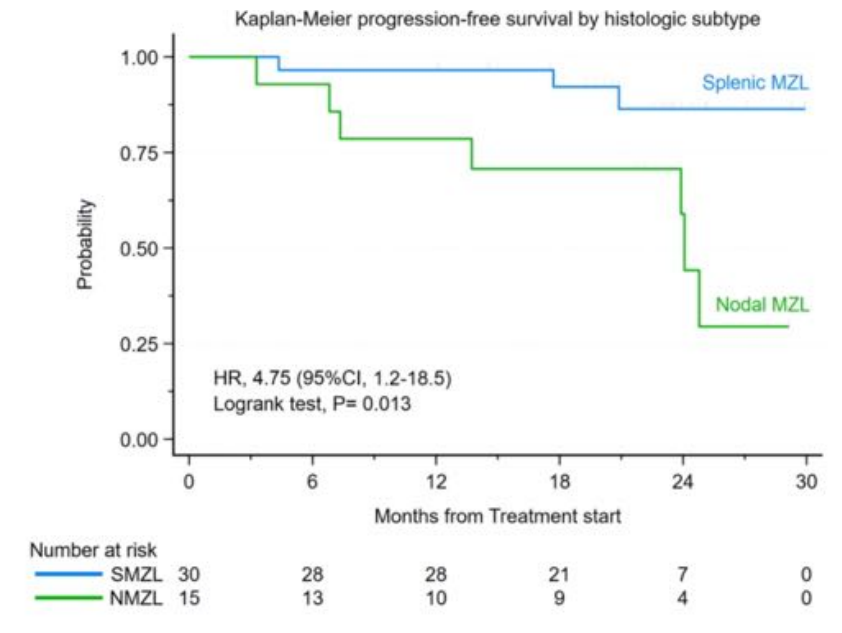
The research was funded by: The research was supported partially by Janssen (financial and drug supply) and Roche (drug supply)

Keywords: extranodal non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, molecular targeted therapies

Conflicts of interests pertinent to the abstract

C. Thieblemont

Honoraria: BMS, Gilead/Kyte, Novartis, Roche, Janssen, Incyte, Abbvie, Miltenyi



IELSG47/MALIBU phase II trial of rituximab and ibrutinib in untreated MZL
Planned subset analysis; median follow-up, 23 months

A. Tedeschi
Consultant or advisory role: Astrazeneca, Janssen, Beigene, Abbvie

A. Stathis
Consultant or advisory role: Janssen, Roche
Research funding: Abbvie, ADC Therapeutics, Amgen, AstraZeneca, Bayer, Cellestia, Incyte, LoxoOncology, Merck, Novartis, Pfizer, Philogen, Roche
Educational grants: AstraZeneca
Other remuneration: Expert testimonies from Bayer, Eli/Lilly

S. Luminari
Consultant or advisory role: Jannsen, Novartis, Beigene, BMS, Gilead, Regeneron, Genmab, Incyte

L. Arcaini
Consultant or advisory role: Roche, Janssen-Cilag, Verastem, Incyte, EUSA Pharma, Celgene/Bristol Myers Squibb, Kite/Gilead, ADC Therapeutics
Research funding: Gilead Sciences
Other remuneration: Speakers' Bureau of EUSA Pharma, Novartis

O. Casasnovas
Consultant or advisory role: Roche, Takeda, BMS, Merck, Gilead, Janssen, ADC therapeutics, Incyte, Astra Zeneca
Honoraria: Roche, Takeda, BMS, Merck, Gilead, Janssen, ADC therapeutics, Incyte, Astra Zeneca
Research funding: Roche, Takeda, Gilead, Abbvie
Educational grants: Roche, Takeda, Janssen, Abbvie

E. Zucca
Consultant or advisory role: from BeiGene, BMS/Celgene, Celltion Healthcare, Curis, Eli/Lilly, Incyte, Ipsen, Janssen, Kyte (a Gilead Company), Merck, Roche
Research funding: AstraZeneca, BMS/Celgene, Incyte, Janssen, Merck and Roche
Educational grants: Abbvie, BeiGene, Janssen and Roche.

A. Conconi
Consultant or advisory role: Regeneron
Other remuneration: speaker fees from Roche, Abbvie, Incyte, Takeda, AstraZeneca

066 | THE IELSG39 TRIAL: EFFICACY OF FIRST-LINE CHLAMYDIA PSITTACI ERADICATION WITH A SIX-MONTH REGIMEN OF DOXYCYCLINE IN PATIENTS WITH STAGE-I MALT LYMPHOMA OF THE OCULAR ADNEXAE

A. J. M. Ferreri[1], M. C. Sassone[1], M. G. Cangi[2], G. Magliacane[2], S. Zanussi[3], F. Marino[1], E. Flospergher[1], N. Vicari[4], L. Bongiovanni[2], E. Dal Cin[2], F. Cavallo[5], F. Re[6], A. Anastasia[7], D. Mannina[8], R. Bassan[9], D Vallisa[10], A. Pulsoni[11], L. Bonomini[12], F. Bertoni[12], R. Dolcetti[3], E. Zucca[13], M. Ponzoni[14]
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Introduction: In geographical areas where ocular adnexal MALT lymphoma (OAML) is frequently associated with *Chlamydia psittaci* (Cp) infection, monotherapy with a 3-week regimen of doxycycline has been associated with an overall response rate (ORR) of 65% and a 2-year progression-free survival (PFS) of 60% (IELSG27 trial; Ferreri, *et al.* JCO 2012). However, successful Cp eradication has been achieved only in half of patients (pts), which strongly conditioned therapeutic results. This could be explained by the well-known prolonged persistence of Cp within macrophages under the form of elementary bodies, a metabolically inert condition, refractory to antibiotics. Accordingly, a prolonged exposure to effective antibiotics could result in a higher bacterial eradication rate and better lymphoma control. This hypothesis was tested in a multicentre phase II trial (IELSG39), where OAML pts were treated with a six-month regimen of doxycycline. Herein, we report primary endpoint results.
Methods: HIV-negative adults with untreated stage-IEA OAML were enrolled and treated with doxycycline 100 mg twice daily for 4 weeks followed by 4 weeks rest, repeated for 3 times. Cp DNA was assessed by real-time PCR on tumor tissue at diagnosis and monitored on conjunctival swabs and PBMC every 6 months. Tumor response (orbit MRI & ophthalmologist exam) was assessed every 6 months. The primary endpoint was the 2-year PFS; the primary objective was to improve the 2-yr PFS achieved in the IELSG27 trial (60%; P0) to 75% (P1). To detect such a difference, 30 pts with *Cp*-positive OAML were required (one-sided test; α 5%; β 80%); whenever ≥17 pts with Cp-pos OAMZL were progression-free at 2 years, the experimental therapy would be considered effective.
Results: 44 pts (median age 58 yo, range 31–85; male:female ratio 0.63) were enrolled between March 2013 and May 2016. Cp DNA was detected in 21 (64%) of 33 assessed pts; PCR analysis is ongoing in 11. Doxycycline was well tolerated; all pts completed the treatment in the planned time. The best objective response was complete in 14 pts and partial in 14, with an ORR of 64% (95% CI = 50–78). The median time to the best response was 9 months (range 3–34).

The primary endpoint was met: 32 pts remain relapse-free at 2 years: 18 had a Cp-pos OAML, 7 were Cp-neg, and PCR results are pending in 7. At a median follow-up of 83 months (range 10–115), 23 pts remain relapse-free, with a 2- and 5-yr PFS of 75% (95% CI 74–77) and 55% (95% CI 49–59), respectively. Pts with Cp-pos OAML had a 2- and 5-yr PFS of 90% (95% CI 90–91) and 65% (95% CI 61–69). All pts are alive. Full data on bacterial eradication rate and monitoring will be presented at the congress.

Conclusions: This six-month regimen of doxycycline was safe and effective in pts with stage-I OAML. This treatment achieved the predetermined efficacy threshold and compares favourably with the 3-week regimen used in the IELSG27 trial, suggesting that a prolonged exposure to antibiotics improves lymphoma control.

Keywords: extranodal non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, Therapeutics and Clinical Trials in Lymphoma - Other

No conflicts of interests pertinent to the abstract.

067 | IMMUNOTHERAPY ALONE VERSUS CHEMOIMMUNOTHERAPY AS FIRST-LINE TREATMENT OF MARGINAL ZONE LYMPHOMA (MZL): A REAL-WORLD ANALYSIS

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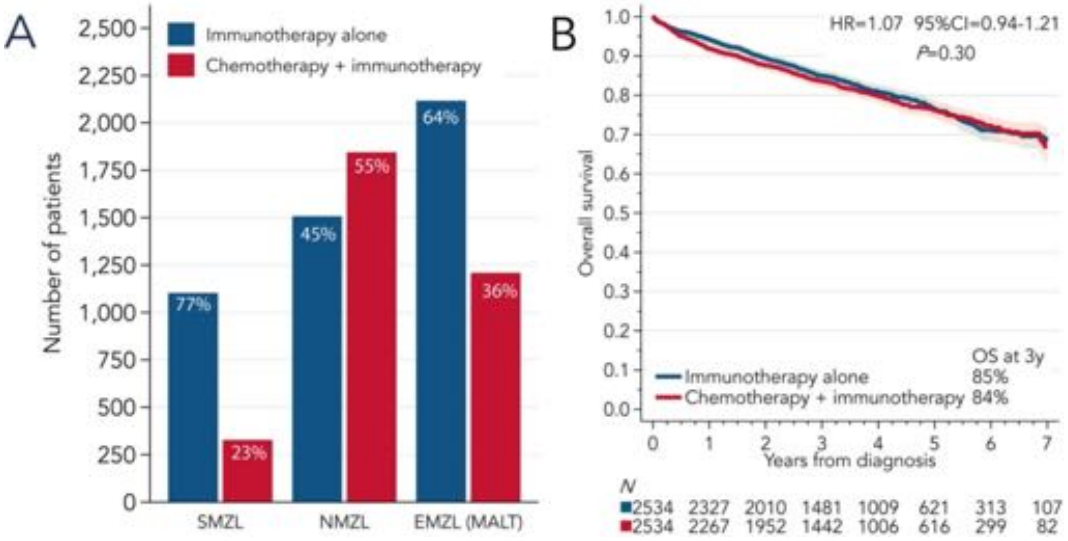
[1]*Brown University, Medicine, Providence, Rhode Island, USA*, [2]*Ohio State University, Columbus, Ohio, USA*, [3]*MD Anderson Cancer Center, Houston, Texas, USA*, [4]*Rhode Island Hospital, Hematology-Oncology, Providence, Rhode Island, USA*

Introduction: First-line treatment options for MZL include immunotherapy alone (Imm: most commonly, rituximab) or chemoimmunotherapy (Ch+Imm: typically, rituximab with alkylator-based regimens). Phase 2 trials support either approach, but comparative evidence is lacking considering the rarity of MZL and its multiple subtypes encompassing splenic (SMZL), nodal (NMZL), and extranodal MZL (EMZL).

Methods: We examined overall survival (OS) after Imm alone or with Ch+Imm for newly diagnosed MZL using 2013–2018 data from the National Cancer Data Base—a hospital-based registry that includes histology, treatment, and OS data from >70% of lymphomas diagnosed in the United States (US). Patients receiving no systemic therapy or only chemotherapy without Imm were excluded. Specific Imm or Ch+Imm agents, laboratory tests, or progression-free survival were not available from the database. We matched groups receiving Imm or Ch+Imm in a 1:1 ratio using a propensity score to minimize treatment selection bias. OS was compared in a Cox model, reporting hazard ratio (HR) with 95% confidence intervals (CI). Separate matching was also fitted in histologic subgroups.

Results: Among 8110 patients (median age 67 years; 56% women; 18% SMZL, 41% NMZL, and 41% EMZL), 58% received first-line Imm and 42% Ch+Imm. These proportions were stable between 2013 and 2018. Patients selected for Ch+Imm were on average younger, more often male, with NMZL (rather than SMZL/EMZL; Figure A), stage 3/4 disease, or B-symptoms. The groups did not significantly differ by comorbidity index or socioeconomic factors. We noted a preference in each hospital for Imm or Ch+Imm ($p < 0.0001$ for a random intercept model)—but no significant differences between academic or community hospitals. We matched 5068 patients receiving Imm or Ch+Imm, eliminating differences by all available confounding factors. In the matched cohort, median OS was not reached, and 3-year OS did not significantly differ between Imm (84.9%; 95% CI, 83.4–86.3) or Ch+Imm (83.6%; 95% CI, 82.0–85.0), with a HR = 1.07 (95% CI, 0.94–1.21; Figure B). There was no significant heterogeneity in subgroups defined by propensity score quintile or age. Using matching

Figure: (A) number of patients with histologic subtypes of MZL receiving first line treatment with immunotherapy alone or chemotherapy with immunotherapy; percentages in each subtype are listed; (B) overall survival in the propensity score-matched cohort, according to first-line therapy received.
SMZL: splenic MZL; NMZL: nodal MZL; EMZL (MALT): extranodal MZL of mucosa-associated lymphoid tissue



within the histologic subtypes, we observed no significant difference in OS between Ch+Imm versus Imm in EMZL (HR = 1.06; 95% CI, 0.85–1.31) or NMZL (HR = 1.08; 95% CI, 0.91–1.28), whereas in SMZL patients receiving Ch+Imm had worse survival (HR = 1.42; 95% CI, 1.04–1.96).

Conclusions: In this real-word analysis including most US patients treated for MZL in 2013–2018, first-line Imm and Ch+Imm resulted in similar survival, except for SMZL where Ch+Imm was associated with worse outcome than Imm alone (possibly due to additional unfavorable molecular features prompting chemotherapy use, or increased toxicity). These results support Imm alone as first-line treatment for MZL and as a potential comparator arm in clinical trials.

The research was funded by: Leukemia and Lymphoma Society

Keywords: cancer health disparities, immunotherapy, indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

A. J. Olszewski

Consultant or advisory role: Schrodinger; TG Therapeutics; Genmab; BCBSRI

Research funding: Precision Bio; Adaptive Biotechnologies; Celldex; Acrotech Biopharma; Genentech

SESSION 12 - LYMPHOMA BIOLOGY

068 | BTG2 SUPER-ENHANCER MUTATIONS DISRUPT TFAP4 BINDING AND DYSREGULATE BTG2 EXPRESSION IN DIFFUSE LARGE B-CELL LYMPHOMA

E. Bal[1], P. De Simone[1], A. B. Holmes[1], L. Hilton[2], K. Basso[1], R. K. Soni[3], R. D. Morin[2], R. Dalla-Favera[1], L. Pasqualucci[1]

[1]*Columbia University, Institute for Cancer Genetics, New York, New York, USA*, [2]*Genome Sciences Center, BC Cancer Research Institute, Vancouver, Canada*, [3]*Proteomics and Macromolecular Crystallography Shared Resource, Columbia University, New York, New York, USA*

Introduction: Diffuse large B-cell lymphoma (DLBCL), the most common lymphoid malignancy, remains incurable in ~40% of patients. Coding-genome sequencing efforts identified several genes/pathways altered in this disease, as well as genetic subgroups of potential clinical relevance. However, the large non-coding portion of the genome remained largely unexplored. We recently identified a pervasive hypermutation mechanism targeting active super-enhancers (SEs) in >90% of DLBCL and leading to dysregulation of multiple genes, including well-known lymphoma oncogenes (Bal et al., Nature 2022). As evidence of oncogenic relevance, we demonstrated that mutational hotspots in the *BCL6*, *BCL2* and *CXCR4* SEs impair the binding of specific transcriptional repressors, preventing the gene negative regulation and creating oncogenic dependencies in DLBCL cells. Here we aimed to define the pathogenic role of mutations targeting the intragenic SE (iSE) of the *BTG2* gene, the second most commonly mutated in DLBCL. *BTG2* encodes a member of the B-cell translocation gene (BTG)/TOB family involved in transcriptional co-activation and modulation of mRNA abundance. *BTG2* is also a recurrent target of somatic missense mutations (6%–11% of DLBCL), suggesting a major role in the pathogenesis of this disease.

Methods: We screened 243 DLBCL cases for the presence of mutational hotspots within the *BTG2*-iSE, and combined in silico prediction, DNA-binding assays (Reverse-ChIP, electromobility-shift assay, ChIP-qPCR), RNA-seq and CRISPR/Cas9 editing approaches in isogenic *BTG2* mutant versus WT DLBCL cell lines to identify transcription factors bound to the SE and disrupted by the mutation.

Results: We identified a recurrent mutational cluster affecting the *BTG2*-iSE in 52/243 (21%) DLBCLs, with preferential enrichment in ST2 subgroup. CRISPR-Cas9 mediated correction of the mutation in 3 DLBCL cell lines led to counter selection and reduced *BTG2* expression, consistent with oncogenic addiction. In silico motif prediction and in vitro DNA-binding assays, followed by validation in multiple isogenic DLBCL cell lines, identified TFAP4 as a major transcription factor that binds to the WT, but not to the mutated site. TFAP4 is an important regulator of B-cell proliferation and cell fate decisions, which can function as a transcriptional activator or repressor in germinal center B-cells, and acts downstream of/in parallel with c-MYC. Of note, introduction of SE hotspot mutations in WT DLBCL cells was associated with increased *BTG2* expression, confirming a direct link between SE mutations and deregulated gene expression through escape from TFAP4-mediated suppression.

Conclusions: These findings suggest a major role for *BTG2* deregulation by SE aberrant somatic hypermutation in the pathogenesis and heterogeneity of DLBCL, with implications for precision classification and potential therapeutic targeting of DLBCL.

Keywords: aggressive B-cell non-Hodgkin lymphoma, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

069 | CLONAL ARCHITECTURE OF RELAPSED OR REFRACTORY FOLLICULAR HELPER T-CELL LYMPHOMA: AN ANCILLARY STUDY OF THE ORACLE TRIAL, A LYSA STUDY

R. Loyaux[1], N. Sako[1], V. Tran Quang[1], E. Bachy[2], F. Morschhauser[3], G. Cartron[4], R. Gressin[5], N. Daguindau[6], S. Le Gouill[7], A. Wolfromm[8], K. Bouabdallah[9], L. Ysebaert[10], O. Casasnovas[11], C. Robe[1], M. Delfau[1], J. Dupuis[1], L. De Leval[12], P. Gaulard[1], I. Sloma[1], F. Lemonnier[1]

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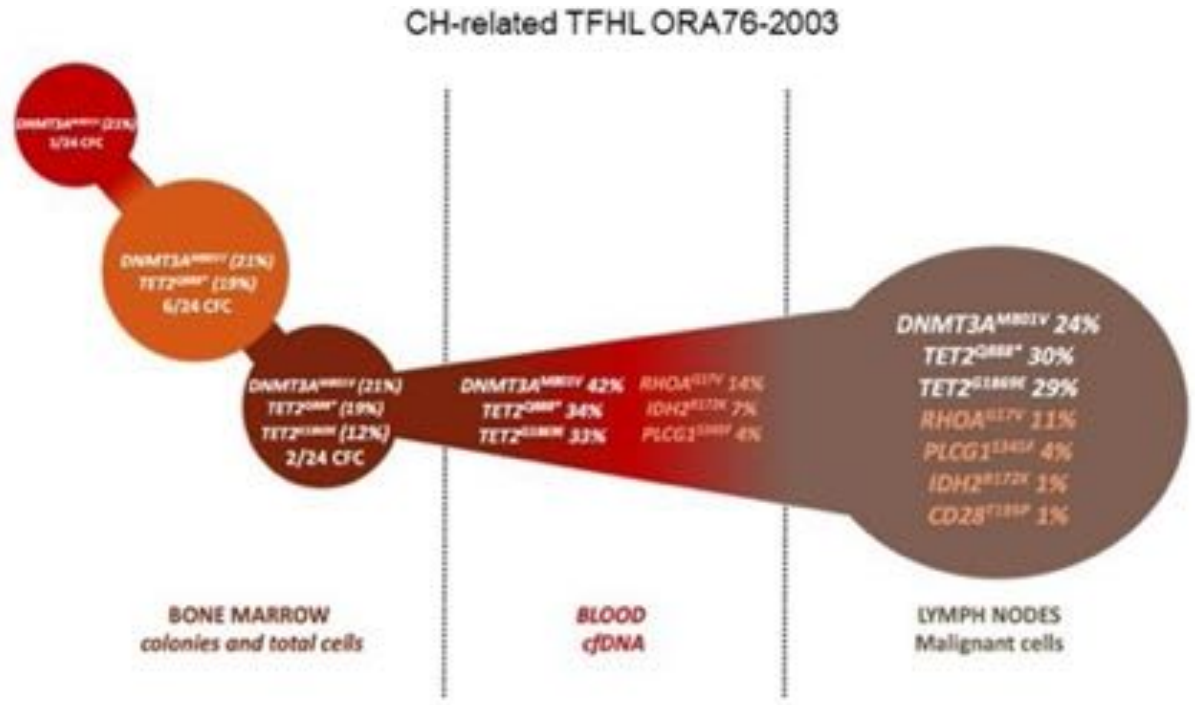
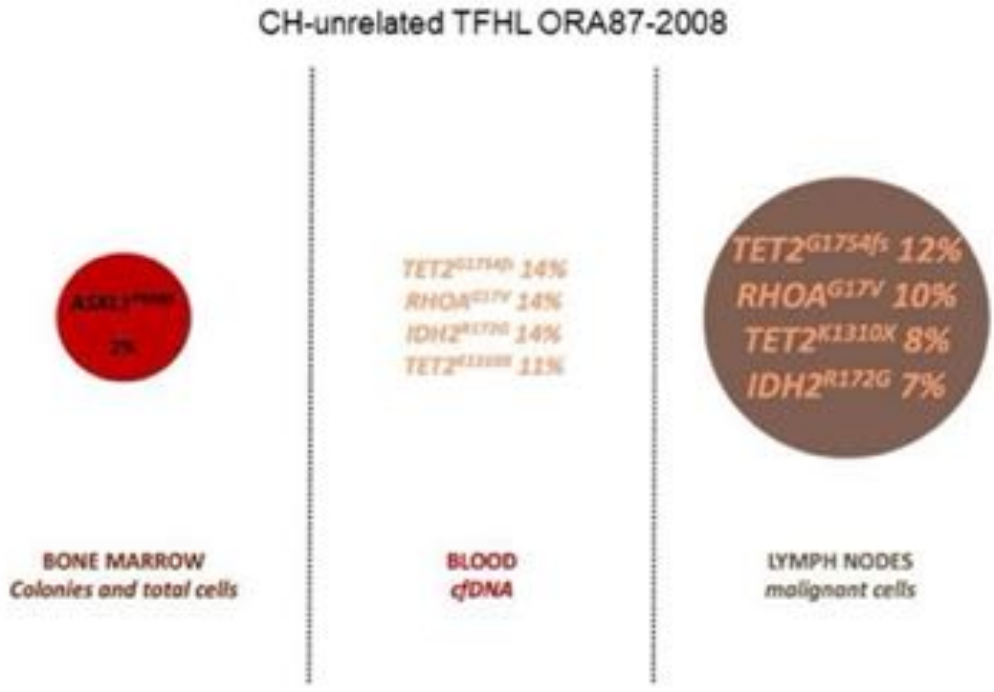
Follicular helper T-cell lymphoma (TFHL) results from the oncogenic transformation of a TFH cell, driven by mutations in genes involved in epigenetic regulation (*TET2*, *DNMT3A*, *IDH2*) and T-cell signaling (*RHOA*). Demonstration of *TET2* and *DNMT3A* mutations in B cells, myeloid cells, or hematopoietic progenitor cells have suggested that TFHL can emerge from clonal hematopoiesis (CH) in a multi-step process. However, the frequency, the extension, and the relevance of such CH in TFHL oncogenesis are unclear.

To describe and characterize the clonal architecture of refractory/relapsed (R/R) TFHL, we collected bone marrow samples of patients included in the ORACLE trial (NCT03593018), a phase 3 trial evaluating the oral 5-azacitidine (CC-486) compared to single-agent chemotherapy in patients with R/R TFHL. Bone marrow (BM) cells





from 32 patients at inclusion were cultured in methylcellulose supplemented with standard growth factors. BFU-E, CFU-GM, and CFU-GEMM were counted and individually harvested. A total of 517 colonies derived from the 32 patients were then individually genotyped by next-generation sequencing (NGS) using a capture-based panel (limit of detection: 1%) covering 43 genes recurrently mutated in CH and/or TFHL, including *TET2*, *DNMT3A*, *IDH2*, and *RHOA*. Meanwhile, bulk BM cells from 29 patients were sequenced with the same NGS panel and then compared to the mutations found in cfDNA (31 patients) and tumor biopsies (28 patients). Overall, the frequency of CH and the phylogenetic link between the myeloid progenitors and the TFHL was evaluable in 30 TFHL patients.

We successfully genotyped 471/517 (91%) colonies. CH defined by at least one somatic mutation detected in at least one myeloid colony or total BM cells was found in 29/30 (97%) patients. Among the 26/29 patients with mutated myeloid colonies, the median percentage of mutated colonies was 21% (IQR 7%–53%) and 7 had subclonal architecture with a median of 3 different clones. The 2 most frequent mutations were *DNMT3A* and *TET2*, detected in 24/30 (80%) and 18/30 (60%) patients' BM, respectively. We confirmed the absence of $RHOA^{G17V}$ and $IDH2^{R172}$ mutations in BM cells of TFHL patients. While 17/18 patients with a detectable *TET2* mutation in CH had a *TET2* mutated TFHL, only 13/23 patients with a *DNMT3A* mutated CH had a *DNMT3A* mutated TFHL. We thus identified 3 groups of patients according to the distribution of mutations found in the BM and the LN lymph nodes: 16/30 (53.3%) patients had a TFHL clonally derived from CH (CH-related TFHL), 13 (43.3%) had TFHL, and clonally distinct CH (CH-unrelated TFHL), and one patient (3.3%) had undetectable CH. No significant difference in patient outcome was observed regarding the presence of CH-related or unrelated TFHL, but our results are limited by the small number of patients and treatment heterogeneity.

In conclusion, CH is very frequent in TFHL, and more than half of them are TFHL-related.

Encore Abstract—previously submitted to EHA 2023

Keywords: aggressive T-cell non-Hodgkin lymphoma, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

070 | MOLECULAR CHARACTERIZATION CONTRIBUTES TO DIAGNOSIS AND PREDICTS OUTCOME IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMAS: A LYSA STUDY

V. Camus[1], P. Viailly[2], P. Sesques[3], F. Drieux[4], E. Veresezan[4], C. Haioun[5], E. Durot[6], M. Patey[7], C. Rossi[8], L. Martin[9], V. Rainville[2], E. Bohers[2], P. Ruminy[2], M. Viennot[2], J. Paillassa[10], O. Tournilhac[11], A. Willaume[12], C. Antier[13], J. Lazarovici[14], E. Lévêque[15], P. Decazes[16], S. Becker[16], D. Tonnelet[16], A. Berriolo-Riedinger[17], P. Gaulard[18], H. Tilly[1], T. J. Molina[19], A. Traverse-Glehen[20], F. Jardin[1]

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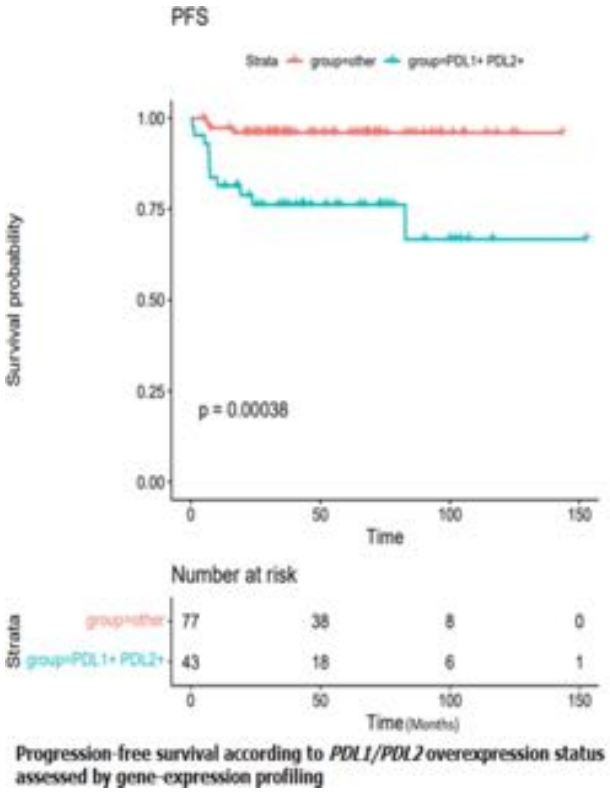
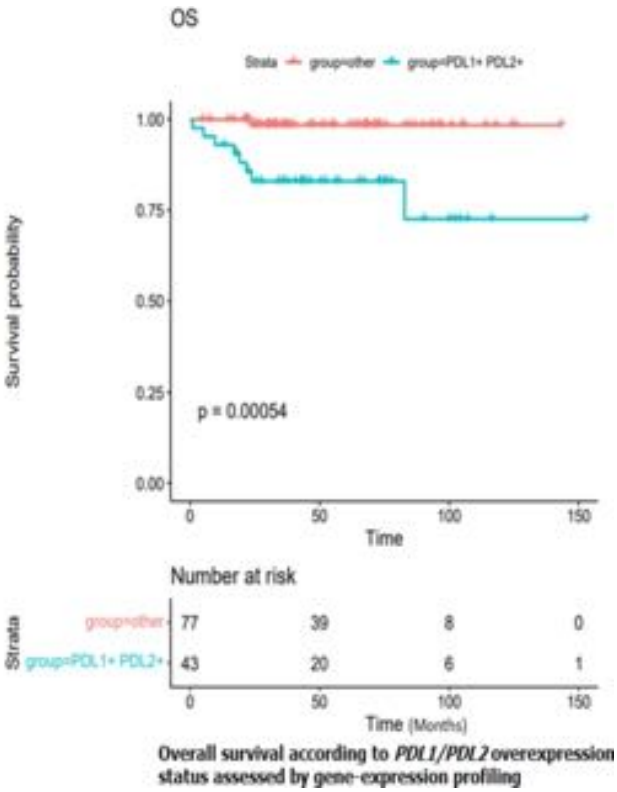
Introduction: Primary mediastinal large B-cell lymphoma (PMBL) is a unique entity with an unusually good prognosis, except for ~15% of refractory patients. Routine diagnosis relies on a clinicopathological confrontation. Tools to detect earlier refractory patients are lacking.

Methods: We implemented a biological characterization of a multicenter retrospective LYSA cohort that previously reported clinical outcomes of 313 adult PMBL patients treated with first-line ACVBP or CHOP plus anti-CD20 between 2007 and 2017. We centrally reviewed 211 cases with available tumor material at diagnosis and then excluded 17 cases (misclassifications/inadequate material). Next, we applied Gene Expression Profiling (GEP) with a 137-genes RT-MLPA assay (LymphoSign signature) and Next-Generation Sequencing (NGS) with a 45-genes panel. Primary endpoints were progression-free survival (PFS) and overall survival (OS) according to molecular data.

Results: We obtained GEP and NGS data for 139 (72%) and 131 (67.5%) cases, respectively. We observed a dominant expression of the PMBL-related driver genes *IL4I1*, *B2M*, *PDL2*, *CD23*, *CD30*, *MAL*, *PDL1*, and *STAT6*. Commonly mutated genes were *SOCS1* (85.5%), *B2M* (61.1%), *STAT6* (51.9%), *IGLL5* (51.1%) and *TNFAIP3* (51.1%). After integration of morphologic and available molecular data, 131/194 cases (67.5%) were considered as PMBL *bona fide* (with typical morphology and molecular profile). Within the PMBL *bona fide* group, we identified a cluster of 43 cases with overexpression of *PDL1/2* genes (*PDL1+/PDL2+*, cutoff ≥median expression of each gene). As compared with others, *PDL1+/PDL2+* cases were as follows: median [range] age of 34 [18–67] years (vs. 33.5 [19–64] years, $p = 0.621$), male sex: 53% (vs. 35%, $p = 0.05$), elevated LDH: 95% (vs. 76.3%, $p = 0.008$), PS 0–1: 79% (vs. 89.6%, $p = 0.12$), stage III–IV: 55.8% (vs. 39%, $p = 0.08$), IPI ≥ 3: 37.2% (vs. 18.4%, $p = 0.027$), extra-nodal involvements: 60% (vs. 45.5%, $p = 0.12$), metabolic tumor volume (MTV) ≥ 360 cm^3: 53% (vs. 25.4%, $p = 0.007$). Treatments in the *PDL1+/PDL2+* group did not differ from other patients: R-ACVBP: 69.8% (vs. 66.2%), R-CHOP14: 18.6% (vs. 20.8%) and R-CHOP21: 11.6% (vs. 14.3%) ($p = 0.411$). *PDL1+/PDL2+* status was associated with poorer PFS (HR = 7, $p < 0.001$) and OS (HR = 15, $p < 0.001$, Figure 1). *B2M* mutations were inactivating and



Progression-free survival according to *PDL1/PDL2* overexpression status assessed by gene-expression profiling



Overall survival according to *PDL1/PDL2* overexpression status assessed by gene-expression profiling

associated with lower PFS ($p = 0.006$). In a multivariate model including IPI ≥ 3, *PDL1/2* status, MTV ≥ 360 and *B2M* mutations, only *PDL1+/PDL2+* status was an independent prognostic factor of adverse PFS (HR = 7.1, 95% CI [1.5;33.1], $p = 0.013$).

Conclusions: The molecular characterization of PMBL using GEP and mutational NGS tools may be a valuable support for the pathologists, through an integrated diagnosis. In particular, RT-MLPA assay could serve as a companion diagnostic. We outlined a subset of PMBL cases with an immune privilege based on a *PDL1/2* overexpression that have poorer outcome with first-line immunochemotherapy.

The research was funded by: This work was supported by grants from the Ligue Contre le Cancer (Comité de Seine-Maritime, AO_2020), the GIP Cancéropôle Nord-Ouest (N°2021/01 and N°2021/13), Force Hémato (N°02-2020) and CALYM (ANR-2020).

Keywords: diagnostic and prognostic biomarkers, extranodal non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

071 | GENE EXPRESSION PROFILING OF *T*(14;18)-NEGATIVE CD23+ FOLLICLE CENTER LYMPHOMA DEMONSTRATES ACTIVATION OF THE IL4/JAK/STAT6 PATHWAY AND A ROLE IN ITS PATHOGENESIS

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Introduction: *t*(14;18)-neg FL cases show similar copy number alterations and mutations as carried by *t*(14;18)-pos FL, but with different frequencies. *STAT6* mutations are significantly more frequent in *t*(14;18)-neg FL than *t*(14;18)-pos FL and correlate with CD23 expression. The consequences of *STAT6* mutations in *t*(14;18)-neg FL have not been investigated, and the impact of STAT6 pathway activation on the tumor microenvironment, which plays a central role in FL, are largely unknown. STAT6 pathway mutations (i.e., *IL4R*), have been demonstrated in primary mediastinal large B-cell lymphoma (PMBL), underlying the importance of STAT6 pathway activation in lymphomagenesis. The aim of this study was to perform gene expression profiling (GEP) on well-characterized *t*(14;18)-neg FL, with mutational analysis on STAT6 pathway associated genes.

Methods: GEP was performed in 52 *t*(14;18)-neg FL including 39 cases with *STAT6* or *SOCS1* mutation ($FLneg^{mut}$), and 13 cases with *STAT6/SOCS1* wild type sequence ($FLneg^{wt}$). Expression of 1392 genes associated with tumor/immune interaction was investigated using the HTG EdgeSeq Immuno-Oncology panel. DESeq2 algorithm was used to determine differentially expressed genes (p-adj < 0.05,

fold change ≥1.5 and ≤−1.5). Gene set enrichment analysis (GSEA, Broad Institute) for *STAT6* pathway genes was performed. An Ampliseq custom panel was used to explore *STAT6* pathway genes *(DUSP2*, *IL4R*, *IL13RA1*, *PTPN1*, *JAK1-3*, *STAT3*, *SOCS3*, *TYK2)*.

Results: GEP of FLneg^{mut} versus FLneg^{wt} showed 32 differentially expressed genes. In FLneg^{mut} a significant upregulation was detected in 23 genes (*CD23*, *IL4R*, *CD83*, *ALOX5*, *ELL3*, *CD40*, *NCF1*, *GPR18*, *CD20*, *CD22*, *CD180*, *HLA-DOB*, *CIITA*, *HLA-DMB*, *LTB*, *PIK3CG*, *PAX5*, *CLEC4A*, *SELL*, *TNFRSF17*, *WASHC4*, *IL13RA1*) and downregulation of 9 genes (*SLAMF7*, *FCRLA*, TNFRSF13B, *CHIT1*, *FCGR1A_FCGR1B*, *MNDA*, *S100A8*, *IRF4*, *FCGR3A_3B*). In FLneg^{mut}, genes associated with germinal center (GC) and activated B cells (ABC) (*CD23*, *IL4R*, *CD83*, *GPR18*) were upregulated, whereas FLneg^{wt} predominantly shows genes upregulated in post-GCB cells (*SLAMF7*, *TNFRSF13B*, *IRF4*), a transcriptional program supporting plasma cell differentiation. In contrast to PMBL, in *t*(14;18)-neg FL, no other mutations in the STAT6 pathway were identified.

Conclusion: GEP identified two distinct groups within *t*(14;18)-neg FL, indicating different stages of differentiation of the neoplastic B cells. FLneg^{mut} shows activation of STAT6 pathway through upregulation of CD23 and IL4R and by enrichment in GSEA and correlates with CD23 expression. Constitutive activation of STAT6 and consequent upregulation of CD23 prevent ongoing B cell differentiation in FLneg^{mut}, precluding the cells from exiting the GC and adopting the state of activated B cell. In contrast, FLneg^{wt} shows a transcriptional program supporting plasma cell differentiation suggesting that the COO is a late GC cell or a post-GCB cell.

Keywords: indolent non-Hodgkin lymphoma, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

072 | IMMUNOGLOBULIN CLASS DICTATES TRANSFORMATION TRAJECTORY AND BCR STATUS OF MYC/BCL2 DOUBLE-HIT LYMPHOMA: BIOLOGY AND CLINICAL IMPLICATIONS

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B cell receptor (BCR) critically contributes to the growth of multiple types of mature B cell neoplasms, representing a preferred target of therapy. In aggressive B-cell non-Hodgkin lymphomas expressing BCL2 and MYC oncoproteins, BCR status remains elusive. Immunohistochemical screening for immunoglobulin (Ig) heavy (H) chains IgM/D/G/A in 331 real-world Diffuse Large B Cell Lymphomas (DLBCL) identified 65% (58/89) of Double-hit (DH) and Triple-hit (TH) lymphomas, carrying MYC/BCL2 (MB2) chromosomal rearrangements, which lacked measurable IgH levels. DHL/THL with undetected IgH (IgH^{UND}) accumulated damaging mutations within Ig variable region genes, presented poor T-cell infiltration and featured transcriptome and mutational profiles sustaining a germinal center (GC) dark zone (DZ)-like molecular program. Conversely, IgH^{+} MB2 DHL/THL were closely related to GC late centrocytes, embedded within an immune-rich microenvironment, permeated by immunosuppressive cytotypes and cytokines, and sustained by mutational signatures evoking active cross-talk with the tumor niche. Strikingly, whereas IgH^{+} DHL/THL GCB lymphomas retained IgM expression, IgH^{UND} lymphomas systematically completed IgH class-switching, yet failed to assemble signaling-competent Ig/CD79B/A BCR complexes. Analyses of metachronous specimens representative of the evolution of Follicular Lymphoma into DHL/THL revealed that the IgH^{UND} status, linked to Ig switching, is established in the FL malignant clone and conserved throughout histological transformation. Our data assign to pre- and post-switched Igs distinctive roles in shaping the transformation trajectory of GC B cells upon consecutive acquisition of BCL2 and c-MYC rearrangements, to ultimately become DHL. In particular, isotype-switched Igs confer to GC DZ B cells highest susceptibility to undergo MYC/BCL2-driven transformation under conditions of chronic BCR silencing. Recurrent BCR downmodulation in DHL/THL and other GC-derived DLBCL urges for IgH assessment in routine diagnostics to select patients who will benefit most from emerging anti-CD79B immunotherapies, while directing those with IgH^{UND} lymphomas to alternative treatments.

The research was funded by: The Italian Association for Cancer Research (AIRC) Italian Ministry for Education, University and Research through the call for Research Projects of National Relevance

Keywords: aggressive B-cell non-Hodgkin lymphoma, microenvironment, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

UCLI - ICML JOINT SESSION

073 | INTRODUCTION OF LYMPHOMA DATABASE OF NATIONAL HEALTH COMMISSION OF THE PEOPLE'S REPUBLIC OF CHINA

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Background: Global burden of diseases 2019 showed China had an aggravating lymphoma burden. There was estimated 101,500 new case and 47,000 deaths due to lymphoma. China had 9500 new cases and 2700 deaths of HL, accounting for 10.8% and 9.8% worldwide. China had 92,000 new cases and 44,300 deaths of NHL, accounting for 20.1% and 17.4% worldwide. Moreover, the age-standardized incidence rate of NHL increased by 14.2%, and the age-standardized mortality rate of NHL increased by 21.9%, respectively, over the past three decades.

Lymphoma database development: The project of lymphoma database is approved by National Health Commission Capacity Building and Continuing Education Center in November 2021. The general responsible person are Professor Jun Ma and Jun Zhu. The consultant are Professor Zhixiang Shen, Yongping Song and Xiaoqiu Li. The project kickoff meeting was hold in January 2022. The database framework was completed in April 2022. The data input was initialed in May 2022.

Representative data: Until March 2023, more than 100 medical centers participated in the project of lymphoma database. There was data of more than 16,000 cases of lymphoma in the database. The data of 100,000 representative cases of lymphoma was chosen and analyzed.

The median age was 54 years (range, 3–93 years). Patients aged <18 years accounted for 2.%, 18–60 years accounted for 63.2%, and >60 years accounted for 34.3%. Male accounted for 55.6% and female accounted for 44.4%. The most common nationality was Han (82.9%), followed by Manchu (0.9%), Zhuang (0.9%), Hui (0.8%), Mongolian (0.6%), Yi (0.3%), Miao (0.2%), Bai (0.2%), Tujia (0.1%), and Yao (0.1%). Non-Hodgkin lymphoma accounted for 89% and Hodgkin lymphoma accounted for 11%. Diffuse large B cell lymphoma was the common histological type (44.4%) of B cell lymphoma, followed by follicular lymphoma (11.3%), and marginal zone lymphoma (5.0%). Natural killer/T cell lymphoma was the most common histological type (5.3%) of mature T/NK cell lymphoma, followed by angioimmunoblastic T-cell lymphoma (3.2%), and peripheral T cell lymphoma not otherwise specified (2.6%).

In the cohort, 11.7% of patients had stage 1 disease, 21.2% had stage 2 disease, 20.2% had stage 3 disease, and 46.9% had stage 4 disease. Almost one third of patients presented B symptom. According to the Eastern Cancer Cooperation Group performance status score, 50.1% of patients scored 0, 36.8% scored 1, 9.9% scored 2, 2.6% scored 3, and 0.6% scored 4.

Keywords: bioinformatics, computational and systems biology, genomics, epigenomics, and other -omics

No conflicts of interests pertinent to the abstract.

074 | 1998–2023 TWENTY-FIVE YEARS OF COMMITMENT TO IMPROVING OUR UNDERSTANDING OF LYMPHOMA

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The International Extranodal Lymphoma Study Group (IELSG) was established in 1998 with the purpose of improving the understanding of extranodal lymphoma. The group's primary objective was to bring together scientists from various institutions to create a collaborative network for collecting data from a large number of patients. This data could then be used to conduct individual studies focusing on specific tissues or organs affected by extranodal lymphoma.

The primary responsibility of the IELSG is to develop and implement study protocols that identify novel treatments and cures for lymphoma. The group aims to create current therapeutic standards for extranodal lymphomas and establish specific prognostic scoring systems and precise response criteria for different extranodal presentations. Over the years, the IELSG has conducted around 50 studies, including both retrospective and prospective trials to address management issues linked to extranodal lymphoma presentations.

These trials have resulted in several publications in leading peer-reviewed medical journals and have led to changes in clinical practice for several extranodal lymphomas, including MALT lymphoma, testicular lymphoma, primary mediastinal lymphoma, and central nervous system lymphoma.

Moreover, the IELSG is conducting translational studies. These studies may enhance our knowledge of the specific biology of extranodal lymphoma entities, refine their classification, and aid in the development of rationally targeted treatments.

Keywords: aggressive B-cell non-Hodgkin lymphoma, extranodal non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

075 | SMART START WITH TISLELIZUMAB AS THE FRONT-LINE TREATMENT IN PATIENTS WITH HIGH-RISK STAGE IIB AND ADVANCED-STAGE CLASSICAL HODGKIN LYMPHOMA

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Introduction: Around 10%–30% of classical Hodgkin's lymphoma (cHL) will relapse or refract after treatment with traditional cytotoxic drug-based chemotherapy, meanwhile the chemotherapy-related toxicity cannot be ignored. In order to balance efficacy and toxicity, we use the concept of 'Smart Start' to explore the efficacy and safety of tislelizumab sequentially combined with AVD regimen in the first-line treatment of cHL in phase II study (NCT04843267).

Method: The study included untreated cHL patients with advanced-stage (III–IV and II_B with unfavorable risk factors). All patients first received 2 cycles of tislelizumab monotherapy and then entered into the PET-CT evaluation (PET-2). According to PET-2, complete response (CR) patients continued to receive 4 cycles of tislelizumab monotherapy, partial response (PR) patients received 4 cycles of tislelizumab and AVD combination therapy, progression disease (PD)/stable disease (SD) patients withdrew from the study. After 6 cycles of the treatment, the patients who still maintained PR according to the PET-CT evaluation (PET-3), could receive 2 additional cycles of tislelizumab and AVD combination therapy. The primary endpoint is the CR rate in PET-2, and the secondary endpoints include overall response rate (ORR), progression-free survival (PFS), overall survival (OS) and safety.

Results: 29 patients were enrolled in this study till 27 February 2023. Among them one patient was removed due to pathological review as peripheral T-cell lymphoma. The basic characteristics of the 28 patients who met the inclusion criteria are shown in Table 1. The median age was 34y (21–68), stage II_B 10.7%, stage III 25.0%, stage IV 64.3%. All 28 patients have received at least two cycles of tislelizumab monotherapy and PET-2 efficacy evaluation, the swimming plot of efficacy and overall survival were shown in Figure 1. After PET-2, the CR rate was 28.6% (8/28), the overall response rate (ORR) was 96.4% (27/28), and one patient (3.6%) developed PD. Up to PET-3, 21 patients completed all treatment, the other 7 were still in the treatment. 19 patients (90.5%,19/21) achieved CR, one (4.8%) achieved PR, and one (4.8%) had PD during the treatment, with the ORR of 95.2%. During the follow-up, six of the 8 CR patients in PET-2 had still maintained CR after 6 cycles of tislelizumab monotherapy without chemotherapy. The safety profile was shown in Table 2. The study was well tolerated, and there was no treatment-related SAE or death. Immune-related AEs were mostly concentrated in grade 1/2, and grade 3/4 hematological toxicities were mainly happened during the combination treatment period.

Conclusion: The study showed great efficacy and safety profile, indicating that cytotoxic drugs could be reduced even ignored in some of advanced-stage cHL patients. Therefore, tislelizumab

Fig 1. Swimming plot of efficacy and overall survival in 28 cHL patients

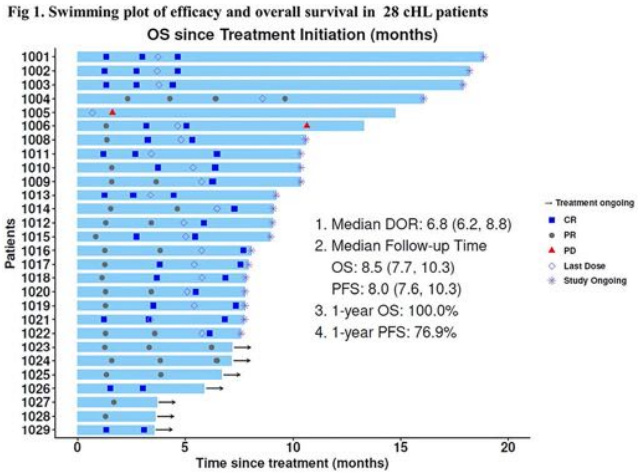

Table 1. Baseline Patient Characteristics (n=28)

Characteristic	Number of assessable patients	(%)
Age (years)		
Range (Median)	21-68(34)	
> 60	3	10.7
≤ 60	25	89.3
≥45	8	28.6
<45	20	71.4
Gender		
Male	17	60.7
Female	11	39.3
B symptoms		
Yes	10	35.7
No	18	64.3
Ann Arbor stage		
Stage II	3	10.7
Stage III	7	25.0
Stage IV	18	64.3
LDH		
> 245 U/L	16	57.1
≤ 245 U/L	12	42.9
Bulky Disease		
Yes	7	25.0
No	21	75.0
CRP		
> 10 mg/L	16	44.4
≤ 10 mg/L	20	55.6
ESR		
≥ 50mm/h	13	46.4
< 50mm/h	15	53.6
β2-MG		
≥ 2.5ng/L	8	28.6
< 2.5ng/L	20	71.4
IPS		
0	2	7.1
1	6	21.4
2	8	28.6
3	7	25.0
4	3	10.7
5	1	3.6
6	1	3.6

Table 2. Toxicity profiles from the tislelizumab sequentially combined with AVD regimen

Toxicity	No. of Adverse Events (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Hematological AEs						
Leukocytopenia	1(3.6)	6(21.4)	2(7.1)	0	0	9(32.1)
Neutropenia	1(3.6)	3(10.7)	6(21.4)	3(10.7)	0	13(46.4)
Non-hematological AEs						
Hyperthyroidism	2(7.1)	1(3.6)	0	0	0	3(10.7)
Hypothyroidism	1(3.6)	0	0	0	0	1(3.6)
Increased transaminases	2(7.1)	2(7.1)	0	0	0	4(14.3)
Fever	1(3.6)	1(3.6)	0	0	0	2(7.1)
Nausea	3(10.7)	1(3.6)	0	0	0	4(14.3)
Vomiting	3(10.7)	0	0	0	0	3(10.7)
Constipation	1(3.6)	0	0	0	0	1(3.6)
Pruritus	0	1(3.6)	0	0	0	1(3.6)
Pancreatitis	1(3.6)	0	0	0	0	1(3.6)
Pneumonitis	0	0	0	1(3.6)	0	1(3.6)
Pharyngitis	0	0	0	1(3.6)	0	1(3.6)
Numbness of figure	3(10.7)	0	0	0	0	3(10.7)
Alopecia	0	1(3.6)	0	0	0	1(3.6)

sequentially combined with AVD regimen is a promising treatment option for first-line treatment of cHL.

Keywords: Hodgkin lymphoma, immunotherapy

No conflicts of interests pertinent to the abstract.

076 | ROLE OF CHECKPOINT INHIBITION IN GERMANY

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Immune checkpoint inhibition (ICI) has demonstrated an overall excellent benefit-to-risk profile in the treatment of classical Hodgkin lymphoma (cHL); however, cure remains an exception to the rule. The German Hodgkin Study Group (GHSG) has identified several areas of unmet need for ICI development in cHL. First, we aim to better understand the role of immune checkpoints in the interplay between Hodgkin/Reed-Sternberg malignant cells and the abundant microenvironment. Second, we aim to improve efficacy of ICI in multiple relapsed/refractory (r/r) cHL patients, as complete response rates are infrequent and median PFS is still quite limited. Therefore, combination therapies with alternative ICIs targeting TIGIT, LAG3, or TIM3, or combinations with conventional cytotoxic drugs need to be investigated. The GHSG has focused on evaluating the abscopal effects of radiotherapy to improve ICI in multiple r/r cHL. Third, the GHSG strongly believes that ICI should be able to improve first-line therapy of cHL. The GHSG is currently conducting clinical trials to de-escalate the chemotherapy intensity. In early favourable stage cHL patients, we hypothesize that ICI can replace chemotherapy in the combined modality therapy approach. In early unfavourable stage cHL, we use our PET-adapted design to select well-responding patients and remove chemotherapy and/or radiotherapy from the treatment strategy. In advanced stage cHL, we aim to reduce cumulative exposure to conventional chemotherapy. We hypothesize that the combination of anti-PD-1 antibody therapy with our intensive chemotherapy should act synergistically and more patients should achieve an early metabolic complete response. These patients could then be treated with only 4 cycles of combined PD1 chemotherapy. Overall, this new treatment principle should serve to overcome chemotherapy resistance and improve the efficacy of established therapeutic regimens, while reducing the treatment burden for our cHL patients.

Keywords: Hodgkin lymphoma, immunotherapy

No conflicts of interests pertinent to the abstract.

077 | NEW DRUG DEVELOPMENT IN LYMPHOMA OF CHINA IS GOING GLOBAL

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In 2018, China contributed to 7.8% of the global drug innovation pipeline and 11.6% of new drug launches, thereby becoming the largest base for new drug R&D in Asia. Statistically, oncology, particularly the field of lymphoma, occupies the major area of innovative drug development. Despite substantial advances, there is still an unmet need to develop better therapies for B-cell lymphomas (BCL), especially for those incurable settings. As an icon of successful drug R&D in China, Zanubrutinib, known as the Best-in-class BTK inhibitor, exhibits more potent kinase selectivity and less off-target toxicites than other BTK inhibitors. In two phase 3 head-to-head trials against ibrutinib, Zanubrutinib showed superior ORR and PFS in R/R CLL/SLLpatients, and deeper durable responses in WM patients. Of note, Zanubrutinib plus obinutuzumab was associated with improved PFS compared with obinutuzumab alone in R/R FL acccording to the ROSEWOOD trial. Moreover, Zanubrutinib plus rituximab versus bendamustine plus rituximab is undergoing Phase III trial in transplant-ineligible, untreated MCL. To date, Zanubrutinib has been approved for 60+ markets across 4 lead indications (CLL/SLL, WM, MCL, MZL) and is pursuing approval for a broader range of indications worldwide. The new BCL-2 inhibitor lisaftoclax (APG-2575) has shown high activity and favorable security as monotherapy and in combination with rituximab or acalabrutinib in patients with treatment-naïve, R/R CLL/SLL from a phase 2 global study. PSB202 is the first-in-class bifunctional antibody that target CD20 and CD37 for the treatment of BCL. It is expected to elicit improved efficacy and reduce resistance/refractivity to initial rituximab treatment. A phase I study evaluating the efficacy and safety of PSB202 in patients with previously treated, relapsed, indolent BCL is in progress. The emergence of these innovative drugs offers possibilities to explore novel combinations in treatment of BCL. In addition to BCL, a phase I/II study demonstrates the antitumor activity and managable safety of Golidocitinib, a selective JAK1 inhibitor, in R/R PTCL. From participation to leadership, from best in class to first in class, China has evolved to one of the largest market of drug development

globally, with high potential to shape the way of future drug development.

Keyword: molecular targeted therapies

No conflicts of interests pertinent to the abstract.

078 | NEW TRENDS IN LYMPHOMA TREATMENT IN WESTERN COUNTRIES

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Immunotherapy with chimeric antigen receptor (CAR) T-cells and bispecific antibodies undoubtedly represent the most advanced frontier in the treatment of lymphomas in Europe and North America. Real world experiences with CAR T-cells both in the United States and at some European institutions have replicated the favourable outcomes of pivotal clinical trials, with the achievement of objective response rates of 45%–55% in patients with diffuse large B-cell lymphoma treated beyond the second line, and yielding 2-year progression-free survival rates of 30%–45%. Importantly, at least 50% of the patients treated on a routine basis would have not qualified for a clinical trial, thus underscoring that CAR T-cells may represent a valuable option for a wide spectrum of patients who have failed chemotherapy and appear ineligible for autologous transplantation because of age or disease status.

Bispecific antibodies realize a T-cell-based immunotherapy in aggressive and indolent B-cell lymphomas: glofitamab, epcoritamab and odronextamab are now being extensively applied in the aggressive lymphoma setting, while mosunetuzumab is mainly given in patients with follicular lymphoma. Results in both aggressive and indolent lymphomas that substantially overlap with those of CAR T-cells along with a more favourable toxicity profile in terms of cytokine release syndrome and neurologic events, make bispecific antibodies an attractive option for multiply treated patients.

Given the experience gained with these agents, CAR T-cells are now being explored as first salvage and frontline treatment in aggressive lymphomas. Trials with bispecific antibodies combined with chemotherapy or targeted agents in less pretreated or untreated patients are ongoing.

Keywords: aggressive B-cell non-Hodgkin lymphoma, aggressive T-cell non-Hodgkin lymphoma, molecular targeted therapies immunotherapy

No conflicts of interests pertinent to the abstract.

SESSION 13 - FOLLICULAR LYMPHOMA

079 | A "FUNCTIONAL CURE" MAY BE ACHIEVABLE IN A SUBSET OF PATIENTS WITH FOLLICULAR LYMPHOMA TREATED WITH CHEMOIMMUNOTHERAPY: 15-YEAR FOLLOW-UP OF PHASE III SWOG-S0016

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Background: Follicular lymphoma (FL) is considered incurable with current therapies which include chemoimmunotherapy as the standard of care for first line. S0016 enrolled patients with untreated advanced FL (bulky stage II or III–IV) between 2001 and 2008 and randomized them to CHOP × 6 followed by (131) I-tositumomab radioimmunotherapy (CHOP-RIT) or CHOP-R × 6; no maintenance was included.

Methods: Fifteen-year PFS and OS were estimated according to the Kaplan–Meier method. Cumulative incidence of disease progression was calculated using the nonparametric Nelson-Aalen estimator with death without progression/relapse treated as a competing risk.

Results: Baseline characteristics between the CHOP-RIT (n = 267) and CHOP-R (n = 264) arms were balanced: age (median 53.4 vs. 54.5 years), B symptoms (26% vs. 29%), path grade 3 (9% vs. 8%), high FLIPI risk (26% vs. 22%), high β2M (55% vs. 53%), marrow involvement (55% vs. 56%) and bulky disease (26% vs. 24%).

After a median follow-up of 15.5 years, the 15-year OS was 70% (95% CI: 65.9%–74.1%) for the entire cohort, 67% (95% CI: 60.7%, 72.6%) for CHOP-RIT and 73% (95% CI: 67.2%, 78.4%) for the CHOP-R (p-value = 0.56) arm. The 15-year estimate of PFS for the entire cohort was 40% (95% CI: 36.0%, 44.7%). The PFS was superior in the CHOP-RIT arm [47% (95% CI: 40.4%, 53.0%)] versus CHOP-R [34% (95% CI: 28.2%, 40.0%)] (p-value = 0.004).

While the overall incidence of progression increased overtime, the average progression rate dramatically decreased: 6.8% (0–5 years), 2.3% (5–10 years), 1.1% (10–15 years) and 0.6% (15%–20%). Cumulative incidence of progression at 15-years for the entire study population was 50.5% (95% CI: 46.5%–54.8%) and was lower in the CHOP-RIT arm vs. CHOP-R arm [42.3% (95% CI: 36.1–48.4%) vs. 58.6% (95% CI: 52.2%–64.4%); p-value = 0.0009]

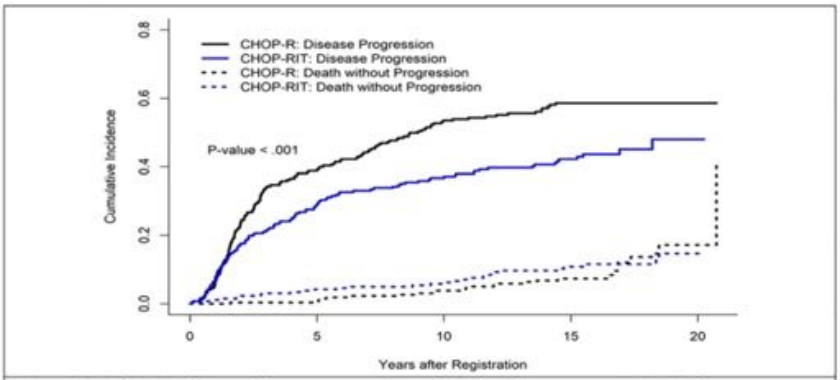

Figure: Cumulative incidence of disease progression and death without progression in both arms

There was no difference between the 2 arms in incidence of 2nd malignancies (19.7% vs. 22.1%; *p*-value = 0.52) or AML/MDS (5.3% vs. 2.2%; *p*-value = 0.08). The estimate of 15-year cumulative incidence of deaths due to 2nd malignancies were 7% and 5.4% in CHOP-RIT and CHOP-R arms (*p*-value = 0.45) but the 15-cumulative incidence of deaths due to AML/MDS was higher in CHOP-RIT arm (4.4% vs. 1.2%; *p*-value = 0.03). The most common causes of death were lymphoma (15.2%), 2nd malignancies (7.2%) and non-cancer medical issues (6.4%) in the CHOP-RIT arm and lymphoma (11.6%), non-cancer medical issues (8.6%) and 2nd malignancies (5.6%) in CHOP-R arm (*p*-value 0.27). The cumulative incidence of death without progression at 15-years was 9.1% (95% CI: 6.7%–11.9%).
Conclusion: With more than 15 years of follow-up, 40% of patients remain alive and progression-free after 6 cycles of CHOP-RIT or CHOP-R without maintenance therapy. The average rate of progression decreased overtime indicating a possibility of achieving a functional cure in a subset of patients. These results provide a benchmark for first-line studies utilizing novel agents.

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Keywords: chemotherapy, combination therapies, indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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Research funding: Merck, I-Mab bio, IgM Bio, Takeda, Gilead, AstraZeneca, Agios, Janssen, BMS, SeaGen, Teva, Genmab

080 | SAKK 35/14 RANDOMIZED TRIAL OF RITUXIMAB WITH OR WITHOUT IBRUTINIB FOR UNTREATED PATIENTS WITH ADVANCED FOLLICULAR LYMPHOMA IN NEED OF THERAPY

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The Swiss Group for Clinical Cancer Research (SAKK) and the Nordic Lymphoma Group (NLG) conducted the SAKK 35/14 randomized phase-2 trial (NCT02451111) to evaluate the safety and efficacy of frontline treatment with ibrutinib plus rituximab compared to rituximab plus placebo in adult patients (pts) with advanced follicular lymphoma in need of therapy. Ibrutinib was administered orally (560 mg once a day) for 24 months (104 weeks), while rituximab was given intravenously (375 mg/m2) on day 1 of weeks 1, 2, 3, and 4, and subsequently every 2 months for 12 maintenance administrations, given either intravenous (375 mg/m2) or subcutaneous (1400 mg flat dose) based on local policy. The primary endpoint was the complete remission (CR) rate at 24 months after randomization determined on PET/CT scans by an independent review panel.

In total, 192 pts were randomized (98 in arm A rituximab + placebo; 94 in arm B rituximab + ibrutinib) with stratification by rituximab maintenance route, lymphoma grade, follicular lymphoma international prognostic index, and bulky (≥6 cm) disease. The CR rate at 24 months was 36% (95% CI, 26%–46%) in arm A and 40% (95% CI, 30%–51%) in arm B with an odds ratio (OR) of 0.80 (95% CI, 0.44–1.46; $p = 0.233$). At a median follow-up of 42 months, the 3-year progression-free survival (PFS) rate was 36% in arm A (95% CI, 19%–54%) and 45% (95% CI, 25%–64%) in arm B, with a hazard ratio (HR) of 1.63 (95% CI, 0.99–2.7; $p = 0.056$). At 3 years after randomization, 45% (95% CI, 36%–56%) of pts in arm A and 39% (95% CI, 30%–50%) in arm B had already required a new treatment, with a HR of 1.47 (95% CI, 0.93–2.32; $p = 0.099$). The 3-year overall survival rate (OS) approximated 96% in both arms (95% CI, ~89%–99%) with a HR of 1.02 (95% CI, 0.29–3.55; $p = 0.979$).

The percentage of pts experiencing at least one adverse event (AE) was similar in the two arms (100% and 99%). However, 29% of pts experienced at least one AE of grade ≥3 in arm A while this was the case for 49% of pts in arm B. The percentage of pts experiencing AEs related to trial treatment was also lower in arm A (67%) than in arm B (84%). A total of 93 SAEs were reported, 42 in arm A, affecting 26% of pts, and 51 in arm B, involving 39% of pts. A total of 7 SUSARS occurred, 1 in arm A and 6 in arm B.

The most frequent AEs of grade ≥3 during treatment were neutropenia (8% in arm A and 14% in arm B), lymphocytosis (5% in arm A and 10% in arm B), hypertension (5% in each arm), and maculopapular skin rash (not observed in arm A, 11% in arm B).

Superiority of the rituximab-ibrutinib combination regimen in terms of CR rates could not be demonstrated. However, the significantly improved (at the pre-specified alpha level of 0.1) PFS, and time to next treatment rates suggest a clinical benefit and potentially higher efficacy (with expected greater but manageable toxicity) that could be further explored in untreated FL. The very good OS in both arms supports the ongoing use of rituximab as a therapeutic partner in clinical trials of novel combinations.

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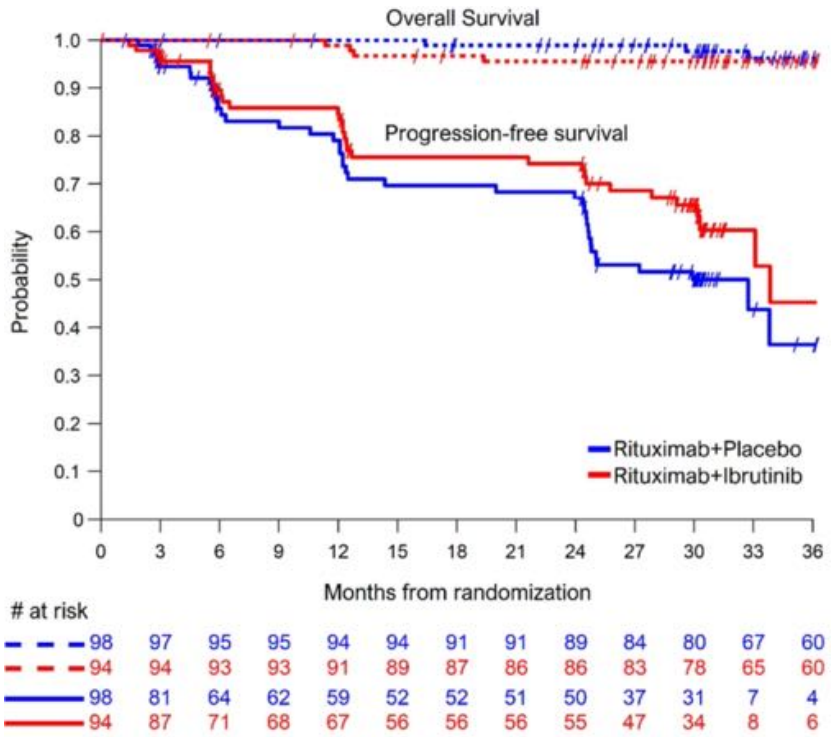

Keywords: immunotherapy, indolent non-Hodgkin lymphoma, molecular Targeted Therapies

Conflicts of interests pertinent to the abstract

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081 | ZANUBRUTINIB PLUS OBINUTUZUMAB VERSUS OBINUTUZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA: UPDATED ANALYSIS OF THE ROSEWOOD STUDY

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Introduction: In an early-phase study, the combination of zanubrutinib plus obinutuzumab (ZO) was well tolerated and associated with an early signal of efficacy in patients (pts) with follicular lymphoma (FL) (Tam et al. *Blood Adv*, 2020). ROSEWOOD (NCT03332017) is a phase 2, randomized study designed to assess efficacy and safety of ZO versus obinutuzumab (O) in patients with relapsed/refractory (*R/R*) FL. Here, we present an updated analysis with a median follow-up of 20.2 months.

Methods: Pts with *R/R* FL (grade 1–3a) who received ≥2 lines of therapy including an anti-CD20 antibody and alkylating agent were randomized 2:1 to receive ZO or O. Zanubrutinib was given at 160 mg twice daily until progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) by independent central review. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), time to next treatment (TTNT), overall survival (OS), and safety.

Results: A total of 217 patients were randomized (145 for ZO; 72 for O). Median age was 64 years. Of the 217 pts, 114 (52.5%) had a high Follicular Lymphoma International Prognostic Index (FLIPI) score at screening and 123 (56.7%) pts had high tumor burden according to Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria. Median number of prior lines of therapy was 3 (range, 2–11). A total of 114 (52.5%) pts were refractory to rituximab; 214 (98.6%) patients received prior immunochemotherapy. Prior exposure to anticancer drugs included anthracyclines (80.6%), cyclophosphamide (94.0%), and bendamustine (54.8%). ORR was 69.0% (ZO) versus 45.8% (O) ($p = 0.0012$). Complete response rate was 39.3% (ZO) versus 19.4% (O); 18-month DOR rate was 69.3% (ZO) versus 41.9% (O); median PFS was 28.0 months (ZO) versus 10.4 months (O) (hazard ratio [HR], 0.50 [95% CI: 0.33, 0.75]; $p = 0.0007$). Median TTNT was not evaluable for ZO and 12.2 months for O (HR, 0.34 [95% CI: 0.22, 0.52]; $p < 0.0001$). Estimated OS rate at 24 months was 77.3% (ZO) and 71.4% (O), with median OS not reached (ZO) and 34.6 months (O). Nonhematologic treatment-emergent adverse events of any grade that occurred more frequently for ZO versus O (>5% difference) were petechiae (6.3% vs. 0%) and herpes zoster infection (6.3% vs. 0%); in contrast, pyrexia (13.3% vs. 19.7%) and infusion-related reaction (2.8% vs. 9.9%) occurred more frequently in patients on O. When adjusted for duration of treatment exposure, incidences of infection and cytopenia were similar, and incidence of all grades of hemorrhage was 2.4 (ZO) versus 1.3 (O) persons per 100 person-months. Two patients in each treatment group reported major hemorrhage. Incidences of atrial fibrillation and hypertension were low and similar in both treatment arms.

Conclusions: ZO demonstrated meaningful activity and a manageable safety profile in patients with heavily pretreated *R/R* FL, representing a potential novel therapy.

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The research was funded by: BeiGene

Keywords: combination therapies, indolent non-Hodgkin lymphoma, molecular targeted therapies

Conflicts of interests pertinent to the abstract

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Adaptimmune, Amgen, Bayer, Cellectis, EMD Serono, Guardant Health, Iovance Biotherapeutics, Kite/Gilead, MorphoSys, Nektar, Novartis, Pfizer, Sanofi, Takeda, Ziopharm Oncology

082 | ODRONEXTAMAB IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA (FL) GRADE 1–3A: RESULTS FROM A PRESPECIFIED ANALYSIS OF THE PIVOTAL PHASE II STUDY ELM-2

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Introduction: Odronextamab is a CD20 × CD3 bispecific antibody (Ab). In the Phase 1 ELM-1 study (NCT02290951), odronextamab demonstrated potent antitumor activity and a generally manageable safety profile in patients (pts) with heavily pretreated FL (Bannerji R, et al. Lancet Haematol, 2022). Here, we present results from a prespecified analysis of the FL cohort from the Phase 2 ELM-2 study (NCT03888105).

Methods: ELM-2 is a global, multicenter study that enrolled adult pts with FL Grade 1–3a who were relapsed/refractory (*R/R*) after ≥2 prior lines of therapy (LOT) including an anti-CD20 Ab and an alkylator. Informed consent was obtained from all pts. IV odronextamab was administered in 21-day cycles with steroid prophylaxis and step-up dosing during Cycle (C) 1. The initial step-up regimen consisted of 1 mg split over C1 Day (D) 1 and C1D2, and 20 mg split over C1D8 and C1D9, then the full 80 mg dose on C1D15 (1/20 regimen). This regimen was revised during the study to further mitigate risk of cytokine release syndrome (CRS), with the modified regimen consisting of 0.7 mg split over C1D1 (0.2 mg) and C1D2 (0.5 mg), 4 mg split over C1D8 and C1D9, and 20 mg split over C1D15 and C1D16, then the 80 mg full dose on C2D1 (0.7/4/20 regimen). 80 mg QW continued until the end of C4, followed by 160 mg Q2W until disease progression or unacceptable toxicity. Primary endpoint was objective response rate (ORR) assessed by independent central review (ICR; response data described here are based on ICR).

Results: As of 15 September 2022, 131 pts had been treated: median age 61 y (range 22–84); male, 53%; median prior LOT, 3 (range 2–13); refractory to last therapy, 71%; progression of disease within 2 y, 48%. Median duration of study follow-up was 22.4 mos. ORR and complete response (CR) rate by ICR were 82% (99/121) and 75% (91/121), respectively, and were consistent across high-risk subgroups. Responses were durable with both a median duration of response and a median duration of CR of 20.5 mos. Median PFS was 20.2 mos (95% CI 14.8–not estimable [NE]) and median OS was not reached (95% CI NE–NE).

TEAEs occurred in all pts, considered treatment-related in 118 (90%). Treatment-related Grade (Gr) 5 AEs were reported for 3 pts (pneumonia, progressive multifocal leukoencephalopathy, systemic mycosis [$n = 1$ each]), and treatment-related AEs led to discontinuation in 10 pts. The most common TEAEs (>30% all grades) were CRS (56%), neutropenia (40%), and pyrexia (31%). With the 0.7/4/20 step-up regimen ($n = 63$), Gr 3 CRS was observed in 1 pt (no Gr 4 or 5 CRS; all CRS events resolved) and no ICANS was reported.

Conclusions: In the ELM-2 study, odronextamab demonstrated compelling efficacy in pts with *R/R* FL, and an acceptable safety profile with the optimized 0.7/4/20 step-up regimen. For this patient population, where prognosis is typically poor, odronextamab may provide a more accessible option with favorable benefit:risk compared with existing therapies.

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Keywords: immunotherapy, indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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083 | MOSUNETUZUMAB DEMONSTRATES DURABLE RESPONSES IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA AND ≥2 PRIOR THERAPIES: UPDATED ANALYSIS OF A PIVOTAL PHASE II STUDY

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Introduction: Mosunetuzumab (Mosun) is a CD20xCD3 T-cell engaging bispecific antibody that redirects T cells to eliminate malignant B cells. In a pivotal Phase II study (NCT02500407), fixed-duration Mosun demonstrated a high rate of complete responses (CRs) and durable responses in patients (pts) with relapsed/refractory (*R/R*) follicular lymphoma (FL) and ≥2 prior lines of therapy. We report efficacy outcomes for pts who achieved CR by end-of-treatment (EOT), with a median follow-up of 28.6 months.
Methods: Eligible pts with *R/R* FL (Grade [Gr] 1–3a) and ≥2 prior therapies were enrolled. Mosun was administered intravenously in 21-day cycles with step-up dosing in Cycle (C) 1 (C1 Day [D] 1, 1 mg; C1D8, 2 mg; C1D15/C2D1, 60 mg; C3D1 and onwards, 30 mg). Hospitalization for treatment was not required. Pts achieving CR by

C8 completed treatment with no further cycles; pts with a partial response (PR) or stable disease received up to 9 further cycles. The primary endpoint was independent review committee-determined CR rate. The association between baseline (BL) total metabolic tumor volume (TMTV; derived using an AI-based model [Jemaa et al., 2022]) and clinical efficacy and safety was assessed.

Results: Ninety pts were enrolled. Of these, 54 pts (60%) achieved CR as best response: 49 pts (54%) achieved CR at EOT; 1 pt with CR experienced disease progression (PD) in C8; and 4 pts achieved CR after EOT. In the 49 pts with CR at EOT, 82% had stage III/IV disease and median number of prior lines of therapy was 3 (range: 2–10). As of July 8, 2022, median time on study was 28.6 months. Among the 49 pts who achieved CR at EOT, median duration of CR (DOCR; investigator-assessed) was not reached (NR); 24-month DOCR rate after first CR was 65% (95% CI: 39–90). Median progression-free survival (PFS) was NR; 24-month PFS rate was 77% (95% CI: 63–91; **Table**). Two years after the end of fixed-duration treatment, 67% of these 49 pts remained free of PD or death.

Of the 54 pts with CR as best response, 33 pts achieved their first CR by the first mandatory tumor assessment at 3 (±0.5) months (early CR) and 21 pts achieved their first CR after the 3 month assessment (late CR). Median duration of response (DOR) was NR in patients with an early or late CR. In pts with PR as best response (n = 16), median DOR was 4 months (95% CI: 3–7). No correlation was observed between BL TMTV and best overall response. A higher rate of Gr ≥2 cytokine release syndrome (CRS) was observed in pts with bone or bone marrow metabolic disease burden (n = 24) versus those without (n = 58; 33% vs. 14%, respectively).

Conclusion: Fixed-duration Mosun monotherapy demonstrated a high CR rate at EOT in pts with *R/R* FL, with many pts remaining event-free 2 years after EOT. Exploratory analyses did not suggest an association between the timing of the first CR and DOR. TMTV at BL was not associated with response to Mosun. Gr ≥2 CRS events were more common in pts with bone or bone marrow metabolic disease burden.

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Keywords: immunotherapy, indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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Table: Efficacy in patients with a complete response at the end of mosunetuzumab treatment.

Efficacy endpoints assessed by investigators	CR at EOT n=49
Median DOCR, months (95% CI)	NR (23–NR)
24-month DOCR rate, % (95% CI)	65 (39–90)
Median PFS, months (95% CI)	NR (26–NR)
24-month PFS rate, % (95% CI)	77 (63–91)
Median OS, months (95% CI)	NR (NR–NR)
24-month OS rate, % (95% CI)	100 (100–100)

CI, confidence interval; CR, complete response; DOCR, duration of complete response; EOT, end of treatment; NR, not reached; OS, overall survival; PFS, progression-free survival.

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084 | EPCORITAMAB WITH RITUXIMAB + LENALIDOMIDE (R2) PROVIDES DURABLE RESPONSES IN HIGH-RISK FOLLICULAR LYMPHOMA, REGARDLESS OF POD24 STATUS

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Introduction: Follicular lymphoma (FL) is a heterogeneous disease. Early progression after initial treatment with chemoimmunotherapy, or POD24, occurs in approximately 20% of patients and strongly predicts poor outcomes. There is no standard treatment approach for patients with high-risk, relapsed or refractory (*R/R*) FL (high-risk subgroups in **Table**). Novel treatment options are needed to improve efficacy in patients with high unmet need. Epcoritamab, a subcutaneous T-cell–engaging bispecific antibody, demonstrated impressive single-agent antitumor activity and a manageable safety profile in *R/R* FL (Hutchings et al. *Lancet*, 2021) and shows promise combined with standards of care. Here we present pooled analyses from cohorts 2a and 2b of the ongoing phase 1/2 EPCORE™ NHL-2 trial (NCT04663347) of epcoritamab with rituximab + lenalidomide (R^2).
Methods: Patients with *R/R* $CD20^+$ FL received subcutaneous epcoritamab + R^2 for 12 cycles (28 d each). Epcoritamab was dosed QW in cycles 1–3, Q2W in cycles 4–9, and Q4W in cycles ≥10 (2a) or QW in cycles 1–2 and Q4W in cycles ≥3 (2b) for ≤2 y.
Results: As of 31 October 2022, 109 *R/R* FL patients had received epcoritamab 48 mg + R^2 in 2a and 2b. Median age was 65 y, 56% of patients had FLIPI 3–5, 61% had stage IV disease, and 59% had only 1

prior treatment line. Most had received alkylating agents (92%) or anthracyclines (62%); 2 had prior CAR T. At a median follow-up of 8.8 mo (range, 1.2–18.5), 82% were still on treatment. The most common treatment-emergent AEs were CRS and neutropenia (48% each), injection-site reactions (38%), and fatigue (33%). CRS events were mostly low grade (G; 46% G1–2, 2% G3) and mostly occurred following the first full dose on cycle 1 day 15; all resolved and none led to discontinuation. ICANS occurred in 2 patients (G1, G2) and resolved. In 101 efficacy-evaluable patients, overall response rate (ORR) was 97%, with complete metabolic response (CMR) in 86%. Median time to any response and CMR was 1.4 mo. Estimated 6-mo progression-free survival was 93%. Notably, patients achieved higher ORR/CMR rates with epcoritamab + R^2 versus their immediate prior treatment line (ORR, 97% vs. 85%; CMR, 86% vs. 60%). In second-line patients with POD24, ORR/CMR rates were 95%/90% (additional high-risk subgroup data in **Table**). Additional data with longer follow-up will be presented.

Conclusions: Epcoritamab + R^2 showed potent antitumor activity and a manageable safety profile in a large *R/R* FL population. Encouraging responses were seen in patients with high-risk disease, suggesting subcutaneous epcoritamab may abrogate negative effects of high-risk features. A separate POD24 cohort is planned, and epcoritamab + R^2 is being studied in the phase 3 EPCORE FL-1 trial (NCT05409066).

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Keywords: immunotherapy, indolent non-Hodgkin lymphoma

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Table. Response rates, overall and among high-risk R/R FL subgroups

Population	ORR (%)	CMR (%)
Efficacy evaluable (n=101)	97	86
Primary refractory[a] (n=39)	97	87
Double refractory[b] (n=39)	92	79
Refractory to last line of therapy (n=40)	93	80
Refractory to prior anti-CD20 therapy (n=49)	94	84
POD24[c] (n=38)	95	82
POD24[c] 2L[d] (n=20)	95	90

[a]No response or relapse within 6 mo after first-line treatment.
[b]Refractory to anti-CD20 and an alkylating agent.
[c]Progression within 2 y of first-line treatment with chemoimmunotherapy.
[d]Patients received epcoritamab in second line.
CMR, complete metabolic response; ORR, overall response rate.

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085 | DOES IT MATTER HOW WE NAME LYMPHOMAS?

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To find the optimal treatment for a disease it is necessary to identify specific biological and clinical entities that are as homogeneous as possible. The history of classifying lymphomas in a clinically useful way is a long and interesting story, beginning with Thomas Hodgkin's initial clinical description. Landmarks along the way include the description of the Reed Sternberg cell that separated Hodgkin lymphoma, and a series of classification systems to subdivide the other lymphomas. These include the Gall and Mallory classification (i.e., reticulum cell sarcoma, lymphosarcoma, and giant follicular lymphoma), The Rappaport classification (i.e., based on cell size, shape, and growth pattern), That Lukes- Collins and Kiel classifications (i.e., that subdivided T cell and B cell lymphomas and recognized that all lymphomas originate in lymphocytes), and the working formulation (i.e., a politically driven attempt to standardize terminology and facilitate research and treatment). More recently the REAL classification began the process of identifying specific entities taking into account clinical/pathological syndromes including new genetic information. This approach was adopted by the WHO classification. We now have a new issue to resolve- that is, the relative merits of the new WHO classification versus the ICC classification. This presentation will compare and contrast these two approaches looking for particular strengths or weaknesses. We must always ask if the proposals are scientifically valid, reproducible by pathologists, and clinically relevant. Either way this will not be the last lymphoma classification as new insights into the biology of the diseases and identification of treatment targets will, hopefully, make our treatments more specific and more effective.

Keyword: pathology and classification of lymphomas

No conflicts of interests pertinent to the abstract.

SESSION 14 - NOVEL AGENTS

086 | HIGH COMPLETE RESPONSE RATE WITH TNB-486, A NOVEL CD19XCD3 T-CELL ENGAGER, IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA: INTERIM RESULTS FROM AN ONGOING PHASE 1 STUDY

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Introduction: Follicular lymphoma (FL) is incurable with a relapsing/remitting pattern and decreasing progression-free survival (PFS) interval per recurrence. In the relapsed/refractory (*R/R*) setting, patients (pts) failing chimeric antigen receptor T-cell therapy (CAR T) or CD20 bispecific T-cell engagers (TCE) have few options. TNB-486 is a novel bispecific CD19xCD3 TCE that induces T-cell–mediated cytotoxicity with reduced cytokine release via a low-affinity αCD3 moiety. We present interim data from a phase 1 dose-escalation study of TNB-486 (NCT04594642).

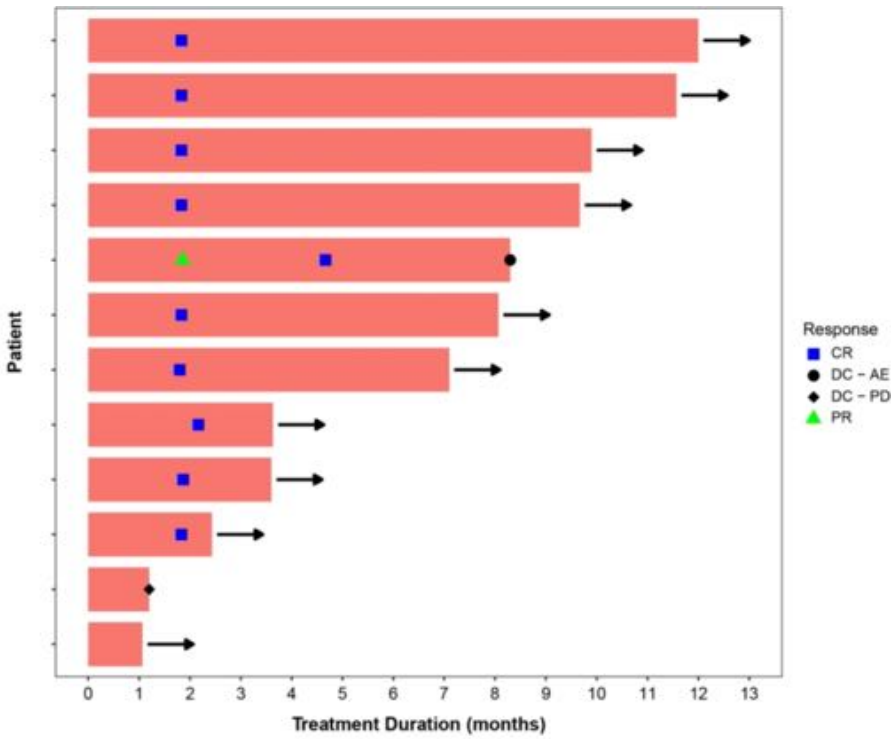
Methods: Third-line+ *R/R* FL pts (grade [G] 1–3a) were enrolled (prior CD19 therapy allowed). Escalating fixed TNB-486 doses (0.03–2.4 mg) without priming were evaluated prior to implementing single (day [D] 1) and double priming doses (D1 & 8) prior to target dose (D15). TNB-486 was given IV every 2 weeks in 28-d cycles (C) for up to 2 y. Response was assessed with RECIL 2017 by central image review. Adverse events (AEs) and cytokine release syndrome (CRS)/immune effector cell-associated neurotoxicity syndrome (ICANS) were graded by CTCAE v5.0 and 2019 ASTCT criteria.

Results: As of 31 December 2022, 17 pts received TNB-486 at target doses 0.03–10 mg (median age 68 y [range 33–86]; 53% male; 65% stage III/IV; 25% CD20-negative disease; median prior lines of therapy [LOT] 3 [range 2–9]). Prior therapies included αCD20 Ab (100%), alkylator (76%), IMiD (47%), CD20 TCE (12%), CD19 CAR T (12%), and autologous stem cell transplant (ASCT) (6%); 53% progressed or started 2nd LOT within 24 months (mo) of initiating 1st LOT (POD24). Median time on study was 7 mo (range 1–22). Eleven pts were response evaluable for efficacy at target doses ≥2.4 mg. Objective response rate (ORR) and complete response (CR) rate were 91% (**Figure**). ORR/CR for pts with CD20-negative disease, prior CD20 TCE, and POD24 was 100%. One pt with 9 prior LOT including ASCT and CAR T, had progression of disease. One pt progressed at C6 after achieving CR with preserved CD19 expression. All others remain in remission to date. The 6-mo PFS rate was 91%. No G3+ CRS occurred (59% G1, 12% G2). Neurologic events consistent with ICANS were reported in 24%, all G1–2 except 1 with a G3 event (confusion). All CRS/neurotoxicity (NT) were transient, resolving in a median of 1.5 d (range 1–5). G3+ treatment-related AEs in >10% of pts included decreased lymphocytes (35%) and neutropenia (12%). No treatment-related deaths or AEs leading to discontinuation occurred (1 pt died and 1 discontinued due to COVID-19). One pt received double step-up priming dosing to date with no CRS/NT. Pharmacokinetic/pharmacodynamic data analysis is ongoing.

Conclusions: TNB-486 induces high complete remission rates during early phase dose escalation. With limited follow-up, responses appear durable in heavily pretreated FL pts, with a manageable safety profile. Dose escalation is ongoing to identify the RP2D.

Encore Abstract—previously submitted to ASCO 2023 and EHA 2023

The research was funded by: AstraZeneca and TeneoTwo



DC - AE: discontinuation due to AE; DC - PD: discontinuation due to progressive disease; PR: partial response; arrow indicates ongoing treatment

Keywords: immunotherapy, indolent non-Hodgkin lymphoma, ongoing trials

Conflicts of interests pertinent to the abstract

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087 | PHASE 1B/2A STUDY OF AZD4573 (CDK9I) AND ACALABRUTINIB IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (*R/R* DLBCL)

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Introduction: AZD4573, a potent and highly selective CDK9i, rapidly induces apoptosis in human haematologic cancer cell lines. In a first-in-human trial, AZD4573 monotherapy had manageable safety in pts with *r/r* haematologic cancers and antitumour activity in those with DLBCL. In the current multicenter, open-label, Phase 1b/2a study (NCT04630756), initial results showed that AZD4573 up to 12 mg QW IV + acalabrutinib 100 mg continuously PO BID had manageable safety (no dose-limiting toxicities [DLTs]) and encouraging activity in pts with *r/r* DLBCL (Strati, ASH 2022, abs 2962). Here we report pooled data from the completed Phase 1b and ongoing Phase 2a expansion.

Methods: Pts were ≥18 years old with ECOG PS ≤2, and had received ≥2 prior lines of therapy (stem cell transplant, T cell engagers [TCEs] and/or CAR-T were allowed). Following a 3-wk intra-pt ramp-up, pts received AZD4573 QW at target doses of 9 mg (Cohort 1) or 12 mg (Cohort 2). Dose escalation used the mTPI-2 model. Objectives included ORR, safety and PK. Responses were assessed by Lugano 2014 criteria and adverse events (AEs) graded using CTCAE v5.0.

Results: As of 2 December 2022, 27 pts were treated: 8 in Cohort 1 and 19 in Cohort 2 (11 pts in escalation, 16 pts in expansion; pooled data is presented by dose). Median age was 60 yrs, 59.3% of pts were male, and median number of prior lines of treatment was 4 (range 2–6). Median duration of AZD4573 treatment was 14.9 wks (range, 1–74) in Cohort 1 and 8.9 wks (range, 1–38) in Cohort 2. Response was evaluable in 24 pts, 8 in Cohort 1 and 16 in Cohort 2; 11/24 had prior CAR-T and 5/24 had prior TCE. The ORR was 50.0% (95% CI 29.1, 70.9) and the CR rate was 25%. Responses occurred in both Cohorts. Median duration of response was 6.8 mos. Responses were noted in 5/11 pts with prior CAR-T (ORR 45.5%; 95% CI 16.7, 76.6), including 3 CRs in Cohort 2 and 2 PRs in Cohort 1. Responses were seen in both GCB (7 evaluable pts; 2 CRs/1 PR) and non-GCB (8 evaluable pts; 2 CRs/2 PRs) subtypes. AZD4573 PK was linear (half-life ~6 hrs) with dose-dependent increases in exposure (C_{max} and AUC) and target coverage. No DLTs were identified and both doses were expanded. Safety was evaluable in 27 pts. The most common TEAEs were primarily laboratory-based. ALT/AST and bilirubin increases were mainly due to down-modulation of hepatic transporter proteins and reduced

Table. Safety and clinical activity

	Cohort 1: AZD4573 9 mg QW + acalabrutinib 100 mg BID	Cohort 2: AZD4573 12 mg QW + acalabrutinib 100 mg BID	Total
Treatment-emergent AEs, n (%)	**(n=8)**	**(n=19)**	**(N=27)**
Any grade AEs	8 (100)	18 (94.7)	26 (96.3)
Grade ≥3 AEs	8 (100)	17 (89.5)	25 (92.6)
Serious AEs	2 (25.0)	12 (63.2)	14 (51.9)
AEs with outcome of death	0	1 (5.3)*	1 (3.7)*
AEs leading to d/c of AZD4573	0	2 (10.5)	2 (7.4)
AEs leading to d/c of acalabrutinib	0	1 (5.3)	1 (3.7)
Antitumor response	**(n=8)**	**(n=16)**	**(N=24)**
Objective response rate, % (95% CI)	50.0 (15.7, 84.3)	50.0 (24.7, 75.3)	50.0 (29.1, 70.9)
Best overall response, n (%)			
Complete response	1 (12.5)	5 (31.3)	6 (25.0)
Partial response	3 (37.5)	3 (18.8)	6 (25.0)
Stable disease	0	1 (6.3)	1 (4.2)
Progressive disease	4 (50.0)	2 (12.5)	6 (25.0)
Missing	0	5 (31.3)†	5 (20.8)†
Median duration of response, months (95% CI)	NR	3.6 (1.1, NC)	6.8 (1.1, NC)
Median progression-free survival, months	NR	4.0 (1.35, 5.78)	4.0 (1.54, 5.78)
Median overall survival, months (95% CI)	NR	9.1 (3.65, NC)	NR

AE, adverse event; BID, twice daily; d/c, discontinuation; NR, not reached; NC, not calculable; QW, weekly

*Unrelated to AZD4573

†Reasons for missing data: overall disease response not recorded at time of data cutoff (n=3), death due to progressive disease, with no scan performed (n=1), and discontinuation (consent withdrawal) before week 8 (n=1).

enzyme clearance, not direct hepatocellular injury; all were short-lived with spontaneous resolution and caused no treatment delays. Neutropenia occurred in 92.6% of pts but was manageable with G-CSF; 4/27 pts (14.8%) had Grade ≥3 infections. One pt discontinued due to AZD4573-related Grade 2 fatigue.

Conclusions: AZD4573 + acalabrutinib had manageable safety with no new signals. Clinical activity was promising with durable responses in heavily pretreated pts, including those with prior CAR-T. More mature data will be presented at the conference.

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Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies

Conflicts of interests pertinent to the abstract

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088 | PHASE 1 STUDY OF JNJ-67856633, A FIRST-IN-HUMAN MALT1 INHIBITOR, IN RELAPSED/REFRACTORY (R/R) B-CELL NON-HODGKIN LYMPHOMA (B-NHL) AND CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Introduction: MALT1 is a key component of the CARD11-BCL10-MALT1 (CBM) complex, which activates the classical NF-κB pathway. JNJ-67856633 (JNJ-6633), a highly selective protease inhibitor of CBM-mediated NF-κB signaling, demonstrated potent anti-lymphoma activity in preclinical models. Here, we present results from a phase 1 dose escalation study of JNJ-6633 in patients (pts) with *R/R* B-NHL and CLL.

Methods: Pts were ≥18 years with *R/R* B-NHL or CLL (per WHO/iwCLL criteria), ECOG PS ≤1, and ≥1 or 2 lines of therapy (LOT). Dose escalation was supported by a modified continual reassessment method to identify recommended phase 2 dose (RP2D). Pts received oral 50–600 mg JNJ-6633 once daily (QD). Loading doses (LD) were explored to accelerate steady-state exposure of JNJ-6633: 2 LD using capsules at 400 mg QD for 14 days followed by 300 mg QD, and 300 mg twice daily for 7 days followed by 300 mg QD. Similar LD were used for tablets.

Results: At a clinical cutoff of 22 January 2023, 109 pts with *R/R* B-NHL or CLL received JNJ-6633 (n = 89, capsules; n = 20, tablets). Median duration of treatment was 10.3 weeks (range 0.57–176.29). Most common histology was diffuse large B-cell lymphoma (n = 65 [59.6%]). Treatment-emergent AEs were reported in 97.2% pts (Table). Hyperbilirubinemia was observed in 44% of pts and taken into consideration when selecting RP2D. Dose limiting toxicities were reported in 5 pts (400 mg, Grade 3 [G3] hyponatremia; 600 mg, G2 bradycardia; 300 mg, G3 febrile neutropenia; 400 mg LD, G3 renal failure; 300 mg LD, G3 acute renal failure); 4 pts continued with same dosing and 1 pt had dose reduction. Maximum-administered dose was 600 mg QD and maximum-tolerated dose was not reached. Based on toxicity profile, RP2D was 300 mg QD and LD 300 mg. No new safety signals were observed with both formulations at different LD. Preliminary pharmacokinetic data showed JNJ-6633 is rapidly absorbed (median T_{max}, range 2–5 h), slowly eliminated at 50–600 mg doses, and accumulated ~8-fold upon multiple dosing. Steady-state exposure of 50 mg capsule increased in an approximately dose proportional manner as the dose increased from 50 to 400 mg. Exposures were comparable between tablet doses of 200 or 240 mg and a capsule dose of 300 mg. Overall response rate (ORR) at RP2D (n = 36) was 27.8% (complete response, n = 4 [11.1%]; partial response, n = 6 [16.7%]). Responses were observed across indolent and aggressive histologic subtypes.

Conclusions: Preliminary data from this phase 1 dose escalation study of JNJ-6633 indicates it has a manageable hematological and non-hematological safety profile. JNJ-6633 demonstrated clinical activity in indolent and aggressive lymphomas. LD may be associated with higher ORR and is further explored in expansion cohorts. Safety and efficacy results from this dose escalation study supported targeting MALT1 in pts with *R/R* B-NHL and CLL and further evaluation of JNJ-6633 in expansion cohorts.

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Keywords: chronic lymphocytic leukemia (CLL), molecular targeted therapies, non-Hodgkin (pediatric, adolescent, and young adult)

No conflicts of interests pertinent to the abstract.

089 | ENHANCER OF ZESTE HOMOLOG 2 (EZH2) INHIBITOR SHR2554 IN RELAPSED OR REFRACTORY (*R/R*) PERIPHERAL T-CELL LYMPHOMA (PTCL): UPDATED OUTCOMES FROM THE FIRST-IN-HUMAN PHASE 1 STUDY

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Table. Summary of TEAEs

Safety	n (%)	
	Any grade	Grade 3-4
TEAEs	106 (97.2)	84 (77.1)
TEAEs in ≥20% of patients		
Hyperbilirubinemia	48 (44.0)	16 (14.7)
Anemia	39 (35.8)	18 (16.5)
Neutropenia	35 (32.1)	29 (26.6)
Diarrhea	26 (23.9)	3 (2.8)
Rash[a]	24 (22)	8 (7.3)
Thrombocytopenia	25 (22.9)	11 (10.1)
Blood creatinine increased	22 (20.2)	0 (0.0)

[a]Includes preferred terms "rash", "rash maculo-papular", "rash macular", "rash erythematous", and "rash papular".

TEAE, treatment-emergent adverse event.

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Introduction: Inhibition of histone methyltransferase EZH2 represents a rational therapeutic strategy for lymphomas. SHR2554 is an oral small-molecule inhibitor exhibiting potent selectivity for EZH2. The multicenter, 2-part, phase 1 study was initiated to assess SHR2554 in patients (pts) with *r/r* lymphomas (NCT03603951). In part I, 350 mg BID was established as the recommended phase 2 dose (RP2D) based on the findings in the dose-escalation and expansion phases; subsequently, pts with selected lymphoma subtypes were recruited in the clinical expansion phase to receive SHR2554 at RP2D (Y Song et al. *Lancet Haematol*, 2022). Here we report the updated results of part I focusing on PTCL pts at RP2D. The prognosis of PTCL is extremely poor due to low response to chemotherapy regimens and limited treatment options thereafter, highlighting an urgent, unmet medical need.

Methods: Pts with histologically confirmed PTCL that had relapsed or were refractory to ≥1 line of prior systemic therapy were eligible for inclusion in part I of this study. Efficacy and safety were assessed in PTCL pts who received at least one dose of SHR2554 at 350 mg BID.

Results: Totally, 28 pts were included in this analysis: median age, 56 y (range 30–70); ECOG PS 1, 64.3% (18/28); median lines of prior systemic therapies, 2 (range 1–14). At data cutoff on 31 August 2022, the median follow-up duration was 11.9 mo (range 0.9–23.9). 17 pts achieved complete or partial response, resulting in a confirmed objective response rate (ORR) of 60.7% (95% CI 40.6–78.5). Responses were still ongoing in 58.8% (10/17) of the responders; estimated median duration of response (DoR) was 12.3 mo (95% CI 7.4–NR). 16 (57.1%) pts had disease progression or died; median progression-free survival (PFS) was 11.1 mo (95% CI 5.3–22.0). 4 (14.3%) deaths occurred; 1-y overall survival rate was 92.2% (95% CI 72.1–98.0). Of the 28 pts, 17 were diagnosed with angioimmunoblastic T-cell lymphoma (AITL), and 11 had PTCL not otherwise specified (PTCL-NOS). AITL pts showed better outcomes than PTCL-NOS pts: ORR, 76.5% versus 36.4%; median DoR, 20.3 versus 3.3 mo; median PFS, 22.1 versus 5.0 mo (Table). Grade ≥3 treatment-related adverse events (TRAEs) occurred in 14 of the 28 pts (50.0%), with the most common being decreased platelet count (32.1%), decreased

Table. Efficacy outcomes of PTCL pts following treatment with SHR2554 at RP2D

	All PTCL (N=28)	PTCL subtypes	
		AITL (N=17)	PTCL-NOS (N=11)
ORR, n (%; 95% CI)	17 (60.7%; 40.6–78.5)	13 (76.5%; 50.1–93.2)	4 (36.4%; 10.9–69.2)
DCR, n (%; 95% CI)	22 (78.6%; 59.0–91.7)	15 (88.2%; 63.6–98.5)	7 (63.6%; 30.8–89.1)
DoR			
Ongoing response, n/N (%)	10/17 (58.8%)	10/13 (76.9%)	0/4 (0%)
Median (95% CI), mo	12.3 (7.4–NR)	20.3 (12.1–NR)	3.3 (1.8–NR)
PFS			
Events, n/N (%)	16/28 (57.1%)	6/17 (35.3%)	10/11 (90.9%)
Median (95% CI), mo	11.1 (5.3–22.0)	22.1 (13.8–NR)	5.0 (0.6–5.5)
OS			
Events, n/N (%)	4/28 (14.3%)	2/17 (11.8%)	2/11 (18.2%)
1-y OS rate, % (95% CI)	92.2% (72.1–98.0)	100% (NE–NE)	77.8% (36.5–93.9)

RP2D, recommended phase 2 dose; PTCL, peripheral T-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; NOS, not otherwise specified; ORR, objective response rate; DCR, disease control rate; DoR, duration of response; PFS, progression-free survival; OS, overall survival; CI, confidence interval; NR, not reached; NE, not estimable.

white blood cell count (14.3%), decreased neutrophil count (14.3%), and anemia (14.3%). One (3.6%) pt discontinued treatment due to TRAE (interstitial lung disease). No treatment-related deaths were reported.

Conclusions: This extended follow-up analysis further provides evidence of potent anti-tumor activity, durable response, and acceptable safety of SHR2554 in pts with *r/r* PTCL.

The research was funded by: The study was sponsored by Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Keywords: aggressive T-cell non-Hodgkin lymphoma, molecular targeted therapies

Conflicts of interests pertinent to the abstract

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090 | OPEN-LABEL PHASE 1/2 STUDY OF CC-99282, A CEREBLON E3 LIGASE MODULATOR (CELMOD) AGENT ± RITUXIMAB, IN PATIENTS WITH RELAPSED/REFRACTORY (*R/R*) NON-HODGKIN LYMPHOMA (NHL)

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Introduction: CC-99282 is a novel, oral, small molecule CELMoD® agent that co-opts cereblon to induce targeted degradation of Ikaros/Aiolos, transcription factors critical for B-cell malignancy development. Compared with immunomodulatory drugs (IMiD), CC-99282 had 10- to 100-fold enhanced antiproliferative and apoptotic activity in preclinical models of diffuse large B-cell lymphoma (DLBCL), while maintaining immunostimulatory effects. We previously reported promising efficacy and a predictable and manageable safety profile of CC-99282 in patients (pts) with *R/R* NHL (Michot et al. EHA, 2022).

Methods: CC-99282-NHL-001 (NCT03930953) is a 2-part, multicentre, first-in-human study with dose escalation of CC-99282 monotherapy (part A) and expansion ± combination partners (part B) in pts with *R/R* DLBCL or follicular lymphoma (FL) who progressed after ≥2 lines of therapy, or pts with *R/R* DLBCL with ≥1 line of standard therapy and transplant-ineligible. Part A dosing is CC-99282 0.2–0.8 mg QD on 3 intermittent schedules of 28 d cycles. Part B dosing is CC-99282 0.2 or 0.4 mg alone on 2 intermittent schedules or with rituximab (RTX). Here, we report updated efficacy results for CC-99282 monotherapy (part A) and new safety data for CC-99282 + RTX (part B).

Results: For part A, as of Sep 14, 2022, 50 pts were treated (38 DLBCL, 12 FL; median age 66 y); 3 pts (6%) completed, 7 (14%) were ongoing and 40 (80%) discontinued, most commonly due to progressive disease ($n = 33$, 66%). Median # of prior systemic anticancer therapies was 3 (range 1–8). For doses ≥0.4 mg on 7/14 or 14/28 d schedules, the overall response rate was 43% (17/40 evaluable pts; 10/30 DLBCL, 7/10 FL), with complete response in 7 and partial response in 10 pts. Responders included pts previously treated with CAR T cell therapy and/or IMiD/CELMoD agents. Responses were durable (Figure), with median duration of response (mDOR) of 299 d (range 48–898; median follow-up [mFU] 293) in pts with DLBCL and mDOR of 448 d (135–930; mFU 572) in pts with FL. For part B, as part of the safety run-in, 12 pts were treated with CC-99282 + RTX (9 DLBCL, 3 FL; median age 61y). With mFU of 6 wks (range 4–28), neutropenia was the most common any-grade treatment-emergent adverse event (AE), occurring in 5/12 (42%) pts, including 25% (3/12) grade 3/4 neutropenia. No febrile neutropenia occurred. There were no dose reductions, discontinuations, or dose-limiting toxicities (DLTs). Severe AEs included fever (n = 2), and dyspnoea and fatigue (n = 1 each). Similar safety profiles were observed at both CC-99282 dose levels, 0.2 and 0.4 mg, combined with RTX.

Conclusions: CC-99282 oral monotherapy continues to show promising efficacy in heavily pretreated pts with *R/R* NHL, achieving durable responses up to 900 d. CC-99282 can be safely combined with RTX, with no DLTs reported. This study is ongoing, with continued

enrolment in the monotherapy and CC-99282 + RTX combination expansion cohorts.

The research was funded by: Celgene, a Bristol-Myers Squibb Company

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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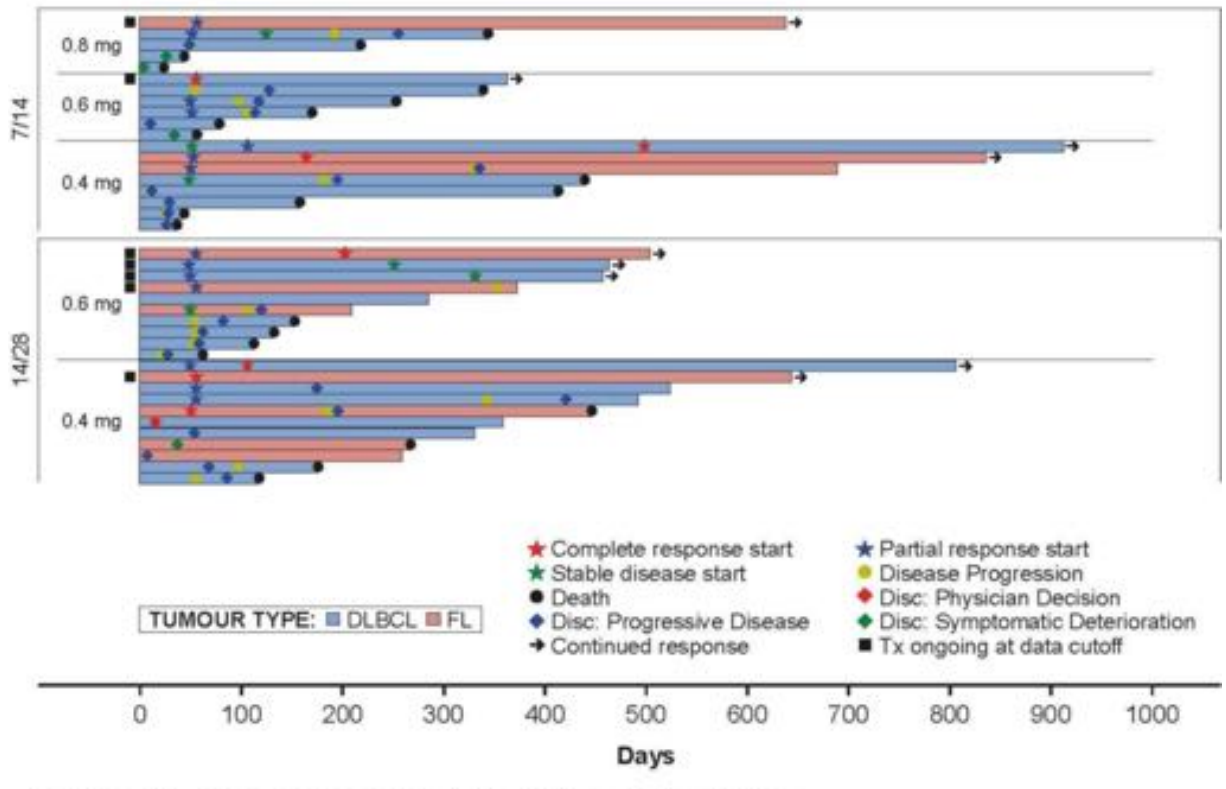
Figure: Duration of response for Part A dose schedules 7/14 and 14/28*



*Each bar starts from treatment start to earliest of death date, cutoff date and last known alive date. Continued response is defined as censored duration of response/duration of stable disease

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091 | COMBINING CD19-4-1BBL (RO7227166) WITH GLOFITAMAB IS SAFE AND SHOWS EARLY EFFICACY IN PATIENTS SUFFERING FROM RELAPSED OR REFRACTORY B-CELL NON-HODGKIN LYMPHOMA

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Introduction: The antibody-like fusion protein RO7227166 simultaneously targets CD19 on B-cells and 4-1BB (CD137) on T cells. RO7227166 activity is strictly dependent on CD19 crosslinking and exhibits no single-agent activity. RO7227166 plus glofitamab shows strong synergy in preclinical models and is being developed for patients (pts) with relapsed/refractory B-cell non-Hodgkin lymphoma (*R/R* B-NHL).

Methods: This first-in-human trial BP41072 (NCT04077723) evaluated the safety, tolerability, pharmacokinetics/dynamics and preliminary activity of RO7227166 in combination with glofitamab. After a single obinutuzumab dose (1000 mg), pts started glofitamab step up dosing receiving the first target dose of 30 mg on C2D1. On C2D8 RO7227166 dose was given intravenously. From C3D1 both drugs were administered Q3W for a maximum of 12 cycles. Dose escalation was conducted using an mCRM EWOC model with overdose control. Response rates were assessed using Lugano criteria.

Results: As of 15 December, 57 pts with aggressive (aNHL) and 23 pts with indolent NHL (iNHL) out of a total of 104 enrolled (all histologies) were evaluable. Aggressive NHL include 42 DLBCL (diffuse large B-cell lymphoma) and 15 trFL (transformed follicular lymphoma). RO7227166 doses ranging from 360 ug up to 75 mg were assessed and the maximum tolerated dose was not reached. Pts (aNHL/iNHL) had median age of 63/62, 39% female, ECOG 0 (56%/74%) or 1 (44%/26%), and stage IV (54%/56%). Patients were heavily pre-treated (median 3 for both [1–8]; 46%/4% had prior CAR-T and 19.7%/9% were primary refractory.

Across the 84 safety evaluable pts (all histologies) who received both glofitamab and RO7227166 at least once, the most common adverse events (>15% of pts) were cytokine release syndrome (CRS, 58.3%), neutropenia (28.6%), COVID-19 (25.0%), anemia (22.6%), diarrhea and rash (19.0% each), fatigue (17.9%) and pyrexia (16.7%). Grade 5 events were reported in 5 pts (6%), related to study treatment in 2 pts. A Grade 5 pneumocystis jiroveci pneumonia, related to glofitamab qualified as dose-limiting toxicity ($n = 1$).

CRS was grade 1 in 50.0%, grade 2 in 16.7% and grade 3 in a single patient, mostly confined to the first two cycles of glofitamab. CRS was considered related to only RO7227166 in 6 pts and were all grade 1. Across all doses investigated, best ORR (aNHL/iNHL) was 70%/ 95.7% with CRR of 53%/74%. The aNHL pts with prior CAR-T had 68% BORR and 42% CRR.

RO7227166 exposure increased in an almost dose proportional manner for doses ≥22 mg. Furthermore, pharmacodynamic analysis showed expansion of primed and activated CD8, and effector memory T-cells, with a reduction of exhausted T cell phenotypes.

Conclusions: Glofitamab can be safely combined with a costimulatory bispecific antibody (RO7227166) in *R/R* B-NHL. The safety profile of the combination was mainly driven by glofitamab and we did not detect an additive safety signal from RO7227166.

Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy, ongoing trials

Conflicts of interests pertinent to the abstract

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SESSION 15 - IMMUNOTHERAPY FOR AGGRESSIVE LYMPHOMAS

092 | GLOFITAMAB PLUS POLATUZUMAB VEDOTIN DEMONSTRATES DURABLE RESPONSES AND A MANAGEABLE SAFETY PROFILE IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Glofitamab (Glofit) is a bispecific CD20:CD3 antibody which redirects T cells to eliminate malignant B cells. The CD79b targeted antibody-drug conjugate polatuzumab vedotin (Pola) is approved in combination with bendamustine and rituximab for the treatment of *R/R* DLBCL. Glofit and Pola have distinct yet complementary mechanisms of action, with little overlap in toxicity profiles. Initial data from an open-label, multicenter Phase Ib/II study (NCT03533283) support the manageable safety and encouraging efficacy of Glofit + Pola in *R/R* DLBCL (Hutchings et al. ASH, 2021). We present updated study results (data cutoff 25 January 2023).

Methods: Patients (pts) received obinutuzumab 1000 mg on Day (D) 1 of the first 21-day cycle (C), to mitigate risk of cytokine release syndrome (CRS). Pola 1.8 mg/kg was given on C1D2 and D1 of C2–6. Glofit was given with C1 step-up dosing (C1D8 2.5 mg; C1D15 10 mg; C2–12 D1, 10/30 mg) for up to 12 cycles. Per protocol, 24-hour hospitalization was only mandatory after the first Glofit infusion. Primary objective: to establish the recommended Phase II dose of Glofit in combination with Pola (identified as 30 mg; Hutchings et al. ASH, 2021). Additional objectives: safety, efficacy, PK (secondary), and biomarkers (exploratory).

Results: As of 25 January 2023, 111 pts received ≥1 dose of study drug. Median age was 68 yrs (range 23–82), 51.5% had *R/R* DLBCL, 24% *R/R* HGBCL, 23% *R/R* trFL, and 2% *R/R* PMBCL. 71% of pts were refractory to their last therapy, median prior lines of therapy was 2 (range 1–7; 39% received 1 prior line), and 25% of pts had prior CAR T-cell therapy. The most common AE was CRS (44%): majority ASTCT criteria Gr 1/2 (30%/14%). One pt had Gr 5 CRS in the context of urosepsis and herpetic stomatitis but declined intensive CRS management. Gr 3/4 AEs occurred in 61% of pts, most commonly neutropenia (30%; one febrile neutropenia event). Glofit-related neurologic AEs potentially consistent with ICANS occurred in 3 pts (Gr 1/2). Pola-related peripheral neuropathy was reported in 21% of pts (all Gr 1/2). SAEs occurred in 59% of pts and Gr 5 AEs in 6% (5/7 Gr 5 events due to COVID-19). 9% of pts discontinued treatment due to an AE (2% due to COVID-19). Of 109 efficacy-evaluable pts, best ORR (BORR) for both dosing cohorts (per Lugano 2014) was 78%, with best CR (BCR) rate of 56%. By histology, BORR and BCR, respectively were: *R/R* DLBCL 86% (48/56) and 61% (34/56); *R/R* trFL 77% (20/26) and 54% (14/26); *R/R* PMBCL 100% (2/2) and 100% (2/2); HGBCL 60%

(15/25) and 44% (11/25). With median FU of 13.0 months (95% CI: 11.8–16.6), median PFS was 10.4 months (95% CI: 5.8–19.0; **Figure**) and median DoR was 17.9 months (95% CI: 10.1–NE).

Conclusions: Glofit + Pola resulted in frequent and durable responses and a manageable safety profile, with mostly low-grade CRS and low ICANS prevalence. The safety profile was consistent with that of the individual drugs. Updated efficacy, PK, and biomarker data will be presented.

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Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy

Conflicts of interests pertinent to the abstract

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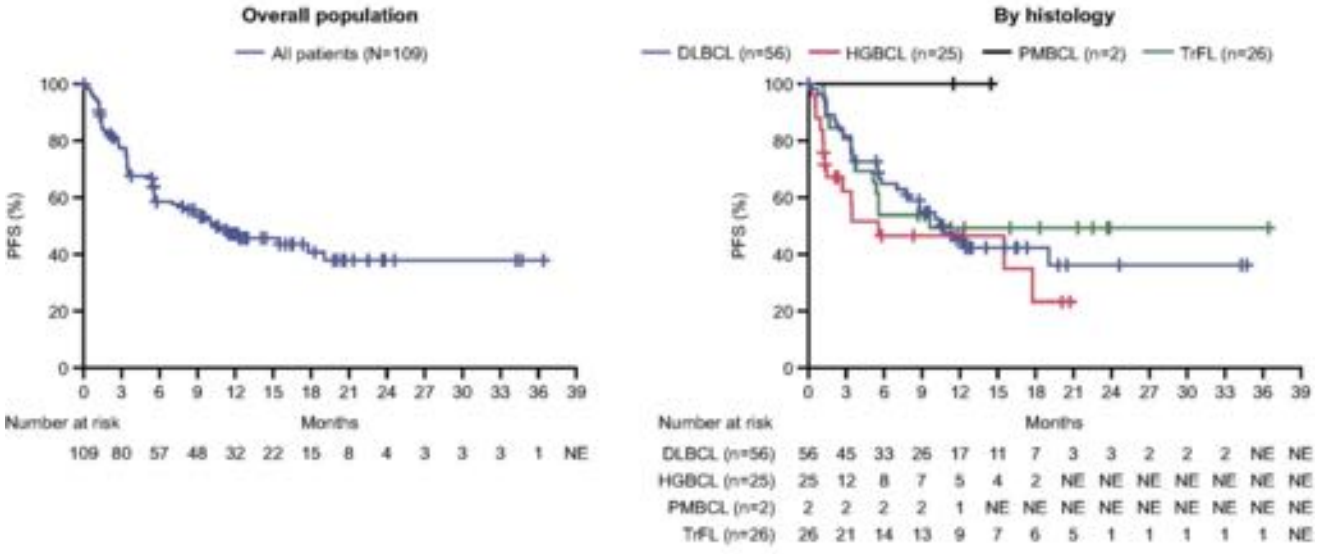
Figure. PFS with Glofit+Pola



DLBCL, diffuse large B-cell lymphoma; Glofit+Pola, glofitamab plus polatuzumab vedotin; HGBCL, high-grade B-cell lymphoma; NE, not estimable; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; TrFL, transformed follicular lymphoma

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093 | ODRONEXTAMAB IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): RESULTS FROM A PRESPECIFIED ANALYSIS OF THE PIVOTAL PHASE II STUDY ELM-2

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Introduction: Odronextamab is a CD20×CD3 bispecific antibody (Ab). In ELM-1 (Ph1, NCT02290951), odronextamab demonstrated encouraging activity and a generally manageable safety profile in patients (pts) with heavily pretreated DLBCL (Bannerji R et al. Lancet Haematol, 2022). Here, we present results from a prespecified analysis of the DLBCL cohort from the ELM-2 study (Ph2, NCT03888105).

Methods: ELM-2 is a global, multicenter study that enrolled adult pts with DLBCL who were relapsed/refractory (*R/R*) after ≥2 prior lines of therapy (LOT) including an anti-CD20 Ab and an alkylator; previous CAR T therapy was not permitted. Informed consent was obtained for all pts. IV odronextamab was administered in 21-day cycles with steroid prophylaxis and step-up dosing during Cycle (C) 1. The initial step-up regimen was 1 mg split over C1 Day (D) 1 and C1D2, and 20 mg split over C1D8 and C1D9, followed by the 160 mg full dose on C1D15 (1/20 regimen). This regimen was revised during the study to further mitigate risk of cytokine release syndrome (CRS), with the modified regimen consisting of 0.7 mg split over C1D1 (0.2 mg) and C1D2 (0.5 mg), 4 mg split over C1D8 and C1D9, and 20 mg split over C1D15 and C1D16, then the full 160 mg dose on C2D1 (0.7/4/20 regimen). 160 mg QW continued until the end of C4, followed by 320 mg Q2W until disease progression or unacceptable toxicity. Primary endpoint was objective response rate (ORR) assessed by independent central review (ICR).

Results: As of 15 September 2022, 140 pts had been treated: median age, 66 y (range 24–88); male, 59%; Ann Arbor stage III–IV, 80%; median prior LOT, 2 (range 2–8); primary refractory, 57%; double refractory to anti-CD20 Ab and an alkylator in any LOT, 66%. Median duration of study follow-up was 21.3 mos. ORR and CR rate by ICR were 49% (64/130) and 31% (40/130), respectively, and were consistent across high-risk subgroups. CRs were durable; median duration of CR was 17.9 mos (95% CI 10.2 mos–not estimable) and the probability of an ongoing CR at 18 mos was 48%.

TEAEs occurred in 139 (99%) pts, considered treatment-related in 123 (88%). Treatment-related Grade (Gr) 5 AEs occurred in 5 pts, and treatment-related AEs led to discontinuation in 11 pts. The most common TEAEs (>30% all grades) were CRS (55%), anemia (42%), and pyrexia (39%). With the 0.7/4/20 regimen ($n = 73$), 1 pt had Gr 3 CRS (no cases of Gr 4 or 5 CRS; no pts required mechanical ventilation or ICU admission for CRS management), and ICANS was reported in only 1 pt (Gr 2).

Conclusions: In the ELM-2 trial, odronextamab showed clinically meaningful efficacy, durable CRs, and a manageable safety profile. These data confirm the efficacy of odronextamab in hard-to-treat, highly aggressive *R/R* DLBCL. The 0.7/4/20 odronextamab step-up regimen mitigates the risk of high-grade CRS, which is consistently observed with other bispecifics and CAR T therapies, and may present an important future option for the management of *R/R* DLBCL.

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094 | SUBCUTANEOUS EPCORITAMAB INDUCES DEEP, DURABLE COMPLETE REMISSIONS IN RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA: LONGER FOLLOW-UP FROM THE PIVOTAL EPCORE NHL-1 TRIAL

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Introduction: Outcomes are poor for patients with relapsed/refractory (*R/R*) large B-cell lymphoma (LBCL). Effective treatments that drive deep, durable responses and long-term benefit are needed. In the pivotal EPCORE™ NHL-1 trial (NCT03625037), single-agent epcoritamab showed high complete response (CR) and MRD-negativity rates and a manageable safety profile as an off-the-shelf, subcutaneous, CD3xCD20 T-cell–engaging bispecific antibody (Thieblemont et al. *J Clin Oncol*, 2022). We present updated results, including longer follow-up, in a challenging-to-treat population.
Methods: Patients with *R/R* $CD20^+$ LBCL received subcutaneous epcoritamab (step-up priming and intermediate doses followed by

Table. Outcomes for complete responders (n=62)

Median duration of response among complete responders, mo	20.8 (95% CI, 17.3–NR)		
Median progression-free survival, mo	NR (95% CI, 18.5–NR)		
Median overall survival, mo	NR (95% CI, NR–NR)		
	9 mo	**12 mo**	**15 mo**
Estimated complete responders remaining in response, %	91.2	85.2	79.0
Estimated progression-free survival, %	91.1	87.2	81.3
Estimated overall survival, %	98.3	95.0	88.3

Kaplan–Meier estimates.

48-mg full doses) in 28-d cycles: QW, cycles 1–3; Q2W, cycles 4–9; Q4W, cycles ≥10 until PD or unacceptable toxicity.

Results: As of 18 November 2022, of 157 patients (median age, 64 y) with LBCL (including DLBCL [*n* = 139; 12/88 double/triple-hit by FISH], HGBCL [*n* = 9], PMBCL [*n* = 4], and FL grade 3B [*n* = 5]), 36 remain on study treatment. Patients had a median of 1.6 y from initial diagnosis to first dose and a median of 3 (range, 2–11) prior treatment lines; 61% of patients had primary refractory disease, and 39% had prior CAR T, of whom 75% progressed within 6 mo of treatment. Median follow-up was 20 mo (range, 0.3+ to 28.2). Patients received a mean of 9.1 cycles. LBCL overall response and CR rates were 63.1% and 39.5%, respectively, and were consistent for DLBCL (61.9% and 39.6%, respectively). The median duration of CR was 20.8 mo. Median time to CR was 2.7 mo; 8 patients converted from partial response to CR at ≥36 wk. Median overall survival was 18.5 mo (95% CI, 11.7–not reached [NR]) for patients with LBCL and 19.4 mo (95% CI, 11.7–NR) for patients with DLBCL. Median overall survival was NR in patients who achieved CR. Additional outcomes for patients with CR are shown in the **Table**. The most common treatment-emergent AEs of any grade (G) were CRS (51%), neutropenia (24%), pyrexia (24%), fatigue (23%), nausea (22%), and diarrhea (21%). Nine patients (6%) had G1–2 ICANS, and 1 patient had a G5 event with confounding factors. Fatal treatment-emergent AEs occurred in 15 patients; 2 were considered related (COVID-19, ICANS). CRS was predominantly low grade (48% G1–2; 3% G3) and occurred following the first full dose (cycle 1, day 15). One patient discontinued treatment due to G1 CRS.

Conclusions: These data with longer follow-up reaffirm single-agent subcutaneous epcoritamab induces durable CRs with improved outcomes and a manageable safety profile in patients with *R/R* LBCL. No new safety signals were observed in these hard-to-treat patients. These impressive data support the ongoing phase 3 studies evaluating epcoritamab across different lines of treatment and in various combinations.

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095 | GLOFITAMAB MONOTHERAPY IN PATIENTS WITH RELAPSED/REFRACTORY (*R/R*) LARGE B-CELL LYMPHOMA (LBCL): EXTENDED FOLLOW-UP AND LANDMARK ANALYSES FROM A PIVOTAL PHASE II STUDY

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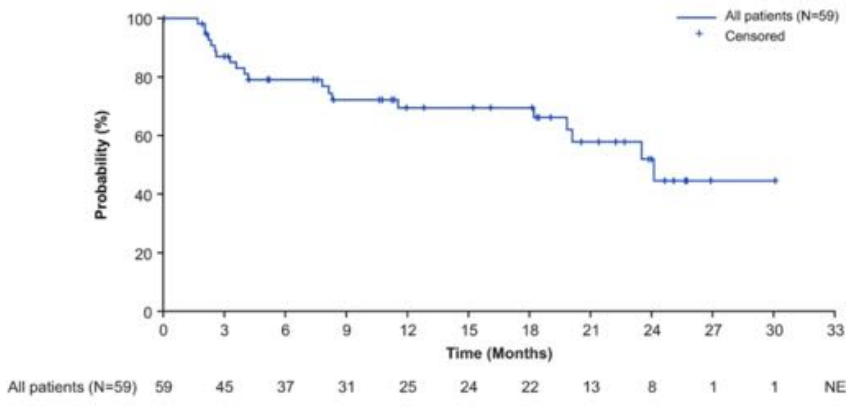
Introduction: Glofitamab is a CD20xCD3 bispecific antibody delivered in a fixed course of 12 three-weekly cycles. In a Phase II study (NCT03075696), glofitamab induced high complete response (CR) rates and had manageable toxicity in pts with *R/R* LBCL (Dickinson et al., 2022). We present an extended follow-up and a landmark analysis to assess the outcomes of pts in CR.

Figure: Duration of complete response in patients with R/R LBCL who received glofitamab monotherapy



LBCL, large B-cell lymphoma; R/R, relapsed/refractory.

Methods: Pts with LBCL and ≥2 prior therapies received 1000 mg obinutuzumab pretreatment 7 days prior to the first glofitamab dose. IV glofitamab was given as step-up doses: 2.5 mg on Day (D) 1 of Cycle (C) 1, 10 mg on C1D8 and 30 mg (target dose) on D1 of C2–12 (21-day cycles). The primary endpoint was independent review committee (IRC)-assessed CR rate. Progression-free survival (PFS) and overall survival (OS) post-hoc analyses were performed in responders (landmark for CR at C3 or end of treatment [EOT]).

Results: As of 10 October 2022, 154 pts had received ≥1 dose of study treatment; baseline characteristics were as previously presented. Median number of prior therapies was 3 (range: 2–7); 33% had received prior CAR T-cells and 85% were refractory to their most recent regimen. Median time on study was 20.1 months (range: 0–32). The investigator (INV)-assessed CR rate (BOR) was 38% (40% by IRC) and overall response rate was 59% (52% by IRC). CR rates were consistent in pts with and without prior CAR-Ts (37% vs. 39%). After a median follow-up of 18.3 months (range: 0–30) in pts with a CR (BOR), most CRs (39/59; 66%) were ongoing. Median duration of CR (DoCR) was 24.1 months (95% CI: 19.8–NE); an estimated 70% of pts with a CR at any time remained in remission at 18 months (Figure). The 18-month OS rate was 41% (95% CI: 32.1–49.3). Landmark analyses at 1 year in pts with a CR pre-C3 (PFS rate: 71%, OS rate: 92%) and in pts with a CR at EOT (PFS rate: 80%, OS rate: 94%) showed that most pts were progression free and alive. In a cohort of 101 pts treated with glofitamab doses below the recommended Phase II dose but ≥10 mg with longer median CR follow-up (31 months, range: 1–49), the median DoCR was 30.1 months (95% CI: 5.5–NE) and 55% of pts were still in remission at data cut-off. This further confirms the highly durable responses achieved with glofitamab.

CRS (by ASTCT) remained the most common adverse event (AE), occurring in 64% of pts and was mostly Grade (Gr) 1 (48%) or Gr 2 (12%); Gr 3 (3%) and Gr 4 (1%) events were uncommon. The incidence of AEs and serious AEs was stable compared with earlier analyses, with one new Gr 3 AE (acute kidney injury), one new Gr 2 neurologic AE (agitation) and no new glofitamab-related Gr 5 AEs reported.

Conclusions: Glofitamab continued to demonstrate durable responses, with most pts in CR at EOT still in remission without new AEs. These data support the potential for favorable long-term outcomes with fixed-duration glofitamab for *R/R* LBCL. Updated analyses, including a larger population with a median CR follow-up of approximately 20 months post-EOT, will be presented.

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Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy

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096 | BISPECIFIC ANTI-CD20/19 CAR-T—ZAMTOCABTAGENE AUTOLEUCEL FOR RELAPSED/REFRACTORY DLBCL—INTERIM ANALYSIS RESULTS OF DALY-II-USA STUDY

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Background: DALY II USA is the first multicenter trial of fresh, bispecific targeted CD20/CD19, chimeric antigen receptor (CAR) T-cell therapy for patients (pts) with *R/R* diffuse large B-cell lymphoma (DLBCL). While CD19 CAR T-cell therapy is an established treatment for pts with *R/R* DLBCL, relapse remains a clinical challenge. One proposed mechanism of resistance is either loss of epitope, recognition, or downregulation of the CD19 receptor. To improve outcomes, dual targeting of B-cell receptors has been proposed. Reported here is the preplanned interim futility analysis after treatment of 22 evaluable pts.

Aim: To assess safety and efficacy of dual CAR-T therapy with zamtocabtagene autoleucel (zamto-cel) administered fresh in *R/R* DLBCL.

Methods: Eligible pts were >18 y, ECOG PS 0–1, with *R/R* DLBCL after ≥2 prior lines of systemic therapy. No bridging chemotherapy was allowed. Apheresis material was shipped fresh without cryopreservation to a central manufacturing site. A fixed 12-day process of CAR-T production was performed using the CliniMACS Prodigy® (Miltenyi Biotec). A single infusion of $2.5x10^6$ cells/kg fresh zamto-cel was administered after lymphodepletion which was initiated during manufacturing to facilitate a fresh infusion. Evaluation of response rate is the primary objective of this study.

Results: As of 1 September 2022, 28 pts have enrolled (All treated) with 22 evaluable per protocol. Most (69%) of treated patients presented advanced disease with IPI score of at least 3 and abnormal baseline LDH and 28% were previously treated with CD19 and or CD79 targeting agents. Six pts were not included in the primary efficacy analysis. One received a frozen product and 5 received a nonconforming fresh product. Per Independent Radiology Committee (IRC) 18 (82%) of 22 evaluable pts had either complete (CR—46%) or partial response (PR—36%) exceeding the preplanned futility threshold. The response rate in the evaluable set was similar to that in the all-treated population (Tbl. 1). Post-progression biopsies were available in 5 pts. There was no isolated CD19 loss, but 1pt had dual target loss CD19+CD20 in relation to the pre-treatment status. PFS at 6 months for evaluable pts was 64% and 61% for all treated. The treatment was well tolerated. Among all 28 treated pts., there were no grade 3–4 CRS events and only two transient and reversible Grade 3 ICANS (9%). There was no treatment-related mortality.

Table 1: Objective Response Rate per IRC and per Site

	Evaluable Set (n=22)		All Treated (n=28)	
	IRC	Per Site	IRC	Per Site
ORR	18 (82%)	17 (77%)	22 (79%)	20 (71%)
CR	10 (46%)	11 (50%)	14 (50%)	13 (46%)
PR	8 (36%)	6 (27%)	8 (29%)	7 (25%)
SD	1 (4%)	2 (9%)	1 (4%)	2 (7%)
PD	3 (14%)	3 (14%)	5 (17%)	5 (18%)

IRC – Independent Radiology Committee

Summary/Conclusion: The prespecified efficacy threshold of zamtocel was exceeded in the interim analysis Treatment demonstrated a favorable safety profile, with promising ORR and PFS in advanced DLBCL population often pre-treated with agents not available in previous similar studies. We also demonstrate the feasibility of a rapid manufacturing process with 100% fresh infusion in eligible pts.

Encore Abstract—previously submitted to EHA 2023

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, immunotherapy

No conflicts of interests pertinent to the abstract.

097 | AXICABTAGENE CILOLEUCEL AS SECOND-LINE THERAPY FOR LARGE B-CELL LYMPHOMA IN TRANSPLANT-INELIGIBLE PATIENTS: FINAL ANALYSIS OF ALYCANTE, A PHASE 2 LYSA STUDY

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Introduction: Patients with relapsed or refractory (*R/R*) large B-cell lymphoma (LBCL) after first-line treatment who are unable to undergo high-dose chemotherapy (HDCT) and hematopoietic stem cell transplantation (HSCT) have poor outcomes and limited treatment options. In the ZUMA-7 study, Axicabtagene ciloleucel (axi-cel) demonstrated superior efficacy over standard of care (SOC) as second-line therapy in patients intended for transplant (Locke et al. NEJM, 2022). The objective of the open-label, phase 2, ALYCANTE study (NCT04531046) was to evaluate the efficacy and safety of axi-cel in patients with *R/R* LBCL after 1 prior line of therapy not intended for HDCT/HSCT owing to age and/or comorbidities.

Methods: Eligible patients were adults with *R/R* LBCL that was refractory to or had relapsed no more than 12 months after first-line chemoimmunotherapy and who were not deemed candidates for HDCT/HSCT based on physician's assessment and at least one of the following criteria: age ≥65 years; age ≥18 years and Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) score ≥3; or age ≥18 years and prior ASCT (as 1st line consolidation). The primary endpoint was the complete metabolic response (CMR) at 3 months from axi-cel infusion based on investigator assessment. The protocol was amended to allow an expansion of 22 additional patients for subgroup comparisons.

Results: At the time of data cut-off, 40 patients (out of 62 infused patients) could be analyzed for the primary endpoint. Median on-study follow-up was 10 months. Median age was 68 years (range, 49–81; 45% ≥70 years), 30% had HCT-CI score ≥3, and 52.5% were refractory to first-line treatment. Overall, 37 patients (92.5%) received bridging chemotherapy (R-GEMOX). Twenty-seven patients (67.5%) were refractory to bridging therapy. The study met its primary endpoint with a CMR at 3 months of 70% versus 12% expected with SOC based on historical controls (Cazelles et al. Leukemia & Lymphoma, 2021). Best OR and CR rates were 92.5% and 80%, respectively. Median PFS was 11 months and median OS was not reached. CRS occurred in 90% of patients, including 10% of grade 3–4. ICANS occurred in 55% of patients, including 20% of grade 3–4. Twelve patients (30%) were admitted to ICU. Seven patients died: 2 due to lymphoma and 5 due to fatal infections. Early evaluation of response showed that 64.7% (22/34) and 44.4% (16/36) of patients had a negative PET-CT and an undetectable ctDNA at day 14 post axi-cel infusion, respectively.

Conclusions: In the ALYCANTE study, axi-cel as second-line treatment in patients with LBCL who were not deemed candidates for HDCT/HSCT appears feasible and induces high response rates. The final analysis with 22 additional patients ($n = 62$ vs. 40 patients at current cut-off) and a longer follow-up will be presented at the meeting, including subgroup analysis.

The research was funded by: Kite/Gilead

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies

Conflicts of interests pertinent to the abstract

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FOCUS ON MANTLE CELL LYMPHOMA

098 | FIVE-YEAR UPDATE OF THE FIRST-LINE IMCL-2015 GELTAMO STUDY. PROLONGED MOLECULAR AND CLINICAL RESPONSES WERE OBSERVED AFTER MRD-DRIVEN IBRUTINIB DISCONTINUATION

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Introduction: A frontline tailored treatment for indolent clinical forms of mantle cell lymphoma (MCL) with ibrutinib in combination with rituximab was evaluated. A high rate of complete remissions (CR) with undetectable minimal residual disease (MRD) was reported, with predictable toxicity (Giné, JCO 2022). We herein present an updated analysis focusing in the data of treatment discontinuation.

Methods: This was an open-label, phase II trial conducted in 14 Spanish GELTAMO sites (NCT02682641). Centralized histology, PET-CT review, MRD studies (qPCR and NGS in peripheral blood) and biological studies were conducted. Previously untreated MCL patients with indolent clinical forms were eligible according to the following criteria: no symptoms attributable to MCL, ECOG 0–1, stable disease without therapy need for at least 3 months, non-blastoid variants, Ki-67 <30% and largest tumor diameter ≤3 cm. Both leukemic non-nodal and nodal forms were acceptable. Patients received ibrutinib 560 mg daily and a total of 8 doses of rituximab 375 mg/m^2 (4 weekly doses during the first 28-day cycle, followed by day 1 of cycles 3, 5, 7 and 9). Ibrutinib could be discontinued after 2 years of treatment in case of sustained undetectable MRD.

Results: Fifty patients (Male 66%; median age 65 years) were enrolled in the study (June 2016 to December 2019, data cut-off 18 October 2022, median follow-up 54 months and next cut-off is planned in March 2023). The overall response (OR) and CR rates at 12 months of treatment were 84% and 80%, respectively (including 4 early discontinuations). Undetectable MRD was reached in 40 (87%) of 46 evaluable cases (sensitivity 10^{-5}). After 24 months, 42 of 44 patients were in response, with OR and CR rates of 86% and 84%, respectively. Undetectable MRD was observed in 35 (80%) of 44 cases. Thirty-two patients discontinued ibrutinib as per protocol (64% of initial series). Twelve patients continued on ibrutinib. Median time on ibrutinib treatment was 29 months (1.7–51+ months). The median duration of undetectable MRD, achieved in 41 cases, was 60 months (95% CI: 29–92), and has not been reached in the 32 cases that stopped ibrutinib as per protocol. Six patients progressed from the disease between 12 and 72 months of follow-up and three of them eventually died of disease progression. Overall, PFS and OS at 48 months were 86% (95% CI: 75–96) and 88% (95% CI: 79–98), respectively. At current follow-up, 6 patients remain on treatment, and up to 13 patients discontinued ibrutinib because of adverse events, including 7 associated to ibrutinib with a hemorrhagic cardiac tamponade being the most severe. Five secondary neoplasms in 4 patients have been reported. Whole-genome sequencing of paired tumor/normal samples from 34 patients was obtained and will be presented.

Conclusions: An MRD-driven strategy allows ibrutinib discontinuation in indolent clinical forms of MCL patients who persist with prolonged MRD and also clinical responses.

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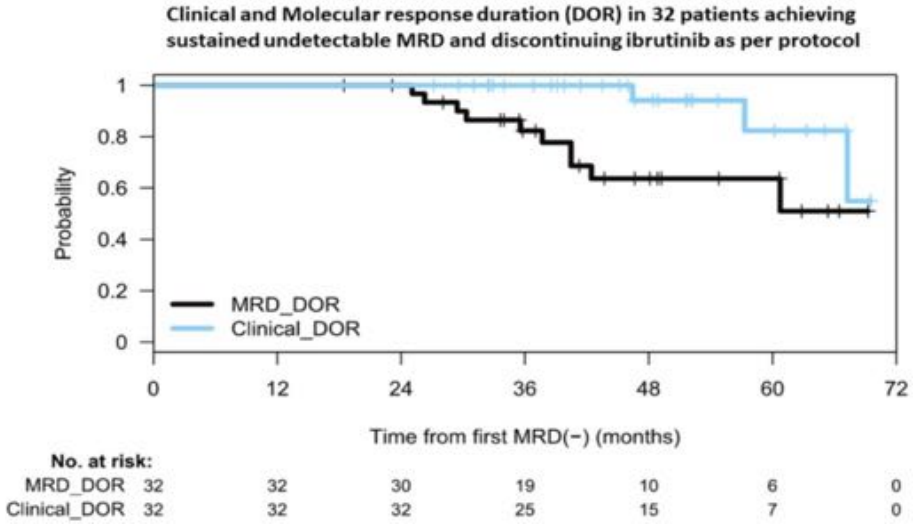

Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies

Conflicts of interests pertinent to the abstract

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099 | ACALABRUTINIB WITH RITUXIMAB AS FIRST-LINE THERAPY FOR OLDER PATIENTS WITH MANTLE CELL LYMPHOMA—A PHASE II CLINICAL TRIAL

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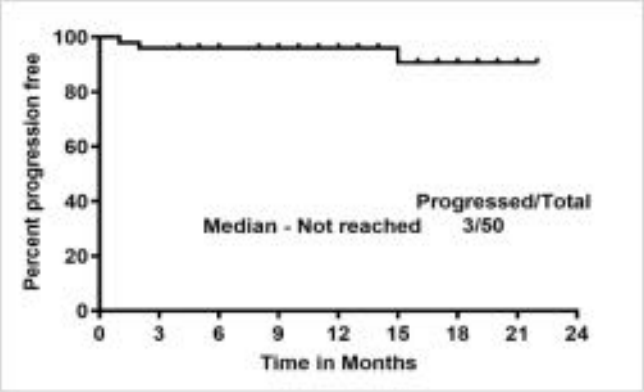
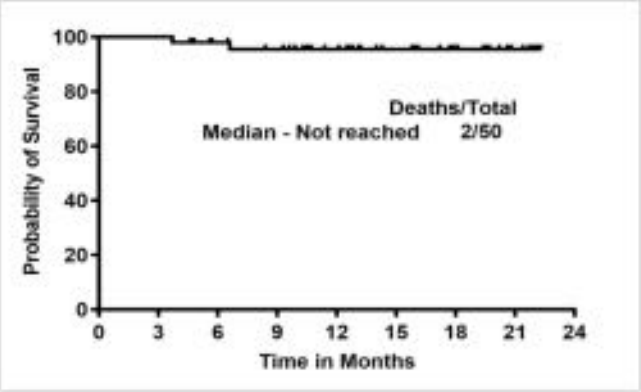
Introduction: Previously, our group reported results from ibrutinib with rituximab in older mantle cell lymphoma (MCL) patients (pts) with an atrial fibrillation rate of 22%. To develop a chemotherapy-free combination for elderly MCL pts, we designed this phase II clinical trial to investigate the efficacy and safety of acalabrutinib with rituximab (AR) as a first line approach in MCL pts (≥65 yrs).
Methods: We enrolled 50 previously untreated pts in this single institution, single arm, phase II clinical trial—NCT05214183. Pts received acalabrutinib 100 mg orally twice a day and intravenous rituximab, weekly for first 4 weeks, followed by once a month for 12 months and subsequently once every 2 months totaling 24 months. Acalabrutinib was continued. The primary objective was to assess best overall response rate (ORR) rate after AR. Responses were assessed as per Lugano response criteria. Clonoseq based minimal residual disease (MRD) assessment was performed. Adverse events were coded as per CTCAE version 5. Genomic studies are ongoing.





Results: Among 50 pts, the median age was 69 years (range: 65–81). Male/female were 36 and 14 respectively. Bone marrow was positive for MCL in 45/50 (90%) and GI tract in 35/47 (74%) pts. Forty-six pts had classic morphology while three were blastoid and one was pleomorphic. Ki-67% was available in 42 pts—13/42 (31%) had high Ki-67% and 29/42 (69%) had a low Ki-67% (<30%). Simplified MIPI risk stratification included: low ($n = 4$), intermediate ($n = 35$) and high risk ($n = 11$). *TP53* aberration status (mutations or deletion) was available in 43/50 pts and 12 pts had aberrant *TP53* while 31/43 did not have aberrant *TP53*. Thirty-nine pts had baseline next generation sequencing (NGS) on tumor tissue biopsy and 25/39 (64%) had ≥ 3 mutations. Median number of AR cycles was 12 (range: 3–24). One pt was not evaluable for response at 12 weeks. Overall, the best response was 94% ORR and 90% CR, 4% PR; 6% were non-responders. Median number of cycles to get complete metabolic response was 3 (range 2–7). Fourteen pts were MRD negative at last follow-up of the 28 evaluable pts.

With a median follow up of 14 months, the median PFS and OS were not reached (2 year 92% and 96% respectively). The median PFS and OS was not reached and not significantly different in pts with high and low Ki-67% or with/without *TP53* aberrations or among pts with low, medium or high-risk categories. Nine pts (18%) came off study—3 for adverse events (syncope, atrial fibrillation, intolerance), 3 for disease progression, one melanoma recurrence, one pt choice and one with an unusual monocytosis. Overall, 2 pts died (1 on trial with primary progression).

The most common all-grade toxicities were fatigue (82%), myalgia (64%), headache (38%), bruising (28%) and <1% were grade 3 or higher. Among 50 pts, 1 pt had recurrence of grade 2 atrial fibrillation (2%) and one pt had recurrence of grade 3 unstable angina.

Conclusions: Chemotherapy-free frontline therapy with AR is highly effective and safe and induced early CR in older pts with MCL.

The research was funded by: Astra Zeneca

Keywords: combination therapies, molecular targeted therapies

Conflicts of interests pertinent to the abstract

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100 | VERY LONG-TERM FOLLOW-UP OF RITUXIMAB MAINTENANCE IN YOUNG PATIENTS WITH MANTLE CELL LYMPHOMA INCLUDED IN THE LYMA TRIAL, A LYSA STUDY.

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Aim: the phase III LYMA trial demonstrated the efficacy (OS, PFS, EFS) and safety of rituximab maintenance (RM) post autologous stem cell transplant (ASCT) in first line for young patients with mantle cell lymphoma (MCL) (Le Gouill et al., NEJM). Herein, we present the first long-term analysis of the LYMA trial.

Patients and methods: 299 patients were included in LYMA trial of whom 240 were randomized to receive 3 years of RM ($n = 120$) or no RM (observation; $n = 120$). Primary endpoint was 3 years EFS. We updated the outcome of all patients enrolled in this trial. Treatment at relapse and cause of death were collected.

Results: At the time of the present analysis, the median follow-up is 7 years (0.2–10). The median EFS and PFS were still statistically superior in favor of RM (not reached [NR] vs. 5.8 years, $p < .0001$ for EFS and NR vs. 6.1 years for PFS in RM and observation arm respectively). The 7 years estimated EFS and PFS were 76.2% (95% CI 67.4%–82.9%) versus 46% (95% CI 36.6%–54.9%) and 78.5% (95% CI 69.9%–85.0%) versus 47.4% (95% CI 37.9%–56.3%), for RM and observation respectively, $p < .0001$). In the RM arm, 22 patients had died (18.3%) versus 33 (27.5%) in the observation arm with a 7-year OS estimate of 83.2% (95% CI: 74.7.7%–89.0%) and 72.2% (95% CI 62.9%–79.5%) in RM and observation arm, respectively ($p = 0.087$). Causes of death were not significantly distinct between the 2 groups, lymphoma being the leading cause in both (50% in both arm), with less than 10% of infectious related death. The end of RM was not associated with an increase in the relapse incidence, since in the RM arm, 17/21 (81%) of the progression occurred during the theoretical 3 years of RM and only 19% after the end of RM. On the contrary, in the observation arm, 32/53 (60%) of the progression/relapses occurred during the theoretical 3 years of maintenance part, and 40% after. Salvage treatments were not different between the RM and observation arm, including anti CD20 and BTK inhibitors administered in 75% versus 79% and 10% versus 15% of the relapsing patients in the RM and observation arms, respectively. Post relapse OS was significantly impacted by previous RM, with a median OS-2 of 1.1 years (95% CI 0.7–2.1) for the 21 relapsing patients in the RM arm versus 4.6 years (95% CI 2-NA) for the 53 relapsing patients in the observation arm. Given the timing of relapses in RM arm, this reflects the aggressiveness of early disease progression during RM.

Conclusion: The benefice in favor of RM in term of EFS (the primary objective), PFS remains after 7 years of FU, but not in OS. The end of RM was not associated with an increase in relapse rate. RM was not associated with an increase in infectious related mortality, making of this strategy a safe standard of care with long term FU. Patients relapsing during RM have a particularly poor outcome and represent an unmet medical need.

Encore Abstract—previously submitted to ASCO 2023 and EHA 2023

Keywords: aggressive B-cell non-Hodgkin lymphoma, chemotherapy, combination therapies

No conflicts of interests pertinent to the abstract.

101 | IBRUTINIB-RITUXIMAB AND VENETOCLAX (IRV) FOLLOWED BY RISK-STRATIFIED R-HYPERCVAD/MTX IN YOUNG PATIENTS WITH UNTREATED MANTLE CELL LYMPHOMA—PHASE-II WINDOW-2 TRIAL

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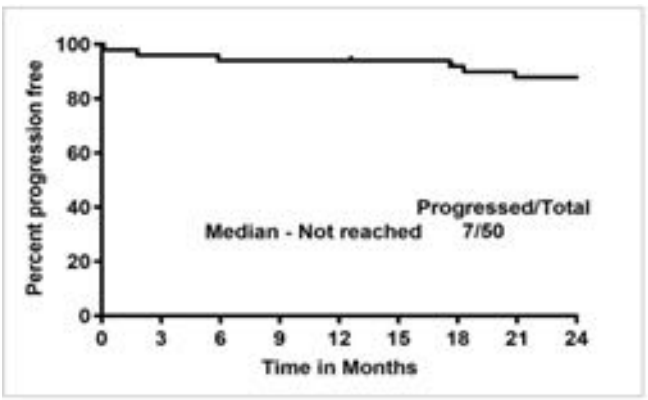
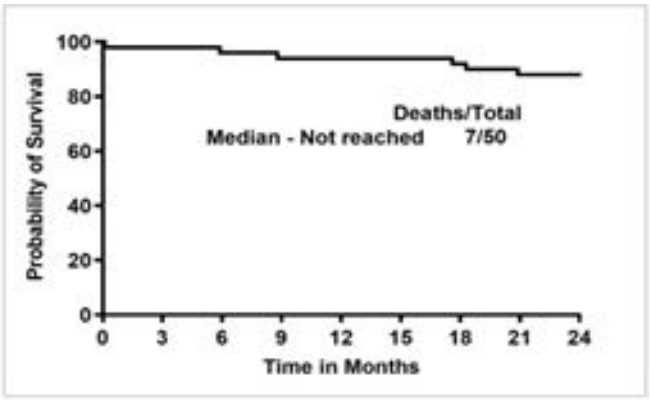
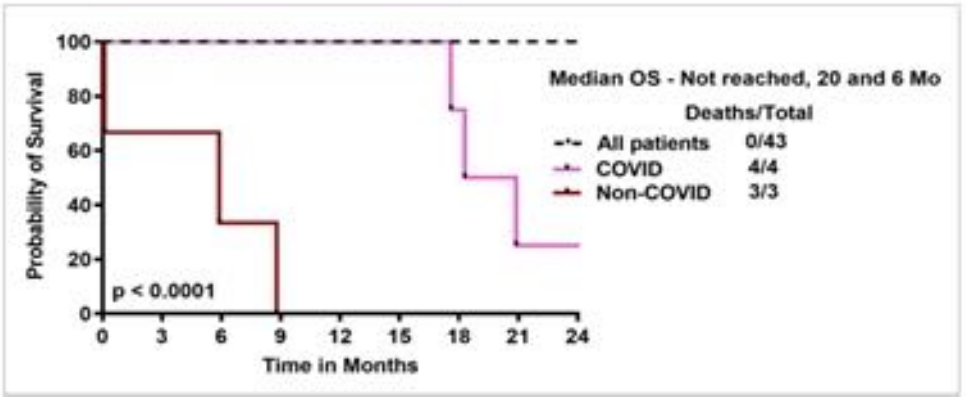
Introduction: We investigated the efficacy and safety of ibrutinib, rituximab (IR) and venetoclax (IRV) followed by risk-stratified short course R-HCVAD/MTX-ARA-C as consolidation and IRV maintenance in previously untreated young patients (pts) (≤65 yrs) with MCL (mantle cell lymphoma). We anticipated that using a triplet chemotherapy-free induction would minimize chemotherapy exposure.

Methods: We enrolled 50 previously untreated pts in this single institution, single arm, phase II clinical trial—NCT03710772. Pts received IR induction (Part-1) and added dose ramp-up venetoclax (400 mg) at cycle 5. Pts were stratified into three risk groups: high, moderate and low risk from baseline data and assigned to R-HCVAD/MTX-ARA-C as consolidation in part 2 (4 cycles, 2 cycles, or no chemotherapy for high, medium and low risk pts respectively). Low risk pts (Ki-67 ≤30%, tumor mass <3 cm, low MIPI score and no high risk features), High risk pts (Ki-67 ≥50%, mutations in the *TP53*, *NSD2* or in *NOTCH* genes, or tumor diameter >5 cm or blastoid/pleomorphic histology). Medium risk pts did not belong to low or high-risk categories. After part 2 consolidation, all pts received 2 years of IRV maintenance. The primary objective was to assess CR rates after IRV induction. Adverse events were coded as per CTCAE version 4.

Results: Among the 50 pts, the median age was 58 years (range: 35–65). There were 21 pts in the high-risk group, 18 pts in the







intermediate-risk group and 11 pts in the low-risk group. Forty-eight pts received IRV. Two pts couldn't start venetoclax due to progression on IR and on-study death prior to venetoclax. Best response to IRV was 100% and CR of 100%. The median number of cycles of triplet IRV to reach best response was 8 cycles (range 2–12). Sixteen pts (30%) did not receive part 2 chemotherapy (11 were low risk and 5 pts other reasons).

With a median follow up of 41 (range: 25–50) months, median PFS and OS were not reached (3 year 85% and 86% respectively). Median PFS and OS were not reached and not significantly different in pts with high and low Ki-67% or with/without *TP53* aberrations or among pts with low, medium or high-risk categories. Twenty-seven pts (54%) came off study—20 for adverse events (9 COVID related and 11 non-COVID related), 3 deaths, and 4 patient choice. Overall, 7 pts died (2 on trial, one off study with progression and 4 due to COVID pneumonia in CR). Grade 3–4 toxicities on part 1 included 10% myelosuppression and 10% each with fatigue, myalgia and rashes and 3% mucositis. One pt developed grade 3 atrial flutter during part 1. None had grade 3–4 bleeding/bruising.

Conclusions: Chemotherapy-free induction with IRV induced deep responses. No patients relapsed regardless of risk category. Pts with low risk MCL may not need chemotherapy. The combination was safe. This combined modality treatment approach significantly improves outcomes of young MCL pts across all risk groups.

Encore Abstract—previously submitted to regional or national meetings (up to <1'000 attendees)

The research was funded by: Janssen and abbvie

Keywords: combination therapies, molecular targeted therapies

Conflicts of interests pertinent to the abstract

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Research funding: Pharmacyclics, Janssen, AstraZeneca, Celgene, Loxo Oncology, Kite Pharma, Juno, BioInvent, VelosBio, Acerta Pharma, Oncternal, Verastem, Molecular Templates, Lilly, Innocare

102 | PIRTOBRUTINIB IN COVALENT BTK-INHIBITOR PRE-TREATED MANTLE CELL LYMPHOMA: UPDATED RESULTS, SUBGROUP ANALYSIS FROM BRUIN WITH >3 YEARS FOLLOW-UP FROM START OF ENROLLMENT

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Introduction: Pirtobrutinib is a highly selective, non-covalent (reversible) BTK-inhibitor (BTKi). Here, we report updated results of pirtobrutinib in patients (pts) with cBTKi pre-treated relapsed/refractory (*R/R*) mantle cell lymphoma (MCL) and more than 3 years follow-up from start of enrollment.

Methods: Pts with cBTKi pre-treated *R/R* MCL received pirtobrutinib monotherapy in a multicenter phase 1/2 BRUIN trial (NCT03740529). Efficacy was assessed in the prespecified primary efficacy cohort that comprised the first 90 enrolled pts who had measurable disease, had received a prior cBTKi, and had no known central nervous system involvement. The primary endpoint was overall response rate (ORR) as assessed by independent review committee. Secondary endpoints included duration of response (DOR) and safety. A data cut of 29 July 2022 was utilized.

Results: Among MCL pts who received a prior cBTKi ($n = 90$), median age was 70 years (range 46–87), median prior lines of therapy were 3 (range 1–8), 82% discontinued a prior cBTKi due to disease progression, and 78% had intermediate/high risk sMIPI score. Of samples available, 17/36 (47%) had *TP53* mutations and 25/34 (74%) had Ki67 ≥30%. The ORR was 57% (95% CI, 46–67), including 19% complete responses ($n = 17$) and 38% partial responses ($n = 34$). At a median follow-up time of 13 months, the median DOR among the 51 responding pts was 17.6 months (95% CI, 7.3–27.2). The 12- and 18-month estimated DOR rates were 58% (95% CI, 41–72) and 45% (95% CI, 27–61), respectively. ORR and DOR by subgroups are shown in the Table. The median progression-free survival was 7.4 months (95% CI, 5.3–13.3). The median overall survival was 23.5 months (95% CI, 15.9-NE). In the MCL safety cohort ($n = 166$), the most frequent treatment-emergent adverse events (TEAE) were fatigue (31%), diarrhea (22%), and anemia (17%). The most common Grade ≥3 TEAE was neutropenia (15%). Grade ≥3 TEAE of hemorrhage (3%) and atrial fibrillation/flutter (2%) were infrequent. Only 5 (3%) pts discontinued due to a treatment-related AE.

Conclusion: Pirtobrutinib continues to show durable efficacy and a favorable safety profile in heavily pre-treated *R/R* MCL pts with prior cBTKi therapy. Responses were observed in pts with high-risk disease features including pts with blastoid/pleomorphic variants, elevated Ki67 index, and *TP53* mutations.

Table. ORR and DOR in cBTKi pre-treated MCL pts and high-risk subgroups

		cBTKi pre-Treated MCL, n	ORR, % (95% CI)	DOR, median (95% CI)
Overall		90	56.7 (45.8-67.1)	17.6 (7.3-27.2)
MCL histology	Classic/Leukemic	70	58.6 (46.2-70.2)	17.6 (7.5-NE)
	Blastoid	8	50.0 (15.7-84.3)	NE (1.4-NE)
	Pleomorphic	12	50.0 (21.1-78.9)	27.2 (3.7-NE)
TP53 mutation	Yes	17	47.1 (23.0-72.2)	17.6 (1.7-NE)
	No	19	57.9 (33.5-79.7)	14.8 (1.9-NE)
Ki-67	<30%	9	66.7 (29.9-92.5)	17.6 (1.6-NE)
	≥30%	25	56.0 (34.9-75.6)	21.6 (1.7-NE)

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Conflicts of interests pertinent to the abstract

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Research funding: AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Biopath, Bristol Myers Squibb, CALIBR, CALGB, Celgene, City of Hope National Medical Center, Constellation Pharmaceuticals, Curis, CTI Biopharma, Fate Therapeutics, Forma Therapeutics, Forty Seven, Genentech, Gilead Sciences, InnoCare Pharma, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Janssen, Kite Pharma, Loxo, Merck, Millennium Pharmaceuticals, MorphoSys, Myeloid Therapeutics, Novartis, Nurix, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Roche, Seattle Genetics, Tessa Therapeutics, TCR2 Therapeutics, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development Corp., Unum Therapeutics, Verastem

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Research funding: Adaptive Biotechnologies, Aptevo Therapeutics, AstraZeneca, Bristol Myers Squibb, CRISPR Therapeutics, Celgene, Curis, Inc, Epizyme, Fate Therapeutics, Genentech/Roche, Kite, Loxo Oncology, MEI Pharma, Nurix, Pharmacyclics/Janssen, Sunesis Pharmaceuticals, Trillium Therapeutics/Pfizer, Velos Bio, Xencor

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Honoraria: BMS/Celgene/JUNO; Genentech/Roche; Gilead/Kite; BeiGene; Pharmacyclics/Abbvie; Jansen; Amgen; Astra-Zeneca; Novartis; MEI Pharma

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Consultant or advisory role: AbbVie, Acerta Pharma, AstraZeneca, BeiGene, BioInvent, Deciphera, InnoCare, Janssen, Kite Pharma, Leukemia & Lymphoma Society, Lilly, Merck, Milken Institute, Oncternal, Parexel, Pepromene Bio, Pharmacyclics, VelosBio

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103 | OUTCOMES OF AUTOLOGOUS TRANSPLANT, ALLOGENEIC TRANSPLANT, AND CAR T CELL THERAPY IN TP53 ALTERED MANTLE CELL LYMPHOMA: A MULTI-INSTITUTION RETROSPECTIVE ANALYSIS

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Introduction: *TP53* alterations are associated with poor prognosis in mantle cell lymphoma (MCL). In trials of intensive chemotherapy and autologous hematopoietic cell transplant (auto-HCT), patients (pts) with *TP53* mutations had an overall survival (OS) of 1.8 years (yrs) compared to 12.7 yrs for unmutated. Optimal treatment to achieve durable remission is unknown. We report transplant and cellular therapy outcomes of a large cohort of pts with *TP53* altered MCL.

Methods: We conducted a multi-site retrospective study of pts with MCL harboring *TP53* mutation, deletion, or overexpression at 25 sites in the United States from 1998 to 2022. For outcomes after auto-HCT, allogeneic transplant (allo-HCT), and chimeric antigen receptor T cell therapy (CAR-T), *TP53* alteration must have been present at time of this therapy. Event free survival (EFS) after auto-HCT, allo-HCT, and CAR-T was defined as time from treatment to relapse, subsequent therapy, or death.

Results: We identified 254 pts with *TP53* altered MCL, with median 4.8 yrs follow up and baseline characteristics described in table 1. TP53 alteration was found in 75% at diagnosis. OS for the total cohort was 6.3 yrs from diagnosis. There was no difference in OS based on type of *TP53* alteration or Ki-67. MIPI high risk ($p < 0.0001$) and blastoid/pleomorphic variant ($p = 0.02$) predicted shorter OS.

There were 75 consolidative auto-HCT eligible pts, defined as age 65 and under with no events within 6 months after first line therapy. Of these, 42 received auto-HCT in first remission. Median EFS was 4.0 yrs in pts who received auto-HCT and 1.5 yrs for no auto-HCT ($p < 0.01$). There was no difference in OS ($p = 1.0$). Among pts with a TP53 mutation, EFS was 2.1 yrs with auto-HCT ($N = 10$) and 2.2 yrs without ($N = 18$) ($p = 0.5$).

Allo-HCT was used in 24 pts, after a median of 2 lines of therapy. 46% had prior Bruton tyrosine kinase inhibitor (BTKi) treatment. Allo-HCT was matched in 74%, related donor in 50%, myeloablative in 25%, using post-transplant cyclophosphamide in 46%, and ATG in 13%. With median follow up 5.9 yrs, median EFS after allo-HCT was 1.5 yrs and OS 5.4 yrs, with no difference according to type of *TP53* alteration. There were 5 pts still in remission over 5 years from allo-HCT. CAR-T was used in 37 pts, with median 3 prior lines of therapy. 92% had prior BTKi and 86% received bridging therapy. With median follow up 1.3 yrs, median EFS after CAR-T was 0.9 yrs and median OS 1.4 yrs, with no difference based on type of *TP53* alteration.

Conclusion: Here we report the largest pooled analysis of transplant and cellular therapy for *TP53* altered MCL. Within this high risk cohort, high MIPI and blastoid/pleomorphic morphology predicted even shorter survival. Auto-HCT was associated with improved EFS

Variable	Total (N = 254)	Auto-HCT Eligible (N = 75)		Allo-HCT (N = 24)	CAR-T (N = 37)
		Auto-HCT (N = 42)	No Auto-HCT (N = 33)		
Age at diagnosis, years, median (range)	64 (35-93)	59 (44-65)	58 (45-65)	58 (35-73)	58 (35-85)
Sex, male, No. (%)	181 (71)	28 (67)	24 (73)	17 (71)	28 (76)
MIPI high, No. (%)	102 (51)	11 (32)	7 (24)	9 (43)	10 (32)
Ki-67 >30%, No. (%)	94 (59)	17 (52)	13 (59)	10 (71)	23 (72)
Blastoid/Pleomorphic, No. (%)	65 (26)	10 (24)	4 (12)	10 (42)	16 (43)
SOX11 positive, No. (%)	70 (55)	18 (69)	7 (58)	6 (60)	14 (67)
TP53 alteration					
Mutation, No. (%)	114 (45)	10 (24)	18 (55)	10 (42)	23 (62)
Deletion, No. (%)	167 (66)	30 (71)	20 (61)	18 (75)	20 (54)
Overexpression, No. (%)	41 (16)	10 (24)	7 (21)	9 (38)	6 (16)

Table 1: Baseline characteristics of patients with TP53 altered MCL

in all *TP53* altered, but not among *TP53* mutated. CAR-T and allo-HCT do not appear to abrogate the poor prognosis conferred by *TP53* mutation, emphasizing the need for targeted clinical trials in this population.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, stem cell transplant

Conflicts of interests pertinent to the abstract

S. D. Smith
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D. Bond
Consultant or advisory role: SeaGen, KITE/Gilead, Nurix
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P. Ramakrishnan Geethakumari
Consultant or advisory role: KITE, BMS, Rafael Pharma, Pharmacyclics LLC, ADC Therapeutics, Cellectar Biosciences, Ono Pharma

FOCUS ON HODGKIN LYMPHOMA

104 | CORRELATION BETWEEN PROGRESSION-FREE AND OVERALL SURVIVAL IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA: A COMPREHENSIVE ANALYSIS OF INDIVIDUAL PATIENT DATA FROM GHSG TRIALS

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Introduction: Progression-free survival (PFS) and overall survival (OS) are predominant measures of treatment efficacy in classical Hodgkin lymphoma (HL). Despite the preference for OS from many regulatory authorities, PFS is most relevant to patients and frequently serves as primary endpoint in clinical trials. The relationship between PFS and OS in HL is of immediate interest but remains unknown to date. We aimed to evaluate correlation of PFS with OS after first-line treatment of HL and its potential to serve as a surrogate parameter.

Methods: We analyzed individual patient data obtained during and after polychemotherapy-based treatment in nine randomized phase III GHSG first line trials (HD7-HD15) between 01/93 and 08/18. PFS was defined as time from randomization until progression, relapse, or death; OS was defined as time from randomization until death. Effects of 16 experimental treatments on PFS and OS on trial level were evaluated by estimation of the treatment effects with Cox proportional hazards (PH) regression and a linear weighted least squares (WLS) regression. On patient level, marginal Cox PH models for multiple endpoints were applied according to the Wei-Lin-Weissfeld method (WLW). Additionally, we correlated risk factor effects with marginal Cox PH models at patient level (WLW) and applied copula models to correlate PFS and OS directly at patient level.

Results: At least one PFS and OS event was recorded in 1682 and 1064 of 10,605 HL patients, respectively. The statistical analysis at trial level revealed a high and significant correlation of treatment effects on PFS and OS ($r = 0.72$, $r^2 = 0.54$, $p < 0.001$, Figure 1). A multiple regression model accounting for different effectiveness of experimental treatments and historical progress over trial generations reached almost perfect fit ($r^2 = 0.93$). The statistical analysis at patient level confirmed a high correlation of treatment effects on PFS and OS. Within the trials, Pearson r was ranging between 0.61 and 0.85 (each $p < 0.001$) and with two exceptions all correlations were $r > 0.70$. In total, Pearson r was 0.74, r being higher in advanced stages of HL ($r = 0.78$) than in limited stages ($r = 0.72$). At patient level, we found similar high correlations between effects of risk factors on PFS and OS (Pearson $r = 0.74$–0.85, each $p < 0.001$, WLW analysis) and when correlating PFS and OS with copula (Pearson $r = 0.72$–0.83, each $p < 0.001$).

Conclusions: In first-line trials of HL, PFS and OS as well as treatment effects and prognostic effects of risk factors on PFS and OS are highly correlated. PFS thereby predicts treatment effects on OS to a high degree and many years before OS can be reliably evaluated.

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Research funding: BeiGene, Bristol-Myers Squibb, MSD Sharp & Dohme, Takeda
Educational grants: Celgene

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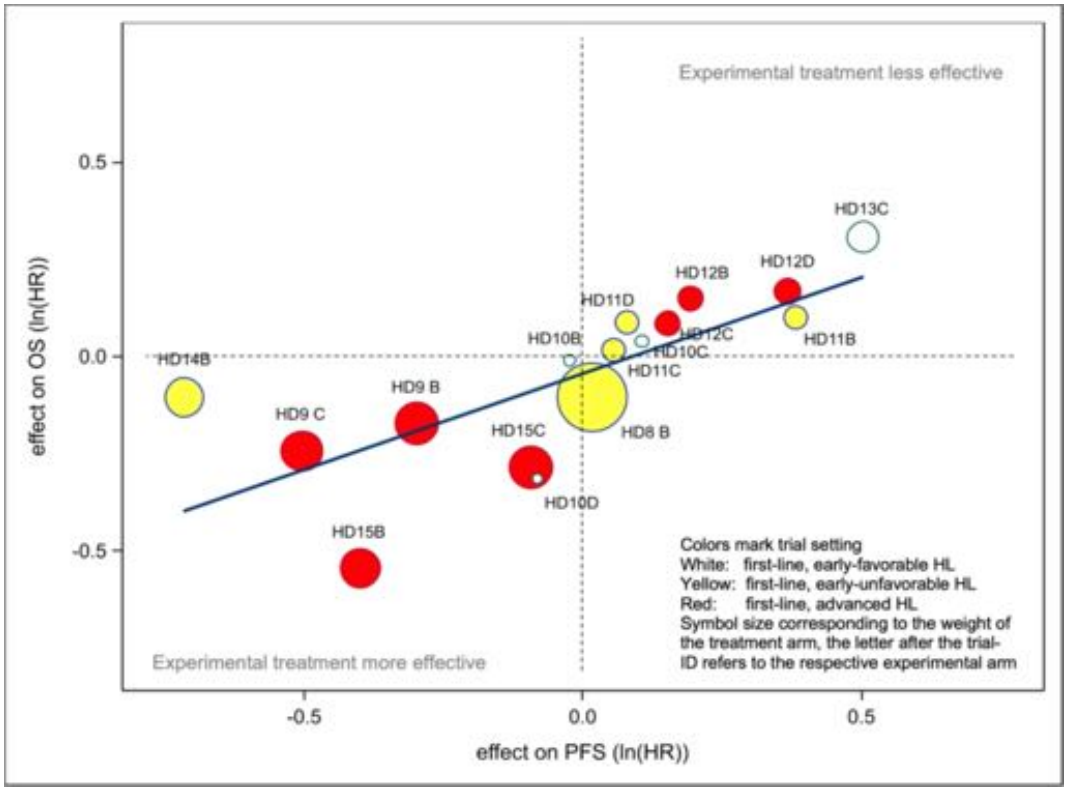

FIGURE 1 Sixteen separately estimated treatment effects on PFS and OS at trial level with resulting linear regression line ($r = 0.721$, 95% CI = 0.350–0.896).

B. von Tresckow

Consultant or advisory role: Allogene, BMS/Celgene, Cerus, Incyte, IQVIA, Gilead Kite, Miltenyi, Novartis, Noscendo, Pentixapharm, Roche, Amgen, Pfizer, Takeda, Merck Sharp & Dohme, and Gilead Kite

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105 | EARLY FDG-PET ADAPTED TREATMENT OF LIMITED STAGE HODGKIN LYMPHOMA (HL): 10Y LONG TERM FOLLOW-UP ANALYSIS OF THE RANDOMIZED INTERGROUP EORTC/LYSA/FIL H10 TRIAL

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Background: Though the outcome of patients with stage I/II HL is excellent with standard combined chemo- and radiotherapy, the H10 trial assessed the possibility of improving tumor control by treatment intensification in early (i.e., after two cycles of ABVD) PET-positive patients and of reducing treatment related toxicity by omission of involved-node radiotherapy (INRT) in early PET-negative patients. Here, we present the results of 10y long term follow-up analysis, focused on progression-free survival (PFS), and overall survival (OS).

Methods: H10 was a randomized trial to evaluate treatment adaptation on the basis of early PET (ePET) after two cycles of ABVD in previously untreated stage I and II HL—according to European Organisation for Research and Treatment of Cancer criteria favorable (F) and unfavorable (U). The standard arm consisted of ABVD followed by involved-node radiotherapy (INRT), regardless of ePET result. In the experimental arm, ePET-negative patients received ABVD only (noninferiority design), whereas ePET-positive patients

switched to two cycles of BEACOPPesc and INRT (superiority design). Primary end point was progression-free survival (PFS). In January 2019, a preplanned analysis on 10y follow-up was launched. So far, out of 1925 patients constituting the original study population, 1419 cases have been updated, and are included in the present analysis; 506 cases showing similar baseline characteristics and 5y OS and PFS than updated patients were excluded so far.

Results: After a median follow-up of 9.5 yrs, a total of 57 deaths and 136 events for PFS were reported in the analyzed population, leading to an overall 10-year OS and PFS rates of 96% and 90% respectively. In ePET-positive patients, 10y PFS increased from 79% for standard ABVD + INRT to 85% for intensification to BEACOPPesc + INRT (hazard ratio [HR] = 0.67; 95% CI, 0.37 to 1.20), although the difference was not statistically significant. The 10y OS rates were 90% and 92%, respectively (hazard ratio [HR] = 0.92; 95% CI, 0.43–1.97). In the F ePET negative group the 10y PFS rates were 99% versus 85% (HR = 13.2; 95% CI, 3.1–55.8) in favor of ABVD + INRT, and the difference was statistically significant. The 10y OS rates were 100% versus 98% for ABVD + INRT and ABVD only arms, respectively (hazard ratio [HR] = 2.80; 95% CI, 0.3–26.9). Finally, in the U ePET negative group 10y PFS rates were 91% and 87% (HR = 1.52; 95% CI, 0.8–2.8) for standard and experimental arm, respectively. The 10y OS rates were 94% versus 95% for ABVD + INRT and ABVD only arms, respectively (hazard ratio [HR] = 0.84; 95% CI, 0.4–2.0).

Conclusion: The present long-term analysis confirms that in F ePET-negative patients, the omission of INRT is associated with lower 10y PFS, although no differences in terms of OS emerged. Moreover, in the U ePET negative and in the ePET positive patients, no significant differences between standard and experimental arms emerged in terms of 10y PFS and OS.

Keyword: Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

106 | PEMBROLIZUMAB AS FIRST THERAPY FOR HODGKIN LYMPHOMA IS DELIVERABLE IN OLDER OR ABVD-INELIGIBLE PATIENTS, ALLOWS SUBSEQUENT THERAPY, AND GIVES ADEQUATE SURVIVAL.

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Background: There is no consensus on the optimal treatment of older (≥60y) patients (pts) who develop classical Hodgkin lymphoma (CHL). CHL in this age group is more likely to present with poor risk features, reduced performance status, advanced disease and concomitant illnesses. In this setting, treatment-related mortality may be as high as 10% with ABVD. The PD1-inhibitor pembrolizumab is active in *R/R* CHL. We hypothesized the efficacy and toxicity profile may be favourable in this population. We report the results of an investigator-initiated, prospective, multicentre, single-arm trial of pembrolizumab monotherapy as first treatment for CHL.

Methods: Eligible patients had to be either considered to be unfit for frontline ABVD for reasons of comorbidity or be aged ≥65; have an ECOG < 3, adequate organ function (including platelets ≥75, neutrophils ≥1.0), GFR ≥ 30mL/min. Key exclusions were autoimmune disease or infection at baseline, or disease that could be completely irradiated. Low-risk other malignancies were allowed. Treatment consisted of pembrolizumab 200 mg q21d, up to 35 cycles. Cessation of treatment for pts achieving CR was optional, and retreatment on progression was permitted. The primary endpoint was response rate. Secondary endpoints were safety and time-dependent survival outcomes. We recorded cumulative index rating scale (CIRS) at baseline and post-protocol therapies.

Results: 27 pts were registered. One was registered in error, another withdrew prior to pembrolizumab; both were replaced and 25pts received treatment. The median age was 77 (range 64–92); 52%/48% were male/female; the median CIRS was 7 (IQR 4–10); 20% had an ECOG performance score of 2. 92% had stage III/IV disease, 48% had B symptoms and 56% had extranodal disease. A median of 11 cycles was delivered (range 1–35). 18/25 (72%) pts responded, 8 (32%) had a CR. The median DOR was 10.6 months (95% CI 3.4-NE). After a median follow-up of 25.1months, the 12-month and 24-month OS estimates were 90% (95% CI 67–98) and 83% (95% CI 55–94). 5 pts died, 12-month survival after PD was 77% (95% CI: 44, 92). There were no treatment-associated deaths. The most common any-cause adverse event (AE) was grade 1/2 arthritis *n* = 7, 28% and pruritis (24%). 8 pts (32%) had a gr 3/4 event, which precluded further therapy in 2. Of the 8pts who went on to subsequent treatment, 5 had a CR, 2 PR, and one had SD.

Conclusion: Pembrolizumab was feasible in an ABVD-unfit, elderly, and significantly comorbid cohort of patients with advanced CHL. Despite the characteristics of the patient group and the development of immune-mediated AEs in some, there were no treatment-related deaths that may occur after conventional chemotherapy in elderly patients. Complete response rates in patients receiving subsequent therapy were reassuring. Further exploration of first therapy with checkpoint inhibitors in frail patients with CHL is warranted.

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Keywords: Hodgkin lymphoma, immunotherapy

Conflicts of interests pertinent to the abstract

M. J. Dickinson
Consultant or advisory role: MSD
Honoraria: MSD
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L. Berkahn

Stock ownership: Beigene

107 | PHASE 2 TRIAL OF NIVOLUMAB PLUS ADRIAMYCIN, VINBLASTINE, DACARBAZINE (N-AVD) AS FRONTLINE THERAPY IN OLDER ADULTS WITH HODGKIN LYMPHOMA

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Background: Outcomes of classical Hodgkin lymphoma (cHL) remain poor in older adults (OA) with 5- year progression free survival (PFS) of 60% even with curative therapy (Cheng, et al. Blood Advances 2022). In the ECHELON-1 study, brentuximab-AVD led to higher incidence of toxicities in OA without any significant benefit in PFS compared to ABVD (Evens, et al. Haematologica 2022). The CheckMate 205 study established the safety of nivolumab plus doxorubicin, vinblastine and dacarbazine (N-AVD), however it included only 6 patients (pts) ≥60 years (y) of age (Ramchandren, et al. JCO 2019). We conducted a multicenter, investigator-initiated, phase 2 trial to evaluate the safety and efficacy of N-AVD specifically in OA with cHL, and to understand the impact of baseline geriatric assessment (GA) on treatment toxicity in this vulnerable population.

Methods: Pts ≥ 60y with newly diagnosed, any stage, cHL were treated with 6 cycles of AVD at standard doses plus nivolumab 240 mg intravenously on days 1 and 15 of each cycle. A GA was performed prior to therapy initiation that included measures of function, comorbidity, cognition, psychological state, social activity/support, and nutritional status. The primary end point was 2-year PFS. We hypothesized that N-AVD would improve the 2-year PFS for OA with cHL from a historical control of 55% (Evens, et al. BJHaem 2013) to 75%. Secondary end points included 2-year overall survival (OS) and safety. The mean scores of each domain of the GA were corelated with grade ³3 toxicities using logistic regressions.

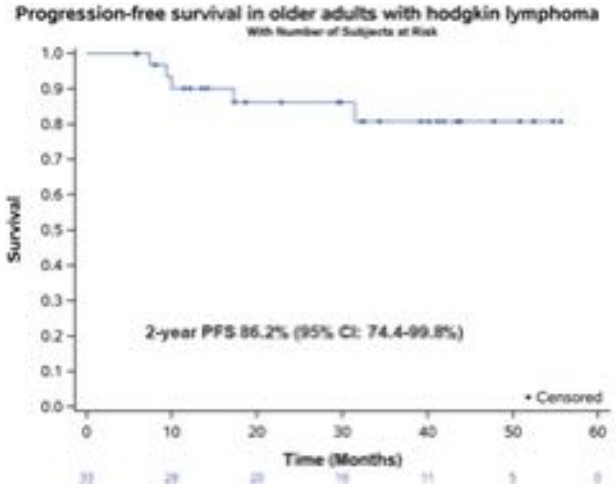
Results: 37 pts enrolled; 33 are evaluable for response (4 too early). Median age was 66 y (range 60–78) with 41% pts ≥70 y. At diagnosis, 78% pts had stage 3/4 disease, 68% had International Prognostic Score of ≥3, 54% had B symptoms and 43% had extranodal disease. Overall and complete response rates were 100% and 97% respectively, one patient had a partial response with biopsy being non-diagnostic. At a median follow-up of 37 months, 5 (14%) pts had HL relapse, and one pt died from HL. The 2 y PFS and OS were 86.2% (95% CI: 74.4%–99.8%) and 96.4% (95% CI: 89.8%–100%) respectively (Figure). Overall, 41% pts experienced grade (gr) 3/4 treatment-related adverse events (TrAE) and 2 (6%) pts stopped therapy due to TrAEs (both nivolumab only). Treatment-related febrile neutropenia occurred in 5% of pts. Endocrine immune-mediated AEs (irAEs) were all Gr 1/2; nonendocrine irAEs included Gr 3 hepatitis ($n = 1$), Gr 2 colitis ($n = 1$), Gr 2 pneumonitis ($n = 1$) and Gr 1/2 rash ($n = 7$). GA data are currently being analyzed and will be reported at the meeting.

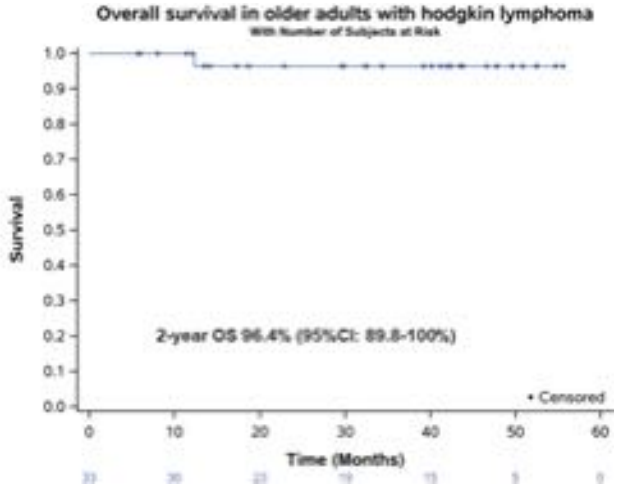
Conclusions: N-AVD is a highly effective and well tolerated frontline regimen in older adults with cHL. With no upper age, the phase 3 Intergroup study comparing N-AVD with brentuximab-AVD that recently completed accrual will provide definitive data on whether N-AVD will become a standard of care regimen in pts with newly diagnosed cHL.

The research was funded by: Bristol Myers Squibb

Keywords: combination therapies, Hodgkin lymphoma, immunotherapy

Conflicts of interests pertinent to the abstract





P. Torka
Consultant or advisory role: Genentech, GenMab, Lilly USA, Seagen

Z. Epstein-Peterson
Honoraria: OncLive
Research funding: Kymera, Amgen, Viracta

A. Kumar
Consultant or advisory role: Genentech
Honoraria: Astra Zeneca, Kite Pharmaceuticals, Janssen, Genentech, and Loxo/Lily Pharmaceuticals
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Research funding: ADC Therapeutics, Affimed, Auxilius Pharma, Celgene, Crispr Therapeutics, Daiichi Sankyo, Kyowa Hakko Kirin, Millennium/Takeda, Seattle Genetics, C4, and Verastem/SecuraBio

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Research funding: Roche, genentech, abbvie, Genmab
Educational grants: Genmab

W. Johnson
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M. Palomba
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Stock ownership: Owkin
Honoraria: Abbvie, Bayer, Incyte, Kite/Gilead, Morphosys, Novartis, Regeneron

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Research funding: MEI Pharmaceuticals, Genentech/Roche, Beigene, SPORE -PI (receives salary support and funds awarded to MSK)

A. Moskowitz
Honoraria: Seagen, Affimed, Bio Ascend, Imbrium Therapeutics L.P./ Purdue, Janpix Ltd., Merck, Seattle Genetics, Tessa Therapeutics and Takeda
Research funding: ADC Therapeutics, Beigene, Miragen, Seattle Genetics, Merck, Bristol-Myers Squibb, Incyte, and SecuraBio

108 | AVELUMAB MONOTHERAPY FOLLOWED BY A PET ADAPTED CHEMOTHERAPY APPROACH IN THE FIRST LINE TREATMENT OF CLASSICAL HODGKIN LYMPHOMA: INITIAL RESULTS FROM THE AVENUE WINDOW STUDY

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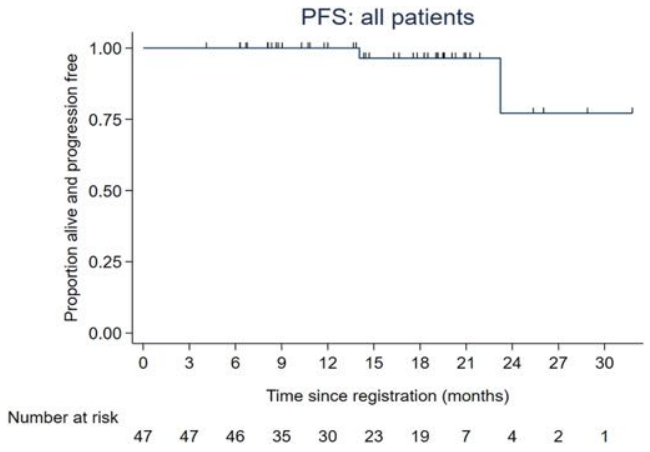
Introduction: Inhibitors of programmed cell death receptor 1 (PD1) used with chemotherapy result in high response rates and durable remissions in the first line (1L) treatment of classical Hodgkin Lymphoma (cHL). Avelumab is an inhibitor of the immune checkpoint PDL1, which is highly expressed by Reed-Sternberg cells, and has demonstrated activity in relapsed/refractory cHL. The AVENuE window study assessed the efficacy and safety of avelumab prior to response adapted chemotherapy as 1L treatment in cHL. It is the first study to report on PDL1 inhibition in this setting. Financial support was provided as an investigator sponsored research grant from Pfizer Ltd.
Methods: Adult patients (pts) with advanced cHL were enrolled in this phase 2 study. Pts received 2 cycles (4 doses) of avelumab then



underwent a PET/CT followed by 2 cycles of ABVD and PET/CT (iPET). iPET neg (Deauville score 1–3) pts received further 4 × AVD and PET pos (DS 4–5), escalated BEACOPP. RATHL study results were used as a historical comparison. The primary endpoint was overall response rate (complete & partial metabolic response: CMR/PMR) after 2 cycles of avelumab with >40% deemed worthy of further study and <20% considered unacceptable (5% 1-sided alpha, 90% power required 47 pts). Response was assessed as per modified Lugano criteria.

Results: 47 pts were eligible. Median age 30 y (range: 17–58); 64% male; 23%, 26% and 51% had high risk stage II, stage III and IV disease respectively; 60% had B symptoms; 40% had IPSS of >2. 44 pts completed 2 cycles of avelumab (2 stopped due to toxicity, 1 due to site concerns over progressive disease (PD); indeterminate response (IR) by modified Lugano). 89% of subsequent ABVD/AVD cycles were delivered without delay (compared with 89% in RATHL). Overall response to 2 cycles of avelumab was 44.7% (90% CI: 32.2–57.7); CMR 11%; PMR 34%. The remainder were IR. iPET after 2 cycles of ABVD was positive in 5 pts (10.6%) (95% CI 3.5–23.1) versus 16.3% in the RATHL study. Pts with IR to avelumab did not show a worse response to ABVD compared with responders (87.5% vs. 88.0%). 5 pts had eBEACOPP of whom 4 converted to PET neg subsequently. With a median follow up of 14 months (range 4–32) there is a 1y PFS of 100% but 2 PDs have been reported at 14 and 23 months. Grade 3 + adverse events at least possibly related to avelumab occurred in 9 pts (20%) including one each of colitis, pneumonitis, autoimmune hepatitis, renal tubular acidosis and 2 reports of tumour flare.

Conclusions: Avelumab as 1L treatment for cHL resulted in a response above the predefined threshold confirming the activity of PDL1 inhibition in this setting. Results from subsequent chemotherapy compared favourably with RATHL in terms of iPET response after 2 cycles of ABVD, deliverability of chemotherapy and response of iPET pos patients to eBEACOPP. 1y PFS is promising but needs more follow up. These results support further study of this and similar agents in the 1L treatment of cHL.

The research was funded by: Pfizer

Keywords: Hodgkin lymphoma, immunotherapy

Conflicts of interests pertinent to the abstract

E. A. Hawkes
Research funding: Merck KgA

109 | FAVEZELIMAB PLUS PEMBROLIZUMAB IN ANTI–PD-1–REFRACTORY CLASSICAL HODGKIN LYMPHOMA (CHL): ESTIMATING THE RELATIVE EFFICACY OF FAVEZELIMAB

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Introduction: There is an unmet need for effective therapeutic options for patients (pts) with relapsed or refractory (*R/R*) cHL whose disease has progressed after a PD-1 inhibitor. Favezelimab is a LAG-3 inhibitor that had tolerable safety and effective antitumor activity when used in combination with pembrolizumab in pts with anti–PD-1–refractory *R/R* cHL in the phase 1/2 MK-4280-003 study (Timmerman J et al. *J Clin Oncol*. 2022;40(16 suppl):7545). ORR in this study was promising, but the contribution of favezelimab is unclear. In this post hoc analysis, we assessed relative efficacy of favezelimab + pembrolizumab versus pembrolizumab alone in pts with anti–PD-1–refractory *R/R* cHL. Because there are no clinical trial data for pembrolizumab alone in this setting, we used historical data from pts with *R/R* cHL who received pembrolizumab beyond disease progression in the phase 2 KEYNOTE-087 study.

Method: Pts from MK-4280-003 with a baseline and postbaseline scan were included. Pts from KEYNOTE-087 who received >2 doses of pembrolizumab beyond progression, had confirmed progression within 12 weeks of the last dose of pembrolizumab (confirmatory scan ≥4 weeks from initial progression), and had postprogression scans available, were included in the historical control arm. Pts in MK-4280-003 received pembrolizumab 200 mg IV Q3W plus favezelimab 200 mg or 800 mg IV Q3W. Pts in KEYNOTE-087 received pembrolizumab 200 mg IV Q3W. For pts in KEYNOTE-087, baseline tumor size was reset at first progression and best change in target lesion size was calculated in the postprogression period. ORR was assessed per Cheson 2007 criteria. A bootstrapping method compared change in target lesion size, with 1000 random samples averaged from pts in KEYNOTE-087.

Results: 27 of 33 pts in MK-4280-003 were included for the radiographic analysis. In KEYNOTE-087, 123 pts developed disease progression on pembrolizumab, of whom 81 received postprogression

pembrolizumab and were included in this analysis. ORR for pts who received favezelimab + pembrolizumab was 31% (range 15–51) compared with 2.5% (range 0–5.9) for pts who received post-sprogression pembrolizumab. Average change from baseline in target lesion size was −46.6% for favezelimab + pembrolizumab compared with −0.37% for postprogression pembrolizumab. 44% of pts who received favezelimab + pembrolizumab had a ≥50% reduction in target lesion size compared with 5% of pts who received postprogression pembrolizumab. Results of the bootstrapping analysis showed a better response for favezelimab + pembrolizumab relative to pembrolizumab monotherapy in 99.4% (26,826 of 27,000) of samples.

Conclusions: In this analysis, favezelimab + pembrolizumab was associated with a higher ORR and deeper responses than pembrolizumab alone in pts with anti–PD-1–refractory *R/R* cHL, indicating that favezelimab contributed substantially to the efficacy observed in MK-4280-003.

Keywords: Hodgkin lymphoma, immunotherapy

Encore Abstract—previously submitted to EHA 2023

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Conflicts of interests pertinent to the abstract

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Honoraria: Merck

Research funding: MSD, BMS, Roche, Adaptive Biotechnologies, Affimed Therapeutics, Genentech, IGM, Kite--a Gilead company

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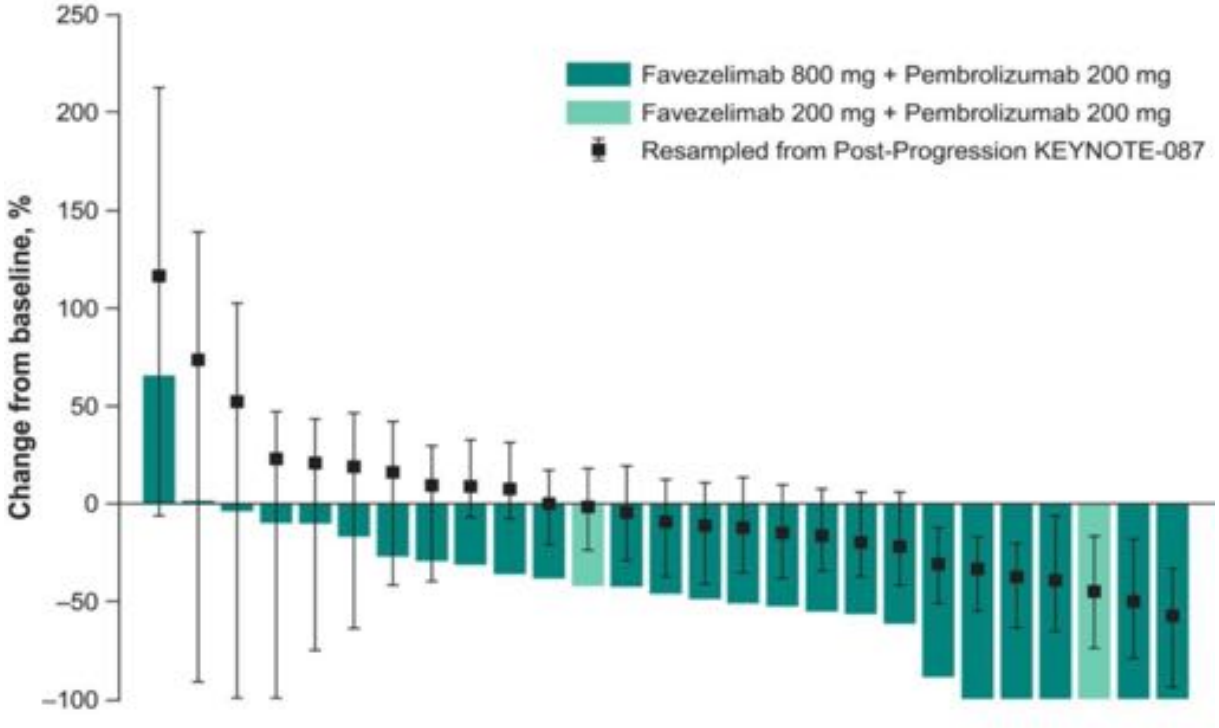
Other remuneration: Speaker bureau--MSD, EUSA Pharma, Novartis

J. Timmerman

Consultant or advisory role: Kite/Gilead, DAVA Oncology, Oncovalent Therapeutics

Honoraria: Kite/Gilead

Figure. Best percentage change from baseline in target lesion size in patients treated with favezelimab + pembrolizumab in MK-4280-003 compared with historical control data from patients who received postprogression pembrolizumab in KEYNOTE-087[a]



[a]Resampled data are median (range) of 1000 random samples obtained from patients who received postprogression pembrolizumab in KEYNOTE-087.

Research funding: BMS, Kite- A Gilead company, Merck
Travel grants: BMS

N. Johnson
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Research funding: BMS, Merck, Genentech/Roche, Kite--a Gilead Company, AstraZeneca, Seattle Genetics, Gilead Sciences, ADC Therapeutics
Travel grants: BMS

FOCUS ON ONGOING TRIALS

OT01 | SAKK 38/19: ASSESSING A CTDNA AND PET-ORIENTED THERAPY IN PATIENTS WITH DLBCL. A MULTICENTER, OPEN-LABEL, PHASE II TRIAL

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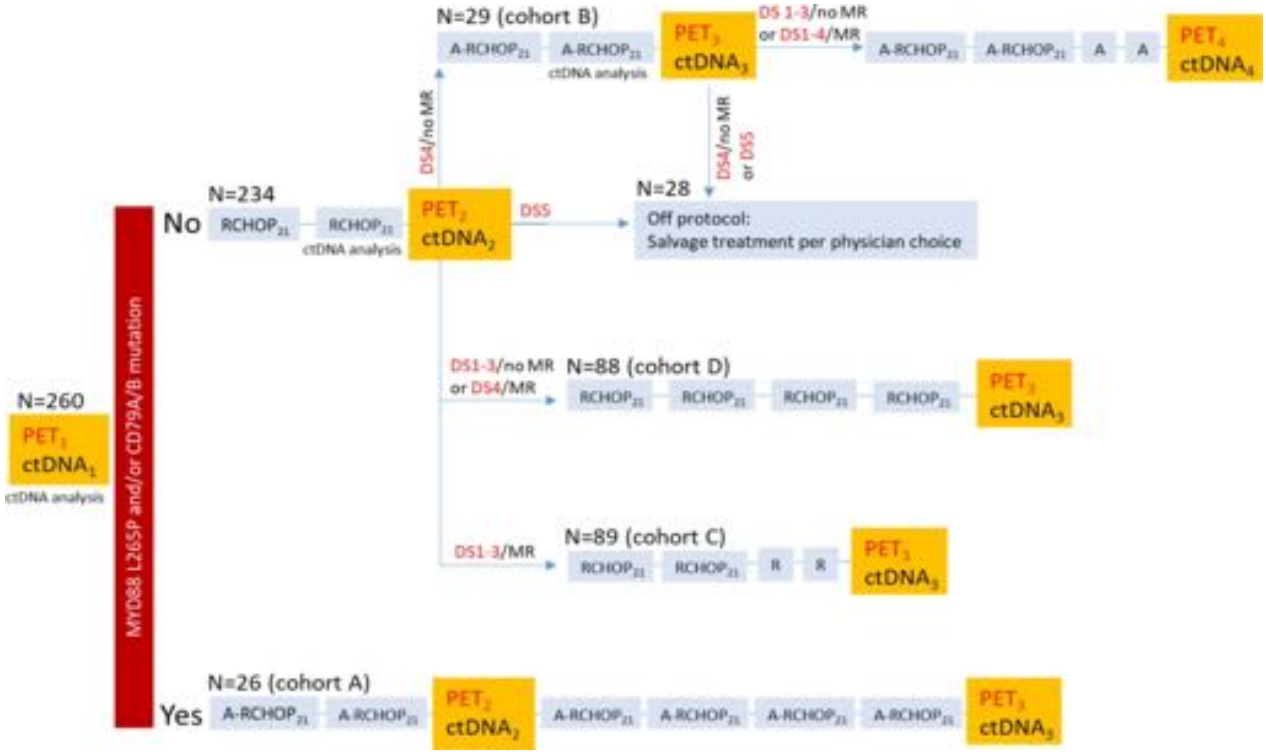
Introduction: Diffuse large B-cell lymphoma (DLBCL) is an aggressive but potentially curable lymphoma. Rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP) is the standard first-line regimen with cure rates nearing 60%. Over the last years many efforts have been made aiming at improving outcomes of first line therapy but none has resulted in improved overall survival over R-CHOP. Recently, genetic subtypes of DLBCL that go beyond the cell-of-origin and have distinct biology, clinical characteristics and different likelihood of response to specific therapies have been identified. One of these entities is represented by the MCD subtype harboring either the MYD88 L265P mutation, the CD79A/B mutation, or both. MCD has a dismal outcome when treated with R-CHOP but is sensitive to BTK inhibition. In addition to the genetic definition of specific subtypes, the possibility to use circulating tumour DNA (ctDNA) response assessment together with PET-response may establishe a new strategy for treatment decisions in patients with DLBCL.

Methods: SAKK 38/19 (NCT04604067) is an ongoing exploratory multicohort phase II trial in patients (pts) with previously untreated DLBCL not otherwise specified (NOS). Adult pts with CD20-positive DLBCL NOS, ECOG performance status 0–2, candidates for 6 cycles of R-CHOP are eligible.

At baseline, a liquid biopsy is perfomed and pts with MCD subtype are treated with the combination of R-CHOP plus acalabrutinib for 6 cycles (cohort A). Non-MCD pts receive 2 cycles of R-CHOP and based on the combined PET and ctDNA response assessment after cycle 2 they are allocated to one of three different cohorts: R-CHOP for 4 additional cycles in combination with acalabrutinib followed by 2 months of acalabrutinib single-agent (cohort B); 2 additional cycles



of R-CHOP and 2 administrations of single-agent rituximab (cohort C); 4 additional cycles of R-CHOP (cohort D).

Co-primary endpoints of the trial are: Progression free survival (PFS) (in Cohorts A, C and D) and complete remission (CR) rate (in Cohort B)

Secondary endpoints: Adverse events in the cohorts treated with acalabrutinib-R-CHOP; overall survival; PFS in cohort B; CR rate in cohorts A, C and D; overall response rate; duration of response.

Enrollment began June 2021. The trial is currently recruiting and plans to enroll 260 pts in Switzerland and Italy.

The research was funded by: -Astra Zeneca -Hubacher Fund

Keywords: aggressive B-cell non-Hodgkin lymphoma, liquid biopsy, ongoing trials

Conflicts of interests pertinent to the abstract

A. Stathis

Honoraria: Eli Lilly, Bayer, Roche, Novartis, Janssen Oncology, AstraZeneca

Research funding: ADC Therapeutics, Pfizer, Roche, Novartis, Bayer, Eli Lilly, MEI Pharma, Cellestia, Debiopharm Group, Merck/MSD, Abbvie, Amgen, AstraZeneca, Incyte, Loxo, and Philogen

F. Hitz

Consultant or advisory role Abbvie, Takeda and Roche

G. Gritti

Consultant or advisory role Roche, Takeda, Kite-Gilead, Ideogen, Genmab

Educational grants: Janssen, Beigene, Sandoz

Other remuneration: Clinigen, Ideogen, Beigene, Incyte, Novartis

T. Zenz

Honoraria: Roche, Abbvie, AZD, Beigene, Janssen, Gilead, Novartis

OT02 | REMODL-A: A RANDOMISED PHASE II EVALUATION OF MOLECULAR GUIDED THERAPY FOR DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) WITH ACALABRUTINIB — ONGOING TRIAL

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Introduction: R-CHOP remains the standard of care in DLBCL yet for up to 40% of patients (pts.) it fails either through refractory lymphoma or relapse after achieving an initial remission. In the phase Ib/

II ACCEPT study (NCT03571308), acalabrutinib (A), a second generation Bruton Tyrosine Kinase inhibitor with enhanced kinase selectivity and a potential for better tolerability, was assessed in combination with R-CHOP in patients with *de novo* DLBCL. There were no dose-limiting toxicities and the maximum tolerated dose was not reached, At the recommended phase II dose of A 100 mg bd, R-CHOP+A demonstrated a 95% 24 month progression-free survival (PFS). In older patients there was no difference in safety and no compromise of delivery of full course R-CHOP. Efficacy was preserved across cell-of-origin and genomic sub-groups. The REMoDL-A study now builds upon these findings to examine efficacy of R-CHOP +A against R-CHOP.

Methods: REMoDL-A is a stratified open-label, multicentre, randomised phase II study. Eligible patients have untreated histologically confirmed DLBCL requiring full course R-CHOP. All patients receive 1 cycle of R-CHOP chemotherapy. FFPE diagnostic pathology blocks have molecular profiling and are assigned subtype Germinal Centre B-cell, Activated B-Cell, Molecular High Grade, Unclassifiable, or failed RNA extraction (GEP Fail). Patients whose biopsies are successfully sub-typed are randomised 2:1 between R-CHOP+A (Arm B) or R-CHOP for a further 5 cycles (Arm A). The randomisation is stratified by molecular subtype, International Prognostic index and age. The primary endpoint for the study is progression free survival (PFS) in the modified intention to treat (ITT) population (non-Fail ITT population). Secondary endpoints include PFS related to the cell of origin and genomic subtypes, duration of response, overall survival, event free survival, toxicity and quality of life. Exploratory analyses will investigate how dynamic molecular (including $_{CT}$DNA) and PET based biomarkers predict risk and can be incorporated into a dynamic risk prediction model. An early interim analysis is planned to explore safety in the ≥65 years population. The trial is powered to detect a hazard ratio of 0.668 with 90% power with 1-sided significance level of 20%. The number of patients to be randomised is 453 (302:151 per arm). To date 155 patients have been recruited. Of the FFPE diagnostic pathology blocks that have undergone molecular profiling, failed RNA extraction (GEP fail) has occurred in only 4 patients.

This is a UK National Cancer Research Institute multicentre trial coordinated by Southampton Clinical Trials Unit. Molecular profiling is performed in HMDS, Leeds. Trial registration: ISRCTN14251143/NCT04546620

The trial has been supported by an investigator initiated grant and drug access from AstraZeneca (ESR-19-20180) and has endorsement from Cancer Research UK (CRUKE/19/017).

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, ongoing trials

Conflicts of interests pertinent to the abstract

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Honoraria: Roche, AstraZeneca

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Research funding: Beigene
Educational grants: Roche, BMS

G. Griffiths
Honoraria: AstraZeneca

P. Johnson
Honoraria: Takeda, InCyte, Genmab, Epizyme

A. J. Davies
Consultant or advisory role Celgene, Roche, Kite, Takeda, Incyte
Honoraria: Celgene, Roche, Kite, Takeda

Research funding: Celgene, Roche, Kite, Takeda, Janssen, GSK
Educational grants: Celgene, Roche

OT03 | BRENTUXIMAB VEDOTIN-NIVOLUMAB ALONE AND THEN WITH RITUXIMAB-CYCLOPHOSPHAMIDE-DOXORUBICIN-PREDNISONE AS FRONTLINE THERAPY OF PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

R. E. Steiner[1], P. Strati[1], C. R. Flowers[1], S. S. Neelapu[1], M. Green[1], L. J. Nastoupil[1], F. B. Hagemeister[1], L. Feng[2], S. Ahmed[1], R. Nair[1], L. Fayad[1], H. J. Lee[1], M. A. Rodriguez[1], J. R. Westin[1]
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Introduction: Primary mediastinal (thymic) large B-cell lymphoma (PMBCL) is a rare, aggressive subtype of diffuse large B-cell lymphoma and affects primarily young adults. PMBCL shares several features with classic Hodgkin lymphoma, such as 9p24.1 amplification, increased programmed cell death protein 1 (PD-1) ligand, and CD30 expression. The trial CheckMate-436 treated relapsed/refractory (rr) PMBCL patients with nivolumab (antibody that binds to PD-1) and brentuximab vedotin ((BV) anti-CD30 antibody-drug conjugate), who showed an overall response rate (ORR) of 73% and complete response rate (CRR) of 43% (Zinzani et al. JCO 2019). Although most PMBL patients can be cured with frontline chemo-immunotherapy (CIT) with or without radiotherapy (XRT), the outcome of patients having rr-PMBCL is generally unfavorable. The discovery of new frontline regimens represents an unmet need for PMBL patients. We hypothesize that BV+Nivolumab will show ORR in frontline therapy at least as high as in the rr setting, may avoid chemoresistance, could deescalate the intensity of CIT, and alleviate the need for consolidative XRT.

Methods: We are conducting a phase II, open-label, single-center clinical trial NCT04745949 combining BV-Nivolumab alone and then combined with rituximab, cyclophosphamide, doxorubicin,

and prednisone (R-CHP) for patients with previously untreated PMBL.

Patients 18 years or older with previously untreated PMBL, stage I to stage IV disease are eligible. However, patients previously treated with up to one cycle of standard-of-care therapy are eligible.

Patients will receive BV 1.8 mg/Kg IV and Nivolumab 240 mg flat dose IV day 1 for cycles 1 and 2, in a 21-day cycle. During cycles 3 and 4, R-CHP will be added to BV-Nivolumab. Patients who have achieved complete response (CR) at PET/CT before cycle 5 will receive 2 more cycles of BV-Nivolumab+R-CHP (cycle 5 and 6) and BV-Nivolumab only for cycles 7 and 8 (A). In case of CR on PET/CT after cycle 8, therapy will be considered completed. Patients in PR on PET/CT before cycle 5 will receive 4 more cycles of BV-Nivolumab +R-CHP (cycles 5–8 (B)).

The primary endpoint is CRR at the end of therapy (EOT). The maximum sample size for the PMBL cohort is 40 patients, with a target CRR at EOT of 70%. The null hypothesis is that the true CRR at EOT is 50%, and the alternative hypothesis is that the true CRR at EOT is 70%. The Simon's optimal two-stage design controls the one-sided type I error rate at 0.06 and yields the power of 0.8.

The secondary endpoints will include the response rate of BV-Nivolumab+R-CHP at the end of the immune lead-in, landmark survival outcomes, safety, and patient-reported outcome. Exploratory analyses include assessing molecular response by sequencing cell-free DNA and multiplex immunofluorescence to analyze the tumor microenvironment.

The trial is actively accruing at MD Anderson Cancer Center, and 8 out of 40 patients have been enrolled.

The research was funded by: Seagen, BMS (drug support only)

Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy, ongoing trials

Conflicts of interests pertinent to the abstract

R. E. Steiner

Research funding: Seagen, BMS, GSK, Rafael Pharmaceuticals

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Research funding: Astrazeneca-Acerta, ALX Oncology and ADC Therapeutics

S. Ahmed

Consultant or advisory role Tessa Therapeutic's advisory committee

Research funding: Seattle Genetics, Merck, Xencor, and Tessa Therapeutics

J. R. Westin

Consultant or advisory role Research funding: Kite/Gilead, BMS, Novartis, Genentech, AstraZeneca, Morphosys/Incyte, ADC Therapeutics, Abbvie, SeaGen, MonteRosa, Regeneron

Research funding: Kite/Gilead, BMS, Novartis, Genentech, AstraZeneca, Morphosys/Incyte, ADC Therapeutics, Kymera, Calithera

OT04 | MAHOGANY: A PHASE 3 TRIAL OF ZANUBRUTINIB PLUS ANTI-CD20 VERSUS LENALIDOMIDE PLUS RITUXIMAB IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR OR MARGINAL ZONE LYMPHOMA

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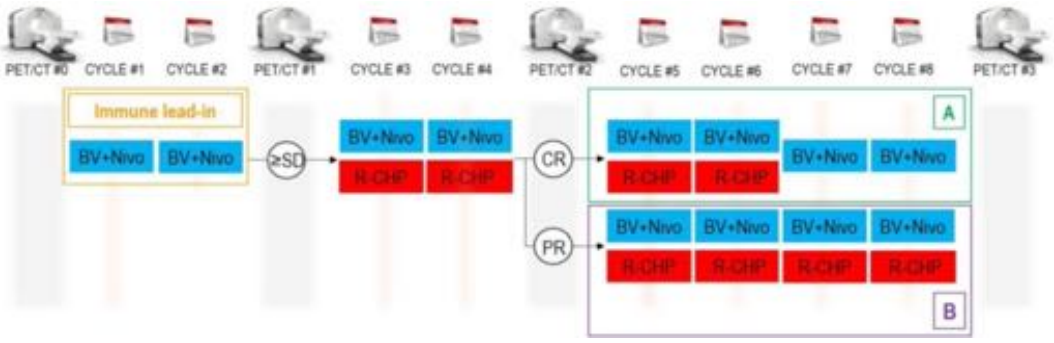

Introduction: Inhibition of Bruton tyrosine kinase (BTK) has emerged as a strategy for treatment of patients (pts) with B-cell malignancies including indolent non-Hodgkin lymphomas. Zanubrutinib is a second-generation, potent, and specific BTK inhibitor and has shown to be more effective and better tolerated than first-generation BTK inhibitors in several diseases including chronic lymphocytic leukemia/small lymphocytic lymphoma and Waldenström macroglobulinemia. Zanubrutinib is approved in >15 countries, including the United States and European Union, for pts with relapsed/refractory (*R/R*) marginal zone lymphoma (MZL) who received ≥1 anti-CD20–based regimen, based on the single-arm MAGNOLIA trial (Opat et al. *Clin Cancer Res* 2021). In *R/R* follicular lymphoma (FL), ROSEWOOD, a phase 2 randomized study of zanubrutinib plus obinutuzumab versus obinutuzumab, met its primary endpoint of increased overall response rate (ORR) at primary analysis (Zinzani et al. *J Clin Oncol* 2022). In this trial, zanubrutinib plus obinutuzumab in pts with *R/R* FL demonstrated deep and durable responses with a favorable safety profile.

Methods: MAHOGANY (BGB-3111-308, NCT05100862) is a phase 3 randomized, open-label trial that compares efficacy and safety of a combination of zanubrutinib plus anti-CD20 monoclonal antibody versus lenalidomide plus rituximab in 2 independent cohorts, for pts with either *R/R* FL or MZL. Key eligibility criteria include histologically confirmed FL (grades 1–3A) or MZL, previously treated with ≥1 anti-CD20-based regimen, relapsed after or refractory to the most recent systemic therapy, in need of treatment, no prior BTK inhibitor exposure, and no prior resistance to a lenalidomide-based regimen. In the FL cohort, pts will be randomized 1:1 to zanubrutinib plus obinutuzumab ($N = 300$) and lenalidomide plus rituximab ($N = 300$). Randomization is stratified by age (≥60 vs. <60 years), number of prior lines of therapy (1–2 vs. >2), and rituximab-refractory status (yes vs. no). The primary endpoint is progression-free survival (PFS) assessed by an independent review committee (IRC) according to Lugano 2014 criteria. Key secondary endpoints are ORR by IRC assessment and overall survival. In the MZL cohort, pts will be randomized 1:1 to zanubrutinib plus rituximab ($N = 75$) and lenalidomide plus rituximab ($N = 75$). Randomization is stratified by age (≥60 vs. <60 years) and number of prior lines of therapy (1–2 vs. >2). The primary endpoint is PFS assessed by IRC according to Lugano 2014 criteria. The key secondary endpoint is ORR by IRC assessment. Zanubrutinib is given at 160 mg twice daily or 320 mg once daily according to investigator, until progression or unacceptable toxicity. Obinutuzumab or rituximab are given for up to 8 infusions. Lenalidomide is given according to approved label for up to 12 cycles. Recruitment is ongoing.

Encore Abstract—previously submitted to ASCO 2023 and EHA 2023
The research was funded by: BeiGene

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies

Conflicts of interests pertinent to the abstract

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Educational grants: Roche, Incyte
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Research funding: Janssen Biotech, Genentech/Roche, Epizyme, Novartis, IgM Biosciences, Gilead Sciences, Allogene Therapeutics, Takeda, BMS/Celgene
Educational grants: Genentech/Roche

OT05 | SUNMO: PHASE III TRIAL OF MOSUNETUZUMAB PLUS POLATUZUMAB VEDOTIN VERSUS RITUXIMAB PLUS GEMCITABINE AND OXALIPLATIN IN RELAPSED/REFRACTORY AGGRESSIVE NON-HODGKIN LYMPHOMA

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Introduction: Aggressive non-Hodgkin lymphomas (aNHL) are a diverse group of neoplasms, of which diffuse large B-cell lymphoma (DLBCL) is the most common subtype (Thandra, 2021). Patients (pts) with relapsed/refractory (*R/R*) DLBCL after one prior therapy who are unable to receive, or relapsed after, an autologous stem cell transplant (ASCT) and/or chimeric antigen receptor T-cell therapy have a poor prognosis (Salles, 2019; Di Blasi, 2022). Mosunetuzumab (Mosun) is an off-the-shelf CD20xCD3 T-cell engaging bispecific antibody that redirects T cells to eliminate malignant B cells (Sun, 2015), with promising efficacy and safety as a single agent, as shown in a Phase I trial in pts with B-cell NHL, including aNHL (Budde, 2022). Mosun has also shown promising safety and efficacy in combination with polatuzumab vedotin (Pola), a CD79b targeted antibody-drug conjugate that delivers the microtubule-disrupting agent monomethyl auristatin E directly to B cells (Dornan, 2009), in a Phase Ib/II trial in pts with *R/R* aNHL (Budde, ASH 2021).
Methods: SUNMO (NCT05171647) is a randomized, open-label, global Phase III trial evaluating the efficacy and safety of subcutaneous Mosun + intravenous (IV) Pola (M-Pola) versus IV rituximab + gemcitabine and oxaliplatin (R-GemOx) in pts with *R/R* aNHL (Figure). Eligible pts have CD20-positive *R/R* aNHL (DLBCL not otherwise specified [NOS], high-grade B-cell lymphoma double/triple hit or NOS, transformed follicular lymphoma [FL], or Grade 3B FL), Eastern Cooperative Oncology Group performance status 0–2, and ≥1 prior systemic therapy (if only one prior line of therapy, pts must be ineligible for ASCT). Exclusion criteria include prior treatment with CD20-directed bispecific antibodies, R-GemOx, or GemOx; prior allogeneic stem cell transplantation; and any central nervous system involvement of lymphoma. Pts will be randomized 2:1, stratified by the number of prior lines of therapy (1 vs. >1) and response to last therapy (relapsed vs. refractory) to receive M-Pola or R-GemOx IV for a fixed duration of up to 8 cycles (6 cycles for Pola; M-Pola, 21-day cycles; R-GemOx, 14-day cycles). The primary endpoint is progression-free survival (PFS) determined by an independent review facility (IRF). Secondary endpoints include overall survival; IRF- and investigator (INV)-assessed complete response (CR) rate, objective response rate, and duration of response/CR; INV-assessed PFS; patient-reported outcomes; and safety. Biomarker analyses include prespecified prognostic subsets from baseline biopsies and circulating tumor DNA at baseline and during treatment. Enrollment is ongoing, and an estimated 75 sites globally will enroll approximately 222 pts (M-Pola, 148 pts; R-GemOx, 74 pts).

Encore Abstract—previously submitted to ASCO 2023

The research was funded by: SUNMO (NCT05171647) is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of all authors, was provided by Martha Warren MSci of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy

Conflicts of interests pertinent to the abstract

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Research funding: Janssen, Genentech, Novartis, Kite/Gilead, BMS, AstraZeneca, Morphosys/Incyte, ADC Therapeutics

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Research funding: Genentech, Adaptive Biotech, Precision Bio, Kymera Therapeutics, Schrodinger

W. S. Kim
Research funding: Sanofi, Beigene, Boryong, Roche, Kyowa-kirin, Donga

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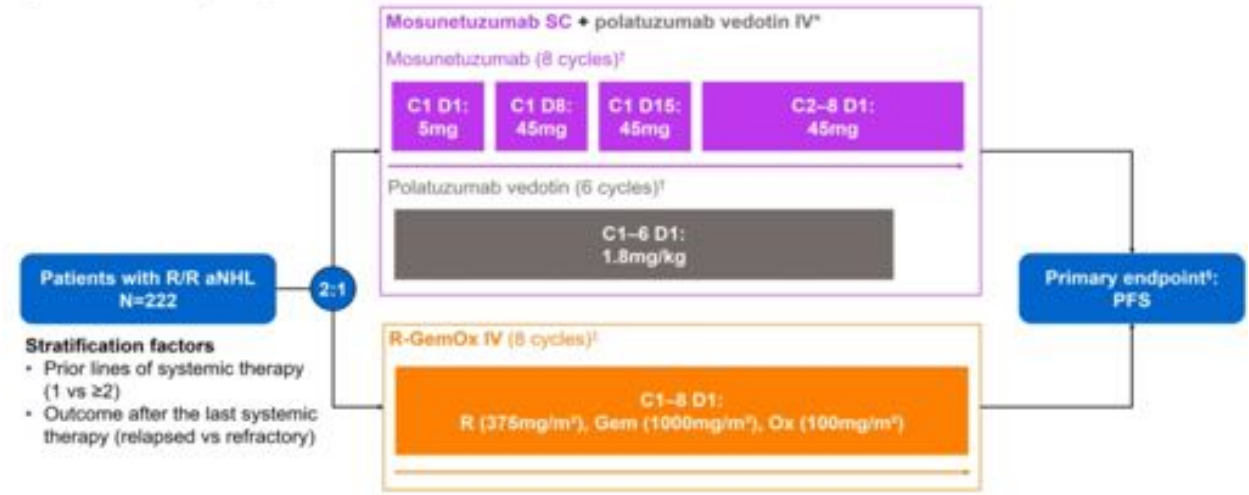
Employment or leadership position: Pusan National University Hospital

Figure. SUNMO study design



*Administered as an outpatient regimen. †One cycle is 21 days. ‡One cycle is 14 days and may be adjusted to 21 days. §Secondary endpoints include: OS, investigator-assessed PFS, CR rate, ORR, DoR/CR, and time to deterioration of patient-reported outcomes.
aNHL, aggressive B-cell non-Hodgkin lymphoma; C, cycle; CR, complete response; D, day; DoR, duration of response; Gem, gemcitabine; IV, intravenous; ORR, objective response rate; OS, overall survival; Ox, oxaliplatin; PFS, progression-free survival; R, rituximab; R/R, relapsed/refractory; SC, subcutaneous.

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S. Pham
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J. Jing
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Research funding: Merck, Amgen, MustangBio, AstraZeneca
Other remuneration: Patents, royalties, other intellectual property—CCR4 CAR T cells for treatment of patients with CCR4 positive cancer, CD33CAR for treatment of patients with CD33+ acute myeloid leukemia; Travel, accommodation, expenses—Roche/Genentech, Kite/Gilead

OT06 | ZUMA-23: A GLOBAL, PHASE 3, RANDOMIZED CONTROLLED STUDY OF AXICABTAGENE CILOLEUCEL VERSUS STANDARD OF CARE AS FIRST-LINE THERAPY IN PATIENTS WITH HIGH-RISK LARGE B-CELL LYMPHOMA

J. Westin[1], C. A. Jacobson[2], J. C. Chavez[3], A. Sureda[4], F. Morschhauser[5], B. Glaß[6], M. Dickinson[7], A. Davies[8], I. W. Flinn[9],

D. G. Maloney[10], M. Chamuleau[11], M. Tees[12], A. Xue[13], S. Shahani[13], O. Nikolajeva[13], J. Kang[13], A. Kaplan[13], M. Schupp[13], H. Miao[13], E. S. Rich[13]

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Introduction: The nearly 40% of patients with large B-cell lymphoma (LBCL) who are refractory to or relapse after current first-line standard-of-care (SOC) regimens, such as R-CHOP (rituximab [R] + cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]) and DA-EPOCH-R (dose-adjusted etoposide [DA-E]), have poor prognoses. High International Prognostic Index (IPI) score and the subtype of high-grade B-cell lymphoma (HGBL) are associated with shorter progression-free and overall survival (PFS and OS; Nastoupil LJ and Bartlett NL. *J Clin Oncol.* 2023). Strategies to improve outcomes in these subgroups have been largely unsuccessful; therefore, therapeutic options with a different mechanism of action are needed.

Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved to treat patients with relapsed/refractory LBCL after demonstrating significant clinical benefit as second line (ZUMA-7; Locke FL, et al. *N Engl J Med.* 2022) and third line and above (ZUMA-1; Neelapu SS, et al. *N Engl J Med.* 2017) therapy. Additionally, in the Phase 2 ZUMA-12 study in patients with refractory first-line LBCL, axi-cel showed a high rate of durable responses with an objective response rate of 89% (complete response rate, 78%) and an ongoing response rate of 73% (median follow-up, 15.9 months; Neelapu SS, et al. *Nat Med.* 2022). ZUMA-23 is the first Phase 3, randomized controlled study to evaluate CAR T-cell therapy as a first-line regimen for any cancer and will assess axi-cel versus SOC in patients with high-risk LBCL, defined as IPI 4–5.

Methods: The Phase 3 trial design will enroll ≈300 adult patients with high-risk, histologically confirmed LBCL based on the 2016 WHO classification, including diffuse large B-cell lymphoma, HGBL, and transformed follicular or marginal zone lymphoma (Swerdlow SH, et al. *Blood.* 2016). Eligible patients will receive 1 cycle of R-chemotherapy and then be randomized 1:1 to receive axi-cel or continue with SOC. Patients in the axi-cel arm will undergo leukapheresis and then receive R-CHOP or DA-EPOCH-R as bridging therapy, followed by lymphodepleting chemotherapy (fludarabine/cyclophosphamide), and a single axi-cel infusion (2×10^6 CAR T cells/kg). Prophylactic corticosteroids may be administered to reduce the incidence and severity of cytokine release syndrome at the investigator's discretion. Patients in the SOC arm will receive 5 additional cycles of R-CHOP or DA-EPOCH-R (investigator's choice).

The primary endpoint is event-free survival by blinded central review. Key secondary endpoints are OS and PFS. Safety, quality of life, and pharmacokinetics will also be assessed. Patients with a history of HIV and/or hepatitis B or C and undetectable viral loads may enroll. Key exclusion criteria include LBCL of the central nervous system. ZUMA-23 is open for enrollment (NCT05605899).

Encore Abstract—previously submitted to ASCO 2023 and EHA 2023
The research was funded by: Kite, a Gilead Company.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, ongoing trials

Conflicts of interests pertinent to the abstract

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Research funding: ADC Therapeutics, AstraZeneca, Bristol Myers Squibb, Calithera, Genentech, Kite, Kymera, Morphosys/Incyte, and Novartis

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Research funding: Kite and Pfizer

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Research funding: Takeda
Educational grants: Kite and Takeda
Other remuneration: Speakers' bureau participation for Takeda

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Research funding: AstraZeneca, Cellcentric, MSD, and Roche
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Research funding: 2seventy bio, AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Biopath, Bristol Myers Squibb, CALIBR, CALGB, Celgene, City of Hope National Medical Center, Constellation Pharmaceuticals, Curis, CTI Biopharma, Epizyme, Fate Therapeutics, Forma Therapeutics, Forty Seven, Genentech, Gilead Sciences, InnoCare Pharma, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Janssen, Kite Pharma, Loxo, Marker Therapeutics, Merck, Millennium Pharmaceuticals, MorphoSys, Myeloid Therapeutics, Novartis, Nurix, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Roche, Seattle Genetics, Step Pharma, Tessa Therapeutics, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development Corp., Unum Therapeutics, Verastem, and Vincerx Pharma

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Honoraria: A2 Biotherapeutics, Amgen, Bristol-Myers Squibb, Celgene, Genentech, Gilead Sciences, Incyte, Janssen, Juno Therapeutics, Kite, Legend Biotech, MorphoSys, Mustang Bio, Navan Technologies, Novartis, Pharmacyclics, and Umoja
Research funding: (To your institution): Celgene, Juno, and Kite
Other remuneration: Data Safety Monitory Board or Advisory Board participation for Bioline Rx and Celgene; rights to royalties from Fred Hutch for patents licensed to Juno; and stock options from A2 Biotherapeutics and Navan Technologies

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Educational grants: Kite

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Stock ownership: Kite

M. Schupp
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H. Miao
Employment or leadership position: Kite, a Gilead Company
Stock ownership: Gilead

E. S. Rich
Employment or leadership position: Kite, a Gilead Company
Stock ownership: Gilead

FOCUS ON LIQUID BIOPSY AND MINIMAL RESIDUAL DISEASE

110 | MOLECULAR CLUSTERING ON CTDNA IMPROVES THE PROGNOSTIC STRATIFICATION OF DLBCL PATIENTS COMPARED TO CTDNA LEVELS

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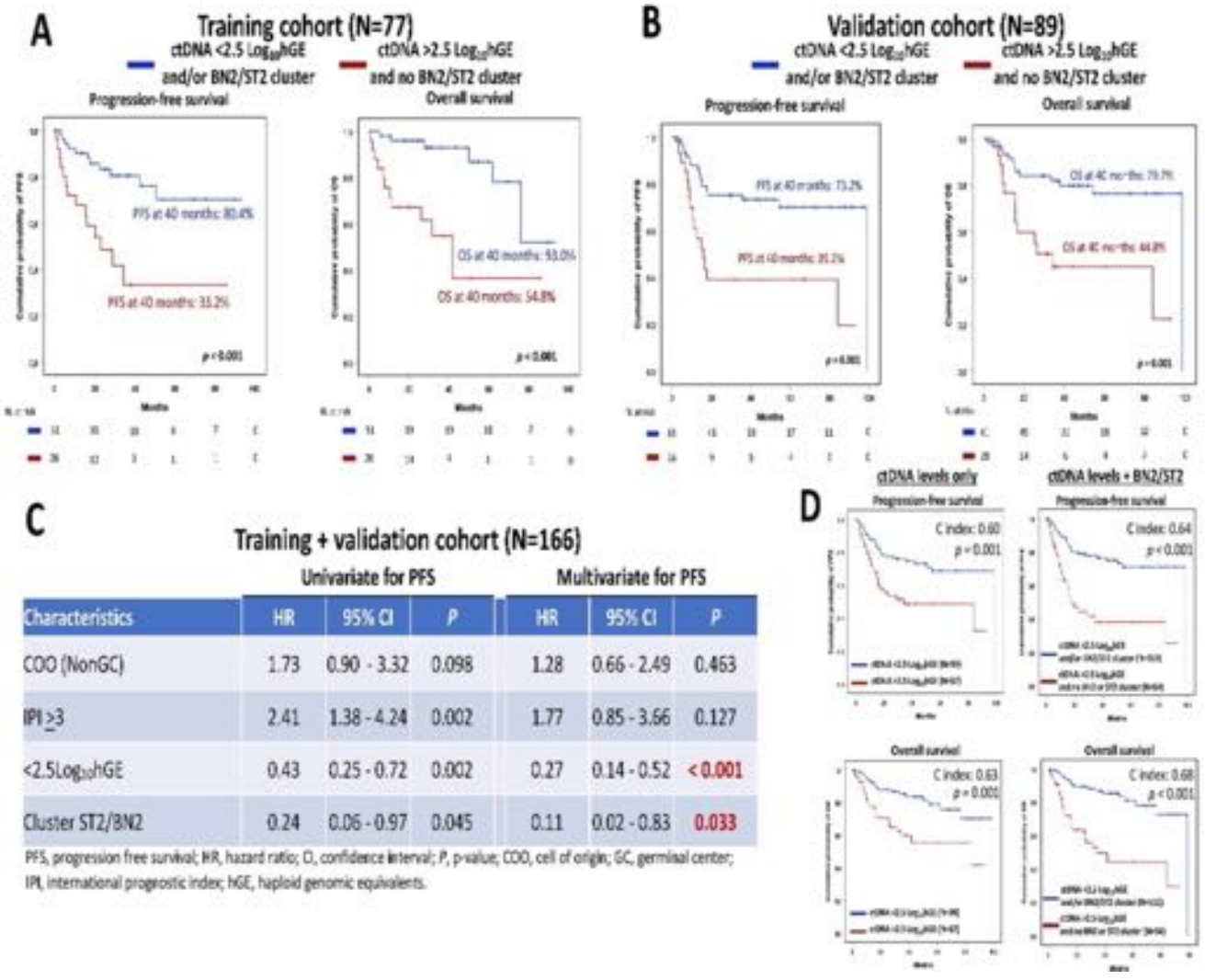
Introduction: The quantification of circulating tumor DNA (ctDNA) on the liquid biopsy at the time of diagnosis allows to stratify the outcome of diffuse large B-cell lymphoma (DLBCL) patients but its integration with molecular clustering has not been evaluated so far. **Methods:** A multicenter cohort of newly diagnosed and homogeneously treated DLBCL provided with ctDNA and with genomic DNA



from lymph node (LN) biopsy represented the training cohort. A validation cohort of newly diagnosed DLBCL patients provided with ctDNA was collected. The CAPP-Seq assay was used.

Results: The training cohort included 77 newly diagnosed DLBCL patients treated with R-CHOP-based therapy. After a median follow-up of 33.9 months, the 40-month progression-free survival (PFS) and overall survival (OS) were 65.2% and 80.2%, respectively. Using the LymphGen tool on ctDNA, 9 patients were classified as MCD, 5 as ST2, 7 as EZB, 5 as BN2 and 1 as molecular composite (BN2/ST2). ST2 and BN2 patients in both ctDNA ($p = 0.032$) and in LN biopsy ($p = 0.007$) displayed an excellent PFS compared to other patients. By recursive partitioning, patients assigned to clusters ST2 or BN2 ($N = 10$) further split the outcome of patients with ctDNA levels $\geq 2.5\text{Log}_{10}$hGE (40-month PFS of 100% compared to 33.2% for patients classified as MCD or EZB or not classified, $p = 0.009$). Therefore, by combining ctDNA levels and molecular clusters identified on the liquid biopsy, patients with $<2.5\text{Log}_{10}$hGE and/or assigned to cluster BN2 and ST2 presented a 40-month PFS and OS of 80.4% and 93.0%, compared to 33.2% and 54.8% for other patients, respectively (both $p < 0.001$) (Figure 1A). Interestingly, 80% of ST2/BN2 patients reached an early molecular response (EMR) and the 2 ST2/BN2 patients who did not achieve an EMR after 1 cycle of therapy are still in complete remission. To validate this finding, a validation cohort of 89 newly diagnosed DLBCL was collected. The PFS and OS of the training of the validation cohort were superimposable ($p = 0.805$ and $p = 0.608$, respectively). Also in the validation cohort, patients with $<2.5\text{Log}_{10}$hGE and/or assigned to cluster BN2 and ST2 presented an excellent outcome with a 40-month PFS and OS of 73.2% and 79.7%, compared to 39.2% and 44.8% for other patients, respectively (both $p = 0.001$) (Figure 1B). By combining the training and the validation cohort, we performed a multivariate analysis on 166 patients. Both a ctDNA $<2.5\text{Log}_{10}$hGE and the BN2/ST2 cluster maintained an independent association with an excellent outcome when adjusted for IPI and cell of origin (Figure 1C). Moreover, compared to ctDNA levels only, the addition of BN2/ST2 cluster improved the C statistics of the model (0.64 vs. 0.60 for PFS and 0.68 vs. 0.63 for OS, Figure 1D).

Conclusions: The combination of ctDNA levels <2.5 Log_{10}hGE and ST2/BN2 molecular clusters on the liquid biopsy represents a powerful biomarker to identify patients who can benefit the most from R-CHOP-based therapy.

Keywords: aggressive B-cell non-Hodgkin lymphoma, liquid biopsy

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No conflicts of interests pertinent to the abstract.

111 | CIRCULATING TUMOR DNA (CTDNA) STATUS AND CLINICAL OUTCOMES IN PATIENTS (PTS) WITH PREVIOUSLY UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) IN THE POLARIX STUDY

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Introduction: In the POLARIX study, pts with previously untreated DLBCL were randomized to Pola-R-CHP or R-CHOP (NCT03274492; Tilly et al., 2022). We previously validated the prognostic value of ctDNA at baseline and after one cycle of therapy in POLARIX (Herrera et al., 2022); here, we evaluate the relationship between ctDNA clearance and PFS and OS.

Methods: Pts were included if baseline and longitudinal ctDNA results were available. Plasma ctDNA was measured at baseline, Cycle (C) 5 Day (D) 1, and end of treatment (EOT), with the AVENIO NHL CAPP-Seq assay (Stokowski et al. 2022). ctDNA clearance was determined as previously described (Herrera et al. 2022). PFS and OS according to ctDNA status were reported as landmarked hazard ratios (HR) and 3-yr rates. HRs were adjusted for IPI score (>2), region, bulky disease (>7.5 cm), age (>60 years), and cell of origin.

Results: At baseline, 654 pts had ctDNA results; 494 (76%) and 519 (79%) pts were evaluable at C5D1 and EOT, respectively. Undetectable ctDNA (ctDNA–) was achieved by 57% (152/265) of Pola-R-CHP-treated pts and 59% (135/229) of R-CHOP-treated pts at C5D1 ($p = 0.79$), and by 66% (172/262) of Pola-R-CHP-treated pts and 67% (172/257) of R-CHOP-treated pts at EOT ($p = 0.83$). Achieving

ctDNA—was prognostic for PFS and OS in each treatment arm at C5D1 and EOT (Table).

Pts in the Pola-R-CHP arm who had complete response (CR) with PET-CT and ctDNA—at EOT had superior PFS and OS compared with pts with CR and detectable ctDNA (ctDNA+) at EOT (PFS HR 0.30, 95% confidence interval [CI]: 0.14–0.66; OS HR 0.20, 95% CI: 0.07–0.60). This was not observed with R-CHOP (PFS HR 0.74, 95% CI: 0.34–1.63; OS HR 1.11, 95% CI: 0.30–4.16). Among pts with CR and ctDNA—at EOT, pts treated with Pola-R-CHP had superior PFS versus R-CHOP (HR 0.41, 95% CI: 0.21–0.82); this was not observed with OS (HR 0.41, 95% CI: 0.14–1.18). There was no statistically significant difference in PFS between treatment arms in pts with CR and ctDNA+ at EOT (PFS HR 1.20, 95% CI: 0.49–2.83).

Conclusions: Achieving ctDNA—at C5D1 and EOT was prognostic for longer survival. Although no difference was observed in the number of pts with ctDNA—at EOT between arms, pts achieving CR and ctDNA—at EOT had superior PFS in the Pola-R-CHP versus the R-CHOP arm, suggesting deeper molecular responses in pts treated with Pola-R-CHP beyond the detection sensitivity of the assay used in this analysis.

Encore Abstract—previously submitted to ASCO 2023

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Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, minimal residual disease

Conflicts of interests pertinent to the abstract

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TABLE

	Landmarked PFS HR (95% CI)	3-yr PFS % (95% CI)	Landmarked OS HR (95% CI)	3-yr OS % (95% CI)
Pola-R-CHP C5D1				
ctDNA+	0.38 (0.23–0.63)	58 (49–70)	0.36 (0.17–0.76)	79 (72–87)
ctDNA−		83 (76–90)		93 (89–97)
R-CHOP C5D1				
ctDNA+	0.52 (0.31–0.87)	61 (52–72)	0.50 (0.23–1.10)	82 (74–90)
ctDNA−		76 (68–85)		93 (89–98)
Pola-R-CHP EOT				
ctDNA+	0.25 (0.14–0.46)	55 (46–66)	0.12 (0.05–0.28)	70 (61–81)
ctDNA−		85 (79–92)		96 (93–99)
R-CHOP EOT				
ctDNA+	0.43 (0.25–0.74)	48 (38–60)	0.21 (0.10–0.45)	76 (67–86)
ctDNA−		78 (70–85)		95 (91–98)

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112 | MRD-NEGATIVITY AFTER FRONTLINE DLBCL THERAPY: POOLED ANALYSIS OF 6 CLINICAL TRIALS

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Introduction: Current lymphoma response criteria rely on metabolic imaging with moderate predictive value. Prior studies showed prognostic utility of circulating tumor DNA (ctDNA) early during therapy. However, accurate MRD detection at the end of therapy (EOT) is difficult using 1st-generation assays with plasma detection limits of ~1e-4. We tested performance of phased variant enrichment and detection by sequencing (PhasED-Seq), an ultrasensitive ctDNA MRD method (LOD ~1e-6), focusing on EOT disease detection.

Methods: We integrated PhasED-Seq MRD from LBCL studies using curative intent 1st-line regimens. We considered 6 prospective trials including investigational combinations of CHOP or EPOCH with rituximab, acalabrutinib, lenalidomide, obinutuzumab, polatuzumab, and/or tafasitimab [ACTRN12609001077257;NCT04002947; NCT00398177;NCT02529852;NCT04231877;NCT04134936]. Samples were profiled by PhasED-Seq at Foresight Diagnostics or Stanford University. Tumor or pretreatment plasma samples were used to identify Phased Variants, which were tracked at MRD timepoints (C2D1, C3D1, C4D1, and EOT).

Results: 407 specimens from 151 pts were evaluable, with 148 pts (97%) successfully genotyped. Plasma samples were available from 119 pts pretreatment, 52 at C2D1, 53 at C3D1, 51 at C4D1, and 93 at EOT. While MRD clearance during therapy stratified PFS, persistent MRD at EOT identified highest risk ($p < 0.0001$, HR = 90, Figure A). EOT MRD+ had 95% Sn for predicting future PFS events, with lead times up to 30 mo before radiologic PD. In total, 23 cases (25%) were MRD+ at EOT, with 18/23 experiencing PFS events to date. Among 5 pts without PFS events to date, 1 received subsequent RT for FDG-avid residual disease, while 2 others have <1-yr follow-up. In contrast, 70 cases were MRD-neg at EOT, with 99% (69/70) remaining alive without progression to date. The 1 MRD-neg case at EOT that experienced later progression presented with isolated CNS relapse at 10 mo. MRD status predicted PFS in multivariate models after adjusting for regimen and ctDNA profiling lab ($p < 0.01$). Clinical Sn, Sp, PPV, and NPV of EOT MRD for subsequent events were 95.0%, 94.5%, 83%, and 99%, respectively.

While analytical Sn of 1e-4 has been used in CLL and myeloma for MRD, detection below this threshold was needed for adequate clinical Sn in DLBCL. When using a threshold of 1e-4 for MRD-detection, performance deteriorated, with clinical Sn dropping to 60% (Figure B), and corresponding degradation in PFS stratification (MRD@1e-4, HR = 16; MRD-Full, HR = 90). Although EOT PET/CT response also predicted PFS ($p < 0.0001$, HR = 8.5), PhasED-seq showed higher Sn (95% vs. 50%, $p = 0.008$).

Conclusions: MRD status at EOT is highly prognostic in DLBCL and holds promise as a surrogate endpoint. Analytical detection ~1e-6 is needed to achieve high clinical Sn and NPV. EOT MRD using an ultrasensitive assay should be considered in the revised Lugano response criteria.

Keywords: aggressive b-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, minimal residual disease

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Conflicts of interests pertinent to the abstract

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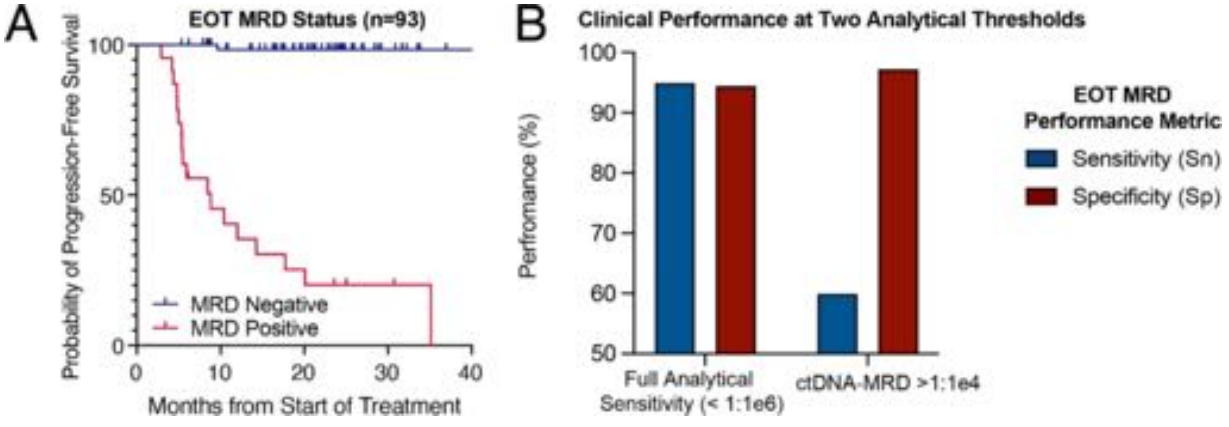

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Foresight Diagnostics: Consultancy, Current equity holder in private company, Patents & Royalties; Gilead: Consultancy, Divested equity in a private or publicly-traded company in the past 24 months, Patents & Royalties; Syncopation: Current equity holder in private company, Patents & Royalties; Roche: Consultancy; Adaptive Biotechnologies: Consultancy; Karyopharm: Consultancy; BMS: Consultancy, Research Funding; Genentech: Consultancy; Cibermed Inc: Consultancy, Current equity holder in private company, Patents & Royalties.

113 | EARLY CTDNA CLEARANCE AFTER CAR T-CELL INFUSION PREDICTS OUTCOME IN PATIENTS WITH LARGE B-CELL LYMPHOMA : RESULTS FROM ALYCANTE, A PHASE 2 LYSA STUDY

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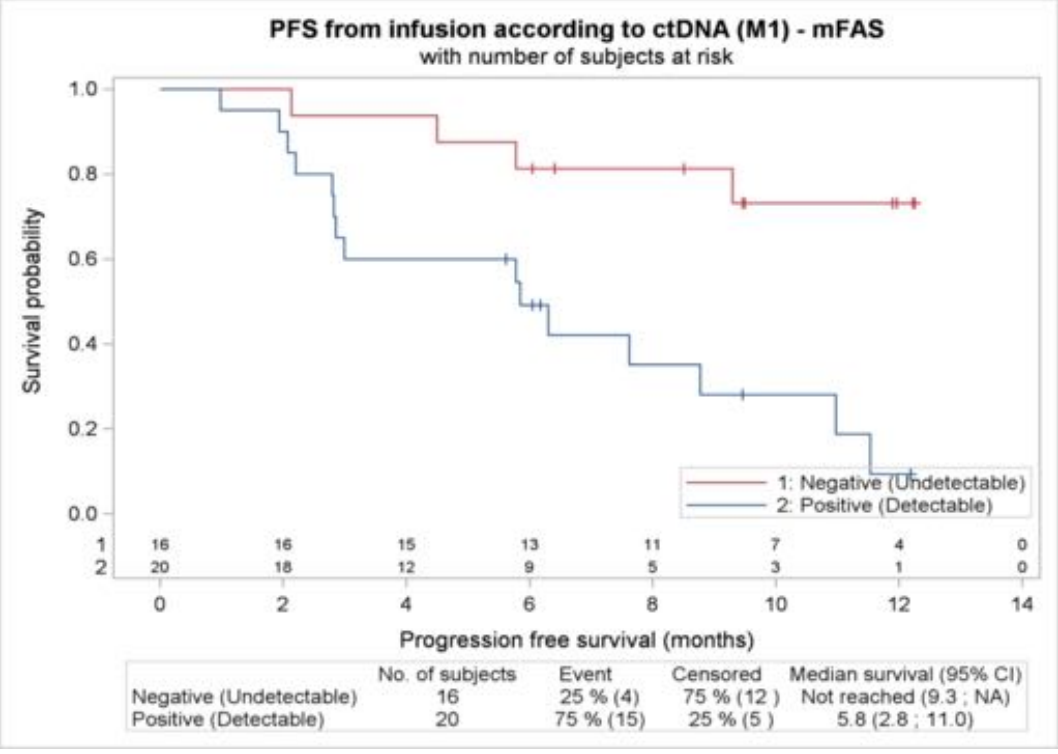
Introduction: CAR T-cells have significantly improved the outcome of patients with relapsed or refractory (*R/R*) large B-cell lymphoma (LBCL). However, more than half of the patients fail to obtain a prolonged remission, resulting in a poor prognosis. Early identification of these patients would allow early intervention to improve their outcome. Circulating tumor DNA (ctDNA) assessment is a promising tool to monitor early response in LBCL, but few data are available regarding ctDNA monitoring after treatment with CAR T-cells. The aim of our study was to monitor ctDNA before and after CAR T-cell infusion and correlate the results with clinical outcome in the ALYCANTE trial.

Methods: Patients' samples were prospectively collected in the ALYCANTE trial, an open-label, phase 2 study (NCT04531046), designed to evaluate the efficacy and safety of axi-cel in 62 patients with *R/R* LBCL not intended for autologous stem cell transplantation after 1 prior line of therapy.

DNA was extracted from 2 to 4 mL of plasma. Libraries were generated from 129 kb captured-DNA custom panel (Agilent, XTHS2). Variant calling and phased variant annotation were performed using Unique Molecular Identifiers (UMI). Concentrations of ctDNA were expressed as hGE/mL and were measured at leukapheresis, after bridging/before lymphodepletion, at time of CAR T-cell infusion (D0) and at day 14 (D14), month 1 (M1), 3, 6, 9, and 12 after infusion. These results were correlated with clinical outcome.

Results: With a median of 85 variants (range 1–707), a mutational profile could be identified from ctDNA in 88% (55/62) of patients at time of leukapheresis ($n = 54$) or after bridging ($n = 1$). The median ctDNA load was 77 hGE/mL (range 0–6803) at leukapheresis and 39 hGE/mL (range 2–17,354) after bridging therapy. Only 2/55 (4%) patients experienced ctDNA clearance after bridging.

To date, we report the clinicobiological correlations for the first 40 patients included in the ALYCANTE trial. Early ctDNA evaluation was performed in 38/40 (95%) patients: at D14 and M1 ($n = 34$), at D14 only ($n = 2$), or at M1 only ($n = 2$). For patients with D14 and M1 evaluation, the results were concordant in 32/34 (94%) patients, either both positive ($n = 19$) or both negative ($n = 13$). A negative ctDNA at D14 ($n = 14/36$, 38.9%) or at M1 ($n = 16/36$, 44.4%) was associated with a complete metabolic response at 3 months in 93% ($p = 0.03$) and 94% ($p = 0.009$) of cases, respectively. After a median follow-up of 10 months, the median progression-free survival was not reached in patients with



negative ctDNA at D14 and M1 versus 7.6 months and 5.8 months for patients with positive ctDNA at D14 and M1, respectively (Figure 1).

Conclusions: Our results suggest that early clearance of ctDNA at D14 and M1 post-infusion is predictive of favorable outcome of CAR T-cell therapy in patients with *R/R* LBCL. An update of these results on 62 patients and with a longer follow-up will be presented at the meeting.

Encore Abstract—previously submitted to EHA 2023

The research was funded by: Kite-Gilead, as a prespecified exploratory analysis

Keywords: cellular therapies, liquid biopsy, minimal residual disease

Conflicts of interests pertinent to the abstract

M. Delfau-Larue
Other remuneration: Education, symposia: TAKEDA, AMGEN, ROCHE, GILEAD, ABBVIE

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Honoraria: Jansen, Gilead, Takeda, Novartis, Milteny.

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Research funding: Amgen, BMS

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Honoraria: Kite/Gilead, Novartis, Incyte, Janssen, MSD, Takeda and Roche

114 | CELL-FREE DNA KINETICS DECIPHER POTENTIAL MECHANISMS OF ACTION OF IBRUTINIB COMBINATION THERAPY IN MANTLE CELL LYMPHOMA (MCL)

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Introduction: The European MCL Network trial TRIANGLE (NCT02858258) evaluated the addition of ibrutinib to standard treatment with autologous stem cell transplantation (ASCT) (arm A +I) in comparison to ASCT alone (arm A) and ibrutinib plus chemo-immunotherapy without ASCT (arm I) demonstrating significant and clinically relevant superiority of additional ibrutinib on outcome.
Cell-free (cf)DNA captures tumor genetics and can be used to assess disease kinetics and minimal residual disease (MRD). We used capture based targeted sequencing for genotyping and MRD monitoring in cfDNA in the TRIANGLE trial to gain insight into the mechanisms of action of Ibrutinib and to identify patients (pts) with high risk of relapse.

Methods: Peripheral blood (PB) and plasma samples from 57 pts with a PB infiltration of ≥10% at baseline (BL) and samples at mid induction (MI, $n = 57$) and end of induction (EoI, $n = 53$) were sequenced using the EuroClonality (EC)-NDC assay (Univ8® Genomics UK) to detect immunoglobulin and T-cell receptor (IG/TR) rearrangements, structural- (SV) and single nucleotide variants (SNVs) in 72 genes. Bioinformatics by ARResT/Interrogate with adaptations for cfDNA. Pts were considered MRD+ by detecting ≥1 read of a lymphoma-specific IG, SV or SNV. MRD in PB was analyzed by ASO-qPCR.

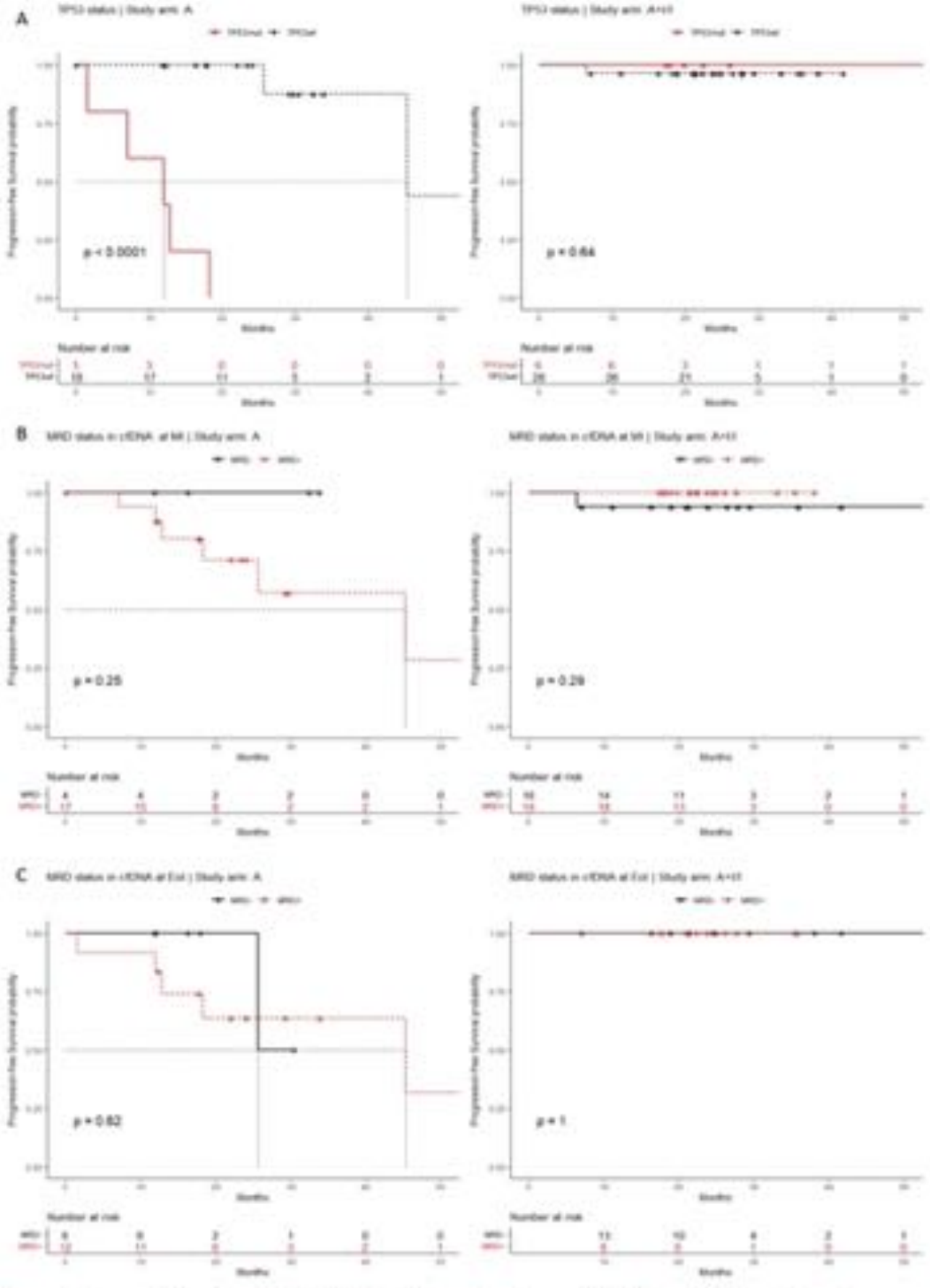

Figure 1 *Progression-free Survival (PFS) depicted by treatment arms. A) Effects of TP53 mutation status on patient outcomes. B,C) Effect of minimal residual disease positivity by cfDNA at Mid-induction (MI) (B) and EoI (C) on patient outcomes.*

Results: cfDNA levels were high at BL (mean 93 ng/mL) and MI (124 mg/mL) and decreased at EoI (12 ng/mL). BL cfDNA levels correlated with MIPI scores and identified pts with poor outcome.

Genotyping by EC-NDC showed fully concordant IG clonotypes and SVs among 57 paired PB gDNA and cfDNA samples. 126 SNVs were identified (VAF 2.7%–75%, median 30%) in genes described as drivers in MCL, *ATM* (44%), *TP53* (19%), *KMT2D* (16%), *SAMHD1* (8%), *CCND1* (8%) and 18 others. On average, 6 MRD markers were identified per patient (range 3-10). Copy number variation analysis revealed deletions in *ATM* (10%), *CDKN2A* (16%) and *TP53* (5%) pts.

TP53 mutations/deletions are a poor prognostic indicator in MCL, but therapy in arms A+I/I ($n = 6$) overcomes this poor outcome in comparison to arm A ($n = 5$).

At MI, total cfDNA and ctDNA levels were significantly increased in arms A+I/I as compared to arm A ($p = 0.049$). 20/57 (35%) pts were MRD+ in PB and 35/55 (64%) in cfDNA. ctDNA was detected in 17/21 pts (81%) in Arm A and 18/34 pts (53%) in Arms A+I/I, suggesting effective disease clearance in the lymph nodes by ibrutinib. ctDNA detection at MI predicted outcome only in arm A.

At EoI 8/53 (15%) pts were MRD+ in PB and 20/40 (50%) pts were MRD+ in cfDNA. ctDNA was detected in 12/18 pts (66%) in Arm A and 8/22 pts (36%) in Arms A+I/I. Similar to MI, ctDNA at EoI predicted outcome only in arm A.

Conclusion: Dynamic monitoring of ctDNA and PB MRD gives relevant hints on the efficacy of ibrutinib in tumor cell clearance of different compartments. Effective cell killing by ibrutinib takes place early during treatment and abrogates the effects of adverse biomarkers like disrupted *TP53* or MRD positivity.

Keywords: combination therapies, liquid biopsy, minimal residual disease

Conflicts of interests pertinent to the abstract

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R. García Sanz
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Educational grants: Janssen

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Research funding: Roche, Janssen, Bayer, AbbVie

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Research funding: Genentech, Roche
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Employment or leadership position: Founder and director of Univ8 Genomics Ltd.

115 | COMBINED USE OF MINIMAL RESIDUAL DISEASE MONITORING AND FDG-PET FOR OUTCOME PREDICTION IN FOLLICULAR LYMPHOMA: RESULTS FROM THE FONDAZIONE ITALIANA LINFOMI (FIL) FOLL12 TRIAL

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Introduction: In follicular lymphoma (FL), FDG-PET is routinely employed to evaluate response at the end of induction (EoI), while minimal residual disease (MRD) analysis is highly reliable in predicting relapse over the entire disease history. Nonetheless, scant data are available describing the integration of these powerful prognostic tools for response evaluation in FL. This issue was investigated in the phase III FIL "FOLL12" trial [Luminari, JCO 2022].

Methods: Only patients with an available molecular marker for MRD and centrally reviewed EoI PET were included. MRD was systematically assessed by RQ-PCR with BCL2::IGH consensus primers in peripheral blood (PB) and bone marrow (BM), as previously reported with inferior follow-up [Ladetto ASH 2021]. PET scans were classified according to Deauville score (DS) criteria: DS1–3 was negative and DS4–5 positive.

Results: Overall, 394 patients out of 780 were included (51%), as expected based on the MRD marker availability. These patients had a slightly better outcome than excluded cases (CR rate 82% vs. 73%, $p = 0.003$, 5y PFS 66% vs. 61%, $p = 0.046$). At EoI, both BM MRD and PET positivity were independent predictors of poor PFS in multivariate analysis (HR 1.66, CI: 1.01–2.71 and HR 2.03, CI: 1.30–3.18). The 68 discordant cases (i.e., MRD+/PET− or MRD−/PET+) showed an intermediate outcome (PFS HR 1.93, CI: 1.28–2.92) between the 314 double negative (reference) and the 10 double positive ones (HR 6.22, CI: 2.99–12.9), Figure 1A. Moreover, both EoI PET+ and the persistence/reappearance of MRD positivity in BM during the 18 months of rituximab maintenance/observation were independently associated to a higher risk of POD24 (HR 5.61, CI: 2.59–12.1, and HR 2.37, CI: 1.15–4.84, respectively). On the other hand, MRD kinetic analysis by non-invasive PB sampling during the rituximab maintenance/observation period substantially updated the risk status over PET results. Indeed, the marginal PFS HR for an MRD+ after an EoI PET negative result increased from 1.36 (CI: 0.47–3.96) at 6 months, to 2.09 (CI: 1.01–4.18) at 12 months, up to 3.60 (CI: 2.30–5.64) at 24 months (Figure 1B, blue curve). This means that patients scoring PET-

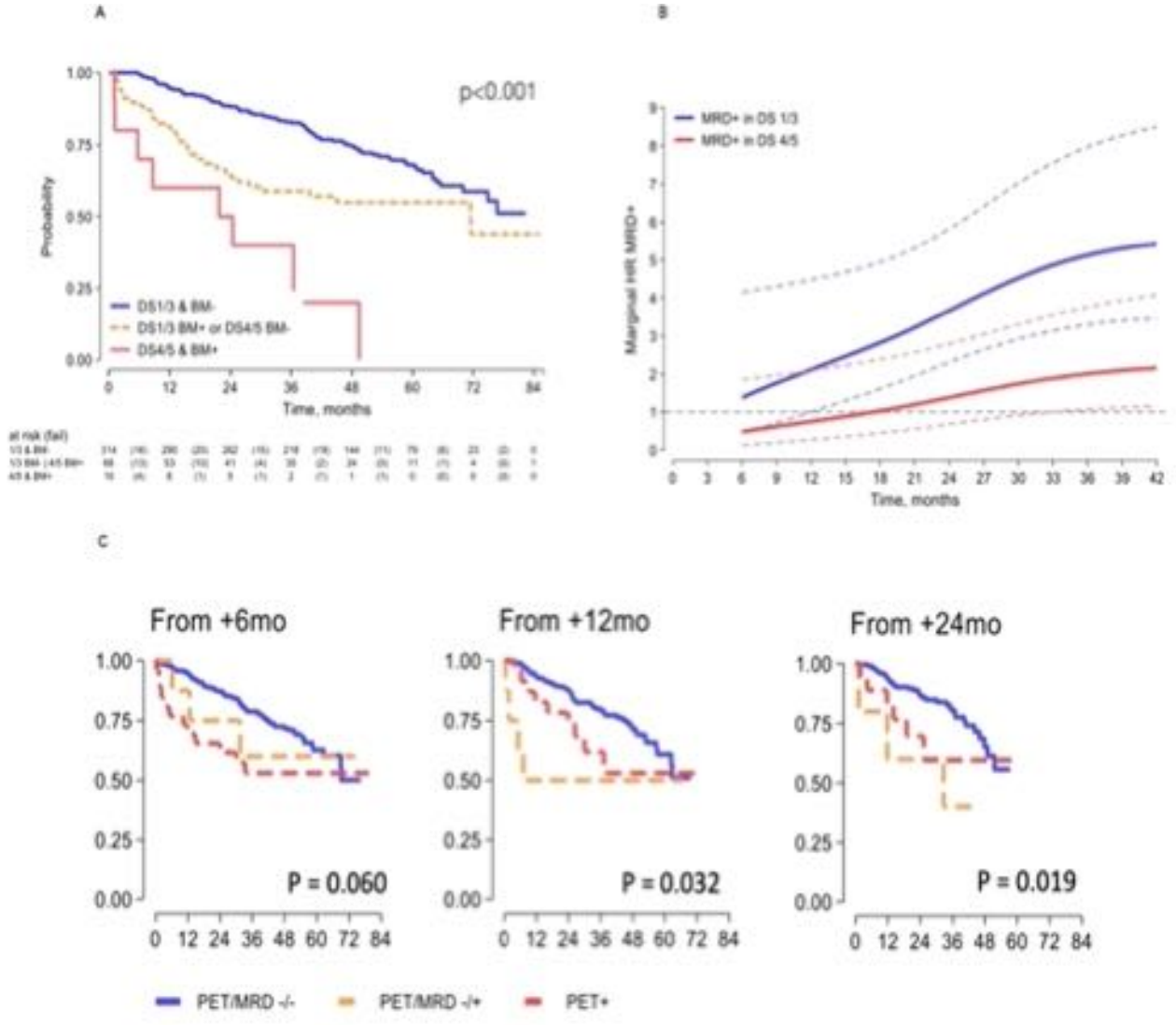

Figure 1. PFS from EoI stratified by PET and BM MRD results (A). Marginal PFS HR for a MRD+ result at given timepoints, stratified for EoI PET result (B). Landmark analysis for PFS stratified by EoI PET and MRD result at given timepoints.

at EoI but showing a persistent or reappearing MRD+ signal during the following 24 months had a dismal PFS, superimposable to that of PET+ patients (Figure 1C). Accordingly, in landmark multivariate analysis PB MRD+ either at 12 or 24 months predicted adverse PFS (HR 3.79, CI: 1.60–8.96 and HR 5.21, CI: 1.88–14.4, respectively), independently from EoI PET result.

Discussion: MRD analysis and PET scan are independent and complementary prognostic tools in FL: a MRD positivity in the two years after immuno-chemotherapy is predictive of POD24 and dismal PFS independently from the EoI PET result. Interestingly, a regular, simple and non-invasive MRD monitoring in PB might identify high risk patients even among PET-negative patients under rituximab maintenance.

Keywords: indolent non-Hodgkin lymphoma, minimal residual disease, PET-CT

Conflicts of interests pertinent to the abstract

S. Ferrero

Consultant or advisory role: Janssen, EUSA Pharma, Abbvie, Incyte, Clinigen, Sandoz, Italfarmaco
Honoraria: Janssen, EUSA Pharma, Servier, Gentili
Research funding: Morphosys, Janssen, Gilead, Beigene
Educational grants: Takeda, Janssen, EUSA Pharma

FOCUS ON MECHANISMS OF TREATMENT RESISTANCE

116 | GENOMIC EVOLUTION AND RESISTANCE TO PIRTOBRUTINIB IN COVALENT BTK-INHIBITOR PRE-TREATED CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS: RESULTS FROM THE PHASE I/II BRUIN STUDY

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Introduction: Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi, demonstrated efficacy in patients (pts) with CLL resistant to cBTKi. Mechanisms of resistance to pirtobrutinib have not been systematically analyzed.

Aim: To explore genomic evolution of pirtobrutinib resistance in cBTKi pre-treated CLL pts.

Methods: Pts treated with pirtobrutinib monotherapy in phase 1/2 BRUIN trial (NCT03740529) who developed disease progression (PD) were included. Targeted NGS of all exons of 74 relevant genes was centrally performed on PBMCs. Somatic mutations were reported with a limit of detection (LoD) of 5% variant allele frequency (VAF). Manual inspection of *BTK* exons with LoD 1% was performed in selected cases.

Results: As of 29 July 2022, 49 cBTKi pre-treated CLL pts who progressed on pirtobrutinib had paired NGS data at baseline and PD. The median age was 69 y (36–86), median number of prior lines was 4 (1–10) and 41 pts (84%) had discontinued prior cBTKi due to PD. Pts received one or more cBTKi: ibrutinib ($n = 44$, 90%), acalabrutinib ($n = 10$, 20%), or zanubrutinib ($n = 1$, 2%). ORR to pirtobrutinib (including PR-L) was 80%.

Most common alterations at baseline were mutations in *BTK* (51%), *TP53* (49%), *ATM* (27%), *NOTCH1* (20%), *SF3B1* (18%), *PLCG2* (10%). Among 25 pts with ≥1 *BTK* mutation at baseline, mutations included C481S ($n = 23$), C481R ($n = 4$), C481Y ($n = 2$), C481F ($n = 1$), T474I ($n = 1$). *BTK* C481 VAF decrease/complete clearance was observed at PD in most pts (92%, 22/24, median VAF decrease=100%). At PD, 71% (35/49) of pts acquired ≥1 mutation, with 55% (27/49) acquiring ≥1 *BTK* mutation. Among these 27 pts, 36 acquired *BTK* mutations were identified; including gatekeeper mutations (T474I/F/L/Y, 17/49, 35%), kinase-impaired (L528W, 9/49, 18%), variants of unknown significance (VUS) proximal to the ATP-binding pocket (6/49, 12%; V416L ($n = 2$), A428D ($n = 2$), D539G/H ($n = 1$), Y545N ($n = 1$)) (Figure). Manual inspection for acquired *BTK* mutations at PD in baseline samples revealed 9 mutations (8 pts) pre-existed at baseline at low VAFs (1%–4%): 6 gatekeeper T474I/L, 2 kinase impaired L528W, 1 VUS A428D. These pts responded to pirtobrutinib (6/8, 75% ORR) and received prior ibrutinib ($n = 5$)/acalabrutinib ($n = 4$). Most commonly acquired non-*BTK* mutations were *TP53* (7/49, 14%) and *PLCG2* (4/49, 8%).

Conclusions: Pts who progressed on pirtobrutinib showed clearance of *BTK* C481 clones and emergence/outgrowth of non-C481 clones (T474, L528W mutations) and other VUS. Many acquired *BTK* mutations were shown to pre-exist at baseline at low VAF, reflecting emergence on prior cBTKi. These *BTK* mutations did not preclude pirtobrutinib efficacy. Approximately half the pts did not acquire *BTK* mutations and 29% did not acquire any mutations in this targeted panel, suggesting alternate resistance mechanisms. Whether similar resistance patterns would manifest if pirtobrutinib was utilized prior to cBTKi treatment remains uncertain.

Encore Abstract—previously submitted to EHA 2023

The research was funded by: Eli Lilly and Company

Keyword: chronic lymphocytic leukemia (CLL)

Conflicts of interests pertinent to the abstract

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Research funding: Adaptive Biotechnologies, Aptevo Therapeutics, AstraZeneca, Bristol Myers Squibb, CRISPR Therapeutics, Celgene, Curis, Inc, Epizyme, Fate Therapeutics, Genentech/Roche, Kite, Loxo Oncology, MEI Pharma, Nurix, Pharmacyclics/Janssen, Sunesis Pharmaceuticals, Trillium Therapeutics/Pfizer, Velos Bio, Xencor

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Figure. Number of patients with acquired mutations according to *BTK* status at baseline and prior type of cBTKi. The color gradient indicates the mean VAF at progression.

KI; Kinase-impaired, VUS; variant of unknown significance, VAF; variant allele frequency
*Patients with multiple acquired BTK mutations are counted more than once

Honoraria: Roche, AstraZeneca, KITE Gilead, Loxo Oncology, Beigene, Incyte, Abbvie, Janssen
Research funding: Astrazeneca, Beigene
Other remuneration: Roche, AstraZeneca, Janssen, Abbive

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Honoraria: Roche, Janssen, Gilead, AstraZenecca, Lilly, TG therapeutics, Beigene, Novartis, Menarini, Daizai, Abbvie, Genmab. BMS
Research funding: BMS, Roche, Abbvie; MSD, Lilly

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Research funding: BMS, AbbVie, AstraZeneca, Janssen

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Research funding: AstraZeneca; AbbVie ; DTRM Biopharma ; Genentech ; Janssen ; BeiGene ; Octopharma ; TG Therapeutics ; Nurix ; Pharmacyclics, LLC ; LOXO ; Genmab ; Johnson & Johnson ; Pfizer ; Acerta

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Other remuneration: GSK/Novartis, Abbvie, Genentech, Pharmacyclics LLC, AstraZeneca/Acerta Pharma, Gilead Sciences, Bristol Myers Squibb (Juno & Celgene), KITE Pharma, Sunesis, Miragen, Oncternal Therapeutics, Inc., Cyclacel, Loxo Oncology, Inc./Lilly, Janssen, Xencor

117 | SINGLE-CELL RNA-SEQ OF CLASSIC HAIRY CELL LEUKEMIA REVEALS DISEASE DRIVERS LINKED TO INTRINSIC TREATMENT RESISTANCE AND IDENTIFIES DUSP1 AS POTENTIAL NEW THERAPEUTIC TARGET

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Introduction: Standard treatment with purine analogs such as cladribine (2-CdA) achieves excellent remissions in classic hairy cell leukemia (HCL), but up to 25% of patients relapse early and there is a non-diminishing risk of late relapse in complete responders. Even when targeting the recurrent genetic driver mutation BRAF V600E, HCL cells frequently persist in the bone marrow suggesting cooperating biologic alterations facilitating disease survival and persistence.
Methods: Single-cell RNA sequencing (scRNA-Seq) was performed in primary HCL cells derived from three long-term (>10 years progression-free survival, PFS) and three short-term responders after 2-CdA treatment (SR, <3 years PFS) and from up to three time points (HCL diagnosis, first, and second relapse). Functional studies were performed using the BRAF D594E-mutated HAIR-M cell line after validating BRAF D594E as an activating mutation with similar downstream signaling and inhibitory potential with BRAF inhibitors as compared to BRAF V600E in primary HCL cells.

Results: scRNA-Seq revealed distinct HCL cell clusters characterized by marked overexpression of DUSP1, FOS and JUND in all six patients that were outgrowing at first and second relapse in all three SR. In these DUSP1^{hi}/FOS^{hi}/JUND^{hi} HCL cells, PROGENy cancer pathway analysis demonstrated induced activation of MAPK pathways and gene ontology analysis found negative regulation of the pro-apoptotic p38-MAPK-cascade as potential underlying biologic alteration. BRAF D594E-mutated HAIR-M cells were selected as substitute for primary HCL cells in cell culture due to comparable changes upon exposure to BRAF inhibitors in BRAF kinase activity conformation as assessed by the modular kinase conformation biosensor platform (KinCon) and similar reduction in ERK phosphorylation levels in HEK293T cells transiently overexpressing either flag-tagged BRAF D594E or BRAF V600E. In HAIR-M, we confirm stable expression levels of DUSP1, FOS and JUND, which were highly increased when co-cultured with HS5 stromal cells. Whereas increased expression of FOS and JUND was reversible upon exposure to BRAF inhibitors, expression of DUSP1, a direct target of BRAF-MEK-ERK signaling, and phosphorylation of p38 remained unaffected. As DUSP1 preferentially dephosphorylates/inactivates p38, we studied exposure of the DUSP1-inhibitor BCI in co-culture and found re-phosphorylated p38.

Conclusion: DUSP1^{hi}/FOS^{hi}/JUND^{hi} HCL cells may represent a distinct subset of HCL cells highly dependent on environmental cues with an inherently more resistant phenotype to treatment with 2-CdA or BRAF-inhibitors. Inhibition of DUSP1 may represent a novel therapeutic approach by effectively truncating HCL cells from extracellular pro-survival stimuli. Finally, our results suggest that BRAF D594E-mutated HAIR-M cells may serve as a representative disease model for functional studies.

Keywords: bioinformatics, computational and systems biology, indolent non-Hodgkin lymphoma, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

118 | IL16 PRODUCTION IS A MECHANISM OF RESISTANCE TO BTK INHIBITORS AND TO R-CHOP

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Introduction: Covalent and non-covalent BTK inhibitors (BTKi) are used or being explored for the treatment of patients with B-cell malignancies, such as marginal zone lymphoma (MZL), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma (DLBCL) of the activated B-cell type (ABC). The identification of mechanisms of resistance can lead to improvements in the current therapeutic approaches. We had reported IL16 production in a MZL model of secondary resistance to ibrutinib (Arribas ENA2019). Here, we expand the initial observation to additional lymphoma types and treatments modalities, performing therapeutic interventions to block it and providing clinical validation data on its expression and role in patients.

Methods: VL51 (marginal zone lymphoma, MZL) parental (PAR) and Ibrutinib-resistant (RES) cells underwent RNA (mRNA & miRNA by RNA-Seq), DNA (promoter methylation, WES) and secretome (Cytokine array) profiling. RES cells exhibited resistance to covalent and non-covalent BTK inhibitors. No DNA copy number variations or mutations were detected by WES in RES compared to PAR cells, including those affecting *BTK* or *PLCG2* genes.

Results: Multi-omics (DNA, mRNA, miRNA, secretome) characterization of RES and PAR cells identified hypomethylation, up-regulation and secretion of IL16 in RES but not in PAR cells. Elevated levels of p-AKT and p-ERK was observed in RES compared to PAR, suggesting a signaling activation in RES cells. Stimulation with recombinant IL16 reduced sensitivity to BTKi not only in VL51 PAR cells, but also in models derived from MCL (REC1) and CLL (MEC1). Conversely, the use of IL16 blocking antibody recovered sensitivity to BTKi in RES cells, along with other lines with high expression of IL16 and low sensitivity to ibrutinib derived from MCL (MAVER1) and MZL (SSK41). IL16 is part of the ABC-DLBCL signature. We observed that high IL16 expression was associated with shorter overall survival in ABC but not in germinal center like DLBCL patients (n = 233, log-rank test p = 0.013, multivariate Cox: HR (95% CI) 0.43 (0.22–0.85), p = 0.016). IL16 stimulation also decreased sensitivity to RCHOP in ABC DBCL cells (OCILy10, HBL1). Finally, secreted levels of IL16 in the serum of CLL patients (n = 17) with resistance to ibrutinib (in absence of *BTK* or *PLCG2* mutations) were significantly higher compared to patients responding to the drug and paired for clinical features.

Conclusions: Starting from a MZL model of secondary resistance to ibrutinib, we showed that IL16 can sustain resistance to BTK inhibitors also in CLL and MCL. Furthermore, increased expression of IL16 associated with shorter outcome in ABC DLBCL patients and the interleukin induced in vitro resistance to RCHOP. The demonstration that IL16 blocking therapies recovered sensitivity to therapies can lead to novel therapeutic approaches to overcome resistance in lymphoma patients.

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Keyword: molecular targeted therapies

Conflicts of interests pertinent to the abstract

A. Arribas
Educational grants: Astra Zeneca

119 | ENHANCER RNAS (ERNAS) PLAY A ROLE IN THE RESPONSE TO SMALL MOLECULES AND IN THE DEVELOPMENT OF ACQUIRED RESISTANCE IN MARGINAL ZONE LYMPHOMA (MZL)

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Introduction: The therapeutic options for MZL patients with disseminated disease include chemotherapy, rituximab alone or rituximab with chemotherapy but several small molecules are also available. Resistance development is always an issue. Stable non-genetic resistance can be acquired by transcriptional adaptation through alternative pattern of enhancers sustaining the expression of survival genes. Most active enhancers are also transcribed in long noncoding RNAs (lncRNAs) called eRNAs. They play a regulatory role helping the correct chromatin conformation required to transactivate promoters. eRNAs can occasionally be stabilized and regulate distal loci in trans. We studied the contribution of eRNAs, but also other lincRNAs, expressed in MZL in the response to agents as inhibitors of PI3K (copanlisib, umbralisib), BTK (ibrutinib), BCL2 (venetoclax) or anti CD20 (rituximab). In particular, for ibrutinib we took advantage of a resistant cell line in vitro stabilized by prolonged exposure to the drug.
Methods: To identify eRNAs expressed in MZL, we applied de novo reconstruction to total RNA-Seq profiling of VL51 parental, ibrutinib-Res and idelalisib-Res derivatives (Arribas et al., Haematologica 2022). We looked for novel and known reconstructed transcripts associated to the superenhancers (SEs), identified by ROSE algorithm. We associated to these eRNAs a TSS derived from publicly available CAGE data sets. We designed 5825 paired gRNAs against 659 targets (312 eRNAs, 255 lincRNAs) and, as controls, 90 essential and 30 not expressed genes. The pgRNAs were included in a custom lentiviral library to infect VL51 expressing dCas9KRAB-ZIM3 mCherry. Cells were kept for 14 days under DMSO, ibrutinib, rituximab, copanlisib, umbralisib or copanlisib/venetoclax and gRNAs dropout was measured.
Results: Unsupervised clustering of eRNAs differentially enriched at day 14 ver sus day0 discriminated parental and ibrutinib-Res cells, indicating the dependency of the cells on different transcriptome program.
A series of eRNAs and lincRNA were significantly enriched after DMSO (12 and 19, respectively) ibrutinib (27 and 28), rituximab (12 and 18), copanlisib (8 and 17), umbralisib (12 and 13) or copanlisib/venetoclax (14 and 15). The inhibition of transcription of those molecules in some cases represented a proliferative advantage under exposure to the drug, in other cases a disadvantage. For further investigation, we considered eRNAs essential under treatment since they may regulate pathways involved in therapeutic escape, as the calcium-calcineurin pathway, or G-protein coupled receptors or molecules already known to interact with epigenetic regulators as EZH2.
Conclusions: Individual eRNAs revealed to be essential in drug response, in a treatment specific manner and to play a role in resistance development, as regulator of relevant pathways.

Encore Abstract—previously submitted to regional or national meetings (up to <1000 attendees)

The research was funded by: Work supported from the Swiss National Science Foundation (SNSF Sparks CRSK-3_190808 and SNSF 310030_197466).

Keywords: genomics, epigenomics, and other-omics, molecular targeted therapies, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

120 | HARNESSING BTKI THERAPY BY CDK4/6I CONTROL OF T CELL SURVEILLANCE

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Introduction: Drug resistance remains a formidable challenge in mantle cell lymphoma (MCL). Cell cycle dysregulation driven by aberrant Cyclin D1 and CDK4 expression is a hallmark for MCL. By inhibition of CDK4/6, we have developed a novel strategy that both inhibits proliferation of MCL cells and reprograms them for cytotoxic killing. In a phase I clinical trial we investigated if inhibition of cyclin D1/CDK4 with palbociclib could reprogram recurrent MCL to deepen and prolong the ibrutinib response, and the mechanism for resistance by longitudinal genomic analysis of sequential samples from individual patients in the context of the clinical response.

Methods: Palbociclib was administered to recurrent MCL patients on days 1–21 of a 28-day cycle; ibrutinib was given continuously. For longitudinal genomic analysis, sequential tissue and blood specimens from 27 evaluable MCL patients before, during therapy and on progression were collected. Single cell RNA-seq (scRNA-seq) of PBMC or the monocytic fractions from bone marrow and lymph node was performed using a unique in house MCL-specific library. The data were then subject to multiplex analysis with whole transcriptome sequencing and whole exome sequencing of purified MCL cells and flowcytometry of the same samples in conjunction with IHC.

Results: Palbociclib appears to deepen and prolong the ibrutinib response; the CR rate was 42% CR, and 5 patients (2 CR and 3 PR) remained on therapy for >8 years. Longitudinal scRNA-seq further revealed that MCL cells comprise 4 major transcriptomically distinct clusters (C)s. Primary resistance and progression on therapy were associated with a marked expansion of either long-live non-proliferating C3 cells or C2 cells that fuel the proliferating C4 cells. Resistance was associated with a profound reduction in MHC I and MHC II expression and disease progression was further accompanied by a rapid loss of both CD8+ and CD+ T cells. This suggests T cell surveillance plays a critical role in maintaining a durable ibrutinib response. Guided by our discoveries, we have restored ibrutinib sensitivity by target patient-specific expansion of C2 or C3 MCL cells ex vivo. In one patient, this led to restoration of CD4+ and CD8+T cells and a CR over 2.5 years.

Conclusion: T cell surveillance plays a critical role in prolonging the ibrutinib response by CDK4/6 inhibition, implicating genome-guided combination therapy to overcome ibrutinib resistance in MCL.

The research was funded by: PO1 grant from the National Cancer Institute MCL-RI grant from Leukemia and Lymphoma Society

Keywords: combination therapies, genomics, epigenomics, and other-omics, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

121 | IMMUNE-DEPLETED TUMOR MICROENVIRONMENT IS ASSOCIATED WITH POOR OUTCOMES AND BTK INHIBITOR RESISTANCE IN MANTLE CELL LYMPHOMA

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Introduction: An understanding of the tumor microenvironment (TME) and its cellular and analyte composition plays a critical role in promoting mantle cell lymphoma (MCL) cell growth, proliferation. To further understand the relevance of the tumor-immune landscape in tissue microenvironments, we performed multiomic profiling to characterize the TME in tissues from MCL patients and examined the relationship between TME subtypes and their impact on clinical outcome and the response to BTKi.

Methods: This cohort study was conducted under an IRB approved protocol for MCL patients at our Center. Tissue biopsies (28 lymph nodes and 13 other tissues) were collected from 41 patients with MCL. We conducted whole exome sequencing (WES; $n = 41$) and RNA-seq ($n = 41$) from MCL tissue biopsies from patients treated with BTKi (ibrutinib, acalabrutinib or zanubrutinib) in combination with the analysis of a published MCL cohort ($n = 122$). Joint WES and RNA-seq mutation calling and TME molecular signatures were categorized based on response to BTKi. All WES and bulk RNA sequencing was performed with Illumina HiSeq4000 using a 76 bp paired end configuration.

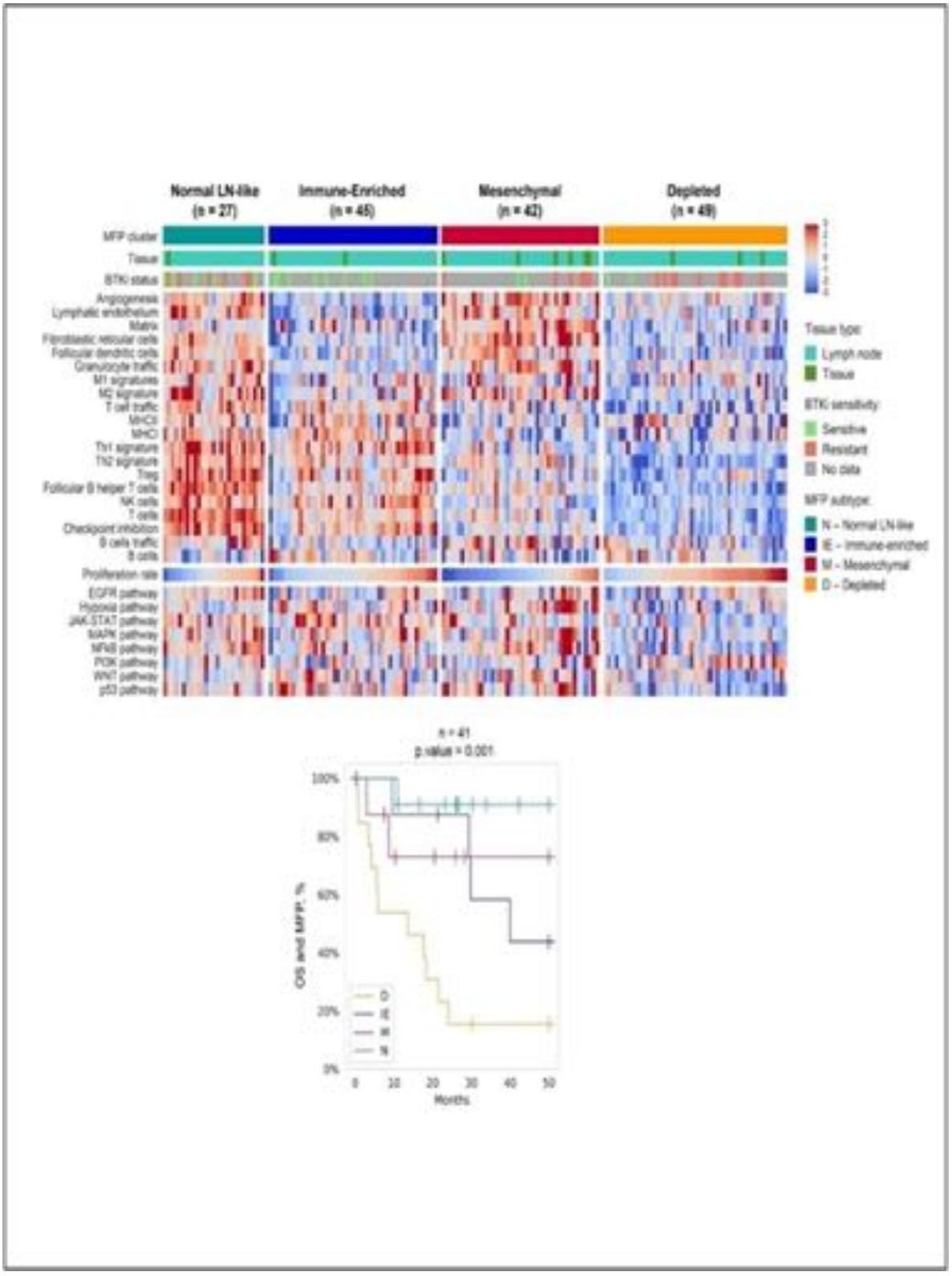
Results: Unsupervised clustering identified four MCL TME subtypes reflecting distinct tumor-immune cell gene signatures. Four distinct groups—normal lymph node ($n = 27$), immune cell-enriched ($n = 46$), mesenchymal ($n = 44$) and immune cell-depleted "**D**" ($n = 51$). "**D**" subtype was predominant in patients with primary BTKi resistance. A high tumor proliferation gene signature was observed exclusively in the "**D**" group. We further observed that Ki-67% from tissue biopsies had a linear correlation with proliferation rate signature genes and significantly overexpressed in the **D** group ($p = 0.002$). Somatic mutations such as *TP53*, *NSD2*, *NOTCH1*, *KMT2D*, *SMARCA4*, which were previously reported in ibrutinib-resistant MCL and/or in refractory high-risk MCL patients, were predominant in the **D**subtype.

Finally, the evaluable patients ($n = 39$) were divided according to response to BTKi- sensitive, primary resistant and acquired resistant and MFP clusters. Patients with primary and acquired resistance had significant proportion of patients with **D** subtype ($p = 0.004$), compared to N and IE subtypes. Primary and BTKi resistant patients had a trend of inferior survival compared to sensitive patients ($p = 0.07$). Furthermore, we demonstrated that the **D** TME group had worse overall survival compared to other TME categories ($p = 0.001$).

Conclusions: Overall, the immune-depleted TME subtype in MCL correlated with BTKi resistance and poor outcomes in patients. Immune depleted TME subtype in MCL is a biomarker to predict BTKi resistance and poor outcomes in MCL patients.

Keyword: microenvironment

The research was funded by: Boston Gene Corp


Normal LN-like (n = 27)
Immune-Enriched (n = 45)
Mesenchymal (n = 42)
Depleted (n = 49)
MFP cluster
Tissue
BTKi status
Angiogenesis
Lymphatic endothelium
Matrix
Fibroblastic reticular cells
Follicular dendritic cells
Granulocyte traffic
M1 signatures
M2 signature
T cell traffic
MHCII
MHCI
Th1 signature
Th2 signature
Treg
Follicular B helper T cells
NK cells
T cells
Checkpoint inhibition
B cells traffic
B cells
Proliferation rate
EGFR pathway
Hypoxia pathway
JAK-STAT pathway
MAPK pathway
NFkB pathway
PI3K pathway
WNT pathway
p53 pathway
Tissue type
Lymph node
Tissue
BTKi sensitivity
Sensitive
Resistant
No data
MFP subtype
N – Normal LN-like
IE – Immune-enriched
M – Mesenchymal
D – Depleted
n = 41
p-value = 0.001
OS and MFP, %
100%
80%
60%
40%
20%
0%
0
10
20
30
40
50
Months

FOCUS ON T-CELL LYMPHOMAS

122 | LACK OF SMARCB1 EXPRESSION CHARACTERIZES A SUBSET OF PERIPHERAL T-CELL LYMPHOMAS ENRICHED IN CHILDREN AND YOUNG ADULTS

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Introduction: Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is a heterogeneous group of malignancies with poor outcome. Because patients respond poorly to current treatment regimens, identification of new therapeutic strategies is required. In a mouse tumor model, conditional deletion of *Smarcb1* encoding a member of the SWI/SNF chromatin remodeling complex causes the majority of mice to develop mature T-cell lymphomas. The human counterpart, *SMARCB1*, is a bona fide tumor suppressor gene associated with the development of for example, rhabdoid tumors and schwannomas, but has also been shown to be involved in lymphocyte development.

Methods: SMARCB1 (INI1) gene and protein expression was assessed in 315 patients with diverse mature T cell lymphomas by array-based mRNA profiling, immunohistochemistry and/or Western Blot. The DNA methylome was analyzed in SMARCB1-negative pediatric PTCL-NOS patients ($n = 5$) and murine T cell lymphomas of the *Cd4-cre::Smarcb1*$^{fl/fl}$ model ($n = 5$) using the Infinium MethylationEPIC and Mouse Methylation BeadChip, respectively. Murine *Smarcb1*-deficient T-cell lymphomas were further studied using droplet-based single cell RNA sequencing (Chromium, 10X Genomics).

Results: *SMARCB1* expression was heterogeneous between and within the 315 different human mature T-cell lymphoma entities. Loss of SMARCB1 expression in PTCL-NOS patients correlated with young age (Wald test, p value = 0.011). Molecular characterization and DNA methylation analysis revealed that loss of *SMARCB1* expression in human PTCL largely occurs via somatic mutation and/or epigenetic silencing, whereas in contrast to rhabdoid tumors, germline *SMARCB1* mutations were not observed. Comparison of the DNA methylome of human and murine PTCL-NOS$^{Smarcb1-}$ showed similar DNA methylation profiles, with hypermethylation of T-cell-related genes and hypomethylation of genes involved in myeloid development. Increase of myeloid cell populations was confirmed in murine tumors by scRNA-seq analyses, which further revealed an immunosuppressive and pro-inflammatory tumor microenvironment (TME). Treatment of tumor-bearing mice with SAHA, a pan-HDACi, triggered remodeling of the TME, promoting replenishment of lymphoid compartments and reversion of the exhaustion phenotype.

Conclusions: Here we describe SMARCB1-negative PTCL-NOS as a potential new molecular subtype of PTCL-NOS significantly enriched in young patients. A strong concordance between naturally occurring SMARCB1-deficient PTCL in humans and in the targeted mouse model were found regarding epigenetic features. Our results provide a rationale for further investigation of potential HDACi combination therapies in SMARCB1-negative PTCL-NOS.

Keywords: aggressive T-cell non-Hodgkin lymphoma, genomics, epigenomics, and other-omics

No conflicts of interests pertinent to the abstract.

123 | CHROMATIN ACCESSIBILITY PROFILING TO INCREASE DIAGNOSTIC ACCURACY AND REFINE CELL-OF-ORIGIN CLASSIFICATION OF MATURE T-CELL LYMPHOMAS

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Mature T-cell neoplasms (MTCN) are heterogeneous diseases with dismal prognosis. Differentiating between the many entities requires specialized pathology expertise, and studies show up to 30% of minor or major diagnostic reclassifications following expert review of cases. Assay for transposase-accessible chromatin sequencing (ATAC-seq) is a simple technique to profile open chromatin regions, which has been shown to be highly discriminative for clustering solid tumors and acute myeloid leukemias. We applied ATAC-seq to MTCN to explore the epigenetic landscape of these different entities, and built a predictive model to aid in diagnosis.

FACS-sorted tumor cells from primary MTCN samples and 50µm sections of frozen tumor tissue from the French TENOMIC T-cell lymphoma consortium were processed according to previously published FAST- and OMNI-ATAC protocols, respectively. In parallel, we applied FAST-ATAC to several normal T and NK cell subsets sorted from PBMC or lymph node suspensions of healthy donors. Sequencing data were processed by an adapted version of the ENCODE ATAC-seq pipeline using a custom Hg38 genome version including HTLV1 sequence.

A total of 678 normal and tumor samples were sequenced to provide a comprehensive landscape of chromatin accessibility in MTCN. Unsupervised clustering of normal NK and T cell subtypes ($N = 49$) and sorted tumoral lymphoma cells ($N = 104$) confirmed that AITL are derived from TFH cells, HSTL and LGL are closely segregated with NK and gd-T cells. We also found that T-PLL likely derive from the transformation of naïve T cells. Epigenetic profiling by ATAC-seq of FACS-sorted tumor samples resulted in a complete segregation of the known MTCN entities (TFH, ALK+ and ALK- ALCL, HSTL, CTCL, ATLL, LGL and T-PLL). Most PTCL-NOS (13/17) clustered with a predefined MTCN subtype (mainly AITL/TFH-phenotype PTCL, CTCL and lymphomas exhibiting cytotoxic features), showing that this waste basket subgroup is merely virtual, at least from an epigenetic point of view. Using unsupervised deconvolution approaches, we were able to discriminate different MTCN subtypes from 223 processed frozen bulk samples. All known MTCN subtypes were identified by ATAC-seq but a novel subset of PTCL-NOS representing ~5% of cases was pinpointed, showing high GATA3 transcription factor activity. Subsequent exome sequencing revealed numerous copy number alterations and TP53 (8/12) and NCOR1 mutations (7/12). A support vector machine model was trained to predict diagnosis and showed accurate classification performance by cross-validation and on external validation cohort collected from 5 tertiary care centers.

ATAC-seq is a rapid and cost-effective technique with high classification accuracy for PTCL subtypes. Among GATA3-expressing PTCL that spread across multiple epigenetic subgroups, we identified a specific entity with recurrent NCOR1 mutations.

Keywords: aggressive T-cell non-Hodgkin lymphoma, genomics, epigenomics, and other -omics, pathology and classification of lymphomas

No conflicts of interests pertinent to the abstract.

124 | BRCA1/2 MUTATIONS IMPACT ON THE DEVELOPMENT OF BREAST IMPLANT-ASSOCIATED LYMPHOMA (BIA-ALCL) IN WOMEN WITH BREAST CANCER RECONSTRUCTED WITH TEXTURED BREAST IMPLANTS

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Introduction: Breast Implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a subtype of T-cell lymphoma arising as a seroma and/or mass in relation to the capsule of textured breast implants. Previous research in a Dutch population suggests a higher-than-expected prevalence of *BRCA1/2* carriers in women with BIA-ALCL. Here we analyze the risk of BIA-ALCL occurrence related to BRCA in a large population of women with implants followed long term after breast cancer (BC) mastectomy.

Methods: We compared the prevalence of *BRCA1/2* pathogenic variants (pv) between women from a large cohort of BC patients treated at Memorial Sloan Kettering Cancer Center (MSKCC) who did and did not develop BIA-ALCL after reconstruction with textured implants. Hazard ratios (HRs) of developing BIA-ALCL were estimated using Cox regression. To best control for age at BC diagnosis and length of follow up, we conducted a nested case-control within the cohort, matching 1:3, analyzed with conditional logistic regression.

Results: Among 3312 women with BC assessed for pv in the context of MSK-IMPACT tumor and normal study at MSKCC the prevalence of BRCA mutations was 5.3%. Among 526 patients with textured implants post BC mastectomy, followed long term at MSKCC (median FU 82 mo, range 12, 316) and clinically assessed for *BRCA1/2*, the prevalence of pv of *BRCA1/2* was 7.8%.

Of 31 BIA-ALCL post-BC cases seen at MSKCC, 16 received capsulectomy at MSKCC and 5/13 (38.4%) were BRCA1–2 positive. Within the cohort of 526 patients with BC tested for BRCA, reconstructed with textured implants and followed long-term, the age-adjusted rate of developing BIA-ALCL for women with BRCA mutations was 11.0 times the rate of BIA-ALCL among women without BRCA (HR 95% CI 3.6, 33.9, $p < .0001$). Carrying bilateral versus unilateral implants (HR 6.9, 95% CI 0.9, 53.2), prior chemotherapy exposure (HR 0.7, 95% CI 0.2, 2.05), prior radiation therapy exposure (HR 0.5, 95% CI 0.1, 2.5) were not significantly associated with the rate of BIA-ALCL.

Within this cohort, 13 BIA-ALCL cases were matched 1:3 with 39 controls. Median ages at BC mastectomy were 47.2 (37, 66) and 46.8 (35, 65) in cases and controls, respectively. The median time between reconstruction for BC and BIA-ALCL was 130 (80, 190) months. The odds ratio of BIA-ALCL associated with carriership of a *BRCA1/2* pathogenic variant was 12.4 (Wald 95% CI 1.4, 109.5 $p = 0.0074$).

Conclusions: In this study, we define the role of *BRCA1/2* mutations as a significant risk factor in the development of BIA-ALCL in patients with BC reconstructed with textured implants. These results will help decision making for women with *BRCA1/2* mutations undergoing breast reconstruction, or with textured implants in place. Analysis of pathogenic variants in other DNA repair genes in this cohort potentially affecting lymphomagenesis is ongoing.

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Keywords: aggressive T-cell non-Hodgkin lymphoma, prevention and cancer interception

No conflicts of interests pertinent to the abstract.

125 | A PHASE 2 TRIAL OF CHOP WITH ANTI-CCR4 ANTIBODY MOGAMULIZUMAB FOR ELDERLY PATIENTS WITH CCR4-POSITIVE ADULT T-CELL LEUKEMIA/LYMPHOMA

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Background: No standard of care for elderly patients with aggressive adult T-cell leukemia/lymphoma (ATL) has been established yet. We assessed the efficacy of an anti-CCR4 antibody, mogamulizumab (Moga)combined with biweekly cyclophosphamide (CPA), doxorubicin (DXR), vincristine (VCR), and prednisone (PSL) (Moga-CHOP-14) for untreated elderly patients with aggressive ATL.

Methods: In this phase 2 trial conducted at 21 centers in Japan, untreated CCR4-positive aggressive ATL patients aged 66 years or older and 56–65 years who were not candidates for allogeneic hematopoietic stem cell transplantation (allo-HSCT) received six cycles of Moga-CHOP-14, followed by two cycles of Moga monotherapy. The primary endpoint was 1-year progression-free survival (PFS), defined as the time from enrollment to the progression/relapse of ATL or death due to any cause, whichever occurred first. Secondary endpoints were complete response rate (CR), overall response rate (ORR), overall survival (OS), 1-year event-free survival (EFS), and the incidence of adverse events. The necessary number of patients calculated by setting the threshold 1-yearPFS at 16% and the expected 1-year PFS at 31% using the exact method based on binomial distribution under the conditions of one-sided level of significance of 5% ($\alpha = 0.05$) and power of 70% was 43.

Results: A total of 50 patients were enrolled from October 2015, until September 2020. Among the 48 evaluable patients, the median age was74 years (interquartile range [IQR], 70–78). ATL subtypes included 31, 9, and 8 patients for the acute, lymphoma, and unfavorable chronic type, respectively. ATL-PI included 9, 31, and 8 patients for high, intermediate, and low risk, respectively. With a median follow-up of 1.6years (IQR, 0.7–2.4), 1-year PFS was 36.2% (90% confidence interval (CI), 24.9–47.6), and a median PFS was 0.7 years (95% CI, 0.5–1.0).CR and ORR were noted in 64.6% (95% CI, 49.5–77.8), and 91.7%(95% CI, 80.0–97.7), respectively. One-year OS was 66.0% (95% CI, 50.6–77.6) and median OS was 1.6 years (95% CI, 1.1–2.8). One-year EFS was 29.9% (95% CI, 17.6–43.2) and median EFS was 0.5 years (95% CI, 0.4–0.7). The most frequent adverse events grades 3/4, which occurred in >10% of patients were lymphocytopenia (97.9%), leukopenia (93.8%), neutropenia (89.6%),

febrile neutropenia (64.8%), anemia (58.3%), thrombocytopenia (45.8%), infection (27.1%), skin rash (20.8%), and hyperglycemia (20.8%). Relative dose intensity (RDI) was calculated for each drug: the mean RDI for Moga was 82.1%, for CPA 71.7%, for DXR 72.7%, for VCR 72.0%, and for PSL 77.3%.

Conclusions: This study demonstrated that Moga-CHOP-14 significantly improved PFS in elderly patients with aggressive CCR4-positive ATL who were ineligible for allo-HSCT. Moga-CHOP-14 is now considered for the preferred first-line treatment in those patients. Clinical trial ID:jRCTs041180130.

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Keyword: combination therapies

Conflicts of interests pertinent to the abstract

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126 | AFM13 IN PATIENTS WITH CD30 POSITIVE RELAPSED OR REFRACTORY (*R/R*) PERIPHERAL T CELL LYMPHOMA (PTCL): RESULTS FROM THE PHASE 2 REDIRECT STUDY

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Introduction: PTCLs are aggressive hematologic malignancies often with poor prognoses; there is no standard of care therapy for patients with *R/R* PTCL. AFM13, a tetravalent, bispecific innate cell engager, binds CD30 when expressed on PTCL cells, and CD16A on innate effector cells, augmenting the innate immune response to $CD30^+$ tumor cells. Phase 1 clinical trials of AFM13 in patients with *R/R* Hodgkin lymphoma (HL) and cutaneous $CD30^+$lymphomas showed a tolerable safety profile and clinical activity; correlative science data in a small group of AFM13-responsive patients with HL showed increased natural killer (NK) cell activity.

Methods: A Phase 2 study (NCT04101331) assessed the efficacy of AFM13 in patients with select *R/R* PTCL subtypes, exhibiting histologically confirmed $CD30^+$expression in ≥1% tumor cells, who had received ≥1 prior systemic therapy. The primary endpoint was to assess the overall response rate (ORR) by FDG-PET per independent review committee. Secondary endpoints included safety, complete response rate (CRR), and duration of response (DoR). Progression-free survival (PFS) and overall survival (OS) were exploratory endpoints. Patients received 200 mg AFM13 intravenously once weekly until disease progression, intolerable toxicity, consent withdrawal or termination by the investigator.

Results: Patients (n = 108; age 21–93; 61% male) received AFM13 with a median (min, max) number of infusions of 9.0 (1, 116). PTCL subtypes assessed (n) were: PTCL not-otherwise-specified (PTCL-NOS, 41); angioimmunoblastic T cell lymphoma (AITL, 30); anaplastic large cell lymphoma (ALCL, 26); other (11). Patients had received a mean of 2.7 prior treatment lines; 46.3% received prior brentuximab vedotin (BV), 17.6% received prior auto-transplant. The ORR was 32.4% (CRR was 10.2%); ORR per subtype was 22.0% (PTCL-NOS), 53.3% (AITL), 23.1% (ALCL), and 36.4% (other). Median DoR, PFS,

and OS were 2.3 months, 3.5 months, and 13.8 months, respectively. AFM13-related treatment emergent adverse events (TEAEs) occurred in 79/108 patients (73.1%); 14 events in 9 patients (8.0%) were considered serious. The most frequent TEAE was infusion-related reactions, as reported by the investigator, seen in 34/108 patients (31.5%), including 12 Grade 3 events in 6 patients (5.7%). Neutropenia was the most frequent Grade ≥3 TEAE occurring in 9.3% of patients.

Conclusion: AFM13 monotherapy demonstrated robust clinical activity in heavily pretreated patients with *R/R* PTCL. The safety profile of AFM13 was well managed and consistent with previously reported data from prior and ongoing clinical studies with AFM13. These data support future evaluation of AFM13 in combination with other immunotherapies, including allogeneic NK cells, to further potentiate anti-tumor immune responses to $CD30^+$ lymphomas.

Keyword: immunotherapy

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Research funding: ADC Therapeutics; Auxilius Pharma; Celgene; CRISPR Therapeutics; Millennium/Takeda; Seattle Genetics; C4 Therapeutics; Verastem/SecuraBio

127 | LACUTAMAB IN PATIENTS WITH ADVANCED MYCOSIS FUNGOIDES (MF): EFFICACY RESULTS ACCORDING TO UPDATED LYMPH NODE (LN) CLASSIFICATION IN THE TELLOMAK STUDY

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Introduction: Cutaneous T-cell lymphoma (CTCL) is a rare form of non-Hodgkin lymphoma. The most common type is Mycosis Fungoides (MF) accounting for 50%–60% of cases with 25% of patients (pts) having advanced disease (median survival of 1–4 years). KIR3DL2 is a killer immunoglobulin-like receptor, expressed in 50% of MF. Lacutamab is a humanized first-in-class monoclonal antibody targeting KIR3DL2-expressing cells. Global response evaluation is based on 4 compartments: skin, blood, lymph nodes (LN) and viscera (Olsen 2011). LN assessment is an important component of staging and response assessment. The radiologic criteria have recognized limitations in CTCL given their adaptation from guidelines for primary nodal lymphomas. However, recent cooperative group collaboration resulted in a clarification of the guidelines. In MF and SS the pathological assessment of nodal lymphoma should fulfil the criteria for N3 designation (Olsen, 2022), highlighting the importance of utilizing relevant and updated guidelines for accurate assessment of activity.

Methods: TELLOMAK is an open-label, phase II trial with multiple cohorts (NCT03902184). Eligible pts received at least 2 prior systemic therapies. MF pts are allocated to one of two cohorts: KIR3DL2 ≥1% MF (Cohort 2) and KIR3DL2 <1% MF (Cohort 3). Lacutamab is administered until progression or unacceptable toxicity. Primary endpoint is Objective Response Rate (ORR). Secondary endpoints include additional efficacy endpoints, safety and quality of life.

The MF cohorts follow a Simon 2-stage design. Stage 1 results were presented at EORTC-CL 2022. Per protocol, Stage N0 LNs were not considered as clinically abnormal and Stage N1, N2, N3 or Nx were considered as clinically abnormal at baseline. Here, we present activity data for the same population with the same data cut-off (DCO), but according to these updated recommendations where the criteria for **N3** designation are fulfilled.

Results: At the DCO of March 04 2022, stage 1 recruitment to cohort 2 and 3 was complete, with 39 pts enrolled, median follow-up was 12.2 months (range: 1–25), median number of previous therapies was 4 (range: 2–15). In cohort 2, among the 21 pts, there were 10 (47.6%) N0, 2 (9.5%) N1, 2 (9.5%) N2, and 7 (33.3%) Nx pts. Global ORR was 28.6% [13.8; 50.0] according to the original classification. According to the updated classification, Global ORR is 42.9% (95% CI [24.5; 63.5]. In cohort 3, among the 18 pts, there were 9 (50%) N0, 3 (16.7%) N1, 1 (5.5%) N2, and 5 (27.8%) Nx pts. Global ORR is 11.1% [3.1; 32.8] according to both classifications.

Conclusion: Within the heavily pre-treated MF population enrolled in TELLOMAK, Lacutamab shows clinical activity in KIR3DL2 expressing MF pts, with higher global ORR according to updated LN evaluation. The future adoption of the revised guidelines is welcomed by the CTCL community.

Reference: Olsen et al. Blood 2022, 140 (5):419–437.

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Keywords: cutaneous non-Hodgkin lymphoma, molecular targeted therapies

Conflicts of interests pertinent to the abstract

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Employment or leadership position: Employment

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FOCUS ON CAR-T CELL

128 | PROTEOMIC PROFILING IDENTIFIES GRANZYME B INHIBITOR SERPIN B9 AS MEDIATOR OF RESISTANCE TO CAR T-CELL AND BISPECIFIC ANTIBODY TREATMENT IN NODAL B-CELL LYMPHOMA

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Introduction: Treatment options for relapsed or refractory (*r/r*) B-cell non-Hodgkin lymphomas (B-NHL) have broadened towards T-cell engaging therapies, including CD19-targeting chimeric antigen receptor T-cells (CD19-CAR) and bispecific antibodies (CD19-BsAb). Although CD19-CAR and CD19-BsAb induce durable responses in some *r/r* B-NHL patients, response remains heterogenous and a significant proportion of patients experience insufficient responses or relapse. A thorough understanding of tumor-intrinsic mechanisms of resistance is crucial for the clinical improvement of T-cell immunotherapy.

Methods: Aiming to identify lymphoma cell-inherent mechanisms that impair response to T-cell engaging therapy, we quantified the in-vitro response of 46 B-NHL cell lines to 3rd generation CD19-CAR and CD19-BsAb. Response was measured using a high-throughput flow cytometry-based assay. In parallel, cell lines were subjected to proteomic profiling and protein abundance was regressed on in-vitro response in order to identify proteomic determinants of response. We further combined CD19-CAR treatment with clinically relevant drugs and assessed how killing of lymphoma cells and expansion of T-cells was altered.

Results: Response to CD19-CAR and CD19-BsAb was highly heterogeneous across cell lines and B-NHL entities, but not significantly

linked to their proliferation rate or CD19 expression. Integration of the proteomic profiles revealed that abundance of Serpin B9, endogenous inhibitor of T-cell effector molecule granzyme B, was associated with poor response to CD19-CAR and CD19-BsAb. This finding was validated in overexpression and knock-out models. Overexpression of *SERPINB9* indeed attenuated response to CD19-CAR and CD19-BsAb, while its knock-out rendered cell lines more sensitive. The observed changes in susceptibility to T-cell-mediated cytotoxicity upon modulation of *SERPINB9* expression were independent of T-cell donor and expression of T-cell activation and proliferation markers. We sought to improve T-cell-mediated cytotoxicity specifically in samples with high *SERPINB9* expression and found that immune checkpoint inhibitors and lenalidomide enhanced expansion of CAR T-cells and increased killing of lymphoma cells. In addition, vorinostat and antibody-drug-conjugate polatuzumab vedotin specifically killed lymphoma cells without affecting T-cell expansion. However, the observed improvement in T-cell-mediated cytotoxicity was independent of *SERPINB9* expression.

Conclusion: This study is the first to investigate proteomic determinants of response to CD19-CAR and CD19-BsAb in B-NHL. With this approach, we identify tumorigenic Serpin B9 as mediator of resistance and provide combinatorial drug treatments to improve response to CD19-CAR. Collectively, these results may contribute to the targeted advancement of T-cell engaging therapy.

Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy, indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

129 | CART-SIE REAL LIFE STUDY: PRIMARY MEDIASTINAL B-CELL LYMPHOMA (PMBCL) HAVE A SUPERIOR OUTCOME COMPARED TO LARGE B-CELL LYMPHOMA (LBCL) TREATED WITH AXICABTAGENE CILOLEUCEL

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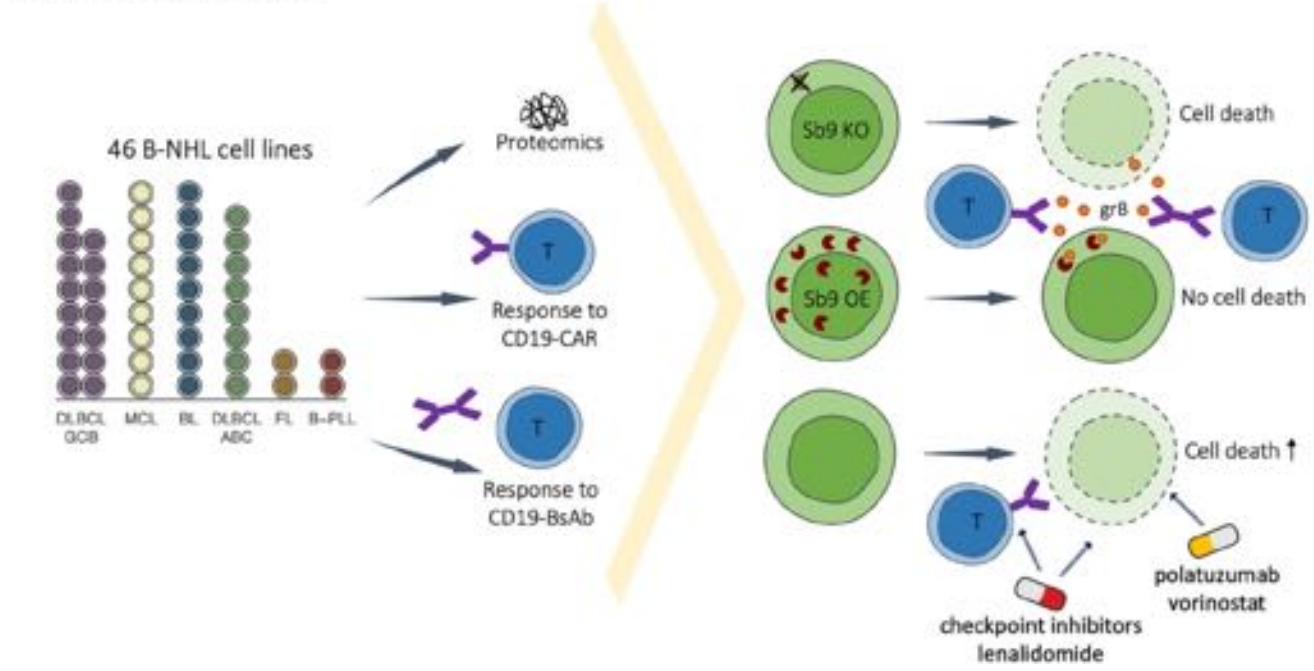
Figure 1. Graphical Abstract



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Introduction: In Italy, axicabtagene ciloleucel (axi-cel) is commercially available for the treatment of LBCL, including diffuse large B-cell lymphoma (DLBCL-NOS), high grade B-cell lymphoma (HGBCL), transformed follicular lymphoma (tFL), and PMBCL patients, relapsed/refractory (*R/R*) after at least two prior treatments.

Methods: The CART-SIE is an ongoing prospective and retrospective study collecting data on the outcome of all consecutive lymphoma patients treated with CAR-T cells. The aim of this analysis was to compare the outcome of PMBCL and LBCL treated with axi-cel in the Italian real life.

Results: From 2019 to 2022, 444 patients were infused. Axi-cel was administered in 192 patients: 57 PMBCL and 135 LBCL, including DLBCL-NOS (85), HGBCL (28) and tFL (22), respectively. The clinical characteristics for PMBCL versus LBCL showed: median age 35 versus 56 ($p = 0.0001$), bulky 33/57 (58%) versus 47/135 (35%) ($p = 0.0035$), limited stage 35/57 (61%) versus 41/135 (31%) ($p = 0.0001$), respectively. Median follow-up time for infused patients was 10.99 months (IQR 4.18, 18.03). The Overall Response Rate (ORR, complete CR + partial PR) at 30-days after the infusion was 44/57 (77%) with 30 (53%) CR in PMBCL, and 97/135 (72%) with 67 (50%) CR in LBCL, ($p = 0.4206$). The 12-months Overall Survival (OS) was 89% (95% CI: 81–98) in PMBCL versus 70% (95% CI: 62–80) in LBCL (log-rank $p = 0.0016$); by different histology subtypes, the 12-months OS was 89% (95% CI: 81–98) in PMBCL versus 74% (95% CI: 63–86) in DLBCL-NOS, 58% (95% CI: 41–81) in HGBCL, 76% (95% CI: 58–100) in tFL (log-rank $p = 0.0013$). The 12-months PFS was 65% (95% CI: 53–80) in PMBCL versus 47% (95% CI: 39–57) in LBCL (log-rank $p = 0.0160$); by different histology subtypes, the 12-months PFS was 65% (95% CI: 53–80) in PMBCL versus 40% (95% CI: 30–54) in DLBCL-NOS, 51% (95% CI: 35–75) in HGBCL, 65% (95% CI: 47–90) in tFL (log-rank $p = 0.0420$). All grades CRS was observed in 49/57 (86%) PMBCL and 118/135 (87%) LBCL patients, with 9 (16%) and 12 (9%) severe (grade 3–4) CRS, respectively; all grades ICANS were reported in 25 (44%) PMBCL patients and in 46 (34%) LBCL, with 12 (21%) and 14 (10%) severe (grade 3–4) ICANS, respectively. Tocilizumab was administered in 41 (72%) PMBCL and in 90 (67%) LBCL; steroids in 20 (35%) PMBCL and in 36 (27%) LBCL patients. Twelve (21%) PMBCL and 15 (11%) LBCL patients were admitted in the intensive care unit. Treatment related mortality was reported in 3 (5%) PMBCL and 3 (2%) LBCL patients. In a multivariable model with all clinically important and unbalanced variables, PMBCL maintained its significantly superior outcome as compared to LBCL, for OS and for PFS.

Conclusions: CART-SIE is the first real-life study comparing the prognosis of patients affected by *R/R* PMBCL and LBCL treated with axi-cel. PMBCL patients had a superior OS and PFS compared to LBCL, with a similar incidence of CRS and ICANS.

Encore Abstract—previously submitted to EHA 2023

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies

Conflicts of interests pertinent to the abstract

A. Chiappella

Consultant or advisory role: Celgene-BMS, Gilead-Sciences, Ideogen, Janssen, Roche, SecuraBIO, Takeda

Other remuneration: Lecture fees/Educational activities: Astrazeneca, Celgene-BMS, Gilead-Sciences, Incyte, Janssen-Cilag, Novartis, Roche, Takeda

130 | IMPACT OF RESPONSE TO SYSTEMIC BRIDGING THERAPY ON CLINICAL OUTCOMES AND CYTOKINE PROFILE IN PATIENTS RECEIVING CAR T-CELL THERAPY FOR AGGRESSIVE B-CELL LYMPHOMA

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Background: It is unclear whether a deeper response to bridging therapy (BT) before chimeric antigen receptor (CAR) T cell therapy improves CAR-T treatment outcome in large B cell lymphoma (LBCL). We studied the impact of response to systemic BT on clinical outcomes and cytokine profiles of LBCL patients (pts) treated with CD19-directed CAR-T.

Methods: We included LBCL pts treated with systemic BT before receiving commercial CD19-CAR-T at two academic centers, and excluded those who received monotherapy with glucocorticosteroids or isolated radiation therapy. BT was classified as Polatuzumab-(pola) based, intensive chemotherapy, lenalidomide/ Bruton tyrosine

kinases inhibitors (len/BTKi), or other. PET/CT scans obtained before and after BT, and after CAR-T were evaluated using Lugano 2014 response criteria. Association between BT and response rates (RR) were examined using Fisher's exact test, and the associations with cytokine levels were examined using Kruskal Wallis tests. Kaplan Meier analysis was used to estimate overall (OS) and progression free survival (PFS) from time of CAR T infusion. Cox proportional hazards models were used for univariable and multivariable analyses.

Results: We identified 148 pts whose median age was 65 (range 23–85), and 96 (65%) were male. BTs included: 62 (42%) pola-based, 48 (32%) intensive chemotherapy, 25 (17%) len/BTKi, and 13 (9%) other BT. Among all pts, 77 (52%) received Axicel, 42 (28%) received Tisacel and 29 (20%) received Lisocel. Median time from apheresis to CAR-T was 35 days. Among evaluable pts RR to BT were: 10 (7%) complete responses (CR), 39 (29%) partial responses (PR), 87 (64%) either stable disease (SD) or progressive disease (PD). RR did not differ among different BT regimens ($p = 0.27$). At day 100 post-CAR-T, RR were: 74 (50%) CR, 27 PR (18%) and 44 (30%) SD/PD. With a median follow up of 18.9 months, PFS was 5.03 months (95% CI: 3.25, 9.53) and median (OS) was 16.1 months (95% CI 12.2–31.3) (Figure 1A). In multivariable analysis, poor response to BT (SD/PD) and elevated LDH prior to CAR-T infusion were associated with worse PFS, but not with OS. LDH (Figure 1B), ferritin, IL-6, IL-10 and C-reactive protein measured prior to lymphodepletion (LD) and at day 0 of CAR-T infusion were significantly higher in pts with SD/PD compared to pts achieving a CR/PR to BT. Ferritin levels prior to LD were higher in pts who received intensive chemotherapy compared to other BT.

Conclusions: Our findings indicate that response to CAR T therapy is more frequent in pts responding to BT. Ferritin, LDH, and other inflammatory cytokine levels at the time of LD differ according to the type and response to systemic BT. Higher levels may reflect inherent disease biology and treatment-refractoriness. Further studies are required to evaluate which BT strategies may reduce tumor burden and optimize the inflammatory cytokine environment for improved outcomes after CAR -T cell therapy.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies

Conflicts of interests pertinent to the abstract

G. L. Shah

Research funding: Janssen, Amgen, Beyond Spring, and BMS. DSMB for ArcellX

M. Scordo

Consultant or advisory role: McKinsey & Company, Angiocrine Bioscience, Inc., and Omeros Corporation; served on ad hoc advisory boards for Kite—A Gilead Company

Honoraria: Received honoraria from i3Health and Medscape for CME-related activity

Research funding: received research funding from Angiocrine Bioscience, Inc., and Omeros Corporation

R. J. Lin

Consultant or advisory role: Kite

G. Salles

Consultant or advisory role: Abbvie, Atbtherapeutics, Bayer, Beigene, BMS/Celgene, Debiopharm, Epizyme, Genentech/Roche, Genmab, Incyte, Ipsen, Janssen, Kite/Gilead, Loxo/Lilly, Molecular Partners, Morphosys, Nordic Nanovector, Novartis, Regeneron, Takeda H

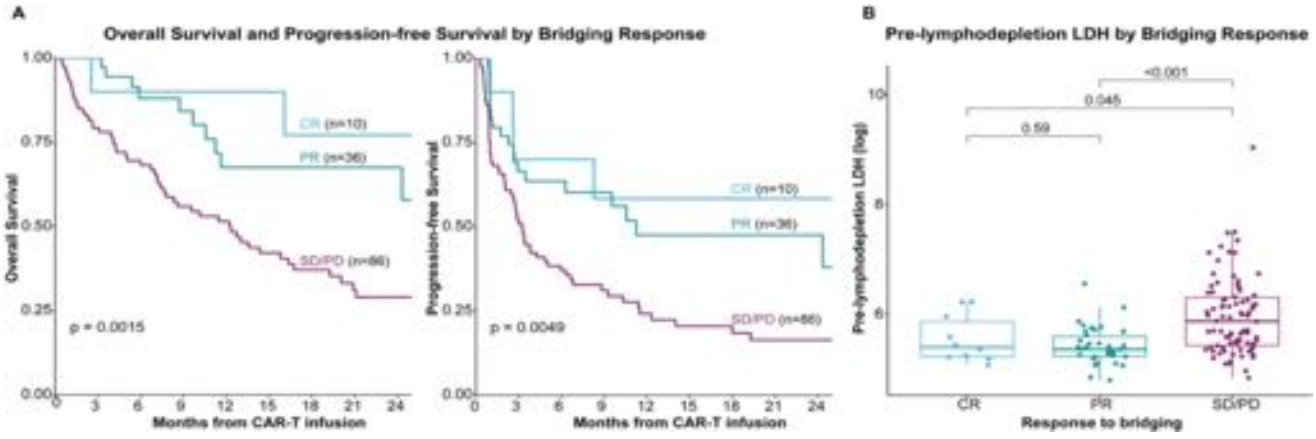
Stock ownership: Owkin

M. Perales

Consultant or advisory role: Adicet, Allovir, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equilium, Exevir, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Syncopation, VectivBio AG, and Vor Biopharma. He serves on DSMBs for Cidara Therapeutics, Medigene, and Sellas Life Sciences, and the scientific advisory board of NexImmune.

Research funding: He has received institutional research support for clinical trials from Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis.

Other remuneration: He has ownership interests in NexImmune, Omeros and OrcaBio.



M. L. Palomba

Consultant or advisory role: Synthekine, Cellectar, Beigene, Kite, BMS

131 | BENDAMUSTINE LYMPHODEPLETION TRIGGERS REDUCED INFLAMMATORY CYTOKINES AND DECREASED TOXICITIES AFTER BOTH 4-1BB- AND CD28-COSTIMULATED CART19 FOR NON-HODGKIN LYMPHOMA

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Introduction: Lymphodepletion (LD) is a key component of anti-CD19 chimeric antigen receptor T cell (CART19) immunotherapy, establishing the proper environment and cytokine milieu before CART infusion. We previously demonstrated that Bendamustine (Benda) LD is as effective as standard fludarabine and cyclophosphamide (Flu/Cy) LD before the 4-1BB-costimulated tisagenlecleucel, but has reduced cytokine-release syndrome (CRS), neurotoxicity (ICANS), and hematological toxicities. However, it remains unknown whether Benda LD is both effective and safe in CD28 costimulated CART19 and what the mechanism is for the reduced toxicities associated with Benda.

Methods: We retrospectively evaluated the outcomes of 54 consecutive non-Hodgkin lymphoma patients (pts), including large B cell lymphomas and follicular lymphoma, treated with commercial CD28-costimulated axicabtagene ciloleucel (axi-cel) at the University of Pennsylvania between 2018 and 2023. Pts were evaluated for response (Lugano), and toxicities (ASTCT, CTCAE) in the 30 days after axi-cel infusion. We also analyzed serum samples, collected pre- and post-LD (CART19 infusion day), for cytokines (Luminex) and metabolomics (Mass Spectrometry) changes due to LD, in a second cohort of 32 pts undergoing CART19 immunotherapy. Cytokine and metabolite levels are expressed as fold change of values post-LD as compared to pre-LD values to reduce inter-patient variability.

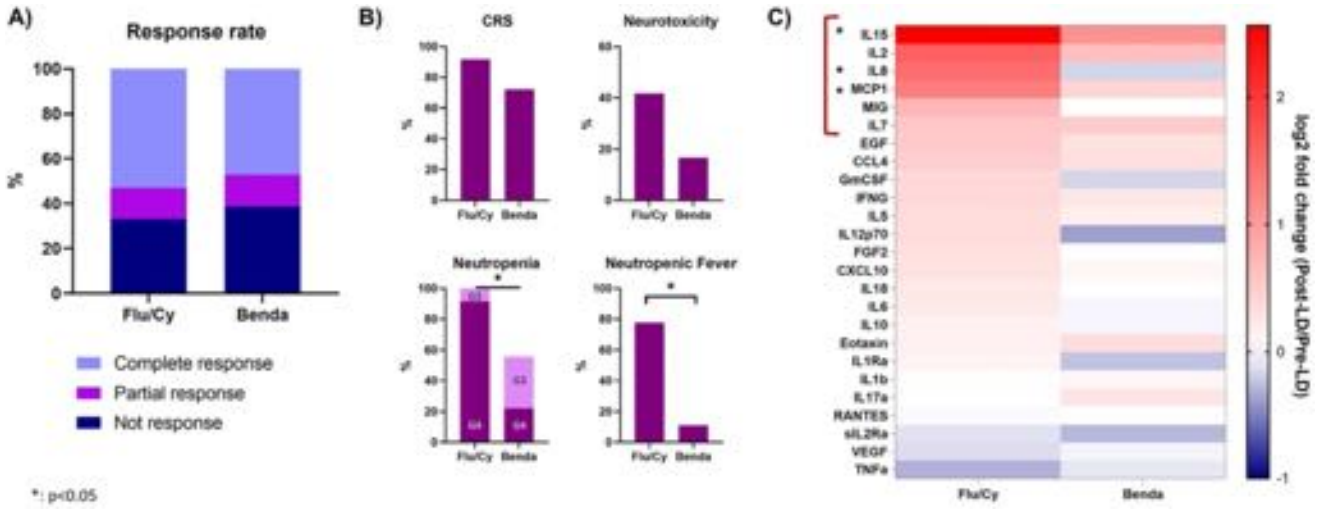
Results: Of 54 pts, 36 received Flu/Cy while 18 Benda LD; LD choice was at the treating physician's discretion. The groups were balanced for most clinical features. The overall response rate was 67% for Flu/Cy and 61% for Benda LD (**Figure 1A**), and complete remission rate was 53% and 47%, respectively. Both any grade CRS and ICANS were more frequent in Flu/Cy pts as compared to Benda pts (any grade CRS 92% vs. 72%; any grade ICANS 42% vs. 17%). Remarkably, Flu/Cy LD was also associated with higher incidence of severe neutropenia (100% vs. 63%), infections (78% vs. 27%) and neutropenic fever (78% vs. 13%) (**Figure 1B**).

We then investigated the possible mechanism for the enhanced toxicities in Flu/Cy pts by analyzing serum cytokines and metabolites. After both Flu/Cy ($n = 7$) and Benda ($n = 25$), we observed increased cytokines levels, in particular, those facilitating CART proliferation (IL7, IL2, IL15). Overall, Flu/Cy pts had a greater increase in cytokine levels compared to Benda pts. Moreover, cytokines previously associated with ICANS (i.e., IL15, IL8, MIG, and MCP1) were enriched in Flu/Cy-treated pts (**Figure 1C**). Metabolomic data will be presented at the meeting.

Conclusions: This study demonstrates that Benda LD is as effective as Flu/Cy in pts receiving CD28-costimulated CART but associated with reduced CRS, ICANS, infections, and cytopenias. Our mechanistic studies identify a significant increase of cytokines associated with neurotoxicity in pts receiving Flu/Cy.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies

No conflicts of interests pertinent to the abstract.



132 | PROGNOSTIC SCORING SYSTEMS FOR SEVERE CRS AND ICANS AFTER AUTOLOGOUS ANTI-CD19 CAR T CELLS IN LARGE B-CELL LYMPHOMA: A DESCAR-T REGISTRY STUDY FORM THE LYSA

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Background: Cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) are common immune-related toxicities associated with chimeric antigen receptor (CAR)–T-cell therapy. Their clinical manifestations can be severe and potentially life threatening.

Aims: Here, we report on specific acute toxicities of CAR-T in a large real-world evidence population treated with axi-cel or tisa-cel for refractory/relapse aggressive B-cell lymphoma (*R/R* ABCL) and we propose two validated prognostic scoring systems to refine the identification of patients at high risk of severe CRS or ICANS before any CAR-T cell infusion.

Methods: We conducted a study in a large cohort of *R/R* ABCL patients (pts) treated with commercial products as third-line therapy. All data were collected through the French DESCAR-T registry. CRS/ICANS were graded according to the ASTCT grading scale. For prognosis scoring system computation, the data set was split into a training set ($N = 555$) to derive optimal predictive models, and the remaining 40% of records were used as a first validation set to test their validity ($N = 370$). Boostrap analyses were used to identify robust prognostic parameters and models in the training set.

Results: Toxicity was analyzed for 925 pts receiving CAR-T cells in third-line setting, with a median follow-up of 12.7 months (range: 0.2–39). CRS of any grade occurred in 778 pts (84.1%) including 74 (8.0%) with grade 3 or higher. ICANS of any grade occurred in 375 pts (40.5%) including 110 (11.9%) with grade ≥3.

Based on the parameters selected by multivariate analyses, two independent prognostic scoring systems (PSS) were derived for grade ≥3 CRS and grade ≥3 ICANS based on weighted coefficients and termed CRS-PSS (4-point scale) and ICANS-PSS (5-point scale) respectively (Table 1). Each score was subsequently divided into 2 classes for convenient routine use with an optimal cut-off set at 2. For severe CRS, the incidence was 6.2% in the low-risk category (CRS-PSS ≤2) compared with 20.7% in the high-risk category (CRS-PSS >2, $p < 0.0001$). For severe ICANS, the incidence was 2.6% in the low-risk category (ICANS-PSS ≤2) compared with 18.3% in the high-risk category (ICANS-PSS >2, $p < 0.0001$). The statistical prognostic significance of both CRS-PSS and ICANS-PSS were confirmed in the DESCAR-T validation cohort ($p = 0.0184$ and $p < 0.0001$, respectively). Performances of CRS-PSS and ICANS-PSS were compared with those of EASIX, modified-EASIX and simplified-EASIX and were consistently better both in the training and the validation cohorts (Table 2). Further external validation is ongoing and will be presented at the meeting.

Conclusion: In this large study, we propose two pre-infusion validated and easy-to-compute scoring systems that allow for the identification of patients at higher risk of grade ≥3 CRS or ICANS for potential tailored medical care.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies

Conflicts of interests pertinent to the abstract

P. Sesques
Honoraria: KITE/GILEAD; BMS; CHUGAI
Educational grants: KITE/GILEAD; JANSSEN

R. Di blasi
Honoraria: Janssen, Pfizer, Bristol Myers Squibb, Kite/Gilead and Novartis.

S. Legouill
Honoraria: Janssen-Cilag, Kite/Gilead and Novartis

G. Cartron
Honoraria: Roche, Bristol Myers Squibb, Onwards Therapeutics, MedxCell, EmerCell, MabQ, Sanofi, Abbvie, Takeda, Roche, Janssen, Roche, Novartis and Myltenyi

D. Beauvais
Honoraria: Kite/Gilead

F. Gros
Honoraria: Bristol Myers Squibb, Novartis and Kite/Gilead

P. Bories
Honoraria: Bristol Myers Squibb, Kite/Gilead, Novartis and Abbvie

Table 1. CRS-PSS (prognostic scoring system) and ICANS-PSS in training and validation sets

	Factors (score computation)[#]	Category	n/N (%) of grade ≥3 AE (CRS for CRS-PSS and ICANS for ICANS-PSS)	
			Training set[1] (N=555)	DESCAR-T validation set[2] (N=370)
CRS-PSS 4 points	• Bulk (> 5cm) (+1) • Platelets < 150 G/L (+1) • No bridge or bridge failure (+1) • CRP > 30 mg/L (+1)	Low (0-2)	29/468 (6.2%)	19/317 (6.0%)
		High (>2)	18/87 (20.7%)	8/53 (15.1%)
ICANS-PSS 5 points	• Female sex (+1) • Platelets < 150 G/L (+1) • No bridge or bridge failure (+1) • Axi-cel (+2)	Low (0-2)	6/233 (2.6%)	5/150 (3.3%)
		High (>2)	59/322 (18.3%)	40/220 (18.2%)

[#]at lymphodepletion
[1]$P<0.0001$ for both CRS-PSS and ICANS-PSS (χ^2 test)
[2]$P=0.0184$ for CRS-PSS and $P<0.0001$ for ICANS-PSS (χ^2 test)

Table 2. Model performance comparisons

		Training set	DESCAR-T validation set
	Score	AUC of the ROC curve (95% Wald confidence limits)	AUC of the ROC curve
Grade ≥3 CRS prediction	CRS-PSS	0.71 (0.63-0.78)	0.63 (0.52-0.74)
	EASIX	0.64 (0.55-0.73)	0.57 (0.46-0.69)
	Modified-EASIX	0.62 (0.52-0.73)	0.61 (0.48-0.73)
	Simplified-EASIX	0.63 (0.54-0.73)	0.57 (0.46-0.69)
Grade ≥3 ICANS prediction	ICANS-PSS	0.75 (0.70-0.80)	0.71 (0.64-0.78)
	EASIX	0.60 (0.52-0.67)	0.56 (0.44-0.67)
	Modified-EASIX	0.53 (0.44-0.62)	0.61 (0.41-0.73)
	Simplified-EASIX	0.58 (0.50-0.65)	0.58 (0.47-0.69)

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133 | SEVERE HEMATOLOGICAL TOXICITY FOLLOWING CD19 CAR-T FOR RELAPSED/REFRACTORY LBCL IS ASSOCIATED WITH SUPPRESSIVE IMMUNE DYSREGULATION AND LIMITED CAR-T EXPANSION

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Background: Hematological toxicity represents the most frequent high-grade toxicity of CD19 CAR-T, but remains poorly understood. We recently proposed a classification system for CAR-T-related hematotoxicity, defining three unique phenotypes of neutrophil recovery: quick ["Q"] versus intermittent ["I"] versus aplastic ["A"].
Methods: In this multicenter observational study of 344 patients receiving standard-of-care CD19 CAR-T for r/r LBCL, we examined the underlying (patho-)physiology of post-CAR-T neutrophil recovery and its relation to clinical outcomes. The phenotypes were defined as:

1. Quick: sustained neutrophil recovery without a second dip below an ANC <1000/μL.
2. Intermittent: neutrophil recovery (ANC > 1500/μL) followed by a second dip with an ANC < 1000/μL after day 21.
3. Aplastic: continuous severe neutropenia (ANC < 500/μL) ≥14 days.

Multivariable binary logistic regression was applied to analyze clinical metadata. CAR T-cell expansion dynamics were studied during the first 4 months post-CAR-T infusion. The plasma proteome was explored in 58 patients across four time points (day 0, 4, 14, 28) using a 92-protein multiplex proximity extension assay (Olink Bioscience). Progression-free (PFS) and overall survival (OS) were studied via Kaplan-Meier estimates.
Results: The distribution of phenotypes was 18%, 42%, and 40% (A vs. I vs. Q). As expected, 'aplastic' patients displayed prolonged severe neutropenia (A vs. I vs. Q: 28 vs. 10 vs. 5 days, $p < 0.001$) and a higher rate of severe infections (40% vs. 22% vs. 18%). On multivariable regression of baseline risk factors ($n = 344$), the aplastic phenotype was independently associated with the presence of BM infiltration ($p = 0.004$), low ANC ($p = 0.002$), and increased ferritin ($p = 0.039$).
When comparing CAR-T expansion among phenotypes, 'intermittent' patients displayed the greatest CAR T-cell expansion over time (Figure 1A). Conversely, 'aplastic' patients displayed low expansion with an unfavorable relationship between CAR-T expansion and baseline tumor burden (Figure 1B). Serum proteomics revealed higher markers of T-cell suppression, endothelial dysfunction, inflammatory cytokines, and macrophage activation in the 'aplastic' phenotype group (Figure 1C). Notably, both PFS and OS was poor in the 'aplastic'patients (1-yr PFS 26%, 1-yr OS 46%). On the other hand, the 'intermittent' phenotype, characterized by recurrent neutrophil dips, was associated with superior survival outcomes (1-yr PFS 51%, 1-yr OS 46%).
Conclusion: In conclusion, prolonged neutrophil aplasia occurs in patients with systemic immune dysregulation with subsequently impaired CAR T-cell expansion and myeloid-related inflammatory changes. Overall, neutrophil recovery patterns reflected survival outcomes after CD19 CAR-T therapy, highlighting critical interactions between host hematopoiesis and the immune state stimulated by CAR T-cell infusion.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, basic and translational science – Basic and Translational Science - Other

Conflicts of interests pertinent to the abstract

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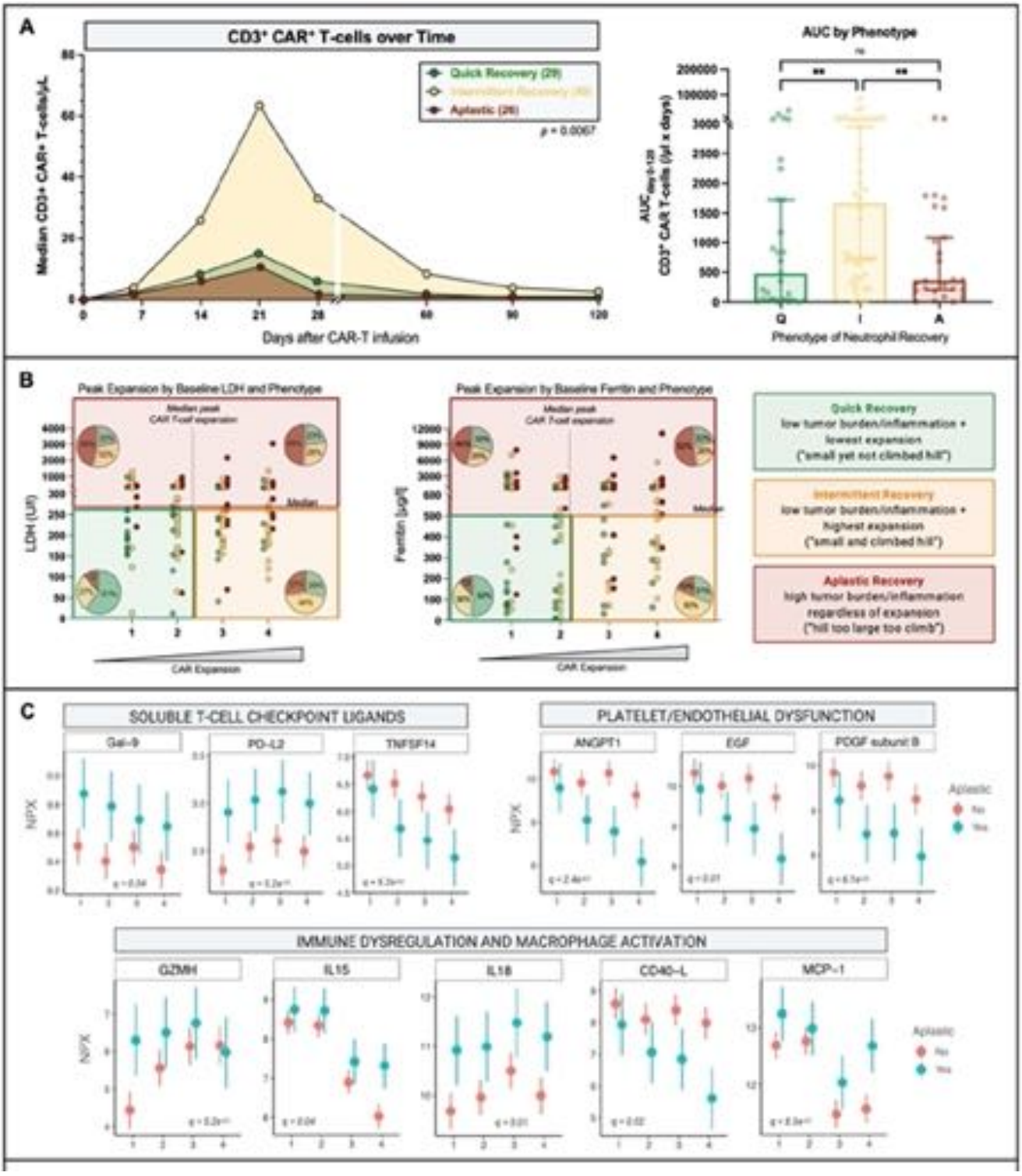

FOCUS ON LARGE B-CELL AND DOUBLE HIT LYMPHOMAS

134 | **MYC/BCL6 DOUBLE HIT LYMPHOMA NEGATIVE FOR *T*(3;8) BCL6::MYC FUSION IS ASSOCIATED WITH INFERIOR SURVIVAL, IN CONTRAST WITH *T*(3;8) POSITIVE PSEUDO-DOUBLE HIT LYMPHOMA**

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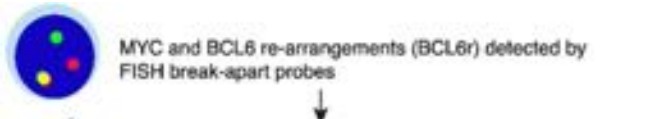
Introduction: A small proportion of large B cell non-Hodgkin lymphoma (NHL) has *MYC* and *BCL6* rearrangements, detectable by fluorescence in-situ hybridisation (FISH) break-apart probes. There are conflicting reports on the prognosis of this group. A proportion of them have a single *t*(3;8) *BCL6*::*MYC*translocation which accounts for both break-apart probe results. The prognostic significance of this *t*(3;8) positive group is unknown.

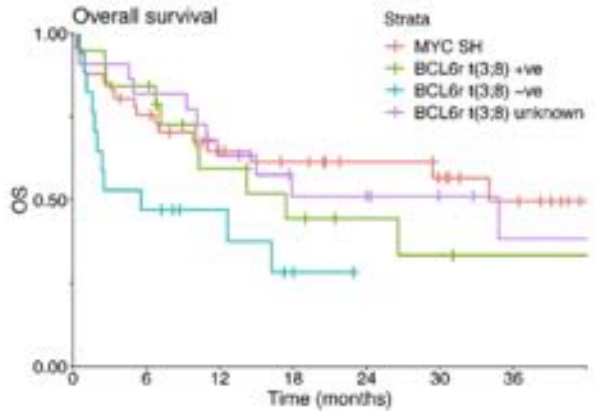
Methods: We conducted a retrospective cohort study of cases of high grade B NHL, excluding Burkitt lymphoma, referred to a regional histopathology and FISH laboratory from 14 hospitals in the West Midlands, UK. Cases of *MYC/BCL2* double-hit lymphoma without *BCL6* rearrangement were excluded. Survival was analysed using univariate and multiple regression with Cox proportional hazards.

Results: Data were collected for 106 cases of high grade B cell lymphoma with *MYC* rearrangements. BCL6 rearrangement by FISH break-apart probe (*BCL6r*) was seen in 61, of which 19/38 tested with a *t*(3;8) fusion probe were positive. The four groups, *MYC* single hit, *BCL6r t*(3;8) positive, *BCL6r t*(3;8) negative, and *BCL6r t*(3;8) untested, were well matched for baseline histological and clinical characteristics. Univariate survival analysis showed that the *BCL6r t*(3;8) negative group had inferior overall survival (OS) and progression-free survival relative to *MYC* single hit (hazard ratio (HR) 2.6 for death, $p = 0.01$), and the association was maintained in a multivariate analysis (HR 3.1, $p = 0.01$). No significant effect on survival was associated with the *BCL6r t*(3;8) positive group.

Conclusions: The *t*(3;8) translocation is a common cause of apparent double hit *MYC* and *BCL6* FISH results but, as expected from a rearrangement leading only to *MYC* overexpression, this group have a similar survival to *MYC* single hit cases. However, large B cell lymphomas with separate *MYC* and *BCL6* rearrangements which are negative for *t*(3;8) are associated with inferior survival, independently of established clinical prognostic factors.



	MYC single hit	MYC-rearrangement plus:		
median or %	n=45	BCL6r t(3;8)+ve n=19	BCL6r t(3;8)-ve n=19	BCL6r t(3;8) unknown n=23
Age	70	71	72	69
Prior low grade	24%	21%	21%	13%
BCL2r	0%	63%	42%	61%
Blastoid	48%	75%	50%	68%
GCB by IHC	79%	92%	100%	80%
LDH ratio	1.5	1.7	2.9	3.0
ECOG PS	1	1	1	0
Stage	4	4	3	4



Univariate		Hazard ratio	HR	p
FISH group	MYC SH			
	BCL6r t(3;8) +ve		1.4	0.43
	BCL6r t(3;8) –ve		2.6	0.01
	BCL6r t(3;8) unknown		1.1	0.75
LDH ratio	0			
	1		2.2	0.09
	2		2.3	0.07
Age			1.0	0.01
Stage			1.6	0.02
ECOG PS			2.0	<1e–05
Extranodal sites	0			
	1		1.5	0.36
	2+		2.0	0.15

1 2 5

Multivariate		Hazard ratio	HR	p
FISH group	MYC SH			
	BCL6r t(3;8) +ve		1.4	0.37
	BCL6r t(3;8) –ve		3.0	0.01
	BCL6r t(3;8) unknown		1.2	0.71
Age			1.0	0.40
Stage			1.6	0.02
ECOG PS			2.0	0

0.5 1 2 5

In high grade B cell lymphoma:

- the presence of t(3;8) is not associated with inferior survival.
- true MYC BCL6 double hit lymphomas, without t(3;8) have inferior survival.
- this association is independent of established prognostic risk factors.

GCB, germinal centre B cell; IHC, immunohistochemistry; LDH, lactate dehydrogenase; ECOG PS, Eastern cooperative oncology group performance status.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, pathology and classification of lymphomas

No conflicts of interests pertinent to the abstract.

135 | HIGH COMPLETE METABOLIC RESPONSE RATES WITH EPCORITAMAB + R-CHOP IN PREVIOUSLY UNTREATED (1L) HIGH-RISK DLBCL, INCLUDING DOUBLE-HIT/TRIPLE-HIT: EPCORE NHL-2 UPDATE

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Introduction: Patients with previously untreated (1L) diffuse large B-cell lymphoma (DLBCL) typically receive rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); however, around 40% of these patients relapse. Complete response rates and long-term outcomes are worse for high-risk patients with International Prognostic Index (IPI) 3–5 or double-hit/triple-hit lymphoma, representing an underserved patient population requiring better curative options. Data from the pivotal study of single-agent epcoritamab, a T-cell–engaging bispecific antibody, demonstrated impressive efficacy and a manageable safety profile (Thieblemont et al., *J Clin Oncol*, 2022). Preliminary data for epcoritamab + R-CHOP in 1L DLBCL from the EPCORE™ NHL-2 phase 1/2 trial (NCT04663347; arm 1) showed encouraging efficacy. Here we present results for a larger cohort with longer follow-up.

Methods: Patients with 1L $CD20^+$ DLBCL and IPI ≥3 received subcutaneous epcoritamab (cycles 1–4, QW; cycles 5–6, Q3W) + R-CHOP for 6 cycles (21 days each) followed by epcoritamab monotherapy Q4W (28-day cycles) up to a total of 1 year.

Results: As of October 31 2022, 47 patients (median age, 64 years) had received epcoritamab 48 mg + R-CHOP with a median follow-up of 11.5 months (range 0.8–15.5). All patients had IPI 3–5, 37 (79%) had stage IV disease, and 11 (44%) of 25 patients with FISH data available had double-hit/triple-hit DLBCL. Median time from diagnosis to first dose was 28 days (range 3–423). Median dose intensity for R-CHOP was ≥95%. The most common treatment-emergent AEs (TEAEs) of any grade (G) were neutropenia (64%), anemia (62%), CRS (60%), fatigue (40%), pyrexia (40%), injection-site reactions (38%), and nausea (38%). TEAEs led to epcoritamab discontinuation in 3 patients; 1 patient had a G5 TEAE (COVID-19, unrelated to treatment). CRS was predominantly low grade (57% G1–2, 2% G3) and occurred mostly after the first full dose (cycle 1, day 15); all cases resolved. One patient experienced G2 ICANS, which resolved in 4 days. All response-evaluable patients (100%) had a response, and 76% had a complete metabolic response (CMR; **Table**). Notably, response rates were similar for patients with double-hit/triple-hit DLBCL (CMR rate, 82% [9/11]). Median progression-free survival, overall survival, and duration of response were not reached. Responses were durable; at 9 months, an estimated 96% of patients with CMR remained in CMR. Updated data will be presented.

Conclusions: Subcutaneous epcoritamab + R-CHOP induces high CMR rates with a manageable safety profile in patients with 1L high-risk DLBCL, including patients with double-hit/triple-hit lymphoma. These results support the ongoing phase 3 study of epcoritamab + R-CHOP in 1L patients (NCT05578976).

Table. Antitumor activity

	Complete metabolic response, n (%)	Partial metabolic response, n (%)	Overall response, n (%)
Total evaluable, n=46	35 (76)	11 (24)	46 (100)
Double-hit/triple-hit, n=11	9 (82)	2 (18)	11 (100)

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Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy

Conflicts of interests pertinent to the abstract

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136 | WAVELINE-004: OPEN-LABEL, PHASE 2 STUDY OF ZILOVERTAMAB VEDOTIN (MK-2140) IN PATIENTS WITH RELAPSED OR REFRACTORY (*R/R*) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Introduction: Patients (pts) with *R/R* DLBCL who are not candidates for autologous stem cell transplant (ASCT) or CAR T-cell therapy have limited treatment options. ROR1 is an oncofetal protein pathologically expressed in several hematologic malignancies, including DLBCL. The ROR1-targeting antibody-drug conjugate zilovertamab vedotin (ZV) had promising antitumor activity and manageable safety in pts with *R/R* DLBCL in the phase 1 waveLINE-001 study. We present early data from the single-arm, open-label, phase 2 waveLINE-004 study (NCT05144841), designed to evaluate ZV monotherapy in pts with *R/R* DLBCL who were ineligible for or had progression after ASCT and CAR T-cell therapy.
Methods: Key eligibility criteria were age ≥18 y, histologically confirmed DLBCL by WHO classification, measurable disease per Lugano 2014 criteria, ECOG PS of 0–2, and PET-positive disease. Pts must have received ≥2 prior lines of therapy, including an alkylating agent, an anthracycline, and an anti-CD20 antibody, and must have been ineligible for or had disease progression after ASCT and CAR T-cell therapy. Pts were treated with ZV 2.5 mg/kg IV Q3W until disease progression, unacceptable toxicity, or withdrawal. The primary end point was ORR per Lugano 2014 criteria. Secondary end points were DOR, safety, and tolerability. Safety was evaluated in pts who received ≥1 dose of ZV. Efficacy was evaluated in pts with ≥3 mo of follow-up data.
Results: Forty pts were enrolled and received ≥1 dose of ZV. Median age was 68.0 y, 29 pts (73%) were male, 37 (93%) had an ECOG PS of 0/1, and 24 (60%) had received ≥3 prior lines of therapy. Ten pts (25%) had received prior ASCT; 11 (28%) received prior CAR T-cell therapy. At data cutoff (16 November 2022), 23 pts (58%) had discontinued ZV and 17 (43%) continued. Median follow-up (range) was 2.6 (0.3–7.9) mo for all pts and 6.0 (3.0–7.9) mo for pts with ≥3 mo of follow-up (n = 20). ORR by investigator review was 30% (95% CI, 11.9–54.3; 2 CR/4 PR). DCR was 55% (95% CI, 31.5–76.9; 5 SD). Treatment-related AEs occurred in 28 pts (70%), most commonly (≥20%) diarrhea (9 [23%]) and anemia (8 [20%]). Grade 3/4 treatment-related AEs occurred in 16 pts (40%), most commonly (≥10%) neutropenia (7 [18%]), anemia (6 [15%]), and neutrophil count decrease (4 [10%]). Treatment-related AEs led to discontinuation of ZV in 1 pt (3%) (diabetic ketoacidosis). Treatment-related peripheral neuropathy (PN) occurred in 6 pts (15%): none was grade ≥3. Treatment-related PN led to dose reduction in 3 pts (8%). No treatment-related infusion reactions or tumor lysis syndrome occurred. No pts died of treatment-related AEs.
Conclusion: This early analysis of waveLINE-004 showed ZV had clinically meaningful antitumor activity in pts with *R/R* DLBCL who are ineligible for or had progression after ASCT and CAR T-cell therapy. The safety profile of ZV was manageable and consistent with that of other monomethyl auristatin E–containing agents.

Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies

Encore Abstract—previously submitted to ASCO 2023 and EHA 2023

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Conflicts of interests pertinent to the abstract

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137 | LONG-TERM RESPONSES WITH LONCASTUXIMAB TESIRINE: UPDATED RESULTS FROM LOTIS-2, THE PIVOTAL PHASE 2 STUDY IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Patients (pts) with diffuse large B-cell lymphoma (DLBCL) who relapse after stem cell transplant or chimeric antigen receptor therapy or are refractory to second-line therapy have poor prognosis and few treatment options (Chow et al., 2019). For these pts, long-term disease control with manageable toxicity is the goal. Loncastuximab tesirine (loncastuximab tesirine-lpyl; Lonca), an anti-CD19 antibody conjugated to a pyrrolobenzodiazepine dimer, demonstrated single-agent antitumor activity in LOTIS-2, the pivotal phase 2 study in heavily pretreated pts with relapsed/refractory (*R*/*R*) DLBCL (Caimi et al., 2021). In previously presented follow-up analyses (median follow-up: 7.8 months [mo; range: 0.3, 31.0]), durable

responses to Lonca were observed (median duration of response [mDOR]: 13.4 mo; median duration of complete response [CR]: not reached [NR]; Zinzani et al. ICML, 2021).

Here, we present updated long-term efficacy and safety from LOTIS-2 (NCT03589469) in pts with *R/R* DLBCL treated with Lonca, including subsets of pts with durable CR.

Methods: LOTIS-2 was a multicenter, open-label, single-arm phase 2 study of Lonca monotherapy in pts with *R/R* DLBCL after ≥2 prior systemic therapies. Lonca was administered every 3 weeks (150 μg/kg for 2 cycles; 75 μg/kg thereafter). The primary efficacy endpoint was overall response rate (Lugano 2014 criteria). Secondary endpoints included DOR; CR rate; and relapse-free, progression-free (PFS; measured from start of therapy), and overall survival (OS). Efficacy and safety analyses were performed for all pts and subsets of pts with CR, and pts with CR who were event-free (no progressive disease or death) for ≥1 and ≥2 years (yr) from cycle 1, day 1.

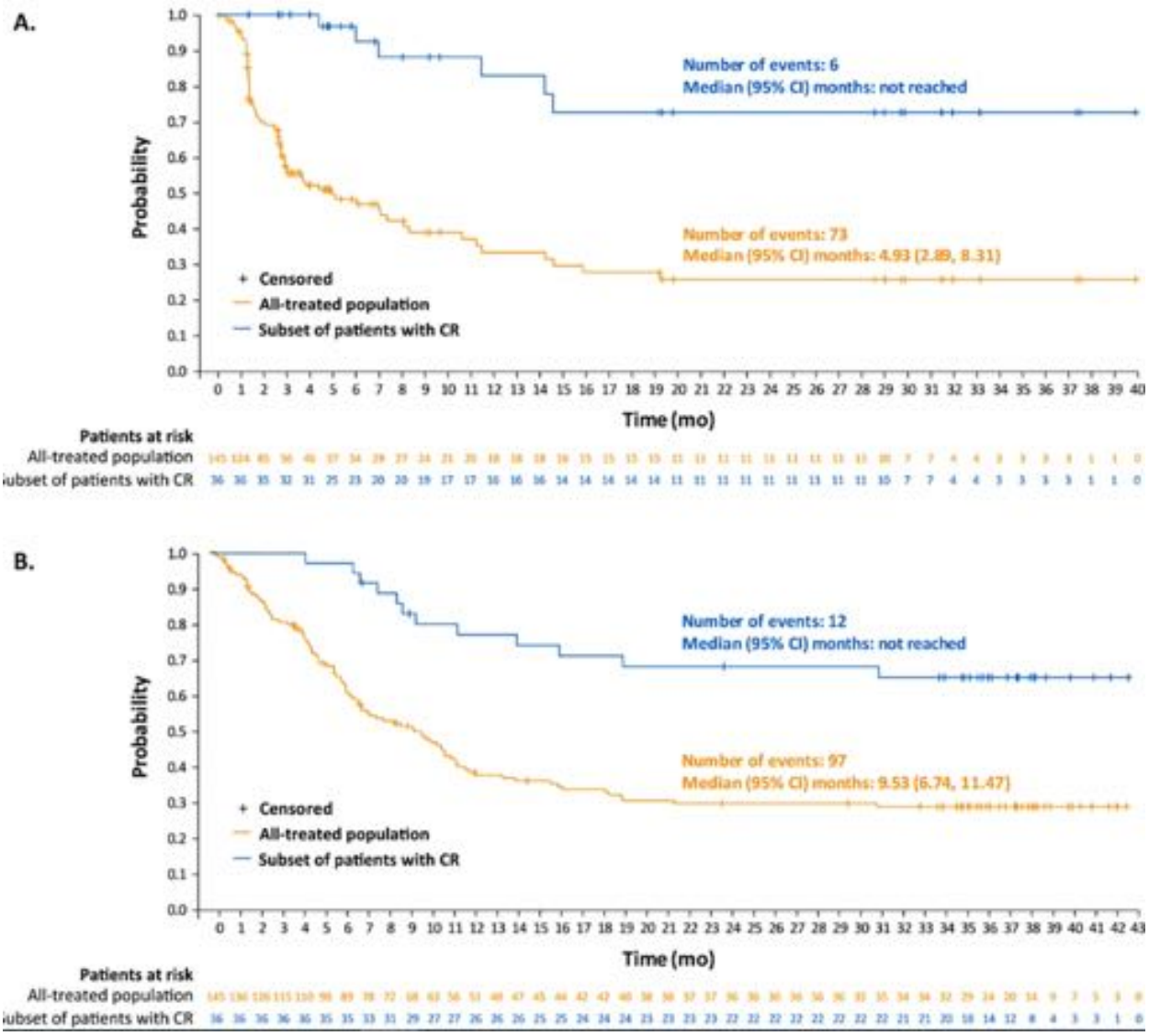
Results: As of final data cutoff (15 September 2022; median follow-up: 7.8 mo [range: 0.3, 42.6]), 70 (48%) of 145 pts achieved response and 36 (25%) pts achieved CR; 16 (44%) and 11 (31%) of the 36 CR pts were event-free for ≥1 and ≥2 yr, respectively. Median numbers of doses were 12.5 and 13.0 for pts with CR who were event-free for ≥1 and ≥2 yr, respectively. All 11 pts with CR who were event-free for ≥2 yr were censored at study end.

Among all pts, the mDOR was 13.4 mo (95% CI: 6.9, -), mPFS 4.9 mo (2.9, 8.3), and mOS 9.5 mo (6.7, 11.5). Among pts with CR, mDOR, mPFS, and mOS were NR (**Figure 1**).

All-grade treatment-emergent adverse events occurring in ≥30% of all pts were increased gamma-glutamyltransferase (42%), neutropenia (40%), and thrombocytopenia (33%).

Conclusions: Among heavily pretreated pts in LOTIS-2, Lonca continued to demonstrate durable, long-term responses in pts with CR with a manageable safety profile; 31% of the 36 CR pts were

Figure 1. Kaplan–Meier curves of (A) progression-free survival and (B) overall survival in the all-treated population and the subset of patients with a complete response (CR)



event-free for ≥2 yr with no evidence of disease and no new anticancer therapy post-Lonca. Further study is needed to identify factors predictive of long-term response to Lonca.

Funding: ADC Therapeutics SA; medical writing: CiTRUS Health Group.

Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies

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138 | LISOCABTAGENE MARALEUCEL (LISO-CEL) VERSUS STANDARD OF CARE (SOC) AS SECOND-LINE THERAPY IN LARGE B-CELL LYMPHOMA (TRANSFORM STUDY): SUBGROUP ANALYSES BY PRIOR THERAPY RESPONSE

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Introduction: The TRANSFORM primary analysis (PA; NCT03575351) confirmed the superior efficacy of liso-cel versus SOC as second-line (2L) therapy in patients (pts) with primary refractory (refr) or early relapsed (rel) large B-cell lymphoma (LBCL) (Abramson et al. *Blood*, 2022). Response to first-line (1L) therapy (refr vs. rel), which was a randomization stratification factor, may influence treatment response. Here, we present results for refr and rel LBCL subgroups from the TRANSFORM PA.

Methods: TRANSFORM is a randomized phase 3 study of liso-cel versus SOC (salvage chemotherapy [CT] followed by high-dose CT [HDCT]/autologous SCT [ASCT]) in adults ≤75 y with LBCL primary refr to or rel ≤12 mo after 1L therapy and eligible for HDCT/ASCT. The primary endpoint was event-free survival (EFS); key secondary endpoints were CR rate, PFS, and OS. In this predefined subgroup analysis, refr was SD, PD, PR, or CR with rel <3 mo after 1L therapy; rel was CR with rel ≥3 mo and ≤12 mo after 1L therapy.

Results: Ninety-two pts were randomized to each arm. Most pts in the liso-cel and SOC arms had refr disease (73% and 76%, respectively; rel disease, 27% and 24%). Baseline characteristics in the refr and rel subgroups, respectively, were generally balanced: median LDH (U/L; liso-cel, 228.5 and 225; SOC, 259 and 259); median SPD (cm^2; liso-cel, 11 and 12; SOC, 15.5 and 18); high-grade B-cell lymphoma (liso-cel, 27% and 16%; SOC, 27% and 9%); diffuse LBCL not otherwise specified (liso-cel, 58% and 56%; SOC, 49% and 73%). Consistent with the overall study population, EFS, CR rate, and PFS favored liso-cel versus SOC in both subgroups (**Table**). Safety was also consistent. Grade ≥ 3 cytokine release syndrome (CRS) and neurological events (NE) were low in refr (1% and 4%) and rel (0 and 4%) subgroups, respectively, with no grade 4/5 CRS or NEs.

Conclusions: In TRANSFORM, liso-cel showed benefits in EFS, PFS, and CR rate versus SOC irrespective of prior response to 1L therapy. As refr LBCL is historically difficult to treat, outcomes for liso-cel in this subgroup are encouraging.

TABLE

	Refr: liso-cel arm (*n* = 67)	Rel: liso-cel arm (*n* = 25)	Total liso-cel arm[1] (*N* = 92)	Refr: SOC arm (*n* = 70)	Rel: SOC arm (*n* = 22)	Total SOC arm[1] (*N* = 92)
EFS[a]	12.0 (6.0–NR)	NR (15.6–NR)	NR (9.5–NR)	2.2 (2.1–2.7)	8.3 (2.9–NR)	2.4 (2.2–4.9)
HR (95% CI)[b]	0.371 (0.244–0.565)	0.294 (0.117–0.739)	0.356 (0.243–0.522)	—	—	—
CR rate, n (%) [95% CI]	46 (69) [56.2–79.4]	22 (88) [68.8–97.5]	68 (74) [63.7–82.5]	23 (33) [22.1–45.1]	17 (77) [54.6–92.2]	40 (43) [33.2–54.2]
PFS[a]	19.2 (6.6–NR)	NR (NR–NR)	NR (12.6–NR)	4.9 (2.3–7.5)	9.0 (6.0–NR)	6.2 (4.3–8.6)
HR (95% CI)[b]	0.441 (0.275–0.708)	0.256 (0.089–0.739)	0.400 (0.261–0.615)	—	—	—
OS[a]	29.5 (22.2–NR)	NR (NR–NR)	NR (29.5–NR)	20.9 (15.1–NR)	NR (17.9–NR)	29.9 (17.9–NR)
HR (95% CI)[b]	0.754(0.447–1.273)	0.535(0.126–2.266)	0.724(0.443–1.183)	—	—	—

[a]Data are median (95% CI), mo;

[b]vs SOC. NR, not reached.

[1]Abramson et al. *Blood*, 2022.

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Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, ongoing trials

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139 | COMPARATIVE ACCURACY OF ALTERNATIVE EARLY MEASURES OF RESIDUAL DISEASE AFTER CAR19 THERAPY OF RELAPSED/REFRACTORY LBCL

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Introduction: Over half of relapsed/refractory large B-cell lymphoma (rrLBCL) patients receiving anti-CD19 chimeric antigen receptor (CAR19) T-cells experience subsequent relapse. Improved methods are therefore needed to predict outcomes, and to accurately measure minimal residual disease (MRD). While PET/CT metabolic response ~4 weeks after CAR infusion is established for such early assessments, several liquid biopsy MRD methods (including IgHTS and CAPP-Seq) have been reported to noninvasively measure responses (Frank et al. *JCO*, 2021; Sworder et al. *ICML-16*). Phased variant enrichment and detection sequencing (PhasED-seq) allows further improved sensitivity to detect circulating tumor-derived DNA (ctDNA) by monitoring of phased-variants (PVs), comprising multiple independent somatic

mutations in individual cell-free DNA fragments. Here, we compared ~week-4 residual disease evaluations by PET/CT, CAPP-Seq, and PhasED-Seq in patients receiving standard of care axicabtagene ciloleucel (axi-cel) CAR19 therapy (Sworder et al., *Cancer Cell*, 2023).

Methods: Tumor or baseline plasma and matched PBMC samples were used to genotype SNVs and PVs, with subsequent evaluation of MRD status in on-treatment samples by CAPP-Seq (SNVs) or PhasED-Seq (PVs). We empirically determined an analytical sensitivity of at least 1:1e5 to result in optimal performance for PhasED-Seq for MRD detection after CAR19. Patients were considered evaluable for such analyses by having week +4 and adequate baseline samples available allowing 1:1e5 analytical sensitivity. PET/CT at week +4 was assessed by Deauville 5-point score per Lugano criteria.

Results: A total of 29 patients were evaluable for all 3 evaluations at week +4 (PET/CT, CAPP-Seq, PhasED-Seq). Patients with detectable MRD by PhasED-Seq at this landmark had inferior event-free survival (EFS) [log-rank $p = 0.00018$, Cox HR = 7.88 (95% CI: 1.9–33.3); **Figure 1A**]. MRD positivity by CAPP-Seq [log-rank $p = 0.0028$, Cox HR = 3.02 (95% CI: 1.4–6.6), **Figure 1B**] and failure to achieve a metabolic complete response (Deauville 1–3) by PET/CT [log-rank $p = 0.015$, Cox HR=2.78 (95% CI: 1.1–6.6); **Figure 1C**] were also associated with inferior EFS, however, PhasED-Seq outperformed both of these methods in predicting clinical outcomes. When considering patients with discordant ctDNA detection between CAPP-Seq and PhasED-Seq at week +4, PhasED-Seq detected ctDNA in an additional 3 patients that ultimately relapsed (**Figure 1D**). Among patients that failed to achieve a complete metabolic response at week +4, PhasED-Seq demonstrated 100% specificity in identifying which of these patients would not experience disease progression **(Figure 1E)**.

Conclusions: Detection of ctDNA MRD using PhasED-Seq is prognostic for outcomes in rrLBCL patients undergoing CAR19 therapy, and has superior performance compared to CAPP-Seq and PET/CT.

Keywords: cellular therapies, diagnostic and prognostic biomarkers, minimal residual disease

Conflicts of interests pertinent to the abstract

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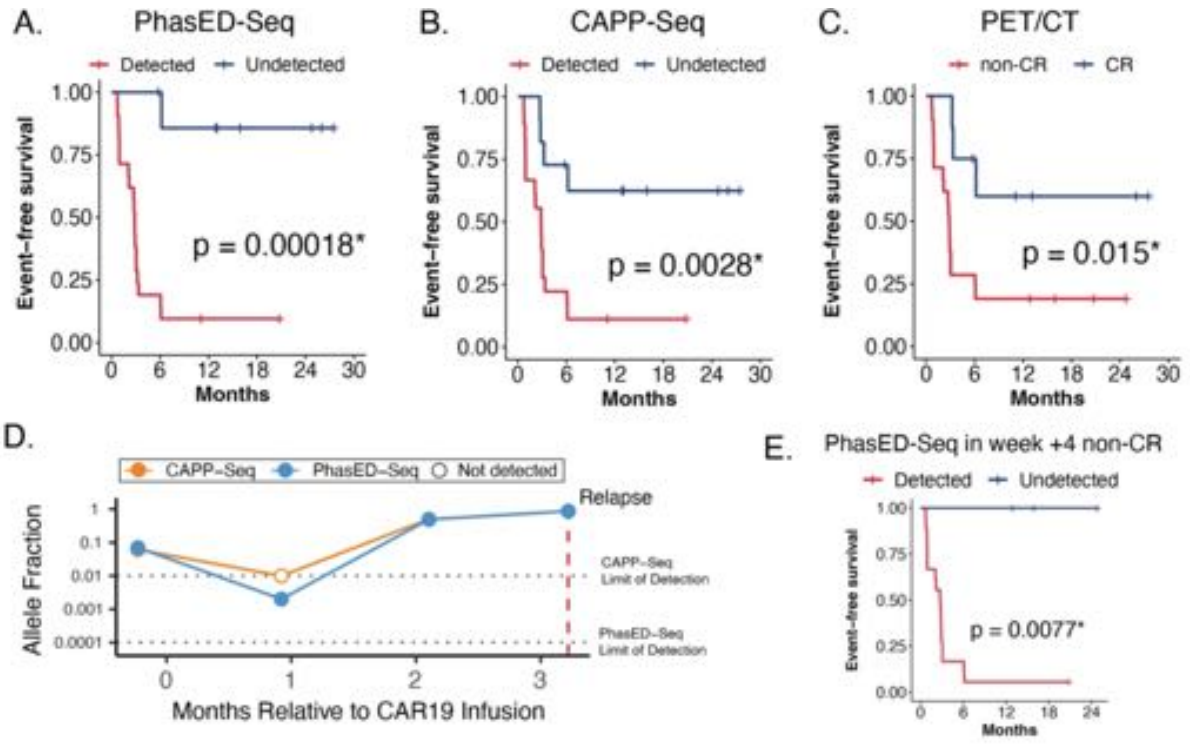

Figure 1 – (A-C) Kaplan-Meier estimates show event-free survival (EFS) for patients stratified by (A) PhasED-Seq MRD detection, (B) CAPP-Seq MRD detection and (C) PET/CT response (CR vs. non-CR) at week +4 following CAR19 infusion. (D) Dynamic changes in mean allele fraction as quantified by PhasED-Seq (blue) or CAPP-Seq (orange) in an exemplar patient in which ctDNA is detected by PhasED-Seq, but not CAPP-Seq, at week +4. (E) Kaplan-Meier estimate shows EFS for patients that did not achieve a complete metabolic response on their week +4 PET/CT, stratified by PhasED-Seq MRD detection. *p<0.05

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Stock ownership: CiberMed Inc., Foresight Diagnostics, FortySeven Inc., CARGO Therapeutics.
Research funding: Celgene, Bristol Myers Squibb, Pfizer

FOCUS ON RADIOTHERAPY

140 | RITUXIMAB-CONTAINING COMBINED MODALITY THERAPY IN LIMITED STAGE FOLLICULAR LYMPHOMA: MATURE FOLLOW UP AND DERIVATION OF A NOVEL PROGNOSTIC SCORE FROM THE TROG99.03 TRIAL

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Introduction: The TROG99.03 represents the only randomised phase III trial of combined modality therapy (CMT) in limited-stage follicular lymphoma 'LSFL', reporting a prolonged progression-free survival (PFS) in the CMT arm (MacManus, *JCO*, 2018). Here, we report extended follow up of this study providing mature data of patients treated with a rituximab-containing CMT regimen and the development of a new gene-expression based prognostic score.

Methods: Patients with LSFL, grade 1–3a were randomised (1:1) to either involved-field radiotherapy alone (IFRT) (30–36Gy) or to CMT consisting of identical IFRT followed by 6 cycles of CVP. Reflecting evolving clinical practice, from 2006 onwards (i.e., 'modern-era'), PET staging was increasingly utilised, and rituximab added to the CMT arm. Digital multiplex gene expression by Nanostring was performed on diagnostic biopsies based on genes previously identified to differentiate LSFL from advanced stage FL 'ASFL' (AM Staiger, *Blood*, 2020).

Results: 150 patients were recruited between 2000 and 2012 with 31/75 patients in each arm recruited in the 'modern-era'. At median follow-up 11.3 years, PFS remained superior for CMT compared to RT (HR 0.6; $p = 0.043$). Although no significant difference in OS was observed (HR 0.45, $p = 0.11$), compared with IFRT, patients in the CMT arm experienced fewer composite (deaths and histological transformation 'HT') events (HR 0.25; $p = 0.045$). With additional

follow up no new non-malignant late toxicities were observed and incidence of secondary malignancies were similar between both arms (11 IFRT vs. 10 CMT, $p = 0.99$).

Patients treated with a rituximab regimen (i.e., IFRT+R-CVP) had a markedly superior PFS compared to those treated without rituximab (i.e., IFRT, or IFRT+CVP), 8 year PFS rates 81% versus 52%, HR 0.42 $p = 0.013$ (Figure 1). Amongst PET staged patients the difference between R-CVP/IFRT versus IFRT increased (HR 0.35 p =0.027) suggesting this effect was not due to stage migration.

No clinical factors were significantly associated with PFS on multivariate analysis. Nor were prognostic associations found for expression level of any individual genes. However, by penalised Cox regression an 8-gene Lasso-weighted prognosticator was identified, termed the 'Bio-LSFL-score'. Genes (*CACNA2D2*, *CD69*, *GZMB*, *IL7R*, *MYCT1*, *SLP1*, *TNFRSF14*, *TNFRSF25*) reflected both B-cells and the microenvironment. The Bio-LSFL-score was highly significant for PFS (HR 0.25, $p < 0.0001$) with 100% patients in the high-risk group relapsing before 8 years.

Conclusions: Particularly when incorporating rituximab, LSFL patients demonstrated significant increases in PFS and reduction in the rates of death and/or HT when treated with CMT compared with IFRT alone. A novel gene expression prognosticator was identified which in this trial cohort showed 'ASFL-like' behaviour by identifying LSFL patients unlikely to experience durable remissions.

Keywords: diagnostic and prognostic biomarkers, indolent non-Hodgkin lymphoma, radiation therapy

Conflicts of interests pertinent to the abstract

C. Cheah

Consultant or advisory role: Roche, Janssen, Gilead, Astra Zeneca, Lilly, TG Therapeutics, Beigene, Novartis, Menarini, Daizai, Abbvie, Genmab, BMS

Research funding: BMS, Roche, Abbvie, MSD, Lilly

J. F. Seymour

Consultant or advisory role: Abbvie, Astra Zeneca, Celgene/BMS, Genentech, Genor Bio, Gilead, Janssen, Morphosys, Roche, Sunesis, TG Therapeutics

Research funding: Celgene/BMS

M. K. Gandhi

Research funding: Beigene, Janssen

141 | RADIOTHERAPY BRIDGING IN LARGE B-CELL LYMPHOMA PATIENTS RECEIVING CD19 CAR-T – THE UK EXPERIENCE

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Background: Radiotherapy (RT) has potential synergistic effects with CAR T but is not widely used as bridging therapy for lymphoma patients due to logistical challenges, uncertainty about patient selection and lack of standardised protocols. Published data on RT bridging are so far restricted to single-centre analyses.

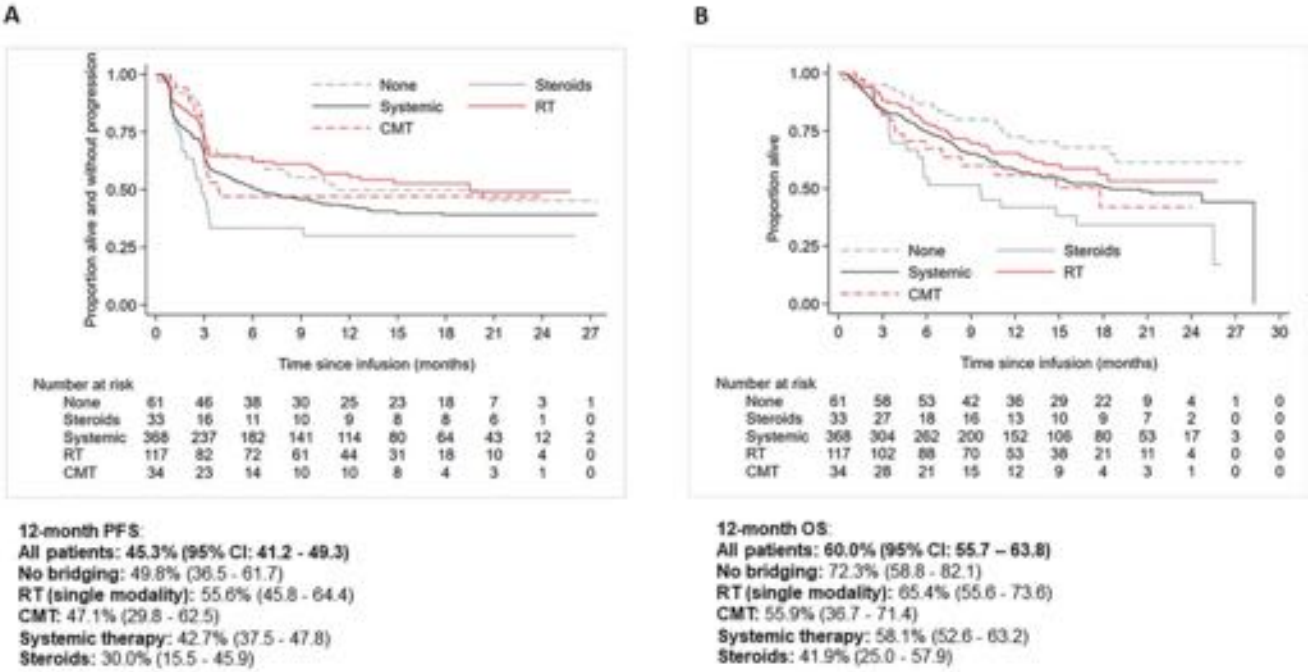
Methods: We analysed RT bridging in a large multi-centre national cohort of large B-cell lymphoma (LBCL) patients approved for 3rd line axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) between December 2018 and October 2022 across 12 UK centres.

Results: Of 763 approved patients, 722 (95%) were leukapheresed, 717 had data available on bridging therapy. 170/717 (24%) received RT bridging, 129 as single modality and 41 as combined modality treatment (CMT). Use of RT bridging varied between centres from 11% to 32%, and increased from 19% (2018–19) to 26% (2021–22; $p = 0.034$).

Median age of RT bridged patients was 60 y. 69% had de novo LBCL, 8% PMBL, 35% tFL and 6% transformed from other low-grade lymphoma. Disease characteristics for RT bridged patients with available data were as follows: 66% advanced stage, 41% bulk, 87% elevated LDH, 42% IPI $\geq$ 3, 17% double/triple hit. Patients given single modality RT were less likely to have advanced stage or $\geq$2 extranodal sites versus those receiving systemic therapy/CMT (61% vs. 85/83% and 18% vs. 30/39%, respectively; $p < 0.05$).

Median time from approval to infusion was 56 days with no difference between bridging modalities. Infusion rates were 88% for RT bridging (vs. 84%, 85%, 85% for no bridging, steroids, or systemic therapy, respectively ($p = 0.41$)). Data on bridging (in-field) response was available for 46 RT patients: 10% CR, 65% PR, 6% SD, 10% PD. Details on RT techniques, anatomical locations and toxicities were

Figure: Progression-free survival (A) and overall survival (B) according to bridging modality.



available for 68 patients and will be provided at the meeting. Doses of 2–39 Gy were used, including combination of multiple doses; 40 patients received IMRT. Only one patient experienced G3–4 toxicity from RT.

The overall incidence of G ≥ 3 CRS was 5.2% and G ≥ 3 ICANS 16.3%, with no significant difference according to bridging approaches. Median follow-up was 16 months. RT bridged patients had favourable outcomes with 1-y PFS of 56% for single modality and 47% for CMT, and 1-y OS of 65% and 56%, respectively (Figure 1). RT bridging was associated with favourable outcomes both in limited and advanced stage (1-y PFS 59% (43—72) and 50% (39–61), respectively.

Conclusion: This is the largest multi-centre cohort of LBCL patients receiving RT bridging prior to CD19 CAR T reported to date. Our results show that RT bridging can be safely and effectively used even in advanced stage and high risk disease, with low dropout rates and excellent outcomes. High-precision, individualised RT protocols allowed successful tumour de-bulking with limited toxicity, providing the basis to develop specific RT bridging protocols in lymphoma.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, radiation therapy

Conflicts of interests pertinent to the abstract

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142 | HIGH RATE OF METABOLIC COMPLETE RESPONSE AFTER LOW DOSE RADIOTHERAPY AND OBINUTUZUMAB IN EARLY STAGE FOLLICULAR LYMPHOMA: INITIAL RESULTS OF THE GAZAI STUDY (GLA 2018-3)

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Introduction: The FORT trial demonstrated a higher complete remission (CR) rate using 12 × 2 Gy compared to 2 × 2 Gy in Follicular Lymphoma (FL) (67% vs. 47%). This benefit resulted also in an improved progression free survival (PFS). The TROG 99.03 trial and the MIR study showed an improved PFS with the addition of Rituximab to radiation therapy of 30–40 Gy in early stage FL. Preclinical data suggest that the anti-CD20 antibody may act synergistic with radiation therapy and therefore enhance the radiation effect of low dose radiotherapy. The prospective, multicentric phase II GAZAI study of the German Lymphoma Alliance (GLA) investigated the efficacy of low dose radiation therapy (2 × 2 Gy) in combination with the anti-CD20 antibody Obinutuzumab in early stage nodal FL. The primary endpoint was the metabolic complete remission at the end of therapy.

Methods: Patients with early stage FL grade 1/2 were recruited in 11 German centers. Ann Arbor stage I or II was confirmed by FDG-PET/CT. Patients received 1000 mg Obinutuzumab flat dose intravenously in weeks 1, 2, 3, 4, 8, 12 and 16. An interim CT scan was performed in week 7 for response evaluation and subsequent treatment planning. Radiation therapy was applied to the initial involved sites (site of diagnostic surgical intervention and PET positive sites) in week 9. The radiation dose was 2 x 2 Gy on two succeeding days. A FDG-PET/CT was performed at the end of therapy in week 18 for evaluation of the metabolic and morphologic response. Minimal detectable/residual disease (MRD) in peripheral blood was monitored at baseline and at week 18 by allel-specific RQ PCR targeting *t*(14;18) translocations and clonal immunoglobulin heavy chain (IGH) rearrangements.

Results: Of 89 patients included in the study, 54 entered the treatment phase showing FDG-PET-positive lymph nodes qualifying for the primary endpoint.

At week 18, metabolic CR (Deauville score (DS) <3) was seen in 46/53 patients (87%; one patient only had a CT without FDG-PET). Partial metabolic remission with a DS 3 was seen in 3 patients (6%) and 3 patients showed a DS 4.

Morphologic (CT based) CR/CRu according to Cheson 1999 criteria was seen in 21/54 patients (39%) at week 7 and in 49/54 patients (91%) at week 18. Morphologic PR was seen in 17 patients (32%) at week 7 and in 4 patients (7%) at week 18; one patient (2%) showed progressive disease (metabolic and morphologic) outside of the radiation field.

13/54 patients (24%) were initially MRD positive. All but one patient converted to MRD negativity at week 18.

Conclusions: Low dose radiation therapy using 2 × 2 Gy in combination with Obinutuzumab is highly effective in early stage FL. Longer follow-up is necessary to investigate if this effectivity also results in a prolonged PFS. Currently, the FORTplus trial is looking for non-inferiority of this regimen in comparison to a conventional radiation dose (12 × 2 Gy) combined with Rituximab.

The research was funded by: Roche Pharma

Keywords: combination therapies, indolent non-Hodgkin lymphoma, radiation therapy

Conflicts of interests pertinent to the abstract

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143 | VERY LOW DOSE RADIATION THERAPY FOR INDOLENT LYMPHOMA: COMPARING "BIG BOOM" (4GY × 1) VERSUS "BOOM BOOM" (2GY × 2)

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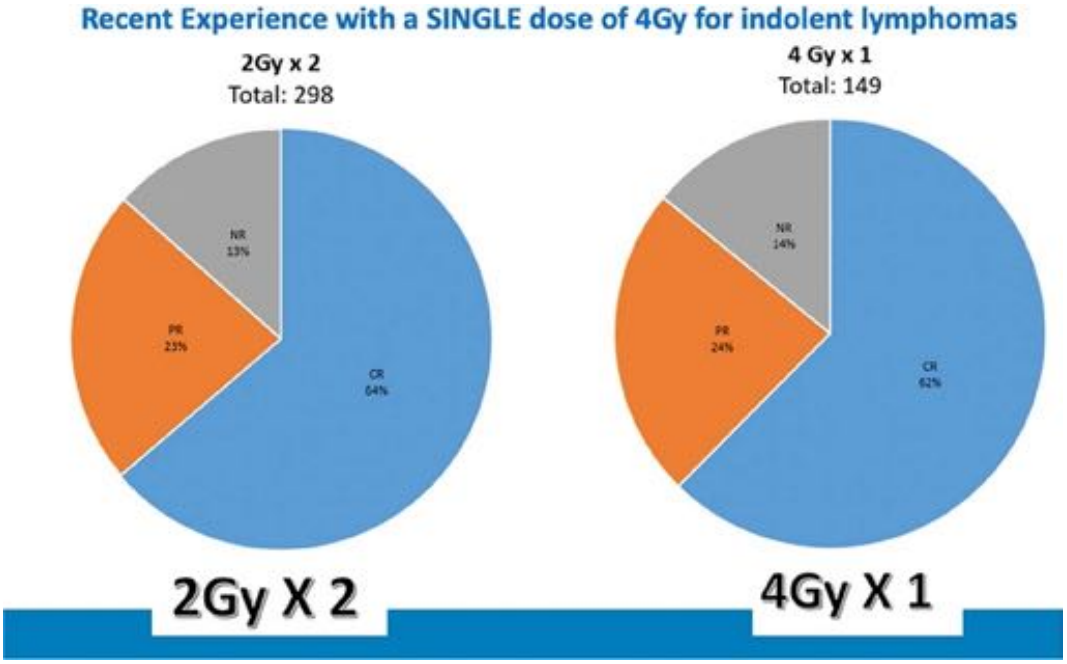
Purpose/Objectives: Indolent lymphomas are exquisitely sensitive to radiation therapy (RT). Programs of 2Gy × 2 were shown to be highly effective in controlling irradiated site(s). During the COVID-19 pandemic, the International Lymphoma Radiation Oncology Group (ILROG) proposed guidelines that offered substitution of the Boom Boom (2Gy × 2) regimen with Big Boom of 4Gy × 1. This report compares our center's experience with both regimens.

Materials/Methods: We included patients with indolent lymphomas in this retrospective single institution study. After April 2020, both options of very low dose and choice of a standard full dose of 24Gy were discussed with the patients. Patients were treated with a definitive or palliative intent depending on disease stage and prior therapy exposure. Patients treated with 24Gy are not included in this report. Overall response rate (ORR) was assessed with Lugano PET criteria at the initial post-RT imaging. Differences between the two groups were examined using the Fisher's exact test and Mann-Whitney test.

Results: We evaluated a total of 471 lesions in 386 patients, including 172 lesions (37%) treated with 4Gy × 1 and 299 lesions (63%) treated with 2Gy × 2. Table 1 summarizes the patient and treatment characteristics. Age at the time of RT and sex were not significantly different between the two groups. The 2Gy × 2 cohort was more likely to have follicular lymphomas (FL) (66% vs. 54%, $p = 0.011$), though the proportion of higher-grade FL was similar between cohorts. The ORR was similar (4Gy × 1 = 86%, 2Gy × 2 = 87%) at the first post-RT evaluation (median of 2 months from RT for both cohorts). There was no significant difference in the rate of complete response, partial response, stable disease, or progressive disease between the cohorts at initial post-RT imaging. For both regimens, no directly related short-term side effects were observed.

Conclusions: Both the 4Gy × 1 and 2Gy × 2 regimens demonstrated excellent ORR at the initial post-RT imaging assessment among patients with indolent lymphomas. While longer term follow-up is

Characteristic	4Gyx1	2Gyx2	*p*-value
Number of patients	136	250	
Number of treated lesions	172	299	
Age at radiation	67 (24, 97)	68 (20, 94)	>0.9
Male Sex	54 (40%)	127 (51%)	0.034
Diagnosis			0.016
FL • FL Grade 3A • FL Grade 3B • FL Grade 1-2	93 (54%) • 7 (4.1%) • 0 • 86 (50%)	197 (6%) • 7 (2.3%) • 2 (0.7%) • 188 (63%)	
Marginal Zone	54 (31%)	80 (27%)	
Other	25 (15%)	22 (7.4%)	
Maximal axial diameter >5 cm			<0.001
• >5 cm • ≤5 cm • Unknown	• 15 (8.7%) • 96 (56%) • 61 (35%)	• 40 (13%) • 259 (87%) • 0	
Time to first follow up (months)	2.37 (0.3, 4.4)	2.1 (0.7, 13.5)	<0.001
Response			
• Complete Response • Partial Response • Progressive Disease • Stable Disease • Not assessed yet	• 93 (62%) • 35 (23%) • 6 (4%) • 15 (10%) • 23	• 190 (64%) • 68 (23%) • 16 (5.4%) • 24 (8.1%) • 1	0.8



required to confirm durability of these findings, our initial experience suggests that 4Gyx1 regimen recommended by ILROG during the pandemic is an effective treatment approach.

Keywords: indolent non-Hodgkin lymphoma, radiation therapy

No conflicts of interests pertinent to the abstract.

144 | SALVAGE RADIOTHERAPY IN RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA AFTER CAR T-CELL THERAPY FAILURE

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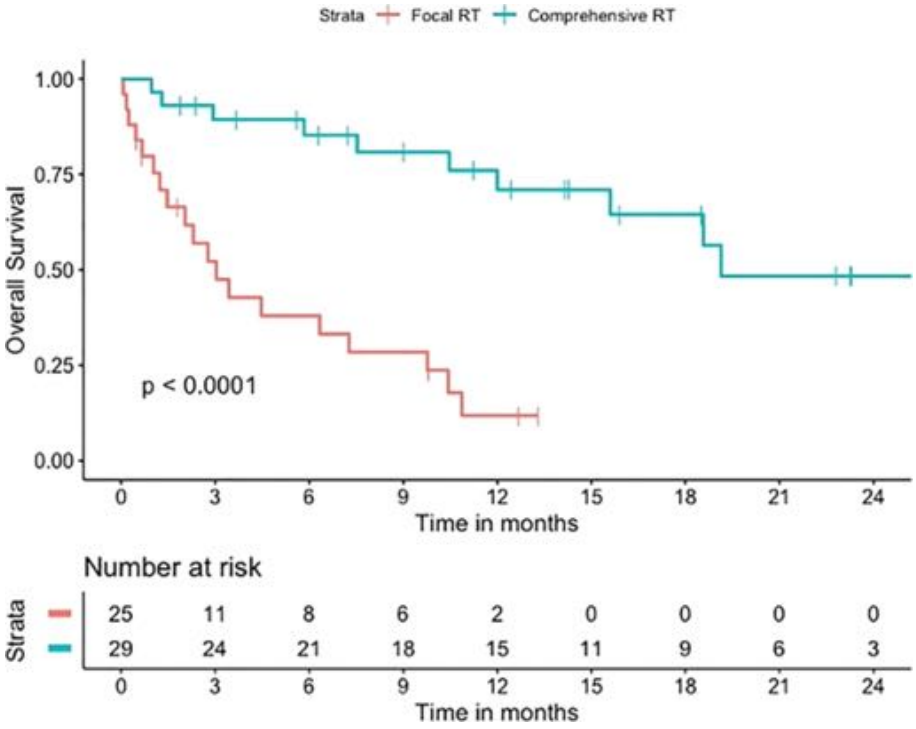
Introduction: We sought to describe our experience with salvage radiation therapy (RT) relative to other therapies in patients with relapsed/refractory large B-cell lymphoma (LBCL) post-CD19-targeted chimeric antigen receptor (CAR T)-cell therapy failure.
Methods: A multi-institutional retrospective study was conducted in a database of 352 consecutive LBCL patients who received axi-cabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) between 2017 and 2021. Patients who relapsed following CAR T-cell therapy and received salvage therapies (RT alone, systemic therapy alone, or combined modality therapy [CMT]) were identified and analyzed. A separate analysis was then conducted for patients who were treated with comprehensive versus focal RT.
Results: A total of 120 patients with post-CAR T relapsed LBCL received salvage therapies (RT alone, 14 patients; CMT, 40 patients; systemic therapy alone, 66 patients). The median follow-up after CAR T-cell infusion was 10.2 months (interquartile range [IQR]: 5.2–20.9 months). Failure occurred in previously involved sites prior to CAR T-cell therapy in 78% of patients ($n = 93$). The median time from CAR T-cell therapy infusion to the start of salvage therapy was 3.4 months (IQR: 1.7–6.5 months). A total of 93 sites were irradiated among the 54 patients who received RT in the RT and CMT cohorts. The median dose/fractionation were 30 Gy (range 4–50.4 Gy) and 10 fractions (range 1–28 fractions). The 1-year local control (LC) rate for the 81 assessable sites was 84%. The median overall survival (OS) from the time of salvage therapy was not reached for the RT group, 10.5 months for the CMT group, and 6.6 months for the ST group ($p = 0.4$). The median OS from the start date of RT was significantly higher among patients who received comprehensive RT versus focal RT (19.1 months vs. 3.0 months, $p \leq 0.001$); 26 of the 29 patients who received comprehensive RT had only a single site of disease, but survival for the 3 patients with >1 site of disease was not statistically different ($p = 0.17$). Receipt of bridging therapy and CAR T construct were not significantly associated with OS after CAR T infusion. On multivariate survival analysis, achieving PR or CR post-CAR T (HR = 0.5, 95% CI: 0.3–0.9, $p = 0.01$) was independently associated with superior OS.



Conclusion: RT provides excellent local control for LBCL relapsed post-CAR-T cell therapy. Patients with limited disease burden who were treated with comprehensive RT had favorable OS relative to patients with more extensive disease who received focal RT. Future prospective studies should investigate combination of RT with other novel strategies, including lenalidomide, polatuzumab vedotin, loncastuximab tesirine, bispecific antibodies, and/or consolidation with allogeneic HSCT to optimize patient outcomes.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, radiation therapy

No conflicts of interests pertinent to the abstract.

145 | BONE MARROW VOLUME IRRADIATED AND RISK OF CYTOPENIAS IN AGGRESSIVE B-CELL LYMPHOMA PATIENTS BRIDGED WITH RADIATION THERAPY FOR CART CELL THERAPY

G. S. Manzar, B. S. Dabaja, S. Y. Wu, L. F. Nasr, S. O. Dudzinski, A. K. Yoder, K. L. Corrigan, J. R. Gunther, S. Ahmed, M. Spiotto, E. J. Shpall, Y. Nieto, M. Daher, H. Rafei, N. Sainai, S. A. Srour, R. Nair, J. Westin, S. S. Neelapu, R. E. Steiner, L. Nastoupil, C. C. Pinnix, P. Strati, P. Q. Fang

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Introduction: Patients (pts) with aggressive B cell lymphomas undergoing anti-CD19-directed chimeric antigen receptor T cell therapy (CART) can benefit from bridging radiation therapy (bRT) as immune priming. Previously, by measuring the bone marrow (BM) volume irradiated in multiple myeloma pts, we established that RT does not adversely affect stem cell collection.[1] Here, we examined the impact of irradiated BM distribution on the risk of acute cytopenias after bRT prior to CART.

Methods: We retrospectively reviewed adults with DLBCL between 2017 and 2022 who received bRT prior to CART, which included axicabtagene ciloleucel, tisagenlecleucel, or lisocabtagene maraleucel. Clinical characteristics, labs, and response were extracted. RT plans were reviewed; % BM irradiated was calculated as described previously with published estimates of skeletal BM distribution.[2] Progression free survival (PFS), disease specific survival (DSS) and overall survival (OS) were modeled using the Kaplan-Meier method. Binary logistic regression and Mann-Whitney U correlated RT distribution with cytopenias (anemia, thrombocytopenia, and neutropenia per CTCAE v4.03).

Results: Fifty-one pts received bRT, of which 13 (25.5%) had bulky disease (≥10 cm). Majority received bRT alone; 16 (31.4%) were additionally bridged with systemic therapy. The median bRT was 30 Gy (range: 4–48 Gy) and 26 pts (51%) pts received ≥30 Gy. Thirty-one pts (61%) received bRT comprehensively to all disease sites. The incidence of ≥Grade 3 cytopenias in timepoints following bRT are shown below.

		0 day post-RT	1 wk post-RT	1 mo post-RT	3 mo post-RT
Grade 3	Anemia (Hgb <8 g/dL)	4.8%	22.2%	42.0%	25.6%
	Thrombocytopenia (Plt <50k)	11.9%	26.7%	50.0%	34.9%
	Neutropenia (ANC <1000)	11.9%	31.8%	61.2%	41.9%
	Any cytopenia	19.0%	46.7%	70.0%	60.5%

The median cumulative % of BM irradiated was 5.05% (range: 0%–50%). Nine pts (18%) received bRT encompassing ≥15% of the BM, for whom there was no increased incidence of ≥Grade 3 cytopenias overall (as well as specifically anemia, thrombocytopenia, and neutropenia) at any timepoint (all $p > 0.2$). Receipt of RT comprehensively to all disease sites, or bridging with both RT + systemic therapy, or delivery of ≥30 Gy bRT did not correlate with the incidence of ≥Grade 3 cytopenias at any timepoint.

Regarding outcomes, 26 pts (51%) had CR at 30 days post-CART. Sixteen had PR (31.4%), and 9 pts (17.6%) had PD or SD. The OS/PFS were 84% (71–92)/78% (64–87) at 1 year, and 59% (44–71)/57% (42–70) at 2 years. Twenty-seven pts (52.9%) remain alive at last follow-up, 19 (70.4%) of whom have no evidence of disease.

Conclusions: bRT is not associated with increased incidence of cytopenias, even for doses ≥30 Gy, when encompassing ≥15% of the BM, or when pts are treated comprehensively to all disease sites. While bRT can be delivered safely, we still urge careful field design to ensure minimum BM is treated to incorporate into pre-CART regimens.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, radiation therapy

Conflicts of interests pertinent to the abstract

R. E. Steiner

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FOCUS ON LYMPHOMA MICROENVIRONMENT

146 | IMMUNE CONTEXTURE ANALYSIS IN POLARIX SUGGESTS RESPONSE TO POLA-R-CHP TREATMENT REDUCES TUMOR MICROENVIRONMENT DEPENDENCY

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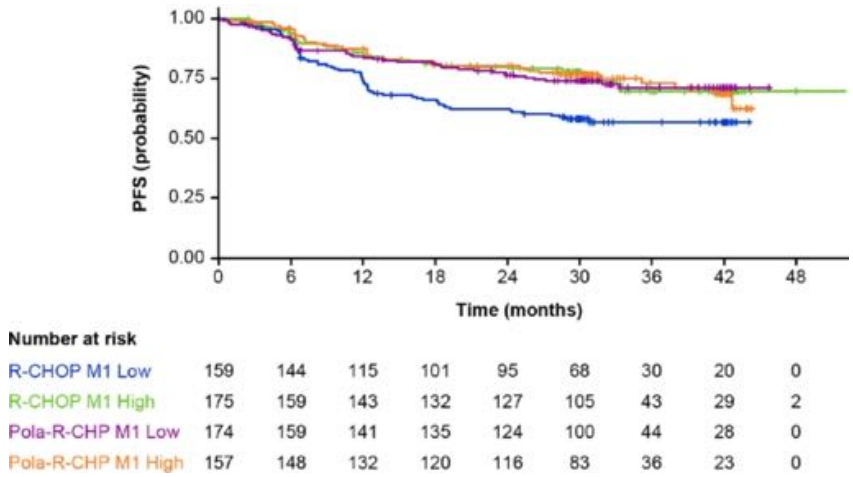
Introduction: The lymphoma microenvironment contributes to clinical treatment outcome. Previously, we showed that enrichment in M1 macrophages was associated with improved clinical outcome in patients with diffuse large B-cell lymphoma (DLBCL) treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; Yan et al., 2020). In the POLARIX study (NCT03274492), polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) demonstrated prolonged progression-free survival (PFS) versus R-CHOP in patients with previously untreated DLBCL (Tilly et al., 2022). Here, we investigate the relationship between the lymphoma microenvironment at baseline and clinical outcomes in patients treated with Pola-R-CHP or R-CHOP in POLARIX.

Methods: Global gene expression patterns of baseline tumor biopsies from patients treated with Pola-R-CHP or R-CHOP in POLARIX were generated by RNA-seq. Immune and stromal cell tumor content was estimated using the xCell and QuanTIseq algorithms. Association of the infiltration scores with PFS was evaluated. Hazard ratios (HR) were adjusted for International Prognostic Index score (2 vs. 3–5), age (≤60 vs. >60 years), and cell of origin (activated B cell, germinal center B cell, unclassified, unknown).

Results: Gene expression data were generated from 665 patients in POLARIX (Pola-R-CHP, $n = 331$; R-CHOP, $n = 334$). M1 macrophage infiltration levels were comparable between treatment arms. Quantity of M1 macrophage infiltration was the primary immune-related positive prognostic factor for PFS in patients treated with R-CHOP. High levels (above median) of M1 macrophages were associated with improved PFS when quantified by either QuanTIseq (HR 0.60, 95% confidence interval [CI]: 0.41–0.88) or xCell (HR 0.57, 95% CI: 0.39–0.84). In contrast, M1 macrophage infiltration did not impact clinical activity of the Pola-R-CHP regimen when quantified by either QuanTIseq (HR 0.90, 95% CI: 0.58–1.38) or xCell (HR 0.95, 95% CI: 0.62–1.46); the treatment benefit in patients with lymphomas with low M1 macrophage levels was similar to that of patients with high



M1 macrophage levels (**Figure**). Enrichment in various immune infiltrates was linked to either improved or poor survival outcomes in the R-CHOP arm; however, PFS appeared to be largely independent of immune infiltration in the Pola-R-CHP arm.

Conclusions: Our results confirm that the efficacy of R-CHOP is associated with a specific lymphoma microenvironment. M1 macrophage levels are the primary positive predictors of treatment outcome. In contrast, Pola-R-CHP may achieve therapeutic responses in patients who lack a favorable immune contexture, suggesting Pola-R-CHP can decouple treatment outcome from the lymphoma microenvironment, likely due to its distinct mechanism of action.

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Keywords: aggressive B-cell non-Hodgkin lymphoma, targeting the tumor microenvironment

Conflicts of interests pertinent to the abstract

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147 | SPATIALLY-RESOLVED TRANSCRIPTOMICS DEFINE CLINICALLY RELEVANT SUBSETS OF MACROPHAGES IN DIFFUSE LARGE B-CELL LYMPHOMA

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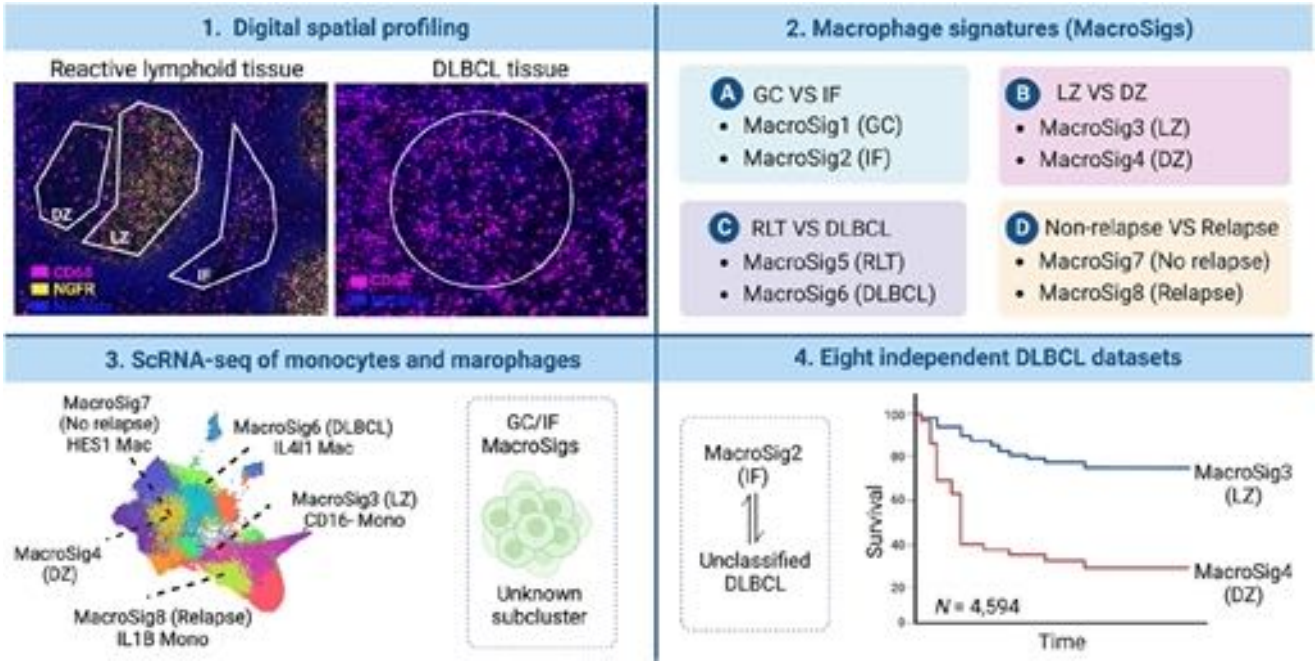
Introduction: Tumor-associated macrophages (TAMs) are abundant immune cells in the microenvironment of diffuse large B-cell lymphoma (DLBCL) and are implicated in tumor progression and therapy resistance. Conventional immunohistochemistry-based studies have



relied on the oversimplified M1/M2 classification of TAMs which does not fully capture the functional diversity of macrophage biology, thus potentially contributing to their inconsistent prognostic significance in DLBCL. Spatial whole-transcriptomic analysis allows in-depth investigation of specific cell types in different spatial regions within normal and malignant lymphoid tissues, enabling detailed macrophage phenotyping. Here, we employed spatial whole-transcriptomic analysis in the characterization of CD68+ cells of DLBCL and reactive lymphoid tissues (RLTs) to identify novel macrophage subsets with biological and clinical significance.

Methods: Digital spatial profiling with whole-transcriptomic analysis of CD68+ cells was performed in 47 DLBCL and 17 RLTs, to define macrophage signatures (termed "MacroSigs") of distinct lymphoid spatial niches and clinical scenarios. Eight independent DLBCL datasets (4594 patients) with complete transcriptomic and survival information were used for validation of these spatial-derived MacroSigs.

Results: Digital spatial profiling revealed previously unrecognized transcriptomic differences between macrophages populating distinct spatial compartments in RLTs (light zone (LZ)/dark zone (DZ), germinal center (GC)/interfollicular (IF) regions), and in between disease states (RLTs and DLBCL with or without relapsed disease). This transcriptomic diversity of macrophages was categorized into eight MacroSigs. Spatial-derived MacroSigs associate with specific cell-of-origin (COO) subtypes of DLBCL, of particular interest being the IF-MacroSig enriched in the unclassified COO ($p < 0.005$, 6/8 datasets). MacroSigs of relapsed-DLBCL and DZ were prognostic for shorter overall survival in multiple datasets ($p < 0.05$ in 5/8 datasets; $p < 0.05$ in 8/8 datasets, respectively). Projection onto a macrophage single-cell RNA-sequencing atlas reveals the Non-relapse-DLBCL MacroSig to depict HES1/FOLR2-like macrophages, while relapse-DLBCL-MacroSig represents IL1B-like monocytes, with unique therapeutic vulnerabilities for each.

Conclusions: This study first provides the spatially-resolved macrophage whole-transcriptomic analysis in reactive and malignant lymphoid tissues. Gene expression signatures of macrophages in the DZ of GC and from relapsed-DLBCL samples are consistently prognostic for survival in multiple datasets and offer insights into novel therapeutic strategies for DLBCL.

The research was funded by: Work in ADJ's laboratory is funded by a core grant from the Cancer Science Institute of Singapore, National University of Singapore through the National Research Foundation Singapore and the Singapore Ministry of Education under its Research Centres of Excellence initiative. CT was supported by the Italian Foundation for Cancer Research (AIRC) Investigator Grant IG ID.22145; 5 × 1000 Grant ID.22759.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

148 | COORDINATED CHANGES IN THE TUMOR MICROENVIRONMENT (TME) ARE ASSOCIATED WITH INCREASED RISK OF THERAPEUTIC FAILURE IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Introduction: Despite advances, 20%–40% of patients with DLBCL do not achieve remission or relapse after an initial response. We aimed to identify immunological factors associated with early clinical failure in DLBCL.

Methods: Patients with DLBCL treated with rituximab and anthracycline-based chemotherapy were prospectively enrolled in the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE). Tissue microarrays (TMAs) containing specimens from diagnosis were analyzed using the Digital Spatial Profiling (DSP) system quantifying expression of 58 proteins (Figure 1A). Event-free survival (EFS) was defined as time from diagnosis to relapse, progression, or death from any cause. Patients with EFS of at least 24 months were classified as achieving EFS24. Following normalization, logistic regression was performed on DSP data to adjust for IPI and cell of origin. Multiplex immunofluorescence (MxIF) using the CODEX system was performed on a biopsy specimen from a representative patient. Machine learning models were used for cell segmentation and classification (Figure 1B).

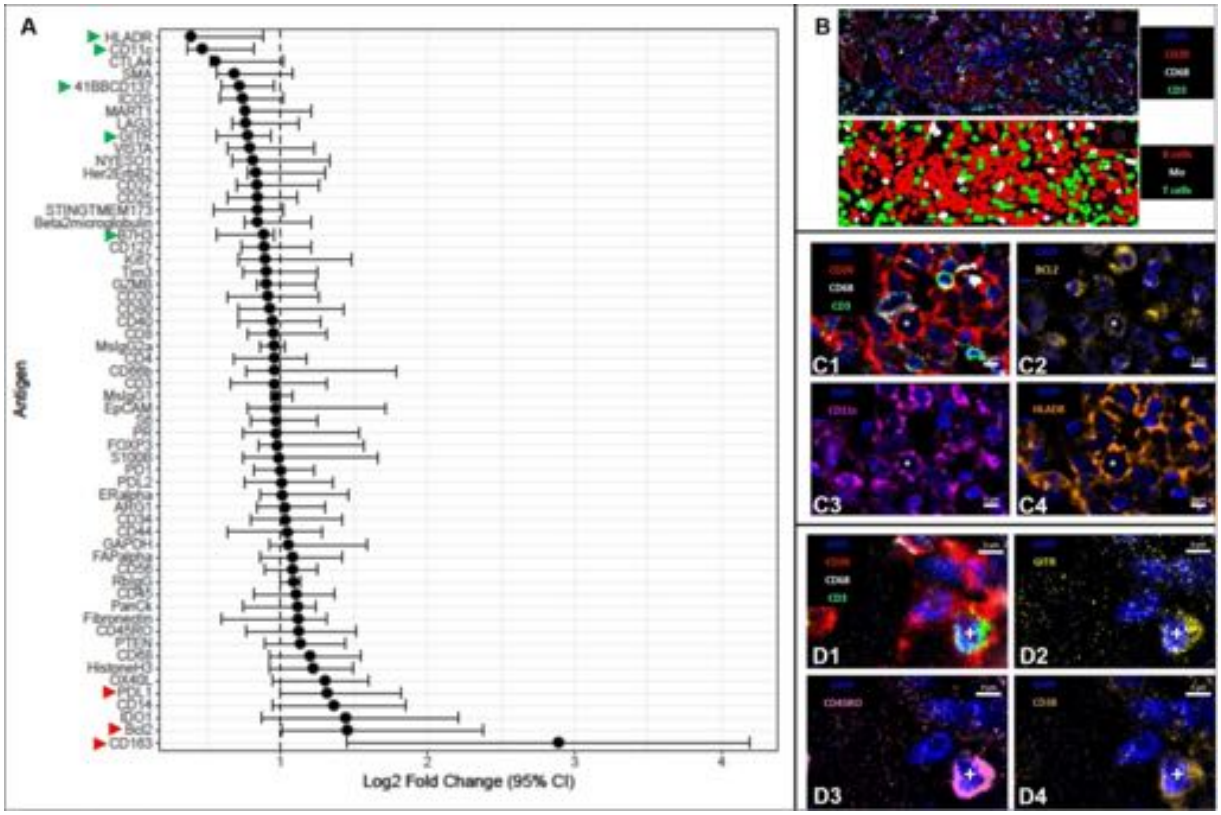
Results: Specimens from 446 DLBCL patients were available on TMAs, of which 321 (72%) achieved EFS24. DSP data was acquired in 395 unique DLBCL patients and showed that increased expression of CD163 (Log2FC = 2.9; $p = 0.0009$), BCL2 (Log2FC = 1.4; $p = 0.047$), and PDL1 (Log2FC = 1.3; $p = 0.05$) were significantly associated with increased risk of EFS24 failure (Figure 1A, red arrows). Conversely, increased expression of CD11c (Log2FC = 0.5; $p = 0.003$), HLA-DR (Log2FC = 0.4; $p = 0.01$), CD357/GITR (Log2FC = 0.8; $p = 0.01$), CD137 (Log2FC = 0.7; $p = 0.02$), and B7H3 (Log2FC = 0.9; $p = 0.02$) were significantly associated with decreased risk of EFS24 failure (Figure 1A, green arrows). A total of 3004 single cell events were acquired using MxIF, of which 55% were classified as B cells, 17% as T cells, 8% as macrophages, and 20% as other cells. Within B cells, 81% were classified as HLA-DR+, 73% as CD11c+, 54% as BCL2+, while; 45% were positive for all 3 antigens (Figure C1–4). GITR expression was confirmed in 3% of T cells and showed a memory (CD45RO+), activated (CD38+) phenotype (Figure D1–4).

Conclusion: Increased expression in the TME of proteins associated with antigen presentation (HLA-DR), cell adhesion (CD11c), and effector cell activation (CD137, GITR, B7H3) are associated with favorable outcomes in DLBCL. Conversely, increased expression of proteins associated with suppression of apoptosis (BCL2), effector cell suppression (PDL1), and M2 macrophages (CD163) are associated with early clinical failure. Using MxIF, we localize the expression of HLADR, CD11c, and BCL2 to tumor cells while confirming expression of GITR in activated memory T cells. These findings suggest a coordinated immunological basis for therapeutic failure in DLBCL and offers rationale for modulation of these targets in this disease.

The research was funded by: Department of Defense (DOD), Lymphoma Research Foundation (LRF), National Cancer Institute (NCI)

Keywords: aggressive B-cell non-Hodgkin lymphoma, genomics, epigenomics, and other -omics, microenvironment

No conflicts of interests pertinent to the abstract.



149 | EZH2 INHIBITION ENHANCES CAR T ANTITUMOR EFFECT BY INDUCING LYMPHOMA IMMUNOGENICITY AND ENHANCING T CELL FUNCTION

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Introduction: Despite recent successes with CAR T-cell therapy against CD19 in patients with B-celllymphomas, only ~30%–40% of DLBCL and FL patients maintain a durable complete long-term remission, and over half of the patients will ultimately relapse. Several factors contribute to the lack of response or relapse, including tumor cell-intrinsic factors, an immunosuppressive tumor microenvironment (TME), and CAR T-cell dysfunction. DLBCL and FL depend on EZH2 for their proliferation and survival. Somatic gain-of-function mutations of EZH2 ($EZH2^{Y641X}$, found in 20%–30% FL and GCB-DLBCL) drive lymphomagenesis at least in part through generating immune evasive phenotypes. Of note, EZH2 inhibitors have potent activity against both wild type and mutated EZH2 FL and DLBCL patients. EZH2 also modulates the TME by increasing Tregs and repressing memory-related transcription factors in CD8 T-cells.
Methods: To explore the effects of EZH2 inhibition and immunotherapy in a relevant physiological context, we developed and exhaustively characterized a genetically engineered mouse model (GEMM)—designed for conditional expression of EZH2Y641F and overexpression of BCL2 ("EZB") in germinal center (GC) B-cells—, that recapitulates low-grade human FL with their immune microenvironment. We further generated murine GC B lymphoma cell lines from these GEMM, which develop immune-depleted aggressive DLBCL when adoptively transferred into immunocompetent mice. To investigate CAR T-cell-mediated tumor killing in human cells in combination with EZH2i tazemetostat, we used the GCB-DLBCL cell lines SUDHL4 ($EZH2^{Y641F}$), OCI-Ly18 and Toledo (WT EZH2).
Results: In vivo tazemetostat treatment of EZB GEMM significantly reduced EZB lymphoma B-cells ($p < 0.05$) and increased of $CD4^+$ and $CD8^+$ cells ($p < 0.05$), while reducing Tregs ($p < 0.01$). We found that EZH2i not only directly affected T-cells, but also increased the immunogenicity of EZB lymphoma cells. Pre-treatment of GEMM-derived EZB murine cell line with tazemetostat significantly increased murine CD19 CAR T-cells ability to kill lymphoma B-cells both in vitro and in vivo. Furthermore, tazemetostat pre-treatment of human GCB-DLBCL cell lines increased CAR T tumor killing and avidity, reflecting a superior CAR T-cell efficiency in binding to cancer cells. Strikingly, exposure of murine CAR T-cells to EZH2i enhanced in vivo CAR T tumor killing by increasing memory CAR T and inhibiting exhaustion. In summary, we show that EZH2i enhances CAR T antitumor effect by inhibiting lymphoma cells growth, inducing lymphoma immunogenicity and ability to synapse with T-cells, modulating the TME and enhancing T-cell function.
Conclusions: We have elucidated a novel strategy to improve CAR T immunotherapy by combining with epigenetic therapy to modulate lymphoma B-cells, CAR T and the TME, that can significantly improve the clinical outcomes of DLBCL and FL patients.

The research was funded by: NIH, Leukemia & Lymphoma Society, The Follicular Lymphoma Foundation, Lymphoma Research Foundation

Keywords: genomics, epigenomics, and other -omics, immunotherapy, microenvironment

Conflicts of interests pertinent to the abstract

M. Ruella
Employment or leadership position: Dr. Ruella has patents related to CART that are managed by the University of Pennsylvania

150 | SINGLE CELL ANALYSIS REVEALS IMMUNE DYSFUNCTION IN LARGE B CELL LYMPHOMA (LBCL) PTS WITH HYPOMAGNESEMIA RECEIVING AXI-CEL: RESULTS FROM ZUMA-1 TRIAL AND MAYO CLINIC COHORT

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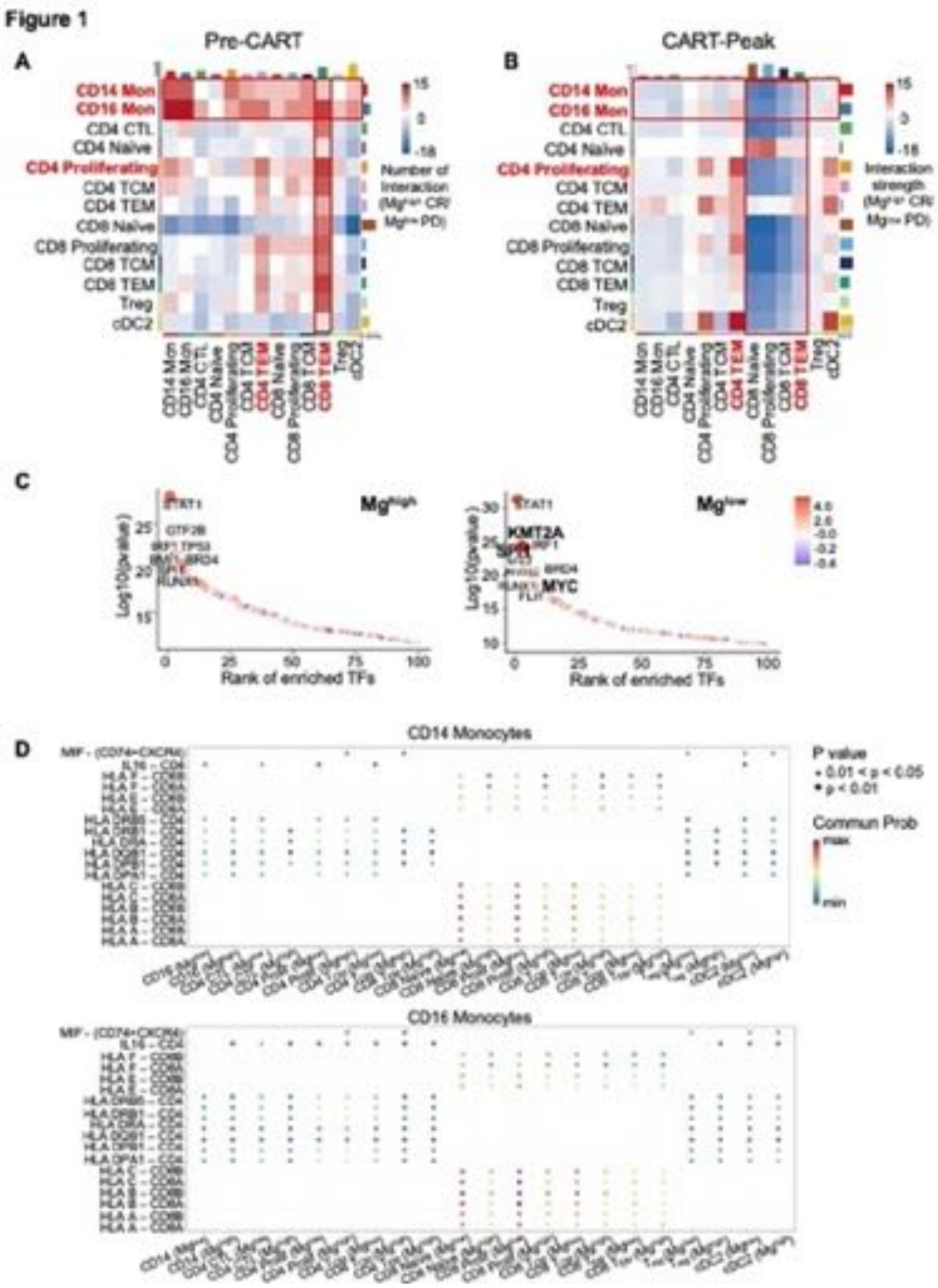
Introduction: Magnesium (Mg) plays a critical role in modulating immune surveillance. While the prognostic impact of hypomagnesemia in patients (pts) with LBCL undergoing stem cell transplant is established, little is known of its role in CART-cell therapy.
Methods: We investigated the effects of Mg levels before lymphodepletion (LD) in 108 relapsed/refractory LBCL pts enrolled in the ZUMA-1 trial and in an independent cohort of 57 LBCL pts receiving axicabtagene ciloleucel (Axi-cel) at Mayo Clinic.
Results: The two groups had similar characteristics. In ZUMA-1, 21% pts had Mg levels lower than 1.7 mg/dL (Mg^{low}), 45% within normal range (Mg^{nl}) and 34% had a high level (Mg^{high}). The Mayo Clinic cohort showed a similar distribution, with 21% Mg^{low}, 53% Mg^{nl} and 26% Mg^{high}. In ZUMA-1, the ORR was 65%, 83% and 92% in the Mg^{low}, Mg^{nl} and Mg^{high} groups ($p = 0.03$). Lower Mg associated with inferior PFS ($p = 0.022$) and OS ($p = 0.001$). Similar results were observed in the Mayo Clinic cohort. Of note, the Mg^{low} group had a higher level of inflammatory cytokines (e.g., IL-6, IL1a, IL-8 and MIP1a), suggesting an immune modulatory effect. To explore the

impact of different Mg levels on immune response, we performed single-cell RNA-seq of peripheral blood cells collected before LD (Pre-CART) and at CART peak. Using CellChat analysis, we found that at Pre-CART pts with Mg^{high} had a higher number of interactions between CD16 and CD14 monocytes and between these cells with CD4 and CD8 T cells compared to those with Mg^{low}. Similarly, CD8 T effector memory (T_{EM}) cells had an increased number of interactions with CD4 cells and CD16 monocytes (Figure **1A)**. Remarkably, at CART peak the same interactions decreased dramatically in pts with Mg^{high}. There was a profound decrease in the interaction strength of all CD8 T cell subsets and T_{EM} cells in the Mg^{high} group (Figure 1B). In contrast, pts with Mg^{low} had significantly increased interactions between CD8 T cells and CD14 monocytes. A transcription factors analysis identified a significant enrichment for *SPI1*, which plays an essential role for monocyte differentiation, in Mg^{low} compared to those Mg^{high} pts. There was also an enrichment of the histone methyltransferase *KMT2A*, which may alter the chromatin accessibility to allow transcription factors binding and gene activation.



Moreover, Mg^{low} pts showed an upregulation of the proto-oncogene *MYC*, which favors cell growth and orchestrates changes in the tumor microenvironment (Figure **1C**). Finally, we performed ligand-receptor analyses which identified a significant downregulation of the interaction of multiple HLA subtypes of CD8 T cells with CD14 and CD16 monocytes, CD4 and CD8 T_{EM} cells in Mg^{high} compared to Mg^{low} pts (Figure **1D)**

Conclusion: Hypomagnesemia is prognostic and associated with altered monocytes to T cell interactions in pts with LBCL receiving CART cells, however whether optimizing Mg levels would improve CART efficacy remains unknown.

The research was funded by: the University of Iowa/Mayo Clinic Lymphoma SPORE CA97274; Mayo Clinic Center for Individualized Medicine, Bernard E. and Edith B. Waterman, Henry J. Predolin Foundation

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

151 | FOLLICULAR LYMPHOMA PATIENT-DERIVED ORGANOIDS FOR BISPECIFIC T-CELL ENGAGER IMMUNOTHERAPY

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Introduction: The follicular lymphoma tumor microenvironment (FL TME) is critical for FL maintenance and associated with clinical outcomes (Tobin et al. JCO, 2019). Novel immunotherapies including bispecific T-cell engagers require an intact TME for immune effector function and cannot be modeled in traditional B-cell monocultures. Organoid systems in non-lymphoid cancers have been proposed as accurate ex vivo models of the TME. We therefore developed a robust patient-derived lymphoma organoid (PDLO) system utilizing primary biopsies from FL patients and assessed response to bispecific T-cell mediated immunotherapy.

Methods: Surgical lymph node biopsies were obtained at diagnosis or relapse, mechanically dissociated into single cell suspensions, cryopreserved, and later prepared as PDLOs on a high-throughput 96-well platform previously developed with human tonsils (Wagar et al. Nature Med, 2021, Figure **A**). PDLOs were assessed at serial timepoints by a multi-modal approach including flow cytometry, CAPP-Seq DNA sequencing, bulk RNA sequencing, immune cell deconvolution with CIBERSORTx (Newman et al. Nat Biotech, 2019), and repertoire profiling of B- and T-cell receptors. For treatment experiments, bispecific antibody (CD19:CD3; HD37 (Anti-CD19); L2K-07 (Anti-CD3); InvivoGen) or corresponding unconjugated monospecific antibodies were added on D4 at a final concentration of 100 ng/mL.

Results: We studied 11 primary specimens including 3 with evidence of transformation (tFL). FL PDLOs formed aggregate clusters similar to healthy tonsil organoids with most viable for 21+ days. Although variable across samples, the proportion of malignant B-cells by flow cytometry remained largely stable (Figure **B**) as did CD4/CD8/Tfh T-cell subsets (Figure **C**,**D**). We assessed mutations pre-culture and at D7/14/21, with mutational stability over 21 days suggesting against strong selective pressure in untreated cultures (Figure **E**).

To assess immunotherapy response, we treated at D4 with CD19:CD3 bispecific antibody or unconjugated anti-CD19 and anti-CD3 as "Control". At D11 treatment with CD19:CD3 induced significant B-cell killing as assessed by flow cytometry and CIBERSORTx, along with expansion in CD8+ effector and regulatory T-cells (Figure **F**). Although total CD4+ T-cells remained stable, an increase in activated subsets was seen during treatment (Figure **G**,**H**). Confirming lymphoma killing, monoclonal BCR was reduced in bispecific-treated cultures (Figure **I**). Treated PDLOs showed significant RNA upregulation of *TIGIT*, *LAG3*, *CTLA4*, and *PD1* (Figure **J**) consistent with T-cell exhaustion associated with continuous bispecific exposure (Philipp et al. Blood, 2022). Data for CD20:CD3 and cell-specific correlates of response will be presented.

Conclusions: FL PDLOs allow ex vivo modeling of T-cell mediated immunotherapies with B-cell killing, activated T-cell expansion, and T-cell exhaustion signatures. PDLOs represent a promising strategy for preclinical evaluation of immunotherapies relying on the TME, and for modeling tumor-intrinsic and -extrinsic mechanisms of resistance.

Keywords: immunotherapy, microenvironment, patient-derived xenograft (PDX) models

Conflicts of interests pertinent to the abstract

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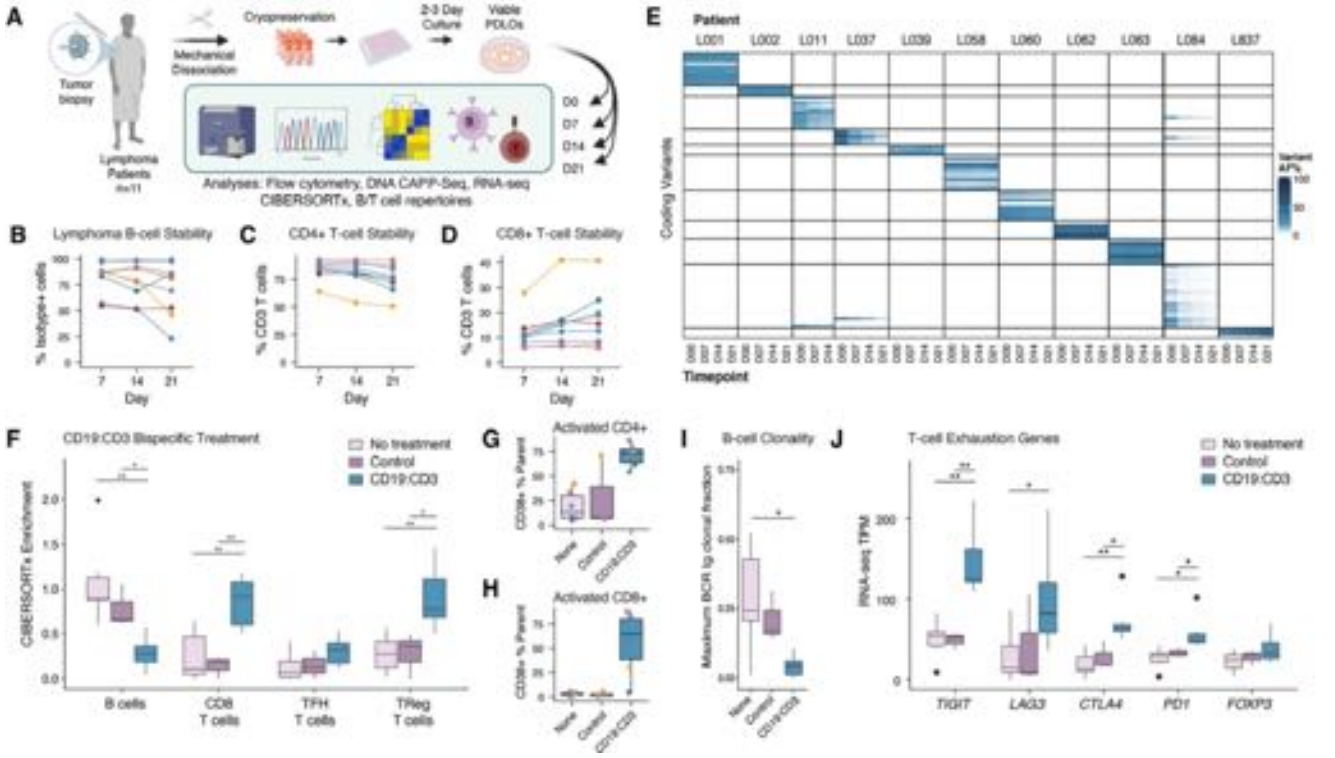

FOCUS ON LONG TERM RESULTS OF CLL TRIALS

152 | 5-YEAR (Y) FOLLOW-UP OF A PHASE 2 STUDY OF IBRUTINIB PLUS FLUDARABINE, CYCLOPHOSPHAMIDE, RITUXIMAB (IFCR) AS INITIAL THERAPY FOR YOUNGER CLL PATIENTS (PTS)

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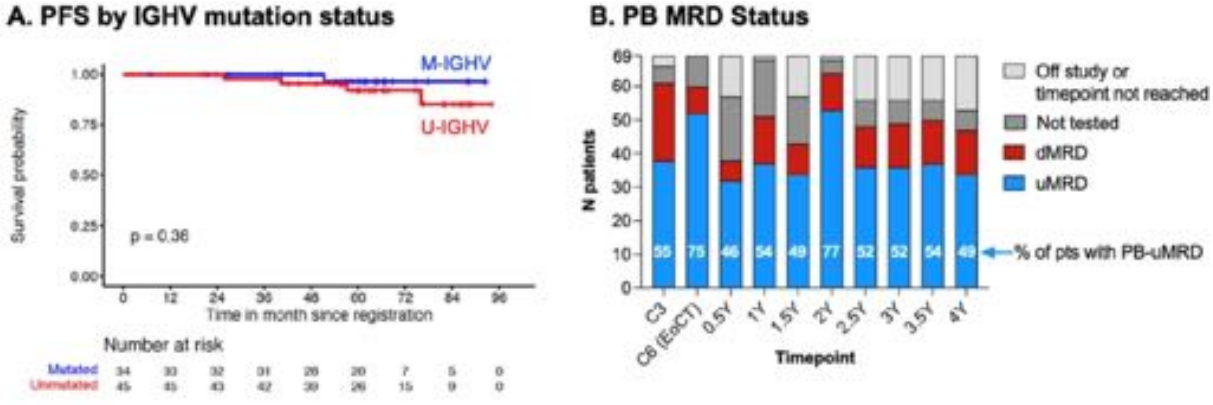
Introduction: This frontline study investigates whether iFCR followed by 2Y ibrutinib (IBR) maintenance (I-M) could provide deep and durable responses in CLL irrespective of IGHV status. We previously reported high rates of bone marrow undetectable minimal residual disease (BM-uMRD) in both IGHV unmutated (U-IGHV, 83%) and mutated (M-IGHV, 82%) pts (Davids et al., *Lancet Haematol*, 2019). Here, we report updated data at a median follow-up of 63 months.

Methods: In this phase 2 investigator-sponsored trial (NCT02251548), eligible pts received up to 6 cycles of iFCR followed by 2Y I-M. Pts with BM-uMRD after 2Y I-M had the option to stop IBR. MRD was assessed with multicolor flow at 10^{-4}. Targeted NGS covering 97 genes was applied to peripheral blood (PB) samples at MRD recurrence.

Results: 85 pts with a median age of 55Y (range 38–65) were treated, including 53% with U-IGHV and 6% with del17p and/or *TP53*^{MUT}. 77 pts (91%) completed 2Y I-M. 20 pts continued IBR beyond 2Y I-M, including 13 with detectable MRD in BM or PB at 2Y. Safety was similar to our previous report; the cumulative incidence of atrial fibrillation was 8%, and second malignancy occurred in 11%, mostly non-melanoma skin cancer. Two pts (2%) had secondary myeloid neoplasms. No new deaths have occurred since the one death reported in the prior publication (sudden cardiac death during I-M).

5Y PFS was 94% (95% CI 89%–100%) and 5Y OS was 99% (95% CI 96%–100%). There was no difference in PFS by IGHV status or duration of I-M (Figure A). Five pts progressed with CLL, all after cessation of IBR. Fourteen pts remained in response on continuous IBR therapy, two of whom had achieved BM-uMRD at 2Y but chose to continue IBR.

We longitudinally tracked PB MRD of 69 pts treated with at least 2Y of I-M with available samples and observed high rates of PB-uMRD post-iFCR (75%) and after 2Y I-M (77%). At 4Y after completion of iFCR, 63% of evaluable pts maintained PB-uMRD (Figure B). Thirteen pts (15%) had MRD recurrence without clinical progression, mostly after stopping IBR; 62% of these pts had U-IGHV, 7% del17p, and 15% *NOTCH1*^{MUT}. *BTK*^{MUT} was not detected in any of the ten pts analyzed at time of MRD recurrence. One pt had *PLCG2*^{MUT} at a low



allele frequency (2%). Driver gene mutations were commonly detected at MRD recurrence (23% with *TP53*^{MUT}, 38% with 1–2 other mutations per pt affecting *NOTCH1*, *SF3B1*, *ATM*, *XPO1*, and/or *BRAF*). Four of six pts (67%) who received IBR retreatment after MRD recurrence achieved PR. Median duration of IBR retreatment was 34 months. Serial PB MRD data from five pts on IBR retreatment revealed that the MRD growth stabilized but was not eradicated during retreatment.

Conclusions: iFCR with 2Y I-M achieved durably deep responses (94% 5Y PFS and 63% 4Y PB-uMRD) in fit pts with diverse CLL genetic markers. U-IGHV and CLL driver gene mutations were commonly found among pts with MRD recurrence. Re-emergent clones lacked *BTK*^{MUT}and retained sensitivity to IBR in most pts upon retreatment.

Keywords: chronic lymphocytic leukemia (CLL), minimal residual disease, molecular targeted therapies

This study was funded by Pharmacyclics, an AbbVie Company.

Conflicts of interests pertinent to the abstract

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Research funding: AbbVie, AstraZeneca, Ascentage Pharma, Genentech, MEI Pharma, Novartis, Surface Oncology, TG Therapeutics

153 | LONG-TERM FOLLOW-UP OF MULTICENTER PHASE II TRIAL OF ZANUBRUTINIB, OBINUTUZUMAB, AND VENETOCLAX (BOVEN) IN PREVIOUSLY UNTREATED PATIENTS WITH CLL/SLL

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Background: Venetoclax-obinutuzumab induces durable undetectable MRD (median time to MRD $\geq 10^{-4}$ of 21 mo) in CLL (Al-Sawaf JCO, 2021) and zanubrutinib is a second-generation BTKi with a favorable safety profile (Brown NEJM 2023). BOVen appeared well-tolerated and achieved frequent uMRD in CLL (Soumerai Lancet Haem 2021), but longer follow-up was needed to evaluate the MRD-driven treatment strategy. Herein, we present the initial report on long-term follow-up of BOVen in CLL.
Methods: In this multicenter phase 2 trial (NCT03824483), eligible pts had CLL/SLL requiring first-line treatment (iwCLL), ECOG PS ≤2, ANC ≥1000, PLT ≥75,000 (ANC ≥0/PLT ≥20,000 if due to CLL). Informed consent was obtained from all pts.
BOVen was administered in 28-day (D) cycles (C): Zanubrutinib 160 mg PO twice daily starting D1; Obinutuzumab 1000 mg IV D1 (split D1–2 if ALC ≥25,000 / LN ≥5 cm), D8, D15 of C1, and D1 of C2–8; Venetoclax ramp up initiated C3D1 (target 400 mg PO daily).
MRD was evaluated by flow cytometry (MRD-FC) with uMRD defined as $\leq 10^{-4}$ for the primary endpoint. ΔMRD400 was evaluated by immunosequencing (Adaptive ClonoSEQ) in 35/39 (13 pending) and defined as ≥400-fold reduction in peripheral blood (PB) MRD level at C5D1.
Treatment consisted of 8–24 cycles (duration determined by pre-specified MRD-FC criteria). Beginning C7D1 then q2 cycles, PB uMRD-FC prompted bone marrow (BM) <14 days. If BM uMRD-FC, PB MRD-FC was repeated after 2 additional cycles. Pts with confirmed uMRD-FC in PB and BM discontinued therapy.
All-cause adverse events (AE) were assessed (CTCAE v5). Median time to PB MRD-FC $\geq 10^{-4}$ was calculated from end-of-treatment (EOT; Kaplan–Meier method).
Results: The study accrued 52 pts (3–10/2019; 7–4/2021): median age 61, 75% male, 75% *IGHV* unmutated, 18.4% del17p/*TP53*M. All evaluable for safety with 50 evaluable for efficacy.
With median follow up of 40 mo (4.1–47.4) and treatment duration of 10 cycles (IQR 8–14), 96% (48/50) were uMRD-FC in PB; 92% (46/50) were uMRD in PB and BM after a median 8 mo (IQR 6–11.5).
The most common AEs were thrombocytopenia (55.8%), fatigue (55.8%), neutropenia (53.8%), diarrhea (46.2%), bruising (44.2%), infusion related reaction (36.5%). The most common grade ≥3 AE were neutropenia (23.1%), thrombocytopenia (7.7%), lung infection (5.8%). No lab/clinical TLS occurred (Howard).
Of 46 pts meeting MRD-FC criteria to end treatment, MRD-FC free survival was 29.8 mo (3.6–35.1; **A**). Of pts who were PB uMRD-FC and evaluable for ΔMRD400, MRD-FC free survival was longer in ΔMRD400 achievers (NR vs. 18.1 mo, log-rank $p = 0.003$; **B**) despite fewer median cycles of therapy (8 vs. 13, $p < 0.001$).
Conclusion: Long-term follow up of BOVen demonstrate high rates of durable uMRD-FC. A phase II trial of BOVen with ΔMRD400-directed treatment duration is planned, and we hypothesize that longer duration of therapy for pts who do not achieve ΔMRD400 (24 vs. 10 mo) will further improve uMRD duration in these pts.

The research was funded by: Beigene, Genentech (Roche), Grais-Cutler Fund, Lymphoma Research Fund, Lymphoma Research Foundation, American Cancer Society, Farmer Family Foundation, and the National Instititutes of Health and National Cancer Institute.

Keywords: chronic lymphocytic leukemia (CLL), molecular targeted therapies

Conflicts of interests pertinent to the abstract

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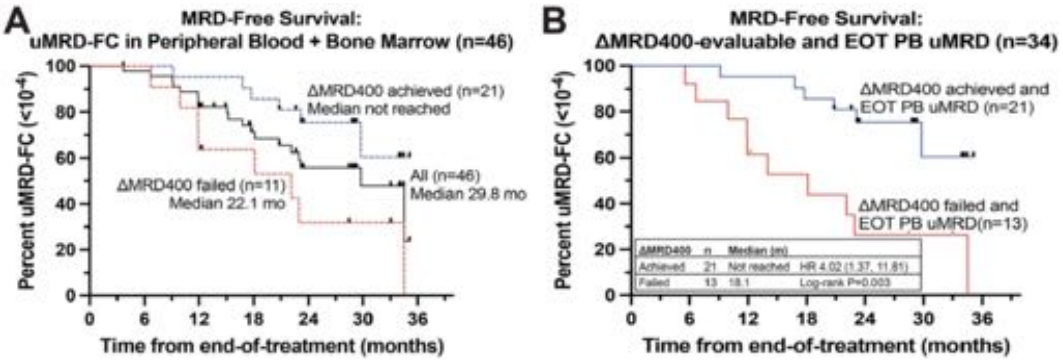

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154 | ZANUBRUTINIB (ZANU) VERSUS BENDAMUSTINE + RITUXIMAB (BR) IN PATIENTS (PTS) WITH TREATMENT-NAïVE (TN) CLL/SLL: EXTENDED FOLLOW-UP OF THE SEQUOIA STUDY

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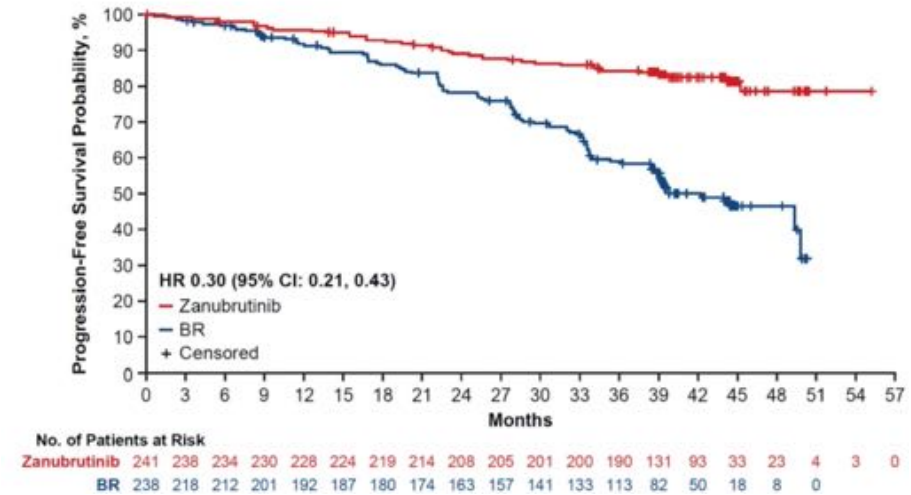
Introduction: Zanu, a next-generation Bruton tyrosine kinase inhibitor (BTKi), demonstrated superior progression-free survival (PFS) by independent review versus BR in pts with TN CLL/SLL without (w/o) del(17p) in the SEQUOIA study (NCT03336333) at a median follow-up of 26.2 mo; pts with del(17p) treated with zanu in a separate cohort had similar outcomes to pts w/o del(17p). Here, updated efficacy and safety results from the SEQUOIA study after 18 mo of additional follow-up (data cutoff 31 October 2022) are reported.

Methods: Patients w/o del(17p) were randomized to zanu or BR. Pts with del(17p) received zanu monotherapy. Investigator-assessed PFS, overall survival (OS), overall response rate, and safety/tolerability were evaluated.

Results: A total of 479 pts w/o del(17p) were randomized (zanu: n = 241; BR: n = 238). At a median follow-up of 43.7 mo, median PFS was not reached (NR) for zanu and was 42.2 mo for BR (Figure). At 42 mo, estimated PFS rates were 82% for zanu. With additional follow-up, PFS for zanu versus BR was improved for pts with mutated IGHV (HR 0.35; 95% CI: 0.19, 0.64); benefit was also sustained for pts with unmutated IGHV (HR 0.23; 95% CI: 0.14, 0.37) or del(11q) (HR 0.26; 95% CI: 0.13, 0.51). Complete response/complete response with incomplete hematological recovery (CR/CRi) rates in pts w/o del(17p) were 17% and 22% with zanu and BR, respectively. While median OS was NR in either arm, HR for OS was 0.87 (95% CI: 0.50, 1.48) for zanu versus BR, and estimated 42-mo rates were 89% versus 88%, respectively. For pts with del(17p) assigned to zanu monotherapy, after a median follow-up of 47.9 mo, the estimated 42-mo PFS and OS rates were 79% and 90%, respectively; the CR/CRi rate was 15%. As of 31 Oct 2022, zanu treatment was ongoing in 75% pts w/o del(17p) and 70% pts with del(17p). The most common causes for treatment discontinuation were adverse events (AEs) and progressive disease for pts w/o del(17p) (15%, 6%) and with del(17p) (14%, 14%, respectively). AEs of interest (AEI) in pts w/o del(17p) (zanu vs. BR) included any-grade (gr) atrial fibrillation/flutter (5% vs. 3%), hypertension (18% vs. 14%), bleeding (49% vs. 12%), infection (73% vs. 63%), anemia (7% vs. 21%), thrombocytopenia (6% vs. 18%), and neutropenia (17% vs. 57%). Gr≥3 AEI included bleeding (6% vs. 2%), infection (24% vs. 22%), anemia (1% vs. 2%), thrombocytopenia (2% vs. 8%), and neutropenia (13% vs. 51%).

Conclusions: With extended follow-up in the SEQUOIA study, zanu efficacy was maintained in pts w/o del(17p) with a safety profile aligned with long-term follow-up for the BTKi class. Longer follow-up showed benefit in pts with mutated IGHV, and pts with del(17p) continued to show PFS benefits consistent with the randomized

Figure: Progression-Free Survival by Investigator Assessment



cohort. Rates of atrial fibrillation remained low, and no new safety signals were identified. Zanu continues to be well tolerated over time, with low rates of treatment discontinuation, and remains a valuable treatment option for TN CLL/SLL.

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Conflicts of interests pertinent to the abstract

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155 | FIXED-DURATION IBRUTINIB + VENETOCLAX IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)/SMALL LYMPHOCYTIC LYMPHOMA (SLL): 4-Y FOLLOW-UP FROM THE FD COHORT OF THE PHASE 2 CAPTIVATE STUDY

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Introduction: CAPTIVATE (PCYC-1142) is a multicenter phase 2 study of first-line ibrutinib (I) + venetoclax (V) in CLL/SLL. Follow-up results from the fixed duration (FD) cohort showed 3-y PFS rate of 88% overall and ≥80% in patients (pts) with high-risk features (Wierda, ASCO 2022). Here we present updated results from the FD cohort with 4-y follow-up.

Methods: Pts aged ≤70 y with previously untreated CLL/SLL received 3 cycles of I then 12 cycles of I+V (I 420 mg/d orally; V ramp-up to 400 mg/d orally). Responses were investigator assessed per iwCLL 2008 criteria. Undetectable minimal residual disease (uMRD; $<10^{-4}$) was assessed by 8-color flow cytometry.

Results: 159 pts were enrolled, including pts with high-risk features of unmutated IGHV (uIGHV) (56%) or del(17p) and/or TP53 mutation (17%). Median time on study was 50 mo (range 1–53). At 4 y of follow-up, best CR rate was 58% and ORR was unchanged at 96%. At 4 y, PFS rate was 79% (95% CI 71–84) and OS rate was 98% (95% CI 94–99). 4 y PFS rates were numerically lower in pts with uIGHV (73%) or del(17p) and/or TP53 mutation (63%), while OS rates remained consistently high (Table). 4 y PFS rates by MRD status 3 mo after end of treatment (EOT+3) were significantly higher in pts with uMRD versus detectable MRD (dMRD) in PB (90% vs. 66%, Table); this difference was minimal at 24 mo (100% vs. 91%). Median TTNT was not reached (range 1–53 mo); 4 y rate of freedom from next treatment was 84% (95% CI 77–89). Second malignancies continue to be collected off treatment; 1 AE of prostate cancer occurred during this y of follow-up.

To date, 19 pts with PD after completing fixed duration I+V in either the FD cohort or MRD cohort placebo arm initiated retreatment with I. Responses in 17 pts with available data were 1 CR, 13 PR, and 1 each PR with lymphocytosis, SD, and PD. Median time on retreatment was 11 mo (range 0–39). The most common AEs (≥10%) with retreatment were diarrhea ($n = 3$), COVID-19 ($n = 3$), and anemia ($n = 2$). In addition, 4 pts have started I+V retreatment to date.

Conclusions: Results of the CAPTIVATE study support I+V as an all-oral, once-daily fixed-duration regimen for previously untreated pts with CLL/SLL. With 4 y follow-up, fixed-duration I+V continues to provide deep, durable remissions with clinically meaningful PFS and time off treatment, including in pts with high-risk disease features. New safety findings off-treatment were expectedly negligible, highlighting the benefits of a fixed duration regimen. Promising responses were observed upon retreatment with I in progressing pts.

	4 y PFS, % (95% CI)	4 y OS, % (95% CI)
FD Cohort ($N = 159$)	79 (71–84)	98 (94–99)
del(17p) and/or *TP53* ($n = 27$)	63 (41–79)	96 (76–99)
uIGHV ($n = 89$)	73 (62–81)	97 (90–99)
uMRD at EOT+3, PB ($n = 90$)	90 (81–95)	100
dMRD at EOT+3, PB ($n = 57$)	66 (52–77)	100

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Conflicts of interests pertinent to the abstract

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156 | MURANO: FINAL 7 YEAR FOLLOW UP AND RETREATMENT ANALYSIS IN VENETOCLAX-RITUXIMAB (VENR)-TREATED PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (*R/R* CLL)

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Introduction: Fixed-duration (FD) VenR treatment (tx) in patients (pts) with *R/R* CLL in the Phase 3 MURANO trial (NCT02005471) resulted in superior progression-free survival (PFS) and overall survival (OS), versus bendamustine (B)R. This was sustained at 5 years (y) median (m) follow up (FU): PFS, 53.6 months [mo] with VenR versus 17.0 mo with BR; 5 y OS rates, 82.1% with VenR versus 62.2% with BR; $p < 0.0001$ for both. We report the final analyses of MURANO at 7 y mFU: specifically, updated PFS and OS, with minimal

residual disease (MRD) evaluation, in pts treated in the main study, and in VenR-retreated pts in the substudy.

Methods: Pts with *R/R* CLL were randomized to VenR (Ven 400 mg daily for 2 y + monthly R for the first 6 mo) or BR (6 mo). In the substudy (2018 onwards), pts with progressive disease (PD) received VenR (to the main study regimen) as re-tx or as crossover from BR. PFS was investigator assessed. Peripheral blood MRD was measured centrally by ASO-PCR and/or flow cytometry. Undetectable (u)MRD was defined as $<10^{-4}$.

Results: Baseline characteristics are shown in the Table. At the final data cut (3 August 2022), mPFS (95% confidence interval [CI]) in VenR-treated pts ($n = 194$) was 54.7 mo (52.3, 59.9) versus 17.0 mo (15.5, 21.7) in BR-treated pts ($n = 195$; hazard ratio [HR] 0.25). Seven y PFS rates (95% CI) were 23.0% (16.1, 29.9) with VenR (no BR-treated pts were progression free at this time point); 7 y OS rates (95% CI) were 69.6% (62.8, 76.5) with VenR and 51.0% (43.3, 58.7) with BR (HR 0.53). M time to next tx with VenR was 63.0 mo versus 24.0 mo with BR (HR 0.30); 37.1% of VenR-treated pts have not had further anti-CLL tx.

Among VenR-treated pts who had uMRD at end of tx (EOT) without PD ($n = 83/118$; 70.3%), mPFS (95% CI) from EOT was 52.5 mo (44.5, 61.5) versus 18.0 mo (8.5, 29.3; $p < 0.0001$) in pts who were MRD+ at EOT ($n = 35$; 29.7%). At 7 y FU, 14 (16.9%) pts had no PD nor confirmed MRD conversion; in the 63 (75.9%) pts with MRD conversion, m time to conversion (95% CI) was 19.4 mo (8.7, 28.0). Among 63 pts who converted, 39 subsequently had PD or died; m time from conversion to PD (95% CI) was 28.3 mo (23.2, 35.0).

In the substudy ($n = 34$), 25 pts received VenR re-tx (Table), 92.0% of whom had ≥1 of the following high-risk features: *IGHV*-unmutated disease, genomic complexity, del(17p) and/or *TP53* mutations; despite this, 14/25 (56.0%) achieved uMRD at EOT in the main study. Best overall response rate (ORR) to re-tx was 72.0% and mPFS (95% CI) was 23.3 mo (15.6, 24.3). M (range) time from the last Ven dose in the main study to Ven ramp-up in the substudy was 2.3 y (1.2–3.1). Eight (32.0%) pts achieved uMRD at the re-tx end of combination tx, but no pts retained uMRD at the re-tx EOT.

No new safety findings were observed.

Conclusions: PFS and OS benefits for VenR versus BR were sustained and uMRD was associated with prolonged PFS. In the high risk VenR-retreated pts, ORR was high and uMRD was attainable. These data support FD VenR in *R/R* CLL, and suggest that VenR re-tx is a viable option for pre-treated pts.

Encore Abstract - previously submitted to EHA 2023

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	Main study		Substudy
	Pts treated with VenR (n=194)	Pts treated with BR (n=195)	Pts retreated with VenR (n=25)
Baseline characteristics			
Mean age, years (SD)	63.9 (10.5)	64.4 (9.6)	65.8 (8.3)
Number of prior cancer therapy, n (%)			
1	111 (57.2)	117 (60.0)	0 (0.0)
2	58 (29.9)	43 (22.1)	20 (80.0)
≥3	25 (12.9)	35 (17.9)	5 (20.0)
del(17p) and/or *TP53* mutation (aCGH), n (%)			
mutated	53 (27.3)	55 (28.2)	14 (56.0)
unmutated	104 (53.6)	98 (50.3)	9 (36.0)
unknown	37 (19.1)	42 (21.5)	2 (8.0)
Genomic complexity, n (%)	n=48	n=46	n=20
3–4	34 (70.8)	29 (63.0)	3 (15.0)
≥5	14 (29.2)	17 (37.0)	8 (40.0)
IGHV, n (%)	n=180	n=180	n=23
mutated	53 (29.4)	51 (28.3)	2 (8.7)
unmutated	123 (68.3)	123 (68.3)	21 (91.3)
unknown	4 (2.2)	6 (3.3)	0 (0.0)
Efficacy results			
Median follow-up, months	85.7	85.7	33.4
Best ORR, %	93.3	67.7	72.0
uMRD at EOCT of main study, n (%)	121 (62.4)	26 (13.3)	16 (64.0)
uMRD at EOCT of substudy, n (%)	N/A	N/A	8 (32.0)
uMRD at EOT of main study, n (%)	83 (70.3)*	N/A	14 (56.0)
uMRD at EOT of substudy, n (%)	N/A	N/A	0 (0.0)
Median PFS, months (95% CI)	54.7 (52.3, 59.9)	17.0 (15.5, 21.7)	23.3 (15.6, 24.3)
3 year OS rate, % (95% CI)	88.4 (83.8, 93.0)	78.9 (72.8, 84.9)	53.1 (25.1, 81.0)

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Keywords: Chronic Lymphocytic Leukemia (CLL), Combination Therapies

Conflicts of interests pertinent to the abstract

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Educational grants: Abbvie, AstraZeneca, Janssen, Roche/Genentech
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Research funding: Ascerta/AstraZeneca; Celgene; Genentech/Roche; Gilead; Janssen; Loxo Oncology; TG Therapeutics; Verastem; Pharmacyclics/AbbVie; Breast Cancer Research Foundation; Md Anderson Cancer Center; Oncternal Therapeutics, Inc.; Specialized Center of Research [SCOR] - The Leukemia and Lymphoma Society [LLS]; California Institute for Regenerative Medicine [CIRM]; National Cancer Institute/NIH; VelosBio, Inc. – Research Agreement
Educational grants: Pharmacyclics/AbbVie, Genentech/Roche, Janssen, Gilead, National Cancer Institute/NIH, Celgene, European Research Initiative on CLL [ERIC], Dava Oncology, Breast Cancer Research Foundation, iwNHL, NCCN CLL/SLL Hairy Cell Leukemia Panel Meeting, OncLive
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WILEY

POSTER PRESENTATIONS

EPIDEMIOLOGY

157 | IMPACT OF THE AFFORDABLE CARE ACT AND MEDICAID EXPANSION ON INSURANCE COVERAGE AND OUTCOMES IN PATIENTS WITH HIV-ASSOCIATED AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMAS

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Introduction: HIV-associated lymphomas affect a uniquely disadvantaged group of patients, who were often denied insurance based on preexisting conditions until the Affordable Care Act (ACA) was signed in 2010. We investigated the impact of ACA and its Medicaid expansion in 2014 which covered the low-income strata, on outcomes among patients with HIV-associated aggressive B-cell non-Hodgkin lymphomas (HIV-aB-NHL).

Methods: We used the National cancer database (NCDB) to identify HIV-associated aB-NHL patients aged 18–64 years from 2004 to 2017. We defined the pre-ACA period up to 2013 and the post-ACA period after 2014. States were grouped as Medicaid expansion adopted or not adopted. To reduce bias from advancements in antiretroviral and chemo-immuno-therapies, we compared survival outcomes between 2010 to 2013 and 2014 to 2017. Kaplan-Meier method and a parametric Weibull model were used for survival analysis.

Results: We identified 10,795 eligible patients with HIV-associated aB-NHL, comprised of 1802 Hispanics (16.7%), 3915 non-Hispanic blacks [NHB (36.3%)], 4727 Non-Hispanic Whites [NHW (43.8%)] and 351 other minorities (3.2%). The predominant diagnoses were diffuse large B-cell lymphoma (63.3%) and Burkitt lymphoma (20.1%). The figure shows the distribution of insurance status at diagnosis in Medicaid expansion ($n = 4611$) and non-expansion ($n = 3091$) states before and after the implementation of ACA stratified by race. Hispanics were more likely to be from residential zip codes in the lower educational quartile. A higher proportion of patients were seen at academic medical centers in expansion states across all races, and this further improved post-ACA. There was a significant improvement in survival seen among NHB ($p < 0.01$) post-ACA though the trend in Hispanics was not significant ($P = 0.36$). A multivariable survival analysis using the Weibull model adjusting for age, sex, insurance status, Charlson-Deyo comorbidity index, income, race, and Medicaid expansion status found statistically significant improvement in the states that adopted Medicaid expansion (HR 0.88, $p < 0.01$) though NHB race predicted poor survival (HR 1.49, $p < 0.01$).

Conclusions: The ACA has resulted in a decrease in uninsured across most races when diagnosed with HIV-associated aB-NHL. However, Hispanics who were more likely to be from less educated neighborhoods were unable to utilize it. Though an improvement in overall survival among non-Hispanic blacks was observed post-ACA, in the overall population, black race was still a negative predictor for survival, reflecting the complex interplay between disease biology and social determinants of health. Strategies must be deployed to help minorities acquire insurance coverage, especially in non-expansion states, which will improve access to treatment at academic centers with access to clinical trials thereby improving outcomes.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cancer Health Disparities

Conflicts of interests pertinent to the abstract.

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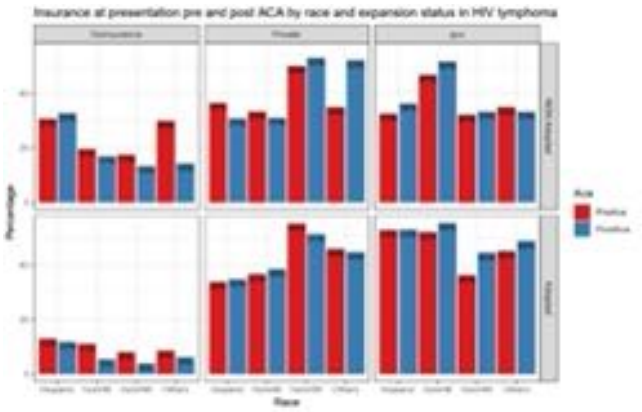

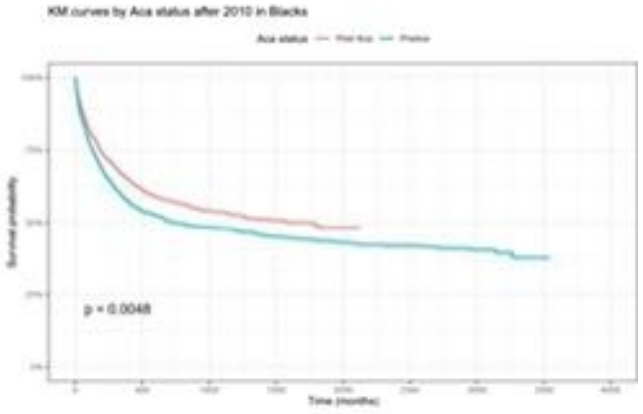

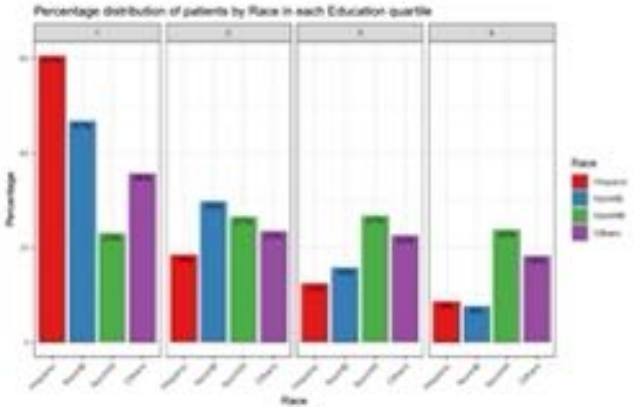

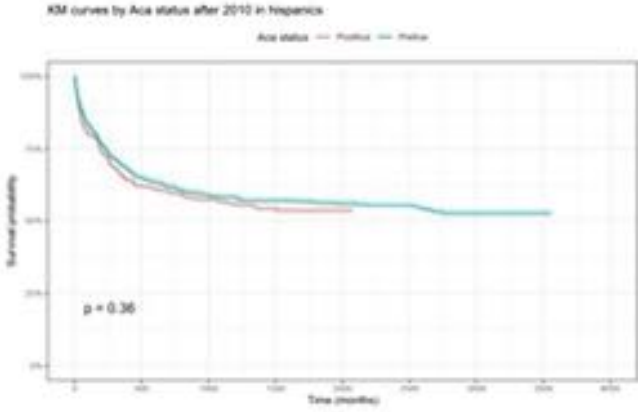

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BIOLOGY

158 | TESTICULAR LARGE B-CELL LYMPHOMA IS GENETICALLY SIMILAR TO PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA AND DISTINCT FROM NODAL DIFFUSE LARGE B-CELL LYMPHOMA

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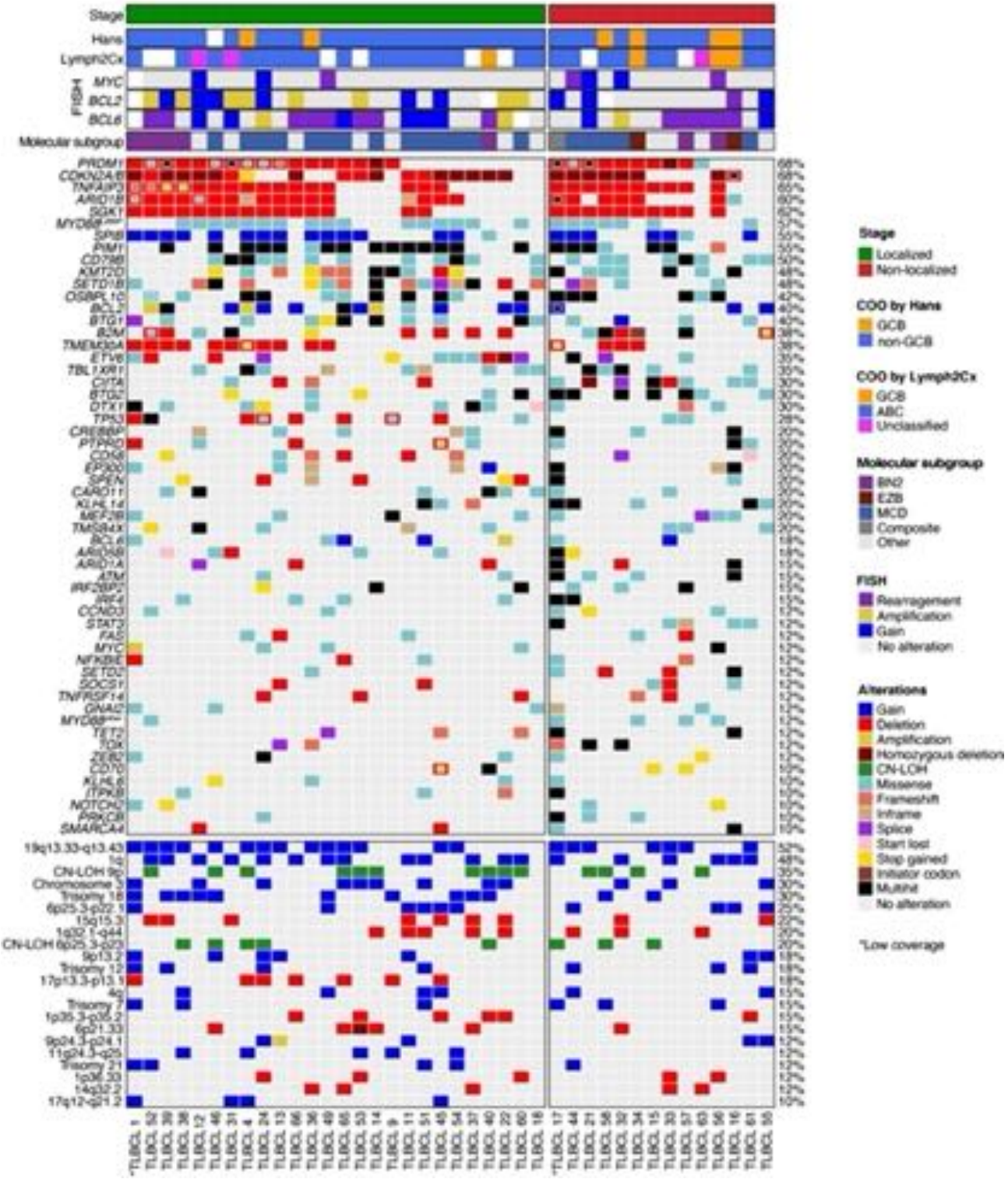
Introduction: Testicular large B-cell lymphoma (TLBCL) is an infrequent and aggressive lymphoma presenting in an immune-privileged site, recently recognized as a distinct entity from diffuse large B-cell lymphoma (DLBCL). Here, we performed the genetic characterization of TLBCL and compare it with a published series of nodal DLBCL and primary central nervous system lymphoma (PCNSL).

Patients and Methods: We collected 61 patients with TLBCL diagnosed between 2002 and 2021. Cell-of-origin was determined by immunochemistry and Lymph2Cx assay. To characterize the genomic profile of TLBCL we performed targeted next-generation sequencing, copy number arrays, and fluorescent in situ hybridization, and compared them to those of DLBCL and PCNSL.

Results: The median age was 70 years and 30% of the patients had disseminated disease at diagnosis, including six cases with CNS involvement. Using Hans' algorithm, 83% (44/53) were identified as a non-germinal center while the Lymph2Cx assay categorized 71% (30/42) as activated B-cell phenotype and 12% (5/42) as unclassified. *BCL6* rearrangements were detected in 36% (17/47) of cases, and no concomitant *BCL2* and *MYC* rearrangements were found. Integrative analysis of 40 cases with single nucleotide variants, indels, and copy number alterations (CNA) data showed that the most frequent alterations (>50%) in TLBCL were *PRDM1*, *CDKN2A/B*, *TNFAIP3*, *SGK1*,

Figure. Recurrent genomic alterations in TLBCL according to disease stage. The Oncoprint encompasses the 40 cases analyzed using next-generation sequencing and copy number analysis.



ARID1B, *MYD88*^{L265P}, *SPIB*, *PIM1*, and *CD79B* (Figure). Concomitant variants in *MYD88*^{L265P}, *CD79B*, and *PIM1* were detected in twelve (29%) cases. Using the LymphGen tool, 71% (30/42) of the cases could be classified into a molecular subgroup, with MCD being the most frequent group (66%, 20/30). Interestingly, patients with localized or disseminated disease displayed similar genomic complexity based on the number of CNAs and the number of mutated genes. Compared with nodal DLBCL, localized and disseminated TLBCL have less CNA complexity ($P = 0.01$ and $P < 0.04$, respectively) but showed a higher number of variants ($P = 0.01$ and $P < 0.001$, respectively). TLBCL also presented more frequently 18q21.32-q23 (*BCL2*) gains and 6q and 9p21.3 (*CDKN2A/B*) deletions. *PIM1*, *MYD88*^{L265P}, *CD79B*, *TBL1XR1*, *MEF2B*, *CIITA*, *EP300*, and *ETV6* variants were enriched in TLBCL, and *BCL10* mutations in nodal DLBCL. There were no genetic differences between TLBCL and PCNSL.

Conclusions: TLBCL has a distinctive genetic profile similar to PCNSL, supporting its recognition as a separate entity from DLBCL and providing decisive information to tailor therapeutic approaches.

Encore Abstract - previously submitted to regional or national meetings (up to <1'000 attendees).

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Keywords: Extranodal non-Hodgkin lymphoma, Pathology and Classification of Lymphomas

Conflicts of interests pertinent to the abstract.

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159 | SUBGROUPING OF BURKITT LYMPHOMA VARIANTS BY DNA METHYLATION IS DRIVEN BY AN EBV-ASSOCIATED EPIGENOTYPE

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Introduction: Burkitt lymphoma (BL) is an aggressive mature B-cell lymphoma, which traditionally has been separated into three epidemiologic variants: endemic (eBL), sporadic (sBL) and immunodeficiency-associated BL (iBL). This subgrouping is strongly confounded by EBV-infection. Indeed, there is evidence from molecular studies that subtyping of BL based on EBV status might better reflect the pathogenetic heterogeneity than epidemiology. As EBV is known to influence epigenetic regulation, we here aimed at a comparative DNA methylation (DNAme) profiling of BL variants with respect to their geographic origin and EBV status.

Methods: We collected DNAme profiles (Infinium HumanMethylation450 and Infinium MethylationEPIC BeadChip) of 116 BL patients (80 sBL: 7 EBV+; 29 eBL: 27 EBV+; 7 iBL: 4 EBV+), 17 BL cell lines and 6 EBV-transformed LCLs. For group determination unsupervised clustering algorithms (K-means, PGMRA, UMAP) were applied. To investigate potential consequences of EBV-associated DNAme we performed a protein-protein interaction network analysis on genes within the EBV-specific DNAme pattern. Moreover, we mined gene expression values from RNAseq in 21 EBV- sBL and 5 germinal-center B-cell populations.

Results: Unsupervised clustering algorithms revealed two distinct DNAme phenotypes, which differentiate EBV+ and EBV- BL based on 1,266 CpGs. This separation is accompanied by a characteristic hypermethylation in EBV+ BLs. Additionally, we identified a subgroup of EBV+ BL with a similar DNAme pattern like the LCLs, possibly indicating latency phase differences within EBV+ BLs. Investigation of the EBV-specific DNAme pattern revealed a network

with UBC as a key interactor, indicating the potential importance of the ubiquitin-proteasome system (UPS) in EBV-induced lymphomagenesis. Among genes differentially methylated between EBV+ and EBV- BL, 19 genes have been reported as recurrently mutated in BL. All except 3 of these genes are expressed in sBL and germinal-center B-cells. All these genes were significantly hypermethylated within regulatory regions in EBV+ BLs ($\sigma/\sigma_{max} = 0.4$, $q \leq 0.01$), including genes with a lower mutational frequency in EBV+ versus EBV- BLs.
Conclusion: The findings of this study show the EBV status to be strongly associated with DNAme subgroups in BL, supporting the subtyping of BL variants based on their EBV status rather than their geographic origin. Moreover, the pattern of DNAme in EBV+ BL might suggest epigenetic silencing and deregulated ubiquitination as means alternative to gene mutation to be involved in the pathogenesis of EBV+ BL.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Genomics, Epigenomics, and Other -Omics, Pathology and Classification of Lymphomas

No conflicts of interests pertinent to the abstract.

160 | A TRANSPOSABLE ELEMENT ATLAS OF AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMAS DEFINES NOVEL CLASSIFICATIONS OF BURKITT LYMPHOMA INDEPENDENT OF EBV STATUS

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Introduction: Clinical and pathological heterogeneity in aggressive B-cell non-Hodgkin lymphomas may be driven by several mechanisms of oncogenesis, such as translocations involving the immunoglobulin locus and proto-oncogenes, the 'cell-of-origin' from the germinal center (GC), and viral associations. Previous classifications of B-cell lymphomas have been defined by one or more of these characteristics and transforming events. However, transposable elements (TEs), which make up roughly half of the human genome and have key regulatory functions, have been previously overlooked in both the healthy GC and in B-cell lymphomas. We hypothesized that unique TE signatures, which may in part be driven by human endogenous retroviruses (HERVs), would allow a novel categorization of B-cell lymphomas. Here we present a comprehensive, locus-specific atlas of TE expression in healthy GC B cells, diffuse large B-cell lymphoma (DLBCL), Epstein-Barr Virus (EBV)-positive and negative Burkitt lymphoma (BL), and follicular lymphoma (FL).
Methods: We obtained RNA-seq data from 529 DLBCLs belonging to the TCGA and NCICCR cohorts, 113 sporadic and endemic BL, and 12 FL from the CGCI cohort for gene and locus-specific TE quantification. RNA-seq data from sorted cells from the healthy GC were obtained from two recent studies (Holmes et al., 2020; Agirre et al., 2019). TEs were quantified with Telescope, which addresses the computational challenges of repetitive and interspersed TE reads, and low read counts using an expectation-maximization algorithm. We used STAR for indexing and alignment, HTSeq for quantifying EBV viral reads in endemic BL samples, DESeq2 to identify differentially expressed TEs, and LRT, Boruta, and Lasso for feature selection.
Results: TE-driven clustering of healthy B cells showed that HERVs could independently distinguish stages of B cell differentiation and specific GC subsets, with plasmablasts and bone marrow plasma cells having the highest number of differentially expressed HERVs. We found HERV loci of interest upstream of POU5F1B and MYC that can differentiate plasmablasts from other GC cells. Furthermore, we describe a map of locus-specific TE expression in DLBCL, BL, and FL. Strikingly, we find that BL can be subdivided into three HERV-driven clusters, which are not obtained with gene-only clustering, and identify 4 HERV loci sufficient to distinguish between clusters. Clusters are independent of EBV status, clinical variant, location of MYC translocation, and display a high number of differentially expressed LINE elements, lncRNAs, and snoRNAs.
Conclusions: Here, we report an atlas of TE expression in BL, DLBCL, and FL, and provide evidence for disease-specific changes in TE expression in B-cell lymphomas. TEs that are selectively expressed in lymphoma subtypes provide opportunities for novel subclassification that may have biological and pathological relevance.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Bioinformatics, Computational and Systems Biology, Pathology and Classification of Lymphomas

No conflicts of interests pertinent to the abstract.

161 | CHARACTERIZATION OF THE GENETIC AND EPIGENETIC LANDSCAPE OF B-CELL NEOPLASMS WITH IG::BCL3-TRANSLOCATION

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Introduction: The *BCL3* gene (19q13) encodes a transcriptional coactivator of the nuclear factor-kappaB (NF-κB) family. It is recurrently deregulated in B-cell neoplasms by a juxtaposition to regulatory elements of one of the immunoglobulin loci, mostly the immunoglobulin heavy chain (*IGH*) locus (14q32). Two distinct subsets of *IG*::*BCL3* translocation-positive B-cell neoplasms, differing in the number of chromosomal aberrations, IGHV mutation status and histopathology, have been described [Martín-Subero et al., 2007]. In B-cell chronic lymphocytic leukaemia (CLL), the *IG*::*BCL3* translocation has been associated with younger age at diagnosis, a more aggressive clinical course and an atypical tumour cell phenotype [Michaux et al., 1997; Au et al., 2002].

Methods: A total of 89 B-cell neoplasms with *IG*::*BCL3* translocation detected by fluorescence in situ hybridisation (FISH), including predominately cases diagnosed as CLL, were studied. Breakpoints at the *BCL3* and *IGH* loci were sequenced in a subset of samples using targeted capture and breakpoint-spanning PCR approaches. Chromosomal aberrations detected by FISH as well as the IGHV mutation status were analysed. In addition, DNA methylation and copy number aberration (CNA) analyses were performed for 48 samples with CLL using the 850K EPIC BeadChip array.

Results: Targeted capture-based sequencing data showed that in the majority of cases *BCL3* translocations are associated with aberrant class-switch recombination at the *IGH* locus, often involving *IGHA* segments ($n = 4/10$). From the 69 *IG*::*BCL3*-translocated cases with available IGHV mutation status, a total of 51 (74%) were classified as unmutated and 18 (26%) as mutated. This indicates an over-representation of cases with unmutated IGHV status among the *IG*::*BCL3*-translocated cases compared to the general CLL population. Based on EPIC BeadChip data (total $n = 48$) 25 (52%) *IG*::*BCL3*-translocated cases carried a trisomy 12, 11 cases (23%) a deletion 13q, 7 cases (15%) a deletion 17p and 3 cases (6%) a deletion 11q. FISH analysis of a partially overlapping set of neoplasms ($n = 54$) was in line with the EPIC BeadChip data and revealed 17 *IG*::*BCL3*-translocated cases (32%) with trisomy 12, 7 cases (13%) with deletion 17p and deletion 13q each, and 4 cases (7%) with deletion 11q. Thus, *IG*::*BCL3*-translocated cases showed a striking skewing towards the presence of trisomy 12 compared to the general CLL population ($p = 0.011$). In the DNA methylation analyses, the *IG*::*BCL3*-translocated CLLs segregated separately from other CLLs with and without *IGH* translocations.

Conclusions: Our large multi-OMICs study of *IG*::*BCL3*-translocated B-cell neoplasms corroborates previous reports on the pathogenetic heterogeneity of these lymphomas and moreover provides evidence that *IG*::*BCL3*-translocated CLL might form a genetically and epigenetically distinct subtype of B-cell neoplasms distinct from common CLL.

Keywords: Chronic Lymphocytic Leukemia (CLL), Genomics, Epigenomics, and Other -Omics

No conflicts of interests pertinent to the abstract.

162 | GENOMIC CHARACTERIZATION OF LYMPHOMAS IN PATIENTS WITH INBORN ERRORS OF IMMUNITY

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Patients with inborn errors of immunity (IEI) have a higher risk of developing cancer, especially lymphoma. However, the molecular basis for IEI-related lymphoma is complex and remains elusive. Here, we perform an in-depth analysis of lymphoma genomes derived from 23 IEI patients. We identified and validated disease-causing or associated germline mutations in 14 of 23 patients involving *ATM*, *BACH2*, *BLM*, *CD70*, *G6PD*, *NBN*, *PIK3CD*, *PTEN*, and *TNFRSF13B*. Furthermore, we profiled somatic mutations in the lymphoma genome and identified eight genes that were mutated at a significantly higher level in IEI-associated diffuse large B-cell lymphomas (DLBCLs) than in non-IEI DLBCLs, such as *BRCA2*, *NCOR1*, *KLF2*, *FAS*, *CCND3*, and *BRWD3*. The latter, *BRWD3*, is furthermore preferentially mutated in tumors of a subgroup of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) patients. We also identified five genomic mutational signatures, including two DNA repair deficiency-related signatures, in IEI-associated lymphomas and a strikingly high number of inter- and intrachromosomal structural variants in the tumor genome of a Bloom syndrome patient. In summary, our comprehensive genomic characterization of lymphomas derived from patients with rare genetic disorders expands our understanding of lymphomagenesis and provides new insights for targeted therapy.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Genomics, Epigenomics, and Other -Omics, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

163 | CHARACTERIZATION OF MECHANISMS OF RESISTANCE IN PREVIOUSLY TREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) FROM A HEAD-TO-HEAD TRIAL OF ACALABRUTINIB VERSUS IBRUTINIB

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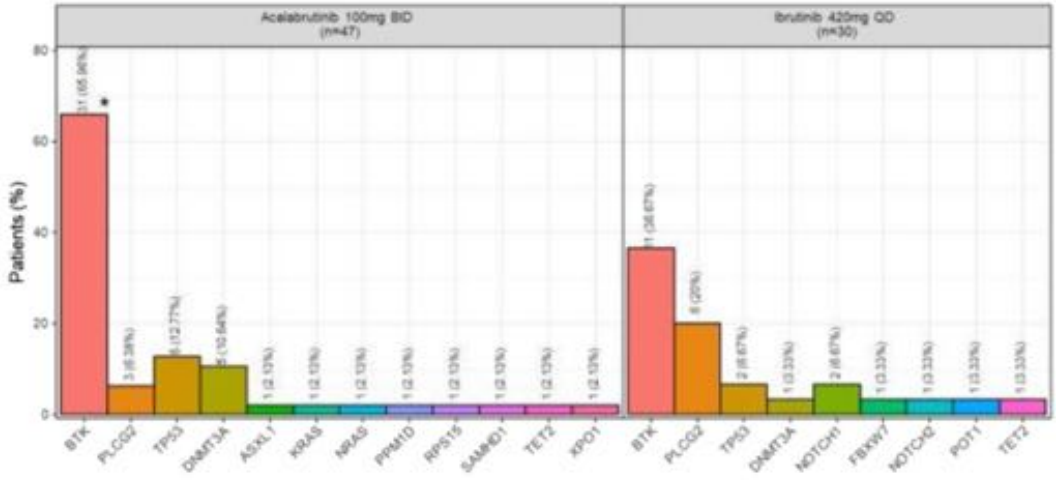
Introduction: Acalabrutinib (Acala) is a highly selective, next-generation covalent Bruton tyrosine kinase inhibitor (BTKi) approved for CLL. In ELEVATE-RR (NCT02477696) at a median follow-up of 41 mo, Acala demonstrated noninferior progression-free survival with fewer cardiovascular adverse events versus ibrutinib (Ibr) in patients (pts) with relapsed/refractory (R/R) CLL. Disease progression on covalent BTKis is often characterized by acquisition of B-cell receptor pathway mutations, but no data have compared mutational profiles of Acala versus Ibr. We report clonal evolution data in pts with CLL progressing on Acala versus Ibr in ELEVATE-RR.

Methods: Peripheral blood samples at baseline and relapse from pts in ELEVATE-RR were used. DNA was extracted from enriched CD19 + cells (RoboSep) and subjected to a 50-gene sequencing assay panel with a sensitivity cutoff for *BTK* and *PLCG2* resistance–associated mutations at 0.5% variant allele fraction (VAF). Forty-eight other CLL-associated genes were assessed at 1%–2% VAF.

Results: Paired (baseline and progression) samples were available for 47 (excluding 1 Richter) and 30 (excluding 6 Richter) pts in the Acala and Ibr groups, respectively. At progression, emergent *BTK* mutations were seen in 31 (66%) Acala versus 11 (37%) Ibr pts ($P = 0.02$) (Figure 1; median VAF: 5.7 vs. 5.8). Emergent *PLCG2* mutations occurred in 3 (6%) Acala vs. 6 (20%) Ibr pts ($P = 0.14$). Only 1 Acala pt had co-occurrence of *BTK* and *PLCG2* mutations versus 4 Ibr pts. *BTK C481S*, *C481Y*, and *C481R* mutations occurred at similar frequency in both groups; a novel *E41V* mutation within the pleckstrin homology domain of *BTK* (median VAF: 16%) was seen in 1 Acala pt. *L528W* and *A428D* co-mutations were observed in 1 Ibr pt. Six Acala pts had *TP53* and *BTK* co-mutations. Emergent *TP53* mutations were seen in both groups (13% [Acala] vs. 7% [Ibr], $P = 0.47$; median VAF: 5% [Acala] versus 37% [Ibr]). Only 2 Ibr pts had *TP53* mutations (1 had *TP53/BTK* co-mutation). No statistical difference was seen in the

Figure 1. Emergent mutations at the time of progression in patients treated with acalabrutinib and ibrutinib



*$P<0.05$ per Fisher's exact test.

Patients could have been included in >1 mutation category but were counted only once in a given single mutation category.

proportions of Acala versus Ibr pts who acquired *BTK* mutations among pts with del(17p) (39% vs. 64%; $P = 0.18$), del(11q) (77% vs. 46%; $P = 0.07$), complex karyotype (58% vs. 73%; $P = 0.48$), unmutated IGHV (90% vs. 100%; $P = 0.55$), or trisomy 12 positivity (3% vs. 18%; $P = 0.16$). Additional mutations (Acala vs. Ibr) included *DNMT3A* (5 vs. 1 pts), *TET2* (1 pt for each), and *NRAS* (1 pt; Acala only).

Conclusions: While common mutations were observed with both treatments, patterns of mutation frequency, mutation VAF, and uncommon *BTK* variants varied with Acala versus Ibr in this R/R CLL population despite shared resistance mutations. Additional studies could help to understand contributions of the differing pharmacologic properties of these 2 BTKis and variations by line of treatment.

The research was funded by: AstraZeneca

Keywords: Chronic Lymphocytic Leukemia (CLL), Genomics, Epigenomics, and Other -Omics, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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Research funding: Abbvie, Janssen, Karyopharm Therapeutics, Loxo/Lilly, Pharmacyclics, Schrodinger

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Stock ownership: AstraZeneca; Gilead Sciences

164 | THE RNA HELICASE DDX21 COOPERATES WITH ETS1 AND FLI1 IN CELL CYCLE REGULATION AND SMALL NUCLEOLAR RNA PROCESSING TO SUSTAIN THE SURVIVAL OF DLBCL CELLS

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Introduction: We have previously shown that the two ETS transcription factors ETS1 and FLI1, co-mapped in the 11q24.3 region, are recurrently gained in up to 25% of diffuse large B cell lymphomas (DLBCL), and largely co-regulate a series of genes involved in B cell signaling, differentiation and cell cycle (Bonetti et al., 2013; Priebe et al., 2020; Sartori et al., 2021). ABC-DLBCL is a more aggressive subtype of DLBCL compared to GCB-DLBCL, and it is associated with poor outcomes when treated with a standard therapy. As a result, there is an urgent need to elucidate new therapeutic venues for this dismal malignancy. While FLI1 is expressed at a higher level in DLBCL of the germinal center B-cell (GCB) type than in the activated B-cell-like (ABC) DLBCL, ETS1 is more expressed in the latter subgroup. We and others have reported preclinical anti-tumor activity in lymphomas and other tumors with small molecules blocking the binding of ETS factors and RNA helicases (Erkizan et al., 2009; Spriano et al., 2019). In this study, we identified additional therapeutic targets related to these transcription factors, by investigating the ETS1 interactome in ABC DLBCL.

Methods: Liquid Chromatography tandem Mass Spectrometry (LC-MS/MS) was done on proteins obtained with pull down of strep-tagged ETS1. Proteins with a spectral count above 4 were considered candidate interactors, and validated by normal and reverse co-immunoprecipitation experiments. RNASeq and small RNASeq analysis was done after DDX21 siRNAs silencing in 2 ABC (HBL1 and U2932) and in 2 GCB (OCI-Ly1 and VAL) DLBCL cell lines. In addition, we performed ChIPSeq for DDX21 on the same 4 cell line models.

Results: Proteins related to RNA processing, more specifically in spliceosome (NOP56 and ALYREF) and in ribosome biogenesis (SF3B1 and DDX21), were among the identified ETS1 interactors in the ABC DLBCL HBL-1 cell line. We focused on the novel ETS1 interactor DDX21, an RNA helicase also regulated by FLI1 (Sartori et al., 2021). DDX21 appeared more expressed in ABC than GCB DLBCL ($P < 0.001$) in 4 datasets (GSE98588, $n = 117$; phs001444.v2.p1, $n = 432$; GSE95013, $n = 33$; GSE10846, $n = 350$). When we silenced DDX21 with siRNAs, toxicity was seen in ABC (U2932) and not in GCB (OCI-Ly1) cell lines. Our results indicate DDX21 is involved in regulating proteins involved in cell cycle (FDR < 0.001), ribosomes (FDR < 0.001), spliceosome (FDR < 0.001) and small nucleolar RNAs (snRNAs).

Conclusions: In ABC DLBCL, ETS1 interacts with proteins involved in spliceosome and in ribosome biogenesis, including DDX21. Highly expressed in ABC than GCB DLBCL, DDX21 sustains the survival of lymphoma cells by regulating cell cycle and RNA processing. Targeting the interaction between ETS1 and DDX21 represents a novel therapeutic modality against ABC DLBCL.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Genomics, Epigenomics, and Other -Omics, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

165 | ALPHA-KETOGLUTARATE SUPPRESSES TUMOR GROWTH OF DIFFUSE LARGE B-CELL LYMPHOMA BY INDUCING FERROPTOSIS

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Background: Metabolic reprogramming is one of the vital characteristics of cancers. Glutamine metabolism is an essential metabolic pathway in tumorigenesis, which provides a ready carbon and nitrogen source to support tumor biosynthesis, energy metabolism, and intracellular homeostasis. As a type of lymphoma with heterogeneity, diffuse large B-cell lymphoma (DLBCL) is characterized by severe metabolic vulnerability represents. Given the importance of glutamine metabolism in human cancer, revealing the characteristics of glutamine metabolism in DLBCL is expected to provide new pathogenesis and effective treatment strategies for patients.

Methods: Peripheral blood serum of 120 DLBCL patients and 60 healthy donors were collected for untargeted metabolomics sequencing, followed by metabolic characteristics analysis. Subsequently, the biological functions and mechanisms of α-ketoglutarate (α-KG) were explored by RNA sequencing. Finally, ROS detection, ATP detection, and lipid peroxidation were used to verify the mechanism of α-KG-induced ferroptosis.

Results: Untargeted metabolomics profiling revealed that the metabolic characteristics of DLBCL patients were significantly different from healthy controls. Among the differentially expressed metabolic pathways, glutamine metabolism accounted for the highest weight, suggesting the importance of glutamine metabolism in the tumorigenesis of DLBCL (Figure 1A). Notably, glutamate, glutamine, and α-KG were the critical metabolites in glutamine metabolism. Clinical data analysis identified that high glutamine concentrations and low decreased α-KG were associated with poor prognosis in DLBCL patients. Subsequently, dimethyl α-ketoglutarate (DM-αKG) was used to reverse glutamine metabolism and increase α-KG concentration. In vitro studies showed that DM-αKG treatment significantly inhibited cell proliferation of DLBCL cells both in vitro and in vivo (Figure 1B). In addition, DM-αKG induced non-apoptotic cell death phenotypes, represented by cell membrane swelling and LDH release. To further explore the functional mechanisms of α-KG in DLBCL, we performed RNA-sequencing in DM-αKG-treated DLBCL cells. As shown in enrichment analysis, DM-αKG treatment showed apparent dysfunction in the hypoxia-inducible factor pathway, oxidative stress response,

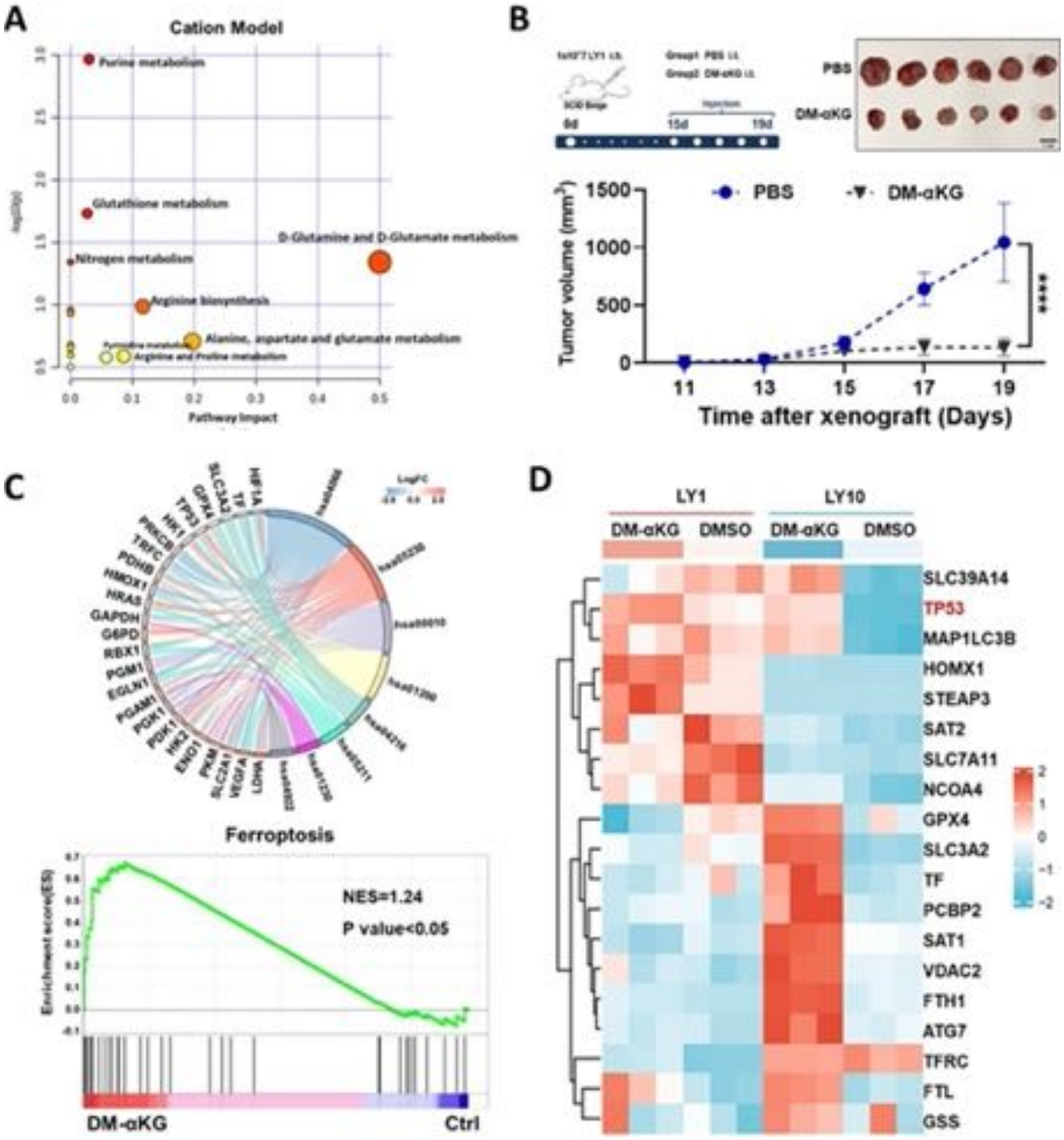
and ferroptosis (Figure 1C). In particular, DM-αKG treatment promoted ROS release and lipid peroxidation, followed by impaired ATP production and decreased mitochondrial pathway expression. Moreover, differentially expressed genes analysis identified an increased expression of TP53 in the ferroptosis pathway, indicating the importance of TP53 in α-KG-induced ferroptosis (Figure 1D).

Conclusion: Our present findings were the first to identify the metabolic characteristics of DLBCL patients and elucidate the anti-tumor effects of α-KG in DLBCL.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Metabolism

No conflicts of interests pertinent to the abstract.

Figure 1



166 | CTPS1 ACTS AS A PROGNOSTIC BIOMARKER AND THERAPEUTIC TARGET IN MANTLE CELL LYMPHOMA

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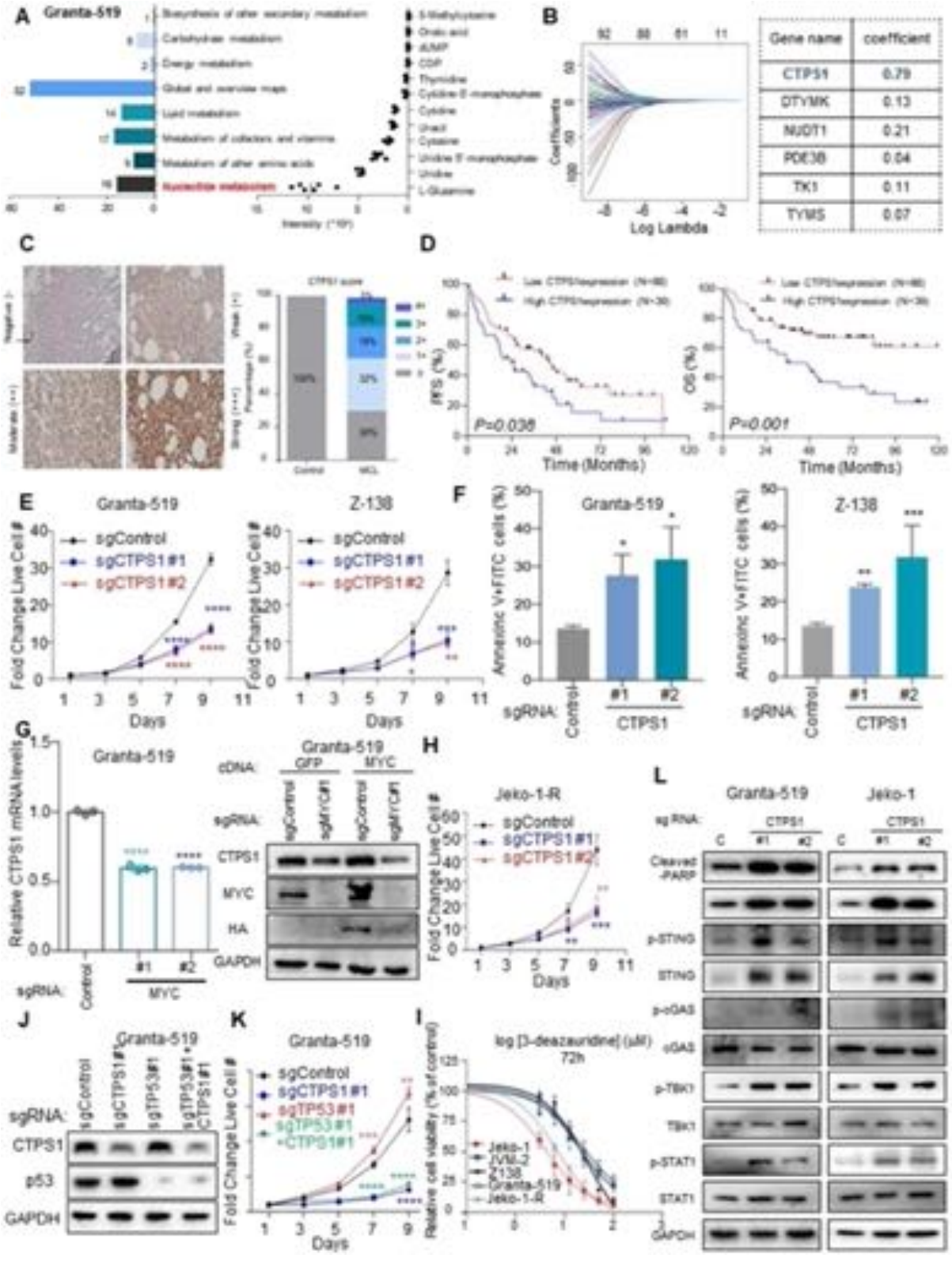
Introduction: Mantle cell lymphoma (MCL) represents 6 to 8% of non-Hodgkin's lymphoma with generally poor prognosis. Cytidine triphosphate synthase 1 (CTPS1) is a critical regulatory enzyme in cytidine metabolism, catalyzing the rate-limiting step in de novo CTP synthesis. Herein, we aim to investigate the clinical significance and functional mechanisms of CTPS1 in MCL patients.



Methods: Lymph node, bone marrow biopsy, peripheral blood specimens and MCL cell lines were utilized as models. Liquid chromatography-coupled tandem mass spectrometry (LC-MS/MS)-based analysis was performed to measure the steady-state level of metabolites. GSE93291 dataset and immunohistochemistry (IHC) staining were utilized to determine the relationship between expression levels of CTPS1 and patient outcome. CRISPR/Cas9 editing was employed to engineer the loss-of-function models of CTPS1 and other key enzymes involved in CTP synthesis.

Results: Metabolic Profiling revealed dramatically aberrant cellular abundance of metabolic intermediates in the CTP synthesis pathway (Figure 1A). For GSE93291 analysis, a nucleotide metabolism related prognostic model was established by bioinformatic analysis and CTPS1 was screened out by highest regression coefficient (Figure 1B). IHC staining of CTPS1 in 105 MCL tissues confirmed that elevated CTPS1 expression was significantly associated with poor PFS ($P = 0.038$) and OS ($P = 0.001$) in MCL patients (Figure 1C-D). Multivariate Cox regression analysis showed that high CTPS1 expression was an independent prognostic indicator of both PFS and OS. CTPS1 depletion significantly impaired outgrowth and increased apoptosis of MCL cells, suggesting that CTPS1 is the major isozyme important for MCL survival (Figure 1E-F). In primary tumor samples, MYC protein levels were significantly correlated with CTPS1 protein levels ($P < 0.001$, $R = 0.638$). MYC knockout blocked CTPS1 mRNA and protein expression prior to induction of cell death, suggesting a requisite role of MYC in CTPS1 transcription regulation (Figure 1G). Remarkably, TP53 aberrant and ibrutinib-resistant MCL cells rely on cytidine metabolism (Figure 1H). Genetic or chemical inhibition (3-deazauridine) of CTPS1 reversed poor responsiveness of MCL cell lines to ibrutinib (Figure 1I). Cytidine level was significantly increased in TP53-deficient MCL cells and the effect of CTPS1 inhibition was independent of TP53 status (Figure 1K). Gene set enrichment analysis of RNA-sequencing revealed that CTPS1 inhibition induced DNA damage and apoptosis. Moreover, CTPS1 inhibition caused cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) activation, which triggered innate immune pathway, leading to cells growth inhibition (Figure 1L).

Conclusions: CTPS1-mediated cytidine metabolism plays an important role in MCL. CTPS1 may serve as a prognostic biomarker and therapeutic target in MCL patients.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, Metabolism

No conflicts of interests pertinent to the abstract.

167 | LIPID METABOLISM REPROGRAMMING ROLES IN MANTEL CELL LYMPHOMA GROWTH AND SURVIVAL

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Introduction: Metabolic reprogramming is a hallmark of cancer progression. However, there are few studies in mantle cell lymphoma (MCL). Protein arginine methyltransferase 5 (PRMT5), catalyzes monomethylation and symmetric demethylation of arginine residues on histone and nonhistone proteins and participates in tumor progression. This study aimed to investigate the mechanism of PRMT5-induced lipid reprogramming in MCL.

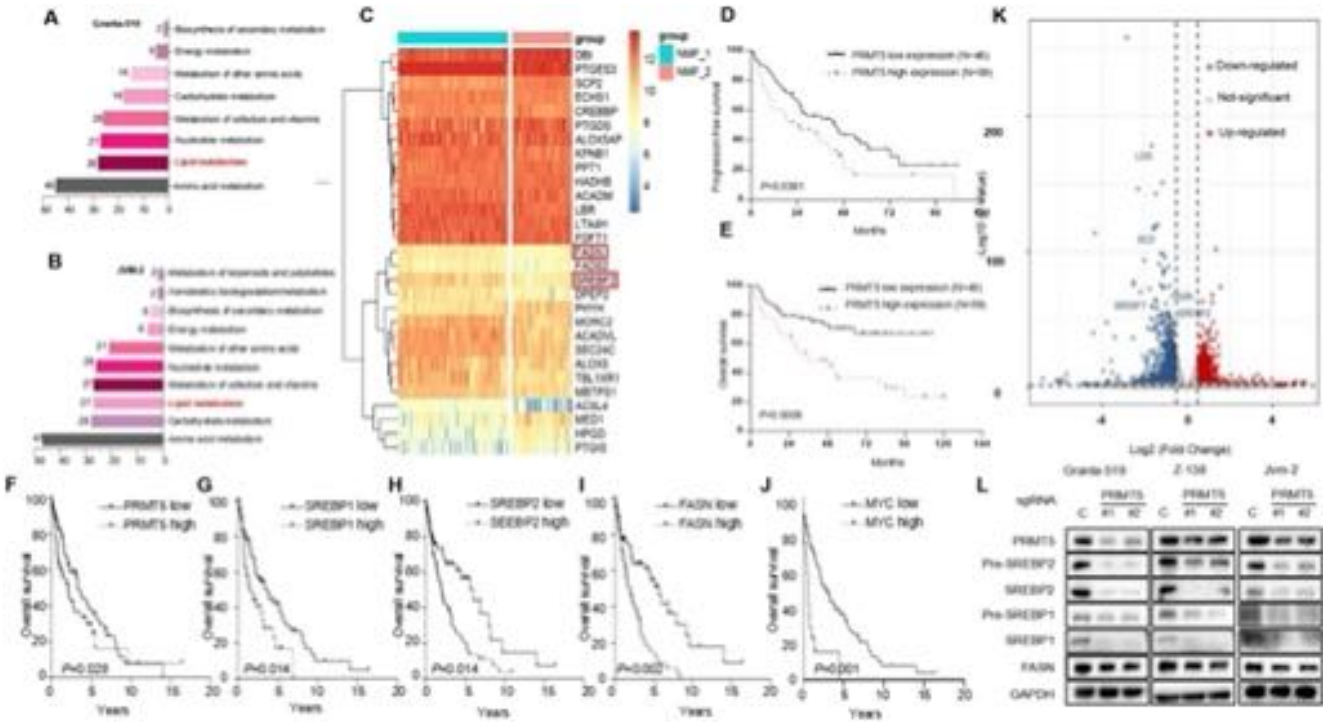
Method: Lymph node, bone marrow biopsy, peripheral blood specimens and MCL cell lines were utilized as models. Liquid chromatography-coupled tandem mass spectrometry (LC-MS/MS)-based analysis was performed to measure the steady-state level of metabolites. GSE93291 dataset and immunohistochemistry (IHC) staining were utilized to determine the relationship between expression levels of PRMT5 and patient outcome. CRISPR/Cas9 editing was employed to engineer the loss-of-function models of PRMT5 and other key genes involved in lipid metabolism.

Result: Non-targeted LC-MS/MS analysis showed that lipid metabolites were rich in MCL cell lines (Figure 1A and 1B). Through systematic analysis of the relationship between lipid metabolism-related genes and MCL prognosis in GSE93291, PRMT5, SREBP1, SRENP2, FASN and MYC were found to be associated with the overall survival (OS) of MCL patients (Figure 1F–1J), which suggested that lipid metabolism reprogramming may be involved in the development of MCL. IHC staining of PRMT5 in 105 MCL tissues confirmed that elevated PRMT5 expression was significantly associated with poor progression free survival (PFS) ($P = 0.039$) and OS ($P < 0.001$) in MCL patients (Figure 1D and 1E). Multivariate Cox regression analysis showed that high PRMT5 expression was an independent prognostic indicator of OS ($P = 0.003$). Gene transcriptome sequencing showed downregulation of the PRMT5 caused the reduced expression of SREBP1/SREBP2 and FASN and change the expression of lipid metabolite (Figure 1K). PRMT5, SREBP1/SREBP2 and FASN depletion significantly impaired outgrowth and increased apoptosis of MCL cells. In primary tumor samples, MYC protein levels were significantly correlated with PRMT5 protein levels ($P < 0.001$). PRMT5 knockout blocked MYC mRNA and protein expression, suggesting a requisite role of PRMT5 in MYC transcription regulation. Further molecular biological methods were used to verify that PRMT5 could participate in lipid metabolism reprogramming through MYC by changing the expression levels of SREBP1/SREBP2 and FASN (Figure 1L).

Conclusion: In this study, we first clarify the role of PRMT5 in lipid metabolism reprogramming in MCL. PRMT5 enhances the expression of lipogenic genes via MYC/SREBPs signaling and SREBPs-mediated lipogenesis is critical for MCL cells growth and metastasis in vitro and in vivo. Meanwhile, PRMT5, SREBP1/2, and FASN are suggested as new prognostic factors in MCL patients.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, Metabolism

No conflicts of interests pertinent to the abstract.



168 | **DECIPHERING THE ROLE OF MSI2 AS A REGULATOR OF STEM-LIKE PROPERTIES IN MANTLE CELL LYMPHOMA**

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Introduction: Mantle cell lymphoma (MCL) is one of the most aggressive mature B-cell neoplasms. MCL frequently responds to initial treatments although later the development of resistance is common, relapsing with a more aggressive disease. Several groups have isolated MCL-cancer stem cells (CSC), presenting self-renewal, clonogenic growth, tumorigenic capabilities, and resistance to standard therapies.

SRY-related HMG-box gene 11 (SOX11) is expressed in progenitors and embryonic stem cells (ESC). Its overexpression has been observed in undifferentiated tumor cell populations with CSC features. In MCL, its overexpression has been associated with more aggresive behavior and worse patient's outcome. SOX11 is regulating several oncogenic mechanisms in MCL. However, nothing is known about its possible stemness role in MCL.

Methods: To search for stem-cell related genes regulated by SOX11 that may contribute to MCL biological and clinical evolution, we compared SOX11+ and SOX11- MCL primary cases differential gene expression profiling (GEP). We analyzed the prognostic value of stem-cell related genes directly regulated by SOX11 and their involvement in stemness features in MCL, using several cellular and molecular approaches.

Results: We observed a significant enrichment of leukemic- and hematopoietic stem cells (HSC)-related genes in the SOX11+ compared to SOX11- MCCL subtype. The RNA-binding protein Musashi-2 (MSI2), that maintains self-renewal and prevents differentiation in ESC and HSC, emerged as one of the most significant stem cell-related gene upregulated in SOX11+ MCL primary cases. Moreover, we have demonstrated that SOX11 binds to *MSI2* promoter and activates its expression. However, *MSI2* intronic superenhancers might be also responsible for MSI2 upregulation in MCL. Moreover, we found that higher expression of MSI2 is significantly associated with poor overall survival, independently of other knows high-risk features in MCL.

MSI2 knockdown (KD) or MSI2 function inhibition with Ro 08-2750 (Ro) changed the GEP, downregulating genes involved in CSC-related pathways whereas upregulating pro-apoptotic genes in MCL cells. MSI2KD or MSI2 Ro-inhibition led to suppress stemness phenotypic features, such as clonogenic growth, chemoresistance and cell survival. Moreover, MSI2KD MCL cells have reduced tumorigenic engraftment into mice bone marrow and spleen compared to control cell lines in vivo, suggesting that MSI2 is an important tumorigenic factor in MCL.

Conclusions: Our findings suggest that MSI2 expression in MCL is upregulated by SOX11 binding to its promoter and to several active *MSI2* intronic superenhancers. MSI2 upregulation might contribute to sustain stemness and chemoresistance to MCL cells, through the post-transcriptional regulation of stem cell-related genes, representing a novel target for therapeutic interventions in aggressive MCL.

Keywords: Genomics, Epigenomics, and Other -Omics, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

169 | LYMPH NODE LOCATION AND RETENTION PROPERTIES OF DC-SIGN ENGAGEMENT WITH THE IMMUNOGLOBULIN OLIGOMANNOSES OF FOLLICULAR LYMPHOMA

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Introduction: The oligomannose-type glycans occupying the surface immunoglobulin antigen-binding site (sIg-Mann) are a tumor-founding post-translational requirement of classic follicular lymphoma (FL). These are universally acquired and a clonal necessity during the entire natural history of FL from the early stages throughout transformation into EZB-DLBCL (*Chiodin G, Blood 2021*, *Odabashian M, Blood 2020*). The low-affinity interaction of sIg-Mann with its specific ligand DC-SIGN distinguishes from conventional high-affinity antigen:Ig protein interactions for promoting prolonged low-level growth and prosurvival signals via PI3K/AKT and not endocytosis (Linley A, Blood 2015). However, the location and function of DC-SIGN remains to be further elucidated. Here, we investigated the hypothesis that the specific DC-SIGN:Ig-Mann interaction functions to promote retention of FL cells in tissue niches maintaining selective survival advantage.

Methods: Immunofluorescence imaging was used to determine DC-SIGN histological location in primary FL lymph nodes. In WSU-FSCCL cells, DC-SIGN effects on sIg redistribution were measured by dSTORM; adhesion to VCAM-1 in presence/absence of inhibitors was measured by flow cytometry.

Results: Immunofluorescence of lymph nodes from FL patients revealed that DC-SIGN was expressed on interfollicular CD163+ macrophages and, remarkably, on CD23+ follicular dendritic cells (FDC), claiming an influence on FL cell retention and survival. dSTORM revealed that DC-SIGN induced less dense and more diffuse surface Ig clusters compared to anti-Ig, reflecting an immature sIg redistribution unable to promote endocytosis and death. However, DC-SIGN efficiently induced adhesion of sIg-Mann+ve lymphoma cells to VCAM-1, known to be expressed on both lymph node macrophages and FDC, and inhibited migration towards SDF-1 in vitro. Blocking of DC-SIGN carbohydrate-recognition domain completely abrogated DC-SIGN-induced adhesion. Although intracellular signals were significantly lower, DC-SIGN induced levels of adhesion similar to those induced by anti-Ig. Adhesion to VCAM-1 was observed at concentrations from 20 μg/ml down to 20 ng/ml, even when AKT and ERK phosphorylation was not detectable. Either proximal inhibition of the PI3K/AKT pathway, or distal inhibition of ARP2/3, formin, and Cdc42 for lamellipodium formation at the surface membrane, suppressed adhesion.

Conclusions: These results reveal an important mechanism of the DC-SIGN:sIg-Mann interaction that fine-tunes signals for membrane adaptation towards tumor cell adhesion, without promotion of cell death. This possibly facilitates FL cell retention in the lymph node protected tumor niche where selective growth and survival signals are maintained. Interrupting this interaction will be a novel way towards tumour-specific targeted therapy in FL patients.

The research was funded by: This research was funded by Blood Cancer UK (grant 18009), Cancer Research UK (ECRIN-M3 accelerator award C42023/A29370, program C2750/A23669, and BTERP project C36811/A29101). D.T. was funded by the Eyles Cancer Immunology PhD scholarship, G.C. was funded by the Eyles Cancer Immunology Fellowship and the Southampton Cancer Immunology Centre Pump-priming award 2021).

Keywords: Indolent non-Hodgkin lymphoma, Microenvironment, Targeting the Tumor Microenvironment

Conflicts of interests pertinent to the abstract.

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Employment or leadership position: University of Siena
Consultant or advisory role: Beigene
Honoraria: Abbvie, Janssen-cilag, Beigene, Astra-Zeneca
Research funding: Cancer Research UK
Educational grants: Beigene, Abbvie
Other remuneration: BC Platform

170 | CD30 PROTECTS EBV-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA CELLS AGAINST MITOCHONDRIAL DYSFUNCTION THROUGH INCREASING BNIP3 EXPRESSION

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Introduction: EBV-positive diffuse large B-cell lymphoma (EBV+DLBCL) predicts poor prognosis. Studies have found that CD30 expression was more frequent in EBV+DLBCL patients compared to EBV-negative (EBV-) DLBCL and high CD30 expression was associated with poor survivals in EBV+DLBCL. All these facts suggested a synergistic effect between CD30 expression and EBV infection.

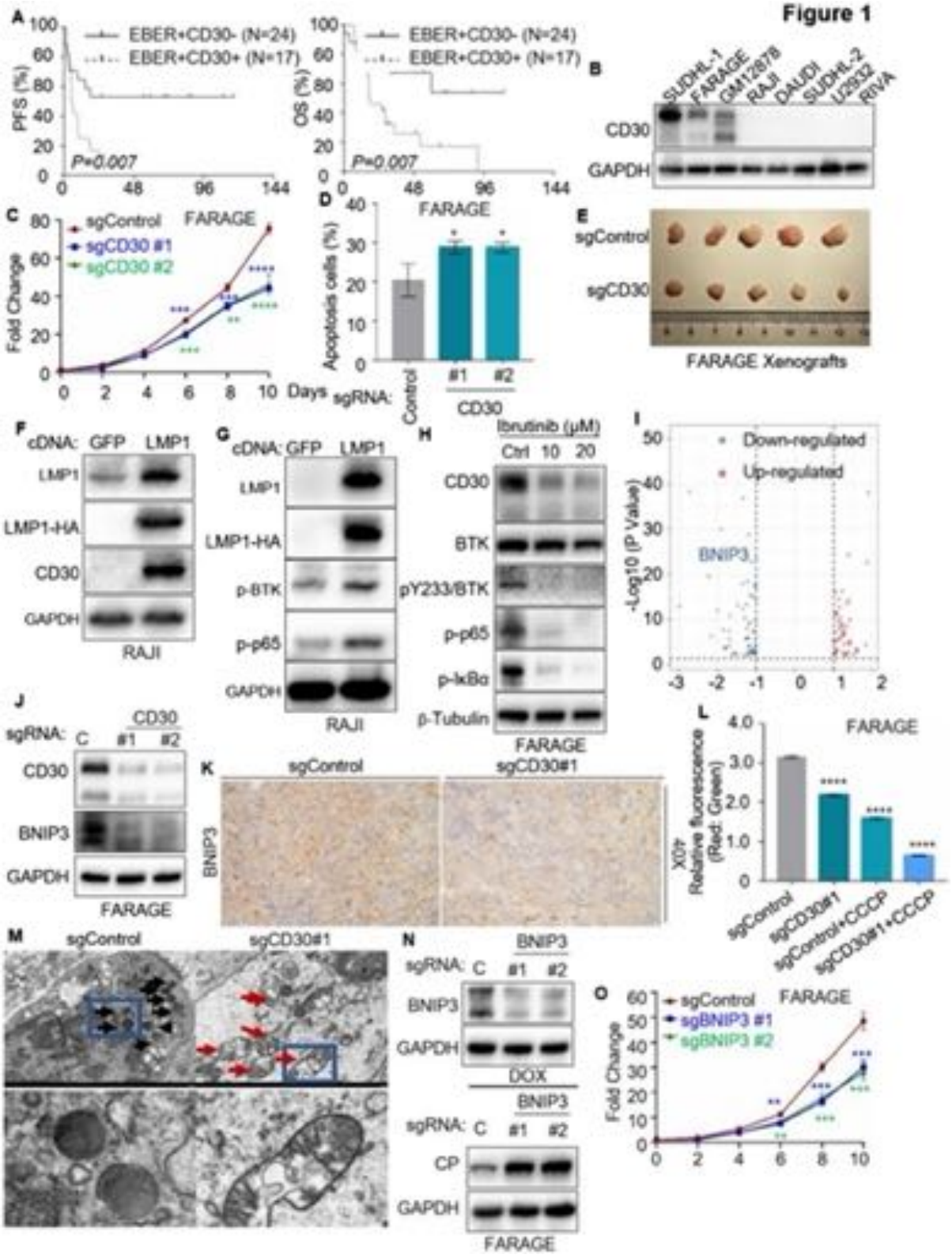
Methods: FARAGE and GM12878 are type II and III latency EBV-infected B cell lines while RAJI and DAUDI are type I. SUDHL-2, U2932 and RIVA are EBV-negative DLBCL cell lines. CRISPR/Cas9 editing was employed to engineer the loss-of-function models of genes involved in this study.

Results: A total of 451 patients were included and the results showed patients had worse PFS ($P = 0.007$) and OS ($P = 0.007$) when CD30 was co-expressed with EBER in DLBCL (Figure 1A). Immunoblot analysis showed that CD30 expression in EBV latency II and III cell lines were higher than EBV latency I and EBV-negative cell lines (Figure 1B). Relevant experiments indicated that the tumor cells with high CD30 expression demonstrated rapid proliferation and were less susceptible to apoptosis (Figure 1C and 1D) and CD30-KO mice

showed significantly smaller tumor size compared to CD30 wild type (WT) mice (Figure 1E).

A LMP1 overexpression resulted in CD30 expression (Figure 1F). To elucidate how LMP1 regulated CD30, we found LMP1 overexpression increased p-Btk and p-p65 (Figure 1G). Immunoblot analysis detected a decrease in CD30 expression when latency II and III cells were treated with ibrutinib (a BTK inhibitor) and ibrutinib also abolished LMP1-induced p-p65 and p-IκBα (Figure 1H).

We performed gene expression analysis following CD30 KO in FARAGE and the results indicated depression of CD30 inhibited



BNIP3 expression (Figure 1I). Immunoblot analysis showed that BNIP3 expression in the KO group were significantly lower compared to those in the control group (Figure 1J). IHC staining results revealed a significant decrease of BNIP3 expression in CD30-KO mice (Figure 1K).

We found that CD30 KO by CRISPR/Cas9 system led to a significant fall in the MMP (Figure 1L). Moreover, the accumulation of damaged mitochondria was observed in CD30-deficient tumor cells in mice by TEM (Figure 1M). Above results suggested that silencing of CD30 resulted in mitochondrial damage and the inhibition of mitochondrial activity. As BNIP3 was identified as a target gene for CD30, we investigated the effect of BNIP3 in EBV+DLBCL. Collectively, our results validated an important role of BNIP3 in promoting EBV +DLBCL survivals (Figure 1N and 1O).

Conclusions: In this study, we have demonstrated that CD30 is regulated by LMP1 through BCR/NF-κB signaling and exerts oncogenic effects in EBV+DLBCL. Furthermore, the current study provided compelling evidence that CD30 could protect against mitochondrial dysfunction through increasing BNIP3 expression to affect cells survival in EBV+DLBCL.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Molecular Targeted Therapies, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

171 | ACTIVATION OF THE NOVEL TUMOR SUPPRESSOR SAMHD1 INHIBITS CELL GROWTH AND INDUCES INTERFERON-BETA (IFN-β) GENE EXPRESSION IN CLASSICAL HODGKIN LYMPHOMA (CHL)

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Introduction: The SAMHD1 protein is a deoxynucleoside triphosphate (dNTP) triphosphohydrolase, which depletes the intracellular dNTP substrates. Mutations of SAMHD1 gene have been linked to Aicardi-Goutières syndrome, and have been detected in a subset of chronic lymphocytic leukemia, mantle cell lymphoma and T-prolymphocytic leukemia. Therefore, SAMHD1 may play a role in lymphomagenesis as a tumor suppressor. We have recently reported that SAMHD1 expression by the neoplastic Hodgkin and Reed Sternberg cells (HRS) correlates with unfavourable clinical outcome in classical Hodgkin lymphoma (cHL) (Xagoraris et al., Br J Haematol 2021;193:488). SAMHD1 activity can be regulated at post-translational level through phosphorylation at residue T592 by Cyclin-CDKs in various cell systems. T592-phosphorylation of SAMHD1 results in decreased hydrolase enzymatic activity, thus inhibiting SAMHD1 functions. The activation (phosphorylation) status of SAMHD1 protein in HRS cells of cHL is still unknown to date.

Methods: The in vitro system included 5 cHL cell lines (MDAV, L1236, HDLM2, L428, KMH2). Expression and phosphorylation of SAMHD1 was analysed by Western blot using specific antibodies. The cHL cell lines were treated with viral protein X (VPX) or control DX to eliminate SAMHD1 as previously described (Herold et al., Nat Med 2017;23:256). Restoration of SAMHD1 activity was achieved by using a CDK4/6 inhibitor (Palbociclib) or Sulforaphane (SFN), which are known to inhibit SAMHD1 phosphorylation at T592. Gene expression of interferons (IFNs) and other immunomodulators, such as IFN-β, CXCL10, IFN-γ, STING, as well as, a control gene (GAPDH), was assessed at the mRNA level by qRT-PCR.

Results: SAMHD1 is differentially expressed and phosphorylated (inactivated) among the cHL cell lines assessed. Depletion of SAMHD1 by VPX resulted in significantly lower levels of IFN-β and CXCL10 mRNA in HRS cells, which was linked to decreased NK cell killing of the cHL cells in vitro. Restoration of SAMHD1 activity through de-phosphorylation, either by Palbociclib or SFN, resulted in significant decrease in cell growth, and to lesser degree in cell viability, which were associated with upregulation of the CDK inhibitors, p21 and p27, pro-apoptotic protein Bax, as well as, down-regulation of Cyclin D2 and anti-apoptotic proteins. SAMHD1 de-phosphorylation/activation also led to increased gene expression of IFN-β by cultured cHL cells but differential effects on CXCL10 and IFN-γ gene regulation. In particular, treatment with SFN was associated with dramatic increase (up to 40-fold) of IFN-β mRNA level in L1236 cells.

Conclusions: The novel tumor suppressor SAMHD1 may be phosphorylated and thus inactivated in HRS cells in vitro. Restoration of SAMHD1 enzymatic activity by agents such as Palbociclib (used in clinical trials in other cancer types) or SFN may have therapeutic implications in patients with cHL.

Keywords: Basic and Translational Science, Hodgkin lymphoma, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

MICROENVIRONMENT

172 | UNRAVELING THE MECHANISMS OF C-MYC-MEDIATED ESCAPE FROM ANTIBODY AND T-CELL BASED ANTI-TUMOR IMMUNE ATTACK IN B-CELL MALIGNANCIES

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Background: Overexpression of the c-MYC oncogene (hereafter MYC) was implicated to suppress tumor immune surveillance and

was shown to associate with poor clinical outcome in several malignancies. Here, we investigated its impact on the anti-tumor effect of antibody and T-cell based immunotherapies in diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL) and multiple myeloma (MM).

Methods: Using CRISPR-Cas9 gene editing technology, we targeted MYC in the DLBCL cell line OCI-LY18 and analyzed 10 randomly selected daughter clones showing partial disruption of the MYC gene. In one clone we repaired the MYC DNA sequence by homologous recombination to confirm the role of MYC in tumor cell lysis via NK-cell mediated (rituximab and daratumumab) and T-cell redirecting (blinatumomab) antibodies, target antigen expression and expression of apoptosis regulatory proteins.

We extended our studies in a panel of DLBCL, BL and MM cell lines using the specific MYC-MAX dimerization inhibitor 10058-F4 to study the effects of MYC on immunotherapeutic treatment strategies in B-cell malignancies.

Results: Rituximab-dependent cellular cytotoxicity (ADCC) was significantly increased in 9/10 MYC-targeted clones and reversed in the MYC repaired subclones, illustrating the direct involvement of MYC in modulating rituximab-mediated ADCC (Figure 1A–C). The increase in ADCC was associated with upregulation of CD20 expression, the target antigen of rituximab (Figure 1D–E).

MYC targeting also increased daratumumab-dependent and blinatumomab-mediated cytotoxicity, but without upregulation of their target antigen expression (CD38 and CD19, respectively), indicating the existence of mechanisms beyond modulation of target antigen expression. In depth analyses revealed that MYC targeting appeared to upregulate the expression of pro-apoptotic PUMA and downregulated the anti-apoptotic BCL2, XIAP, Survivin and MCL-1, attributing a role to MYC in development of resistance to apoptosis, a key death mechanism induced by NK- and T-cells (Figure 1F).

Furthermore, blinatumomab induced a significantly higher level of T-cell activation and cytokine release in response to MYC targeted versus parental cells, revealing a hitherto unknown T-cell suppressive mechanism mediated by MYC overexpression in tumor cells.

Finally, the efficacy of these immunotherapies were significantly improved in several DLBCL, BL and even MM cell lines and primary cells derived from DLBCL patients after inhibition of MYC with a small molecule 10058-F4, extending the results in various B-cell malignancies.

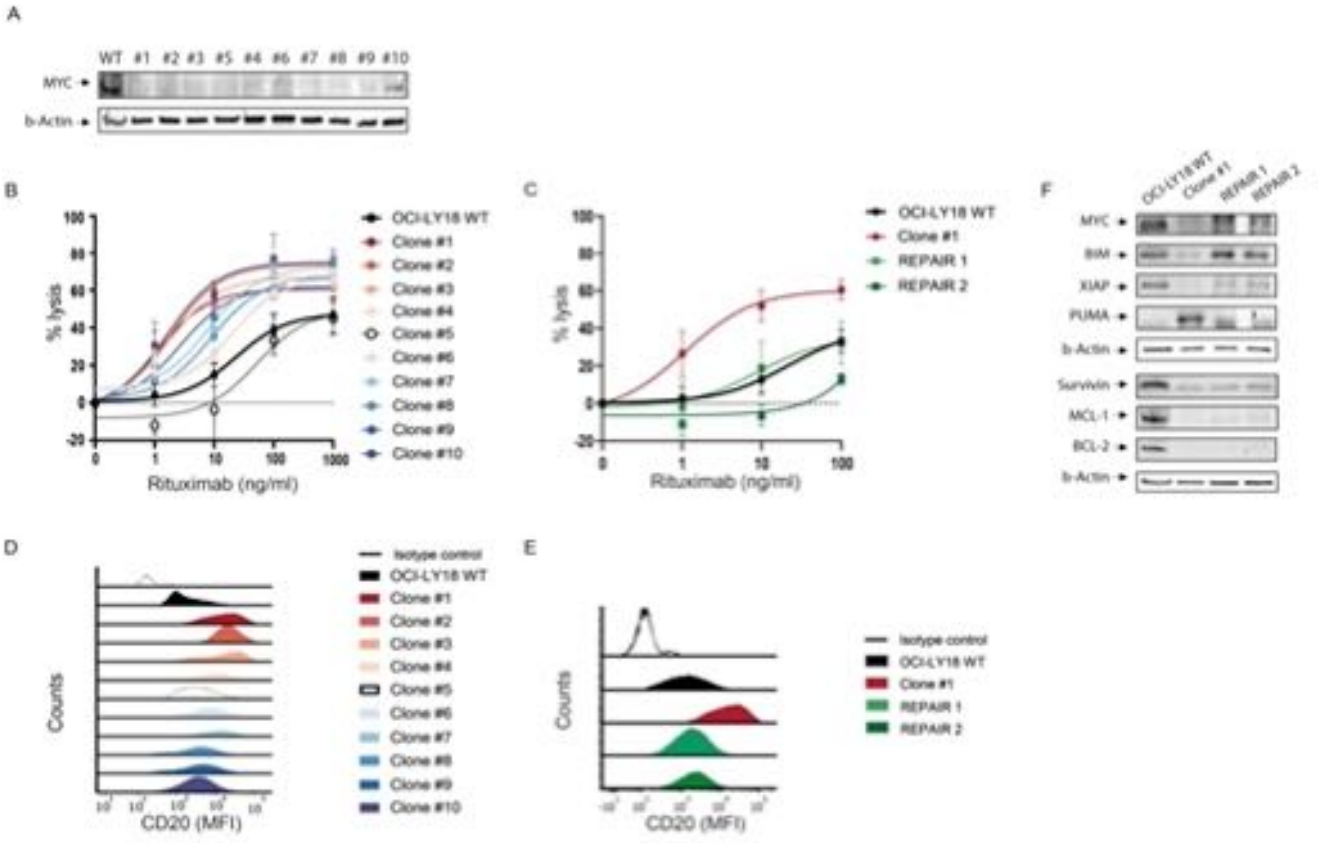

Figure 1: MYC is involved in escape from antibody and T-cell based immunotherapies that is beyond target antigen downregulation and involves downregulation of anti-apoptotic proteins. A) MYC protein expression in OCI-LY18 parental cell line (WT) and MYC targeted daughter clones. B) Rituximab-mediated ADCC in OCI-LY18 WT (black) and MYC targeted clones (colored). C) Rituximab-mediated ADCC in OCI-LY18 WT (black), MYC targeted clone #1 (red) and MYC repaired subclones (green). D) CD20 expression level in OCI-LY18 WT (black) and MYC targeted clones (colored). E) CD20 expression level in OCI-LY18 WT (black), MYC targeted clone #1 (red) and MYC repaired subclones (green). F) Immunoblot of apoptosis regulatory proteins in OCI-LY18 WT, MYC targeted clone #1 and MYC repaired subclones.

Conclusion: We demonstrate a proof-of-concept that MYC is involved through several mechanisms in escape from NK-cell ad T-cell mediated anti-tumor immune attack in B-cell malignancies. These findings may contribute to the development of improved immunotherapeutic strategies in MYC overexpressing tumors.

Encore Abstract - previously submitted to regional or national meetings (up to <1'000 attendees)

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Immunotherapy, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

173 | DECIPHERING THE ROLE OF MACROPHAGES AND T CELLS IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA: TUMOUR AGGRESSIVENESS AND RESPONSE TO IMMUNOTHERAPIES

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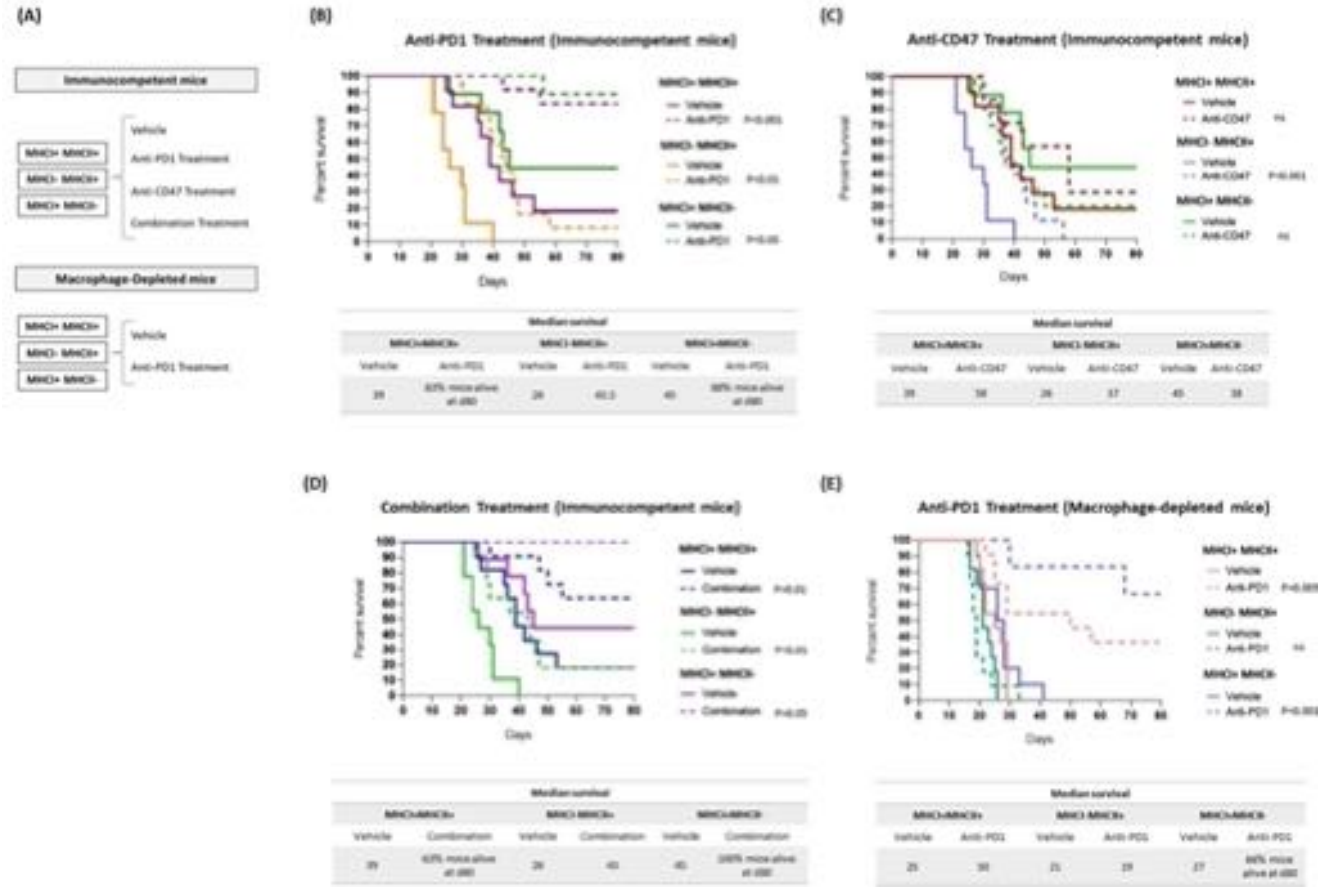
Introduction: Primary Central Nervous System Lymphoma (PCNSL) represents 5% of extranodal lymphomas. The brain has low immunosurveillance which contributes to an inefficient immune response against PCNSL cells. Of notice, up to 70% of patients have mutations in MHC genes and amplifications in PD-L1, which increases immune evasion by hampering T cell response. Macrophages are supressed by the MHCI in cancer cells, rendering cells that downregulate it more exposed to phagocytosis. Against this background, we aimed to decipher the differential role of macrophages and T cells in PCNSL tumour growth and response to immunotherapy.

Methods: Luciferase-expressing A20 murine B-cell lymphoma cells were genetically modified to knock-out MHCI or MHCII by CRISPR-Cas9 and injected into the brain of immunocompetent (IC) or macrophage-depleted (MD) mice. Once tumours were stablished, mice were treated intravenously with seven injections, twice/week, of anti-PD1, anti-CD47 or the combination of both (Figure 1A). Survival and tumoral growth were studied. Also, brains were obtained from mice treated with three injections for macrophage, B and T cell analysis by flow cytometry and IHC.

Results: In IC mice, all anti-PD1 treated mice showed significant differences in tumoral growth and survival compared to vehicle; however, MHCI- tumours had the lowest overall survival (Figure 1B). With anti-CD47, only MHCI- PCNSL mice had increased

Figure 1



survival compared to vehicle (Figure 1C). Combination was effective in all groups, but no drug synergy was seen (Figure 1D). In MD mice, all tumours were more aggressive than in IC mice. With anti-PD1, MHCI+ PCNSL mice achieved a complete tumour regression and survived longer in comparison to vehicle. On the contrary, MHCI- PCNSL mice didn't respond to anti-PD1 (Figure 1E). MHCI+ PCNSL in both MD and IC models had a higher infiltration of active T cells when treated with anti-PD1. In MHCI- PCNSL, infiltrated T cells had less expression of activation markers in both models and macrophages were polarized to an M2 phenotype in IC mice.

Conclusions: We observed a complete response to anti-PD1 therapy in MHCI+ PCNSL regardless of the presence of macrophages, meaning T cells would be responsible for tumour regression. In line with that, blocking CD47 in MHCI+ PCNSL was not enough to recover macrophage phagocytosis. MHCI- PCNSL induces a very aggressive disease; anti-PD1 is less effective probably because these tumours can only be controlled by macrophages, which is confirmed by the lack of treatment response in a MD microenvironment. Our results show that macrophages control the growth and response to therapy of CNS lymphomas, especially when MHCI expression is lacking. Anti-PD1 therapy works better when macrophages are present, indicating T cells are not the only player in this tumoral scenario. The study suggests that targeting both T cells and macrophages could be a promising approach for treating PCNSL.

Keywords: Extranodal non-Hodgkin lymphoma, Targeting the Tumor Microenvironment, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

174 | THE IMMUNOBIOLOGY OF HISTOLOGIC TRANSFORMATION IN FOLLICULAR LYMPHOMA: A MULTI-OMIC CASE-CONTROL STUDY

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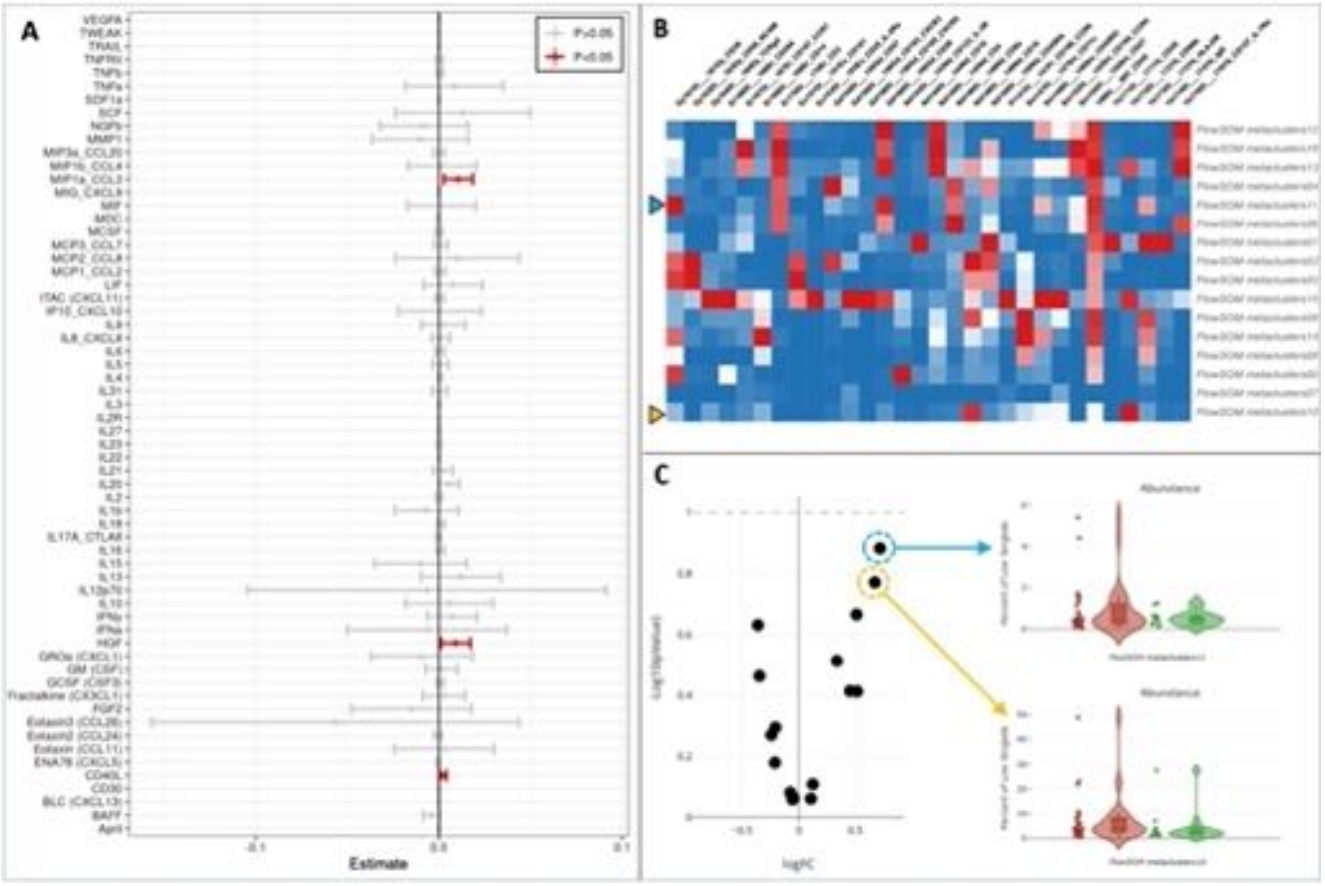
Introduction: Histologic transformation (HT) is a singular event in the natural history of patients with follicular lymphoma (FL) which dramatically change the clinical course and portends a poor prognosis. Efforts to date in understanding the pathobiology of HT in FL (HT-FL) have been focused on genomic factors leading to clonal evolution of lymphoma cells. In the present study we aimed to investigate the contribution of the host immune system in the pathobiology of HT-FL.

Methods: Patients with newly diagnosed FL grade 1-3a were prospectively enrolled in the Molecular Epidemiology Resource (MER) of the University of Iowa/Mayo Clinic Specialized Program of Research



Excellence (SPORE). HT was defined as histopathological confirmation of a subsequent FL grade 3b, large cell lymphoma, or another high grade B-cell malignancy. Patients with composite lymphomas, FL grade 3b, or evidence of transformation at the time of initial FL diagnosis were excluded. Cases (HT-FL) were selected based on availability of biospecimens and then matched to controls (no HT) for baseline characteristics including FLIPI score, treatment, and duration of follow-up. Cryopreserved cells and plasma isolated from blood obtained at time of diagnosis were used for mass cytometry (CyTOF) and multiplex ELISA respectively. Hazard ratio (HR) was calculated by comparing plasma concentration of 65 soluble factors between HT-FL cases and controls. Single cell events from CyTOF were analyzed via unsupervised hierarchical clustering followed by differential abundance analysis.

Results: A total of 52 patients with newly diagnosed FL were included in the analysis, of which 36 (69.2%) were subsequently diagnosed with HT-FL (cases). Median age at diagnosis was 59 years, 47 (90.4%) had grade I–II FL, and 40 (76.9%) had stage III–IV disease. Plasma concentration of the following soluble factors (at diagnosis) were associated with a subsequent diagnosis of HT-FL (Figure 1A): MIP1α (HR 0.01, $p = 0.012$), CD40L (HR 0.002, $p = 0.021$) and HGF (HR 0.0092, $p = 0.029$).A subset of these patients ($n = 45$) had samples available for CyTOF analysis, of which 32 (71%) were subsequently diagnosed with HT-FL (cases). Over 13 million live single-cell events were analyzed and 16 metaclusters were identified (Figure 1B). Increased abundance of activated (CD45RO+ HLADR+ CD38+) cytotoxic T cells (Figure 1C, blue arrow) and eosinophils (Figure 1C yellow arrow) were found in the peripheral blood (at diagnosis) from patients who subsequently developed HT-FL.

Conclusions: Our data suggests that immunological features such as soluble factors and peripheral blood immune cell profile, measured at the time of diagnosis of FL, may be associated with subsequent risk of HT. These findings provide rationale for further investigation of immunological factors in the pathobiology of HT-FL and potential use of immune biomarkers to identify patients at high risk for transformation.

The research was funded by: National Cancer Institute (NCI), Mayo Clinic

Keywords: Genomics, Epigenomics, and Other -Omics, Indolent non-Hodgkin lymphoma, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

175 | SPATIAL TRANSCRIPTOMIC PROFILING: THE "NEXT GENERATION DIAGNOSIS" DISTINGUISHING BETWEEN EBV+ LYMPHOPROLIFERATIONS WITH HODGKIN-LIKE FEATURES

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Introduction: Epstein-Barr virus positive (EBV+) lymphoproliferative disorders (LPD) with Hodgkin-like features include indolent, localised conditions such as EBV+ mucocutaneous ulcer (EBVMCU) through to systemic lymphomas, such as EBV+ classical Hodgkin lymphoma (EBVcHL) and EBV+ diffuse large B-cell lymphoma (EBVDLBCL). The diagnostic distinction between these LPD is imperative to guide management, but can prove problematic, owing to the dearth of reliable diagnostic markers. The biological underpinning resulting in close pathological similarities but different clinical behaviours is also uncertain.

Methods: Utilising immunohistochemistry with CD30 and CD68 to guide sampling, Nanostring GeoMX spatial transcriptomic characterisation of the whole transcriptome in the HRS/HRS-like and macrophage compartments was performed in EBVMCU ($n = 6$; 27 regions of interest (ROI)), EBVcHL ($n = 8$; 11 ROI) and EBVDLBCL ($n = 6$; 12 ROI) on formalin fixed paraffin embedded (FFPE) tissue sections. Differential gene expression and gene set enrichment analyses were performed to identify characteristic signatures and explore novel diagnostic discriminators in EBV+ Hodgkin-like LPD.

Results: Dimensionality reduction (tSNE) based on the transcriptomic profiles in the HRS/HRS-like and macrophage compartments showed that EBVMCU, cHL and EBVDLBCL clustered distinctly from one another. Differential gene expression using a linear mixed effects model and gene set enrichment analysis revealed expression pathways that discriminate between the Hodgkin-like EBV+ LPD. EBVMCU was distinguished from EBVDLBCL in the HRS-like compartment by upregulation of pathways involved in T-reg differentiation (odds ratio (OR) 40; $p = 0.0001$), interleukin 2 (OR 40; $p = 0.0001$) and interferon response signalling, whilst the EBVDLBCL macrophage compartment was distinctive from EBVMCU by negative regulation of pathways involved in T-cell activation (OR 80; $p = 0.00001$) and IL10 production (OR 40; $p < 0.0001$). The HRS-like cells in EBVMCU were distinguished from the HRS cells of CHL by upregulation of T-cell chemotaxis (OR 120; $p = 0.00001$) and migration pathways (OR 120; $p = 0.00001$), whilst the macrophage compartment was distinguished by upregulation of interferon-alpha production (OR 40; $p < 0.0004$) and interferon-beta responses (OR 40; $0 < 0.0004$).

Conclusion: Gene expression profiling of the HRS/HRS-like and macrophage compartments diagnostically discriminates EBVMCU from EBVcHL and EBVDLBCL. The findings demonstrate a scope for spatial transcriptomics in FFPE tissue to represent the "Next Generation Diagnosis" in Cellular Pathology.

The research was funded by: Jean Shanks/The Pathological Society of the UK

Keywords: Diagnostic and Prognostic Biomarkers, Hodgkin lymphoma, Genomics, Epigenomics, and Other -Omics

No conflicts of interests pertinent to the abstract.

176 | COMBINED SINGLE-CELL AND SPATIALLY-RESOLVED MAPPING OF LYMPH NODE ECOSYSTEMS REVEALS PRINCIPLES OF LYMPHOMA TISSUE ORGANIZATION

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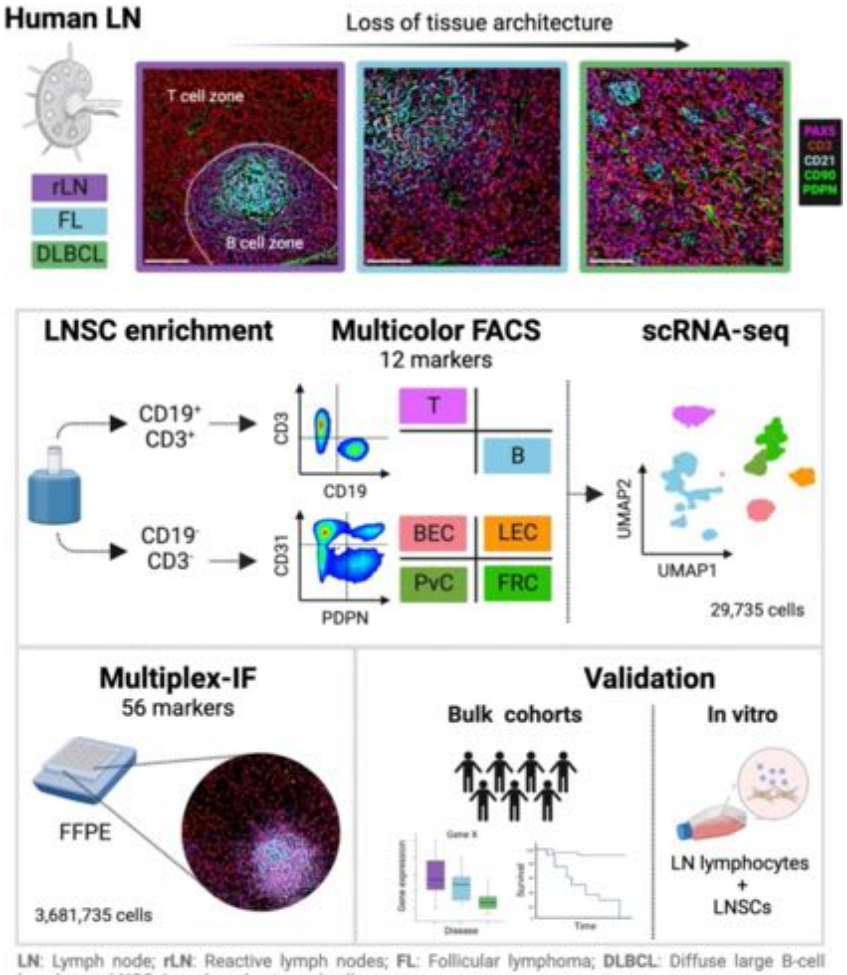
Introduction: Non-Hodgkin lymphoma (NHL) NHL arise in lymph nodes whose normal architecture is variably altered by different NHL subtypes. While follicular lymphoma maintains a germinal center-like growth program, diffuse large B cell lymphomas (DLBCL) is characterized by a diffuse growth pattern. To uncover driving forces of these distinct growth patterns we studied lymph node derived immune cell subsets and stroma cells (SC) which are known to function as tissue organizers through chemokine gradients that enable the compartmentalization of specific immune cell subsets into functionally specialized microdomains (Figure 1).

Methods: Here, we utilized a combined single-cell and spatially-resolved mapping approach of lymph node derived stroma cells, lymphoma infiltrating T-cells and malignant B-cells to dissect the pathophysiological mechanisms underlying the gradual loss of tissue organization in indolent and diffusely growing aggressive lymphomas. We validated altered chemokine gradients in large lymphoma patient cohorts and in-vitro SC co-culture lymphocyte co-culture models.

Results: First, we characterized and quantified how lymph node resident cells organize into spatially distinct cellular



neighborhoods and how these functional units are disturbed and disrupted in diffusely growing lymphomas using ultra-high-plex immunofluorescence (CODEX). To determine the molecular programs underlying loss of tissue organization, we employed holistic single-cell transcriptomic mapping of the lymph node ecosystem, covering major lymph node resident cell types, including rare mesenchymal and endothelial populations. Combined with transcriptomic and outcome data from patient cohorts, this approach revealed that highly specialized mesenchymal cells, which create chemokine gradients in normal lymph nodes, downregulate chemokines responsible for the maintenance of tissue organization and enter a dysfunctional state characterized by inflammatory and fibrotic phenotypes. In silico modelling of intercellular attractions based on receptor ligand expression levels recapitulated lymphoma specific cellular neighborhoods and revealed that DLBCL specific chemokine signatures were sufficient to explain the loss of lymph node organization in DLBCL. In addition to the loss of mesenchymal-derived chemokine gradients, inflammatory immune cells create ectopic sources of chemokines in diffusely growing lymphomas, further disturbing the highly orchestrated chemokine gradients.

Summary/Conclusion: In summary, we demonstrate that a reprogramming of the lymph node microenvironment underlies loss of compartmentalization in aggressive lymphomas, illustrating the power of combined single-cell and spatially-resolved technologies for deciphering molecular pathomechanisms.

Ongoing Trial

Keywords: Bioinformatics, Computational and Systems Biology, Genomics, Epigenomics, and Other -Omics, Microenvironment

No conflicts of interests pertinent to the abstract.

177 | DIGITAL SPATIAL PROFILING OF THE TUMOR MICROENVIRONMENT IN HODGKIN-LIKE ADULT T-CELL LEUKEMIA/LYMPHOMA

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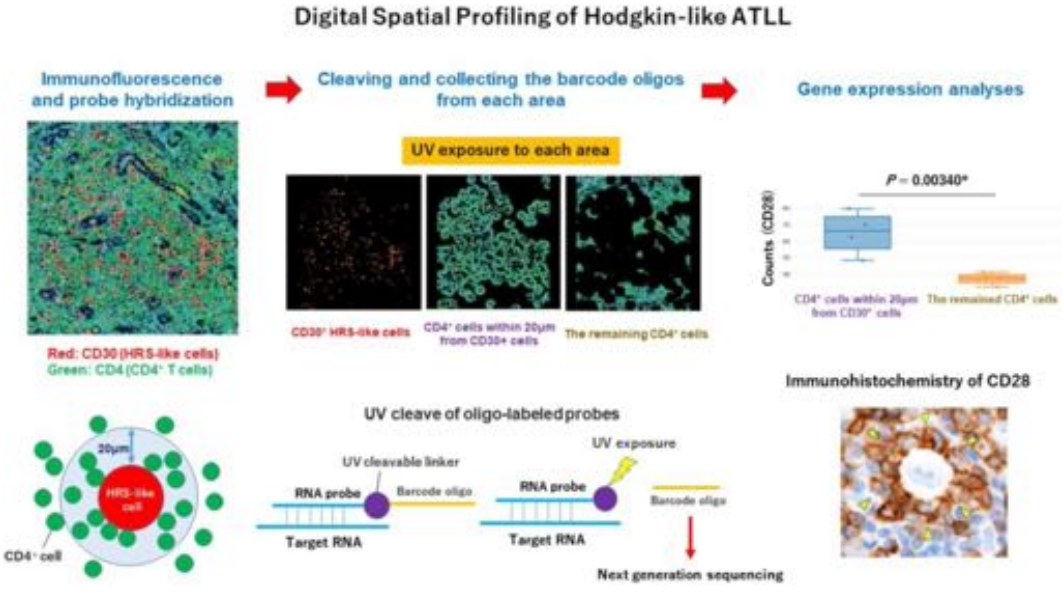
Introduction: Hodgkin-like adult T-cell leukemia/lymphoma (ATLL) is a rare subtype of ATLL harboring $CD30^+$ Hodgkin and Reed–Sternberg (HRS)-like cells and small to medium $CD4^+$ T cells infected with human T-cell lymphotropic virus type I (HTLV-1), which mimics classic Hodgkin lymphoma (CHL) histologically. Interaction between HRS cells and $CD4^+$ T cells is considered important in the tumor microenvironment (TME) of CHL. The TME of Hodgkin-like ATLL remains unclear. Digital spatial profiling (DSP) enables the comprehensive gene expression profiling of the specific cells and areas in formalin-fixed paraffin-embedded (FFPE) slides. Here, we performed DSP and immunohistochemistry (IHC) to elucidate the interaction between $CD30^+$ HRS-like cells and $CD4^+$ T cells in patients with Hodgkin-like ATLL.

Methods: DSP of four patients was performed using a GeoMx digital spatial profiler (NanoString Technologies, Seattle, WA, USA) (summarized in the Figure). Three areas were selected from each region of interest in FFPE slides using immunofluorescence : $CD30^+$ HRS-like cells, $CD4^+$ cells located within 20 μm from $CD30^+$ HRS-like cells, and the remaining $CD4^+$ cells present further away. A barcoded RNA probe mix targeting 18,000+ genes was hybridized on the FFPE slide, and barcode oligos were then separately cleaved from each area by ultraviolet exposure. A sequencing library constructed from the obtained oligos was paired-end sequenced using the NovaSeq 6000 instrument (Illumina, San Diego, CA, USA). The obtained data were



analyzed using GeoMx DSP Control Center software (NanoString Technologies).

Results: DSP revealed significantly higher expression of genes encoding co-stimulatory molecules, CD28 and inducible T cell co-stimulator (ICOS), in $CD4^+$ cells located within 20 μm from HRS-like cells than in the remaining $CD4^+$ cells. IHC was performed on 11 patients, identified distinct $CD4^+$ T cells expressing CD28 in a rosette-like manner around HRS-like cells. HRS-like cells widely expressed CD80 and CD86, suggesting that CD28–CD80/CD86 interaction is important in the constitutive activation of HTLV-1 infected $CD4^+$ T cells in Hodgkin-like ATLL. T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) and programmed cell death -1 (PD-1) were also variably expressed in $CD4^+$ T cells surrounding HRS-like cells, suggesting the interaction between HRS-like cells and $CD4^+$ T cells via immune chockpoint molecules.

Conclusion: Our findings indicate the interaction between HRS-like cells and $CD4^+$ T cells via co-stimulatory and immune checkpoint molecules in Hodgkin-like ATLL. Our study provides new insights into the TME of Hodgkin-like ATLL and implicates a new therapeutic strategy targeting these molecules.

The research was funded by: Grants-in-Aid from the Japan Society for the Promotion of Science (KAKENHI); grant 20K07381 (K. Ohshima), grant JP20K16206 (M. Takeuchi), JP22K06950 (M. Takeuchi), and grant 20K16208 (K. Yamada).

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, Microenvironment

No conflicts of interests pertinent to the abstract.

178 | SINGLE-CELL RNA SEQUENCING REVEALS THE SPATIAL HETEROGENEITY IN BTKI-RESISTANT PROLIFERATIVE DRIVE CLL PATIENTS

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Introduction: The underlying mechanisms of proliferative drive (PD) CLL including transformation of CLL to aggressive B-cell lymphoma (Richter transformation, RT) and accelerated CLL (aCLL) has not been fully disclosed yet, especially progressing after BTK inhibitor (BTKi).

Methods: scRNA-seq of paired lymph nodes (LNs) and peripheral blood (PB) was performed among 4 CLL. P1 and P2 were treated with BTKi and then progressed to RT. P3 were initially diagnosed as aCLL. P4 was treated with BTKi for 54 months and progressed to aCLL.

Results: BTKi-resistant PD CLL showed MYC activation and metabolic reprogramming, high proliferative cells enriched in LN showed downregulation of MHC class I. GSVA analysis showed significant activation of MYC targeted pathways and oxidative phosphorylation in 3 BTKi-resistant PD CLL. Trajectories of tumor cells were constructed and cells from PB were distributed in the front of trajectories with the enrichment of G1 phase cells, while cells from LNs were distributed in the terminal with S and G2M cells, indicating that PD CLL might evolve from PB indolent CLL. Gradual downregulation of MHC class I genes were found in those high proliferative cells, suggesting their escape from immune surveillance.

BTKi-resistant PD CLL showed strengthened crosstalks with T cells, activation of receptor-ligands contributed to exhausted T enrichment in LNs. Distribution of T cell subsets showed great spatial heterogeneity. PB of all four patients showed similar T cells distribution. However, LNs of two RTs displayed significant enrichment of CD8+ exhausted T. Cell-cell interaction showed that BTKi-resistant aggressive tumor displayed strengthened interactions with T cells. Analysis of receptor-ligand interactions showed activation of CD70-CD27 and LGALS9-HAVCR2 between BTKi-resistant tumor cells and CD8+ effective and exhausted T, indicating the underlying mechanism leading to T cell exhaustion.

Heterogenous distribution of CD8+ exhausted T cells, with terminally enhausted T cells specifically enriched in LNs. Evolutionary trajectories of T cells showed that CD8+ naïve T were distributed in the front of trajectories while exhausted T showed heterogeneous evolution with two different ends. Four clusters of exhausted T were splited, with C1 mostly in PB, showing highest cytotoxicity and lowest exhaustion feature. C2 was distributed scantly in PB while mostly in LNs, showing highest cycling and proliferation score. C3 was LNs specific, showing highest exhaustion and lowest cytotoxicity score, indicating its terminally exhausted character.

Conclusion: This study disclosed spatial heterogeneity of tumor and immune microenvironment among BTKi-resistant PD CLL. High proliferative tumor cells enriched in LNs showed downregulation of MHC class I and strengthened crosstalk with T cells, contributing to T cell exhaustion through activation of CD70-CD27 and LGALS9-HAVCR2.

Encore Abstract - previously submitted to EHA 2023

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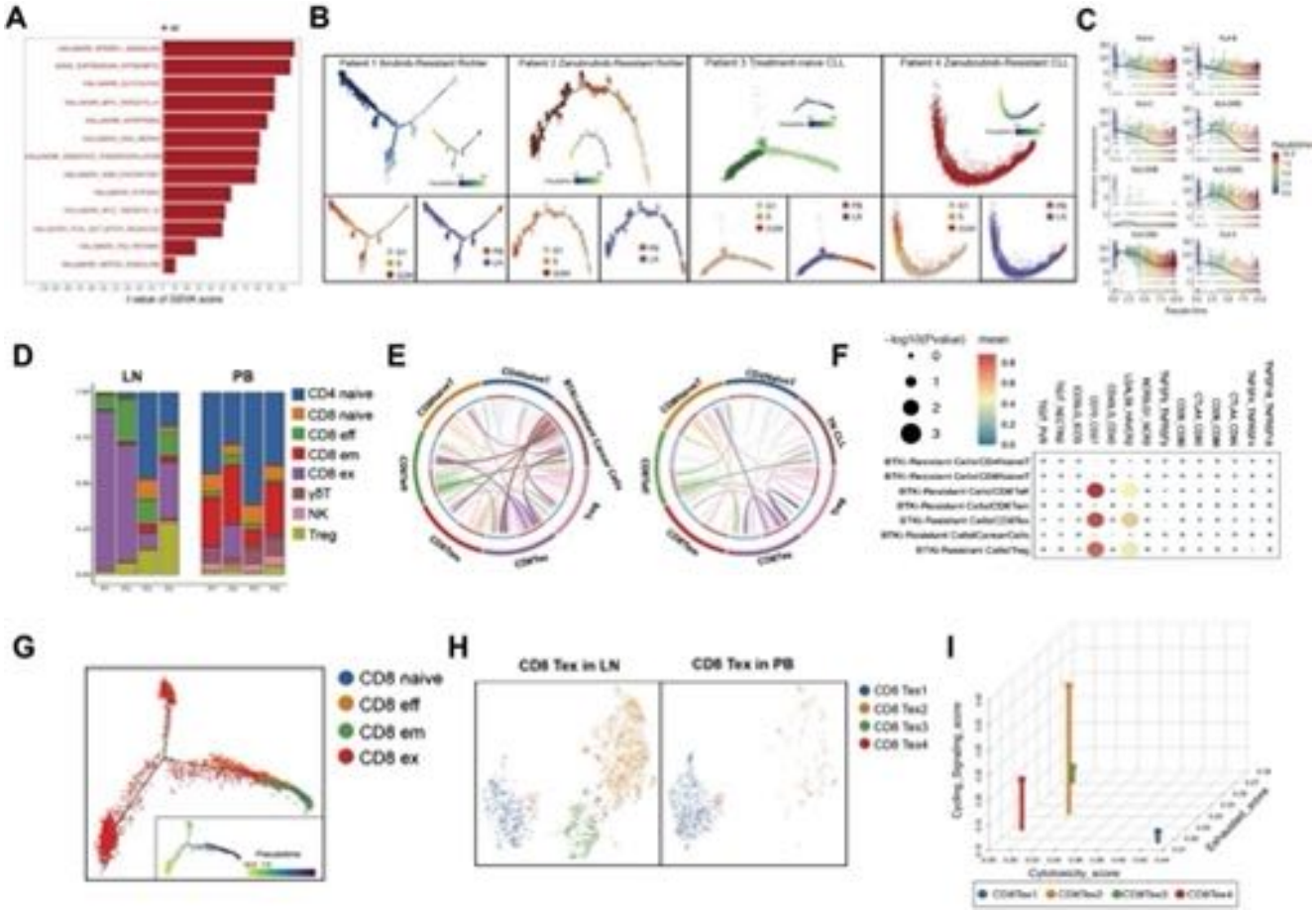
Keywords: Chronic Lymphocytic Leukemia (CLL), Microenvironment, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.



179 | CHARACTERIZATION OF THE TUMOR MICROENVIRONMENT IN CLASSIC HODGKIN LYMPHOMA: DETERMINING THE DEEP IMMUNOPHENOTYPIC SIGNATURE OF T CELLS USING MASS CYTOMETRY

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Classic Hodgkin lymphoma (cHL) is a B-cell malignancy characterized by a rich non-malignant immune infiltrate. Previous efforts to characterize T cell subsets in cHL tumor microenvironment (TME) showed conflicting results. PD-1 inhibitors have provided further insight into the complex interactions of the TME in cHL. Most studies of the TME in cHL relied on flow cytometry and immunohistochemistry, techniques limited in the number of markers that can be analyzed at once. Given the complexity of the TME in cHL, a comprehensive approach is needed. In this study we utilized mass cytometry or CyTOF (cytometry at time-of-flight), to analyze the deep phenotypic composition of T cells within the cHL TME.

We examined single-cell suspensions of lymphoid tissue from 15 patients (8 newly diagnosed cHL and 7 control patients [CP]) using a 33-protein surface marker CyTOF panel. Over 4.7 million CD45+ single cell events were analyzed by an automated pipeline (Figure 1/A). Analysis of major immune cell groups showed a 3-fold increase in the T:B cell frequency ratio between cHL lymph nodes (ratio 1.02) and CP (ratio 0.32) (Figure 1/B1).

Most memory cells within the classical Helper T cell (Th) subset in cHL were classified as central memory (Th-CM; 71.4% ± 10%) as opposed to effector memory (Th-EM; 28.6% ± 10%). Both Th-EM and Th-CM cells favored a Th1 polarization (TH1-P). Those not polarized towards TH1-P demonstrated Th17 polarization (Th17-P). No cHL samples demonstrated polarization toward Th2 (Figure 1/C).

Regulatory T cells (Treg) corresponded to 10% (±7.1%) of all T cells in cHL samples compared to 7.9% (±2.1%) in CP. In contrast, follicular helper T cells (Tfh) were more prevalent in CP (9.3% ± 3.1%) compared to cHL (2.1% ± 2.4%). Treg subsets showed higher frequency of a unique CXCR3+ memory phenotype in cHL compared to CP (Figure 1/D).

Cytotoxic T cells (Tc) corresponded to 20.1% (±8.4%) of all T cell events in cHL, distributed between memory (54.9% ± 20.5%) and non-memory phenotypes (45.1% ± 20.5%). Within the non-memory Tc subset, naïve phenotypes predominated (74% ± 13.3%) over effector phenotypes (26% ± 13.3%). The distribution of T cell subsets within the cytotoxic (CD8+) compartment was similar between cHL and CP (Figure 1/B2).

PD-1 expression was highly variable within Th-EM T cells across cHL samples. The percentage of PD-1+ cells was similar across Th1-,

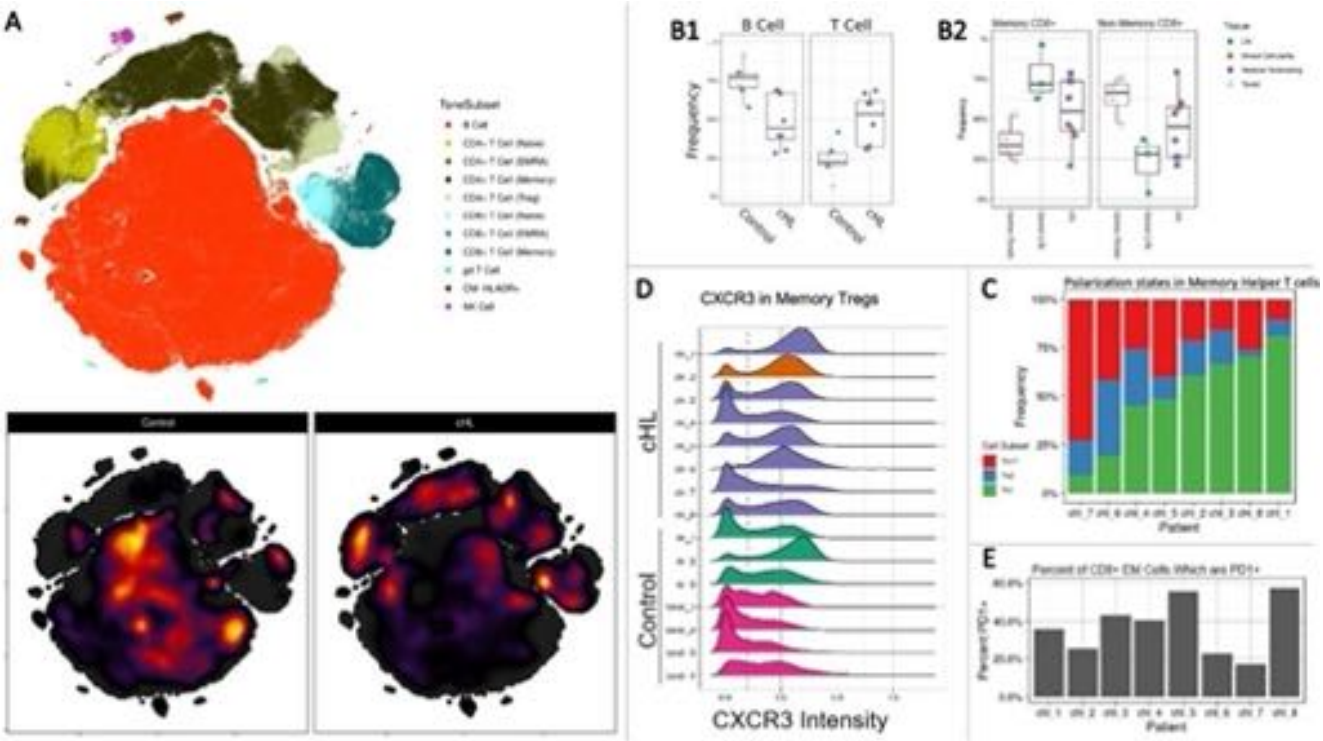

Figure 1. A. Dimensionality reduction projection of immune cell groups identified within lymphoid tissue using CyTOF (top) with density map stratified by tissue origin (bottom). **B1.** Frequency of B- & T-cells (as % of total CD45+ cells) in classic Hodgkin Lymphoma and control patient lymphoid tissue. **B2.** Distribution of memory and non-memory CD8+ cytotoxic T-cells (as % of total T cells) in Hodgkin Lymphoma and controls (stratified by tissue type). **C.** Percentage of TH1, TH2, and TH17 polarization inside Helper T cell compartment for each classic Hodgkin Lymphoma patient. **D.** Histogram of CXCR3 intensity within memory Treg cell compartment. **E.** Percentage of PD-1+ cells inside effector memory cytotoxic T cell compartment in cHL samples. Threshold of PD-1 positivity determined by measuring background PD-1 expression in naive CD8+ cytotoxic cells for each patient.

Th2-, and Th17-P Th-EM T cells in 7 of 8 cHL samples. PD-1 expression was observed in a minority of EM Tc in cHL (Figure 1/E). Our analysis demonstrates substantial differences in the lymphoid microenvironment between cHL and CP. In addition, PD-1 expression was variable and only found in a small proportion of EM Tc suggesting that PD1 blockade responses in cHL are mediated by mechanisms different from that of solid tumors. The identification of a unique CXCR3+ Treg population in cHL deserves further investigation as a potential therapeutic target.

Keywords: Hodgkin lymphoma, Microenvironment, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

180 | PROGNOSTIC VALUES OF CIRCULATING TREM2+ AND ARG1+ MREG CELLS IN ADULTS WITH TREATMENT-NAïVE DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Novel Trem2$^+$ (triggering receptor expressed on myeloid cells 2) and Arg1$^+$ (arginase 1) regulatory myeloid cells (Mreg) that lead to the dysfunction of CD8$^+$ T cells and facilitate tumor growth were recently discovered in a murine cancer model by Yonatan Katzenelenbogen et al. However, as the roles of Mreg cells have never been examined in human cancer patients, we aim to elucidate the clinical impact of circulating Mreg cells on patients with treatment-naive B-cell NHL, especially focusing on DLBCL.

Methods: This prospective, observational study enrolled 102 adults with newly diagnosed and treatment-naïve B-cell NHL, including 62 DLBCL, 25 FL (4 grade 3B), 4 MCL, 4 MZL, 2 LPL, 2 BL, and 3 mature B-cell neoplasms, from December 2020 to November 2022. We obtained human circulating TREM2$^+$ and ARG1$^+$ Mreg cells from freshly isolated peripheral blood and calculated their percentages among CD45$^+$ and CD15$^-$ cells by flow-cytometry analysis. Non-stain (NS) and fluorescence minus one (FMO) controls were used for gating positive levels of surface TREM2 and intracellular ARG1, respectively.

Results: Among 102 patients with B-cell NHL, those with high-risk IPI had significantly higher percentages of circulating Mreg cells than patients with intermediate or low-risk IPI (5.46% vs. 1.71% vs. 0.63%, $P_{H\ vs.\ L} < 0.001$, $P_{H\ vs.\ I} = 0.032$, $P_{I\ vs.\ L} = 0.005$); patients with aggressive subtypes (including grade-3B FL) had significantly higher

percentages of circulating Mreg cells than patients with indolent subtypes (1.89% vs. 0.93%, $P = 0.023$). For 62 DLBCL patients, those with high IPI risk (9.18% vs. 1.25%, $P < 0.001$), bulky mass ≥ 7.5 cm (5.08% vs. 1.18%, $P = 0.057$), or DEL (5.13% vs. 1.21%, $P = 0.036$) had significantly higher percentages of circulating Mreg cells (Figures A–F). More importantly, DLBCL patients with circulating Mreg cells ≥4.5% had significantly worse PFS and OS than those with Mreg cells <4.5% after a median follow-up of 14 months (Figures G and H); when utilizing multivariate Cox regression analysis, "circulating Mreg cells ≥4.5%" remained an independent prognostic factor for both PFS and OS after adjusting for confounding factors, including age, sex, high-risk IPI, bulky mass ≥7.5 cm, BM involvement, non-GCB type, and DEL.

Conclusion: A higher percentage of circulating TREM2$^+$ and ARG1$^+$ Mreg cells among CD45$^+$ and CD15$^-$cells in peripheral blood is a poor prognostic factor of both PFS and OS in treatment-naïve DLBCL patients, and it warrants further investigation about the immunomodulatory effect of Mreg cells in DLBCL patients.

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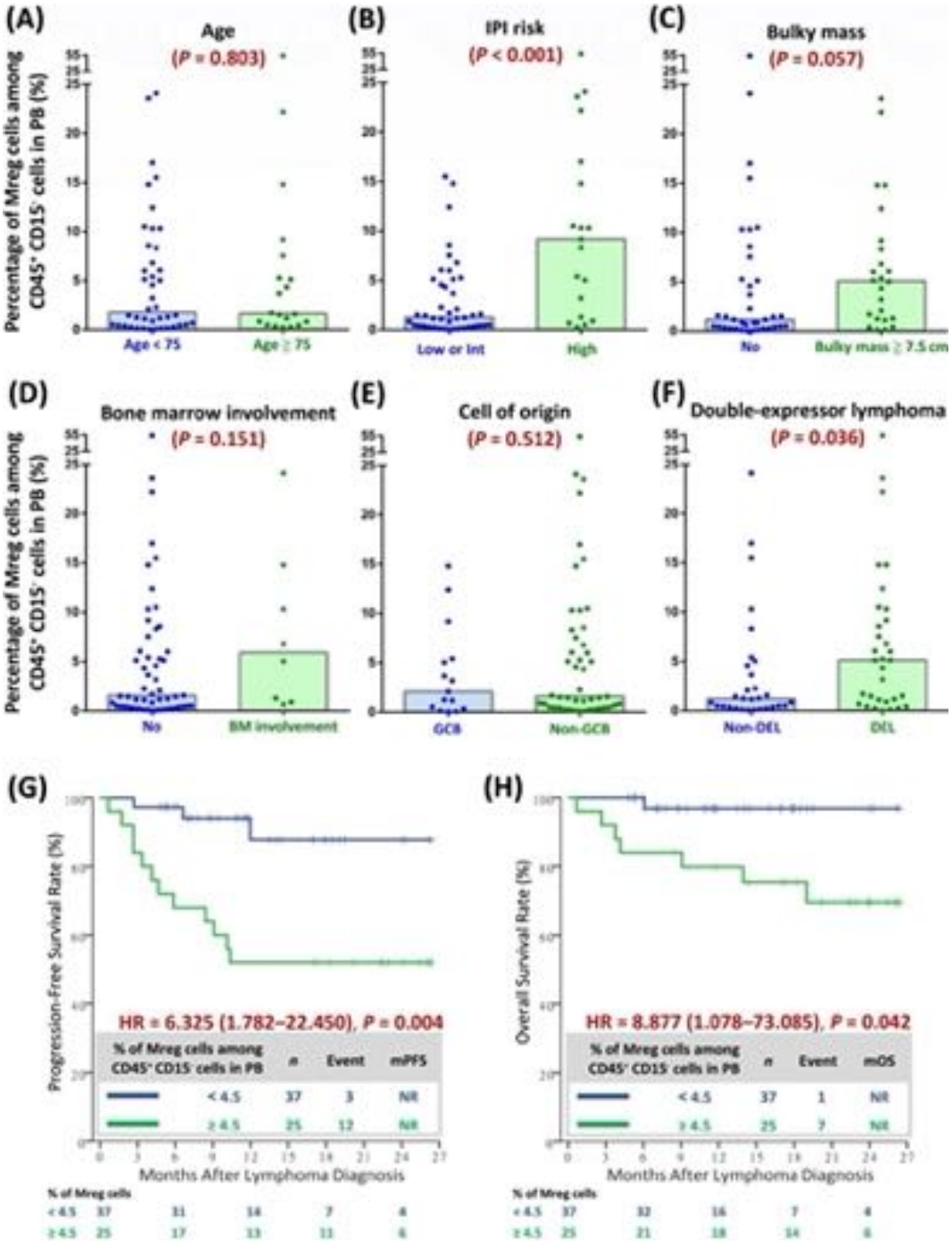

012), (3) the Chong Hin Loon Memorial Cancer and Biotherapy Research Center, (4) the Melissa Lee Cancer Foundation, and (5) the Taiwan Clinical Oncology Research Foundation.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers

No conflicts of interests pertinent to the abstract.

181 | PEMBROLIZUMAB IN COMBINATION WITH EPIGENETIC THERAPY IS SAFE AND ACTIVE IN HEAVILY TREATED PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA AND CUTANEOUS T-CELL LYMPHOMA

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Introduction: Peripheral T-cell lymphomas are uniquely sensitive to epigenetic modifiers. We have shown that decitabine and 5-azacytidine (Marchi et al.; Br. J. Haematol. 171; 2015) induce the expression of cancer testis antigens in pre-clinical models of PTCL, and that pralatrexate modulates genes involved in cytokine production, viral response and apoptosis. These data suggest a role for the incorporation of the immune-checkpoint inhibitor, pembrolizumab, to epigenetic agents. Herein we report on the clinical activity of this approach in patients with relapsed or refractory (R/R) PTCL and CTCL.

Methods: This is a phase 1b study of pembrolizumab combined with pralatrexate (Arm A), pralatrexate + decitabine (Arm B), or decitabine (Arm C) in patients with R/R PTCL and CTCL. A 3+3 dose-escalation/de-escalation is applied in Arms A and C while a DLT-adapted partial order continual reassessment method for dose-finding with combinations of agents is applied in Arm B. Changes in serum cytokine levels were assessed during cycle 1 using a Luminex-based immunoassay. T-cell subpopulation profiling in peripheral blood was performed using a multi-color flow cytometry assay (Cytek® Aurora).

Results: Patient characteristics, toxicity data, and response analysis are shown in table 1. Serum levels of three cytokines, TNFα, MIP-3α and IL-10, measured at day 1 pre-treatment were significantly elevated ($p = 0.0001$, 0.011 and 0.0017, respectively) in trial patients compared to healthy controls. Patients who responded to treatment demonstrated a more consistent decline in levels of TNFα, MIP-3α, and IL-10 during cycle 1, whereas non-responders showed stable to increased levels of these cytokines. T-cell subpopulation analysis ($n = 6$) showed mean CD4:CD8 ratio of 0.5 in trial patients prior to treatment compared to 1.5 for healthy age and sex-matched controls ($p = 0.016$). No significant change in the proportion of PD1+CD8+ central memory cells was seen in trial patients between D0 and D28 of treatment ($p = 0.12$), and between D0 in comparison to healthy controls ($p = 0.11$). The proportion of PD1+CD8+ effector T cells was lower in trial patients relative to healthy controls both before and after treatment ($p = 0.04$ and 0.001, respectively). There was no difference in the proportion of PD1+CD8+ effector T cells among trial patients from D0 to D28 of treatment ($p = 0.19$). Patients who responded to treatment ($n = 3$), had a lower proportion of PD1+CD8+ effector cells at the start of treatment relative to non-responders ($p = 0.002$).

Conclusions: These clinical data suggest that the integration of pembrolizumab on an epigenetic backbone is safe and demonstrates encouraging responses in heavily treated patients with PTCL and CTCL. These correlative data suggest that specific cytokines (TNFα, MIP-3α, and IL-10) and changes in circulating T-cell subpopulations may have predictive value as biomarkers of disease response.

The research was funded by: Merck and Co.
Ongoing Trial

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Combination Therapies, Ongoing Trials

Conflicts of interests pertinent to the abstract.

N. N. Benani
Consultant or advisory role: Vividion Therapeutics, Kymera, Secura Bio, Affirmed GmbH, Astellas Pharma, Acrotech Biopharma LLC

M. E. Williams
Consultant or advisory role: Astra Zeneca, Gilead, Janssen, Kite Pharma, Kymera, TG Therapeutics
Honoraria: International Oncology Network, Research to Practice
Research funding: Janssen, Kymera, Pharmacyclics

J. S. Manavalan
Research funding: Astex

O. A. O'Connor
Employment or leadership position: TG Therapeutics
Stock ownership: TG Therapeutics

E. Marchi
Employment or leadership position: Myeloid Therapeutics
Consultant or advisory role: Myeloid Therapeutics

Table 1. Patient characteristics, toxicities and responses (n=16)

Median age (range)	65 (38 - 77)
Sex	
Male	8
Female	8
Race	
White/Non-Hispanic	9
White/Hispanic	1
Black	4
Asian	2
Histology	
PTCL, NOS	6
AITL	3
MF	4
ATLL	1
Sezary Syndrome	1
PCAECTL	1
Stage at diagnosis	
I	2
II	2
III	5
IV	5
Tumor Stage	2
Median number of prior therapies (range)	3 (1-7)
Adverse Event, Grade 3/4, n (%)	
Thrombocytopenia	2 (14.3)
Neutropenia	4 (28.6)
Anemia	1 (7.1)
Fatigue	1 (7.1)
Vomiting	1 (7.1)
Hyponatremia	1 (7.1)
Rash	1 (7.1)

Dose Limiting Toxicities (DLT)	Total DLT, n (type)
Arm A	1 (failure to meet required blood parameters prior to C2)
Arm B	1 (febrile neutropenia)
Arm C	3 (failure to meet required blood parameters prior to C2 x2; G3 rash and hyponatremia)

Response analysis				
Arm (evaluable/total)	CR	PR	SD	PD
Arm A (3/6)	0	1	0	2
Arm B (3/4)	1	1	0	1
Arm C (4/6)	0	0	2	2

Honoraria: Kyowa Kirin

Research funding: Merck and Co., Celgene/BMS, Astex, NomoCan Pharmaceuticals

Other remuneration: University of Virginia (Patents & Royalties: 3062/170 PROV), Daiichi Sankyo (advisory board)

182 | GENOMIC ABNORMALITIES INVOLVING CLASS I HLA ARE COMMON IN ADVANCED CUTANEOUS T-CELL LYMPHOMA

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Introduction: Immunotherapy is an effective treatment for cutaneous T-cell lymphoma (CTCL) and an active area of investigation. Genomic biomarkers may aid in identifying CTCL patients likely to benefit from immunotherapies. Somatic mutations involving HLA have been previously reported in CTCL. However, there has not yet been a dedicated study of HLA in CTCL, so the frequency of genomic aberrations of HLA remains unknown. We thus aimed to characterize the occurrence of class I HLA abnormalities in patients with advanced CTCL.

Methods: We sequenced skin and/or blood specimens with matched germline from a cohort of 49 patients with advanced mycosis fungoides (MF) or Sézary syndrome (SS). Targeted DNA sequencing was performed with a 225-gene panel including coverage of HLA loci. Somatic mutations of class I HLA were called using POLYSOLVER and validated by Sanger sequencing. Loss Of Heterozygosity in Human Leukocyte Antigen (LOHHLA) was used to identify loss of heterozygosity (LOH). Single-cell RNA-sequencing (scRNA-seq) was

performed on 8 samples from 6 patients. Allele-specific expression of class I HLA at a single-cell level was used to validate LOH. Progression-free survival (PFS) was determined from the time of initial diagnosis until the first progression event.

Results: Nine unique somatic HLA mutations were identified among 6 patients. In contrast, only one patient had a coding mutation involving *B2M*. LOH of class I HLA was common, affecting 20 patients (41%), and was due to both focal and non-focal deletions (Figure 1A). In two patients with SS, we validated HLA LOH through HLA allele-specific scRNA-seq analysis. Imbalanced expression of HLA alleles occurred exclusively in the malignant T-cell population. In one patient, LOH involving HLA appeared to be clonal (Figure 1B-C), but in the other, LOH was identified in a phenotypically distinct subclonal population. scRNA-seq data for a third patient confirmed expression of an HLA-B splice site mutation restricted to malignant T-cells.

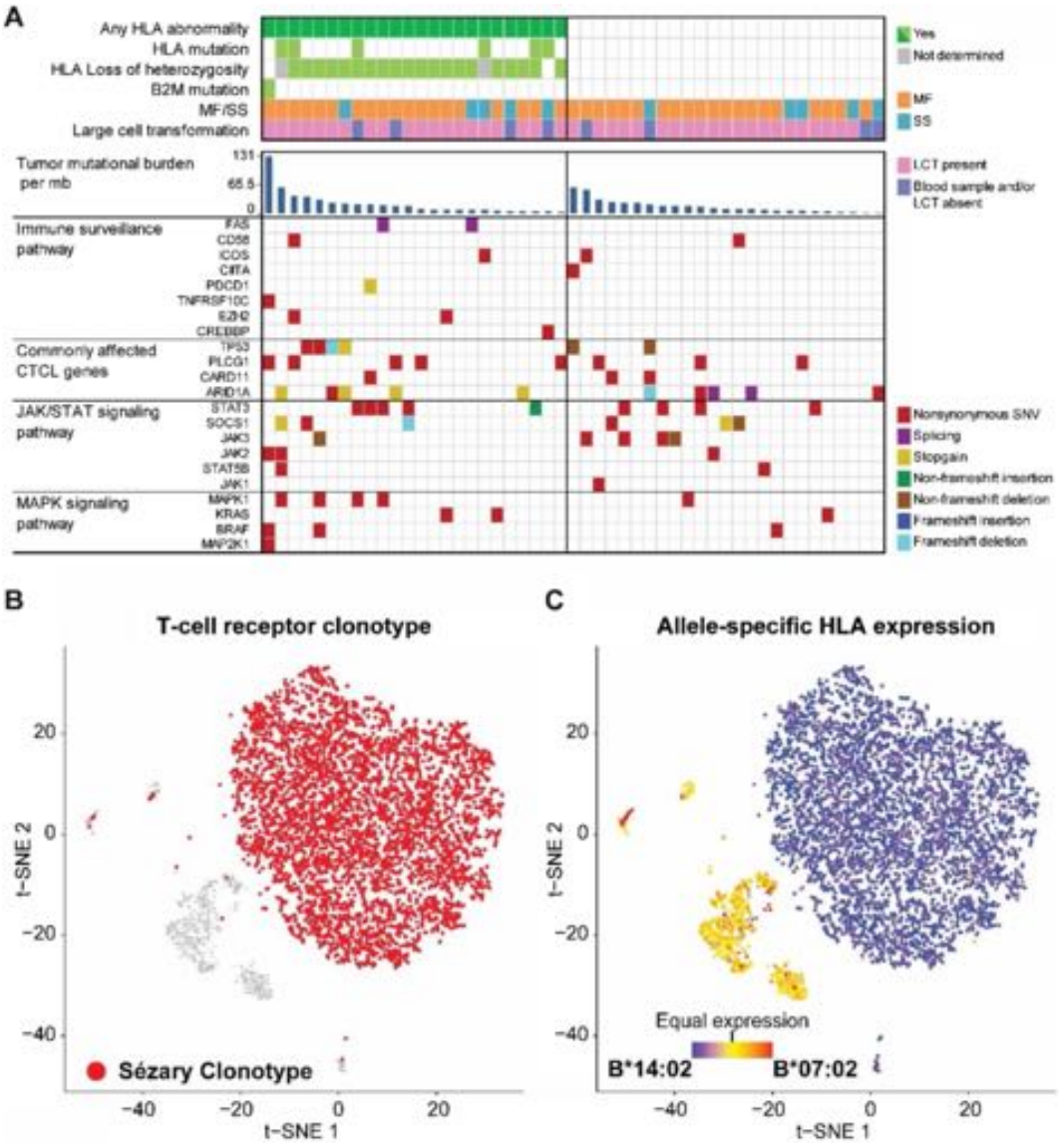
In total, at least one HLA abnormality was detected in 24/49 patients (45%). Patients were categorized by HLA status for correlation with clinical characteristics and outcomes. There were no differences in CTCL subtype (MF vs. SS), stage, or age. There were also no differences in estimated tumor mutational burden. The solitary patient with an abnormality of*B2M* had a hypermutated phenotype with 131 mutations per megabase. Patients with genomic abnormalities of HLA had significantly worse PFS than those without (median PFS 31.7 months vs. 98.9 months, respectively; $P = 0.016$).

Conclusions: Our findings show that genomic class I HLA abnormalities are common in advanced CTCL. Further investigation is necessary to explore potential links between HLA abnormalities, disease prognosis, and responses and/or resistance to immunotherapy.

The research was funded by: Grant K08 CA207882 and Haas Family Foundation.

Keywords: Cutaneous non-Hodgkin lymphoma, Genomics, Epigenomics, and Other -Omics, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.



183 | T CELL CD62L EXPRESSION FOLLOWING NIVOLUMAB THERAPY IS ASSOCIATED WITH RESPONSE TO RITUXIMAB-NIVOLUMAB IN TREATMENT NAïVE FOLLICULAR LYMPHOMA: THE 1ST FLOR STUDY

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Introduction: Inter-tumoral T cell dysfunction and efficacy of immune checkpoint inhibitors (ICI) in follicular lymphoma (FL) has been well described. However, few studies have examined peripheral blood immunity at diagnosis or the impact of frontline ICI on circulating immunity in FL. We hypothesised that immune dysregulation in peripheral blood would be present in treatment naïve FL and would correlate to response to frontline ICI.

Methods: PBMC samples from 34 untreated FL patients receiving rituximab (R) and nivolumab (nivo) in the 1st FLOR trial (Hawkes JCO 2021) were collected at baseline, post 4 cycles of nivo and after 6 months of nivo±R. Immune profile was assessed using a single-tube 29 antibody FACS panel on a spectral flow cytometer and compared to the profile of 12 age matched healthy donors. Results were correlated with centrally determined PET response (Lugano criteria).

Results: Compared to healthy donors, FL patients had increased proportions of TRegs ($P < 0.0001$) with decreased HLA-DR+ ($P < 0.01$) and increased PD-1+ ($P < 0.01$) populations. NK cells were increased ($P < 0.05$) with a 2-fold increase in TIM3 expression ($P < 0.01$). While total T cells were unchanged, expression of PD-1, TIM3, HLA-DR and 4-1BB were significantly increased in T cells from FL patients.

Treatment with nivo significantly increased the populations of TRegs expressing 41BB, LAG-3, TIM3 or PD-L2 ($P < 0.05$) with a decreased PD-L1 positive population at PET-CT2. Expression of immune checkpoints on T cells was unchanged by therapy.

To assess biomarkers of response, patients were stratified into sustained CR (CR achieved by PET-CT4 and maintained for 6 months without evidence of relapse, $n = 15$) vs. PR/PD ($n = 21$). At baseline, sustained CR was associated with a trend for increased proportions of Naïve CD4 and CD8 T cells and decreased TRegs and PD-L2 expressing TRegs. Baseline expression of PD-1 on T and NK cells did not correlate with sustained response.

Most strikingly, expression of CD62L was significantly downregulated across total CD4 and CD8 T cells and TRegs at PET-CT2 in PR/PD patients ($P < 0.05$) and maintained at baseline levels in those patients who achieved a sustained CR. At this early timepoint final patient responses had not been established with most patients having either progressive or stable disease, suggesting that dysfunctional downregulation of CD62L in response to nivo may reflect the inability of patient's T cells to activate and/or migrate to the tumour site and facilitate tumour clearance and long-term treatment responses.

Conclusions: Grade 1-3A treatment naïve FL is associated with significant dysregulation of peripheral blood T and NK cells prior to therapy. Early downregulation of CD62L on T cells of patients treated with nivo was associated with the inability to achieve long term complete responses and may indicate aberrant T cell activation and/or function which impacts on long term response to therapy.

Encore Abstract - previously submitted to EHA 2023

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Keywords: Basic and Translational Science, Diagnostic and Prognostic Biomarkers

Conflicts of interests pertinent to the abstract.

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Research funding: Bristol Myers Squibb, Roche, Merck KgA, Astra Zeneca

184 | RHOA DEFICIENCY DRIVES DECREASED CD19 EXPRESSION AND IMMUNE DYSREGULATION IN CAR-T RESISTANT DIFFUSE LARGE B-CELL LYMPHOMA

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Background: CD19-directed chimeric antigen receptor T-cell (CAR-19) therapies are promising new options in relapsed or refractory diffuse large B-cell lymphoma (DLBCL), but over half of patients still progress. Recent whole-genome sequencing data published by our lab revealed that deletion of *RHOA* (3p21.31) is strongly associated with poor response ($p = 0.0013$). In newly diagnosed DLBCL, 20% of patients harbor a *RHOA* deletion and another 5% have loss-of-function mutations. To date, no work has comprehensively identified the role of RHOA in DLBCL or how its inactivation may protect CAR-19 resistant tumors.

Methods: RHOA loss-of-function (LoF) lymphoma cell lines were generated using shRNA and CRISPR approaches. Diminished RHOA activity was confirmed via active RHO pulldowns. RNA-sequencing in conjunction with western blotting and flow cytometry was conducted to uncover deregulated pathways in RHOA-deficient lymphoma. Cell proliferation, migration, and viability were assessed to phenotype RHOA LoF and uncover signaling pathways activated in RHOA-deficient lymphoma. CD19-directed murine and human CAR-T cells were co-cultured with corresponding RHOA LoF systems to assess CAR-T engagement and killing.

Results: RNA-seq analysis of RHOA-deficient cell lines revealed enrichment of gene sets associated with cell-cycle progression and interferon signaling pathways, and cell proliferation and chemotaxis assays both demonstrated increased activation. Western blotting revealed upregulated pAKT, but strikingly RHOA LoF systems showed enhanced sensitivity to PI3K, AKT, and mTOR inhibition. We assessed if RHOA LoF associates with previously described decreased CD19 driving CAR-19 resistance and found consistent downregulation by flow cytometry in both A20 sh*Rhoa* ($p = 0.0002$) murine lymphomas and RIVA human cell line CRISPR het *RHOA* knockouts ($p = 0.0031$), confirmed by western blotting in both systems. RNA-seq analysis of 74 DLBCL patients (PCAWG data) revealed a strong positive correlation between expression *CD19* and *RHOA* ($p < 0.001$, $R^2 = 0.236$). Impedance-based serial cell viability assessments and flow cytometry cytotoxicity assays with CAR-19 and RHOA LoF cells revealed a statistically significant decrease in CAR-19 killing of RHOA-deficient lymphomas ($p = 0.0005$ and $p < 0.0001$).

Conclusion: RHOA-deficient lymphoma relies on PI3K/AKT/mTOR signaling for proliferation that works in parallel with decreased CD19 to decrease CAR-19 killing. Upregulation of interferon signaling pathways gives evidence of increased immunoinhibitory ligands that could promote exhausted CAR19 products. Further research will challenge in vivo RHOA-deficient tumors with CAR-19 cells and employ scRNA-seq to reveal transcriptomic changes within RHOA-deficient lymphoma responsible for CAR-19 resistance.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Immunotherapy, Microenvironment

No conflicts of interests pertinent to the abstract.

185 | SHELTER IN PLACE: LIVE CLL CELLS INSIDE THE BONE MARROW FIBROBLASTS AND ITS IMPLICATION IN DRUG RESISTANCE

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Introduction: Cell-in-cell (CIC) describes a century old observation where an intact cell can be seen inside another whole cell. It has been associated with human cancers, especially hematopoietic malignancies. However, most observations have been published as case reports. In the absence of systematic studies of case cohorts, understanding of the pathological significance of live CIC remains challenging.

Methods: In this investigation, we studied primary CLL samples using an ex vivo co-culture model system which mimics the CLL tumor microenvironment (TME). In these TME models, CLL cells were cocultured with bone marrow fibroblasts (BMF) in the presence of B-cell growth factors. The tumor cells survive for weeks, become larger, downregulate surface CXCR4 and upregulate Ki67 expression. Phenotypically, tumor cells proliferate and divide into daughter cells. Collectively, these features recapitulate the behavior of lymph node-resident CLL cells. In this study, cells were observed and analyzed with confocal microscopy and 3D reconstruction.

Results: We observed that CLL cells were actively internalized by BMF in 41 CLL cases studied. The internalized CLL cells were alive and mobile within the BMF's cytoplasm. Moreover, the tumor cells were seen leaving their BMF host and re-entering into other BMFs. The number of internalized CLL cells were quantified and correlated with patients' clinical and pathological parameters. No correlations were found between cell internalization and widely used CLL prognostic indicators, including cytogenetic features and IGHV mutational status. However, we have found that treated patients had higher level of CIC than those not treated.

We hypothesized that live CIC may contribute to drug resistance and internalization may be an important mechanism for tumor cells to evade harmful drug insult and survive as residual disease. To test the hypothesis, we exposed CLL cells in the TME models to BTK inhibitors including ibrutinib and pirtobrutinib. Our results showed that the drug exposure drove CLL cells into BMF. Additionally, we observed that increased CIC was associated with higher cellular proliferation capacity. Importantly, chemokine CXCL12-CXCR4 axis played a critical role in this process. Specifically, CXCL12 ligand promoted cell internalization, while a CXCR4 antagonist partially prevented CIC from occurring.

Conclusion: Our study represents the first report implicating the cell-in-cell phenomenon in drug resistance using a cohort of patient-derived CLL cells assessed with 3D imaging and quantitative

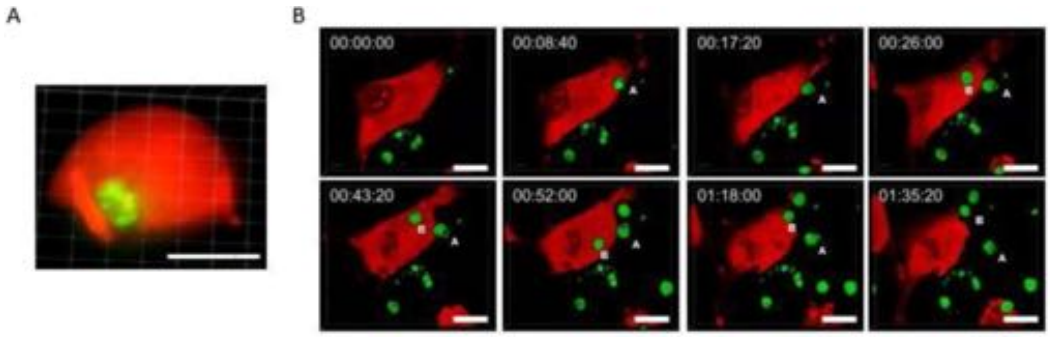

Fig. 1. CLL cells (green) are internalized by the bone marrow fibroblasts (red), actively move within the BMF and exit internalization. (A) 3D Image generated by Lattice Light Sheet Bessel Beam Illumination Microscope. A CLL cell was enwrapped inside the BMF. **(B)** Still Confocal images from time-lapsed microscopy. At time 08:40-17:20, cell "A" was leaving the BMF. At 26:00, cell "A" had left and cell "B" emerged. Cell "B" moved around (43:40-52:00) and was exiting the BMF at 01:18:00. By 1:35:20, both cells had completed the exit and were lingering nearby the BMF.

approach. These findings suggest that live CIC may be an important mechanism used by tumor cells to avoid harmful drug insult, survive, persist, proliferate and become an origin for future relapse. Targeting the CXCL12-CXCR4 axis may become a potential therapeutic strategy to minimize residual disease and future relapse.

The research was funded by: NCI

Keywords: Chronic Lymphocytic Leukemia (CLL), Microenvironment, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

186 | DEGRADATION OF CD47-SIRPα AXIS BY POMALIDOMIDE POTENTIATES CD20 ANTIBODY-DEPENDENT CELLULAR PHAGOCYTOSIS AGAINST B-CELL LYMPHOMA

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Introduction: Anti-CD20 monoclonal antibodies (mAbs) have revolutionized the treatment of B-cell lymphomas (BCL). The chemo-free combination with lenalidomide (Len) and rituximab (R^2) as a first-line therapy has shown promising activity in indolent lymphomas. However, the efficacy of R^2 regimen is yet unsatisfactory in aggressive settings, thereby novel synergistic strategy with next-generation CD20 mAbs and/or newer immunomodulatory drugs (IMiD) are urgently needed. Pomalidomide (Pom) is more powerful than Len in immunomodulatory properties including redirection of tumor-associated macrophages (TAM), which may confer a therapeutic opportunity to potentiate antibody-dependent cellular phagocytosis (ADCP) in elimination of lymphoma cells. This study aimed to evaluate the macrophage-based anti-lymphoma activities of Pom plus CD20 mAbs.

Methods: BCL cell lines (SU-DHL-4, Raji and Daudi) were co-cultured with human monocyte-derived macrophages and treated with various combinations with IMiDs (Len or Pom) plus CD20 mAbs (rituximab or obinutuzumab). Phagocytosis and cell viability of lymphoma cells were tested by flow cytometry. Protein mass spectrometry and co-immunoprecipitation (co-IP) were performed to identify Pom-redirected neosubstrates of cereblon (CRBN). IMiD-responsive *Crbn*^{I391V} mice were bred to Eμ-Myc lymphoma mice to evaluate the in vivo immunomodulatory effects of Pom on macrophages.

Results: In vitro co-culture systems showed that Pom plus obinutuzumab elicited the strongest ADCP effects, resulting in robust phagocytosis of tumor cells by macrophages and markedly decreased tumor cell number, when compared to other combinations including Len plus rituximab (R^2), Len plus obinutuzumab (GALEN) or Pom plus rituximab. Mechanistically, we identified CD47, a well-known negative regulator of macrophage phagocytosis, as a novel CRBN neosubstrate in BCL cells using mass spectrometry screening and co-IP validation. Interestingly, we found that only Pom rather than Len or thalidomide could efficiently induce degradation of total and surface CD47 in SU-DHL-4 cells. We further confirmed that knockdown of *CRBN* abrogated Pom-induced CD47 degradation, indicating the on-target effect. More importantly, based on the murine spontaneous lymphoma models (Eμ-Myc *Crbn*^{I391V} mice), we found administration of Pom elicited a shift from M2 (CD206$^+$) to M1 (CD86$^+$) phenotype of tumor-associated macrophages and significant decrease of SIRPα$^+$ populations in both M1 and M2 subtypes.

Conclusion: Our study provides evidence for the superior effects of Pom plus obinutuzumab by harnessing the anti-lymphoma activity of TAMs, and suggests degradation of CD47-SIRPα axis as a novel mechanism underlying the drug synergy. Further preclinical and clinical investigations are needed to determine the in vivo synergistic efficacy and potential toxicity of this combined treatment.

The research was funded by: This study was supported by the National Natural Science Foundation of China (No. 81470336 to KZ).

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Immunotherapy

No conflicts of interests pertinent to the abstract.

187 | TARGETING MONOCYTIC-MYELOID SUPPRESSOR CELLS THROUGH CSF1R-BLOCKADE ENHANCES CD19-CAR T-CELL RESPONSE IN DLBCL

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Introduction: Adoptive immunotherapies such as chimeric antigen receptor (CAR) T cell therapy have strongly improved the outcome of patients with diffuse large cell lymphoma (DLBCL) that are relapsed or refractory after standard chemo-immunotherapy. However, approx. 50% of patients with DLBCL are not durably responding to CAR T cell therapy. CAR T cell expansion is associated with durable responses. However, the molecular mechanisms that mediate suppression of CAR T cells leading to resistance still remain elusive.

Methods: We performed bulk RNA sequencing of DLBCL patients before CAR T cell therapy. We performed gene set enrichment analysis (GSEA) using signatures derived from published genes associated with an immunosuppressive lymphoma microenvironment. To investigate CAR T cell therapy in an immunocompetent autochthonous mouse model we established murine CD19-redirected CAR-T cells that were generated using splenic T cells isolated from mice harbouring a C57BL/6N background. We treated DLBCL derived from PPMBC (PRDM1-KO, Myd88 + BCL2 overexpression, CD19: Cre) mice with this murine CD19 CAR-T cells in combination with an anti-CSF1R targeted antibody compared to controls.

Results: We found increased immunosuppressive metabolic characteristics in CD19 CAR T refractory DLBCL patients indicated by increased glycolysis, hypoxia and elevated reactive oxygen species (ROS) in GSEA analysis. This metabolic signature was associated with an enriched monocytic-myeloid cell signature and a lack of expansion of effector T cells in CD19 CAR T refractory DLBCL. CSF1-CSFR1 (CD115) signaling is one major pathway that mediates the differentiation of myeloid derived cells into immunosuppressive MSCs. CD115-positive MSCs are important immune regulators in the tumor microenvironment that mediate inhibition of T cells and induce the proliferation of Tregs. We therefore hypothesize that combined treatment with a CSFR1 inhibitor will enhance CAR T cell expansion and thus improve CAR T cell response. We show that CSF1R blockade shifts the immunosuppressive lymphoma microenvironment into an proinflammatory environment in CD19 CAR T cell treated mice with DLBCL and abrogation of the expansion of lymphoma associated myelo-monocytic suppressor cells (LAMMs). This shift into an immunosupportive lymphoma microenvironment was accompanied with an increase of T cell expansion within the tumor and expansion of CD19-CAR T cells. We next evaluated whether the combination of CD19-CAR T cell therapy with CSF1R inhibition improves therapeutic outcome PPMBC DLBCL mice. Strikingly, we show that CSF1R Inhibition displays synergistic efficacy in combination with CD19 CAR T cell therapy.

Conclusions: Our data strongly indicates that CSF1R inhibition improves CD19-CAR T expansion, promotes an immunosupportive microenvironment and could enhance CD19-CAR T cell therapy efficacy in patients with DLBCL.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Microenvironment

No conflicts of interests pertinent to the abstract.

188 | SAR442257, A CD38/CD28/CD3 TRISPECIFIC ANTIBODY, POTENTIATES CAR T-CELL ACTIVITY AGAINST LARGE B-CELL LYMPHOMA

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CART cell therapy has significantly improved outcomes of patients with relapsed/refractory large B cell lymphoma (rrLBCL), but many do not experience long term benefit. The mechanisms of failure are multifaceted including CAR T exhaustion. Understanding these mechanisms are likely to identify therapeutic avenues for improving outcomes.

13 rrLBCL tumors (7 CART naïve, 6 CART refractory), were subjected to scRNA-seq. Clustering was performed and frequency, clonal dominance, and expression of major cells and subclusters were compared. The effect of SAR442257, a CD38/CD28xCD3 trispecific antibody, was assessed in cytotoxicity assays and

compared to control antibodies without CD38 or CD38/CD3/CD28 targeting regions. RL and HT cell lines were CRISPR modified to knock-out CD19 and isogenic WT used as target cells. CD19 CAR T were constructed from PBMCs of rrLBCL patients obtained at time of apheresis using a construct like axicabtagene ciloleucel. For cytotoxicity assays, cell lines were co-cultured at E:T ratios of 1:1 for 24 h or 48 h.

scRNA-seq revealed that CART refractory rrLBCL tumors possessed higher fractions of terminally exhausted LAG3+TIM3+CD38+ CD8 T-cells ($CD8_{TEX}$) with high expression of T-cell dysfunction and TEX signatures compared to CAR T naïve tumors. $CD8_{TEX}$ were most frequent in CART refractory tumors and enriched within CAR+CD8 T-cells detected. TCR clonotype analysis revealed highly expanded T-cell clones within the $CD8_{TEX}$ cluster, significantly increased clonal dominance, and reduced clonal diversity of $CD8_{TEX}$ cells in CAR T refractory compared to CART naïve tumors. Single cell differential gene expression revealed significantly increased expression of LAG3, TIM3, and CD38 in CD8 T-cells from CART refractory compared to CART naïve tumors.

We hypothesized that SAR442257 could boost the activity of CD19 CART-cells from rrLBCL patients through dual antigen targeting of CD19 and CD38 on lymphoma cells and by fratricide of CD38-expressing $CD8_{TEX}$ cells. Cytotoxicity assays showed that SAR442257 significantly increased the killing of CAR T-cells against HT and RL WT (CD19+/CD38+) cells (24-h HT *P*-value = 3e-4, 24-h RL *P*-value = 1e-2) that persisted at 48 h. Addition of SAR442257 to CART-cells allowed killing of HT and RL CD19KO (CD19-/CD38+) (24-h HT *P*-value = 8e-7, 24-h RL *P*-value = 2e-8) at a level similar to the combination in WT. Addition of antibodies lacking CD38 or CD38/CD3/CD28-targeting regions did not boost cytotoxicity or rescue killing of CD19KO targets. We observed significant T-cell fratricide, which was beneficial or non-detrimental in light of increased lymphoma cell killing.

The tumor microenvironment of CART refractory rrLBCL is enriched in clonally expanded and terminally exhausted CD8 T-cells expressing CD38. The CD38/CD28xCD3 trispecific antibody SAR442257 boosted CART-cell activity through recognition of CD38 on the tumor, costimulation of CART-cells, and induced fratricide of CD38+ T-cells. In addition, SAR442257 allowed CD19 CART-cells to kill CD19-/CD38+ LBCL cells.

Encore Abstract - previously submitted to EHA 2023

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Bioinformatics, Cellular therapies, Computational and Systems Biology

Conflicts of interests pertinent to the abstract.

P. Kim
Employment or leadership position: Sanofi

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Employment or leadership position: Sanofi

H. Van De Velde
Employment or leadership position: Sanofi

H. Wang
Employment or leadership position: Sanofi

189 | PROGNOSTIC IMPACT OF HLA-I NEOANTIGEN-SPECIFIC CD8+ T CELLS IN LIMITED-STAGE FOLLICULAR LYMPHOMA

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Introduction: Follicular lymphoma (FL) is the most common indolent NHL. Recently, we demonstrated in limited and advanced stage FL (LSFL, ASFL), that patients with longer remissions had raised clonally expanded intratumoral CD8+ T cells (Tobin, JCO 2019). Durable remissions occur in ~50% of LSFL patients whereas ASFL is incurable. However, little is known regarding the immunological features associated with this difference. We hypothesized HLA-I neoantigen (neoAg)-specific CD8+ T cells may play a role.

Methods: The discovery cohort comprised 101 patients with diagnostic paraffin embedded tissue from the TROG99.03 LSFL clinical trial (MacManus, JCO 2018), in which stage I/II patients were randomized to involved field radiation (IFRT) only or combined modality therapy between 2000 and 2012 (PET from 2006). Contemporaneous validation cohorts were (a) AusLSFL: 60 PET staged, stage I FL patients from Australia (treatment miscellaneous), and (b) CanLSFL: 60 PET staged, stage I FL patients drawn principally from Canada (IFRT only). Digital gene expression (NanoString), targeted sequencing (330 genes), and germline HLA-typing was performed. Mutations observed by sequencing were used to predict neoAgs in TROG99.03 tissues using 8 algorithms (PVACseq) and filtered according to strong binding affinity to HLA-I over wild-type (TESLA consortium guidelines; Wells, Cell 2020).

Results: CD8A gene expression was tested for prognostic significance. In TROG99.03, elevated intratumoral CD8A (by MaxStat) was associated with ~2-fold improvement in PFS for all patients: HR 0.45 (CI: 0.77–0.26, $p = 0.0053$) and stage I only patients: HR 2.4 (CI: 1.2–4.6, $p = 0.036$). In keeping with a relationship between CD8+ T cell infiltration and tumor antigen presentation, raised expression of NLRC5 (a transcriptional HLA-I activator) was also associated with superior PFS: HR 0.48 (CI: 0.99–0.24, $p = 0.024$). CD8A significance was confirmed in both validation cohorts (whereas NLRC5 was validated in AusLSFL only). In keeping with recent IHC CD8 protein data (Los-de Vries, Bld Adv 2022), CD8A gene expression was raised in stage I LSFL vs. 68 ASFL patients treated with immunochemotherapy ($p = 0.02$).

Mutational profiling was concordant with published LSFL data, with *CREBBP* and *KMT2DA* most frequent. NeoAg calling methods including functional assays for neoAg peptide binding were confirmed in a separate cohort of fresh FL tissues. 59% of TROG99.03 tissues had ≥1 neoantigens detected. Importantly, unsupervised hierarchical clustering showed 2-fold enrichment of samples with neoantigens among those with high vs. low HLA-I.

Conclusions: Raised CD8A is associated with favorable prognosis in LSFL. Our data suggests disease control involves populations of expanded HLA-I neoAg-specific T cells. These findings have implications for novel immunotherapeutic strategies designed to increase the rate of durable remissions.

The research was funded by: National Health and Medical Research Council, Australia; Leukaemia Foundation; Mater Foundation

Keywords: Diagnostic and Prognostic Biomarkers, Indolent non-Hodgkin lymphoma, Microenvironment

Conflicts of interests pertinent to the abstract.

C. Keane
Honoraria: Takeda, Roche, AZ, MSD, Beigene

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Honoraria: BMS, Roche, Abbvie; MSD, Lilly

R. Kridel
Research funding: Abbvie
Educational grants: Eisai

M. K. Gandhi
Research funding: Beigene, Janssen

190 | METABOLIC REPROGRAMING OF EXHAUSTED INTRATUMORAL CD8+ T-CELL UNDERLIES ANTI-TUMOR ACTIVITY OF SUMOYLATION INHIBITORS IN LARGE B CELL LYMPHOMA

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Immune checkpoint inhibitors targeting PD1 have revolutionized our approach to solid tumors and Hodgkin lymphoma, but they have not been effective in treating Large B Cell Lymphoma (LBCL). In prior work, we used single cell spatial profiling to show that CD8 and regulatory T cell populations were associated with PD1 resistance in LBCL. Here we used syngeneic model of LBCL to show that this model is sensitive to checkpoint blockade during the early disease phase when tumors are small, and resistant when tumors are large and established. We demonstrate that CD8+ T-cell basal metabolic rate (BMR) is lower in larger tumor and speculated that metabolic dysfuction of CD8 cells contribute to PD1 checkpoint resistance in LBCL. Small ubiquitin-like modifiers (SUMO) proteins regulate a variety of cellular processes in tumor and immune cells and inhibitors of SUMOylation have shown anti-tumor activity in a variety of preclinical tumor models with potential synergy with checkpoint inhibitors targeting PD-1. Here we show that SUMOylation inhibition leads to a robust anti-tumor response which is dependent on CD8+ T-cells. (Figure 1A) Using single cell metabolic studies, we demonstrate that SUMOylation inhibition increases the BMR, glycolytic dependency and proliferative capacity of tumor infiltrating PD1+ CD8+ T-cells. (Figure 1B-D) SUMOylation inhibition is known to increased IFN1 production and we show that the increased BMR was not IFN1 dependent suggesting a direct modulation of immune cell metabolism. PD-1 signaling in CD8+ T-cells has been shown to shift CD8+ Tcells away from glucose-dependent respiration towards fatty acid oxidation which is thought to be responsible for decreased effector functions intratumorally. As SUMOylation inhibition appears to reverse this metabolic shift, we hypothesize that metabolic reprograming of CD8 T-cells is the basis for synergy between SUMOylation inhibition and immune checkpoint inhibitors in LBCL.

The research was funded by: NIH/NCI R01CA266544 to AAM

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Metabolism, Targeting the Tumor Microenvironment

No conflicts of interests pertinent to the abstract.

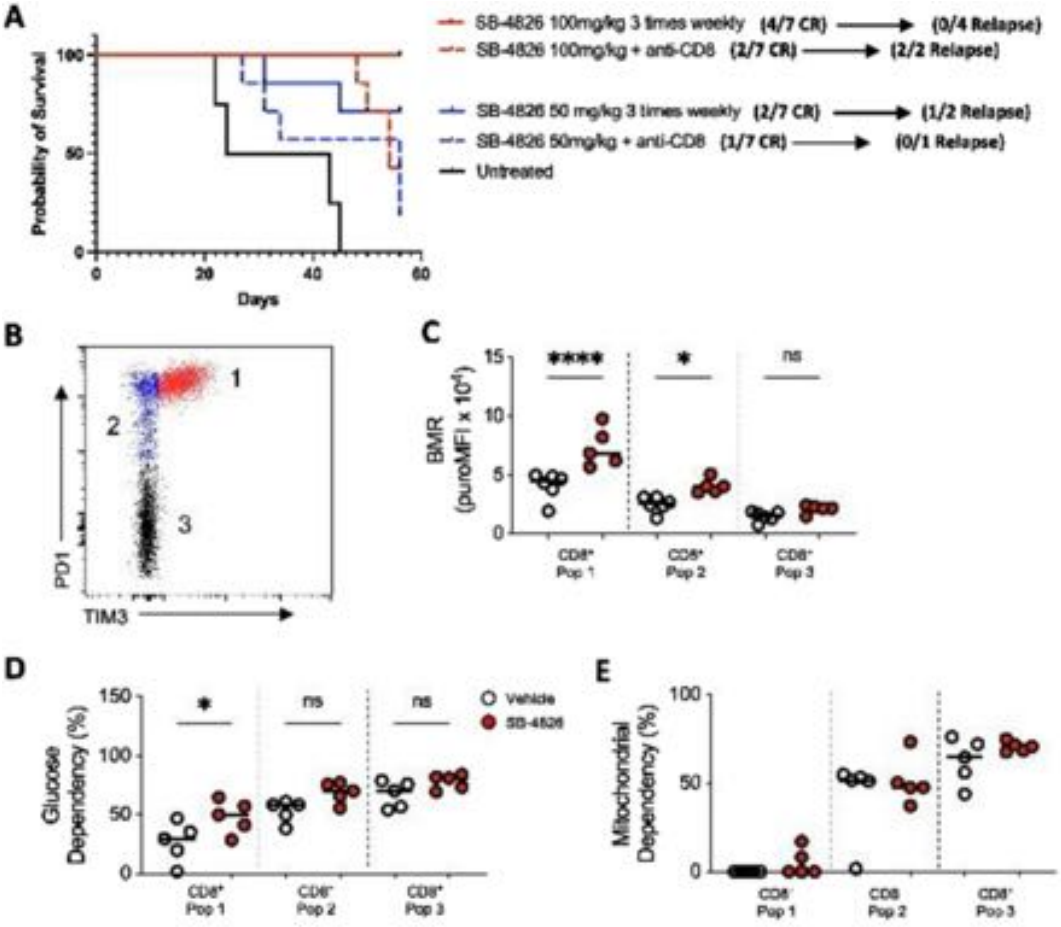

Figure 1: SUMO inhibition causes CD8 T-cell metabolic reprogramming. (A) Survival plot of A20 tumor bearing mice (n=7 per group). (B) Representative flow cytometry data highlight CD8+ T-cell populations for C-E. (C) Basal metabolic rate (BMR) of indicated CD8 tumor infiltrating T-cell populations using flow cytometry based metabolic rate calculations, based off SCENITH. Metabolic rate is relative to puromycin incorporation during a 30 minute incubation. (D) Glucose dependency is relative to the decrease in puromycin incorporation following 2DG treatment. (E) Mitochondrial dependency is relative to the decrease in puromycin incorporation following oligomycin treatment.

191 | GENE EXPRESSION AND SPATIAL TRANSCRIPTOMIC ANALYSIS OF PAIRED DIAGNOSIS AND RELAPSE DLBCL BIOPSIES SHOW A REDUCTION IN T CELL INFILTRATION AND FUNCTION AT RELAPSE

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Introduction: Patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) continue to have poor outcomes despite introduction of innovative immune based therapies. Defining immune changes that occur within tumours at relapse is crucial to understanding treatment failure. We performed comprehensive immune gene expression and spatial transcriptome analysis in a large cohort of R/R DLBCL patients with paired diagnosis and relapse biopsies to explore the evolution of the tumour microenvironment (TME) across treatment timepoints.

Methods: Archived biopsies from 122 R/R DLBCL patients were collected from 5 Australian centres. Gene expression profiling using the Nanostring PanCancer Immune panel of 770 immune-related genes was performed on 85 diagnostic and 85 R/R biopsies with cell of origin (COO) markers spiked in. Nanostring GeoMx spatial whole transcriptome assay was performed on 17 diagnostic and 6 R/R biopsies, segmented into CD20, CD8 and CD68 regions.

Results: 42 R/R patients were assigned germinal B centre (GCB) COO, 31 activated B cell (ABC), and 11 were unclassified. Only one patient (relapsing at 4.5 years) had COO discordance. Differential gene expression (corrected for false discovery) on 68 pairs of diagnosis and R/R biopsies demonstrated profound changes in the T cell compartment, with T cell associated genes (*CD3E*, *CD5*, *CD7*, *CD8A*, *CXCL9*: $p < 0.044$), PD-L1 pathway genes (*IKBKB*, *JAK2*, *STAT3*, *LCK*, *RELA*, MYD88: $p < 0.028$), immune checkpoint gene *TIGIT* (p 0.003), and genes involved in antigen presentation (*HLA-DRB3*, *TAP2*, *TAPBP*: $p < 0.049$) significantly downregulated at relapse [Figure 1a]. Of note, high expression of CD8 and CXCL9 are highly specific for response to immune checkpoint therapy in solid organ tumour cohorts, most likely due to enrichment in neo-antigen T cells (Litchfield et al, Cell, 2021). Gene set enrichment analysis (GSEA) showed suppressed T cell receptor signalling and PD-L1/PD-1 pathways [Figure 1b] as the most significantly altered pathways. Analysis of cell abundance scores revealed a marked reduction in overall T cell abundance scores, but in particular CD8/exhausted CD8 T cell subtypes (*p* 0.015).

Spatial whole transcriptome pathway analysis of CD8 segments demonstrated reduced immunogenic cell death signalling at relapse while upstream analysis predicted severe interferon-gamma and tumour necrosis factor inhibition within CD8 and CD68 segments at relapse.

Conclusions: Key differences in the TME are evident in DLBCL across treatment timepoints with reduced T cell infiltration and function at relapse demonstrated by immune gene expression and spatial transcriptome analysis. These findings have implications for clinical practice as they may explain poor response to immune checkpoint therapy at relapse and could have implications for predicting responses to newer T cell directed therapies such as bispecific T cell and CAR T therapies.

The research was funded by: Metro South Hospital and Health Service Study Grant (SERTA)

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Microenvironment, Tumor Biology and Heterogeneity

Conflicts of interests pertinent to the abstract.

D. Talaulikar
Honoraria: CSL, EUSA, Janssen, Amgen, MSL, Beigene, Roche, Antengene
Research funding: Roche, Janssen

M. K Gandhi
Research funding: Janssen, Beigene

C. Keane
Honoraria: Takeda, Roche, AZ, MSD, Beigene

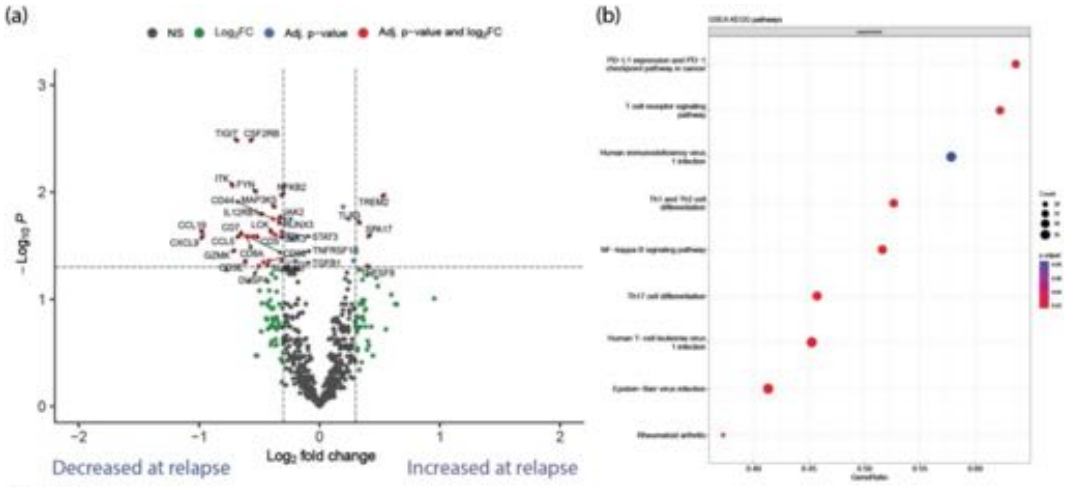

Figure 1:
(a) Volcano plot of paired differential immune gene expression in diagnostic and relapse biopsies showing downregulation of T cell genes, PD-L1 pathway genes, checkpoint gene TIGIT and genes involved in antigen presentation at relapse
(b) Gene set enrichment analysis (GSEA) demonstrating markedly suppressed PD-L1/PD-1 and T cell receptor signalling pathways at relapse compared with paired diagnostic biopsies

192 | ENHANCING T-CELL RESPONSES TO GCB-LIKE LYMPHOMAS WITH IMMUNE-CHECKPOINT-BLOCKADE-BASED THERAPIES

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Introduction: Germinal center B-cell(GCB)-like diffuse large B-cell lymphomas and follicular lymphomas resemble GCB cells, which are normally controlled by $CD4^+$ T follicular helper (Tfh) cells. Gain-of-function (GOF) mutations in the methyltransferase EZH2 (e.g., $EZH2^{Y641F}$) contribute to these diseases by downregulating antigen presentation molecules for T-cell recognition, including MHC-II. Cytolytic T cells have a limited capacity to enter GCs, which facilitates the outgrowth of lymphomas in these sites. Conversely, immunosuppressive $CD4^+Foxp3^+$ regulatory T cells (Tregs) infiltrate GCs (as follicular Tregs, Tfr) and increase the stringency of Tfh survival signals for GCB cells. Immune checkpoint blockade (ICB) therapy targeting CTLA-4 and PD-1 can substantially impact Tfh (PD-1^{hi}) and Tfr (PD-1^{hi}CTLA-4^{hi}) cells. This offers an opportunity to clarify the role of these cells in GCB tumors using clinically available immunotherapies.

Methods: We used a genetically engineered mouse model (GEMM) and derived cell lines expressing $EZH2^{Y641F}$ along with Bcl2 in GCB cells to mimic human EZB lymphomas. We examined how T-cell responses are affected in these models and reinvigorated by ICB alone or with EZH2 inhibition (tazemetostat), by performing flow cytometry and immunofluorescence staining. These effects were correlated with tumor progression (BLI, MRI) and survival. Peripheral blood samples from lymphoma patients treated with ICB were tested by flow cytometry for similar effects.

Results: In the GEMM, EZB cells showed MHC-II and CD86 downregulation, according to EZH2 GOF. Of note, normal B and/or GCB cells in lymphoma-bearing vs. control mice also downregulated MHC-II, pointing to aberrant B:$CD4^+$ T-cell interactions overall. Yet, $CD4^+$ T cells were not excluded from these tumors; rather, $CD4^+Foxp3^-$ T cells (Teff) and PD-1^{hi} Teff were more abundant in lymphoma vs. normal secondary lymphoid organs. EZH2 inhibition with tazemetostat in combination with CTLA-4 blockade increased MHC-II^+CD86^+ EZB cells in GEMM mice and achieved more rapid anti-tumor responses, but without survival improvements. Moreover, this combination did not counteract lymphoma-driven expansion of PD-1^{hi} Teff, and instead promoted their Tfh differentiation (CXCR5 expression), potentially favoring their recruitment near EZB cells. Conversely, combining PD-1 blockade—which can target Tfh cells—with anti-CTLA-4 therapy achieved complete regressions of systemic aggressive tumors in 80% of mice and potent long-lasting immunological memory fully controlling a second tumor injection.

Conclusions: These data suggest that PD-1^{hi} Teff and Tfh cells sustain GCB-like lymphomas and that combined ICB can be used to control these tumors. This aligns with our observation that Tfh cell reductions in lymphoma patients upon treatment with anti-PD-1-based ICB therapy correspond to longer-lasting clinical benefit.

The research was funded by: Leukemia & Lymphoma Society; Parker Institute for Cancer Immunotherapy; AstraZeneca Pre-Clinical & Retrospective Translational Research.

Keywords: Immunotherapy, Microenvironment

Conflicts of interests pertinent to the abstract.

A. Melnick

Consultant or advisory role: Astra Zeneca, BMS, Epizyme, Constellation, ExoTherapeutics, Daiichi Sankyo and Janssen

Research funding: from Janssen, Astra Zeneca, Epizyme, Daiichi Sankyo, and Sanofi

193 | ITK INHIBITOR INDUCES TH1 SKEWING AND HOST ANTI-TUMOR RESPONSE MEDIATED BY CD8+ TEMRA CELLS IN REFRACTORY T CELL LYMPHOMA PATIENTS

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Interleukin 2 inducible T cell kinase (ITK) is involved in both T cell receptor (TCR) signaling and differentiation of helper T cells. ITK-/- mice have defects in Th2 differentiation resulting in skewing toward Th1 cells that secrete IFN-γ. CPI-818 is a selective covalent inhibitor of ITK (Kd 2.5 nM). Its activity was assessed in murine T cell lymphoma EL4 model and demonstrated anti-tumor activity by increasing infiltration of normal CD8+ T cells in the tumors. In vivo CD8 and CD4 depletion reduced CPI-818 anti-tumor activity, indicating that tumor microenvironment infiltrating normal T cells are essential for the anti-tumor activity. Similar results were observed in murine syngeneic B cell lymphoma A20 and colon cancer CT26 models supporting a role for host anti-tumor immunity. CPI-818 is now being evaluated in an ongoing Phase 1 trial in refractory T cell lymphoma (TCL).

Fifty-four patients (pts) with TCL were enrolled in a dose escalation trial receiving doses of 100–600 mg bid of CPI-818 until progression. Pts had a median age of 62 years and a median of four prior therapies. In vitro studies and clinical response data indicated that the optimum dose was 200 mg bid; a dose associated with effects on T cell differentiation based on demonstration of Th1 skewing in vitro and in vivo. In the 200 mg cohort ($N = 20$ enrolled with 13 evaluable)

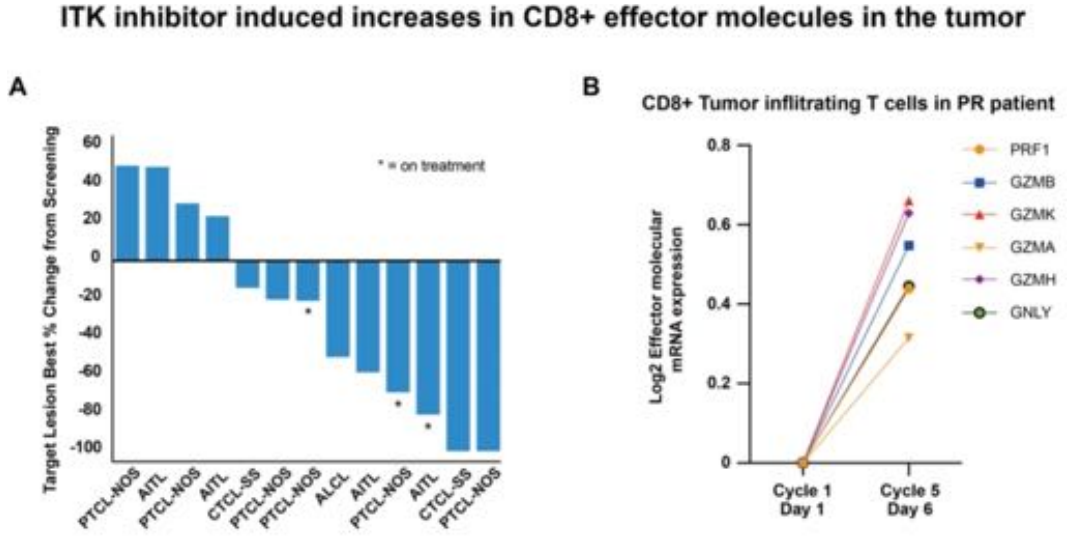

Figure 1. (A) The waterfall plot respresents the best change in target lesion size in patients receiving ITK inhibitor treatment at 200mg BID. (B) The single cell RNA-seq analysis of gene expression profiles of CD8+ infiltrating T cells in patient with partial response (PR). p-values are as follows for comparison of pre and post treatment: perforin-1 (PRF1), 0.04; granzyme B (GZMB), 0.004; granzyme K (GZMK), 0.04; granzyme A (GZMA), 0.02; granzyme H (GZMH), 0.0003; granulysin (GNLY), 0.001.

there have been 1 CR 25 months (PTCL), 1 nodal CR 21 months (CTCL), 1 PR 12+ mo (PTCL) and 1 PR 7 months (ALCL). Ten pts remain on therapy. 1 PR also was seen in a pt receiving 600 mg bid (PTCL). Drug related Grade 3/4 AEs reported in 4/0 pts. Single cell RNA-seq analyses using peripheral blood and tumor tissue samples was performed and revealed that treatment: reduced malignant T cell proliferation by down-regulating cell cycle and DNA replication pathways; increased PRF1+, IFNG+, and GZMB+ CD8 subpopulations; induced clonal expansion of normal CD8 T cells; inhibited Treg cell activity by decreasing the expression of FOXP3 and IL2RA. Flow cytometry of peripheral blood from 3 PR patients revealed higher levels of Th1 cells (CD3+/CD4+/CD8-/CD183+/CD196-) and CD8+ terminally differentiated T effector memory cells (TEMRA CD3+/CD4-/CD8+/CD197-/CD45RA+) compared to baseline.

Our findings suggest that selective ITK blockade has an immunomodulatory effect, which could represent a potentially novel immunotherapy approach for the treatment of T cell lymphomas and other tumors.

The research was funded by: The research was funded by Corvus Pharmaceuticals and Angel Pharmaceuticals.

Keywords: Immunotherapy, Molecular Targeted Therapies, Targeting the Tumor Microenvironment

Conflicts of interests pertinent to the abstract.

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Stock ownership: Corvus Pharmaceuticals

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194 | DETERMINANTS OF RESPONSE TO T-CELL STIMULATION BY CD27 ANTIBODY THERAPY IN LYMPHOMA: THE RIVA TRIAL

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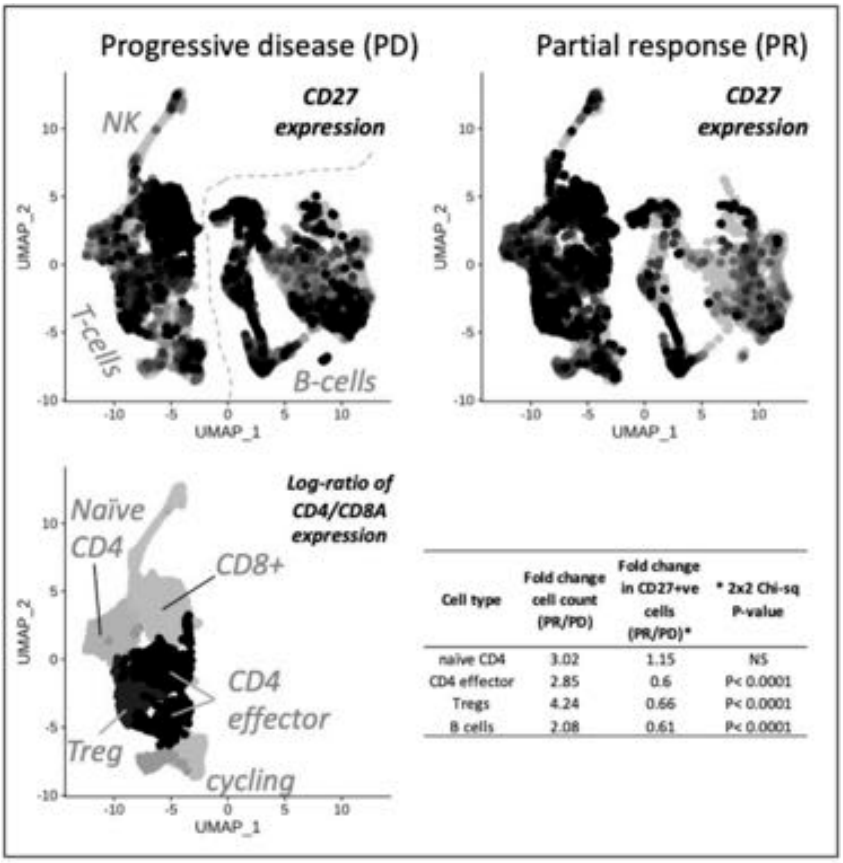
Introduction: T-cell immunostimulatory antibodies invoke potent anti-tumour responses in murine models but their ability to induce T-cell immunostimulation in the immunosuppressive tumour microenvironment (TME) of patients, or induce clinical responses, is lacking. Agonistic CD27 antibody stimulation of T cells enhanced tumour killing by anti-CD20 in murine models led to the RiVa trial (NCT3307746): a phase IIa study of rituximab (ritux) and varlilumab (varli, anti-CD27) in relapsed/refractory B-cell lymphoma. Here, we describe the immunological effects of the combination in pre- and post-treatment biopsies, and their association with clinical responses.
Methods: Patients with relapsed/refractory $CD20^+$ B-cell lymphoma were randomised to arms A (ritux on Cycle 1 Day 1 (C1D1)/varli (C1D2)) or B (ritux (C1D1)/ varli (C1D8)). C2-6 are identical in both arms (D1 ritux (C2-6); D2 varli (C3 and C5); Q2W. The primary endpoints were overall response and safety. Intratumoral biopsies were taken pre-treatment and on C1D7/8 post treatment, i.e., post-ritux/varli in arm A, and post-ritux alone in arm B, and processed by bulk and single cell RNA sequencing (scRNAseq) for analysis by CIBERSORTx and gene set enrichment analysis (GSEA).
Results: Safety and efficacy data were previously reported (Lim et al *ASH* 2022). 27 patients were randomised (16 indolent B-cell non-Hodgkin lymphoma cases (NHL) and 11 aggressive B-NHL; median age 71 (range 49–87); median lines of previous treatment were 4 (range 1–13). The overall response rate was 37.5% (90% CI, 17.8–60.9) for indolent B-NHL and 20% (90% CI, 3.7–50.7) for aggressive B-NHL (4 partial responders (PR) (2 aggressive B-NHL, 2 indolent B-NHL; duration 54 days to >1 year) and 4 with stable disease (SD) (all indolent B-NHL; duration >11 days to >1 year)).
Comparing pre- vs. post-treatment biopsies by bulk RNAseq, pathways enriched in TCR and costimulatory signalling (normalised enrichment score (NES) 1.97–2.51, q-value = 0.001) were observed in ritux/varli-treated cases, which were absent in ritux only cases. CIBERSORTx analysis showed >100-fold increased CD4 T cell infiltration in responders vs. non-responders ($p = 0.027$). Pre-treatment



Cell type	Fold change cell count (PR/PD)	Fold change in CD27+ve cells (PR/PD)*	* 2x2 Chi-sq P-value
naïve CD4	3.02	1.15	NS
CD4 effector	2.85	0.6	P< 0.0001
Tregs	4.24	0.66	P< 0.0001
B cells	2.08	0.61	P< 0.0001

Figure. scRNA-seq of RIVA patient biopsies. Top: UMAPs of CD27 mRNA expression in partial responders (n=3) versus those with progressive disease (n=3). Black = high scaled expression. Cell types shown as indicated. **Bottom:** UMAP of log-ratio of CD4/CD8A expression in T cell clusters. Light grey shading indicates the lowest log-ratio for all clusters, these were labelled as CD8+ cells. **Table insert:** Fold change in cell counts and associated significance as indicated between PR and PD cases. Cell numbers normalised by down-sampling to 1400 cells/case.

samples of responders were enriched in T-cell signalling and Th1 signatures (NES 2.52, q = 0.02).
scRNAseq analysis of pre-treatment biopsies (3 PR vs. 3 progressive disease (PD)) showed 2.08–4.24-fold higher CD4 T-cell frequencies and 0.61-fold less CD27-expressing B-cells ($p < 0.0001$) in PR vs. PD cases (see Figure).
Conclusions: T-cell immunostimulatory antibodies can overcome the immunosuppressive TME to produce clinical responses when combined with rituximab. In the case of anti-CD27, clinical responses were associated with higher CD4+ T cell numbers and T-cell signalling activity in the pre-treatment tumours. Further studies to exploit therapeutic T-cell agonistic antibodies in lymphoma are warranted.

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Keywords: Combination Therapies, Immunotherapy

Conflicts of interests pertinent to the abstract.

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195 | GUT MICROBIOME IN DLBCL PATIENTS UNDERGOING FIRST-LINE R-CHOP REGIMEN—THE ONCOPASSPORT STUDY

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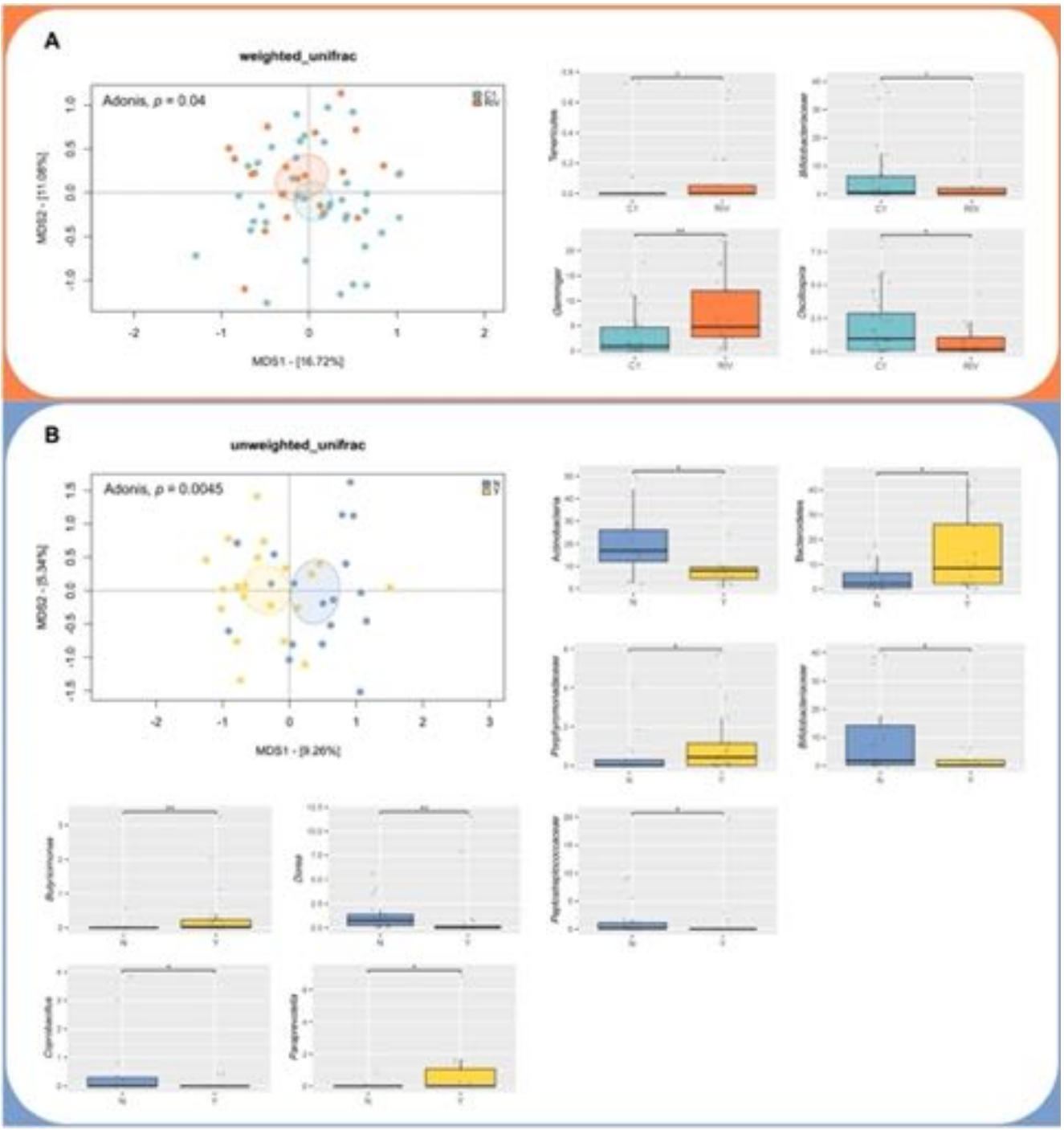
Introduction: The search of biomarkers that can predict and influence treatment outcomes of diffuse large B-cell lymphoma (DLBCL) is constantly evolving, especially in the front-line setting. Preclinical studies have shown that gut microbiome (GM) diversity and specific bacterial species can have a direct impact on drug efficacy and immune-related toxicity. Although R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) remains the gold standard as first-line treatment for DLBCL patients, about 40% of them relapsed or are refractory to this regimen. In addition, major adverse events (AEs) related to this combination, such as hematological toxicity, including febrile neutropenia (FN), and gastrointestinal (GI) AEs, do not affect all treated populations and could influence the role of GM in the tolerability and response to R-CHOP. Reconstructing GM dynamics in DLBCL patients from diagnosis to the end of R-CHOP may provide important information for patient management.
Methods: Fifty DLBCL patients undergoing first-line R-CHOP regimen were enrolled (NCT03797170; RF-2016-02363730). Stools were collected at baseline, before each therapy cycle, and at response assessment (after 3 cycles and at the end of therapy), to profile GM compositional changes. Additional samples were collected upon occurrence of FN and GI AEs. GM was analyzed by 16S rRNA amplicon sequencing.
Results: Of 50 enrolled patients, 45 provided at least one fecal sample. Interim and final overall response rate were 91.1% (36 complete response). Specifically, 4 patients worsened their

response between cycles 3 and 6, and 4 patients improved their response. At the end of treatment, only 3 patients had progression of disease. Three patients had FN (all grade 4) and 24 patients had at least one GI AE. Beta diversity analysis showed separation between baseline and end-of-therapy GM structures (Figure 1A). In particular, the phylum Tenericutes and the genus *Gemmiger* increased, while the family *Bifidobacteriaceae* and the genus *Oscillospira* decreased. Additionally, patients reporting GI AE or FN segregated at baseline from those who did not report them, being enriched in Bacteroidetes and *Butyricimonas*, while depleted in Actinobacteria, *Peptostreptococcaceae*, *Dorea*, and *Coprobacillus* (Figure 1B).

Conclusions: Identifying factors that may modify the response and tolerance to first line is crucial to improving lymphoma patients outcome and adherence to therapy. To date, numerous efforts have been made to recognize biologic factors that can identify patients with DLBCL at increased risk of relapse and toxicity to R-CHOP, with poor results. Interestingly, in our series, putative early GM signatures of GI AE or FN were identified, paving the way for new personalized GM-based intervention strategies to improve patient prognosis.



The research was funded by: Italian Ministry of Health, RF-2016-02363730

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers

No conflicts of interests pertinent to the abstract.

196 | MICROBIOTA DIVERSITY IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA AND IMMUNE-PRIVILEGED SITES LYMPHOMA

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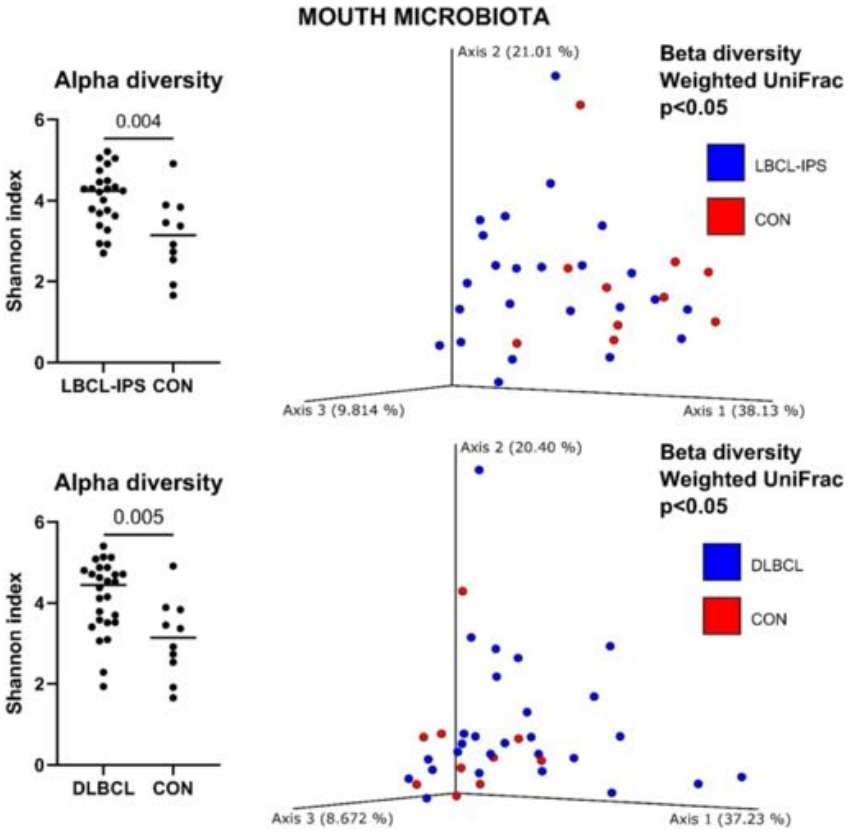
Background: Microbiota (MB) participates on the host immune system regulation. There is data that MB could be connected with immunotherapy effect in several cancers e.g. melanoma. It may play important role in the pathogenesis or therapy of lymphoma as well. There is however still limited knowledge about MB diversity in different lymphoma subtypes especially in large B-cell lymphoma of immune-privileged sites (LBCL-IPS). We present first data of prospective microbiota project in lymphoma.

Methods: We have analyzed 10 healthy donors (CON, age med. 67) and 55 pts with lymphoma—31 patients with systemic diffuse large B-cell lymphoma (DLBCL, age med. 66) and 24 pts with LBCL-IPS (age med. 67). LBCL-IPS group consists of 18 Primary CNS lymphoma (PCNSL), 5 vitreoretinal lymphoma (VRL) and 1 primary testicular lymphoma (PTL). We have collected fresh fecal samples (gutMB) and buccal swab samples (oralMB) and processed them for bacterial16S ribosomal RNA gene sequencing by Illumina. To compare oralMB and gutMB of both lymphoma groups with CON, we used Shannon diversity index for α-diversity analysis and the Principle Coordinate Analysis (PCoA) based on weighted UniFrac distance and the Linear discriminant analysis Effect Size (LEfSe) for the description of β-diversity.



M. Tenglerova share co-first authorship

M. Trneny co-share senior authorship

Results: The non-GC subtype was detected in 19 (61%) out of 31 DLBCL pts and in 7 (41%) out of 17 evaluable PCNSL pts. Both DLBCL as well as LBCL-IPS showed a significantly higher α-diversity ($p < 0.005$), as well as a significant shift in β-diversity ($p < 0.05$) of their oralMB compared to CON (Figure 1). This shift was associated with an increased relative abundance of microbes from the order Fusobacteriales and family Lachnospiraceae in DLBCL and from the order Fusobacteriales and family Prevotellaceae in LBCL-IPS. GutMB of DLBCL had significantly lower α-diversity ($p < 0.05$) compared to CON whereas LBCL-IPS showed only borderline decrease ($p = 0.06$). In addition, only gutMB of LBCL-IPS showed significant shift in β-diversity ($p < 0.05$) vs. CON. GutMB of DLBCL was associated with increased relative abundance of pathobionts from genera *Escherichia/Shigella*, *Ruminococcus gnavus* group and *Bilophila*, and LBCL-IPS microbiota had higher abundance of genera *Akkermansia* and *Veillonella*.

Conclusions: Both lymphoma groups—diffuse large B-cell lymphoma as well as large B-cell lymphoma of immune-privileged sites—are characterized by unique microbiota composition. Both the oral and fecal microbiota of lymphoma patients differ from those of healthy individuals. The follow-up studies are focused on microbiota composition and therapy outcome.

The research was funded by: The study is supported by the Cooperation Program, research area "Oncology and Haematology" and NU20-03-00253 and NU22-03-00370.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

197 | TAYLORING LYMPHOMA THERAPY WITH IMMUNE ESCAPE SIGNATURES FROM 3D AVATARS OF B-CELL NHL

F. Gava[1], C. Faria[2], P. Gravelle[1], J. Garcia-Valero[3], C. Quelen[1], N. Serrat[3], N. Gower[4], F. Morschhauser[4], J. Fournié[1], F. Bouquet[5], C. Fonseca[6], S. Herter[6], L. Codarri[6], R. McCord[7], E. Chiang[7], C. Laurent[8], P. Perez-Galan[3], L. Ysebaert[9], C. Bezombes[1]

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Relapsed/refractory B-cell NHLs are made up with a heterogeneous array of incurable diseases, whose outcomes in the rituximab era are unclear, despite patients benefit from new therapeutic strategies. In most cases, the choice of therapy is based on age, comorbidities, and duration of last response to immuno-chemotherapy. We lack predicting factors able to dictate this choice on a patient-per-patient basis, as exemplified by immune checkpoint blockade since we often do not understand why these drugs fail or succeed in our patients. One strategy to improve the rate of success of new cancer drugs prioritization in the clinic, would be to more closely align the cellular models used in our translational scientific projects to patients' tumors.

Here, we present a new preclinical follicular lymphoma (FL) 3D model called Patient-Derived Lymphoma Spheroid (FL-PDLS) that recapitulates the FL pathogenesis and the B cells-immune tumor microenvironment crosstalk. We established a workflow allowing their full characterization and present evidences that PDLS, which are mainly composed of tumor B cells and autologous T cells, exhibit an exhausted immune phenotype typical of FL lymph node, including a medium to high expression of several ICP TIGIT, PD1, TIM3 or LAG3 that can be targeted. These 3D avatars constitute a platform for high-throughput screening of therapeutic antibodies. Among functional assays available, we can assess the ability of lymphomatous cells to grow in 3D and ability of T cells to infiltrate/kill 3D autologous models and/or 3D cell lines models of NHL.

Thus, in the era of personalized medicine FL-PDLS appear a promising preclinical model to predict patient response and discover new therapeutic target. This system can evolve towards full FL-TME reconstituted organoids and therefore become powerful theragnostic biomaterials that combine therapy with diagnosis necessary for individualized therapies for patients.

The research was funded by: This research collaboration was supported through the imCORE network on behalf of F.Hoffmann-La Roche.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Immunotherapy, Risk Models

Conflicts of interests pertinent to the abstract.

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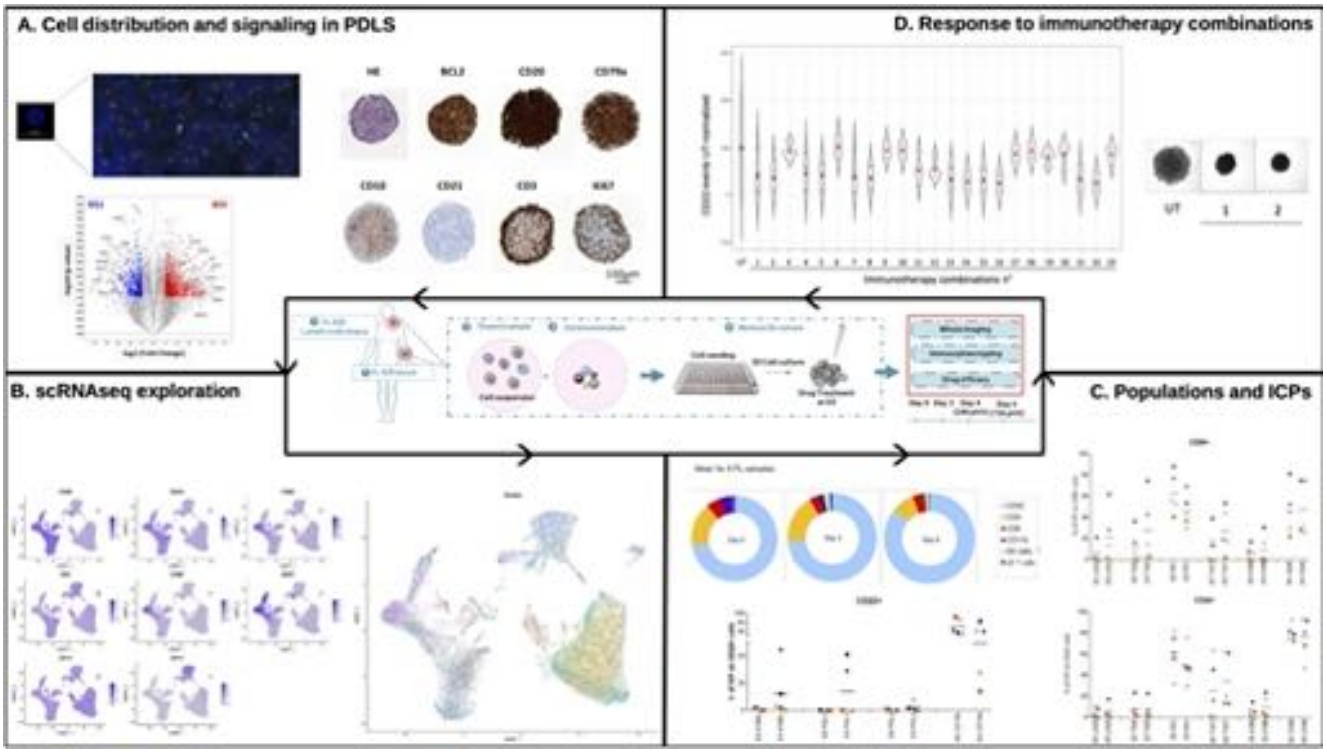

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198 | STUDY OF THE EFFICACY OF NOVEL BISPECIFIC ANTIBODIES TARGETING IMMUNE CHECKPOINTS IN A 3D MODEL OF B NON-HODGKIN LYMPHOMA

N. Gower[1], F. Gava[2], L. Rimailho[2], C. Faria[3], P. Gravelle[2], P. Perez-Galan[4], N. Serrat[4], F. Bouquet[5], C. Fonseca[6], S. Herter[6], L. Codarri[6], R. McCord[7], E. Chiang[7], F. Morschhauser[1], L. Ysebaert[8], C. Laurent[9], C. Bezombes[2]

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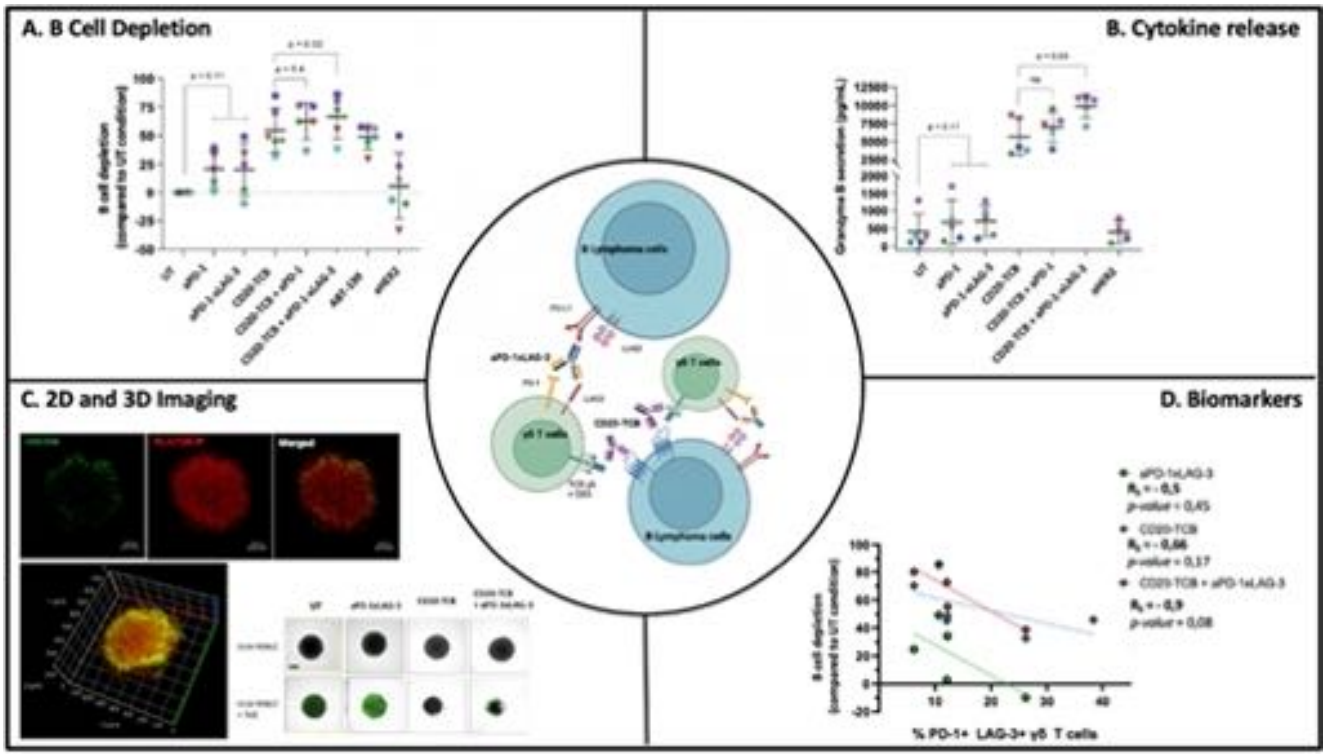
Despite therapeutic advances, follicular lymphoma (FL) remains an incurable disease. In addition to tumour-specific genomic alterations, the tumour microenvironment plays an essential role in the progression of the disease by participating in immuno-escape mechanisms. Among them, the PD-1/PDL1 axis has been widely studied but the efficacy of anti-PD-1 remains limited in FL suggesting additional immune escape mechanisms such as LAG-3. In order to decipher this issue, we tested the efficacy of a bispecific antibody targeting both PD1 and LAG-3 ICPs in a 3D model of FL co-cultured with PD-1/LAG-3 expressing γαμμαδελταT cells.

Therefore, we studied γαμμαδελταT cells infiltration and measured their activation as well as tumour B cell depletion by flow cytometry and high throughput 2D/3D analyses. Our results showed that aPD-1xLAG-3 bispecific antibody enhances CD20-TCB efficacy by increasing γδT cells infiltration into 3D model and their activation as attested by an increase of Granzyme B and IFNγαμμα secretion. Consequently, a decrease of 3D area correlated with a potent B cell depletion was observed after combination treatment. Finally, we observed that percent of PD-1+/LAG3+ γαμμαδελταT cells negatively correlates with drug efficacy. 3D cell cultures from FL biopsies



(Patient-Derived Lymphoma Spheroids-PDLS) will allow us to confirm these results in relevant preclinical models.
As PD-1^{+}LAG-3^{+} T cells predict a poor outcome in FL patients, our findings open encouraging perspectives for the use of new antibodies blocking both PD-1 and LAG-3 thus specifically targeting the exhausted T-cell population and may therefore represent a promising future treatment strategy in FL patients.

The research was funded by: This research collaboration was supported through the imCORE network on behalf of F.Hoffmann-La Roche.

Keywords: Immunotherapy, Indolent non-Hodgkin lymphoma, Risk Models

Conflicts of interests pertinent to the abstract.

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Honoraria: Chugai (scientific lectures)

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Educational grants: Janssen

TRANSLATIONAL STUDIES, B-CELL LYMPHOMAS

199 | IDENTIFICATION OF AN ACTIVATED/MEMORY B-CELL SIGNATURE OF POOR OUTCOME AND SENSITIVITY TO LENALIDOMIDE IN FOLLICULAR LYMPHOMA PATIENTS

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Introduction: The RELEVANCE randomized trial showed that the combination of lenalidomide + rituximab (R^2) has similar efficacy to rituximab + chemotherapy (R-chemo) in patients (pts) with advanced-stage, previously untreated follicular lymphoma (FL) after 6 years of follow-up. In this study, using RNA sequencing we identify high-risk patients benefiting from R^2.

Methods: RNAseq on FFPE biopsies was performed for 324 enrolled pts (grade 1–2 and 3A) at diagnosis. Using unsupervised clustering, gene signatures (GS) were identified, scored in individual pts and tested for their association with progression free survival (PFS).

Results: Of the total 46 identified GS, two GS displayed opposite and treatment-dependent associations with PFS. The first GS (179 genes) was enriched for genes expressed in ABC-subtype diffuse large B cell lymphomas and normal memory B cells; while the second GS (213 genes), strongly anti-correlated with the first one, was enriched for genes expressed in GCB-subtype DLBCLs.

We combined the two GS into a 20-genes based Linear Predictor Score (LPS20) which could classify pts into either an ABC/MEM-like FL subtype (n = 160 patients) or a GCB-like FL subtype (n = 164 patients). In the R-chemo arm, the 6 years PFS of ABC/MEM-like pts (45% [35–59]) was significantly shorter than GCB-like pts (67% [59–80]) (HR = 2.13[1.30–3.51], p = 0.003). In the R^2 arm, both subgroups had comparable PFS (65% vs. 62%; HR = 1.04[0.61–1.77], p = 0.9). In a multivariate model including FLIPI, the association between subtype and outcome remained significant for R-chemo pts (adjusted HR = 2.15[1.31–3.53], p = 0.002) and the treatment dependence as well (interaction subtype*treatment p = 0.041). A marked benefit of R^2 compared to R-chemo was observed (HR = 0.46[0.28–0.75], p = 0.002) for ABC/MEM-like pts with FLIPI ≥ 2.

We validated these prognostic correlations in two independent R-chemo treated FL cohorts from the LYSA (PRIMA, n = 134) and BCCA (GSE119214, n = 137). In PRIMA, the ABC/MEM-like subtype was associated with a shorter PFS (vs GCB-like) but only among FLIPI ≥ 2 pts (n = 111, HR = 1.72[1.01–2.93], p = 0.044). In the BCCA cohort, the ABC/MEM-like subtype was associated with inferior FFS (HR = 1.78[1.1–2.87], p = 0.019) and overall survival (HR = 2.13 [1.18–3.82], p = 0.012).

Exome sequencing data revealed that ABC/MEM-like FLs were enriched for mutations in genes from the mTOR/autophagic pathway, while GCB-like FLs were enriched for mutations in*EZH2* and *TNFRSF14*, hinting different genetic drivers.

Conclusions: These results confirm that FL tumors can be sub-categorized into cell of origin-based ABC/MEM- vs. GCB-like subtypes, as recently suggested (PMID 34991156). The herein described LPS20 predictor has theragnostic potential in identifying ABC/MEM-like FL pts as a high-risk subgroup with inferior outcome when treated with R-chemo, but the R^2 regimen overcame this poor prognosis.

CL, PT and BT contributed equally to this work. FM, AKG and LX contributed equally to this work

The research was funded by: Bristol Myers Squibb

Keywords: Diagnostic and Prognostic Biomarkers, Genomics, Epigenomics, and Other -Omics, Indolent non-Hodgkin lymphoma

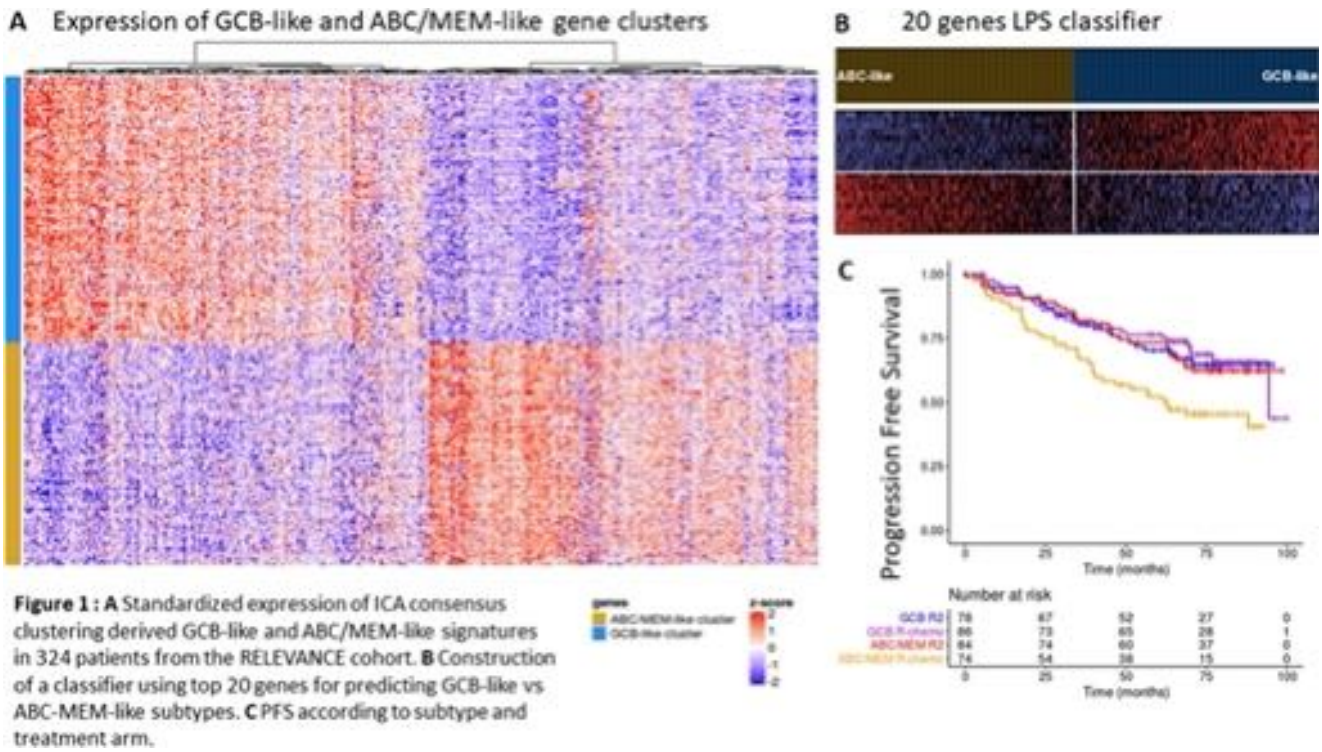

Figure 1 : A Standardized expression of ICA consensus clustering derived GCB-like and ABC/MEM-like signatures in 324 patients from the RELEVANCE cohort. **B** Construction of a classifier using top 20 genes for predicting GCB-like vs ABC-MEM-like subtypes. **C** PFS according to subtype and treatment arm.

Conflicts of interests pertinent to the abstract.

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200 | A LOW LYMPHOCYTE-TO-MONOCYTE RATIO (LMR) PREDICTS PFS, POD24 AND OS IN PREVIOUSLY UNTREATED, HIGH TUMOR BURDEN FOLLICULAR LYMPHOMA (FL): AN ANALYSIS FROM THE RELEVANCE TRIAL

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Introduction: The peripheral blood LMR has been postulated as an accessible piece of information about the composition of the tumor microenvironment. In a single-center, retrospective, unselected cohort of FL, a low LMR was shown to be associated with an older age and higher tumor burden and to predict for a shorter progression-free and overall survival (PFS, OS) and a higher risk of histological transformation and second primary malignancies (*Mozas, Leuk & Lymph, 2020*). We explored the impact of the LMR in patients included in the phase III RELEVANCE trial (*Morschhauser, NEJM, 2018 and JCO, 2022*), which compared rituximab-chemotherapy (R-chemo) with rituximab-lenalidomide (R^2) in patients with previously untreated, high tumor burden FL.

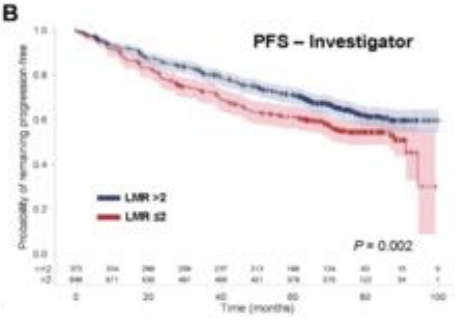
Methods: Xtile and the *maxstat* package of R software were used to find the best LMR cutoff based on PFS data and then validated using a truncated power basis spline method. Baseline characteristics, PFS per investigator assessment, early relapse (POD24) and OS were compared between LMR risk groups. Multivariable Cox regression models including the FLIPI score and the treatment arm were built for survival analyses and uni/multivariable logistic regression was used for POD24 analysis.

Results: Among the 1030 patients included in the RELEVANCE study, 1018 had LMR data available. The median LMR was 2.5 (range, 0–93) and a LMR cutoff of 2 was found to best predict PFS. Patients with a LMR $\leq$2 (n = 372, 37%) were older and displayed higher-risk features (Figure A). In the global cohort, a LMR $\leq$2 was predictive of a shorter

A

	LMR		All patients	P value
	≤2	>2		
Number of patients, n (%)	372 (37)	646 (63)	1018 (100)	-
Male sex, n (%)	192 (52)	305 (47)	497 (49)	0.2
Median age, years	61	58	59	**<0.001**
ECOG PS 2, n (%)	14 (4)	13 (2)	27 (3)	**0.03**
B symptoms, n (%)	91 (25)	179 (28)	270 (27)	0.3
Ann-Arbor stage III-IV, n (%)	349 (94)	599 (93)	948 (93)	0.6
Histological grade 1-2, n (%)	305 (82)	555 (86)	860 (85)	0.1
>1 extranodal sites, n (%)	167 (45)	339 (53)	506 (50)	**0.02**
Bulky mass, n (%)	190 (51)	222 (34)	412 (41)	**<0.001**
Hemoglobin <120 g/L, n (%)	92 (25)	96 (15)	188 (19)	**<0.001**
β2-microglobulin ≥3 mg/L, n (%)	130 (37)	214 (34)	344 (35)	0.4
Elevated LDH, n (%)	120 (33)	168 (26)	288 (28)	**0.03**
High-risk FLIPI score, n (%)	213 (57)	281 (44)	494 (49)	**<0.001**
Treatment				
R-chemotherapy, n (%)	185 (50)	324 (50)	509 (50)	0.95
R-lenalidomide, n (%)	187 (50)	322 (50)	509 (50)	

B



C

	LMR			All patients
	≤2	>2	P value	
POD24, n (%)	75 (20)	78 (12)	**<0.001**	153 (15)
5-y PFS, % (95% CI)	62 (56–68)	71 (67–74)	**0.002**	68 (65–71)
5-y OS, % (95% CI)	89 (85–92)	92 (89–94)	**0.05**	91 (89–93)

	LMR ≤2 – Univariable analysis			LMR ≤2 – Multivariable analysis		
	OR or HR	95% CI	P value	HR or OR	95% CI	P value
POD24	1.84	1.30–2.60	**0.0006**	1.71	1.20–2.43	**0.003**
PFS	1.39	1.13–1.71	**0.002**	1.31	1.06–1.62	**0.01**
OS	1.44	1.001–2.07	**0.05**	1.30	0.90–1.87	0.16

LMR, lymphocyte-to-monocyte ratio; HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; FLIPI, Follicular Lymphoma International Prognostic Index; POD24, progression of disease within 24 months of frontline treatment initiation; PFS, progression-free survival; OS, overall survival; CI, confidence interval. Statistically significant values are highlighted in bold.

PFS (HR = 1.39 Figure B and C) and OS (HR = 1.44), but its negative impact in the multivariable model remained statistically significant solely for PFS (HR for LMR = 1.31). Likewise, a LMR ≤2 was associated with a higher risk of POD24 (univariable OR = 1.84; multivariable OR = 1.71). No significant interaction was observed in the PFS analysis between treatment arms and the LMR, despite the fact that the LMR was significantly associated to PFS only in the R-chemo arm ($P = 0.001$) and not in the R^2 arm ($P = 0.08$).

Conclusions: In this RELEVANCE subanalysis, we demonstrated that the LMR is a strong predictor of PFS and early relapse in high tumor burden FL patients. Whether treatment with immunomodulators such as lenalidomide may abrogate its negative prognostic impact needs to be further investigated.

The research was funded by: The RELEVANCE trial was supported by Celgene, a Bristol Myers Squibb Company, and the Lymphoma Academic Research Organisation (LYSARC).

Keywords: Diagnostic and Prognostic Biomarkers, Indolent non-Hodgkin lymphoma, Targeting the Tumor Microenvironment

Conflicts of interests pertinent to the abstract.

A. Martín García-Sancho
Other remuneration: Janssen, Roche, BMS, Kyowa Kirin, Clinigen, Eusa Pharma, Novartis, Gilead/Kite, Incyte, Lilly, Takeda, ADC Therapeutics America, Miltenyi, Ideogen, Abbvie

P. Abrisqueta
Consultant or advisory role: Janssen, Roche, Abbvie, BMS, Astrazeneca, Gilead, Beigene
Honoraria: Janssen, Roche, Abbvie, BMS, Astrazeneca, Gilead
Educational grants: Janssen, Abbvie, Roche

M. Crump
Other remuneration: Kyte/Gilead, Novartis

F. Morschhauser
Consultant or advisory role: Roche, Gilead, Genmab, Novartis, Abbvie
Honoraria: Chugai (scientific lectures)

201 | GENETIC ALTERATIONS IN FOLLICULAR LYMPHOMA PREDICT RESPONSE TO VERY LOW DOSE RADIOTHERAPY

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Introduction: Follicular lymphoma (FL) is typically indolent, but relapses and transformation to higher grade disease are common. FL is often sensitive to radiotherapy (RT) and can show a complete response (CR) even to very low dose radiotherapy (VLDRT, 4 Gy). We identified genetic signatures of FL radiosensitivity to aid in patient selection for VLDRT.

Methods: We analyzed an institutional database, identified 110 FL patients with 113 tumors treated with RT, and obtained targeted exon sequencing data and patient/tumor traits including BCL2 translocations. The presence of mutant (mut) genes compared to wild type (WT) were associated with RT response using logistic regression. Log-rank testing and Cox proportional hazards models were used to analyze local progression free survival (LPFS), censored at start of unplanned therapy, with 2-year (2y) survival reported.

Results: The patient and tumor characteristics are summarized in Table 1. For the overall cohort, only prior DLBCL ($p < 0.01$) and prior

chemoimmunotherapies ($p = 0.02$) were significantly associated with LPFS on multivariate Cox modeling, and there were no associations with odds of CR.

The most altered gene was CREBBP ($n = 75$, 66%) and only 14 tumors had TP53 mutations. BCL2 translocations were seen in 42 tumors with 20 tumors having both BCL2 mut and translocation (mut/trans). We identified a BCL2-altered signature with shorter LPFS after RT ($p = 0.01$). BCL2 mut or mut/trans had shorter LPFS for the overall cohort ($p < 0.01$ for both), while for VLDRT, only BCL2 mut/trans was associated with shorter LPFS ($p = 0.02$). Among altered genes, only CREBBP mut was associated with increased odds of CR (OR: 2.28 (95% CI: 1.01–5.15, $p = 0.04$)).

Most CREBBP mutations occurred in a histone acetyltransferase (HAT) domain ($n = 66$, 88%), and HAT mut had improved LPFS (2y LPFS 67% WT vs. 77% mut, $p = 0.05$). This was also seen in the VLDRT cohort (2y LPFS 54% WT vs. 73% mut, $p = 0.04$) but not for >4 Gy RT ($p = 0.50$). For the VLDRT cohort, BCL2 mut/trans and HAT WT had a 2y LPFS of 28% whereas BCL2 mut/trans and HAT mut had a 2y LPFS of 53% ($p < 0.01$).

Conclusions: Incorporating genetic signatures associated with radiosensitivity, and specifically alterations involving BCL2 and CREBBP, may independently improve patient selection for RT. CREBBP HAT domain mutations are potentially targetable and may have important implications for augmenting radiosensitivity to VLDRT.

Keywords: Genomics, Epigenomics, and Other -Omics, Indolent non-Hodgkin lymphoma, Radiation Therapy

TABLE 1 Patient, treatment, and tumor characteristics

Variable		Overall ($n = 113$)	VLDRT ($n = 66$)
		Median (IQR) or *n* (%)	
Grade	1–2	92 (82%)	57 (88%)
Site	Pelvis	43 (38%)	15 (23%)
Size		3.2 cm (2.1–4.6)	3.3 cm (2.1–4.4)
Prior DLBCL		7 (6%)	6 (9%)
Prior treatment	Transplant	5 (4%)	2 (3%)
	Chemoimmunotherapy	45 (41%)	26 (40%)
PET-staged		112 (99%)	65 (98%)
Stage at RT	Stage 1 or 2	80 (71%)	39 (59%)
Intent	Curative	72 (64%)	34 (52%)
Response by Imaging	CR	72 (64%)	37 (56%)
	PR	31 (28%)	20 (30%)
	No Response	9 (8%)	9 (14%)
Local Progression		31 (27%)	23 (35%)

Conflicts of interests pertinent to the abstract.

E. Joffe
Consultant or advisory role: AstraZeneca, Epizyme outside scope of this work

A. Dogan
Consultant or advisory role: Seattle Genetics, Takeda, EUSA Pharma, AbbVie, Peerview, Physicans' Education Resource outside scope of this work
Research funding: Roche/Genentech outside scope of this work

A. D. Zelenetz
Employment or leadership position: data safety monitoring committee membership for BMS, Celgene, and Juno, data safety monitoring committee members outside scope of this workhip chair for Beigen
Consultant or advisory role: Adaptive Biotechnologies, Abbvie, Amgen, AstraZeneca, Beigene, Bristol Myers Squibb, Celgene, Genentech/Roche, Gilead, MEI Pharma, MorphoSys, NCCN, Novartis, and Verastem outside scope of this work
Research funding: MEI Pharma, Gilead, Beigene, and Roche outside scope of this work

G. Salles
Consultant or advisory role: bbvie, Beigene, BMS/Celgene, Debiopharm, Genentech/Roche, Genmab, Incyte, Kite/Gilead, Milteniy, Morphosys, Novartis, Velosbio outside scope of this work

B. S. Imber
Honoraria: GT Medical Technologies Inc outside scope of this work

202 | PROTEOMIC PROFILING IDENTIFIES APOPTOTIC DEREGULATION PREDICTIVE OF HISTOLOGICAL TRANSFORMATION IN FOLLICULAR LYMPHOMA

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Introduction: Follicular lymphoma (FL) is a lymphoid neoplasia arising from germinal center B cells, characterized by the t(14;18) translocation and subsequent upregulation of anti-apoptotic B-cell lymphoma 2 (BCL2) proteins. While characterized by an indolent nature and favorable prognosis, FL remains generally incurable. Furthermore, histological transformation (HT) to a high-grade lymphoma

histology, is associated with markedly aggressive clinical behavior and remains the leading cause of FL-related death.

We performed a large-scale mass spectrometry-based proteomics study on diagnostic FL biopsies, in which proteins predictive of HT were identified. Of interest, proteins involved in apoptotic regulation, namely caspase 3 (CASP3), induced myeloid leukemia cell differentiation protein (MCL1), BCL-2-associated X protein (BAX), B-cell lymphoma-extra-large (BCL-xL), and BCL2-like 13 (BCL-rambo) were differentially expressed in comparison with HT.

Methods: Protein expression levels in pre-therapeutic lymphoma biopsies from FL patients, either with (subsequently-transforming FL (st-FL); $n = 20$) or without (non-transforming FL (nt-FL); $n = 33$) subsequent transformation, and in paired high-grade biopsies from the transformed lymphomas (transformed FL (tFL); $n = 20$) were analyzed by label-free quantitative nano liquid - tandem mass spectrometry. Differential expression of CASP3, MCL1, BAX, BCL-xL, and BCL-rambo were further evaluated by immunohistochemistry and digital image analysis.

Results: At time of initial diagnosis, samples from st-FL patients had higher expression levels of CASP3 ($p < 0.001$), MCL1 ($p = 0.015$), BAX ($p = 0.003$), BCL-xL ($p = 0.025$), and BCL-rambo ($p = 0.057$) compared with samples from nt-FL patients. Expression levels of all five apoptotic markers showed a significantly ($p < 0.05$) strong positive correlation to each other (correlation coefficient $\rho = 0.34$–0.62, $p < 0.05$). In addition, all markers showed correlation to both/either low HgB levels and/or lymphopenia. Shorter transformation-free survival (TFS) was significantly associated with high expression levels of CASP3 ($p < 0.001$), MCL1 ($p = 0.002$), and BAX ($p = 0.007$). Combining the five markers to a risk score based on expression levels showed inferior TFS with increasing numbers of markers with high expression levels. Notably, this was even more evident when analyzing exclusively intra follicular areas.

Conclusion: Our data show differential protein expression in FL lymphoma tissues, here with focus on biomarkers that indicate apoptotic deregulation in relation to FL-patients subsequent experience of transformation. Importantly, a risk-score based on expression levels of these markers was able to identify the majority of st-FL.

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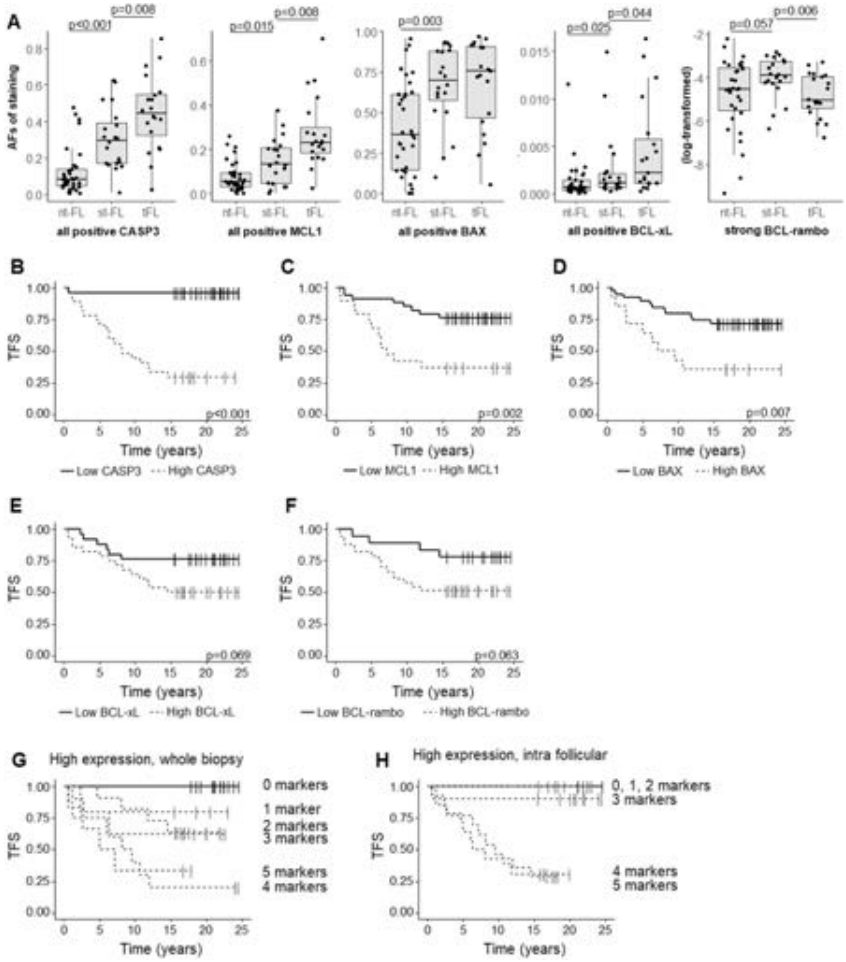

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Keywords: Diagnostic and Prognostic Biomarkers, Genomics, Epigenomics, and Other -Omics, Indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

203 | ASSESSMENT OF HELICOBACTER PYLORI (HP) NEGATIVE GASTRIC MALT LYMPHOMA FOR NON-H.PYLORI HELICOBACTER USING MULTIPLEX PCR: A RETROSPECTIVE ANALYSIS

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Background: The rate of HP-negative gastric MALT-lymphoma is reported to be increasing. However, successful therapeutic application of HP-eradication leading to lymphoma regression has been reported. In addition, recent data from Asia have shown the presence of non-*H. pylori* Helicobacter-species as assessed by PCR in a relevant number of patients. In view of this, we have assessed the presence of non-*H. pylori* Helicobacter species using multiplex PCR in patients with localized gastric MALT-lymphoma rated as HP-negative who had undergone HP-eradication at our institution.

Methods: Twenty patients (6 female, 14 male) with newly diagnosed gastric MALT-lymphoma rated HP-negative receiving HP-eradication and in whom sufficient material for analysis was available were assessed for outcome and multiplex PCR with primers for HP (positive control) and *H. suis*, *H. bizzozeronii*, *H. salomonis* and *H. heilmanii* s. s. was performed from gastric biopsies obtained from lymphoma as well as normal mucosa before antibiotic therapy. Commercially available primers were chosen in analogy to the data reported for patients from Korea, and both negative as well as positive controls were run in parallel to triplicate testing of paraffin-embedded material from our patients. Definition of HP-negativity had included histological assessment as well as negative breath-test and negative serology for HP.

Results: In total, 6/20 patients (30%) developed a complete response following antibiotic therapy targeting HP, with a median PFS of 25 months. All patients except one, in whom a weak signal for HP was detected were confirmed as HP-negative by PCR, suggesting that our clinical definition of HP-negativity is indeed stringent and can be reliably applied in such patients. As opposed to results from Korea demonstrating infection with non-*H. pylori* Helicobacters in 55% of patients, no signal for the presence of any non-*H. pylori* Helicobacter infection was detected in our pilot series.

Conclusion: In addition to confirming the clinical assessment of HP-negativity by combined histology, breath test and serological negativity, our results do not suggest infection with non-*H. pylori* Helicobacters as a potential explanation for successful antibiotic therapy of gastric lymphomas in such patients. In addition, our data again suggest a potential geographic difference in infection rates with non-*H. pylori* Helicobacters for gastric MALT-lymphomas based on the scarce data published so far.

Keywords: Diagnostic and Prognostic Biomarkers, Extranodal non-Hodgkin lymphoma, Microenvironment

No conflicts of interests pertinent to the abstract.

204 | IMPACT OF THE DARK ZONE SIGNATURE ON CENTRAL NERVOUS SYSTEM RELAPSE IN A REAL-WORLD DIFFUSE LARGE B-CELL LYMPHOMA POPULATION

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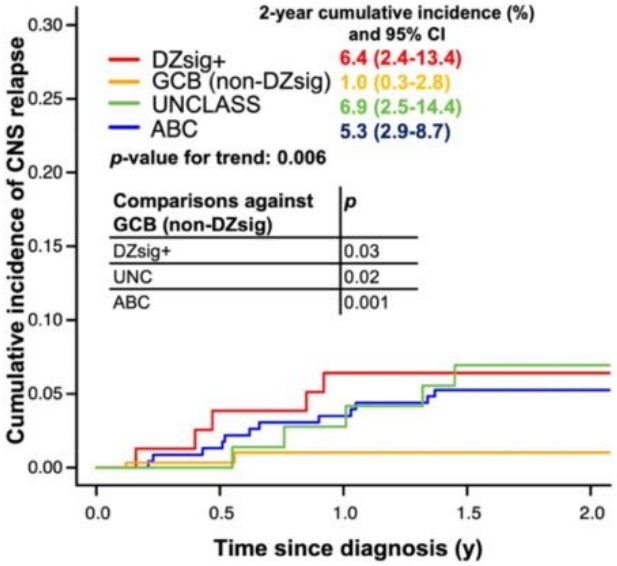
Introduction: Central nervous system (CNS) relapse in diffuse large B-cell lymphoma (DLBCL) is associated with dismal outcomes necessitating the identification of high-risk patients (pts). To refine CNS risk stratification, a better understanding of the role of molecular risk factors is required. We previously described the dark zone signature (DZsig), which refines the cell of origin (COO) classification and identifies pts within germinal centre B-cell-like (GCB) DLBCL with inferior outcomes. Within DZsig expressing tumours (DZsig+) of DLBCL morphology, ~40% harbour 'double hit' *MYC* and *BCL2* rearrangements (DH), whereas ~60% lack DH (Ennishi et al JCO 2018, Alduaij et al Blood 2022). Here we report the incidence and characteristics of CNS relapse in DZsig+ DLBCL in relation to DH status and the CNS International Prognostic Index (CNS-IPI) in an unselected, real-world DLBCL population.

Methods: All pts with de novo tumours of DLBCL morphology diagnosed in British Columbia, Canada, during 2005–2010 with evaluable diagnostic biopsies, without confirmed CNS involvement at diagnosis and treated with curative intent, were included. Evaluable biopsies were profiled by fluorescence in situ hybridization (FISH), immunohistochemistry and digital gene expression profiling (GEP) to assign COO and DZsig. Cumulative incidence of CNS relapse was estimated while accounting for the competing risk of death from other causes.

Figure 1: Cumulative incidence of CNS relapse according to molecular subgroup



Cumulative incidence of CNS relapse was estimated while accounting for the competing risk of death from other causes. GCB (non-DZsig) refers to patients with GCB DLBCL that lacks DZsig expression. Comparisons against GCB (non-DZsig) are based on regression modeling of subdistribution functions in competing risk analysis.

Results: Of 1149 pts, 804 had evaluable GEP results, 797 had no CNS involvement at diagnosis and 670 were treated with curative intent, mostly R-CHOP (Table 1). With a median follow-up of 12.4 years (y), the cumulative incidence of CNS relapse at 2 y in DZsig+ was significantly higher than in non-DZsig GCB (6.4% vs. 1.0% p = 0.03, Figure 1) regardless of the presence of DH by FISH (DZsig+ *without* DH 6.8% vs. DZsig+ with DH 6.7% p = 0.99). CNS relapse events in DZsig+ occurred more frequently in pts with a high CNS-IPI (2 y risk: 20% high vs. 3.4% low/intermediate (int) p = 0.02). In a multivariable competing risk analysis that included COO and CNS-IPI, high CNS-IPI was significantly associated with CNS relapse (hazard ratio with 95% confidence interval [CI]: 3.7 [1.1–12.6] p = 0.035) with a trend towards higher risk in DZsig+ relative to non-DZsig GCB (3.2 [0.95–10.5] p = 0.06). All CNS relapses in DZsig+ occurred early (<1 y from diagnosis) and more frequently involved the leptomeninges than non-DZsig GCB or ABC (p = 0.01, Table 1). **Conclusion:** DZsig identifies a population within GCB DLBCL with a higher CNS relapse risk, irrespective of DH status, and an increased tendency for early leptomeningeal relapse. Overall, the risk is modest (6.4% at 2 y), and the CNS-IPI remains predictive of CNS relapse in

Table 1: Baseline characteristics of the study population (2005-2010)

Patient Characteristics	Total	DZsig+	GCB (non-DZsig)	UNC	ABC	p*
Total (n)	670	78	292	72	228	
Age, Median (range, years)	67 (20-93)	64 (35-88)	67 (22-92)	65 (20-93)	69 (31-93)	.19
Female (n, %)	289 (43)	28 (36)	124 (43)	27 (38)	110 (48)	.17
CNS IPI factors (n/available,%)						
Age > 60	447/670 (67)	51/78 (65)	192/292 (66)	45/72 (63)	159/228 (70)	.69
Stage III/IV	336/645 (52)	45/77 (58)	126/281 (45)	38/69 (55)	127/218 (58)	**.013**
Elevated lactate dehydrogenase	261/573 (46)	45/71 (63)	99/248 (40)	27/72 (42)	90/189 (48)	**.005**
Performance status >1	205/628 (32)	27/77 (35)	78/274 (28)	24/66 (36)	76/211 (36)	.28
Extranodal sites >1	129/645 (20)	17/77 (22)	52/281 (19)	12/69 (17)	48/218 (22)	.69
Kidney/adrenal involvement	17/645 (3)	1/77 (1.3)	5/281 (2)	2/69 (3)	9/218 (4)	.38
Testicular involvement (n/available, %)	22/645 (3)	0/77 (0)	2/281 (1)	3/69 (3)	17/218 (8)	**<.0001**
CNS IPI risk group (n, %)						
Low (0-1)	207 (35)	21 (28)	106 (41)	21 (32)	59 (30)	**.01**
Intermediate (2-3)	278 (47)	38 (51)	120 (47)	31 (48)	89 (45)	
High (4-6)	111 (19)	15 (20)	32 (12)	13 (20)	51 (26)	
Not calculable	74	4	34	7	29	
Treatment regimen (n, %)						
R-CHOP	618 (92)	70 (89.7)	274 (93.8)	66 (91.7)	208 (91.2)	.14
R-CHOP-IT†	10 (1.5)	0	5 (1.7)	1 (1.4)	4 (1.8)	
R-CEOP	38 (5.7)	5 (6.4)	13 (4.5)	5 (6.9)	15 (6.6)	
Intensive‡	4 (0.6)	3 (3.9)	0	0	1 (0.4)	
Double-hit status, (n, %)						
MYC/BCL2	41 (6.4)	30 (41)	9 (3)	1 (1)	1 (0.5)	**<.0001**
MYC/BCL6	10 (1.6)	4 (5)	2 (1)	0	4 (1.8)	
Non-Double-hit	586 ((2)	40 (54)	262 (96)	69 (99)	215 (97.7)	
NA	33	4	19	2	8	
MYC/BCL2 DPE (n/available, %)	148/561 (26)	35/65 (54)	17/251 (7)	12/60 (20)	84/184 (46)	**<.0001**
CNS relapse characteristics (n, % of relapses)						
CNS relapses (n, %)	34 (5.1)	5 (6.4)	5 (1.7)	5 (6.9)	19 (8.3)	**.002**
Site						
Parenchymal only	26 (76)	2 (40)	5 (100)	2 (40)	17 (89)	**.011**
Leptomeningeal only	8 (24)	3 (60)	0	3 (60)	2 (11)	
Both	0	0	0	0	0	
Extent						
Isolated CNS	25 (74)	2 (40)	4 (80)	3 (60)	16 (84)	.20
CNS and systemic	9 (26)	3 (60)	1 (20)	2 (40)	3 (16)	
Occurrence						
First	30 (91)	4 (80)	4 (80)	5 (100)	18 (95)	.41
Second or subsequent	3 (9)	1 (20)	1 (20)	0 (0)	1 (5)	

*Comparison of the four molecular subgroups by Chi sqaure, Fisher's exact or multi-factor ANOVA tests †intrathecal methotrexate/cytarabine was used in this era for CNS prophylaxis in select patients with high-risk extranodal site involvement prior to the introduction of high-dose intravenous methotrexate. ‡Intensive: CODOX-MR/IVAC-R or R-CHOP followed by consolidative autologous hematopoietic cell transplant, DZsig+: dark zone signature, GCB: Germinal centre B-cell-like DLBCL that lacks DZsig expression (non-DZsig), UNC: unclassified, ABC: Activated B-cell-like, IPI: International Prognostic Index DPE: Dual protein expressor. NA: not available

DZsig+ DLBCL. This highlights the importance of clinical risk factors in refining risk, including identifying 80% of DZsig+ DLBCL pts with low/int CNS-IPI who may forgo CNS-directed procedures and prophylaxis.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers

Conflicts of interests pertinent to the abstract.

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Research funding: Abbvie, AstraZeneca, Janssen

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Honoraria: AbbVie, Acerta, Amgen, Apobiologix,AstraZeneca, BMS/Celgene, Gilead, Incyte,Janssen, Kite, Karyopharm, Lundbeck, Merck, Morphosys, Sandoz, Seattle Genetics, Servier,Takeda, TG Therapeutics, Verastem, Chugai, Teva, Roche/Genentech
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Research funding: Janssen, Roche
Other remuneration: NanoString- Patents and Royalties

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Consultant or advisory role: Seagen
Honoraria: BMS, Merck, Astra Zeneca, Janssen, Abbvie
Other remuneration: Regeneron (DSMC), Beigene (Steering committee)

205 | IDENTIFICATION OF BIOMARKERS FOR PREDICTING CENTRAL NERVOUS SYSTEM INVOLVEMENT IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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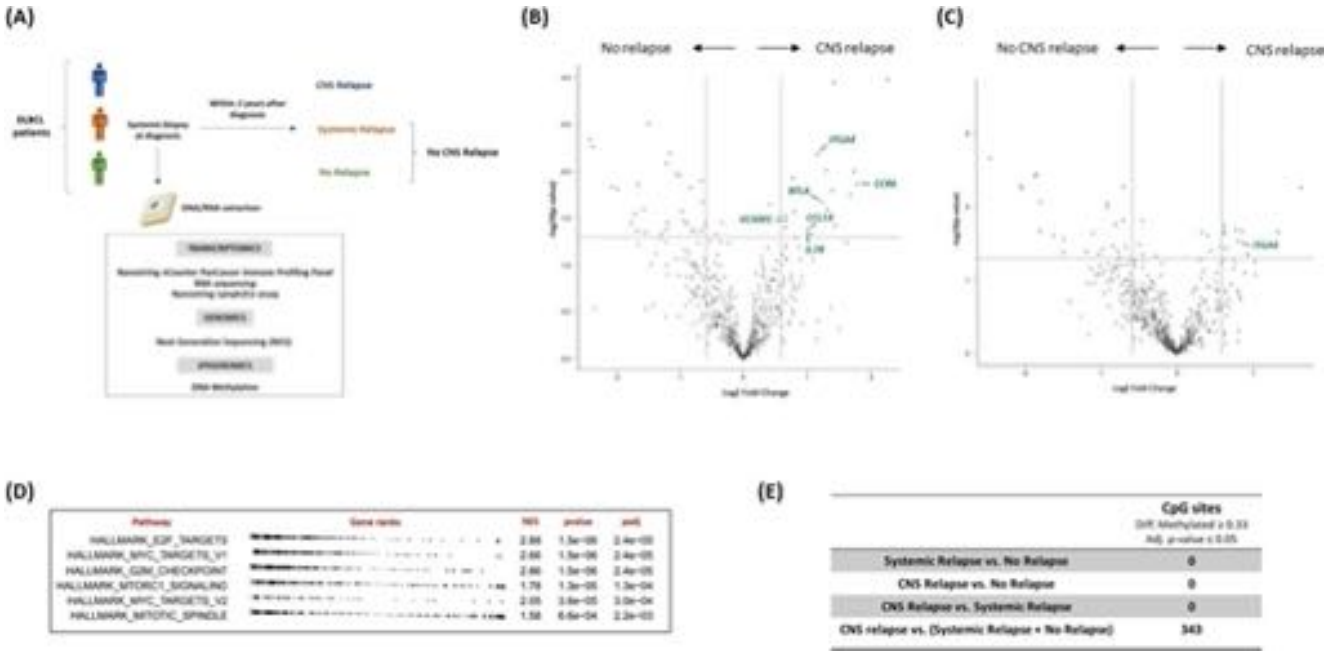
Introduction: Central Nervous System (CNS) involvement in Diffuse Large B Cell Lymphoma (DLBCL) is a rare complication associated with bad prognosis. The CNS Prognostic Index identifies patients in high risk of CNS relapse; however, its specificity is limited and not accurate. Biomarkers that can predict CNS relapse are still missing. For that reason, we aimed to characterize the transcriptomic, genomic and epigenomic hallmarks of systemic tumors at diagnosis of patients that will relapse in the CNS.

Methods: We conducted a retrospective study including 38 patients with nodal DLBCL that relapsed within the first two years after diagnosis: 12 with CNS relapse and 26 with systemic relapse. As controls, we included 21 patients that did not relapse. DNA and RNA were extracted from tumors at diagnosis. Immune infiltration was evaluated using the nCounter PanCancer Immune Profiling Panel (Nanostring); COO was determined using the Lymph2Cx assay. Transcriptomic profiles were generated by bulk RNA sequencing; mutational analysis was performed using a custom targeted NGS panel. Methylation profiles were described using the Illumina Infinium MethylationEPIC Array 850K (Figure 1A).

Results: Immune cell composition was similar between groups; however, several genes were overexpressed at diagnosis in patients with CNS relapse. Genes related to chemokine signaling as *CCL14*, *IL7R*, and *CCR6*; adhesion like *VCAM1* and *ITGA4*; and immune checkpoints as *BTLA* were upregulated in the CNS relapse group in comparison to patients without relapse (Figure 1B). Among these, the *ITGA4* gene was also found to be overexpressed in the CNS relapse group when compared to both systemic and no relapse groups together (Figure 1C). No differences in COO were observed between groups. Whole transcriptomic data showed enrichment in genesets related to proliferation and survival in CNS relapse group in comparison to all others (Figure 1D). Patients with CNS relapse had increased mutation load and frequency in *PIM1*, *IGLL5* and *KMT2D* genes. A total of 343 CpG sites were differentially methylated in CNS relapse group in comparison to No CNS relapse, involving 211 genes (Figure 1E).

Conclusions: Results show a higher chemokine, adhesion and proliferation signaling in DLBCL patients that will relapse in the CNS. Of notice, BTLA, CCR6 and IL7R proteins have been previously reported to be implicated in B cell CNS entrance in B-cell malignancies. Also, the *ITGA4* gene codifies for the integrin α4 subunit (CD49d) of the Very Late Antigen-4, which is required for B cell migration across the BBB. Herein, we proved that DLBCL cells at diagnosis already own



specific hallmarks towards a higher capacity to infiltrate the CNS; these results could improve specific selection of patients and prophylactic CNS-directed therapies. Further in vivo experiments are planned altogether with increasing the number of samples and validation of results using CNS biopsies at relapse.

Keywords: Diagnostic and Prognostic Biomarkers, Extranodal non-Hodgkin lymphoma, Genomics, Epigenomics, and Other -Omics

No conflicts of interests pertinent to the abstract.

206 | PREDICTING CELL OF ORIGIN FROM DIGITIZED IMAGES OF HEMATOXYLIN AND EOSIN-STAINED SLIDES OF DIFFUSE LARGE B-CELL LYMPHOMAS USING A CELL-BASED DEEP-LEARNING MODEL

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Introduction: Based on gene expression profiling, diffuse large B-cell lymphoma (DLBCL) can be classified by cell of origin (COO) as activated B-cell-like (ABC) or germinal center B-cell-like (GCB) tumors. These differ in prognosis, which means that timely and accurate classification is important to stratify patients and provide appropriate treatment. Determining COO using immunohistochemistry can be time-consuming and weakly reproducible, and poorly reflects underlying tumor biology. We developed a deep-learning (DL) model to perform COO classification using whole-slide images (WSIs) of hematoxylin and eosin (H&E)-stained pathology slides from patients with DLBCL.

Methods: Algorithms were trained, validated and tested using data from the phase 2 CAVALLI (NCT02055820) and phase 3 GOYA (NCT01287741) trials. The slides from GOYA were split into a training set and a test set for model tuning, containing (ABC/GCB/total) 106/202/308 and 21/46/67 WSIs, respectively. The CAVALLI slides were used as an independent holdout set for further validation of the final model to prevent overfitting, and contained (ABC/GCB/total) 57/110/167 WSIs. For COO prediction, a transformer was used to aggregate extracted features and predict the WSI label in a weakly supervised manner. We compared the performance of two types of features as the input to the transformer: a tile-based model that extracted tumor regions from WSIs and a nucleus-based model that used automatically segmented nuclei from the same tiles. For each model, a fixed network pretrained with digital pathology images was used to extract features, which were used to make patch-level predictions that were aggregated at slide level.

Results: Using the tile-based model, the areas under the receiver operating characteristic curves (AUCs) for the test set and holdout set were 0.73 and 0.67, and the average F1 scores were 0.68 and 0.61 respectively; the nucleus-based model had AUCs of 0.63 and 0.70, and average F1 scores of 0.61 and 0.64 using the same test settings. Visual inspection of the highest-scoring tiles and nucleus patches revealed a higher density of tumor cells and larger overall cell size for ABC than for GCB DLBCL. Similarly, the ratio of tumor cells to nontumor cells, and the average tumor cell size, were significantly larger for ground truth ABC images than GCB images ($p < 0.001$ for all data sets).

Conclusions: Our DL models demonstrated reasonable performance in COO classification of DLBCL using WSIs of H&E-stained slides without use of ancillary techniques. In addition, our models may be

able to identify novel cellular features that differentiate ABC from GCB DLBCL. With rigorous validation and regulatory approval, the models may have the potential to supplement the pathologist's diagnostic tool kit with a reliable method of COO classification.

Encore Abstract - previously submitted to EHA 2023

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers

Conflicts of interests pertinent to the abstract.

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207 | MYC NEGATIVELY IMPACTS TREATMENT OUTCOMES IN STAGE II, BUT NOT STAGE I DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Diffuse large B-cell lymphoma (DLBCL) patients with limited stage (LS) disease (Ann Arbor stage I or II) generally have a favorable prognosis. A rearrangement of the MYC oncogene (MYC-R) is considered a negative prognostic factor in patients with stage III or IV DLBCL. The prognostic value of a MYC-R in LS DLBCL remains unclear as this has only been studied in limited numbers of patients. (Torka Blood Adv 2020, Augustyn Leuk Lymphoma 2021) In this population-based study, we assessed the impact of MYC-R on outcome among LS DLBCL patients in the Netherlands.

Methods: We selected 1,446 LS DLBCL patients with a known MYC-R status diagnosed between 2014 and 2020 and treated with R-CHOP(-like) regimens, using the Netherlands Cancer Registry. Survival follow-up (FU) was until February 2022. We performed separate analyses for stage I and stage II patients as stage I patients generally receive less intensive treatment. Patients were divided in 4 treatment groups: 1) 6–8 cycles R-CHOP, 2) abbreviated R-CHOP plus radiotherapy (RT), 3) less intensive R-CHOP-like regimens, and 4) more intensive R-CHOP-like regimens such as R-CHOEP, DA-EPOCH-R. Patients with only a MYC-R were defined as single hit (SH), patients with a MYC-R, BCL2 and/or BCL6 rearrangement as double or triple hit high grade B-cell lymphoma (HGBL). The primary endpoint was overall survival (OS) defined as time from diagnosis until death by any cause. Multivariable analysis was performed using Cox regression.

Results: In total, 742 (51%) patients had stage I and 704 (49%) stage II.

In stage I patients, 84 (11%) had a MYC-R of which 37 were HGBL. Most stage I patients (48%) received abbreviated R-CHOP plus RT, 44% 6–8 cycles R-CHOP, 7% less intensive regimens and 1% more intensive regimens. With a median FU of 38 months, 2-year OS was 96% irrespective of MYC-R status (Figure 1A). In multivariable analysis, older age, male sex and IPI score 2–3 were associated with poorer outcome, while treatment and SH and HGBL were not.

In stage II patients, 90 (13%) had a MYC-R of which 39 were HGBL. Most stage II patients (86%) received 6–8 cycles R-CHOP, 3% abbreviated R-CHOP plus RT, 7% less intensive regimens and 3% more intensive regimens. With a median FU of 38 months, the 2-year OS rates were 86% and 94% for patients with or without MYC-R, respectively (Figure 1B). In multivariable analysis, older age and HGBL, but not SH, negatively impacted outcome. Among 21 patients with MYC-R stage II disease, a more intensive chemotherapy did not improve OS ($p = 0.61$).

Conclusions: The outcome of stage I DLBCL patients treated with R-CHOP(-like) regimens is excellent, irrespective of MYC-R status. With a 2-year OS of 96%, there is no justification for more intensive treatment. However, among stage II DLBCL patients, a double or triple hit HGBL was associated with an inferior outcome. More intensive regimens did not seem to improve this, warranting new treatment strategies for stage II HGBL patients.

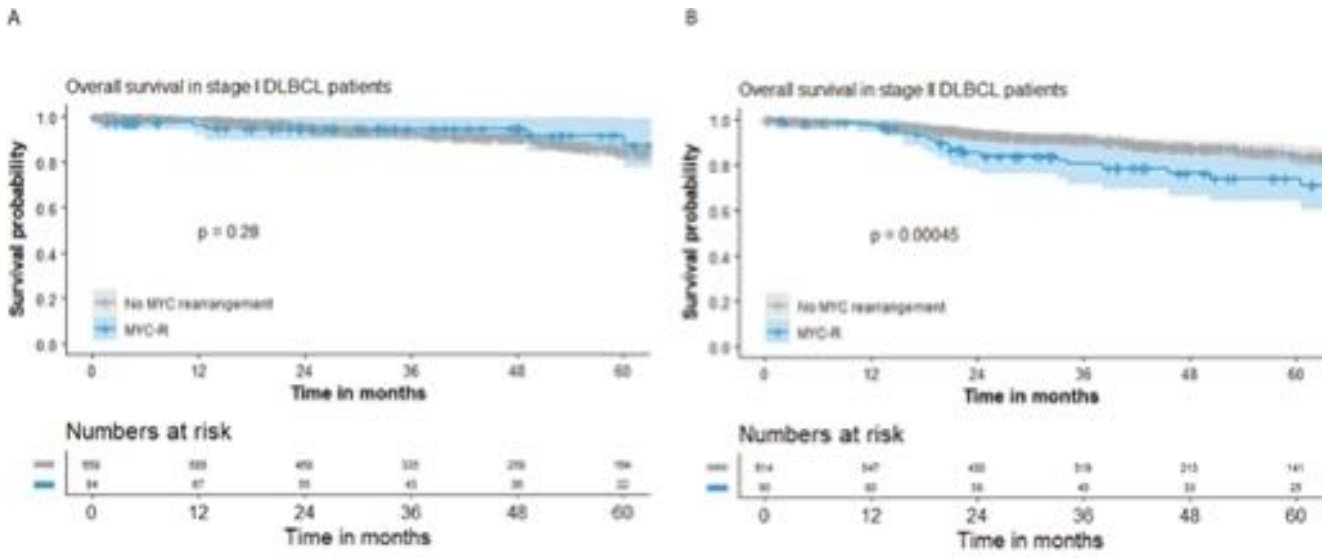

Figure 1. Overall survival in (A) stage I DLBCL patients with and without a MYC rearrangement, (B) stage II DLBCL patients with and without a MYC rearrangement

Keyword: Aggressive B-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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Research funding: Takeda

208 | A SUB-POPULATION OF CELLS EXPRESSING MYC AND BCL2 WITHOUT BCL6 REFINES THE DEFINITION OF DOUBLE EXPRESSOR LYMPHOMA (DEL)

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Introduction: 'Double Expressor Lymphomas' (DEL) refer to high-risk diffuse large B-cell lymphoma (DLBCL) that are positive for MYC and BCL2 by immunohistochemistry (IHC). We recently demonstrated using single-cell resolved analysis that the extent of cells with a unique co-expression pattern of high MYC and BCL2 but lacking BCL6 (M+2+6-) drives prognosis in DLBCL. We now present a follow-up study evaluating clinical utility of the M+2+6- subpopulation with relation to DEL, and its relation to spatial and immune phenotypes in DLBCL.

Methods: We measured M+2+6- percentage by multiplexed fluorescent IHC (mfIHC) in DEL cases from a DLBCL cohort classified by chromogenic IHC (British Columbia Cancer Agency (BCA), $n = 89$). A mathematical method to predict M+2+6- percentage extent was used to extend the analysis to DEL cases from two independent mRNA-based cohorts (GSE117556, $n = 67$; GOYA, $n = 175$). To evaluate for immune phenotypes and therapeutic vulnerabilities in cases with high M+2+6-, we performed Digital Spatial Profiling (DSP) analyses, applying the protein-based nCounter method (29 immune markers) to 110 DLBCL samples, and the Whole Transcriptome Atlas (WTA) analysis (18,000 genes) to CD3+ enriched regions of 47 DLBCL samples.

Results: The M+2+6- percentage stratified DEL cases for survival in the BCA cohort, albeit at borderline statistical significance (BCA: OS, $p = 0.077$, PFS, $p = 0.101$). However, with larger numbers of DEL cases available in mRNA-based measurement cohorts, there was a statistically significant stratification for PFS (GSE117556: OS, $p = 0.084$, PFS, $p = 0.031$; GOYA: OS, $p = 0.065$, PFS, $p = 0.047$), suggesting that the following formula refines the current DEL definition and improves its prognostic value:

$$M + 2 + 6 - \% = \left(\frac{MYC\%}{100} \times \frac{BCL2\%}{100} \times \frac{(100 - BCL6\%)}{100}\right) \times 100\%$$

Using a pan-immune protein-marker DSP panel, we identified that the T-cell immune regulators ICOS and 4-1BB were negatively correlated with M+2+6- percentage extent ($r = -0.27$, $p = 0.0046$; $r = -0.22$, $p = 0.019$, respectively), suggesting a potential role for ICOS or 4-1BB stimulatory therapeutics (e.g. feladilimab, utomilumab) in combination with chemotherapy for high M+2+6- cases. To molecularly characterize T-cells in relation to the presence of M+2+6- cells, we performed a DSP WTA analysis in CD3+ expressing cells in our DLBCL cohort. T-cells in cases with high M+2+6- fraction expressed distinct genes and pathways, and single-cell atlas mapping revealed an intriguing enrichment of naïve CD4 and CD8 populations.

Conclusions: A simple mathematical formula for estimation of MYC +BCL2+BCL6- cells in DLBCL refines the DEL diagnosis, and could be of value in selecting high risk DLBCL for trials of novel agents. High M+2+6- DLBCL display unique T-cell infiltrates, and immunomodulation by ICOS and 4-1BB agonists could represent a therapeutic vulnerability for this high-risk subgroup.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, Pathology and Classification of Lymphomas

Conflicts of interests pertinent to the abstract.

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A. Bottos
Employment or leadership position: Alessia Bottos is an employee of Roche

A. D. Jeyasekharan
Consultant or advisory role: Roche, Gilead, Turbine Ltd, AstraZeneca, Antengene, Janssen, MSD and IQVIA
Research funding: Janssen and AstraZeneca

209 | MOLECULAR HETEROGENEITY OF BCL2/MYC DOUBLE EXPRESSOR LYMPHOMA UNDERLIES SENSITIVITY TO HISTONE DEACETYLASE INHIBITOR

Z. Shi, Y. Fang, P. Xu, H. Yi, J. Li, Y. Dong, Y. Zhu, M. Liu, D. Fu, S. Wang, Q. Shi, R. Shen, C. Wang, S. Cheng, L. Wang, F. Liu, W. Zhao
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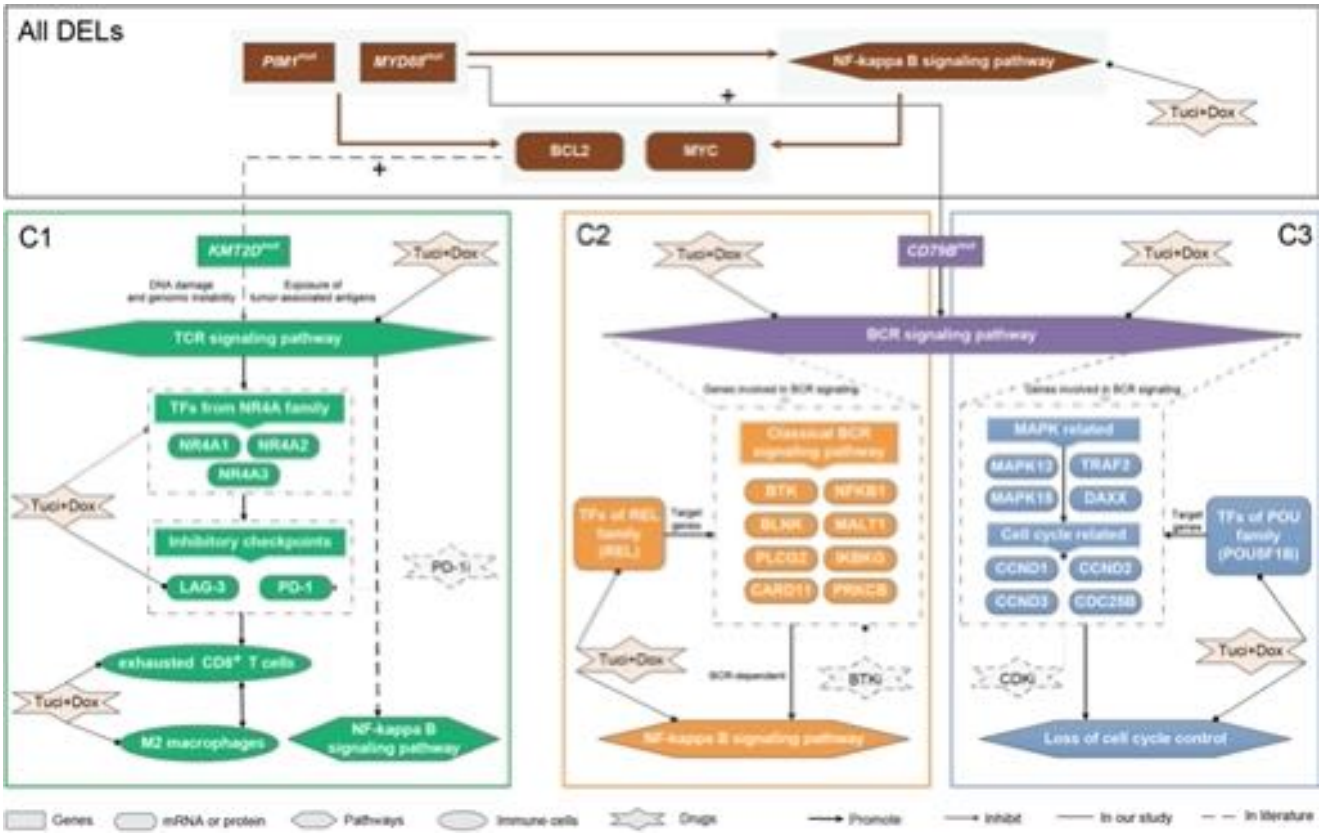

Introduction: Double expressor lymphoma (DEL) concurrently overexpressing BCL2 and MYC protein represent a high-risk phenotypic entity of diffuse large B-cell lymphoma. Evidence suggested that DEL may be molecularly heterogeneous. The aim of this study was to identify molecular subtypes of DEL with distinct biological features and potential therapeutic implications.

Methods: Unsupervised transcriptome-based clustering was performed on tumor samples from 157 patients with DEL. Genomic, transcriptomic, and tumor microenvironmental alterations were integrated, as compared to 160 patients double negative for BCL2 and MYC protein. Preclinical models including cell lines and patient-derived xenograft models were established to investigate the effect of histone deacetylase inhibitor tucidinostat combined with doxorubicin on each DEL subtype.

Results: We identified three molecular subtypes of DEL, namely, cluster 1 (C1, $n = 48$), cluster 2 (C2, $n = 63$), and cluster 3 (C3, $n = 46$), which shared recurrent high-frequency mutations of *PIM1* and *MYD88*, and upregulation of NF-kappa B signaling pathway. Moreover, C1 was characterized by *KMT2D* mutations, upregulation of T-cell receptor signaling pathway, and increased infiltration of exhausted $CD8^+$ T cells and M2 macrophages within the tumor microenvironment. Both C2 and C3 were characterized by *CD79B* mutations and upregulation of B-cell receptor (BCR) signaling pathway, but differed in oncogenic transcriptional factors, with REL family in C2 and POU family in C3. Tucidinostat combined with doxorubicin targeted the immune cell dysfunction in C1, and the closure of chromatin and downregulation of target genes involved in BCR signaling pathway in C2 and C3.

Conclusions: In conclusion, we identified three molecular subtypes of DEL, unveiled distinct genetic, transcriptional, and microenvironmental properties, and highlighted epigenetic therapeutic approaches for targeting histone acetylation in DEL.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Genomics, Epigenomics, and Other -Omics, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

210 | BIOLOGICAL AND CLINICAL RELEVANCE OF CD79 PROTEIN AND GENE EXPRESSION IN DIFFUSE LARGE B-CELL LYMPHOMA

Y. Naoi[1], R. Chijimatsu[1], T. Urata[1], K. Sunami[2], T. Imai[3], Y. Nawa[4], Y. Hiramatsu[5], K. Yamamoto[6], S. Fujii[7], I. Yoshida[8], T. Yano[9], K. Ikeuchi[1], H. Kobayashi[1], K. Tani[1], Y. Sato[10], M. Boyle[11], A. Jiang[11], Y. Maeda[1], D. W. Scott[11], D. Ennishi[1]

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Introduction: CD79B is a target of polatuzumab vedotin, an antibody–drug conjugate, which may improve the prognosis of both previously untreated and relapsed/refractory patients with diffuse large B-cell lymphoma (DLBCL). However, the biological and clinical significance of CD79B protein and gene expression in DLBCL is largely unknown.

Methods: We retrospectively analyzed de novo DLBCL patients, who were diagnosed and received rituximab-based immunochemotherapy from 2008 through 2018 in the Okayama Hematology Study Group from Japan. Immunohistochemistry (IHC) staining was performed using a CD79B antibody (AT107-2), and protein expression was assessed based on H-score according to a previous study (Sehn L et al. JCO 2020). We also performed gene expression profile-based cell-of-origin (COO) classification, including double-hit signature (DHITsig) which has been renamed to dark zone signature (DZsig) (Waleed A et al. Blood 2022), using the NanoString DLBCL90 assay.

Results: CD79B IHC expression was evaluable in 602 cases. We defined two groups according to median H-score of CD79B expression: $CD79B^{high}$ and $CD79B^{low}$. The COO subtypes were assigned as follows: 308 patients (51%) with activated B-cell-like (ABC)-DLBCL, 196 (33%) with germinal center B-cell-like (GCB)-DLBCL, 32 (5%) with DZsig-pos DLBCL and 66 (11%) with unclassified (UNC). H-score of CD79B was the lowest in patients with ABC-DLBCL followed by GCB-DLBCL and DZsig-pos DLBCL in ascending order (Kruskal–Wallis test $P < .00001$; Figure A). Indeed, $CD79B^{low}$ tumors were significantly enriched in ABC-DLBCL (57%) compared to GCB-DLBCL (40%) and DZsig-pos DLBCL (22%), respectively (both, $P < .001$). Consistently, using publicly available DLBCL datasets (Schmitz et al. NEJM 2018 and Ennishi et al. JCO 2019), we revealed that *CD79B* gene expression was the lowest in ABC-DLBCL compared to GCB- and DHITsig-DLBCL (Kruskal–Wallis test $P = .01$; Figure B and C). The association of *CD79B* expression with COO prompted us to evaluate *CD79B* expression in normal germinal center B cells. Notably single-cell transcriptomic analyses of six reactive lymphoid tissues from publicly available datasets revealed that the lowest expression of *CD79B* was found in plasmablasts followed by light zone B cells and dark zone B cells in ascending order (Kruskal–Wallis test $P < .0001$), supporting the differential expression of *CD79B*according to COO subtype.

$CD79B^{low}$ group had significantly shorter overall survival (OS) in the total DLBCL cohort (log-rank, $P < .001$) and within ABC-DLBCL ($P = .001$, Figure D and E). Moreover, CD79B protein expression was significantly associated with OS after adjusting for International Prognostic Index in the total cohort (Cox regression model; $P < .001$).

Conclusion: Our findings provided novel biological and clinical insights into CD79B protein and gene expression in DLBCL.

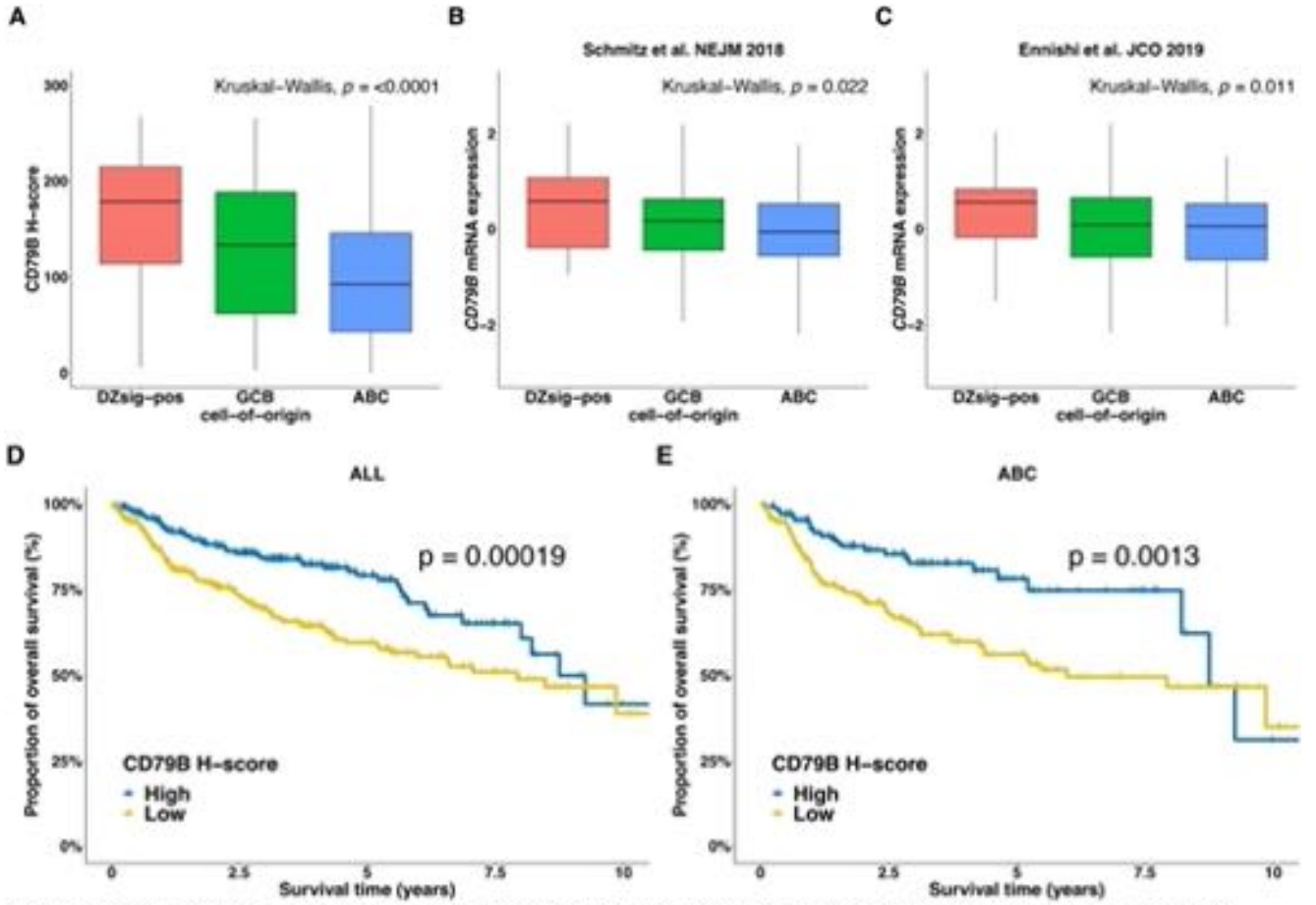

Figure1. Boxplot for CD79B H-score in DLBCL and comparison among cell-of-origin (A). Boxplots for *CD79B* mRNA level in two recent representative cohorts of DLBCL and comparison among cell-of-origin (B,C). Proportion of overall survival according to CD79B H-score groups in the total cohort (D) and in ABC-DLBCL (E).

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers

Conflicts of interests pertinent to the abstract.

K. Sunami
Honoraria: Celgene, Sanofi, BMS, Ono, Janssen
Research funding: Takeda, AbbVie, GSK, Chugai, Otsuka, MSD, Novartis, Astellas Amgen, Pfizer, Parexel, Kyowa Kirin, Symbio, Agios

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D. Ennishi
Honoraria: Chugai, Eisai, Kyowa Kirin
Research funding: Nipponshinyaku, Chugai

211 | GENETIC AND TRANSCRIPTOMIC ANALYSES OF DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS WITH POOR OUTCOMES WITHIN TWO YEARS OF DIAGNOSIS

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Background: R-CHOP immunochemotherapy is the first-line treatment for DLBCL, but approximately 30%–40% of patients still experience refractory or relapsed (R/R) disease. We aimed to characterize the molecular features of DLBCL derived from patients with early R/R disease and develop a prognosis model to identify those high-risk patients.

Methods: We performed a comprehensive genomic and transcriptomic characterization on 161 R-CHOP-treated DLBCL samples. These patients were grouped by follow-up outcome status after R-CHOP treatment. The first group had R/R disease within two years of diagnosis (poor outcome; n = 50), and the second group remained in remission at two years following R-CHOP treatment (good outcome; n = 111). In an addition, external cohorts were included in the validation analysis (GSE117556, n = 374; GSE181063, n = 810).

Results: Patients with poor outcomes more often had an advanced stage of the disease, a high international prognostic index (IPI) and a non-GCB subtype of the tumor. We identified a set of frequent somatically mutated targets (Figure 1A), including *PIM1*, *TP53*, *MPEG1* and *ROBO1*, as well as a specific mutational signature (activation-induced cytidine deaminase related) in DLBCLs with poor outcomes. Transcriptomic analyses further showed a distinct gene expression pattern and a less inflamed tumor microenvironment in these patients (Figure 1B). Finally, we developed an 11-gene signature as an independent prognostic marker for DLBCL patients treated with R-CHOP (Figure 1C). The 11-gene signature could further stratify DLBCL patients based on their IPI scores (Figure 1D). Additionally, the use of 11-gene signature to identify high-risk patients was also validated in two independent cohorts, suggesting the robustness of the risk model. Furthermore, our model effectively identified high-risk patients, including those with double-hit and MCD genetic subtypes that are associated with poor survival outcomes.

Conclusions: Our study provides insight into understanding the molecular features of DLBCL with early R/R disease treated with R-CHOP and identifies an 11-gene signature that could help to identify high-risk patients. This signature may improve prognostic accuracy and guide individualized treatment strategies for DLBCL patients.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, Genomics, Epigenomics, and Other -Omics

No conflicts of interests pertinent to the abstract.

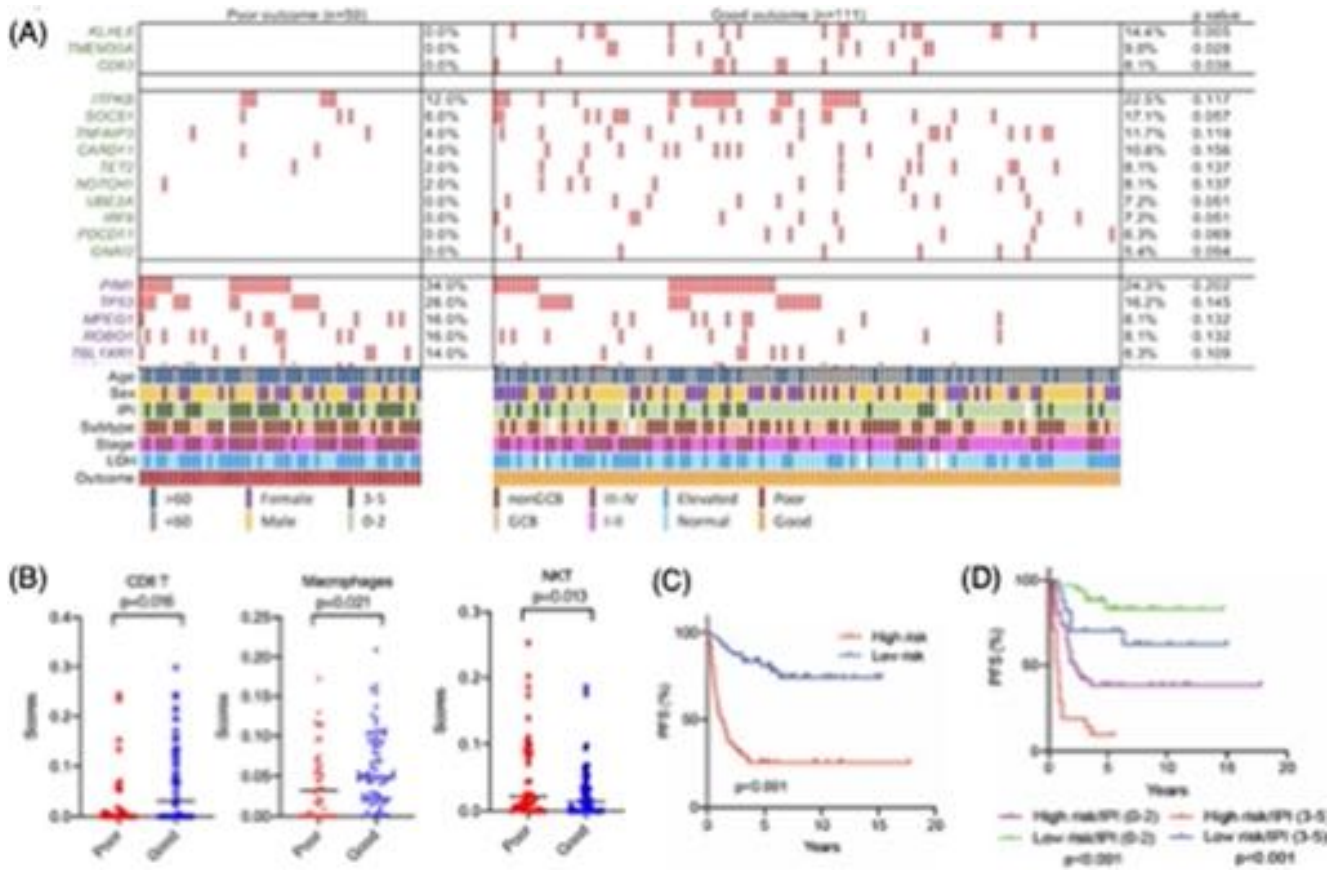

FIGURE 1 (A) The mutation pattern between poor outcome and good outcome DLBCLs. (B) Tumor-infiltrating immune cells in DLBCL patients with poor and good outcomes. (C-D) Kaplan–Meier survival analysis of PFS between high-risk and low-risk groups (C) and the association of 11-gene risk scores and IPI risk groups (D).

212 | GENOMIC CORRELATES OF RADIOSENSITIVITY IN DIFFUSE LARGE B CELL LYMPHOMA

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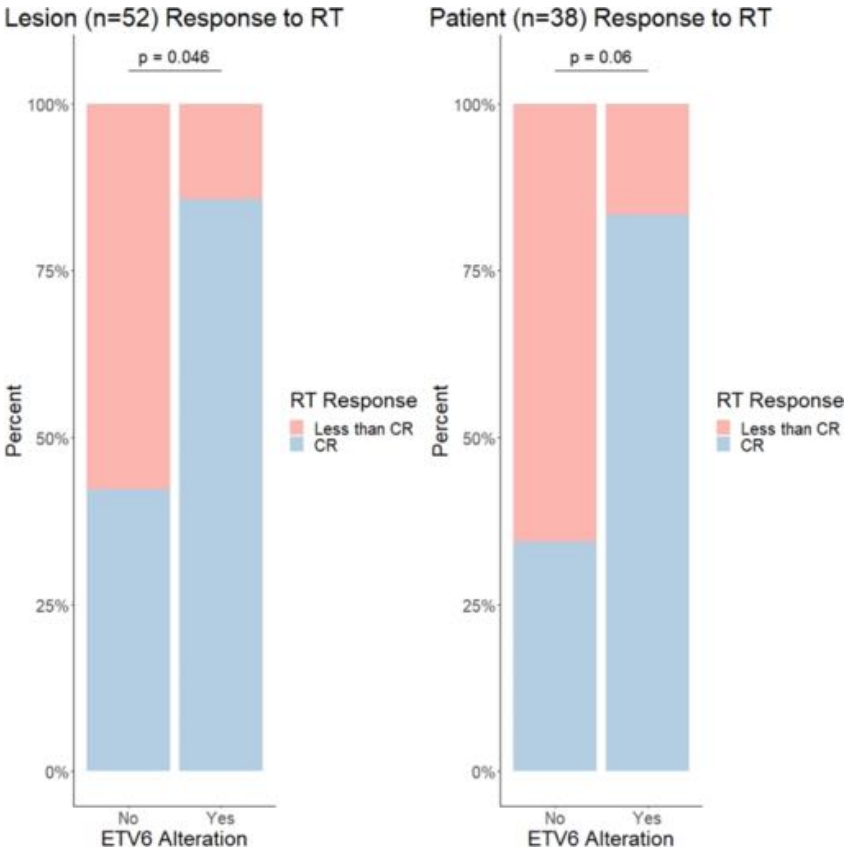
Introduction: Radiotherapy (RT) is beneficial for select patients with localized diffuse large B cell lymphoma (DLBCL), in both early stage and in relapsed/refractory settings. Genomic predictors of local response to RT have yet to be adequately explored. We sought to identify genomic signatures of radiosensitivity in localized DLBCL.

Methods: We analyzed our database of DLBCL patients with localized measurable disease treated with RT between 2007 and 2022 with pre-existing targeted exome sequencing. This included both Ann Arbor stage I/II patients and those with isolated sites of relapsed/refractory disease in order to increase cohort size. The public NCI LymphGen algorithm was used to further classify genomic subgroups. Using Fisher's exact test and logistic regression we tested for univariable correlation between specific gene alterations and LymphGen subgroups with initial radiation response, defined by Lugano criteria and decrease in maximum SUV.

Results: We identified 38 patients with 52 irradiated tumors. The median (range) RT dose was 36 Gy (4–54), with 35 (67%) tumors receiving at least 30 Gy. 21 (40%) tumors were treated in the early stage setting (10% definitively, 90% as consolidation), while 31 (60%) were treated in the localized relapsed/refractory setting. 54% of tumors were GCB subtype, 31% were ABC subtype, and 15% were not classified. The median (range) of prior lines of systemic therapy were 1 (0–2) and 1 (1–7) in the early stage and localized relapsed/refractory settings respectively.

The median (range) lesion SUV at the time of RT was 7.7 (1.1–46.0). 48% of tumors were in complete response (CR) at time of first imaging after RT (median 3.12 months) and the mean (SD) percent decrease in SUV was 60% (43%). The most commonly altered individual genes were KMT2D (37%), MYD88 (33%), and TP53 (31%). LymphGen classified 21% of cases as EZB subtype, 14% as MCD, 2% as BN2, 2% as ST2; 62% were unclassified. Alteration in ETV6 (13% of tumors) was associated with a significantly higher CR rate in response to RT (86% with alteration, 42% without, $p = 0.046$). After restricting each patient to their first course of RT, ETV6 alteration trended towards significantly higher CR (83% with alteration, 34% without, $p = 0.06$). Lesions with vs. without ETV6 alteration had similar SUV ($p = 0.88$) and size ($p = 0.8$) at time of RT. Alteration in ETV6 ($p < 0.0001$), PIM1 ($p < 0.0001$), MYD88 ($p < 0.0001$), and TNFAIP3 ($p = 0.01$) were associated with greater reductions in SUV. The LympGen MCD subgroup trended towards increased odds of CR post-RT (log odds 1.9, $p = 0.078$) and greater reduction of SUV ($p = 0.12$) compared to the EZB subgroup.



Conclusion: Alterations in ETV6, PIM1, MYD88, TNFAIP3, and the MCD LymphGen subgroup may be associated with better response to radiotherapy. This result is hypothesis generating and warrants further study with larger, prospective cohorts to validate the ability of genomic signatures to predict RT response.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Genomics, Epigenomics, and Other -Omics, Radiation Therapy

Conflicts of interests pertinent to the abstract.

G. Salles

Consultant or advisory role: AbbVie, Aptitude Health, Bayer, BeiGene, Ltd., Bio Ascend, Bristol-Myers Squibb, Celgene, Epizyme, Everest Clinical Research Corporation, GenMab, Genentech, Gilead Pharmaceutical, Incyte, Ipsen, Janssen Pharmaceuticals, Inc., Loxo Oncology, Miltenyi Biotec Incorporated, MorphoSys AG, Nordic Nanovector ASA, Novartis, Physicians' Education Resource, RAPT Therapeutics, Regeneron Pharmaceuticals, Inc., Roche, Scientific Education Support Ltd., Takeda Millennium

Stock ownership: Owkin, Inc.

213 | DEEP LEARNING CAN PREDICT PRESENCE OF TP53 ABERRATIONS AND IGHV MUTATIONAL STATUS FROM PERIPHERAL BLOOD SMEARS OF CHRONIC LYMPHOCYTIC LEUKEMIA

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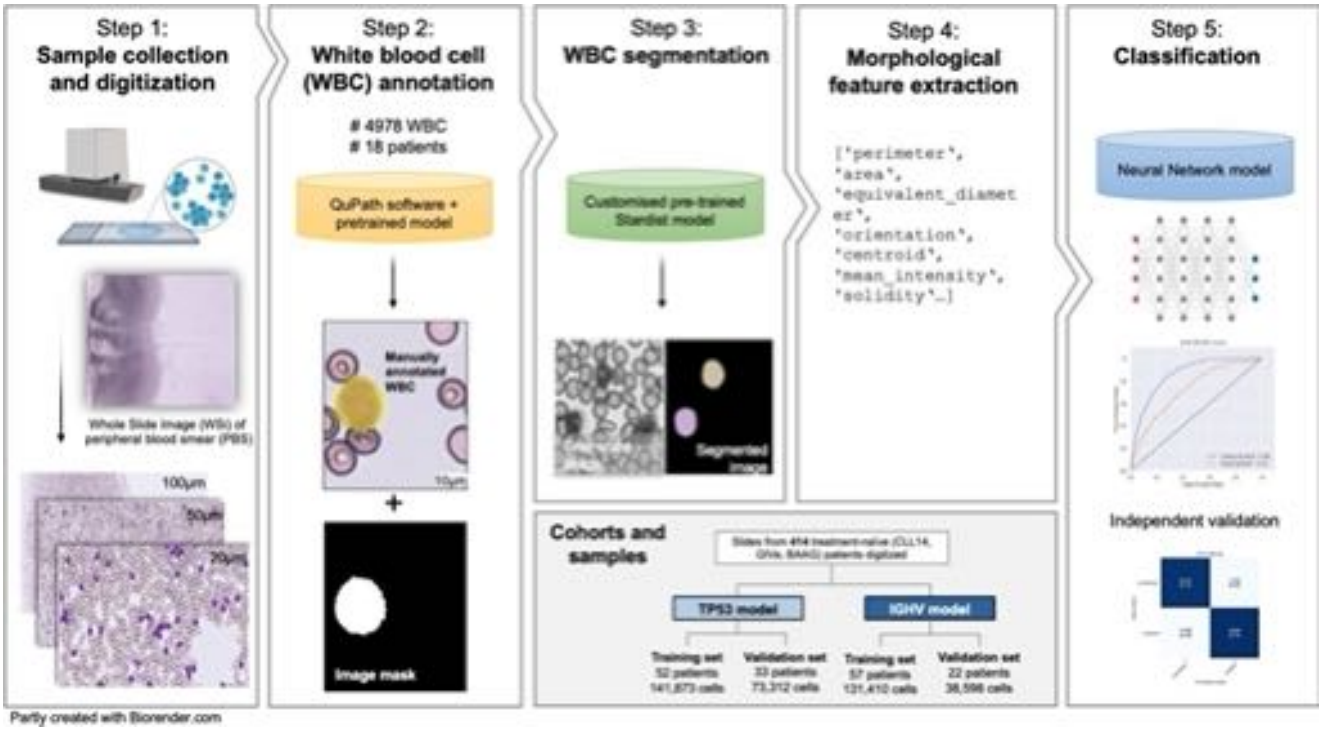
Introduction: Patient stratification based on genomic biomarkers is critical to optimize treatment of chronic lymphocytic leukemia (CLL). Using digitized, genomically annotated peripheral blood smears (PBS) of patients with CLL, we evaluated whether deep learning can predict presence of *TP53* aberrations (del[17p] and/or *TP53 mutation*) and unmutated IGHV status solely based on cytomorphology.

Methods: The workflow consisted of sample collection and digitization, manual annotation, segmentation, morphological feature extraction, and aberration classification. Whole slide images were generated from PBS of 414 patients with previously untreated CLL (CLL14, GIVe, BAAG). Manual annotation was conducted using Qupath software (v0.3.2) with ImageJ. A tailored Stardist model was used for semantic segmentation. Morphological features were collected from each segmented white blood cell (WBC) and fed into the classification model. Two neural network (NN) models were generated for each aberration (*TP53* and IGHV) based on a cohort split into 70/30% training and testing datasets. The models were evaluated using AUC (Area Under the Curve of ROC [Receiver Operating Curve]).

Results: In preparation of model training, 4,962 manual cells from 18 randomly selected patients were manually annotated.



For the *TP53* classifier, 141,873 WBC from 52 patients were segmented using the Stardist model. For the IGHV classifier, 131,410 WBC from 57 patients were segmented. The model was trained on 256 × 256 pixels patches obtained from original images with 200 epochs and 100 batch_size whilst making use of data augmentation. An intersection over union (IoU) value of 89.6% confirmed good model performance, i.e. accurate WBC segmentation.

Lymphocyte cells were then segmented on each frame image. In total, 28 single-cell morphological features were captured and 8 best representatives fed into the NN model. The collected metadata vector features were randomly assigned to non-overlapping training and testing sets. Separate datasets were used for the *TP53* and IGHV classifier. On a single-cell level, the models achieved an AUC of 86% for *TP53* aberrations and IGHV status, respectively. For independent validation, the *TP53* and IGHV classifiers were tested on a set of unseen images of 33 and 22 patients, respectively. AUC values of 78% and 72%, respectively, were achieved, confirming good model performance. To classify individual patients, a threshold of ≥50% positive cells/image was used to either classify a patient as *TP53* aberrated or IGHV unmutated. Using this approach, 70% of patients with *TP53* aberration and 68% with IGHV unmutated status were accurately classified.

Conclusions: This study demonstrates that deep learning models can predict presence of *TP53* aberrations and IGHV mutational status based on cytomorphological features of CLL cells. Further model validation and optimization is warranted to confirm clinical utility.

Keywords: Bioinformatics, Chronic Lymphocytic Leukemia (CLL), Computational and Systems Biology, Diagnostic and Prognostic Biomarkers

No conflicts of interests pertinent to the abstract.

214 | NEXT GENERATION SEQUENCING IN ROUTINE DIAGNOSTICS OF MATURE NON-HODGKIN'S LYMPHOMAS. A SINGLE-CENTER REAL-LIFE DATA STUDY

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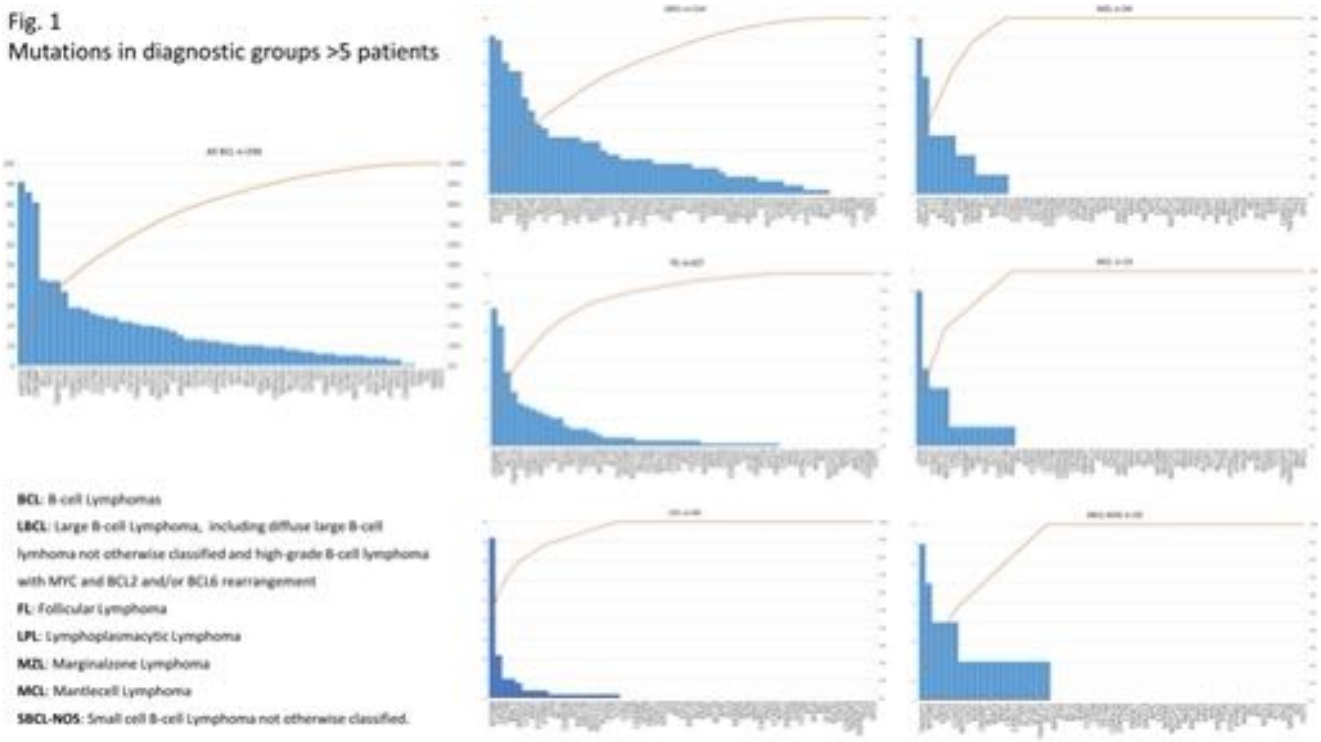
Introduction: Precision medicine requires equivalently precise diagnostic methods. The lymphoma diagnoses are primarily based on characteristic patterns of morphology and protein expression detected by immunohistochemistry (IHC). However, integral molecular characterization of lymphomas in clinical diagnostics may improve subclassification and risk-stratification. To accommodate this growing need we implemented a next generation sequencing (NGS) analysis as part of routine diagnostic work up of all mature non-Hodgkin lymphoma (NHL). We present data of mutational profiles with potential complementary diagnostic, prognostic and predictive value detected in our consecutive non-selected cohort of NHL patients.

Methods: NGS results from 320 individual consecutive non-selected diagnostic patient samples with a mature NHL were included as a single center study. Patients with both newly diagnosed and relapsed/refractory or progressive disease were included. Diagnoses were according to WHO (4.rev edition). NGS was performed as routine analysis together with standard diagnostic work-up using a custom-made amplicon PCR-based multiplex NGS-panel covering all coding exons and consensus splice sites in 59 genes.

Results: Patients are presented in Table 1. Mutations were detected in 93% of the 320 samples. Most B-cell lymphomas (BCL) could be

Diagnosis	Cases (n)	Relapsed/ Refractory/ Transformed	Age years, mean (range)	Gender, male	Samples with mutations	Total no. mutations	Mutations/ sample, mean (range)
Large B-cell Lymphoma (LBCL)	114	34	71 (36-100)	64 (56%)	110 (96%)	511	4,5 (0-11)
Burkitt Lymphoma (BL)	4	1	76 (72-80)	1 (25%)	4 (100%)	20	5 (2-8)
Follicular Lymphoma (FL)	67	14	71 (48-92)	36 (54%)	66 (99%)	301	4,5 (0-11)
Lymphoplasmacytic Lymphoma (LPL)	45	8	73 (46-87)	29 (64%)	44 (98%)	85	1,9 (0-6)
Mantle Cell Lymphoma (MCL)	19	4	72 (56-91)	15 (79%)	15 (79%)	32	1,6 (0-4)
Marginal Zone Lymphoma (MZL)	20	9	69 (42-89)	10 (50%)	18 (90%)	37	1,9 (0-5)
Hairy Cell Leukemia (HCL)	5	0	63 (50-75)	4 (80%)	4 (80%)	6	1,5 (0-3)
Small B-cell Lymphoma, not specified (SBCL-NOS)	24	6	75 (56-95)	10 (42%)	19 (79%)	29	1,2 (0-3)
T-cell Lymphoma (TCL)	22	5	73 (47-99)	12 (55%)	17 (77%)	35	1,6 (0-7)
Total	320	81	71,5 (36-100)	181 (57%)	297 (93%)	1056	3,4 (0-11)



classified definitively and had characteristic mutational profiles as shown in Figure 1, but 24 cases were classified as small cell B-cell lymphomas without defining characteristics (SBCL-NOS). 50% (12/24 cases) of SBCL-NOS could retrospectively be assigned a likely diagnostic subtype according to mutational findings. (1 FL, 6 MZL, 3 LPL and 2 Small lymphocytic lymphoma).

Conclusion: Implementation of NGS in routine diagnostics of mature B-cell NHL added diagnostic value to 50% of unclassified cases and provided in a total of 93% of all cases possible biomarkers for disease monitoring as well as potential diagnostic, prognostic and predictive markers for future studies.

The research was funded by: Department of Pathology, Herlev-Gentofte Hospital, Denmark

Keywords: Diagnostic and Prognostic Biomarkers, Pathology and Classification of Lymphomas

No conflicts of interests pertinent to the abstract.

215 | MACHINE LEARNING-BASED STEM CELL-LIKE PHENOTYPE IDENTIFICATION AND NOVEL RISK STRATIFICATION IN DIFFUSE LARGE B-CELL LYMPHOMA: MULTI-OMICS DATA FROM MULTICENTER STUDIES

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Background: Previous researches have mainly focused on the discussion of whether cancer stem cells exist in diffuse large B-cell lymphoma (DLBCL). However, some subgroups with dismal prognosis that exhibit stem cell-like characteristics have been overlooked.

Methods: Using an innovative one-class logistic regression (OCLR) machine learning algorithm, we calculated *stemness indices* and systematically assessed their ability to reflect the oncogenic dedifferentiation-like characteristics of DLBCL. Next, we identified signatures associated with oncogenic dedifferentiation-like features and prognosis using LASSO and SVM-RFE algorithms and developed a proportional hazards model (Riskscore) for DLBCL through Cox regression. Then we stratified the risk of DLBCL (n = 2133) and evaluated the prognostic value of the risk model across known clinical and molecular subgroups. We further compared the characteristics of high- and low-risk DLBCL with Burkitt lymphoma. Finally, we investigated the mechanisms of poor prognosis in high-risk DLBCL using transcriptomics, genomics (n = 576) and single-cell RNA sequencing (n = 19) data, as well as cell experiments and internal validation cohorts.

Results: In this study, we identified and validated a DLBCL subgroup (25.6% of DLBCL) with stem cell-like characteristics and dismal prognosis. This high-risk group was defined as polyamine metabolism-cold immune tumor with upregulated polyamine metabolic key enzyme (ODC1) and desert-like immune infiltration, and had a poor prognosis with lower 3-year OS rate (54.3% vs. 83.6%,

$p < 0.0001$) and PFS rate (42.8% vs. 75.2%, $p < 0.0001$) compared to the low-risk group. We found that some patients with MYC rearrangement, double-hit, double-expresser, or complete remission may have either favorable or poor prognosis, which can be accurately identified by our risk stratification model. Additionally, the high-risk group exhibited malignant proliferative phenotypes similar to Burkitt lymphoma. Genomic analysis revealed widespread copy number losses in the chemokine and interferon coding regions 8p23.1 and 9p21.3 in the high-risk group. Bulk and single-cell transcriptome analysis indicated that the upregulation of ODC1 might mediate the cold immune microenvironment of DLBCL, and knocking down ODC1 effectively inhibited DLBCL cell proliferation. Promisingly, our model effectively identified patients who were insensitive to immunotherapy (CAR-T and immune checkpoint antibodies).

Conclusions: Our model effectively simplifies the risk stratification of DLBCL and reveals that polyamine metabolism and the immune microenvironment jointly shape a group of DLBCL patients with extremely poor prognosis. Targeting polyamine metabolism may regulate immune therapy and effectively improve the prognosis of DLBCL patients, providing new insights into immunotherapy for DLBCL.

The research was funded by: This work was supported by grants from the National Natural Science Foundation of China (grant no. 81873450, 82170181), Beijing Hospitals Authority Youth Programme (code: QML20200201), and Beijing Natural Science Foundation (No. 7222027) to Liang Wang.

Keywords: Bioinformatics, Computational and Systems Biology, Microenvironment, Risk Models

No conflicts of interests pertinent to the abstract.

216 | LONG-TERM FOLLOW-UP AND GENE EXPRESSION PROFILES ASSOCIATED WITH OUTCOME IN PATIENTS WITH RELAPSED AGGRESSIVE B- OR T-CELL LYMPHOMAS TREATED IN THE NORDIC P[R]EBEN TRIAL

T. Relander[1], S. Leivonen[2], T. S. Larsen[3], P. Brown[4], J. M. Jørgensen[5], S. Mannisto[2], P. Lugtenburg[6], H. Holte[7], U. M. Fagerli[8], G. F. Lauritzsen[7], P. Meyer[9], K. Liestøl[10], H. Toldbod[5], S. Leppä[2], F. d'Amore[5]

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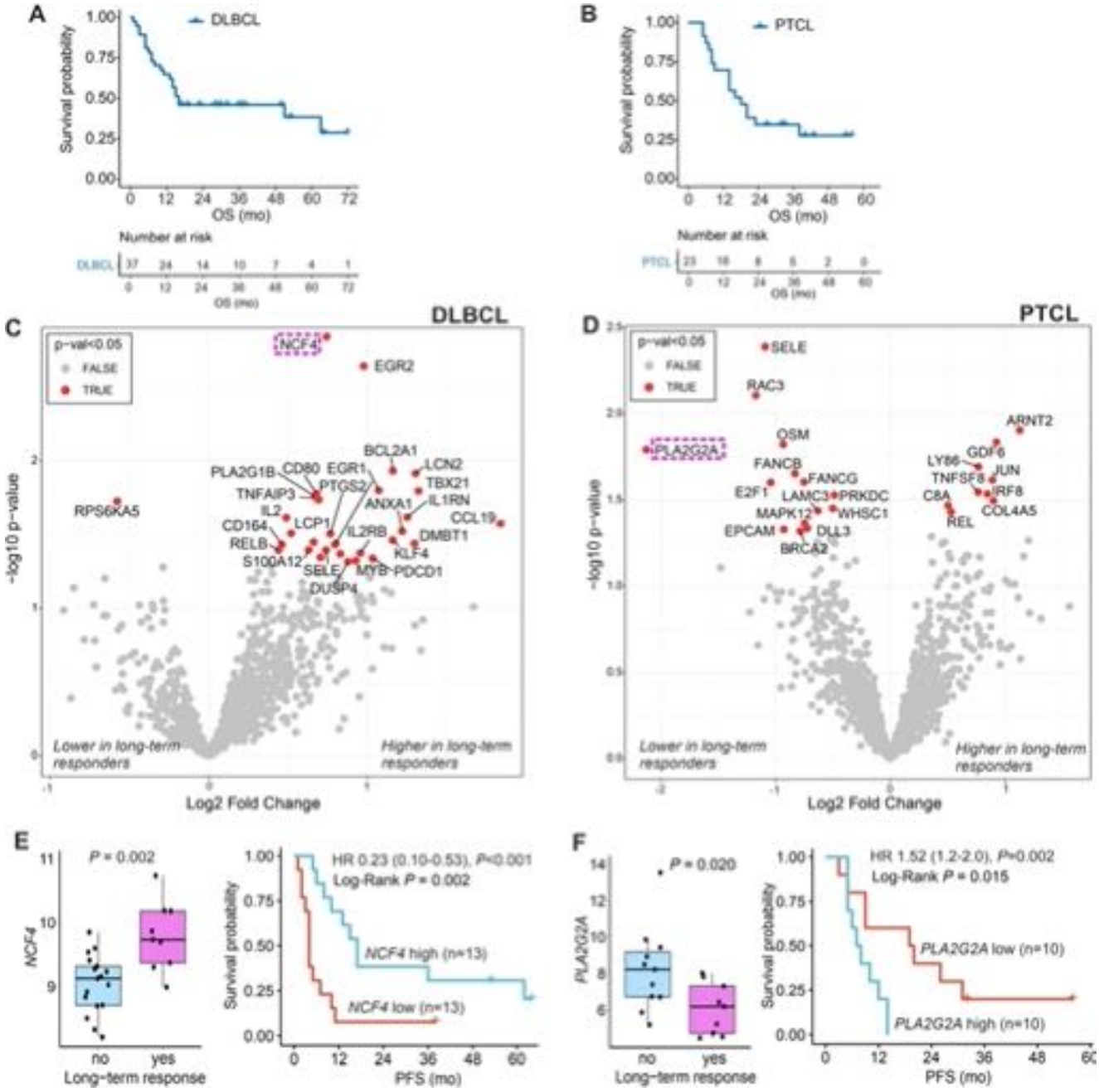

T. Relander and S. Leivonen shared first author

S. Leppä and F. d'Amore shared last author

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Introduction: The Nordic Lymphoma Group (NLG) performed a dose-finding/expansion trial evaluating pixantrone, etoposide, bendamustine and, in CD20+ lymphomas, rituximab (P[R]EBEN) in patients (pts) with relapsed diffuse large B-cell (DLBCL) or peripheral T-cell (PTCL) lymphomas. The regimen was out-patient based, and applicable in frail, heavily pre-treated pts. Here we present a long-term follow-up of the trial and a per-protocol correlative biological analysis of pre-therapeutic tumour biopsies looking for gene expression profiles associated with long-term response.

Methods: We enrolled 60 pts (37 DLBCL and 23 PTCL; age range: 39–84 yrs, median: 71 yrs). Time to event parameters were analyzed by Kaplan-Meier estimates, log-rank test and Cox regression models. Pre-therapeutic biopsies from 42 pts (25 DLBCL, 17 PTCL) were analyzed for gene expression by NanoString PanCancer Pathways and Immune profiling panels (altogether 1348 genes).

Results: Of the original 60 patients, 22 were alive at the time of the present analysis. The median follow-up of surviving pts was 41 mo (range 26–76 mo). The 38 deaths were due to: lymphoma (24; 63%), infections (3; 8%) and other causes (11; 29%: 1 lung carcinoma, 5 acute myeloid leukemia-AML, 1 myelodysplasia-MDS, 1 lung embolism, 1 allotransplant related and 2 unknown). Of the 6 pts with AML/MDS, 5 were PTCL and 1 DLBCL. Of 58 evaluable pts, 38 (65%) had a complete (CR) and 1 (3%) a partial response (B: 51%; T: 70%). The median duration of response (DoR) of the 38 CR pts was 17 mo (range 0.5–55 mo; B: 18 mo; T: 17 mo). Four pts were bridged to allogeneic transplant. The overall 5-yr OS and PFS were 33% and 19%, respectively. The median OS for DLBCL was 16.0 mo [IQR 7.0>] and for PTCL 18.0 mo [IQR 8.0>]. The median PFS for DLBCL was 10.0 mo [IQR 4.0–32.0] and for PTCL 10.0 mo [IQR 5.0–26.0].

To better understand molecular alterations underlying the delay of relapse in this heavily pre-treated elderly population, we determined differentially expressed genes between short (<12 mo) and long term (>12 mo) responders. In DLBCL, 31 genes showed significant differential expression between short- and long-term responders ($P < 0.05$). The latter had higher expression of genes related to transcription factor activity. The gene most significantly associated with long-term response was Neutrophil Cytosolic Factor 4 (*NCF4*). In PTCL, 23 genes were differentially expressed between short- and long-term responders, the latter showing enrichment in Ras signaling pathway genes (e.g., Rac Family Small GTPase 3, *RAC3*, and phospholipase A2 group IIA, *PLA2G2A*).

Conclusion: The P[R]EBEN regimen is feasible on an out-pt basis and shows encouraging response rates and DoR. In PTCL, we observed an overrepresentation of AML/MDS, possibly related to the use of etoposide in multiple treatment lines. Gene expression analysis identified signatures and single genes predictive of long-term response.

The research was funded by: Servier Laboratoires

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Aggressive T-cell non-Hodgkin lymphoma, Combination Therapies

No conflicts of interests pertinent to the abstract.

TRANSLATIONAL STUDIES, PCTL AND cHL

217 | INTERACTION BETWEEN GUT MICROBIOME AND IMMUNE CHECKPOINT INHIBITOR TREATMENT IN LYMPHOMA PATIENTS: FINAL RESULTS OF THE MICRO-LINF STUDY

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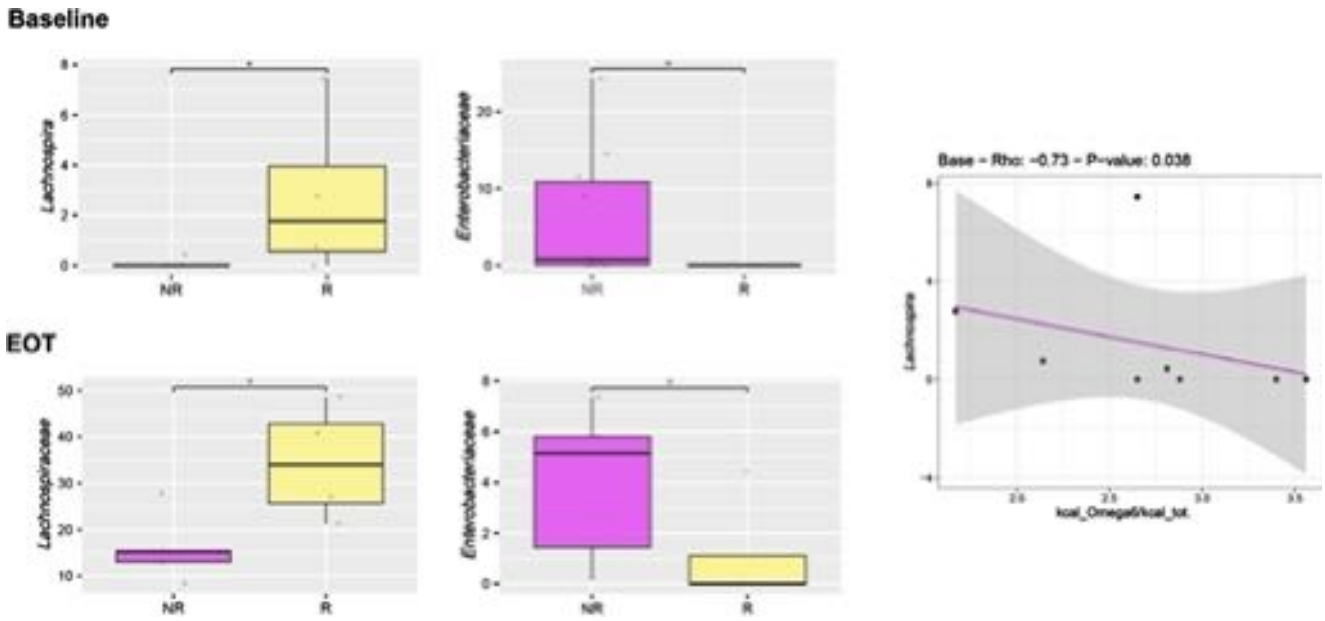
Introduction: Over the last decades, a revolution has occurred in oncology with the development of immune checkpoint inhibitors (ICIs). Following tremendous successes in solid tumors, interest has risen to explore these inhibitors also in hematologic malignancies, especially lymphomas. Biomarkers for ICIs response and resistance include PD-L1 expression and other environmental factors, among which the gut microbiome (GM) is gaining increasing interest. Several studies have demonstrated a connection between GM compositional and functional patterns and ICIs efficacy in solid tumors, but no data in lymphomas have yet been published. We hypothesize that GM dynamics in lymphoma patients during ICIs therapy correlate with treatment response and toxicities.

Methods: We enrolled 20 patients (15 with classical Hodgkin lymphoma [cHL] and 5 with primary mediastinal B-cell lymphoma [PMBCL]) treated with ICIs due to relapsed/refractory (R/R) disease. Feces were collected at baseline, before each therapy cycle and at response assessment, and profiled through Illumina sequencing. Sequencing data were processed using a bioinformatics pipeline combining PANDASEQ and QIIME 2. At each time point, patients compiled a 7-day weighted food intake record that was analyzed by MètaDieta (METEDA). All statistical analysis was performed in R (4.4.2).

Results: The two groups of patients did not differ for baseline characteristics, thus both clinical outcomes and GM results are reported as pooled. Nineteen patients were refractory to last therapy, with a median of previous treatments of 3 (range 2–8). The median number of ICIs cycles was 14 (1–39). The overall response rate (ORR) was 30.5%, with a median progression-free survival of 11 months and a median disease survival not reached, at a median follow-up of 28.9



months. No association was found between clinical characteristics and response/survival outcomes. Three patients developed 6 hematological toxicities and 18 patients developed 58 extra-hematological toxicities; 4 patients had SAE, of which 2 were judged as drug related. As for GM (Figure 1), responding patients showed a peculiar enrichment of *Lachnospira* at baseline ($p = 0.013$). The relative abundance of this taxon negatively correlated with dietary intake of Omega-6 ($p = 0.038$). On the other hand, non-responders showed higher basal levels of *Enterobacteriaceae* ($p = 0.041$). These features were also maintained at the end of the treatment, even if only as trends ($p < 0.1$).

Conclusions: Recognizing patient-related factors that may influence response and toxicity to ICIs is becoming critical to optimize the treatment pathway of heavily pretreated, young patients with a potentially long-life expectancy. In our series, albeit small, we identified a potential early GM and dietary signatures of therapeutic response in lymphoma patients, which could pave the way for new adjuvant strategies to improve prognosis in these individuals.

Keywords: Diagnostic and Prognostic Biomarkers, Immunotherapy

No conflicts of interests pertinent to the abstract.

218 | MATURE T AND NK CELL LYMPHOMAS CLASSIFIED ACCORDING TO 2016 WHO CLASSIFICATION. A REPORT OF 741 CASES REGISTERED IN THE INTERNATIONAL PROSPECTIVE T-CELL PROJECT 2.0.

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Introduction: Mature T and NK-cell lymphomas represent a heterogeneous group of rare lymphoid disorders arising from mature T cells of post-thymic origin. The T-cell Project 2.0 (TCP2) was launched in 2018 with the aim of better understanding this group of

rare disorders, capturing a real-life snapshot of the evolving landscape of T-cell lymphoma biology, treatment strategies, and outcome. Here we report preliminary data on histotype distribution, disease characteristics, front line treatment, and short-term outcome of patients registered between 2018 and 2021.

Methods: The TCP2 (ClinicalTrials.gov Identifier: NCT03964480) is a prospective, longitudinal, international, observational study of patients with Peripheral T-cell lymphoma (PTCL). For this analysis we considered cases based on the diagnosis made locally according to the WHO2016 classification. The study was approved by each participating center and required patients to sign informed consent.

Results: Between October 2018 and December 2021, 741 eligible cases with newly diagnosed PTCLs were registered by 94 Institutions across 17 Countries. Overall, PTCL-NOS, AITL, ALCL ALK-, ALCL ALK+, ENKTCL, and ATLL resulted the most frequent 6 subtypes, accounting for 91% of cases, while the remaining 9% were represented by few cases of 13 different subtypes. Of note, only 16 cases (2.1%) were classified according to entities not considered in the previous WHO 2008 classification. The median age at diagnosis was 57 years (18–93), 56.5% of patients were male, the presence of systemic symptoms was reported in 30% of cases, 7.4% had ECOG-PS 3–4, 71% advanced disease and 36.6% bone marrow involvement. Overall, 88% were treated with combination chemotherapy and 28% of patients with advanced stage disease in complete or partial remission after chemotherapy were consolidated with high dose therapy and stem cell transplantation.

After a median follow-up of 21 months, the 2-year PFS and OS of the whole series were 38% and 52%, respectively. At the same time point, the PFS and OS (in brackets) were: PTCL-NOS (24% and 43%); AITL (40% and 50%); ENKTL (44% and 53%); ALCL ALK- (52% and 67%); ALCL ALK+ (71% and 85%) and ATLL (14% and 27%).

Comparing the distribution of cases enrolled in the present study with those in the previous TCP1 (2008–2018), we found a 6% and 3% decrease in the frequency of PTCL-NOS and EATL, respectively, whilst the frequency of other histotypes remained almost unchanged. Of note, no statistically significant differences emerged in terms of PFS and OS for the comparable histotypes of TCP1 and TCP2.

Conclusions: Based on the analysis of this large series of cases of PTCL prospectively registered in the TCP2, it seems "Nothing new under the sun": no improvement in terms of outcome and a very limited effect of the WHO2016 in classification of cases in the real world.

The research was funded by: Angela Serra Association for Cancer Research

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Pathology and Classification of Lymphomas

No conflicts of interests pertinent to the abstract.

219 | ANGIOIMMUNOBLASTIC T CELL LYMPHOMA PROGNOSTIC INDEX IN ASIAN POPULATION IDENTIFIES LOW RISK PATIENTS WITH UNIQUE GENE EXPRESSION PROFILES

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Introduction: Angioimmunoblastic T cell Lymphoma (AITL) is a subtype of peripheral T cell lymphoma and prognosis is generally felt to be poor. Molecular characteristics differentiating good or poor risk AITL has not been identified. In our Asian multicentre study, we investigate the clinical prognostic factors affecting the outcomes of our AITL patients. We also interrogate the gene expression profiles in our patients to identify if there may be different immune and cell signalling signatures in different risk groups.

Methods: Patients who were diagnosed with AITL and seen at National Cancer Centre Singapore, Singapore General Hospital and National University Cancer Institute, Singapore between June 1999 and December 2019 were retrospectively analysed. Relevant demographical and clinical characteristics were collected. Outcomes of interest were that of 5-year overall survival (OS) and 5-year progression free survival (PFS). Kaplan-Meier curves were plotted to estimate survival for each individual clinical parameter. Parameters found to be significant on univariate analysis were subsequently used in the generation of multivariate cox regression models. NanoString PanCancer IO360 panel (NanoString Technologies, Seattle, WA, USA) was used to interrogate gene expression on AITL FFPE tissue, following manufacturer's protocol using the nCounter platform.

Results: A total of 174 patients were identified. Median duration of follow up was 20.4 months. Median PFS and OS was 1.8 years and 5.6 years respectively. In multivariate analyses, Age >60, bone marrow Involvement, Total white cell count and serum Lactate dehydrogenase were associated with poorer PFS and OS. A prognostic index (AITL-PI) differentiated patients into low (0–1 factors, $n = 64$), moderate (2 factors, $n = 59$) and high-risk (3–4 factors, $n = 49$) subgroups with 5-year OS of 84.0%, 44.0% and 28.0% respectively ($p < 0.0001$). Gene expression studies performed in 23 patients found disparate immune cell type profiles and oncogenic signalling pathway signatures in the low risk as compared to the intermediate and high-risk groups. In the low risk

group, neutrophilic, T-regulatory and Th-1 cell profiles were predominant whereas cytotoxic cell profile was predominant in the intermediate and high-risk groups. The low risk group was more active in the myeloid compartment, WNT, cytokine and chemokine, TGF-β and hedgehog signalling pathways whereas cytotoxicity, interferon and lymphoid compartment signalling signatures returned higher in the intermediate and high-risk groups.

Conclusion: Our AITL-PI identified 3 different subgroups of patients with disparate outcomes based on their presenting clinical parameters. Low risk patients had 5-year OS exceeding 80%. Gene expression profiling found unique immune and oncogenic signalling profiles in the low risk group that would allow for further dissection in future molecular analyses.

Figure 1. Classification of patients by the AITL Prognostic Index

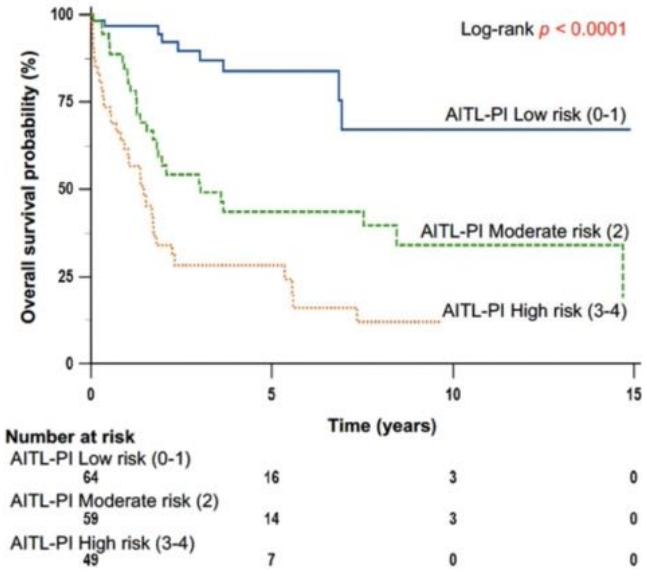
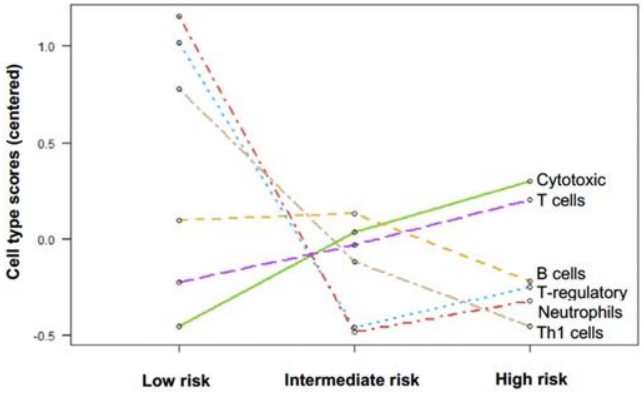


Figure 2. Gene expression profiling of immune cell types across the AITL-PI risk groups



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Keywords: Aggressive T-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers

No conflicts of interests pertinent to the abstract.

220 | IDENTIFYING THE MECHANISTIC DIFFERENCES BETWEEN HYPOMETHYLATING AGENTS FOR THE TREATMENT OF PERIPHERAL T CELL LYMPHOMA

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Introduction: Peripheral T-cell lymphomas (PTCL) are a rare and heterogeneous group of malignancies that share a unifying feature of epigenetic dysregulation. Recent evidence suggests that PTCL, unlike other forms of cancer or even lymphoma, exhibits a marked vulnerability to hypomethylating agents (HMAs) alone and especially in combination with HDAC inhibitors. HMAs like azacitidine (AZA) and decitabine (DAC) have been shown to reverse transcriptional repression secondary to hypermethylation. Cladribine (CLAD) is FDA-approved for the treatment of hairy cell leukemia and is postulated to inhibit both DNA and histone methylation. Here, we sought to define the mechanistic differences between different DNA HMAs in order to inform a rationale on the optimal combinations that might exploit the epigenetic vulnerabilities of PTCL.

Methods: Cell viability, caspase activity assay, and western blotting (WB) were performed on a panel of T-cell lymphoma cell lines to identify the effects of AZA/DAC/CLAD on cell survival, apoptosis, and DNA methyltransferase (DNMT) levels. Liquid chromatography-based mass spectrometry (LC-MS) was done to quantify 5-methyl cytosine (5-mC) levels.

Results: Cell viability analysis confirmed that the dose and time-dependent sensitivity of the six PTCL cell lines differed following exposure to AZA/DAC/CLAD, where CLAD showed the lowest IC50 value (0.1–1 μM) across all cell lines, followed by AZA (IC50: 1–10 μM), and DAC had the least effect on cell viability (IC50: >100 μM, except T-ALL). A differential threshold of caspase activation was observed across the PTCL cell lines where CLAD showed the most

superior caspase activity leading to the highest apoptotic potential. However, WB analysis showed that after 24 hours of treatment, DNMT1 and DNMT3A protein levels were significantly depleted at low concentrations of DAC (<0.01 μM) compared to AZA whereas CLAD did not affect the DNMT1 and DNMT3A levels. LC-MS-based quantification of 5-mC showed a similar relationship in methylation, with initial changes observed at doses >0.01 μM of DAC and >0.1 μM of AZA/CLAD. Taking the short half-life of AZA/DAC into account, cell viability assays with daily addition of AZA/DAC showed increased cell cytotoxicity for AZA/DAC treated samples, which was comparable to CLAD. Ongoing analyses of gene expression and metabolism of the universal methyl donor S-adenosylmethionine (SAM) will help to understand the mechanistic difference between these HMAs.

Conclusions: These data suggest that the HMAs have a distinct mechanism of action for hypomethylation. While AZA/DAC induces hypomethylation by depletion of DNMTs, CLAD acts in a DNMT depletion-independent pathway. A mechanistic understanding of AZA/DAC/CLAD will inform how best to use them in clinic as well as assist in the strategic development of biological correlates to further support their therapeutic application.

The research was funded by: Translational Orphan Blood Cancer Research Initiative Fund and RO1 # FD-R-006814-01.

Keywords: Genomics, Epigenomics, and Other -Omics, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

221 | SERUM TRIGLYCERIDE AND APOLIPOPROTEIN A1 AS BIOMARKERS FOR EXTRANODAL NATURAL KILLER/T CELL LYMPHOMA (ENKTL): A MULTICENTER STUDY

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Background: Although clinical outcome of extranodal NK/T cell lymphoma (ENKTL) has been improved recently, some patients resistant to Asp-based chemotherapy suffered poorer survival. Therefore, reliable and convenient biomarkers become more important.

Methods: We retrospectively analyzed 1017 ENKTL patients with available clinical data between December 2003 and August 2021. Demographics and serum lipid data of 500 healthy controls were reviewed. The median values at baseline were selected as the cutoff values for serum lipid.

Results: The baseline serum levels of high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein A1 (ApoA1) were lower, while the levels of triglyceride (TG) was higher in ENKTL patients than those in age- and gender-matched healthy controls (all $p < 0.001$). Besides conventional predictive factors, baseline serum TG (PFS: $p = 0.017$; OS: $p = 0.018$) and ApoA1 (PFS: $p = 0.007$; OS: $p = 0.002$) were identified as independent prognostic factors. Among patients with high levels of TG (or low levels of ApoA1) at baseline, those who exhibited objective responses had a significant serum TG decrease (or ApoA1 increase) after treatment (all $p < 0.001$) (Figure A-B). However, no significant change of TG or ApoA1 was observed in patients without satisfactory response. Compared with baseline levels, further increased levels of TG and decreased levels of ApoA1 after first-line treatment were associated with significantly shorter PFS and OS (all $p < 0.001$) (Figure C-D). We developed and validated a pre-treatment nomogram containing TG and ApoA1 at baseline and a post-treatment nomogram containing serum lipid at best response (Figure E-F). Compared with pre-treatment nomogram and PINK, the post-nomogram prognostic model was proved to possess a higher predictive power of survival for ENKTL with significantly higher concordance index and the area under the curve (AUC) and lower integrated Brier score (IBS) for 5-year OS. Subgroup analysis showed that Asp-containing regimens were associated with significant survival benefits among patients with low levels of LDL-C and high levels of HDL-C and ApoA1 at baseline (all $p < 0.001$). Furthermore, the comprehensive transcriptome analysis provided evidence for intratumoral lipid metabolic disorders and dysregulated classical tumor-related signaling pathways, including NOTCH and MAPK, among patients with high levels of TG (or low levels of ApoA1) at baseline (Figure G-H)

Conclusion: This study suggests that ENKTL is accompanied by dyslipidemia. Baseline levels and change trends of TG and ApoA1 could contribute to risk stratification, disease status monitoring and treatment outcome prediction. Patients with dyslipidemia also have intratumoral lipid metabolic disorders and dysregulated classical tumor-related signaling pathway.

Encore Abstract - previously submitted to EHA 2023

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Keyword: Extranodal non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

222 | SOLUBLE IMMUNE CHECKPOINTS HVEM AND TIM-3 ARE PROGNOSTIC BIOMARKERS FOR OUTCOME IN CLASSICAL HODGKIN LYMPHOMA

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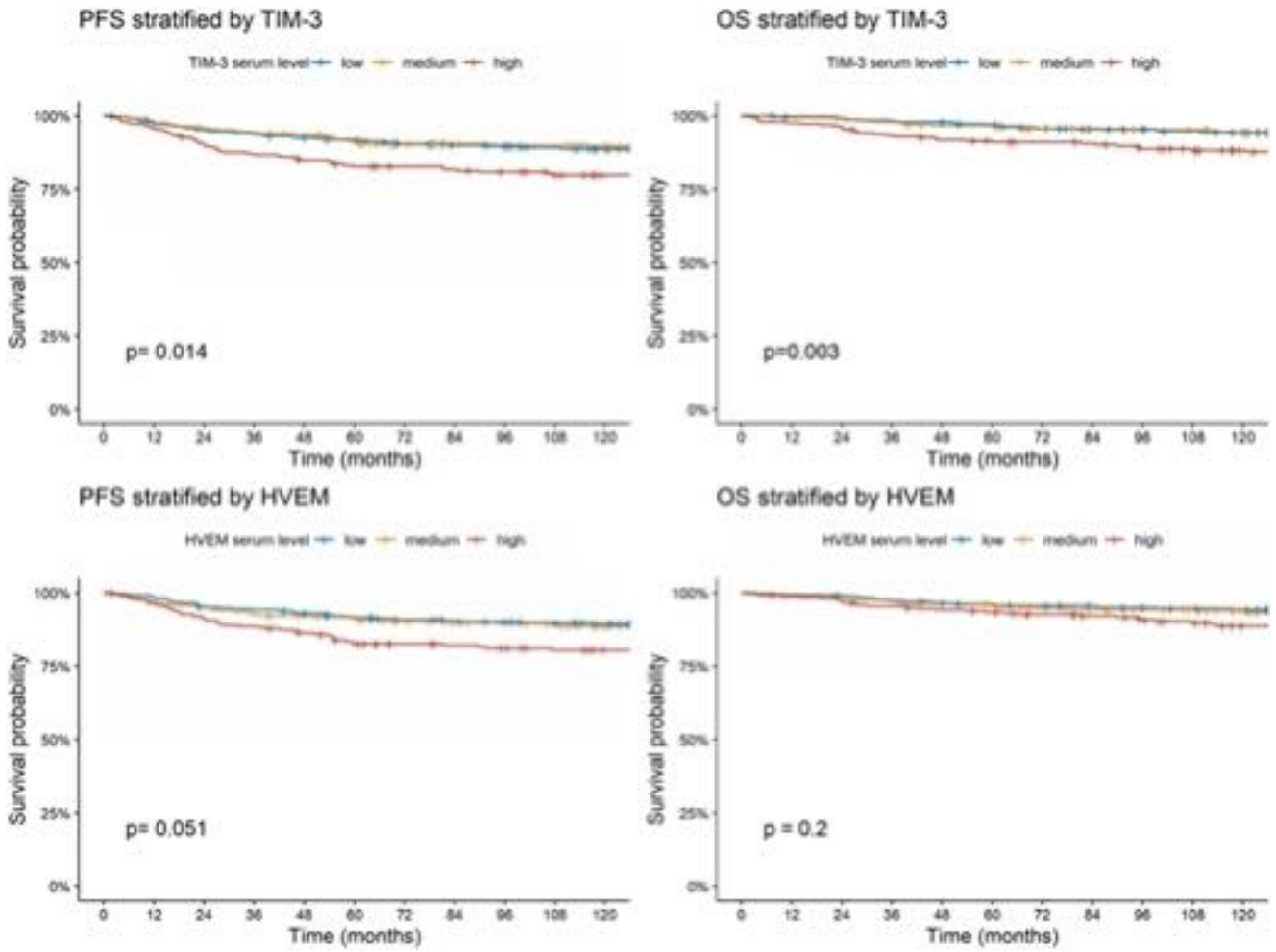
Introduction: Immune checkpoints expressed in the tumor microenvironment (TME) play a key role in the immune evasion of cancer in general and in classical Hodgkin lymphoma (cHL) in particular. While few studies reported elevated PD-L1 serum levels in cHL compared to healthy individuals, the distribution and prognostic significance of soluble immune checkpoints (sCP) in the serum of cHL patients remains unclear. We therefore analyze the prognostic value of 14 different baseline sCP levels in prospectively treated patients with primary cHL.

Methods: We measured serum levels of soluble BTLA, CD27, CD80, CTLA-4, GITR, GITR-L, HVEM, MICA, MICB, PD-L1, TIM-3, ULBP-1, ULBP-3, ULBP-4 with multiplex cytokine arrays in patients treated in the German Hodgkin Study Group (GHSG) trials HD7, HD8 and HD9. We designed a PFS-event-enriched study cohort from these patients. sCP levels were analyzed descriptively. In absence of validated thresholds, associations of sCP serum levels with PFS and OS were first tested using weighted cox-regression stratified for stage, age and sex, modeling sCP levels as continuous variables before performing secondary analyses separating levels into three groups: low, medium and high. All analyses of PFS and OS were weighted with respect to the



proportion of progressions and relapses in the total study population to correct for event-enrichment.

Results: Of 308 patients with measured sCP levels, 176 (57.1%) had advanced stage disease and median follow-up was 144 months. Weak correlations were noted among sCPs (median r = 0.12, IQR 0.24). Only TIM-3 and HVEM were significantly associated with PFS and OS by cox-regression modeling sCP levels as continuous variables. Interestingly, no associations of soluble PD-L1 with outcome was observed (PFS: $p = 0.22$, OS: $p = 0.54$). PFS and OS differed significantly when the cohort was split by TIM-3 sCP levels ($p = 0.014$ and 0.003, respectively for PFS and OS) but not when split by HVEM sCP levels ($p = 0.051$ and 0.2). In detail, Patients with TIM-3 serum levels in the upper third of levels had a higher risk of progression (HR 2.3, CI95: 1.3–4.0) or death (HR: 2.5 CI95: 1.2–5.4) compared to those in the lower third. High HVEM was associated with significantly shorter PFS (HR 1.8, CI95: 1.1–3.2) but not shorter OS (HR 1.6, CI95: 0.6–3.2). Exploratory separation by median rendered similar results.

Conclusions: We provide a reference for baseline serum levels sCP in a large cohort of patients with cHL across all stages with very long follow up. Further, we identify soluble HVEM and TIM-3 as novel prognostic biomarkers in cHL. Investigations into the origin of these sCP using primary tumor tissue are ongoing. Since antibodies targeting TIM-3 are already in advanced clinical development, our findings call for further investigation of this immune checkpoint in cHL.

Keywords: Diagnostic and Prognostic Biomarkers, Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

223 | A GENE EXPRESSION SIGNATURE TO PREDICT DISEASE PROGRESSION FOR HODGKIN LYMPHOMA PATIENTS WHO ACHIEVE A COMPLETE METABOLIC RESPONSE AFTER 2 ABVD COURSES

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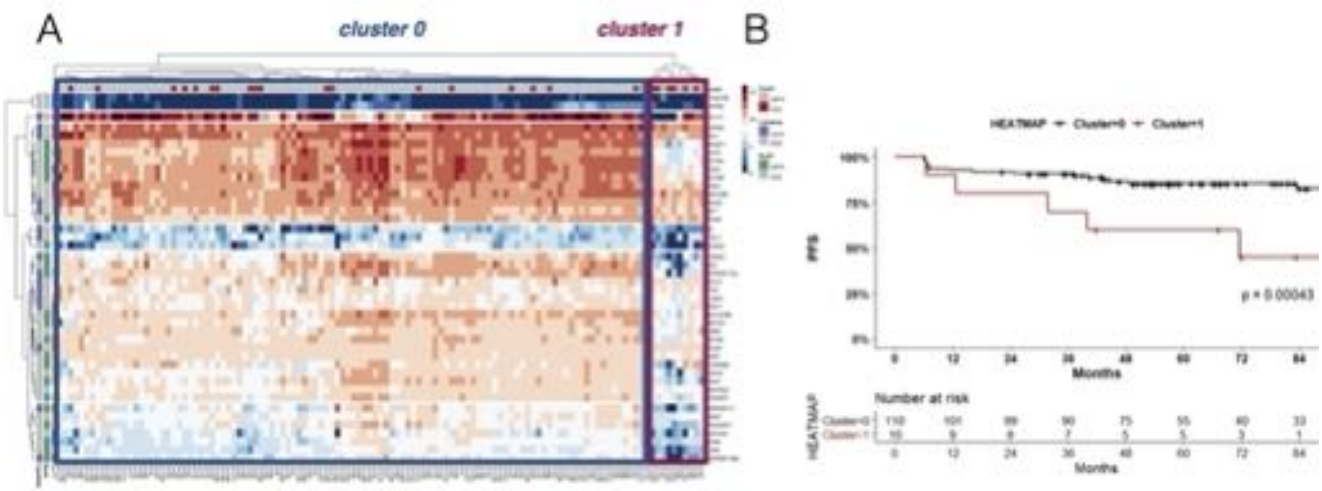
Background: Classical Hodgkin Lymphoma (cHL) is one of the most manageable human cancers. The early identification of patients who experience relapse after completion of front-line therapy, regardless of their initial stage currently represent an unsolved need. It is likely that disease progression reflects some innate features that escape the current prognostic criteria but that can be revealed by a deep analysis of the molecular assets of the lesions. We employed a deep gene expression analysis searching for molecular determinants that could anticipate the risk of relapse among patients who achieve a complete metabolic response after 2 ABVD courses (iPET-).

Patients and methods: We conducted a retrospective search of our local clinical archives to include patients with the following characteristics: confirmed cHL histology, age >18, iPET negative after 2 ABVD course (Deauville score 1–3). We retrieved the baseline diagnostic biopsy to conduct a gene expression analysis by nCounter Nanostring Technology using the PanCancer Immune-panel. Genomic data were correlated with clinical and laboratory data and with patients' outcomes. Primary endpoint of this analysis was Progression Free Survival (PFS).

Figure 1



A) Unsupervised clustering of iPET- cHLs based on the expression of 43 protective genes identifies two clusters.
B) Kaplan Meier curves showing PFS for cluster 0 and cluster 1

Results: Out of 215 cHL patients seen in our institution from 2004 to 2019, 148 achieved a negative iPET after 2 ABVD course. FFPE material was available for 120 iPET- cases which constitute the study population. Forty percent of patients were older than 45 years, 38% had stage III-IV, and 15% had Bulky disease. With a median follow up of 63 months (range, 7–139 months) we recorded 31 events for PFS. The resulting 4 year PFS rate was 77% (95% CI: 71.1–84.9).

Analysis performed by Cox Proportional Hazard model identified 54 genes whose expression was significantly associated with PFS ($p \leq 0.05$). Of these, 43 were positively associated with improved PFS indicating a potential protective role of these factors. Vice versa, only 11 genes were significantly associated with reduced survival probability. Gene Ontology analysis showed that protective genes were enriched in B-cells related pathways and response to cytokines, pointing to a shielding function of the microenvironment with respect to disease aggressiveness. Unsupervised clustering analysis using the 43 genes protective signature identify two separate clusters of patients (Figure 1A). Kaplan Meyer curve analysis showed that Cluster 2 patients had a significative reduced PFS as compared to Cluster 1 ($p = 0.00043$), supporting the prognostic relevance of these genes (Figure 1B).

Conclusions: Even if preliminary, these data indicate that gene expression analysis helps in the early identification of relapsing iPET-cHLs and that progression in this disease is restrained by an immune-protective microenvironment of which B-cells are crucial component.

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Keywords: Genomics, Epigenomics, and Other -Omics, PET-CT, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

224 | DEREGULATED HSA-MIR-23A-3P AND HSA-MIR-148A-3P INFLUENCE KEY PROCESSES IN CLASSIC HODGKIN LYMPHOMA (CHL) PATHOGENESIS

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Introduction: We previously performed global miRNA expression profiling of cHL vs. non-Hodgkin lymphoma (NHL) cell lines and sorted germinal centre B-cells (GCB). In the group of 79 deregulated miRNAs ($p < 0.05$) we became particularly interested in the upregulated miR-23a-3p, a potential oncomiR, predicted to regulate the expression of *TNFAIP3* and the downregulated miR-148a-3p, a potential tumor suppressor miRNA, predicted to regulate the expression of *IL15*. Therefore, we aimed to decipher the role of miR-23a-3p and miR-148a-3p in cHL pathogenesis.

Methods: Expression analyses were performed with TaqMan Advanced miRNA Assays versus two miRNA controls. Laser capture microdissection was used for primary HRS collection. 1,000 (miRNA expression) and 2 × 200 (DNA methylation) HRS cells were collected per case. Bisulfite pyrosequencing assay was designed using the PyroMark Software and sequencing performed using the PyroMark Q24 sequencer.

MiRNA-mRNAs interactions were validated with Dual-Glo Luciferase Assay using respective miRNA mimics. For overexpression pre-miRNAs were cloned into the pCDH-CMV-MCS-EF1α-GreenPuro vector and transductions were performed in triplicate.

Cell proliferation was measured using CCK-8 in four replications in three independent reactions by the GloMax®96 Microplate reader.

Results: We confirmed the overexpression of miR-23a-3p ($p < 0.001$) and downregulation of miR-148a-3p ($p < 0.014$) in microdissected HRS cells ($n = 10$) vs. GCB cells ($n = 10$). Moreover, we observed inverse correlation of miR-148a-3p expression with DNA methylation level of an adjacent CpG island ($r = -0.72$, $p < 0.01$; cHL $n = 7$, NHL $n = 10$). Elevated DNA methylation of this CpG island was detected also in 2/6 cHL primary cases.

Next, we validated interactions between miR-23a-3p and miR-148a-3p and their target genes. A reduction by 34% ($p < 0.001$) and 40% ($p < 0.01$) of the luciferase signal was observed in consequence of the interaction of miR-23a-3p mimic—*TNFAIP3* 3'UTR and miR-148a-3p mimic—*IL15* 3'UTR, respectively. Moreover, the abundance of TNFAIP3 protein was reduced after overexpression of the miR-23a (coexpressed with miR-27a) in L428 ($p = 0.0018$) and GCB6-16 ($p = 0.0083$) cell lines, compared to empty vector transductions. Whereas overexpression of miR-148a in three cHL cell lines caused a 32% decrease ($p < 0.05$) in proliferation in the KM-H2 cell line compared to empty vector transductions.

Conclusions: MiR-23a-3p and miR-148a-3p are recurrently deregulated in cHL and show significant affinity towards the *TNFAIP3* and *IL15* transcripts respectively. As *TNFAIP3* is a frequent target of inactivating mutations in HRS cells we suggest that miR-23a-3p has a complementary function in attenuating *TNFAIP3*. Moreover, we suggest that epigenetic repression of miR-148a-3p contributes to the phenotype of HRS cells which includes expression of IL15 of known growth, pro-survival and pro-inflammatory function.

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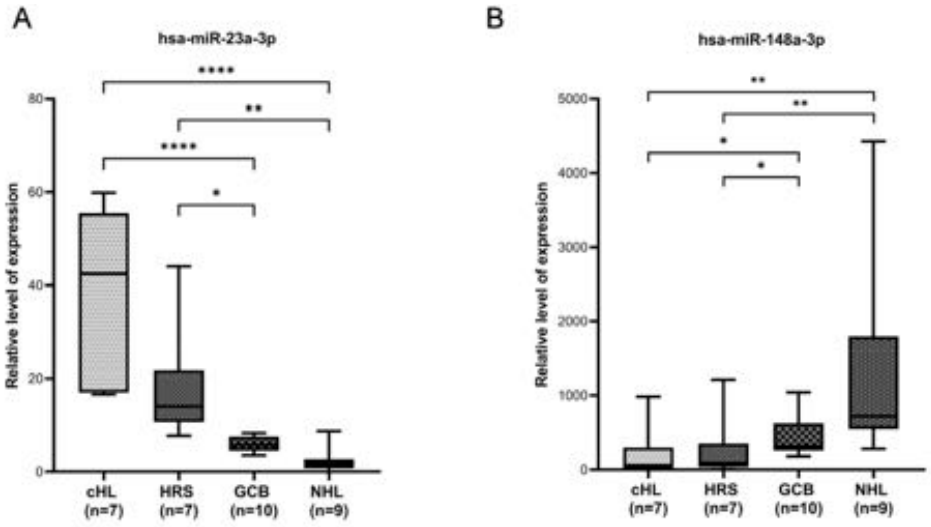

Figure 1. Expression level of (A) hsa-miR-23a-3p and (B) hsa-miR-148a-3p in cHL cell lines, microdissected HRS cells from cHL cases, sorted GCB cells and NHL cell lines. Statistical significance was calculated using Mann–Whitney U test * - $p<0.05$; ** - $p<0.01$, **** - $p<0.0001$.

Keywords: Hodgkin lymphoma, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

225 | STING IS EXPRESSED BY HODGKIN AND REED STERNBERG (HRS) CELLS IN A SUBSET OF CLASSICAL HODGKIN LYMPHOMA (CHL) AND CORRELATES WITH TUMOR MICROENVIRONMENT AND IMMUNE RESPONSE

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Introduction: Cytosolic DNA of exogenous or endogenous origin triggers activation of cyclic GMP-AMP synthase (cGAS), a cytosolic DNA sensor, that activates innate immune responses through activation of the adaptor protein STING. The latter, in turn, activates TBK1 and IKK kinases that, in turn, activate IRF3 and NF-κB transcription factors, which induce expression of interferons (IFNs), chemokines and cytokines involved in anti-tumor immune responses. The expression patterns of STING in Hodgkin and Reed-Sternberg (HRS) cells and the potential role of cGAS-STING pathway in anti-tumor immune responses in classical Hodgkin lymphoma (cHL) remain unknown to date.
Methods: In this prospective study, STING expression was immunohistochemically analysed in a cohort of 52 previously untreated patients with cHL and available tissue for flow cytometry (FC) analysis and histology as well as available peripheral blood samples for FC. An arbitrary 10% cutoff was used for positivity in HRS. The in vitro system included 6 cHL cell lines (MDAV, L1236, L428, L540, HDLM2, KMH2). Gene (mRNA level) and protein expression/activation of cGAS-STING components at baseline and experimental conditions were analysed by quantitative RT-PCR (RT-qPCR) and Western blot, respectively. The cHL cell lines were treated with a STING agonist or were subjected to silencing of STING gene using transient transfection with specific STING siRNA construct. The gene expression of cGAS-STING-associated IFNs and cytokines, including IFN-β, CXCL10, IFN-γ, STING, and a control gene (GAPDH), was analysed with RT-qPCR.
Results: STING was positive in HRS cells of cHL in 22 of 52 (42%) patients. STING positivity in HRS significantly correlated with lower numbers of STING+ T-lymphocytes ($p < 0.0001$) and CD3+ T-lymphocytes ($p = 0.04$) but higher numbers of CD20+ B-cells assessed by FC in the tissues. In peripheral blood samples assessed by FC at presentation, STING expression by HRS correlated with higher numbers of CD3+ T-cells ($p = 0.005$) but lower numbers of NK-cells ($p = 0.02$). STING expression did not correlate with clinical features at presentation, including age, gender, Ann Arbor stage, B-symptoms, tumor burden, bulky disease, anemia, or other hematologic values. STING expression at the mRNA and protein level was substantially higher in L1236, L428 and HDLM2 compared to other cHL cell lines. Treatment with STING agonists stimulated gene expression of IFN-β and/or CXCL10 at a variable level indicating functional cGAS-STING pathway in HRS. Knocking down STING gene resulted in dramatic increase in CXCL10 gene expression in cHL cells.
Conclusions: STING is expressed by HRS in a subset of cHL and significantly correlates with the lymphocytic populations in the tumor microenvironment and peripheral blood. The cGAS-STING pathway is functional in HRS suggesting that STING agonists may have therapeutic implications in patients with cHL.

Keywords: Diagnostic and Prognostic Biomarkers, Hodgkin lymphoma, Microenvironment

No conflicts of interests pertinent to the abstract.

226 | PROTEOMIC PROFILING DIFFERENTIATES CLASSIC HODGKIN LYMPHOMA WITH AND WITHOUT SKELETAL INVOLVEMENT AT THE TIME OF DIAGNOSIS

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Introduction: Classic Hodgkin lymphoma (cHL) is a highly curable disease, even in advanced stages. It is controversial whether bone involvement has a negative effect on overall- and progression-free survival in patients treated with intensive chemotherapy. cHL is characterized by a unique tumor microenvironment (TME) consisting of few, scattered neoplastic Hodgkin and Reed-Sternberg (HRS) cells, embedded in an abundant background of reactive immune and stromal cells. When cHL disseminates, the new disease sites also contain both HRS cells and TME cells. Whether cases that present with bone lesions, harbour specific TME features is unknown. We investigated protein expression in lymph node biopsies from cHL patients with and without skeletal involvement at diagnosis, using nano liquid chromatography—tandem mass spectrometry (nLC-MS/MS), to identify potential markers of skeletal disease.

Methods: Protein expression patterns in pre-therapeutic formalin-fixed, paraffin-embedded lymphoma samples from 69 cHL patients diagnosed at Aarhus University Hospital, Denmark between 2009 and 2018 were analysed by nLC-MS/MS. Patients were grouped according to diagnostic ^{18}F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/computed tomography (CT). FDG PET/CT scans were reviewed specifically for bone involvement. The study cohort included 50 patients with nodal cHL (n-cHL) and no skeletal involvement, and 19 patients with both skeletal and nodal disease (s-cHL).

Results: We identified 2,298 proteins; comparison of the protein profiles between the s-cHL and n-cHL groups revealed 220 unique proteins significantly differentially expressed ($p < 0.05$) and with a fold change of at least 25%. Of these, 117 proteins were upregulated (fold change 1.25–3.94), and 103 were downregulated (fold change 0.44–0.80) in s-cHL. In hierarchal clustering based on an even higher significance threshold ($p < 0.001$), i.e., 25 significantly differentially expressed proteins, two clusters were observed: (i) a skeletal-group comprising 12 s-cHL and 4 n-cHL samples; and (ii) a nodal-group of 46 n-cHL and 7 s-cHL samples. Of particular interest among the differentially expressed proteins, we identified isocitrate dehydrogenase (IDH1) and WD repeat- and FYVE domain-containing protein 4 (WDFY4). This pattern of protein expression suggests disturbance in cytoplasmic NADPH production, antigen processing/presentation, and B-cell survival in cHL patients with skeletal involvement compared to those without.

Conclusion: Our data show differential protein expression in cHL lymphoma tissues that correlate with the presence or absence of concomitant bone involvement at diagnosis. This indicates that certain biological pathways are affected among those presenting with disease disseminated to the skeletal system.

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Keywords: Genomics, Epigenomics, and Other -Omics, Hodgkin lymphoma, Microenvironment

No conflicts of interests pertinent to the abstract.

TRANSLATIONAL STUDIES, LIQUID BIOPSY

227 | CLINICAL UTILITY OF CIRCULATING TUMOR DNA QUALIFICATION AND QUANTIFICATION IN CLASSICAL HODGKIN LYMPHOMA

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Background: Classical Hodgkin lymphoma (cHL), the most common lymphoma in young adults, is a disease of poorly understood heterogeneity. The need for enriching tumor cells before assaying has limited the granularity of its molecular sub-classification. Although the cure rates of patients with cHL have increased over time, new biomarkers are still needed for more precise treatment decision-making in this complex patient population. Patients with cHL frequently have significant amounts of circulating tumor DNA (ctDNA), suggesting an alternative approach for studying this enigmatic tumor.

Methods: IOSI-EMA003 (NCT03280394) is a prospective, observational, multi-center study of adult patients with newly diagnosed cHL aiming at: (i) identifying subgroups of patients with phenotype- and outcome-associated molecular signatures; (ii) testing and validating baseline ctDNA load as a prognostic biomarker; (iii) testing if ctDNA can be used as biomarker for the early identification of chemoresistance. Blood samples were collected at staging and disease response assessment. PET scans were centrally and blindly reviewed. ctDNA was analyzed by using deep targeted and low pass whole genome sequencing to measure ctDNA load, capture mutations and profile ctDNA fragmentation patterns. Single-cell RNA sequencing has been used to deconvolute the composition of the tumor microenvironment.

Results: A total of 215 patients were enrolled. Based on ctDNA fragmentation patterns reflecting chromatin accessibility in the regulatory region of germinal center (GC) B-cell genes, we segregated cHL into two previously unknown subgroups that we named SNCD (for sub-nucleosomal cfDNA) and NCD (for nucleosomal cfDNA). We hypothesized that SNCD cHL stems from a cell that is closer to the GC B-cell differentiation stage than NCD cHL. SNCD cHL and NCD cHL differed in many aspects, including activation induced cytidine deaminase (AID)-hypermutation profile, neoantigen load, immune editing mechanism and response to chemotherapy and checkpoint inhibitors. Clinically, SNCD cHL displayed less sensitivity to both chemotherapy and anti-PD1 antibodies. Immune editing of SNCD cHL points loss of MHC-I, recruitment of Treg and upregulation of LAG3 as prominent immune checkpoint. High load of pre-treatment ctDNA nominated high-risk patients more accurately than clinico-radiological features. In addition, persistence of residual ^{18}FDG avid lesions along with measurable ctDNA after two chemotherapy courses was a better proof of chemoresistance than the sole persistence of residual ^{18}FDG avid lesions. Also, persistence of measurable ctDNA after the end of therapy invariably predicted progression.

Conclusions: Collectively, our results provide a roadmap for cHL subtyping and for the clinical use of ctDNA as a biomarker to aid risk stratification and guide treatment decisions in a more personalized approach.

Encore Abstract - previously submitted to ASCO 2023

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Keywords: Diagnostic and Prognostic Biomarkers, Hodgkin lymphoma, Liquid biopsy

Conflicts of interests pertinent to the abstract.

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228 | DISTINCT MOLECULAR DETERMINANTS OF TREATMENT-FAILURE IN ELDERLY HODGKIN LYMPHOMA IDENTIFIED BY CELL-FREE DNA PROFILING: A LYSA STUDY

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Introduction: While nearly all younger patients (pts) with Hodgkin's lymphoma (HL) are cured with conventional chemotherapy, outcomes are significantly worse in those over age 60. Intriguingly, among older HL pts, those with EBV+ disease have even poorer outcomes (Keegan et al., JCO 2005), yet the biological basis for this phenomenon is not understood. The paucity of malignant cells in HL tumors has hampered genomic studies. Circulating tumor DNA (ctDNA) profiling can overcome these limitations, allowing noninvasive genotyping and risk stratification in HL (Spina et al., Blood 2018; Alig et al., ASH 2022). Here, we use a fully non-invasive approach for genomic profiling of elderly HL pts, focusing on the impact of ctDNA and EBV status on clinical outcomes.

Methods: We profiled 57 pts (64%) from NCT02414568, a prospective, multicenter phase II LYSA-PVAB study of newly diagnosed classical HL >60 years (Ghesquières et al., ASH2019). All pts received 6 cycles of PVAB (prednisone, vinblastine, doxorubicin, and bendamustine). Plasma cfDNA was genotyped using Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq); MRD was monitored using Phased variant Enrichment and Detection Sequencing (PhasED-Seq). Pts were classified into high and low pretreatment ctDNA levels using a threshold of 2.5 log hGE/mL (Alig et al., ASH2022). We defined EBV status either by LMP1 staining of FFPE tumor tissue or by VirCAPP-Seq targeting 180 viral species, where a predefined threshold of 32 genomes/ml was previously validated as 94% accurate (Garofalo et al., ASH 2022).

Results: Pretreatment ctDNA was detected in 94% of pts with a median concentration of 2.2% (MAF), which was significantly correlated with disease burden measured by TMTV ($p = 0.034$). Pts with high pre-treatment ctDNA levels (39%) had significantly worse PFS (HR = 2.3, $p = 0.039$). EBV+ pts also had inferior PFS (HR = 2.2, $p = 0.04$) and OS (HR = 3.1, $p = 0.028$) (Figures A-B). In multivariate analysis, both indices remained independently associated with worse outcomes (HR = 2.5, $p = 0.01$ for pre-treatment ctDNA and HR = 2.7, $p = 0.01$ for EBV status). Interestingly, pre-treatment ctDNA levels did not differ between EBV+ and EBV- tumors ($p = 0.92$), while specific genetic aberrations were significantly associated with respective EBV status (Figure C). Among evaluable pts for MRD monitoring, detection of ctDNA after four cycles of chemotherapy was highly associated with risk of death (Figure D).

Conclusions: Noninvasive ctDNA genotyping and EBV profiling capture distinctive molecular features of elderly HL pts. Both ctDNA burden and dynamics (MRD) and EBV positivity are associated with risk of treatment failure after conventional chemotherapy. Older HL pts, especially those with high baseline ctDNA levels and/or EBV+ tumors, have an exceedingly high risk of treatment failure with conventional chemotherapy, and likely require future risk-adapted strategies.

The research was funded by: NIH/NCI R01 R01CA257655

Keywords: Diagnostic and Prognostic Biomarkers, Genomics, Epigenomics, and Other -Omics, Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

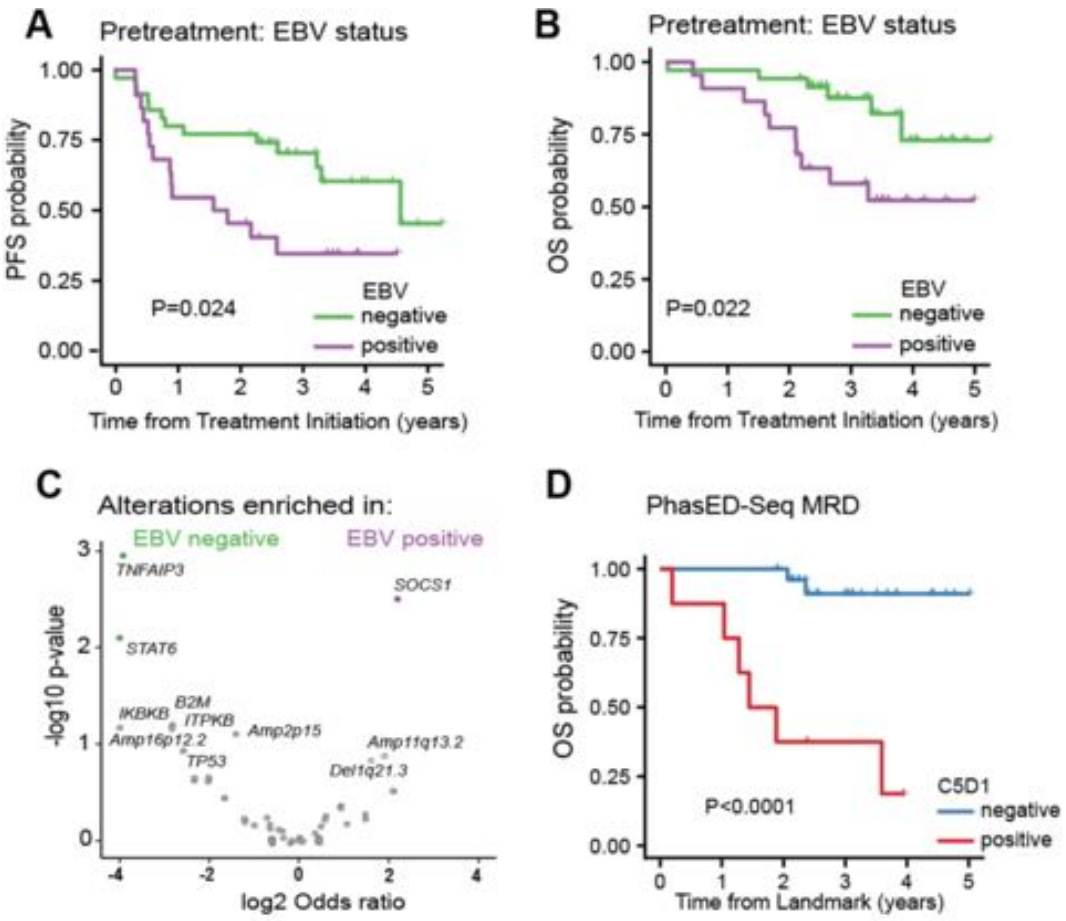

Figure 1: EBV status, and MRD detection on treatment each stratify the outcomes of elderly patients with Hodgkin lymphoma. (A) Progression-free survival (PFS) and (B) Overall survival (OS) stratified by EBV status at time of diagnosis (C) Volcano plot summarizing differentially genetic abnormalities between EBV+ and EBV- patients with significant p-values (P<0.05) are in green and purple (D) MRD status at C5D1 stratifies OS.

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229 | PET INTERIM RESULTS COULD PROMPTLY SELECT FOLLICULAR LYMPHOMA PATIENTS IN NEED OF MAINTENANCE THERAPY. POTENTIAL ADDITIONAL VALUE OF CTDNA

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Background: Follicular Lymphoma (FL) patients frequently achieve long remissions with frontline chemoimmunotherapy (CIT);

nevertheless, a subset of patients will experience early progression and a poor outcome. Fluoro-[18F]-deoxy-2-D-glucose positron emission tomography (PET/CT) and liqBio-MRD performed at the end of CIT induction can identify patients at significantly higher risk of relapse. The aim of this study is to analyze if an interim PET/TC scan could earlier identify high-risk FL.

Methods: We retrospectively identified 121 patients grade 1–3A FL patients who had end of treatment (EOT) and interim PET/CT (after 4 cycles of frontline CIT) between 2012 and 2022. PET/CT were analyzed using Deauville score (DS). Interim cell free DNA (cfDNA) was available in 15 patients, so we could measure MRD by NGS (Jiménez-Ubieto 2023).

Results: Most patients were treated with R-CHOP ($n = 94$; 78%) or rituximab-bendamustine ($n = 24$; 20%). Rituximab maintenance (RM) was used in 87%. Median follow-up was 34 months (3–115). A total of 34 patients (28%) relapsed, 21 (17.5%) within 24 months after CIT (POD24). Histological transformation (HT) rate was 2.5%. The EOT CR rate was 81.5%. PET/CT_{EOT} were predictive of relapse, with 2-years PFS 47% in PET/CT_{EOT}(+) vs. 89% in PET/CT_{EOT}(-) ($p < .001$). On iPET/CT, 41 (34%) patients were PET/CT(+).The estimated 5 year-PFS at was 72% in patients with a negative iPET/CT versus 29% in those with a positive iPET/CT ($p < 0.001$) (Figure 1a). POD24 was found in 34% and 7.6% of patients with iPET/CT(+) and (-)respectively, ($p < 0.001$; HR 7.89). iPET/CT(-) presented a negative predictive value of 94% for POD24. Additionally, in 78 patients with iPET/CT(-) and 93 patients with PET/CT_{EOT}(-) MR was not relevant to predict POD24 (2-year PFS of 93.5%/85.7% and 91.3%/87.5%, respectively) (Figure 1b). Notwithstanding, patients with iPET/CT(+) or $_{EOT}$PET/CT(+) MR had a clear impact in PFS ($p < 0.05$). Additionally SUVmax >3,7 in the iPET/CT(-) was predictive for HT, regardless of being iPET/CT(-) (6-year TFS of 81.9% vs. 100%).

We found trackable mutations in 14 of 15 patients with interim cfDNA MRD analysis (93%). 4/14 patients relapsed after a median of 8.5 months. 3/4 of the relapsing patients had a MRD interim (+) and all the non-relapsing patients a negative MRD test ($p < .001$). Interestingly, of the 10 non-relapsing patients, 2 have iPET/CT(+) (mesenteric masses). A biopsy excluded lymphoma, confirming the false positive value of the PET/CT.

Conclusion: Response assessment by PET/CT at mid-induction can identify FL patients at high risk of failure early on during first line ICT and is able promptly select patients in whom maintenance therapy could be avoided. Clinical trial focus on decreasing treatment should be investigated in iPET/CT(-) patients. Additionally, LiqBIO-MRD is a promising technique able to identify the non-depreciable rates of false positive PET/CT scans.

Encore Abstract - previously submitted to EHA 2023

Keywords: Indolent non-Hodgkin lymphoma, Liquid biopsy, PET-CT

No conflicts of interests pertinent to the abstract.

230 | GENETIC CHARACTERIZATION IN TISSUE AND CFDNA IN MARGINAL ZONE LYMPHOMAS

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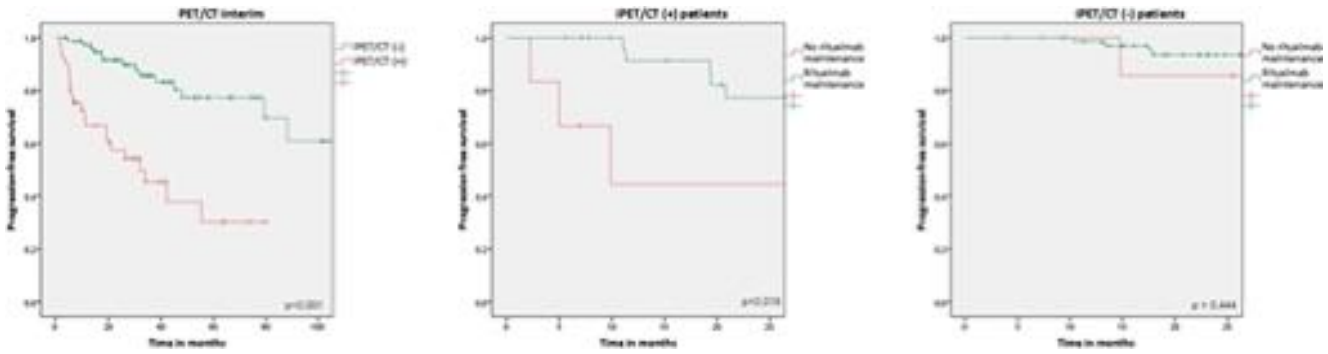
Introduction: Marginal zone lymphoma (MZL) is a group of non-Hodgkin lymphomas that originate from the marginal zone of lymphoid follicles. The WHO/ICC classifies MZL in primary splenic (SMZL), primary nodal (NMZL) and extranodal lymphoma of the mucosa-associated lymphoid tissue (EMZL). Their diagnosis remains difficult as they do not have pathognomonic features. Thus, integration of all the diagnostic available tools including genetic characterization is crucial. Circulating cell-free DNA (cfDNA) analysis is being incorporated in the study of some lymphoma types, but there are no studies in MZL.

Methods: 98 patients were identified between 2014 and 2022 (33 SMZL, 32 EMZL, 6 NMZL, 16 monoclonal non-CLL B cell lymphocytosis (MZ-CBL) and 11 unclassified B-cell lymphoproliferative syndromes (LPS-NOS) with MZL clinico-biological features). DNA for tissue analysis was extracted from the diagnostic samples (54 from



mononuclear cells from peripheral blood, 44 from formalin-fixed paraffin embedded tissues). cfDNA was extracted from paired plasma in 34/98 patients (17 SMZL, 6 EMZL, 4 NMZL, 6 MZ-CBL and 1 LPS-NOS). Libraries were prepared using a custom panel covering 31 MZL-associated genes (Qiagen Hilden, Germany) and sequenced with NextSeq (Illumina, San Diego CA).

Results: We found mutations in 77% of the tissue-based samples (88% SMZL, 59% EMZL, 100% NMZL, 69% MZ-CBL and 91% LPS-NOS). The most frequently mutated genes in SMZL were *KLF2* (27%), *DNMT3A* (24%), *TP53* (21%), *TNFAIP3* (18%), *KMT2D* (18%), *ARID1A* (18%), *CCND3* (12%) and *MYD88* (12%); in EMZL *TNFAIP3* (19%), *TET2* (19%) and *KMT2D* (9%); in NMZL *KMT2D* stood out (50%); in MZ-CBL *DNMT3A* (19%), *CCND3* (19%), *MYD88* (19%) and *TP53* (13%); in LPS-NOS *TP53* (36%), *MYD88* (27%), *CCND3* (18%) and *BIRC3* (18%) (Figure 1). *KLF2* was overrepresented in SMZL ($p < 0.05$) and *TP53* was underrepresented in EZML ($p < 0.05$) compared to the other MZL types. Overall, 14/98 patients were *TP53*mut (8/14 multi-hit, 7 with cooccurrence of 17p deletion and 1 with 3 mutations). When comparing SMZL and MZ-CBL, *KLF2* mutations defined SMZL over MZ-CBL (9/33 vs. 0/16, $p < 0.05$). The ability to find any tissue mutation in cfDNA was 94% in SMZL, 33% in EMZL, 100% in NMZL and 100% in MZ-CBL. Besides, in 76% of SMZL we detected the 100% of the tissue mutations. cfDNA revealed mutations not present in the tissue in 41% of SMZL, 33% of MALT, 100% of NMZL and 0% of MZ-CBL (86%, 50% and 50% of these mutations respectively were found in clonal hematopoiesis (CH) potentially related genes: *DNMT3A*, *TET2*, *ASXL1* and *TP53*).

Conclusions: NGS allows the molecular characterization of patients with MZL. MZ-CBL share a similar genetic profile to SMZL but with lower *KLF2* mutations. *TP53* involvement (in many cases multi-hit) seems frequent in MZL except for EMZL. cfDNA is a useful tool for the genetic characterization of MZL where apart from detecting tissue mutations we can identify additional mutations and CH not visible in the tissue.

The research was funded by: FIS/FEDER PI19/00034, SEHH, SCHH

Keywords: Diagnostic and Prognostic Biomarkers, Genomics, Epigenomics, and Other -Omics, Indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

231 | SERIAL CIRCULATING TUMOR DNA SEQUENCING REVEALS CLONAL DYNAMICS AND CAN OFFER TREATMENT GUIDANCE IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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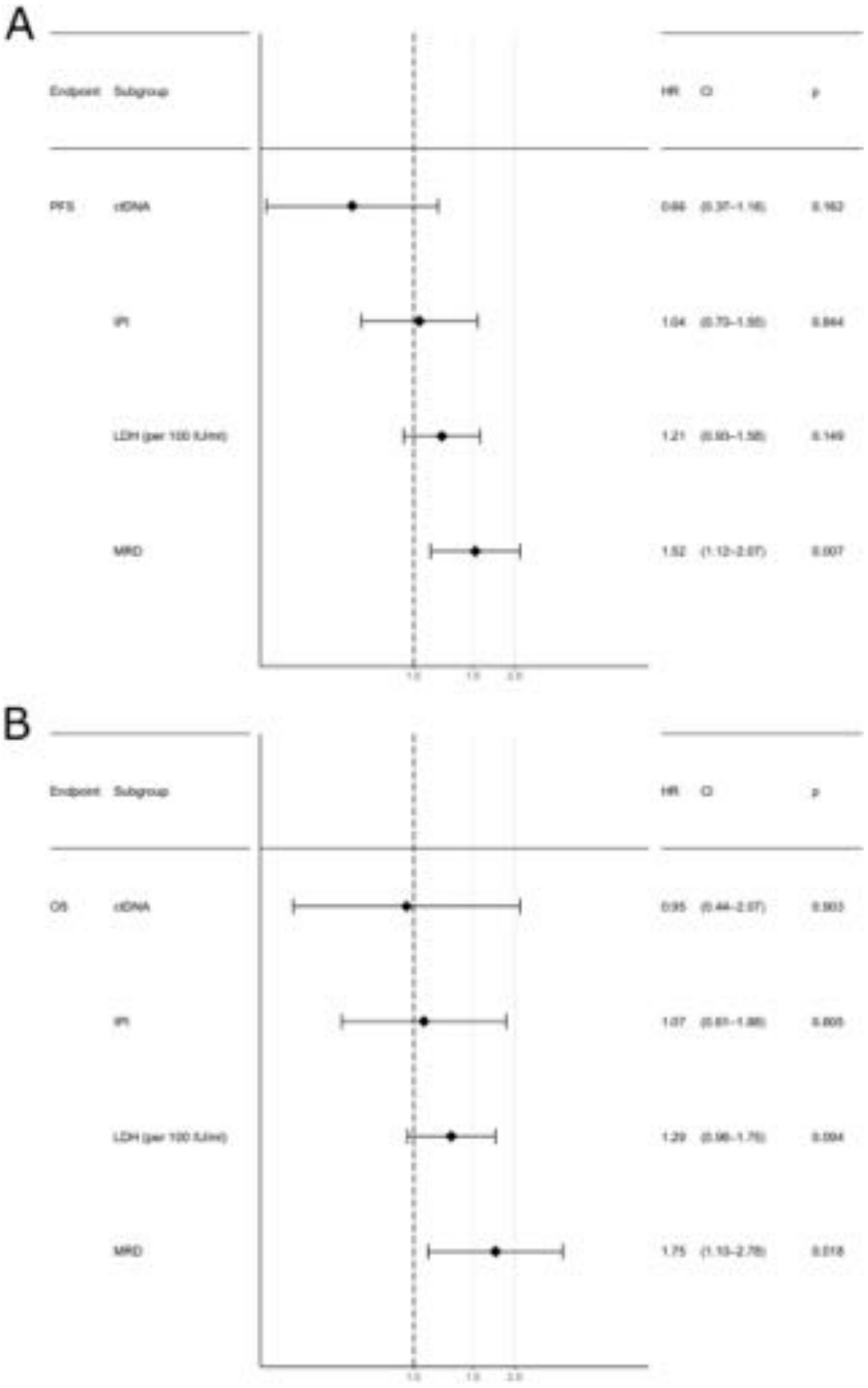
Introduction: Despite recent advances in the treatment of relapsed/refractory (rr)DLBCL, most patients still face progression and death. Current clinical challenges include allocation of patients to the

Figure 1. Heatmap plot showing all the pathogenic/presumed pathogenic mutations detected.

variety of available treatment options and early detection of insufficient response. While recent evidence suggests utility of circulating tumor (ct)DNA derived biomarkers for CAR-T cell treated patients (Sworder et al, 2023), data on ctDNA in diversely treated rrDLBCL is scarce.

Methods: We applied ctDNA sequencing to 197 blood samples of consecutive patients with rrDLBCL presenting at the University Hospitals Cologne and Essen, Germany. An extension of the cohort to >300 samples is ongoing. Samples were analyzed as previously described (Sobesky et al., 2021; Heger et al., 2022).



Results: Most patients presented with stage III/IV disease (88.4%), intermediate (58.1%) or high risk (31.4%) international prognostic index (IPI), and received CAR-T cells, high-dose chemotherapy and autologous stem cell transplantation, or other approved treatments. The mean ctDNA concentration at baseline closely correlated with lactate dehydrogenase (LDH) levels ($R = 0.61$, $p < 0.001$). Mutations were most frequently detected in *IGLL5* (31.4%), *KMT2D* (30.2%), and *TP53* (24.2%), matching previous reports (Chapuy et al, 2018; Meriranta et al, 2022; Sworder et al, 2023). No significant association between the most frequently mutated genes and outcome was observed. When assessing minimal residual disease (MRD) dynamically during and after treatment, we observed significantly impaired progression-free (PFS, $p = 0.025$) and overall survival (OS, $p = 0.019$) in MRD-positive patients. In a multivariable model, MRD $\log_{10}$ levels had a significant impact on PFS (HR 1.52, 95% CI: 1.12–2.07, $p = 0.007$) and OS (HR 1.75, 95% CI: 1.10–2.78, $p = 0.018$), while LDH, IPI and ctDNA concentration at baseline did not (Figure 1). In patients with ≥5 samples available, assessment of clonal evolution revealed at least two different patterns of clonal dynamics—one consisting of reemergence of a largely similar clone at relapse and one reflecting expansion of one or more subclones acquiring novel genetic lesions, such as *TP53* mutations. Examining clonal evolution in the context of treatment choices revealed subclone-specific treatment effects. For example, in a patient with chemo-resistant disease, CAR-T cells were able to eliminate all but one clone. Intriguingly, this clone drove early progression of disease but was successfully overcome by allogeneic stem cell transplantation.

Conclusions: Risk stratification strategies established in previously untreated DLBCL are not transferable to rrDLBCL. In contrast, ctDNA-based detection of MRD allows for reliable identification of patients at high risk for disease progression. Studying longitudinal clonal evolution patterns with serial ctDNA sequencing might help to guide treatment.

The research was funded by: J.M.H. was supported by a MD Research Stipend of the Else Kröner Forschungskolleg Clonal Evolution in Cancer, University Hospital Cologne, Cologne, Germany. Sequencing infrastructure was supported by DFG Research Infrastructure as part of the Next Generation Sequencing Competence Network [INST 216/981-1], and next-generation sequencing (NGS) analyses were carried out at the production site WGGC Cologne. The research was partly funded by grants BO5316/3-1 and BO5316/2-1 from the Deutsche Forschungsgemeinschaft (DFG) as well as a grant by the Frauke Weiskam, Christel Ruranski Foundation, and Else Kröner Fresenius Stiftung (Kolleg, 2016).

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Liquid biopsy, Minimal residual disease

Conflicts of interests pertinent to the abstract.

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Educational grants: Kite-Gilead, Novartis

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Research funding: Novartis, Merck Sharp & Dohme, Takeda
Educational grants: AbbVie, AstraZeneca, Kite-Gilead, Merck Sharp & Dohme, Takeda, Novartis

S. Borchmann
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232 | EVALUATION OF CTDNA IN A PHASE I/II TRIAL IN RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA OF EPCORITAMAB, A NOVEL, SUBCUTANEOUS CD3XCD20 BISPECIFIC T-CELL–ENGAGING ANTIBODY

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Introduction: The emergence of novel, more potent therapeutics in the treatment of patients with large B-cell lymphoma (LBCL) has resulted in higher rates of responses and highlighted a need for additional methods, such as minimal residual disease (MRD), to determine the depth and quality of response and potentially guide duration of treatment. Epcoritamab (DuoBody®-CD3xCD20) is a subcutaneously (SC) administered bispecific antibody (bsAb) that simultaneously binds to CD3 on T cells and CD20 on malignant B cells, inducing activation and cytotoxic activity of T cells for the killing of malignant CD20 B cells. In the pivotal epcoritamab trial, a correlation was demonstrated between MRD by clonoSEQ® (Adaptive Biotechnologies) and long-term outcomes. These findings led to additional analyses to further clarify the clinical use of ctDNA.
As the evaluation of ctDNA in LBCL has not been standardized, we have expanded our investigation of the utility of ctDNA measurements from the initial analysis with the clonoSEQ assay to the

AVENIO ctDNA assay (Roche). Here we present additional exploratory analyses of ctDNA using the AVENIO assay.

Methods: Patients with relapsed/refractory (R/R) LBCL enrolled in EPCORE NHL-1 expansion phase (NCT03625037) received SC epcoritamab administered in 28-d cycles. ctDNA was measured using the clonoSEQ and AVENIO ctDNA assays at protocol-specified timepoints. Specimens were collected in EDTA and Streck cfDNA tubes, respectively, based on the recommended sample type at the time of study initiation. Plasma ctDNA levels were quantified per sample as count per mL (CPM) and mutant molecules per mL (MMPM) for clonoSEQ and AVENIO, respectively.

Results: ctDNA quantification was concordant between the assays when within the dynamic range of the clonoSEQ assay (>80% in paired samples tested); however, a greater sensitivity of the AVENIO assay was observed, allowing further exploratory analyses of ctDNA using this platform.

Consistent with prior observations, baseline ctDNA levels were associated with key clinical parameters, including LDH, TMTV, ECOG, and IPI. In patients who responded to epcoritamab, ctDNA levels decreased rapidly, with the majority of patients achieving CR having a deep ctDNA response by C3D1. Additional patients achieved MRD-negative status at later evaluations with continued therapy. MRD-negative status at C3D1, measured as absolute or relative change from baseline, was associated with longer progression free survival (PFS) and sustained MRD negativity throughout the duration of treatment.

Conclusions: To our best knowledge, this is the first comprehensive, prespecified report of ctDNA data for patients treated for R/R LBCL with a CD3-directed bsAb. These findings warrant additional analyses of the utility of ctDNA in patients with R/R DLBCL. Further evaluations are ongoing in additional PhII/III epcoritamab clinical trials.

The research was funded by: Genmab A/S and AbbVie

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Liquid biopsy, Minimal residual disease

Conflicts of interests pertinent to the abstract.

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Educational grants: AbbVie, Amgen, BMS/Celgene, Cellectis, Gilead Sciences, Kite, Novartis, Roche

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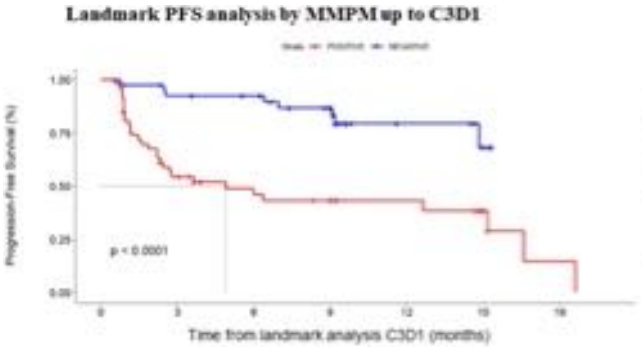

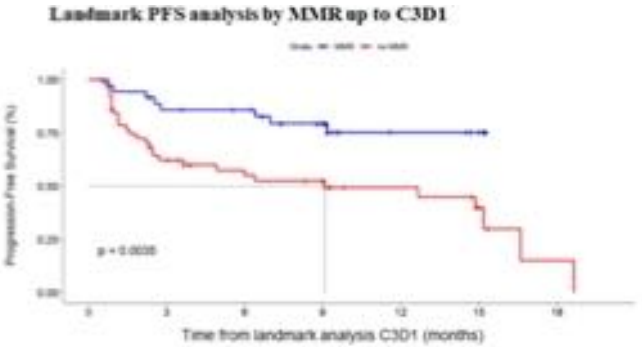

Landmark MRD PFS Analysis

As the majority of the patients who achieved MRD negative status was by cycle 3 day 1, this protocol-specified time point was selected for landmark analysis. Since the criteria for MRD has not been established for RR DLBCL, MRD was explored using a cut-off of < 1 mutant molecule per ml (MMPM) and by having a major molecular response (MMR) of ≥ 2.5 log reduction at C3D1. Patients who had a PFS event or were censored before cycle 3 day 1 were excluded.

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Research funding: Celgene, Genentech, Genmab, Incyte, Janssen, Novartis, Roche, Takeda (All Paid to Institution)

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Honoraria: Takeda, BMS/Celgene, Novartis, Janssen, MSD, Amgen, GSK, Sanofi, Kite
Research funding: Takeda
Educational grants: Takeda, BMS/Celgene, Roche
Other remuneration: Takeda, BMS/Celgene, Novartis, Janssen, MSD, Amgen, GSK, Sanofi, Kite: Speakers Bureau

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233 | CIRCULATING TUMOUR DNA CONCENTRATION AND GENETIC CLASSIFICATION IMPROVE RISK STRATIFICATION IN NEWLY DIAGNOSED PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is a genetically heterogeneous disease with poor outcomes for the 40% of patients who relapse or are refractory to upfront therapy, and current prognostic tools are unable to identify many of those patients. Recently, novel prognostic biomarkers like genetic classification and circulating tumor DNA (ctDNA) have been developed. Here we explore the value these biomarkers to improve prognostic stratification in DLBCL.

Methods: DNA was extracted from 2 to 5 ml of plasma and formalin-fixed paraffin-embedded (FFPE) tumor tissue obtained at diagnosis from patients with DLBCL treated with R-CHOP-like regimes. Samples were sequenced in an Illumia NovaSeq using a panel of 112 genes that are recurrently mutated in lymphoid neoplasms, and variants were called using a pipeline that follows GATK best practices. Genetic subtype (GS) was determined using LymphGen tool, excluding A53, as copy number variation data was unavailable. ST2, EZB MYC negative and BN2 subtypes were considered favorable, while N1, MCD, EZB *MYC* positive and other were considered unfavorable. ctDNA levels were reported as haploid genome equivalents per mL of plasma and expressed as a base 10 logarithm (log hGE/mL)

Results: We included 46 patients with median age of 64.8 years, 58% advanced stage (III-IV) and 65% germinal center DLBCL by Hans's algorithm. Somatic mutations were detected in FFPE in all patients and in ctDNA in 40 (87%) patients. Most frequently mutated genes were *KMT2D*, *CREBBP*, *TP53*, *ARID1A*, *MYD88* and *CARD11*.

The sensitivity of ctDNA to detect mutations present in paired FFPE samples was 66% (for all variants) and 74.5% (for variants with >5% allelic frequency in FFPE samples). 67.4% of patients were successfully classified by LymphGen, with a concordance between ctDNA and FFPE of 84.7%. Patients without detectable ctDNA presented localized disease (Ann Arbor stage I) and low DNA concentration in plasma (<15 ng/ml).

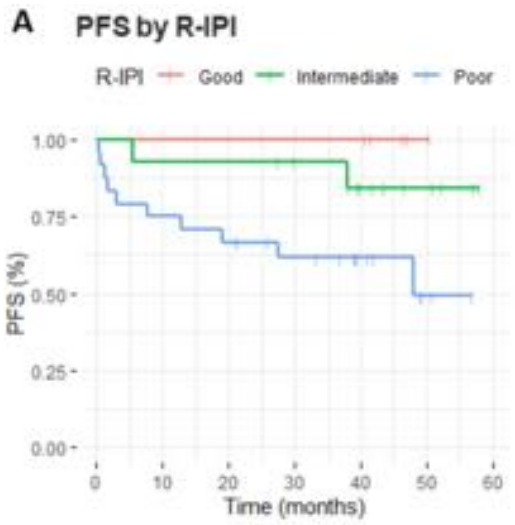
In our cohort, 24 patients presented a poor R-IPI score with a 3-year progression-free survival (PFS) of 61.5% (Figure 1A). These patients were further stratified by ctDNA levels and GS, and those unfavorable GS or ctDNA concentration >4 log hGE/ml presented worse PFS and OS than without risk factors a 3-year PFS of 34.6% and 90.9%, respectively (Figure 1B).

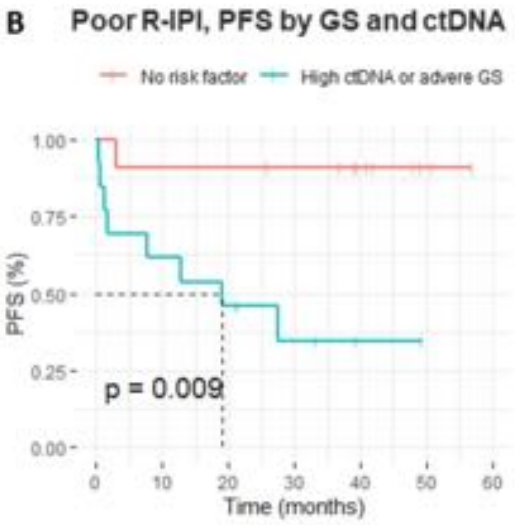
Patients were classified into three groups according IPI score modified by ctDNA levels (Figure 1C), with a 3-year PFS of 94.7%, 81.2% and 18.8%, and a 3-year overall survival (OS) of 100%, 87.5% and 37.5%, respectively (Figure 1D–E).

Conclusions: Our results suggest that genetic classification and ctDNA concentration can improve risk stratification in newly diagnosed patients with DLBCL treated with R-CHOP-like regimes.

Keywords: Diagnostic and Prognostic Biomarkers, Genomics, Epigenomics, and Other -Omics

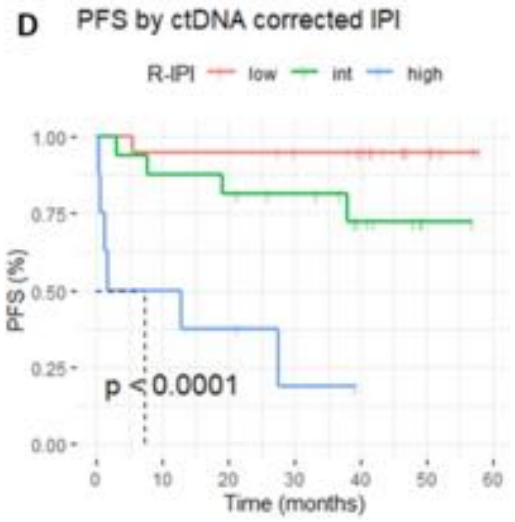
No conflicts of interests pertinent to the abstract.

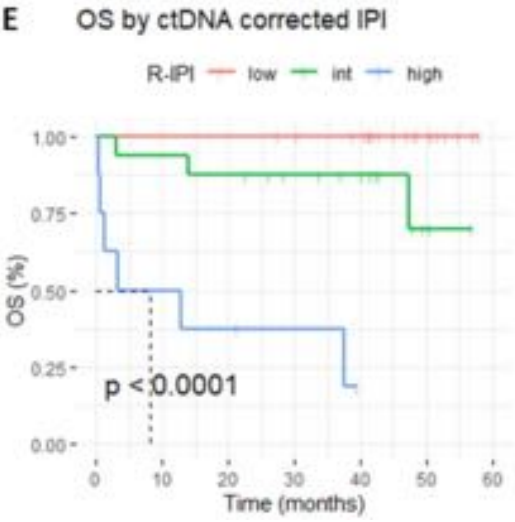




C **IPI score:** ECOG >2, >1 EN location, age >60 years, elevated LDH, stage III or IV
ctDNA correction:
- >4 log10 hGE: +1p
- <2.5 log10 hGE -1p

Risk Group	Points	3y-PFS	3y-OS
Low	0-2	94.7%	100%
Intermediate	3-4	81.2%	87.5%
High	5-6	18.8%	37.5%





234 | **CIRCULATING TUMOR DNA (CTDNA) BY CLONOSEQ TO MONITOR RESIDUAL DISEASE AFTER AXICABTAGENE CILOLEUCEL (AXI-CEL) IN LARGE B-CELL LYMPHOMA (LBCL)**

B. R. Miles[1], D. Mao[1], S. Vardhanabhuti[1], C. To[1], M. Schupp[1], S. Shahani[1], H. Xu[1], J. L. Munoz[2], J. Westin[3], R. Shen[1], S. Filosto[1]
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Introduction: Most patients (pts) with LBCL respond to axi-cel, but many will eventually experience disease progression (Jacobson et al. *JCO*. 2020). Monitoring of ctDNA from blood, a minimally invasive diagnostic tool, has been used to assess measurable residual disease (MRD) with prognostic value, including in pts with diffuse LBCL treated with axi-cel in the third line of therapy (3L; Frank et al. *JCO*. 2019). Here, we explored the value of ctDNA to predict outcomes in LBCL after axi-cel across lines of treatment.

Methods: Pts with LBCL from ZUMA-12 (Phase 2 axi-cel in 1L), ZUMA-7 (Phase 3 axi-cel or standard of care [SOC] in 2L), and ZUMA-14 (Phase 2 axi-cel + rituximab in 3L) were included. All studies included initial MRD testing ≈30 days post axi-cel infusion. ClonoSEQ MRD assay (limit of detection ≈0.0001%–0.00001%) was used to define the lymphoma B-cell clonotype in formalin-fixed, paraffin-embedded (FFPE) biopsy tissue prior to axi-cel infusion and to track ctDNA in blood after treatment. Positive predictive value (PPV; MRD+ pts who relapsed or were nonresponders/total MRD+ pts ×100) and negative predictive value (NPV; MRD- pts in ongoing

response/total MRD- pts ×100) were assessed at Day 28, Month (Mo) 3, and Mo 5 for 3L; Days 50, 100, 150, Mo 9, and Mo 24 for 2L; and Day 28, Mo 3, and Mo 6 for 1L.

Results: In 3L, the PPV at Day 28 was 88% (7/8) and NPV was 83% (10/12). NPV remained 83% at Mo 3 (10/12) and increased to 100% (8/8) at Mo 5. Overall, 83% (5/6) of relapsed pts had MRD detected at any time; of those 5, 100% (5/5) had MRD detected at any time prior to or at progression with a median detection of 43 days prior to progression.

In 2L, the MRD+ detection rate among evaluable pre-infusion samples was only 69% (11/16). At Day 50, PPV was 100% (7/7) in the SOC arm, whereas it was only 57% (4/7) in the axi-cel arm. PPV increased over time in the axi-cel arm, reaching 100% by Mo 9 (2/2). At Day 50, NPV was 53% (8/15) in the axi-cel arm and 38% (5/13) in the SOC arm. Overall, 47% (9/19) of relapsed pts on the axi-cel arm had MRD detected at any time; of those 9, 78% (7/9) had MRD detected prior to or at progression with a median of 35 days prior to progression.

In 1L, most pts (11/14) remained in ongoing response by data cut off. The PPV at Day 28 was 50% (1/2): of the two pts who had detectable MRD at Day 28, one subsequently became MRD negative at Mo 3 yet relapsed just after Mo 3, while the second became negative by Mo 3 and had ongoing response up to Mo 24. The NPV at Day 28 was 88% (7/8).

Conclusions: The prognostic value of MRD assessment by clonoSEQ varied across lines of therapy in pts with LBCL treated with axi-cel. A relatively high rate of undetectable MRD at baseline in the 2L setting and prior to relapse in the 2L and 1L settings warrants exploration of more sensitive ctDNA monitoring methods.

Encore Abstract - previously submitted to ASCO 2023

The research was funded by: The research was funded by Kite, a Gilead Company

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Diagnostic and Prognostic Biomarkers

Conflicts of interests pertinent to the abstract.

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Research funding: ADC Therapeutics, AstraZeneca, Bristol-Myers Squibb, Genentech, Gilead, Kite, a Gilead Company, Morphosys/Incyte, MonteRosa, Novartis

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Employment or leadership position: Employment with Kite, a Gilead Company
Stock ownership: Kite
Other remuneration: Patents, royalties, other intellectual property from Tusk Therapeutics.

235 | CLINICAL IMPLICATIONS OF CTDNA IN PREDICTING THE GENETIC SUBTYPE, CNS INVOLVEMENT AND OUTCOMES OF NEWLY DIAGNOSED DIFFUSE LARGE B CELL LYMPHOMA

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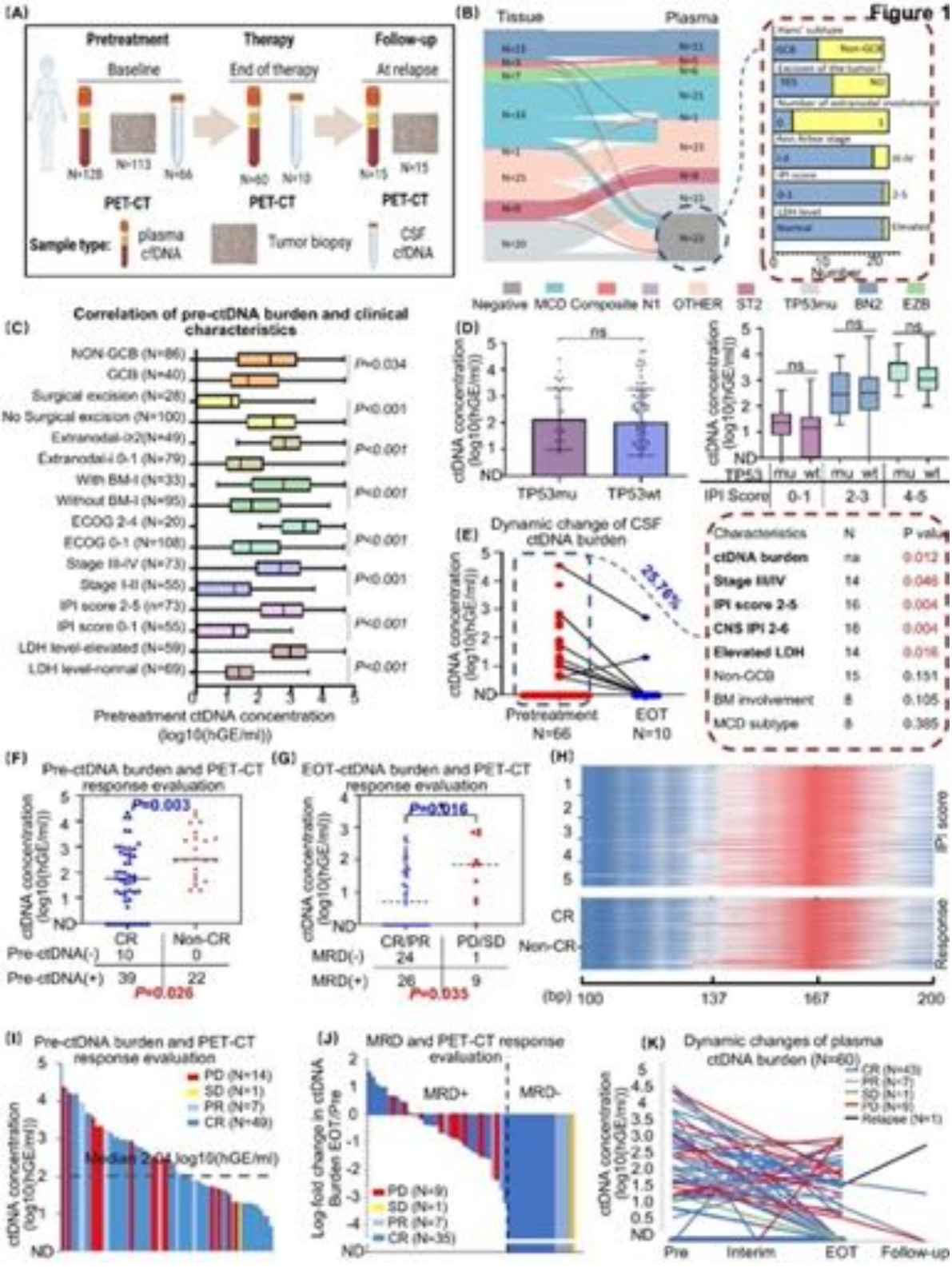
Introduction: Diffuse large B cell lymphoma (DLBCL) is the most common entity of non-Hodgkin lymphoma with high clinical and biological heterogeneity. The value of circulating tumor DNA (ctDNA) in DLBCL need to be further explored.

Methods: A total of 128 DLBCL patients (pts) were included in our study. We obtained plasma, tissue and cerebrospinal fluid (CSF) samples before and after first-line therapy for a lymphoma-specific sequencing.

Results: The detailed sample collections were shown in Figure 1A. We compared genetic subtypes based on the mutations detected respectively in tissue and plasma, the overall coincidence rate was 77.8%. The characteristics of pts with negative pretreatment ctDNA



(pre-ctDNA) burden were shown in Figure 1B. Pts with elevated lactate dehydrogenase (LDH) level ($P < 0.001$), higher international prognostic index (IPI) score ($P < 0.001$), advanced stage ($P < 0.001$), ECOG 2–4 ($P < 0.001$), multiple extranodal involvement ($P < 0.001$), non-GCB subtype ($P = 0.034$) and no surgical excision of the tumor ($P < 0.001$) had significantly higher pre-ctDNA burden (Figure 1C). However, no significant differences of pre-ctDNA burdens were identified between TP53 mutation and TP53 wild type groups or among different genetic subtype groups (Figure 1D).

A significantly high CNS involvement (CNSi) rate (25.8%, 17/66) was detected by pretreatment CSF. Among the 17 pts, only 3 pts (17.6%) had typical radiographic findings or CSF cytomorphology. CNSi was significantly associated with clinical characteristics, including advanced stage ($P = 0.046$), elevated LDH level ($P = 0.016$), high IPI ($P = 0.004$), CNS-IPI score ($P = 0.004$) and higher pre-ctDNA burden ($P = 0.012$) (Figure 1E). Among the 17 CNSi pts detected by CSF ctDNA, 15 pts received BTK inhibitor or high-dose methotrexate (HD-MTX) treatment. Six pts achieved CSF clearance among the 8 pts who had CSF ctDNA detection at the end of therapy (EOT).

As regard to pretreatment cell free DNA fragmentation patterns, all samples were characterized by a prominent mono-nucleosomal fragments abundance (167 bp), whereas the samples with high IPI scores or non-complete response (CR) at the EOT had a more prominent shift towards shorter cfDNA size (Figure 1H). A significant difference of pre-ctDNA burden existed between CR and non-CR group, and pre-ctDNA burden negative group presented with higher CR rate at the EOT (Figure 1F and 1I). Furthermore, minimal residual disease (MRD) negative (EOT-ctDNA negative) group was associated with higher remission rate (Figure 1G and 1J). Among the 60 pts who had plasma samples at the EOT, all but 1 of the 25 pts with MRD negative achieved CR. All 9 pts who experienced progressive disease (PD) were all MRD positive. However, not all the pts with CR achieved MRD negative (Figure 1K).

Conclusions: CtDNA is a promising noninvasive tool for genetic subtype classification, CNSi assessment and prognosis prediction for newly diagnosed DLBCL.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers

No conflicts of interests pertinent to the abstract.

236 | MOLECULAR CHARACTERIZATION OF DIFFUSE LARGE-B CELL LYMPHOMA BY LIQUID BIOPSY AT DIAGNOSIS AND DURING FOLLOW-UP. OBO "EUROCLONALITY-NGS GROUP" & "GRUPO COLABORATIVO LINFOMAS Y SLP DE CYL"

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Introduction: Circulating tumor DNA (ctDNA) is the leading liquid biopsy approach in lymphomas for genotyping and minimal residual disease (MRD) detection. In the present study we evaluated the clinical and prognostic value of ctDNA in a series of DLBCL patients at baseline and during the first-line treatment using a NGS approach targeting single nucleotide variations (SNVs) and structural variants (SVs, both translocations and immunoglobulin gene rearrangements). In parallel responses were monitored by metabolic imaging.

Methods: Blood samples from 68 DLBCL patients homogeneously treated with R-CHOP were collected at diagnosis. Paired tumour tissue biopsy was available in 19 cases for validation purposes. MRD studies after 2-cycles of treatment were performed in 59 cases.

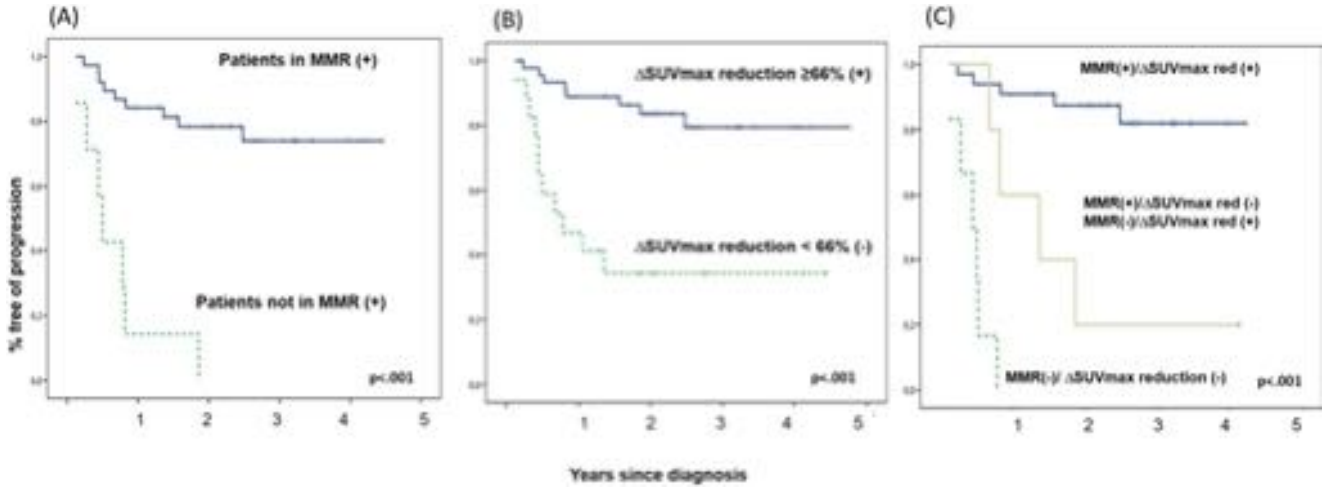
QIAamp circulating nucleic acid kit™(Qiagen) was used for cell free DNA (cfDNA). Library preparation was performed using the Kapa Hyper Prep Kit™ (Roche) with a minimum input of 30 ng of cfDNA and hybrid selection was performed with EuroClonality-NDC panel (Univ8 Genomics). Pooled libraries were sequenced on the NextSeq 550 (Illumina) and results were analyzed with customized bioinformatic pipeline.

ctDNA concentrations (hGE/ml) during treatment were normalized to basal levels at diagnosis and expressed as a log-fold change. We employed 2.5-log drop in ctDNA after 2-cycles of treatment as a threshold to define patients achieving major molecular response (MMR).

Results: Paired tumour tissue biopsies displayed a molecular profile highly concordant to ctDNA: 88% SNVs (VAF >15%), 95% for translocations and 84% for *IGH* rearrangements.

The NGS capture panel was able to identify a molecular marker in 62 out of 68 (91%) ctDNA samples at diagnosis. The median amount of ctDNA was 2.9 log hGE/ml [range 1.9–4.7]. High levels of ctDNA significantly correlated with elevated LDH ($p < 0.001$), advanced Ann-Arbor stages [(III-IV) vs. (I, II) $p = 0.028$], high risk IPI [(3, 4, 5) vs. (0, 1, 2) $p = 0.021$] and a trend to shorter PFS than those with low levels (80% vs. 62% at 2 years; p = NS).

We obtained valuable NGS data for molecular response assessment after 2-cycles of treatment in 45 cases. Based on the 2.5-log drop in ctDNA, 38 cases achieved MMR and 7 cases did not. PFS curves displayed statistically significant differences among those achieving MMR *vs.* those not achieving MMR (2 yr PFS of 74% vs. 0%, $p < 0.001$; Figure 1A). Similarly, more than 66% reduction in ΔSUVmax



by PET/CT (2 yr PFS of 84% vs. 34%; $p < 0.001$ Figure 1B) identified two subgroups with different prognosis. Combining both approaches MMR and ΔSUVmax reduction, a better stratification was observed (2 yr PFS of 87% vs. 20% vs. 0%, $p < 0.001$; Figure 1C).

Conclusions: The Euroclonality-NDC panel allows the detection of a molecular marker in the ctDNA in >90% of DLBCL. ctDNA reduction at 2 cycles and its combination with PET interim allows the identification of patients with significantly different PFS. These results should be validated in larger series.

Encore Abstract - previously submitted to regional or national meetings (up to <1'000 attendees)

The research was funded by: This study has been funded by Instituto de Salud Carlos III (ISCIII) through the projects "PI13/02644" "PI21/00109" and co-funded by the European Union. Addtional funding: GRS 2271/A/2020, FUCALHH 2017,GRS 1652/A/17, GRS 1661/A/17 and Gilead GLD18/0063.

Keyword: Liquid biopsy

No conflicts of interests pertinent to the abstract.

237 | PERSONALIZED MONITORING OF CIRCULATING TUMOR DNA BY A SPECIFIC SIGNATURE OF TRACKABLE MUTATIONS AFTER CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY IN NON-HODGKIN B CELL LYMPHOMA

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Introduction: CAR-T therapy has produced a paradigm shift for the treatment of non-Hodgkin B-cell lymphomas (NHBcL). Strategies to optimize the disease surveillance after this therapy are increasingly necessary. This study aims to explore the potential value of a circulating tumor DNA (ctDNA) monitoring with an innovative signature of personalized trackable mutations.

Methods: Twenty-five NHBcL treated with CD19 CAR-T cell therapy were included in 2 academic hospitals (10 follicular lymphoma-FL and 15 large B-cell-LBCL). Clinical outcomes are shown in Table 1. Genomic profiling was performed in relapse FFPE biopsy to detect somatic mutations by a custom capture enrichment panel (Twist, USA) of 134 genes (NextSeq, Illumina) suitable for liquid biopsy MRD monitoring (LiqBio-MRD) (Jiménez Ubieto 2023).

A total of 93 peripheral blood samples were collected to isolate plasma at day +7, +14, +30, +90 and before progression (45 LBCL and 48 FL). The potential VAF sensibility of the test was below 10^{-4}. PET/CT examinations were performed on day +90, +180, +365 and every 6 months in FL, and the same but also adding day +30 for LBCL.

Results: We found 136 trackable mutations suitable for MRD monitoring in all the patients (mean of 5.44 per patient). The most frequently mutated genes were CREBBP (80%), KMT2D (50%) and EP300 (30%) in FL and CREBBP (43.7%), KMT2D (37.5%), TP53 (37.5%) and TNFRSF14 (31.2%) in LBCL.

The dynamics of the baseline mutations in the 25 patients were shown in Figure 1. Among the 15 patients who progressed, 11 presented LiqBio-MRD + result (ctDNA) in all samples before progression. Regarding the remaining: DLCBL2 had a single in relapse; DLCBL7 had two negative MRD samples and subsequently a LiqBio-MRD + sample before progression; and FL107 had one negative MRD sample and subsequently a LiqBio-MRD + sample before progression. All LBCL patients who didn't progress achieved persistent MRD−status since month one. However, 4 out of 6 FL patients who had MRD + status at month one became negative in the following samples and didn't progress. As shown in Figure 2, ctDNA surveillance exhibited high agreement with the PET-CT results. Remarkably,

	LBCL (n=15)	FL (n=10)
Clinical variables		
Age, years (mean, range)	56 (29-75)	58 (38-69)
Gender (nº, %)		
Male	9 (60)	6 (60)
Female	6 (40)	4 (40)
anti-CD19 CART		
Axi-cel	9 (60)	2 (20)
Tisa-cel	6 (40)	8 (80)
Follow-up, (mean-range)	days. 404 (31-1147)	months. 36 (18-58)
Outcome (nº)		
Progression	9	0
Relapse	2 (one only CNS)	2
Complete response rate (%)		
3 months	40	100
PFS (%)		
1 months	60	100
3 monhts	40	100
1 year	25	80

Table 1. Baseline demographic and outcome of patients.

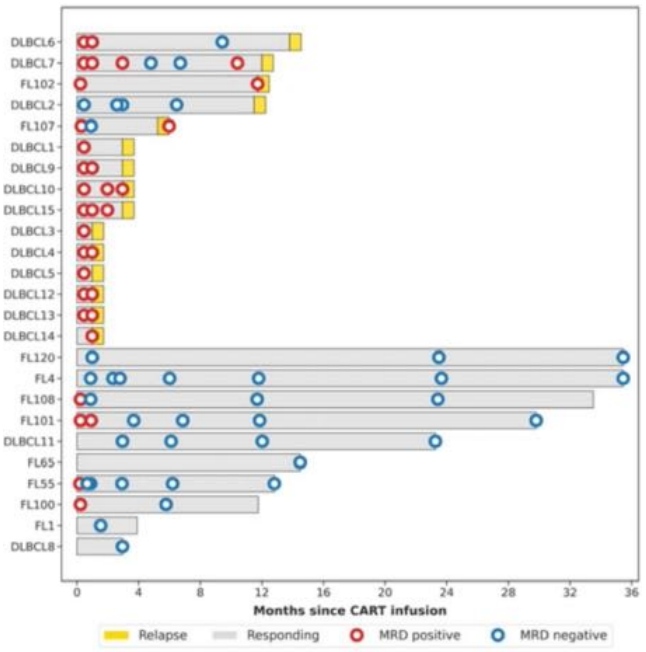

Figure 1. Swimmer plot of the different follow-up time-points screened for all patients under CART treatment.

33/36 negative PET-CTs (91.7%) were consistent with a LiqBio-MRD−determination, and 11/13 positive PET-CTs (85%) were LiqBio-MRD +. Patients with PET-CT positive but LiqBio-MRD−(n = 2) resulted as false positive PET/CT (cervical mass confirmed by biopsy and mesenteric mass becoming negative in the next PET/CT analysis). Furthermore, patients with PET-CT negative and LiqBio-MRD + (n = 3) presented progression.

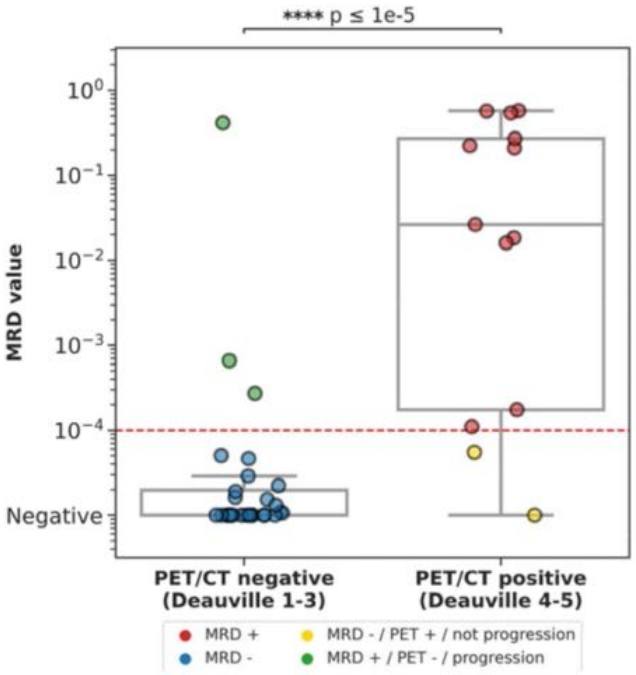

Figure 2. Correlation of Liqbio-MRD and PET/CT.

Conclusions: In the case of FL undergoing CAR T-cell, this is the first in FL study demonstrating the utility of a non-invasive personalized MRD evaluation in liquid biopsy. Our LiqBio-MRD test is able to predict LBCL and FL outcome and could be of high utility to detect false positives or negatives PET/CT assessments during follow-up.

Keywords: Cellular therapies, Liquid biopsy, Minimal residual disease

No conflicts of interests pertinent to the abstract.

238 | LIQUID BIOPSY FOR EARLY, NON-INVASIVE DIAGNOSIS OF EBV-POSITIVE BURKITT LYMPHOMA IN RESOURCE LIMITED SETTINGS

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Introduction: Burkitt Lymphoma (BL) is an aggressive B- cell malignancy that is highly prevalent in Sub-Saharan Africa (SSA), contributing to 50% of paediatric cancer. In this region where Epstein Barr virus (EBV) is endemic, more than 90% of cases of BL are associated with EBV (EBL). Survival rate for BL in SSA is less than 50%, largely due to late presentation of advanced disease coupled with mis- or delayed diagnosis all of which delays initiation of effective chemo-immunotherapy. An accurate diagnosis of BL via immunohistochemistry is dependent upon obtaining a tissue biopsy. The limited number of histopathologists, infrastructural challenges and lack of reagents for immunohistochemistry are largely implicated in the diagnostic delays resulting from this diagnostic modality. We developed a liquid biopsy test for the detection of EBL that complements tissue histopathology while circumventing these challenges.

Methods: We designed a custom sequencing panel of approximately 140 kb targeting genes commonly mutated in BL, the full *MYC* gene and its common translocation partners and three EBV genes (*EBER1*, *EBER2* and *EBNA2*). Our sample set of 150 samples was split into a training cohort and a test cohort. The training cohort was used to develop the test, which was then validated on the test cohort. Three diagnostic models were tested using logistic regression; a clinical model (with clinical parameters predictive of EBL), a liquid biopsy model (using *MYC* translocation and the presence/absence of EBV DNA) and a combined model (combining the clinical and the liquid biopsy parameters). The model with the best performance was then validated on the test cohort and performance assessed by means of AUC, sensitivity and specificity. Histopathology diagnosis with a limited IHC panel was used as the gold standard.

Results: In the training cohort, the combined model performed best (AUC: 0.95, sensitivity 87% and specificity 83%), followed by the liquid biopsy model (AUC: 0.90, sensitivity 93% and specificity of 74%). Upon validation using the test cohort, the combined model had an AUC of 0.96 (CI: 0.4, 1.0) with sensitivity of 92% and specificity of 82%.

Conclusion: The presence of clinical features characteristic of EBL in children and young adults in SSA, combined with results from a liquid biopsy test using the presence of EBV DNA and *MYC* translocation, is diagnostic of EBL with appreciable sensitivity and specificity. This technology has the potential of revolutionizing the management of EBL by providing early non-invasive diagnosis to thousands of patients in need.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, Non-Hodgkin (Pediatric, Adolescent, and Young Adult)

No conflicts of interests pertinent to the abstract.

239 | CLINICAL IMPACT OF EPSTEIN–BARR VIRUS DNA IN AGGRESSIVE NK-CELL LEUKEMIA

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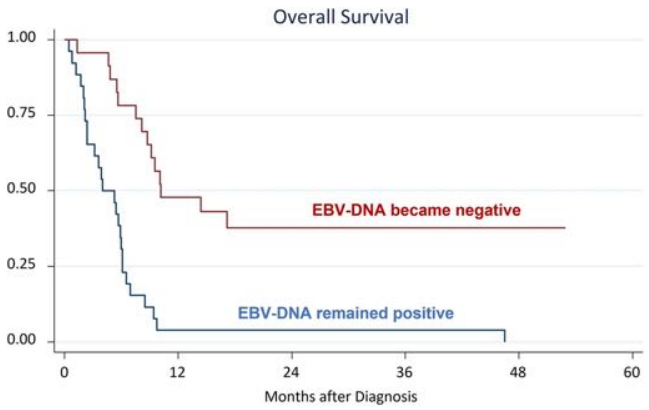
Background: Aggressive NK-cell leukemia (ANKL) is an uncommon leukemic form of mature NK-cell neoplasm with poor prognosis, which is strongly associated with the Epstein–Barr virus (EBV). The information on EBV-DNA in the blood is limited.

Method: We performed a nationwide survey of ANKL patients diagnosed between 2002 and 2021 at 65 institutes in Japan (ANKL22 study). The significance of EBV-DNA in ANKL was retrospectively analyzed.

Results: A total of 101 patients with ANKL were enrolled in the ANKL22 study. Patients' median age was 49 years (range, 17–90) and males accounted for 56%. EBV-DNA in peripheral blood was positive in 70 of 80 patients evaluated (88%). EBV encoded small RNA in situ hybridization (EBER-ISH) of the tissue samples was positive in 59 of 67 patients (88%). The positivity of EBV was consistent with that in the previous reports. Among patients of whom both EBV-DNA and EBER were assessed, the concordance rate was 91%. The median overall survival (OS) was 5.5 months and the 1-year OS of all ANKL patients was 25.2%. OS was not considerably different between EBV-positive ($N = 77$, either EBV-DNA or EBER-ISH) and EBV-negative patients ($N = 10$) ($P = 0.29$). The subjects for the EBV-DNA in peripheral blood measurement varied. EBV-DNA was measured in the whole blood in 54 of 67 patients tested (81%), 8 in plasma (12%) and 5 in serum (7%). Among patients whom EBV-DNA was measured in the whole blood, the EBV-DNA was detected at a median level of 765,000 copies/ml. Among those who received multi-agent chemotherapy, all patients with high EBV-DNA exceeding 10^6 copies/ml at diagnosis eventually died within 1 year ($N = 12$). The prognosis of patients with undetectable EBV-DNA after treatment initiation had a significantly better prognosis than those with identifiable EBV-DNA (median OS: 10.2 months vs. 4.0 months; $P < 0.001$). The median day of initial undetectable EBV-DNA was 92 days after diagnosis. The proportion of EBV-DNA negativity was significantly higher in patients who achieved complete response (CR) after initial chemotherapy than in the others (80% vs. 33%). Sixteen of 24 patients (67%) who achieved CR were treated with SMILE chemotherapy (dexamethasone (steroid), methotrexate, ifosfamide, L-asparaginase,

and etoposide). The patients of whom EBV-DNA decreased more than 3 logs from the initial level around 2 months after treatment initiation (17%) had significantly better prognosis than the others (median OS: 10.2 months vs. 5.7 months; $P = 0.04$).

Conclusion: The EBV-DNA copy levels in the blood, which represent the tumor load, can be an accurate predictor for response to chemotherapy and prognosis of EBV-positive ANKL patients. Further analyses for EBV-negative ANKL are required. The positioning of EBV-negative ANKL itself should also be discussed in the future.



Keywords: Aggressive T-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, Extranodal non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

A. Fujimoto
Honoraria: Chugai Pharmaceutical Co., Ltd., Meiji Seika Pharma, Sanofi

T. Maeda
Honoraria: Bristol Myers Squibb, Chugai, Janssen, Nippon Shinyaku, Novartis, Ono, Sanofi

N. Fukuhara
Honoraria: Chugai pharma, Genmab, Abbvie, Takeda, Eli Lilly, astrazeneca, Meiji Seika, Ono Pharmacuetical, Janssen, Bristol-Myers Squibb, Eisai, Kyowa-Hakko Kirin, Symbio and Novartis
Research funding: Chugai pharma, Genmab, Abbvie, Takeda, Eli Lilly, Incyte and Chordia Therapeu

K. Miyazaki
Honoraria: Chugai Pharma, SymBio Pharmaceuticals, Janssen, Eisai, Nippon Shinyaku, AstraZeneca, Bristol-Myers Squibb Japan, Meiji Seika Kaisha, Abbvie, Novartis, Incyte, and Asahi Kasei
Research funding: Eisai, Takeda, Nippon Shinyaku, Otsuka, Chugai Pharma, Asahi Kasei, Sumitomo Dainippon Pharma Oncology and Zenyaku Kogyo

M. Yamaguchi
Honoraria: AbbVie, Bristol Myers Squibb, Chugai Pharma, Janssen, Kyowa Kirin, Meiji Seika Pharma, MSD, Nippon Shinyaku, SymBio pharmaceuticals, Takeda Pharmaceutical
Research funding: AstraZeneca, Chugai Pharma, Genmab, Incyte, Kyowa Kirin

F. Ishida
Honoraria: Janssen, Pfizer, CSL Behring, Astra Zeneca
Research funding: Chugai Pharmaceuticals, CSL Behring, Daiichi-Sankyou, Kyowa Kirin

R. Suzuki
Honoraria: Kyowa-kirin, Chugai, Bristol-Meyer Squib, Eisai, MSD, Shionogi, Janssen, Abbvie, Takeda, Meiji Seika, Ohtsuka, Sumitomo Dainippon, Novartis, AstraZeneca, Nippon Shinyaku
Research funding: Kyowa-kirin, Chugai, Taiho, Ohtsuka, Takeda, Shionogi, Eisai, Meiji Seika, Sysmex

240 | MOLECULAR FEATURES POSSESSED IN THE CTDNA REVEAL HETEROGENEITY AND PREDICT OUTCOME IN NEWLY DIAGNOSED PERIPHERAL T-CELL LYMPHOMA

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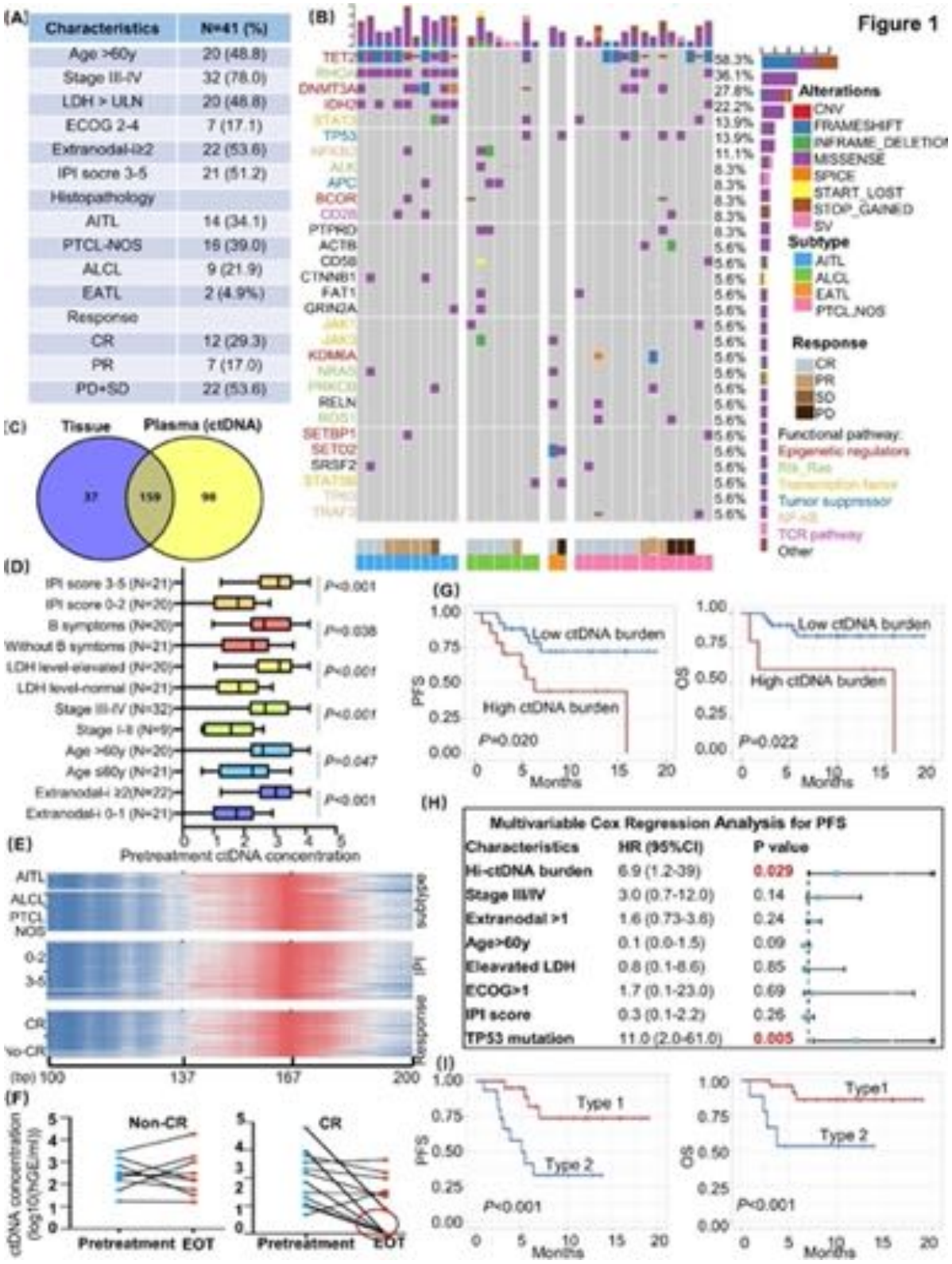
Introduction: Circulating tumor DNA (ctDNA) has been proven to be a promising tumor-specific biomarker in tumors, but its clinical utility in risk stratification and early prediction of relapse for peripheral T cell lymphoma (PTCL) has not been well explored.

Methods: Using a lymphoma-specific sequencing panel, we assessed the prognostic and predictive utilities of ctDNA measurements before and after first-line therapy in 41 PTCL patients.

Results: For the 41 patients, we obtained a total of 36 primary tumor specimens, 41 pretreatment blood samples and 21 serial blood samples before and after first-line therapy. By the last visit in March 2023, the median follow-up duration was 10.0 (range, 2.5–18.8) months. The clinical characteristics of the 41 patients were shown in Figure 1A. All patients received CHOP-like regimen. The top 30 somatic mutations of tissues were shown in Figure 1B. Pretreatment ctDNA (Pre-ctDNA) achieved an overall sensitivity of 81.3% (159/196) in detecting variants verified in tumor, indicating that ctDNA is a reliable source for PTCL genotyping. In addition, ctDNA allowed for the identification of additional 98 somatic mutations that were undetectable in tumor gDNA, which demonstrated that ctDNA could overcome tumor spatial heterogeneity (Figure 1C). Pre-ctDNA burden was significantly associated with clinical characteristics, including extranodal involvement ($P < 0.001$), lactate dehydrogenase

(LDH) levels ($P < 0.001$), age ($P = 0.047$), B symptoms ($P = 0.038$), stage ($P = 0.008$) and international prognosis index (IPI) score ($P < 0.001$) (Figure 1D). The cell-free (cfDNA) fragments profoundly reflects both genomic and chromatin characteristics. Our results suggested that all samples had a more prominent mono-nucleosomal fragments abundance (167 bp), whereas the samples of angioimmunoblastic T-cell lymphom (AITL) and the samples with high IPI scores or non-complete response (CR) in the mid-stage of treatment had a more prominent shift towards shorter cfDNA size (Figure 1E). Similarly, when we analyzed the response to treatment, significant decline



in ctDNA levels was observed at end of treatment (EOT) in patients with CR compared with those who did not achieved CR. The 4 patients with CR and EOT ctDNA negative achieved continuous CR until now (Figure 1F). Furthermore, high pre-ctDNA levels presented unfavourable PFS ($P = 0.002$) and OS ($P = 0.020$) (Figure 1G). Multivariate cox regression analysis showed that high pre-ctDNA burden ($P = 0.029$) and TP53 mutation ($P = 0.005$) (Figure 1H). Subgroup analysis showed that patients without these 2 risk factors (Type 1) had longer PFS than the other patients with more than 0 risk factor (Type 2) ($P < 0.001$) (Figure 1I).

Conclusions: ctDNA is a promising noninvasive tool for prognosis prediction, response assessment and early relapse prediction for newly diagnosed PTCL.

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers

No conflicts of interests pertinent to the abstract.

241 | CELL-FREE DNA SEQUENCING ALLOWS THE IDENTIFICATION OF THE MUTATIONAL PROFILE OF TFH LYMPHOMAS AND HAS A PREDICTIVE VALUE: A LYSA STUDY

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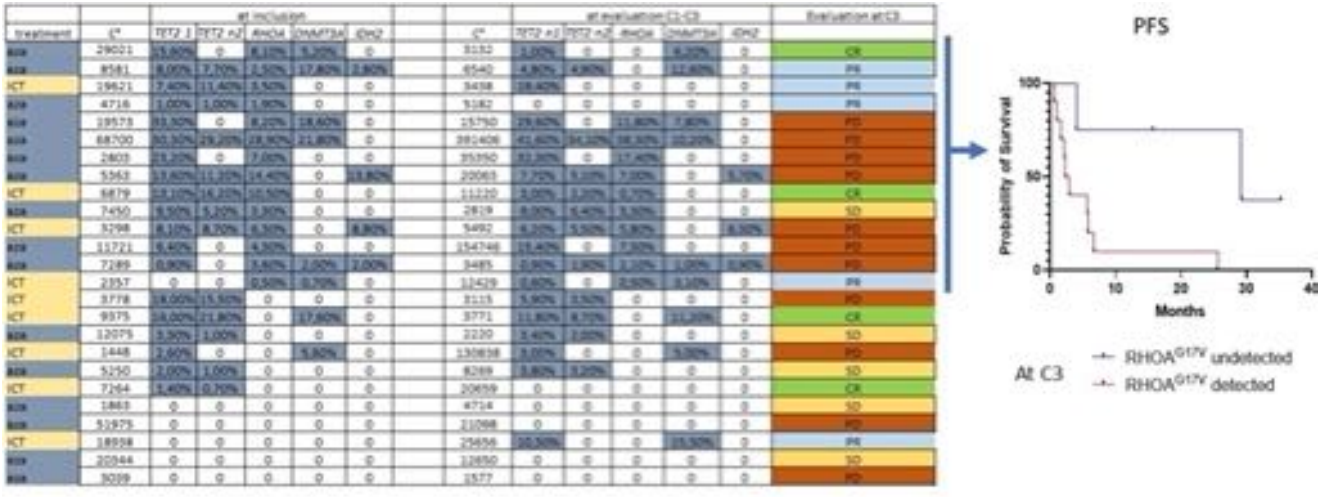
Introduction: TFH lymphomas (TFHL) commonly harbor mutations in *TET2*, *RHOA*, *DNMT3A* and *IDH2*. While *RHOA* and *IDH2* appear restricted to the neoplastic cells, *TET2* and *DNMT3A* mutations occur in a significant proportion of cases in a hematopoietic progenitor cell and can also be detected in B or myeloid cells. Cell-free DNA (cfDNA) sequencing allows the detection of circulating tumor DNA in solid cancers or B-cell lymphomas, with predictive value, but few data exist on cfDNA sequencing in TFHL.

Methods: In the frame of the ORACLE study, a phase 3 trial comparing oral azacitidine to investigator choice treatment in relapsed or refractory TFHL patients, we collected tumor biopsies and plasma in streck tube at inclusion, after 3 cycles, and at progression. Tumour and cfDNA were sequenced by NGS using 9 genes, amplicon-based libraries. Median sequencing depth was 2386X in tumor and 3519X in cfDNA.

Results: Among patients with confirmed TFHL treated in LYSA centers, we collected 45 samples at inclusion, 16 after cycle 3, and 14 at progression. The median cfDNA concentration at each time point was respectively 7507 (IQR 3418–19414), 5182 (3438–12429), and 15750 (7316–26953) hEG/mL. Results of cfDNA at inclusion and tumor sequencing were compared in 43 patients. Common *TET2* mutations were detected in the tumor of 36/43 (84%) and in cfDNA of 33/43 (77%) patients, with a median variant allele frequency (VAF) of 17.75% vs. 9.8% respectively. $RHOA^{G17V}$ was detected in 29/43 (67%, VAF 10%) and in 24/43 (59%, VAF 4.4%), *DNMT3A* in 13/43 (30%, VAF 17.9%) and 15/73 (35%, VAF 17.9%), and *IDH2* in 12/43 (28%, VAF 5.9%) and 8/43 (19%, VAF 5.4%) of tumor biopsies and cfDNA samples respectively. Only one patient had detectable *TET2*, *DNMT3A*, *IDH2*, and *RHOA* mutations in the cfDNA and not in the tumor biopsy, corresponding to a tumor with low neoplastic cell



Aza: treatment with oral azacitidine, ICT: investigator choice treatment (bendamustine or gemcitabine), C°: concentration of cfDNA in haplotype equivalent genome/mL (hEG/mL), %: variant allele frequency of mutation, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

content. By contrast, 3 patients had *DNMT3A* mutations, not affecting the R882 residue, detected in the cfDNA but not in the tumor likely corresponding to clonal hematopoiesis not related to the TFHL. We also compared 25 paired cfDNA samples collected at inclusion and after cycle 3 (including progression sample if occurring at cycle 3 or before). In all but one patient, we observed the persistence of *TET2* and *DNMT3A* mutations, even in responding patients, confirming that these mutations are not restricted to neoplastic cells, and suggesting that treatment, especially with 5-azacitidine, does not affect the clonal hematopoiesis. By contrast, among the 14/25 patients with a detectable *RHOA* mutation in cfDNA at inclusion, progression-free survival was longer in the 4 patients with the disappearance of the *RHOA* mutations in cfDNA at cycle 3 than in the 10 others (median 29 vs. 3 months, $p = 0.01$).

Conclusion: cfDNA sequencing allowed the detection of the *RHOA* mutation in 77% of mutated patients, and the disappearance of *RHOA* mutation at cycle 3 predict prolonged PFS.

The research was funded by: BMS Force Hémato

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Liquid biopsy, Minimal residual disease

No conflicts of interests pertinent to the abstract.

IMAGING

242 | THE IMPACT OF SPLEEN METABOLIC TUMOR VOLUME ON TOTAL METABOLIC TUMOR VOLUME AND PROGNOSIS IN PATIENTS WITH FOLLICULAR LYMPHOMA ENROLLED IN FOLL 12 TRIAL

L. Guerra[1], S. Chauvie[2], L. Marcheselli[3], F. Bergesio[2], R. Durmo[4], S. Peano[5], A. Franceschetto[6], F. Fallanca[7], A. Pinto[8], C. Ghiggi[9], A. Pulsoni[10], M. Merli[11], L. Farina[12], M. Tani[13], C. Boccomini[14], G. Musuraca[15], B. Falini[16], F. Ballerini[17], P. Stefani[18], S. A. M. Bolis[19], G. Pietrantuono[20], M. Manni[21], M. Federico[21], S. Luminari[22], A. Versari[4]

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Introduction and Aim: Recently, in an ancillary study of FOLL12 trial (NCT02063685), total Metabolic Tumor Volume (tMTV) assessed before treatment has been demonstrated to be an independent predictor of PFS in patients receiving frontline immune chemotherapy (1). During the segmentation procedure, it has been observed that frequently spleen MTV (sMTV) heavily influenced the tMTV value, particularly in case of diffuse spleen uptake included in tMTV calculation. High tMTV could be a negative prognostic factor as it represents the tumor burden. On this basis, the aim of the current study was to evaluate the effect of the sMTV defined on baseline PET on tMTV calculation and its impact on outcome, particularly 5y-PFS (Progression Free Survival), in follicular lymphoma patients.

Methods and Results: Overall, 690 patients with baseline PET were included in the analysis, 48% were older than 60 years, 89% had stage III-IV disease and 40% had a high-risk FLIPI-2 score. Overall, the 5y-PFS was 79% (95% CI, 76%–82%). Among 690 patients 469 (67.9%) did not have spleen involvement while 128 (18.5%) and 93 (13.4%) showed focal and diffuse spleen involvement, respectively. The 5y-PFS (95% CI) according the spleen status was 67% (62–72), 58% (48–67) and 61% (49–61) in patients without, with focal and with diffuse spleen involvement, respectively (p not significant). MTV calculation was performed with a threshold of 41% for segmentation. In the whole population of 690 patients, the tMTV threshold to categorized low and high tumor burden was 224 and 194 ml with and without sMTV, respectively. Assuming 200 ml as a tMTV threshold, only 16/693 pts (2.3%) changed from low to high tumor burden when the sMTV was included in the tMTV. Including sMTV in tMTV, with a threshold of 200 ml, the 5y-PFS in patients with low and high tMTV was 73% (95% CI: 67–78) and 58% (95% CI: 53–64), respectively, with a HR of 1.83 ($p < 0.001$). Excluding sMTV from tMTV, the 5y-PFS in patients with low and high tMTV was 72% (95% CI: 67–77)

and 58% (95% CI: 52–64) with a HR of 1.80 ($p < 0.001$). In the two groups, HRs values for tMTV >200 ml showed negligible difference, independently from sMTV inclusion.

Conclusion: These preliminary data of the FOLL12 trial showed that tMTV correlated with outcome in terms of PFS; on the contrary the metabolic spleen status defined in the baseline PET do not seem to show any prognostic added value, neither in case of focal nor in case of diffuse uptake. Finally, the inclusion/exclusion of the sMTV into the tMTV did not significantly change either the risk classification of the patients or the outcome in terms of PFS. Larger patients population are needed to confirm these data.

References: R. Durmo, L. Guerra, S. Chauvie et al. "Total Metabolic Tumor Volume and tumor dissemination calculated from PET/CT scan before first line therapy are predictors of outcome in patients with follicular lymphoma" Eur J Nucl Med Mol Imaging (2022) 49 (Suppl 1): S1–S751; OP 629

Keywords: Diagnostic and Prognostic Biomarkers, PET-CT

No conflicts of interests pertinent to the abstract.

243 | COMPARISON OF MACHINE LEARNING APPROACHES FOR POD24 PREDICTION BASED ON PRETREATMENT PET IN FOLLICULAR LYMPHOMA PATIENTS (ON BEHALF OF CALYM/LYSA GROUPS)

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Introduction: Follicular Lymphoma (FL) is the second most common non-Hodgkin lymphoma in adults and is heterogeneous with 20% of poor-outcome patients relapsing/progressing within 24 months (POD24) of first treatment start (Casulo et al., JCO 2015). Early identification of those POD24 patients is critical but remains elusive. We initiated a collaboration between the academic CALYM Carnot Institute and the private company Euranova aiming at developing interpretable artificial intelligence (AI) models based on Positron Emission Tomography (PET) images to predict POD24.

Methods: The dataset was based on the LYSA group RELEVANCE (RE) trial (Morshhauser et al, NEJM 2018) and on real-life (RL) datasets from two french hospitals (Dijon, Toulouse). Patients with FL diagnosis confirmation on biopsy, high tumor burden criteria (GELF >0) and PET images were enrolled in this retrospective study (Table 1). The input data, including PET images, tumor segmentation masks if available, and clinical data, are hosted on CALYM's cloud based data lake Lymphoma Data Hub. After quality controls and data preprocessing, several POD24 predictive models based on pretreatment images were developed. A deep convolutional neural network with 3D ResNet architecture pretrained on 3D medical images and enriched with clinical data was trained on PET images with a binary cross entropy loss. A machine learning (ML) model based on the XGBoost boosting algorithm was trained on tabular radiomics features after extraction of 851 radiomics features for each tumor and features aggregation at patient's level by using only the 3 tumors with largest volumes. Models were cross-validated on the RE cohort with leave-one-out method and tested on the RL cohorts (Figure 1).

Results: The ML approach achieved more promising results than the deep learning (DL) model on the RE cohort with an AUC of 0.61 for ML vs. 0.56 for DL. Interestingly, in this ML model, SUVmax and new radiomics features, such as major axis length, came out as the most predictive features. For now the external validation of the ML model on RL cohorts is slightly more limited with an AUC of 0.51. Improvement of this result is expected owing to the ongoing enrichment of the cohort with additional external data. Finally, regarding the treatment's impact on the model's performance, preliminary data showed better results when training on the R-CHOP cohort only. Validation is underway, and will be presented at the meeting.

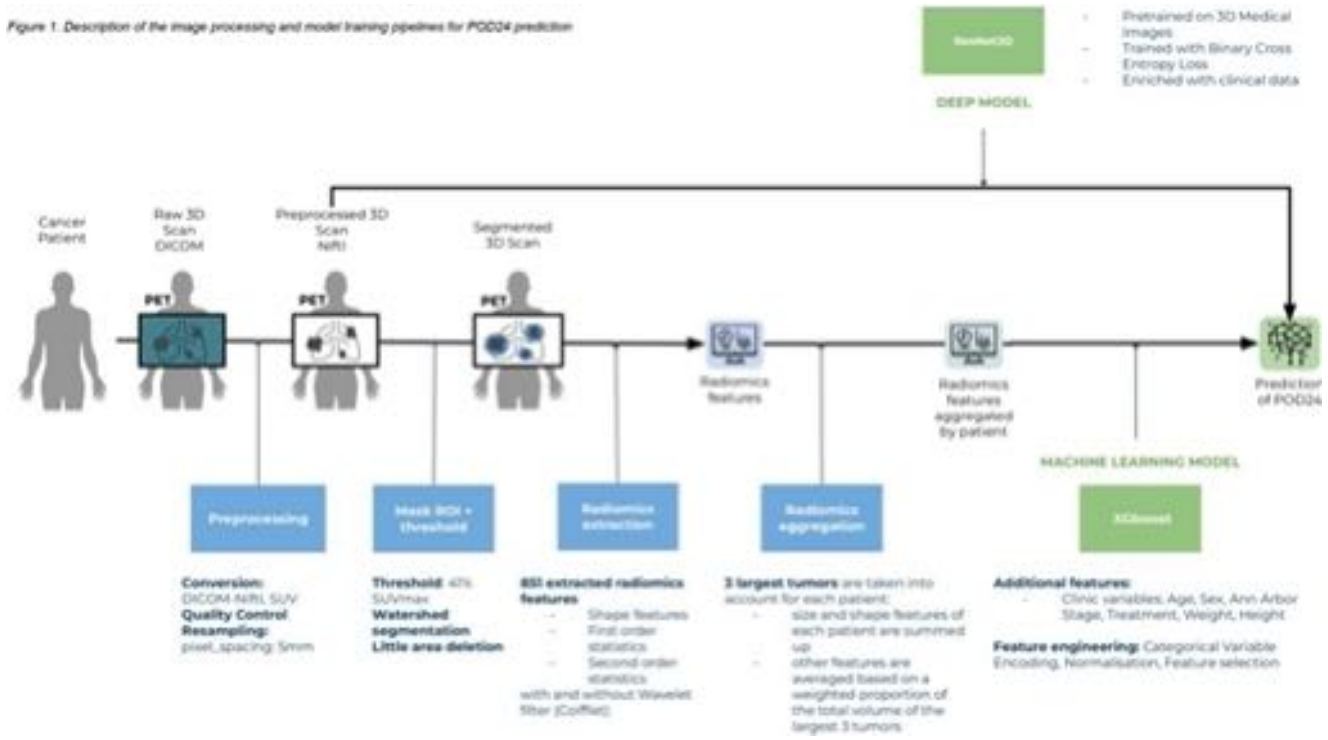
Conclusion: Our study demonstrates the feasibility of POD24 prediction in FL patients through a radiomics based ML approach. Such predictive models could help clinicians for early identification of poor-outcome patients and decision-making, and ultimately improve patient care.

Keywords: Bioinformatics, Computational and Systems Biology, Indolent non-Hodgkin lymphoma, PET-CT

No conflicts of interests pertinent to the abstract.

TABLE 1 Description of the population (RE: relevance trial, RL: real life cohorts)

Cohorts	Treatment	Number of patients
RE	R-Len	214
	R-CHOP	208
	R-CVP	14
RL	R-Len	5
	R-CHOP	74



244 | **AUTOMATED FDG PET/CT RADIOMICS FOR RISK STRATIFICATION IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)**

J. T. Shreve[1], A. Z. Hazim[1], A. M. Bock[1], J. C. Pritchett[1], M. J. Maurer[2], M. V. Shah[1], M. Binder[1], T. E. Witzig[1], Y. Wang[1], G. S. Nowakowski[1], A. J. Novak[1], J. R. Young[3], J. R. Cerhan[2], T. M. Habermann[1], S. M. Ansell[1], J. Paludo[1]

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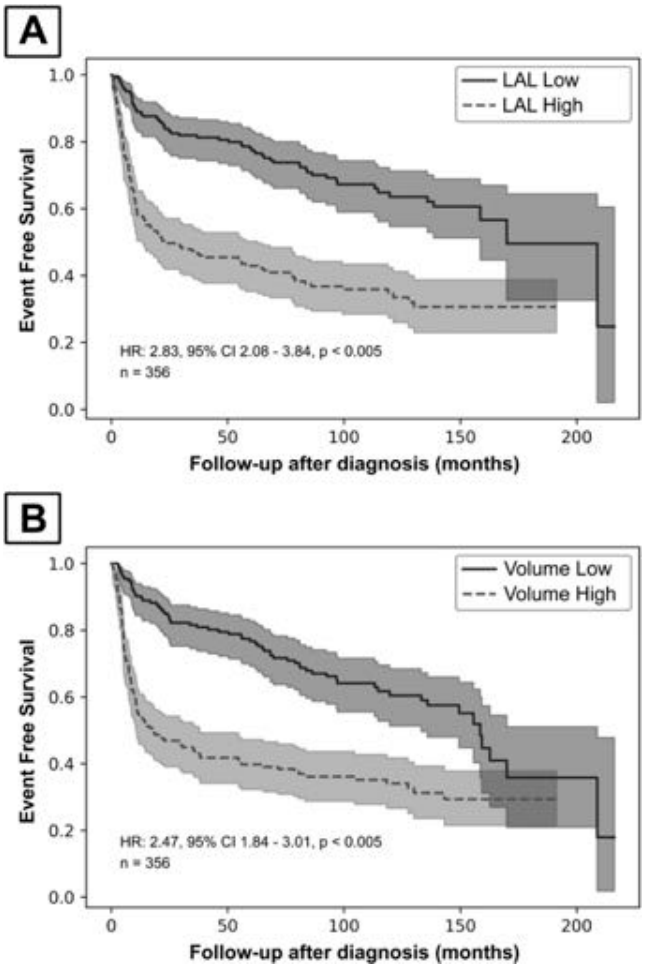
Introduction: Pre-treatment PET/CT scans have not yet been incorporated into risk stratification models despite being the imaging modality of choice in DLBCL. Deep learning computer algorithms have consistently demonstrated the ability to analyze imaging data and identify features that are not readily apparent to the human eye. Therefore, to assess the prognostic performance of pre-treatment PET/CT scans in patients with DLBCL, we compared automatically extracted radiomics features using a convolutional neural network with a standard prognosticating tool (NCCN-IPI).

Methods: Native DICOM images from FDG PET/CT scans of newly diagnosed DLBCL patients were preprocessed for regularity and then segmented using the nnU-Net architecture with an external lymphoma-specific model. Feature extraction and SUV characterization were accomplished with PyRadiomics and NiBabel. Our computational method included no manual segmentation correction. Individual radiomics features (n = 115) were evaluated for association with event free survival (EFS) via univariate Cox regression analysis and by Kaplan Meier log rank testing of upper and lower feature quartiles. Additionally, Spearman and Pearson correlation matrices were used to guide feature selection while minimizing collinearity. We then assessed the association of the highest scoring radiomics features with EFS.

Results: Radiomics features were automatically extracted from a cohort of 713 newly diagnosed DLBCL patients with pre-treatment PET/CT scans treated at Mayo Clinic between 2003 and 2015 and followed through 2023. Median age at diagnosis was 64 years (range 18–93), 41% were females. NCCN-IPI composition and outcomes of our cohort was comparable to the previously published NCCN cohort, with patient distribution and 5-year OS as follows: Low (11%, 5-y OS 89%), Low-intermediate (42%, 5-y OS 72%), High-intermediate (38%, 5-y OS 53%), High (9%, 5-y OS 25%). Log rank testing found numerous radiomics features were associated with EFS including least axis length (LAL) (HR: 2.83, 95% CI: 2.08–3.84, $p < 0.005$, Figure A) and volume (HR: 2.47, 95% CI: 1.84–3.01, $p < 0.005$, Figure B). As a reference, NCCN-IPI univariate Cox regression analysis of EFS produced a Harrell's C-statistic (c) of 0.633. Single radiomics features of sphericity, volume, surface area, and least axis length individually produced unadjusted c-statistics of 0.624, 0.629, 0.636 and 0.638, respectively. Combinations of radiomics features (surface area + least axis length) demonstrated cumulative benefit (c = 0.642).

Conclusion: Radiomics features automatically extracted from pre-treatment PET/CT scans of DLBCL patients were associated with event free survival and appear to be promising prognostic markers, but will need external validation. In addition, improvement in stratification when combining radiomics with clinical and genomic variables is warranted.



Keywords: Aggressive B-cell non-Hodgkin lymphoma, PET-CT, Risk Models

Conflicts of interests pertinent to the abstract.

T. M Habermann

Consultant or advisory role: Data Monitoring Committee: Seagen, Tess Therapeutics, Eli Lilly & Co. Scientific Advisory Board: Morphosys, Incyte, Biegene, Loxo Oncology. No personal compensation is received for these activities, any compensation is received by my institution.

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245 | AN AUTOMATED QUANTIFICATION ALGORITHM FOR EVALUATING TOTAL METABOLIC TUMOR VOLUME IN PATIENTS WITH FDG-AVID LYMPHOMAS USING A DEEP LEARNING MODEL

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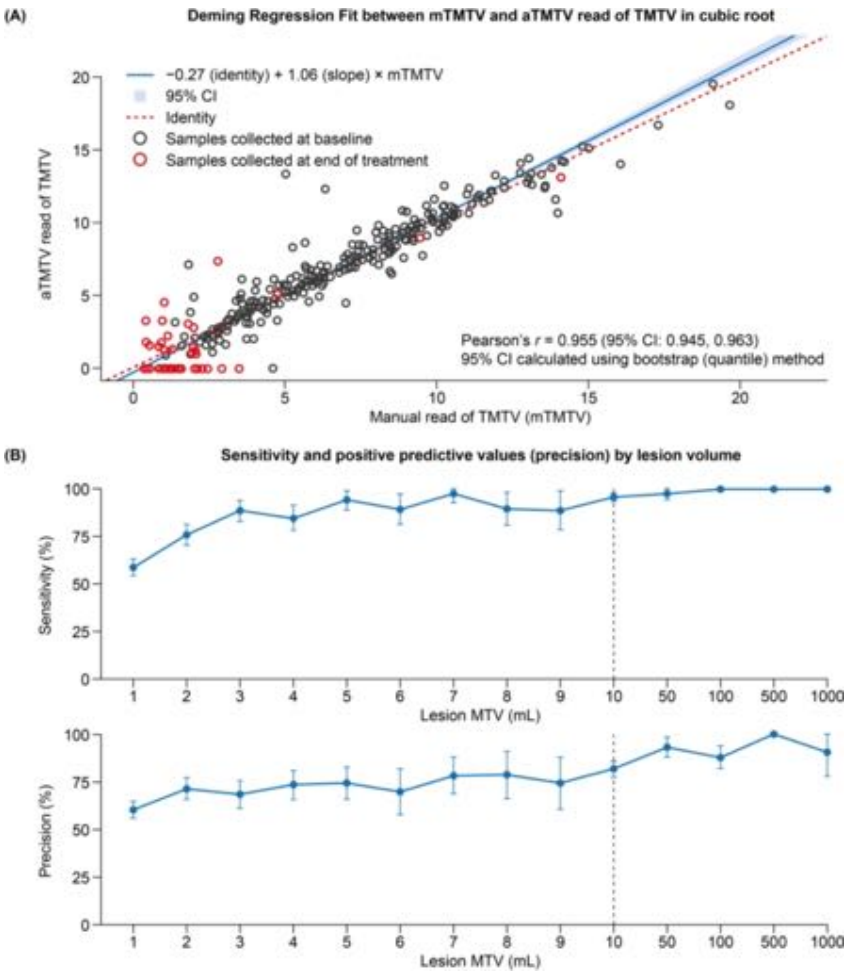
Introduction: Total metabolic tumor volume (TMTV) holds promise as a method for quantifying tumor burden in patients with F-18 fluorodeoxyglucose (FDG)-avid lymphomas and, with further validation, has potential as a prognostic biomarker. We have developed a deep learning model for the automatic detection of lesions and quantification of TMTV from FDG-positron emission tomography/computed tomography (FDG-PET/CT) scans (Jemaa *et al.*, 2020, 2022). We aimed to further evaluate the model and identify factors that may influence the performance of lesion detection and TMTV quantification in patients with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).

Methods: The test data set was compiled using baseline and post-treatment FDG-PET/CT scans from the phase 3 GOYA (NCT01287741) and GALLIUM (NCT01332968) clinical trials, which included 166 patients with DLBCL and 201 patients with FL, respectively. The model was trained using an independent data set from GOYA (n = 836). FDG-PET/CT images were assessed manually (mTMTV) and by the algorithm (aTMTV). Pearson's correlation coefficient (r) was used to determine the overall performance of aTMTV versus mTMTV. Bias was assessed using the slope and intercept from a weighted Deming regression. Lesion detection performance was evaluated based on sensitivity (the proportion of mTMTV-detected lesions identified by aTMTV) and positive predictive value (PPV; the proportion of aTMTV-detected lesions identified by mTMTV). Performance was compared among patient populations with different demographics and clinical characteristics, and across images from different PET/CT scanner manufacturers.

Results: aTMTV quantification highly correlated with mTMTV in the test data set (n = 367; Figure A). No systematic bias was observed between aTMTV and mTMTV (slope, 1.06 [95% CI: 1.02, 1.09]; intercept, −0.27 [95% CI: −0.52, −0.03]; mean difference between methods, 0.10 [standard deviation (SD): 1.15]). Agreement between aTMTV and mTMTV was consistent among patients with different baseline demographics and clinical characteristics, and across scans from different PET/CT scanner manufacturers. Overall mean sensitivity and PPV for lesion detection were both >0.8 (Figure B). Performance was lower for lesions ≤10 mL (mean sensitivity, 0.67; mean PPV, 0.72) than for lesions >10 mL (mean sensitivity and PPV >0.95).

Conclusions: The aTMTV algorithm demonstrated good performance for the measurement of TMTV in patients with non-Hodgkin lymphoma and good generalizability across patient subpopulations and PET/CT scanner manufacturers. Reduced algorithm performance for small lesions (≤10 mL) may be the result of higher variability among readers in the determination of small lesions; future work aims to refine and optimize performance of the algorithm for use as a prognostic tool in clinical practice.

Encore Abstract - previously submitted to EHA 2023



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Keywords: Diagnostic and Prognostic Biomarkers, Indolent non-Hodgkin lymphoma, PET-CT

Conflicts of interests pertinent to the abstract.

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246 | DEPTH OF METABOLIC RESPONSE AT INTERIM PET AND SURVIVAL OUTCOMES AMONG PATIENTS WITH PRIMARY REFRACTORY OR EARLY RELAPSING DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Background: Total metabolic tumor volume (TMTV) and maximum standardized uptake value (SUVmax) may improve upon standard 18F-fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT)-based assessment during treatment. We report the association of TMTV and SUVmax response by interim PET (PET2) on survival outcomes in patients with primary refractory DLBCL (prDLBCL) and early relapsing DLBCL (erDLBCL).
Methods: Adult patients with prDLBCL (less than a complete response at EOT or progression during treatment) or erDLBCL (CR at EOT with a relapse within 12 months) between 2005 and 2019 and seen at Mayo Clinic Rochester were included. The % change (Δ) from baseline to PET2 (after 2 cycles of 1L immunochemotherapy) of TMTV and maximum SUV uptake (SUVmax) were measured. A PET segmentation threshold of 1.5 liver mean SUV + two standard deviations with a minimum volume constraint of 0.5 mL was utilized (MIM Software, Inc., Cleveland OH, USA) with manual input as needed. Functional spline analysis showed a ΔSUVmax decline ≥65% and a ΔTMTV decline ≥75% at PET2 were associated with improved OS and determined threshold for further analysis.
Results: 131 patients with prDLBCL or erDLBCL, 131 had complete PET-CT data available (N = 79 prDLBCL, N = 52 erDLBCL). Median baseline TMTV was 939.5 cm^3 (range 13.1–6840.4) in prDLBCL and 670.4 cm^3 (0.9–5464.5) in erDLBCL (p = 0.01). Baseline median SUVmax was 22.2 (3.1–52.6) in prDLBCL and 19.1 (2.0–49.7) in erDLBCL (p = 0.02). The 2-year estimated OS rate was 21% (95% CI: 13–34) for prDLBCL and 58% (95% CI: 45–75) for erDLBCL. At a median follow up of 77.6 months, 81 patients had died. Among all patients, Two-year OS rate was 53% (95% CI: 42–67) for patients with a PET2 ΔSUVmax decline ≥65% compared to 15% (95% CI: 7–29) for patients with a PET2 ΔSUVmax decline <65% (p < 0.001) (Figure A). PrDLBCL had a 2-year OS rate of 48% (95% CI: 31–74) for a ΔSUVmax ≥65% compared to 7% (95% CI: 2–21) for patients with a ΔSUVmax <65% (p < 0.001)(Figure B), which captured 58% of prDLBCL patients (N = 46). Among all patients, 2-year OS rate was 43% (95% CI: 34–54) for patients with a ΔTMTV ≥75% compared to 5% (95% CI: 1–35) for patients with a ΔTMTV <75% (p < 0.001) (Figure C). All patients with a ΔTMTV <75% had prDLBCL. PrDLBCL had a 2-year OS rate of 28% (95% CI: 18–44) for a ΔTMTV ≥ 75% (Figure D). The outcomes for ΔSUVmax <65% and ΔTMTV <75% at PET2 remained significant in a cox regression model when adjusted for IPI and bulky disease (>10 cm).
Conclusion: A ΔTMTV decline <75% or a ΔSUVmax decline <65% at PET2 identified an ultra-high-risk subgroup of prDLBCL with particularly poor outcomes that was still significant after adjusting for IPI and baseline bulky disease. Depth of metabolic response by PET2 may identify patients at high risk for frontline treatment failure who may benefit from alternative PET-adapted treatment strategies.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, PET-CT

Conflicts of interests pertinent to the abstract.

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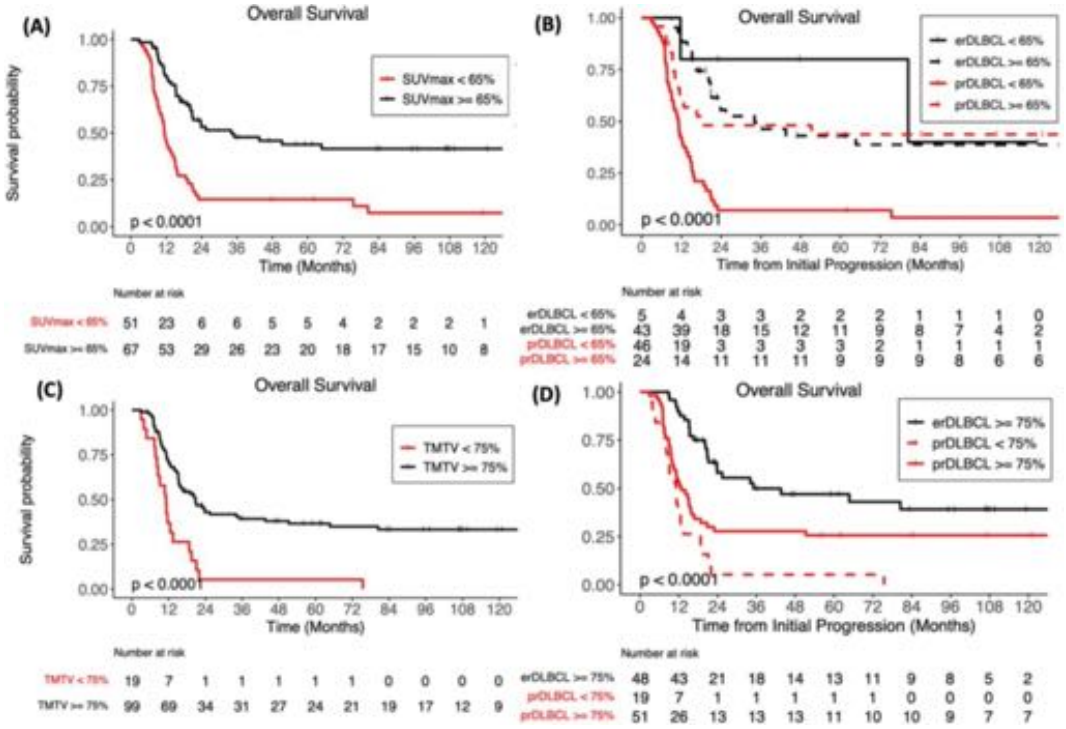

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247 | DIFFERENCES IN BASELINE PET/CT LYMPHOMA DISTRIBUTION PATTERNS BETWEEN DLBCL-NOS AND HIGH-RISK DLBCL PATIENTS

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Introduction: Approximately 8%–10% of diffuse large B-cell lymphoma (DLBCL) patients have genetic aberrations, known as high grade B-cell lymphoma double-hit and triple-hit (HGBL-DH/TH, with *MYC/BCL2* and *MYC/BCL2/BCL6* rearrangements). However, it is unknown whether these subtypes have different distribution patterns on baseline PET/CT compared to cases without rearrangements

(wild-type), or with only a single *MYC* (SH) arrangement, or *MYC/BCL6* rearrangements (hereafter collectively referred to as DLBCL-NOS (Not Otherwise Specified)). The aim of this study was to analyze the frequencies in which different nodal stations and extra-nodal sites were involved, with secondary endpoints including: bulky disease (BD), the number of lesions, the number of nodal stations, the number of extranodal sites and metabolic tumor volume (MTV).

Methods: Baseline PET/CT scans from the HOVON-84 (2006-005174-42), HOVON-130 (2014-002654-39) and HOVON-152 (2017-003631-12) were reviewed. Lesions were included if the uptake was above SUV4.0 using the ACCURATE software tool, which was also used to calculate MTV.Differences in frequencies of involved nodal stations, extranodal sites and the occurrence of BD were determined with X^2- and Fisher exact tests. The number of lesions, number of nodal stations, number of extranodal sites, and MTV were analyzed with unpaired T-tests and Mann-Whitney U tests.

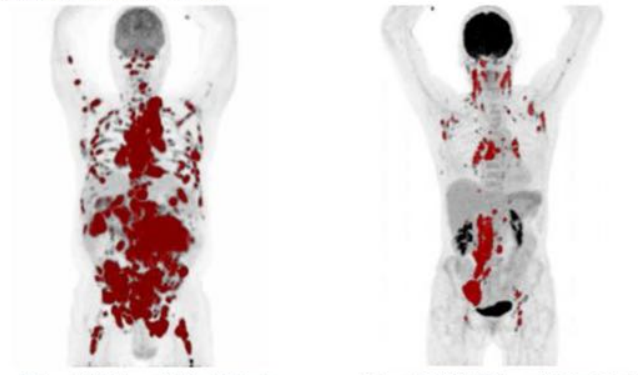
Results: 88 DLBCL-NOS patients (66 wild-type, 16 SH and 6 *MYC/BLC6*) were compared to 38 HGBL cases (26 DH, 12 TH). The HGBL patients showed more frequent involvement of para-aortic (68.4% vs. 48.2%, $p = 0.043$) and mesenteric (71.1% vs. 37.5%, $p < 0.001$) nodal stations, and a higher occurrence of gastro-intestinal- (44.7% vs. 21.6%, $p = 0.008$), pancreatic- (23.7% vs. 8.0%, $p = 0.021$) and peritoneal (15.9% vs. 3.4%, $p = 0.022$) extranodal involvement compared to DLBCL-NOS cases. Renal- (18.4% vs. 6.8%, $p = 0.061$) and dermal (13.2% vs. 3.4%, $p = 0.053$) localizations were also more common in HGBL than in DLBCL-NOS. In contrast, splenic- and pulmonary hilar node involvement occurred more often in DLBCL-NOS; 27.2% versus 10.5% ($p = 0.029$) and 28.4% versus 10.5% ($p = 0.05$) respectively. Furthermore, the total number of extranodal sites involved was found to be higher in HGBL patients (median 2 vs. 1, $p = 0.011$), as was the MTV (median 777 vs. 305 mL, $p = 0.021$) and the rate at which BD occurred (57.9% vs. 23.9%, $p < 0.001$). No difference in the total number of lesions and the total number of involved nodal stations was observed between the two groups.

Conclusions: DLBCL-NOS and HGBL show a remarkably different distribution pattern on baseline PET/CT, with significant differences in nodal- and extranodal localizations, and a higher MTV and number of extranodal sites in HGBL. These findings might indicate high-risk disease at baseline. Moreover, they suggest a different biology, corroborating HGBL's recently allocated status as a separate disease entity.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, PET-CT

No conflicts of interests pertinent to the abstract.

Figure 1: Examples of two analyzed patients in ACCURATE. Included lesions are depicted in red.



A) Stage IV HGBL scan (MTV = 2377 mL) B) Stage IV DLBCL-NOS scan (MTV = 219 mL)

248 | PROGNOSTIC VALUE OF LYMPHOPENIA AND TOTAL METABOLIC TUMOR VOLUME IN DIFFUSE LARGE CELL LYMPHOMA OF B PHENOTYPE IN THE RT3 AND REMARC TRIALS—A LYSA RETROSPECTIVE ANALYSIS

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Introduction: New prognostic factors have emerged such as total metabolic tumor volume (TMTV) assessed by PET-CT in large B cell lymphoma (DLBCL). Normal T, B and NK cells are also involved in antitumoral response. What is the impact of lymphopenia at the time of diagnosis on a large population?

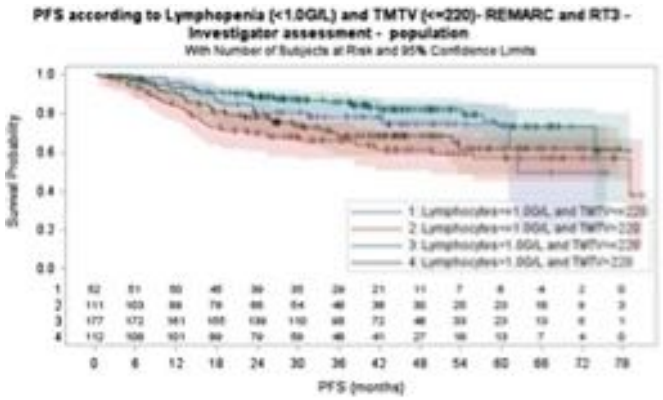
Methods: We pooled 1095 patients from 3 LYSA studies (GAINED, RT3 and REMARC) with TMTV and Lymphocytes available.

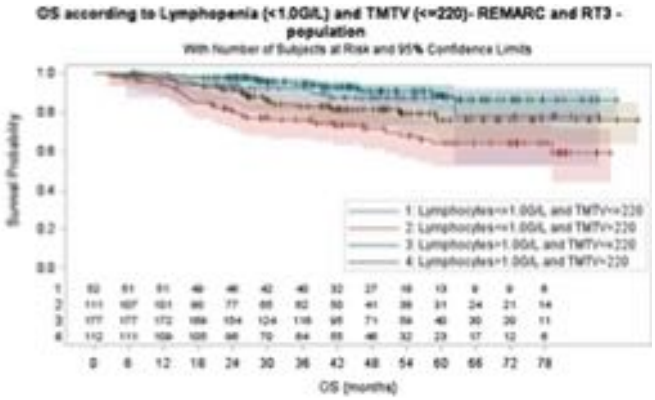
Results: The three studies differ for mean age at diagnosis: GAINED patients were younger (median 48; IC: 18–61) than in RT3 (66; 20–92) and REMARC (68, 64–73).

Patients with lymphocytes ≤1.0 G/L differed from patients with lymphocytes >1.0 G/L in terms of presence of B symptoms (44.5% vs. 30.0%, $p < 0.001$), number of extra-nodal sites involved (median of 2 vs. 1, $p < 0.001$), ECOG ≥ 2 (17.4% vs. 11.8%, $p = 0.011$), Ann Arbor stage III-IV (85.3% vs. 80.4%, $p = 0.037$), LDH > Upper limit (76.6% vs. 57.8%, $p < 0.001$), Albumin (median of 36.7 vs. 39.0 g/l, $p < 0.001$), IPI 3–5 (57.8% vs. 42.8%, $p < 0.001$), and TMTV (median of 389.3 vs. 165.3, $p < 0.001$).

Patients with Lymphocytes ≤1.0 G/L were 39.8% and were different between the 3 studies ($p = 0.008$). 42.5% ($n = 273$ GAINED), 28.8% ($n = 44$ RT3) and 39.7% ($n = 119$ REMARC). Median TMTV was 242 cm^3 overall and was different between the 3 studies ($p < 0.001$), 257 cm^3 (GAINED), 147 (RT3) and 237 (REMARC).

PFS assessment was different between RT3 and REMARC. Patients from RT3 had a higher risk of PFS (HR of 1.48 (95% CI. 1.0–2.2, $p = 0.044$)). No difference of OS was observed between the 3 studies ($p = 0.44$)





An impact of TMTV was observed on PFS ($p < 0.001$) and OS ($p < 0.001$). Patients with TMTV > 220 cm^3 had higher risk (HR = 1.71 (95% CI: 1.3–2.2) for PFS and HR = 2.06 (95% CI: 1.4–2.9) for OS). At a threshold of 1.0 G/L, PFS was not different ($p = 0.14$) but OS was different between patients with lymphocytes ≤1.0 G/L and patients >1.0 G/L (HR = 0.70 95% CI: 0.5–0.97 for patients with lymphocyte >1.0G/L, $p = 0.033$). No difference was observed for PFS ($p = 0.98$) and OS ($p = 0.90$) in the GAINED study. No difference was observed for PFS ($p = 0.18$) but OS differed between both groups (HR = 0.36 95% CI: 0.1–0.92 for patients with lymphocytes >1.0 G/L, $p = 0.036$) in the RT3 study. PFS and OS differed in the REMARC study ($p = 0.021$ and $p = 0.0074$, respectively). Patients with lymphocytes >1.0 G/L had lower risk of PFS (HR = 0.59 95% CI: 0.4–0.93) and OS (HR = 0.49 95% CI: 0.3–0.8).

Conclusion: The analysis of these studies reveals the important impact of lymphocytes and probably especially of T cells. In the era of CAR-T cells, it is not surprising that native T cells also have their role to play. The pooled analysis of these 3 studies reveals that lymphopenia seems, logically enough, to have a greater impact in older patients (REMARC and RT3) than in younger patients (GAINED), perhaps reflecting a still preserved lymphopoiesis capacity. Choosing less lymphotoxic chemotherapy could be necessary as the use of lymphopoiesis stimulating agent.

Keywords: Diagnostic and Prognostic Biomarkers, PET-CT

No conflicts of interests pertinent to the abstract.

249 | MODIFICATION OF LUGANO CRITERIA BY PRE-INFUSION TUMOR KINETICS IMPROVES EARLY SURVIVAL PREDICTION FOR LYMPHOMA PATIENTS UNDER CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY

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Purpose: Chimeric antigen receptor T-cell therapy (CART) is effective for patients with refractory or relapsed (r/r) lymphoma with prolongation of survival. We aimed to improve the prediction of Lugano criteria for overall survival (OS) at 30-day follow-up (FU1) by including the pre-infusion tumor growth rate ($TGR^{pre\text{-}BL}$) and its early change to 30-day FU1 imaging ($TGR^{post\text{-}BL}$).

Methods: Consecutive patients with pre-baseline (pre-BL), baseline (BL) and FU imaging around day 30 with CT or PET/CT before/after CART were included. TGR was defined as change of Lugano criteria-based tumor burden between pre-BL, BL and FU examinations in relation to days between imaging exams. For the pre-BL timepoint, the last imaging exam before BL was applied, unless the time interval was less than 2 weeks or more than 6 months; this was intended to limit time bias in the calculation of TGR. Overall response and PFS were determined based on Lugano criteria. Proportional Cox regression analysis studied association of TGR with OS. For survival analysis, OS was analyzed using Kaplan-Meier survival curves.

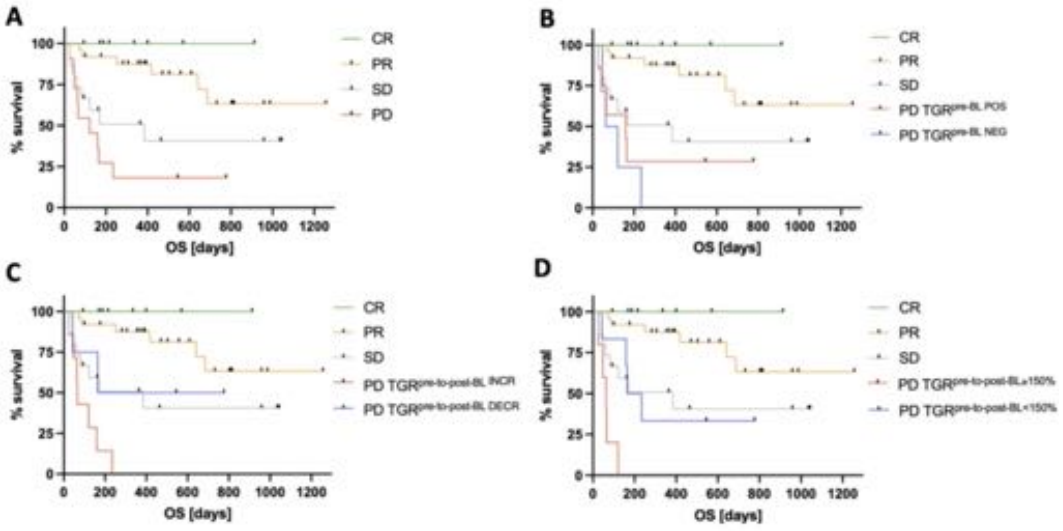
Results: 59 out of 81 patients met the inclusion criteria. At 30-day FU 8 patients (16%) had a CR, 25 patients (42%) a PR, 15 patients (25%) a SD, and 11 patients (19%) a PD according to Lugano criteria. The Median $TGR^{pre\text{-}BL}$ was −0.6 mm^2/d, 24.4 mm^2/d, −5.1 mm^2/d, and 18.6 mm^2/d and the median $TGR^{post\text{-}BL}$ was −16.7 mm^2/d, −102.0 mm^2/d, −19.8 mm^2/d and 8.5 mm^2/d in CR, PR, SD, and PD patients, respectively. PD patients could be subclassified into a cohort with an increase in TGR (7 of 11 patients [64%], PD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ INCR}$) and a cohort with a decrease in TGR (4 of 11 patients [36%], PD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ DECR}$) from pre- to post-BL. In general, the Lugano criteria at 30-day FU1 performed well for OS stratification (Figure 1A; $p < 0.001$). Interestingly, when PD patients were subdivided according to their $TGR^{pre\text{-}BL}$, those with a positive $TGR^{pre\text{-}BL}$ showed longer OS compared to the $TGR^{pre\text{-}BL\ NEG}$ group (Figure 1B; $p < 0.001$). The most interesting result was observed when PD patients were divided into a cohort with an increase in TGR (PD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ INCR}$) and a second cohort with a decrease in TGR (PD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ DECR}$) from pre- to post-BL. PD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ DECR}$ exhibited similar OS to patients

Table 1. Influence of pre- and post-BL TGR on PFS and OS

	No. of Patients	Median $TGR^{pre\text{-}BL}$	Median $TGR^{post\text{-}BL}$	Median PFS	Median OS
CR $TGR^{pre\text{-}to\text{-}post\text{-}BL\ INCR}$	3 (38%)	-29.7 mm2/d	-3.4 mm2/d	not reached	not reached
CR $TGR^{pre\text{-}to\text{-}post\text{-}BL\ DECR}$	5 (62%)	+15.7 mm^2/d	-54.5 mm^2/d	not reached	not reached
PR $TGR^{pre\text{-}to\text{-}post\text{-}BL\ INCR}$	1 (4%)	-18.8 mm^2/d	-16.8 mm^2/d	343 d	not reached
PR $TGR^{pre\text{-}to\text{-}post\text{-}BL\ DECR}$	24 (96%)	+25.5 mm^2/d	-103.8 mm^2/d	641 d	not reached
SD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ INCR}$	7 (47%)	-23.8 mm^2/d	-12.9 mm^2/d	97 d	384 d
SD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ DECR}$	8 (53%)	+2.9 mm^2/d	-21.9 mm^2/d	56 d	126 d
PD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ INCR}$	7 (64%)	-14.5 mm^2/d	+88.9 mm^2/d	30 d	65 d
PD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ DECR}$	4 (36%)	36.1 mm^2/d	-96.6 mm^2/d	39 d	471 d

Shown are the number (No.) of patients, median tumor growth rate pre- ($TGR^{pre\text{-}BL}$) and post-baseline ($TGR^{post\text{-}BL}$), median progression-free survival (PFS), and overall survival (OS) according to their Lugano response overall response at FU1. The color coding also corresponds to the Lugano response categories with complete response (CR; green), partial response (PR; orange), stable disease (SD; grey), and progressive disease (PD; red).

Figure 1. Overall Survival Stratification with TGR-modified Lugano Criteria at 30 Days



Analysis of overall survival (OS) by 30-day Lugano overall response modified by TGR. **A** depicts Kaplan-Meier curves for OS ($p<0.001$) by Lugano response category. **B** shows OS data ($p<0.001$) with modification of PD category by grouping patients into a group with positive pre-baseline (PD $TGR^{pre\text{-}BL\ POS}$) and negative pre-baseline TGR (PD $TGR^{pre\text{-}BL\ NEG}$). **C** demonstrates OS analysis by separation of PD patients to a cohort with an increase of TGR ≥100% (PD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ INCR}$) and a second cohort with increase <100% or decrease in TGR (PD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ DECR}$) from pre- to post-baseline, while **D** depicts a dichotomization by 150% increase in TGR.

classified as SD, while PD $TGR^{pre\text{-}to\text{-}post\text{-}BL\ INCR}$ had significantly shorter OS (65 days vs. 471 days; Figure 1C; $p < 0.001$). Further, increasing the threshold for TGR pre- to post-BL change showed no additional benefit in OS stratification, as shown for a cut-off of 150% (Figure 1D).

Conclusion: In the context of CART, the additional use of $TGR^{pre\text{-}BL}$ and its change to $TGR^{post\text{-}BL}$ determined at 30-day FU1 showed better OS prognostication for patients with overall progressive disease according to Lugano criteria. Therefore, this modification of the Lugano classification should be explored as a potential novel imaging biomarker of early response.

The research was funded by: No funding to report.

Keywords: Diagnostic and Prognostic Biomarkers, Imaging and Early Detection, PET-CT

No conflicts of interests pertinent to the abstract.

250 | BASELINE PET TOTAL METABOLIC TUMOR VOLUME HAS A PROGNOSTIC ROLE IN PTCLS—DATA FROM INTERNATIONAL PROSPECTIVE T-CELL PROJECT 2.0

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Introduction: Peripheral T-cell lymphomas (PTCLs) are a rare, heterogeneous group of hematological malignancies with extremely poor prognosis for almost all subtypes. Functional imaging based on 18-fluorodesoxyglucose positron emission tomography (PET), used for all other lymphoma subtypes, is challenging in PTCLs. Recently, also radiomics, i.e., the extraction of features from the images describing several underlying characteristics of the tumor such as heterogeneity, has demonstrated to provide a better characterization of the disease and reserve some prognostic value, but in this case, no experience in PTCLs lymphoma is available. It has been reported the prognostic value of TMTV in predicting the disease prognosis PTCLs through pre-treatment PET/CT imaging. However, these are limited data on pretreatment evaluation.

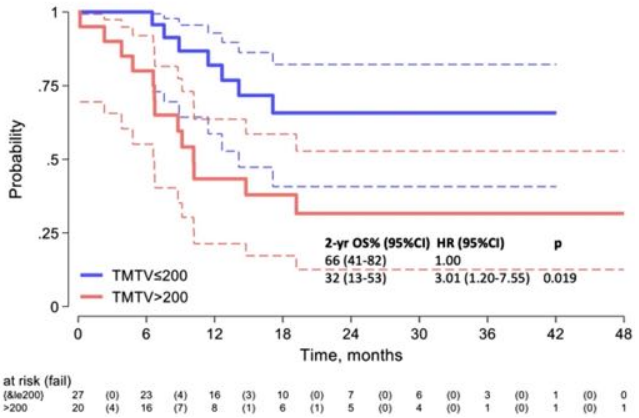
Patients and methods: This study aimed to investigate whether the metabolic parameters on baseline PET could be used to predict the outcome of PTCL patients, and was conducted as a retrospective analysis of the prospective T-Cell Project 2.0 (NCT03964480). Patients were eligible if a baseline PET was available for central review. Anonymized PET images acquired within TCP 2.0 underwent a central review on WIDEN platform by a pool of nuclear medicine physicians. Tumor segmentation was performed with a percentage threshold of 41% of SUV_{max} in a lesion. TMTV was defined as sum of MTV through all the lesion of the body.

Results: Sixty-six PTCLs patients were enrolled in this study from 8 international centers, and 48 were confirmed eligible and were evaluated in the present study. Median follow-up time was 18 months. PFS and OS at 2 years were 43% and 58% respectively. Median TMTV was 93 ml (25%–75% 30–419). A TMTV of 200 ml was chosen as threshold between high and low risk group for PFS. The same threshold was applied to OS. Overall, 27 patients (56%) were identified as having high TMTV without meaningful **differences among PTCL subtypes**. Patients with TMTV >200 ml had shorter 2y-PFS and -OS rates (27% and 35%, respectively), compared to patient with lower TMTV (62%, and 82%, respectively) describing both as statistically significant behavior (log-rank of 0.019 for PFS and 0.01 for OS).

In univariate analysis, in addition to TMTV >200 ml, B-symptoms, PS >1, stage III/IV, ALC $< 1 \times 10^9$/L, were adverse prognostic features for PFS, while LDH > UNL, PS > 1, Hb < 12 g/dL, albumin < 3.5 g/dL, and ALC $< 1 \times 10^9$/L were correlated with lower OS rates.

Conclusion: The preliminary data in this study confirms that TMTV is a strong prognostic factor for both PFS and OS in patients with PTCL. It warrants further validation as a biomarker for development of first-line PET-adapted approaches in PTCL.

Figure 1. **Progression-free survival, TMTV >200**



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Keywords: Aggressive T-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, PET-CT

No conflicts of interests pertinent to the abstract.

251 | INTERIM 3-DIMENSIONAL VOLUMETRIC RESPONSE (3DVR) IS ASSOCIATED WITH BETTER OVERALL SURVIVAL OF PATIENTS (PTS) WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)

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Introduction: PCNSL outcome risk determination is currently not standardized and the prognostic role of 2-Dimensional (2D) response assessment is controversial (van de Meulen 2021). 3DVR; defined as a reduction of at least 65%, is predictive of solid brain tumour outcomes (Ellingson 2018). Here we report the associations of baseline 3-Dimentional Volume (3DV), and interim 3DVR, with PCNSL survival.

Methods: This is a retrospective multicentre study of the impact of MRI-measured 3DV on outcomes in adult PCNSL pts receiving immunochemotherapy. 3DV was calculated centrally using MIMvista software. 2D response was determined according to standard PCNSL response criteria (Abrey 2005). EZR on R commander was used for statistical analysis. An optimal threshold for 3DVR was explored by ROC analysis as well as solid tumour cut offs used; Kaplan-Meier survival curve methodology and logrank tests were used for survival comparisons. Fisher's exact test was used to compare the distribution of pt characteristics (age, sex, LDH, ECOG) between groups.

Results: 78 pts were identified between 2009 and 2021, 60 had paired baseline & interim MRIs. Median age was 66.5y (range 22–86); 59% were male. All pts received rituximab & methotrexate-based chemotherapy: R-MPV (54%), R-MATRIX (13%), other-including single-aged methotrexate (33%). No pts underwent transplant. Median follow-up was 63 months, 5-year OS was 62.5%. Median baseline 3DV was 11.8 mLs (range 0.23–331.5 ml). Baseline 3DV did not correlate with overall survival (OS). As expected, interim 2D overall response (complete response; CR, or partial response;PR) was associated with longer OS compared to stable disease or progression ($p = 0.01$). However, in pts with 2D interim response (CR or PR; $n = 56$), there was no OS difference between CR versus PR ($p = 0.6$, Figure 1a). In contrast, 3DVR <65% was strongly associated with inferior OS (median OS 11.8m vs. not reached; $p < 0.001$, Figure 1b) in the 56 responding pts. ROC analysis determined 58% as the optimal 3DVR cutoff in our analysis. 3DVR < 58% retained association with inferior OS ($p < 0.001$). There were no significant differences in outcomes according to age >60 years, sex, elevated LDH and ECOG 2–4 between groups with CR versus PR, 3DVR ≥ or <65%, ≥ or <58%.

Conclusion: An association between baseline 3DV and OS was not observed in our analysis. Standard interim 2D assessment of CR versus PR did not correlate with OS in PCNSL, however 3DVR is associated with inferior OS in pts with chemotherapy responsive PCNSL. Interim 3DVR assessment potentially improves identification of poor prognosis PCNSL.

Keyword: Imaging and Early Detection

No conflicts of interests pertinent to the abstract.

HODGKIN LYMPHOMA

252 | BASELINE-PET DERIVED METRICS ARE THE MOST RELEVANT FACTORS FOR RISK STRATIFICATION IN EARLY-STAGE NONBULKY HL: PRELIMINARY RESULTS OF THE RAFTING TRIAL

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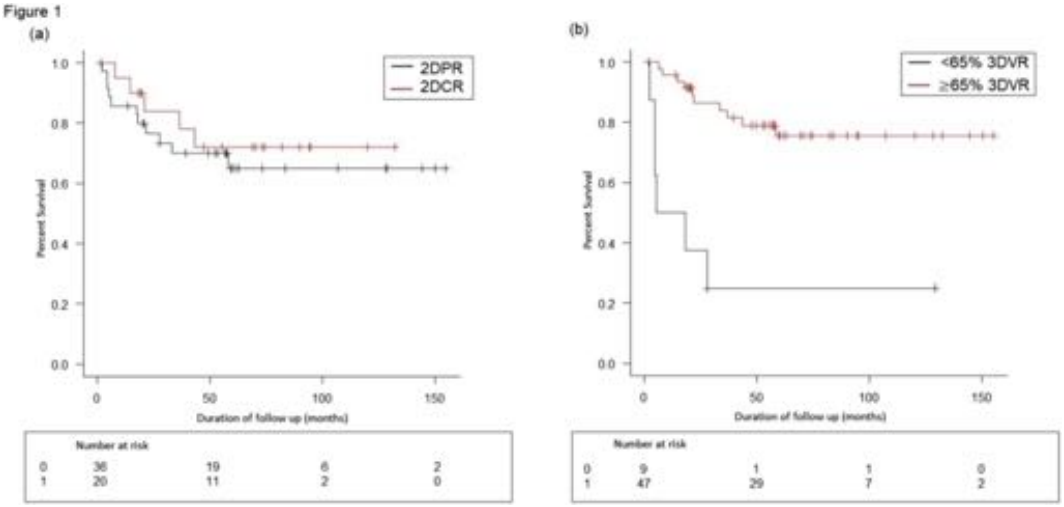

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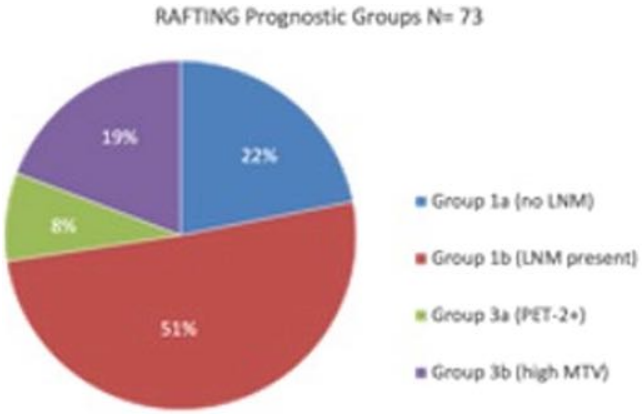
Introduction: The efficacy of combined-modality treatment (Tx) with chemotherapy (CT) and radiotherapy (RT) in early-stage Hodgkin Lymphoma (eHL) is offset by long-term morbidity, with a cumulative incidence of 2nd primary malignancy at 40 years of 48.5% (Schaapveld 2015). The RAFTING trial (NCT Id. 04866654) is a phase-2 prospective single-cohort international study to explore the effectiveness of a risk-adapted Tx in non-bulky stage I-IIA eHL, based on the risk of CT failure (TxF) in a single-patient (p.) basis and in a personalized medicine design.

Methods: p. are first stratified in 3 classes of TxF risk, depending on (a) modified EORTC criteria (m-EORTC), in which bulky is replaced by a Large Nodal Mass (LNM), defined by a longest ∅ measuring ≥5 cm in CT or PET/CT, (b) Metabolic Tumor Volume (MTV), with a SUVmax threshold method of 41% and cutoff value of 84 ml, and (c) PET-2 result (5-point scale). Tx stratification: Group 1: PET-2 neg. & low MTV p., treated either with 2 (group 1a) or 4 (group 2b) ABVD depending on no or ≥1 m-EORTC criterion presence, addressed, once in CR, to a 3-monthly cell-free tumor DNA (ctDNA) assay (CAPPSeq. Method, Spina 2018); Group 2: group 1 p. with < CR after ABVD or in "limited" relapse (LR), defined by eHL relapse in old and up to 3 new nodal areas, addressed to Involved-Node RT (INRT) and Nivolumab (N), 240 mg. i.v. twice a month for 24 doses; Group 3: PET-2+ and/or high MTV p., treated with the triplet ABVD × 4, INRT, 20 or 30 Gy (A-RxT-N). All PET/CT scans are centrally reviewed by an expert panel. The trial primary endpoint is a 3-Y PFS ≥90% in group 1 p. The secondary endpoints are: (a) Effectiveness of RxT (36 Gy) and N (same schedule of Group 3), in rescue p. with LR (b) effectiveness of the triplet A-RxT-N in high-risk (Group 3) eHL; (c) predictive value of ctDNA in detecting an impending eHL relapse after CT alone.

Results: Preliminary results of risk stratification upon enrolment of the first 104/180 (58%) of the pre-planned sample size: in a per-protocol analysis, 88/104 (85%) turned out eligible and 73 stratified for risk. Non-eligibility reasons were higher HL stage, or bulky (10 p.) and early Tx stop, for p./investigator decision: (6p.). Out of 73 p. stratified, 53 (73%) were low-risk (Group 1), and 20 (27%) high risk (Group 3). Out of 53 low-risk p., 16 were in Group 1a: one of them was addressed to salvage Tx with ASCT because of an extended relapse 3 months after CT end. As many as 37 (70%) of low-risk p. belonged to Group 1b, mostly because of the presence of a LNM; two of them had a LR (entering Group 2) and started RxT-N rescue. Twenty p. (27%) had high-risk disease, most (14) for a high MTV, and a minority (6) for a positive PET-2. Updated results will be presented.

Conclusions: LNM and MTV, both assessed in baseline PET/CT, turned out as the most frequently used tools to guide treatment in RAFTING trial, superseding PET-2 and possibly paving the way to future eHL Tx options based on new metrics in baseline PET/CT.



The research was funded by: Polish Medical Agency ABM
Ongoing Trial

Keywords: Liquid biopsy, Ongoing Trials, PET-CT

No conflicts of interests pertinent to the abstract.

253 | PET-ADAPTED THERAPY WITH NIVOLUMAB PLUS ADRIAMYCIN, VINBLASTINE, AND DACARBAZINE FOR NEWLY DIAGNOSED STAGE III OR IV HODGKIN LYMPHOMA

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Introduction: Interim PET is highly predictive of outcome for patients (pts) with stage III or IV Hodgkin lymphoma (HL) treated with 6 cycles of Adriamycin, Bleomycin, Vinblastine, Dacarbazine (ABVD). The RATHL study showed that PET-2 negative (neg) pts receiving 6 cycles

of ABVD can stop bleomycin after 2 cycles without compromising efficacy. Furthermore, PET-2 positive (pos) pts appear to have improved outcomes if treatment is intensified with BEACOPP (Johnson, et al. NEJM 2016). We hypothesized that introduction of programmed death (PD)-1 blockade may also improve outcomes for PET-2 pos pts and allow them to avoid BEACOPP-associated toxicity.

Methods: We conducted a multicenter, investigator-initiated phase II study for pts with newly diagnosed stage III or IV HL. Pts initially received 2 cycles of ABVD. PET-2 neg pts (defined as Deauville score of 3 or better) received 4 additional cycles of AVD. PET-2 pos pts received 4 cycles of AVD plus nivolumab (240 mg IV every 14 days). Pts could receive cycles 1 and 2 of ABVD off-study and enroll if PET-2 was determined to be positive (Deauville score 4 or 5). The primary endpoint was 2-year progression-free survival (PFS) for PET-2 pos pts. The study was initially designed to enroll 26 PET-2 pos pts however due to slow accrual, the study was closed after 19 PET-2 pos pts enrolled.

Characteristic, n (%)	Total (n=39)	PET-2 negative (n=20)	PET-2 positive (n=19)
Median age (range)	35 (19-58)	35 (21-58)	35 (19-58)
Male	23 (58%)	12 (60%)	11 (58%)
Race			
White	31 (79%)	15 (75%)	16 (84%)
Black	3 (8%)	2 (10%)	1 (5%)
Asian	4 (10%)	2 (10%)	2 (11%)
Unknown	1 (3%)	1 (5%)	0 (0%)
Stage			
III	10 (26%)	7 (35%)	3 (16%)
IV	29 (74%)	13 (65%)	16 (84%)
B symptoms	20 (51%)	11 (55%)	9 (47%)
IPS score			
0-2	21 (53%)	10 (50%)	11 (57%)
3-7	18 (46%)	10 (50%)	8 (42%)
PET-2 Deauville			
1		2 (10%)	
2		13 (65%)	
3		5 (5%)	
4			14 (74%)
5			4 (21%)
missing			1 (5%)
PET-6 Response			
Negative	36 (92%)	19 (95%)	17 (89%)
Positive	3 (8%)	1 (5%)	2 (11%)

Results: 39 pts enrolled, including 20 PET-2 neg and 19 PET-2 pos. 26 pts received cycles 1 and 2 of ABVD on-study. Among them, 20 (77%) were PET-2 neg and 6 (23%) PET-2 pos. An additional 13 pts received cycles 1 and 2 of ABVD off-study and enrolled based upon PET-2 positivity. Among the 39 pts, median age was 35 years (19–58), 74% had stage IV disease, and 46% had IPS score of 3–7 (Table). Among PET-2 neg pts there were 3 events; 1 pt with biopsy confirmed refractory HL and 2 with biopsy-confirmed relapse of HL 6 and 23 months after treatment completion. Among PET-2 pos pts there were 6 events; 2 pts remained PET-positive on PET-6 and end of treatment biopsies showed gray zone lymphoma and T-cell/histiocyte rich B cell lymphoma, respectively. 4 PET-2 pos pts developed biopsy-confirmed relapse of HL 7–18 months after treatment completion. 2-yr PFS (Figure) for PET-2 neg and pos pts were 90% (95% CI: 78–100) and 65.7% (95% CI: 46.6–92.6), respectively. After a median follow-up of 36 months, there was 1 death (in a PET-2 neg pt who experienced sudden death while in remission 3 years after treatment completion).

Conclusion: In HL pts treated with ABVD, those with PET-2 pos responses may benefit from switching to nivolumab plus AVD. Larger, randomized studies are needed to confirm the role of changing therapy for pts with PET-2 pos disease. Incorporation of modern risk factors, such as metabolic tumor volume or circulating tumor DNA, may help identify pts most likely to benefit from change in treatment.

The research was funded by: Bristol Myers Squibb; Adam R. Spector Foundation

Keywords: Chemotherapy, Hodgkin lymphoma, Immunotherapy

Conflicts of interests pertinent to the abstract.

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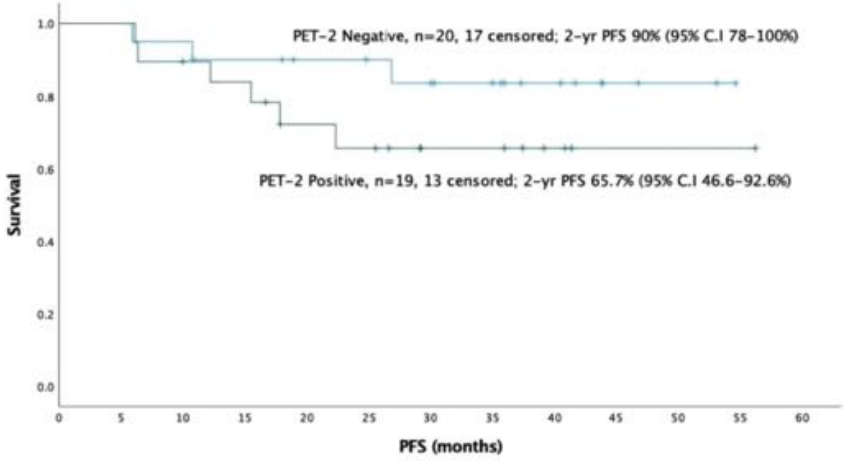
Progression Free Survival for PET-2 negative and PET-2 positive patients



Z. Epstein-Peterson
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A. Kumar
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Honoraria: stra Zeneca, Kite Pharmaceuticals, Janssen, Genentech, and Loxo/Lily Pharmaceuticals
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Stock ownership: Owkin
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Consultant or advisory role: Genentech, GenMab, Seagen and Lilly USA

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Consultant or advisory role: Incyte, EUSA Pharma, Loxo
Research funding: Roche and Takeda.

254 | BRENTUXIMAB VEDOTIN, NIVOLUMAB, DOXORUBICIN, AND DACARBAZINE FOR EARLY-STAGE CLASSICAL HODGKIN LYMPHOMA: UPDATED RESULTS FROM AN ONGOING PHASE 2 STUDY (SGN35-027 PART C)

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Introduction: Brentuximab vedotin (BV) and nivolumab are well tolerated, active treatments for patients (pts) with classical Hodgkin lymphoma (cHL) (Advani 2021; Yasenchak 2020). Herein, we present updated efficacy and safety results from an ongoing phase 2 study of a novel combination of BV + nivolumab with doxorubicin and dacarbazine among pts with early-stage cHL (SGN35-027 Part C).

Methods: SGN35-027 (NCT03646123) Part C enrolled pts with Ann Arbor stage I or II cHL without bulky disease (single node or nodal mass with a diameter <10 cm on computed tomography imaging). Pts received 4 cycles of AN + AD (BV 1.2 mg/kg [A], nivolumab 240 mg [N], doxorubicin 25 mg/m^2 [A], and dacarbazine 375 mg/m^2 [D] administered intravenously on Days 1 and 15 of each 28-day cycle). Radiation was not included. The primary endpoint was the complete response (CR) rate at end of treatment (EOT). Secondary endpoints

included safety and tolerability, objective response rate (ORR), duration of response, duration of complete response, and progression-free survival.

Results: Part C enrolled 156 pts and 154 pts received at least 1 dose of study treatment. The majority of pts were white (84%), <65 years old (92%), and female (55%). Median age was 31.0 years (range: 18, 77). Pts had stage I (11%) or II (89%) cHL without bulky disease.

All data are based on a cutoff of 28 November 2022. The Efficacy Evaluable population (completed an EOT response assessment) had 147 pts. A 92% CR rate and 98% ORR were observed among these pts (see table for efficacy data). The planned 4 treatment cycles were completed by 94% of pts. Three percent of pts discontinued treatment (all study drugs) because of treatment-emergent adverse events (TEAEs). Thirty-three percent and 3% of pts experienced Grade ≥3 treatment-related TEAEs and Grade ≥3 treatment-related peripheral sensory neuropathy, respectively. Treatment-emergent immune-mediated adverse events (IMAEs) were experienced by 21% of pts, and 6% of pts experienced Grade ≥3 treatment-emergent IMAEs. Treatment-related serious TEAEs were experienced by 13% of pts. No deaths occurred.

Part C is ongoing with 85% of pts in long-term follow-up.

Conclusions: Updated results indicate that AN + AD has promising efficacy and an acceptable safety profile in pts with early-stage cHL without bulky disease. No new safety signals were observed.

Response	All Treated N=154 % (95% CI)	Efficacy Evaluable N=147 % (95% CI)
ORR at EOT (CR+PR)	94 (88.4, 96.8)	98 (94.2, 99.6)
CR	88 (81.4, 92.4)	92 (86.2, 95.7)
Partial response (PR)	6 (2.7, 10.8)	6 (2.8, 11.3)
Stable disease	0	0
Progression	0	0
Indeterminate response[a]	2	2
Not evaluable	5	Not applicable

a. Confirmatory scan pending at time of data cutoff. Two pts' responses converted to CR after cutoff. No pts received any additional antilymphoma therapy.

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Keywords: Combination Therapies, Hodgkin lymphoma, Immunotherapy

Conflicts of interests pertinent to the abstract.

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Research funding: Bristol-Myers Squibb, Celgene, Octernal Therapeutics, Seagen, Takeda, Pharmacyclics

255 | IMPACT OF PET-2 GUIDED TREATMENT DE-ESCALATION ON TIME-TO-RECOVERY FROM CANCER-RELATED FATIGUE IN ADVANCED STAGE HODGKIN LYMPHOMA: RESULTS FROM THE GHSG HD18 STUDY

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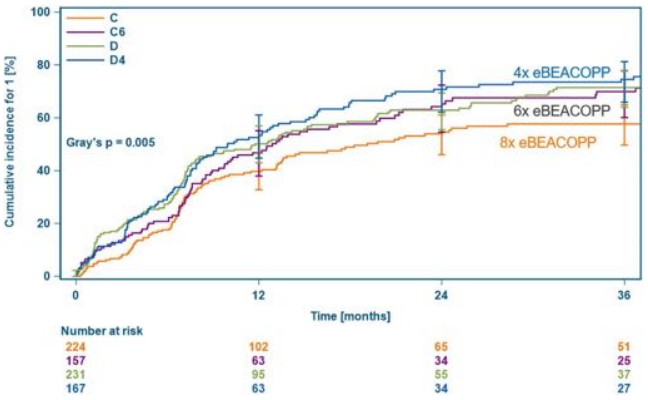
Introduction: Persisting cancer related fatigue (CRF) has impact on health related quality of life (HRQoL) and social re-integration of patients with Hodgkin lymphoma (HL). The GHSG HD18 trial established treatment PET-2 guided de-escalation of treatment for advanced-stage HL as new standard. Here, we investigate the impact of treatment de-escalation in HD18 on long-term HRQoL domains and time-to-recovery from fatigue (TTR-F).

Methods: Mean fatigue scores (FA) of the EORTC QLQ-C30 questionnaire are reported descriptively for baseline, interim, end-of-treatment, and yearly follow-up. TTR-F was defined as time from end of chemotherapy until first occurrence of FA <30 or the time of last questionnaire (censored). TTR-F was analyzed and compared using time-to-event methods including cumulative incidence and cox proportional hazard models, as recommended by the SISAQoL consortium. Effect of disease, patient and treatment characteristics on 2y HRQoL domains was analyzed using multiple regression.

Results: 2101 patients aged 18–60 years with advanced-stage HL were recruited in HD18, of whom 156 were found ineligible before or after randomization. PET-2 negative Patients were randomized between 8x eBEACOPP (arm C, $n = 288$) and 4x eBEACOPP (arm D; $n = 285$), and between 6x eBEACOPP (arm C6; $n = 216$) and 4x eBEACOPP (D4; $n = 216$). HRQoL questionnaires at baseline were available in 83.9% of all randomized patients. Overall, baseline FA and age were significantly associated with TTR-F, whereas sex was not. TTR-F differed between trial arms for PET-2 negative, but not for PET-2 positive patients. Particularly, treatment reduction from 8 to 4 cycles of eBEACOPP led to a significantly shorter TTR-F (HR 1.41, $p = 0.008$). Reducing the cycle number of eBEACOPP from 8 to 6 cycles (HR 1.21, $p = 0.2$) or 6 to 4 cycles (HR 1.22, $p = 0.18$) speeded TTR-F accordingly but was not statistically significant. For PET-positive patients a significantly slower TTR-F was observed with addition of Rituximab (HR 0.7, $p = 0.0163$). In PET-2-negative patients, median TTR-F was 19 months (CI95: 13–28) in arm C, 13 months (CI95: 10–20) in arm C6, 12 months (CI95: 8–15) in arm D and 10 months (CI95: 8–13) arm D4. HRQoL at baseline and age were the main determinants of 2y HRQoL domains.

Conclusion: Individualized PET-2-guided de-escalation of first-line treatment for patients with advanced-stage HL significantly shortens the time to recovery from CRF and increases the proportion of patients without clinically relevant long-term CRF. We encourage



reporting TTR-F as patient reported outcome in randomized clinical trials of HL. Our analysis supports the development of highly active therapeutic regimens for HL with short treatment times to improve recovery from CRF.

The research was funded by: Deutsche Krebshilfe, Swiss State Secretariat for Education and Research, and Roche Pharma AG.

Keywords: Chemotherapy, Hodgkin lymphoma, Late Effects in Lymphoma Survivors

No conflicts of interests pertinent to the abstract.

256 | REPLACING PROCARBAZINE WITH DACARBAZINE IN ESCALATED BEACOPP REDUCES CLINICAL TOXICITY WITH NO LOSS OF EFFICACY YET PROTECTS STEM CELLS FROM EXCESS SOMATIC MUTATIONAL DAMAGE

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Internationally it has become increasingly common practice to modify escalated BEACOPP (eBPP) by replacing procarbazine with dacarbazine to reduce haematopoietic stem cell and gonadal toxicity in Hodgkin lymphoma (HL) patients. A similar replacement of procarbazine in COPP (to COPDac) has reduced gonadal toxicity and conferred comparable long-term event-free survival in children (EuroNet-PHL-C1 trial; Mauz-Körholz et al. Lancet Oncol 2021).

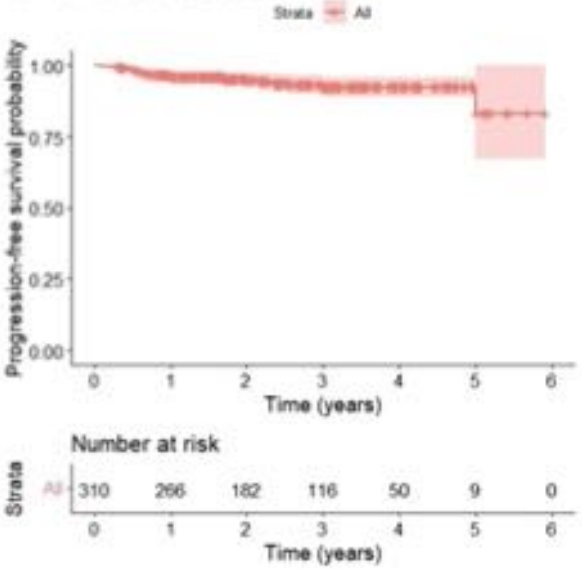
Using a real-world multi-centre dataset of 25 UK, Ireland and France centres we have 2.5 years median follow-up of 311 high risk advanced stage HL patients treated with first-line escalated BEACOPDac (eBPDac). We have compared toxicity data with 73 UK patients treated with eBPP and outcome data with 2073 patients treated in the German HD18 trial. We show eBPDac patients have a reduced blood transfusion requirement and earlier return of menstrual periods compared with real-world eBPP patients (Figure 1A). We have observed 16 relapses, 3 non-lymphoma deaths and an estimated 3 yr PFS of 92.4% with progression-free survival (PFS) and overall survival (OS) comparable to HD18 (Figure 1B). Through collaboration with the GHSG we are performing a case matched analysis with the HD18 cohort and will present the results at 17-ICML.

The differential impact of procarbazine and dacarbazine-containing regimens on stem cell genomic toxicity was investigated by whole genome sequencing (WGS) of haematopoietic stem and progenitor cell (HSPC) colonies from patients treated with eBPP, eBPDac and ABVD. We found that HSPCs from ABVD and eBPDac-treated patients had similar minor excess somatic mutation burdens compared to age-matched normal HSPCs of 183 (CI95% = 110–256) and 291 (CI95% = 242–340) mutations respectively. In contrast, the HSPCs from eBPP-treated patients had a dramatically increased excess mutation burden of 1153 (CI95% = 937–1369). Analysis of the mutational profiles revealed that every patient who received procarbazine had a clear SBS25-like mutational signature, demonstrating that SBS25 is attributable to procarbazine. We have also identified the SBS25 signature in malignant and non-malignant non-haematopoietic tissue in patients previously exposed to procarbazine, suggesting this drug induces the SBS25 signature in multiple somatic tissues. To determine whether procarbazine also induces SBS25 in germ cell DNA we performed duplex sequencing of sperm from an eBPP-treated male, and WGS of buccal DNA from 3 children with pre-conception maternal exposure to eBPP × 6 cycles. Reassuringly, SBS25 was not found in the germline of all 3 children, while the results of the sperm mutation analysis are expected imminently. In summary, our data suggest that eBPDac is highly efficacious HL therapy. Replacing procarbazine with dacarbazine is unlikely to compromise the efficacy of eBPP and the substitution improves the clinical and genomic toxicity of the regimen.

Baseline Characteristics	Escalated BEACOPP N=73	Escalated BEACOPDac N=311	p-value
Median Age (range)	26 (16-57)	26 (16-62)	U=11192, p=0.852
Male sex [%]	37 (51%)	185 (59%)	Fisher_p=0.189
Stage IB / IIA / IIB	15 (21%)	52 (17%)	
3	9 (12%)	50 (16%)	Fisher_p=0.620
4	49 (67%)	209 (67%)	
IPS 0-2	17 (23%)	116 (37%)	
3-4	40 (55%)	152 (49%)	
5-7	16 (22%)	42 (14%)	Fisher_p=0.038
IPS 3+	56 (77%)	194 (63%)	
Unknown	0	1	
Toxicity Outcomes			
Mean day 8 ALT (cycles 1-4) [SD]	58.8 (±29.5)	46.0 (±29.2)	t(101)=1.78, p=0.0780
Mean day 8 neutrophils (cycles 1-4) [SD] (GCSF day 9)	3.00 (±1.95)	2.55 (±2.18)	t(132)=1.56, p=0.120
(GCSF day 4)	6.95 (NA)	6.29 (±6.22)	
Mean days non-elective admission (cycles 1-4) [SD]	5.23 (±7.23)	3.32 (±6.06)	U=7727, p=0.040
Mean number of red cell units transfused (cycles 1-4) [SD]	3.69 (±3.89)	1.72 (±2.78)	U=5838, p<1.10E-6
Median follow-up from diagnosis in months [range]	72.1 (5.0-153)	50.0 (0.92-71.1)	U=2919, p<2.2E-16
Mean number of months for return of menstrual period post-chemotherapy [SD]	8.77 (±5.57)	5.04 (±3.07)	t(30)=3.18, p=0.00357
Mean number of cycles completed by women <35 years of age [SD]	5.74(±0.59)	4.83 (±0.93)	U=459, p<2.92E-7

Figure 1A. Patient characteristics and toxicity outcomes of eBPDac cohort vs real-world eBPP cohort

Figure 1B. Kaplan-Meier estimate of progression-free survival of the eBPDac cohort



The research was funded by: Addenbrooke's Charitable Trust

Keywords: Chemotherapy, Hodgkin lymphoma, Late Effects in Lymphoma Survivors

Conflicts of interests pertinent to the abstract.

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Educational grants: Takeda

257 | 'ACOPP' CHEMOTHERAPY FOR OLDER AND LESS FIT PATIENTS WITH HODGKIN LYMPHOMA—A MULTICENTRE, RETROSPECTIVE STUDY

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Introduction: Patients (pts) aged ≥60 years comprise 20%–30% of classical Hodgkin lymphoma (cHL) diagnoses, but are significantly underrepresented in clinical trials and outcomes for this group have not improved in line with advances seen in younger counterparts. Whilst there is evidence that anthracycline-containing regimens result in superior outcomes, older pts typically have poor tolerance of the chemotherapy regimens used in younger pts. We modified the BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) by removing bleomycin and etoposide and dose-reducing cyclophosphamide for use in older pts with co-morbidities. Here we present data from the first 41 pts treated with ACOPP across 3 UK centres.

Methods: The ACOPP regimen comprises doxorubicin 35 mg/m^2 and cyclophosphamide 650 mg/m^2 intravenous infusion day (D) 1, vincristine 1.4 mg/m^2 intravenous injection D8, oral procarbazine 100 mg/m^2 D1-7, prednisolone 40 mg/m^2 D1-14 and subcutaneous G-CSF D9-13. Each centre retrospectively analysed consecutive patients receiving ACOPP for cHL with data recorded in a secure, anonymised database. Medical co-morbidities were quantified using the Cumulative Illness Rating Scale-Geriatric (CIRS-G). Lymphoma diagnosis was not included in the score. Interim assessment after 2 cycles with either computed tomography (CT) or positive emission tomography (PET-CT) was recommended. Statistical analysis was performed using SPSS v28.0.

Results: Forty-one pts previously untreated for cHL were included, with median age 74 and median CIRS-G of 5. The majority (78%) had advanced stage disease. Six cycles of ACOPP were planned for 38/41 patients, of whom 68% completed treatment. Nine pts (22%) had dose reductions, most commonly with vincristine (6/9). Sixty-one percent required hospital admission during treatment, the majority having 1–2 admissions (22/25). Grade 3+ neutropenia was seen in 34%, with a relatively low rate of febrile neutropenia (15%). Neuropathy was seen in 15 patients (37%), all grade 1–2. Six pts died

during the study, only 1/41 (2%) had a direct treatment related death.

Overall response rate was 39/41 (95%), with 34/41 (83%) achieving CR. With median follow-up of 17 months, estimated 2-year PFS and OS were 74% (95% CI: 58–90) and 87% (95% CI: 75–99) respectively.

Conclusion: The ACOPP regimen can be delivered to older pts with significant co-morbidity, with a relatively favourable toxicity profile and promising efficacy. Although only a pilot study, the outcomes in this multicentre study are more favourable than expected in this in this patient group. Treatment of older patients with cHL continues to be an area of unmet need. Whilst treatment in clinical trials should be considered optimal therapy, enrolment in this group remains challenging and the ACOPP regimen offers promising outcomes in a difficult to treat population.

Keywords: Chemotherapy, Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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Other remuneration: Support for medical education: Novartis, Takeda, Roche

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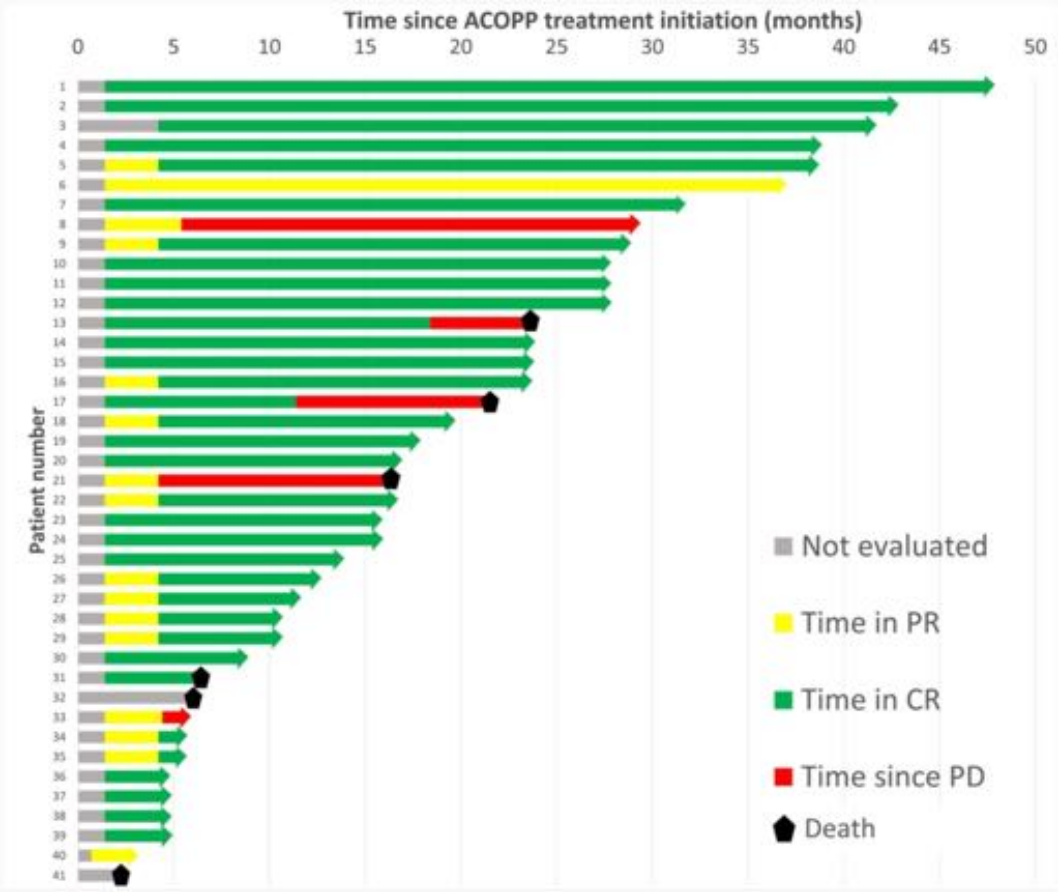

258 | BRENTUXIMAB VEDOTIN (BV) + AVD FOR NEWLY DIAGNOSED CLASSIC HODGKIN LYMPHOMA (CHL): INCIDENCE AND MANAGEMENT OF PERIPHERAL NEUROPATHY (PN) IN A MULTI-INSTITUTION COHORT

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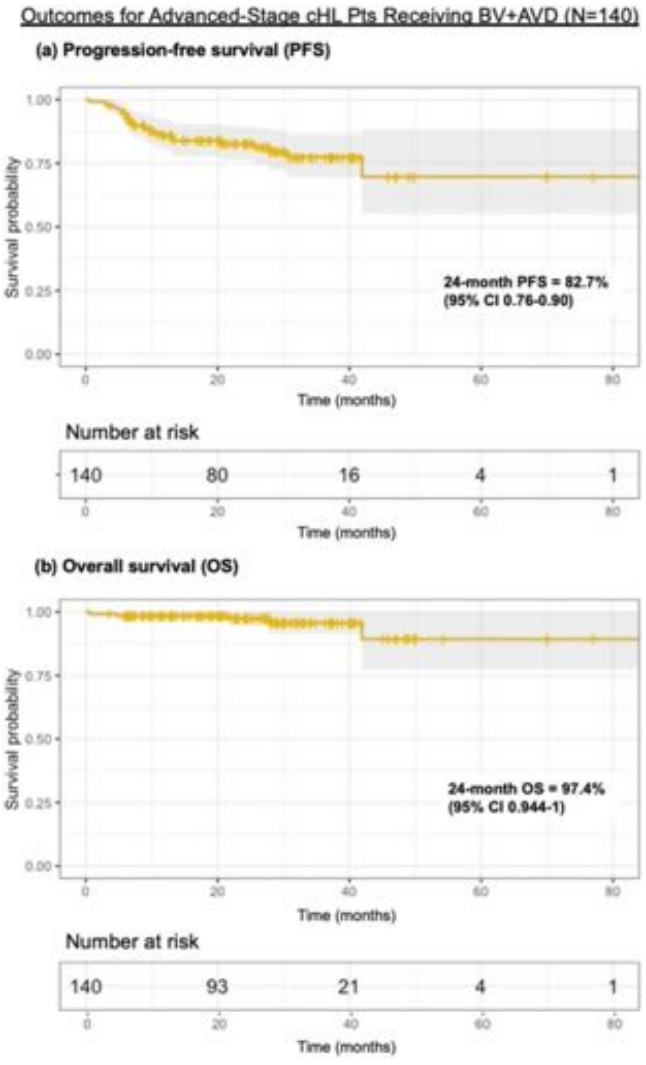
Introduction: BV in combination with doxorubicin, vinblastine, and dacarbazine (AVD) is the new standard of care for newly diagnosed stage III/IV cHL. In the pivotal ECHELON-1 trial, PN was the most common toxicity, seen in 67% of patients (pts) and leading to discontinuation of BV in 6.6%. However, PN from BV+AVD in cHL has not been studied in a non-trial setting, where clinicians may have different strategies for managing it.

Methods: We conducted a multi-site, retrospective study to characterize PN in pts who were planned to receive 6 cycles of BV+AVD for newly diagnosed cHL before 9/2022. Data was obtained from medical records and PN was graded retrospectively using CTCAE v5.0 criteria. Multivariable logistic regression was used to assess factors associated with PN. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan Meier method. A Cox proportional hazards model was used to test the effect of discontinuation on PFS.

Results: 153 pts from 10 US institutions were eligible. Median age was 35 years (range 18–76) with 22% of pts over 60 years old. Thirty-four pts (22%) had at least 1 ineligibility criteria for ECHELON-1, including stage (8% stage I/II), performance status (3% ECOG 3+), preexisting PN (6%), or other comorbidities including HIV and other malignancies (10%). Of advanced stage pts, 41% had IPS 4–7. Median no. BV+AVD cycles was 6 (range 1–6). PN was reported by 80% of pts during treatment; 39% experienced grade (G) 1, 31% G2, and 10% G3. In total, BV was modified in 44% of pts due to PN leading to BV discontinuation in 23% with median no. of doses omitted of 4 (range 1–10), dose reduction in 17% and temporary dose hold in 4%. Vinblastine was modified in 17% of pts due to PN including discontinuation or temporary hold in 10% and dose-reduction in 7%; in 35% of pts with vinblastine modification, BV was continued. None of the factors assessed (age, sex, baseline PN, diabetes mellitus) predicted development of any grade PN. However, higher initial dose of BV in mg (based on weight) was associated with increased risk of grade 2+ PN (OR 1.03, 95% CI: 1.01–1.05, p = 0.002). With median follow up of 24 months (range 0.33–87), PN resolution was documented in 36% and improvement in 33% at last follow up. Ongoing G2+ PN was present in 13% of pts at last follow up. 2-year PFS for the advanced stage patients (n = 140) was 82.7% (95% CI: 0.76–0.90) and OS was 97.4% (95% CI: 0.944–1). Discontinuation of BV due to neuropathy did not affect PFS (HR 1.1, 95% CI: 0.45–2.5).

Conclusions: In the non-trial setting, BV+AVD was associated with a high incidence of PN. In our cohort, which includes pts who would not have been eligible for the pivotal ECHELON-1 trial, BV discontinuation rates were higher than previously reported, but 2-year outcomes remain comparable; discontinuation of BV was not associated with inferior PFS.



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J. Svoboda
Consultant or advisory role: Seagen, BMS, Astrazeneca, Pharmacyclics, Adaptive Biotechnologies, Atara
Research funding: Seagen, Celgene, Pharmacyclics, Merck, BMS, Incyte, AstraZeneca, Adaptive Biotechnologies

259 | BEGEV AS SALVAGE REGIMEN IN FIRST SETTING FOR RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA

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Introduction: One of the most critical issues in the management of Hodgkin lymphoma (HL) patients who resulted as primary relapsed or refractory is to obtain a minimal disease status before autologous stem cell transplantation (ASCT) with a salvage regimen able to induce this status without severe toxicity.

Methods: A single-center retrospective study was conducted to assess effectiveness and safety of BEGEV (bendamustine, gemcitabine, and vinorelbine) regimen as first salvage setting. Patients with HL who were refractory to or had relapsed after one previous chemotherapy line were eligible. The primary end point was complete response (CR) rate after four cycles of therapy. Secondary end points were: overall response rate, stem-cell mobilization activity, and toxicity. Progression-free and overall survival were also evaluated on an intention to treat analysis taking into account ASCT outcomes too.

Results: Fifty-seven patients were eligible for this retrospective analysis. Median age at BEGEV therapy was 36.2 years (range 18–70), and the median time from frontline therapy to the first cycle of BEGEV was 5 months. At the end of BEGEV, 50 patients achieved a complete response (CR, 87.7%), with an overall response rate of 89.5%. Fifty-five patients harvested CD34+ cells and 50 ones underwent ASCT with 49 patients in CR at the end of the therapeutic pathway. With a median follow-up of 31.4 months, 7 CR patients had disease relapse, yielding an estimated disease-free survival of 73.9% at 34 months. The estimated 2-year progression-free survival was 83.4% (median not reached). Six patients had an early BEGEV discontinuation due toxicity, but they were still able to perform ASCT with a CR.

Conclusions: Real-life data on BEGEV regimen as first salvage setting showed a relevant rate of objective responses and a limited myelotoxicity with no impairment of a subsequent mobilization of peripheral blood stem cells. BEGEV regimen was well tolerated, and reversible adverse events were the most common ones.

Keywords: Chemotherapy, Hodgkin lymphoma, Stem Cell Transplant

No conflicts of interests pertinent to the abstract.

260 | EFFICACY OF BRENTUXIMAB CONSOLIDATION BY METABOLIC RESPONSE IN AN INTERNATIONAL REAL-WORLD COHORT OF CLASSIC HODGKIN LYMPHOMA AT HIGH RISK FOR PROGRESSION AFTER ASCT

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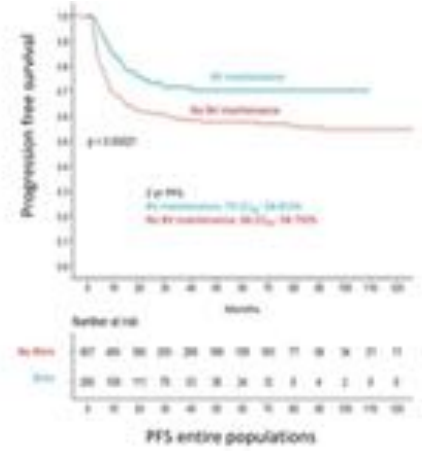
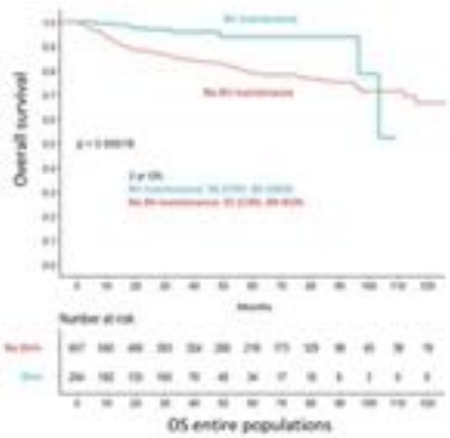
Background: Salvage chemotherapy and autologous stem cell transplant (ASCT) have cure rates of 60–70% in relapsed refractory (R/R) classic Hodgkin lymphoma (cHL). Pre-ASCT compete metabolic response (CMR) compared to partial metabolic response (PMR), is associated with significantly better progression free survival (PFS) and overall survival (OS). Post-ASCT brentuximab vedotin (BV) consolidation improves PFS in pts with high-risk relapse as per ATHERA criteria: early relapse [ER], primary refractory disease [PRD] or extra nodal disease (END). Impact of BV consolidation by pre-ASCT PET-based response is not well characterized. Here we report outcomes of BV consolidation on PFS and OS by pre-ASCT PET-based response in real world cohort of R/R cHL.

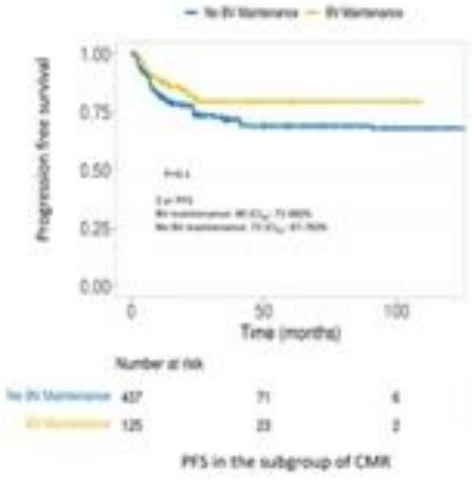
Methods: From a multicenter, international, observational cohort of 15 institutions of US and Czech Republic, adult pts with cHL and high-risk relapse per ATHERA criteria, who had ASCT were included in this study. Demographics, time to relapse, extranodal disease, B symptoms, stage, lines of salvage therapies, ASCT era, BV consolidation were collected. Pre-ASCT metabolic response was determined institutionally according to PET-based Lugano criteria. Study objectives were PFS and OS from date of ASCT. Association of BV consolidation with PFS and OS was assessed in the subgroup of pre-ASCT CMR and PMR using propensity score weighted analysis.

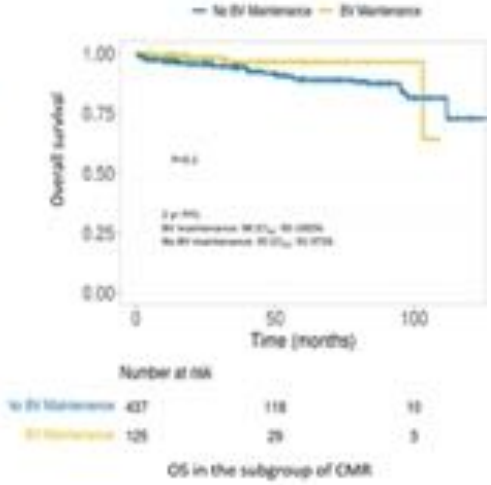
Results: Out of 1158 pts enrolled from January 2011 to December 2020, 880 met ATHERA criteria. Median age was 32 (12–72), 473 (54%) were male, 511 (59%) had advanced stage, 389 (45%) had END, 385 (45%) had B symptoms, 266 (30%) had PRD, 484 (55%) had ER, and 259 (29%) required ≥2 line of salvage pre-ASCT. 527 (60%) had CMR and 222 (25%) had PMR pre-ASCT. 208 received BV consolidation. Median follow up was 37 (0.3–137) months. In all pts, 2-yr PFS was 64% (CI_{95}: 61–68) and OS was 90% (CI_{95}: 88–93). Receipt of BV consolidation was associated with significantly higher 2 yr PFS (HR: 0.7, CI_{95}: 0.5–0.9, $p = 0.0002$) and OS (0.4, CI_{95}: 0.1–0.9, $p = 0.0002$) compared with no BV maintenance. In univariate analysis, increasing age and salvage therapy lines, ER, PRD, END, accounting for age, relapse <12 months, PRD, extranodal disease, salvage therapy lines and ASCT era, BV consolidation was not significantly associated with PFS (0.7, CI_{95}: 0.4–1.2, $p = 0.1$) or OS (0.5, CI_{95}: 0.2–1.4, $p = 0.2$) in the group of pts with pre-ASCT CMR. In pts with pre-ASCT PMR, BV consolidation was associated with higher PFS (0.5, CI_{95}: 0.3–0.9, $p = 0.01$) and OS (0.4, CI_{95}: 0.1–0.8, $p = 0.02$).

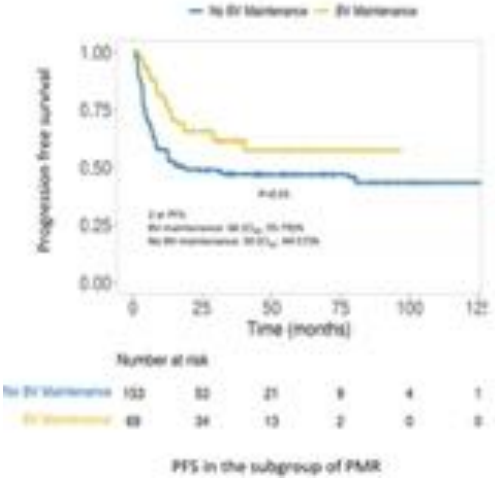
Conclusions: In this cohort of patients with R/R cHL, post-ASCT BV consolidation was associated with better PFS and OS. In propensity score weighted analysis, BV consolidation was associated with better survival in the subgroup of pre-ASCT PMR but not pre-ASCT CMR.

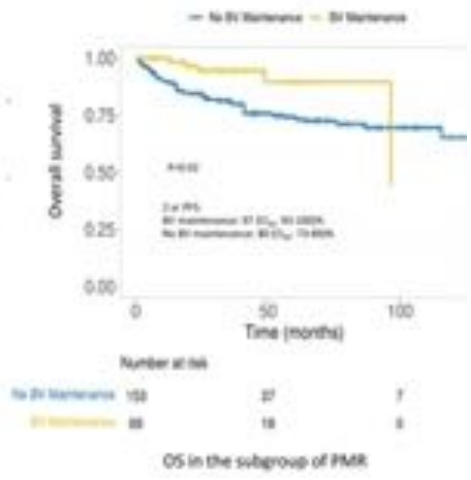












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261 | TOXICITIES AT ONE YEAR FOLLOW-UP IN PATIENTS WITH ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA: RESULTS FROM THE RANDOMIZED PHASE III HD21 TRIAL BY THE GERMAN HODGKIN STUDY GROUP

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Introduction: The HD21 trial compares BrECADD with eBEACOPP for the first-line treatment of advanced stage classical Hodgkin Lymphoma (AS-cHL). We previously reported a superior acute tolerability profile for BrECADD. However, persisting treatment sequelae as peripheral neuropathy or gonadal dysfunction are a major concern for survivors of AS-cHL. Accordingly, resolution of organ toxicities is highly relevant from the patient´s perspective. Therefore, we report treatment-related toxicities at twelve months follow-up (FU12) after treatment in HD21.

Methods: Adult patients ≤60 years of age with AS-cHL were included in this ongoing international open label randomized phase III trial and randomized in a 1:1 ratio to receive PET2-guided 4–6 cycles of either standard eBEACOPP or experimental BrECADD treatment. For detection of treatment sequelae at FU12, non-hematological adverse events and serum levels of FSH levels are reported. The trial was registered at clinicaltrials.gov (NCT02661503) and conducted according to ICH-GCP guidelines.

Results: Between July 2016 and August 2020, we enrolled 1,500 patients from 9 countries. Baseline characteristics were well balanced between treatment arms. Documented FU12 was available in 1395/1470 (94.9%) patients in the ITT cohort. 557 (80.8%) and 566 (80.2%) patients had no documented toxicity following eBEACOPP and BrECADD, respectively. At FU12, grade 2 or higher PNP was reported for 17 (2.7%) patients following eBEACOPP and for 12 (1.9%) patients following BrECADD; however, no or only grade 1 PNP was reported for most patients in both treatment groups with 97.3% for eBEACOPP and 98.1% for BrECADD. Rate of PNP was numerically higher in patients receiving 6 cycles of chemotherapy (3.0%) compared to 4 cycles (1.9%). FSH levels at FU12 were available for 597 patients and were higher for patients who received eBEACOPP (mean FSH 29.4 and 31.8 after 4 and 6 cycles, respectively) compared to BrECADD (mean FSH 18.3 and 20.5 after 4 and 6 cycles, respectively. Other than PNP, most frequent organ toxicities at FU12 were classified as respiratory, thoracic or mediastinal disorders (4.4%), and cardiac disorders (2.9%). All other organ toxicities were rare and equally distributed between trial arms.

Conclusions: Complete resolution of acute adverse events is frequent following either regimen in the GHSG HD21 study. However, less patients report higher grade PNP or impaired gonadal function at FU12 after treatment with BrECADD than after eBEACOPP. Accordingly, persisting toxicities were reported in only few patients after BrECADD. Although these results are indicate good overall tolerability, they still need to be complemented by patient-reported outcomes for which analyses are ongoing. The non-inferiority of the experimental BrECADD regimen also remains to be demonstrated to draw definitive conclusions.

The research was funded by: Takeda

Keywords: Hodgkin lymphoma, Molecular Targeted Therapies, Ongoing Trials

Conflicts of interests pertinent to the abstract.

P. Borchmann
Consultant or advisory role: Takeda Oncology, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, Amgen, Miltenyi Biotech
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Research funding: Takeda Oncology, Roche, Novartis, Merck Sharp & Dohme, Amgen

262 | OUTPATIENT TREATMENT WITH 2 CYCLES OF BENDAMUSTINE, GEMCITABINE AND DEXAMETHASONE IS EFFECTIVE AND SAFE IN R/R HODGKIN LYMPHOMA—POLISH LYMPHOMA RESEARCH GROUP STUDY

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Introduction: BURGUND is a phase II study evaluating the combination of bendamustine, gemcitabine and dexamethasone (BGD) as the first salvage therapy in patients with refractory or relapsed Hodgkin lymphoma (r/r HL).
Patients and Methods: Patients (pts) with r/r HL during or after induction with ABVD were eligible. BGD regimen included bendamustine 90 mg/m^2 iv days 1,2, gemcytabine 800 mg/m^2 iv days 1,4, dexamethasone 20–40 mg po/iv days 1–4 in 3–4 weeks intervals for 2 cycles. The response was evaluated according to the LUGANO criteria. Pts in complete or partial metabolic response (CMR, PMR) after 2 BGD proceeded to autologous hematopoietic cell transplantation (aHCT). Treatment could be extended up to 4 cycles if aHCT was not available immediately after BGD. Treatment was discontinued in case of stable or progressive metabolic disease (SMD, PMD), serious adverse events or patient withdrawal. Pts with PMR were referred for aHCT at the physician's discretion.
The primary endpoint was CMR rate after two BGD cycles. Secondary endpoints were: overall response rate (ORR), 2-y progression-free survival (PFS), 2-y overall survival (OS) and toxicity.
Results: From 10/2017 to 11/2022, 112 pts were enrolled: 45 (40%) male, median age (IQR) 37 (29–49) years. 55 pts (49%) were primary refractory. Pts received 1 ($n = 3$), 2 ($n = 58$), 3 ($n = 28$), or 4 ($n = 23$) cycles of BGD. CD34 mobilization was performed in 6 pts after the 1st, 55 the 2nd, 34 the 3rd, and in 4 after the last BGD. The ORR was 71% ($n = 80$) with 67% CMR ($n = 76$). 75 pts proceeded to aHCT. 31 pts were off-study because of toxicity ($n = 3$) or non-response ($n = 28$). 23 of those pts proceeded to aHCT after third-line treatment.
With a median follow-up of 29 months, the 2-y PFS and OS rates for all pts were 62.6% (95% CI: 53.2%–72.0%) and 90.6% (95% CI: 85.1%–96.1%), whereas in pts who achieved CMR 2-y PFS and OS were 86.0% (95% CI: 77.4%–94.6%) and 97.3% (95% CI: 93.6%–100%). 2-y PFS for relapsed and refractory populations were 75.8% (95% CI: 64.0%–87.6%) and 49.3% (95% CI: 35.8%–62.8%) $p = 0.023$, respectively. There was no difference in OS.
BGD was given mainly outpatient. Primary GCSF prophylaxis was used for 74% of pts ($n = 83$). Grade 3/4 anemia occurred in 8% ($n = 9$) and 10.7% ($n = 12$), thrombocytopenia in 0.9% ($n = 1$) and 3.6% ($n = 4$), neutropenia in 3.5% ($n = 4$) and 7% ($n = 8$) of pts during 2 cycles and extended BGD, respectively. Infections occurred in 18% ($n = 20$) of pts during 2 BGD, 24% ($n = 27$) if treatment was extended, majority of them were GRADE <3. Skin toxicity occurred in 22% ($n = 25$) and 23% ($n = 26$) of pts after 2 and 3–4 BGD cycles. 16 pts died (14%) from HL progression ($n = 2$), COVID-19 ($n = 3$), other infections ($n = 3$), secondary malignancy ($n = 1$), alloHCT complications ($n = 2$), other reasons ($n = 5$).
Conclusions: Two cycles of BGD are feasible and effective salvage chemotherapy even in primary refractory HL. A combination of BGD with immunotherapy may improve efficacy of the BGD regimen.

Keywords: Chemotherapy, Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

263 | AN OPEN-LABEL PHASE 1/2 STUDY OF FAVEZELIMAB PLUS PEMBROLIZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA WITH/WITHOUT PREVIOUS ANTI-PD-1 TREATMENT

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Introduction: Dual blockade of PD-1 and lymphocyte-activation gene (LAG-3) has shown antitumor activity; however, the activity of the combination for patients (pts) with relapsed or refractory (R/R) classical Hodgkin's lymphoma (cHL) is unclear. Initial results of a multicohort phase 1/2 study (NCT03598608) showed that the anti–PD-1 inhibitor pembrolizumab (200 mg Q3W) combined with the anti–LAG-3 inhibitor favezelimab (800 mg Q3W) showed promising antitumor activity and acceptable safety in pts with R/R cHL who either were anti–PD-1 naive (cohort 1) or had progression after anti–PD-1 therapy (cohort 2) (Johnson NA et al. *J Clin Oncol*. 2022;40(16 suppl):7516; Timmerman J et al. *J Clin Oncol*. 2022;40(16 suppl):7545). Updated data with additional follow-up from both cohorts are presented.

Methods: Pts in cohorts 1 and 2 had R/R cHL after autologous stem cell transplant (ASCT) (or were ineligible for ASCT) or did not respond to salvage chemotherapy and had an ECOG PS of 0 or 1. Pts in cohort 1 had no prior anti–PD-1 therapy; pts in cohort 2 had progression within 12 weeks after ≥2 doses of anti–PD-1 therapy, per Cheson 2007 criteria. Pts received pembrolizumab 200 mg Q3W plus favezelimab at the established RP2D (800 mg Q3W) for ≤35 cycles (~2 years). Primary end points were safety and RP2D. The secondary end point was ORR. DOR, PFS, and OS were exploratory.

Results: At the data cutoff (Aug 31, 2022), median follow-up (range) was 25.5 (18.0–37.2) months and 29.3 (9.0–43.4) months in cohort 1 and cohort 2, respectively. Anti–PD-1 was the most recent therapy for 17 pts (50%) in cohort 2. In cohort 1, 47% (14 pts) of pts discontinued treatment, and 74% (25 pts) discontinued treatment in cohort 2. ORR was 80% in cohort 1 (95% CI, 61%–92%, 10 CR, 14 PR) and 29% in cohort 2 (95% CI, 15%–47%, 3 CR, 7 PR). Additional efficacy analyses are included in the Table. Treatment-related adverse events (AEs) occurred in 26 pts (87%) and 28 pts (82%) in cohorts 1 and 2, respectively. The most common treatment-related AEs were hypothyroidism (27%) in cohort 1 and hypothyroidism and nausea (18% each) in cohort 2. Grade 3/4 AEs occurred in 7 pts (23%) in cohort 1 and in 6 pts (18%) in cohort 2. No treatment-related deaths occurred.

Table. Additional Efficacy Outcomes.	Cohort 1 *N* = 30	Cohort 2 *N* = 34
DOR (range), months	25.6 (0.0+ to 28.8+)	21.9 (0.0+ to 24.0)
DOR ≥15 months, %, (Kaplan-Meier estimate)	54	52
PFS, median (95% CI), mo	19.4 (9.0–28.5)	10.7 (5.1–14.7)
PFS at 15 mo, % (Kaplan-Meier estimate)	53	33
OS, median (95% CI), mo	NR (NR-NR)	NR (25.7-NR)
OS at 15 mo, % (Kaplan-Meier estimate)	93	87

Conclusion: With additional follow-up, the combination of favezelimab plus pembrolizumab continued to show antitumor activity and manageable safety in anti–PD-1–naive pts with R/R cHL and in pts whose disease progressed after anti–PD-1 therapy.

Encore Abstract - previously submitted to EHA 2023

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Keywords: Hodgkin lymphoma, Immunotherapy

Conflicts of interests pertinent to the abstract.

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264 | OVERALL SURVIVAL IN CLASSIC HODGKIN LYMPHOMA PTS WHO PROGRESS AFTER AUTOLOGOUS STEM CELL TRANSPLANT IN THE ERA OF NOVEL AGENTS

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Introduction: Approximately 20% of patients (pts) with classic Hodgkin lymphoma (cHL) relapse after frontline therapy. Salvage

Characteristics	Overall (N, %) (total N=299)
Age	
- Median (IQR)	32 (26-43) yr
Male sex	153 (51.2)
TTP_categories	
<3	59 (19.7)
3-6	88 (29.4)
6-12	75 (25.1)
12-24 months	45 (15.1)
>24	32 (10.7)
TTP_categories_2	
<6	147 (49.2)
>6	152 (50.8)
No. theray lines	2 (1-9)
BV maintenance	53 (18.7)
Nivo first	60 (20.1)
Nivo at any point	124 (41.5)
BV first	140 (46.8)
BV at any point	165 (55.2)
Received alloBMT	74 (24.7)

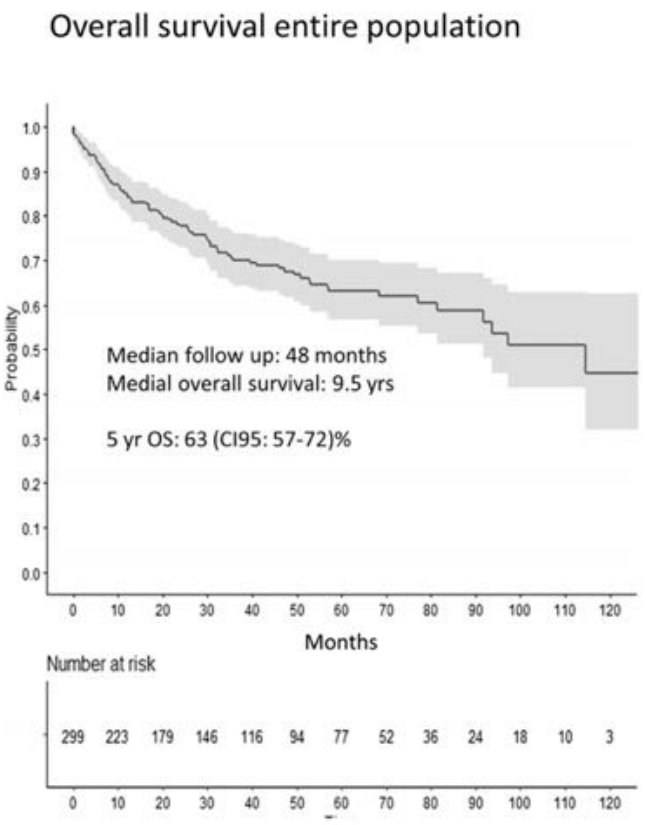

Figure 1

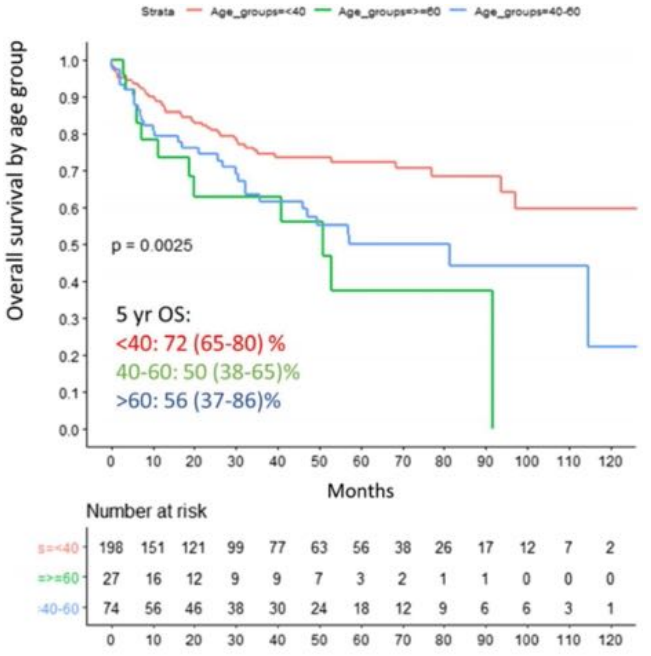

Figure 2

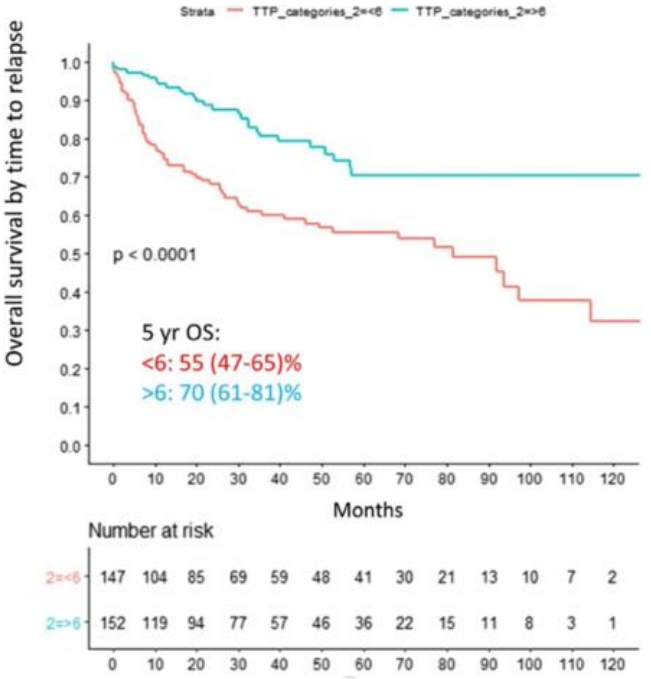

Figure 3

chemotherapy and autologous stem cell transplant (ASCT) have cure rates of 60%–70%. Prior to brentuximab vedotin (BV) and checkpoint inhibitors (CPI), the median overall survival (OS) of pts with cHL relapse after ASCT was 2–3 years. Recently, CPI and BV have improved progression free survival (PFS) in this population whereas the impact on OS has not been well-described in the literature. Herein we report on OS of pts progressing after ASCT in the era of novel agents.

Methods: In this multicenter retrospective study of 14 participating institutions, adult pts with cHL who progressed after ASCT were included. Age, sex, time to relapse (TTR) from ASCT, details of treatments for post-transplant progression were collected. Study

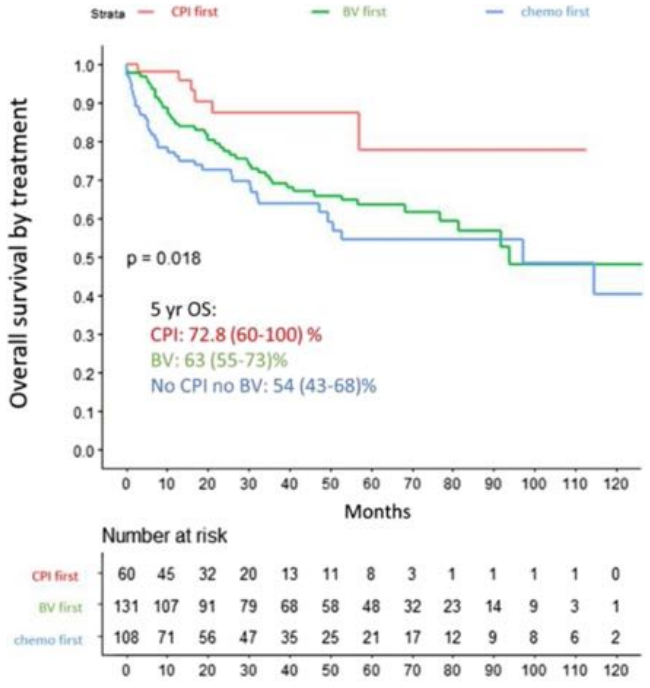

Figure 4

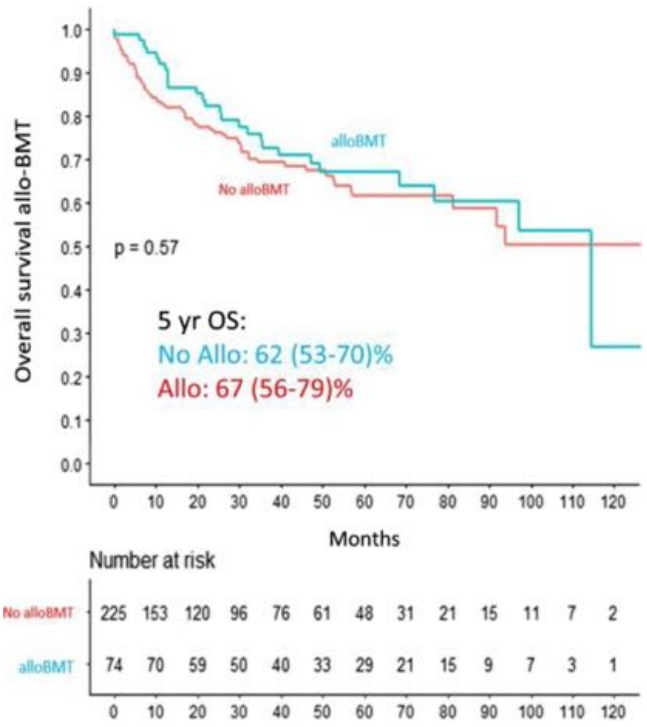

Figure 5

objective was post-progression OS, defined as the time from post-transplant progression to death or last follow up.

Results: Among 986 pts with cHL who underwent ASCT, 300 pts progressed. Median age was 32 (26–43) yr, 153 (51%) were male, 147 (49%) had TTR <6 months, 269 (89%) had TTR <24 months. Median prior lines were 2 (range: 1–9). 52 (19%) pts progressed after BV maintenance. 223 (74%) pts received BV or CPI at any point after post-ASCT progression. To assess impact of BV/CPI sequencing for post-ASCT progression on OS, pts were divided into 3 groups on the basis of first therapy received after progression: 60 (20%) received CPI first (CPI group), 140 (47%) received BV (BV group) and 108 (36%) received chemotherapy or radiation as first post-ASCT progression regimen (chemorad group). Of 140 pts in BV group, 55 (39%) received CPI as subsequent line of therapy. Of 108 pts in the chemorad group, 64 (59%) received CPI and 25 (23%) received BV as subsequent regimen for progression. 74 (47%) pts had allogeneic stem cell transplant (alloSCT). Median follow up was 4 years (0.07–11). Median OS was 9.5 (7-NA) yrs; 5-year OS was 63%, CI_{95}: 57–72, f). In univariate analysis, age <40 and TTR >6 months were associated with higher OS (Figures 2 and 3). When adjusted for age and TTR, CPI was associated with superior OS compared to chemorad group but not BV group (Figure 4). Progression on BV maintenance was also associated with higher OS. Receipt of alloSCT was not significantly associated with OS in uni- and multivariable analysis (Figure 5).

154 pts received more than 1 line of therapy for progression. Significantly higher proportion of pts in CPI group were alive without requiring further lines of therapy compared to BV or chemo group [44 (73%), 66 (47%); 59 (52%), $p < 0.005$].

Conclusions: In the era of novel agents, pts with relapsed cHL after ASCT were found to have a median OS reaching almost a decade. Age >40 years and TTR < 6 months of ASCT were associated with shorter OS. Employing CPI earlier in the course may be associated with higher OS. AlloSCT was not associated with improved OS in this population.

Keyword: Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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Research funding: BMS, Seatle Genetics

265 | ROLE OF AUTOLOGOUS STEM CELL TRANSPLANTATION OR SALVAGE CHEMOTHERAPY IN RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA PATIENTS AFTER IMMUNE CHECKPOINT INHIBITORS

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Introduction: Programmed death-1 (PD1) blockade is an efficient and safe therapeutic option in patients with relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL). However, many patients progress or lose the response to immune checkpoint inhibitors (CPIs). In this setting, two options can be explored to improve patients outcomes: 1) salvage chemotherapies (CHT) for those patients with an unsatisfactory response to anti-PD1 treatment (less than a partial response), and 2) autologous stem-cell transplantation (ASCT) as a consolidation treatment in those HL patients who obtained at least a partial response (PR) after CPI.

Methods: We retrospectively investigated the effectiveness of both salvage therapies for unsatisfactory response to anti-PD1 therapy (cohort 1) and ASCT as consolidation (cohort 2) in patients with R/R cHL treated with pembrolizumab or nivolumab at our Institution. Overall response rates (ORR) were chosen as primary endpoint in the two settings, whereas progression-free survival (PFS), disease-free survival (DFS) and overall survival (OS) were analyzed as secondary endpoints starting from the first dose of CHT (intended as a conditioning regimen for consolidation pathway or other drugs in the case of salvage treatments after CPIs failure). Adverse events (especially cumulative toxicities) were also assessed.

Results: Forty-eight heavily pre-treated patients were eligible for this retrospective analysis (median of previous therapies 4, range 3–9; 77% primary refractory). Thirty-one patients underwent further CHT (cohort 1) after a median time of 1.4 months from last CPI dose. Specifically, 21 patients received a single-agent treatment and 10 received a multi-agent regimen. Seventeen patients underwent ASCT to consolidate the response (15 in complete response [CR]) obtained with CPIs (cohort 2) with a median time to last CPI dose of 2 months days. In cohort 1, the final ORR was 32.3% (6 CR and 4 PR), while in cohort 2, we observed an ORR of 88.2% (all CR). After a median follow-up of 5 years, in cohort, median OS and DFS were still not reached, while median PFS was 11.6 months. In cohort 2, for OS, PFS, and DFS the median was not reached. No unexpected or cumulative toxicity was observed.

Conclusions: Our results indicated that ASCT can be considered an effective consolidation strategy in patients with cHL who have achieved at least a partial response after CPI, despite a large number of prior lines of therapy. In addition, treatment with CPI, regardless of its success, appears to promote sensitization to subsequent chemotherapy regimen in a setting of heavily pretreated and chemo-refractory patients. In this context, post CPI chemo-sensitization may pave the way for eventual subsequent transplant consolidation, increasing the chances of cure.

Keywords: Chemotherapy, Immunotherapy, Stem Cell Transplant

No conflicts of interests pertinent to the abstract.

266 | SECONDARY CANCER IS THE LEADING CAUSE OF DEATH 15 YEARS OR MORE AFTER DIAGNOSIS OF EARLY-STAGE HODGKIN LYMPHOMA

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Introduction: Classical Hodgkin lymphoma (cHL) often occurs in early adulthood and disease control is achieved by several treatment strategies, including radiotherapy (RT) added to chemotherapy in early stage disease. Long-term treatment-related toxicity is therefore an important issue, in particular with regard to toxicity from RT. Even if the latter seems to be reduced as methods of delivery are being refined, repeated investigations of long-term results are warranted.

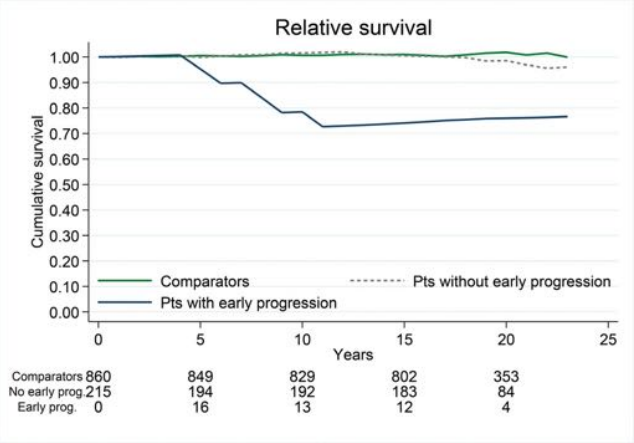
Methods: A Swedish population-based cohort, $n = 215$, of stage I-IIA cHL treated with 2–4 cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and 30 Gy limited field RT, between 1999 and 2005 is followed by linkage to health registries. Limited field being a modification of involved field, with a reduction of the target volume. In a first report (Br J Haematol. 2020) no excess mortality was detected. In a later report (J Clin Oncol. 2022) excess morbidity in secondary cancer and diseases of the circulatory system was seen when comparing with matched comparators. Relative survival rate (RSR) is now updated using the Ederer II method for all patients, patients with and without early progression (<5 years from diagnosis), and for comparators. Mortality is analyzed by years of life lost to secondary cancer and to diseases of the circulatory system, according to cause of death. Years of life lost are calculated in relation to expected survival, from the time of death, derived from life tables.

Results: Median age at time of diagnosis is 34 years (range 18–77). Median follow-up for survival is 20 years (range 16–23) with 34 deaths occurring among patients of which 14 are seen more than 15 years after diagnosis. RSR for all patients is 0.97 (95% CI: 0.90–1.02) at 20 years. RSR at 20 years for patients with and without early progression is 0.76 (95% CI: 0.47–0.93) and 0.99 (95% CI: 0.92–1.04), respectively (Figure 1). Analyzing the impact on the whole cohort of deaths later than 15 years from diagnosis, years of life lost to

secondary cancer are 0.22 years per patient and 0.07 per comparator ($p < 0.001$). In the same period years of life lost to diseases of the circulatory system are 0.14/patient and 0.20/comparator ($p < 0.001$).

Conclusions: In this cHL cohort treated with chemotherapy and RT, survival is very good 20 years after diagnosis. A trend towards excess mortality can be seen, starting 15 years after diagnosis. The small group with early progression has significant excess mortality with an impact on RSR for the whole cohort. The excess mortality is correlated in time with a significantly higher risk for death from a secondary cancer. Thus, the appearance of excess secondary cancers among patients seems to impact survival. There is, so far, no signs of a comparable effect from the excess morbidity in diseases of the circulatory system.

FIGURE 1 Relative survival for patients with, and without early progression (<5 years from diagnosis) and comparators.



The research was funded by: Cancerfonden and Stiftelsen onkologiska klinikens i Uppsala forskningsfond.

Keyword: Late Effects in Lymphoma Survivors

No conflicts of interests pertinent to the abstract.

267 | OVERALL SURVIVAL AND CAUSES OF DEATH IN ELDERLY PATIENTS WITH HODGKIN LYMPHOMA—A NORWEGIAN POPULATION-BASED CASE-CONTROL STUDY

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Background: Elderly Hodgkin Lymphoma (HL) patients (pts) are poorly characterized and underrepresented in high-quality studies. Populations-based studies with individual disease- and treatment-factors together with causes of death are lacking.

Methods: Pts ≥60 years diagnosed with HL between 2000 and 2015 were identified by Cancer Registry of Norway. Hospital and other health-care records were reviewed and pts grouped according to treatment into ineligible (no HL directed treatment), palliative (intended dose intensity <50%) or curative (>50% intended dose intensity of HL regimens or curative radiotherapy only). Pts' causes of death were obtained from records and compared to The Norwegian Cause of Death Registry providing date and cause of death for pts and cancer-free controls matched 1:10 based on age, sex and place of residency.

Overall survival was analyzed by Kaplan-Meier statistics. Cumulative incidence functions were calculated using the Aalen-Johansen estimator and compared using Gray's test. Risk differences between pts and controls were calculated for each competing event at 2, 5 and 10 years.

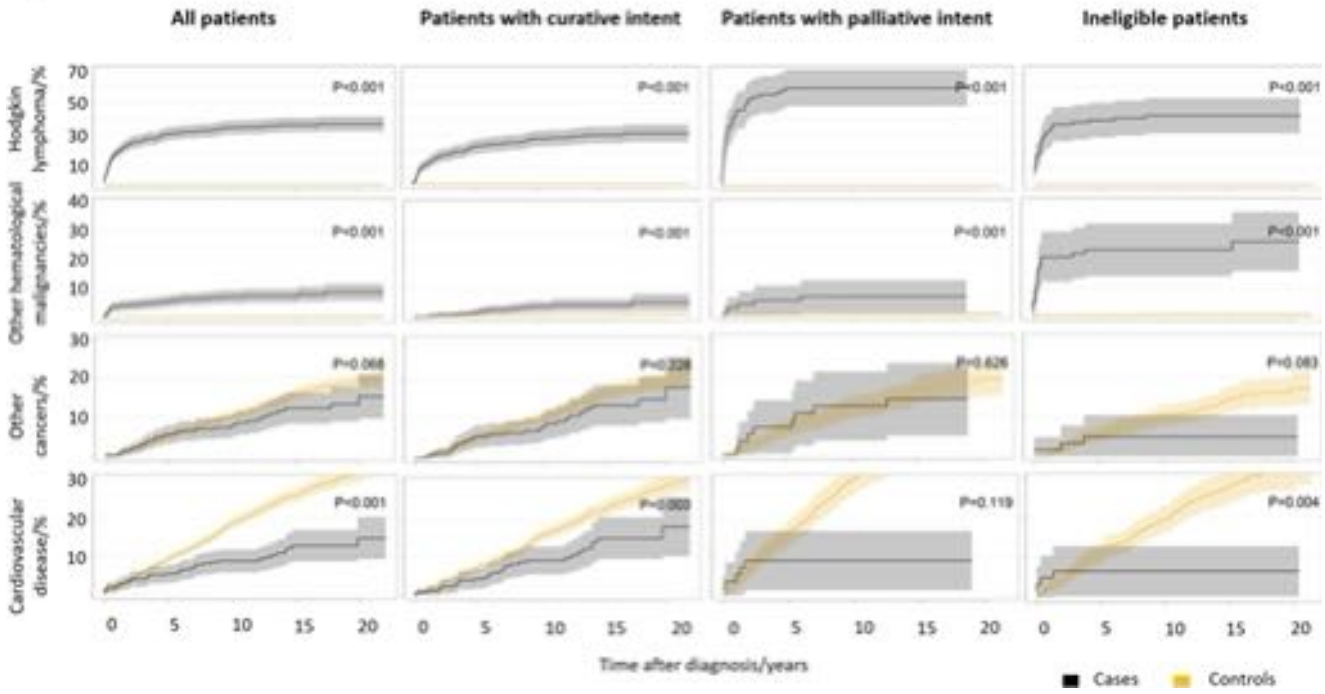
Results: Of 492 pts, 81 (16.5%) were ineligible for the analysis of treatment outcomes, due to composite lymphoma ($n = 51$), diagnosis after death ($n = 13$), severe comorbidity ($n = 16$) or incomplete patient data ($n = 7$). 74 (15%) and 337 (68.5%) pts were treated with palliative or curative intent, respectively, most commonly with CHOP.

Median overall survival in the ineligible, palliative and curative groups were 0.5 (95% Confidence interval [CI] 0.4–0.6), 0.8 (0.4–1.2) and 9.1 (7.5–10.7) years, respectively. With 359 deaths, the most common cause was HL in all groups, with 30% dying from HL, 8% from treatment-related mortality and 62% from other causes.

The risk difference of dying from HL compared to controls increased from 16% (95% CI: 12%–20%) at 2 years to 28% (23%–33%) after 10 years for the curative group, compared to 59% (48%–71%) and 42% (31%–53%) after 10 years in the palliative and ineligible groups, respectively. There was an increased risk of dying from other hematological malignancies, including Non-Hodgkin lymphoma in all groups, but not from other causes of death (Figure 1).

Conclusion: In this national population-based study, 32% of pts received either palliative or no treatment directed specifically at HL, and these accounted for a substantial proportion of excess mortality of HL. 10% of pts had other previous or concomitant malignant lymphoproliferative diseases. In curatively treated pts, long-term HL-specific survival corrected for competing causes of death was 72%, indicating adequate disease control in a majority. In all pts, there was a significantly increased risk of dying from other hematological malignancies over time, but not from other

Figure 1: Cumulative incidence functions for competing causes of death in elderly HL patients.



causes, indicating a low rate of excess mortality from long-term treatment complications.

Keyword: Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

INDOLENT LYMPHOMAS

268 | INTEGRATIVE GENOMIC AND TRANSCRIPTOMIC ANALYSIS REVEALS GENETIC ALTERATIONS ASSOCIATED WITH THE EARLY PROGRESSION OF FOLLICULAR LYMPHOMA

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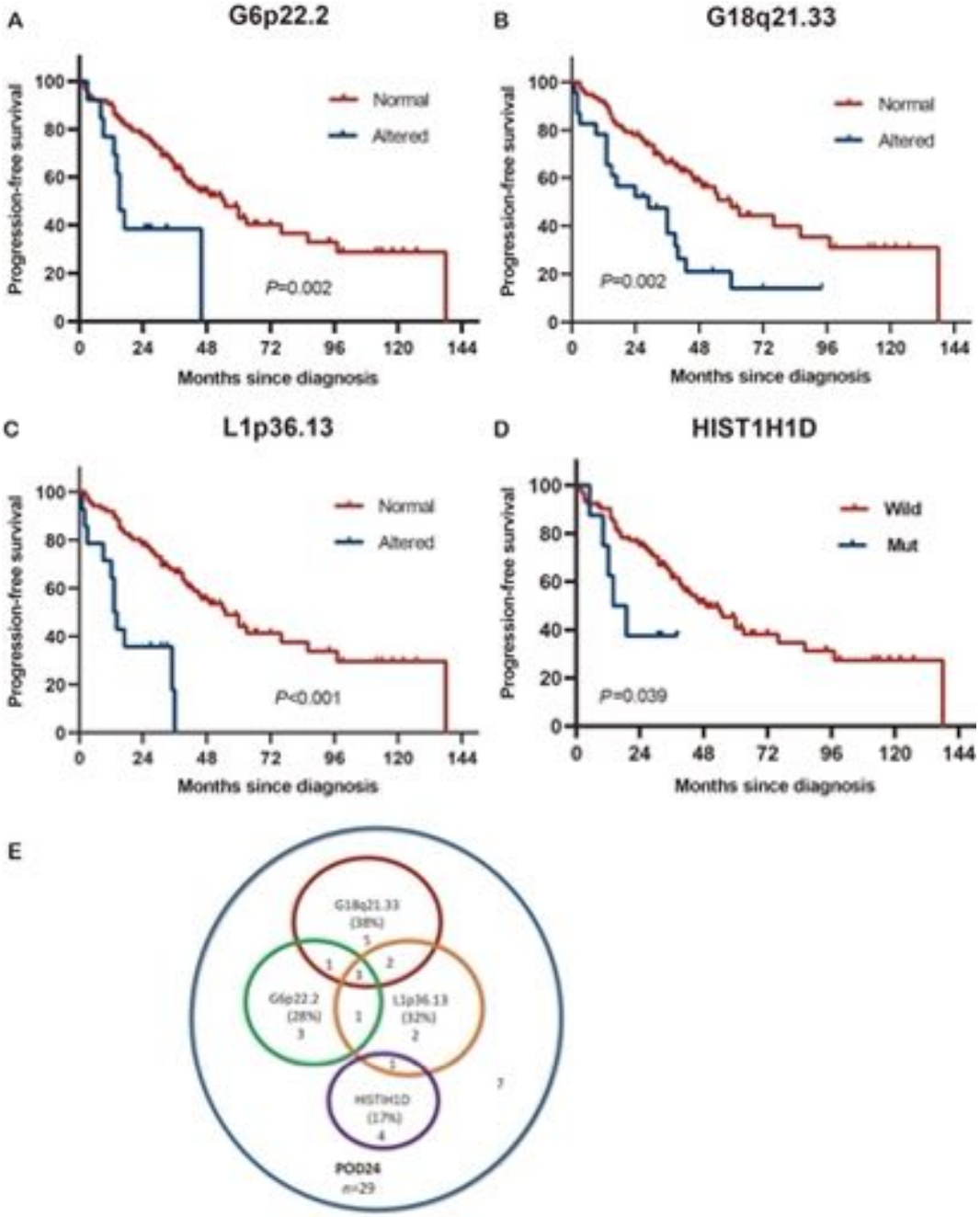
Introduction: Follicular lymphoma (FL), the most common indolent lymphoma, is a clinically and genetically heterogeneous disease. Progression of disease within 24 months (POD24) is strongly associated with poor outcome. Therefore, prediction of POD24 at diagnosis is essential to support the precision medicine treatment strategies making in clinical practice. However, risk factors associated with POD24 remain uncertain in FL patients. In addition, the prognostic value of driver gene mutations and copy number alterations has not been systematically assessed in FL.

Method: We analysed clinical-biological features of 415 FL patients to identify variables associated with POD24. In addition, we integrated whole exome sequencing (WES) and transcriptomic analysis of 102 these patients with FL to identify genetic alterations associated with early progression.

Result: POD24 occurred in 21% of evaluable FL patients, with a 5-year OS rate of 82.9% compared with 96.2% for those without POD24 (HR, 5.03; 95% CI, 2.15–11.72; $P < 0.01$). Patients with B symptoms, elevated lactate dehydrogenase and β2-microglobulin levels, unfavourable baseline haemoglobin levels, advanced stage, and high-risk FL International Prognostic Index (FLIPI) scores had an increased risk of POD24, with FLIPI being the most important factor in logistic regression. Among all the somatically occurring non-silent mutations, twenty-three genes were considered cancer drivers. HIST1H1D, known as a driver mutation, was significantly correlated with POD24. Gains of 6q22.2 (HIST1H1D) and 18q21.33 (BCL2) and loss of 1p36.13 (NBPF1) predicted POD24 independent of FLIPI. Integration of the four variants led to the identification of 76% of POD24 patients. Gene expression profiling (GEP) of 41 FL samples showed that the POD24 cohort was significantly enriched in the inflammatory response (mediated by interferon and tumour necrosis factor) and cell cycle regulation (transcription, replication and proliferation) sets.

Conclusion: In summary, we present the first comprehensive genomic and transcriptomic study that associated with POD24 in FL patients. We showed that FL patients with POD24 had distinct clinical, genetic, and molecular features. The genetic alterations identified in this study may also provide opportunities for development of novel therapeutic strategies.



Keywords: Diagnostic and Prognostic Biomarkers, Genomics, Epigenomics, and Other -Omics, Indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

269 | REAL-WORLD TREATMENT PATTERNS AND CLINICAL OUTCOMES AMONG FOLLICULAR LYMPHOMA PATIENTS IN THE SEER-MEDICARE POPULATION

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Introduction: Follicular lymphoma (FL) is the second most common lymphoma with annual estimated new cases of approximately 14,000 in the US. Survival outcomes in FL patients vary depending on various risk factors. Patients generally respond well to anti-CD20 monoclonal antibody (mab) with or without chemotherapy. However, majority of patients require multiple lines of therapy and treatment sequencing is very heterogeneous (Casulo et al., *Lancet Haematol* 2022). Progression of disease within two years (POD24) of first-line chemoimmunotherapy (CIT) and receiving third-line therapy within

three years of diagnosis (3L36) have shown to be associated with shorter overall survival (OS). The aim of the study was to characterize the real-world evidence of treatment patterns and outcomes in FL patients in the US.

Methods: Patients aged ≥65 who were diagnosed with FL between 2000 and 2017 were identified from the SEER-Medicare database based on ICD-O-3 codes (9695/3, 9691/3, 9698/3, 9690/3). A new line of therapy (LOT) was defined when next lymphoma directed treatment was started (including retreatment of anti-CD20 mab) after 180 days from completion of previous treatment. Event-free survival (EFS) was used as a proxy of treatment success in this study and an event was defined as initiation of next lymphoma treatment, transformation or death from any cause. OS by POD24 and 3L36 were estimated by landmark analysis (Casulo et al., *Blood* 2022), which included patients with ≥24 months of follow-up from 1L CIT (for POD24 analysis) or ≥36 months from diagnosis (for 3L36 analysis). Cox models were conducted to evaluate the association between prognostic factors and OS.

Results: Of 14,077 patients with incident FL (median age: 76 years), 64%, 23%, 9%, and 4% received at least 1, 2, 3, and 4 LOTs, respectively. CIT, the most common treatment regimen across all LOTs, was used in 60%, 45%, 42% and 42% of patients in 1L, 2L, 3L, and 4L, respectively. Anti-CD20 mab monotherapy was used in 31%, 40%, 38%, and 36% of patients in 1L, 2L, 3L, and 4L, respectively. Median follow-up time was 56.8 months after 1L initiation and decreased to 23.6 months following 4L. The median EFS was 33.9, 20.0, 15.9 and 13.4 months for patients in 1L, 2L, 3L and 4L, respectively. The median OS was 81.9, 49.6, 35.1, and 27.1 months for patients in 1L, 2L, 3L, and 4L, respectively. Patients experiencing POD24 showed shorter OS than other patients (median OS: 67.5 vs. 103.8 months; hazard ratio [HR] 1.61; 95% CI: 1.46, 1.79). The median OS was 38.2 and 88.2 months in patients with or without receiving 3L36 (HR 1.78; 95% CI: 1.57, 2.02).

Conclusions: This study confirmed the negative impact of POD24 and 3L36 on survival in older patients with FL. The median EFS becomes shorter with later lines of treatment, indicating unmet needs for effective and tolerable therapies in patients with FL.

The research was funded by: Genmab A/S and AbbVie

Keywords: Cancer Health Disparities, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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270 | ANALYSIS OF REAL-WORLD TREATMENT PATTERNS AND OUTCOMES AMONG PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA INCLUDING POD24 PATIENTS

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Introduction: Although follicular lymphoma (FL) is an indolent disease, there is much heterogeneity in outcomes. Patients with early relapsed disease within 24 months (POD24) have been reported to be a poor prognostic subgroup, although this finding has not been confirmed in several recent real-world studies. This study describes treatment patterns, prognostic factors, and outcomes in patients with relapsed/refractory (R/R) FL, including those who progress through multiple lines of therapy (LOTs).

Methods*:* This study was conducted using the COTA database, which is comprised of electronic health records drawn from academic centers (50%) and community practices (50%) in the US. Patients included in this study had a confirmed diagnosis of FL (index date) between 1 January 1990 and 31 December 2022, were ≥18 y of age at index date, were administered treatment for FL, and were followed >3 months after first-line (L) treatment initiation. The utilization of novel treatment options was captured progressively throughout the study period. Patients who progressed from 1L chemoimmunotherapy (CIT) within 24 months were identified as POD24 patients. A landmark approach was taken to assess the overall survival (OS) of the POD24 patients who had at least 24 months of follow-up from 1L CIT versus non-POD24 patients as described in previous studies (Casulo et al.,

Blood 2022). Patient demographics, treatment patterns, and OS were also assessed by LOT.

Results: Overall, 3568 FL patients met inclusion criteria. Among these, 2465 received 1L CIT, with 459 (18.6%) identified as POD24. Of these POD24 patients, 264 had ≥24 months of follow-up from 1L CIT and were included in the landmark analysis. This sub-group of POD24 patients had a median age of 64 y at diagnosis and 86.6% had stage III/IV disease. Non-POD24 patients (n = 2006) had a median age of 61 y at diagnosis and 81.4% had stage III/IV disease. POD24 patients had worse OS (hazard ratio [HR] 2.24; 95% confidence interval [CI] 1.79, 2.80) versus non-POD24 patients. Of the 3568 1L FL patients, 862 continued to 2L, 328 continued to 3L, 146 continued to 4L, and 59 continued to 5L+ treatment. Across all LOTs, the most common therapy was rituximab or obinutuzumab + chemotherapy. The utilization of novel treatments (ie, kinase inhibitors, CAR T-cell therapy, tazemetostat) increased through LOTs, with 6.4% utilization at 3L, 9.6% at 4L, and 20.7% at 5L. Patients who progressed through successive LOTs experienced worsening OS (Figure 1).

Conclusions: This study confirms findings from previous reports demonstrating poorer outcomes in POD24 versus non-POD24 patients and the worsening of outcomes in patients following successive LOTs in a real-world setting. Within this cohort, CIT remained the most common treatment in 3L+ patients and the use of novel therapies was low. These findings underscore the need to increase the utilization and development of novel therapies for patients with R/R FL.

The research was funded by: This study was funded by Genmab A/S and AbbVie Inc.

Keywords: Cancer Health Disparities, Late Effects in Lymphoma Survivors

Conflicts of interests pertinent to the abstract.

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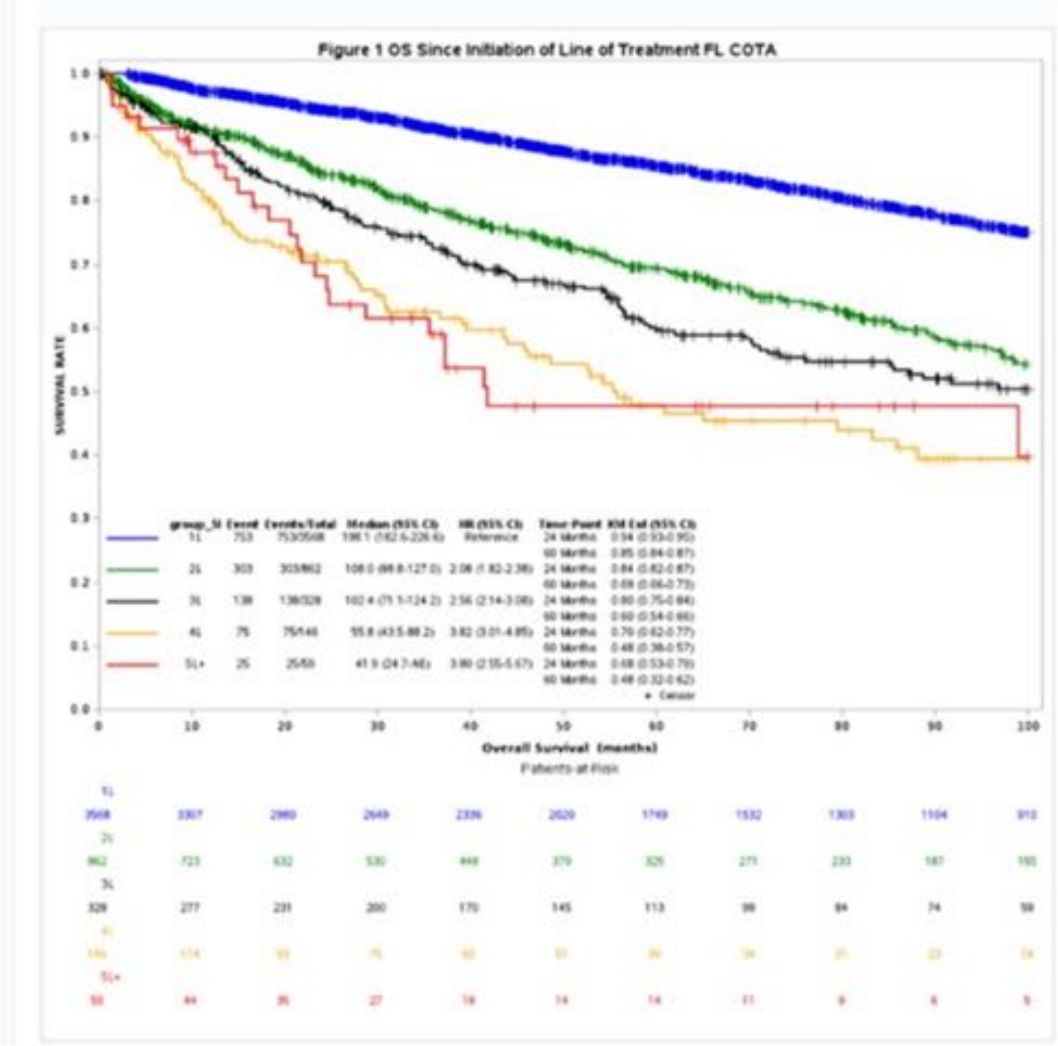
Consultant or advisory role: AbbVie, Bayer, BeiGene, BMS/Celgene, Epizyme, Genentech/Roche, Genmab, Incyte, Janssen, Kite/Gilead, Loxo, Miltenyi, MorphoSys, Novartis, Rapt, Regeneron, Takeda

Figure 1. Overall survival since initiation of 1st line of treatment.



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271 | REAL-WORLD EARLY OUTCOMES OF AXICABTAGENE CILOLEUCEL FOR RELAPSED OR REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL)

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Background: Axicabtagene ciloleucel (axi-cel) is an autologous CAR T-cell therapy approved for adult patients (pts) with R/R FL after ≥2 lines of systemic therapy. In the primary analysis of the pivotal ZUMA-5 trial, 94% of pts who received axi-cel to treat R/R FL achieved an objective response, with a 79% CR rate (Jacobson et al. *Lancet Oncol.* 2022). Grade ≥3 cytokine release syndrome (CRS) and neurologic events occurred in 6% and 15% of pts, respectively. Here, we present real-world outcomes of pts receiving axi-cel for R/R FL, including those who would have been ineligible for ZUMA-5.

Methods: A total of 230 pts from 72 US centers receiving first axi-cel for R/R FL in the real-world setting between March 2021 and October 2022 were identified from the CIBMTR registry. The following pts were excluded: no consent, prior non-transplant cellular therapy, and FL grade 3b or 3a/3b unspecified. Of the 230 pts, 151 had post-infusion assessments and were included in the analysis of outcomes. Effectiveness outcomes were ORR, CR, DOR, PFS and OS. Adverse events included CRS, immune effector cell–associated neurotoxicity syndrome (ICANS) and prolonged cytopenia.

Results: Of the 230 pts, median age was 62 years and 60% were male. Prior to infusion, 98% had an ECOG performance score of 0–1, 33% had elevated LDH, and 66% were chemo-resistant. Clinically significant comorbidities were present in 74% of the pts. Ninety-two (40%) pts would have been ineligible for ZUMA-5, mainly due to comorbidities. Pts had a median of 4 (range 1–13) lines of prior therapy including 14% who also underwent prior ASCT. Median time from leukapheresis to infusion was 28 days (IQR 26–34). 9% of pts received bridging therapy.

Outcomes were analyzed among the 151 pts with follow-up (median 6.2 mo). ORR and CR rates were 93% (95% CI: 88%–97%) and 84% (95% CI: 77%–89%), respectively. Estimated PFS and OS at 6 mo were 88% (95% CI: 81%–92%) and 96% (95% CI: 91%–98%), respectively. Grade ≥3 CRS (ASTCT consensus) and ICANS (ASTCT consensus) occurred in 2% (95% CI: 0%–6%) and 13% (95% CI: 8%–19%) of pts, respectively. Median cumulative incidence estimate for CRS resolution was 5 days; for ICANS resolution was 4 days. Among pts alive at Day 30 ($n = 150$), 11% experienced prolonged cytopenia (4% neutropenia, 9% thrombocytopenia).

PFS and OS at 6 mo were comparable regardless of ZUMA-5 eligibility, while pts eligible for ZUMA-5 had fewer Grade ≥3 ICANS (10% vs. 16%) and more rapid ICANS resolution (92% vs. 71% resolved ≤2 weeks). Pts aged ≥65 versus <65 years had comparable effectiveness and safety profiles.

Conclusion: This is the first report on axi-cel to treat R/R FL in real-world settings. Despite a broader pt population, early results demonstrate effectiveness and safety profiles consistent with those observed in the ZUMA-5 trial. The intent is to present findings from an updated dataset with longer follow-up. Overall, these findings support the continued broad use of axi-cel to treat R/R FL.

Encore Abstract - previously submitted to ASCO 2023 and EHA 2023

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Keywords: Cellular therapies, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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272 | THE PROGNOSTIC VALUE OF PROGRESSING WITHIN 24 MONTHS OF FRONTLINE CHEMOIMMUNOTHERAPY (POD24) IN RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL)—A SCHOLAR-5 ANALYSIS

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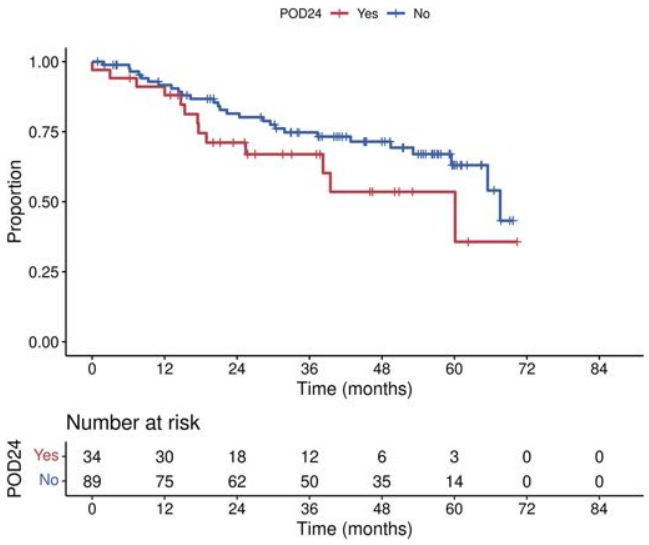
Introduction: FL has a heterogeneous prognosis with multiple risk factors associated with shorter overall survival (OS). Whilst patients whose FL progresses within 24 months (POD24) after frontline chemo-immunotherapy (CIT) have poor OS (50% at 5 year vs. 90% non-POD24, HR of 7.17, 95% CI: 4.83–10.65, Casulo et al. [J Clin. Oncol., 33(23):2516–2522 (2015)]). The role of POD24 as a prognostic factor in later lines is less clear. We sought to investigate whether POD24 remains a key prognostic factor in R/R FL patients initiating ≥3rd line of therapy (LoT).
Methods: The electronic medical record (EMR) component of the SCHOLAR-5 cohort of R/R FL patients served as the evidence base for this analysis. POD24 was defined as relapse within 24 months of

initiating frontline CIT (Patients who relapsed within 24 months of initiating rituximab monotherapy or another class of frontline therapy were non-POD24). Analyses included LoT, gender and stem-cell transplant in current LoT as covariates. OS was analyzed using Cox regression with time-dependent variables and a single outcome for each patient. Progression-free survival (PFS) was analyzed using repeated measures Cox regression. Overall response rate (ORR) and complete response (CR) were analyzed using repeated measures logistic regression producing an odds ratio. Additional sensitivity analyses explored alternate definitions of POD24 and different model specifications.

Results: A total of 123 patients met the inclusion criteria, with 34 (27.6%) defined as POD24. Patient characteristics at initiation of frontline therapy were comparable between POD24 and non-POD24 groups. At first eligible LoT (≥3rd), POD24 patients were notable for a significantly shorter time since initial diagnosis, and a higher probability for being refractory to their last line of therapy. POD24 was associated with shorter OS OS (Figure 1) with a hazard ratio (HR) of 1.92 (95% confidence interval [CI]: 1.16, 3.16). Although all estimates for other clinical outcomes were in the same direction they were not statistically significantly s (PFS HR: 1.27; 95% CI: 0.96, 1.69, ORR odds ratio: 1.44; 95% CI: 0.80, 2.97, CR odds ratio: 1.45; 95% CI% 0.65, 3.30). Patients refractory to their last LoT were at increased risk of progression (HR: 1.48; 95% CI: 1.05, 2.09), but this was not associated with OS.

Conclusions: This study suggests that POD24 remains a prognostic factor for OS in R/R FL patients initiating ≥3rd LoT, albeit with a less pronounced effect than among patients initiating 2nd LoT.

Figure 1: Kaplan-Meier curve of OS by POD24 (unadjusted analysis)



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Keywords: Cellular therapies, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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Research funding: Gilead/Kite

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Honoraria: Gilead/Kite, Merck, BMS, Novartis, Celgene, Pfizer, Allogene Therapeutics, Cell Medica/Kuur, Incyte, Precision Biosciences, Adicet Bio, Legend Biotech, Calibr, Unum Therapeutics, Bluebird Bio, Medscape, Bio Ascend
Research funding: Gilead/Kite, Merck, BMS, Celgene, Allogene Therapeutics, Precision Biosciences, Adicet Bio, Unum Therapeutics, Aptitude Health, Poseida, Cellectis, Karus Therapeutics, Acerta
Other remuneration: Gilead/Kite, Merck, BMS, Novartis, Celgene, Pfizer, Allogene Therapeutics, Cell Medica/Kuur, Incyte, Precision Biosciences, Legend Biotech, Adicet Bio, Calibr, Unum Therapeutics, Takeda Pharmaceuticals

J. G. Gribben
Honoraria: Janssen, AbbVie, AstraZeneca, Amgen, BMS, Gilead/Kite, Novartis
Research funding: Celgene, AstraZeneca, BMS
Other remuneration: Janssen, AbbVie, Roche/Genentech

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Employment or leadership position: Gilead/Kite
Research funding: Gilead/Kite

273 | PROGNOSTIC VALUE OF THE END OF INDUCTION PET IN PATIENTS WITH FOLLICULAR LYMPHOMA: RESULTS FROM THE ANALYSIS OF FOLL 12 TRIAL

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Aim: To assess the prognostic value of the PET metabolic response using the Deauville Score at the end of induction (EoI) therapy.

Methods: FOLL12 trial (NCT02063685) is a multicenter, phase III, randomized study with the primary objective to evaluate whether a FDG-PET (PET) and MRD (molecular residual disease) response-based maintenance therapy (experimental arm) is more effective in terms of Progression-Free Survival (PFS) than a standard maintenance therapy with Rituximab (standard arm) in patients with follicular lymphoma. Adult patients with untreated grade 1–3a FL and stage II-IV were randomized to receive standard immunochemotherapy followed by rituximab maintenance versus standard immunochemotherapy followed by a response adapted post-induction management (i.e. non-maintenance for patients in CMR and with MRD negative, short rituximab therapy for CMR (complete metabolic response) and MRD +ve cases and radioimmunotherapy followed by rituximab maintenance for non-CMR patients). EoI-PET was mandatory. All PET scans were centralized on WIDEN® platform and classified according to Deauville score (DS) in a blind independent central review. DS1-3 was considered negative (CMR), whereas DS4-5 was considered positive (not CMR). The primary endpoint was PFS. Main secondary endpoint was Overall Survival (OS)

Results: Overall, 729 follicular lymphoma patients, 52% women, 89% stage III-IV disease and 40% with a high-risk FLIPI-2 score, were included in the analysis. DS at the EoI-PET resulted 1,2,3,4, and 5 in 361(49.5%), 168(23.1%), 112(15.4%), 49(6.7%) and 39 (5.3%) patients, respectively. EoI-PET resulted positive in 88/729 (12%). Among the reviewers, the overall agreement (OA) on PET pos/neg result was 0.92, while agreement on positive and negative cases were 0.77 and 0.94, respectively. In the whole population of 729 patients, 5 yrs PFS (95% CI) for DS1-3 and DS4-5 was 69% (65–73) and 35%(25–46) with HR3.32(2.45–4.50), $p < 0.001$, respectively. The 5 yrs OS (95% CI) in DS1-3 and DS4-5 was 94% (92–96) and 81%(71–88), HR4.72(2.69–8.32), $p < 0.001$. The prognostic role of CMR was confirmed both in the standard and in the experimental arm of the study. In the whole population, the 5 yrs PFS (95% CI) in DS1-2, DS 3 ad DS4-5 was 74% (69–78), 55% (44–65; HR1.90 (1.36–2.66) $p < 0.001$) and 37%(26–48; HR 4.01 (2.90–5.54) $p < 0.001$); DS3 patients had an intermediate 5 yrs PFS rates between those of DS1-2 and DS4-5 patients. OS in DS3 patients had similar values to those with DS1-2. Applying a different definition of CMR (i.e., DS1-2 only) the rate of positive EoI-PET rose to 27%.

Conclusion: In FOLL12 trial, EoI-PET according DS criteria was a reliable tool to stratify PFS and OS in advanced follicular lymphoma patients treated with immunochemotherapy; in addition, these data showed DS3 patients as a new category with an intermediate prognosis in terms of PFS.

Keywords: Diagnostic and Prognostic Biomarkers, PET-CT

No conflicts of interests pertinent to the abstract.

274 | TREATMENT OUTCOMES OF LIMITED STAGE GRADE 3A FOLLICULAR LYMPHOMA

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Introduction: While radiotherapy is an established standard of care for limited stage, low grade follicular lymphoma (FL), the management of localized FL grade 3A (FL3A) disease remains controversial. We reviewed the outcomes of grade 3A patients treated with definitive RT, combined modality therapy (CMT), or systemic therapy (ST) alone.

Methods: We retrospectively analyzed a single institution database to identify newly-diagnosed, grade FL3A patients with Ann Arbor stage I/II disease treated between 2000 and 2021. Patients were stratified by definitive treatment modality including RT monotherapy, CMT, or ST. Best post-RT imaging response was evaluated using Lugano criteria for all by CT, and by PET if available. Rate of complete response (CR) was compared between the three treatment modalities. Progression-free survival (PFS) and Overall survival (OS) were calculated using Kaplan Meier from first day of treatment. Univariable Cox regression was used to assess possible clinicodemographic associations with PFS.

Results: 84 patients (median age 62, 38% male) were analyzed with median follow-up of 6.9 years from initiation of treatment. Patients were stage I (73%) or II (27%) and 92% were initially PET staged at diagnosis. 29 (35%) had extranodal disease. The median (IQR) maximum SUV and size prior to treatment were 9.8 (5.4, 14.0) and 3.2 (2.0, 4.5) cm respectively.

RT was the most common treatment modality ($n = 48$, 57%), followed by CMT ($n = 21$, 25%), then ST ($n = 15$, 18%). For RT/CMT patients the planned RT dose was most commonly 36 Gy (32%, range 4–40 Gy). 2 patients (3%) received very low dose of 4 Gy. Of the CMT/ST patients the most common regimen was 3–4 cycles of R-CHOP (53%). 3 patients (8%) received Rituximab alone. Compared to RT patients, ST patients were most likely to have been diagnosed after 2010 ($p = 0.002$) and have stage II disease ($p < 0.001$), while CMT patients were more likely to be female ($p = 0.03$) and have grade 3 disease not further characterized ($p = 0.002$).

The rates of CR post-treatment were 88% for RT, 100% for CMT, and 87% for ST. Factors significantly associated with PFS univariably included the treatment modality (CMT vs. RT HR 0.30, 95% CI: 0.10–0.91, $p = 0.03$), and presence of low-grade FL component in the biopsy (HR 3.33, 95% CI: 1.43–7.78, $p = 0.005$). Age, sex, stage, extranodal status, Ki67 score, size, and SUV were not predictive of PFS. The probability of transformation to DLBCL was 4.2% (95% CI: 1.1%–11%) at 5 years after treatment. Overall survival was excellent for all treatment modalities with median OS of 18 years for CMT, and not reached for RT or ST.

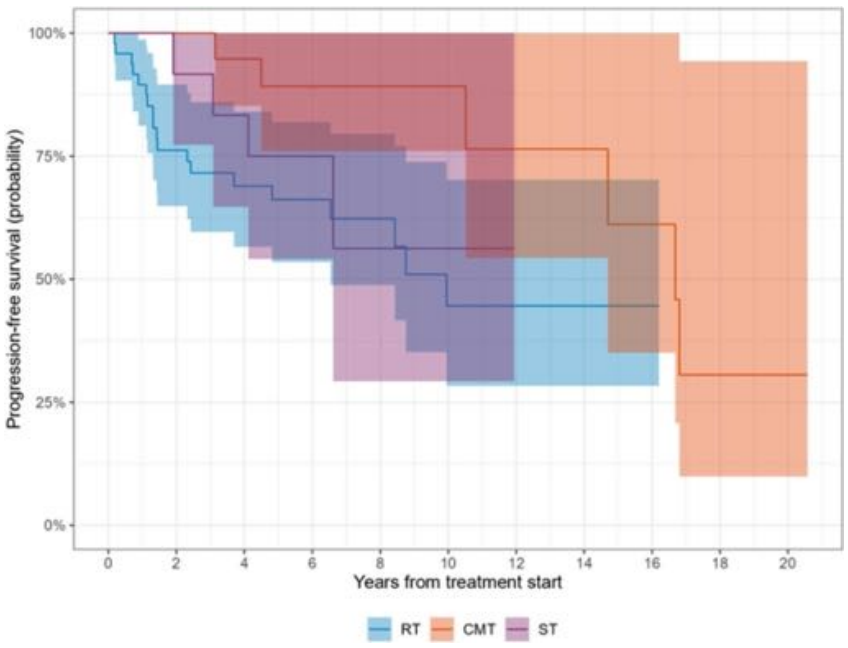
Conclusion: To our knowledge, this is the largest study of the outcomes of early stage FL3A after therapy. CMT had the highest rate of CR in our cohort, and was associated with a statistically significantly lower hazard of PFS compared to RT. However, OS is excellent regardless of treatment modality suggesting all may be appropriate options.

Keywords: Combination Therapies, Indolent non-Hodgkin lymphoma, Radiation Therapy

Conflicts of interests pertinent to the abstract.

A. Zelenetz

Consultant or advisory role: ADC Therapeutics, AbbVie, Adaptive Biotechnologies Corp Arvinas, Inc. AstraZeneca BeiGene, Ltd. Bristol-Myers Squibb, Curio Science LLC, Dava Oncology, Genentech, Instituto de Ciencias Integradas, Kyowa Kirin Co., Ltd. MEI Pharma, Inc., Medscape, Oncopeptides, AB Sandoz, Inc., Secura Bio, Inc., Suzhou Liang Yihui Network Science and Technology Company, Limited



G. Salles

Consultant or advisory role: AbbVie, Aptitude Health, Bayer, BeiGene, Ltd., Bio Ascend, Bristol-Myers Squibb, Celgene, Epizyme, Everest Clinical Research Corporation, GenMab, Genentech, Gilead Pharmaceutical, Incyte, Ipsen, Janssen Pharmaceutical, Nordic Nanovector ASA, s, Inc., Loxo Oncology, Miltenyi Biotec Incorporated, MorphoSys AG, Novartis, Owkin, Inc., Physicians' Education Resource, RAPT Therapeutics, Regeneron Pharmaceuticals, Inc., Roche, Scientific Education Support Ltd., Takeda Millennium

J. Yahalom

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275 | OUTCOMES IN PRIMARY GASTROINTESTINAL (GI) FOLLICULAR LYMPHOMA (FL): RESULTS FROM A MULTICENTER ANALYSIS

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Introduction: GI FL is a rare disease, accounting for less than 5% of GI non-Hodgkin's lymphomas (NHL). We formed a consortium to clarify baseline features, common practices and survival outcomes in primary GI FL.

Methods: A retrospective analysis of 182 patients (pts) with primary GI FL from 8 institutions was conducted. Overall survival (OS) and progression-free survival (PFS) were assessed. Cox regression models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI).

Results: Median age at diagnosis (dx) was 60 years (yrs) (IQR: 51–68). 89% (n = 141) of pts had low-grade FL by histology, and most presented with a low-risk score by FLIPI (68%, n = 111) or FLIPI-2 (76%, n = 103). At presentation, 18% (n = 32) of pts were asymptomatic, and 71% (n = 124) had at least one GI symptom, most commonly abdominal pain (40%, n = 70). 5% (n = 9) of pts presented with overt GI bleeding, and 9% (n = 15) with bowel obstruction. The most common first-line strategy was observation (33%, n = 59), of which 36% (n = 21) underwent surgical resection at dx. Other regimens included single-agent rituximab (R) (22%, n = 39), chemoimmunotherapy (CI) with R-bendamustine (18%, n = 32) or R-CHOP (11%, n = 19), and radiation therapy (5%, n = 9). The remainder received other CI combinations or R-lenalidomide. For those observed, median time to first treatment (tx) was 4.6 yrs. For those treated, overall response rate was 83% (95% CI, 76%–89%), and median time to second-line tx was 3.7 yrs. With median follow-up of 5.7 yrs, median OS was not reached. 5-yr PFS and OS were 71% (95% CI, 64%–79%) and 93% (95% CI, 89%–98%), respectively. Relevant factors that did not show a significant effect on PFS/OS included advanced disease by Paris and Ann Arbor staging systems, high-risk disease by FLIPI or FLIPI-2, B symptoms, GI symptoms, location of disease within the GI tract, and bone marrow involvement. Patients who were initially observed had similar OS to those who were treated up-front; PFS/OS did not improve significantly with use of maintenance rituximab. Factors that significantly impacted PFS and/or OS are outlined in Table 1.

Conclusion: This multi-institutional analysis describes characteristics of the largest cohort of pts with GI FL to date. Observation or tx with rituximab ± chemotherapy were common initial approaches. Patients in this cohort had a good overall prognosis. While some factors including age, grade and BCL-2 expression by immunohistochemistry (IHC) predicted survival, traditional prognostic indices and staging systems did not.

The research was funded by: No funding to disclose.

Keyword: Extranodal non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

T. Alrifai

Consultant or advisory role: Previous independent consultancy for MJH Life Sciences; completed in June of 2022.

	OS		PFS	
Variable	HR	*P* value	HR	*P* value
Age ≥60	4.47 (1.28, 15.6)	0.019	1.30 (0.75, 2.25)	0.3
Male sex	2.07 (0.80, 5.35)	0.13	1.87 (1.08, 3.23)	0.026
Grade (3A vs. 1–2)	4.85 (1.51, 15.5)	0.008	6.13 (3.00, 12.5)	< 0.001
BCL-2 expression positive by IHC	0.14 (0.04, 0.53)	0.004	0.53 (0.19, 1.49)	0.2
Surgical resection at dx	3.22 (1.22, 8.33)	0.018	1.18 (0.64, 2.17)	0.6

J. Kline

Employment or leadership position: Speaker for Kite Pharma, Inc./Gilead. B.A.D

Consultant or advisory role: Advisory boards for Merck, Kite Pharma, Inc./Gilead, Seattle Genetics, and Verastem Oncology

Honoraria: Has received advisory board fees from Janssen, Sanofi, and consulting fees from COTA Healthcare.

Research funding: Research support from Merck, iTeos, and Verastem Oncology

R. Karmali

Employment or leadership position: Speakers Bureau: AstraZeneca, BeiGene, Morphosys

Consultant or advisory role: Advisory Board: BMS, Gilead Sciences/Kite Pharma, Janssen, Pharmacyclics, Morphosys, Epizyme, Genentech/Roche, Calithera, Miltenyi, Lilly Oncology

Research funding: Grants/Research Support: BMS, Takeda, BeiGene, Gilead Sciences/Kite, Calithera

276 | IBRUTINIB AND VENETOCLAX IN RELAPSED AND REFRACTORY FOLLICULAR LYMPHOMA

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Background: Ibrutinib (I) and venetoclax (V) have modest single-agent activity in relapsed/refractory follicular lymphoma (FL) (Gopal A, JCO 2018; Davids M, JCO 2017). Preclinical data have shown synergy I and V (Kuo H, Mol Cancer Ther 2017). Based on these data, we conducted the first phase I/II trial to combine I and V in FL (NCT02956382). We previously presented results from the phase Ib portion of this multi-institutional trial (Ujjani C, Blood 2020). Here, we present data from the phase II study.

Methods: Enrolling sites include Fred Hutch CC, Lombardi CCC, and John Theurer CC. Eligibility criteria were WHO grade 1-3a FL, >1 prior systemic therapy, measurable disease warranting therapy by standard criteria or physician discretion, ECOG PS ≤2, adequate marrow, hepatic, renal function. In the phase II study, patients (pts) received I 560 mg and V 600 mg daily. There was no dose ramp up of V based on experience in FL. Pts at high risk for tumor lysis syndrome (TLS) (node ≥8 cm and/or significant lymphocytosis) were hospitalized for initial dose. Pts received therapy until progression or unacceptable toxicity. Response was assessed by Lugano criteria.

Results: Fourteen pts received treatment at the RP2D between May 2019 and April 2021. Patient characteristics are listed in Table 1. One pt was considered high risk for TLS. Pts received a median of 1 prior therapy (range 1–8).

Grade 3/4 adverse events (AE) included neutropenia (NTP) (21%), febrile NTP (14%), diarrhea (21%), nausea (14%), hypertension (14%), thrombocytopenia (7%), atrial fibrillation (7%), vomiting (7%), ALT/AST elevation (7%), COVID pneumonia (7%). Grade 1/2 AE occurring in > 30% of pts were rash (64%), diarrhea (57%), bruising (50%), abdominal pain (36%), fatigue (36%), nausea (35%), and mucositis (35%). There were 2 SAEs: febrile NTP and COVID. There was no clinical TLS.

The ORR amongst the 14-patient cohort was 64% (0.35, 0.87); CR 21%. One of these 14 developed a prolonged, severe COVID infection resulting in study withdrawal before a response evaluation could be performed. One other pt also discontinued for toxicity (mucositis, malaise, arthralgia). Nine discontinued for progression. Two responding pts chose to discontinue further treatment. Median PFS was 8.6 months (2.73, NA) (Figure 1). Duration of response is displayed in Figure 2. Median DOR for 6 pts with PR was 5.7 months; 3 pts with CR was NA. The study closed early due to poor accrual during the COVID pandemic.

Conclusion: In the first trial to combine a BTK and BCL-2 inhibitor in relapsed/refractory FL, we found the I-V doublet to demonstrate a toxicity profile similar to that seen in CLL. Importantly, there was no evidence of clinical TLS, despite omission of the V ramp up. Preliminary results of anti-tumor activity are encouraging. The combination of BTK and BCL2 inhibitor may provide an effective option for FL, utilizing a targeted approach distinct from other approved novel agents.

The research was funded by: Pharmacyclics and Abbvie

Keywords: Combination Therapies, Indolent non-Hodgkin lymphoma, Molecular Targeted Therapies

Table 1: Patient Characteristics

Characteristic	N=14 (%)
Median Age in years (Range)	64 (40-75)
Male sex	8 (57%)
ECOG Performance Status	
0	11 (79%)
1	3 (21%)
Stage	
I/II	2 (14%)
III/IV	12 (86%)
Grade	
1 or 2	12 (86%)
3a	2 (14%)
FLIPI score	
0 or 1	1 (7%)
2	6 (43%)
3-5	7 (50%)
FLIPI-2 score	
0	2 (14%)
1-2	9 (64%)
3-5	3 (22%)
Number of prior therapies	
1	8 (58%)
2	3 (21%)
≥3	3 (21%)
Prior Regimens	
Bendamustine + anti-CD20 monoclonal antibody	5
CHOP + anti-CD20 monoclonal antibody	4
Proteasome inhibitor + anti-CD20 monoclonal antibody	3
PD-1 Inhibitor	3
Lenalidomide-based regimen	3
anti-CD20 monoclonal antibody monotherapy	2
PI3K inhibitor	1
Radioimmunotherapy	1
Anti-CD20 Bispecific T-cell Engager	1
Anti-CD19 CART	1
Other chemotherapy	5
Time since last anti-lymphoma therapy	
< 2 years	10 (71%)
≥ 2 years	4 (29%)

Figure 1: Progression-free Survival (months)

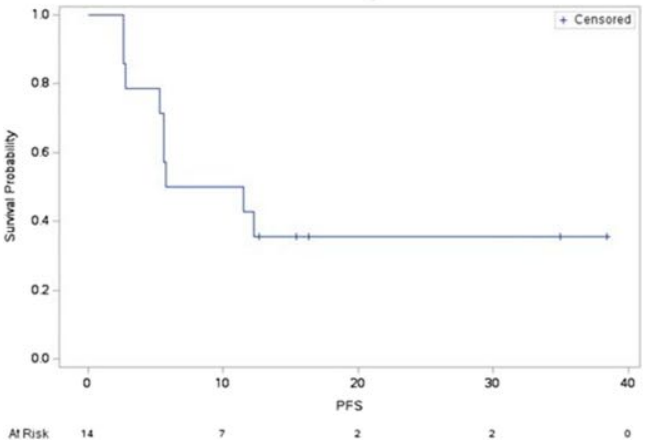
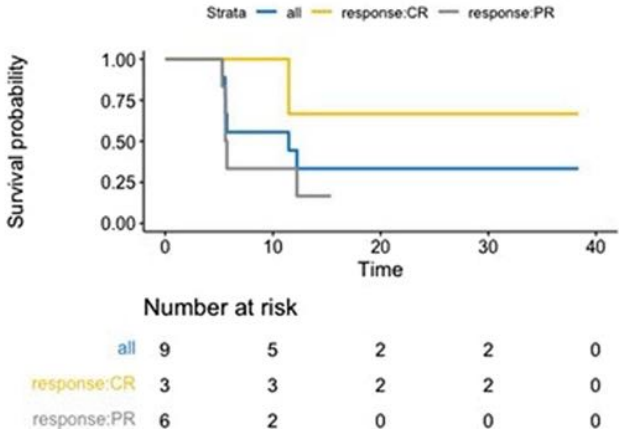


Figure 2: Duration of Response (months)



Conflicts of interests pertinent to the abstract.

C. Ujjani

Consultant or advisory role: Abbvie, Janssen, Pharmacyclics, Beigene, Lilly, Astrazeneca, Epizyme, Atara, Incyte, Genentech

Research funding: Abbvie, Pharmacyclics, Astrazeneca, Lilly

A. Gopal

Consultant or advisory role: Incyte, Kite, Morphosys/Incyte, ADCT, Acrotech, Merck, Karyopharm, Servier, Beigene, Cellectar, Janssen, SeaGen, Epizyme, I-Mab bio, Gilead, Genentech, Lilly, Caribou, Fresenius-Kabi

Stock ownership: Compliment Corporation

Research funding: Merck, I-Mab bio, IgM Bio, Takeda, Gilead, AstraZeneca, Agios, Janssen, BMS, SeaGen, Teva, Genmab

C. Lai

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M. Shadman

Consultant or advisory role: abbvie

S. D. Smith

Consultant or advisory role: ADC Therapeutics, Astrazeneca, Beigene, Epizyme, Karyopharm, KITE pharma, Incyte, Numab Therapeutics AG, Abbvie, Coherus Biosciences, advisory board (spouse), Genentech

Research funding: ADC Therapeutics, Astrazeneca, Ayala (spouse), Bayer, Beigene, Bristol Myers Squibb (spouse) De Novo Biopharma Enterome Genentech Ignyta (spouse), Incyte Corporation, Kymera Therapeutics, Merck, Sharp and Dohme Corp, MorphoSys, Nanjing Pharmaceuticals Co., Ltd., Portola Pharmaceuticals, Viracta Therapeutics

B. D. Cheson

Consultant or advisory role: Abbvie, Pharmacyclics, Morphosys, Lilly, Beigene, Reddy Biosimilar, Genmab

K. Dunleavy

Consultant or advisory role: Astra Zeneca, Abbvie, ADC Therapeutics, Cellectar, Beigene, ONO, Incyte

Research funding: Genentech, ONO, Kymera

277 | A PHASE II INVESTIGATOR INITIATED STUDY OF ACALABRUTINIB, LENALIDOMIDE AND RITUXIMAB (AR2) IN PATIENTS WITH PREVIOUSLY UNTREATED HIGH TUMOR BURDEN FOLLICULAR LYMPHOMA

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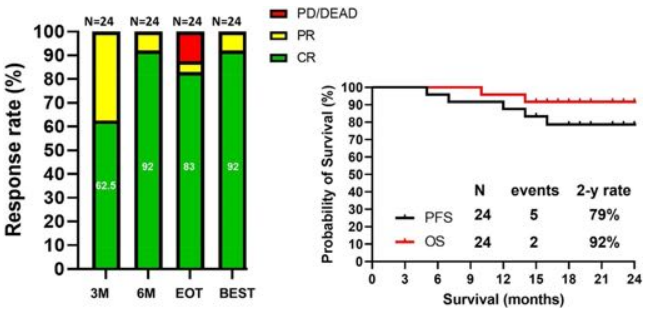
Background: The efficacy of lenalidomide and rituximab (R^2) is comparable to chemoimmunotherapy in patients with previously untreated follicular lymphoma (FL). We previously reported pro-tumoral macrophage enrichment may be associated with resistance to R^2. As pre-clinical studies show that BTK inhibition can mitigate the crosstalk between macrophages and FL B cells, we hypothesized that acalabrutinib, a specific BTK inhibitor, may synergize with R^2 without increasing toxicity. In agreement with this, the combination of acalabrutinib and R^2 (aR^2) was shown to be safe and effective in patients with relapsed FL.

Methods: This phase 2 single arm study (NCT04404088) was conducted between 09/2020 and 09/2021 (data cutoff 02/2023). Adult patients with previously untreated FL, grade 1 to 3A, stage 3–4, and with high tumor burden (per GELF criteria) were included. Dosing included acalabrutinib 100 mg PO twice a day in a 28-day cycle for 13 cycles, lenalidomide 20 mg PO daily on days 1–21, starting from cycle 2, and rituximab 375 mg/m^2 IV weekly during cycle 2, and on day 1 of subsequent cycles. Response was assessed per Lugano 2014 criteria. The primary endpoint was best complete response (CR) rate, and an exact binomial test was used for sample size calculation ($N = 24$; H_0 50%, H_A 80%, power 80%, 2-sided alpha level 0.05).

Results: Twenty-four patients were enrolled. Median age was 62 years (range, 40–82), 18 (75%) were male; median largest lymph node size was 6.2 cm (range, 1.9–15), median SUV_{max} was 14 (range, 6–36), and 17 (61%) patients had an intermediate-high FLIPI. Median number of cycles was 13 (range, 6–13) and 15 (62.5%) patients experienced a cycle delay, due to COVID-19 in 11 (46%) cases; 6 (25%) patients required dose reduction of lenalidomide, but none discontinued, and 2 (8%) required dose reduction of acalabrutinib and 1 discontinued. The most common (>5% of patients) grade 3–4 adverse events were neutropenia (58%), liver function test elevation (17%), infection (12.5%; 2 out of 3 related to COVID-19), anemia (8%) and skin rash (8%). Best ORR was 100% and best CR rate was 92%, as early as after 6 cycles (Figure). After a median follow-up of 22 months (95% CI: 20–24 months), 4 patients had disease progression, including 2 who transformed at 5 and 7 months, while in partial response (both with pre-treatment bulky disease and SUVmax >17), and 1 who transformed at end of treatment, after initial CR. The 2-year PFS rate was estimated at 79% (95% CI, 56%–91%). At data cutoff, 2 patients have died, 1 due to COVID-19 (while in CR, at 14 months) and 1 due to transformed lymphoma (at 10 months), both 4 months after study discontinuation. The 2-year OS rate was estimated at 92% (95% CI, 71%–98%) (Figure).

Conclusion: Our results indicate that aR^2 is a safe and effective frontline non-chemotherapy regimen for FL patients, resulting in high CR rates. The study has been expanded to include 26 additional patients treated with only 6 cycles.



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278 | OUTPATIENT ADMINISTRATION OF MOSUNETUZUMAB IN US COMMUNITY PRACTICE SETTINGS: PERSPECTIVES AND LEARNINGS FROM THE PHASE II MORNINGSUN STUDY

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Introduction: Mosunetuzumab (mosun) is a CD20xCD3 T-cell engaging bispecific monoclonal antibody that redirects T cells to eliminate malignant B cells. The Phase II MorningSun study evaluates subcutaneous (SC) mosun in select B-cell non-Hodgkin lymphomas (B-NHLs), including follicular lymphoma (FL). As intravenous mosun is

already FDA-approved for relapsed/refractory FL after ≥2 prior treatments (txs), there is also a need to understand how to manage patients (pts) at risk for cytokine release syndrome (CRS), especially in an outpatient setting. We present interim safety data from the MorningSun first-line (1L) high tumor burden FL cohort and describe the approach to monitoring/managing CRS from the community practice perspective.

Methods: MorningSun is an open-label, multicenter trial of SC mosun monotherapy in B-NHL (NCT05207670). Mosun is given as step-up dosing in Cycle (C) 1 (5 mg Day [D] 1, 45 mg D8, 45 mg D15) then 45 mg on D1 of each 21-day C for up to 17 Cs (1 year) in pts with high-tumor burden 1L FL. Pts with partial/complete metabolic response may receive additional maintenance therapy. The primary endpoint in the FL cohorts is progression-free survival rate at 24 months. Secondary endpoints include safety, pharmacokinetics, time to next tx, duration of response, overall survival, and objective response rate. Prophylaxis for CRS is mandatory for the first 2 Cs and optional thereafter. Pre-tx with acetaminophen and/or diphenhydramine may also be given. The study allows for outpatient tx in academic medical centers/community practice sites.

Results: Safety analyses in the high-tumor burden FL cohort were based on a cutoff date of Aug 10, 2022, at which time 23 sites were active (all non-academic community sites). Eighteen pts had completed ≥1 C of mosun, of whom 16 (88.9%) were still on tx and 2 (11.1%) had progressive disease. Median age was 64 (range 28–79) years; sex was equally balanced. With a median follow up of 2.1 months, 15 (83.3%) pts experienced ≥1 adverse event (AE). Serious AEs occurred in 4 (22.2%) pts, with Grade (Gr) ≥3 AEs in 3 (16.7%) pts. Twelve (66.7%) pts had ≥1 tx-related AE. The most common AEs (≥20%) were injection-site reaction (n = 6, 33.3%) and CRS (n = 4, 22.2%; no oxygen, steroids, tocilizumab, or vasopressors required; Table). All pts had complete resolution of CRS events and continued tx. One pt (5.6%) had 2 neurologic AEs (headache Gr 1 and insomnia Gr 2), both of which resolved.

Community sites created a support network to help pts, their treating physicians, and other colleagues monitor for, identify, and manage CRS. Additional details of this process will be presented at the meeting.

Conclusions: MorningSun is the first study to evaluate SC mosun in 1L FL. Early safety data support its continued evaluation in this setting. These findings, along with best practice examples, illustrate that community practices can safely manage pts receiving mosun in an outpatient setting.

The research was funded by: The MorningSun study is sponsored by Genentech, Inc. Third-party medical writing assistance, under the direction of the authors, was provided by Martha Warren, MSci, and Roisin Weaver, MSc, of Ashfield MedComms, an Inizio company, and was funded by Genentech, Inc.

Keywords: Immunotherapy, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

Table. Summary of CRS events and their consequent management in pts with 1L high-tumor burden FL.

	1L high-tumor burden FL (N=18)
Any Grade CRS*, n	**4** (22.2)
Grade 1, n (%)	**3** (16.7)
Grade 2, n (%)	**1** (5.6)
Serious AE of CRS (any Grade)	
Criteria: Inpatient hospitalization, n (%)	**3** (16.7)
Median time to CRS onset†, days (range)	**1.5** (1–24)
Median CRS duration, days (range)	**2.5** (2–4)
CRS management (n=4)	
Treated with low-flow oxygen, n (%)	**0**
Corticosteroids, n (%)	**0**
Tocilizumab, n (%)	**0**
Fluids, n (%)	**1** (25)
CRS resolved (n=4), n (%)	**4** (100)

*CRS events were graded according to ASTCT criteria (Lee et al. 2019).
†From first mosun dose.
1L, first-line; AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; FL, follicular lymphoma; pts, patients.

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279 | THE IMPACT OF CHOP VERSUS BENDAMUSTINE ON BONE MINERAL DENSITY IN PATIENTS WITH FOLLICULAR LYMPHOMA ENROLLED IN THE GALLIUM STUDY

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Introduction: A standard treatment with CHOP or CVP includes a cumulative dose of 3,000–4,000 mg prednisone. Observational studies have shown increased risk of fractures in patients treated with R-CHOP/R-CVP. However, it is not clear whether reductions in

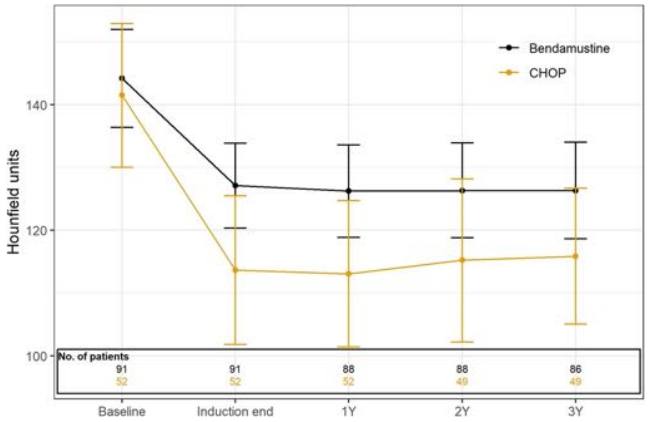
bone mineral density (BMD) are mainly caused by glucocorticoids or the combined impact of chemotherapy and glucocorticoids. The objective of this study was to investigate the impact of G/R-bendamustine versus G/R-CHOP on BMD in patients with follicular lymphoma (FL) enrolled in the GALLIUM study.

Methods: Patients enrolled in the GALLIUM study, an international randomized phase 3 trial of first-line treatment for FL, were included if they were ≥60 years at inclusion and in complete remission following treatment with G/R-bendamustine or G/R-CHOP. Exclusion criteria were treatment with anabolic or antiresorptive therapies prior to baseline, co-existing medical conditions associated with low BMD, and new anti-lymphoma treatment during the initial 5 years of follow-up.

CT scans were performed at baseline, induction treatment completion (ITC), and annually in five years after inclusion. Hounsfield units (HU) measured in an ovoid region in the anterior of L1 were used as surrogate for BMD, which has been shown to correlate with BMD measurements from conventional dual-energy X-ray absorptiometry (DXA). Low HU values represent lower bone density while high values represent more dense bone. Vertebral compression fractures were defined as vertebral height loss of ≥20%.

Results: At ITC, 244 patients ≥60 years old were in CR. Of those, 155 fulfilled the inclusion criteria, 55 (35%) received G/R-CHOP and 100 (65%) received G/R-bendamustine. CT scans with contrast were performed at baseline and ITC in 143 patients. Baseline characteristics, including age and gender, were balanced between groups. The mean baseline HU was 143.8 in the CHOP group and 141.5 in the bendamustine group ($P = 0.74$). The mean HU decrease from baseline to ITC was 27.8 after CHOP versus 17.1 after bendamustine, corresponding to a difference of 12.5 (95% CI: 5.5–19.5) after adjusting for age, sex, B-symptoms, and baseline HU. BMD remained at the ITC level, and thus below baseline, during the first 3 years of follow-up. During treatment and 5 years follow up, a total of nine new compression fractures were recorded in five patients. One patient in the bendamustine group and four patients in the CHOP group developed new vertebral fractures.

Conclusion: CHOP induction treatment for FL was associated with a significantly greater loss in BMD as compared to bendamustine. Fractures were numerically more frequent in the CHOP treated group. The results suggest that considerations regarding use of primary prophylaxis against BMD loss in lymphoma patients are warranted, in particular for patients selected for glucocorticoid containing regimens.



Keywords: Indolent non-Hodgkin lymphoma, Late Effects in Lymphoma Survivors

No conflicts of interests pertinent to the abstract.

280 | EVALUATION OF THE GELTAMO GUIDELINES FOR SURVEILLANCE IN FOLLICULAR LYMPHOMAS AFTER FIRST-LINE IMMUNOCHEMOTHERAPY: A REAL-WORLD PROSPECTIVE STUDY

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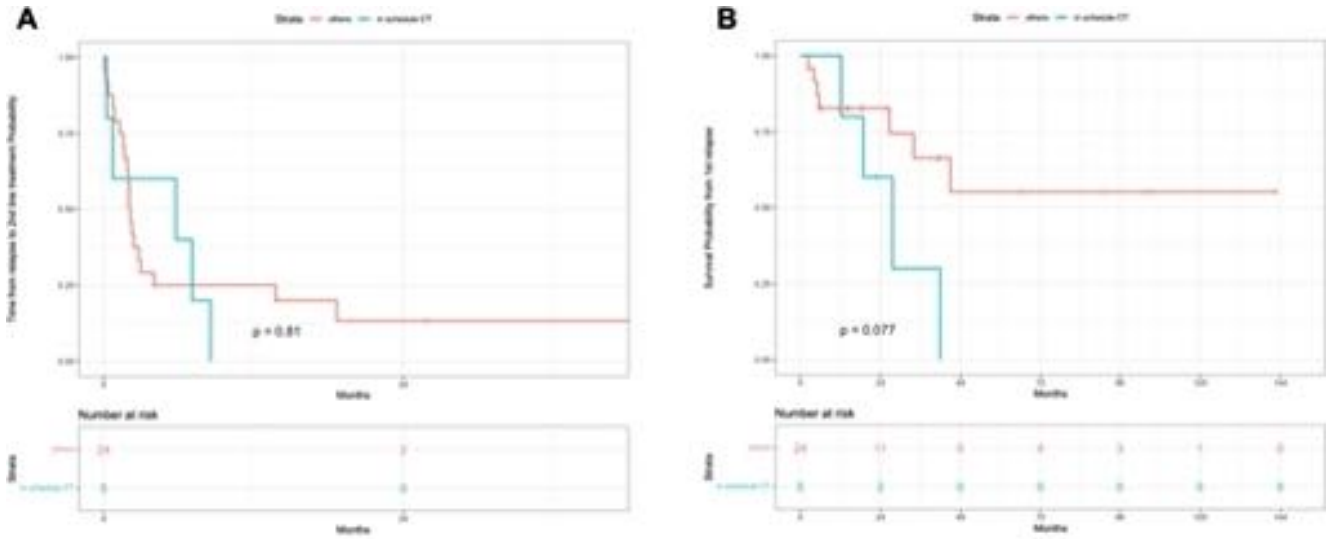
Introduction: CT scans have been traditionally recommended in the surveillance of patients (pts) with follicular lymphoma (FL) by international societies. In asymptomatic FL pts responding to first line (1L) immunochemotherapy, the Spanish GELTAMO FL guidelines recommends CT scan every 6 months for 2 years (during rituximab maintenance). The real value of surveillance with CT scans remains an open question, even more after the incorporation of PET in the response evaluation of FL. Our aim was to evaluate the detection rate of relapses by CT surveillance according to GELTAMO guidelines in FL pts with complete metabolic response (CMR) or partial metabolic response (PMR).

Methods: observational prospective study in a single center between 2008 and 2020. Newly diagnosed FL who had CMR or PMR to 1L therapy were identified. Evaluation for both relapse and method of relapse detection, having special interest in the CT surveillance according to GELTAMO guidelines.

Results: From 108 FL treated pts, 81 were included in the final analysis. Median age and female proportion were 59 years (range 24–83) and 49.4%. Treatment: R-CHOP/R-CHOP-like 63%, R-CVP 15% and rituximab 22%. Response: CMR 82%, PMR 18%. Median follow-up was 79.7 months (IQR 57.8–117.3).

A total of 29 pts relapsed or progressed (35.8%) during the whole study period: 24 from CMR and 5 from PMR. Of these pts, 9 relapsed in the first 2-y (31.0% of all relapses and 11.1% of all patients) and were more common in pts in PMR versus CMR (60% vs. 25%, $p = 0.1238$). Relapse detection method in the first 2-y was: 5 (55.5%) by CT scan, 2 by physical examination and 2 by other methods. Beyond 2-y, 12 (60%) were detected by physical examination, 5 (25%) by CT scan, 2 (10%) by blood tests and 1 (5%) by ultrasound echography.



Protocol adherence was 75.3%. A total of 262 CTs were performed in first 2-y with only 5 positive CT scans in this time-lapse (diagnostic yield 2%). Globally, 17.2% of all relapses were diagnosed by GELTAMO recommended surveillance CT scans. Time from first relapse to second line treatment was 4.02 months in those with relapse detected by CT in schedule versus 2.03 months in those detected by other methods ($p = 0.81$) (Figure 1A). In relapsed pts, OS at 3-y from relapse was 30.0 months in those with relapse detected by CT in schedule versus 66.2 months in the other patients ($p = 0.077$) (Figure 1B), probably because of the enrichment of POD24 cases in the first group. However, OS at 3-y from relapse in those patients in which relapse was detected by CT at any time (in or out schedule) was 43.8 months versus 66.9 months in those detecting relapse by other methods ($p = 0.19$).

Conclusions: Our results show no benefit from routine surveillance CT scans during the first 2-y of follow-up among FL patients in CMR after first-line therapy. However, the value of this strategy in PMR remains to be defined, since surveillance CT scans during the first 2-y can identify POD24 cases, a condition that predicts reduced survival.

Keywords: Imaging and Early Detection, Indolent non-Hodgkin lymphoma, PET-CT

No conflicts of interests pertinent to the abstract.

281 | REALMA: SUBSET OF PATIENTS WITH MARGINAL ZONE LYMPHOMAS FROM THE FRENCH NATIONWIDE REALYSA REAL-WORLD PROSPECTIVE COHORT.

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Background: Marginal Zone Lymphomas (MZL) are a heterogeneous group of lymphomas that include three subtypes: extranodal MZL (EMZL), splenic MZL (SMZL) and nodal MZL (NMZL). Since most of the knowledge comes from clinical trials (with stringent inclusion criteria and limited representativeness), there is a crucial need for real-world evidence in MZL. In 2018 the French REALYSA (Real world dAta in LYmphoma in Adults) study was initiated as a nationwide multicentric prospective cohort of patients newly diagnosed with lymphoma. By Dec 31, 2021, a total of 207 patients with MZL were included in the study.

Methods: Patients were recruited in **35 French hematology centers** and received routine care. Data were collected from medical records and questionnaires. A first abstraction was performed on Jan 1, 2023, to parse out the available data regarding MZL patients with >1 year of follow-up. Each case was reviewed by medical and pathological experts, and treatments were classified on an intent-to-treat basis.

Results: Of the **207 patients** with MZL included up to Dec 31, 2021, 111 (53%) presented with EMZL, 47 (23%) with SMZL and 49 (24%)

with NMZL. At baseline, median age was of 67 years old (IQR 60,75), 53% of patients were females, 5.5% of patients had a PS of 2–4, 70% were stage III-IV, 19% presented with B-symptoms, 20% had a bulky mass >7 cm and 5.8% had a compressive syndrome. Only 7% of patients reported an auto-immune disease. Diagnosis of MZL was mostly evoked by general practitioners (48%) but patients were finally treated by hematologists (98%). Only 9 patients were referred to an onco-geriatrician. Regarding the **initial workup**, while at least one imagery was offered in 97% of patients, ^{18}FDG-PET/CT (EMZL 78%, SMZL 62%, NMZL 78%) was performed more frequently than CT-scan at baseline (EMZL 73%, SMZL 62%, NMZL 71%), although 47% patients underwent both procedures. Among the 207 patients, 58 (28%) were not treated. Only 10 patients exclusively received **local therapy** (radiotherapy $n = 6$, surgery $n = 2$, antibiotics $n = 2$). Regarding **systemic therapies**, rituximab-chlorambucil was mainly offered in patients with EMZL (40%), while rituximab-monotherapy was preferred in SMZL (60%). For patients with NMZL, physicians mainly offered RCHOP (33%) and rituximab-bendamustine (27%). Only 7 patients with EMZL received the combination of ibrutinib and rituximab. At end of 1st line, 93% of patients had responded to therapy and **75% were in complete response**. Among patients assessed with ^{18}FDG-PET/CT, a metabolic complete response was observed in 52/58 (90%) of cases.

Conclusion: This is the first analysis describing **real-world data** of patients with MZL in France. Our cohort features high-quality data both on **epidemiological and clinical outcomes**. When the total number of patients will increase and data will mature, this dataset will provide insightful information regarding both endpoints and treatment evaluations.

Keyword: Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

C. Bommier

Research funding: Inserm/AvieSan/ITMO Cancer, LYSA/ELI (Bertrand Coiffier Prize), Philippe Foundation, Institut Servier

282 | MATCHING-ADJUSTED INDIRECT COMPARISON (MAIC) OF ZANUBRUTINIB (ZANU) VERSUS IBRUTINIB (IBRU) IN RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA (R/R MZL)

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Introduction: ZANU is a Bruton tyrosine kinase inhibitor (BTKi) that has been evaluated for the treatment of R/R MZL in two phase 2, single-arm trials (MAGNOLIA, $n = 66$, NCT03846427; BGB-3111-AU-003, $n = 20$, NCT02343120). At 28 and 35 months of study follow-up in MAGNOLIA and BGB-3111-AU-003, respectively, median progression-free survival (PFS) and overall survival (OS) were not reached. IBRU, a first-generation BTKi, has also been evaluated for R/R MZL in a phase 2, single-arm trial (PCYC-1121, $n = 60$ [Noy et al. *Blood* 2017; Noy et al. *Blood Adv* 2020]). Here, we conducted an unanchored MAIC to estimate the comparative efficacy of ZANU versus IBRU in R/R MZL.

Methods: The MAIC utilized study-level data from PCYC-1121 and pooled individual patient-level data from MAGNOLIA and BGB-3111-AU-003. A logistic propensity score model (PSM) was used to estimate weights for patients in the ZANU trials so that weighted mean baseline characteristics matched those in PCYC-1121. Number of prior lines of therapy, MZL subtype, response to prior therapy, and age were identified as key prognostic factors and included in the base case PSM. A sensitivity analysis was conducted including additional characteristics (B symptoms, time since last therapy, prior anti-CD20 therapy, bulky disease [>5 cm], and lactate dehydrogenase above normal). Comparisons were conducted for OS, PFS, and objective response rate (ORR) by independent review committee using weighted statistical models with relative treatment effects presented as hazard ratios (HRs), odds ratios (ORs), and 95% confidence intervals (CIs).

Results: After applying weights estimated from the base case PSM, the effective sample size (ESS) for ZANU was 68 (Table). Compared with IBRU, ZANU significantly reduced the risk of progression (HR 0.38; 95% CI: 0.21, 0.69; $p = 0.001$) and was associated with a higher ORR (OR 2.37; 95% CI: 1.13, 4.96; $p = 0.022$). OS was comparable for ZANU and IBRU, which is consistent with expected survival for indolent lymphomas. The sensitivity analysis accounting for additional prognostic factors suggested the 2 treatments were comparable across all outcomes, owing in part to the low ESS (24) for ZANU associated with the expanded model. A leave-one-out analysis showed improved PFS (HR 0.33–0.45) for ZANU when excluding B symptoms, time since last therapy, or bulky disease from the expanded model.

Conclusions: This MAIC demonstrated ORR and PFS benefits for ZANU versus IBRU in R/R MZL.

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Keywords: Indolent non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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Table: Efficacy outcomes

Covariates, %	IBRU (n=60)	ZANU unweighted (n=86)	ZANU weighted (ESS=68)
2 prior lines	30.0	30.2	30.0
≥3 prior lines	33.3	25.6	33.3
Nodal MZL	28.3	36.6	28.3
Splenic MZL	21.7	22.0	21.7
Refractory to last therapy	22.2	30.1	22.2
Aged ≥65 years	60.0	65.1	60.0
Results ZANU vs IBRU (95% CI)			
ORR OR		2.64 (1.32, 5.28)	2.37 (1.13, 4.96)
PFS HR		0.38 (0.22, 0.65)	0.38 (0.21, 0.69)
OS HR		0.61 (0.30, 1.22)	0.68 (0.34, 1.39)

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283 | ORELABRUTINIB, A NEW-GENERATION BRUTON TYROSINE KINASE INHIBITOR, DEMONSTRATES SAFETY AND EFFICACY IN RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA

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Introduction: Marginal zone lymphoma (MZL) is an indolent type of non-Hodgkin lymphoma that develops through pathological B cell receptor signaling. Orelabrutinib, a new-generation oral small molecule Bruton's tyrosine kinase (BTK) inhibitor, was evaluated in relapsed/refractory (r/r) MZL patients.

Methods: Previously treated r/r MZL patients received orelabrutinib 150 mg once daily in a phase 2, multicenter, single-arm study conducted in China. The primary endpoint was overall response rate (ORR) assessed by an Independent Review Committee (IRC) based on the Lugano 2014 classification. Other efficacy, safety, and pharmacokinetic parameters were evaluated as secondary outcome measures.

Results: Between April 2019 and November 2021, 111 Chinese patients with a median age of 60 y/o (range 23–77) were enrolled. Among those, 83 patients who received at least 1 prior therapy with an anti-CD20 antibody-containing regimen were confirmed with MZL by the central pathological review, who were mainly with extranodal MZL of mucosa-associated lymphoid tissue (MALT, 45.8%) and nodal MZL (36.1%). The majority had late-stage diseases, the stage IV

accounting for 75.9%. After a median follow-up of 22.3 months, the IRC-assessed ORR was 57.8% (95% CI, 46.5% to 68.6%). Ten patients achieved a complete response (CR, 12%), and 38 achieved a partial response (PR, 45.8%). The IRC-assessed median duration of response (DoR) and median progression-free survival (PFS) was 34.3 months and 36.0 months, respectively, with a 12-month PFS rate of 84.3% (95% CI, 73.9% to 90.8%). The rate of overall survival (OS) was 91.5% (95% CI, 82.9% to 95.8%) at 12 months. Treatment was well tolerated with most treatment-related adverse events (TRAE) being grade 1 or 2. In all the 111 patients, common all-grade TRAEs included anemia (27.9%), neutrophil count decrease (23.4%), white blood cell count decrease (18.0%), platelet count decrease (17.1%), rash (14.4%), and upper respiratory tract infection (10.8%). Thirty-four patients (30.6%) experienced grade 3 or higher TRAEs. Serious TRAEs occurred in 18 patients (16.2%), of which pneumonia (5.4%) was the most common. Seven patients (6.3%) discontinued orelabrutinib due to TRAEs.

Conclusions: Orelabrutinib demonstrated high response rates with durable disease remission and was well tolerated in Chinese patients with r/r MZL. This trial is registered at ClinicalTrials.gov as NCT03797456.

Keyword: Indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

284 | LONG-TERM EFFICACY AND SAFETY OF ZANUBRUTINIB (ZANU) IN RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA (R/R MZL): FINAL ANALYSIS OF THE MAGNOLIA (BGB-3111-214) TRIAL

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Introduction: ZANU (BGB-3111), a potent next-generation Bruton tyrosine kinase inhibitor, is approved in various countries for R/R MZL based on the MAGNOLIA study (NCT03846427) primary analysis. At a median follow-up of 28 months (mo), we present the MAGNOLIA study final analysis.

Methods: Eligible adult patients (pts) received ZANU 160 mg twice daily until disease progression/unacceptable toxicity. Primary endpoint was overall response rate (ORR) by independent review committee (IRC) in accordance with Lugano 2014 classification. Secondary endpoints included ORR by investigator assessment, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Efficacy was assessed by positron emission tomography (PET)-based Lugano criteria for pts with IRC-confirmed fluorodeoxyglucose (FDG)-avid disease at baseline; non-avid pts were assessed by computed tomography (CT)-based criteria. A sensitivity analysis using only CT-based criteria was also performed.

Results: As of May 4, 2022, 68 pts were enrolled and treated (70 [range: 37–95] median years); 66 pts were efficacy-evaluable (median follow-up 28.0 mo [range: 1.6–32.9]; median treatment duration 24.2 mo [range: 0.9–32.0]). Pts had the following MZL subtypes: 38.2% extranodal (mucosa-associated lymphoid tissue), 38.2% nodal, 17.6% splenic, 5.9% unknown. Sixty-one (89.7%) pts had IRC-assessed FDG-avid disease. IRC-assessed ORR (complete response [CR] + partial response [PR]) was 68.2% (CR 25.8%; Table). ORR (CR rate) was 64.0% (40.0%) in extranodal, 76.0% (20.0%) in nodal, 66.7% (8.3%) in splenic, and 50.0% (25.0%) in unknown subtypes. Median DOR, PFS, and OS were not reached. At the 2-year landmark by IRC, >70.0% of pts were alive/progression-free. Sensitivity analysis using only CT-based criteria (n = 66) by IRC showed an ORR of 66.7% (CR 24.2%). Median DOR and median PFS were not reached. At study completion, 31 (45.6%) pts deriving benefit rolled over to a long-term extension study (NCT04170283); 24 (35.3%) discontinued due to disease progression (investigator assessed); 5 (7.4%) to adverse events (AEs), 2 (2.9%) required prohibited medications, and 1 (1.5%)

Table. Baseline Characteristics, Efficacy, and Safety Outcomes

Baseline Characteristics	**R/R MZL (N=68)[a]**		
Male sex, n (%)	36 (52.9)		
ECOG PS 0-1, n (%)	63 (92.7)		
Bone marrow involvement, n (%)	29 (42.6)		
Extranodal sites, n (%)	53 (77.9)		
Stage III/IV, n (%)	59 (86.8)		
Efficacy	**(N=66)[b]**		
	IRC		**INV**
	PET and/or CT	CT only	PET and/or CT
ORR, n (%) [95% CI]	45 (68.2) [55.6, 79.1]	44 (66.7) [54.0, 77.8]	50 (75.8) [63.6 85.5]
Best response, n (%)			
CR	17 (25.8)	16 (24.2)	19 (28.8)
PR	28 (42.4)	28 (42.4)	31 (47.0)
SD	13 (19.7)	16 (24.2)	10 (15.2)
PD	6 (9.1)	5 (7.6)	5 (7.6)
DOR rate at 24 months, % [95% CI]	72.9 [54.4, 84.9]	66.8 [46.4, 81.0]	60.8 [44.8, 73.6]
PFS rate at 24 months, % [95% CI]	70.9 [57.2, 81.0]	64.9 [51.2, 75.6]	57.9 (44.8, 68.9]
OS rate at 24 months, % [95% CI]	85.9 [74.7, 92.4]		
Safety[c]	**(N=68)[a]**		
Any TEAE, n (%)	68 (100)		
Grade ≥3 TEAE, n (%)	33 (48.5)		
Drug-related grade ≥3 TEAE, n (%)[d]	10 (14.7)		
Serious TEAE, n (%)	30 (44.1)		
Drug-related serious TEAE, n (%)[d]	7 (10.3)		
TEAE leading to dose interruption, n (%)	25 (36.8)		
Drug-related TEAE leading to dose interruption, n (%)[d]	8 (11.8)		
TEAE leading to dose reduction, n (%)	0		

Data cutoff: May 4, 2022.

[a]Safety analysis set is defined as all patients who received at least 1 dose of study drug.

[b]Efficacy analysis set is defined as all patients in the safety analysis set with centrally confirmed diagnosis of MZL. Two pts were excluded from analysis owing to centrally confirmed transformation to diffuse large B-cell lymphoma. One pt discontinued study before first response assessment.

[c]TEAE is defined as an adverse event that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days after study drug discontinuation or initiation of a new anticancer therapy. Worsening of an event to grade 5 beyond day 30 after last dose of study drug is also considered a TEAE (if it is before start of new anticancer therapy).

[d]Based on assessment by the investigators.

CR, complete response; CT, computed tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PR, partial response; pt, patient; R/R, relapsed/refractory; SD, stable disease; TEAE, treatment-emergent adverse event.

withdrew consent. Most common treatment-emergent AEs in >20% of pts were bruising (23.5%) and diarrhea (22.1%). Neutropenia (8.8%) and COVID-19 pneumonia (5.9%) were the most common grade ≥3 AEs. Five (7.4%) pts died due to unrelated AEs (2 COVID-19 pneumonia, 1 acute myeloid leukemia [prior alkylating agent exposure], 1 myocardial infarction [preexisting coronary artery disease], 1 septic encephalopathy [pt in CR]). Hypertension occurred in 3 (4.4%) pts, atrial fibrillation and atrial flutter in 1 (1.5%) pt; none led to treatment withdrawal.

Conclusions: With >2 years of median study follow-up, ZANU continues to demonstrate high response rates, durable disease control, and is well tolerated with no new safety signals observed.

Encore Abstract - previously submitted to EHA 2023

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Keywords: Indolent non-Hodgkin lymphoma, Molecular Targeted Therapies, Targeting the Tumor Microenvironment

Conflicts of interests pertinent to the abstract.

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285 | A SINGLE-CENTER EXPERIENCE OF LOW-DOSE RADIOTHERAPY FOR PRIMARY EXTRANODAL MARGINAL ZONE LYMPHOMA OF BRONCHUS-ASSOCIATED LYMPHOID TISSUE (BALT)

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Introduction: Extranodal marginal zone lymphoma of bronchus-associated lymphoid tissue (BALT) is a rare cancer for which optimal treatment strategies are not well defined. Retrospective analyses show equivalent or superior outcomes with surgical resection compared to systemic therapy or active surveillance. Despite a well established role for radiotherapy in the management of other types of extranodal marginal zone lymphoma (MZL), its role in BALT lymphoma is underexplored.

Methods: We screened 153 patients with a diagnosis of primary BALT lymphoma treated at a single institution from 1995 to 2022. Inclusion criteria comprised patients aged 18 years or older, histologically confirmed BALT lymphoma, and receipt of radiotherapy at initial presentation or disease progression/recurrence. We excluded patients with synchronous evidence of lymphoma involving non-thoracic extranodal sites and/or lymphadenopathy outside of the mediastinum and hilum, as these patients might represent MZL with secondary lung involvement as opposed to primary BALT lymphoma. All patients underwent baseline PET/CT staging. We extracted patient, tumor, imaging, and treatment characteristics from the electronic medical record. We defined active surveillance as at least 3 months of follow up prior to initiating active therapy combined with documentation of this plan in the medical record. We assessed treatment response using the RECIL 2017 criteria.

Results: We report the largest to date single-center retrospective analysis of 13 patients (median age 67 years, range 33–84 years) with localized BALT lymphoma treated with radiotherapy. The median tumor size was 3.6 cm (range 0.8–8.2 cm) with a median SUV of 3.9 (range 1.3–11.4). Most patients (n = 8, 62%) received radiotherapy for BALT lymphoma after failing first-line treatment, including active surveillance (n = 3), surgical resection (n = 2), or systemic therapy (n = 3). Of 15 irradiated lesions, most (n = 10, 67%) received very low-dose radiotherapy (VLRDT) of 4 Gy (range 4–36 Gy). With a median follow-up of >50 months, only 3 patients experienced progression of disease, none within the irradiated field (1 following VLDRT and 2 following full-dose RT). Among all treated lesions, the overall response rate was 100% (n = 5, 33% partial response [PR] and n = 10, 67% complete response [CR]). Among 10 lesions treated with VLDRT, 6 (60%) achieved CR; among 5 lesions treated with full-dose RT, 4 (80%) achieved CR. There were no events of secondary lung cancers within or in proximity to the irradiated field.

Conclusions: Radiotherapy, including VLDRT, is a feasible, well tolerated, non-invasive and effective treatment strategy for primary BALT lymphoma that can be considered in both the upfront and recurrent treatment settings.

Table 1. Treatment Outcomes

Sex, age (y)	Initial management strategy	Tumor maximum diameter (cm)	RT dose (Gy)/ fractions	Treatment response	Recurrent disease	Outcome	Follow-up from diagnosis (mo)
M, 64	Radiotherapy	6.2	4 Gy/2	CR	No	Alive	24
F, 52	Radiotherapy	1.0	4 Gy/2	CR*	No	Alive	21
M, 80	Initial wedge resection for solitary LUL mass with bilateral lung recurrence (including at site of prior LUL mass) 5 y later s/p rituximab (8 cycles) (progressive disease in bilateral lung masses 1 y later)	5.8, 3.6	4 Gy/2	PR*, PR*	No	Dead	94
F, 49	Rituximab (4 cycles) for bilateral lung masses with oligoprogressive RUL lesion 6 y later s/p rituximab (8 cycles) (oligoprogressive RUL lesion 2 y later)	5.8	4 Gy/2	CR	No	Alive	176
F, 69	Rituximab (1 cycle, stopped for DVT) for bilateral lung masses (progressive disease in bilateral lungs 1 y later)	8.2, 4.5	4 Gy/2	PR, CR	Regional recurrence in RUL 2 mo later	Alive	59
F, 71	Active surveillance for solitary RUL mass (progressive disease in RUL lesion 1 y later)	1.7	4 Gy/2	CR	No	Alive	24
M, 79	Active surveillance for solitary RUL mass (progressive disease in RUL lesion later)	5.9	4 Gy/2	PR	No	Alive	13
F, 67	Active surveillance for solitary LUL mass	1.7	4 Gy/1	CR	No	Alive	10
F, 65	Radiotherapy	2.7	24 Gy/12	PR	No	Alive	27
M, 68	Radiotherapy	0.8	30 Gy/20	CR	Distant recurrence in portacaval lymph node 78 mo later	Alive	122
F, 84	Rituximab (4 cycles) for solitary right lung mass (local progression 1 y later)	3.6	30 Gy/20	CR	No	Dead	139
F, 48	Initial right middle lobectomy for solitary RML mass with LUL recurrence 2 y later s/p wedge resection (oligoprogressive RUL lesion 6 y later)	2.3	30 Gy/15	CR*	Regional recurrence in RLL 17 mo later	Alive	194
M, 33	Radiotherapy	5.3	36 Gy/20	CR	No	Alive	81

*CT-based response-assessment only

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Keywords: Extranodal non-Hodgkin lymphoma, Indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

286 | CLINICOPATHOLOGICAL CHARACTERISTICS OF EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMA OF THE INTESTINE: A SINGLE CENTER ANALYSIS

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Extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid tissue (MALT-lymphoma) is mot commonly diagnosed in the stomach (30%–35%), but is exceedingly rare in the intestinal tract (2%). Consequently, data on this special subgroup are scarce.

Out of 484 patients with MALt-lymphoma diagnosed and treated at our institution from 1999 to 2020, 42 (11%) had intestinal involvement (24 primary and 18 secondary) and were restrospectively analyzed. Out of 18 patients rated as secondary intestinal invlevement, 14 patients had gastric MALT-lymphoma as the primary origin. Median age at diagnosis was 67 years (interquartile range (IQR) 53–72) and the median follow-up time was 47 months (IQR 32–102). Patients presenting with lymphoma-associated symptoms were significantly more common in the group of primary versus secondary intestinal MALT lymphomas (52% vs. 20%, $p = .047$). Nine patients each, i.e. 9/18 secondary and 9/24 primary intestinal MALT lymphomas were found positive for Helicobacter pylori. Intestinal organs involved included the colon ($n = 19$), duodenum ($n = 11$), small intestine ($n = 8$) and rectum ($n = 5$). MALT-IPI could be calculated for 39 patients, with low MALT-IPI documented in 37/39 cases. Seven patients were found to be positive for translocation t(11;18)(q21;q21), 6 of whom had primary gastric MALT lymphoma, suggesting the presence of the translocation as highly suggestive for secondary involvement.

Treatment data were available in 41 our of those 42 patients. Eleven patients (27%) received local therapy (ten surgery, and one radiotherapy, complete response rate 90%), 16 (38%) systemic therapy (overall response rate 87%) and 9 (22%) had only antibiotic therapy (complete response rate 38%). in 4/41 patients, only watchfuil waiting was applied. Eighteen patients progressed during follow-up; the median progression free survival following first line therapy was 50 mos (CI: 38.4–53.7 mos), with anumerical trend towards longer PFS in primary (134 mos) versus secondary MALT lmyphoma (35.5 mos). The estimated overall survival was 301 months, with 6 patients having died during follow up (two from lymphoma progression, the other 4 from unrelated conditions). A comparison in terms of PFS and Os with the cohort of 144 patients with gastric MALT-lmyphoma showed no significant difference in terms of outcome.

Overall, patients with intestinal MALT-lymphoma appear to have a good prognosis irrespcetive of primary or secondary involvement, whichbappears to be comparable to our data obtined in gastric MALT-lymphoma.

Keyword: Extranodal non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

287 | AUTOLOGOUS AND ALLOGENEIC STEM-CELL TRANSPLANTATION FOR TRANSFORMED WALDENSTRöM MACROGLOBULINEMIA

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Introduction: The prognosis of histological transformation (HT) in Waldenström macroglobulinemia (WM) is unfavourable despite the use of diffuse large B-cell lymphoma-directed chemo-immunotherapy. The aim of this study was to evaluate the outcomes after autologous stem-cell transplantation (autoSCT) or allogeneic stem-cell transplantation (alloSCT) in patients with transformed WM.

Methods: Patients who received autoSCT or alloSCT between January 1996 and December 2021 were identified in an international multicenter database of 285 patients with transformed WM. The primary end-point was overall survival (OS), calculated from the date

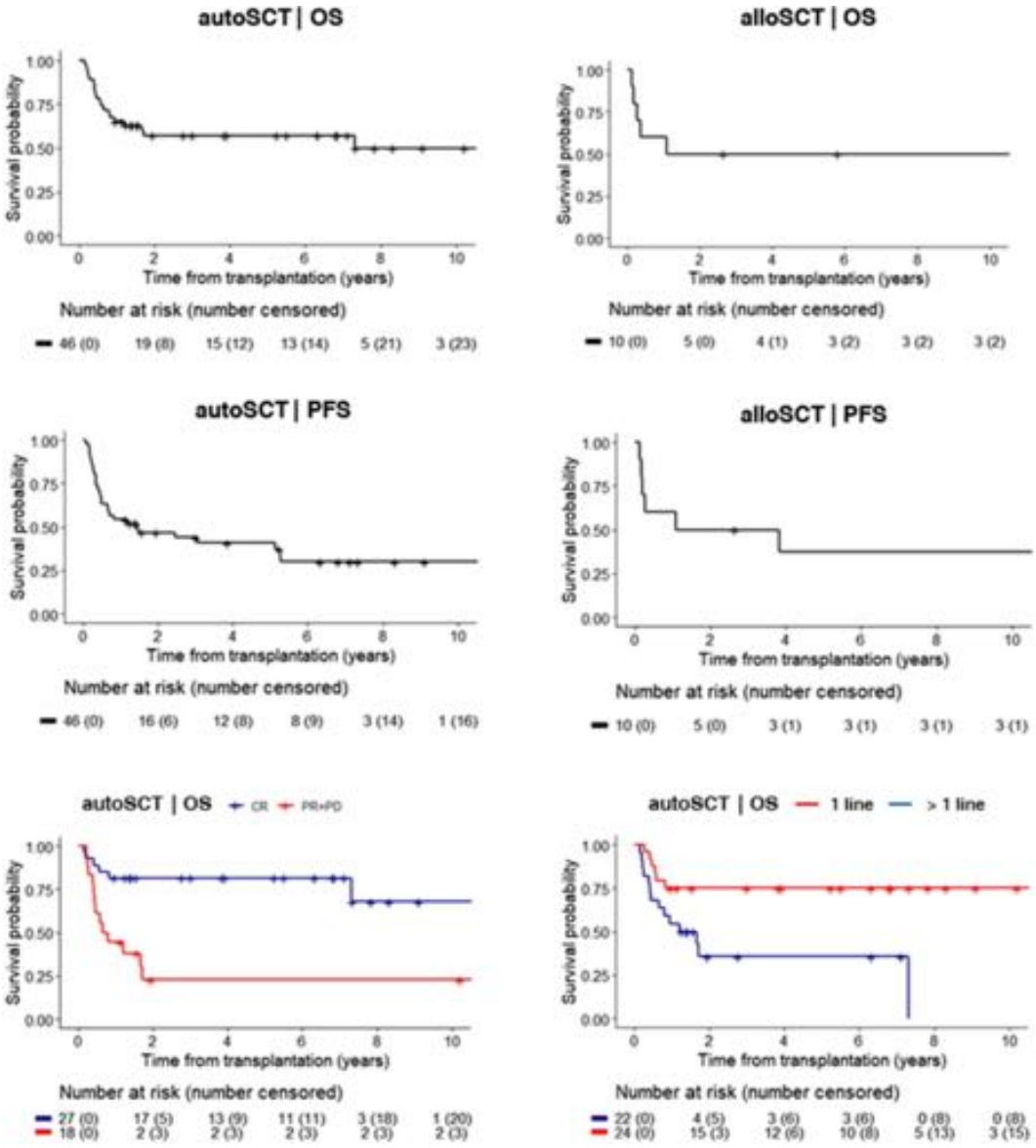
of SCT to death from any cause. Secondary end-points were progression-free survival (PFS), incidence of relapse/progression and non-relapse mortality (NRM). Univariate and multivariate analyses were performed using the Cox proportional hazards model for OS and PFS only for the autoSCT cohort, due to the small sample size of the alloSCT cohort.

Results: Fifty-six patients were included, 46 had received autoSCT and 10 alloSCT. The median time from HT diagnosis to SCT was 8 months (range, 2–76 months) for autoSCT and 7 months (range, 3–49 months) for alloSCT. The patients received a median of 2 lines of treatment for HT before SCT (range, 1 to 6 for autoSCT and 1 to 3 for alloSCT), and 89% (complete response (CR): 59%) and 80% (CR: 50%) of the patients had chemosensitive disease at the time of autoSCT and alloSCT, respectively. For autoSCT, the conditioning regimen was BEAM in 76% of the patients, and for alloSCT, reduced-intensity conditioning was used in 70% of the cases. The median follow-up time for the surviving patients was 5.5 years (95% CI, 2.8–7.1 years) from autoSCT and 12.6 years (95% CI, 2.7–14.4 years) from alloSCT. The 3-year estimates of OS, PFS and cumulative incidences of relapse and NRM were 57%, 44%, 54%, and 2% for autoSCT and 50%, 50%, 30%, and 20% for alloSCT, respectively. In the autoSCT cohort, CR at SCT was found to be associated with superior OS and PFS (3-year OS, 81% for CR vs. 23% for less than CR, $P = 0.001$ and 3-year PFS, 62% vs. 21%, $P < 0.001$) and less than 2 lines of therapy for HT with superior OS (3-year OS, 75% for 1 line vs. 36% for >1 line, $P = 0.01$).

Conclusion: This multicenter retrospective study shows that durable remission can be achieved with autoSCT or alloSCT in transformed WM, in particular for patients in complete response before SCT.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Stem Cell Transplant

No conflicts of interests pertinent to the abstract.



288 | INDOLENT LYMPHOMA: BENDAMUSTINE, RITUXIMAB AND ACALABRUTINIB IN WALDENSTROMS MACROGLOBULINEMIA (BRAWM)

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Background: Waldenström's macroglobulinaemia (WM) is an uncommon lymphoproliferative disorder. Many options are available, however, an optimal first-line therapy for WM has not be defined. We postulated that combining bendamustine and rituximab (BR) with a next generation BTK inhibitor would result in deeper responses as measured by complete response (CR) and very good partial response (VGPR) rates, and provide a longer duration of response.

Objectives: The primary objective of this trial is to document the CR and VGPR rates

Methods: The BRAWM clinical trial combines BR with acalabrutinib in a fixed duration treatment course including six cycles of BR and 12 months of acalabrutinib. This trial is taking place at 8 clinical sites across Canada and 33 patients have been enrolled, with a recruitment goal of 59.

Results: A pre-defined interim analysis of the first 30 enrolled patients showed; median age of patients was 66; 25 were male; two patients were low risk, 14, intermediate and 15 high risk. Seventeen patients completed combination therapy, 9 completed monotherapy and 2 were followed-up at 18 months (6 months post therapy). Clinical results to date:

Two patients discontinued treatment early; 1 at cycle 7 (with a VGPR) but experienced an adverse event requiring treatment; 1 at cycle 3 with possible disease progression. There were 186 treatment related adverse events (TRAEs) among 25 of 30 participants; 5 participants did not experience a TRAE; 163 of these occurred during combination therapy; 23 during monotherapy in 7 of 17 participants, where 10 participants did not experience a TRAE. During combination therapy, 16 of the 163 TRAE's were grade 3; neutropenia (n = 8), including 2 that were febrile neutropenia, n = 1 for each: atrial fibrillation, transaminitis, cellulitis, fatigue and pulmonary emphysema. An additional five were also considered serious and included febrile neutropenia (n = 2), and n = 1 for each fever, allergic reaction and bowel obstruction. During monotherapy, there were no serious TRAEs. There were 2 grade 3 events during monotherapy in two different patients; decreased neutrophil count, and syncope. There were 21 dose interruptions in 11 participants, all but one of whom returned to regular dosage. Of assessed patients, 20/20 have MyD88 mutations, 4/20 have a CXCR4 mutation, and none had a TP53 mutation. Minimal residual disease (MRD) analysis using next generation sequencing of the IgV regions will be reported.

Conclusions: Bendamustine, rituximab and acalabrutinib front-line therapy for WM is safe and well tolerated and initial clinical results show that this treatment induces a high percentage of VGPRs.

The research was funded by: AstraZeneca

Keywords: Combination Therapies, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

N. L. Berinstein
Consultant or advisory role: AstraZeneca
Research funding: AstraZeneca, Merck, IMV

N. Forward
Honoraria: AstraZeneca, AbbVie, BeiGene, Celgene/BMS, IMV, Kite, Janssen, Pfizer, Roche, Servier
Research funding: Astellas, AstraZeneca, IMV, Merk, MorphoSys, Seattle Genetics, Roche
Other remuneration: Speaker Fees: Pfizer, BeiGene, AstraZeneca

M. Shafey
Consultant or advisory role: Jansen, Roche Canada, Kite/Gilead, Novartis, BeiGene, Incyte, Abbvie, BMS, AstraZeneca

A. Nikonova
Consultant or advisory role: Forus, Janssen, Astra Zeneca, Apotex, Incyte
Educational grants: Janssen

	Screening (30)	Month 7 (n=17) Post combination therapy	Month 12 (n=9) Post monotherapy	Month 18 (n=2) Post therapy
Hb (median)	106	120.4*	126	142
IgM (median)	35.7	1.78*	1.1	0.42
CR			1/9 (11%)	
VGPR		12/17 (70%)	8/9 (89%)	2/2 (100%)
PR		3/17 (18%)		

*Data being confirmed on 1 participant

D. MacDonald

Honoraria: Abbvie, Astra Zeneca, Beigene, BMS, Incyte, Kite Gilead, Roche, and Seattle Genetics

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Honoraria: AZ, BeiGene, Janssen, Roche, Kite/Gilead, Merck, BMS/Celgene, ONO Pharmaceuticals.
Research funding: Roche, AstraZeneca

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Honoraria: Celgene/BMS, Kite/Gilead, Janssen, Sanofi, FORUS, Pfizer

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Consultant or advisory role: Jansen, Sanofi, Pfizer, Beigene

J. Larouche

Consultant or advisory role: Incyte, Gilead
Research funding: Incyte, Astra-Zeneca, Genmab

289 | SINGLE-AGENT RITUXIMAB AS AN EFFECTIVE SALVAGE THERAPY IN PRE-TREATED HAIRY CELL LEUKEMIA

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Introduction: Hairy cell leukemia (HCL) patients usually experience multiple disease relapses during the course of their disease. The CD20 antigen is highly expressed on the surface of hairy cells. Single-agent rituximab can be a suitable treatment options in patients relapsing after repeated courses of purine analogs, if purine analogs are contraindicated (e.g., in case of poor bone marrow cellularity, high disease infiltration predicting long-lasting aplasia), especially if newer agents (such as moxetumomab or vemurafenib) are not easily available (as it happens in several countries).

Methods: Our institutional series of HCL patients receiving single-agent rituximab as salvage therapy was retrospectively reviewed. Patients received rituximab at the standard dose of 375 mg/m^2 weekly for 4 weeks. The main study objectives were overall response rate (ORR), time-to-next treatment (TTNT), progression-free survival (PFS) and overall survival (OS). Responses have been categorized according to the Consensus Resolution Criteria.

Results: Thirty-three patients received 39 courses of rituximab (4 patients received it twice, one patient three times), in median as third line of therapy (range 2–8). First rituximab was given at a median age of 61 years and at a median time from disease diagnosis of 65 months. Out of 39 courses, a complete response was obtained in 28.2% of cases, a partial response in 23.1% and a minimal response in 20.5%, yielding an ORR of 71.8%. In 28.2% of patients, we observed no response. Median TTNT was reached at 33 months (65% at 2 years), while median PFS was reached at 24 months (51% at 2 years). Median OS resulted of 154 months (22% at 20 years). Among the 5 patients receiving rituximab more than once, all responded after the first course, although the ORR after the second or later course was only 50%. Median TTNT following the first rituximab was 38.5 months in these patients, ranging from 15 to 205 months.

Conclusions: To our knowledge, this is the widest series of HCL patients receiving single-agent rituximab for disease relapse. Rituximab is an effective salvage therapy in pretreated HCL patients after failure of purine analogs, as it permits an adequate disease control with considerably long TTNT periods. It may be repeated if no alternatives are available, although it seems to reduce its efficacy in the following courses.

Keywords: Immunotherapy, Lymphoid Cancers

No conflicts of interests pertinent to the abstract.

290 | INTRALESIONAL RITUXIMAB IN THE TREATMENT OF PRIMARY CUTANEOUS B-CELL LYMPHOMAS: A SINGLE-CENTER EXPERIENCE

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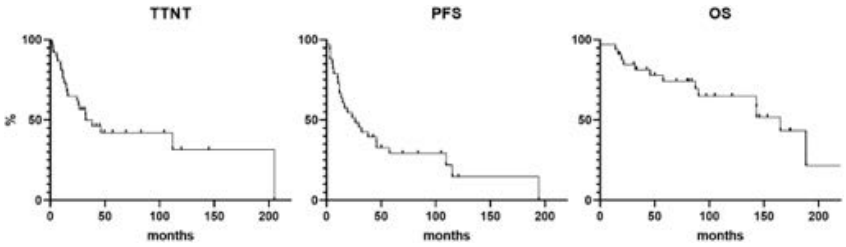

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Introduction: Primary cutaneous B-cell lymphomas (PCBCL) are rare lymphoproliferative disorders characterized by an indolent course and a life-long tendency to relapse. The management has always been based on radiotherapy and/or intravenous rituximab (IVR). To minimize toxicity, intralesional rituximab (ILR) has been applied with encouraging results.

Methods: We retrospectively collected data on patients diagnosed with primary cutaneous marginal zone lymphoma (PCMZL) and follicular center lymphoma (PCFCL) who received at least one cycle of ILR from 2010 to 2022 at our Center. A cycle consisted of three doses in a week of intralesional rituximab (10 mg each). In some patients, subsequent cycles were administrated to reach a deeper response. Statistical analysis was conducted to identify variables associated with response and recurrence. Cox regression models were used to estimate hazard ratios and their 95% confidence intervals.

Results: With a median follow-up of 86 months (range 1–153), ILR was administered to 26 patients, 73% with PCMZL histology. The median age at diagnosis was 51 years, with a predominance of males (62%). Fourteen (54%) were classified as T2 according to TNM staging and 11 (42%) patients presented with 3 or more lesions (Table 1). All patients experienced at least a partial response (PR), with 58% of complete responses (CR), the majority (80%) reached with only one ILR cycle. Patients with head localization presented a lower CR rate (17%, p-value = 0.007), without other significant factors associated to CR. Twenty-one (81%) patients relapsed, in a median time of 7 months (range 2–118) and the median time to next treatment was 10.8 months (range 4–119). Sixteen patients (62%) were retreated with ILR, achieving an overall response of 93% (CR 81%). PCFCL histology showed a significant association with recurrence (HR = 4.07, 95% CI, 1.29–12.87). Neither infusion reactions nor infectious complications were seen. The median progression-free survival was 7 months (2–134 months), and 6 patients are still in CR.

Conclusion: Our study confirms the efficacy and safety of ILR in the management of PCBCL. With a very well-tolerated profile, all patients achieved at least PR, without losing efficacy at retreatment. Factors such as the localization of lesions and the subtype of lymphoma emerged associated with response and relapse, respectively.

	N=26 (%)
Median age at diagnosis (yrs)	51 (22-81)
Male	16 (62)
Histology	
PCMZL	19 (73)
PCFCL	7 (27)
TNM	
1	8 (31)
2	14 (54)
3	4 (15)
Number of lesions	
1	8 (31)
2	7 (27)
>=3	11 (42)
Localization	
Head	6 (23)
Upper limb	5 (19)
Lower limb	3 (12)
Trunk	6 (23)
Multiple	6 (23)
High β-2-microglobuline	3 (12)
High LDH	1 (5)
Median Ki67	13% (5-40%)
>15%	5 (19)
Previously treated	13 (50)
Number of RIL	
1	19 (73)
>1	7 (27)
Response	
CR	15 (58)
PR	11 (24)
Relapse	21 (81)

Keywords: Cutaneous non-Hodgkin lymphoma, Immunotherapy

No conflicts of interests pertinent to the abstract.

EXTRANODAL LYMPHOMAS NON MZL

291 | PATTERNS OF DISEASE FAILURE BY RESPONSE TO INDUCTION THERAPY IN A LARGE COHORT OF PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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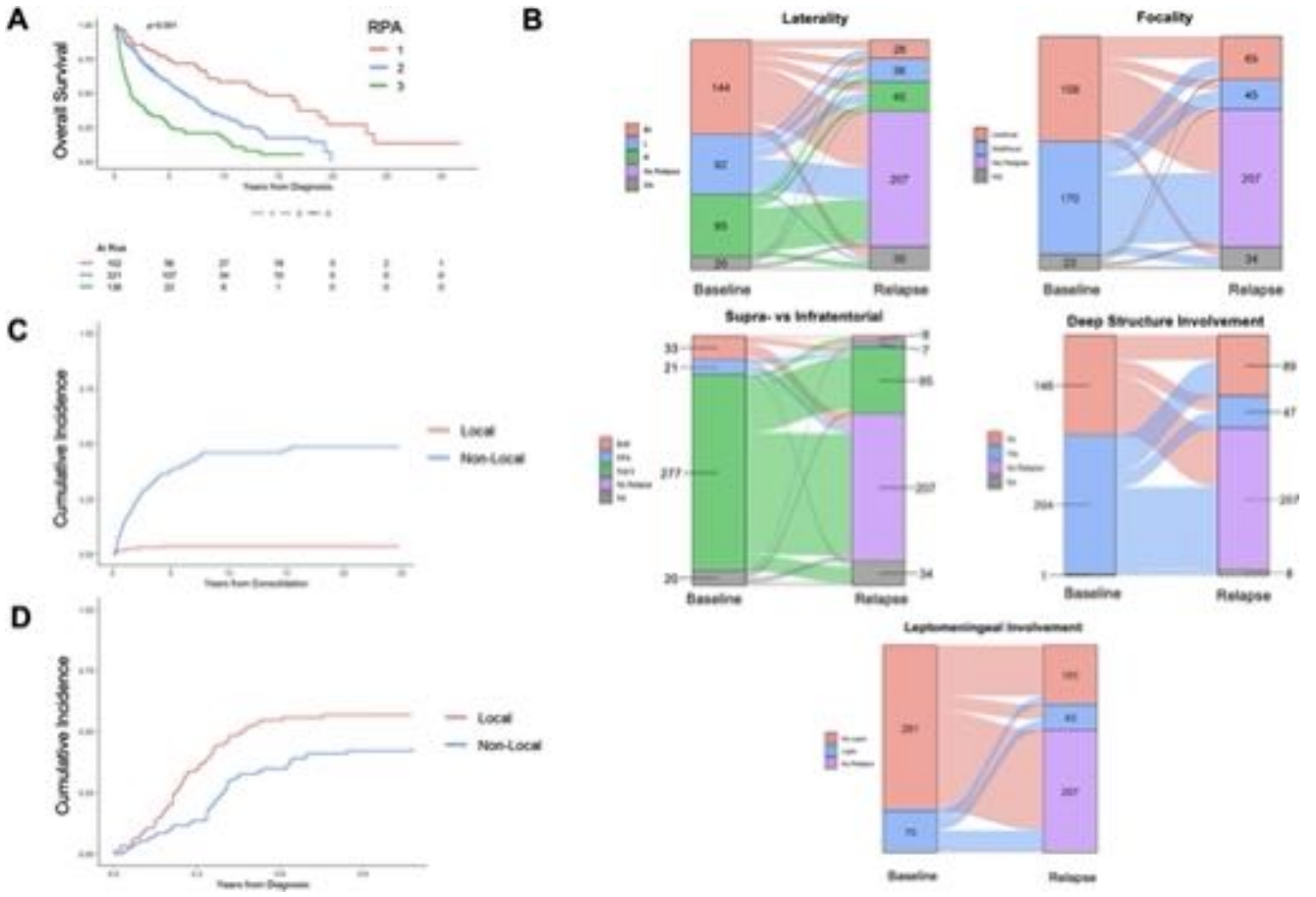
Introduction: Primary central nervous system lymphoma (PCNSL) is an aggressive disease historically considered incurable and disseminated throughout the neuroaxis. Contemporary outcomes and detailed relapse patterns are lacking. We analyzed factors associated with relapse in a large cohort.

Methods: Patients with PCNSL (diffuse large B-cell) from 1983 to 2020 were analyzed. Initial T1 post-contrast-enhancing disease was characterized by site and largest dimension. Patients were stratified by response (complete [CR], partial, stable, progression [POD]) to induction and consolidation (autologous hematopoietic cell transplantation, whole brain radiotherapy [≤24 Gy reduced-dose vs. >24 Gy standard-dose], cytarabine, other). Refractory was defined as POD on induction or relapse within 3 mos of induction. Site of first relapse was characterized as local (involving/adjacent to baseline site) versus distant intraparenchymal, leptomeningeal (CSF and/or MRI), or other. Progression-free (PFS) and overall survival (OS) were estimated using the Kaplan Meier method. Cox Proportional Hazards regression was used to evaluate associations with OS/PFS. Univariable associations with local relapse were examined using Fine-Gray competing risks regression with death without local relapse as a competing risk.

Results: Median follow-up was 7.4y among 559 patients. Median age was 63y (IQR 54–72); most (321, 57%) were MSKCC recursive partitioning analysis (RPA) class 2 (age ≥50, KPS ≥70). Most presented with supratentorial (420, 81%), multifocal (274, 53%), bilateral (224, 43%), and deep structure involvement (314, 56%). Nearly all received methotrexate-based induction (532, 95%). PFS and OS differed significantly by RPA (log-rank $p < 0.001$) with best outcomes for RPA 1: 1- and 10-y OS of 95% (95% CI: 91–99) and 58% (95% CI: 48–72; Figure A). 1- and 5-y PFS for the 351 (91%) who achieved CR to consolidation was 80% (95% CI: 76–84) and 46% (95% CI: 41–53). Baseline disease distribution was not associated with relapse (Figure B). Relapses were mostly distant from initial sites: 1-y cumulative incidence (CuI) from consolidation of non-local versus local POD of 15% versus 1.8% (Figure C).



Of the 97 refractory patients, 1-y CuI from diagnosis of local versus non-local POD was 57% (95% CI: 55–57) versus 42% (95% CI: 41–43; Figure D), with median OS only 1.0y from diagnosis (95% CI: 0.8–2.2). Deep structure involvement (HR 1.9, 95% CI: 1.1–3.3, $p = 0.02$) was associated with local failure, while tumor size (HR 1.2, 95% CI: 0.99–1.5, $p = 0.057$) was marginally associated.

Conclusions: For the first time, we report comprehensive relapse patterns in a large PCNSL cohort. We confirmed that relapses post-CR to consolidation are often distant and unpredictable; yet, we found a relatively high cumulative incidence of local relapse among refractory patients. These findings suggest a potential role for focal involved site radiotherapy in this particularly high-risk subset.

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Keywords: Extranodal non-Hodgkin lymphoma, Imaging and Early Detection, Radiation Therapy

Conflicts of interests pertinent to the abstract.

M. Scordo
Other remuneration: Provision of services: Medscape, Omeros

C. Grommes
Other remuneration: Provision of services: BTG International, Ono Pharma, Roche

292 | IBRUTINIB IN COMBINATION WITH IFOSFAMIDE, ETOPOSIDE, AND RITUXIMAB FOLLOWED BY IBRUTINIB MAINTENANCE THERAPY IN PATIENTS WITH R/R-PCNSL: A MULTICENTER PHASE II STUDY

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Introduction: Primary CNS lymphoma (PCNSL) is a rare subtype of extranodal lymphoma with a dismal prognosis. Treatment options for patients with relapsed or refractory disease are extremely limited. Based on previously documented single-agent activity of ibrutinib, a BTK inhibitor, we conducted a phase II study to investigate the efficacy and safety of combining ibrutinib with ifosfamide, etoposide, and rituximab (IBER) followed by ibrutinib maintenance therapy in patients with relapsed or refractory PCNSL (R/R-PCNSL).

Methods: Eligible patients had R/R-PCNSL with histologically confirmed $CD20^+$ diffuse large B-cell lymphoma, age $\geq$18, ECOG score of $\leq$2, and had received one or more prior lines of therapy. The IBER induction chemotherapy consisted of ibrutinib 560 mg/d on days 1–21, ifosfamide 3.75 g/m^2 on day 2, etoposide 100 mg/m^2 on days 2–4, and rituximab 375 mg/m^2 on day 1 (days 1/8/15 in cycle 1), and was administered for up to 6 cycles (21-day cycle). Patients who achieved a better than partial response to induction therapy received maintenance therapy with ibrutinib 560 mg/d for up to 6 months. The primary endpoint was the best overall response rate (ORR).

Results: Between February 2020 and February 2022, 30 PCNSL patients were enrolled. The median follow-up time was 14.8 months (range 0.23–28.8 months) as of 31 December 2022. The median age was 65.0 years (range 37–79), and 13 were women. Performance status was ECOG 1 in 18 patients and ECOG 2 in 12 patients. All patients had brain parenchymal lesion(s) measurable with MRI. Objective response was evaluable in 27 patients. Of these, complete response (CR) was achieved in 16 patients (53.3%), partial response (PR) in 6 patients (20.0%), and the ORR of induction and maintenance therapy was 73.3% (95% CI, 57.2%–89.4%). Among responders, the median duration of response was 9.8 months (95% CI, 6.9–12.7 months). A total of 17 patients completed 6 cycles of induction therapy, and maintenance therapy with ibrutinib was initiated in 15 patients. The median progression-free survival (PFS) was 11.5 months (95% CI, 8.3–14.8 months), and the median overall survival (OS) was not reached. The safety of IBER induction and ibrutinib maintenance therapy was also evaluated. Grade 3/4 hematologic toxicities included thrombocytopenia in 9 patients (30.0%), neutropenia in 6 patients (20.0%), and anemia in 5 patients (16.7%). Febrile neutropenia was observed in 3 patients (10.0%). COVID-19 pneumonia was confirmed in 4 patients during the study period. No treatment-related mortality was observed.

Conclusions: Our data suggest that IBER induction followed by ibrutinib maintenance therapy is an effective and well-tolerated salvage strategy for patients with R/R-PCNSL. This novel approach of combining ibrutinib with active cytotoxic agents and extending the duration of ibrutinib exposure may effectively improve the survival of these patients.

The research was funded by: The study was supported by research grant and investigational products from Janssen Korea Ltd.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Extranodal non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

293 | INDUCTION (MATRIX) FOLLOWED BY TRANSPLANTATION IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA. EXPERIENCE OF THE GELTAMO (GRUPO ESPAñOL DE LINFOMA Y TRASPLANTE DE MEDULA ÓSEA)

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Introduction: The prognosis of primary central nervous system lymphoma (PCNSL) is still unfavorable. In recent years, several studies focused on frontline strategy have been performed. The aim of our study was to analyze immunocompetent newly diagnosed PCNSL patients following clinical guidelines of the GELTAMO group based on immunochemotherapy plus autologous transplant (ASCT) in terms of response, toxicity, and outcome.

Methods: From March 2019 to September 2022, 71 patients diagnosed with PCNSL from 17 centers of the GELTAMO were analyzed. They were planned to receive 4 cycles of the MATRix scheme (rituximab, methotrexate, cytarabine and thiotepa). Responders [complete response (CR), partial response (PR), stable disease (SD)] after 2 cycles completed the 4 cycles. Those who achieved CR or PR after 4 cycles underwent ASCT conditioned with low dose thiotepa and carmustine.

Results: In the whole series, mean age was 57 years (range 25–71); 38M/33F; 45% had a single lesion, 45% frontal involvement and 35% ECOG ≥2. All patients received at least 2 cycles of MATRix and 48 (67.6%) completed 4 cycles. Of 59 patients evaluated after induction, the response rate was: CR 54%, PR 39% and SD 7%. Of a total of 250 cycles administered (out of 284) grade 3–4 toxicities were: hematological 16.4%, hepatic 6%, renal 0.8%, neurological 0.8%, digestive 0.8% and infections 2.8%. Among the patients ($n = 23$) that did not complete the 4 cycles the causes were: toxicity ($n = 15$), progression ($n = 4$), others ($n = 4$). Induction treatment-related mortality was 7%. The apheresis was performed in 50 patients (70.4%). At the time of the analysis (February 2023), 40 patients had been consolidated with ASCT. From the remaining 31 patients, 18 did not go into the procedure because of toxicities/physician's decision, 7 due to disease progression, 4 had mobilization failure and 2 are pending. With a median follow-up of the whole series of 11 months (range 0.75–40.5), 2-year progression-free survival (PFS) was 49.7% (95% CI: 36.2%–68.1%) and 2-year overall survival (OS) was 59.7% (95% CI: 46.4%–76.8%). The 2-year OS for patients achieving CR or PR after induction, were 75% (95% CI: 55%–95%) and 62% (95% CI: 33%–91%), respectively. The 2-year OS for autografted patients was 75% (95% CI: 57%–93%) versus 41% for non-ASCT (95% CI: 17%–65%), ($p = 0.004$). Transplant related mortality was 0%. At the time of analysis, 21 patients had died and 8 patients had relapsed after ASCT. Causes of death were: progression, 13 patients, pneumonia, 7 and cerebral hemorrhage in 1 patient.

Conclusions: This is a "real-life" study assessing the feasibility and efficacy of the MATRix regimen followed by ASCT as frontline therapy in immunocompetent PCNSL patients, performed on behalf of GELTAMO group. Our results showed a high ORR after induction (93%) with manageable toxicity, allowing sustained survival over time in almost half of the patients, especially for those consolidated with ASCT.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Extranodal non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

294 | EVOLVING CONSOLIDATION PATTERNS AND MODERN OUTCOMES FOR A LARGE LONGITUDINAL COHORT OF PRIMARY CNS LYMPHOMA PATIENTS

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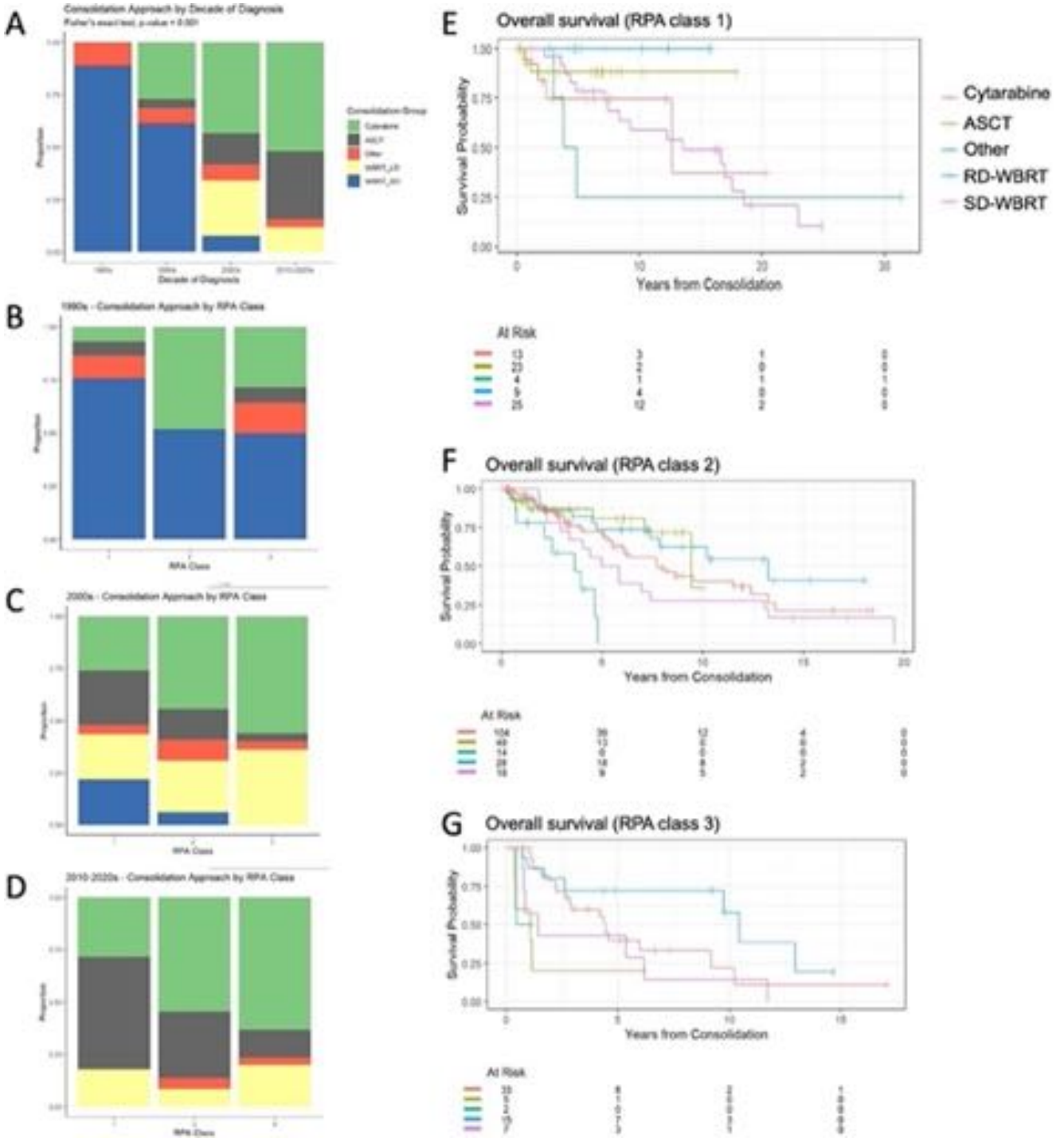
Introduction: There are several suitable consolidation strategies for primary central nervous system lymphoma (PCNSL) after induction therapy including whole brain radiotherapy [≤24 Gy reduced-dose, RD-WBRT or >24 Gy standard-dose, SD-WBRT], non-myeloablative chemotherapy (e.g., cytarabine, cyt) or autologous hematopoietic cell transplant (AHCT). We analyzed contemporary use patterns and associated outcomes in a large cohort.

Methods: PCNSL patients (diffuse large B-cell subtype) from 1983 to 2020 were identified from an institutional database. Longitudinal consolidation patterns were analyzed by Fisher exact test. Consolidation strategies and outcomes were stratified by decade and MSKCC recursive partitioning analysis (RPA) class 1 (age <50), 2 (age ≥50, KPS ≥ 70) or 3 (age ≥50, KPS < 70). Associations with consolidation strategy were analyzed by multinomial logistic regression. Progression free (PFS) and overall survival (OS) were estimated by Kaplan-Meier from consolidation date.

Results: Of 645 evaluated, 559 were eligible and 385 (69%) were consolidated. Median follow-up was 7.4y and median OS was 5.7y. Median age was 63y (IQR 54–72); most (n = 321, 57%) were RPA class 2. Over the study period, there was significant change in consolidation with declining use of WBRT+cyt (61% in 1990s vs. 12% in 2010s) and rising use of AHCT (4% in 1990s vs. 32% in 2010s) and cyt (27% in 1990s vs. 52% in 2010s) [Figure A, p < 0.001]. This temporal evolution was seen across RPA classes, with greater cyt use for higher RPA in the recent era (Figure B-D).



Adjusting for diagnosis decade and induction response, RPA class 2 was significantly less likely to receive AHCT (odds ratio, OR 0.23, $p = 0.001$), RD-WBRT (OR 0.31 $p = 0.02$) or SD-WBRT (OR 0.08, $p < 0.001$) vs. cyt compared to RPA class 1. Those with partial response to induction were also less likely to receive AHCT (OR 0.36, $p = 0.02$), controlling for decade and RPA.

Among the 351 with complete response to consolidation, on multivariable analysis, only receipt of R-MPV induction was associated with better PFS (HR 0.5 $p = 0.006$). There was no significant PFS association with any consolidation strategy. RPA class 3 was associated with poorer OS (HR 1.8, $p = 0.03$). For RPA class 1 and 2, among all strategies, those treated with AHCT and RD-WBRT had similar and most favorable OS outcomes (Figure E-G). For RPA class 1, median OS was not reached for AHCT or RD-WBRT and 13y post cyt. For RPA class 2, median OS was 9.4y post AHCT, 13y post RD-WBRT and cyt and 7.7y post cyt alone.

Conclusion: We report a significant change in consolidation approach for PCNSL in recent years with decreased use of WBRT+cyt and increased use of AHCT and cyt alone. RD-WBRT is associated with favorable outcomes across RPA classes. Given preliminary data from the ongoing RTOG 1114 trial showing significantly improved PFS and no early neurotoxicity signal, RD-WBRT could be more strongly considered, particularly for higher RPA classes.

The research was funded by: Connecticut Cancer Foundation, a Lacher Fellowship in Lymphoma Radiation Oncology and the Memorial Sloan Kettering Cancer Center Support Grant [P30 CA008748]

Keywords: Extranodal non-Hodgkin lymphoma, Radiation Therapy, Stem Cell Transplant

Conflicts of interests pertinent to the abstract.

M. Scordo

Consultant or advisory role: McKinsey & Company, Angiocrine Bioscience, Inc., and Omeros Corporation, Kite – A Gilead Company
Honoraria: i3Health and Medscape for CME-related activity
Research funding: Angiocrine Bioscience, Inc., and Omeros Corporation

C. Grommes

Consultant or advisory role: BTG International, Roche, Ono Pharmaceuticals

295 | BONE MARROW ASSESSMENT MAY BE OMITTED IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMAS WITH PRIMARY CNS INVOLVEMENT

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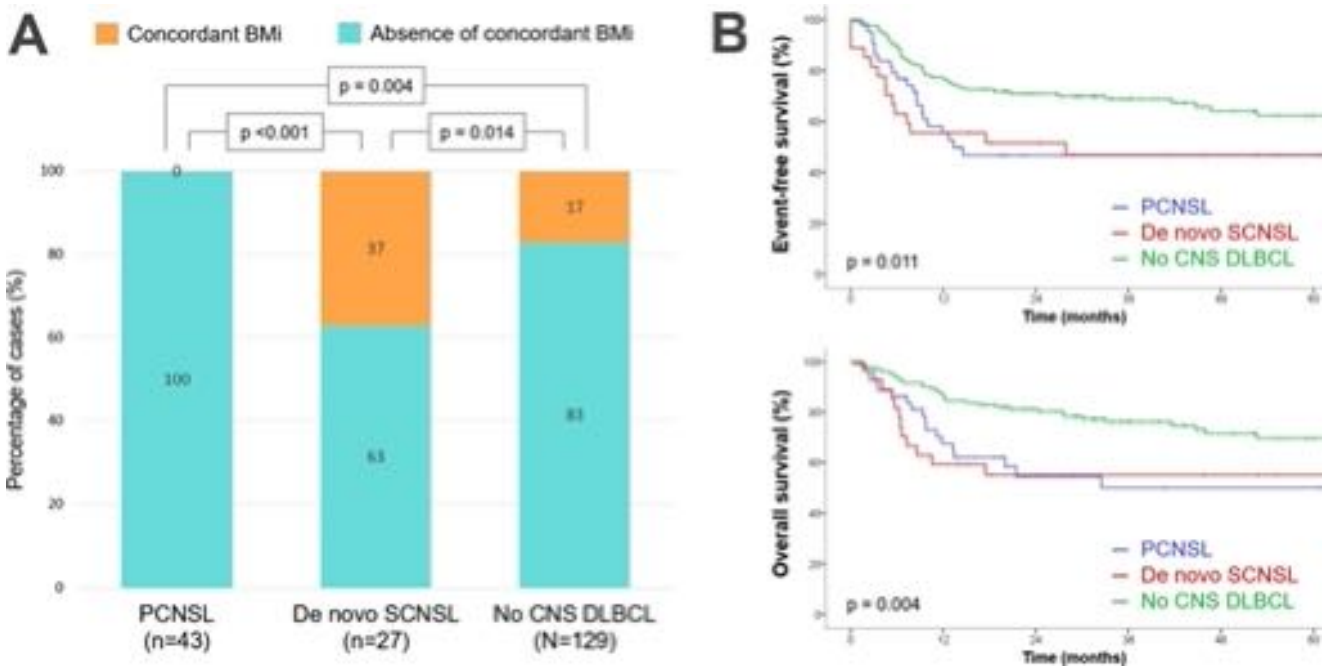
Background: Central nervous system (CNS) involvement in diffuse large B-cell lymphoma (DLBCL) patients may be primary (PCNSL) or secondary (SCNSL). Bone marrow (BM) assessment is still recommended at PCNSL diagnosis, although its usefulness is debatable.

Methods: Retrospective multicenter study including three cohorts of newly DLBCL: (1) PCNSL ($N = 43$); (2) synchronous CNS and systemic DLBCL at diagnosis (SCNSL, $N = 27$); and (3) DLBCL with no evidence of CNS spread ($N = 129$). A complete BM assessment and a whole-body PET-CT (92%) or CT (8%), was available in all 199 cases prior to first-line therapy. The proportion of concordant BM infiltration (BMi), as well as other clinical and biological characteristics, were compared among groups. Survival analysis was evaluated by Kaplan Meier curves (log rank test).

Results: Median age and male proportions were 62 years (IQR 50–66) and 56% in PCNSL, 64 years (IQR 59–71) and 44% in SCNSL, and 67 years (IQR 56–75) and 52% in no-CNSL. ECOG ≥2 at presentation: 8/43 PCNSL (19%), 16/27 SCNSL (59%), and 17/129 no-CNSL (13%). Lower median levels of lactate dehydrogenase (LDH, U/L) and beta-2 microglobulin (β2M, mg/dL) were detected in PCNSL (190 [IQR 154–266] and 1.9 [IQR 1.5–2.3], respectively) compared with SCNSL (LDH 517 [IQR 383–1,046] and β2M 2.9 [IQR 2.4–3]) and no-CNSL (LDH 248 [IQR 199–408] and β2M 2.6 [IQR 2.2–3.9]), while hemoglobin (g/dL) was higher in PCSNL (13.6 [IQR 12.5–14.5]) than in SCNSL and no-CNSL (11 [IQR 9.3–13.9] and 12.5 [IQR 11–14], respectively). Nodal involvement was not seen in PCNSL, while it was found in 93% and 91% SCNSL and no-CNSL cases, respectively. In addition to CNS, 23/27 SCNSL (85%) presented extranodal involvement at other sites. No extranodal infiltration far from CNS was seen in PCNSL; the comparison among BMi between groups is presented in Figure 1A. Among the 10/27 SCNSL patients with BMi, all of them had nodal disease. Two patients of the SCNSL group presented without nodal involvement: 1 primary breast DLBCL, and 1 testicular involvement. Treatment was heterogeneous in PCNSL and SCNSL groups. In the PCNSL cohort, 42/43 (98%) received first-line therapy including systemic high-dose methotrexate, being MATRix (51%) and B-RAM (26%) the most common approaches. With a median follow-up of 14 months (IQR 8–41) in PCNSL, 18 months (IQR 7–64) in SCNSL, and 34 months (IQR 20–60) in no-CNSL, event-free and overall survival curves are presented in Figure 1B.



Conclusions: This research suggests that BM assessment is not needed in de novo DLBCL patients with CNS involvement and absence of nodal or extranodal non-neurological disease, thus, BM evaluation might be omitted in PCNSL. Patients with SCNSL presented with a more aggressive disease, although their prognosis did not differ from PCNSL patients. The aim is to validate these results in a larger series on behalf of the Spanish Lymphoma Group GELTAMO.

Keywords: Diagnostic and Prognostic Biomarkers, Extranodal non-Hodgkin lymphoma, PET-CT

No conflicts of interests pertinent to the abstract.

296 | COMBINATION OF RITUXIMAB AND METHOTREXATE FOLLOWED BY RITUXIMAB AND CYTARABINE IN ELDERLY PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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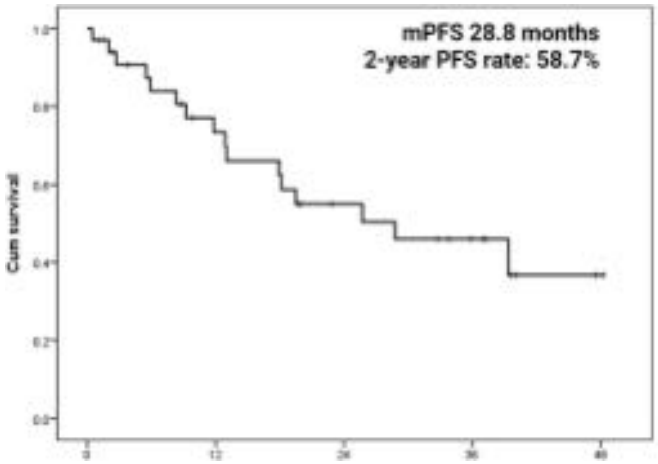
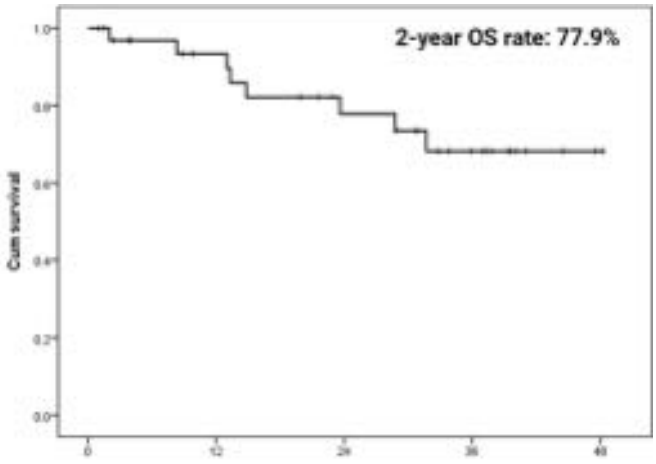
The long-term outcomes of PCNSL remains poor which is partially explained by that more than half of patients are diagnosed over the age of 65 years. The optimal treatment strategy for newly diagnosed PCNSL has not been established, especially in the elderly. While the backbone treatment for young patients consist of high-dose methotrexate (MTX) and cytarabine, their feasibility has not been widely tested in the elderly. Moreover, the addition of rituximab has demonstrated inconsistent findings. We have carried out a phase II study to evaluate the efficacy and safety of rituximab plus high-dose MTX followed by rituximab plus cytarabine in newly-diagnosed PCNLS patients aged ≥60 years.

Patients received 5 cycles of MTX (3.5 g/m^2) with rituximab (500 mg/m^2) every 2 weeks. If CR was not achieved after 5 cycles, 2 additional cycles were applied (total 7 cycles). Patients without progressive disease further received 2 cycles of cytarabine (3000 mg/m^2 × 2 days) plus rituximab (500 mg/m^2) every 4 weeks. The primary end-point was 2-year progression free survival (PFS) rate, and if 9 or more out of 32 evaluable patients achieved 2-year PFS, the null hypothesis would be rejected. This study was registered at clinicaltrials.gov (NCT03569995).

Between Nov. 2018 to November 2020, we enrolled 35 patients from 13 tertiary institutes. The median age was 73 (range 60–81), and 15 patients were male. With 21 (62%) patients were ECOG PS 0–2, 6 (17%), 8 (51%), and 11 (31%) patients were categorized as favorable, intermediate, and high-risk group by IELSG classification, respectively. One patient was immediatedly withdrawn because of rapid deterioration, and 34 patients received at least one cycle of induction treatment. Twenty-nine patients completed 5 cycles of induction





which resulted in 55% of CR ($n = 16$) and 41% of PR ($n = 12$). Twelve patients who had residual disease further received 2 cycles of induction and 3 patients achieved CR (25%) and 7 patients remained in PR. The median dose density of MTX was 100% (range, 65–100). Twenty-six patients proceeded to consolidation treatment, and all could complete it. Among 7 patients who still had residual disease, 4 patiens was converted to CR after consolidation. After a median follow-up duration of 36.0 months (95% CI: 33.2–38.8), 2 year PFS rate was 58.7% (± 9.2%) and 10 patients achieved 2-yr PFS. There was a trend for prolonged PFS for those who achived ≥90% of relative dose intensity of MTX (mPFS 28.8) compared to those who did not (mPFS 13.0). Treatment was generally well-tolerated as only 2 patients were withdrawn from the study due to toxicity, and no treatment-related mortality was reported. In total of 230 person-cycle, delay of treatment occurred in 21 times. The mOS wasn't reached and the 2-year OS rate was 77.9%.

The current study met its primary end-point which suggests the feasibility of high-dose MTX plus cytarabine in elderly PCNSL patients, and the positive role of additive rituximab.

The research was funded by: The Celltrion Inc. provided rituximab (truxima (R)) for in gratis, but was not involved in study analysis.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chemotherapy, Immunotherapy

No conflicts of interests pertinent to the abstract.

297 | PRELIMINARY RESULTS OF PENPULIMAB COMBINED WITH RMA (RITUXIMAB, METHOTREXATE, AND CYTARABINE) FOR NEWLY DIAGNOSED PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)

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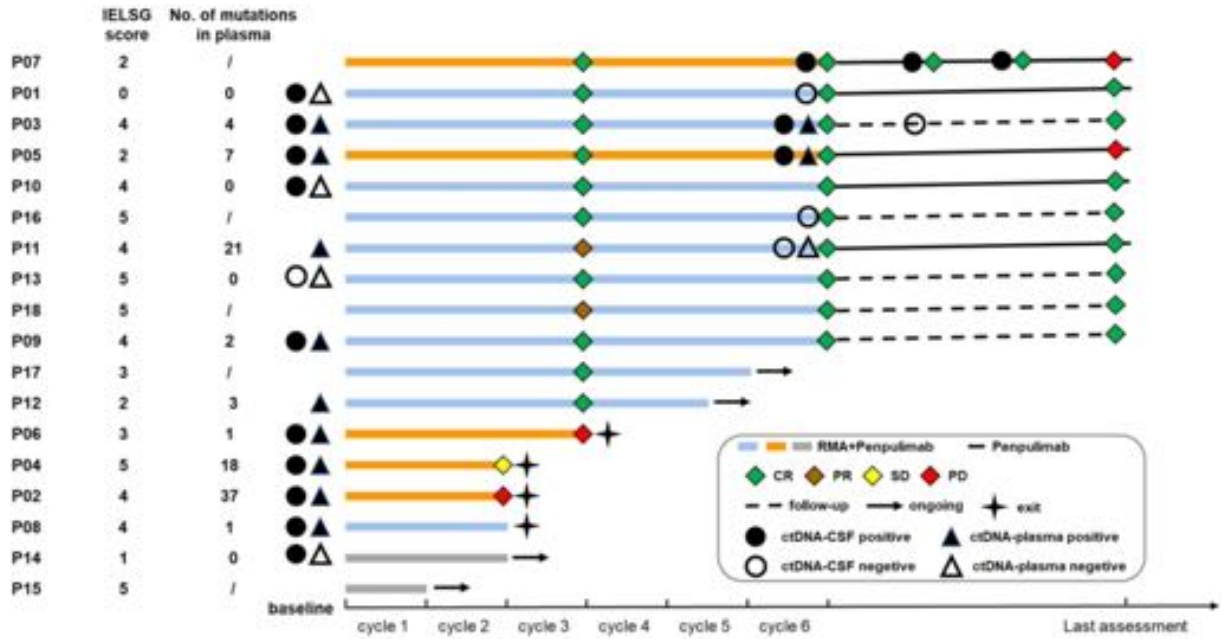
Background: Primary central nervous system lymphoma (PCNSL) has a very poor survival. The efficacy of high-dose methotrexate was suboptimal with a short remission time and low response rate. The discovery of the frequent 9p24.1/PD-L1/PD-L2 copy number alterations and increased expression of PD-L1 in PCNSL provide the rationale to evaluate the efficacy of PD-1antibody in PCNSL.

Methods: NCT05347641 is a Phase II, single-center, single-arm, open-label study. An estimated 23 newly diagnosed PCNSL patients will be enrolled. Eligible patients are aged 18–75 years, and ECOG performance status of 0–4. The Pen-RMA induction treatment includes rituximab 375 mg/m^2, d0; methotrexate 3.5 g/m^2, d1; cytarabine 1–2 g/m^2, q12h, d2–3; penpulimab (anti-PD1 antibody) 200 mg, d5; 21d/cycle. After six cycles, patients who achieve CR/CRu/PR will undergo ASCT (for patients ≤60 yr), patients who achieve CR after ASCT will receive 8 cycles of penpulimab as maintenance therapy, or receive whole brain radiotherapy (WBRT) combined with 8 cycles of penpulimab if reach PR. Patients over 60 yr who achieve CR will receive 8 cycles of penpulimab, or receive WBRT combined with 8 cycles of penpulimab if reach PR. Tissue samples and cerebrospinal fluid (CSF)/plasma samples are performed targeted next-generation sequencing (NGS) in Nanjing Geneseeq Technology Inc.

Results: Between April 2022 and February 2023, 18 newly diagnosed PCNSL patients were enrolled. The median age was 64 (45–74) yr. The median cycles of treatment were 6 (1–6). Grade 3/4 toxicities included neutropenia (3, 18.8%), thrombocytopenia (2, 12.5%) and renal dysfunction (1, 6.25%). The mutational profiles of baseline samples from 14 cases revealed 2 frequent mutations of MYD88L265P and PIM1, 12 cases were classified into MCD subtype and 1 was BN2 subtype. Three of 15 patients who were evaluable after 3 cycles had disease progressed, the ORR was 80.0% (CRR was 66.7%). Of the 13 evaluable patients after 6 cycles, 10 patients have completed 6 cycles and they all reached CR (both ORR and CRR were 76.9%). Five of them had entered the maintenance phase while 5 patients delayed due to COVID 19 pneumonia. The median follow-up time was 9.5 months (1–11), the median PFS and OS were not reached. CSF circulation tumor DNA (ctDNA) monitoring was performed in 6 patients after 6 cycles. Three of them had imaging CR



and CSF ctDNA clearance. Three patients were assessed as CR by imaging but the CSF ctDNA was still positive, 2 of them relapsed while 1 patient had CSF ctDNA clearance during the maintenance phase (Figure 1).

Conclusion: Our preliminary results suggested that the 9p24.1/PD-L1/PD-L2 copy number alterations were less than reported, but Pen-RMA also achieved excellent responses in newly diagnosed PCNSL patients. CSF ctDNA could be leveraged to overcome the limitations of tissue biopsies for diagnosis and assessed more sensitively compared with imageology-based response evaluation.

Keywords: Combination Therapies, Immunotherapy, Ongoing Trials

No conflicts of interests pertinent to the abstract.

298 | RADIOTHERAPY AS AN EFFECTIVE BRIDGE FOR CHEMO-REFRACTORY OR PROGRESSIVE SECONDARY CNS LYMPHOMA

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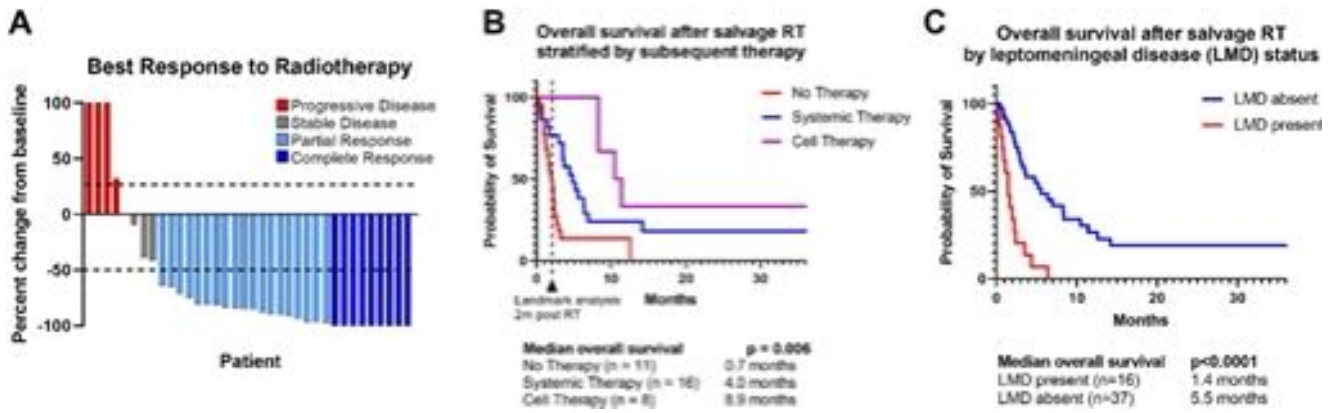
Introduction: Secondary CNS lymphoma (SCNSL) is observed in 2%–5% of patients with diffuse large B cell lymphoma (DLBCL). Progression of SCNSL after first line CNS-directed systemic therapy is particularly challenging, without clear standard of care. We studied the outcomes of patients who received brain radiotherapy (RT) for progressive SCNSL.

Methods: We identified SCNSL patients with DLBCL who received brain RT after radiographic or clinical progression on at least 1 line of SCNSL-directed therapy between 1999 and 2023 at MSKCC. SCNSL-directed therapy is defined as systemic therapy for active SCNSL, as opposed to prophylaxis. Overall survival (OS) was determined from RT start using Kaplan-Meier. OS comparing subsequent therapy was landmarked 2 months (m) post RT to minimize immortal time bias. RT response was evaluated with contrast MRI or CT using International Primary CNS Lymphoma Collaborative Group or Response Assessment in Neuro-oncology radiographic criteria for parenchymal or leptomeningeal disease (LMD), respectively. LMD was declared by cytology and/or imaging. The risk of intracranial failure post RT was calculated by Gray's test with death as competing risk.

Results: 53 patients received brain RT for progressive SCNSL with median follow up of 3.2 m. 36 patients were evaluable for response; the remainder were lost to follow up/hospice ($n = 8$), lacked suitable imaging ($n = 4$), died with progressive neurologic symptoms ($n = 4$) or other cause ($n = 1$). At RT, median age was 63 (interquartile range 49–71), median KPS was 70 (60–80), and 87% had neurologic symptoms. Patients received a median 2 lines of SCNSL-directed therapy prior to RT (1–3), 90% received a methotrexate-based regimen. Median RT dose was 30 Gy in 10 fractions delivered to whole brain ($n = 44$), partial brain ($n = 7$), or craniospinal axis ($n = 2$). The overall response rate was 77% (25% complete response, 52% partial response). 30/53 patients (57%) were successfully bridged to subsequent systemic therapy ($n = 21$), hematopoietic stem cell transplant ($n = 5$), or CAR T ($n = 4$), with median interval of 34 days (21–59). Median OS for the entire cohort was 3.4m, and was improved for those who were successfully bridged ($p = 0.006$). Chemo-resistant LMD was associated with inferior survival (median 1.4 vs. 5.5 m, $p < 0.0001$) and increased risk of intracranial failure ($p = 0.04$).



Conclusion: RT referrals for progressive SCNSL represent a high-risk cohort characterized by treatment-resistant, symptomatic neurologic disease. RT confers a high response rate in this chemo-resistant population. Thus, RT is an effective tool in the management of SCNSL, especially as a bridge to subsequent therapy in otherwise refractory patients. Persistent leptomeningeal disease is a poor prognostic factor and warrants further investigation of craniospinal RT or combined-modality approaches.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Radiation Therapy

Conflicts of interests pertinent to the abstract.

G. Salles
Stock ownership: Owkin, Inc.
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299 | GERIATRIC ASSESSMENT SCORES: PREDICTORS OF PROGNOSIS AND PREMATURE END OF TREATMENT IN THE MARTA AND MARITA STUDY POPULATION OF ELDERLY PCNSL PATIENTS >65 YEARS

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Introduction: Short induction followed by high-dose chemotherapy and autologous stem cell transplantation (HCT-ASCT) has been shown to be feasible and highly effective in newly diagnosed elderly PCNSL patients (Schorb et al. Blood Advances 2021; Schorb et al. ASH 2022). However, getting patients to undergo HCT-ASCT remains a major clinical challenge. Geriatric assessment (GA) can be helpful in assessing prognosis, but standardized GA for PCNSL patients is lacking. Our aim was to analyze the impact of GA scores on survival parameters and to develop an algorithm to predict eligibility for HCT-ASCT.
Methods: Our cohort consists of 64 patients >65 years treated in the prospective bicentric MARiTA (DRKS 00008900) and the subsequent phase II multicenter MARTA study (DRKS 00011932). The planned

study treatment consisted of 2 cycles of rituximab, HD-MTX and cytarabine followed by busulfan- and thiotepa-based HCT-ASCT. Baseline characteristics, including comorbidities and GA scores at the time of diagnosis were analyzed for progression-free survival (PFS), overall survival (OS), and non-relapse premature end of treatment (pEOT), defined as not reaching HCT-ASCT. Univariate analyses (UVA) were performed using logistic and Cox regression, and relevant variables were included in a multivariate analysis (MVA) model.

Results: After a median follow-up of 22 months, PFS and OS at 12 months from time of diagnosis was 68.8% (95% CI: 55.9%–78.6%) and 70.3% (95% CI: 57.5%–79.9%), whereas PFS and OS at 12 months from time of HCT-ASCT was 80.0% (95% CI: 66.0%–88.7%) and 84.0% (95% CI: 70.5%–91.7%). Looking at pEOT, ECOG PS ≥2, geriatric screening according to Lachs (Lachs) >20% and Cumulative Illness Rating Scale-Geriatric (CIRS-G) ≥6 were significantly associated in UVA, while Barthel Index of Activities of Daily Living (ADL) almost reached statistical significance ($p = 0.088$, OR 4.12, 95% CI: 0.8–21.0). In MVA, CIRS-G ≥ 6 ($p = 0.031$; OR 7.17; 95% CI: 1.2–42.8), ECOG ≥ 2 ($p = 0.070$; OR = 4.56; 95% CI: 0.9–23.5.4), ADL < 20 ($p = 0.361$; OR = 2.38; 95% CI: 0.4–15.3) and Lachs >20% ($p = 0.459$; OR = 2.46; 95% CI: 0.2–26.4) still had an impact on pEOT. A composite sum score including ECOG PS ≥ 2, Barthel Index of ADL < 20 and Lachs >20% was significantly associated with the risk of pEOT using a cut-off of >1 ($p = 0.022$; OR = 6.50; 95% CI: 1.3–32.1). Importantly, 26/28 (92.9%) of those patients with at most 1 score outside the respective cut-off reached HCT-ASCT. In addition, ECOG PS ≥ 2, Barthel Index of ADL <20, and the above mentioned composite sum score were significantly associated with decreased PFS and OS.

Conclusions: This is the first study to report the impact of different GA tools on outcome parameters in a prospectively and uniformly treated elderly PCNSL patient population. Our results have been incorporated into the randomized, phase III PRIMA-CNS trial to validate the findings and their role in guiding individualized treatment decisions.

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Keyword: Aggressive B-cell non-Hodgkin lymphoma

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300 | PRIMARY MEDIASTINAL B-CELL LYMPHOMA, A NATIONWIDE REAL-LIFE RETROSPECTIVE STUDY FROM FONDAZIONE ITALIANA LINFOMI (FIL)

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Introduction: PMBCL is an uncommon neoplasia showing unique clinicopathologic and demographic features. Front-line chemo-immunotherapy (R-CHT) plus consolidative radiotherapy (RT) allows a 5 yr OS of 80%. However, several issues still need to be debated.

Methods: We designed a retrospective cohort study including 37 hematological centers throughout the national territory to describe presenting features, first-line and consolidation strategies adopted, and the outcomes in a real-world setting. All adult patients were eligible, provided they had a clinical picture coherent with that of the PMBCL, were registered in the local databases from 1/1/2007 to 31/12/2019 with a histological diagnosis of PMBCL, and were treated with an RCHT.

Results: Data from 891 patients with PMBCL were retrieved. The median age was 35 yrs (IQR 28–44), and 62% were females. ECOG >2, Stage >II, LDH ratio >1, and bulky mediastinum were present in 21%, 22%, 74%, and 72% of patients, respectively. All patients received treatment with rituximab plus CHOP21 (n = 98), CHOP14 (n 181), megaCHOP (n 31), VACOPB (n 179), MACOPB (n 225), and DAEPOCH (n 179). In addition, 66 (7.5%) were consolidated with autologous stem cell transplant (ASCT), and 589 patients (66.2%) received RT. The RT consolidation rates significantly differed across therapeutic groups (p = 0.01); the lower (31%) and the higher values (90%) were reported in the R-DAEPOCH and in the R-megaCHOP groups, respectively. Final PET response assessment was available in 97% of patients, and CR was recorded in 81%. Both CR and primary failure rates were comparable across the different regimens. With a median follow-up of 5.1 years [QR: 3.5–7.6], the 5-yr PFS and OS of the entire series were 83% (95% CI: 80–85) and 91% (95% CI: 89–93), respectively. PFS curves according to different therapeutic groups and multivariate Cox proportional-hazards models are shown in Figure 1. The 5-yrs PFS and OS rates with R-MACOPB, which is the treatment of choice in Italy, were 86% (95% CI: 81–90) and 91% (95% CI: 86–94), respectively and comparable to others reported in the literature. In multivariate analysis, compared to the R-MACOPB group, R-CHOP21 treated patients showed a significantly worse PFS (HR = 2.00 95% CI: 1.08–3.72). Concerning OS, there was no substantial difference among the different R-CMTs. The IPI score (one class increase) was significantly associated with the risk of primary refractoriness, worse PFS, and OS. The presence of >1 extranodal site conferred a higher prognostic weight than the other IPI parameters.

Conclusions: Our preliminary nationwide real-world analysis indicates that R-CHOP21 is a suboptimal treatment for patients with PMBCL. All other regimens allow PFS and OS rates that do not significantly differ from the original R-MACOPB.

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Conflicts of interests pertinent to the abstract.

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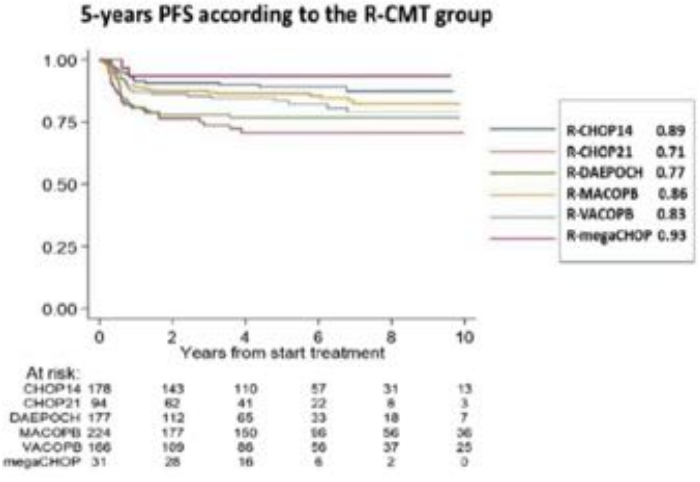

Univariable and multivariable Cox model for PFS.

Univariable			
CHOP21	2.34	1.27-4.32	0.006
VACOPB	1.31	0.85-2.03	0.223
MACOPB	1.00	1.00-1.00	-
DAEPOCH	2.09	1.12-3.91	0.021
CHOP14	0.80	0.41-1.58	0.519
megaCHOP	0.34	0.07-1.61	0.166
Multivariable			
CHOP21	2.00	1.08-3.72	0.028
VACOPB	1.24	0.80-1.91	0.334
MACOPB	1.00	-	-
DAEPOCH	1.70	0.92-3.13	0.090
CHOP14	0.76	0.39-1.48	0.421
megaCHOP	0.33	0.05-1.95	0.218
IPI score (1 point increase)	1.57	1.29-1.91	<0.001
AA Stage III-IV	1.56	1.03-2.35	0.034
ECOG PS>=2	1.37	0.91-2.05	0.131
LDH (proxy)	0.82	0.50-1.33	0.431
>1 extranodal site	1.98	1.26-3.12	0.003
Age, per 5-year increase	1.00	0.91-1.07	0.961
Male sex	1.20	0.86-1.67	0.275
Systemic B symptoms	1.53	1.09-2.14	0.014
Bulky mediastinum > 10 cm	1.41	0.91-2.19	0.125
Pericardial or Pleural effusion	1.20	0.80-1.74	0.372

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301 | REAL-LIFE EXPERIENCE WITH RITUXIMAB-DOSE-ADJUSTED EPOCH (R-DA-EPOCH) IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL): A MULTINATIONAL ANALYSIS OF 274 PATIENTS

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Background: Real-life studies of moderate size have shown satisfactory but less impressive results compared with the original R-da-EPOCH publication for PMLBCL. However, large studies are needed efficacy and toxicity of R-da-EPOCH, the use of radiotherapy (RT) and significance of the compliance with the strict dose escalation strategy of the protocol.

Aim: To assess the clinical outcomes after R-da-EPOCH, the use of RT and protocol compliance in a multinational real-life setting.

Patients and Methods: 274 patients (pts) were enrolled from 18 Greek, Israeli, Turkish, Saudi, Cypriot and Maltese centers (n = 143, 66, 34, 22, 5 and 4 pts respectively). Consolidative RT was given at the treating physician's discretion and was highly affected by PET/CT results.

Results: The median age of the pts was 33 years (16–63), 62% were females, 38% had B-symptoms, 33% extranodal involvement (E or stage IV), 18% PS ≥ 2, 83% elevated LDH (34% highly elevated ≥2x normal). RT was spared in the overwhelming majority of responders.

The 5-year Freedom From Progression (FFP) was 85%. However, 5 pts developed therapy-related (t-)AML at 10.5–24 months from treatment initiation, while in 1st remission, and one Hodgkin lymphoma. The 5-year overall survival (OS) was 91% with 20 disease-related deaths (1 toxic). Protocol violations were common (54% of 245 patients with available data so far), mainly consisting of insufficient dose escalation despite the absence of prohibitive toxicity. Among 258 pts with available data, 60% reached level ≥3 and 30% ≥4 (73% and 44% among those with strict protocol adherence). The 5-year FFP was 89% versus 83% for pts with strict protocol adherence or not ($p = 0.19$); 5-year OS was not also different (91% vs. 92%, $p = 0.74$). FFP and OS did not differ according to the final level reached (≥3 or ≥4). A more detailed analysis of outcome according to the degree of protocol violations is currently ongoing. Pts with both risk factors according to the prognostic systems including any extranodal involvement and highly elevated LDH (≥2x) or bulk had inferior outcomes but still better than those achieved by R-CHOP in high-risk pts.

Conclusions/Discussion: In the largest series reported so far for R-da-EPOCH in PMLBCL, FFP appeared somewhat but not impressively better than the expected with R-CHOP, but this was achieved with the safe omission of RT was in >85% of responders. OS was >90%. The appearance of 5 cases of t-AML among 274 pts is worrisome. Significant dose-escalation violations were recorded in the real-life; their impact on outcomes appears to be modest and is further evaluated. A final analysis on 290–300 pts will be presented at the Meeting.

Keyword: Aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

302 | AXICABTAGENE CILOLEUCEL (AXICEL) FOR RELAPSED/REFRACTORY PRIMARY MEDIASTINAL B-CELL LYMPHOMA (R/R PMBCL) COMPARED TO DLBCL-NOS: A GLA/DRST REGISTRY STUDY.

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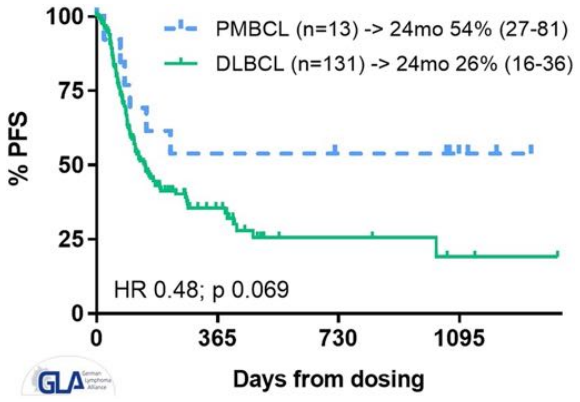
Introduction: Axicel is approved for treatment of r/r PMBCL beyond the 2nd treatment line (>2L). However, real-world data on axicel safety and efficacy in this orphan entity is limited. Here, we present a comparison of standard-of-care axicel treatment in r/r PMBCL >2L versus diffuse large B-cell lymphoma, not otherwise specified (DLBCL).

Methods: The previously published German Lymphoma Alliance (GLA)/ German Registry for Stem Cell Transplantation (DRST) dataset (Bethge et al., Blood 2022) was screened for PBMCL patients treated with axicel. Investigators were consulted for follow-up data and confirmation of diagnosis. Axicel-treated patients with DLBCL from the same dataset served as comparators.

Results: Altogether, 13 patients with PMBCL were identified in the total sample of 173 patients treated with axicel, along with 131 DLBCL patients. PMBCL patients were significantly younger (median age 39 (20–48) years versus 60 (20–83) years for DLBCL), but were comparable to DLBCL for all other baseline parameters, including performance status, prior treatment lines, prior transplantations, IPI, LDH, and disease status at lymphodepletion. Specifically, in the PMBCL population, IPI was high/high-intermediate in 54% of patients and 92% had active disease at lymphodepletion due to omission of bridging attempts in 38% and unsuccessful bridging in 54% of patients. Only 18% each had received prior radiotherapy and checkpoint inhibitor treatment, respectively. With rates of grade ≥3 CRS and neurotoxicity of 15% each, and 8% of patients without neutrophil recovery at day 30, safety outcomes of the PMBCL patients did not significantly differ from the DLBCL cohort. Non-relapse deaths did not occur in the PMBCL group. Regarding efficacy, the best overall response rate (ORR) in PMBCL was 85%, with 54% complete responses (CR), and thus not significantly different from the DLBCL cohort (ORR 71%, CR 42%). With a median follow-up of 35 months, 2-year progression-free survival (PFS) and overall survival (OS) of the PMBCL group was 54% and 75%, respectively, and compared favorably with DLBCL outcomes (PFS 26%, $p = 0.069$; OS 36%, $p = 0.011$). Of note, in the PMBCL group, progression events beyond 8 months did not occur (Figure), and patients not responding to bridging had 2-year PFS similar to patients without bridging or with bridging response (57% vs. 50%).

Conclusions: Although limited by small sample size, safety outcomes after axicel treatment for PMBCL >2L seem comparable to those observed in DLBCL. Unlike in DLBCL, late progression events in PMBCL do not occur, and bridging failure is not associated with poorer outcome. Along with reduced post-axicel failure mortality, this results in substantially better survival of axicel-treated patients with PMBCL compared to DLBCL. Thus, axicel is a highly effective salvage option for r/r PMBCL, and exploration in earlier treatment lines should be considered.



Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies

Conflicts of interests pertinent to the abstract.

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303 | PRIMARY LYMPHOMA OF THE FEMALE GENITAL TRACT: A RETROSPECTIVE SURVEY OF THE INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP (IELSG35)

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Introduction: Primary lymphoma of the female genital tract (PLFGT) is an uncommon extranodal lymphoma. There are few reported series of PLFGT in the literature, and most of them are case reports.
Methods: We retrospectively collected and analyzed data on presentation, treatment, and outcome of 60 female patients (pts) diagnosed with PLFGT between 1982 and 2013. Our aim was to investigate baseline features associated with patient outcome (including age, stage, LDH, IPI, PS, bulky disease, primary site, aggressive histology, and use of rituximab). Univariable and

multivariable analyses were performed using the log-rank test and a stepwise Cox regression, respectively.

Results: The median age at diagnosis was 52 years. Ann Arbor stage I-II was observed in 32 pts while 38 pts had localized disease according to the FIGO staging systems. Uterus was the primary site in 26 pts, 23 had ovarian involvement and 11 had vaginal or vulvar involvement. Fourteen pts had multiple gynecologic sites affected at diagnosis. Diffuse large B-cell lymphoma (DLBCL) was the most common subtype, occurring in 39 patients, followed by extranodal marginal zone lymphoma and follicular lymphoma (6 patients each). Surgery alone was given to 2 patients as first-line therapy, while systemic therapy was administered to 58, 16 of whom had undergone previous major surgery. Consolidation radiotherapy was given to 13 patients, all but one of whom had pelvic lesions. Six patients received central nervous system (CNS) prophylaxis (4 high-dose methotrexate, 1 intrathecal methotrexate, and 1 unspecified prophylaxis). Fifty-four patients responded to treatment (49 complete and 5 partial responses), while 20 experienced disease progression or relapse. Of those, 6 relapsed in the CNS (which was the only recurrence site in 5). All but one patient with CNS relapse had ovarian involvement, 3 had bulky disease, and none had received previous prophylaxis. With a median follow-up of 60 months, progression-free survival (PFS) at 5 and 10 years was 66% and 57%, respectively. At the last follow-up, 44 patients were alive (42 of whom were in complete remission), 13 had died from lymphoma, and 2 had died from other causes, while 1 patient was lost to follow-up. The median overall survival was 12.7 years with 5- and 10-year overall survival (OS) of 77% and 68%, respectively. Only FIGO advanced disease remained significantly associated with poorer PFS and OS at multivariable analysis.

Conclusions: This PLFGT survey showed the prognostic impact of gynecological staging procedures and a sizeable risk of CNS relapse. These findings may have treatment implications and highlight the utility of multidisciplinary management, as well as the need for further research to identify predictive factors for CNS relapse

Keyword: Extranodal non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

DLBCL

304 | COMPARISON BETWEEN AAIPI, LAB-PI, NCCN-IPI AND GELTAMO-IPI TO PREDICT PROGNOSIS IN ELDERLY PATIENTS WITH DIFFUSE LARGE-B CELL LYMPHOMA WHO UNDERGO R-CHOP/R-MINICHOP

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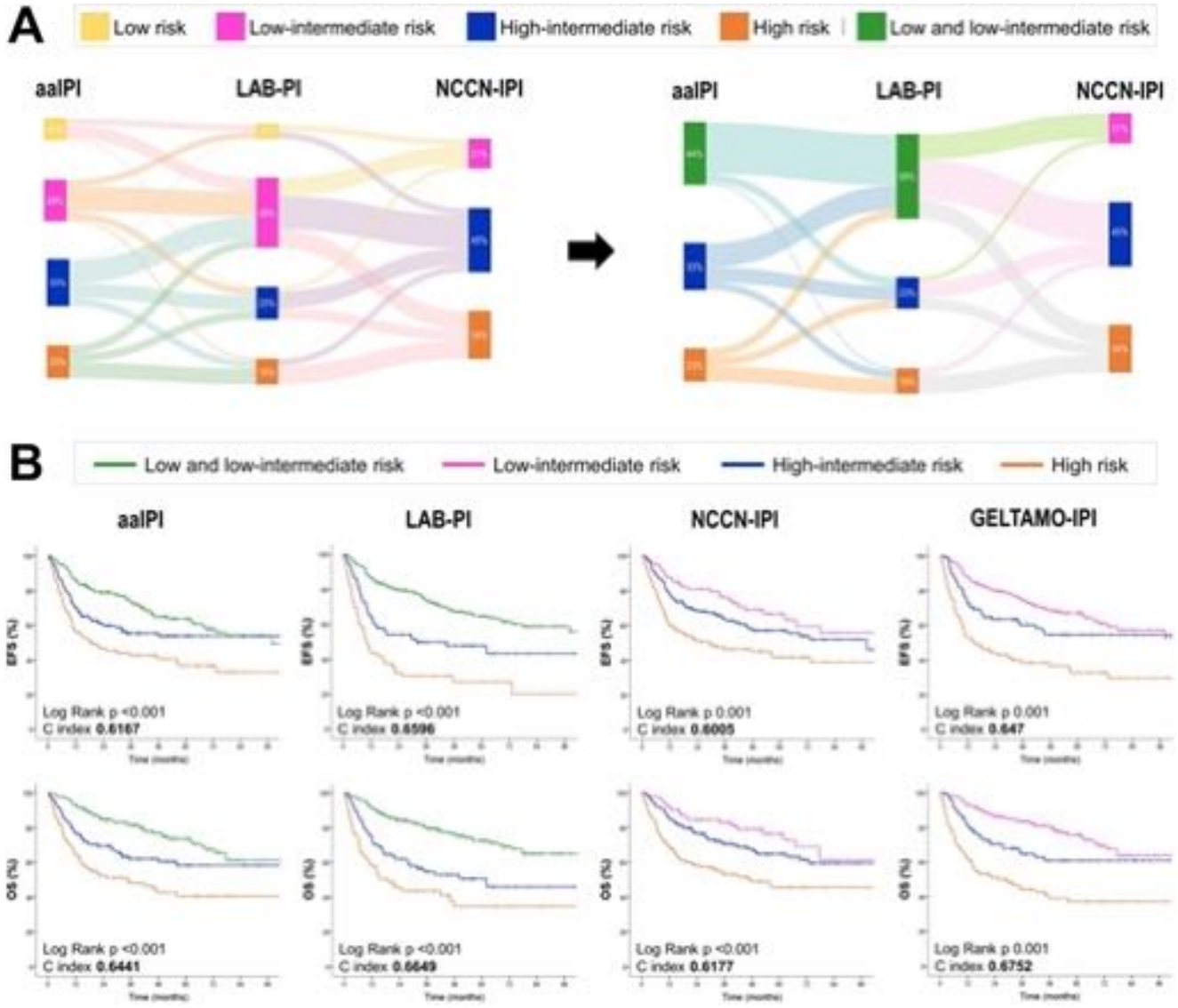
Background: Elderly patients with diffuse large B-cell lymphoma (DLBCL) need thorough evaluation at diagnosis to select the most suitable approach. Different scores are used to stratify DLBCL cases according to their prognosis, but data are scarce in old patients. The Laboratory Prognostic Index (LAB-PI) [Martin-Moro. ASH 2022; abstract 320] has emerged as an interesting tool for this group of patients, due to its simplicity and accessibility, as it only includes three variables routinely tested in peripheral blood at DLBCL diagnosis: lactate dehydrogenase, hemoglobin, and beta-2 microglobulin. The aim was to compare the prognostic usefulness of validated prognostic indexes in old DLBCL patients, with a special focus on the LAB-PI score.

Methods: Retrospective multicenter study (on behalf of the Spanish Lymphoma Group GELTAMO) including de novo DLBCL patients with ≥70 years old at diagnosis who received first-line therapy (N = 386). Four prognostic scores were calculated prior to treatment initiation: aaIPI, LAB-PI, NCCN-IPI, and GELTAMO-IPI. Descriptive statistics were applied to compare the different prognostic scores, which were analyzed for both event-free survival (EFS) and overall survival (OS) by Kaplan Meier curves and by the concordance C-index. In each score, risk clusters which showed no EFS difference, calculated by univariate hazard ratio (UV HR) Cox regression analysis, were grouped.

Results: The series was composed of 386 DLBCL patients with a median age at diagnosis of 76 years (IQR 73–80) and a male:female ratio of 0.8:1. Patients presented with advanced stage were 254/386 (66%). The distribution of the prognostic groups (low, low-intermediate, high-intermediate, and high) among the four indexes was heterogeneous, as shown in Figure 1A when comparing LAB-PI with aaIPI and NCCN-IPI. No statistical EFS difference was seen between low and low-intermediate risk groups for aaIPI (UV HR 1.4, 95% CI: 0.8–2.6) and LAB-PI (UV HR 1.2, 95% CI: 0.8–1.9), so these



clusters were grouped in each index. Three hundred and seventy-four patients (97%) were treated with anthracycline-based regimens (R-CHOP or R-miniCHOP). The median follow-up of the cohort was 34.2 months (IQR 15–61). EFS and OS curves according to each prognostic score are presented in Figure 1B. According to C-index, the most useful score to predict EFS was the LAB-PI (0.66).

Conclusions: The prognostic scores analyzed in this study (aaIPI, LAB-PI, NCCN-IPI, and GELTAMO-IPI) are useful to predict both EFS and OS in old patients with DLBCL who receive first-line therapy with R-CHOP/R-miniCHOP, although variability among the distribution of risk groups was noted between scores. The LAB-PI score is postulated as a more objective, easier to apply and reproducible tool which may be assessed in elderly DLBCL patients. Its potential in therapeutic decision-making remains to be evaluated.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, Risk Models

No conflicts of interests pertinent to the abstract.

305 | PATIENT- VERSUS CLINICIAN-REPORTED SYMPTOMS IN THE POLARIX STUDY

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Introduction: The safety profiles of novel agents are mainly based on clinician-reported adverse events (AEs) from clinical trials. Patient-reported outcomes (PROs) may better represent the treatment burden experienced by patients (pts) compared with clinician-reported AEs. Using data from POLARIX, a double-blind, placebo-controlled, randomized Phase 3 international study (NCT03274492), we previously presented PRO and clinician-reported data showing similar rates of neuropathy (Trněný et al., 2022). Here, we evaluate the reporting of other common symptoms using PRO and clinician-reported data in POLARIX.

Methods: POLARIX methods were previously described (Tilly et al., 2022); this analysis included all pts with PRO data. PRO and clinician-reported data described the incidence and severity of fatigue, constipation, diarrhea, nausea, and vomiting. Clinician-reported severity grading was based on the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0. PROs were collected using the European Organisation Research and Treatment of Cancer Quality of Life-Core 30 questionnaire (EORTC QLQ-C30), which was administered to pts at clinic visits on Day 1 of Cycles 1 (baseline), 2, 3, and 5, and end of treatment (EOT). PRO severity scores included 'A little', 'Quite a bit', and 'Very much'.

Results: Overall, 825 pts were evaluable. From baseline to EOT, PROs showed a higher incidence of symptoms compared with clinicians for fatigue (98% vs. 27%), constipation (68% vs. 29%), diarrhea (56% vs. 26%), nausea (58% vs. 40%), and vomiting (24% vs. 15%). PRO severity scores of 'Quite a bit' or 'Very much' were reported in 33% of pts for fatigue, 29% for constipation, 17% for diarrhea, 19% for nausea, and 7% for vomiting (Table). Clinicians reported Grade ≥2 symptoms in 11% of pts for fatigue, 11% for constipation, 11% for diarrhea, 14% for nausea, and 6% for vomiting (Table).

Conclusions: In POLARIX, pts reported a higher incidence and severity of symptoms compared with clinicians. Although distinct scales were used, the differences in symptom rates reported by pts and clinicians were clinically meaningful. These data may have implications for symptom management, including physician evaluation and communication of symptom expectations for pts. Reporting of symptoms by PROs should be incorporated into clinical trials as an adjunct to standard AE reporting to better characterize the patient experience.

Encore Abstract - previously submitted to ASCO 2023

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Table:

Symptom,* n (%)	Clinician-reported severity†	Patient-reported severity‡		
	Grade ≥2	'A little'	'Quite a bit'	'Very much'
Fatigue	88 (10.7)	532 (64.6)	245 (29.7)	28 (3.4)
Constipation	93 (11.3)	330 (40.2)	143 (17.4)	91 (11.1)
Diarrhea	87 (10.5)	316 (38.4)	90 (10.9)	52 (6.3)
Nausea	119 (14.4)	317 (38.5)	112 (13.6)	46 (5.6)
Vomiting	46 (5.6)	143 (17.4)	33 (4.0)	25 (3.0)

PRO-evaluable population: n=825.

*From baseline to EOT; †Based on NCI-CTCAE v4.0; ‡Based on EORTC QLQ-C30.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies

Conflicts of interests pertinent to the abstract.

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306 | SUBGROUP ANALYSIS OF ELDERLY PATIENTS (PTS) WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) IN THE PHASE 3 POLARIX STUDY

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Introduction: In the Phase 3 POLARIX study (NCT03274492), polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and

prednisone (Pola-R-CHP) significantly improved progression-free survival (PFS) compared with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), with a similar safety profile in pts aged 18–80 years with previously untreated DLBCL (Tilly et al., 2022). Combination regimens may be associated with higher rates of toxicity in elderly pts. We report the efficacy and safety of Pola-R-CHP versus R-CHOP in pts aged ≥70 years enrolled in POLARIX.

Methods: POLARIX methods were described by Tilly et al. (2022). Pts with previously untreated DLBCL were randomized 1:1 to receive 6 cycles of Pola-R-CHP or R-CHOP, plus 2 cycles of rituximab. This analysis focused on pts aged ≥70 years at enrollment.

Results: Overall, 284 pts were analyzed for efficacy (Pola-R-CHP, $n = 141$; R-CHOP, $n = 143$) and 280 pts were analyzed for safety (Pola-R-CHP, $n = 137$; R-CHOP, $n = 143$). Median age was 74 years (range 70–80), and 69.7% had an International Prognostic Index score of 3–5. Most pts in either arm received all 6 doses of polatuzumab vedotin or vincristine (88.3% and 91.6% in the Pola-R-CHP and R-CHOP arms, respectively).

At data cutoff (June 28, 2021; median follow-up: 24.2 months), the risk of progression, relapse or death was lower with Pola-R-CHP versus R-CHOP (hazard ratio [HR] 0.64; 95% confidence interval [CI]: 0.41–0.99) (Table). Death by any cause occurred in 14.2% and 19.6% of pts treated with Pola-R-CHP and R-CHOP, respectively. Overall survival (OS) and disease-free survival (DFS) results are presented in the Table.

Safety profiles were generally comparable for Pola-R-CHP versus R-CHOP, including rates of Grade 3–5 adverse events (AEs), Grade 5 AEs, serious AEs, peripheral neuropathy (any grade), neutropenia (Grade 3–4), and infection (Grade 3–4) (Table).

Conclusions: Pola-R-CHP and R-CHOP demonstrated similar safety profiles in pts aged ≥70 years with previously untreated DLBCL. The risk-benefit profile favored Pola-R-CHP versus R-CHOP.

Encore Abstract - previously submitted to ASCO 2023

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies

Conflicts of interests pertinent to the abstract.

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	Pola-R-CHP	R-CHOP
Efficacy, % (95% CI)	**n=141**	**n=143**
2-year PFS rate	77.1 (69.98–84.19)	67.0 (59.15–74.79)
	*HR 0.64 (0.41–0.99)	
2-year OS rate	86.2 (80.47–91.98)	82.8 (76.51–89.05)
	*HR 0.74 (0.41–1.31)	
2-year DFS† rate	80.6 (73.37–87.78)	73.4 (65.11–81.72)
	*HR 0.65 (0.38–1.11)	
Safety	**n=137**	**n=143**
Total no. pts with ≥ 1 AE, n (%)		
Grade 3–5	101 (73.7)	100 (69.9)
Grade 5	5 (3.6)	7 (4.9)
Serious	59 (43.1)	55 (38.5)
Any grade peripheral neuropathy	72 (52.6)	67 (46.9)
Grade 3–4 neutropenia	42 (30.7)	50 (35.0)
Grade 3–4 infection	22 (16.1)	18 (12.6)

*Unstratified analysis; †DFS-evaluable population, n=125 (Pola-R-CHP); n=124 (R-CHOP).

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307 | A RETROSPECTIVE ANALYSIS OF CLINICAL CHARACTERISTICS, TREATMENT, AND OUTCOMES IN LARGE B-CELL LYMPHOMAS WITH SYNCHRONOUS SYSTEMIC AND CENTRAL NERVOUS SYSTEM INVOLVEMENT

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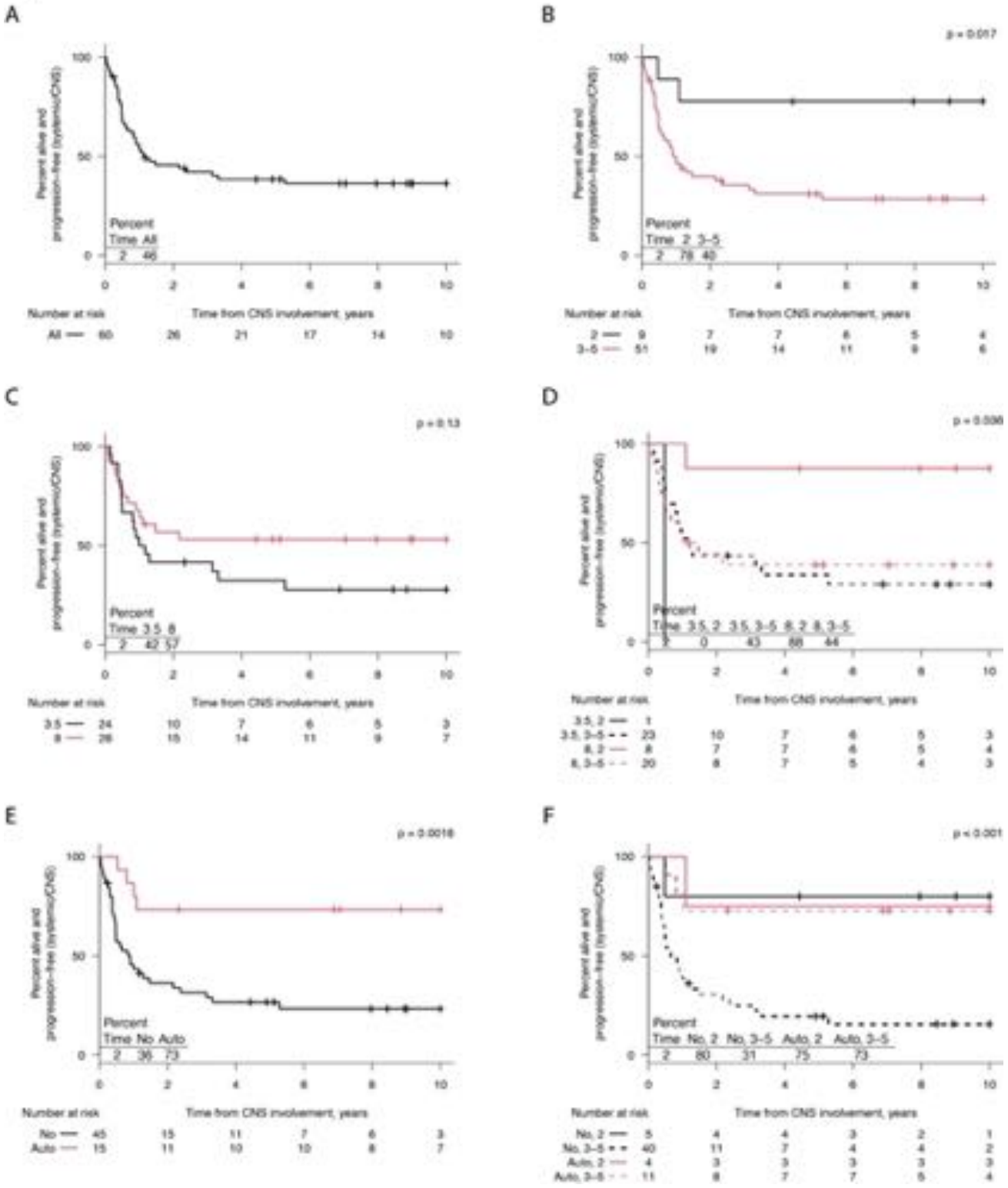
Introduction: Large B-cell lymphoma with synchronous systemic and central nervous system (CNS) involvement at diagnosis is a rare entity with a poor prognosis. Prior data come from small heterogenous retrospective studies, and there is no consensus on optimal treatment.
Methods: Using our IRB-approved Research Patient Data Repository, we identified 60 consecutive pts presenting with synchronous systemic/CNS large B-cell lymphoma between 6/2002-6/2021.
Results: The median age was 64 years (range: 38–89), and 23 (38%) were female. Most pts (73%) had diffuse large B-cell lymphoma (47% GCB; 53% non-GCB). There were 6 high grade B-cell lymphomas (4/6 double hit). Six cases were intravascular LBCL. The most common CNS site was brain parenchyma (60%), followed by leptomeninges (58%), intraocular (7%), and spinal cord (2%); 23% of pts had >1 CNS site at diagnosis. The median IPI score was 3 (range 2–5) and baseline LDH was elevated in 60%. Almost all pts (93%) had non-CNS extranodal disease, with a median of 2 sites (range 1–7). The most

common non-CNS extranodal sites were testis (18%), adrenal/renal (17%), and bone marrow/leukemic (17%).

Most pts received R-CHOP-like regimens (85%) and 14% received EPOCH-R or R-CODOX/IVAC. The most common CNS therapy was intravenous (IV) methotrexate (MTX) in 88%. Among MTX-treated pts, the target dose was 8 g/m^2 in 53% (median cycles 6, range 2–20) and 3.5 g/m^2 in 45% (median cycles 6, range 1–11). Other CNS therapies were intrathecal (IT) MTX (22%) and IT liposomal cytarabine (15%). Fifteen (25%) pts underwent consolidative autologous stem cell transplant (ASCT).

Figure 1



The best overall response rate was 91% (95% CI: 81%–97%) and best complete response rate was 79% (95% CI: 66%–89%). With 8.4 years of median follow up, the median progression-free survival (PFS) was 1.2 years (range 0–10) (Figure 1A) and the median overall survival (OS) was 7.9 years (range 0–10). The 2-year PFS and OS were 46% and 61%, and the 6-year PFS and OS were 36% and 52%, respectively. The 2-year PFS by IPI was 78% for IPI 2 and 40% for IPI ≥3 ($p = 0.017$, Figure 1B). The 2-year PFS by IV MTX dose was 42% for 3.5 g/m^2 and 57% for 8 g/m^2 ($p = 0.13$, Figure 1C). The 2-year PFS for pts with IPI < 3 who received 8 g/m^2 IV MTX was 88% ($p = 0.036$, Figure 1D). The 2-year PFS for pts undergoing consolidative ASCT was 73%, compared to 36% for non-transplanted pts ($p = 0.0018$, Figure 1E). Pts with IPI ≥3 who underwent ASCT had a 2-year PFS of 73% compared to 31% in non-transplanted pts ($p < 0.001$, Figure 1F).

Conclusions: Half of pts with synchronous systemic/CNS LBCL treated with chemoimmunotherapy are alive at 8 years. Improved outcomes were observed for pts with lower IPI, as well as for pts consolidated with ASCT. Pts presenting with synchronous systemic/CNS LBCL can have durable remission and survival when treated with frontline systemic and CNS-directed chemoimmunotherapy.

Keyword: Aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

308 | POLA-R-CHP VERSUS R-CHOEP IN YOUNG PATIENTS WITH HIGH-RISK DIFFUSE LARGE B-CELL LYMPHOMA

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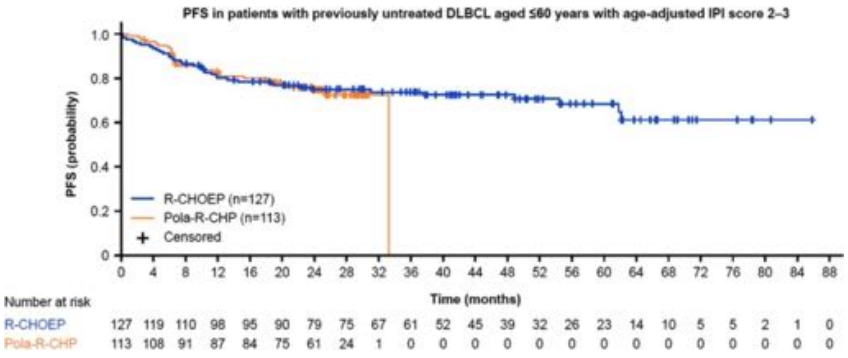
Introduction: The best treatment for young patients with high-risk diffuse large B-cell lymphoma (DLBCL) is still a matter of debate. Results of the phase 3 R-MegaCHOEP study showed promising results using etoposide in combination with R-CHOP (R-CHOEP). Progression-free (PFS) and overall survival (OS) rates for young patients (18–60 years) with high-risk (age-adjusted IPI 2, 3) DLBCL treated with R-CHOEP were among the best reported for such patients. Recently, the combination of polatuzumab vedotin and R-CHP (pola-R-CHP) was approved for the treatment of DLBCL patients based on the data of the POLARIX study that showed an improvement of PFS following treatment with pola-R-CHP compared to R-CHOP in DLBCL patients with an IPI 2–5. To obtain further insights into the optimal treatment of young (age ≤60 years), high-risk (aaIPI 2, 3) DLBCL patients we retrospectively compared outcomes of such patients treated with pola-R-CHP or R-CHOEP.

Methods: Treatment consisted of 6 cycles pola-R-CHP followed by 2 cycles of rituximab (R) given every 3 weeks or 8 cycles of CHOEP given every two weeks plus 6 cycles of R. Event-free survival (EFS), PFS, and OS of DLBCL patients ≤60 years with aaIPI 2, 3 were calculated and major toxicities compared. The Kaplan-Meier method was used to estimate EFS, PFS, and OS in each group. Hazard ratios with 95% CI and log-rank tests comparing pola-R-CHP with R-CHOEP were calculated. *P*-values <0.05 were considered significant.

Results: 113 patients treated with pola-R-CHP and 127 patients treated with R-CHOEP were analyzed. Major patient characteristics differed in aaIPI with more patients in the R-CHOEP group showing an aaIPI of 3 (28% vs. 12%). Two-year EFS-, PFS-, and OS-rates for patients treated with pola-R-CHP were 65.9% (CI: 56.7%, 74.8%), 74.8% (66.5%, 83.0%), and 88.3% (82.3%, 94.3%) as compared to 70.5% (62.5%, 78.5%), 74.9% (67.3%, 82.6%), and 84.6% (78.3%, 91.0%) for patients treated with R-CHOEP with no significant differences for any of these endpoints between treatment regimens. Patients treated with R-CHOEP experienced more hematological toxicity and infections (29.9% ≥ grade 3 infections in R-CHOEP-treated vs. 15.0% in pola-R-CHP treated patients) with 4 treatment-related deaths occurring in patients treated with R-CHOEP and 2 treatment-related deaths following pola-R-CHP, respectively.

Conclusions: Both regimens gave excellent results with around 85% of patients surviving at 2 years. R-CHOEP caused cytopenias and infections in more patients compared to pola-R-CHP. For R-CHOEP-treated patients secondary neoplasms have been reported while



these were not observed following pola-R-CHP-treated patients with limited follow-up. In summary, pola-R-CHP is a safe and effective treatment regimen in young high-risk DLBCL patients. Treatment with R-CHOEP may be considered as an alternative especially in situations in which pola-R-CHP is not readily available.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies

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309 | GLOFITAMAB PLUS R-CHOP OR POLATUZUMAB VEDOTIN-R-CHP IS DELIVERABLE WITH HIGH OVERALL RESPONSE IN PATIENTS ≤65 YEARS OF AGE WITH HIGH-RISK DLBCL: INTERIM ANALYSIS OF COALITION

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Background: Improved treatments are needed for patients (pts) with high-risk (HR) DLBCL. Intensification of R-CHOP has not improved outcomes. Furthermore, pts with HR disease are frequently excluded from trials due the need for rapid treatment initiation, an independent predictor of poor outcome.

Glofitamab (glo) is a CD20/CD3 bispecific antibody achieving 39% complete remission (CR) rate R/R DLBCL (Dickinson, NEJM 2023). We present an interim analysis of an ongoing investigator-initiated, parallel-arm, phase I/II study of glo in combination with R-CHOP or polatuzumab vedotin (pola)-R-CHP in younger pts with HR DLBCL.

Methods: Eligible pts include untreated DLBCL, age 18–65, and at least one HR feature: IPI ≥3, NCCN-IPI ≥4, or proven double-hit status. To minimise treatment delay, enrolment is allowed after 1 cycle of R-CHOP and ECOG <4 at baseline or <2 at C2 is permitted. Pts receive 5 cycles of glo (2.5 mg & 10 mg step-up in C2, 30 mg in C3-6) in combination with R-CHOP (Arm A) or Pola-R-CHP (Arm B), followed by 2 cycles of glo consolidation.

Primary endpoints are safety, relative dose intensity (RDI) and rate of treatment discontinuation. Responses are evaluated after cycles 2, 4 and 6 and then 3–6 monthly. Adverse events (AEs) are graded using CTCAE V5.0, except cytokine-release syndrome (CRS) and neurotoxicity (ICANS) graded by ASTCT criteria.

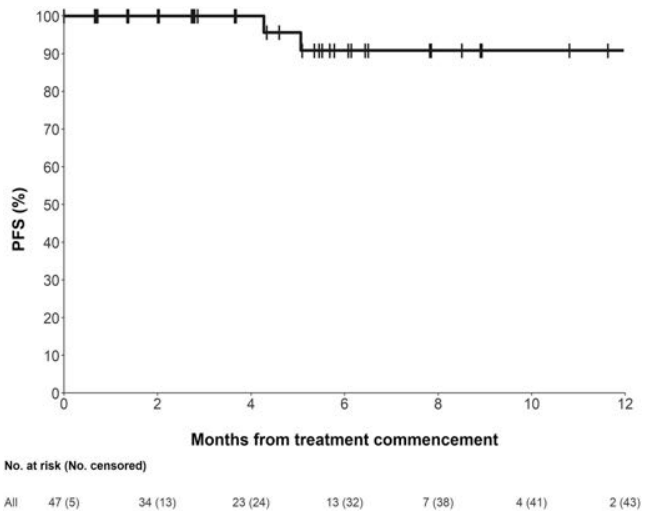
Results: 47 patients have received ≥1 dose of study treatment at Nov 1, 2022 (25 Arm A, 22 Arm B). 42 (89%) have de novo DLBCL and 5 (11%) have transformed indolent lymphoma. Median age was 52 years (range 24–65), IPI was ≥3 in 81%, and NCCN-IPI was ≥4 in 81%. The median TMTV was 673 cm^3 (IQR 249–1221 cm^3). Median time from diagnosis to first R-CHOP was 15 days (IQR 11–21.5).

Grade (Gr) ≥3 AEs were seen in 10/25 (40%) (Arm A) and 11/21 (52%) (Arm B). There were no Gr 5 AEs. Febrile neutropenia was observed in 1/25 (4%) and 6/21 (29%) and CRS Gr 1 in 5/25 (20%) and 5/21 (24%), respectively. There was 1 episode of Gr 2 CRS in Arm A. Neuropathy was limited to Gr 1–2 in 11/25 (44%) and 5/21 (24%) respectively. No ICANS was observed.

The RDI was ≥90% for cyclophosphamide, doxorubicin, pola, vincristine and glo in 93%, 93%, 100%, 76% and 88% of patients, respectively. There was 1 dose interruption of doxorubicin and 3 interruptions to glo, 2 for infection and 1 for rash.

41 treated pts had at least 1 efficacy assessment, with best overall response rate 100%. Of 25 pts who reached the end of induction (EOI) assessment, 19 (76%) demonstrated CR, 5 (20%) PR and 1 (5%) PD. At a median follow up of 3.7 months (mo), the estimated PFS at 6-mo was 91% (Figure). Of the 5 pts with PR at EOI, none has progressed with median follow up 6.1 mo.

Conclusion: Glo with R-CHOP or Pola-R-CHP was deliverable with low-grade CRS and maintenance of RDI. The ability to enrol after 1 cycle of R-CHOP resulted in short time to treatment initiation and inclusion of pts with high burden disease. Efficacy appears promising in this HR pt population.



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Conflicts of interests pertinent to the abstract.

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310 | ZANBRUTINIB, LENALIDOMIDE PLUS R-CHOP (ZR2-CHOP) AS THE FIRST-LINE TREATMENT FOR NON-GCB DIFFUSE LARGE B-CELL LYMPHOMA: AN UPDATED ANALYSIS OF EFFICACY AND TOLERABILITY

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Aims: To evaluate the safety and efficacy of zanubrutinib, lenalidomide plus R-CHOP (ZR2-CHOP) as the first-line treatment for non-GCB DLBCL patients, we updated the results in our cohort.

Methods: We enrolled patients aged 18–75 with high-risk non-GCB DLBCL (including double expression and other molecular characteristics). Oral zanubrutinib was given continuously (160 mg twice daily) from Day 0, lenalidomide 25 mg daily Day 1–7. Patients were administered intravenously rituximab (375 mg/m^2 Day 0), cyclophosphamide (750 mg/m^2 Day 1), doxorubicin (50 mg/m^2 Day 1), vincristine (1.4 mg/m^2 Day 1), and oral prednisone (100 mg Day 1–5). All patients were recommended to receive 6 cycles of ZR2-CHOP (R-CHOP or R2-CHOP were allowed in cycle 1 due to poor physical condition or inaccessible molecular characteristics at treatment) and patients older than 70 years old were administered ZR2-miniCHOP. Prophylaxis was mandatory with G-CSF in all patients and entecavir in patients with seropositive occult HBV (HBsAg negative but HBcAb positive). CT or PET-CT scans were applied to mid-term efficacy and PET-CT scan was conducted after 6 cycles. ctDNA was dynamically detected baseline, after 3 and 6 cycles to evaluate tumor mutational burden. The primary endpoint was complete response ratio (CRR) at mid-term and after 6 cycles. The secondary endpoint was overall response rate (ORR), ctDNA dynamics and adverse events (AE). AEs were graded based on CTCAE (version 5.0).

Results: 30 treatment-naïve non-GCB DLBCL patients were enrolled in this cohort between July 2020 and October 2023. The median age was 55.5. 19 patients (63%) were diagnosed as double-expression (Table 1). At data cutoff (March 2023), the median follow-up was 17 (6–32) months with 27 patients have completed 6 cycles. The ORR was 97% (29/30), with 22 patients achieved CR and 7 patients achieved PR after 3 cycles; 26 (96%) patients achieved CR after 6 cycles (Figure 1). 4 patients have received autologous stem cell transplantation for consolidation after 6 cycles. Molecular subtypes were determined in 18 patients as shown in Figure 2. ctDNA was dynamically detected in 18 patients. 15 (83%) patients achieved

Figure 1. Treatment response

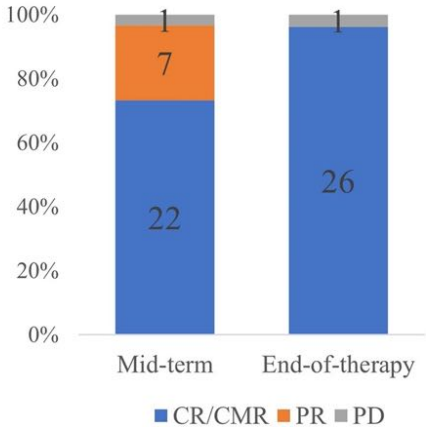

Figure 2. Molecular subtypes

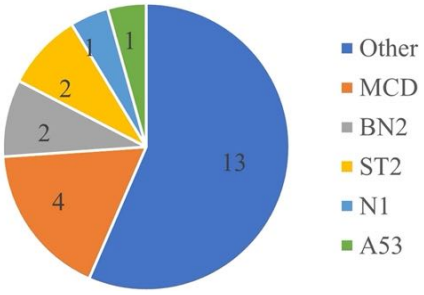

Table 1. Patient characteristics

Age	Median 55.5	ECOG-PS	
<60	20 (67%)	0	17 (57%)
≥60	10 (33%)	1	3 (10%)
Gender		2	8 (27%)
Male	17 (57%)	3	2 (7%)
Female	13 (43%)	IPI	
Stage		0-1	7 (23%)
I	2 (7%)	2	6 (20%)
II	5 (17%)	3	8 (27%)
III	5 (17%)	4-5	9 (30%)
IV	18 (60%)	NCCN-IPI	
B symptoms	12 (40%)	0-1	4 (13%)
Bulky disease	8 (27%)	2-3	6 (20%)
Bone marrow involvement	9 (30%)	4-5	17 (57%)
Elevated LDH	17 (57%)	6-8	3 (10%)
Double expressor	19 (63%)	Double hit (n=29)	0
TP53 deletion (FISH, n=27)	5 (19%)		

Figure 3. Survival curves

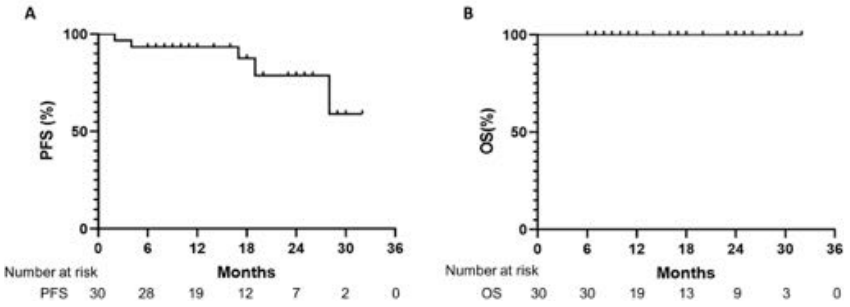

Table 2. Characteristics of patients with progressive disease

Pts.	Age	Gender	Stage	Molecular subtype	IPI	Double expression	p53-IHC	PFS (month)	OS status	OS (month)	Genetic aberrations at baseline
1	42	Male	IIIA	Other with TP53 deletion	2	No	Negative	28	Alive	32	TP53 deletion, B2M mutation, IRF4 mutation
2	71	Male	IVB	MCD	5	Yes	Scatter +	17	Alive	28	CD79A mutation, MYD88 L265P mutation, DTX1 mutation, PIM1 mutation
3	59	Male	IA	MCD	0	Yes	60%	19	Alive	28	CD79B muataion, MYD88 L265P mutation, B2M mutation, CIITA mutation, PIM1 mutaiton
4	67	Male	IVA	NA	4	No	80%+	4	Alive	6	NA
5	55	Female	IVA	MCD	4	Yes	NA	2	Alive	6	TP53 deletion, PIM1 mutation, TBL1XR1 mutation, BCL6 mutation, SYK mutation, KDM5A mutation, RUNX1 mutation CDKN2A mutation, MYD88 L265P mutation, BCOR mutation, MEF2B mutation, BTG2 mutation

undetectable ctDNA after 3 cycles. The 2-year PFS was 79% and the 2-year OS was 100% (Figure 3). The characteristics of 5 patients with progressive disease were listed in table 2. Among them, 3 were of the MCD subtype, 2 had TP53 deletion, 1 had p53 overexpression (80%). Grade 3–4 neutrophil count decreased, thrombocytopenia and anemia occurred in 40%, 30% and 20% of patients, respectively. 6 patients had grade 3 pneumonia and received intravenous antibiotics. **Conclusion:** ZR2-CHOP for high-risk non-GCB DLBCL patients with fair physical condition could achieve high CRR and early-stage undetectable ctDNA. The overall tolerability was under control.

Ongoing Trial

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies

No conflicts of interests pertinent to the abstract.

311 | IBRUTINIB + BORTEZOMIB + R-CHOP FOR HIGHER-RISK DLBCL: FEASIBILITY, EFFICACY AND MOLECULAR PREDICTORS

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Introduction: Most recent phase III trials investigating single targeted treatment additions to R-CHOP in patients with diffuse large B-cell lymphoma (DLBCL) failed, at least in part, due to the high heterogeneity of this disease. While re-analyses of negative trials (*e.g.* PHOENIX R-CHOP ± ibrutinib or REMoDL-B R-CHOP ± bortezomib) unveiled molecular subgroups that strongly benefitted, we pursued in our explorative single-arm open-label phase I/II ImbruVeRCHOP (ibrutinib + bortezomib + R-CHOP) investigator-initiated study (IIS) a proximal and distal BCR/NF-κB double-targeting strategy for higher-risk all-comer patients (i.e., independent of any molecular pre-selection) that utilizes repeated lymphoma biopsies for multi-omics profiling in the course of therapy to identify molecular signatures indicative of lasting responsiveness.

Methods: 37 IPI ≥2 newly diagnosed DLBCL patients 61–80 years of age were enrolled in the ImbruVeRCHOP multi-center IIS (EudraCT number 2015-003429-32, ClinicalTrials.gov identifier NCT03129828). Patients received six 21d-cycles of R-CHOP plus ibrutinib (420 mg/d p.o.) and bortezomib (1.3 mg/m^2 s.c. d1 + 8) followed by two subsequent applications of single-agent rituximab. Patients underwent lymphoma and liquid biopsies prior to, acutely under the first treatment cycle and, in case of a residual and reasonably accessible tumor manifestation, once again at interim CT imaging prior to cycle 3.

Results: The study enrolled patients at 12 German and Austrian centers until April 2022. Workup of the multi-omics analyses started at the end of 2022. Based on 34 patients completing all treatment cycles, the median follow-up is 11.5 months and the CT-based overall response rate is 44% (15 CR, 19 PR—with no mandatory PET/CT certainly underestimating metabolic CR). Median 2-year progression-free-survival, the primary endpoint, has not been reached yet. R-CHOP dose adherence was high (91%—compared to 73% in patients over 60 years in the PHOENIX trial), and toxicities—under strongly recommended quadruple prophylaxis (G-CSF, ciprofloxacin, acyclovir, cotrimoxazole)—beyond those expected from R-CHOP were moderate and mostly grade 1 + 2 (71%, compared to 29% grade 3 + 4). No grade 5 toxicities were observed during treatment and within 30 days after end of therapy. First results from whole exome and RNA sequencing analyses are currently being obtained.

Conclusions: The ibrutinib + bortezomib extension of R-CHOP is feasible and effective in this elderly higher-risk all-comer first-line population. Our meeting report will give an updated analysis of treatment outcome, first insights into candidate molecular response signatures, and shed light on potential underlying modes of biological action. With two years of median follow-up, we will be able to compare the cohort with prior study populations (RICOVER-60, REMoDL-B and PHOENIX).

The research was funded by: The ImbruVeRCHOP trial is an investigator-initiated study, which was partly funded by Janssen-Cilag.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Ongoing Trials

Conflicts of interests pertinent to the abstract.

U. Keller

Other remuneration: reports personal fees from Janssen Cilag, outside the submitted work (Advisory board fees, speakers honorary, and travel support)

R. Marks

Consultant or advisory role: participated in an Advisory board with Janssen-Cilag

C. A. Schmitt

Honoraria: receives honoraria for medical advice from Roche and Janssen-Cilag

Research funding: coordinates clinical research (namely the ImbruVeRCHOP trial) partly funded by Janssen-Cilag

312 | PIXANTRONE CONTAINING R-CPOP AS FIRSTLINE TREATMENT IN ELDERLY DLBCL PATIENTS WITH CONGESTIVE HEART FAILURE OR HIGH RISK OF ANTHRACYCLINE INDUCED CARDIOTOXICITY

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Background: R-CHOP remains the standard of care for fit patients with DLBCL up to 80 years. However, anthracyclines as well as liposomal anthracyclines are contraindicated for patients with impaired cardiac function, especially congestive heart failure (CHF). Pixantrone showed reduced cardiotoxicity in vitro compared to standard anthracyclines. Data by Herbrecht et al. (Ann Oncol, 2013, 24:2618) comparing first line R-CHOP with R-CPOP (substituting doxorubicin with pixantrone, 88 mg/m^2) in patients with DLBCL resulted in similar PFS with reduced grade 3 CHF rates in R-CPOP patients.

Methods: In a prospective, explorative, non-randomized, multicenter phase 2 trial two DLBCL patient cohorts (1. with an age >75, 2. with impaired cardiac function/CHF determined by left ventricular ejection fraction (LVEF) >40% and ≤50%) were recruited. In addition to cohort 2, we conducted a retrospective analysis from patients with even lower LVEF or other strict contraindications to anthracyclines, like prior use, in our center. Patients received up to six cycles of R-CPOP followed by additional 2 cycles of rituximab every 21 days.

Results: From 2016 to 2021 we included 51 patients in our analysis (23 and 10 patients in the prospective multicenter trial cohort 1 and 2, respectively; 18 patients in the retrospective analysis). In cohort 1 with a median age of 81.9 years, 2y-PFS and OS of 40% and 47% could be observed. In the combined group of 28 DLBCL patients with an impaired cardiac function the median age was 76 years (range 51–85). 71% had an advanced Ann Arbor stage (III/IV), 71% had an IPI ≥3. The median LVEF was 45% (range 25–63%), 79% patients had a LVEF ≤50%. Median NT-ProBNP was 1814 pg/ml (range: 103–15895). The median number of R-CPOP cycles delivered was 5 (range 1–6). ORR was 82.1%, with 17 patients (60.7%) achieving CR after induction. With a median follow up of 24.7 months, estimated 2y-PFS and OS were 66.5% and 69.2%, respectively. Two patients died during induction (one progression, one by CHF). Concerning serologic parameters for cardiac function, there was no significant change of the median NT-ProBNP from start of induction (654 pg/ml, range 103–1598) to end of treatment (646 pg/ml, range 96–2199) in 15 patients which received at least 4 cycles R-CPOP and achieved a CR.

Conclusion: With this trial we could show feasibility and encouraging efficacy of R-CPOP in elderly DLBCL patients with CHF and/or high

risk of anthracycline induced cardiotoxicity which invites further trials to establish R-CPOP as standard first line treatment in this patient cohort.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chemotherapy, Late Effects in Lymphoma Survivors

Conflicts of interests pertinent to the abstract.

R. Marks
Honoraria: Kite/Gilead, Novartis, Abbvie
Research funding: CTI, Servier

313 | FINAL ANALYSIS OF AUSTRALASIAN LEUKAEMIA & LYMPHOMA GROUP NHL29: A PHASE II STUDY OF IBRUTINIB, RITUXIMAB AND MINI-CHOP IN VERY ELDERLY PATIENTS WITH NEWLY DIAGNOSED DLBCL

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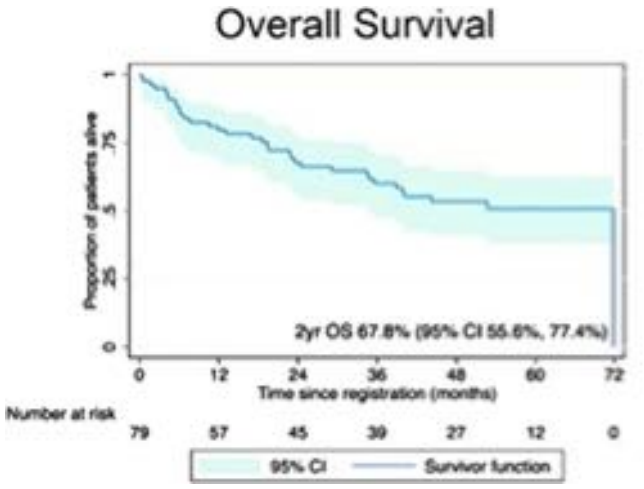
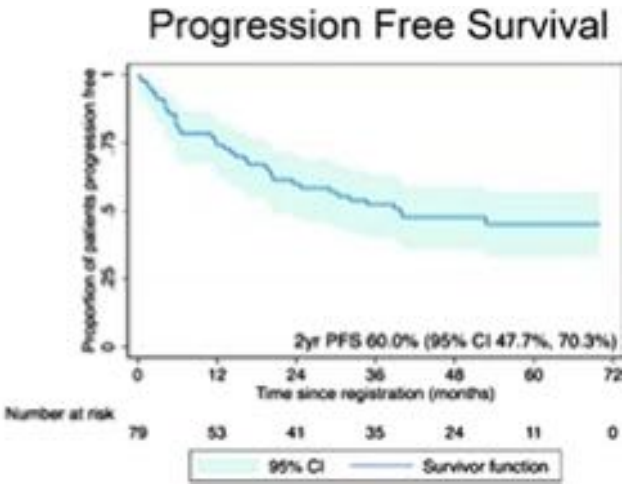
Introduction: The optimal treatment for very elderly patients (pts) with newly diagnosed Diffuse Large B Cell Lymphoma (DLBCL) remains controversial. R-mini-CHOP is an established standard of care in elderly patients with DLBCL, with a 2 yr OS of 59% and PFS of 47% (Peyrade et al., Lancet Oncol 2011). We present our final data from this prospective Phase II study of ibrutinib, rituximab and mini-CHOP in pts ≥75 yrs with newly diagnosed DLBCL.

Methods: Pts received six 21-day cycles of ibrutinib 560 mg daily and R-mini-CHOP (Rituximab 375 mg/m^2, cyclophosphamide 400 mg/m^2, doxorubicin 25 mg/m^2, vincristine 1 mg on day 1 & prednisone 40 mg/m^2 or 100 mg/d × 5) followed by an additional two 21 day cycles of rituximab + ibrutinib (or high dose methotrexate for CNS prophylaxis). Primary endpoints were deliverability and 2 year overall survival (OS). Sample size calculations were made using a one-sample two-sided approach to detect a 15% improvement on the fixed Peyrade reference OS (59%) and PFS (47%) rates.

Results: Eighty pts were recruited from Nov 2015 to Nov 2018. One died prior to receiving treatment and is not included in the analysis. Median age was 82 yrs (75–95); 81% stage III/IV; 54% age adjusted IPI 2–3. With a median follow-up of 35.5 months (m) (0.2, 71.7) (data cut 6 September 2022), there was a non-significant trend towards improvement in 2-year OS of 68% (55.6%, 77.4%) compared to the reference Peyrade cohort of 59% (p = 0.11). Median OS was 72 m (95% CI 35 m to not reached (NR)). Median 2-year PFS of 60.0% (47.7%, 70.3%) was significantly improved compared to the reference cohort of 47% (p = 0.03), with a median PFS of 40 m (95% CI 20.41, NR). Overall response assessment assessed by investigators at the end of treatment was 76% (61/80 pts), with a complete response rate of 70% (56/80 pts). All 6 cycles of R-mini-CHOP were completed in 63/79 pts (80%) and 57/79 pts (71%) completed all 8 cycles of therapy. The median Average Relative Total Dose and Average Relative Dose Intensity for the entire regimen was 97% (IQR 82, 100; 88, 100). 34/79 pts (43%) have died, 17 due to progressive disease and 5 were treatment-related. 67% pts experienced an SAE. Most common AEs were infections and diarrhoea (majority grade 1–2). In the EORTC QLQ-





C30 there was an improvement in functional and symptom scales and on the EQ-5D-5L survey, there was a significant improvement in the median health state classification score and median visual analogue scale thermometer score over time.

Conclusion: The addition of ibrutinib to R-mini-CHOP was deliverable with an improved 2-yr PFS compared to R-mini-CHOP alone. While there was a trend towards improvement in 2-yr OS, our target 15% increase was not achieved in this small sample size. Despite considerable and not unexpected toxicity in this elderly cohort, the QOL and functional improvements in survivors are promising. These data support further study of the addition of BTK inhibitors to R-mini-CHOP in elderly patients with DLBCL.

Encore Abstract - previously submitted to EHA 2023

The research was funded by: Janssen-Cilag Pty Ltd.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies

Conflicts of interests pertinent to the abstract.

E. Verner
Research funding: Janssen-Cilag Pty Ltd.

E. Hawkes
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T. Cochrane
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C. Y. Cheah
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M. K. Gandhi
Research funding: Janssen-Cilag Pty Ltd.

B. E. Butcher
Other remuneration: Janssen Cilag Pty Ltd.

J. Trotman
Research funding: Janssen-Cilag Pty Ltd.

314 | THE TREATMENT OF BURKITT LYMPHOMA WITH THE BERLIN-FRANKFURT-MüNSTER PROTOCOL WITH RITUXIMAB AND AUTOLOGOUS TRANSPLANTATION

A. Broccoli[1], L. Argnani[1], G. Gugliotta[2], V. Stefoni[1], C. Pellegrini[2], B. Casadei[2], L. Nanni[1], P. E. Coppola[1], E. Sutto[1], M. Cantelli[1], A. Morigi[1], G. Bagnato[1], M. Gentilini[1], S. Zoli[1], M. Carella[1], G. Lolli[1], P. L. Zinzani[1]

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Introduction: Burkitt lymphoma (BL) is a highly aggressive B-cell lymphoma; because of its fast growing rate, it often represents a clinical emergency. Intensive treatment approaches are required for adult BL, although a univocal standard of care still does not exist. The use of frontline autologous transplantation (ASCT) is debated.

Methods: Between 2004 and 2020, 50 HIV-negative BL patients were treated with the Berlin-Frankfurt-Münster (BFM) protocol at our institution. Treatment plan consisted of 3 blocks, A (ifosfamide, vincristine, methotrexate, etoposide, cytarabine), B (vincristine, cyclophosphamide, methotrexate, doxorubicin) and C (vindesine, methotrexate, etoposide, cytarabine), each repeated twice, every 28 days. Patients elder than 60 years did not receive block C, thus blocks A and B were repeated 3 times. Rituximab was given at day 1 each block. Central nervous system (CNS) prophylaxis with intrathecal cytarabine, methotrexate and dexamethasone was given once per each block. Autologous stem cells were harvested after the 4th or 5th cycles, with reinfusion (ASCT) at the end of the 6-blocks after BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning, when feasible.

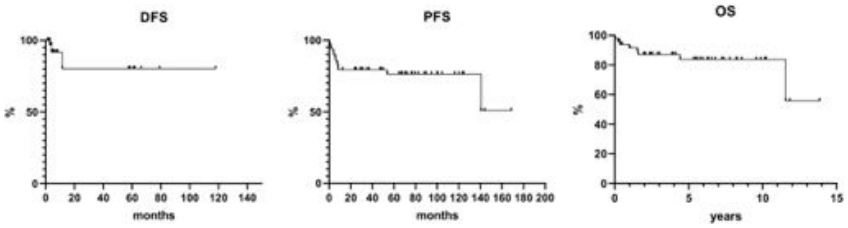
Results: Median age at onset was 38 years (range 16–72); 387 patients were male and 12 female. Stage III-IV disease was observed in 82% of cases; bulky disease occurred in 44% of the patients, with B-symptoms in 38%. Two patients did not receive rituximab because of adverse reaction and early death. Intrathecal prophylaxis was given in 96% of patients. Stem cell harvest was performed in 70% of patients, who all received a subsequent ASCT. The full 6-blocks treatment was completed in 70% of the patients; 8% received 5 cycles and 22% received $\leq$3 cycles. Early treatment interruption occurred because of disease progression (12%), toxicity (8%), death (4%) or other causes (4%).

The overall response rate was 74%, with a complete response rate of 60%. Three patients could not be evaluated because of early progression/death. Ten-year overall survival and progression-free survival were 83.7% and 76.0%, respectively, with both curves exhibiting a plateau. Likewise, 10-year disease-free survival was 80.3%. Eight patients had died because of disease progression (3 patients), infection or sepsis (4 patients) or cardiac arrest (1 patient). Grade 3–4 neutropenia, thrombocytopenia, anemia and mucositis were seen in 96%, 60%, 32% and 24% of patients, respectively. Infections occurred in 60% of patients, with grade 4 and fatal sepsis in 14% and 8% of cases, respectively. Methotrexate-related hepatic and renal toxicity occurred in 16% and 12% of patients, respectively, with complete recovery in all cases.

Conclusions: Intensive treatment according to BFM protocol, with rituximab and ASCT, appears feasible, safe and highly effective in adult patients with BL, as confirmed by long-term survival rates.

Keywords: Chemotherapy, Immunotherapy, Stem Cell Transplant

No conflicts of interests pertinent to the abstract.



315 | QUALITY OF LIFE AND RESPONSE SHIFT EFFECT OF DIFFUSE LARGE B-CELL LYMPHOMA FRENCH PATIENTS INCLUDED IN PROSPECTIVE REAL-LIFE REALYSA COHORT IN THE FIRST YEAR AFTER DIAGNOSIS

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Introduction: Few quality of life (QoL) data are available for diffuse large B-cell lymphoma (DLBCL) patients during the first year of diagnosis. Due to the disease and treatment, patients can adapt to their condition and then change their criteria to assess QoL over time, resulting in a response shift (RS) effect. This study aims to provide QoL level for DLBCL patients at diagnosis and after 1 year, and to assess the occurrence of a RS effect.

Methods: Data from DLBCL patients prospectively included in the French multicentric cohort REALYSA were used. QoL was collected at diagnosis and at 1 year using the EORTC QLQ-C30 and QLQ-NHL-HG29 (non-Hodgkin high-grade lymphoma) questionnaires. The recently validated QLQ-NHL-HG29 specific questionnaire assesses 5 symptomatic dimensions: symptom burden (SB), neuropathy (NP), physical condition/fatigue (PC), emotional impact (EI), worries/fears about health and functioning (WF). A score is generated per dimension on a 0 to 100 scale.

Analyses were done on patients who received standard first-line immunochemotherapy regimen, with QoL questionnaire at diagnosis and at 1 year, and without relapse before 1 year questionnaire completion to avoid bias related to second line therapy.

Scores were reported according to age, gender, performance status (PS) and disease stage. We examined the prevalence of clinically important problems/symptoms on QLQ-C30 scales at patient level using validated thresholds (Giesinger et al. J Clin Epidemiol. 2020).

The potential occurrence of a RS effect was explored using the Oort procedure.

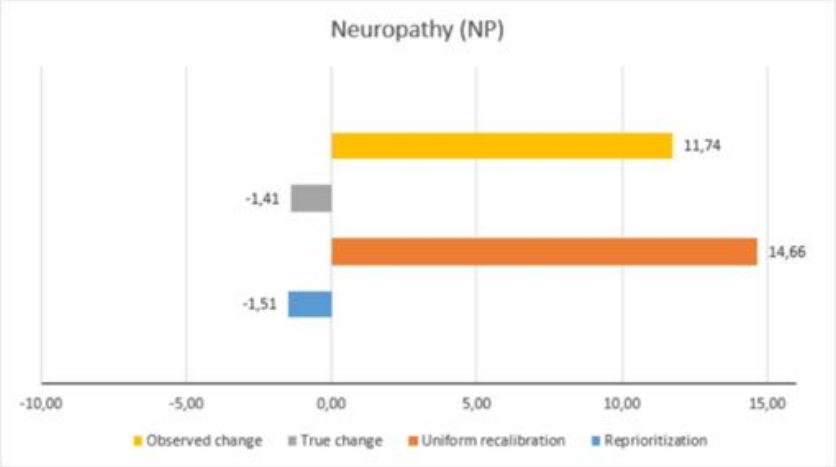
Results: Between Nov 2018 and Dec 2021, 3116 patients were enrolled in REALYSA including 1198 DLBCL. Among 964 patients without relapse at 1 year, 523 had completed questionnaires at baseline and 1 year.

For Global QoL, 57% of patients presented clinically important problems at baseline and 42% at 1 year. Regarding the QLQ-NHL-HG29, the mean PC score was 32 (SD 25) [PS 0–1 vs. 2: 29 (SD 24) vs. 47 (SD 25)] at baseline and 23 (SD 21) [PS 0–1 vs. 2: 22 (SD 20) vs. 27 (SD 22)] at 1 year; the mean NP score was 12 (SD 20) [PS 0–1 vs. 2: 11 (SD 19) vs. 16 (SD 26)] at baseline and 23 (SD 28) [PS 0–1 vs. 2: 23 (SD 27) vs. 24 (SD 29)] at 1 year.

Among the QLQ-NHL-HG29, a RS effect was observed for NP, PC and WF. The highest effect was observed for NP (Figure 1), suggesting that there is no increase in NP level at 1 year compared to baseline (mean change of -1 points (SD 1)). If no RS effect was considered, it would have been concluded that the NP level had increased at 1 year compared to diagnosis (mean change of 12 points (SD 11)).

Conclusions: These results are the first obtained on a real-life DLBCL cohort with specific lymphoma questionnaire and provide reference

Fig 1. Response shift effect occurring for the neuropathy scale with the observed change (without taking into account response shift), the true change (taking into account response shift), and the two components of response shift (recalibration, ie respondent's internal standards of measurement, and reprioritization, ie change in the value of the scale)



data. We showed that a RS effect was observed on several scales. This effect may have important consequences in terms of interpretation of QoL change over time. These results will be useful for clinical practice and design of future studies focused on QoL.

The research was funded by: Institut National du Cancer (INCa, N° 2021-130)

Keyword: Aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

316 | TRENDS IN RELATIVE SURVIVAL OF DIFFUSE LARGE B-CELL LYMPHOMA IN SWEDEN IN THE ERA OF TARGETED AND CELLULAR THERAPIES

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Introduction: Most patients diagnosed with diffuse large B-cell lymphoma (DLBCL) are cured with primary immunochemotherapy, but about one in four experience relapsed/refractory (R/R) disease with worsened outcome. In recent years, new targeted and cellular treatments are becoming available in trials or clinical routine primarily in the R/R setting. However, only a fraction of R/R DLBCL patients are offered these new treatments. We aimed to assess the impact of new treatment options on trends in survival among all patients with DLBCL in Sweden.

Methods: We identified all patients diagnosed with DLBCL in the Swedish Lymphoma Register (SLR) 2007–2021, and followed through 31 December 2022. Patients with primary CNS, mediastinal B-cell or transformed low-grade lymphoma were excluded. SLR holds data on age, sex, performance status, stage and lactate dehydrogenase at diagnosis, enabling calculation of the age-adjusted International Prognostic Index (aaIPI) score. We estimated overall (OS) and relative survival (RS) by calendar year of diagnosis in three-year periods. Two-year RS was estimated with the Pohar-Perme method adjusting for age, sex, diagnosis year and aaIPI. Differences in RS were evaluated using the log-rank type test proposed by Graffeo et al.

Results: Overall, 8,808 patients were diagnosed with DLBCL during the study period (median age 72 years, range 18–105, 57% male). In the full cohort, 2-year OS was 66% among patients diagnosed 2007–2009, increasing to 71% for 2019–2021 ($p_{overall} < 0.001$, Figure 1A). Improvements in 2-year RS were noted across all groups by age, sex and aaIPI score. However, by age, improvements were primarily observed among patients aged 60–69 and 80+ years (Figure 1B). By risk group, improvements were mainly noted among young high-risk patients (aaIPI 2–3, age <70 years) and among older patients (70+ years) independently of aaIPI (Figure 1C). In young high-risk patients, the 2-year RS increased from 71% among patients diagnosed 2007–2009, to 83% among patients diagnosed 2019–2021 ($p_{overall} < 0.001$).

Conclusion: In this nationwide population-based cohort, we note a clear improvement in 2-year survival over calendar time among DLBCL patients across all ages and risk groups. We speculate that the higher survival rate among young high-risk patients may be driven by the introduction of CAR-T in the last few years, whereas the more general and successive improvement among older patients

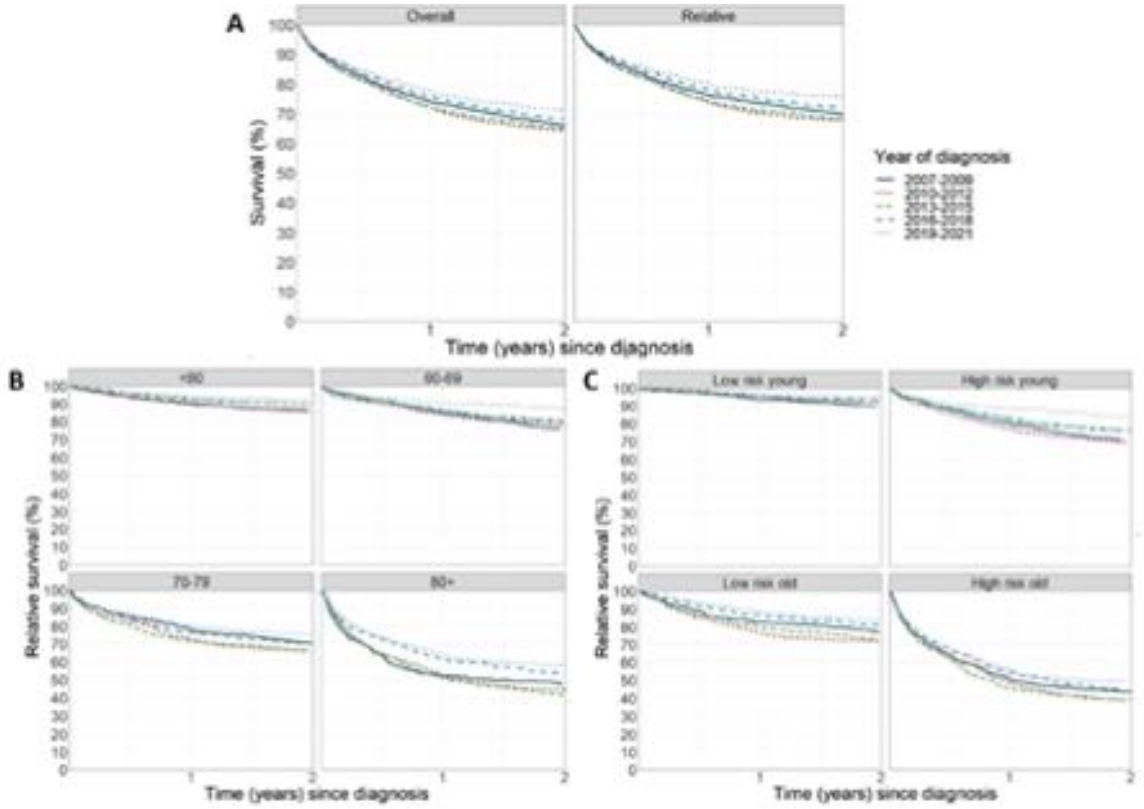

Figure 1. Overall and relative survival among patients diagnosed with diffuse large B-cell lymphoma in Sweden by calendar period 2007-2021 (A), relative survival stratified by age group (<60, 60-69, 70-79 and 80+ years) (B), and relative survival stratified by age-adjusted international prognostic index (aaIPI) score into low-risk young (aaIPI 0-1, age <70 years), high-risk young (aaIPI 2-3, age <70 years), low-risk old (aaIPI 0-1, age 70+ years) and high-risk old (aaIPI 2-3, age 70+ years) patients (C).

could be due to intensified treatment schemes in the primary as well as relapsed settings.

The research was funded by: Swedish Cancer Society

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies

No conflicts of interests pertinent to the abstract.

317 | DEFINING PRIMARY REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) BASED ON SURVIVAL OUTCOMES

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Background: DLBCL that fails to achieve a complete response (CR) or relapses early after standard immunochemotherapy (IC, e.g., R-CHOP or similar) is referred to as primary refractory DLBCL (prDLBCL) and has a poor prognosis. Different definitions of prDLBCL have been used in literature, and it is uncertain which definition of primary refractory correlates most closely with survival outcomes. In this study, we examined the association of time to refractory status with survival outcomes in patients with prDLBCL.

Methods: Adult patients diagnosed with DLBCL between 2015 and 2020 and seen at an academic center included in the lymphoma epidemiology of outcomes (LEO) cohort were included. PrDLBCL was defined as no response or progressive disease (PD) during frontline IC (primary progressive disease, PD), partial response (PR) at end of treatment (EOT PR), or relapse with 12 months after achieving CR at EOT (early relapse). Clinical characteristics, treatment and response data (by Lugano 2014 response criteria), and follow-up data were abstracted from LEO.

Results: Out of 2747 DLBCL patients, 310 (11.3%) had prDLBCL, 147 with PD, 66 with EOT PR, and 97 with early relapse. No significant differences in age, gender, race, number of extranodal sites,

stage, IPI, or cell of origin were found between the 3 groups. The proportion of *MYC* and *BCL2/BCL6* rearrangements or Myc/Bcl2 double expressor was small and not different among the 3 groups. Salvage therapies were mainly platinum based high-dose chemotherapy (57%), MTX-based therapy for CNS relapse (12%), or targeted therapies (9%). Patients with PD had significantly lower CR/PR rates (19.6%/19.6%) to second line therapy compared to patients with EOT PR (32.1%/30.4%) or early relapse (50.6%/19.1%)($P < 0.001$). The 2-year overall survival (OS) rate was 31% for patients with PD, which was significantly worse compared to patients with EOT PR (2-year OS 50%) or early relapse (2-year OS 58%)($P = 0.001$)(Figure 1A). In patients with early relapse, the 2-year OS was not significantly different among those who relapsed within 3 months or between 3 and 6 months but appeared better for those relapsing between 6 and 12 months (Figure 1B). Our findings validate the results in our previously reported Mayo cohort, other than the survival improvement in early relapsing patients between 6 and 12 months in LEO.

Conclusion: Our data suggest that broadly defined primary refractory DLBCL has heterogenous survival outcomes. DLBCL patients with primary progressive disease represent an ultra-high-risk group that has particularly poor survival outcomes with current standard salvage regimens. This subgroup should be clearly defined and novel therapies such CAR T-cell therapy or targeted agents should be studied in this patient population. In contrast, patients who only achieve PR at EOT and those who relapse within 12 months of achieving CR had better OS.

Keyword: Aggressive B-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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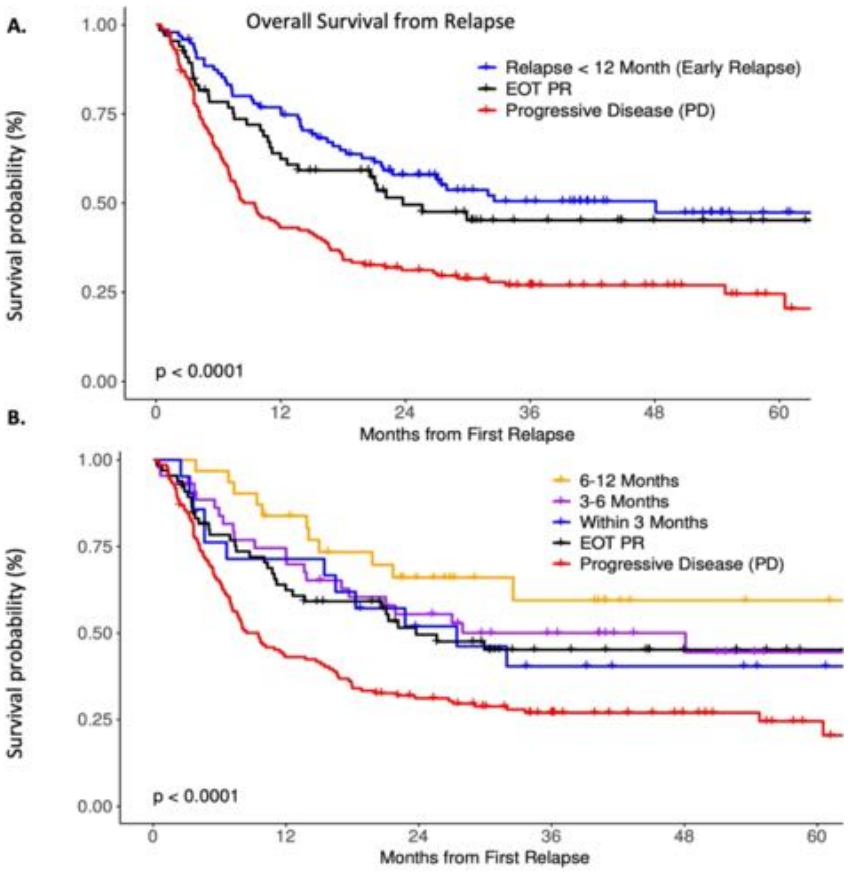

Figure 1. Overall survival from time of relapse by timing of refractory status

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318 | CAUSE OF DEATH AND PROGNOSIS OF PATIENTS (PTS) WITH PRIMARY REFRACTORY DISEASE, AND PROGNOSIS OF PTS REACHING PFS24: DESCRIPTIVE ANALYSIS OF POLARIX

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Introduction: In the past decade, disease progression has been reported as the main cause of death in pts with diffuse large B-cell lymphoma (DLBCL) treated with first-line (1L) R-CHOP. Outcomes in pts with primary refractory disease were poor (Crump et al. 2017). Being alive and disease-free at 24 months (m) was defined as a robust endpoint for disease-related outcomes (Maurer et al. 2014). Since then, newer treatment options, such as Pola-BR, CAR-T, and Tafa-Len, have been introduced in the relapsed/refractory setting. In the POLARIX study (NCT03274492), Pola-R-CHP demonstrated improved PFS versus R-CHOP in 1L DLBCL, with a similar safety profile (Tilly et al. 2022). We report an ad hoc analysis of data from POLARIX to evaluate (1) cause of death and prognosis of pts with primary refractory disease and (2) prognosis of pts who are progression-free at 24 m (PFS24) after 1L treatment.

Methods: Cause of death was classified as progression, adverse event, or other cause. Three pt populations were defined based on response to 1L therapy: pts who were primary refractory (lack of CR or relapse within 12 m after treatment completion), pts who were non-primary refractory (CR and no relapse within 12 m after treatment completion), and pts who reached PFS24 (no PFS events during the 24 m after treatment initiation). Time-to-event data were described using Kaplan–Meier curves and cumulative incidence functions.

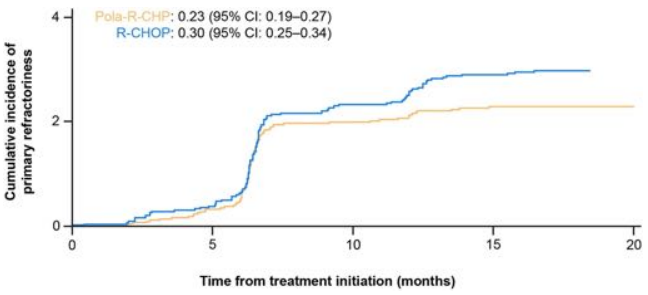
Results: At dasta cutoff (15 June 2022; median follow up: 39.7 m), 14.7% of pts treated with Pola-R-CHP and 15.8% with R-CHOP had died; the main cause of death was disease progression (safety-evaluable population; Table).

Based on a landmark analysis, risk of death was 7.4-fold higher for pts with primary refractory versus non-refractory disease (OS HR: 0.14, 95% CI: 0.07–0.25). The cumulative incidence of refractory disease was 23% (95% CI: 19–27) with Pola-R-CHP and 30% (95% CI: 25–34) with R-CHOP (subdistribution HR: 0.75, 95% CI: 0.58–0.99; Gray's test for equality: $p = 0.0376$; Figure). Mortality as a competing risk was similar between treatment arms.

Overall, 77.0% of pts were progression-free at 24 m with Pola-R-CHP versus 70.4% with R-CHOP (stratified HR: 0.75, 95% CI: 0.57–0.98). As of 18 m after reaching PFS24, 90.3% of pts were progression-free with Pola-R-CHP versus 88.7% with R-CHOP; corresponding OS rates were 98.3% and 98.9%, respectively.

Conclusions: These results confirm disease progression as the main cause of death in pts with DLBCL. Pts who reached PFS24 had excellent outcomes, while pts with primary refractory disease continue to have unmet medical needs. In 1L DLBCL, Pola-R-CHP reduced the risk of refractory disease and increased the likelihood of achieving PFS24 compared with R-CHOP. These results reinforce the value of Pola-R-CHP in this setting.

Cause of death, n (%)	Pola-R-CHP ($n = 435$)	R-CHOP ($n = 438$)
Progression	34 (7.8)	35 (8.0)
Adverse event	13 (3.0)	11 (2.5)
Other cause	17 (3.9)	23 (5.3)



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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies

Conflicts of interests pertinent to the abstract.

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319 | COMPARISON OF CLINICAL OUTCOMES IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA TREATED WITH EPCORITAMAB VERSUS CHEMOIMMUNOTHERAPY

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Introduction: There is currently no clear standard of care for patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) who have failed ≥2 prior lines of therapy (LOTs); although chemoimmunotherapy (CIT) regimens are the most commonly used therapies, outcomes are not optimal. Epcoritamab has demonstrated deep and durable responses among patients with R/R LBCL. We compared the efficacy of epcoritamab with that of CIT in R/R LBCL.
Methods: This indirect treatment comparison utilized individual patient data (IPD) from the EPCORE™ NHL-1 trial (NCT03625037) based on the January 2022 data cut, and longitudinal IPD from

multiple US clinical centers collected in the COTA electronic health records database. The CIT cohort included adult patients diagnosed with LBCL and treated with CIT between January 2010 and March 2022 after failing ≥2 prior LOTs. Inverse probability of treatment weighting (IPTW) was used to create balanced cohorts based on demographic and clinical characteristics and outcomes were compared across these cohorts. Overall response rate (ORR) and complete response (CR) rate were compared using weighted logistic models, and progression-free survival (PFS) and overall survival (OS) were compared using weighted Cox proportional-hazard models.

Results: A total of 179 patients were included in the CIT cohort and compared with all 157 patients treated with epcoritamab for LBCL. Both cohorts were balanced on: absence of prior CAR T exposure (61.1% vs. 62.2%); International Prognostic Index score ≥3 (52.2% vs. 49.2%); primary refractory (61.2% vs. 61.8%); refractory to last LOT (82.8% vs. 85.3%); refractory to most recent anti-CD20–containing regimen (85.4% vs. 83.7%); time since last LOT (6.1 vs. 5.3 mo); sex/male (59.9% vs. 63.5%); and age at diagnosis (62.3 vs. 60.3 years). ORR in the epcoritamab cohort was higher versus the CIT cohort (63.1% vs. 41.8%). CR rate was also higher in the epcoritamab cohort versus the CIT cohort (38.9% vs. 9.4%). Adjusted odds ratio (95% CI) for ORR and CR rate in the epcoritamab versus CIT cohorts was 1.51 (1.20, 1.89; $P = 0.0004$) and 4.12 (2.39, 7.09; $P < 0.0001$), respectively. Median PFS (95% CI) for the epcoritamab cohort (4.4 mo [3.02, 7.85]) was higher versus the CIT cohort (2.6 mo [1.65, 2.84]). Adjusted hazard ratio (HR) (95% CI) for PFS in the epcoritamab versus CIT cohorts was 0.48 (0.37, 0.63; $P < 0.0001$). With the median OS for epcoritamab not reached at the time versus 4.9 mo for CIT, the adjusted HR (95% CI) for OS in the epcoritamab versus CIT cohorts was 0.5 (0.37, 0.69; $P < 0.0001$).

Conclusions: Compared with CIT, epcoritamab significantly increased the likelihood of achieving response and reduced the risk of progression and mortality. These results underscore the therapeutic benefits of epcoritamab in R/R LBCL in the third-line or later setting. Comparative analyses conducted outside of a randomized clinical trial are subject to limitations.

Encore Abstract - previously submitted to EHA 2023

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Immunotherapy

Conflicts of interests pertinent to the abstract.

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320 | NOVEL THERAPIES FOR THE TREATMENT OF RELAPSED-REFRACTORY AGGRESSIVE B-CELL LYMPHOMA INCREASE SURVIVAL. ANALYSIS FROM THE RELINF REGISTRY OF THE GELTAMO GROUP

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Introduction: Several new therapeutic agents have been introduced in recent years for the treatment of relapsed/refractory (r/r) aggressive B cell lymphoma (ABCL) (diffuse large B cell lymphoma [DLBCL] and high-grade B cell lymphomas [HGBCL]), such as new monoclonal antibodies (MA), bispecific antibodies (BA) and CAR-T cell therapy. The objective of our study was to evaluate the frequency of use of these new therapies (NT) in Spain and to analyze their impact on survival.

Methods: This is a multicentre retrospective study performed in 17 centers in Spain, 3 of which are CAR-T cell providers. We identified patients with a histologic diagnosis of ABCL from the RELINF platform. Cases were included from 01/2014 to 12/2022.

Results: From 3270 identified, 2853 patients were included in the analysis. The median age was 68 yrs. (16–104), and 49.5% were female. 2474 (87%) DLBCL, and 334 HGBCL (170 double/triple HIT [DH/TH]).

Seven hundred thirty-eight patients relapsed, 492 (67%) early relapses (ER), and 246 (33%) late relapses (LR). Among ER, 268 (55%) were in patients over 65 y/o and 137 (28%) over 79 y/o. For LT the distribution was 142 (57%) and 72 (28%), respectively. Regarding histologies, early relapses were significantly higher in DH/TH HGL (34%) and T-cell-rich DLBCL (29%) compared to DLBCL (16%) ($p < 0.001$).

From the relapsed patients, 236 patients received NT, with the following distribution: CAR-T ($n = 144$), BA ($n = 68$), polatuzumab (pola)-based ($n = 86$), tafasitamab-lenalidomide (TL) ($n = 10$). 38 patients received NT in 1st relapse, 11 (3%) CAR-T, 15 (4%) pola-based, 5 (1%) TL, and 11 (3%) BA. From 354 patients that received >2 lines of treatment, 130 (37%) received CAR-T cell therapy, 69 (19%) pola-based, 5 (1%) TL, 55 (15%) BA, and 299 (84 %) did not receive NTs.

With a median follow-up or 49 months (mo) (95% CI: 47–51), the median PFS and OS were 54 (95% CI: 48–61) and 82 mo (95% CI: 74–90), respectively. Median OS (mOS) for relapsed patients was 32

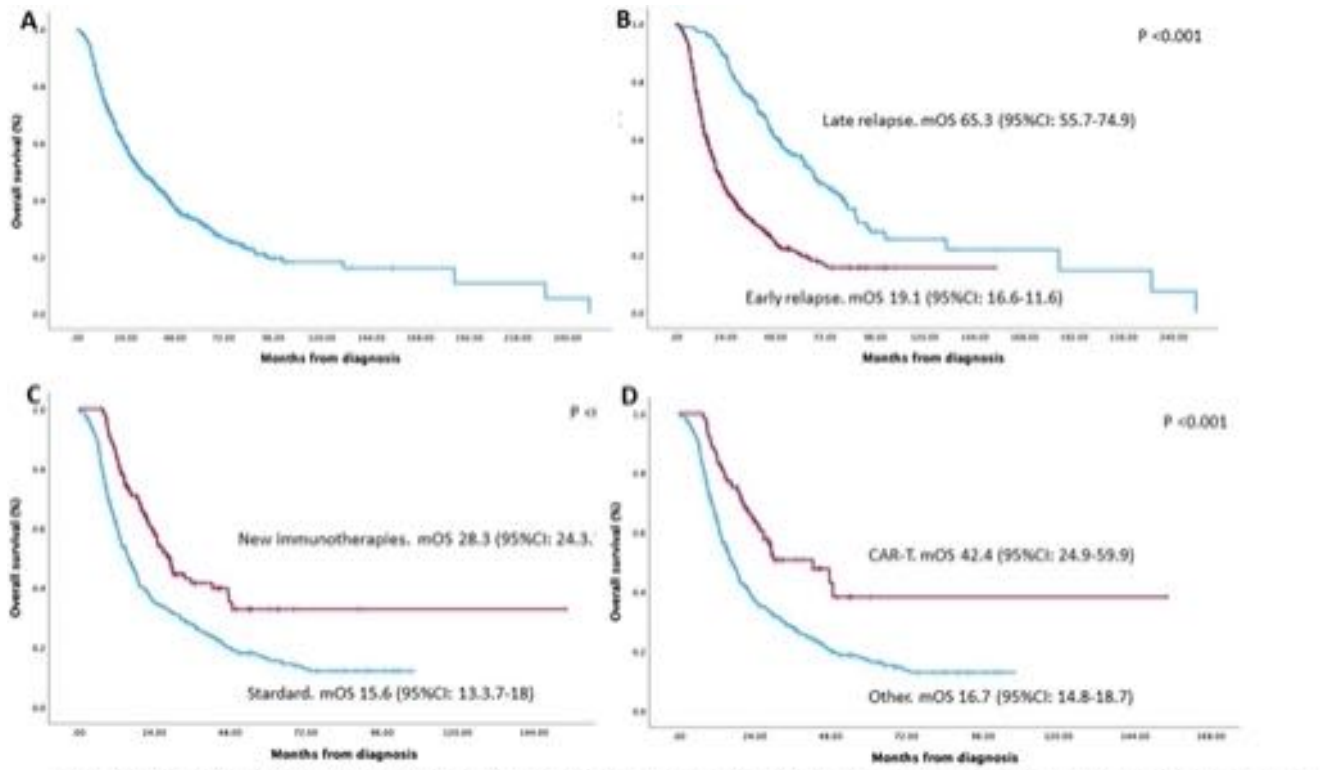

Figure 1. A) Overall survival for the relapsed patients; B) Survival for early and late relapses; C) Survival according to the use of new therapies; D) Survival for early relapses according to CAR-T cell therapy

mo (95% CI: 27–36) (Figure 1A), and for the group of patients with >2 lines was 33 mo (95% CI: 28–39).

Median OS for ER was 19 mo (95% CI: 17–12) versus 65 mo (95% CI: 56–75) for LR ($p < 0.001$) (Figure 1B). mOS for relapsed patients treated with NT was 48 mo (95% CI: 37–58) versus 26 mo (95% CI: 21–30) for the standard treatment ($p < 0.001$) (Figure 1C). Considering only ER, mOS for patients who received CAR-T cell therapy was 42 mo (95% CI: 25–60) versus 17 (95% CI: 15–19) who did not ($p < 0.001$) (Figure 1D).

In multivariate analysis ER [HR 2.91 (IC95%: 2.35–3.6) ($p < 0.001$)], number of total lines [HR 1.4 (IC95%: 1.14–1.71)], age over 65 y/o [HR 1.83 (IC95%: 1.17–2.86) ($p = 0.008$)], age over 75 y/o [HR 2.86 (IC95%: 1.84–4.46) ($p < 0.001$)], use of CAR-T therapy [HR 0.67 (IC95%: 0.47–0.96) ($p = 0.029$)] and NT HR 0.49 (95% CI: 0.38–0.64) impacted on OS.

Conclusions: Our analysis confirms the negative impact of early relapses on the survival of patients with ABCL, which was especially frequent in patients with HGDH. According to our results, the introduction in recent years of NT for the treatment of r/r DLBCL and HGBCL has markedly improved survival.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Immunotherapy

No conflicts of interests pertinent to the abstract.

321 | VENETOCLAX COMBINED WITH R-ICE (VICER) FOR SECOND LINE TREATMENT OF DIFFUSE LARGE B CELL LYMPHOMA REFRACTORY OR RELAPSED AFTER INITIAL CHEMOIMMUNOTHERAPY

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Introduction: Patients (pts) with diffuse large B cell lymphoma (DLBCL) refractory or relapsed (r/r) after initial therapy have poor survival. The overall response (OR) rate to platinum-based second line therapy is approximately 50% with complete response (CR) rate of 30%. Preclinical studies indicate venetoclax (VEN) may sensitize DLBCL to chemotherapy. We conducted a phase 1–2 trial evaluating the combination of VEN with rituximab, ifosfamide, carboplatin and etoposide (VICER).

Methods: Adult, transplant-eligible pts with r/r DLBCL after ≤2 lines of therapy, including anthracycline and rituximab were eligible. Pts received up to 3 cycles of treatment. In phase 1 ($n = 18$), VEN was given on days 1–10 of each cycle. Dose escalation followed a 3 + 3 schema; the MTD of VEN was 800 mg/day (Blood (2018) 132;(Suppl 1): 397). In phase 2, a shorter course VEN was given (days 1–5) to decrease risk of cytopenias. VEN dose was initially 800 mg/day ($n = 29$); the protocol was amended to reduce VEN dose to 400 mg/day ($n = 19$) to evaluate efficacy and hematologic toxicity at lower dose.

Results: 66 pts enrolled. Median age was 59 years (range 27–77). 49 pts (74%) had primary refractory disease or relapsed <12 months after initial therapy. Median number of cycles was 3 (range 1–3); 3 pts discontinued treatment after 1 cycle (disease progression, toxicity, and pt preference, 1 each).

The most frequent grade ≥3 TEAEs were thrombocytopenia (70%), neutropenia (59%) and anemia (47%). Among 174 VICER cycles, there were 23 febrile neutropenia events (13%) in 19 pts; with a lower rate for pts treated with 400 mg of VEN (2/22 vs. 17/41, $p < 0.01$).

64 pts were evaluable (1 pt died prior to response assessment, 1 pt withdrew consent). OR rate was 81%, CR rate was 63%. There were no statistically significant differences in OR and CR rates based on Bcl-2 expression or dose level. Eight pts in CR did not proceed to ASCT (mobilization failure, 2; pt preference, 3, CAR-T consolidation, 3) while 39 pts underwent ASCT (CR, 33; PR, 6). Eight pts had consolidative CAR-T cell therapy (CR, 3; PR, 5).

Median follow up was 26 months (IQR 13–32), 32 (48%) pts had progressive disease. Median progression-free survival (PFS) was 25 months (95% CI: 16–33), with 2-year PFS estimate of 52%. Median PFS was not reached for patients in CR and 16 months for pts in PR. Median OS was 33 months (95% CI 18-NR). 2-year OS estimate was 59%. 7 pts died from non-relapse causes (MDS, 2; sepsis during transplant, 2; sepsis during VICER; COVID 19; and unknown, 1 each).

Conclusions: The combination of VEN and RICE (VICER) achieves high OR rates including CR in a majority of pts with r/r DLBCL, including those with high-risk disease. Toxicities of VEN were dose dependent and manageable at a dose of 400 mg. This chemoimmunotherapy + targeted combination should be evaluated further as second line option for r/r DLBCL pts eligible for ASCT as well as those requiring disease control prior to CAR-T cell therapy.

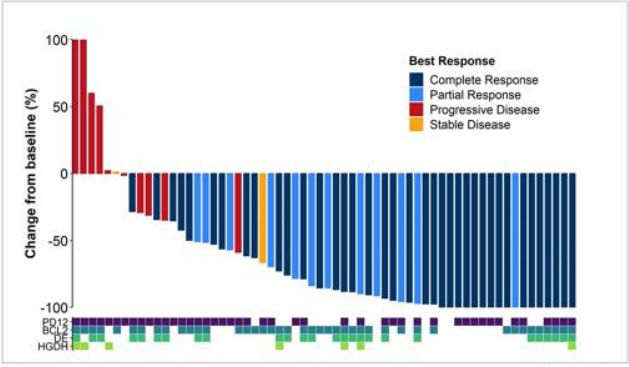

Figure 1. Waterfall plot showing best response to VICER (bars show percentage change from baseline in the product of the sum of the diameters). Colors represent response assessment based on Lugano response criteria. N = 62 patients with measurable disease. Risk factors are shown in the tile marker under the bars. PD12: primary refractory disease or relapse <12 months; BCL2: Bcl-2expression by IHC; DE: double expressor of Myc and Bcl-2; HGDH: High grade lmphoma with MYC and BCL2 and/or BCL6 rearrangements.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies

Conflicts of interests pertinent to the abstract.

P. F. Caimi
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Research funding: Genentech, ADC Therapeutics, Abbvie

322 | COMBINATION OF PIXANTRONE WITH RITUXIMAB, IFOSFAMIDE AND ETOPOSIDE IN RELAPSED/REFRACTORY AGGRESSIVE NON-HODGKIN LYMPHOMA. RESULTS FROM A PHASE II LYSA STUDY (PIVER)

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Introduction: The prognosis of patients with relapsed/refractory aggressive non-hodgkin lymphoma (R/R aNHL) remains poor with conventional immunochemotherapies. Pixantrone is an aza-anthracenedione agent designed to improve the efficacy and reduce the toxicity associated with anthracyclines and anthracenediones. In this context, we conducted a phase II trial combining pixantrone with ifosfamide, etoposide and rituximab (PIVeR) in R/R aNHL. The primary objective was to assess the efficacy measured by the overall metabolic response (OMR) rate after 2 cycles.

Methods: Patients were eligible if they had a histologically proven CD20+ aNHL (de novo diffuse large B-cell lymphoma (DLBCL) or transformed low-grade NHL or grade 3B follicular lymphoma). R/R disease was defined as follows: (1) autologous stem-cell transplantation (ASCT) eligible patients who failed to achieve a CR after at least one salvage therapy, (2) patients in first relapse after ASCT or (3) patients not eligible for ASCT who failed to achieve a CR after at least one prior treatment. First response evaluation by PET-scan was performed after 2 cycles. Responders could then proceed, if eligible, to ASCT or CAR T-Cells therapies after a third optional cycle. Others responding patients were treated with four additional cycles.

The study was designed in order to detect an OMR rate increase from 40% to 55%, assuming an 80% power at a 5% (1-sided) significance level using a two-stage phase II design. A total of 84 evaluable patient was expected.

Results: Between March 2018 and December 2021, 74 patients were enrolled. The median age was 70 y (range 35–87). The majority of the patients had a diagnosis of de novo DLBCL (85.1%) and 43.2% were primary refractory.

After 2 cycles, the OMR rate was 59.5% (90% CI = 49.2%–69.1%) with 18.9% complete metabolic response (CMR). A total of 44 patients completed the treatment. At the end of treatment, the OMR rate was 36.5% with 24.3% CMR. With a median follow-up of 16.6 mo, median PFS and OS were respectively 3.7 mo (95% CI = 2.6–5.6) and 19.2 mo (95% CI = 11.9–36.5). Three patients had an ASCT and 16 were treated with CAR T-Cells. For patients treated with CAR T-Cells, the OMR rate after CAR T-Cells was 31.3% and median OS was not reached.

A total of 53 patients (71.6%) reported at least one AE. The most frequent grade 3–4 AEs were neutropenia (28.4%), thrombocytopenia (18.9%) and anemia (17.6%). Cardiac AEs occurred in 6 patients (11.3%) and 5 (9.4%) had a grade 3–4 heart failure. Serious AEs occurred in 30.9% of the patients, leading to treatment discontinuation in 3 cases.

Conclusion: The primary objective of this trial was met with a high OMR rate of 59.5% after 2 cycles of the PIVeR regimen. The safety profile appeared manageable with few grade 3–4 cardiac AEs. Based on these results, the use of pixantrone in salvage treatment of R/R aNHL should be further evaluated, in particular in the context of bridging therapy before CAR T-Cells.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chemotherapy

No conflicts of interests pertinent to the abstract.

323 | FIVE-YEAR EFFICACY AND SAFETY OF TAFASITAMAB IN PATIENTS WITH RELAPSED OR REFRACTORY DLBCL: FINAL RESULTS FROM THE PHASE II L-MIND STUDY

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Introduction: Tafasitamab, an anti-CD19 immunotherapy that enhances antibody-dependent cellular cytotoxicity and phagocytosis, received accelerated approval in the USA and conditional authorization in Europe in combination with lenalidomide (LEN) for patients (pts) with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) ineligible for autologous stem cell transplant (ASCT) based on the results of the open-label, multicenter, single-arm, Phase II L-MIND study (NCT02399085; Salles G., et al. Lancet Oncol 2020, Duell J., et al. Haematologica 2021). Here, we report the final, 5-year follow-up of L-MIND. Data cut-off was 14 November 2022.

Methods: Pts were aged ≥18 years with ASCT-ineligible R/R DLBCL, 1–3 prior systemic therapies (including a CD20-targeting regimen), and ECOG PS 0–2. Tafasitamab (12 mg/kg) was given for up to 12 cycles in combination with LEN (25 mg), then as monotherapy until disease progression (PD) or unacceptable toxicity. The primary endpoint was best objective response rate (ORR; complete response [CR] or partial response [PR], by independent radiology committee). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and incidence and severity of adverse events (AEs). Exploratory analyses evaluated efficacy endpoints by prior lines of therapy (pLoT).

Results: Of 81 pts enrolled, 80 were treated (full analysis set [FAS]). The ORR (FAS) of 56.2% [95% CI: 44.7–67.3], with CR of 40.0% [29.2–51.6] (n = 32) and PR of 16.2% [8.9–26.2] (n = 13), was generally consistent with the primary and 3-year analyses. Median DoR was not reached (NR) with median follow up (mFU) of 43.7 months [29.9–58.4]. Median PFS was 11.6 months [5.7–45.7] (mFU 36.7 [22.9–59.2]) and median OS was 33.5 months [18.3–NR] (mFU 65.6 [59.9–70.3]). At data cut-off, OS was >60 months in 21 pts (18 with best response of CR, 1 PR, 1 stable disease and 1 PD), including 14 with 1 pLoT and 7 with ≥2 pLoT. Pts with 1 pLoT (n = 40) in the FAS had higher ORR (65%; 50% CR [n = 20] and 15% PR [n = 6]) compared to pts with ≥2 pLoT (n = 40; 47.5%; 30% CR [n = 12] and 17.5% PR [n = 7]). However, median DoR was not reached for both subgroups, indicating similar long-term efficacy for responders. AEs were consistent with previous reports and manageable; incidence declined after transition from combination to tafasitamab monotherapy and again with monotherapy >2 years.

Conclusions: The final, 5-year analysis of L-MIND showed prolonged durable responses with tafasitamab + LEN combination therapy, followed by long-term tafasitamab monotherapy, in pts with R/R DLBCL ineligible for ASCT, with median DoR not reached after 43.7 months mFU. No new safety signals were identified, confirming the tolerability profile observed with earlier data cuts. These long-term data suggest that this immunotherapy may have curative potential that is being explored in further studies.

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Conflicts of interests pertinent to the abstract.

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Honoraria: Roche/Genentech, Janssen, Celgene, Gilead Sciences, Novartis, AbbVie, MorphoSys AG

324 | FIVE-YEAR SUBGROUP ANALYSIS OF TAFASITAMAB + LENALIDOMIDE FROM THE PHASE II L-MIND STUDY IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Background: The Phase II L-MIND study led to accelerated US approval and EU conditional authorization of the CD19-targeted immunotherapy, tafasitamab, + lenalidomide (LEN) followed by tafasitamab monotherapy for patients (pts) with R/R DLBCL ineligible for autologous stem cell transplant (ASCT). Long-term L-MIND data further support the regimen. Here we present exploratory analyses of final 5-year (yr) efficacy in subgroups of interest.

Methods: Pts (≥18 years) with ASCT-ineligible R/R DLBCL, 1–3 prior systemic therapies (incl. ≥1 targeting CD20) and ECOG PS 0–2 received tafasitamab for ≤12 28-day cycles (+ LEN), then alone until disease progression. Primary endpoint was objective response rate (ORR). Secondary endpoints included duration of response (DoR), progression-free survival (PFS) and overall survival (OS). Exploratory subgroup analyses including by International Prognostic Index (IPI) and time to progression after 1L (in pts with only 1 prior line) used Kaplan-Meier estimates of 5-yr endpoints.

Results: As of 14 November 2022 in the full analysis set (FAS; *n* = 80), ORR was 57.5% [95% CI: 45.9–68.5]. Median treatment duration was 9.0 months (mo) [0.5–73.6] and median follow-up (mFU) for OS was 65.6 mo [59.9–70.3]). Median DoR was not reached (mFU: 44.0. mo [29.9–57.0]). Of 18 patients in follow-up for ≥5 years, 9 received tafasitamab until end of study per protocol, 9 discontinued while in remission. RR and 5-yr rates for DoR, PFS and OS showed long-term clinical activity in all pt subgroups (Table).

Conclusion: In this 5-yr subgroup analysis, a long-term clinical benefit with tafasitamab + LEN followed by tafasitamab monotherapy was observed in all subgroups of clinical interest, including pts with poor prognosis risk factors. These data suggest this immunotherapy may have curative potential, which is being explored in further studies.

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Keyword: Aggressive B-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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Table: Subgroup analysis

		N	ORR, % [95% CI]	PFS*	OS*	DoR*
FAS		80	56.2 [44.7–67.3]	36.1 [23.7–48.6] (9)	40.3 [29.0–51.3] (21)	58.7 [39.9–73.4] (5)
Age	≤70 yr	35	60.0 [42.1–76.1]	40.8 [22.4–58.4] (4)	45.9 [27.9–62.2] (9)	63.8 [35.3–82.3] (3)
	>70 yr	45	53.3 [37.9–68.3]	32.6 [16.7–49.5] (5)	35.8 [21.8–50.1] (12)	55.5 [30.2–74.8] (2)
IPI score	0–2	40	65.0 [48.3–79.4]	57.0 [38.2–72.0] (7)	58.0 [40.9–71.8] (17)	80.3 [54.5–92.4] (4)
	3–5	40	47.5 [31.5–63.9]	12.2 [2.7–29.3] (2)	20.3 [8.6–35.4] (4)	29.5 [8.7–54.3] (1)
Bulky disease (≥7.5 cm)	Yes	14	42.9 [17.7–71.1]	27.7 [5.3–57.0] (1)	33.4 [9.3–60.2] (2)	NE (0)
	No	65	60.0 [47.1–72.0]	37.4 [23.6–51.1] (8)	42.3 [29.7–54.3] (19)	58.9 [38.4–74.6] (5)
Time to progression after 1L therapy†	<12 mo‡	20	50.0 [27.2–72.8]	38.8 [17.0–60.2] (3)	44.9 [21.9–65.6] (8)	70.0 [32.9–89.2] (1)
	≥12 mo	20	80.0 [56.3–94.3]	46.2 [19.5–69.4] (4)	57.0 [32.0–75.8] (6)	51.4 [21.2–75.2] (2)

*5-yr rate estimate, % [95% CI] (5-yr n at risk). †Pts with 1 prior line of therapy. ‡Includes primary refractory. NE, not estimable.

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325 | TAFASITAMAB PLUS LENALIDOMIDE VERSUS STANDARD OF CARE AS SECOND-LINE (2L) THERAPY FOR PATIENTS WITH R/R DLBCL: A POST HOC INTERNAL 2L ANALYSIS OF L-MIND (IN 2L-MIND)

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Background: Tafasitamab (tafa) is an anti-CD19 immunotherapy that enhances antibody-dependent cellular cytotoxicity and phagocytosis. L-MIND (NCT02399085), a phase 2 single-arm study, demonstrated efficacy of tafa plus lenalidomide (tafa/len) in autologous stem cell transplantation (ASCT)–ineligible adult patients (pts) with relapsed or refractory (R/R) DLBCL, and led to tafa/len accelerated approval in the US and conditional approval in Canada and Europe. Using the L-MIND 35-month follow-up data (October 30, 2020 data cutoff), the IN 2L-MIND post hoc analysis assessed 2L clinical outcomes in pts evaluated in 2 cohorts: pts treated with tafa/len as 2L therapy during the study (tafa/len cohort) and pts who received 2L systemic therapy prior to entering L-MIND (SOC cohort).
Methods: Methodology for L-MIND as well as independent review committee– and investigator (INV)-assessed outcomes have been previously published (Salles et al., *Lancet Oncol* 2020). The primary endpoint of IN 2L-MIND was INV-assessed progression-free survival (PFS) after 2L treatment (defined as the time from initiation of 2L therapy [index date] until disease progression or death from any cause); secondary endpoints included objective response rate (ORR) and duration of response (DOR). Observable time was defined as time from initial DLBCL diagnosis until initiation of 2L treatment. Primary refractory pts enrolled in L-MIND prior to protocol amendment had disease that relapsed or progressed between 3 and 6 months after completing 1L therapy.
Results: Total of 80 pts (tafa/len, $n = 40$; SOC, $n = 40$) were analyzed. Pt characteristics for the tafa/len and SOC cohorts were as follows: median age at diagnosis was 70 and 67 years, and male pts comprised 52.5% and 55.0%, respectively; 35 pts (87.5%) in each cohort had confirmed DLBCL diagnosis. In the tafa/len and SOC cohorts, median total observable time was 18.96 and 22.60 months, 6 and 9 pts had primary refractory disease, and 20 and 16 pts relapsed within 12 months of 1L therapy, respectively. Based on 35-month data, median

PFS in the IN 2L-MIND analysis was 16.2 months (95% CI, 7.0-not evaluable [NE]) in the tafa/len cohort and 7.2 months (95% CI, 4.1–11.4) in the SOC cohort (Figure), and median DOR was 43.9 months (95% CI, 6.5-NE) and 7.9 months (95% CI, 3.2–13.8), respectively. ORR was 75.0% in the tafa/len cohort and 52.5% in the SOC cohort (CR, 37.5% vs. 25.0%; PR, 37.5% vs. 27.5%, respectively). PFS and ORR results were similar in a sensitivity analysis excluding pts without confirmed DLBCL diagnosis.

Conclusions: From the IN 2L-MIND analysis, pts receiving tafa/len as 2L therapy in L-MIND had longer PFS than pts who received 2L SOC prior to study enrollment. Results of this post hoc internal control analysis support potential benefit of tafa/len as a 2L treatment option for ASCT-ineligible pts with R/R DLBCL, as demonstrated in L-MIND.

The research was funded by: Incyte Corporation

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chemotherapy, Combination Therapies

Conflicts of interests pertinent to the abstract.

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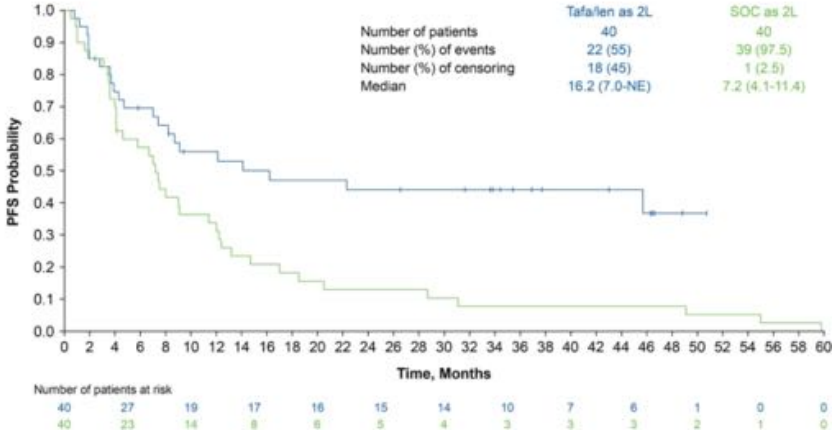
Figure. Progression-free survival (PFS) in patients with relapsed or refractory DLBCL receiving tafasitamab plus lenalidomide (tafa/len) or standard of care (SOC) as 2L therapy



326 | COMBINATION OF ACALABRUTINIB WITH RITUXIMAB AND LENALIDOMIDE IN RELAPSED/REFRACTORY B CELL NON-HODGKIN LYMPHOMA

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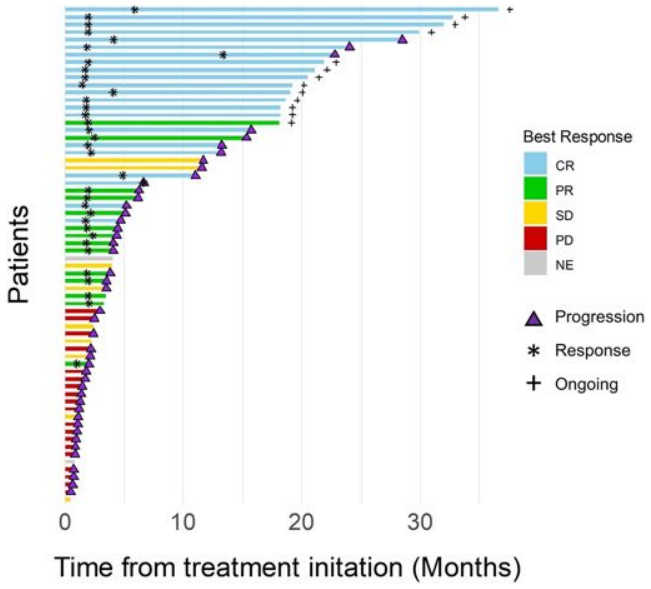
Introduction: Previous studies have shown that combination of acalabrutinib with rituximab and lenalidomide has a synergistic effect in killing NHL cells. We hypothesized that the R2A regimen would show satisfying efficacy for relapsed/refractory B cell NHL and a tolerable toxicity profile.

Methods: In this single-arm, phase 2, multicenter study in Republic of Korea, 66 patients (median age 67.5, range 20–87) with relapsed/refractory B cell NHL were included. Patients who were diagnosed with mantle cell lymphoma were excluded. The patients received the R2A regimen, a cycle of which consisted of 28 days with acalabrutinib 100 mg twice daily from day 1 to day 28, rituximab 375 mg/m^2 on day 1, and lenalidomide 20 mg once daily from day 1 to day 21. The patients received R2A up to 6 cycles, and those who responded and remained in response to R2A received maintenance acalabrutinib 100 mg twice daily up to 1 year. The primary outcome of the study was objective response rate (ORR) by Lugano criteria. The secondary outcome of the study includes complete remission (CR) rate, duration of response (DoR), progression free survival (PFS), and biomarker analysis from next generation sequencing. (ClinicalTrials.gov identifier: NCT04094142)

Results: Among the 66 patients, 47 patients (71.2%) had non-germinal center B cell like (non-GCB) subtype diffuse large B cell lymphoma (DLBCL) and 11 patients (16.7%) had GCB subtype DLBCL. All patients had received at least one previous line of treatment and 34 patients (51.5%) had 2 or more previous lines of treatment. The ORR was 54.5% [36 patients, 95% confidence interval (CI) 42.4–66.4] and CR rate was 33.3% (22 patients, 95% CI: 22.4–45.4). ORR in the non-GCB subtype DLBCL was 61.7% (95% CI: 46.8–74.8), which tended to be higher than the GCB subtype DLBCL which was 36.4% (95% CI: 13.5–66.8, $p = 0.18$). The median DoR was 12.9 months for all responders (95% CI: 4.3—not available) and 24.4 months for CR patients (95% CI: 13.8—not available). Total of 13 patients have not experienced progressive disease at the time of data cutoff (Figure 1). At median follow-up duration of 9.1 months, median PFS was 4.4 months (95% CI: 3.5–11.6). A total of 7 patients were found to have *MYD88* mutation. Among these patients, total of six patients with MYD88 mutation showed objective response to the R2A regimen with three CR patients. A total of 39 patients (59.1%) experienced adverse events (AE) of any grade. The most common AEs were neutropenia (31.8%), skin rash (25.8%), thrombocytopenia (9.1%) and pruritus (9.1%). One patient was off study due to a drug reaction with eosinophilia and systemic symptom syndrome.

Conclusion: R2A regimen showed meaningful efficacy and durable clinical response in patients with relapsed/refractory B cell NHL with tolerable toxicity profiles. Further clinical trial on patients enriched with potential biomarkers is warranted.



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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

327 | INTERIM REPORT FROM A PHASE 2 MULTICENTER STUDY OF ANTI-PD-1 ANTIBODY (PENPULIMAB) PLUS LENALIDOMIDE, RITUXIMAB, GEMCITABINE AND OXALIPLATIN IN RELAPSED/ REFRACTORY DLBCL

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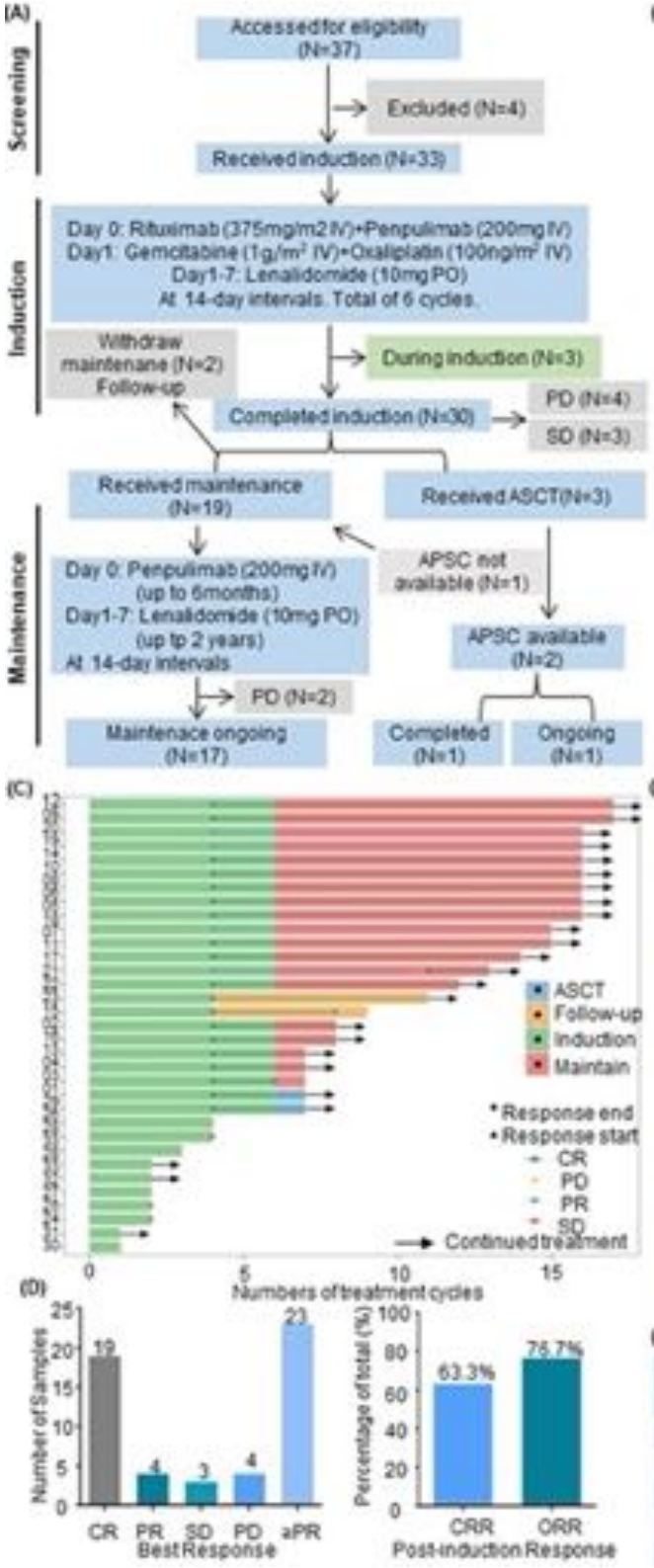
Introduction: Immunodeficiency is a well-known risk factor for diffuse large B cell lymphoma (DLBCL), and microenviromental inteations between programmed death receptor-ligand (PD-L1) expression and effector cells are also involved in DLBCL pathogenesis. Penpulimab is a newly developed humanized high-affinity IgG1 anti-PD-1 monoclonal antibody intended for treatment of various malignancies. This study evaluates the efficacy and safety of penpulimab plus lenalidomide, rituximab, gemcitabine and oxaliplatin (R2-GemOx) in patients with relapsed/refractory (R/R) DLBCL (NCT05186558).



(B) Patients characteristics at entry

Characteristics	N=33
Age, median (range)	**66 (19-80)**
> 60y	**21 (63.6)**
≤ 60y	**12 (36.3)**
Sex, n (%)	
Female	**10 (30.3)**
Male	**23 (69.6)**
Ann Arbor stage	
I-II	**8 (24.2)**
III-IV	**25 (75.7)**
Extranodal involvement, n (%)	
0-1	**21 (63.6)**
>2	**12 (36.3)**
LDH > ULN	
Yes	**14 (42.4)**
No	**19 (57.6)**
ECOG PS, n (%)	
0-1	**30 (90.9)**
2	**3 (9.1)**
IPI score	
0-2	**19 (57.5)**
3-5	**14 (42.4)**
Previous lines of therapy	
1	**29 (87.8)**
≥ 2	**4 (12.2)**

(E) Treatment-related adverse events

Term	All grades	Grades 1-2	Grade 3-4
Hematologica			
Leukopenia	15	15	2
Neutropenia	10	10	2
Thrombocytopenia	5	5	0
Anemia	15	15	0
Non-hematologica			
Thrombocytopenia	7	7	0
Poor appetite	15	14	1
Vomit	15	14	1
Nausea	15	14	1
Rash	3	3	0
Dianheas	5	5	0
Bacterial pneumonia	2	2	1
Pyrexia	2	2	0
Pruritus	1	1	0

(F) Immune-related adverse events

Term	All grades	Grades 1-2	Grade 3-4
Hypothyroidism	9	8	1
Rash	4	3	1
Elevated transminase	3	3	0
Hyperthyroidism	2	2	0
Cardiac toxicity	0	0	0

Methods: All patients are intended to receive 6 cycles of penpulimab plus R2-GemOx (P-R2-GemOx). Afterwards, patients who achieve complete response (CR)/unconfirmed (CRu)/partial response (PR) assessed by positron emission tomography/computedtomography (PET-CT) are eligible for autologous stem cell transplantation (ASCT) will undergo ASCT. Patients who achieve CR/CRu/PR assessed by PET-CT are not eligible for ASCT will directly receive penpulimab (penpulimab for a maximum of 6 months) and lenalidomide (lenalidomide monotherapy for 18 months) as maintenance treatment. Patients who achieve stable disease (SD) or progression disease (PD) assessed by PET-CT will withdraw from this study. The primary endpoint is CR rate (CRR). The second endpoint is 2-years overall survival (OS) and progression-free survival (PFS).

Results: Until March 2023, 33 patients were enrolled, and the details of the enrollment were shown in Figure 1A. Median age was 66y (range 19–80y) and median prior lines of chemotherapy was 1 (range, 1–4); 23 patients (69.7%) were non-GCB subtype and 14 patients (42.4%) were with high international prognostic index (IPI) score of 3–5 at entry (Figure 1B). Twenty-one patients had genotyping (5 with BN2 subtype, 1 with EZB subtype, 2 with MCD subtype, 1 with N1 subtype, 1 with ST2 subtype and 11 patients with other subtype). The duration and depth of response are presented in the siwmmer's plot (Figure 1C). Among the 30 patients who completed the induction therapy, the best overall response rate (ORR) was 76.7% (95% CI, 43.9%–80.1%) with 63.3% CR (19/30) and 13.4% PR (4/30); the primary endpoint was met (Figure 1D). Among the 7 patients with TP53 mutation who completed the induction therapy, 4 patients (57.1%) achieved CR. We also depicted the responses after the 6 cycles of penpulimab plus R2-GemOx in each prespecified sub-group classified with clinical characteristics and gene subtypes, and no significant tests were conducted. There were 128 adverse events (AEs) recorded, of which 94.4% were grade 1 or 2. Leukopenia and neutopenia were the most common grade 3 or 4 AEs (Figure 1E and F).

Conclusion: Preliminary results of this study show that penpulimab plus R2-GemOx demonstrated promising antitumor activity with manageable toxicities as a salvage treatment for R/R DLCBL. Enrollment is ongoing.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chemotherapy, Combination Therapies

No conflicts of interests pertinent to the abstract.

328 | PREDICTORS OF LONG-TERM SURVIVAL OUTCOMES FOLLOWING RECEIPT OF AUTOLOGOUS STEM CELL TRANSPLANTATION FOR PATIENTS WITH DIFFUSE LARGE/HIGH GRADE B CELL LYMPHOMA

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Introduction: Per the CORAL study, response to salvage immunochemotherapy (IC) for patients (pts) diagnosed with relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL) and high grade B cell lymphoma (HGBL) was predicted by time to relapse, International Prognostic Index (IPI) score and prior receipt of rituximab. However, it is unclear if these risk factors or others predict for survival in R/R DLBCL/HGBL pts with chemosensitive disease following salvage IC who receive high dose chemotherapy/autologous stem cell transplantation (HDC/ASCT), an understanding of which may inform future efforts to risk-stratify R/R DLBCL/HGBL pts who are candidates for this therapy.

Methods: Included pts were age ≤75 years who received HDC/ASCT at the University of Pennsylvania between 3/1/13 and 3/1/21. All pts received prior rituximab and anthracycline. Response to salvage IC was determined by PET-CT. Freedom from treatment failure (FFTF) was defined as the interval between receipt of HDC/ASCT and proven/suspected relapse of DLBCL/HGBL or last follow-up (f/u) in remission. Overall survival was defined as the interval between receipt of HDC/ASCT or CART19 and death or last f/u while alive. Data were censored on 3/1/23.

Results: Characteristics at the time of start of salvage IC as well as treatment characteristics for 100 consecutive HDC/ASCT pts are listed in the Table. With a median length of f/u of 62.7 months (mo), the estimated (est) rates of freedom from treatment failure (FFTF) and overall survival (OS) at 60 mo were 57% (95% confidence interval [CI]: 46%–67%) and 71% (95% CI: 60%–80%). On univariate analysis, only history of indolent lymphoma was associated with a lower risk of TF at 60 mo (hazard ratio 0.22, 95% CI: 0.07–0.73, $P = 0.01$). As seen in the Figure, est rates of FFTF at 60 mo did not differ by time to diagnosis of R/R disease, primary refractory disease status, IPI score or response to salvage IC.

Conclusions: Pts with R/R DLBCL/HGBL demonstrating chemosensitive disease by PET-CT following salvage IC and receiving HDC/ASCT may experience prolonged FFTF even if harboring features which may predict for resistance to salvage IC. These findings support additional efforts to risk-stratify pts who are candidates for HDC/ASCT, such as molecular testing, which may predict response to salvage IC.

Keyword: Aggressive B-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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Research funding: Curis, Calithera, Epizyme

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Research funding: Pharmacyclics, Roche, Rafael, FortySeven

J. Svoboda

Consultant or advisory role: SEAGEN, Pharmacyclics, Incyte, Genmab, BMS, Atara, Astra Zeneca, Adaptive, ADCT

Characteristic	*n*
Sex (male/female)	64/36
Time to relapse following initial diagnosis (<12/≥12 months)	54/46
Primary refractory disease (yes/no)	28/72
IPI score (<3/≥3)	76/24
Transformed indolent lymphoma (yes/no)	23/77
Prior lines of therapy (1/≥2)	90/10
Histology (DLBCL/HGBL)	95/5
COO (germinal/non-germinal center)	48/36
MYC rearrangement (yes/no)	8/45
Double hit lymphoma (yes/no)	5/46
First line IC (R-CHOP/intensive)	91/9
Salvage IC (R-ICE/R-DHAP)	89/11
Response to salvage IC (metabolic PR/CR)	40/60
High dose therapy (BCV/BEAM)	80/20
Maintenance therapy (yes/no)	12/88

Research funding: TG, SEAGEN, Pharmacyclics, Merck, Incyte, BMS, Astra Zeneca

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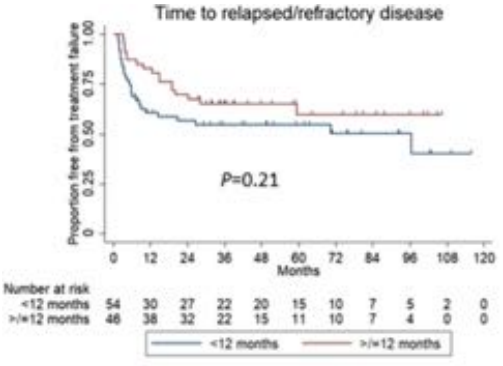

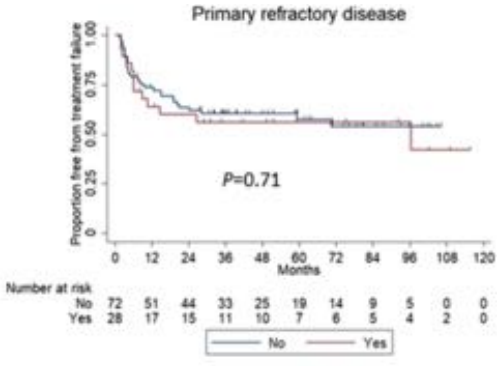

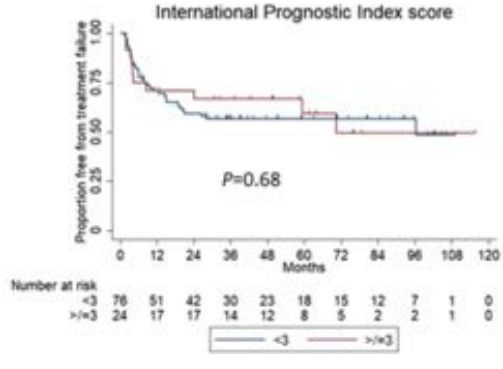

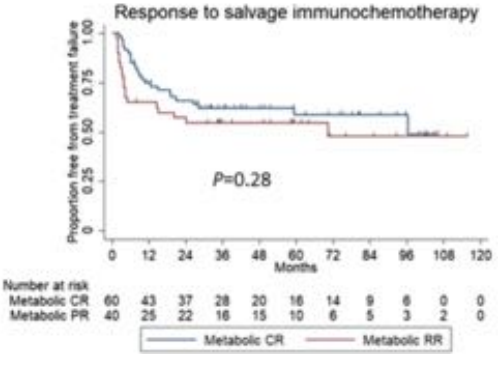

Research funding: Novartis, Tmunity Therapeutics, Janssen, Crispr Therapeutics

E. A. Stadtmauer

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Research funding: Novartis

329 | AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION (AUTOHCT) FOR T-CELL/HISTIOCYTE-RICH LARGE B-CELL LYMPHOMA (THRLBCL): AN EBMT LYMPHOMA WORKING PARTY STUDY

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Introduction: THRLBCL is an orphan entity of large B-cell lymphomas (LBCL). It is dominated by stromal and immune components—especially T-cells and histiocytes—with similarities to nodular lymphocyte-predominant Hodgkin lymphoma. This microenvironment can produce immunomodulating molecules with therapeutic implications since recent reports suggest THRLBCL resistance to chimeric antigen receptor T-cells (CART). As CART-based therapies are challenging the role of autoHCT as second line consolidation for relapsed/refractory LBCL, we aimed to study the efficacy of autoHCT in THRLBCL in comparison with diffuse LBCL not other specified (DLBCL).

Methods: Eligible for this EBMT registry analysis were adult patients who underwent a first autoHCT for THRLBCL between 2016 and 2020. These were compared to adult patients with DLBCL who received a first autoHCT during the same time period. Statistical analysis was descriptive and employed univariate and multivariate comparisons for the impact of baseline characteristics on survival endpoints. A 1:2 matching comparison was performed to better adjust for baseline differences between THRLBCL and DLBCL, respectively.

Results: In total 11,151 patients (10,831 DLBCL, 320 THRLBCL) were identified. THRLBCL patients were younger (52 vs. 58 years), predominantly male (76% vs. 59%), had better performance status (ECOG 0: 97% vs. 92%) and less comorbidity (HCT-CI 0: 78% vs. 68%), and had a longer time from diagnosis to transplant (13 vs. 11 months) than DLBCL patients. In contrast, there were no significant differences regarding the proportion of patients receiving autoHCT during second-line (2L) treatment (87% vs. 82%) and sensitive disease status at autoHCT (95% vs. 92%) between THRLBCL and DLBCL, respectively. On logrank comparisons including all patients, THRLBCL was associated with a better 2-year overall survival (OS; 79% vs. 73%; $p = 0.05$) and progression-free survival (PFS; 72% vs. 61%) than DLBCL. However, when comparing 139 THRLBCL with 278 DLBCL patients matched for age, sex, disease status, performance status (PS), comorbidities (HCT-CI), and time from diagnosis, the outcome differences were no longer significant. Multivariate analyses adjusting for age, gender, disease status, PS, HCT-CI, and time from diagnosis identified higher age, refractory disease, >12 months from diagnosis, and poorer PS as significant risk factors for reduced OS and PFS. Of note, diagnosis THRLBCL was an independent predictor of reduced relapse risk (HR 0.73; $p = 0.04$).

Conclusions: AutoHCT is an effective salvage therapy for relapsed/refractory THRLBCL sensitive to salvage therapy. Superior outcome of autoHCT for THRLBCL compared to DLBCL may be partly explained by more favorable baseline features of the THRLBCL group in terms of age, and PS. The 72% PFS-benchmark shown for autoHCT here has to be considered when deciding about 2L treatment strategies for THRLBCL.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Stem Cell Transplant

Conflicts of interests pertinent to the abstract.

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330 | OUTCOMES OF DIFFUSE LARGE/HIGH GRADE B CELL LYMPHOMA PATIENTS FOLLOWING RECEIPT OF AUTOLOGOUS STEM TRANSPLANTATION OR CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELLS

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Introduction: High dose chemotherapy/autologous stem cell transplantation (ASCT) and CD19-directed chimeric antigen receptor-modified T cells (CART19) are potentially-curative treatment options for patients (pt) diagnosed with relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL) and high grade B cell lymphoma (HGBL). Analysis of a large series of pt receiving ASCT and/or CART19 has not been performed and may reveal differences in treatment failure (TF) which could inform efforts to optimize pt selection for these therapies.

Methods: Included pt were age ≤75 years who received ASCT and/or CART19 for R/R DLBCL/HGBL at the University of Pennsylvania between 3/1/13 and 3/1/21. All ASCT pt demonstrated either partial or complete metabolic response to salvage immunochemotherapy (IC). Freedom from TF (FFTF) was defined as the interval between receipt of cell infusion and proven/suspected relapse of lymphoma (DLBCL/HGBL for ASCT pt or any lymphoma for CART19 pt) or last follow-up (f/u) in remission. Data were censored on 3/1/23.

Results: Characteristics at the time of relapse preceding ASCT or CART19 are listed in the Table. Minimum prior LOT was 1 for ASCT and 2 for CART19 pt. With a median length of f/u of 62.7 months (mo) for ASCT pt and 37.6 mo for CART19 pt, the estimated (est) rate of FFTF at 36 mo were 59% and 24%, respectively. Cox regression analysis of characteristics predictive of TF at 36 mo revealed history of tIL (hazard ratio [HR] 0.23, $P = 0.016$) for ASCT pt, and history of tIL (HR 0.48, $P = 0.004$) as well as IPI score ≥3 (HR 2.7, $P < 0.001$) for CART19 pt. As depicted in the Figure, ASCT pt experienced significantly higher est rates of FFTF at 36 mo if achieving actual FFTF at 3 mo (64% vs. 38%, $P = 0.002$), 6 mo (76% vs. 52%, $P = 0.02$), 12 mo (84% vs. 62%, $P = 0.03$) and 24 mo (95% vs. 78%, $P = 0.03$) post-infusion as compared to CART19 pt. For characteristics which predict for TF at 36 mo (no history of tIL and IPI score ≥3), the incidence was either similar or significantly lower for CART19 versus ASCT pt who achieved actual FFTF at 3, 6, 12 and 24 mo.

Conclusions: Pt with R/R DLBCL/HGBL receiving ASCT following response to salvage IC may experience prolonged est rates of FFTF at 36 mo if achieving actual FFTF at landmark time points as compared to those receiving CART19, which is not explained by the presence of characteristics which predict for TF. These findings support additional efforts to risk-stratify pt who are candidates for ASCT, such as molecular testing, which may predict response to salvage IC.

Keyword: Aggressive B-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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Educational grants: Novartis

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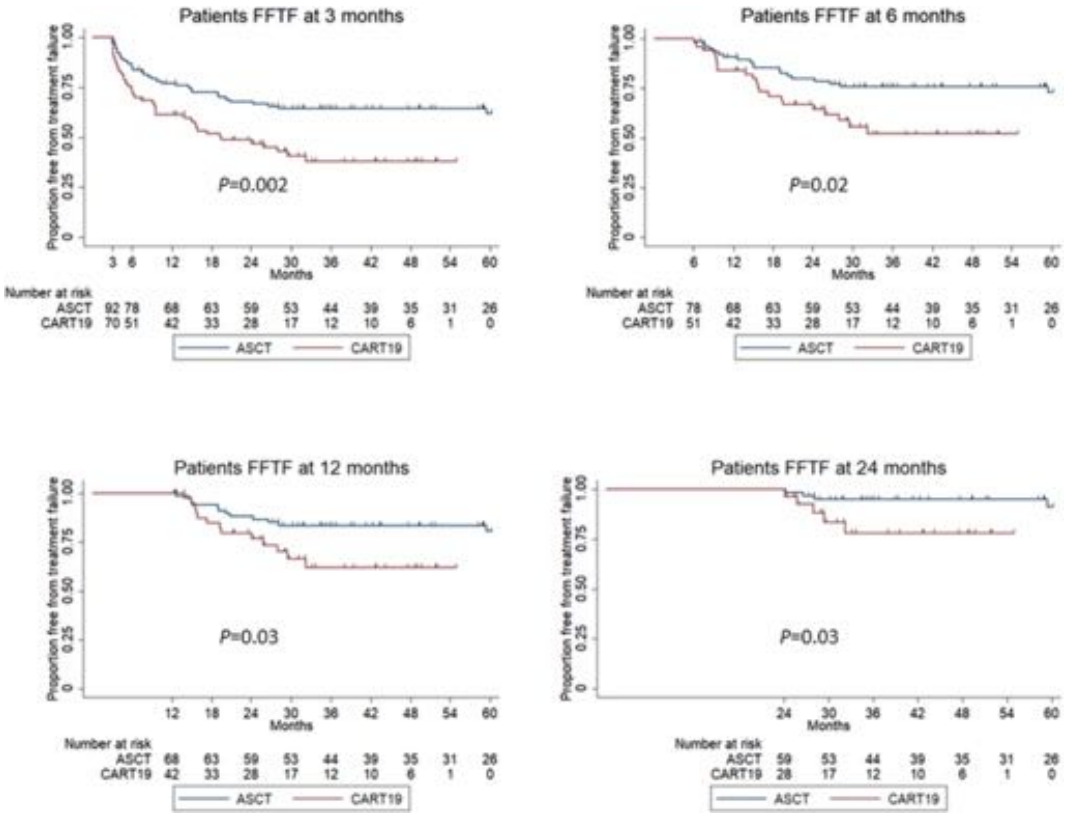
Characteristic	ASCT (*n*=100)	CART19 (*n*=109)
R/R disease <12 months from diagnosis	54	38
Primary refractory disease	28	47
International Prognostic Index (IPI) score ≥3	24	28
Transformed indolent lymphoma (tIL)	23	40
Intensive first-line IC	11	24
GCB cell of origin	48	70
MYC rearrangement	8	29
Double hit lymphoma	5	21
Complete response (CR) prior to cell infusion	60	21
Cellular therapy received after minimum prior lines of therapy (LOT)	90	71



Honoraria: Acrotech, Seagen, Kyowa Kirin

E. A. Chong

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Research funding: Novartis, Tmunity Therapeutics, Janssen, Crispr Therapeutics

E. A. Stadtmauer

Research funding: BMS, Celgene, Abbvie, Sorrento

N. V. Frey

Consultant or advisory role: Sana Biotechnology, Kite Pharma, Syndax Pharmaceuticals

Research funding: Research Funding

D. L. Porter

Consultant or advisory role: Novartis, Kite/Gilead, Incyte, Janssen, Jazz, DeCart, BMS, Bluebird Bio, Angiocrine, Mirror Biologics, Capstan Therapeutics, Instill Bio

Research funding: Novartis

331 | PROGNOSTIC FACTORS FOR CELLULAR THERAPIES - CART AND ALLOGENEIC SCT - IN RELAPSED /REFRACTORY LARGE B CELL LYMPHOMA (LBCL)

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Introduction: Allogeneic stem cell transplantation (alloSCT) was the only curative option for younger patients (pts) with relapsed/ refractory (r/ r) LBCL (DLBCL, tFL, PMBCL). Anti-CD19 CAR T-cells (CART) entered the clinical arena around 5 years ago now being considered standard of care for such patients. As >50% of LBCL pts progress or relapse after CART treatment we were interested in identifying prognostic factors for both modalities and their relative role in the treatment of advanced r/r LBCL.

Methods: Pts registered with the EBMT database from 1/2016 to 5/2021 having received either a first alloSCT or commercially available CART therapy (Yescarta® or Kymriah ®) as ≥3rd therapy of LBCL were analyzed. To correct for imbalances in patient characteristics we did propensity score analyses considering only pts with complete information on IPI including LDH at the time of cell therapy. We performed multivariate analyses in patients with either low- or high-risk r/r LBCL according to LDH level at cell therapy in pts treated with alloSCT or CART.

Results: We identified 515 pts with full information on IPI at cell therapy (212 alloSCT and 303 CART). Patient groups differed significantly in median age, IPI score, and disease status at cell therapy. Median follow up was 46.3 months after alloSCT and 22.1 months after CART treatment. In univariate analysis, type of cell therapy, disease status, and IPI at cell therapy had a significant impact on OS. Amongst IPI risk factors LDH, performance status, and number of extranodal sites had a significant impact on OS, PFS an RI. At 24 months, OS was 41% after allo SCT and 49% after CART. In a propensity score analysis using all IPI factors as covariates, CART was superior to alloSCT in terms of OS (HR 0.62, 95% CI: 45–0.84, $p = 0.0193$) but not PFS, RI or NRM. In multivariate analysis patients with IPI (o-2) low risk at cell therapy show better OS (HR 0.81, 95% CI 0.59–1.1, $p < 0.0001$) and PFS (HR 0.62, CI: 0.46–0.83, $p = 0.00145$), comparable RI and lower NRM (HR 0.21 CI: 0.11–0.42, $p = 0.00001$) with CART compared to allo SCT. In IPI (3–5) high-risk patients, CART showed significantly higher RI (HR 1.45, CI: 1.03–2.04, $p = 0.03549$) but lower NRM (HR 0.21, CI: 0.11–0.42), $p = 0.00001$) compared to allo SCT. OS and PFS did not significantly differ. Refractory disease was an independent adverse prognostic factor for OS (HR 1.74, CI: 1.3–2.33, $p = 0.0002$), PFS (HR 1.61 CI: 1.23–2.1, $p = 0.0006$) and RI (HR 1.79 CI: 1.29–2.49, $p = 0.0006$) but not for NRM. Results at 2 years are given in Table 1.

Conclusion: IPI assessed at cell therapy is of prognostic impact for both CART and allo SCT. Overall, pts given CART for ≥3rd line treatment of DLBCL showed better OS than pts treated with alloSCT. In patients with high intermediate/high IPI results of CART must be improved and allogeneic SCT remains a valuable treatment strategy due to its high anti-lymphoma activity.

Table 1	OS		PFS		RI		NRM	
LOW IPI (N=325)								
Allo SCT	42% (35-50)	p < 0.001	33% (26-41)	p = 0.136	36% (29-43)	p = 0.0056	31% (24-38)	p < 0.001
Car-T	58% (51-67)		43% (36-52)		50% (42-58)		7% (3-11)	
HIGH IPI (N=190)								
Allo SCT	37% (25-55)	p = 0.472	27% (17-45)	p = 0.788	47% (31-61)	p = 0.0931	26% (14-40)	p = 0.0016
Car-T	38% (31-47)		30% (23-38)		62% (54-70)		8% (4-13)	

Keyword: Cellular therapies

Conflicts of interests pertinent to the abstract.

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Consultant or advisory role: Kite, BMS, Novartis, Milteneyi, Roche, Janssen, Jazz, Abbvie

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Honoraria: Allogene
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Educational grants: Allogene, Milteneyi

332 | COMPARISON OF OVERALL SURVIVAL OF LISOCABTAGENE MARALEUCEL (LISO-CEL) VERSUS STANDARD OF CARE (SOC) ADJUSTING FOR CROSSOVER IN SECOND-LINE (2L) R/R LARGE B-CELL LYMPHOMA

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Introduction: TRANSFORM (NCT03575351) is a multinational, phase 3 study that compared efficacy and safety of liso-cel versus SOC, including overall survival (OS) as a key secondary endpoint, as a 2L treatment for patients (pt) with relapsed/refractory (R/R) large B-cell lymphoma who were eligible for transplant. The study design permitted pts treated with 2L SOC to receive liso-cel as third line (3L) treatment if protocol-defined conditions were met and requested by investigators. The intention-to-treat (ITT) analysis of OS for liso-cel versus SOC in TRANSFORM addressed a specific research question that did not account for treatment switching. Additionally, as real-world use of chimeric antigen receptor (CAR) T cell therapies in 3L may be less common compared with TRANSFORM, the ITT analysis may provide a conservative estimate of the treatment effect for liso-cel versus SOC on OS. Here, we conducted a complementary analysis of OS to adjust for crossover and estimate the relative effect of liso-cel versus SOC in the absence of 3L CAR T cell therapy.

Methods: An external control arm based on external data from the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) phase 3 study (NCT00137995) was created using the inverse probability of treatment weighting (IPTW) method. CORAL provided relatively mature survival data and reflects OS in the absence of CAR T cell therapies, which were not available at the time CORAL was conducted. After aligning inclusion/exclusion criteria of the 2 studies, 258 pts from CORAL were retained. To control for confounding, the 2L SOC cohort from CORAL was weighted to match the baseline distributions of prognostic factors and treatment effect modifiers of the liso-cel population in TRANSFORM. Relative efficacy was estimated by fitting a weighted Cox regression model to survival data for the external SOC arm from CORAL and the liso-cel arm from TRANSFORM.

Results: After population adjustment via IPTW, the effective sample size (ESS) for SOC (CORAL) was 43.6% of the unadjusted sample size. The IPTW approach generally reduced imbalances in baseline characteristics between the 2 populations. The adjusted hazard ratio (HR; 95% CI) for liso-cel versus SOC was 0.50 (0.32–0.78), indicating that liso-cel was associated with a survival benefit in comparison with SOC in the absence of treatment switching (Table).

Conclusions: These analyses demonstrated that liso-cel is associated with prolonged OS in comparison with SOC under a scenario of no 3L CAR T cell therapy, and the consideration of external data is a suitable alternative to existing statistical methods to adjust for treatment switching.

Table. Descriptive Statistics for OS Before and After Population Adjustment

Arm	N (ESS)	Number of deaths (%)	Median (95% CI), months	HR (95% CI)
Liso-cel (TRANSFORM)	92	28 (30.4)	NR (29.5–NR)	–
Unadjusted SOC (CORAL)	258	153 (59.3)	17.1 (13.8–32.3)	–
Adjusted SOC (CORAL)	258 (112.5)	67.9 (60.4)	18.7 (13.2–64.0)	–
Unadjusted (liso-cel versus SOC)				0.48 (0.32–0.71)
Adjusted (liso-cel versus SOC)				0.50 (0.32–0.78)

NR, not reached.

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Keyword: Cellular therapies

Conflicts of interests pertinent to the abstract.

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Employment or leadership position: Conor Chandler is employed by Evidera, an independent research company that provides consulting services to life science companies; in his salaried position, he works with a variety of companies and is precluded from receiving payments or honoraria directly from these organizations for services rendered. Evidera received payment from Bristol Myers Squibb for the conduct of this study.

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Other remuneration: Grants from Janssen, AstraZeneca, Abbvie

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Honoraria: Regeneron, AstraZeneca, Janssen, Bristol-Myers Squibb
Research funding: Seattle Genetics, AI Therapeutics, Bristol-Myers Squibb/Celgene

333 | CAR T TREATMENT ACCESS AND OUTCOMES IN PATIENTS WITH LARGE B-CELL LYMPHOMA ACCORDING TO ETHNICITY AND SOCIOECONOMIC DEPRIVATION

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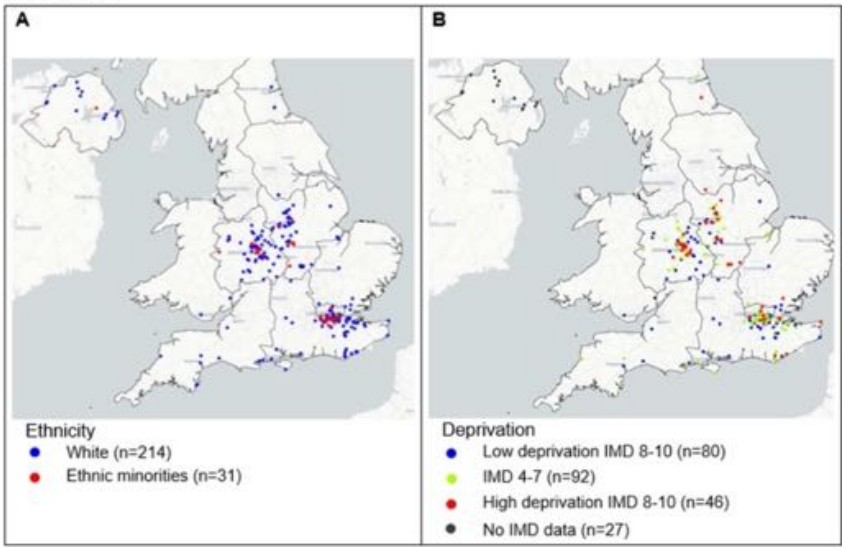
Background: CAR T-cell therapy has revolutionised treatment of relapsed/refractory (r/r) large B-cell lymphoma (LBCL), but it is unclear whether access and clinical benefit is equal for ethnic minorities and deprived communities. We analysed outcomes of LBCL patients approved for CD19 CAR T at 2 UK centres serving a large and diverse population, according to ethnicity and socioeconomic deprivation.

Figure 1: Patients approved for CAR T according to (A) ethnicity and (B) socioeconomic deprivation.



Methods: Consecutive patients with r/r LBCL approved for 3L axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) between January 2019 and December 2022 at King's College Hospital London and University Hospital Birmingham were included. Data on deprivation was obtained through the Index of Multiple Deprivation (IMD) 2020 according to patients' postcode. The IMD ranks between 1 and 10 and includes different factors relating to healthcare inequalities (e.g., income, employment, education). Patients were grouped into high (IMD 1–3) and low deprivation (8–10).

Results: 245 patients were included, 193 approved for axi-cel, 52 for tisa-cel. Deprivation data were available for 218 patients. The product choice did not differ according to ethnic or deprivation groups. Patients' median age was 61y. Ethnic groups were as follows: 214/245 (87%) White, 22 (9%) Asian, 7 (3%) Afro-Caribbean, 2 mixed race. 21% of patients were from areas of high deprivation. 53% of patients travelled >50 km to the CAR T centre, 25% >100 km. 82% patients were infused, with no significant difference according to ethnicity, deprivation or distance to the centre.

Ethnic minority patients came from more deprived areas versus white patients (med. IMD 7 vs. 5 vs. 4 in White, Asian and Afro-Caribbean patients, respectively; $p = 0.04$). Distance to the CAR T centre was longer in white versus ethnic minority patients (med. 59 vs. 18 km, $p = 0.03$). There were more patients with ECOG PS 0 from low deprivation areas (46% vs. 31%; $p = 0.04$), otherwise no significant differences of baseline characteristics, i.e., LDH, bulk, stage, IPI, bridging response, or vein-to-vein time according to ethnicity or deprivation.

No difference was observed in high-grade ICANS, incidence of CRS, ICU requirement, tocilizumab/steroid use or non-relapse mortality with respect to ethnicity or deprivation.

CAR T response and progression-free survival were similar across ethnic and deprivation groups. Among patients who progressed after CAR T, those from areas of low deprivation were more likely to receive further therapies (79% vs. 48%, $p = 0.02$). Patients from low deprivation areas had better overall survival (OS; 1-y OS 61% vs. 45%, $p = 0.04$).

Conclusions: CAR T related outcomes were similar in ethnic minority or deprived patients. However, patients from more deprived areas had inferior overall survival and access to post-CAR T therapies, underscoring healthcare inequalities in these patients. Ethnic minorities appear underrepresented relative to the centre's catchment area population and potential inequity of access to CAR T should be further investigated.

Keywords: Cancer Health Disparities, Cellular therapies, Immunotherapy

No conflicts of interests pertinent to the abstract.

334 | EFFICACY OF SUBCUTANEOUS EPCORITAMAB VERSUS AXI-CEL IN R/R DLBCL CAR T-NAIVE AND CAR T-ELIGIBLE PATIENTS: AN INDIRECT COMPARISON

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Introduction: Epcoritamab, an off-the-shelf, subcutaneous CD3xCD20 T-cell–engaging bispecific antibody that redirects T cells to

eliminate malignant CD20+ B cells, showed single-agent efficacy in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) with a manageable safety profile. The phase 1/2 EPCORE NHL-1 trial (NCT03625037) of epcoritamab in patients with R/R DLBCL who received ≥2 prior lines of systemic therapy showed high complete response (CR) and minimal residual disease rates.

Methods: This matching-adjusted indirect comparison included published data on overall response rate (ORR), CR rate, and overall survival (OS) for axi-cel (ZUMA-1 trial, $N = 101$) and individual patient-level data (IPD) for epcoritamab (EPCORE NHL-1 trial). Patients in EPCORE NHL-1 with prior CAR T therapy were excluded as ZUMA-1 included only patients without prior CAR T therapy. Analyses were adjusted for imbalances in baseline characteristics between IPD from EPCORE NHL-1 and aggregate data from ZUMA-1. Propensity score weights were applied to estimate risk differences for ORR and CR rate; weighted Cox proportional-hazards models were used to estimate OS hazard ratio (HR). Subgroup analyses of CAR T-eligible patients assessed patients with more similar clinical characteristics.

Results: Compared with the ZUMA-1 population, the majority of patients enrolled in EPCORE NHL-1 ($N = 86$) were men (61.6% vs. 23.8%) with a median age of 69.5 y (vs. 58.0 y), and were refractory to ≥2 consecutive lines of therapy (62.8% vs. 53.5%). Among the CAR T-adjusted matched population, response rates were not statistically different in those treated with epcoritamab versus axi-cel (ORR: 73.4% vs. 74.3%, respectively; difference in ORR: −0.8%; $P = 0.927$; CR rate: 48.5% vs. 54.5%; difference in CR rate, −6.0%; $P = 0.583$). In a subgroup of CAR T-naive patients that were CAR T eligible and treated with epcoritamab ($n = 50$), response rates also did not significantly differ from those in patients treated with axi-cel (ORR 72.7% vs. 74.3%, respectively; difference in ORR: −1.6%; $P = 0.873$; CR rate: 47.7% vs. 54.5%; difference in CR rate, −6.8%; $P = 0.576$). In all CAR T-naive patients, OS was not statistically different between those treated with epcoritamab versus axi-cel (HR: 0.695; 95% CI: 0.351, 1.376; $P = 0.297$). Likewise, the CAR T-eligible subpopulation treated with epcoritamab did not have statistically different OS versus axi-cel (HR: 0.708; 95% CI: 0.309, 1.626; $P = 0.416$).

Conclusions: Findings from this cross-study comparison suggest that epcoritamab is a promising, emerging, novel therapy with no statistically significant difference in efficacy versus axi-cel in patients with highly refractory, hard-to-treat DLBCL. Additional analyses are needed to better understand the therapeutic potential of epcoritamab as an off-the shelf, subcutaneously delivered core therapy for these patients.

Encore Abstract - previously submitted to EHA 2023

The research was funded by: Epcoritamab is jointly developed by Genmab A/S and AbbVie Inc.; AbbVie and Genmab are sponsoring this study.

Keyword: Aggressive B-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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335 | EFFICACY AND TOXICITY OF CAR T-CELL THERAPY IN PATIENTS WITH PRIMARY AND SECONDARY CENTRAL NERVOUS SYSTEM LYMPHOMA—AN ANALYSIS OF THE EBMT LYMPHOMA WP AND THE GOCART COALITION

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Introduction: The prognosis of patients (pts) with diffuse large B-cell lymphoma (DLBCL) and involvement of the central nervous system (CNS) remains dismal. Anti-CD19 chimeric antigen receptor T-cells (CART) are considered standard treatment for pts with refractory or relapsed (r/r) DLBCL. Pts with involvement of the CNS were excluded from most CART trials; however, anecdotal reports suggest that CART might be an effective treatment option for such pts. This EBMT registry study aimed at compiling data of a larger cohort of pts with primary (PCNSL) or secondary CNS lymphoma (SCNCL) to better define the role of CART in these settings.

Methods: All centres contributing to the EBMT database were asked for consecutive cases of PCNSL and SCNSL, which had been treated with any type of CART between January 2018 and December 2021. Reported pts were identified in the database and analysed for major patient characteristics, pre-treatment aspects, and major clinical endpoints. Kaplan Meier estimates were used to calculate overall survival (OS) and progression-free survival (PFS), whereas cumulative incidence was used for relapse incidence (RI), and non-relapse mortality (NRM).

Results: 74 pts with PCNSL ($n = 10$) or SCNSL ($n = 64$) and complete information on major endpoints after CART and a median follow-up of 20.2 months [CI: 13.25–23.5] were analysed. Median age was 61.6 years (range 31–80), 31 pts were female. 37 of 57 pts (64.9%) had three or more prior treatment lines, 36.5% of pts had undergone autologous hematopoietic cell transplantation. 14 of 70 pts (20%) had ECOG ≥2. Disease-status at CART was complete (CR) or partial remission (PR) for 31.5% (6.8% and 24.7%, respectively) of pts, 68.5% of pts were in relapse, refractory, or had progressive disease. For one patient information on disease status was missing. 40 pts received axicabtagene ciloleucel (Yescarta®), 34 pts were treated with tisagenlecleucel (Kymriah®). OS- and PFS-rates at 12 months were 51.1% [CI: 40.2–64.8] and 33.7% [CI: 24.3–46.7] for the whole cohort. RI at 12 months was 59.4% [CI: 46.9–69.8]. NRM was 7% [CI: 2.5–14.5]. OS and PFS for pts in CR/PR were 53.0% [CI: 35.5–79.3] and 42.1% [CI: 25.9–68.7]. For the refractory cohort OS and PFS were 51.7% [CI: 38.7–69.0] and 30.6% [CI: 19.9–46.9], respectively.

Conclusion: With a 51% OS-rate at 12 months CART seem to be a very effective therapeutic option in heavily pre-treated r/r PCNSL or SCNSL, particularly for pts being refractory to prior therapy. These results compare favourably with those of conventional treatment (including a minority of pts treated with autoSCT) in SCNSL with a median overall survival of 3.5 months (Schmitz et al., 2016) and 12-months OS-rate of 20% (Thieblemont et al., 2023). Pts with CNS involvement and r/r LBCL should be considered for treatment with CART.

The research was funded by: Lymphoma Working Party of the EBMT GoCART coalition

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies

Conflicts of interests pertinent to the abstract.

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Other remuneration: Speaker's bureau: Takeda, Non-profit organisations: Presidency of the GETH-TC, Presidency of the EBMT

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Honoraria: Allogene

Research funding: Astra Zeneca, Janssen, Roche
Educational grants: Allogene, Miltenyi

B. Glaß

Honoraria: Novartis, JAZZ, Gilead, BMS, Roche, Abbvie, Miltenyi
Research funding: Riemser, Roche

336 | TREATMENT WITH ANTI CD19 CAR-T CELLS IS SAFE AND EFFECTIVE IN PATIENTS WITH RELAPSED REFRACTORY LARGE B-CELL LYMPHOMA WITH ACTIVE CENTRAL NERVOUS SYSTEM INVOLVEMENT

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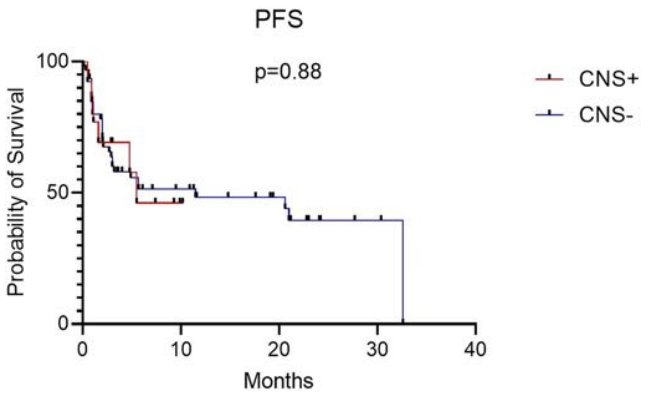
Introduction: Central nervous system (CNS) involvement in patients with refractory or relapsed large B-cell lymphoma (LBCL) is associated with an extremely poor prognosis. Autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy is an approved treatment for patients with refractory or relapsed (R/R) LBCL that has changed the prognosis of patients with chemoresistant LBCL. However, data regarding efficacy and safety of CART cell treatment in patients with active CNS involvement are limited since they are excluded from most of clinical trials.

Methods: We retrospectively collected data from 75 patients with LBCL, treated with CART cells from January 2020 to January 2023 in Henri Mondor Hospital. We identified 13 patients with active CNS involvement at the time of CAR-T cell treatment decision: 12/13 had abnormal neurological examination, 8/11 had head and/or medullar MRI abnormalities consistent with lymphoma and 9/10 had detectable lymphoma cells in the cerebrospinal fluid. We compared the characteristics of the 13 patients with CNS involvement (CNS+) with 62 patients without evidence of active CNS disease (CNS-). Median age was 69 and 59 years, respectively ($p = 0.05$). CNS+ patients received a median of 2 previous lines of treatment versus 3 for CNS- patients ($p = 0.34$). Performance status prior to CART-cell injection was 2 or more in 9/13 (69%) and 11/62 (18%) $p < 0.001$, respectively. 5/13 (38%) CNS+ patients had high grade B-cell lymphomas versus 11/62 (18%) CNS- ($p = 0.13$). CAR-T-cell was axi-cel in 10/13 (77%) CNS+ patients versus 42/62 (68%) CNS– ($p = 0.74$). It is noteworthy that 7/13 (54%) CNS+ patients had pre-existing low-grade B-cell lymphomas versus 15/62 (24%) CNS- ($p = 0.046$).

Results: The best overall response rate was identical in both groups: 12/13 (92%) in CNS+ patients versus 51/61 (92%) in CNS-, including 11/13 (85%) and 44/61(72%) complete metabolic response. As shown in the figure, median progression free survival and overall survival was 5.5 and 8.4 months, respectively in CNS+ patients versus 11.5 and 21 months in CNS- patients (not significant). Regarding safety, 13/13 (100%) CNS+ patients had a cytokine release syndrome (10 grade 1–2 and 3 grade 3) versus 54/62 (87%) CNS- (49 grade 1–2 and 5 grade 3–4) and 10/13 (77%) experienced ICANS (6 grade 1–2 and 4 grade 3–4) versus 28/62 (45%) CNS- (27 grade 1–2 and 1 grade 3–4) ($p = 0.06$ and 0.02 for grade 3–4). Transfer into an intensive care unit occurred in 4/13 (31%) CNS+ patients versus 9/62 (15%) CNS- ($p = 022$). Median time of hospitalization was 37 days for CNS+ patients versus 20 days for CNS- patients ($p = 0.007$). Six CNS+ patients died from which 5 died of progression and 1 of infection.

Conclusion: Although associated with a higher rate of grade 3–4 ICANS and a prolonged hospitalization, treatment with CAR-T-cells in CNS+ R/R LBCL is associated with manageable toxicity and with a high rate of complete metabolic response and prolonged survival, thus should be considered for these patients.



Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Immunotherapy

Conflicts of interests pertinent to the abstract.

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L. Roulin
Educational grants: Kite gilead, Novartis, Bristol myers squibb

337 | EFFICACY AND SAFETY OF AXICABTAGENE CILOLEUCEL (AXI-CEL) FOR THE TREATMENT OF RELAPSE/REFRACTORY NON-HODGKIN LYMPHOMA: FIRST REAL-WORLD DATA IN CHINESE POPULATION

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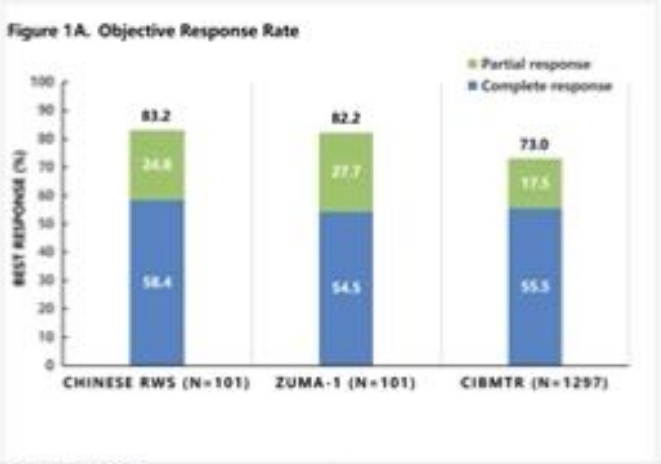
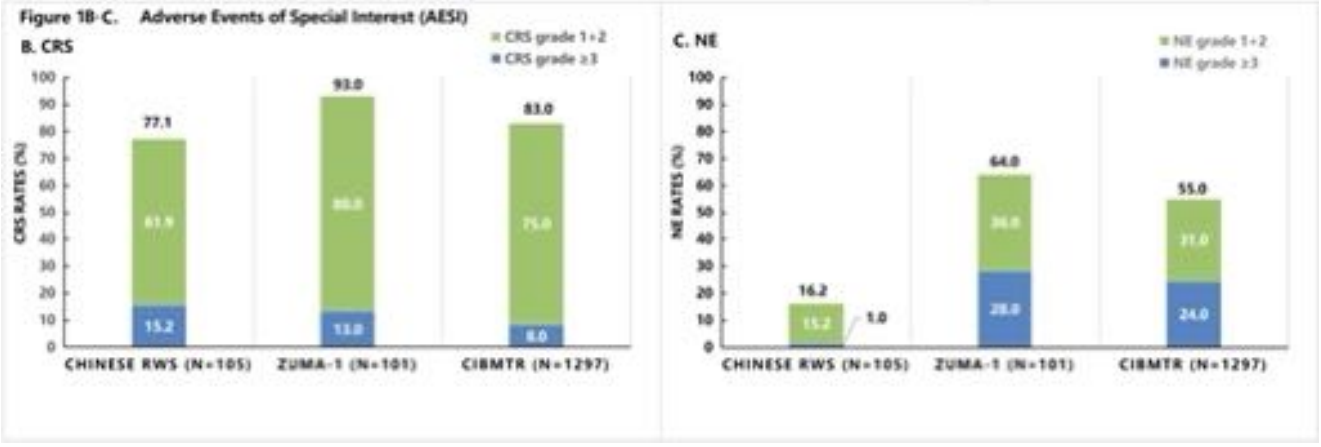
Background: Axi-cel was approved by NMPA to treat R/R LBCL adult patients who had received 2 or more prior treatments in 2021 June.





For better understanding the efficacy and safety of commercial Axi-cel in Chinese R/R NHL patients in real world setting, we conducted this multi-center, non-interventional study (ChiCTR2100047990). The accrual goal is 200 patients, and the primary endpoint is median OS. Here we made an interim analysis and reported clinical outcomes of Chinese patients treated by commercial CAR-T products in real world for the first time.

Methods: R/R NHL patients treated with commercial Axi-cel in 17 authorized treatment centers from 11/2021 to 02/2023 were included. All patients signed written informed consents. We reported best objective response rate (bORR), best complete response (bCR) rate and adverse events.

Results: A total of 101 R/R NHL patients were efficacy-evaluable. The median age was 56.8 years old, and 25 (24.8%) patients were ≥65 years. Fifty-nine patients were male. Baseline characteristics, including 80 (79.2%) with DLBCL, 4 (4.0%) with PMBCL, and 6 (5.9%) with high grade B-cell lymphoma. Forty-two (44.2%) patients had IPI ≥3 and 18 (24.3%) patients ECOG PS were ≥2. The median prior lines of therapy was 2, including 36 (35.6%) patients got ≥3 previous treatments and 10 patients had history of ASCT. Eighty-four patients were resistant to previous therapy, and the primary refractory subgroup reached 47 (46.5%). Bridging therapy was given in 56 (55.4%) patients, while combination therapy in 29 (28.7%) patients.

The median follow-up was 9.2 months. The bORR and bCR was 83.2% (95% CI, 74.4 to 89.9) and 58.4% (95% CI, 48.2 to 68.1) respectively (Figure 1A). Response rates were consistent across key covariates, including disease type, disease stage, IPI score, cell-of-origin subtype, etc. Patients ≥65 years had favorable ORR [92.0% (95% CI, 74.0–99.0)] and CR rate [80.0% (95% CI, 59.3–93.2)]. Median PFS was 12.0 months (95% CI, 7.3 to NA). The median DOR and OS were not reached.

No new safety signal was observed in Chinese patients. The most common ≥ grade 3AE were white-cell count decreased (in 87.6% of the patients), neutropenia (in 82.9%), pyrexia (in 73.3%). Eighty-one patients experienced cytokine release syndrome (CRS) of any grade, and 16 (15.2%) patients occurred grade 3 or higher. Any grade of neurologic events (NE) occurred in 17 (16.2%) patients, and only 1 (1.0%) patients were grade 4. No grade 5 CRS or NE appeared (Figure 1B-C). Fifty-five percent received tocilizumab and 52% received glucocorticoids to manage CRS and/or NE. The median cumulative cortisone-equivalent corticosteroid dose was 2000 mg, which was similar to ZUMA-1 cohort6 and much smaller than ZUMA-1 cohort1+2.

Conclusions: This interim analysis showed global consistent efficacy and lower NE incidence of Axi-cel in Chinese R/R NHL patients.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies

No conflicts of interests pertinent to the abstract.

CLL

338 | IBRUTINIB PLUS FLUDARABINE, CYCLOPHOSPHAMIDE AND RITUXIMAB (IFCR) AS INITIAL TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKEMIA/ SMALL LYMPHOCYTIC LEUKEMIA: A SINGLE-ARM STUDY

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Introduction: BTK inhibitors (BTKi) monotherapy has introduced the concept of continuous treatment in CLL/SLL until disease progression, leading to several concerns like lack of deep remission, increasing risk of toxic effects and substantial cost. Therefore, time-limited treatment strategies as first line treatment of CLL/SLL were comprehensively explored and BTKi combined with chemo-immunotherapy was one of these options which could induce durable responses in young fit patients.

Methods: CLL/SLL patients who were treated with iFCR as initial therapy in the First Affiliated Hospital of Nanjing Medical University were included without any genomic restrictions. Ibrutinib (420 mg daily) was given continuously for 2 years and intravenously rituximab (375 mg/m^2 in day 0 of cycle 1; 500 mg/m^2 in day 0 of cycle 2–6), fludarabine (25 mg/m^2, days 1–3) and cyclophosphamide (250 mg/m^2, days 1–3) were administered every 28-day cycle, up to maximal 6 cycles. Patients who achieved complete remission or complete remission with incomplete recovery (CR/CRi) and bone marrow (BM) undetectable MRD (uMRD) 2 years after iFCR initiation were feasible to discontinue ibrutinib maintenance.

Results: 34 previously untreated, young fit CLL/SLL patients who received iFCR regimen between January 2019 and March 2021 were included in our cohort. The median age was 55 years (IQR: 48–56). IGHV was unmutated in 21 of 34 (61.8%) patients; complex karyotype was present in 11 of 34 (32.4%) patients; TP53 mutation or del (17p) was detected in 6 of 34 (17.6%) patients. CR/CRi rate and BM uMRD rate was 35.3% (12/34) and 41.2% (14/34) after 3 cycles of iFCR and increased to 55.9% (19/34) 2 months after 6 cycles in both patients who received 3 or 4 and 6 cycles of iFCR. The best CR/CRi and BM uMRD rate were both 73.5% (25/34). With the median follow-up of 33 months (range 7–42 months), the 3-year PFS and OS rate was 80.0% and 95.5% respectively. CR/CRi rate and BM uMRD rate was comparable between patients with IGHV mutated and unmutated status without TP53 aberration, while all patients with TP53 aberration failed to achieve sustainable CR/CRi or BM uMRD. Patients who achieved MRD 10^{-6} negative post 3 cycles of iFCR sustained remission and discontinued ibrutinib maintenance. The most common hematological adverse events were neutropenia (25/34, 73.5%) and thrombocytopenia (24/34, 70.6%), grade 3–4 neutropenia and thrombocytopenia occurred in 67.6% (23/34) and 35.3%

(12/34) patients respectively. The most common non-hematological adverse events were nausea (21/34, 61.8%), fatigue (16/34, 47.1%) and vomiting (15/34, 44.1%).

Conclusion: The iFCR regimen could achieve high response rate and uMRD rate as initial treatment for young fit CLL/SLL patient without TP53 aberrations with acceptable tolerability. MRD-guided iFCR courses adjustment in patients who achieved early phase remission could achieved sustainable response and reduced toxicity.

Encore Abstract - previously submitted to regional or national meetings (up to <1'000 attendees)

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Keywords: Chronic Lymphocytic Leukemia (CLL), Combination Therapies

No conflicts of interests pertinent to the abstract.

339 | ZANUBRUTINIB SAFETY/TOLERABILITY PROFILE AND COMPARISON WITH IBRUTINIB PROFILE IN B-CELL MALIGNANCIES: POST HOC ANALYSIS OF A LARGE CLINICAL TRIAL SAFETY DATABASE

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Introduction: Bruton tyrosine kinase inhibitors (BTKi) block B-cell receptor pathway signaling, leading to growth inhibition and cell death in malignant B-cells. First-generation BTKi, ibrutinib (ibr) revolutionized treatment; however, inhibition of off-target kinases such as EGFR, HER2, TEC, and CSK may be associated with toxicities, including diarrhea, rash, bleeding, and atrial fibrillation (Afib), that limit its use. Zanubrutinib (zanu), a potent and selective next-generation BTKi, maximizes BTK occupancy and minimizes off-target effects. Here, we characterized the overall safety/tolerability of zanu and compared it with ibr in patients (pts) with B-cell malignancies using the zanu clinical safety database.

Methods: Safety data were pooled from 10 clinical trials of zanu monotherapy; 2 of the included studies (ASPEN; ALPINE) compared zanu head to head with ibr. Pts with CLL/SLL, MCL, MZL, WM, FL and other B-cell malignancies were included. Treatment-emergent adverse events (TEAEs) were summarized using MedDRA preferred terms; adverse events of special interest (AESI) were defined using pooled terms. Rates of TEAEs, exposure-adjusted incidence rates (EAIRs), and prevalence over time of AESI were assessed.

Results: Pooled analyses included 1550 pts treated with zanu. Median zanu exposure was 28.6 months with 31.2% of pts having treatment exposure of ≥36 mo. Most common nonhematologic AEs were upper respiratory tract infection (29.0%), diarrhea (19.9%), contusion (19.4%), cough (17.2%), and rash (16.2%); grade ≥3 nonhematologic AEs occurring in ≥5% of pts included pneumonia (7.9%) and hypertension (7.4%). The most common serious AE was pneumonia (7.5%). Zanu discontinuation due to AE occurred in 12.3% of pts; AEs leading to dose reduction occurred in 9.6%. Disease progression was the most common cause of death (7.2%); deaths attributed to AEs occurred in 5.6% of pts, and most (3.2%) were due to infections including COVID-19-related AEs.

The most common AESI in the pooled zanu population and in ibr-treated pts from ASPEN and ALPINE (N = 422) were infections and hemorrhage (Table). With the exception of neutropenia, EAIRs were numerically lower for zanu versus ibr, most notably hypertension (0.57 vs. 1.15 person/100 person-months), anemia (0.54 vs. 0.84 person/100 person-months), and atrial fibrillation or flutter (0.15 vs. 0.70 person/100 person-months). Prevalence of zanu AESI tended to remain constant or decrease with longer follow-up.

Conclusions: As BTKi therapy requires continuous treatment, long-term tolerability and low treatment discontinuation rates are needed for successful outcomes. zanu was well tolerated, with generally mild-to-moderate AEs that tended not to lead to treatment discontinuation. Prevalence of AESI generally trended down over time without emergence of new safety signals, supporting zanu as a good option for long-term treatment.

Table. Overall and EAIR for Adverse Events of Special Interest in the Pooled Zanubrutinib or Ibrutinib Populations

	Pooled zanubrutinib population (N=1550)		Pooled ibrutinib population (N=422)	
	n (%)	EAIR (person/100 person-months)	n (%)	EAIR (person/100 person-months)
Infections	1096 (70)	6.18	287 (68)	6.67
Opportunistic infections	*36 (2)*	*0.08*	*13 (3)*	*0.14*
Hemorrhage	785 (51)	3.26	191 (45)	3.44
Major hemorrhage	*81 (5)*	*0.17*	*26 (6)*	*0.28*
Neutropenia	458 (30)	1.32	97 (23)	1.19
Thrombocytopenia	265 (17)	0.64	66 (16)	0.75
Hypertension	235 (15)	0.57	91 (22)	1.15
Anemia	236 (15)	0.54	2 (17)	0.84
Secondary primary malignancies	228 (15)	0.53	49 (12)	0.55
Skin cancers	*136 (9)*	*0.31*	*34 (8)*	*0.38*
Atrial fibrillation/flutter	72 (5)	0.15	62 (15)	0.70

EAIR, exposure-adjusted incidence rate.

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Conflicts of interests pertinent to the abstract.

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340 | IBRUTINIB (IBR) DOSE MODIFICATION FOR MANAGEMENT OF EARLY CARDIAC ADVERSE EVENTS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: POOLED ANALYSIS OF 7 CLINICAL TRIALS

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Introduction: Sustained progression-free survival (PFS) has been demonstrated with continuous Ibr-based therapy and with time-limited treatment (tx) with the Ibr + venetoclax (Ven) combination in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). Adverse events (AEs), including cardiac AEs, have been observed with all BTK inhibitors; for Ibr, they are more frequent in the first year of tx. Active management of AEs with dose reductions may facilitate continuation of Ibr tx and optimize outcomes.

Methods: Pooled data from 1210 evaluable patients from the primary analyses of 7 clinical studies evaluating continuous single-agent Ibr (PCYC-1102 [n = 48]; PCYC-1112 [n = 195]; RESONATE-2 [n = 136]), continuous Ibr-based combination therapy (iLLUMINATE [n = 113]; HELIOS [n = 289]), or time-limited tx with Ibr + Ven (CAPTIVATE [n = 323]; GLOW [n = 106]) were analyzed to evaluate incidence of early cardiac AEs and outcomes of subsequent Ibr dose reductions (for any AE), both occurring within 12 months of Ibr-based tx initiation in patients with CLL/SLL. Cardiac AEs were identified using terms under the system organ class for cardiac disorders. AE recurrence (same or worse grade) was evaluated by preferred term and measured up to 30 days after last dose of Ibr or start of next-line therapy, whichever occurred first.

Results: 212 patients had a cardiac AE; the majority were grade 1–2, with only 72 patients having a grade 3–4 cardiac AE. Of those, 52 (25%), 75 (35%), and 85 (40%) patients received single-agent Ibr, Ibr + anti-CD20, and Ibr + Ven, respectively. In total, 17/212 (8%) patients had dose reductions of Ibr (to 280 mg, n = 8; to 140 mg, n = 9); only 4 patients had a dose reduction specifically following a cardiac AE. Among these 17 patients, 3 (18%) received single-agent Ibr, 5 (29%) received Ibr + anti-CD20, and 9 (53%) received Ibr + Ven. Eight of 9 patients (89%) who received Ibr + Ven and had a dose reduction went on to complete tx. Patients with cardiac AEs with

versus without dose reductions tended to be older (≥75 y: 29% vs. 19%), were less heavily pretreated (≥1 prior line of tx: 12% vs. 41%), had less bulky disease (29% vs. 42%), and had fewer cytogenetic abnormalities (del[17p]: 6% vs. 12%; del[11q]: 12% vs. 26%; mutated *TP53*: 0% vs. 9%; Table). Median follow-up was 21.8 and 16.0 months for patients with and without dose reductions, respectively. No patient with a dose reduction had recurrence of the same cardiac AE at the same or worse severity, both overall and as a serious AE (vs 22% and 11% in patients without dose reduction, respectively). No patient died due to recurrence of the same cardiac AE, regardless of dose reduction. PFS was not negatively impacted by dose reduction ($n = 17$; median PFS not reached, 24-month PFS: 94%).

Conclusions: Dose reduction following early cardiac AEs may enable patients to continue benefiting from Ibr tx while mitigating risks for recurrence or worsening of cardiac AEs.

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Baseline characteristics	Pts with grade 1-4 cardiac AEs occurring ≤12 mo of Ibr initiation		
	With dose reductions due to any AE (n=17)	Without dose reductions due to any AE (n=195)	Total (N=212)
Median age (range), y	67 (48-83)	68 (37-87)	68 (37-87)
Age ≥65 y, n (%)	12 (71)	124 (64)	136 (64)
Age ≥75 y, n (%)	5 (29)	37 (19)	42 (20)
Male, n (%)	9 (53)	133 (68)	142 (67)
ECOG score, n (%)			
0	8 (47)	91 (47)	99 (47)
1	7 (41)	101 (52)	108 (51)
2	2 (12)	3 (1)	5 (2)
Prior lines of therapy, n (%)			
0	15 (88)	116 (59)	131 (62)
1	0	27 (14)	27 (13)
≥2	2 (12)	52 (27)	54 (25)
Bulky disease ≥5 cm, n (%)	5 (29)	81 (42)	86 (41)
Cytogenic status, n/N (%)			
del(17p)	1/17 (6)	21/174 (12)	22/191 (12)
del(11q)	2/17 (12)	46/174 (26)	48/191 (25)
TP53 mutated	0	15/174 (9)	15/191 (8)
Cardiac risk factors at baseline*, n (%)	16 (94)	168 (86)	184 (87)

ECOG, Eastern Cooperative Oncology Group.
*At least 1 of the following at baseline: arrythmias; coronary artery disease; peripheral vascular disease; age ≥65 y; body mass index ≥30; myocardial infarction; ischemic central nervous system vascular conditions; hypertension; cardiac failure; diabetes mellitus; dyslipidemia.

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341 | ZANUBRUTINIB VERSUS IBRUTINIB IN RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LYMPHOMA (R/R CLL/SLL): IMPACT ON HEALTH-RELATED QUALITY OF LIFE

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Introduction: Zanubrutinib (zanu) is a potent and highly selective next-generation Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize off-target effects. In the ALPINE study (NCT03734016), zanu demonstrated superiority to ibrutinib (ibr) in both progression-free survival (PFS) and overall response rate and a more favorable safety profile in R/R CLL/SLL. The purpose of this analysis was to assess health-related quality of life (HRQOL) in patients (pts) treated with zanu and ibr. Results from the data cutoff related to recent PFS analysis (8 Aug 2022) are reported here.
Methods: HRQOL was measured by EORTC QLQ-C30 and EQ-5D-5L at baseline, cycle 1, and every 3rd 28-day cycle until end of treatment. Key pt-reported outcome (PRO) endpoints included global health status (GHS), physical and role functions, fatigue, pain, diarrhea, and nausea/vomiting. Descriptive analysis was conducted on all the scales; a mixed-model repeated-measure analysis using key PRO endpoints at the key clinical cycles of cycles 7 (6 months) and 13 (12 months) was performed. Adjusted completion rates were defined as the number of pts who completed the questionnaires at each cycle divided by number still on treatment. Clinically meaningful was defined as a $\geq$5% mean change difference from baseline.
Results: A total of 652 pts were randomized to receive zanu (n = 327) or ibr (n = 325); baseline characteristics were generally similar between arms, although the zanu arm had fewer males versus ibr arm (65.1% vs. 71.4%). At baseline, GHS, functional, and symptom scales scores were similar between arms. Although more ibr-treated pts discontinued treatment due to adverse events versus zanu (22.2% vs. 15.4%), adjusted PRO completion rates were high at cycles 7 and 13 in both the zanu (89.6% and 94.3%) and ibr arm (87.7% and 92.3%), respectively. By cycle 7, GHS scores were improved with zanu versus ibr and by cycle 13, the difference in GHS scores from baseline was no longer significant (Table). Pts in the zanu arm experienced clinically meaningful improvements in physical and role functioning as well as pain and fatigue at cycles 7 and 13, but the difference between arms was not significant. Although pts in the zanu arm reported lower diarrhea scores, the difference between treatments was not significant. Nausea/vomiting scores were maintained in both arms with no measurable difference. VAS scores showed greater improvement from baseline at both cycle 7 (7.92 vs. 3.44) and cycle 13 (7.75 vs. 3.92) of treatment with zanu versus ibr, respectively.
Conclusions: In ALPINE, pts with R/R CLL/SLL treated with zanu demonstrated improvement versus ibr in the QLQ-C30 GHS/QoL scale at cycle 7. Other endpoints continued to improve, suggesting treatment with zanu positively affected and improved HRQOL over

Table. LS Mean Differences (95% CI) From Baseline Within and Between Treatment Arms

	Cycle 7 (6 months)			Cycle 13 (12 months)		
	Zanubrutinib N=327 Difference within the arm	Ibrutinib N=325 Difference within the arm	Difference between the arms	Zanubrutinib N=327 Difference within the arm	Ibrutinib N=325 Difference within the arm	Difference between the arms
GHS	8.18 (6.25, 10.12)	5.18 (3.20, 7.17)	**3.00 (0.23, 5.77)***	7.28 (5.41, 9.15)	5.93 (3.97, 7.89)	1.34 (-1.37, 4.06)
Physical functioning	6.55 (4.96, 8.15)	4.73 (3.08, 6.38)	1.82 (-0.47, 4.12)	5.46 (3.87, 7.04)	4.31 (2.65, 5.97)	1.15 (-1.15, 3.44)
Role functioning	6.95 (4.85, 9.06)	6.32 (4.14, 8.50)	0.63 (-2.40, 3.66)	6.81 (4.61, 9.02)	5.01 (2.69, 7.33)	1.80 (-1.40, 5.00)
Fatigue†	-12.54 (-14.47, -10.60)	-10.63 (-12.63, -8.62)	-1.91 (-4.70, 0.87)	-11.13 (-13.19, -9.08)	-10.78 (-12.93, -8.63)	-0.35 (-3.32, 2.62)
Nausea/vomiting†	-1.21 (-2.03, -0.38)	-0.92 (-1.77, -0.07)	-0.29 (-1.48, 0.89)	-0.92 (-1.94, 0.10)	-0.40 (-1.47, 0.66)	-0.51 (-1.99, 0.96)
Pain†	-5.06 (-7.21, -2.91)	-3.63 (-5.85, -1.42)	-1.43 (-4.51, 1.66)	-5.18 (-7.38, -2.97)	-2.75 (-5.06, -0.44)	-2.43 (-5.62, 0.77)
Diarrhea†	-2.11 (-3.80, -0.42)	-0.52 (-2.27, 1.22)	-1.59 (-4.01, 0.84)	-3.23 (-4.79, -1.66)	-1.38 (-3.03, 0.27)	-1.85 (-4.12, 0.43)

Data cutoff: 08 August 2022.
*Nominal *P* value <0.05.
†Negative values indicate improvement.

time. As expected, given the generally good HRQOL at baseline in both arms, the differences between the arms were small and not significant.

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342 | IBRUTINIB (IBR) FOR TREATMENT OF RELAPSED-REFRACTORY (R/R) CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A MATCHING-ADJUSTED INDIRECT COMPARISON OF 3 RANDOMIZED PHASE 3 TRIALS

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Introduction: Ibr is a standard therapy for CLL with demonstrated efficacy in first-line and R/R settings. Within R/R CLL, single-agent Ibr was evaluated in 3 randomized phase 3 trials: RESONATE (vs. ofatumumab), ALPINE (vs. zanubrutinib), and ELEVATE-RR (vs acalabrutinib in pts with del(11q) or del(17p)). This analysis evaluated outcomes of Bruton's tyrosine kinase inhibitor (BTKi) treatment in pts with R/R CLL by comparing the efficacy of Ibr in RESONATE to ALPINE and ELEVATE-RR using a matching-adjusted indirect comparison analysis.

Methods: Individual patient data (IPD) of Ibr-treated pts from RESONATE (NCT01578707) were separately match-adjusted to Ibr-treated arms of 1) ALPINE (NCT03734016) and 2) ELEVATE-RR (NCT02477696) for key baseline characteristics: age ≥75 y, bulky disease, ≥3 or ≥4 prior treatments, b_2 microglobulin >3.5 mg/L, and del(11q) or del(17p). For comparison with ELEVATE-RR, only pts with del(17p) or del(11q) from RESONATE were included. After matching, adjusted ORR (CR + CRi + nPR + PR) and PFS from RESONATE were compared with published outcomes from ALPINE and ELEVATE-RR; for PFS, IPD for ALPINE and ELEVATE-RR were extracted from published Kaplan-Meier curves. Hazard ratios (HRs) were calculated using a weighted Cox model.

Results: The analysis comprised 785 Ibr-treated pts across RESONATE ($n = 195$), ALPINE ($n = 325$), and ELEVATE-RR ($n = 265$). After omission of pts with missing values and the adjustment procedure, the effective RESONATE sample size was 95 pts (vs ALPINE) and 69 pts (vs ELEVATE-RR). Median follow-up was 36.0 versus 29.6 mo (RESONATE adjusted vs. ALPINE published) and 36.1 versus 40.9 mo (RESONATE adjusted vs. ELEVATE-RR published). 2-y PFS (95% CI) for Ibr-treated pts in RESONATE adjusted sample and ALPINE was 81% (74–90) and 66% (60–71), respectively; median PFS was 40.7 and 34.2 mo, with an HR (95% CI) of 0.57 (0.39–0.84) favoring RESONATE, $P = 0.0048$ (Figure). ORR (95% CI) was 90% (86–94) and 74% (69–79), respectively ($P < 0.0001$). Compared with the ELEVATE-RR Ibr arm, which included more pts with high-risk genetic features than ALPINE, the RESONATE adjusted sample had greater 2-y PFS (79% [69–89] vs. 69% [64–75], not statistically significant). Median PFS was 41.2 vs. 44.1 mo (HR [95% CI] 0.85 [0.55–1.31], $P = 0.46$), respectively; ORR was 89% (83–95) and 80% (75–85) ($P = 0.0381$).

Conclusions: In phase 3 randomized trials in R/R CLL, continuous Ibr was associated with robust PFS and ORR benefits. Ibr outcomes were consistent between RESONATE and ELEVATE-RR; however, significant differences in the performance of Ibr within ALPINE were identified. Indirect comparisons have limitations, since each trial, protocol, and patient profile are unique; however, these results highlight the need for further research on which elements of protocol design, center selection, or treatment delivery may lead to a significant impact on the performance of a given BTKi in clinical trials.

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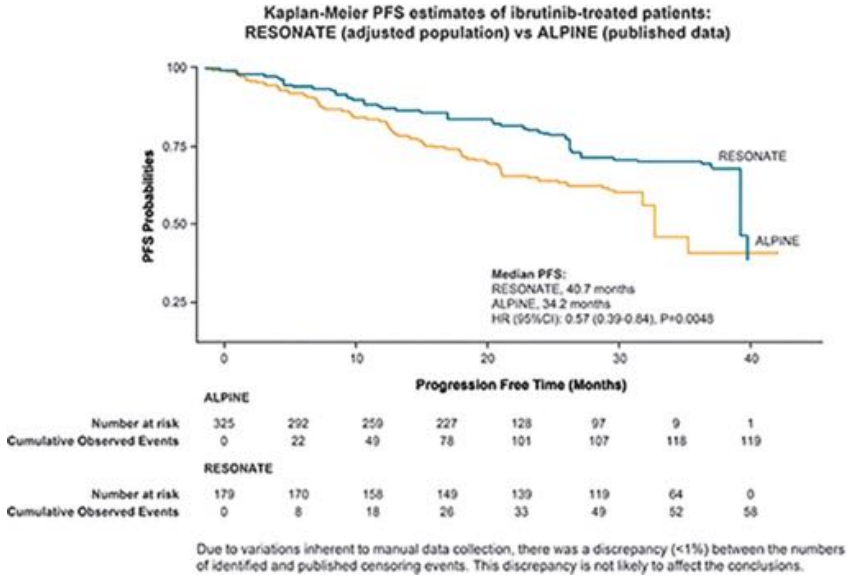

Keywords: Chronic Lymphocytic Leukemia (CLL), Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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343 | INITIAL RESULTS OF A MULTICENTER PHASE 2 STUDY OF VENETOCLAX IN COMBINATION WITH R-CHOP (VR-CHOP) FOR PATIENTS WITH RICHTER SYNDROME

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Introduction: We previously reported promising efficacy for venetoclax (V) plus da-R-EPOCH (VR-EPOCH) for 26 patients (pts) with CLL who developed Richter Syndrome (RS), with a CR rate of 50% and median OS of 19.6 mo.; however, hematologic and infectious complications were common (Davids et al., Blood, 2022). We hypothesized that de-intensifying the chemoimmunotherapy backbone while keeping the venetoclax could potentially preserve efficacy while mitigating the toxicities observed with this approach. Here, we report for the first time on an ongoing study of VR-CHOP in RS.
Methods: This is a single-arm, phase 2, investigator sponsored trial of VR-CHOP for RS (NCT03054896) open at 3 US sites. We treated pts with CLL and biopsy-confirmed DLBCL with R-CHOP for 1 cycle, then after count recovery with accelerated inpatient daily V ramp-up (20/50/100/200/400 mg), then VR-CHOP outpatient for up to 5 additional 21d cycles (V 400 mg qd, d1–10 of each cycle) with mandatory G-CSF support. Responders could then receive daily V 400 mg qd maintenance in 28d cycles or elect to come off study for

alloHCT. Response was by Lugano criteria with PET/CT, toxicity by CTCAE v4.03.

Results: As of 24 Feb 2023, 27 pts have started study treatment. Median age: 72 yrs (range 42–80), 37% had del(17p) or *TP53* mut, 26% had *NOTCH1* mut. Median # prior CLL treatments was 1 (range 1–9), including 44% post-BTKi and 17% post-V; 4 pts (15%) had prior treatment for RS. Median # of VR-CHOP cycles to date in this ongoing study is 4 (range 1–6). ≥Gr 3 heme toxicity included: neutropenia (36%), anemia (32%), thrombocytopenia (40%). Additional ≥Gr 3 toxicities in ≥10% of pts included: febrile neutropenia (32%) and peripheral neuropathy (12%). No TLS occurred with daily V ramp-up after 1 cycle of R-CHOP. Two pts on active treatment have not yet reached the first response eval. In the remaining 25 pts, ORR: 68% (17/25), CR: 48% (12/25). 7 pts have died: 4 due to PD (including 2 prior to starting V) and 3 due to infection ($n = 2$ sepsis, $n = 1$ COVID-19). 8 pts with initial CLL marrow involvement had re-staging marrows, and 88% (7/8) were uMRD for CLL by flow at 10–4. 7 pts in remission electively went to alloHCT. With a median follow-up of 6.1 mo (range 0.1–21.4), median PFS is 7.2 mo (Figure A), median OS is 19.5 mo (Figure B).

Conclusions: Our initial data suggest that VR-CHOP achieves similar efficacy results as our historical results with VR-EPOCH (48% vs. 50% CR, median OS 19.5 vs. 19.6 mo.) with less toxicity (≥Gr 3 neutropenia 36% vs. 65%) and mostly outpatient treatment, though infectious complications still occurred. These early data support the continued exploration of VR-CHOP in this ongoing study.

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Keywords: Chemotherapy, Chronic Lymphocytic Leukemia (CLL), Combination Therapies

Conflicts of interests pertinent to the abstract.

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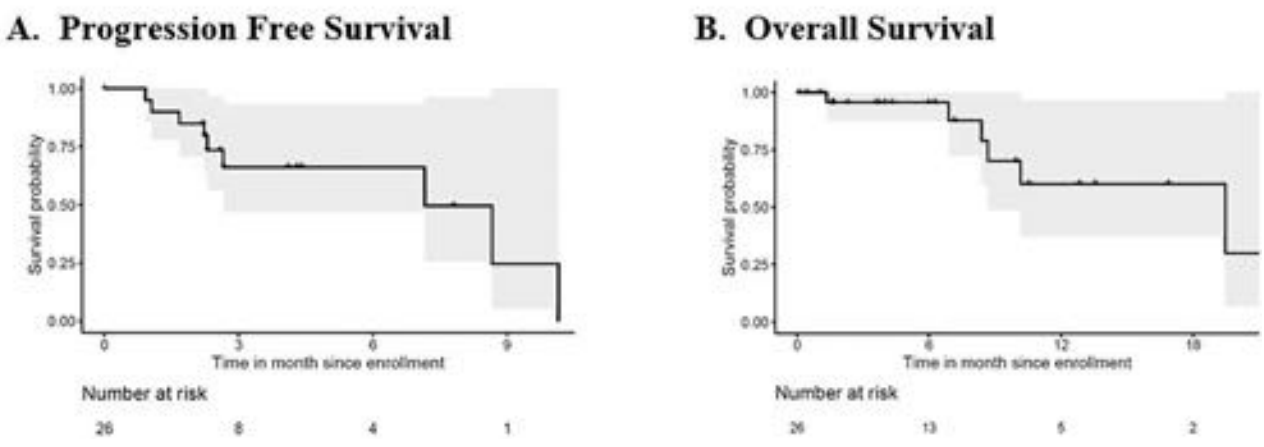
Figure



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344 | SAFETY OF ACALABRUTINIB TREATMENT IN VERY OLD (≥80 Y) AND/OR FRAIL PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA - INTERIM SAFETY ANALYSIS OF THE ONGOING PHASE II CLL-FRAIL TRIAL

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Introduction: BTK-inhibitors have revolutionized treatment of CLL. However, although patients (pts) above 80 years of age represent roughly 20% of the general CLL-population they remain underrepresented in clinical trials. Comorbidities, frailty, and organ dysfunction have a high prevalence in older pts and significant impact on efficacy and tolerability of treatments as well as survival. The CLL-Frail trial aims to evaluate the efficacy and safety of acalabrutinib monotherapy in pts ≥80 years of age and/or a FRAIL scale score of ≥3. The FRAIL scale score is a 5-item questionnaire for pts correlating with Fried's frailty phenotype.

Methods: Pts in need of treatment with previously treated and untreated CLL and ≥80 years of age and/or a FRAIL scale score ≥3 were eligible. A maximum of one previous therapy was allowed. At least 50% of pts needed to fulfil frailty criteria. Pts received acalabrutinib 100 mg BID until progression or intolerance. The primary endpoint was overall response rate at initial response assessment (cycle 7, day 1 = ~6 months after initiation of therapy). A pre-planned interim safety analysis was conducted once 30 pts reached cycle 7, day 1.

Results: 30 pts were enrolled in the first 12 months of recruitment. Median age was 82 years, 50% had a FRAIL scale score of ≥3. Median CIRS score was 10, with 73% of pts having a score >6. Median ECOG-Score was 1. Most pts had a Binet stage A (77%). Unmutated IGHV and TP53mut/del was present in 63% and 10%, respectively. 19 pts (63%) were treatment naïve. In the previously treated cohort, prior lines of treatment included chemoimmunotherapy in 73% and ibrutinib + obinutuzumab + venetoclax, bendamustine + ibrutinib + ofatumumab and obinutuzumab + venetoclax in 9% of pts each. At the data cut in November 2022 the median observation time was 8 months, 21 pts remained on therapy. Reasons for discontinuation were adverse events in five (56%) and death and withdrawn consent in two (22%) pts each, respectively. All pts experienced at least one AE, totalling in 200 AEs of which 35 (18%) were CTC grade >3 (patient level analysis is shown in Table 1). 15 severe adverse events were reported, of which eight (53%) were assessed as treatment-related by the investigator. There were no cases of severe (Grade ≥3) bleeding, two pts (6%) experienced atrial fibrillation with CTC grade two and three, respectively. Two cardiac SAEs termed cardiac failure were reported in pts who both had prior existing hypertension and atrial fibrillation. Four pts (13%) died, of which one death was deemed treatment related. Causes of death were infection in three cases (one bacterial and two COVID-19 pneumonia) and concomitant disease in one case.

Conclusions: The first interim analysis of this international phase II study evaluating treatment with acalabrutinib in very old and/or frail pts with CLL did not show unexpected safety signals in comparison to prior published data.

Table 1: Safety

Adverse Events (Patient level)		
All patients, N (%)	**30**	
	All grades	**Grade ≥ 3**
AEs	**30 (100)**	**18 (60)**
Haematoma	11 (36.7)	0
COVID-19	9 (30)	2 (6.7)
Anemia	5 (16.7)	4 (13.3)
Headache	5 (16.7)	0
Constipation	5 (16.7)	0
Diarrhoea	5 (16.7)	1 (3.3)
Fatigue	5 (16.7)	0
Pneumonia	4 (13.3)	3 (10)
Weight decreased	4 (13.3)	0
Dehydration	4 (13.3)	0
Thrombocytopenia	3 (10)	1 (3.3)
Vertigo	3 (10)	0
Nausea	3 (10)	0
Vomiting	3 (10)	0
Oedema	3 (10)	0
Hyperkalaemia	3 (10)	0
Hypokalaemia	3 (10)	1 (3.3)
Back Pain	3 (10)	0
Muscular weakness	3 (10)	0
Rash	3 (10)	1 (3.3)
Atrial Fibrillation	2 (6.7)	1 (3.3)
Cardiac Failure	2 (6.7)	1 (3.3)
Palpitations	2 (6.7)	0

Table 1: Safety. Patient-level analyses were performed for PTs with an occurrence equal or larger than 10%.Only frequent AEs (≥10% of patients) and cardiac events are depicted.

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345 | A PHASE 2 STUDY OF ZANUBRUTINIB IN PREVIOUSLY TREATED B-CELL MALIGNANCIES INTOLERANT TO IBRUTINIB AND/OR ACALABRUTINIB: PRELIMINARY RESULTS FOR PATIENTS WITH CLL/SLL

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Introduction: Patients (pts) with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) treated with Bruton tyrosine kinase inhibitors (BTKi) can have adverse events (AEs) that lead to treatment (tx) discontinuation. Interim data from BGB-3111-215 (NCT04116437) suggests that zanubrutinib (zanu), a next generation BTKi, is well-tolerated in pts with B-cell malignancies who are intolerant to ibrutinib (ibr) or acalabrutinib (acala). Preliminary safety results for pts with CLL/SLL treated with zanu after intolerance to ibr or acala are presented here.

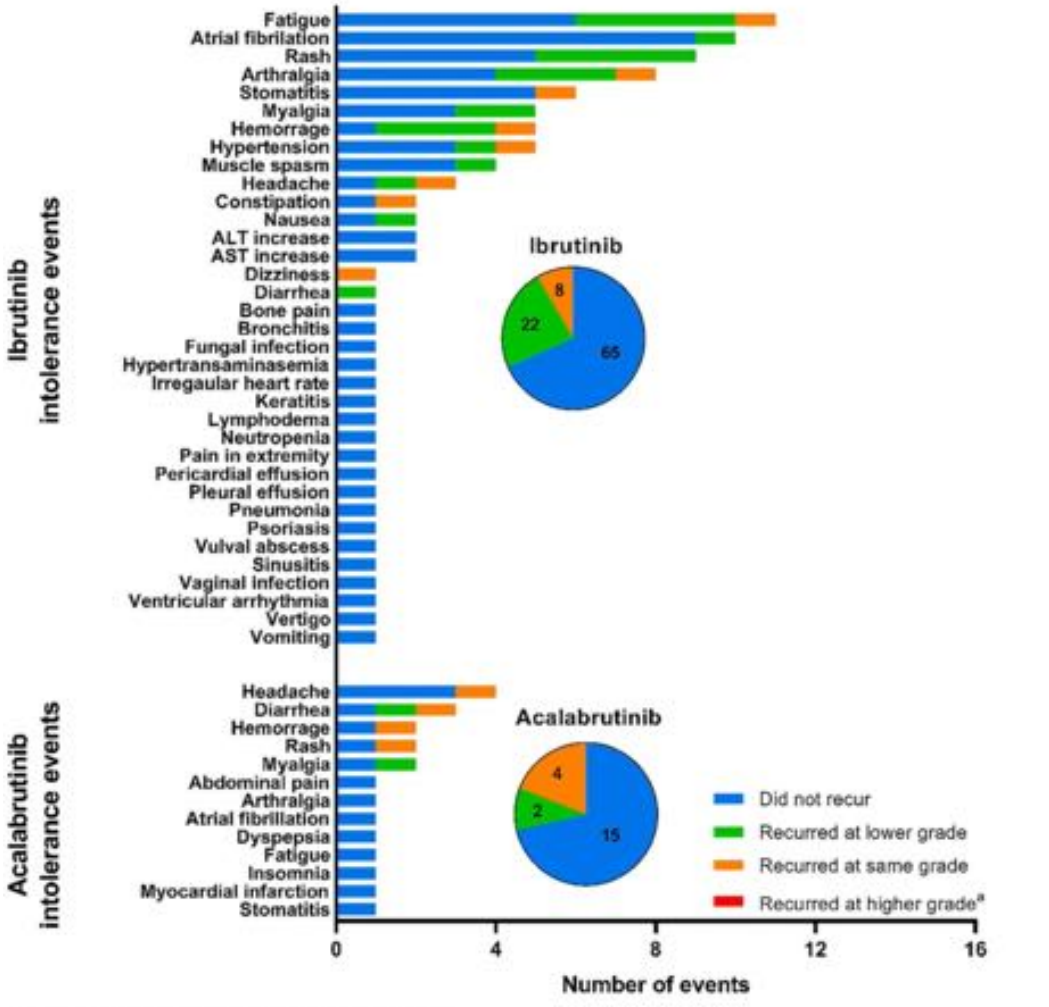
Methods: Pts with CLL/SLL intolerant to ibr, acala, or both (without progression on prior BTKi) were given zanu monotherapy (160 mg twice daily [BID] or 320 mg once daily [QD]). Safety, including

recurrence of AEs that led to intolerance on ibr and/or acala, and efficacy were assessed.

Results: As of 3 January 2023 (median follow-up: 25.6 mo), 61 pts with CLL/SLL (44 intolerant to only ibr, 17 acala intolerant [9 intolerant to acala only; 8 intolerant to acala and ibr]) were enrolled and received ≥1 zanu dose (160 mg BID: 43 [70%], 320 mg QD: 18 [30%]). Median age was 71 y (range, 49–91), median duration of tx was 23.7 mo (range, 0.5–36.2). The most common prior BTKi intolerance AEs were fatigue (n = 12 events), rash (n = 11) and atrial fibrillation (n = 10). On zanu, 61% of pts did not experience recurrence of any prior BTKi-related intolerance AE. At the event level, 68% (65/95) of ibr- and 71% (15/21) of acala-intolerance AEs did not recur with zanu (**Figure**). Of the ibr-intolerance AEs that did recur, 73% (22/30) recurred at a lower grade and 27% (8/30) recurred at the same grade. Of the acala-intolerance AEs that did recur, 33% (2/6) recurred at a lower grade and 67% (4/6) recurred at the same grade. No intolerance AEs recurred at a higher grade. At data cutoff, 41 pts remained on tx; 20 discontinued tx (progressive disease, 6; AEs, 5; other, 9) and 12 discontinued the study (death, 6; pt withdrawal, 4; lost to follow-up, 2). Most common tx-emergent AEs (TEAEs): fatigue (n = 18, 30%), COVID-19 (n = 14, 23%), contusion (n = 13, 21%), diarrhea (n = 12, 20%), arthralgia, myalgia, and cough (n = 10 each, 16%). Grade ≥3 TEAEs were reported in 31 pts (51%); most common Grade ≥3 TEAE: neutropenia (n = 7, 11%). Serious TEAEs were reported in 16 pts (26%), TEAEs requiring dose interruption in 30 pts (49%), and TEAEs leading to dose reduction in 15 pts (25%). One pt experienced a TEAE (COVID-19 pneumonia) that led to death. Among 57 efficacy evaluable pts, the disease control and the overall response rates were 95% (n = 54) and 72% (n = 41), respectively. Progression-free survival rates at 6- and 12-mo were 95% and 88%, respectively.

Conclusions: AEs that previously caused pts to discontinue ibr or acala tx were unlikely to recur with zanu and their disease continued to be controlled, suggesting pts intolerant to ibr or acala are likely to continue receiving clinical benefit by switching to zanu.

Figure. Recurrence and severity change of intolerance adverse events from prior ibrutinib or acalabrutinib exposure during zanubrutinib treatment in patients with CLL/SLL



[a]No intolerance adverse events recurred at a higher grade.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

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Keywords: Chronic Lymphocytic Leukemia (CLL), Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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MCL

346 | TIMING OF DISEASE PROGRESSION AND IMPACT ON SURVIVAL IN SWEDISH MANTLE CELL LYMPHOMA PATIENTS—A NOVEL ILLNESS-DEATH MODEL STUDY

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Background: In mantle cell lymphoma (MCL), time to relapse is a critical factor, and patients experiencing disease progression within 24 months from treatment start (POD24) have inferior survival. However, the cut-off at 24 months is arbitrary and potentially overly simplified. We aimed to quantify the impact of the timing of disease progression on overall survival, stratified by the most common first-line treatment concepts (Nordic-MCL, R-Bendamustin, and R-CHOP).
Methods: Using the population-based Swedish lymphoma register, we identified all systemically treated MCL patients diagnosed between 2006 and 2018. We supplemented this with information on progression and relapse from medical chart reviews through 2022. Patients were categorized based on first-line treatment (Nordic MCL regimen, R-Bendamustin, R-CHOP, and others). POD was defined as a lack of response to primary therapy (progressive disease [PD]) or an

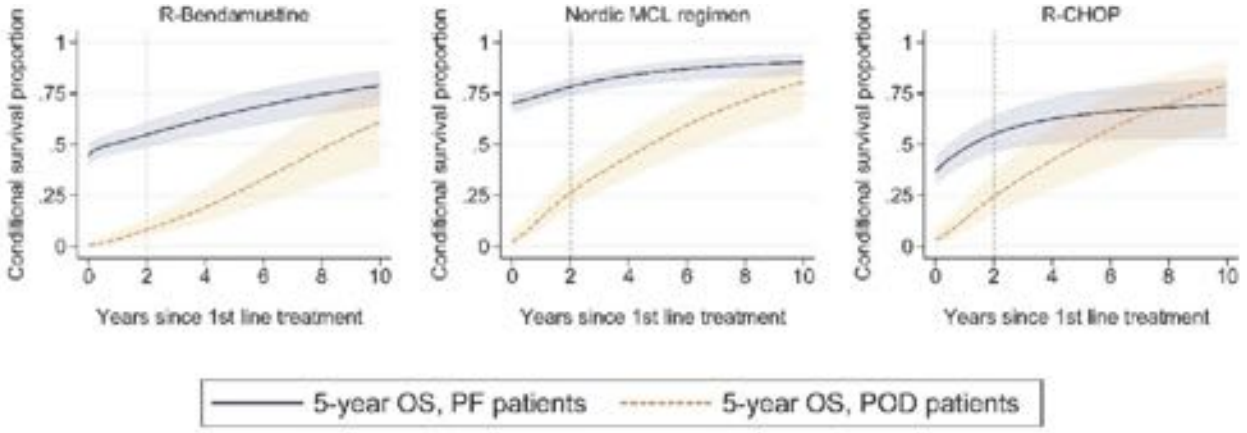

Figure 1: Five-year overall survival among patients who were still progression-free, PF (blue curve), or experienced progression of the disease, POD (yellow curve) as a function of time since the start of first systemic treatment (in years), by type of treatment (R-Bendamustine, Nordic-MCL regimen or R-CHOP). The vertical gray dashed line represents POD24. The gap between the two lines shows the difference in 5-year overall survival between patients experiencing POD (at different time points) and patients still progression-free at that time point.

initial response followed by a relapse. To assess the impact of POD timing on survival, we used an illness-death model with transition rates estimated using flexible parametric survival models to predict the five-year overall survival (OS) conditional on either being progression-free or experiencing POD as a smooth function of time since primary treatment.

Results: A total of 1193 patients receiving systemic treatment were included. The median age at diagnosis was 70 years, and patients were followed for a median of 4 years (range 0–16 years, alive patients, six years). 33% of patients received R-Bendamustin (n = 387, median age 75 years), 30% received the Nordic MCL regimen (n = 351, median age 62 years), and 23% received R-CHOP (n = 276, median age 72 years). Almost half of the patients (48%, n = 571) experienced POD during follow-up. The five-year OS from treatment start was 47%, and progression-free survival was 32%. **Among patients treated in the first line with either R-Bendamustin or the Nordic MCL protocol, those with a POD had substantially lower 5-year OS compared to patients who remained progression-free, also for POD occurring up to six years after primary treatment.** For patients treated with R-CHOP, the impact of POD was largest if it occurred within 2–3 years after first-line therapy.

Conclusion: Our population-based study of Swedish MCL patients shows that disease progression is always associated with worse survival in immunochemotherapy-treated patients. Survival continues to be much lower among progressing patients even beyond the initial 24-month period, particularly in R-Bendamustin and Nordic MCL-treated patients. Our results indicate that a strict POD24 focus may be too simplified and highlight the need for continued monitoring, improved first-line regimens, and maintenance therapy (for example, rituximab or BTK inhibitors) to sustain remission and optimize outcomes for MCL patients.

Keyword: Aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

347 | MULTICOHORT STUDY OF CONDITIONAL SURVIVAL AND CAUSE OF DEATH AFTER ACHIEVING EVENT-FREE SURVIVAL AT 24 MONTHS (EFS24) IN PATIENTS WITH MANTLE CELL LYMPHOMA (MCL)

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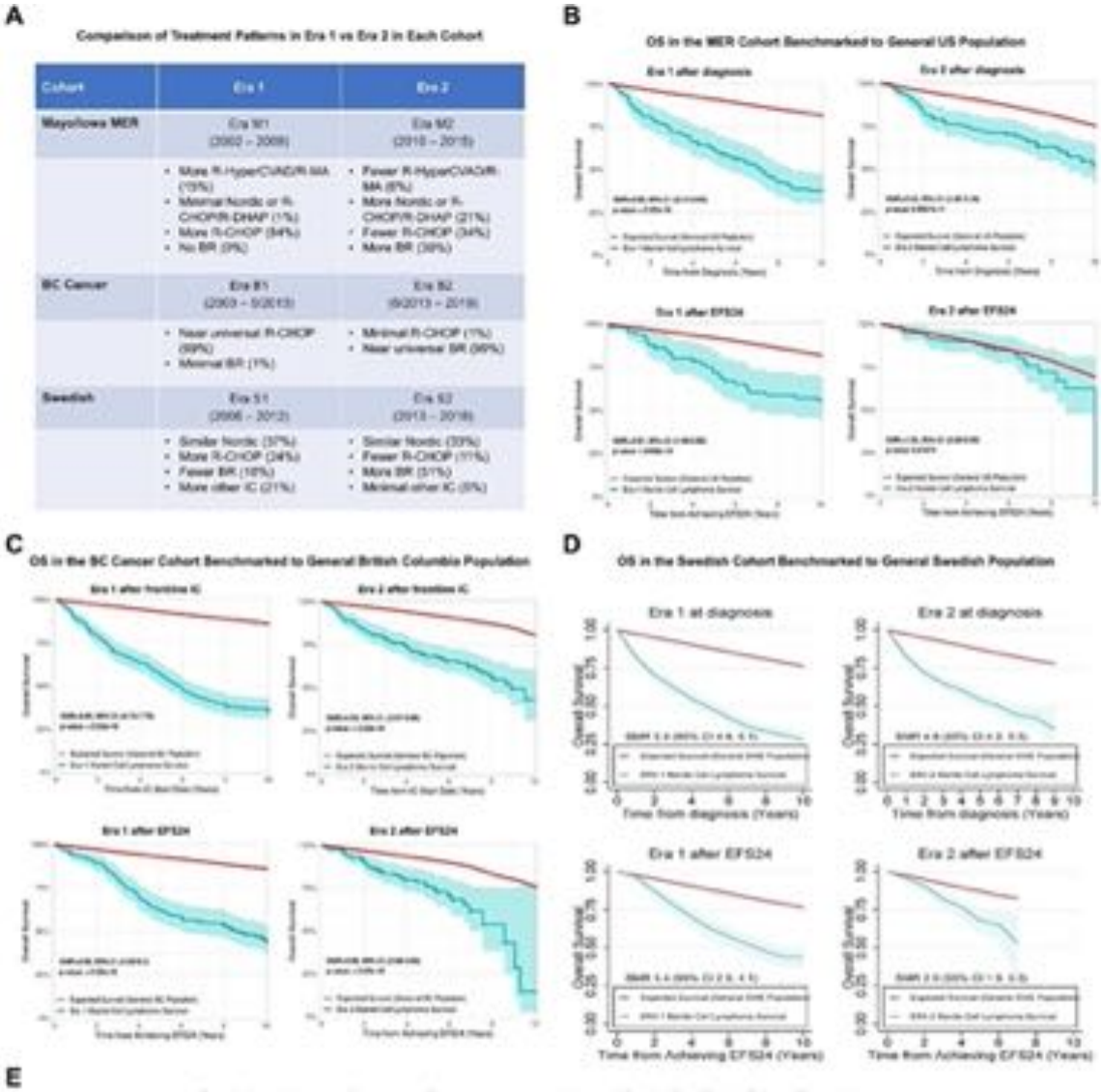
Background: MCL is considered incurable, but outcomes are improving in the evolving treatment landscape. Event-free survival status at a landmark (e.g., 24 months) after frontline IC may help identify patients who will subsequently do well, which would be useful for patient counseling, care planning, and trial design. We evaluated conditional survival and cause of death in MCL patients who achieve EFS24 after frontline immunochemotherapy (IC).

Methods: Outcomes after frontline IC were evaluated in 3 cohorts: Mayo/Iowa MER prospective clinic-based cohort, BC Cancer retrospective population-based cohort, and Swedish Lymphoma Register. For each cohort, 2 treatment eras were defined based on the

specifics of local treatment patterns (Figure 1 A). Overall survival (OS) after diagnosis and after achieving EFS24 was compared to the background age and sex matched general population using a standardized mortality ratio (SMR). Cumulative incidences of cause-specific deaths were analyzed using a competing risk model.

Results: In the MER, patients treated in Era M1 (2002–2009; n = 110) and M2 (2010–2015; n = 127) both had inferior OS compared to the US general population. A lower SMR (2.43 vs. 3.95) in Era M2 suggested a narrower gap in OS versus the general population. Lymphoma was the leading cause of death in both eras. In Era M1,



Cohort	Era 1	Era 2
Mayo/Iowa MER	Era M1 (2002 – 2009)	Era M2 (2010 – 2015)
	• More R-HyperCVAD/R-MA (19%) • Minimal Nordic or R-CHOP/R-DHAP (1%) • More R-CHOP (64%) • No BR (9%)	• Fewer R-HyperCVAD/R-MA (6%) • More Nordic or R-CHOP/R-DHAP (21%) • Fewer R-CHOP (34%) • More BR (39%)
BC Cancer	Era B1 (2003 – 5/2013)	Era B2 (5/2013 – 2019)
	• Near universal R-CHOP (99%) • Minimal BR (1%)	• Minimal R-CHOP (1%) • Near universal BR (99%)
Swedish	Era S1 (2006 – 2012)	Era S2 (2013 – 2018)
	• Similar Nordic (37%) • More R-CHOP (24%) • Fewer BR (16%) • More other IC (21%)	• Similar Nordic (33%) • Fewer R-CHOP (11%) • More BR (31%) • Minimal other IC (5%)

E

Cumulative Incidences of Lymphoma Related vs Lymphoma Unrelated Deaths Stratified by Cohort, Era, and Landmark

Cohort	Era	Cause of death	Cause-specific mortality rate			
			2 years from diagnosis	5 years from diagnosis	2 years from achieving EFS24	5 years from achieving EFS24
Mayo/Iowa MER	Era M1 (2002 – 2009)	Lymphoma	0.14 (0.09 – 0.22)	0.26 (0.19 – 0.35)	0.06 (0.02 – 0.16)	0.21 (0.13 – 0.32)
		Non-Lymphoma	0.01 (0.00 – 0.07)	0.06 (0.03 – 0.12)	0.06 (0.02 – 0.16)	0.06 (0.03 – 0.16)
		Unknown	0.05 (0.02 – 0.11)	0.06 (0.03 – 0.13)	0	0
	Era M2 (2010 – 2015)	Lymphoma	0.15 (0.10 – 0.23)	0.20 (0.14 – 0.28)	0	0.01 (0.00 – 0.06)
		Non-Lymphoma	0.02 (0.00 – 0.07)	0.06 (0.03 – 0.12)	0.05 (0.03 – 0.13)	0.05 (0.02 – 0.13)
		Unknown	0	0.03 (0.01 – 0.09)	0	0.08 (0.04 – 0.17)
BC Cancer	Era B1 (2003 – 5/2013)	Lymphoma	0.18 (0.15 – 0.24)	0.40 (0.34 – 0.47)	0.09 (0.06 – 0.15)	0.33 (0.26 – 0.41)
		Non-Lymphoma	0.02 (0.01 – 0.05)	0.04 (0.02 – 0.07)	0.01 (0.00 – 0.05)	0.06 (0.03 – 0.10)
	Era B2 (5/2013 – 2019)	Lymphoma	0.14 (0.10 – 0.20)	0.23 (0.17 – 0.30)	0.06 (0.03 – 0.11)	0.12 (0.07 – 0.18)
		Non-Lymphoma	0.02 (0.01 – 0.06)	0.09 (0.06 – 0.14)	0.04 (0.02 – 0.13)	0.13 (0.08 – 0.20)
Swedish	Era S1 (2006 – 2012)	Lymphoma	0.23 (0.20 – 0.27)	0.41 (0.36 – 0.46)	0.08 (0.05 – 0.12)	0.23 (0.18 – 0.29)
		Non-Lymphoma	0.08 (0.04 – 0.09)	0.10 (0.07 – 0.13)	0.05 (0.02 – 0.09)	0.14 (0.10 – 0.19)
	Era S2 (2013 – 2018)	Lymphoma	0.24 (0.20 – 0.28)	0.33 (0.29 – 0.38)	0.04 (0.02 – 0.07)	0.13 (0.09 – 0.18)
		Non-Lymphoma	0.05 (0.03 – 0.07)	0.12 (0.09 – 0.16)	0.05 (0.03 – 0.09)	0.19 (0.13 – 0.26)

patients achieving EFS24 still had inferior OS compared to the general population (SMR = 2.81, 95% CI: 1.98–3.88), and lymphoma remained the leading cause of death. However, in Era M2, patients achieving EFS24 had similar OS compared to the general population (SMR = 1.35, 95% CI: 0.83–2.09), and lymphoma was no longer the leading cause of death (Figure 1 B&E).

In the BC cohort, patients treated in Era B2 (6/2013–2019; $n = 188$) versus Era B1 (2003–5/2013; $n = 250$) had a narrower gap in OS compared to the British Columbia population (SMR 4.53 vs. 6.69). Lymphoma was the leading cause of death in both eras. For patients achieving EFS24, the gap in OS was narrower in Era B2 versus B1 (SMR 3.56 vs. 4.99). After achieving EFS24, lymphoma was the leading cause of death for patients in Era B1 but not in Era B2 (Figure 1 C&E).

Similar results were seen in the Swedish cohort. The gap in OS compared to the general Swedish population was narrower in Era S2 (2013–2018; $n = 439$) vs. S1 (2006–2012; $n = 442$), both after frontline IC (SMR 4.8 vs. 5.4) and after achieving EFS24 (SMR 2.6 vs. 3.4). After achieving EFS24, lymphoma was the leading cause of death for patients in Era S1 but not in Era S2 (Figure 1 D&E).

Conclusion: In all 3 cohorts, overall survival in patients who achieve EFS24 after frontline IC improved in the more recent treatment era and moved closer to the background expected mortality. Of particular note, after achieving EFS24, lymphoma-related mortality was no longer the leading cause of death in the more recent era. EFS24 following frontline treatment may become a critical landmark for predicting subsequent outcomes in patients with MCL in the modern era.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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Honoraria: Kite (to my institution)

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Consultant or advisory role: Genentech, MEI Inc

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Consultant or advisory role: Janssen, BeiGene, AstraZeneca, Merck, Kite/Gilead, BMS/Celgene, AbbVie, ONO therapeutics, Zetagen, Roche

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348 | OUTCOMES OF YOUNGER PATIENTS WITH MANTLE-CELL LYMPHOMA EXPERIENCING LATE RELAPSE (>24 MONTHS): THE LATE-POD STUDY

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Introduction: Patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) have poor outcome. Time to first relapse or progression (POD) has been consistently shown to be an independent predictor of survival, with patients experiencing early-POD, within 2 years since the diagnosis, representing a subgroup at greater risk of

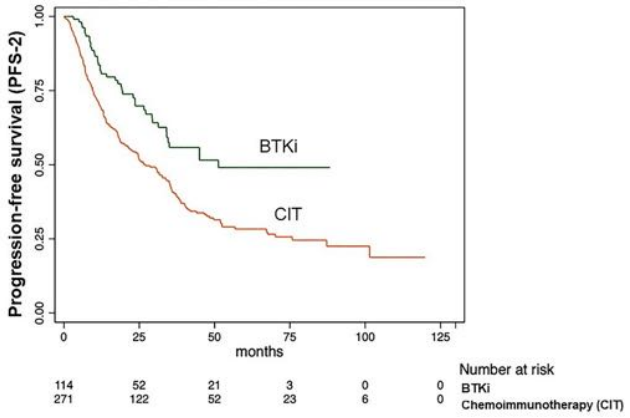
death. On the contrary, there is a paucity of large-scale treatment data on patients experiencing relapse beyond 2 years (late-POD).

Methods: In this international, observational cohort study, we evaluated the outcomes amongst patients with first R/R MCL and late-POD, after upfront standard regimens including high dose cytarabine. Patients treated upfront with Bruton tyrosine kinase inhibitors (BTKi) were excluded. The primary objective was progression-free survival (PFS) of BTKi versus chemoimmunotherapy (CIT) as second line therapy. For sample size calculation 100 patients treated with drug 1 (BTKi), and 200 with drug 2 (CIT) were needed to compare PFS of drug 1 versus drug 2, assuming that CIT and BTKi would have a median PFS of 36 and 60 months, respectively. After accrual, all patients were prospectively followed-up. Overall survival (OS-2) and PFS-2 were estimated from the time of salvage therapy.

Results: Overall, 386 late-POD patients were included from 10 countries. Median age was 59 (19–70), and 77% were males. Median follow-up from time of first relapse was 53 months (12–144). Overall, 114 patients had second-line BTKi (drug 1), while CIT (drug 2) was delivered to 271 patients, consisting of rituximab-bendamustine (R-B, $n = 101$), R-B and cytarabine (R-BAC, $n = 70$), or other regimens (mostly CHOP or platinum-based, $n = 100$). The two groups were balanced for clinicopathological features, and median time to first relapse (48 months for both). Overall, BTKi was associated with significantly longer median PFS-2 than CIT [51 versus 26 months, respectively, $P = 0.0003$, Figure 1], and OS-2 [88 and 56 months, $P = 0.03$]. The performance of BTKi and R-BAC were similar, both in terms of PFS-2 and OS-2, and significantly superior to R-B or other regimens ($P = 0.0003$, and $P = 0.01$, respectively). Multivariate Cox regression showed that ibrutinib was associated with inferior risk of death than R-B and other regimens (HR 2.41 for R-B, 2.17 for others), but similar to R-BAC. Blastoid variant, age, and time to POD as continuous variable were also independent predictors of OS-2. Nine patients with *TP53* mutation had inferior OS-2 compared to *TP53* wild-type patients ($n = 48$, $P = 0.04$).

Conclusions: This is the first report comparing CIT with targeted therapy in patients with MCL and late-POD. BTKi was superior to CIT in late-POD patients (as it had been shown for early-POD). Despite R-BAC had similar outcomes than ibrutinib, the latter may be preferred, especially in CAR-T cell candidates. These results establish BTKi as the preferable second line approach in BTKi naïve patients with MCL.

Figure 1. Progression-free survival calculated from time of first relapse (PFS-2)



The research was funded by: The research was funded in part by Janssen, as part of a Clinical IIS Research Application

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

349 | SECONDARY MALIGNANCIES IN MANTLE CELL LYMPHOMA PATIENTS—A NATIONWIDE POPULATION-BASED STUDY IN SWEDEN

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Introduction: With modern treatments, mantle cell lymphoma (MCL) patients may experience long-lasting remission resulting in a growing population of long-term survivors. Follow-up care includes identification and management of treatment-related late effects, such as secondary malignancies (SM). We conducted a population-based study to describe the burden of SM in MCL patients in Sweden.

Methods: All Swedish patients with a primary diagnosis of MCL, aged >18 years and diagnosed between 2000 and 2017 were included, along with 6–10 matched population comparators. Patients and comparators were followed from twelve months after diagnosis/matching until death, emigration, or December 2019, whichever occurred first. Rates of SM among patients and comparators were estimated using the Anderson-Gill method (accounting for multiple events) and presented as hazard ratios (HR) with 95% confidence intervals (CI) adjusted for age, calendar year, sex and a time-dependent variable indicating the number of previous events.

Results: Overall, 1452 patients and 13 992 comparators were followed for 6.6 years on average. Among patients, 230 (16%) developed at least one SM and a total of 264 SMs were observed. Relative to comparators, patients had a higher rate of SM, $HR_{adj} = 1.6(1.4–1.8)$ (Figure 1). Higher rates in patients were observed across all primary treatment groups: Nordic-MCL2 protocol (250 patients, $HR_{adj} = 1.4(1.0–2.0)$), R-CHOP single (144 patients, $HR_{adj} = 2.0(1.3–2.9)$), R-bendamustine (302 patients, $HR_{adj} = 2.2(1.7–2.7)$), lenalidomide (16 patients, $HR_{adj} = 4.3(2.0–9.0)$) (Figure 1), R-CHOP/Cytarabine (145 patients, $HR_{adj} = 1.6(1.0–2.5)$), and ibrutinib (9 patients,

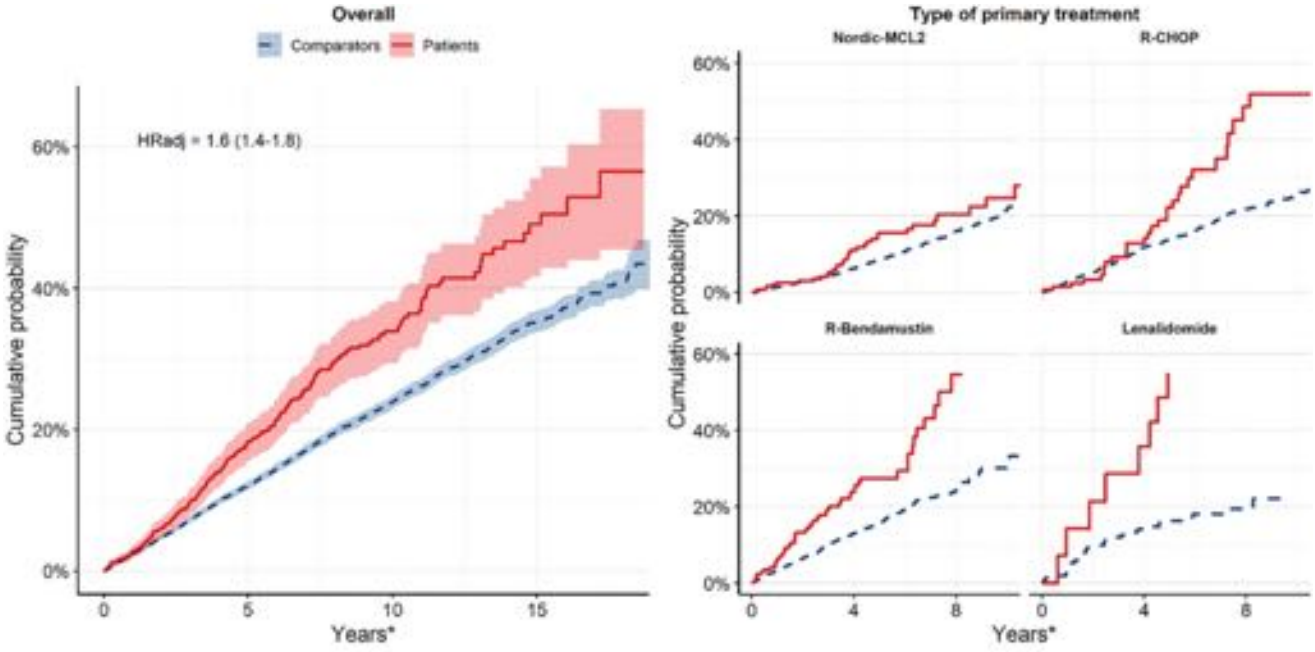

Figure 1: Crude cumulative probability (1- Kaplan Meier, in percentage) of secondary malignancies in mantle cell lymphoma patients (red solid line) and matched population comparators (blue dashed line), overall (left panel) and stratified by type of first line treatments (right panel), twelve months from the diagnosis (matching) date.

Years: Number of years of follow-up starting from twelve months after diagnosis (matching date for comparators). HRadj: Hazard ratio (and 95% confidence interval) adjusted for age at diagnosis, year of diagnosis, sex and a time-dependent variable indicating the number of previous events. Comparators are the reference group. R-bendamustine: rituximab-bendamustine, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone. Nordic-MCL2 protocol: R-CHOP/R-cytarabine, high dose treatment and consolidation with an autologous stem cell transplant.*

HR_{adj} = 4.8(1.2–18.7)) contrasted with comparators. Compared to Nordic-MCL2, treatment with R-bendamustine was independently associated with an increased risk of SM, HR_{adj} = 2.0(1.2–3.3). Within patient groups, higher rates of SM were also seen with increasing age at diagnosis (p-trend < 0.001), for males (p = 0.006) and for patients with a family history of lymphoma (p = 0.009). Melanoma/skin cancer (n = 109, 41%), cancer of male genital organs (n = 38, 14%), digestive organs (n = 38, 14%), respiratory (n = 18, 7%), urinary tract (n = 17, 6%) and lympho-hematopoietic malignancies (excluding MCL, n = 17, 6%) were the most frequent SM.

Conclusions: MCL survivors have an increased risk of SM, particularly patients given primary treatment with R-bendamustine, but also patients treated with other chemotherapies or novel targeted drugs (lenalidomide, ibrutinib), though only few patients were included in the latter group and the results should be interpreted accordingly. The intensive treatments needed for long-term remissions are a concern, and transition to protocols with treatments with remained efficacy but with less risk of SM and a careful surveillance for long-term survivors with MCL are needed.

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Keyword: Late Effects in Lymphoma Survivors

No conflicts of interests pertinent to the abstract.

350 | HOW TO CHOOSE BETWEEN CURATIVE RADIOTHERAPY OR CHEMOTHERAPY IN LOW STAGE MCL?—A POPULATION-BASED ANALYSIS OF OUTCOME IN PATIENTS WITH STAGE I-II MCL IN SWEDEN

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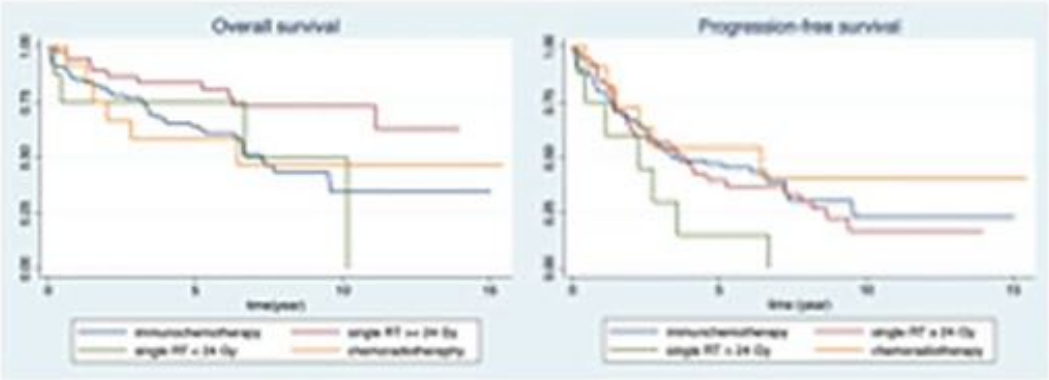
Introduction: The optimal primary treatment of mantle cell lymphoma is not yet defined with respect to long-term disease control and manageable toxicity. A few patients with MCL present with limited stage disease and for these, involved node radiotherapy may be a well tolerable alternative to immunochemotherapy regimens. Here, we aim to evaluate progression free survival (PFS) and overall survival (OS) in relation to given treatment and prognostic factors in patients with stage I-II MCL.

Figure 1a-b Progression-free and overall survival according to Kaplan-Meier estimates in patients diagnosed in Sweden with stage I-II MCL 2006-2018. Estimates were calculated from end of treatment until progression (PFS), death or last follow-up (PFS + OS)



Methods: The study was based on patients diagnosed with MCL in Sweden 2006–2018 according to the Swedish Lymphoma Register (SLR), which is a nationwide population-based register with a reported coverage of 95%. Data were supplemented by review of medical records for all patients. Survival analyses were made by Kaplan-Meier estimates with end of given treatment as start of follow-up (FU).

Results: Out of all patients ($n = 1412$), we identified a cohort of 173 patients reported with Ann Arbor I-II or Musshoff PeI according to standard staging procedure. Median age was 71(22–93) years, 88% had ECOG 0–1 and 31% were scored high-risk MIPI at diagnosis. Primary treatment included single RT ($n = 48$, 28%) of which curative radiation dose ≥24 Gy in 37 (21%) patients, Immunochemotherapy (ICT) ($n = 94$, 54%) including R-bendamustine ($n = 34$), Nordic MCL2 protocol ($n = 28$), R-CHOP ($n = 14$), and ICT with consolidative RT in 12 (7%) (CRT). At a median FU time of 5.40 (0.01–15.46) years (y), median OS in the cohort was 9.56 y (95% CI: 6.60-NR). 5-y-OS (95% CI) after ICT was 0.64(0.53–0.73), after single RT ≥24 Gy 0.84(0.67–0.92) and 0.58 (0.27–0.80) after CRT (Figure 1a). Median progression-free survival (PFS) in the cohort was 3.55 y (95% CI: 2.53–6.08). 5-y-PFS (95% CI) was 0.47 (0.36–0.58) after ICT, 0.40 (0.24–0.55) after single RT ≥24 Gy and 0.55 (0.23–0.78) after CRT (Figure 1b).

Conclusions: Our analysis demonstrates excellent outcome after curative radiotherapy in localized MCL both in terms of PFS and OS. By being a well tolerable and less resource demanding strategy, the results clearly support its use upfront. Further analysis on subgroups and relapse pattern will increase understanding and enable further interpretation of the results.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chemotherapy, Radiation Therapy

No conflicts of interests pertinent to the abstract.

351 | ENHANCED CTDNA PROFILING REVEALS MOLECULAR DETERMINANTS OF RESPONSE AND RESISTANCE IN RELAPSED AND REFRACTORY MANTLE CELL LYMPHOMA (NLG-MCL7-VALERIA)

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Introduction: Deciphering molecular determinants of response to targeted treatments and early detection of refractoriness in patients with relapsed and refractory (R/R) mantle cell lymphoma (MCL) could individualize treatment, improve outcomes and limit unnecessary toxicities. Circulating tumor DNA (ctDNA) allows non-invasive profiling and measurement of treatment responses. Yet, increased sensitivity for detection and distinction from confounding biological signals are warranted. Enhanced ctDNA detection can be achieved using duplex sequencing or tracing of phased variants. Poor recovery of complementary strands and low number of phased variants limit the feasibility of these approaches separately in MCL.

Methods: Thus, we developed and optimized a hybrid ctDNA sequencing platform, which combines strand- and phasing-aware error correction methods for improved specificity and sensitivity of non-invasive B-cell lymphoma profiling, quantification and detection (Figure 1A). We applied this platform to profile ctDNA in serial

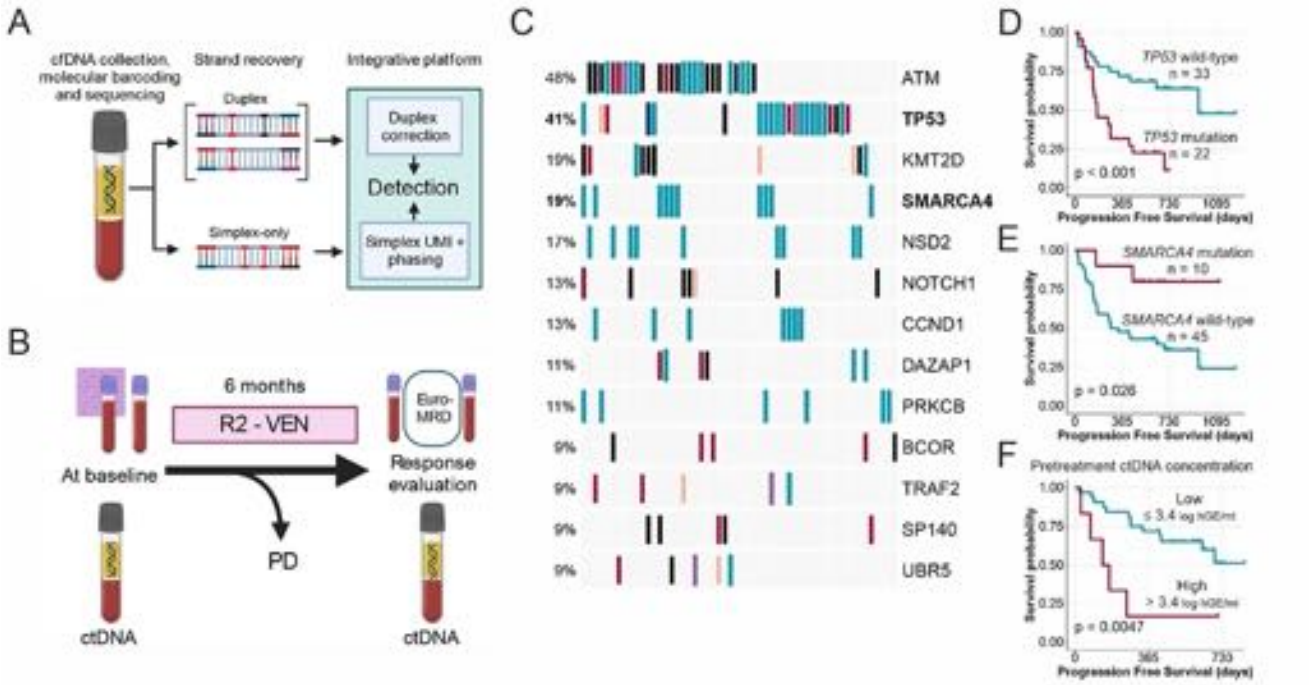

Figure1. Analysis of circulating tumor DNA in MCL-7 (VALERIA) trial. A) Developed method with our hybrid strategy for ctDNA analysis combining duplex sequencing adapters and variant phasing. UMI; unique molecular identifier. B) Sample collection, treatment and Euro-MRD measurements according to the study protocol. C) Genomic driver landscape of recorded mutations in joint analysis of genotyping tissues at baseline. D-F) Kaplan-Meier survival estimates according to baseline (D) *TP53* and (E) *SMARCA4* mutation status and (F) elevated pretreatment ctDNA concentration. log hGE/ml; log10-transformed haploid genome equivalents per milliliter of plasma.

plasma samples from 59 patients with R/R MCL treated with lenalidomide, venetoclax and rituximab in the Nordic phase II trial (NLG-MCL7; VALERIA). We compared the results with outcomes and real-time quantified PCR (RQ-PCR, 'Euro-Minimal Residual Disease (MRD')) data from bone marrow (BM) and peripheral blood (PB) samples that guided therapy in the trial (Figure 1B).

Results: Joint analysis of targeted sequences from pretreatment tumor, PB, BM, and plasma samples revealed MCL genotypes for ctDNA tracing even in the patients who failed primer designs for Euro-MRD (Figure 1C). Comparison between genotyping of samples from different compartments from individual patients mitigated confounding clonal hematopoiesis background and revealed spatially-confined MCL mutations. *TP53* mutated MCL conferred resistance to therapy, whereas *SMARCA4* mutations translated into durable molecular remission (Figure 1D-E). Elevated pretreatment ctDNA concentration was associated with multiple clinical risk factors, leukemic disease, and poor outcome (Figure 1F).

After six months of therapy, ctDNA levels dropped in all studied patients. The responses in the ctDNA were highly concordant with concomitant Euro-MRD and extended to patients not evaluable by RQ-PCR. Notably, contrasting ctDNA clearance, the analysis of the post-therapy cell-free DNA revealed positive selection of clonal hematopoiesis drivers following therapy exposure, such as *TP53* mutations in 77% of the patients.

Conclusions: We found that pretherapeutic and dynamic patterns in the ctDNA of R/R MCL predict different responses to treatment with lenalidomide, venetoclax and rituximab. Our enhanced ctDNA platform is applicable in R/R MCL and can overcome limitations of concurrent prognostication and MRD methods even in a challenging genetic background including marked clonal hematopoiesis.

The research was funded by: Academy of Finland, iCAN Flagship, University of Helsinki, Helsinki University Hospital, Finnish Cancer Organisation, Sigrid Juselius Foundation and Abbvie.

Keywords: diagnostic and prognostic biomarkers, liquid biopsy, molecular targeted therapies

No conflicts of interests pertinent to the abstract.

352 | LONG TERM FOLLOW-UP OF UNTREATED/RELAPSING MCL PATIENTS WITH THE IBRUTINIB, OBINUTUZUMAB, AND VENETOCLAX COMBINATION

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Backgrounds: Targeted therapies (such as Ibrutinib and Venetoclax) have improved Mantle Cell Lymphoma (MCL) patients' outcomes. OAsIs trial has evaluated the efficacy and toxicity of the Ibrutinib Obinutuzumab plus venetoclax combination in both R/R and untreated MCL patients (NCT02558816, Le Gouill et al. Blood 2021). In the present work, we updated the outcome of patients enrolled in OASIS trial.

Methods: The OASIS trial was a 3 arms multicenter prospective phase 1/2 trial. Arm A (n = 9) enrolled R/R patients who were treated with Obinutuzumab (Obi, 1000 mg) and Ibrutinib (Ibru, 560 mg). Patients in Arm B (R/R; n = 24) and C (newly diagnosed MCL; n = 15) were treated with Obi+Ibru+Venetoclax (Ven, 400 mg). Patients' characteristics have been described in the original manuscript.

Results: In cohorts A (n = 9) and B (n = 24), overall response rates were 89% and 71%, respectively. Median Follow-ups were 71.6 and 48m, the 4-y PFS were 67% and 50%, respectively. No safety signals appeared during long term FU. Patients who progressed were treated with Bendamustine-containing regimen (6 out of 10) and one patient received Odronextamab and anti-CD22xCD3 bispecific antibodies.

For Cohort C (n = 15), the median follow-up was 46m (36, 49m). Median PFS and DOR were not reached, the estimated 48m-PFS and 36m-DOR were 80% (Figure 1A). Two patients prematurely discontinued, one early PD (after 4m) and one for Adverse Event (neuropathy after 9m). The early PD patient harbored no adverse event, especially no *TP53* alteration. One patient with *TP53* mutation is still experiencing long-term disease control. One patient experienced atrial fibrillation and one patient had acute cardiac failure. Regarding infections, one patient died of a progressive multifocal leukoencephalopathy after the completion of treatment. Two patients prematurely discontinued the treatment, one patient had a PD at C4 and has subsequently been treated with R-CHOP, one patient relapsed after treatment completion and has been treated with Glofitamab. In all, 2 patients progressed and 1 died in arm C (PML), hence, the 4-y OS is estimated to be 93% (Figure 1B).

Conclusion: The Ibrutinib-Venetoclax-Obinutuzumab triplet is associated with a sustained disease control, in both R/R (4-y PFS of 50%) and newly diagnozed (4y-PFS of 80%) patients presenting with high risk-profil (no low-MIPI patients were included in the Oasis Trial). The anti-CD20+Ibrutinib versus anti-CD20+Ibrutinib+Venetoclax combinations are currently under investigation in OASIS-II trial (NCT04802590) for untreated patients with MCL.

Encore Abstract - previously submitted to EHA 2023

The research was funded by: Roche SAS supplied obinutuzumab, Janssen-Cilag supplied ibrutinib and AbbVie supplied venetoclax. Roche SAS, Janssen-Cilag and AbbVie funded the trial

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, targeting the tumor microenvironment

Conflicts of interests pertinent to the abstract.

S. Rule

Employment or leadership position: AstraZeneca

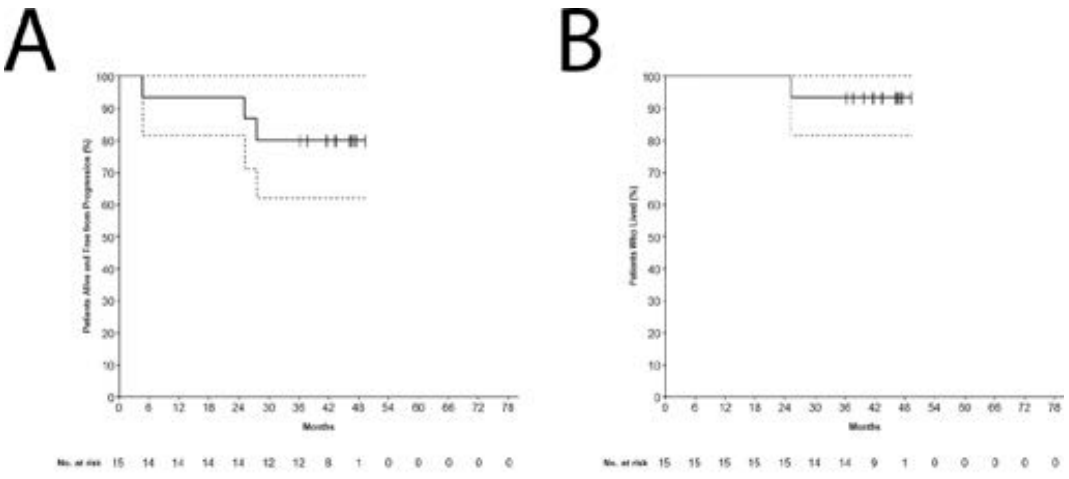

Figure 1. PFS (A) and OS (B) for STEP-C Cohort
MCL patients at diagnosis, treated with Obin-Ibru-Ven, mFU=46m)

353 | LONG-TERM SAFETY WITH ≥12 MONTHS OF PIRTOBRUTINIB IN RELAPSED/REFRACTORY B-CELL MALIGNANCIES

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Introduction: While Bruton tyrosine kinase inhibitors (BTKi) can induce sustained remissions, ongoing response requires continuous treatment and thus long-term safety/tolerability is critical for adherence, maintaining dose intensity, and delivering maximum efficacy. Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi approved by the FDA in January 2023 for relapsed/refractory (R/R) mantle cell lymphoma after 2 prior lines of therapy including a BTKi. Pirtobrutinib has demonstrated promising efficacy with low discontinuation and dose reduction rates in patients (pts) with multiple subtypes of R/R B-cell malignancies. However, the long-term safety and tolerability of pirtobrutinib has not yet been reported. Here we report the clinical safety in pts with long-term (≥12 months) pirtobrutinib treatment from the phase 1/2 BRUIN trial.

Methods: Pts with R/R B-cell malignancies who received ≥12 months of pirtobrutinib were included. Median time to onset, dose reduction, discontinuation, and cumulative incidence rates were determined for treatment emergent adverse event (TEAE) that occurred in ≥20% of pts and select AE of interest associated with BTKi.

Results: As of 29 July 2022, 773 pts were enrolled, and 326 (42%) pts received treatment for ≥12 months. Among these 326 pts, median time on treatment was 19 months (IQR: 16.25), with 231 (71%) remaining on pirtobrutinib. The most common TEAE (all grade, regardless of attribution) in this long-term 326 pt cohort were fatigue (32%), diarrhea (31%), Covid-19 (29%), contusion (26%), cough (25%), and back pain (21%). TEAE leading to dose reduction or discontinuation occurred in 23 (7%) and 11 (3%) pts, respectively. Four (1%) pts discontinued due to a treatment-related AE, and 1 pt had a fatal treatment-related AE (Covid-19 pneumonia). Select AE of interest for the long-term pts are shown in the Table. Comprehensive safety analyses describing the frequency of TEAE over time will be presented.

Conclusion: Prolonged pirtobrutinib therapy continues to demonstrate a safety profile amenable to long-term administration at the recommended dose without evidence of new or worsening toxicity signals. The safety and tolerability observed in pts on therapy for ≥12 months was similar to previously published safety analyses on all pts enrolled regardless of follow-up.

Encore Abstract - previously submitted to ASCO 2023

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Conflicts of interests pertinent to the abstract.

Y. Wang

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Honoraria: Kite

Research funding: Incyte, InnoCare, LOXO Oncology, Novartis, Genentech, MorphoSys, Genmab

C. C. Coombs

Consultant or advisory role: LOXO/Lilly, AbbVie, AstraZeneca, Beigene, Genentech

Select AE of interest associated with BTKi in pts with ≥12 months exposure (N=326)

AE	Any-Grade TEAE %	Grade ≥3 TEAE %	Median time (months) to first occurrence (Q1, Q3)	Leading to dose reduction %	Leading to drug discontinuation %	Cumulative incidence rate (6, 12, 24 months) %
Bruising[a]	31	0	1.8 (0.5, 5.6)	<1	0	23, 27, 29
Arthralgia	21	1	7.4 (2.9, 12.0)	0	0	9, 16, 20
Rash[a]	20	<1	2.4 (0.7, 9.1)	0	0	13, 15, 18
Hemorrhage/ Hematoma[a]	17	2	5.8 (1.9, 13.7)	0	0	9, 11, 16
Hypertension	16	3	6.9 (2.1, 11.6)	<1	0	7, 12, 16
Atrial fibrillation/ flutter[a]	3	1	10.2 (3.8, 15.0)	0	0	1, 2, 2

[a]Consolidated Terms.

Stock ownership: CTI Biopharma
Research funding: LOXO/Lilly, AbbVie, Genentech, AstraZeneca, Beigene, Novartis, TG Therapeutics, MEI Pharma
Other remuneration: AbbVie

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Research funding: Miltenyi Biotec
Other remuneration: Incyte

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Research funding: Astrazeneca, Beigene
Other remuneration: Roche, AstraZeneca, Janssen, Abbive

354 | LONG-TERM ANALYSIS OF THE RIBVD PHASE II TRIAL REVEALS THE UNFAVORABLE IMPACT OF TP53 MUTATIONS AND HYPOALBUMINEMIA IN ELDERLY MANTLE CELL LYMPHOMA PATIENTS. FOR THE LYSA GROUP.

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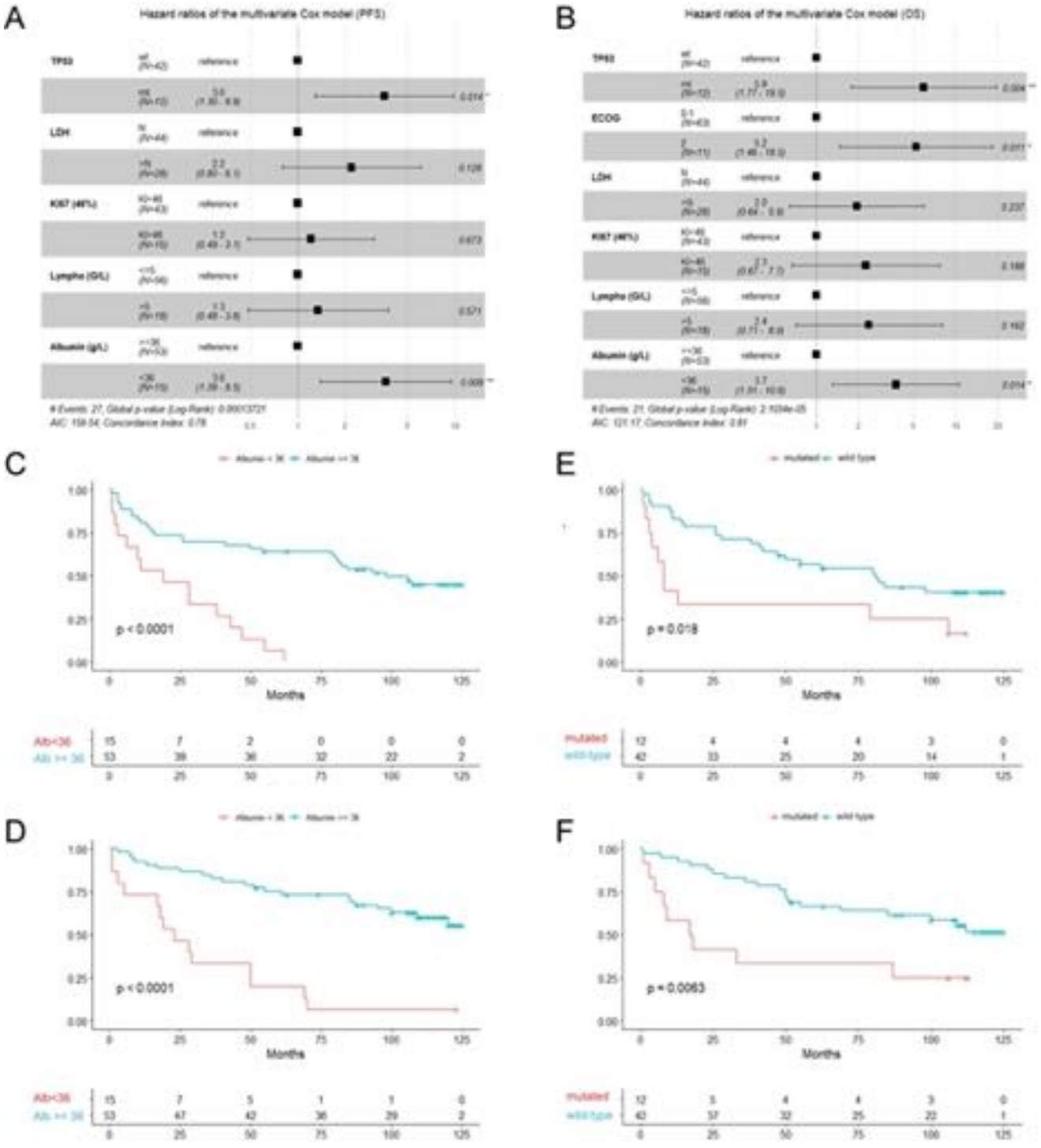

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Introduction: Alterations in *TP53* are a well known negative factor in young mantle cell lymphoma (MCL) patients eligible for intensive therapies, but their impact in elderly subjects remains poorly characterized.

Between 2011 and 2012, the LYSA group conducted a phase II trial evaluating the safety and efficacy of 6 cycles of the combination RiBVD (Rituximab, Bendamustine, Velcade and Dexamethasone) without maintenance Rituximab (RM) in patients aged over 65, which allows a median PFS (mPFS) of 5 years to be reached. In this update of the study, we re-examined the classic prognostic factors (PF) for survival by adding the assessment of the mutation status of *TP53*.

Results: Seventy-four patients (median age 73 years) were treated with the RiBVD combination. The median Progression Free Survival (mPFS) and median Overall Survival (mOS) of the whole population were 62.5 months (5.2 years) and 90 months (7.5 years), respectively. In total, *TP53* mutation status was available in 54/74 (73%) patients. *TP53* mutations were found in 12 patients (22.2%) (*TP53*mt). Among the significant prognostic factors in univariate analysis, only *TP53*mt and an albumin level below 36 g/L (Alb < 36g/L) were independently associated with a shorter PFS in multivariate analysis with an HR of 3.16 (1.3–9.9, $p = 0.014$) for *TP53*mt versus *TP53*wt and 3.6 (1.39–9.5, $p = 0.009$) for alb < 36 g/L versus alb ≥ 36 g/L. Three PFs were associated with a shorter OS in multivariate analysis; *TP53*mt, Alb < 36 g/L and ECOG = 2 with HR of, respectively 5.9 (1.77–19.5, $p = 0.004$), 5.2 (1.46–18.5, $p = 0.011$) and 3.7 (1.31–10.6, $p = 0.014$).

Discussion: With a median follow-up of 9.6 years, we confirm the long-term efficacy of RiBVD as first-line treatment of elderly patients with MCL with a median PFS of 5.2 years and an median OS of 7.5 years. We also show that the presence of *TP53* mutation and hypoalbuminemia (<36 g/L) are 2 independent PF for PFS and OS in elderly MCL patients included in the cohort. Finally, the *TP53* status and the serum albumin allow to discriminate 3 populations of patients according to the presence of 0, 1 or 2 PF with an mPFS of respectively 7.8y, 28 months and 2.5 months.

Conclusion: We confirm with a prolonged follow-up the efficacy of the RiBVD regimen regarding other non-maintenance immunochemotherapy regimens. We also suggest that RiBVD also compares favorably to other newer regimens incorporating maintenance and/or the addition of an iBTK to BR induction. In this population of elderly patients, *TP53* mutational status and hypoalbuminemia appear to be strong independant prognostic factors that can easily be integrated to guide therapeutic strategies.

The research was funded by: ARAMIS association

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

355 | RITUXIMAB COMBINED WITH CHEMOTHERAPY AND ACALABRUTINIB PRIOR TO AUTOLOGOUS STEM CELL TRANSPLANTATION IN MANTLE CELL LYMPHOMA: THE RECTANGLE TRIAL

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Introduction: In the European MCL Network Triangle study the addition of ibrutinib to frontline rituximab-containing chemotherapy and subsequent maintenance therapy improved failure-free survival in young, fit patients with mantle cell lymphoma (MCL). Ibrutinib was administered with R-CHOP, but not with R-DHAP, during the induction phase.

Continuous, uninterrupted Bruton Tyrosine Kinase (BTK) inhibition could maximize the benefit of front-line therapy given that responses develop over time. Acalabrutinib is a second generation BTK inhibitor with less off-target inhibition than ibrutinib. We hypothesize that combining continuous acalabrutinib with R-CHOP may result in a tolerable, outpatient, highly active regimen producing favorable outcomes.

Methods: NCT04566887 is a phase II, non-randomized, single-arm study conducted across 5 academic centres in Canada. Patients ≥18 years of age with previously untreated MCL, ECOG performance status 0–2, adequate organ function and considered fit for autologous stem cell transplantation (ASCT) were included. Patients received 6 cycles of R-CHOP at standard doses plus acalabrutinib 100 mg twice per day orally. Responding patients proceeded with ASCT and maintenance rituximab and acalabrutinib for a total of 2 years.

The primary endpoint was the complete response (CR) rate after 6 cycles of induction with centrally reviewed PET/CT using the Lugano Criteria. The total sample size is $n = 54$. We present the results of a preplanned interim analysis when the first 24 subjects completed response assessments after 6 cycles of induction. The study would be terminated if <15/24 patients achieved a CR.

Results: The median age was 60 years (range 38–69), 16 (67%) were male, 23 (96%) had performance status 0–1, 19 (79%) Ann Arbor stage IV, 19 (79%) bone marrow involvement, 4 (17%) high risk MIPI, 3 (13%) blastoid/pleomorphic morphology, 7 (29%) Ki67 ≥30%. All patients completed 6 cycles of induction and proceeded to ASCT. The overall response rate was 100%, and 19 (79%) patients achieved a CR.

Table 1. Common AE, including all grade 3 and 4 AE regardless of frequency during the 6 cycles of induction with R-CHOP + acalabrutinib (n=24).

ADVERSE EVENT	Grade 1	Grade 2	Grade 3	Grade 4	Total
PERIPHERAL SENSORY OR MOTOR NEUROPATHY	10	4	0	0	14
HEADACHE	8	4	0	0	12
NAUSEA	6	4	0	0	10
NEUTROPENIA	0	2	5	2	9
FATIGUE	8	0	0	0	8
BLEEDING OR BRUISING	6	1	0	0	7
ORAL MUCOSITIS	5	2	0	0	7
VOMITING	1	5	0	0	6
INFECTIONS AND INFESTATIONS.	1	4	0	0	5
DIARRHEA	4	0	0	0	4
DIZZINESS	4	0	0	0	4
DYSPEPSIA	2	2	0	0	4
LOWER EXTREMITY EDEMA	4	0	0	0	4
FEBRILE NEUTROPENIA	0	2	1	0	3
MUSCLE CRAMP	3	0	0	0	3
ANEMIA	0	0	1	0	1
HEART FAILURE	0	0	1	0	1
PLATELET COUNT DECREASED	0	0	1	0	1

With a median follow up of 12 months by the reverse Kaplan-Meier method, the 12-month PFS was 89.4% (95% CI: 63.8–97.3), and OS 100% (95% CI not calculable). Three subjects have developed PD so far, all with adverse clinical and biological factors:

- Baseline high-risk MIPI and Ki67 70%; biopsy at relapse TP53 positive by immunohistochemistry (IHC),
- Baseline intermediate risk MIPI and Ki67 60%; biopsy at relapse with pleomorphic morphology, TP53 positive by IHC, Ki67 100%,
- Baseline high risk MIPI, Ki67 ≥30%, and blastoid morphology.

Table 1 lists adverse events (AE) during the 6 cycles of induction. There were no grade 5 AE. Most infections were respiratory including 1 case with mild COVID-19.

Conclusions: Acalabrutinib + R-CHOP is associated with a 79% CR rate with low rates of grade 3–4 AE expected for this combination. The study is ongoing, with expected full accrual by April 2023.

The research was funded by: This investigator-initiated trial was funded by AstraZeneca.

Keywords: combination therapies, indolent non-Hodgkin lymphoma, molecular targeted therapies

Conflicts of interests pertinent to the abstract.

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Other remuneration: Patents using gene expression to subtype aggressive lymphoma, including one licensed to Veracyte

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356 | VENETOCLAX BASED COMBINATION THERAPY DOES NOT OVERCOME POOR OUTCOMES IN BTKI-REFRACTORY MANTLE CELL LYMPHOMA: PHASE 2 TRIAL OF UMBRALISIB, UBLITUXIMAB, AND VENETOCLAX

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Introduction: Novel agents such as the Bruton's tyrosine kinase inhibitors (BTKi) have improved care for patients with mantle cell lymphoma (MCL), yet progression during BTKi is associated with poor outcomes. Ibrutinib resistance is associated with activation of phosphatidylinositol 3-kinase (PI3K) signaling. However, in xenograft

models, inhibition of PI3K appears to overcome BTK resistance and the addition of BCL2 inhibition is synergistic.

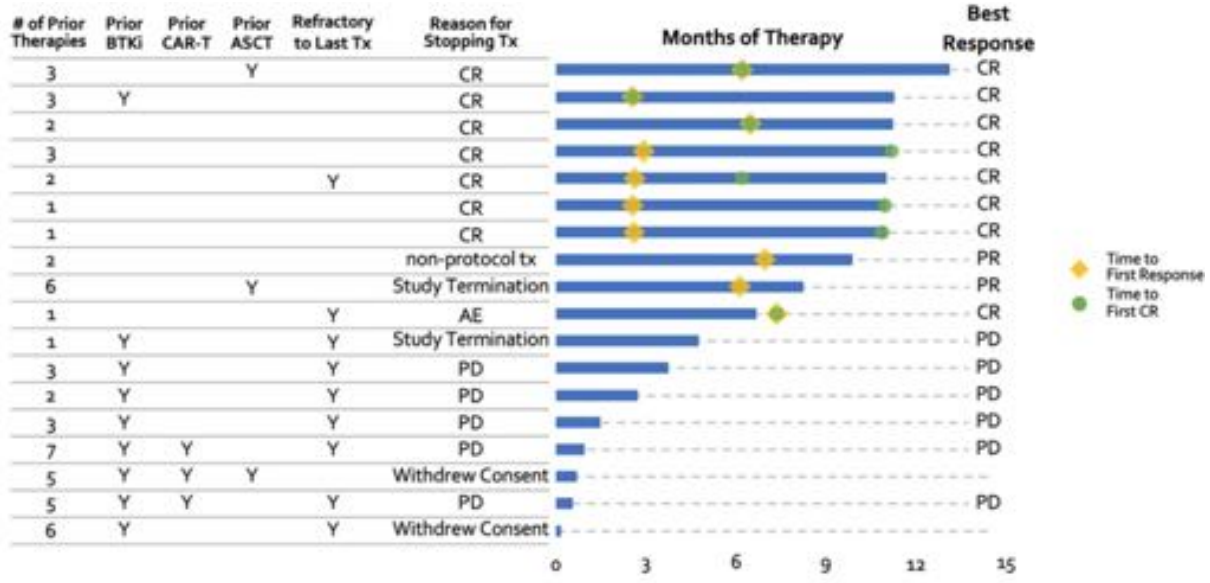
We therefore conducted a phase 2 trial to investigate the activity of the PI3Kδ/CK1ε inhibitor umbralisib (umbra) with anti-CD20 monoclonal antibody ublituximab (ubli) and the BCL2 inhibitor venetoclax (U2Ven) in patients with relapsed or refractory MCL. The primary objective was safety with secondary objectives of overall response rate (ORR), complete response (CR) rate, and progression-free survival (PFS).

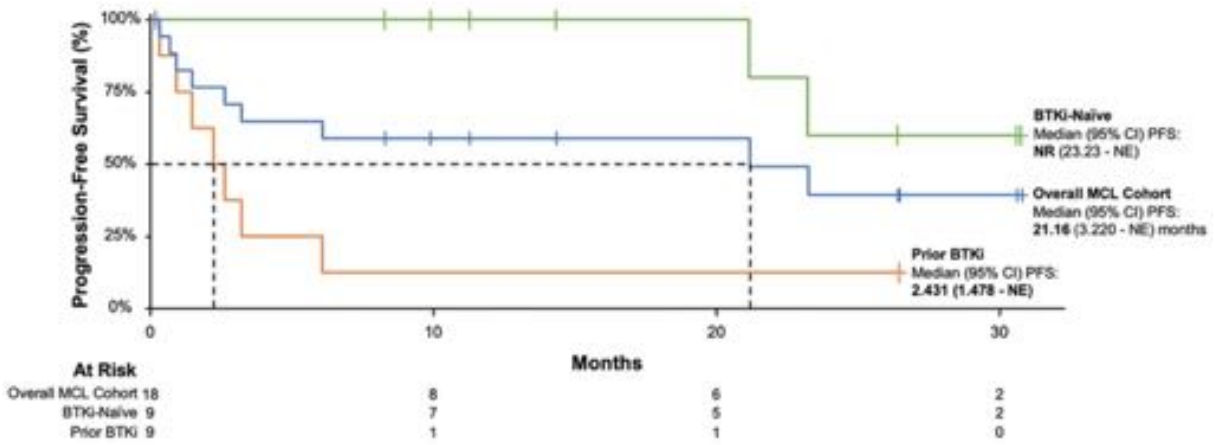
Methods: Patients received umbra 800 mg daily and ubli 900 mg on days 1, 8, 15 of the first 28-day cycle followed by umbr daily, ubli on day 1 of cycles 2–6, and ven 400 mg (via the standard weekly ramp-up) starting with cycle 2. Response assessments were performed with CTs prior to cycles 3 and 7, and with a PET prior to cycle 12. Patients in CR stopped therapy following 12 cycles; those not in CR remained on umbra. The study was halted by the FDA for PI3K safety concerns.

Results: 18 patients were enrolled with a median age of 70 (range 51–85) and a median of 3 (range 1–7) prior therapies, including 50% who were refractory and 50% who had received a BTKi. Two patients withdrew consent shortly after initiation of therapy and are excluded from efficacy analyses; all 18 are included in safety reporting. With a median follow-up of 21 months, there was a 63% (n = 9) ORR, including a best CR rate of 50% (n = 8) and a partial response rate of 13% (n = 2). Seven patients were able to stop therapy due to achieving a CR. The median PFS was 21.2 months, and the median OS was not reached. 100% of BTKi naïve patients responded to therapy versus only 14% in those with prior BTKi exposure. Median PFS was not reached for the BTKi naïve patients versus 2.4 months following BTKi.

The most common grade 1–2 adverse events were ubli infusion reactions (50%), anemia (33%), fatigue (33%), cough (28%), lymphocytopenia (28%), thrombocytopenia (22%) and nausea (22%). Grade 3 or 4 adverse events occurring in ≥2 patients included thrombocytopenia and ALT increase, including 1 discontinuation for alcoholic hepatitis. There was no reported colitis, pneumonitis, or tumor lysis syndrome.

Discussion: Time-limited U2Ven had a higher ORR and CR rate than would be expected with monotherapy, supporting the preclinical data suggesting synergy with inhibition of the BCL2 and PI3K axes. This otherwise potent combination including ven was unable to overcome





the poor outcomes seen after BTKi progression. Cellular therapies should be prioritized for these patients for whom there is a critical ongoing need for novel treatment options.

The research was funded by: TG Therapeutics

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, molecular targeted therapies

Conflicts of interests pertinent to the abstract.

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Research funding: Abbvie, AstraZeneca, Beigene, Juno, Janssen, Loxo, TG Therapeutics
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357 | ANALYSIS OF IMMUNE AND HIGH-RISK BIOMARKERS IN PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA TREATED WITH GLOFITAMAB MONOTHERAPY

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Introduction: Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin lymphoma with no recognized standard of care in the relapsed or refractory (R/R) setting. Glofitamab is a CD20xCD3 T-cell-engaging bispecific antibody with a novel 2:1 configuration that confers bivalency for CD20 (B cells) and monovalency for CD3 (T cells), redirecting T cells to eliminate malignant B cells. In an ongoing Phase I/II study (NCT03075696), glofitamab monotherapy demonstrated high response rates and a manageable safety profile in patients (pts) with R/R MCL (Phillips et al. ASH 2020). Here, we present a preliminary biomarker analysis in pts with R/R MCL to characterize the pharmacodynamic effect of glofitamab and assess response to glofitamab in high-risk pts.

Methods: Eligible pts had R/R MCL and had received ≥1 prior therapy. Pts received intravenous (IV) obinutuzumab pretreatment (1000 mg or 2000 mg) 7 days prior to the first dose of glofitamab on Day (D) 1. IV glofitamab step-up dosing was then given on D8 (2.5 mg) and D15 (10 mg) of Cycle (C) 1, followed by either 16 mg or 30 mg glofitamab on D1 of C2–12 (21-day cycles). Peripheral T cells were evaluated by flow cytometry. Baseline (BL) tumor biopsies were assessed by CD20+/PAX5+ immunohistochemistry and CD8+/Ki67+ immunofluorescence. Plasma interferon (IFN)-γ levels were evaluated by enzyme-linked immunosorbent assay. Bulk RNA-sequencing

analysis from tumor biopsies included gene set variation analysis and xCell cell type enrichment.

Results: As of 10 October 2022, 49 pts with R/R MCL were evaluable for efficacy. Investigator-assessed best overall response rate was 83.7% (41/49) and complete metabolic response rate was 75.5% (37/49). In total, 32.4% of pts (12/37) achieving a complete response showed biomarkers of poor prognosis at BL, including high Ki67 expression, *TP53* mutation, high MCL International Prognostic Index score, and a high MCL35 gene signature. Pharmacodynamic analysis showed that glofitamab induced T-cell activation characterized by margination, an increase in the percentage of CD4+ and CD8+ T cells expressing activation markers, and increased IFN-γ levels. Analysis of BL tumor biopsies showed no association between CD20 expression levels and response. Tumor CD8+ T-cell count tended to be higher in responders versus non-responders. Additionally, gene expression analysis of BL tumors ($n = 27$) showed a trend towards higher T-cell signatures and lower tumor proliferation-related signatures, in responders versus non-responders.

Conclusions: Glofitamab monotherapy induces activation of peripheral T cells in pts with R/R MCL. Analysis of BL tumor characteristics suggests that an immune-enriched environment, but not CD20 expression levels, may favor a better response to glofitamab in R/R MCL. Importantly, analysis of biomarkers of poor prognosis at BL shows that glofitamab could drive responses in high-risk MCL.

* equal contributors

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Keyword: tumor biology and heterogeneity

Conflicts of interests pertinent to the abstract.

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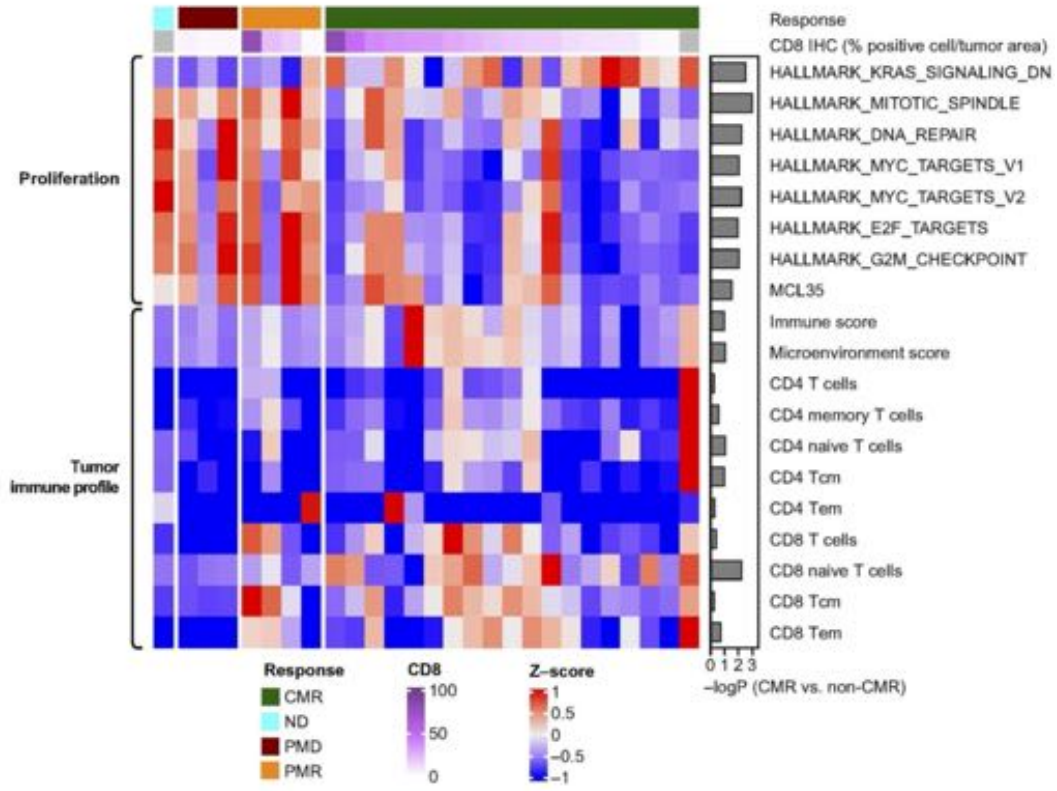
Employment or leadership position: Roche/Genentech, Inc.

Stock ownership: Roche/Genentech, Inc.

Figure: Summary of tumor proliferation and tumor environment profile by RNA-sequencing from patients with R/R MCL treated with glofitamab monotherapy



CMR, complete metabolic response; DN, downregulated; IHC, immunohistochemistry; MCL, mantle cell lymphoma; ND, no metabolic disease; PMD, progressive metabolic disease; PMR, partial metabolic response; R/R, relapsed or refractory; Tcm, central memory T cells; Tem, effector memory T cells

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358 | REAL-WORLD OUTCOMES OF BREXUCABTAGENE AUTOLEUCEL (BREXU-CEL) FOR RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA (R/R MCL): A CIBMTR SUBGROUP ANALYSIS BY PRIOR TREATMENT

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Introduction: Brexu-cel is a CAR T-cell therapy approved for adult patients (pts) with r/r MCL. In a 3-year follow-up of ZUMA-2 (Wang et al. 2022), ORR was 91% (CR, 68%). Median DOR, PFS, and OS were 28.2, 25.8, and 46.6 mo, respectively. Here, we describe real-world outcomes with brexu-cel analyzed by prior receipt of BTK inhibitor (BTKi), bendamustine, or autoHCT, and 1–2 versus ≥3 prior lines (L) of therapy.
Methods: From July 2020 to August 2022, 397 pts who received brexu-cel for r/r MCL in 79 US centers were registered in the CIBMTR observational database. This analysis included 272 pts (median follow-up, 6.6 mo; range, 0.3–16.5), excluding pts with prior non-HCT cellular therapy ($n = 7$), missing data on prior treatment, or no follow-up. Descriptive analyses were used for all outcomes.
Results: Median age was 65.8 y (range, 34.1–84.9); most pts were male (78%). Prior to infusion, 7% had ECOG PS ≥2; 76% had clinically significant comorbidities; 4% had extranodal CNS involvement. At diagnosis, Ki-67 ≥30%, Ki-67 ≥50%, and TP53/17p deletion were reported in 69% ($n = 111/160$), 44% ($n = 70/160$), and 19% ($n = 29/153$) of pts, respectively. Pts had a median of 4L of prior therapy (range, 1–12L; 6% as 2L). Prior to leukapheresis, 87% and 54% of pts had received BTKi or bendamustine, respectively, and 31% were autoHCT recipients. Median time from leukapheresis to infusion was 28 d (IQR, 26–34 d); 18% of pts received bridging therapy.

Overall ORR was 89% (CR, 78%). At 6 mo, cumulative incidence of relapse/PD was 21%; DOR, PFS, and OS were 76%, 73%, and 83%, respectively. Grade ≥3 (ASTCT consensus) CRS and ICANS occurred in 9% and 27% of pts, respectively (88% and 62% for any grade). Most CRS (94%) and ICANS (79%) resolved within 3 weeks. Prolonged cytopenia by 30 d occurred in 23% of pts. NRM at 100 d and 180 d were 3% and 6%, respectively, mainly due to infections.

ORR in BTKi-naive (n = 36) versus -exposed (n = 233) pts was 85% (CR, 79%; 6-mo DOR, 84%) versus 89% (CR, 77%; 6-mo DOR, 74%); in pts with (n = 145) versus without (n = 124) prior bendamustine was 88% (CR, 75%; 6-mo DOR, 75%) versus 89% (CR, 80%; 6-mo DOR, 77%); in pts with (n = 83) versus without (n = 188) prior autoHCT was 90% (CR, 82%; 6-mo DOR, 83%) versus 88% (CR, 76%; 6-mo DOR, 72%). CR rates were higher in pts with brexu-cel as 2/3L (n = 56) versus 4L+ (n = 213) (91% vs. 74%; ORR, 92% vs. 88%; 6-mo DOR, 77% vs. 75%). Safety profiles were similar regardless of prior BTKi or autoHCT. Pts with prior bendamustine had lower rates of Grade ≥3 ICANS (19% vs. 36%) but higher prolonged cytopenia (29% vs. 16%) versus those without.

Conclusions: These early findings suggest that real-world outcomes with brexu-cel are consistent regardless of prior BTKi, bendamustine, or autoHCT. Use of brexu-cel in earlier lines may help achieve a higher CR rate. Further studies with longer follow-up are warranted to contextualize response rates in relation to long-term clinical benefits of brexu-cel. Updated data with longer follow-up will be presented.

NA and SK contributed equally.

Encore Abstract - previously submitted to ASCO 2023 and EHA 2023

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Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, immunotherapy

Conflicts of interests pertinent to the abstract.

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359 | OUTCOMES OF BRIDGING AND SALVAGE RADIOTHERAPY IN RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA PATIENTS UNDERGOING CD19-TARGETED CAR T-CELL THERAPY

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Introduction: We sought to describe our early experience of using bridging and salvage radiation therapy (RT) in patients with relapsed/refractory mantle cell lymphoma (MCL) undergoing CD19-targeted chimeric antigen receptor (CAR) T-cell therapy.

Methods: A retrospective study was conducted for consecutive MCL patients who were treated with commercially available CD19-targeted CAR T-cell therapy between 2020 and 2022 at a single institution. Patients who received RT pre-and post-CAR T-cell therapy were identified and analyzed using descriptive and statistical analysis. Overall survival (OS) from the date of CAR T infusion was estimated with the Kaplan-Meier method. The duration of local control (LC) was defined as the time between the start date of RT and the date of in-field progression/relapse. Response to RT was analyzed based on the total number of irradiated sites.

Results: A total of 21 patients with MCL who received CD19-targeted CAR T-cell therapy were identified (17 brexu cel, 3 tisa-cel, and 1 liso-cel) with a median follow-up of 15.3 months (24 days-36.2 months). The median age was 65 years at time of apheresis (43–83 years). The median OS for the entire cohort following CAR T-cell therapy was 24.5 months (95% CI: 21.5 months-not reached). Of the 21 patients, 1 patient received bridging RT prior to CAR T infusion, 1 patient received RT pre-and post-CAR T, and 5 patients received salvage RT post-CAR T with a total of 23 irradiated sites. Sites of RT include: extremities (10), central nervous system (3), pelvis/groin (3), head and neck (3), chest (2), abdomen (1), and multiple sites (1). The median dose/fractionation were 15 Gy (range, 3.6–45 Gy) and 5 fractions (range, 2–16 fractions). The in-field responses of the 21 evaluable sites were as follows: complete response (CR) (n = 18, 86%) and partial response (PR) (n = 3, 14%), translating into an LC rate of 100%; the remaining 2 sites were not evaluable since the patient died shortly after receiving RT due to progressive lymphoma. Notably, there was no correlation between RT dose and LC; 10 sites received low-dose RT (3.6–6 Gy) with responses as follows: CR (n = 7, 70%) and PR (n = 3, 30%). Only 1 patient experienced grade 3–4 RT-related toxicities. At the time of the last follow-up, 4 patients remained alive, and 3 patients succumbed to progressive lymphoma.

Conclusion: As no studies exclusively focusing on CAR T-cell therapy and bridging or salvage RT have been published among relapsed/refractory MCL patients, our early experience underlines that using RT as a bridging and salvage approach is associated with excellent in-field control and limited toxicity in the peri-CAR T setting. Low-dose RT for MCL appears to be very effective in this highly refractory population and warrants further investigation.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies

No conflicts of interests pertinent to the abstract.

PTCL

360 | LONG TERM OUTCOME OF PERIPHERAL T CELL LYMPHOMAS: 10Y FOLLOW-UP ANALYSIS OF THE INTERNATIONAL PROSPECTIVE T CELL PROJECT NETWORK

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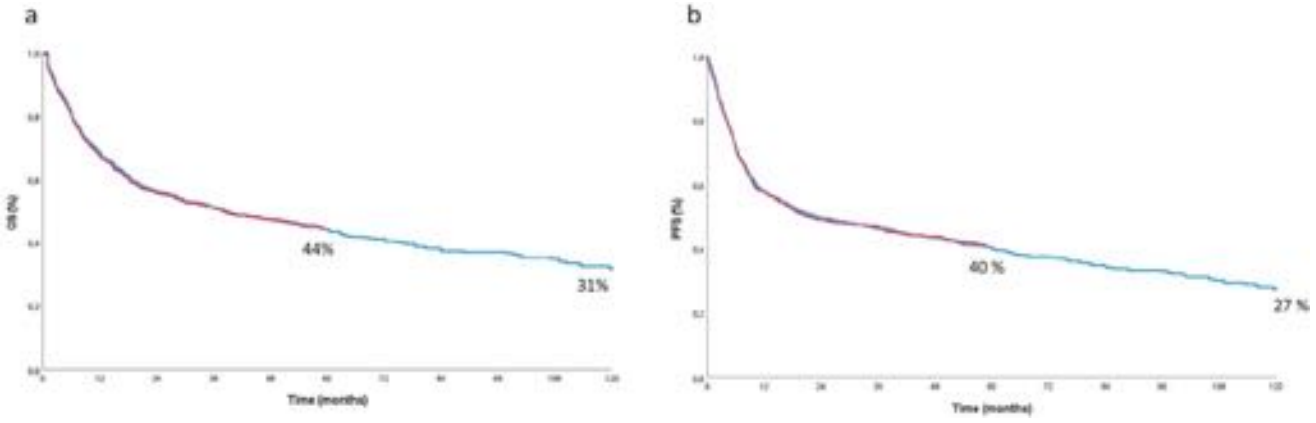
Introduction: Peripheral T cell lymphomas (PTCLs) are a rare, heterogeneous group of hematological malignancies with too often poor prognosis for almost all subtypes. The T-Cell Project (TCP; registered at clinicaltrials.gov identifier: 01142674) was a prospective cohort study aimed at better understanding clinical characteristics and outcome of patients with PTCL. Here we report the results of 10-year follow up, focused on late relapses and long term survival.

Methods: The TCP started in September 2006 as a prospective registry of patients with mature PTCLs. Between December 2006 and March 2018, 1669 patients were registered and 1,553 patients were eligible in the study. Recently, a survey was launched asking for the willingness of the centers to provide long term follow up data. So far, out of 1,553 eligible patients, 713 were referred by Centers that provided information on long-term follow-up and have been included in the present analysis; 840 cases, referred by centers that did not participate to this long term survival analysis were excluded. However, both groups showed similar baseline characteristics and 5y OS (44% vs. 44%) and PFS (37% vs. 35%), thus minimizing selection biases

Result: Out of these 713 patients, 255 patients (36%) had a diagnosis of PTCL NOS, 133 (19%) of AITL, 124 (17%) of ALCL ALK-, 62 (8%) of ACL ALK- and 13 (2%) of NKTCL. The median age at diagnosis was 56 years (range, 18–88 years), with a slight male predominance (55%). B symptoms were present in 44% and extranodal involvement in 56% of patients. Patients receiving chemotherapy alone and radiotherapy alone comprises 58% and 3% respectively; while the 18% received CHT+RT. Of evaluable patients, 60% received anthracycline-based chemotherapy, 24% anthracycline/etoposide and 12% etoposide alone. A minority (16%) of the total cohort underwent high-dose chemotherapy with autologous stem cell support as first-line consolidation.

After a median follow-up of 82 months, 35 (12%) of patients had an event of progression or death beyond 5 years.

The 5- and 10-year rates of both overall survival and progression-free have decreased from 44% and 40%, to 31% and 27%, respectively (Figure 1).



For those patients alive at 5 years, the chance of surviving the subsequent 5 years was 83% (95% CI: 61–99). Furthermore, for patients progression free at 5 years the probability of being disease alive and free in the subsequent 5 years was 78% (95% CI: 60–96).
Ten year OS and PFS rates for patients alive at 5 years were: 77% and 73% for PTCL NOS, 85% and 76% for AITL, 88% and 87% for ALCL ALK-, 100% and 100% for ALCL ALK+), and 78% and 80% (for NKTCL).
Conclusions: Based on the results of this survey, the risk of death in the subsequent five years of patients with PTCL surviving at least five years since initial diagnosis is much lower (25%) than the risk of death in the first 5 years (55%).

Keyword: aggressive T-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

361 | DIAGNOSIS AND MANAGEMENT OF ADULT T-CELL LEUKEMIA/LYMPHOMA IN A BRAZILIAN COHORT. T-CELL BRAZIL PROJECT

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Introduction: Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell malignancy caused by human T-cell leukemia virus type I (HTLV-1), endemic in some areas of the world, such as Brazil. Between 3% and 5% of HTLV-1-infected individuals develop ATL after a long latency. The clinical features are heterogeneous and classified into acute, lymphoma, chronic and smoldering types. Acute and lymphoma types are defined as aggressive whereas the others as indolent ATL. On April 2017, the T-cell Brazil project was launched.
Methods: Ambispective observational study design collected 90 ATL patients from 606 registered cases in the T-Cell Brazil Project. Its main goal is to describe demographic and clinical features, analyze the overall and progression-free survival (OS and PFS), and try to identify factors that could influence them. REDcap Platform has been used to collect and store data, and the IBM-SPSS version 24 for statistical analysis.
Results: The median age was 50 years (23–88), 59% female; 50% was lymphoma subtype, followed by 33% acute (both aggressive), 12% chronic and 5% smoldering (indolent); 87% had advanced stage disease (III-IV, Ann Arbor), 57% had B symptoms and 11% had Central Nervous System involved. Both indolent and aggressive had elevated serum LDH levels. 25% received chemotherapy plus immunotherapy, whilst 46% took chemotherapy alone with anthracycline-based regimens (46% CHOEP; 33% CHOP; 21% others). The best response (complete plus partial) after 1st line of treatment reached 50%; 31% had no response or progression; 13% was undetermined due early death; 5% were on treatment, and 1% had stable disease (without treatment). Median follow-up was ten months (0–78) and 18 months for 35% of alive cases. OS for 24 months was 34% (95% CI: 24%–44%), whereas 24-month PFS was 20% (95% CI: 12%–28%). Indolent presented better OS and PFS when compared with Aggressive; 86% versus 33%, $P = 0.001$ for OS and 45% versus 12%, $P = 0.002$ for PFS. Public medical care had worst OS and PFS than private ($P = 0.14$ and $P = 0.05$). The multivariate Cox Regression for OS resulted hypoalbuminemia - albumin <3.5 g/dL (HR 2.13 CI95% 1.10–4.12, $P = 0.024$) plus LDH twice the normal value (HR 2.49 CI95% 1.17–5.32, $P = 0.018$) as predictors. And for PFS were male (HR 1.83 CI95% 1.03–3.24, $P = 0.037$), ECOG > 1 (HR 2.01 CI95% 1.10–3.70, $P = 0.023$) and hypoalbuminemia (HR 3.35 CI95% 1.82–6.17, $P < 0.0001$).

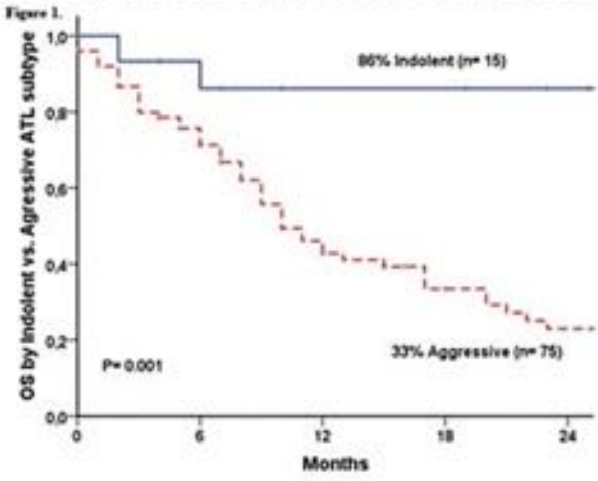

Figure 1. OS by Indolent vs. Aggressive ATL

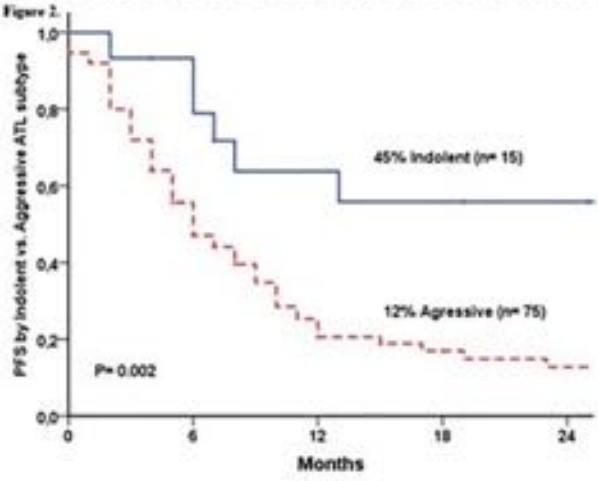

Figure 2. PFS by Indolent vs. Aggressive ATL

Conclusion: Prognosis of ATL remains dismal and is associated with the high incidence of aggressive subtypes. Our median age was younger than the literature, and the best response was achieved in half cases. However, the maintenance therapy did not avoid an early relapse, and Brazilian public medical care showed worst results.

The research was funded by: Educational Support by Takeda

Keyword: aggressive T-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

362 | NEWLY DIAGNOSED EXTRANODAL NATURAL KILLER/T CELL LYMPHOMA (ENKTL) TREATED BY ANTI-PD-1 ANTIBODY PLUS HISTONE DEACETYLASE INHIBITOR FOLLOWED BY P-GEMOX REGIMEN

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Background: ENKTL is a highly aggressive NHL with a higher incidence in Asia. In 2020 ASH meeting, we reported Sintilimab(anti-PD-1 antibody) plus Chidamide(an oral subtype-selective HDACi) yielded effective antitumor activity, durable response with mild toxicity in patients with relapsed or refractory ENKTL. We then initiated this exploratory study to investigate the efficacy and safety of Sintilimab plus Chidamide(SC) for patients with newly diagnosed ENKTL.

Methods: This trial enrolled eligible patients with newly diagnosed ENKTL(ND-ENKTL); ECOG score ≤2; at least one measurable or evaluable lesion. All patients received 2–3 cycles of Sintilimab (200 mg) plus Chidamide (30 mg, twice a week). For patients with early stage, 2 cycles of SC were given, subsequent 2–4 cycles of P-GemOx regimen administered and followed by involved field radiotherapy (IFRT). For advanced stage, patients were treated with 3 cycles of SC and 3–6 cycles of P-GemOx. The primary study endpoints are the ORR of SC and end of treatment assessed according to the lymphoma response to immunomodulatory therapy criteria (LYRIC). Key secondary endpoints included DOR, PFS, OS and safety.

Results: From July 2019 to Nov 2021, 42 eligible patients were enrolled from Sun Yat-sen University Cancer Center. The median age was 47.5 (range, 20–81) years, 16(38%) patients with stage III-IV, 15 (31%) patients with PINK-E score≥3. All patients were evaluated for efficacy. For stage I-II, 21(81%) patients achieved response, including 18(69%) CR patients with SC. After 2 cycles of SC, 17(94%) of 18 CR patients chosen to continue SC treatment. Only 1 (6%) PR patients accepted 2 cycles of P-GemOx and got CR after chemotherapy. Twenty-five (96%) patients obtained CR after IFRT. For stage III–IV, 9(56%) patients achieved response with 13%(2/16) CR, 3(33.3%) patients experienced rapid progression disease (RPD) in SC portion. Ten (63%) patients entered P-GemOx portion including 1 RPD patient. Thirteen (81%) patient got ORR with 69% (11/16) CR after whole treatment. The median follow-up time was 24.1(5.4–44.3) months. The 2-year PFS and OS rate were 76% and 78%, the prognosis of early stage is better than advanced stage (Fig. 1). Two RPD patients died within one month. Circulating EBV-DNA clearance after SC significantly correlated with superior outcome. Forty(95.2%) patients reported treatment-related adverse effects (TRAEs). The most common TRAEs (≥10%) were neutropenia (43%), thrombocytopenia (38%), elevated transaminase (29%), and anemia (24%). The most common grade 3 TRAEs (≥10%) was elevated transaminase (10%), no grade 4 TRAEs.

Conclusion: Sintilimab plus Chidamide yielded effective antitumor activity and manageable toxicities in ND-ENKTL. It may be a

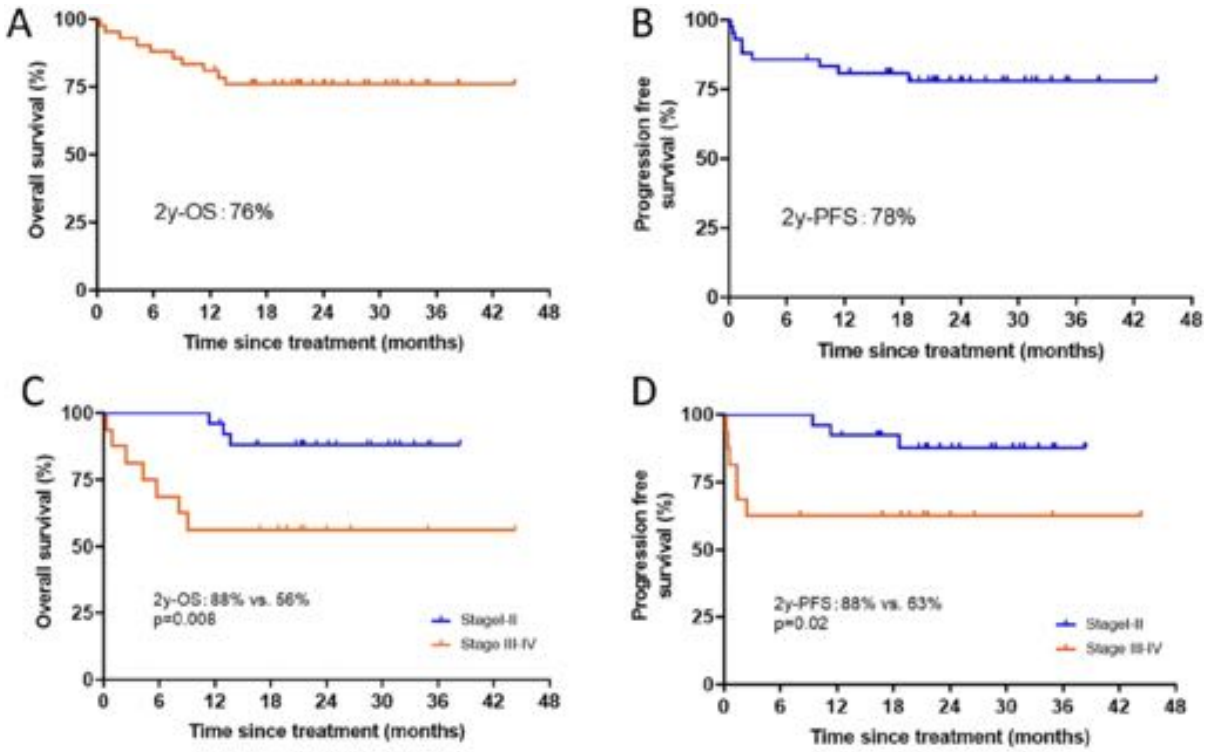

Fig 1. Long-term survival. (A)OS of whole cohort, (B)PFS of whole cohort,(C) OS of stageI/II vs. III/IV, (D) PFS of stageI/II vs. III/IV

promising chemo-free induction therapeutic portion for this population, especially for early-stage patients.

Keywords: aggressive T-cell non-Hodgkin lymphoma, extranodal non-Hodgkin lymphoma, immunotherapy

No conflicts of interests pertinent to the abstract.

363 | ENTEROPATHY ASSOCIATED T-CELL LYMPHOMA: A POPULATION-BASED COHORT STUDY ON INCIDENCE, TREATMENT AND OUTCOME IN THE NETHERLANDS

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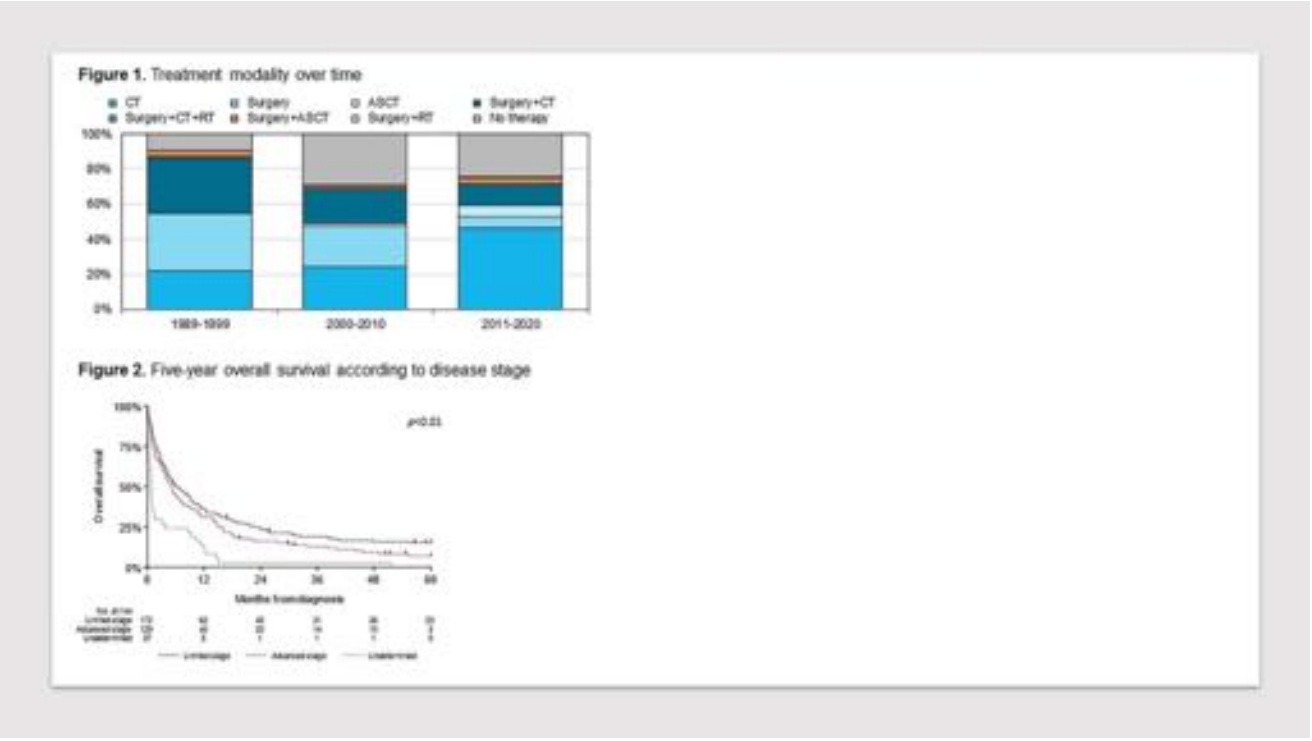
Introduction: Enteropathy associated T-cell lymphoma (EATL) is a rare peripheral T-cell lymphoma (PTCL) associated with celiac disease that has a poor prognosis. Treatment of EATL is challenging due to the lack of clinical trials. In PTCL, the preferred chemotherapeutic regimen is cyclophosphamide, doxorubicine, vincristine and prednisone (CHOP), either with or without etoposide (CHOEP) followed by consolidative autologous stem cell transplantation (ASCT). This nationwide Dutch study describes the incidence, treatment and outcome of all reported EATL cases.

Methods: All patients diagnosed with EATL between 1989 and 2020 were identified in the Netherlands Cancer Registry with survival follow-up through February 1, 2022, thereby excluding post-mortem diagnoses. Baseline characteristics, treatment modality and survival outcomes were collected. Patients were categorized into three periods (1989–1999, 2000–2010, 2011–2020) and in limited (I/II) or advanced (III/IV) stage disease. For patients diagnosed as of 2014, detailed information on treatment regimens was available. Overall survival (OS) was defined as the time from diagnosis to all-cause-death. Multivariable analysis of OS was performed using Cox regression.



Results: We included 338 patients (median age 67 years [range 37–90 years], 57% male) in our study. Limited stage disease was more common than advanced stage (51% versus 38%, 11% undetermined). Treatment consisted of surgery (18%), chemotherapy (CT; 33%), CT followed by ASCT (3%), surgery and CT (19%), surgery and CT followed by ASCT (3%), surgery and RT (1%) or no treatment (23%). Between 2014 and 2020, the most commonly used CT regimens were CHOP (54% in limited stage and 66% in advanced stage disease) and CHOEP (32% in all stages). Over time, the use of CT increased from 22% to 46%, whereas resection only and resection combined with CT became uncommon (decrease from 33% to 7%, and 23% to 5% respectively; Figure 1). Two-year OS improved from 19% in 1989–1999 to 26% in 2011–2020. The 6-month, 2-year and 5-year OS for limited stage were 51%, 24% and 15% (median OS 6.3 months) and for advanced stage 44%, 16% and 7% (median OS 5.1 months), respectively (Figure 2). In multivariable analysis, surgery only (hazard ratio [HR] 1.97; 95% confidence interval [CI] 1.41–2.74), no therapy (HR 3.66; 95% CI: 1.72–3.76) and advanced stage disease (HR 1.31; 95% CI: 1.02–1.70) were independent predictors of poor prognosis, whereas ASCT (HR 0.38; 95% CI: 0.17–0.81) was associated with improved OS.

Conclusion: The prognosis of patients with EATL is dismal with a high mortality rate early after diagnosis and a lack of a survival plateau up to 5 years after diagnosis. The prognosis for limited stage is only marginally better than for advanced stage disease. There has not been a clinically significant improvement in OS over time and the development of novel therapeutic strategies is urgently needed.

Keyword: aggressive T-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

364 | COMPARISON OF CHOP-LIKE WITH OR WITHOUT TUCIDINOSTAT IN THE FIRST-LINE TREATMENT OF PERIPHERAL T-CELL LYMPHOMA: A RETROSPECTIVE PROPENSITY SCORE-MATCHED STUDY

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Introduction: Peripheral T cell lymphoma (PTCL) is a group of highly heterogeneous malignancies with a high rate of disease relapse or progression.Tucidinostat (formerly known as chidamide(C)),a novel histone deacetylase inhibitor, has shown promising results in T-cell lymphomas by multiple mechanisms and is currently approved by the Chinese FDA for relapsed/refractory PTCL.In this retrospective study,we compared the efficacy of Tucidinostat with CHOP-like (C+CHT) and CHOP-like (CHT) alone in newly diagnosed PTCL.

Methods: We reviewed 132 patients with PTCL diagnosed at the Shanxi Provincial Cancer Hospital Hematology Oncology Center from January 2015 to July 2021,of whom 109 patients were diagnosed with newly diagnosed PTCL,with last follow-up as of November 2022.Those in the C+CHT group who achieved complete remission received Tucidinostat maintenance therapy.The two groups of patients were subjected to 1:1 propensity score matching, according to whether the Prognostic index for PTCL-NOS(PIT) ≥2, pathological subtype, age > 60 years, and gender (matching tolerance = 0.024),36 pairs ($n = 72$) were matched. The primary study endpoint

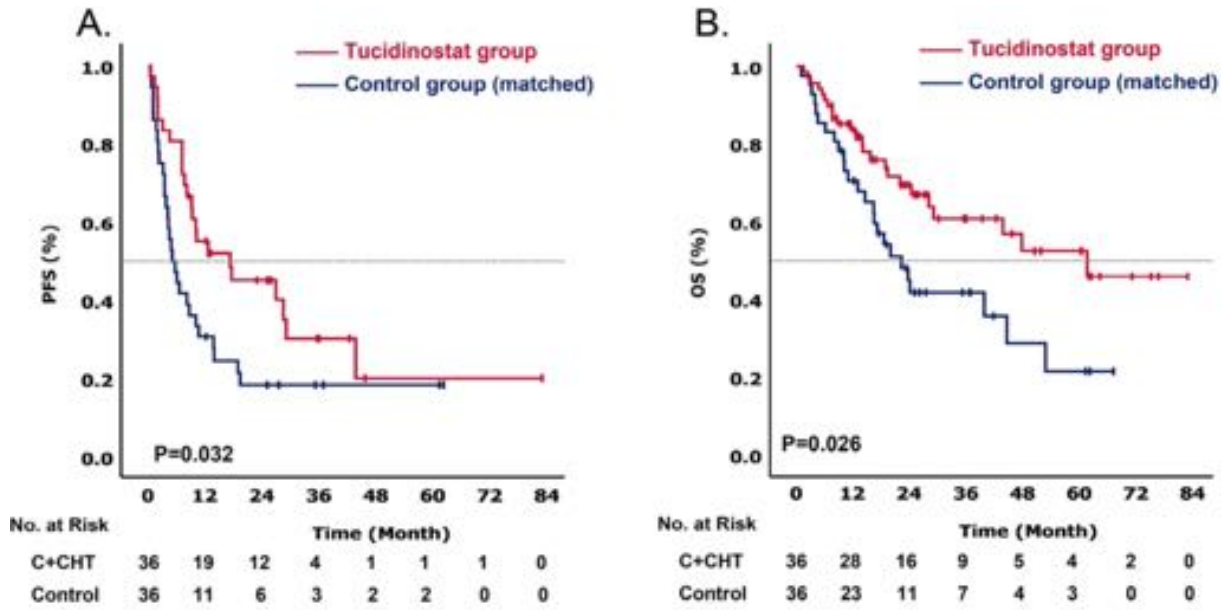

Figure 1. (A) and (B): PFS and OS curves of Tucidinostat group and the matched Control group;

of this study was progression-free survival (PFS), and the secondary study endpoints were overall survival (OS), objective remission rate (ORR) at the end of the first-line chemotherapy regimen, CR rate and adverse events (AEs).

Results: After matching,no statistical difference was found in baseline characteristics between C+CHT ($n = 36$) and control ($n = 36$) groups (all $P > 0.05$).The ORR for C+CHT group and control group were 72.2% and 52.8% ($p = 0.088$), with the CR rate of 44.4% and 33.3% ($p = 0.334$). After median follow-up of 18.7 (range 1.0–82.8) months, the median PFS in C+CHT group and control group were 17.2 and 5.0 months, respectively; the 2-year PFS was 67.9% and 25.3%, respectively; the median OS was 43.7 and 18.5 months, respectively; and the 2-year survival rate was 65.6% and 35.7%, respectively. Compared with control group, C+CHT group displayed significantly longer PFS(HR = 0.553, 95% CI: 0.319–0.959,$p = 0.035$, Figure 1A) and OS(HR = 0.483, 95% CI: 0.251–0.930, $p = 0.029$, Figure 1B). Cox analyses further verify that the effect values were basically consistent with the matching results (PFS HR = 0.552, OS HR = 0.469).

Common grade 3–4 hematological AEs in the C+CHT group were leukopenia (55.9%), neutropenia (52.9%), thrombocytopenia (26.5%), and anemia (20.6%), the incidence of AEs was comparable to that of the control group. Common non-hematological AEs, the incidences of elevated AST and ALT were higher in the C+CHT group than in the control group($p = 0.028$ and $p = 0.021$, respectively), but they were mainly grade 1 AEs, which could be resolved with supportive treatment.

Conclusions: Our study preliminarily shows that Tucidinostat with CHOP-like sequential Tucidinostat maintenance may be an effective treatment for newly diagnosed PTCL patients.

Keyword: aggressive T-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

365 | ROLE OF UPFRONT AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN ADULTS WITH T-NHL IN FIRST COMPLETE REMISSION (CR1): A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

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Introduction: There is currently no consensus on the role of upfront ASCT for patients with T cell Non-Hodgkin lymphomas (T-NHL), especially in patients who have achieved complete remission (CR1) following induction chemotherapy. To date, no randomized control trials (RCTs) exist and available data is conflicting, especially with regards to T-NHL subtypes that might benefit. A systematic review and meta-analysis of all comparative studies (randomized, non-randomized and observational) was hence performed to address this question.

Methods: A comprehensive, systematic search (from 1/2000 to 2/2022) of MEDLINE/PubMed, EMBASE and Cochrane databases was performed. PRISMA and Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were followed. Studies were screened based on predefined inclusion/exclusion criteria, and were critically appraised for outcomes of interest [progression free survival (PFS) and overall survival (OS)]. Quality of studies was assessed using Newcastle-Ottawa Scale. Hazard ratios (HRs) and corresponding 95% Cis were calculated, and the meta-analysis was performed using the random-effects model. Test for heterogeneity was performed using I2 statistic.

Results: Of 3297 unique records, 17 studies (prospective = 6, retrospective = 11) were included. Median follow up in these

Figure 1a: PFS in the AITL subgroup

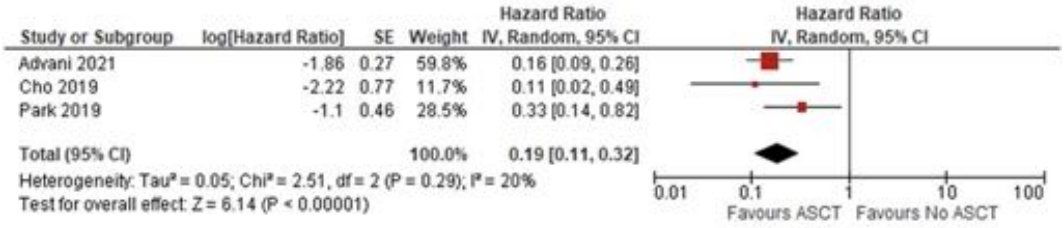
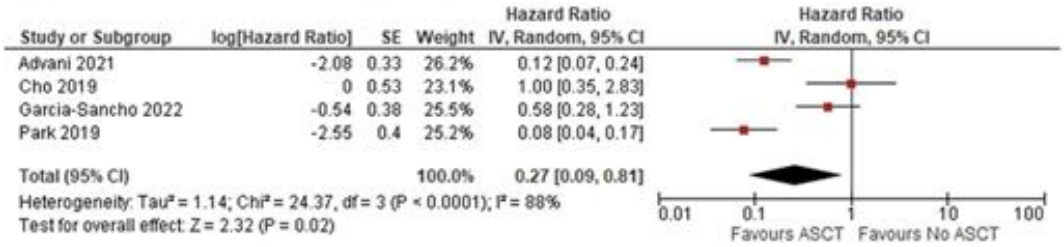


Figure 1b: OS in the AITL subgroup



studies ranged from 22 to 94 mths. Ten studies compared upfront ASCT versus No ASCT in patients with complete remission (CR1), while in 7 patients achieving either PR1 (first partial remission) or CR1 were included[MS1]. Of these, 9 studies included only transplant eligible patients. The T-NHL subtypes included in the studies were also heterogenous, with nodal T-NHLs, in particular Angioimmunoblastic T-NHL (AITL) being amongst the most common subtypes.

Results: from the meta-analysis showed that PFS in T-NHL patients who underwent ASCT benefited (HR 0.64, 95% CI: 0.46–0.89, I2 = 74%) compared to not undergoing ASCT; however similar benefit was not observed in OS (HR 0.67, 95% CI: 0.36–1.23, I2 = 89%). Sensitivity analyses including only studies with patients transplanted in CR1, and studies involving transplant eligible patients showed similar findings. In the studies that evaluated patients with the AITL subtype, ASCT showed a significant benefit in PFS and OS, compared to not undergoing ASCT (PFS = HR 0.19, 95% CI: 0.11–0.32, I2 20%; OS = HR 0.27, 95% CI: 0.09–0.81, I2 88 (Figure 1).

Conclusions: In the absence of RCTs, the results of this systematic review/meta-analysis represents the best evidence supporting PFS benefits of upfront ASCT consolidation in patients with T-NHL in CR1 or CR1/PR1 after frontline chemotherapy. In particular, AITL patients showed significant PFS and OS benefits with upfront ASCT.

Keyword: stem cell transplant

No conflicts of interests pertinent to the abstract.

366 | A RANDOMIZED PHASE II TRIAL OF CHOP VERSUS ICED AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN NEWLY DIAGNOSED T-CELL LYMPHOMA

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Purpose: Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of non-Hodgkin lymphomas, and their prognoses are still poor because of frequent relapses and the absence of optimal standard therapy. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been the backbone of frontline chemotherapy for PTCL for many years. However, it is not clear whether anthracycline-based chemotherapies such as CHOP could be standard induction therapy for PTCL. Thus, we conducted a randomized phase II study to compare the efficacy of CHOP with fractionated ifosfamide, carboplatin, etoposide, and dexamethasone (ICED).

Patients and Methods: This study was a phase II, multicenter, open-label randomized trial at 21 hospitals that belonged to the Consortium for Improving Survival of Lymphoma (CISL) in Korea (CISL-1504/ROSE study). Eligible participants were patients aged 20–65 years with previously untreated histologically confirmed PTCLs based on the World Health Organization classification 2008 including PTCL-not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), ALK-negative anaplastic large-cell lymphoma (ALCL), enteropathy-associated T-cell lymphoma (EATL), and hepatosplenic T-cell lymphoma (HSTL). Patients with ALK-positive ALCL, extranodal NK/T-cell lymphoma, and mycosis fungoides/sezary syndrome were not included in the study. Patients were randomized at a 1:1 ratio to receive either CHOP or ICED every 3 weeks for 6 cycles. Upfront autologous stem cell transplantation (ASCT) was done for patients achieving complete or partial response and the primary end point was progression-free survival (PFS).

Results: Between September 2015 and March 2021, 145 patients were screened, and 138 patients were enrolled. The characteristics were not different between CHOP ($n = 69$) and ICED ($n = 66$), and PTCL-NOS ($n = 60$) and AITL ($n = 53$) were dominant. The objective response rate was not different between CHOP (41/69, 59.4%) and ICED (37/66, 56.1%), and the 3-year PFS was not different between CHOP (36.7%) and ICED (33.1%, $P = 0.709$). Around 80% of patients who completed either CHOP or ICED followed by upfront ASCT showed 3-year overall survival (Figure 1). There was no statistically significant difference in PFS between the CHOP and ICED arms for any subgroup analyzed except AITL. CHOP was favored over ICED in AITL patients, whereas ICED was favored over CHOP in EATL/HSTL patients. ICED was associated with more anemia, neutropenia, and thrombocytopenia of all grades and grade 3 or worse, and the frequency of febrile neutropenia was higher in the ICED arm.

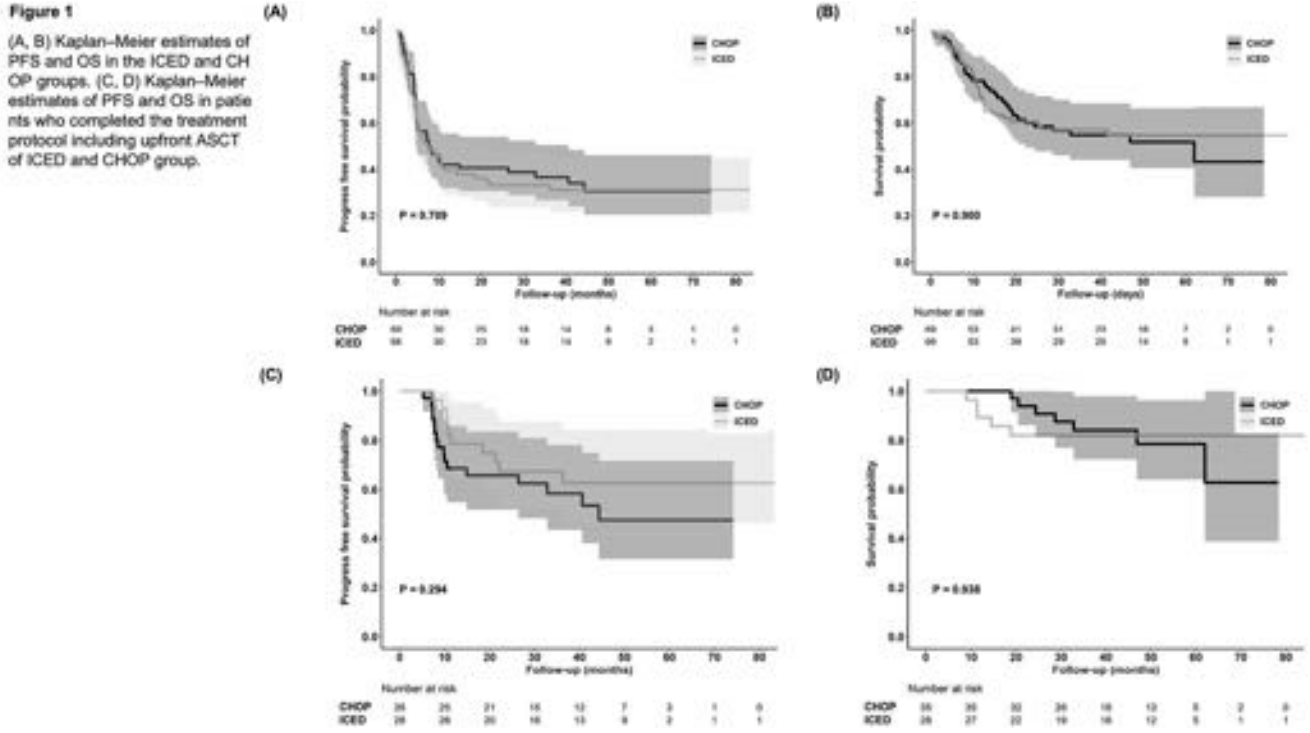

Figure 1
(A, B) Kaplan–Meier estimates of PFS and OS in the ICED and CHOP groups. (C, D) Kaplan–Meier estimates of PFS and OS in patients who completed the treatment protocol including upfront ASCT of ICED and CHOP group.

Conclusion: Our study showed no therapeutic difference between CHOP and ICED, and the role for upfront ASCT as a consolidation of complete response. In AITL, CHOP should remain the reference regimen based on its better outcome.

Keywords: aggressive T-cell non-Hodgkin lymphoma, chemotherapy, stem cell transplant

No conflicts of interests pertinent to the abstract.

367 | DUVELISIB IN PATIENTS WITH RELAPSED/REFRACTORY PERIPHERAL T-CELL LYMPHOMA FROM THE PHASE 2 PRIMO TRIAL EXPANSION PHASE: OUTCOMES BY BASELINE HISTOLOGY

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Introduction: Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of aggressive lymphomas with a poor prognosis for relapsed/refractory disease. The WHO classification of NK and T-cell lymphomas includes 39 entries; the 3 most common subtypes in the US are PTCL-NOS (not otherwise specified), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL).

Except for brentuximab vedotin in CD30-positive disease, agents were generally approved based on overall response rates (ORR) of less than 30%. The PRIMO Trial (NCT03372057; sponsored by Secura Bio, Inc.) evaluated duvelisib (DUV), an oral dual inhibitor of phosphatidylinositol 3-kinase (PI3K)-δ and PI3K-γ isoforms in PTCL. Anti-tumor activity of single agents may not be uniform across different PTCL subtypes. Here we present data on 3 specific subtypes of some of the patients (pts) included in the PRIMO trial (fully enrolled as of January 2022).

Methods: Eligibility criteria included adults with pathologically confirmed PTCL after ≥2 cycles of at least 1 prior standard regimen. A criterion for CD4 lymphocyte count ≥50/mm^3 was added for the Expansion Phase (EP). Based on dose optimization results, the EP dose was DUV 75 mg BID for 2 cycles, to maximize disease control, followed by 25 mg BID, to mitigate late toxicities, until progressive disease/unacceptable toxicity. *Pneumocystis jirovecii* prophylaxis was required; herpes simplex and varicella zoster virus prophylaxis were indicated as needed. The primary endpoint was ORR by IRC assessment (Lugano 2014 criteria); efficacy is or will be assessed in all pts who received ≥1 dose of DUV. Secondary objectives included additional outcome measures, safety, and pharmacokinetics. Exploratory endpoints included pharmacodynamics and biomarkers.

Results: The PRIMO study included 101 pts from the EP (data cutoff October 1, 2021), with a median follow-up of 8.7 months (mo) from time of first response. In the overall PRIMO study (N = 101), pts had a median age of 67.0 (21–92) years, a median of 3 (1–9) prior lines of therapy, an ORR (by IRC) of 49%, a CR rate of 34%, and a median PFS of 3.6 mo. Pts with the 3 most common histology subtypes from the PRIMO study are included in the current analysis (n = 97); these are PTCL-NOS (n = 52), AITL (n = 30), and ALCL (n = 15). Median PFS stratified by baseline histology was 3.5 mo (PTCL-NOS), 9.1 mo (AITL), and 1.5 mo (ALCL). Table 1 shows additional outcomes by histology. Adverse events seen were consistent with those observed previously in the PRIMO trial with no additional unexpected treatment-related toxicities.

Conclusions: The ORR (by IRC) of DUV was higher in pts with PTCL-NOS (48%) and AITL (67%), compared with ALCL (13%). This corresponded to a longer median PFS of 3.5 mo in PTCL-NOS and 9.1 mo in AITL compared with 1.5 mo in ALCL. Although not powered for subset analyses, this analysis suggests activity of DUV may not be uniform across different types of lymphomas.

Encore Abstract - previously submitted to EHA 2023

Table 1. Outcomes from the PRIMO Expansion Phase stratified by baseline histology

Outcome (n=97)*	PTCL-NOS (n=52)	AITL (n=30)	ALCL (n=15)
ORR by baseline histology, n (%)	25/52 (48.1)	20/30 (66.7)	2/15 (13.3)
Best overall response, n (%)			
Complete response (CR)	14/52 (26.9)	16/30 (53.3)	2/15 (13.3)
Partial response (PR)	11 (21.2)	4 (13.3)	0 (NC, NC)
Median PFS by IRC, months (95% CI)	3.5 (1.8, 8.1)	9.1 (6.2, NC)	1.5 (0.7, 1.7)
Median OS, months (95% CI)	10.9 (5.1, NC)	15.5 (9.5, 18.0)	4.8 (1.7, 15.7)
Median time to response (range)	1.7 (1.7, 0.5)	1.8 (1.9, 0.5)	2.6 (2.6, 1.3)
Median DOR by IRC, months (95% CI)	5.5 (2.0, 9.2)	8.8 (7.7, NC)	1.9 (1.9, 2.0)
Median DOR for patients achieving CR	7.4 (6.4, NC)	7.9 (3.3, NC)	1.9 (1.9, 2.0)

*In the current analysis (n=97), four patients discontinued prior to first scheduled scan due to progressive disease.
NC, not calculated.

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Keywords: molecular targeted therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

N. Mehta-Shah
Consultant or advisory role: AstraZeneca, Celgene/BMS, C4 Therapeutics, Celgene, Corvus, Daiichi Sankyo, Genentech/Roche, Innate Pharmaceuticals, Karyopharm, Kyowa Kirin, ONO Pharmaceuticals, Secura Bio, Verastem

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368 | IMPROVED PROGNOSIS OF ADVANCED-STAGE EXTRANODAL NK/T-CELL LYMPHOMA: RESULTS OF THE NKEA-NEXT STUDY

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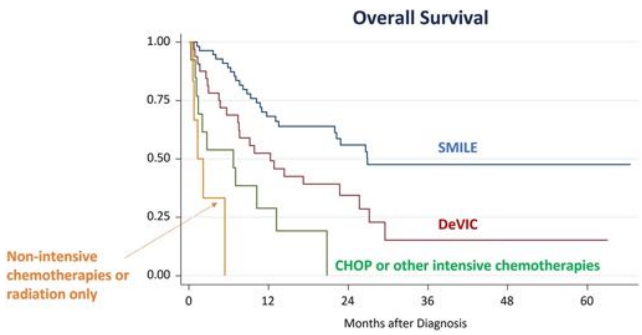
Background: Extranodal NK/T-cell lymphoma (ENKL) is a particular subtype of lymphoma that is characterized by the expression of multi-drug resistance-associated P-glycoprotein. Although the advent of non-anthracycline-based and L-asparaginase containing chemotherapy has contributed to enhancing the prognosis of ENKL patients, recent clinical results of ENKL patients have not been well assessed.

Method: A cooperative NKEA-Next study (UMIN 000046300) was performed in Japan to gather data on ENKL patients diagnosed between 2014 and 2021. Data from advanced-stage ENKL patients were examined. Results of limited-stage patients were presented elsewhere (ASCO 2023).

Results: A total of 351 patients with ENKL were included in the NKEA-Next study. Among these, 116 patients (33%; 5 with stage III and 111 with stage IV) were in an advanced stage. The median age of the advanced-stage patients was 59.5 years (range: 19–90) and 59% were male. Thirty-five percent of the advanced-stage patients had poor performance status (2–4), and 53% had B symptoms at diagnosis. Of the 111 patients with stage IV disease, 94 (85%) had two or more extranodal involvement, including nasal/paranasal area (65%), bone or bone marrow (44%), skin (44%), lung (18%), liver (17%),

spleen (14%) and central nervous system (10%). The most common first-line treatment was SMILE (52%), followed by DeVIC (30%) and CHOP (10%), although 10 patients did not receive any treatments due to poor general condition. The 2-year overall survival (OS) of the advanced-stage patients was 38.2%, which was significantly improved in the recent era (25.2% for the year 2014–2017 vs. 49.8% for the year 2018–2021; $P = 0.01$). Patients treated with SMILE had significantly longer survival time than those treated with DeVIC or CHOP (2y-OS: 57.1%, 35.8% and 0%, respectively; $P < 0.001$). The overall response rate was significantly higher in patients treated with SMILE (74%) than those treated with DeVIC (58%) and CHOP (18%). The proportion of patients who underwent subsequent hematopoietic stem cell transplantation (HSCT) was also significantly higher in patients treated with SMILE than the other regimens (65% vs. 18%, $P < 0.001$). The prognosis was significantly better in patients who underwent HSCT than in those who did not (2-year OS: 66.8% vs. 17.6%, $P < 0.001$). Multivariate analysis confirmed that patients who underwent HSCT had significantly better OS [hazard ratio (HR) 0.2, 95% confidence interval (CI) 0.1–0.5, $P < 0.001$] and treatment with SMILE was identified as almost significant factor for better OS (HR 0.6, 95% CI: 0.3–1.0, $P = 0.06$).

Conclusion: The prognosis of advanced-stage ENKL was improved in recent years. The use of the SMILE regimen and subsequent HSCT was considered to contribute to the improvement. Further studies are warranted to enhance the prognosis of advanced-stage ENKL patients.



Keywords: Aggressive T-cell non-Hodgkin lymphoma, Chemotherapy, Extranodal non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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Honoraria: Chugai pharmaceutical co. ltd, Meiji Seika Pharma, Sanofi

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K. Yakushijin
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W. Munakata
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Research funding: Kyowa-kirin Chugai Taiho Ohtsuka Takeda Shionogi Eisai Meiji Seika Sysmex

369 | EFFICACY OF ANTI-PD1 THERAPY IN RELAPSED OR REFRACTORY NK/T CELL LYMPHOMA: A MATCHED COHORT ANALYSIS FROM THE LYSA

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Extranodal NK/T cell lymphoma (ENKTCL) is a rare subset of peripheral T lymphoma of which Asparaginase containing regimens are the standard of care. Despite recent improvements in the therapeutic strategy, patient's prognosis remains poor, especially for those who experienced relapsed or refractory (R/R) disease. Recent studies highlighted that immune escape mechanisms are involved in ENKTCL pathogenesis. Particularly, the frequent PD-L1 upregulation led to assess the efficacy of anti-PD1 (aPD1) therapy in small cohorts of R/R ENKTCL patients, with encouraging results.

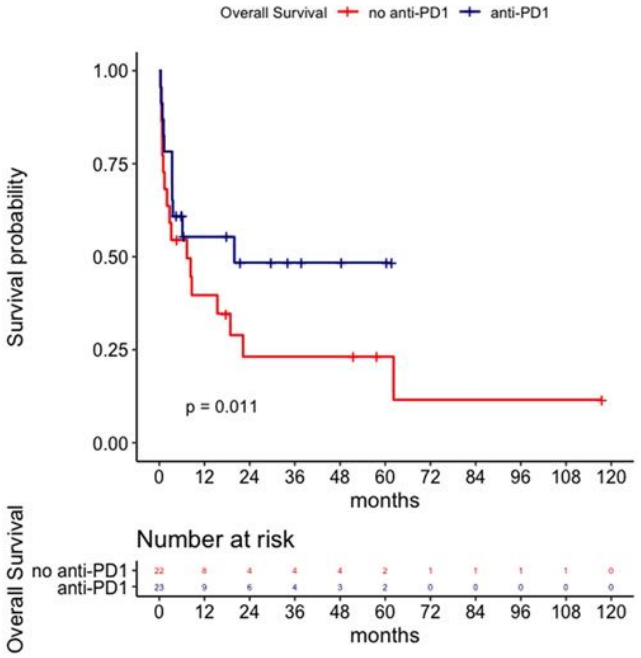
Our study aims to evaluate the efficacy of aPD1 therapy alone or in combination in 37 patients with R/R ENKTCL. We also performed a comparative analysis with a historic cohort of 38 patients treated for R/R ENKTCL before immunotherapy era.

37 patients from 24 French centers, with R/R ENKTCL treated with at least one cycle of aPD1 as salvage therapy between 2017 and 2022 were analyzed in this study. Among them, 12 were included in the prospective ACSE Unicancer study and received aPD1 as monotherapy.

The historic cohort used for the comparative analysis was established from the ENKTCL national observatory and composed of 38 R/R ENKTCL patients who received at least one cycle of first salvage therapy without aPD1 between 2006 and 2019. All patients were treated with Asparaginase-containing regimen as frontline therapy.

Patient characteristics were as follows: median age of 52 years (19–79), sex ratio M/F of 2/1, disseminated stage and high PINK score respectively in 57% and 41% of the cases.

The overall response rate at the last follow-up was 40.5% in the aPD1 group. With a median follow-up time of 6.5 months for the whole cohort and 23.4 months for survivors, progression free survival and overall survival (OS) at 2 years were 22.4% and 50.2%.



Among the 22 patients who experienced progression or relapse after aPD1 initiation, 14 patients (64%) received salvage therapy, mostly containing gemcitabine in association with immunotherapy continuation.

This cohort was then compared to the historic cohort after matching on a propensity score. 23 patients in each group were included in this analysis. OS was significantly improved in patients treated with aPD1 as salvage therapy alone or in combination (48.4% versus 23.1%, $p = 0011$).

We report here the largest cohort of R/R ENKTCL treated with aPD1. Our study confirms the efficacy of aPD1 therapy in R/R ENKTCL and highlights its superiority as compared to other types of salvage therapy used in this setting before immunotherapy era.

Our results will prompt us to now prospectively evaluate the benefit of aPD1 therapy as first line therapy in patients with high risk disseminated stage of ENKTCL, in combination with chemotherapy agents able to enhance anti-tumor immunity.

To improve response to immunotherapy, it is crucial to identify biomarkers predictive of response to immune checkpoint blockade.

Encore Abstract - previously submitted to regional or national meetings (up to <1'000 attendees), EHA 2023

Keywords: Extranodal non-Hodgkin lymphoma, Immunotherapy

No conflicts of interests pertinent to the abstract.

370 | INTERIM ANALYSIS OF A PROSPECTIVE MULTICENTER PHASE II STUDY FOR ADVANCED-STAGE OR RELAPSED/ REFRACTORY NATURAL KILLER/T CELL LYMPHOMA

W. Liu[1], L. Zhao[2], C. Wu[3], H. Yu[4], Z. Li[5], L. Liu[6], D. Gao[7], Y. Sun[8], X. Wei[9], Y. Wu[10], Y. Song[1], J. Zhu[1]

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Background: Advanced-stage or relapsed/refractory (r/r) natural killer/T cell lymphoma (NKTCL) has a poor prognosis. The anti-programmed death 1 (PD-1) antibody has demonstrated satisfactory efficacy and good tolerance in treating r/r NKTCL. In this report, we present the interim analysis results of a prospective multicenter phase II study.

Methods: Patients with advanced-stage or r/r NKTCL were eligible for participation. The DAPT regimen chemotherapy was administered as the protocol treatment, which included dexamethasone 10 mg on days 1–3, azacytidine 100 mg on days 1–5, pegaspargase 3750 IU on day 1, and tislelizumab 200 mg on day 6. Cycles were repeated every 21 days. The primary endpoint was the overall response rate (ORR) after the protocol treatment.

Results: A total of 29 eligible patients were enrolled, with a median age of 52 years (range, 35 to 72 years) and a male-to-female ratio of 2.2:1. Eighteen patients had newly diagnosed disease with stage IV, while 11 had r/r disease. Among 21 patients with available response, the ORR and complete response rates were 76% and 33% for the entire cohort, 85% and 39% for newly diagnosed stage IV disease, and 63% and 25% for r/r disease, respectively. Six patients underwent autologous hematopoietic stem cell transplantation. The median progression-free survival was 10.7 months (range, 1.3–20.9 months). The most common adverse events were neutropenia (17%), elevated alanine aminotransferase (13%), and decreased fibrinogen (10%). No treatment-related deaths were observed.

Conclusion: The DAPT regimen chemotherapy is an effective and tolerable treatment for advanced-stage or r/r NKTCL.

The research was funded by: Clinical research fund for distinguished young scholars of Beijing Cancer Hospital (Grant No. QNJJ202106

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Combination Therapies

No conflicts of interests pertinent to the abstract.

371 | PEGARSPARGASE AND SINTILIMAB FOR NEWLY DIAGNOSED, ADVANCED STAGE NATURAL KILLER T-CELL LYMPHOMA, NASAL TYPE: AN OPEN-LABEL, SINGLE-ARM, PHASE 2 STUDY

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Shanghai Institute of Hematology, Shanghai, China

Introduction: Natural killer/T-cell lymphoma (NKTL) is a highly aggressive lymphoma that usually treated with intensive

chemotherapy. To explore a more effective and less toxicity treatment for newly diagnosed stage III/IV NKTCL, we conducted a phase II study of pegarspargase and sintilimab chemo-free regimen.

Methods: Patients with newly diagnosed stage III/IV disease and a performance status of 0 to 2 were eligible. Eligible patients were treated with induction treatment of pegaspargase 2500 IU/m^2 intramuscularly on day 1 and sintilimab 200 mg intravenously on day 2 for 6 cycles, as well as maintenance treatment of sintilimab monotherapy. The primary end point was the complete remission (CR) rate at the end of induction treatment. The secondary end points include overall response rate (ORR), 2-year overall survival (OS) and progression-free survival (PFS), duration of remission (DOR), blood EBV DNA levels, treatment-related mortality (TRM), and adverse effect (AE) rate.

Results: A total of 22 eligible patients were enrolled. The median age was 51 years (range, 14 to 74) and the male: female ratio was 16: 6. The CR and ORR after induction treatment was 59.1% (95% CI, 42.7 to 78.8) and 68.2% (95% CI, 47.3 to 83.6). 10 patients continued maintenance treatment of sintilimab and 2 patients underwent autologous hematopoietic stem-cell transplantation after induction treatment. With a median follow up of 18.2 months (range, 3.2 to 37.2) for PFS and 20.2 months (range, 4.7 to 39.2) for OS, the estimated 2-year PFS and OS for chemo-free cohort were 62.3% (95% CI, 33.5% to 81.5%) and 84.4% (95% CI, 58.3% to 94.8%), respectively. Grade 3/4 AEs were observed in 45% (n = 10) patients, including neutropenia (32%, n = 7), hypofibrinogenemia (18%, n = 4), leukopenia (9%, n = 2), anemia (5%, n = 1), thrombocytopenia (5%, n = 1), hypoalbuminemia (5%, n = 1), AST/ALT elevation (5%, n = 1), heart failure (5%, n = 1), which were manageable and led to no discontinuation of treatment. The comprehensive characterization of responders and non-responders were further investigated according to clinical parameters and exploratory multi-omic analysis. Dynamically monitoring of blood EBV DNA levels and the peripheral immune cell profile at diagnosed were potential prognostic markers.

Conclusions: The chemo-free regimen is an effective treatment for newly diagnosed, advanced stage NKTCL with significantly prolonged PFS and OS, as well as reduced and manageable AEs.

Keywords: Extranodal non-Hodgkin lymphoma, Immunotherapy

No conflicts of interests pertinent to the abstract.

372 | IMATINIB-INDUCED COMPLETE AND LONG-TERM SUSTAINED REMISSION IN CHEMOTHERAPY-RESISTANT SYSTEMIC ALK-POSITIVE ANAPLASTIC LARGE CELL LYMPHOMA

A. Pichler[1], C. Kornauth[2], I. Garces-de-los-Fayos-Alonso[3], L. Kazianka[1], H. Alachram[4], A. Zibat[4], T. Pemovska[1], G. Heller[5], R. Greil[6], L. Kenner[3], U. Jäger[1], P. Staber[1]

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Background: Platelet-derived growth factor receptor (PDGFR) is expressed in nucleophosmin–anaplastic lymphoma kinase (NPM-ALK) positive anaplastic large cell lymphomas (ALCL ALK+). Our previous preclinical research suggested that PDGFR blockade by the Abl/c-Kit/PDGFR kinase inhibitor imatinib could be an effective treatment strategy for ALCL ALK+. A young indicator patient whose ALCL cells expressed PDGFR and who failed three treatment lines (including autologous stem cell transplantation) achieved complete remission (CR) with imatinib.

Methods: We report imatinib treatment of 6 relapsed/refractory (r/r) ALK-positive ALCL patients, 4 of which were treated in a prospective clinical trial (EudraCT No.: 2013-003505-26). Median follow-up was 40 months (160 weeks, range 4–428). Patients were characterized by whole exome sequencing, bisulfite sequencing, and immunological prnofiling. Whole exome sequencing data were integrated and compared to 25 additional ALK+ ALCL patients (Larose et al. Haematologica, 2021).

Results: 4 out of 6 patients achieved a CR that was maintained throughout the follow-up of 3.3–8.9 years. 5-year progression-free survival (PFS) was 67%. Lymphoma cells of the two non-responding patients did not express PDGFRA/B. Cytoplasmic co-expression of both ALK and PDGFRA/B in ALCL tumor cells was associated with imatinib response in ALCL ALK+ patients. Methylation profiling confirmed a differentially activated PDGFR axis between responders and non-responders and identified a specific protein kinase profile that included a significant upregulation of HGFAC, VEGFa, and TNFa. Additionally, non-responders were characterized by an exclusive mutational signature of genes linked to vesicular endocytosis and signaling as a resistance mechanism to pan-kinase inhibitors.

Conclusion: PDGFRA/B expression in tumour cells of therapy-resistant ALK-positive ALCL patients can discriminate genetically and functionally distinct lymphoma subgroups that are directly related to long-term treatment response to kinase inhibitor imatinib.

EA - Encore Abstract: Regional or national meeting (≤1'000 attendees)

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

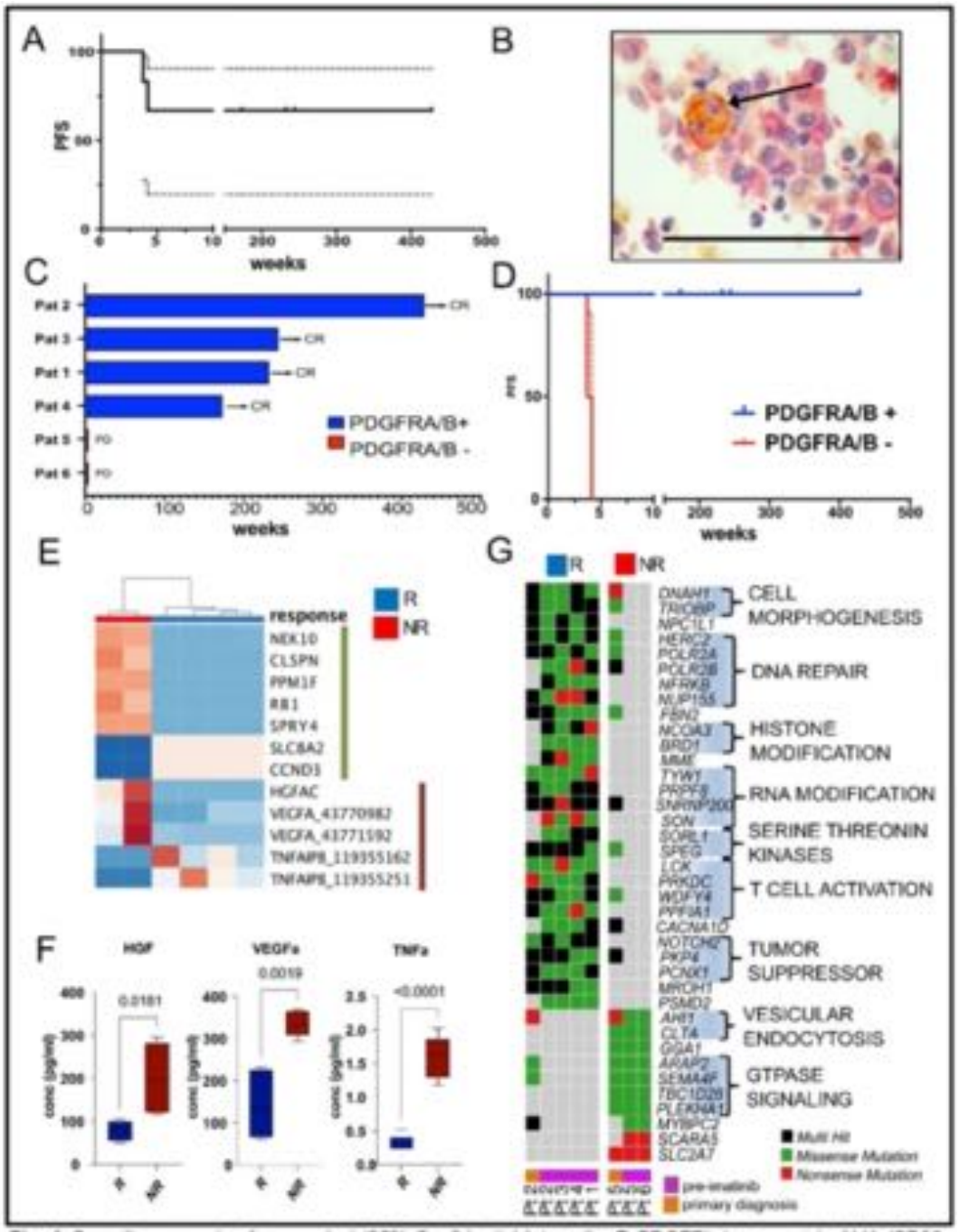

Fig. A Overall progression-free-survival (95% Confidential Interval) . **B** PDGFRb is present in ALK+/CD30+ ALCL cells. Double IHC staining of an ALCL-case showing co-expression of both ALK (magenta) and PDGFRb (brown) in a tumor cell (arrow). **C and D** Imatinib-induced long-term progression free survival stratified by PDGFRA/B positivity. **E.** Differentially methylated genes in Non - responder vs Responder. Protein kinase activity (green bar), cytokines (dark red bar). **F** Corresponding serum cytokine levels are increased in Non-responders. G. Exclusively mutational signature in R and NR.

373 | **BRIGATINIB IN PATIENTS WITH ALK-POSITIVE ANAPLASTIC LARGE CELL LYMPHOMA WHO HAVE FAILED BRENTUXIMAB VEDOTIN**

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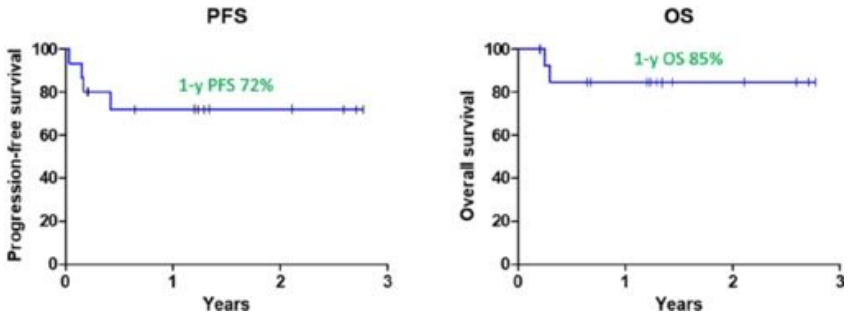

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ALK-positive anaplastic large cell lymphoma (ALK+ ALCL) patients (pts) who have failed brentuximab vedotin (BV) have a poor prognosis with a median OS after BV failure of 2.9 months and 2-year OS of 27.1% (Chihara D, 2019). ALK-inhibitors have shown interesting results in relapsed ALK+ ALCL, but in these studies, most pts had not received prior BV, which does not correspond to current standards of treatment in adults. Furthermore, there are currently several ALK-inhibitors, but too few pts available to test them in this rare and difficult-to-treat population. It is therefore important to evaluate these ALK-inhibitors in preclinical studies, before selecting one for a clinical study.

We carried out a preclinical study and then a real-life clinical study. We generated a patient-derived xenograft (PDX) model from a fresh lymph node biopsy of a 41-year-old man newly diagnosed with ALK+ ALCL. Our PDX closely mimicked the patient's primary tumor, as assessed by pathology, FISH, TCR gene rearrangement, WES and RNA-seq. We used this model to assess 8 ALK-inhibitors (alectinib, brigatinib, ceritinib, crizotinib, ensartinib, entrectinib, lorlatinib, gilteritinib).

We selected and recommended brigatinib for clinical off-label use based on our preclinical results and the safety profile in pts with ALK-positive non-small cell lung cancer (NSCLC). Between Jan 2020 and Oct 2022, 15 French adults who have failed BV started brigatinib. At brigatinib initiation, the median age was 35 y (19–73; 2 pts > 60 y), 8/15 were male, the median number of prior treatment lines was 2 (1–8), 4/15 (27%) had received prior crizotinib, including 3 crizotinib-resistant (crizo-R) and 1 crizotinib-sensitive (crizo-S) who relapsed after discontinuation of the drug. 4 pts had previously undergone stem cell transplantation (3 autoSCT, 1 alloSCT). ALCL was refractory to the last treatment in 10/15 pts. 10/11 pts had detectable ALK transcript in blood by RT-PCR. Pts received brigatinib at a dose of 180 mg once daily (with a 7-day lead-in period at 90 mg), as recommended in ALK-positive NSCLC. The best ORR was 93% (14/15) with 73% (11/15) CR according to Lugano response criteria. 2 crizo-R and the crizo-S pts achieved CR, and 1 crizo-R pt reached PR. Time to achieve CR ranged from 8 to 325 days. 9 pts were monitored for ALK transcript in blood over time and kinetics correlated with response. 5 CR pts were bridged to alloSCT. There were 4 progressions/relapses after brigatinib initiation, all occurring within the first 6 months. After a median follow-up of 1.3 years, 1-year PFS and OS were 72% and 85%, respectively. There was no permanent discontinuation of brigatinib related to adverse event (AE), and 3 pts had dose reduction for moderate AE (1 dyspnea and 2 cramps), with complete resolution.

Brigatinib showed high efficacy, including in pts who have failed crizotinib, and was well tolerated. These results should be confirmed in prospective studies.

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

D. Sibon
Consultant or advisory role: Takeda, AbbVie, Janssen, Roche

374 | LONG-TERM OUTCOMES WITH MOGAMULIZUMAB ALONE OR IN COMBINATION WITH OTHER THERAPIES FOR THE TREATMENT OF CUTANEOUS T-CELL LYMPHOMA

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Introduction: Mogamulizumab (MOGA) is an anti-CCR4 monoclonal antibody approved for mycosis fungoides (MF) or Sézary syndrome (SS). The MAVORIC trial comparing MOGA versus vorinostat showed superior overall response rates (ORR) (28% vs. 4.8%, $P < 0.0001$) and progression free survival (PFS) (7.7 vs. 3.1 months (mo), $P < 0.0001$) with MOGA. We report the long-term outcomes of patients (pts) treated with MOGA at Stanford. Moreover, we describe the impact of MOGA-associated rash (MAR) and MOGA combination therapies (combotx) in the treatment outcomes.

Methods: We obtained the data from MF and SS pts who were treated with MOGA from 2009 to 2022. We evaluated ORR (consensus criteria), duration of response (DOR), time to next treatment (TTNT), PFS, OS, impact of MAR and of combotx. Combotx was defined as the intended use of concurrent or sequential treatment(s) to augment clinical response and/or as a supportive therapy for MAR. TCR clonality data was used to confirm MAR. TTNT was defined as time from initiation of MOGA mono or combination therapy to the initiation of the next systemic therapy for lymphoma.

Results: A total of 65 pts were included: MF = 16, SS = 49. Median age was 68 (26–90). At the time of treatment, 20% had measurable nodal (N3) disease, 14% had a biopsy showing large cell transformation (LCT) within 5 years prior to MOGA, and 92% had disease stage IIB-IV. Median prior lines of systemic therapies was 3 (0–18). Median follow-up was 42 mo (1.3–148).

Overall, median TTNT was 15 mo (95% CI: 10–23), PFS 25 mo (95% CI: 14–30), OS 127 mo (95% CI: 45–135). ORR was higher for SS (74% vs. 25%, $p < 0.01$); PFS and TTNT were longer in SS but not significant. LCT and N3 disease were associated with worse TTNT.

Combotx was used in 32% pts, SS = 86%. ORR was higher in pts that received combotx compared to monotherapy (monotx) (95% vs. 45%, $p < 0.0001$). Combotx led to significant improvement in the rate of objective response lasting ≥12 mo (ORR12) (90% vs. 55%, $p = 0.03$), TTNT (38 vs. 10 mo, $p = 0.0018$) and PFS (39 vs. 14 mo, $p = 0.0274$). Proportion of LCT and N3 between groups was not significantly different. Agents used in combotx included methotrexate, oral retinoids, total skin electron beam therapy, and magrolimab.

MAR occurred in 49% pts (MAR+), SS = 88%. ORR was 91% in MAR+ versus 33 % without MAR (MAR-). MAR+ had significant improvement in the ORR12 (86% vs. 36%, $p = 0.0037$), TTNT (30 vs. 7.5 mo, $p < 0.0001$) and PFS (30 vs. 11.5 mo, $p = 0.0049$). Proportion of LCT and N3 between groups was not significantly different. Duration of MOGA exposure was similar between MAR+ and MAR- and responders versus non-responders [figure].

Conclusions: Our real-world experience with MOGA supports promising ORR, PFS, TTNT, and a subset with durable responses. Moreover, pts with MAR or that received combotx had better outcomes. Thus, future trials should explore combination regimens with MOGA not only as a supportive therapy for MAR, but also to augment clinical activity, and ultimately improve outcomes.

Keywords: Cutaneous non-Hodgkin lymphoma, Immunotherapy

Conflicts of interests pertinent to the abstract.

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Consultant or advisory role: Corvus, CRISPR Therapeutics, Innate

Honoraria: Kyowa Kirin, Citius, CRISPR, Takeda

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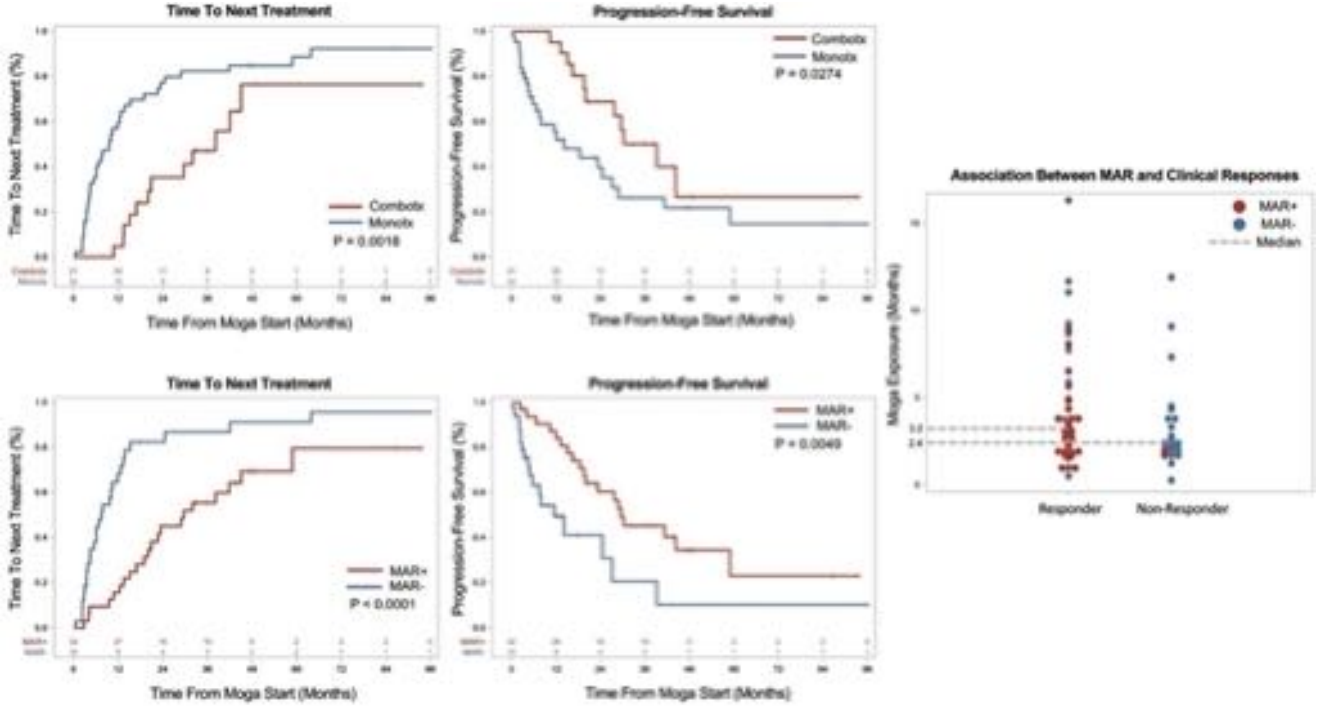

375 | COMBINATION OF GEMCITABINE, PEGASPARGASE, ETOPOSIDE, AND DEXAMETHASONE (GPED) IN THE TREATMENT OF ADVANCED EXTRANODAL NK/T-CELL LYMPHOMA

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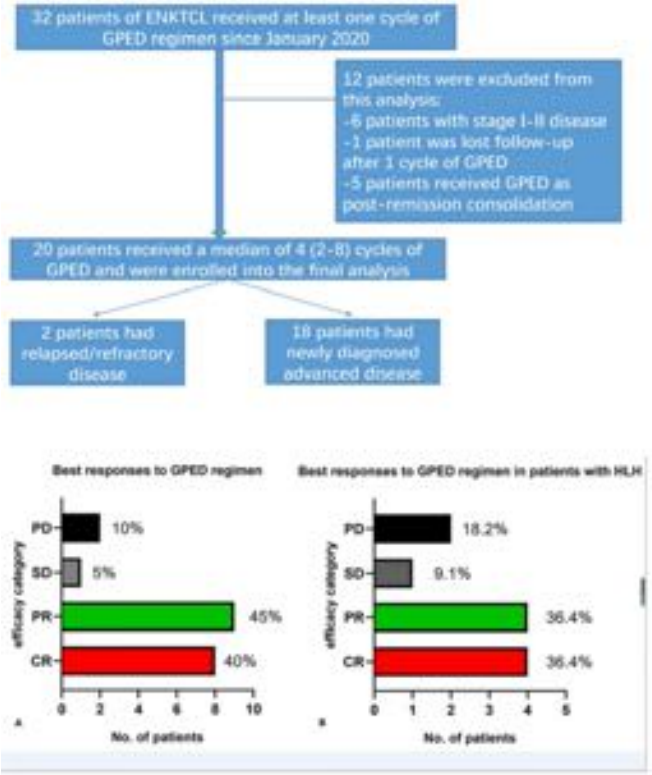
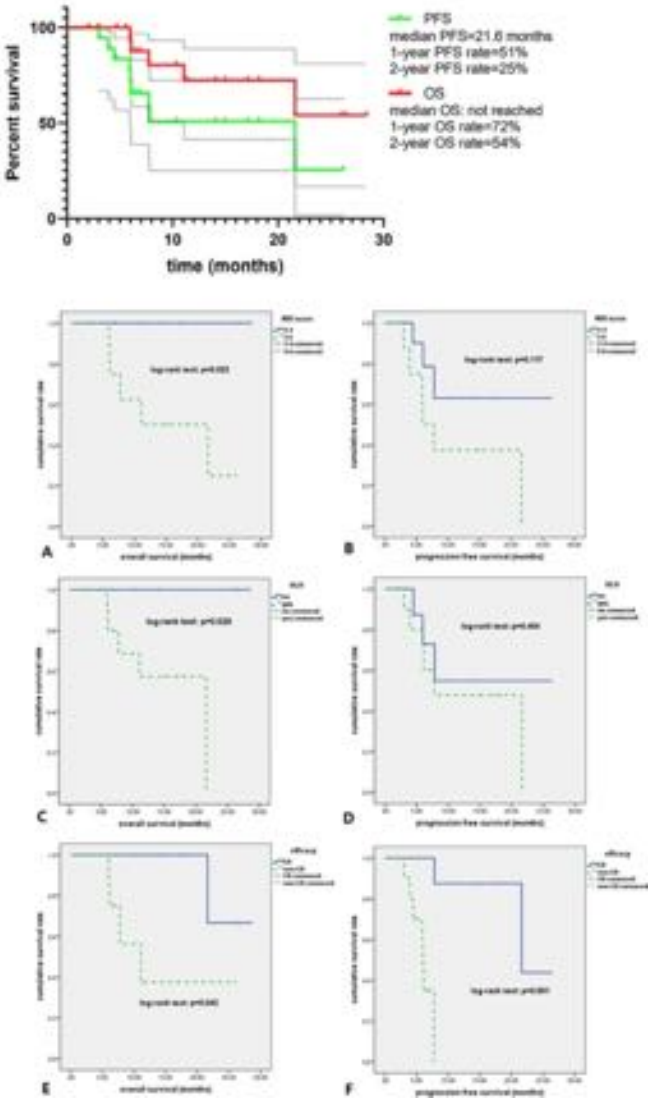
Purpose: Extranodal NK/T-cell lymphoma (ENKTCL) is a highly aggressive lymphoma, with dismal outcomes for patients with advanced disease. No standard chemotherapy regimens were defined yet, especially for those with concurrent hemophagocytic lymphohistiocytosis (HLH).

Methods: Patients with advanced stage ENKTCL were treated with combination of gemcitabine, pegaspargase, etoposide, and dexamethasone (GPED) since January 2020 in our center. The clinical characteristics, short-term efficacy, long-term survival outcomes, safety profiles, and potential prognostic biomarkers were analyzed.

Results: Up to June 2022, a total of 20 patients with stage IV ENKTCL were treated with a median of four cycles of GPED regimen (range, 2–8). All patients had NRI score of 3 or more. Concurrent HLH were confirmed in 11 patients. The best responses to GPED regimen were complete remission (CR) in 40% of patients, partial remission (PR) in 45% of patients, rendering an overall response rate (ORR) of 85%. For the 11 patients with concurrent HLH, the CR rate was 36.4%, and the ORR was 72.8%. At a median follow-up time of 14.5 months (range, 2.1–28.4), nine patients had disease progression at a median of 6 months (3–21.6), and 5 patients died of ENKTCL. The predicted 1- and 2-year progression free survival (PFS) rate was 51% and 25%, respectively, and the overall survival (OS) rate was 72% and 54%, respectively. The major adverse events (AE) were hematologic, with grade 3 or severer leukopenia in 65% of patients, and 20% had grade 1 neutropenic fever.

Conclusions: GPED regimen was effective in advanced ENKTCL, especially those with concurrent HLH, and well tolerated with major grade 3–4 AEs being hematologic. Our findings need to be validated in well-designed prospective, randomized clinical trials.





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Keywords: Aggressive T-cell non-Hodgkin lymphoma, Chemotherapy, Combination Therapies

No conflicts of interests pertinent to the abstract.

376 | SAFETY AND EFFICACY OF BRENTUXIMAB VEDOTIN IN CHINESE ADULTS WITH CD30+ PERIPHERAL T-CELL LYMPHOMA: AN INTERIM ANALYSIS FROM A PROSPECTIVE, OBSERVATIONAL, REAL-WORLD STUDY

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Introduction: Brentuximab vedotin (BV) is an anti-CD30 antibody–drug conjugate approved for the treatment of Chinese adults with refractory/relapsed (R/R) classical Hodgkin lymphoma, systemic anaplastic large cell lymphoma (ALCL), primary cutaneous ALCL, and CD30-expressing mycosis fungoides who have received prior systemic therapy. BV is also approved for frontline CD30+ peripheral T-cell lymphoma (PTCL) in western countries. This real-world (RW) study reported the outcomes of BV treatment in Chinese patients (pts) with CD30+ PTCL.

Methods: This is an interim analysis from a prospective, observational, RW study (BRAVE; NCT04837222) evaluating the safety and efficacy of BV-based regimens in frontline and R/R settings in Chinese adult pts with CD30+ lymphoma (targeted sample size: 1000). The primary outcome was serious adverse events (SAEs). Secondary outcomes were adverse events (AEs), adverse drug reactions (ADRs), patient characteristics, and objective response rate (ORR) (complete response, CR; partial response, PR).

Results: Overall, 82 pts across 17 centers were included (cutoff date: Nov 30, 2022): 58 (70.7%) pts in frontline settings (>90% frontline pts received BV-CHP) and 24 (29.3%) pts in R/R settings (R/R pts received more than 10 BV-based regimens like BV + Chemo, BV + Chemo + Chidamide, BV + Chemo + PD-1 inhibitors). The median age was 55 years (age range, 41–66). Among all, 15 (18.3%) had stage III advanced disease and 13 (64.6%) had stage IV advanced disease. Overall, 55 (67.1%) pts had extranodal involvement of whom 30 (36.6%) pts had bone marrow infiltration. Pathologically, most pts either had angioimmunoblastic T-cell lymphoma (24; 29.3%), ALCL anaplastic lymphoma kinase-positive (ALK+) (21; 25.6%), or ALCL ALK− (14; 17.1%) (Figure 1).

In 58 frontline pts, 27 (46.6%) had quantifiable CD30+ expression ranging from 5% to 20% ($n = 11$), 25%–60% ($n = 6$), 70%–90% ($n = 6$), and 100% ($n = 4$). In 24 R/R pts, 7 (29.2%) pts had quantifiable CD30 + expression ranging from 0% to 20% ($n = 3$), 30%–60% ($n = 3$), and 95% ($n = 1$).

Of the 82 pts, 80 (97.6%) experienced AEs and 19 (23.2%) had SAEs, which were similar to the events observed in the ECHELON-2 study (AEs, 99%; SAEs, 39%). ADRs, serious ADRs, and ADRs grade ≥3 were reported in 51 (62.2%), 7 (8.5%), and 19 (23.2%) pts, respectively. Overall, only one pt experienced an ADR that resulted in death.

The data cutoff for this analysis was performed in 34 frontline and 7 R/R pts who had at least one follow-up effectiveness assessment. In frontline settings, ORR was 82.4% (28/34) with CR in 20 (58.8%) and PR in 8 (23.5%) pts. The median time to CR and PR was 2.61 months and 2.49 months, respectively. In R/R settings, ORR was 71.4% (5/7) with CR in 2 (28.6%) and PR in 3 (42.9%) pts. The median time to PR was 2 months.

Conclusions: BV-based treatment regimens are safe and effective options in frontline and R/R settings in CD30+ PTCL pts.

The research was funded by: Takeda (China) International Trading Co., Ltd.

Keyword: Aggressive T-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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Characteristics	PTCL [N=82]	PTCL (FL) [N=58]	PTCL (R/R) [N=24]
Age (years), Median (Q1; Q3)	55.0 (41.0; 66.0)	56.0 (45.0; 66.0)	50.5 (38.5; 59.5)
Age ≥65 years, n (%)	24 (29.3)	20 (34.5)	4 (16.7)
Male Gender, n (%)	51 (62.2)	37 (63.8)	14 (58.3)
Weight (Kg), Median (Q1; Q3)	65.00 (57.20; 71.00)	65.00 (57.00; 71.00)	65.00 (58.60; 72.00)
ECOG score, n (%)			
0	29 (35.4)	23 (39.7)	6 (25.0)
1	18 (22.0)	13 (22.4)	5 (20.8)
2	8 (9.8)	6 (10.3)	2 (8.3)
3	8 (9.8)	6 (10.3)	2 (8.3)
4	3 (3.7)	3 (5.2)	-
Pathological Classification - Mature T and NK Cell Tumors, n (%)			
AITL	24 (29.3)	17 (29.3)	7 (29.2)
ALCL, ALK-	21 (25.6)	16 (27.6)	5 (20.8)
ALCL, ALK+	14 (17.1)	12 (20.7)	2 (8.3)
NOS	11 (13.4)	9 (15.5)	2 (8.3)
MF	5 (6.1)	2 (3.4)	3 (12.5)
ATL	3 (3.7)	1 (1.7)	2 (8.3)
CPD-NKs	1 (1.2)	-	1 (4.2)
ENKL	1 (1.2)	-	1 (4.2)
SPTCL	1 (1.2)	-	1 (4.2)
SS	1 (1.2)	1 (1.7)	-
IPI Score, Median (Q1; Q3)	2.0 (1.5, 3.0)	3.0 (2.0, 3.0)	2.0 (1.0, 2.0)
IPI Score, n (%)			
0	5 (6.1)	3 (5.2)	2 (8.3)
1	11 (13.4)	7 (12.1)	4 (16.7)
2	20 (24.4)	14 (24.1)	6 (25.0)
3	15 (18.3)	14 (24.1)	1 (4.2)
4	10 (12.2)	9 (15.5)	1 (4.2)
5	3 (3.7)	3 (5.2)	-
Clinical staging before first use of BV (Ann Arbor staging), n (%)			
I	2 (2.4)	2 (3.4)	-
II	9 (11.0)	7 (12.1)	2 (8.3)
III	15 (18.3)	10 (17.2)	5 (20.8)
IV	53 (64.6)	38 (65.5)	15 (62.5)
Unknown	2 (2.4)	1 (1.7)	1 (4.2)
Bulky lesion ≥ 5cm, n (%)	22 (26.8)	17 (29.3)	5 (20.8)
Extranodal involvement, n (%)	55 (67.1)	44 (75.9)	11 (45.8)
Bone marrow infiltration, n (%)	30 (36.6)	20 (34.5)	10 (41.7)
No. of recurrences/ relapse, n (%)			
1st	7 (8.5)	-	7 (29.2)
2nd	8 (9.8)	-	8 (33.3)
3rd	4 (4.9)	-	4 (16.7)
Other	5 (6.1)	-	5 (20.8)

PTCL= Peripheral T-Cell Lymphoma, ECOG= Eastern Cooperative Oncology Group, AITL= Angioimmunoblastic T-cell Lymphoma, ALCL= Anaplastic large cell lymphoma, NOS= not otherwise specified, MF= Mycosis fungoides, ATL= Adult T-cell lymphoma/leukemia, CPD-NKs=Chronic NK cell proliferative disease, ENKL= Extranodal NK/T-cell lymphoma, nasal type, SPTCL= Subcutaneous panniculitis-like T-cell Lymphoma, SS= Sezary syndrome, IPI= International Prognostic Index, BV= Brentuximab vedotin

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377 | OUTCOMES OF CONTEMPORARY NOVEL AGENT INCORPORATION IN RELAPSED/REFRACTORY PTCL

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Background: Conventional salvage chemotherapy has limited efficacy in relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL). In the last decade, several novel agents have been approved; however, their impact on real world survival remains to be defined. In this multi-center retrospective analysis, we assessed survival following initial progression with respect to novel agent exposure in patients who did not receive stem cell transplant (SCT).

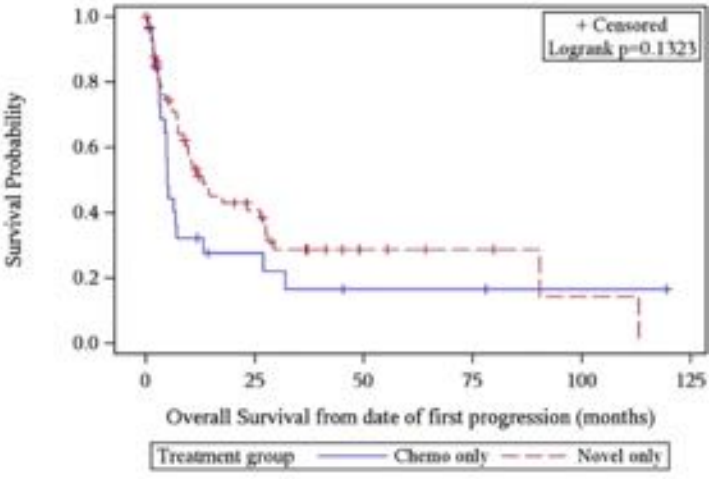
Methods: Patients with PTCL from 1998 to 2021 at Columbia and Cornell were included after IRB approval. Medical records were reviewed for baseline characteristics, treatment including (1) novel agents, (2) chemotherapy, and (3) auto- and/or allo-SCT across all lines of therapy. Event-free survival (**EFS**) was calculated as time from 1st progression to 2nd progression, re-treatment, or death. Subsequent OS (**sOS**) was calculated from date of first progression to death or last follow-up. Kaplan-Meier method was used to estimate

Figure 1A: Baseline characteristics of patients with R/R PTCL

Clinical Feature, n (%)		Treatment Regimens, n (%)	
Total No. Patients	189 (100)	First Line*	
Female	85 (45)	CHOP	51 (27.3)
Male	104 (55)	EPOCH	44 (23.5)
Age		CHOEP	21 (11.2)
> 60	81 (42.9)	Other Chemo	33 (17.9)
≤ 60	108 (57.1)	Novel Agent +	38 (20.1)
Ann Arbor Stage		Romidepsin	11 (5.8)
I-II	31 (18.6)	Brentuximab	8 (4.2)
III-IV	136 (81.4)	Belinostat	3 (1.6)
ECOG		Azacitidine	2 (1.1)
0-1	131 (73.6)	Other Biologics	13 (7)
2-4	47 (26.4)	Transplant	26 (13.8)
LDH > wnl	73 (62.9)	Auto	16 (61.5)
LDH ≤ wnl	43 (37.1)	Allo	10 (38.5)
IPI Score		Second Line*	
0-1	18 (15.4)	ICE	29 (15.8)
2	36 (30.8)	GemOx	11 (5.8)
3	35 (29.9)	Other Chemo	42 (22.2)
4-5	28 (23.9)	Novel Agent +	83 (43.9)
Subtype		Romidepsin	40 (21.2)
AITL	52 (27)	Brentuximab	23 (12.2)
PTCL_NOS	41 (21.7)	Pralatrexate	11 (5.8)
ATLL	33 (17.5)	Azacitidine	5 (2.6)
ALCL Alk -	13 (6.9)	Belinostat	4 (2.1)
ALCL Alk +	10 (5.3)	Transplant	29 (15.3)
T-PLL	14 (7.4)	Auto	10 (34.5)
ENKTL	11 (5.8)	Allo	19 (65.5)

*3rd and 4th lines of treatment, including SCT in later lines, are not shown in this table.

1B: sOS from First Progression in Novel Agent vs Chemo-Only



Group* (n)	Median (95% CI)
Chemo-Only (27)	4.9 (3.4 - 13.3)
Novel Agent Containing Regimen Only (66)	13.0 (8.8 - 27.0)

*Does not include patents who underwent SCT.

survival probability. Survival difference was tested by log-rank and Cox regression analysis.

Results: A total of 348 patients with PTCL were identified, of which 189 had R/R disease and 156 had sufficient data for analysis. The median follow-up was 45.4 m from 1st progression. Baseline characteristics are shown in Figure 1A. The major PTCL subtypes were AITL (N = 52, 27%), PTCL-NOS (N = 41, 21.7%), ATLL (N = 33, 17.5%), and ALCL (N = 23, 12.2%). Median age at diagnosis was 58. Following initial progression, 21 (11.1%) received auto-SCT, and 42 (22.2%) received allo-SCT in second or later lines. Out of those patients who did not undergo SCT (n = 93), 66 (70.9%) received novel-agent-containing regimen only and 27 (29%) received chemo-only in second and later lines. Median sOS from date of initial progression for the entire cohort was 21.3 m. In patients who did not receive SCT, sOS for chemo-only versus novel-agent-containing regimen only was 4.9 m versus 13.0 m, respectively (p = 0.132) with hazard ratio 0.66 (95% CI: 0.39–1.14, p = 0.1349), illustrated in Figure 1B. EFS from first progression in novel-agent-containing regimen only was 4.2 m versus chemo-only 3.6 m (p = 0.6131) with hazard ratio 0.88 (95% CI: 0.54–1.44, p = 0.6137).

Conclusion: This multi-center study represents one of the largest retrospective R/R PTCL real world cohorts in the novel agent era with sOS of 21.3 m, which compares favorably to historical data collected a decade ago reporting a sOS of 5.5 m in R/R patients receiving chemo-only (Mak 2013); however, compares similarly to more recent data from the COMPLETE study (Lansigan 2019). Our data suggest that novel-agent-containing regimens trend toward a sOS benefit compared to chemo alone. However, EFS remains disappointing, underscoring the need for more effective agents and optimal treatment sequencing. Future analysis interrogating role of novel agents in context of SCT and clinical trial enrollment is currently underway.

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

M. R. Seshadri
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Consulting for Gilead and Beigene
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378 | ALLOGENEIC TRANSPLANTATION IN T-CELL LYMPHOMA: LESSONS FROM THE AATT STUDY

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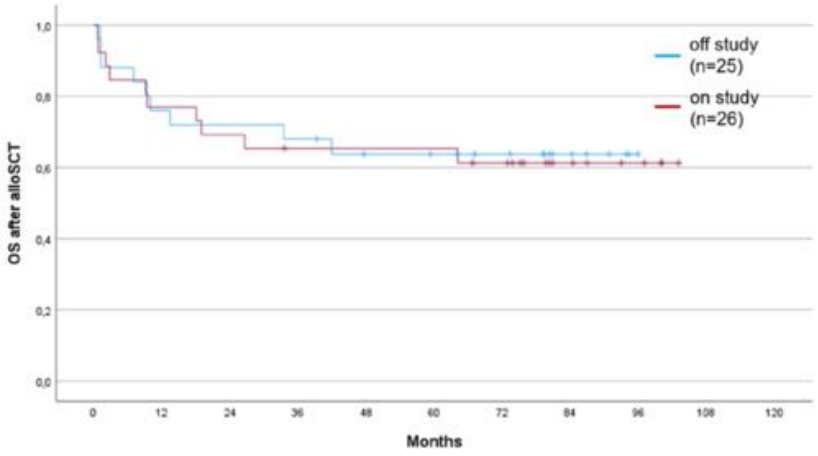
Treatment of non-cutaneous mature T-cell lymphoma (PTCL) remains difficult. Results of the AATT study (Schmitz et al. Blood 2021) demonstrated that standard 1st line chemotherapy followed by alloSCT did not improve outcome of PTCL patients (pts) when compared to autoSCT. We sought to investigate long-term outcomes of AATT patients focusing on the role of alloSCT in pts transplanted on and off study.

AATT was a randomized trial comparing alloSCT and autoSCT in younger pts (18–60 yrs) with newly diagnosed PTCL who achieved CR, PR, or SD after 4 xCHOEP and 1xDHAP. These pts were to receive autoSCT or alloSCT from matched related or unrelated donors for consolidation. Detailed reports on all therapy given until last follow up or death were retrieved to calculate long-term event-free (EFS) and overall survival (OS) focusing on patients receiving alloSCT on study as well as off study for primary refractory disease or after failing autoSCT.

103 pts (median age 50 years) randomized to autoSCT (n = 54) or alloSCT (n = 49) formed the full analysis set (FAS), 67 pts (65%) received autoSCT (n = 41) or alloSCT (n = 26) (per protocol set, PPS) on study. 36 pts went off study mainly for early progression (n = 29) or change of diagnosis (n = 4). With a median observation time of 7 years EFS and OS were 36% [95% CI: 27%–46%] and 58% [48–68] for all 103 pts with no significant differences between treatment arms. For patients transplanted 7-year-EFS and -OS were 50% [34–66] versus 61% [42–80] and 72% [58–86] versus 61% [42–80] after autoSCT versus alloSCT.

After autoSCT, 20 of 41 pts progressed (n = 5) or relapsed (n = 15) and 10 could be allografted off study. In the alloSCT arm (n = 26) only 1 pt each progressed or relapsed after alloSCT, these pts were not

Figure 1: OS after alloSCT transplantation done either on study (alloSCT arm of the AATT) or off study (salvage treatment after relapse post autoSCT or early progression).



allografted again. Among 29 pts with early progression before transplantation 15 were allografted off study. Thus, 25 of 49 pts (51%) who had early progression before transplantation or had failed autoSCT received alloSCT. Five-year OS rate for these 25 pts was 64% [45–83] with no significant differences between pts allografted for early progression or relapse after autoSCT. Surprisingly, OS after alloSCT for 26 pts transplanted on study and 25 pts transplanted off study was superimposable with a 5-year OS-rate of 65% [47–84] for on study patients (Figure 1). Pts with progression or relapse not proceeding to alloSCT had a dismal.

AlloSCT results in long-term survival of approximately 60% of younger PTCL pts transplanted for consolidation, early progression, or relapse after autoSCT and should be the preferred option for relapsed/refractory PTCL. Our observation that survival rates after consolidative alloSCT and salvage alloSCT after relapse or progression did not significantly differ supports the notion not to perform alloSCT for consolidation after 1st line therapy. Because relapsing/progressing pts not undergoing alloSCT had a dismal outcome any effort should be made to swiftly find a suitable donor and proceed to alloSCT as soon as possible.

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Keywords: Aggressive T-cell non-Hodgkin lymphoma, Cellular therapies

Conflicts of interests pertinent to the abstract.

O. Tournilhac
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Honoraria: Takeda
Educational grants: Takeda

PLASMA CELL NEOPLASMS AND AMYLOIDOSIS

379 | PREDICTORS OF RESPONSE TO RADIATION THERAPY AND OF PROGRESSION TO MULTIPLE MYELOMA IN PATIENTS WITH SOLITARY BONE AND EXTRAMEDULLARY PLASMACYTOMAS

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Introduction: Radiation therapy (RT) plays an important role in treating Solitary Extramedullary (EMP) and Solitary Bone (SBP) Plasmacytomas. The objective of this study is to review the effectiveness of RT in locally controlling the disease and looking at factors that predict progression to Multiple Myeloma (MM) in the PET scanera.

Methods: We performed a retrospective analysis of consecutive plasmacytoma patients (pts) treated at our high-volume center. We identified 94 pts, of which 62 were diagnosed with SBP and 32 with EMP, without evidence of MM at diagnosis (end-organ damage, >10% bone marrow involvement, >1 plasmacytoma). We identified 94 total pts, largest series to date in the literature, treated with RT (no pts received systemic therapy) between January 1, 2000, through December 31, 2020. Of the 94 pts, 62 were diagnosed with SBP and 32 with EMP, without evidence of MM at diagnosis (end-organ damage, >10% bone marrow involvement, >1 plasmacytoma). We utilized radiographic staging including PET scans and clinical assessments to determine patient outcomes. Outcomes include initial radiographic responses using the European Expert Panel Response Criteria, local control (LC), overall survival (OS), and progression to MM. Kaplan-Meier was used to assess LC and OS. Univariable analysis was done using age, sex, race, plasmacytoma type (EMP vs.

SBP), PET scan at staging versus other modalities, first post-RT response (CR, no CR), Pre-RT SUV of lesion, RT dose (≥45 Gy) and overall response to RT (if CR was achieved).

Results: Patient and treatment characteristics are summarized in table 1. 24 (66%) EMPs and 54 (84%) SBPs received a radiation dose ≥45 Gy. After excluding 8 patients who were lost to follow up, 81% of patients with EMPs and 81% with SBPs achieved complete response (CR) with a median time to CR being 11 months (range 0.53–38.9) for EMP and 8 months (range 0.6–89.2) for SBP. All pts achieving a CR were treated with doses ≥40 Gy. Only 1 (3%) EMP and 2 (3%) SBPs had an in-field failure after CR. The 5-year OS was 68% for EMPs and 94% for SBPs [$p = 0.007$]. Out of 94 pts, 19 died, and cause of death was not related to the plasma cell neoplasm in 7 EMP pts. The 5-year rate of progression to MM was 28% in the EMP group, and 64% in the SBP group [$p = 0.006$], with progression-free survival (PFS) of 61% In the EMP group and 35% in the SBP group [$p = 0.041$]. On univariate analysis, sex, age, RT dose (<45 Gy, ≥45 Gy), staging PET, location [EMP vs. SBP] and achieving a CR after RT

	EMP N=32 (%)	SP N=62 (%)
Sex (M/F)	21 (66) / 11 (34)	41 (66) / 21 (34)
Age at Diagnosis		
<60	11 (34)	27 (44)
>/= 60	21 (66)	35 (56)
Prior Cancer Diagnosis		
Yes *	10 (31)	14 (23)
No	22 (69)	48 (77)
Treatment for Plasmacytoma		
RT alone	10 (31)	40 (65)
Surgery (including excisional bx)+RT	22 (69)	22 (35)
Chemo + RT	0 (0)	0 (0)
Staging Modality		
PET	21 (65.6)	54 (87)
CT	8 (25)	5 (8)
MRI	3 (9.4)	2 (3)
Skeletal Survey	0 (0)	1 (2)
Pre-RT SUV Mean [range]	4.36 [0-14.7]	8.07 [0-32.2]
Pre-RT Maximum Tumor Size, cm	2.56 [0.7-5.1]	5.46 [1.2-11.1]
<5	7 (21.9)	14 (22.6)
5.1-10.0	1 (3.1)	14 (22.6)
>/= 10.1	0	1 (1.6)
Unknown	24 (75)	33 (53.2)
Lesion Site	Head and Neck 20 (62.5)	Axial Skeleton 38 (61)
	Other 12 (37.5)	Appendicular Skeleton 24 (39)
Total Delivered Dose (cGY)		
< 4500 [range]	11 (34) [3000-4000]	10 (16) [2000-4400]
>/= 4500 [range]	21 (66) [4500-6000]	52 (84) [4500-5040]
Complete Response (CR) Achieved	12.3 [12.3]	134.8 [66.03-203.47]
Yes	26 (81)	50 (80.65)
No	1 (3)	9 (14.52)
Unknown (lost to FU, no imaging)	5 (16)	3 (4.83)
Time to CR Median value [range], months	11.0 [0.53-38.9]	7.93 [0.57-89.2]
Re-Occurrence		
None	22 (69)	18 (29)
In-field Only	0 (0)	0 (0)
Out of field Only	6 (19)	40 (65)
In-field + out of field	1 (3)	2 (3)
Unknown (lost to FU)	3 (9)	2 (3)
Time to in-field failure from CR (months)	12.3	134.8
Time to first OOF Median value [range], months.	12.67 [3.2-28.7]	33.5 [1.2-134.0]
Progression to MM		
Yes	7 (21.8)	43 (69)
No	20 (62.5)	18 (29)
Unknown	5 (15.6)	1 (2)

(at first post-RT response and CR at any time) were analyzed. Pts with EMP were at significantly lower risk for progression to MM (HR 0.3, 95% CI: 0.2, 0.8; $p = 0.009$) Additionally, Pts with CR on first post-RT imaging were at lower risk for progression to MM (HR 0.6, 95% CI: 0.3, 1.0, $p = 0.05$).

Conclusion: Our data indicates that definitive RT for EMP and SBP can provide excellent LC. Progression to MM remains the main problem and is more common among pts with SBP, which is concordant with previously published literature.

Keyword: Multiple Myeloma

Conflicts of interests pertinent to the abstract.

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380 | RADIATION IN A NEW ERA OF MULTIPLE MYELOMA MANAGEMENT: PATTERNS OF UTILIZATION, CLINICAL, RADIOLOGIC, AND BIOCHEMICAL OUTCOMES, AND POSSIBLE GENOMIC CORRELATES OF RESPONSE

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Background/Objectives: Systemic therapies for multiple myeloma (MM) have advanced considerably, improving patient outcomes. Yet, the use of radiotherapy (RT) has remained heterogeneous, and even controversial, due to minimal data on outcomes. With the ultimate goal of guiding the design of prospective trials incorporating RT, we initiated a study of our institutional experience treating MM with RT since 1/1/2000. Here we report a preliminary feasibility analysis of an initial sample cohort, identifying patterns of RT utilization, outcomes, and impact of RT on radiographic and biochemical markers, with genomic characterization for more recently treated patients.

Materials/Methods: 506 pathologically confirmed MM patients who received RT to 1190 sites between 1/1/2000 and 6/1/2022 were identified. Patient, disease, and treatment characteristics were analyzed for 50 consecutive patients treated in 2019 and tested for association with local and distant failure (LF, DF) using univariable and multivariable analysis. Genomic data was obtained via next generation sequencing using an institutional targeted sequencing panel.

Results: Among the 50 patients analyzed (median 63 years), 90 lesions were treated with RT, 33% with concurrent systemic therapy, to median dose of 20 Gy (8–46 Gy) over a median of 5 fractions (1–25). RT Indications were pain (56%), critical structure involvement (25%), peri-operative (9%), salvage/consolidation (8%), and bridging therapy (2%). Median size of RT-treated lesions was 4.2 cm (1.4–7.9) and included non-vertebral bones (62%), spine (24%), and extramedullary sites (14%). The median number of lines of pre-RT therapy was 7 (1–14) and 51% had >9 lesions on imaging, 47% involving both medullary and extramedullary sites. With median follow-up of 12.4 months (0.5–46), LF occurred in 5% of treated sites and 89% had DF, most commonly in both medullary + extramedullary (51.4%) sites. Absolute decreases 1-week to 1-month post-RT were observed in % of marrow plasma cell (median 4.0%), M spike (0.30 g/dL), total protein (0.3 g/dL), K:L ratio (0.01), lesion size (1.5 cm), and lesion SUV (3.1) but in this limited sample, none were significantly associated with disease control. A cohort of 62 RT-treated MM patients from 2016 to 2022 had genomic data available; most common tumor mutations were in TP53 (35%), HIST1 (34%), NRAS (34%), and KRAS (23%).

Conclusion: In this pilot analysis of a sampling cohort of RT-treated MM, we report on patterns of utilization, outcomes, and biochemical and radiographic correlates. At the meeting, we will present the analysis of a larger cohort of MM patients and further analyze emerging genomic data. We aim to characterize the role of RT in the modern era of systemic therapy to guide the design of future prospective trials and to inform novel approaches for incorporating RT into the treatment paradigm.

Keywords: Diagnostic and Prognostic Biomarkers, Multiple Myeloma, PET-CT

No conflicts of interests pertinent to the abstract.

CAR-T (CELLULAR THERAPIES)

381 | SAR444245, A NON-ALPHA IL2, RESCUES CHRONIC ANTIGEN AND CAR-DRIVEN T-CELL DYSFUNCTION

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T cell dysfunction from chronic antigen stimulation limits the efficacy of T cell therapies. SAR444245 is a PEGylated, non-alpha IL2; PEG is attached to a novel amino acid such that it prevents binding to the alpha subunit of the IL-2 receptor, avoiding drug toxicities and expansion of regulatory T-cells, yet retains binding to the beta-gamma receptors that expand tumor-killing T cells.

T-cell assays: CD8 T cells isolated from healthy donors were repetitively stimulated with antigen over 12 days to establish exhausted CD8 T cells. They were then exposed to SAR444245 for 7 days. Proliferation and co-inhibitory marker expression were measured as well as cytokine production by Luminex. CART cell assays: CD19 CAR T cells were generated from relapsed LBCL patient PBMCs obtained at the time of leukapheresis. Short term CAR T cell cytotoxicity was assessed by co-culture with 2 LBCL cell lines in the presence or absence of SAR444245 over 48 hours. Chronic CART stimulation was modelled in vitro by repeat addition of target tumor cells to CAR T cells every 48 hours over 8 days in the presence or absence of SAR444245. Live T cell and lymphoma cell counts as well as T-cell immunophenotyping were obtained at baseline and days 4 and 8. In vivo: Luciferase expressing Raji cells were injected into NSG mice. Tumor burden was monitored via BLI. Mice were either treated with anti-CD19/22 CAR T cells alone or in combination with SAR444245 (weekly treatment for 3 doses). Blood samples were obtained from mice on days 11 and 18 days post-CART infusion to immunophenotyping.

Seven days following exposure to SAR444245, exhausted CD8 T cells demonstrated enhanced IFNγ and TNFα secretion, decreased co-inhibitory expression, and increased proliferation compared to cells not exposed to SAR444245. CD8 T cells exposed to SAR444245 on the day of initial activation, followed by repetitive antigen exposure, proliferated and maintained IFNγ similar to acutely stimulated CD8 T cells. Cytokine analysis of treated CD8 T cells demonstrated robust expression of cytokines and effector molecules, and increased polyfunctionality. In short term assays, SAR444245 induced T cell expansion without significant increase in cytotoxicity. However, in long-term assays mimicking chronic CAR stimulation and exhaustion, addition of SAR444245 to CAR T-cells resulted in enhanced CART-cell proliferation through day 8, and enhanced control of tumor cells. In an in vivo Raji model, the combination of SAR444245 with CD19/CD22 CART cells demonstrated enhanced CART expansion and sustained anti-tumor efficacy compared to CAR T cells alone.

SAR444245 treatment of exhausted CD8 or CAR T cells restored functionality and alleviated T cell dysfunction. These data suggest that SAR444245 rescue of T cell exhaustion through maintenance of T cell proliferative capacity, cytotoxicity, and polyfunctionality and provide rationale for future clinical study of SAR444245.

Encore Abstract - previously submitted to EHA 2023

The research was funded by: Sanofi

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Immunotherapy

Conflicts of interests pertinent to the abstract.

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Research funding: Sanofi

382 | CELLULAR DYNAMICS AND THEIR IMPACT ON OUTCOME IN PATIENTS WITH MANTLE CELL LYMPHOMA DURING TREATMENT WITH CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS

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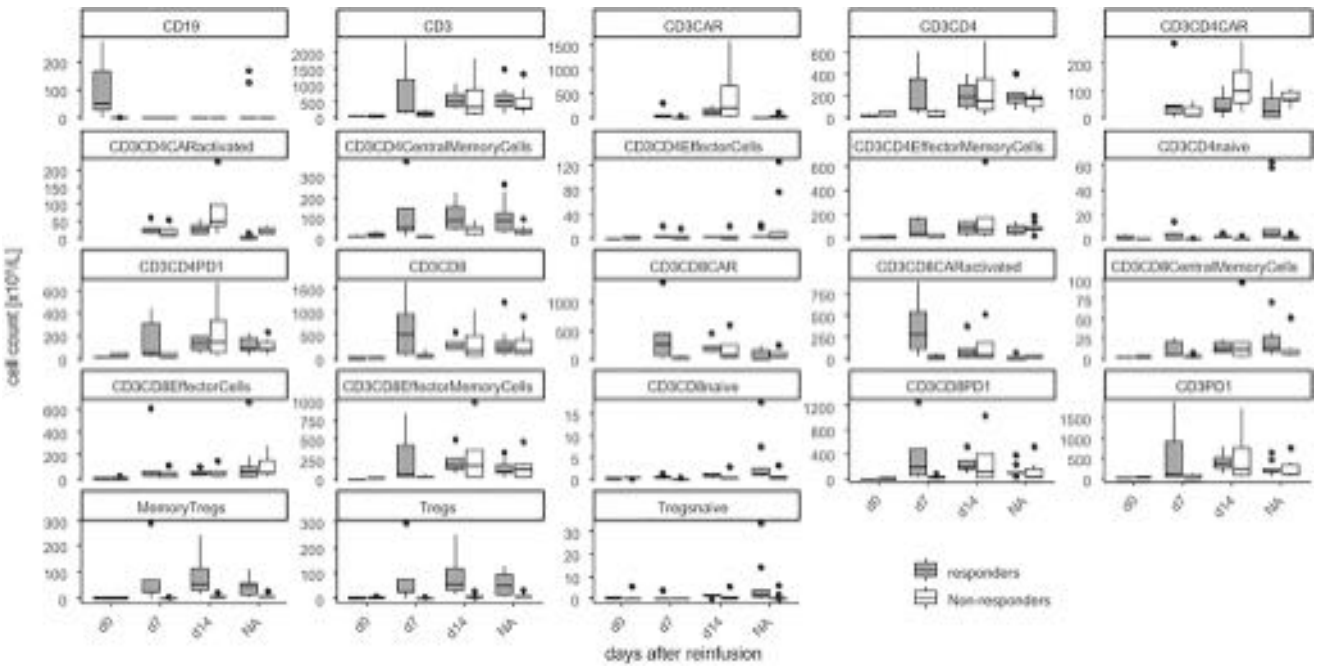
Introduction: Brexucabtagene autoleucel (brexu-cel) is an effective chimeric antigen receptor (CAR) product for the treatment of patients (pts) with refractory or relapsed (r/r) mantle-cell lymphoma (MCL). Cellular biomarkers predicting response to brexu-cel have not been studied systematically so far.

Methods: Therefore, comprehensive multiparemteric flow-cytometric analyses (16 parameter) of peripheral blood were performed before (d0), and on days 7, 14, 28 and 100 after brexu-cel reinfusion to assess changes of the cellular immune system and to approximate their impact on outcomePts were stratified according to their response in the contrast-enhanced computed tomography one month after reinfusion, as responders (complete morphological response) and non-responder. Moreover, CAR T cells isolated from pts were incubated with CD19 Raji cells in vitro to assess their cytotoxicity.

Results: A total of 10 pts (9 male, 1 female) with a median age 63 years (51–75) were investigated. CD3CAR and CD3CD8CAR cells peaked both on d14 with 105.39 $\times$ 10^6/L (8.19–1590.2) and 134.68 $\times$ 10^6/L (11.0–595.65) respectively, whereas the CD3CD4CAR cells peaked on d28 with 64.75 $\times$ 10^6/L (0–137.25). Tregs peaked on d28 with 24.2 $\times$ 10^6/L (5.2–128.1) compared to baseline.

In respect to the immune cell composition at baseline (d0), we could not detect any differences in responders and non-responders.

However, on d7 the responders showed significantly higher counts of activated CD3CD8CAR T cells ($p = 0.02$), CD4 central memory cells



($p = 0.03$) and CD3CD4naïve cells ($p < 0.01$), but also higher counts of T regulatory cells (Tregs) ($p = 0.02$) and memory Tregs ($p = 0.02$) on day 7.

On d14 the responders had higher counts of Tregs ($p = 0.02$) and memory Tregs ($p = 0.03$) were higher in responders, without differences in the counts of CD3CAR T cells ($p = 0.77$), C3CD8CAR T cells ($p = 0.25$) and CD3CD4CAR T cells ($p = 0.56$).

Responders also expressed higher counts of naïve CD4 cells ($p < 0.05$) on d28 and d100 ($p = 0.02$). The regeneration of CD19 cells on d100 was detected in one responder and one non-responder.

In vitro cytotoxicity of pts' CAR T cells was confirmed in five patients (4 responder, 1 non-responder) thus indicating their general functional activity but also highlighting that additional factors in-vivo may mitigate the potential of infused CART-cells.

Conclusion: Within our cohort of pts undergoing treatment with brexu-cel, we identified an association of the kinetics of CD3CD8CAR T cells, CD4 central memory cells and CD3CD4naïve as well as Treg cells with response to treatment. Further studies are warranted to elucidate the impact of cellular and microenvironmental factors on therapy response.

Keyword: Cellular therapies

Conflicts of interests pertinent to the abstract.

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383 | RESPONSES AFTER ALLOGENEIC NK CELL THERAPY FOR LYMPHOMA: CORRELATIVE ANALYSIS REVEALED IMPACT OF HOST MONOCYTES AND ROBUST T CELLS TUMOR TRAFFICKING

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Background: Natural killer (NK) immune effectors are being explored for cancer immunotherapy. GDA-201 is a novel nicotinamide ex-vivo expanded metabolically fit allogeneic NK cell product with augmented resistance against exhaustion. We conducted a phase 1 study of GDA-201 (NCT03019666) and reported 19 patients (pts) with relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL).

Methods: R/R NHL patients (10 follicular lymphoma, 8 DLBCL, 1 MCL) received lymphodepleting chemotherapy followed by 2 infusions of GDA-201 (days 0, 2) combined with rituximab and low dose IL2. We performed comprehensive analysis of the host innate immunity and T cell repertoire using CyTOF and Clonoseq. "On treatment" lymphoma biopsies obtained between 4 and 16 days after GDA-201 infusion were examined using CODEX spatial proteomic profiling and CyTOF.

Results: We previously reported that the best overall response rate for 19 NHL patients was 74% and 62% achieved complete response. The median duration of response was 16 months (range 5–36 months). GDA-201 cells persisted in peripheral blood for 7–14 days (2–92% NK cells were GDA-201) but were no longer detected after day 14.

At baseline, number of classical monocytes varied widely (266–730 cells/uL) among patients. Responders had lower levels of classical monocytes and PMN myeloid derived suppressor cells (MDSC) at baseline compared to non-responders (monocytes median 342 vs. 624 cells/uL; $p = 0.093$; PMN-MDSC 0.04 vs. 0.6 cells/uL; 0.049). At day 7 after GDA-201, we observed expansion of host T cell subsets, particularly regulatory T cells, CD8 effector memory and CD4 effector memory subsets characterized by high Ki67 expression. CD4 cells had increased expression of CCR4 and CXCR3 chemokines. T cell clonality data will be presented.

Tumor tissue biopsies obtained 4–16 days after GDA-201 revealed a low number of viable B-cell lymphoma cells with areas of necrosis. CODEX analysis demonstrated NK cells in lymphoma tissue increased from <1% at baseline to 10% after GDA-201 infusion. Remarkably, host T cells comprised most of cells at tumor sites (~ 50–65% of cellularity). Both CD8 and CD4 subsets have been detected, including regulatory T cells (10–25%). Tumor infiltrating T cells were predominantly characterized by terminal effector or effector memory phenotype, activation (↑ HLA-DR, CD69), expression of suppressive receptors TIGIT, PD1 and increased expression of chemokine receptors CXCR3 and CCR4. The high proportion of $CXCR4^+$ $CD4^+$ T cell in both blood and tissues suggests a role for chemokine recruitment and trafficking.

Conclusion: Overall, our findings showed that responses after allogeneic NK cell therapy are influenced by levels of pre-treatment monocytes and PMN MDSCs. Our results suggest that immune microenvironment changes after allogeneic NK therapy stimulate influx of host T cells into tumor sites and support cross-talk between innate and the adaptive arms to enhance lymphoma elimination.

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Keywords: Cellular therapies, Microenvironment

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384 | THE ITALIAN CART-SIE REAL LIFE MULTICENTER OBSERVATIONAL STUDY ON CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY FOR LARGE B-CELL (LBCL) AND MANTLE CELL (MCL) LYMPHOMAS

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Introduction: Axi-cel and tisa-cel are reimbursed for the treatment of LBCL relapsed/refractory (R/R) after at least two treatments; brexu -cel for R/R MCL failing a BTK inhibitor.
Methods: The CART-SIE is a multicenter study collecting data on all consecutive lymphoma patients treated with CAR-T. The aim of this analysis was to evaluate outcome [overall response rate (ORR), overall survival (OS), progression free survival (PFS)], and safety [cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS)] of the different CAR-T products.
Results: From 2019 to 2022, 499 patients were enrolled and leukapheresed; 426 infused patients with adequate follow-up were analyzed. Clinical characteristics were as follows: median age 57 years (IQR: 46–65), stage III/IV 300 (70%); median number of prior lines 2 (IQR: 2–3), 295 (69%) refractory to the last treatment. According to local pathology reports, 44 (10%) were MCL and 382 (90%) LBCL, including 236 (55%) DLBCL, 89 (21%) HGBCL, 57 (13%) PMBCL. Median follow-up time for infused patients was 10.99 months (IQR: 4.18–18.03). Brexu-cel was infused in 43/44 (98%) MCL; the ORR at 30-days was 33/44 (75%), with 24 (56%) CRs; the 12-months OS and PFS were 76% (95% CI: 56–100) and 59% (95% CI: 35–97). In the 382 LBCL, axi-cel was infused in 192 (50%), and tisa-cel in 190 (50%); the ORR at 30-days was 255/382 (67%), with 174 (46%) CRs; the 12-months OS and PFS were 71% (95% CI: 66–76) and 45% (95% CI: 39–50). By histotype, the 12-months OS was 89% (95% CI: 81–98) in PMBCL, 70% (95% CI: 64–78) in DLBCL, 58% (95% CI: 47–71) in HGBCL; the 12-months PFS was 65% (95% CI: 53–80) in PMBCL, 42% (95% CI: 35–50) in DLBCL, 38% (95% CI: 29–50) in HGBCL. In the whole population, all grade CRS was observed in 355/426 (83%) patients, with 47 (11%) severe (grade 3–4); ICANS in 103 (24%) patients, with 39 (9%) severe (grade 3–4). Tocilizumab was administered in 272 (64%) and steroids in 108 (25%); 46 patients (11%) were admitted in the intensive care unit. Treatment related deaths were 9 (2%). CAR-T expansion kinetics by flow cytometry was evaluated in a cohort of 150 patients with a positive correlation with disease response and survival (p-value 0.0076 and 0.036 respectively). A sub-analysis comparing axi-cel and tisa-cel was performed in the DLBCL and HGBCL cases (although unbalanced for histotypes and disease status); no differences between axi-cel and tisa-cel were reported in 12-months OS 71% (95% CI: 62–80) and 64% (95% CI: 56–73) (log-rank $p = 0.6792$); an

advantage of axi-cel compared to tisa-cel was observed in 12-months PFS 47% (95% CI: 38–57) and 37% (95% CI: 30–45), respectively (log-rank $p = 0.0354$).

Conclusions: The outcome and safety of patients treated with CAR-T were similar to those reported by other real life studies with a low non-relapse mortality. CR rate in MCL seems lower than in pivotal trial.

Encore Abstract - previously submitted to EHA 2023

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies

Conflicts of interests pertinent to the abstract.

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Other remuneration: Lecture fees/educational activities: Astrazeneca, Celgene-BMS, Gilead-Sciences, Incyte, Janssen-Cilag, Novartis, Roche, Takeda

385 | 3-YEAR OUTCOMES OF ADULTS WITH RELAPSED OR REFRACTORY B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH BREXU-CEL IN ZUMA-3 BY AGE, PRIOR THERAPIES, AND SUBSEQUENT TRANSPLANT

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Background: Brexucabtagene autoleucel (brexu-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved in the US for adults with relapsed or refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) and in the EU for adults ≥26 years with R/R B-ALL based on positive results of ZUMA-3. After 3-years follow-up in ZUMA-3, brexu-cel demonstrated an overall complete remission (CR)/CR with incomplete hematologic recovery (CRi) rate of 71% and a median overall survival (OS) of 26.0 mo in all treated pts ($N = 55$) and 38.9 mo in pts with CR ($n = 31$; Shah et al. EU CAR T 2023. Abstract 34). Here we report 3-years outcomes by age, prior therapies, and subsequent allogeneic stem cell transplant (alloSCT).

Methods: Pts (≥18 years) had R/R B-ALL and received 1 brexu-cel infusion (1×10^6 CAR T cells/kg) following leukapheresis and conditioning chemotherapy. The primary endpoint was overall CR/CRi rate per independent review. Post hoc subgroup analyses were exploratory, with descriptive statistics reported.

Results: As of July 23, 2022, the median follow-up in Phase 2 ($N = 55$) was 38.8 mo (range, 32.7–44.6). The CR/CRi rate (95% CI) was 67% (35–90) for pts <26 years ($n = 12$) and 72% (56–85) for pts ≥26 years ($n = 43$). The median (95% CI) OS was 28.6 mo (0.6-not estimable [NE]) for pts <26 years and 34.1 mo (15.9-NE) for pts ≥26 years. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 92% of pts <26 years and in 88% of pts ≥26 years.

For pts with 1 prior therapy ($n = 10$), the CR/CRi rate was 90% (95% CI, 55–100) and for pts with ≥2 prior therapies ($n = 45$), the CR/CRi rate was 67% (95% CI, 51–80); medians (95% CI) for OS were not reached (NR; 2.1-NE) and 25.6 mo (14.2–38.9), respectively. The incidence of Grade ≥3 TRAEs was 90% for pts with 1 prior therapy and 89% for pts with ≥2 prior therapies.

The CR/CRi rates (95% CI) for pts with ($n = 25$) and without ($n = 30$) prior blinatumomab (blina) were 60% (39–79) and 80% (61–92). The median (95% CI) OS was 14.2 mo (3.2–26.0) for pts with prior blina and NR (18.6-NE) for pts without prior blina; Grade ≥3 TRAEs occurred in 80% and 97% of pts, respectively.

For responders (CR/CRi) who did ($n = 10$) or did not ($n = 29$) proceed to subsequent alloSCT, the median (95% CI) OS was NR (7.6-NE) and 38.9 mo (18.6-NE), respectively.

Similar efficacy results were observed in a pooled subgroup analysis of Phase 1 and 2 pts treated at the pivotal dose ($N = 78$), with a median follow-up of 41.6 mo (range, 32.7–70.3).

Conclusions: Adults with R/R B-ALL benefitted from brexu-cel, regardless of age, number of prior therapies, prior blina exposure, or subsequent alloSCT status. Survival appeared longer in pts with fewer prior therapies and in blina-naïve pts; however, small pt numbers and unmatched baseline characteristics limit interpretation of these results. Additional studies are needed to determine the impact of prior therapies and/or subsequent alloSCT on outcomes of pts who receive brexu-cel.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Immunotherapy

Conflicts of interests pertinent to the abstract.

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386 | MATCHING-ADJUSTED INDIRECT COMPARISON OF AXICABTAGENE CILOLEUCEL VERSUS MOSUNETUZUMAB IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA PATIENTS AFTER 2 PRIOR SYSTEMIC TREATMENTS

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Introduction: Follicular lymphoma (FL) is an indolent form of non-Hodgkin's lymphoma; however, relapsed/refractory (R/R) FL patients tend to have poor outcomes. Axicabtagene ciloleucel (axi-cel) was the first chimeric antigen receptor (CAR) T-cell therapy approved for R/R FL patients. More recently, mosunetuzumab was the first bispecific monoclonal antibody approved in R/R FL. We sought to conduct a matching-adjusted indirect comparison (MAIC) to estimate the comparative efficacy and safety of axi-cel and mosunetuzumab for the treatment of 3rd line or higher (3L+) FL.

Methods: The evidence base consisted of individual patient data (IPD) from the single-arm axi-cel trial, ZUMA-5, and publications identified through a systematic review pertaining to the mosunetuzumab trial (NCT02500407). For each outcome, prognostic factors—including progression within 24 months of frontline initiation (POD24), refractory status, double refractory, prior stem cell transplant—were a priori identified through quantitative analysis and clinical experts. Outcomes were progression-free survival (PFS), duration of response (DoR), objective response rate (ORR), complete response rate (CRR), and safety. Analyses used independent central review for both trials, where possible. Overall survival (OS) was not analyzed as mosunetuzumab data were immature and not reported in the latest publication. As IPD for axi-cel and aggregate data for mosunetuzumab were available, unanchored MAICs were conducted to align ZUMA-5 to the patient characteristics of the mosunetuzumab trial. Hazard ratios (HRs) from Cox regression were used to compare time-to-event outcomes using pseudo-IPD extracted from published Kaplan-Meier plots for mosunetuzumab and the remaining outcomes were compared using odds ratios (ORs). Index date for ZUMA-5 was date of leukapheresis and included all enrolled patients.

Results: Patient characteristics were generally well-aligned between trials leading to large effective-sample sizes after matching, ranging from 99.2 to 109.9, for ZUMA-5 (n = 127). In comparisons to mosunetuzumab (n = 90), axi-cel was associated with improved PFS (HR: 0.38; 95% confidence interval [CI]: 0.23–0.61) and DoR (HR: 0.45; 95% CI: 0.26–0.77). Results were consistent for response outcomes (Figure 1). Sensitivity analyses led to similar results. Although axi-cel was associated with a higher rate of all-grade cytokine release syndrome (CRS) and neurological events (NE), differences in Grade ≥3 (G3+) CRS and treatment-related adverse events (TRAEs) were not statistically significant. Differences in G3+ NE were not evaluable.

Conclusions: Findings from this comparative analysis of axi-cel and mosunetuzumab for the treatment of 3L+ FL show improved efficacy and more durable response with axi-cel, with increased odds of all-grade CRS and NE, but not G3+ CRS and TRAEs. More data are needed for OS comparisons.

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Keywords: Cellular therapies, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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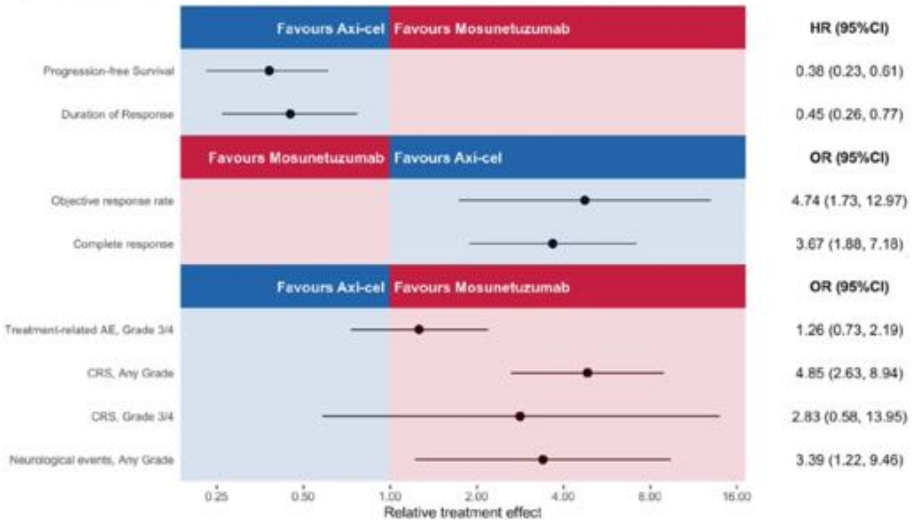
Figure 1: Outcomes from axi-cel versus mosunetuzumab MAIC in 3L+ R/R FL



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Honoraria: Pfizer, Gilead

387 | OUTCOMES IN PATIENTS WITH EBV+ PTLD TREATED WITH ALLOGENEIC EBV-SPECIFIC T-CELL IMMUNOTHERAPY (TABELECLEUCEL) UNDER AN EXPANDED ACCESS PROGRAM (EAP) IN EUROPE

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Introduction: Patients (pts) with relapsed or refractory (r/r) Epstein–Barr virus-positive (EBV$^+$) post-transplant lymphoproliferative disease (PTLD) in Europe have had historically poor overall response rates and median overall survival (OS) with no approved treatment options.

Tabelecleucel, an off-the-shelf, allogeneic EBV-specific T-cell immunotherapy has shown clinical benefit and favorable safety profile in the treatment of EBV$^+$ PTLD failing rituximab ± chemotherapy (Prockop EBMT 2021, ATC 2021, ASH 2021, Mahadeo ASH 2022). Its recent European marketing authorization (EMA) represents the first approval of an allogenic T-cell immunotherapy globally.

Methods: Atara Bio supported expanded access requests for tabelecleucel in Europe. Here we report new and updated real-world effectiveness and safety data for r/r EBV$^+$ PTLD pts who provided consent for research between September 2020 and December 2022.

Results: 74 EAP requests were received from 10 countries for pts with r/r EBV$^+$ diseases. 27 EBV$^+$ PTLD pts consented to secondary use of data and 24 pts had received ≥1 dose of tabelecleucel, including 4 pts with primary central nervous system (PCNS) PTLD.

16 of 24 (66.7%) EBV$^+$ PTLD pts achieved a partial (PR) (33.3%) or complete (CR) (33.3%) response, with median time to response (TTR) of 1.0 months (mo) (0.8–2.2). Response rate for PCNS PTLD pts was 75% (1 CR, 2 PR).

1-year OS Kaplan–Meier (KM) estimate rates in EBV$^+$ PTLD were 73.7% (95% CI: 47.3, 88.3) overall, 87.5% in allogeneic hematopoietic stem cell transplant (HCT) and 66.5% in solid organ transplant (SOT), with a median follow-up time of 9.9 (2.4–13.9) and 6.0 (0.7–18.0) mo, respectively.

Serious treatment-emergent adverse events (TESAEs) were reported in 7 (29.2%) pts, including 1 fatal event of disease progression. Predefined risks for tabelecleucel were reported in 3 pts; 1 (4.2%) SOT pt had a TESAE of liver transplant rejection (grade 2) and 2 (8.3%) HCT pts had non-serious TEAEs of chronic graft-versus-host disease (grade 1 and 2). No cases of cytokine release syndrome or tumor flare reaction were reported. No AEs were reported as related to tabelecleucel by the treating physician.

Conclusions: These real-world results for pts with r/r EBV$^+$ PTLD post-HCT or post-SOT, including those with EBV$^+$ PCNS PTLD, treated in the European EAP continue to reinforce the favorable risk: benefit profile of tabelecleucel and are in line with clinical study data supporting its recent EMA approval.

Table: Effectiveness outcomes in tabelecleucel treated r/r EBV$^+$ PTLD pts

	EBV$^+$ PTLD post-HCT (N=8)	EBV$^+$ PTLD post-SOT (N=16)	All (N=24)
Responders*	7 (87.5)	9 (56.3)	16 (66.7)
95% CI	(47.3, 99.7)	(29.9, 80.2)	(44.7, 84.4)
CR	4 (50.0)	4 (25.0)	8 (33.3)
PR	3 (37.5)	5 (31.1)	8 (33.3)
Median TTR, mo (range)	1.0 (0.9–1.6)	1.0 (0.8–2.2)	1.0 (0.8–2.2)
Median follow-up, mo (range)	9.9 (2.4–13.9)	6.0 (0.7–18.0)	7.4 (3.4–11.8)
1-yr OS KM rate (95% CI)	87.5 (38.7, 98.1)	66.5 (32.7, 86.2)	73.7 (47.3, 88.3)

*Best overall response, n (%); CI, confidence interval

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388 | COMBINED AUTOLOGOUS CD30.CAR-T CELLS AND NIVOLUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA AFTER FAILURE OF FRONTLINE THERAPY (ACTION STUDY)

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Introduction: Autologous CD30.CAR-T therapy has demonstrated promising antitumor activity with favorable safety profile in relapsed or refractory (r/r) classical Hodgkin Lymphoma (cHL) patients. Hodgkin Reed-Sternberg cells, the target of CD30.CAR-T, frequently over-express PD-L1/PD-L2. Checkpoint inhibitors (CPI) of PD-1, including nivolumab (nivo), have shown effective and safe in r/r cHL. Pre-clinical studies suggest that combination of CPI and CAR-T therapy could enhance the survival of CAR-T cells and promote tumor cell death.

Methods: A single-arm, phase 1b, multicenter study (NCT# 05352828) is being conducted to evaluate safety and antitumor activity of combined CD30.CAR-T and nivo in r/r cHL patients after frontline therapy failure, with 15 patients to be enrolled. Patients are treated with 2 cycles of nivo, followed by a single infusion of CD30.CAR-T preceded by lymphodepletion (LD) chemotherapy. An additional 2 cycles of nivo are then given, followed by response assessment by PET/CT per Lugano 2014 criteria. Patients without progressive disease may undergo either autologous stem cell transplant or continue nivo up to 6 additional cycles per physician and patient preference.

Results: A total of 15 patients were enrolled (Table 1). To date, all patients were treated with at least 2 cycles of nivo, and 10 patients treated with CD30.CAR-T (median dose: 2.4 [range: 2.0–2.7] $\times 10^8$ cells/m^2).

Combined therapy was well tolerated. 86.7% (13/15) patients experienced at least one AE with 46.7% patients having grade ≥3 AEs which were hematologic toxicities mainly due to LD chemotherapy. Two patients had cytokine release syndrome (Grade 1), which resolved without use of steroid or tocilizumab. No neurotoxicity was observed.

Among 5 patients treated with CD30.CAR-T and 4 cycles of nivo, there were 4 complete response (CR) and one stable disease (SD). ctDNA-MRD was assessed with PhasED-Seq (Foresight Diagnostics) in 3 patients where samples were available to date, all with radiographic CR. All 3 patients (100%) had undetectable ctDNA-MRD at this timepoint, demonstrating deep molecular response.

Conclusion: Preliminary data demonstrated favorable safety profile and promising anti-tumor responses of CD30.CAR-T combined with nivo in r/r cHL patients after failure of frontline therapy. Evaluation of 15 patients enrolled is ongoing, and the clinical and ctDNA-MRD data will be presented at the meeting.

Table 1: Patient Demographics

Characteristics	All patients (N=15)
Age, median (range)	35 (27-76)
Sex, % (n)	
- Male	7 (46.7)
- Female	8 (53.3)
ECOG Performance Status, n (%)	
- 0	11 (73.3)
- 1	4 (26.7)
Lugano Classification Stage, n (%)	
- II	6 (40.0)
- III	4 (26.7)
- IV	5 (33.3)
Prior First-line Treatment	
- ABVD	9 (60.0)
- BV+AVD	5 (33.3)
- Other	1 (6.7)
Relapsed/ Refractory, n (%)	
- Relapsed	10 (66.7)
- Primary Refractory	5 (33.3)
B Symptoms, n (%)	6 (40.0)
Bulky Disease, n (%)	6 (40.0)
Extranodal Involvement, n (%)	7 (46.7)

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Conflicts of interests pertinent to the abstract.

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389 | FIRST IN HUMAN DATA OF NKX019, AN ALLOGENEIC CAR NK FOR THE TREATMENT OF RELAPSED/REFRACTORY (R/R) B-CELL MALIGNANCIES

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Background: Autologous CAR T-cell therapies have altered the treatment landscape for many patients (pts) with advanced B-cell malignancies, however custom manufacturing precludes prompt treatment and can result in manufacturing failure. T-cell mediated toxicities are common and can be severe, thereby limiting the population of eligible pts. These challenges limit CAR T-cell therapy administration to certified treatment centers, further restricting patient access.

NKX019 is a cryopreserved, allogeneic CD19-targeting CAR NK-cell therapy, derived from healthy donor NK cells, with CD3 zeta and OX40 costimulatory domains and a separate membrane bound IL-15 for activation. NKX019 has shown encouraging in vitro and in vivo cytotoxicity. Development of an on demand allogeneic NK-cell therapy may address challenges associated with CAR-T therapy.

Methods: This is an open label, phase 1 trial (NCT05020678) for adults with r/r B-cell malignancies with ≥2 prior lines of therapy excluding prior auto CD19 CAR T-cell therapy. Following 3 days of lymphodepletion (LD) with fludarabine and cyclophosphamide, pts received NKX019 at 3 dose levels (3×10^8, 1×10^9, or 1.5×10^9 CAR^+ NK cells/dose on days 0, 7, and 14 of a 28-day cycle). Additional cycles were allowed to deepen response. Tolerability, anti-tumor activity, cellular kinetics, and immune responses were evaluated.

Results: As of November 2022, 19 pts in the US and Australia with r/r B-cell malignancies (14 with non-Hodgkin lymphoma (NHL) (LBCL, FL, MZL, or MCL) and 5 with leukemia (ALL or CLL)) received NKX019. Median age was 59 years (range 21–82), with median 4 prior lines of therapy. RP2D of 1.5×10^9 cells was determined.

Grade 3/4 hematologic toxicity was 84%, consistent with expected myelosuppression related to LD. There was one grade 3 infection. There were no treatment related AEs leading to discontinuation of NKX019. No dose limiting toxicities, neurotoxicity, or GvHD were reported. Five of 19 pts (26%) developed transient fever within 8 hours of NKX019 dosing, but no pts developed signs of cytokine release syndrome beyond 24 hours after cell infusion.

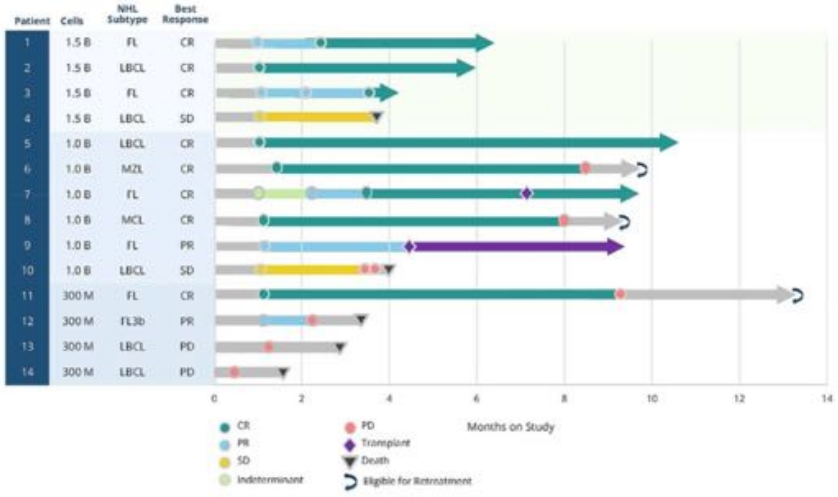
Responses for pts with NHL were as follows: 2 out of 4 (3×10^8 dose level), 5 out of 6 (1×10^9 dose level) and 3 out of 4 (1.5×10^9 dose level). Of the 8 patients who achieved CR, 3 with indolent lymphoma subsequently relapsed, each after more than 6 months of remission. One pt with CLL had stable disease.

Pharmacokinetic data showed a correlation between higher cell doses and higher peak concentration (Cmax), with a trend toward higher Cmax in pts achieving CR. No association was observed between clinical response and elevation of serum cytokines.

Conclusion: These data suggest that NKX019 has a manageable safety profile with activity across multiple NHL histologies. Expansion cohort enrollment is ongoing evaluating the RP2D in CAR-T naïve LBCL, CAR-T exposed LBCL, and combination with rituximab.

Encore Abstract - previously submitted to EHA 2023

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Ongoing Trials



Conflicts of interests pertinent to the abstract.

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390 | A PHASE I STUDY OF CD19-TARGETED 19(T2)28Z1XX CAR T CELLS IN ADULT PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Background: The redundancy of CD28 and CD3 signaling in a CAR design incorporating all 3 immunoreceptor tyrosine-based activation motifs (ITAMs) might negatively affect T cell differentiation and promote exhaustion. Therefore, we created a novel CD19 CAR construct with calibrated CAR signaling potential by mutating 2 of the 3 ITAMs, termed 1XX. In mouse models, 19-28z1XX CAR successfully induced tumor eradication at low CAR T cell doses with improved survival compared to conventional 19-28z CAR and with enhanced persistence of functional CAR T cells. We report on adult pts with DLBCL treated with 19(T2)28z-1XX CAR T cells (NCT04464200).
Methods: This is a single center, phase I, dose-escalation and expansion trial of 19(T2)28z1XX CAR T cells in adult pts with R/R DLBCL. Pts received lymphodepleting chemotherapy followed by escalating doses of CAR T cells: 25–200 $\times$ 10^6. The primary objective was to evaluate safety and tolerability and determine the recommended phase 2 dose. Secondary objectives include overall response rate and duration of response.
Results: Sixteen pts were treated on the dose escalation phase of the study. Median age was 62 (range, 50–80), and median number of prior treatments was 2 (range, 1–5). 4, 6, 3 and 3 pts were treated at DL1, DL2, DL3 and DL4 CAR T cells, respectively. 15 pts (94%) experienced cytokine release syndrome (CRS): grade 1 ($n = 9$), grade 2 ($n = 6$). No pts experienced $\geq$ grade 3 CRS. Two pts (13%) experienced neurotoxicity (NTX): 1 pt with grade 1 and 1 pt with grade 3. NTX was transient and reversible in both cases.Ten of 16 pts (63%) achieved a complete response (CR) and 2 pts (13%) achieved a partial response (PR), with overall response rate (ORR) of 75%. One pt who achieved initial PR spontaneously converted to CR without further treatment after month 6, resulting in best CR rate of 69%. Responses were seen across all dose levels. With a median follow-up of 155 days (range, 33–667), no pt in CR has experienced relapse including 7 pts with >6 months of follow-up (Figure 1). Peak CAR T cell expansion occurred at a median of 14 days after CAR T cell infusion (range, 7–83.3 days). CAR T cell detection beyond 350 days has been noted. DL 1 (25 $\times$ 10e6 cells) was chosen as the recommended dose for the expansion phase. Updated responses in the dose escalation cohort and the full expansion cohort, as well as PK data, will be presented.
Conclusions: Treatment with 19(T2)28z1XX CAR T cells was safe. No severe CRS was observed and only 1 pt experienced transient grade 3 NTX. The overall CR rate was 69% and durable with no relapse observed with a median follow-up of 155 days. CRs were observed at DL1, which was chosen for the expansion phase. These findings

corroborate our preclinical data and suggest that the 1XX signaling domain may lead to enhanced efficacy of CD19 CAR and allow infusion of a lower T cell dose with favorable toxicity profile.

Keyword: Cellular therapies

Conflicts of interests pertinent to the abstract.

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391 | OUTCOMES WITH BENDAMUSTINE LYMPHODEPLETION AND BREXUCABTAGENE AUTOLEUCEL FOR MANTLE CELL LYMPHOMA

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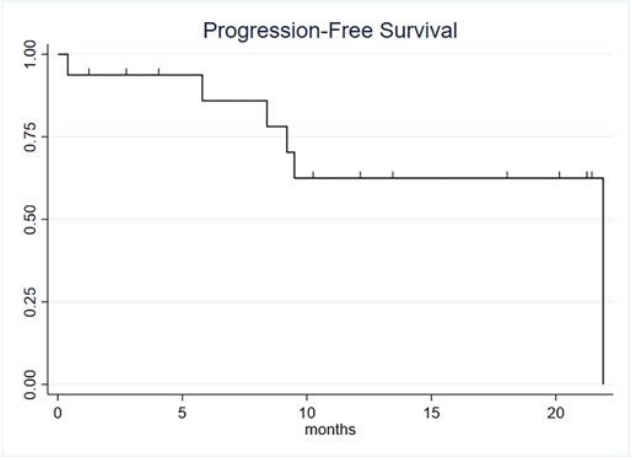
Introduction: Brexucabtagene autoleucel (brexu-cel) is approved for relapsed/refractory mantle cell lymphoma (MCL). Cyclophosphamide/fludarabine for lymphodepletion (LD) is standard LD prior to brexu-cel. Due to a recent fludarabine shortage, we have utilized alternatives to fludarabine-based LD prior to brexu-cel, primarily bendamustine. We have previously reported our institutional experience with bendamustine LD prior to another anti-CD19 CAR T cell product.

Methods: We retrospectively examined all patients with MCL who were treated with bendamustine LD followed by brexu-cel at our center from 2020 to 2022. Progression-free survival (PFS) was analyzed by Kaplan-Meier survival analysis. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT consensus criteria.

Results: Of 26 patients who received brexu-cel, 16 patients received bendamustine followed by brexu-cel. Median age was 65 years (range: 54–76). Median number of prior therapies was 3 (range: 3–8). All patients (100%) had received a BTK inhibitor prior to brexu-cel; 9/16 (56%) were BTKi refractory. 14/16 (88%) had received bridging therapy. 14/16 (88%) patients developed CRS; 11/14 (79%) had grade 1–2 CRS and 3 (19%) had grade 3 or greater CRS. 5 (31%) patients had ICANS; 2 (12.5%) had grade 1–2 ICANS, and 3 (19%) had grade 3 or greater ICANS. 10 (63%) patients received tocilizumab, 8 (50%) received dexamethasone, and 3 (19%) received anakinra for management of CRS and/or ICANS. Best objective response rate (ORR) was 81% with 11 (69%) patients achieving CR. Median follow-up was 13.4 months. Six month progression-free survival was 86% (95% CI: 54%–96%) and 12-month progression-free survival was 63% (95% CI: 32–82). Of 6 patients who had disease progression, two have died; median time to progression was 8.8 months.

Conclusions: Bendamustine LD prior to brexu-cel for MCL is feasible. Patients have comparable outcomes to that reported in real world brexu-cel data (Y Wang et al. J Clin Oncol 2023) and ZUMA-2 (M Wang et al. NEJM 2020).



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392 | REASONS FOR DISCORDANCE AMONG IMAGING-BASED RESPONSE CRITERIA IN LYMPHOMA PATIENTS RECEIVING CAR T-CELL THERAPY

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Introduction: Chimeric antigen receptor T cell therapy (CART) has emerged as an effective cell-based immunotherapy using patient-derived T cells. Modified CAR T cells are used for the treatment of relapsed or refractory (r/r) lymphoma with expression of a CD19 antigen specific receptor. CART prolongs survival for patients with r/r lymphoma compared to historical controls. In the currently ongoing phase III trials, treatment response is assessed using the Lugano criteria from 2014. In the recent years, new imaging criteria for lymphoma have been published. Discrepancies among these different response criteria for lymphoma under CART were recently shown. We evaluated reasons for discordance among different response criteria and their relation to overall survival (OS).

Methods: Consecutive large B-cell lymphoma (LBCL) and mantle-cell lymphoma (MCL) patients with baseline and follow-up imaging 30, and 90 days after CART infusion were included. For each patient, up to 6 Tagret lesions, non-target lesions, and the spleen were 3D-segmented. Overall response was determined based on Lugano criteria, Cheson criteria, response evaluation criteria in lymphoma (RECIL) and lymphoma response to immunomodulatory therapy criteria (LYRIC). Overall response rate (ORR) and rates of progressive disease (PD) were determined. For each criterion reasons for PD were analyzed in detail.

Results: 41 patients were included (median age: 64 years, 41% female). ORR was 68%, 68%, 63%, and 68% at FU2 by Lugano, Cheson, RECIL, and LYRIC, respectively. PD rates differed among criteria with 32% by Lugano, 27% by Cheson, 17% by RECIL, and 17% by LYRIC. Dominant reasons for PD according to Lugano were target lesion (TL) progression (84.6%), new appearing lesions (NL; 53.8%), non-TL progression (27.3%), and progressive metabolic disease (PMD; 15.4%). Deviations among the criteria were largely explained by PMD of preexisting lesions that are defined as PD only by Lugano and non-TL progression, which is not defined as PD by RECIL and in some cases classified as indeterminate response by LYRIC. Interestingly, grouping patients according to focality of progressive target lesions showed a significant trend for OS stratification ($p = 0.036$).

Conclusions: While the ORR was comparable between the different criteria (A), considerable discordance in reasons for definition of PD were observed (B, C). Response assessment by LYRIC exhibited superior association between PFS and OS. In addition, we could detect a significant trend for OS stratification by grouping according to focality of progressive target lesions. The response assessment method must therefore be considered when interpreting the impact of imaging endpoints on outcomes in clinical trials. Considering the heterogeneity, our results argue for standardization and harmonization across centers.

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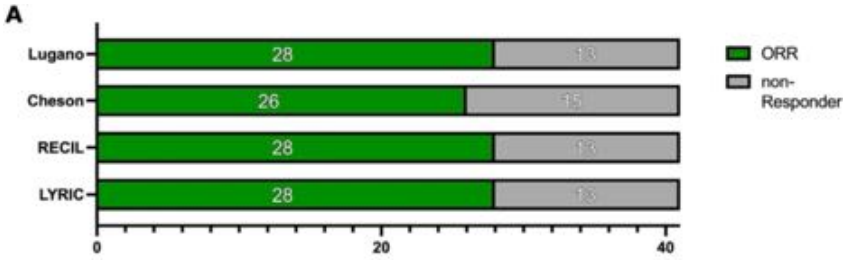
Keywords: Cellular therapies, Diagnostic and Prognostic Biomarkers, PET-CT



C

Criteria	TL PD	Focality of Progressive Lesions			NTL PD	NL PD				New Organ Lesion	PMD
		Uni	Oligo	Multi		Total	Nodal	Extra-nodal	Both		
Lugano	10	4	1	5	3	7	2	1	4	Bone (3) Muscle (3) Peritoneal (2) Fat tissue Kidney Liver Lung Pancreas Pleura	2
Cheson	10	4	1	5	3	7	2	1	4		0
RECIL	7	1	1	5	0	7	2	1	4		0
LYRIC	6	0	1	5	1	6	1	1	4		0

Conflicts of interests pertinent to the abstract.

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Research funding: Amgen, BMS/Celgene, Gilead, Janssen, Miltenyi Biotec, Morphosys, Novartis, Roche, Takeda

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393 | CNS RADIOTHERAPY AS BRIDGING PRIOR TO CAR T-CELL THERAPY FOR HEMATOLOGIC MALIGNANCIES

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Introduction: Up to 80% of patients who receive CAR T-cell therapy for central nervous system lymphoma (CNSL) require bridging therapy, yet optimal regimens remain undefined. Bridging radiotherapy (BRT) is an established strategy for extracranial lymphoma that provides beneficial cytoreduction. However, BRT for CNSL (CNS-BRT) is controversial due to concerns of potential enhanced neurotoxicity. We explored the safety and response profiles for CNS-BRT prior to CAR T therapy.

Methods: We identified CAR T patients with hematologic malignancy at MSKCC who received CNS-BRT, defined as treatment delivered between cell collection and infusion to targets in CNS parenchyma, leptomeninges, or epidural space. Safety was evaluated by cytokine release syndrome (CRS), immune effector associated neurotoxicity syndrome (ICANS), and immune effector cell encephalopathy (ICE) scores, as documented by primary physician. Response was evaluated within the RT field for patients with baseline measurable disease using the International Primary CNS Lymphoma Collaborative Group (IPCG), Response Assessment in Neuro-Oncology (RANO), and Response Evaluation Criteria in Lymphoma (RECIL) radiographic criteria for parenchymal, leptomeningeal, and epidural lesions, respectively.

Results: 11 patients received CNS-BRT with median follow up of 10.1 months (range: 1.1–25.9). At RT, median age was 51 (25–79), median KPS was 80 (50–90), and 9/11 patients had progressive CNS disease. 8/11 patients received prior methotrexate (high dose $n = 7$, intrathecal $n = 1$) with median 39-day interval to RT (0–179). Disease was localized to the brain parenchyma ($n = 6$), leptomeninges ($n = 2$), and epidural spine ($n = 3$). RT targets included whole brain ($n = 3$), involved site (partial) brain ($n = 4$), and involved site spine ($n = 4$), with median dose 24 Gy (20–30). Patient and CAR T cell characteristics are shown in Table 1. 4/10 patients experienced ICANS ($n = 1$ grade (G) 1, $n = 1$ G2, $n = 1$ G3, and $n = 1$ G4). 8/10 patients experienced CRS ($n = 2$ G1, $n = 5$ G2, and $n = 1$ G3). 6/11 patients required tocilizumab and/or steroids. Patients with G3/4 ICANS had decreased baseline ICE scores of 5 and 6, respectively. Median change in lesion size prior to CAR T infusion was -43.6% (-3.1% to -74.5%) among 7 evaluable patients. Best response included 6 partial responses (PR) and 4 complete responses (CR) at median 4.2 months (0.5–10.4). There were 3 CNS treatment failures, 1 in the leptomeninges and 2 in the paraspinal/epidural space.

Conclusion: Preliminary data suggest CNS-BRT can achieve cytoreduction as bridging therapy prior to CAR T therapy, and may not increase the risk of high-grade CRS and ICANS, though the sample size is limited. Patients with baseline neurologic impairment may be at increased risk of severe ICANS. These data support further study of RT, and exploration of involved site RT, as an effective bridging modality for CAR T-cell therapy in CNSL.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Radiation Therapy

Conflicts of interests pertinent to the abstract.

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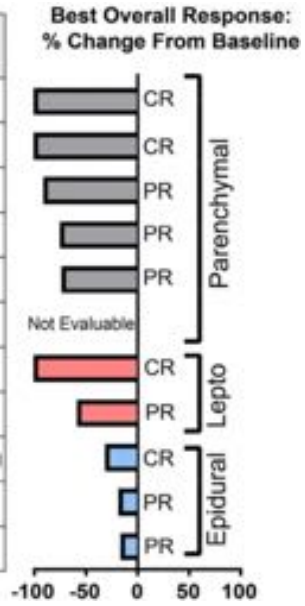
Age	Diagnosis	CNS Site	CAR T Product	RT Site	Dose (cGY)	Fraction	Baseline ICE	ICANS	CRS	Best Response	CNS Failure
66	DLBCL	Brain Parenchyma	Tisagenlecleucel	Partial Brain	3000	10	10	0	0	CR	No
41	PCNSL	Brain Parenchyma	Tisagenlecleucel	Whole Brain	2400	12	10	0	2	CR	No
48	DLBCL	Brain Parenchyma	Lisocabtagene Maraleucel	Whole Brain	2400	12	6	4	2	PR	No
30	DLBCL	Brain Parenchyma	Lisocabtagene Maraleucel	Partial Brain	3300	11	10	Not Available	Not Available	PR	No
71	DLBCL	Brain Parenchyma	Lisocabtagene Maraleucel	Partial Brain	3000	10	10	2	2	PR	No
25	Lymphoblastic Lymphoma	Brain Parenchyma	Tisagenlecleucel	Partial Brain	2400	12	Not Evaluable	0	1	Not Evaluable	No
36	Burkitt	Lepto	Tisagenlecleucel	Whole Brain	2000	5	Not Available	1	0	CR	No
74	DLBCL	Lepto	Tisagenlecleucel	Partial Spine	2000	5	5	3	3	PR	Lepto
70	Mantle Cell	Epidural	Lisocabtagene Maraleucel	Partial Spine	2000	5	10	0	2	CR	Paraspinal
51	DLBCL	Epidural	Axicabtagene Ciloleucel	Partial Spine	2000	5	10	0	1	PR	Epidural
79	Multiple Myeloma	Epidural	Idecabtagene Vicleucel	Partial Spine	3000	10	10	0	2	PR	No



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394 | DEVELOPING CAR-T-SPARING RADIOTHERAPY - EARLY DOSIMETRIC RESULTS

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Background/objective: Radiotherapy (RT) is an effective treatment for residual lymphoma following CD19 chimeric antigen receptor T-cell (CAR-T) therapy. However, there are concerns regarding the potential effect of RT on CAR-T, particularly early after infusion. We initiated a prospective protocol to explore the effect of different RT planning parameters and techniques on dose to the blood, and thus CAR-T cells, in order to develop a "CAR-T sparing RT" for early RT after CAR-T therapy.
Methods: We analysed 33 RT treatment plans for 11 lesions in 7 patients. Each lesion was planned 3 times; (1) a conventional plan using volumetric modulated arc therapy (VMAT) technique, (2) a plan with optimisation for blood vessels in the region as well as blood-rich organs and bone marrow, and (3) same as plan 2 but delivered with Flattening Filter-Free (FFF) beams to increase dose rate. Plans were compared with regards to planning target volume (PTV) coverage, dose homogeneity, organs at risk (OAR) doses including blood vessels, dose rate and beam-on time.
Results: Using CAR-T sparing techniques, the mean dose to major blood vessels was reduced by a mean of 12% compared to the conventional VMAT plan. The beam-on time was reduced by a mean of 60% due to the increase in dose rate. The blood-rich organ doses were not significantly affected. There was no detrimental effect on the overall quality of plans in terms of PTV coverage and dose homogeneity. The effect of different planning measures employed varied in different cases depending on the PTV volume, the anatomical location, and the proximity of blood vessels. Examples of clinical cases will be presented in the meeting.
Conclusion: Reduction of radiation dose to the blood is possible using a variety of technical adjustments as well as reduction of the beam-on time. Further work continues to understand the relative contribution of the individual parameters and optimise RT in the post-CAR-T setting.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Radiation Therapy

Conflicts of interests pertinent to the abstract.

N. G. Mikhaeel
Honoraria: Gilead, Educational meeting honoraria, Oct 2022

395 | MULTICENTER EXPERIENCE WITH RADIOTHERAPY FOR RELAPSE AFTER CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY IN NON-HODGKIN LYMPHOMA

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Introduction: Approximately half of patients relapse following chimeric antigen receptor T-cell therapies (CAR T), a challenging clinical scenario without established treatment paradigms. Salvage radiotherapy (SRT) may be an important strategy for this population with rapidly growing, often chemotherapy-refractory disease. Limited data are available regarding SRT utilization and outcomes.

Methods: We reviewed all patients with Non-Hodgkin Lymphoma treated with SRT for any intent post CAR T from 2016 to 2022 at four US cancer centers. Comprehensive SRT was defined as including all sites with PET avidity > liver max. Failure sites were classified as pre-existing (present pre SRT) versus new, and as in field, marginal (within 1 cm of), or distant with respect to SRT prescription dose region. Toxicities were graded by CTCAE v5.0. Event free and overall survival (EFS/OS) were measured from SRT start by Kaplan Meier. EFS was defined as freedom from progression, initiation of subsequent therapy, or death. Clinicodemographic associations with outcomes were assessed by Cox univariate proportional hazards.

Results: 121 patients with diffuse large B cell lymphoma (DLBCL; n = 110), mantle cell lymphoma (n = 8), and primary mediastinal B cell lymphoma (n = 3) were included. Patients received axicabtagene (n = 62), tisagenlecleucel (n = 27), lisocabtagene (n = 17), experimental CAR T (n = 12), and brexucabtagene (n = 3). For 49%, SRT was the first post-CAR T therapy. SRT indications included palliation (n = 72), consolidation (n = 5), bridging to allogeneic transplant (allo; n = 5) or 2nd CAR T (n = 3), and other (n = 33). At SRT, 29 (24%) had localized disease of which 28 were treated comprehensively; overall 37% of SRT was comprehensive. Median dose was 30 Gy (4–50.4). 27% received concurrent systemic therapy.

SRT was well tolerated: 8% (n = 10) had ≥ grade 2 (G2) acute adverse events (G3 = 1, no G4/5). Objective response rate was 74% (41% complete) within the SRT field and 38% (22% complete), overall. With a median follow up of 6 mo, 78 patients (64%) progressed. First failure sites were 64% pre-existing/mixed and 38% in field/marginal. For DLBCL patients, median EFS was 4.2 mo in limited stage and 1.2 mo in advanced ($p < 0.001$). Median OS was 59.6 mo and 3.4 mo in localized and advanced DLBCL relapse ($p < 0.001$). Median OS for RT as bridging to allo/CAR T, consolidation, and palliation was unreached, 6.7 mo, and 3.0 mo ($p < 0.001$). Localized relapse and receipt of comprehensive SRT were associated with improved EFS ($p < 0.001$) while primary refractory disease to CAR T ($p = 0.02$), elevated LDH pre SRT ($p = 0.02$), and SRT for palliation ($p = 0.03$) or for ≥*2nd*salvage post CAR T (0.04) were associated with shorter EFS.

Conclusions: SRT has diverse utility after CAR T, particularly in patients with limited relapse or when feasible to irradiate comprehensively. SRT bridging to additional definitive options like allo/second CAR T warrants further study.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Radiation Therapy

Conflicts of interests pertinent to the abstract.

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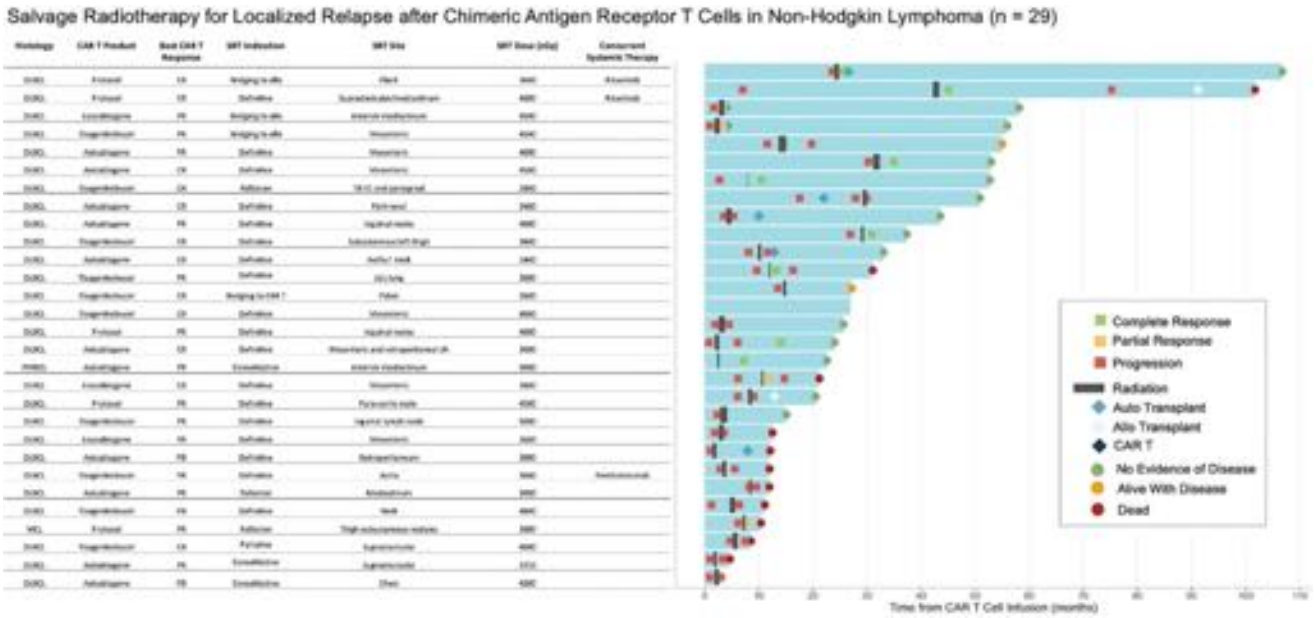

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396 | PREDICTING ICANS BY MEANS OF PLASMA CAR-T CELL DERIVED EXTRACELLULAR VESICLES IN PATIENTS UNDERGOING INFUSION OF ANTI-CD19 CAR-T CELLS

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Introduction: Immune effector cell-associated neurotoxicity syndrome (ICANS) is a life-threatening adverse effect of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy that usually occurs within 5–7 days after cell infusion. Although several clinical and biochemical parameters have been associated with ICANS, it is still a matter of debate how to predict its onset at the patient level. We here tested the hypothesis that CAR-T cell derived extracellular vesicles (EV) carrying the engineered CAR protein and produced early after CAR-T cell activation can be used as predictive biomarker of ICANS. Purposely, we measured plasma CAR+ EV in lymphoma patients underwent anti-CD19 CAR-T cell therapy.
Methods: Seventy-one patients with aggressive r/r B-cell lymphomas were admitted to the advanced cell therapy unit of IRCCS AOU of Bologna (NCT04892433) for anti-CD19 CAR-T cell infusion. Included patients received tisa-cel ($n = 27$), axi-cel ($n = 34$), or brexu-cel ($n = 10$) after a median number of 3 prior lines of treatment (2–11); median age was 62 years (19–76) and no patients had CNS disease at the time of CAR-T cell infusion. Twenty out of 71 patients (28%) had ICANS of any grade: 5 patients (7%) ICANS grade 1, 7 patients (10%) ICANS grade 2 and 8 patients (11%) ICANS grade ≥3 (3 patients ICANS grade 3, 3 patients ICANS grade 4 and 2 patients ICANS grade 5 with diffuse cerebral edema). ICANS was classified according to Lee et al. The median time from CAR-T cell infusion to ICANS onset was 5 days (3–12). Available plasma samples at day +1 after CAR-T cell infusion were analyzed for CAR+ EV by FACS analysis. Data analysis was performed with Prism software v9.1.3 (GraphPad).
Results: CAR+ EV were already detectable +1 day after CAR-T cell infusion in 58 patients. The median onset of ICANS was at day +5 (3–12). Patients with ICANS of any grade showed higher CAR+ EV level compared to no-ICANS ones ($p < 0.0001$). CAR+ EV anticipated the median ICANS onset of 2 to 11 days. CAR+ EV ROC analysis showed that a concentration >187.5 CAR+ EV/µl at day +1 after infusion predicts ICANS onset with sensitivity of 100% and specificity of 83.33% ($p < 0.0001$).
Conclusions: These findings lead us to hypothesize that the plasma level of CAR+ EV mirrors target engagement by CAR-T cells, and their massive release is related to ICANS. Thus, CAR+ EV level could be considered a putative early predictor of ICANS onset; further analyses in larger cohorts are warranted to confirm this finding.

Keywords: Cellular therapies, Diagnostic and Prognostic Biomarkers

Conflicts of interests pertinent to the abstract.

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397 | TRANSFUSION NEEDS AFTER CD19 CAR T-CELLS FOR LARGE B-CELL LYMPHOMA: PREDICTIVE FACTORS AND IMPACT ON OUTCOME. A DESCAR-T STUDY.

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Introduction: Patients undergoing CAR T-cell therapy may experience severe cytopenias due to lymphodepleting chemotherapy and/or CAR T-cells. Transfusion needs represent a surrogate marker of severe anemia and thrombocytopenia. Transfusion needs may impact patients' quality of life and CAR T-cells efficacy through transfusion-related immunomodulation. Here, we aimed to describe transfusion needs of patients receiving commercial CD19 CAR T-cells for relapse or refractory large B-cell lymphoma (LBCL), identify predictive factors associated with transfusions and search for correlations with CAR T-cells efficacy.

Methods: Clinical data were collected form the DESCAR-T registry, the French national real-life registry for all patients treated with commercial CAR T-cells. Transfusion data were collected from the French national blood bank. We included all LBCL patients with at least 6-months follow-up from CAR T-cell infusion. Patients were censored for transfusions at relapse, new treatment onset, or death.

Results: From August 2018 to September 2022, 671 patients in the DESCAR-T registry met the eligibility criteria. Overall, 382 patients (56.9%) received at least one transfusion after CAR T-cell infusion: 53.5% at the early phase (i.e. within the first month), and 37.8% at the late phase (i.e. beyond one month). Only 6% of the patients required transfusions beyond 3 months. The mean number of red blood cells (RBC) units and platelets transfusion per patient after CAR T-cell therapy were 3.5 (range, 0–90) and 5.1 (range, 0–127), respectively. Factors associated with transfusion needs after CAR T-cells therapy are presented in Table 1. Age, international prognostic index, primary refractory status, prior ASCT, bulk disease, and severe cytokine release syndrome (CRS) were associated with early but not late RBC transfusions. Early and late platelets transfusion shared the same risk factors except for severe CRS. No association was found between transfusions and response rate after CAR T-cell therapy. However, early transfusions (RBC and platelets) were associated with a shorter progression-free survival (median PFS = 3.2 vs. 6.0 months, $p = 0.0168$) and overall survival (median OS = 9.3 vs. 23.6 months, $p < .0001$). Late platelets transfusions were associated with decreased PFS (median = 5.6 vs. 12.0 months, $p = 0.0072$) and OS (median = 13.8 vs. NR, $p < .0001$) whereas late RBC transfusions did not impact PFS nor OS.

Conclusion: In our study, 56.9% of patients received transfusions after CAR T-cell therapy. We identified risk factors associated with early and late transfusion needs. Early transfusions (RBC and platelets) and late platelets transfusion were associated with worse survival. Our data shed light on the mechanisms of early and late anemia and thrombocytopenia, and on the potential impact of transfusions on CAR T-cells efficacy.

Encore Abstract - previously submitted to EHA 2023

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies

Conflicts of interests pertinent to the abstract.

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Honoraria: Kite, a Gilead Company, Bristol Myers Squibb, Novartis, Pfizer, Incyte, ADC Therapeutics

Research funding: Amgen, BMS

Other remuneration: Kite, a Gilead Company, Bristol Myers Squibb, Novartis, Pfizer

	Transfusion in the early phase (<1 month)		Transfusion in the late phase (>1 month)	
	RBC	Platelets	RBC	Platelets
Age > 65 years at infusion	X			
PS ≥ 2 at infusion	X	X	X	X
aaIPI ≥ 2 at diagnostic	X	X		X
Refractory to first treatment	X			
Prior ASCT	X			
Prior chemotherapy within 6 months (excluding bridge)	X	X		X
Prior chemotherapy within 6 months (including bridge)	X	X	X	X
Chemotherapy as bridging therapy	X	X	X	X
Bulk disease (>5 cm) at infusion	X			
CAR-HEMATOTOX score ≥ 2 at infusion	X	X	X	X
RBC and/or platelets transfusions < 6 months before CAR T-cell infusion	X	X	X	X
Axi-cel (vs Tisa-cel)	X	X	X	X
CRS grade ≥ 3	X	X		
ICANS ≥ 3	X	X	X	X
Tocilizumab use	X	X	X	X
Corticosteroids use	X	X	X	X
EPO use after CAR T-cell infusion	X	X	X	X
G-CSF use after CAR T-cell infusion	X	X	X	X

Table 1: factors associated with transfusion after CAR T-cell therapy. The abbreviation PS denotes performance status, aaIPI age-adjusted international prognostic index, ASCT autologous stem cell transplantation, RBC red blood cells, CRS cytokine release syndrome, ICANS immune effector cell-associated neurotoxicity syndrome, EPO erythropoietin and G-CSF granulocyte-colony stimulating factor. Factors tested but not predictive were Hematopoietic Cell Transplant- Comorbidity Index, LDH, number of previous therapies, bone marrow involvement, other types of bridging therapy, best overall response rate and complete response at any time.

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398 | NEUROTOXICITY IN PATIENTS WITH CNS LYMPHOMAS TREATED WITH CAR-T CELL THERAPY. A LOC NETWORK STUDY

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Introduction: CAR-T cell therapy represents one of the major progress of the last years in aggressive B-cell lymphomas. Its use in central nervous system (CNS) lymphomas has been limited due to the fear of neurotoxicity but several recent studies have showed promising efficacy in this setting. The aim of this study was to focus on neurotoxicity in CNS lymphoma patients treated with CAR-T cells.
Methods: Patients with isolated CNS relapse of DLBCL treated with commercial CAR-T cells at Pitié-Salpêtrière hospital were retrospectively selected. We considered only neurological deterioration for which other causes than CAR-T cell toxicity had been reasonably ruled out.
Results: Thirty patients (median age: 65, 17 women, 19 primary, 11 secondary CNS lymphomas, median of 3 previous lines) received CAR-T cells (Tisa-cel: $N = 23$, axi-cel, $N = 7$) between May 2020 and December 2022. At the time of CAR-T, 15 (50%) had stable or progressive disease, median Karnofsky Performance Status (KPS) was 70, median Montreal Cognitive Assessment (MoCA) score was 22 and median immune effector cell-associated encephalopathy (ICE) score was 10. Twelve (40%) patients didn't experience any neurotoxicity after CAR-T, whereas 9 (30%), 3 (10%), 2 (7%), 4 (13%) patients experienced grade 1, 2, 3 or 4 toxicity according to ASTCT classification. The signs of neurotoxicity began at a median of 5 days after CAR-T. The most common symptoms were cognitive disorders ($N = 18$), motor deficit ($N = 4$), balance disorders ($N = 8$), consciousness disorders ($N = 5$), seizures ($N = 3$) and movement disorders ($N = 3$). Among cognitive symptoms, there was predominantly a worsening of pre-existing symptoms regarding memory impairment (12/15 patients) or dysexecutive syndrome (11/13), while dysgraphia or dyscalculia were

most frequently new symptoms (in 14/15 and 7/11 patients). Brain MRI showed pseudo-progression in 4 cases. On lumbar puncture, median IL-6 level and median cellularity were higher in patients with grade 2 to 4 neurotoxicity compared to other patients (243 vs. 41 pg/ml, 15 vs. 3 cells/mm^3). We found no association between risk of neurotoxicity and age, gender, pre-CART KPS, MoCA or ICE score, primary vs. secondary CNS lymphoma or type of CAR-T. Twelve patients (40%) received steroids, for a median of 10 days, leading to an improvement in a median of 5 days; one received anakinra. Median duration with neurological impairment was 13 days, but was >3 months in 3 patients, including one who finally died from neurotoxicity.

Conclusions: The majority of CNS lymphoma patients didn't experience severe neurotoxicity following CAR-T cells, so that this treatment shouldn't be contraindicated in this population. However, the percentage of severe and prolonged neurotoxicity is probably higher than in systemic lymphomas and a close neurological follow-up is warranted in these complex situations. Further studies are needed to better predict severe neurotoxicity.

Keyword: Cellular therapies

Conflicts of interests pertinent to the abstract.

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399 | FACTORS ASSOCIATED WITH INCREASED RISK OF MAJOR CARDIOVASCULAR EVENTS FOR PATIENTS UNDERGOING CAR T THERAPY

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Introduction: Chimeric antigen receptor (CAR)-T cell therapy use has increased exponentially following its approval for multiple indications in non-Hodgkin lymphomas, multiple myeloma, and acute lymphoblastic leukemia. While cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and cytopenias are well-described and frequently encountered side effects, a significant proportion of patients experience major adverse cardiovascular events (MACE). This study investigates factors associated with increased risk for MACE.

Methods: We performed a retrospective analysis of a consecutive cohort of patients treated with CAR-T therapy at our center between 2018 and 2022. Clinical, laboratory, and imaging parameters were collected. MACE were defined as acute myocardial infarction (AMI), stroke or transient ischemic attack, cardiovascular death, unstable angina, life-threatening arrhythmias, and heart failures. Data was analyzed using SPSS v23. Categorical variables were compared using univariate chi-square test.

Results: A total of 126 patients were included. Of these, ten patients (12.5%) had a MACE event. Baseline characteristics including age, sex, body mass index, coronary artery calcium, lipid profile, baseline medications, preceding anthracycline or carfilzomib exposure, cancer type, CRS, ICANS, and tocilizumab use are summarized in Table. The median follow-up period was 8.9 months. Patients who experienced MACE versus no MACE had a significantly higher age at CAR-T cell therapy (74.5 years vs. 64.9 years, $p = .009$), higher peak C-reactive protein (CRP) with a median of 116.7 mg/dL versus 73.85 mg/dL, $p = 0.006$ respectively. CRS and ICANS grades were associated with MACE events ($p = 0.008$ and 0.005, respectively). No echocardiographic differences were found. No progression free or overall survival differences were observed in the groups ($p = 0.67$ and 0.16, respectively).

Conclusions: Our results indicate that patients undergoing CAR-T cell therapy who are older and who experience an increased degree of inflammatory response, reflected by peak CRP level, were associated with MACE. These data suggest that inflammatory markers may be clinically relevant predictors of subsequent MACE in CAR-T therapy-treated patients. Prospective inflammation monitoring combined with trials incorporating anti-inflammatory strategies may mitigate the risk of MACE in this patient population.

Keywords: Cellular therapies, Diagnostic and Prognostic Biomarkers, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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Honoraria: BluePrint Medicines, GERON, OncLive, MD Education, Sierra Oncology, Stemline Therapeutics, Blueprint Medicines, Morphosys, Taiho Oncology and Novartis
Educational grants: Blueprint Medicines and Morphosys.

Table 1. Analysis of clinical, laboratory, and imaging data in patients treated with CART therapy.

MACE (composite of myocardial infarct, heart failure event, transient ischemic attack, cerebrovascular accident, or new arrhythmia)		No MACE N = 116	MACE N = 10	p
Age (median [IQR]) (years)		64.9 (16.0)	74.5 (12.5)	0.009
Sex (%)	F	47 (41)	4 (40)	0.761
	M	69 (59)	6 (60)	
BMI (median [IQR]) (kg/m2)		27.7 (6.6)	27.2 (10.5)	0.846
Diagnosis Group (%)	LBCL	71 (61)	6 (60)	0.729
	MCL	10 (9)	0	
	MM	34 (29)	4 (40)	
	ALL	1 (1)	0	
Disease status prior to CAR T infusion	Primary Refractory	27 (23)	2 (20)	0.922
	Refractory second or higher line of therapy	46 (40)	5 (50)	
	Relapse post-SCT	42 (36)	3 (30)	
CAR T product (%)	Idecabtagene vicleucel	30 (26)	4 (40)	0.522
	Brexucabtagene autoleucel	11 (10)	0	
	Axi-cel	67 (58)	4 (40)	
	Liso-cel	4 (4)	0	
	Tisagenlecleucel	0	1 (10)	
	Others	4 (4)	1 (10)	
Time from diagnosis to CAR T (median [IQR]) (yrs)		2.2 (4.0)	1.7 (2.3)	0.821
Prior anthracycline (AC) exposure (%)		82 (71)	5 (50)	0.317
Time from AC Exposure to CAR T (mean (SD)) (days)		846.8 (1477.3)	283.4 (156.9)	0.397
Prior Carfilzomib exposure (%)		18 (16)	1 (10)	0.994
Beta blocker (%)		35 (30)	5 (50)	0.498
ACEi or ARB (%)		35 (30)	5 (50)	0.348
Statin (%)		47 (41)	6 (60)	0.388
Tocilizumab (%)		81 (70)	9 (90)	0.322
Charleston Comorbidity Index Score (%)	0-6	106 (91)	8 (80)	0.515
	7-12	10 (9)	2 (20)	
CRS grade (%)	0-2	114 (98)	9 (90)	0.008
	3-5	2 (2)	1 (10)	
ICANS grade (%)	0-2	100 (86)	8 (80)	0.392
	3-5	16 (14)	2 (20)	
Creatinine on day prior to infusion (median [IQR]), mg/dL		0.80 (0.36)	0.80 (0.40)	0.814
CRP on day prior or day of infusion (median [IQR]), mg/dL		12.75 (22.10)	22.20 (76.50)	0.057
CRP peak (median [IQR]), mg/dL		73.85 (73.25)	116.70 (78.40)	0.006
HgbA1c (median [IQR]), mg/dL		6.60 (1.85)	6.0 (0.50)	0.316
Total cholesterol within 365d of infusion (mean [SD]), mg/dL		176.36 (46.97)	144.50 (43.13)	0.350
LDL within 365d of infusion (mean [SD]), mg/dL		98.22 (35.33)	68.50 (44.55)	0.250
HDL within 365d of infusion (mean [SD]), mg/dL		45.29 (17.31)	56.50 (6.36)	0.369

400 | **HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA TREATED WITH LISO-CEL IN TRANSCEND CLL 004**

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Introduction: Patients (pt) with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), especially those with progression on Bruton tyrosine kinase inhibitors (BTKi) and venetoclax failure, have limited treatment options and poor pt-reported outcomes (PRO)/health-related quality of life (HRQOL). The CD19-directed chimeric antigen receptor T cell therapy lisocabtagene maraleucel (liso-cel) is being evaluated in R/R CLL/SLL in the phase 1/2 TRANSCEND CLL 004 study (NCT03331198). Here, we report PRO/ HRQOL for pts in the phase 2 part of TRANSCEND CLL 004.

Methods: Pts completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-30 items (C30), EORTC QLQ-17 items for CLL (CLL17), and EQ-5D-5L at baseline (≤7 days before lymphodepletion), pre-infusion on the day of liso-cel infusion (Day 1), and 30, 60, 90, 180, 270, 365, 455, 545, and 730 days after infusion. The primary domains of interest were EORTC QLQ-C30 global health status (GHS)/quality of life (QOL), physical functioning, role functioning, cognitive functioning, and fatigue and EORTC QLQ-CLL17 symptom burden and physical condition/fatigue. The PRO-evaluable population was defined as pts with baseline and ≥1 postbaseline PRO assessment, among all leukapheresed pts in the phase 2 portion. Observed scores and mean changes from baseline were calculated across postbaseline visits. Intra-pt meaningful changes from baseline were calculated using prespecified change thresholds.

Results: Of 112 pts in the PRO-evaluable population and 70 in the BTKi progressed/venetoclax failure subset, baseline completion rates were 61% in both populations, with rates of 40%–70% across most visits for all measures. The main reasons for not completing PROs were COVID-19–related restrictions. Outcomes were similar in both populations. Mean baseline scores were worse than those of the United States general population for many domains. After initial deterioration in HRQOL after liso-cel infusion, the observed mean changes from baseline showed improvement starting at Day 60 for all primary domains (representative domains shown in Figure) except for cognitive functioning score, which was comparable with the general population at baseline and maintained over time. The proportion of pts with meaningful improvement increased over time for multiple domains, including fatigue-related domains and GHS/QOL on the EORTC QLQ-C30 and EORTC QLQ-CLL17. From Day 90 through Day 730, the proportions of pts with meaningful improvement or no change on the primary domains exceeded the proportion with meaningful deterioration.

Conclusions: Liso-cel either improved or maintained HRQOL from baseline in pts with heavily pretreated R/R CLL/SLL. Meaningful improvements were achieved in the key CLL symptom of fatigue and overall QOL.

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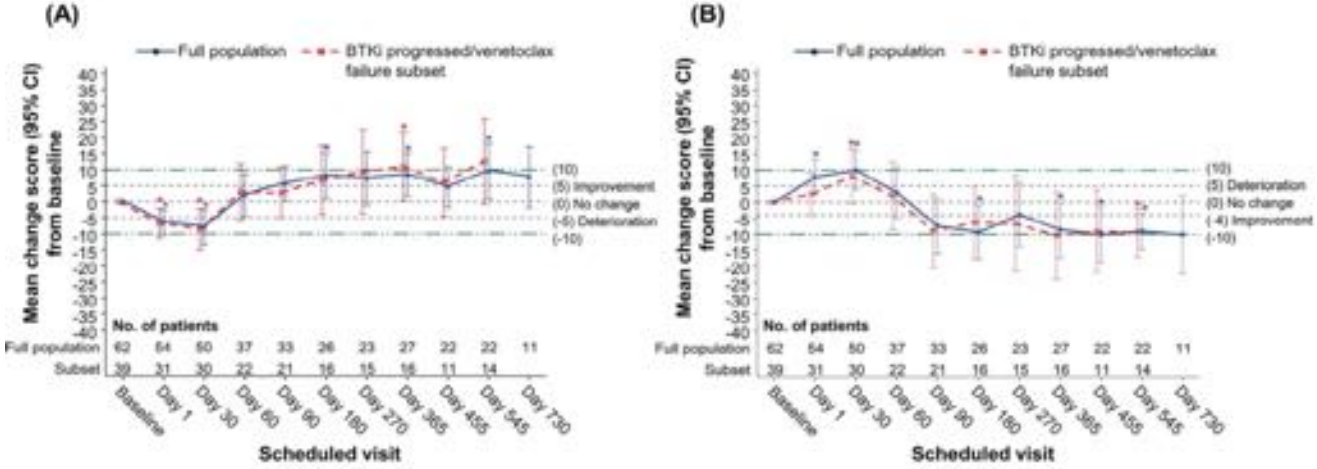
Keyword: Cellular therapies

Figure. Observed mean changes from baseline in select primary domains of (A) EORTC QLQ-C30 GHS/QOL and (B) fatigue



Higher score for GHS/QOL (A) indicates better overall HRQOL, while higher score for symptom domain (fatigue [B]) indicates worse symptoms. Dashed lines represent minimally important difference thresholds.
*Observed change from baseline was statistically significant based on nominal $P < 0.05$.
CI, confidence interval.

Conflicts of interests pertinent to the abstract.

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Other remuneration: Patents and Royalties: Novartis, Humanigen, MustangBio, Mettaforge, Sendero; DSMB: Humanigen

401 | 'DON'T KEEP ME WAITING': ESTIMATING THE IMPACT ON LIFETIME SURVIVAL AND QALYS OF REDUCED VEIN-TO-VEIN TIME FOR LBCL PATIENTS TREATED WITH CAR T IN THE 3L+ SETTING

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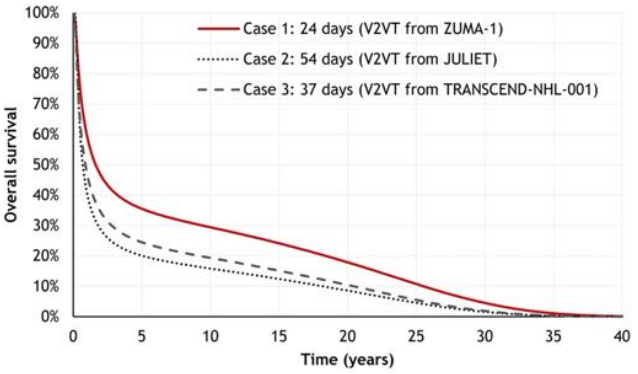
Introduction: Chimeric antigen receptor (CAR) T-cell therapies have revolutionised the treatment of haematological cancers. However, production requires a complex multistep process from leukapheresis, manufacturing, transport and storage before final infusion. This time is known as the vein-to-vein time (V2VT) during which the patient's condition may deteriorate, thus highlighting the potential importance of V2VT on patients outcome. This modelling study was designed to compare potential outcomes of a 'long' versus 'short' V2VT for relapsed/refractory large B-cell lymphoma (r/r LBCL) patients treated with CAR T-cell therapy in the 3L+ setting.

Methods: A hypothetical cohort of patients enter a decision tree model at leukapheresis, they are then assigned a probability of successful infusion based on V2VT. Patients then enter a partition survival model which estimates life-years (LYs) and quality-adjusted life years (QALYs) over a lifetime horizon, which were based on real world axi-cel OS data. Other CAR T efficacy data were not included to provide conservative estimates and to avoid confounding. Model inputs were sourced from the published literature and the ZUMA-1 trial. An epidemiological model was used to extrapolate results to CAR T-eligible US patients. Finally, scenario analyses were performed to assess the robustness of results to key assumptions.

Results: Reducing V2VT from 54 days (tisa-cel median V2VT; JULIET) to 24 days (axi-cel median V2VT; ZUMA-1) led to a 3-year gain in life expectancy (4.2 vs. 7.7 LYs), and an additional 2 QALYs (2.9 vs. 5.3) per patient. This translates to 9,328 additional LYs and 6,385 additional QALYs every year, if all ≈ 2,710 eligible patients in the US received a 'short' V2VT. Using a smaller difference in V2VT (24 vs. 37 days [liso-cel median V2VT; TRANSCEND-NHL-001]) produced 2.6 and 1.8 additional LYs and QALYs, respectively, equating to population level gains of 7,040 LYs and 4,819 QALYs (Figure 1). Outcomes were consistently positive across all sensitivity analyses.

Conclusions: Our study is the first to quantify potential lifetime survival and QALY outcomes for r/r LBCL patients treated with CAR T cells in the 3L+ setting associated with reducing V2VT utilising currently available evidence. V2VT is an important predictor of outcomes and aiming for short manufacturing, product release, shipment and infusion are key to further improve CAR T cell outcomes. We find that moderate difference in V2VT may lead to pronounced effects on life expectancy.



The research was funded by: Kite, A Gilead Company

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Genomics, Epigenomics, and Other -Omics

Conflicts of interests pertinent to the abstract.

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402 | REMOTE MONITORING OF CAR T-CELL TREATED PATIENTS BY A SPECIALIZED NURSE TO DETECT AND MANAGE LATE COMPLICATIONS: REPORT OF THE CARAMA PROGRAM

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Introduction: CAR T-cells have been approved for the treatment of relapse/refractory (R/R) large B-cell lymphoma (LBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), acute lymphoblastic leukemia (ALL), and multiple myeloma (MM). Although acute toxicities of CAR T-cells are well managed during hospitalization, delayed complications (including cytopenias, infections and relapses) are more challenging to manage owing to the distance. To address this issue, we initiated a program consisting in a remote monitoring of CAR T-cell treated patients by a specialized nurse (CARAMA) to detect and manage delayed complications.
Methods: Patients treated with CAR T-cells at the University Hospital of Rennes (France) were prospectively followed remotely (by phone) by a CARAMA nurse after hospital discharge. Adverse events and interventions were prospectively collected by the CARAMA nurse who called patients after hospital discharge daily until day 21, twice a week until day 28, once a week until month 2, every other week until month 3, once a month until month 6, and once every 3 months until month 12 or relapse/progression.
Results: Between September 2019 and December 2022, 151 patients have been followed in the CARAMA program (113 LBCL, 11 MCL, 11 FL, 9 ALL, 7 MM). Median age was 64 years (range, 16–80). A total of 2,573 phone calls were given to the patients by the CARAMA nurse which represents a median of 15 calls/patient (range, 0–41).

The CARAMA nurse:

- identified complications requiring intervention including cytopenias (111 patients, 73.5%) requiring transfusions (44 patients, 29.1%) and/or growth factors (110 patients, 72.8%), and infections requiring antibiotics (37 patients, 24.5%);
- was able to detect disease relapse before medical consult in 24 out of 65 patients (36.9%);
- referred 75 patients (49.7%) in consult to their general practitioner ($N = 71$), their hematologist ($N = 24$), and/or other physicians ($N = 29$);
- requested hospitalization for 41 patients (27.2%) due to infection (48.8%), cytopenias (14.6%), disease relapse (17.1%), and/or other causes (19.5%);
- organized supportive measures for 63 patients (41.7%), including physical therapy ($N = 38$), psychological support ($N = 24$), social worker ($N = 14$), hypnosis ($N = 11$), sexology consult ($N = 7$), or dietician ($N = 4$).

A survey evaluating patients' satisfaction (0 = useless, 10 = indispensable) at 3 months of the CARAMA program ($N = 43$) showed a median score of 10/10 (range, 7–10).
Conclusions: Remote monitoring of patients treated with CAR T-cells by a specialized nurse allows early detection and management of delayed complications (adverse events and/or relapse). It also saves medical time and resources. Finally, this close follow-up is reassuring for the patients and contributes to their well-being. Ours results support the development of CARAMA nurses in CAR T-cell centers.

Keyword: Aggressive B-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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PRECLINICAL NEW DRUGS

403 | DRUG-RESISTANCE MUTATIONS IN BTK OCCUR IN DISTINCT ENZYMATIC CLASSES AND ARE OVERCOME BY BTK DEGRADATION

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Introduction: Increasing use of covalent Bruton tyrosine kinase (BTK) inhibitors ibrutinib, acalabrutinib, and zanubrutinib as well as noncovalent inhibitors nemtabrutinib and pirtobrutinib, have elucidated a series of acquired BTK mutations, some of which can confer cross-resistance to other BTK inhibitors in patients with B-cell

malignancies. Our biochemical and biological assays revealed that in addition to impeding drug binding, some BTK drug resistance mutations have diminished or absent enzymatic function and reduced autophosphorylation of tyrosine 223 (Y223), a marker of BTK activation. Our data suggest that recurrent kinase domain BTK mutations occur in distinct enzymatic groups: certain BTK mutations are kinase proficient (T474I/F and C481S mutations), while others reduce enzymatic activity (M437R mutation), and some mutations render BTK kinase dead (V416L, C481Y/R/F and L528W, see Figure). Despite their lack of BTK activation, upon B-cell receptor (BCR) stimulation kinase dead BTK mutants showed enhanced activation of downstream BCR signals and hyperactivated calcium release.

Methods: To identify the signaling mechanisms of kinase dead BTK mutants, we generated CRISPR-CAS9 knockin mutant cells and utilize several orthogonal proteomic approaches in BTK-dependent human lymphoma B cells expressing WT or mutant (C481S, V416L, T474I and L528W) BTK. We performed global phosphoproteomics, kinobead assays, BTK immunoprecipitation mass spectrometry studies, and 2D differential gel electrophoresis to unbiasedly elucidate a novel scaffolding function of BTK.

Results: Collectively our data revealed enhanced physical interactions of kinase dead BTK with protein kinases HCK and ILK as well as activation of multiple signaling moieties in malignant B cells. Given the newly discovered scaffolding function of BTK, we decided to test strategies to eliminate, rather than inhibit mutant BTK proteins. While other PROTAC degraders of BTK have been demonstrated to target wild-type or C481S-mutant forms of BTK in preclinical studies, we now demonstrate the first clinical-stage (clinicaltrials.gov #NCT04830137) degrader of BTK, NX-2127, which binds to each drug resistant BTK mutant proteoform (as demonstrated by biophysical and structural data) and induces their proteasomal degradation causing inhibition of BCR signaling. Treatment of chronic lymphocytic leukemia (CLL) patients with NX-2127 achieves >80% degradation of BTK and we demonstrate proof-of-concept therapeutic benefit in patients with CLL (Figure).

Conclusions: These data reveal a distinct oncogenic scaffolding function of kinase dead BTK which confers resistance across FDA-approved BTK inhibitors. Importantly, regardless of enzymatic group, each recurrent BTK mutant is susceptible to BTK degradation preclinically and in patients currently being treated in a Phase 1b dose expansion in CLL with NX-2127.

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Keyword: Chronic Lymphocytic Leukemia (CLL)

Conflicts of interests pertinent to the abstract.

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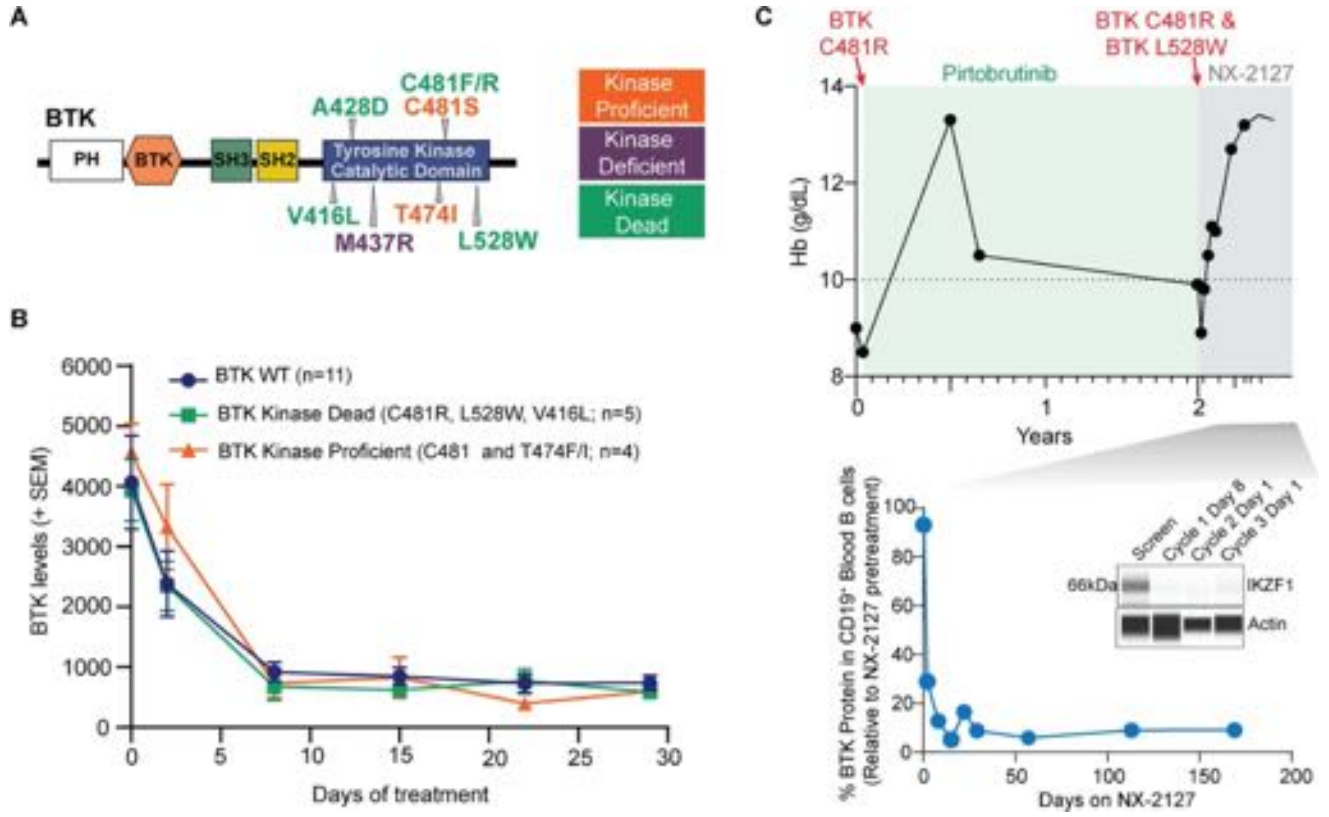

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Research funding: H3B Biomedicine, Nurix Therapeutics, Minovia Therapeutics, and LOXO Oncology

404 | BTM 3566, A NOVEL ACTIVATOR OF THE MITOCHONDRIAL STRESS RESPONSE INDUCES ROBUST THERAPEUTIC RESPONSES IN DIFFUSE LARGE B-CELL LYMPHOMA IN VITRO AND IN VIVO

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Introduction: Relapsed/refractory diffuse large B-cell lymphomas (r/r-DLBCL) are a therapeutic challenge, especially in patients not suitable for high dose chemotherapy, stem cell transplantation or patients who fail CAR-T-cell therapy. r/rDLBCLs exhibit considerable heterogeneity. BTM-3566, a novel compound demonstrating efficacy against diverse B-cell malignancies, with the most pronounced impact observed in DLBCL. BTM-3566 initiates the mitochondrial integrated stress response (ISR) via a unique mechanism governed by the mitochondrial protein FAM210B.

Methods: Human cell line xenograft models were established using SU-DHL-10 cells (ATCC Cat# CRL-2963,RRID:CVCL_1889).For the patient derived xenograft models, all tumors were sourced from Crown Bio. Models were established in female mice with an average body weight of 25 grams.

Results: BTM-3566 induces rapid apoptosis and in DLBCL cell lines with an IC_{50} of 400 nM. Responsive DLBCL cell lines include ABC, GCB, and double-hit and triple-hit lymphoma lines. In xenograft models using the DLBCL line SU-DHL-10, BTM-3566 once-daily oral treatment resulted in complete regression in all tumor-bearing animals. Most importantly, no subsequent tumor growth occurred for 2 weeks after cessation of therapy, indicating that treatment with BTM-3566 resulted in a durable complete remission in this model of double-hit DLBCL. Expansion studies into human DLBCL PDX models harboring a range of high-risk genomic alterations, including MYD88 mutations and MYC and BCL2 rearrangements, demonstrated response in 100% of the lines with complete tumor regression in 6 of 8 PDX models tested (Table 1).

Pharmacokinetic studies in mice showed suitability for once daily dosing, with >50% of oral bioavailability and close to 6 hours of serum half-life. 14-day dosing in mice and dogs demonstrated excellent tolerability at therapeutic doses. BTM-3566 showed stability in human hepatocytes (IC < 5 ml/min*kg) as well and a favorable in vitro safety profile.

TABLE I BTM-3566 is efficacious in DLBCL PDX models

PDX-model	% TGI	BTM-3566 response: Complete regression	Partial regression	Tumor stasis
(1) ABC, MYD88 L265P, BCL6 translocation	97	1	1	1
(2) GCB, MYC Translocation	100	3	0	0
(3) ABC/GCB	89	0	1	2
(4) ABC/GCB	100	3	0	0
(5) GCB	100	3	0	0
(6) ABC/GCB	100	3	0	0
(7) ABC/GCB	100	3	0	0
(8) ABC, MYD88 L265P	100	3	0	0

Conclusions: BTM-3566 is an oral small molecule based on a pyrazolothiazol-backbone, developed for treatment of diffuse large B-cell lymphoma (DLBCL). Here we describe a novel, highly potent activator of the mitochondrial ISR, which is well tolerated in mice and dogs, has favorable pharmacokinetics and induces robust DLBCL regression *in-vivo*. An IND application in mature B-cells malignancies has been cleared by the FDA and Phase 1 study is ready to enroll in the second half of 2023.

The research was funded by: Bantam Pharma

Keywords: Genomics, Epigenomics, and Other -Omics, Patient-Derived Xenograft (PDX) Models

Conflicts of interests pertinent to the abstract.

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405 | MALT1 PROTEASE INHIBITION OVERCOMES BTK INHIBITOR RESISTANCE AND SHOWS SYNERGISTIC ACTIVITY WITH VENETOCLAX IN MODELS OF B CELL LYMPHOMA AND LEUKEMIA

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Introduction: Specific B cell malignancies, including CLL and the aggressive non-GCB subtype of DLBCL, are driven by constitutive activation of the B cell receptor (BCR) pathway and the transcription factor NF-κB. Pharmacological inhibition of MALT1 protease, a key mediator of the BCR/NF-κB signal transduction pathway, may therefore provide an attractive treatment option for patients with these cancers. Further, as combination therapy is often required for the treatment of aggressive B cell malignancies, the identification of therapies that synergistically combine with MALT1 inhibitors could afford additional and promising treatment options.

Experimental Procedures: A highly potent and orally bioavailable MALT1 protease inhibitor (ABBV-MALT1) was used to test the hypothesis that MALT1 inhibition will abrogate the proliferation of preclinical models of B cell malignancies in vitro and in vivo. Tumors treated with ABBV-MALT1 were subjected to transcriptomic and functional proteomic assays to elucidate molecular mechanisms of action and rational combination partners.

Results: Mechanistic studies reveal that ABBV-MALT1 effectively inhibits signal transduction of the BCR pathway and reduces NF-κB gene activation in non-GCB DLBCL cell lines resulting in cell cycle arrest and diminished viability. In vivo, oral administration of this compound demonstrates robust tumor growth inhibition in several models of B cell tumors, including non-GCB DLBCL models that are resistant to Bruton's tyrosine kinase (BTK) inhibitors.

NF-κB target genes include the pro-survival family members BCL-X_L and BCL2-A1, which aid in regulation of the intrinsic apoptosis pathway. As ABBV-MALT1-induced inhibition of the NF-κB pathway resulted in downregulation of these genes, we hypothesized that the associated tumor models would become increasingly dependent on the pro-survival family member BCL-2. To test this hypothesis, combination studies of ABBV-MALT1 and the selective BCL-2 inhibitor venetoclax were performed in both cell line and patient-derived xenograft models of DLBCL. Herein we show that concomitant administration of ABBV-MALT1 and venetoclax results in dramatic antitumor activity in all models tested in vivo. This efficacy also translates to primary patient CLL cells in vitro where the combination confers greater levels of apoptosis compared to either agent alone.

Conclusion: ABBV-MALT1 demonstrates robust single agent antitumor activity in malignant B cell models that are resistant to BTK inhibitors. Moreover, combination of ABBV-MALT1 with the BCL-2 inhibitor venetoclax shows synergistic cell killing of B cell tumors in vitro and dramatic tumor regression in vivo. Together, these data indicate that MALT1 inhibition may overcome BTK inhibitor resistance and combine with venetoclax to effectively treat patients with DLBCL, CLL and other B cell malignancies.

Encore Abstract - previously submitted to AACR 2023

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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406 | DIFFUSE LARGE B-CELL LYMPHOMA CELL-CYCLE PROGRESSION REQUIRES THE CYCLIN-G ASSOCIATED KINASE (GAK), A NOVEL DRUG TARGET FROM MACHINE LEARNING-ENABLED PHENOTYPIC SCREENING

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Background: Recurrent genomic alterations in specific cancers reveal tumor drivers that inform the development of therapeutic approaches. In diffuse large B-cell lymphoma (DLBCL), oncoprotein-focused drug development has achieved limited success. Phenotypic screening is an emerging alternative that can be leveraged through machine-learning analysis. Under this paradigm, we reveal strong therapeutic potential in DLBCL of inhibiting the cyclin-G associated kinase (GAK). GAK participates in clathrin-mediated endocytosis and regulates mitotic-spindle alignment. GAK has been minimally explored in cancer therapeutics and is a novel target in DLBCL.

Methods: We performed a first-of-its-kind screen of kinase inhibitors in DLBCL followed by machine learning-based analysis using our in-house target identification platform, idTRAX. We analyzed gene-expression data for 414 previously untreated DLBCL patients (Lenz cohort). Immunofluorescent microscopy was performed to visualize the mitotic effect of GAK inhibition.

Results: Our screen of kinase inhibitors revealed GAK as a strong target for both activated B-cell (ABC) and germinal center B-cell (GCB) derived cell lines with complete sparing of peripheral-blood mononuclear cells. Analysis of gene-expression data found tumors with high *GAK* expression had dramatically worse overall survival compared to those with low expression ($p = 0.0002$). We found that GAK inhibition in DLBCL results in profound disruption of progression through mitosis, potently triggering the spindle assembly checkpoint and causing accumulation in G2 before onset of apoptosis. Additionally, gene-expression data showed correlation between high *GAK* expression and low expression of *RB1*, encoding the tumor suppressive master cell-cycle regulator retinoblastoma-associated protein (RB, $p < 0.0001$). The DLBCL cell lines RIVA and U2932 completely lack RB expression and show high sensitivity and accumulation in G2 in response to GAK inhibition. Pooled analyses of DLBCL cell lines show increased sensitivity to GAK inhibition in ABC-derived lines (mean EC50 0.2817 μM) compared to GCB (mean EC50 0.6517 μM, $p = 0.0078$). Immunofluorescent microscopy revealed profound disruption of mitotic spindles and shattering of chromosomes in these cells. Multiple participant molecules in mitotic progression are implicated as candidate GAK substrates and are under investigation to define key mechanisms.

Conclusion: GAK is a novel kinase therapeutic target in DLBCL revealed by our target identification platform, idTRAX. GAK's role in mitotic-spindle alignment represents a critical kinase dependency for DLBCL tumors, in particular with cell-cycle deregulation due to loss of RB function. Our synthesis of novel inhibitors of GAK and synergistic targets may reveal new therapeutic strategies for translation to clinical trials for DLBCL patients with unmet clinical needs.

The research was funded by: Florida Department of Health Bankhead-Coley Cancer Research Program

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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407 | BTK DEGRADATION AS A NOVEL THERAPEUTIC STRATEGY IN RELAPSED CNS LYMPHOMA: PROOF OF CONCEPT STUDIES IN INTRACRANIAL PRECLINICAL INCLUDING PATIENT-DERIVED MODELS

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Introduction: There is substantial need for more effective therapeutic strategies for relapsed, refractory primary and secondary CNS lymphomas. Bruton's tyrosine kinase (BTK) is a key driver of NF-kB activation and an important target in primary CNS lymphoma, largely dependent on B-cell receptor (BCR) signaling. Limitations of current covalent and non-covalent BTK inhibitors include the susceptibility to mutational escape as a basis for resistance.

Recent evidence also suggests a potential scaffolding function of BTK, active in the setting of catalytically inactive BTK kinase mutations and not antagonized by kinase inhibitors, that permits downstream growth pathway activation.

BTK degradation represents a unique therapeutic strategy. NX-5948 is a novel oral small molecule that induces BTK degradation via recruitment of the cereblon E3 ligase complex. NX-5948 is being evaluated in a Phase 1 trial as treatment for patients with B cell malignancies who have progressed despite prior treatment with covalent and/or non-covalent BTK inhibitors or in B cell indications where treatment with BTK inhibitors has been less effective. NX-5948 induces sub-nanomolar potency degradation of both wild-type and mutant forms of BTKin vitro, demonstrating rapid in vivo degradation in mouse and non-human primate B cells within four hours of oral administration. In mice, NX-5948 inhibits growth of subcutaneously implanted ABC-type DLBCL, TMD8 tumors, harboring BTK wild type or ibrutinib resistant C481S mutation. In addition, NX-5948 crosses an intact blood-brain barrier in mice and promotes BTK degradation in microglia and brain-resident lymphoma cells.

Methods: Here we evaluated the pharmacodynamic properties of NX-5948 in an intracranial model of CNS lymphoma using patient-derived SC1 cells. SC1 cells are derived from a patient with highly refractory CD79b and EVT6-mutant large B-cell secondary CNS lymphoma, resistant to R-CHOP, high-dose methotrexate/rituximab, etoposide, Ara-C and RT.

Results/Conclusions: Upon intracranial implantation, SC1 cells grow aggressively and exhibit diffuse bi-hemispheric brain infiltration in RAG-/- mice, with localization along brain microvasculature. Oral administration of NX-5948 for three days at 90 mg/kg in mice bearing established intracranial SC1 tumors yielded 98% degradation of BTK in SC1 lymphoma cells isolated six hours after NX-5948 dosing, as quantified by immunoblot analysis. Daily treatment with NX-5948 was associated with marked prolongation of survival in mice with intracranial SC1 CNS lymphoma compared to control, $p = 5.6 \times 10^{-5}$ and to mice treated with daily ibrutinib $p = 8.6 \times 10^{-5}$ ($N = 6$ mice/cohort). Survival prolongation was further evident following cessation of dosing at 100 days. Taken together, these preclinical results support, in part, the rationale for a phase I study of NX-5948 in relapsed primary CNS lymphoma (NCT05131022).

The research was funded by: Nurix

Keywords: Molecular Targeted Therapies, Patient-Derived Xenograft (PDX) Models

Conflicts of interests pertinent to the abstract.

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408 | DIFFERENTIAL IBRUTINIB SENSITIVITY IN CD79B-MUTANT AND WILDTYPE SUBTYPES OF A NOVEL MYD88-DRIVEN DLBCL MOUSE MODEL

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Introduction: Recent efforts have established distinct subtypes of DLBCL by clustering cases based on their mutational profiles. Mutations associated with the MCD/C5 cluster include *MYD88* p.L265P, *CD79B* p.Y196X and *BCL2* amplifications. Several recurring MCD-associated mutations affect transcription factors involved in regulating B cell differentiation (*BCL6*, *SPIB*, *PRDM1*, *TBL1XR1*). We previously established an autochthonous mouse model mimicking B cell-specific expression of $MYD88^{L265P}$, *BCL2* amplification and loss of *PRDM1*. These animals develop a disease that resemble many features of MCD DLBCL and thereby provide a valuable tool for DLBCL research. Here, we aimed to advance this existing model by introducing a *Cd79b* ITAM mutation.

Methods: We generated an allele that allows the conditional expression of *Cd79b* p.Y195H (the murine orthologue of *CD79B* p.Y196H) from the endogenous locus and bred it to our established DLBCL mouse models. The developing lymphomas were characterized by exome, transcriptome and B cell receptor sequencing. We

performed flow cytometric analyses, phosphoproteomics and proximity ligation assays to assess the activation status of the BCR pathway in our models. Lastly, we conducted MRI-guided treatment experiments with the BTK inhibitor ibrutinib.

Results: By including a B-cell-specific *Cd79b* p.Y195H mutation, we refined our mouse model to gain novel insights into MCD/C5 DLBCL characteristics. Mice developed highly proliferative, (oligo-)clonal lymphomas. While mouse models with an engineered loss of *Prdm1* formed lymphomas that were $B220^{+}CD138^{-}$ and enriched for pre-memory and light zone gene signatures, the $B220^{-}CD138^{+}$ tumors developing in *Prdm1*-deficient lines showed plasmablastic features on a transcriptional level. The *Cd79b* status had no effect on the putative precursor population of the malignant B cells, however the highest frequency of spontaneous mutations in genes associated with MCD DLBCL was observed *Prdm1*-deficient lymphomas carrying both *Myd88* and *Cd79b* activating mutations. Futhermore, the presence of the *Cd79b* p.Y195H allele increased BCR pathway activation levels in both the *Prdm1*-proficient and -deficient mouse lines. This activated state of the BCR pathway in *Cd79b*-mutated murine lymphoma translated into an increased sensitivity of those tumors to BTK inhibition by ibrutinib.

Conclusions: Taken together, we refined existing *Myd88* p.L252p and *BCL2*-driven MCD/C5 DLBCL mouse models by co-expressing the *Cd79b* p.Y195H mutation. *Cd79b*-mutant murine lymphomas exhibited increased BCR activation levels, resulting in an increased sensitivity towards BTK inhibition, when compared to *Cd79b* wt control tumors. These findings indicate that patients with *CD79B* ITAM mutations might be particularly sensitive to BTK inhibitor treatment.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Basic and Translational Science

Conflicts of interests pertinent to the abstract.

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Research funding: AstraZeneca, Gilead

409 | SYNTHESIS AND PRECLINICAL DEVELOPMENT OF A PROMISING NOVEL ROMIDEPSIN NANOPARTICLE FOR THE TREATMENT OF PERIPHERAL T-CELL LYMPHOMA (PTCL)

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Introduction: The HDAC inhibitors are important drugs for the treatment of PTCL. While these drugs produce ORR of 25–30% with short PFS, responses can last over a year. There is still debate on the optimal ways to use HDAC inhibitors. Most HDAC inhibitors are oral with prolonged AUC of exposure. Romidepsin (R) is administered IV and exhibits a half-life of only 3 hours, though biological effects on chromatin may persist for 24–48 hours. A failed Phase 4 study led to the withdrawal of R for R/R PTCL. In an effort to try and create improved alternatives to R with better efficacy and safety, we deployed a proprietary nano-chemistry platform to synthesize NanoRomidepsin (NR) particles, identifying a lead molecule that is comparable to or better than the predecessor R.

Methods: Using a combinatorial strategy of solvent screening and polymer chemistry, we developed a first-in-class NR therapeutic with a unique and specific Drug/ Polymer/Surfactant ratio. We utilized dynamic Light Scattering (DLS), cryo-electron microscopy (EM) and liquid chromatography-mass spectrometry (LC-MS) to characterize the size, morphology, and drug encapsulation efficiency of the NR nanoparticles. Cell viability, flow cytometry and western blotting (WB) were performed to determine the effect of NR on cytotoxicity, apoptosis, and histone acetylation across a panel of PTCL cell lines. The maximum tolerated dose of NR was based on an in vivo single-dose and repeated dose toxicity study. Pharmacokinetic studies were performed in mice treated at ½ MTD with quantitation of plasma drug levels by LC-MS.

Results: Cryo-EM and DLS confirmed that NR had a poly-dispersity index (PDI) between 0.16 to 0.27 and a z-average of 60–70 nm, indicating uniform size and homogenous particle distribution in the desired ranges. The cell viability assays demonstrated that R and NR produced comparable cytotoxicity (IC50 in range of 0.7–1.9 nM). Flow cytometry and WB analysis demonstrated that NR induced apoptosis and increased acetylation of H3/H4 in a time and concentration-dependent manner. In vivo single-dose and repeated dose toxicity assays revealed a clear correlation between dose and weight loss and/or clinical score in both R and NR treated groups. Pharmacokinetic analyses revealed a substantially greater AUC for NR, which was 3- and 25-fold higher compared to R for IP and IV routes of administration respectively. Interestingly, the markedly greater AUC for NR did not appear to be associated with increased in vivo toxicity.

Conclusions: We have synthesized a lead nanotherapeutic of R that will be translated to the clinic. In keeping with other nanotherapeutic drugs, nanosizing drugs tend to increase their volume of distribution (Vd), AUC and markedly improve their tolerability. Large scale in vivo modeling of NR is underway. Data on the development and differentiation of our lead NR asset will be presented, as will the strategy for clinical development.

The research was funded by: IVY grant, Translational Orphan Blood Cancer Research Initiative Fund

Keyword: Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

410 | FUNCTIONAL PRECISION ONCOLOGY FOR FOLLICULAR LYMPHOMA WITH PATIENT-DERIVED XENOGRAFT IN AVIAN EMBRYOS

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Introduction: Follicular lymphoma (FL) is an incurable type of B-cell malignancy that accounts for 25 percent of all lymphomas. Although most patients achieve remission with immuno-chemotherapy, almost all of them will experience multiple relapses after treatment. The prognosis is especially poor for around 20 percent of FL patients who relapse within two years after treatment initiation. The understanding of the heterogeneity of treatment responses is limited by the absence of in vitro or in vivo experimental models, mainly due to the strong dependence of tumor cells on their surrounding environment to survive.

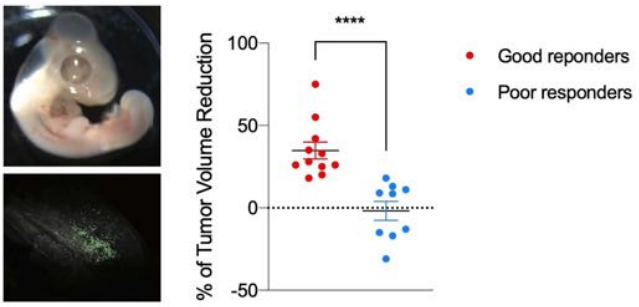
The aim of this project is to develop a primary FL cell xenograft model in chicken embryos to capture treatment response heterogeneity and analyze the mechanisms of response to immune-chemotherapy.

Methods: The FL-AVI-PDX^{TM} model was developed by transplanting primary FL cells into chicken embryos. We transplanted 20 biopsy samples, including good (n = 11) and poor clinical responders (POD24, n = 9), and treated each set of embryos with either RCHOP or vehicle intravenously. The effects of treatment were evaluated 24 hours later with tumor volume measurement by light-sheet microscopy and transcriptomic analysis at the single-cell level (scRNAseq).

Results: All samples engrafted successfully in the aorto-gonado-mesonephros of chicken embryos. Tumor volume reduction achieved with RCHOP in the avian embryo was strongly correlated to patient's clinical outcome (mean tumor volume decreased by 35% in the good responders (n = 11) compared to an increase of 2% in the poor responders (n = 9), $p < 0.05$).

Transcriptomic analysis of individual cells was conducted on 14 patients in three different conditions (before and after transplantation with RCHOP or vehicle treatment). We found a robust signature of 21 genes whose expression increased after exposure to RCHOP in all the patients. Among these genes was BAX, a key effector of the mitochondrial outer membrane permeabilization (MOMP), whose inactivation (by CRISPR-CAS9) conferred resistance to RCHOP in cell lines. Furthermore, venetoclax, a BCL2 inhibitor that lowers the threshold of BAX level required for MOMP, had synergistic effects with RCHOP in cell lines and primary samples in vivo, validating the findings in the model.

Conclusion: FL-AVI-PDX^{TM} enables to study primary FL samples, and to capture the heterogeneity of clinical response to a complex therapeutic regimen. Moreover, it provides a unique opportunity to analyze the mechanisms of response to immune-chemotherapy and to identify therapeutic targets (such as BAX) that can be functionally assessed in the avian embryo.



Light sheet microscopy of chicken embryo and primary FL cells in green (left panel). Mean percentage of tumor volume reduction achieved with RCHOP in samples from good and poor responders. Error bars indicate SEM. **** p Val<0.0001, Mann-Whitney test (right panel).

Encore Abstract - previously submitted to regional or national meetings (up to <1'000 attendees)

Encore Abstract - previously submitted to EHA 2023

Keywords: Indolent non-Hodgkin lymphoma, Patient-Derived Xenograft (PDX) Models, Tumor Biology and Heterogeneity

Conflicts of interests pertinent to the abstract.

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411 | CFT7455, A NOVEL IKZF1/3 DEGRADER, DEMONSTRATES POTENT ACTIVITY IN PERIPHERAL AND CNS MODELS OF NHL AS A SINGLE AGENT OR IN COMBINATION WITH CLINICALLY APPROVED AGENTS

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Immunomodulatory drugs, such as pomalidomide and lenalidomide are approved for the treatment of multiple subtypes of NHL. These drugs induce an interaction between Ikaros family zinc finger proteins 1 and 3 (IKZF1/3) and cereblon (CRBN), an E3 ligase, resulting in IKZF1/3 degradation. Clinically, immunomodulatory drugs are active as single agents or when used in combination with several classes of targeted therapies, in both first line and relapsed/refractory NHL subtypes.

We previously described the preclinical characterization of CFT7455 as a novel IKZF1/3 degrader with 800-fold increased potency over pomalidomide in CRBN binding. We demonstrated that this increased activity translates into dramatically greater efficacy compared to pomalidomide in cellular and in vivo preclinical models of multiple myeloma and NHL. Here we show that the increased catalytic activity and improved potency of CFT7455 also translates into potent antitumor activity as a single agent or in combination with clinically approved agents in multiple in vivo models of NHL. In addition, the enhanced activity of CFT7455 demonstrates CNS activity in both the Raji and OCI-Ly10 intracranial xenograft models. CFT7455 (100 μg/kg/day) led to a significant increase in survival probability in comparison to pomalidomide (3000 μg/kg/day) and two investigational IKZF1/3 degraders in both models.

The combination of immunomodulatory drugs with CD20, BTK, or HDAC targeting agents shows promising clinical activity in the treatment of NHL. Studies were conducted with CFT7455 dosed in combination with rituximab (anti-CD20 antibody), ibrutinib (BTK inhibitor), or romidepsin (HDAC inhibitor) in several models of NHL. In the MCL model, Mino, the combination of CFT7455 with rituximab demonstrated enhanced activity and complete tumor regression. In the DLBCL model, TMD8, the combination of ibrutinib and CFT7455 was synergistic and resulted in a significant increase in survival probability. Synergistic activity was also observed with the combination of CFT7455 and romidepsin in two models of ALCL. In the intracranial NHL model, OCI-Ly10, the combination of CFT7455 with rituximab or ibrutinib led to increased survival probability, highlighting the therapeutic potential of this combination in CNS disease. In conclusion, CFT7455 is a potent, selective degrader of IKZF1/3, with single agent and combination antitumor activity in DLBCL, ALCL, and MCL, supporting clinical investigation of CFT7455 for NHL. CFT7455 is currently being studied in NHL in an ongoing Phase 1/2 clinical trial (NCT04756726).

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Aggressive T-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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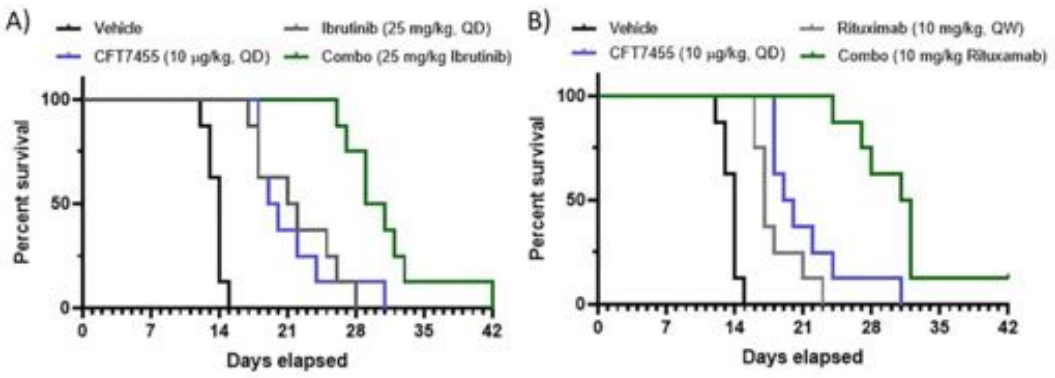

Figure 1. CFT7455 treatment shows improved survival probability in a CNS model of OCI-LY-10 as a single agent or in combination with ibrutinib or rituximab. Panel A. Kaplan-Meier survival curves of 4 animal cohorts bearing intracranial OCI-LY-10 xenografts following vehicle, CFT7455 (10 μg/kg QD), ibrutinib(25 mg/kg QD) or CFT7455 and ibrutinib combination treatments. Panel B. Kaplan-Meier survival curves of 4 animal cohorts bearing intracranial OCI-LY-10 xenografts following vehicle, CFT7455 (10 μg/kg QD), rituximab (10 mg/kg QD) or CFT7455 and rituximab combination treatments. CFT7455 + ibrutinib showed a 121.4% increase in median survival time ($p<0.001$). CFT7455 + rituximab showed a 92.9% increase in median survival time ($p<0.001$).

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412 | ORTHOTOPIC XENOGRAFTS MODELS IN RELAPSE/REFRACTORY LYMPHOMAS: A PRECLINICAL MODEL FOR THERAPEUTIC, MECHANISTIC AND FUNCTIONAL STUDIES

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Introduction: Novel targeted therapies have improved the treatment of relapse/refractory lymphomas, although overcoming therapy resistance is still a main clinical challenge and an overriding priority for patients and treating physicians. Patient-derived orthotopic xenografts (PDOXs), in which a human tumor biopsy is implanted in an immunodeficient mice in the same organ as the tumor is grown in the patient, are the most advanced in vivotumor preclinical models, as they reproduce better patient tumor behavior and therapeutic responses.

Aim: To generate and characterize PDOXs for refractory and relapsed lymphomas from different histologies and to derive cell lines from these PDOX in order to obtain advanced preclinical models to examine the mechanisms involved in drug resistance through therapeutic, mechanistic and functional studies.

Material and Methods: Systematic and prospective study in which a fragment of the patients' biopsy has been used to generate PDOXs. Fresh tumor biopsies were grafted in spleen and/or mesenteric lymph nodes or in extranodal sites (according to the location where the tumor grow in the patient), in 1–3 (depending on tissue availability) NOD/LtSz-scid/IL-2Rychain^{null} (NSG) mice. Once the tumor grows, the animal was sacrificed and the tumor was re-implanted (2–3 fragments) in the same location in additional animals to expand it for histological, IHQ and molecular characterizations and posterior therapeutic studies. Genetic match between the PDOX and the paired patient tumor from which they derived was assessed using 6 microsatellites by PCR followed by capillary electrophoresis with fluorescence detection. Fusions, point mutations, and expression levels in 125 genes linked to lymphomas were simultaneously detected using Archer® FusionPlex® Lymphoma Kit.

Results: We have generated 15 patient derived xenografts (PDX) based in orthotopic implantation from aggressive B and T cell lymphomas, including resistant DLBCLs, adult Burkitt's lymphoma,

Hodgkin lymphoma, marginal zone lymphomas and aggressive anaplastic and angioimmunoblastic T-cell lymphomas, among other histologies (Table). All of them mimic the histology of the tumor there were derived and showed genetic match with their respective patient tumor. From 10 of these orthotopic PDX, we have derived cell lines to have paired in vitro and in vivo models. These models are now molecularly characterized using a targeted next generation sequencing assay. In vivo massive pharmacologic screening in this models are ongoing.

Conclusions: To our knowledge, these are one of the first orthotopic PDX lymphoma models generated, that can allow us to expand patients' refractory tumors in order to extensively study molecular features of them and target effective drug profiles.

PDOX code	Histology		Passages in mice	Derived cell line
Ly4	Diffuse large B cell lymphoma		#2	
Ly8	Diffuse large B cell lymphoma		#10	
Ly9	Primary cutaneous large B-cell lymphoma, leg type		#10	Cell-ly9
Ly10	Burkitt lymphoma		#10	Cell-ly10
Ly11	Hodgkin lymphoma		#3	
Ly13	T cell lymphoma		#10	Cell-ly13
Ly15	Hodgkin lymphoma		#4	
Ly17	Splenic marginal zone B cell lymphoma transformed to Hodgkin		#9	Cell-ly17
Ly18	Lymphoplasmacytic lymphoma	Ly18	#8	Cell-ly18
		Ly18-IF (liver implant)	#10	Cell-ly18-IF
Ly20	Diffuse large B cell lymphoma + follicular lymphoma grade 3a		#9	Cell-ly20
Ly22	Angioimmunoblastic T cell lymphoma		#6	Cell-ly22
Ly26	Anaplastic T-cell lymphoma		#3	Cell-ly26
Ly27	Marginal zone B cell lymphoma		#1	
Ly29	Plasmacytic lymphoma post-transplant		#3	Cell-ly29

Keywords: Patient-Derived Xenograft (PDX) Models, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

413 | COMBINATION OF IMVOTAMAB AND LONCASTUXIMAB TESIRINE SHOWS ENHANCED ANTI-TUMOR ACTIVITY IN A PRECLINICAL MODEL OF NON-HODGKIN'S LYMPHOMA

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Introduction: Non-Hodgkin's lymphoma (NHL) is among the most common cancers in the United States and Europe. Systemic chemoimmunotherapy, consisting of alkylating-based chemotherapy plus a CD20-directed monoclonal antibody therapy, is a mainstay of treatment for advanced-stage disease. Unfortunately, once NHL becomes refractory to this standard treatment, the overall prognosis is poor, with limited long-term survival. Given that malignant B cells demonstrate broad and consistent expression of CD19 and CD20, combining therapies that target both CD19 and CD20 may improve treatment outcomes among patients with relapsed or refractory (r/r) NHL. We evaluated the combination of imvotamab, an engineered bispecific anti-CD20 IgM antibody T cell engager (TCE) that eliminates CD20+ lymphoma cells by T cell and complement-mediated killing, and loncastuximab tesirine, a FDA and EMA-approved CD19-directed antibody drug conjugate (ADC) in a preclinical model of NHL.

Methods: To evaluate the combination of imvotamab and loncastuximab tesirine in vitro, the human B lymphoma Raji cell line that expresses CD19 and CD20 was co-cultured with healthy human peripheral blood mononuclear cells (PBMCs) and subsequently evaluated for T cell activation and T cell-dependent cellular cytotoxicity (TDCC). The in vivo anti-tumor activity of imvotamab and loncastuximab tesirine was assessed in mice that had been reconstituted with a human hematopoietic system, implanted subcutaneously with Raji tumor cells, and then measured for tumor growth inhibition (TGI) relative to vehicle-treated animals. Additionally, immunohistochemistry (IHC) staining of CD19 and CD20 was conducted on formalin-fixed paraffin-embedded Raji xenograft tumors to confirm target expression in treated animals.

Results: T cell activation induced by imvotamab is similar with or without loncastuximab tesirine. In TDCC assays with healthy donor effector T cells, the killing of Raji cells was enhanced with the combination of imvotamab and loncastuximab tesirine. In vivo, the combination of imvotamab and loncastuximab tesirine resulted in up to 100% TGI with several mice reaching complete responses, and enhanced overall survival compared to treatment with either single agent at study endpoint. IHC confirmed CD19 and CD20 expression in the Raji tumors on treatment.

Conclusions: Our preclinical data indicate that combining imvotamab with loncastuximab tesirine results in potent anti-tumor activity and supports the rationale for testing this combination in the clinic. Imvotamab is currently being studied as monotherapy in a Phase 1/2 clinical trial for r/r NHL, where it has been generally well tolerated, with both complete and partial responses observed (NCT04082936). Clinical testing will be initiated this year to evaluate the combination of imvotamab with loncastuximab tesirine in r/r NHL patients

Keywords: Combination Therapies, Non-Hodgkin (Pediatric, Adolescent, and Young Adult)

Conflicts of interests pertinent to the abstract.

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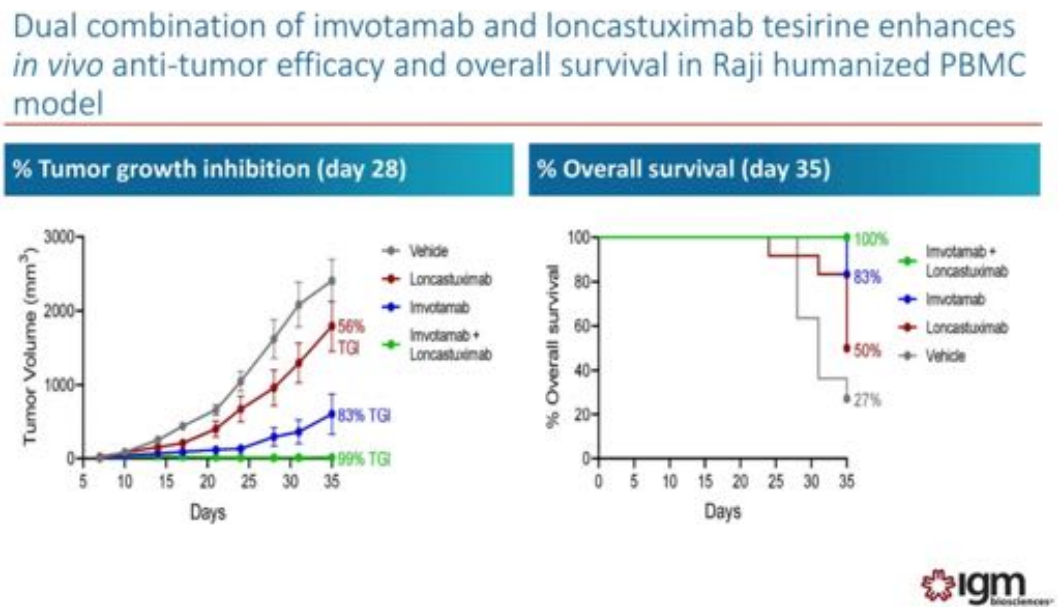

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414 | PROLONGED CELL CYCLE ARREST BY THE CDK4/6 ANTAGONIST NARAZACICLIB RESTORES IBRUTINIB RESPONSE IN PRECLINICAL MODELS OF BTKI-RESISTANT MANTLE CELL LYMPHOMA

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Introduction: Bruton tyrosine kinase inhibitors (BTKi) have transformed the therapeutic landscape of mantle cell lymphoma (MCL); however, primary and acquired resistance to these agents remains a challenge. Previous studies have suggested that narazaciclib (ON123300), a second-generation, orally bioavailable and clinical-stage CDK4/6 inhibitor (CDKi), may trigger cell cycle arrest and significant tumor growth inhibition (TGI) in BTKi-resistant MCL models.
Methods: We compared the efficacy and safety of narazaciclib with the health authority approved CDKi in association with different BTKi, in a panel of 10 MCL cell lines with distinct sensitivity to the first-in-class BTKi, ibrutinib. We used the CellTiter-Glo proliferation assay, FACS-mediated quantification of cell cycle and apoptosis, and RNA sequencing followed by gene set enrichment analysis (GSEA), RT-PCR and western blot validations. In addition, we evaluated the safety and efficacy of narazaciclib/ibrutinib combo in vivo in an immune-competent chicken embryo chorioallantoic membrane (CAM) MCL xenograft.

Results: Narazaciclib exhibited the highest antitumor activity among MCL cell lines (mean IC_{50}: 3.61 ± 2.1 μM), regardless of their sensitivity to ibrutinib. Although there was no correlation between CDKi sensitivity and activation of the CDK4/CDK6-pRb pathway in MCL, transcriptomic and phenotypic analyses revealed a predominant downregulation of E2F target genes and G2/M checkpoint response (NES > 2.5) upon narazaciclib treatment. This feature was associated to intracellular accumulation of p21, p16, and phospho-p27, decreased mitotic index, G1 cell cycle blockade, and apoptosis onset. When combined with ibrutinib, but not with the second generation therapeutic acalabrutinib, narazaciclib achieved significant synergistic antitumor activity in both BTK-sensitive and BTK-resistant cells. The combination was not associated with improved apoptosis, but rather with a slight but constant (+10%–15%) augmentation in G1 phase blockade and the down-modulation of cell cycle-associated transcriptome. Both the downregulation of phospho-histone H3 and the upregulation of p-p27/p27 and p16, also underwent a 10%–15% improvement in combination-treated cells. In vivo, while narazaciclib single agent achieved a 28% TGI in the CAM model, the narazaciclib-ibrutinib combination reduced tumor spreading by 65% and allowed a 50% reduction in malignant B cell infiltration into the bone marrow, with no detectable toxicity.
Conclusions: Narazaciclib, due to its completely distinct MoA from BTKi involving the direct modulation of the cell cycle, can achieve significant synergistic activity with ibrutinib in vitro and in vivo, especially in BTKi-resistant models of MCL. Ongoing phospho-proteomics and genetic edition assays will help deciphering the molecular bases of this unique drug cooperation at the cell cycle level.

Encore Abstract - previously submitted to AACR 2023

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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415 | MICRORNAS REGULATE NOVEL SIGNALING PATHWAYS TARGETABLE BY PI3K, MEK, BCL6 AND EZH2 INHIBITORS IN IBRUTINIB RESISTANCE MANTLE CELL LYMPHOMA

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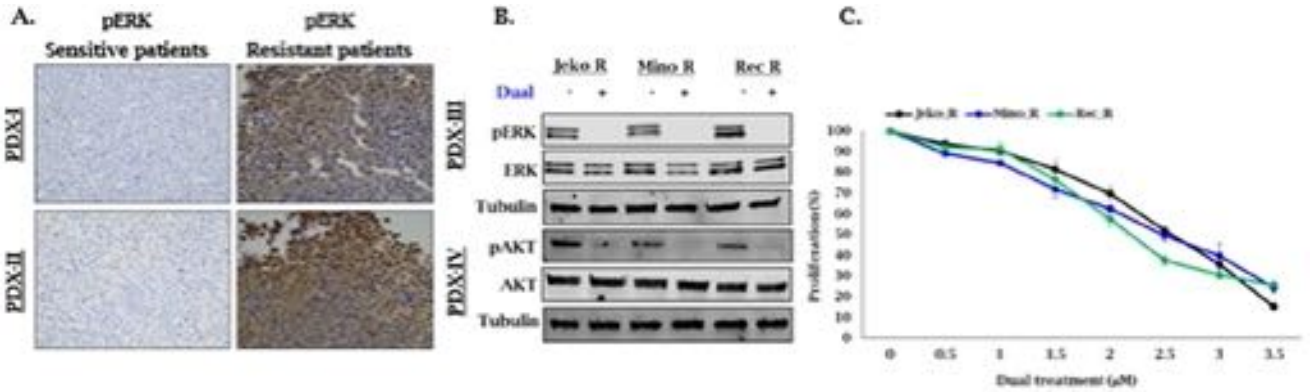
Background: Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin's lymphoma. Bruton's tyrosine kinase (BTK) is a key component of B-cell receptor (BCR) signalling, implicated in B-cell cancers and an effective therapeutic target in MCL. Resistance to the BTK inhibitor ibrutinib is a major clinical challenge that has prompted a search for alternative therapeutic options for this patient population. MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by silencing messenger RNA (mRNA) targets. MiRNAs have an important role in cancer development and drug response. We hypothesized that miRNA-mRNA interactions may help identify the molecular mechanism involved in ibrutinib resistance in MCL and may suggest novel therapeutic options for patients with ibrutinib-reistant disease.
Methods: We generated 3 ibrutinib-resistant cell lines: Jeko_R, Rec_R and Mino_R by gradually increasing ibrutinib dosage over time. MiRNA and mRNA expression profiles were determined using small-RNA and RNA next-generation sequencing, respectively. MiRNA/gene and protein expression profiles were validated in sensitive and resistant cell lines, in patient-derived xenograft (PDX) models (n = 10) and in patient biopsies (n = 25) by qRT-PCR, Western analyses and immunohistochemistry (IHC). MEK, PI3K, BCL2, BCL6 and EZH2 inhibitors were used to target overexpressed signaling pathways in ibrutinib-resistant cells.
Results: Ibrutinib-sensitive cells had different miRNA and mRNA expression signatures compared with those of ibrutinib-resistant



(A) Immunohistochemistry staining of tissues from MCL patient derived xenograft (PDX) model. pERK is highly expressed in ibrutinib resistance patients (PDX-III and PDX-IV) compared to ibrutinib sensitive patients (PDX-I and PDX-II) **(B)** MCL resistance cells were treated for 48h with both MEKi (cobimetinib) and PI3Ki (idelalisib), which resulted in downregulation of pERK and pAKT proteins and (C) reduced cell proliferation at IC50 of 2.5 μM as measured by WST assay.

cells. Crossing of miRNA binding site sequences (seed region) with their mRNA target sequences revealed potential involvement of miRNAs in regulating pro-cancerous pathways (e.g., MAPK, PI3K-AKT, mTOR, NFkB) and mitochondrial energy-related pathways (Oxphos signaling and the tricarboxylic acid cycle) in ibrutinib-resistant cell lines. A subset of miRNAs (miRs-221, 146a, 182, 342 and the let-7 family members), which regulate the survival pathways MAPK-ERK and PI3K cascade, were downregulated in ibrutinib-resistant cell lines, PDX, and in patients with ibrutinib-resistant MCL. Moreover, MCL-resistant cells overexpressed pERK, pAKT, BCL6 and EZH2 proteins. Treatment of the resistant cells with specific inhibitors such as cobimetinib (MEKi), idelalisib (PI3Ki), FX1 (BCL6i), and tazemetostat (EZH2i) resulted in significant downregulation of these proteins and reduced cell proliferation.

Conclusions: Overall, our data show that miRNAs upregulate pro-survival signaling pathways in patients with ibrutinib-resistant MCL, suggesting a mechanism for drug resistance. These pathways may be targeted by existing inhibitors, providing novel strategies for combating resistance.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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Research funding: H3B Biomedicine, Nurix Therapeutics, Minovia Therapeutics, and LOXO Oncology.

416 | INTERLEUKIN-2-INDUCIBLE KINASE REPRESENTS A NOVEL THERAPEUTIC TARGET FOR NK/T-CELL LYMPHOMA TREATMENT

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Background: Natural killer T-cell lymphoma (NKTCL) is a highly aggressive non-Hodgkin lymphoma with more incidence in Asian and South American populations. Patients suffered from advanced stage disease have limited treatment options and dismal prognosis. Therefore, the development of novel therapeutic targets for the treatment of this debilitating disease is urgently needed. ITK (interleukin-2-inducible kinase, ITK), one of the Tec kinase family, is predominantly expressed in T and natural killer T cells. Though redundant ITK expression was reported in NKTCL, the role of ITK in NKTCL has not been fully investigated. In this study, we elucidate the important role of ITK within the pathogenesis of NK/T cell lymphoma.

Methods: Expression level of ITK and p-ITK in NKTCL cell line and patients were performed by immunoblotting and immunohistochemistry, respectively. The lentivirus containing dox-induced ITK targeting shRNA or ITK overexpression plasmid were used to mediate conditional ITK knockdown or stable overexpression of ITK. NKTCL cell line stably transfected dox-induced shRNA or control shRNA plasmids was engrafted in opposite lateral of the same NCG mice to investigate the effect of ITK knockdown in vivo, 4 mg/mL dox in drinking water was administrated to induce ITK knockdown in vivo. The cell viability of tumor cells was analyzed through Cell Titer-Glo® Luminescent Cell Viability Assay. Soft agarose colony forming assay was employed to determine the influence of ITK inhibitor on colony-forming ability of NKTCL cell lines.

Results: The expression level of ITK were first analyzed in NKTCL cell lines (KHYG-1, YT, NK-YS and YTS). The KHYG-1 and YT cell showed high level of phosphorylation of ITK activation. Meanwhile, the activation and expression of ITK protein could also be observed in NKTCL patients ($n = 17$). Next the ITK overexpression plasmid were transfected into NK-YS and YTS cells, which promoted the proliferation of tumor cells. On the other hand, the conditional knockdown of ITK significantly suppressed the growth of KHYG-1 and YT cells. Furthermore, in vivo ablation of ITK in YT mouse model obviously delayed the progression of NKTCL tumors, showing smaller tumor size and lower weight compared with control group, highlighting ITK is a new fragility of NKTCL cells.

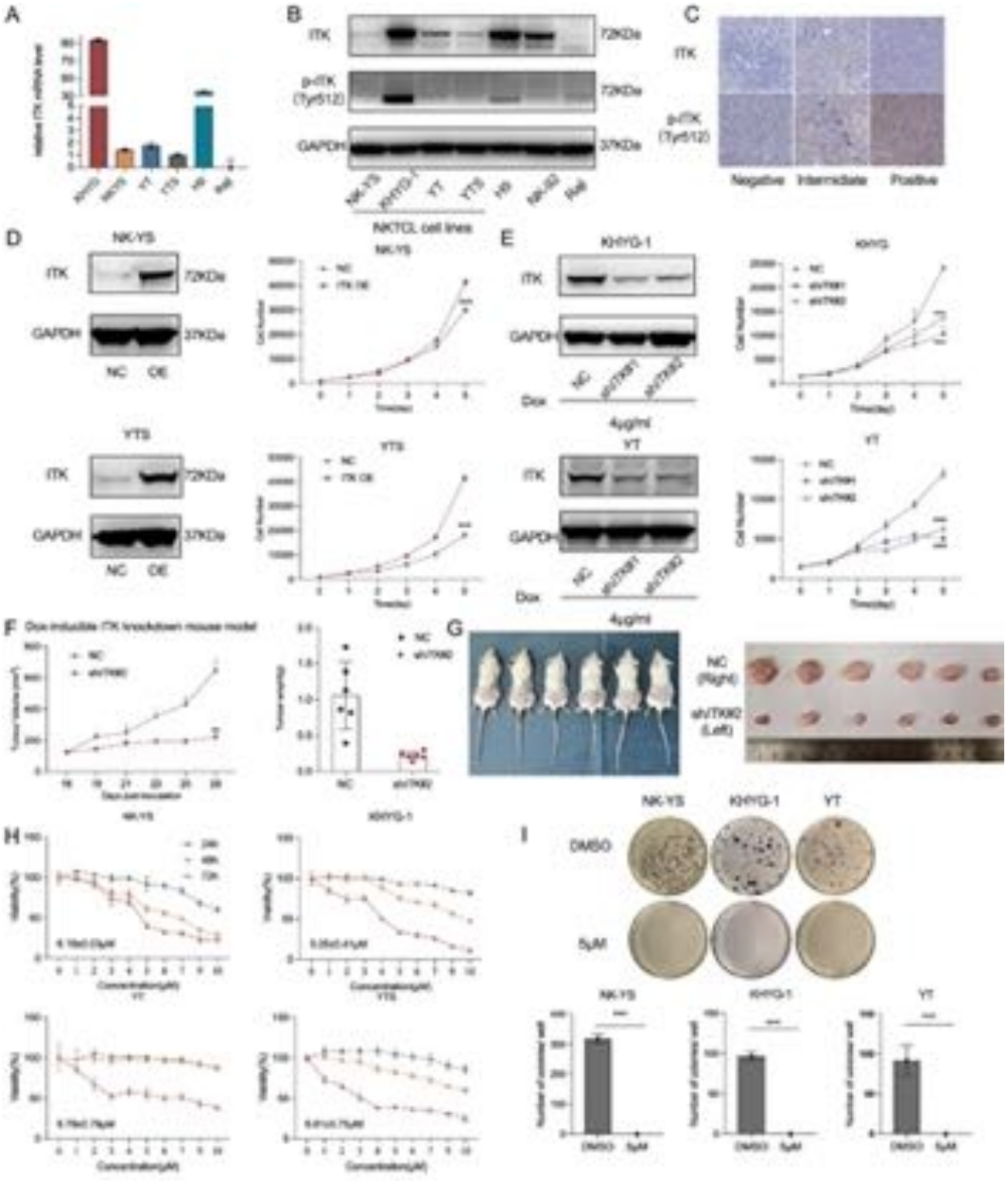

Figure 1. (A) and (B) ITK mRNA and protein expression in NKTCL cell lines were detected by qRT-PCR and WB; (C) ITK and p-ITK staining in NKTCL patients (n=17); (D) the expression levels of ITK in NK-YS and YTS cells transfected control (NC) or ITK overexpression (OE) plasmids is detected by WB, respectively; (E) KHYG-1 and YT cells containing Dox-inducible shRNA plasmids were treated with 4μg/ml Dox for 48h. ITK protein was analyzed by immunoblot analysis; cell viabilities were used to calculated cell number in (D) and (E); (F)The Dox-inducible ITK knockdown cells bearing mice (n=6) were treated with Dox (4mg/mL). The growth of tumors was monitored every 2d; (G) representative pictures of mice bearing tumor were shown; (H) cell viabilities were utilized to determine IC50 after treatment with different concentrations of ITK inhibitor; (I) Soft agarose colony forming assay, colonies were stained with MTT and taken photos after 10-16d culture, colony numbers were calculated by ImageJ. Statistical analysis was performed using Student's t test. *$p < 0.05$, **$p < 0.001$, ***$p < 0.0001$ compared with the control group.

To further validate this therapeutic effect, NKTCL cells were treated with ITK inhibitors for 24h, 48h and 72h in vitro, The ITK inhibitors repressed the viability of these NKTCL cells in a concentration and time-dependent manner. Furthermore, ITK inhibitors treatment abolished the colony formation of NKTCL cells, which indicated the ITK might represent the potential therapeutic target for NKT cell lymphoma. Taking together, targeting ITK is a promising strategy for treatment NKTCL.

Conclusion: Our results indicated the therapeutic role of ITK in NKTCL, which may represent the novel treatment approach for NKTCL patients.

Encore Abstract - previously submitted to regional or national meetings (up to <1'000 attendees)

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

417 | BRINCIDOFOVIR INDUCES POTENT ANTI-TUMOR ACTIVITY IN MYC-DRIVEN NATURAL KILLER/T-CELL LYMPHOMA WITH LOSS OF TRANSCRIPTIONAL REPRESSOR TLE1

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Introduction: Natural killer/T-cell lymphoma (NKTCL) is an aggressive Epstein-Barr virus (EBV)-associated malignancy which is prevalent in Asian countries. Brincidofovir (BCV), a lipid conjugated form of cidofovir, is a biologically-active acyclic nucleoside phosphonate recently shown to exhibit both antiviral and antitumor properties.

Methods: We investigated BCV in NKTCL cell-lines (n = 11) and mouse xenograft models. Whole exome sequencing, bulk RNAseq and single cell RNAseq (scRNAseq) were employed to examine mechanisms of action, and validated using orthogonal assays.

Results: BCV inhibited viability in all NKTCL cell-lines in a dose- and time-dependent manner. Highest sensitivity was demonstrated in four cell-lines KAI-3, NK-S1, NK-92 and KHYG-1 (IC50 36.0 to 303.6 ng/ml). Intraperitoneal BCV (40 mg/kg, 2X per week) inhibited tumor growth in NOD/SCID mice NK-S1 xenografts, compared with vehicle alone (p = 0.0005, two-tailed t-test). Whole exome sequencing of the cell-lines revealed widespread mutations in the JAK/STAT and DNA repair pathways, with no clear correlation observed with BCV sensitivity. RNAseq and Hallmark gene set enrichment analysis showed that *MYC* target pathways (FDR q < 0.001) were prominently upregulated in the four sensitive cell-lines compared to the rest. RNAseq of BCV-treated cell-lines (KAI-3 and NK-S1) revealed striking downregulation of *MYC* target pathways. scRNAseq revealed distinct temporal cell states evoked by BCV, including appearance of cell clusters enriched for p53 and apoptosis pathways, cell cycle and DNA repair pathways, as well as type I/II interferon and cytokine signaling. Western blot and quantitative PCR showed that markers of replication stress, DNA damage and STING signaling were potently upregulated, implicating an immunogenic form of cell death. Notably, *TLE1*, a known transcriptional repressor of the *MYC* oncogene, was the topmost downregulated gene (log2FoldChange -7.39, adjusted p = 3.51E-31) in the four BCV-sensitive cell-lines on RNAseq. This finding was verified on qPCR (p = 0.0061, Mann-Whitney test) and Western blot. In keeping with this result, RNAseq on NKTCL patient samples (n = 36) showed that *TLE1*-low tumors were enriched for *MYC* target pathways, which conferred worse progression-free survival (HR 3.44, 95% CI: 1.23–10.49, p = 0.0301).

Conclusions: Taken together, these results suggest that BCV may play a novel role in the treatment of MYC-driven NKTCL. Loss of TLE1, a putative predictive biomarker, implies that BCV may favour patients in this poor prognostic subgroup.

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Keywords: Diagnostic and Prognostic Biomarkers, Extranodal non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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418 | THE MTOR KINASE INHIBITOR EVEROLIMUS SYNERGISTICALLY ENHANCES THE ANTI-TUMOR EFFECT OF THE JANUS KINASE 1 (JAK1) INHIBITOR AZD4205 ON PERIPHERAL T CELL LYMPHOMA

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Introduction: Peripheral T-cell lymphoma (PTCL) constitute a heterogenous group of non-Hodgkin lymphomas, which is distinguished by their aggressive courses and poor clinical outcomes.

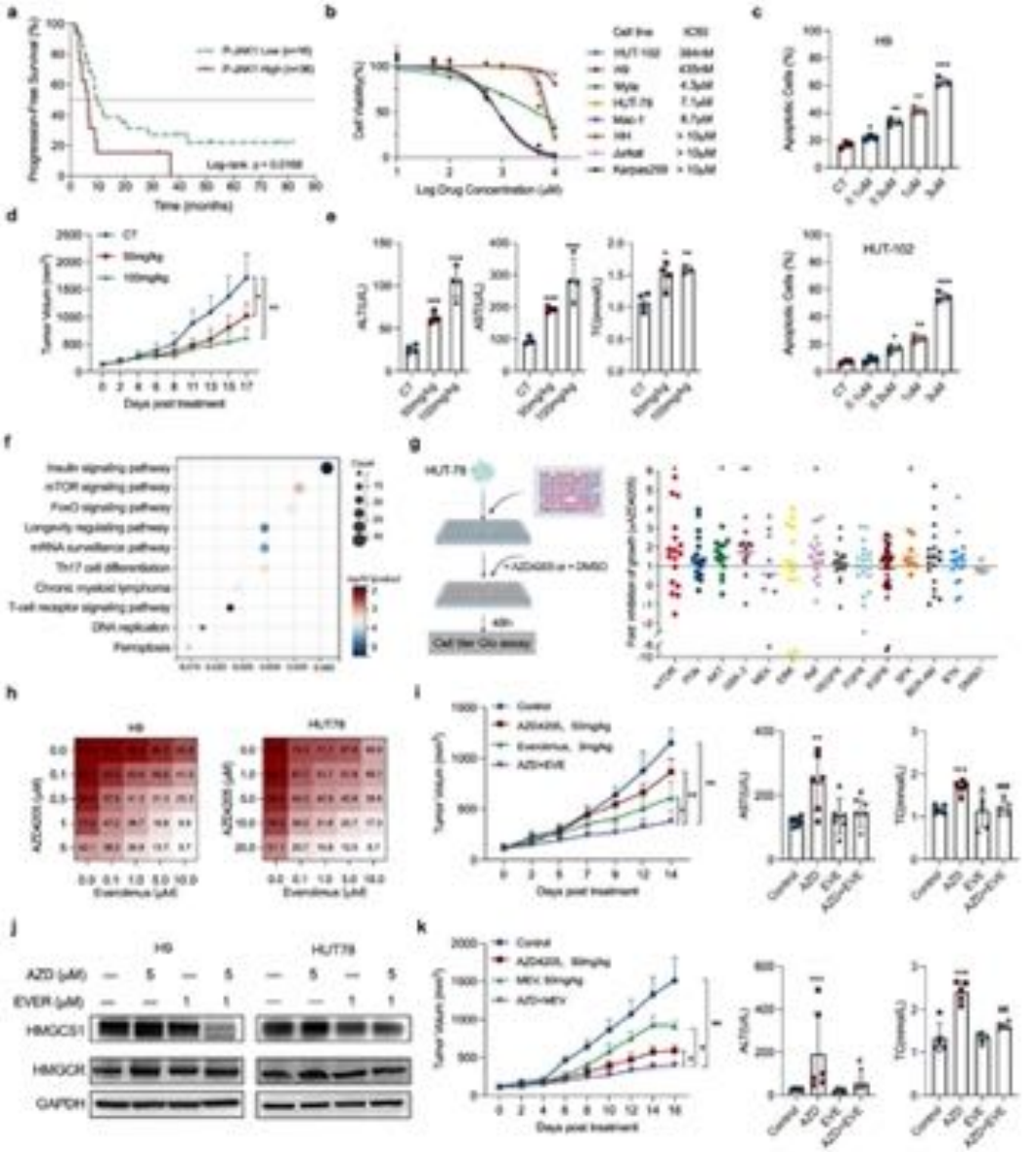

Figure 1: (a). Kaplan-Meier curves for univariate analysis. Stratified by high or low expression of phosphorylated JAK1. (b). Cell viability of T cell lymphoma cell lines treated with the indicated concentrations of the JAK1 inhibitor AZD4205 for 72h. (c). Apoptotic cells of H9 and HUT-78 were quantified using flow cytometry after treating with AZD4205 for 48h. (d). PDX model was established. AZD4205 (50 mg/kg QD, 100 mg/kg QD) was administrated to mice for 14 days when the tumor volume reached 100 mm^3 (n=6). The tumor volume of mice was measured every 3 days during the treatment. (e) The ALT, AST, and total cholesterol (TC) level in mouse serum were detected at the end of administration. (f) KEGG analysis of RNA-seq data of HUT-78 cells after 24-hour treatment with 5.0 μM AZD4205 (AZD4205 v.s. CT). (g) An overview of growth inhibition of HUT-78 by various pathway inhibitors ± AZD4205. Fold inhibition of growth by the combination of each compound with AZD4205 was compared with each compound alone. (h). Cell viability of H9 and HUT-78 cells treated with the indicated concentrations of AZD4205 and everolimus for 48h. (i & k). Tumor volume curves of PDX models during 14-days administration with the indicated agents. The AST and TC level in mouse serum were detected at the end of administration. (j). HMGCS1 and HMGCR expression level of H9 and HUT-78 cells were detected by western blot after treatment with indicated concentrations of AZD4205 for 48h. Data are expressed as Mean ± SD. Statistical analysis was performed using Student's t test or Mann-Whitney U test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with control group.

Multiple researches have indicated that the JAK/STAT pathway acts as an important role in the mechanism of TCL pathogenesis. Preliminary results from related clinical studies showed that JAK inhibitors have a high remission rate and durable response in PTCL patients. AZD4205 is a potent JAK1-selective inhibitor currently evaluated in phase II clinical studies in PTCLs, which could reduce the side effects caused by JAK2 blockade by selectively targeting JAK1. Therefore, the aim of this study is to explore the efficacy and appropriate combination regimen of the novel JAK1 inhibitor AZD4205 in PTCL and to decipher the underlying anti-tumor mechanism.

Methods: We analyzed the expression of JAK/STAT pathway in PTCL tissues via bioinformatics analysis and IHC. In vitro cell viability was assessed by using Cell Titer-Glo Luminescent assay. Induction of cell apoptosis was measured by flow cytometry. Western blot was utilized to identify the influence of AZD4205 on the intracellular relevant signaling pathways. The effects of AZD4205 on the transcriptome of PTCL cells were analyzed via transcriptome sequencing technology. High-throughput compounds screening was applied to explore potential combination therapeutic targets of AZD4205. Tumor-bearing mouse models were established to validate the efficacy and safety of AZD4205 and the combination regimen.

Results: High expression of phosphorylated JAK1 in PTCL tissues are potential poor prognostic factors. The JAK1 inhibitor AZD4205 inhibited the proliferation of PTCL cells and down-regulated the activation of JAK/STAT signaling pathway. In addition, AZD4205 induced apoptosis in PTCL cells, and showed anti-tumor effects in vivo. However, AZD4205 also induced adverse effects of hepatic impairment and dyslipidemia in vivo. Transcriptome sequencing analysis revealed that AZD4205 treatment upregulated the expression of mTOR pathway-related genes. Moreover, high-throughput screening assay showed that the mTOR inhibitor everolimus significantly enhanced the inhibitory efficacy of AZD4205. We further confirmed that AZD4205 combined with the mTOR inhibitor everolimus exerted synergistic anti-PTCL efficacy both in vitro and in vivo, and the combination regimen significantly reduced AZD4205-induced adverse effects. The RNA-seq results suggested that the combination treatment affected the cholesterol homeostasis pathway and a further validation of the combined anti-PTCL effect of mevastatin and AZD4205 was confirmed in mouse models.

Conclusions: The mTOR inhibitor everolimus could enhance the anti-tumor effects and attenuate the side effects induced by AZD4205, which may be indicated as the potential therapeutic strategy for PTCL patients.

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Combination Therapies, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

419 | AFM13 ENHANCES THE ANTI-TUMOR ACTIVITY OF AB-101 TOWARDS CD30+ TUMORS, CONFERRING TUMOR GROWTH CONTROL IN VIVO

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Introduction: Bispecific antibodies targeting CD16A and a tumor antigen have the potential to specifically redirect the cytotoxic potential of NK cells towards cancer cells through antibody-dependent cellular cytotoxicity (ADCC). It has been demonstrated that the bispecific CD16AxCD30 innate cell engager AFM13 significantly enhances the cytotoxic activity of $CD16A^+$ NK cells towards $CD30^+$ tumor cells. Combination of AFM13 with adoptive NK cell transfer achieved unprecedented clinical response rates in patients with relapsed/refractory (R/R) Hodgkin lymphoma (ORR 94.2% for patients treated with RP2D), while maintaining a favorable toxicity profile. AB-101 is a non-engineered, allogeneic, off-the-shelf, cryopreserved cord blood-derived NK cell product, currently being tested in a Phase 1/2 clinical trial as monotherapy and in combination with rituximab in patients with R/R B cell NHL. AB-101 is optimized for ADCC through pre-selection for the KIR-B haplotype and the natural high-affinity variant of CD16A (158V/V).

In the present study, we investigated whether the combination of AFM13 with AB-101 leads to enhanced anti-tumor activity in vitro and in vivo.

Methods: Cellular cytotoxic activity was assessed in 4-h calcein-release cytotoxicity assays. Cell viability, degranulation/CD107a expression and IFN-γ production were measured by flow cytometry. Tumor growth control in vivo was determined in a hematologic (Karpas-299 $CD30^+$ T-cell lymphoma) human IL-15 NOG mouse xenograft model by whole body bioluminescence imaging.

Results: We demonstrate robust, homogenous binding of AFM13 to AB-101 as assessed by flow cytometry when AB-101 cells were combined with AFM13 after thawing. Overall, the binding pattern of AFM13 was congruent to the binding pattern of high CD16A expression on AB-101, suggesting saturated loading of CD16A molecules by AFM13 on the surface of AB-101. Combination with AFM13 enhanced the cytotoxic activity of AB-101 towards $CD30^+$ Karpas-299 tumor cells. AFM13-induced cytotoxic activity was associated with an increased functional activation status of AB-101, reflected by increased degranulation/CD107a expression and IFN-γ production in response to Karpas-299 tumor cells. Of note, viability of AB-101 cells was maintained upon exposure to AFM13 in the absence or presence of $CD30^+$ tumor cells. Importantly, adoptive transfer of AB-101 co-administered with AFM13 conferred tumor growth control in vivo in a human IL-15 NOG mouse xenograft model.

Conclusion: This study demonstrates synergistical anti-tumor activity in vivo for the combination of AFM13 and AB-101. Building on our clinical data with fresh cord blood-derived stimulated/expanded NK cells combined with AFM13 (NCT04074746), co-administration of cryopreserved AB-101 with AFM13 offers a promising highly scalable off-the-shelf immunotherapeutic treatment for patients with $CD30^+$ malignancies.

The research was funded by Affimed GmbH and Artiva Biotherapeutics

Keywords: Cellular therapies, Combination Therapies, Immunotherapy

Conflicts of interests pertinent to the abstract.

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PHASE I-II

420 | FINAL SAFETY AND EFFICACY RESULTS OF COPANLISIB MONOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY INHL: 6-YEAR FOLLOW-UP OF CHRONOS-1

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Introduction: The phosphatidylinositol 3-kinase inhibitor copanlisib was approved for use in the US in 2017 as monotherapy in patients with relapsed follicular lymphoma (FL) who have progressed after ≥2 therapies based on results from the Phase II CHRONOS-1 study in patients with relapsed or refractory indolent non-Hodgkin lymphoma (iNHL) (Dreyling et al. *J Clin Oncol* 2017). Here, we describe efficacy and safety data at the 6-year follow-up.

Methods: CHRONOS-1 enrolled patients with FL, marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and Waldenström macroglobulinemia/lymphoplasmacytoid lymphoma (WM/LPL) who had received ≥2 therapies. Copanlisib 60 mg was administered intravenously on days 1, 8, and 15 of a 28-day cycle. The primary efficacy endpoint was objective response rate (ORR) per independent radiologic review (Cheson et al. *J Clin Oncol* 2007). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), and overall survival (OS). CTCAE v4.03 was used to grade adverse events (AEs).

Results: 142 patients with iNHL (104 FL, 23 MZL, 8 SLL, 6 WM/LPL, 1 other) received treatment. 99.3% of patients had discontinued treatment by the data cut-off (June 30, 2022). During follow-up, 74% of patients (n = 105) received ≥1 line of subsequent systemic anti-cancer therapy, including 46% of patients treated with rituximab-based regimens. ORR was 59.9% (n = 85) with complete responses in 23 patients (16.2%). Median DoR was 14.9 months (mos) (range 0–80.6). With a median follow-up of 14 mos (95% confidence interval [CI] 10.3, 20.7), median PFS was 11.3 mos (range 0–82.1) with a 2-year PFS rate of 33%. With a median follow-up of 82.3 mos (95% CI: 79.3, 84.2), median OS was 59.1 mos (73 events, range 0.2–100.6) with a 6-year OS rate of 45% (Figure). Median duration of treatment was 6.0 mos (range 0.23–81.0). Transformation to aggressive lymphoma (diffuse large B-cell lymphoma) was not observed. Treatment was discontinued primarily due to radiologic disease progression (35.2%; n = 50) and AEs not associated with clinical disease progression (28.2%; n = 40). Copanlisib safety data were consistent with the 2-year follow-up (Dreyling et al. *Am J Hematol* 2020). The most common treatment-emergent AEs (all grades/grades 3–4) were infusion-related hyperglycemia (50.7%/39.4%), diarrhea (35.9%/8.5%), hypertension (29.6%/23.9%), neutropenia (29.6%/24.7%), and pyrexia (26.8%/4.2%).

Conclusions: With 6 years of follow-up in CHRONOS-1, copanlisib continued to show durable responses in patients with relapsed or refractory iNHL. The safety profile remained manageable without evidence of late-onset severe toxicities or worsening treatment-emergent AEs. To our knowledge, these results constitute the most favorable OS observed to date in patients with iNHL having failed 2 or more prior treatments including an alkylating agent and rituximab.

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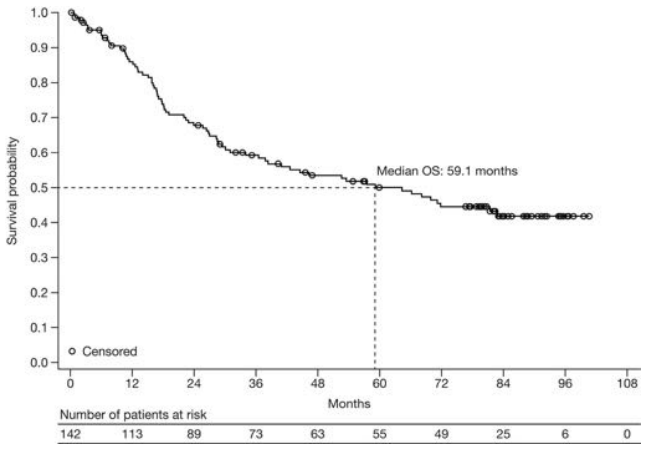
Keyword: Indolent non-Hodgkin lymphoma



Conflicts of interests pertinent to the abstract.

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Other remuneration: PATENTS, ROYALTIES, OTHER INTELLECTUAL PROPERTY: P201731067. Prognosis methods for patients with folicular lymphoma. España. 16/05/2017. FIBHUPH; PCT/ES2018/070463. Method for designing

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421 | A PHASE II, OPEN-LABEL, MULTICENTER STUDY OF CAPIVASERTIB, A POTENT, ORAL PAN-AKT INHIBITOR, IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN LYMPHOMA (CAPITAL)

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Introduction: The PI3K/AKT/mTOR pathway is an established therapeutic target in indolent B-cell non-Hodgkin lymphoma (B-NHL). Several PI3K inhibitors (PI3Ki) have been approved to treat relapsed/refractory (R/R) follicular lymphoma (FL) and marginal zone lymphoma (MZL). Nonetheless, potential class-specific and PI3K isoform-related toxicities may limit their clinical utility. Capivasertib is an oral, potent, selective pan-AKT inhibitor that has demonstrated evidence of survival benefit in phase 2 clinical studies in patients with solid tumors. Capivasertib has also shown a manageable safety profile and unlike PI3Ki, colitis or pneumonitis do not feature as noted toxicities. Here, we report preliminary safety and efficacy data from a phase II

study evaluating capivasertib in pts with R/R B-NHL (NCT05008055).

Methods: Eligible pts were adults (≥18 years) with R/R NHL including histologically confirmed FL, MZL, and mantle cell lymphoma (MCL). Pts received capivasertib 480 mg orally twice daily using an intermittent schedule of 4 days on/3 days off in 28-day cycles until disease progression or unacceptable toxicity. Response was assessed by investigators based on the modified Lugano Classification lymphoma response criteria (Cheson, et al. JCO 2014). Baseline PTEN status and genomics will be correlated with clinical efficacy.

Results: At data cut off (DCO; December 21, 2022), 15 pts with R/R B-NHL had been treated (histology: FL [$n = 11$], MZL [$n = 2$], MCL [$n = 2$]). Pts had a median age of 55 (range 40–87) years and had received a median of 3 prior lines of therapy (2–5), including prior PI3Ki ($n = 6$), and autologous stem cell transplant ($n = 1$). Six (40%) pts were refractory to their most recent therapy. Median follow-up for dosed pts was 5 (range 1–11) months. Treatment was ongoing in 9 (60%) pts. 11/13 pts with FL or MZL were evaluable for efficacy (FL 10/11, MZL 1/2). ORR was 54%; 8% of pts had a CR, 46% had a PR, 23% had SD, and 8% had PD. No response data are available for the MCL cohort because both pts were not evaluable at DCO. Grade ≥3 TEAEs occurred in 3 pts: COVID-19, QT prolongation, and rash; no grade ≥3 infections other than COVID-19 were reported. No immune-mediated adverse events or treatment-related deaths occurred. One (7%) pt discontinued due to TEAE (grade 3 QT prolongation). The most common TEAEs (≥25% of patients) were diarrhea (93%), fatigue (27%), and nausea (27%). Diarrhea events were all grade 1 (57%) or 2 (43%) and mainly occurred on dosing days.

Conclusions: Capivasertib demonstrated single-agent activity and a manageable safety profile in pts with heavily pretreated R/R FL. Notably, no immune-mediated events and no treatment-related deaths were observed. Capivasertib has the potential to be an alternative therapeutic option for pts with R/R B-NHL, with a non-overlapping safety profile compared to currently available PI3Ki.

Encore Abstract - previously submitted to EHA 2023

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Keywords: Indolent non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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422 | A PHASE 2 STUDY OF ZILOVERTAMAB VEDOTIN AS MONOTHERAPY OR IN COMBINATION IN PATIENTS (PTS) WITH AGGRESSIVE AND INDOLENT B-CELL MALIGNANCIES: WAVELINE-006

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Background: The transmembrane protein ROR1 is overexpressed in hematologic malignancies. Additionally, targeting Bruton tyrosine kinase (BTK) has been found to be a viable therapeutic option. Zilovertamab vedotin (ZV) is a humanized IgG1 monoclonal anti-ROR1, with a proteolytically cleavable linker and the antimicrotubule agent monomethyl auristatin E. Nemtabrutinib is a reversible inhibitor of BTK. With different mechanisms of action and nonoverlapping toxicities, the combination of ZV and a BTKi has the potential for improved responses in B-cell malignancies. The waveLINE-006 study (NCT05458297) will be conducted to investigate safety and efficacy of ZV in pts with B-cell malignancies, as monotherapy or in combination with nemtabrutinib.

Methods: Approximately 275 pts will be enrolled (cohorts A-F; see table). Pts ≥18 years old with biopsy-proven and/or histologically confirmed mantle cell lymphoma (MCL), Richter transformation (RT), chronic lymphocytic leukemia (CLL), or follicular lymphoma (FL), with relapsed or refractory (R/R) disease, ECOG performance status of 0 to 2, and adequate organ function are eligible. In cohorts A and B, patients will receive ZV 2.5 mg/kg IV Q3W. In cohort C, 30 patients will be enrolled in a safety run-in phase of ZV in combination with nemtabrutinib, then an additional 15 patients will receive the RP2D of the combination. Patients in cohort D (schedule optimization) will be randomly assigned 1:1 to receive ZV 2.5 mg/kg IV Q3W (arm 1) or ZV 2.0 mg/kg IV Q2/3W (arm 2). Patients in cohorts E and F (efficacy expansion) will receive the dose and schedule of ZV determined during schedule optimization. Each pt will receive ZV and/or nemtabrutinib until disease progression, unacceptable toxicity, or other discontinuation criteria are met. The primary end points are the safety and tolerability of ZV alone (cohort D) and in combination with nemtabrutinib (cohort C), and the objective response rate of ZV alone (cohorts A, B, D, E, and F) and in combination with nemtabrutinib (cohort C). The secondary end points are the duration of response of ZV alone (cohorts A, B, D, E, and F) and in combination with nemtabrutinib (cohort C) and the safety and tolerability of ZV alone (cohorts A, B, E, and F). Tumor scans will be performed at baseline, then Q12W up to week 108, and Q24W thereafter. Adverse events will be monitored and graded per NCI CTCAE v5. Enrollment is ongoing.

Cohort	Inclusion Criteria	n	Treatment
A	R/R MCL after ≥2 therapies including a BTKi and either received or was ineligible for CAR-T cell therapy	40	ZV 2.5 mg/kg IV Q3W
B	R/R RT after ≥1 prior therapy	50	
C	R/R MCL to ≥1 prior therapy and no prior exposure to noncovalent BTKi	45	ZV 2.0 to 2.5 mg/kg IV Q3W + Nemtabrutinib 65 mg PO QD
D	R/R CLL or FL after ≥2 prior therapies	80	ZV 2.5 mg/kg IV Q3W (arm 1) or ZV 2.0 mg/kg IV Q2/3W (arm 2)
E	R/R FL after ≥2 prior therapies	30	ZV on dose and schedule determined in cohort D
F	R/R CLL after ≥2 prior therapies	30	

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Indolent non-Hodgkin lymphoma, Ongoing Trials

Conflicts of interests pertinent to the abstract.

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423 | UPDATED FOLLOW-UP OF BELLWAVE-001: AN OPEN-LABEL, SINGLE-ARM, PHASE 1/2 STUDY OF THE EFFICACY AND SAFETY OF NEMTABRUTINIB FOR THE TREATMENT OF B-CELL MALIGNANCIES

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Background: Bruton tyrosine kinase inhibitors (BTKis) are standard of care for chronic lymphocytic leukemia/small lymphocytic

lymphoma (CLL/SLL), but resistance can develop, most commonly because of BTK mutations. Nemtabrutinib inhibits both wild-type and C481S-mutant BTK. Initial results from the phase 1/2 BELLWAVE-001 study (NCT03162536) showed that the recommended phase 2 dose (RP2D) of nemtabrutinib (65 mg QD) had a manageable safety profile and promising antitumor activity in heavily pretreated patients (pts) with relapsed or refractory (R/R) CLL/SLL, including pts whose disease progressed after prior covalent BTKis. We present updated analyses on the efficacy and safety of the RP2D of nemtabrutinib in pts with hematologic malignancies.

Methods: Pts with CLL/SLL were enrolled in cohort A (R/R CLL/SLL with ≥2 prior therapies, including a covalent BTKi, with C481-mutated BTK) or cohort B (R/R CLL/SLL with ≥2 prior therapies, intolerant to a BTKi, without C481-mutated BTK) and pts with B-cell non-Hodgkin lymphoma were enrolled in cohorts C-I. Pts received nemtabrutinib 65 mg QD until unacceptable toxicity, disease progression, or other discontinuation criteria were met. Primary end points were ORR (for CLL/SLL pts, per 2018 iwCLL criteria by investigator), and RP2D. Secondary end points were DOR and safety. Efficacy and safety analyses included all pts who received ≥1 dose of nemtabrutinib.

Results: 112 pts were enrolled and treated with nemtabrutinib 65 mg; 57 had CLL/SLL. Among pts with CLL/SLL, median age was 66 years (range, 45–86), 16 (28%) were female, and 51 (89%) had ECOG PS ≤1. Among pts with CLL/SLL, the median number of prior lines of therapy was 4 (range, 2–18), all pts received prior BTKi therapy, 27 (47%) received prior BTKi and BCL2i therapy, and 36 (63%) had C481S-mutated BTK. At data cutoff (October 28, 2022), median follow-up for pts with CLL/SLL treated with nemtabrutinib 65 mg was 9.4 months (range, 0.1–45.5). Among pts with CLL/SLL treated with nemtabrutinib 65 mg, 32 had an objective response (ORR, 56% [95% CI, 42–69]; 2 CR; 15 PR; 15 PR with residual lymphocytosis [PR-L]); median DOR was 26.0 months (95% CI, 13.9-not reached [NR]). ORR for pts in cohorts A ($n = 25$) and B ($n = 10$) were 56% (95% CI, 35–76; 4 PR; 10 PR-L) and 40% (95% CI, 12–74; 1 CR; 2 PR; 1 PR-L), respectively; median DOR was 16.6 months (95% CI, 5.7–26.0) and NR, respectively. Among all pts with hematological malignancies treated with nemtabrutinib 65 mg, 82 (73%) had any-grade treatment-related AEs, most common (≥15%) were dysgeusia (21%) and decreased neutrophil count (20%). Grade 3 or 4 treatment-related AEs occurred in 47 pts (42%); most commonly (≥5%) decreased neutrophil count (17%) and decreased platelet count (7%). No deaths were attributed to treatment.

Conclusion: With ~9 months of follow-up, nemtabrutinib 65 mg QD continued to show antitumor activity with manageable safety in pts with R/R CLL/SLL.

The research was funded by: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chronic Lymphocytic Leukemia (CLL), Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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424 | PHASE 1 TRIAL OF KT-333, A STAT3 DEGRADER, IN PATIENTS WITH RELAPSED OR REFRACTORY LYMPHOMAS, LARGE GRANULAR LYMPHOCYTIC LEUKEMIA AND SOLID TUMORS

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Background: KT-333 is a first-in-class, potent, highly selective, heterobifunctional small molecule degrader of the signal transducer and activator of transcription 3 (STAT3) protein. Aberrant activation of STAT3 resulting from activating mutations or deregulated cytokine signaling is known to underlie a variety of malignancies including peripheral T-cell lymphomas (PTCL), cutaneous T-cell lymphoma (CTCL), and large granular lymphocytic leukemia (LGL-L). However, selective targeting of STAT3 has been a therapeutic challenge. In preclinical xenograft studies, treatment with KT-333 resulted in durable tumor regressions in STAT3-dependent T cell lymphomas. Pharmacokinetic (PK) and pharmacodynamic (PD) analysis demonstrated that STAT3 degradation of >90% in tumor for 48 h is required for anti-tumor efficacy.

Methods: The ongoing multicenter Phase 1a/1b study evaluates the safety, tolerability, PK, PD and preliminary clinical activity of KT-333 administered as a weekly IV infusion in 28-day cycles. The Phase 1a will identify the recommended phase 2 dose based on dose limiting toxicity (DLT) observed in Cycle 1. Eligible patients include those with advanced solid tumors and relapsed or refractory B- and T-cell lymphomas, Hodgkin's lymphoma, and LGL leukemia. Serial blood samples are collected in Cycle 1 and Cycle 2 to measure KT-333 plasma concentrations and STAT3 protein expression in PBMCs (using targeted mass spectrometry). STAT3 degradation and the impact on tumor biology is measured in patients with accessible tumors.

Results: As of February 3, 2023, seven patients have been treated in the first two dose levels (DLs) in Phase 1a, including patients with CTCL and PTCL with median age of 65 (range 57, 74) and performance status of 0 ($n = 1$) and 1 ($n = 6$). No DLTs have been observed and no patients have discontinued KT-333 due to an adverse event. The most common adverse events are Grade 1 and 2 and include constipation, fatigue, abdominal pain, dizziness, and nausea. PD data in blood demonstrated robust and sustained STAT3 degradation with mean maximum decrease of PBMC STAT3 levels after dosing on Days 1 and 8 of 66% in DL1 ($n = 4$) and 70% in DL2 ($n = 2$). PK results were in line with the modeled predictions.

Conclusion: The emerging clinical data suggest that KT-333 is a potent degrader of STAT3 as demonstrated in PBMCs at doses that are well tolerated. These data provide the first evidence of STAT3 targeted protein degradation in humans and point to the potential of

heterobifunctional degraders for targeting previously undruggable targets. It is projected that higher doses of KT-333 will achieve the predicted degradation profile in tumors that may translate into clinical benefit in patients with STAT3-dependent T cell malignancies. Accrual into the study is ongoing, and analyses from additional patients will be presented at the meeting.

The research was funded by: Kymera Therapeutics

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Cutaneous non-Hodgkin lymphoma, Therapeutics and Clinical Trials in Lymphoma

Conflicts of interests pertinent to the abstract.

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425 | ENCOURAGING COMPLETE RESPONSES (CRS) WITH CDK9 INHIBITOR AZD4573 IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) PERIPHERAL T-CELL LYMPHOMA (PTCL): EARLY TRIAL ANALYSIS

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Introduction: Pts with r/r PTCL have limited treatment options and poor outcomes to standard of care therapy. CDK9 regulates transcription elongation through phosphorylation of RNA polymerase II. AZD4573 is a highly potent and selective CDK9 inhibitor that downregulates short-lived transcripts and labile proteins such as MCL1, BFL1, and MYC, which are overexpressed in haematologic tumours including T cell lymphoma. Preclinical studies demonstrate that AZD4573 induces apoptosis and inhibits tumour growth of PTCL cell lines and patient samples in vitro and in vivo (Cidado, CCR 2020;26:922–34). In a phase 1, first-in-human study in pts with haematologic cancers, the recommended phase 2 dose of AZD4573 monotherapy was 12 mg IV QW (Brümmendorf, ASH 2022, abs 1353). Here we report the efficacy and safety of AZD4573 monotherapy in a phase 2a study of pts with r/r PTCL (NCT05140382).
Methods: Pts in this single-arm, open-label study were ≥18 years old, had ECOG PS ≤2, and ≥1 prior line of therapy including an alkylating agent and/or anthracycline. Primary cutaneous and primary leukemic PTCL subtypes were excluded. Each pt received an intra-pt ramp-up of AZD4573: 6 mg on day 1, 9 mg on day 8, then the target dose of 12 mg on day 15, continuing QW thereafter. The primary objective was efficacy by investigator-assessed ORR (Lugano 2014 criteria); secondary objectives included efficacy by complete response (CR) rate, duration of response, progression-free survival and overall survival; safety and tolerability; and pharmacokinetics (PK).
Results: Eighteen pts received AZD4573; median age was 63.0 years (range 45–83), 66.7% were male and median number of prior regimens was 3.0 (range: 1–9). At the 1 Feb 2023 data cutoff, efficacy was evaluable in 12 pts who had received at least one 12 mg dose. The ORR was 3/12 (25.0%, all CRs) in the efficacy-evaluable set (Table). The CRs lasted 7.7 wks to 17.4+ wks. An additional complete metabolic response (CMR) was observed in a pt after initial progressive disease (PD). Safety was evaluable in 18 pts who received ≥1 dose. Treatment-emergent adverse events (TEAEs) occurred in 16 pts (88.9%), all of which were Grade ≥3. Key Grade ≥3 TEAEs were

neutropenia (55.6%) and increased AST (22.2%). Two pts (11.2%) discontinued due to TEAEs (hospitalisation and septic shock, $n = 1$ each). Serious TEAEs were reported in 72.2% and were deemed treatment-related by investigators in 61.1%. Grade 5 treatment-related AEs were reported in 2 pts (11.1%, both septic shock). AZD4573 exhibited linear PK (half-life ~6 hrs) with dose-dependent increases in C_{max} and AUC.

Conclusions: Preliminary results show encouraging clinical activity with AZD4573 monotherapy in pts with r/r PTCL, including 3 CRs and one CMR after initial PD. Safety and PK profiles are consistent with the phase 1 study with no unexpected findings, and the study continues to expand in the PTCL population. Previously submitted to EHA 2023.

Table. Complete response rates.

	Complete response rate, n/total evaluable (%)
Intention-to-treat population	3/18 (16.7)
Patient completed ≥1 intended dose (12 mg)	3/12 (25.0)
Patient completed ≥2 cycles of treatment	3/5 (60.0)

Encore Abstract - previously submitted to EHA 2023

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Keywords: Aggressive T-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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426 | PROOF OF CONCEPT OF NX-2127, A FIRST-IN-CLASS BRUTON'S TYROSINE KINASE (BTK) DUAL-TARGETED PROTEIN DEGRADER WITH IMMUNOMODULATORY ACTIVITY, IN PATIENTS WITH DLBCL

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Introduction: Despite advances in cell- and immune-based therapies, relapsed diffuse large B cell lymphoma (DLBCL) remains a high unmet medical need. Preclinical data suggest that drugs modulating E3 ligases may synergize with BTK inhibition in certain subtypes of DLBCL [Yang et al. 2012]. Combination therapy with ibrutinib, lenalidomide and rituximab demonstrated clinical activity in recurrent DLBCL [Goy et al. 2019], and ibrutinib + lenalidomide + R-CHOP was effective in de novo DLBCL [Westin et al. 2023]. BTK degradation may further potentiate anti-tumor activity by modulating protein non-kinase function (e.g., scaffolding). NX-2127 is an oral, first-in-class, dual-function small molecule degrader that combines the activity of a targeted BTK degrader with the immunomodulatory activity of an Ikaros and Aiolos degrader. Preliminary safety of NX-2127 in all patients and efficacy in patients with chronic lymphocytic leukemia (CLL) have been presented [Mato et al. 2022]. Here we report overall safety and initial findings of activity in patients with non-germinal center B cell (non-GCB) DLBCL.

Methods: NX-2127-001 (NCT04830137) is a first-in-human, multicenter, US-based, open-label, phase 1 dose-escalation (phase 1a) and cohort-expansion (phase 1b) trial, evaluating the safety, tolerability, and preliminary efficacy of NX-2127 in adults with relapsed/refractory B cell malignancies, including CLL, DLBCL, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, and Waldenstrom's macroglobulinemia. NX-2127 is administered orally once daily in 28-day cycles starting at 100 mg.

Results: As of 21 September 2022, 36 patients have been enrolled at 100, 200 and 300 mg dose levels. Patients were predominantly male (63.9%) with a median age of 75 (range 50–92) years and a median of 4 (range 2–11) prior lines of therapy. The most common all-grade adverse events were fatigue (52.8%), neutropenia (38.9%), and contusion (27.8%). Adverse events resulting in treatment discontinuation included: atrial fibrillation ($n = 3$), cognitive disorder ($n = 2$), anemia ($n = 1$), confusional state ($n = 1$), fatigue ($n = 1$), pain in extremity ($n = 1$), and ventricular tachycardia ($n = 1$). NX-2127 led to robust BTK degradation of >80% across dose levels and degradation of cereblon neosubstrates. Two patients with non-GCB DLBCL were enrolled: one patient experienced stable disease followed by progressive disease at the 100 mg dose; a second patient with four prior lines of therapy experienced complete response at the 300 mg dose at the time of first response assessment (week 8), which was maintained at week 16.

Conclusions: In this first-in-human, first-in-class study of a BTK degrader, NX-2127 was well tolerated and showed promising activity in a patient with non-GCB DLBCL. These data support further clinical development of NX-2127 in B cell lymphoid malignancies including DLBCL.

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Keyword: Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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427 | ZILOVERTAMAB VEDOTIN (MK-2140) IN RELAPSED OR REFRACTORY (R/R) NON-HODGKIN LYMPHOMA (NHL): 14-MONTH FOLLOW-UP OF THE PHASE 1 WAVELINE-001 STUDY

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Introduction: The ROR1-targeting antibody-drug conjugate zilovertamab vedotin (ZV) had a manageable safety profile and promising antitumor activity in patients (pts) with R/R NHL in the phase 1 waveLINE-001 study (NCT03833180). We present updated results after 14 months of follow-up for pts with diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and Richter transformation (RT).

Methods: Eligible pts were ≥18 y; had a histologic diagnosis of NHL and an ECOG PS of 0–2. Pts must have had disease progression during or relapse after prior systemic therapy. waveLINE-001 includes 3 dosing schedules; schedule 1 data are presented. Pts received ZV IV at a starting dose of 0.5 mg/kg Q3W increasing to 2.5 mg/kg using an accelerated 3 + 3 dose escalation. Primary end point was MTD and/or the recommended dosing regimen (RDR). Safety, ORR, DOR, PFS, and OS were secondary.

Results: 56 pts were enrolled in schedule 1, of whom 30 received ZV at the previously established RDR (2.5 mg/kg). Median follow-up at data cutoff (Nov 27, 2022) was 14.3 mo (range, 0.5–44.2). Median age was 70.0 y, 59% of pts were male, 48% had an ECOG PS of 0. Pts with DLBCL (n = 17) received a median (range) of 4 (1–9) prior lines of therapy, 71% received prior CAR-T or CAR-NK and 47% had germinal center B cell–like subtype. Pts with MCL (n = 17) received a median (range) of 4 (1–9) prior lines of therapy and none received prior CAR-T or CAR-NK. 71% of MCL pts were Ann Arbor stage IV and 53% had mutated TP53. Pts with RT (n = 7) received a median (range) of 6 (1–10) prior therapies, and all had the DLBCL subtype. Any-cause AEs occurred in 54 pts (96%). Treatment-related AEs occurred in 41 pts (73%). Grade 3/4 treatment-related AEs occurred in 27 pts (48%), most frequently (≥10%) neutrophil count decreased (32%) and platelet count decreased (11%). No pts died because of a treatment-related AE. Peripheral neuropathy occurred in 27 pts (48%). No infusion-related reactions or tumor lysis syndrome occurred. Any-cause AEs led to discontinuation of ZV in 12 pts (21%) and interruption or reduction of ZV in 24 (43%). ORR was 29%, 53%, and 57% for pts with DLBCL, MCL, and RT respectively. ORR (95% CI) for pts with MCL and mutated TP53 was 44% (14–79). Additional efficacy results are in the table.

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	All n = 56	DLBCL n = 17	MCL n = 17	RT n = 7
ORR (95% CI), %	32 (20–46)	29 (10–56)	53 (28–77)	57 (18–90)
CR, n (%)	6 (11)	3 (18)	2 (12)	1 (14)
PR, n (%)	12 (21)	2 (12)	7 (41)	3 (43)
DOR, median (range), mo	n = 18 9.6 (0.0–21.5)	n = 5 4.6 (2.9–21.5)	n = 9 10.0 (0.0–20.3)	n = 4 2.8 (0.0–2.8)
PFS, median (95% CI), mo	4.5 (3.9–7.5)	3.9 (0.7–7.0)	11.4 (4.0–NR)	4.7 (0.7–NR)
OS, median (95% CI), mo	20.1 (10.1–NR)	9.1 (2.7–NR)	18.0 (7.1–NR)	19.4 (2.7–NR)

Conclusion: After 14 months of follow-up, ZV had a manageable safety profile and promising antitumor activity in pts with heavily pretreated DLBCL, MCL, and RT. These results are consistent with prior findings of waveLINE-001 and support continued investigation of ZV in NHL.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chronic Lymphocytic Leukemia (CLL), Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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428 | ROBUST BRUTON'S TYROSINE KINASE (BTK) DEGRADATION WITH NX-5948, AN ORAL BTK DEGRADER, IN A FIRST-IN-HUMAN PHASE 1A TRIAL IN RELAPSED/REFRACTORY B CELL MALIGNANCIES

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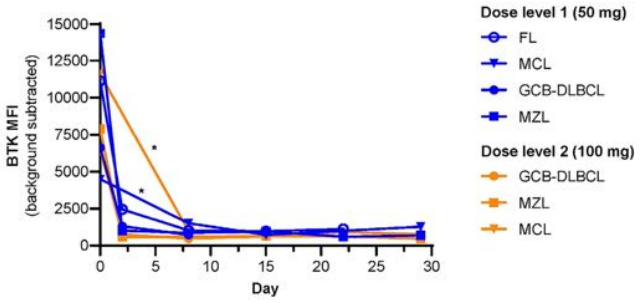
Introduction: Although BTK inhibitors are widely used for treating B cell malignancies, acquired resistance mutations represent a growing clinical challenge. NX-5948 is a novel oral small molecule that induces BTK degradation via recruitment of the cereblon E3 ligase complex. NX-5948 is being evaluated as treatment for tumors with resistance to BTK inhibitors or in B cell indications where treatment with BTK inhibitors is less effective. NX-5948 induces sub-nanomolar potency degradation of wild-type and mutant BTK in vitro, demonstrating rapid in vivo degradation in mouse and non-human primate B cells within 2 h of oral administration. NX-5948 crosses the blood-brain barrier and degrades BTK intracranially, translating to preclinical efficacy in brain lymphoma disease models. Here we report preliminary PK/PD findings from a phase 1a trial of NX-5948 in B cell malignancies.

Methods: NX-5948-301 is a first-in-human, dose-escalation (phase 1a) and cohort-expansion (phase 1b) study designed to evaluate the safety, tolerability, and clinical activity of NX-5948 in relapsed/refractory B cell malignancies (NCT05131022). Phase 1a will evaluate safety and tolerability of NX-5948 in patients (pts) with relapsed/refractory CLL, SLL, non-GCB DLBCL, FL, MCL, MZL, and WM, including those with secondary CNS involvement in any disease indication plus PCNSL. Key eligibility criteria: ≥2 prior lines of therapy; measurable or other evaluable disease per indication specific response criteria; ECOG PS 0–1. NX-5948 is given orally, once daily, with dose escalation (3+3 design). Approximately 110 pts (30 in phase 1a, 80 in phase 1b) may be enrolled and treated until confirmed disease progression or unacceptable toxicity. Pharmacokinetic parameters are generated using non-compartmental analysis. Pharmacodynamic biomarkers are assessed in whole blood longitudinally using a 10-color flow cytometry assay designed to quantify BTK.

Results: As of Dec 1, 2022, 7 pts have been enrolled in phase 1a and received NX-5948 at 50 mg (n = 4) or 100 mg (n = 3). Baseline demographics/disease characteristics: median age 59.0 (range 46.0–79.0) years; male/female 57.1%/42.9%; white 100%; ECOG PS 0/1 42.9%/57.1%; median time since diagnosis 7.6 (range 2.9–23.5) years. Primary diagnosis: DLBCL (n = 2), MCL (n = 2), MZL (n = 2), FL (n = 1). Most pts (n = 6) have received ≥4 prior lines of therapy. NX-5948 exhibited dose-proportional PK, with a half-life of ~12 h, and a T_{max} of 2–3 h. Rapid, robust and sustained BTK degradation was observed in all pts dosed, regardless of their absolute BTK starting level, tumor type, or dose level of NX-5948.

Summary/conclusion: Preliminary findings suggest that NX-5948 exhibits dose-proportional PK and supports daily dosing, resulting in rapid, robust and sustained BTK degradation. Additional indications, including CLL, and additional dosing levels are currently being explored.

Figure. Flow cytometry analysis of BTK expression in patients treated with NX-5948



*Day 2 data for two patients not available for analysis at time of submission

FL (follicular lymphoma), GCB-DLBCL (germinal center B cell diffuse large B cell lymphoma), MCL (mantle cell lymphoma), MZL (marginal zone lymphoma)

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Conflicts of interests pertinent to the abstract.

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429 | HIGHLY SELECTIVE ALLOSTERIC MODULATOR OF THE PHOSPHOINOSITIDE 3-KINASE DELTA (PI3Kδ) ROGINOLISIB IN PATIENTS WITH REFRACTORY/RELAPSED FOLLICULAR LYMPHOMA

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Introduction: PI3Kδ inhibitors are very active in patients with lymphomas, but their clinical development has been hampered by toxicity (Brown et al, Lancet Oncol 2022). Roginolisib (IOA-244) exerts an allosteric modulation of the PI3Kδ C terminus and functions as a non-ATP competitive PI3Kδ inhibitor, delivering a selective inhibition without off-target effects typically seen with other PI3K inhibitors (Johnson et al, Cancer Res Commun 2023). Using the recommended phase 2 dose (RP2D) of 80 mg QD established in solid tumors patients, patients with refractory/relapsed (r/r) follicular lymphoma (FL) were treated to investigate its safety profile in pts with hematologic malignancies (NCT04328844).
Methods: In Part A of the FiH dose escalation study, roginolisib was investigated at 20 and 80 mg QD in pts with r/r FL. Primary objective: safety of the RP2D established in solid tumor pts. Secondary objectives: PK; PD (e.g., changes in immune cell subsets in peripheral blood); Lugano-based responses; PFS and OS. Roginolisib was in vitro combined with 474 other compounds (each given at 5μM, over 72 hrs) in two cell lines (mantle cell lymphoma SP-53; cutaneous T cell lymphoma HH) to look for combination partners.
Results: In Part A for pts with r/r FL, there were two cohorts: (a) Cohort 1: 20 mg QD daily (4/4; 2 female, 2 male); (b) Cohort 2: 80 mg QD (4/4; 3 female, 1 male). There were no DLT observed and no dose modifications were needed. The mean time on treatment was 1.9 months (20 mg QD) and 3.7 months (80 mg QD), with one patient at the 80 mg still on treatment after 6 mo. More than 4 prior lines of treatment were in 3/8 pts. Transient (lasting less than 48 hrs) platelet reduction (G3) and AST/ALT elevation (G3) were observed in 2/8 pts, which improved while pts continued without a treatment intervention, such as dose modification or medical treatment with steroids. Lugano-based PRs were observed in 2/4 pts at the 80 mg QD dose and none at the 20 mg QD. At the 80 mg QD dose a third pt had a clinical response manifested by improvement in night sweats and fever, reduction in cervical palpable lymph nodes and relief from chronic pleural effusion. This clinical improvement lasted less than 5 weeks.
The in vitro screen identified various roginolisib-containing combinations with synergistic anti-proliferative activity. Active combination partners included BCL2 and HDAC inhibitors and chemotherapy agents.
Conclusions: The safety profile of roginolisib in pts with r/r FL appears to match that in pts with solid malignancies. In contrast to other PI3Kδ inhibitors, roginolisib is highly selective for binding to PI3Kδ, favoring an inactive confirmation of PI3Kδ and functions as a non-ATP competitive inhibitor. The observed early signs of clinical activity are promising, alongside the reported non-clinical data on selectivity and combination possibilities.

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430 | LIPOSOMAL DOXORUBICIN SUPERCHARGE-CONTAINING FRONTLINE TREATMENT FOR DIFFUSE LARGE B-CELL LYMPHOMA OR CLASSICAL HODGKIN LYMPHOMA: PRELIMINARY RESULTS OF A PHASE II STUDY

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Myocet™ is doxorubicin encapsulated in a non-pegylated liposomal membrane of phosphatidylcholine and cholesterol (NPLD) that spares the heart muscle from the direct cytotoxic drug. NPLD was suggested for the treatment of elderly or cardiopathic patients with DLBCL or c-HL, instead of hydroxydaunorubicin, constituting new regimens of R-COMP (Rituximab, cyclophosphamide, NPLD and vincristine) and MBVD (NPLD, bleomycin, vinblastine and dacarbazine) respectively. We designed a dose-intensified (DI) version of both R-COMP and MBVD scheme by using a supercharge dose of NPLD (named R-COMP-DI and MBVD-DI). In this prospective study, patients with newly diagnosed advanced-stage DLBCL received R-COMP-DI for a total of 3 cycles followed by 3 cycles of R-COMP (with NPLD at standard dose), and patients with newly diagnosed advanced-stage c-HL received MBVD-DI for a total of 2 cycles followed by 4 cycles of MBVD (with NPLD at standard dose). The primary end-point was the activity of this strategy in terms of interim-FDG-PET negativity (according to the Deauville scale [DS] 5-point scoring system). Secondary end-points were end-of-treatment (EoT) responses, toxicity (including cardiologic side-effects by using the echocardiography [ECG] assessment of global systolic longitudinal myocardial strain [GLS], as well as left ventricular ejection fraction [LVEF]), feasibility and Progression Free survival (PFS).

In this phase II study (2016–2022), 92 adult patients, admitted to the Federico II Hematology Department, with advanced-stage DLBCL ($n = 60$) and c-HL ($n = 32$) received front-line R-COMP-DI and MBVD-DI. In R-COMP-DI, 70 mg/m^2 of NPLD was employed for 3 cycles (followed by 3 cycles with NPLD de-escalated at 50 mg/m^2); MBVD-DI consisted of 35 mg/m^2 of NPLD for 2 cycles (followed by 4 cycles with NPLD de-escalated at 25 mg/m^2). Patients underwent R-COMP-DI and MBVD-DI with a median dose intensity of 91% and 94%, respectively. At interim-FDG-PET, 81/92 patients (one failed to undergo interim-FDG-PET due to early death) had a Deauville score of ≤3 reaching the primary end-point of the trial in terms of complete response incidence at interim imaging assessment with a Complete Metabolic response rate significantly higher (89% [95% CI: 83%–96%]; $p = 0.0015$) than the pre-specified minimum efficacy threshold. At end of treatment, 90% of patients reached complete responses. In all, 20 patients had Grade ≥3 adverse events, and four of them required hospitalization. According to the definition of cardiotoxicity for cancer treatment of ESC, there were very small changes, i.e. <10% point reductions in median values of GLS and LVEF at interim, EoT and 6-month follow-up, when they were compared with the median values at baseline. At a median 21-months of follow-up, the progression-free survival of the entire population was 77.3% (95% confidence interval 68%–88%). Our data suggest that the NPLD supercharge-driven strategy in high-risk DLBCL/c-HL may be a promising option to test in phase III trials, for improving negative interim-FDG-PET cases incidence.

Keyword: Chemotherapy

No conflicts of interests pertinent to the abstract.

431 | PHASE 2 KEYNOTE-B68 STUDY: PEMBROLIZUMAB EVERY 6 WEEKS IN RELAPSED/REFRACTORY (R/R) CLASSICAL HODGKIN LYMPHOMA (CHL) OR PRIMARY MEDIASTINAL B-CELL LYMPHOMA (PMBCL)

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Table. Main efficacy results of liposomal doxorubicin supercharge-based front-line strategy for advanced-stage DLBCL or c-HL.

	Total	R-COMP-(DI)	MBVD-(DI)
Patients	92	60	32
At interim			
i-FDG-PET cases	91	59	32
Negative	82/91 (89) [82-95]	51/60 (85) [75-95]	31/32 (96) [89-100]
Positive	9 (10) [3-17]	8 (13) [4-22]	1 (4)
Not done	1 (1)	1 (2)	0
At the end-of-treatment			
EoT-FDG-PET cases	90	58	32
CR	82/91 (90) [83-96]	51/58 (87) [78-96]	31/32 (96) [89-100]
PR	2 (2.5)	1 (2)	1 (4)
PD	4 (5)	4 (8)	0
Not done	2 (2.5)	2 (4)	0

Data are reported as n (%) [CI%] if not indicated otherwise.

DLBCL: Diffuse large B-cell lymphoma; c-HL: Classic-Hodgkin lymphoma; R-COMP-(DI): Rituximab, Cyclophosphamide, MyocetTM, Vincristine and Prednisone (dose-intensified); MBVD-(DI): MyocetTM, Bleomycin, Vinblastine and Dacarbazine (dose-intensified); CI: Confidence interval; i-FDG-PET: interim-2-deoxy-2[F-18] fluoro-D-glucose positron emission tomography; EoT: end-of-treatment; CR: complete response; PD: disease progression; PR: partial response.

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Introduction: Pembrolizumab (pembro) was originally approved by the FDA for the treatment of R/R cHL and R/R PMBCL at 200 mg every 3 weeks (Q3W). Recently, the FDA granted accelerated approval for pembro 400 mg Q6W in all approved indications based on data from solid tumors. The open-label, single-arm, phase 2 KEYNOTE-B68 study (NCT04875195) is evaluating the efficacy and safety of pembro 400 mg Q6W in patients (pts) with R/R cHL or R/R PMBCL. Results after 9 months of follow-up are presented.

Methods: Pts were ≥18 y old, had histologically confirmed cHL or PMBCL, measurable disease per Lugano criteria, an ECOG PS of 0 or 1, and no prior anti–PD-1 therapy. Pts with cHL must have either relapsed during their last regimen for cHL or within 12 months after completing their last regimen, or had relapsed after or failed to respond to ≥1 prior line of multiagent therapy or autologous stem cell transplant (ASCT). Pts with PMBCL must have relapsed after or failed to respond to ASCT, or if ineligible for ASCT, must have relapsed after or failed to respond to ≥2 prior lines of therapy including rituximab. All pts received pembro 400 mg Q6W for ≤18 cycles or until progressive disease (PD), unacceptable toxicity, or withdrawal. The primary end point was ORR per Lugano criteria by investigator review. Secondary end points were DOR and safety. PFS and OS were exploratory.

Results: At data cutoff (Oct 18, 2022), 66 pts had been enrolled (R/R cHL, $n = 60$; R/R PMBCL, $n = 6$). Median follow-up was 8.9 mo (range, 1–15.9) for pts with R/R cHL and 10.6 mo (range, 5.1–15.4) for R/R PMBCL. ORR was 65% (95% CI, 51.6–76.9; 20 CR/19 PR) for pts with R/R cHL and 50% (95% CI, 11.8–88.2; 2 CR/1 PR) for R/R PMBCL. Median DOR was NR (range, 0.0+ to 8.6+) for pts with R/R cHL and 9.7 mo (range, 2.6–9.7) for R/R PMBCL. Additional efficacy data are summarized in the table. Treatment-related AEs occurred in 24 pts (40%) with R/R cHL and 2 (33.3%) with R/R PMBCL; grade ≥3 treatment-related AEs occurred in 3 pts (5%) and 1 pt (16.7%), respectively. No grade 5 treatment-related AEs occurred. Immune-mediated AEs were reported in 13 pts (21.7%) with R/R cHL and 1 pt (16.7%) with R/R PMBCL; 2 pts (3.3%) with R/R cHL had grade ≥3 immune-mediated AEs (1 grade 3 infusion reaction; 1 grade 3 severe skin reaction).

	cHL n = 60	PMBCL n = 6
ORR, n (% [95% CI])	39 (65.0 [51.6-76.9])	3 (50.0 [11.8-88.2])
CR	20 (33.3)	2 (33.3)
PR	19 (31.7)	1 (16.7)
DOR, median (range), mo*	NR (0.0+ to 8.6+)	9.7 (2.6-9.7)
9-mo DOR, %	NR	66.7
OS, median (95% CI), mo*	NR (NR-NR)	NR (0.1-NR)
12-mo OS, %	91.8	62.5
PFS, median (95% CI), mo*	6.3 (5.6-NR)	4.1 (0.1-NR)
12-mo PFS, %	37.9	33.3

NR, not reached; *Kaplan-Meier estimate; "+" no PD at last assessment.

Conclusions: With approximately 9 mo of follow-up, pembro 400 mg Q6W had robust antitumor activity in pts with R/R cHL and R/R PMBCL, with ORR similar to that with pembro 200 mg Q3W. No new safety signals were reported. These results support the use of pembro 400 mg Q6W in hematologic indications.

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Conflicts of interests pertinent to the abstract.

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432 | RESPONSE-ADAPTED MOSUNETUZUMAB FOR UNTREATED FOLLICULAR AND MARGINAL ZONE LYMPHOMAS: SIGNIFICANT MONOTHERAPY ACTIVITY SEEN IN RESULTS OF AN INTERIM EFFICACY ANALYSIS

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Introduction: Mosunetuzumab (mosun) is a CD3:CD20 bispecific antibody that has been FDA-approved for relapsed/refractory follicular lymphoma after two prior lines of therapy. We hypothesized that mosun would be even more active in patients (pts) without prior lymphotoxic therapy. Therefore, we designed a response adapted study for pts with untreated follicular lymphoma (FL) and marginal zone lymphoma (MZL).

Methods: This is a single center, open label, investigator initiated clinical trial in untreated pts with FL or MZL with indication for treatment. Pts received subcutaneous mosunetuzumab monotherapy for 8 cycles (21 day cycle, Part A) employing step up dosing in cycle 1 (5 mg, 45 mg, 45 mg). A PET/CT was performed after 8 cycles, and pts in CR were observed without further treatment. Pts with SD or PR could receive 6 cycles (21 day cycle, Part B) of polatuzumab vedotin and obinutuzumab, followed by an end of treatment (EOT) PET/CT. Total planned accrual is 42 pts. The primary endpoint is complete response (CR) rate. A pre-planned interim efficacy analysis is being performed after 20 enrolled pts. If 14 or fewer of the first 20 subjects do not achieve an objective response, the study will be suspended to enrollment.

Results: 20 pts enrolled on study between March 24, 2022, and March 11, 2023, and as of the submission date 17 pts are evaluable for safety, and 15 pts are evaluable for efficacy. Patient characteristics are listed in the table. All treatment was delivered as an outpatient. Two pts experienced SAEs (one pt with G3 lung infection followed by G3 shingles, and one pt observed overnight with G1 cytokine release syndrome (CRS). The only other G3 AE observed was diarrhea (1, 6%). Seven (41%) pts experience G1 CRS, with no G2 or higher CRS observed or any grade ICANS observed. No pts required tocilizumab. All CRS events occurred during cycle 1. No heme toxicity greater than Grade 1 was observed (neutropenia 12%, anemia 6%, thrombocytopenia 59%). Three (18%) pts experienced a treatment delay due to G2 hyperglycemia, G2 upper respiratory infection, and G3 pneumonia. No dose modifications were required and all pts have received expected doses of mosun. Nearly all pts (94%) experienced at least one injection site reaction, which were all G1. Since 14/15 (93%) pts so far have achieved an objective response at any time point meeting the interim efficacy threshold, the study is proceeding with total enrollment of up to 42 pts. Among patients who have received all 8 cycles of mosun, 9/11 (82%) have achieved a CR. All pts remain alive and progression-free. Updated data will be presented at the meeting.

Patient Characteristic	N = 20
Age, median (range)	63 (42-83)
Age Category, n (%)	
<60yr	7 (35%)
≥60yr	13 (65%)
Gender, n (%)	
Female	9 (45%)
Male	11 (55)
Baseline disease characteristics, n (%)	
Stage at Diagnosis, n (%)	
I	0 (0%)
II	1 (5%)
III	8 (40%)
IV	11 (55%)
Histology	
Follicular lymphoma, grade 1-2	15 (75%)
Follicular lymphoma, grade 3a	4 (20%)
Marginal zone lymphoma	1 (5%)
B symptoms	5 (25%)
Extranodal disease	11 (55%)
Elevated LDH	4 (20%)
FLIPI 3-5	9 (45%)
Indications for treatment (can have > 1)	
Symptomatic disease	15 (75%)
Threatened organ function	1 (5%)
Cytopenias	0 (0%)
Steady progression	7 (35%)
Bulk > 7 cm	4 (20%)
Hepatomegaly	0 (0%)
Splenomegaly	3 (15%)

Conclusion: Mosun is safe and highly active in untreated pts with follicular lymphoma with no G2+ CRS and no ICANS of any grade. The trial met its initial efficacy target allowing full study accrual to proceed. To our knowledge this represents the first presented safety and efficacy data for mosunetuzumab in untreated pts with FL or MZL.

The research was funded by a research grant from Genentech

Keywords: Combination Therapies, Immunotherapy, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

R. C. Lynch
Consultant or advisory role: Cancer Study Group, SeaGen, Foresight Diagnostics
Research funding: TG Therapeutics, Incyte, Bayer, Cyteir, Genentech, SeaGen, Rapt

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Research funding: Genentech

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Research funding: Mustang Bio, BMS
Other remuneration: Patent- Mustang Bio

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Research funding: Genentech

C. Ujjani
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A. K. Gopal
Consultant or advisory role: Incyte, Kite, Morphosys/Incyte, ADCT, Acrotech, Merck, Karyopharm, Servier, Beigene, Cellectar, Janssen, SeaGen, Epizyme, I-Mab bio, Gilead, Genentech, Lilly, Caribou, Fresenius-Kabi
Research funding: Merck, I-Mab bio, IgM Bio, Takeda, Gilead, Astra-Zeneca, Agios, Janssen, BMS, SeaGen, Teva, Genmab
Other remuneration: Stock Options: Compliment Corporation

433 | PHASE 2 STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF IMC-001, ANTI-PD-L1 ANTIBODY, IN PATIENTS WITH RELAPSED OR REFRACTORY EXTRANODAL NK/T CELL LYMPHOMA, NASAL TYPE: DISTINKT STUDY

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Introduction: IMC-001 is a fully human IgG1 monoclonal antibody that binds to human PD-L1 to enhance T cell activation and retains Fc effector function to stimulate antibody-dependent cell-mediated cytotoxicity. The preclinical results of IMC-001 are comparable to the data of approved PD-1/PD-L1 targeting drugs. Preliminary clinical data in the literature suggest that certain cancers studied in the IMC-001 program, such as extranodal natural killer (NK)/T cell lymphoma (ENKTL), nasal type, are responsive to PD-L1 inhibition. We present efficacy and safety of the phase 2 study of IMC-001 in patients with relapsed or refractory extranodal NK/T cell lymphoma (R/R ENKTL), nasal type.

Methods: Patients with histologically confirmed ENKTL who failed to at least one prior systemic therapy including asparaginase-based regimen were enrolled. Patients received IMC-001 20 mg/kg intravenously every two weeks for up to 2 years until disease progression or unacceptable toxicity. The primary endpoint is the objective response rate (ORR) determined by centralized independent review per the Lugano criteria with LYRIC modification for lymphoma. Tumor assessments were performed every 12 weeks using PET-CT/CT. Safety was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: Between October 2020 and February 2023, 15 patients were enrolled. The median age was 59 years (range 46–79), and 13 patients (87%) were male. All patients had a good ECOG performance status of 0–1. Nine patients (60%) were an extranasal type. The median number of prior systemic therapy was 2 (range 1–4). Ten patients (67%) received radiotherapy. Of the 10 efficacy-evaluable patients, 6 patients had a complete response (CR) and an ORR of 60%. A total 6 patients with CR, most of whom received long-term treatment (the median duration of 39 cycles, range 3–52).

Most treatment-emergent adverse events (TEAEs) were grade 1–2, and the common TEAEs were fatigue (20%), rash (20%), hypothyroidism (13%), abdominal pain (13%), headache (13%), pruritus (13%), and covid-19 (13%). Grade 2 infusion-related reactions (IRR), grade 3 uveitis, grade 2 hypothyroidism, and grade 2 fatigue suspected to related to IMC-001 were observed in 1 patient each. No TEAEs or serious TEAEs that resulted in death. No long-term toxicity was observed in 4 patients treated for more than 1 year.

Conclusions: PD-L1 blockade with IMC-001 is highly effective in patients with R/R ENKTL failing L-asparaginase containing regimens. IMC-001 has a good safety profile without long-term toxicity. We will present updated data for efficacy and safety. (Clinical Trial Identification: NCT04414163)

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Immunotherapy

Conflicts of interests pertinent to the abstract.

J. Oh
Employment or leadership position: Employee

S. Y. Lee
Employment or leadership position: Employee

H. T. Kim
Employment or leadership position: Chief Executive Officer

434 | FIRST-IN-HUMAN (FIH) STUDY OF THE FULLY-HUMAN KAPPA-LAMBDA CD19/CD47 BISPECIFIC ANTIBODY TG-1801 IN PATIENTS WITH B-CELL LYMPHOMA

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Introduction: CD19 is an established target of multiple B-cell lymphoma therapies. Blockade of CD47, a macrophage immune checkpoint inhibitory ligand, induces tumor-cell phagocytosis. TG-1801 is a CD19/CD47 bispecific antibody designed to selectively block CD47 on CD19+ cells, while retaining a functional IgG1 Fc domain. Herein we report updated results from the FIH study.

Methods: The primary objectives of this phase I 3+3 study were to characterize the safety profile and determine the recommended phase 2 dose (RP2D) as monotherapy and in combination with ublituximab. Pharmacokinetics, pharmacodynamics, and preliminary antitumor activity were also assessed. Eligible patients (pts) had relapsed/refractory (R/R) B-cell lymphoma after ≥1 prior standard therapy. TG-1801 doses evaluated included: 20 mg, 60 mg, 180 mg, 360 mg, & 500 mg. In the monotherapy arm, treatment consisted of weekly fixed dosing 1h-infusions of TG-1801 in a 4-week cycle: day (D)1, D8, D15, and D22 of cycle (C) 1 and C2. Pts who had at least stable disease after 2 cycles continued with TG-1801 once every 4 weeks for 4 further infusions. Intra-pt dose escalations were permitted. A second arm explored the combination of TG-1801 with ublituximab; an anti-CD20 mAb. Pts received TG-1801 and ublituximab, IV every 4 weeks: D1, D8, and D15 of C1; D1 of C2-C6; and D1 of C9 and every 3 cycles thereafter, up to 24 cycles. 2 dose levels of TG-1801 (300 mg and 400 mg) with 900 mg of ublituximab were tested. Responses were assessed by Lugano 2014 criteria.

Results: As of October 2022, 14 pts (MZL = 5, DLBCL including Richter's transformation = 5, FL = 4) received monotherapy and 16 pts received combination therapy (DLBCL = 9, FL = 4,

MZL = 2, MCL = 1). Pts had a median of 3 prior therapies (range, 1–8) with 16 pts (53%) refractory to their last therapy. One DLT of grade (G) 4 thrombocytopenia occurred at 500 mg monotherapy. Most frequent (>20%) treatment emergent adverse events (TEAEs) at monotherapy doses of 20 mg to 360 mg (n = 10) included fatigue, thrombocytopenia, and infusion-related reaction (3 pts each), with no G3/4 TEAEs occurring in >20% of pts. Combination therapy was also well tolerated (TG-1801 at 300 mg N = 3, 400 mg N = 13) without DLT. Most common TEAEs (≥20%) for combination therapy were anemia, headache, and fatigue (5 pts each), with no G3/4 TEAEs occurring in >20% of pts. 2 pts permanently discontinued therapy due to TEAEs (1 infusion reaction [500 mg monotherapy], 1 rash [360 mg monotherapy]). Among 13 evaluable monotherapy pts, there were 3 (ORR = 23%) partial responses (PR). In combination (n = 16), a 44% ORR was observed with 1 complete response (CR) in a pt with FL and 6 PR (5 pts with DLBCL and 1 pt with FL) for a 56% ORR in DLBCL and 50% ORR in FL.

Conclusions: TG-1801 monotherapy and combination therapy demonstrates clinical activity, particularly in R/R DLBCL, with an acceptable preliminary safety profile. This study (NCT03804996) has completed enrollment.

The research was funded by: TG Therapeutics Inc.

Keywords: Combination Therapies, Immunotherapy, Targeting the Tumor Microenvironment

Conflicts of interests pertinent to the abstract.

E. A. Hawkes
Consultant or advisory role: Advisory board and speaker fees (institutional or personal) from Roche, Merck Sharpe & Dohme, Astra Zeneca, Gilead, Antigene, Novartis, Regeneron, Janssen, Specialised Therapeutics, outside the submitted work
Research funding: Roche, Bristol Myers Squibb, Merck KgA, Astra Zeneca and Merck

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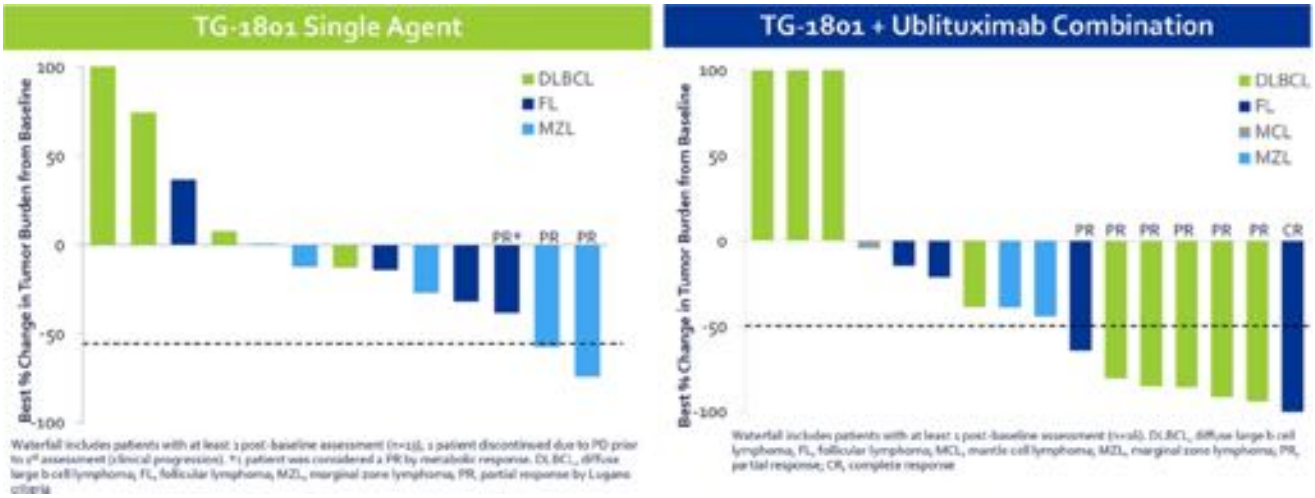
Honoraria: Roche, Janssen, Gilead, AstraZenecca, Lilly, TG therapeutics, Beigene, Novartis, Menarini, Daizai, Abbvie, Genmab. BMS
Research funding: BMS, Roche, Abbvie; MSD, Lilly



435 | PHASE 1 TRIAL OF EO2463 PEPTIDE-BASED IMMUNOTHERAPY AS MONOTHERAPY AND IN COMBINATION WITH LENALIDOMIDE AND RITUXIMAB IN INDOLENT NON-HODGKIN LYMPHOMA; EONHL1-20/SIDNEY

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Introduction: T cells normally recognize bacterial proteins originating from the gut microbiome, including some that cross-react with normal host B cell-specific proteins. A peptide-based strategy designed to activate and expand such pre-existing memory CD8+ T cells recognizing and driving anti-tumor activity against B cell malignancies was developed. EO2463 includes 4 synthetically produced peptides corresponding to cytotoxic CD8 HLA-A2 restricted epitopes which exhibit molecular mimicry with the B cell antigens CD20, CD22, CD37, and CD268 (BAFF-receptor), as well as a helper CD4 peptide, UCP2, derived from hTERT. Memory CD8+ T cell clones can be detected in the peripheral blood of healthy donors recognizing the EO2463 mimic peptides; in vitro, such cells can kill target T2 cells loaded with mimic or human counterpart peptides.

Methods: This first-in-human trial include HLA-A2+ patients (pts) with follicular lymphoma (FL) and marginal zone lymphoma (MZL). In the safety lead-in dose-finding part, EO2463 is administered subcutaneously every other week (w) × 4, followed by monthly administrations for a max of 12 months. After 6 w of EO2463 monotherapy, oral lenalidomide (20 mg/day for 21/28 days up to 12 cycles) is added, and if no complete remission (CR) at w 19, rituximab (375 mg/m^2 IV, weekly × 4, followed by q4 w infusions × 4) is also added. The peptide-dose is evaluated in a 3-by-3 safety design, starting at 150 μg/peptide, max escalation to 300 μg.

Results: Pts in the 1st (150 μg dose; 3 pts) and 2nd (300 μg dose; 3 pts) cohorts received EO2463 monotherapy without related grade ≥3 adverse events. Three more pts are being enrolled at the 300 μg dose, prior to starting expansion cohorts. Among the initial 6 pts, 5 had FL and 1 MZL; median number of prior therapies was 1 (range 1–4). Objective response rate 67%, including 50% CR (at w18, w18, w42), and 17% partial remission (at w18; ongoing treatment). On EO2463 monotherapy (at w6), 3 stable disease (including one metabolic response in 5 of 6 target lesions), 2 indeterminate responses (increased FDG uptake, no size change), 1 progressive disease. Combination therapy toxicity; grade 3 thrombocytopenia, rash, anemia, atrial fibrillation, bronchitis and sepsis (all $n = 1$); in addition, grade 4 neutropenia ($n = 2$). Expansion of specific CD8+ T cells against the mimic peptides and targeted B cell proteins was detected in 4/6 pts, including in 2 pts with no measurable B cells at baseline (prior anti-CD20). Immune response was maintained even following addition of rituximab. In vitro expanded EO2463 specific CD8+ T cells from pts with immune response can kill malignant HLA-A2 B cell lines.

Conclusions: EO2463 is well tolerated as monotherapy, and without additional safety signals when combined with lenalidomide and rituximab. We find evidence of on-target immune activation, and preliminary complete response rate is encouraging. Expanded data to be presented. NCT04669171.

Keywords: Combination Therapies, Immunotherapy, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

A. A. Pinto

Consultant or advisory role: Scientific Advisory Boards (F. Hoffmann-La Roche AG, Merck Sharp and Dohme, Incyte-Italy)

Honoraria: Speaking engagements – Educational Lectures (F. Hoffmann-La Roche AG, Incyte –Italy, Merck Sharp and Dohme, Servier Affaires Medicales, BMS-CELGENE)

Other remuneration: Speaker's Bureau: Incyte-Italy, F. Hoffmann-La Roche AG

S. D. Smith

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Research funding: ADC Therapeutics, Astrazeneca, Ayala (spouse), Bayer, Beigene, Bristol Myers Squibb (spouse), De Novo Biopharma, Enterome, Genentech, Ignyta (spouse), Incyte Corporation, Kymera Therapeutics, Merck Sharp and Dohme Corp., MorphoSys, Nanjing Pharmaceuticals Co., Ltd., Portola Pharmaceuticals, Viracta Therapeutics

L. Arcaini

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Research funding: Gilead Sciences

Other remuneration: Speakers' Bureau: EUSA Pharma, Novartis

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Research funding: Merck, Bristol Myers Squibb, Genmab, Genentech/Roche

S. Ansel
Research funding: Bristol Myers Squibb, SeaGen, Takeda, Regeneron, AstraZeneca, Pfizer, Affimed and ADC Therapeutics.

P. Armand
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Honoraria: Merck
Research funding: Kite, Merck, BMS, Adaptive, Genentech, IGM

P. L. Zinzani
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Other remuneration: Speaker's Bureau: Celltrion, Gilead, Janssen-Cilag, BMS, Servier, MSD, AstraZeneca, Takeda, Roche, Eusa Pharma, Kyowa Kirin, Novartis, Incyte, Beigene

436 | PHASE 1 TRIAL OF RUXOLITINIB COMBINED WITH NIVOLUMAB IN PATIENTS RELAPSED/REFRACTORY HODGKIN LYMPHOMA AFTER FAILURE OF CHECK-POINT INHIBITOR (CPI)

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Background: Recent studies demonstrated that classical Hodgkin lymphoma (cHL) is characterized by chromosome 9p24.1 amplification with associated overexpression of PD-1 ligands and JAK2 tyrosine kinase activation. JAK2 signaling augments tumor cell proliferation. Given this biology, we tested the combined inhibition of PDL1 pathway and JAK2 signaling in cHL patients who had progressed after prior PD-1 blocking therapy.
Methods: This is a Phase I/II multicenter, open-label, dose escalation/dose-expansion study to evaluate the safety and tolerability of JAK2 inhibitor ruxolitinib when combined with nivolumab in patients with R/R cHL (NCT03681561) who fail prior check-point inhibitor. Ruxolitinib was administered at 3 dose levels: 10, 15 or 20 mg orally twice a day continually with nivolumab at fixed dose 3 mg/kg IV every 2 weeks. Planned duration of therapy was 2 years.
Results: We enrolled 21 patients with median age 41 years (range 22–76); 67% were males. Patients were 3.4 years from diagnosis (median; range 0.9–16.7 years), 81% had stage III-IV and 89% had prior stem cell transplant. All patients had experienced progressive disease following prior CPI; 78% were resistant to CPI. Ruxolitinib MTD of 20 mg BID was reached without DLTs. Median cycles administered was 9 (range 3–28). The combination was well tolerated; most AEs were grade 1 and 2. Three patients experienced immune mediated adverse events (LFT elevation: 3 Gr 1 and 1 Gr 2; 1 Gr 3 pneumonitis); all were reversible. Median follow-up was 20.7 months (range 3–52 months).
In 19 patients evaluable for response (by LYRIC criteria), best disease control rate was 63% (12 of 19); including 5 complete response (26%), 3 partial response (16%) and 3 patients had stable disease (SD, 16%; with tumor bulk reduction ranging from 3 to 48%). One patient had indeterminate response (negative biopsy of new PET-avid site). Median duration of responses was 16.5 months (range 5.8 to 20.4 months). Two patients died, both with progressive disease and one from complications of subsequent experimental therapy. Progression-free survival at 2 years was 45% (95% CI: 22–66%). Correlative analysis demonstrated a ruxolitinib-driven modulation of classical monocytes and myeloid derived suppressor cells suggesting a synergistic antitumor effect with nivolumab. Correlative and in vitro data on mechanism of synergy will be presented.
Conclusions: Therapy combining ruxolitinib with nivolumab is well tolerated and yield encouragingly high remission rates and durable responses in patients who failed previous CPI. Pharmacodynamic and correlative analyses suggest synergistic effect on adaptive and innate immune systems.

The research was funded by: Incyte and BMS sponsored this trial as investigator initiated study

Keywords: Hodgkin lymphoma, Immunotherapy

Conflicts of interests pertinent to the abstract.

V. Bachanova
Research funding: Incyte and BMS supported this trial

437 | VENETOCLAX, IBRUTINIB, PREDNISONE, OBINUTUZUMAB, AND LENALIDOMIDE (VIPOR) IN RELAPSED/REFRACTORY (R/R) AND TREATMENT-NAïVE (TN) MANTLE CELL LYMPHOMA (MCL)

C. J. Melani[1], R. Lakhotia[1], S. Pittaluga[1], J. D. Phelan[1], Y. Yang[1], T. Davies-Hill[1], J. Simard[1], J. Muppidi[1], D. W. Huang[1], C. J. Thomas[2], M. Ceribelli[2], F. A. Tosto[2], A. Pradhan[1], A. M. Juanitez[1], L. M. Rimsza[3], A. Jacob[4], H. Simmons[4],

S. M. Steinberg[1], E. S. Jaffe[1], L. M. Staudt[1], M. Roschewski[1], W. H. Wilson[1]

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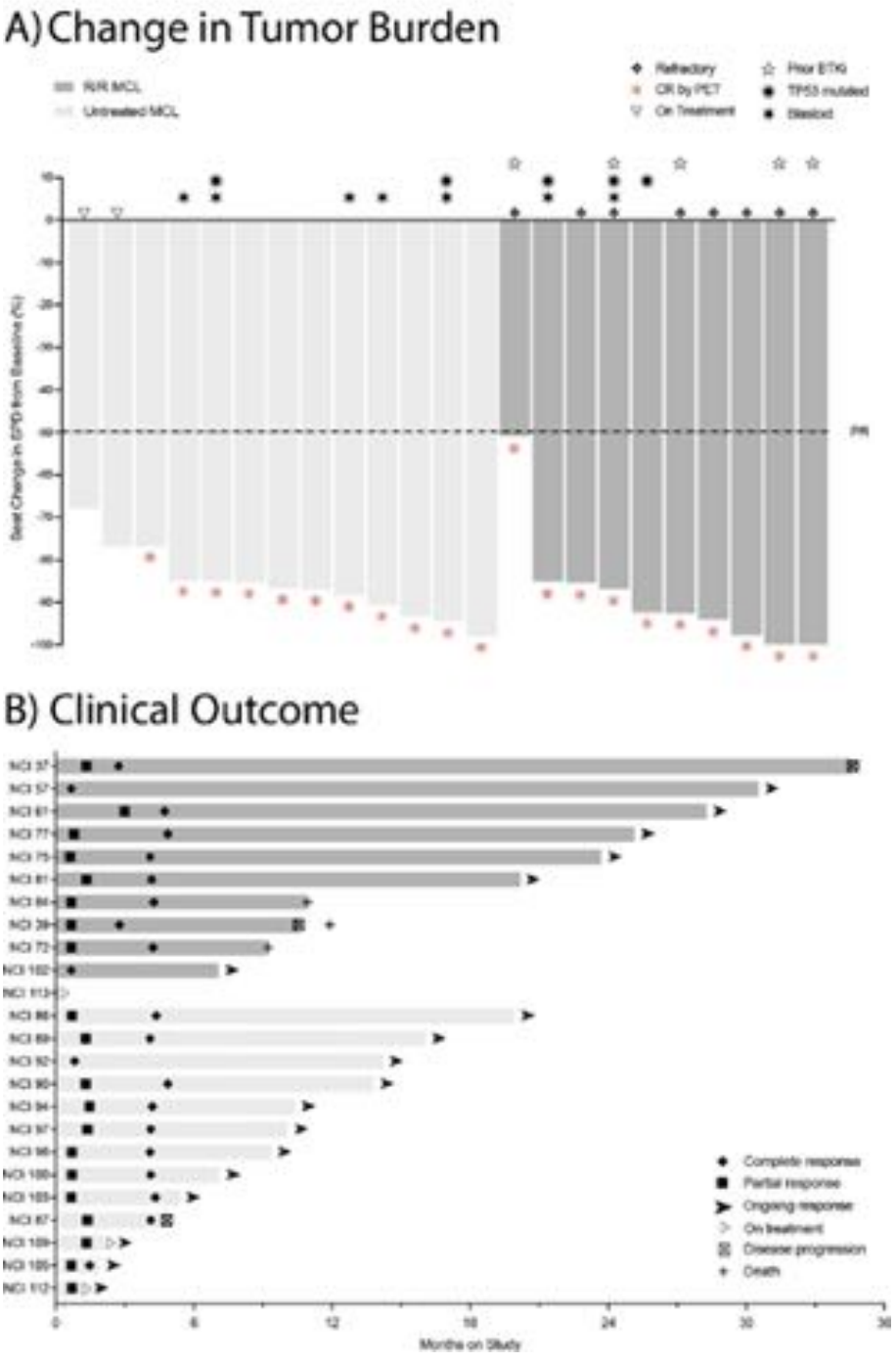
Introduction: MCL is incurable with standard chemotherapy. Although oral targeted agents are active in MCL, they fail to induce deep responses as monotherapy and require extended duration. We developed a multi-agent targeted regimen (ViPOR) and showed it to be safe and able to induce durable CRs in R/R B-cell lymphomas (Melani et al. *Blood*. 2020). Here, we present data for the MCL cohort of the ongoing ViPOR study.

Methods: R/R and TN MCL pts with adequate organ function were eligible. In Ph1, R/R pts were tx at 2 DLs of VEN (200 and 400 mg) to identify the RP2D. VEN was given PO D2-14 on C2-6 with an initial inpatient 12d ramp-up on C2, with fixed-dose IBRUT 560 mg PO D1-

FIGURE 1



14, PRED 100 mg PO D1-7, OBIN 1000 mg IV D1-2, and LEN 15 mg PO D1-14 on C1-6. In Ph2, R/R and TN MCL pts were treated at the RP2D. ViPOR q21d × 6C was given without maintenance. TLS, G-CSF, and PCP ppx was given to all pts and VTE ppx was per PI discretion. Baseline CT, PET, BM, and tumor bx was performed with CT after C1, 2, 4, and 6 and PET after C6. CT was then performed q3m × 1y, q4m × 1y, q6m × 1y, and q12m × 2y. MRD was assessed in plasma ctDNA using clonoSEQ at baseline, during tx, and in f/u.

Results: 24 MCL pts (11 R/R & 13 TN) have been enrolled. 71% were male with a median (range) age of 67y (41–82). Blastoid morphology, Ki-67 ≥30%, and TP53 mutations occurred in 29%, 38%, and 26%, respectively. High-risk MIPI and MCL35 proliferation score was noted in 21% and 19%, respectively. Median (range) prior tx in R/R was 3 (1–4) with prior BTKi in 45% and 73% refractory to last tx.

No DLTs occurred and VEN 400 mg was used in Ph2. Heme AEs were most common and included G3-4 (% cycles) thrombocytopenia (17%), anemia (9%), and neutropenia (9%), with no febrile neutropenia across 126 cycles. The only non-heme G3 AE in >10% pts was hypokalemia (22%), with any grade observed in 78%. Other common non-heme AEs (% pts) included diarrhea (65%) and rash (52%). G3 A. fib occurred in 2 pts with 1 G3 VTE and no major bleeding. No TLS or tx-related mortality occurred. Dose reductions occurred in 25%, and 86% completed all 6C.

All 21 (100%) off-tx pts achieved CR, including 7 blastoid, 5 TP53 mutated, 5 post-BTKi, and 8 refractory pts (Figure 1A). CRs occurred across all MIPI and MCL35 risk groups. With a median f/u of 17m, 78% of responses are ongoing (Figure 1B), with a 1y TTP, PFS, and OS of 87%, 74%, and 80%, respectively. 1y TTP was 88% in R/R, 90% in TN, 42% in blastoid, and 67% in TP53 mutated MCL.

Baseline ctDNA was identified in 95% (21/22) pts, with 95% (19/20) MRD- at EOT. Median (range) duration of MRD negativity was 6m (0–25). All 3 pts with relapse after CR experienced molecular relapse prior to imaging, with a median (range) lead-time of 4m (1–6).

Conclusions: Fixed-duration ViPOR × 6C without maintenance induces a high rate of MRD-CRs in MCL, including blastoid, TP53 mutated, post-BTKi, and refractory pts. ViPOR with a 12d VEN ramp-up on C2 is safe in MCL pts of all ages without significant TLS or febrile neutropenia when given with G-CSF.

The research was funded by the intramural program of the National Cancer Institute of the National Institutes of Health.

Keywords: Indolent non-Hodgkin lymphoma, Minimal residual disease, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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Other remuneration: Named inventor on the MCL35 assay.

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438 | CC-99282 PLUS R-CHOP IN PATIENTS (PTS) WITH PREVIOUSLY UNTREATED AGGRESSIVE B-CELL LYMPHOMA (A-BCL): EARLY SAFETY AND EFFICACY RESULTS FROM A PHASE 1B STUDY

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Introduction: Up to 30–40% of pts with diffuse large BCL relapse/become refractory after first-line chemo-immunotherapy with R-CHOP. CELMoD agent CC-99282 builds on the efficacy of immunomodulatory agents by optimizing degradation of target proteins Ikaros/Aiolos, enhancing antiproliferative and apoptotic activity; it showed a manageable safety profile with promising clinical activity as monotherapy in relapsed/refractory non-Hodgkin lymphoma in a phase 1 study (Michot et al. *Blood* 2021). CC-220-DLBCL-001 (NCT04884035) is an open-label, multicenter, dose-escalation and expansion trial to assess safety and preliminary efficacy of CC-99282 or CC-220 plus R-CHOP for untreated a-BCL. We report initial results from the CC-99282 escalation phase.

Methods: Pts aged ≥18 y had untreated a-BCL with measurable disease (Lugano 2014), with ECOG performance status ≤2 and International Prognostic Index (IPI) score 0–5. Pts received R-CHOP in 21-d cycles (C) plus CC-99282 at 3 dose levels (DLs): DL-1 (0.2 mg, d1–7), DL1 (0.4 mg, d1–7), and DL2 (0.4 mg, d1–10). Treatment (tx) continued for 6 C or until disease progression/unacceptable toxicity/study withdrawal. Primary endpoints: maximum tolerated dose and recommended phase 2 dose based on dose-limiting toxicity (DLT).

Results: Of 25 pts enrolled and treated (DL-1, $n = 9$; DL1, $n = 10$; DL2, $n = 6$), median (range) age was 64.0 (31–81) y; 60.0% were male;

most had IPI score 3–5 at diagnosis (60.0%), Ann Arbor stage III–IV disease (68.0%), and germinal center B-cell (GCB) as cell of origin (COO) (52.0%; 12.0% activated B-cell; 24.0% non-GCB). Four pts discontinued tx, 17 remain on tx, and 4 completed tx.

In total, 22 (88.0%) pts experienced a grade (Gr) 3/4 tx-emergent adverse event (TEAE), most commonly neutropenia (88.0%); 12.0% had infections. Gr 3/4 febrile neutropenia occurred in 2 (8.0%) pts; neutrophil recovery was prompt, 24 (96%) pts reaching absolute neutrophil count >1000 by d15. Gr 3/4 thrombocytopenia occurred in 9 (36.0%) pts. Seven (28.0%) pts had a serious TEAE. Overall, 28.0% of pts had CC-99282 reduction and 1 pt permanently discontinued tx at DL2. R-CHOP was delayed in 3 (12.0%) pts, and vincristine dose was reduced due to AE in 2 (8.0%) pts. Median relative dose intensity for CC-99282 and CHOP components was >90%. DLTs occurred in 1/9, 1/10, and 2/4 pts at DL-1, DL1, and DL2, respectively. DL2 exceeded the predefined threshold for toxicity.

In the efficacy evaluable population, complete response and complete metabolic response rates were highest at DL1 (100.0%, 95% CI: 59.0–100.0; 71.4%, 95% CI: 29.0–96.3, respectively). Overall response rate was 100.0% at all DLs.

Conclusions: CC-99282 showed a manageable safety profile with timely delivery and uncompromised R-CHOP dose intensity. Preliminary efficacy data indicated early and robust response to DL1 irrespective of COO. Low DLTs were observed at DL1 and DL-1; these DLs will be used in the expansion phase.

The research was funded by: Bristol Myers Squibb

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Immunotherapy

Conflicts of interests pertinent to the abstract.

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Honoraria: Targeted Oncology, OncView, Curio, Kyowa, Physicians' Education Resource, and Seattle Genetics
Research funding: Bayer, Gilead/Kite Pharma, Celgene, Merck, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, Millennium
Other remuneration: Speaker's bureau – Gilead/Kite Pharma, Kyowa, Bayer, Pharmacyclics/Janssen, Seattle Genetics, Acrotech/Aurobindo, Beigene, Verastem, AstraZeneca, Celgene/BMS, Genentech/Roche

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Research funding: AbbVie, Amgen, Bristol Myers Squibb, Dr. Reddy's, Karyopharm, Mei, Merck, Pfizer, Roche, Takeda,

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Research funding: Celgene, MorphoSys AG, NanoString Technologies

439 | SAFETY AND EFFICACY OF ACALABRUTINIB, BENDAMUSTINE, AND RITUXIMAB IN PATIENTS WITH TREATMENT-NAIVE OR RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA: PHASE IB TRIAL

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Background: Acalabrutinib (A) is a next-generation Bruton tyrosine kinase inhibitor approved for relapsed/refractory (R/R) mantle cell lymphoma (MCL). Bendamustine (B) + rituximab (R) is used for treatment-naive (TN) and R/R MCL. We present updated ABR safety and efficacy data in patients (pts) with TN or R/R MCL.

Methods: Eligible adults received ABR (phase 1b; NCT02717624) as follows: ABR for 6 28-d cycles, maintenance A+R for up to 2 y (TN cohort responders), then oral A continuously until progressive disease (PD) or treatment discontinuation due to toxicity (both cohorts). Primary endpoint was safety. Secondary endpoints were overall response rate (ORR), progression-free survival (PFS), and duration of response (DOR), all per Lugano.

Results: Overall, 38 pts were enrolled (TN, $n = 18$; R/R, $n = 20$) with median age 66 y (range 47–86). Baseline characteristics were (TN and R/R cohorts, respectively): stage IV disease, 88.9% and 95.0%; high-risk simplified MIPI score, 11.1% and 15.0%; bulky disease >5 cm, 16.7% and 30.0% or ≥10 cm, 5.6% and 10.0%; blastoid morphology, 5.6% and 15.0%. R/R pts had a median of 2 prior lines of therapy. At data cutoff (6/15/22), 6 (33.3%) TN pts and 4 (20.0%) R/R pts were receiving A monotherapy (Table). Most common any-grade AEs were nausea ($n = 14$, 77.8%; TN) and neutropenia ($n = 11$, 55.0%; R/R). Grade 3–4 AEs occurred in 13 (72.2%) TN pts and 17 (85.0%) R/R pts, most commonly neutropenia ($n = 7$, 38.9% [TN]; $n = 10$, 50.0% [R/R]). Serious AEs occurred in 11 (61.1%) TN pts and 13 (65.0%) R/R pts. There were no reports of ventricular tachyarrhythmia. Grade 3 atrial fibrillation occurred in 1 pt outside the safety reporting period and was unrelated to study treatment. Grade ≥3 major hemorrhage was reported in 2 (11.1%) TN pts and 3 (15.0%) R/R pts. Grade ≥3 hypertension was reported in 3 (16.7%) TN pts and 2 (10.0%) R/R pts. Five TN pts died (AE: pneumonitis, $n = 1$; unknown, $n = 4$) and 6 R/R pts died (AE: COVID and cerebrospinal meningitis, $n = 2$; PD, $n = 2$; unknown, $n = 2$). ORR was 94.4% ($n = 17$) in the TN cohort and 85.0% ($n = 17$) in the R/R cohort, with CR rates of 77.8% ($n = 14$) and 70.0% ($n = 14$), respectively. Median DOR was not estimable (NE) in the TN cohort and 43.5 mo in the R/R cohort. Median PFS and overall survival were NE in the TN cohort (median follow-up 47.6 mo) and 28.6 mo and NE, respectively, in the R/R cohort (median follow-up 20.4 mo).

Conclusions: Triple-combination ABR was tolerable and effective in pts with TN or R/R MCL.

Encore Abstract - previously submitted to ASCO 2023 and EHA 2023

The research was funded by: AstraZeneca

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

T. Phillips

Consultant or advisory role: Seattle Genetics, Pharmacyclics, Incyte, Genentech, Genmab, Bayer, Gilead Sciences, Curis, Kite/Gilead, Celgene, Genmab, TG Therapeutics, ADC Therapeutics, Abbvie, Eli Lilly, Beigene, BMS, Merck, Morphosys, Xencor

Research funding: Abbvie, Pharmacyclics/Janssen, Bayer, Genentech

Educational grants: Abbvie

Table. Disposition

Patients, n (%)	TN (n=18)	R/R (n=20)	Total (N=38)
Time on study, median (min–max), mo	47.6 (0.6–72.4)	20.4 (1.2–64.2)	26.4 (0.6–72.4)
Completed 6 cycles of BR	15 (83.3)	10 (50.0)	25 (65.8)
Completed 6 cycles of ABR	14 (77.8)	10 (50.0)	24 (63.2)
Receiving A at end of study	6 (33.3)	4 (20.0)	10 (26.3)
Discontinued A	12 (66.7)	16 (80.0)	28 (73.7)
AE	6 (33.3)	9 (45.0)	15 (39.5)
Disease progression	2 (11.1)	5 (25.0)	7 (18.4)
Withdrawal by PI	2 (11.1)	1 (5.0)	3 (7.9)
Other	2 (11.1)	1 (5.0)	3 (7.9)

M. Wang

Consultant or advisory role: AbbVie, Acerta Pharma, ADC Therapeutics America, Amphista Therapeutics Limited, AstraZeneca, Be Biopharma, BeiGene, BioInvent, Deciphera, DTRM Biopharma (Cayman) Limited, Genentech, InnoCare, Janssen, Kite Pharma, Leukemia & Lymphoma Society, Lilly, Merck, Miltenyi Biomedicine, Milken Institute, Oncternal, Parexel, Pepromene Bio, Pharmacyclics, VelosBio

Honoraria: AbbVie, Acerta Pharma, AstraZeneca, Bantam Pharmaceutical, BeiGene, BioInvent, Bristol Myers Squibb, CAhon, Dava Oncology, Eastern Virginia Medical School, Genmab, IDEOlogy Health, Janssen, Kite Pharma, Leukemia & Lymphoma Society, Medscape, Meeting Minds Experts, MD Education, MJH Life Sciences, Merck, Moffit Cancer Center, Nurix, Oncology Specialty Group, OncLive, Pharmacyclics, Physicians Education Resources (PER), Practice Point Communications (PPC), Scripps, Studio ER Congressi, WebMD

Research funding: Acerta Pharma, AstraZeneca, BeiGene, BioInvent, Celgene, Genmab, Genentech, Innocare, Janssen, Juno Therapeutics, Kite Pharma, Lilly, Loxo Oncology, Molecular Templates, Oncternal, Pharmacyclics, VelosBio, Vincerx

Educational grants: AstraZeneca, Celgene, DAVA Oncology, Kite/a Gilead Company, Physician's Education Resources (PER)

T. Robak

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Research funding: AstraZeneca, BeiGene, Janssen

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Research funding: AstraZeneca, Xencor, Pharmacyclics, Curis, Bristol-Meyers Squibb, Celgene, MEI Pharma, Trillium Therapeutics, Kite/Gilead, Roche/Genentech, Fate Therapeutics, Takeda, Epizyme, Aptevo Therapeutics, Nurix, Loxo/Lilly, Century Therapeutics

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Research funding: ADC Therapeutics, Astrazeneca, Ayala, Bayer, Beigene, Bristol Myers Squibb (spouse), De Novo Biopharma, Enterome, Genentech, Ignyta, Incyte Corporation, Kymera Therapeutics, Merck Sharp and Dohme Corp., MorphoSys, Nanjing Pharmaceuticals Co., Ltd., Portola Pharmaceuticals, Viracta Therapeutics

440 | PHASE 1/2 STUDY OF ZILOVERTAMAB AND IBRUTINIB IN MANTLE CELL LYMPHOMA (MCL), CHRONIC LYMPHOCYTIC LEUKEMIA (CLL), OR MARGINAL ZONE LYMPHOMA (MZL)

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Background: Zilovertamab (Zilo) is a humanized monoclonal antibody that inhibits the tumor promoting activity of the cancer stem cell receptor, ROR1, which is highly expressed in many hematologic malignancies but not on normal adult tissues.

Methods: Patients (Pts) with relapsed or refractory (RR) MCL or MZL or treatment-naïve (TN) or RR CLL were enrolled. Part 1 (Dose Escalation in CLL & MCL) evaluated multiple doses up to Zilo 600 mg IV q4wks + Ibr 420 mg (CLL) or 560 mg (MCL) daily which was selected for Part 2 (Dose Expansion in CLL, MCL & MZL) and Part 3 (CLL only; pts randomized 2:1 to Zilo+Ibr vs. Ibr alone).

Results: To date, 33 MCL, 62 CLL & 4 MZL (99) pts were treated in Parts 1, 2 & 3. In Parts 1&2, 28 RR MCL and 34 CLL (12 TN and 22 RR) on zilo+ibr were efficacy evaluable (MZL not yet evaluable). In Part 3, 23 CLL pts on Zilo+Ibr (16) or Ibr (7) were evaluable. Safety & efficacy results were as of 11 October 2022.

Safety in MCL and CLL: The most frequent (≥30%) treatment emergent adverse events (TEAEs) for all MCL & CLL pts on Zilo +Ibr (n = 85) were diarrhea & fatigue (45.9%), contusion (38.8%) and cough (30.6%). The most frequent (≥5%) grade ≥3 TEAEs were hypertension (10.6%), pneumonia (8.2%), atrial fibrillation (AF) & neutropenia (7.1%), and fatigue (5.9%). For all MCL & CLL pts on zilo+ibr, grade ≥3 hematologic lab abnormalities were decreases in neutrophils (11.8%), platelets (4.7%), and hemoglobin (3.5%).

Efficacy in MCL: The ORR was 89.3% (42.9% CR); 18% had achieved CR at 3 mos which suggests rapid response; median duration of response (mDOR) was 34.1 mos. Median PFS (mPFS) was not reached (NR) (95% CI: 33.2, NE) with median follow-up (mf/u) of 19.5 mos. Pts with 1 prior line of therapy (LOT) and >1 prior LOT had mPFS of 33.2 mos and NR, respectively. In pts with poor prognostic factors, 7 pts with TP53 mutation had ORR of 85.7% with mPFS NR and 14 pts with Ki-67 ≥30% had ORR of 85.7% with mPFS 33.2 mos. Overall, median OS was NR (95% CI: 22.46, NE).

Efficacy in CLL: In parts 1–3, mPFS was NR with mf/u of 40 mos for parts 1&2 and ~30 mos in part 3. In pooled analysis of all parts, mPFS in 10 pts (5 TN, 5 R/R) with TP53/del(17p) was NR and landmark PFS and OS were 100% at 42 & 40 mos, respectively.

Conclusions: Zilo+Ibr is well-tolerated with a safety profile that is comparable to Ibr alone. AF (all grades) occurred in 9.4% of all pts treated which appears lower than rate in Ibr alone studies. The combination is very promising in pts with RR MCL (ORR 89.3%, CR 42.9%, mPFS NR). For CLL pts with TP53 mut/del(17p), Zilo+Ibr is also very active, maintaining 100% PFS and OS at ~42 mos. This Zilo + Ibr data after >3 years of f/u is very encouraging in reference to the ALPINE results which reported estimated PFS at 36 mos of ~55% for Zanubrutinib and ~42% for Ibr in RR CLL pts with TP53 mutation. The study is currently enrolling MZL pts and has provided a strong rationale for conducting a Phase 3 pivotal study in RR MCL (ZILO-301).

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chronic Lymphocytic Leukemia (CLL), Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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441 | CCTG LY18-A PHASE I MASTER PROTOCOL OF NOVEL COMBINATION THERAPY FOR PATIENTS WITH RELAPSED OR REFRACTORY LYMPHOMA - THE RGDP-VENETOCLAX SUBSTUDY

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Introduction: Therapies for relapsed/refractory (r/r) large B cell lymphomas are expanding. Chemo-immunotherapy and autologous stem cell transplant (ASCT) remains an important therapeutic option with survival benefit. About 50% of patients (pts) have an adequate response to salvage therapy which is required to proceed to ASCT. Novel salvage regimens may increase response and transplantation rate.

Methods: LY.18 is a Canadian Cancer Trials Group Phase I platform trial of novel salvage regimens for patients with r/r large B cell lymphoma. RGDP (rituximab, gemcitabine, dexamethasone, cisplatin) plus venetoclax (RGDP-V) was evaluated in adult pts with diffuse large B cell lymphoma, primary mediastinal B cell lymphoma, transformed follicular lymphoma, or high-grade B cell lymphoma after one prior line of therapy. RGDP was administered at standard doses (Crump, JCO, 2014) for up to 3 cycles pre-transplant. V was administered at increasing dose levels (200–800 mg) according to a 3 +3 design, with dose limiting toxicity (DLT) assessed in cycle one. The recommended Phase 2 dose (RP2D) was the primary outcome. Pts with a partial or complete response (PR or CR) could proceed to ASCT. Response was assessed using both the Lugano criteria and RECIL.

Results: Since Sept 2020, 18 pts have been treated at 5 dose levels. Severe myelotoxicity was noted in the first dose level with 2 DLTs observed in the first 4 pts. The trial was amended to mandate G-CSF days 9 to 14 with each cycle of therapy (Table 1). Median age was 59, 4 pts were ≥65 years, 8 were female, median ECOG was 1 (range 0 to 3). Two of 3 pts experienced a DLT at the 800 mg dose. The recommended phase 2 dose (RP2D) is RGDP-V 400 mg days 4 to 10 of cycle 1, and days 1 to 10 of cycles 2 and 3. There were 7 serious adverse events in 5 pts, including febrile neutropenia ($n = 3$); grade 2 bacteremia ($n = 1$); and grade 3 abdominal pain, C2 fracture from fall, and supraventricular tachycardia ($n = 1$ each), all unrelated. There were 4 deaths on trial; 3 disease related, 1 from transplant-related complications. All grade treatment emergent adverse events occurring in at least 20% of patients were tinnitus, abdominal pain,

Table 1

Dose Level	Regimen RGDP plus Ven	Patients* n=18	DLT n=4	Nature of DLT	Best Response (Lugano)	ORR (CR+PR)
Dose level 1	Ven 200mg/day C1: days 4-10 C2,3: days 1-10	4	2	• Grade 4 neutropenia >7 days • Grade 4 neutropenia, thrombocytopenia >7 days	2 PR 1 PD 1 INEVAL	50%
Dose level -1	Ven 200mg/day C1: days 4-8 C2,3: days 1-5 G-CSF	3	0	N/A	1 CR 2 PR	100%
Modified Dose llevel 1	Ven 200mg/day C1: days 4-10 C2,3: days 1-10 G-CSF	5	0	N/A	1 CR 3 PR 1 INEVAL	80%
Modified Dose level 2	Ven 400mg/day C1: days 4-10 C2,3: days 1-10 G-CSF	3	0	N/A	3 PR	100%
Modified Dose llevel 3	Ven 800mg/day C1: days 4-10 C2,3: days 1-10 G-CSF	3	2	• Grade 4 neutropenia >7 days • Febrile Neutropenia	1 PD 2 still on treatment	

*17 diffuse large B Cell Lymphoma, 1 mixed follicular/high grade B cell
DLT dose limiting toxicity; CR complete response; PR partial response; progressive disease; ORR overall response rate; INEVAL inevaluable; Ven venetoclax; RGDP rituximab gemcitabine, dexamethasone, cisplatin;
G-CSF granulocyte colony stimulating factor

constipation, diarrhea, dyspepsia, fatigue, pain, headache, and back pain. Grade 3 or greater anemia was seen in 33%, neutropenia in 78%, and thrombocytopenia in 61% of pts. The ORR in 16 evaluable pts was 75% (12/16) (95% CI: 51.7%–92.4%) by both Lugano criteria and RECIL; 2 pts were in CR by Lugano criteria and 3 pts by RECIL. Responses were seen across all dose levels. Stem cell collection >2.0 $\times$ 10^6 CD34+cells/kg was achieved in 9 of 10 pts in whom it was attempted. All 10 pts were successfully transplanted. 4 pts received CART therapy, 1 following progression post ASCT.

Conclusion: RGDP-V 400 mg is safe and feasible with encouraging early response rates. Neutropenia was a key toxicity and can be mitigated with prophylactic G-CSF. LY.18 will expand to include 6 more patients at the RP2D.

The research was funded by: AbbVie Corporation, Hoffmann-La Roche Ltd

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies

Conflicts of interests pertinent to the abstract.

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442 | FIRST INTERIM ANALYSIS OF A PHASE 1 STUDY OF ZANUBRUTINIB (ZANU) + LENALIDOMIDE (LEN) IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Introduction: Effective therapies for R/R DLBCL are limited in China, especially for patients (pts) who are ineligible for high-dose therapy/stem cell transplantation (HDT/SCT). Preclinical data suggest synergy of len and zanu, a potent and selective Bruton tyrosine kinase inhibitor approved for various B-cell malignancies (Guo et al. *J Med Chem* 2019). Here, we present the interim analysis of an ongoing phase 1, open-label, dose-escalation/expansion study of zanu + len in R/R DLBCL in China (NCT04436107).

Methods: Pts with R/R DLBCL ineligible for HDT/SCT with ≥1 prior line of adequate systemic therapy were enrolled. Dose escalation (part 1): Len 15 mg, 20 mg, or 25 mg orally once daily on days 1–21 of each 28-day cycle. Dose expansion (part 2): Len 25 mg. Zanu 160 mg was given orally twice daily continuously in parts 1 and 2. Primary

endpoints were safety and recommended phase 2 dose (RP2D) of len (part 1) and overall response rate (ORR) by investigator based on Lugano classification (part 2). Interim analysis was performed when the 19th pt in part 2 completed first tumor assessment. Pts who received len 25 mg (RP2D) in parts 1 and 2 were analyzed separately.
Results: As of 8 November 2022, 46 pts were treated and included in the analysis (27 in part 1; 19 in part 2; 30 at RP2D). Median age was 60 years (range, 29–82), 83% had stage III-IV disease, 37% had refractory disease, 70% had non-germinal center B-cell (non-GCB)-like disease; and median number of prior systemic therapies was 1 (range, 1–5).
Median exposure to zanu and len was 3.9 months (range, 0.4–24.9), median follow-up was 6.6 months (range, 0.5–25.5). ORR was 46% overall (95% CI: 30.9, 61.0; complete response [CR]: 24%) and 57% at RP2D (95% CI: 37.4, 74.5; CR: 30%). At RP2D, ORR was 61% (95% CI: 38.5, 80.3; CR: 35%) for pts with non–GCB-like disease and 50.0% (95% CI: 11.8, 88.2; CR: 17%) for GCB. At RP2D, median duration of response was not reached and 6-month event-free rate was 59% (95% CI: 23.8, 82.8). The 9-month progression-free survival rate was 37% (95% CI: 17.6, 57.4).
Overall, 46 (100%) pts experienced ≥1 treatment-emergent adverse event (TEAE). At RP2D, grade ≥3 TEAEs occurred in 60% of pts, most commonly neutrophil count decreased (43%), white blood cell count decreased (23%), and pneumonia (13%). One patient (2%) had febrile neutropenia (grade 3) but recovered within 2 days. TEAEs led to discontinuation of both len and zanu in 2 pts (cardiopulmonary failure unrelated to treatment [part 1, len 20 mg], pulmonary embolism [part 1, len 25 mg]) and discontinuation of len in 2 pts (platelet count decreased [part 1, len 20 mg], rash [part 2]). Two TEAEs leading to death were assessed as unrelated to treatment.
Conclusions: Zanu 160 mg + len 25 mg combination showed an acceptable safety profile with promising efficacy. Further evaluation of the combination in a larger sample size is planned in future analysis.

Encore Abstract - previously submitted to ASCO 2023 and EHA 2023

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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443 | TAFASITAMAB LENALIDOMIDE IN RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMAS: A MULTICENTRIC REAL-WORLD FRENCH EXPERIENCE STUDY

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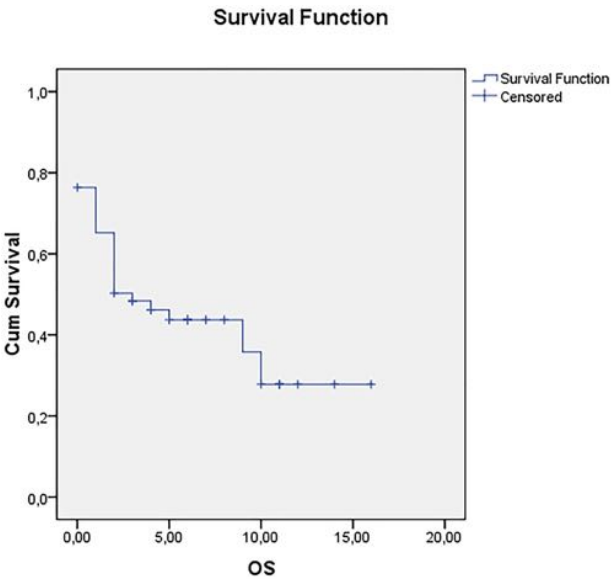
Introduction: Tafasitamab in association with Lenalidomide (TAFA LEN) has shown its efficacy in relapse/refractory diffuse large B-cell lymphomas (R/R DLBCL) in the L-MIND study. In this study, the best overall response rate (BORR) was 60%, the best complete response (CR) rate 43%, and the median overall survival (OS) was not reached. We aimed to study the efficacy and safety of TAFA LEN in the real-world setting in France.
Methods: Real-Tafa Study is a multicentric, retrospective, real-world study including consecutive patients with R/R large B-cell lymphomas. Included patients were treated in 6 French LYSA (Lymphoma Study Association) centers. TAFA LEN was available thanks to an early access program initiated in January 2022. As in the L-MIND study, Tafasitamab was given intravenously at 12 mg/kg and Lenalidomide orally at 25 mg for 12 induction cycles, then Tafasitamab monotherapy for maintenance in case of stable disease (SD) or better.
Results: Between February 2021 and February 2023, 56 patients were treated with TAFA LEN were included. The median age was 72 years (range 37–91). The majority of them had comorbidities. Thirty-nine had diffuse large B-cell lymphoma, not otherwise specified (24 non-GC, 10 GC, 5 unknown), 11 transformed from a low-grade lymphoma, 3 T-cell/histiocyte-rich large B-cell lymphomas, 2 high

grade B-cell lymphomas, and 1 grey zone lymphoma. The median number of prior lines was 2 (range 0–9), with 88% of patients who had received ≥2 prior lines and 77% refractory to their last treatment. Twenty-one percent had received prior Chimeric Antigen T-cells (CAR T-cells). The BORR was 33%: 29% in CR, 4% in partial response (PR), 15% in SD, 52% in progressive disease (PD). Sixty-three percent of patients died, mainly from PD. The median number of induction cycles was 2, most patients stopped TAFA LEN because of PD. The median OS was 3.0 months (95% CI: 0.5–5.0 months) (Figure 1). There was no statistically significant difference in terms of BORR between CD19 negative and CD19 positive patients, but the data was only available for 11 patients. There was a trend toward a lower BORR for patients with ≥2 prior lines versus <2 prior lines (30% vs. 50%) and for patients with prior CAR T-cells versus no prior CAR T-cells (17% vs. 38%), but the difference was no statistically significant. The small number of patients precluded any conclusion. As in the L-MIND study, most toxicities were cytopenias, with 29%, 36%, and 32% of patients experiencing grade 3–4 anemia, thrombocytopenia, and neutropenia, respectively. One third of patients had an infection. Half of the patients experienced an interruption or a reduction of Lenalidomide because of adverse events.

Conclusion: In this real-world study with heavily pre-treated R/R large B-cell lymphoma patients, TAFA LEN did not reach the favorable outcome found in clinical trials, especially for patients previously treated with more than 2 lines and CAR T-cells.



Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Immunotherapy

Conflicts of interests pertinent to the abstract.

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444 | FINAL RESULT OF DIAL (NCI10089), RANDOMIZED PHASE 2 TRIAL OF VARLILUMAB COMBINED WITH NIVOLUMAB IN PATIENTS WITH RELAPSED/REFRACTORY AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMA

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Introduction: The prognosis for patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (r/r B-NHL) is poor. The efficacy of combining nivolumab (PD-1 inhibitor) and varlilumab (CD27 agonist) was tested in this population in the multi-center randomized phase II DIAL study (Dual Immunomodulation in Aggressive Lymphoma).

Methods: Patients with r/r B-NHL were randomized to treatment with nivolumab alone or combined with varlilumab (Figure 1A). Cross-over (group 1 to 2) was allowed for progression. Primary endpoint was overall response (ORR) per LYRIC criteria, by intention-to-treat. A sample size of 48 patients per arm would provide 80% power to detect increase in ORR from 25% to 45% using a one-sided test ($p = 0.15$). Pre-specified interim analysis occurred after half of patients completed first radiologic assessment. Secondary endpoints included overall survival (OS), progression-free

survival (PFS), and adverse events (AEs). Exploratory endpoints included tumor genomic assessment and immune profiling of blood and tumor.

Results: 51 patients were enrolled (25 in group 1; 26 in group 2) between November 2017 and August 2022 with median follow-up of 8.8 months. Mean age was 65.5 years, 36 (71%) were male, and 90% of patients had at least 3 prior lines of therapy. Prior CAR-T cell therapy was confirmed in 33 (65%) patients. Baseline characteristics were balanced between arms. There were no treatment-associated deaths. Proportion of grade ≥3 AEs were similar in both groups. ORR was achieved in 6 patients (12%), not statistically different between arms; 4 responses were complete (Figure 1B). Seven patients crossed over (1 responded after crossing). Median OS (9.3 vs. 7.3 months; $p = 0.24$; Figure 1C) did not differ between arms and median PFS (2.6 vs. 1.4 months; $p = 0.04$; Figure 1D) was statistically higher in group 1. Subgroup analysis of patients with confirmed prior CAR-T cell therapy showed similar ORR compared to overall cohort (5/33; 15%), not statistically different between arms; 3 responses were complete (Figure 1B). In this subgroup, median OS (9.3 vs. 10.9 months; $p = 0.5$) and PFS (2.8 vs. 1.4 months; $p = 0.05$) did not differ between arms. Correlative analysis results including CyTOF, whole exome, and whole transcriptome sequencing will be presented at conference. The trial met pre-specified futility criterion on interim analysis and is permanently closed.

Conclusion: Dual immunomodulatory therapy did not enhance anti-tumor activity or increase toxicity in patients with aggressive r/r B-NHL compared to nivolumab alone. Response rates were low, and survival was poor, consistent with previous studies of checkpoint inhibitors (CPI) in this population. DIAL is the largest prospective study to evaluate the efficacy of CPI in post CAR-T failure. In this setting, response rates and survival were equally dismal, suggesting that CPI is not an effective salvage strategy in post CAR-T failure.

The research was funded by: National Cancer Institute (NCI), Department of Defense (DOD), Mayo Clinic, Lymphoma Research Foundation (LRF).

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Immunotherapy

Conflicts of interests pertinent to the abstract.

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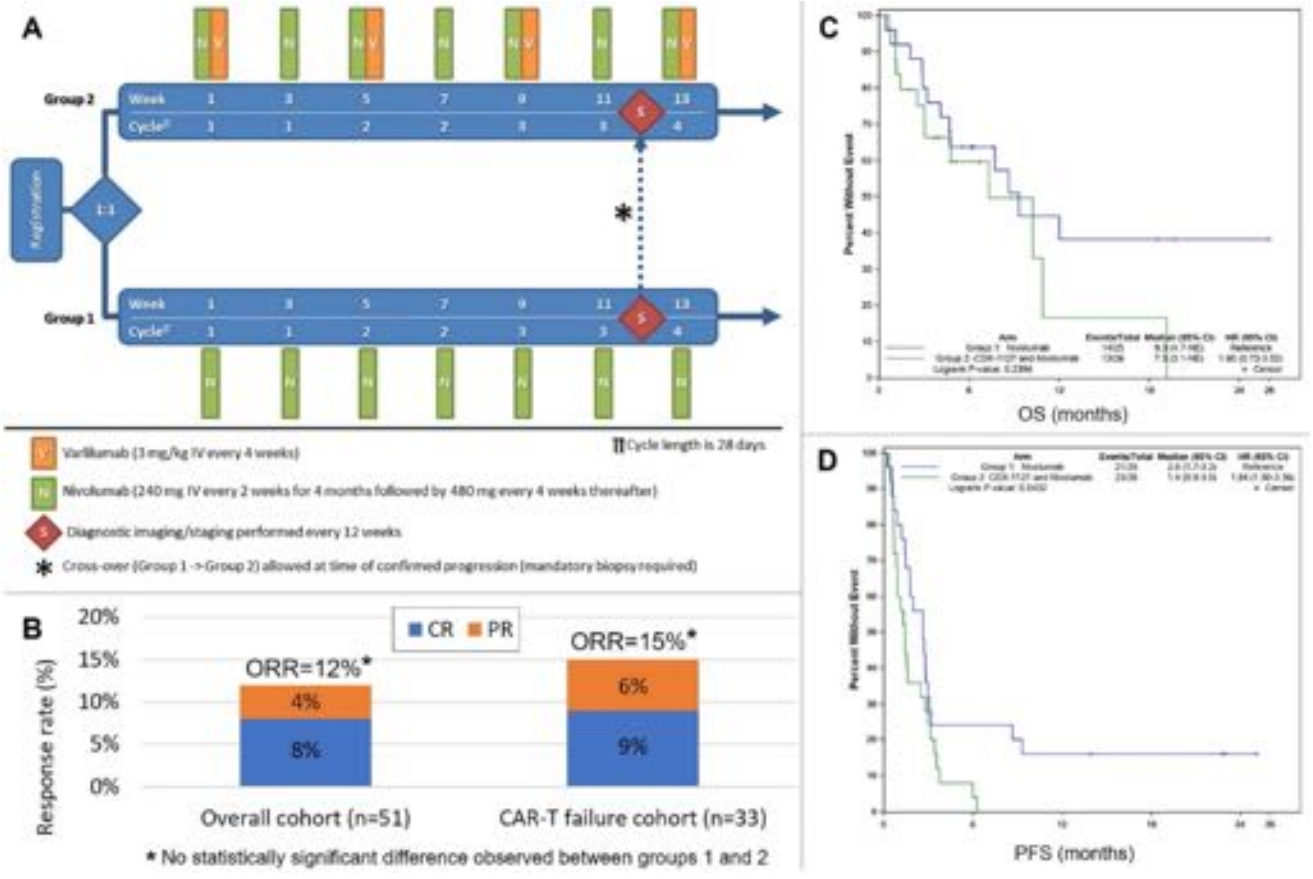

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445 | COMBINATION OF EVEROLIMUS AND ITACITINIB IN PATIENTS WITH HODGKIN LYMPHOMA RELAPSED/ REFRACTORY TO BRENTUXIMAB VEDOTIN (BV) AND CHECKPOINT INHIBITORS (CPI)

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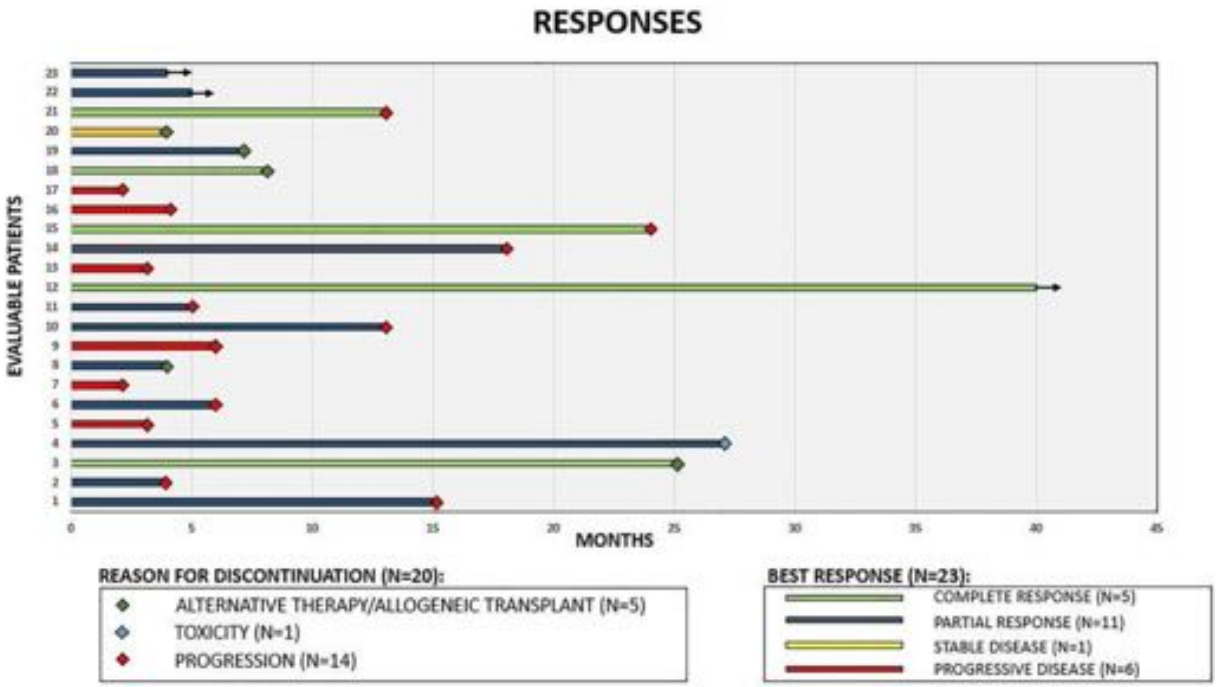
Introduction: Patients (pts) with classic Hodgkin lymphoma (cHL) who have failed or are intolerant of BV and CPI have few available treatment options. Genetic alterations in JAK/STAT pathway are frequently detected in cHL tumors making them an ideal therapeutic target. Since pre-clinical studies showed synergistic activity of JAK and mTOR inhibition in JAK-mutated cell lines, we designed a combination trial using an oral JAK inhibitor with potent selectivity for JAK1, itacitinib adipate, and an oral mTOR inhibitor, everolimus, for patients with cHL relapsed/refractory (R/R) to BV and CPI.

Methods: We conducted an open-label, investigator-initiated, phase I/II trial using everolimus and itacitinib for pts with cHL who had at least 2 prior lines of therapy. Eligible pts were R/R to BV and CPI (or intolerant/not a candidate for either agent). A 3+3 design was used to define the recommended phase II dose (RP2D). Therapy was continued until progression or intolerance. All pts received PJP and anti-viral prophylaxis. DLT was defined as the occurrence of any ≥ grade 3 non-hematological or selected grade 4 hematological adverse event (AE) during Cycle 1 (by CTCAE v5 criteria). Responses were evaluated by Lugano 2014 criteria. Enrollment began in Feb 2019 with data cut off in Jan 2023.

Results: We enrolled 23 cHL pts with median age 38 yrs (22–67), 65% male. Median number of prior treatments was 6 (2–12) including 74% post auto-SCT, 17% post allo-SCT and 15% post CD30 CART. All pts had prior BV and 21 (91%) had prior CPI except for 2 due to GVHD. No DLTs occurred in phase I and the RP2D was everolimus 5 mg and itacitinib 400 mg daily. All pts experienced at least one AE during the study, but most were manageable and low grade. Hematological events included thrombocytopenia (78%), anemia (57%) and neutropenia (39%). Most common non-hematological AEs included hypercholesterolemia (57%), hyperlipidemia (43%), hypertension (35%), acneiform rash (39%) and stomatitis (17%). These were attributed to everolimus and managed with supportive care. There were no study-related deaths. Six (26%) pts experienced grade at least one 3/4 non-hematological AE (all reversible) and one patient discontinued study treatment due to toxicity (infection/hypoxia). The best overall response rate was 70% (95% CI: 50%–85%) and complete response rate was 22% (95% CI: 12%–50%). At median follow-



up 30 months (range 3–47), the 2-year PFS was 23% (95% CI: 12%–46%) and OS was 74% (95% CI: 59%–92%).

Conclusions: In cHL patients R/R to BV and CPIs, the combination of everolimus and itacitinib was well tolerated and produced high response rates that compare favorably to historical reports of mTOR or JAK inhibitors as monotherapies. Further analysis of the biopsy samples may define those who would particularly benefit from this novel combination.

The research was funded by: Incyte

Keywords: Combination Therapies, Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

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Research funding: TG, Seagen, Pharmacyclics, Merck, Incyte, BMS, Astra Zeneca, Adaptive

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Research funding: Beckman Coulter, NanoString, AbClon

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Research funding: Merck, AbbVie, BMS, Genentech, TG, DTRM, Adaptive, Roche, Pharmacyclics, Novartis, Incyte

446 | GLOFITAMAB PLUS IMMUNOCHEMOTHERAPY DEMONSTRATES DURABLE EFFICACY WITH MANAGEABLE SAFETY IN RELAPSED/REFRACTORY NON-HODGKIN LYMPHOMA (R/R NHL): UPDATE OF A PHASE IB STUDY

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Introduction: Glofitamab (Glofit) is a novel T-cell engaging bispecific antibody. Its 2:1 molecular configuration allows bivalent binding to CD20 on B cells and monovalent binding to CD3 on T cells, enabling combination with anti-CD20 antibody therapies such as rituximab. This Phase Ib study, NCT03467373, was designed to assess the safety, tolerability, and efficacy of Glofit in combination with R-CHOP in patients (pts) with R/R NHL prior to assessing this combination as a first-line therapy for pts with diffuse large B-cell lymphoma. Here, we present the updated efficacy and safety of Glofit plus R-CHOP in pts with R/R NHL from the dose-escalation phase after ≥2 years' follow-up.

Methods: Pts with R/R NHL received pretreatment with R- or obinutuzumab-CHOP in Cycle (C) 1. From C2 onwards, pts received R-CHOP plus increasing Glofit doses in separate cohorts (70 µg, 1800 µg, 10 mg, 30 mg) for 6–8 21-day cycles. In the 70 and 1800 µg cohorts, Glofit was given as a fixed dose on C2 Day (D) 8 onwards; in the 10 and 30 mg cohorts, pts received step-up dosing (SUD) in C2 (C2D8, 2.5 mg; C2D15, 10 mg; C3D8 onwards, target dose). Pts with a complete response (CR), partial response or stable disease were permitted to receive Glofit maintenance at their fixed or target dose every 2 months for up to 2 years. Efficacy endpoints included investigator-assessed best overall response rate (BORR) and duration of response (DoR).

Results: At data cut-off (14 November 2022) 31 pts (23 follicular lymphoma [FL]; 6 transformed FL; 1 marginal-zone lymphoma; 1 mantle-cell lymphoma) had been enrolled and treated with Glofit plus R-CHOP (SUD, $n = 20$; fixed dose, $n = 11$). Median time on study was

30.7 months (range: 1–47); median age was 62 years (range: 34–78); median prior lines of therapy was 2 (range: 1–5). In the fixed-dose cohort, BORR during treatment was 82% (9/11 pts) and complete metabolic response (CMR) rate was 64% (7/11 pts). The median DoR and duration of complete response (DoCR; months) were not reached (NR; 95% CI: 6.1– not estimable [NE] for DoR and DoCR; Figure); median progression-free survival (PFS) was NR (95% CI: 7.7–NE). In the SUD cohort, the BORR during treatment was 95% (19/20 pts); CMR rate was 95% (19/20 pts). The median DoR was 28.4 months (95% CI: 21.6–NE), median DoCR was 25.4 months (95% CI: 17.9–NE; Figure); median PFS was 30.7 months (95% CI: 14.6–NE).

Grade (gr) ≥3 adverse events (AEs) occurred in 29/31 pts (94%); serious AEs occurred in 23/31 pts (74%); 3 pts (10%) had fatal AEs ($n = 2$, COVID-19 pneumonia; $n = 1$, acute myeloid leukemia). Six pts (19%) withdrew from treatment due to an AE; cytokine release syndrome (CRS) occurred in 16/31 pts (52%; gr 1/2, 12 pts; gr 3/4, 4 pts).

Conclusions: This trial demonstrated that Glofit plus R-CHOP demonstrated high BORR and CMR rates in pts with R/R NHL, with durable responses observed after ≥2 years' follow-up. The safety profile was manageable, with CRS events predominantly low grade.

The research was funded by: Study NCT03467373 was sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of all authors, was provided by Ellie Sherwood, MPhil, and Emily Lynch, PhD, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Immunotherapy, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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Honoraria: F. Hoffmann-La Roche Ltd., Takeda, Gilead, Incyte

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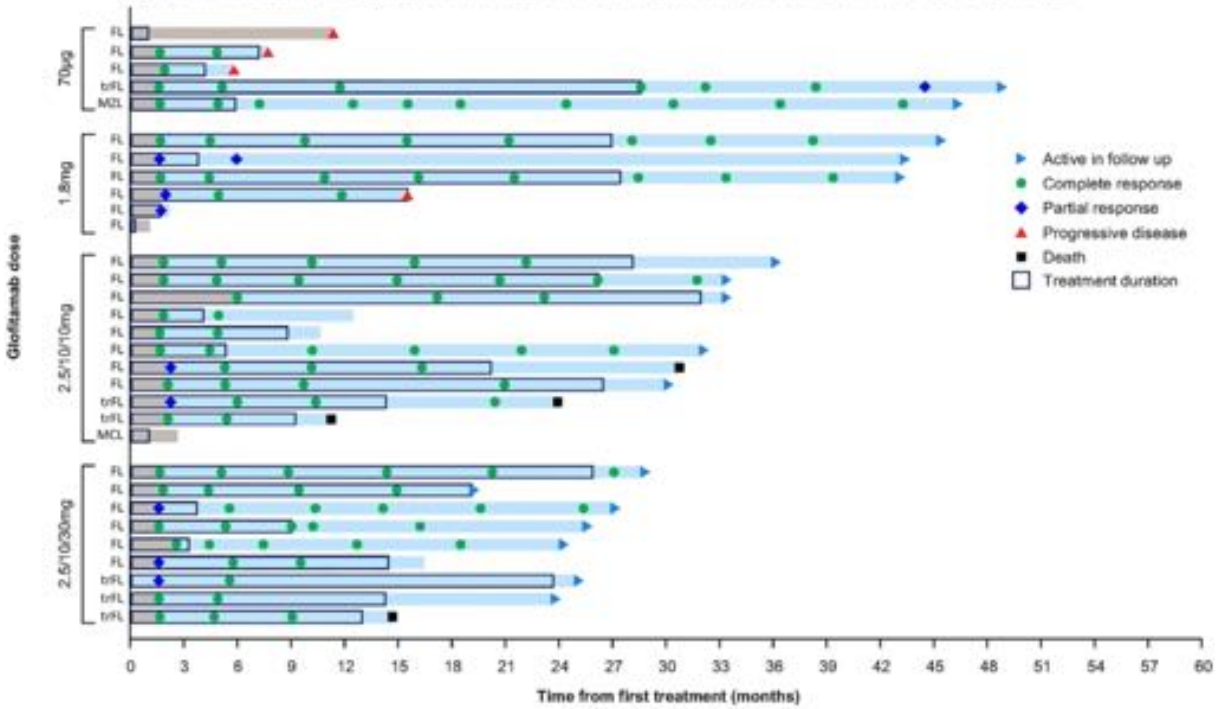
Figure: Duration of response and time on treatment for the SUD and fixed-dose cohorts.



FL, follicular lymphoma; MCL, mantle-cell lymphoma; MZL, marginal-zone lymphoma; SUD, step-up dosing; trFL, transformed follicular lymphoma.

Research funding: Novartis, F. Hoffmann-La Roche Ltd., Takeda, Celgene, MSD, AbbVie, Lilly
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Research funding: TG Therapeutics, Genentech/Roche, Bristol Myers Squibb, Gilead, Morphosys, AbbVie
Other remuneration: Speaker's bureau - Gilead, AstraZeneca, Bristol Myers Squibb, Phamacyclics, Janssen, Epizyme

447 | COMBINATION OF THE PD-1 INHIBITOR NIVOLUMAB AND IMMUNOMODULATORY DRUG LENALIDOMIDE IN RELAPSED HODGKIN AND LARGE B-CELL LYMPHOMA: RESULTS FROM A PHASE I/II STUDY

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Introduction: Lenalidomide (len) and nivolumab (nivo) each have single agent activity in relapsed Hodgkin lymphoma (HL) and large B-cell lymphoma (LBCL) with potential for additive or synergistic activity. The immunomodulatory properties of this combination may salvage response to prior adoptive cellular therapy. We conducted a multicenter, open label, phase 1/2 study to determine the recommended phase 2 dose (RP2D) of len and nivo, and to assess the toxicity and preliminary efficacy of the combination in relapsed HL and LBCL.

Methods: Adults with relapsed LBCL ineligible for autologous transplant (ASCT) or relapsed HL with ≥2 prior lines of therapy were eligible. Nivo 240 mg IV every 2 weeks for cycles 1–4 (28 day cycle) and 480 mg IV every 4 weeks beginning cycle 5 was given for up to

12 cycles. Len was given days 1–21 according to dose level (DL) and continued until progression.

Results: Thirty-six patients signed informed consent and were treated, including 10 in the phase I cohort, 10 in the phase Ib HL cohort, and 16 in the phase II LBCL cohort. Dose limiting toxicity (DLT) occurred in 2/4 patients at DL 1 (len 15 mg) and included grade 3 rash and grade 3 generalized weakness. Six patients were treated at DL -1 (len 10 mg) with no DLT and thus 10 mg len was selected as the RP2D. The most common adverse events (AE) included diarrhea (44%), rash (42%), and hypothyroidism (25%). Grade ≥3 AE included SARS CoV2 infection (11%), fatigue (8%), pulmonary embolism (3%), and Stevens-Johnson Syndrome (SJS) (3%).

Baseline characteristics for the phase Ib HL cohort included median age 28.5 (range 19–43), male sex in 9/10 patients, classical HL in 9 and nodular lymphocyte predominant HL in 1, prior brentuximab in 8/10, prior ASCT in 5/10, prior PD-1 inhibitor in 1/10, and a median of 3 prior treatments (range 2–9). The overall response rate (ORR) was 70% including 30% complete response (CR). The median progression free survival (PFS) and overall survival (OS) were not reached (Figure). Two patients completed 12 cycles of nivo and remain on len treatment. In total 6 patients (2 from phase I and 4 from phase 1b) with HL underwent consolidative ASCT ($n = 2$) or allogeneic transplant (allo-HCT) ($n = 4$) directly following discontinuation of study treatment, and all 6 remain alive and relapse-free at data cut-off.

For the phase 2 LBCL cohort, the median age was 62, 12/16 patients were male, 14/16 had prior CAR-T, and the median prior treatments were 4 (range 2–5). The ORR was 37%, including 12% CR. The median PFS was 2.6 months with a median OS of 12.3 months. Both patients with CR received CAR-T as the prior treatment and responses were ongoing beyond 12 months.

Conclusions: The combination of nivo and len has an acceptable toxicity profile and a high response rate in HL, including utilization as salvage prior to consolidative transplant. In LBCL, while the ORR was similar to len monotherapy, two patients with prior CAR-T achieved sustained responses.

Encore Abstract - previously submitted to EHA 2023

The research was funded by: Bristol Myers Squibb

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Hodgkin lymphoma, Immunotherapy

Conflicts of interests pertinent to the abstract.

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Research funding: Novartis, Nurix Therapeutics

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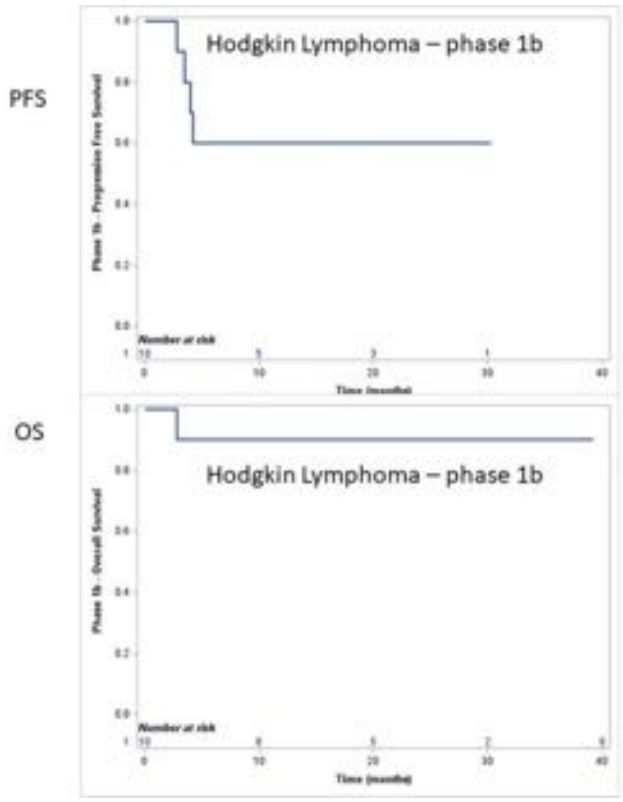
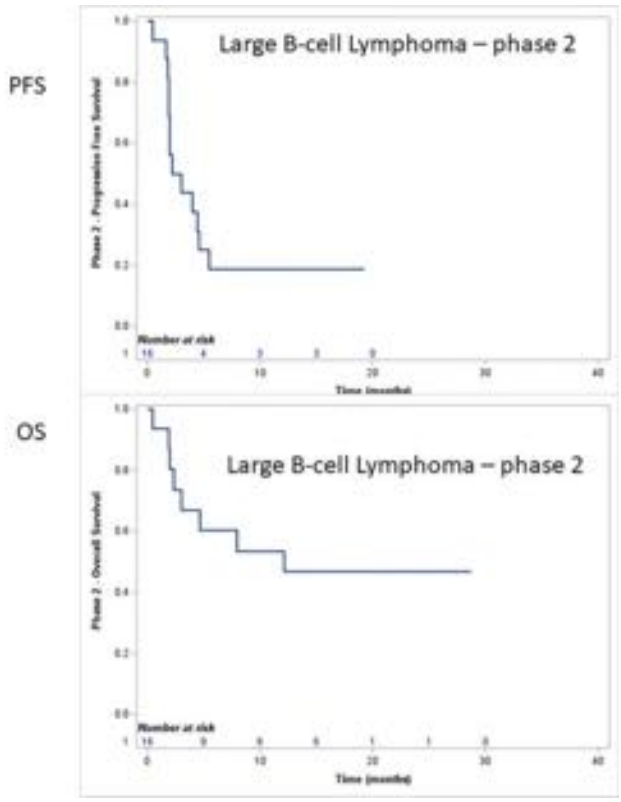
Research funding: Genentech, Acerta, Millenium, Bristol-Myers Squibb





448 | **RADIOTHERAPY (RT) & DURVALUMAB IN RELAPSED/ REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) & FOLLICULAR LYMPHOMA (FL). THE PHASE I "RADD" STUDY**

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Introduction: DLBCL & FL are exquisitely radiosensitive. RT offers durable in-field remissions & good palliation in relapsed/refractory (RR) disease. RT also stimulates anti-tumour immunity through several mechanisms and is synergistic with immunotherapy such as PD1/PDL1 inhibitors in preclinical & solid tumour studies. PD1/PDL1 inhibitors are highly efficacious in some lymphomas, but monotherapy in heavily pre-treated DLBCL & FL pts is disappointing. RT to multiple disease sites may broaden the spectrum of tumour antigen release and overcome clonal variation between disease sites further augmenting local & distant (abscopal) therapeutic response when given with PD1/PDL1 inhibition.

We describe primary results of a phase I study of RT treatment dose- & volume-escalation with concurrent durvalumab-a PDL1 inhibitor, in RR DLBCL & FL.

Methods: RaDD (NCT03610061) is a phase I, 3+3 dose escalation study in adult transplant-ineligible RR DLBCL & FL. Pts received 5 or 10 fractions of external beam RT dose range 2.5–30 Gy to between 1 and 3 target sites plus continuous Durvalumab 1500 mg IV 4-weekly starting Day 2 of RT until PD (RT+D). Primary endpoint was recommended phase two dose (RP2D) of RT. Secondary endpoints were response rate (Lugano criteria), toxicity, progression-free & overall survival (PFS & OS). The DLT period was 28 days. Correlative blood & tissue markers, including targeted paired-biopsy analyses and a novel PET substudy of ^{89}Zr-Durvalumab & CD8 minibody ^{89}Zr-Df-IAB22M2C were performed.

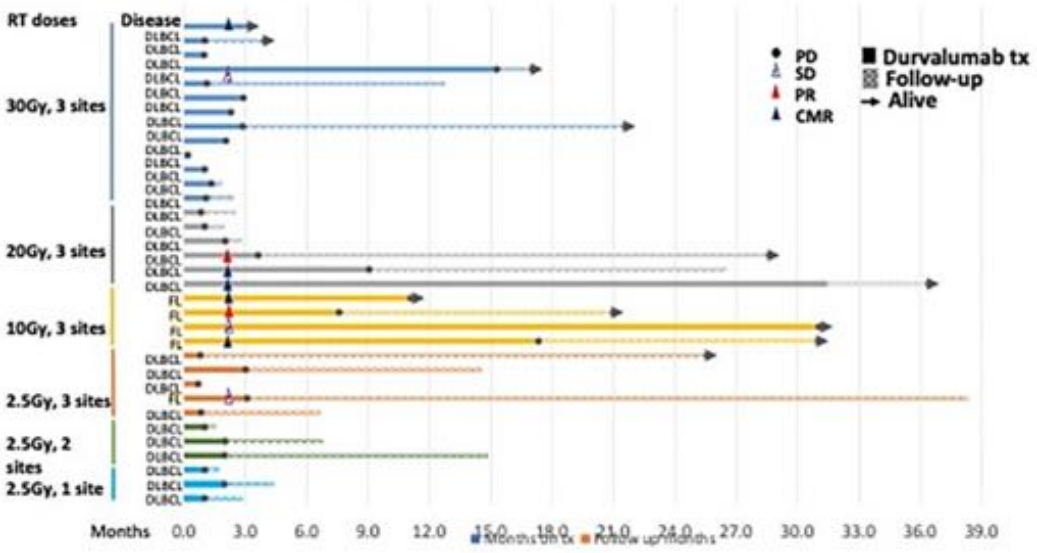
Results: 34 pts were eligible; 5 FL, 29 DLBCL. Median age was 74y (range 49–87) median prior lines was 2 (range 1–3). No DLTs occurred. RT RP2D was 20 Gy/5# to 3 sites in FL & 30 Gy/10# to 3 sites in DLBCL (Figure 1). Most common treatment emergent G3-4 adverse events were anaemia (9%, n = 3), neutropenia (11%, n = 4), liver enzyme elevation (5%, n = 2) No pts stopped Durvalumab due to AEs. 66% (16/24) of evaluable pts achieved some reduction in target lesion tumour burden, (11/19 DLBCL and 5/5 FL) with 33% of pts achieving shrinkage >50%. ORR by Lugano criteria was 60% in FL (CMR 40%); 14% in DLBCL (CMR 10%), all occurred at RT doses of 10 Gy or higher to 3 sites. Median duration of response was 5.6 months (10 months FL; 3 months DLBCL), median PFS & OS were 1.9 months and 4.3 months respectively.

PET and correlative biomarker substudy results will be presented separately.

Conclusions: RT+D with RT doses up to 30 Gy/10# to 3 disease sites is safe with minimal toxicity and offers promising response rates in FL. Activity was seen in >50% of DLBCL lesions although overall response rates were low. These data are broadly applicable to both lymphoid and solid malignancies receiving PD1/PDL1i requiring multi-site radiotherapy and the RT/PDL1i combination is being further explored with an anti-CD20 monoclonal antibody in FL (NCT04962126).

The research was funded by: Astra Zeneca who supplied durvalumab and research funding. The Victorian Cancer Agency, and ^{89}Zr-Df-IAB22M2C was supplied by imaginab.

Figure 1: Summary of responses according to RT dose level & disease



Keywords: Aggressive B-cell non-Hodgkin lymphoma, Indolent non-Hodgkin lymphoma, Radiation Therapy

Conflicts of interests pertinent to the abstract.

E. A. Hawkes
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Research funding: Institutional research funding from Astra Zeneca, Roche, Bristol Myers Squibb, Merck KgA and Merck
Educational grants: Astra Zeneca

J. Shortt
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Honoraria: Mundipharma, Novartis
Research funding: Amgen, BMS, Astex outside the submitted work

A. M. Scott
Research funding: astra zeneca for the submitted work, supply of CD8 imaging probe (IAB22M2C) from ImaginAb for conduct of the study (to Institution),

M. Macmanus
Research funding: astra zeneca (to institution)

449 | RISKS AND BENEFITS OF PHASE 1 CLINICAL TRIALS FOR PATIENTS WITH RELAPSED OR REFRACTORY LYMPHOMA, FROM 2008 TO 2023

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Introduction: Previous reviews of phase 1 trials in oncology have reported a treatment response rate of 4%–6% and a toxicity-related mortality rate of 0.5%. These results may not reflect current Phase 1 trial rates for patients with lymphoma.

Methods: All non-pediatric phase 1 trials for relapsed or refractory (R/R) lymphoma approved by the Cancer Therapy Evaluation Program of the Institut Gustave Roussy between 2008 and 2023 (cut-off date 05 January 2023) were reviewed. We reported on overall survival (OS), treatment response rates, treatment-related deaths, and the number of patients who benefit to have received a drug in clinical trial which was further approved by the health authorities (FDA or EMA).

Results: We analyzed 50 trials involving 447 participants (pts) with R/R lymphoma who received at least one dose of treatment. All patients were assessed for toxicity and 382/447 (85%) for treatment response. The median (range) age of patients was 64.9 (19.2–88.5) years. The median of treatments received before entering the trial was 3 (1–13). The main types of lymphoma were DLBCL (n = 253; 56.6%), PTCL (n = 45; 10.1%), Hodgkin (n = 40; 8.9%) and FL (n = 39; 8.7%). The overall response rate (i.e complete and partial responses) was 23.6%. Drug classes in trials included epigenetic modifiers (n = 99 pts; 22.1%), Proteolysis Targeting Chimeras (PROTAC) (n = 90; 20.1%), IO (n = 77; 17.2%), anti-apoptotic inhibitor (n = 50; 11.2%), molecular targeted therapy (n = 46; 10.3%), T-Cell Engagers (n = 23; 5.1%), antibody drug conjugated (n = 20; 4.5%), monoclonal antibody (n = 17; 3.8%), cycle cellular inhibitor (n = 8; 1.8%), gamma secretase inhibitor (n = 8; 1.8%), chemotherapy (n = 5; 1.1%), antiangiogenic (n = 4; 0.9%). Trials including drug further approved by health authorities involved 84/447 (18.8%) of patients and had an overall response rate of 32.9% (26/79 evaluable pts). The overall rate of deaths due to toxic events was 0.45% (2/447 pts). The median OS of patients was 14.1 (CI95% 11.7–17.9) months, with significant variation among lymphoma types ($p < 0.0001$) (Figure 1). Poor OS was observed for

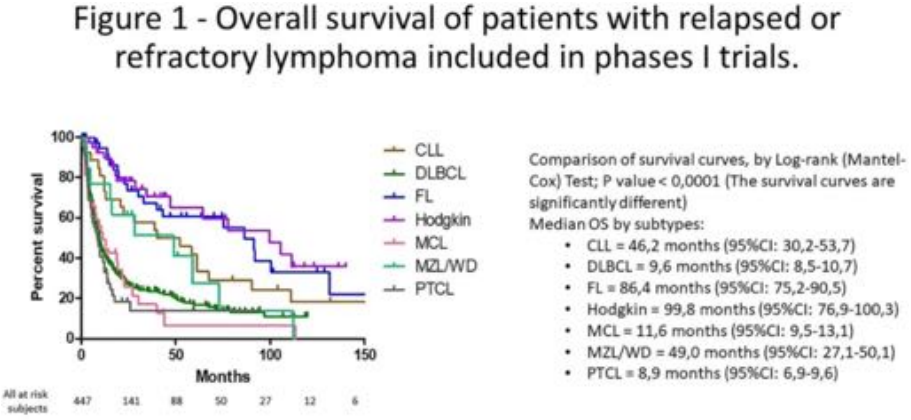

FIGURE 1 Overall survival of patients with relapsed or refractory lymphoma included in phase 1 trials from 2008 to 2023, according to the lymphoma type (CLL = Chronic lymphoid leukemia; DLBCL = Diffuse large B cell lymphoma; FL = Follicular lymphoma; MCL = Mantle cell lymphoma; MZL = Marginal zone lymphoma; WD = Waldenstrom disease; PTCL = Peripheral T cell lymphoma).

patients with relapsed or refractory with peripheral T-cell lymphoma (8.9 months CI95% 6.9–9.6) (Figure 1).

Conclusion: Overall response rates among phase 1 trials for patients with R/R lymphoma are higher than those reported with phase 1 in oncology. Toxicity-related mortality rates are similar those reported with phase 1 in oncology.

The research was funded by: Ideogen (funding for clinical data analysis)

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Aggressive T-cell non-Hodgkin lymphoma, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

J. M. Michot
Honoraria: Ideogen (clinical data analysis)

450 | REGULATORY APPROVALS AND SURVIVAL BENEFIT FOR NOVEL LYMPHOMA DRUGS FROM 2013–2022

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Increasingly, novel agents are approved for the treatment of lymphoma by the US Food and Drug Administration (FDA) via accelerated approval and using single arm trials and surrogate efficacy measures, which leave uncertainty as to their clinical benefit.

Methods: We reviewed the FDA website and Drugs@FDA to identify approvals, conversions and withdrawals of novel agents for lymphoma from 2013 to 2022. From FDA approval summaries, we collected efficacy outcomes for pivotal trials, trial design, and type of approval (accelerated or regular). We extracted confirmatory trial characteristics and results from PubMed.

Results: The FDA approved 19 novel drugs and 4 cellular therapies across 38 lymphoma indications. 25 (66%) indications received accelerated approval. All initial approvals were based on changes to surrogate measures: 7 (18%) on progression-free survival, 11 (29%) on overall response rate (ORR) plus duration of response, and 20 (53%) on ORR alone. 27 (71%) indications were approved based on single arm trials (22 accelerated, 5 regular). Just 6 (16%) indications have shown overall survival (OS) benefit in randomized trials. Of 25 accelerated approval indications, 4 (16%) have been converted, while 4 have been withdrawn due to toxicity (all Pi3K inhibitors).

Conclusions: Many lymphoma therapies are FDA-approved based on single-arm trials and surrogate measures, while few have confirmed OS benefit. Timely randomized trials with meaningful clinical endpoints can help patients and clinicians choose among therapeutic options.

	Approval Year	Indication	Accelerated Approval	Efficacy outcome	Subsequent OS benefit	Accelerated approval outcome: Ongoing (O), Converted (C), withdrawn (W)
Obinutuzumab	2013	CLL	-	PFS	Y	-
	2016	FL	-	PFS	Y	-
Lenalidomide	2013	MCL	-	ORR	N	-
	2019	FL, MZL	-	PFS	Y	-
Ibrutinib	2013	MCL	Y	ORR	N	O
	2014	CLL	Y	ORR	Y	C
	2015	WM	-	ORR	N	-
	2017	MZL	Y	ORR	-	O
Belinostat	2014	PTCL	Y	ORR	-	O
Idelalisib	2014	FL/SLL	Y	ORR	N	W
	2014	CLL	-	PFS	N	-
Nivolumab	2016	HL	Y	ORR + DOR	-	O
Venetoclax	2016	CLL	Y	ORR	N	C
Pembrolizumab	2017	HL	Y	ORR	N	C
	2018	PMBCL	Y	ORR	-	C
Copanlisib	2017	FL	Y	ORR	N	O
Acalabrutinib	2017	MCL	Y	ORR	-	O
	2019	CLL	-	PFS	N	-
Duvelisib	2018	FL	Y	ORR	-	W
	2018	CLL	-	PFS	N	-
Polatuzumab vedotin	2019	DLBCL	Y	CRR + DOR	Y	O
Zanubrutinib	2019	MCL	Y	ORR	-	O
	2021	MZL	Y	ORR + DOR	-	O
	2021	WM	-	ORR	N	-
Tazemetostat	2020	FL	Y	ORR + DOR	-	O
Selinexor	2020	DLBCL	Y	ORR + DOR	-	O
Tafasitamab	2020	DLBCL	Y	ORR	-	O
Umbralisib	2021	MZL	Y	ORR + DOR	N	W
	2021	FL	Y	ORR + DOR	-	W
Loncastuximab tesirine	2021	LBCL	Y	ORR + DOR	-	O
Mosunetuzumab	2022	FL	Y	ORR	-	O
Tisagenlecleucel	2018	LBCL	-	ORR	N	-
	2022	FL	Y	ORR + DOR	-	O
Axicabtagene ciloleucel	2017	LBCL	-	ORR	N	-
	2021	FL	Y	ORR + DOR	-	O
Brexucabtagene autoleucel	2020	MCL	Y	ORR	-	O
Lisocabtagene maraleucel	2021	LBCL	-	ORR + DOR	N	-

The research was funded by: Arnold Ventures

Keyword: Therapeutics and Clinical Trials in Lymphoma

Conflicts of interests pertinent to the abstract.

E. R. S. Cliff
Research funding: Arnold Ventures

W. B. Feldman
Research funding: Arnold Ventures

A. S. Kesselheim
Research funding: Arnold Ventures

451 | ASSOCIATION BETWEEN GERIATRIC IMPAIRMENTS AND QUALITY OF LIFE IN OLDER ADULTS WITH LYMPHOMA ON ORAL TARGETED THERAPIES: A ONE-YEAR PROSPECTIVE STUDY

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Background: While oral targeted therapies (OTT) have transformed the care of patients (pts) with lymphoma, adherence, cost, and chronic low-grade toxicities with subsequent impact on health-related quality of life (HRQoL) remain challenging issues. There are limited data on HRQoL in older adults (OA), who tend to be more vulnerable to treatment-related adverse effects. We prospectively evaluated the role of geriatric assessment (GA) in predicting HRQoL and adherence in OA with lymphoma on OTT.

Methods: Pts ≥70 years (yrs) with lymphoma, initiating or already on OTT were included. A GA was performed at baseline; pt, disease, and OTT characteristics were recorded. Pts were followed monthly for the first 3 months (mos), then every 3 mos for 1 year. QoL was measured at each visit using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30 (EORTC QLQ-C30) and EORTC QLQ- chronic lymphocytic leukemia 16 (EORTC QLQ-CLL16) modules. The log QoL scores were modeled as a function of visit and mean scores at 12 months were compared to baseline using a linear mixed model.

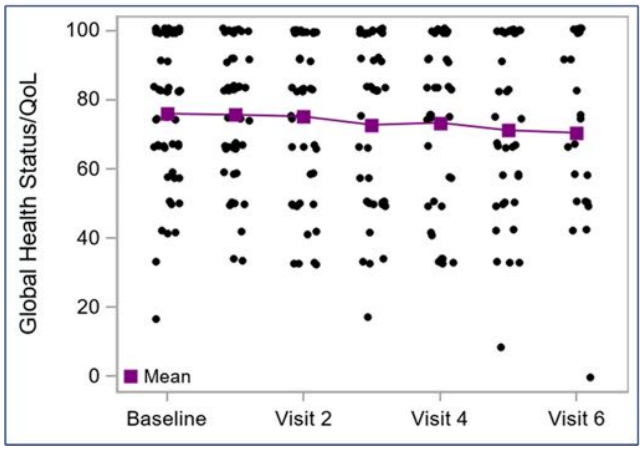
Results: We enrolled 50 pts. Median age was 77 yrs (70–93 yrs) with 88% pts having at least 1 geriatric syndrome (GS), including cognitive impairment (22%), depression (24%), polypharmacy (86%) and falls (16%); 50% pts had ≥2 GS; 50% having an impaired 4-meter gait speed (<1 m/s); 46% having an abnormal timed-up-and-go (TUG) time (>10s) and 86% had an adjusted CIRS-G score of ≥6. OTT included ibrutinib (54%), venetoclax (26%) and acalabrutinib (12%).

At baseline, advancing age, activities of daily living (ADL) dependence, and instrumental activities of daily living (IADL) dependence were associated with inferior global health status, physical functioning, role functioning, and cognitive functioning scores. IADL dependence was also associated with worse social functioning and most symptoms scores. An abnormal TUG was associated with lower global health score ($p = 0.002$) and cognitive functioning ($p = 0.003$).

At the end of 1 year, there was a statistically significant worsening of global health status (mean difference -8.4, $p = 0.003$) without any changes in other functional scales; however, it did not reach the predefined criterion for clinical relevance (absolute difference of >10, Figure 1). Only impaired baseline TUG was associated with significant worsening of global health status (-1.9 vs. -23.2, $p = 0.048$), physical (4.1 vs. -8.2, $p = 0.031$), role (1.3 vs. -18.5, $p = 0.026$) and social functioning (5.1 vs. -24.1, $p = 0.016$), and increasing fatigue scale (-11.5 vs. 20.4, $p < 0.001$) over 1 year. Other geriatric impairments did not impact changes in HRQoL over time.

Conclusions: An abnormal baseline TUG is associated with longitudinal decline in HRQoL in OA with lymphoma on OTT and could be used as a screening tool to determine need for early intervention and closer monitoring in this vulnerable population.

Figure 1. Trends in global health status during 12-month follow up in older adults with lymphoma on oral targeted therapies



The research was funded by: Roswell Park Alliance Foundation

Keywords: Cancer Health Disparities, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract.

P. Torka
Consultant or advisory role: Genenetech, GenMab, Lilly USA, Seagen

PEDIATRIC / YOUNG ADULTS

452 | WHAT DRIVES PEDIATRIC BURKITT LYMPHOMA? TIMING EVENTS IN THE EVOLUTION OF CANCER USING SINGLE-CELL WHOLE GENOME SEQUENCING

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Princess Maxima Centre for Pediatric Oncology, Utrecht, The Netherlands

Introduction: Burkitt lymphoma (BL) is a rare but highly aggressive B-cell non-Hodgkin lymphoma. BL exhibits a characteristic immunophenotype that is positive for pan-B cell markers and CD10. The genetic hallmark of BL is the translocation of the MYC oncogene under the regulation of an immunoglobulin (IG) heavy or light chain enhancer, resulting in MYC protein overexpression. Notably, MYC translocation by itself is not sufficient for BL oncogenesis and a variety of cancer genes are recurrently mutated. BL can be divided epidemiologically but also, more recently, genetically based on driver mutations including DGG-BL (DDX3X, GNA13, and GNAI2), IC-BL (ID3 and CCND3), and Q53-BL (quiet TP53). Despite high survival rates, pediatric BL patients suffer from long-term side effects and relapses are usually fatal.

In order to develop more targeted and less toxic therapies, a better understanding is needed of the ethology of the disease. Therefore, our aim is to characterise the cell-of-origin (COO) and dissect the life history of BL subtypes, by pinpointing when during tumorigenesis somatic mutations play a role and by identifying the rate-limiting steps of malignant transformation.

Method: We collected single-cell suspensions of BL patient samples, including lymph node biopsies, bone marrow aspirates, as well as ascites and pleural fluid. To perform flow cytometry, single cells were stained with DAPI and a panel of antibodies: CD10/CD45/CD19 or CD10/CD3/CD20. Live B cells were separated with the DAPI-CD45+ CD19+ or DAPI-CD3-CD20+ phenotype. Subsequently, CD10+ B cells and CD10- B cells were sorted in 96-well plates (Figure 1). To confirm the presence or absence of the IG::MYC translocation a PCR was perfomed using patient-specific primers that flank the translocation locus. Whole genome amplification was carried out on the DNA of single cells using the Primary Template-directed Amplification (PTA) technique that was subsequently whole genome sequenced.

Results: From a bone marrow sample of a 4-year-old female BL patient we found that 1% of immune cells were CD10+ B cells, while 17% of B cells were negative for the CD10 marker (Figure 2A). In the lymph node sample from the same patient, we found that 87% of B cells were CD10+ and 9% were CD10- (Figure 2B). PCR confirmed the MYC translocation in 2/6 CD10+ and 0/6 CD10- bone marrow-derived B cells (Figure 3).

Conclusions: We have successfully isolated malignant (i.e., myc-translocated) and non-malignant B cells from a BL patient. Upon sequencing these cells, we will study the different mutational

Fig. 1

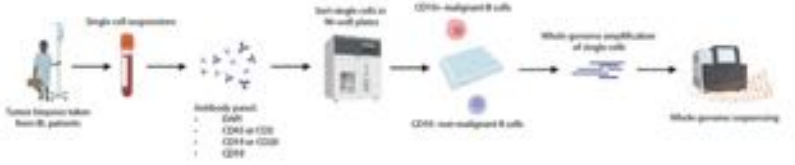


Fig. 2A

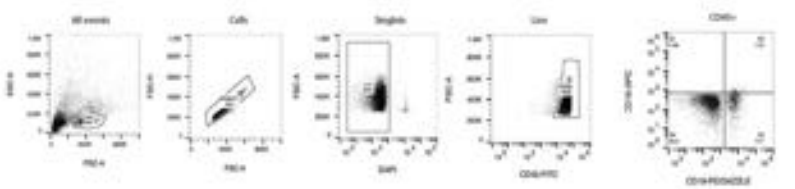


Fig. 2B

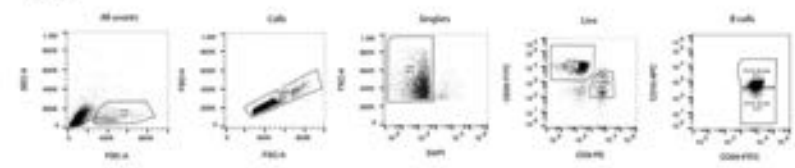


Fig. 3

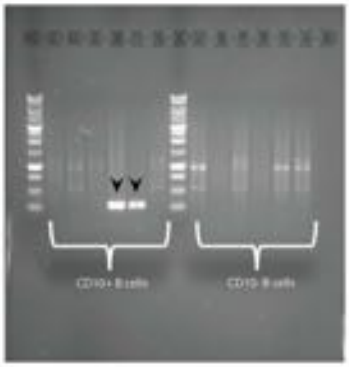
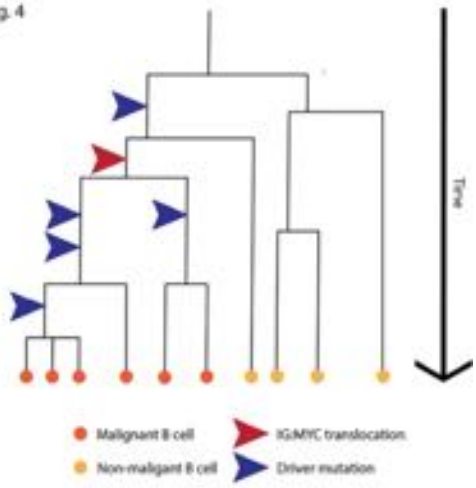


Fig. 4



processes that occur during tumorigenesis, and time driver events using phylogenetic inference (Figure 4). Indeed, we plan to sort more patient material to better understand the heterogeneity within and between patients which could be influenced by factors such as age, sex, or BL subtype.

Keywords: Genomics, Epigenomics, and Other -Omics, Non-Hodgkin (Pediatric, Adolescent, and Young Adult), Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

453 | ANALYSES OF A PATIENT WITH 3 SEQUENTIAL POST TRANSPLANT LYMPHOPROLIERATIVE DISEASE (PTLD) BIOPSIES REVEAL PERSISTENCE OF HISTONE 1 GENE MUTATION, SUSPECTED TO MEDIATE PTLD

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Introduction: Post allograft transplant patients are prone to develop a continuum of lympho-proliferative diseases (PTLD) that exhibit distinct clinicopathological forms that range from benign to malignant. The molecular pathogenesis of PTLD is not well established.

Methods: We analyzed an unusual case of a 15 year old child who received a lung transplant at age 7 and developed PTLD first in the right tonsil (polymorphic PTLD) 4 months post transplant and then in the left shin and associated lymph node (PTLD-Burkitt Lymphoma) 4 years later. Histopathology and immunohistopathology (IHC) features of the left shin mass were typical for Burkitt Lymphoma with diagnostic features of CD20+, CD10+ve, TdT-ve, EBER+ve, IGH clonal for B cells and *Ig-cMyc* fusion positve by FISH analysis. The child received chemotherapy and was in remission for 3 years. At 8 years post transplant, he developed an enlargement of the left tonsil. Histopathology and IHC lack evidence of recurrent Burkitt Lymphoma as the B cells are polyclonal, CD10-ve and EBV-ve. FISH was negative for *Ig-cMyc* fusion. A diagnosis of a polymorphic PTLD was made. With the recently available TruSight RNA Pan-Cancer assay, RNA was extracted from the two most recent tissue samples and NGS libraries were enriched using the 1385 gene panel.

Results show the PTLD- Burkitt Lymphoma has additional mutations in the *cMyc* locus and *TP53*. The distinctly common mutations notable for Pediatric Burkitt Lymphoma in immunocompetent patients such as *ID3*, *DDX3X*, *ARID1A and SMARCA4* that are noted in our database and described in a recent publication by B. Burkhardt et al (Nature communication 13:3881;2022) are absent. *cMyc*, *TP53* and all of these mutations are absent in the post chemotherapy polymorphic PTLD in the right tonsil. However, a mutation of Linker *Histone 1 (H1-4)* gene is detected in the Burkitt PTLD mass and this recurrent polymorphic PTLD tonsil.

Conclusions: This result shows there is a persistence of non clonal B cells that are chemotherapy resistant. The patient is currently stable under clinical surveillance. The pathological consequence of *H1ST-1 (1-4)* mutation in the B cells of this patient appears to be supported by a study in a preclinical mouse model that Histone H1 loss drives lymphoma by disrupting 3D chromatin structure (N. Yusufova et. al. Nature 589:299-305; 2021). In this study, knock-in mice carying this mutation alone have prolonged survival as compared with knock-in mice with genetic constructs that contain additional oncogenic driver genes. Based on our findings of the persistence of lymphoid cells with a mutation of gene encoding for a epigenomic gene[*HIST-1 (1-4)*], we suspect this mutation plays a role that drives the development of PTLD in this patient.

Keywords: Diagnostic and Prognostic Biomarkers, Non-Hodgkin (Pediatric, Adolescent, and Young Adult), Pathology and Classification of Lymphomas

No conflicts of interests pertinent to the abstract.

454 | ABBREVIATED WHOLE-BODY MRI FOR FOLLOW-UP IN PEDIATRIC LYMPHOMA: RESULTS OF A MULTICENTER PROSPECTIVE STUDY

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Introduction: The evaluation of treatment response in pediatric lymphoma is critical for making informed treatment decisions and improving patient outcomes. Positron emission tomography/computed tomography (PET/CT) and traditional whole-body magnetic resonance imaging (MRI) are the most commonly used imaging modalities for assessing treatment response in lymphoma. However, PET/CT exposes patients to ionizing radiation, and its high cost and limited availability may limit its use for routine follow-up. Traditional whole-body MRI is a noninvasive alternative, but it has some limitations, including prolonged acquisition time and the need for sedation, which can be burdensome for pediatric patients. Abbreviated whole-body MRI (AWBMRI) has emerged as a promising imaging modality for monitoring treatment response in pediatric lymphoma. AWBMRI requires less time and is typically performed without

Table 1: Abbreviated Whole-Body Diffusion-weighted MRI Protocols

	DWIBS	T2-dixon	T2-STIR	T2WI+fs	T2-HASTE
Plane	axial	axial/coronal	axial/coronal	axial	coronal
body part	whole-body	neck	thorax	abdomen/pelvis	abdomen/pelvis
TR/TE,ms	8290/72	4230/72	4270/69	3350/106	1200/98
Inversion time,ms	240	NA	220	NA	NA
Field of view ,mm²	430×349	280×280/240×195	380×297/450×309	340×340	350×350
Acquisition matrix	128×104	256×179/320×182	320×175	256×256	256×256
Acquired Voxel Size ,mm³	3.36×3.36 ×5	1.09×1,56×3/1.33×1.0 7×4	1.19×1.70×5.5/1.41×1.7 7×5	1.33×1.33×5	1.37×1.37×5
B-values (s/mm²)	b50、b800				
No. of signals averaged	1	1	2	1	1
Total scan time (min)	9-11min	3-5min	3-5min	3-10min	1min

sedation, making it a potentially more feasible and patient-friendly alternative to traditional MRI for routine follow-up.

Methods: A multicenter prospective study was conducted, enrolling 103 pediatric patients aged 0 to 18 years with pathologically confirmed lymphoma. All patients underwent both PET/CT and abbreviated whole-body MRI at baseline and during follow-up. Image quality of abbreviated whole-body MRI was evaluated using a 5-point Likert scale, and interobserver agreement was assessed. Sensitivity, specificity, and accuracy of abbreviated whole-body MRI for detecting residual or recurrent disease were calculated, with PET/CT used as the reference standard.

Results: Image quality of abbreviated whole-body MRI was rated as good or excellent in 97% of cases, with high interobserver agreement. Abbreviated whole-body MRI demonstrated a sensitivity of 90%, specificity of 96%, and accuracy of 94% for detecting residual or recurrent disease, with excellent agreement between abbreviated whole-body MRI and PET/CT findings.

Conclusion: Abbreviated whole-body MRI is a feasible and accurate imaging modality for follow-up of pediatric lymphoma patients undergoing various treatments, with high diagnostic performance and excellent image quality. The non-invasive nature and lack of radiation exposure make it a favorable option compared with PET/CT, especially for pediatric patients.

Keyword: Other

No conflicts of interests pertinent to the abstract.

455 | CHARACTERIZATION OF CLONAL EVOLUTION IN PEDIATRIC LYMPHOMA USING SINGLE-CELL TRANSCRIPTOMICS

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Lymphomas are the third most common type of malignancy among children, affecting 10%–15% of all new childhood cancer patients. Lymphomas are divided into three main categories: B (40%) and T (20%) cell lymphomas and Hodgkin lymphomas (HL, 40%). Current treatments are based on radiotherapy, chemotherapy, or monoclonal antibodies. Despite effectiveness, these intensive treatments are associated with severe adverse effects, including infertility, secondary malignancies, and heart failure. Moreover, drug resistance is associated with relapse and leads to poor survival. Therefore, there is an unmet need to develop precision treatment in both primary and relapse lymphoma.

The aim of our research is to identify how changes in gene expression in individual B and T cells lead to cell transformation and lymphoma. We hope to identify signaling pathways in B and T cells that are dysregulated in pediatric lymphoma and then formulate future treatments.

We performed single-cell RNA sequencing on pediatric lymphoma and blood samples and compared them with reactive lymph nodes as control samples. This allowed us to identify molecular alterations at the single-cell level providing insights into the intratumoral heterogeneity. Moreover, we performed VDJ sequencing of the B cell receptor (BCR) and the T cell receptor (TCR) genes to track the clonality of lymphoma cells and to identify major and minor expanded clones. Our preliminary analysis of B cell lymphoma from two pediatric patients identified clonal expansions of dominant transformed clones based on BCR sequencing within each patient. Furthermore, these expanded clones were enriched for proliferative genes. Immunohistochemistry and flow cytometry will be used as validation methods for our single-cell analysis.

Overall, our study has the potential to provide insights into the cellular and molecular mechanisms underlying pediatric lymphoma by identifying unique features of each tumor for future precision medicine treatment.

Keywords: Genomics, Epigenomics, and Other -Omics, Non-Hodgkin (Pediatric, Adolescent, and Young Adult), Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

INFECTIONS

456 | PREDICTING COVID-19 INFECTION RISK IN LYMPHOMA BY IMMUNE MONITORING

R. Wijaya[1], N. Campbell[1], M. Johnson[2], B. Stuart[3], A. Kelly[1], N. Tipler[1], A. Coleman[4], A. Turaj[1], T. Menne[5], M. Ahearne[6], V. Willimott[7], A. Bowzyk Al-Naeeb[8], C. P. Fox[9], G. P. Collins[10], A. O'Callaghan[11], A. J. Davies[1], D. Goldblatt[2], S. H. Lim[1]

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Introduction: Patients with B-cell lymphoma have poorer antibody responses to COVID-19 vaccines compared to patients with other malignancies. However, the immune responses are heterogeneous and its association with clinical outcomes are poorly understood. Here, we study the association between antibody and cellular responses with the outcomes from COVID-19 infection from the PROSECO study.

Methods: THE UK PROSECO study is a prospective observational cohort study evaluating COVID-19 vaccine response in people with lymphoma. Peripheral blood antibody titres (anti-spike (S) IgG by Mesoscale Discovery), antibody avidity (surface plasmon resonance) and IFNγ T-cell responses (ELISpot) against spike protein after two to four COVID-19 vaccines, and clinical outcomes data were collected.

Results: 524 patients (92 Hodgkin lymphoma, 180 aggressive B non-Hodgkin lymphoma (B-NHL), 234 indolent B-NHL and 18 peripheral T-cell lymphoma) were included: 334 (84·3%), 315 (79·5%) and 266 (67·1%) participants were eligible for post-two, three and four vaccine dose analysis, respectively. Breakthrough infections (BTI) occurred in 20 (5.9%), 40 (12.7%) and 36 (13.5%) participants after two, three and four vaccine doses. Of 96 participants with BTI, 12 (12.5%) needed hospitalisation. No deaths were observed due to COVID-19 infection. No differences were observed in T-cell responses between BTI and non-BTI groups, but 4/9 (44.5%) hospitalised BTI cases had undetectable cellular and antibody responses. There was no association between antibody titres and infection episodes after two vaccine doses, but antibody titres were associated with lower BTI risk after three or four vaccine doses on multivariable analysis. Intriguingly, the antibody threshold associated with infection risk was lower after four than three vaccine doses (41 vs. 820 BAU/mL). We also observed stronger antibody binding avidity to SARS-CoV-2 spike receptor-binding domain (RBD) proteins from Wuhan and Omicron BQ.1 variants, with increasing vaccine doses, i.e., fourth versus third dose: 10-fold increase (p: <0.01); fourth versus second dose:100-fold-increase than the second dose (p: <0.0001) (see Figure).

Conclusion: Anti-S antibody titres can predict the risk of COVID-19 infection after three or more vaccine doses in patients with lymphoma. Repeated COVID-19 vaccination drives antibody affinity maturation and consequently improves the strength of antibody binding to virus spike proteins. Nearly half of participants who required hospitalisation for COVID-19 had undetectable antibody and cellular immunity to vaccination. Altogether, these data show the importance of booster vaccine doses and immune monitoring post COVID-19 vaccination to identify lymphoma patients who still continue to be at risk from severe COVID-19, and thus the best prophylactic and therapeutic strategies.

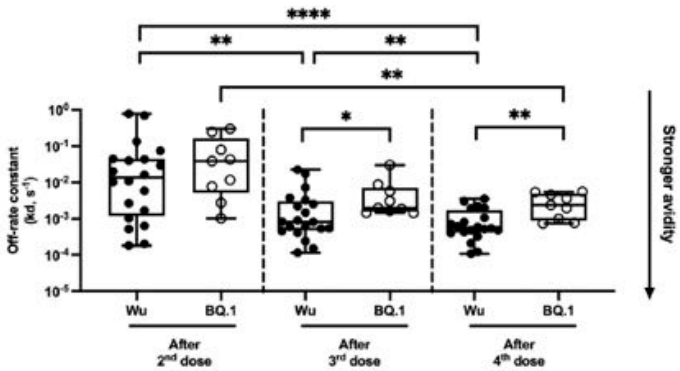

Figure. Antibodies avidity after two, three, and four vaccine doses in lymphoma. The antibody off-rate constant (kd, s^{-1}), a surrogate marker for antibody avidity, was determined from human plasma binding to SARS-CoV-2 receptor-binding domain (RBD) proteins from Wuhan-Hu-1 (Wu) and Omicron (BQ.1) strains by surface plasmon resonance. Statistical significance was performed through the Friedman test with subsequent Dunn's multiple comparisons and Mann-Whitney test, *p<0.05, **p<0.01, ****p<0.0001

The research was funded by: the Blood Cancer UK Vaccine Research Collaborative, which is led by Blood Cancer UK in partnership with Myeloma UK, Anthony Nolan and the British Society for Haematology; a Cancer Research UK Advanced Clinician Scientist Fellowship to SH Lim; Cancer Research UK/National Institute for Health Research (NIHR) Southampton Experimental Cancer Medicine Center; NIHR Southampton Clinical Research Facility (Southampton Research Biorepository) and NIHR Southampton Biomedical Research Center; NIHR Great Ormond Street Biomedical Research Center and the NIHR Oxford Biomedical Research Center and CRUK Experimental Cancer Medicines Center.

Keywords: Lymphoid Cancers, Other: Covid-19, Therapeutics and Clinical Trials in Lymphoma, vaccination

Conflicts of interests pertinent to the abstract.

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457 | IMPACT OF COVID-19 INFECTION ON BISPECIFIC ANTIBODIES TREATMENT IN PATIENTS DIAGNOSED WITH B-CELL LYMPHOPROLIFERATIVE DISORDERS

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Introduction: Bispecific antibodies (BsAbs) are a promising therapeutic approach for the treatment of B-cell lymphoproliferative disorders. Limited data is available regarding the impact of COVID-19 in patients treated with BsAbs. We assessed the impact of COVID-19 infection on BsAbs treatment and evaluated the severity of COVID-19 infection and the seroconversion rate.

Methods: Patients treated with BsAbs at our institution were reviewed from March 2020 to January 2023. Severity of COVID-19 infection was defined according to World Health Organization (WHO) criteria. Seroconversion rate was assessed using chemiluminescence immunoassays for the determination of antibodies against SARS-CoV2 spike glycoprotein (cutoff, 40 BAU/mL). Patients who received convalescent plasma, sotrovimab or AZD7442 (cilgavimab and tixagevimab) were excluded from the seroconversion analysis.

Results: One hundred and nine patients (median age, 62 years old) were included. Most frequent diagnoses were Diffuse Large B-Cell Lymphoma (73%) and Follicular Lymphoma (18%). Median number of previous lines was 2. Ninety-four patients (86%) received an anti-CD20/CD3, 13 (12%) an anti-CD22/CD3 and 2 (2%) an anti-CD19/4-1-bb. Anti-CD20 agents in the prior 6 months had been administered alone or in combination in 61 patients (56%). Twenty-two (20%) patients had received prior CAR-T cell therapy for a median of 5 months. Eighty-six patients (79%) were vaccinated (in general with Spikevax), with an average of 3 doses. COVID-19 infection was diagnosed in 61 patients (56%); 23 (38%) presented mild COVID-19 infection, 20 (33%) moderate, 11 (18%) severe and 7 (11%) critical. Ten patients were diagnosed with a second COVID-19 episode; of these, sequencing results confirmed a reinfection in 2 patients and a persistent infection in 8 patients. Median time to first negative PCR was 34 days and 62 days for those who presented a second infection. Twenty-five patients became infected during treatment causing 84% delays and 20% discontinuations. At the time of infection, 76% of the patients had negative serology. A higher seroconversion rate was observed in the post treatment setting with BsAbs after a median of 6 months. No differences were evidenced according to recent exposure to an anti-CD20 agent (figure 1D). Patients with positive serology (24%) presented milder infection ($p = 0.009$). After a median follow up of 34.3 months, 32 patients died (29%), 19 due to progressive disease, 6 from COVID-19 pneumoniae (10%, 5 of which were in complete response), 5 from other infections and 2 of unknown causes.

Conclusions: COVID-19 infection had a significant impact on patients treated with bispecifics, with prolonged viral shedding and 80% suffering therapy delays. As with anti-CD20 agents, bispecifics affected seroconversion rate for at least 6 months. Reduced humoral immunity was associated with moderate/severe disease and mortality.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Immunotherapy, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract.

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A

		Total (n=108) (%)	(/)
Age median (range)		61,83 (30-86)	
Sex			
	Male	58,7	64/109
	Female	41,3	45/109
Diagnosis			
	Diffuse Large B Cell Lymphoma	73,4	80/109
	Follicular Lymphoma	18,3	20/109
	Mantle Cell Lymphoma	5,5	6/109
	Chronic Lymphocitic Leukemia	0,9	1/109
	Primary Mediastinal B Cell Lymphoma	0,9	1/109
	Richter's Syndrome	0,9	1/109
Number previous lines median (range)		2,0 (0,0-6,0)	
Previous rituximab or in combination			
	No	44,0	48/109
	Yes	56,0	61/109
Previous CAR-T			
	No	79,8	87/109
	Yes	20,2	22/109
Previous ASCT			
	No	89,9	98/109
	Yes	10,1	11/109
BITE combination agent			
	No combination	57,8	63/109
	Chemotherapy	11,0	12/109
	Immunotherapy	31,2	34/109
Vaccination			
	Unknown	0,9	1/109
	No	20,2	22/109
	Yes	78,9	86/109
Number doses median (range)		3,0 (0,0-5,0)	
AZD7442 administration			
	No	79,8	87/109
	Yes	20,2	22/109
Seroconversion			
	Not available	30,3	33/109
	No	25,7	28/109
	Yes	44,0	48/109
Follow up median (range)*		34,3 (1-35,3)	

CAR-T, Chimeric Antigen Receptor T
ASCT, Autologous Stem Cell Transplantation
BITE, Bispecific T cell Engager
AZD7442, cilgavimab and tixagevimab

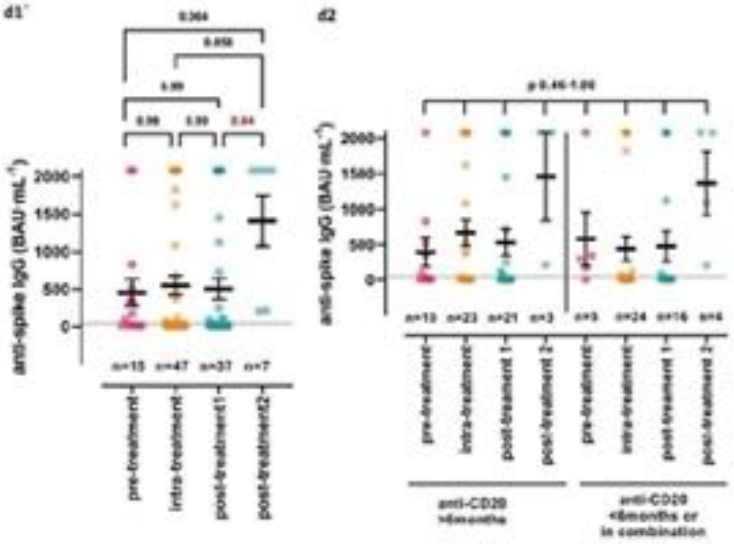
B

	COVIDpositive (n=61) (%)	(/)
COVID infection		
No	44,0	48/109
Yes	56,0	61/109
COVID infection severity		
Mild	37,7	23/61
Moderate	32,8	20/61
Severe	18,0	11/61
Critical	11,5	7/61
COVID treatment		
No treatment	36,1	22/61
Treatment	63,9	39/61
COVID specific treatment		
Remdesivir	76,9	30/39
Sotrovimab	51,3	20/39
Tocilizumab	25,6	10/39
Convalescent plasma	33,3	13/39
Paxlovid	28,2	11/39
First COVID infection median days for negativization (range)	34,0 (1,0-783,0)	
Second COVID infection median days for negativization (range)	61,0 (5,0-180,0)	
COVID infection before treatment (*)		
No	83,3	45/54
Yes	16,7	9/54
COVID infection during treatment (*)		
No	53,7	29/54
Yes	46,3	25/54
COVID infection after end of treatment		
No	55,6	30/54
Yes	44,4	24/54
BITE interrupted		
No	16,0	4/25
Yes	84,0	21/25
BITE discontinuated		
No	80,0	20/25
Yes	20,0	5/25

C

	Negative serology (n=87) (%)	(/)	Positive serology (n=12) (%)	(/)	p-value
COVID infection severity					
Mild	16,9	7/37	58,3	7/12	0,009 *
Moderate	40,5	15/37	25,0	3/12	0,332
Severe	21,6	8/37	16,7	2/12	0,711
Critical	18,9	7/37	0,0	0/12	0,104

D



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458 | EFFICACY AND TOXICITY OF HYPOFRACTIONATED RADIATION THERAPY FOR PATIENTS WITH HEMATOLOGIC MALIGNANCIES: UPDATE ON A COVID ERA ILROG COLLABORATIVE REPORT

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Purpose/Objectives: During COVID19, shorter radiation therapy (RT) courses were considered to minimize patient exposure, ensure staff safety, and conserve healthcare resources. Due to concerns with the safety of systemic therapy, RT demands were also increased. In response, guidelines were published by the International Lymphoma

	N (%)
Age in years at RT start (median, range)	68 (24-100)
Sex (male)	151 (131)
ECOG (median, range)	1 (0-4)
Diagnosis(n = 282)	
Classic Hodgkin Lymphoma	5 (2)
(DLBC): Diffuse Large B Cell	59 (21)
Mantle Cell	10 (4)
Marginal Zone	27 (10)
Follicular Grade 1-2	42 (15)
Follicular Grade 3 (A and 3B)	4 (1)
Multiple Myeloma	61 (22)
Solitary Plasmacytoma	3 (1)
Mycosis Fungoides	21 (7)
Peripheral T cell	2 (1)
Nodular Lymphocyte Predominant Hodgkin Lymphoma	2 (1)
Leukemia (including myeloid sarcoma)	12 (4)
Other	34 (12)
Therapy Intent (n=279)	
Definitive	60 (21)
Consolidative	29 (10)
Salvage	12 (4)
Palliative	170 (60)
Bridge to CAR T-cell therapy	8 (3)
If prior systemic therapy (ST) (n=156)	
Prior ST regimens >3	62 (40)
Response to ST (n=155)	
CR	37 (24)
PR	29 (19)
SD	2 (1)
PD	97 (63)
Treatment site (n=282)	
Head and neck	57 (20)
Thorax	64 (23)
Abdomen	15 (5)
Pelvis	61 (22)
Extremity	57 (20)
Central Nervous System	26 (9)
Other	2 (1)
Radiation Dose in Gy (median, range)	12 (4-36)
Fractions (median, range)	3 (1-13)
Dose/Fractionation (n=282)	
4 Gy / 1 fx;	91 (32)
7 Gy / 2fxs;	1 (1)
8 Gy / 1 fx;	25 (9)
8 Gy / 2 fxs;	10 (4)
9 Gy / 3 fxs;	1 (1)
10 Gy / 2 fxs;	1 (1)
10.5 Gy / 3 fxs;	8 (3)
12 Gy / 3 fxs;	17 (6)
14 Gy / 4 fxs;	2 (1)
16 Gy / 4 fxs;	17 (6)
17.5 Gy / 5 fxs;	6 (2)
18 Gy / 6 fxs;	2 (1)
20 Gy / 5 fxs;	43 (15)
25 Gy / 5 fxs;	14 (5)
27 Gy / 9 fxs;	25 (9)
30 Gy / 6 fxs;	10 (4)
36 Gy / 12 fxs;	7 (3)
39 Gy / 13 fxs;	2 (1)
Prior RT received in field	38 (13)
Concurrent ST	18 (6)

Radiation Oncology Group (ILROG) to guide the treatment of hematologic malignancies patients with hypofractionated radiation therapy (hRT) regimens. These guidelines suggested hRT dose/fractionation schemes based on the known radiosensitivity of various hematologic malignancies with consideration of the biologically equivalent doses in the hRT setting. However, the outcomes for these dose/fractionation regimens in terms of efficacy and toxicity are unknown.

Materials/Methods: In collaboration with ILROG, we performed a retrospective multinational, multicenter study. We included any patient treated from 1/1/2020 to 8/31/2020 with hRT given according to the published ILROG guidelines or hRT given at >3 Gy per fraction. We abstracted patient and treatment data from the respective institutional databases. CTCAE v5.0 was used to grade toxicity.

Results: We included 237 patients from 8 different institutions treated with 282 RT courses. Patient and treatment details are reported in Table 1. Median RT dose was 12 Gy (range 4–39) in a median of 3 fractions (range 1–13). Median follow up was 181 days, with 174 patients (73%) alive at last follow up. Response within the RT field was assessed in 228 sites: complete response (CR) ($n = 143$, 63%); partial response (PR) ($n = 59$, 26%); stable disease (SD) ($n = 15$, 7%); and progressive disease (PD) ($n = 11$, 5%). Maximal toxicities reported were Grade 1 ($n = 45$), Grade 2 ($n = 24$), Grade 3 ($n = 4$) and Grade 4 ($n = 1$). Grade 3 toxicities occurred with the following treatment regimens: 12 Gy in 3 fx to extremity (dermatitis, given concurrent with methotrexate); 30 Gy in 6 fx to extremity (dermatitis); 20 Gy in 5 fx to pelvis (pain); 25 Gy in 5 fx to abdomen (pain). One grade 4 toxicity occurred with 12 Gy in 3 fx to the CNS (hematologic toxicity).

Conclusions: Treatment of hematologic malignancies patients with hRT was generally well tolerated with few unexpected toxicities. Evaluation of efficacy is limited by patient and treatment heterogeneity but appears to be reasonable. These data can provide guidance for emergency situations requiring minimization of patient and staff exposure. Perhaps more importantly, hRT could be considered even in routine settings to spare patients time on treatment, especially for certain patient subgroups.

Keyword: Radiation Therapy

Conflicts of interests pertinent to the abstract.

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Research funding: Varian, ViewRay, Danish Cancer Society

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ABSTRACTS SELECTED FOR PUBLICATION

EPIDEMIOLOGY

459 | REAL WORLD AND MENDELIAN RANDOMIZATION ANALYSES OF THE IMPACT OF AUTOIMMUNE DISEASE ON CLINICAL CHARACTERISTICS IN LYMPHOMA

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Background: Previous studies have shown associations between the risk of lymphoma and autoimmune diseases (AIDs). Mendelian randomization (MR) can estimate causal effects of a modifiable exposure on outcomes. Herein, we estimated causal effects of AID on lymphoma using MR and analyzed clinical signatures in patients of AID-associated lymphoma.

Methods: A two-sample MR framework was conducted to estimate the causal effect of genetic liability for AID on lymphoma. We enrolled in patients with a history for at least one year of AID, who diagnosed with lymphoma at Shandong Provincial Hospital. For each lymphoma case, 1 lymphoma-free AID individual was identified as a control. Measures of relative risk were calculated using conditional logistic regression.

Results: Strong evidence of a potential causal effect of AID on the risk of lymphoma was found ($p = 0.040$). Slopes of MR regressions and causal estimates associated with each SNP are illustrated (**Figure 1**). In the examination of the association between single autoimmune disease and lymphoma, the only potential causal effect of Sjögren syndrome (SS) was detected ($p < 0.01$). There was no heterogeneity, and these effects were robust to various MR assumptions.

55 cases of lymphoma were collected and matched to 110 controls randomly selected. The number of patients according to AID lymphoma subtypes were described using heatmap (**Figure 2**). The median age at AID was 60 years, and the median lymphoma-diagnosing age was 40 years. The clinical course from AID to lymphoma varies considerably, with a median time of 10 years. There was a female predominance ($n = 29$, 52.7%). Cases with a history of rheumatoid arthritis (RA) accounted for 32.73% ($n = 18$), followed by psoriasis (PsO) ($n = 9$). Baseline characteristics of patients and controls did not significantly differ in sex, age at AID onset, age of matching time or duration of AID. Cohorts as generated by the matching process were balanced.

The most represented subtype was NHL ($n = 45$), of which 15 were DLBCL. Among those patients, 7 were GCB type and 1 was non-GCB type. According to incomplete IHC results, 23/28 patients expressed CD20. Ki67 index of 15 patients was greater than or equal to 60%. Median follow-up for surviving patients was 49.5 months. The 1-, 3-, and 5-year OS rates were 72.5%, 45%, and 22.5%, respectively.

On univariate analysis, factors including sex, type of AID, age at AID/lymphoma and disease duration were not related to lymphoma risk. The assessment of ORs for the history of RA and PsO revealed no significantly increased risks for lymphoma (OR 1.027 for RA, 1.022 for PsO).

Conclusions: Our study first reported the potential causality of AID on lymphoma through MR analysis. There was a strong relationship between SS and risk of lymphoma. Meanwhile, in this study, indicators including sex, type of AID, age at AID/lymphoma and disease duration were validated not related to an increased risk of lymphoma.

Keyword: aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

Figure 1 Scatter plot of SNPs associated with AID and their risks of lymphoma.

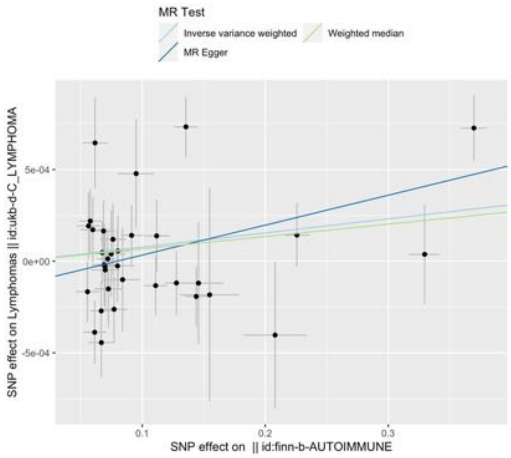
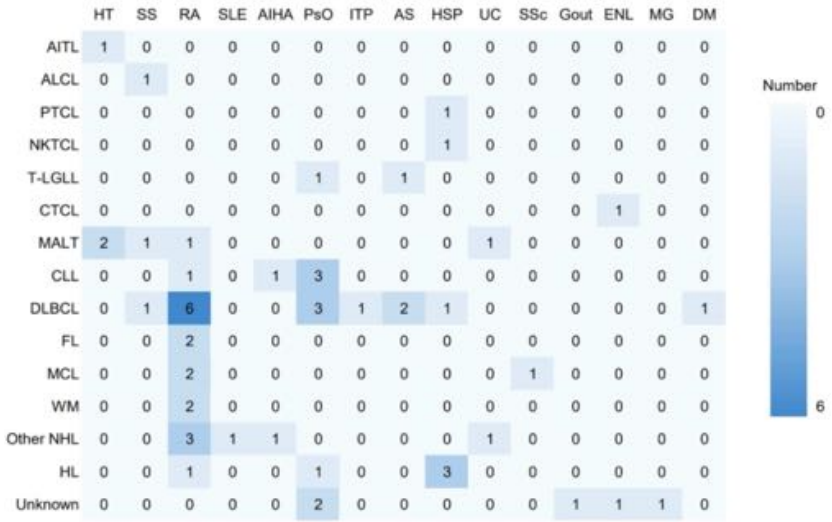


Figure 2 Heatmaps of the patients with AID associated lymphoma (n=55).

Abbreviation: AID, autoimmune disease; HT, Hashimoto's thyroiditis; SS, Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; AIHA, autoimmune hemolytic anemia; PsO, psoriasis; ITP, immune thrombocytopenia; AS, ankylosing spondylitis; HSP, Henoch-Schönlein purpura; UC, UC, ulcerative colitis; SSc, systemic sclerosis; ENL, erythema nodosum leprosum; MG, myasthenia gravis; DM dermatomyositis.



460 | **TOBACCO SMOKING IMPAIRS SURVIVAL IN LYMPHOMA PATIENTS IN TWO FINNISH POPULATION-BASED COHORTS**

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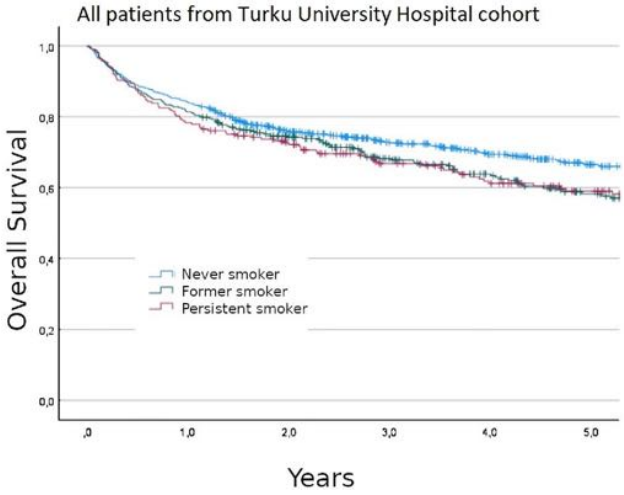
Introduction: A few studies have explored the effect of smoking status on the survival after the diagnosis of lymphoma during the modern immunochemotherapy era. Shorter overall survival (OS) has been reported especially in patients with the most pack years smoked.

Methods: Deep learning-based algorithm was used to classify smoking status (persistent, former or never) at the time of the diagnosis from medical records from Turku and Tampere University Hospitals in Finland. Lymphoma patients excluding Hodgkin lymphoma from years 2009 to 2019 were identified based on histological diagnosis and followed up for OS and cancer-specific survival. Currently detailed baseline demographics and treatment data are available from Turku cohort only. Survival was analyzed with Kaplan-Meier analysis and hazard ratio for death was calculated using Cox regression with 95% confidence interval.

Results: Turku cohort included 1814 and Tampere cohort 1027 patients; 1223 with diffuse large B-cell lymphoma (DLBCL) and 513 with follicular lymphoma (FL). Median follow-up time was 69 months. Smoking status was unavailable for 885 patients (31%). Among the DLBCL patients 583 (57%) had never smoked, 238 were former smokers (23%) and 198 (19%) were persistent smokers. For FL patients respective numbers were 248 (57%), 90 (21%) and 97 (22%). Among all patients from Turku median OS was 127 months for never smokers (reference), 82 months for former (HR 1.30 [1.06–1.60]) and 93 months for persistent smokers (HR 1.30 [1.02–1.65]). Among DLBCL patients median OS was 117 months for never (reference), 56 months for former (HR 1.45 [1.09–1.95]) and 57 months for persistent smokers (HR 1.37 [0.97–1.95]). 5-year survival rate was 63%, 50% and 48% in Turku and 59%, 55% and 40% in Tampere, respectively. Among FL patients, median OS was not reached and their 5-year survival rates were 73%, 75% and 70% in Turku and 81%, 70% and 79% in Tampere, respectively.

In Turku cohort, DLBCL patients' baseline Ann Arbor stage was advanced (stage III-IV) in 68%, 69% and 76% never, former and persistent smokers respectively ($p = 0.47$) and in FL patients the baseline Ann Arbor stage was III-IV in 65%, 70% and 51% ($p = 0.14$) respectively. Persistent smokers were slightly younger compared to former and never smokers (62 years, 67 yrs and 65 yrs for DLBCL ($p = 0.03$) and 57 yrs, 67 yrs and 67 yrs for FL ($p < 0.001$)). Persistent and former smokers were more often male than never smokers (66%, 67% and 45% respectively in DLBCL, ($p < 0.001$) and 64%, 57% and 43% for FL ($p = 0.04$)).

Conclusion: Our preliminary results concerning OS suggest a significantly shorter median OS among DLBCL patients who continued to smoke compared to never smokers. Former smokers had equally worse prognosis compared to persistent smokers, therefore a lifelong non-smoking status appears to be important.



The research was funded by: This study was financially supported by Finnish Cancer Foundation, State Competitive Research Funds and Juho Vainio Foundation.

Keywords: aggressive B-cell non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, late effects in lymphoma survivors

No conflicts of interests pertinent to the abstract.

461 | ABO BLOOD GROUP TYPE AND RISK OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH LYMPHOMA

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Introduction: Risk of venous thromboembolism (VTE) is increased in patients with cancer owing to various pathophysiological mechanisms that generate prothrombotic state. Lymphoma patients are well known to be at significant risk for VTE development. Recently, non-O blood type was associated with increased risk of VTE in patients with cancer and it has been proposed as time-dependent predictor of VTE in that group of patients. The aim of the study was to examine ABO blood group as a risk factor for VTE development in patients with lymphoma.
Methods: A total of 600 patients with lymphoma (newly diagnosed and relapsed) have been included in the study. All the patients have been treated at Lymphoma Center, Clinic for Hematology, University Clinical Center of Serbia. Data regarding VTE events was collected for all the patients included in the study, from the time of diagnosis to 3 months after the last cycle of therapy. ABO blood group has been determined prior to treatment initialization through standard institutional procedure. VTE was diagnosed objectively based on radiographic studies, clinical examination, and laboratory evaluation.
Results: The median patients' age was 57 years (range 18–89 years); 55.5% were males. The majority of the patients were newly diagnosed (88.8%). The distribution of the diagnosis was following: indolent NHL 140 (23.3%), aggressive NHL 366 (61%), and Hodgkin lymphoma 94 (15.7%), respectively. The rate of VTE was 10.3% (62 patients), with the highest rate in aggressive NHL group of patients (7.7%, 46 patients). VTE was diagnosed before the specific hematological treatment initiation in 46.8% of lymphoma patients, whilst 53.2% of lymphoma patients have been diagnosed with VTE after the hematological treatment commencement. A blood type was the most common in our group of patients (41.6%), followed by O blood type (33.3%), B blood type (15.8%) and AB blood type (9.3%), respectively. There was no statistically significant association between VTE development and ABO group type ($p = 0.495$). Non-O blood type lymphoma patients with VTE had significantly more often developed VTE prior to the treatment initiation in comparison with O blood type lymphoma patients with VTE (2.5% vs. 1%, $p = 0.04$), whereas VTE in O blood type lymphoma patients was significantly more often after the initiation of hematological treatment in comparison with VTE in non-O blood type patients (3.8% vs. 3%, $p = 0.04$). Logistic regression model demonstrated that non-O blood type is a predictor of pre-treatment VTE development in lymphoma patients (odds ratio [OR] = 3.19, confidence interval [CI]: 1.03–9.88, $p = 0.044$).
Conclusions: While there is no association between frequency of ABO blood group and the rate of VTE in lymphoma patients, non-O blood type in lymphoma patients has shown to be a predictor of VTE development prior to specific hematologic treatment commencement.

Encore Abstract—previously submitted to EHA 2023

Keywords: diagnostic and prognostic biomarkers, Lymphoid Cancers - Other

No conflicts of interests pertinent to the abstract.

462 | RACIAL AND ETHNIC REPRESENTATION IN LARGE B-CELL LYMPHOMA TRIALS AND REAL-WORLD DATABASES

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Introduction: In large B-cell lymphoma (LBCL) trials, racial and ethnic representation is difficult to determine due to underreporting in some regions, or because some patients may not provide data. It is difficult to understand the full extent of any underrepresentation of specific races or ethnicities in these trials relative to the prevalence of LBCL in clinical practice. The objective of this study was to characterize racial and ethnic representation in LBCL real-world databases and recently published LBCL studies.
Methods: Analyses of the distribution of different racial and ethnic categories were conducted across 6 real-world clinical practice databases from the United States (US): SEER-Medicare, COTA,

Medicare, Optum Market Clarity, Optum CDM, and Concert AI RWD. In addition, a targeted review of recently published studies in patients with LBCL was conducted to identify reported race and ethnicity distributions. Distributions were described using counts and percentages for each race (Asian, Black, White, and other/unknown/not reported) and ethnicity (Hispanic, non-Hispanic, and other/unknown/not reported) category.

Results: Patients with LBCL from the databases included: COTA (N = 5848), SEER-Medicare (N = 102,548), Medicare (N = 136,466), Optum Market Clarity (N = 19,649), Optum CDM (N = 22,175), and Concert AI (N = 1828). Race and ethnicity distributions are reported in Table 1. Across databases, Asian (2%–6%) and Black (5%–8%) races were substantially lower than White race (69%–88%). Across various lines of therapy, distributions were similar: 3%–5% Asian, 3%–5% Black, and 78%–82% White. Hispanic ethnicity (5%–22%) was substantially lower than non-Hispanic ethnicity (70%–91%). In the targeted review, 14 publications of LBCL therapies were identified; of these, 10 did not report racial/ethnic composition. In 4 publications (Salles et al., 2020; Sehn et al., 2020; Bannerji et al., 2022; and a real-world study by Shenoy et al., 2011), Asian, Black, White, and other/unknown/not reported represented 2%–13%, 0%–7%, 71%–89%, and 1%–11%, respectively.

Conclusions: Information on racial and ethnic distributions in LBCL studies is underreported, particularly in global trials. If this information was reported and reflective of LBCL in clinical practice in the US, the numbers of Asian and Black patients would be low at ≤8%, and most patients would be expected to be White and non-Hispanic.

Encore Abstract—previously submitted to ASCO 2023

The research was funded by: Genmab A/S and AbbVie

Keywords: aggressive B-cell non-Hodgkin lymphoma, cancer health disparities

Table 1. Racial and ethnic distributions in patients with LBCL across US databases

Database	Asian	Black	White	Race Other/Unknown/ Not Reported	Hispanic Ethnicity	Non-Hispanic Ethnicity	Ethnicity Other/Unknown/ Not Reported
COTA (2010–2022)	3%	5%	80%	12%	22%	70%	NA
SEER-Medicare (1999–2017)	6%	6%	88%	0%	9%	91%	NA
Medicare (2015–2020)	2%	6%	87%	6%	6%	83%	5%
Optum Market Clarity (2016–2021)	2%	6%	78%	14%	5%	77%	19%
Optum CDM (2016–2021)	3%	8%	70%	19%	NA	NA	NA
ConcertAI RWD (2016–2021)	2%	8%	69%	12%	5%	78%	17%

Conflicts of interests pertinent to the abstract

J. Munoz
Consultant or advisory role Pharmacyclics/AbbVie, Bayer, Gilead/Kite Pharma, Pfizer, Janssen, Juno/Celgene, BMS, Kyowa, Alexion, Fosunkite, Innovent, Seattle Genetics, Debiopharm, Karyopharm, Genmab, ADC Therapeutics, Epizyme, Beigene, Servier, Novartis, MorphoSys/Incyte, Secura Bio, TG Therapeutics, MEI, Lilly/Loxo
Honoraria: Targeted Oncology, OncView, Curio, Kyowa, Physicians' Education Resource, Seattle Genetics
Research funding: Bayer, Gilead/Kite Pharma, Celgene, Merck, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, Millennium
Other remuneration: Speaker's Bureau: Gilead/Kite Pharma, Kyowa, Bayer, Pharmacyclics/Janssen, Seattle Genetics, Acrotech/Aurobindo, BeiGene, Verastem, AstraZeneca, Celgene/BMS, Genentech/Roche.

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463 | POLATUZUMAB AND THE PROGRESSION-FREE SURVIVAL (PFS) PREDICAMENT: A COMPARATIVE ANALYSIS OF HEALTH TECHNOLOGY ASSESSMENT AGENCY (HTA) REVIEWS

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As more cancer drugs are approved based on changes in surrogate measures such as PFS, greater controversy surrounds their clinical benefit and economic value. In the POLARIX trial for untreated diffuse large B cell lymphoma (DLBCL), polatuzumab (Polivy), as part of the PolaRCHP regimen, achieved superior PFS than RCHOP (76.7% vs. 70.2%) with no difference in overall survival (OS) – challenging the 20-year standard of care.

We examined reviews of PolaRCHP by international HTAs to understand how international expert organizations view a new cancer drug that marginally improves PFS without OS benefit.

Methods: We searched NAVLIN (Eversana, Milwaukee, WI), a global HTA database, to determine which HTA organizations have reviewed polatuzumab in untreated DLBCL. We then extracted key summary documents from each group's website to investigate the rationale provided.

Results: Among 14 HTAs that reviewed pola, 5 assessed its use in frontline DLBCL. HTAs in Germany and the UK recommended reimbursement, while those in France and Australia did not. The UK was willing to tolerate an uncertain impact on OS due to acceptable cost effectiveness, while a "hint" of non-quantifiable benefit was sufficient to earn reimbursement in Germany (Table). Conversely, Australia and France emphasized that unchanged overall and complete response rate undermined the PFS benefit (suggesting that PolaRCHP may neither achieve more responses nor deeper responses among responders), as well as the uncertain impact on OS, given the aggressive nature of DLBCL. HTAs considered price differently: the UK found pola's incremental cost-effectiveness ratio (ICER) acceptable while Australia considered its budget impact too high. France and Germany did not factor price into assessments.

Conclusions: Polatuzumab offers insights into how HTAs value PFS: in some countries, a marginal PFS benefit in the absence of OS benefit was sufficient to warrant reimbursement, while other HTAs felt the difference in PFS was undermined by lack of improvement in response rate and depth and OS. Our study is limited by undisclosed negotiated discounts, which may influence reimbursement decisions in different jurisdictions.

Understanding how HTAs interpret trial results is essential to ensure optimal design of future clinical trials and improve patient access to effective novel agents.

The research was funded by: Arnold Ventures

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies

Conflicts of interests pertinent to the abstract

E. R. S. Cliff
Research funding: Arnold Ventures

A. J. N. Raymakers
Consultant or advisory role Adam Raymakers reports serving as a member of the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) with the Canadian Agency for Drugs and Technologies in Health (CADTH).

464 | CLINICAL FEATURES AND PROGNOSIS OF PATIENTS COEXISTING WITH FOLLICULAR LYMPHOMA AND DIFFUSE LARGE B-CELL LYMPHOMA: A RETROSPECTIVE OBSERVATIONAL STUDY

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Introduction: The clinical features and prognosis of patients coexisting follicular lymphoma and diffuse large B-cell lymphoma remain unclear. This retrospective observational study was conducted to explore theclinical characteristics and prognosis of this particular pathological type lymphoma patients treated with R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone)-based treatment.

Country	Australia	France	Germany	United Kingdom
HTA	PBAC	HAS	IQWIG/G-BA	NICE
Reimbursement Decision	No	No	Yes	Yes
HTA Findings	- No benefit in OS or overall RR - optimistic ICER - high financial impact	- modesty of PFS benefit; median PFS not reached - No benefit in complete RR or OS - No formally demonstrated reduced toxicity or improved quality of life (QoL)	- Unclear PFS benefit due to low magnitude of benefit & endpoint limitations - Insufficient patient reported data to assess QoL - "A hint for a non-quantifiable additional benefit of PolaRCHP is identified since the scientific data does not allow quantification"	- high unmet need of DLBCL - PFS benefit, effect on OS highly uncertain - ICER likely to be within acceptable range

Methods: From January 2016 to August 2022, 33 patients with coexisting follicular lymphoma and diffuse large B-cell lymphoma were enrolled in the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. All patients received R-CHOP-based immunochemotherapy. All patients received a total of 205 cycles of chemotherapy, with a median of 6 (2–8) cycles. As of January 2023, the median follow-up period was 48 months (3–72). The clinical characteristics, progression-free survival, and overall survival time of all patients were summarized, and the factors related to the prognosis were analyzed.

Results: 33 patients with coexisting both follicular lymphoma and diffuse large B-cell lymphoma were included in this retrospective observational study. Among them, 72.7% of the patients were less than 60 years old. Advanced patients accounted for 57.6%. B symptoms were absent in 90.6% of the patients .66.7% of the patients had less than 2 extranodal sites involved, and 21.2% of the patients had IPI scores of 3–5. Among the tumor components, diffuse large B-cell lymphoma accounted for 63.6%, and follicular lymphoma accounted for 57.6%. In follicular lymphoma, grade 3A accounted for 33.3% and grade 3B accounted for 63.6%. One patient with follicular lymphoma could not be graded. After receiving R-CHOP treatment, the response rate was 75.8%, and the primary refractory patients accounted for 24.2%. The PFS for 24 months and 48 months was 71.2%, 71.2%. The OS for 24 months and 48 months was 78.4%, and 65.6%, respectively. The factors related to the prognosis of patients included primary refractory, high IPI, and the interim PET efficacy evaluation. The proportion of diffuse large B-cell lymphoma and the grade of follicular lymphoma in tumor tissue was not related to the poor prognosis.

Conclusions: Compared with the historical database, patients with coexisting both follicular lymphoma and diffuse large B-cell lymphoma have a higher incidence of primary refractory. The prognosis of patients is related to IPI, primary refractory, and the interim PET efficacy evaluation, but it needs to be confirmed by a larger sample of prospective studies.

Keywords: aggressive B-cell non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

BIOLOGY

465 | SINGLE CELL LANDSCAPE OF MULTICENTRIC CASTLEMAN DISEASE IN IDENTICAL TWINS

E. C. Y. Lee, J. W. Loh, B. Kannan, J. Q. Lim, H. Liany, B. Y. Lim, J. Y. Lee, K. Lim, J. C. H. Ha, C. C. Ng, T. K. Ko, D. Huang, D. Y. B. Seow, C. L. Cheng, S. H. Chan, J. Ngeow, B. T. Teh, S. T. Lim, C. K. Ong, J. Y. Chan

National Cancer Center Singapore, Singapore, Singapore

Idiopathic Multicentric Castleman Disease (iMCD) is a rare IL-6-driven hematological disorder characterized by systemic lymphadenopathy, elevated immunoglobulin levels, and prominent plasmacytosis in the bone marrow and lymph nodes. An unusual occurrence of iMCD in identical twins provided a unique opportunity to answer genetic and molecular features of this disease, including the cell-of-origin of IL-6 signals, and the immune milieu within affected lymphoid organs and in circulation. Germline whole genome sequencing of the affected twins identified pathogenic homozygous mutations of *NCOA4* c.G1322A and monoallelic mutations of *TRAF3* c.G1504A – both genes recently implicated in IL-6 signaling and B-cell regulation. Their unaffected sister was heterozygous mutant for *NCOA4* and homozygous wildtype for *TRAF3* loci. Via single cell sequencing of 63,519 cells from bone marrow, lymph node, and peripheral blood mononuclear cells, we identified nodal endothelial cells and fibroblastic reticular cells (FRC) as the source of IL-6 signals. The latter are composed of mainly T-cell zone FRCs (CCL19+/CCL21+/IL7+/PDPN+/MADCAM1-) and a minor population of follicular dendritic cells (FDCs) (CD21+/CD35+/CXCL13+). An "inflammatory" peripheral monocytosis enriched for the expression of S100A family genes was evident in both twins, as well as a group of monocytes expressing cytotoxic gene signatures in the affected twin with milder clinical manifestations. Their unaffected sister mainly carried monocytes enriched for expression of major histocompatibility complex (MHC) class II genes. In conclusion, we provided evidence of a genetic cause of iMCD, identified the putative cell-of-origin of IL-6 signals in this rare disease, and described a distinct monocytic immune response phenotype.

Encore Abstract—previously submitted to AACR 2023

The research was funded by: This work was supported by the Tanoto Foundation Professorship in Medical Oncology, New Century Foundation Limited, Ling Foundation, Singapore Ministry of Health's National Medical Research Council Research Transition Award (TA21jun-0005), Large Collaborative Grant (OFLCG18May-0028), and TETRAD II Collaborative Centre Grant (CG21APR2002).

Keywords: genomics, epigenomics, and other -omics, Lymphoid Cancers - Other, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

466 | A SINGLE-CELL ATLAS OF DIFFUSE LARGE B CELL LYMPHOMA

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Diffuse large B-cell lymphoma (DLBCL) is one of the most common yet aggressive types of B-cell lymphoma and remains incurable in 40% of patients. Herein, we profiled the transcriptomes of 94,324 cells from 17 DLBCLs and 3 control samples using single-cell RNA-sequencing technology, creating a comprehensive single-cell map for tumor and infiltrating immune cells for DLBCL. High degrees of inter- and intratumor heterogeneity were revealed, and we identified 73 gene expression programs expressed in malignant B cells. We further characterized 8 nonmalignant B-cell subclusters and 16 T-cell subclusters from the tumor microenvironment. Six myeloid subclusters were also identified, including the *LAMP3*$^{+}$ DC subcluster enriched in ABC-DLBCL. More than 2000 likely cell-cell interactions were further predicted in DLBCL, illustrating a complex and highly dynamic DLBCL tumor microenvironment. Unique to B cell lymphomas, a strong costimulatory CD70-CD27 interaction was predicted between malignant cells and T cells. Furthermore, coinhibitory signals mediated by TIM-3 or TIGIT seemed to be the main driving force for T-cell exhaustion. Finally, we discovered that chronic hepatitis B virus infection may have a significant impact on tumor cell survival and immune evasion in DLBCL. Our results provide new insights into B-cell lymphomagenesis and may facilitate the design of targeted immunotherapy strategies.

The research was funded by: Swedish Cancer Society, STINT, CIMED, Radiumhemmet, the Swedish Research Council, and the Knut and Alice Wallenberg Foundation, the Guangdong Enterprise Key Laboratory of Human Disease Genomics, the Shenzhen Key Laboratory of Single-Cell Omics

Keywords: aggressive B-cell non-Hodgkin lymphoma, genomics, epigenomics, and other -omics, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

467 | ELUCIDATING THE MOLECULAR MECHANISMS OF CLONAL EVOLUTION IN MULTIPLE MYELOMA THROUGH SINGLE-CELL RNA SEQUENCING

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Background: Myeloma cells respond differently to therapeutic pressure, with sensitive clones being cleared and some more resistant clones being screened as major clones after treatment. This phenomenon of clonal resistance and clonal evolution, in which different clones compete with each other and change before and after treatment, is the underlying cause of the failure of minimal residual disease (MRD) clearance and myeloma recurrence. Previous studies have confirmed that clonal evolution in MM occurs at the cytogenetic level as early as after induction therapy and that different patterns of clonal evolution have a significant impact on the prognosis of MM patients. However, there is a gap in the study of MRD compared to myeloma cells at diagnosis in terms of cell composition and transcriptional heterogeneity. To elucidate the cellular composition, transcriptional differences, and interrelation ship with the tumor microenvironment between MRD and myeloma cells at diagnosis, we performed single-cell RNA sequencing on primary and post-induction therapy myeloma bone marrow samples.

Methods: In this study, we collected paired bone marrow samples from 19 cases before and after 2–4 courses of induction therapy with the VRD regimen; and from 10 normal controls (8 of which were from the Human cell atlas database). We generated single-cell transcriptome libraries by the Single Cell 3' Library Kit V3 (10x Genomics, CA, USA), following the manufacturer's instructions. Once prepared, indexed complementary DNA (cDNA) libraries were sequenced on a NovaSeq 6000 platform (Illumina) with paired-end mode according to the manufacturer's instructions. Seurat and Harmony were then applied to perform dimensionality reduction, clustering and visualization.

Results: Three types of clonal evolution patterns were identified by comparing plasma cell genetic abnormalities and transcriptional differences before and after induction treatment: (1) MRD-negative patients exhibited a clonally clearance of residual plasma cells after treatment, while MRD-positive patients exhibited clonal resistance and clonal selection; (2) Clonal resistance cells showed high proliferation activity and unfolded protein-responsive drug resistance pathways were activated. And unfolded protein-responsive drug resistance pathways and the NF-kB signaling pathway were activated in clonal selection cells; (3) Clonal selection cells showed more significant cellular communication with the microenvironment cells.

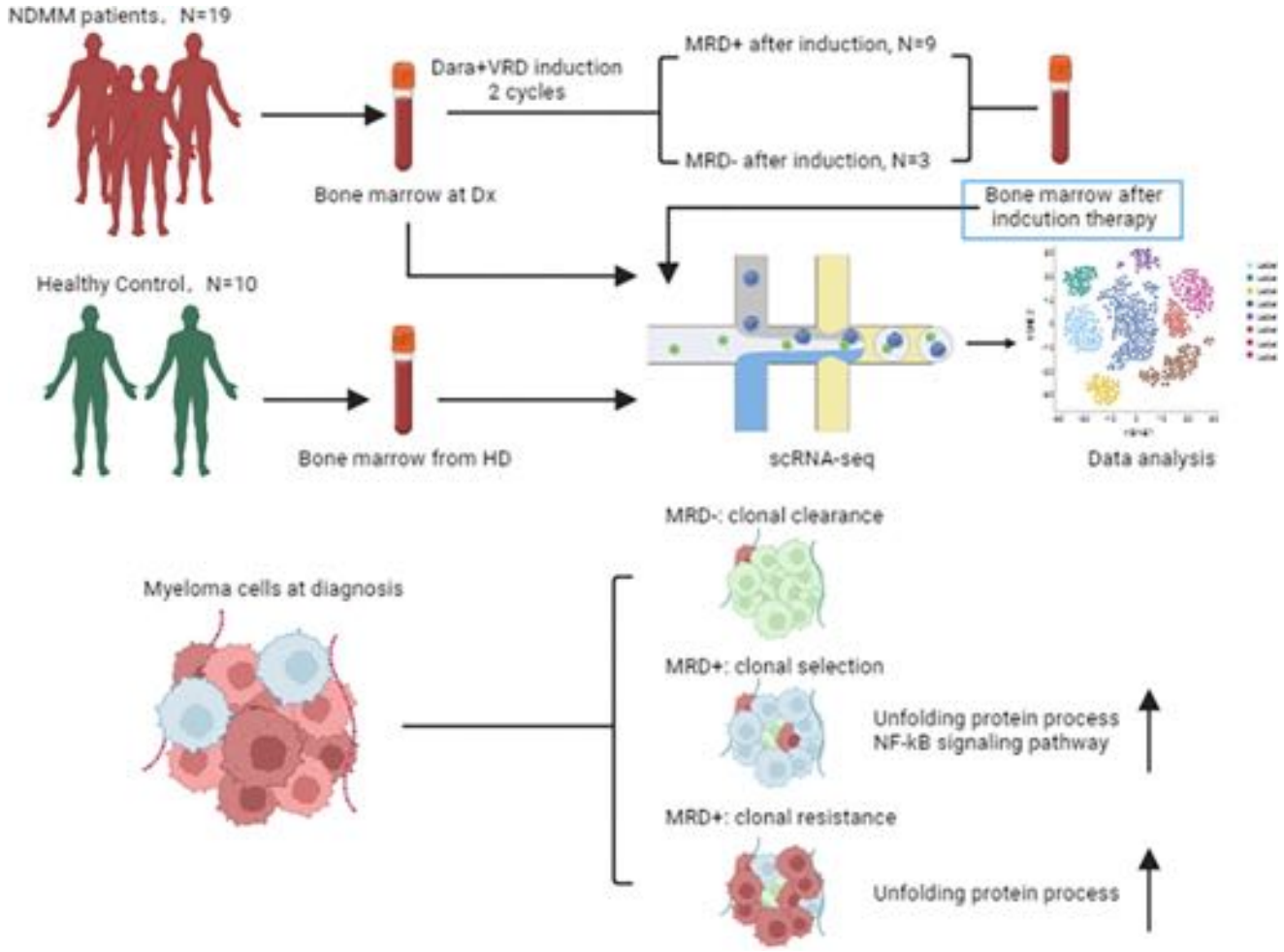
Conclusion: The application of single cell RNA sequencing allows for the observation of clonal evolution and the onset of drug resistance early after induction therapy. Clonal selection cells exhibit activation of unfolded protein responses while gaining support from the tumor microenvironmental.

Encore Abstract—previously submitted to EHA 2023

The research was funded by: This investigation was supported by the International Cooperation Projects of National Natural Science Foundation (grants 81920108006), CAMS Innovation Fund for Medical Sciences (CIFMS) (grants 2022-I2M-1-022), the National Natural Science Foundation (grants 81630007; grants 82270218, 81670202; grants 81900214).

Keywords: microenvironment, multiple myeloma, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.



468 | **PIM1 GENETIC ALTERATIONS ASSOCIATED WITH DISTINCT MOLECULAR PROFILES, PHENOTYPES AND DRUG RESPONSES IN DIFFUSE LARGE B-CELL LYMPHOMA**

Y. Lu, T. Zhang, X. Wang, H. Zhang

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Background: PIM1 is one of somatic hypermutation genes in diffuse large B-cell lymphoma (DLBCL). Characterization of a specific molecular subtype with PIM1 genetic alterations is warranted in order to design better personalized therapy for this inferior prognosis patients. The study aims to explore PIM1 genetic alterations and its value in identifying high risk patients and guiding individualized treatment strategies.

Methods: NGS targeted sequencing was performed on 162 samples from 2008 to 2018 at Tianjin Medical University Cancer Institute&Hospital to detect 307 lymphoma-related gene mutations. All patients' genomic landscape, PIM1 mutation type and gene mutual exclusivity and co-occurrence were analysed. Transcriptome sequencing was performed on 140 DLBCL patients and differential gene expression analysis, protein-protein interaction analysis, Gene Ontology (GO) and Kyoto Encyclopedia of Genesand Genomes (KEGG) analyses were also performed. Besides, a PIM1 mutation-related gene signature was established and predicted the therapeutic response of common chemotherapeutic and targeted drugs.

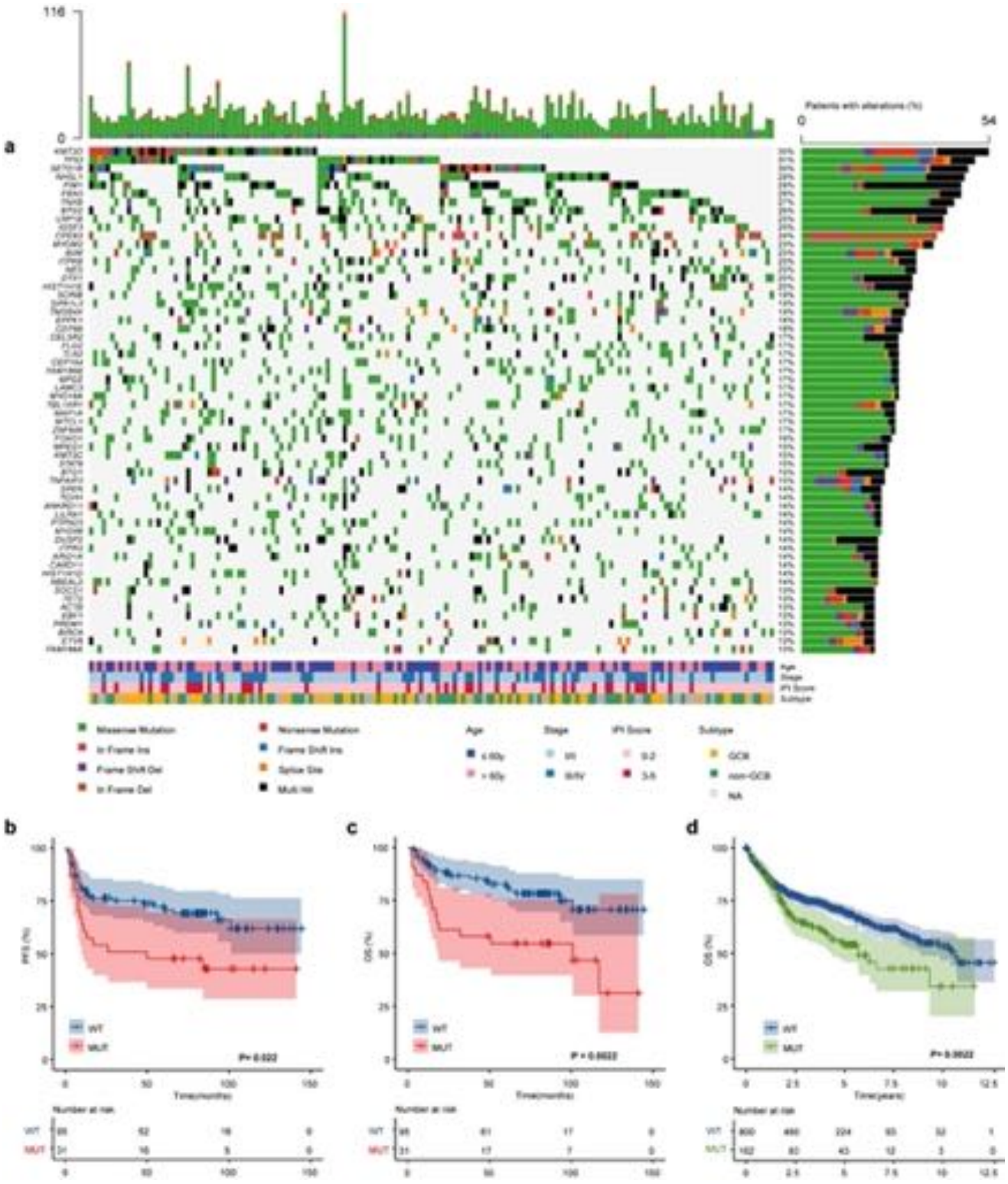
Results: We observed that PIM1 mutations characterized by predominant missense and nonsense mutations and frameshift deletions mainly occurred in protein kinases domain, leading to a deleterious event, and uncovered that SETD1B, CD79B, MYD88 and PRDM1 mutations were enriched and SPEN mutation excluded with PIM1 mutations. Besides, PIM1-mutated DLBCL conferring a typical mutational signature involved in disorder the tumor microenvironment, JAK-STAT and NF-κB signaling pathways. Patients with PIM1 mutations were characterized by higher IPI scores, more frequent disease relapse and testis and/or CNS involvement, as well as inferior progression-free survival and overall survival. A novel PIM1 mutation-related gene signature indicated distinct phenotypes and served as a promising biomarker for risk stratification. Patients with high-risk score had higher response to TGFβ receptor inhibitors (SB525334, SB505124), Lenalidomide, NF-κB inhibitors (Parthenolide, TPCA-1) and JAK inhibitors (Ruxolitinib, TG101348).

Conclusions: Taken together, our findings provide novel insights into the pathogenic role of PIM1 mutations and highlights personalized therapy strategies for treatment of PIM1-mutated DLBCL patients.

Keywords: diffuse large B-cell lymphoma, Genetic alterations, PIM1, personalized therapy

Keywords: aggressive B-cell non-Hodgkin lymphoma, bioinformatics, computational and systems biology, diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.



469 | ALK-POSITIVE LARGE B-CELL LYMPHOMA IS A TERMINALLY DIFFERENTIATED B-CELL NEOPLASM FEATURING FREQUENT EPIGENETIC DYSREGULATION AND MUTATIONS INVOLVING MYC AND THE JAK-STAT PATHWAY

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Background: Anaplastic lymphoma kinase-positive large B-cell lymphoma (ALK+ LBCL) is a rare neoplasm of large B-cells with a plasmablastic immunophenotype and ALK expression due to *ALK* rearrangements. The molecular genetic profile of the disease, however, remains largely unknown.

Design: Clinicopathologic features of 10 cases with ALK+ LBCL and 12 cases with ALK-negative plasmablastic lymphoma were retrospectively analyzed. The mutational landscapes were revealed by screening a targeted panel of 136 genes using next-generation sequencing and formalin-fixed, paraffin-embedded tumor samples.

Results: Compared with the control group, ALK+ LBCL cases were more frequently associated with a younger age (≤50 yrs) ($p = 0.043$) and histologically, a sinusoidal growth pattern ($p < 0.0001$). Cytologically, the immunoblastoid tumor cells with prominent nucleoli resembling HRS cells were more frequently seen in ALK+ tumors ($p < 0.0001$). Immunophenotypically, ALK+ LBCL cases featured high-level expression of PD-L1 ($p = 0.007$). In addition, 2 cases demonstrated a CD33+ phenotype. Gene mutations involving epigenetic regulation, including *EP300*, *TET2*, *SF3B1*, *KMT2C*, and *KMT2D*, were frequently detected in ALK+ LBCLs. Additional aberrations might include mutations involving *MYC* as well as some candidates related to the *JAK-STAT* signaling pathway ($p < 0.01$).

Conclusions: ALK+ LBCL carries frequently genetic aberrations involving *MYC* and the *JAK-STAT* pathway-related genes. Epigenetic dysregulation, which is peculiar for this post-germinal center B-cell neoplasm, might have suggested a complex genetic background of tumorigenesis. These findings may constitute a rational basis for the therapeutic strategies of targeting these pathways.

The research was funded by: The research was funded by "Chinese Society of Clinical Oncology (No. HYXH2021045), Science and Technology Commission of Shanghai Municipality (No. 22YF1408200) and Shanghai Anticancer Association (No. HYXH2021082)".

Keywords: aggressive B-cell non-Hodgkin lymphoma, pathology and classification of lymphomas

No conflicts of interests pertinent to the abstract.

470 | A 9-LNCRNA SIGNATURE FOR PREDICTING PROGNOSIS AND IMMUNE RESPONSE IN DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Diffuse large B-cell lymphoma (DLBCL) is a biologically and clinically heterogeneous disease that requires personalized clinical treatment. To assign patients into different risk categories, cytogenetic abnormalities and genetic mutations have been widely applied to the prognostic stratification of DLBCL. Increasing evidence has demonstrated that deregulated epigenetic modifications and long noncoding RNAs (lncRNAs) contribute to the initiation and progression of DLBCL. However, specific lncRNAs that affect epigenetic regulation and their value in predicting prognosis and therapy response remain uncertain.

Methods: LncRNA expression profiles and clinical features of DLBCL samples were collected from the GEO database and 188 DLBCL patients in our center was as a validation cohort. A linear regression based on the modified LASSO algorithm was performed to construct a predictive model named lncRNA-regulating epigenetic event signature (ELncSig).

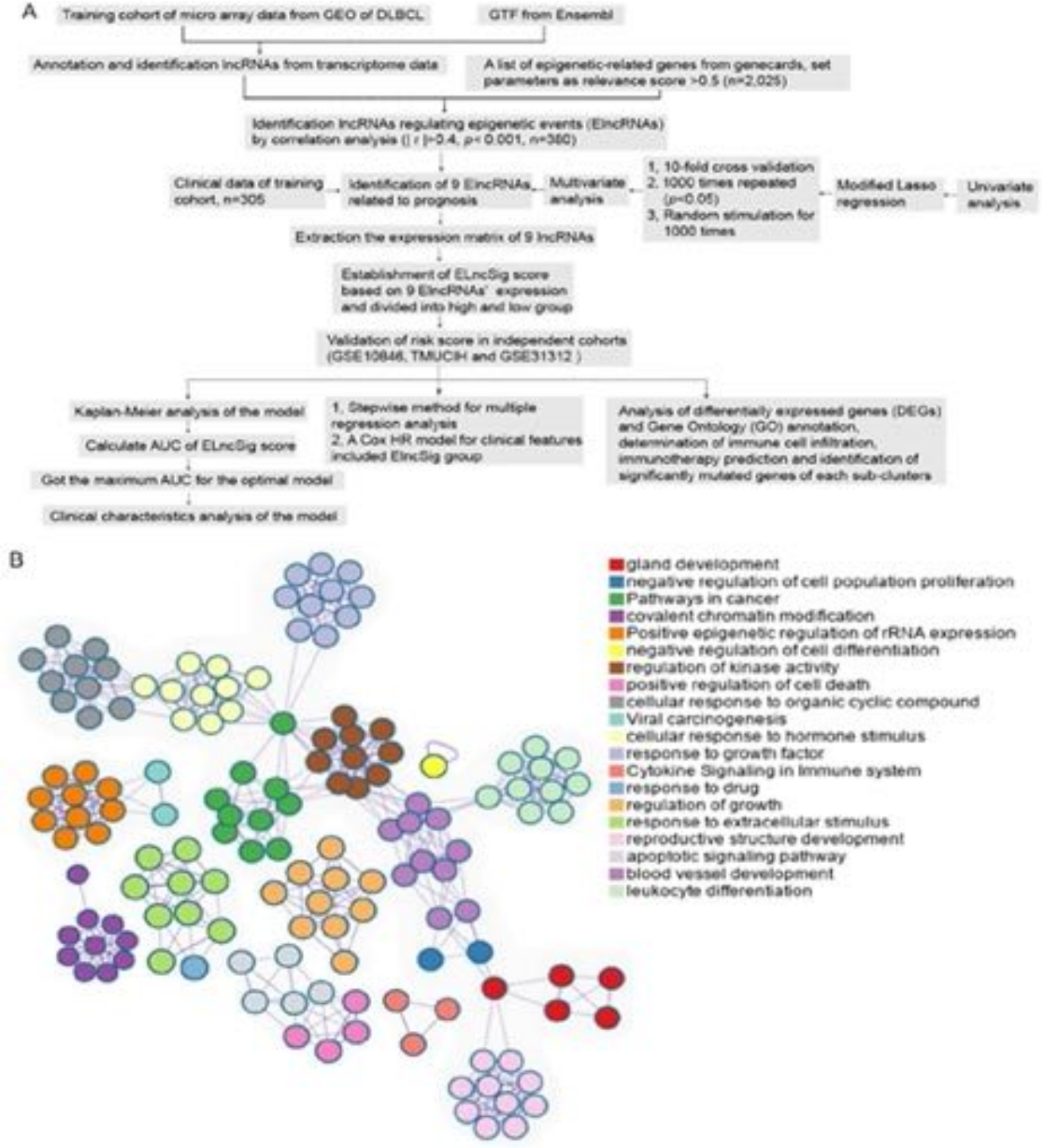
Results: A list of 2,025 epigenetic regulatory genes was generated from GeneCards and 9 lncRNAs (PRKCQ-AS1, C22orf34, HCP5, AC007389.3, APTR, SNHG19, ELFN1-AS1, LINC00487, and LINC00877) were tested and validated to establish the ELncSig which could distinguish different survival outcomes. Functional characterization of ELncSig showed that it could be an indicator of the immune microenvironment and is correlated with distinctive mutational characteristics. Univariate and multivariate analyses showed that ELncSig was independent of traditional prognostic factors.

Conclusions: We constructed a lncRNA signature based on epigenetic-related genes to predict the prognosis of DLBCL and also proved that this new signature could affect other coding proteins in addition to epigenetic genes. Importantly, ELncSig might be associated with immune infiltration levels and even the efficacy of tumor immunotherapy.

Keywords: diffuse large B-cell lymphoma, immune infiltration, prognosis, risk score, signature

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, risk models

No conflicts of interests pertinent to the abstract.



471 | **THE RNA M6A READER YTHDF2 REGULATES ACER2-CERAMIDE METABOLIC AXIS TO PROMOTE TUMORIGENESIS OF DIFFUSE LARGE B-CELL LYMPHOMA**

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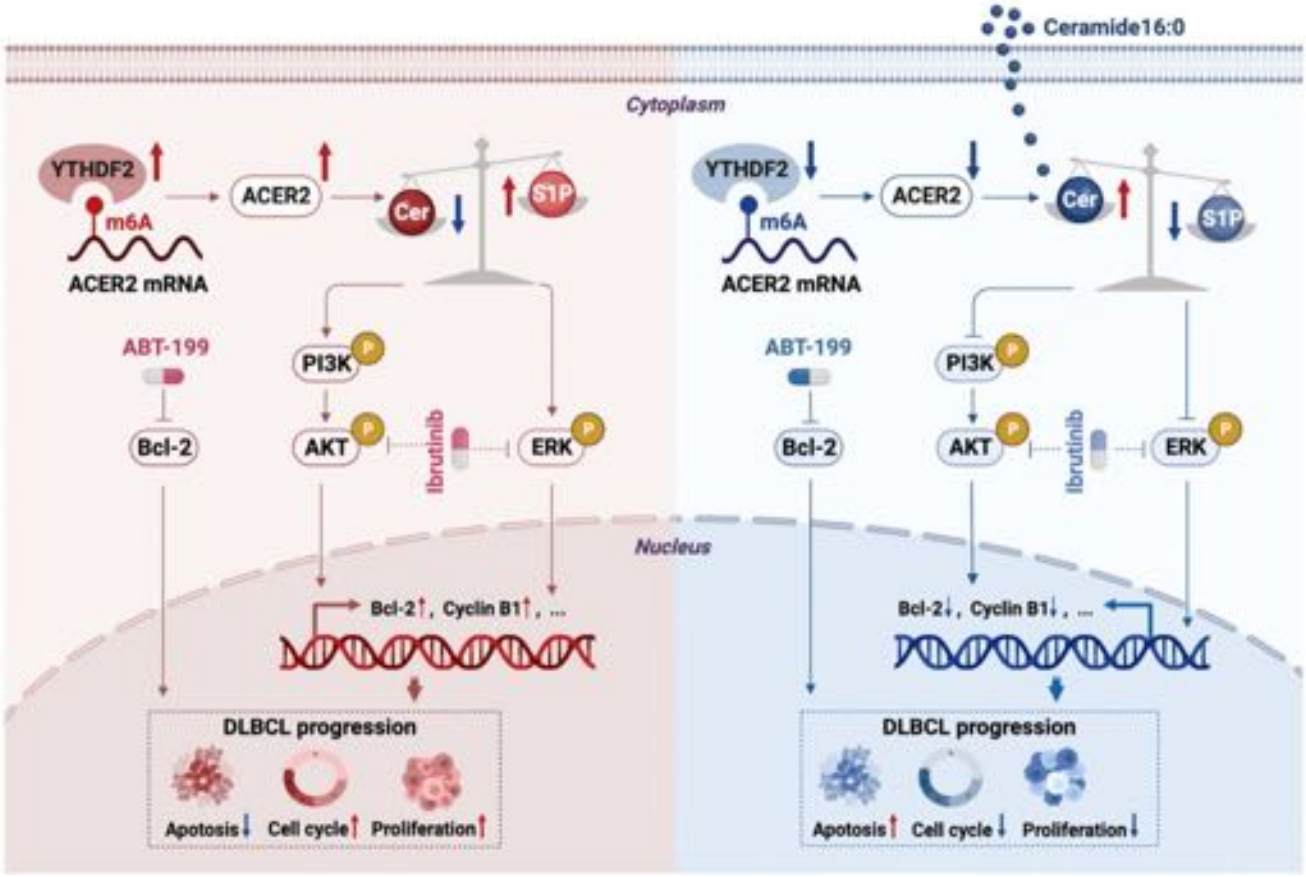
Introduction: N6-methyladenosine (m6A) is the most abundant modification in eukaryotes and plays an important biological function in human diseases. YTHDF2 is an important m6A reading protein, which could specifically bind to m6A-modified RNA and mediate its degradation. Here, we explored the functional significance and regulatory mechanism of YTHDF2 in diffuse large B-cell lymphoma (DLBCL), expecting to propose a novel therapeutic strategy.

Methods: Lymph node biopsies from 120 de novo DLBCL patients and 20 reactive hyperplasia cases were collected with informed consent. The biological function of YTHDF2 was evaluated via constructing YTHDF2 stable knockdown and overexpression models and



CRISPR/Cas9 mediated genomic deletion. RNA-seq and lipidomic sequencing were conducted to detect the dysregulated RNA in YTHDF2-knockout DLBCL cells. MeRIP-seq, m6A methylation assays and dual-luciferase reporter assay were performed to explore the functional mechanism of YTHDF2. Xenograft DLBCL mice model was simultaneously established. Animal experiments were performed in accordance with the principles of the Institutional Animal Care.

Results: The upregulation of YTHDF2 mRNA and protein in DLBCL cells was found, and high YTHDF2 expression was associated with aggressive disease process. Knockdown of YTHDF2 impaired cell proliferation, induced cell cycle arrest and triggered cell apoptosis in vitro, and repressed tumor growth in vivo. Furthermore, By RNA-seq, lipidomics, and MeRIP-seq analysis, YTHDF2 was found to regulate ceramide metabolism in DLBCL cells. The exogenous ceramide treatment suppressed tumor growth in DLBCL cells. YTHDF2 bound to ACER2 mRNA at m6A sites, promoting the expression and stability of ACER2. As ACER2 expression was enhanced, ceramides were hydrolyzed, disrupting ceramide and sphingosine-1-phosphate (S1P) balances, activating ERK and PI3K/AKT pathways, and promoting DLBCL tumorigenesis (Figure 1).

Conclusions: Our present study provides in vitro and in vivo evidence for the significance of YTHDF2 in lymphomagenesis and highlights the regulatory mechanism of YTHDF2 on ACER2-ceramide metabolic axis in DLBCL. Further investigations on the specific inhibitors of YTHDF2 in DLBCL will outline a promising therapeutic option in DLBCL therapy.

Keywords: ACER2, Ceramide, DLBCL, m^{6}A, YTHDF2

Keywords: aggressive B-cell non-Hodgkin lymphoma, genomics, epigenomics, and other -omics, molecular targeted therapies

No conflicts of interests pertinent to the abstract.

472 | KIAA1429 REGULATES HIPPO-YAP PATHWAY TO MAINTAIN THE TUMORIGENICITY OF DIFFUSE LARGE B-CELL LYMPHOMA VIA AN M6A-DEPENDENT MANNER

X. M. Chen[1], T. Lu[1], Y. Cai[1], Y. Han[2], M. Ding[1], Y. Chu[1], X. Zhou[2], X. Wang[1]

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Introduction: N^6-methyladenosine (m^{6}A) is the most abundant form of chemical modification in eukaryotes. m^{6}A methylation is dynamically modulated by diverse types of regulators, including methyltransferases ('writers'), RNA binding proteins ('readers'), and

demethylases ('erasers'). Growing evidence has shown that m^{6}A methylation plays an essential role in the development and progression of multiple cancers. However, the functions of m^{6}A methyltransferase KIAA1429 in diffuse large B-cell lymphoma (DLBCL) remain undefined. Here, we aimed to unravel an epitranscriptomic mechanism mediated by the m^{6}A methyltransferase KIAA1429 in DLBCL.

Methods: Collecting lymph node biopsy samples from 60 de novo DLBCL patients and 20 reactive hyperplasia cases after informed consent. The biological function of KIAA1429 was evaluated using CRISPR/Cas9 mediated genomic deletion and CRISPR/dCas9-VP64 activation. RNA-seq, MeRIP-seq, RIP assays, luciferase activity assay, RNA stability experiments, and co-immunoprecipitation were performed to explore the regulatory mechanism of KIAA1429 in DLBCL. DLBCL cells were subcutaneously injected into SCID-Beige mice to establish xenograft models. The Institutional Animal Care guidelines were followed during the animal experiments.

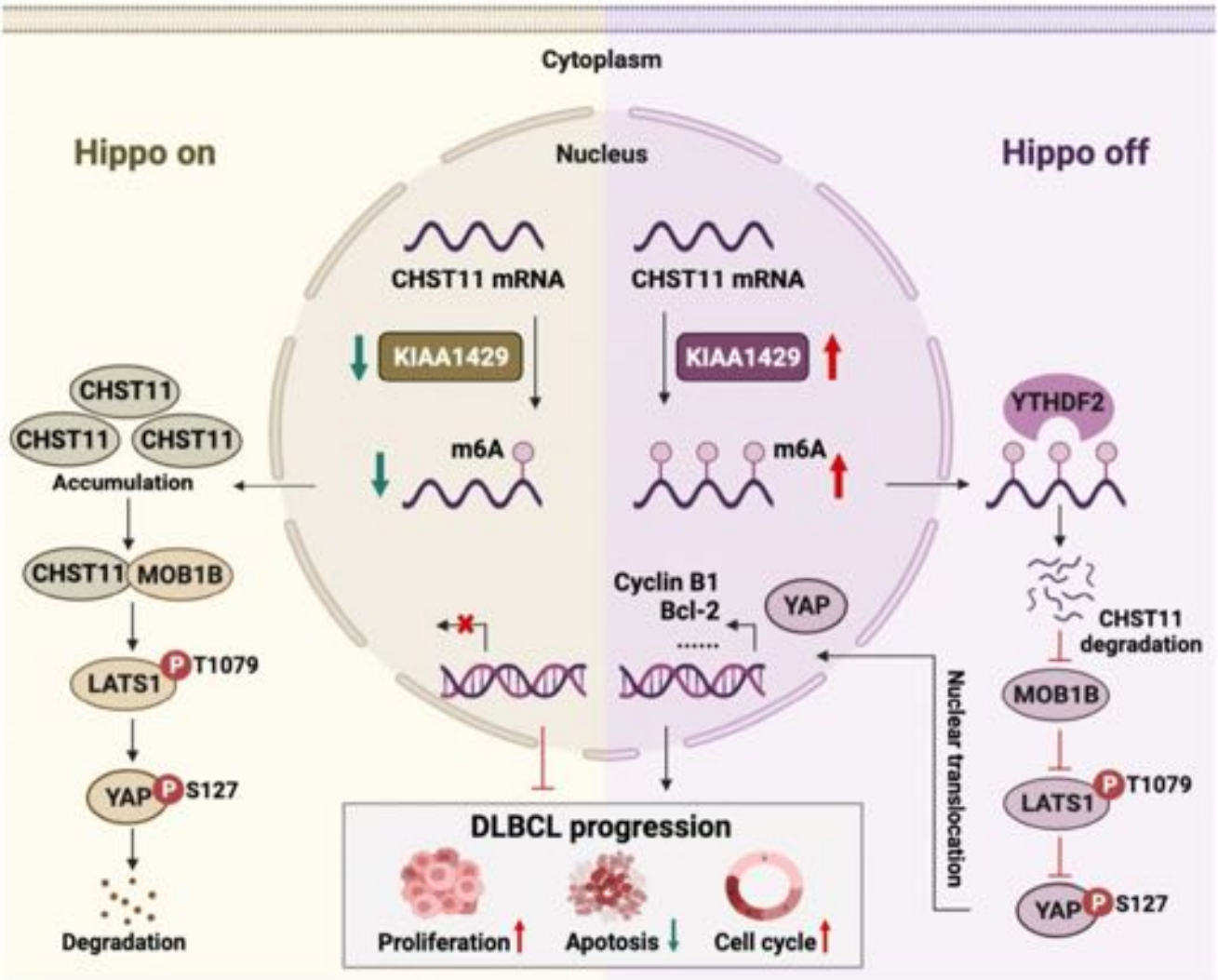
Results: m6A regulators were dysregulated in DLBCL, and a predictive model based on m6A score was developed. KIAA1429 expression was found to be elevated and associated with poor prognosis. KIAA1429 knockout inhibited DLBCL cell proliferation, induced cell cycle arrest in the G2/M phase, promoted apoptosis in vitro, and repressed tumor growth in vivo. Furthermore, KIAA1429 mediated m6A modification of CHST11 mRNA and recruited YTHDF2 to reduce the stability and expression of CHST11. By decreasing MOB1B expression, CHST11 inhibited Hippo-YAP signaling, reprogramming the expression of Hippo target genes (Figure 1).

Conclusions: In summary, we identified for the first time that m^{6}A methylation regulators were dysregulated, and its risk score could exert as an independent prognostic indicator in DLBCL. More importantly, our study identified a novel mechanism in which KIAA1429/YTHDF2-coupled epitranscriptional repression of CHST11 inactivates the Hippo-YAP pathway in DLBCL, highlighting the potential of KIAA1429 as a novel predictive biomarker and therapeutic target for DLBCL progression.

Keywords: DLBCL, Hippo-YAP pathway, KIAA1429, m^{6}A, mechanism

Keywords: aggressive B-cell non-Hodgkin lymphoma, bioinformatics, computational and systems biology, genomics, epigenomics, and other -omics

No conflicts of interests pertinent to the abstract.



473 | NAT10 REGULATES THE AMPK SIGNALING PATHWAY TO PROMOTE DLBCL PROGRESSION VIA AC4C ACETYLATION OF SLC30A9 MRNA

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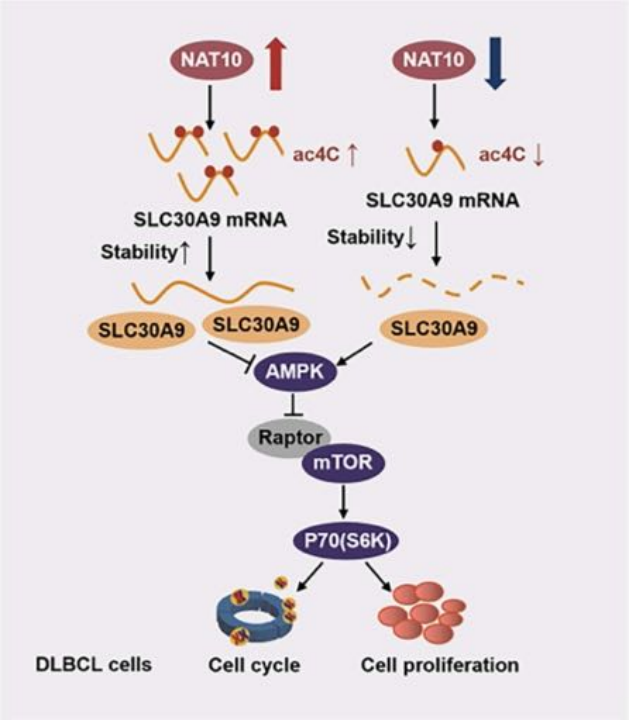
Introduction: N-acetyltransferase 10 (NAT10) is the only confirmed regulator to mediate the N4-acetylcytidine (ac4C) modification of mRNA and is crucial for mRNA stability and translation efficiency. However, its role in diffuse large B-cell lymphoma (DLBCL) development and prognosis has not yet been explored. Herein, we explored the functional significance and regulatory mechanism of NAT10 mediated mRNA ac4C modification in DLBCL, which is expected to propose novel therapeutic strategy.
Methods: The expression levels of NAT10 were evaluated in DLBCL cell lines and lymph node biopsies tissues, and its prognostic value in patients was further analyzed. Stable NAT10 knockout DLBCL cell lines were constructed using CRISPR/Cas9 mediated genomic deletion. The biological functions of NAT10 in DLBCL cells were analyzed in vitro by cell proliferation and cell cycle assays. Xenograft models were used to analyze the effect of NAT10 on the tumorigenesis of DLBCL cells in vivo. RNA sequencing, acetylated RNA immunoprecipitation sequencing (acRIP-seq), LC-MS/MS, RIP and RNA stability analyses were performed to explore the mechanism by which NAT10 functions in DLBCL progression.
Results: NAT10 was upregulated in DLBCL cell lines and tissues. NAT10 high expression was associated with poor patient prognosis. Knockout of NAT10 impaired cellular phase progression and proliferation of DLBCL. Further analysis revealed that NAT10-mediated ac4C acetylation of SLC30A9 transcript and subsequently stabilized SLC30A9 mRNA, leading to activation of AMPK signaling and thereby facilitating DLBCL progression **(Figure 1)**.
Conclusions: Taken together, these results revealed that NAT10 regulated the AMPK signaling pathway to promote DLBCL progression by affecting SLC30A9 mRNA stability in an ac4C-dependent manner, suggesting that NAT10 could be a novel prognostic and therapeutic target in DLBCL.



Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, genomics, epigenomics, and other -omics

No conflicts of interests pertinent to the abstract.

474 | DNP73 PROMOTES DRUG RESISTANCE AND IMMUNE EVASION IN MULTIPLE MYELOMA VIA UPREGULATING MYC AND N-MYC

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Introduction: Multiple myeloma (MM) remains an incurable malignancy of plasma cells. The complex bone marrow microenvironment promotes resistance to both current anti-myeloma agents and emerging immunotherapies. Crosstalk between the NF-κB and p53 can play a pivotal role in various hematologic malignancies. DNp73, an inhibitor of the p53 tumor suppressor family, drives drug resistance and cancer progression in several solid malignancies. However, the biological functions and molecular mechanisms of DNp73 in MM remain unclear. In this study, we investigated the role of DNp73 in the drug resistance of MM, and disclosed the corresponding mechanism of how DNp73 promotes the immune escape of MM cells.
Methods: We constructed DNp73 overexpression and sh-RNA interference plasmids to obtain stable cell lines. The effects of DNp73 on proliferation and drug sensitivity were determined by flow cytometry and xenotransplantation model. RNA-seq and CHIP-seq were performed to detect the mechanisms of drug resistance in MM cells. The DNA damage repair and invasion ability of MM cells were detected by immunofluorescence and transwell assay. To validate the role of DNp73 in immune escape, we performed phagocytosis assays.
Results: Our previous study reported that miR-15a was down-regulated in MM cells and correlated with the inferior outcome of MM patients. Further analysis demonstrated that DNp73 was a direct target of p65, loss of miR-15a led to the activation of NF-κB-p65 pathway in MM cells. In addition, the level of miR-15a was negatively correlated with the expression of DNp73 in MM cells of patients ($r = -0.672$, $p < 0.05$). After DNp73 was down-regulated, cell proliferation and drug resistance were effectively inhibited.

Further in vivo study indicated the tumor volume in DNp73 knockdown group was reduced, and increased sensitivity to the carfilzomib, epirubicin and pomalidomide was observed ($p < 0.01$). Of note, RNA-seq analysis indicated that DNp73 expression was positively correlated with MYCN, MYC and CDK7 transcriptional programs in MM. GSEA analysis showed that MYC targets and DNA damage repair pathways were significantly enriched in DNp73-OE cells. Compared to control group, DNp73-OE cells were resistant to irradiation-induced cell death ($p < 0.01$). Meanwhile, DNp73 knockdown significantly reduced the migration and invasion of cells ($p < 0.01$). CHIP-seq data showed that DNp73 could bind to the promoter region of MYCN. DNp73 overexpression protects MM cells from phagocytosis, treated with anti-human CD47 antibody increased phagocytosis of macrophages ($p < 0.01$).

Conclusions: We demonstrated that miR-15a downregulation activated NF-κB, which promoted DNp73 expression at transcription level. DNp73 promotes drug resistance and immune escape in multiple myeloma by modulating Myc and N-Myc signal pathway.

The research was funded by: the CAMS Innovation Fund for Medical Sciences (2022-I2M-1-022), the Natural Science Foundation of China (82170194), the Non-profit Central Research Institute Fund of the Chinese Academy of Medical Sciences (2018RC320012), the Natural Science Foundation of China (81920108006), the Non-profit Central Research Institute Fund of the Chinese Academy of Medical Sciences (2018PT31006)

Keywords: multiple myeloma, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

475 | PTGDS PROMOTES TUMORIGENESIS OF PERIPHERAL T CELL LYMPHOMA THROUGH REGULATING IRON METABOLISM

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Introduction: Accumulating evidence indicates that ferroptosis, an iron-dependent cell death, is involved in the development of tumors, and targeting ferroptosis offers great potential in tumor therapy. However, the regulatory networks of ferroptosis in peripheral T cell lymphoma (PTCL) remain unclear.

Methods: Paraffin-embedded tissues of 112 PTCL patients and 38 reactive hyperplasia cases were collected with informed consents. Lentiviral vectors were stably transfected into PTCL cell lines. Tandem mass tag (TMT)-mass spectrometry and RNA-sequencing (RNA-seq) were performed for downstream analysis. Co-IP and confocal immunofluorescence were performed to verify protein–protein interaction. Xenograft models were established using SCID Beige mice.

Results: Firstly, both mRNA and protein levels of PTGDS were found to be higher in PTCL cells and patients' tissue (Figure 1A–C). Survival analysis revealed that the positive expression of PTGDS was closely associated with worse prognosis in PTCL patients (Figure 1D). PTGDS overexpression could significantly promote the proliferation of PTCL cells while PTGDS knockdown inhibited it in vitro and in vivo (Figure 2A,B). Besides, PTCL cells with PTGDS knockdown displayed a higher apoptosis rate (Figure 2C). PTGDS specific inhibitor AT56 could significantly inhibit the proliferation of PTCL cells, in a dose- and time-dependent manner (Figure 2D). Moreover, AT56 treatment induced the cell cycle arrest at G0/G1 phase in PTCL cells (Figure 2E).

Analysis based on TMT-mass spectrometry found that AT56 treatment significantly regulated the expression of ferroptosis-related molecules (Figure 3A) in PTCL cells. The anti-tumor effects of sorafenib and erastin, classic ferroptosis inducers, was significantly enhanced by AT56 treatment, and Fer-1, ferroptosis inhibitor, rescued the inhibitory role of AT56 on cell proliferation (Figure 3B, C). Moreover, AT56 promoted erastin/sorafenib-induced accumulation of lipid ROS (Figure 3D), a classic biomarker of ferroptosis. Further *in-vivo* experiments observed that AT56 treatment enhanced the anti-tumor effects of sorafenib (Figure 3E).

Mechanically, structure analysis of differentially expressed molecules in TMT-mass spectrometry identified HMOX1, a regulator of heme catabolism, as PTGDS interactive protein. Co-IP and confocal immunofluorescence assays verified their co-localization and interaction in PTCL cells (Figure 4A,B). Moreover, AT56 treatment increased the level of intracellular iron, and HMOX1 knockdown could rescue it (Figure 4C).

Conclusions: Taken together, our investigations firstly identified the high expression of PTGDS and its prognostic significance in PTCL patients. In-vitro and in-vivo investigation revealed that targeting PTGDS might promote tumorigenesis of PTCL through regulating HMOX1-mediated iron metabolism.

Keywords: aggressive T-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, molecular targeted therapies

The research was funded by:

National Natural Science Foundation (No. 82270200, No. 82170189, No. 82070203, No. 81800194, No. 81770210); Key Research and Development Program of Shandong Province (No. 2018CXGC1213); China Postdoctoral Science Foundation (No. 2021T1404223); Translational Research Grant of NCRCH (No. 2021WWB02, No. 2020ZKMB01); Shandong Provincial Natural Science Foundation (ZR2021YQ51); Taishan Scholars Program of Shandong Province; Shandong Provincial Engineering Research Center of Lymphoma; Academic Promotion Programme of Shandong First Medical University (No. 2019QL018).

No conflicts of interests pertinent to the abstract.

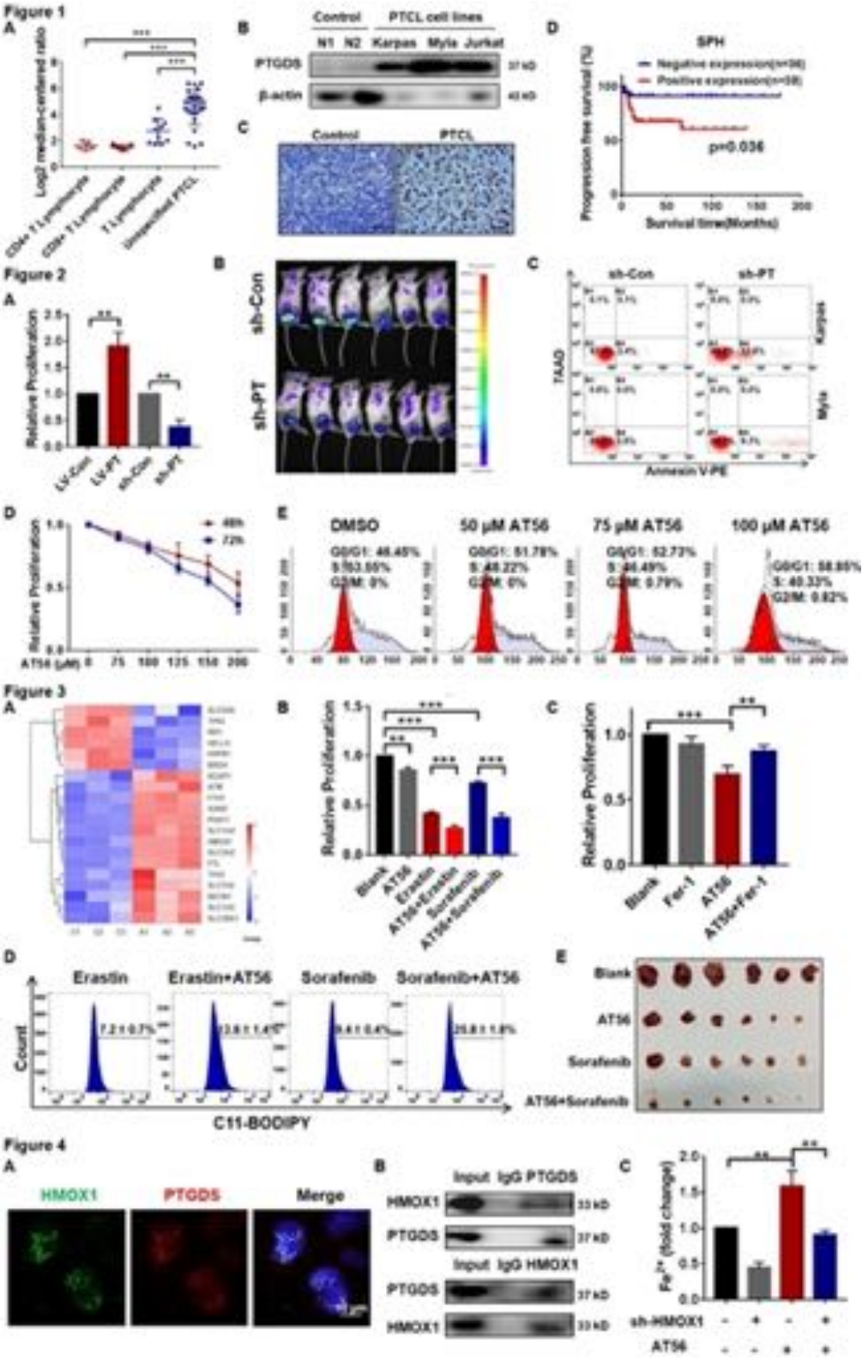
Figure 1
Figure 2
Figure 3
Figure 4
Control
PTCL cell lines
N1 N2 Karpas Myla Jurkat
PTGDS
β-actin
SPH
p=0.036
sh-Con
sh-PT
DMSO
50 μM AT56
75 μM AT56
100 μM AT56
Erastin
Erastin+AT56
Sorafenib
Sorafenib+AT56
C11-BODIPY
Blank
AT56
Fer-1
AT56+Fer-1
HMOX1
PTGDS
Merge
Input IgG PTGDS
Input IgG HMOX1

MICROENVIRONMENT

476 | PENTOSE PHOSPHATE PATHWAY INHIBITION ACTIVATES MACROPHAGES TOWARDS PHAGOCYTIC LYMPHOMA CELL CLEARANCE

A. Beielstein[1], E. Izquierdo-Alvarez[2], S. Blakemore[2], N. Nickel[2], S. Chawan[2], M. Michalik[2], R. Brinker[2], H. Bartel[2], D. Vorholt[2], J. Nolte[2], R. Linke[2], C. Raissa Costa Picossi[3], J. Saiz[3], A. Villaseñor[3], H. Winkels[4], M. Hallek[1], M. Krueger[1], C. Barbas[3], C. Pallasch[1]

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Introduction: Treatment response in lymphoma depends on the interaction of macrophages as important effector cells for tumor cell clearance by antibody-dependent cellular phagocytosis (ADCP). In the tumor microenvironment there is an altered supply of nutrients which implicates metabolic reprograming of immune cells such as diminished phagocytic capacity of macrophages. We aimed to identify metabolic pathways regulating macrophages to improve their effector cell function in lymphoma therapy.

Methods: We addressed macrophage lymphoma cell co-cultures using macrophage cell lines, primary human and murine macrophages, humanized aggressive lymphoma cell model hMB, and primary CLL patient cells. For pathway inhibition specific compounds and shRNA-mediated knockdowns were used. Macrophages were studied by immunophenotyping, SeaHorse, (phospho)-proteomic and metabolomic assessment. Lymphoma bearing NSG and C57BL/6 mice were used for in vivo treatment with the pentose phosphate pathway inhibitor S3, analysis of macrophage reprogramming, and overall survival.

Results: Inhibition of the pentose phosphate pathway (PPP) induced an increased therapeutic efficacy of lymphoma cell phagocytosis by macrophages. Under PPP inhibition, an increased metabolic activity and a pro-phagocytic reprogramming of macrophages was observed, accompanied by an increased pro-inflammatory cytokine secretion. PPP inhibition in macrophages reduced primary CLL cell survival support in co-culture. The increased lymphoma cell clearance and phenotypic alterations were also observed in PPP enzyme knockdown macrophages and by inhibiting the PPP in primary human macrophages. In a multiomics assessment, a connection between PPP inhibition, subsequent suppression of glycogen synthesis and a changed immune profile by modulation of the Stat1-Irg1-itaconate axis was identified and validated. In humanized lymphoma mouse model the addition of the PPP inhibitor S3 led to significant prolonged overall survival and an increased macrophage maturation, pro-inflammatory polarization and phagocytic activity.

Conclusions: We have identified the PPP as therapeutic target for reprogramming macrophage activity towards lymphoma cell phagocytosis. This effect is driven by Stat1-Irg1-itaconate signalling axis, connecting metabolic activity and immune-phenotype of macrophages. We hypothesize the PPP as a key regulator of macrophage function determining the capacity of lymphoma cell clearance and propose PPP inhibition as a therapeutic booster of antibody dependent regimens in B cell lymphoma.

The research was funded by: Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) KFO28 and SFB1530, Studentische Forschungsfoerderung/ Begabtenfoerderung of Koeln Fortune program

Keywords: metabolism, microenvironment, targeting the tumor microenvironment

No conflicts of interests pertinent to the abstract.

477 | THE ASSOCIATION OF THE EMERGING TICK-BORNE BACTERIAL PATHOGEN NEOEHRLICHIA MIKURENSIS WITH MALIGNANT B CELL LYMPHOMA

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The development of some lymphomas has been associated with infections caused by bacterial species discovered in the 1980s, for example, *Helicobacter pylori* and *Borrelia burgdorferi s.l.* The first cases of human infection with a bacterial species that was first described in 2004, the tick-borne bacterium *Neoehrlichia mikurensis* were published in 2010. Patients with malignant B cell lymphomas emerged as a risk group for severe cases of infection, presenting with fever of unknown cause and venous thromboembolism. The infection is missed by routine microbiologic diagnostic procedures such as blood culture and can only be detected by PCR. Vascular endothelium is a likely target of *N. mikurensis* infection. Asymptomatic carriage of the infection for months to years appears to occur. We hypothesized that *N. mikurensis* causes latent infections that can reactivate when B cell defenses are compromised. It was whilst conducting a study of patients with malignant B cell lymphomas scheduled to receive treatment with rituximab that we discovered several patients who had the infection already before the start of treatment. This led us to hypothesize that persistent latent infections with *N. mikurensis* might contribute to the development of certain cases of malignant B cell lymphoma. Splenic engagement, restricted repertoires of the Immunoglobulin heavy chain variable (*IGHV*) regions, and mutations of the *IGHV* regions from the germline configuration featured among these cases of lymphoma, which encompassed chronic lymphocytic leukemia, splenic marginal zone lymphoma, mantle cell lymphoma and non-classified indolent splenic lymphoma. Remarkably, three out of five patients could cease

lymphoma therapy after eradication of the infection. Our aim is to confirm and expand these findings of a possible causality between *N. mikurensis* infection and the development of malignant B cell lymphomas. To this end, we are starting a prospective study of the prevalence of *N. mikurensis* infection in newly diagnosed patients with malignant B cell lymphomas, and the response of such lymphomas to eradication of the infection. We will also attempt to identify a genetic signature of *N. mikurensis* infection by studying *IGHV* gene usage, the mutations induced by somatic hypermutations, as well as the physicochemical properties of the complementarity-determining region 3 (CDR3), the most hypervariable part of the B cell receptor of infected patients. This will help establish if it is mainly post-germinal center B cells that undergo malignant B cell transformation in cases of *N. mikurensis*-associated lymphoma.

The research was funded by: the Swedish Research Council, the Swedish Cancer Society, the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement, and the Cancer and Allergy Foundation.

Keywords: indolent non-Hodgkin lymphoma, tumor biology and heterogeneity, chronic lymphocytic leukemia (CLL)

No conflicts of interests pertinent to the abstract.

478 | PATTERNS OF CIRCULATING NK CELL DYSFUNCTION IN PATIENTS WITH LYMPHOMA

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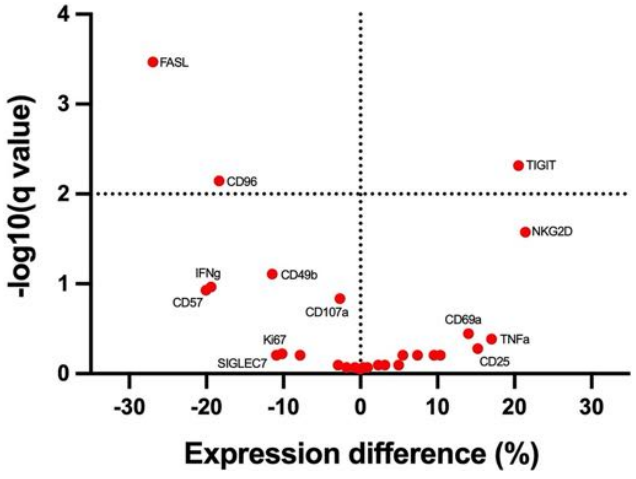
Background: Cancer is a recognized condition of secondary immunosuppression. Lymphoma patients often show a decrease in absolute lymphocyte counts and in peripheral blood gamma-globulin levels. However, less is known about how NK cells are altered in lymphoma patients. The aim of this study was to evaluate the patterns of circulating NK cell dysfunction in lymphoma patients.
Methods: We performed a cross-sectional study of patients with a recent diagnosis of nodal lymphoproliferative disorder. Patients with active anticancer treatment or steroid use were excluded. Peripheral blood samples in EDTA were analyzed by multicolor flow cytometry. A custom panel of 30 markers was applied to all samples to test for major subpopulations, maturation, and functional markers. Results were compared to healthy controls. Clinical data were obtained from the electronic database. This study was approved by the institutional IRB and Clinical Ethics Committee.
Results: A total of 30 patients were examined between October 2021 and November 2022. The median age was 62 years (range 15–88) and 45.7% were female (16). Patients had the following subtypes: large B-cell lymphoma (LBCL; 9), follicular lymphoma (FL; 9), Hodgkin lymphoma (HL; 5), mantle cell lymphoma (MCL; 4), marginal zone lymphoma (MZL; 2), Waldenström macroglobulinemia (WM; 1). Most patients had advanced stage disease (20).
Compared to healthy controls ($n = 10$), lymphoma patients showed a significant decrease in absolute NK cell counts (ANKC, 319.7 vs. 131.1 cells/mm^3; $p < 0.0001$). MCL patients had the lowest ANKC (68.8) and Hodgkin patients the highest (165.6). Advanced stage disease correlated with lower ANKC compared to localized disease (99.85 vs. 148.9; p = ns). The pattern of maturation was altered in lymphoma patients compared to controls ($p = 0.0092$). Patients had a higher proportion of immature CD56-bright NK cells (4.97% vs. 2.88%) and lower levels of CD16 expression in the mature CD56-dim subpopulation (68.12% vs. 85.94%). Lymphoma patients also showed dysfunctional expression of receptors and activation markers (Figure). There was a significant increase in the levels of FAS-L, IFNg, CD49b, CD57, CD96, and CD107a, while the levels of TIGIT and NKG2D were significantly decreased. Differences in the expression of immune checkpoints (PD-1, LAG-3, TIM-3), as well as additional activating, inhibitory, and chemokine receptors were not significant. 22 of 30 patients (73.3%) achieved a complete response. All patients with ANKC above 135 cells/mm^3 at diagnosis achieved sustained complete remission.
Conclusions: Patients with lymphoma show a quantitative and qualitative dysfunction of circulating NK cells. Patients without a decrease in ANKC have good clinical outcomes. Identification of NK cell dysfunction could serve as a dynamic biomarker. Further validation is warranted.



The research was funded by: Fondecyt 11200805 Clínica Alemana de Santiago ID1025

Keyword: diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

479 | IMMUNE PROFILE IN THE PERIPHERAL BLOOD (PB) OF PATIENTS WITH FOLLICULAR LYMPHOMA (FL) AT DIAGNOSIS AND UPON RELAPSE

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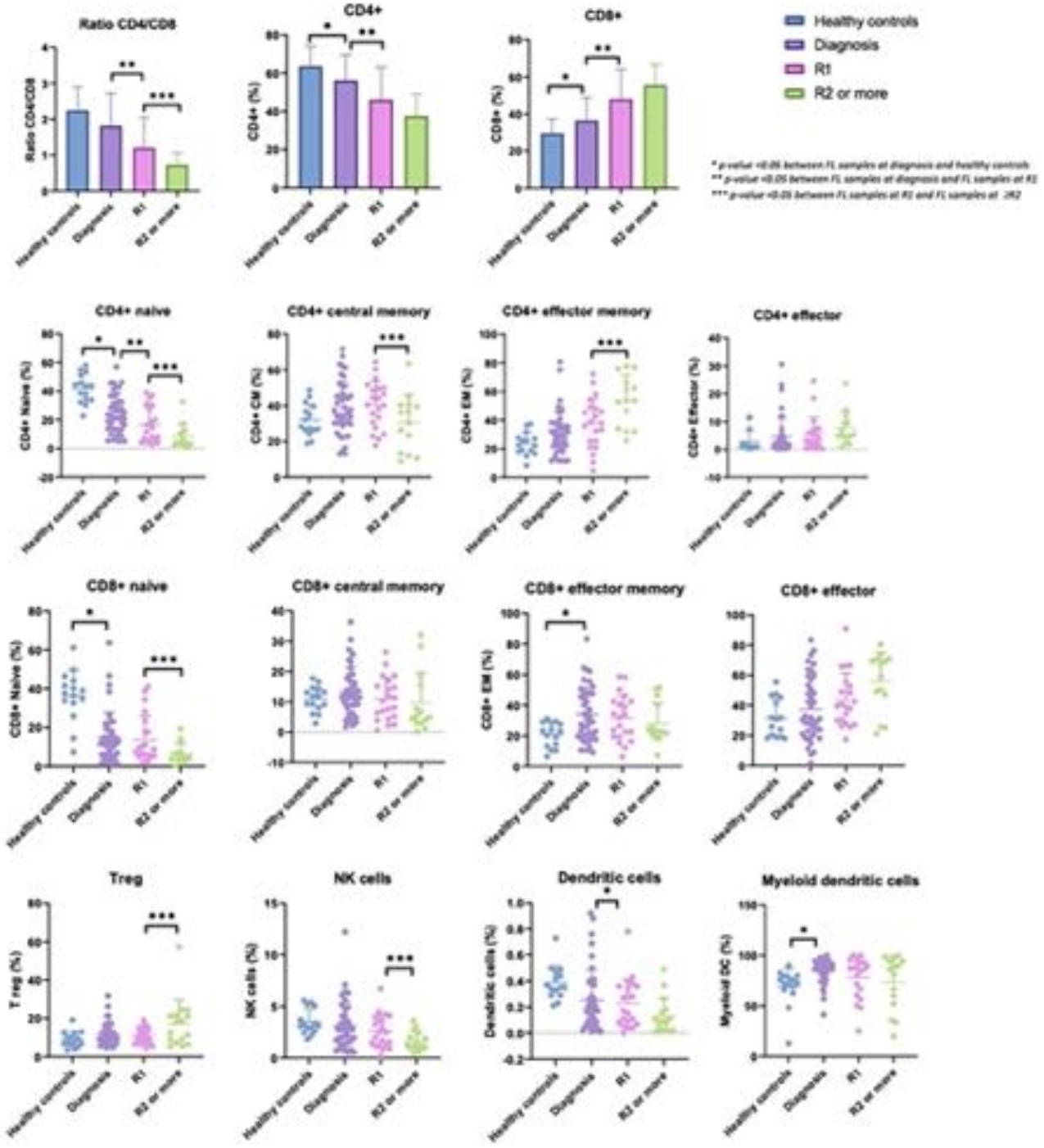
Introduction: FL is characterized by a heterogeneous clinical course. The biologic importance of the tumour microenvironment in FL

Image. Most relevant immune populations in patients with FL and healthy controls



pathogenesis is well established. However, detailed information on the immune profile in PB has not been previously investigated, which becomes very relevant in the current era of the immunotherapy. The aim of this study was to characterise the PB immune profile of FL patients at diagnosis, first relapse (R1) and subsequent relapses (>R^2) and compare them with healthy controls. Moreover, R1 was also analysed according to histological transformation (HT) and POD24 status.

Methods: We collected PB samples of FL patients at diagnosis ($n = 42$), R1 ($n = 22$) and >R2 ($n = 16$) from April 2019 to August 2022 (median age at diagnosis: 65 years [30–82]; 22M/20F). 15 PB samples from healthy donors were also obtained (median age: 31 years [28–65]; 5M/10F). All individuals signed informed consent. The identification of major subsets of T-cells, B-cells, NK cells, monocytes, neutrophils, eosinophils, basophils, dendritic cells (DC) and myeloid suppressor cells (MSC) was performed by multiparameter flow cytometry. Euroflow methodology was used to set up the Omnicyt™ flow cytometer and acquired at least 150.000 events. All data were analysed using Infinicyt™ software version 2.0 (Cytognos, Salamanca, Spain).

Results: Compared with healthy controls, FL patients showed a lower $CD4^+/CD8^+$ ratio due to an increase in $CD8^+$ lymphocytes and a decrease in total $CD4^+$ lymphocytes. In addition, FL patients had a significantly lower percentage of naïve T lymphocytes, a higher percentage of effector memory and effector lymphocytes, both $CD4^+$ and $CD8^+$. Of note, regulatory T lymphocytes (Treg) and Th1 cells were increased in FL patients, while NK-cells were diminished. Interestingly, differences in DC and MSC were also found between healthy controls and FL patients (**Figure**). These differences remained when comparing the immune populations between diagnosis and relapse and deepened with each relapse. No differences were observed between groups in the percentage of neutrophils, monocytes, eosinophils, or total B lymphocytes. A subanalysis performed in R1 samples according to HT and POD24 status revealed that HT-R1 presented significantly a smaller $CD8^+$ central memory population compared with non HT-R1. POD24 patients displayed a lower $CD4^+/CD8^+$ ratio and a higher proportion of Th1 cells ($p < 0.05$). In both adverse prognostic groups, the percentage of myeloid DC and neutrophils was significantly lower.

Conclusions: FL patients showed an immunological profile in PB that is significantly different from that observed in healthy controls, and deeper differences are observed with subsequent relapses. The knowledge of these immune alterations may contribute to the understanding of FL behaviour and might help design immunotherapy strategies adapted to the patient´s immunological profile.

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Keywords: indolent non-Hodgkin lymphoma, microenvironment

No conflicts of interests pertinent to the abstract.

480 | M6A-REGULATOR EXPRESSION SIGNATURES IDENTIFY A SUBSET OF FOLLICULAR LYMPHOMA HARBORING AN EXHAUSTED TUMOR MICROENVIRONMENT

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Background: The role of N6-methyladenosine (m6A) modification in tumor microenvironment has rarely been explored in follicular lymphoma (FL).

Methods: To examine the role of m6A modification in biological behavior, especially the immune landscape of FL, we utilized the Gene Expression Omnibus database to determine the expression signatures of m6A-regulators by unsupervised clustering, and then condense into a risk score, which was validated in an external cohort from the Tianjin Medical University Cancer Institute and Hospital.

Results: 16 m6A-regulators in 351 FL patients were evaluated and two m6A clusters were identified, characterized by differences in prognosis and biological behaviors. The m6A score was further developed based on 20-genes to quantify the m6A-regulator expression signature in each patient with FL. The low m6A score was associated with inferior prognosis of patients, with a median survival time of 8.84 (95% confidence interval [CI]: 7.251–10.429) years, which was remarkably shorter than that of patients with high m6A scores (15.73 years, 95% CI: 11.729–19.731; $p < 0.0001$). Genes like TNFRSF14, CREBBP, and CARD11 were shown to be more often mutated in the low m6A group. This group was enriched with immune/inflammatory response but along with the abundant infiltration of exhausted T cells and the upregulated PD-1 and PD-L1 expression. Finally, we verified the m6A score could predict the response to anti-PD-L1 antibodies in an immunotherapy cohort.

Conclusions: To conclude, the m6A score recognizes a section of FL patients harboring an exhausted tumor microenvironment and may help guide more effective immunotherapy strategies for patients with FL.

Keywords: bioinformatics, computational and systems biology, indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

481 | GENETIC CHARACTERISTICS INVOLVING THE PD-1/PD-L1/L2 AND CD73/A2AR AXES AND THE IMMUNOSUPPRESSIVE MICROENVIRONMENT IN DLBCL

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Background: Targeting the PD-1/PD-L1/L2 pathway combined with other immunosuppressive signaling, such as CD73/A2aR adenosine signaling, has emerged as a promising strategy for cancer treatment. The genetic characteristics of these immune checkpoints need to be further investigated in diffuse large B-cell lymphoma (DLBCL).

Methods: We performed whole-exome sequencing/targeted deep sequencing to investigate the genetic characteristics of PD-1/PD-L1/L2 and CD73/A2aR. The immunosuppressive effect of these two pathways on the tumor microenvironment was evaluated via RNA sequencing. Single-cell RNA sequencing was further applied to investigate the dysfunctional CD8+ T cells. In addition, multiplex immunofluorescence staining was used to quantitatively assess the expression of dysfunctional CD8+ T cells in DLBCL.

Results: SP140 was identified as a novel translocation partner for PD-L1, and a new inversion was detected between PD-L1 and PD-L2, both leading to the upregulation of PD-L1 expression. CD73 genetic mutations did not increase mRNA and protein expression. Patients with genetically altered CD73 tended to have a better overall survival than patients with wild-type CD73. Both PD-1/PD-L1 and CD73/A2aR signaling mediated the immunosuppressive microenvironment in DLBCL. The numbers of CD8+ T cells with PD-1 and A2aR expression were positively correlated with the number of dysfunctional CD8+ T cells ($R2 = 0.974$, $p = 0.013$). According to the grades of dysfunctional CD8+ T cells we defined, grade 1 dysfunctional CD8+ T cells, with either PD-1+ or A2aR+, were significantly associated with poorer survival than grade 0 dysfunctional CD8+ T cells, with both PD-1- and A2aR-; and patients with grade 2 dysfunctional CD8+ T cells showed the worst clinical outcomes.

Conclusions: This study describes the additional genetic basis of PD-L1 overexpression and characterizes certain genetic alterations of CD73/A2aR in DLBCL. The degree of T cell dysfunction is correlated with clinical outcomes. Strategies that reverse T cell dysfunction by inhibiting PD-1/PD-L1/L2, particularly in combination with CD73/A2aR, may show potential as effective therapeutic options for DLBCL.

Keywords: aggressive B-cell non-Hodgkin lymphoma, microenvironment

No conflicts of interests pertinent to the abstract.

482 | PLASMA PROTEIN PROFILING USING MULTIPLEX EXTENSION ASSAY IN DLBCL. A DESCRIPTIVE STUDY EXPLORING PLASMA PROTEIN PATTERN EVOLUTION IN DLBCL TREATED WITH R-CHOP

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Background: In a previous study utilizing multiplex protein extension assay (PEA) we were able to highlight significant differences in pre-treatment plasma proteins in lymphoma and leukemia patients compared to age and gender matched controls.

In this study we intended to explore the pattern of changes in plasma proteins throughout the venture of treatment with R-CHOP for patients with DLBCL and possible association to clinical outcome and prognosis.

Materials and methods: Frozen plasma samples from 94 DLBCL patients 41(44%) female, 53 (56%) male, median age of 64 years (27–87 years), and 60 age and gender matched controls were used. Samples were collected before the start ($n = 93$), midway through ($n = 30$), at progressive disease ($n = 5$) at relapse ($n = 5$) and after completion of chemotherapy in complete remission ($n = 51$).

A total of 182 plasma proteins were measured using customized protein panels utilizing PEA technique.

Results: Multivariate modelling using partial least square discriminant analysis revealed significant distinctions in protein patterns at diagnosis compared to controls and between samples collected at different stages of the illness. Striking differences in protein levels before and after treatment in patient who responded to treatment were evident (Figure 1). The three top proteins were TCL1A, CXCL13 and IL2RA. Moreover, particular proteins were significantly associated with established clinical risk factors such as age < versus ≥60 years (top CXCL17), A versus B-symptoms (top BLM hydrolase), Stage I+II versus III+IV (top CD163) and IPI 0–1 versus 3–5 (top BLM hydrolase).

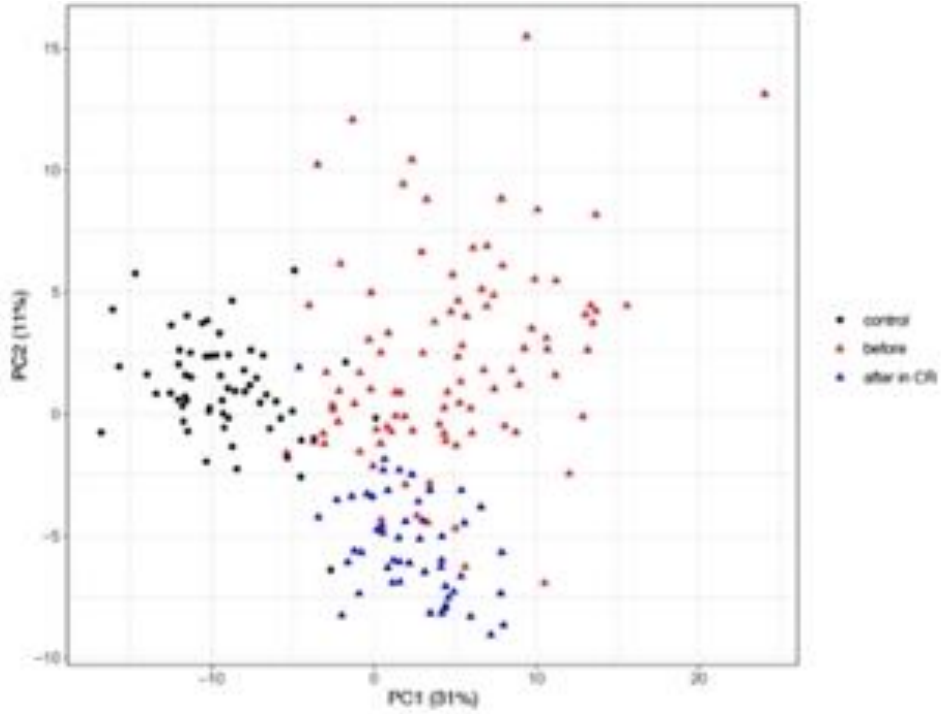
Furthermore, proteins well linked to mitogen activated protein kinase (MAPK) cascade, inflammatory response, cell differentiation were prominent when comparing pre and post treatment samples and controls. Cox regression analysis revealed multiple proteins significantly linked to overall survival, lymphoma specific survival and relapse free survival. Finally, there were profound differences between patients in CR and controls.

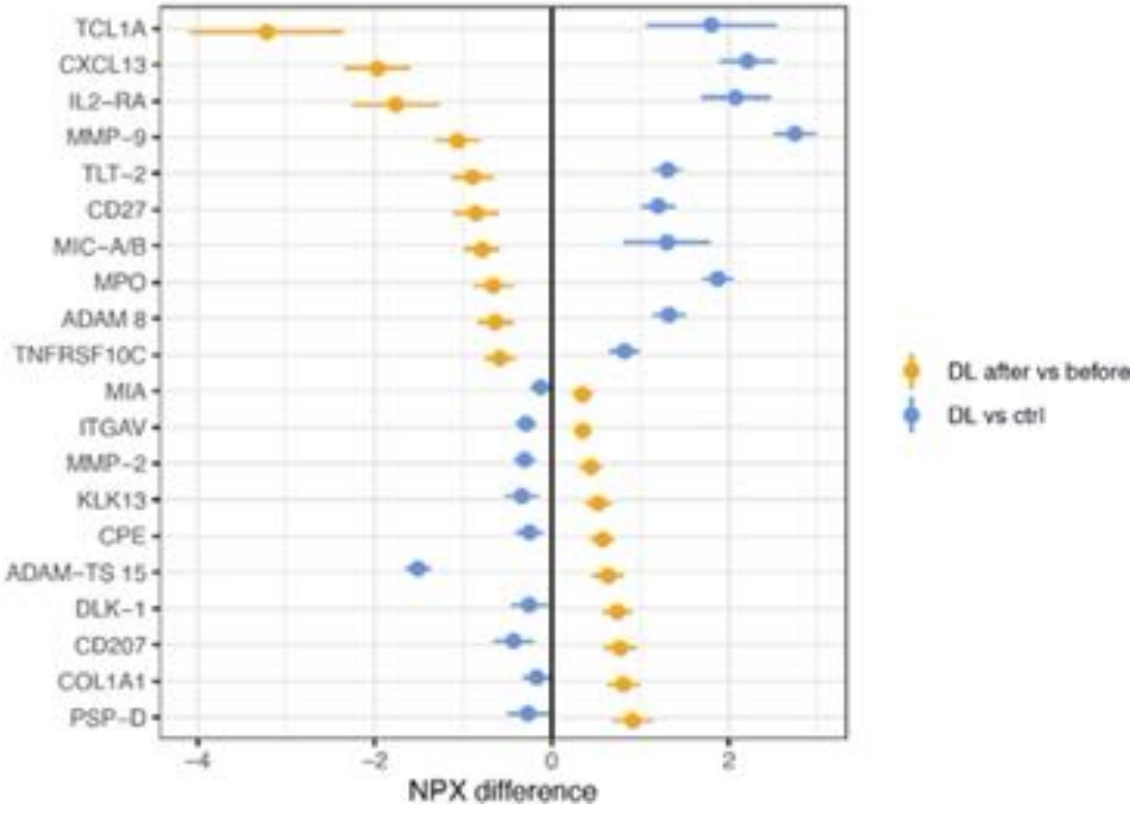
Conclusion: Plasma protein profiling could add valuable insight to the biological changes in DLBCL patients undergoing treatment with R-CHOP and may aid the quest for biomarkers predicting response to treatment and prognosis. The intriguing differences between patients in CR and controls demands further studying.

Abbreviations:

DLBCL: Diffuse Large B-Cells Lymphoma

RCHOP: Rituximab, Cyclophosphamide, Doxorubicin hydrochloride, Vincristine sulfate, and Prednisone





PEA: protein extension assay

TCL1A: T-cell leukemia/lymphoma protein 1A

CXCL13: Cyclin-dependent kinase inhibitor 1

IL2RA: Interleukin-2 receptor alpha chain

BLM Hydrolase: Bleomycin hydrolase

CD163: Cluster of Differentiation 163

MAPK: Mitogen activated protein kinase

Figure 4: PCA of controls and DLBCL before and after

Forest plot over proteins that differ significantly between DLBCL before and controls and between DL after versus before, but in opposite directions. Only top 10 for after versus before in each direction are shown.

Keyword: diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

483 | **TRACES OF EPSTEIN BARR VIRUS (EBV) ARE NOT INVOLVED IN THE PATHOGENESIS OF DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)**

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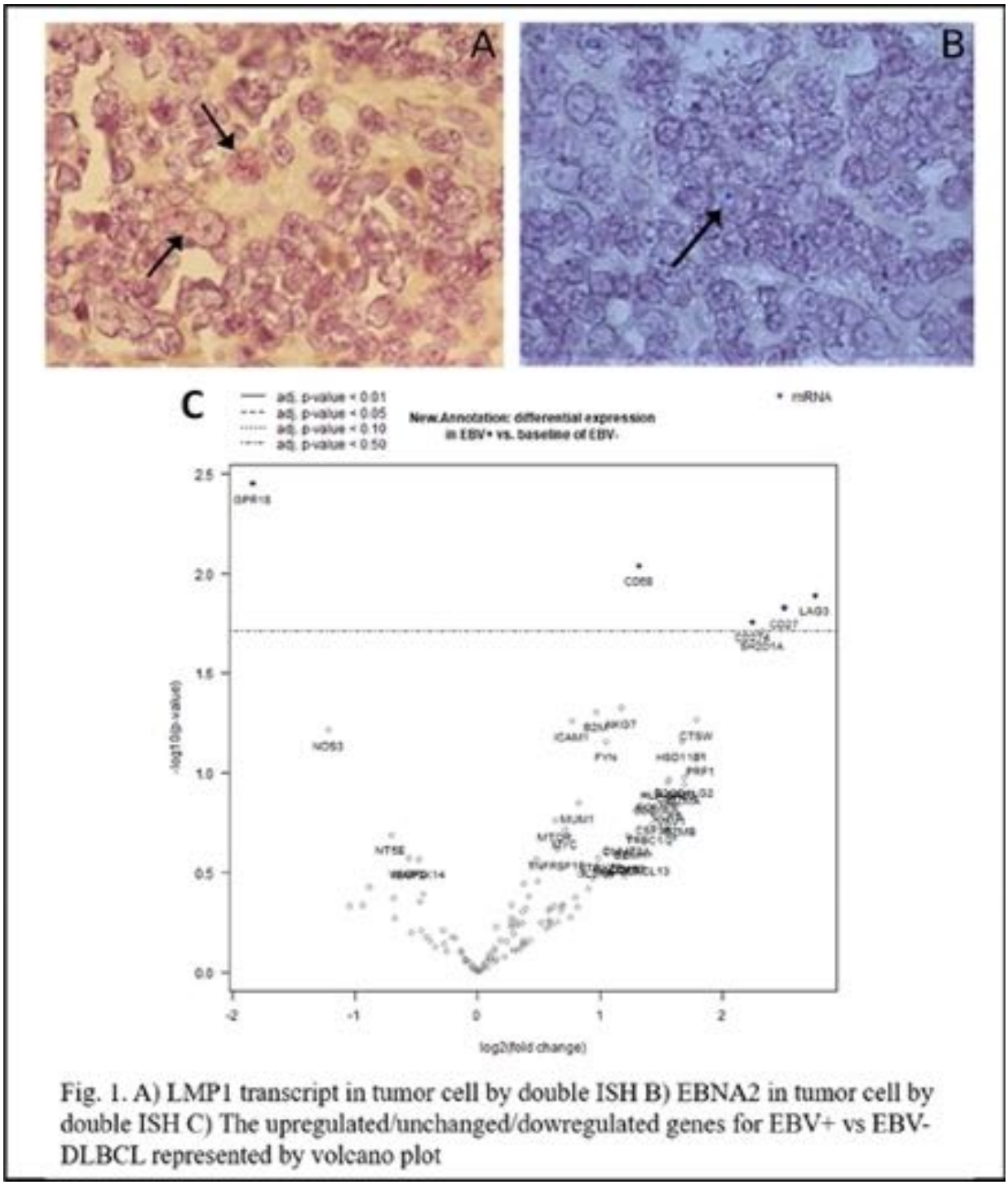

Fig. 1. A) LMP1 transcript in tumor cell by double ISH B) EBNA2 in tumor cell by double ISH C) The upregulated/unchanged/dowregulated genes for EBV+ vs EBV- DLBCL represented by volcano plot

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Introduction: Epstein-Barr virus-positive DLBCL (EBV+ DLBCL) was defined by the WHO, with >80% EBERs+ cells, although 20% was used as cut off. The detection of traces of EBV was reported by more sensitive methods than EBERs in situ hybridization (ISH). The aim was to analyze immune response markers in EBV+ DLBCL, and to compare them in cases with or without traces of EBV infection.

Methods: Fifty DLCBL cases were studied by EBERs ISH. The expression of immune response genes was evaluated by Lymph2Cx. LMP1 and EBNA2 transcripts were detected by double ISH with ViewRNA ISH Tissue 2-Plex Assay to define the presence of traces of EBV. LMP1+, EBNA2+, and double LMP1+/EBNA2+ cells were counted in tumor cells. Viral load was measured by RT- qPCR. Immunohistochemistry (IHC) for CD68, CD163, LAG3 and PDL1 at the TME, and PDL1/PAX5 in tumor cells was performed.

Results: EBV was detected by EBERs ISH in 12/50 cases. A cut-off of 20% of EBERs+ cells was used to define EBV+DLBCL. Viral transcripts were detected in 19/45 cases (5 EBV+ and 14 EBV-) with good quality for analysis. 19 and 5 cases expressed LMP1 and EBNA2 transcripts, respectively (Figure 1A,Bfig1). Only EBV+DLBCL cases displayed detectable viral load. When the expression of immune response genes by Lymph2Cx was compared in EBV+ versus EBV- DLBCL, higher expression of CD274 (PDL1), LAG3, CD68, among others, was observed (Figure 1C). This increased expression was not observed when cases with traces of viral transcripts were compared with its negative counterpart. The expression of LAG3, CD68 and PDL1 in the TME and PDL1/PAX5 in tumor cells was assessed by IHC to validate gene expression results. PDL1+/ PAX5+ and CD68+ cell count was higher in EBV+ DLBCL ($p < 0.05$), whereas no difference was observed in LAG3 and PDL1 expression in TME. M1 polarization profile prevailed in the entire cohort. However, when cases with traces of EBV transcripts were compared with cases without them, no differences were proved in CD68, LAG3, PDL1 and PDL1/ PAX5 cell count.

Conclusion: This study provides further evidence that traces of EBV could be detected by a sensitive method. However, since differences were only demonstrated in cases with more than 20% of EBERs+ cells as cut off, traces of EBV would not be involved in the pathogenesis of DLBCL, in contrast to the hit-and-run theory. In EBV+ DLBCL PDL-1 and CD68 expression is upregulated in tumor cells and in the TME, respectively.

The research was funded by: grants from National Agency for Science and Technology Promotion (PICT 2018 0966, PIDC 2018 0052), CONICET (PUE 0048)

Keywords: microenvironment, non-Hodgkin (pediatric, adolescent, and young adult), tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

484 | A NOVEL IMMUNE-RELATED EPIGENETIC SIGNATURE BASED ON THE TRANSCRIPTOME FOR PREDICTING THE PROGNOSIS AND THERAPEUTIC RESPONSE OF PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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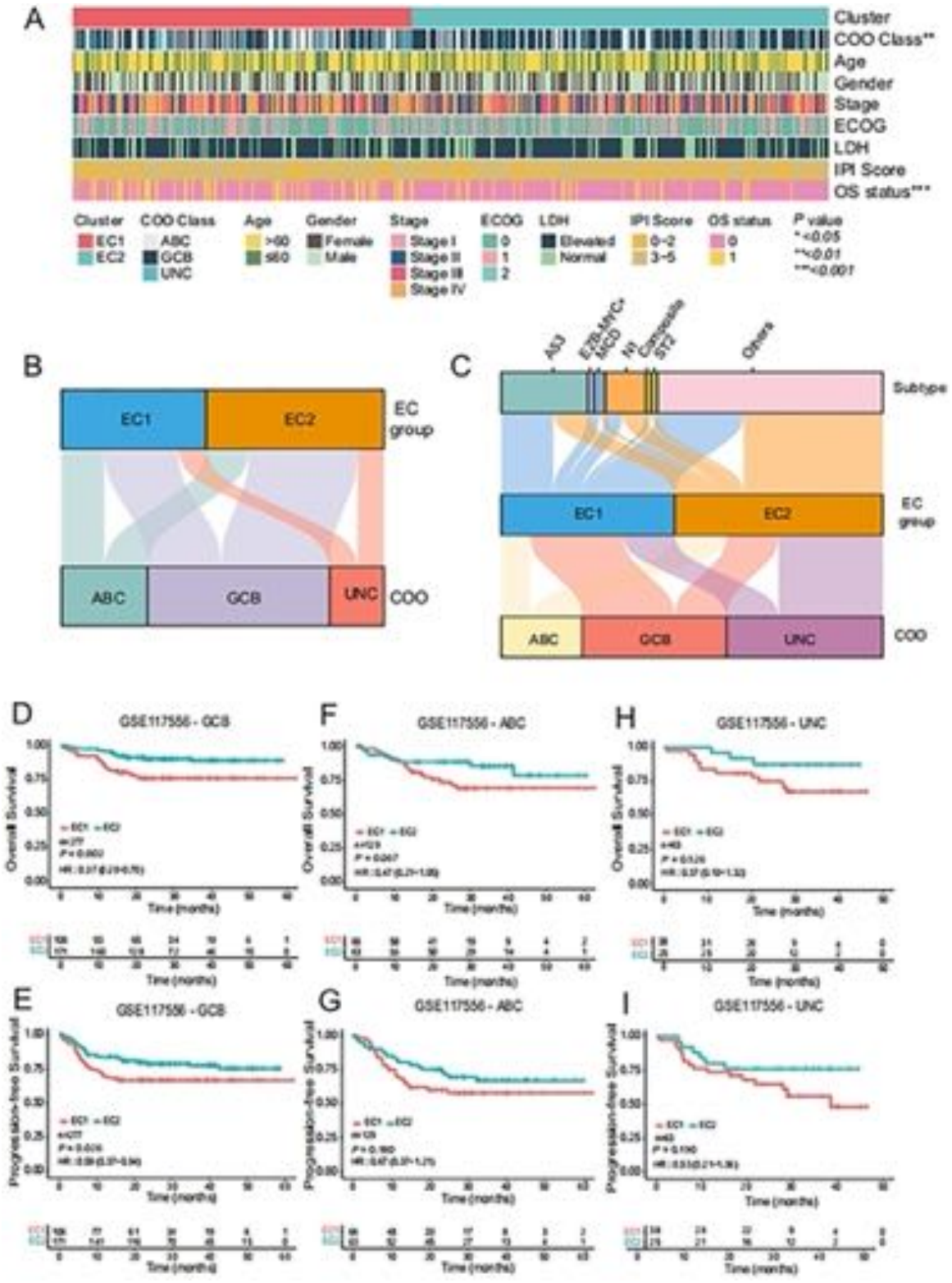
Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid neoplasm in adults. The poor prognosis of patients who failed R-CHOP therapy prompted efforts to discover new combination therapies. Epigenetic genes play a crucial role in the development and progression of lymphoma, and it has been shown that epigenetic dysfunction can induce lymphomagenesis. From a comprehensive perspective, how epigenetic factor-related genes affect the immune regulation and tumor microenvironment of DLBCL is still unclear. Implementing R-CHOP-based combined epigenetic therapy to reverse the immune-resistant phenotype is critical for the precise treatment of DLBCL.

Methods: The DLBCL dataset GSE117556 was selected, and 469 patients treated with R-CHOP or R-CHOP-like regimen were selected as a discovery dataset, and 910 epigenetic-related molecules were obtained through GeneCards and EpiFactors. Epigenetic genes related to survival were obtained by Cox regression analysis. Unsupervised nonnegative matrix factorization (NMF) using R language to determine the best grouping. At the same time, 66 DLBCL patients with R-CHOP or R-CHOP-like treatment who were diagnosed and treated in our cancer institute from 2008 to 2018 were selected. Genetic genes do NMF clustering to get the best grouping. At the same time, the external validation set GSE98588 is used to do NMF clustering with the same method as above to obtain the best grouping.

Result: We performed an expression clustering analysis and identified two epigenetic-related clusters (EC1 and EC2). EC1 presented abundant TP53, MYD88, HIST1H1D, HIST1H1C, KMT2D and EZH2 mutations and an inferior prognosis. Pathways involved in the regulation of DNA methylation/demethylation, histone methyltransferase activity, and protein methyltransferase activity were significantly enriched in EC1. However, EC2 was frequently accompanied by B2M, CD70 and MEF2B mutations, which presented with enrichments in DNA damage repair, cytokine-mediated and B-cell activated immune signaling, increased levels of CD8+ T-, γδT- and T helper-cells, as well as immune scores and immunogenic cell death (ICD) modulators. According to the prediction, EC1 was more sensitive to vorinostat, serdemetan and navitoclax. However, ruxolitinib, cytarabine and CP466722 were more suitable treatments for EC2.

Conclusions: The novel immune-related epigenetic signature exhibits promising clinical predictive value for DLBCL, particularly for guiding



epigenetic therapeutic regimens. R-CHOP based combination treatment regimens are suggested.

Keywords: DLBCL, prognosis response, epigenetic, immune infiltration signature.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, genomics, epigenomics, and other -omics

No conflicts of interests pertinent to the abstract.

485 | ENDOTHELIAL ACTIVATION AND STRESS INDEX IS AN INDEPENDENT PROGNOSTIC FACTOR OF DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH STANDARD IMMUNOCHEMOTHERAPY

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Background: The natural history of diffuse large B-cell lymphoma (DLBCL) is heterogeneous. Several prognostic models have been investigated to predict treatment outcomes of patients with DLBCL. Endothelial activation and stress index (EASIX) is a surrogate of endothelial dysfunction in various conditions including cancer. An elevated EASIX score was associated with inferior outcomes in patients with multiple myeloma, low-risk myelodysplastic syndrome and patients treated with cell-based immunotherapy. However, the data of EASIX in DLBCL is limited and warrants exploration. We evaluated the prognostic implication of EASIX score in patients with DLBCL treated with immunochemotherapy.

Methods: This is a single center study enrolling adult patients with newly diagnosed DLBCL receiving immunochemotherapy at the University hospital between January 2013 and December 2022. Clinicopathological data were abstracted from medical record. EASIX score was calculated using serum creatinine, lactate dehydrogenase and platelet according to the original report by Luft et al. The optimal cutoff of EASIX for survival outcomes was determined by the time-dependent receiver operating characteristic curves (ROC). Relevant survival endpoints including progression free survival (PFS) and overall survival (OS) were analyzed using Kaplan Meier Estimate. Cox proportional hazards analysis was performed to explore the impact of EASIX on survival outcomes.

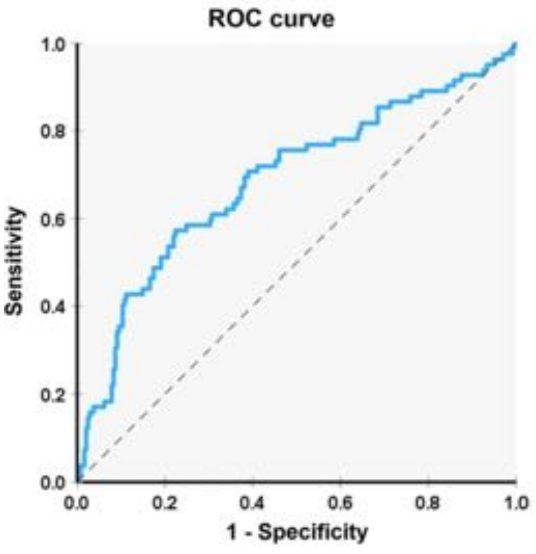
Result: A total of 323 patients with newly diagnosed DLBCL were included. The median EASIX score was 1.00 (range, 0.17–136.94). The optimal EASIX cutoff by ROC analysis was 1.07 stratifying patients into the low EASIX (n = 174, 53.9%) and high EASIX (n = 149, 46.1%) groups (Figure). In the high EASIX group, there was a significantly higher proportion of patients with advanced stage, bulky disease, and impaired performance status. Patients with high EASIX score significantly presented with higher-risk diseases as determined by the International Prognostic Index. Of 290 evaluable patients, the overall response rate of the entire cohort was 91.7% (complete remission, CR 67.9%). Patients with high EASIX score had a significantly lower CR than those with low EASIX score (89.6% vs. 73.8%, $p < 0.001$). After a median follow up of 34.6 months, 79 patients (24.4%) relapsed, and 96 patients (29.7%) had died. Patients with high EASIX score had a significantly worse 2-year PFS (53.4% vs. 81.5%, $p < 0.001$) and 2-year OS (64.4% vs. 88.7%, $p < 0.001$) than patients with low EASIX score (Figure). Multivariate analysis revealed that older age, bulky disease, impaired performance status, and high EASIX score were associated with an unfavorable OS.

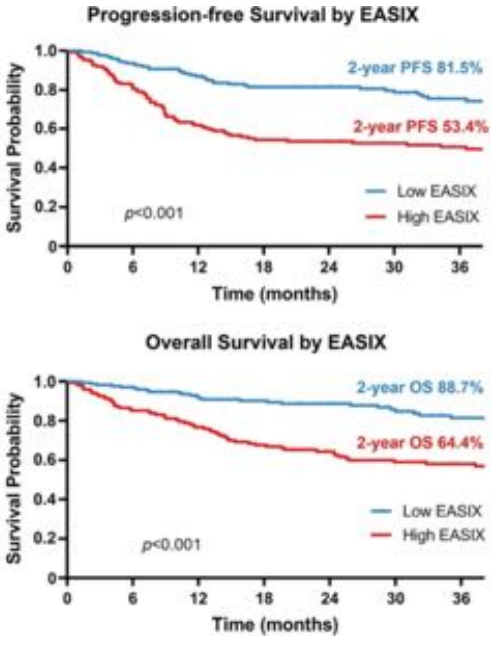
Conclusion: In patients with DLBCL, a high EASIX score is an independent prognostic factor of an unfavorable survival outcome. Further studies in larger patient cohorts are warranted to validate its prognostic implication.

Encore Abstract—previously submitted to EHA 2023

Keyword: aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.





486 | IDENTIFYING A NOVEL DEFINED PYROPTOSIS-ASSOCIATED SIGNATURE CONTRIBUTES TO PREDICTING PROGNOSIS AND TUMOR MICROENVIRONMENT OF DIFFUSE LARGE B-CELL LYMPHOMA

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Emerging evidence shows that pyroptosis plays a crucial role in the development and progression of multiple types of cancer. However, there is a limited understanding of the role of pyroptosis in DLBCL. The study aimed to identify pyroptosis-related signatures, develop a novel prognostic model, and investigate immune infiltration profiles in DLBCL.

The expression profiles of pyroptosis-related genes (PRGs) in DLBCL and normal samples were examined, and the clinical characteristics of DLBCL patients. LASSO Cox regression analyses were performed to develop a prognostic model based on six PRGs. The expression of differentially expressed PRGs in DLBCL cell lines was validated using qRT-PCR.

To explore the expression profile characteristics of PRGs in DLBCL, the mRNA expression levels of PRGs were evaluated in DLBCL and normal samples. The results revealed that the majority of PRGs were dysregulated in DLBCL samples.

The clinical significance of PRGs in DLBCL was further evaluated. 19 genes were significantly associated with OS of DLBCL patients in the univariate Cox regression. Six PRGs were selected for the risk model according to the minimum criteria of the LASSO Cox regression, and DLBCL patients were divided into groups of high and low. The low-risk group exhibited lower mortality rates and longer OS than the high-risk group (Figure 1A). Significantly shorter OS was observed in DLBCL patients with high risks (Figure 1B). To further verify the expression levels of PRGs in DLBCL, we assessed the mRNA expression levels of the above six PRGs by qRT-PCR in DLBCL cell lines. Compared with normal samples, CASP8, CASP9, NLRP1, NLRP6, and TIRAP were significantly down-regulated in DLBCL cell lines, while SCAF11 was significantly up-regulated. These results revealed the outstanding predictive efficacy and superiority of this model.

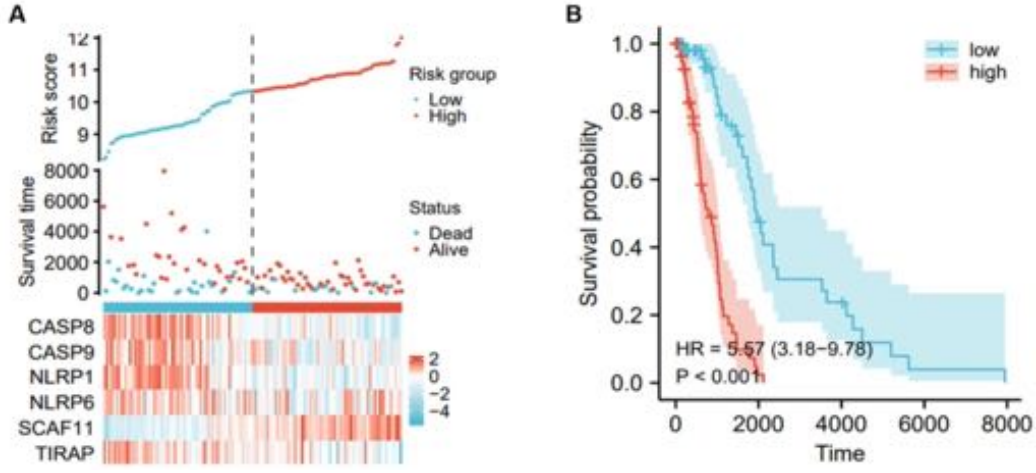
The potential biological role and the mechanism of PRGs causing different risks were further explored. GO and KEGG enrichment illuminated that these PRGs may be involved in cellular protein modification processes and regulation of JAK-STAT signaling pathway. Given the strongly correlation with tumor immune environment, we analyzed the immune status of different risk groups. The low-risk group showed higher activity immune infiltration and immune checkpoint pathways than the high-risk group. We found that the risk scores corresponded with the immune profile, and the elevated immune activity might contribute to the antitumor effect of DLBCL.

In conclusion, our study identified for the first time that pyroptosis is closely associated with the development and progression of DLBCL. Moreover, we developed a comprehensive prognostic model based on the characteristics of PRGs in DLBCL that accurately predicts the prognosis of patients. Combining pyroptosis-targeting with immunotherapies could be a feasible alternative treatment for DLBCL.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

Figure 1



487 | IDENTIFICATION OF TUMOR IMMUNE INFILTRATION-ASSOCIATED SNORNAS FOR IMPROVING THE PROGNOSIS OF PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Diffuse large B-cell lymphoma (DLBCL) is a highly aggressive non-Hodgkin lymphoma. Most studies on reliable biomarkers to better predict the immunity regulation and the tumor microenvironment. This study aims to establish a model of small nucleolar RNAs (snoRNAs) derived from immune infiltration-related cells for risk stratification and improving clinical outcomes of DLBCL.
Methods: we established a computational framework to identify an immune cell infiltration-related snoRNA signature (IMMsno) through integrative analysis for snoRNA of immune cell lines and 551 DLBCL patients with gene expression profiles (GSE10846 and GSE87371), validated in GSE181063 containts 1310 patients with the overall survival (OS). IMMsno was developed with Least Absolute Shrinkage and Selector Operation (LASSO) regression and visible by nomogram integrating clinical and pathological information (cell of origin, International Prognostic Index and clinical stage). Then the influence of the IMMsno clusters on the molecular functional enrichment and immunotherapy in DLBCL was comprehensively investigated.
Results: Six tumor immune infiltration-associated snoRNAs (SNHG1, SNHG5, SNHG6, SNHG12, SNHG16, SNHG19) and LASSO selected five of them to develop IMMsno. The IMMsno stratified DLBCL patients into the high-score group and low-score group, and a high IMMsno score was associated with poor DLBCL prognosis (HR = 2.049, 95% CI = 1.628–2.578, *p*-value = 0.001). Cox multivariate analysis conformed that IMMsno score is an independent predictive prognosis factor adjusted by other clinical characters. Further analysis accounting for IMMsno linked to the biological functions of antigen processing and presentation and signaling pathway of Complement and coagulation cascades, implying a better response in low-score IMMsno group to immunotherapy.
Conclusions: Our finding suggested the potential biological effects of snoRNAs in evaluating the tumor immune microenvironment, also as a predictive biomarkers of DLBCL prognosis.

The research was funded by: This project was supported by the National Natural Science Foundation of China (No. 81773524, No. 81502878, and No. 82273720

Keywords: bioinformatics, cancer health disparities, computational and systems biology, diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

488 | THE ROLES OF CD8+ CTLS, CD163+ TAMS, PDL1 IN TUMOR MICROENVIRONMENT IN THE PROGNOSIS OF PRIMARY CENTRAL NERVOUS SYSTEM

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Introduction: In order to explore the immune cell infiltration and PDL1 expression in the tumor microenvironment (TME) of primary central nervous system lymphoma (PCNSL), we conducted this research and discussed the therapeutic importance and prognostic significance of TME.
Methods: Immunohistochemical staining was performed on paraffin-embedded tumor tissues of 36 patients diagnosed with PCNSL. 3–5 fields were taken to represent the whole TME. CD8 and CD163 positive cells were manually counted (numbers/HPF). PDL1 was quantified by H-Score scoring method in the tumor center and around the tumor (within 3 cm outside the tumor area) respectively. The Kaplan-Meier method was used to reveal the prognostic significance of TME.
Results: We found obvious infiltration of $CD8^+$ CTLs and $CD163^+$ TAMs in the TME of PCNSL, and the average number of $CD8^+$ CTLs was 59/HP and $CD163^+$ TAMs was 38 /HP. The $CD8^+$ CTLs is more than $CD163^+$ TAMs ($p = 0.012$). Meanwhile, PDL1 was expressed in tumor center as well as around the tumor. The average PDL1 H-Score in the tumor center was 20.98, and which around the tumor was 37.38. The expression of PDL1 around the tumor was significantly higher than that in the tumor center ($p < 0.0001$). It is notable that the expression of PDL1, both in the tumor center and around the tumor, was significantly correlated with $CD163^+$ TAMs (PDL1 in the tumor center: $r = 0.42$, $p = 0.015$, PDL1 around the tumor: $r = 0.40$, $p = 0.021$). The cut-off values of $CD8^+$ CTLs, $CD163^+$ TAMs and PDL1 were obtained by ROC curve, then the survival analysis showed that high $CD8^+$ CTLs ($p = 0.027$) and high PDL1 expression in the tumor center ($p = 0.012$) were significantly correlated with longer overall survival (OS). High $CD8^+$ CTLs ($p = 0.044$) and high $CD163^+$ TAMs ($p = 0.040$) were associated with longer progression-free survival (PFS). There was no significant correlation between PDL1 around the tumor and prognosis. Furthermore, the patients were divided into ORR group and non-ORR group according to whether they achieved objective response to treatment or not. We found that $CD163^+$ TAMs was increased in ORR group ($p = 0.012$). Finally, the χ^2 test showed that the $CD163^+$ TAMs was related to age ($p = 0.042$), and the expression of PDL1 around the tumor was related to serum LDH level ($p = 0.002$).
Conclusion: There are significant infiltration of $CD8^+$ CTLs and $CD163^+$ TAMs, and high expression of PDL1 in TME of PCNSL. They are all have influence on the prognosis of PCNSL, but only $CD163^+$ TAMs is correlated with curative effect. In addition, the TME is affected by age and serum LDH, indicating that the TME is regulated by the basic clinical characteristics of patients.
The research was funded by: the National Natural Science Foundation of China [grant number 8226010026] and the "Cui Ying

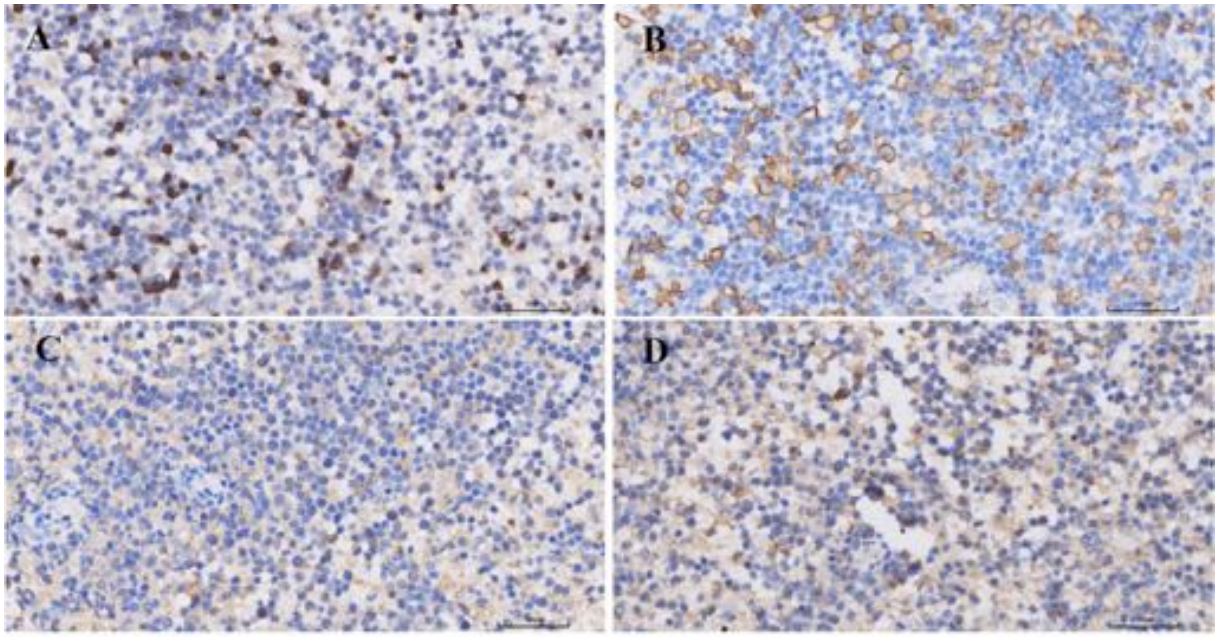

Figure 1 400×HPF A: CD8 B: CD163 C: PDL1 in tumor center D: PDL1 around the tumor

graduate instructor" training program of Lanzhou University Second Hospital [grant number 201710].

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, extranodal non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

489 | RELATIONSHIP BETWEEN GENE MUTATION CHARACTERISTICS AND TUMOR IMMUNE MICROENVIRONMENT IN 18 CASES OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Objective: To explore the relationship between gene mutation characteristics of 18 cases of primary central nervous system lymphoma (PCNSL) and tumor immune microenvironment.

Methods: Taking 18 patients with PCNSL (pathological type: DLBCL) as the study object, whole exome sequencing and immunohistochemical staining were performed on their tumor tissue samples. CD8 and CD163 were analyzed by manual counting of positive cells (unit: cells/HP), and PDL1 was analyzed by H-Score score (unit: pixels/HP). 3–5 visual fields were taken from the center of the tumor and around the tumor (area within 3 cm outside the tumor area) for quantitative analysis. The sequencing results were analyzed by data processing and bioinformatics, and the mutation panorama and characteristics of the entire cohort were obtained.

Results: In all 18 patients, obvious somatic mutations were detected. More than 90% of mutations were missense mutations, the main type of mutations was C > T (50.2%); The KEGG pathway enrichment analysis of all somatic mutations found that the mutant genes were significantly enriched in 20 pathways, of which the ECM-receptor interaction pathway was the most significant one. Analysis showed that among the top 15 high-frequency mutation genes, PSD3, DUSP5, MAGEB16, TELO2, FMO2, TRMT13, AOC1, PIGZ, SVEP1, IP6K3 and TIAM1 were the driving genes; the enrichment results of the driver gene pathway showed that the driver gene was significantly enriched in the RTK-RAS, WNT, NOTCH, Hippo, and Cell-Cycle signal pathways. In PCNSL tumor microenvironment, CD163 +TAMs cells and CD8+CTLs cells were significantly infiltrated, with an average of 30 CD163+TAMs cells/HP and 68 CD8+CTLs cells/HP; PDL1 was expressed in the tumor center and around the tumor, the average PDL1 H-score in the tumor center was 13.05, and the PDL1 H-score around the tumor was 33.26. The analysis of the relationship between the tumor mutation gene and the tumor immune microenvironment showed that the infiltration of CD163 + TMAs in the tumor microenvironment of the FMO2 gene mutation group was decreased ($p = 0.016$), and the infiltration of CD8 + CTLs in the tumor microenvironment of the TIAM1 gene mutation group was increased ($p = 0.027$). The residual gene mutation did not have a significant correlation with the immune cells in the tumor microenvironment.

Conclusion: Missense mutations of somatic cells frequently occur in PCNSL tumor tissues, the enrichment analysis of KEGG pathway of somatic cell mutations shows that ECM-acceptor interaction pathway is the most significant pathway. In the tumor microenvironment of PCNSL, there were obvious infiltration of CD163 +

TAMs, CD8 + CTLs and PDL1. Among the high-frequency mutation genes, FMO2 and TIAM1 gene mutations are related to the degree of infiltration of different immune cells in the tumor microenvironment.

Keywords: aggressive B-cell non-Hodgkin lymphoma, genomics, epigenomics, and other -omics

No conflicts of interests pertinent to the abstract.

490 | CLASSICAL HODGKIN DISEASE: PRESENCE OF TIGIT MRNA IN PERITUMORAL LYMPHOCYTES

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Background: T cell Ig and ITIM domains (TIGIT) has been recognized as an immune checkpoint receptor able to negatively regulate T cell functions. Our group (Annibali O et al. Sci Rep. 2021) demonstrated TIGIT expression in lymphocytes around the RS cells using immunohistochemistry in 56% of evaluated patients. (19/34) Aim of this study was to assess the in situ TIGIT mRNA expression in CHL, in order to verify the effective intracellular transcription of TIGIT receptor in peritumoral lymphocytes that resulted positive at immunohistochemical analysis.

Material and methods: 34 formalin fixed-paraffin embedded samples, in which was tested TIGIT protein expression, were selected. The TIGIT protein expression status was determined by immunohistochemical investigations with TiGIT antibody, as previously described. Seriate sections from FFPE lymph nodes were submitted for RNAscope Assay.

Results: Among 34 enrolled cases, 15 resulted negative for TIGIT immunohistochemistry on lymphocytes within the tumor environment and were classified score 0. 10 cases showed a sparse, faintly stained non-tumoral lymphocytes within the tumor environment, near the HRS cells and were classified as score 1. 5 cases showed the presence of a discrete quote of non-tumoral lymphocytes with moderate membrane staining around the HRS cells and were reported as score 2. 4 cases demonstrated evidence of a circle of non-tumoral lymphocytes with intense membrane staining, surrounding the HRS cells corresponding to the score 3.RNAscope was successfully applied to the whole FFPE histological sections of the 34 HL cases. TIGIT probe is represented as red dots/spots within the lymphocytes surrounding the RS cell. After slides were visualized, each case was assigned a semi-quantitative score based on the mRNA expression level of the TIGIT gene according to the scoring system provided by the RNAscope manufacturer. The remaining cases scored a 0 with no mRNA probe signals observed in the lymphocytes. Low mRNA expression was observed in ten cases marked as 1 which is equivalent to 1–3 probe signals per positive lymphocyte. Five cases showed moderate mRNA expression with a score of 2 representing 4–10 probe signals per positive lymphocyte. 4 cases showed high mRNA expression with a score of 3, representing > 11 probe signals per positive lymphocyte. With QuPath software, we observed an increase in the number of positive cells in relation to protein expression status. In fact, at score 0 corresponds 0% positive cells, at score 1+ corresponds 8% positive cells, at score 2+ corresponds 33% positive cells and at score 3+ corresponds 54.9% positive cells.

Conclusion: Our results confirm the presence of immunoescape through the expression of TIGIT in patients with HL, based on the expression of the mRNA coding for TIGIT and validate the score system proposed for the immunohistochemical reaction.

Encore Abstract—previously submitted to EHA 2023

Keyword: Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

491 | GLOBAL CHARACTERIZATION OF MONOCYTE REVEALS A STRESS SIGNATURE INDUCED BY MULTIPLE MYELOMA THROUGH SINGLE-CELL RNA SEQUENCING

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Background: A growing body of evidence has indicated impaired function or compositional changes of monocytes in inflammatory disorders, such as acute respiratory syndrome and covid-19. In myeloma tumor microenvironment, activation of type I interferon pathway and dysregulated expression of major histocompatibility complex type II genes are observed in classical monocytes, which result in loss of antigen presentation of monocytes. The proportions of BAFF+PD-L1+ monocytes in the bone marrow also correlate with survival of myeloma patients following chimeric antigen-receptor T cell therapy. Nevertheless, the mechanisms underlying PB and BM monocytes defects in myeloma remain poorly addressed, at least in part by the lack of large scale scRNA-seq studies. To resolve the heterogeneous bone marrow and peripheral blood monocyte subpopulations and their transcriptional factors between healthy donors and multiple myeloma patients.

Methods: We conducted scRNA-seq on monocytes of 7 newly diagnosed myeloma patients and 12 healthy donors. Specifically, 3 and 5 bone marrow aspirates and 9 and 7 peripheral blood samples of 12 healthy controls and 7 newly diagnosed patients were obtained, respectively.

Results: Heterogeneous bone marrow and peripheral blood monocyte subpopulations and their transcriptional factors were resolved.

The function characteristics of monocyte were compared between MM patients and healthy donors, which indicated a stress signature induced by multiple myeloma. Furthermore, we identified two monocyte differentiation pathways, and discovered that bone marrow monocyte feature type I IFN-associated differentiation dysregulation in patients with MM as well as dysregulated patterns at transcriptome. Finally, we included 10 MM patients as a validation cohort, by tracking the stress signature over time in those patients undergoing first-line treatment, we founded that the stress signature was partially overcome by antitumor therapy.

Conclusion: Our results provided further insight into transcriptional and differentiation changes occurring in the bone marrow and peripheral blood monocytes from patients with multiple myeloma and hint and mechanisms of immune evasion.

Encore Abstract - previously submitted to EHA 2023

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Keywords: genomics, epigenomics, and other -omics, microenvironment, multiple myeloma

No conflicts of interests pertinent to the abstract.

TRANSLATIONAL STUDIES (B-CELL LYMPHOMAS, PCTL AND cHL)

492 | ULTRASONOGRAPHY-GUIDED CORE-NEEDLE BIOPSY OF LYMPHADENOPATHIES SUSPECTED OF LYMPHOMA: ANALYSIS OF EFFICACY AND SAFETY OF 1000 BIOPTIC PROCEDURES IN A MULTICENTER ITALIAN STUDY

C. Giordano[1], M. Picardi[1], E. Vigliar[2], N. Pugliese[1], R. Della Pepa[1], R. Accarino[3], S. Varricchio[3], M. Mascolo[3], D. Russo[3], G. Troncone[2], G. Muccioli Casadei[1], M. Ciriello[1], D. P. Abagnale[1], M. Esposito[1], I. Cozzolino[4], P. Zeppa[5], R. Accarino[3], M. Persico[6], F. Pane[1]

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Patients with clinical suspect of lymphoma require prompt and correct diagnosis through the histological examination.

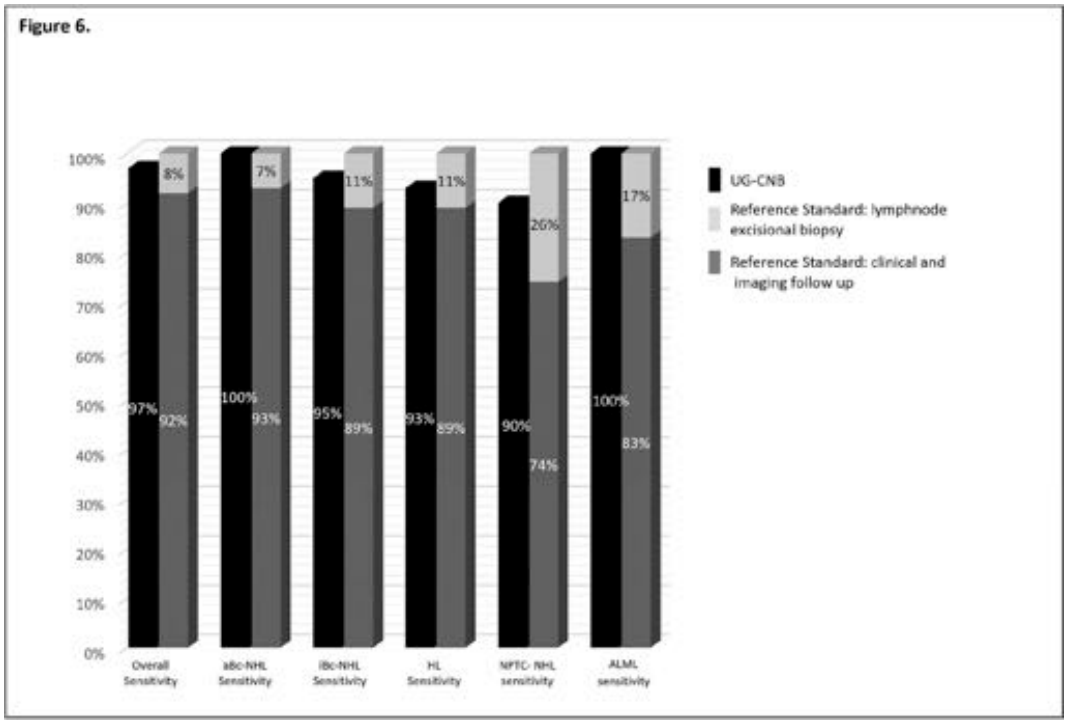
The aim of this study was to evaluate the reliability and safety of the front-line ultrasonography guided core needle biopsy (UG-CNB) of suspected lymphadenopathies in a large series of patients from 4 southern Italian clinical units. Inclusion criteria were: (i) lymphadenopathy power Doppler ultrasonography retrospectively assessment on recorded video clips and/or images; (ii) 16-gauge CNB with powered automatic suction and 1.6 mm needle diameter sample; (iii) availability of lymph node sections fixed in formalin and embedded in paraffin; (iv) morphological and immunohistochemical information (assessed retrospectively by haematopathologists); and (v) information of an accepted diagnostic reference standard (either the lymphadenopathy surgical resection or follow-up assessment with 2-deoxy-2[F-18] fluoro-D-glucose positron emission tomography [FDG PET]-computed tomography [CT] showing decreased FDG uptake and/or decreased size after specific antineoplastic treatment according to the histological subtype, as well as spontaneous regression for the benign conditions).

We retrospectively collected the data of 1048 patients who underwent UG-CNB between 1 July 2009 and 1 January 2022 for suspected pathological lymphadenopathies. In total, out of the 1000 UG-CNBs yielding macroscopically adequate material for histological diagnosis, the 90% (n = 900) resulted in lymph-nodes positive for malignancy. Most patients were suffering from lymphomas (aggressive B-cell non-Hodgkin lymphoma [aBc-NHL], 309 cases; indolent B-cell [iBc]-NHL, 266 cases; Hodgkin lymphoma [HL], 198 cases; and nodal peripheral T-cell [NPTC]-NHL, 27 cases) and 100 cases from metastatic carcinoma; 70 patients were negative for malignancy (diagnosis of atypical lymphadenopathies mimicking lymphomas [ALML]). The remaining 3% were inconclusive at CNB: the morphologic, immunohistochemical and/or molecular investigations did not allow a final diagnosis.

The overall diagnostic accuracy rate was 97%, that is, results accurate in 970 of 1000 samples. For aBc-NHL neoplasms, the sensitivity rate was 100%, that is, 309 of 309 aBc-NHL samples were correctly identified; for iBc-NHL, was 95% with a false negative rate of 5% (13 inconclusive results); for HL, the sensitivity rate was 93% with a false negative rate of 7% (14 inconclusive results); and for NPTC-NHL, the sensitivity rate was 90% with a false negative rate of 10% (3 inconclusive samples). Finally, the sensitivity rate for ALML was 100%, that is, 70 of 70 samples positive for ALML according to the reference standard were correctly identified by UG-CNB. The complication rate was low (6% for all complications) without complications of grade >2 according to the Common Terminology Criteria for Adverse Events. Lymph node UG-CNB as first mini-invasive diagnostic procedure is effective with minimal risk for the patient.

Keyword: imaging and early detection

No conflicts of interests pertinent to the abstract.



493 | LYMPHOMA DIAGNOSTIC EFFICIENCY: PREDICTORS FOR DIAGNOSTIC DELAY AND PROLONGED REFERRAL TO TREATMENT TIME

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St Vincents University Hospital, Dublin, Ireland

Introduction: Lymphoma is one of the most prevalent cancers diagnosed in the Republic of Ireland, with approximately 800 cases of Non-Hodgkin lymphoma and 150 cases of Hodgkin lymphoma (HL) diagnosed annually. Previous studies have demonstrated that time to diagnosis can range substantially, with diagnosis to treatment interval associated with survival outcomes.

Aims & Methods: The primary aim of this study was to compare the diagnostic efficiency according to histology specimen type. The secondary aims included time to lymphoma diagnosis, and predictors associated with diagnostic delays.

A retrospective analysis was performed on all patients diagnosed at a tertiary (non-fee paying) centre in Ireland between 2016 and 2021. Baseline demographic data and diagnostics were obtained from electronic records. Referral to treatment interval (RTI) was calculated from the date of initial review in the referral centre to commencement of therapy.

Results: A total of 225 new lymphoma diagnoses were made during the study period. The median age was 63.3 years (IQR 44.2, 73.6) Males accounted for 54.7% (n = 123) of the population. DLBCL was the most common subtype (n = 94; 41.8%); followed by classical HL (n = 40; 17.8%) and Follicular lymphoma (n = 32; 14.2%). Fifty four percent (n = 122) had their diagnostic histology attained during an inpatient episode. The median time to diagnosis was 24 days (IQR 13.0, 58.0).

A total of 350 histology specimens were attained. Core biopsy yielded a diagnosis in 64% (n = 144), excision biopsy in 35.6% (n = 80) and FNA in 0.4% (n = 1). The positive diagnostic rate was 69.5% for core biopsy, 93% for excision biopsy and 1.7% for FNA. The median financial cost of diagnosis was €13714 (IQR €4050, €24044). The total cost for this patient group was €3.7 million over a 5 year period.

The median RTI was 47 days (IQR 23.0, 91.0). In the univariate analysis, we confirmed patients with older age are more likely to have longer RTI (p = 0.0007). Diagnostic biopsy performed as inpatient was associated with a shorter RTI ($p \leq .0001$). Patients referred direct to haematology services had a longer RTI (p = 0.0004).

In the multivariable analysis, patients with older age remained significant associated with prolonged RTI (p = 0.0251). Diagnostic biopsy performed as an inpatient remained significant ($p \leq .0001$). Similarly, patients referred directly to Haematology services has significantly longer RTI (p = 0.0051).

Conclusion: In this review, we confirm the higher diagnostic yield of excision biopsy for diagnosis. Older age at presentation and referral direct to haematology was associated with longer RTI. Inpatient diagnostic's was associated with shorter RTI. We confirm an over reliance on inpatient diagnostics. With the increasing financial burden of healthcare and increased demand on resources including bed utilisation, the appropriate choice of investigations and diagnostic sampling is ever more critical.

Encore Abstract - previously submitted to regional or national meetings (up to <1000 attendees)

Keywords: cancer health disparities, diagnostic and prognostic biomarkers, Imaging and Early Detection - Other

No conflicts of interests pertinent to the abstract.

494 | IMPACT OF TUMOR MUTATIONAL BURDEN ON THE RESPONSE TO IMMUNOCHEMOTHERAPY IN FOLLICULAR LYMPHOMA

M. Lafuente[1], R. Diez-Feijóo[2], C. Fernández-Rodríguez[3], R. Longarón[3], L. Fernández-Ibarrondo[1], N. García-Gisbert[3], M. García-Recio[4], B. Sánchez-González[2], S. Pinzón[2], J. Gibert[3], L. Camacho[3], L. Colomo[5], A. Gutierrez[4], B. Bellosillo[3], A. Salar[2]

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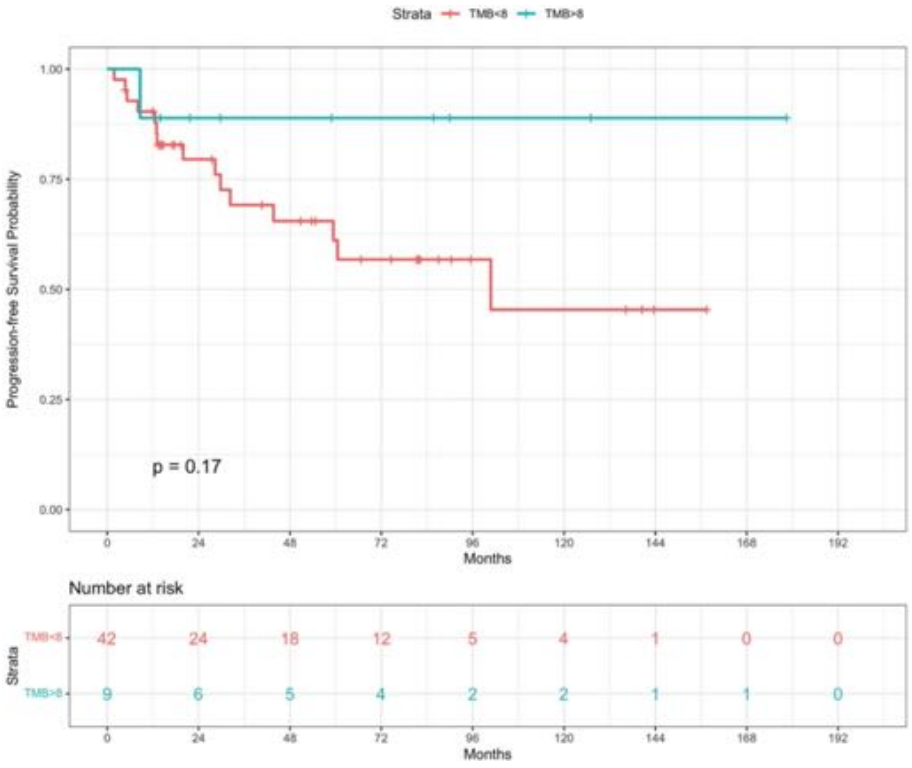
Introduction: Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma. It is typically an indolent entity, however, patients who progress or relapse within 24 months of front-line immunochemotherapy (ICT), have a poor outcome. Tumor mutational burden (TMB) is defined as the number of somatic mutations/megabase (mut/Mb) and has been proposed as a biomarker for predicting response to immune checkpoint inhibitors in some cancers. This study aimed to explore the role of TMB in FL.

Methods: The study included 51 patients with FL grade 1–3a treated with first line ICT (rituximab, R-CHOP, R-CVP or R-bendamustine). TMB was determined in diagnostic lymph node biopsies by Next Generation Sequencing (NGS), using the Oncomine Tumor Mutational Load Assay (Thermo Fisher), which covers 409 genes. Sequencing was performed on the Ion GeneStudio S5 system with >300X mean coverage. In addition, the mutational profile of 27 of the 51 patients was analyzed using a QIAgen custom DNA panel which covered 64 genes frequently mutated in FL. Sequencing was performed using MiSeq (Illumina) with >3000X mean coverage. Variants were analyzed and interpreted for pathogenicity using several databases.

Results: Median age at time of treatment was 64 years (mean 62; range 24–83), with 84% of patients diagnosed with stage III-IV disease. All patients presented at least one mutation using the custom panel, and showed a median TMB value of 5.22 mut/Mb (range 1.69–14.66 mut/Mb). The number of mutations identified correlated with TMB value at diagnosis ($p = 0.003$). We did not find statistically significant differences in clinical parameters according to basal TMB. However, patients harboring the *t*(14;18)(q32;q21) translocation and patients with mutations in genes involved in migration, had a higher TMB at diagnosis (mean 6.57 vs. 4.18 mut/Mb, $p = 0.017$; 8.52 vs. 4.74 mut/Mb, $p < 0.001$, respectively). Moreover, patients with mutations in genes involved in the BCR pathway showed a trend towards a higher TMB (6.79 vs. 4.73 mut/Mb, $p = 0.061$). Patients were then stratified in two groups according to their basal TMB value, with



a cutoff of 8 mut/Mb that corresponded to the upper quartile. The high-TMB group was enriched in patients harboring mutations in BCR signaling pathway or migration genes ($p = 0.016$, $p = 0.009$ respectively) and showed a trend towards having the *t*(14;18) translocation or mTORC1 pathway mutations ($p = 0.106$, $p = 0.144$ respectively). Patients in the high-TMB subgroup had a trend towards a longer progression free survival (PFS) ($p = 0.17$) (Figure 1). 5-years PFS was 88.9% (95% CI: 10.5–70.6) in high-TMB patients and 61.1% (95% CI: 46.0–81.2) in low-TMB patients.

Conclusions: FL patients harboring *t*(14;18) or mutations in genes of the BCR signaling pathway or involved in migration have higher TMB values at diagnosis. High TMB (≥8 mut/Mb) shows a tendency for longer PFS in FL patients treated with ICT.

The research was funded by: FIS/FEDER PI19/00034, ISCIII Spanish Ministry of Education (FPU21/02671)

Keywords: diagnostic and prognostic biomarkers, genomics, epigenomics, and other -omics, indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

494 bis | THE ROLE OF CD5+ AS AGGRESSIVE BIOMARKER IN DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Diffuse large B-cell lymphoma (DLBCL) is a clinical and biological heterogeneous subtype of lymphoma. The better knowledge of its biology let to identify some factors associated with worse outcomes. In this setting, the expression of CD5 emerged as a possible biomarker of lymphoma aggressiveness. Hereby we describe a single-center series of DLBCL with CD5 expression.

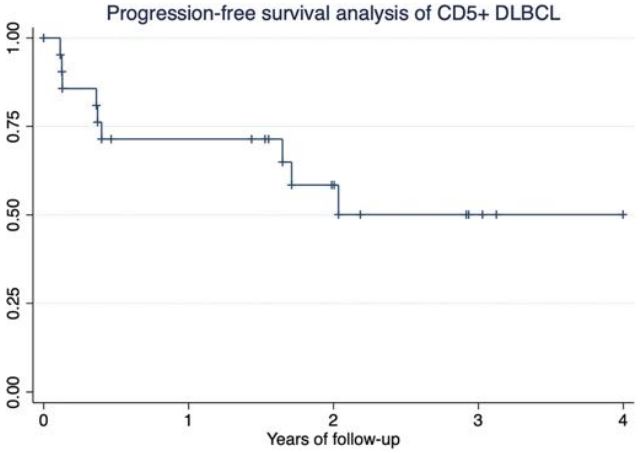
Methods: We retrospectively analyzed patients with DLBCL expressing CD5 by immunohistochemistry (IHC) diagnosed from 2010 to 2022 at Institute Catalan of Oncology Hospitalet. For Kaplan-Meier analysis, relapse, progression or death were considered an event.

Results: Among 559 total DLBCL patients registered, 25 (4.5%) were CD5-positive. At diagnosis, median age was 69 years (33–85), 12 (52%) were males, 15 (60%) had Ann Arbor stage III-IV, all patients had extranodal involvement (10 with >1 site), 8 (32%) presented B-symptoms, 14 (56 %) had IPI 3–5, and 10 (40%) presented bulky disease (>5 cm). LDH was elevated in 20 (80%) and beta2microglobuline in 16 (64%). Regarding histology, 60% were DLBCL NOS, 16% transformed DLBCL, 8% EBV-positive DLBCL, 8% leg-type, 4% double hit and 4% intravascular DLBCL. By IHC, 54% had non-germinal center phenotype according to Hans algorithm, 17 (71%) expressed MUM1, 10 (40%) expressed MYC 40%, 20 (80%) expressed Bcl2 50%, and 9/12 (75%) were double-expressors. Median Ki67 was 85% (range 30–100), P53 (median of 20%) was expressed in 5/10 (50%). MYD88 L265P mutation was detected in 2/5 (40%) cases. R-CHOP/R-CHOP-like was the most used treatment in first-line (22 patients), combined with radiotherapy in 6 patients (all with localized disease), and 3 (12%) patients received palliative regimens due to frailty. Treatment was not completed in 6 patients, mainly due to infectious complications. Complete response rate was 72%. With a median follow-up of 2 years (range 0–4), 7 (28%) patients progressed/relapsed at a median time of 11.1 months (1.4–18.9). The median progression-free survival and overall survival at 2 years were 53% (CI 95%, 31%-73%) and 66% (CI 95%, 44%-82%), respectively.

Conclusions: CD5+ DLBCL patients have diverse histologies, some of them related to poor prognosis, as leg-type, intravascular or EBV-positive DLBCL, which make difficult to believe that they constitute a homogeneous biological group, with BCL2 expressed in most of the cases. Of note, all the patients had extranodal involvement and many of them presented other features of poor prognosis at diagnosis, as high LDH and bulky disease. We will perform further comparisons between CD5+ and CD5- DLBCL cohorts to determine the real impact of this biomarker on survival.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.



495 | IMMUNOPHENOTYPIC CHARACTERIZATION OF RICHTER SYNDROME DIFFUSE LARGE B-CELL LYMPHOMA TYPE AND COMPARISON WITH THE ORIGINAL CHRONIC LYMPHOCYTIC LEUKEMIA

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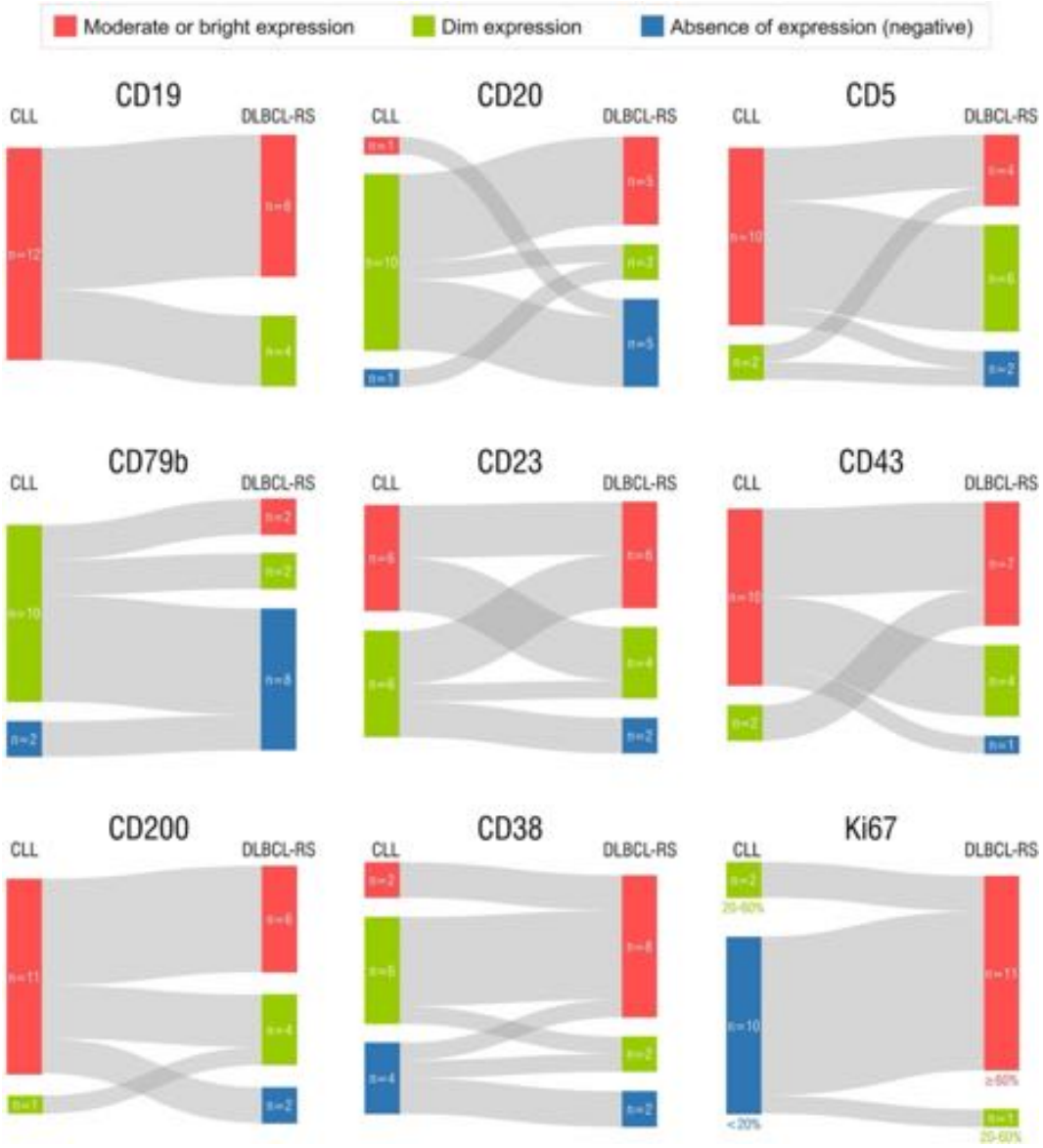
Introduction: Biological mechanisms undergoing Richter Syndrome diffuse large B-cell lymphoma type (DLBCL-RS) from a previous chronic lymphocytic leukemia (CLL) arouse a great scientific interest, but the pattern of markers expressed in DLBCL-RS cases has been scarcely studied. Our aim was to immunophenotypically characterize DLBCL-RS and compare it with the prior CLL population.

Methods: Retrospective unicenter study of patients histologically diagnosed with DLBCL-RS (*DLBCL not otherwise specified* subtype) from a prior or concomitant CLL (N = 12). Multiparametric flow cytometry (FCM) and immunohistochemistry (IHC) were used to cluster cases according to their expression level for each marker: bright or moderate (positive), low (dim), or absent (negative). Comparisons were made between CLL and DLBCL-RS in available tissues (lymph node, blood, bone marrow, and others).

Results: Median age at DLBCL-RS diagnosis was 74 years (IQR 65-79) and 42% were males. Three cases were concomitantly diagnosed with CLL and DLBCL-RS; the median time of transformation in the remaining 9/12 was 76 months (IQR 51-112), and all of them had received at least 1 therapeutic line for the CLL (median 2). Clonal relationship was demonstrated in 9/10 cases with available



information. Figure 1 shows the most relevant phenotypic comparisons between CLL and DLBCL-RS populations. Although phenotypic variability was seen for all antigens, some of them showed tendency to increase or decrease their pattern of expression. CD19, CD20, CD5, CD79b, and CD200 tended to lose expression in the DLBCL-RS phase (3/5 DLBCL-RS CD20 negative cases had received anti-CD20 therapy during the 12-month period prior to transformation). On contrary, CD38 and Ki67 were constant in the increasing of expression. Other markers such as CD23, CD43, CD22, and CD11c presented higher variability. One case showed CD10 dim expression of the DLBCL-RS, while it remained negative in the other 11/12. The light-chain restriction was the same in 10/12 (κ:λ ratio of 1.5:1); 1/12 presented a switch from κ to λ, and 1/12 DLBCL-RS showed negativity for κ/λ, when κ was restricted in the CLL phase. p53 expression was available in 7 cases, being negative in CLL tissue in all of them: 3/7 retained p53 negativity in the DLBCL-RS, while 4/7 showed p53 overexpression after transformation. Treatment for the DLBCL-RS was initiated in 8/12 cases, being 92% death at data cut-off date (median follow-up 6.5 months from DLBCL-RS diagnosis, IQR 2.4–9.7).

Conclusions: As far as the authors know here is presented the largest series which compares the phenotype between CLL and its DLBCL-RS. The markers CD19, CD20, CD5, CD79b, CD38, Ki67, and p53 showed relevant changes at the moment of histological transformation. This research enhances the importance of validating reproducible assays to follow hematological malignancies with potential of transformation to more aggressive diseases.

Keywords: diagnostic and prognostic biomarkers, pathology and classification of lymphomas, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

496 | IDENTIFY TRULY HIGH-RISK TP53-MUTATED DLBCL AND EXPLORE THE UNDERLYING BIOLOGICAL MECHANISMS

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Introduction: TP53 mutation (TP53-mut) correlates with inferior survivals in many cancers, whereas its prognostic role in diffuse large B-cell lymphoma (DLBCL) is still in controversy. TP53-mut is frequently enriched in A53 subtype and also can be found in other gene subtypes. However, A53 subtype which was associated with fatal prognosis cannot be identified using the next-generation sequencing (NGS) which used mostly in clinical practice. Therefore, more precise risk stratification is need to be further explored for TP53-mut DLBCL patients.

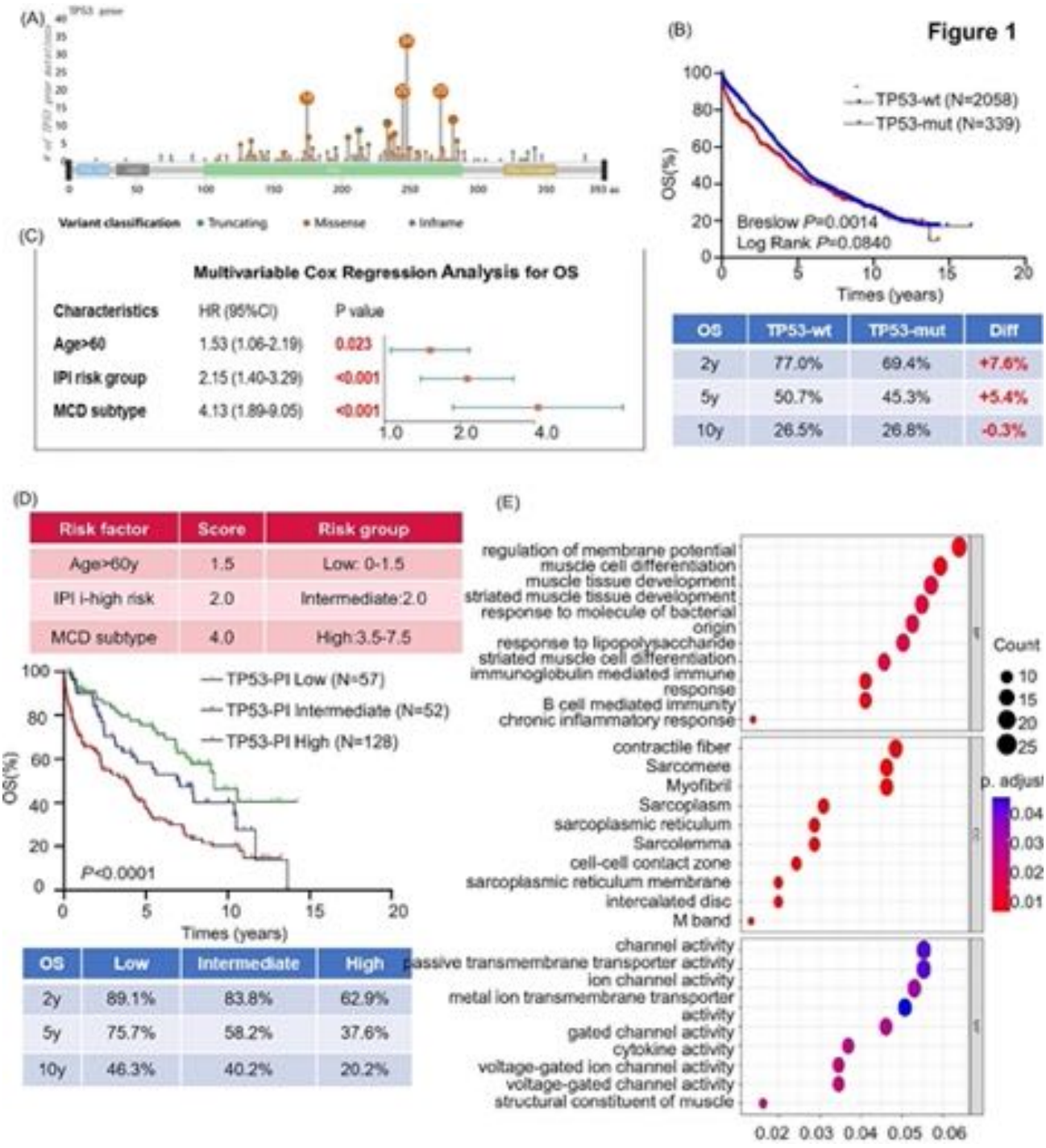
Methods: The available clinical information and corresponding mutation data of DLBCL were retrieved and obtained from published articles. Ultimately, 2637 DLBCL patients in six cohorts were enrolled in the final analysis. Among the 109 DLBCL patients in the Jiangsu Province Hospital (JSPH) study cohort, all tumor tissue samples were collected to perform NGS while 104 samples were analyzed the gene expression levels using RNA-seq.

Results: Among the 2637 DLBCL patients from the integrated cohort, 14.0% patients (370/2637) had TP53-mut. The distribution of mutation events was mainly located in the DNA binding domain (N = 333, 83.3%), containing 34 at Arg248, corresponding to the TP53 hotspots in non-Hodgkin lymphoma described in previous studies (**Figure 1A**). Compared with TP53 wild type (TP53-wt) patients, significant p value was generated by Breslow test (p = 0.0014), whereas Log Rank test uncovered border-line p value for overall survival (OS) (p = 0.0840). Such a result indicated that adverse survival of TP53-mut patients just occurred during early survival while the 10-year OS was even slightly better than the TP53-wrt patients (**Figure 1B**). Accordingly, we sought to construct a model to identify the truly high-risk patients. As shown in **Figure 1C**, three variables (age, international prognostic index score and MCD subtype) retained independent prognostic factors for progression free survival (PFS) and OS in TP53-mut patients. The TP53 prognostic index (TP53-PI) model could significantly distinguish the prognosis of TP53-mut DLBCL patients ($p < 0.0001$, **Figure 1D**). To calculate the weight of each selected factor, a nomogram was generated, which was used to predict the survival rates.

Differential expression analysis by RNA-seq analysis in JSPH cohort offered insights into the underlying biological mechanisms of poor survivals for high TP53-PI risk DLBCL patients. The immune-associated biological processes occupied a large proportion in the result of Gene Ontology functional enrichment analysis between low and high TP53-PI risk DLBCL patients (**Figure 1E**). Of note, the TP53-mut group had a unique immune microenvironment.

Conclusions: In conclusion, TP53-PI model could further identify the adverse prognosis of TP53-mut DLBCL patients. The mechanism driving different survivals outcomes may be explained by the unique immune microenvironments.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, microenvironment



497 | NOVEL AUTOANTIBODIES PANEL PREDICTED PROGNOSIS OF DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH R-CHOP THERAPY

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Introduction: DLBCL patients treated with R-CHOP regimen have prolonged survival, but 20%–40% of patients survive less than 5 years. Autoantibodies (AAbs) have the advantages of easy specimen acquisition and dynamic real-time monitoring. Blood-based autoantibodies have stratified lymphoma patients outcomes in previous studies, such as anti-ALK autoantibody titers were found to predict

anaplastic large B-cell lymphoma (ALCL) recurrence risk stratification. This study was designed to find prognostic AAbs biomarkers for early progression, PFS, and OS in DLBCL patients treated with R-CHOP by utilizing a proteomic test based on autoantibodies.

Patients and methods: Plasma samples from 325 DLBCL patients and FFPE samples from 37 DLBCL patients with biopsy confirmation were retrospectively collected between 2006 and 2020. All patients were previously untreated and collected before first-line R-

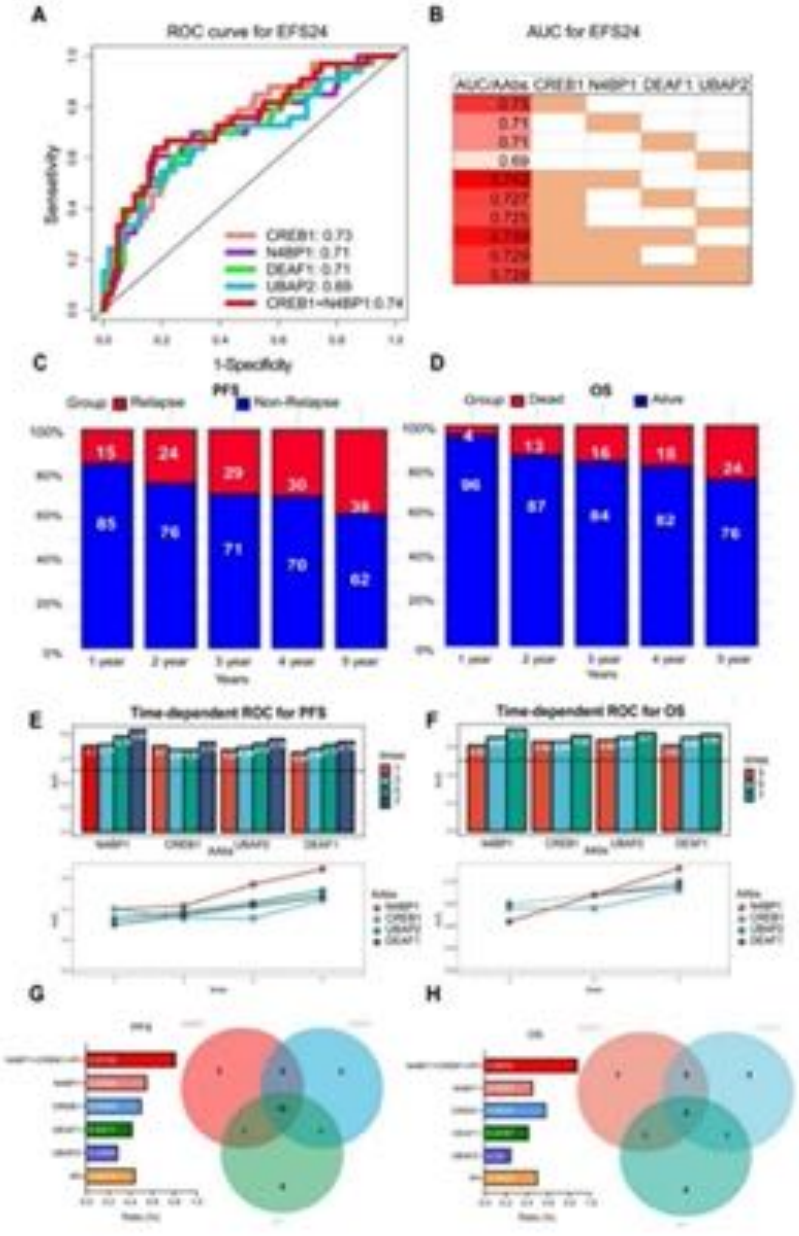

Figure 1. PFS and OS 4 AAbs performance of PFS and OS predictions in validation phase. **A.** ROC curves of 4 AAbs for EFS24, respectively. **B.** AAbs combination performance by logistic models. **C/D.** PFS and OS changes in 1–5 years in the validation phase. **E/F.** Time dependent ROC curves for PFS and OS based on the 4 AAbs, separately. **G/H.** AUC comparison between 4 AAbs, IPI and N1BP1+CREB1+IPI in PFS and OS.

CHOP and had complete clinical data. Patients were divided into relapse and non-relapse groups based on EFS24. There were three cohorts in this study. In the discovery phase, 20 samples were conducted comprehensively high-throughput protein microarray (~20 K proteins, HuProtTM). In the verification phase, 181 samples were conducted low-density focused array (200 proteins). And in the validation phase, 135 samples were conducted for ELISA detection. Besides, exploratory analyses revealed the expression difference of prognostic AAbs target proteins in DLBCL FFPE samples.

Results: Global autoantibody profiling of DLBCL patients were observed. Four autoantibodies were significantly different in relapse and non-relapse patients ($p < 0.05$) and associated with superior survival outcomes (PFS and OS) both in the verification phase ($n = 181$) and validation phase ($n = 135$). Based on the AUC for EFS24, 2 AAbs were chosen for the riskscore model conduction. 2 AAbs signature riskscore model was predictive of PFS with AUC of 0.72, 0.76 and 0.82 at 1, 3 and 5 years independent of IPI score in validation phase. Combining with the IPI score, 2 AAbs signature riskscore identified a more poor prognosis group (5-year PFS rate: 17.86%) versus IPI score high group (33.3%), a mediate group(56.49%) versus IPI score high_inter/low_inter group (46.3% and 48.2%) and a more favorable group (89%) versus IPI score low group (85.78%). Furthermore, 2 AAbs target proteins were also higher in DLBCL patients with superior outcomes ($p < 0.05$).

Conclusions: We have demonstrated the extensive profiling of autoantibodies in DLBCL patients, and identified a novel prognostic AAbs panel and it can also contribute to improving the prognostic stratification ability of IPI score.

Keywords: autoantibody, biomarker, diffuse large b-cell lymphoma, protein microarray

No conflicts of interest pertinent to the abstract.

Encore Abstract - previously submitted to regional or national meetings (up to <1000 attendees), EBMT 2023, AACR 2023, ASCO 2023, EHA 2023

The research was funded by: China National Major Project for New Drug Innovation (2017ZX09304015, 2019ZX09201-002)

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, risk models

No conflicts of interests pertinent to the abstract.

498 | EXPRESSION OF HUMAN LEUKOCYTE ANTIGENS GENETIC POLYMORPHISMS IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Diffuse Large B- cell Lymphoma (DLBCL) is characterized by genetic and clinical heterogeneity. Different loci within the human leukocyte antigen (HLA) region have been implicated in susceptibility and disease control of DLBCL.

Methods: HLA typing was performed using Sequence-Specific Oligonucleotide (SSO) and Sequence-Specific Primer (SSP) in 60 DLBCL patients and 250 healthy adult donors from local Bone Marrow registry. Statistical analysis was conducted with version 29.0 of IBM SPSS. The phenotypic frequencies of HLA-A, HLA-B, HLA-C, HLA-DRB1 and HLA-DQB1 between patients and controls were compared with the 2-sided Fisher's exact test. Results with p-value < 0.05 were considered statistically significant. Odds Ratios (OR) with 95% Confidence Intervals were calculated to further strength the results. Additionally, a follow-up analysis was performed by calculating Bonferroni-adjusted p-values (pc). Thereafter HLA polymorphisms that showed statistically significant difference were included in univariate and multivariate survival analysis together with the patients clinical-biological characteristics (age, stage, LDH, R-IPI). The R programming language, version 4.2.2 and specifically the "survivalAnalysis" package version 0.3.0. were used to investigate the associations of each factor with the Overall Survival (OS) and the Progression Free Survival (PFS). Results: DLBCL patients displayed a lower frequency of HLA-C*12 (6.7% vs. 34.7%, $p = 0.001$, pc = 0.00001, OR = 0.13, 95% CI [0.05, 0.38]), HLA-DRB1*16 (15% vs. 29.7%, $p = 0.02$, pc = 0.04, OR = 0.42, 95% CI [0.19, 0.89]) and HLA-DRB1*03 (58.3% vs. 77.5%, $p = 0.02$, pc = 0.01, OR = 0.40, 95% CI [0.22, 0.74]) compared to healthy individuals. In univariate analysis only advanced stage, high LDH and low versus high R-IPI had statistically significant impact on OS (p values 0.007, 0.003 and 0.002 respectively) and PFS (p-values 0.001, 0.002 and <0.001 respectively). Interestingly the Cox regression analysis used to evaluate the impact of LDH together with the HLA-DQB1*03 polymorphism on

OS showed that although normal LDH is a good prognostic factor with HR = 0.33 95% CI [0.17 – 0.65] *p*-value = 0.001), the combination of normal LDH with DQB1*03 with HR 2.07 95% CI [1.06–4.07] indicates a significantly increased risk of death (*p*-value = 0.034). Regarding PFS the LDH- DQB1*03 model displayed also statistical significancy ($p = 0.001$) in a similar way with DQB1*03 increasing the risk of death while keeping LDH within normal ranges.
Conclusions: Our results suggest that DLBCL patients express certain genetic types of HLA in lower frequency compared to healthy individuals. Antigens represented less frequently may act protectively in the development of the DLBCL. However, the presence of rarely represented HLA types failed to prove any positive impact on OS and PFS indicating the complexity of DLBCL pathogenesis.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

499 | NOTCH PATHWAY MUTATION CONTRIBUTES TO INFERIOR PROGNOSIS IN HBV-INFECTED CHRONIC LYMPHOCYTIC LEUKEMIA

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Chronic lymphocytic leukemia (CLL) patients with hepatitis B virus (HBV) infection have a poor prognosis, underlying mechanism remains unclear. NOTCH mutations are frequent in CLL and associated with disease progression and drug resistance. It is also reported to be associated with hepatitis infection in lymphoid malignancies. In order to investigate the relation between NOTCH pathway and HBV-associated CLL, we studied 98 previously untreated HBV positive CLL patients and 244 HBV-negative CLL. A total of 342 treatment naïve patients diagnosed with CLL at the First Affiliated Hospital of Nanjing Medical University from 1 January 2010 to 31 October 2021 were enrolled in our study. The mutation hotspots of NOTCH pathway genes were analyzed by Next Generation Sequencing (NGS) of DNA that used PCR for the identification of genomic mutation. Fisher exact and χ^2 tests were used to assess the correlation between HBV infection and clinical, demographic factors in CLL patients. Survival curves were generated by Graphpad 9.5. NOTCH mutations were more frequent in HBV positive CLL subgroup (17.3% vs. 7.4%, $p = 0.033$). By survival analysis, HBV infection was associated with disease progression and poor survival ($p = 0.0099$ for overall survival [OS] and $p = 0.0446$ for time-to-treatment [TTT]). Any lesions of the NOTCH pathway (NOTCH1, NOTCH2 and SPEN) aggravated prognosis. In multivariate analysis, NOTCH mutation retained an independent significance for HBV-infected patients ($p = 0.016$ for OS and $p = 0.023$ for TTT). However, HBV positive with NOTCH unmutated had no statistical difference in prognosis compared with HBV negative patients ($p = 0.1706$ for OS and $p = 0.2387$ for TTT), which indicated that NOTCH pathway mutation contributed to inferior prognosis in HBV-infected CLL. In conclusion, a cohort of CLL patients with HBV positive displayed a worse clinical outcome and the status of NOTCH signaling pathway might play a crucial role.

Keywords: chronic lymphocytic leukemia (CLL), diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

500 | INCREASED SOLUBLE SERUM CD163 (SCD163) LEVELS PREDICT A SHORT DISEASE FREE SURVIVAL IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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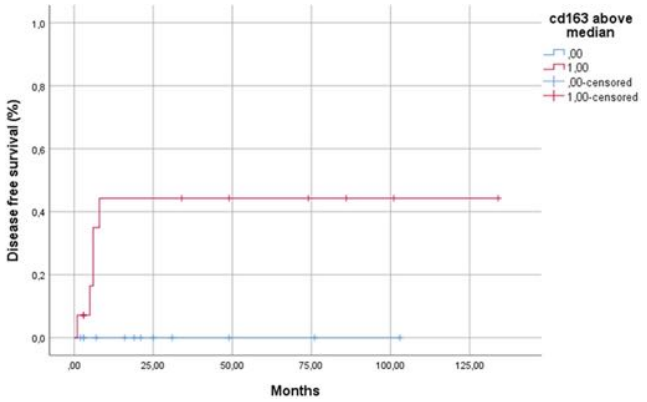
Introduction: Monocyte counts were found of prognostic significance in DLBCL, implying the possible contribution of monocyte-macrophage lineage cells in disease pathogenesis. These cells secrete among others sCD163, the role of which has not been investigated yet.
Aims: To study eventual correlation of serum sCD163 levels with prognosis in DLBCL.
Patients and Methods: Twenty-six DLBCL patients were studied with a median follow-up time of 21 months (2–138). Ten were diagnosed in early stages (1 and 2) while the resting majority was in advanced stages (3 and 4). Six patients (23%) relapsed early during disease course. Seven patients succumbed to their disease and other 3 from other causes.
SerumCD163 measurements were performed by ELISA (Duo-Set R&D Quantiquine) according to the manufacturer's instructions in frozen sera kept at diagnosis. The SPSS v.26 software was used for statistical analysis and survival curves were drawn by Kaplan-Mayer method and compared by the log-rank test.
Results: Serum sCD163 levels ranged from 34072 to 164912 pg/mL (median 134672 pg/mL) in patients and from 104420 to >140000 pg/mL (median 117952 pg/mL) in 15 healthy individuals. Patients with serum sCD163 levels above median had a higher probability of relapse and a shorter disease free survival ($p = 0.004$), compared to the others (figure). Overall survival was not affected by sCD163 levels.
Conclusions: In this small series increased soluble serum CD163 (sCD163) levels constituted a prognostic marker of early relapse. Larger series are needed to confirm this interesting preliminary result.



Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, targeting the tumor microenvironment

No conflicts of interests pertinent to the abstract.

501 | CHARACTERISTICS AND TREATMENT OUTCOMES OF AGGRESSIVE HIGH GRADE B CELL LYMPHOMA WITH MYC AND BCL 6 REARRANGEMENTS

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According to the International Consensus Classification of Lymphomas (Blood 2022: 140: 1229–53), a new provisional *entity* high grade B cell lymphoma with *MYC* and *BCL 6 rearrangements* (HGBCL-DH-*BCL6*) was introduced. HGBCL-DH-*BCL6* occurred very rare, in less than 10% of patients with HGBCL with rearrangements. Here we assessed clinicopathological features and treatment outcomes of HGBCL-DH-*BCL6*.

We retrospectively collected clinic-pathological data of patients with HGBCL with *MYC/BLC6*-rearrangements. All cases were evaluated by h*istopathological*/immunohistochemical/flow-cytometry examination (IHC/FCM), with a broad panel of antibodies, including CD10/CD38/MYC/LMO2/ BCL2/BCL6. Gene status *(MYC/BCL2/BCL6*) was examined using fluorescence in situ hybridization (FISH), karyotype was successfully achieved in 70% of patients. We identified 18 patients with *MYC*-rearrangement (median *MYC*-R: 49% of examined cells; range: 5%–93%), and *BCL6*-rearrangements (median *BCL6*-R: 50% of examined cells; range: 5%–93%) with no *BCL2*- rearrangements was found. Expression of MYC-protein was found only in 22% of patients. Eleven and seven patients, respectively, had DLBCL and BCL-u morphology. Median age at diagnosis was 57 years (range: 18–84). Advanced stage, extranodal disease, increased dehydrogenase lactate were found in 78%, 33%, 83% of patients, respectively. Only 15 patients received immunochemotherapy: 8 were treated with R-CHOP and CNS prophylaxis, other 7 patients had more intensive therapy: GMALL, CODOX/IVAC or DAEPOCH-R. Six patients had consolidative auto-SCT. Morphology of disease, age and intensity of immunochemotherapy had no impact on response and survival. Only 36% of patients achieved complete remission. Median overall survival (OS) and progression free survival (PFS) were 5.6 months and 3.0 months, respectively. OS and PFS for 1 year were 34% and 28% respectively. Actually, 4 patients are alive with no active disease.

HGBCL-DH-*BCL6* is a rare and aggressive B-cell lymphoma, often without the IHC-protein MYC deletion, with advanced disease presenting at diagnosis. The outcomes is poor and less than 40% of patient are alive from one year from diagnosis. Intensive therapy has not improved treatment results.

Keywords: aggressive B-cell non-Hodgkin lymphoma, pathology and classification of lymphomas

No conflicts of interests pertinent to the abstract.

502 | PROGNOSTIC SIGNIFICANCE OF KAT2A AS A HISTONE ACETYLATION REGULATOR IN DIFFUSE LARGE B-CELL LYMPHOMA

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Diffuse large B-cell lymphoma (DLBCL) is a highly heterogeneous lymphoid neoplasm with variations in the expression of genes and genetic alterations. Histone acetylation is one of the epigenetic alterations associated with lymphoma pathogenesis. Among the many types of cell death, ferroptosis has distinct properties and has been found to be associated with physical conditions as well as various cancers.

Using consensus clustering, we categorized DLBCL patients based on histone acetylation regulators and ferroptosis-related genes (HFGs) expression. LASSO Cox regression was used to calculate risk scores. Kaplan-Meier survival analysis, univariate and multivariate Cox regression analysis, and ROC curve analysis were performed. qRT-PCR was used to validate the expression of four HFGs in DLBCL cell lines.

According to the study, CREBBP had the highest mutation frequency. Based on CREBBP mutations, patients were divided into mutant and wild groups, and several histone acetylation regulators were overexpressed in the mutant group.

To demonstrate the potential malignant mechanisms of HFGs in DLBCL development and their prognostic value. A significant positive self-correlation was observed in HAGs and FRGs. A negative correlation was found between KAT2A, the HA writer, and the majority of FRGs (Fig. 1A). 36 genes were selected ($p < 0.05$) by univariate regression correlations with clinical prognosis. Consensus clustering was used to categorize the expression of DLBCL patients. K-M survival analysis showed that HFcluster B had a worse prognosis.

Based on HFGs, we developed a high-quality and high-accuracy gene signature prediction model. Following LASSO Cox regression, a four-gene signature model was identified. Patients with DLBCL in the high-risk group had a significantly shorter OS ($p < 0.001$, Figure 1B). ROC curves, univariate and multivariate Cox regression analyses also revealed that riskScore served as an independent indicator for patients with DLBCL ($p < 0.001$). Analyses revealed that molecular mechanisms mediate histone acetylation and ferroptosis. The results of PCR in CD19+ B cells and DLBCL cell lines also confirmed the accuracy of the model.

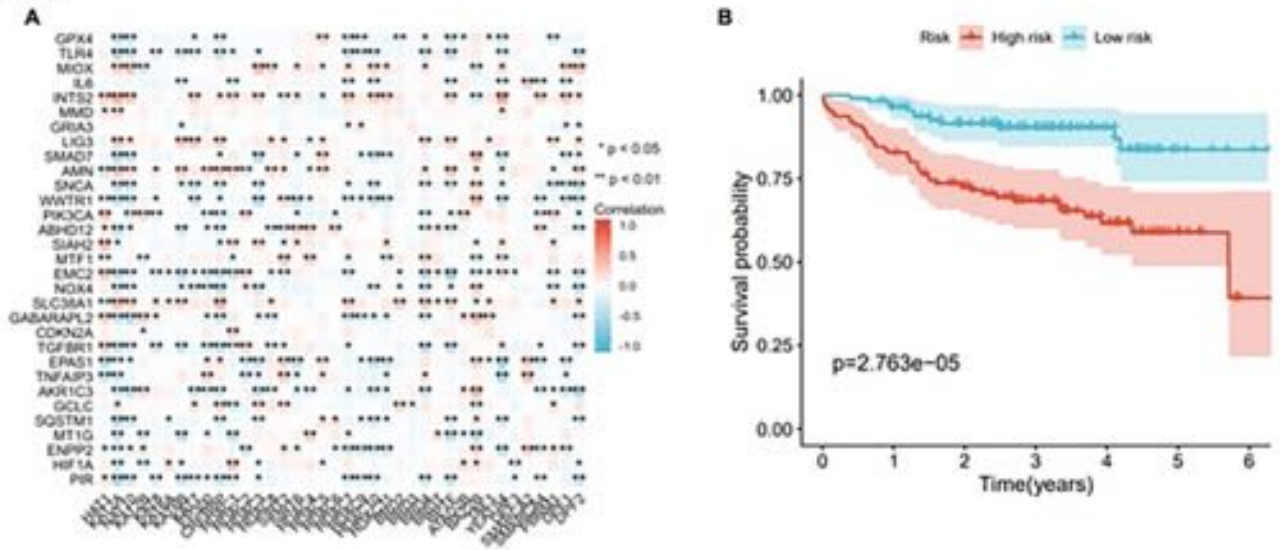
Due to its close relationship to ferroptosis-related genes, KAT2A was explored in greater depth. Further study revealed that KAT2A was significantly correlated with age ($p = 0.028$) and IPI ($p = 0.016$). In univariate analysis, KAT2A was an independent indicator of DLBCL patients ($p < 0.001$). The expression level of KAT2A was negatively correlated with OS in DLBCL patients ($p = 0.003$).

There were significant correlations among these HFGs, indicating their potential role in DLBCL development and predictive value for prognosis. Additionally, our study shows that KAT2A is associated with prognosis in patients with DLBCL. Further study of the mechanisms of KAT2A in DLBCL may help clinicians to individualize the treatment of this patient population.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

Figure 1



503 | EXPLORING THE POTENTIAL CORRELATION BETWEEN NEUTROPHIL EXTRACELLULAR TRAPS AND PROGNOSIS IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA AND HODGKIN'S LYMPHOMA

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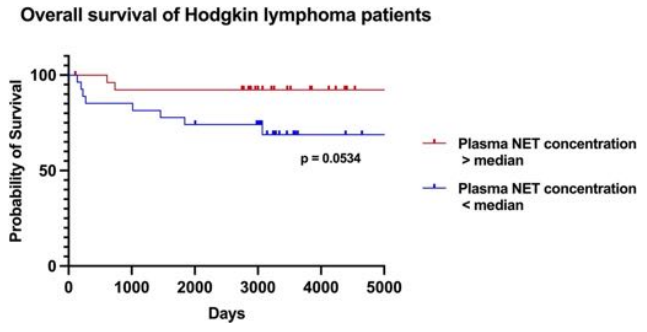
Introduction: Neutrophil extracellular traps (NETs) are web-like structures of decondensed chromatin and granule proteins that are released from neutrophils in response to infection. NET-release also occurs and contributes to inflammation, organ dysfunction and thrombosis in patients with non-infectious inflammatory conditions, such as cancer. In several solid cancer types, NETs have been associated with poorer prognosis by facilitating tumour growth and metastasis. One study has associated NETs with tumour progression and poorer prognosis in diffuse large B-cell lymphoma (DLBCL), however the knowledge of the role of NETs in lymphoma is sparse. Here, NETs were measured in plasma from patients with DLBCL and Hodgkin's lymphoma (HL), and correlated to blood counts and clinical outcome of the patients.

Methods: Plasma samples from patients with DLBCL ($n = 72$) and HL ($n = 54$), diagnosed between 2010 and 2015, were obtained from the Swedish Uppsala Umeå Comprehensive Cancer Consortium (U-CAN) biobank. The lymphoma samples, as well as healthy controls ($n = 11$), were analysed using a commercial enzyme-linked immunosorbent assay (ELISA) targeting citrullinated histone 3 in complex with externalized DNA, a biomarker considered specific for NETs. Data collected from patient records, including routine blood counts at diagnosis, clinical background and disease outcome, was correlated to the obtained plasma concentrations of NETs.

Results: DLBCL and HL patients showed significantly elevated concentrations of NETs in plasma compared to healthy controls (median concentrations 60.07, 65.24 and 5.366 ng/mL, $p < 0.0001$). In both DLBCL and HL, trends towards better overall survival ($p = 0.3308$ and 0.0534 respectively) and better progression free survival ($p = 0.2777$ and 0.1056) were seen for patients with concentrations of NETs above median. While there was no correlation between sex or age and NET levels in DLBCL patients, HL patients under the age of 50 years showed a significant correlation with higher levels of NETs ($p = 0.0021$). In both DLBCL and HL patients, plasma NET-levels showed a positive correlation with the neutrophil count in blood at diagnosis ($p = 0.0087$ and 0.0001 respectively). A neutrophil-lymphocyte ratio above 3.0, a known predictor of worse outcome in cancer patients, showed a trend towards being correlated with worse prognosis in DLBCL patients, but this was less evident for HL patients.

Conclusions: In contrast to the previous understanding of NETs as being unfavourable for the prognosis in cancer, we here show a trend towards better survival of DLBCL and HL patients with significant elevation of NETs in plasma. The NET-levels correlated significantly to the neutrophil count in blood. More DLBCL and HL plasma samples will be analysed to confirm these findings, and in order to investigate a possible association between NETs and other comorbidities in the lymphoma patients.



Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

504 | MYC ALTERATIONS IN HIV-ASSOCIATED B CELL LYMPHOMAS: RESULTS OF "EUROMYC" STUDY (A EUROPEAN RETROSPECTIVE STUDY)

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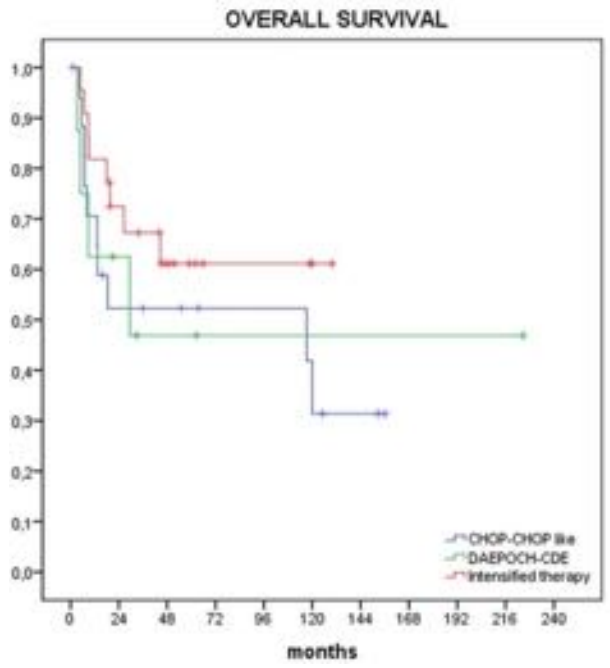
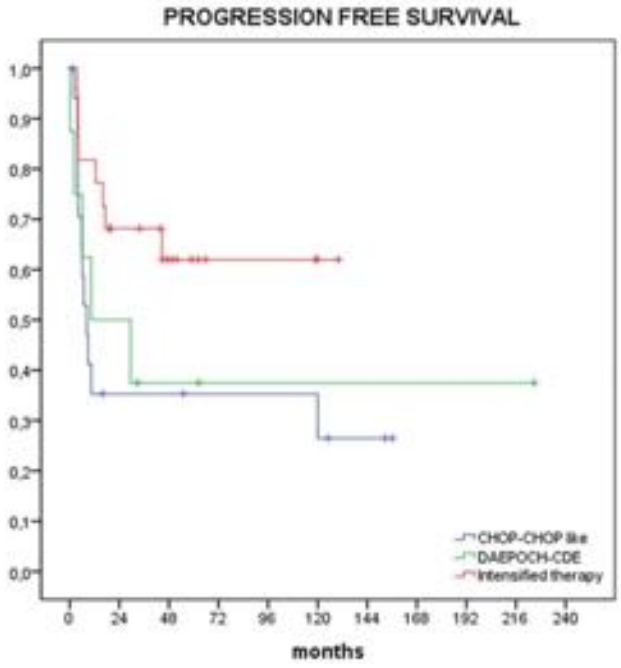
Introduction: HIV negative patients (pts) with B cell lymphoma (Ly) carrying *MYC* rearrangements and *BCL2*+/-*BCL6* translocations [double hit (DHL) or triple hit Ly (THL)] have shown a dismal prognosis when treated with standard chemotherapy. Data about the prognosis of "single hit" Ly, (SHL) are more controverse. In HIV-associated B cell lymphomas (HIV+Ly), scanty data are available on the prevalence and prognostic impact of *MYC* rearrangements.

Methods: This is a retrospective study conducted in 11 European centers with the aim to evaluate the clinical and prognostic impact of *MYC* rearrangement, evaluated by FISH analysis, in HIV+Ly. We compared HIV+ Ly [diffuse large B cell Ly (DLBCL), B cell Ly unclassifiable, with features intermediate between DLBCL and Burkitt (BCLU), and High grade B cell Ly (HGBL)] with (*MYC*+) and without (*MYC*-) *MYC* rearrangements, treated with standard (R-CHOP or CHOP like) or intensive therapy (iCT) that is, CODOX-IVAC, Carmen trial, GMALL.

Results: A total of 161 consecutive pts were enrolled: 49 (30%) were *MYC*+ and 112 (70%) *MYC*-. *MYC*+ pts had higher involvement of central nervous system (CNS) at presentation, higher ki67%, more frequent histology other than DLBCL, translocation of *BCL2* and germinal center B phenotype. *MYC*+ pts received more frequently iCT (45% vs. 20%, $p = 0.002$). With a median follow-up of 57 months, there were no significant differences in overall survival (OS) and progression-free survival (PFS) between *MYC*+ and *MYC*- pts (5 years (y) OS and PFS 55% and 47% in *MYC*+ and 59% and 53% in *MYC*- pts). DHL/THL were 10 (13 *MYC*+ pts did not have data on *BCL2*/*BCL6*): compared to 26 SHL they had similar clinical characteristics, but worse outcome with 5y PFS (30% vs. 60%, $p = 0.02$) and 5y OS (50% vs. 67%, $p = 0.07$).

In univariate analysis IPI≥3, ECOG≥ 2, increased LDH and ki67 < 90% were related to worse OS and PFS while *BCL2* translocation with shorter PFS. In multivariate analysis ECOG≥2, elevated LDH and ki67 < 90% maintained their negative impact. In *MYC*+ pts, iCT was related to better PFS compared to standard therapy (5 y PFS 62% and 35%, $p = 0.04$) and to a trend of better OS (5 y OS 61% and 52%, $p = 0.25$) (Figure 1). No pts treated with iCT died from toxicity.





Conclusion: In this analysis, *MYC*+ pts had slightly clinical differences compared to *MYC*- pts, including higher proliferative index and more CNS involvement at diagnosis. OS and PFS survival were similar in the 2 groups. However, more *MYC*+ pts were treated with iCT, and this allowed to obtain better outcome compared to standard therapy.

Keyword: aggressive B-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

M. Spina
Honoraria: GILEAD, Servier, Novartis, Incyte, BeiGene, Istituto Gentili
Research funding: MENARINI

L. Arcaini
Consultant or advisory role Roche, Janssen-Cilag, Verastem, Incyte, EUSA Pharma, Celgene/Bristol Myers Squibb, Kite/Gilead, ADC Therapeutics
Research funding: Gilead Sciences
Other remuneration: Speakers' Bureau: EUSA Pharma, Novartis

D. Dalu
Educational grants: Roche, Gentili, Lilly and Eisai
Other remuneration: Gentili, Daikii Sanchio

A. Tucci
Consultant or advisory role Gentili, Sanofi, Jannsen
Honoraria: Kiowa Kyrin, Takeda

505 | EXPLORING DIFFERENTIAL MUTATIONAL DISTRIBUTION BY TARGETED SEQUENCING IN A R-CHOP TREATED COHORT OF DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS

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Background: Diffuse large B-cell lymphoma (DLBCL) harbors striking clinical and molecular heterogeneity, which continues to encumber risk stratification with a consequently high rate of refractory/relapsed patients (pts). Though the genomic landscape of DLBCL has been comprehensively uncovered, the search for eligible molecular biomarkers continues. Exploratively, we set out to retrospectively evaluate differential mutational distributions in a DLBCL cohort using targeted sequencing.

Patients and method: A cohort of 105 de novo DLBCL pts, uniformly treated with first-line R-CHOP, were studied. Thirty pts relapsed, of which 70% had early relapses (<2 years after completing therapy), while 30% had late relapses (≥2 years). Targeted next-generation sequencing (90 gene panel) was applied on archival paraffin-embedded diagnostic samples and, if available, first relapse samples.

Results: In total, 118 samples were sequenced, each displaying a median of 12 (range 1–46) putative somatic protein-coding

mutations. Germinal center B-cell (GCB) DLBCL ($n = 60$) displayed a differential somatic signature with enrichment of *EZH2*, *TNFRSF14*, *BCL2*, *ACTB*, *SOCS1*, and *FAS* mutations (Fisher's Exact, $p < 10^{-4}$), whereas mutations in *CDKN2A*, *PRDM1*, *MYD88*, and *CD79B* were significantly enriched in non-GCB pts ($p < 10^{-4}$, $n = 44$). Survival analysis confirmed inferior overall survival (OS) in non-GCB DLBCL (5-year OS, log-rank (Mantel-Cox), $p = 0.01$, hazard ratio (HR) 1.7). Pts with double-hit biology (DHB), defined as either *MYC* and *BCL2* and/or *BCL6* fluorescent in situ hybridized positive and/or with *MYC* and *BCL2* immunohistochemical double expression ($n = 32$), did not display a significant mutational signature or differential OS. However, a subgroup of DHB pts characterized by mutations in *MYC*, *PRDM1*, or *IRF4* ($n = 15$) had markedly inferior OS (5-year OS, log-rank, $p = 0.0003$, HR 3.34) compared to negative non-DHB pts ($n = 55$) or negative non-DHB/DHB pts ($p = 0.0017$, HR 2.7, $n = 72$). Noticeably, *ACTB* mutations were only present in non-DHB pts. The mutational distribution at diagnosis did not differ between pts with relapse and in sustained remission. However, in the relapse group, *GNA13* mutation at diagnosis was more frequent in early relapses than late relapses (43% vs. 0%, Fisher's Exact without correction, $p = 0.03$). The presence of *GNA13* in the entire cohort showed a trend towards inferior survival.

Conclusion: Differential distribution with significant mutational signatures were expectedly found in GCB versus non-GCB, but not in subgroups with DHB or relapse. Interestingly, mutations in *MYC*, *PRDM1* or *IRF4* identified a distinct subset of DHB pts with inferior survival. Furthermore, *GNA13* mutations were significantly enriched in early relapse pts. These preliminary findings call for validation of *GNA13* as a potential marker of early relapse as well as the prognostic value of *MYC*, *PRDM1* and *IRF4* mutations in DHB DLBCL.

The research was funded by: The Danish Cancer Society and The Vissing Foundation

Keywords: aggressive B-cell non-Hodgkin lymphoma, genomics, epigenomics, and other -omics, tumor biology and heterogeneity

Conflicts of interests pertinent to the abstract

T. S. Larsen
Consultant or advisory role Roche, Gilead, Novartis, Celgene/BMS
Research funding: Genentech

506 | ENHANCING MORPHOLOGICAL ANALYSIS OF PERIPHERAL BLOOD CELLS IN CHRONIC LYMPHOCYTIC LEUKEMIA WITH AN ARTIFICIAL INTELLIGENCE-BASED TOOL

Y. Wang, H. Liu, H. Wang, Y. Wu, H. Qiu, C. Qiao, L. Cao, J. Zhang, J. Li, L. Fan, R. Wang
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital, Nanjing, China

Background: Real-time monitoring of chronic lymphocytic leukemia (CLL) is crucial for effective patient management. Peripheral blood (PB) is the preferred source for obtaining CLL cells due to its ease of access and lower cost. However, traditional methods of evaluating PB films have several drawbacks, such as lack of automation, reliance on personal experience, and low repeatability and reproducibility. To address these limitations, we developed an artificial intelligence-based tool that objectively evaluates morphologic features in the blood cells of CLL patients from a clinical perspective.

Methods: We conducted a retrospective study on 284 patients newly diagnosed with CLL at Jiangsu Province Hospital from December 1, 2013 to December 31, 2020. To train and test our machine-learning algorithm, we randomly split the cohort into a training set (75%) and a testing set (25%). We obtained high-quality whole-slide images from blood films using the Bionovation CSFA-80 scanner, and developed an automated algorithm using a deep convolutional neural network (CNN) to precisely identify regions of interest. Additionally, we used the well-established Visual Geometry Group-16 CNN as the encoder to segment cells and extract morphological features. This tool enabled us to extract precise morphological features of all lymphocytes for subsequent analysis.

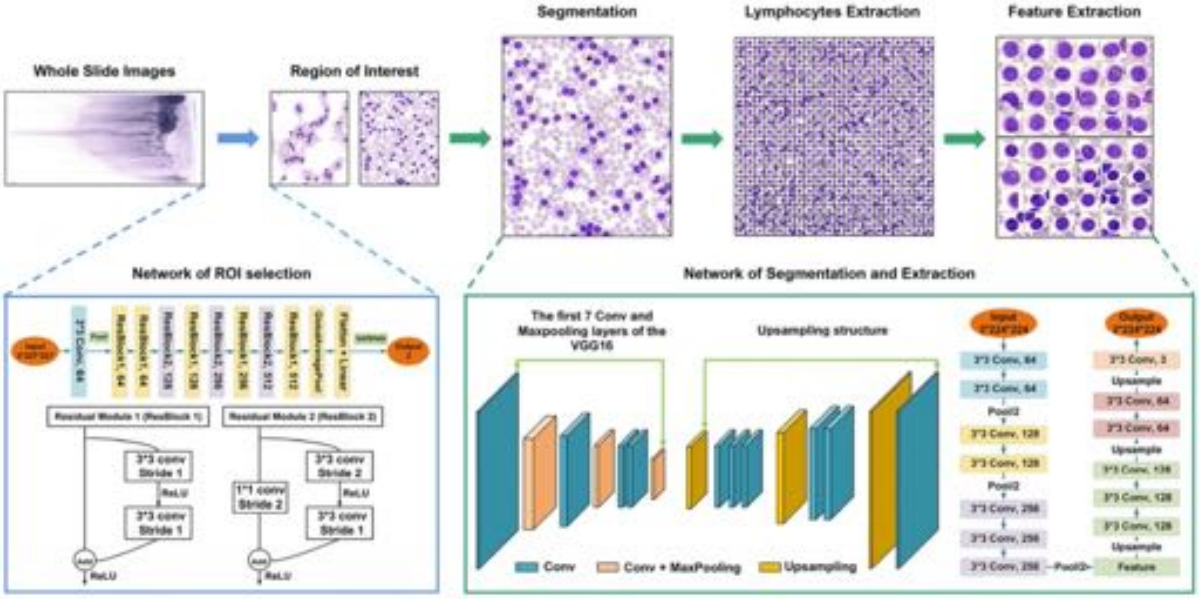
Results: Our study's lymphocyte identification had a recall of 0.96 and an F1 score of 0.97, making it suitable for future applications. Cluster analysis identified three clear, morphological groups of lymphocytes that reflect distinct stages of disease development to some extent. To investigate the longitudinal evolution of lymphocyte, we extracted cellular morphology parameters at various time points from the same patient. These time points included the initial diagnosis period without treatment indications, the pretreatment period with indications beginning to appear, and the diagnosed phase of large cell transformation. The results showed some similar trends to those observed in the aforementioned cluster analysis. Correlation analysis further supports the prognostic potential of cell morphology-based parameters.

Conclusions: Our methodology offers a strong basis for future research on cell morphology and its impact on disease management. With an automated, user-friendly approach that eliminates biases from manual inspection and enhances repeatability, we believe our approach could significantly contribute to the clinical understanding and management of diseases. To validate and establish the clinical utility of our approach, we propose conducting multicenter retrospective validation and prospective longitudinal studies.

The research was funded by: National Natural Science Foundation of China [82100211]; Beijing Xisike Clinical Oncology Research Foundation [Y-Roche2019/2-0090]; Science Foundation Project of Ili & Jiangsu Joint Institute of Health [yl2021ms04]; and Science and Technology Development Fund Project of Pukou branch of Jiangsu People's hospital [KJ2021-4].

Keywords: diagnostic and prognostic biomarkers, Imaging and Early Detection - Other, chronic lymphocytic leukemia (CLL)

No conflicts of interests pertinent to the abstract.



507 | SOLUBLE SERUM CD163 (SCD163) LEVELS IS A MARKER OF DISEASE ACTIVITY IN LYMPHOPLASMACYTIC LYMPHOMA (LPL). PRELIMINARY RESULTS

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General Hospital of Athens Laiko, 1st Haematology Department of Propaedeutic and Internal Medicine, Athens, Greece

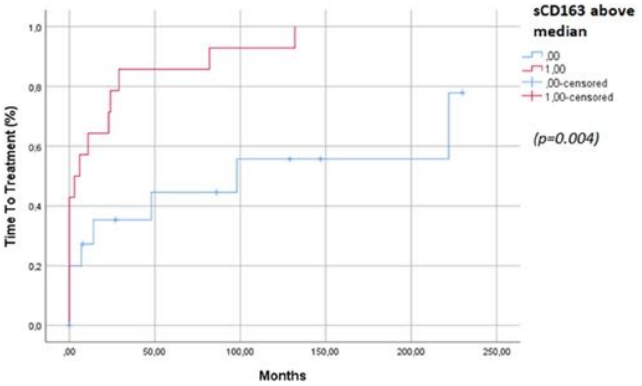
Introduction: sCD163 is secreted by monocyte-macrophage lineage cells, including Tumor-Associated Macrophages (TAM) that participate in neoplastic and immune regulation. LPL is a lymphoproliferative neoplastic disorder, the spectrum of which comprises Waldenstrom's macroglobulinaemia (WM) in its symptomatic, asymptomatic and precursor forms as well as non-secreting or IgG/IgA-secreting cases. sCD163 eventual role in LPL has not been investigated so far.

Aims: To determine sCD163 levels in a series of LPL patients at diagnosis and evaluate possible correlations with disease activity.

Patients and Methods: Twenty-nine patients were studied (24 WM of whose 5 asymptomatic, 2 IgM-MGUS with related peripheral neuropathy and 3 LPL) after their informed consent. Clinical and routine laboratory data were collected. Median time to treatment (TTT) was 11 months and median overall survival (OS) 128 months. Serum sCD163 was tested in frozen sera of patients collected at diagnosis and in 15 healthy individuals (HI). Measurements were performed by ELISA (Duo-Set R&D Quantiquine) according to the manufacturer's instructions. Statistical analysis was performed with the SPSS v.26 software and survival curves were drawn by the Kaplan-Mayer methods and compared by the log-rank test.

Results: Median serum sCD163 was 109000 pg/mL and 117952 pg/mL in patients and HI respectively. Time to treatment was significantly shorter in patients with serum sCD163 values above median ($p = 0.004$), compared to the others (figure). In addition sCD163 levels were correlated with platelet number, the presence of lymphadenopathy and IgM in WM-only patients.

Conclusions: Our results revealed that increased serum sCD163 is related to a shorter TTT in LPL suggesting a role for monocyte-macrophage lineage cells in disease biology. Further research is needed.



Keywords: diagnostic and prognostic biomarkers, indolent non-Hodgkin lymphoma, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

508 | THE INCIDENCE, CLINICAL APPLICATION AND PROGNOSTIC SIGNIFICANCE OF MYD88 AND CXCR4 MUTATION IN CHINESE PATIENTS WITH LYMPHOPLASMACYTIC LYMPHOMA/WALDENSTRöM MACROGLOBULINEMIA

Y. Yu, Y. Yan, J. Wang, W. Xiong, Y. Yao, Y. Huang, R. Lyu, T. Wang, Q. Wang, W. Liu, G. An, W. Sui, Z. Xiao, Y. Xu, W. Huang, D. Zou, L. Qiu, S. Yi
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Introduction: Waldenström macroglobulinemia (WM)/lymphoplasmacytic lymphoma (LPL) is a rare, B-cell lymphoma with highly prevalent somatic mutations including MYD88, and CXCR4. The mutation rates of LPL/WM in China and the direct comparison among different deletion means are still not clear.

Methods: 387 patients with LPL/WM were included in this study. Tumor cells were collected from 357 un-sorted BM 28 PB and 2 lymph nodes (FFPE). MYD88^{L265P} mutation were detected by Sanger sequencing (FGS), NGS, allele-specific quantitative polymerase chain reaction (ASPCR), and droplet digital polymerase chain reaction (ddPCR). CXCR4 mutation were detected by Sanger sequencing, NGS, and ASPCR.

Results: 386 patients were assessed for MYD88^{L265P} mutation, of whom 263 were tested by FGS, 235 by NGS, 311 for AS-PCR, 118 for ddPCR. The MYD88^{L265P} mutation was found in 88.6% of the patients. ASPCR and ddPCR had the highest sensitivity of 97.1% and 96.8%. FGS and NGS failed to detected the mutation in low tumor load. A high false-negative rate (FNR) for MYD88 by FGS and NGS was observed in patients with tumor load less than 10% (FNR: 35.5% and 20%). There was no significant difference in the MYD88 mutation rate detected by ddPCR and ASPCR among patients with different tumor load groups ($p = 0.794$). MYD88 mutation was detected in a high incidence of 88.5% in less than 1% infiltrated WM tumor cells specimens by ddPCR and ASPCR.

CXCR4 mutation testing was performed in 358 patients of LPL/WM, comprising 301 with FGS, 236 with NGS, and 311 with ASPCR. Overall, 31.2% patients were identified as having the CXCR4 mutation. NGS exhibited the highest sensitivity among the three detection means.

MYD88 wild-type patients had a significantly lower Hb levels (median 79 g/L vs. 90 g/L, $p = 0.015$), lower proportion of males (54.5% vs. 51.8%, $p = 0.012$) and a significantly higher proportion elevated β2-MG (84.2% vs. 65.6%, $p = 0.021$), and LDH (30.2% vs. 11.9%, $p = 0.001$). However, there were no significant differences in either PFS or OS between MYD88^{L265P} wild-type and MYD88^{L265P} mutation group ($p = 0.35$, $p = 0.42$).

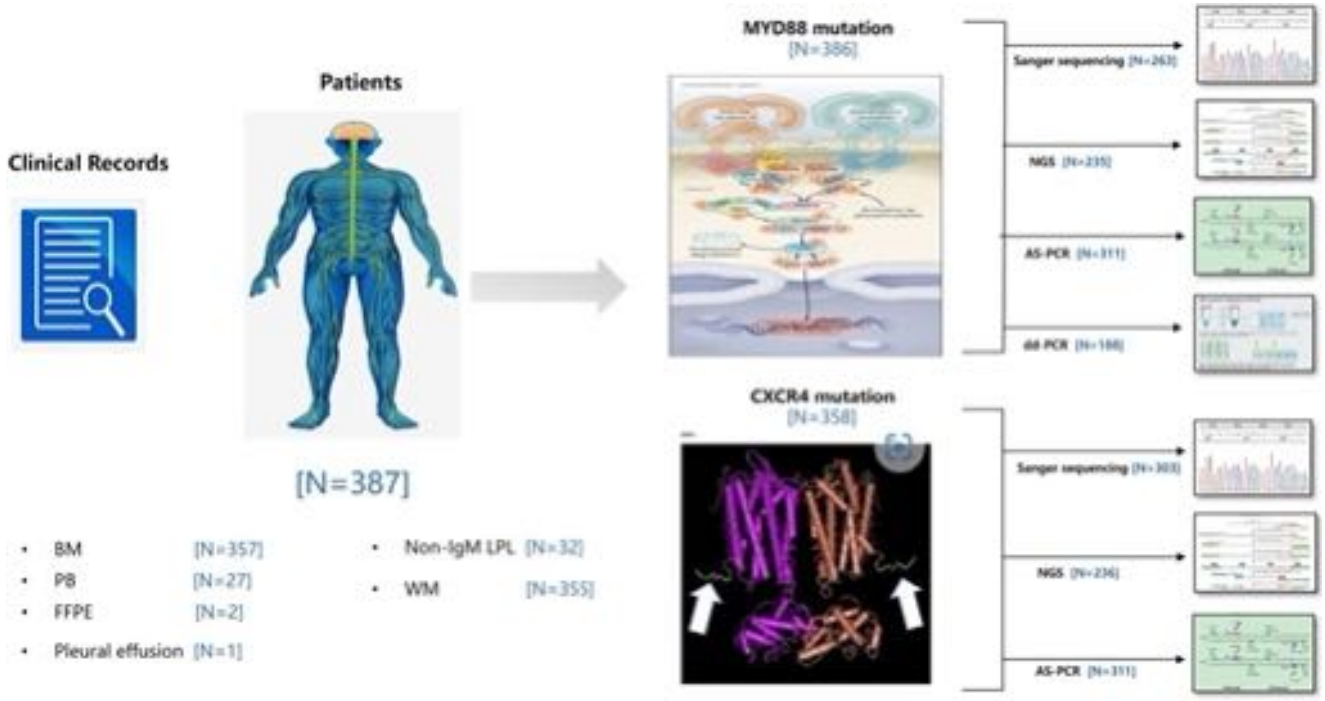
Patients with CXCR4 mutation tended to be older (median 64 vs. 60, $p < 0.001$) and displayed lower hemoglobin level (median 81 g/L vs. 93 g/L, $p = 0.008$), higher serum IgM level (median 36.1 g/L vs. 31.6 g/L, $p < 0.001$), and higher baseline BM involvement (by FCM, median 15.1% vs. 7.1%, $p < 0.001$) compared with CXCR4 wild-type patients. Notably, CXCR4 mutation group had significantly worse survival compared with the wild-type group ($p = 0.03$, $p = 0.02$).

Conclusions: Here, we conducted a large cohort to further explore the incidence, clinical application and prognostic significance of MYD88 and CXCR4 mutation in Chinese WM/LPL. ASPCR and ddPCR exhibited the highest sensitivity in MYD88 mutation detection, and were effective and accurate enough for un-sorted low infiltrated WM specimens. And NGS was the most sensitive method to detect CXCR4 mutation.

The research was funded by: National Nature Science Foundation of China (81970187, 82170193, 81920108006, and 81900203) and the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2022-I2M-1-022, 2021-I2M-C&T-B-081)

Keywords: diagnostic and prognostic biomarkers, indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.



509 | PROGNOSTIC SIGNIFICANCE OF A NOVEL AMINO ACID METABOLIC INDEX IN CHRONIC LYMPHOCYTIC LEUKEMIA

M. Liu, Y. Zhang, L. Feng, P. Li, K. Lu, Y. Jiang, X. Wang
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Introduction: Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the western world, with a highly variable clinical course, which makes the study of prognostic influences and treatment options for CLL patients particularly important. Cancer cells readjust their metabolic pathways to accommodate their nutritional demands for reducing equivalents, increased energy and cellular biosynthesis. Altered amino acid metabolism is one way to achieve these demands. Amino acid metabolism plays an important role in the development and progression of CLL. However, there is still a lack of clinical biochemical indicators associated to amino acid metabolism to evaluate the prognosis of CLL patients. The study aimed to investigate the impact of clinical indicators related to amino acid metabolism on the prognosis of CLL patients and to develop a novel amino acid metabolism scoring system to optimize the risk assessment of CLL patients.

Methods: CLL patients who were treated in Shandong Provincial Hospital between October 2010 to April 2022 were assessed from the Shandong Provincial Hospital CLL (SPHCLL) database. The univariate Cox regression analysis and multivariate Cox regression analysis were applied to evaluate the prognostic values of clinical indicators related to amino acid metabolism. Survival curves were constructed using the Kaplan-Meier method. The prognostic capacities of the novel scoring system were measured by areas under the curve (AUCs) of receiver operating characteristic curves.

Results: A total of 634 CLL patients were randomly assigned to the training set (n = 432) and validation set (n = 202). Independent prognostic significance of hemoglobin (Hb, p = 0.004), cystatin (Cys, p = 0.018) and glutamyl transpeptidase (GGT, p = 0.006) was determined in the training set by univariate and multivariate Cox regression analysis. The clinical indicators related to amino acid metabolism, Hb, CysC and GGT, were selected for establishing a novel amino acid metabolism score system (AAMS) model in CLL patients: AAMS = −1.082*Hb+0.862*CysC +0.842*GGT. CLL patients in the training set were divided into low and high subgroups based on the median AAMS. AAMS had independent prognostic significance in the prognosis of CLL patients (p = 0.017), and a higher AAMS indicates a poorer prognosis for CLL patients. AAMS (AUC = 0.755) also showed better predictive performance compared with Binet stage (AUC = 0.568) and Rai stage (AUC = 0.592) in CLL patients of the training set. These conclusions are well proved in the validation set.

Conclusion: AAMS was an independent prognostic factor for CLL patients. This study analyzed the prognostic effects of clinical indicators related to amino acid metabolism in patients with CLL and developed a new scoring system to optimize accurate risk assessment in CLL patients.

Keywords: amino acid metabolism, chronic lymphocytic leukemia, prognosis, risk score

The research was funded by: This research was funded by National Natural Science Foundation (No. 82270200, No. 82000195, No. 82070203 and No. 81770210); China Postdoctoral Science Foundation (No. 2022M721981); Key Research and Development Program of Shandong Province (No. 2018CXGC1213); Translational Research Grant of NCRCH (No. 2021WWB02, No. 2020ZKMB01); Taishan Scholars Program of Shandong Province; Shandong Provincial Natural Science Foundation (No. ZR2020QH094); Shandong Provincial Engineering Research Center of Lymphoma; Academic Promotion Programme of Shandong First Medical University (No. 2019QL018).

Keywords: chronic lymphocytic leukemia (CLL), diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

510 | RESEARCH ON COHORT OF PATIENTS RELAPSED ON BRUTON TYROSINE KINASE INHIBITORS (BTKI)

L. Dai, Y. Sha, S. Qian, X. Lu, T. Qiu, Y. Miao, S. Qin, Y. Xia, L. Fan, W. Xu, J. Li, H. Zhu
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Introduction: Acquired *BTK/PLCG2* mutations remain to be the driver of drug resistance. The underlying mechanisms need to be further explored. In this study, we retrospectively analyzed the clinical and biological characteristics of fifty-five BTKi-resistant CLL patients in our center and mapped the mutational landscape.

Method: Fifty-five CLL patients who relapsed on BTKis were included and analyzed. 31 patients had matched sequencing data. High sensitivity droplet digital PCR (ddPCR) was additionally used for the detecting certain *BTKC481S* mutation.

Result: The median age at the time of progression on BTKis was 57 years (Table 1). 86.3% (44/51) pts were IGHV unmutated. The most commonly used fragments were 1–69 (n = 10), 4–39 (n = 9), 3–9 (n = 6), and 3–48 (n = 6) (Figure 1). Resistance to BTKi occurred at a

median exposure of 27.6 m in our cohort, medium exposure were 11.23 and 30.59 m for Richter transformation and CLL progression, respectively, $p < 0.001$).

At progression time, 46.9% (23/49) had TP53 mutation, 24.5% (12/49) had ATM mutation, 22.4% (11/49) had EGR2 mutation, 22.4% (11/49) had SF3B1 mutation, 16.3% (8/49) had NOTCH1 mutation, and 10.2% (5/49) had KMT2D mutation. Mutational landscape is shown (Figure 2). No significant shift of mutation landscape was shown between these two timepoints.

By integrating NGS and ddPCR results, BTK/PLCG2 mutation was detected in 49.0% (24/49) pts. ddPCR method may not available for the patients relapsed on the Ibrutinib, this may account for the low rate of acquired mutations detected in patients treated with Ibrutinib. Besides, spatial clonal heterogeneity affect the detection of acquired mutations. In 2 pts presented as LN enlargrment at progression, acquired mutations were not detected by NGS (bone marrow sample) while mutation was detected by ddPCR method or lymph node sample was used. The most com-

TABLE 1

Characteristics		Number (%) or Median (range) At initiation	At progression
Age (y)		55 (30–70)	57 (32–73)
Male: Female	32:23		
Number of prior therapies	0 (1–4)		
Rai stage	I–II	15/45 (33.3)	
	III–IV	30/45 (66.7)	
	Not applicable	8	
	Missing	2	
Binet stage	B	17/45 (37.8)	
	C	28/45 (62.2)	
	Not applicable	8	
	Missing	2	
IGHV mutation status	unmutated	44/51 (86.3)	
	Cannot be defined	1	
	Missing	3	
LDH (IU/L)		289.3 (146–579)	254 (127–959)
β2-MG (mg/L)		4.37 (2.52–7.18)	2.68 (1.4–8.38)
Bulky disease (≥5 cm)	≥5 cm	16/46 (34.8)	16/44 (36.4)
	≥10 cm	5/46 (10.9)	4/44 (9.1)
	Missing	9	11
FISH	17p-	18/42 (42.9)	24/39 (61.5)
	11q-	16/35 (45.7)	4/16 (25)
	13q14-	12/35 (34.3)	4/14 (28.6)
	+12	3/34 (8.8)	5/14 (35.7)
TP53 mutation	Yes	10/34 (29.4)	24/50 (48)
	Missing	21	5
TP53 Disruption	Yes	21/38 (55.3)	31/42 (73.8)
	Missing	17	13
Complex karyotype	≥3	12/32 (37.5)	16/35 (45.7)
	Missing	23	20

TABLE 2

Characteristics	RT (n = 13)	CLL progression (n = 42)	Entire cohort (n = 55)	P value
Median age (range)	57 (42–67)	55 (30–70)	55 (30–70)	ns
Male: Female	7:6	25:17	32:23	ns
Number of prior therapies (range)	1 (0–4)	1 (0–4)	1 (0–4)	ns
LDH (IU/L)	257 (179–400)	293.5 (146–579)	289.3 (146–579)	ns
β2-MG (mg/L)	4.8 (2.8–6.12)	4.37 (2.52–7.18)	4.37 (2.52–7.18)	ns
IGHV unmutated (%)	11/11 (100)	33/40 (100)	44/51 (86.3)	ns
Bulky disease (≥5 cm) (%)	3/9 (33.3)	18/37 (48.7)	21/46 (45.7)	ns
TP53 mutation (%)	3/9 (33.3)	7/25 (28.0)	10/34 (29.4)	ns
17p- (%)	4/10 (40.0)	14/32 (43.8)	18/42 (42.9)	ns
TP53 disruption (%)	5/8 (62.5)	16/30 (53.3)	21/38 (55.3)	ns
11q- (%)	6/10 (60.0)	10/25 (40.0)	16/35 (45.7)	ns
13q14- (%)	5/11 (45.5)	7/24 (29.2)	12/35 (34.3)	ns
+12 (%)	1/10 (10.0)	2/24 (8.3)	3/34 (8.8)	ns
CK (≥3) (%)	3/5 (60.0)	9/27 (33.3)	12/32 (37.5)	ns

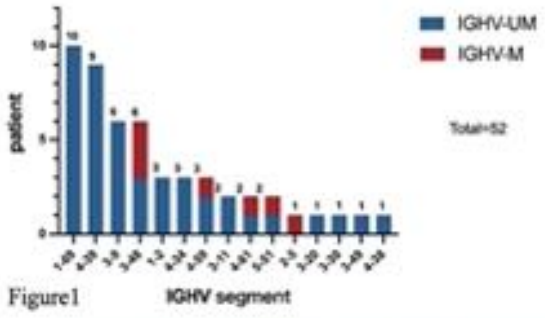

Figure1

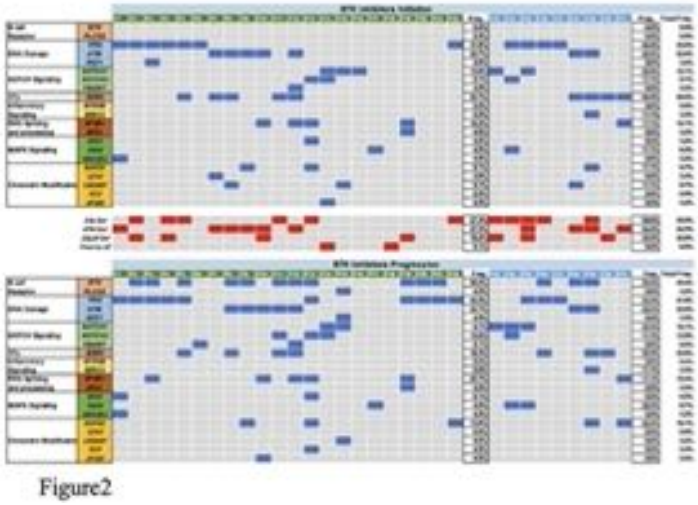
Figure2

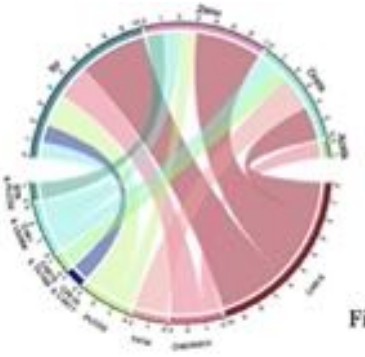
Figure3

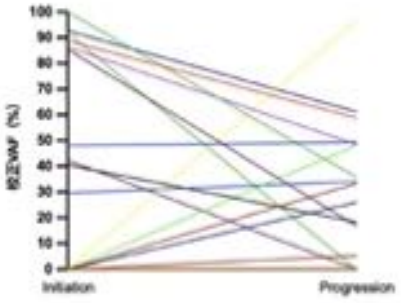

Figure4

mon mutation was C481S (Figure 3), other mutations at the C481 site include C481R, C481Y, C481F. BTK T474 and L528 mutation were also found, concurrent with BTK 481 mutation or alone. 4 patients had PLCG2 mutations, including one concurrent with BTK mutation.

TP53 mutations were analyzed among pts with paired gene mutation results. 16/31 pts were TP53 wildtype at both timepoints. No significant differences in TP53 mutation burden were shown (Figure 4). 4 pts gained TP53 mutation at disease progression, including one carried two different clones. 8/11 pts showed a reduction of existing clone (including 2 disappeared); 2 showed an expansion of existing clone; 1 carried a stable clone at low VAF (detected by ctDNA).

Conclusion: IGHV unmutated status was dominant in our cohort and the most frequently used fragment were 1–69(n = 10), followed by 4–39(n = 9). Acquired BTK/PLCG2 mutations remained to be factors of BTKis resistance and the most common mutation was C481S in our cohort. No significant difference in TP53 mutation burden was found during the treatment of BTKis.

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Keywords: chronic lymphocytic leukemia (cll), molecular targeted therapies

No conflicts of interests pertinent to the abstract.

511 | INTEGRATING MULTI-OMICS ANALYSIS AND ASPARAGINASE ACTIVITY CURVE TO EXPLAIN DRAMATIC PROGNOSIS DIFFERENCES BETWEEN EARLY AND ADVANCED-STAGE IN ENKTL PATIENTS

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Introduction: Asparaginase is the footstone drug for extranodal NK/T cell lymphoma (ENKTL) patients. However, dramatic prognosis differences were shown between early and advanced-stage ENKTL patients. We aimed to explore the underlying biological mechanisms between early and advanced-stage ENKTL.

Methods: Gene expression profiling data was analyzed in 47 ENKTL patients using GSE90597 data. Metabolomic assay of 16 patients (10 for early-stage and 6 for advanced-stage) were detected using serum samples at diagnosis. Dynamic asparaginase activity was available for 10 patients at various time points over 21 days of therapy.

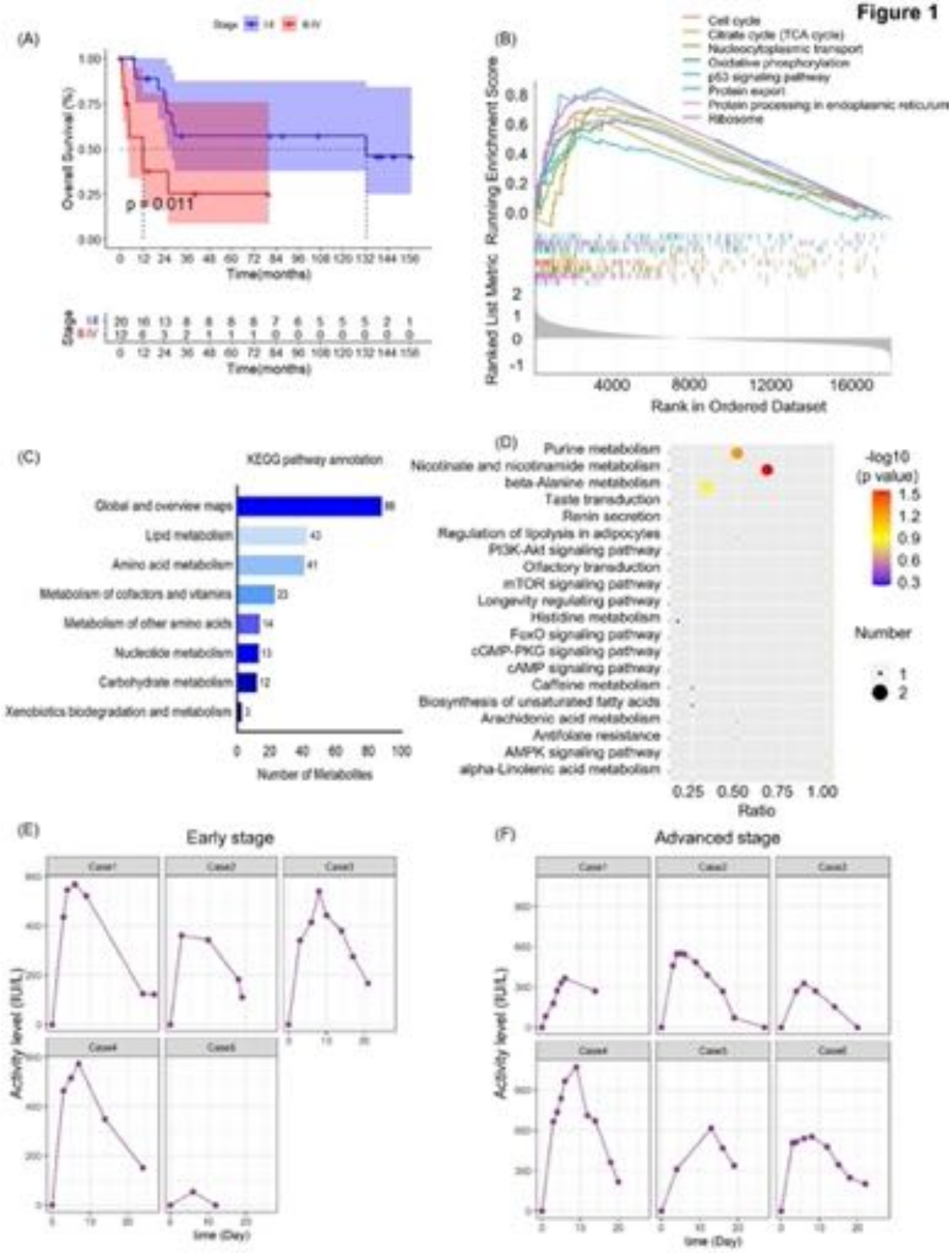
Results: Patients with advanced-stage had shorter overall survivals compared with early-stage (**Figure 1A**). Differential expressed genes (DEGs) which included 196 up-regulated and 13 down-regulated genes were identified between early and advanced-stage patients. The gene set enrichment analysis showed that the DEGs were mainly enriched in metabolism-related pathways, including TCA cycle and oxidative phosphorylation (**Figure 1B**). Untargeted metabolomic profile identified a total of 732 distinguished metabolites including 55 amino acids, 43 lipids and 13 nucleotides (**Figure 1C**). Pathway enrichment analysis was performed using the Kyoto Encyclopedia of Genes and Genomes pathway database by differential metabolites. Statistically significant pathways overrepresented by significant metabolites unique to advanced-stage versus early-stage patients included various metabolism and oncogene-related pathways, particularly purine metabolism, and beta-Alanine metabolism (**Figure 1D**). Asparaginase activity has been well described in acute lymphoblastic leukemia patients for whom asparaginase is the standard component. However, its activity has not been described in ENKTL. As illustrated in **Figure 1E and 1F**, asparaginase activity curves were plotted for 6 early-stage and 4 advanced-stage patients, respectively. The mean peak value of serum asparaginase enzymatic activity was 580.67 $\pm$ 242.18 IU/L and 419.20 $\pm$ 198.08 IU/L for early and advanced-stage patients respectively, and the peak values occurred between d3 and d13. Of particular note, case 5 in advanced-stage had an asparaginase activity level below the effective activity level (>100 IU/L) on the sixth day following the second dose and activity of asparaginase completely depleted on the twentieth day. After that, the patient experienced disease progression.

Conclusions: Collectively, the poor prognosis of advanced-stage ENKTL might due to a distinct metabolism signature and inactivation of asparaginase.

Keywords: aggressive T-cell non-Hodgkin lymphoma, genomics, epigenomics, and other -omics, tumor biology and heterogeneity

No conflicts of interests pertinent to the abstract.

Figure 1


(A)
Overall Survival (%)
p = 0.011
Time(months)
Stage
(B)
Cell cycle
Citrate cycle (TCA cycle)
Nucleocytoplasmic transport
Oxidative phosphorylation
p53 signaling pathway
Protein export
Protein processing in endoplasmic reticulum
Ribosome
Running Enrichment Score
Ranked List Metric
Rank in Ordered Dataset
(C)
KEGG pathway annotation
Global and overview maps
Lipid metabolism
Amino acid metabolism
Metabolism of cofactors and vitamins
Metabolism of other amino acids
Nucleotide metabolism
Carbohydrate metabolism
Xenobiotics biodegradation and metabolism
Number of Metabolites
(D)
Purine metabolism
Nicotinate and nicotinamide metabolism
beta-Alanine metabolism
Taste transduction
Renin secretion
Regulation of lipolysis in adipocytes
PI3K-Akt signaling pathway
Olfactory transduction
mTOR signaling pathway
Longevity regulating pathway
Histidine metabolism
FoxO signaling pathway
cGMP-PKG signaling pathway
cAMP signaling pathway
Caffeine metabolism
Biosynthesis of unsaturated fatty acids
Arachidonic acid metabolism
Antifolate resistance
AMPK signaling pathway
alpha-Linolenic acid metabolism
Ratio
-log10 (p value)
Number
(E)
Early stage
Activity level (IU/L)
time (Day)
(F)
Advanced stage
Activity level (IU/L)
time (Day)

512 | INTEGRATION OF T-CELL CLONALITY SCREENING USING TRBC-1 IN LYMPHOMA SUSPECT SAMPLES BY FLOW CYTOMETRY

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Background: The diagnosis of T-cell non-Hodgkin lymphomas (NHL) is challenging. Many cases of T-NHL have normal immunophenotypes, and currently available T-cell clonality assays have limitations, including suboptimal sensitivity. The development of a monoclonal antibody (mAb) specific for T-cell receptor β constant region 1 (TRBC1) provides an alternative to discriminate clonal T cells. The aim of this study was to evaluate the diagnostic potential of an anti-TRBC1 mAb for the identification of T-NHL.

Materials and Methods: We performed a cross-sectional diagnostic analytic study of samples tested for lymphoma. All samples sent for lymphoma screening were first evaluated using the standard Euroflow Lymphoma Screening Tube (LST), to which a second additional custom-designed T-cell clonality assessment tube was added. LST tube included CD45/CD3/CD4/CD5/CD8/CD19/ CD20/CD38/ TRCγδ/CD56 and the second CD45/TRBC1/CD2/CD7/CD4/TRCγδ/ CD3. The results of TRBC1 expression in patient samples were compared to the normal expression of TRBC1 in 10 normal samples of peripheral blood (PB). Flow cytometry reports were compared with morphological and molecular tests. Clinical data were obtained from the electronic database. This study was approved by the institutional IRB and Clinical Ethics Committee.

Results: 69 samples were evaluated. 10 healthy controls, and 59 patient samples. Overall, individuals had a median of 52 years (interquartile range [IRQ], 35–70 years) and 53.6% were female.

Normal TRBC1 expression was assessed in 10 normal PB samples. Within the T-cell population (CD45+/CD3+), CD4+ cells expressed (±SD) TRBC1 in 42% (4.2), while CD8+ cells in 38% (4.7). This resulted in a TRBC1+/- ratio of 0.72 ± 0.13 for CD4+ and 0.61 ± 0.13 for CD8+ T cells. Cut-off percentages in the CD4+ cells were from 29.4% to 54.6%, and from 23.9 to 52.1% in CD8+ T-cells. Cut-off ratios in CD4+ T cells were from 0.33 to 1.1, and in CD8+ T cells between 0.22 and 1.0.

Using predefined normal cut-off values, 18 of 59 (30.5%) samples showed a restricted (monotypic) expression of TRBC1. 6/18 were monotypic positive (33.3%) and 12/18 were monotypic negative (66.6%). A final diagnosis of a T-NHL was confirmed by IHC in 15 of the 18 cases (83.3%). A molecular TCR gene rearrangement assay

Characteristic	Donors	Non-neoplastic	T-cell NHL
n	10	41	18
Age, median (y; IQR)	42 (35 – 45)	53 (32 – 71)	56 (44 – 66)
Sex (n; %)			
Female	7 (70%)	22 (54%)	8 (44%)
Male	3 (30%)	19 (46%)	10 (56%)
Sample (n)			
PB	10	3	9
BM	0	7	3
Tissues	0	24	5
Seroma	0	6	0
Pleural fluid	0	1	1
CD4 / CD8 ratio			
Abnormal	0	23 (56%)	12 (67%)
TRBC1			
Polytypic	10 (100%)	41 (100%)	0
Monotypic	0	0	18 (100%)

Abbreviations: NHL, Non-Hodgkin's lymphoma; IQR, interquartile range; PB, peripheral blood; BM, bone marrow

was available in 3/15 cases, which confirmed clonality. The 3 discordant cases were 2 samples from an EBV+ primary effusion lymphoma (PEL) and 1 of lung adenocarcinoma. There were no cases of a diagnosis of a T-NHL by morphology / IHC with normal TRBC1 expression. Non-neoplastic patient samples behaved between predefined TRBC1 cut-off values.

Conclusions: Expression of TRBC1 provides a robust method for T-cell clonality assessment, with very high sensitivity and good correlation with complementary methods. TRBC1 can be integrated into routine lymphoma screening strategies via flow cytometry to improve T-NHL diagnosis capacities.

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Keyword: diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

513 | RANDOMIZATION IS AN INFREQUENTLY USED METHOD IN INTERVENTIONAL PHASE II CLINICAL TRIALS OF ADULT PATIENTS WITH LYMPHOMA

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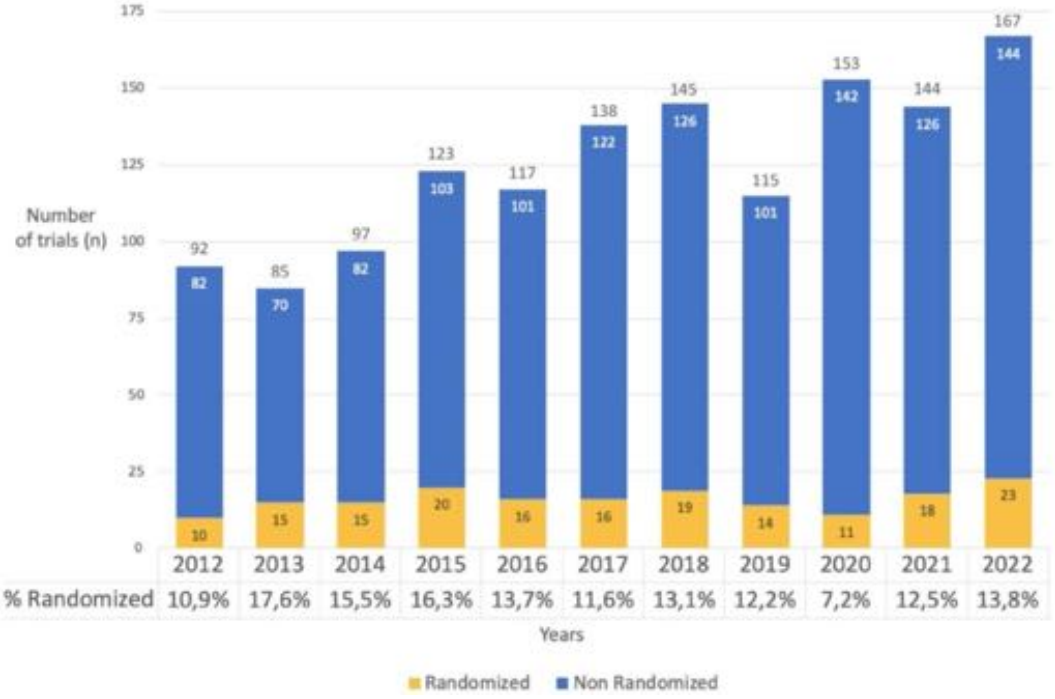
Introduction: Clinical trials are important to inform decision making and to improve outcomes for patients with lymphoma. Phase II trials are designed to determine if a new treatment has enough promising efficacy and safety to warrant further investigation in a phase III trial. Randomized controlled trials have historically received the greatest consideration in providing reliable evidence of a drug's safety and efficacy. However, Single Arm Non-Randomized Studies (SANRS) have been considered as a valid option by regulators. It has been reported that 66% (49/74) of approvals granted between 1999 and 2014 from the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) were based on nonrandomized experiments in oncology including hematological malignancies, and lymphoma is one of the most common cancer types that has single arm FDA drug approval. The aim of this report is to evaluate the proportion and evolution in time of the use of randomization in interventional phase II clinical trials in adult patients with lymphoma, using a sample of the ClinicalTrials.govdatabase.

Methods: We conducted a predefined search in the United States National Library of Medicine clinical trials database (ClinicalTrials.gov) in the field “condition or disease” for the term "lymphoma" with filters for "interventional studies", "phase 2 studies” and “adults =

Figure 1. Frequency of randomization in interventional phase II clinical trials in adult patients with lymphoma from 2012 to 2022



>18–64 years old" plus "older adults = 65 years and older". We examined all clinical trials that met the inclusion criteria from January 1st, 2012, through December 31st, 2022. We excluded trials with overlapping terminology that did not enroll patients with mature lymphoid neoplasms, such as precursor b-lymphoblastic lymphoma/leukaemia, anaplastic lymphoma kinase (ALK) non-small-cell lung cancer and trials involving very broad disease categories such as "advanced cancer", "hematological malignancies" or "high risk populations" with the exception when a significant proportion of patients with lymphoma was expected to be enrolled. Difficult cases were discussed and decided at the discretion of the authors.

Results: Our search returned 2085 clinical trials, of those we included 1376 in the analysis according to our inclusion/exclusion criteria. We found that between 2012 and 2022 randomization was performed in 12.8% (177/1376) of interventional phase II clinical trials of adult patients with lymphoma. The histogram (Figure 1) shows that the number of trials increased during the analysis period, but the number of randomized clinical trials remained proportionally low.

Conclusions: A small proportion of interventional phase II clinical trials of adult patients with lymphoma use randomization when assessing efficacy and safety of their interventions. The use of data derived from SANRS for clinical decision making should be used with caution by health providers. Randomization should be encouraged by stakeholders.

Keywords: therapeutics and clinical trials in lymphoma, other

No conflicts of interests pertinent to the abstract.

TRANSLATIONAL STUDIES, LIQUID BIOPSY

514 | GENOMIC ABERRATIONS DETECTED IN CIRCULATING TUMOR DNA FROM CEREBROSPINAL FLUID AND PLASMA OF PATIENTS WITH PRIMARY AND SECONDARY CNS LYMPHOMAS WITH NEGATIVE FLOWCYTOMETRY

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Introduction: Primary or secondary central nervous system lymphomas (PCNSL, SCNSL) represent aggressive malignancies with poor prognosis. Their diagnosis is based on magnetic resonance imaging and brain biopsy or cerebrospinal fluid (CSF) analysis by cytology or flow cytometry (FC). The biopsy is highly invasive, with a risk of complications. Cytology and FC have high specificity but limited sensitivity, showing up to 40% of false negative results. The analysis of circulating tumor DNA (ctDNA) in plasma and CSF has the potential to identify the presence of tumor in CNS. The aim of our work was to map the genomic alterations in ctDNA of CNS lymphoma cases with negative FC results.

Methods: We analyzed paired samples (plasma and CSF) of 7 PCNSL and 5 SCNSL patients. Peripheral blood (20 mL) and CSF (10 mL) were collected in special tubes with stabilizing agent (CELL-FREE DNA BCT®, Streck). After double centrifugation, plasma, CSF pellet, and CSF supernatant were obtained. ctDNA was extracted using the QIAamp Circulating Nucleic Acids kit (QIAGEN) and analyzed by custom NGS panel LYNX (PMID: 34082072) together with DNA from CSF pellets. NGS library was prepared by SureSelectXT HS kit (Agilent Technologies) and sequenced on NextSeq (Illumina). LYNX panel enables analysis of various genomic biomarkers in lymphoproliferative disorders—mutations in 67 genes, genome-wide copy number alterations, antigen receptor rearrangements, and common lymphoma translocations.

Results: Our cohort of 12 patients with CNS lymphoma comprised six men and six females of median age 66.5 years, diagnosed during 2021–2022 at our clinic. Genomic aberrations and clonal immunoglobulin rearrangements detected in ctDNA from plasma and CSF supernatant are summarized in Table 1. At diagnosis, we detected clonal abnormalities only in CSF of PCNSL, whereas in SCNSL, plasma was also infiltrated with ctDNA. In relapse or progression of the systemic disease to SCNSL, ctDNA was detected in CSF, not in plasma. In all PCNSL cases, we found pathogenic *MYD88* L265P mutation (in one patient, CSF pellet but not supernatant was positive), clonal IG rearrangements, and in majority of cases complex chromosomal changes. In ctDNA, we also detected *IGH*::*BCL2* in two SCNSL patients and a *BCL6*::*IGH* translocation in one case.

Conclusions: Despite the small number of patients in our cohort, we showed that CSF is the relevant material for the analysis of lymphoma genomic markers in ctDNA, which seems to be a feasible and reliable approach for identifying lymphoma CNS infiltration. Importantly, we were able to confirm the CNS involvement even in samples with negative FC results.

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The research was funded by: Supported by MH CZ - DRO (FNBr, 65269705), AZV_NU22-08-00227, MUNI/A/1224/2022, NPO-NUVR LX22NPO5102.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, liquid biopsy

Conflicts of interests pertinent to the abstract

A. Janikova
Consultant or advisory role ROCHE, NOVARTIS, GILEAD, TAKEDA
Educational grants: ROCHE, GILEAD

Table 1

ID	Diagnosis	Disease status at sampling	Flowcytometry of CSF	Affected genes	Chromosomal changes	Clonal IG rearrangement	Translocation	ctDNA detected in CSF	ctDNA detected in plasma
P1	PCNSL	new dg	10 cells CD19+ kappa+	*MYD88, ETV6, JAK3, NOTCH2, CD79B, PIM1*	ND	IGH	ND	yes	no
P2	PCNSL	new dg	only T-lymphocytes	*MYD88, KMT2D, IKZF3, PIM1, PAX5*	complex	IGK	ND	yes	no
P3	PCNSL	new dg	only T-lymphocytes	*MYD88, BTG1, CD79A, EP300, PAX5*	complex	IGK	ND	yes	no
P4	PCNSL	new dg	inconclusive	*MYD88, BTG1, CARD11, CD79B, MYC, NOTCH1, PIM1*	complex	IGH IGK IGL	ND	yes	no
P5	PCNSL	new dg	only T-lymphocytes	*MYD88, CXCR4, PIM1*	complex	IGH IGK IGL	ND	yes	no
P6	PCNSL	new dg	4 B-lymphocytes CD19+CD20+	*MYD88, CD79A*	ND	IGH	ND	yes	no
P7	PCNSL	relaps	only T-lymphocytes	*MYD88, TP53, BCL2, CDKN2A*	complex	IGH IGK IGL	ND	yes	NA
P8	agressive B-NHL with CNS infiltration	new dg	inconclusive	*KMT2D, BTG1, CREBBP, BCL2, EP300, NOTCH2*	complex	IGK IGL	BCL2/IGH	yes	no
P9A	DLBCL with CNS infiltration	new dg	negative including cytology	*TNFRSF14, ARID1A, KMT2A, KMT2D, CREBBP, TP53, MEF2B, CARD11*	complex	IGK IGL	BCL2/IGH	yes	yes
P9B	DLBCL with CNS infiltration	relaps	only T-lymphocytes	*TNFRSF14, ARID1A, KMT2A, KMT2D, CREBBP, TP53, MEF2B, CARD11, XPO1*	complex	IGK IGL	BCL2/IGH	yes	no
P10A	DLBCL	new dg	NA*	*MYD88, KMT2D, FOXO1, MYC, P2RY8*	complex	IGK	ND	NA*	yes
P10B	DLBCL with CNS infiltration	relaps	negative	*MYD88, KMT2D, MYC, FOXO1, P2RY8*	complex	IGK	ND	yes	no
P11	DLBCL NOS	new dg	inconclusive	*TP53, MYD88, IKZF3, BCL6*	complex	IGH IGK IGL	BCL6/IGH	NA	yes
P12	BL with CNS infiltration	new dg	lymphocytes CD10+CD19+CD20+	*TP53*	complex	IGH IGK IGL	ND	yes	yes

ND - not detected; NA - not analyzed due to the low amount of ctDNA; NA* - not analyzed due to the absence of neural symptoms

515 | CIRCULATING TUMOR DNA MEASUREMENT AND TOTAL METABOLIC TUMOR VOLUME BY PET/CT AS PARAMETERS FOR TUMOR BURDEN AND CLINICAL RESPONSE IN DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Circulating tumor DNA (ctDNA) derives from cell-free DNA (cfDNA) and has been described as a diagnostic and prognostic test in diffuse large B cell lymphoma (DLBCL). Its quantification may be used as a surrogate of tumor burden. Besides, total metabolic tumor volume (TMTV) measured by PET/CT can quantify tumor burden.

Methods: We followed prospectively 18 patients with DLBCL and collected cfDNA before treatment and 2 months after end of chemotherapy. For ctDNA evaluation, after cfDNA extraction, we used next-generation sequencing (NGS) with a panel of 11 genes selected by relevance (*KMT2D*, *TP53*, *CREBBP*, *LRP1B*, *PIM1*, *MYD88*, *PCLO*, *B2M*, *CARD11*, *CD79B and HIST1H1E*). As previously demonstrated, quantitative levels of ctDNA were measured in haploid genome equivalents per milliliter (hGE/mL), determined as the product of total cfDNA concentration and the mean allele fraction of somatic mutations. TMTV was calculated at diagnosis and end of treatment.

Results: The median patients' follow-up was 24.9 months (4.6–46.1). Median age at diagnosis was 59 y (24–84), with 55% female patients and mostly white (78%). Seven patients (39%) were primary gastric lymphoma at presentation, with 5 localized and 2 advanced diseases, according to Lugano TGI lymphoma classification. Among the non-gastric lymphoma patients (n = 11), 5 were localized and 5 had bulky disease. IPI-NCCN was low-intermediate (LI-IPI) in 55% and high-intermediate (HI-IPI) in 33% of patients. After treatment, 14 patients had complete remission (CR) with RCHOP. There were 4 deaths. 9 patients had the ctDNA measurement at diagnosis (DNA1) with higher value then the ctDNA measurement at end of treatment (DNA2). Within this group, 8 patients had CR and the other case died before response assessment. In the other hand, DNA2 was higher than DNA1 in 8 patients, with 4 of these in CR without relapse so far. The other 4 patients had 1 CR with early relapse and 3 with primary refractory disease. One patient had similar results of DNA1 and DNA2 measurement (patient with CR). Higher DNA2 was common in patients with HI-IPI (4 pts, 67%). TMTV at diagnosis correlated with DNA1 (Spearman test ρ 0.69 and p value = 0.03). However, TMTV at end of therapy didn't correlate with DNA2 (ρ 0.34 and p value = 0.25).

Conclusions: With a small sample size and limited NGS painel, we were able to demonstrate a correlation between ctDNA measurement in hGE/mL and clinical response. Patients with a decrease in DNA2 compared to DNA1 had complete remission. DNA2 higher than DNA1 occurred also in patients with response, which could point to a low specificity. TMTV at diagnosis showed good correlation with quantification of disease by ctDNA measurement. To best of our knowledge, this is the first cohort of DLBCL patients from South America with ctDNA evaluation for tumor burden and clinical response.

The research was funded by: Laboratório Fleury and Fundação de Amparo à pesquisa do estado de São Paulo (FAPESP)

Keywords: diagnostic and prognostic biomarkers, liquid biopsy, PET-CT

No conflicts of interests pertinent to the abstract.

516 | DYNAMIC CHANGES IN CIRCULATING EBV-DNA LOAD DURING TREATMENT HAVE PROGNOSTIC VALUES IN EBV+ DLBCL-NOS: A CHINESE COHORT STUDY

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Introduction: EBV-positive diffuse large B-cell lymphoma, not otherwise specified (EBV^+ DLBCL-NOS), is an EBV-positive clonal B-cell lymphoid proliferation and circulating EBV-DNA is a great indicator for prognosis among EBV associated disease. However, the prognostic role of EBV DNA for EBV+ DLBCL-NOS was not identified, especially the dynamic change of EBV-DNA.

Methods: In this retrospective study, we report 66 EBV^+ DLBCL cases among 2137 DLBCL-NOS cases diagnosed from 2013 to 2021 (prevalence of 6.0%). The peripheral whole blood sample was collected for each patient at these time points: at initial diagnosis before treatment, after 3 cycles of treatment, at the end of treatment, and during the follow-up. EBV-DNA copy number in whole blood was quantified by a real-time quantitative PCR. The detection sensitivity was 500 copies per mL and EBV-DNA copy number less than 500 copies/mL was defined as negative.

Results: After a median follow-up of 27 months, progression-free survival (PFS) and overall survival (OS) at 2 years were 39.5% ± 6.2% and 53.6% ± 6.4%, respectively (Figure 1A,B). According to the pretreatment EBV-DNA status, the pretreatment EBV-DNA positive group and pretreatment EBV-DNA negative group had comparable PFS and OS (p = 0.7726 and p = 0.9040, respectively) (Figure 1C,D). Dynamic changes in circulating EBV-DNA copy number were available for 58 out of 66 patients. Patients were divided into three subgroups according to dynamic changes of EBV-DNA status: EBV-DNA persistently negative group (PNG, 24/58), EBV-DNA persistently positive group (PPG, 16/58), and EBV-DNA transformed from positive to negative group (TNG, 18/58); among the three groups, PPG had a clear trend toward worse PFS and OS (p = 0.0527 and p =

Figure1

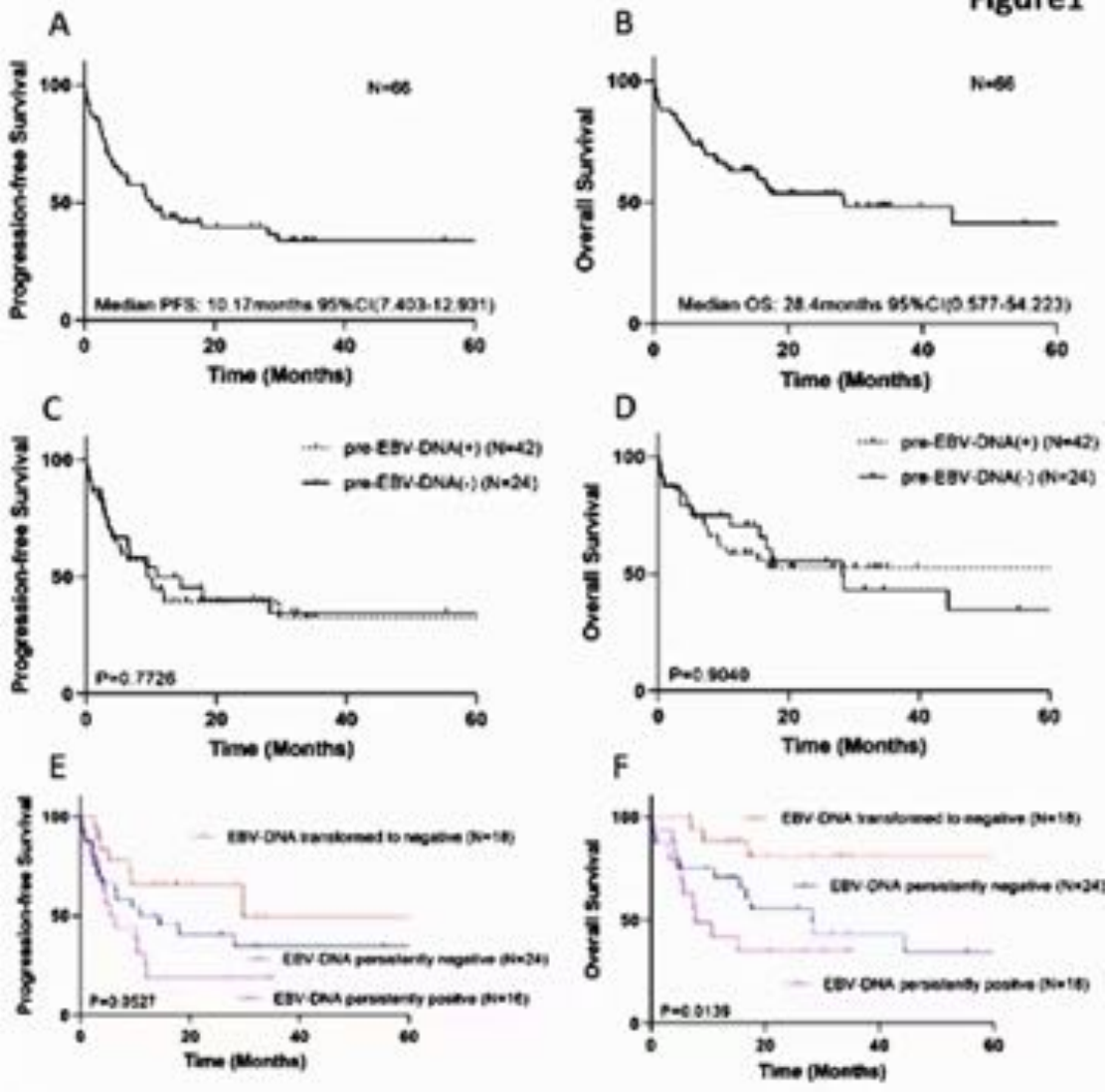

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Table 1. The relation between dynamic Epstein-Barr virus (EBV) DNA and therapy response.

		Total, n		CR		PR		NR		*P* value
		58		25		12		21		
Dynamic EBV-DNA	transformed to negative	18	31.00%	11	44.00%	4	33.30%	3	14.30%	0.044
	persistently positive	16	27.60%	4	16.00%	6	50.00%	6	28.60%	
	persistently negative	24	41.40%	10	40.00%	2	16.70%	12	57.10%	
post-EBV-DNA	positivity	16	38.10%	4	16.00%	6	50.00%	6	28.60%	0.095
	negativity	42	72.41%	21	84.00%	6	50.00%	15	71.40%	
		66		27		12		27		
pre-EBV-DNA	positivity	42	63.60%	17	63.00%	10	83.30%	15	55.60%	0.249
	negativity	24	36.40%	10	37.00%	2	16.70%	12	44.40%	

CR, complete response; NR, no response PR, partial response.

0.0139, respectively) (Figure 1E,F). Decline in EBV copies correlated significantly with treatment response as well; it is noteworthy that dynamic changes of pretreatment EBV-DNA positivity cases rather than post treatment EBV-DNA status were strongly associated with therapy response of CR ($p = 0.034$ and $p = 0.086$, respectively) (Figure 1G).

Conclusion: In conclusion, circulating EBV-DNA level played a vital role in prognostic and monitoring marker for EBV$^+$ DLBCL-NOS.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, risk models

No conflicts of interests pertinent to the abstract.

517 | APPLICABILITY OF IMMUNOGLOBULIN SEQUENCING TO ACCURATELY MONITOR DISEASE: AN ANALYSIS OF UNIQUENESS AMONG DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS TESTED BY CLONOSEQ

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Introduction: Diffuse Large B-Cell Lymphoma (DLBCL), an aggressive form of non-Hodgkin lymphoma, most commonly affects older adults. ~80% of patients achieve complete response to frontline therapy; roughly half are cured while half relapse and receive salvage treatment such as transplant or CAR-T therapy which may be curative. Due to the aggressiveness of DLBCL and therapies offering potential cure, there is growing interest in a monitoring tool that provides more accurate information than standard clinical imaging. clonoSEQ® is a next-generation sequencing assay, which monitors measurable residual disease (MRD) levels from plasma of DLBCL patients. Using data from 1268 patients we assessed Ig loci uniqueness.

Methods: Following identification of a dominant sequence(s) in a high tumor burden sample, the clonoSEQ algorithm quantifies tumor-associated sequences in MRD samples. The algorithm assigns a uniqueness score to each dominant sequence based on analyses of Ig locus V, D, and J segments and non-templated nucleotides. This score reflects the probability a sequence could be independently recreated in a non-malignant cell, including in another person, and is incorporated into the limit of detection (LOD). Sequences with a lower uniqueness must be observed at a higher rate to be above the LOD and reflect confidence they are tumor related.

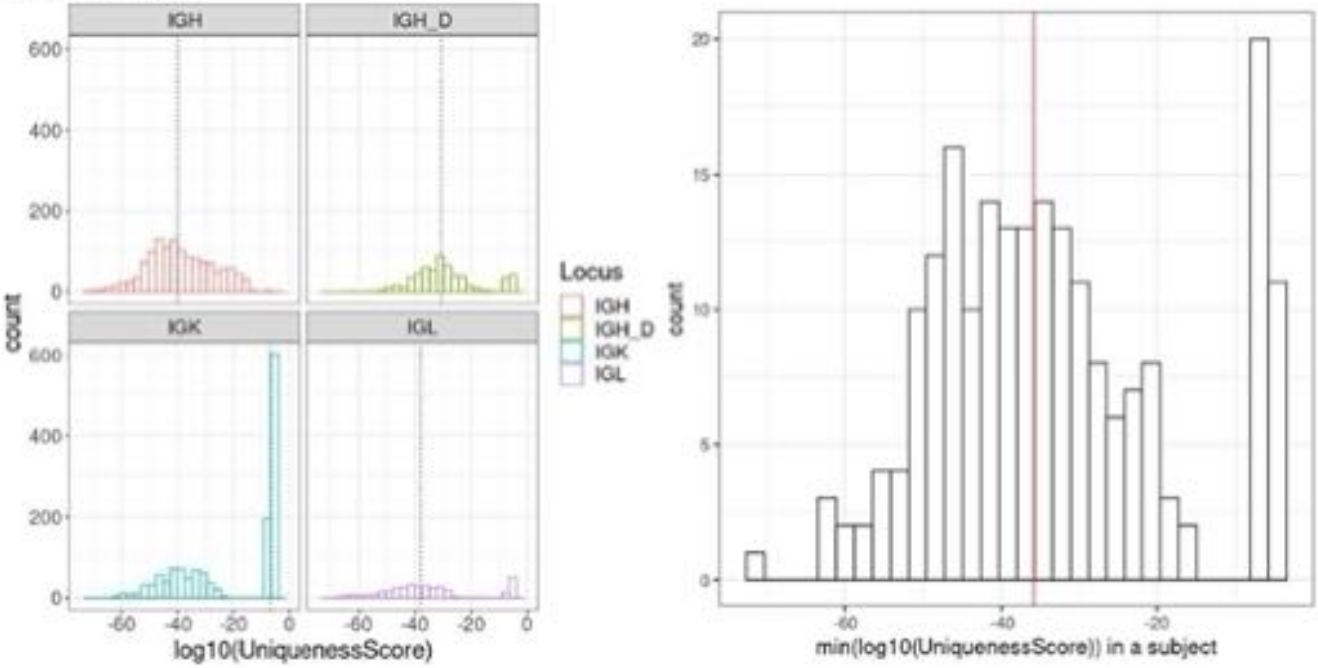
To assess the uniqueness of sequences detected across DLBCL patients, we examined our database containing 3657 dominant sequences from 1268 patients. 969 of these patients are from 27 clinical studies, and 302 are from use of the commercial assay. We assessed the dominant sequences for their uniqueness distribution across IgH, IgK, and IgL loci.

Results: Across the population of 1268 DLBCL patients and 3657 dominant sequences, there was a range of 1–9 dominant sequences with 1115 (87.9%) patients having 1–4 (avg 2.89; med 3). We found that 1187 (93.6%) patients had at least one dominant IgH sequence. The remaining 81 (6.4%) patients had only dominant light chain sequences with 66 (5.2%) patients having IgK only.

We assessed the distribution of uniqueness across the Ig loci in these patients. Figure 1a shows that IgH sequences were most unique, followed by IgL, IgH (D-J segments), and IgK. Figure 1b indicates the uniqueness score for each patient with only one dominant sequence, with just 31 (2.4%) subjects with expected 'backgrounds' of >1/100,000 of all Ig sequences.

Conclusions: Our analysis of >1200 patients demonstrates that the majority rely on multiple dominant sequences for disease tracking. In a small subset of patients (2.4%), disease is only trackable using a lower uniqueness sequence. In these cases, the LOD serves as a guide to discern the probability of the sequence being present above background.

Figure 1a & b



Keyword: diagnostic and prognostic biomarkers

Conflicts of interests pertinent to the abstract

A. Jacob
Employment or leadership position: Adaptive Biotechnologies
Stock ownership: yes, as an employee

L. W. Lee
Employment or leadership position: Adaptive Biotechnologies
Stock ownership: yes, as an employee

K. Akers
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I. Kirsch
Employment or leadership position: Adaptive Biotechnologies
Stock ownership: yes, as an employee

H. Simmons
Employment or leadership position: Adaptive Biotechnoloigies
Stock ownership: yes, as an employee

IMAGING

518 | COMBINING BASELINE TOTAL METABOLIC TUMOR VOLUME AND BETA-2-MICROGLOBULIN LEVELS PREDICTS OUTCOMES IN HIGH BURDEN FOLLICULAR LYMPHOMA

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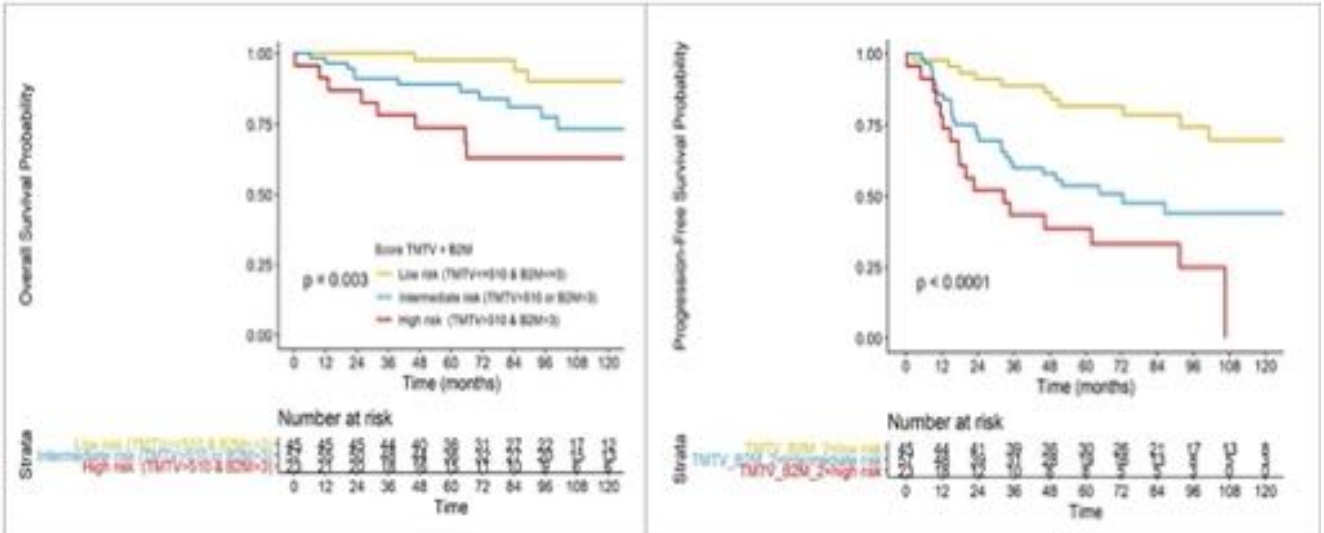
Introduction: Follicular lymphoma (FL) usually presents an indolent course with repeated events of disease progression but treatment-free time intervals and patients' survival are reduced at each relapse. Many prognostic scores exist but few are used in practice due to their complexity. Total metabolic tumor volume (TMTV) has demonstrated a strong prognostic value in FL and its routine use is increasing in academic centers. We aim to explore the predictive value of a simple prognostic score based on TMTV and beta-2-microglobulin (B2M) levels at baseline in high tumor burden FL to identify patients with the highest unmet medical need.

Methods: In this monocentric retrospective analysis, we enrolled adult patients admitted to our hospital between 2006 and 2018 and fulfilling the following inclusion criteria: grade 1 to 3A FL with at least one high tumor burden criteria defined by the Groupe d'Etude des Lymphomes Folliculaires (GELF), available PET-CT images collected before first-line standard immunochemotherapy start and suitable for TMTV assessment. Baseline TMTV was determined using the 41% SUVmax threshold method. B2M levels were routinely measured at diagnosis. Primary endpoints were progression-free survival (PFS) and overall survival (OS) according to a score combining TMTV and B2M.

Results: We included 126 FL patients in this analysis. Median age at time of treatment was 61 years (55; 57). Patients displayed advanced-stage disease (n = 112, 88.9%), intermediate (n = 51, 40.8%) or high (n = 62, 49.6%) FLIPI and intermediate (n = 40, 33.3%) or high (n = 31, 25.8%) PRIMA-PI scores. Median baseline SUVmax and TMTV were 12.1 (10; 17) and 606 mm^3 (268;1219), respectively. Baseline B2M levels were measured for 125 (97%) patients and >3 mg/L in 30 (24%). Treatment regimens used were mostly R-CHOP



like (n = 109, 86.5%) and R-lenalidomide (n = 9, 7.1%). 80 patients (63.5%) received a maintenance therapy during 24 months. We defined three risk categories : (i) Low risk (n = 45, 36%): TMTV ≤510 mm^3 and B2M ≤3 mg/L; (ii) Intermediate risk (n = 57, 45.6%) : TMTV >510 mm^3 or B2M >3 mg/L ; (iii) High risk (n = 23, 18.4%) : TMTV >510 mm^3 and B2M >3 mg/L. With a median follow-up of 83 (52; 116) months, the 5-year PFS was 81.7% (95% CI: 71–94), 53.7% (95% CI: 41.8–69) and 38.6% (95% CI: 23–65) in the low, intermediate and high risk groups, respectively ($p < 0.0001$). Five-year OS was based on 14 deaths and estimated at 96.1% (95% CI: 91–100), 89.1% (95% CI: 81.2–97.7) and 73.7% (95% CI: 57.6–94.2) in the low, intermediate and high risk groups, respectively ($p = 0.003$).

Conclusion: Combining TMTV and B2M in a simple score in previously untreated FL patients with high tumor burden may help physicians to identify very high risk patients with poorer outcomes. Novel therapeutic approaches in first-line are warranted in this population. A large prospective cohort study is needed to reproduce and confirm the relevance of this prognostic score.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, PET-CT

No conflicts of interests pertinent to the abstract.

519 | PROGNOSTIC VALUE OF METABOLIC PARAMETERS OF BASELINE PET/CT IN PATIENTS WITH DOUBLE EXPRESSION TYPES OF DIFFUSE LARGE B-CELL LYMPHOMA

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Purpose To explore the value of baseline PET/CT parameters for predicting prognosis in patients with double expression lymphoma (DEL).

Methods We retrospectively analyzed the clinical and [^{18}F]FDG PET/CT imaging data of 118 patients diagnosed with DLBCL by pathological examination at two hospitals: 58 cases at the Nanjing Drum Tower Hospital and 60 cases at the First Affiliated Hospital of Nanjing Medical University, from October 2015 to September 2022. We used receiver operating characteristic (ROC) curve analysis to determine the optimal threshold for the maximum standardized uptake value (SUVmax), the total metabolic tumor volume (TMTV), and the total lesion glycolysis (TLG) in predicting overall survival (OS) rate. Kaplan-Meier survival analysis, univariate and multivariate analyses were performed to predict OS rate, construct a survival prediction model, plot a calibration curve for the model, a time-dependent area under the ROC curve (tdAUC), and a decision curve analysis (DCA) curve, and calculate the C-index of the model.

Results: As of the last follow-up, 25 patients had died, and the OS rate was 78.8%. The area under the curve (AUC) of the ROC curve for TMTV was 0.705, with corresponding cutoff values of 230.9 cm^3. In multivariate analysis, Eastern Cooperative Oncology Group performance status (ECOG PS) (HR = 3.989, $p = 0.002$) and TMTV (HR = 4.042, $p < 0.008$) were identified as independent predictors of OS. A combined model of ECOG PS and TMTV was found to be superior to IPI in predicting OS.

Conclusion: TMTV, a metabolic index, and ECOG PS, a clinical risk factor, are independent predictors of OS in patients with DEL, and their combination can provide more accurate prognostic predictions.

Keywords: [^{18}F]FDG-PET/CT, diffuse large B-cell lymphoma, double expression lymphoma, Eastern Cooperative Oncology Group performance status, prognosis, total metabolic tumor volume

Encore Abstract - previously submitted to EHA 2023

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, PET-CT

No conflicts of interests pertinent to the abstract.

520 | PROGNOSTIC SIGNIFICANCE OF SEQUENTIAL 18F-FDG PET/CT DURING THE TREATMENT OF ANTHRACYCLINE-CONTAINING FRONTLINE CHEMOTHERAPY IN PERIPHERAL T CELL LYMPHOMAS

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Introduction: Despite the prognostic significance of ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography-computed tomography (PET/CT) assessment has important implications on determining the response-adapted therapy in patients with peripheral T-cell lymphomas (PTCLs), an optimal timing of the use and clinical application of PET/CT-based response are still up in the air. The aim of this study was to explore the prognostic impact of sequential ^{18}F-FDG PET/CT analysis in patients with newly diagnosed PTCLs who treated with frontline anthracycline-based chemotherapy.

Methods: Between February 2006 and September 2022, 143 patients with newly diagnosed PTCLs were included. All patients were treated with 6 cycles of anthracycline-containing chemotherapy.

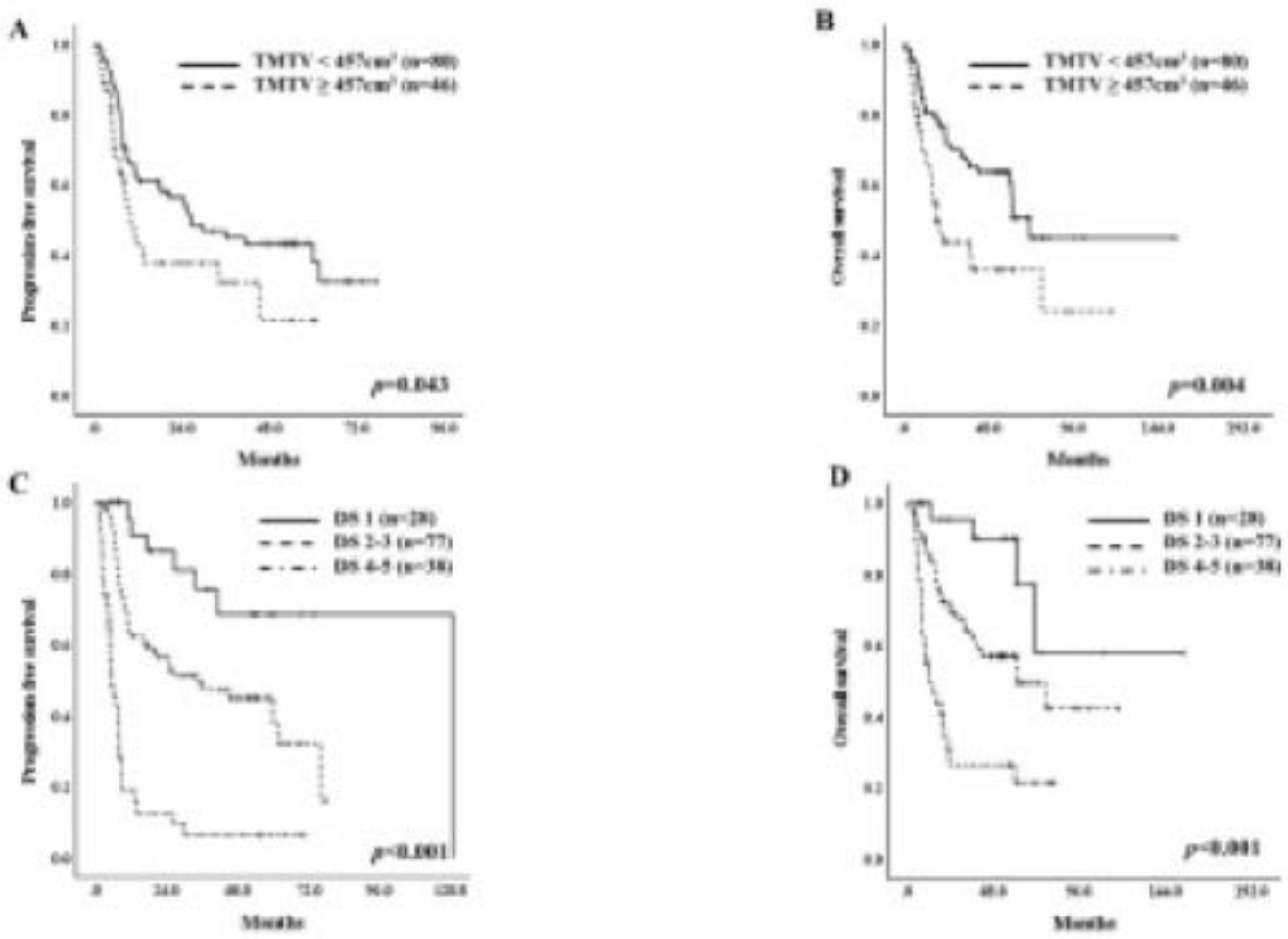
Sequential ^{18}F-FDG PET/CT were obtained at the time of diagnosis, after three cycles of chemotherapy and finally at the end of chemotherapy. Baseline total metabolic tumor volume (TMTV) was computed with the sum of SUV2.5 threshold method, and the PET/CT response were assessed using the five-point scale (5-PS) of Deauville criteria.

Results: Baseline MTV could be calculated in 126 patients, and the cut-off value of TMTV according to ROC analysis was 457.0 cm^3 (Sensitivity 45.0%, specificity 74.0%). With a median follow-up of 52.0 months (range 3.8–153.9 months), patients with high TMTV more than cut-off value had inferior PFS and OS than those with low TMTV (PFS, 9.8 months vs. 26.5 months, HR 1.600, 95% CI 1.010–2.671, $p = 0.043$; OS, 18.9 months vs. 71.2 months, HR 2.135, 95% CI 1.261–3.615, $p = 0.004$, Figure 1A, B). Interim ^{18}F-FDG PET/CT assessment was available in all 143 patients. When patients were categorized with three subgroups as response with grade 1, grade 2 and 3, and grade 4–5, PFS and OS showed significant difference according to interim visual assessment (PFS, 120.7 months vs. 34.1 months vs. 5.1 months, $p < 0.001$; OS, not reached vs. 61.1 months vs. 12.1 months, $p < 0.001$, Figure 1C, D), respectively. Among 77 patients who were assessed as grade 2 or 3 in interim PET/CT analysis, 19 patients (26.3%) turned over a remnant tumor metabolism or progressed at final PET response assessment. Moreover, the outcome of patients with interim grade 2 or 3 showed the significant differences based on the final achievement of complete metabolic response or not in PFS and OS (PFS, 59.9 months vs. 7.2 months, HR 4.754, 95% CI 2.267–9.971, $p < 0.001$; OS, not reached vs. 24.0 months, HR 3.706, 95% CI 1.592–8.630, $p = 0.001$), respectively.

Conclusion: High baseline TMTV could indicate a poor response for the anthracycline-based chemotherapy in PTCLs. Interim PET/CT response based on visual assessment could be a valuable prediction factor of disease progression and survival outcome in the treatment of PTCLs. Particularly, patients with grade 4 out of interim 5-PS should be considered with an alternative therapeutic plan or intensified chemotherapy.

Keywords: aggressive T-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.



521 | INVESTIGATING THE SAFETY AND EFFICACY OF IV FENTANYL FOR BROWN FAT MITIGATION IN ^{18}FDG-PET/CT IN PEDIATRIC ONCOLOGY: A MULTI-INSTITUTIONAL EXPERIENCE

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Background: Brown fat is a metabolically active tissue which can take up the ^{18}FDG tracer used in PET/CT scans, potentially leading to diagnostic uncertainty. Metabolically active brown fat is more prevalent in children than adults with recent studies demonstrating an incidence of brown fat uptake in 34%–40% of children with cancer. The resultant diagnostic uncertainty can impact clinicians' ability to interpret scans in pediatric oncology patients and has the potential to result in unnecessary invasive procedures, upstaged risk stratification, or additional therapy. A lack of clinical consensus remains regarding the safest and most effective method for suppressing brown fat uptake of ^{18}FDG.

Objective: We report the first multi-institutional analysis of the use of fentanyl to mitigate brown fat uptake of ^{18}FDG in patients receiving PET/CT scans with a focus on safety in pediatric oncology patients.

Methods: This is a multi-institutional, retrospective review of pediatric (aged >1 year to <25 years) oncology patients undergoing ^{18}FDG-PET/CT scans following pretreatment with fentanyl from April 2021 to January of 2023. Scans were conducted per institutional treatment regimens. Patients received a weight based dose of fentanyl 10 min prior to tracer injection. Vital signs, clinical outcomes, and presence of brown fat was recorded. Similar data was recorded on patients who underwent PET/CT scans without fentanyl premedication during this same time period to serve as the control group.

Results: Seventy scans were completed with fentanyl pre-treatment. Patients were evenly split by sex (n = 34, 49% male) with median age of 15 (range 3 y–23 y). Eleven patients (16%) had brown fat uptake and was most common in cervical (n = 9, 82%) supraclavicular (n = 9, 82%), intercostal (n = 2, 18%) and pararenal (n = 4, 36%) areas. There were no adverse events including zero incidents of bradycardia, hypoxia, or hypotension in the pretreated fentanyl cohort.

Conclusion: Fentanyl, used for brown fat mitigation in pediatric oncology patients, was well tolerated without any adverse safety events. The observed incidence of brown fat tracer uptake in patients receiving fentanyl pre-medication was higher than previously reported in the literature (16% vs. 6.7%) but lower than reported baseline incidence in the literature (16% vs. 34%–40%). Larger, prospective, multi-institutional clinical trials are warranted to further explore the efficacy of fentanyl for brown fat mitigation pediatric oncology patients.

Keyword: PET-CT

No conflicts of interests pertinent to the abstract.

HODGKIN LYMPHOMA

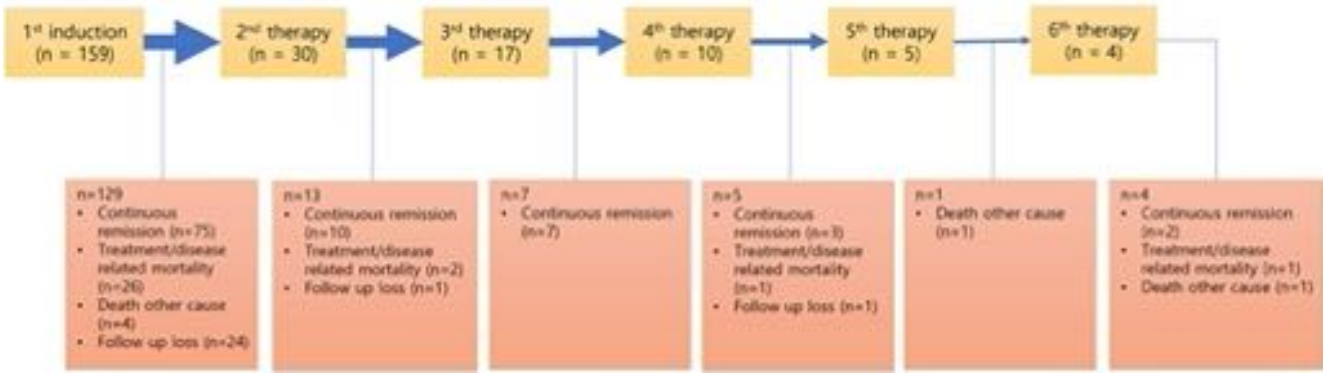
522 | OUTCOMES IN ELDERLY HODGKIN LYMPHOMA: RESULTS FROM KOREAN MULTICENTER COHORT

E. Lee[1], H. Eom[1], D. H. Yoon[2], K. Kang[3], S. Y. Oh[4], H. J. Kim[5], W. S. Kim[6], B. S. Sohn[7], J. Park[8], J. H. Yi[9], Y. Mun[10], J. Jo[11], S. I. Lee[12], J. Kwak[13], M. K. Kim[14], J. H. Won[15], H. J. Jun[16]
[1]*National Cancer Center, Goyang-si, Gyeonggi-do, Korea,* [2]*Asan Medical Center, University of Ulsan College of Medicine, Departments of Oncology, Seoul, Korea,* [3]*Korea University College of Medicine, Division of Hematology-Oncology, Department of Internal Medicine, Seoul, Korea,* [4]*Dong-A University College of Medicine, Department of Internal Medicine, Busan, Korea,* [5]*Hallym University Sacred Heart Hospital, Anyang, Korea,* [6]*Samsung Medical Center, Sungkyunkwan University School of Medicine, Division of Hematology and Oncology, Department of Medicine, Seoul, Korea,* [7]*Sanggye Paik Hospital, Inje University College of Medicine, Department of Internal Medicine, Seoul, Korea,* [8]*Gachon University Gil Medical Center, Incheon Regional Cancer Center, Gachon University College of Medicine, Department of Internal Medicine, Incheon, Korea,* [9]*Chung-Ang University Hospital, Department of Internal Medicine, Seoul, Korea,* [10]*Ewha Womans University College of Medicine, Seoul, Korea,* [11]*Ulsan University Hospital, University of Ulsan College of Medicine, Department of Hematology and Oncology, Ulsan, Korea,* [12]*Dankook University Hospital, Dankook University College of Medicine, Division of Hematology-Oncology, Department of Internal Medicine, Cheonan, Korea,* [13]*Chonbuk National University Hospital, Department of Internal Medicine, Jeonju, Korea,* [14]*Yeungnam University College of Medicine, Department of Internal Medicine, Daegu, Korea,* [15]*Soonchunhyang University Hospital, Soonchunhyang University College of Medicine, Department of Hematology-Oncology, Seoul, Korea,* [16]*Seoul Medical Center, Hematology and Medical Oncology, Department of Internal Medicine, Seoul, Korea*

Introduction: Hodgkin lymphoma (HL) is a rare disease especially in Asian known to have good prognosis. However, in elderly patients (pts), due to comorbidities and poorer tolerance to treatment, the survival rate is not as good as in younger pts. This study aims to enhance understanding of current status of elderly HL pts in Korea.

Methods: We analyzed a total of 159 HL pts who were diagnosed between 1999 and 2018 from 16 medical centers in Korea retrospectively. Pts aged 60 years (yrs) or older were included and clinical data were collected.

Results: The median age at diagnosis was 69 yrs (range 60–85) and male was predominant (n = 110, 69.2%). More than half were between the ages of 60 to 69 yrs (n = 86, 54.1%), 39.6% (n = 63) was between 70 to 79 yrs, 6.2% (n = 10) was older than 80 yrs. Forty-eight pts (30.2%) had at least 2 comorbidities or prior malignancy history. Advanced disease as Lugano stage III and IV were presented in 72.3% (n = 115) of patients. Pts with absence of B symptoms (n = 99, 62.3%), non-bulky disease (n = 152, 95.6%) and absence of bone marrow involvement (n = 109, 68.5%) were predominant. Elevation of lactate dehydrogenase (LDH) was observed in 44.0% (n = 70).



Most of pts (n = 143, 89.9%) presented CD30 positive malignant cells.

Among 159 pts, 1 was cured by radiotherapy alone and the other 158 received induction chemotherapy. Median 5 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was the most common first (1st) line treatment (n = 148, 93.1%). The average dose intensity of ABVD was 86.7% for each cycle. Average intensity of bleomycin dosage was 84.9% for each cycle and 41.9% (n = 62) of pts received reduced dose of bleomycin. Except 39 pts whose treatment responses were not evaluable, response rate including complete remission and partial remission after 1st line therapy was 96.7% in total population. Thirty pts received second (2nd) line chemotherapy. The major cause of not proceeding to 2nd line therapy was continuous remission after 1st treatment (n = 75, 58.1%).

Grade 3, 4 adverse events (AE) were observed in 46.8% (n = 74). Cytopenia was the most common grade 3, 4 AE. Among 148 pts who received ABVD induction, pneumonitis was observed in 27.0% (n = 40) and among these pts, 55.0% presented grade 3, 4 AE.

The 1st 3-yr progression-free survival rate was 73.1% (95% confidence interval [CI], 63.38–80.64) and 5-yr overall survival (OS) was 65.1% (95% CI 55.53–73.04). B symptom (hazard ratio [HR] 1.96, $p = 0.016$), poor performance status (HR 1.95, $p = 0.000$), elevated LDH (HR 1.17, $p = 0.031$), relapse/refractory disease (HR 1.27, $p = 0.000$), pulmonary AE (HR 2.50, $p = 0.001$) were adverse factors for OS.

Conclusions: Although the major portion of Korean elderly HL pts presented advanced-stage disease and received reduced intensity of induction, treatment response was adequate. Pneumonitis was the most important adverse factor for OS.

Keyword: Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

523 | THE LOW-RISK EARLY-STAGE HODGKIN LYMPHOMA PATIENTS WITH INADEQUATE RESPONSE TO CHEMOTHERAPY. THE PRELIMINARY EXPERIENCE FROM THE RAFTING TRIAL

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Introduction: Early-stage Hodgkin Lymphoma (eHL) treated with a combined modality approach (CMT): chemotherapy (CT) and radiotherapy (RT) is a highly curable disease. However, for 70% of eHL patients (pts.) CT alone might be sufficient for cure. The RAFTING trial is a phase 2, multicenter, international prospective study investigating risk-adapted treatment strategy in eHL pts. We hypothesized that CT alone will be sufficient for to cure low-risk pts. Here we would like to present the clinical characteristics of low-risk pts. for whom CT was not sufficient to achieve a complete response (CR).

Methods: Treatment intensity in RAFTING is tailored to two risk categories: low or high risk. Low-risk pts. are defined by low baseline metabolic tumor volume (MTV) and negative interim PET after 2 ABVD cycles. High-risk pts. were defined by high baseline MTV and/or positive iPET2. Within the low-risk group the pts. without any risk factors according to modified EORTC (mEORTC) criteria (largest nodal mass (LNM) 5–10 cm, Age > 50 yo, ESR > 50 mm/h, ≥4 nodal areas (NA)) (group 1a) are treated with 2 ABVD cycles only whereas pts. with at least 1 risk factor (group 1b)—with 4 ABVD cycles. High-risk pts. (group 3) receive "triple" therapy (4 ABVD cycles, RT and nivolumab for 12 months; RT-NIV). In case of "limited relapse" (i.e., within initially involved lymph nodes and/or up to 3 new nodal areas) pts. receive delayed RT-NIV.

Results: In a per-protocol analysis, out of 77 stratified pts. in March 2023, seven pts. (9%) with low-risk disease, had inadequate response to ABVD alone (defined as achievement less than CR or early relapse (<6 months after the end of the CT): 2 pts. from group 1a and 5 pts. from group 1b. Specifically, one pt. from Group 1a had an extended and symptomatic (B symptoms) relapse, and underwent salvage therapy with ASCT and two pts. from group 1b were withdrawn due to PI decision. While 4 pts. (1 in Group 1a and 3 in Group 1b) with less than CR (2 pts.) or early relapse (2 pts.) received RT + NIV.

The most frequent risk factor among 1b pts. was LNM, which was observed in 4 pts., age >50 yo—in 2 patients, and ≥4 NA—in 1 pt. More than 1 risk factor had 2 pts. In 4 cases the confirmatory biopsy was done and was positive for HL in 3 out of 4 cases.

Conclusion: The frequency of inadequate response after CT alone observed in the RAFTING trial was similar to that reported by the literature. The most frequent adverse prognostic factor presented in these small pts. subset was a LNM.

Keywords: combination therapies, Hodgkin lymphoma, radiation therapy

No conflicts of interests pertinent to the abstract.

524 | ESCALATED BEACOPP X 2 + ABVD X 4 IS SUPERIOR TO ABVD X 6 IN ADVANCE STAGE CLASSICAL HODGKIN LYMPHOMA: EXPERIENCE IN A TERTIARY CENTER

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Introduction: Classical Hodgkin lymphoma (cHL) is a curable disease but results in advanced stages are suboptimal when treated with standard treatment ABVD with 10%–15% of primary refractoriness and 30% of relapses, although 5 years overall survival (OS) around 88%–90%.

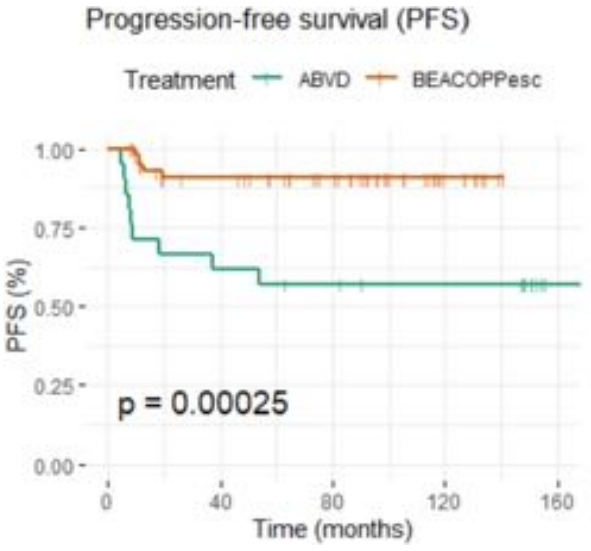
First-line treatment with more intensive schemes such as escalated BEACOPP has improved progression-free survival (PFS) in these patients, although associating greater toxicity. However, escalated BEACOPP did not improve OS when compared to ABVD due to the efficacy of rescue treatments, but assuming a high toxic cost. We present our experience to optimize first-line treatment in advanced cHL.

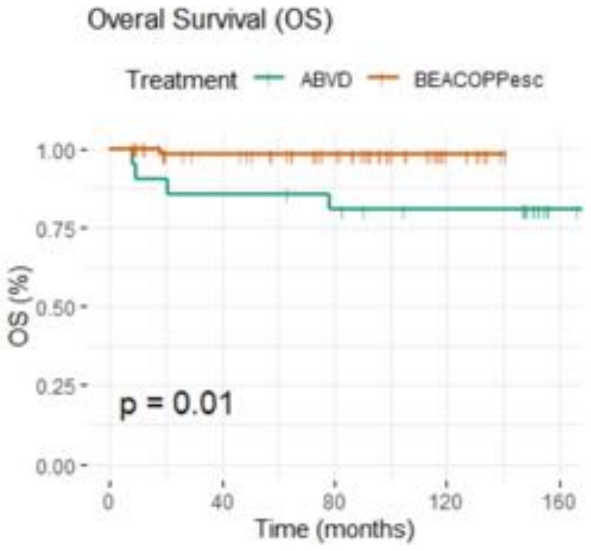
Methods: We retrospectively analyzed patients with advanced stage cHL (IIB-IV) treated with curative intent in our center between December 2008 and December 2022 (Table 1). In the period 2008–2011, patients were treated with ABVD x 6. During the period 2011–2022, we implemented a strategy intermediate PET guided (PET2) after escalated BEACOPP (x 2). With PET2 negative, we continued with ABVD/AVD x 4; in PET2 positive patients we continued with escalated BEACOPP x 4. Both groups received radiotherapy on bulky masses. We evaluate the efficacy of this strategy by comparing results and toxicity in the two study periods.

Results: In the 2008–11 period, 21 patients received standard treatment with ABVD and during the 2011–22 period, 60 the intensified one (S). In PET2, 55 (91.6%) of patients in the intensified

TABLE 1 Patients characteristics.

	Standard $N = 21$	Intensified $N = 60$	p overall
Age, median (range)	36.6 (21-69)	34.8 (15-61)	0.527
Male	16 (76.2%)	32 (53.3%)	0.115
Histological subtype			0.750
MC	4 (19%)	10 (16.7%)	
NE	12 (57.1%)	28 (46.7%)	
Stage			
IIB	10 (47.6%)	13 (21.7%)	0.253
IIIA–B	3 (14.28%)	17 (28.3%)	
IVA–B	8 (38.1%)	30 (50%)	
Median IPS	2 (1-6)	2 (0-6)	0.282





group achieved CR and 5 (8.4%) PR versus 5 (23.8%) CR, 14 (66.7%) PR and 2 (9.52%) refractory patients in the ABVD group. At the end of treatment, 58 patients (96.6%) achieved CR in the intensified treatment group and 15 (71.4%) in the ABVD group. There where 4 (19%) refractory patients in ABVD group versus 2 (3.3%) in the intensified group. PFS for the intensified treatment group was 90.8% at 5 years versus 57.1% for the ABVD group ($p = 0.00025$). OS for the intensified treatment group was 98.1% versus 85.7% for the ABVD group at 5 years ($p = 0.01$).

The incidence of admissions for febrile neutropenia tended to be higher in the intensified group (15% vs. 4.76%, $p = 0.44$) and no significant differences were observed in the incidence of secondary malignancies or infertility. There were no toxic deaths in any group.

Conclusions: Our strategy in advanced cHL guided by PET2 decreases the rate of primary refractories and relapses with a high PFS. In addition, it has shown an adequate initial safety profile and limited long-term toxicity by avoiding rescue treatments with other intensive regimens and/or hematopoietic stem cell transplantation.

Keywords: Hodkin lymphoma, PET-CT

No conflicts of interests pertinent to the abstract.

526 | PROSPECTIVE REAL WORLD EVIDENCE: USE OF BRENTUXIMAB VEDOTIN AS CONSOLIDATION THERAPY AFTER AUTOLOGOUS TRANSPLANT IN HODGKIN LYMPHOMA. AN INTERIM ANALYSIS, ON BEHALF OF GATLA

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Introduction: Consolidation therapy with brentuximab vedotin (BV) after autologous stem cell transplant (auto-HCT) in the AETHERA trial, reported improved progression free survival (PFS) in patients with classical Hodgkin lymphoma (cHL) with high risk of relapse but no difference in OS. Few retrospective reports of this indication have been published. The aim of this study is to describe with a prospective Argentinian registry of all patients who undergo Auto-SCT, the selection criteria, outcomes and safety of BV as consolidation therapy.

Methods: We prospectively enrolled relapsed/refractory (R/R) HL who underwent auto-HCT between September 2021 and March 2023 from different transplant centers in Argentina. We analyzed patients' characteristics, previous lines of treatment, response before and after transplant. We recollected information regarding factors that influenced BV indication and safety of the treatment. All patients are being followed for PFS and OS.

Results: Sixty-one patients from 13 centers were reported. Twenty-eight (59%) of 47 evaluated patients received BV as consolidation therapy. Sixty-eight % of the patients treated with BV had 1 high risk criteria from the AETHERA trial, 25% had 2 and only 3% had all 3. The most frequent of these criteria was primary refractory disease, seen in 64% patients, followed by early relapsed in 36%. The median time from auto-HCT to first infusion of BV was 2.5 months (IQR 1.7–4.9). The median cycles of BV was 10.5 (IQR7.5-15-5).

Of the 53 evaluable patients, 57% only received 1 salvage therapies, 24% 2 and 19% received 3 or more salvage therapies before Auto-SCT. Twenty-nine (55%) patients received BV before auto-HCT. All patients had PET CT before auto-SCT, a Deauville score (DS) of 1–3; 4; 5 was reported in 89%, 6% and 2% respectively. After auto-SCT, 86%, of 36 evaluated patients were in complete metabolic response with a DS 1–3.

Fourteen patients (26%, of 53 evaluated) had an adverse event (AE). The most common were peripheral neuropathy in 13%, and infections in 6%. Of all AE, 6 (43%) were grade 1, 7 (50%) grade 2 and 1 (7%) grade 3, no grade 4 or 5 AE were reported. BV was temporarily suspended in 4 (28%) patients, and permanently discontinued in 2 (14%). Finally, 2 (14%) patients had complete resolution of the adverse event while 11 (78%) are still active.

Conclusions: This is the only prospective evidence describing the acceptance and indication of consolidation therapy with BV in a patient with RR HL. Most of the indications were in patients with high-risk features according to the pivotal trial. This real world cohort includes a higher proportion of patients with complete metabolic response at time of auto-SCT compared with the AETHERA Trial. Follow-up time is still short, and recruitment continues. With a larger number of patients and longer follow up progression-free survival and overall survival will be reported.

The research was funded by: GATLA received a grant from Takeda

Keyword: Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

527 | TREATMENT STRATEGIES AND PROGNOSTIC FACTORS FOR THE OUTCOME OF PATIENTS WITH HODGKIN LYMPHOMA EXPERIENCING VERY LATE RELAPSES AFTER CHEMOTHERAPY ± RADIOTHERAPY

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Background: Despite the excellent long-term outcome of patients with Hodgkin Lymphoma (HL), some cases will be primary refractory or will eventually relapse, mainly within the first 2 years from diagnosis. Patients with sustained complete remission (CR) for ≥5 years are generally considered "cured". However, Very Late Relapses (VLRs), occurring ≥5 years after treatment initiation, are a non-negligible event and possibly comprise a distinct entity with unique characteristics.

Aim: The aim of the current study is to describe the treatment strategies adopted for patients with VLRs as well as their outcome and relevant prognostic factors.

Patients/Methods: Patients with HL who experienced VLRs ≥5 years after treatment Initiation with chemotherapy ± radiotherapy (CT±RT), were identified retrospectively from the databases of 8 referral centers. Statistical endpoints were the estimation of time to second failure (TT2F) and Overall Survival after failure (O2S).

Results: 145 patients with VLRs were identified. The median age was 49 years (19–82), 69% were males and 18% were ≥65 years old. In 23% of the patients, relapse occurred >15 years after the initial diagnosis. Reinduction with the same regimen was given in 24% of the cases, and 26% were indented to proceeded to high-dose therapy and autologous stem cell transplantation (HDT/ASCT). The 5- and 10-year TT2F were 57% and 53% and the 10-year and 15-year O2S were 59% and 46% respectively. Among 52 deaths, only 28 were disease-related whereas others were attributed to secondary malignancies or unrelated causes. Re-induction with the same regimen did not significantly affect TTF2 and O2S. Despite the numerical difference regarding 5-year FF2P for patients <65 years old who received HDT/ASCT, this was not statistical significant and there was no difference at 10 years. In multivariate analysis B-symptoms, extranodal disease, age ≥65 at relapse, and occurrence of relapse <15 years from diagnosis were independent adverse prognostic factors for TT2F (p = 0.03, 0.003, 0.005 and 0.006 respectively). Anemia, age ≥ 65 and extranodal disease at relapse were also associated with impaired O2S (p = 0.02, <0.001 and 0.044 respectively). We assigned one point to each of the aforementioned unfavorable factors and constructed prognostic scores. Patients combining 2–3 adverse characteristics had significantly compromised outcomes. None of the patients survived at 10-years with the 10-year disease-free-survival being only 36%.

Conclusion: The prognosis of VLRs does not appear very favorable, however a considerable proportion of patients were ≥65 years old at the time of relapse when treatment options are limited and also, many patients succumb to disease-unrelated causes. Treatment approaches were heterogenous. In our study B-symptoms, extranodal disease and age ≥65 at relapse were the most important prognostic factors for the outcome of patients with VLRs.

Keyword: Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

528 | LATE EFFECTS AFTER TREATMENT OF HODGKIN LYMPHOMA, A SINGLE CENTRE EXPERIENCE

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Introduction: Classical Hodgkin Lymphoma (cHL) has an incredibly high survival rate, exceeding 80% at 10 years. Continuous improvement in treatment strategies led to an increased number of survivors in the community. Most common complications encountered are secondary malignant neoplasms (SMN) and cardiovascular (CV) toxicity.

Methods: We conducted a single-centre retrospective study including 157 patients diagnosed and treated for cHL between 1974 and 2016.

Results: Median age at diagnosis in our cohort is 30 years old. Ninety-six patients (61%) had a stage 1 or 2 disease. Front line treatment consisted of radiotherapy alone for 3 patients (2%), chemotherapy alone for 74 patients (47%) and combined modalities for 80 patients (51%). Our median follow-up time is 11 years.

We reported 96 cardiovascular events in 75 patients (48%). Median time to CV event was 10 years. Most of the events were graded 1 or 2 (71%) and were related to valvular heart disease. Grade 3 and 4 CV events ($n = 21$) were mainly due to coronary heart disease (43%) while most of the deaths related to CV toxicity were consequent to heart failure (57%).

Twenty-seven patients (17%) were diagnosed with SMN, with a median time to SMN of 10 years. Most of them were solid malignancies (71%), including 6 lung cancers and 2 breast cancers (both BRCA2+). We encountered 2 secondary leukaemia, 3 myelodysplastic syndromes and 2 Non-Hodgkin Lymphoma.

Overall survival rate in our cohort is 76% at 10 years. We observed 38 deaths, at a median age of 60 years old. Six patients (16%) died from cHL, and main causes of non-lymphoma deaths were secondary malignant neoplasms (10 pts, 28%) and cardiovascular events (7 pts, 18%).

Discussion: Long-term complications in Hodgkin Lymphoma survivors are well-known and focus on how to decrease treatment related toxicity is constantly growing. Special attention is brought to the use of anthracyclines and mediastinal radiotherapy.

Regarding CV toxicity, we tend to review our patients annually and to offer periodic screening with heart imaging. Our study showed that we detected CV events in almost half of our patients. Those events were mostly low-grade valvular disease not requiring treatment. However, more than 1 out of 4 CV event was graded 3 or more. The impact of the doses of anthracycline and/or radiotherapy received in our population still need to be determined.

With a median time to CV event and to SMN of 10 years, we can confirm that long-term surveillance is recommended for the survivors.

Conclusion: Cure is no longer enough when managing cHL. Our past and previous treatments led to an increasing number of survivors who are at higher risk of long-term complications. Recommendations for long-term surveillance programmes are emerging and are mostly experts-based opinions. More data are needed to identify high-risk patients and to provide them with an adequate monitoring.

Keywords: Hodgkin lymphoma, late effects in lymphoma survivors, prevention and cancer interception

No conflicts of interests pertinent to the abstract.

529 | FERTILITY PRESERVATION IN ADULT LYMPHOMA PATIENTS: A CONSENSUS-BASED POSITION PAPER BY THE FONDAZIONE ITALIANA LINFOMI (FIL) & SOCIETà ITALIANA DELLA RIPRODUZIONE UMANA (SIRU)

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Background: In this consensus-based position paper, the scientific societies Fondazione Italiana Linfomi (FIL) and Società Italiana della Riproduzione Umana (SIRU) reviewed main aspects and identified the optimal paths aimed to preserve and monitor fertility in patients diagnosed with lymphoma.

Methods: The multi-disciplinary working group for this consensus-based position paper was composed by 5 onco-hematologists, 4 gynecologist or andrologists, 1 embryologist and 1 biologist, with the supervision of an international expert leader. A series of rank-ordering key questions were proposed according to the clinical relevance focusing on patients diagnosed with non-Hodgkin's lymphomas and Hodgkin lymphoma. The agreement among all the Panelists was scored by a web-based questionnaire according to the Delphi methodology (two rounds). All statements were newly discussed in a round robin way and confirmed for the drafting of the final recommendations.

Results: Chemotherapy-induced gonadotoxicity is influenced by the type of agent, the dose intensity (high risk of infertility ≥80%, intermediate risk 40%–60%, low risk <20%, very low risk and unknown risk, and in women, also by age at treatment. The correct

timing for onco-fertility counseling is as soon as possible, ideally at time of diagnosis, in order to increase patient's awareness and to allow timing optimization to apply FP techniques. An urgent referral pathway needs to be established between the Hematological and The Reproductive Centers with the aim to offer the onco-fertility counseling within 24–48 h. Blood and specialist exams to be performed during the pre-therapy counseling have been summarized. Oocyte cryopreservation is a well-established FP technique that should be proposed to patients after a personalized onco-fertility counseling, and the possibility to delay treatment of 10–14 days. Ovarian tissue cryopreservation could be proposed as a unique technique in patients with: therapeutic urgency, when chemotherapy has to be started within 10–14 day, when there is a high/moderate gonadotoxic risk, and if the patient's clinical conditions are feasible for surgery. To improve the safety of ovarian tissue transplantation for patients in complete and prolonged survival after lymphoma, the ovarian samples have to be analyzed in order to exclude the presence of neoplastic cells by using molecular and histological analyses prior to graft, especially for aggressive NHL histotypes. Post-pubertal males should be offered sperm cryopreservation. GnRHa should not be considered an alternative option for FP with cryopreservation techniques unless for women for whom these latter are contraindicated due to treatment start delay or safety issues. Indications on fertility tests to be carried out in the period following chemotherapy (1–5 years and >5 years) has been also discussed.

Conclusion: These recommendations would be useful for clinicians who take care of young lymphoma patients to guarantee an evidence-based onco-fertility assessment and treatment during the oncologic pathway.

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Keywords: Late Effects in Lymphoma Survivors

No conflicts of interests pertinent to the abstract.

530 | EVALUATION OF GONADAL FUNCTION IN YOUNG MEN AND WOMEN DIAGNOSED WITH HODGKIN LYMPHOMA

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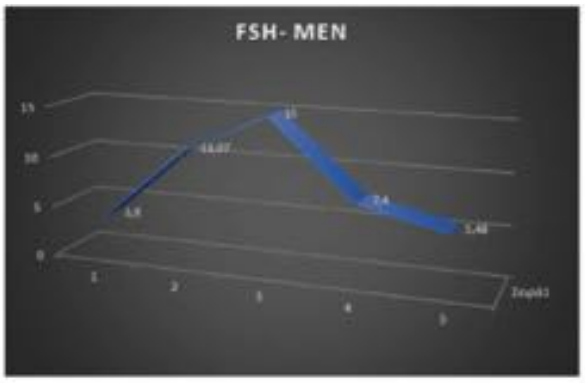
Background: ABVD or escBEACOPP chemotherapy (CT) ± radiation is the treatment approach for Hodgkin lymphoma (HL) patients. As a result of treatment improvement, long-term survivors and treatment-related complications are recognized, among which, gonadal insufficiency plays a cenrtal role. Moreover, little is known about the kinetics of gonadal function and sex hormones during CT to guide contraceptive measures.

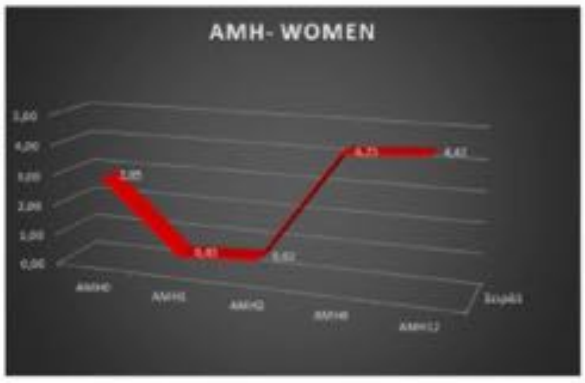
Subjects and Methods: This is a prospective study of gonadal function in HL patients, with an age limit of ≤40 years in women and ≤45 years in men. We present our results on 94 patients. Measurements were performed at pre-specified time points: before treatment (t0), during CT(t1), at the end of CT(t2) and every six months (t6, t12) thereafter. The following hormones were measured: follicle-stimulating hormone (FSH), lutenizing hormone (LH), progesterone (PG), estradiol (E2), anti-Mullerian hormone (AMH) in women and FSH, LH, AMH, testosterone in men.

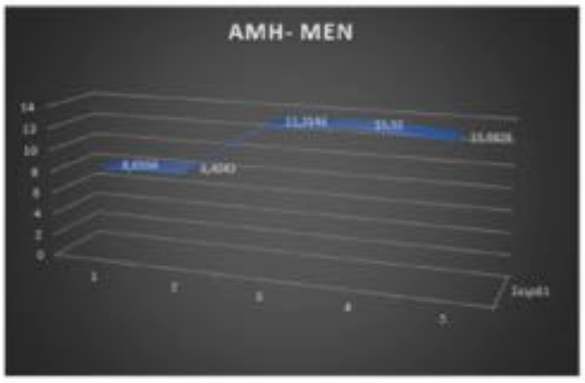
Results: The study included 55 men (median age 30 years) and 39 women (median age 29 years) with HL, all in first-line treatment with ABVD. In men, FSH increased from the start of treatment, peaked at the end and remained high 6 months after the end of CT: [t0 = 3.8 IU/mL, t1 = 11.07 IU/mL, t2 = 15 IU/mL, t6 = 7.4 IU/mL, fsh0–1 $p < 0.001$, fsh0–2 $p < 0{,}001$, t0–6 $p = 0.001$], while it normalized at 12 months. AMH increased progressively from the beginning to the end of treatment and remained high up to 12 months after the end of CT: (t0 = 8, 05 ng/mL, t1 = 8.40 ng/mL, t2 = 13.21 ng, t6 = 13, 52 ng/mL, t12 = 13.04 ng/mL amh0–1 $p = 0.002$, amh0–2 $p < 0.001$, amh0–6 $p < 0.001$, amh0–12 $p = 0{,}05$). Testosterone increased during treatment: (t0 = 407 ng/dL, t1 = 523 ng/dL, t2 = 535 ng/dl, t0–1 $p = 0.001$, t0–2 $p = 0{,}001$), and returned to normal levels at the end of CT.

In women, FSH showed an increase from the start of CT, peaked in the middle and remained high for up to 6 months after the end: (t0 = 4.1 U/mL, t1 = 8.8 U/mL, t2 = 7.7 IU/mL, t6 = 6.6 U/mL, fsh0–1 $p < 0{,}001$, fsh0–2 $p < 0.01$, fsh0–6 $p = 0.05$). AMH showed a decrease in the middle of treatment, its levels remained low until the end: (t0 = 2.85 ng/mL, t1 = 0.45 ng/mL, t2 = 0.62 ng/mL, amh0–1 $p < 0.001$, amh0–2 $p < 0.001$), and progressively returned to normal levels 6 months later. Sex hormones were unaffected.

Conclusion: Gonadal function in HL patients is affected during CT in both sexes. In men, spermatogenesis (Sertoli cells), reflected by the increased levels of FSH, was impaired for 1 year after the end of CT, while testosterone transiently increased, possibly as a result of treatment toxicity to Leydig cells. Regarding the increase in AMH observed in men, it is a finding that needs further investigation as its biochemical function in male reproductive system is not sufficiently studied. In women, gonadal dysfunction was evident (rapid decrease in AMH, increase in FSH), but resolved 1







year after the end of treatment. AMH proved as a more sensitive marker compared to FSH.

Keywords: Hodgkin lymphoma, late effects in lymphoma survivors, other

No conflicts of interests pertinent to the abstract.

531 | MY HODGKIN, MY HEALTH: FEASIBILITY OF A MOBILE APPLICATION TO COLLECT LONG TERM FOLLOW UP DATA ABOUT HODGKIN PATIENTS

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Introduction: There is increasing utility of novel agents in the treatment of Hodgkin lymphoma (HL), and the role of radiotherapy is evolving. Whilst there is a large body of research into the long-term outcomes of HL, this data is mostly related to conventional radiotherapy and chemotherapy regimens. With the advent novel therapies, our understanding of the long-term toxicities is also undergoing a period of dynamic change. Whilst recent trials provided abundant high-level short term follow up data, they fail to provide a full picture of the long-term morbidity and mortality associated with current therapy.

The My Hodgkin, My Health (MHMH) app will be the first app designed to collect patient-derived data from HL patients. The purpose of this study is to demonstrate feasibility of this novel construct by meeting pre-specified recruitment and retention targets. Given the good overall survival of HL, and the paucity of long-term data in an era of novel therapies, we feel this is the ideal space in which to develop this app to capture this data conveniently and economically.

Methods: This will be a pilot study to with initial recruitment targeted at Australian participants of the Risk-Adapted Therapy for Advanced Stage Hodgkin Lymphoma (RATHL) study. This is a well-defined population who are familiar with study procedures and well connected with investigators who will disseminate recruitment information. To prove feasibility, the primary outcome of this study is to recruit ≥30% of Australian RATHL study participants. Secondary endpoints will include disease status and relapse rates, fertility, and other long-term sequelae from HL treatment.

Screening and consent procedures will be done electronically. Subjects will complete a baseline survey including details of their treatment and disease status, as well as information about any treatment complications. Subjects will be encouraged every six months via push notifications to save or update their data.

If the primary endpoint is met, the project will continue with a focus on the secondary endpoints. We also envisage collaboration with international investigators and global uptake of the app. Ideally MHMH will be an invaluable database for researchers moving forward and will facilitate clinical trials aimed at optimising treatment efficacy whilst balancing quality of life and treatment sequelae.

Keywords: Hodgkin lymphoma, ongoing trials

No conflicts of interests pertinent to the abstract.

INDOLENT LYMPHOMAS

532 | THE PROGNOSTIC INDEX PRIMA-PI COMBINED WITH KI67 AS A BETTER PREDICTOR OF PROGRESSION OF DISEASE WITHIN 24 MONTHS IN FOLLICULAR LYMPHOMA

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Introduction: Follicular lymphoma (FL) is one of the common sbutypes of non-Hodgkin's lymphoma (NHL). The disease progresses slowly and has a long median survival but is difficult to treat and prone to recurrent relapse. Notably, disease progression within 24 months after first-line treatment (POD24) has been found to be a risk factor for poor survival in follicular lymphoma, but there is no optimal prognostic model to accurately predict patients with early disease progression. Given the technical complexity as well as the cost, bioclinical prediction is currently difficult to be popularized in the clinical setting, so simple and efficient tumor microenvironment assays are a current research hotspot. How to combine traditional prognostic models with new indicators to establish a new prediction system to predict the early progression of FL patients more accurately is a future research direction.
Methods: The study retrospectively analyzed patients with newly diagnosed FL patients in Shanxi Provincial Cancer Hospital from January 2015 to December 2020. Date from patients undergoing immunohistochemical detection (IHC) were analyzed using chi-square test and multivariate Logistic regression. Also, we built a nomogram model based on the results of LASSO regression analysis of POD24, which was validated in both the training set and validation set, and additional external validation was performed using a dataset ($n = 74$) from another center.
Results: The multivariate Logistic regression results suggest that high-risk PRIMA-PI group, Ki-67 high expression represent risk factors for POD24 ($p < 0.05$). Next, PRIMA-PI and Ki67 were combined to build a new model, namely, PRIMA-PIC to reclassify high and low-risk groups. The result showed that the new clinical prediction model constructed by PRIMA-PI with ki67 has a high sensitivity to the prediction of POD24. Compared to PRIMA-PI, PRIMA-PIC also has better discrimination in predicting patients' progression-free survival (PFS) and overall survival (OS). In addition, we built nomogram models based on the results of LASSO regression (histological grading, NK cell percentage, PRIMA-PIC risk group) in the training set, which were validated using internal validation set and external validation set, we found that C-index and calibration curve showed good performance.
Conclusions: As such, the new predictive model-based nomogram established by PRIMA-PI and Ki67 could well predict the risk of POD24 in FL patients, which boasts clinical practical value.

Keyword: diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

533 | DEVELOPMENT AND VALIDATION OF A MACHINE LEARNING MODEL FOR PREDICTING EARLY PROGRESSION/RELAPSE IN FOLLICULAR LYMPHOMA

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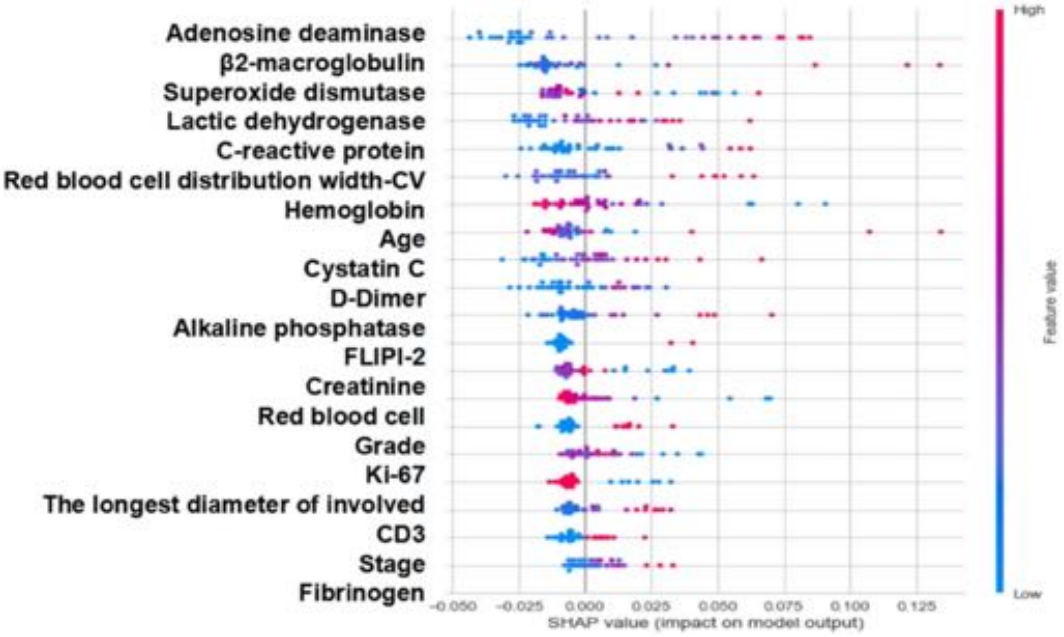
[1]*Shandong Provincial Hospital, Shandong University, Jinan, China*, [2]*Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China*

Introduction: Follicular lymphoma (FL) is the most frequently occurring indolent lymphoma, and progression/relapse of disease within 24 months (POD24) is now established as a predictor for poor survival, being the leading cause of death. Machine learning (ML) offers a novel technology and has several advantages compared with conventional models. We aimed to establish a comprehensive model which could predict the early POD (E-POD) of FL patients.
Methods: Data from a retrospective cohort of 139 patients (training cohort) diagnosed with FL were analyzed to build a model to predict E-POD and the model was tested in the validation cohort ($n = 57$). Demographic information and laboratory values were included as covariates. Furthermore, we compared the features of FL patients with early (<2 years) and late (>5 years) POD.
Results: Of 196 patients, 38 (19.4%) had at least one POD. The ML algorithm with the highest predictive performance was random forests (RF) and the five highest importance variables were adenosine deaminase (ADA), β2-macroglobulin (β2-MG), superoxide dismutase (SOD), lactic dehydrogenase (LDH), and C-reactive protein (CRP). Furthermore, we established a model which could predict E-POD



using the above risk factors. Late POD patients, in comparison with those who experienced E-POD, showed a more favorable risk profile at presentation: low pathological grade (1–2, $p = 0.047$), and no mutation of the CARD11 ($p = 0.050$) and a trend toward a better outcome was also observed.

Conclusion: This study identified biomarkers capable of predicting the risk of E-POD before initial intervention using the ML algorithm. Further validation in the future will hopefully facilitate the incorporation of these simple biomarkers into clinical decision-making tools to prevent adverse outcomes and promote personalized treatment options.

Keyword: diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

534 | KI-67 PROLIFERATION PATTERNS ARE PREDICTIVE OF EARLY PROGRESSION AND INFERIOR OUTCOMES IN GRADE 1–2 FOLLICULAR LYMPHOMA

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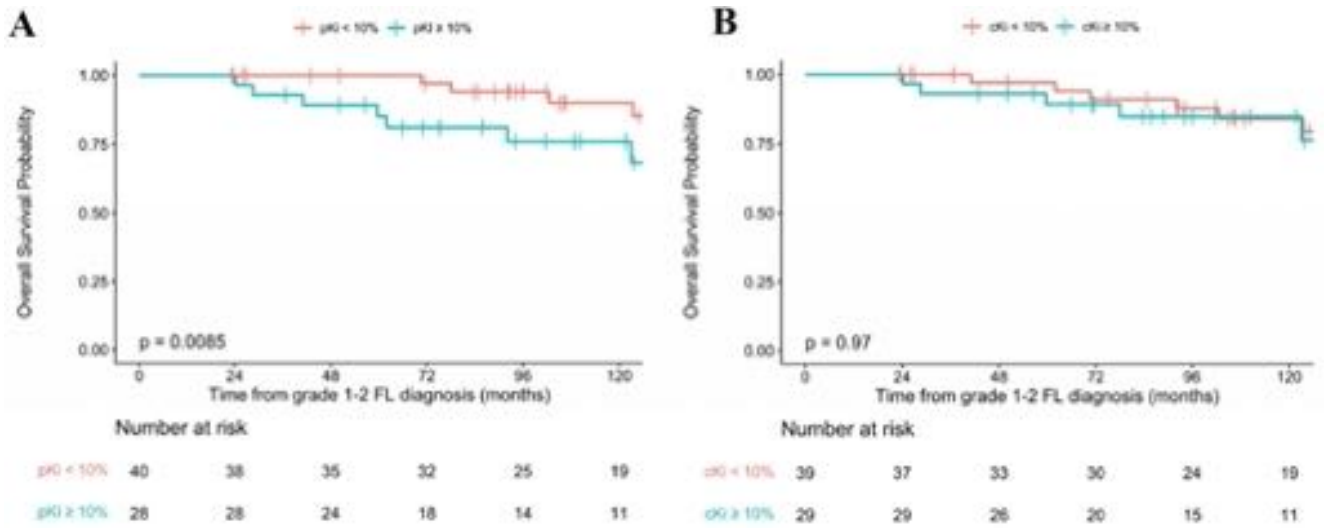
Background: Follicular lymphoma (FL) is the most prevalent indolent B-cell non-Hodgkin lymphoma (B-NHL). Progression of disease within 24 months (POD24) and transformation to large B-cell lymphoma (LBCL) are known adverse outcomes in grade 1–2 FL. There is a need to develop practical and sensitive biomarkers to risk-stratify these patients (pts) at diagnosis. Ki-67 staining is a widely available biomarker without a defined role in FL, however has potential to better highlight the tumor microenvironment (TME) based on its known colocalization with subsets of T-cells. We thus set out to characterize high-risk pt features based on Ki-67 immuno-architectural patterns of grade 1–2 FL at diagnosis.

Methods: Diagnostic biopsy slides from 68 pts with grade 1–2 FL without concurrent LBCL treated at the University of Chicago were collected from 11/2001 to 2/2021. Grade 1–2 histology was confirmed by H&E-stained slides, and Ki-67 stained slides were scored for immuno-architectural features including peripheral follicular pattern Ki-67% (pKI), central/diffuse follicular pattern Ki-67% (cKI), and extrafollicular Ki-67% (eKi). Outcomes were assessed by overall survival (OS), occurrence of POD24 from time of initial treatment, and transformation to LBCL. Outcomes were compared with log-rank and Mann-Whitney tests of significance.

Results: Median age at diagnosis was 61 years (yrs) (IQR 52–69 yrs), and 57% of pts were male. Eleven (16%) pts experienced POD24 from time of first treatment, and 17 (25%) subsequently transformed to LBCL. Median follow-up time was 9.0 yrs (IQR 6.1–11.7 yrs). Median pKi for pts with POD24 was 20% (IQR 11%–40%) versus 3% (IQR 0%–15%) for those without POD24 ($p = 0.01$). Median cKi for pts with POD24 was 20% (IQR 9%–30%) versus 5% (IQR 2%–15%) for those without POD24 ($p = 0.02$). Median eKi for pts with POD24 was 5% (IQR 4%–6%) versus 3% (IQR 1%–3%) for those without POD24 ($p = 0.04$). There was no association between



pKi, cKi, or eKi with transformation to LBCL. Pts with pKI ≥ 10% also had significantly inferior 5-yr OS of 85% (95% CI: 73%–99%) compared with 100% for those with pKi < 10% ($p < 0.01$) (Figure 1A). A cKI score ≥ 10% was not associated with inferior survival outcomes (Figure 1B).

Conclusions: Immuno-architectural patterns of higher focal Ki-67 staining in grade 1–2 FL are significantly associated with POD24, and high Ki-67 staining in peripheral patterns is associated with inferior 5-yr OS. These findings suggest that Ki-67 staining patterns may be an accessible biomarker of FL TME features, and may serve a biological role in the early progression of FL through changes in immune cell colocalization within follicles. Our work suggests that more nuanced, spatial profiling of Ki-67 staining patterns may be able to better identify pts at higher risk for adverse outcomes in grade 1–2 FL pts at diagnosis, and further work is planned with digital image analysis to refine prognostication of these patterns.

Keywords: diagnostic and prognostic biomarkers, indolent non-Hodgkin lymphoma, pathology and classification of lymphomas

Conflicts of interests pertinent to the abstract

G. Venkataraman
Consultant or advisory role EUSA Pharma
Honoraria: ASH

J. P. Kline
Consultant or advisory role Janssen, Sanofi, COTA Healthcare
Honoraria: Kite Pharma Inc./Gilead
Research funding: Merck, Kite Pharma Inc./Gilead, Seattle Genetics, Verastem Oncology

P. A. Riedell
Consultant or advisory role Abbvie, Genmab, ADC Therapeutics, Pharmacyclics, Novartis, BMS, Kite/Gilead, Nurix Therapeutics, Nektar Therapeutics, Takeda, Intellia Therapeutics, Sana Biotechnology, BeiGene, Janssen, CVS Caremark
Honoraria: Novartis, Kite Pharma
Research funding: BMS, Kite/Gilead, Novartis, MorphoSys, CRISPR Therapeutics, Calibr, Xencor, Fate Therapeutics, Tessa Therapeutics

M. R. Bishop
Consultant or advisory role Celgene, Kite Pharma Inc./Gilead, CRISPR Therapeutics, Takeda, Novartis
Honoraria: Kite Pharma Inc./Gilead, BMS, Incyte, Agios, Celgene
Other remuneration: Novartis

535 | CLINICAL OUTCOMES BY PROGRESSION OF DISEASE WITHIN 24 MONTHS (POD24) IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL) TREATED WITH LINPERLISIB

L. Qiu[1], X. Sun[2], L. Qiu[3], H. Su[4], J. Cao[5], Z. Li[6], Y. Song[7], L. Zhang[8], D. Li[9], H. Wu[10], W. Zhang[11], J. Li[12], K. Zhou[13], H. Zhou[14], Y. Yang[15], Z. Li[16], H. Cen[17], Z. Cai[18], Z. Zhang[19], T. Wang[1], W. Fu[20], J. Jin[21], F. Li[22], W. Wu[23], X. Gu[24], W. Zhu[25], L. Liu[26], Z. Li[1], S. Yi[1]

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Introduction: Linperlisib, a PI3Kδ inhibitor, has shown clinically efficacy and manageable safety profile as third- or further-line treatment in patients with R/R FL from a multicenter phase 2 trial (NCT04370405). We aimed to perform a subgroup analysis to evaluate the impact of POD24, a well-established indicator of poor survival, on the efficacy of linperlisib.

Methods: This phase 2 study was conducted at 25 sites in China between April 2019 and September 2020. Linperlisib 80 mg was given orally once daily until disease progression, intolerable toxicity or withdrawal from the study. Response was assessed by an independent review committee according to the International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). The primary endpoint was objective response rate (ORR).

Results: The POD24 group had a lower median age (49 vs. 53 years) and lower proportion of patients with at least three lines of prior therapies (73.8% vs. 87.0%) than the non-POD24 group. All patients in both groups had received prior anti-CD20 antibody and alkylating agent.

	POD24 subgroup (n = 61)	Non-POD24 subgroup (n = 23)	Total (n = 84)
Objective response rate, *n* (%)	47 (77.1)	20 (87.0)	67 (79.8)
95% CI	64.5, 86.9	66.4, 97.2	69.6, 87.7
Duration of response			
6-month rate, % (95% CI)	76.4 (60.5, 86.5)	89.2 (63.1, 97.2)	80.0 (67.4, 88.1)
12-month rate, % (95% CI)	56.3 (39.0, 70.5)	52.1 (23.2, 74.8)	55.3 (40.6, 67.8)
Median, months (95% CI)	13.0 (9.3, NR)	12.3 (6.6, NR)	12.3 (9.3, 15.9)
Progression-free survival			
6-month rate, % (95% CI)	79.4 (65.9, 88.1)	77.3 (53.7, 89.8)	78.6 (67.5, 86.3)
12-month rate, % (95% CI)	55.8 (40.7, 68.5)	46.4 (22.3, 67.6)	53.1 (40.3, 64.3)
Median, months (95% CI)	13.7 (11.1, 19.4)	11.5 (8.2, NR)	13.4 (11.1, 16.7)
Overall survival			
6-month rate, % (95% CI)	96.7 (87.3, 99.2)	100 (100, 100)	97.6 (90.6, 99.4)
12-month rate, % (95% CI)	89.9 (78.9, 95.3)	95.5 (71.9, 99.3)	91.4 (82.7, 95.8)
Median, months (95% CI)	NR (NR, NR)	NR (21.7, NR)	NR (NR, NR)
Common grade ≥3 treatment-related adverse events, n (%)			
Neutrophil count decreased	9 (14.8)	4 (17.4)	13 (15.5)
Infectious pneumonia	12 (19.7)	4 (17.4)	16 (19.0)
Interstitial lung disease	3 (4.9)	0	3 (3.6)

The ORR (77.1%, 47/61) in the POD24 group was numerically lower than that (87.0%, 20/23) in the non-POD24 group, but without statistical significance ($p = 0.314$). Both groups showed similar progression-free survival (13.7 months vs. 11.5 months). The most common grade ≥3 treatment-related adverse events were infectious pneumonia (19.7%), decreased neutrophil count (14.8%), and interstitial lung disease (4.9%) in the POD24 group, and decreased neutrophil count (17.4%) and infectious pneumonia (17.4%) in the non-POD24 group (Table).

Conclusions: For R/R FL, patients with POD24 could also benefit from subsequent linperlisib treatment, with similar prognosis to those without POD24. Linperlisib could be an appropriate option for this difficult-to-treat population.

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Keyword: molecular targeted therapies

No conflicts of interests pertinent to the abstract.

536 | OUTCOME OF HIGH DOSE CHEMOTHERAPY PLUS AUTOLOGOUS STEM CELL TRANSPLANTATION (HDT-ASCT) IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA: EXPERIENCE OF A SINGLE ITALIAN INSTITUTION

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Introduction: Patients (pts) with follicular lymphoma (FL) can have long survival, nevertheless most of them have subsequent relapses with disease-free intervals progressively shorter. In the present *chemo-free era* the role of transplantation has been questioned and its right place in the treatment plan of relapse/refractory (R/R) disease is still challenging.

The aim of this analysis was to collect long-term follow-up data on pts treated with HDT-ASCT in our Institution focusing on outcome and toxicity.

Methods: All patients with R/R FL, consecutively treated with HDT-ASCT in our Institution in the last 18 years were considered. Response assessment was made as recommended by International Workshop criteria and survival analysis were calculated with Kaplan-Meyer method.

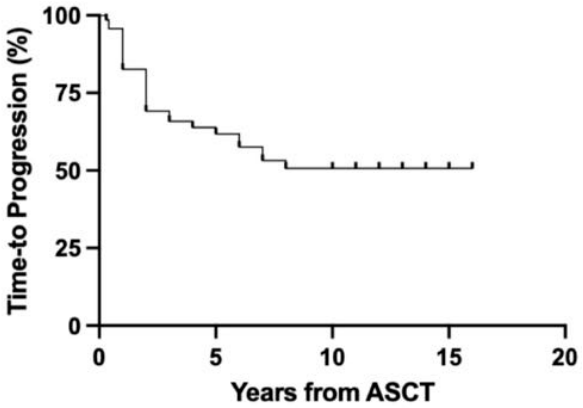
The primary end point was overall survival (OS). Secondary end points included progression-free survival (PFS), time to progression (TTP), and second tumors.

Survival analysis were also focused on different subgroups of pts divided according to early (POD24) or late (noPOD24) relapse or the timing of transplant procedure.

Results: Between June 2003 and May 2021, 87 pts underwent ASCT, and 70 of them had complete data to be considered for the analysis. Median age was 58 yrs (range 37–75) and 53% were early relapse (POD24).

With a median follow-up of 110 months from ASCT (range 4–197), the 5-years(yrs) and 10-yrs OS were 80% and 69%, PFS 55% and 39% and TTP 62% and 51% respectively, with a plateau around 8 years after ASCT (**Figure 1**). No survival difference was recorded in pts receiving ASCT in second line (80%) or later (20%). In a cohort of 45 pts transplanted in 2nd-line who received 1st-line therapy within the first year of diagnosis, 10 yrs OS was 62% versus 79% ($p = 0.26$) in pts with POD24 versus noPOD24, respectively. No Transplant Related Mortality was observed. Thirty pts (43%) had relapse or progression, 2, pts (3%) had histological transformation into diffuse large B-cell lymphoma. Nineteen pts (27%) developed 2nd tumors [10 (53%) hematological, 8 (42%) solid and 1 (5%) both]. The majority of them (84%) have previously received purine analogues or Ibritumomab tiuxetan or both. Twenty pts (29%) died [4 (20%) for lymphoma, 12 (60%) for 2nd tumors and 4 (20%) for infections including 3 covid-19].

Conclusions: This long term follow up analysis confirms that HDT-ASCT is a safe and effective treatment for R/R FL. The plateau of TTP curve suggests that this approach is potentially curative for a non-negligible subset of pts, that may become larger if the incorporation of novel agents in the induction therapy will reduce the occurrence of 2nd malignancies. This procedure is still competitive with chemo-free second line therapies, in particular for pts with more aggressive disease requiring therapy within 12 months and a POD24 after first line.



N° Patients	N° events	TTP median	5-year TTP	10-year TTP
70	30	Undefined	62%	51%

Keyword: indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

537 | PROSPECTIVE KOREAN MARGINAL ZONE LYMPHOMAS COHORT STUDY: INITIAL DATA ANALYSIS OF 407 CASES

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Background: Marginal zone lymphoma (MZL) is a distinct subgroup of non-Hodgkin's lymphoma (NHL), which is typically characterized by an indolent clinical course and long survival duration. In Korea, MZL accounts for 21% of all B-cell lymphoma and is the second most frequent histologic subtype following diffuse large B-cell lymphoma. Because of its rarity, prospective clinical trial is difficult to conduct. Therefore we want to make prospective MZL patients' cohort for several observations including clinical presentation, evaluation patters, treatment modality, results, and side effects.

Methods: Histological newly diagnosed patients with MZL were eligible. We received official approval from each study site their local IRB. All patients gave written informed consent prior to study participation. Patients' data was collected via e-CRF on the Web.

Results: In total, 407 patients were enrolled (median age: 56 years, range: 20–86 years) between July 2010 and September 2019 from twenties hospitals of the Consortium for Improving Survival of Lymphoma (CISL). Male-to-female ratio was about 1.2 to 1 (219 vs. 188). Nodal MZLs were observed in 48 patients (11.8%). Almost of registered MZL patients was MZL of MALT type 359 (88.2%). The most common site of involvement was orbit and ocular adnexa (29.7%) followed by stomach (17%), multiple MALT sites involved (15.7%), and lung (5.4%). Ninety-four percent (384) of the patients initially presented with Ann Arbor stage I/II. BM involvement was detected in 7.3% (28 of 384). Bulky mass and B symptom was observed in only 3 patients, respectively. 71% of the patients (290 of 407) and 36 patients (8.8%) were categorized as the low and low-intermediate risk group according to the IPI, respectively. Initial treatment was conducted by Patients' disease status; ten percentage of patients were observed without treatment. Chemotherapy alone 106 (26%), RT alone 80 (19.7%), Surgery + Chemotherapy 46 (11.3%), *H. pylori* eradication 35 (8.6%), Surgery alone 26 (6.4%). 5 years PFS and OS duration were 89.4% (32 events) and 97.3 (11 events). Eleven cases of hepatitis reactivation were observed during treatment.

Conclusion: This is a first large scale prospective MZL cohort study in Korea. The results showed that the characteristics of MZL that survives for a long time and causes frequent recurrence were well represented. However, for accurate characteristic analysis, it is necessary to collect continuous survival-related data for the next five years or more. This study will replacing 207 retrospective studies published in 2004 and can be used as basic data to determine survival changes after Rituximab is used (ClinicalTrials.gov ID: NCT02732236).

The research was funded by: The research was funded by JW pharmaceutical.

Keyword: indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

538 | COMORBIDITY, AGE AND SEX IN RELATION TO SURVIVAL AMONG 2264 PATIENTS WITH WALDENSTROM'S MACROGLOBULINEMIA—A SWEDISH LYMPHOMA REGISTRY STUDY

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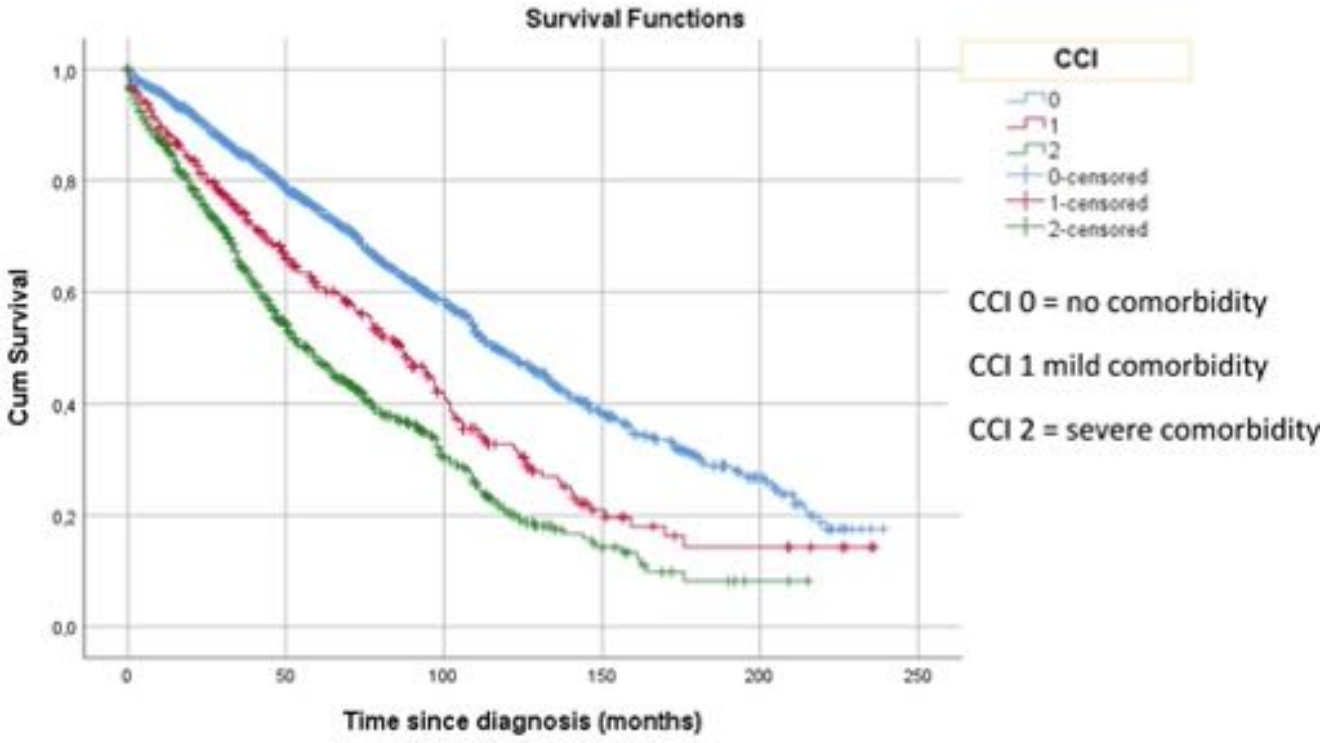
Introduction: Waldenstroms macroglobulinemia (WM) is a rare indolent B-cells lymphoma mainly affecting elderly persons. With increasing age many patients develop comorbidities, affecting the choice of treatment and mortality. The median survival is 7–10 years and many patients dies from other reasons than WM. WM is an incurable disease. Treatment is only required when the disease becomes symptomatic and should be individualized.

A large population based cohort of WM patients from a national registry are characterized regarding clinical characteristics, gender,

Fig 1: Kaplan-Meier curves for OS for CCI and All WM patients



morbidity and mortality with the intent to facilitate treatment decisions.

Methods: All patients with WM or lymphoplasmacytic lymphoma registered in the Swedish Lymphoma Registry (SLR) between 1 January 2000 to 31 December 2019 and matched controls were included in the study. Clinical characteristic and prognostic factors at the time of diagnosis were collected from SLR. Information on comorbidities within 10 years prior to diagnosis were obtained from the Swedish Patient Register. Comorbidity was classified according to the Charlson comorbidity index (CCI) CCI 0, 1 or 2. The Swedish Cause of Death Register and the Longitudinal Integrated Database (LISA) were also used.

Results: We identified 2 264 patient with WM, 1378 (61%) males and 886 (39%) females, diagnosed between the years 2000 to 2019 and registered in SLR, and 22 595 matched controls. The median age at diagnosis was 73 years and 1 696 (76%) ≥65 years.

Most of the WM patients had performance status (PS) 0 at diagnosis and the PS was worsen with increasing age; PS 0 ≤ 65 years $n = 473$ (77.8 %), PS 0 66–75 years $n = 493$ (67.7 %) PS 0 and ≥76 years $n = 432$ (45.6 %).

The education level was higher in WM patients compared with the controls; ≤ 9 years $n = 807$ (35.6%) and $n = 9068$ (40.1%), and ≥13 years $n = 578$ (25.5%) and $n = 4703$ (20.8%) ($p < 0.001$).

The median follow-up time was 98 months and in the end of the observation time 1 143 (50.5%) had died. Using CCI, 1187 (52%) of the WM patient and 12573 (55.6%) of the controls had CCI 0 (p-value < 0.001.) WM patients had significant more often rheumatic diseases, renal and severe liver diseases, other malignancies, but significantly less often myocardial infarction, cerebrovascular diseases or dementia compared with the controls. CCI was increasing with age. The median overall survival (OS) for the WM patients were for CCI 0: 117, CCI 1: 87 and CCI ≥ 2: 47 months, respectively (Figure 1).

The median OS in the same CCI group differed between males and females. The difference was most pronounced for elderly males in CCI 2; median OS for males ≥76 years was 36 months compared with 48 for females.

Conclusions: Elderly males have an inferior prognosis than females, analyses of the reasons for this is ongoing. With increasing age and comorbidity the risk of non-WM related death is significant. This fact influences the choice of therapy especially for elderly patients.

The research was funded by: Norrbotten County Council

Keyword: indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

539 | RITUXIMAB VERSUS BORTEZOMIB PLUS CYCLOPHOSPHAMIDE AND DEXAMETHASONE IN NEWLY DIAGNOSED SYMPTOMATIC WALDENSTRöM MACROGLOBULINEMIA: A RANDOMIZED CONTROLLED PHASE 3 TRIAL

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Waldenström macroglobulinemia (WM) is a rare type of lymphoma, for which rituximab- or bortezomib-based regimens are commonly used as first-line treatment. However, the optimal treatment regimen remains unknown. This study was a randomized, phase 3 clinical trial to compare the efficacy of rituximab, cyclophosphamide, and dexamethasone (RCD) with bortezomib, cyclophosphamide, and dexamethasone (BCD) in newly diagnosed WM patients (NCT02844322). Between March 2016 and November 2020, 38 patients were randomly assigned into groups. The overall response rate was 89·5% in both groups. The proportion of patients who achieved a very good partial response or better was higher in the RCD group than in the BCD group (42·1% vs. 26·3%, $p = 0.305$). Over a median 55-month follow-up, the 5-year PFS rate was 69·4% (95% CI: 35%–88%) in the RCD group versus 35·5% (95% CI: 15%-57%) in the BCD group ($p = 0.009$). The 5-year overall survival rate was also significantly higher in the RCD group (88·9% vs. 71·3%, $p = 0.034$). The most common adverse event in both groups was hematological toxicity. No serious non-hematological grade ≥3 adverse events occurred in either group. In conclusion, the rituximab-based regimen was superior to the bortezomib-based regimen for newly diagnosed patients with WM.

Keywords: combination therapies, indolent non-Hodgkin lymphoma, ongoing trials

No conflicts of interests pertinent to the abstract.

540 | DUODENAL-TYPE FOLLICULAR LYMPHOMA, A RARE ENTITY: CLINICAL ASPECTS, TREATMENT AND OUTCOMES OF BRAZILIAN PATIENTS

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Introduction: Duodenal-type follicular lymphoma (DFL) is a rare entity, presented mostly as localized disease and excellent long-term outcomes. Its pathogenesis and peculiar predilection for the duodenum is not clear. Wide use of endoscopy for several reasons seems to highlight this disease and increase its diagnosis, since many patients are asymptomatic. Environment aspects, such as diet and local infections, could play a role in its clinical presentation and evolution.
Methods: We evaluated 53 patients with diagnosis of DFL based on the current WHO classification on lymphoid neoplasms. Reference Brazilian centers in hematology reported their cases to this retrospective analysis. Cases were reviewed in electronic charts after ethical approval by each center.
Results: The median follow-up of the whole cohort was 2.9 years (range 0.1–11). Median age at diagnosis was 58.2 y (33–85). Using the Lugano TGI classification, 75% ($n = 40$) were stage I. There were 2 patients with concomitant involvement of the jejunum and 1 with colonic infiltration of follicular lymphoma. Endoscopic lesions were mainly nodules (56%) and in the second portion of the duodenum (85%). Bone marrow involvement (BMi) was present in 4 cases. Close to half of the population (51%) was asymptomatic and had the diagnosis after a screening endoscopy, while 45% had some form of mild gastrointestinal symptom that preclude the exam. Only one patient had constitutional symptoms. FLIPI 0-1 in 81% of patients, with LDH elevated in 3 patients (mean of 262.8, range 116–487). Most patients were followed with regular observation (watch and wait in 60.4%), rituximab monotherapy was administered for 15 patients (28.3%) and radiotherapy for 3 (5.7%). Only 3 patients received chemotherapy (one consolidated with radiotherapy). GI symptoms were the major cause ($n = 8$) for starting treatment, followed by nonspecific cause in 7 cases (many described by patient anxiety). Rituximab maintenance was performed in 9 patients, 7 treated with rituximab monotherapy and 2 with rituximab plus chemotherapy. Three patients had progression of disease (1 after watch and wait, 1 treated with rituximab monotherapy and no maintenance and 1 progressed after receiving chemotherapy for advanced disease). Within these patients, 2 had BMi. Table 1 summarize the main findings. No patient died. Within the watch and wait group, most patients didn't perform a follow up endoscopy however three patients had a spontaneous complete remission observed by endoscopy.
Conclusions: This is the first cohort of Brazilian or Latin American patients with DFL published so far. Most patients were asymptomatic or with mild gastrointestinal symptoms at diagnosis. Small multiple nodules in the second portion of the duodenum were the principal

	Total (N=53)
Gender, n (%)	
male	27 (50.9%)
female	26 (49.1%)
AD (years)	
Range	34.0,90.0
Mean (SD)	61.0 (12.5)
Median (IQR)	61.0 (53.0, 68.0)
GI_CS, n (%)	
I	40 (75.5%)
II1	2 (3.8%)
II2	4 (7.5%)
IIE	1 (1.9%)
IV	5 (9.4%)
NA	1 (1.9%)
GIS, n (%)	
yes	24 (45.3%)
no	28 (52.8%)
NA	1 (1.9%)
FLIPI, n (%)	
	0 19 (35.8%)
	1 24 (45.3%)
	2 6 (11.3%)
	3 1 (1.9%)
NA	3 (5.7%)

Treat, n (%)	
Watch and wait	32 (60.4%)
R monotherapy	15 (28.3%)
RDT	3 (5.7%)
RCVP	1 (1.9%)
Others	1 (1.9%)
RDT + RCHOP	1 (1.9%)
Response, n (%)	
CR	21 (41.2%)
PR	2 (3.9%)
SD	2 (3.9%)
NA	26 (51.0%)
IOT, n (%)	
GI symptons	8 (15.1%)
B symptons	1 (1.9%)
Advanced disease	2 (3.8%)
Organ compression	1 (1.9%)
Not specified	7 (13.2%)
Local progression	2 (3.8%)
Not treated	32 (60.4%)
Relapse, n (%)	
No	50 (94.3%)
Yes	3 (5.7%)

Table 1 (clinical and treatment aspects).

AD = Age at diagnosis; GI_CS = gastrointestinal clinical staging; GIS = gastrointestinal symptoms; NA = not available; RDT = radiotherapy; R = rituximab; RCVP = rituximab, cyclophosphamide, vincristine and prednisone; RCHOP = rituximab, cyclophosphamide, doxorrubicin, vincristine and prednisone; CR = complete remission; PR = partial remission; SD = stabel disease; IOT = indication of treatment; GI = gastrointestinal.

appearance. Patients tended to have low FLIPI, localized disease and good prognosis. Watch and wait strategy seems safe and spontaneous CR can occur.

Keyword: indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

541 | MINIMAL RESIDUAL DISEASE STATUS IMPROVED THE RESPONSE EVALUATION IN PATIENTS WITH WALDENSTRöM'S MACROGLOBULINEMIA

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Minimal residual disease (MRD) has been recognized as an important prognostic factor for survival in hematological malignancies. However, the prognostic value of MRD in Waldenström's macroglobulinemia (WM) remains largely unexplored. We analyzed 108 newly diagnosed WM patients receiving systematic therapy and assessed MRD by multiparameter flow cytometry (MFC) in the bone marrow. At best response, 34 patients (31.5%) achieved undetectable MRD (uMRD). Hemoglobin > 115 g/L ($p = 0.03$), serum albumin >35 g/L ($p = 0.01$), β2-MG ≤ 3 mg/L ($p = 0.03$), and low-risk International Prognostic Scoring System for WM (IPSSWM) stage ($p < 0.01$) were associated with a higher rate of uMRD. Improvements in IgM ($p < 0.01$) and hemoglobin ($p = 0.03$) were more evident in uMRD patients compared with MRD-positive patients. The 3-year progression-free survival (PFS) was better for uMRD patients compared with those MRD-positive patients (96.2% vs. 52.8%; $p = 0.0012$). Landmark analysis also showed that uMRD patients had a better PFS than MRD-positive patients after 6 and 12 months. Patients who achieved partial response (PR) and uMRD had a 3-year PFS of 100%, which was significantly higher than that patients with MRD-positive PR (62.6%, $p = 0.029$). Multivariate analysis showed that MRD positivity was an independent factor for PFS (HR 2.55, $p = 0.03$). Moreover, the combination of the 6th International Workshop on WM assessment (IWWM-6 Criteria) and MRD had a higher 3-year AUC compared with the IWWM-6 criteria only (0.71 vs. 0.67). MRD based on MFC was an independent prognostic factor for survival in WM, which could improve the precision of response evaluation, especially for patients who had obtained PR.

Keywords: diagnostic and prognostic biomarkers, indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

542 | COMBINED MODALITY ULTRA-LOW-DOSE ADAPTIVE RADIOTHERAPY AND RITUXIMAB AS TREATMENT STRATEGY FOR INDOLENT NON-HODGKIN LYMPHOMAS: THE UT SOUTHWESTERN EXPERIENCE

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Introduction: For indolent non-Hodgkin lymphomas (iNHL), ultra-low-dose radiation therapy (ULDRT) with 4 Gy (2 Gy × 2 or "boom-boom") has demonstrated durable local control (70%), though distal relapses may occur. Concurrent systemic chemotherapy with RT extends PFS but is often avoided due to toxicity. We hypothesize that the combination of adaptive ULDRT and single-agent rituximab results in excellent local and systemic control with minimal toxicity.
Methods: We conducted an IRB approved retrospective review of patients with iNHL who were treated with both ULDRT and rituximab (4 weekly doses of 375 mg/m^2) as frontline therapy, either concurrently, or within a short interval (median 13 days), at our institution from 2017-2023. Treatment response and disease control (local and distant) were measured. Overall and progression-free survival (OS and PFS) were analyzed using the Kaplan-Meier method.
Results: Baseline patient characteristics and treatment sites are shown in Table 1.

The overall response rate at first follow up was 21/22 (95%), of which 17 sites (77%) achieved complete response (CR), 4 (18%) partial response (PR), and 1 (5%) stable disease (SD). Of those with PR, 1 had residual disease in-field, 1 out-of-field, and 2 both in- and out-of-field of RT. Repeat ULDRT was given to sites of PR with all achieving CR except for 1 patient with both in and out-of-field PR who declined salvage RT and was managed with active surveillance with SD on last follow up.

Two patients experienced mild acute RT-related toxicities (diarrhea and dysgeusia), and 1 patient with Sjogren's syndrome experienced long-term mild dry mouth. There were no major toxicities associated with rituximab. Of 14/22 initially symptomatic treatment sites, 12/14 (86%) noted resolution after treatment.

In our cohort, the 2-year PFS and OS were 86% and 100%, respectively. The median time to relapse was 23 months. Of the patients who relapsed, 1 relapsed in-field, and 2 relapsed both in- and out-of-field of ULDRT. Two of these patients were retreated with ULDRT, while one is undergoing systemic treatment with bendamustine/rituximab.

Conclusion: The combination of rituximab and ULDRT demonstrates sustained local and distant disease control with minimal side effects in iNHL. In situations where there is prohibitive toxicity risk for chemotherapy and/or higher radiation doses, this strategy presents a reasonable alternative. Further studies are needed to elucidate potential mechanisms of synergy and define the optimal use of this treatment paradigm.

Table 1. Baseline characteristics

Disease Characteristics		N (Median (range))	%
Age (years)		75 (25-90)	
ECOG PS		1 (0-2)	
Gender	Male	12	67
	Female	6	33
Stage	I	7	39
	II	5	28
	III	4	22
	IV	2	11
Histologic Subtype	Follicular	8	44
	Nodal MZL	4	22
	MALT Lymphoma	5	28
	Other	1	6
Treatment Sites	Pelvis	5	23
	Parotid	4	18
	Abdomen	5	23
	Mediastinum	2	9
	Head and Neck	4	1
	Other	5	23

Keywords: combination therapies, indolent non-Hodgkin lymphoma, radiation therapy

Conflicts of interests pertinent to the abstract

G. Kaur
Employment or leadership position: SANOFI, BMS, Janssen, Cellectar, Arcellx
Consultant or advisory role Advisory

EXTRANODAL LYMPHOMAS NON MZL

543 | PRELIMINARY FINDINGS OF A PHASE II STUDY OF CHEMO-FREE COMBINATION OF POMALIDOMIDE, ORELABRUTINIB, RITUXIMAB WITH SEQUENTIAL HIGH-DOSE METHOREXATE IN NEWLY DIAGNOSED PRIMARY CNS LYMPHOMA

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Background: High-dose methotrexate (HD-MTX) is widely used as front-line treatment in patients with primary central nervous system lymphoma (PCNSL). Both preclinical models and clinical data suggested pomalidmide and orelabrutinib were effective in PCNSL and the combination of them may have synergy in DLBCL.
Aims: We aimed to evaluate the tolerability and efficacy of pomalidomide, orelabrutinib and rituximab (POR) with the sequential addition of HD-MTX chemotherapy in newly diagnosed PCNSL.

Methods: This is an investigator-initiated, single-arm phase II study, and immunocompetent patients with untreated PCNSL were enrolled.

Patients were treated with pomalidomide 4 mg once per day on days 1-14, orelabrutinib 150 mg once daily continuously, and rituximab 375 mg/m^2 intravenous once on day 1 of each 21-day cycle. After four cycles, HD-MTX chemotherapy was sequentially added for two additional cycles. The primary endpoint was overall response rate (ORR) at the end of four cycles of POR. Circulating tumor DNA detection of cerebrospinal fluid was performed. This trial was registered at www.clinicaltrials.gov (#NCT 05390749).

Findings: The data cut-off date was 15 February 2023, and thirteen patients were enrolled in this study. The median age was 58 years (range 34-79 years). Four patients had eye involvement and one patient had leptomeninges involvement. Eight patients performed ctDNA analysis and all had *MYD88 I265p* mutation. One patient discontinued the experimental treatment due to treatment-related adverse events (TRAE) and eleven patients finished four cycles of POR and were evaluable. The ORR after four cycles of POR was 90.1% and the complete response rate was 36.4%. Twelve patients who finished at least 1 cycle were evaluated for safety analysis. The most common grade 3 or 4 AEs were neutropenia (G3, $n = 1$; G4, $n = 2$), thrombocytopenia (G3, $n = 2$), rash (G3 $n = 1$, G4 $n = 1$), ALT increased (G3, $n = 1$) and anemia (G3, $n = 1$). With a median follow-up of 4 months, one patient relapsed and died of PCNSL.

Conclusion: This is the first study to treat newly diagnosed PCNSL with a targeted therapy combination before chemotherapy. POR produced a high ORR with good tolerance. This suggested the potential of noncytotoxic first-line therapies for PCNSL.

Encore Abstract—previously submitted to EHA 2023

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Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy, molecular targeted therapies

No conflicts of interests pertinent to the abstract.

544 | AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL). REAL-WORLD REPORT OF POLISH LYMPHOMA RESEARCH GROUP.

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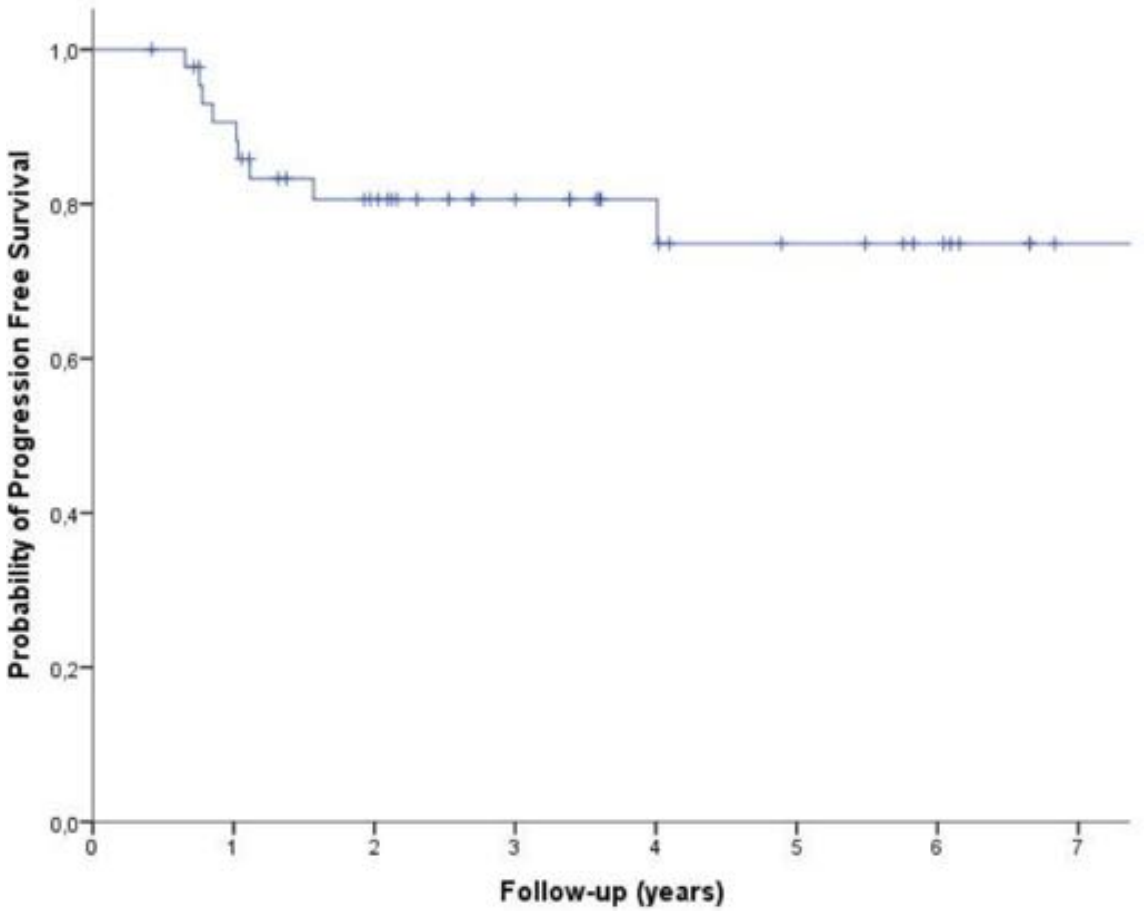
Introduction: High-dose chemotherapy with autologous stem-cell transplantation (HDC-ASCT) is now the preferred consolidation strategy for young PCNSL patients. The optimal conditioning regimen is unknown. The data suggests that BEAM (carmustine, etoposide, cytarabine, melphalan) is ineffective, BCNU/TT (carmustine/thiotepa) is well-tolerated with treatment related mortality (TRM) 1%–3%, but late relapses are common, and TBC (thiotepa, busulfan, cyclophosphamide) is highly effective but with higher TRM 11%.

Methods: The aim of the study was to analyze the safety and efficacy of consolidation based on conditioning regimen consisted of carmustine, etoposide and thiotepa (BET)1 followed by ASCT. We evaluated the outcome of 45 immunocompetent adult patients with PCNSL treated in 4 Polish centers between Feb. 2015 and Oct. 2022. Six cycles of induction with rituximab, methotrexate (3.5 g/m^2), ifosfamide and vincristine (R-MIV) and one cycle of cytarabine with thiotepa (AT)2 were given. Patients with a complete or partial response (CR/PR) proceeded to consolidation with carmustine 400 mg/m^2 on day -5, etoposide 150 mg/m^2 on day -5,-4, -3, and thiotepa 5 mg/kg every 12 h on days -4 and -3 (total 4 doses), followed by ASCT.

Results: Median age (range) of 45 transplanted patients was 57 years (19-66) with 15 (33%) patients ≥60 years old. At the end of induction 29 (64.5%) patients obtained CR/CRun (19/10 respectively), with additional 5 (11%) patients with no evidence of disease at baseline, and 11 (24.5%) in PR, based on standard CT/MRI assessment. For 32 (71%) patients with ^{18}FDG PET/CT done before ASCT, metabolic-CR was confirmed. Mean (range) number of 584.4 (187–2642) $\times$ 10^6 CD34+ peripheral blood stem cells were collected, corresponding to 7.2 $\times$ 106 cells/kg (2.55–34.7 $\times$ 10^6 cells/kg). Mean hospitalization time from the day of ASCT was 15 days. Mean time to hematologic recovery with PLT > 25 G/L and NEU > 0.5/ > 1.0 G/L was 9 and 9/10 days, respectively. The most common grade 3–4 non-haematological toxicities were diarrhea (12 patients, mean 4 days) and mucositis (18 patients, mean 5 days). Febrile neutropenia occurred in 21 patients (mean 2.5 days). Blood cultures did not reveal any relevant pathogens except one patient with confirmed Enterobacter cloacae-ESBL and Klebsiella oxytoca. Two patients (TRM



4.4%) died of transplant-related complications: septic shock and neurotoxicity. At a median (range) follow-up of 41 (13-92) months, 3-year progression free survival (PFS) and overall survival (OS) was 78% (95% CI: 65-91) and 81% (95% CI: 68-93). Relapse occurred in 9 patients, in all but one within first 11 months after ASCT. Causes of death were: lymphoma progression ($n = 6$), TRM ($n = 2$), accident ($n = 1$) and concomitant diseases ($n = 2$).

Conclusion: HDC-ASCT based on conditioning regimen consisted of carmustine, etoposide and thiotepa (BET) is a relatively safe and highly effective treatment for PCNSL patients.

Keywords: aggressive B-cell non-Hodgkin lymphoma, stem cell transplant

No conflicts of interests pertinent to the abstract.

545 | A RETROSPECTIVE STUDY OF 222 PATIENTS WITH NEWLY DIAGNOSED PRIMARY CNS LYMPHOMA—OUTCOMES INDICATIVE FOR IMPROVED SURVIVAL OVERTIME

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Introduction: Primary central nervous system lymphoma (PCNSL) is a rare disease with an incidence of 0.4/per 100,000 person-years. As there is a limited number of prospective randomized trials in PCNSL, large retrospective studies on this rare disease may yield information that might prove useful for the future design of randomized clinical trials.

Methods: We retrospectively analyzed the data of 222 newly diagnosed PCNSL patients treated in 5 referral centers in Israel between 2001 and 2020. During this period, combination therapy became the treatment of choice, rituximab has been added to the induction therapy, and consolidation with irradiation was largely laid off and was mostly replaced by high-dose chemotherapy with or without autologous stem cell transplantation.

Results: Patients older than 60 comprised 67.5% of the study population. First-line treatment included high-dose methotrexate (HD-MTX) in 94% of patients with a median MTX dose of 3.5 gr/m^2 (range 1.14–6 gr/m^2) and a median cycle number of 5 (range 1–16). Rituximab was given to 136 patients (61%) and consolidation treatment to

TABLE 1: Patients' characteristics at diagnosis.

Characteristic	Median (range) or %
Number of patients	222
Age	66 years (28–94)
50≥	36 (16%)
51–60	36 (16%)
61–70	71 (32%)
71–80	61 (27.5%)
80≤	18 (8%)
Sex- M/F	109/113 (Ratio 0.96)
ECOG PS	
0	17/219 (8%)
1	70/219 (32%)
2	59/219 (27%)
3	45/219 (20%)
4	28/219 (13%)
Elevated LDH	101/208 (49%)
Number of enhancing lesions	
Single	106/218 (49%)
Multiple	112/218 (51%)
Deep Brain Lesions	107/203 (53%)
Mode of diagnosis	
Craniotomy	27/221 (12%)
Stereotactic Biopsy	184/221 (83%)
CSF cytology	7/221 (3%)
Vitrectomy	3/221 (1.5%)
Vitreoretinal involvement	29/164 (18%)
Elevated CSF protein	86/140 (61%)
Positive CSF cytology	24/155 (15.5%)
Histopathologic diagnosis	
Diffuse large B-cell lymphoma	210/222 (95%)
Non-GCB	83/93 (89%)
GCB	10/93 (11%)
High grade lymphoma	5/222 (2%)
T-cell lymphoma	1/222 (0.5%)
Others	6/222 (3%)

Abbreviations: F, female, GCB, germinal center B-cell like, M, male.

124 patients (58%). Patients treated after 2012 received significantly more treatment with HD-MTX and rituximab, more consolidation treatments, and autologous stem cell transplantation. The overall response rate was 85% and the complete response (CR)/unconfirmed CR rate was 62.1%. After a median follow-up of 24 months, the median PFS and OS were 21.9 and 43.5 months respectively with a significant improvement since 2012 (PFS:12.5 vs. 34.2 $p = 0.006$ and OS: 19.9 vs. 77.3 $p = 0.0003$). A multivariate analysis found that the most important factors related to OS were obtaining a CR followed by rituximab treatment and ECOG performance status.

Conclusions: The observed improvement in outcomes may be due to multiple components such as an intention to treat all patients regardless of age with HD-MTX- based combination chemotherapy, treatment in dedicated centers, and more aggressive consolidation with the introduction of HDC-ASCT.

The research was funded by: No funding

Keywords: diagnostic and prognostic biomarkers, combination therapies, aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

546 | THE ROLE OF UPFRONT LENALIDOMIDE MAINTENANCE FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA PATIENTS RESPONDING TO FIRST-LINE MTX TREATMENT

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Background: Consolidation therapy improves duration of response in primary central nerves system lymphoma (PCNSL). Lenalidomide maintenance has shown potential activity in elder adults with PCNSL. However, the efficacy of front-line lenalidomide maintenance in non-elder PCNSL has never been elevated. We aim to evaluate the effect of lenalidomide maintenance on duration of response in newly-diagnosed PCNSLs

Method: This is a retrospective, single-center analysis. The patients with PCNSL who achieved complete remission or partial remission after high-dose methotrexate induction therapy were enrolled. Lenalidomide maintenance of 25 mg/d was administered orally for 21 days of every 28-day for 24 months in 35 patients, and no further treatment in the observe group. The efficacy and safety data were analysis.

Results: 69 patients were enrolled at Peking Union Medical College Hospital from 2003 to 2021. The median age was 58.0 years, and 50.7% ($n = 35$) were male. Patients totaling to 57 (82.6%) achieved CR and 12 (18.4%) achieved PR status. Thirty-five patients received lenalidomide maintenance, the median duration of lenalidomide was 18 (2–36) months. It was well tolerated and barely affected the quality of life. After a median follow-up of 32.6 months, there were fewer relapsing and death events in the maintenance group.

However, the median PFS was similar between groups (36.1 months vs. 30.6 months, HR 0.78, $p = 0.446$), and so did the median OS (HR 0.4263, $p = 0.091$). In the PR patients after induction, lenalidomide maintenance improved PFS and OS significantly.

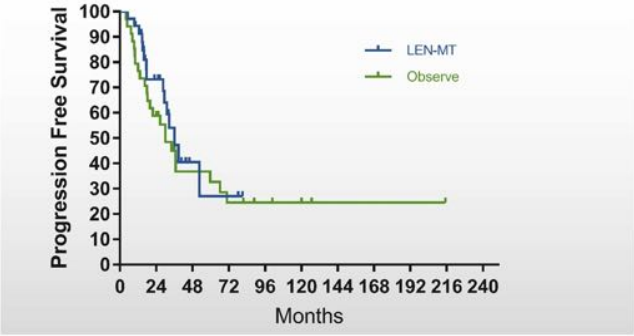
Conclusion: This is the first study to compare lenalidomide maintenance with observation as frontline treatment in PCNSL, the improvement of PFS and OS were not observed, although the safety profile was satisfied.

Encore Abstract—previously submitted to EHA 2023

The research was funded by: CAMS Innovation Fund for Medical Sciences (CIFMS) 2021-I2M-C&T-B-005.

Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy

No conflicts of interests pertinent to the abstract.



547 | REAL WORLD EXPERIENCE OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA IN A MULTI-ETHNIC ASIAN COHORT

Y. H. Tan[1], S. Zhou[2], M. Tao[1], S. T. Lim[1], M. Poon[3], E. Chan[3], K. W. Yeoh[4], E. Chang[1], E. Poon[1], N. Somasundaram[1], V. Yang[1], J. Chiang[1], M. F. Harunal Ras[1], T. Tang[1], J. Y. S. Chan[1]

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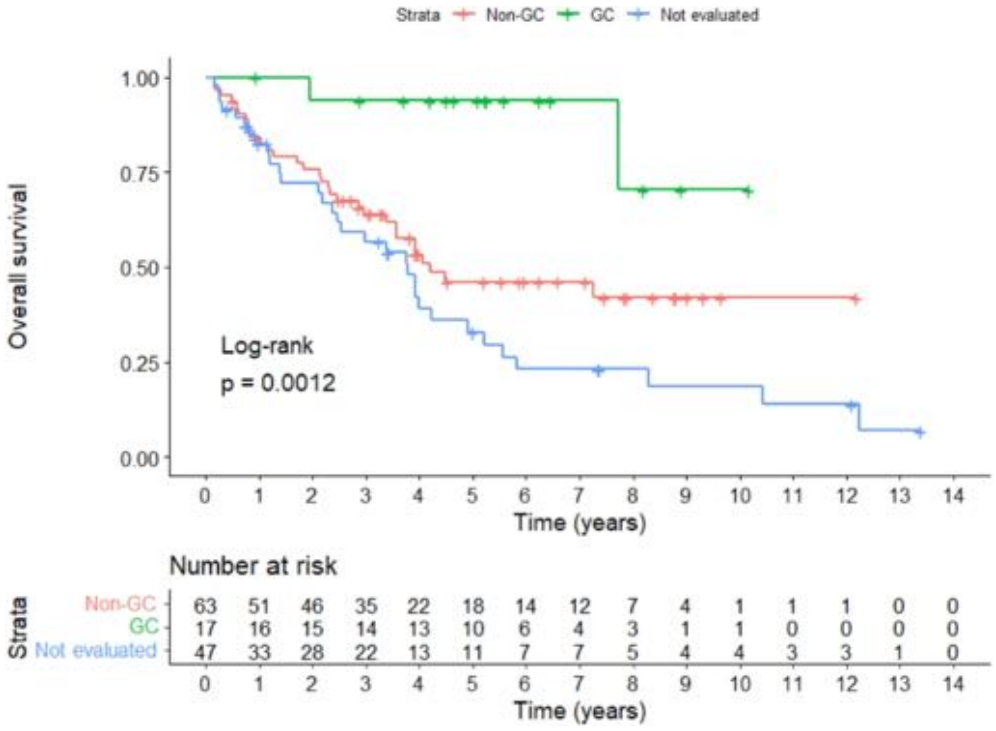
Introduction: Primary Central Nervous System Lymphoma (PCNSL) is a rare and intractable disease with a dismal prognosis. There is a paucity of data on Asian patients' outcome, we aimed to review the clinicopathologic characteristics and prognostic factors influencing survival patterns of Asian patients with PCNSL.

Methods: A retrospective review of adult PCNSL patients treated with frontline chemotherapy (ChT) consisting of methotrexate, vincristine, procarbazine (MVP) with or without rituximab (R-MVP), at two tertiary cancer centres in Singapore, between year 2000 and 2019 was conducted. We recorded data on demographics, ChT regimen, radiotherapy doses, treatment response and survival outcomes. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan-Meier method. Univariate associations were derived using a Cox regression model. All statistical analyses were performed using R.

Results: A total of 127 patients were analysed. Seventy-five (59%) were male and median age at diagnosis was 59 years (range: 20–78).



Ethnic subgroups included 86 (67.7%) Chinese, 27 (21.3%) Malay, 7 (5.5%) Indian and 7 (5.5%) others. Median follow-up duration was 5.9 years (IQR 3.82 to 8.79 years). Most patients (n = 116, 91%) had ECOG performance status of 0-2. We observed that deep brain structure involvement was common (n = 99, 78%). Of the 80% patients with data on cerebrospinal fluid and intraocular involvements, these events were rare at 13.4% and 16.5% respectively. Classification by cell-of-origin revealed that 49.6% were of non-germinal centre (GC) subtype and 13.4% were GC subtype, while the rest were unknown. All patients received the MVP induction chemotherapy regimen with (40.9%) or without (59.1%) rituximab. Consolidation radiotherapy was administered to 100 patients (78.7%), while consolidation chemotherapy using cytarabine was administered to 69 patients (54.3%). None of the patients underwent upfront stem cell transplant. Approximately half the cohort (48.8%) received at least a single dose of intrathecal methotrexate. The median systemic methotrexate dose was 2.5 g/m^2 and median radiotherapy dose was 36 Gy.

The best overall treatment response rate was 94%, with 77% attaining complete response. Median OS was 4.5 years and median PFS was 3.6 years. 2-year PFS was 63.4% and 2-year OS was 76.9%. On univariate analysis, GC subtype was associated with improved PFS (HR = 0.13, 95% CI 0.03–0.55, p = 0.006) and OS (HR = 0.17, 95% CI 0.04-0.71, p = 0.015). Addition of rituximab to ChT and radiotherapy conferred survival advantage though this was not statistically significant.

Conclusion: Contemporary R-MVP induction chemotherapy for Asian PCNSL patients yielded comparable results to published trial data. Cell-of-origin may be a prognostic biomarker that requires further validation.

Keywords: aggressive B-cell non-Hodgkin lymphoma, extranodal non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

548 | BTK INHIBITORS IN CNSL AND HIGH-RISK/REFRACTORY DLBCL PATIENTS: A REAL-WORLD STUDY

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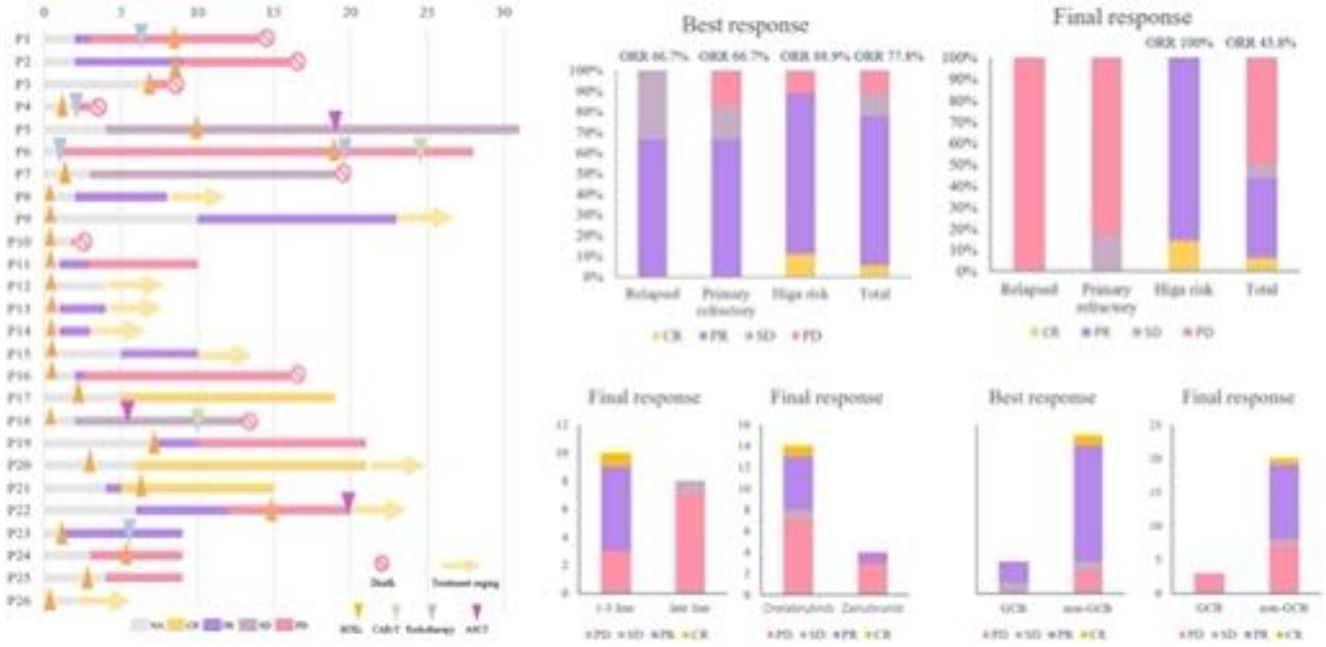
Objective: The effectiveness and prognosis of a BTki-containing regimen in first-line treatment and relapsed/refractory patients were assessed in this study.

Methods: There were 26 patients with DLBCL. BTKi was administered to patients with newly diagnosed, relapsed, refractory primary PCNSL and high-risk/refractory systemic DLBCL, and the effectiveness and PFS were evaluated.

Results: The BTKi therapy study included 26 participants (16 PCNSL, 10 DLBCL). Among PCNSL,3 patients who had achieved PR following MTX-based first-line chemotherapy were given BTKi as a monotherapy for disease recurrence. BTKi patients lived for an average of 5 (1–8) months before dying from disease progression, which is 5 months longer than the typical patient survival period following chemotherapy recurrence. After three rounds of MTX-based chemotherapy, none of the six patients with refractory PCNSL achieved PR. After BTKi was utilized as second-line therapy, the average survival time was increased by 12 (2–21) months. Three patients received early treatment, while the remaining three received BTKi after the third round of medicine. Early patients had a longer average survival period than late ones (11 months vs. 10 months). The remaining seven high-risk patients received first-line chemotherapy and BTKi treatment. The median follow-up duration was 5 months, the ORR was 100%, and neither the median PFS nor the median OS were achieved. The mean maintenance time was 8 months. Among 10 patients with DLBCL, 8 of them are high risk group, and 2 had refractory disease. When the disease of two SCNSL patients advanced, BTKi was used in conjunction with chemotherapy as a salvage treatment, and BTKi was kept up for an



average of 5 months. The efficacy was evaluated as PD. The ORR was 80% (4/5, 1 case was not assessed) and CR rate was 100% in high risk group. Four of these CNS-IPI high-risk DLBCL patients had adrenal involvement and a high IPI score, with BTKi maintained for an average of 6 months, two of them achieved CR, one of PD, and 1 case was not evaluated. The efficacy evaluation was CR in the other two high-risk CD5+ patients, whose BTKi was sustained for 12 months and 6 months, respectively. After receiving standard chemotherapy, the remaining 2 refractory patients kept getting worse. One patient with hepatitis B cirrhosis had elevated AST and ALT levels after one course of medication, so BTKi was stopped. The other patient was kept on BTKi alone for 4 months, but the efficacy was still PD. Patients with PCNSL have a dismal prognosis, in particular, the average survival time for R/R patients is less than two months.

Conclusion: Although the long-term benefit of BTK inhibitors on patients who have experienced relapse is limited, early treatment and combination therapy can further improve their prognosis. Early use of BTK inhibitors may be advantageous for patients with DLBCL who are at high risk, particularly those who are at high risk for CNS-IPI.

The research was funded by: National Natural Science Foundation of China (8226010026), Natural Science Foundation of Gansu Province (22JR11RA053)

Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies, combination therapies

No conflicts of interests pertinent to the abstract.

549 | EFFICACY AND SAFETY OF BTK INHIBITORS IN VITREORETINAL LYMPHOMA: A SINGLE-CENTER RETROSPECTIVE ANALYSIS OF 24 PATIENTS

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Purpose: Vitreoretinal lymphoma (VRL) is a rare subtype of lymphoma. The optimal treatment strategy is not yet defined. 60%–90% of VRL will progress to PCNSL. Therefore, central nervous system (CNS) prophylaxis for VRL patients is critical. Our previous studies have shown that BTK inhibitors monotherapy can replace repeated intravitreal injection of low-dose methotrexate, with rapid effect and a certain preventive value for the CNS. This study aimed to expand the sample size and extend the follow-up time to retrospectively analyze the efficacy and safety of BTK inhibitors in VRL.

Method: A total of 24 VRL patients admitted to the Department of Hematology in Beijing Tongren Hospital from May 2020 to December 2022 were included. The clinical characteristics, treatment methods, treatment outcomes, survival status and treatment-related adverse reactions were retrospectively analyzed.

Results: The median age was 62 years. There were 18 primary VRLs (PVRLs). The IL-10 in aqueous humor at baseline was significantly increased, and the IL-10/IL-6 ratio was greater than 1. There was no evidence of CNS involvement in 23 patients. All patients were treated with a BTK inhibitors (zanubrutinib 160 mg bid, or orelabrutinib 150 mg qd), and nine of them were also treated with intraocular injection of methotrexate. After 1 month of treatment, 21 patients had CR (87.5%) and 2 patients had PR (8.3%). The IL-10/IL-6 levels of aqueous humor were lower than 1 in all patients. The median duration of BTK inhibitors was 10 months. At a median follow-up of 17 months, 15 patients (62.5%) developed disease progression, including 11 with CNS infiltration and 4 with intraocular recurrence. The median PFS was 11.9 months, and the median OS was not reached. The 1-year PFS rate was 34% and the 1-year OS rate was 96%. The recurrence rate was 33.3% in the combined treatment group and 80.0% in the monotherapy group. Three patients died, all from CNS progression. BTK inhibitors were well tolerated, with grade 1-2 hypertension of 16.7%, grade 1 hypotension of 4.2%, grade 1 joint pain of 8.3%, grade 1 subcutaneous bleeding and ecchymosis of 25.0%. Four patients developed COVID-19 infection and BTK inhibitor medication was suspended. All patients had negative COVID-19 test within 2 weeks and did not develop significant pneumonia.

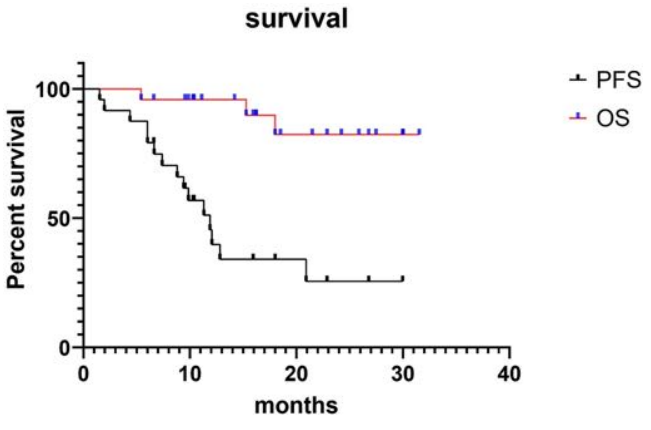
Conclusion: BTK inhibitors showed rapid local control of VRL and were well tolerated. However, monotherapy with BTK inhibitors does not provide adequate central nervous system prophylaxis, and the combination of BTK inhibitors with other drugs, such as high-dose methotrexate, should be explored.

Keywords: BTK inhibitor, CNS prophylaxis, methotrexate, vitreoretinal lymphoma

The research was funded by: This work was supported by grants from the National Natural Science Foundation of China (grant No. 81873450, 82170181), Beijing Hospitals Authority Youth Programme (code: QML20200201), and Beijing Natural Science Foundation (No.7222027) to Liang Wang.

Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies

No conflicts of interests pertinent to the abstract.



550 | EFFICACY AND SAFETY OF FIRST-LINE COMBINATION THERAPY VERSUS MONOTHERAPY FOR PRIMARY VITREORETINAL LYMPHOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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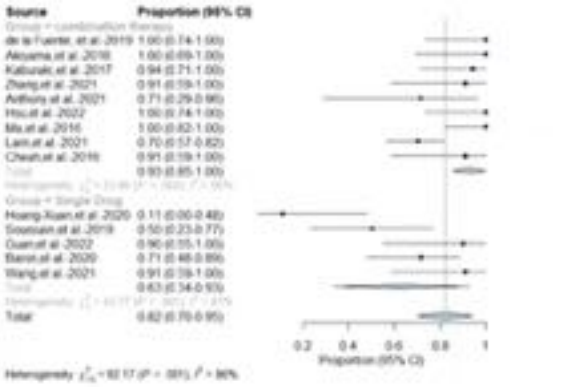
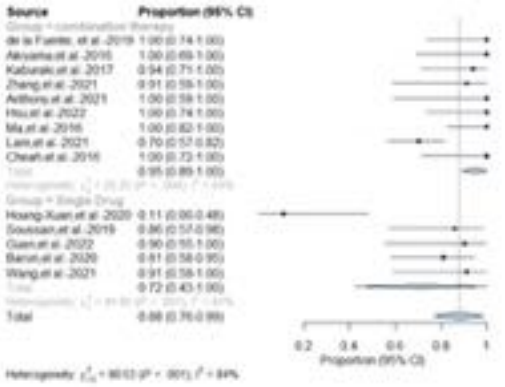
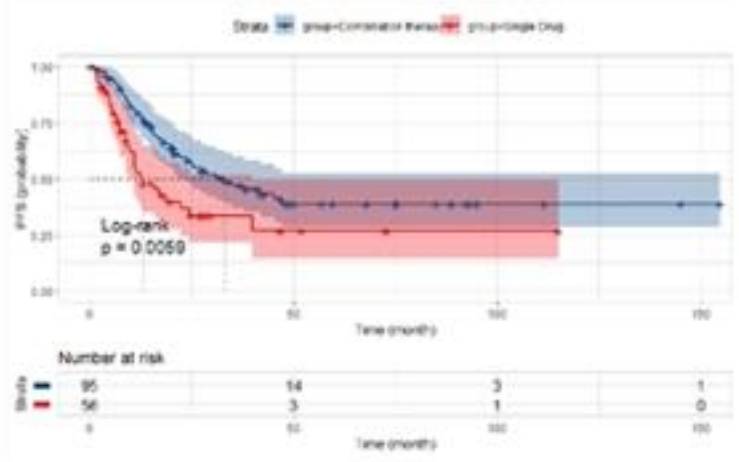
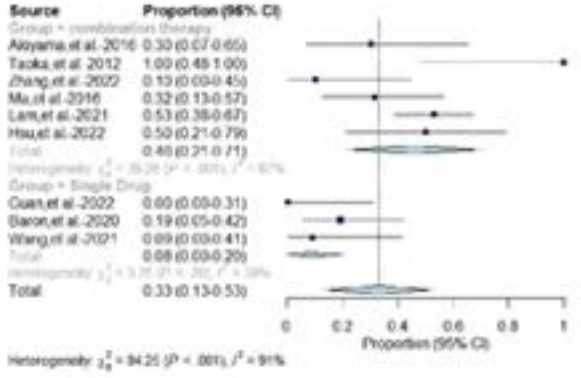
Objective: Primary vitreoretinal lymphoma (PVRL) is a rare primary central nervous system lymphoma (PCNSL) that affects vitreous and/or retina, 90% of which will eventually progress to CNS involvement, and no optimal treatments have been defined yet. PVRL is typically treated with intraocular methotrexate, high-dose intravenous methotrexate, or local radiotherapy as first-line modalities, which are often used in combination to enhance efficacy. Recently, we demonstrated the value of BTK inhibitors in the treatment of PVRL in a prospective phase 2 clinical trial. However, The effectiveness and safety of BTK inhibitors, lenalidomide, and temozolomide as monotherapy for PVRL remain uncertain.

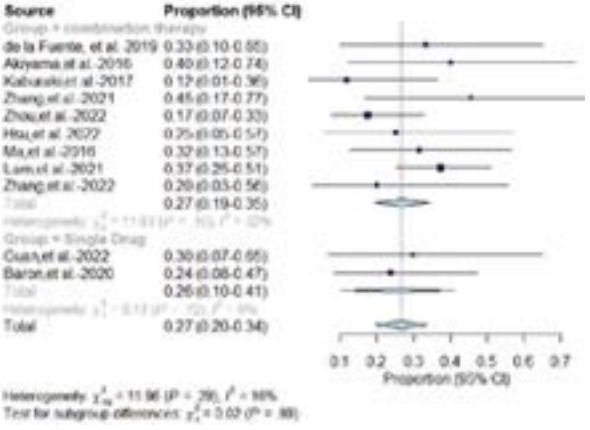
Methods: A systematic review and meta-analysis of clinical trial data and conference abstracts in PVRL patients treated with combination therapy and monotherapy were conducted through a search of PubMed, Embase, and Scopus databases until December 2022. A total of 17 studies comprising 278 patients were included, and











survival data were extracted from 151 patients due to inconsistent units across studies.

Results: The combinational therapy strategies often include intraocular injection of methotrexate (ioMTX)+ intravenous injection of high-dose MTX (ivMTX), ocular radiotherapy+ivMTX, ioMTX+lenalidomide/BTK inhibitors. The monotherapy strategies include BTK inhibitors monotherapy, lenalidomide monotherapy, ioMTX monotherapy, ivMTX monotherapy. Overall, combination therapy resulted in higher overall response rate (ORR) and complete response rate (CRR) compared to monotherapy (ORR: 95% vs. 72%, CRR: 94% vs. 63%). There was a significant difference in median progression-free survival (PFS) between the two groups, with a longer PFS observed in the combination treatment group (33 months vs. 13 months, $p = 0.0059$). However, the combination therapy group had a higher incidence of grade 3/4 toxicity than the monotherapy group (46% vs. 8%), mainly catract, bone marrow suppression, and keratitis.

Conclusion: This study found that combination therapy had better OR and CR rates, longer PFS, and more toxicity compared to monotherapy in the treatment of PVRL. Although monotherapy like BTK inhibitors showed good tolerability, its long-term efficacy needs to be further explored through prospective studies.

Keywords: BTK inhibitors, meta-analysis, primary central nervous system lymphoma, vitreoretinal lymphoma

The research was funded by: This work was supported by grants from the National Natural Science Foundation of China (grant No. 81873450, 82170181), Beijing Hospitals Authority Youth Programme (code: QML20200201), and Beijing Natural Science Foundation (No. 7222027) to Liang Wang.

Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies, combination therapies

No conflicts of interests pertinent to the abstract.

551 | MR-GUIDED ADAPTIVE RADIOTHERAPY FOR GASTRIC LYMPHOMA, PRELIMINARY RESULTS FROM ONGOING STUDY

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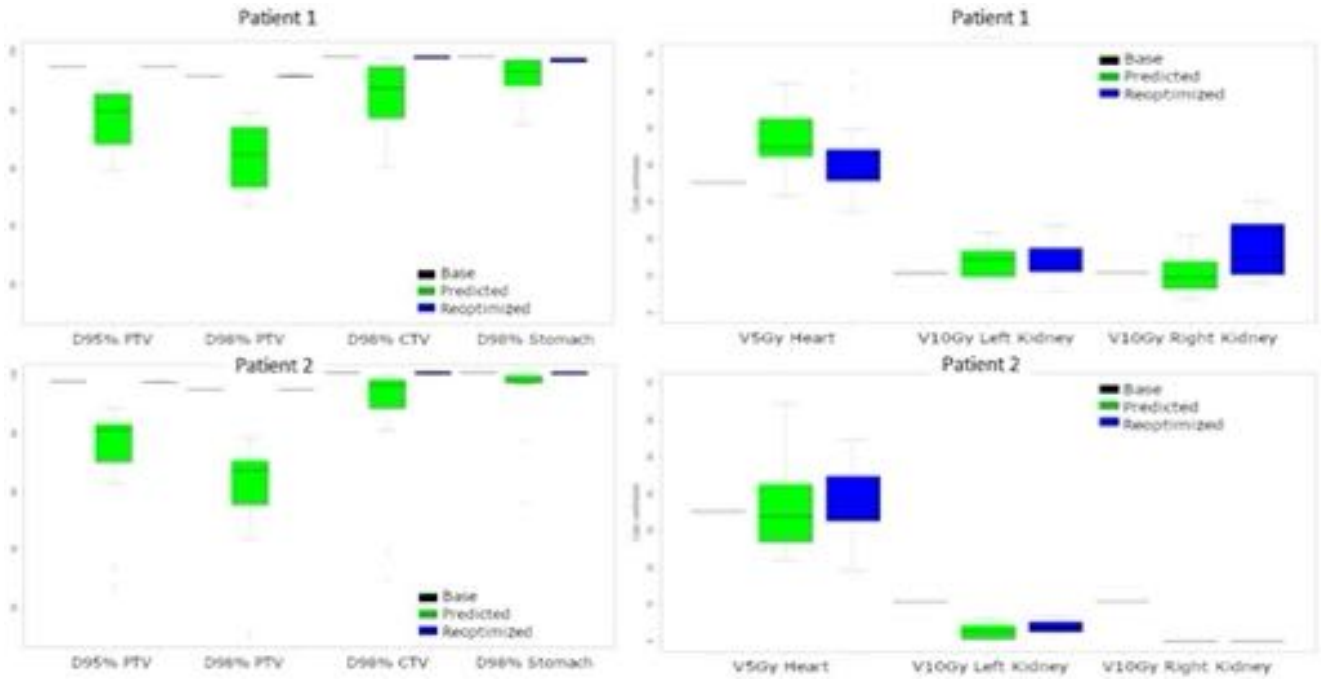
Radiotherapy is a curative treatment in indolent lymphoma and an important part of the combined treatment for aggressive gastric lymphoma. New technologies have changed the options for normal tissue sparing with same target dose coverage substantially. One of the new technologies, MR-guided daily adaptive radiotherapy (MR-ART) is a modality that could be advantageous for patients who need radiotherapy for gastric lymphoma due to the improved soft tissue contrast for daily image guidance, possibility of tracking and gating on internal anatomy, and the ability to account for large daily anatomical variations, so the treatment can be delivered with the intended dose to the stomach with reduced dose to the heart and left kidney.

The purpose of this study is to report a preliminary analysis from an ongoing protocol for MR-ART for patients with gastric lymphoma and investigate if daily adaption with MR-ART improves target coverage relative to no adaption.

Materials/Methods: At present 4 patients with gastric lymphoma have been recruited to participate in our protocol for MR-ART and provided written informed consent. All patients were planned in



(comfortably deep) inspiration breath-hold on the MR-linac (MRIdian, ViewRay) using intensity modulated radiotherapy (IMRT) for the base plan. The prescription dose was 24 Gy in 12 fractions in 3 patients and 2 Gy × 20 in one patient. All patients were treated on the MR-linac with MR-ART, with internal gating on the superior region of the stomach near the heart.

Results: In this ongoing trial, we have performed analyses of the treatment with daily adaption with MR-ART improved target coverage relative to the predicted plan for the first two patients (base plan recalculated on the daily anatomy) (Figure 1). For example, the dose to 95% of the target (D95%) improved from 77% to 95% of the prescription dose for the predicted plan compared to the adapted plan for patient 1 and from 72% to 98% for patient 2 (mean of all fractions). The results for the volume (cubic centimeters) of the heart and kidneys risk receiving 5 Gy or 10 Gy (V5Gy or V10Gy) were kept at the same level when comparing the predicted plan to the reoptimized adapted plan (Figure 2).

Conclusion: Preliminary results from this novel protocol on MR-ART for patients with gastric lymphoma show large improvements in target coverage with similar doses to organs at risk for patients treated with MR-ART relative to the predicted plan with no adaption. Treatment planning, daily recontouring, reoptimization of the plan, tracking and gating, and treatment delivery on the MR-linac were feasible, and further analysis will be performed in the two patients undergoing treatment now and when more patients have been accrued.

Keywords: extranodal non-Hodgkin lymphoma, ongoing trials, radiation therapy

No conflicts of interests pertinent to the abstract.

552 | RADIATION THERAPY IN THE MANAGEMENT OF PRIMARY GASTRIC DIFFUSE LARGE B-CELL LYMPHOMAS: LONG-TERM OUTCOMES OF 82 PATIENTS

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Introduction: Our group has recently published its long-term experience treating gastric MALT lymphomas with involved site radiation therapy (ISRT) and supported the use of RT alone as standard of care for H pylori independent MALT. For primary gastric (PG) diffuse large B-cell lymphomas (DLBCL), R-CHOP is the mainstay of therapy, but RT to the stomach primarily as consolidation has rarely been analyzed. In this study, we focus on patients (pts) with PG DLBCL who received combined modality therapy.

Methods: 285 consecutive pts with PG lymphomas treated with RT between 1/2000 and 1/2021 at our institution were retrospectively identified. Baseline characteristics and follow-up data were abstracted. Overall response rate (ORR) was assessed with Lugano PET criteria and endoscopy. Overall survival (OS) was calculated using Kaplan-Meier. Toxicity was assessed with CTCAE v4.0.

Results: Of 285 pts, 203 (71%) had PG MALT and 82 (29%) PG DLBCL. Baseline characteristics are summarized in Table 1. In the DLBCL pts, 74 (90%) received consolidation RT after limited (3-4 cycles) or full (6 cycles) chemoimmunotherapy (CT), 4 (5%) received RT after 2 lines of CT, 2 (3%) received first line RT followed by CT, 1 (1%) had 3 lines of CT and RT, and 1 (1%) was treated with surgery, 2

	MALT (n=203)	DLBCL (n= 82)
Sex (M/F)	86 (42) / 117 (58)	40 (49) / 42 (51)
Race		
White	174 (85.7)	71 (86.6)
Black	7 (3.4)	3 (3.7)
Asian	5 (2.5)	1 (1.2)
Unknown/Other	17 (8.4)	7 (8.5)
Transformed FL	-	3 (4)
Transformed MALT	-	9 (11)
No Transformation	-	70 (85)
Baseline Radiographic Staging		
PET	83 (40.9)	49 (60)
CT	58 (28.6)	20 (24)
MRI	2 (1.0)	0 (0)
No Imaging	60 (29.5)	13 (16)
Baseline EGD	201 (99)	82 (100)
Lugano Staging (Baseline)		
Stage I	182 (89.7)	55 (67.1)
Stage II	11 (5.4)	17 (20.7)
Stage IV	7 (3.4)	6 (7.3)
Unknown	3 (1.5)	4 (4.9)
Bulky Tumor (*≥6 cm*)	5 (2.5)	8 (9.8)

lines of CT, and RT. In the 74 pts who received CT+RT as first line treatment, the median RT dose was 3060 cGy (range 1620-3600). Based on post-chemo pre-RT EGD and PET, 61 (82%) pts were in CR, 7 (10%) had PR, 3 (4%) had SD and 3 (4%) pts were not assessed. Overall, 66 (89%) pts who received RT after CT achieved a CR. Of the remaining 8 (11%) pts who did not achieve a CR after RT, 4 had PR, 1 had SD, 1 was lost to FU, 1 started additional CT before response assessment and 1 pt died. The 2 pts in the DLBCL group who received first line RT achieved CR after RT. Side effects after RT were mild and limited to nausea and fatigue. The median follow-up time was 5.4 years (95% CI 0.4, 20.4) in DLBCL pts and 6.3 yrs (95% CI 0.3, 22.1) in MALT pts. The 5-year OS was 80% (95% CI 71%–90%) for DLBCL and 96% (95% CI 93%–99%) for MALT.

Conclusion: Adding stomach RT following chemoimmunotherapy is feasible, well-tolerated and safe. More in depth analysis PG DLBCL is underway, with a plan to compare outcomes of patients treated with CT alone versus CT followed by RT, and further analyze treatment-related toxicities, progression-free survival, and patterns of recurrence.

Keyword: aggressive B-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

B. Imber
Honoraria: GT Medical Technologies

553 | CLINICAL CHARACTERISTICS AND PATHOLOGICAL DISTRIBUTION IN NON-HODGKIN LYMPHOMA OF WALDEYER'S RING FROM SINGLE INSTITUTION IN CUBA

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Incidence of non-Hodgkin's lymphoma (NHL) has been increasing in Cuba in the last decades. Waldeyer's ring (WR) is the most common site of NHL involving the head and neck. In this study we retrospectively analyzed the clinicopathological characteristics of patients diagnosed from NHL of WR from January 2000 to December 2019 at the Institute of Oncology and Radiobiology in Havana, Cuba. A total of 97 patients (53 male and 44 female) were included. Median age of 67 years old (range 18-92), 66.0% over 60 years. The main symptom at diagnosis included odynophagia 41.2% and otalgia 12.3%; b-symptoms were presented only in 10.3% of patients, and regional lymph nodes were involved in 66% of patients. The tonsils were the predominant affected subsite 78.3%. Most of the patients were diagnosed in localized stages 73.2% (24 stage I, 42 stage II) Diffuse large B-Cell Lymphomas was the most common histologic subtype (65 patients, 67.0%), followed by peripheral T-cell lymphoma (8 patients, 8.2%) and mantle cell lymphoma (8 patients, 8.2%). Combined treatment of chemotherapy (CT) ± rituximab with involved field radiotherapy (IFRT) was the main therapeutic approach (51.2%), followed by CT ± rituximab in 40.1% of cases. Objective response was achieved in 76.3% (complete response 64.0%). Five years overall survival of the entire series was 59.2% (diffuse large B-cell lymphoma 62.4%). International Prognostic Index (IPI) related factors such as age over 60 years, advanced stage at diagnosis or elevated level of LDH; high intermediated or high IPI and also treatment related factors such as not be treated with IFRT, and to not achieve complete response were significatively associated with worse five-years overall survival. In conclusion, diffuse large B-Cell lymphoma found to have the higher incidence, combined treatment of CT+IFRT was the most prescribe treatment. IPI-related factors, being treated with IFRT and to achieve completed response were established as factors to impact in overall survival.

Keyword: extranodal non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

554 | CLINICOPATHOLOGICAL CHARACTERISTICS OF PATIENTS WITH NON-HODGKIN LYMPHOMA OF THE OCULAR ADNEXA

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The most common malignant tumors of the ocular adnexa are non-Hodgkin lymphomas (NHL). The aim of this study was to describe the clinicopathological characteristics of patients diagnosed from NHL from ocular adnexa (OAL) at the Institute of Oncology and Radiobiology in Havana, Cuba. Data of patients from January 2008 to December 2019 were retrospectively reviewed. A total of 74 patients (41 male, 33 female) were included. The median age was 63 years old (range 29–89), 62.2% ≥ 60 years, most were Caucasian (70.3%). The main symptom at diagnosis included ocular mass (83.8%), proptosis (41%); lymph nodes were involved in only 17.4% of patients. Indolent lymphomas (marginal zone lymphoma 28, small cell lymphocyte 10,

follicular 5 and mantle cell lymphoma 3) were more frequent 62.2% versus aggressive 37.8% (diffuse large B-cell lymphoma 24, peripheral T-cell Lymphoma 4, Burkitt's 1). Most of the cases were diagnosed in localized stage 68.9% (43 stage I, 8 stage II). Involved field radiotherapy (IFRT) was the main treatment for indolent localized stage lymphomas while chemoimmunotherapy ± IFRT for aggressive one's. The overall survival at 5 and 10 years for patients diagnosed from aggressive OAL was 66.4% and 53.2% respectively while for indolent was 79.9% and 74.0%. In conclusion most of the OAL occurred in patients over 60 years old with predominance of indolent lymphomas, specifically marginal zone lymphoma and have confirmed that IFRT is the main choice for treating localized indolent OAL. Excellent outcomes were achieved with the standard approach.

Keyword: extranodal non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

555 | PRIMARY BREAST LYMPHOMA: PATIENT CHARACTERISTICS, TREATMENT OPTIONS AND OUTCOMES: A MULTI-CENTER STUDY OF THE HELLENIC COOPERATIVE LYMPHOMA GROUP

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Introduction: Primary Breast Lymphoma (PBL), defined as lymphoma primarily arising on the breast in the absence of previously detected lymphoma localizations, is a very rare entity, representing approximately 1% of non-Hodgkin Lymphomas (NHL), 2% of extranodal lymphomas and 0.5% of all breast tumors. It is histologically diverse with Diffuse Large B-cell lymphoma (DLBCL) being the most common type, followed by Marginal Zone (MZL) and Follicular Lymphoma (FL). Due to its low prevalence and high histologic diversity there is a scarcity on both the recommendations for its treatment and the data on its outcomes.

Methods: We retrospectively analyzed data of consecutive patients diagnosed with PBL in 8 medical centers in Greece. Data were summarized using descriptive statistics, and survival was analyzed using the Kaplan-Meier method.

Results: Between 9/1997 and 10/2022, 30 patients were diagnosed with PBL (female/male: 28/2) at a median age of −60 (range, 31-86) years. In most patients (97%) there was unilateral involvement with a slight predominance of the right (n = 18) versus the left breast (n = 11). Histologic subtypes were DLBCL in 22 patients (74%), MZL in 7 (23%) and FL in 1 (3%). Nobody had B symptoms at diagnosis. All patients with aggressive NHL underwent a lumbar puncture for assessment of Central Nervous System (CNS) involvement. All were negative for CNS infiltration. Nineteen patients had Ann Arbor Stage IE and 11 IIE with involvement of regional lymph nodes. In 86% of cases lactate dehydrogenase was normal. One third of the patients had increased beta-2-microglobulin.

Eighteen patients with DLBCL (81%) received Rituximab-based chemoimmunotherapy and 3, in the pre- Rituximab era, received chemotherapy without anti-CD20. In 4 cases adjuvant radiotherapy was administered. One elderly patient received Radiation therapy only. Five patients with indolent lymphoma were treated with Rituximab monotherapy and 1 underwent surgical excision of the tumor as only treatment. It is noteworthy that CNS prophylaxis was offered on half (n = 11) of the DLBCL cases but no CNS relapse occurred in any patient. Three documented DLBCL relapses occurred in the bones, the original breast and the mediastinum lymph nodes respectively. Two of the relapsed patients were promptly put into CR with second line therapy and only the patient with the mediastinum relapse died to his lymphoma. Three patients with MZL had relapsed or refractory disease, but all of them were promptly put into remission with second line treatment. With a median follow up of 84 months (range 5–210), the median disease free survival and overall survival were not reached.

Conclusions: PBL has an excellent outcome across all histologic subtypes. Importantly, our data show that the aggressive histologic subtype is not correlated with CNS involvement or relapse.

Keyword: Extranodal non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

556 | CLINICAL PRESENTATION, OUTCOME, AND PROGNOSTIC FACTORS IN PATIENTS WITH INTRAVASCULAR LARGE B-CELL LYMPHOMA: THE ASIA EXPERIENCE FROM A SINGLE-CENTER RETROSPECTIVE STUDY

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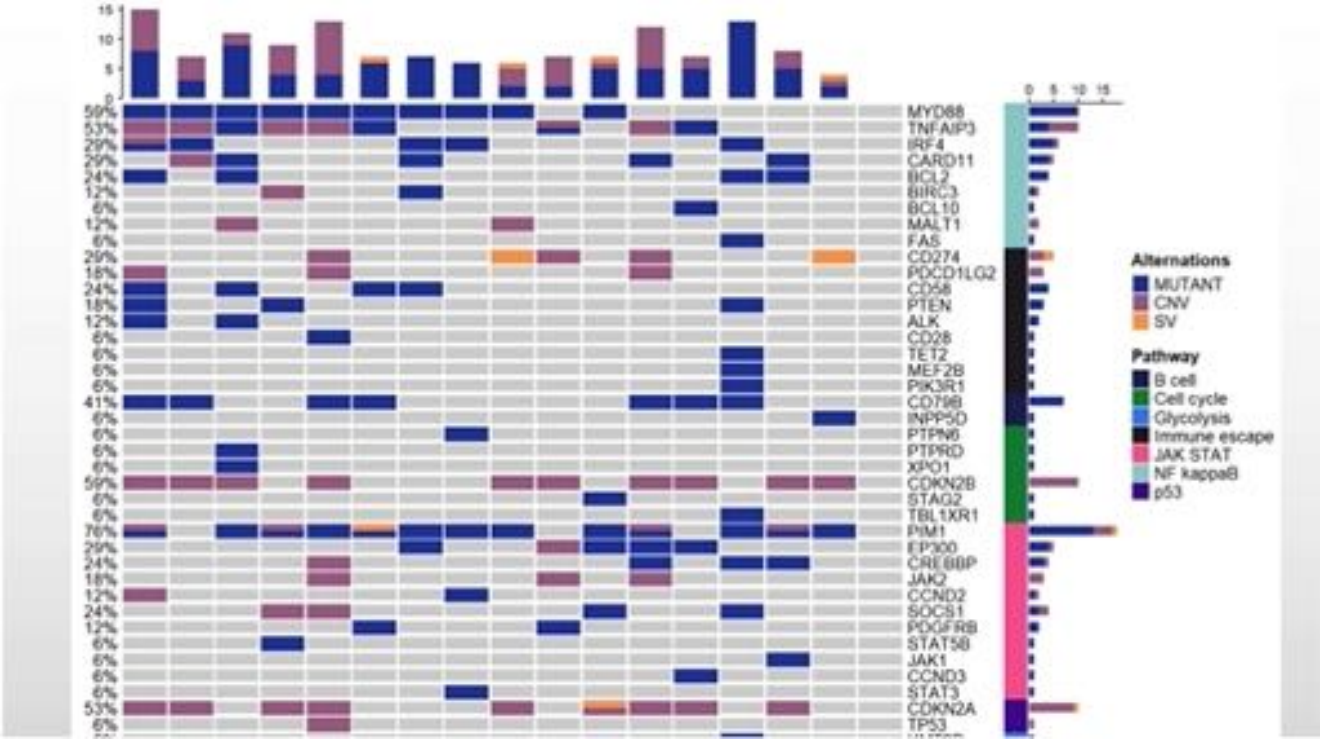
Introduction: Intravascular large B-cell lymphoma (IVLBCL) is a rare, clinically aggressive lymphoma for which there is no available standard treatment. IVLBCL characterized by selective growth in the lumina of small vessels in systemic organs usually presents with many



nonspecific signs and symptoms such as fever of unknown origin and involvement of the central nervous system and skin.

Methods: This is a retrospective, single-center study of 59 patients. Only HIV-negative, immunocompetent patients with untreated IVLBCL were included. The demographics, diagnostic details, therapeutic management, and outcome in patients with untreated IVLBCL were analyzed.

Results: 59 patients were identified in a PUMCH from December 2010 to February 2023. The median age at diagnosis was 58 (range 32–77). 30 (51.8%) were male. 43 patients (72.9%) had an IPI score >3 and 47 patients (79.7%) had a performance status ≥2. All patients belonged to Ann Arbor stage IV and 52(88.1%) had B symptoms. The most frequent extra-nodal locations were skin (n = 30; 50.8%), lung (*n* = 25; 42.4%), central nervous system (*n* = 24; 40.7%), and bone marrow (*n* = 20; 33.9%). Fever, hypoxemia, and edema were the most common presenting symptoms. Diagnosis of IVLBCL was made by random skin biopsy (25), other lesions biopsy (15), bone marrow biopsy (11) and TBLB (8). Plasma cell-free DNA has been detected in 17 patients and these patients frequently had mutations of PIM-1 (76%), MYD88 (59%), CDKN2B (59%) and TNFAIP3 (53%). All of the 40 patients who have detected serum IL-10 concentration had elevated IL-10 concentration (≥5 pg/mL, range 11.5–1000 pg/mL). 23 patients received zanubrutinib plus R-CHOP therapy, 22 received a regimen of anthracycline-based chemotherapy containing rituximab, and 5 received systemic chemotherapy without Rituximab. 18 of all patients also received intrathecal or systemic methotrexate to prevent CNS relapse. After a median follow-up of 22.8 months, the estimated median progression-free survival and overall survival for the entire cohort were 119.8 and 122.9 months. The use of methotrexate and zanubrutuinib was not associated with better PFS or OS.

Conclusions: This is the largest reported series of IVLBCL in Asia and highlights the aggressive clinical picture of IVLBCL in the real world. The outcome was not satisfied in the R-CHOP regimen-based era and new therapies are in demand.

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Keywords: aggressive B-cell non-Hodgkin lymphoma, chemotherapy

No conflicts of interests pertinent to the abstract.

557 | EVALUATION OF FERTILITY IN WOMEN TREATED WITH THE R-DA-EPOCH REGIMEN FOR PRIMARY MEDIASTINAL B CELL LYMPHOMA (PMBCL)

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Background: R-DA-EPOCH and R-CHOP ± radiotherapy are the most commonly used regimens in PMBCL, a disease that primarily affects young women. The cure rate exceeds 80%. Consequently, treatment-related complications are increasingly recognized, with gonadal failure and amenorrhea playing a fundamental role, causing significant psychological and social impact. This is more prevalent in female patients, in whom collection and cryopreservation of oocytes/ovarian tissue are not applied in everyday clinical practice. Published data are scarce on this subject.

The aim of this study is the prospective evaluation of gonadal function in young women with PMBCL who are receiving chemotherapy (CT) with the R-DA-EPOCH regimen. We present our preliminary results on 13 patients.

Subjects and Methods: Women ≤40 years, receiving first-line treatment with 6 cycles of R-DA-EPOCH, were included. Up to date, 13 patients have been analyzed, with a median age of 27.5 years: 12 PMBCL, 1 grey zone lymphoma. Hormonal measurements were performed at pre-specified time points: before treatment (t0), during CT(t1), at the end of CT(t2) and every six months (t6, t12) thereafter. The following hormones were measured: follicle-stimulating hormone (FSH), lutenizing hormone (LH), progesterone (PG), estradiol (E2), anti-Mullerian hormone (AMH). FSH reflects gonadal function in women (increased levels indicate gonadal dysfunction). AMH is considered to be the most sensitive biomarker for gonadal reserve (decreasing values correlate with ovarian insufficiency). E2 and progesterone are the major sex hormones.

Results: Gonadal damage, reflected by the decrease in AMH, was evident [median values: 16.6 pmol/L(t0), 0.16 pmol/L(t1), 3,28 pmol/L (t2), amh0-1 $p = 0.005$, amh0-2 $p = 0.028$]. AMH values sharply decreased from the beginning to the middle of CT and remained low throughout the treatment period. After the end of CT, AMH remained low, and returned to normal values a year after the end of treatment. In contrast to AMH, no clear alteration was seen with FSH and LH possibly because 50% of the patients received prophylactic treatment with GnRH analogues, that blocks their release from the pituitary. Estradiol and progesterone did not change significantly. As far as the menstrual cycle is concerned, all patients reported cycle disorders, with 80% developing amenorrhea after the first cycle of immunochemotherapy.

Conclusion: Gonadal function in female patients with PMBCL malignant lymphomas is affected by the R-DA-EPOCH regimen. Gonadal dysfunction was evident from treatment initiation and normalized a year after the end of CT, indicating a chemotherapy-dependent genotoxic effect. AMH proved as a more sensitive marker compared to FSH, as it is independent of menstrual cycle phases and of prophylactic GnRH analogue administration.

Keywords: aggressive B-cell non-Hodgkin lymphoma, other, late effects in lymphoma survivors

No conflicts of interests pertinent to the abstract.

558 | PRIMARY HEPATIC LYMPHOMA: ROLE OF LOW-DOSE RADIOTHERAPY AND PAIRED LITERATURE REVIEW

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Introduction: Primary hepatic lymphomas (PHL) are a rare form of non-Hodgkin lymphoma for which there are no established treatment guidelines. Available literature is largely comprised of small case reports and there are no reports on low-dose radiotherapy (RT) for indolent PHL. We report our institutional experience treating PHL within the context of existing literature to better understand the role of RT. We hypothesize that low-dose RT offers comparable outcomes to observation (obs), surgery and systemic therapy (ST) in select patients.

Methods: We conducted a single-institution retrospective analysis of all biopsy-proven PHL patients (pts) diagnosed from 2000-2021 without other lymphomatous solid organ involvement. Subgroup analysis was performed for diffuse large B-cell lymphoma (DLBCL) and indolent lymphoma (IL). Univariable (UVA) and multivariable analysis (MVA) for overall survival (OS) was performed using the Cox proportional hazards model. Literature review was conducted using key words including "liver", "lymphoma", and "treatment" to identify all available reported cases of PHL.

Results: We identified 30 PHL pts within our institution and 192 pts from literature review, with subgroup analysis of DLBCL and IL pts in the institutional cohort ($n = 15, 9$) and literature review ($n = 78, 76$), respectively (Table 1). Among the IL institutional cohort ($n = 9$), 3 pts underwent obs and 2 each received RT, ST and surgery. There were no recurrences among pts treated with RT, surgery or obs with median OS of 12.4 years, whereas both ST pts experienced either transformation to DLBCL or recurrence. Both RT patients received low-dose RT of 4Gy in 2 fractions. Literature review identified only 1 case report of RT use for IL with a dose of 41.4Gy.

Conclusions: There is limited literature regarding use of RT in indolent PHLs. We present the first report of low-dose RT for indolent PHL with comparable outcomes to alternative modalities. PHL DLBCL is predominantly treated with ST in both our institutional experience and in the literature. Although our data is limited by the small cohort size reflective of the rarity of disease, our results are encouraging for the consideration of low-dose RT as a management option for appropriate patients with indolent PHL.

Keywords: extranodal non-Hodgkin lymphoma, radiation therapy

No conflicts of interests pertinent to the abstract.

DLBCL Subgroup	MSKCC Cohort (n=15)			Literature Review (n=76)
	N (%)	Odds Ratio	p-value	N (%)
Median Age	67 (48-89)		0.07	64 (19-82)
Sub-Type	15 (100)			-
Germinal Center	7 (44)			
NOS	6 (38)			
Activated B-Cell	2 (13)	6.0	0.06	
ECOG				-
0	11 (73)	**0.68**	**0.02**	
1-2	4 (27)			
Lugano Staging				
I-II	11 (73)	**0.71**	**0.04**	74 (97)
III-IV	4 (26)			2 (3)
Treatment Modality				
Systemic Therapy	14 (93)	0.98	0.12	43 (57)
Surgery	2 (13)	1.02	0.11	21 (28)
Observation	1 (7)			4 (5)
Radiation therapy	-			4 (5)
Response to Therapy				
Complete Response	12 (80)			31 (41)
Partial Response	1 (7)			3 (4)
Progression of Disease	1 (7)			16 (21)
Lost to Follow-up	1 (7)			2 (3)
Indolent Lymphoma Subgroup	**MSKCC Cohort (n=9)**			**Literature Review (n= 78)**
	N (%)	**Odds Ratio**	**p-value**	**N (%)**
Median Age	67 (42-77)		0.03	62 (30-89)
Subtype				
Marginal Zone Lymphoma	5 (56)			66 (85)
Follicular Lymphoma, G1-2	3 (33)			10 (13)
Low-Grade BCL, NOS	1 (11)			2 (3)
ECOG 0	9 (100)			-
Lugano Staging				
I-II	8 (89)	0.9	0.17	78 (100)
III	1 (11)			
Treatment Modality				
Radiation	2 (22)	3.4	0.14	1 (1)
Systemic Therapy	2 (22)	1.0	0.24	30 (38)
Surgery	2 (22)	0.54	0.61	40 (51)
Observation	3 (33)			6 (6)
Response to Therapy				
Complete Response	6 (66)			40 (51)
Progression	2 (22)			6 (77)
Lost to Follow-up	1 (11)			1 (1)

AGGRESSIVE LYMPHOMAS

559 | VALIDATION OF SIMPLIFIED GERIATRIC ASSESSMENT AND ELDERLY PROGNOSTIC INDEX IN OLDER PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA IN CHINA

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Introduction: Diffuse large B-cell lymphoma (DLBCL), with a median age of 66 years at diagnosis, is the most common malignant lymphocytic tumor and predominantly affects elderly individuals. To

predict the prognosis of elderly DLBCL patients, the Fondazione Italiana Linforni (FIL) developed the simplified geriatric assessment (sGA; shown in Figure 1A) and Elderly Prognostic Index (EPI; shown in Figure 1B). Both sGA and EPI are associated with overall survival (OS) and progression-free survival (PFS) of older patients with DLBCL, while EPI could predict early mortality in these cohorts. However, whether sGA and EPI are suitable for elderly patients with DLBCL in China has not been further explored.

Methods: The study included 257 patients with DLBCL aged ≥65 years who were newly diagnosed in Beijing Hospital and Peking

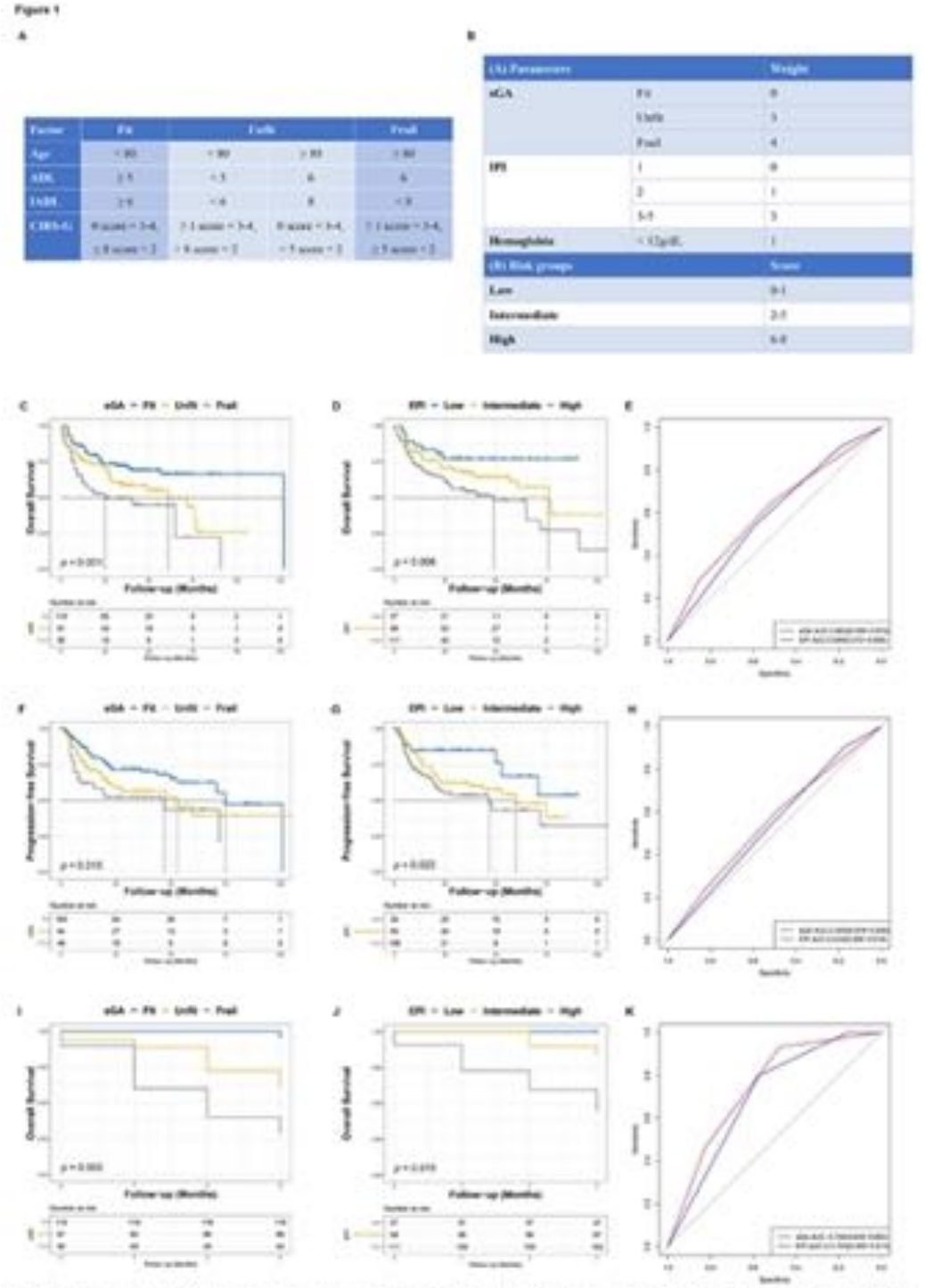

Figure 1. The prognostic value of Simplified Geriatric Assessment (sGA) and Elderly Prognostic Index (EPI) in older patients with diffuse large B-cell lymphoma (DLBCL). (A) The sGA model. (B) The EPI model. (C) Kaplan-Meier curve of sGA for OS in older patients with DLBCL. (D) Kaplan-Meier curve of EPI for OS in older patients with DLBCL. (E) ROC curves of sGA and EPI for OS in older patients with DLBCL. (F) Kaplan-Meier curve of sGA for PFS in older patients with DLBCL. (G) Kaplan-Meier curve of EPI for PFS in older patients with DLBCL. (H) ROC curves of sGA and EPI for PFS in older patients with DLBCL. (I) Kaplan-Meier curve of sGA for early mortality in older patients with DLBCL. (J) Kaplan-Meier curve of EPI for early mortality in older patients with DLBCL. (K) ROC curves of sGA and EPI for early mortality in older patients with DLBCL.

University Third Hospital from December 2007 to December 2020. Kaplan-Meier curves were performed to evaluate the prognostic value of sGA and EPI. The receiver operating characteristics curve (ROC) was used to assess the sensitivity and specificity.

Results: According to the criteria of sGA, 257 patients were stratified into fit (45.1%), unfit (35.4%) and frail (19.5%) groups. Due to insufficient information in the medical records, the 247 patients were identified as low-risk group (15.0%), intermediate-risk group (40.1%) and high-risk group (44.9%). The median follow-up was 23 months (range 1–127 months). As shown in Figure 1C and Figure 1D, both sGA ($p < 0.001$) and EPI ($p = 0.008$) were related to OS of elderly patients with DLBCL. ROC curves showed that both sGA (AUC: 0.602; 95% CI: 0.530–0.674; $p = 0.006$) and EPI (AUC: 0.584; 95% CI: 0.512–0.656; $p = 0.027$) could predict the OS of elderly patients with DLBCL (shown in Figure 1E). Similarly, both sGA ($p = 0.015$; shown in Figure 1F) and EPI ($p = 0.023$; shown in Figure 1G) were related to the PFS of elderly patients with DLBCL. Regrettably, ROC curves showed that neither sGA (AUC: 0.555; 95% CI: 0.479–0.630; $p = 0.158$) nor EPI (AUC: 0.544; 95% CI: 0.468–0.619; $p = 0.268$) could predict the PFS (shown in Figure 1H). The next section of the study was concerned with the predictive value of sGA and EPI in early mortality of elderly patients with DLBCL. Figure 1I and Figure 1J indicated that sGA ($p = 0.002$) and EPI ($p = 0.015$) were associated with the early mortality of elderly patients with DLBCL, separately. ROC curves explicated that both sGA ($p = 0.002$; AUC: 0.744; 95% CI: 0.634-0.853) and EPI ($p = 0.009$; AUC:0.703; 95% CI: 0.590-0.815) could predict the early mortality of elderly patients with DLBCL (shown in Figure 1K).

Conclusions: Our study confirmed that sGA and EPI were good-to-use tools to predict OS and early mortality of older patients with DLBCL in China for the first time. Otherwise, to predict PFS, the modified model remains further studied.

The research was funded by: grants from the National High Level Hospital Clinical Research Funding (No. BJ-2022-127), CAMS Innovation Fund for Medical Sciences (CIFMS, No. 2021-I2M-C&T-A-020), the Beijing Natural Science Foundation (No. 7232137), and Beijing Health Technologies Promotion Program (No. BHTPP2022094).

Keywords: non-Hodgkin (pediatric, adolescent, and young adult), other

No conflicts of interests pertinent to the abstract.

560 | A POPULATION-BASED STUDY REVEALS THE UNIQUE CLINICAL CHARACTERISTICS AND LONG-TERM SURVIVAL OF PATIENTS WITH GRAY ZONE LYMPHOMA

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Background: Gray zone lymphoma (GZL) is a rare disease entity with pathological features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (HL). Given its rarity, a relative paucity of clinical data exists describing GZL, constraining our ability to better understand the clinical features and outcomes of GZL.

Objective: In this study, we analyzed detailed clinical features, outcomes, and prognostic factors of patients with GZL.

Methods: Chemotherapy-treated patients with GZL diagnosed between 2000 and 2018 were selected. Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) 18 registries database. Cox and Fine-Gray regression models were used to evaluate overall and GZL-specific survival, respectively.

Results: A total of 211 patients were selected. Most patients were aged 55 years or older (51.7%). The lymph node was the most common primary site (85.3%). Patients with nodal primary sites presented more often with B symptoms ($p = 0.041$) and advanced-stage disease ($p < 0.001$). The 5-year overall survival (OS) rates and lymphoma-specific death rates of treated GZL patients were 75.1% (95% CI: 69.0%–81.2%) and 20.8% (95% CI: 15.1%–26.5%), respectively. Patients receiving combined radiotherapy had improved OS ($p = 0.011$) and lymphoma-specific survival (LSS, $p = 0.031$). Other independent prognostic factors included age, ethnicity and race. Patients who received combined radiotherapy, without B symptoms, Hispanic, and younger than 55 years generally had higher 3-year conditional survival (CS) rates.

Conclusion: This study set an age cutoff of 55 years, which provided an excellent estimate for the prognosis of GZL. It identified that B symptoms, ethnicity and race were the prognostic factors for OS, LSS and CS. It is found that combined radiotherapy improved OS and LSS, and treated GZL patients may achieve long-term survival.

Keyword: gray zone lymphoma; clinical characteristics; overall survival; lymphoma-specific survival; conditional survival

Encore Abstract—previously submitted to EHA 2023

Keyword: aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

561 | LOCALIZED NODAL DIFFUSE LARGE B CELL LYMPHOMA: IS RADIOTHERAPY NEEDED?

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is clinically, morphologically and genetically a heterogeneous group of malignant

proliferation of large B-cell lymphoid cells. At diagnosis, 25% of DLBCL presents as a localized disease.

Therapeutic options for localized DLBCL include short-course or extended-course chemotherapy regimens such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) with or without radiotherapy. Regarding the number of cycles, the choice differs in the different oncology services and the role of radiotherapy remains controversial. Another frequent issue regarding this pathology is the prognosis of the cell of origin (COO) in the localized form. In the literature, non-germ center (N-GC) subtype is correlated with lower overall survival (OS) when compared to germinal center (GC) . This lower overall survival of the non-GC subtype has not been reported in patients with localized DLBCL.

Objectives: The primary objective is to compare progression-free survival (PFS) and overall survival (OS) at 5 years of different therapeutic strategies, including 3-4 cycles of chemotherapy with or without radiotherapy and 6 cycles of chemotherapy with or without radiotherapy. The study's secondary objective is to compare the prognostic significance of COO, GC and non-GC phenotypes in localized DLBCL.

Methods: This is a single-center Brazilian, observational, retrospective, descriptive and analytical study, to be carried out at the referenced Brazilian cancer center. The study included patients aged 18 years and over, with a nodal DLBCL diagnosis located in the period between 2007 and 2020. PFS and OS curves were performed in 5 years of the population stratified by treatment and cell of origin.

Results: A total of 90 patients with limited-stage nodal DLBCL were included. The group that received 3 or 4 cycles of chemotherapy (n = 5) had PFS and OS at 5 years of 75%. The second group received 6 cycles of chemotherapy (n = 41) and had PFS and OS at 5 years of 89% and 92%, respectively. The third group (n = 17) received 3 or 4 cycles of chemotherapy and radiotherapy, and had 100% PFS and OS at 5 years. The fourth group (n = 27) received 6 cycles of chemotherapy and radiotherapy and had PFS and OS at 5 years of 87%. There was no statistical difference between the groups. A total of 76 patients had immunohistochemical data extracted from pathology reports to determine COO by Hans' algorithm. A GC phenotype was observed in 47% of patients (n = 36). At 5 years, the PFS and OS for the GC cohort were 94% for both, and for the non-GC cohort 85% and 87% respectively.

Conclusion: There was no significant difference in PFS or OS for the therapeutic strategies, including 3–4 cycles of chemotherapy with or without radiotherapy and 6 cycles of chemotherapy with or without radiotherapy. The cell of origin did not show a difference in 5 year PFS or OS for localized nodal DLBCL.

Keyword: aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

562 | FRONT-LINE RISK-ADAPTED THERAPY PRESENTED FAVORABLE OUTCOMES FOR YOUNG PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: RESULTS FROM A CONSECUTIVE COHORT IN CHINA

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Background: Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous disease. Young patients with high-risk diseases treated with standard chemotherapy have poor outcomes, and the optimal therapy has not been established yet.

Aims: To improve the outcome of young DLBCL patients with clinically or biologically high-risk features by a risk-adapted treatment paradigm.

Methods: Patients with untreated DLBCL from the National Longitudinal Cohort of Hematological Diseases in China (NCT04645199) were prospectively included in the protocol from April 2012 to April 2021. Patients in high-risk (HR) group (aaIPI $\geq$2) were assigned to receive intensive immunochemotherapy (IIC) (mainly DA-EPOCH-R). Patients in the low-risk (LR) (aaIPI <2) group were usually administered R-CHOP, while those diagnosed with biological high-risk (bio-HR) features including double/triple hit (DH/TH), double-expressor lymphoma (DEL), 17p/TP53 deletion, or CD5 positivity (CD5+) were also treated with IIC.

Results: Three hundred and ten cases were included in this study, with 128 in the HR group and 182 in the LR group, respectively. The median age for all patients was 49 years (range, 14 to 65 years). The baseline clinicopathological characteristics of all patients are summarized in **Table 1:** 51.6% were male, 58.7% had stage III/IV diseases, 45.3% had elevated LDH, 62.0% had extranodal involvement and 56.1% had non-germinal center B-cell like (non-GCB) subtype disease. Regarding the bio-HR features, more patients in the HR group had DEL (39.8% vs. 20.1%), MYC-R (20% vs. 9.8%), and DH/TH status (10.6% vs. 5.2%) compared to those in the LR group. The median number of chemotherapy cycles was six (2–8 cycles). The end-of-treatment response was assessable in 308 patients who received at least two cycles of treatment. The overall response rate (ORR) of all patients was 91.3%, and 252 (79.9%) patients had CR or CRu.

With a median follow-up of 42.8 months, the estimated 5-year progression-free survival (PFS) and overall survival (OS) rates for the entire cohort were 75.1% and 84.4%, respectively. Patients in the HR group achieved a 5-year PFS of 63.5% and OS of 73.5%, and frontline ASCT had a positive impact among patients in remission (p = 0.024 for PFS). The outcome was excellent for patients in the LR group with 5-year PFS and OS rates at 83.7% and 92.2%. In both HR

Table 1. Baseline patient characteristics (n = 310)

variables	All(n=310)	High-risk group(n=128)	Low-risk group(n=182)
Median age (range)	49(14-65)	50(14-65)	48(14-65)
Sex			
Male	160(51.6)	56(43.9)	104(57.1)
Female	150(48.4)	72(56.3)	76(42.9)
Ann Arbor Stage			
I-II	128(41.3)	1(0.8)	127(69.8)
III-IV	182(58.7)	127(99.2)	55(30.2)
ECOG PS			
0-1	267(87.3)	89(70.1)	178(99.4)
≥2	39(12.7)	42(29.9)	1(0.6)
Missing	4	1	3
Extranodal involvement			
0	118(38.0)	16(12.5)	102(56.0)
1	105(33.9)	43(33.6)	62(34.1)
≥2	87(28.1)	69(53.9)	18(9.9)
BMI			
Yes/available	33/305(10.8)	30/126(23.8)	3/170(1.7)
Bulk disease > 7.5cm			
Yes/available	45/309(14.6)	29/127(22.8)	16/182(8.8)
LDH elevated			
Yes/available	136/306(44.4)	119/127(93.7)	19/181(10.5)
aaIPI risk group			
0	111(35.8)	0	111(61.0)
1	71(22.9)	0	71(39.0)
2	96(31.0)	96(75.0)	0
3	32(10.3)	32(25.0)	0
COO			
GCB	130(43.9)	46(39.3)	84(46.9)
Non-GCB	166(56.1)	71(60.7)	95(53.1)
Missing	14	11	3
CD5 positive			
Yes/available	40/288(13.9)	20/119(16.8)	20/169(11.8)
DEL			
Yes/available	74/267(27.7)	41/103(39.8)	33/131(20.1)
FISH rearrangements			
MYC-R	30/217(13.8)	17/85(20.0)	13/132(9.8)
BCL2-R	22/208(10.9)	12/80(15.0)	10/122(8.2)
BCL6-R	46/176(26.1)	22/72(30.6)	24/104(23.1)
DH/TH	17/238(7.1)	10/104(10.6)	7/134(5.2)
17p/TP53 del	47/188(25.0)	18/84(21.4)	29/104(27.9)

ECOG PS, Eastern Cooperative Oncology Group Performance Score; BMI, bone marrow involvement (monoclonal B cells≥10%); LDH, lactate dehydrogenase; aaIPI, age-adjusted International Prognostic Index; COO, cell of origin; GCB, germinal center B-cell like; DEL, double expressor lymphomas; FISH, fluorescence in situ hybridization; R, rearrangement; DH/TH, double hit/triple hit.

and LR groups, no difference in survival was observed for patients with at least one of these features versus those without, indicating bio-HR features could be partly overcome by IIC. However, DH/TH and 17p/TP53 deletion were still associated with a poorer OS in the HR group ($p = 0.004$ and 0.014).

Conclusion: This is the first and largest single-center study in China to report the treatment of young DLBCL patients with risk-adapted therapy, in which IIC was applied to selected patients with clinically or biologically high-risk features and showed favorable results.

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies

No conflicts of interests pertinent to the abstract.

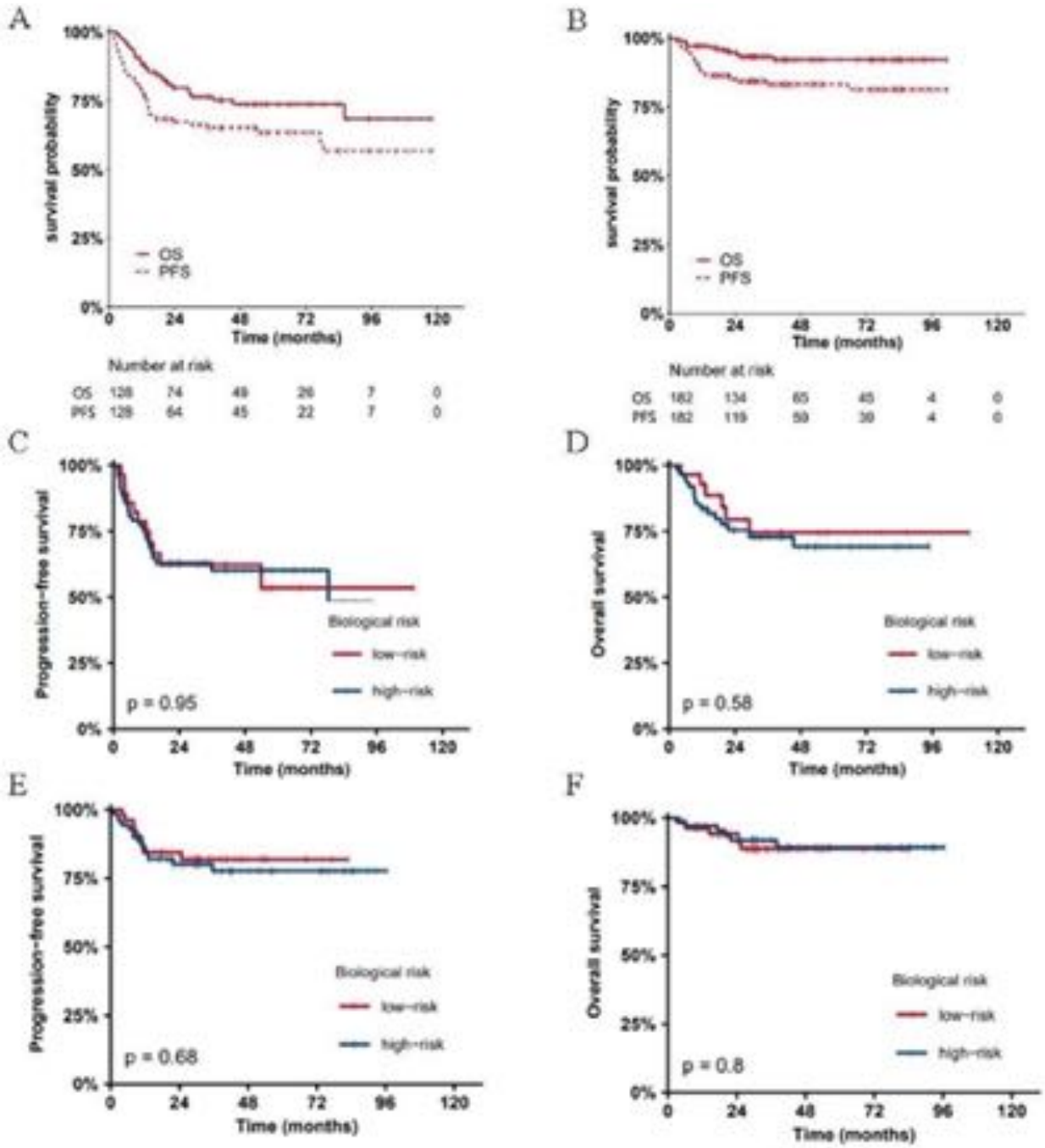

Figure 1. Survival outcome of the 310 DLBCL patients treated by risk-adapted strategy. (A-B) Kaplan-Meier estimates of PFS and OS for the high-risk (aaIPI≥2; n=128) and low-risk group (aaIPI < 2; n=182), respectively. (C-D) Kaplan-Meier estimates of PFS (P = 0.962) and OS (P = 0.621) for patients with (n=62) or without (n=27) adverse biological markers in the high-risk group. (E-F) Kaplan-Meier estimates of PFS (P = 0.68) and OS (P = 0.80) for 123 patients with (n=70) or without (n=53) biological high risks in the low-risk group.

563 | DARATUMUMAB AND EPOCH FOR HIV+/- PLASMABLASTIC LYMPHOMA: A FEASIBILITY STUDY OF THE AIDS MALIGNANCY CONSORTIUM (AMC 105)

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Background: Plasmablastic lymphoma (PBL) is a high-grade neoplasm with features of both lymphoma and myeloma. It was originally described primarily in people with HIV in the pre-antiretroviral era and nearly always fatal. However, a recent study of the AIDS Malignancy Consortium with EPOCH showed a 70% two-year event free survival (Ramos, Blood 2020). Currently, the majority of PBL patients do not have HIV (Ciaccio, ASH 2020). We sought to improve outcomes by adding daratumamb (dara), a monoclonal antibody targeting CD38 and used therapeutically in myeloma, to the EPOCH backbone. The primary endpoint of this ongoing study is feasibility of completing ≥3 cycles of protocol therapy.

Methods: Patients (pts) with or without HIV and stage II-IV disease are eligible after no more than one prior cycle of CHOP- or EPOCH-like therapy. The target sample size is 15. Dara is administered in cycle 1-3 weekly and held for platelets <25K or ANC <500. In cycles 4–6 dara is given on day 1 only. Missed dara doses are not made up. A total of 12 doses of dara is possible. Pts entering after one cycle of RCHOP/REPOCH-like treatment received 5 cycles on protocol with 11 possible doses. The study was to be stopped if 4 of the first 5-6 patients could not tolerate at least 3 cycles of dara-EPOCH. EPOCH was dose adjusted as reported previously. (Sparano, Blood 2010) If dara was held for 2 complete cycles at any time, pts continued on EPOCH alone.

Results: Seven pts have been enrolled, and 5 are evaluable for the primary study endpoint and toxicity. Patient characteristics include HIV (2), Stage II (1), stage IV (4), Ki-67 >80% (4). Two patients had 1 prior cycle off protocol. All five pts received ≥3 cycles of dara-EPOCH. Two pts with 1 pre-protocol cycle completed 5 cycles on study; 2 pts completed 6 total cycles on study. One pt completed 5 cycles on study and is still in treatment. All but 2 doses of planned dara were given for a dose density of 96%. Thus far, 2 pts had grade 4 heme toxicity (2 thrombocytopenia, 1 neutropenia); 3 had grade 3 infection; 1 with grade 3 mucositis. To date, after a median follow up of 10.8 months, 1 patient died of progressive lymphoma after cycle 6. No other disease progression has been noted.

Conclusion: We have added daratumumab to EPOCH for PBL, and the early stopping rule has not been invoked following treatment of the first 5 patients. Dose density for planned dara was 96%. Toxicity preliminarily is comparable to EPOCH. The study is enrolling additional patients.

The research was funded by: This work was supported by US National Institutes of Health (NIH), National Cancer Institute (NCI) grant UM1 PO1568. It was also supported by US NIH, NCI award P30 CA008748 to Memorial Sloan Kettering Cancer Center. All authors are supported by the US NCI sponsored AIDS Malignancy Consortium

Keywords: aggressive B-cell non-Hodgkin lymphoma, chemotherapy, immunotherapy

No conflicts of interests pertinent to the abstract.

564 | DIFFUSE LARGE B-CELL LYMPHOMA: REAL-WORLD CLINICAL EXPERIENCE WITH RITUXIMAB PLUS CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE AND PREDNISOLONE IN CUBA

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Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders. Diffuse large B-Cell Lymphoma (DLBCL) is the most common NHL in adults, it accounts around 30-40% of all NHL. Chemoimmunotherapy regimen based on Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is the standard of care for DLBCL patients. The present study investigated its application in the real-world clinical practice at a single institution in Cuba. Data of patients diagnosed from DLBCL and treated with R-CHOP from January 2008 to June 2019 were retrospectively analyzed. A total of 183 patients (57.4% male, 42.6% female) were included, median age 51 years old (range 19–84) 67.2% under 60 years. Extra nodal disease occurred in 47.3% of cases. Most of the cases (66.5%) were diagnosed in localized stage (I–II). Patients were categorized as International Prognostic index (IPI) low 61.3%; low-intermediate 25.2%; high intermediate 11% and high 2.5%. Revised IPI (R-IPI) categories were grouped at very good 15.4%, Good 71.0% and Poor 13.6%. Radiotherapy was associated with the R-CHOP regimen in 45.4% of cases. The objective response rate achieved was 73.8% (complete response [CR] 66.7%). After a median follow-up of 5.7 years, the 5 years overall survival (OS) rate was 71.4%. The 5 years OS rates by age <60 versus ≥60 years (74.1% vs. 66.2% $p = 0.02$), performance status 0-1 vs. 2-4 (73.5% vs. 52.9%; $p = 0.042$) stage I–II versus III-IV (81.2% vs. 52.9%; $p < 0.001$), R-IPI very good versus good versus poor (89.8% vs. 74.5% vs. 49.8%; $p = 0.001$), CR versus No CR (84.1% vs. 38.8%; $p < 0.001$). Multivariate analysis

established that R-IPI very good category (Hazard Ratio [HR] = 2.51; 95% CI 1.14–5.51) and achieve complete response (HR = 6.89; 95% CI 3.4–13.95) were independent favorable risk factors for OS. In conclusion, this analysis of patients with DLBCL treated with R-CHOP in the real-world setting indicated that excellent outcomes are achieved, similar to those reported in the clinical trials.

Keyword: aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

565 | CGA-DRIVEN THERAPEUTIC DECISION IN ELDERLY PATIENTS WITH PREVIOUSLY UNTREATED DLBCL IN CHINA: A MULTICENTER, PROSPECTIVE, OBSERVATIONAL, CONTROLLED COHORT STUDY

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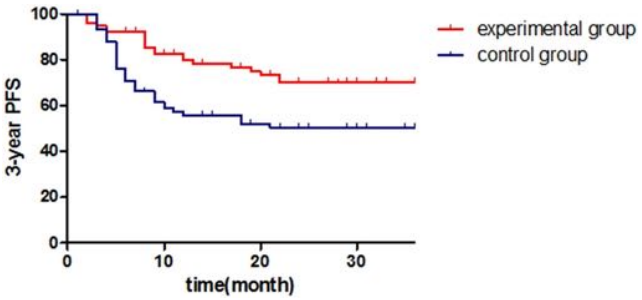
Introduction: Diffuse large B-cell lymphoma (DLBCL) is an aggressive, potentially curable cancer. Although a standard regimen R-CHOP has been shown to cure majority of elderly DLBCL patients. However, some elderly patients can't tolerate the full-dose of R-CHOP due to age, poor physical condition, and severe comorbidities. The Italian Lymphoma Foundation has showed that comprehensive geriatric assessment (CGA) in elderly DLBCL patients can help to objectively and accurately identify patients who were fit for the full-dose of R-CHOP regimens. This multicenter, prospective, observational, controlled cohort study aims to investigate the effectiveness and safety of comprehensive geriatric assessment (CGA) to guide the treatment in elderly patients with previously untreated diffuse large B-cell lymphoma (DLBCL) in China.

Methods: 155 patients from 4 centers in Beijing were enrolled between February 1st 2016 and February 1st2021 (ChiCTR1800016732). Physicians with the same level of academic title in each center were divided into two groups: experimental group and controlled group. In the experimental group, physicians were required to decide treatment based on the results of CGA. In the control group, physicians were blind to CGA results and decided the treatment based on their own clinical experience. 78 patients in the experimental group who will received CGA-driven therapy, 77 patients in the controlled group will received therapy based on clinical judgement. The primary endpoint was 3-year Progression Free Survival (PFS) between two group, the secondary endpoint were Objective Response Rate (ORR), 3-year Overall Survival (OS), or treatment-related adverse events between two groups.

Results: the baseline clinical characteristics of two groups were comparable. According to CGA, 78 patients in the experimental group were classified into three groups: fit (41 patients, 52.6%), unfit (4 patients, 5.1%) and frail group (33 patients, 42.3%). the ORR was 94.9% (74/78), including CR rate was 70.5% (55/78). 3-year OS rates was 79.2%, 3-year PFS rates was 72.9%. however, in the controlled group, the ORR was 81% (62/77), including CR rate was 52% (40/77). 3-year OS rates was 66.2%, 3-year PFS was 54.5%. there was significant difference between the two groups (ORR: $x^2 = 7.421$, $p = 0.006$; CR: $x^2 = 5.629$, $p = 0.018$; 3-year PFS rates: $x^2 = 5.5$, p = 0.019). the toxicity between two group was similar. the number of patients who had lymphoma progression or relapse in the controlled group was higher than that in the experimental group (45.5% vs. 23.4%, $p < 0.05$). lymphoma progression rather than toxicity was the main cause of death among controlled group.

Conclusions: This study suggests that compared with therapy based on clinical judgement, using CGA to guide therapy for elderly patients with previously untreated DLBCL will have better efficacy in China.



Keywords: aggressive B-cell non-Hodgkin lymphoma, Therapeutics and Clinical Trials in Lymphoma - Other

No conflicts of interests pertinent to the abstract.

566 | EFFICACY AND SAFETY OF SELINEXOR COMBINING WITH R-CHOP IN THE TREATMENT OF UNTREATED HIGH RISK (IPI 3-5) GCB SUBTYPE DLBCL PATIENTS: A MULTICENTER REAL-WORLD STUDY FROM CHINA

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Background: Diffuse large B-cell lymphoma (DLBCL) is a highly heterogeneous lymphoma, and it is more difficult to treat for high risk group. The 3-year overall survival (OS) rate of patients with IPI score of 0–1, 2, 3, 4–5 were 91%, 81%, 65% and 59%, respectively. The efficacy for high risk patients was limited even after intensive chemotherapy under R-CODOX-M/R-IVAC (ORR 74.5%; CR 47.3%).

GCB subtype has better prognosis, but 20% of patients still relapsed after R-CHOP [6], and no more benefit was achieved by modifying regimen with new agent like pola-R-CHP. Selinexor is the only approved oral selective nuclear exportin inhibitor which shown a 34% of ORR in GCB subgroup as a monotherapy in relapsed/refractory DLBCL. To provide real world setting data in the patients with IPI score of 3-5 and GCB subtype, we retrospectively analyzed 17 newly diagnosed (ND) high risk (IPI 3-5) GCB subtype DLBCL patients treated with Selinexor and R-CHOP from 4 centers in China.

Methods: We included 17 ND high risk (IPI 3-5) GCB subtype DLBCL patients from 4 clinical sites treated with Selinexor and R-CHOP by January 31, 2023. The objective response, overall survival, and safety data were evaluated.

Results: The median age was 60 years (range 30–74, 35% ≥ 65 yrs), with 8 males (47.1%). All patients were in advanced stage according to Ann Arbor staging system, with 16 patients in stage IV, and 1 in stage III. All patients were treated with Selinexor and standard R-CHOP except for 1 patient who is old (74 years old) and frail treated with R-miniCHOP+ Selinexor. Selinexor was given 40/60 mg (8/9 patients) QW initially.

The ORR and CR were 94.1% and 58.8%, respectively. The ORR and CR in 5 patients with double expressor lymphoma (DEL) were 100% and 60%; 2 patients with molecular high grade lymphoma (MHGL) both responded (1CR 1PR); 8 of 13 patients with ≥2 extranodal lesions completely responded (CR 61.5% ORR 92.3%). Median PFS and OS were not reached yet with a median follow-up of 5 months (range

Characteristics of pts		n（17pts）	%
Age	<65yrs	11	64.7%
	≥65yrs	6	35.3%
Sex	Male	8	47.1%
	Female	9	52.9%
ECOG	1	9	52.9%
	2	7	41.2%
	Unknown	1	5.9%
Ann Arbor staging	IV	16	94.1%
	III	1	5.9%
IPI score	3	12	70.6%
	4-5	5	29.4%
Extranodal lesion number	⩾2	13	76.5%
	<2 or none	4	23.5%
LDH level before treatment	Elevated	8	47.1%
	Normal	8	47.1%
	Unknown	1	5.9%
Ki-67	>80%	9	52.9%
	≤80%	7	41.2%
	Unknown	1	5.9%
MYC expression	<40%	14	82.4%
	≥40%	2	11.8%
	Unknown	1	5.9%
Molecular profile	DEL	5	29.4%
	MHGL	2	11.8%
	Unknown	1	5.9%
Treatment regimens	R-CHOP+X	16	94.1%
	R-miniCHOP+X	1	5.9%
Initial dosage of Selinexor	40mg QW	8	47.1%
	60mg QW	9	52.9%
*IPI: International Prognostic Index			

Table 1. Characristics of patients.

2-14 months). 2 patients got progressed disease in 2 months, and the other 2 progressed after 4 months of treatment.

Common treatment-relate adverse events (all grades, grade 3/4) included: neutropenia (63%, 56%), anemia (50%, 25%), thrombocytopenia (50%, 19%), leukopenia (44%, 44%), fatigue (38%, 0%), anorexia (31%, 0%), hypertriglyceridemia (31%, 0%), nausea/vomiting (25%, 6%). All AEs can be managed with appropriate supportive care and dose adjustments. 6 out of 9 patients got dose reduction of Selinexor to 40 mg (initial in 60 mg QW) due to AE, with 1 happened in C2 and the other 5 happened in C4–C5. All patients were continuously treated after dose reduction, and no treatment-related death occurred. Overall, 10 patients finished 6 cycles of Selinexor+R-CHOP treatment, 3 patients were still receiving therapy.

Conclusion: Once weekly Selinexor can be safely combined with R-CHOP in ND high risk (IPI 3–5) GCB subtype DLBCL patients with ORR $\geq$ 94% and CR of 59%.

Encore Abstract—previously submitted to EHA 2023

Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies

No conflicts of interests pertinent to the abstract.

567 | PHARMACOKINETICS, EFFICACY AND SAFETY OF SUBCUTANEOUS VERSUS INTRAVENOUS RITUXIMAB IN CHINESE PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: A RANDOMIZED TRIAL

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin's lymphoma (NHL) in China. The standard of care for DLBCL is intravenous (IV) rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Compared with IV administration, subcutaneous (SC) administration of rituximab is faster, less invasive, and reduces patients' treatment burden. Global trials have shown that SC rituximab, dosed at 1400 mg, had non-inferior rituximab serum levels and comparable efficacy and safety to IV rituximab at 375 mg/m^2 in patients with NHL; however, data in Chinese patients are lacking.

Methods: This was a Phase II, randomized, controlled, open-label study conducted in nine centers in China from February 2021 to May 2022 (NCT04660799). Patients aged 18–80 years with untreated CD20-positive (CD20+) DLBCL were randomized 1:1 to receive either one cycle of IV rituximab plus seven cycles of SC rituximab (R^{SC}-CHOP), or eight cycles of IV rituximab (R^{IV}-CHOP); both combined with six or eight cycles of CHOP every 3 weeks. IV and SC rituximab were dosed at 375 mg/m^2 and 1400 mg, respectively. Patients were stratified during randomization based on International Prognostic Index (IPI) scores (IPI 0–2 versus 3–5). The primary endpoint was the ratio of trough rituximab serum concentration of SC to IV rituximab ($C_{trough,SC}/C_{trough,IV}$) at Cycle 7. Non-inferiority of $C_{trough,SC}$ versus $C_{trough,IV}$ will be shown if the lower limit of the two-sided 90% confidence interval (CI) exceeded 0.80. Complete response rate (CRR) was assessed by an Independent Review Committee (IRC) using Lugano Response Criteria for Malignant Lymphoma. Safety, tolerability and immunogenicity were also evaluated.

Results: Fifty patients were enrolled: 26 received R^{SC}-CHOP and 24 received R^{IV}-CHOP. Median age was 61.5 (range 19–79) years. The baseline stratification characteristics of IPI scores were well-balanced between both arms; 21 (42.0%) patients had an IPI score of 3–5. Most patients in both SC (24/26, 92.3%) and IV (19/24, 79.2%) rituximab arms completed all eight cycles of rituximab. Geometric mean ratio of $C_{trough,SC}/C_{trough,IV}$ at Cycle 7 was 1.52 (90% CI 1.28–1.79), demonstrating non-inferiority for SC rituximab versus IV rituximab (**Table 1**). The IRC-assessed CRR in the SC rituximab arm (80.8%; 95% CI 60.7–93.5) was similar to that in the IV rituximab arm (62.5%; 95% CI 40.6–81.2). There were no new clinically relevant safety findings, and the incidence of adverse events was comparable between both arms, in line with previous global studies on SC rituximab.

Conclusion: SC rituximab demonstrated non-inferior rituximab serum trough levels and comparable efficacy and tolerability to IV rituximab in Chinese patients with previously untreated CD20+ DLBCL. SC rituximab is a viable route of administration, with potential to reduce burden of administration.

Encore Abstract—previously submitted to EHA 2023

Table 1. Trough serum concentration at Cycle 7, 21 days post-rituximab dose

	IV rituximab[a] (n=17)		SC rituximab[a] (n=22)		Geometric mean ratio[b] (90% CI)
	Geometric mean	CV (%)	Geometric mean	CV (%)	
Trough serum concentration (µg/mL)	90.7	21.1	137.4	36.3	1.52 (1.28–1.79)

[a]Given in combination with CHOP. [b]Geometric mean ratio adjusted for tumor load at baseline.
CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CI, confidence interval; CV, coefficient of variation; IV, intravenous; SC, subcutaneous.

The research was funded by: This study was sponsored by F. Hoffmann-La Roche Ltd.

Keywords: aggressive B-cell non-Hodgkin lymphoma, chemotherapy, combination therapies

Conflicts of interests pertinent to the abstract

S. Grange
Employment or leadership position: Susan Grange is an employee of F. Hoffmann-La Roche Ltd.

L. Bu
Employment or leadership position: Lilian Bu is an employee of F. Hoffmann-La Roche Ltd.

Q. Wang
Employment or leadership position: Qianming Wang is an employee of F. Hoffmann-La Roche Ltd.

Y. Wang
Employment or leadership position: Yanjie Wang was an employee of F. Hoffmann-La Roche Ltd, but is no longer with F. Hoffmann-La Roche Ltd as of 9 March 2023.

568 | CHECK POINT INHIBITORS IN RELAPSED/REFRACTORY GRAY ZONE LYMPHOMA

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Introduction: Gray zone lymphomas have overlapping features between primary mediastinal B-cell lymphoma (PMBCL) and classic Hodgkin lymphoma (cHL). It is a rare and aggressive entity without standard treatment. For relapsed/refractory cases, salvage regimens followed by autologous transplant are recommended. However, many cases are resistant to immunochemotherapy. cHL and PMBCL have high response rates to check point inhibitors (CPI) that could therefore be useful in GZL. We report our single center experience with CPI in this entity.

Methods: In this retrospective, single-center study we identified 21 patients (pts) diagnosed with GZL between 2010 and 2021 (11F, 10M, median age 34). Diagnosis was based on WHO 2016 classification criteria; all cases were reviewed by an expert pathologist. CPI were used as salvage in 9 pts, including pembrolizumab in 5 and nivolumab in 4; in 4 cases CPI were combined with Brentuximab vedotin (BV).

Results: At diagnosis, 76% had B-symptoms, 67% were in stage III/IV, 79% had elevated LDH, 48% had extranodal (EN) involvement and 20% had poor-risk R-IPI score. There were no significant differences between nonmediastinal (n = 8) versus mediastinal (n = 13) cases, except for EN involvement (75% vs. 31%, p = 0.049) and R-IPI score (poor risk in 50% vs. 0% respectively, p = 0.02). First line treatment included ABVD (2), R-CHOP (15), R-CHOEP (2) and R-DA-EPOCH (2). With a median follow up of 50.1 (16.1 to 140.6) months, progression-free (PFS) and overall survival (OS) of the whole series at 3 years were 32% and 90%, respectively. Nine patients were treated with CPI (Figure 1): 7 in third line and 2 in fourth line (78% refractory to the most recent regimen). Median number of CPI cycles was 10 (1–22). Four grade 3–4 adverse events were observed in 2 pts (cholecystitis and cholestasis in 1 patient, neutropenia in 2 pts), both treated with CPI-BV. Overall response rate was 89%, including six pts with complete remission (CR), 2 pts with partial response (PR) and 1 refractory. Median time to CR was 3.3 months. All 5 mediastinal cases obtained CR (including the 4 cases treated in combination with BV), while only 1 nonmediastinal patient attained CR (p = .048). Three pts stopped CPI to proceed to allogeneic hematopoietic transplant (SCT), 3 are still on treatment (referred to SCT) and 3 stopped due to progression. Two nonmediastinal patients (with PR and PD with CPI) died of disease progression. Twelve pts did not

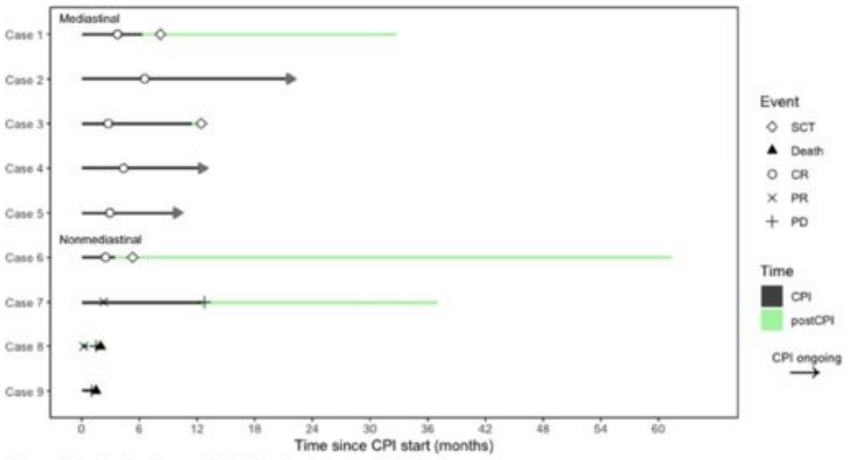

Figure 1. Survival swimmer plot of 9 patients treated with CPI.
CPI: check-point inhibitors; SCT: stem-cell transplant; CR: complete remission; PR: partial remission; PD: progressive disease

receive CPI: 7 with sustained CR after first line and 5 with PR that responded to subsequent therapies (3 consolidated with autologous transplant).

Conclusions: in chemorefractory GZL cases, CPI offered high CR rates with acceptable toxicity, and could be used as a bridge to allogeneic SCT. The combination with BV was well tolerated with 100% response rate. The difference in response between mediastinal and nonmediastinal GZL supports the distinction of these entities in the newer classifications.

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, immunotherapy

Conflicts of interests pertinent to the abstract

M. G. da Silva
Consultant or advisory role Janssen, Roche, Abbvie, Gilead
Educational grants: AstraZeneca

569 | THE OUTCOME OF GLOFITAMAB THERAPY IN PATIENTS WITH AGGRESSIVE REFRACTORY B-NHL IN REAL CLINICAL PRACTICE

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Background: Previous data of clinical trials demonstrated high efficacy of bispecific antibody glofitamab (G) in the therapy of patients with refractory aggressive B-cell non-Hodgkin lymphomas (B-NHL). More than 70% of patients who achieve CR maintain a response within a year according to clinical studies [M. Hutchings et al., 2021]. At the moment, it is required to study this issue in the framework of real clinical practice.

Methods: This study included 24 pts with r/r B-NHL who were treated with G within the Russian Named Patient Program. G was prescribed in escalated regimen: 2.5 mg D8C1, 10 mg D15C1, 30 mg D1C2-12. Anti-CD20 antibody was administrated 1 week before G therapy initiation. Efficacy was analyzed by PET-CT after C3, C7 and C12 using Lugano criteria. Adverse events (AEs) were graded according to NCI CTCAE 5.0.

Results: Median age at G initiation was 47 (27-70), male/female ratio −8/16 (33%/67%). Median number of therapy lines before G was 3 (3-8). Prior autologous SCT was performed in 6 (25%) pts, polatuzumab vedotin in 7 (29%) pts. All patients had active disease at G initiation, ECOG > 1 was in 6 (25%) pts, B symptoms in 5 (21%) pts and bulky disease in 7 (29%) pts. Median follow up was 11 (1-21) months.

At analysis all pts discontinued therapy due to therapy completion (n = 9, 38%), PD (n = 8, 33%), severe COVID-19 (n = 5, 21%) and other reason (n = 2, 8%). Median number of cycles was 7 (2–12).

Overall response rate was 71% (complete response (CR) n = 14, 58%; partial response n = 3, 13%). Nine patients died during G therapy including 6 (18%) pts due to PD and 3 pts—severe COVID-19. Median OS in all patients was not reached, 1-year OS was 62.5% (CI 95%: 40.3-78.4); median PFS was 10.8 months (CI 95%: 3.7-NA), 1-year PFS 50% (CI 95%: 29.1-67.8).

Fourteen patients (58%) achieved CR during G therapy. Median follow up in this group was 12 (8-21) months. At the moment of analysis 1 of 14 pts had a disease relapse and started additional therapy and 1 pt died due to severe COVID-19 pneumonia in CR. Median OS and PFS in patients with CR were not reached, 1-year OS was 92.9% (CI 95%: 59.1–99), 1-year PFS 85.7% (CI 95%: 53.9–96.2).

AEs were presented in 24 (100%) pts including grade 3-4 AEs in 13 (62.5%) and grade 5 AEs (COVID-19) in 3 (12.5%) pts. CRS developed in 13 (54%) pts (grade 1-2 n = 12, grade 3 n = 1). Viral infections occurred in 14 (58%) pts including COVID-19, cytomegalovirus and Varicella zoster virus.

In all patients who had an insufficient response to G therapy the allo-HSCT was considered. However, at the moment of analysis only 1 patient was undergone allo-HSCT after additional therapy.

Conclusions: G therapy demonstrated favorable activity with frequent and durable CR in real practice. At the same time, adverse events were observed in all patients, therefore clinical caution is needed during G treatment considering risk of CRS syndrome and cases of severe viral infections.

Encore Abstract—previously submitted to EHA 2023

Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy

No conflicts of interests pertinent to the abstract.

570 | POLATUZUMAB VEDOTIN IN RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS: A MATCHED-CONTROL ANALYSIS FROM THE THAI LYMPHOMA STUDY GROUP (TLSG)

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Treatments of patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) represent an unmet clinical need. Polatuzumab vedotin (Pola), an anti-CD79b antibody-drug-conjugate (ADC), combined with bendamustine-rituximab (BR), has recently been approved for these patients. However, there were limited data on real-life studies in R/R DLBCL, especially in Thailand. R/R DLBCL patients who received Pola-based regimens as a salvage treatment between 1 April 2021 and 30 March 2022 from the nationwide multi-center in Thailand were included in determining efficacy and safety in the real-world setting. Age, sex, and prior treatments-matched controls were selected from the database of the Thai lymphoma registry. The Pola group and historical control R/R DLBCL patients were compared. Thirty-five patients who received Pola-based treatment (Pola-BR 54.3% and Pola-R 45.7%) were included. The median age was 66 years (IQR 58–79), and the median number of prior treatments was 2 (range 1–4). The overall response rate (ORR) was 62.8%, with complete remission and partial remission of 17.1% and 45.7%. With a median follow-up of 11.8 months, the median progression-free survival (PFS) and overall survival (OS) were 10.6 months and 12.8 months, respectively. Grade 3–4 adverse events (AEs) were mainly hematological: anemia (8.6%), thrombocytopenia (5.7%), neutropenia (22.5%), and febrile neutropenia (8.6%). Compared with 180 matched patients who received non-pola-based therapy, there was a significantly higher ORR in Pola-based salvage treatments (62.8% vs. 33.3%, hazard ratio [HR] 3.52, 95% confidence interval [CI] 1.39-8.95, $p < 0.01$). The survival outcomes were also significantly superior in the Pola group: the median PFS 10.6 versus 4.2 months (HR 0.49; 95% CI, 0.29-0.85; $p = 0.015$), median OS 12.8 versus 7.5 months (HR 0.53; 95% CI, 0.34-0.84; $p = 0.017$). The use of Polatuzumab vedotin combination as a salvage treatment in R/R DLBCL demonstrated promising results with tolerable toxicities in the real-world setting.

Keywords: aggressive B-cell non-Hodgkin lymphoma, chemotherapy, immunotherapy

No conflicts of interests pertinent to the abstract.

571 | INFERIOR OUTCOMES WITH POLATUZUMAB VEDOTIN, BENDAMUSTINE AND RITUXIMAB FOR TREATMENT OF RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA AFTER >1 PRIOR LINE OF THERAPY

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In the pivotal trial, the addition of polatuzumab vedotin to bendamustine and rituximab (Pola-BR) improved overall survival (OS) for stem cell transplant (SCT)-ineligible patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL). However, the optimal position of Pola-BR in the treatment pathway for patients who receive it as a 'stand-alone' treatment, without planned SCT consolidation or CAR T-cell therapy, remains an open question. 71% of patients in the pivotal trial received Pola-BR in 3rd line or beyond but detailed analysis of outcomes by lines of therapy were not presented and published real-world data for this cohort are lacking. We previously reported results of our real-world study of Pola-BR and we now present further analysis of efficacy according to prior treatment exposure.

Methods: Retrospective data were collected for consecutive patients treated with Pola-BR at 28 UK hospitals via the UK Regulatory Agency's Early Access to Medicines Scheme (EAMS) which ran from June 2019 to Jan 2020 prior to marketing authorisation. Patients with R/R LBCL after ≥1 prior treatment were eligible. Treatment was administered according to the marketing authorisation, dose reductions or delays were permitted according to physicians' discretion. Responses were investigator assessed, time to event was measured from the start of Pola-BR.

Results: Pola-BR was administered as stand-alone treatment for 76 of 106 patients who received it via EAMS, treatment intent for the remaining patients was bridge to CAR-T or SCT. Of the stand-alone cohort, 43 received it 2nd line (2L) and 33 at 3rd line or later (≥3L). The median age was 75 years (range 41-88), 71.1% were male. Patients in the ≥3L group were younger and tended to have later stage disease, other characteristics including sex, performance status, IPI and the presence of bulk were well balanced between the groups. 55.8% and 57.6% respectively, were refractory to their last treatment. The objective response rates (ORR) were 73.2% (95% CI 57.1–85.8) and 54.5% (95% CI 36.4%-71.9%) for the 2L and ≥3L groups respectively ($p = 0.1$). The complete response (CR) rates were 48.8% (32.9–64.9) and 30.3% (15.6-48.7) ($p = 0.1$). A best response of progressive disease to Pola-BR was found for 22.0% and 36.4% in the 2L and ≥3L groups respectively.

The 6-month progression free survival (PFS) rates were 54.2% (95% CI 37.9–67.9) and 35.9% (95% CI 20.1–52.0) for the 2L and ≥3L groups respectively (HR 2.17 (95% CI 1.19–3.95), $p = 0.01$). The 6-month OS rate was 68.4% (95% CI 51.8–80.4) in the 2L group and 49.2% (95% CI 30.9–65.2) in the ≥3L group (HR 2.15 (95% CI 1.12–4.14), $p = 0.02$). Longer follow up will be presented.

Conclusion: When used as a stand-alone treatment for SCT-ineligible patients with R/R LBCL, Pola-BR is most effective after 1 prior line of treatment. Survival is limited after 2 or more prior lines and more effective approaches are needed for this difficult to treat group.

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies

Conflicts of interests pertinent to the abstract

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Honoraria: Roche

R. Auer
Honoraria: Beigene

C. Burton
Honoraria: Roche

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Consultant or advisory role: Celgene, Roche, Gilead, Incyte, Abbvie
Honoraria: Celgene, Roche, Gilead, Janssen, Acerta Pharma/AstraZeneca, ADC Therapeutics, Incyte, Abbvie
Research funding: Celgene, Roche, Gilead, Janssen, Acerta Pharma/AstraZeneca, ADC Therapeutics, BioInvent
Educational grants: Celgene, Roche

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Honoraria: Roche
Educational grants: Roche

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W. Townsend
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Honoraria: Roche, Gilead, Incyte
Educational grants: Roche, Takeda

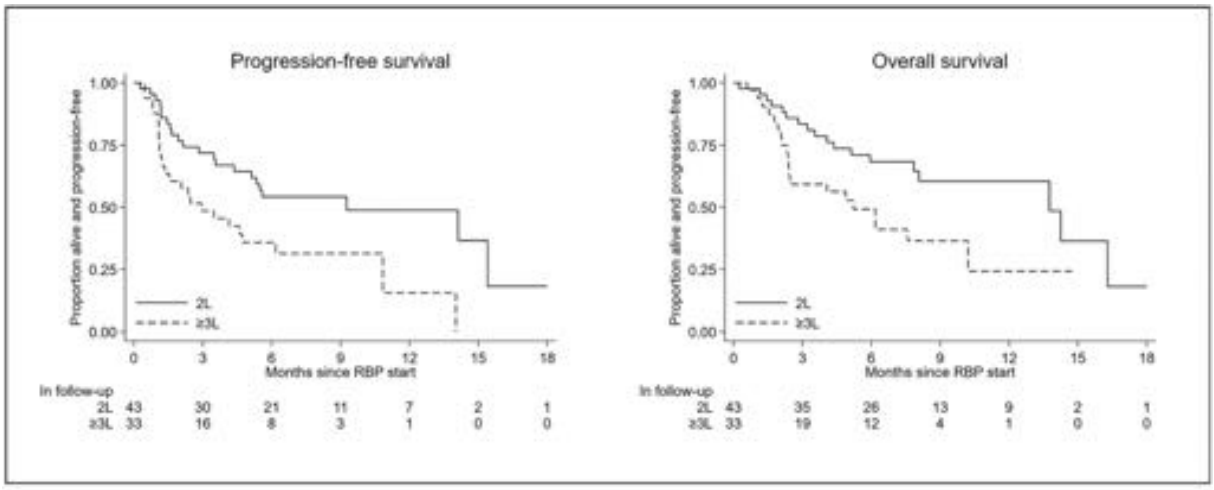

Figure: Progression-free survival and overall survival according to number of lines of prior treatment

572 | POLATUZUMAB, BENDAMUSTINE & RITUXIMAB EFFICACY IN RELAPSED/REFRACTORY TRIAL-INELIGIBLE LARGE B CELL LYMPHOMA PATIENTS: AN AUSTRALIAN LYMPHOMA REGISTRY (LARDR) STUDY

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Introduction: RRDLBCL outcomes remain poor despite autologous transplant and CAR-T therapies offering potential cure to a minority. Evidence for current therapies is mostly from phase II trials with stringent eligibility criteria. Applicability to real-world populations is poorly understood. PolaBR efficacy in RR DLBCL was shown in the landmark GO29365 study (BCT02600897; Sehn Blood Adv 2022). However, the efficacy of PolaBR in routine care RR DLBCL patients (pts) who fail to meet original study eligibility criteria is unknown. Here we report outcomes of Australian RR DLBCL pts receiving compassionate PolaBR according to their eligibility for the GO29365 trial.

Methods: This was a retrospective study of RR DLBCL pts ≥18y receiving Pola ≥ BR from the Australian Lymphoma Registry (LaRDR). Data analysed included: demographics, pt demographics, disease & prior therapy details, trial eligibility criteria, outcomes and toxicity. Descriptive statistics were used to report frequency. Kaplan-Meier method and the Cox proportional hazard model were used for comparison of survival & comparisons according to prognostic factors.

Results: 58 pts were identified between 2019 and 2022, median age 63.0 y, 62% were male; 86% had stage III-IV disease; 61% had R-IPI ≥3. 70% had ≥2 prior therapies (38% >3 prior lines) with most treatment lines being chemotherapy with rituximab.

74% failed ≥1 eligibility criteria of the landmark PolaBR study and 47% failed ≥2 ineligibility criteria (Table 1). Pola was given with BR in 59%, Ritux only in 24%; and single-agent in 8%. Just 27% completed all 6 planned cycles. Reasons for cessation included progressive disease 52%; bridging to other therapy 10%; death 6%; toxicity 4%. 8 pts received up to 2 subsequent lines of therapy, with 2 receiving CAR-T therapy.

Overall response rate was 38% (25% CR). Median follow up was 3.2 m (range 0–31). Median overall survival was 3.9 m (95% CI 2.9–7.3 m). Median PFS was 2.5 m (95% CI 1.9–4.1 m). No difference in OS or PFS was observed for eligible versus non-eligible pts and failure of any one eligibility criteria category did not impact outcome. No difference in OS observed between pola-BR and pola-R ($p = 0.32$).

Conclusion: While response rates were similar to other real-world studies (Northend et al. 2022; Dimou et al., 2021; Wang et al., 2022) they were lower than the registration trial. The high proportion of pts ineligible for the landmark pola-BR registration study and limited access to subsequent therapy potentially explain inferior response and survival outcomes in our cohort. Although acknowledging our modest sample size impacts the results, outcomes of novel therapies in real-world pts are likely influenced by factors outside of those related to trial eligibility such as adverse disease biology and additional comorbidites.

Encore Abstract—previously submitted to EHA 2023

Keyword: aggressive B-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

A. Johnston
Consultant or advisory role MSD, Roche, Link, Beigene, Sanofi, Eusa pharma, Novartis

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Honoraria: Roche, Janssen, Gilead, AstraZenecca, Lilly, TG therapeutics, Beigene, Novartis, Menarini, Daizai, Abbvie, Genmab. BMS
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Honoraria: Celgene (in 2019)
Research funding: Beigene

Table 1: Eligibility criteria that failed to be met and outcomes according to eligibility.

Factor	N (%)	Pts with data (n)	PFS Hazard Ratio (95%CI) pvalue	OS Hazard Ratio (95%CI) pvalue
Failed eligibility for the for the original GO29365 trial	43 (74)	58	0.80 (0.38-1.67) p = 0.55	0.99 (0.47-2.08) p = 0.97
Number of failed eligibility criteria		58		
0	15 (26)			
1	16 (28)		1.35 (0.57-3.16) p = 0.50	1.72 (0.72-4.89) p = 0.22
2	16 (28)		0.77 (0.32-1.85) p = 0.56	0.83 (0.34-2.05) p = 0.69
3 or more	11 (19)		0.50 (0.20-1.28) p = 0.15	0.67 (0.26-1.77) 0.42
Number of significant co-morbidities*		58		
0	39 (67)			
1	11 (19)		1.26 (0.60-2.62)p = 0.54	1.15 (0.53-2.51) p = 0.72
≥2	8 (14)		0.61 (0.25-1.48) p = 0.28	0.63 (0.24-1.66) p = 0.36
Treatment related failed eligibility				
Treatment with CART cell therapy within 100 days prior to commencing Polatuzumab	7 (13)	53	1.96 (0.81-4.70) p = 0.13	2.04(0.7805.38) p = 0.15
Autologous transplant eligible	15 (33)	46	0.51 (0.25-1.03) p = 0.06	0.47 (0.22-1.02) p = 0.06
Disease-related failed eligibility			0.50 (0.26-0.99) p = 0.05	0.51 (0.24-1.06) p = 0.07
Transformed from indolent ineligible	13 (26)	51	0.51 (0.24-1.09) p = 0.08	0.49 (0.21-1.13) p = 0.10
No measurable disease	8 (17)	46		
Presence of CNS involvement	5 (10)	52	1.18(0.40-3.17) p = 0.83	1.18 (0.36-3.85) p = 0.79
Co-morbidity related ineligibility				
ECOG >2	4 (8)	49	0.90 (0.32-2.53) p = 0.84	0.90 (0.27-2.94) p = 0.86
Ineligible due to co-morbidities	19 (33)	58	0.89 (0.48-1.66) p = 0.73	0.89 (0.46-1.71) p = 0.73
Failed Organ function eligibility			1.11 (0.56-2.19) p = 0.76	0.99 (0.49-2.01) p = 0.97
Renal Creatinine >135 umol/L	11 (22)	50		
Haematological	11(31)	36	0.95 (0.43-2.10) p = 0.90	0.86 (0.37-1.98) p = 0.72
Haemoglobin ≤80 g/L	6 (12)	52		
Platelet count ≤50 x10⁹/L	7 (14)	52		
International Normalized Ratio (INR) >2.0	2 (6)	34		
Hepatic	7 (14)	51	1.28 (0.56-2.89) p = 0.56	0.81 (0.28-2.80) p = 0.68
Bilirubin >30 umol/L	3 (6)			
Alanine transaminase (ALT) >100 u/L	5 (10)			
Viral	4 (8)	52	1.04 (0.32-3.38) p = 0.95	1.22 (0.37-3.99) p = 0.75
Positive test results for HBV infection	4 (8)			
Positive test results for HCV antibody	2 (4)			
Neuro: Peripheral neuropathy >1 ineligible	3 (6)		2.50 (0.75-8.40) p = 0.14	4.04 (1.15-14.21) p = 0.03

G. Chong

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S. Opat

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Consultant or advisory role Roche, Merck Sharpe & Dohme, Astra Zeneca, Gilead, Antigene, Novartis, Regeneron, Janssen, Specialised Therapeutics

Research funding: Roche, Bristol Myers Squibb, Merck KgA, Astra Zeneca and Merck

573 | REAL-WORLD OUTCOMES WITH NOVEL THERAPIES IN R/R DLBCL

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Introduction: Outcomes have historically been poor for patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). Despite an increase in approved R/R DLBCL treatment options, clinical outcomes of these therapies remain less certain. Novel treatments for these patients include chimeric antigen receptor T-cell (CAR T) therapy, polatuzumab vedotin plus bendamustine and rituximab (pola-BR), tafasitamab plus lenalidomide (tafa-len),

loncastuximab (lonca), and selinexor. This study examined real-world outcomes of these novel therapies.

Methods: US patient data from the COTA electronic health records database (2010–2021) were used for this retrospective study. Patients had a DLBCL diagnosis after 1/1/2010, with ≥1 prior line of systemic antineoplastic therapy (including an anti-CD20 antibody), and treatment with any of these novel therapies. Patients receiving variations of pola-BR or tafa-len regimens were included. Outcomes included overall response rate (ORR), complete response (CR) rate, median progression-free survival (mPFS), and median overall survival (mOS). Outcomes were analyzed for those treated with any novel therapy following prior CAR T exposure.

Results: A total of 175 R/R DLBCL patients were included (median age 63 y, 60.6% male, median of 2 prior therapies); 29.1% had an international prognostic index score ≥3, 61.7% had stage III/IV disease, and 65.7% had primary refractory disease. A total of 73, 69, and 27 patients were treated with CAR T, pola-BR, and tafa-len regimens, respectively. Only 6 patients were treated with lonca and 0 patients received selinexor. Among 169 patients treated in the 2L+ setting with tafa-len, pola-BR, and CAR T, the CR rate was 11.1%, 18.8%, and 52.1%, respectively (Table). A total of 112 patients were treated in the 3L+ setting with CR rate of 10.0%, 13.5%, and 41.8%, for tafa-len, pola-BR, and CAR T, respectively. Outcomes in the 18% of patients treated with any novel agent following CAR T exposure were ORR of 19.1%, CR of 4.8%, and mPFS and mOS of 1.4 mo and 2.3 mo, respectively.

Conclusions: Outcomes of pola-BR and tafa-len regimens in the 2L+ and 3L+ R/R DLBCL setting remain suboptimal, with worse outcomes as patients advance through lines of therapy. Outcomes are particularly poor when these agents are used following CAR T therapy.

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Keywords: aggressive B-cell non-Hodgkin lymphoma, cancer health disparities, combination therapies

Conflicts of interests pertinent to the abstract

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Research funding: AbbVie, Bayer, Merck, and Genentech/Roche

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Employment or leadership position: Genmab

Table. Clinical Outcomes by Line of Therapy and Treatment Type

Outcome (95% CI)	2L+ setting			3L+ setting		
	CAR T (n=73)	Pola-BR (n=69)	Tafa-len (n=27)	CAR T (n=55)	Pola-BR (n=37)	Tafa-len (n=20)
ORR (%)	76.7 (65.4, 85.8)	59.4 (46.9, 71.1)	40.7 (22.4, 61.2)	74.6 (61.0, 85.3)	62.2 (44.8, 77.5)	35.0 (15.4, 59.2)
CR (%)	52.1 (40.0, 63.9)	18.8 (10.4, 30.1)	11.1 (2.4, 29.2)	41.8 (28.7, 55.9)	13.5 (4.5, 28.8)	10.0 (1.2, 31.7)
mPFS (mo)	6.7 (4.0, 10.0)	3.1 (1.9, 3.8)	1.9 (0.8, 3.5)	5.6 (2.9, 7.4)	3.4 (2.1, 4.4)	1.7 (0.7, 4.4)
mOS (mo)	26.5 (13.6, NE)	7.8 (5.6, 11.4)	6.3 (1.6, 16.2)	17.8 (9.6, NE)	7.4 (4.3, 10.9)	6.3 (1.6, 16.2)

574 | CNS PROPHYLAXIS IN PATIENTS WITH DLBCL: A REAL WORLD EXPERIENCE ON BEHALF OF THE LYMPHOMA SUBCOMMITTEE OF THE ARGENTINE SOCIETY OF HEMATOLOGY

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Introduction: Although central nervous system (CNS) relapse in patients with Diffuse Large B-Cell Lymphoma (DLBCL) is an infrequent event, the mortality rate is high. The efficacy of strategies currently used to prevent it, has been challenged. We aimed

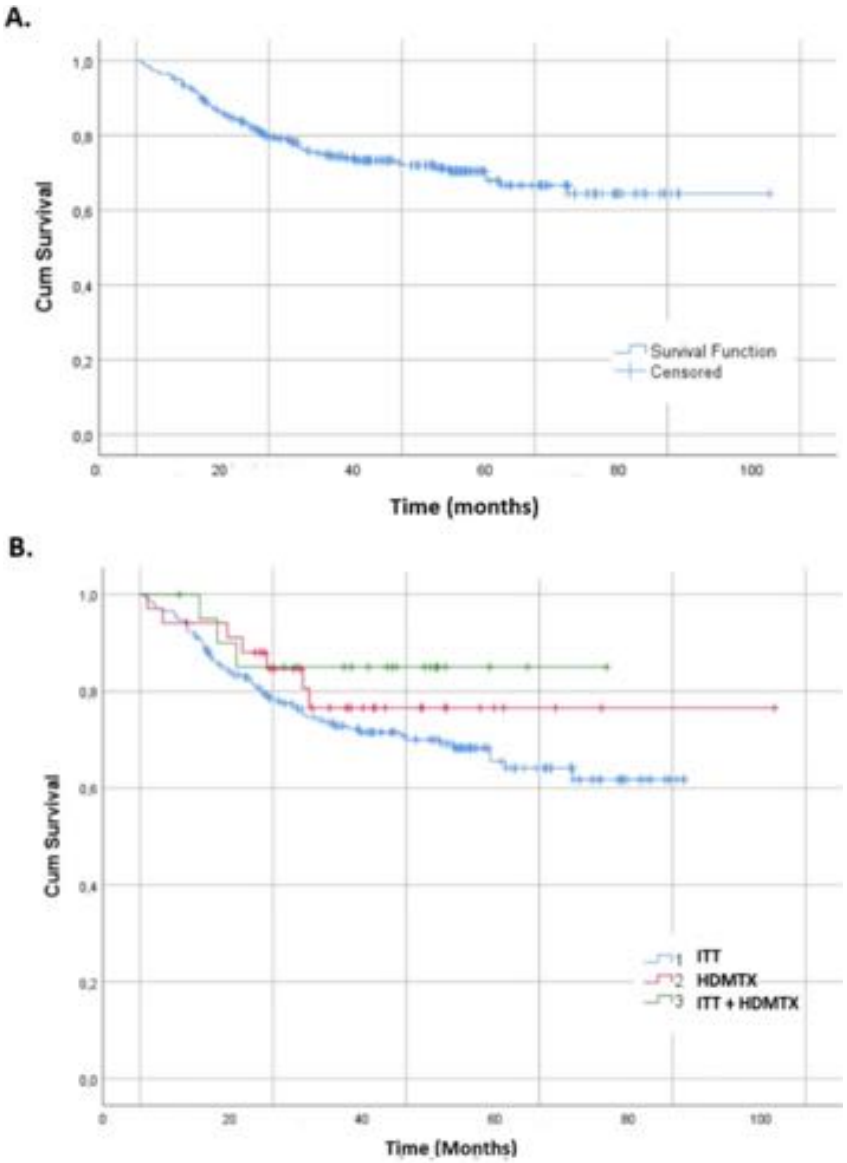

Figure 1. A: Overall survival. **B.** Overall Survival by prophylaxis

to evaluate the incidence of CNS relapse, overall survival (OS) and progression-free survival (PFS) in an Argentinian cohort of patients that received CNS prophylaxis as part of their front line treatment.
Methods and statistical analysis: Retrospective multicenter national analysis, including patients diagnosed with DLBCL, high grade B-cell lymphoma NOS, double/triple hit, who received CNS prophylaxis from January 2016 to December 2020. We used a Fine and Grey regression model to estimate time to CNS relapse and Kaplan Meier curves for PFS and OS.
Results: Two hundred sixty-two patients were included with a median age of 63 years (IQR 53–71), 141 (54%) were male, 222 (85%) had extranodal involvement and 190 (72%) had stage IV at diagnosis. Most frequent extranodal sites were bone (n = 52, 20%), gastrointestinal tract (n = 42, 16%) and bone marrow (n = 37, 14%). IPI was high or intermediate/high in 157 cases (60%), while CNS IPI was intermediate and high in 122 (47%) and 83 (32%), respectively. All patients received immunochemotherapy at diagnosis: 192 (73%) R-CHOP, 62 (24%) R-DA-EPOCH, 8 (3%) others. Two hundred and seven (79%) patients achieved complete response, 18 (6.9%) partial response, 7 (2.7%) stable disease and 30 (11.4%) were primary refractory.

Two hundred and seven (79%) patients received intrathecal therapy (ITT), 34 (13%) high doses of methotrexate (HDMTX) and 21 (8%) both. Median ITT was 4 (IQR 3–6). Intercalated HDMTX was administered to 28 (52%) patients, while 26 (48%) received HDMTX at the end of treatment. Forty-one (16%) patients developed toxicity, causing cycling-delays or prophylaxis withdrawal in 20 (8%), respectively.

Twenty patients (7.7%) had CNS relapse with an incidence of 2.8% (95% CI 1.4–5.6), 5.8% (95% CI 3.4–9.5) and 7.7% (95% CI 4.9–11.9) at 6, 12 and 24 months, respectively: all of them died of disease progression. We found differences at 24 months between CNS-IPI: 4%, 6.5% and 12% for low, intermediate and high score (p = 0.05). No difference according to type of prophylaxis was found.

PFS and OS for the full cohort at 6, 12 and 24 months was 85% (95% CI 80–88), 74% (95% CI 68–79), 62% (95% CI 56–68) and 94% (95% CI 90–96), 83% (95% CI 78–87), 67% (95% CI 61–73), respectively. No statistically significant differences were found in OS and PFS according to type of prophylaxis, no significant risk factors for CNS relapse were found in the bivariate analysis.
Conclusion: In this retrospective analysis, ITT prophylaxis was preferred over HDMTX, showing discrepancies with the most recent recommendations in international guidelines. We describe an incidence of 7.7% of CNS relapse with no difference according to type of prophylaxis.

Keyword: aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

575 | CNS RELAPSE OF DIFFUSE LARGE B-CELL LYMPHOMA AND ROLE OF UPFRONT PROPHYLAXIS: A 10-YEAR SINGLE CENTER EXPERIENCE

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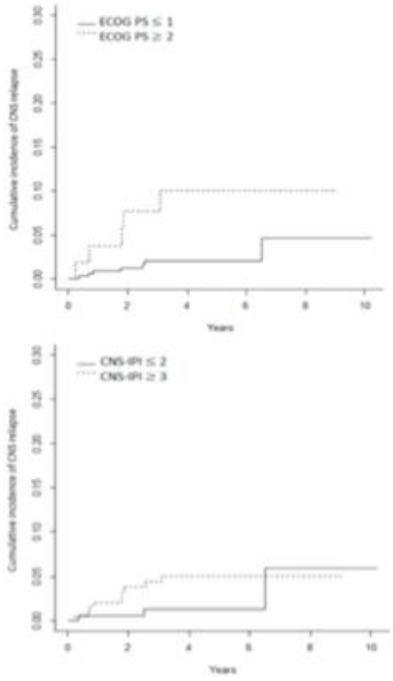
Introduction: Central nervous system (CNS) relapse of diffuse large B-cell lymphoma (DLBCL) is a rare event, occurring in about 5% of patients (pts) and correlating with a very dismal prognosis. Much debate has surrounded the use of strategies to avert CNS disease recurrence. Nowadays, CNS prophylaxis is mostly based on high-dose intravenous (iv) methotrexate (HD-MTX), but its effectiveness is controversial.

Our study focuses on pts with CNS relapse of DLBCL in order to evaluate their clinical and biological features, the validity of known prognostic scores, the efficacy of CNS prophylaxis, prognosis and treatment at the time of relapse.
Methods: All pts with DLBCL diagnosed between January 2010 and December 2021 at AOU Città della Salute e della Scienza di Torino and treated with curative intent were selected: 498 cases with at least 12 months of follow-up were identified. Pts with primary mediastinal lymphoma, primary testicular lymphoma or CNS disease at diagnosis were excluded.
Results: The case series included 406 pts. Mean age was 67 years, 56/400 had ECOG PS $\geq$ 2 (14%), 231/400 elevated LDH levels (58%), 251/404 were stage IV (62%), 192/374 IPI score $\geq$ 3 (51%), 189/373 CNS-IPI 2–3 (51%), 91/373 CNS-IPI 4–6 (24%). 95/397 pts received CNS prophylaxis (24%): 59 by intrathecal (IT) route only (15%) (n 26 CNS-IPI 2-3; n 29 CNS-IPI 4-6), 25 by iv MTX only (6%) (n 17 HD-MTX $\geq$3 g/mq; n 6 CNS-IPI 2-3; n 16 CNS-IPI 4-6), and 11 by combined route (3%) (n 5 CNS-IPI 2-3, n 6 CNS-IPI 3–6). 12 pts experienced CNS relapse; 8/12 exclusively CNS and 4/12 along with systemic recurrence. The cumulative incidence at 3 years was 2.8%. In univariate analysis CNS relapse risk was significantly influenced by ECOG PS and elevated LDH levels, while the use of prophylaxis was not shown to impact the risk of CNS recurrence. However, none of the pts who received systemic MTX prophylaxis had subsequent CNS disease, while 2/59 pts who received exclusive IT prophylaxis had CNS relapse with an incidence superimposable to the whole cohort (3.3%). In multivariate analysis, only ECOG PS confirmed significant correlation with the risk of such disease recurrence (Figure 1). With a mean follow-up of 36 months, the 3-year overall survival for pts with SNC recurrence was 30%.

	HR	IC 95%	p-value
ECOG PS ≥ 2	3.41	1.07; 10.82	0.038
CNS-IPI ≥ 3	2.51	0.69; 9.09	0.161
Profilassi IT e/o EV	0.32	0.07; 1.51	0.149



Conclusions: Data from our case series confirm the limited benefit of IT prophylaxis. Although a statistically significant benefit from the use of HD-MTX prophylaxis is not shown, probably due to the limited sample size and the number of overall events, the abandonment of this therapeutic strategy is not justified. The results of univariate and multivariate regression analyses agree in reporting that the CNS-IPI score is not always reliable. The identification of new predicting factors of CNS relapse may help in intensifying and directing prophylactic strategies on a more selected very high-risk population.

Encore Abstract—previously submitted to EHA 2023

Keyword: aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

575 bis | FEASIBILITY AND SAFETY OF HIGH-DOSE METHOTREXATE INTERCALATED WITH R-CHOP IN DIFFUSE LARGE B-CELL LYMPHOMA: A SINGLE-CENTER EXPERIENCE

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Background: Central nervous system (CNS) relapse still represents an often-fatal event in diffuse large B cell lymphoma (DLBCL). Efforts to prevent it aimed to identify higher risk patients and to administer adequate prophylaxis. In this setting, unmet needs such as the type of prophylaxis (high-dose methotrexate, HD-MTX vs. triple intrathecal therapy) and its timing are still under debate. Hereby, we report our experience of DLBCL patients undergoing CNS prophylaxis with systemic HD-MTX intercalated with systemic chemotherapy.

Methods: We retrospectively collected data of DLBCL patients receiving CNS prophylaxis with at least 1 cycle of HD-MTX from 2017 to 2022. The administration of HD-MTX was based on CNS-IPI and on lymphoma histology/clinical presentation in those cases who may not tolerate more intensified chemo-immunotherapy regimens. We performed a Kaplan-Meier analysis to estimate overall survival.

Results: Twenty-one patients received HD-MTX. The mean age at diagnosis was 62 years (range 33–77), with 66% of patients over 60 years. The median Cumulative Illness Rating Scale (CIRS) was 8 (range 4–13). At presentation, 76% of patients had advance stage disease (III-IV) with more than 1 extranodal localization in 15 cases. Median IPI and CNS-IPI were 3 (range 0–5) and 3 (range 0–5), respectively. According to immunohistochemistry, a non-germinal center phenotype was shown in 24% and 52% patients had double-expressor profile. Patients received R-CHOP (71%) or R-COMP (29%) associated with variable HD-MTX dose, adjusted on age and comorbidities. At a mean delay of 2 days after R-CHOP, a median number of 3 HD-MTX cycles were administered at a mean dosage of 2 g/mq (range 1–3). Regarding safety, 19% of patients experienced acute renal injury (ARI), among them 2 in patients over 60 years and only one grade 3 ARI. We observed a complete response (CR) in 67% of patients, up to 79% if considering over 60 years. Particularly patients over 60 years were more likely to achieve CR ($p = 0.052$), even in those who delayed R-CHOP. At a mean follow-up of 24 months, 82% of patients over 60 years patients are alive (Figure 1). A substantial difference in overall survival was seen in patients reaching CR than others (100% vs. 33%) ($p = 0.001$). Six patients relapsed at a median time of 3 months, among them 4 died from lymphoma.

Conclusions: Our report confirms the feasibility of HD-MTX in the treatment of DLBCL patients with high-risk features and high co-morbidity burden. Patients over 60 years showed higher rate of complete remission without significant toxicity, independently on chemotherapy delay suggesting a good balance between response and toxicity with MRCHOP/COMP in this setting. Further studies with longer follow-up are needed to draw more definitive conclusions, especially in frail patients such as elderly.

Keywords: aggressive B-cell non-Hodgkin lymphoma, chemotherapy

No conflicts of interests pertinent to the abstract.

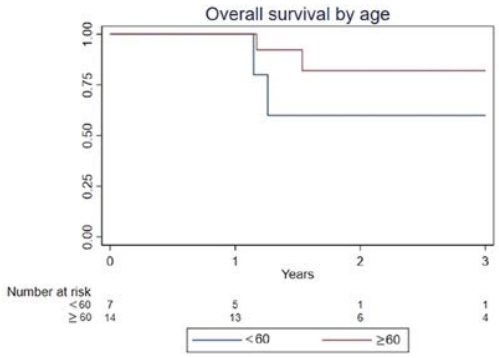

Figure 1. Kaplan-Meier survival of population study according to age at diagnosis

576 | HIGH-DOSE METHOTREXATE PLUS RCHOP: EFFICACY AND TOXICITY IN THE PREVENTION OF CENTRAL NERVOUS SYSTEM RELAPSE IN PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: Prophylactic high dose methotrexate (HD-MTX) is widely used for preventing central nervous system (CNS) relapse in patients with diffuse large b cell lymphoma (DLBCL), as intravenous HD-MTX achieves excellent blood-brain barrier penetration. Despite most of the published studies analyzing the efficacy of HD-MTX when combined with anthracycline based chemotherapy as front-line therapy advocate the administration of methotrexate midcycle (between days 10 and 15 after the RCHOP), the optimal dose and timing of methotrexate when combined with RCHOP remains unclear. Here, we aim to evaluate the efficacy, tolerability and toxicity of the combination HD-MTX-RCHOP.

Methods: We report our experience of HD-MTX-RCHOP in patients with DLBCL and high risk of CNS relapse from 2017 to 2022. The regimen consisted in HD-MTX (dose ≥ 3 g/m^2) administered as a 4-hour intravenous infusion on day 1 of the cycle followed by standard RCHOP on day 3, as 21-days cycles. Patients received HD-MTX as inpatient regimen. Nephrotoxicity was prevented with hyperhidration and urine alcalinization. Urinary pH was monitored every 3 hours and plasmatic MTX levels every 24 hours until clearance.

Results: Nineteen patients receiving a total of 65 cycles of HD-MTX-RCHOP were included in the study. Patients received a median of 4 cycles (range 1-6) of HD-MTX-RCHOP as CNS prophylaxis. CNS-IPI score classified 9 patients (47.3%) as high risk of CNS relapse, 5 (26.3%) as intermediate risk and 5 (26.3%) as low-risk. These low-risk CNS-IPI patients received HD-MTX due to the involvement of high-risk sites.

HD-MTX-RCHOP presented a favorable toxicity profile. Most common adverse event was oral mucositis (29.2% of cycles), with grade ≥ 3 mucositis in 7.69% of cycles. All reported hepatotoxicity was grade 1 (9.2% of cycles). MTX clearance was achieved at a median of 48 hours (range 24–69) after administration and only one case of nephrotoxicity was documented (1.5% of cycles) (table 1).

TABLE 1

Adverse events HD-MTX-RCHOP	*N*(%) cycles	*N*(%) patients
Renal Failure	1 (1.5%)	1 (5%)
Hepatotoxicity	6 (9.2%)	4 (21%)
Febrile neutropenia	8 (12.3%)	6 (31%)
Mucositis	19 (29.2%)	13 (68%)
Delays of 7 days or more	9 (13.8%)	5 (8%)

Overall, only 13% of cycles were delayed by more than 7 days and 13 (68%) patients finished all programmed HD-MTX-RCHOP cycles without any delay. The most frequent cause of delay was neutropenic fever after RCHOP.

With this treatment, 17 (89.47%) patients achieved complete response without relapse in the CNS in any of them. Overall, only one CNS relapse was observed, which occurred during treatment with HD-MTX-RCHOP (primary refractory DLBCL).

Conclusion: Our data suggest that HD-MTX administration on day 1 of the RCHOP cycle is a feasible strategy, with a good safety profile that does not result in unacceptable delays in the administration of RCHOP. Although new prospective studies are needed to confirm these results.

Keyword: aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

577 | POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD) AFTER SOLID ORGAN TRANSPLANTATION (SOT): 15 YEARS OF MONOCENTRIC EXPERIENCE IN A REFERRAL CENTRE

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Background: Post-transplant lymphoproliferative disorder (PTLD) is a rare complication of solid organ transplantation (SOT) and is composed of a heterogeneous spectrum of predominantly B-cell disorders. Epstein-Barr Virus (EBV) is involved in a substantial number of cases. In this single Center retrospective analysis we described our PTLD series.

Methods: PTLD after SOT were identified by Electronic Medical Records database of our Department. Inclusion criteria were age ≥18 years at the time of diagnosis, PTLD occurrence from 2007 to 2022

and receipt of therapy at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Results: A total of 34 PTLD patients were followed for a median of 23 months (Inter Quartile Range: 8–80 months). With a median age at diagnosis of 46 years (range 18–82 years), 59% (20/34) were male. The half of patients were ≥50 years old at PTLD onset. The overall median time from SOT to PTLD was 6.1 years. Considering organ, 41% of patients received liver, 38% kidney and 21% lung respectively. Median time from graft to PTLD diagnosis was 3 months for lung, 99 and 101 months for liver and kidney transplantation respectively. Regarding EBV status, 62% (13/21) of patients presented associated EBV infection. Histologic PTLD diagnosis are reported in Table 1.

Only 32% of patients received reduction of immunosuppression (RIS), 24% were treated with rituximab monotherapy and 82% underwent chemo/chemo-immunotherapy because of aggressive disease or failure of response with previous treatment. At the time of analyses, 38% (13/31 of patients were alive. The median survival time was 35 months (Figure 1A).

Lung transplanted showed higher mortality than kidney ones (hazard ratio (HR) 2.3, 95% confidence interval (CI) 0.6-8.7). At PTLD diagnosis, lung recipients were more frequently EBV-DNA positive (6/7) than those liver transplanted (1/11) (p = 0.001). EBV-DNA positivity was associated with mortality (HR 1.9, 95% CI: 0.7-5.4), but a joint analysis of the role of transplanted organ and EBV-DNA status is not feasible because of sparse data. Neither RIS nor rituximab treatment (Figure 1B,C), but first-line chemo/chemo-immunotherapy were predictive of better survival (HR 0.4, 95% CI: 0.9-1.7) (Figure 1D).

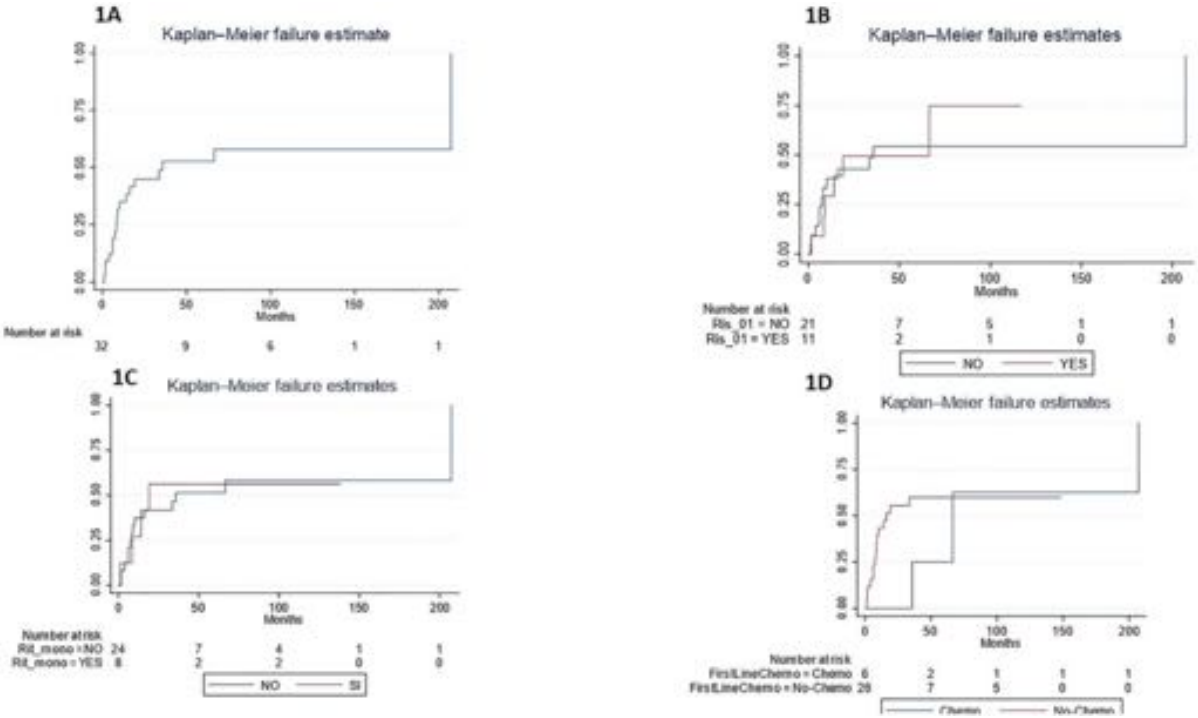
Conclusions: Some variables emerge in line with what has been already described in literature: median time from SOT to PTLD onset, of 5.5–6 years, incidence of EBV positive PTLD, 55%–65%, of cases and histological prevalence of B cell cases. The novelty of our experience is the observation that lung PTLD were more frequently EBV positive and associated with a worse outcome than kidney/liver ones. Differently from the literature, EBV status was found to be a significant predictor for overall survival.

Keyword: aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

TABLE 1

Organ	PTLD *polimorphic*	DLBCL *EBV+*	DLBCL *EBV-*	DLBCL *NA*	HL *EBV+*	HL *EBV−*	*PTCL-NOS* *EBV+*	*PTCL-NOS* *EBV−*	*ALCL* *EBV+*	*ALCL* *EBV−*	Monomorphic plasmacytoma	Total
Lung	1	6	-	-	-	-	-	-	-	-	-	**7**
Liver	-	4	7	1	-	-	1	-	-	-	1	**14**
Kidney	-	4	3	1	2	1	-	-	1	-	-	**12**



578 | HYPOGAMMAGLOBULINEMIA AT DIAGNOSIS IS ASSOCIATED WITH INFERIOR SURVIVAL AND HIGHER RISK OF INFECTIONS IN DIFFUSE LARGE B CELL LYMPHOMA: A RETROSPECTIVE STUDY FROM SWEDEN

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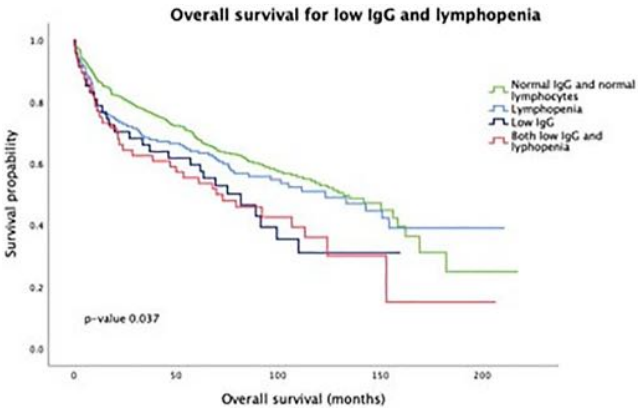
Introduction: Low level of antibody production does not only increase the risk of infections, but also the incidence of malignancies, especially lymphoma. The primary aim of this study was to explore if hypogammaglobulinemia in untreated diffuse large B cell lymphoma (DLBCL) was associated with inferior overall survival (OS) or inferior progression free survival (PFS). Secondary aims were to assess the relationships between low immunoglobulins (Ig), other laboratory tests and infections.

Methods: Using data from the Swedish Lymphoma Register (SLR), we identified all adult patients (18 years or older) diagnosed with DLBCL, receiving anthracycline-based curative therapy during year 2001–2015 in two health regions in southern Sweden (one university hospital and one region hospital). Data from the SLR were supplemented by patient record review, including data on baseline Ig levels and infections of CTC-AE grade 3–5 (in-hospital stay and intravenous antibiotics). Survival was analyzed by Kaplan-Meier estimates. Simple and multivariate linear regression were performed to determine relationships between laboratory tests and number of infections.

Results: 596 patients were included, median age was 69 years (20–96), 57% were men, median OS 72 months, and median PFS 64 months. Median follow-up time for living patients was 106 months (62–117). 25% had low Ig, defined as any deficiency, 18% had low IgG, 37% lymphopenia and 13% both low Ig and lymphopenia. Hypogammaglobulinemia was associated with inferior OS (HR 1.4, 95% CI 1.0–1.9, *p*-value 0.018) and inferior PFS (HR 1.3, 95% CI 1.0–1.7, *p*-value 0.032). The combination of low Ig and lymphopenia aggravated OS (HR 1.2, 95% CI 1.0–1.2, *p*-value 0.023) and PFS (HR 1.2, 95% CI 1.0–1.3, *p*-value 0.002). Hypogammaglobulinemia was also associated with a higher number of infections (*p*-value 0.021), adjusted for International Prognostic Index (IPI) the associations weakened (*p*-value 0.097). The combination of low Ig and lymphopenia was not related to more infections than low Ig alone.

Conclusions: In this cohort of untreated patients with DLBCL, hypogammaglobulinemia was a frequent finding, and was associated with inferior OS and PFS alone and in combination with lymphopenia. Furthermore, hypogammaglobulinemia was associated with an increased risk of severe infections, indicating that hypogammaglobulinemia is common in DLBCL at diagnosis and may have clinical impact in terms of treatment complications and outcome.



Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers

No conflicts of interests pertinent to the abstract.

579 | INCIDENCE AND PREDICTIVE FACTORS OF PLATINUM-ASSOCIATED NEPHROTOXICITY IN PATIENTS WITH LYMPHOID MALIGNANCIES; A 15-YEAR EXPERIENCE OUTSIDE CLINICAL TRIALS

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Introduction: Platinum-based chemotherapy is widely used in patients with lymphoma either in first or successive lines of treatment. However, platinum is well known to be nephrotoxic and could impact in clinical outcomes.

Methods: An unicentric retrospective cohort study was carried out including lymphoma patients who received platinum-based chemotherapy between 2007 and 2022. Renal failure (RF) was defined as a decrease in creatinine clearance by 50% or an elevation of plasma creatinine a 50% over the previous level. Patients who received treatment in first line and those who were intended to proceed to cellular therapy were included. Patients on clinical trials were excluded. The final cohort was assessed for incidence of RF and clinical and laboratory variables were evaluated as risk factors.

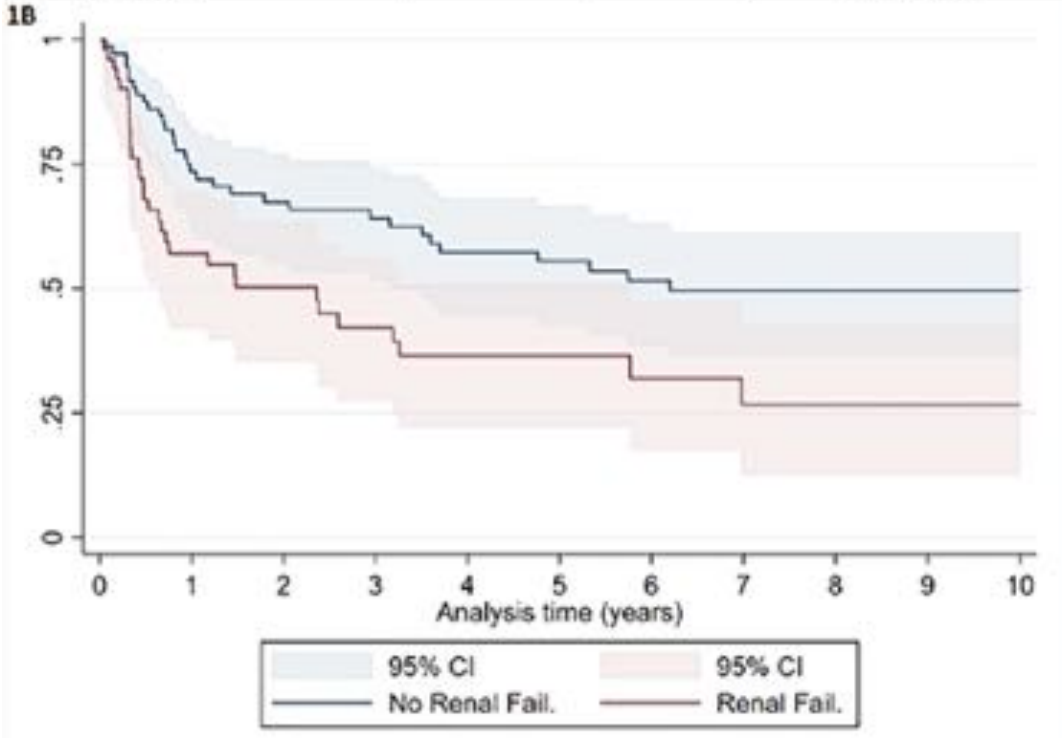
Results: A total of 123 patients were included. Baseline characteristics are summarized in Figure 1A. The incidence of RF was 41.5% (51/123). Median time to RF was 6 days (range: 1–28). RF persisted until data cut-off date in 20/51 (39.2%), and 4/51 (7.8%) patients

required dialysis. Following variables: sex, body mass index, diabetes, dyslipidemia, use of anti-CD20 and the type of chemotherapy were not associated to an increased risk of RF. Administration of magnesium supplements and mannitol had no impact on RF. Significant differences were observed between the RF and the no-RF groups in age (58.3 vs. 48.3 years; $p < 0.001$), hypertension (41.2% vs. 13.9%; $p < 0.001$), albumin (3.2 vs. 3.7 g/dL; $p < 0.001$) and hemoglobin (10.9 vs. 12.5 g/dL; $p < 0.001$). We used the cut-off of 51 years (assessed by the optimal point of the ROC curve) for age to be included in a logistic regression model with categoric predictors. The cut-off values of 3.5 g/dL for albumin and 10 g/dL of hemoglobin were chosen based on a biological basis. These four variables were associated with an increased risk of RF showing univariable odds ratio (OR) of 3.7 (1.7–8) for age, 4.3 (1.8–10.4) for hypertension, 4.3

1A

	No Renal Failure (n=72)	Renal Failure (n=51)
Age, mean (range)	48.3 (17-75)	58.3 (29-74)
Sex (% females)	43.1	41.2
ECOG (%)		
- 0	84.7	82.4
- 1	9.7	13.7
- 2	5.6	3.9
Hypertension (yes %)	13.9	41.2
Diabetes (yes %)	5.6	17.7
Dyslipemia (yes %)	6.9	7.4
Diagnosis		
- Diffuse B large cell lymphoma	23/72 (31.9%)	21/51 (41.2%)
- Follicular lymphoma	15/72 (20.8%)	9/51 (17.7%)
- Mantle cell lymphoma	10/72 (13.9%)	8/51 (15.7%)
- Hodgkin lymphoma	18/72 (25%)	7/51 (13.7%)
- T cell lymphoma	5/72 (6.9%)	2/51 (3.9%)
- Other	1/72 (1.4%)	4/51 (7.8%)
Chemotherapy		
- DHAP	56/72 (77.8%)	45/51 (88.2%)
- ESHAP	10/72 (13.9%)	6/51 (11.8%)
- Other	6/72 (8.3%)	-
Anti-CD20 (yes %)	38.9	47
Line of treatment		
- 1st	6/72 (8,3%)	6/51 (11.8%)
- 2nd	66/72 (91.7%)	38/51 (74.5%)
- Successive	-	7/51 (13.7%)

1B



(2–9.2) for albumin and 4.3 (1.8–10.4) for hemoglobin. A multivariable logistic regression model was built including these variables; having hypertension and hemoglobin <10 remained as significant predictors – OR: 1.8 (1.1–2.9) and 2.8 (1.1–7.6) respectively –, whereas age <51 and albumin kept an OR of 1.9 (0.8–4.9) and 2.3 (0.9–5.5) which resulted non statistically significant. Developing renal failure after platinum treatment was associated with a significant decrease in overall survival (OS); median OS in RF and no-RF groups were: 2.4 versus 6.2 years respectively (Figure 1B, log-rank test: 6.67; $p = 0.009$).

Conclusions: Platinum-related nephrotoxicity is a frequent event related to treatment and is associated with impaired survival. We identified hypertension, age, serum albumin and hemoglobin as potential risk factors. Efforts should be made to ameliorate these factors and novel therapeutic approaches should be considered in older patients.

Keywords: late effects in lymphoma survivors, other, risk models

No conflicts of interests pertinent to the abstract.

CLL

580 | A MULTICENTER RETROSPECTIVE STUDY TO UNDERSTAND THE CLINICAL CHARACTERISTICS FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: INTERIM RESULTS FROM THE CREEK STUDY

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Introduction: The rapidly expanding treatment landscape for Chronic Lymphocytic Leukemia (CLL) calls for appropriate patient and treatment selection and sequencing with existing agents. Data describing CLL management are fragmented across different regions, with marked cross-country differences in treatment practices and patient outcomes. Therefore, we have established the observational study CREEK, CLL retrospective real-world evidence key data from the Middle East and North Africa, Asia, and Latin America. This interim analysis aimed to describe the patient and disease characteristics of CLL-treated (CLL-Tx) patients in international countries and CLL treatment-naïve (CLL-N) patients in the Gulf Cooperation Council (GCC) states.

Methods: Data from 976 patients were collected, including 845 CLL-Tx patients who started treatment between 01 June 2016 and 12 months before data collection and a pilot cohort of 131 CLL-N patients. Patients' demographics, disease characteristics, laboratory assessments, and comorbidities were recorded.

Results: The average age for CLL-Tx and CLL-N was 63.5 and 63.4 years, respectively. Most patients were males, 66.7% in CLL-Tx and 71.0% in CLL-N. Around 11% of patients in CLL-Tx and 12% in CLL-N were current smokers. Most CLL-Tx (62%) had an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1, and the same was for CLL-N (56.4%). As per the Cumulative Illness Rating Scale (CIRS), moderate to severe musculoskeletal ($p < 0.0025$), and endocrine-metabolic ($p < 0.0001$) comorbidities were more frequent in CLL-Tx. All laboratory parameters, except neutrophils and eGFR categories, showed a significant difference ($p < 0.05$) between CLL-Tx and CLL-N. The average days from diagnosis to enrollment were 475 and 59 days in CLL-Tx and CLL-N ($p < 0.0001$), respectively. Patients with CLL-Tx had a worse prognosis compared to CLL-N based on Rai and Binet Staging Scores ($p < 0.0001$). The testing rate for IGHV mutation status was low, with 23.5% in CLL-Tx and 38.9% in CLL-N, and the percentage of mutated IGHV was significantly lower ($p = 0.0006$) in CLL-Tx (9.8%) compared to CLL-N (26.7%). Whereas cytogenetic abnormalities (del "17p"—del "11q"—Complex karyotype), TP53 Aberrations, and cytogenetic abnormalities and TP53 aberrations (del "17p" and TP53 aberrations—TP53 aberrations without del "17p") didn't show a significant difference ($p > 0.05$) between CLL-Tx and CLL-N.

Conclusions: This interim analysis demonstrated a preliminary understanding of the patients and disease characteristics of CLL-Tx and CLL-N patients. The study showed that patients with CLL-Tx and CLL-N had comparable demographic characteristics; however, patients with CLL-Tx had a higher prevalence of moderate to severe comorbidities, worse ECOG scores, worse prognosis based on Rai and Binet staging scores, and a lower prevalence of mutated IGHV.

Keywords: chronic lymphocytic leukemia (CLL), CLL treatment naïve, cytogenetic abnormalities

The research was funded by AstraZeneca UK Limited

Conflict of interest

P. Kantharaju
Employment or leadership position: Pushpalata Kantharaju is an employee for AstraZeneca

F. J Gonzalez
Employment or leadership position: Francisco Gonzalez is an employee for AstraZeneca

A. Ishikawa
Employment or leadership position: Akemi Ishikawa is an employee for AstraZeneca

581 | A MULTICENTER RETROSPECTIVE STUDY TO UNDERSTAND THE CLINICAL CHARACTERISTICS FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: ASIAN SUBGROUP ANALYSIS OF CREEK STUDY

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Introduction: The prevalence of Chronic Lymphocytic Leukemia (CLL) in Asia-Pacific countries is generally lower than in Western countries. However, due to the highly variable patient and disease characteristics, there is a critical need for more disease-related information on Asian CLL patients to manage the disease effectively. To address these gaps, we have established a multicenter, registry-based study called CREEK: CLL REtrospective real-world Evidence Key data from Middle East and North Africa, Asia, and Latin America. This interim analysis of the CREEK Study aimed to describe patient and disease characteristics of CLL in four Asia-Pacific countries.

Methods: The CREEK study is a retrospective observational study to describe disease characteristics, treatment patterns, treatment-related outcomes, and resource utilization for Chronic Lymphocytic Leukemia (CLL). This interim analysis included 258 CLL patients who received treatment between 1 June 2016 and 12 months before data collection in four Asian-Pacific countries: India, Malaysia, Taiwan, and Singapore. Patients' demographics, clinical characteristics, laboratory investigations, comorbidities, and risk groups were recorded. Summary statistics and statistical tests were performed using IBM-SPSS.

Results: The study enrolled 258 patients with an average age of 63.3 ± 11.85 years, of whom the majority were males (73.3%). The Eastern Cooperative Oncology Group (ECOG) score was reported in 162 (62.9%) patients, with 153 (59.3%) of patients scored 0-1, while 9 (3.5%) scored >1. As per the Cumulative Illness Rating Scale (CIRS), severe comorbidities, including musculoskeletal (0.4%), hepatic and pancreatic (0.4%), and cardiac (1.2%) comorbidities, were reported. Around 8.5% and 8.9% of eligible patients were current and former smokers, respectively. The International Prognostic Index (IPI) for CLL was documented in 47 patients (18.2%), with four (1.5%) classified as very high-risk, 11 (4.3%) as high-risk, 18 (7%) as intermediate, and 14 (5.4%) as low-risk. About 21.7% of patients had mildly impaired renal function with eGFR of 60–89 mL/min. The average number of days from diagnosis to study enrolment (treatment start) was 650 days.

Conclusions: This interim analysis showed that most patients had a normal ECOG score, and low rates of severe comorbidities, with a male-to-female ratio higher than described for western countries. The International Prognostic Index (IPI) for CLL was documented in a minority of patients mainly because the low testing rate for IGHV mutational status and TP53 alterations. Further analyses are ongoing, including assessment of treatment patterns, treatment-related outcomes, and resource utilization.

Keywords: Asian-Pacific, chronic lymphocytic leukemia; clinical characteristics

The research was funded by AstraZeneca UK Limited

Conflict of interest:

F. Gonzalez

Employment or leadership position: Francisco Gonzalez is an employee for AstraZeneca

D. H. Shankar

Employment or leadership position: Drupad Shankar is an employee for AstraZeneca

582 | CLINICAL AND BIOLOGICAL FEATURES AND OUTCOMES OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: A REAL-WORLD STUDY OF 2005 PATIENTS IN CHINA

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Introduction: Chronic lymphocytic leukemia (CLL) is less common in Han Chinese compared with persons of Europeans. The data about the clinical and biological features and outcomes of Chinese with CLL are limited, thus promoting us to perform this analysis on a large cohort of 2005 patients with CLL in China.

Methods: Clinical data of 2005 patients with CLL were analyzed in Blood Diseases Hospital, Chinese Academy of Medical Sciences from February 2000 to December 2020.

Results: In this cohort, the median age of patients at diagnosis was 61(20-92) years, which was younger than that for Western CLL patients (65-70 years). Patients showed similar male predominance as Europeans with CLL with an M:F ratio of about 1.8. 69.3% of patients had Binet stage B or C at diagnosis, higher than those of predominately European descent (20%-40%). A higher proportion of mutated immunoglobulin heavy chain variable region (*IGHV*) (64.0%) was shown in patients with CLL in this cohort than Europeans. *IGHV*4-34 rather than *IGHV*1-69 was the most commonly used fragment. Compared with Europeans, patients in this cohort had a higher proportion of subset eight stereotype and a lower proportion of subset two. The most frequent abnormality detected by FISH was *RB1* deletion (21.1%), followed by trisomy 12 (20.4%),

IGH translocation (16.8%), del(17p) (11.4%) and del(11q) (10.9%), respectively. It was shown that the frequencies of the chromosomal abnormalities in this study population were similar to the frequencies in Western countries. Of the 1476 patients for whose treatment data were available, 1191 (80.7%) received treatment. Median time to first treatment (TTFT) for CLL patients was 7 months. Among patients treated, chemotherapy, immunochemotherapy and targeted therapy accounted for 69.6%, 14.1% and 16.3% of first line, yielding 68.4%, 90.0% and 94.2% of overall response rate (ORR), respectively. After median 75-month follow up, median progression free survival (PFS) was 42 months, 5-year and 10-year PFS rate was 35.5% and 12.5%, respectively. Median overall survival (OS) was 130 months, 5-year and 10-year OS rate was 74.9% and 52.3%, respectively. The outcomes were similar to those reported in previous Chinese and Western studies. As expected, PFS and OS were better in CLL patients receiving immunochemotherapy and targeted therapy than those receiving chemotherapy. In addition, patients who achieved partial remission (PR) or complete remission (CR) after first-line treatment had a longer PFS and OS. Interestingly, females with CLL had a longer OS than males.

Conclusions: This is the largest real-world study involving Chinese patients with CLL so far, which might lay a foundation for clinical investigation of Chinese CLL in future. Although the patients were younger, had a later stage at diagnosis and had different genetic backgrounds compared with Europeans, the outcomes were not different from those reported in Western studies.

Keyword: chronic lymphocytic leukemia (CLL)

No conflicts of interests pertinent to the abstract.

583 | LOW SERUM CHOLESTEROL LEVEL AS A SIGNIFICANT PROGNOSTIC FACTOR IMPROVES CLL-IPI IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Hypocholesterolemia possibly due to increased demand and uptake is correlated with elevated cancer risk and mortality. However, hardly any current prognostic factor or model for chronic lymphocytic leukemia (CLL) is established on reprogramed lipid metabolism, which suggests the importance of nutritional status or tumor metabolism during leukemogenesis has been neglected. Our study aims to investigate the association between CLL and serum lipid profile, evaluate the prognostic value of cholesterol levels in CLL and develop a prognostic nomogram incorporating lipid metabolism to facilitate risk stratification.

Methods: In our study, 761 newly-diagnosed CLL patients between January 2007 and January 2021 with a median follow-up of 78 months were enrolled and divided into derivation (n = 507) and internal validation (n = 254) cohorts (2:1). Prognostic nomogram was constructed based on variables associated with cancer-specific survival (CSS) in multivariate Cox regression analyses. Predictive performance of models was evaluated using C-index, area under the curve (AUC), calibration and decision curve analyses.

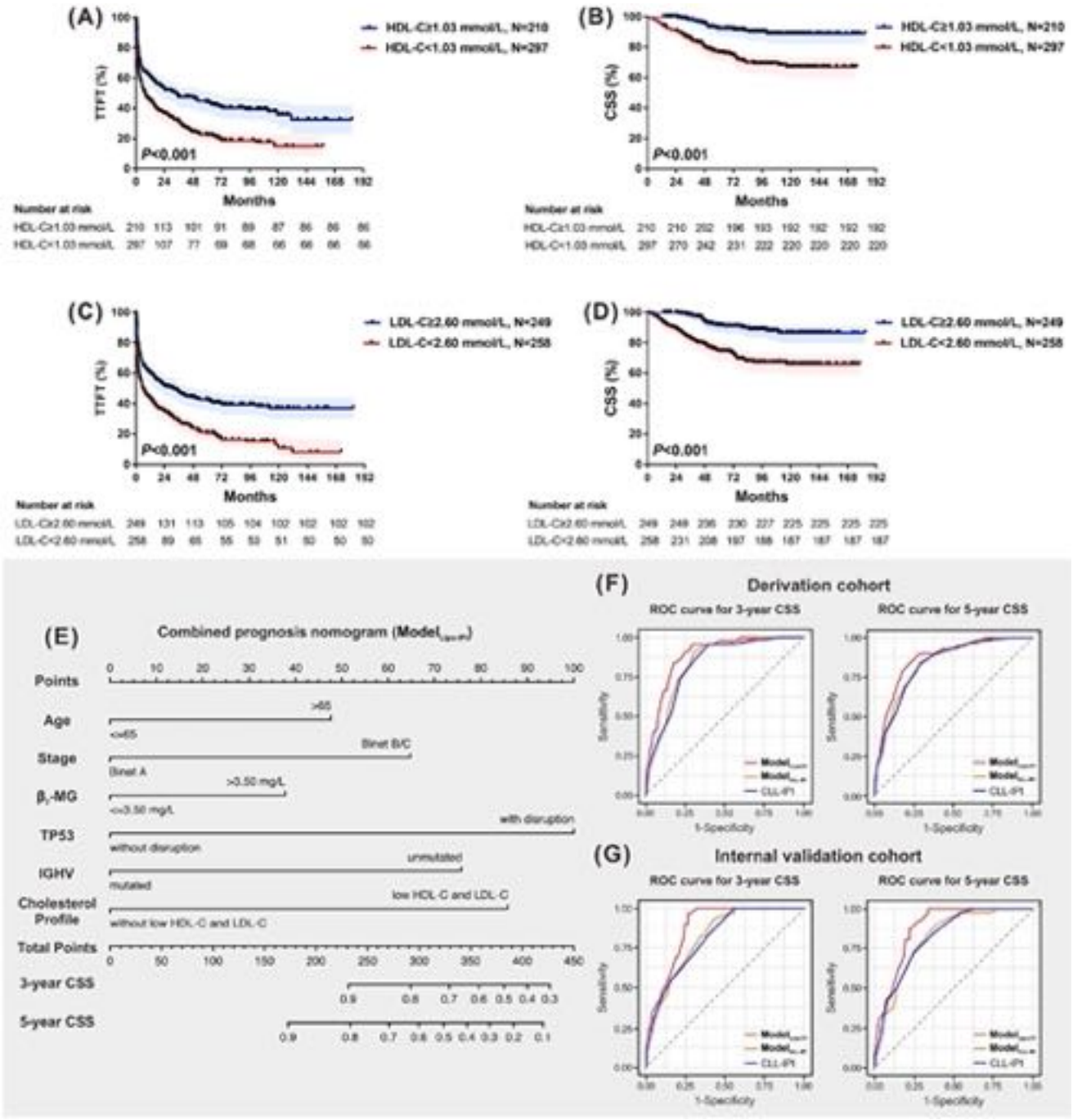
Results: Decreased levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) at diagnosis were significantly associated with worse time-to-first-treatment (TTFT) and CSS (**Figure 1A–D**). Patient with concurrently low HDL-C together with low LDL-C had remarkably worse TTFT and CSS compared with those having only low HDL-C, only low LDL-C, or normal HDL-C and LDL-C. Multivariate Cox regression analyses showed that synchronously low HDL-C and LDL-C was an independent prognostic indicator for both TTFT (HR = 1.488; 95% CI: 1.187−1.865; p = 0.001) and CSS (HR = 2.907; 95% CI: 1.848−4.572; $p < 0.001$). CLL patients who achieved complete remission or partial remission had significant increases in post-chemotherapeutic TC, HDL-C and LDL-C levels as compared with baseline, and these elevations were correlated with favorable survival. Furthermore, we developed a prognostic nomogram ($Model_{Lipo\text{-}IPI}$) for CSS that integrates all the significant factors in the multivariate analyses, including age, stage, β_2-MG level, *TP53* and *IGHV* status, and lipid profile (**Figure 2E**). $Model_{Lipo\text{-}IPI}$ augmenting CLL-international prognostic index (CLL-IPI) with low cholesterol levels yielded better predictive accuracy and discrimination capacity for 3-year and 5-year CSS with highest C-index, largest AUCs and most desirable clinical net benefit both in derivation and internal validation cohorts as compared with the reduced $Model_{CLL\text{-}IPI}$ or CLL-IPI alone (**Figure 2F, G**).

Conclusions: Cholesterol profile as a cheap and readily accessible tool has great potential for predicting prognosis in CLL clinical practice, and the application of $Model_{Lipo\text{-}IPI}$ may materially improve risk stratification of CLL patients.

The research was funded by: National Natural Science Foundation of China (grant number 82200887), Jiangsu Science and Technology Department (grant number BK20220716) and China Postdoctoral Science Foundation (grant number 2022M711404).

Keywords: metabolism, diagnostic and prognostic biomarkers, chronic lymphocytic leukemia (CLL)

No conflicts of interests pertinent to the abstract.



584 | **IDENTIFY THE MOST COMMONLY MUTATED GENES IN CHRONIC LYMPHOCYTIC LEUKEMIA AND THE SIGNIFICANCE ON PROGNOSIS**

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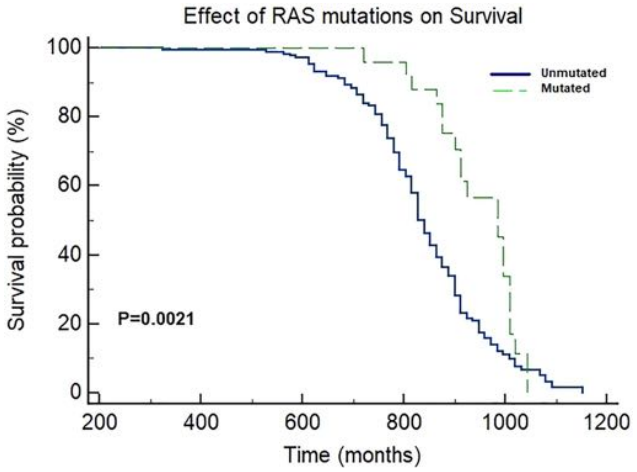
Introduction: The prognosis of chronic lymphocytic leukemia (CLL) varies widely individually. The clinical staging systems by Rai and Binet, cytogenetics/FISH, and mutational status of IGHV have been commonly used as clinical prognostic factors for CLL patients. The advent of molecular panels by next-generation sequencing might provide additional markers to predict the outcome of CLL patients. In this study, we evaluate gene mutation profiles as well as IGVH mutation status for its application to predicting survival outcomes among these CLL patients.

Methods: We performed next-generation sequencing (NGS) sequencing in 196 clinically characterized CLL samples in OSU James Cancer Hospital and analyzed the IGVH mutation status of 172 patients from the same cohort. In addition, clinic-pathological data include age, gender, immunophenotyping, and cytogenetics/FISH.

Results: 50 genes in the NGS mutation panel and IGVH mutation status are explored for a sequencing-based prediction model. Five genes (TP53, NOTCH1, SF3B1, and RAS including KRAS and BRAF)

are identified as the most commonly mutated genes in the order of frequencies from 24.1%, 14.2%, 13.4%, and 11.6%, respectively. There are 66.9% unmutated IGVH genes but has no significant correlation between the outcomes ($p = 0.48$). However, the patients with unmutated IGVH have a substantial correlation to mutated TP53 and NOTCH1, but not SF3B1 and RAS mutations. The outcome in this cohort is significantly correlated to the pathogenic mutations present among these four genes ($p < 0.001$, $n = 139$, Cochran's Q test). However, both Kaplan-Meier and Cox Regression survival analyses reveal that mutated RAS (BRAF and KRAS) is the only one that has a significant correlation to a favorable survival outcome.

Conclusion: Five genes, TP53, NOTCH1, SF3B1, and combined BRAF and KRAS, are the most common mutated molecular markers in CLL but only mutated RAS showed favorable outcomes. In summary, our results indicate the molecular mutation profiles might be used as a unique predictive marker for survival.



Keywords: chronic lymphocytic leukemia (CLL), genomics, epigenomics, and other -omics, risk models

No conflicts of interests pertinent to the abstract.

585 | COMORBIDITY & CLL DIFFERENT SCORES – DIFFERENT RESULTS

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Introduction: Due to the implementation of the outpatient centres, our network provides care for 50% of the patients with hematological diseases in Vienna. Here we analyse the influence of our own CIRS Score on survival of CLL patients. Additionally we focus on renal comorbidities.

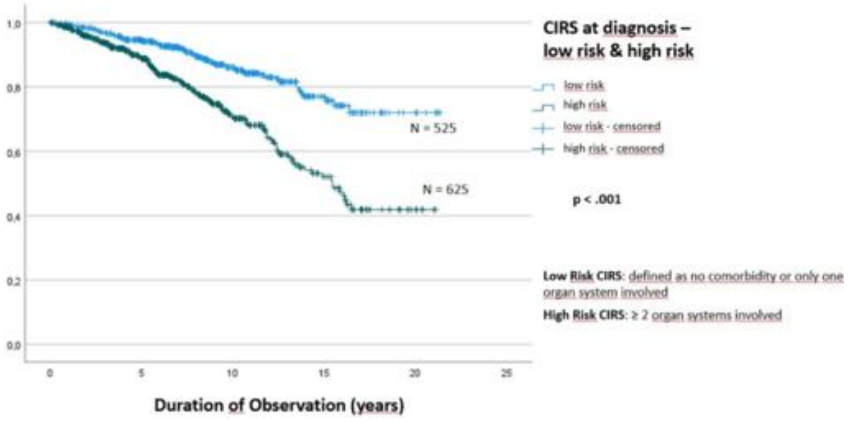
Methods: 1150 CLL patients who were diagnosed, observed and treated between 2011 and 2021 within our haematological network were analysed. Study data was generated by reviewing electronic and paper medical records. Comorbidities were assessed with the conventional CIRS Score including utilizing our own Version where we did not focus on severity to detect more patients. We differentiated between 2 groups: low risk pts. without any or with just one existing co-morbidity and high-risk patients with 2 or more organ systems involved, regardless of the severity. Moreover we demonstrate a Composite Comorbidity Score "Severe4" with <3 or >3 points, validated in 4 Organ Systems as shown on ASH 2022 by Shouse et al. and the cut-off Score of 6 points as used by the German CLL Study Group. Furthermore the Cockcroft-Gault formula (GFR).

Results: 55% of the patients were male. The median age at diagnosis was 68 years. IGHV was mutated in 53% of patients, del(17p) was present in 7,4% of patients. 27% of our 1150 patients received CLL specific treatment. As shown in Figure 1 our own interpretation of the CIRS-Score was able to identify 625 pts. classified as high risk with a significant lower OS. Regardless of the Severity, the involvement of 2 or more organ systems was more relevant than just one. Similarly to the Severe4 Score we could also show a significant OS difference in 167 pts. using a cut-off Score of 3 Points in at least one category. A highly significant OS difference can also be shown in 245 pts when using the established cut-off Score of 6 points. Emphasizing the weakness of the CIRS Score in detecting renal comorbidity due to the high threshold concerning the Serum Creatinine of 1,5 mg/dl we were able to demonstrate that 144 of our pts. had a GFR of <60 mL/min at time of diagnosis, which reflects Stage 3 CKD, resulting in a significant lower OS. When using the CIRS Score alone only 31 pts. would have been classified as renal impaired.

Conclusion: One third of our CLL patients showed an indication for treatment. Different comorbidity scores were prognostic, our feasible Version of the CIRS score is a fast method of assessment, able to discriminate pts. with shorter survival due to their co-morbidities. We were able to detect more patients ($n = 625$) with worse outcome compared to the established cut-off values of ≥3, ($n = 167$) respective ≥6, ($n = 245$). Although CIRS Score is more sensitive in detecting Co-Morbidities than the HCT-CI or CCI, there is a weakness in detecting renal co-morbidity. Pts. with a GFR <60 alone had a shortened OS, but most of them are not displayed in the CIRS Score. Updated results will be presented at the meeting.

Keyword: chronic lymphocytic leukemia (CLL)

No conflicts of interests pertinent to the abstract.



586 | REAL-WORLD OUTCOMES OF PATIENTS (PT) WITH RELAPSED OR REFRACTORY (R/R) CLL/SLL AND PRIOR TREATMENT (TX) WITH BOTH A BRUTON TYROSINE KINASE INHIBITOR (BTKI) AND VENETOCLAX

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Introduction: Despite recent therapeutic advances, in particular the development and regulatory approvals of BTKi and venetoclax, current therapies are not curative in CLL/SLL, and evidence remains limited regarding outcomes of pts with R/R CLL/SLL previously treated with both BTKi and venetoclax. The aims of this real-world evidence (RWE) study are to describe pt/disease characteristics and tx patterns, and to assess clinical outcomes of pts with R/R CLL/SLL who were previously treated with both a BTKi and venetoclax.

Methods: This retrospective study includes pt-level data from multiple RWE pt databases from the United States and Europe. Eligible pts were ≥18 y of age at CLL/SLL diagnosis. Pts in the double-exposed (DE) group had prior tx with both BTKi and venetoclax and received ≥1 subsequent tx with available response assessment by the time of data cutoff. Pts in the BTKi progression/venetoclax failure (DF) group received ≥2 prior lines of therapy (LOT) with progressive disease (PD) while on a BTKi and either no objective response, PD, or intolerance with venetoclax. Pts with Richter's transformation or another primary malignancy before the index date and those enrolled in a clinical trial or treated with cell therapy during the study period were excluded. LOT was adjudicated by clinicians.

Results: The study identified 84 patients who initiated a subsequent LOT after previous tx with BTKi and venetoclax. After applying additional eligibility criteria, there were 32 pts in the DE group and 11 pts in the DF group. In the 2 groups, median age was 70 and 65 y, 65.6% and 81.8% were male, median length of follow-up was 7.9 and 3.5 mo, and 59.4% and 54.5% had ECOG performance status ≤1 (scores were not available in 7 and 4 pts), respectively. Pts in both groups had a median of 4 prior LOTs (range, 1–10 and 2–11, respectively). Pts in the 2 groups, respectively, received a subsequent index regimen of BTKi-based tx (40.6% and 18.2%), venetoclax-based tx (25.0% and 18.2%), chemoimmunotherapy (18.8% and 36.4%), phosphoinositide 3-kinase inhibitors (18.8% and 45.5%), and other tx (9.4% and <1.0%). Complete response rate was 6.3% and 0%, and overall response rate was 62.5% and 45.5% for the DE and DF groups, respectively. Median duration of response was 12.3 and 3.5 mo, respectively. Median progression-free survival (PFS) was 9.6 and 3.3 mo with PFS at 12 mo of 48.5% and 27.7%, respectively (**Figure A,B**). Median overall survival (OS) was 15.9 and 4.6 mo with OS at 12 mo of 68.2% and 27.7%, respectively (**Figure C,D**).

Conclusions: Pts with R/R CLL/SLL previously treated with a BTKi and venetoclax have very poor clinical outcomes and short PFS/OS, particularly among those who received ≥2 prior LOTs with PD while on a BTKi and failure of venetoclax, defined as either no objective response, PD, or intolerance. Novel therapies are needed for this population with high unmet medical needs.

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Keyword: Chronic Lymphocytic Leukemia (CLL)

Conflicts of interests pertinent to the abstract

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Research funding: Research funding paid to institution from Adaptive Biotechnologies, Beigene, BostonGene, Genentech/Roche, GlaxoSmithKline, Moderna, Takeda, TG Therapeutics

L. Wang
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Stock ownership: Bristol Myers Squibb

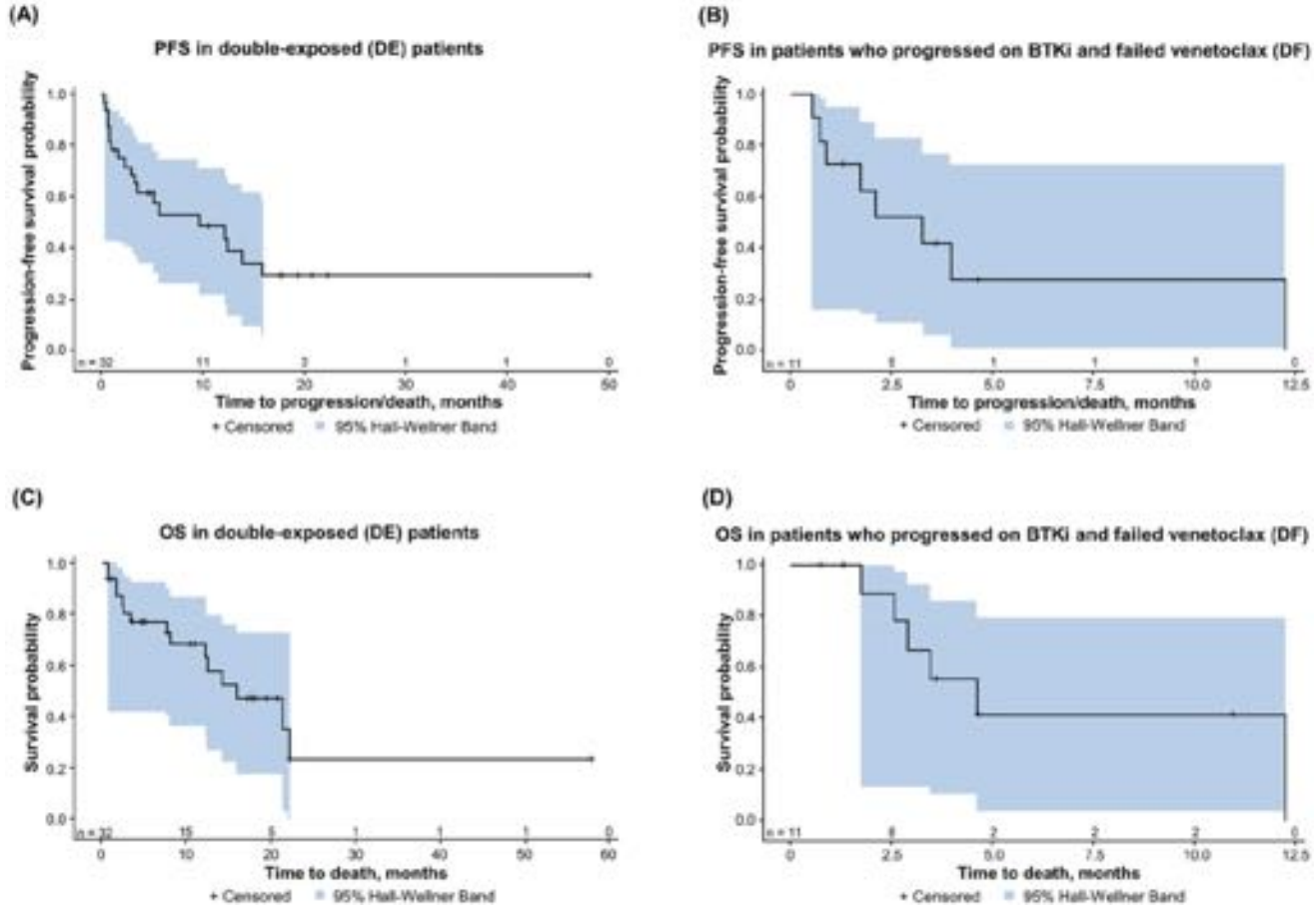

Figure. Survival outcomes in DE pts (A, C) and DF pts (B, D)

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587 | REAL-WORLD TREATMENT PATTERNS, DISCONTINUATION AND CLINICAL OUTCOMES IN PATIENTS WITH B-CELL LYMPHOPROLIFERATIVE DISEASES TREATED WITH BTK INHIBITORS IN CHINA

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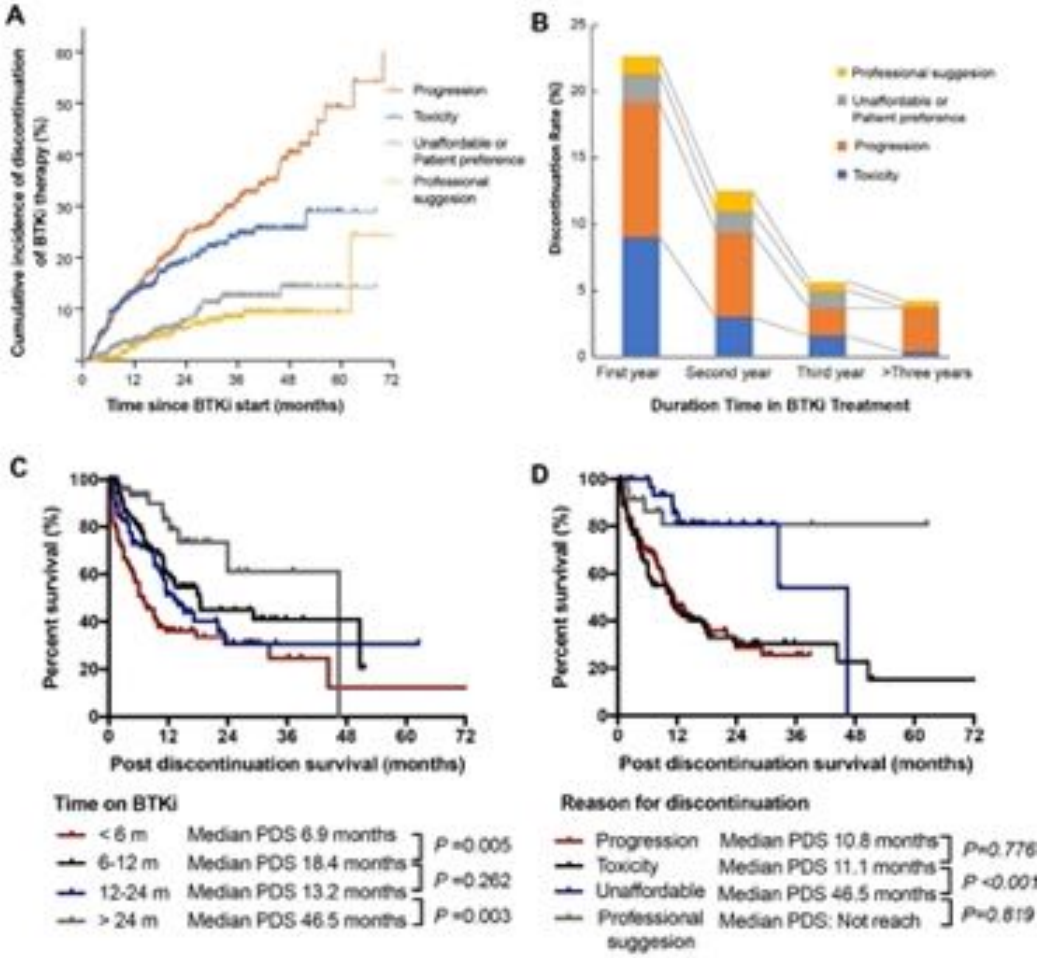
Backgrounds: Bruton tyrosine kinaseinhibition (BTKi) is an effective treatment approach for patients with B-cell lymphoproliferative diseases (BLPD). Despite the remarkable benefits gained from the use of BTKi, the high rates of discontinuation by reason of toxicity or economics are not supposed to be ignored. The real-world evidence in China on BTKi usage is limited.

Methods: A retrospective cohort study was conducted focused on 673 Chinese patients with BLPD receiving at least 1 month of BTKi treatment. Demographic data of the study cohort, lactate dehydrogenase (LDH) level, cytogenetic abnormalities, previous treatment lines, treatment regimen, adverse events (AE), and mortality data were collected. The effect of duration time on BTKi treatment as well as reasons for discontinuation on survival were analyzed.

Results: At the time of data cutoff, 673 of the 6177 patients (11.4%) were included in the study with a median follow-up of 28.8 months since BTKi starts. The most common diagnosis in BTKi treated BLPD patients was CLL (62.0%), followed by WM/LPL (28.4%), MCL (13.2%). Median age at BTKi initiation was 60 years. The median duration on BTKi treatment of the whole cohort was 36.4 months. BTKi-based treatment was permanently discontinued in 288 (43.8%) patients during follow-up, mostly owing to progressive disease. 76 patients (26.3%) experienced early discontinuations within 6 months on BTKi. The risk of drug withdrawal during follow-up in patients treated with ibrutinib was higher than those with zanubrutinib

Figure



E

Multivariate analysis on post-BTKi survival

Variable	HR (95% CI)	*P* value
Category of disease (MCL vs. CLL/WM)	1.8 (1.1-3.1)	**0.021**
Age (>65 vs. ≤65)	1.6 (1.0-2.4)	**0.045**
LDH (Elevated vs. Normal)	1.4 (0.9-2.2)	0.145
Complex karyotype (Yes vs. No)	1.2 (0.8-1.9)	0.369
17p deletion (Yes vs. No)	2.7 (1.7-4.3)	**0.001**
Line of therapy (Non-first line vs. First line)	2.3 (1.5-3.6)	**0.001**
Best response of BTKi (CR vs. PR/SD/PD)	0.6 (0.3-1.2)	0.167
Clinical trial participation (Yes vs. No)	0.7 (0.4-1.2)	0.177
Withdrawal BTKi by toxicity (Yes vs. No)	2.4 (1.4-3.9)	**0.001**
Withdrawal BTKi within 6 months (Yes vs. No)	6.4 (4.0-10.3)	**0.001**

(47.2% vs. 29.1%, $P < 0.001$). The frequency of BTKi discontinuation varied by regimen, with the higher rate among BTKi combined with CHOP-like regimen-treated patients (60.0% vs. other regimens 41.7%, $P = 0.027$). The estimated median post-BTKi failure free survival (FFS) of the entire cohort was 50.9 months, with 2-year and 5-year FFS of 70.8% and 42.3%, respectively. The median post-BTK survival was not reach.

Patients with early discontinuation had extreme worse outcome with a median post-discontinuation survival of only 6.9 months. On multivariate analysis, withdrawal BTKi by toxicity and withdrawal BTKi within 6 months retained to be independent predictors of post-BTK survival when taking account of the response depth, lines of therapy and baseline cytogenetics including 17p deletion. Whether BTKi as monotherapy versus combination therapy, as well as the

choice of first or second generation BTKi exerted no significant impact on survival.

Conclusions: These results expand the real-world evidence on BTKi in China. We concluded that BTKi is an effective and well-tolerated treatment for long-term use in Chinese patient population. Nevertheless, it should be underlined that a proportion of patients experienced early discontinuation and resulted in inferior outcome. This study emphasized the impact of adherence to ibrutinib on clinical outcomes in real-world patients.

Keywords: diagnostic and prognostic biomarkers, indolent non-Hodgkin lymphoma, molecular targeted therapies

No conflicts of interests pertinent to the abstract.

588 | REAL-WORLD DURATION OF VENETOCLAX TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LYMPHOMA

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Introduction: Venetoclax (V) is an approved fixed-duration treatment (tx) for chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL), as a 12-cycle regimen (~12 mos) with obinutuzumab (O) in the first-line (1L) setting or as a 24-cycle regimen (~24 mos) with rituximab (R) in the relapsed/refractory (R/R) setting. We analyzed real-world tx patterns of V+O in 1L and V+R in R/R settings in patients (pts) with CLL/SLL in the United States.

Methods: A retrospective cohort analysis was conducted using the IQVIA PharMetrics® Plus database to identify pts ≥18 y treated with V+O (1L cohort; May 2019 to September 2021) or V+R (R/R cohort; June 2018 to September 2021). Start of tx regimen was defined as the index date. All pts were required to have ≥1 diagnosis code for CLL/SLL and continuous enrollment 12 mos prior to and ≥3 mos after index date. Duration of tx (DoT) was defined as time from index date to earliest of either tx discontinuation (i.e., ≥60-d gap in V prescription refills) or censoring (i.e., end of follow-up). Fixed-duration tx cycle was defined as 12- or 24-cycle dosing (days 336−364 for 1L setting and days 707−735 for R/R setting, based on the dosing schedule plus 28 days). Kaplan-Meier analysis was used to estimate the probability of remaining on tx for the 1L and R/R cohorts.

Results: A total of 116 pts in 1L setting (mean age, 62.3 y) and 145 pts in R/R setting (mean age, 64.2 y) were identified; 48.3% of R/R pts had prior targeted therapy. Median (95% CI) DoT in V+O pts (n = 115) was 12.4 (11.5, 13.4) mos over a median follow-up of 11.4 mos; probability of remaining on tx at 12, 18, and 24 mos was 56.4%, 20.2%, and 5.1%. Median (95% CI) DoT in V+R pts (n = 133) was 24.5 (13.4, 25.2) mos over a median follow-up of 15.5 mos; probability of remaining on tx at 24, 30, and 36 mos was 53.8%, 19.0%, and 19.0%. Among V+O pts, 47.8% (55/115) had ≥12 mos follow-up, of whom 9.1% had fixed cycles and 38.2% discontinued early (median DoT: 4.6 mos). Among V+R pts, 29.3% (39/133) had ≥24 mos follow-up, of whom 5.1% had fixed cycles and 46.2% discontinued early (median DoT: 7.1 mos). The remaining pts in each cohort had DoT >12 or 24 cycles (**Table**).

Conclusions: While median DoT was approximately 12 mos for V+O-treated pts (1L setting) and 24 mos for V+R-treated pts (R/R setting), a high number of pts did not maintain the fixed-dosing schedule. This study provides evidence that a V-based approach may not be suitable for all pts with CLL/SLL.

Encore Abstract—previously submitted to regional or national meetings (up to <1'000 attendees), EHA 2023

The research was funded by: AstraZeneca

Keyword: Chronic Lymphocytic Leukemia (CLL)

Conflicts of interests pertinent to the abstract

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Table. Index tx cycles.

Measures	1L cohort with V+O and ≥12 mos follow-up (n = 55)	R/R cohort with V+R and ≥24 mos follow-up (n = 39)
Index tx duration relative to fixed duration, n (%)		
Treated for fixed duration (1L 336−364 d; R/R 707−735 d)	5 (9.1)	2 (5.1)
Treated beyond fixed duration (1L >364 d; R/R >735 d)	29 (52.7)	19 (48.7)
Early tx discontinuation (1L <336 d; R/R <707 d)	21 (38.2)	18 (46.2)
Median duration of index tx regimen, mos (Q1, Q3)	4.6 (2.3, 8.3)	7.1 (3.4, 11.1)

Q1, quartile 1; Q3, quartile 3.

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Research funding: AstraZeneca Pharmaceuticals. IQVIA received research funding from AstraZeneca to conduct this study.

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Research funding: AstraZeneca Pharmaceuticals. IQVIA received research funding from AstraZeneca to conduct this study.

589 | EPIC: A NON-INTERVENTIONAL, OBSERVATIONAL UK STUDY OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) PATIENTS TREATED WITH FIRST-LINE ACALABRUTINIB. INTERIM ANALYSIS UP TO 24 MONTHS

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Introduction: Clinical trials of acalabrutinib, a second-generation Bruton's tyrosine kinase inhibitor, show high response rates and an acceptable safety profile in patients with CLL. However, there is a lack of real-world data on the use of acalabrutinib in the first-line treatment of CLL. This interim analysis (IA) presents baseline demographics, clinical characteristics, and treatment patterns of patients with CLL up to 24 months post-initiation of first-line acalabrutinib via the UK Early Access Programme (EAP).
Methods: EPIC is a retrospective multi-centre cohort study involving data collection from medical records (ClinicalTrials.gov: NCT05557695). Eligible patients were treatment-naïve CLL patients who initiated acalabrutinib between 1st April 2020 and 1st April 2021 as part of the EAP and were recruited from 5 sites in England for this IA. Data collected included baseline clinical and demographic characteristics, and acalabrutinib treatment patterns. This study has planned follow-up of up to 60 months from the date of acalabrutinib start (index date). Data cut for this IA was 23rd January 2023.
Results: This IA includes 54 patients. Median age at index was 74.5 years (Interquartile range (IQR), 69.0–78.6); 59% (32/54) of patients were male, 84% (43/51) were White British. At index, 53% (20/38) of patients had creatinine clearance <60 mL/min. 7% (4/54) of patients had a confirmed ATM mutation, 6% (3/54) had a confirmed TP53 mutation, 2% (1/54) of patients had a confirmed IGHV mutation (≥2% difference from germline), and none had a chromosome 17p13.1 deletion. Median time between CLL diagnosis and index was 3.1 years (IQR, 1.4–7.3). The median duration of follow up was 27.4 months (IQR, 24.6–29.9); 87% (47/54) and 76% (41/54) of patients had durations of observation ≥1 year and ≥2 years, respectively. 43 patients remained on treatment at 12 months, 10 had discontinued (1 patient not recorded). The continuation rate at 12 months was 81.1% (95% CI, 71.3%–92.4%; $n = 53$). Of 54 patients with relevant medical records at the time of data cut, 28% (15/54) had discontinued acalabrutinib. Of the 14 recorded reasons given for treatment discontinuation, 64% (9/14) were due to adverse events, 7% (1/14) were patient decision and 29% (4/14) other; no discontinuations were recorded due to progressive disease. The median real-world overall time on treatment ($n = 53$; up to 12 months) was 12.0 months (IQR, 11.6–12.0). Of 27 patients with relevant medical records, 70% (19/27) had a recorded diagnosis of COVID-19; of these, 89% (17/19) had diagnoses confirmed via a test. The most common treatment received for COVID-19 (for 32% of patients; 6/19) was sotrovimab.
Conclusions: This first IA shows an 81.1% (95% CI, 71.3%–92.4%; $n = 53$) acalabrutinib real-world continuation rate at 12 months in treatment-naïve patients with CLL. Future analyses are aiming at including retrospective data from around 40 clinical sites with approximately 350 eligible patients.

Encore Abstract—previously submitted to EHA 2023

The research was funded by: AstraZeneca

Keyword: Chronic Lymphocytic Leukemia (CLL)

Conflicts of interests pertinent to the abstract

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590 | SAFETY AND EFFECTIVENESS IN R/R CLL PATIENTS TREATED WITH VENETOCLAX IN COMBINATION WITH RITUXIMAB UNDER REAL-WORLD CONDITIONS IN AUSTRIA, GERMANY, AND SWITZERLAND

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Introduction: In clinical trials, treatment of chronic lymphocytic leukemia (CLL) with venetoclax (Ven) has shown promising efficacy and good tolerability.[1,2] However, patients treated in clinical trial are often not representative in daily practice. Prospective real-world data on Ven usage are limited.

Objective: We conduct a prospective non-interventional observational study assessing effectiveness, safety, and quality of life in relapsed/refractory patients (RR) treated with Ven in Austria, Germany, and Switzerland. The population enrolled is representative for patients treated with Ven according to local label.[3] This report focuses on patients treated with Ven in combination with rituximab (R).

Methods: Adult patients with CLL requiring therapy treated with Ven +R according to local label are eligible for the study. Patient's visits are scheduled at the physician's discretion and according to clinical practice. Study documentation is possible at baseline, weekly during ramp-up, monthly until the end of 6 months and 3-monthly afterwards up to a maximum of 3 years. Response assessment according to iwCLL criteria can be documented at the end of ramp-up, after 3, 12, and 24 months.

Results: Until Nov 4th, 2022, 106 patients receiving VenR were enrolled, 105 with at least one dose of Ven (= safety population), for 87 treatment response had been documented at least once (= effectiveness population). Median age at therapy start was 74 years, 72.6% of patients were male, 76.4% had at least one comorbidity, most commonly cardiovascular (57.5%) and 73.6% received comedication. Patients were pre-treated with a median of 1 (range 1-10) line of therapy, e.g., chemo-immuno-therapy (CIT: 75.5%) or B-cell receptor inhibitors (34.9%). Del(17p), *TP53* mutation, and presence of unmutated IGHV had been diagnosed in 23.6%, 24.5%, and 40.6%, respectively (excl. missing data: 28.7%, 30.6%, 69.4%). With a median observation time of 652 (range 14-1364) days, 93.3% of patients experienced at least one AE, 58.1% experienced CTCAE grade 3/4 AEs, SAEs were reported in 41.0%. Grade 5 AEs were reported in 10 patients, tumor lysis syndrome (TLS) in 12 patients (11.4%). The median for progression-free survival (PFS) and overall survival (OS) has not been reached, the 24-month estimates were 80.1% (PFS) and 84.1% (OS).

The reported best overall response at 24 months was 88.5% (CR+CRi 59.8%; PR: 28.7%). Remissions continue to deepen with longer treatment duration.

Conclusions: Under real-world conditions, VenR is used in elderly patients with comorbidities. The treatment was well tolerated. Most patients receive VenR in 2L of therapy after initial CIT. The response rate in patients presenting with high risk features, e.g., del(17p), *TP53* mutation or unmutated IGHV, was high. Despite the advanced age of the enrolled patient population, PFS and OS estimates are comparable to pivotal phase III trial MURANO.

The research was funded by: AbbVie sponsored this study and contributed to the design, study conduct.

Keywords: molecular targeted therapies, ongoing trials

Conflicts of interests pertinent to the abstract

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591 | MATCHING-ADJUSTED INDIRECT COMPARISON OF PIRTOBRUTINIB VS VENETOCLAX CONTINUOUS MONOTHERAPY IN PATIENTS WITH RELAPSED/REFRACTORY CLL TREATED WITH COVALENT BTK INHIBITOR

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Introduction: Venetoclax-based therapy is standard for pts with relapsed/refractory (R/R) CLL previously treated with a covalent BTK inhibitor (cBTKi). Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi designed to overcome pharmacologic limitations of cBTKi and restore BTK inhibition and has demonstrated marked efficacy and a favorable safety profile. This unanchored MAIC estimates the treatment effect of pirtobrutinib (BRUIN) vs venetoclax continuous monotherapy in pts with R/R CLL treated with a cBTKi.

Methods: Data from pts with R/R CLL previously treated with at least 1 cBTKi and without prior venetoclax exposure who received pirtobrutinib were analyzed (n = 146). Only 1 prospective trial of venetoclax (administered as a continuous monotherapy) for pts previously treated with a cBTKi (n = 91) was identified. Progression-free survival (PFS), overall survival (OS), investigator-assessed overall response rate (ORR), and grade ≥3 treatment-emergent adverse events (TEAEs) regardless of attribution were evaluated. Pt-level data from pirtobrutinib cohort were re-weighted to match the venetoclax cohort using method of moments, adjusting for well-established prognostic factors reported in both studies (age, IGHV mutation status, *TP53* aberrancy, del(17p), del(11q); number of prior lines of therapy, reason for cBTKi discontinuation). Kaplan-Meier PFS and OS curves from the venetoclax trial were digitized (using WebPlotDigitizer) for time-to-event analyses. Fishers exact test was used to compare proportional outcomes (ORR, TEAEs); time-to-event outcomes (PFS, OS) were compared using Cox regression model and log-rank test.

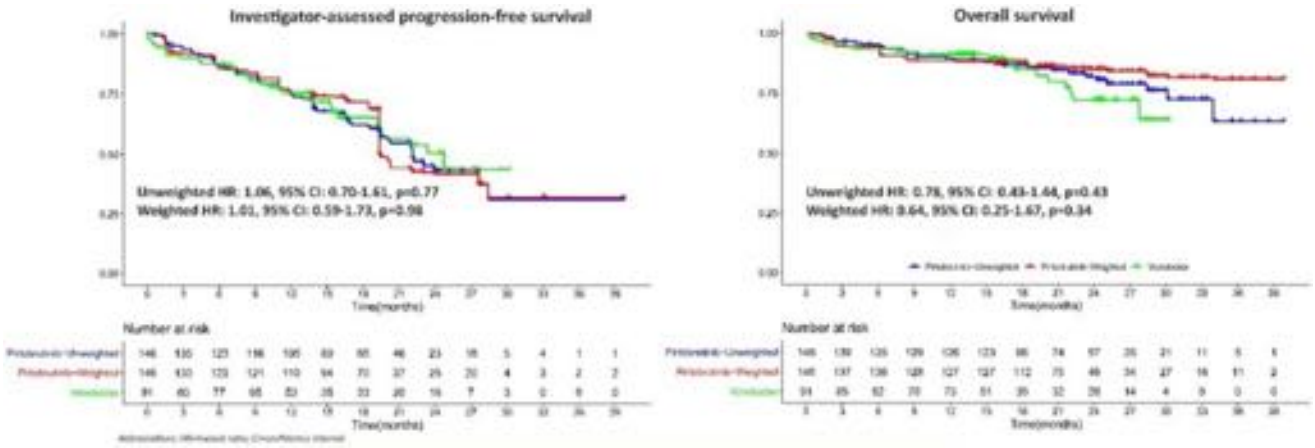
Results: The median age in pirtobrutinib and venetoclax cohorts was 66.5 and 66.0 years; all other prognostic factors were well matched; median follow-up was 21.3 months and 14 months.

PFS and OS were comparable with no significant differences noted for pirtobrutinib versus venetoclax ($p > .05$; Figure). ORR was 80% for pirtobrutinib (inclusive of PR-L) versus 65% for venetoclax (p = .01).

Grade ≥3 TEAEs indicated febrile neutropenia, neutropenia, anemia, and thrombocytopenia were significantly lower for pirtobrutinib vs venetoclax in adjusted analyses (all $p < .01$). No differences were observed for pneumonia (p=.06) or discontinuation due to TEAEs (3% vs 7%, p = .32). Unadjusted results were consistent with the adjusted analyses.

Conclusions: Pirtobrutinib efficacy was comparable to venetoclax in pts with R/R CLL previously treated with cBTKi. Pirtobrutinib was associated with improved ORR and favorable overall safety profile for TEAEs vs venetoclax, raising questions on optimal treatment sequencing of pirtobrutinib and venetoclax in cBTKi-treated CLL, but lack of prospective direct comparisons and limited long-term follow-up preclude definitive conclusions.

Randomized Phase 3 studies of pirtobrutinib in pts with CLL are ongoing.



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Conflicts of interests pertinent to the abstract

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592 | IMPROVED EFFICACY AND SAFETY OF ZANUBRUTINIB VERSUS IBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (R/R CLL) IN CHINA: A SUBGROUP OF ALPINE

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Introduction: Zanubrutinib is an irreversible, potent, next-generation Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize off-target inhibition. In a randomized phase 3 study (ALPINE; NCT03734016), zanubrutinib was compared head to head with ibrutinib as a treatment for R/R CLL (including small lymphocytic lymphoma [SLL]). In the predefined progression-free survival (PFS) final analysis, zanubrutinib demonstrated superior efficacy and a favorable safety profile versus ibrutinib (Brown et al. *NEJM* 2022). Data from the prespecified subgroup in pts from China are reported here.

Methods: Patients (pts) with R/R CLL/SLL who had received ≥1 prior line of therapy and had measurable disease by imaging were randomized (1:1) to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily, until disease progression or unacceptable toxicity. Randomization included stratification by geographical region (China vs. non-China). Data from the subgroup in pts from China were descriptively analyzed.

Results: A total of 90 pts in China with R/R CLL/SLL (zanubrutinib, $n = 47$; ibrutinib, $n = 43$) were enrolled. Disease characteristics and baseline demographics were balanced between zanubrutinib and ibrutinib (aged ≥65 y [40% vs. 37%]; unmutated IGHV [59.6% vs. 62.8%]; del17p/*TP53* mutated [34.0% vs. 32.6%]) with a median age of 60 and 61 y, respectively. Median number of prior therapies was 1. At a median follow-up of 25.3 mo, PFS by independent review committee (IRC) was improved with zanubrutinib versus ibrutinib (hazard ratio [HR]: 0.24; 95% CI 0.09-0.64; nominal 2-sided $P = 0.002$) with 18-mo landmark PFS rates of 88.9% versus 71.6% for zanubrutinib and ibrutinib, respectively (**Figure**). Additionally, zanubrutinib was more favorable in high-risk del17p/*TP53* mutation (18-mo landmark 80.0% vs. 64.3%; HR: 0.51; 95% CI 0.12-2.13). ORR also favored zanubrutinib over ibrutinib (87.2% vs. 76.7%; 95% CI 0.93-1.38) by IRC. The treatment discontinuation rate was lower with zanubrutinib (14.9%) versus ibrutinib (41.9%) with most due to progressive disease (6.4% vs. 20.9%) and adverse events (AEs; 6.4% vs. 14.0%). Rates of grade ≥3 AEs (64.4% vs. 72.1%) and serious AEs (35.6% vs. 51.2%) were lower with zanubrutinib versus ibrutinib. With zanubrutinib, 4 deaths (8.5%) were reported compared to 8 deaths (18.6%) with ibrutinib (HR: 0.45; 95% CI 0.14–1.50).

Conclusions: Zanubrutinib showed improved PFS over ibrutinib in the ALPINE study in pts from China, including high-risk pts, consistent with that of the global population. A favorable safety profile was also observed in pts from China with zanubrutinib compared with ibrutinib, with lower rates of treatment discontinuations and serious AEs in patients with R/R CLL/SLL.

Keywords: Chronic Lymphocytic Leukemia (CLL), Molecular Targeted Therapies

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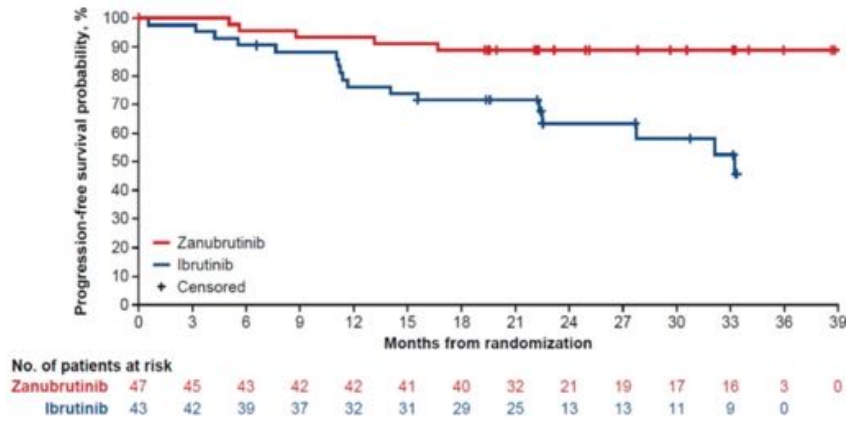
Figure. Kaplan-Meier Plot of PFS by IRC for the Subgroup in pts from China



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Research funding: BeiGene, Gilead, iOnctura, Loxo/Lilly, MEI Pharma, TG Therapeutics

593 | A MATCHING-ADJUSTED INDIRECT COMPARISON OF THE EFFICACY AND SAFETY OF ACALABRUTINIB VERSUS ZANUBRUTINIB IN RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: Next-generation Bruton tyrosine kinase inhibitors (BTKis) acalabrutinib (acala) and zanubrutinib (zanu) were compared with the standard of care BTKi ibrutinib in relapsed/refractory chronic lymphocytic leukemia (RR CLL) in the head-to-head randomized clinical trials (RCTs) ELEVATE-RR and ALPINE, respectively. However, differences in these RCT's populations prevent comparison of acala and zanu. ASCEND, another RCT assessing acala, had a similar population to ALPINE but a different comparator. Thus, we used unanchored matching-adjusted indirect comparison (MAIC) to compare the efficacy and safety of acala vs zanu using individual patient data (IPD) from ASCEND and published aggregate data from ALPINE.

Methods: Acala IPD from ASCEND were weighted to match zanu baseline data from ALPINE. This reduced differences in variables that were prognostic/effect-modifying of progression-free survival (PFS) in an exploratory multivariate cox regression analysis of ASCEND. These included sex, ECOG PS, bulky disease, prior chemo-immunotherapy, del(11q), del(17p), *TP53* without del(17p), IGHV status, region, age, prior lines of therapy and Rai stage. An efficacy analysis assessed investigator-assessed PFS (INV PFS) in randomized patients with baseline data (acala, n = 149; zanu, n = 327). Pseudo IPD for INV PFS for zanu were obtained from Kaplan-Meier curves. A safety analysis assessed odds ratios (ORs) of adverse events (AEs) in treated patients with baseline data (acala, n = 148; zanu, n = 324). To compare the incidence of AEs, an artificial data cut-off (Feb 21, 2020) was imposed for acala to match the zanu median treatment exposure (both 28.4 months).

Results: After matching, the effective sample size of acala was 99 (66.6%; 65% male; median age 66 years). 12- and 24-month INV PFS are shown in Table 1. The MAIC hazard ratio (HR) for INV PFS is similar for acala vs zanu: HR 0.90, 95% confidence interval (CI) 0.60–1.36. The risk of having grade ≥3 AE (OR 0.66, 95% CI 0.41–1.05), atrial fibrillation (AF; OR 1.32, 95% CI 0.56–3.08), grade ≥3 AF/atrial flutter (OR 0.60, 95% CI 0.12–2.89), grade ≥3 hemorrhage (OR 0.61, 95% CI 0.19–2.03) or an AE leading to discontinuation (OR 1.14, 95% CI 0.61–2.13) was similar with acala vs zanu. The risk of having a serious AE (OR 0.61, 95% CI 0.39–0.97), hypertension (any grade: OR 0.18, 95% CI 0.09–0.37; grade ≥3: OR 0.22, 95% CI 0.09–0.54), any grade hemorrhage (OR 0.54, 95% CI 0.34–0.87) or an AE leading to dose reduction (OR 0.30, 95% CI 0.14–0.67) favored acala vs zanu.

Conclusions: Acala and zanu have a similar efficacy in RR CLL, while acala has a lower risk of grade ≥3 hemorrhage, any grade and grade ≥3 hypertension and dose reduction due to AEs vs zanu. Limitations of MAICs mean results should be viewed as hypothesis-generating.

TABLE 1 INV PFS.

Treatment		INV PFS %, 95% CI	
		12-month	24-month
Acala	Unweighted	89, 83–93	75, 68–81
	Weighted	91, 84–95	76, 66–84
Zanu		92, 88–94	78, 73–83

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Keyword: Chronic Lymphocytic Leukemia (CLL)

Conflicts of interests pertinent to the abstract

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594 | A META-ANALYTIC ENDPOINT VALIDATION OF SURROGATES USED IN CLINICAL TRIALS EVALUATING THE EFFICACY OF THERAPIES IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Introduction: Regulatory bodies can approve treatments based on surrogate endpoints, which can be measured earlier than true endpoints. While approvals based on surrogate endpoints are increasing, many have not demonstrated a correlation with clinically meaningful outcomes. This study evaluated the validity of objective response rate (ORR) as a surrogate endpoint for progression-free survival (PFS) and overall survival (OS), and PFS as a surrogate endpoint for OS in CLL.

Methods: A systematic literature review of randomized controlled trials (RCTs) for CLL published between January 2015 and January 2022 was conducted in line with NICE (2022) requirements and Cochrane methodology. RCTs reporting at least 2 endpoints of interest (ORR, PFS, OS) were included. Two independent reviewers extracted relevant data on comparative effectiveness measures reported in the trial publications, which were used in a surrogate endpoint validation in alignment with health technology assessment guidelines. Two-stage validation was used: the overall magnitude of the comparative effect of the surrogates was estimated using a bootstrapped DerSimonian-Laird random-effects model, then correlation and regression analyses assessed the association between surrogate and final endpoints. Analyses were performed across all trials and separately across trials investigating either kinase inhibitor (Ki) or Bruton tyrosine Ki (BTKi).

Results: A total of 69 RCTs were identified; 28, 25, and 29 trials were available for the ORR vs PFS, ORR vs OS, and PFS vs OS comparisons, respectively. Respective numbers for Ki/BTKi trials within each comparison were 14/10, 13/10, and 13/11. Based on all trials, the overall magnitudes of the comparative effect of the surrogate were 0.18 (95% CI: 0.13, 0.23) for the absolute difference in ORR, 0.52 (0.41, 0.64) for the hazard ratio for PFS, and 0.80 (0.72, 0.89) for the hazard ratio for OS. Significant treatment effects were also observed in the Ki and BTKi subgroups. Statistically significant correlations for ORR vs PFS were found across all therapies (r = 0.67; 95% CI: 0.40, 0.84), as well as in the Ki (0.68; 0.24, 0.89) and BTKi (0.75; 0.22, 0.94) subgroups (Figure). The correlation observed between ORR and PFS was categorized as moderate in the BTKi trials. No clear correlation between the comparative effect on ORR and OS was observed. A statistically significant association between the comparative effect on PFS and on OS based on all trials was shown (r = 0.58; 0.27, 0.78). For Ki and BTKi subgroups, significant associations between comparative effects on PFS and OS were observed after weighting the regression by patient number.

Conclusions: We found robust evidence that ORR serves as a surrogate for PFS in CLL, especially when evaluating the treatment effect of BTKis, some evidence of an association between PFS and OS, and no clear evidence of ORR as a surrogate for OS.

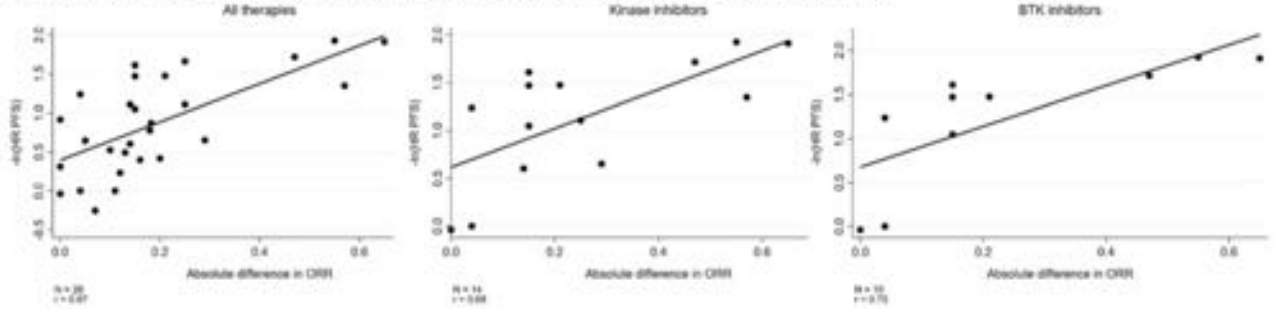
Encore Abstract—previously submitted to EHA 2023

The research was funded by: BeiGene

Keyword: chronic lymphocytic leukemia (CLL)

Conflicts of interests pertinent to the abstract

Figure. Scatterplot displaying the correlation between ORR and PFS



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595 | **PATTERNS OF IMMUNOGLOBULIN G TESTING AND INFECTION OUTCOMES IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA RECEIVING IMMUNOGLOBULIN REPLACEMENT THERAPY**

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Introduction: Infections lead to mortality in up to 50% of patients (pts) with chronic lymphocytic leukemia (CLL). Immunoglobulin G (IgG) testing detects hypogammaglobulinemia (HGG; <500 mg/dL), a secondary immunodeficiency and risk factor for severe infections (SI) in pts with CLL. We hypothesized that increased IgG testing is associated with improved identification of HGG and reduced risk of SI in CLL.
Methods: This retrospective study used de-identified patient data (structured data only) from the Mass General Brigham Research Registry. Eligible adults with CLL (diagnosed post-2010) had ≥12 months of clinical data and ≥3 visits/year. IgG levels and rates of HGG and SI pre- and post-immunoglobulin replacement therapy (IgRT) were compared. A multivariable logistic regression model examined the association of SI with IgG testing, controlling for IgRT, HGG, treatment, age, and sex.
Results: Of 2842 pts with CLL and median (IQR) follow-up of 4.2 (2.2, 6.8) years, 1352 (47.6%) underwent IgG testing; 464 (34.3%) had HGG; 179 (6.3%) received IgRT; and 75.2% were treatment-naive. IgRT use (median [IQR] administrations of 2.0 [1.0, 4.0]) increased IgG levels (502.0 mg/dL [397.0, 615.0] vs. 367.0 mg/dL [245.0, 454.0]) and reduced rates of HGG (38.0% vs. 80.3%, $p < 0.0001$) and SI (33.7% vs. 51.0%, P=0.003) in the 12 months post-IgRT. IgG testing and IgRT use were independently associated with a significantly lower SI risk (**Table**). Pts with ≥3 versus 1-2 IgG tests were more likely to be identified with HGG (51.5% [321/623] vs. 19.6% [143/729], $p < 0.0001$), and pts with HGG who had ≥3 IgG tests were more likely to receive IgRT (32.7% [105/321] vs. 13.3% [19/143], $p < 0.0001$).
Conclusions: Increased IgG testing was independently associated with lower risk of SI. Greater HGG risk awareness and more standardized IgG testing might reduce SI in pts with CLL.

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Keywords: chronic lymphocytic leukemia (CLL), immunotherapy, late effects in lymphoma survivors

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Conflict of interest:

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Table. Odds of SI in Pts With CLL (N=2842)

Variable	Odds Ratio (95% Confidence Interval)
Number of IgG tests[a]	
0	Reference
1	0.34 (0.25, 0.45)[c*]
2	0.27 (0.18, 0.42)[c*]
≥3	0.11 (0.07, 0.16)[c*]
IgRT use[a]	0.38 (0.18, 0.80)[d*]
HGG[a]	1.52 (0.99, 2.35)[e]
Cytotoxic chemotherapy[b]	3.58 (2.49, 5.14)[c*]
CD20 monoclonal antibody[b]	1.39 (0.99, 1.96)[f]
Oral targeted therapy[b]	2.34 (1.79, 3.08)[c*]
Immunomodulatory drugs[b]	4.90 (1.24, 19.32)[g*]
Corticosteroids[b]	5.23 (4.26, 6.42)[c*]
Hematopoietic stem cell transplantation[b]	3.50 (1.63, 7.53)[h*]
Chimeric antigen receptor T-cell therapy[b]	15.22 (4.21, 54.97)[c*]
Age (continuous)	1.02 (1.01, 1.03)[c*]
Sex	
Male	Reference
Female	0.85 (0.70, 1.03)[i]

[a]For patients with an infection, IgG testing, IgRT use, and HGG (lowest IgG <500 mg/dL) was measured 12 months before the infection date; [b]Measured at any time point; [c]$P<0.0001$*; [d]$P=0.011$*; [e]$P=0.058$; [f]$P=0.060$; [g]$P=0.023$*; [h]$P=0.001$*; [i]$P=0.089$.

*Statistical significance ($P<0.05$)

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596 | RETROSPECTIVE STUDY OF BURDEN OF INFECTION IN PATIENTS WITH AND WITHOUT SECONDARY IMMUNODEFICIENCY DISEASE FOLLOWING DIAGNOSIS OF CHRONIC LYMPHOCYTIC LEUKAEMIA

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Introduction: Patients with lymphoid malignancies such as chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) are at risk of developing secondary immunodeficiency disease (SID), which can lead to increased susceptibility to severe, recurrent or persistent infections. This study evaluated burden of infection in patients with and without SID following diagnosis of CLL/SLL.

Methods: This observational, retrospective cohort study was conducted using anonymized data from the Optum-Humedica database in the USA (1-Oct-15–10-Mar-20). Patients with SID (SID cohort) and without SID (no-SID cohort) were identified 1-Apr-16–10-Mar-19 (selection window). The definition of SID included International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) hypogammaglobulinaemia (HGG) codes, low immunoglobulin G (IgG) levels (<5.0 g/L) and signs/symptoms of SID. The SID index date was the earliest occurrence of an ICD-10-CM HGG code or record of low IgG levels. In patients without SID, the index date was randomly assigned to replicate the distribution of index dates in the SID cohort.

CLL/SLL diagnosis and baseline characteristics were identified during a 6-month pre-index period. Included patients were aged ≥18 years with a confirmed diagnosis of CLL/SLL. Infection-related outcomes and overall survival were assessed in patients with ≥12-month and ≥3 months follow-up post-index date, respectively.

Results: Of patients with CLL/SLL, 502 and 3928 with and without SID, respectively, were included (SID vs no-SID: mean [standard deviation; SD] age 70.6 [9.7] vs. 71.6 [10.5] years; 59.2% vs 57.7% male).

At 12-month follow-up, a larger proportion of patients with SID had ≥1 infection than those without SID (SID: 70.1%; no-SID: 30.4%; $p <$ 0.001). Compared with the no-SID cohort, in the SID cohort there was also a higher number of infections (SID vs no-SID: mean [SD]: 8.4

[12.7] vs. 4.1 [5.4]; $p < 0.001$), proportion of patients with ≥1 SBI (SID: 39.8%; no-SID: 9.2%; $p < 0.001$) and proportion of patients with ≥1 infection-associated hospitalization (SID: 27.7%; no-SID: 5.8%; $p < 0.001$). The most common type of infection was bacterial (SID: 63.7%; no-SID: 24.9%); in those patients who experienced an SBI, the most frequently reported infection was bacterial pneumonia.
To assess overall survival, 646 and 4719 patients with and without SID, respectively, were included. Overall survival at 24 months was lower in the SID cohort (77.3%) than the no-SID cohort (87.2%).
Conclusions: Patients with CLL/SLL who subsequently developed SID had a greater burden of infection than patients who did not develop SID. Increasing understanding of this burden of infection may help to improve outcomes in this population

Encore Abstract—previously submitted to EHA 2023

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Keywords: cancer health disparities, chronic lymphocytic leukemia (CLL), indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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MCL

597 | SOLUBLE MACROPHAGE MARKER SCD163 PREDICTS OUTCOME IN BOTH CHEMOIMMUNOTHERAPY AND TARGETED THERAPY TREATED MANTLE CELL LYMPHOMA

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Introduction: The outcome for patients with mantle cell lymphoma (MCL) has drastically improved with new treatments directed towards the tumor immune microenvironment, where macrophages play an important role. In MCL, the presence of M2 macrophages defined by CD163 expression in diagnostic biopsies has been associated with a worse prognosis. An alternative way to assess the abundance of M2 macrophages is by measuring the level of soluble CD163 in serum (sCD163).
Method: We aimed to investigate the prognostic value of sCD163 in 131 MCL patients. sCD163 was analyzed with ELISA and the cut-off was á priori set to median level.
Results: We found that high sCD163 at diagnosis was associated with shorter progression-free survival (PFS) and shorter overall survival (OS) (log rank test $p = 0.002$ and $p < 0.001$, respectively) in 81 newly diagnosed patients that were subsequently treated with chemoimmunotherapy. The same was seen in a cohort of 50 relapsed,

heavily pretreated, MCL patients mainly treated within the phase II Philemon-trial with rituximab, ibrutinib and lenalidomide (log rank test, PFS $p = 0.016$ and OS $p = 0.035$).

Low levels of sCD163 at diagnosis identified patients with a very good prognosis, as shown by a five-year OS of 97%.

There was a moderate correlation between sCD163 and tissue CD163 from MCL lymph nodes ($r = 0.64$, $p = 0.014$).

sCD163 was higher in TP53-mutated/p53 high cases. However, the association of high sCD163 with a poor prognosis was independent of MIPI, Ki67, p53 status and blastoid morphology, as assessed in a multivariable cox proportional hazards model. Here, high sCD163 was associated with both shorter PFS (HR 3.48 95% CI: 1.42–8.54) and shorter OS (HR 4.33 95% CI: 1.32–14.2).

Conclusion: Our results show that a high level of the M2 macrophage marker sCD163 is a negative prognostic factor in MCL, both in the chemoimmunotherapy and the ibrutinib/lenalidomide eras. This is especially interesting since many of the established treatments in MCL, including BTK inhibitors, affect the tumor immune microenvironment and the M2 macrophages. Our results also support the ongoing investigations of new strategies to target M2 macrophages in MCL.

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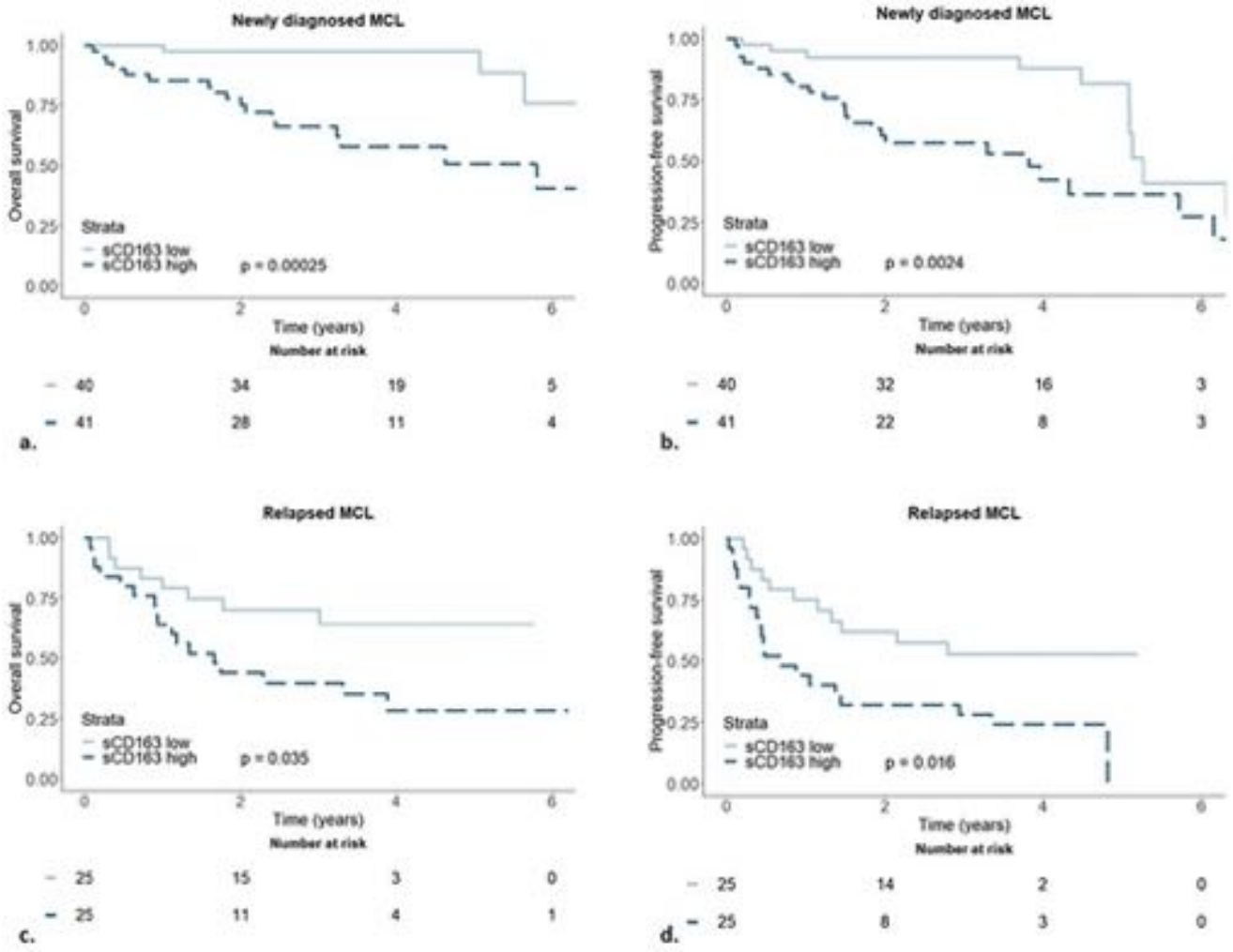

Prognostic impact of sCD163 levels in newly diagnosed and relapsed MCL patients. Probability of a. overall survival and b. progression free survival by sCD163 level (dichotomized by median level 3211 ng/ml) in newly diagnosed MCL patients. Five-year overall survival was 97% vs 51% in patients with low sCD163 vs high sCD163.

c. Probability of overall survival and d. probability of progression-free survival by sCD163 level (dichotomized by median level 2963 ng/ml) in relapsed MCL patients.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, microenvironment

Conflicts of interests pertinent to the abstract

M. Jerkeman
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597 bis | MIPI53. A NEW PROGNOSTIC INDEX FOR MANTLE CELL LYMPHOMA

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Introduction: Mantle Cell Lymphoma (MCL) is an aggressive subtype of non-Hodgkin's lymphoma with an overall survival (OS) of more than 5 years with optimal treatment, but with a highly heterogeneous clinical behavior. The Mantle Cell Lymphoma International Prognostic Index (MIPI) allows risk stratification of patients based on clinical variables and is widely used to establish the prognosis of these patients. However, there are still certain limitations, such as the presence of low-risk MIPI patients who exhibit aggressive behavior. The inclusion of molecular markers could improve stratification models.
Our objective was to analyze the role of TP53 mutations in MCL patients and combine it with clinical variables to establish a prognostic model that improves MIPI. We evaluated response to first-line treatment, progression-free survival (PFS), and overall survival (OS).
Patients and Methods: We included 115 patients diagnosed of MCL between 2003 and 2022 with t(11;14) demonstrated by FISH and/or PCR. TP53 variants (single nucleotide polymorphism and insertions/deletions) were studied using the International Agency for Research on Cancer (IARC) Sanger sequencing protocols, evaluating the prognostic value of each alteration using the Seshat database. Survival analyses were performed using Kaplan-Meier curves and the log-rank test. Untreated patients were excluded from PFS. A multivariate model was generated using the Cox regression method. MIPI 53 model was developed using Cox Regression coefficients to correlate significant variables. Patient groups were distributed following the minimal p-value approach. MIPI53 and MIPI was compared using Akaike information criterion (AIC).
Results: Median age of the patients was 64 years, with a 3:1 male-female distribution. The median follow-up of the series was 67.8 months. Patients with TP53 mutations had lower overall response rate to first line (65% vs. 89%, $p < 0.05$), lower 5-year PFS (30% vs. 66%, $p < 0.0001$), and lower 5-year OS (52% vs. 91%, $p < 0.0001$). N = 80 patients were included in the multivariate analysis. TP53 mutations (HR: 8.3, 95% CI: 3.1-21.8), ECOG>1 (HR: 4.4, 95% CI: 1.2-16.7), LDH levels (HR: 9.0, 95% CI: 1.1-78.7), and age (HR: 1.1, 95% CI: 1.0-1.1) were associated with lower OS ($p < 0.05$ for all variables). These results allowed the construction of a new prognostic model, MIPI53, which was able to separate the patients into 3 groups with different PFS (78% vs. 48% vs. 13% at 5 years, $p < 0.001$) and OS (100% vs. 85% vs. 27% at 5 years; $p < 0.0001$). The MIPI53 model showed a better fit than the MIPI regarding PFS (AIC 240.9 vs. 245.9) and OS (AIC 120.25 vs 135.85).
Conclusions: The combination of TP53 mutations with clinical variables seems to improve the prognostic value of MIPI. A further external validation is required to assess its potential application in clinical routine.

Keywords: aggressive B-cell non-Hodgkin lymphoma, risk models, diagnostic and prognostic biomarkers

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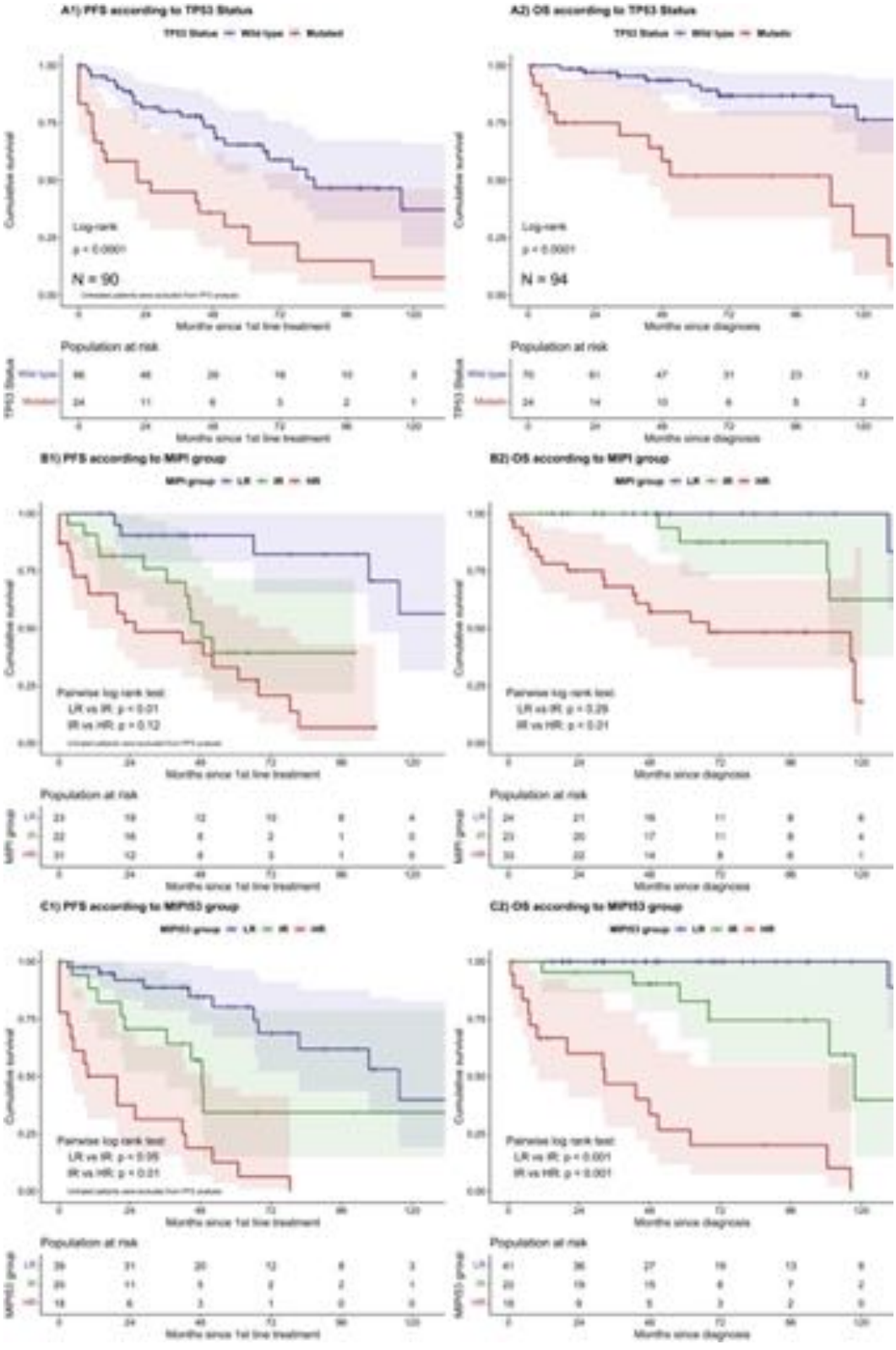
No conflicts of interests pertinent to the abstract.



598 | **TYPE OF ATM ABERRATION HAS A DIFFERENT IMPACT ON SURVIVAL PARAMETERS IN MANTLE CELL LYMPHOMA**

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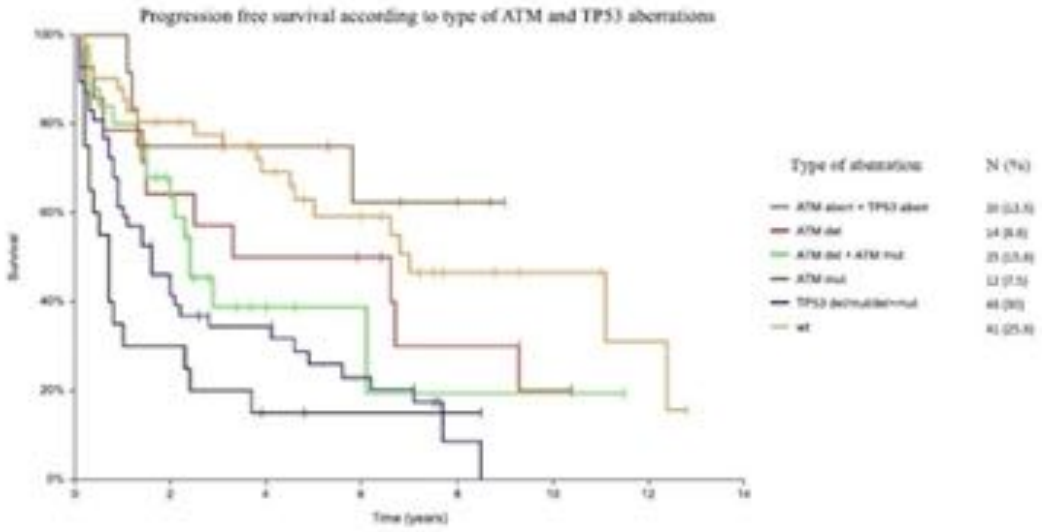
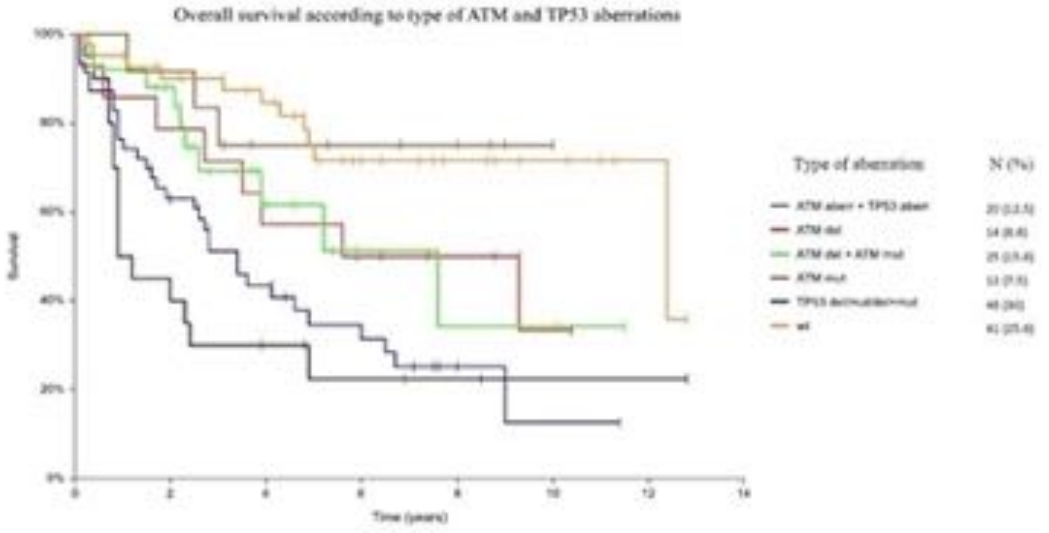
Introduction: The ataxia–telangiectasia mutated (ATM) gene plays an important role in the cellular response to DNA damage. Whether different types of ATM aberrations (mutation and/or deletion of (del) 11q) differentially affect survival in mantle cell lymphoma (MCL) has not yet been reported.

Methods: We analyzed 160 consecutive MCL patients (pts) treated in two Czech university centers (Prague, Olomouc) from 11/2006 to 12/2021. Both fluorescence in situ hybridization (FISH) and next generation sequencing (NGS, Illumina), were performed in all pts to identify ATM and TP53 gene aberrations on tumoral tissue (peripheral blood, bone marrow); the cutoff value for ATM and TP53

Kaplan-Meier estimate of MCL patients according to type of *ATM* and *TP53* aberrations





mutation was 3% variant allele frequency. Peripheral blood and/or bone marrow had at least 5% MCL involvement as analyzed by flow cytometry. Variables were compared by chi-squared test. Kaplan-Meier method was used to calculate the probabilities of progression and overall survival (PFS, OS); the log rank test was used for univariate comparisons of survival curves. PFS and OS were calculated from the date of diagnosis.

Results: The median age at diagnosis was 67 (30-87) years. All pts had advanced disease (IV). MIPI score was low, intermediate and high in 15.6%, 26.3% and 58.1% pts, respectively. Treatment approaches used were as follows: watch and wait in 5.0%, R-CHOP/R-CHOP-like in 50.6%, intensive R-HDAC-containing in 34.4% and non-anthracycline/palliative regimen in 10.0% of pts. Complete and partial response was achieved in 56.3% and 21.9% of pts, respectively. Stable and progressive disease was observed in 13.1% of pts. Almost 29% of pts underwent autologous stem cell transplant. Sixty percent of pts received rituximab maintenance. Overall, 71 (44.4%) and 68 (42.5%) pts had ATM and TP53 aberration(s) (del/mut/del+mut), respectively. Of these, 20 (12.5%) pts had aberrations in both genes. Disruption of ATM gene was related to B-symptoms ($p \leq 0.005$). Age, sex, ECOG PS, cytomorphology, Ki67 index, MIPI and treatment response did not correlate with ATM aberration.

With a median follow-up of 3.8 years, 2-year PFS and 2-year OS in all pts was 58.1% and 74.6%, respectively. Median PFS in pts with ATM mutation, ATM deletion and ATM+TP53 aberration was not reached, 3.3 and 0.7 years, respectively ($p \leq 0.005$). Median OS in pts with ATM mutation, ATM deletion and ATM+TP53 aberration was not reached, 5.6 and 0.9 years, respectively ($p \leq 0.005$). No significant difference in OS was found between ATM mutated and wild-type pts. (Survival graph below)

Conclusions: Deletion but not mutation of ATM gene correlates with shorter survival in MCL. Patients with concurrent disruption of the ATM and TP53 genes have extremely poor outcomes and call for innovative treatment.

Keywords: aggressive B-cell non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, indolent non-Hodgkin lymphoma

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599 | STAGE I-II MANTLE CELL LYMPHOMA: CHARACTERISTICS AT DIAGNOSIS, THERAPY USED AND OUTCOME

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Introduction: Survival of mantle cell lymphoma (MCL) patients has improved in recent years, although it remains an incurable disease. Data about patients diagnosed in early stage are sparse, and the best therapy is not well established.

Patient and Methods: From January 2000 to May 2022, 24 patients with Ann-Arbor stage I-II MCL (out of 306 patients) were identified at the centers of the Catalan Institute of Oncology in Spain. Progression Free Survival (PFS) and Overall Survival (OS) were determined by the Kaplan–Meier method, and differences in actuarial survival were analyzed by the log-rank method.

Results: Localized MCL represented 7% of all MCL. Characteristics at diagnosis were: median age 68 years (range: 43–82), 18 (75%) male, 8 (33%) pleomorphic/blastoid histological variants; 13/15 (87%) Ki-67 > 30%; 15 (62%) Ann Arbor stage II; 1 bulky disease (>5 cm); 9 (37%) extranodal disease (head and neck as the most frequent location) and 17 (70%) high risk MIPI. First line therapy consisted in chemotherapy (CT) alone: 8 (33.3%) patients (5 R-CHOP, 2 R- HyperCVAD, 1 RCOP); CT (3 R-CHOP, 2 R- HyperCVAD, 3 others) + radiation therapy (RT): 8 (33.3%) patients; RT alone: 6 (25%), surgery 1, lost to follow-up 1. Two patients received autologous stem cell transplantation, 1 patient rituximab maintenance. Twenty-three patients were evaluable for response: CR 21 (91%), PR 1 (4%) and progression 1. With a median follow-up in survivors of 7.1 years (range: 0.4-17), 11 (46%) patients relapsed, 5 relapse in stage I-II. Median time to relapse was 42 months (limits, 9–116 months). After relapse, 7 received systemic therapy (ibrutinib 3, R-CHOP/R-DHAP 1, R-bendamustine 1, R-ESHAP 1, chlorambucil 1), 2 RT, and 2 died without treatment. Median PFS was 4.4 years (95% CI 2.1-6.7), median OS was 8.3 years (95% CI 2.5-14.1).

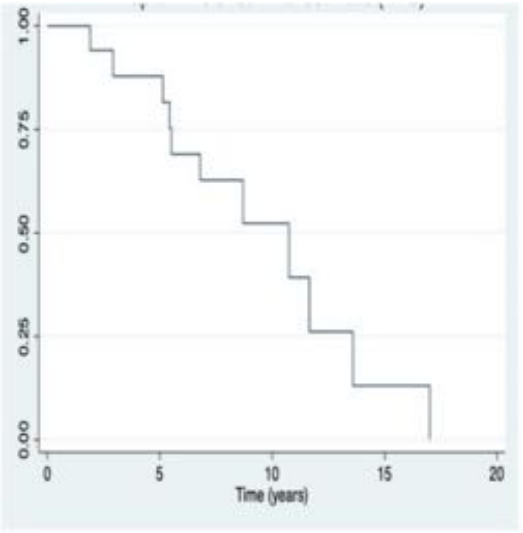

Figure 1. Progression-free survival

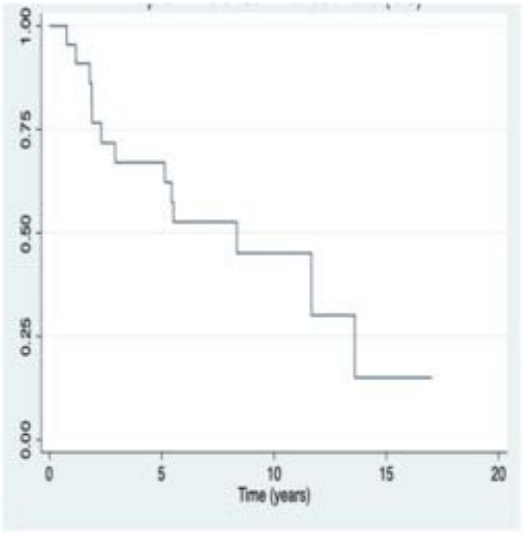

Figure 2. Overall Survival

Variables included in the study of prognostic factors at diagnosis for OS and PFS included age, gender, stage (I vs II), histological subtypes (pleomorphic/blastoid vs classic), nodal vs extranodal disease, head and neck sites vs others, Ki67, LDH, β2-microglobulin, MIPI score. Only age >65 years ($p = 0.04$) showed worse prognosis for OS.

Conclusions: Localized MCL is infrequent. One third of patients are diagnosed with high-risk histologic variants, and around 40% as extranodal disease, involving mainly the head and neck area. The treatments used are heterogeneous, and there is not a plateau in survival curves. These patients represent an unmet clinical need, for whom clinical trials are needed.

Keyword: aggressive B-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

600 | ORELABRUTINIB-LENALIDOMIDE-RITUXIMAB (OLR) IN PATIENTS WITH UNTREATED MANTLE CELL LYMPHOMA (MCL): A PROSPECTIVE, MULTICENTER, SINGLE-ARM PHASE 2 POLARIS STUDY IN CHINA

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Introduction: In recent years, chemo-free regimens have become one of the hot spots for the exploration of first-line therapy for mantle cell lymphoma (MCL). Orelabrutinib (O), a novel highly selective bruton tyrosine kinase inhibitor, has shown high activity and good tolerability in MCL. Orelabrutinib combined with rituximab could preserve NK cell-mediated ADCC induced by rituximab and enhance the apoptosis of tumor. We aimed to explore the efficacy and safety of O plus lenalidomide (L) and rituximab (R) in untreated MCL.

Methods: This multicenter, phase 2 study (NCT05076097) enrolled patients (pts; ≥18 y) with untreated MCL. Pts received OLR-induction therapy on a 28-day cycle for 6 cycles (O, 150 mg/d; L, 15 mg on days 1-21, then 20 mg of cycles 2-6 if tolerated or 10 mg if not tolerated; R, 375 mg/m^2 on days 1, 8, 15, 22, then day 1 of cycles 3, 5), followed by OLR-maintenance therapy for up to 18 cycles. Peripheral blood MRD (PB-MRD) and bone marrow MRD (BM-MRD) were evaluated using qPCR ($<10^{-6}$). The gene mutation profile and circulating tumor DNA (ctDNA) were assessed by next-generation sequencing (NGS). The primary endpoint was complete response rate (CRR) after 6 cycles of induction therapy. Secondary endpoints were objective response rate (ORR), duration of response (DOR), time to response (TTR), progression-free survival (PFS), overall survival (OS), and safety.

Results: As of March 8, 2023, 24 pts with MCL were enrolled (male, 87.5%; median age, 57.5 y [range, 51.5-63.5]; median follow-up, 7.4 months). The 24 pts were characterized with 79.2% stage III-IV disease, 95.8% ECOG PS of 0-1, 79.2% low- and 20.8% intermediate-risk MIPI scores, 41.7% Ki67 index (<30%), 33.3% bone marrow involvement, and 58.3% maximum lesion diameter of ≥5 cm. Eighteen pts have completed induction therapy. Among the evaluable pts ($n = 18$), the ORR was 100%, including 14 (77.8%) CR (**Figure 1**). Meanwhile, 16 of 18 pts were available for MRD analysis, and PB-MRD and BM-MRD of these 16 pts were negative. The results in CRR were observed in several specific subgroups as classified by MIPI scores (low vs. intermediate, 84.6% and 60.0%) and maximum lesion diameter (<5 cm

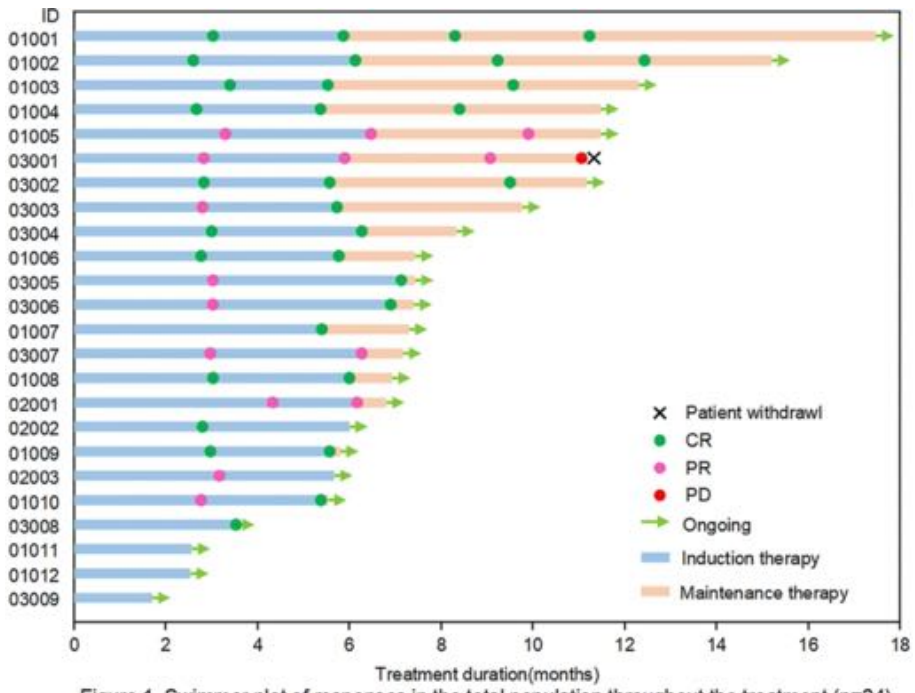

Figure 1. Swimmer plot of responses in the total population throughout the treatment (n=24)

vs. ≥5 cm, 85.7% and 72.7%). Throughout the treatment, the median TTR was 3.0 months (range, 2.8–3.2). The median DOR and median PFS were not reached. One pt had disease progression at cycle 12. The most common adverse events (AEs; any grades, ≥3 grades) were neutropenia (45.8%, 33.3%), leukopenia (41.7%, 8.3%), COVID-19 infection (29.2%, 4.2%), lymphopenia (25.0%, 4.2%), and thrombocytopenia (25.0%, 4.2%). At the data cutoff, 23 pts remained on study (**Figure 1**). No deaths were reported.

Conclusions: The preliminary data indicated that the OLR exerted synergistic antitumor activity, with manageable toxicity in MCL. More updated data will be presented in this ongoing study.

Keyword: MCL Orelabrutinib-Lenalidomide-Rituximab

Keywords: aggressive B-cell non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

601 | ZANUBRUTINIB PLUS BENDAMUSTINE AND CD20 MONOCLONAL ANTIBODY AS TREATMENT FOR MANTLE CELL LYMPHOMA

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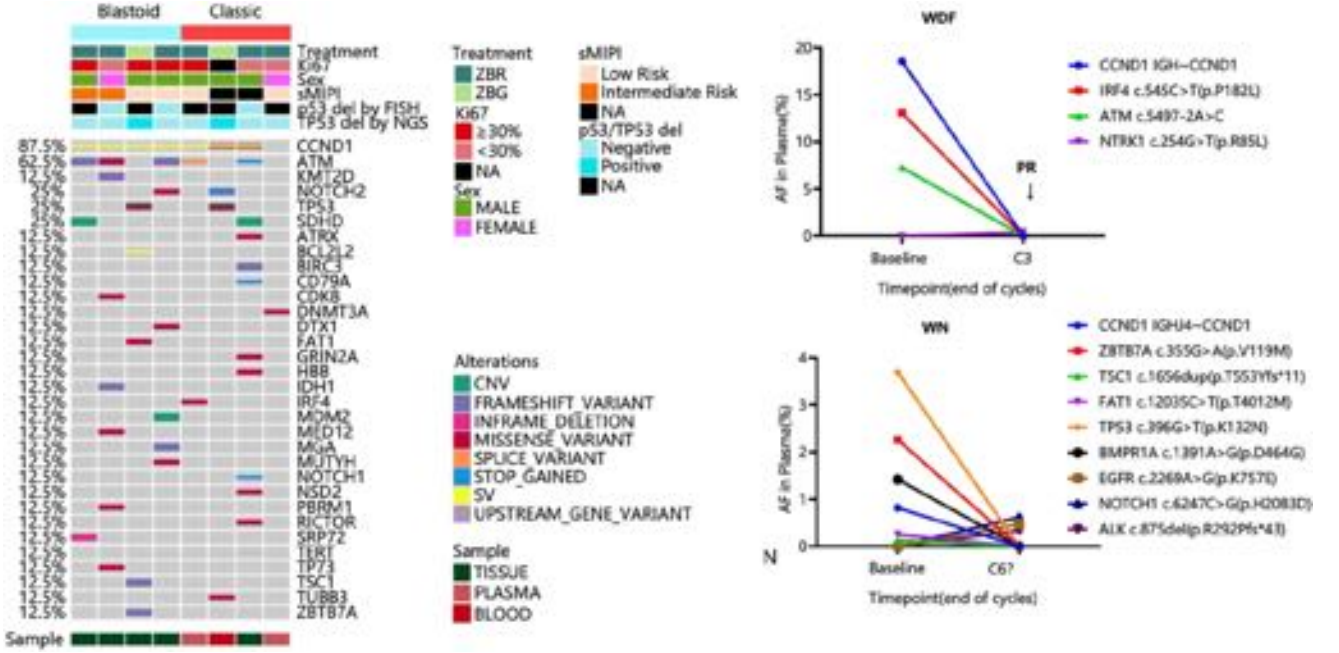
Introduction: To evaluate the safety and efficacy of Zanubrutinib Plus Bendamustine and CD20 monoclonal antibody As Treatment for Mantle Cell Lymphoma patients.

Methods: We analyzed 15 MCL patients aged who received ZBR/G as treatment in our cohort between July 2020 to March 2023. 12 (80%) patients received ZBR/G as their initial treatment, while 3 patients received ZBR/G as their 2nd line treatment. Oral Zanubrutinib was given continuously (160 mg twice a day) from day 0, then intravenously rituximab (375 mg/m^2 in day 0) or Obinutuzumab (1000 mg in day 0), Bendamustine (70 mg/m^2, days 1–2), every 28-day cycles. All the patients received 6 cycles of ZBR/G.

Results: The median follow-up was 14.3 months. 13 of 15 patients achieved mid-term evaluation. Generally, the best overall response rate (ORR) was 100%, among which 61.5% patients achieved CR. Eight patients completed EOT evaluation after 6 cycles, the best overall response rate (ORR) was 100% and 75% patients achieved CR. Among them, one patient whose efficacy was evaluated as PR after 6 cycles reached CR after 3 cycles of rituximab maintenance. Four patients with bone marrow involvement at baseline and CR at mid-term evaluation all achieved uMRD in bone marrow. In terms of adverse events (AEs), two patients had grade 3 and grade 4 neutropenia AEs in cycle 3 and 4 respectively, and no other grade 3–4 AEs were observed. Four cases of classical type and mother cell variant were submitted for ctDNA detection. The mutation map of 8 patients is shown in Figure 1, and 5 cases (62.5%) detected ATM gene mutations. Among them, 2 patients with classic type had CCND1 gene mutation. Two patients had matched sequencing data at baseline and evaluation time points, which were evaluated as CR and PR respectively, and the plasma mutation abundance was significantly lower than before (Figure 2).

Conclusion: ZBR/G as treatment for MCL patients with fair physical condition could achieve high response rate. The overall tolerability was under control.



The research was funded by: This study was supported by National Natural Science Foundation of China (Grant No. 82170166, No. 82100207, No. 81970146)

Keyword: Combination Therapies

No conflicts of interests pertinent to the abstract.

602 | LIFETIME TREATMENT BURDEN OF PATIENTS WITH MANTLE CELL LYMPHOMA: SIMULATION-BASED ANALYSIS OF REAL-WORLD DATA FROM 20 YEARS

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Background: Mantle cell lymphoma (MCL) is a rare subtype of B-cell lymphoma that is currently considered incurable, yet treatable condition with increasing amount of treatment options. Alas, the availability of novel therapies is often limited to later treatment lines due to their excessive cost. In this study, we aimed to conduct a baseline analysis on the lifetime treatment burden of MCL patients treated with conventional chemoimmunotherapy regimes. Specifically, we wanted to estimate the number of treatment lines received during 20-year follow-up to determine the number of MCL patients that could potentially receive novel, targeted therapies during the follow-up period.

Methods: A real-world data set of 548 patients diagnosed and treated for MCL between the years 2000 and 2020 was collected from seven Finnish hospitals and one Spanish hospital. First, this data was analyzed using the traditional methods of survival analysis for overall survival, time to progression and follow-up time. From these initial results, we estimated the risk of progression from the first treatment line to subsequent treatment lines, to death from MCL, or death from other causes. These estimates were then applied in our competing risk analysis based on Weibull distribution and the data was completed by dynamic imputation of health event histories using discrete semi-Markov transitions in a limited time space to extrapolate the censored variables from our data set up to 20 years of follow-up for each patient. A state distribution plot from our analysis is shown below (Figure 1).

Results: In our original data set, the median duration of follow-up was three years (range 0 to 18 years). At 10 years of simulated follow-up, 525 (95.8%) patients had received first-line therapy, 307 (56.0%) had received second-line therapy, 148 (27.0%) had received third-line therapy and 64 (11.7%) had received fourth-line therapy. A total of 262 (47.8%) patients had died from MCL and 113 (20.6%) from other causes. After 20 years of simulated follow-up, the respective figures were 525 (95.8%), 373 (68.1%), 192 (35.0%) and

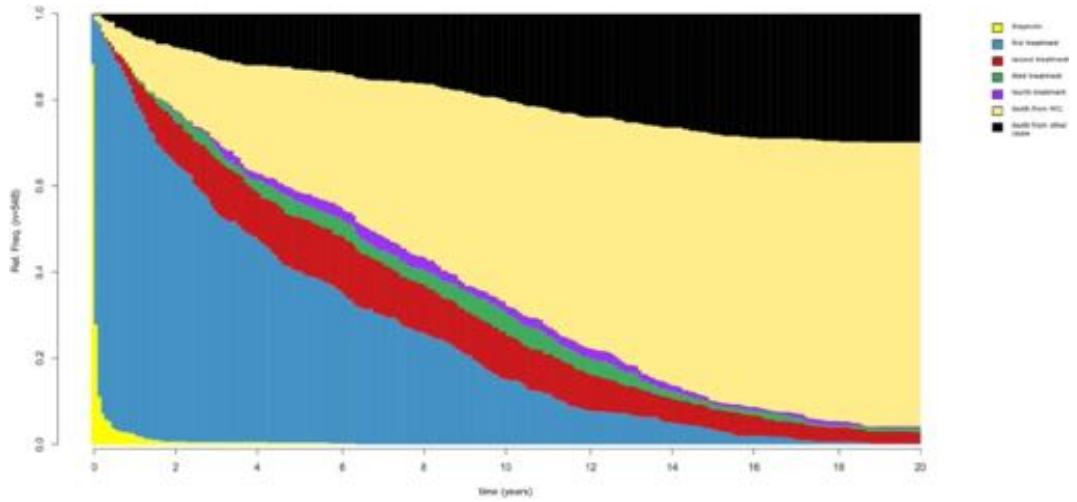

Figure 1. State distribution plot from 20-year follow-up

85 (15.5 %). A total of 362 (66.1%) of patients had died from MCL and 166 (30.3%) from other causes. The median number of treatment lines received both at 10 and 20 years of follow-up was three.

Conclusions: In this study, we estimated the number of treatment lines patients with MCL receive during a 20-year follow-up. The estimation we provide serves as a tool to determine the number of MCL patients that could potentially receive novel therapies during each stage of follow-up. This would contribute to the accuracy of evaluation of health economical costs, thus, allocation of the new, expensive cancer treatments.

The research was funded by: North Ostrobothnia Health Care District

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cancer Health Disparities

No conflicts of interests pertinent to the abstract.

603 | UNMET NEED IN RELAPSED/REFRACTORY (R/R) MANTLE CELL LYMPHOMA (MCL) POST-BRUTON TYROSINE KINASE INHIBITOR (BTKI): A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

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Background: Most patients with MCL, a rare B-cell non-Hodgkin lymphoma, will relapse or become refractory to treatment. While the introduction of BTKis has been transformative, options for patients who fail to respond or whose disease progresses on BTKis remain limited and largely palliative in nature. We sought to characterize and quantify the unmet clinical need of patients with R/R MCL in the post-BTKi setting.

Methods: MEDLINE, Embase, and CENTRAL were systematically searched to October 2022—supplemented with hand searches of select conferences—to identify studies reporting overall survival (OS), progression-free survival (PFS), and/or response outcomes of patients receiving non-CAR-T treatments or brexucabtagene autoleucel (brexu-cel) in the post-BTKi setting. Random effects bivariate meta-analyses of OS/PFS were conducted based on studies with published Kaplan-Meier (KM) curves from which individual patient data could be estimated. Response outcomes, based on the best response achieved, were meta-analyzed using a generalized linear mixed model. Outcomes were evaluated separately for patients treated with non-CAR-T and brexu-cel.

Results: Twenty-six studies (23 observational; 3 trials), reporting the outcomes of 1845 patients treated from 2005 to 2022, were included, where patients were initially enrolled for treatment with a BTKi (12 studies) or for treatment post-BTKi (14 studies). The non-CAR-T interventions varied, with most studies reporting outcomes from cohorts of patients receiving a variety of interventions. Across the included studies, most patients were male (65-94%) and older, with the median age varying from 63 to 77 years.

OS and PFS KM curves were published in 10 and 3 studies, respectively, for non-CAR-T outcomes. The pooled median OS/PFS for these patients was 9.1 and 7.6 months, respectively (Table 1). The pooled objective response rate (ORR) and percentage of patients achieving a complete response (CR) were 45% and 23%, respectively. The median OS/PFS of patients who received brexu-cel was 32.1 and 14.9 months, based on 5 and 6 studies with KM curves, respectively, with ORR/CR rates of 89% and 74%. Analyses were not sensitive to different survival distributions or fixed/random effects models.

Conclusions: Treatment options in the post-BTKi setting are heterogeneous and a significant unmet clinical need persists. Though longer

Table 1: Pooled survival and response outcomes

		non-CAR-T treatments	Brexu-cel
OS	N	669	371
	Median, months (95% CI)	9.1 (7.3 – 11.3)	32.1 (25.2 – 41.2)
	Survival % at 12 months	42	77
PFS	N	80	418
	Median, months (95% CI)	7.6 (3.9 – 14.6)	14.9 (10.5 – 21.0)
	Survival % at 12 months	33	56
ORR	N	414	546
	% (95% CI)	45 (34 – 57)	89 (86 – 91)
CR	N	360	546
	% (95% CI)	23 (14 – 34)	74 (68 – 80)

CI: Confidence interval

follow-up is needed for survival outcomes, treatment with brexu-cel is emerging as a promising option in this difficult-to-treat setting.

The research was funded by: This study was funded by Kite, a Gilead company.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies

Conflicts of interests pertinent to the abstract

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Consultant or advisory role Astra Zeneca, Beigene, BMS/Celgene, Gilead/Kite, Janssen, Lilly/Loxo, Novartis, Roche
Research funding: Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche
Educational grants: Janssen, Roche
Other remuneration: Astra Zeneca, Gilead/Kite, Janssen, Lilly, Novartis, Roche

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Consultant or advisory role Pepromene Bio; Takeda
Honoraria: Kite/Gilead; BMS; Novartis; Amgen; Pfizer; Beigene; Adaptive; Century Therapeutics; Autolus
Research funding: Kite; Servier; Jazz Pharma
Educational grants: Kite/Gilead; Takeda
Other remuneration: Chair, NCCN Adult ALL subcommittee

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M. J. Zoratti
Research funding: RainCity Analytics has received funds from for-profit healthcare companies for research

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Research funding: RainCity Analytics has received funds from for-profit healthcare companies for research

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Consultant or advisory role AbbVie; Acerta Pharma; ADC Therapeutics America; Amphista Therapeutics Limited; AstraZeneca; Be Biopharma; BeiGene; BioInvent; Deciphera; DTRM Biopharma (Cayman) Limited; Genentech; InnoCare; Janssen; Kite Pharma; Leukemia & Lymphoma Society; Lilly; Merck; Miltenyi Biomedicine; Milken Institute; Oncternal; Parexel; Pepromene Bio; Pharmacyclics; VelosBio
Honoraria: AbbVie; Acerta Pharma; AstraZeneca; Bantam Pharmaceutical; BeiGene; BioInvent; Bristol Myers Squibb; CAHON; Dava Oncology; Eastern Virginia Medical School; Genmab; i3Health; IDEOlogy Health; Janssen; Kite Pharma; Leukemia & Lymphoma Society; Medscape; Meeting Minds Experts; MD Education ; MJH Life Sciences; Merck; Moffit Cancer Center; Nurix; Oncology Specialty Group; OncLive; Pharmacyclics; Physicians Education Resources (PER); Practice Point Communications (PPC); Studio ER Congressi

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604 | TREATMENT PATTERNS IN PATIENTS WITH MANTLE CELL LYMPHOMA: UPDATED REPORT OF THE ASIA-PACIFIC MULTINATIONAL RETROSPECTIVE REGISTRY STUDY

W. S. Kim[1], D. H. Yoon[2], H. Cho[2], J. Y. Chan[3], D. J. Kim[4], K. Kang[5], J. Kwak[6], S. Tan[7], J. Lee[8], S. Y. Oh[9], Y. R. Do[10], H. Eom[11], S. H. Jeong[12], H. J. Kang[13], Y. Koh[14], U. Bunworasate[15], H. J. Kim[16], J. Jo[17], S. Kim[18], J. H. Won[19], Y. H. Park[20], E. Chan[21], T. Lin[22], T. Chen[23], D. H. Yang[24], K. Kato[25], Q. Cai[26], S. C. Ng[27]

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Introduction: We conducted a multinational, multicenter retrospective registry study to better define the treatment patterns and survival outcomes of newly diagnosed patients with mantle cell lymphoma (MCL) in the Asia-Pacific region.

Methods: Data were collected from newly diagnosed MCL patients between January 2008 and September 2019 from 27 hospitals in Asian countries, including China, Malaysia, Japan, Singapore, South Korea, Taiwan, and Thailand. The first interim analysis with 191 patients was previously reported. An updated analysis of 289 patients was performed at the data cutoff date of December 19, 2022.

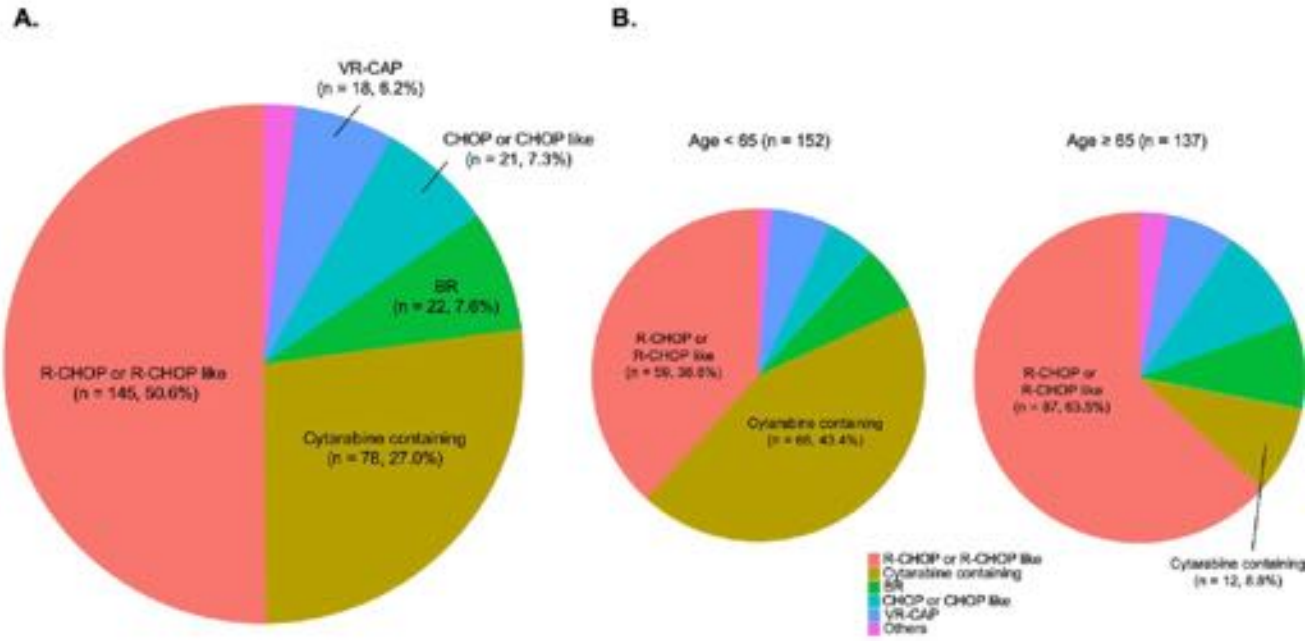
Results: The median age was 64 years (range, 26–90), and 213 patients were male (73.7%). The majority of the patients had stage 3 or 4 diseases (n = 249, 86.2%). The most frequently administered 1st line regimen was R-CHOP or R-CHOP-like regimens (n = 146), followed by cytarabine-containing regimens (n = 78) including R-Hyper-CVAD (n = 56), and bendamustine-rituximab (n = 22) (Figure 1A). Higher proportion of elderly patients received R-CHOP or R-CHOP-like regimens, while cytarabine-containing regimens were more frequently administered in young patients (Figure 1B). The overall response rate (ORR) and the complete response (CR) rate among these patients were 94.7% and 59.0%, respectively. The ORR and CR rates for each regimen were as follows; R-CHOP or R-CHOP-like regimens (ORR 97.0%, CR 52.2%), cytarabine-containing regimens (ORR 94.6%, CR 65.3%), and bendamustine-rituximab (ORR 95.2%, CR 76.2%). Median progression-free survival (PFS) was 47.6 months, and median overall survival (OS) was 75.7 months. The median PFS was 41.1 months for R-CHOP or R-CHOP-like regimens, 60.8 months for cytarabine-containing regimens, and 71.0 months for bendamustine-rituximab. Twenty-nine patients received rituximab maintenance treatment, and the survival outcomes regarding maintenance therapy will be updated and presented at the ICML 2023.

There were no significant differences in PFS and OS between the ASCT (n = 103) and non-ASCT (n = 35) groups among transplant-eligible patients (n=138), with a 5-year PFS rate of 48.6 versus 32.5% (P = 0.29) and 5-year OS rate of 73.7 versus 73.7% (P= 0.13), respectively.

A total of 152 patients were given the 2nd line regimens. The most commonly used regimen was ibrutinib (n = 45), followed by cytarabine-based regimens (n = 38). The median 2nd PFS was 17.3 months.

Conclusion: Our study demonstrated that the majority of MCL patients in the Asia-Pacific region were treated with rituximab-based regimens in the contemporary era. R-CHOP or R-CHOP-like regimens were the most commonly used 1st line regimen. Compared to previous studies, our real-world analysis showed improved survival

Figure 1. (A) First-line regimens in entire patients (n = 191). (B) First-line regimens according to age; young (age < 65, n = 152) versus elderly patients (age ≥ 65, n = 137)



outcomes. However, the rate of upfront ASCT and usage of rituximab maintenance was relatively low, and there was no significant difference in survival outcomes according to upfront ASCT.

Keyword: Aggressive B-cell non-Hodgkin lymphoma

The research was funded by:
The work was funded by a research grant from Janssen Pharmaceuticals Ltd.

No conflicts of interests pertinent to the abstract.

605 | COMPARISON OF BLEEDING-RELATED EVENTS IN PATIENTS WHO RECEIVED PIRTOBRUTINIB WITH AND WITHOUT ANTITHROMBOTIC AGENTS

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Introduction: Bruton tyrosine kinase inhibitors (BTKi) are associated with increased risk of bleeding events. Pirtobrutinib, a non-covalent (reversible) BTKi FDA approved for treatment of R/R MCL after 2 lines of therapy including a BTKi, demonstrated efficacy and tolerability across B-cell malignancies. Bleeding events in pts treated with pirtobrutinib and concomitant antithrombotic therapy have not been specifically reported. We analyze bleeding events in pts from BRUIN who received pirtobrutinib with antithrombotic therapy.

Methods: Pts with B-cell malignancies (317 CLL, 166 MCL, 290 other) enrolled in open-label, multicenter Phase 1/2 BRUIN were analyzed. Concomitant antithrombotic therapy (direct factor XA inhibitors, heparin anticoagulants, platelet aggregation inhibitors) at time of enrolment was permitted (excluding warfarin). Pirtobrutinib was administered QD (28-day cycles) until disease progression/discontinuation due to toxicity. CTCAE V5.0 determined grade and type of bleeding events. Descriptive analyses were performed.

Results: 773 pts (29 July 2022) received at least 1 pirtobrutinib dose; 216 with concomitant antithrombotic therapy (median age: 72 years [IQR 65-77]; % ≥75 years: 34%). Median time on pirtobrutinib with and without antithrombotic therapy: 10.6 (IQR 4.0–19.9) and 9.3 months (IQR 3.1–17.3). Any-grade bleeding events were reported in 44.9% (97/216) pts with antithrombotic therapy vs 32.5% (181/557) without. A summary of bleeding events is shown (Table). Most (>90%) were grade ≤2. Most common bleeding events (≥3%) in pts with antithrombotic therapy were contusion (22.7%), hematuria (5.6%), epistaxis (5.1%), petechiae (3.7%), hematoma (3.2%). Of 6 (2.8%) pts on antithrombotic therapy with grade 3 bleeding event, 2 (0.9%) were deemed related to pirtobrutinib by investigators: upper GI bleeding with anemia and hemarthrosis from a knee injury (1 each). Grade ≥3 bleeding events occurred in 11 (2%) pts not taking antithrombotics. Any-grade hemorrhage/hematoma occurred in 13/79 (16.5%) pts who received direct factor XA inhibitors, 10/39 (25.6%) who received heparins, 18/112 (16.1%) who received platelet

Table: Summary of bleeding events in patients who received pirtobrutinib with or without antithrombotic medication.

	Pirtobrutinib Monotherapy N=773			
	Concomitant Antithrombotic N=216		No Concomitant Antithrombotic N=557	
Summary of Bleeding Events	All Grades n (%)	Grade ≥3[e] n (%)	All Grades n (%)	Grade ≥3 n (%)
Bleeding[a,b]	97 (44.9)	6 (2.8)	181 (32.5)	11 (2.0)
Bruising[c]	60 (27.8)	0 (0.0)	123 (22.1)	0 (0.0)
Hemorrhage/hematoma[d]	34 (15.7)	4 (1.9)	54 (9.7)	10 (1.8)
Hematuria	12 (5.6)	0 (0.0)	15 (2.7)	0 (0.0)
Gingival bleeding	3 (1.4)	0 (0.0)	2 (0.4)	0 (0.0)
Hemoptysis	3 (1.4)	0 (0.0)	1 (0.2)	0 (0.0)
Median Time to First Onset, Weeks (IQR)	8.1 (2.6-24)		4.1 (1.3-16.1)	
Median Duration, Weeks (IQR)	2.1 (0.6-4.3)		4.0 (1.1-7.9)	
Bleeding Events Requiring Dose Reduction or Discontinuation	0 (0.0%)		1 (0.2%)	
Bleeding Events Requiring or Prolonging Hospitalization	5 (2.3%)		9 (1.6%)	

IQR = interquartile range. [a]Patients may appear in more than one subcategory. Events occurring in ≥1% of patients are presented. [b]Adverse events shown are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechia, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including hemorrhage or hematoma. [e]No grade 4-5 bleeding events occurred in patients with concomitant antithrombotic therapy.

aggregation inhibitors (some >1 class). Among pts with antithrombotic therapy, median time to onset of any-grade bleeding event was 8.1 weeks (IQR 2.6–24) and median duration of a bleeding event was 2.1 weeks (IQR 0.6-4.3). Among pts who received antithrombotic therapy, bleeding events required dose interruption of pirtobrutinib in 5 pts (2.3%) and no bleeding events led to dose reduction/permanent discontinuation of pirtobrutinib.

Conclusion: Concomitant antithrombotic therapy with pirtobrutinib was associated with increased rate of bleeding events vs pirtobrutinib alone; most events were grade ≤2. High-grade bleeding events were infrequent (<2%). This supports safety of pirtobrutinib in pts requiring antithrombotic therapies.

Encore Abstract - previously submitted to EHA 2023

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606 | **EFFICACY OF FRONT-LINE IMMUNOCHEMOTHERAPY FOR TRANSPLANT-INELIGIBLE MANTLE CELL LYMPHOMA: A NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS**

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Background: In the past 20 years, there have been significant advances in the prognosis of mantle cell lymphoma (MCL) patients because of the introduction of rituximab. However, there is still no cure, and the relapse is inevitable. The earlier MCL patients progress after the first-line therapy, the worse the prognosis, especially for those who progress within 6 months after first-line therapy. There is no standard first-line immunochemotherapy regimen for transplant-ineligible patients with MCL currently, and the efficacy of various treatment remains unclear.

Methods: Network meta-analysis (NMA) can compare the relative treatment effects of multiple interventions by synthesizing evidence from a network of randomized controlled trials (RCTs), which can be very useful for the choice of clinical treatment plans. We conducted a Bayesian NMA of all eligible randomized controlled trials. Pairwise comparisons and ranking of different first-line treatment options were performed.

Results: nine studies were included in the NMA, involving a total of 2,897 MCL patients. The BR-Ibrutinib+R regimen showed the best progression-free survival (PFS), with a surface under the cumulative ranking curve (SUCRA) of 0.89 (Figure 1a) and probability of being the best treatment (PbBT) of 69%, followed by the BR+R regimen (SUCRA 0.76, PbBT 11%) and the BVR regimen (SUCRA 0.64, PbBT 13%). The VR-CAP regimen was the most potential intervention to improve overall survival (OS), with a SUCRA of 0.89 (Figure 1b) and PbBT of 63%, followed by the BR regimen (SUCRA 0.74, PbBT 22%) and the R-CHOP regimen (SUCRA 0.65, PbBT 1%). Compared with the R-CHOP regimen, the BR regimen achieved a better PFS (hazard ratio [HR] 0.45 [95% credible interval 0.2–0.96]). The BR-Ibrutinib+R regimen (HR 0.14 [0.02–0.99]), BR+R regimen (HR 0.19 [0.034–0.99]), and BR regimen (HR 0.19 [0.08–1.03]) were superior to CHOP regimen with better PFS. The R-FC regimen (HR 2.27 [1.01–5.21]) or FC regimen (HR 3.17 [1.15–8.71]) was inferior to the VR-CAP regimen with a worse OS.

Conclusions: Our study is the first NMA of first-line treatment options for transplant-ineligible MCL patients. It overcame the disadvantages of other RCTs which could only compare two regimens at the same time and could not compare multiple regimens involving

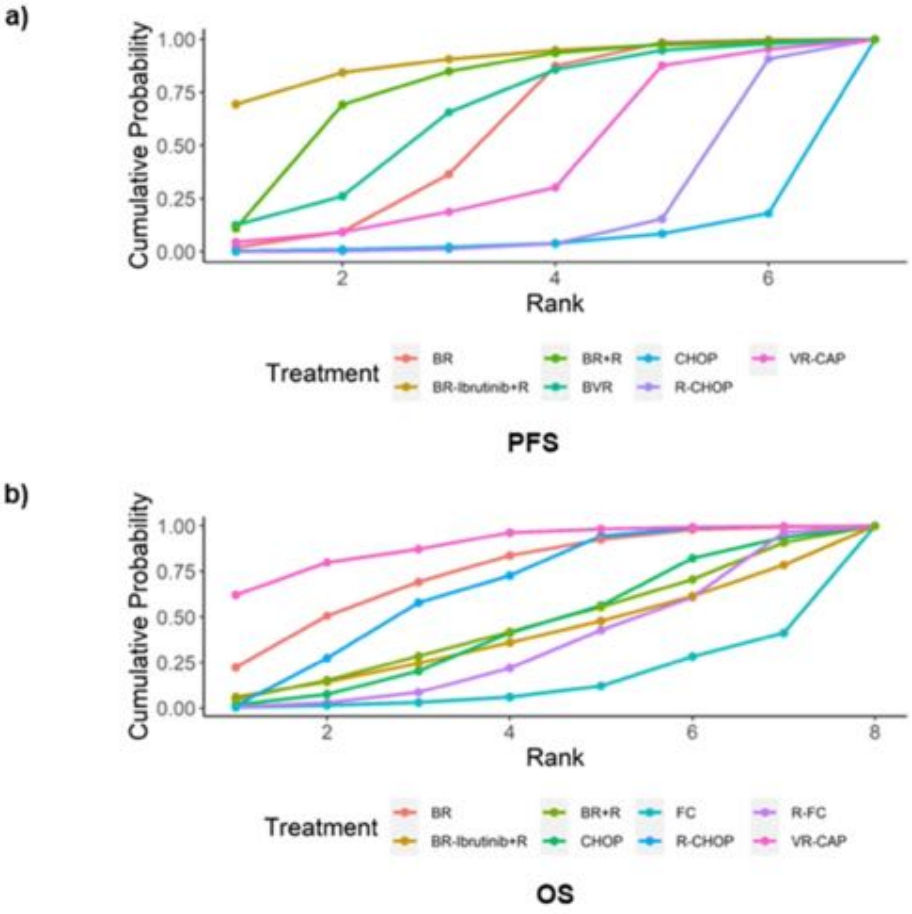

Fig. 1 Surface under the cumulative ranking (SUCRA) curves

new drugs. Itpresents the most promising first-line treatment strategy for transplant-ineligible MCL patients in terms of PFS and OS, which provides innovative treatment strategy for MCL treatment.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chemotherapy, Immunotherapy

No conflicts of interests pertinent to the abstract.

PTCL

607 | PERIPHERAL T CELL LYMPHOMA (PTCL) AND TREATMENT OUT-COME SINGLE CENTRE RETROSPECTIVE STUDY

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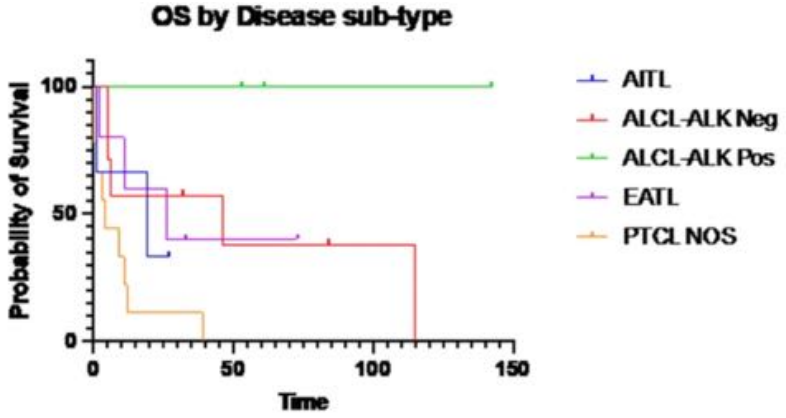
Introduction: Mature T-cell lymphomas comprise 15% to 20% of all aggressive non-Hodgkin lymphomas (NHL) and 5% to 10% of all NHLs. Compared to their B-cell counterparts, PTCLs remain largely unexplored and the optimal treatment ill-defined due to disease rarity and biological heterogeneity. CHOP-type chemotherapy has been the mainstay of therapy for PTCL with some exception in NK/T cell lymphoma, but with the notable exception of ALK-positive ALCL, outcome has been uniformly disappointing[3-5]. For the main nodal PTCLs (AITL, PTCL-NOS, and ALK– ALCL), the 2- and 5-year progression-free survival (PFS) is approximately 35% and 25%, and the 2- and 5-year overall survival (OS) is 45% and 35%, respectively[6-8]. Progressions/relapses of PTCLs are frequent (approximately 70% of patients), occur most often early (during the first year after initial diagnosis), and have a poor outcome, with a median OS of approximately 6 months [9-11].

Methods: Patients were identified through pathology database and informed consent obtained. Patient's demographic characteristics, clinical features, initial / subsequent treatment and survival were analysed. Data cut-off was 31/01/2023.

Results: Twenty-seven patients were included in this study, with male predominance (70%), the median age was 69 years (Rang 17-84 years) and the majority with advanced disease (67%). The common histology subtype was ALCL in 10 patients (37%) (Alk-Neg =7 & Alk-Pos =3) followed by PTCL in 9 patients (33%). While EATL, AITL subtypes were reported in 5(18%), 3(11%) patients respectively. Chemotherapy was the main initial treatment modality in our cohort (26 patients / 96%) (CHOP based /19 patients, CHOEP in 4 patients, and GDP based /3 patients) and 1patient (4%) was not suitable for any therapy. Complete response (CR) was achieved in 16 patients (59%) and 8 patients (30%) subsequently relapsed, while other treated patients (10/37%) experienced disease progression. At relapse GDP and Brentuximab Vedotin therapy were used for in 8 and 3 patients respectively resulted in CR in 2 patients and



	AITL	ALCL-ALK Neg	ALCL-ALK Pos	EATL	PTCL NOS
Median survival	19	46	Undefined	26	4

P value	0.0083

progression disease in the reminder. Autologous bone marrow transplant consolidation was used in 3 patients (10%), and radiotherapy was used in 5patients (15%). At time of study data analysis (31/01/2023), 8 patients (30%) were still alive and 19 patient (70%) had died mostly lymphoma related death (18 patients).

Conclusion: This study reflects a real world data on peripheral T cell lymphoma and the impact of patient age and disease sub-type. We confirmed the previously reported poor prognosis of this disease with exception of ALCL ALK positive subtype. High grade T cell lymphoma continue to be challenging to treat. Recent molecular understanding and availability of target therapy have resulted in some treatment out-come improvement and clinical trials enrolment are of great importance.

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Pathology and Classification of Lymphomas

No conflicts of interests pertinent to the abstract.

608 | HOW WE ARE SUCCESSFUL IN THERAPY OF T-CELL LYMPHOMA PATIENTS (≥70 YEARS). REAL-WORDL ANALYSIS FROM THE CZECH LYMPHOMA STUDY GROUP REGISTRY (NIHIL).

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Background: T-cell lymphomas (TCL) belong to the malignancies with poor prognosis. Up to now, the core of treatment is based on chemotherapy. The best results are reached with intensive regimen (etoposide-based; CHOEP) and autologous stem cell transplantation (autoTx). In the patients ≥70 years is not usually possible to apply this strategy.

Methods: In total 1 432 patients (pts) with newly diagnosed T-cell lymphomas (1999–2020) was enrolled in NIHIL database (Clinical Trial gov. NCT03199066), 503 patients with a diagnosis other than PTCL, AITL and ALCL, and 23 patients with no follow-up information were excluded. We selected 240 patients ≥70 years at lymphoma diagnosis with the ALCL, PTCL-NOS and AITL/TFH-TCL (around 67% patients).

Results: In the cohort of 240 patients ≥70 years, PTCL-NOS (131/240; 54.6%) was the most frequent, followed by ALCL (61/240; 25.4%) and AITL (48/240; 20%). Median age was 75 yrs (range; 70-95), 131/240 (54.6%) were men, ECOG >2 had 45/240 (19.3%) pts, advanced disease (stage III or IV) was in 180/240 (76.2%) pts, and 161/240 (68.8%) pts had LDH above normal range.

First-line therapy received 233/240 (97.1%) patients, systemic chemotherapy was administered in 201/240 (83.8%), the most frequent regimen was CHOP in 114/201 (56.7%), COP in 15%, etoposide-based regimens were administered in 6.5% patients only; no patients received alloTx or autoTx, monoclonal antibody (brentuximab vedotin, alemtuzumab, rituximab) was given in 11/201 (5.5%) cases. Best response after first-line treatment included 83 (34.6%) CR/Cru, 32 (13.3%) PR, 10 (4.2%) SD and 37 (15.4%) PD, but there were 58 (24.2%) pts with not evaluable and 20 (8.3%) pts with unknown response. Median OS (95% CI) was 1.2 yrs (0.9–1.5), and median PFS 0.8 yrs (0.7–1.0). From the subgroup of 78 patients with unknown/unevaluable response, 94.6% died with median 0.32 yrs (range; 0.14-5.6).

Conclusion: TCL of elderly ≥70yrs represents difficult subgroup of patients with increasing proportion of prognostically worse subtypes (PTCL-NOS, AITL). Despite chemotherapy is administered in majority of cases, the response is reached in half of them only, but around another third of patients died early during or immediately after therapy.

Keyword: Aggressive T-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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Educational grants: Roche, Gilead Sciences

H. Mocikova
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Educational grants: Janssen, Takeda

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609 | BRENTUXIMAB VEDOTIN IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED CD30-POSITIVE PERIPHERAL T-CELL LYMPHOMAS: REAL-WORLD DATA

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Background: Based on the results of ECHELON-2 trial, Brentuximab vedotin (BV) in combination with cyclophosphamide, doxorubicin and prednisone (CHP) has been approved by EMA for the treatment of newly diagnosed systemic anaplastic large cell lymphoma (ALCL) and become the standard of care for this patient population. In Czech Republic, BV plus CHP is approved as 1st line treatment for CD30-positive peripheral T-cell lymphomas (PTCL), including non-ALCL PTCL since 8/2020. The aim of this analysis is to provide real world data with this combination.

Methods: Using the prospective observational NiHiL project (NCT03199066), we identified patients (pts) ≥ 18 years of age with histologically confirmed CD30+ PTCL (diagnosed between August 2020 to October 2022), who received BV in combination with chemotherapy as 1st line treatment.

Results: A total of 63 pts were recruited; 31 (49%) had ALCL (12 ALK +, 19 ALK-) and 32 (51%) had non-ALCL PTCL (16 with PTCL NOS, 14 with AITL, and 2 with EATL). Median age was 60 years (range; 19-82). Most pts showed adverse clinical features at lymphoma diagnosis, including Ann Arbor stage III-IV ($n = 46$; 73%) or elevated LDH ($n = 34$; 54%). Of note, 18 (29%) pts had ECOG performance status ≥ 2 (incl. 6 pts ECOG 3 and 1 pt ECOG 4). By IPI, 16 (25%), 18 (29%), 12 (19%), and 17 (27%) pts belonged to low, low-intermediate, high-intermediate, and high-risk groups, respectively.

The most common chemotherapy backbone was CHP administered in 45 (71%) pts, followed by CHP + etoposide administered in 13 (21%) pts. Five (8%) pts received attenuated regimen. Nine (14%) pts underwent pre-planned consolidative autologous stem cell transplant. Sixty (95%) pts received G-CSF prophylaxis.

The most common grade ≥3 adverse events were neutropenia (49%), anaemia (30%), febrile neutropenia (19%), thrombocytopenia (19%), and infections (18%). Neuropathy (all grades) occurred in 21 pts (33%); grade 3 neuropathy in 3 pts (5%). Grade 5 AE occurred in 2 (3%) pts, sepsis in both cases.

Out of 63 there were 56 (89%) pts evaluable for response (PET/CT) at the time of database lock. The overall objective response rate (ORR) was 80% with 63% complete response (CR). The ORR/CR rates in ALCL ($n = 26$) versus non-ALCL ($n = 30$) pts were 89%/73% versus 73%/53%, respectively. The median follow-up of surviving pts is 16.6 months (range; 4.3- 31.3). The overall 18-months PFS and OS probability were 61.8% and 73.7%, respectively **(Figure 1).** By lymphoma subtype, the 18-months PFS and OS probability were 77.6% and 83.5% in ALCL and 50.3% and 65.9% in non-ALCL, respectively (**Figure 1**). Evaluation of the relationship between % of CD30+ neoplastic cells and clinical outcome is ongoing.

Conclusion: The outcome of the pts treated in real world setting seems to be similar to ECHELON-2 data, although the follow up is shorter and our patient cohort characteristic is slightly more unfavourable compared to ECHELON-2 population. Of note is the outcome of non-ALCL pts.

The research was funded by: The study is supported by the Cooperation Program, research area "Oncology and Haematology" and NU20-03-00253 and NU22-03-00370.

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Combination Therapies

Conflicts of interests pertinent to the abstract

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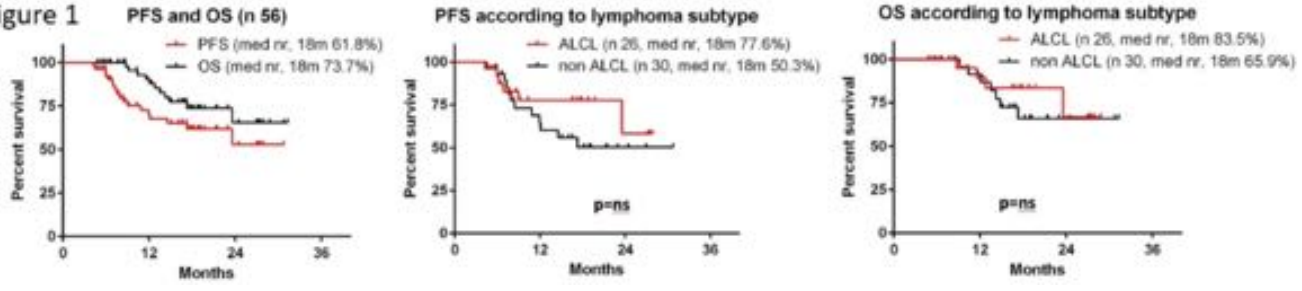
Other remuneration: ROCHE, GILEAD, TAKEDA

Figure 1



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Honoraria: Takeda

610 | ANALYSIS OF PATIENTS IN THE FIRST RELAPSE OR PROGRESSION OF T-CELL LYMPHOMA. REAL WORLD DATA FROM CZECH LYMPHOMA STUDY GROUP REGISTRY (NIHIL).

A. Janikova[1], D. Belada[2], M. Klanova[3], R. Chloupkova[4], N. Kopalova[5], V. Campr[6], K. Kamaradova[7], V. Prochazka[8], K. Benesova[9], H. Mocikova[10], J. Duras[11], M. Trneny[12]
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Background: Systemic T-cell lymphoma (TCL) is heterogeneous group of hematological malignancies with extremely poor prognosis. The prognosis of relapsed/ progressed disease is much worse, but there are sporadic data about this group of patients only. We focused on the most frequent subsets ALCL, PTCL-NOS and AITL/TFH-TCL) representing around 70% of all systemic T-cell lymphoma.

Methods: For this analysis, ALCL, PTCL-NOS and AITL patients at first progression (n = 441) were selected from the NIHIL registry (initial diagnosis 1999-2021). We tried to characterize this group of patients by calculation of PFS, OS, OS2 and interval from-relapse-to-therapy. We compared the subgroup of patients with early vs. late progression.

Results: At the first relapse (R1), there were 117 (26.5%) ALCLs, 74 (16.8%) AITLs, and 250 (56.7%) PTCLs, median age was 63 yrs (range; 19-91); 274/441 (62%) were men. First-line therapy included CHOP (254; 57.6%), CHOEP/CEP (110; 24.9%), and 52 (11.8%) pts were autotransplanted. Median since diagnosis to R1 was 0.72 yrs (range; 0.3–15.2), median OS2 from progression was 0.41 yr (0–10.28). Majority of patients 293/441 (66%) progressed early within 1 year including 168 (57%) of primary progression, whereas 58 (13%) pts only relapsed 2.5 years or later, remaining 90 (20%) pts relapsed between 1 and 2.5 years.

Patients with early relapse (<1 year) with median age (61 yrs), 65% were men, median OS2 was 0.31 year (0-8.9); median interval from-relapse- to-therapy was 8 days (range; 0-370). The most frequent therapy administered in R1 were platinum-based (28%) a gemcitabine-based (16%) regimen, 40 (13.6%) pts were transplanted (including 20 alloTx); whereas 26% patients did not start any therapy. Patients with late relapse (≥2.5 years) had median age 65 yrs, 55% were men, OS2 was longer with median 0.97 year (range; 0.05-10.2); median interval from-relapse- to-therapy was longer with median 34 days (range; 0-273). The patients were treated by gemcitabine (28%) and platinum-based regimens (22%), whereas 17% patients were not treated at all, autoTx was administered in 14% cases.

Conclusions: Our analysis demonstrates that relapse of TCL is usually fatal event for majority of patients with very short survival (in order of months), which occurs very early (in two thirds of pts within 1 yr since diagnosis). Because of lack of data from big clinical trials, these results could serve as a supporting evidence for administration of case-driven targeted therapy.

Conflicts of interests pertinent to the abstract

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Non-Hodgkin (Pediatric, Adolescent, and Young Adult)

D. Belada
Consultant or advisory role Gilead, Roche, Novartis, Takead
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H. Mocikova
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J. Duras
Consultant or advisory role Roche, Takeda, Celgene

611 | A NOVEL CONDITIONING REGIMEN OF CHIDAMIDE, CLADRIBINE, GEMCITABINE, AND BUSULFAN (CHICGB) IN THE AUTOLOGOUS STEM CELL TRANSPLANTATION OF AGGRESSIVE T-CELL LYMPHOMA

Q. Zeng[1], H. Zhang[1], P. Kuang[1], J. Li[1], X. Chen[1], T. Dong[1], Q. Wu[2], C. Zhang[1], C. Chen[3], T. Niu[1], T. Liu[1], Z. Liu[1], J. Ji[1]

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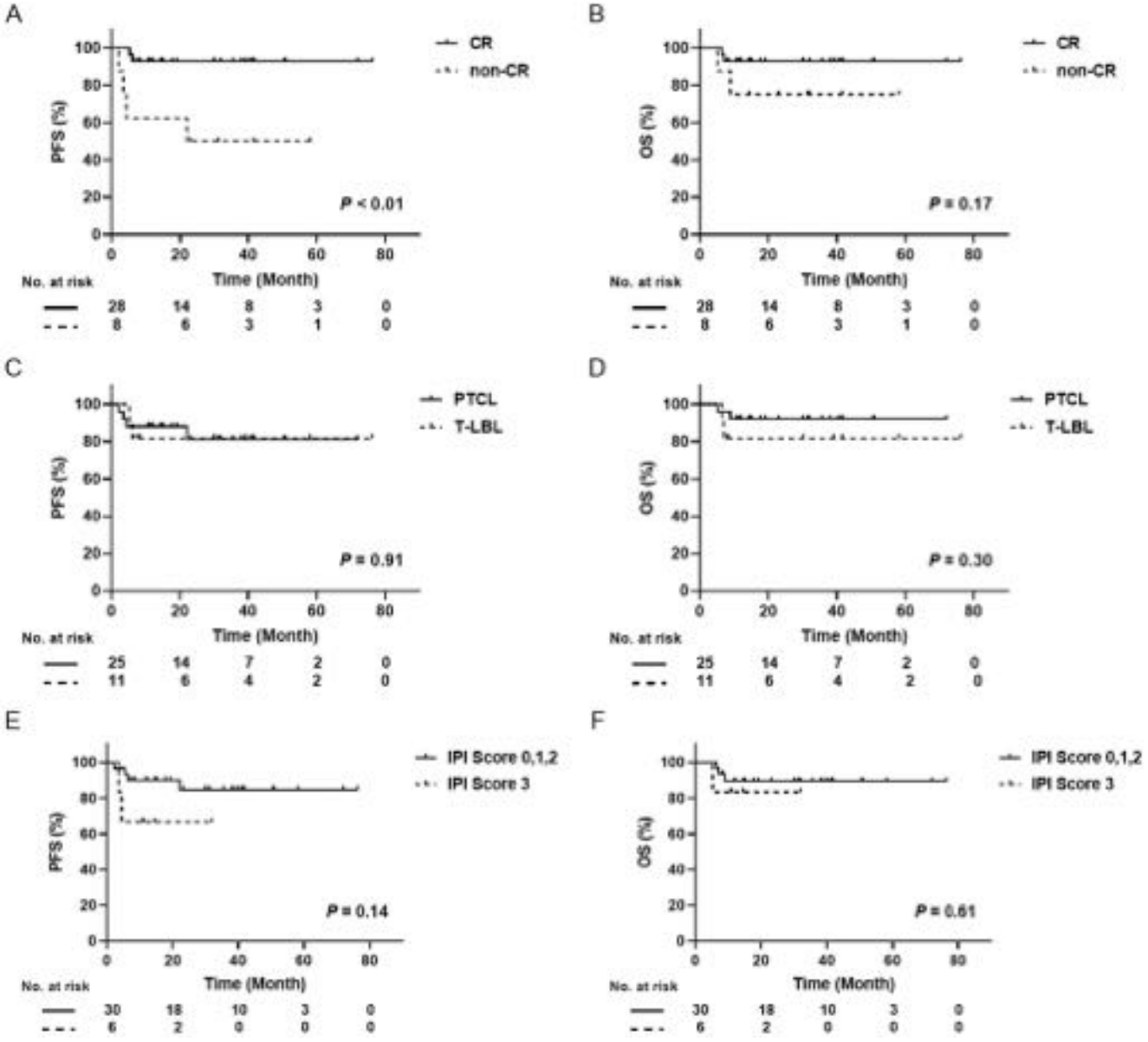
Background: The prognosis of patients with peripheral T-cell (PTCL) or lymphoblastic T-cell lymphoma (T-LBL) remains poor under current conditioning regimens before receiving autologous stem cell transplantation (ASCT).

Methods: Patients with PTCL or T-LBL were enrolled to receiviing ASCT using the conditioning regimen of chidamide, cladribine, gemcitabine and busulfan (ChiCGB). Positron emission tomography-computed tomography (PET/CT) was used to evaluate the response to ASCT. Overall survival (OS) and progression-free survival (PFS) were employed to assess patient outcome, and adverse events were used to assess the safety of the regimen. The survival curve was estimated via the Kaplan-Meier method.

Results: Twenty-five PTCL and 11 T-LBL patients were recruited. The median time to white blood cell (WBC) and platelet engraftments were 10 days (8–13 days) and 13 days (9–31 days), respectively. The 3-year PFS and OS were 81.3 ± 7.2% and 88.5 ± 5.4% for all patients; 92.0 ± 5.4% and 81.2 ± 8.8% for PTCL patients; and both 81.8 ± 11.6% for T-LBL patients, respectively. The 3-year PFS and OS were both 92.9 ± 4.9% for patients with complete response (CR), but 50.0 ± 17.7% and 75.0 ± 15.3% for patients with non-CR,



respectively. Infection was the most common non-hematological toxicity, and all toxicities were mild and controllable.

Conclusions: ChiCGB was a potentially effective and well-tolerated conditioning regimen to improve the prognosis of patients with aggressive T-cell lymphoma. Future randomized controlled trials are needed to further assess ChiCGB as conditioning regimen for ASCT.

Keywords: aggressive T-cell lymphoma, ASCT, busulfan, chidamide, cladribine, gemcitabine

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Chemotherapy, Stem Cell Transplant

No conflicts of interests pertinent to the abstract.

612 | A REAL-WORLD STUDY OF CHIDAMIDE FOR PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA IN CHINA

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Background: Peripheral T-cell lymphoma (PTCL) is featured with a poor survival outcome. Targeting histone deacetylases (HDACs) has become a novel treatment option for PTCL. Chidamide is the first oral selective HDAC inhibitor.

Objective: This observational study aimed to investigate the efficacy and safety of Chidamide in patients with PTCL.

Methods: From June 2015 to April 2022, 49 PTCL patients treated with Chidamide were included in this study. Objective responses, progression-free survival (PFS), overall survival (OS), and safety were analyzed.

Results: The median age was 59 years (range, 30–85 years). Angioimmunoblastic T-cell lymphoma (AITL, 57.1%) was the main pathological subtype, followed by PTCL-not otherwise specified (PTCL-NOS, 14.3%), NK/T-cell lymphoma (NKTCL, 8.2%), anaplastic large cell lymphoma (ALCL, 6.1%) and other subtypes (14.3%). 77.6% of patients were previously untreated. 91.8% of patients had stage III/IV disease. Thirty-three patients achieved objective responses with an overall response rate (ORR) of 67.4%, including 21 patients with complete response (CR). The 2-year PFS rate and 2-year OS rate were 51.5% and 68.5%, respectively. Among the 27 previously untreated patients who received Chidamide combined with chemotherapy, the ORR of all various PTCL subtypes, AITL and PTCL-NOS were 85.2%, 68.8% and 75.0%, respectively. The most common adverse events (AEs) were hematological toxicities. 24.5% of patients reduced the dosage or stopped using Chidamide due to AEs. No treatment-related death occurred.

Conclusion: The favorable efficacy and safety profiles indicate that Chidamide would be a new therapeutic option in patients with PTCL.

Encore Abstract - previously submitted to EHA 2023

Keyword: Aggressive T-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

613 | CLINICAL EFFICACY OF CD34 POSITIVE SELECTION EX-VIVO PURGING DURING AUTOLOGOUS STEM CELL TRANSPLANTATION IN PERIPHERAL T CELL LYMPHOMA

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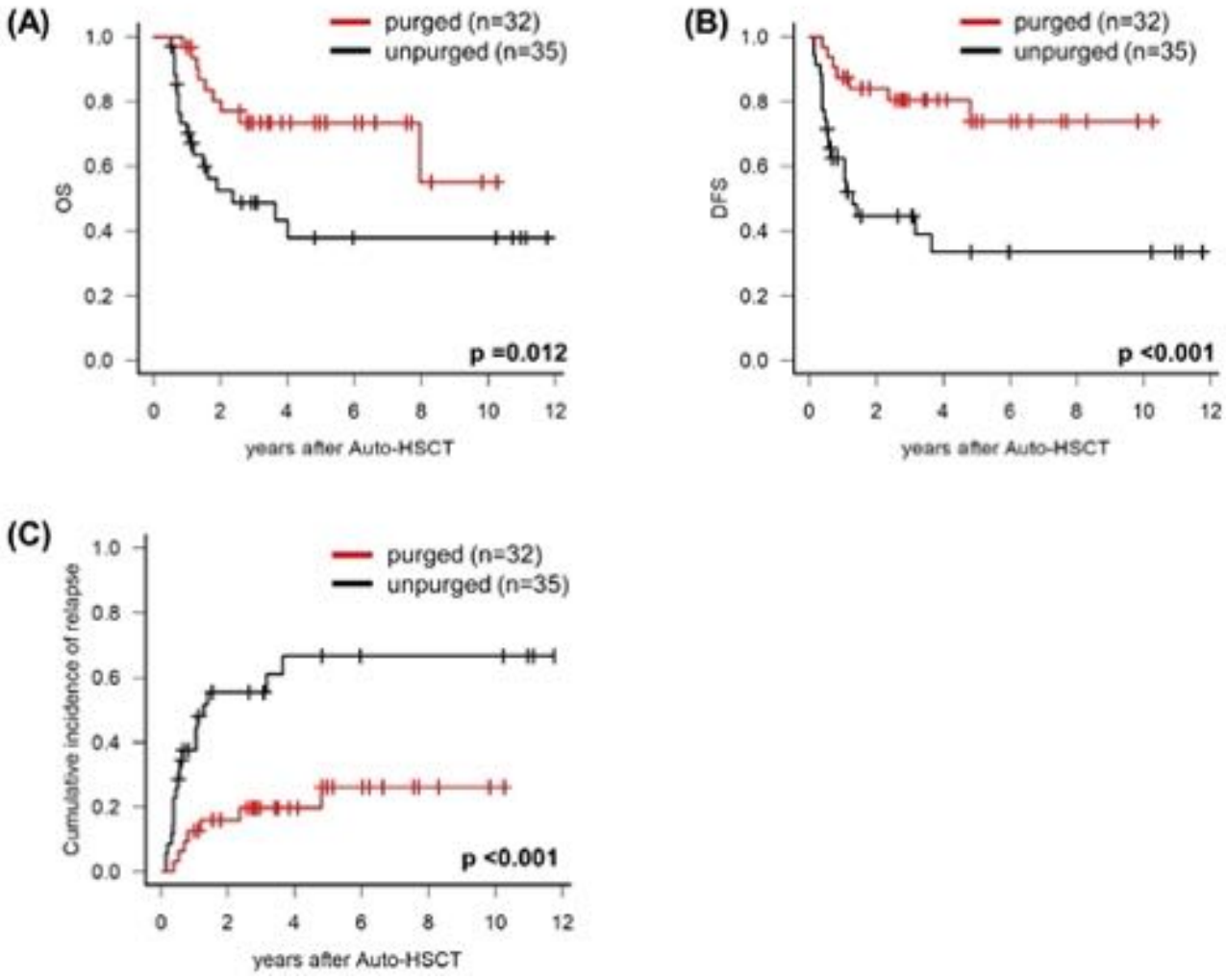
Background: Autologous stem cell transplantation (ASCT) is the standard treatment for peripheral T-cell lymphomas (PTCLs). Strategies that reduce the relapse rate and treatment-related mortality are essential for successful ASCT. Because in vivo/in vitro purging methods using rituximab are not appropriate for T-cell lymphomas, an ex vivo CD34+ selective purging system using CliniMACS is the most reliable method to reduce autograft tumor cell contamination in these tumors. In the present study, we retrospectively analyzed the clinical outcomes of HDT/ASCT after ex vivo purging via the CD34+ selective method in T-cell NHL patients.

Methods: We retrospectively investigated the influence of *ex vivo* purging with CD34+ selection to maximize the effects of ASCT. Of 67 consecutive PTCL patients, 32 and 35 underwent purged and unpurged ASCT.

Results: The purged group had improved overall survival (OS), disease-free survival (DFS), and cumulative incidence of relapse (hazard ratio [HR] = 2.68, $p = 0.016$; HR = 3.97, $p = 0.002$; and HR = 3.65, $p = 0.004$, respectively), compared to the unpurged group. Prognostic factor analysis showed that unpurged ASCT, chromosomal abnormalities at initial diagnosis, high risk, and pre-ASCT disease status were associated with poor survival outcomes. Subgroup analysis demonstrated that purging was most appropriate for International Prognostic Index high-risk patients who underwent upfront ASCT (HR = 3.35 [OS] and = 6.59 [DFS]). In purged ASCT group, NK cell activity and the lymphocyte-to-monocyte ratio known as an independent prognostic factor were increased after ASCT with statistical significance; the lymphocyte-to-monocyte ratio (LMR) was significantly increased after ASCT in the purged group (mean difference = 1.484, 95% CI = 0.407–2.560; $p = 0.009$). Also, Engraftment was achieved in all patients with no need for unpurged autologous stem cell backup in purged group. There were no engraftment failures or differences in adverse events including of transplant-related viral infections between the two groups.

Conclusions: CD34+ ex vivo purging ASCT is safe, effective, and may improve survival outcomes, particularly in high-risk PTCL patients. Successful ASCT for lymphoma is based on patient selection, conditioning, transplant timing, and minimal residual disease, and purged

Figure 1



autologous stem cells have been shown to improve survival outcomes.

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Keywords: Aggressive T-cell non-Hodgkin lymphoma, Stem Cell Transplant

No conflicts of interests pertinent to the abstract.

614 | PRELIMINARY RESULTS OF GEMCITABINE, ETOPOSIDE, MITOXANTRONE HYDROCHLORIDE LIPOSOME AND DEXAMETHASONE REGIMEN FOR NEWLY DIAGNOSED EARLY NUAT OR ADVANCED STAGE ENKTL

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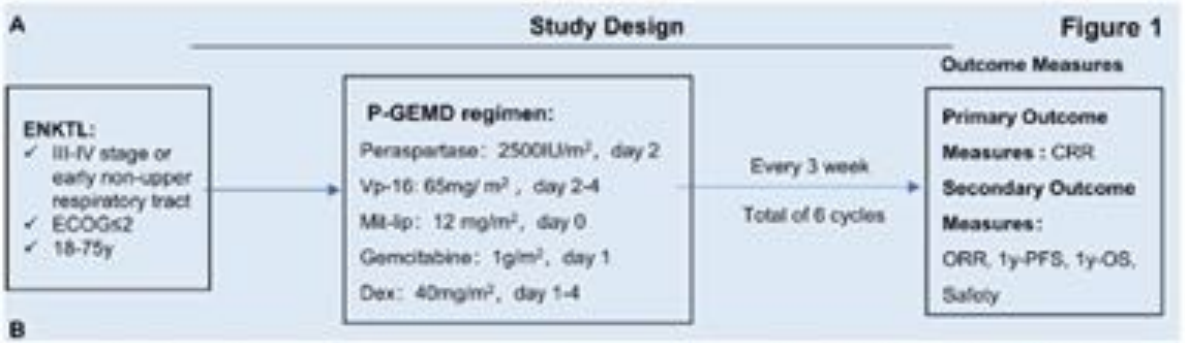
Introduction: Extra-nodal NK/T-cell lymphoma (ENKTL) is an aggressive disease common in Asia but rare in the West. More than two-thirds of persons have stage I/II disease of the upper aero-digestive tract (UAT), which have relatively superior prognosis. However, patient of early non-UAT (NUAT) or advanced stage show an aggressive clinical course with extremely poor prognosis and low survival rates. Mitoxantrone hydrochloride liposome has reported to have efficacy in relapsed/ refractory (R/R) ENKTL in a phase II clinical trial. Furthermore, patient of early NUAT or advanced stage always have hemophagocytic lymphohistiocytosis (HLH) at diagnosis. Therefore, etoposide and high dose dexamethasone were also important for these patients. Based on these facts, this study evaluates the efficacy and safety of the regimen of gemcitabine, etoposide, mitoxantrone hydrochloride liposome, and dexamethasone (P-GEMD) in patients of newly diagnosed early NUAT or advanced stage ENKTL.

Methods: Patients diagnosed as ENKTL in early NUAT and advanced stage form 18–80 years with ECOG of 0–2 were eligible for enrollment. We planned a maximum of 6 cycles of P-GEMD regimens for patients. The P-GEMD regimen was administered intravenously every 3 weeks until disease progression (PD) or unacceptable toxicity as follows (Figure 1A): pegaspargase at 2500 IU/m^2 d2; gemcitabine at 1000 mg/m^2, d1; etoposide at 65 mg/m^2, d2–4; mitoxantrone hydrochloride liposome at 12 mg/m^2, d1; dexamethasone at 40 mg/d, d1–4. The primary endpoint is complete response rate (CRR). The second endpoint are overall response rate (ORR), duration of



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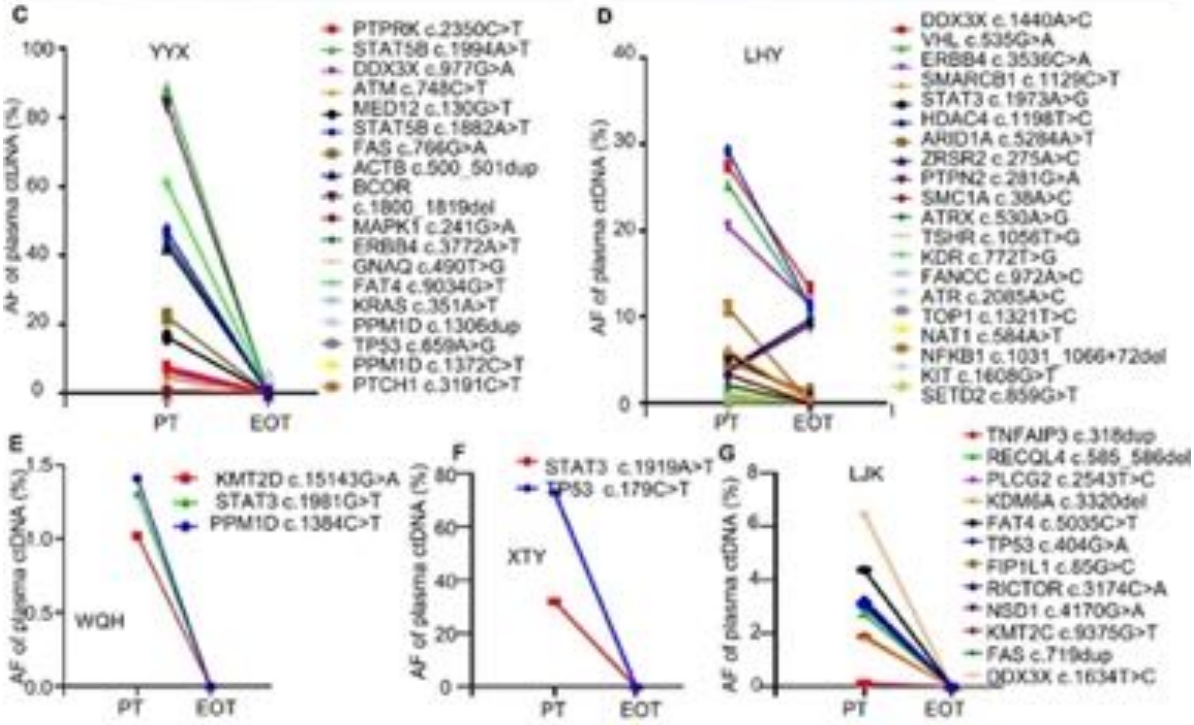
Age	Sex	Year	Stage	PINK/PINK-E score	Regimens	Response for interim evaluation	Response for end evaluation
YYX	M	50	IV, B	PINK=2, PINK-E=3	P-GEMD*6 cycles	CR	CR
WQH	M	44	IV B	PINK=2, PINK-E 3	P-GEMD*6 cycles	CR	CR
LJK	M	65	IV B	PINK=4, PINK-E=4	P-GEMD*6 cycles	CMR	CMR
LHY	F	60	IV B	PINK=3, PINK-E=4	P-GEMD*3 cycles	PD	--
XTY	F	51	IV B	PINK=2, PINK-E=3	P-GEMD*6 cycles	CMR	CMR



H

Treatment-related adverse events

Hematologic	All grades	Grades 1-2	Grade 3-4	Non-hematologic	All grades	Grades 1-2	Grade 3-4
Leukopenia	5	5	0	Hypo-fibrinogenemia	5	4	1
Neutropenia	5	5	0	Hypo-albuminemia	5	4	1
Anemia	4	4		Asparate transaminase increase	5	3	2
Thrombocytopenia	1	1	0	Infection	0	0	0

response (DOR) and 1-year overall survival (OS) and progression-free survival (PFS).

Results: Five patients were preliminarily planned for P-GEMD regimens. Median age was 51y (range 44–60 y). All the five patients were advanced stage with B symptoms. The median PINK and PINK-E score was 2 (range 2–4) and 3 (range 3–4), respectively. Two patients experienced HLH at diagnosis. All the five patients completed the induction of P-GEMD regimens with the median cycles of 6 (range 3–6). Only 1 patient experienced PD while the other 4 patients were evaluated as CR by PET-CT. Therefore, the CRR is 80% (Figure 1B). Furthermore, the 4 patients with CR evaluated by PET-CT were all negatively for minimal residual disease (circulating tumor DNA) checked by next generation sequencing (NGS) while the ctDNA burden of patient with PD was positive (Figure 1C-G). There were 30 adverse events (AEs) recorded, of which 86.7% were grade 1 or 2. Hypo-fibrinogenemia, hypo-albuminemia and asparate transaminase increase were the most common grade 3 or 4 AEs (Figure 1H).

Conclusion: Overall, from these preliminary data, P-GEMD regimen demonstrated promising antitumor activity with manageable toxicities as a fronnt-line treatment for early NUAT or advanced stage ENKTL. Further enrollment of this clinical trial is warranted.

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Chemotherapy, Combination Therapies

No conflicts of interests pertinent to the abstract.

615 | A MULTI-CENTER RETROSPECTIVE STUDY OF PEMBROLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY EXTRANODAL NK/T-CELL LYMPHOMA

J. Y. Lee[1], J. H. Kwon[2], J. Y. Hur[3], D. H. Yoon[4], Y. R. Do[5], J. Jo[6], H. J. Kang[7], Y. Koh[8], W. S. Lee[9], S. Lim[10], J. Lee[1]

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Background: Extranodal natural killer T-cell lymphoma (ENKTL) is an aggressive malignancy with a dismal prognosis. PD-1 blockade with pembrolizumab has shown promising activity in relapsed/refractory (R/R) ENKTL in case series. Real-world data about the efficacy of pembrolizumab in R/R ENKTL patients are limited.

Methods: We performed a multicenter retrospective study to evaluate pembrolizumab efficacy and safety in patients with R/R ENKTL from 10 academic centers in South Korea. Pembrolizumab 100 mg was administered intravenously every 3 weeks.

Results: A total of 24 patients were enrolled. The median age was 67 years old (range, 36–87) and 29.2% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or greater. Pembrolizumab was administered as 2nd-, 3rd- and 4th or greater line chemotherapy in 9 (37.5%), 9 (37.5%), and 6 (25.0%) patients, respectively, and median 3 cycles (range 1–21) of pembrolizumab were given. In response evaluation, complete remission (CR) and partial response (PR) was achieved in 6 (25.0%) and 3 (12.5%), respectively. The median progression-free survival and overall survival were 2.0 months (95% CI, 0.9–3.0) and 8.0 months (95% CI, 0.0–22.4), respectively. Multivariate analysis indicated that ECOG PS was the only significant predictor of PFS after pembrolizumab treatment (hazard ratio, 5.33; 95% confidence interval, 1.09–26.1; $P = .039$) Overall, 14 (58.3%) patients experienced adverse events (AEs), with fatigue ($n = 7$, 29.1%) being the most common Eight patients (33.3%) developed G3-4 AEs, the most frequent of which was neutropenia (4,16.7%)

Conclusion: Pembrolizumab could be a therapeutic approach for the control of R/R ENKTL.

Keyword: Aggressive T-cell non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

616 | THE OUTCOME OF MODIFIED-SMILE REGIMEN AS THE FIRST-LINE TREATMENT FOR NEWLY DIAGNOSED FRAIL ADVANCED HIGH-RISK NK/T CELL LYMPHOMA: A RETROSPECTIVE OBSERVATION STUDY

F. Zhu, L. Zhang, J. Li, T. Liu, X. Liu, Q. Li, G. Wu

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Introduction: To explore an effective and well-tolerant treatment for newly diagnosed advanced high-risk extranodal natural killer/T cell lymphoma (NKTCL) patients with poor performance status. We analyzed the efficacy and toxicity of modified-SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide) regimen in untreated advanced high-risk NKTCL patients retrospectively.

Methods: Ten newly diagnosed advanced high-risk extranodal natural killer/T cell lymphoma (NKTCL) patients with a performance status of 2 were included in Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology from May 2017 to May 2019. At least two cycles of modified-SMILE chemotherapy were administered as the first-line treatment. The primary endpoint was overall survival (OS) and progression-free survival (PFS). The secondary endpoint was the adverse effects of the treatment.

Results: A total of 10 patients with newly diagnosed advanced high-risk NKTCL were enrolled, with a median age of 31.5 years (18-57 years). The male: female ratio was 7:3. The performance status of all patients was 2. Seven patients had B symptoms at the initial diagnosis, all presenting as hyperpyrexia. Extranodal organs involvement at the initial diagnosis included nasal cavity (8/10), skin (5/10), bone (4/10), lung (3/10), breast (2/10), pancreas (2/10), liver (1/10), stomach (1/10), intestine (2/10), adrenal glands (1/10) and uterine adnexa (1/10). Bone marrow involvement was present in 3 patients, and the spleen was involved in 2 patients. The prognostic index of NKTCL with Epstein-Barr virus DNA (PINK-E) of all patients was higher than 3. The median OS and PFS were 9 months (2-53 months) and 3 months (1-53 months), respectively. The main adverse effects were hematological toxicities including neutropenia, thrombocytopenia, and decreased fibrinogen. The grade 3/4 neutropenia happened in 2 patients, and the grade 4 thrombocytopenia happened in 1 patient. All toxicities were tolerable. To Mar 2023, the median follow-up period was 9 months (2-53 months), and the median OS was 9 months (2-53 months). Nine patients died and 1 patient survived. Of the 9 patients who died, all patients were diagnosed with Lymphoma-associated haemophilic syndrome (LAHS).

Conclusions: The prognosis of advanced high risk NKTCL is very poor because of the poor tolerance to the intensive chemotherapy and the high incidence of LAHS. The modified-SMILE regimen might be an effective and well-tolerance chemotherapy to this intractable condition.

Keywords: Chemotherapy, Combination Therapies

No conflicts of interests pertinent to the abstract.

617 | PRELIMINARY RESULTS OF A PHASE 2 STUDY OF CHIDAMIDE, GEMCITABINE, VINORELBINE, AND MITOXANTRONE LIPOSOME (CHI-GVM) IN RELAPSED/REFRATORY PERIPHERAL T-CELL LYMPHOMA

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Introduction: Patients with relapsed or refractory peripheral T-cell lymphoma (R/R PTCL) have a poor prognosis. There is no effective treatment for these patients. Mitoxantrone hydrochloride liposome showed high antitumor activity and low toxicity in lymphoma. In a phase II clinical study of mitoxantrone hydrochloride liposome monotherapy for R/R T-cell lymphoma, the overall response rate (ORR) and complete remission rate (CRR) of PTCL, not otherwise

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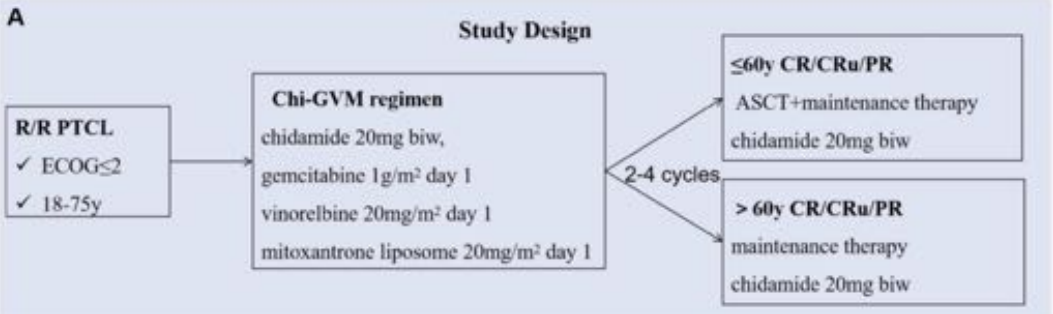

B

General information

Patient	Sex	Age	Stage	Diganose	PIT Score	Cycles	Best Response
Pt.1	Male	70	IV	PTCL,NOS	1(Age)	2	PD
Pt.2	Male	51	I	PTCL,NOS	1(LDH)	1	PD
Pt.3	Male	58	II	PTCL,NOS	0	3	CR
Pt.4	Female	47	IV	ALCL,ALK-	0	2	CR
Pt.5	Male	52	IV	MEITL	0	1	lost follow-up
Pt.6	Female	55	III	ALCL,ALK-	0	1	-
Pt.7	Male	66	IV	MEITL	1(Age)	1	-

Pt.6 and Pt.7 did not reach the assessment time; LDH: lactate dehydrogenase

C

Treatment-related adverse events

Hematologic	Grades 1-2	Grades 3-4	Non-Hematologic	Grades 1-2	Grades 3-4
Leukopenia	2	1	Hepatic insufficiency	0	1
Neutropenia	2	2	Nausea	2	0
Thrombocytopenia	2	0	Infection	0	0

specified (PTCL, NOS) reached 34.4% and 18.8%. Our study aimed to explore whether the combination chemotherapy regimen containing mitoxantrone liposomes can improve the efficacy and survival of R/R PTCL.

Methods: A Phase II, multicenter, single-arm, open-label study is planned at our center. All patients enrolled are R/R PTCL and will receive induction therapy with chidamide (20 mg, twice a week), gemcitabine (1 g/m^2, d1), vinorelbine (20 mg/m^2, d1), and mitoxantrone hydrochloride liposome (20 mg/m^2, d1) (Chi-GVM) for 2–4 cycles. Patients aged 60 years or younger with complete remission (CR) / unconfirmed complete remission (CRu) / partial remission (PR) after 2–4 cycles of induction therapy received autologous stem cell transplantation (ASCT) prior to maintenance therapy. Patients after ASCT or patients over 60 years old with CR/CRu/PR receive maintenance therapy of chidamide (20 mg twice a week) until intolerance or disease progression (PD). Efficacy was assessed by contrast-enhanced CT or PET-CT every 2 cycles during treatment. The primary endpoint of the study was ORR and secondary endpoint was duration of remission (DOR) and1-year progression-free survival (1y-PFS).

Results: A total of 7 patients were treated with Chi-GVM between September 2022 and February 2023, including 3 patients with PTCL, NOS; two patients with ALK negative anaplastic large cell lymphoma (ALCL, ALK-); and 2 patients with monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). Five male and two female were included, with a mean age of 57 years, and one patient was post-ASCT. Two patients were re-staged of stage I–II and five of stage III–IV prior to treatment, extranodal lesions including stomach, skin and intestinal. Four patients were evaluable for efficacy, 1 patient was lost to follow-up, and 2 patients did not reach the assessment time. Of the evaluable patients, 2 patients had a best response of CR and 2 patients experienced PD, one patient achieved CR and received consolidation therapy with ASCT. Grade 2 or 3 adverse events occurred in 5 patients, including 3 cases of leukopenia, 4 cases of neutropenia, 2 case of thrombocytopenia, and 1 case of hepatic insufficiency. One patient had myocardial damage before treatment, and kept stable after mitoxantrone hydrochloride liposome used.

Conclusion: For R/R PTCL, Chi-GVM is an alternative effective regimen and the adverse effect is acceptable and controllable.

Keywords: Aggressive T-cell non-Hodgkin lymphoma, Chemotherapy, Late Effects in Lymphoma Survivors

No conflicts of interests pertinent to the abstract.

618 | SINGLE AGENT BRENTUXIMAB VEDOTIN AS BRIDGE TO ALLOGENEIC STEM CELL TRANSPLANT IN ADOLESCENTS WITH RELAPSED ANAPLASTIC LARGE CELL LYMPHOMA (ALCL): THE UCLH EXPERIENCE

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Introduction: Optimal treatment for relapsed ALCL in children and adolescents is still subject of debate. We present here the results of our salvage strategy in the TYA Unit at UCLH, using single agent brentuximab vedotin (BV) as bridge to allogeneic stem cell transplant (alloHSCT).

Methods: Between 2011 and 2021 we treated 7 patients with relapsed ALCL; all patients had received first line treatment according to ALCL99 guidelines. All relapses were biopsy proven and centrally reviewed if not performed at UCLH.

Brentuximab Vedotin was given at the standard dose of 1.8mg/kg intravenously every 3 weeks.

Results: All 7 patients were male; median age at diagnosis was 16 (range 13–19). Baseline characteristics were as follows: 7/7 were CD30+, 3/7 were CD3+, 6/7 biopsies were ALK positive, and 3/7 presented with a small cell/lymphohistiocitic (SC/LH) pattern. Six/7 patients had stage IV disease, 4/7 had skin involvement, bone marrow involvement was seen in 3/7 cases (infiltrate between 2 and 10%); 1/7 patients had bulky disease.

Of the 7 patients, 3 had primary progressive disease, while 4/7 patients initially achieved a complete metabolic response (CMR), but had a very early relapse, between 2 and 3 months after completion of treatment.

6/7 patients received BV as first line of salvage treatment, 1 as second salvage, after failing ICM (ifosfamide, carboplatin, mitoxantrone), which was still our standard of care in 2011. Median number of doses of BV received was 3 (range 2–5); 6/7 (86%) patients obtained a complete metabolic remission, after a median of 3 doses (range 3–5). One patient progressed on BV; after failing crizotinib he achieved CMR with vinblastine-dexamethasone, then proceeded to transplant and is in long term remission.

All 6 patients who achieved a complete remission after BV proceeded to alloHSCT, 1/6 from fully matched sibling donor, 3/6 from haploidentical donors, 2/6 from matched unrelated donors.

Conditioning regimen was myeloablative for 5/6 patients, using Cyclophosphamide/total body irradiation +/- Campath depending on donor source; one patient received intermediate intensity conditioning with BEAM (BCNU, etoposide, cytarabine, melphalan)-Campath.

With a median follow up of 55 months (range 4–133), all 6 patients are alive and 5/6 (83%) remain in remission with no need for further treatment; 1/6 patients relapsed 8 months post-transplant.

This patient was re-challenged with BV, with the addition of donor lymphocytes infusions (DLI) and achieved a complete remission.

Conclusions: Salvage treatment with single agent BV followed by alloHSCT is effective in adolescents with relapsed ALCL and lead to durable responses in a cohort of patients with high prevalence of high-risk features (advanced stage, SC/LH pattern, CD3+, early relapse after first line treatment). Interestingly, in one patient who relapsed after alloHSCT, BV and DLI were successful in inducing another complete remission.

Keywords: Molecular Targeted Therapies, Non-Hodgkin (Pediatric, Adolescent, and Young Adult), Stem Cell Transplant

No conflicts of interests pertinent to the abstract.

619 | LYMPH NODE AND SKIN SCORING GROWTH KINETICS PREDICT OUTCOMES IN CUTANEOUS T-CELL LYMPHOMA: AN INTERIM ANALYSIS

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In cutaneous T-cell lymphoma (CTCL), skin scoring and lymph node (LN) assessment are essential for scoring disease response in both clinical practice and in trials. Current assessment methods rely on calculating relative changes in the Modified Severity-Weighted Assessment Tool (mSWAT) and target LN size during a patient's treatment course. However, measuring relative changes fails to account for mixed treatment effects comprising the simultaneous regression of treatment-responsive cells and growth of treatment-resistant cells. Additionally, the clinical significance of LN size on imaging scans remains uncertain in CTCL. LNs are currently measured using linear dimensions that may not capture the extent of nodal involvement or be sensitive enough to track clinically meaningful changes over time.

The aim of this study was to perform kinetic analysis using mSWAT data and computed tomography LN measurements from the MAVORIC trial to determine if dynamic changes over time correlate with overall survival (OS) in CTCL. Kinetic modeling evaluated simultaneous rates of growth (***g***) and regression (***d***) using a two-phase equation. Unidimensional and volumetric LN sizes were measured using a novel radiomics imaging platform. Tumor doubling times can be estimated based on ***g***, using the equation $\mathbf{dt = 0.693/g.}$

An initial cohort of 119 patients were included, and in most patients, ***g*** and ***d*** values could be estimated. Patients were divided into two groups based on ***g***, and correlation with OS was evaluated. The median ***g*** was $0.0013d^{-1}$ in the half with slowest rate of increase in SWAT scores (doubling time = 533 days); with ***g*** of 0.0057d1 in those with fastest growth (doubling time = 122 days). For unidimensional LN size, volumetric LN size, and mSWAT, ***g*** was highly correlated with OS; faster rates of nodal growth or increase in SWAT scores were associated with shorter OS. Median OS for patients with faster unidimensional LN, volumetric LN, and mSWAT growth rates were 29, 27.7, and 17 months, respectively, whereas median OS were not reached for patients with slower growth rates ($p = 0.012$, 0.0035, and 0.0012, respectively).

Our interim analysis demonstrates that skin scoring and lymph node growth kinetics predict survival in CTCL. Thus, ***g*** has potential as a novel biomarker for prognostication and treatment response assessment. It may also serve as a clinical trial endpoint that allows for earlier readout of trial results than conventional survival endpoints. Further validation in a larger cohort, and ultimately with prospective studies, is needed.

The research was funded by: Kyowa Kirin

Keywords: Diagnostic and Prognostic Biomarkers, Cutaneous non-Hodgkin lymphoma, Imaging and Early Detection - Other

Conflicts of interests pertinent to the abstract

L. J. Geskin
Consultant or advisory role Kyowa Kirin
Research funding: Kyowa Kirin

620 | A CASE SERIES OF PATIENTS WITH CUTANEOUS T-CELL LYMPHOMA TREATED WITH COMBINATION MOGAMULIZUMAB AND OTHER THERAPIES AFTER SINGLE AGENT MOGAMULIZUMAB

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Introduction: Mogamulizumab (moga) is an anti-CCR4, monoclonal antibody approved as monotherapy for the treatment of relapsed/refractory mycosis fungoides (MF) and Sezary syndrome (SS). Combination therapies are frequently utilized in cutaneous T-cell lymphoma (CTCL), in part due to the variation in response across blood, nodal, and skin compartments. Little is known about moga in combination with other therapies.

Methods: We conducted a single institution retrospective analysis of MF/SS patients who were treated with moga in combination with other systemic therapies, including peginterferon alpha-2a (IFNα), bexarotene, extracorporeal photopheresis (ECP), and oral methotrexate between March 2019 and March 2023. Baseline characteristics and clinical outcomes were recorded and summarized. Responses were assessed by Olsen staging criteria (Olsen et al., 2022).

Results: We identified 9 patients treated with moga combination therapy at our institution (Table 1). Six of 7 patients transitioned

Table 1. Summary of demographic and clinical features of patients with Mycosis Fungoides and Sezary syndrome treated with mogamulizumab monotherapy and combination therapy.

ID	Age at treatment	Gender	No. of prior treatments	TNMB at start of treatment	Best Response (TNMB)	Time to best response (days)	Time to next treatment (days)	Status
Mogamulizumab monotherapy								
1	69	M	6	T2N0M0B2	T2N0M0B2	N/A	156	Alive
2	57	M	7	T4N0M0B2	T1N0M0B1	140	159	Alive
3	76	F	3	T2N0M0B0	T3N0M0B0	28	42	Alive
4	61	M	2	T1NxM0B1	T1NxM0B1	N/A	104	Alive
5	86	M	2	T4N0M0B1	T4N0M0B1	N/A	46	Deceased
6	73	M	4	T2N0M0B0	T1N0M0B0	180	197	Alive
8	68	F	2	T4N0M0B2	T2N0M0B2	88	201	Alive
9	91	F	10	T3N0M0B0	T1N0M0B0	188	330	Alive
Mogamulizumab + IFN α								
1	70	M	7	T4N0M0B2	T1N0M0B2	154	Ongoing	Alive
2	58	M	10	T2N0M0B1	T2N0M0B1	N/A	224	Alive
3	79	F	6	T2N0M0B1	T1N0M0B1	N/A	196	Alive
7	65	M	4	T4N3M0B1	T4NxM0B1	N/A	171	Alive
Moga + bexarotene								
2	58	M	9	T2N0M0B1	T2N0M0B1	N/A	91	Alive
8	69	F	3	T2N0M0B2	T2N0M0B2	N/A	Ongoing	Alive
Moga + ECP								
2	58	M	8	T1N0M0B1	T1N0M0B1	N/A	98	Alive
4	62	M	4	T1NxM0B1	T1NxM0B1	N/A	175	Alive
Moga + TSEB								
5	86	M	3	T4N0M0B1	T2N0M0B1	24	24	Deceased
6	74	M	5	T2N0M0B0	T1N0M0B0	103	103	Alive
Moga + NBUVB								
4	61	M	3	T1NxM0B1	T1NxM0B1	N/A	186	Alive
Moga + IFNα + ECP								
4	62	M	5	T1NxM0B1	T1NxM0B1	N/A	Ongoing	Alive
7	66	M	5	T4N3M0B1	T4N3M0B1	N/A	39	Alive
Moga + methotrexate								
9	92	F	11	T3N0M0B0	T3N0M0B0	N/A	Ongoing	Alive

Abbreviations: number (No.). Time to best response not applicable (N/A) where patient only had stable disease.

from mono to combination therapy due to progressive disease or stable disease with uncontrolled symptom burden. Median time to next treatment was 157.5 days (range 42-330) for moga monotherapy. The best response observed in the 8 patients to single agent moga was classified as: 4 (50%) partial responses (PR), 3 (37.5%) stable disease (SD), and 1 (12.5%) progressive disease (PD).

We identified a total of 7 different treatment combinations in our 9 patients (6 systemic therapies and 2 skin-directed), which included IFNα (n = 4), bexarotene (2), ECP (2), total skin electron beam radiation (TSEB) (2), narrow band ultraviolet-B therapy (NBUVB) (1), IFNα + ECP (2), and oral methotrexate (1). Multiple patients received more than one combination treatment. Among the combination therapies, the median time to next treatment was 137 days (range 24-224 days) with 2 out of 6 patients having ongoing responses to moga + IFNα +/- ECP. The patient with PR on moga + IFNα received 7 prior therapies. His skin involvement improved from T4 to T1 but significant disease in the blood persisted (B2). He continues moga + IFNα now 846 days later.

Conclusions: Mogamulizumab has improved outcomes for MF/SS patients, but global complete responses are rare with the best responses seen in blood. In our series, the addition of IFNα provided clinical benefits to patients with SD or PD on single agent moga. One patient achieved a lengthy partial response despite persistent disease seen in peripheral blood samples. We speculate the combination of moga + IFNα may augment antibody-dependent cellular cytotoxicity thereby improving efficacy of moga. Additionally, combinatorial approaches may improve responses in skin, nodes, and viscera where lower responses are observed to single agent moga. Further investigations of moga combinations are needed.

Keywords: Combination Therapies, Cutaneous non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

621 | EXCELLENT OUTCOMES OF SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA TREATED WITH CYCLOSPORIN-BASED REGIMEN, A MULTICENTER RETROSPECTIVE STUDY IN THAILAND

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Background: Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare form of cytotoxic T-cell lymphoma, characterized by primary cutaneous tissue involvement mimicking inflammatory panniculitis. Treatment for this disease is still under debated between conventional chemotherapy or immunosuppressive agents like cyclosporin and prednisolone.

Material and Methods: A multicenter retrospective study was conducted among adult patients who was diagnosed as subcutaneous panniculitis-like T-cell lymphoma from January 2013 to December 2020, in 15 medical centers in Thailand. The patient demographic data, treatment regimens which divided into conventional chemotherapy or immunosuppressive agents, and treatment outcomes were retrieved from the Thai lymphoma registry database. All of aspects were analyzed and compared between the treatment group.

Results: A total of 34 patients were reviewed in this cohort. The median age was 30 years (range;16–64) with female predominance (67.6%). The majority of patients was diagnosed as advanced stage of disease as Ann Arbor stage IV (58.8%). All patients presented with skin and subcutaneous involvement while one-fourth of them had extra-cutaneous lesions including liver (14.7%) and bone marrow (11%). B symptom was observed in 64% and elevated LDH level in 70.6% of the patients which represented the high disease burden. However, almost all of our patients were in good performance status (ECOG 1–2). For treatment options, 41% of the patients received conventional chemotherapy, mostly CHOP, while 38% received cyclosporin containing regimens. The overall response rate (ORR) was 64% in chemotherapy group and 76% in cyclosporin group, which was comparable. Precisely 57% and 76% of the patients in conventional chemotherapy and cyclosporin treatment, respectively, had complete remission. Patients with Ann Arbor stage IV were received conventional chemotherapy as first-line treatment for 69%, on the other hand, 31% received cyclosporin-based treatment, which was in complete remission around 60% on both groups. With median follow up time of 35.2 months, the overall survival and progression free survival were not reached in both groups.

Conclusions: Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare form of cytotoxic T-cell lymphoma which predominantly affects young female and usually presents with extranodal lesions especially skin and subcutaneous tissues, bone marrow, and liver. Patients were responded well to cyclosporin-based treatment both limited and advanced stages of the disease.

Keywords: chemotherapy, cyclosporin, Subcutaneous panniculitis-like T-cell lymphoma

Keyword: Cutaneous non-Hodgkin lymphoma

No conflicts of interests pertinent to the abstract.

622 | OPTIMISING HOLISTIC CARE OF WOMEN AT RISK OF OR LIVING WITH BIA-ALCL: A SURVEY OF UK HEALTH CARE PROFESSIONALS

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Introduction: Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) was classified by the World Health Organisation in 2016. As of December 2021 there have been 86 reported cases within the UK. Raising awareness amongst clinicians of this novel entity is crucial in order to provide effective clinical care.

Psycho-social support forms a vital arm of care, both for affected women but also for the now millions at risk or those considering new implants. This survey aims to assess the current awareness and experiences of health care providers potentially involved in the care of patients with BIA-ALCL with a particular focus on psycho-social support requirements.

Methods: We performed an online survey using categorical and open-ended questions. The questionnaire was distributed amongst professional associations that have an interest in the topic researched, e.g., The Association of Breast Surgeons (ABS), British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS). In addition the survey was distributed amongst multidisciplinary teams that are likely to encounter these patients, e.g. Breast and Lymphoma. The survey was designed in Qualtrics and sent via a link. Data has been collated and analysed within SPSS. Research approval was obtained from Leeds Beckett University.

Results: There were a total of 78 respondents who completed the survey. Breast surgeons made up the largest proportion of respondents (36%, 28/78) with over half of respondents having cared for a patient with BIA-ALCL (58% 42/78). The largest proportion of respondents reporting using ABS/BAPRAS joint guidelines in their clinical practice (46%, 36/78). High median confidence scores were reported in both diagnosing/managing, 7/10 (3) and having conversations with patients regarding BIA-ALCL, 7/10 (5) although a large range in responses was noted. The most frequently selected test to work up a case of suspected BIA-ALCL was 'core biopsy of any associated peri-implant mass' (82%, 64/78) with mammography the least selected (42%, 33/78). 45% (35/78) reported seeing women requesting reassurance or implant removal despite an absence of symptoms or signs of BIA-ALCL. The average degree of distress upon receiving a diagnosis was reported as 7/10 (2). 70% (54/77) of respondents felt patients diagnosed with BIA-ALCL or those awaiting test results would benefit from psychological support. Only 38 (29/76) % of respondents however, confirmed that breast implant patients have access to any psychological support as part of routine care.

Conclusion: This survey demonstrates that although there is relatively high confidence in managing and conducting discussions with patients regarding BIA-ALCL, there is a large variability amongst healthcare providers. The findings suggest there is urgent need for psycho-social support for both patients diagnosed with BIA-ALCL and asymptomatic women seeking reassurance.

Keyword: Aggressive T-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

D. Cunningham

Consultant or advisory role Ovibio on scientific advisory board
Research funding: Medimmune/AZ, Clovis, Eli Lilly, 4SC, Bayer, Celgene, Roche - institution recipient

PLASMA CELL NEOPLASMS AND AMYLOIDOSIS

623 | EXOSOME MIRNAS PROFILING IN SERUM AND PROGNOSTIC EVALUATION IN PATIENTS WITH MULTIPLE MYELOMA

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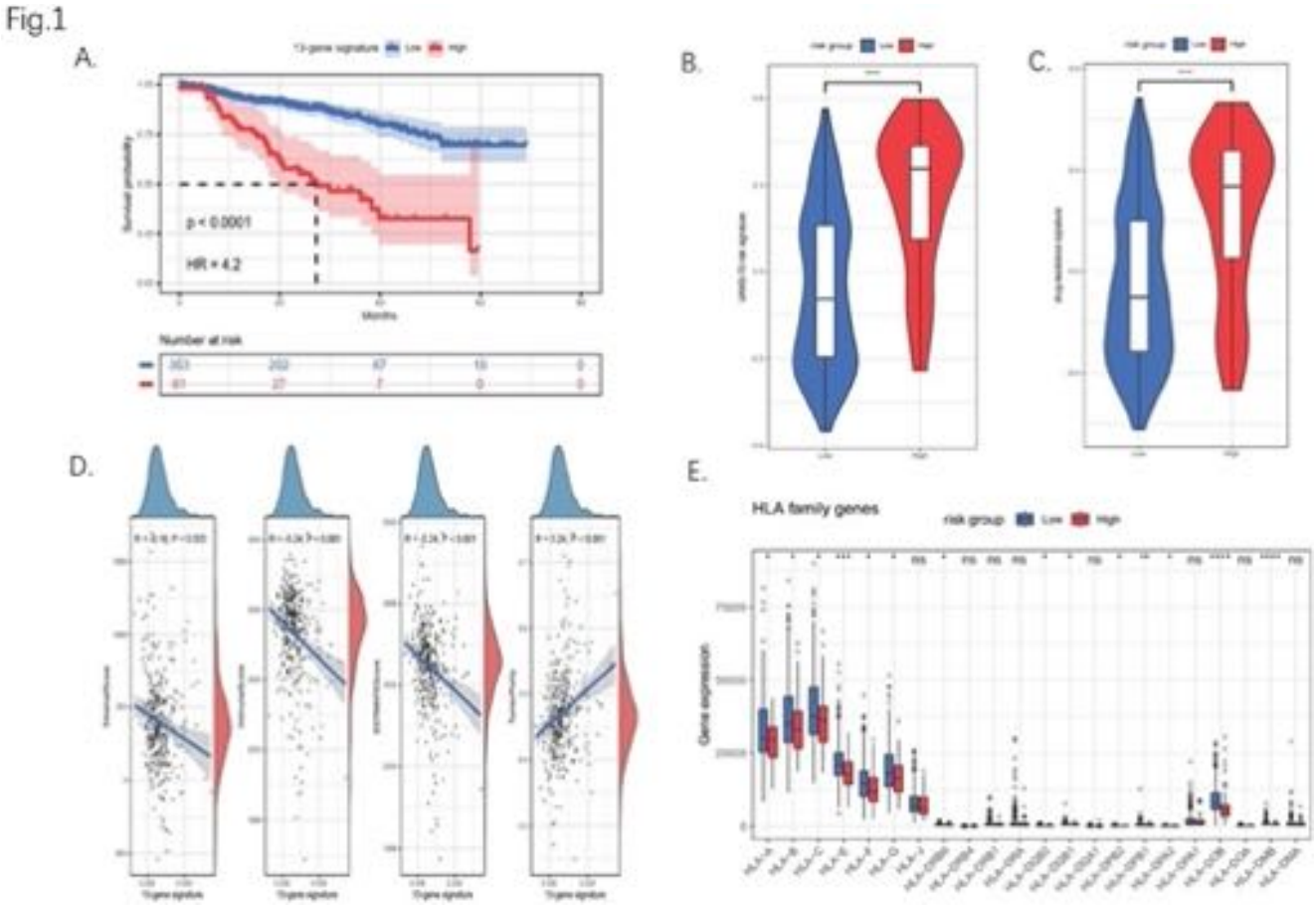
Introduction: Multiple Myeloma (MM) is an incurable hematological malignancy. Tightly crosstalk through microRNAs (miRNAs) carried by exosomes between the bone marrow microenvironment and MM cells plays pivotal roles in MM. Our study aimed to identify the expression profile of exosomal miRNAs (exo-miRNAs) in the serum of MM patients and investigate the regulation network and their potential functions.

Methods: Exosomes in serum from 19 newly diagnosed multiple myeloma patients and 9 healthy donors were isolated and the miRNA profile was investigated by small RNA sequencing. Differential expression of exo-miRNAs was calculated and target genes of miRNAs were predicted. CytoHubba was applied to identify the hub miRNAs and core target genes. The LASSO Cox regression model was utilized to develop the prognostic model, and the ESTIMATE immune score was calculated to investigate the correlation between the model and immune status in MM patients.

Results: Our study clarified 313 differentially expressed serum exo-miRNAs between MM patients and HD. GO analysis of target genes of differential miRNAs showed that these target genes are mainly involved in the critical biological processes related to MM pathogenesis such as proteasome-mediated ubiquitin-dependent protein catabolic process, indicating the indispensable roles of these miRNAs in MM pathogenesis.

Top six hub differentially expressed serum exo-miRNAs (hsa-miR-4728-5p, hsa-miR-455-3p, hsa-miR-6779-5p, hsa-miR-124-3p, hsa-miR-615-3p, and hsa-miR-7106-5p) were identified. 513 target genes of six hub exo-miRNAs were confirmed to be differentially expressed in MM cells in Zhan Myeloma microarray dataset. Functional enrichment analysis indicated that these target genes mainly involved mRNA splicing, cellular response to stress, and deubiquitination. Thirteen core exo-miRNA target genes were applied to create a novel prognostic signature to facilitate the risk stratification of MM patients, and two groups of MM patients with diverse outcomes were recognized (Figure 1A). The high-score patients identified by thirteen core genes signature displayed a higher 70 high-risk gene set (UAMS-70) score and the 56 drug-resistance genes set score, which might partly explain their inferior outcomes (Figure 1B–C). Additionally, our results suggest that the thirteen core genes signature model was highly correlated with the status of the immune microenvironment, and patients in the low-score group had higher immune cell



infiltration levels (Figure 1D). Besides, patients in the high-risk group displayed lower HLA family gene expression (Figure 1E).

Conclusion: Our study comprehensively investigates the exo-miRNA profiles in MM patients. A novel prognostic signature was constructed to facilitate the risk stratification of MM patients with distinct outcomes, which is associated with the immune microenvironment of MM patients as well.

Encore Abstract - previously submitted to EHA 2023

Keywords: Bioinformatics, Computational and Systems Biology, Diagnostic and Prognostic Biomarkers, Risk Models

No conflicts of interests pertinent to the abstract.

624 | KAPPA MYELOMA ANTIGEN (KMA) AND LAMBDA MYELOMA ANTIGEN (LMA) ARE EXPRESSED ON B CELL MALIGNANCIES AND ARE PROMISING NOVEL TARGETS ON MALIGNANT PLASMA CELLS

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Introduction: The kappa myeloma antigen (KMA) and the lambda myeloma antigen (LMA) are found on the surface of malignant plasma cells (PCs) in multiple myeloma (MM), other plasma cell dyscrasia patient bone marrow (BM) samples, human myeloma cell lines and in patient BM samples from plasmacytomas, lymphoplasmacytoid and B cell lymphoproliferative disorders (BLPD). KMA and LMA are not present on normal B cells in BM but are found on occasional mononuclear cells in tonsillar tissue and secondary mucosal lymphoid tissue. KappaMab is a therapeutic antibody that specifically targets KMA and a phase IIb study in combination with lenalidomide and dexamethasone has recently been completed. In early clinical trials, KappaMab was shown to have an excellent safety profile, with low-grade infusion-related reactions and no haematological toxicities. Two human therapeutic LambdaMabs (10B3 and 7F11) bind specifically to LMA expressed only on malignant cells in lambda restricted B cell diseases. Here we compare the expression of KMA and LMA to that of BCMA in MGUS, newly diagnosed MM and relapsed, refractory (RRMM) myeloma BM samples. We describe the difference in phenotype between KMA and LMA expressing malignant PCs and their enrichment in RRMM compared to early disease stages.

Methods: Patient BM samples (κ = 70 and λ = 40) were analysed using multiparametric FCM immunophenotyping with APC labelled LambdaMab (10B3) and KappaMab Fab'2 fragments, CD38, CD138, CD269 (BCMA), CD319 (SLAM F7), CD56 and CD45 monoclonal antibodies. PCs were identified by initial gating using CD38 and

CD138. LMA and KMA expression was determined and compared with the other cell markers.

Results: KMA was expressed on the majority of kappa restricted BM PCs from MGUS through to RRMM, on lymphoplasmacytoid cells in 2 out of 3 BM samples and in all 4 plasmacytoma BM samples. LMA was expressed on the surface of BM PCs in lambda restricted MGUS through to RRMM and in all 4 AL amyloidosis BM samples.

KMA and LMA antigen densities were both higher than BCMA in the RRMM population: KMA mean 1899 (range 468–7943) versus BCMA mean 1426 (range 350-2630) and LMA mean 2439 (range 263–6664) versus BCMA mean 817 (range 537–1065) molecules of PE/cell.

Conclusions: Although there are smaller numbers of samples from other B cell malignancies such as lymphoplasmacytoid, amyloidosis and BLPDs, we have demonstrated that KMA or LMA are expressed on malignant BM PCs. In the myeloma cases, the antigen density of both KMA and LMA was increased compared to BCMA on RRMM BM PCs, which suggests a clonal advantage of KMA and LMA expressing plasma cells that are resistant to standard of care treatments. These data suggest that KappaMab and LambdaMabs have therapeutic potential in RRMM where the combination of high antigen density and restriction of the target antigen to the malignant subpopulation of PCs may confer clinical benefit by retaining normal plasma cells following treatment.

Keywords: Immunotherapy, Multiple Myeloma

Conflicts of interests pertinent to the abstract

D. Gottlieb

Consultant or advisory role David sits on the Scientific Advisory Board for HaemaLogiX Ltd.

R. Dunn

Employment or leadership position: Employee at HaemaLogiX Ltd.
Stock ownership: Yes

625 | A PREDICTIVE MODEL FOR ULTRA-HIGH RISK IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: A SINGLE-CENTER STUDY IN CHINA

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Introduction: Although novel therapies have significantly improved the prognosis of multiple myeloma (MM) patients, there are still a subgroup of MM patients experienced early relapse or disease progression. To early identify the patients with compromised prognosis in our center, the study aimed to establish a predictive model for ultra-high risk (UHR) in MM.

Methods: A study from a tertiary hospital in western China analyzed the patients with newly diagnosed MM (NDMM) receiving bortezomib and/or lenalidomide-included regimens from January 2015 to June 2021. The last follow-up date was December 31, 2022. The patients were randomly divided (2:1) into training and validation cohorts, and the patients with progression-free survival (PFS) less than 12 months were defined as UHR. Univariate and multivariate Cox regression analyses were performed for clinical feature selection. Independent baseline factors were incorporated and scored to develop the predictive model. The UHR group was then defined beyond the optimal cut-off value of total scores.

Results: A total of 314 MM patients were enrolled and 102 (32.5%) patients underwent autologous hemopoietic stem cell transplantation (ASCT). The median time of follow-up was 36.6 months. Disease progression and death occurred in 178 (56.7%) and 69 (22.0%) patients. The median PFS (mPFS) was 36.5 months, and the median overall survival (mOS) was not reached. The mPFS of patients stratified into R-ISS III, R2-ISS III, R2-ISS IV, IMWG high-risk and mSMART double/triple hit was 23.8, 25.6, 10.0, 17.2 and 10.5 months, respectively. Among 54 patients at UHR, less than half of them could be identified by the aboved stratification systems. In the training cohort, elevated LDH, hypercalcemia, 1q21 gain/amplification (1q+) and the presence of extramedullary disease (EMD) showed significant association with UHR in NDMM. Referring to the results, the UHR predictive model was developed as 5 points for elevated LDH, 6 points for hypercalcemia, 7 points for 1q+ and 10 points for EMD. Patients with total scores of more than 12 points can be predicated as UHR. This model identified UHR and non-UHR groups with significantly different mPFS (9.8 v. s. 37.5 months, HR = 3.24, 95% CI:2.09-5.03, $P < 0.001$) and 5-year OS (63.3% vs. 83.8%, HR = 2.92, 95% CI: 1.47-5.81, $P = 0.002$). The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was 0.77, and in the validation cohort, the UHR model kept good discrimination (AUC: 0.79) at the latest follow-up.

Conclusions: In this study, elevated LDH, hypercalcemia, 1q+ and EMD were selected and scored to develop the UHR model for NDMM patients. At present, the extension of follow-up time and expansion of sample size in the validation cohort are still ongoing. External validity is also designed to verify the generalizability of the model.

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Keywords: Risk Models, Multiple Myeloma

No conflicts of interests pertinent to the abstract.

626 | **EARLY RELAPSE WITHIN 18 MONTHS (ER18) IS A POWERFUL DYNAMIC PREDICTOR FOR PROGNOSIS AND COULD REVISE STATIC RISK DISTRIBUTION IN PATIENTS WITH NEWLY-DIAGNOSED MULTIPLE MYELOMA**

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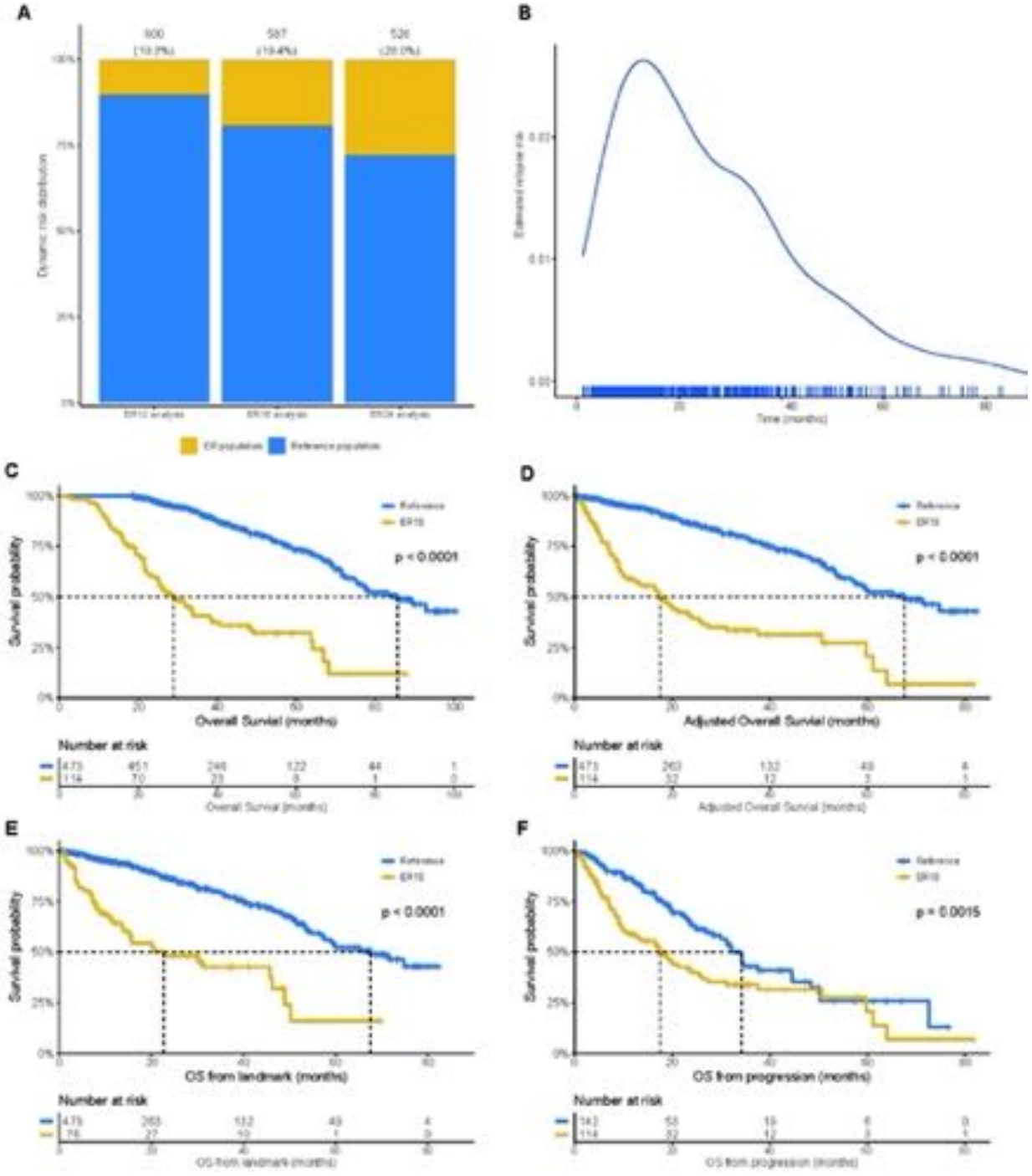
The duration of response to treatment is a major prognostic factor and early relapse (ER) strongly predicts inferior survival in multiple myeloma (MM) patients. But the definitions of ER in MM varied from study to study. In this study, we aimed to identify the best ER timepoint which we integrated with initial traditional risk features to formulate a novel prognostic classification incorporating both static and dynamic risk. The study was based on the National Longitudinal Cohort of Hematological Diseases in China (NCT04645199) and a total of 629 patients diagnosed with NDMM were included in this study.

Figure 2



We first summarized all studies about ER published to date and found that relapse within 18 months from the initial treatment or within 12 months from SCT was mostly used to define early PD in many studies. Our findings indicate that ER18 could effectively balance the bias of ER definitions for patients with or without ASCT, as well as fulfill all requirements for a dynamic risk predictor. The ER18 population (114/587; 19.4%) presented with more aggressive biologic features compared to a reference cohort ($P < 0.001$), with a significant short median overall survival (OS) of 28.9 months. We also described the specific transitions from static risk profile to dynamic risk distribution in our cohort and then constructed a mixed-risk pattern to identify four novel populations with distinct survival outcomes ($P < 0.001$). A total of 367 (67.0%) patients presented with at least one high-risk feature: those with ISS III stage, elevated LDH, and HRCAs were classified as baseline high-risk (BHR) group; 86 (23.4%) patients experienced ER18 and further defined as mixed high-risk (MHR) population, and the remaining patients were classified as static high-risk (SHR). Within patients without BHR features, the dynamic risk event (ER18) occurred in 21(11.6%) patients, defined as functional high-risk (FHR). As expected, the MHR population had the worst outcomes with a median OS of 25.9 months ($P < 0.001$). Of note, FHR patients had similar survival compared to SHR patients (OS: not reached vs. 71.4 months; $P = 0.235$; Figure 3B), supporting the importance of dynamic risk factor (ER18) as a prognostic factor and further suggesting that lack of durable response could exert an adverse impact on prognosis similar to baseline high-risk variables. Moreover, we confirmed that ER18 refined the predictive accuracy of the Revised International Staging System stage (R-ISS).

ER18 maintains its significance as a predictor of prognosis in the multivariate analysis even after adjustment for clinical stage, cytogenetics, therapeutic options, and response depth. The underlying correlation between clinical features at diagnosis and dynamic predictor (ER18) was demonstrated. Our results further indicated that ER18 was a refining factor for the R-ISS staging system and that the refined model could actualize a more valuable risk distribution.

Encore Abstract - previously submitted to EHA 2023

Keywords: Diagnostic and Prognostic Biomarkers, Multiple Myeloma, Risk Models

No conflicts of interests pertinent to the abstract.

627 | STEM CELL MOBILIZATION AND AUTOLOGOUS STEM CELL TRANSPLANTATION AFTER BENDAMUSTINE, PREDNISONE AND BORTEZOMIB INDUCTION IN MULTIPLE MYELOMA PATIENTS WITH RENAL IMPAIRMENT

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Background: High-dose therapy followed by autologous stem cell transplantation (ASCT) is the standard first line treatment for younger patients (<70 years) with multiple myeloma (MM). Approximately 20%–50% of all patients already display an impaired kidney function at diagnosis. However, MM patients with severe renal dysfunction are excluded from most ASCT studies. Bortezomib and bendamustine have both been identified as quickly acting and well-tolerated drugs for patients with MM-induced renal failure. In this retrospective study we analyzed the efficacy of a BPV induction therapy prior ASCT in newly diagnosed MM patients depending on the severity of renal impairment.

Methods: Between October 2008 and November 2019, 135 patients with newly diagnosed MM were treated with a BPV-induction therapy consisting of bendamustine 60 mg/m^2 on days 1 and 2, bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 and prednisone 100 mg on days 1, 2, 4, 8 and 11 followed by chemomobilization with cyclophosphamide (1-4 g/m^2) and ASCT.

Results: The majority of patients (n = 117; 87%) responded after the BPV-induction with median of 2 (range 1–6) cycles with 9 sCR (7%), 3 CR (2%), 12 nCR (9%), 39 VGPR (29%), and 54 PR (40%). Stem cell counts of CD 34+ ≥20 × 106/L in the peripheral blood were achieved in 131 (97%) patients after a median of 12 (range 9–17) days. Further four patients with poor stem cell mobilization on day 15 received additional plerixafor. After first ASCT ORR increased to 99% with 33 sCR (24%), 10 CR (7%), 32 nCR (24%), 41 VGPR (30%) and 17 PR (13%). With a median observation time of 51 months, median PFS was 47 months and 60 months OS was 67%. Transplant related mortality was 0.7% ($n = 1$). Patients were divided into four groups depending on the severity of renal impairment: group A 13 patients with eGFR <15 mL/min, group B 15 patients with eGFR 15–29 mL/min, group C 19 patients with eGFR 30–59 mL/min and group D 88 patients with eGFR ≥60 mL/min. At the time of diagnosis, 8 of 13 patients in group A were dialysis dependent. We observed no significant difference in the median PFS between patients with normal/mild (D), moderate (C), severe renal dysfunction (B) and renal failure/dialysis (A) (50 vs 47 vs 34 vs 24 months, p = 0.053) and in the 60 months OS (69 vs. 72 vs 58 vs. 70%, $p = 0.23$). In 23 of 38 patients with eGFR ≤50mL/min, we found rapid recovery of renal function during the first two BPV cycles, with four of eight dialysis-dependent patients reverting to independence. BPV induced a rapid reduction in light chain production in the first few days of treatment, potentially

preventing the development of irreversible renal failure. Following the ASCT, the renal response rate improved from 61% after BPV induction to 74% with 18 CRrenal (47%), 3 PRrenal (8%) and 7 MRrenal (18%).

Conclusions: Our results indicate that the BPV induction followed by high-dose therapy and ASCT is feasible, effective and well tolerated in patients with MM-induced renal failure.

Encore Abstract - previously submitted to EBMT 2023

Keywords: Combination Therapies, Multiple Myeloma, Stem Cell Transplant

No conflicts of interests pertinent to the abstract.

628 | RADIATION THERAPY AS A BRIDGING AND SALVAGE STRATEGY IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA UNDERGOING BCMA-TARGETED CAR T-CELL THERAPY

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Introduction: Radiation therapy (RT) may be a useful bridging and/or salvage approach prior to and following B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T-cell therapy in patients with relapsed or refractory multiple myeloma (MM). Thus, we sought to report our early experience evaluating the potential role of RT in bridging and salvage settings in MM patients undergoing CAR T-cell therapy.

Methods: A multi-institutional retrospective study was conducted for consecutive MM patients who received CAR T-cell therapy between 2018 and 2022. Patients who were administered bridging RT pre-CAR T and salvage RT post-CAR T failure were identified and analyzed using descriptive and statistical analysis.

Results: We retrospectively reviewed 13 patients who have been treated with RT pre- and/or post-CAR T-cell therapy infusion at two tertiary care centers [5 patients received bridging RT pre-CAR T, 4 patients received salvage RT post-CAR T failure, and 4 patients received both bridging and salvage RT]. A total of 17 sites were treated with bridging-RT with a median dose of 20 Gy (range, 4–24 Gy) and a median of 5 fractions (range, 1–12 fractions). Twelve sites were treated with salvage RT with a median dose/fractionation of 20 Gy (range, 4–30 Gy) and 5 fractions (range, 1–12 fractions). No worsening in CAR T-related toxicities occurred among the patients who were treated with bridging RT, and no significant RT-related toxicities were observed post-bridging or salvage RT. For the entire cohort, the median overall survival was 16.2 months (95% CI: 8.6 months-not reached), and the median progression-free survival was 4.1 months (95% CI: 1.07 months-not reached). The local control rate for patients receiving bridging RT and/or salvage RT was 100%, with a median follow-up after each RT course of 7.3 months.

Conclusion: Our findings suggest that using RT as a bridging and salvage strategy is safe and feasible, and offers excellent local control among relapsed/refractory MM patients treated with CAR T-cell therapy infusion. Future larger studies with translational correlatives are required to assess the optimal role of RT in these settings.

Keywords: Cellular therapies, Multiple Myeloma

No conflicts of interests pertinent to the abstract.

629 | UPFRONT RADIATION THERAPY FOR POST-STEM CELL TRANSPLANT MULTIPLE MYELOMA PATIENTS WITH OLIGO-RELAPSE/PROGRESSIVE DISEASE: FACTORS ASSOCIATED WITH FAVORABLE OUTCOMES

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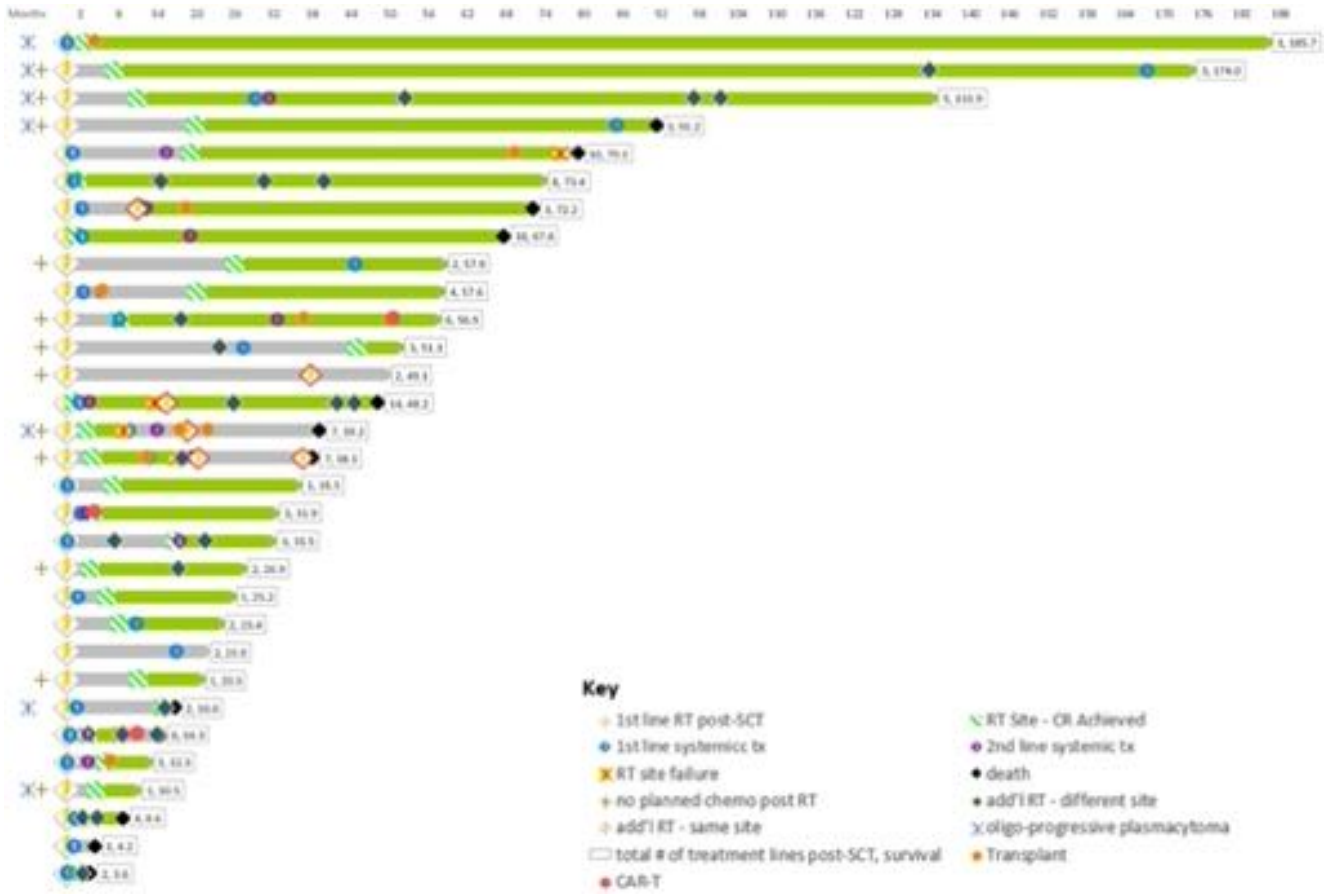
Introduction: MM patients (pts) remaining refractory or presenting with a relapse after stem cell transplant (SCT) may have a dismal prognosis. Yet, RT may still provide an effective tool for control of localized disease. We report on the impact of RT for the treatment of oligo-relapse and oligo-progressive plasmacytomas post-SCT and factors associated with favorable long-term outcomes.

Methods: We identified 31 consecutive MM pts who were treated with upfront RT for oligo-relapse or oligo-progressive plasmacytoma post-SCT between 2000 and 2021. We excluded pts who began systemic therapy for evidence of MM progression pre-RT, >10% bone marrow involvement, >3 sites of active disease at time of RT, or never achieved a stringent CR (sCR), complete response (CR), very-good partial response (VGPR), or serologic CR post-SCT. The International Myeloma Working Group's response criteria was used to assess transplant and post-RT response.

Results: Figure 1 summarizes post-SCT treatment characteristics. Of the 27 pts with radiographic evaluation pre-SCT, 67% (18) were assessed with PET, 22% (6) skeletal survey, 3.7% (1) MRI/CT, 3.7% CT scan, 3.7% (1) X-ray; of the full cohort, 48% (13) pts were noted to have radiographic progression. 23% (7) pts had sCR, 23% (7) CR, 10% (3) serologic CR, and 45% (14) VGPR to SCT; of the 18-pts assessed radiographically (including BM bx and/or labs) post-SCT, 67% (12) were in radiographic CR at time of re-staging. Median time from SCT to oligo-relapse plasmacytoma (new sites [never active pre-SCT] of disease) (20, 64.5%) was 31 months (3.2–117.5) and 9 months (3.4–



15.9) for oligo-relapse from pre-existing plasmacytomas that were not active prior to SCT (4, 12.9%); 22.6% (7) are oligo-progressive plasmacytomas (active prior to SCT). 94% (29) pts had pre-RT PET, median SUV of targeted plasmacytoma was 4.4 (2.6–7.2). Solitary bone (77%) and extramedullary (23%) plasmacytomas were treated to median dose of 30 Gy (8–19 Gy). 77% (24) had PET at 1st RT response scan and 42% (13) achieved a CR at 1st scan. Of the 18 that did not achieve CR at 1st response, 15 went on have CR in median time of 7 months (1.7–44.5) and 1 received additional RT for stable disease 27 months post-RT (response unavailable for 2 remaining pts). 87% (27) pts received systemic therapy post-RT in a median time of 3.2 months (.1–165.1) and 4 (13%) did not receive additional systemic treatment post-RT; median number of treatment lines post-RT is 3 (1–17). Median survival time for full cohort was 38 months (3.5–37.9).

Conclusions: RT to limited refractory or relapsed MM post-transplant combined with modern systemic therapies is an effective therapeutic tool. Prospective studies with defined imaging criteria will help in identifying the best candidates for this approach. At the meeting, we will present further analysis on the relationship between radiographic and biochemical features and outcome with upfront RT approach.

Keyword: Multiple Myeloma

Conflicts of interests pertinent to the abstract

B. Imber
Honoraria: GT Medical Technologies

630 | INTERMEDIATE-DOSE ARAC+G-CSF IS MORE EFFECTIVE THAN CY+G-CSF AND PLERIXAFOR+G-CSF IN HEMATOPOIETIC STEM CELL MOBILIZATION IN POOR MOBILIZERS

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Background: High dose chemotherapy with autologous hematopoietic stem cell transplantation (autoHSCT) is an effective treatment option for lymphomas and multiple myeloma (MM). Peripheral blood stem cell (PBSC) is associated with faster hematological reconstitution and engraftment compared to bone marrow stem cell and preferentially used as a hematopoietic stem cell source. Despite using novel agents and improving algorithms, there are patients who fail to mobilize sufficient number of CD34+ cells. Thus, finding new approaches is still a current challenge.

Table 1. Patients characteristics	
Median age, years	52 (22–66)
Sex: male/female	39/55 (46%/64%)
Mobilization regimen	
ID-AraC + G-CSF	28 (33%)
Cy + G-CSF	28 (33%)
Plerixafor + G-CSF	29 (34%)
Diagnosis	
B-cell lymphoma	29 (34%)
T-cell lymphoma	12 (14%)
Hodgkin lymphoma	14 (17%)
MM	30 (35%)

Based on these considerations we aimed to retrospectively assess the efficacy of Intermediate-dose (ID) AraC+G-CSF as mobilization regimen in comparison to Cy+G-CSF and Plerixafor+G-CSF in patients with hematological malignancies.

Methods: A retrospective analysis was performed on 85 consecutive lymphoma and MM patients who met at least one criterion of "predicted poor mobilizers" according to classification proposed by Gruppo Italiano Trapianto di Midollo Osseo [1] (Table 1).

From April 2019 to August 2022 patients were mobilized either with ID-AraC+G-CSF or Cy+G-CSF or Plerixafor+G-CSF. Ara-C was administered at a dose of 0.4 g/m^2 twice daily on days 1 and 2 (total dose 1.6 g/m^2) plus G-CSF 10 mg/kg/day from day 7 until the end of PBSC collection. Cy was administered at a dose of 2–4 g/m^2 on day 1 plus G-CSF 10 mg/kg/day from day 5 until the end of PBSC collection. Plerixafor was given at a dose of 0.24 mg/kg/day from day 5 of treatment with G-CSF 10 mg/kg/day.

The apheresis procedure was started when CD34+ cells reached 20 $\times$ 10^6/L in peripheral blood. The target CD34+ cell yield of 2.0 $\times$ 10^6 CD34+/kg for lymphoma patients and 4 $\times$ 10^6 CD34+/kg for MM patients.

Results: Peak concentrations of circulating CD34+ cells in peripheral blood were significantly higher in ID-AraC+G-CSF (median 153, IQR 106–334) compared to Cy+G-CSF (median 129, IQR 74–355) and Plerixafor+G-CSF (median 33, IQR 28–39, $p = 0.005$). The median number of collected CD34+ cells was also higher in patients mobilized with ID-AraC+G-CSF (10.2, IQR 5.2–16.9) vs with Cy+G-CSF (7.2, IQR 4.4–9.9) or Plerixafor+G-CSF (2.5, IQR 1.4–4.0, $p < 0.0001$). A single apheresis was sufficient to collect the target number of CD34+ cells in 96% patients in the Ara-C group compared to 46% in the Cy group and 76% in the Plerixafor group ($p < 0.0001$).

Conclusion: Intermediate dose AraC+G-CSF is more effective for stem cell mobilization than Cy+G-CSF or Plerixafor+G-CSF in patients who are at risk of mobilization failure. ID-AraC could be a preferable mobilization regimen in this setting.

Encore Abstract - previously submitted to EHA 2023

Keywords: Chemotherapy, Stem Cell Transplant, Therapeutics and Clinical Trials in Lymphoma - Other

No conflicts of interests pertinent to the abstract.

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631 | AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA WITH DIALYS-DEPENDENT RENAL IMPAIRMENT

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Introduction: The one of the most frequent complications of multiple myeloma (MM) is renal impairment (RI). At the diagnosis time in 2%–4% of patients with newly diagnosed MM develop dialysis-dependent RI. That is associated with early mortality and a high complications' incidence.

Aim: To compare PFS and OS depending on the achievement of renal response and autoHSCT in patients with newly diagnosed MM develop dialysis-dependent RI.

Materials and methods: 39 patients with newly diagnosed MM III B stage (Durie-Salmon) with dialysis-dependent RI for the period from 2000 to 2020 are included in this study. 58 years is the median age (range 36 to 76), 24 (61.5%) of patients were male. In accordance with the criteria of IMWG-2014 was established the diagnosis. In 17 (43.6%) patients was performed cytogenetic examination. 4 (10.2%) patients have high–risk translocation t (4;14). The median CKD-EPI was 7 ml/min/1.73 m^2 (ranged 2 to 10 ml/min/1.73 m^2), median creatinine level was 631 mkmol/L (range 448 to 2138) at the disease onset. The following programs: CyBorD – 10 (25.6%), VCP – 6 (15.4%), CP – 14 (35.9%) VAD – 7 (17.9%), VMCP – 2 (5.1%) – were used as induction therapy.16 patients (41%) were received bortezomib-containing regimens. For autoHSCT the candidates were 30 (77%) patients. In 8 (20.5%) patients was performed high-dose melphalan (140–200 mg/m^2) with autoHSCT, in 3 (7.7%) cases – tandem autoHSCT. After 3–4 courses of induction therapy and on the 100th day after autoHSCT was evaluated an antitumor response. Using the Statistica program (version 10.0) were subjected the results of the study to statistical processing. Using the Kaplan–Meier method was carried out the survival analysis.

Results: During induction therapy 25 patients (64.1%) achieved renal response: no response – 14 (35.9%) patients, minimal response -14 (35.9%) patients, partial response – 10 (25.6%) patients, complete response – 1 (2.6%) patient. With an improvement in the indicators

median of 3-year PFS 61.1% (95%CI 43.7, 76.1) vs. 17.7% (95% CI 6.8, 23,9) (p = 0.045), median 3-year OS 72.2% (95%CI 58.2, 86,1) vs. 38.1% CI (27.6, 48,2) (p = 0.049) respectively was associated the achievement of any renal response.

To compare with patients who were the candidates for autoHSCT, but didn't undergo autoHSCT: median 3-year PFS 17,9% (CI 9.7, 31,2), 3-year OS – 33,7% (CI 16.7, 57.3) ($p = 0,036$) – median 3-year PFS in patients who underwent autoHSCT was 48,6% (CI 35.8, 67,2), median 3-year OS – 67,2% (CI 46.8, 78.9). There wasn't mortality associated with transplantation.

Conclusions: Achieving at least a minimal renal response during induction therapy and performing autoHSCT improve the PFS and OS in patients with newly diagnosed MM with dialysis-dependent RI.

Keywords: Multiple Myeloma, Stem Cell Transplant

No conflicts of interests pertinent to the abstract.

CAR-T (CELLULAR THERAPIES)

632 | PHASE-2 FIRST-IN-INDIA INDUSTRY STUDY OF VARNIMCABTAGENE AUTOLEUCEL (IMN-003A) IN RELAPSED REFRACTORY B CELL MALIGNANCIES: IMAGINE STUDY B-NHL SUBANALYSIS

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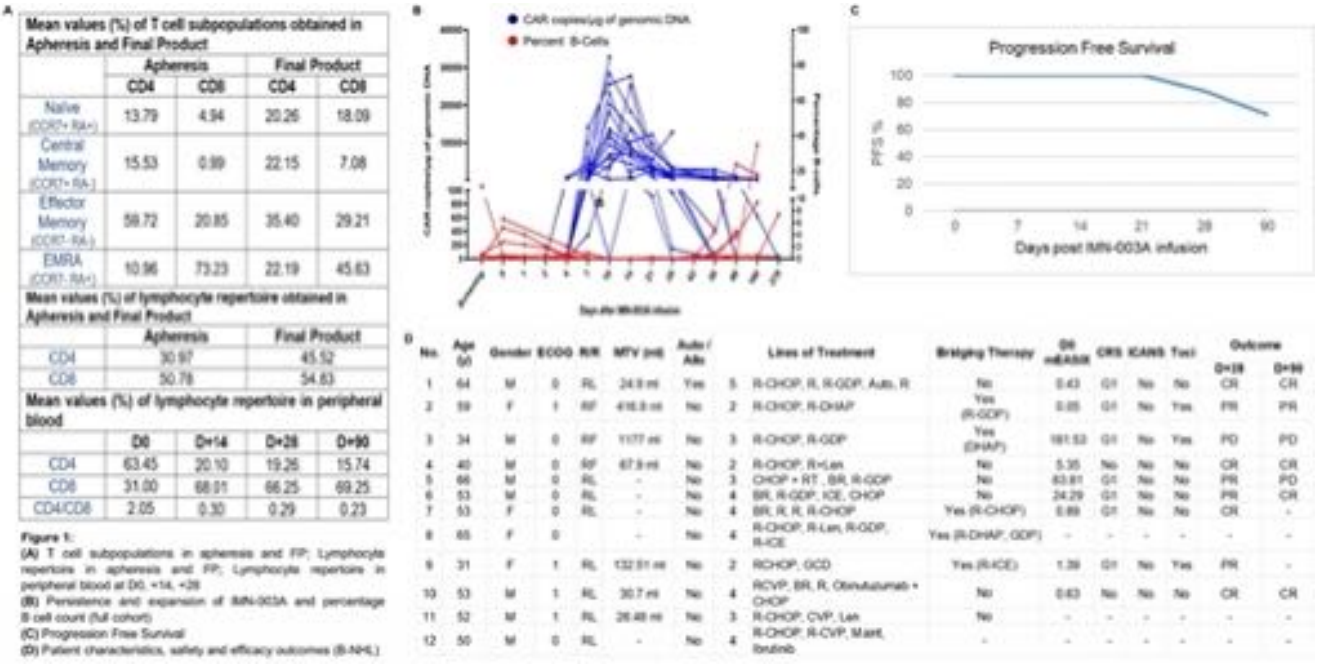
Introduction: Varnimcabtagene autoleucel (IMN-003A) is an autologous CD19 directed CAR-T with 4-1BB co-stim domain and A3B1 binder, a non-FMC63 murine scFv, manufactured in India for phase 2 study in patients (pts) with relapsed / refractory (r/r) B cell malignancies (CTRI/2022/03/041162). Target dose (B-ALL: 1×10^6 CAR+ cells/kg; B-NHL: 5×10^6 CAR+ cells/kg) was infused as 3 fractions (10%, 30%, 60%) after Flu-Cy lymphodepletion. B-NHL subanalysis is presented here.

Methods: Pts ≥ 18 yrs with r/r B-NHL, measurable disease, ≥1 prior regimen and ECOG 0-1 were eligible. IMN-003A persistence was evaluated by ddPCR. Manufacturing was in CliniMACS Prodigy. CAR-T % transduction and T cell subsets were analyzed by flow. Primary objectives were overall response rate (ORR: CR + PR; IWG criteria) at day +90, and occurrence of adverse events.

Results: Of 23 pts in study, 11 pts with B-NHL (median 53 yrs, range 31–66) underwent apheresis with 100% manufacturing success (median time 15d; range 11–27). Two needed second apheresis. Mean % transduction was 28.27% (range 8.50–51.07) with median transgene copies / genome of 2.36 (range 0.76–4.16). Mean CD4/CD8 ratio was 0.31 (apheresis); 0.62 (final product FP); 2.05 (Day 0) and 0.23 (Day 90) with reversal post infusion. Mean proportion of naïve cells (CCR7+ RA+) was >35% in FP (Fig 1A). Median Product Doubling time was 1.03d (range 0.88–2.12) and Apheresis to Infusion time was 30d (range 21–95).

Max IMN-003A expansion (Tmax) was at median 10d (range 7–21) with median Cmax 122,029 CAR copies / µg gDNA (range 24,624–284,498). IMN-003A persistence was 100% at D+28 and 40% at D +90 (range 28–NR) with concurrent B cell aplasia (Fig 1B) range 90–



A

Mean values (%) of T cell subpopulations obtained in Apheresis and Final Product	Apheresis		Final Product	
	CD4	CD8	CD4	CD8
Naive (CCR7+ RA+)	13.79	4.94	20.26	18.09
Central Memory (CCR7+ RA-)	15.53	0.89	22.15	7.08
Effector Memory (CCR7- RA-)	59.72	20.85	35.40	29.21
EMRA (CCR7- RA+)	10.96	73.23	22.19	45.63

Mean values (%) of lymphocyte repertoire obtained in Apheresis and Final Product	Apheresis	Final Product
CD4	30.97	45.52
CD8	50.78	54.83

Mean values (%) of lymphocyte repertoire in peripheral blood	D0	D+14	D+28	D+90
CD4	63.45	20.10	19.25	15.74
CD8	31.00	68.01	66.25	69.25
CD4/CD8	2.05	0.30	0.29	0.23

Figure 1:
(A) T cell subpopulations in apheresis and FP; Lymphocyte repertoire in apheresis and FP; Lymphocyte repertoire in peripheral blood at D0, +14, +28
(B) Persistence and expansion of IMN-003A and percentage B cell count (full cohort)
(C) Progression Free Survival
(D) Patient characteristics, safety and efficacy outcomes (B-NHL)

B

C

D

No.	Age (y)	Gender	ECOG	R/R	MTV (ml)	Auto / Allo	Lines of Treatment	Bridging Therapy	D0 mBAIDE	CRS	ICANS	Toci	Outcome D+28	Outcome D+90
1	64	M	0	RL	24.9 ml	Yes	5 R-CHOP, R, R-GDP, Auto, R	No	0.43	G1	No	No	CR	CR
2	59	F	1	RF	416.8 ml	No	2 R-CHOP, R-DHAP	Yes (R-GDP)	0.05	G1	No	Yes	PR	PR
3	34	M	0	RF	1177 ml	No	3 R-CHOP, R-GDP	Yes (DHAP)	181.53	G1	No	Yes	PD	PD
4	40	M	0	RF	67.9 ml	No	2 R-CHOP, R+Len	No	5.35	No	No	No	CR	CR
5	66	M	0	RL	-	No	3 CHOP + RT , BR, R-GDP	No	63.81	G1	No	No	PR	PD
6	53	M	0	RL	-	No	4 BR, R-GDP, ICE, CHOP	No	24.29	G1	No	No	PR	CR
7	53	F	0	RL	-	No	4 BR, R, R, R-CHOP	Yes (R-CHOP)	0.89	G1	No	No	CR	-
8	65	F	0		-	No	4 R-CHOP, R-Len, R-GDP, R-ICE	Yes (R-DHAP, GDP)	-	-	-	-	-	-
9	31	F	1	RL	132.51 ml	No	2 RCHOP, GCD	Yes (R-ICE)	1.39	G1	No	Yes	PR	-
10	53	M	1	RL	30.7 ml	No	4 RCVP, BR, R, Obinutuzumab + CHOP	No	0.43	No	No	No	CR	CR
11	52	M	1	RL	26.48 ml	No	3 R-CHOP, CVP, Len	No	-	-	-	-	-	-
12	50	M	0	RL	-	No	4 R-CHOP, R-CVP, Mant, Ibrutinib	-	-	-	-	-	-	-

NR. CD4+ T cell count recovery (>200/μL) was seen at median of 24.5 days (range 7- 42) post infusion.

Of 9 pts infused, 4 (44.4%) needed bridging therapy (patient characteristics in Figure 1D). Median follow-up was 99 days (range 58–226).

Overall response rate (ORR) was 88.8% at D+28 and 71.4% at D+90. Median time to first response was 28 days.

Median progression-free survival (PFS) and overall survival (OS) were not reached (Figure 1C).

AESIs reported were CRS (Grade [G] 1 77.8%; G3+ 0%; overall 77.8%); ICANS (G1 0%; G3+ 0%; overall 0%); hypogammaglobulinemia (8/9, 5 recd IVIg) neutropenia (G3+ 100%); anemia (G3+ 55.6%); and thrombocytopenia (G3+ 22.2%). CRS median onset was D+3 and duration 3 days. No G3+ ICANS was reported. Tocilizumab usage was in 33.3% pts (majority for persistent G1 CRS). There was no treatment related mortality with one death due to disease progression.

Conclusions: This First-In-India Industry study (IMAGINE) for varnimcabtagene autoleucel (IMN-003A) in B-NHL has demonstrated 100% manufacturing success with excellent safety and efficacy outcomes and durable responses including absence of neurotoxicity. This offers a significant benefit for patients in India.

The research was funded by: Immuneel Therapeutics Private Limited

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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633 | PRELIMINARY DATA FROM A FIRST-IN HUMAN PHASE II STUDY OF SEQUENTIAL USE OF SELINEXOR AND CD19 CART THERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN LYMPHOMA

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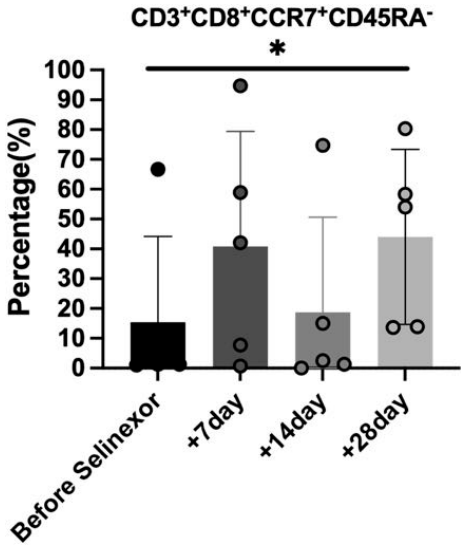
Background: Preclinical trial has demonstrated that sequential use of Selinexor and Anti-CD19 directed chimeric antigen receptor modified T-Cell therapy (CART19) cells might improve the anti-tumor efficacy of CART 19 cells against lymphoma cells. However, the efficacy and safety of CART19 combined with Selinexor in lymphoma patients is unknown. We report preliminary data from a phase 2 trial of sequential use of Selinexor and CART19 in patients with relapsed or refractory B-cell non-Hodgkin lymphoma (R/R B-NHL).



Methods: We performed a multicenter, prospective, phase II, open-label clinical study of sequential use of Selinexor and CART19 in R/R B-NHL. Patients received Selinexor as a bridging therapy (40–60 mg) with a weekly for three weeks prior to CART19 infusion. Over all response (ORR), duration of response (DOR) and safety were evaluated as primary objectives. This study is registered with ClinicalTrials.gov, NCT05322330.

Results: Between February 10, 2022, and February 10, 2023, 6 patients were enrolled. Four patients with diffuse large B-cell lymphoma, one mantle cell lymphoma and one Burkitt lymphoma received Selinexor 40mg and CART19 treatment. The median age was 55.5 years (range 34–77), 3 (50.0%) of 6 patients had refractory disease, 5 (83.3%) of 6 patients had extranodal involvement and the median prior systemic therapy was 2 (range 2–5), 5 (83.3%) of 6 patients had evaluated LDH prior to Selinexor administration. Median on-study follow-up was 9.68 months (range 2.53–12.17). 4 (66.7%) of 6 patients had an overall response. Cytokine release syndrome (CRS) was the most common adverse event, occurring in all 6 (100.0%) patients [66.7% was grade 1–2 and 33.3% was grade 3]. No neurotoxicity was observed. The most common grade 3–4 adverse events were neutropenia (5 [83.3%] of 6 patients), thrombocytopenia (4 [66.7%]), and anemia (3 [50.0%]). No treatment-related grade 5 adverse event occurred. Furthermore, our data showed that the use of Selinexor resulted in a higher proportion of $CD8^+$central memory T cell phenotypes ($P = 0.04$) while having no effect on $CD4^+$ central memory T cell phenotypes (Figure 1).

Conclusion: These results demonstrated that sequential use of Selinexor and CART19 in R/R B-NHL is effective and well tolerated in patients with R/R B-NHL. This study is ongoing and patients being recruited, more results should be evaluated in future.

Encore Abstract - previously submitted to ASCO 2023

Keywords: Cellular therapies, Combination Therapies, Ongoing Trials

No conflicts of interests pertinent to the abstract.

634 | DURABLE LONG-TERM REMISSION IN HIGH-RISK RELAPSE REFRACTORY LYMPHOMA—20 YEARS' EXPERIENCE OF ALLOGENEIC HAEMOPOIETIC STEM CELL TRANSPLANT IN SINGAPORE

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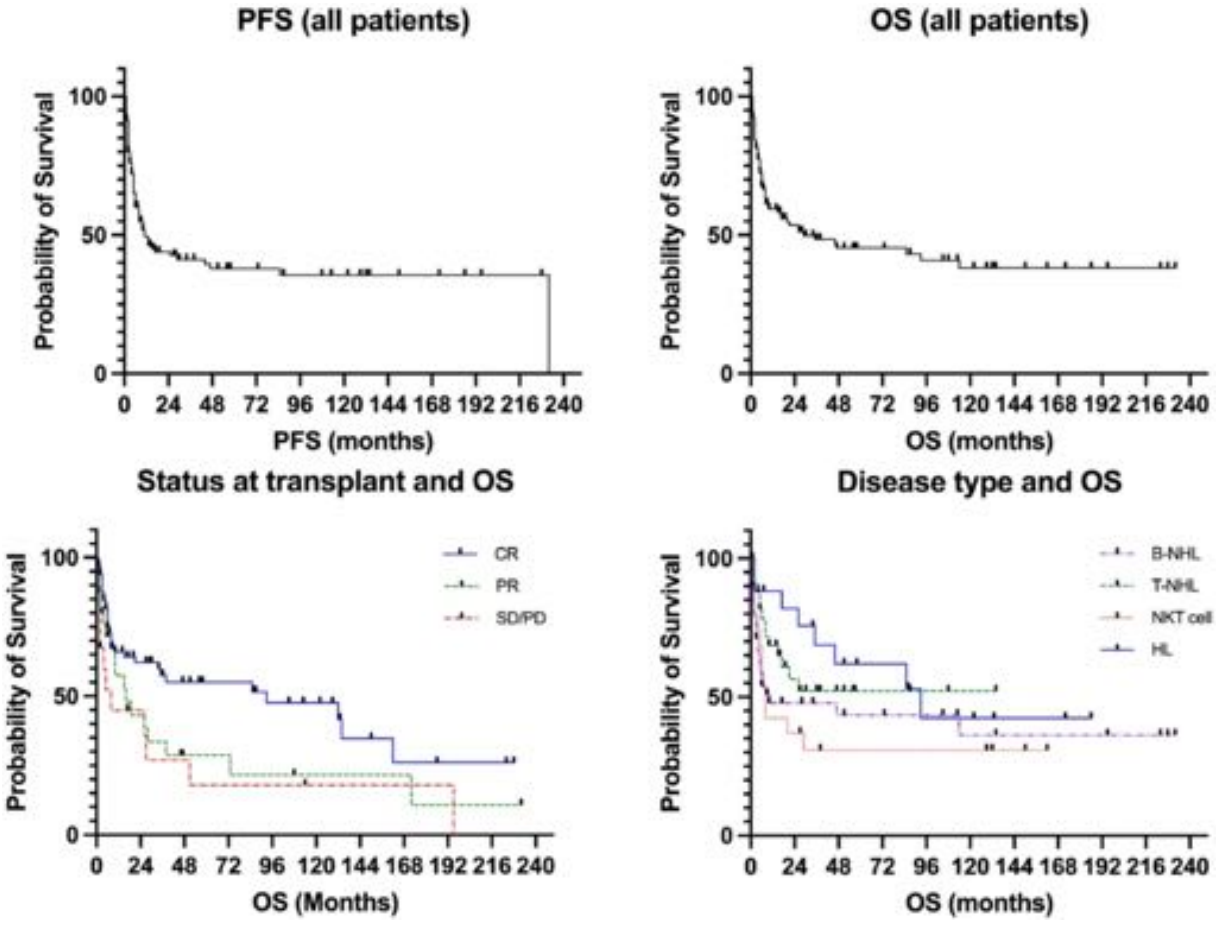

Background: Allogeneic hematopoietic stem cell transplantation (AlloHSCT) is a curative option for those who have high risk relapsed/refractory lymphoma in the era of novel and cellular therapies including CAR-T cell. There is a paucity of data evaluating the long term outcomes of AlloHSCT in Asian lymphoma patients. We performed a retrospective analysis of 20 years to evaluate the prognostic factors and outcomes of AlloHSCT for lymphoma patients in Singapore.

Methods: We evaluated 121 lymphoma patients (both non-Hodgkin (NHL) and Hodgkin lymphoma (HL)) from two major transplant centres in Singapore who had AlloHSCT over a 20-year period (2003–2022).

Results: The 121 patients have a median age of 41 (range 16–71). Diagnoses include B-NHL ($N = 41$, diffuse large B cell lymphoma $n = 21$, follicular lymphoma $n = 2$, mantle cell lymphoma $n = 6$, primary mediastinal B cell lymphoma $n = 5$, chronic lymphocytic leukemia $n = 7$), T-NHL ($N = 38$, peripheral T cell lymphoma $n = 32$, other T-NHL $n = 6$), NK T cell ($N = 24$) and HL ($N = 18$). 84% received reduced intensity conditioning (RIC), and 27.3% had a previous transplant. Donor types include matched sibling donor ($N = 54$), matched unrelated donor ($N = 35$), Haplo-identical donors ($N = 23$) and Cord blood ($N = 9$). With a median duration of follow up of 56 months (range 0–232 months), the 4-year progression free survival (PFS) and overall survival (OS) were 38% and 45% respectively. The non-relapse mortality was 11.6% at day 100 and 24% at 1 year. The cumulative incidence of acute graft-versus-host disease (GvHD) was 36.4% with 5 patients having grade IV acute GvHD. On univariate analysis, patients who were in complete remission (CR) at the time of AlloHSCT and those who have been given RIC had improved OS.

Subset analyses showed that the outcomes of AlloHSCT for relapsed/refractory Hodgkin lymphoma were the most favourable (4-year PFS and OS at 61.2% and 62% respectively), whereas patients with T-NHL, B-NHL and NK T cell lymphoma had lower survival rates (4-year PFS 35%, 44%, 19%; 4-year OS 52%, 43%, 30% respectively).

Conclusions: AlloHSCT resulted in long term disease control in patients with high risk relapsed/refractory lymphomas especially for HL. It has a long track record and plays a crucial role despite the advent of novel and cellular therapies.

Keyword: Stem Cell Transplant

No conflicts of interests pertinent to the abstract.

635 | REMISSION AFTER CAR T-CELLS: DO PATIENTS RECOVER A NORMAL LIFE?

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Introduction: CD19 CAR T-cells can induce prolonged remission in a significant number of patients with relapse/refractory (R/R) lymphoma. However, little is known about patients' life after CAR T-cell therapy. Here, we conducted a prospective study to evaluate health-related quality of life (HRQol), as well as physical, social and professional outcomes after CAR T-cell therapy.

Methods: This prospective study was conducted at the University Hospitals of Rennes and Toulouse (France). All adult patients with R/R lymphoma treated with CAR T-cells were eligible. HRQol changes were assessed using the FACT-Lym questionnaire. Other questionnaires evaluated cognitive state (FACT-Cog), fatigue (FACT-Fatigue), anxiety and depression (HAD scale), post-traumatic stress disorder (PTSD), and sexuality (Vican). Questionnaires were collected at baseline (before leukapheresis), immediately before CAR-T infusion, 3 and 6 months after CAR T-cell infusion. Patients were censored in case of relapse or death. Among patients in remission after 12 months, professional, physical, sexual and global life information were collected.

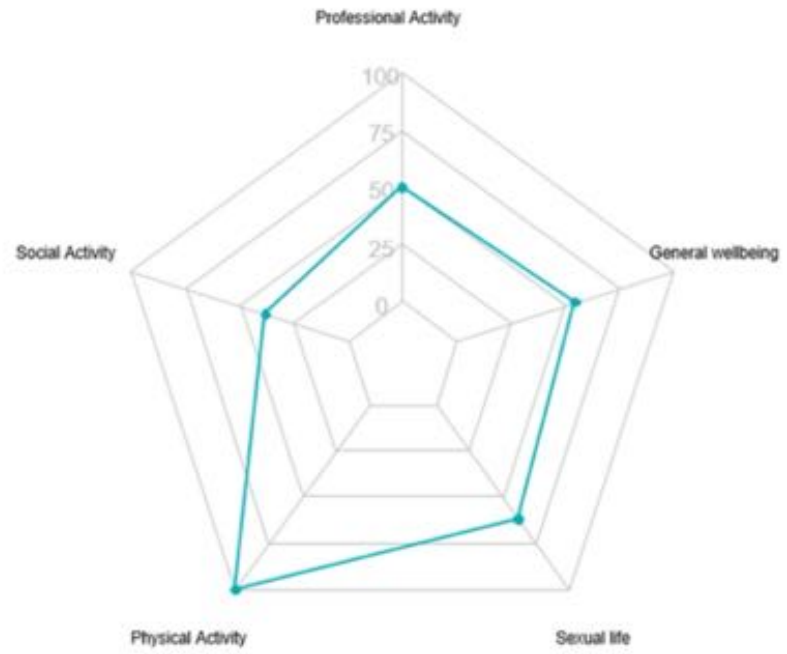
Results: From March 2020 to August 2022, 59 patients were included in the study (46 LBCL, 5 MCL, 8 FL). Median age was 63 years (range, 19–78). Patients were treated with axi-cel ($N = 37$), tisa-cel ($N = 18$) or brexu-cel ($N = 3$). The median follow-up after CAR T-cell infusion was 11 months. There were 53 and 38 still in remission at 3 and 6 months after CAR T-cell infusion, respectively. The FACT-Lym score showed a clinically relevant improvement of HRQol, with a mean change from baseline of 10.9 points (95%CI 5.8; 16.1) and 12.2 (95%CI 4.2; 20.1), respectively. The fatigue subscale showed a clinically relevant improvement at 3 and 6 months, with a mean change from baseline of 5.9 points (95%CI 2.9; 8.8) and 4.7 (95%CI 0.2; 9.2), respectively. The FACT-Cog score did not show any clinically relevant change. The HAD score showed that 43% and 24% of patients presented anxiety and depression at baseline, respectively, versus 26% and 7% after 6 months. Overall, 26% of patients presented a significant PTSD (i.e., >44) at 6 months.

Among patients in remission beyond 12 months ($N = 22$) after CAR T-cell infusion (Figure):

- 54.5% of the patients considered that their life was back to normal (before lymphoma diagnosis);
- 68.2% patients were satisfied with their sexual life, 59.1% considered that it was back to normal;
- 54% felt less fit than before lymphoma;
- 21/21 patients practicing a physical activity before lymphoma resumed their activity;
- 3/8 resumed their social activity;
- Among the working age population ($n = 10$), 50% patients had returned to work.

Conclusions: Our study shows an improvement in HRQol after CAR-T cells therapy and a clinically significant improvement in anxiety, depression, sexual satisfaction, and general well-being. Nevertheless, only half of the working age population returned to work.

Figure : Radar plot of the proportion of patients (in percentage) returned to their professional (N=10), physical (N=21), social (N=8) activities (i.e. involved in associations) after CAR T-cells among patient practicing before lymphoma diagnosis and satisfaction about sexual life (N=22) and general wellbeing (N=22) compared to before lymphoma diagnosis.



Encore Abstract - previously submitted to EHA 2023

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Other

Conflicts of interests pertinent to the abstract

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636 | REAL-WORLD OUTCOMES OF INTRAVENOUS IMMUNOGLOBULIN FOR HYPOGAMMAGLOBULINEMIA AFTER CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Takeda Development Center Americas, Inc., Cambridge, Massachusetts, USA

Introduction: Chimeric antigen receptor T-cell (CAR-T) therapy is a treatment for patients with diffuse large B-cell lymphoma (DLBCL) and is associated with toxicities, including hypogammaglobulinemia (HGG). Intravenous immunoglobulin (IVIG) is often used to manage HGG and prevent recurrent infections after CAR-T therapy, but more real-world evidence is needed to support this.

Aim: To describe the real-world incidence of HGG and the effectiveness of IVIG after CAR-T therapy in patients with DLBCL.

Methods: This observational cohort study used de-identified data from the nationwide (US-based) electronic health record (EHR)-derived Flatiron Health database. Patients were aged ≥18 years, diagnosed with DLBCL, had ≥2 visits in the Flatiron network on/after 1-Jan-11 and had received CAR-T therapy (tisagenlecleucel or axicabtagene ciloleucel) in any treatment line after 1-Jan-18. Baseline characteristics were identified in the 60 days prior to the index date (date of first CAR-T therapy administration). Outcomes, including HGG, were measured from index date until patient death or end of

data availability (cut-off: 30-Apr-21). In this ad-hoc analysis, the primary objectives were to evaluate HGG incidence and IVIG use in patients with DLBCL who received CAR-T therapy. Exploratory objectives were to describe overall survival (OS) and progression-free survival (PFS) by IVIG treatment. Proportions and medians were used for patient characteristics. The Kaplan–Meier method was used for clinical outcomes.

Results: Overall, 91 patients were included. During follow-up, 14 patients (15.4%) developed HGG, of which six cases were 'directly attributed' and one case 'possibly attributed' to CAR-T therapy; attribution was not documented for seven patients. Among these 14 patients, eight received treatment for HGG and six had no documented record of treatment. In total, 14/91 patients received IVIG (IVIG cohort). The IVIG cohort was younger (median [range] age 59 [32–67] vs 63 [28–83] years), had more females (50.0% vs 37.7%), had more patients with an Eastern Cooperative Oncology Group score of 2 (14.3% vs 6.5%) and was more frequently treated in a community setting (64.3% vs 49.4%) than the non-IVIG cohort. In the IVIG and non-IVIG cohorts, median (95% confidence interval [CI]) OS was not reached (NR; 5.6–NR) and 18.3 (9.1–NR) months, respectively and median (95% CI) PFS was NR (2.3–NR) and 3.0 (2.7–7.4) months, respectively.

Conclusions: In this real-world study, half of the 14 HGG cases in patients with DLBCL were directly/possibly attributed to CAR-T therapy. This may be an underestimate because HGG is primarily assessed using laboratory data but here it was identified using EHRs. Despite a small sample size, the hypothesis-generating analyses of IVIG effectiveness and management outcomes support further evaluation of IVIG for the treatment of HGG in patients with DLBCL after CAR-T therapy.

The research was funded by: Takeda Development Center Americas, Inc. Writing support was funded by: Takeda Pharmaceuticals International AG.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Immunotherapy

Conflicts of interests pertinent to the abstract

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637 | COMPARATIVE EFFECTIVENESS OF SALVAGE CHEMOTHERAPY AND CHIMERIC ANTIGEN T-CELL RECEPTOR THERAPIES IN R/R DLBCL: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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David Hodgson and John Kuruvilla are co-senior investigators

Introduction: The optimal salvage chemotherapy (SC) regimen for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) prior to autologous stem cell transplant (ASCT) remains unclear. Head-to-head comparison of chimeric antigen receptor T cell (CAR-T) therapies for second line use in primary refractory DLBCL is lacking. Given these limitations, we conducted a systematic review and network meta-analysis (NMA) of randomized clinical trials (RCTs) to assess the efficacy and safety of SC and CAR-T therapies for R/R DLBCL.

Methods: We searched MEDLINE, EMBASE and CENTRAL from Jan 1 2006 to July 7 2022 for RCTs enrolling patients diagnosed with R/R DLBCL following treatment (trt) with at least 1 prior regimen. The primary outcome was overall survival (OS), and secondary outcomes were progression free survival (PFS) and grade $\geq$ 3 adverse events (AEs). NMA was conducted using a fixed-effect model to synthesize evidence. Surface under the cumulative ranking curve was used to rank the relative effect of compared trt.

Results: A total of 22 RCTs (n=4505) met eligibility criteria, 13 included for qualitative synthesis only. NMA of SC (6 RCTs, n=1831) compared 7 trt: GDP (gemcitabine, dexamethasone, cisplatin), rituximab (R)-GDP, ICE (ifosfamide, mesna, carboplatin, etoposide), R-ICE, DHAP (dexamethasone, cytarabine, cisplatin), R-DHAP, ofatumumab (O)-DHAP, ESHAP (etoposide, cytarabine, cisplatin, methylprednisolone). Results indicated that R-GDP had improved OS and PFS over other regimens (Table), and ranked highest for OS and PFS. NMA of AEs showed no differences for infection. NMA of 3 CAR-T RCTs (axi-cel, liso-cel, tisa-cel; n=733) showed that axi-cel and liso-cel had improved PFS over SC and ASCT, while no OS difference was observed. Comparing between CAR-T products, both axi-cel and liso-cel had improved OS and PFS over tisa-cel. Liso-cel ranked highest for PFS. NMA of AEs showed that tisa-cel and axi-cel had higher risk of cytokine release syndrome over SC, while axi-cel had higher risk of neurologic toxicity over SC.

Conclusions: Our results suggest that R-GDP may be the optimal regimen for R/R DLBCL prior to ASCT. Both axi-cel and liso-cel had improved PFS over SC and ASCT, while tisa-cel did not. Although liso-cel ranked highest for PFS, longer follow-up is required for comparative survival analysis as data matures.

	OS HR (95% CI)	PFS HR (95% CI)
R-GDP vs.		
GDP	0.53 (0.29-0.97)*	0.56 (0.33-0.93)*
DHAP	0.52 (0.28-0.98)*	0.55 (0.32-0.95)*
ESHAP	0.34 (0.16-0.72)*	0.36 (0.19-0.71)†
O-DHAP	0.35 (0.16-0.77)*	0.44 (0.22-0.87)*
R-DHAP	0.39 (0.19-0.82)*	0.39 (0.21-0.75)*
CAR-T vs SC		
Axi-cel	0.73 (0.53-1.01)*	0.49 (0.37-0.65)†
Liso-cel	0.51 (0.26-1.00)*	0.41 (0.25-0.67)*
Tisa-cel	1.24 (0.83-1.85)*	1.07 (0.82-1.40)*
Between CAR-T		
Axi-cel vs tisa-cel	0.59 (0.35-0.98)*	0.46 (0.31-0.67)*
Liso-cel vs tisa-cel	0.41 (0.19-0.90)*	0.38 (0.22-0.67)*
Axi-cel vs liso-cel	1.43 (0.68-3.02)‡	1.20 (0.68-2.01)‡

GRADE was used to assess certainty of evidence: ‡ = very low; * = low; † = moderate.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Therapeutics and Clinical Trials in Lymphoma - Other

No conflicts of interests pertinent to the abstract.

638 | SALVAGE TREATMENTS FOR RELAPSED/REFRACTORY SECONDARY CNS LYMPHOMA IN THE CAR T ERA: A REAL-WORLD COMPARISON

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Introduction: Secondary central nervous system lymphoma (SCNSL) is a rare and aggressive subtype of non-Hodgkin lymphoma that involves the neuraxis. Patients with refractory or relapsed (r/r) disease have limited treatment options and poor outcomes. Chimeric antigen receptor T-cell therapy (CAR T) has shown promise in clinical trials but lacks mature data in the r/r SCNSL setting. In this retrospective, real-world review, we evaluated salvage treatment patterns and survival outcomes of patients with r/r SCNSL, comparing historic regimens to CAR T.

Methods: We retrospectively reviewed medical records of SCNSL patients treated at our institution between 2008 and 2022. Patients were included if they had r/r disease and received salvage treatment. Progression-free (PFS) and overall survival (OS) from initiation of first salvage therapy were calculated using the Kaplan-Meier method.

Results: We identified 28 r/r SCNSL patients, 11 with de novo CNS disease and 17 with CNS relapse. Initial treatments were based on intrathecal or high-dose methotrexate. Six patients underwent consolidative autologous stem cell transplant. Upon relapse, 7 patients received supportive care with steroids only with rapid disease progression and death within one month. The remaining 21 patients had a median age of 60 years (range, 34-77 years) and median Karnofsky performance status of 80. The most common histological subtype was diffuse large B-cell lymphoma (DLBCL) (n=19, 90%). CNS disease was mostly parenchymal (52%), followed by spinal cord (29%) and leptomeningeal (19%) involvement.

Salvage regimens included combinations of radiation (RT, $n = 14$), immunologic, targeted and chemotherapies [(rituximab, ibrutinib, polatuzumab; $n = 15$), methotrexate ($n = 11$), temozolomide ($n = 8$)], and CAR T ($n = 7$). The overall response rate was 67% for initial salvage therapy, with 9 patients having a sustained response. Median OS was 23 months and median PFS was 10 months.

Seven patients who underwent salvage anti-CD19 CAR T had improved PFS and OS compared to other salvage regimens ($p = 0.0014$, Figure 1). Four of these patients received bridging therapy, either with RT ($n = 2$) or chemo-immunotherapy ($n = 2$). The majority (6/7) remain alive, and 4/7 patients remain in complete remission past 1.5 years. 6/7 patients had grade 1-2 CRS and 4/7 had grade 2-3 ICANS that was successfully managed per institutional guidelines. Median OS for other salvage regimens was 6.2 months. The addition of radiation to systemic therapy trended to improve OS.

Conclusion: R/R SCNSL carries a guarded prognosis with no established salvage regimens. Our study shows promising results with CAR T in the real-world setting with improved survival over historic options. Future studies are needed to optimize CAR T timing and elucidate the role of bridging therapies, like RT, to maximize efficacy in this patient population.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Extranodal non-Hodgkin lymphoma

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Conflicts of interests pertinent to the abstract

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Honoraria: BluePrint Medicines, GERON, OncLive, and MD Education
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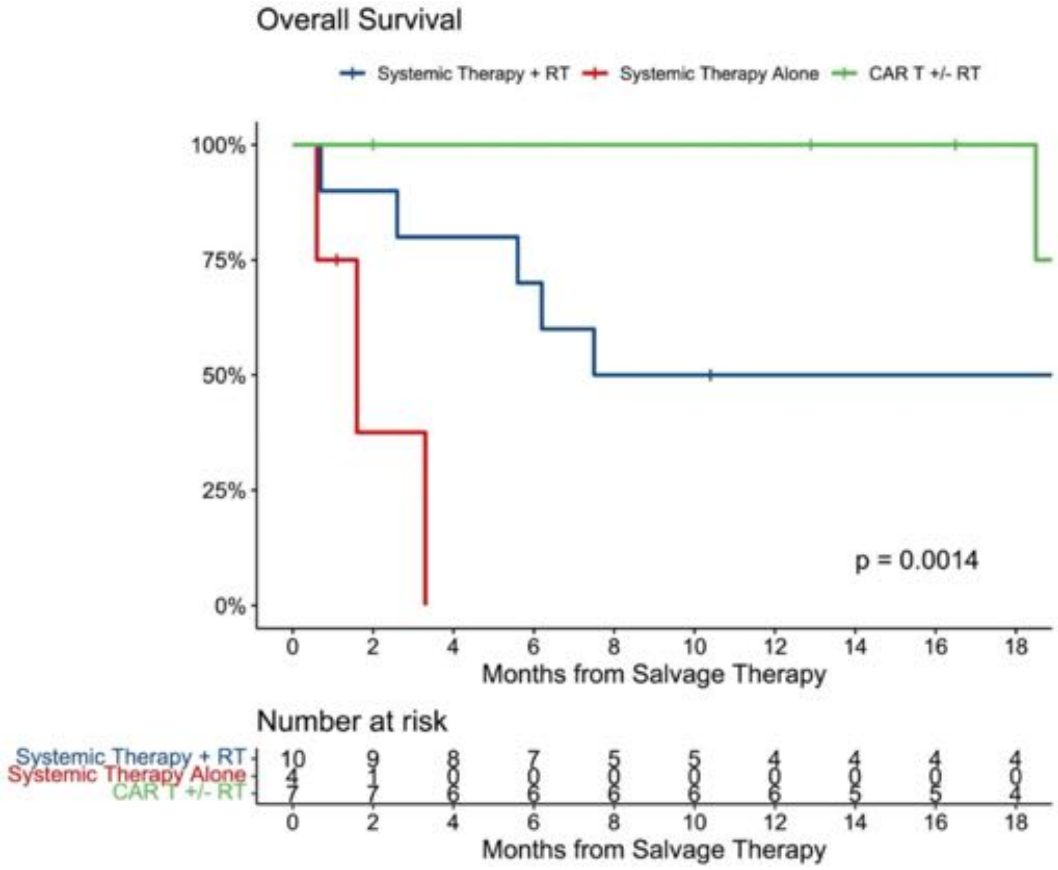

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Consultant or advisory role: PRG has provided consultancy services to Kite Pharma, Bristol Myers Squibb and Rafael Pharma and served on the advisory boards of Pharmacyclics LLC, ADC Therapeutics, Cellectar Biosciences and Ono Pharma.

639 | COMPARISON OF THE EFFICACY OF EPCORITAMAB VERSUS CHIMERIC ANTIGEN RECEPTOR THERAPIES, POLATUZUMAB-BASED REGIMENS, AND TAFASITAMAB-BASED REGIMENS

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Introduction: Epcoritamab, an off-the-shelf subcutaneous CD3xCD20 T-cell–engaging, bispecific antibody that redirects CD3+ T cells to eliminate malignant CD20+ B cells, has shown deep and durable responses in relapsed/refractory (R/R) large B-cell lymphoma (LBCL) patient populations, including those with difficult-to-treat LBCL. In the absence of head-to-head trials, there is a need to assess the comparative efficacy of epcoritamab versus novel therapies recently approved for R/R DLBCL. We compared the efficacy of epcoritamab versus chimeric antigen receptor T-cell (CAR T) therapy, polatuzumab-based (pola-based) regimens, and tafasitamab-based (tafa-based) regimens in R/R diffuse large B-cell lymphoma (DLBCL) and LBCL.

Methods: This study compared individual patient data from the EPCORE™ NHL-1 trial (NCT03625037; Jan 2022 cutoff) and multiple US academic and community clinical practices in the COTA electronic health records database (2010–2022), including adult patients with R/R DLBCL and LBCL treated with CAR T, pola-based, and tafa-based regimens with ≥2 prior lines of therapy (LOTs). Inverse probability of treatment weighting was used to create balanced cohorts on key demographic and clinical characteristics. Overall response rate (ORR) and complete response (CR) rate were compared using weighted logistic models; progression-free survival (PFS) and overall survival (OS) were compared using weighted Cox proportional-hazard models.

Results: A total of 96 CAR T-naive LBCL patients were included in the epcoritamab cohort versus 55 in the CAR T cohort, and 139 DLBCL patients in the epcoritamab cohort versus 37 receiving pola-based and 20 receiving tafa-based regimen. Cohorts were balanced on several factors including but not limited to prior CAR T exposure (in epcoritamab versus pola-based and tafa-based regimens), number of prior LOTs, and refractoriness to last LOT. For epcoritamab versus CAR T, CR rate was 38.9% versus 36.5%. For epcoritamab versus

Table. Clinical Outcomes

Outcome	Treatment after failing ≥2 prior LOTs				
	Epcoritamab		CAR T[a] (N=55)	Pola-based regimens[b] (N=37)	Tafa-based regimens[c] (N=20)
	CAR T-naive LBCL (N=96)	DLBCL (N=139)			
ORR (95% CI)	68.8% (59.5, 78.0)	61.9% (53.8, 69.9)	72.0% (62.6, 81.4)	60.7% (51.7, 69.7)	34.9% (26.4, 43.4)
Odds ratios (95% CI) for ORR for epcoritamab vs			0.95 (0.79, 1.15) *P*=0.626	1.02 (0.84, 1.24) *P*=0.853	1.77 (1.34, 2.34) *P*<0.0001
CR (95% CI)	41.7% (31.8, 51.5)	38.9% (30.8, 47.0)	36.5% (26.4, 46.5)	10.7% (5.1, 16.5)	11.2% (5.5, 16.8)
Odds ratios (95% CI) for CR for epcoritamab vs			1.14 (0.79, 1.64) *P*=0.472	3.60 (2.04, 6.37) *P*<0.0001	3.48 (2.01, 6.01) *P*<0.0001
mPFS (mo)	5.4	4.4	5.6	3.3	1.9
Hazard ratios (95% CI) for PFS for epcoritamab vs			0.78 (0.55, 1.11) *P*=0.169	0.44 (0.33, 0.60) *P*<0.0001	0.49 (0.36, 0.65) *P*<0.0001
mOS (mo)	NR	NR	15.0	5.6	6.6
Hazard ratios (95% CI) for OS for epcoritamab vs			1.08 (0.70, 1.69) *P*=0.724	0.44 (0.32, 0.62) *P*<0.0001	0.53 (0.38, 0.75) *P*=0.0003

CAR T, chimeric antigen receptor T-cell; CI, confidence interval; CR, complete response; LOTs, lines of therapy; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate.

[a]Treatment types include: axicabtagene ciloleucel, lisocabtagene maraleucel, tisagenlecleucel, and unknown CAR T.

[b]Treatment types include: polatuzumab vedotin plus bendamustine and rituximab, polatuzumab vedotin plus bendamustine, polatuzumab vedotin plus rituximab, and polatuzumab vedotin plus obinutuzumab.

[c]Treatment types include: tafasitamab plus lenalidomide and tafasitamab alone.

pola-based and tafa-based regimens, CR rate was 38.9% versus 10.7% and 11.2%, respectively. Adjusted odds ratio (95% CI) for CR for epcoritamab versus CAR T was 1.14 (0.79, 1.64; *P*=0.472); for epcoritamab versus pola-based regimens was 3.60 (2.04, 6.37; *P*<0.0001); and for epcoritamab versus tafa-based regimens was 3.48 (2.01, 6.01; *P*<0.0001). Adjusted hazard ratio (95% CI) for OS for epcoritamab versus CAR T was 1.08 (0.70, 1.69; *P*=0.724); for epcoritamab versus pola-based regimens was 0.44 (0.32, 0.62; *P*<0.0001); and for epcoritamab versus tafa-based regimens was 0.53 (0.38, 0.75; *P*=0.0003). Other clinical outcomes are summarized in the Table.

Conclusions: Epcoritamab provides significantly better efficacy versus pola-based and tafa-based regimens, with no significant difference versus CAR T, in patients with R/R DLBCL and LBCL who received ≥2 prior LOTs. These findings are subject to limitations consistent with comparative analyses conducted outside of a randomized clinical trial.

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Keyword: Aggressive B-cell non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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Honoraria: Targeted Oncology, OncView, Curio, Kyowa, Physicians' Education Resource, Seattle Genetics

Research funding: Bayer, Gilead/Kite Pharma, Celgene, Merck, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, Millennium

Other remuneration: Speaker's Bureau: Gilead/Kite Pharma, Kyowa, Bayer, Pharmacyclics/Janssen, Seattle Genetics, Acrotech/Aurobindo, BeiGene, Verastem, AstraZeneca, Celgene/BMS, Genentech/Roche.

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640 | OUTCOMES OF THE TREATMENT AFTER ANTI-CD19 CAR-T THERAPY FAILURE IN PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMA—ANALYSIS OF DATA FROM THE CZECH REPUBLIC

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Introduction: In patients with aggressive B-cell lymphomas (BCL), the long-term progression-free survival (PFS) after anti-CD19 CAR-T therapy is around 30-40%. The prognosis of patients with progression/relapse after this therapy is poor. There are currently limited data on treatment approaches to improve the prognosis of this group of patients (p) and optimal management is not yet defined. Based on the published data, it seems that some of the new drugs being tested in clinical trials (polatuzumab vedotin, bispecific antibodies, lenalidomide, tafasitamab, selinexor, loncastuximab tesirine) could be used as a "bridge" to allogeneic transplantation, which remains a potentially curative treatment option for some of these patients.

Methods: We analyzed patients with aggressive BCL (diffuse large B-cell lymphoma /DLBCL/ – 64p, transformed DLBCL – 19p, high-grade BCL – 12p and primary mediastinal large BCL – 11p) who were treated with anti-CD19 CAR-T cells (tisagenlecleucel 79p and axicabtagene ciloleucel 27p) between Dec 2019 and Dec 2022. This is a multicentre retrospective analysis from 5 university hematological centres, where the patients were referred for CAR-T therapy after ≥ 2 lines of treatment failure from the Czech Republic and Slovakia. We focused on the group of patients who did not respond to this treatment.

Results: 106p were treated with anti-CD19 CAR-T therapy. The median follow-up (FU) was 16.4 months. The median PFS and overall survival (OS) were 4.3 and 26.4 months. The overall response rate (ORR) was observed in 63p (60%) with 52% complete response (CR). We further analyzed subsequent therapy in a subgroup of 60p who did not respond to CAR-T treatment (progression in 37p/stable disease in 6p) or had relapse (9p) or progression (8p) after initial response (CR/partial remission). The median FU for failed patients was 9.5 months. Overall, 42p in our cohort received therapy; 18p rapidly progressed and were not treated. 4p were treated with radiotherapy (2p achieved CR) and 38p with systemic therapy (glucocorticoids – 6p, lenalidomide+-rituximab – 6p, chemotherapy+-rituximab – 16p, polatuzumab+bendamustine and rituximab – 6p, CAR-T reinfusion – 2p, other 2p). The ORR after systemic therapy was observed in 17% of patients. Patients who were not treated had more likely massive involvement > 5cm at the time of apheresis ($p = 0.02$). Of the 60p with CAR-T treatment failure, 39p (65%) died. Median OS for CAR-T therapy failed patients (n=60) was 3.1 months from diagnosis of progression/relapse after CAR-T treatment (6-month and 1-year OS 34.9% and 26%). The median OS were 4.7 for treated and 0.2 months for untreated patients from diagnosis of progression/relapse after CAR-T.

Conclusion: Our results confirm the poor prognosis of patients with relapsed/refractory aggressive BCL who failed CAR-T treatment. The ORR to the treatment was insufficient and the lymphoma progressed in most patients.

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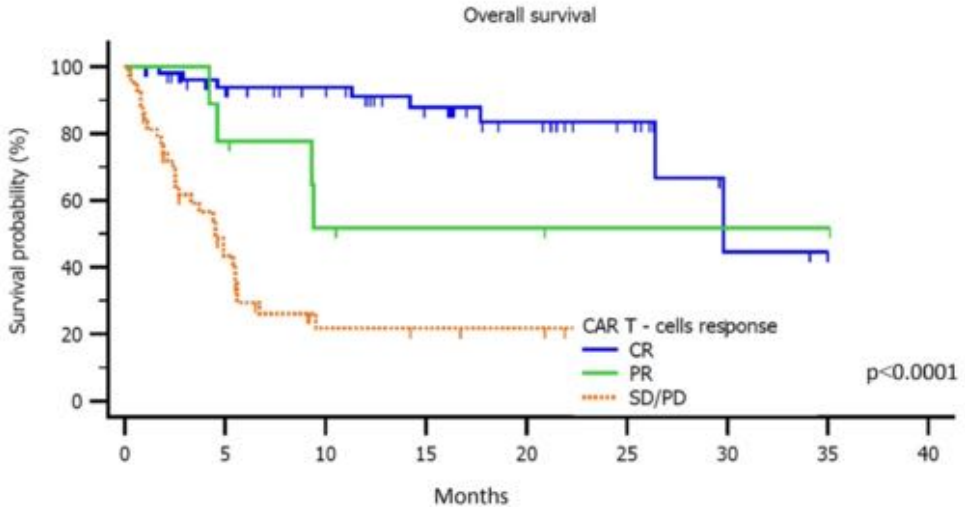
Figure 1 Overall survival of patients after anti-CD19 CAR T therapy according to treatment response



Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies

Conflicts of interests pertinent to the abstract

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PRECLINICAL NEW DRUGS

641 | A NOVEL ANTHRACYCLINE MNPR-202 DISPLAYS A DISTINCT IMMUNOMODULATORY PROFILE TO DOXORUBICIN IN DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: Diffuse large B cell lymphoma (DLBCL) is the most common subtype of aggressive lymphoma. Although the combination therapy of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is curative, around 40% of patients relapse after first line treatment. Due to cardiotoxicity of doxorubicin (dox), patients are unable to tolerate or maintain dose-intensity of R-CHOP, increasing the relapse risk. Camsirubicin (MNPR-201; GPX-150; 5-imino-13-deoxydoxorubicin), a novel analog of dox, has not shown any irreversible heart damage to date in two Phase 1 trials and a Phase 2 trial. Here we report on early pre-clinical studies of MNPR-202, a camsirubicin analog which retains the non-cardiotoxic backbone but is modified at other sites to circumvent drug-resistant pathways.

Methods: A comparative in vitro study between dox and MNPR-202 was performed by treating 8 DLBCL cell lines and donor-derived macrophages. Phenotypes such as cell proliferation, apoptosis, DNA damage, and immune gene transcription were investigated using routine methods. The impact of both drugs on macrophage polarization were evaluated using DLBCL-macrophage co-culture experiments. RNA-seq was conducted to explore the immunomodulatory

pathway differences between macrophages treated with dox or MNPR-202. A drug screen with ~200 compounds was carried out to identify synergistic combinations of dox and MNPR-202, respectively.

Results: We demonstrated that in DLBCL cells, dox and MNPR-202 had similar effects on cell proliferation with comparable IC50s. After 24-48 hours, MNPR-202 was more potent than dox in inducing apoptosis and DNA damage. In contrast, Dox, but not MNPR-202, induced the expression of innate immunomodulatory genes. Macrophage co-culture experiments revealed that MNPR-202 mitigated, more strongly than dox, the lymphoma-induced polarization of macrophages towards the pro-tumor M2-like phenotype; this effect was more pronounced upon direct treatment of macrophage monocultures. RNA-seq analysis showed that the TNF-α/NF-κB pathway was upregulated in MNPR-202-treated macrophages, with respect to dox. Strikingly, this analysis also demonstrated that the cardiac hypertrophic response pathway was downregulated with MNPR-202 lending credence to its cardioprotective properties. Finally, the drug screen revealed distinct differences in the synergy profile between dox and MNPR-202, e.g., with respect to volasertib.

Conclusions: To conclude, dox and MNPR-202 have similar cytotoxic potencies, but likely work through different cellular pathways and have distinct drug synergies. Overall MNPR-202 appears to have greater immunomodulatory potential. Indeed, MNPR-202 ostensibly improves the anti-tumor response by exerting a stronger suppressive effect on M2-macrophage polarization. These findings support further in vivo studies and clinical investigation of MNPR-202 as a promising non-cardiotoxic substitute for dox in DLBCL.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract

R. R. Nair
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A. D. Jeyasekharan
Consultant or advisory role ADJ has received consultancy fees from Roche, Gilead, Turbine Ltd, AstraZeneca, Antengene, Janssen, MSD and IQVIA; and research funding from Janssen and AstraZeneca.

642 | APR-246 TRIGGERS FERRITINOPHAGY AND FERROPTOSIS OF DIFFUSE LARGE B-CELL LYMPHOMA CELLS WITH DISTINCT TP53 MUTATIONS

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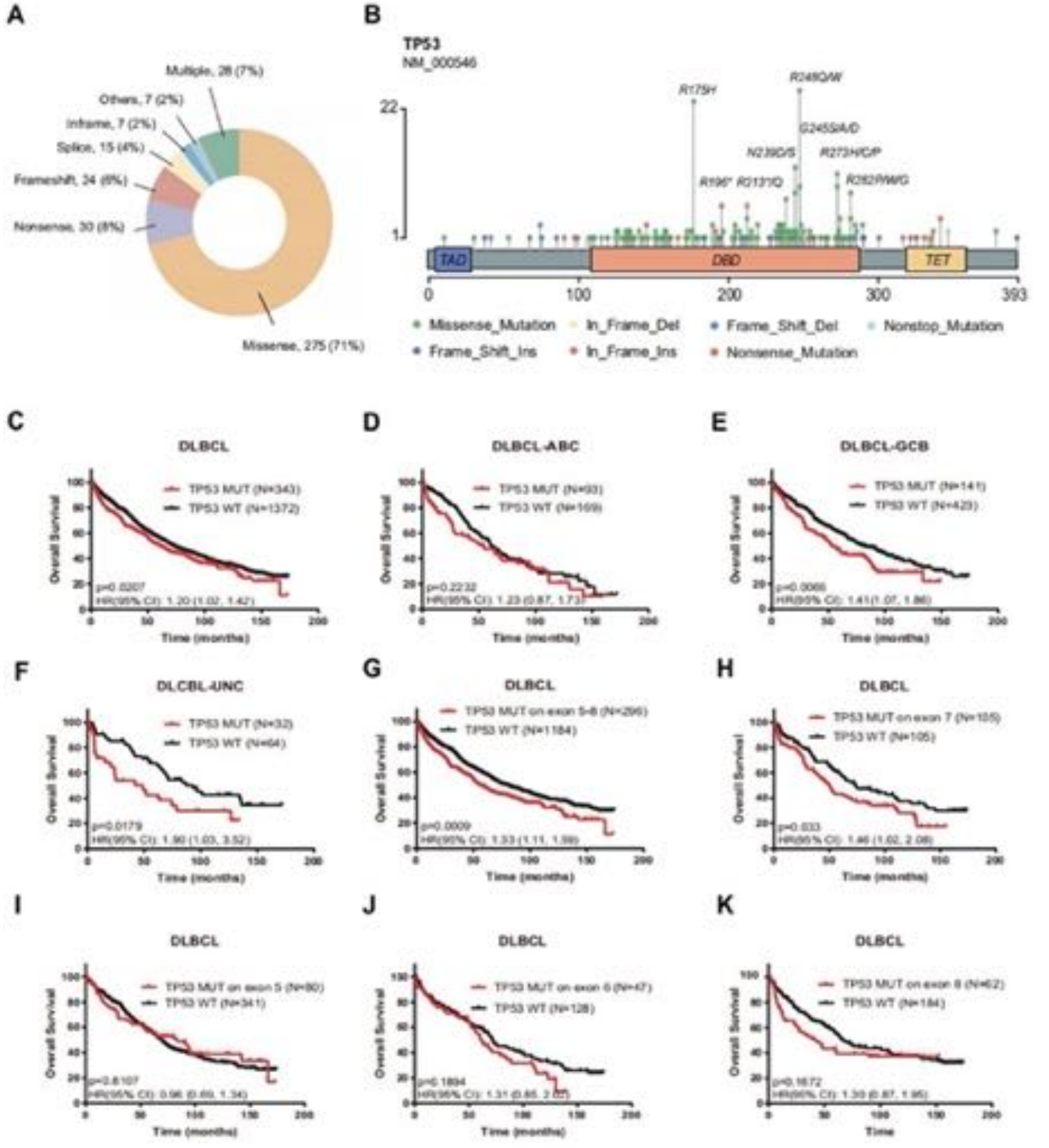
Purpose: Recently, seven diffuse large B-cell lymphoma (DLBCL) genotypes were defined, among which the A53 type showed adverse outcomes. Thus, it is necessary to explore promising anticancer drugs and therapies for *TP53* dysfunction patients. APR-246 is a promising compound to combat mutant p53 in solid and hematological tumors, but the effect of APR-246 on DLBCL remains unclear.

Methods: A set of 2464 DLBCL cases from multiple cohorts including our center, was integrated to identify the type and localization of *TP53* mutations and clinical impacts. APR-246 was applied in *TP53*-mutated DLBCL cells and xenograft mouse models to explore the anti-tumor effect and the underlying mechanism.

Results: Of all patients, 16% contained *TP53* mutations. *TP53* mutations correlated with poor overall survival (OS) and progression-free survival (PFS) in all cases. Notably, *TP53*single mutations in the DBD (exons 5-8) resulted in poor OS and PFS, but those on the exons (3-4, 9-11) outside the DBD.

DLBCL cells carrying exons 5 and 7 or intact *TP53* mutations showed more sensitivity to APR-246 than those containing spliced mutations or null *TP53*. DLBCL cells with knocked-out *TP53* showed less sensitivity to APR-246. APR-246 also significantly inhibited the DLBCL tumor growth in xenograft animal model. The decreased cell viability induced by APR-246 was almost completely rescued by either the iron chelater deferoxamine (DFO) or ferrostatin-1 (Fer-1), indicating that ferroptosis mediates cell death. APR-246-induced cell death is an action involving ROS production, which was not altered by knockout of *TP53* in OCI-LY7. However, only ferroptosis was induced by APR-246 in OCI-LY3, TMD8 and *TP53*-knockout OCI-LY7 cells, indicating that APR-246-induced autophagy in OCI-LY7 was *TP53*-dependent. Further, the cells re-expressing wild-type p53 showed the similar response as OCI-LY3 harboring wild-type p53 to APR-246, while the cells with re-expressed p53 mutant showed the similar response as OCI-LY7 to APR-246.

The expression of *ALOX5*, *ALOX12*, and *ALOX15* were increased in DLBCL cells after APR-246 treatment for 24 h. The *LC3-II* level was enhanced while the autophagy substrate *SQSTM1* was reduced by APR-246 treatment, confirming APR-246 induces autophagy in OCI-LY7 cells. Additionally, *FTH1*, *NCOA4* and *HERC2* were also examined in *TP53* knockout DLBCL cells, and the data demonstrated that APR-246 had no effect on the level of these proteins, indicating that APR-246 restored p53 was involved in ferritinophagy in OCI-LY7 cells.



These findings were further confirmed in OCI-LY7 *TP53*-KO cells with re-expressing mutant or wild-type p53.

Conclusions: *TP53* mutations on exons 5, 6 and 7 are predictors of progression and survival. Targeting mutant p53 by APR-246 is a promising therapeutic approach for DLBCL patients. Finally, our study highlights that the induction of non-apoptosis may represent a new target in DLBCL. The effect of *TP53* induction-based treatments on lymphoid malignancies and their value compared to that of standard-of-care DLBCL therapies will be important to evaluate in the future.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Diagnostic and Prognostic Biomarkers, Genomics, Epigenomics, and Other - Omics

No conflicts of interests pertinent to the abstract.

643 | NX-0255 AND NX-1607, SMALL MOLECULE INHIBITORS OF CBL-B, ARE EFFICACIOUS IN COMBINATION WITH ADOPTIVE CELL THERAPY OR RITUXIMAB IN PRECLINICAL MOUSE MODELS OF LYMPHOMA

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The E3 ubiquitin ligase Casitas B-lineage lymphoma B (CBL-B) is expressed in leukocytes, negatively regulating signaling pathways in T and NK cells, thereby significantly limiting their antitumor effector function. CBL-B attenuates cellular activation initiated by TCR engagement, in part by mediating the requirement for CD28 co-stimulation, thus setting the threshold for T cell activation. In NK cells, CBL-B similarly functions downstream of TAM receptors and negatively regulates cytokine production and cytotoxicity.

We developed two potent small molecule inhibitors of CBL-B, NX-0255 and NX-1607, for*in vitro* and *in vivo* use, respectively. We previously reported that NX-0255 enhances the *in vitro* growth and efficacy of drug-enhanced adoptive cell therapy (DeACT-0255). Addition of NX-0255 during *in vitro* treatment of tumor-specific T cells improves the efficacy of ACT in tumor-bearing mice by increasing the frequency and absolute number of less exhausted CD8+ memory T cells. NX-1607 can be administered orally and demonstrates tumor growth inhibition in multiple murine solid tumor models.

Here, we show that NX-1607 treatment of immunocompetent mice bearing the A20 B cell lymphoma leads to robust, T-cell dependent, tumor regression. Moreover, we show that in the setting of disseminated disease (Raji cell Non-Hodgkin lymphoma model)the combination of daily NX-1607 administration with Rituximab enhanced tumor growth inhibition and tumor rejection when compared to single agent activity ($p<0.0001$). Importantly, the survival benefit provided by NX-1607 was abrogated with depletion of NK cells in this xenogeneic model.

We also characterized the antitumor effect of post-infusion treatment with NX-1607 in the DeACT-0255 model. *In vitro* generated, NX-0255-treated OT-I cells were adoptively transferred in mice bearing established E.G7-OVA lymphomas. Mice treated with or without oral NX-1607 and evaluatedat 7 and 14 days following ACT demonstrated that NX-1607 increased circulating OT-I cells which showed a central-memory and less exhausted cytotoxic phenotype. This suggests that DeACT-0255 could be further enhanced with oral administration of NX-1607.

NX-1607 enhances both innate and adaptive immune responses, both of which are important for overcoming the suppressive TME of lymphoid neoplasms. The observed activities of NX-0255 and NX-1607 support their potential use in cell-based therapeutics or in combination with antibody therapy to enhance their antitumor efficacy for patients with hematopoietic malignancies.

We have initiated a clinical trial with NX-1607 (NCT05107674) in patients with advanced cancer including solid tumors and malignant lymphoma, including large B cell lymphoma. Nurix has also completed the safety run-in portion of a Phase 1 trial evaluating NX-0255 in the production of an investigational drug-enhanced TIL therapy, DeTIL-0255 (NCT05107739).

Keywords: Cellular therapies, Combination Therapies, Immunotherapy

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Conflict of interest:

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644 | BV6, AN ANTAGONIST OF INHIBITOR OF APOPTOSIS PROTEINS, SENSITIZES RESISTANT MANTLE CELL LYMPHOMA CELLS TO VENETOCLAX

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Introduction: Although Bruton's tyrosine kinase inhibitors (BTKi) and CAR T-cell therapy have achieved remarkable efficacy in the treatment of mantle cell lymphoma (MCL), it remains incurable due to the inevitable development of therapeutic resistance. The BCL-2 inhibitor venetoclax is effective in many relapsed MCL patients, including those who progressed on BTKi, but subsequent relapse to venetoclax yields poor clinical outcomes. Hence, novel therapeutics and combination therapies are required to tackle the clinical challenges. Here, we investigated BV6, an antagonist of inhibitor of apoptosis proteins (IAPs), alone and in combination with venetoclax in multiple therapy-resistant MCL models.
Methods: We performed single-cell RNA-seq to assess gene expression in ibrutinib-sensitive, ibrutinib-resistant, and dual ibrutinib-/CAR T-resistant MCL patients. Cell lines with acquired resistance to ibrutinib or venetoclax, as well as primary tumor cells from patients who relapsed after multiple therapies, were used as models of MCL resistance. CellTiter-Glo® luminescent assay was used to measure cell viability; annexin V/PI staining was used to measure the induction of apoptosis; and western blotting was used to assess IAP and apoptosis signaling protein expression across MCL cell lines after drug treatment.
Results: The single-cell RNA-seq analysis demonstrated that IAP gene expression was not influenced by patient response to ibrutinib and CAR T-cell therapy, and western blotting showed that IAP proteins were broadly expressed across all MCL cell lines. To determine the on-target effects of BV6, we treated JeKo-1, JeKo-IBN-R, Mino, and Mino-VEN-R cells with BV6 and examined the expression of IAPs. BV6 treatment for 4h markedly reduced c-IAP1 and c-IAP2 expression, and moderately reduced XIAP expression. BV6 inhibited cell viability in both ibrutinib- and venetoclax-resistant cell lines, and BV6 treatment for 24 h dose-dependently induced apoptosis in MCL cells, including not only cell lines with acquired resistance but also patient primary cells, independent of their resistance to ibrutinib, venetoclax, and CAR T-cell therapy. We observed a striking and significant synergy in the cell viability assay when ibrutinib- or venetoclax-resistant cells were treated with BV6 combined with venetoclax (combination index < 1), and a dramatic enhancement of apoptosis ($p < 0.001$). The combination eradicated c-IAP1 and c-IAP2 expression, while XIAP was synergistically diminished. This was accompanied by strong caspase-3 activation and PARP cleavage. This combination therapy is currently under evaluation in venetoclax-resistant mouse model *in vivo*.
Conclusions: Our findings indicate that a combination of IAP antagonists with apoptosis inducers can be exploited as a rational strategy to overcome therapeutic resistance in MCL.
This study was supported by philanthropic funds from the Kimmel Research fund and various donor funds.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

645 | COMBINATION STRATEGIES OVERCOME TREATMENT RESISTANCE DRIVEN BY GAIN-OF-FUNCTION BCL10 MUTATIONS IN DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Diffuse large B cell lymphoma (DLBCL), the most common lymphoma diagnosis, has heterogeneous biology and prognosis. Frontline R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), used regardless of subtype, cures ~60%, but relapsed/refractory patients have persistently poor prognosis. Efforts to improve frontline and establish subtype-targeted therapy have largely failed. Post-hoc analysis of the negative PHOENIX trial suggested younger patients with specific subtypes benefited from adding a Bruton's tyrosine kinase inhibitor (BTKi) to R-CHOP, but BN2 (LymphGen)/Cluster 1 (Chapuy clusters) cases did not. *BCL10*, encoding a key oncoprotein promoting NF-kB activation through formation of the CBM complex with CARD11 and MALT1, is mutated in DLBCL (~5%), clustering strongly in BN2 (~40%). While these gain-of-function mutations alter CBM complex dynamics and promote BTKi resistance, therapeutic strategies to overcome them are minimally defined. We find resistance to multiple drug classes is driven by BCL10 mutants, but rational combinations can restore treatment sensitivity, informing biomarker-driven strategies for clinical translation.
Methods: We established gain-of-function models for two classes of BCL10 mutants: a recurrent R58Q CARD-domain alteration and truncations of the ST-rich domain. We probed impact through RNA-seq and transcription-factor (TF) analyses. We assessed deregulation of cytokines and downstream signaling, performed drug screens and validations and assessed drug combinations.
Results: Both mutation classes promote constitutive CBM activation (NF-kB: p65/IKBα; AP-1: JNK/cJUN). Consistent with CBM biology, RNA-seq showed activation of IL6-JAK-STAT3 and TNFα signaling

via NF-kB but implicated novel cytokines including CXCL10 and IL7, confirmed by ELISA assays. BCL10 mutant biology converged on TFs downstream of CBM (RELA, JUN) and cytokine signaling (STAT1, STAT2). As previously reported, BCL10 mutants drove BTKi resistance, including the non-covalent inhibitor pirtobrutinib. We sought drug vulnerabilities using the TargetMol Epigenetic library, revealing additional BCL10-mutant resistances. Confirmed across multiple lines in dose-response viabilities, these targets included PI3K, BCL2, PIM, and AKT. Given lack of single drug activities in DLBCL, we sought rational combinations. MALT1 activity is critical in BCL10-mutant cells and the combination of MALT1i with BTKi was additive. MALT1i-independent combinations showed striking synergy between BTKi and BCL2i (pirtobrutinib+venetoclax), even though both independently are resistant, informing a rational combination with non-covalent BTKis.

Conclusions: Gain-of-function BCL10 mutants drive oncogenesis and drug resistance through persistent signaling and cytokine activation which is overcome by novel drug combinations.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

646 | LYMPHOMA TISSUE EXPLANTS TO ANTICIPATE RESPONSE TO TARGETED THERAPIES

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The concept of precision medicine emerged to match targeted therapies with the genomic fingerprint of each cancer patient. However, the cellular composition and architecture of tumor tissues are additional parameters that influence response to therapies. B-cell lymphomas are a heterogenous group of tumors emerging from B cells in different stages of differentiation in specialized areas of the lymph nodes. Therefore, in order to reliably anticipate responses to treatment, lymphoma models must preserve the spatial organization and the functional interdependency between the malignant and non-malignant cells. Modeling lymphoma *ex vivo* has been hampered by the lack of suitable 3D models and the complexity of translating organoid technology - which is mainly based on the presence of tumor sustaining cancer stem cells- from other cancer types into lymphoma. To address these challenges, we have designed an *ex vivo*culture system for lymphoma tissues using murine models. FACS analyses, single-cell RNA sequencing, and high-plex spatial proteomic analyses confirm that our system is able to support tumor growth and tissue architecture. As they retained histological, cellular, and molecular characteristics distinctive of the original tissue, we called them *lymphomoids*. To anticipate sensitivity to anti-cancer therapies, we tested response to targeted therapies on lymphomoids obtained from human primary lymphomas. Histopathological and spatial transcriptomic analyses showed patient-specific sensitivity to particular compounds and revealed features on the tumor tissue composition associated with resistance or response to therapies. Importantly, in three cases the response to therapy observed in the lymphomoids anticipated the patient's clinical outcome. All in all, lymphomoids represent an innovative tool to assess therapy response in lymphoma patients and uncover novel aspects of lymphoma biology.

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Keywords: Microenvironment, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

647 | CREATION OF ISOGENIC CELL LINE MODELS OF 17P DELETION TO STUDY CLONAL EVOLUTION AND MECHANISMS OF THERAPY RESISTANCE IN CLL AND DLBCL

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Introduction: A deletion of chromosome 17p (del17p), on which the tumour suppressor gene *TP53* is located, is a prevalent genetic aberration in many cancer types. In chronic lymphocytic leukaemia (CLL), diffuse large B-cell lymphoma (DLBCL), and other B cell malignancies this chromosomal mutation is associated with high fitness advantage in the setting of therapy, and the most adverse clinical outcome. Whilst resistance to the chemoimmunotherapies often used in the treatment of CLL and DLBCL can be explained by the functional loss of p53, such deactivation does not explain the increase in aggressive behaviour of the malignant cells. To study this, we aimed to develop in-vitro models of 17p deletion in CLL and DLBCL by creating *TP53* (15.6 kbp) and 17p (20.5 Mbp) deletions by means of CRISPR-Cas9 genome editing.

Methods: The efficiency of the gene editing machineries were firstly assessed in the adherent human colorectal cancer cell line HCT116 prior to their application on the B-cell lines, which are less amenable to genetic manipulation. *TP53* gene removal (15.6 kbp) was performed by transient transfection of a vector encoding Cas9 as well as single guide (sg) RNAs targeting upstream and downstream of the *TP53* coding region. For deletion of 17p (20.5 Mbp) sgRNAs targeting exon 2 of GEMIN4 (telomeric) and intron

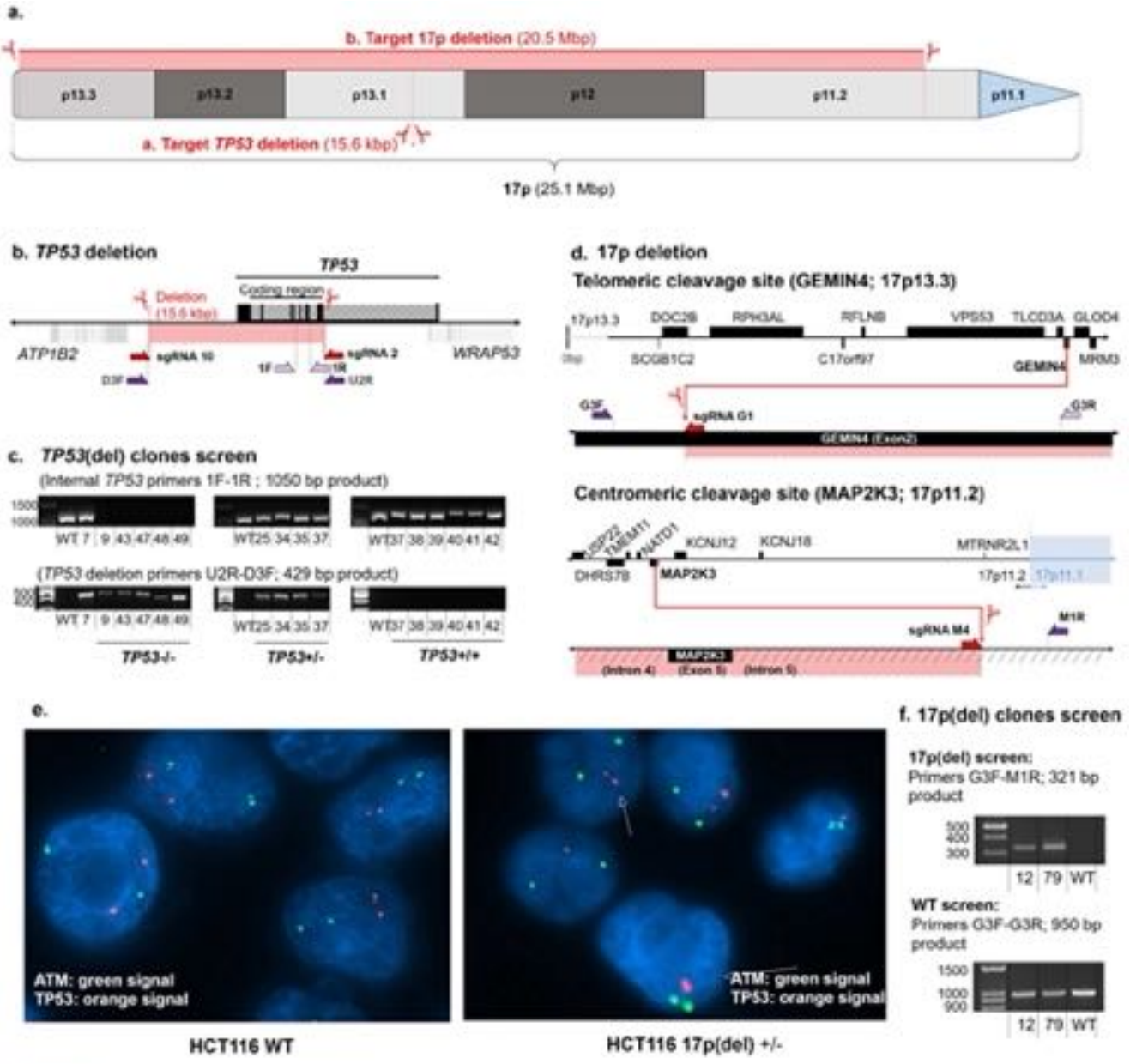

FIGURE 2. **17p and *TP53* deletions by CRISPR/Cas9. a)** Schematic representation of the size and location of the target 17p and *TP53* deletions relative to the wild-type 17p chromosome arm. **b)** . Schematic overview of the genomic locations of the sgRNAs and genotyping primers in relation to the *TP53* gene (sgRNAs; red, sequencing primers; purple). **c)** Genotyping HCT116 clones for *TP53*(del) and zygosity status by PCR amplification. **d)** . Schematic overview of the genomic locations of the sgRNAs and genotyping primers at the telomeric (*GEMIN4*) and centromeric (*MAP2K3*) target cleavage sites for deletion of 17p. **e)** FISH analysis for 17p(del) in HCT116 wildtype and HCT116 17p(del)+/- cells denoted by the presence of 2 green signals for ATM, and 2 or 1 orange signal for *TP53*, respectively. **f)** Genotyping two HCT116 clones (#12 and #79) for *17p*(del) status by PCR amplification.

5 of MAP2K3 (centromeric) were designed. PCR was used to confirm deletions.

Results: Isogenic HCT116 cell lines with hemizygous and homozygous *TP53* deletion, as well as hemizygous 17p deletion were obtained (Figure 1). HG-3 cells, a CLL cell line, were successfully transduced with inducible-Cas9, and subsequently with the sgRNAs for removal of *TP53* and 17p.

Conclusion: This work shows generation of the first isogenic cell lines bearing the loss of *TP53* and 20.5Mbp of the short arm of chromosome 17. Further work will include gene expression analysis of the wild-type, 17p(del) and *TP53*(del) isogenic cell lines for identification of associated gene expression signatures that can be applied back into primary CLL cells from patients with 17p deletion.

Keyword: Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

648 | CRIP1 INDUCES PIS RESISTANCE BY FORMING A COMPLEX WITH USP7 /PA200 AND ENHANCING PROTEASOME ACTIVITY AND AUTOPHAGY IN MULTIPLE MYELOMA

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Introduction: Multiple myeloma (MM) is a plasma malignancy characterized by an accumulation of misfolded immunoglobulins in the cell. Although proteasome inhibitor (PI) can treat MM by inhibiting ubiquitin-proteasome system (UPS), autophagy as a compensatory protein clearance mechanism, it still leads to drug resistance. The discovery of new targets that can simultaneously inhibit UPS and autophagy will provide great potential for the treatment of MM.
Methods: The proliferation, invasion, migration, proteasome activity and autophagy were detected in CRIP1- knockdown /overexpression and control MM cells. Co-IP (Co-Immunoprecipitation) with TAP/MS (Tandem affinity purification/Mass spectrum) was performed to detect the binding of USP7, CRIP1 and PA200. Myeloma xenograft model was used to determine the role of CRIP1 to promote proliferation of MM cells and induce BTZ resistance in vivo.
Results: The levels of CRIP1 were significantly increased in plasma cells from NDMM (newly diagnosed multiple myeloma) compared to healthy donors, and further increased in patients with RRMM (relapsed/refractory multiple myeloma). Moreover, the high expression of CRIP1 is significantly related to the poor prognosis of MM patients, especially those treated with BTZ. Our results in vitro and in vivo showed that CRIP1 knockdown noteworthy inhibited the cell growth, invasion, migration. MM cells were more sensitive to PIs-induced cell growth arrest when CRIP1 knockdown. The proteasome activity and the protein level of LC3B-II of the MM cells were significantly reduced with CRIP1 knockdown. Co-IP analysis showed that CRIP1 formed a complex with USP7/PA200. The protein level of CRIP1 decreased and the ubiquitination CRIP1 increased with USP7 inhibition. These data suggested that CRIP1 is the substrate of USP7. CRIP1 promotes the de-ubiquitination and stabilization of PA200 mediated by USP7 by interacting with USP7 and PA200, which in turn promotes MM cell survival and drug resistant. Functional inhibition of CRIP1 by knocking down of USP7 or PSME4 in CRIP1 OE MM cell line led to a decrease of the activity of proteasome and autophagy, thus enhancing the sensitivity to PIs in intro and in vivo.
Conclusion: CRIP1 plays a critical role in MM progression and PIs resistance by formation of CRIP1/USP7/PA200 complex. High level of CRIP1 is a biomarker for high-risk MM patients. CRIP1 is a potential target for MM therapy, can simultaneously inhibit proteasome activity and autophagy.

Encore Abstract - previously submitted to EHA 2023

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Keywords: Diagnostic and Prognostic Biomarkers, Multiple Myeloma, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

649 | NANOSECOND PULSED ELECTRIC FIELD MODULATES IMMUNOPHENOTYPE OF LYMPHOCYTES

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Introduction: Nanosecond pulsed electric fields (nsPEFs) have been shown to have anticancer effects, but little is known about the mechanisms modulating the immune landscape. According to the applied parameters (voltage, pulse duration, pulse delivery frequency, and a number of pulses), it is possible to achieve a specific effect modulating the immunophenotype of cancer cells. This study aims to identify changes in the expression profile of antigens defining lymphocyte maturity and function.
Materials and Methods: We treated the Jurkat cell line with PEF. We tested different parameters of electroporation (2.5, 5, 7.5, 10, and 12.5 kV/cm, 100, 200 and 100 ns pulses, 25, 100, 250, and 500 pulses, 1, 10 and Hz). For the detection of cell permeabilization, Yo-Pro-1 and flow cytometry were employed. Cell viability was analyzed after 24h by MTT Assay. ATP levels in culture were measured using Cell-Titer-Glo® Assay after 24 hours. The expression of cell markers was determined using flow cytometry.
Results: The obtained results confirmed that electroporation permeabilizes the cell membrane and modulates the immunophenotype of Jurkat cells. Moreover, we observed that the ATP release increases when higher electric fields are applied. Application of 10kHz-100Hz and 25 pulses of nsPEF induces an increase in the expression of CD154 costimulatory molecule, which regulates the immune response by priming T cells and activating immune cells. Simultaneously, we increase the expression of the early activation marker CD69, indicating the ability to activate lymphocytes. The application of the 10kHz parameter upregulated the expression of antigens involved in the recruitment of inflammatory cells (CD183), controlling homeostasis of peripheral T lymphocytes (CD127) and regulating platelet adhesion (CD61). Importantly, we thus noted there was no alteration in the expression of CD95,

which can mediate the induction of apoptosis in cancer cells. On the contrary, significant CD7 subexpression was observed when 10Hz nsPEF was applied.
In general, the cells have not undergone cell death with lower electric field parameters but have modified their immunophenotype.
Based on our studies, we propose a mechanism in which the cells: (1) permeabilize the cell membrane, (2) increase the expression of lymphocyte-activation antigens, and (3) downregulate the expression of CD7.
Conclusions: Concluding, we can state that nsPEF can be a promising approach in immunotherapy via enhancing the presentation of lymphocyte-activation antigens. Also, we proved that application of electric field treatment could modulate the expression profile of lymphocytes while avoiding cell death.

Encore Abstract - previously submitted to regional or national meetings (up to < 1'000 attendees)

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Keywords: Diagnostic and Prognostic Biomarkers, Basic and Translational Science - Other

No conflicts of interests pertinent to the abstract.

650 | EFFECTS OF ALTERNATING MAGNETIC FIELD ON THE EXPRESSION OF ACTIVATION MARKERS CD154 AND CD69 IN JURKAT CELL LINE

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Introduction: Modulating membrane antigens by physical methods is currently an interesting attempt in oncology. The magnetic field treatment remains a novel approach in the therapy of cancer via its combination with ferromagnetic compounds. The drugs act as magneto-sensitizers in the therapy. The magnetic field also affects the metalloenzymes and thus may be used to modify the cells. This study aims to evaluate the potential of alternating magnetic fields (AMF) in activating the Jurkat cell line.
Materials and methods: In the study, we subjected Jurkat lymphocytes to the alternating magnetic field of 10 mT amplitude. First, the time of effective irradiation was established. Then, the MMP-2 activity was examined in the enzymatic assay. Afterward, we assessed the immunophenotype of the cells via flow cytometry studies. In the end, we performed the presto blue viability tests and simulated the conditions of magnetic field treatment.
Results: We assessed the overexpression of CD69 and CD154 activation markers with flow cytometry. Additionally, we tested CD7—the costimulatory antigen, CD25—receptor of IL-2, CD95—death receptor, and adhesion molecules CD61 and CD162. The proliferation of the cells, ATP content, and the activity of MMP-2 were evaluated as well. Before the experiments, we optimized the conditions of AMF treatment to avoid heating and affect the cells only with the alternating electric field. The optimal time of irradiation is 60 minutes, then MMP2 is less active (about 60%), and we observe the loss of signal in the fluorescence imaging studies. Results suggest that the magnetic field activates Jurkat cells and induce the overexpression of the CD69 (115%) and CD154 (130%) molecules. Besides, CD95 and CD25 expressions were elevated because of the MMP-2 deactivation. The expression of CD61 integrin was steadily decreased (20%).
Conclusions: We propose a mechanism in which the AMF interferes with the metalloproteinases' activity and thus affects the expression of MMP-regulated antigens. The study presents the potential of AMF in the activation of lymphocytes, however more research should be done in this field.

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Keywords: Radiation Therapy, Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

651 | CRISPR/CAS9 SCREENING REVEALS SOS1 PARTICIPATE IN ASPARAGINASE RESISTANCE IN NK/T CELL LYMPHOMA

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Introduction: Extranodal nature killer/T cell lymphoma (NKTCL) accounts for about 6% of all kinds of lymphoma. Asparaginase based chemotherapy regime greatly improved the outcome of NKTCL. However, asparaginase resistance still exists and patients who failed first line asparaginase treatment appeared a poor prognosis. At present, the mechanism of asparaginase resistance in NKTCL was few elucidated. CRISPR/Cas9 genome-wide screening has been widely used to explore disease mechanisms and novel drug targets. In this study, we explored asparaginase-resistant mechanism in NKTCL by CRISPR/Cas9 whole-genome screening, and sequencing after inducing resistant cells from sensitive cells, with a view to improve the clinical efficacy of asparaginase.

Methods: Exploring the sensitivity to asparaginase of NKTCL cell lines in our center, and selecting relative drug-resistant cell line for subsequent screening process. CRISPR/Cas9 library was transfected and whole genome knockout was performed. The transfected cells were selected by puromycin, and the transfection efficiency was controlled at about 30%. After treated with PEG-asparaginase or PBS as control group, DNA was extracted and sent for sequencing to explore drug-resistant genes. Long-term drug treatment was performed in sensitive cell lines to induce drug-resistant cell lines, and then RNA-Sequencing was conducted in parental and induced cells. Drug resistant targets were selected and in vitro validation was performed.

Results: CRISPR/Cas9 whole genome knockout library (TKvO3) was first transfected into KHYG-1 cells to screen the asparaginase resistant genes. The transfected cells were treated with asparaginase or vehicle for 5 days, the DNA of transfected cells was extracted for amplification and sequencing. Compared with the control group, SOS1 was one of the genes most significantly depleted in asparaginase-treated cells. Next the SOS1 targeting sgRNA were transfected into KHYG-1 cell line and improved the sensitivity of KHYG-1 towards asparaginase treatment. And then the SOS1 overexpression plasmid induced KHYG-1 cells more resistant to asparaginase treatment. Besides CRISPR/Cas9 whole genome screening, we also developed the asparaginase resistant cell lines by a long time of low-dose asparaginase treatment in NKYS and YT cells. The gene expression profile analysis indicated that SOS1 associated KRAS signal pathway was also significantly enriched in these related resistant cell lines.

Conclusions: Through CRISPR/Cas9 genome-wide knockout screening and long-time low-dose asparaginase treatment and then

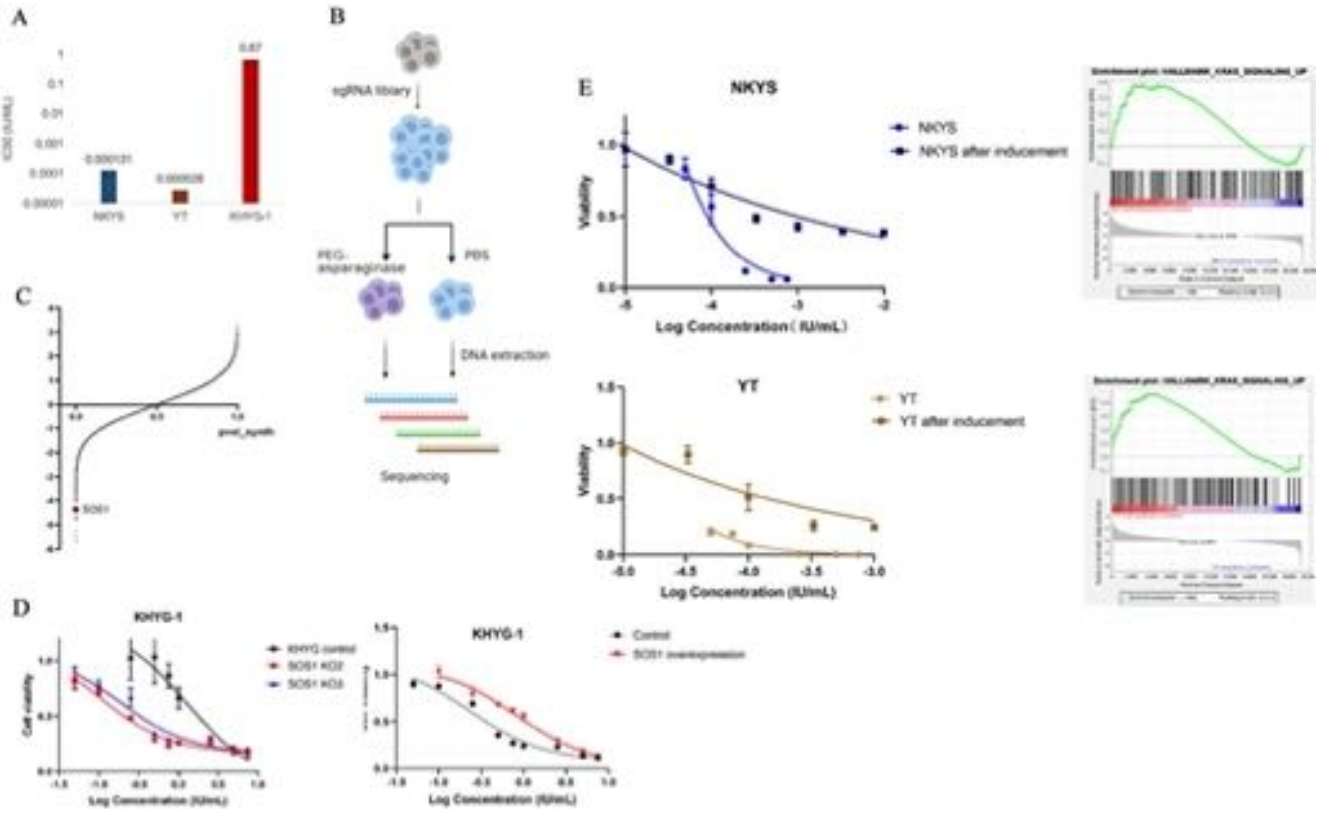

Figure 1: (A). Sensitivity of NKTCL cell lines to PEG-asparaginase. (B). KHYG-1 cells were transduced with the TKvO3 genome-wide guide RNA library in biologic duplicates, split into treatment with vehicle or asparaginase (0.25 IU/mL), and guide RNA representation was assessed after 5 days of treatment. (C). Significance of gene depletion in asparaginase-treated conditions, as assessed using MAGeCK analysis. (D). The indicated cell line was transduced with the indicated sgRNAs or overexpression plasmid, and treated with the indicated doses of asparaginase. Relative viability was assessed after 3 days of treatment by counting viable cells. (E). IC50 (median inhibitory concentration) graphs of parental NKTCL cell lines and induced resistant cell lines. GSEA enrichment depicted KRAS signaling pathway was significantly up-regulated.

sequencing comparing with parental cell lines, we found that SOS1 gene can significantly affect asparaginase sensitivity in NKTCL. Although more *in vivo* and *in vitro*validations are still needed, this study provides a potential therapeutic option for overcoming asparaginase resistance in NKTCL.

Keywords: Extranodal non-Hodgkin lymphoma, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

652 | A HYBRID ENERGY- AND AI-BASED SCREENING FOR NOVEL INHIBITORS OF LCK FOR THE TREATMENT OF T-CELL LYMPHOBLASTIC LYMPHOMA

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Introduction: T-cell lymphoblastic lymphoma (T-LBL), also known as T-cell acute lymphoblastic leukemia (T-ALL) when tumor cells massively infiltrate bone marrow (>20%), is an aggressive hematological malignancy with a particularly dismal prognosis in patients with relapsed diseases. Recent studies have discovered that approximately 40% of T-LBL/T-ALL cases exhibit constitutive activation of Lymphocyte-specific protein tyrosine kinase (LCK), which may predispose to oncogenesis with pre-TCR signaling during early T-cell development. Dasatinib, a promising LCK inhibitor, has demonstrated significant anti-leukemic efficacy both in vitro and in vivo, but its response is limited to a small subtype of samples with only transient effects and frequent drug resistance. The aim of this study was to screen novel clinical available agents with more potent and selective inhibitory activity toward LCK.

Methods and Results: To identify potential inhibitors, a structure-based hybrid high-throughput virtual screening (HTVS) protocol and the DeepDock algorithm were utilized to obtain 10 novel compounds from an "in-house" database (over 9000 compounds). The further biological evaluations revealed that compound ALK-IN-1 exhibited an IC_{50} value of 1.84 nM in in vitro kinase activity assay, resulting in a >10-fold higher cytotoxicity than that of dasatinib (LD_{50}: 0.36 μM vs. 4.75 μM) in the T-ALL cell lines MOLT3 and Jurkat. To better illustrate the activity of ALK-IN-1, a 500 ns molecular dynamics (MD) simulation was conducted to verify the binding conformation, providing more details of their interactions.

Conclusions: These findings suggest that ALK-IN-1 may represent a highly effective inhibitor with potential therapeutic value for T-LBL/T-ALL patients. Finally, we believe that further structural optimization and preclinical evaluation are warranted to validate its therapeutic promise.

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Keywords: Aggressive T-cell non-Hodgkin lymphoma, Bioinformatics; Computational and Systems Biology, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

PHASE I-II

653 | UPDATED RESULTS FROM A PHASE 1B STUDY OF AMDIZALISIB, A NOVEL INHIBITOR OF PHOSPHOINOSITIDE 3-KINASE-DELTA (PI3Kδ), IN PATIENTS WITH RELAPSED OR REFRACTORY LYMPHOMA

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Introduction: Amdizalisib (HMPL-689) is an oral, potent and highly selective small molecule phosphoinositide 3-kinase-delta inhibitor, which showed tolerable safety profile and promising clinical activity in patients (pts) with relapsed/refractory (R/R) B-cell lymphoma, particularly for follicular lymphoma (FL) pts (2021 ESMO). Here, the updates from this phase 1b study to present the safety in all pts at recommended phase 2 dose and efficacy in pts from 4 cohorts will be reported.

Methods: Six cohorts were enrolled in phase 1b study, including FL, marginal zone lymphoma (MZL), mantle cell lymphoma (MCL),

TABLE 1 Efficacy of amdizalisib for R/R lymphomas.

	FL (N = 26)	MZL (N = 16)	MCL (N = 19)	PTCL (N = 31)	Total (N = 92)
Median follow up duration, months	22.1	20.3	22.0	11.1	19.4
ORR, n (%)	22 (84.6)	9 (56.3)	11 (57.9)	10 (32.3)	52 (56.5)
CR, n (%)	9 (34.6)	1 (6.3)	1 (5.3)	4 (12.9)	15 (16.3)
Median TTR, months	1.9	1.9	1.9	1.9	1.9
DoR					
Median, months	NR	NR	4.9	12.0	NR
6 month, %	86.1	87.5	50.0	100.0	81.4
12 month, %	65.9	87.5	25.0	NR	61.9
PFS					
Median, months	NR	26.8	3.9	2.8	11.0
6 month, %	84.6	85.1	36.9	34.8	59.2
12 month, %	67.7	85.1	18.5	29.8	49.3

peripheral T cell lymphoma (PTCL), diffuse large B-cell (DLBCL) and Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Pts who failed or had no eligible standard of care received amdizalisib 30 mg qd, until disease progression or intolerable toxicity. The primary efficacy endpoint was overall response rate (ORR).

Results: As of January 31, 2023, 153 pts were eligible for safety analysis with median age of 58 years and mean exposure duration of 8.7 months. They received a median of 3 prior anti-tumor therapies (range 1 to 11). Treatment emergent adverse events (TEAEs) were reported in 149 (97.4%) pts, and grade ≥3 TEAEs were reported in 94 (61.4%) pts. Common (≥5%) grade ≥3 TEAEs were pneumonia (15.7%), neutrophil count decreased (12.4%), lipase increased (7.8%), and rash (5.9%). 71 (46.4%) pts had TEAE leading to drug interruption, and 18 (11.8%) pts reported TEAE leading to discontinuation. There was no updates for DLBCL and CLL/SLL cohorts compared with 2021 ESMO presentation. Ninety-two pts from the rest 4 cohorts were evaluable for efficacy with a median follow-up duration of 19.4 months (Table 1). Fifteen pts (16.3%) achieved complete response (CR) and 37 pts (40.2%) achieved partial response (PR). They had median progression-free survival (PFS) of 11.0 months. The ORR, CR and 12-month duration of response (DoR) rate were 84.6%, 34.6% and 65.9% for FL pts. In MZL cohort, ORR was 56.3%, 12-month DoR rate was 87.5%. In MCL cohort, ORR was 57.9% and 6-month DoR rate was 50.0%. Four PTCL pts achieved CR, and ORR was 32.3%. All responded PTCL pts had a longer median DoR of 12 months.

Conclusion: Amdizalisib showed an acceptable safety profile and promising anti-tumor activity in R/R lymphoma, providing evidence for future investigations.

Clinical trial information: NCT03128164.

Keyword: Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

654 | ACTIVITY AND SAFETY OF PRECLINICAL AND A PHASE 1 STUDY OF PURINOSTAT MESYLATE, A UNIQUELY POTENT AND SELECTIVE HDAC I/IIB INHIBITOR IN RELAPSED OR REFRACTORY LYMPHOMA

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Introduction: Purinostat Mesylate (PM) is a uniquely potent and selective HDAC I/IIb inhibitor. This study evaluated the efficacy and safety of PM in preclinical studies and phase 1 clinical trial for the treatment of relapsed or refractory (R/R) lymphoma.

Methods: This open-label, non-randomized, first-in-human, phase 1 two-center trial enrolled adult patients with lymphoma who were refractory to or relapsed after ≥1 prior regimens. PM was administered by 30-minute intravenous infusion ranging from 4.0 mg/m^2 to 15.0 mg/m^2 in a standard 3 + 3 dose escalation design. Eligible patients received a single dose (Day 1) and multiple doses (Day 8, 11, and 15) followed by extended doses (Day 1, 4, 8, 11 in 21-day cycles). Additionally, multiple cell lines, xenograft mouse models of diffuse large B-cell lymphoma (DLBCL) were used to evaluate the PM activity and mechanism in vitro and in vivo.

Results: A total of 18 R/R lymphoma patients were enrolled. Among them, 11 patients with R/R DLBCL achieved objective responses rate (ORR) of 63.6% and the disease control rate (DCR) was 72.7% (4

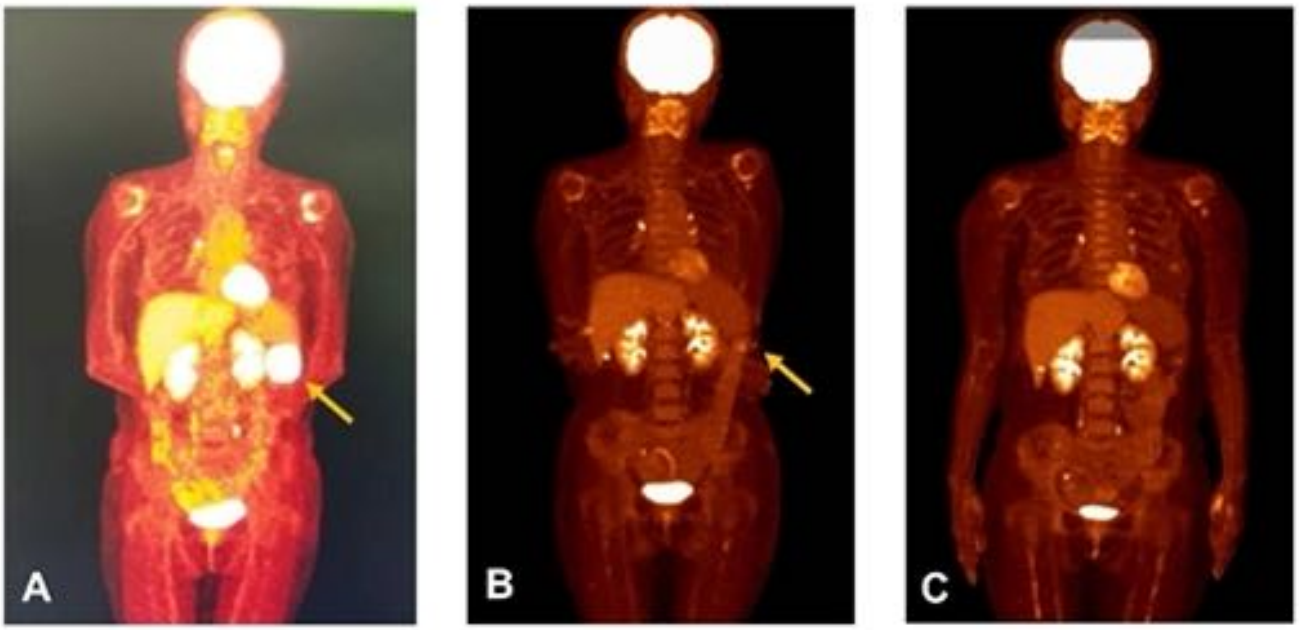
complete remissions [CR], and 3 partial remissions [PR]), and 1 stable disease [SD]). Notably, one patient with double-expression DLBCL who was refractory to two lines of therapy, including chidamide combined with R-CHOP and R-ICE regimen, obtained PR in cycle 3 and CR in cycle 5. Additionally, two out of 4 follicular lymphoma patients relapsed after 2~3 lines therapy achieved ORR of 50%. Most adverse events (AEs) were grade 1 to 2 and recovered with observation or symptomatic manageme. The most common Grade ≥3 AEs were thrombocytopenia (n = 48.1%), neutropenia (n = 48.1%), and anemia (11.1%), which occurred primarily during the extended dosing stages. Dose limiting toxicities (DLTs) have not been observed with dose escalation to the protocol-set maximum dose of 15.0 mg/m^2. Similarly, preclinical studies have also demonstrated the potent therapeutic activity of PM on DLBCL. In vitro, PM had better inhibitory activity against DLBCL cell lines than other HDAC inhibitors, such as chidamide and panobinostat. In several PDX models of

Table 1. Clinical characteristics and response assessment of 11 patients with RR DLBCL.

No.	Gender	Age	Histological feature	Stage	Prior therapy lines	Other HDAC inhibitor	ASCT	Dose	Response after cycle 1	Best efficacy to date	Cycles to date
11	Male	55y	nonGCB, double-expression	III	2	Chidamide	No	6.0 mg/m^2	PD	PD	1
15	Female	58y	non-GCB	IV	1	No	No	8.4 mg/m^2	PR	CR (in cycle 3)	8
16	Male	47y	GCB	III	1	No	No	11.2 mg/m^2	PR	CR (in cycle 3)	7
17	Female	71y	non-GCB	IV	1	No	No	8.4 mg/m^2	PR	PR	7
19	Male	51y	not available	IV	2	No	Yes	11.2 mg/m^2	SD	PR (in cycle 3)	5
20	Female	64y	non-GCB, double-expression	IV	2	No	No	8.4 mg/m^2	SD	SD	4
21	Male	22y	non-GCB	IV	1	No	No	11.2 mg/m^2	PR	CR (in cycle 3)	8
23	Male	34y	GCB, double-expression	II	1	No	Yes	11.2 mg/m^2	PD	PD	1
25	Female	36y	non-GCB	IV	3	No	No	11.2 mg/m^2	PD	PD	1
26	Female	55y	non-GCB, double-expression	IV	2	Chidamide	No	15.0 mg/m^2	MR	CR(in cycle 5)	11
28	Female	57y	GCB	II	1	No	No	15.0 mg/m^2	MR	PR(in cycle 3)	6

non-GCB: non-germinal center B-cell; GCB: germinal center B-cell; ASCT: autologous stem cell transplantation; CR: complete remission; PR: partial remission; MR: minimal remission; SD: stable disease

Figure 1. Comparison of pre- and post-treatment PET-CT in a 55-year-old female patient with double-expression RR DLBCL who was refractory to two lines of therapy, including chidamide combined with R-CHOP and R-ICE regimen. (A) Before treatment; (B) PR achieved after 3 cycles; (C) CR achieved after 5 cycles.



DLBCL, the tumors of the PM-treated mice completely regressed, and the activity was significantly superior to selinexor, R-CHOP, and chidamide combined with R-CHOP, with controlled toxicity. Mechanistically, PM can significantly down-regulate the proteins c-MYC, EZH2, and mutated P53, which are closely related to the development of DLBCL. More importantly, we found that PM showed strong inhibitory activity against TP53-mutated DLBCL cell lines.

Conclusions: PMdemonstrated promising clinical activity and an acceptable safety profile in R/R lymphoma, especially good objective response in patients with DLBCL. Preclinical studies have also confirmed the potent anti-tumor activity of PM in DLBCL.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

No conflicts of interests pertinent to the abstract.

655 | TREATMENT OF B-CELL MALIGNANCIES WITH DZD8586 THROUGH OVERCOMING BOTH BTK-DEPENDENT AND BTK-INDEPENDENT RESISTANCE

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Introduction: Two types of clinical resistance mutations, the C481S mutation, and BTK loss-of-activity mutations, have been identified to covalent (ibrutinib, acalabrutinib, and zanubrutinib) and non-covalent BTK inhibitors (pirtobrutinib). A safe and effective drug to treat patients who relapsed or were refractory to BTK inhibitor treatment is urgently needed.

DZD8586 was designed to inhibit both BTK-dependent and BTK-independent BCR signaling pathways, with full blood-brain barrier (BBB) penetration. In the ongoing phase I/II studies (TAI-SHAN1, CTR20220558), DZD8586 demonstrated reasonable pharmacokinetic (PK) properties, safety profiles and preliminary anti-tumor activities in patients with relapsed or refractory (r/r) B-cell malignancies.

Methods: The anti-tumor activities of DZD8586 were evaluated in pre-clinical cell and animal models driven by wildtype as well as various mutant BTKs. A healthy volunteer clinical study (TAI-SHAN2, NCT05176873) was conducted to investigate PK, pharmacodynamics (PD), and the safety of DZD8586, offering insight into the drug mechanism of action. The ongoing TAI-SHAN1 study in patients included dose escalation and extension cohorts. Patients with r/r B-NHL who failed systemic therapy were enrolled to determine its recommended phase II dose (RP2D). Different subtypes of B-cell Non-Hodgkin Lymphoma, including chronic lymphocytic leukemia (CLL) who failed BTK inhibitor treatment, central nervous system lymphoma (CNSL), follicular lymphoma (FL), marginal zone lymphoma (MZL) and diffuse large B-cell lymphoma (DLBCL), are eligible. PD biomarkers were assessed.

Results: DZD8586 showed equal potencies against wildtype and C481S mutant BTKs, as well as BTK mutations resistant to pirtobrutinib.

In healthy subjects, exposure of DZD8586 increased approximately in a dose-proportional manner from 20 mg to 180 mg. Similar PK characteristics were observed between patients and healthy subjects with a half-life of ~20 h. At the doses of ≥25 mg, near complete inhibition of pBTK was observed.

A multinational dose escalation is ongoing. Patient characteristics: histological subtypes: FL, DLBCL, MZL, and MCL; median prior systemic therapies (range): 3 lines (2–6). Preliminary anti-tumor efficacies were observed in multiple B-NHL subtypes starting at 25 mg once daily. No patients experienced ≥ grade 3 treatment-related adverse events, per investigators' assessment.

Conclusion: DZD8586 is a promising investigational drug which could overcome BTK-dependent and BTK-independent resistance. In the ongoing clinical study, DZD8586 showed good safety profile and encouraging anti-tumor efficacy in heavily pre-treated r/r B-NHL patients. The updated data will be presented at the conference.

Encore Abstract - previously submitted to ASCO 2023

Keyword: Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract

Y. Bai
Employment or leadership position: Dizal Pharmaceutical

K. Fang
Employment or leadership position: Dizal Pharmaceutical

656 | PRECLINICAL AND A PHASE 1 STUDY OF PURINOSTAT MESYLATE, A NOVEL HDAC I/IIB SELECTIVE INHIBITOR, FOR THE TREATMENT OF RELAPSED OR REFRACTORY MULTIPLE MYELOMA

J. Wang[1], L. Yang[2], Q. Qiu[2], Y. Wen[2], H. Li[1], A. Zhao[1], P. Zhao[3], J. Wang[3], J. Xiang[4], J. Miao[4], L. Zheng[4], Y. Wang[4], L. Wang[5], W. Zhao[5], L. Chen[2], T. Niu[1]
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Introduction: Purinostat Mesylate (PM) is a uniquely potent and selective HDAC I/IIb inhibitor. This study evaluated the efficacy and safety of PM in preclinical studies and phase 1 clinical trial for the treatment of relapsed or refractory(R/R) Multiple Myeloma (MM).

Methods: This open-label, non-randomized, first-in-human, phase 1 two-center trial enrolled adult patients with MM who were refractory to or relapsed after ≥1 prior regimens. PM was administered by 30-minute intravenous infusion ranging from 1.2 to 8.4 mg/m^2 in a standard 3+3 dose escalation design. Eligible patients received a single dose (Day 1) and multiple doses (Day 8, 11, and 15) followed by extended doses (Day 1, 4, 8, 11 in 21-day cycles). MM cell lines and multiple mouse models were used to evaluate the antitumor activity of PM alone or in combination in vitro and in vivo.

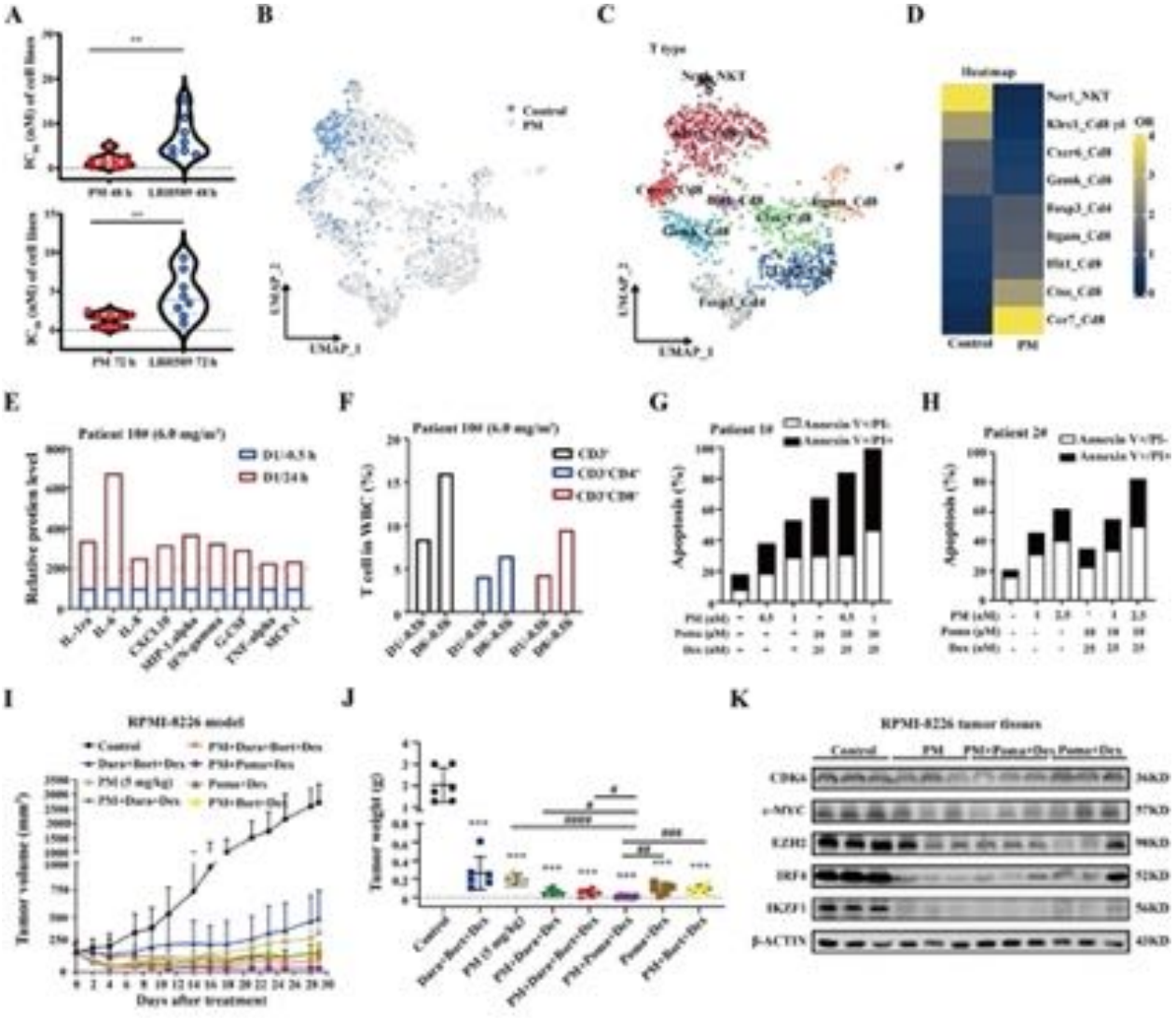

Fig.1 PM treatment of MM activates immunity and shows potent anti-myeloma activity. (A) Antiproliferative activity IC_{50} of PM and LBH589 treated 8 human MM cell lines for 48 and 72 hours, respectively. Each dot represents a cell line. (B-D) A single dose of Control and PM 10 mg/kg was used to treat 5TMM model mice for 24 hours, and single-cell sequencing was used to analyze its effect on T cells in the bone marrow of the model mice. (E) and (F) Patient 10#, a patient who obtained CR after PM treatment, measured serum cytokines and peripheral blood CD3⁺, CD3⁺ CD4⁺, CD3⁺ CD8⁺ T cell levels 0.5 hours before and 24 hours after treatment on the first day (or before the second dose) of PM. (G) and (H) Analysis of the primary cell apoptosis from relapsed plasma cell leukemia patients induced by PM combined with pomalidomide (Poma) and DXM (Dex). (I-K) The activity of PM combined with pomalidomide and DXM in the treatment of RPMI-8226 mouse model and its effect on key proteins in tumor tissues. All data represent mean ± SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, compared with Control group. # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$, #### $p < 0.0001$, compared with the specified group.

Additionally, various methods were used to study the mechanism of PM, such as Bulk RNA sequencing and single-cell RNA sequencing, Luminex high-throughput detection of cytokines, and others.

Results: A total of 11 heavily pretreated MM patients were enrolled. All evaluable 11 patients achieved the disease control rate (DCR) of 72.7%. Eight patients had stable disease after the first cycle of administration and entered the extended stage with a maximum of 6 extended cycles, of which one patient achieved a minimal remission. No dose-limiting toxic effects were observed.

At low nanomolar concentrations, PM exhibited superior antiproliferative activity and apoptosis induction compared to LBH589 in MM cell lines and patient-derived MM cells. In vivo studies demonstrated that PM alone was better than LBH589, or lenalidomide, bortezomib, and dexamethasone (DXM) triple-drug combinations in treating multiple MM mouse models. Mechanistically, PM significantly inhibited the key proteins for MM survival, including c-MYC, IRF4, EZH2, IKZF1, and IKZF3, and activated the innate and adaptive immune response in MM model mice. Combining PM with pomalidomide and DXM has strong antiproliferative effects and reduces key proteins for MM survival in MM1S and MM1R cell lines [CI index = 0.092]. In mouse models, this combination treatment is more effective than PM alone and other triple-drug combination therapies (selinexor, pomalidomide, and DXM, and daratumumab, pomalidomide, and DXM) without significant toxicity.

Conclusions: PM showed low toxicity and potent efficacy in R/R MM by downregulating key proteins for MM survival and activating immunity in preclinical and phase 1 studies. The triple-drug combination of PM, pomalidomide and DXM has demonstrated strong synergistic anti-tumor activity, laying the foundation for phase 2 clinical trials.

Keywords: Molecular Targeted Therapies, Multiple Myeloma

No conflicts of interests pertinent to the abstract.

657 | PHASE 1 TRIAL OF KT-413, A DEGRADER OF IRAK4 AND IMID SUBSTRATES, IN ADULT PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMAS

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Background: Oncogenic mutations in myeloid differentiation primary response 88 (MYD88) occur in about 25% of diffuse large B-cell lymphoma (DLBCL), including approximately one-third of activated B-cell (ABC) nodal DLBCL and 70-80% of ABC-like primary extranodal lymphomas, and are associated with poor survival. MYD88 mutations also occur in up to 90-95% of patients with Waldenström's Macroglobulinemia (WM). These mutations result in activation of the NF-κB pathway via interleukin-1 receptor associated kinase 4 (IRAK4), as well as IMiD substrate (Ikaros and Aiolos)-dependent upregulation of IRF4, which further activates NF-kB while also downregulating Type I IFN signaling, thereby preventing oncogene-induced cell death. KT-413 is a first-in-class, potent, highly selective, heterobifunctional small molecule degrader of IRAK4, Ikaros and Aiolos. Degradation of these 3 targets has been shown to maximize NF-κB inhibition and upregulate the Type I IFN response in MYD88-mutant DLBCL, leading to potent cell killing. In mouse xenograft models of MYD88-mutant DLBCL, KT-413 achieved complete tumor responses associated with >60% IRAK4 and >90% Ikaros/Aiolos degradation for at least 48 hours in tumors.

Methods: Ongoing Phase 1a/1b study to evaluate the safety, identify the recommended phase 2 dose (based on dose limiting toxicity (DLT) observed in Cycle 1 (Phase 1a)), PK, PD, and preliminary clinical activity of IV infused KT-413 on Day 1 of 21-day cycles in patients with R/R B-cell NHL. Blood samples are collected in Cycles 1 and 2 to measure KT-413 plasma concentrations and target degradation in PBMC and perform immunophenotyping. Serial tumor biopsies, when available, are also evaluated for PD.

Result: As of February 3, 2023, three patients have been treated in the first 3 dose levels (DLs) in Phase 1a, including transformed ABC-DLBCL, follicular lymphoma and marginal zone lymphoma that were all MYD88 wild-type. No DLTs were observed and the most common adverse events across all three dose levels were Grade 1 and 2 fatigue and pyrexia. Plasma PK results were in line with the modeled predictions and dose-dependent, sustained target knockdown in PBMC was observed by flow cytometry starting at DL1, with up to 57% reduction in IRAK4 and 96-100% reduction in Ikaros and Aiolos by DL3. Degradation measured by mass spectrometry was achieved in serial tumor biopsies obtained in DL1.

Conclusion: Initial clinical data with KT-413 demonstrate degradation of IRAK4 and Ikaros/Aiolos in PBMC and tumor. It is anticipated that higher doses will achieve the predicted degradation profile in tumors that may confer clinical benefit in MYD88-mutant patients. Dose escalation is ongoing, and analyses from additional patients will be presented at the meeting.

The research was funded by: Kymera Therapeutics

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Extranodal non-Hodgkin lymphoma, Therapeutics and Clinical Trials in Lymphoma - Other

Conflicts of interests pertinent to the abstract

J. K. Lue
Consultant or advisory role TG Therapeutics, Epizyme

E. Ayers
Consultant or advisory role ADC Therapeutics and Genentech

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Employment or leadership position: Kymera Therapeutics
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Stock ownership: Kymera Therapeutics, Pfizer

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Stock ownership: Kymera Therapeutics

658 | SELINXOR COMBINED WITH LENALIDOMIDE AND RITUXIMAB (R2) IN ADULTS WITH DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) AND INDOLENT NON-HODGKIN'S LYMPHOMA (INHL) (SWATCH STUDY)

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Background: Patients (pts) with relapsed/refractory (R/R) DLBCL and iNHL who are ineligible for, or relapse after, high-dose chemotherapy (HDC)/autologous stem cell transplantation (ASCT) have a poor prognosis and limited treatment options. Selinexor, a selective inhibitor of nuclear export has been approved by the US Food and Drug Administration for the treatment of R/R DLBCL. We hereby present the preliminary results of a phase I/II study (NCT05265975) evaluating the safety and tolerability of selinexor in combination with R2 for R/R DLBCL and iNHL.

Methods: Pts with R/R DLBCL or iNHL were eligible for study enrollment but only R/R DLBCL were permitted in dose-escalation phase. Bayesian Optimal Interval (BOIN) design was used to determine the safety, tolerability, maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D). Eligible pts were treated with 6 cycles of rituximab (375 mg/m^2 on day 1), lenalidomide (25 mg on d1-10) and selinexor (dose level: 40mg, 60mg, or 80mg on days 1, 8, 15 of each 28-day cycle), followed by selinexor and lenalidomide maintenance until disease progression. Dose limiting toxicities (DLT) was defined as the occurrence of severe toxicities during the first cycle: grade 3 febrile neutropenia> 5 days, grade 4 neutropenia or thrombocytopenia >7 days, grade 3/4 thrombocytopenia with hemorrhage, or any grade 3 non-hematologic toxicity >7 days.

Results: From May 2022 to December 2022, 10 pts were enrolled in dose-escalation phase. No DLT occurred among the first 3 pts in the 40 mg cohort and 1 out of 3 pts achieved partial response (PR). In 3 pts in the 60mg cohort, no DLT and serious adverse events (SAEs) were observed in continuous treatments and among 2 efficacy evaluable pts, one pt achieved complete response (CR) and another achieved PR. No DLT was observed among the first 4 pts in 80 mg cohort and one pt had a lasting grade 3 to 4 thrombocytopenia (SAE). Among 3 efficacy evaluable pts, two pts achieved CR and another achieved PR. Most AEs were grade 1 or 2 among the 10 pts. The most common grade 3 or 4 AEs were neutropenia (60%), leukopenia (50%), thrombocytopenia (40%), lymphocytopenia (30%) and were reversible with supportive care or dose modification. At data cutoff (March 1, 2023), 6 pts were still receiving treatment and no pt came off study due to intolerability or AEs. MTD was not reached, however, based on the comparable safety and efficacy results between 60 and 80 mg cohorts and clinical consideration that chemo-free regimen was mainly used in pts ineligible for HDC/ASCT, selinexor 60 mg on days 1, 8,15 + R2 is the recommended RP2D for a possible safer and durable regimen.

Conclusion: Selinexor in combination with lenalidomide and rituximab showed encouraging preliminary efficacy and tolerable toxicity with an ORR of 75% and CR of 37.5% in all evaluable dose level pts. The study is ongoing to further confirm the safety and tolerability of RP2D.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies

Conflicts of interests pertinent to the abstract

L. Pei
Employment or leadership position: employee of Antengene Company

Table 1: The Characteristics of the patients

No.	Age	IPI	Number of previous systemic regimens	Refractory to the most recent regimen	Primary refractory disease	Selinexor dose level	DLT in cycle1
1	35	2	1	yes	yes	40	no
2	57	1	5	yes	yes	40	no
3	45	1	2	yes	yes	40	no
4	60	1	2	yes	Yes	60	no
5	68	2	3	yes	yes	60	no
6	77	2	1	yes	yes	60	no
7	23	0	2	yes	no	80	no
8	50	2	3	yes	yes	80	no
9	30	2	1	no	no	80	no
10	52	2	1	yes	yes	80	no

659 | ORIENT STUDY: REGIMEN OF ORELABRUTINIB PLUS R-CHOP-LIKE FOR PATIENTS WITH NEWLY DIAGNOSED UNTREATED NON-GCB DLBCL

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Introduction: Orelabrutinib (O), as a novel highly selective bruton tyrosine kinase inhibitors (BTKi), preserved NK-cell-mediated antibody-dependent cellular cytotoxicity (ADCC) induced by rituximab (R) and thus boost antitumor effect of R-based regimen. We aimed to analyze efficacy and safety of O plus R-CHOP-like (O+R-CHOP) for untreated non-germinal center B-cell-like diffuse large B-cell lymphoma (non-GCB DLBCL) patients (pts) who benefited from induction therapy of O plus R (OR).

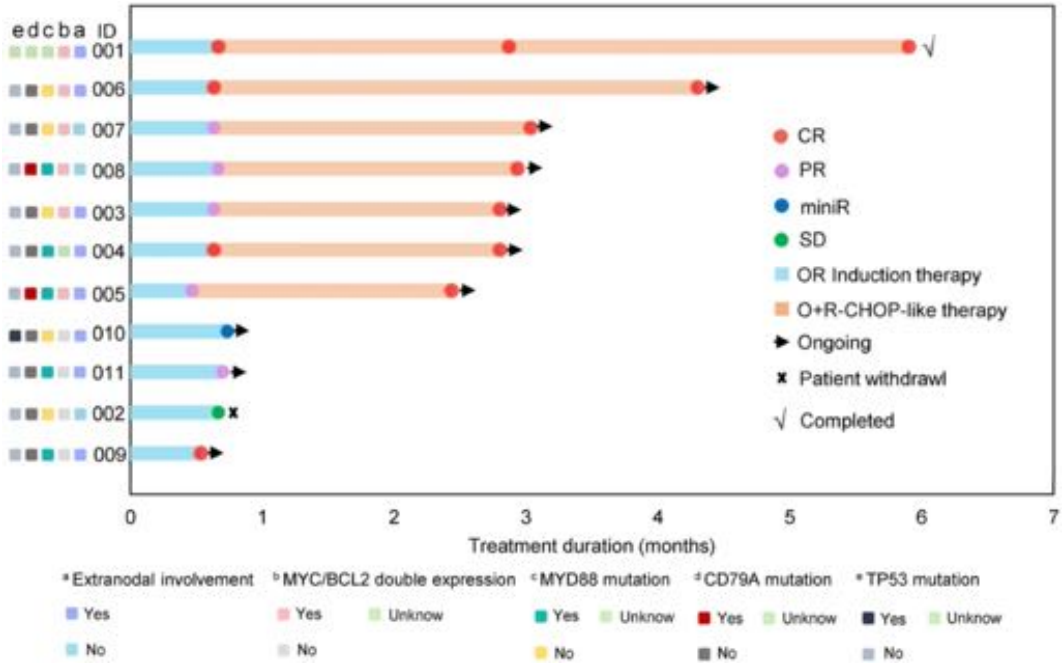
Methods: Pts with untreated non-GCB DLBCL were enrolled in the ongoing, multicenter, phase II study (NCT05498259). Pts received O (150 mg/day) and R (375 mg/m^2, day 1) at induction stage for 21 days. Then, pts with reduction in a lesion of ≥25% received O (150 mg/day) + R-CHOP on a 21-day cycle for 6 cycles. Primary endpoint was complete remission (CR) rate after 6 cycles of O+R-CHOP. Secondary endpoints were mini or better response rate (mRR, defined as percentage of pts with CR, partial remission [PR], and mini response [miniR, lesion reduction 25%–50%]) after OR, overall response rate (ORR) and progression-free survival after O+R-CHOP, and safety.

Results: Eleven pts (median age, 62 years) were enrolled by the cutoff date (March 6, 2023). Most had extranodal involvement (72.7%) and MYC/BCL2 double expression lymphoma (DEL, 54.5%). All had stage III-IV disease. Among them, 5, 2, and 1 pt had detected MYD88, CD79A, and TP53 mutations, respectively.

All 11 completed induction therapy, 10 pts attained response, and mRR was 90.9% (CR 36.4%; PR 45.5%; miniR 9.1%) and then 10 continued to receive O+R-CHOP (median, 4 cycles). Seven (70.0%) pts completed ≥3 cycles of O+R-CHOP and all achieved CR at the end of cycle 3; among whom 1 (10.0%) sustained CR at the end of cycle 6 (Figure 1). Throughout therapy, 8 (80.0%) of the 10 pts had achieved CR, with ORR of 90.0%. No progressive disease or death was reported. By subgroup analysis of 11 pts after induction stage, pts with DEL had better mRR (100.0% vs. 75.0%) than non-DEL. A similar result was observed in pts with extranodal involvement over those without (mRR 100.0% vs. 66.7%). Besides, pts with DEL and extranodal involvement had CRR of 100.0% and 75.0%, respectively while pts with MYD88 and CD79A mutations obtained CR of 80.0% and 100.0%, respectively among 10 pts with O+R-CHOP.

At OR stage, 4 (36.4%) pts had adverse events (AEs), with grade 1–2 hematological AEs. Throughout therapy, AEs occurred in 8 (72.7%) pts, with 3 (27.3%) grade ≥3 (1 lymphocyte count decreased, 1 pulmonary infection, 1 white blood cell decreased, and 1 neutrophil count decreased). No deaths or treatment discontinuation due to AEs were observed.

Conclusions: Despite preliminary, responders to OR induction therapy may attain synergistic antitumor effect and high CRR when receiving subsequent O+R-CHOP. Safety was favorable. More updated data will be reported from this ongoing study.



Encore Abstract - previously submitted to EHA 2023

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Keywords: Molecular Targeted Therapies, Lymphoid Cancers - Other

No conflicts of interests pertinent to the abstract.

660 | **PHASE I TRIAL OF 'RE-PRIMING' RADIATION THERAPY FOR RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS IN INCOMPLETE RESPONSE AFTER CAR-T THERAPY**

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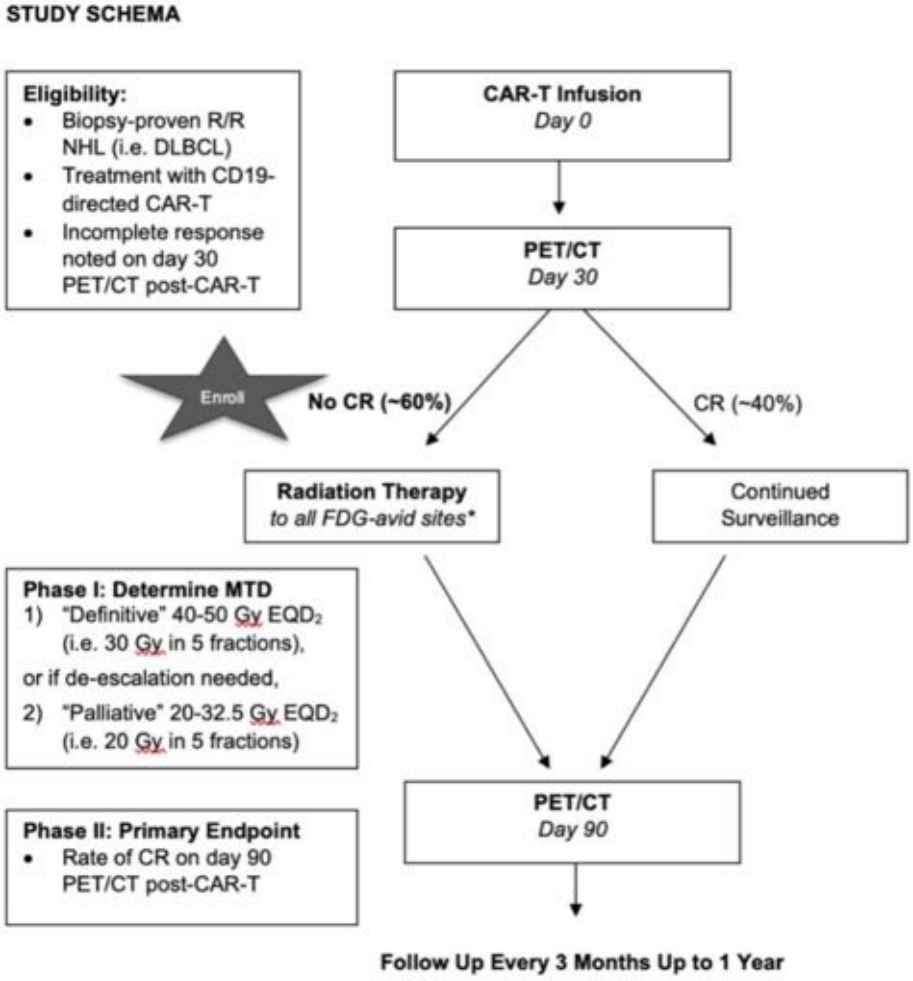
Introduction: In patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) treated with CD19-directed chimeric antigen receptor T-cell therapy (CAR-T), the large majority (~70%) ultimately fail. Early intervention to *'re-prime'* CAR-T with focal RT to partial responding sites may improve outcomes, based upon studies suggesting immune augmentation when combining RT with CAR-T. We report results of the phase I portion of a prospective phase I/II clinical trial hypothesizing that early focal RT to poor responding sites of disease identified on FDG-PET/CT after CAR-T in R/R DLBCL patients is safe (phase I) and will improve conversion to CR versus historical control to 58% (phase II).

Methods: We opened a single-arm, open-label, phase I/II prospective clinical trial at our institution for R/R DLBCL patients treated with CD19-directed CAR-T, and with incomplete response on day 30 post-CAR-T PET/CT scan (defined as Lugano ≥4). The phase I component used a 'Rolling 6' design with 6 patients enrolled concurrently at the "definitive" dose level (40-50 Gy EQD_2 [i.e. 30 Gy in 5 fractions]), with de-escalation to "palliative" dose level (20–32.5 Gy EQD_2 [i.e. 20 Gy in 5 fractions]) if >2 dose-limiting toxicities (DLT) were observed (Figure 1). Hypofractionated regimens (i.e. 5 fractions) directed only to residual FDG-avid disease were recommended to minimize lymphopenia and potentially result in a more favorable immune microenvironment. DLT was defined as toxicity occurring within 60 days of RT by the following criteria: CTCAE v5.0 grade 4+ hematologic, grade 3+ dermatitis, pneumonitis, enteritis, or other toxicity attributable to RT, as well as new grade 3+ cytokine release syndrome (CRS) or neurotoxicity (ICANS) per ASTCT consensus guidelines.

Results: Between April 2021 and July 2022, 6 patients with DLBCL were enrolled. Three patients (50%) had transformed disease from



low-grade follicular lymphoma. Two patients (33%) had primary refractory DLBCL, while the other 4 (66%) had median 2.5 lines of treatment prior to CAR-T. No patient had prior RT to their site(s) of residual FDG-avid disease on day 30 post-CAR-T PET/CT. Five patients were treated to 30 Gy in 5 fractions, with the remaining patient was treated to 36 Gy in 10 fractions. No specified DLTs were observed in the 60-day post-RT period. RT related toxicities included grade 1 alopecia, grade 1 radiation pneumonitis, grade 1 nausea & vomiting, and grade 2 skin infection. No delayed grade 3+ CRS or ICANS were observed.

Conclusion: Early hypofractionated salvage focal "definitive" dose RT to sites of incomplete response on day 30 post-CAR-T for R/R/ DLBCL patients was safe without any dose de-escalation required. This dose will be used in the subsequent phase II component of the trial.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cellular therapies, Radiation Therapy

Conflicts of interests pertinent to the abstract

P. Ramakrishnan Geethakumari
Consultant or advisory role Kite Pharma: Consultancy, Bristol Myers Squibb, Rafael Pharma, Pharmacyclics LLC, ADC Therapeutics, Cellectar Biosciences and Ono Pharma

F. T. Awan
Consultant or advisory role Genentech, AstraZeneca, Abbvie, Janssen, Pharmacyclics LLC, Gilead Sciences, Kitę Pharma, Celgene, Karyopharm, MEI Pharma, Verastem, Incyte, BeiGene, Johnson and Johnson, Dava Oncology, BMS, Merck, Cardinal Health, ADC Therapeutics, Epizyme, Caribou Biosciences, Cellectar Biosciences

PEDIATRIC / YOUNG ADULTS

661 | CORRELATION BETWEEN SOMATIC MUTATIONS AND PROGNOSIS IN PEDIATRIC MATURE B-CELL LYMPHOMA

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Introduction: To investigate the prognostic factors of childhood mature B-cell lymphoma (MBL), especially the significance of somatic *mutations* in the clinical features and prognosis, by analyzing the clinical chartacteristics, genetic *mutation* results and prognosis of 133 children with MBL.

Methods: Children and adolescents (≤18 years old) with MBL who were admitted from November 2017 to February 2023 were enrolled, and patients with somatic *mutations* were detected using next-generation sequencing (NGS). The diagnosis includes the completion of pathological examination and center consultation, and the staging is based on the international children's St. Jude staging system, primary patients were treated with the modified LMB89/96 protocol. Refractory or recurrent (r/r) patients were treated with second-line chemotherapy based on ICE and/or CAR-T-cell sequential therapy with different B-cell targets. The factors related to curative effect and prognosis, especially the correlation between the gene *mutation* spectrum and prognosis, were analyzed.

Results: The mutant gene spectrum of 133 patients is shown in Fig.a. According to the time of specimen collection, there were 77 cases of initial diagnosis (initial treatment group) and 56 cases of r/r patients (r/r group). The clinical feature and survival of the 133 patients are summarized in Figure b, c, d, e ($P < 0.001$) and g. The results showed that patients with a large tumor focus, serous cavity effusion and delayed chemotherapy during treatment had significant difference in prognosis and significantly shortened survival. The top three genes in the initial treatment group were *ID3* (53%), *TP53* (47%), and *CCND3* (30%) (Figure h). The top three genes in the r/r group were *TP53* (82%), *ID3* (58%), and *ARID1A* (40%) (Figure j). *TP53* was significantly different between the initial treatment group and r/r patients ($P < 0.001$). Of the 133 patients grouped by efficacy, 70 progressed/relapsed, and 59/70 received CAR T therapy, with an overall response rate (ORR) of 83%. Survival analysis is shown in the figure f. A total of 11/70 patients received second-line chemotherapy, and only 1 patient survived to receive treatment. Compared with second-line chemotherapy, CAR T-cell treatment significantly improved the

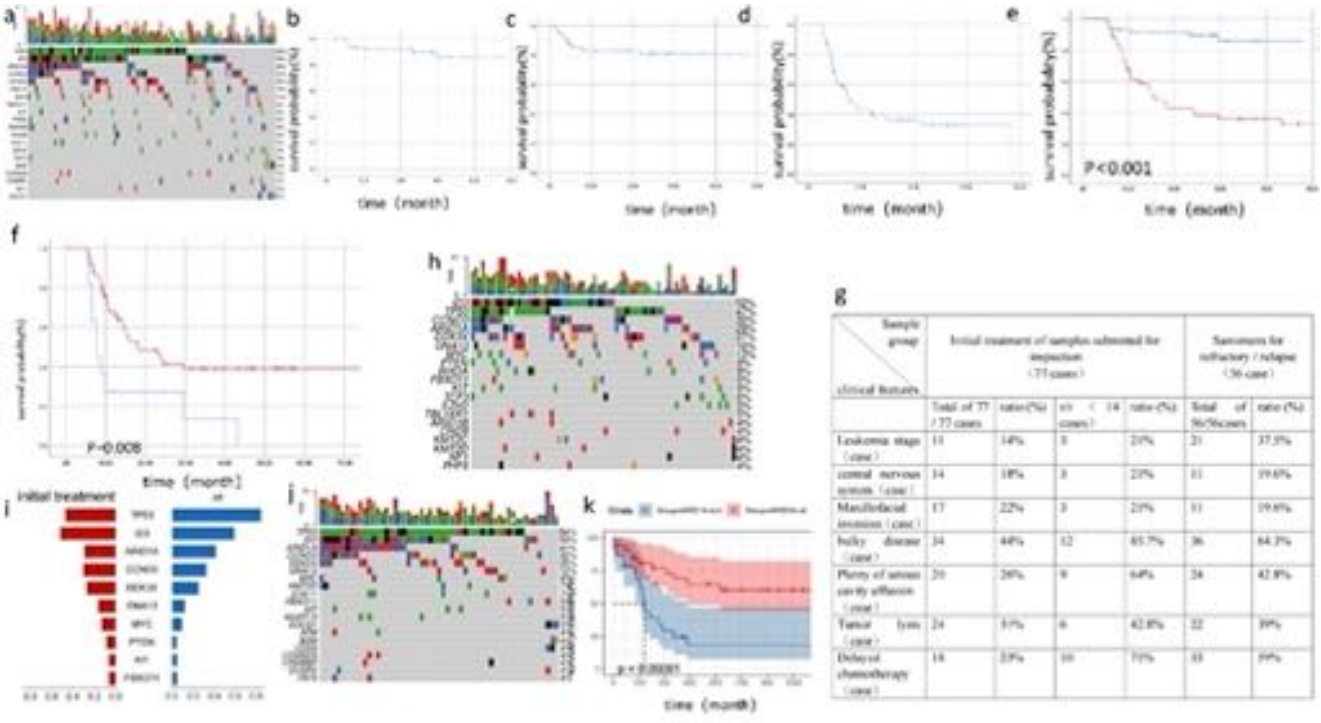

Figure (a) the mutations ladscapes of 133 MB-NHL. EFS (b) and OS (C) of the initial treatment group.(d) OS of r/r MBL.(e) Comparison of OS between initial treatment group and r/r groups. (f)Comparison of OS between the treated with CAR-T and without CAR-T.(g)clinical feature of 133 MBLs. (h) The somatic mutations landscape of 77 initial treament samples with MB-NHL. (i) Comparison of mutations profiling between initial remission patients with MBL (left, red) and r/r MBL (right, blue).(j) The somatic mutations landscape of 77 initial treament samples with MB-NHL.(K) Overall survival (OS) by *TP53* status in MB-NHL pediatric patients.

survival rate ($P = 0.008$). *ARID1A*was significant in patients with poor prognosis after CAR T therapy ($P = 0.00081$) (Figure k).

Conclusion: The frequency of *TP53* and *ARID1A* in the r/r group of mature B-cell lymphoma in children was significantly higher than that in the initial treatment group, while the incidence of *ID3* was relatively lower, suggesting that the change in the *mutation* frequency of tumor genes after treatment might be related to the change in the main clone gene after chemotherapy. The prognosis of patients with a large tumor focus, serous cavity effusion and delayed chemotherapy during treatment is poor. CART treatment can significantly prolong the survival rate and total survival period of r/r patients, but it cannot improve the prognosis of r/r patients with *ARID1A*.

Keywords: Chemotherapy, Diagnostic and Prognostic Biomarkers, Non-Hodgkin (Pediatric, Adolescent, and Young Adult)

No conflicts of interests pertinent to the abstract.

INFECTIONS

662 | THE INCIDENCE OF INTERSTITIAL PNEUMONIA IN NEWLY TREATED DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS DURING THE COVID-19 PANDEMIC: A SINGLE-CENTER, RETROSPECTIVE ANALYSIS OF CONSECUTIVE CASES

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Background: During 2020-2022, the COVID-19 pandemic has had a significant impact on overall medical management and the daily life of people in China. With the popularization of chest CT screening before admission to hospital, we can detect interstitial pneumonia in a more timely and accurate rate. Previous studies reported that the incidence of interstitial pneumonia (IP) caused by rituximab treatment was 3.7% to 16.7%, while the combination of rituximab and liposomal doxorubicin (R-CDOP) resulted in 28.95% incidence of IP.

Purpose: A total of 121 newly diagnosed diffuse large B-cell lymphoma (DLBCL) patients admitted to the Department of Hematology of Beijing Tongren Hospital from January 2020 to December 2022 were included in this single-center, retrospective analysis. All patients were treated with R-CHOP or R-CDOP. The incidence of treatment-related IP in DLBCL patients during the epidemic period and its correlation with clinical features were determined by chest CT screening before admission and mid-term PET-CT evaluation.

Method: All patients received R-CHOP (rituximab 375 mg/㎡ d0, cyclophosphamide 750 mg/㎡,d1, doxorubicin 50 mg/㎡,d1, vindesine 3 mg/㎡,d1, prednisone 60 mg/㎡ D1-5) or R-CDOP (liposomal doxorubicin 40 mg/㎡, maximum 60 mg, in replace of doxorubicin);R-miniCHOP or miniCDOP was used in patients older than 70 years old. The baseline clinical and pathological characteristics were collected. The occurrence of IP was evaluated by chest CT or PET-CT examination. The short-term response rate (ORR or CR rate) was determined according to the modified Lugano response evaluation criteria.

Results: Twenty-three of 121 patients developed IP during treatment, with an overall incidence of 19%. The median time to occurrence of IP was after about 4 cycles of rituximab, and the median duration of treatment for IP was 8 days. A total of 15 patients received steroids-containing regimens for IP, 16 patients terminated rituximab treatment after the onset of IP, and 7 patients stopped liposomal doxorubicin. All patients with IP recovered after treatment. The incidence of IP was increased in patients treated with liposomal doxorubicin containing regimen (27.3 % vs. 14.3 %, $P = 0.080$), smoking (25.8 % vs. 16.7%, $P = 0.263$), advanced age (22.8 % vs. 11.9%, $P = 0.146$) and underlying disease (20.0% vs. 16.1%, $P = 0.636$) were associated with a higher incidence of IP. After R-CHOP or R-CDOP treatments, the CR rate of all patients reached 49.6% in the interim response evaluation, and 75.2% in the final evaluation. Compared with full-dose R-CHOP regimen, the rate of end-of-treatment CR rate increased from 70.0% to 82.1% and the incidence of IP increased from 16.4% to 30.0% with full-dose R-CDOP.

Conclusion: The occurrence of interstitial pneumonia should be vigilant after rituximab-containing treatments in patients with diffuse large B-cell lymphoma, especially in those with smoking, old age and underlying diseases. The prevention and monitoring of interstitial pneumonia should be strengthened after the application of liposomal doxorubicin.

The research was funded by: This work was supported by grants from the National Natural Science Foundation of China (grant No. 81873450, 82170181), Beijing Hospitals Authority Youth Programme (code: QML20200201), and Beijing Natural Science Foundation (No. 7222027) to Liang Wang

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chemotherapy, Prevention and Cancer Interception

No conflicts of interests pertinent to the abstract.

663 | LOW MORTALITY FROM COVID-19 IN PATIENTS WITH B CELL LYMPHOMA AFTER BISPECIFIC CD3 X CD20 THERAPY

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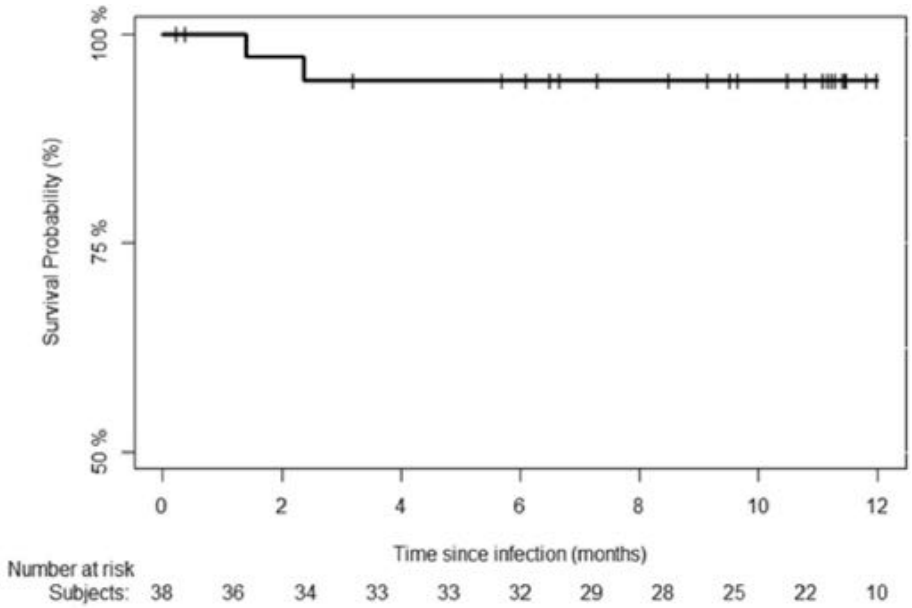

Figure 1. COVID-19 attributable survival probability after infection of B-cell lymphoma patients who have received bispecific antibodies. Patients who died of lymphoma with a resolution of COVID-19 symptoms are censored.

Introduction: Patients with hematological malignancies are at an increased risk of morbidity and mortality from COVID-19. Especially patients treated with CAR-T cell therapy for B-cell malignancies have poor outcomes after COVID-19, with case mortality rates >40%. Outcomes of COVID-19 in patients treated with CD20xCD3 bispecific antibodies have not been reported.

Methods: We identified all patients treated with bispecific antibodies in Denmark from December 2019 to December 2022. We collected data on date and variant of positive SARS-CoV-2 PCR tests, symptoms, reactivations, resolution of disease (either clinical, confirmed by negative PCR test or at death), vaccination status and treatments using electronic health charts and national registries. We assessed time from infection to death, reactivation or resolution and used a univariable cox regression to assess risk factors of reactivation of COVID-19.

Results: Of 130 treated patients we identified 43 patients infected with SARS-CoV-2, 5 were infected prior to CD20xCD3 treatment, and 38 were infected during CD20xCD3 treatment or after end-of-treatment. Five out of thirty-eight patients infected with SARS-CoV-2 died, but only in two patients was death related to COVID-19. The resulting COVID-19 attributable case mortality rate was thus 5.2% (95% CI 1,5% to 17.3%, Figure 1), while overall mortality was 13.2% (95%CI 5,75% to 27,3%) with a median follow-up of 11.2 months. Of the 5 patients who died during follow-up, 4 had refractory/relapsed lymphoma, at the time of the first infection with SARS-COV-2. Data on SARS-CoV-2 variants were available in 21 patients, whereof 19 were infected with omicron and 2 patients with delta.

Seventeen out of thirty-eight patients had at least one reactivation of COVID-19. The mean number of reactivations was 2.9 (95%CI 1.5 to 4.3), ranging from 1 up to 9. In univariable Cox regression, the significant factors associated with reactivation were hospitalization during the first SARS-CoV-2 infection and prior treatment with bendamustine (HR: 4.36, 95%CI 1.47-12.9, p=0.008 and HR: 4.68, 95%CI 1.63-13.5, p=0.004, respectively).

The median time to clinical resolution of COVID-19 was 13.5 days (IQR: 9) and the median time to virologic (PCR) resolution was 66 days (IQR: 52).

Conclusions: To our knowledge, this study presents the first data on COVID-19 incidence and severity in patients with relapsed/refractory lymphoma who received CD20xCD3 bispecific antibodies. The data indicate that there may be less severe complications of COVID-19 with this type of treatment when compared to CAR-T cell therapy. However, the distribution of virus variants was different from prior studies of COVID-19 in CAR-T cell recipients. Overall, it seems relatively safe to prescribe bispecific CD20xCD3 antibodies for patients with lymphoma who have been vaccinated against COVID-19 with the currently circulating variants.

The research was funded by:
The project was supported by grants from Rigshospitalets Research foundation, “Sejer perssons og Lis Klüver Perssons legat” and “Frk. Amalie Jørgenens legat”.

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Immunotherapy, Late Effects in Lymphoma Survivors

No conflicts of interests pertinent to the abstract to be declared.

664 | REPEATED VACCINATION TO MAXIMUM ANTIBODY RESPONSE AND ANTI-VIRAL THERAPY IN CLL AND MBL RESULT IN VERY LOW COVID MORTALITY AND HOSPITALISATION RATES

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Introduction: Patients with chronic lymphocytic leukemia (CLL) or monoclonal B-lymphocytosis (MBL) have impaired immunity. During the COVID pandemic, these patients are at high risk of severe COVID infection, hospitalisation, intensive care (ICU) admission and death. Mortality was very high during early pandemic waves at 30%–40%, and remains high at 10–15% during later waves. We adopted an approach of measuring anti-spike antibody (Ab) response following multiple COVID vaccine doses to assess the optimum individual response. Compared to post-2 vaccine doses (Shen, BJH, 2022), seroconversion and anti-spike Ab levels significantly increased in CLL and MBL after multiple sequential doses (Shen, Blood, 2022). After lifting most COVID restrictions in December 2021, infections rose from ~200 to >40,000 cases/day. Tixagevimab + cilgavimab (T+C) prophylaxis was not available until August 2022.

Methods: We evaluated infection, hospitalisation, ICU admission, and mortality rates, and anti-nucleocapsid (NC) Ab from PCR or RAT confirmed COVID infection in CLL and MBL patients.

Results: Of 184 patients (150 CLL and 34 MBL), 77 CLL (51.3%) and 18 MBL (52.9%) had confirmed COVID infection; 4 had a second infection. There were 4 (5.2%) CLL patients hospitalized (duration 3-8 weeks), no patient required ventilation, with 1 death (1/77 = 1.3%) due to acute anuric renal failure at 4 weeks. No MBL patient was hospitalised or died. Of the total 67 CLL and MBL infected patients with data, 21 received no medication and 20 had symptom-relief only, while 35/67 (52.2%) received antiviral therapy; molnupiravir (15), nirmatrelvir + ritonavir (15) or remdesivir (5). Only 6 received prophylactic T+C prior to COVID infection. There were 89 patients with positive anti-spike data (91.8%, 89/98, excluding post-T+C prophylaxis). The anti-spike levels in infected patients prior to infection (6036.5 AU/mL, 60 positive, 7 negative) were significantly lower compared to those never infected (14319.1 AU/mL, 50 positive, 0 negative) (p=0.038) (Figure 1). Anti-NC Ab was detected in 15 of 43 infected patients (34.9%) within 2 months; 6 of 11 (54.5%) followed >6 months lost detectable NC Ab.

Conclusion: The overall hospitalization rate of 5.2% and mortality rate of 1.3% in our COVID-infected CLL and clinical MBL cohort were significantly lower than those reported in early waves, and lower than rates reported in North America and Europe in late 2022. This suggests that a multiple dose vaccination strategy targeted to achieve a measured, optimum, anti-spike Ab level, with associated neutralising Ab and T-cell responses, is the key factor, as well as relatively easy access to anti-viral therapy. Prophylactic T+C in 6/67 patients may have contributed in this small group. CLL patients have an impaired seroconversion of anti-NC Ab at 34.9%, and half lose these by 6 months.

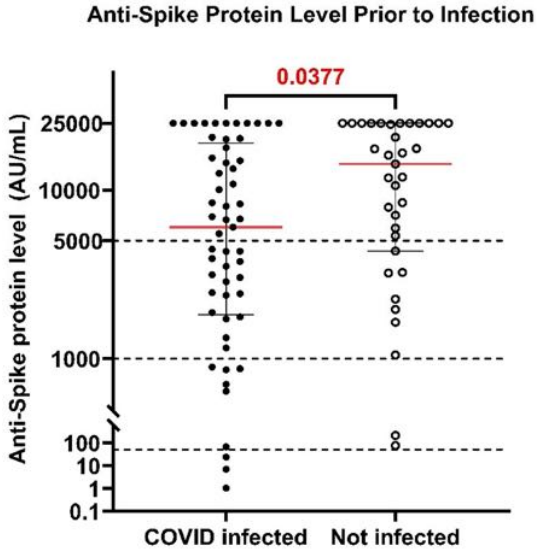

Figure 1. Anti-spike protein levels prior to infection.

Encore Abstract - previously submitted to EHA 2023

No conflicts of interests pertinent to the abstract to be declared.

665 | FACTORS INFLUENCING SURVIVAL AND PROLONGED VIRAL REPLICATION IN PATIENTS WITH LYMPHOMA AND COVID-19: AN OBSERVATIONAL COHORT STUDY FROM GELTAMO SPANISH GROUP

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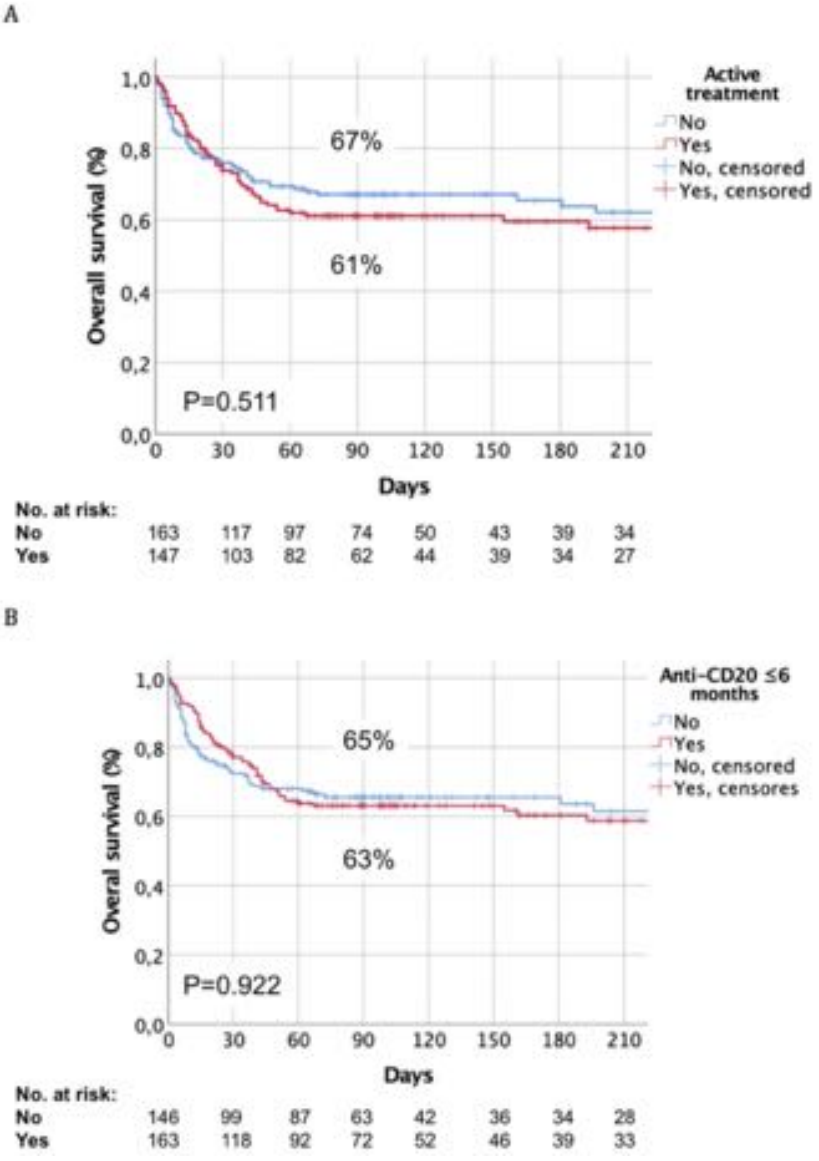
Introduction: Lymphoma patients may be especially vulnerable to COVID-19, due to the immune dysregulation caused by the

Figure 1. Overall survival in hospitalized patients according to active antitumoral treatment (A), and exposure to rituximab or obinutuzumab in the last 6 months (B)



lymphoma itself and the antitumor treatments. Prolonged viral replication represents a major threat for both, patients and the public health. However, information about viral evolution is scarce. We aimed to describe the risk factors affecting survival and prolonged viral replication in patients with lymphoma after developing COVID-19.

Methods: This is a retrospective multicenter study which included patients with a histological diagnosis of lymphoma and confirmed SARS-COV-2 infection before November 30, 2021. The primary outcome was overall survival (OS) 90 days after a COVID-19 diagnosis in hospitalized patients. The secondary outcome was prolonged viral replication, defined as patients with a prolonged positive real-time reverse transcription polymerase chain reaction at ≥3 weeks since diagnosis. For this analysis, we discarded all patients who died within the first 3 weeks of diagnosis.

Results: A total of 399 patients (median age 67 [21–94] years, 56% male) from 32 centers were included; 164 patients had an indolent B-cell non-Hodgkin's lymphoma (NHL), 129 aggressive B-cell NHL, 38 mantle-cell lymphoma, 29 peripheral T-cell lymphoma, and 29 Hodgkin's lymphoma. 44.1% of patients were on active treatment at the time of COVID-19 diagnosis. 79% of patients were hospitalized, and 13% were admitted in the intensive care unit.

With a median follow-up of 137 days (6–597), 118 patients have died (102 from COVID-19), with an estimated 90-day OS of 72% (95% CI 67%–76%) and 64% (95% CI 58%–69%) in the overall series and hospitalized patients, respectively. In the multivariate analysis, age ≥70 years (HR 2.85, 95% CI 2.17–4.72, $p < 0.001$), chronic heart disease (HR 1.80, 95% CI 1.11–2.91, $p = 0.017$), active lymphoma (HR 1.58, 95% CI 1.07–2.34, $p = 0.022$) and previous lines ≥3 (HR 1.76, 95% CI 1.08–2.87, $p = 0.023$) had independent influence on OS. Active antitumoral treatment and rituximab or obinutuzumab exposure in the last 6 months did not significantly impact OS (Figure 1). In contrast, active antitumoral treatment (12.9% vs. 7.1%, $p = 0.073$) and rituximab or obinutuzumab exposure in the last 6 months (15.2% vs. 4.6%, $p = 0.001$) were the single factors that increased the risk of prolonged viral replication, although only the last had significant influence in the multivariate analysis (RR 3.67, 95% CI 1.60–8.44, 0.002).

Conclusions: Our results confirm a high mortality in patients with lymphoma hospitalized before 2022 for COVID-19, especially in those ≥70 years old, with cardiac comorbidities, heavily pretreated or with active lymphoma. Recent exposure to anti-CD20 antibodies did not significantly impact on OS but was associated to a high incidence of prolonged viral replication. Analysis of Omicron wave and impact of vaccination in our series is ongoing.

Encore Abstract - previously submitted to regional or national meetings (up to <1'000 attendees)

Keyword: Lymphoid Cancers - Other

No conflicts of interests pertinent to the abstract.

666 | ASSOCIATION OF COVID-19 PANDEMIC WITH INDOLENT LYMPHOMA CARE DELIVERY AND OUTCOMES IN ONTARIO, CANADA: A POPULATION-BASED ANALYSIS

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Background: Due to concern for infection risk, the coronavirus disease 2019 (COVID-19) pandemic presented a unique challenge for optimal management of indolent non-Hodgkin lymphoma (iNHL). We examined treatment (trt) selection, healthcare utilization, and COVID-19 outcomes of pts with iNHL receiving first-line (1L) systemic treatment during pre-pandemic vs. pandemic period.

Methods: We performed a retrospective cohort study using administrative databases in Ontario, Canada, comparing outcomes in pts with iNHL who initiated trt from January 1, 2015 to December 31, 2018 (pre-pandemic cohort) and September 1, 2019 to August 1, 2020 (pandemic cohort), with end of follow-up March 31 2022. The primary outcome was trt pattern (e.g., 1L regimen, rituximab [R] maintenance use); secondary outcomes were death, toxicities, healthcare utilization (emergency department visit [ED], hospitalization), SARS-CoV-2 outcomes (infection, ED visit, hospitalization/death). Adjusted hazard ratios (aHR) from cause-specific proportional hazards models were used to estimate associations between factors and outcomes.

	Pandemic	Pre-pandemic	*P* value
1L Therapy			
BR	586 (91.0%)	2,328 (90.3%)	0.88
R-CVP	34 (5.3%)	147 (5.7%)	
R	24 (3.7%)	102 (4.0%)	
No. cycles	5.4 (1.3)	5.4 (1.3)	0.8
No. delays over 6 cycles	0.13 (0.40)	0.13 (0.38)	0.78
R maintenance	448 (69.6%)	1,957 (75.9%)	0.0009
Full course (q3 mns × 8)	329 (48.7%)	903 (56.3%)	0.0008
Outcome			
ED visit	0.94 (1.62)	1.23 (1.97)	0.0006
Hospitalization	0.49 (0.95)	0.63 (1.15)	0.0028
ICU	0.06 (0.26)	0.08 (0.31)	0.18
Death	50 (7.4%)	226 (8.5%)	0.27

Reported as *n* (%) or mean (SD)

Results: We identified 4,143 pts (1,079 pandemic, 3,064 pre-pandemic), median age 69 yrs, 44% female. In both pre- and pandemic periods, bendamustine (B)+R was the most frequent prescribed regimen, with no difference in number of cycles or delays (Table). During the pandemic, fewer pts received R maintenance and completed the full course (aHR 0.81, 95% confidence interval [CI] 0.71–0.92, $p = 0.0010$). Pts treated during the pandemic had less healthcare utilization (ED visit aHR 0.77, 95% CI 0.68, 0.88, $p < 0.0001$; hospitalization aHR 0.81, 95% CI 0.70–0.94, $p = 0.0067$) and trt-related complications (infection aHR 0.69, 95% CI 0.57–0.82, $p < 0.0001$; febrile neutropenia aHR 0.66, 95% CI 0.47–0.94, $p = 0.020$), with no difference in death (aHR 0.79, 95% CI 0.58–1.08, $p = 0.14$). R use (first dose to 1 yr post last dose) was associated with higher risk of SARS-CoV-2 infection (aHR 1.56, 95% CI 1.09–2.24, $p = 0.015$) and COVID-19 complications (ED visit aHR 4.28, 95% CI 1.79–10.26, $p = 0.0011$; hospitalization/death 1.81, 95% CI 1.11–2.93, $p = 0.016$).

Conclusion: During the pandemic, BR remained the preferred regimen for iNHL trt, while R maintenance use was less. Despite the similar 1L regimen, healthcare utilization and infectious complications were less in the pandemic cohort. R use was associated with nearly 2-fold risk of COVID-19 hospitalization/death.

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Conflict of interest:

A. Prica
Honoraria: Astra-Zeneca, Abbvie and Kite Gilead

M. Crump
Consultant or advisory role: Novartis and Kyte-Gilead

667 | IDENTIFYING FACTORS THAT AFFECT BARRIERS TO LYMPHOMA TREATMENT DURING THE COVID - 19 PANDEMIC

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Introduction: Barriers to therapy for patients with lymphoma are an essential topic. The Lymphoma Coalition biennial global patient survey collects data on patient experiences, including challenges or limitations patients face in seeking medical attention or access to treatment. Due to COVID-19, patients with lymphoma have experienced high barriers. This study aims to rank the influence of core demographic variables in their ability to predict barriers to lymphoma treatment in 2020 and 2022.

Methods: The survey was deployed globally to lymphoma patients and caregivers in 2020 and 2022. The outcome variable was the identification of any barrier to receiving lymphoma treatment. Logit regression was used to model the outcome against core demographics. Variable importance was quantified with independent Monte Carlo resampling.

Results: Barriers were significantly elevated in all regions in 2022 ($p < 0.0001$). Those who are of older age were found to have fewer barriers to treatment: Unit OR = 0.965; 95%CI [0.962–0.968]. Age was consistently a variable of high importance across most regions in both survey years (Table 1). In 2022, treatment delay due to concerns over COVID-19 was the second-ranked variable of importance in three regions.

Conclusions: Barriers to treatment for patients with lymphoma increased dramatically across all regions from 2020 to 2022. Increased barriers to treatment in those of younger age were an unexpected finding. Heterogeneity in the impact of variables that influence access to treatment appears to be enhanced by participants' psychosocial impacts due to the pandemic was noted and needs further study. Policymakers and providers should actively rectify access disparities and prepare plans for future health emergencies to lessen the impact in the future.

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Keyword: Cancer Health Disparities

No conflicts of interests pertinent to the abstract.

Table 1. Assessment of variable importance for encountering barriers to lymphoma treatment with the top two contributors to the model for each region displayed in bold.

Global Patient Survey 2020					
Variables	**Asia-Pacific**	**Europe**	**Middle East & Africa**	**North America**	**South America**
N	**2116**	**2476**	**30**	**820**	**99**
Percent with barrier	50.3%	11.7%	40.0%	18.9%	13.1%
Age	**0.473**	**0.286**	0.087	**0.493**	**0.309**
Education	0.148	0.029	**0.322**	0.011	0.004
Household Status	0.006	**0.432**	0.074	0.157	0.149
Indolent/Aggressive	0.014	0.126	0.199	**0.189**	0.150
Local Area	**0.353**	0.112	**0.316**	0.059	**0.483**
Sex/Gender	0.052	0.047	0.104	0.011	0.074
Global Patient Survey 2022					
Variables	**Asia-Pacific**	**Europe**	**Middle East & Africa**	**North America**	**South America**
N	**1573**	**2224**	**32**	**871**	**52**
Percent with barrier	85.7%	46.7%	88.9%	54.7%	76.1%
Age	**0.720**	**0.465**	0.001	**0.320**	0.067
COVID Delay	**0.157**	**0.386**	0.002	0.145	**0.294**
Education	0.001	0.008	0.195	0.046	0.033
Household Status	0.003	0.014	0.173	0.069	0.182
Indolent/Aggressive	0.052	0.007	**0.546**	0.053	**0.312**
Local Area	0.141	0.058	**0.304**	**0.375**	0.256
Sex/Gender	0.026	0.056	0.152	0.013	0.023

Age is treated as a continuous variable. COVID delay represents a deliberate delay in seeking lymphoma treatment due to fear of contracting COVID-19. Education was binary with the cut-point between secondary and post-secondary. Household status refers to those who are either single or with a partner. Indolent/Aggressive refers to typical clinical behaviour of a lymphoma subtype. Local Area refers to whether a respondent lives in an urban, suburban, or rural setting. Sex/Gender refers to biological sex in the absence of stated gender.

669 | TIXAGEVIMAB-CILGAVIMAB THERAPY IN THE PREVENTION OF SARS-COV2 INFECTION IN NON HODGKIN-B LYMPHOMAS AND HODGKIN LYMPHOMAS UNDER TREATMENT: OUR EXPERIENCE

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Patients with B-cell malignancies who become infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are at an increased risk of morbidity and mortality due to advanced age, use of B-cell-depleting therapies, and immunodeficiency. Despite development of COVID-19 messenger RNA vaccines, the majority of patients with B-cell malignancies fail to develop anti-SARS-CoV-2 spike antibodies in response to vaccination, and mortality rates secondary to COVID-19 infection over 10% have been reported. Preexposure prophylaxis with tixagevimab-cilgavimab may be an alternative strategy to decrease the incidence or severity of COVID-19 for patients with NHL B-cell malignancies. Tixagevimab-cilgavimab is a monoclonal antibody (MoAb) that inhibits attachment of the SARS-CoV-2 spike protein to the surface of cells, thereby preventing viral entry and infection by the COVID-19 virus. In December 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for its use in individuals 12

years and older with moderate to severe immunodeficiency. Tixagevimabcilgavimab was authorized based on results of the phase III PROVENT study, which demonstrated a breakthrough infection rate of 0.5% in unvaccinated adults at an increased risk of inadequate response or exposure toCOVID-19. However, only 7% of patients had cancer or a history of cancer, and 3% were actively receiving immunosuppressive therapy. The aim of the study is to evaluate the impact of prevention with texagevimab-cilgavimab in a cohort of patients, observed in our Division, with non-Hodgin B lymphoma or Hodgkin's lymphoma under treatment or who had finished treatment in the previous 6 months. From 1 July 2022 to 31 January 2023, we evaluated 101 pts 48 F and 53 M with a median age of 65 years (range 16–91 years) a cohort of patients (pts), who started or were under specific treatment, to whom we performed tixagevimab-cilgavimab in the prevention of SARS-CoV-2. 95% of pts had previously received the recommended vaccine doses, median 2 (range 2–4 doses). 12HD; 88 NHLs; 1 HCL. In 33 (33%) pts has been effectued before the start of treatment and 68 (67%) during treatment. 47 (46.5%) were on induction treatment, 47 (46.5%) on maintenance therapy with anti-CD20 or imbruvica or venetoclax and 7 (7%) had finished treatment within the previous 3 months. Of the 101 pts, 21% were developed covid infection during observation: 12 M and 9 F median age 65 years (range 21–83 years) 2 HD and 19 NHL. 14 pts were in maintenance therapy (9 rituximab; 4 Obinutuzumab and 1 pc ibrutinib + Rituximab) and 7 in induction treatment (2 AdAVD;1 G-CVP;2 R-MACOP-B;1 R-BAC and 1 R-COMP) . 12 pts (57%) had mild symptoms (median age 55 years) while 9 (43%) had severe symptoms who has required hospitalization (median age 75 years). 6 patients (28.5%), with a median age of 75 years, died of COVID. In 9/21 pts (43%) the treatment was not interrupted (4 patients in induction therapy and 5 patients in maintenance therapy) all with mild COVID symptoms, no COVID-related complication was documented in these patient. 4 pts regularly terminated the treatment while 5 are still in treatment. Of the patients who died, 1 had finished induction therapy (R-BAC) while 5 were on maintenance therapy (3 rituximab and 2 obinutuzumab). From our experience, prevention therapy does not seem to have changed the incidence and prognosis of the SARS-COV2 infection, certainly variables that seem to influence are age (75 vs 55 years) and the total IgG value (patients with severe symptoms had a median IgG of 415 mg/dl vs 817 mg/dl in patients with mildly symptomatic COVID), further in patients with mild symptoms the COVID infection did not interfere with the continuation of the specific treatment, we do not know if in these cases it could to helping the preventive therapy. A larger cohort of patients is needed to consolidate or confirm the data of our observation.

Encore Abstract - previously submitted to EHA 2023

No conflicts of interests pertinent to the abstract.

670 | B CELLS WITH VIRUS-NEUTRALIZING IGHV1-69 MUTATIONS SHOW LYMPHOMA-LIKE TRANSCRIPTOMES IN PATIENTS WITH CHRONIC HEPATITIS C INFECTION

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Introduction: Chronic hepatitis C virus (HCV) infection leads to a complex interplay with adaptive immune cells that may result in B cell dyscrasias such as type II mixed cryoglobulinemia and lymphoma. The introduction of direct-acting antiviral (DAA) therapy has reduced the burden of severe liver damage and its clinical consequences. However, the effect of viral elimination on extrahepatic manifestations of HCV such as the accompanying B cell dyscrasia remains to be defined.

Methods: We sequenced B cell repertoires in patients with chronic HCV infection and HCV patients with a sustained virological response (SVR) after DAA therapy. This data set was mined for highly neutralizing HCV antibodies and compared to a diffuse large B cell lymphoma data set. The TKO model was used to test signaling strength of selected B cell receptors (BCRs) in vitro. Single-cell RNA sequencing of chronic HCV and HCV SVR samples was performed to analyze the transcriptome of B cells with HCV-neutralizing antigen receptor.

Results: The majority of HCV patients showed a B cell fingerprint with high richness and somatic hypermutation. Convergence to specific immunoglobulin genes produced complementarity-determining region 3 (CDR3) sequence networks with high connectivity. IGHV1-69 CDR1 and CDR3 mutations characterizing highly neutralizing HCV antibodies corresponded to recurrent point mutations found in the clonotypic BCRs of high-grade lymphomas. These mutations did not confer autonomous BCR signaling but lowered the threshold for activation-induced BCR signaling. In addition, B cells carrying these point mutations showed a persisting oncogenic transcriptome signature with dysregulation in signaling nodes such as CARD11, MALT1, RelB and MAPK, and NFAT pathways.

Conclusions: We provide evidence that lymphoma-like cells may derive from the anti-HCV immune response. In many patients, these cells persist for years after SVR and can be interpreted as mechanistic basis for HCV-related B cell dyscrasias and increased lymphoma risk even beyond viral elimination.

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Keywords: Non-Hodgkin (Pediatric, Adolescent, and Young Adult), Tumor Biology and Heterogeneity

No conflicts of interests pertinent to the abstract.

671 | DIFFERENT TYPES OF ANTIVIRAL THERAPY (AVT) IN PATIENTS WITH VIRAL HEPATITIS C-ASSOCIATED DIFFUSE B-CELL LYMPHOMA (HCV + DVCL)

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The etiopathogenetic link between HCV and B-cell non-Hodgkin's lymphoma is thought to be proven in marginal zone cell lymphoma. Another serious therapeutic challenge is posed by HCV + DVCL, especially in terms of hepatotoxicity during immunochemotherapy (IHT). The emergence of direct-acting antiviral drugs (DAAs) has created an excellent opportunity for rapid HCV irradiation, while the timing of initiation, type and duration of DAAs in HCV + DBCL continues to be debated.

The aim of our study was to investigate the effect of different modes of AVT on the feasibility and efficacy of antitumor treatment in pts with HCV + DBCL.

The study included 64 pts with HCV + DBCL, who received IHT with AVT from 2010 to 2022. The median follow-up was 53 mths. The median age was 51 years (32–76), male-to-female ratio was 1:1.3. The majority of pts (91%) had advanced stage III-IV; B-symptoms were determined in 42 (65%) pts. Extranodal lesions were noted in 46 (72%): spleen -62%, liver -55% and bone marrow -31% involvement at the diagnosed. Thrombocytopenia was in 26(41%) pts, anemia -in 21 (33%). ALT – 53 (91%), AST – 42 (65%), GGTP and ALP were elevated in 35 (55%) pts, LDH—in 58 (91%) pts. Liver cirrhosis was in 4 (6%)pts. Viral load ranged from 3×10^3 to 1×10^8MU/ml (median – 2.6×10^6 MU/ml), genotype 1 was in 38 (61%) pts, genotypes 2–3 were in 26 (39%) pts.

All pts with HCV + DBCL received IHT according to the R-CHOP regimen. The pts were divided into two groups (G1 and G2) according to the type of AVT administered.

In G1 33 pts received ABT with INF + Riv for 12–30 mths (median 21 mths). In G2, 31 pts received DAAs for 3 -8 mths (median 4 mths).

Viral remission was achieved in G1 24 (73%) pts, and in G2 in all 31 (100%) ($p = 0.003$). At the time of IHT in both groups there was no hepatotoxicity in any pts.

Antitumor treatment was more effective in pts G1- the of complete remissions was 63% (21pts), and only 52% in G2 (16pts) ($p = 0.05$). Median PFS was 48 mths in G1 and 14 mths in G2 ($p = 0.001$); median OS was 67 mths (G1) and 28 mths (G2), respectively ($p = 0.0003$).

Conclusions: HCV + DBCL has characteristic clinical features: relatively young age of pts, more common stages of disease with frequent liver and spleen involvement. Virological response is rapidly in pts on DAA therapy, but the course of the disease and long-term results are significantly better in pts who received INF in a long-term regimen. Perhaps—combination of DAAs and INF will improve the results of treatment of pts with HCV + DBCL.

Encore Abstract - previously submitted to regional or national meetings (up to <1'000 attendees)

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Chemotherapy, Immunotherapy

No conflicts of interests pertinent to the abstract.

672 | INCIDENCE OF HBV REACTIVATION IN PATIENTS WITH DIFFUSED LARGE B CELL LYMPHOMA IN ERA OF PROPHYLACTIC ANTIVIRAL THERAPY

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Introduction: Patients with Diffused large B cell lymphoma (DLBCL) who are also co-infected with Hepatitis B virus (HBV) may experience HBV reactivation during immunochemotherapy which can delay or prematurely terminate anti-tumor treatment. It is usually considered that patients who are hepatitis B surface antigen-positive (HBsAg+) have a higher rate of HBV reactivation and a poorer prognosis compared with patients who have resolved hepatitis B virus infection (HBsAg+/anti-HBc+). However, limited data exists regarding the incidence of HBV reactivation and survival outcomes in DLBCL patients with HBsAg+ who receive prophylactic antivirals and HBsAg+/anti-HBc+ patients who adopt HBV DNA monitoring-guided antiviral strategies.

Methods: Patients newly diagnosed with DLBCL who were HBsAg+ or HBsAg+/anti-HBc+ and received at least 4 cycles of R-CHOP (rituximab, prednisone, vincristine, doxorubicin, and cyclophosphamide) or CHOP-like regimens between 1 January 2007 and 30 June 2021 in Peking University Cancer Hospital were reviewed retrospectively. We started the patients with HBsAg+ on prophylactic antiviral treatment from the start of antitumor therapy and

continued it for at least 1 year after completion of the last cycle of antitumor therapy.

Results: A total of 160 DLBCL patients with HBsAg+ and 317 patients with HBsAg+/anti-HBc+ were enrolled. Among patients with HBsAg+, 125 (78.13%) patients received entecavir, 30 (18.75%) patients received lamivudine, and 5 (1.5%) patients received adefovir or telbivudine. Most patients with HBsAg+/anti-HBc+ adopted HBV DNA monitoring-guided antiviral strategy, including 225 (71.0%) who did not receive any antiviral therapy, while 40 (12.6%) received entecavir and 52 (16.40%) received lamivudine. In patients with HBsAg+ group, 45 (28.12%) patients' HBV DNA load was between 10 and 2000 IU/mL, 55 (34.28%) had a high load of HBV DNA (≥2000 IU/mL) and the rest were negative (<10 IU/mL). While, in patients with HBsAg+/anti-HBc+ group, 269 (84.86%) patients had tested HBV DNA level at baseline, 5 (1.58%) patients' HBV DNA load was between 10 and 2000 IU/mL, 1 (0.31%) patient had a high load of HBV DNA (≥2000 IU/mL) and the rest were negative (<10 IU/mL). After a median follow-up of 60.0 months, HBV reactivation was observed in 10 (6.25%) patients in the HBsAg+ group and 11(3.47%) patients in the HBsAg+/anti-HBc+ group ($P = 0.139$). The median time from the beginning of chemotherapy to HBV reactivation were 1.5 months (range: 1.0–4.0 months) and 3.5 months (range: 1.0–6.0 months) in the two groups, respectively. No patients experienced HBV-associated hepatitis.

Conclusion: The incidence of HBV reactivation was significantly lower in the prophylactic antiviral era, even in patients with HBsAg+ lymphoma.

Keywords: Antiviral Agents; Diffuse; Hepatitis B virus; Infections; Lymphoma, Large B-Cell, Survival

The research was funded by: CSCO-HaoSen Oncology Research Fund 183 (Grant No. Y-HS202202-0104)

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Immunotherapy

No conflicts of interests pertinent to the abstract.

673 | VACCINATION STRATEGIES FOR PATIENTS WITH LYMPHOMA: A REAL-WORLD PRACTICE SURVEY AMONG FONDAZIONE ITALIANA LINFOMI CENTERS

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Introduction: Patients with hematological malignancies are at increased risk for various infections, including some (e.g., influenza and invasive pneumococcal disease) that are vaccine preventable. In particular, patients with lymphoma have impaired T cell or B cell immunity, and B cell immunity is further affected by the use of anti-B cell antibodies. Vaccination is an area often influenced by cultural differences, even among health-care workers, in compliance to vaccines. The aim of this study was to assess the attitudes on vaccination of different centers affiliated with Fondazione Italiana Linfomi (FIL) in Italy.

Methods: A survey questionnaire assessing vaccine uptakes and general opinion about vaccination was provided to 144 FIL centers between May 2022 and December 2022.

Results: Responses from 67 centers (46%) were received. All respondents reported information about vaccine strategies in the centers. Prior to starting chemotherapy, 67% of clinicians verify the vaccination history of patients, paying particular attention to the inactivated anti-influenza virus (83%), pneumococcal (71%), and varicella-zoster virus (46%). There is minor attention to vaccinations for diphtheria, tetanus, and pertussis (DTP) or measles, mumps, and rubella (MMR).

In fact, 83% of the centers recommend annual influenza vaccination while pneumococcal vaccination is reserved for 32% of the centers for patients over 65 years of age and 25% of the centers for splenectomized patients or with respiratory comorbidities. Only 7% recommend it to all patients. In 96% of the centers, the vaccination status against SARS-CoV-2 is checked, and 20% also perform anti-Spike antibody testing before starting treatment. 37% of clinicians administer pre-exposure prophylaxis with tixagevimab-cilgavimab (Evusheld) in patients with lymphoma who are candidates for or undergoing treatment, and 20% in patients undergoing treatment with anti-CD20. This practice has allowed to delay the fourth vaccine dose from 1 to 4 months in 46% and 16% respectively, while it does not change the vaccination attitude for 25% of the centers. Almost all centers dispense the anti-SARS-CoV-2 booster dose even during maintenance therapy. In 63% of centers, vaccination with the new recombinant subunit vaccine for Varicella-Zoster Virus is recommended for patients with indolent lymphoma who are candidates for immuno-chemotherapy maintaining while antiviral prophylactic therapy is maintained in 70% of cases.

Conclusions: This survey shows a particular sensitivity among hematologists towards the vaccination for SARS-CoV-2 and initial interest towards VZV vaccination. Further effort is needed to make clinicians' attitudes more homogeneous.

Keyword: Late Effects in Lymphoma Survivors

No conflicts of interests pertinent to the abstract.

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PUBLICATIONS ONGOING TRIALS OT07 - OT33

OT07 | PHASE 1B OPEN-LABEL STUDY OF LONCASTUXIMAB TESIRINE IN COMBINATION WITH OTHER ANTICANCER AGENTS IN PATIENTS WITH RELAPSED/REFRACTORY B-CELL NON-HODGKIN LYMPHOMA (LOTIS-7)

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Introduction: Combining agents with different mechanisms of action may enhance treatment (Tx) efficacy in patients (pts) with relapsed/refractory (*R/R*) B-cell non-Hodgkin lymphoma (B-NHL). Loncastuximab tesirine (loncastuximab tesirine-lpyl; Lonca), an FDA-approved, CD19-directed, antibody-drug conjugate indicated for *R/R* diffuse large B-cell lymphoma (DLBCL), showed significant efficacy and manageable toxicity in a phase 2 trial in pts with *R/R* DLBCL. In preclinical models, Lonca + polatuzumab vedotin (Pola) showed improved efficacy. CD20 × CD3 T-cell–engaging antibodies and Lonca target different antigens; combining these is expected to increase efficacy. The safety and activity of Lonca combined with other agents in pts with *R/R* B-NHL will be evaluated in LOTIS-7.

Methods: LOTIS-7, a phase 1b, open-label, multicenter, multiarm study (NCT04970901), will enroll ~200 pts with B-NHL in part 1 (dose escalation, 60 pts) and part 2 (dose expansion, 140 pts). Part 2 may include specific subpopulation(s) of B-NHL informed by part 1. Primary endpoints are frequency and severity of adverse events (AE), serious AE, dose-limiting toxicities, and frequency of AE-related dose modifications. Secondary endpoints are overall response rate; duration of response; complete response rate; progression-free, relapse-free, and overall survival; Lonca concentrations; and antidrug antibody titers.

Planned arms include Lonca + Pola (arm C), glofitamab (arm E), or mosunetuzumab (arm F). Arm C enrollment is open: pts are treated with Lonca + Pola as an outpatient infusion. In part 1, arm C pts receive Lonca at escalating doses (90-150 μg/kg) and Pola (1.8 mg/kg) on day 1 of each 3-week cycle; pts in arms E and F will receive Lonca 150 μg/kg for 2 cycles, then 75 μg/kg for subsequent cycles + glofitamab (2.5 mg on cycle [C]1 day [D]8, 10 mg on C1D15, and 10 or 30 mg for C2-12 D1, arm E) or mosunetuzumab subcutaneously (5 mg on C1D1, 15 or 45 mg for C1D8, and 45 mg for C1D15 and C2-8 D1, arm F) after initial step-up dosing. Lonca Tx may continue for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria. Key eligibility criteria include age ≥18 years, pathologic diagnosis of *R/R* B-NHL (2016 WHO classification), measurable disease (2014 Lugano classification), Tx failure/intolerance, ≥2 lines of prior therapy (LOT) for part 1 (≥1 LOT for part 2), and ECOG performance status of 0-2. Pts previously receiving a study drug could not enroll in that respective study arm. Pts who received a stem-cell transplant within 60 days (100 days for arms E/F) before study Tx; received allogeneic stem cell or solid organ transplant (arms E/F); have lymphoma with active CNS involvement, ascites, edema, or effusion; or have significant comorbidities are excluded.

The study opened in December 2021; as of January 2023, 12 pts have been enrolled and 9 treated in the Lonca + Pola arm.

Encore Abstract - previously submitted to ASCO 2023

The research was funded by: ADC Therapeutics SA; medical writing: CiTRUS Health Group.

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

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Research funding: MSD Oncology, Celgene, Bristol-Myers Squibb, Amgen, Pfizer
Educational grants: Roche, Takeda
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OT08 | NATHALI-01: A PHASE 1/2A TRIAL OF UCART20X22, AN ALLOGENEIC DUAL CAR T-CELL THERAPY FOR PATIENTS WITH RELAPSED/REFRACTORY B-CELL NON-HODGKIN LYMPHOMA (NHL)

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Introduction: Autologous CAR T-cell therapies have been transformative in the treatment of selected blood cancers. Despite this remarkable success, long term studies on patients treated with CD19 or CD22 CAR T-cells revealed the emergence of relapses often due to antigen loss. The therapeutic options after CAR T-cell relapses are limited, underscoring the urgent need to develop novel therapies to improve current survival rates. In addition, there is a need to develop allogeneic "off-the-shelf" therapies that are readily available at the time of treatment decision and that overcome the development limitations of current autologous approaches. To address these challenges, UCART20x22, the first allogeneic dual CAR T-cell product candidate targeting two well-validated antigens in B-cell malignancies, CD20 and CD22, was generated from normal healthy donor T cells using a bicistronic lentiviral construct to express both CARs. TALEN® gene editing technology was used to inactivate the *TRAC* and *CD52* genes to both minimize Graft-vs-Host Disease and allow for the use of alemtuzumab (an anti-CD52 monoclonal antibody) in the lymphodepleting regimen. UCART20x22 displays strong activity against tumor cell lines with diverse CD20/CD22 antigen combinations, as well as increased activity against cells presenting both targets simultaneously using in vitro cytotoxic and proliferation assays. The activity of UCART20x22 cells persists against tumor cells expressing both antigens (CD20, CD22) or only one. In a pre-clinical in vivo model carrying subcutaneous lymphoma tumors expressing different antigen combinations in a single mouse, UCART20x22 cells provide efficient in vivo clearance of tumor cells expressing one or two antigens in a dose dependent manner. Furthermore, in primary NHL patient samples expressing diverse CD22 and CD20 antigen levels, UCART20x22 displays robust and specific cytotoxic activity and IFN-γ release in all tested combinations.

Methods: NatHaLi-01 (NCT05607420) is a Phase1/2a open-label dose-finding and dose-expansion study to evaluate the safety, expansion, persistence, and clinical activity of UCART20x22 in subjects with relapsed or refractory B-Cell NHL. Primary endpoints are safety, tolerability, and determining the MTD/RP2D of UCART20x22. Additional endpoints are anti-lymphoma activity and describing the expansion and trafficking of UCART20x22. Eligibility criteria include

age 18–80y, lymphoma cell expression of either or both CD20 and CD22, and ≥ 2 prior treatment regimens including autologous CD19 CAR T-cell therapy if eligible. After lymphodepletion with FCA (fludarabine 30 mg/m^2 × 3d, cyclophosphamide 0.5g/m^2 × 3d, alemtuzumab 12 mg on D1, 24 mg on D2, D3), patients will receive a single infusion of UCART20x22 at a flat dose level ([DL]; DL1-50 × 10^6 cells, DL2-150 × 10^6 cells, and DL3-450x10^6 cells). The trial is currently open for enrollment.

The research was funded by: Cellectis, S.A.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

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OT09 | A PHASE I STUDY OF SPLIT-COURSE BRIDGING RADIOTHERAPY (SC-BRT) PRIOR TO COMMERCIAL CD19 CAR T-CELL THERAPIES FOR PATIENTS WITH RELAPSED OR REFRACTORY B-CELL LYMPHOMAS

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Introduction: Despite remarkable responses after chimeric antigen receptor T-cells (CART), most relapse within 6 mos and only 35%–50% achieve sustained remission. Numerous strategies are under study to improve CART outcomes and several potential roles for radiotherapy (RT) are being explored. Given greater disease burden is

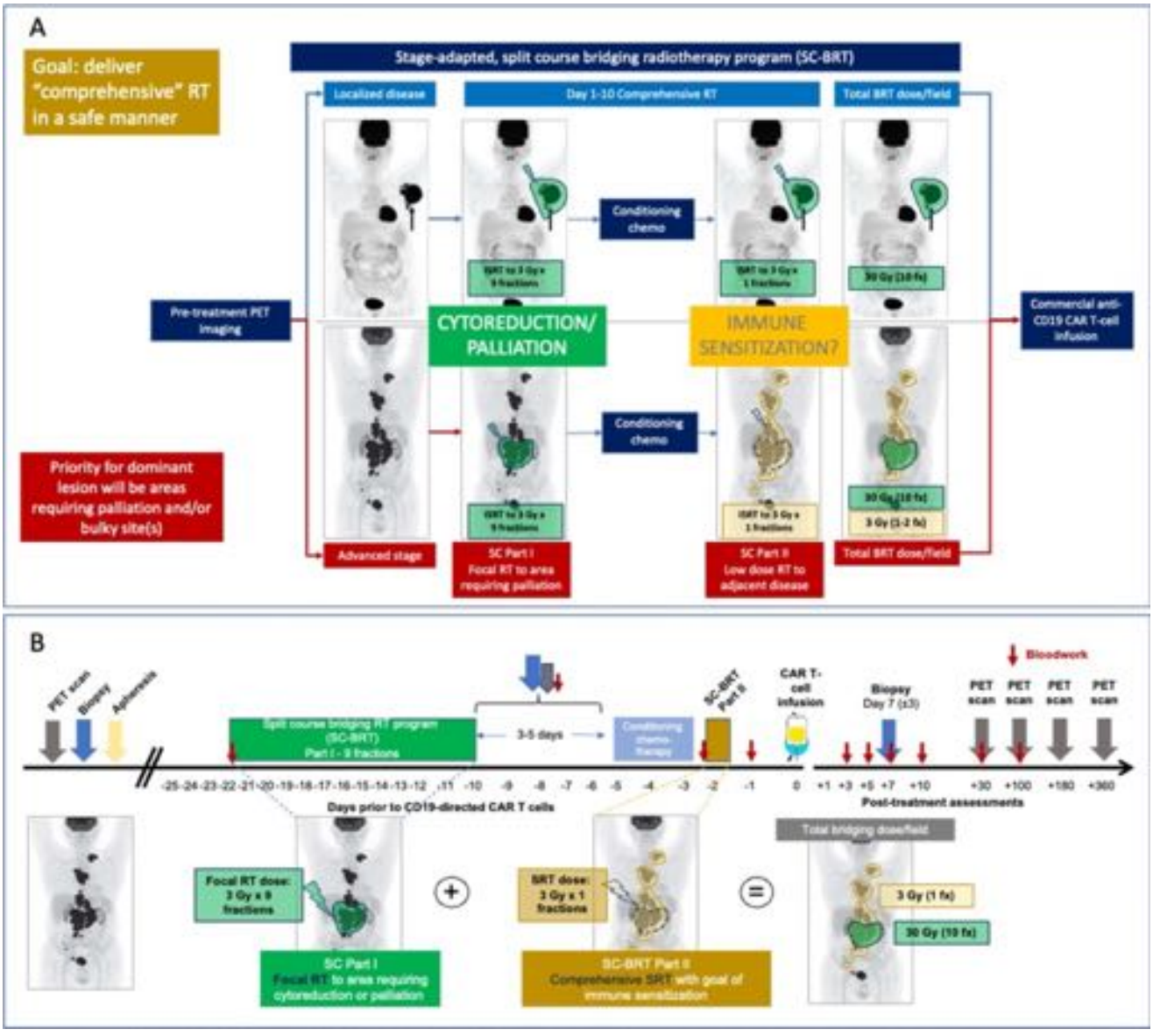
associated with poorer CART outcomes, we and others have demonstrated a rapid cytoreductive or palliative role for RT in the "bridging period" between apheresis and CART infusion. Preclinical data from our institution suggests there is also a potential role of sublethal dose radiotherapy in modulating the tumor microenvironment and thus bolstering CART-mediated response. Our translational study (NCT05574114) is designed to test these hypotheses.

Methods: This is a Phase I trial in which adult B-cell lymphoma patients planned for commercial anti-CD19 CART undergo bridging RT (BRT). All receive our institutional standard of 3 Gy × 10 fractions. However, we deliver a novel stage-adapted, split-course bridging RT (SC-BRT) program where BRT is given before and after conditioning lymphodepleting chemotherapy (LDC) with the intent of debulking disease and to potentially trigger an augmented immune effect.

Phase I of BRT (27Gy in 9 fractions) is delivered only to symptomatic or dominant/bulky site(s) prior to LDC (**Fig A**). This is followed by a repeat PET scan to quantitatively assess cytoreduction and a tissue biopsy. Patients then go on to receive LDC and immediately prior to CART cell infusion (day-2, optimal timing from animal models), they will receive BRT Phase II which is comprehensive, low dose RT (3 Gy × 1 fraction) to all baseline PET-avid sites with a goal of immune sensitization/augmentation. The BRT fields are designed per baseline extent of PET avid disease using ILROG guidelines with multidisciplinary consensus.

Patients then receive standard of care commercial CART (axicabtagene, tisagenlecleucel or lisocabatagene). They are followed closely in the post CAR period for safety events and repeat biopsy is performed at day +7 (±3) ideally of a tumor which received low dose RT. Repeat PET imaging is performed day +30, +100 and +180.

Primary objective is to confirm safety of SC-BRT prior to CD19-directed CAR T-cell therapies (BRT+CAR T) given the theoretical potential for immune augmentation and associated increased toxicity



when combining RT with immunotherapies. A further goal is to gain initial perspectives on efficacy and patterns of failure. Our tumor and blood correlative program aims to generate important insights on potential mechanisms of RT-associated immune enhancement. The study is structured to begin with a Phase 1a pilot cohort designed using 3 + 3 early phase trial principles (**Fig B**). Assuming no unacceptable safety signals in the Phase 1a, the study will proceed to a Phase 1b expansion cohort (up to 20 patients total) with the primary goal of safety.

The research was funded by: The Memorial Sloan Kettering Cancer Center Comedy vs Cancer Grant Program, the Connecticut Cancer Foundation, the Steven A. Greenberg Award in Lymphoma, as well as the Memorial Sloan Kettering Cancer Center Support Grant [P30 CA008748].

Keywords: cellular therapies, ongoing trials, radiation therapy

Conflicts of interests pertinent to the abstract.

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Other remuneration: Seres, Juno, and Wolters Kluwer

OT10 | EPCORITAMAB MONOTHERAPY AND COMBINATIONS IN RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA OR RICHTER'S SYNDROME: NEW ESCALATION AND EXPANSION COHORTS IN EPCORE CLL-1

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Introduction: Targeted therapies have dramatically changed the treatment landscape of chronic lymphocytic leukemia (CLL). Current paradigms include combinations with small molecules (Bruton tyrosine kinase and B-cell lymphoma 2 inhibitors), chemotherapy, and anti-CD20 monoclonal antibodies. Although chemotherapy-free regimens, such as single-agent venetoclax and venetoclax + rituximab, have shown efficacy in heavily pretreated CLL, the disease is generally considered incurable, and novel options are needed, especially for patients with early relapse, who have a poor prognosis and very limited options in later lines of therapy. In vitro data support the potential efficacy of bispecific T-cell engagers, but additional clinical data are needed. Epcoritamab, a subcutaneous (SC), T-cell–engaging, bispecific antibody, binds to CD3 on T cells and CD20 on B cells to induce T-cell–mediated killing of malignant B cells. In the EPCORE™ CLL-1 trial, epcoritamab monotherapy has shown a manageable safety profile and antitumor activity in heavily pretreated patients with high-risk relapsed or refractory (*R/R*) CLL (Kater AP et al., ASH 2021) or Richter's syndrome (RS; Kater AP et al., ASH 2022). Preclinical data suggest that epcoritamab activity may be potentiated by venetoclax (Mhibik M et al., ASH 2021) or other standard therapies (Chiu CW et al., AACR 2021), including lenalidomide and a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), in CLL or RS, respectively. Here we describe new dose-escalation cohorts and expansion arms in EPCORE CLL-1.

Methods: EPCORE CLL-1 is an open-label, multicenter, phase 1b/2 trial evaluating the safety and efficacy of epcoritamab alone or in combination in adults with *R/R* CLL or RS (**Figure**). Epcoritamab + venetoclax will be evaluated in patients with *R/R* CLL requiring treatment per iwCLL. In dose escalation for this combination, patients will receive SC epcoritamab with step-up dosing to full doses QW in cycles 1–3 (28-d cycles, except for 35-d cycle 1 for full doses >48 mg), Q2W in cycles 4–9, and Q4W in cycles ≥10 until disease progression or unacceptable toxicity. Patients will also receive oral venetoclax 400 mg QD for 28 d/cycle up to 26 cycles, following a standard 5-wk ramp-up prior to epcoritamab dosing. Based on dose escalation, an expansion dose will be selected. The primary endpoint of this expansion arm (arm 3) is overall response rate by independent review committee. Secondary efficacy endpoints include complete and partial response rates, duration of response, time to response, time to new anticancer therapy, progression-free survival, and overall survival. Epcoritamab + lenalidomide (arm 2B) or R-CHOP (arm 2C) in RS will be described in detail at the meeting. Enrollment is ongoing in the United States, Belgium, Denmark, Germany, and the Netherlands, and expanding into additional countries (NCT04623541).

The research was funded by: This study was funded by Genmab A/S and AbbVie.

Keywords: Chronic Lymphocytic Leukemia (CLL), Immunotherapy, Ongoing Trials

Conflicts of interests pertinent to the abstract.

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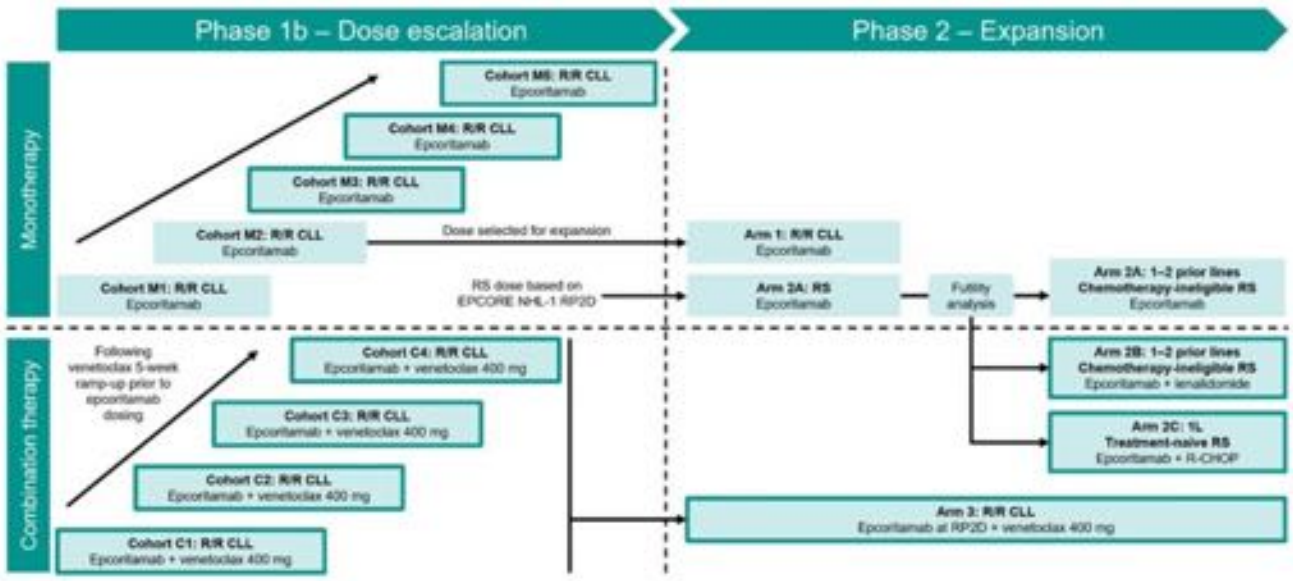
Educational grants: BeiGene
Other remuneration: AbbVie, AstraZeneca, BeiGene, Janssen, Roche, MSD: Speakers Bureau

Figure. EPCORE CLL-1 Study Design



New dose-escalation cohorts (M3–5 and C1–4) and expansion arms (2B, 2C, and 3) are outlined. Arm 1 is no longer recruiting.

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Honoraria: AbbVie
Research funding: AbbVie, Janssen, AstraZeneca, BMS, Roche/Genentech
Other remuneration: Janssen, AstraZeneca, Genmab, Lava: Steering Committee

OT11 | A PHASE 1 STUDY EVALUATING PRT2527, A POTENT AND HIGHLY SELECTIVE CDK9 INHIBITOR, IN PATIENTS WITH SELECT RELAPSED/REFRACTORY B-CELL MALIGNANCIES

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Introduction: PRT2527 is a potent, highly selective cyclin-dependent kinase 9 (CDK9) inhibitor. CDK9 is a key regulator of transcription elongation and has been studied as a potential target for therapy in transcriptionally addicted cancers, which are dependent on oncogenic drivers with short half-lives. Although most of these drivers do not respond to direct inhibition, studies suggest that a subset of drivers with short half-lives such as *MYC*, *MYB*, and *MCL1* may be targeted indirectly through CDK9 inhibition in select hematological malignancies and solid tumors. Preclinical data with PRT2527 have demonstrated evidence of on-target inhibition of *MYC*, *MYB*, and *MCL1*, as well as induced apoptosis, as measured by cleaved caspase 3 in cell lines and translational models (e.g.,

patient-derived xenograft [PDX] models) (Zhang Y et al., AACR-NCI-EORTC 2021).

Methods: PRT2527-02 is a phase 1, open-label, multicenter, dose-finding study to evaluate the safety, tolerability, recommended phase 2 dose (R2PD), and preliminary efficacy of PRT2527 in patients with select B-cell malignancies such as aggressive B-cell lymphoma subtypes, mantle cell lymphoma, and chronic lymphocytic lymphoma/small lymphocytic lymphoma (e.g., Richter syndrome). Aggressive B-cell lymphoma subtypes, including diffuse large B-cell lymphoma not otherwise specified, gray zone lymphoma, follicular lymphoma grade 3b, high-grade B-cell lymphoma, and primary mediastinal large B-cell lymphoma or large B-cell lymphoma transformed from indolent B-cell, are eligible to enroll. Patients must have relapsed or be refractory to or ineligible for standard-of-care therapy. Other key eligibility criteria include measurable disease or requirement for treatment in accordance with standard disease-specific criteria for the hematologic malignancies under study, Eastern Cooperative Oncology Group performance status of 0–1, and adequate bone marrow, renal, and liver function.

The study consists of dose escalation with successive cohorts of patients receiving escalating doses of intravenous PRT2527 once weekly in a 21-day cycle. PRT2527 treatment will continue until disease progression or unacceptable toxicity, whichever comes first. Dose escalation and de-escalation decisions will be guided by the Bayesian optimal interval design method based on the number of participants with dose-limiting toxicities (DLTs) observed at the dose level under evaluation until a maximum tolerated dose and R2PD have been determined. The primary endpoints include safety, tolerability, DLTs, and RP2D of PRT2527. Secondary endpoints include objective response rate, duration of response, duration of complete response, and pharmacokinetic profile of PRT2527. The study has been open to enrollment since February 2023. Clinical trial information: NCT05665530.

The research was funded by: Prelude Therapeutics

Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

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OT12 | A PHASE 1/2 STUDY OF STP938, A FIRST IN CLASS INHIBITOR OF CTP SYNTHASE 1, IN PATIENTS WITH RELAPSED/REFRACTORY B OR T CELL LYMPHOMA

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Background: Chemotherapy-induced inhibition of DNA synthesis has proven efficacy in the treatment of lymphoma. Selective targeting of DNA synthesis has the potential to surpass this efficacy by maximizing pathway inhibition whilst avoiding the dose limiting toxicities of chemotherapy. The rate limiting step in de novo pyrimidine synthesis is catalysed by two homologous enzymes, CTPS1 and CTPS2. CTPS1 is essential for lymphocyte proliferation, whereas CTPS2 is sufficient in non-haemopoietic cells, raising expectations of a therapeutic window for selective CTPS1 inhibition. STP938 is a first in class oral CTPS1 inhibitor showing >1300-fold selectivity over CTPS2. In preclinical studies, STP938 induced death of cancer cells by apoptosis at nanomolar concentrations,

and inhibited tumour growth in in vivo models of haematological malignancies.

Methods: The study employs a seamless dose escalation, dose expansion design. The phase 1 dose escalation follows a standard 3 + 3 approach. Intra-patient dose escalation will be permitted. The recommended phase 2 dose (RP2D) will be nominated based on safety, target engagement and early signs of efficacy. An additional six patients will be treated at the RP2D with a preliminary assessment of food effect. Key phase 1 endpoints are safety and tolerability. Key phase 2 endpoints are objective response rate and duration of response.

The study is open to adult patients following at least 2 prior lines of therapy who have no treatment options known to provide clinical benefit. The phase 1 study is recruiting patients with B or T cell lymphoma; the phase 2 study will be limited to cohorts of patients with specific lymphoma subtypes, which may include T cell lymphoma (peripheral or cutaneous), mantle cell lymphoma, indolent B cell lymphoma and diffuse large B cell lymphoma. Standard exclusion criteria apply; patients with ECOG performance score >2 or known CNS involvement by lymphoma are not eligible.

The phase 2 study will follow a Simon two-stage design with an interim analysis for futility based on predefined, lymphoma subtype specific response rates. In the case of STP938 showing promising efficacy, provision is included in the protocol to expand a cohort using an adaptive approach based on early efficacy signals (Mehta & Pocock, 2011).

Target engagement is assessed by measuring cytokine release (TNFα, IFNγ, IL2, IL8) from *ex vivo* stimulated patient T cells. Exploratory studies include pre- and on-treatment lymphoma biopsies to assess biomarkers of response and mechanism of action. Tumour genomics will be assessed by sequencing of circulating tumour DNA prior to treatment and at disease progression using a bespoke genomic assay designed to elucidate biomarkers of response and understand mechanisms of resistance.

The phase 1 study (NCT05463263) opened to enrolment in the US and UK in September 2022. The phase 2 study will include additional centres in France.

The research was funded by: Step Pharma SAS

Keywords: aggressive B-cell non-Hodgkin lymphoma, aggressive T-cell non-Hodgkin lymphoma, molecular targeted therapies

Conflicts of interests pertinent to the abstract.

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Research funding: BeiGene
Educational grants: Roche

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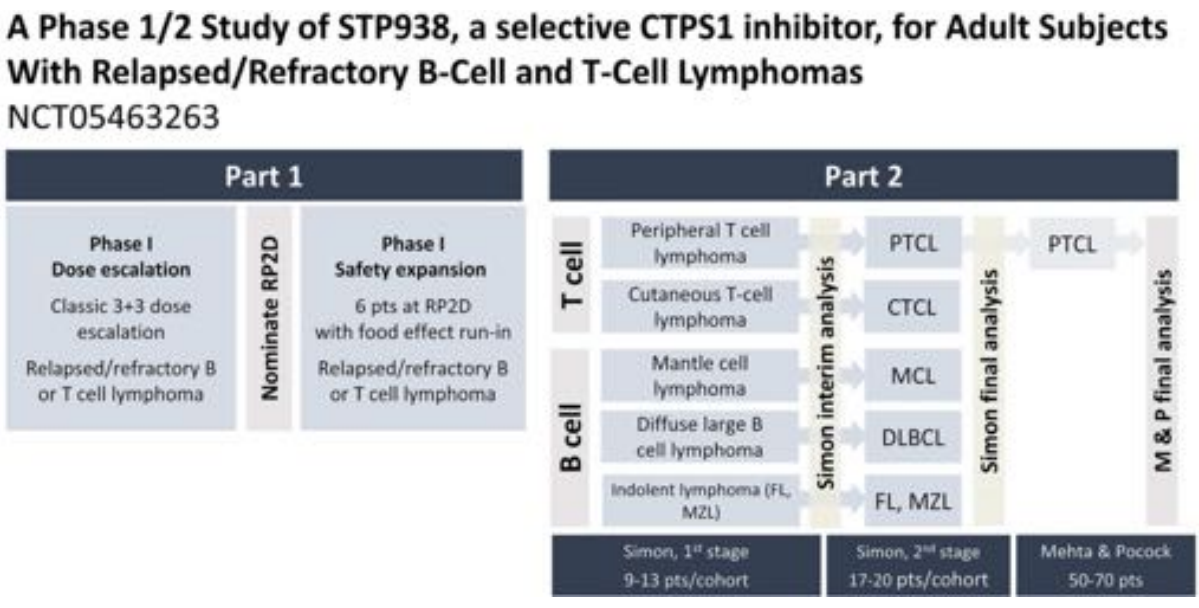

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OT13 | SGR-1505-101: A PHASE 1, OPEN-LABEL, MULTICENTER, DOSE-ESCALATION STUDY OF SGR-1505 AS MONOTHERAPY IN SUBJECTS WITH MATURE B-CELL MALIGNANCIES

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Background: MALT1 (Mucosa-associated lymphoid tissue lymphoma translocation protein 1) is a component of the MALT1-BCL10-CARD11 complex downstream from the Bruton Tyrosine Kinase (BTK) on the B-cell receptor signaling pathway. MALT1 is a key mediator of the nuclear factor kappa B (NF-κB) signaling, which is the main driver of a subset of B-cell lymphomas. MALT1 is considered a potential therapeutic target for several subtypes of non-Hodgkin B-cell lymphomas and chronic lymphocytic leukemia (CLL), including tumors with acquired BTK inhibitor (BTKi) resistance. In particular, constitutive activation of the NF-κB is a molecular hallmark of activated B cell-like diffuse large B cell lymphoma (ABC-DLBCL), and MALT1 may have utility as a treatment option for ABC-DLBCL.

SGR-1505 is an oral potent small molecule allosteric inhibitor of MALT1 that inhibits MALT1 enzymatic activity, and demonstrates anti-proliferative activity in ABC-DLBCL cell lines, both BTKi-sensitive (OCI-LY10) and BTKi-resistant (OCI-LY3). SGR-1505 administered as a single agent and in combination with the approved Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, demonstrates tumorostatic and regressive antitumor activity in ABC-DLBCL cell line-derived xenograft and patient-derived xenograft models.

Aims: These data suggest that SGR-1505-mediated MALT1 inhibition has therapeutic potential and may expand therapeutic options for patients with selected B-cell lymphomas supporting further evaluation of SGR-1505 in clinical trials.

Methods: SGR-1505-101 (NCT05544019) is a phase 1, multicenter trial of SGR-1505 as monotherapy in subjects with mature B-cell malignancies. At present, the study has been activated in 3 sites in the United States. The primary objective is to evaluate safety and tolerability of SGR-1505 as monotherapy and to identify the maximum tolerated dose (MTD) and/or recommended dose (RD). Secondary objectives are to evaluate the pharmacokinetic (PK) profile, food effect, drug-drug interaction, and preliminary anti-tumor activity of SGR-1505. Key inclusion criteria are: history of mature B-cell malignancy (including aggressive and indolent B-cell lymphomas, Waldenström macroglobulinemia, and CLL); measurable or detectable disease according to the applicable disease-specific classification system (Lugano, iwCLL, WWM6); Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2. Patients with indolent B-cell lymphomas or CLL must have an indication for treatment and not require immediate cytoreductive therapy. Subjects with symptomatic or active CNS involvement, and other conditions or laboratory findings placing them at increased risk to the use of an investigational drug are excluded.

SGR-1505 is initially dose-escalated using an accelerated titration design in cohorts of 1–6 subjects, and at higher dose levels using a conventional 3+3 design.

Encore Abstract—previously submitted to EHA 2023

The research was funded by: Schrodinger

Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

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OT14 | ETCTN P10500: PHASE 1/EXPANSION STUDY OF TAZEMETOSTAT PLUS BELINOSTAT FOR THE TREATMENT OF RELAPSED OR REFRACTORY LYMPHOMA

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New findings have identified several DLBCL clusters, including the EZB-GC-DLBCL subtype that is enriched in mutations of CREBBP, EP300, and EZH2 (Wright 2020; Schmitz 2018; Chapuy 2018). More than 1/3 of patients with EZB-DLBCL will relapse following standard immunochemotherapy. Given the critical importance of recurrent derangements in epigenetic modifiers in germinal center (GC)-lymphomas, combined targeting of epigenetic machinery with tazemetostat and belinostat may induce profound epigenetic modification, leading to induction of cell death. The EZH2 inhibitor tazemetostat has an overall response rate of 29% in EZH2 mutated DLBCL. HDAC inhibitors used as single agents only indirectly target CREBBP/EP300 mutations, and have response rates of ~10% in B-cell lymphomas. However, preclinical data generated in our lab has demonstrated that when combined in discrete subsets of DLBCL they lead to highly synergistic interactions via modulation of both histone acetylation and methylation, and prolonged survival in murine models (Lue, 2019). Based on these observations, the ETCTN 10500 clinical trial was designed to study tazemetostat plus belinostat in rel/ref lymphoma (NCT05627245).

The phase 1 portion of the study will determine the maximum tolerated dose and dose limiting toxicities of tazemetostat and belinostat in combination in patients with rel/ref non-Hodgkin lymphoma. Patients will be enrolled based on a standard 3-by-3 phase 1 design. Patients will be treated on a 21-day cycle with tazemetostat orally twice daily at doses between 600 and 800 mg, and belinostat intravenous daily for 5 days between doses of 600–1000 mg. The pharmacokinetic profile will be determined for the combination. Following determination of a recommended phase 2 dose, an expansion study will be performed in 12 patients with GC-derived large cell lymphoma (including transformed disease) as defined by the Hans immunohistochemistry algorithm. The expansion cohort will be stratified by EZH2 mutation status, with a goal of enrolling 6 mutated and 6 wild-type EZH2 lymphoma patients. In addition, baseline EP300 and CREBBP mutation status will be assessed. A gene signature for response to combined epigenetic therapy will be determined with baseline primary lymphoma RNA sequencing. Other correlative studies will include evaluating paired samples for change in gene expression by RNA sequencing and change in histone acetylation and methylation in tumor tissue by mass spectrometry. An exploratory goal will to be to assess immune response to therapy by evaluating changes in T cell subsets and activation in the peripheral blood.

The goal of the ETCTN P10500 study is determine if dual epigenetic targeting with tazemetostat and belinostat is safe for lymphoma patients, to determine the phase 2 dose, and to explore potential biomarkers for response. The hope is to create a strategy to target discrete mutations, like EZH2, EP300 and CREBBP, driving DLBCL.

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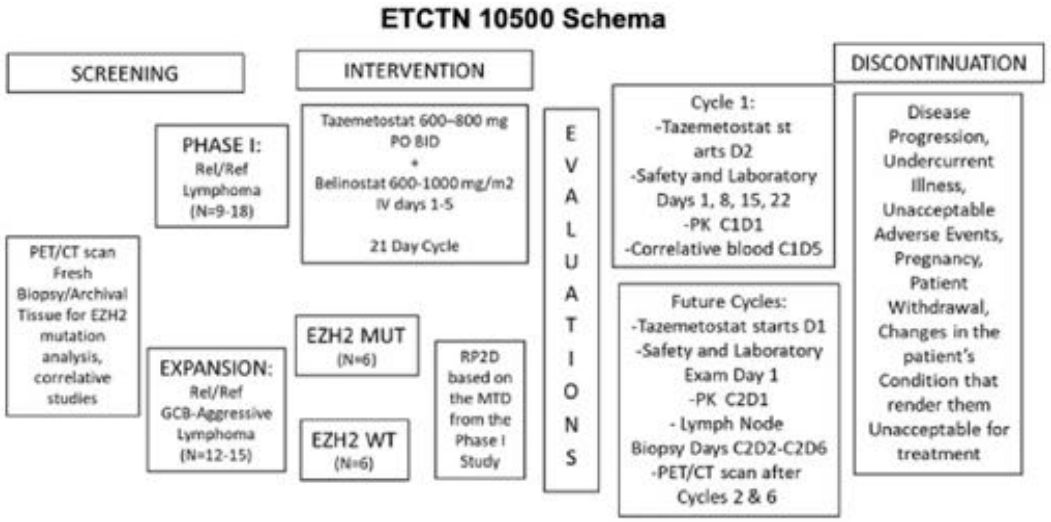
The research was funded by: 2UM1CA186689



Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies, ongoing trials

No conflicts of interests pertinent to the abstract.

OT15 | PHASE 1 STUDY OF PRT1419 (MCL1 INHIBITOR) AS MONOTHERAPY OR IN COMBINATION WITH AZACITIDINE OR VENETOCLAX IN PATIENTS WITH RELAPSED/REFRACTORY MYELOID OR B-CELL MALIGNANCIES

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Introduction: PRT1419 is a potent and selective inhibitor of myeloid cell leukemia-1 (MCL-1). MCL-1 is frequently amplified or overexpressed in hematologic malignancies and is associated with higher grade malignancy and poor prognosis (Xiang et al., *Onco Targets Ther* 2018). Azacitidine (AZA) treatment was shown to induce several proapoptotic changes in primary acute myeloid leukemia (AML) isolates, including a decrease in MCL-1 protein levels (Tsao et al, *Ann Hematol* 2012; Jin et al, *Clin Cancer Res* 2020). Several mechanisms of primary and acquired resistance have been described in patients (pts) with AML treated with venetoclax (VEN)-based regimens, including the loss of dependence on BCL-2 and upregulation of MCL-1 (Saliba et al., *Cancer Drug Resist* 2021; Pei et al., *Cancer Discov* 2020). Considering that MCL-1 upregulation is a mediator of VEN resistance and AZA downregulates MCL-1, PRT1419 may confer additive or synergistic benefits to AZA or VEN in treatment-resistant myeloid or B-cell malignancies.

Methods: PRT1419-03 is a phase 1, open-label, multicenter, dose-finding study to evaluate the safety, tolerability, recommended phase 2 dose (R2PD), and preliminary efficacy of PRT1419 as monotherapy or in combination with AZA or VEN in pts with selected relapsed/refractory myeloid or B-cell malignancies. Pts must have progressed on prior treatment without access to, or eligibility for, further approved therapies. Adult pts with confirmed diagnosis of AML, CMML, MDS, MDS/MPN Overlap Syndrome, CLL/SLL, or B-cell NHLs (mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma) are eligible for this study. Other key eligibility criteria include Eastern Cooperative Oncology Group performance status of 0 to 2 and adequate organ and cardiac function as assessed by echocardiogram or biochemical markers of cardiac damage.

As monotherapy, pts will receive escalating doses of intravenous PRT1419 once weekly in a 28-day cycle using a 3 + 3 dose escalation design until a maximum tolerated dose (MTD) or RP2D dose has been reached. Once the RP2D for monotherapy has been defined, pts will receive escalating doses of PRT1419 in combination with AZA (myeloid malignancies) or VEN (myeloid malignancies; B-cell malignancies) until MTD/RP2D is reached. Pts will then be enrolled into indication-specific dose confirmation cohorts. PRT1419 treatment will continue until relapse/disease progression, intolerance, or pt withdrawal. The primary endpoints include safety, tolerability, dose-limiting toxicities (DLTs), and RP2D of PRT1419 as monotherapy.

Secondary endpoints include safety, tolerability, DLTs, RP2D for PRT1419 in combination

The research was funded by: Prelude Therapeutics

Keywords: combination therapies, molecular targeted therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

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Honoraria: AbbVie, Astellas, BMS, Jazz, Novartis, Pfizer, Servier
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Research funding: Novartis Canada

OT16 | PHASE 1/2A CLINICAL TRIAL OF BI-1206, A MONOCLONAL ANTIBODY TO CD32B (FCGRIIB), IN COMBINATION WITH RITUXIMAB IN SUBJECTS WITH INDOLENT B-CELL LYMPHOMA

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Introduction: Anti-CD20 antibodies, such as rituximab, are an essential therapy resource in patients with B-cell lymphomas. However, approximately 15% of patients are refractory to treatment, and 25% relapse within 3 years following treatment. Non-clinical and retrospective clinical data indicate that the inhibitory Fc receptor CD32b promotes resistance through mechanisms acting on tumor and immune effector cells. Expressed on tumor B cells, CD32b triggers rituximab internalization, and tumor CD32b expression correlates inversely with response to rituximab or rituximab-containing therapy in MCL, FL, and DLBCL. BI-1206 is a human recombinant anti-CD32b (FcγRIIB) antagonistic IgG1 antibody that blocks

rituximab internalization and, in non-clinical experimental models, enhances efficacy and overcomes rituximab resistance.

During early clinical development of BI-1206, frequent infusion-related reactions were observed after intravenous (IV) administration. The development of a novel pre-medication regimen using two doses (16–24 h and 1 h) of corticosteroids prior to IV administration, as well as of a subcutaneous (SC) administration, have been shown to improve the tolerability of BI-1206 significantly, and both methods of administration are evaluated in the current trial.

Methods: The current phase 1/2a multicenter clinical trial includes relapsed or refractory B-cell lymphoma, including FL (except FL grade 3B), MZL, and MCL. This trial will evaluate the safety and tolerability of IV and SC BI-1206 administered in combination with rituximab. The ivRP2D has been established, and enrollment of patients to SC BI-1206 to establish scRP2D has started. Ph2a of the trial will consist of cohorts of at minimum 6 and maximum 12 subjects each, receiving ivRP2D, scRP2D, and potential additional dose levels of interest.

During induction therapy, patients receive one dose of single-agent rituximab (375 mg/m^2) followed by dosing of BI-1206 with subsequent rituximab on weeks 2, 3, and 4. Patients showing clinical benefit (complete response [CR], partial response [PR], or stable disease [SD]) at week 6 are eligible for continued maintenance therapy with dosing of BI-1206 and rituximab every 8 weeks for up to 7 cycles.

The research was funded by: BioInvent

Keywords: Combination Therapies, Immunotherapy, Ongoing Trials

Conflicts of interests pertinent to the abstract.

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Keywords: combination therapies, immunotherapy, ongoing trials
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OT17 | SMART STOP: A PHASE II CLINICAL TRIAL OF LENALIDOMIDE, TAFASITAMAB, RITUXIMAB, AND ACALABRUTINIB ALONE AND WITH RESPONSE ADAPTED CHEMOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED DLBCL

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Background: Diffuse Large B-cell Lymphoma (DLBCL) is cured in ~60% of patients by a chemotherapy-based approach which is largely unchanged for decades. We have previously shown the feasibility and significant efficacy of a targeted therapy combination as initial treatment for patients with newly diagnosed LBCL (Smart Start, Westin et al, JCO 2023). BTK inhibitors like acalabrutinib (A) and the immunomodulatory agent lenalidomide (L) have activity as single agents, and result in synthetic lethality when combined in non-GCB DLBCL models. Both the CD19 antibody tafasitamab (T) and CD20 antibody rituximab (R) demonstrated significant clinical activity with L in patients with relapsed DLBCL. L, T, R, and A are also immunomodulatory, shifting from a tumor-mediated immune anergy to an anti-tumor immune response.

Study Design and Methods: Smart Stop is a phase II, open-label, single-center clinical trial combining LTRA alone and with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) for patients with previously untreated DLBCL (NCT04978584). Eligibility criteria include adult patients with previously untreated DLBCL with adequate organ and bone marrow function.

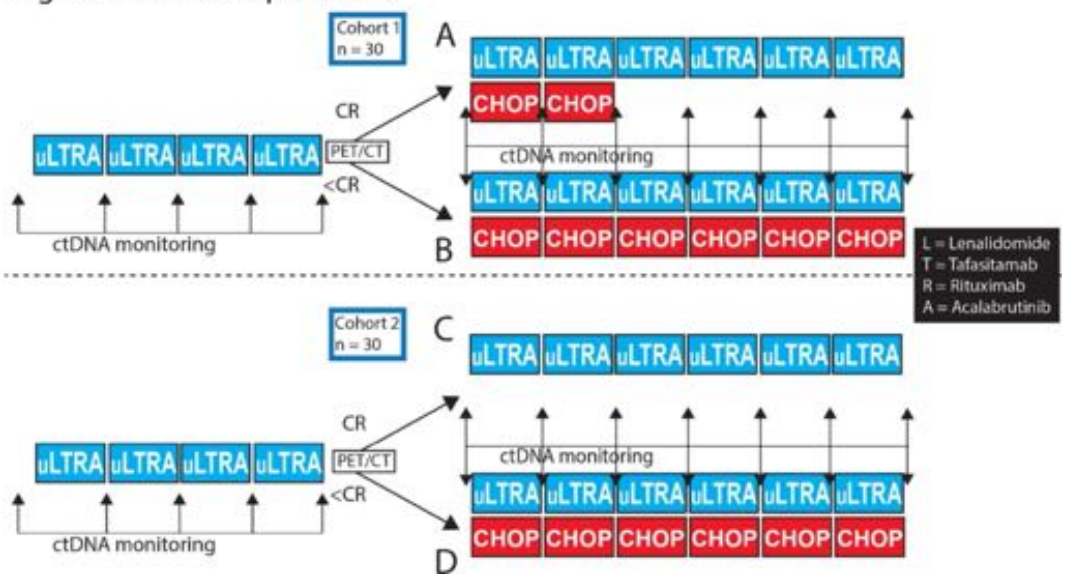
Patients receive lenalidomide (L) 25 mg daily days 1-10, tafasitamab (T) 12 mg/kg IV weekly, rituximab (R) 375 mg/m^2 IV day 1, and acalabrutinib (A) 100 mg PO twice daily during a 21 day cycle. All patients receive LTRA for four cycles, unless clinical suspicion of disease progression. PET/CT scan using the 5 point Deauville score (5PS) will determine response, with complete response (CR) defined as a 5PS of 1, 2, or 3. The trial will have two sequential cohorts of 30 patients each. Patients who achieve CR will receive 6 additional cycles of uLTRA, which will include CHOP for 2 cycles (Cohort 1, Group A) or no CHOP (cohort 2, Group C). Patients who achieve less than a CR (Group B or D) will receive LTRA-CHOP for 6 cycles, for a planned 10 cycles of therapy for all patients. We will utilize two decision rules based upon results from cohort 1 to open and complete cohort 2: 1) the probability in Group A of sustained CRR at the end of therapy, 2) the probability in Group A of sustained response at 7 months after end of therapy in the first 10 patients.

The primary objectives are to determine the 1A: overall response rate after 4 cycles of LTRA and 1B: CR rate of LTRA +/-CHOP at the end of therapy. The maximum sample size is 60 patients. Secondary objectives include survival outcomes, safety, and outcomes of LTRA without CHOP, LTRA with 2 or 6 cycles of CHOP. Exploratory objectives include determining ctDNA response, immune modulation driven by LTRA, and LTRA response associated characteristics. The trial opened in 5/2022 and is actively recruiting patients.

The research was funded by: Incyte/Morphosys, AstraZeneca, and BMS

Keywords: ongoing trials

Figure 1: Smart Stop Schema



Conflicts of interests pertinent to the abstract.

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Research funding: Kite/Gilead, BMS, Novartis, Genentech, AstraZeneca, Morphosys/Incyte, ADC Therapeutics, Kymera, Calithera

OT18 | KILT: A RANDOMIZED NON-COMPARATIVE PHASE II LYSA STUDY OF LACUTAMAB WITH GEMOX VERSUS GEMOX IN RELAPSED/REFRACTORY PERIPHERAL T-CELL LYMPHOMA

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Background: Peripheral T-cell Lymphoma (PTCL) is a heterogeneous group of mature T-cell lymphomas (TCL) with adverse outcomes. Current treatment options for relapsing PTCL are limited. KIR3DL2 is a killer immunoglobulin-like receptor that is expressed across different subtypes of TCL, including approximately 40% of PTCL. Lacutamab is a humanized first-in-class monoclonal antibody designed to deplete KIR3DL2-expressing cells via ADCC and phagocytosis. In a previous phase I trial in relapsed/refractory cutaneous TCL, lacutamab showed adequate safety profile with no dose limiting toxicities and a global response rate of 43%. TELLOMAK multi-cohort phase II trial (NCT03902184) in advanced TCL is ongoing. Lacutamab has not been previously investigated as a combination therapy. Preclinical studies have shown that lacutamab selectively killed KIR3DL2-positive primary cells *ex vivo* from patients with PTCL. A combination of lacutamab with gemcitabine and oxaliplatin (GemOx) enhances NK cell anti-tumor activity in vitro.
Methods: This is an open label, multi-center, international, randomized non-comparative phase II trial to compare the safety and efficacy of lacutamab in combination with GemOx *vs.* GemOx alone in patients with any subtypes of relapsed/refractory KIR3DL2-positive PTCL. The design is non comparative meaning that the control arm will ensure that the assumptions used for sample size calculation are verified. For that reason, randomization is unbalanced in favor of the experimental arm (2:1). Patients are stratified according to *R/R* status and should have received ≤2 prior systemic therapies. In the experimental arm, patients are treated for 6 cycles of lacutamab 750 mg (intravenous infusion) + GemOx every 3 weeks as induction, and with lacutamab every 4 weeks as maintenance for up to a maximum of 2 years if they reached at least a partial response after induction. All patients should have a KIR3DL2 expression ≥1% as assessed centrally by immunohistochemistry. The primary endpoint is the median modified progression-free survival using the Lugano 2014 criteria. Secondary endpoints include safety, other efficacy endpoints and exploratory biomarker analyses. 56 patients are planned to be enrolled in France, Belgium, Spain and Germany. The trial is currently enrolling in 37 medical centers in France and Belgium. The sponsor of the trial is the Lymphoma Academic Research Organisation (LYSARC) in collaboration with Innate Pharma. Trial registration: NCT04984837.

The research was funded by: The research was funded by Innate Pharma

Keywords: aggressive T-cell non-Hodgkin lymphoma, immunotherapy, ongoing trials

Conflicts of interests pertinent to the abstract.

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OT19 | SWOG 2114: A RANDOMIZED PHASE II TRIAL OF CONSOLIDATION THERAPY FOLLOWING CD19 CAR T-CELL TREATMENT FOR RELAPSED/REFRACTORY LARGE B-CELL OR GRADE IIIB FOLLICULAR LYMPHOMA

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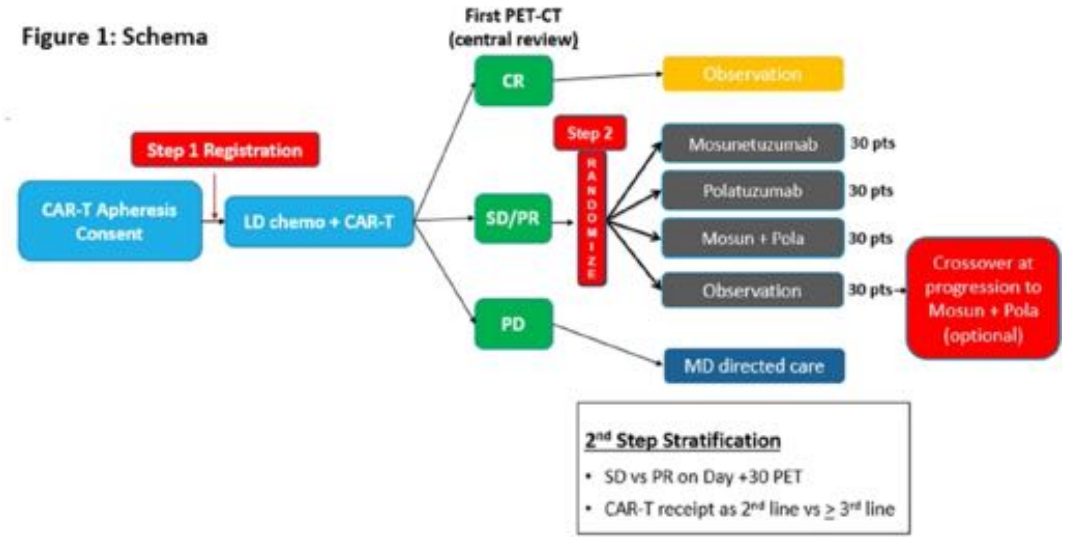
Introduction: CD19 CAR T-cell therapy (CD19 CTCT) is now the standard of care for many patients (pts) with relapsed/refractory large cell lymphoma (LCL), but nearly two-thirds of patients will still progress. Relapsed disease post CD19 CTCT is poorly responsive to subsequent therapies, and patient survival is dismal. (Spiegel JY, et al. Blood, 2021) Thus, we designed a clinical trial to assess the safety and efficacy of new consolidation regimens for LCL pts at high risk for relapse, which we define as stable disease (SD) or partial remission (PR) at one month PET-CT after CD19 CTCT. Polatuzumab vedotin (P) and mosunetuzumab (M) have proven efficacy in LCL, anticipated safety post CD19 CTCT, and lack of detriment to circulating CAR T-cells. The objective of this trial is to prevent relapse in this high-risk population with safe and effective consolidation therapies in order to improve outcomes.

Methods: This is an NCI sponsored phase II study with two registration steps. (Figure 1)

Step 1 registration: All pts with relapsed/refractory LCL or FL grade 3b who are candidates for FDA approved ≥2nd line CD19 CTCT including tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel will be eligible. Pts must enroll prior to the start of lymphodepleting chemotherapy preceding the CD19 CTCT infusion. Bridging therapy is allowed after apheresis as long as it does not include P or M. Previous P is allowed outside of bridging unless pt has progressed within 6 months of last dose.

Step 2 randomization: All pts enrolled in step 1 will undergo one month PET-CT between days +25-40 post CD19 CTCT which will be centrally reviewed by the Imaging and Radiation Oncology Core (IROC). Pts with SD/PR by central review will be eligible for randomization to one of three consolidation arms (M, P, M+P) or observation (O) in a 1:1:1:1 fashion. Those in CR will continue to be followed on the biomarker assay/PRO portion of the protocol



without any therapy initiated while those with progressive disease will be treated per MD discretion. All pts will be followed for survival outcomes.

Primary endpoint: Compare the 1-year PFS of each consolidation arm vs observation (M vs O, P vs O, M+P vs O). An estimated 120 pts (30 in each arm) are needed to detect a hazard ratio of 2 from estimated 25% 1 year PFS of the observation arm to 50% 1 year PFS of the each consolidation arm. It is estimated that 396 pts will need to be enrolled in step 1 registration to randomize 120 pts with SD/PR at one month PET-CT in the step 2 randomization.

Cross-over design: Pts with SD/PR randomized to the observation arm are eligible to receive M+P if they have definitive progression within 1 year of CD19 CTCT infusion.

Correlatives/PRO: Correlative and PRO assessments will occur at scheduled imaging timepoints for all pts registered to step 1. Minimal residual disease will be a focus and be followed in all pts regardless of one month PET-CT response post CD19 CTCT.

Keywords: cellular therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

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Research funding: TG, SEAGEN, Pharmacyclics, Merck, Incyte, BMS, Astra Zeneca, Adaptive

OT20 | A RANDOMIZED PHASE II STUDY OF MB-CART2019.1 COMPARED TO STANDARD OF CARE IN PATIENTS WITH RELAPSED/REFRACTORY DLBCL INELIGIBLE FOR ASCT – DALY 2-EU TRIAL

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Introduction: Elderly patients with relapsed or refractory (*r/r*) diffuse large B-cell lymphoma (DLBCL) represent a distinct patient population with often limited treatment options. CAR-T cell treatment can offer a curative approach to this comorbid patient population, but data directly comparing standard chemotherapy with CAR-T cell therapy are scarce. MB-CART2019.1 (Zamtocabtagene autoleucel) is a tandem CAR-T cell product targeting CD20 and CD19 and is manufactured in a 12-day process, with a vein-to-vein time of 14 days. MB-CART2019.1 was introduced in a Phase I dose finding study (NCT03870945) in mainly elderly patients with *r/r* B-cell lymphoma. It demonstrated encouraging safety with a low incidence of neurotoxicity and cytokine release syndrome. Five out of the 12 patients in the Phase I trial achieved a complete response which were durable at two-year follow-up. The favorable safety profile and encouraging early efficacy results provided the rationale for further investigation.

Trial design and Methods: This study is a pivotal Phase II randomized, multi-center, open-label study comparing the efficacy and safety of MB-CART2019.1 to standard of care (SoC) therapy in participants with *r/r* diffuse large B-cell lymphoma who are not eligible for high-dose chemotherapy (HDC) and ASCT (Clinical trial information: NCT04844866).

A total of 168 adult patients with *r/r* DLBCL will be randomized to receive MB-CART2019.1 with a dose of 2.5×10^6 CAR+ T-cells per kg body weight or SoC therapy. MB-CART2019.1 is intended to be infused as a non-cropreserved product after standard lymphodepleting chemotherapy. The comparator treatment consists of R-GemOx (rituximab, gemcitabine and oxaliplatin) or Pola-BR (polatuzumab vedotin, bendamustine and rituximab). Main criteria for inclusion are i) histologically proven DLBCL and associated subtypes, according to the WHO 2016 classification ii) patients with either refractory disease after 1st-line chemo-immunotherapy or relapsed disease within ≤12 months from the completion of 1st-line therapy, and iii) patients ineligible for ASCT due to a HCT-CT score >3 or age ≥65 years and documented organ dysfunction or age ≥70 years. The primary endpoint of the trial is progression-free survival. In addition to safety endpoints, secondary endpoints in the experimental arm include persistence of MB-CART2019.1, phenotype and immune cell compositions.

In summary, this trial (DALY 2-EU) evaluates the superiority of 2nd-line CAR-T cell treatment with MB-CART2019.1 compared to SoC in an elderly high-risk population of patients with *r/r* DLBC. It is planned to be performed in up to 50 clinical trial sites in 12 countries in Europe. The study is actively enrolling patients since August 2021. In addition, a separate pivotal Phase II trial in the USA is currently enrolling patients with *r/r* DLBCL who have failed at least two lines of prior systemic therapy (NCT04792489).

The study is sponsored by Miltenyi Biomedicine

Keywords: cellular therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

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OT21 | P+R-ICE: PEMBROLIZUMAB IN COMBINATION WITH R-ICE CHEMOTHERAPY IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA - ONGOING TRIAL

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Introduction: Approximately one third of patients with diffuse large B-cell lymphoma (DLBCL) have disease which either fails to respond to initial chemo-immunotherapy, or relapses after initial remission. These patients have a poor prognosis.

Rituximab plus Ifosfamide, Carboplatin and Etoposide (R-ICE) is a well established standard of care for relapsed / refractory patients suitable for autologous stem cell transplant (ASCT), after results from Kewalramani et al. (Blood (2004) 103 (10): 3684–3688) showed a doubling of CR rates with the addition of rituximab to ICE and the CORAL study (NCT00137995) found comparable rates of efficacy between R-ICE and R-DHAP.

Pembrolizumab (P) is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Results from trials conducted in other cancers indicate pembrolizumab, in combination with standard chemotherapy regimens, appears to add efficacy to treatment outcomes whilst remaining tolerable.

The P+R-ICE trial aims to evaluate the activity of a novel agent pembrolizumab in addition to the current best available treatment

(R-ICE) for relapsed refractory DLBCL patients who are fit for autologous stem cell transplant (ASCT).

Methods: P+R-ICE is an open-label, multicentre, randomised phase II trial.

Eligible patients have relapsed or refractory DLBCL following first or second line therapy, fit for high dose therapy and ASCT, and ECOG score 0–1.

Patients are randomised 1:3 to either control R-ICE for 3 cycles or experimental P+R-ICE for 3 cycles. Patients in a CR or PR on the post treatment PET-CT scan will have an ASCT and patients on the experimental arm will follow this with maintenance pembrolizumab every 3 weeks for 1 year. Randomisation is stratified by relapse within or >12 months of first line therapy.

The primary endpoint for the study is event free survival (EFS) at 12 months. Secondary endpoints include progression free survival, overall survival, number of patients achieving sufficient stem cells on harvest, response rates and toxicity. There will be an early interim analysis to monitor safety and the ability to collect required stem cells post treatment.

The trial is powered for the experimental arm using an A'hern design with 80% power, 10% significance, an uninteresting 12 month EFS rate of 20% (p0) and promising rate of 35% (p1) requires 44 patients. The treatment will warrant evaluation if 13/44 are event free at 12 months. With 10% drop out 65 patients will be randomised (16:49 per arm).

This is a UK National Cancer Research Institute multicentre trial coordinated by Southampton Clinical Trials Unit. Trial registration: ISRCTN86607306.

The trial has been supported by an investigator-initiated grant and drug access from MSD (Ref -56804).

Keywords: aggressive B-cell non-Hodgkin lymphoma, immunotherapy, ongoing trials

Conflicts of interests pertinent to the abstract.

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Honoraria: Roche
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Educational grants: Takeda, Janssen

A. J. Davies
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Honoraria: Celgene, Roche, Kite, Takeda
Research funding: Celgene, Roche, Kite, Takeda, Janssen, GSK
Educational grants: Celgene, Roche

OT22 | S2207: RANDOMIZED PHASE II STUDY OF THE ADDITION OF TARGETED AGENTS TO TAFASITAMAB-LENALIDOMIDE IN TRANSPLANT INELIGIBLE PATIENTS WITH RELAPSED/REFRACTORY LBCL

J. E. Amengual[1], P. Reagan[2], H. Li[3], H. Saeed[4], R. Vaidya[3], J. M. Unger[3], A. Danilov[5], M. LeBlanc[3], J. W. Friedberg[2], S. M. Smith[6]

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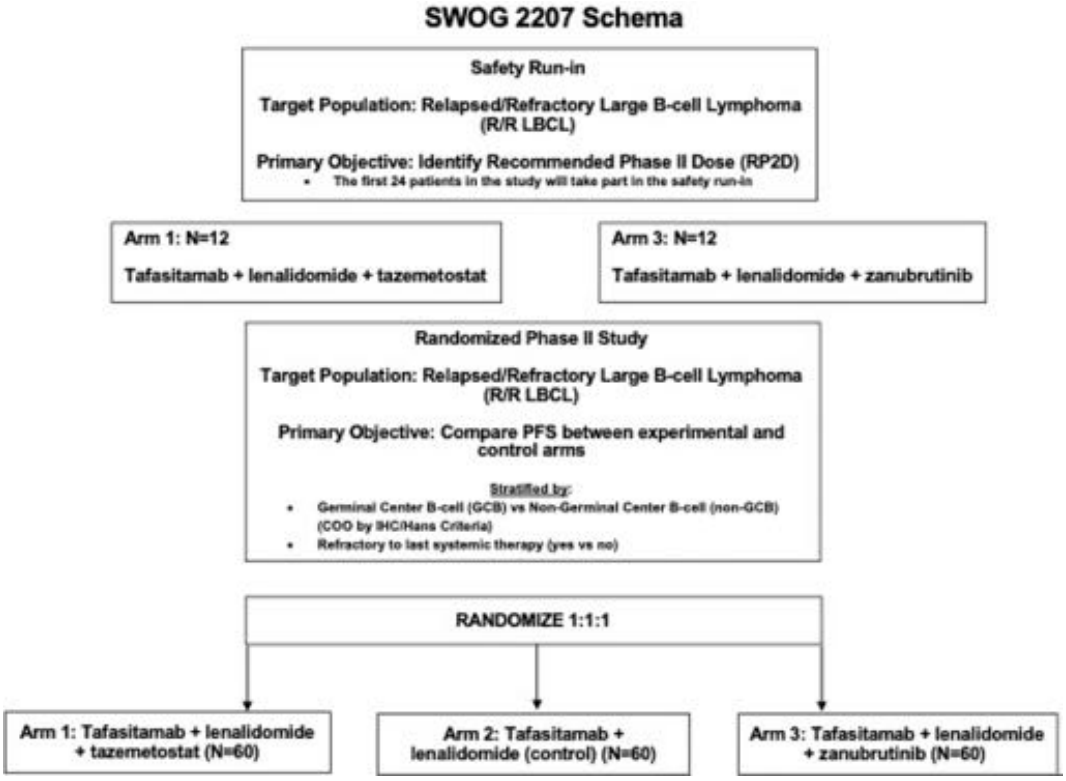
Large B-cell lymphoma (LBCL) is the most common lymphoma worldwide. About 40% of patients relapse, and most are not eligible for transplantation due to chemoresistant disease, advanced age, comorbidities, or lack of access to tertiary care. Similarly, CAR-T remains inaccessible for the majority of patients due to poor fitness, aggressive disease, lack of social support, to name a few. Thus, *R/R* LBCL is an area of great unmet need, with median survival measuring <1 yr. Recently, several less intensive regimens designed for outpatient administration have been approved in the United States. Tafasitamab-lenalidomide is a promising regimen, with durable remissions comparable even to CAR T-cell in some analyses. We hypothesize that if tafa-len is a well-tolerated and effective backbone, then the addition of biologically targeted agents could lead to improved outcomes while limiting toxicity. The SWOG 2207 trial will test the addition of tazemetostat or zanubrutinib to the tafa-len backbone in a randomized study open nationwide. Furthermore, we will evaluate the impact of cell-of-origin (COO) on efficacy.

Following a safety run-in of 12 patients per each experimental arm, the randomized Phase II study will enroll 180 patients to Arm 1: tafa-len + tazemetostat; Arm 2: tafa-len (control); or Arm 3: tafa-len + zanubrutinib (Figure 1). The primary objective of the phase II portion is to compare the PFS of patients treated on the experimental arms with the control. Secondary objectives will include estimating hazard ratios for PFS based on GCB and non-GCB subtypes for each experimental treatment arm. Other objectives will include exploring PFS by molecular profile and genetic subtypes. Frailty and its correlation to outcome will be assessed. In addition, patient-reported lymphoma specific symptoms by PRO-CTCAE will be measured, as well as, quality of life using the FACT-Lym, and will be compared between arms.

Patients will be treated on a 28-day cycle for no more than 13 cycles. Tafa-len will be administered per package insert. Tazemetostat or zanubrutinib will be dosed at the RP2D twice daily for 28 of 28 days. Eligibility will allow for patients to have histologically confirmed *R/R* LBCL as defined by WHO guidelines, FL grade 3B, transformed lymphoma, and HGBCL with/without *MYC*, *BCL2* and/or *BCL6* rearrangements. Patients must have COO determination by Hans



immunohistochemistry algorithm. Patients must not be a candidate for or have declined transplant. Those who have disease progression following transplant or CAR-T are eligible. Disease assessment with PET-CT or contrast enhanced CT, and patient reported outcomes will occur at baseline and by cycle 3, 6 and EOT. The goal of the SWOG 2207 study is to improve outcomes of patients with *R/R* LBCL who are not candidates for transplant with potentially biologically targeted, well tolerated therapy. Funding: NIH/NCI/NCTN grants U10CA180888/U10CA180819.

The research was funded by: NIH/NCI/NCTN grants U10CA180888/U10CA180819

Keywords: aggressive B-cell non-Hodgkin lymphoma, molecular targeted therapies, ongoing trials

No conflicts of interests pertinent to the abstract.

OT23 | ZUMA-24: A PHASE 2, OPEN-LABEL STUDY OF AXICABTAGENE CILOLEUCEL IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA GIVEN OUTPATIENT WITH CORTICOSTEROIDS

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Introduction: Axicabtagene ciloleucel (Axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of adults with relapsed or refractory (*R/R*) large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy and for *R/R* LBCL within 12 months of first-line chemoimmunotherapy. Cohorts (C)1+2 of the ZUMA-1 study of axi-cel in refractory LBCL showed an objective response rate (ORR) of 83% (complete response [CR] rate, 58%), and Gr ≥3 cytokine release syndrome (CRS) and neurologic events (NEs) were experienced by 11% and 31% of patients (pts), respectively, after ≥2 years median follow-up (Locke et al. *Lancet Oncol*. 2019). ZUMA-7 (Locke et al. *N Engl J Med*. 2022) examined axi-cel versus standard of care in pts with *R/R* LBCL after 1 line of prior therapy and showed efficacy (ORR, 84%; CR rate, 65%) and safety (Gr ≥3 CRS, 6%; Gr ≥3 NEs, 21%) consistent with ZUMA-1 C1+2.

Owing in part to this safety profile, most pts received commercial axi-cel in an inpatient setting. ZUMA-1 C6, which evaluated whether improved safety outcomes were observed with prophylactic corticosteroids and earlier use of corticosteroids and/or tocilizumab to manage CRS and NEs, demonstrated no Gr ≥3 CRS and 18% Gr ≥3 NEs with high, durable response rates (ORR, 95%; CR rate, 80%) after ≥2 years median follow-up (Oluwole et al. ASH 2022. #705). To further advance safety management strategies with axi-cel, ZUMA-24, a Phase 2, open-label, multicenter study, will evaluate the safety and efficacy of axi-cel with prophylactic corticosteroid use in pts with *R/R* LBCL after 1 prior line of therapy in the outpatient setting.

Methods: ZUMA-24 will enroll ≈40 adult pts with histologically confirmed *R/R* LBCL who received adequate prior therapy (anti-CD20 monoclonal antibody and anthracycline-containing chemotherapy). Pts will undergo leukapheresis, followed by lymphodepleting chemotherapy (fludarabine/cyclophosphamide) and a single axi-cel infusion (2×10^6 CAR T cells/kg). Prior to axi-cel infusion on Day 0 and on Days 1 and 2, pts will receive prophylactic dexamethasone (10 mg). Pts will undergo daily outpatient monitoring to manage AEs for ≥7 days after axi-cel infusion as set forth by institutional outpatient monitoring program. The primary endpoint is incidence and severity of CRS and NEs. Key secondary endpoints are time to onset and duration of CRS and NEs, rate and duration of hospitalization after axi-cel infusion due to AEs, and measures of efficacy including ORR, CR rate, duration of response, progression-free survival, and overall survival.

Additional key inclusion criteria are ECOG 0-1 and adherence to prespecified institutional clinical monitoring requirements. Key exclusion criteria include >1 prior line of therapy for LBCL, prior stem cell transplant, and prior anti-CD19 or CAR T-cell therapy. The study is open and actively accruing pts at United States sites (NCT05459571).

Encore Abstract - previously submitted to ASCO 2023 and EHA 2023

The research was funded by: The research was funded by Kite, a Gilead Company.

Keywords: aggressive B-cell non-Hodgkin lymphoma, cellular therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

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Research funding: (To your institution): 2seventy bio, AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Biopath, Bristol Myers Squibb, CALIBR, CALGB, Celgene, City of Hope National Medical Center, Constellation Pharmaceuticals, Curis, CTI Biopharma, Epizyme, Fate Therapeutics, Forma Therapeutics, Forty Seven, Genentech, Gilead Sciences, InnoCare Pharma, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Janssen, Kite Pharma, Loxo, Marker Therapeutics, Merck, Millennium Pharmaceuticals, MorphoSys, Myeloid Therapeutics, Novartis, Nurix, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Roche, Seattle Genetics, Step Pharma, Tessa Therapeutics, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development Corp., Unum Therapeutics, Verastem, and Vincerx Pharma

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OT24 | PILOT PHASE II STUDY OF SELINEXOR IN COMBINATION WITH IFOSFAMIDE, ETOPOSIDE AND DEXAMETHASONE IN PATIENTS WITH RELAPSED OR REFRACTORY PERIPHERAL T-CELL LYMPHOMAS (*R/R* PTCLS)

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Introduction: The prognosis of *R/R* PTCLs is very poor. Selinexor is an oral, first in class, potent selective inhibitor of nuclear exportin, that shown promising overall response rate (ORR) and complete response (CR) in a phase I study of selinexor in combination with high-dose dexamethasone, ifosfamide, carboplatin and etoposide in *R/R* PTCLs, Tang et al (Haematologica 2021). These results are very preliminary and need to be confirmed; for this reason, we designed the PTCL S-IDE study (EudraCT number 2021-006229-23).
Methods: S-IDE is a phase II multicenter pilot study of Selinexor in combination with Ifosfamide, Etoposide and Dexamethasone in patients with *R/R* PTCLs. We decided to omit carboplatin in order to reduce nausea and hematologic toxicity, in addition the activity of carboplatin in PTCL is uncertain. Key inclusion criteria are: age 18–75 years, *R/R* histologically confirmed PTCL (PTCL-NOS, angioimmunoblastic T cell lymphoma - AITL, anaplastic large cell ALK negative—ALK neg, T-helper follicular—TFH) after at least one course of anthracycline containing regimen chemotherapy (including or not high dose chemotherapy and stem cell transplantation - SCT), PS ECOG $\leq$2, adequate organ function. All patients will receive intravenous S-IDE on a 21-day cycle: Selinexor (40 mg on day 3, 5 and 7); Ifosfamide 5 g/mq on day 2; Etoposide 100 mg/mq on days 1–3; Dexamethasone 20 mg/day on days 3–7. Patient in CR at the end of the 4 courses receive a maintenance with selinexor (selinexor 60 mg weekly, until progression or unacceptable toxicity) or proceed to allo-SCT or auto-SCT according to donor availability, patient age and comorbidities. The primary endpoint is ORR at the end of 4 courses of S-IDE; the secondary endpoints are duration of response, 18-months PFS and OS, treatment related mortality, CR by histotypes, rate of patients able to undergo SCT, and adverse events. Exploratory biological analyses are ORR in subgroups based on GATA3 and TBX21 expression; loss of tumor suppressor genes on the CDKN2A/B-TP3 axis and PTEN-PI3K pathways as well as genetic gains and amplification of STAT3 and MYC; the presence of mutations described as associated with a poor prognosis, including CD28 mutations in AITL; TP63 rearrangement, loss of TP53, and loss of PRDM1 in ALK− ALCL; GATA3 , TP53, and/or CDKN2A in ALK− ALCL; and alterations in histone methyltransferase genes KMT2A, KMT2B, or KDM6A and FAT1 in PTCL-NOS; XPO1 expression; circulating tumor DNA (ctDNA). The sample size is 30 patients, with enrollment 18 months in 9 Italian centers. The sample size calculation refers to the primary endpoint; a sample size of 30 patients will allow to achieve a statistical power of more than 90% (94%) to test an increase of 30% of ORR (from 50% under null hypothesis to 80% under the alternative one) using a two-sided one sample binomial test with alpha =5%. The accrual is ongoing; at the end of February 2023, 2 patients have been enrolled.

Keywords: aggressive T-cell non-Hodgkin lymphoma, combination therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

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OT25 | TRIAL IN PROGRESS: ODRONEXTAMAB, A CD20×CD3 BISPECIFIC ANTIBODY, FOR THE TREATMENT OF RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA (*R/R* MZL)—A COHORT FROM THE ELM-2 STUDY

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Introduction: MZL is a heterogeneous disease comprising 3 subtypes, extra-nodal MZL of mucosa-associated lymphoid tissue, nodal MZL, and splenic MZL. Treatment of *R/R* MZL is similar to other indolent B-cell non-Hodgkin lymphoma (B-NHL) subtypes (e.g., follicular lymphoma [FL]), comprising rituximab-based immunochemotherapy regimens that achieve an objective response rate (ORR) of ~45%–80%. Options after progression on rituximab-based regimens include the BTK inhibitor ibrutinib, which demonstrated an ORR of 46%, but a compete response (CR) rate of only 3%, in its pivotal trial in *R/R* MZL. Overall, limited options are available after progression on current therapies, and a need remains for more effective treatments for *R/R* MZL.

Odronextamab is a bispecific antibody that binds CD20-expressing B-NHL cells and CD3 on T cells. In the Phase 1 ELM-1 study, odronextamab monotherapy showed antitumor activity and a manageable safety profile in a range of *R/R* B-NHL subtypes, including MZL ($n = 6$; ORR 67%) (Bannerji et al. Lancet Haematol, 2022). In the Phase 2 ELM-2 study, odronextamab elicited an ORR of 82% and CR rate of 75% in patients with heavily pretreated *R/R* FL (Kim, et al. ASH, 2022). These positive data in an indolent B-NHL subtype support evaluation of odronextamab in *R/R* MZL.

Methods: ELM-2 (NCT03888105) is an open-label study of odronextamab in patients with *R/R* B-NHL comprising 5 disease-specific cohorts: FL, diffuse large B-cell lymphoma, mantle cell lymphoma, MZL, and other B-NHLs. Each cohort will be evaluated separately, and patients recruited from sites across North America, Europe, and Asia-Pacific regions. The MZL cohort is planned to include 78 patients, who will receive IV odronextamab monotherapy until disease progression or other protocol-defined reason for treatment discontinuation. Odronextamab is administered according to a step-up regimen during the first 21-day cycle (C), consisting of 0.7 mg split over C1 Day (D) 1 (0.2 mg) and C1D2 (0.5 mg), 4 mg split over C1D8 and C1D9, and 20 mg split over C1D15 and C1D16. The full 80 mg dose is given QW during C2 to C4, then 160 mg Q2W from C5 onwards. If a patient achieves a CR and has a durable response for ≥9 months after initial determination of the CR, then dosing interval will be decreased from Q2W to Q4W.

Patients eligible for the MZL cohort will be ≥18 years of age; relapsed/refractory to ≥2 prior lines of systemic therapy; ECOG performance status ≤1; and have adequate bone marrow and hepatic functions. Patients with prior allogeneic stem cell transplant or CAR T treatment will be excluded.

Primary endpoint is ORR (Lugano classification; assessed by independent central review). Key secondary endpoints include ORR (investigator evaluation); CR rate; progression-free survival; overall survival; duration of response; safety; pharmacokinetics; and patient-reported quality of life outcomes.

As of January 2023, 19 patients with MZL had enrolled.

Encore Abstract—previously submitted to ASCO 2023 and EHA 2023

The research was funded by: Regeneron Pharmaceuticals, Inc.

Keywords: indolent non-Hodgkin lymphoma, immunotherapy, ongoing trials

Conflicts of interests pertinent to the abstract.

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OT26 | R-CHOP WITH SINTILIZUMAB IN FIRST-LINE TREATMENT OF LARGE B-CELL LYMPHOMA PATIENTS WITH TP53 MUTATIONS AND PD-L1 EXPRESSION: A RANDOMIZED, MULTICENTER CLINICAL STUDY

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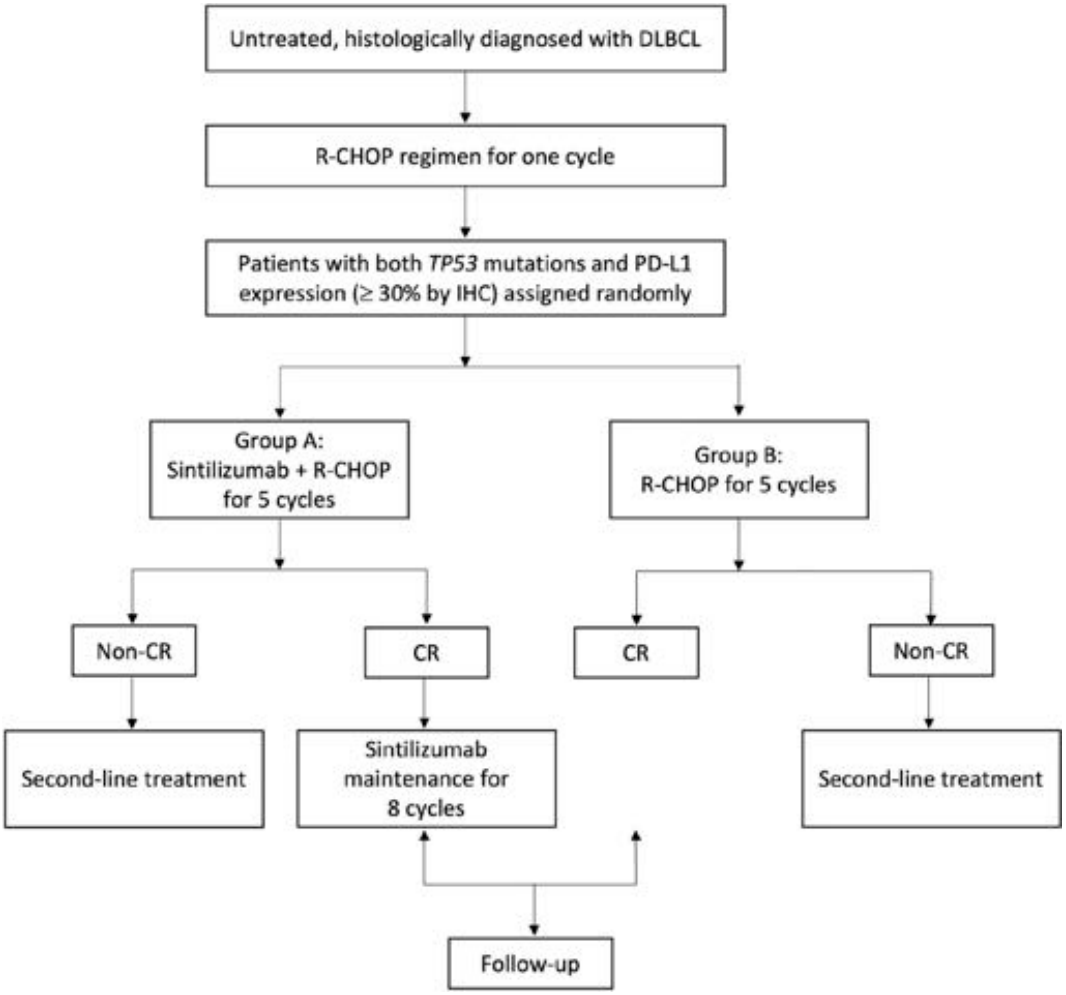
Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common type of malignant lymphoma, which accounts for approximately 30%–40% of all cases of non-Hodgkin lymphoma (NHL). Although 60% of patients can be cured by standard R-CHOP (rituximab plus cyclophosphamide, doxoru bicin, vincristine, and prednisone) as frontline therapy, patients with resistance to primary chemoimmunotherapy have a poor prognosis. It has been well demonstrated that *TP53*mutations and PD-L1 expression correlate with therapeutic resistance. Accordingly, in our preliminary observation, we found that sintilizumab (a PD-1 inhibitor) exerts remarkable efficacy and acceptable tolerance in PD-L1 expressing patients with relapsed or refractory (*R/R*) DLBCL. Therefore, we further initiate a clinical trial to investigate if sintilizumab can enhance the efficacy of R-CHOP in untreated DLBCL patients with *TP53* mutations and PD-L1 expression.

Methods: This randomized, multicenter study performs in at least 10 clinical sites in China. Patients aged 18 years or older with histologically diagnosed with DLBCL, untreated and a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 are eligible for inclusion. Patients will receive one cycle of R-CHOP regimen and *TP53* status and PD-L1 expression will be examined by PCR and immunohistochemistry (IHC), respectively. Afterwards, patients with *TP53* mutations and PD-L1 expression (≥30% by IHC) are randomly assigned (1:1) to receive either sintilimab plus R-CHOP regimen (group A) or R-CHOP only (group B) for 5 cycles, until disease progression, unacceptable toxicity or withdrawal of consent. To avoid the interference of prednisolone, sintilizumab (200mg, every 3 weeks) is administered intravenously at day 10 after chemotherapy. Patients achieving CR in group A will continue to receive sintilizumab for 8 cycles. The primary endpoint of this study is complete response rate (CR) according to Lugano classification. Secondary endpoints include objective response rate (ORR) and 1-year progression free survival (PFS). Tumor measurements are assessed by PET/CT at baseline, at weeks 9 and 18, and then by CT scan every 3 months for 1 year. In addition, blood circulating tumor DNA (ctDNA) and PD-L1 are also under evaluation accordingly. Safety was assessed in all treated patients. The study is registered with www.chictr.org, NCT05280626 and is ongoing.

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, ongoing trials

No conflicts of interests pertinent to the abstract.



OT27 | PHASE II/III STUDY OF R-MINICHOP ± ORAL AZACITIDINE IN PARTICIPANTS AGE 75 YEARS OR OLDER WITH DIFFUSE LARGE B CELL AND RELATED LYMPHOMAS

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Introduction: Diffuse large B cell lymphoma (DLBCL) is an aggressive but potentially curable malignancy. Nearly one-third of patients are >75 y, and advanced age is an adverse prognostic variable. R-miniCHOP, a dose attenuated version of standard R-CHOP, offers a 2-year progression-free survival (PFS) of 47% based on phase II data (Peyrade F et al, 2011). For comparison, patients age 60-80 have about a 75% 2-year overall survival (OS) with R-CHOP chemotherapy (Coiffier B et al., 2002).

A key dilemma is identifying which older patients with DLBCL should be considered for curative intent chemoimmunotherapy. The FIL (Fondazione Italiana Linfomi; Italian Lymphoma Foundation) has developed a tool accounting for age, comorbidities, and ability to perform daily and instrumental activities to classify patients as fit, unfit, or frail (Tucci A et al, 2015), with a key observation being improved survival when curative intent chemoimmunotherapy was delivered to fit and unfit patients. (Merli F et al., 2021). However, there is no prospective validation of frailty assessment and treatment outcomes.

Epigenetic deregulation is a feature of DLBCL in older patients. Preclinical models show that pre-treatment with hypomethylating agents improves the anti-tumor effect of the agents contained in R-

CHOP (Clozel T et al., 2013). Early studies of azacitidine with R-CHOP showed promising efficacy and acceptable toxicity (Martin P et al., 2022). The availability of oral azacitidine is appealing, reduces the infusion burden of treatment, and is agnostic to cell-of-origin.

Methods: S1918 is a randomized trial of R-miniCHOP ± oral azacitidine in patients >75 y with newly diagnosed aggressive B-cell non Hodgkin lymphomas (NCT04799275). This is the first randomized study in this population conducted in North America by the National Clinical Trials Network (NCTN) and will enroll 384 patients. Patients receive prephase therapy with prednisone 60–100 mg × 4–7 days to improve performance status and decrease early treatment-related mortality (Owens CN et al., 2015; Pfreundschuh M et al., 2008). A safety run-in has been completed.

The phase II objective is to determine if oral azacitidine + R-miniCHOP should be tested further against R-miniCHOP based on estimates of 1-year PFS. The phase III objective is to compare OS at 2 years between arms.

S1918 incorporates the FIL Tool for baseline frailty assessment and a serial comprehensive geriatric assessment to evaluate effects of therapy on quality of life and functional status. Key correlative tests include circulating tumor DNA (ctDNA) assays to explore if ctDNA quantity and methylation patterns correlate with response.

S1918 has potential to impact future trial design and change the standard of care for patients > 75 y with aggressive lymphoma with its randomized design, incorporation of baseline frailty and geriatric assessments, and utilization of ctDNA correlatives.

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Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

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OT28 | PHASE 3 TRIAL OF SUBCUTANEOUS EPCORITAMAB + R-CHOP VERSUS R-CHOP IN PATIENTS (PTS) WITH NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): EPCORE DLBCL-2

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Introduction: In pts with newly diagnosed DLBCL, standard treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has a 5-year progression-free survival (PFS) rate of 67.0%, 58.4%, and 45.8% for International Prognostic Index (IPI) 2, 3, and 4–5, respectively (Ruppert et al., *Blood* 2020). Epcoritamab is a subcutaneously administered, bispecific antibody that binds CD3 on T cells and CD20 on B cells, inducing potent and selective T-cell–mediated killing of malignant CD20+ B cells (Hutchings et al., *Lancet* 2021). Epcoritamab monotherapy demonstrated deep and durable responses (overall response rate [ORR], 63%; complete response rate, 39%; median duration of response, 12 months) and was generally well tolerated in pts with relapsed/refractory (*R/R*) aggressive, large B-cell lymphoma (LBCL) (Thieblemont et al., *J Clin Oncol* 2022). Results from an ongoing phase 1/2 study in high-risk pts with newly diagnosed DLBCL (EPCORE NHL-2 arm 1; NCT04663347) show that epcoritamab + R-CHOP has promising efficacy and a manageable safety profile in high-risk pts with IPI 3–5. Among efficacy-evaluable pts ($n = 31$), ORR was 100% and complete metabolic response (CMR) was 77%; cytokine release syndrome (CRS) events ($n = 17/33$; 52%) were mostly low-grade, had predictable timing, and did not lead to treatment discontinuation (Falchi et al., ASCO 2022, abstract 7523). These encouraging data support further evaluation of epcoritamab + R-CHOP for the treatment of newly diagnosed DLBCL.

Methods: This phase 3, global, multicenter, open-label study (NCT05578976) evaluates the efficacy and safety of epcoritamab + R-CHOP in adults newly diagnosed with one of the following CD20

+ DLBCL (de novo or transformed from follicular lymphoma [FL]): 1) DLBCL, not otherwise specified (NOS); 2) high-grade B-cell lymphoma with *MYC* and *BCL-2* and/or *BCL-6* rearrangement; 3) T-cell/histiocyte–rich LBCL; 4) Epstein-Barr virus–positive DLBCL, NOS; or 5) FL grade 3b. Other key eligibility criteria include IPI ≥2 (pts with IPI 2 not to exceed ~30% of total pts), ECOG PS 0–2, and ≥1 measurable disease site. Approximately 900 pts will be randomized 2:1 to either epcoritamab + R-CHOP (6 cycles, followed by 2 cycles of epcoritamab) or R-CHOP (6 cycles, followed by 2 cycles of rituximab). The primary efficacy endpoint is PFS in pts with IPI 3–5 (based on IRC assessment per Lugano criteria). The secondary efficacy endpoints are PFS in pts with IPI 2–5, event-free survival, CMR, overall survival, and minimal residual disease negativity. Safety endpoints include incidence and severity of treatment-emergent adverse events (AEs), serious AEs, and AEs of special interest (CRS, immune cell–associated neurotoxicity syndrome, and clinical tumor lysis syndrome). Enrollment began in January 2023 globally.

The research was funded by: This study was funded by AbbVie and Genmab.

Keywords: aggressive B-cell non-Hodgkin lymphoma, combination therapies, immunotherapy

Conflicts of interests pertinent to the abstract.

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Research funding: Janssen, Bayer, MorphoSys, AstraZeneca
Other remuneration: Invited Speaker: Roche, BMS, Novartis, AbbVie, Incyte, Sobi, Hexal

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OT29 | LOTIS-5, AN ONGOING PHASE 3 RANDOMIZED STUDY OF LONCASTUXIMAB TESIRINE WITH RITUXIMAB (LONCA-R) VERSUS IMMUNOCHEMOTHERAPY IN PATIENTS WITH *R/R* DLBCL

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Introduction: Patients with relapsed or refractory (*R/R*) diffuse large B-cell lymphoma (DLBCL) typically have poor outcomes following standard treatment. Loncastuximab tesirine (loncastuximab tesirine-lpyl; Lonca), an antibody-drug conjugate (ADC) comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin, received accelerated (US) and conditional (EU) approval in *R/R* DLBCL after ≥2 lines of systemic therapy, based on data from the phase 2 LOTIS-2 trial (Caimi PF et al. *Lancet Oncol.* 2021;22[6]:790). Rituximab (R), an anti-CD20 monoclonal antibody, is part of standard immunotherapy for DLBCL, both as frontline therapy and in subsequent treatments. Preclinical evidence suggests the addition of R to anti-CD19 ADC therapy may result in prolonged tumor control (Ryan MC et al. *Blood.* 2017;130 [18]:2018). LOTIS-5 aims to evaluate Lonca-R vs standard immunotherapy of R + gemcitabine + oxaliplatin (R-GemOx) in *R/R* DLBCL.
Methods: This is a phase 3, randomized, open-label, 2-part, 2-arm, multicenter study of Lonca-R in patients with *R/R* DLBCL (NCT04384484). The study consists of a safety run-in phase with Lonca-R (part 1) and a randomized phase evaluating efficacy and safety of Lonca-R vs R-GemOx (part 2). Approximately 350 patients will be enrolled across both parts: part 1 has completed; part 2 will enroll approximately 330 patients (randomized 1:1) to achieve 262 events for the primary end point analysis of progression-free survival by independent central review.
Secondary end points include overall survival, overall response rate (2014 Lugano classification), complete response rate, duration of response, frequency and severity of adverse events, change from baseline in laboratory values, concentration and pharmacokinetic parameters of Lonca (conjugated and total antibody and unconjugated PBD), and changes in patient-reported outcomes from baseline. The dosing regimen for Lonca-R is Lonca 150 μg/kg + rituximab 375 mg/m^2 every 3 weeks (Q3W) for 2 cycles, then Lonca 75 μg/kg + rituximab 375 mg/m^2 Q3W for up to 6 cycles. The dose regimen of R-GemOx is rituximab 375 mg/m^2, gemcitabine 1000 mg/m^2, and oxaliplatin 100 mg/m^2 every 2 weeks for up to 8 cycles.
Key eligibility criteria include age ≥18 years, pathologic diagnosis of DLBCL (including patients with DLBCL transformed from indolent lymphoma) or high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, ≥1 line of prior systemic therapy, previous stem cell transplant >30 days (autologous) or >60 days (allogenic) prior to start of study drug or stem cell transplant ineligibility, and measurable disease. The randomized part of LOTIS-5 began in January 2022 and has an estimated primary completion date of June 2025; enrollment continues, with a total of 45 active sites across the US, Canada, Spain, France, Belgium, Italy, Switzerland, Czech Republic, Poland, and China.

The research was funded by: ADC Therapeutics SA; medical writing: CiTRUS Health Group

Keywords: molecular targeted therapies, combination therapies, ongoing trials

Conflicts of interests pertinent to the abstract

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OT30 | A PHASE 3 TRIAL OF ACALABRUTINIB, OBINUTUZUMAB AND VENETOCLAX COMPARED TO OBINUTUZUMAB AND VENETOCLAX IN PATIENTS WITH HIGH RISK CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: Fixed-duration treatment with targeted agents, particularly venetoclax and obinutuzumab (GVe), have led to significantly improved treatment outcome as compared to chemo-immunotherapy (CIT) in patients (pts) with chronic lymphocytic leukemia (CLL) and genetic risk factors, such as *TP53* aberrations and complex karyotype (CKT). However, pts with high risk still progress earlier than pts with low risk CLL. Recently published results of the phase 2 CLL2-GIVe study suggest that a triple combination of monoclonal antibodies with a BTK- and BCL2-inhibitor is highly active in pts with *TP53* aberrant disease. Within the phase 3 GAIA/CLL13 study recruiting only patients without TP53 aberrations, the triple combination of obinutuzumab, ibrutinib and venetoclax was superior to CIT, but not to GVe. A comparison in high risk CLL is missing yet, so further investigation in a randomized phase 3 trial is warranted. The CLL16 trial of the GCLLSG was set up to compare GVe to the triple combination of acalabrutinib, obinutuzumab and venetoclax (GAVe).

Methods: The CLL16 trial is a prospective, open-label, multicenter, randomized, phase 3 trial comparing GVe to GAVe in previously untreated pts with high risk CLL exhibiting a 17p deletion, *TP53* mutation or CKT. 178 pts are randomly assigned to 12 cycles of venetoclax plus 6 cycles of obinutuzumab with or without 14 cycles of acalabrutinib. In the triplet arm, pts with persisting measurable residual disease after cycle 14 will continue treatment with acalabrutinib for up to 24 cycles. Screening procedures include local immunophenotyping and testing for *TP53* aberrations by FISH and sequencing, as well as central testing for CKT. The primary endpoint of the study is progression-free survival (PFS). The 3-year PFS rate for GVe is assumed with 71% and it is expected to increase with GAVe to 86%. The superiority of GAVe will be estimated based on a required hazard ratio of 0.44, with 48 events providing approximately 80% power. Secondary endpoints include event-free survival, overall survival and safety as assessed by CTCAE V5.0.

Results: The study recruits in 80 study sites in Germany and Austria. 19 pts with a median age of 62 years (range 46–75) and a median CIRS score of 3 (range 1–6) have already been included, eight of the pts are female. Four serious adverse events (SAEs) have been reported so far: one infusion related reaction, one increase of liver enzymes and one ascites, all of them CTC grade 3, and furthermore one CTC grade 2 COVID infection. A Data Monitoring Committee is established for safety overview in this study, after the first meeting the study can continue as planned.

Conclusions: The objective of this trial is to prove the superiority of a triple combination with GAVe over a standard treatment with GVe in pts with CLL and adverse risk factors defined as *TP53* alterations and CKT. No safety concerns have been identified to date and the study continues as planned.

The research was funded by: AstraZeneca

Keywords: chronic lymphocytic leukemia (CLL), combination therapies, ongoing trials

Conflicts of interests pertinent to the abstract.

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OT31 | ZUMA-22: A PHASE 3, RANDOMIZED CONTROLLED STUDY OF AXICABTAGENE CILOLEUCEL (AXI-CEL) VS STANDARD-OF-CARE THERAPY IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

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Introduction: Patients with relapsed/refractory (*R/R*) follicular lymphoma (FL) experience progressively shorter remissions with each successive line of therapy, and the disease is largely considered incurable (Batlevi et al. *Blood Cancer J.* 2020). Patients who relapsed <24 months after initiating first-line chemoimmunotherapy (POD24) have inferior overall survival compared with those who did not experience POD24 (Casulo, Barr. *Blood.* 2019). However, outcomes of *R/R* FL have improved with the introduction of novel options including chimeric antigen receptor (CAR) T-cell therapy, a highly effective approach with potential to change the treatment paradigm (Jacobson et al. *Lancet Oncol.* 2021; Freedman, Jacobson. *Am J Hematol.* 2020). Axi-cel, an autologous anti-CD19 CAR T-cell therapy, is approved for the treatment of *R/R* FL. In ZUMA-5, a single-arm, Phase 2 study of axi-cel in indolent non-Hodgkin lymphoma, patients with FL (n=127) had a median progression-free survival of 40.2 months and median overall survival not yet reached after median follow-up of 41.7 months, with manageable long-term safety (Neelapu et al. ASH 2022. Abstract 4660). In ZUMA-5, POD24 did not adversely affect progression-free survival or overall survival. ZUMA-22 is a Phase 3, open-label, multicenter, randomized controlled trial that will evaluate the efficacy and safety of axi-cel compared with standard-of-care therapy in patients with *R/R* FL.

Methods: The study will enroll approximately 230 adult patients with FL (Grades 1-3a) who have either had 1 prior line of therapy and experienced POD24 or had ≥2 prior lines of systemic therapy. Patients will be randomized 1:1 to receive axi-cel or standard-of-care therapy. Patients in the standard-of-care therapy arm will receive investigator's choice of either rituximab + lenalidomide, rituximab + CHOP, or rituximab + bendamustine. Patients in the axi-cel arm will undergo leukapheresis, followed by optional bridging therapy, lymphodepleting chemotherapy (fludarabine/cyclophosphamide), and a single axi-cel infusion (2×10^6 CAR T cells/kg). The primary endpoint is progression-free survival by blinded central assessment per Lugano classification (Cheson et al. *J Clin Oncol.* 2014). Secondary endpoints include complete and overall response rates, duration of response, overall survival, event-free survival, time to next treatment, safety, and quality-of-life assessments.

Additional key inclusion criteria are ECOG 0-1, presence of ≥1 measurable lesion, and adequate bone marrow and organ function.

Those with HIV or hepatitis B or C and an undetectable viral load are eligible. Key exclusion criteria are a history of large B-cell lymphoma or transformed FL, and FL Grade 3b. The study is currently open and actively accruing patients at several sites globally (NCT05371093).

Encore Abstract - previously submitted to ASCO 2023 and EHA 2023

The research was funded by: Kite, a Gilead Company

Keywords: cellular therapies, indolent non-Hodgkin lymphoma, ongoing trials

Conflicts of interests pertinent to the abstract.

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Research funding: 2seventy bio, AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Biopath, Bristol Myers Squibb, CALIBR, CALGB, Celgene, City of Hope National Medical Center, Constellation Pharmaceuticals, Curis, CTI Biopharma, Epizyme, Fate Therapeutics, Forma Therapeutics, Forty Seven, Genentech, Gilead Sciences, InnoCare Pharma, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Janssen, Kite Pharma, Loxo, Marker Therapeutics, Merck, Millennium Pharmaceuticals, MorphoSys, Myeloid Therapeutics, Novartis, Nurix, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Roche, Seattle Genetics, Step Pharma, Tessa Therapeutics, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development Corp., Unum Therapeutics, Verastem, and Vincerx Pharma

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Research funding: BMS/Celgene, Caribou, Genentech, IGM, Janssen, Kite, Novartis, and Takeda

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Educational grants: Roche

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Honoraria: AbbVie, BeiGene, Celltrion, Gilead Sciences, Incyte, Janssen, Morphosys, Novartis, Pfizer, Regeneron, and Roche/Genentech
Research funding: Amgen, Bayer, Celltrion, Janssen, MSD, Pfizer, and Roche/Genentech
Other remuneration: Speaker's bureau participation with AbbVie, BeiGene, Celltrion, Gilead Sciences, Janssen, Pfizer, and Roche

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Honoraria: AbbVie, ADC Theraputics, Amgen, BeiGene, Celgene, Daiichi Sankyo, Eli Lilly, GSK, Incyte, Janssen, Kite, KyowaKirin, Nerviano Medical Science, Novartis, Roche, Sanofi, SOBI, and Takeda
Educational grants: AbbVie, Amgen, Bristol Myers Squibb, Celgene, Janssen, Kite, Novartis, Roche, and Takeda

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Educational grants: Kite
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Educational grants: Gilead Sciences
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Educational grants: Kite and Clovis Oncology
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OT32 | DISCOVERING TARGETABLE IMMUNE POPULATIONS IN CUTANEOUS T-CELL LYMPHOMA

A. Johansson[1], E. Kalliara[1], A. Porwit[2], E. Belfrage[3], K. Drott[4], S. Ek[1]
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Introduction: Mycosis fungoides (MF) is the most common type of Cutaneous T-cell Lymphoma (CTCL). Most patients with MF patients are diagnosed at an early stage with chronic characteristics and exhibit a good prognosis with a 5-year survival of 89%–98%. However, 25%–30% of those patients will progress to an advanced stage associated with extracutaneous involvement, unpredictable treatment response and dismal prognosis. The exact biological mechanisms underlying disease progression and treatment response are still unknown. Therefore, to acquire an in-depth understanding of the molecular events associated with disease progression and to identify potential treatment predictive biomarkers, a prospective clinical trial for MF patients, called BIO-MUSE, was inaugurated at Skåne University Hospital in Lund in 2021. The interdisciplinary BIO-MUSE clinical trial recognizes six distinct endpoints: I) identification of serum-protein markers, II) immune cell profiling in blood, III) immune cell profiling in skin, IV) analysis of the lymphoma microenvironment in skin, V) skin barrier and skin microbiology profiling and VI) investigations of epigenetic changes in malignant and non-malignant T-cells. Getting access to longitudinal samples from the BIO-MUSE trial followed by applying combinatorial tools of spatially resolved and single cell omics technologies, concerning endpoint II-IV, will enable unique deep molecular investigations to empower early identification of MF patients who will progress and thus allow future personalised treatment strategies, see Figure 1.
Methods: Participants in the BIO-MUSE trial are all consenting patients with Mycosis Fungoides or Sezary Syndrome. In total, the trial aims to enroll 50 patients and 20 healthy volunteers. The participants will be followed for a three-year period and translational sampling will take place every three months. Treatment is given according to clinical routine.
Single cell RNA-sequencing. Gene expression profiles of tumor cells and bulk T cells from peripheral blood will be analyzed by single cell RNA sequencing. In brief, the pool of CD3+ cells will be sorted and the T-cell receptor repertoire and 5' gene expression will be investigated using the 10x Genomics platform.
Digital Spatial Profiling technology. Skin biopsies from MF patients will be analyzed using the nCounter™ GeoMx Digital Spatial Profiling technology. In brief, FFPE tissue sections will be mounted on slides and processed according to corresponding standard protocol, involving staining with morphology markers to identify cell types of interest and subsequently analyzed with a large panel of genes covered by the GeoMx Cancer Transcriptome Atlas.

Keywords: cutaneous non-Hodgkin lymphoma, diagnostic and prognostic biomarkers, genomics, epigenomics, and other -omics

No conflicts of interests pertinent to the abstract.

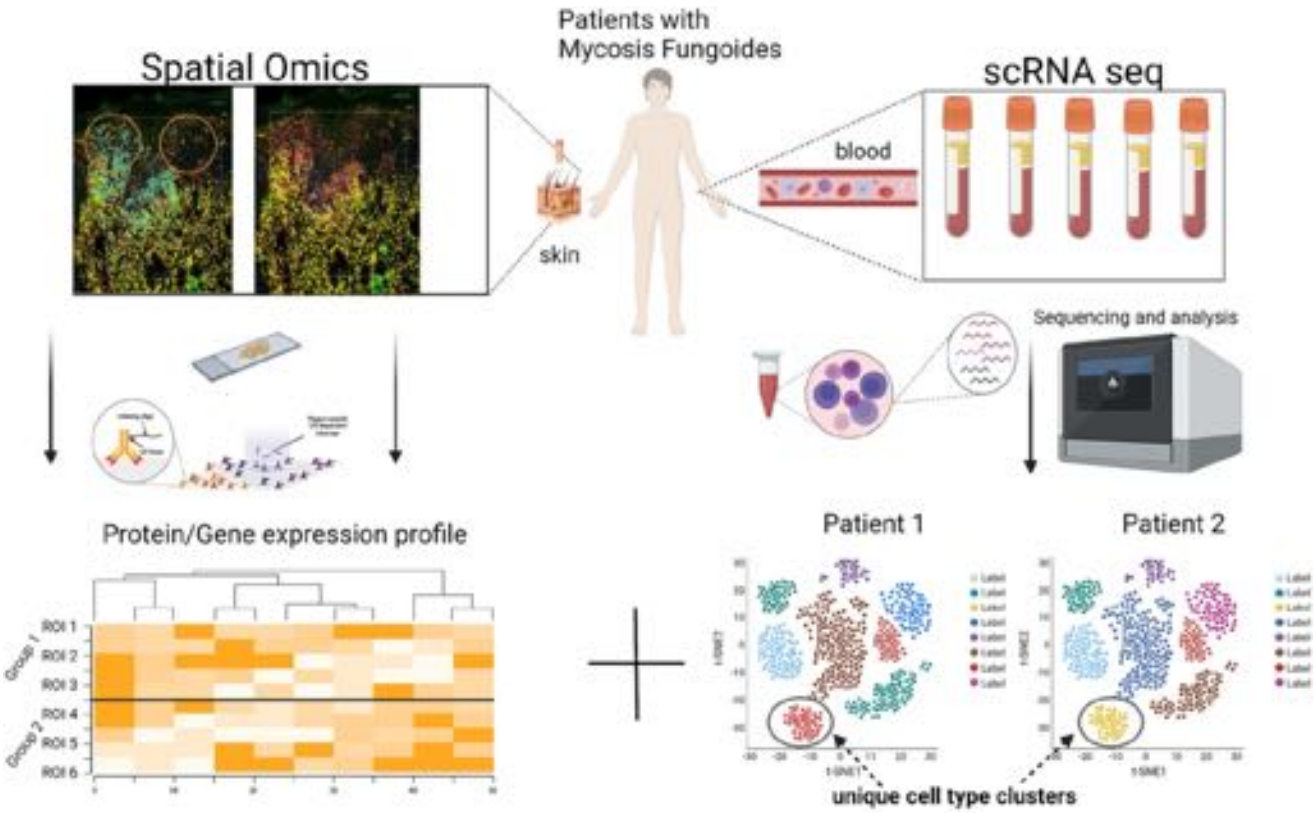

Figure 1. Skin and blood samples from patients enrolled in the BIO-MUSE clinical trial will be analysed with spatial omics and singe cell RNA sequencing tools for identification of targetable immune cell populations.

OT33 | ONKOFRAIL: PERSONALIZATION OF A PHYSICAL EXERCISE PROGRAM IN OLDER PATIENTS WITH LYMPHOMA

M. Martinez De Rituerto Zeberio[1], M. Rua Gomez[2], B. Mendibil Esquisabel[2], J. Garcia[3], M. Pelaez Puente[1], A. Rodriguez Larrad[3], H. Arrieta[4], I. Olazabal Eizaguirre[2], I. Zeberio Etxetxipia[2], L. Basterreceha Badiola[5]

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Several authors highlight the importance of including a physical exercise program during and after cancer treatment, based on the positive effects shown by several studies in young patients.

However, there is very little evidence on the effects of physical exercise during cancer treatment in older patients with lymphoma.

Recommendations of different scientific societies are based on the expert's opinion and studies with younger patients with non-hematological cancer. Therefore, this is an unknown area and it is a priority to promote research projects in order to generate effective interventions for this population. Different studies in cancer patients have shown that physical exercise reduces loss of functionality, attenuates frailty during cancer treatment, reduces toxicity and improves treatment completion rate. Recent studies have shown that physical exercise during chemotherapy is safe and that it may benefit in reducing toxicity and maintaining physical and mental well-being.

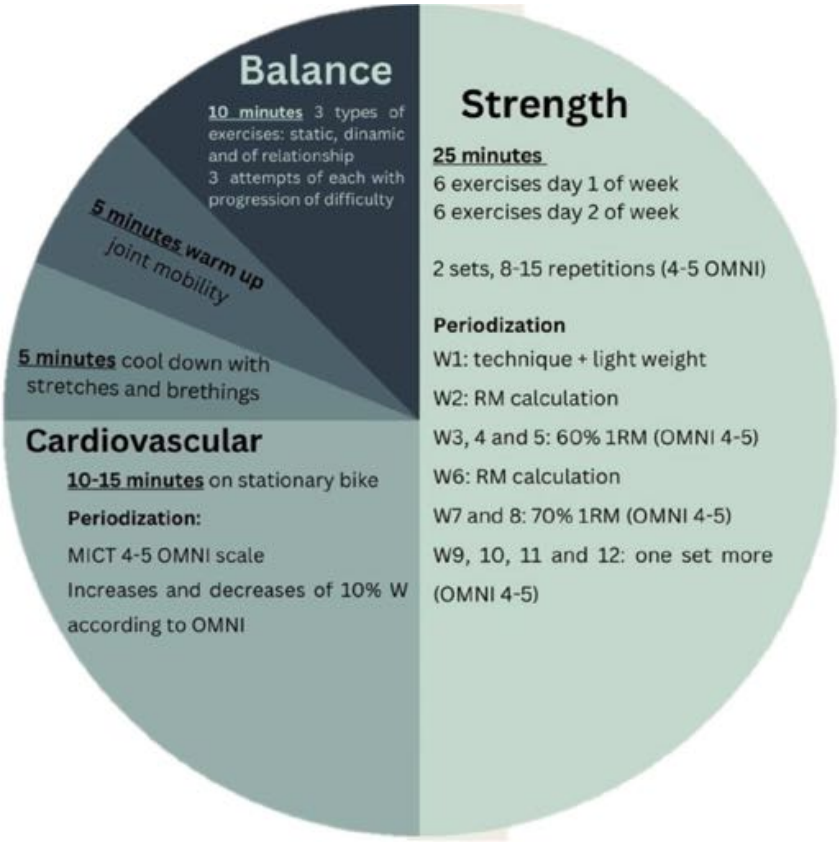
For all these reasons, this research study analyzes the role of supervised physical exercise in older people with lymphoma in an innovative way, with the aim of generating new hypotheses that overcome existing limitations and facilitate the introduction of this type of intervention in the health system.

For this purpose, a randomized controlled multicenter study has been designed.

All patients over 70 years of age diagnosed with lymphoma who require systemic treatment will be invited to participate. The control group will receive the usual care and movement hygiene recommendations, while the intervention group will add an individualized, progressive, moderate-intensity, supervised physical exercise program of 12 weeks duration, with the content described in Figure 1.

All eligible patients will be assessed before receiving a systematic treatment and after 12 weeks.

The Comprehensive Geriatric Assessment (CGA) will assess comorbidity, functional capacity, and nutritional status, emotional/cognitive and social status.



The evaluation also includes the SPPB test (Short Physical Performance Battery) the Fried Frailty Phenotype, the 8 foot up and go and Steep Ramp Test, the Montreal Cognitive Assessment (MoCA test), PROs (patient reported outcomes) and the level of physical activity and sedentary behavior measured by accelerometer.

The study will also analyze certain biomarkers associated with vulnerability that provide objective information complementary to the clinical assessment and allow a more robust stratification of these patients. This study was approved by the Committee on Drug Research Ethics (CEIm) of the Basque Country (Euskadi).

The Trial is ongoing and we have already included 17 patients.

The research was funded by: Biodonostia

Keyword: ongoing trials

No conflicts of interests pertinent to the abstract.

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SUPPLEMENT ARTICLE

17-ICML ABSTRACT BOOK

INDUSTRY PROGRAM—SATELLITE SYMPOSIUM AGENDA (updated to May 10, 2023)

TUESDAY, JUNE 13

11:30–13:00 Room A	Kite, A Gilead Company
	Improving outcomes in R/R DLBCL: Learning from challenging cases
	Chair: Marie-José Kersten, Amsterdam, NL
	Every patient is different, and, due to the patient demographic in DLBCL, some can have multiple health-related issues. How do we manage those more complex cases? This interactive symposium will explore the use of CAR T for complex R/R DLBCL cases based on real-world experiences. Speakers will share cases, highlighting the challenges they faced and the solutions they used, then the panel will discuss the patient management and treatment decision-making. Audience questions are encouraged to ensure a lively, discussion-led symposium that offers the opportunity to share experiences to improve outcomes for patients with R/R DLBCL treated with CAR T-cell therapy.
11:30	Introduction
	Marie-José Kersten, Amsterdam, NL
11:35	Challenges in R/R DLBCL: Overview
	Marie-José Kersten, Amsterdam, NL
11:45	Case study 1
	Chris Fox, Nottingham, GB
	All faculty (moderator: Marie-José Kersten, Amsterdam, NL)
12:00	Case study 2
	Wendy Osborne, Newcastle, GB
	All faculty (moderator: Marie-José Kersten, Amsterdam, NL)
12:15	Case study 3
	Olalekan Oluwole, Nashville, TN, US
	All faculty (moderator: Marie-José Kersten, Amsterdam, NL)
12:30	Case study 4
	Miguel-Angel Perales, New York, NY, USA
	All faculty (moderator: Marie-José Kersten, Amsterdam, NL)
12:45	Q&A
	All faculty (moderator: Marie-José Kersten, Amsterdam, NL)

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11:30–13:00 Room B1	Regeneron
	Optimizing Treatment Paradigms for Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) and Diffuse Large B-cell Lymphoma (DLBCL) With the Emerging Class of Bispecific Antibodies
11:30	Bispecifics: Novel Mechanisms for Immunotherapies in Follicular Lymphoma and DLBCL
	Pier Luigi Zinzani, Bologna, IT
11:38	Disease State and Unmet Needs in Follicular Lymphoma
	Stefano Luminari, Reggio Emilia, IT
11:48	Expanding Treatment Options With Bispecifics in R/R FL
	Stefano Luminari, Reggio Emilia, IT
12:06	Panel Discussion on Follicular Lymphoma
	All Faculty
12:19	Disease State and Unmet Needs in Diffuse Large B-cell Lymphoma
	Jason Westin, MD, Houston, Texas, USA
12:27	Expanding Treatment Options With Bispecifics in DLBCL
	Jason Westin, MD, Houston, Texas, USA
12:45	Panel Discussion on DLBCL
	All Faculty
11:30–13:00 Room B2	Eli Lilly and Company
	Transforming Relapsed/Refractory MCL: Exploring New Options for Your Patients
	Treatment for R/R MCL is complicated, as the disease typically presents in elderly, unfit patients; however, emerging targeted therapy options have shown great promise based on excellent results in clinical trials. In this symposium, expert faculty will present therapeutic options, established by evidence-based practice guidelines, for patients with R/R MCL. Engage with expert faculty as you 'Build Your Own Case' study live. You and your peers can vote on patient demographics and parameters such as treatment, dosing frequency, and adverse events. The experts will craft their lecture to follow your suggestions allowing the case studies to reflect the patients you see. The symposium will conclude with a discussion on engagement between healthcare providers and patients to improve clinical outcomes.
	Welcome and introductions
	Mats Jerkeman, Lund, SE
	The evolving landscape of treatment options for R/R MCL
	All faculty
	Case Studies:
	Differentiate between 2nd and 3rd line therapy for patients with or without prior exposure to BTKi therapy in R/R MCL
	All faculty
	Review of dosing, dosage adjustment, and mode of administration
	All faculty
	Address safety concerns, including monitoring for and mitigating adverse reactions
	All faculty
	The importance of collaboration between providers and patients
	All faculty

(Continues)

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		Q&A
		All faculty
14:00–15:30	Room A	Kite, A Gilead Company
		Evolving survival outcomes with CAR T in 2L DLBCL
		Chair: Anna Sureda, Barcelona, ES
		Patients with DLBCL who progress after initial therapy require effective treatment options but the last change in standard of care was nearly 30 years ago. This symposium will examine challenges and unmet medical need in 2L DLBCL. An update on the latest advances with CAR T at first relapse will be provided, looking at how this is changing the 2L treatment landscape. Our experts will discuss their clinical experience and share insights into patient selection and management. We encourage you to take the opportunity to interact with the authors of these studies to bring benefit to your patients.
14:00		Introduction
		Anna Sureda, Barcelona, ES
14:05		Defining the unmet need in 2L DLBCL
		Michael Dickinson, Melbourne, AU
14:20		How has CAR T changed the 2L DLBCL treatment landscape?
		Frederick Locke, Tampa, FL, USA and Matthew Lunning, Omaha. NE, USA
14:50		CAR T in 2L DLBCL: a case study
		Jason R. Westin, Houston, TX, USA
15:00	Interactive patient management panel discussion	
15:15		Q&A
		All faculty
15:25		Close
		Anna Sureda, Barcelona, ES
14:00–15:30	Room B1	Novartis
		Using Real-World Experience to Optimize CAR-T Cell Therapy in Lymphoma
		Chair: Thorsten Zenz, Zurich, CH
		Real-world experience is invaluable for informing treatment decisions and optimizing outcomes in patients with relapsed/refractory (r/r) lymphomas. In this symposium, the expert faculty will share best practices and learnings from day-to-day clinical experience for management of r/r diffuse large B-cell lymphoma and r/r follicular lymphoma using chimeric antigen receptor (CAR) T-cell therapies. Patient case-based discussions will center around optimizing patient identification, pre-infusion patient management, and current barriers to timely referral. Professors Thorsten Zenz, Ulf Schnetzke, and Roch Houot will look to the future and discuss the impact next-generation CAR-T cell therapies will have on clinical practice.
		Introductions and opening remarks
		Thorsten Zenz, Zurich, Switzerland
		Real-world patient identification and management for CAR-T cell therapy—Third-line r/r DLBCL
		Summary of real-world data
		Thorsten Zenz, Zurich, CH
		Patient identification and clinical outcomes
		Thorsten Zenz, Zurich, CH
		Pre-infusion patient management

(Continued)

		Ulf Schnetzke, Jena, DE
		Real-world patient identification and referral for CAR-T cell therapy—r/r FL
		Optimizing patient identification and timing of referral for CAR-T cell therapy
		Roch Houot, Rennes, FR
		Looking forward to next-generation CAR-T cell therapies—DLBCL and FL
		Potential impact of next-generation CAR-T cell therapies on patient identification and clinical outcomes
		Ulf Schnetzke, Jena, DE
		Roch Houot, Rennes, FR
		All faculty, moderated by Thorsten Zenz, Zurich, CH
		Q&A live session
		All faculty, moderated by Thorsten Zenz, Zurich, CH
		Closing Remarks
		Thorsten Zenz, Zurich, CH
14:00–15:30	Room B2	Incyte
		What to do when CAR Ts are not the most appropriate option in 2L DLBCL.
		Current treatment options for transplant-ineligible patients
		Chair: Björn Chapuy, Berlin, DE
		In this innovative session, our distinguished faculty will share their valuable expertise on currently approved treatments for 2L DLBCL. How do you address treatment decisions for patients with R/R DLBCL who cannot receive ASCT or CAR T in 2L? First, we will focus on shared decision-making to examine how to recognise patient needs and preferences in treatment choices, featuring unique insights from a representative of the patient advocacy group, Lymphoma Coalition. This will be followed by a dynamic debate around the available treatments for 2L DLBCL, including patient cases and live voting on the treatments discussed.
14:00		Introduction
		Björn Chapuy, Berlin, DE
14:05		Part 1: Shared decision-making: when 1L fails
		Philipp Staber, Vienna, AT and Natacha Bolaños, Lymphoma Coalition, EU
14:30		Part 2: Controversy: Available treatments in 2L DLBCL today: Clinical case discussions
		Eva González Barca, Barcelona, ES
		Gabriel Brisou, Marseille, FR
15:20		Conclusion
		Björn Chapuy, Berlin, DE
14:00–15:30	Auditorium	MSD
	West Campus USI	
		Aggressive B-cell lymphomas, ROR1 modalities and ADCs: Why it Matters
		Chair: Thomas Kipps, La Jolla, CA, USA
		Please join the MSD live symposium on 13 June 2023 at 14:00 CEST. Our distinguished faculty, Thomas Kipps, Michael Wang and Pier Luigi Zinzani will discuss the role of ROR1 inhibitors in aggressive NHL, review the ROR1 treatment options in development across aggressive NHL, and discuss the most recent data on ADCs throughout the DLBCL treatment landscape. Attendees will have the opportunity to their questions answered by the expert panel, enhancing the interactivity of this symposium.

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14:00	Welcome and Introduction
	Thomas Kipps, La Jolla, CA, USA
14:10	ROR1 as a Target in aNHL
	Thomas Kipps, La Jolla, CA, USA
14:30	ROR1 Modalities in aNHL
	Michael Wang, Houston, TX, USA
14:50	ADCs in DLBCL: Current & Future
	Pier Luigi Zinzani, Bologna, IT
15:10	Panel Discussion and Q & A
	All faculty
15:25	Closing Remarks
	Thomas Kipps, La Jolla, CA, USA
16:30–18:00 Room A	Bristol Myers Squibb
	Advances in the Management of B Cell Malignancies: Updates and Future Directions
	Chair: Jeremy Abramson, Boston, MA, USA
	Dr. Jeremy Abramson, chair and speaker, will start this 90-minute symposium by presenting the key aspects of the recent developments in CAR T cell therapy for the management of LBCL patients. Dr. Francesc Bosch will then provide an overview of the latest clinical efficacy and safety data regarding the existing CAR T cell therapies in CLL, followed by Dr. Emmanuel Bachy who will discuss current and emerging approaches in the treatment of non-Hodgkin lymphoma. Finally, attendees will have the opportunity to ask questions to the panel of experts.
16:30	Welcome and introduction
	Jeremy Abramson, Boston, MA, USA
16:35	Advancing CAR T cell therapies in DLBCL
	Jeremy Abramson, Boston, MA, USA
16:55	CAR T cell therapy in CLL: latest data and perspectives
	Francesc Bosch, Barcelona, ES
17:20	Novel approaches for immunomodulatory treatment of NHL
	Emmanuel Bachy, Lyon, FR
17:45	Q&A and discussion
	All faculty, moderated by Jeremy Abramson
	Closing remarks
16:30–18:00 Room B1	Genmab
	Beyond the Horizon: Perspectives on the Treatment of Later-Line Large B-Cell Lymphoma (LBCL)
	Chair: Chan Cheah, Perth, AU
	The treatment landscape for relapsed/refractory large B-cell lymphoma (LBCL) has changed dramatically in the last few years. In this symposium, Professors Pau Abrisqueta, Chan Cheah, and Martin Hutchings will discuss the current landscape and efficacy and safety of novel treatments for later-line LBCL and how these will impact the treatment of patients in the coming years.
	Relapsed/refractory LBCL: Exploring chemo-free treatment alternatives
	Pau Abrisqueta, Barcelona, ES
	Epcoritamab monotherapy for third-line or later LBCL
	Chan Cheah, Perth, AU

(Continued)

		Advances in response assessments for LBCL and other hematologic malignancies
		Martin Hutchings, Copenhagen, DK
16:30–18:00	Room B2	Roche
		T-cell engaging bispecific antibodies in the management of relapsed/refractory follicular lymphoma
		Chair: Graham Collins, Oxford, GB
		This satellite symposium at ICML 2023 will offer the opportunity to learn from experts about the use of T-cell engaging bispecific antibodies in the management of relapsed/refractory follicular lymphoma (FL). Efficacy and safety of emerging bispecific antibodies including mosunetuzumab, epcoritamab, odronextamab and glofitamab will be reviewed, as will the management of common side effects, such as CRS. The prognostic value of PET and its role in response-adapted therapy will be presented and discussed. The impact of emerging T-cell engaging therapies on the FL treatment landscape will be explored along with factors influencing their use and adoption in clinical practice.
16:30		Introduction and welcome
		Graham Collins, Oxford, GB
16:35		New treatment options in R/R FL
		Kai Hübel, Cologne, DE
16:55		Clinical guidance on the use of bispecific antibodies in R/R FL
		Matthew Matasar, New Jersey, NJ, USA
17:15		Assessing treatment efficacy in FL
		Judith Trotman, Sydney, NSW, AU
17:35		The future of bispecific antibodies in the evolving treatment landscape
		Graham Collins, Oxford, GB
17:45		Panel discussion and Q&A
		All faculty
16:30–18:00	Auditorium	Satellite symposium organized by PeerView, supported by AstraZeneca
	West Campus USI	**Taking the Leap in MCL: New Opportunities With BTK Inhibitors and Other Innovative Strategies**
		Chair: Martin Dreyling, Munich, DE
		In this MasterClass & Case Forum event, our panel of experts will use a blended lecture and case-based approach to provide learners with insight on the latest clinical evidence supporting novel therapeutics, including BTKi, bispecific antibodies, and cellular therapy in MCL treatment. Each session will provide guidance on the differences between covalent BTKi options that can inform treatment selection and utilization strategies for novel therapeutic options across the spectrum of MCL care. Adapt your practice to reflect the growing role of targeted agents within a multipronged treatment model for MCL, and improve patient outcomes—register today!
16:30		Welcome & MasterClass Prep: Laying the Foundation for Better MCL Care
		Martin Dreyling, Munich, DE
		MasterClass: Sifting Through the Evidence With BTKi and Other Innovative Strategies
		Toby A. Eyre, Oxford, GB and Kami Maddocks, Columbus, OH, USA
		Case Forum: Seizing Opportunities to Challenge Conventional Care
		Martin Dreyling, Munich, DE, Toby A. Eyre, Oxford, GB and Kami Maddocks, Columbus, OH, USA
		Symposium Summary and Audience Q&A

(Continues)

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18:00	Adjourn
19:00–20:30 Room A	Roche
	What does the future hold for DLBCL treatment and prognosis?
	Chair: Franck Morschhauser, Lille, FR
	Our understanding of DLBCL disease biology continues to evolve, and with this comes the possibility of improving patient outcomes with a precision-based approach. In this symposium, an esteemed expert faculty will discuss the latest advances in DLBCL treatment and prognosis, focusing on molecular insights into the disease. The panel will examine the relative contributions of all-comer and molecularly informed studies, and what the future of clinical trials in DLBCL may look like. This session will include a panel discussion, as well as a live and interactive Q&A in which you will have the opportunity to ask the faculty your questions.
19:00	Treating DLBCL: Where are we now?
	Franck Morschhauser, Lille, FR
19:05	New molecular insights into DLBCL disease and prognosis
	Björn Chapuy, Berlin, DE
19:30	A new era for clinical trials in DLBCL?
	Andrew Davies, Southampton, GB and Anna Sureda, Barcelona, ES
20:10	Experts in conversation: Future perspectives in DLBCL
	All faculty; live and interactive Q&A
19:00–20:30 Room B1	Sobi
	Closing the gap: Unmet Needs and Emerging Treatments in Relapsed/Refractory Diffuse Large B-cell Lymphoma (DLBCL)
	Chair: Georg Lenz, Münster, DE
	Despite advances in diffuse large B-cell lymphoma (DLBCL) therapies, a significant number of patients still experience relapsed or refractory (R/R) disease. CAR T-cell therapy may be a curative option for some patients, but a significant proportion don't receive CAR T-cell therapy or will subsequently relapse. In this symposium, Prof. Pier Luigi Zinzani will discuss challenges in treating patients with R/R DLBCL, Prof. Georg Lenz will present emerging data on antibody-drug conjugates, and Prof. Mehdi Hamadani will discuss practical insights on managing 3L patients with R/R DLBCL sharing clinical cases. Attendees will have the opportunity to engage with the speakers.
	Welcome and Introduction
	Georg Lenz, Münster, DE
	Challenges in the Current Treatment of RR DLBCL
	Pier Luigi Zinzani, Bologna, IT
	Future Advances in Later Lines of DLBCL Therapy: Can Antibody Drug Conjugates be a Solution?
	Georg Lenz, Münster, DE
	Third Line Management of R/R DLBCL and Sequencing CD19 Therapies: Real-world Experience From the USA
	Mehdi Hamadani, MilwaGBee, WI, USA
	Ask the Experts Q&A
	All faculty
	Closing Remarks
	Georg Lenz, Münster, DE

(Continued)

19:00–20:30 Room B2	AbbVie
	Optimizing Treatment Strategies for Patients with Chronic Lymphocytic Leukemia (CLL): An Expert Discussion
	Chair: Thorsten Zenz, Zurich, CH
	Over the past decade, advancements in chronic lymphocytic leukemia (CLL) therapeutics have led to an evolution in diagnosis and treatment considerations from a clinical perspective. With the increasing number of treatment options with unique clinical profiles, the patient perspective and their involvement in treatment decision making in CLL has never been more significant. Please join us as Professor Thorsten Zenz chairs a structured roundtable discussion with Dr. Carol Moreno and Dr. Othman Al-Sawaf to consider Optimizing Treatment Strategies for Patients with CLL.
19:00	Introduction: Evolving Concepts in Chronic Lymphocytic Leukemia (CLL)
	Thorsten Zenz, Zurich, CH
19:05	Decisions at Diagnosis: Incorporating Disease Factors and Patient Perspectives
	Thorsten Zenz, Zurich, CH
19:20	Panel Discussion
	Thorsten Zenz, Zurich, CH
19:30	Treatment Strategies in First-Line CLL: Continuous Duration Therapies
	Carol Moreno, Barcelona, ES
19:45	Treatment Strategies in First-Line CLL: Fixed Treatment Duration Therapies
	Othman Al-Sawaf, Cologne, DE
20:00	Panel Discussion
	Thorsten Zenz, Zurich, CH
20:10	Roundtable Discussion: Optimizing Treatment for Patients with Relapsed/Refractory CLL & Future Perspectives
	Thorsten Zenz, Zurich, CH
20:25	Closing
	Thorsten Zenz, Zurich, CH
WEDNESDAY, JUNE 14	
19:00–20:30 Room A	AbbVie
	Navigating the Rapidly Changing Treatment Landscape in DLBCL
	Chair: Georg Lenz, Münster, DE
	Historically there have been limited changes in the treatment landscape for DLBCL. However, recent data are challenging the standard care in first-line as well as expanding the available options in second- and third-line. The complexity of the treatment landscape has evolved with regard to treatment sequencing and patient selection due to the advent of target therapies. Professor Georg Lenz will chair a structured roundtable discussion with Professors Chris Fox, Jeremy Abramson and Catherine Thieblemont to consider how to navigate the rapidly changing treatment landscape in DLBCL.
19:00	Welcome and Introduction
	Georg Lenz, Münster, DE
19:05	Challenging the Standard of Care in First-Line
	Chris Fox, Nottingham, GB
19:25	Selecting an Optimal Second-Line Treatment Strategy in an Evolving Landscape
	Jeremy Abramson, Boston, MA, USA

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19:55		Navigating the Complexities of Third-Line Treatment
		Catherine Thieblemont, Paris, FR
20:25		Closing
		Georg Lenz, Münster, DE
19:00–20:30	Room B	Takeda
		The future of therapy for CD30+ lymphomas: addressing challenges and driving progress
		Chair: Anna Sureda, Barcelona, ES
		Recent advances in frontline treatment for advanced (stage III/IV) Hodgkin lymphoma have resulted in many patients achieving curative responses, but incorporation of targeted therapies and innovative strategies may further improve patient outcomes. Our expert faculty will discuss the future of therapy for CD30+ lymphomas, specifically advanced (stage III/IV) Hodgkin lymphoma and peripheral T-cell lymphoma (PTCL). Novel biomarkers for determining a patient's prognosis and likelihood of response to treatment will also be reviewed, focusing on their importance in selecting appropriate therapy for advanced Hodgkin lymphoma. In PTCL, ongoing research is expanding our understanding of effective treatment strategies, and we will explore recent advances and potential future directions in this area. The symposium aims to provide valuable insights that may help inform a tailored approach to patient care.
19:00		Welcome and Introduction
		Anna Sureda, Barcelona, ES
19:05		Successes, challenges, and future directions in frontline advanced Hodgkin lymphoma
		Anna Sureda, Barcelona, ES
19:30		Emerging biomarkers of risk/response in the treatment of advanced Hodgkin lymphoma
		Sven Borchmann, Cologne, DE
19:55		Progress in peripheral T-cell lymphoma and current frontline management approaches
		Tim Illidge, Manchester, GB
20:20		Q&A
		All faculty
20:25		Closing remarks
		Anna Sureda, Barcelona, ES
19:00–20:30	Auditorium	BeiGene
	West Campus USI	
		Targeting BTK across B-Cell Malignancies—Selecting the right treatment for patients with lymphoma or CLL
		Chairs: Stephen Stilgenbauer, Ulm, DE
		This symposium, chaired by Professor Stephan Stilgenbauer, will discuss current and emerging BTKi-based treatments for B-cell malignancies with a particular focus on chronic lymphocytic lymphoma (CLL) and follicular lymphoma (FL). Professor Stilgenbauer will present the treatment landscape for CLL patients—the concepts of continued versus fixed duration treatment, switching from first to next generation BTKi, and how genetic subtypes influence the treatment selection will be discussed. Professor Zinzani will present the status and current treatment status in FL including emerging data from the randomized Phase 2 ROSEWOOD trial in patients with relapsed or refractory FL (zanubrutinib in combination with obinutuzumab vs. obinutuzumab monotherapy). Professor Stilgenbauer will then lead the panel discussion with the full faculty to discuss the key criteria, supported by additional patient cases, for selecting a BTKi versus other treatment options for CLL, FL, MZL and WM, especially for difficult-to-treat patients.

(Continued)

19:00	Welcome & introduction
	Professor Stilgenbauer, Ulm, DE
19:05	CLL: Contemporary Treatment of CLL—Selection of best treatment for your patient
	Stephan Stilgenbauer, Ulm, DE
	FL: Future Direction in Management of r/r FL patients
	Pier Luigi Zinzani, Bologna, IT
19:30	Panel discussion about key criteria for selecting BTKi for CLL and lymphoma
	All faculty
19:50	Audience Q&A
	All faculty
20:15	Wrap-up
	Professor Stilgenbauer, Ulm, DE
THURSDAY, JUNE 15	
19:00–20:30 Room A	Kite, A Gilead Company
	How do we improve outcomes for underserved populations with B-cell malignancies?
	Chair: Davide Rossi, Bellinzona, CH
	Clinical trial populations should be diverse in order to ensure that the full range of biological variabilities are represented. However, trial populations do not always adequately represent the full range of patients seen in clinic. This is due, in part, to the need to create homogeneous populations for controlled trials. In this non-promotional, interactive symposium, speakers will discuss the management of populations with B-cell malignancies with unmet needs, how to increase diversity and inclusion in clinical studies and how we can improve outcomes for such populations in the future and ensure equitable treatment access for all.
19:00	Introduction
	Davide Rossi, Bellinzona, CH
19:05	Are we ensuring diversity and inclusion in clinical studies?
19:15	Q&A
	All faculty
19:25	Are we addressing the unmet needs for all B-cell lymphomas?
	Kate Cwynarski, London, GB and Barbara F. Eichhorst, Cologne, DE
19:45	Q&A
	All faculty
19:55	Roundtable discussion: How do we improve outcomes for the underserved populations with B-cell lymphoma?
	Davide Rossi, Bellinzona, CH
20:15	Q&A
	All faculty
20:25	Close
	Davide Rossi, Bellinzona, CH
19:00–20:30 Room B	Janssen
	Optimizing treatment for patients with CLL and MCL now and in the future
	Following advances in recent years there are now a number of highly efficacious and tolerable therapeutic approaches available for patients with CLL or MCL. In this symposium the faculty will evaluate how data updates are impacting the clinical

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		management of patients with CLL and MCL, they will discuss results from recent studies that challenge the current standards of care and they will highlight the potential of new treatment options to further improve outcomes in patients with CLL and MCL.
		Chair: John Gribben, London, GB
19:00		Introduction
		John Gribben, London, GB
19:05		Fixed duration or MRD-guided therapy: what's the latest data in CLL?
		Carol Moreno, Barcelona, ES
19:25		Panel discussion
		All faculty, moderated by John Gribben, London, GB
19:45		How BTK inhibitors are changing the treatment algorithm for patients with MCL
		Martin Dreyling, Munich, DE
20:05		Panel discussion
		All faculty, moderated by John Gribben, London, GB
20:25		Summary and closing remarks
		John Gribben, London, GB
19:00–20:30	Auditorium	Follicular Lymphoma Foundation
	West Campus USI	**What will it take to cure Follicular Lymphoma?**
		Chair: Mitchell Smith, CMO at the FLF
		Supported by an independent educational grant from AstraZeneca.
		Sponsorship support from BeiGene, Novartis, and BioInvent International AB.
		The progress in the last 20-30 years within basic science, technology and therapeutics means we are inching ever closer to turning what once was considered science fiction into science fact. For Follicular Lymphoma (FL) patients, the new age of cellular therapy (CAR-T, bispecific antibodies) along with the technological advances and deeper understanding of the underlying complex biological mechanisms (MRD, clonal dynamics), means that we now have a unique opportunity to change the existing paradigm—to cure FL. Join us at the FLF symposium where Dr. Mitchell Smith along with the expert faculty will review recent advances in Follicular Lymphoma (FL) therapy and pathophysiology, before opening an engaging discussion on how we can leverage these key advances to develop and assess future curative approaches for FL patients.
19:00		T-cell engaging therapies—CAR-T and bispecific antibodies in FL: Is there evidence of curing subsets of FL patients?
		Loretta J. Nastoupil, Houston, TX, USA
19:15		The biology of Common Precursor Cells (CPCs) and approaches to eradicating them:
		What are the therapeutic barriers to reaching a cure in FL?
		Jessica Okosun, London, GB
19:30		Minimal Residual Disease (MRD) assays—today and tomorrow:
		How can we show FL patients are cured, without waiting a lifetime?
		Marco Ladetto, Turin, IT
19:45		The role of epigenetic mutations—in FL, resistance, and as treatment targets:
		How can we optimally use epigenetic and other targeted approaches?
		Ari M. Melnick, New York, NY, USA
20:00		Full panel discussion: Laying the pathway to cure

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SUPPLEMENT ABSTRACT

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INDUSTRY PROGRAM - SATELLITE SYMPOSIUM ABSTRACTS

Tuesday, 13 June 2023 from 16:30 to 18:00 CEST (Room B2)

T-CELL ENGAGING BISPECIFIC ANTIBODIES IN THE MANAGEMENT OF RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

During this satellite symposium, an esteemed expert faculty will discuss the use of T-cell engaging bispecific antibodies in the management of relapsed/refractory (R/R) follicular lymphoma (FL). The panel will share their experience managing patients receiving these treatments and will examine the role of positron emission tomography (PET) and how it can potentially aid treatment decisions.

FL is characterized by relapsing disease and increasing refractoriness to treatment, with decreasing progression-free survival (PFS) with each subsequent line of therapy.[1,2] Currently available treatments for patients with R/R FL who have received ≥2 prior therapies are limited by low response rates and/or poor tolerability.[3–6]

Mosunetuzumab is a CD20xCD3 T-cell engaging bispecific antibody that redirects T cells to eliminate malignant B cells.[7–9] Based on findings of a pivotal Phase II study (including an overall response rate [ORR] of 78% and a complete response rate of 60%),[10,11] fixed-duration mosunetuzumab monotherapy has become the first bispecific antibody regimen to be approved for the treatment of patients with R/R FL who have received ≥2 prior systemic therapies, without the need for mandatory hospitalization upon administration.[10–13]

Other CD20xCD3 T-cell engaging bispecific antibodies currently undergoing clinical development for R/R FL and showing encouraging efficacy as monotherapy or as part of a combination regimen include epcoritamab, odronextamab, and glofitamab.[14–19]

Bispecific antibodies are generally associated with manageable safety;[20] the most commonly observed adverse event (AE) is cytokine release syndrome (CRS; predominantly low grade and reversible). Step-up dosing and premedication are recommended to mitigate CRS risk.[10,11] Other AEs of clinical interest include immune effector cell-associated neurotoxicity syndrome, and haematological and infectious AEs.[10,11,17–19]

With bispecific antibodies, we observe high and durable response rates in patients with R/R FL. Early response assessment is becoming part of routine patient management, and several approaches, including PET, may be useful in assisting with treatment decisions.[21] End-of-induction and end-of-treatment PET have both been shown to predict survival outcomes in FL,[22,23] although it is yet to be determined if baseline PET metrics can be used to predict PFS, as observed in other settings.[24,25] PET-adapted decision-making is complex, and further research is required to fully understand the role of PET in R/R FL.[21]

As clinical experience with bispecific antibodies for the treatment of late-line R/R FL grows, further investigation of novel treatment regimens and efficacy assessment is warranted. Optimal therapeutic sequencing for individual patients remains a challenge.[26] Ongoing Phase II/III trials will further define the role of these treatments in R/R and front-line FL.[20]

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Tuesday, June 13, 2023 from 19:00 to 20:30 h (Room A)

WHAT DOES THE FUTURE HOLD FOR DLBCL TREATMENT AND PROGNOSIS?

Chair: F. Morschhauser, Lille (France)

TREATING DLBCL: WHERE ARE WE NOW?

F. Morschhauser, Lille (France)

NEW MOLECULAR INSIGHTS INTO DLBCL DISEASE AND PROGNOSIS

B. Chapuy, Berlin (Germany)

A NEW ERA FOR CLINICAL TRIALS IN DLBCL?

A. Davies, Southampton (UK) and A. Sureda, Barcelona (Spain)

EXPERTS IN CONVERSATION: FUTURE PERSPECTIVES IN DLBCL

All; live and interactive Q&A

WHAT DOES THE FUTURE HOLD FOR DLBCL TREATMENT AND PROGNOSIS?

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous disease with variable clinical presentations and prognoses.[1,2] After first-line treatment with R-CHOP, around 60% of patients with DLBCL are cured.[1] Studies investigating R-CHOP in combination with a variety of therapies and regimens failed to improve patient outcomes until the POLARIX study, which showed significantly improved progression-free survival with polatuzumab vedotin plus R-CHP versus R-CHOP with a similar safety profile in previously untreated DLBCL.[3] In addition to this potentially practice-changing result in the first-line setting, the treatment landscape in relapsed/refractory DLBCL is evolving.

In recent years, clinical research in the second-line setting and beyond has diversified to include novel treatments such as CAR T-cell therapies, bispecific antibodies, antibody–drug conjugates, and small-molecule inhibitors.[4] With modern technological advancements, our understanding of DLBCL disease biology is evolving and therapeutic options continue to expand. Multiple subtypes that are associated with distinct patient outcomes have been identified, providing new insights into disease pathogenesis and the potential for new therapeutic approaches.

Two clinical research strategies present the opportunity for identification of safe and efficacious therapies for patients with DLBCL: all-comer studies based on clinical characteristics (POLARIX,[3] ZUMA-7,[5] NP30179[6]), and molecularly informed studies, which select or stratify patients based on the molecular profile of their lymphoma (ROBUST,[7] PHOENIX,[8] REMoDL-B[9]). Although there is room for discussion surrounding their respective advantages and disadvantages, both of these strategies have important roles to play as we look to the future of DLBCL treatment. Optimally designed clinical trials, accurate diagnostic tools, and individual cancer pathologies must be considered for the improvement of patient management and prognosis.

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LATE BREAKING ABSTRACTS

LBA1 | GENOME-WIDE ASSOCIATION STUDY OF CHILDHOOD BURKITT LYMPHOMA IN EAST AFRICA IDENTIFIES A NOVEL GERMLINE SUSCEPTIBILITY LOCUS ON CHROMOSOME 21

D. Dutta[1], B. Gorman[2], M. Gouveia[3], M. D. Ogwang[4], P. Kerchan[5], S. J. Reynolds[6], C. N. Tenge[7], P. A. Were[8], R. T. Kuremu[7], W. N. Wekesa[7], N. Masalu[9], E. Kawira[10], T. Kinyera[11], I. Otim[11], I. D. Legason[11], H. Nabalende[11], H. Dhudha[9], M. Mumia[8], L. W. Ayers[12], K. Bhatia[1], J. J. Goedert[1], M. Manning[1], N. Cole[1], W. Luo[1], A. Hutchinson[1], B. Hicks[1], G. Chagaluka[13], W. T. Johnston[14], N. Mutalima[14], E. Borgstein[13], G. N. Liomba[13], S. Kamiza[13], N. Mkandawire[13], C. Mitambo[15], E. Molyneux[13], R. Newton[14], S. Glaser[16], H. Kretzmer[17], A. A. Adeyemo[3], C. N. Rotimi[3], S. J. Chanock[1], M. Dean[1], R. Siebert[16], M. Yeager[1], L. Prokunina-Olsson[1], S. M. Mbulaiteye[1]

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Introduction: Burkitt lymphoma (BL) is an aggressive B-cell lymphoma with hallmark somatic *IG*::*MYC* chromosomal translocations. BL is responsible for a significant proportion of childhood cancers in equatorial Africa, where exposure to Epstein Barr Virus (EBV) and *P. falciparum* are established risk factors. Host genetic factors are suspected to modify risk but are currently undefined, with exception of the sickle cell trait that is protective against severe malaria and childhood BL in Africa. Discovery of novel host genetic susceptibility in BL would suggest new directions to understand the biology of BL, particularly the link between host and environmental cofactors.

Methods: We conducted the first genome-wide association study (GWAS) of BL among 4,645 children (800 with BL) aged 0–15 years enrolled in the Epidemiology of Burkitt lymphoma in East African Children and Minors (EMBLEM) study in Uganda, Kenya, and Tanzania (2010–2016) and the Childhood Infections and Cancer case-control study in Malawi (2005–2008). Genotypes at approximately 4.6 million sites were determined using the Infinium Omni5Exome-4 v1.3 BeadChip (Illumina) and imputation was performed using the African Genome Resources reference panel (Sanger Imputation Service), with rigorous quality control to filter unreliable calls. GWAS based on logistic mixed model was performed in SAIGE, adjusting for age, sex, and ancestry using population-specific principal components, and country of origin. Additional analyses were performed using genomic, epigenomic and expression data from the BL and ICGC MMML-Seq genome sequencing projects to provide insight into the potential mechanisms by which the novel loci may influence BL risk in African children.

Results: Considering variants with a minor allele frequency threshold of ≥5%, we identified one genome-wide significant locus at 21q22.12 (Figure 1A) upstream of *RUNX1*. The index SNP (rs111457485, ref/effect: *C*/*T*, effect size: −0.57; p-value = 5.7×10^{-9}; Figure 1B) is common in Africans (frequency of allele *T*: 10.2%) and rare in Europeans (allele frequency of *T*: 0.7%) in the 1000 Genomes populations. Fine mapping in this locus using the Sum of Single Effects (SuSiE) model revealed a credible set of 17 variants spanning 76 kb including the causal variant at the locus with 95% probability (Figure 1C). This associated region contains enhancer elements linked to *RUNX1* expression that are differentially methylated in BL as compared to follicular lymphoma. Moreover, mining of RNA-seq data identified a novel spliced transcript expressed in BL and germinal center B cells. In secondary transcriptome-wide analyses in whole blood and spleen, we identified statistically significant association with additional loci at 19p13.2 in region previously identified to harbor somatic mutations in BL.

Conclusion: We report significant statistical association between childhood BL and a signal upstream of *RUNX1* on chromosome 21q22.12 in the first BL GWAS conducted in Africa. The ancestral

BL-protective allele rs111457485-T is enriched in African individuals and rare elsewhere, suggesting possible selection for retention of this allele in Africa. Our integrative analysis using omics data from BL genome sequencing studies suggests potential molecular mechanisms of this GWAS association. Our results increase support for the hypothesis that host genetic factors influence BL risk, provide support for utilizing GWAS for discovery of host genetic risk factors for BL, and encourage expanding BL GWAS to other geographic areas and adults to better understand the genetic architecture of BL.

The research was funded by: National Cancer Institute, National Institutes of Health, US Department of Health and Human Services

Keywords: Aggressive B-cell non-Hodgkin lymphoma, Cancer Health Disparities, Genomics, Epigenomics, and Other-Omics

No conflicts of interests pertinent to the abstract.

LBA2 | IBRUTINIB PLUS BR OR R-CHOP IN PREVIOUSLY TREATED PATIENTS WITH FOLLICULAR OR MARGINAL ZONE LYMPHOMA: THE PHASE 3 SELENE STUDY

L. J. Nastoupil[1], G. Hess[2], M. A. Pavlovsky[3], I. Danielewicz[4], J. Freeman[5], A. M. García-Sancho[6], V. Glazunova[7], A. Grigg[8], J. Hou[9], A. Janssens[10], S. J. Kim[11], Z. Masliak[12], P. McKay[13], F. Merli[14], W. Munakata[15], H. Nagai[16], M. Özcan[17], M. Preis[18], T. Wang[19], J. Zhu[20], M. Rowe[21], R. Qin[22], T. Henninger[22], M. Curtis[21], D. B. Caces[22], C. Thieblemont[23], G. Salles[24]

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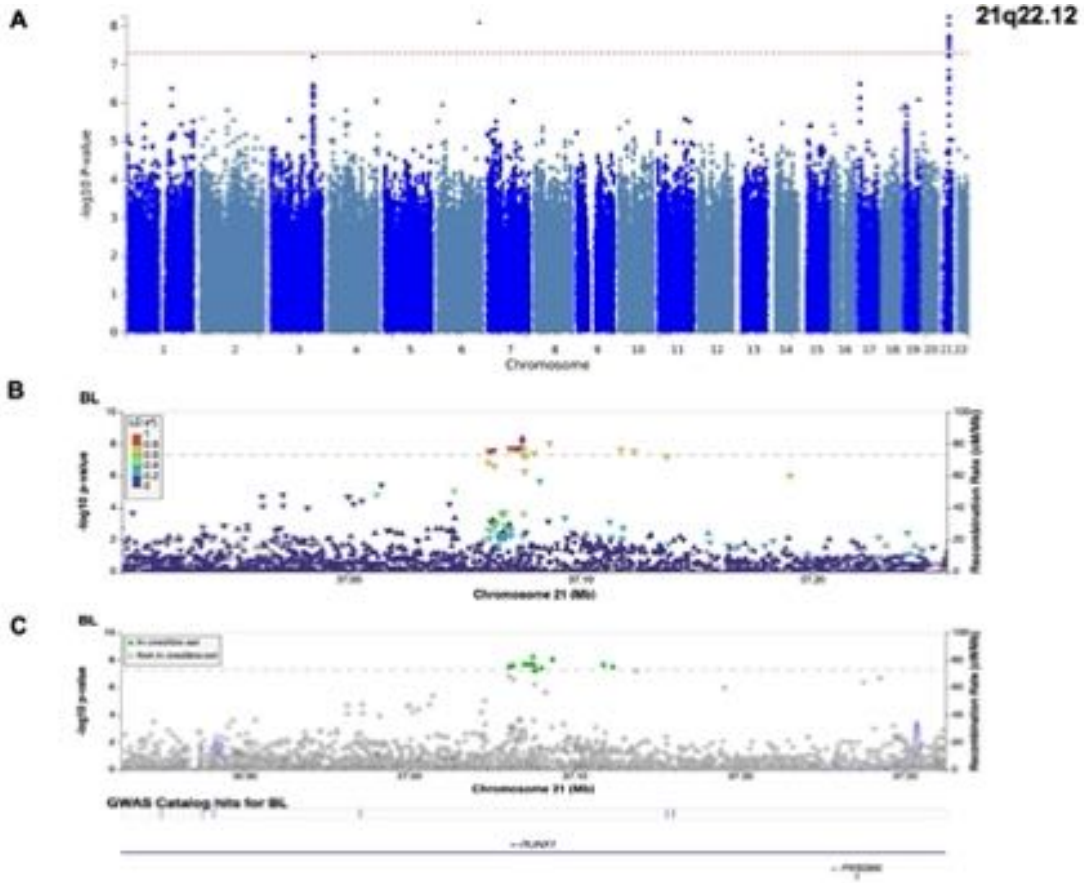

Figure 1. Association results for childhood BL in Africa. (A) Manhattan plot of the GWAS of 800 childhood BL cases and 3,845 childhood controls without BL. (B) Regional plot for the significant locus at 21q22.12 with the index SNP (C) SNPs included in the 95% credible set after fine-mapping.

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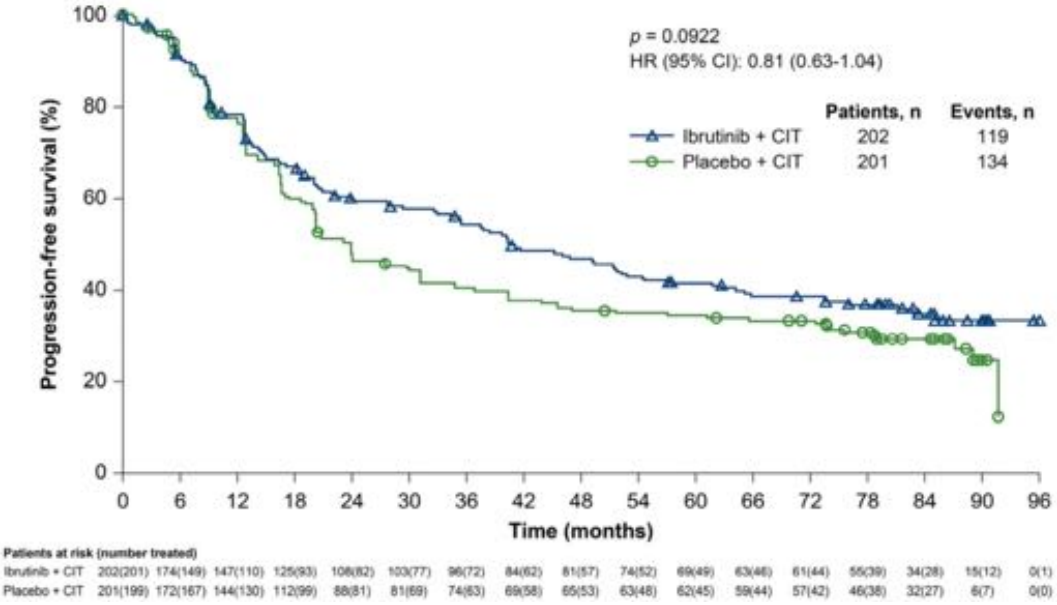
Introduction: For patients with relapsed/refractory (R/R) follicular lymphoma (FL) or marginal zone lymphoma (MZL), chemo-immunotherapy (CIT; bendamustine and rituximab [BR] or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) is recommended by international clinical practice guidelines. However, as prognosis remains poor, particularly with repeated lines of therapy, there is still an unmet need for more effective treatment. The double-blind phase 3 SELENE study evaluated ibrutinib + BR or R-CHOP in patients with R/R FL or MZL who had received prior treatment with an anti-CD20–containing CIT regimen to determine if the addition of ibrutinib would prolong progression-free survival (PFS).

Methods: Adult patients diagnosed with FL or MZL who had received ≥1 prior line of CIT were randomized 1:1 to receive 6 cycles of BR or R-CHOP plus continuous ibrutinib (560 mg) or placebo daily (until progressive disease or unacceptable toxicity). The primary end point was investigator-assessed PFS. Secondary end points included overall survival (OS), overall response rate (ORR), complete response (CR) rate, duration of response (DOR), and safety.

Results: A total of 403 (FL, n = 347; MZL, n = 56) patients were randomized to ibrutinib + CIT (n = 202) or placebo + CIT (n = 201). Most patients (90.3%) received BR as background CIT. After a median follow-up of 84 months, the median PFS was 40.5 months for the ibrutinib + CIT arm and 23.8 months for the placebo + CIT arm (hazard ratio [HR], 0.806 [95% confidence interval (CI), 0.626–1.037]; p = 0.0922) (Figure). For the MZL subgroup, the median PFS was not reached for ibrutinib + CIT and 91.6 months for placebo + CIT (HR [95% CI], 0.725 [0.312–1.682]; p = 0.451). The ORR (91.6% vs. 90.5%) and CR rate (55.0% vs. 50.2%) were similar between the ibrutinib + CIT and placebo + CIT arms, respectively. Median DOR was 44.3 (95% CI, 32.9–60.0) versus 21.7 (95% CI, 17.6–32.4) months in the ibrutinib + CIT versus placebo + CIT arms,

Figure. Investigator-assessed progression-free survival.



respectively. Median OS was not reached in either arm (HR [95% CI], 0.980 [0.686–1.400]; $p = 0.9115$). Treatment-emergent adverse events (TEAEs) of grade ≥3 were reported in 85.6% of patients in the ibrutinib + CIT arm versus 75.4% in the placebo + CIT arm. Thirteen patients in each arm experienced a TEAE leading to death.

Conclusions: In patients with R/R FL or MZL, the addition of ibrutinib to CIT showed clinical activity (median PFS 40 vs. 24 months with ibrutinib + CIT vs. placebo + CIT, respectively) but the improvement in PFS did not reach statistical significance. No new safety signals were identified, and although the addition of ibrutinib to CIT resulted in additive toxicity, there was no detriment to overall survival. Further analyses are needed to explore whether FL/MZL subgroups could benefit from extended treatment with ibrutinib following CIT.

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Keywords: Combination Therapies, Indolent non-Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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LBA3 | LISOCABTAGENE MARALEUCEL (LISO-CEL) IN R/R MCL: PRIMARY ANALYSIS RESULTS FROM THE MCL COHORT OF THE SINGLE-ARM, MULTICENTER, SEAMLESS DESIGN TRANSCEND NHL 001 STUDY

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Introduction: Patients (pts) with R/R MCL after ≥2 prior lines of therapy, including Bruton tyrosine kinase inhibitor (BTKi), have a poor prognosis. Liso-cel is an autologous, CD19-directed, CAR T cell product administered at equal target doses of $CD8^+$ and $CD4^+$ CAR^+ T cells. The phase 1, seamless design, dose-finding TRANSCEND NHL 001 study (NCT02631044) evaluated liso-cel in pts with R/R NHL. Here we report primary analysis results from the MCL cohort.

Methods: Eligible pts had PET-positive R/R MCL after ≥2 lines of prior therapy, including a BTKi, alkylating agent, and CD20-targeted agent. Pts received liso-cel at a target dose level (DL) of 50 (DL1) or 100×10^6 CAR^+ T cells (DL2) after lymphodepleting chemotherapy (LDC). Bridging therapy was allowed. Primary endpoints were treatment-emergent AEs (TEAEs) and ORR by IRC (Lugano 2014 criteria); secondary endpoints included CR rate (key), DOR, PFS, and OS. Primary (null hypothesis [H_0]: ORR ≤40%) and key secondary (H_0: CR rate ≤18%) efficacy hypothesis testing was hierarchical and based on the primary analysis set (PAS) of pts treated at DL2 with PET-positive disease per IRC at baseline (before LDC, after bridging therapy). The safety set included all pts who received liso-cel (DL1 + DL2). The efficacy set included all pts in the safety set who had PET-positive disease per IRC at baseline (DL1 + DL2).

Results: At data cutoff (01/19/2023), of 104 leukapheresed pts, 88 received liso-cel (safety set; DL1, $n = 6$; DL2, $n = 82$). Median (range) age was 68.5 y (36–86), median (range) prior systemic lines of therapy was 3 (1–11), 69% had refractory disease, 53% were BTKi refractory, 33% had prior HSCT, 75% had Ki67 ≥30%, 31% had blastoid morphology, 23% had *TP53* mutations, and 8% had active CNS disease. Median (range) on-study follow-up was 16.1 mo (0.4–60.5). The primary and key secondary endpoints were met based on the PAS ($n = 74$; ORR, 86.5% [95% CI, 76.5–93.3], $P < 0.0001$; CR rate, 74.3% [95% CI, 62.8–83.8], $P < 0.0001$). In the efficacy set ($n = 83$), ORR was 83.1% (95% CI, 73.3–90.5) with CR rate of 72.3% (95% CI, 61.4–81.6). Responses were durable: median DOR, 15.7 mo; median PFS, 15.3 mo (Table). As most pts were enrolled during the COVID-19 pandemic and 6 pts in ongoing CR died due to COVID-19, DOR, PFS, and OS were also analyzed censoring for COVID-19 deaths. In the safety set ($n = 88$), 86% of pts had gr ≥3 TEAE, primarily cytopenias (Table). Four gr 5 TEAEs occurred (3 related to liso-cel and/or LDC). Rate of any-grade cytokine release syndrome (CRS) was 61% (gr 3–4, 1%; no gr 5) and neurological events (NE) was 31% (gr 3–4, 9%; no gr 5). Rate of gr ≥3 infections was 15%, and prolonged cytopenia was 40%. Cellular kinetics and B-cell aplasia will be presented.

Conclusions: Liso-cel demonstrated high ORR and CR rate that were durable and was well tolerated with low rates of gr ≥3 CRS, NE, and infections, thus representing a potential new treatment option for pts with high-risk, aggressive R/R MCL.

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Keyword: Cellular therapies

Conflicts of interests pertinent to the abstract

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Table . Summary of time to event efficacy and safety endpoints

Efficacy	Efficacy set[a] (n = 83)	COVID-19 sensitivity analysis set[b] (n = 83)
DOR, median (95% CI), mo	15.7 (6.2–24.0)	17.5 (7.6–24.0)
Continued response at 18 mo, % (95% CI)	42.7 (29.9–54.9)	48.8 (34.8–61.4)
DOR follow-up, median (95% CI), mo	22.8 (16.7–23.0)	22.6 (16.2–22.8)
PFS, median (95% CI), mo	15.3 (6.6–24.9)	17.8 (7.6–24.9)
PFS rate at 18 mo, % (95% CI)	43.9 (31.8–55.4)	49.9 (36.9–61.7)
PFS follow-up, median (95% CI), mo	23.5 (17.7–23.8)	18.2 (12.4–23.7)
OS, median (95% CI), mo	18.2 (12.9–36.3)	24.8 (15.7–NR)
OS rate at 18 mo, % (95% CI)	50.8 (39.2–61.2)	56.0 (43.9–66.6)
OS follow-up, median (95% CI), mo	24.0 (23.7–24.2)	23.8 (23.6–24.2)
Safety	**Safety set[c] (n = 88)**	
Grade ≥ 3 TEAEs,[d] n (%)	76 (86.4)	
Grade ≥ 3 TEAEs in ≥ 10% of patients, n (%)		
Neutropenia	49 (55.7)	
Anemia	33 (37.5)	
Thrombocytopenia	22 (25.0)	
Grade 5 TEAEs,[d] n (%)	4 (4.5)	
Cryptococcal meningoencephalitis[e]	1 (1.1)	
Cardiopulmonary arrest[f]	1 (1.1)	
Lung infection (COVID-19 pneumonia)[e]	1 (1.1)	
Tumor lysis syndrome[g]	1 (1.1)	
TEAEs of special interest, n (%)		
Any-grade CRS	54 (61.4)	
Grade ≥ 3 CRS	1 (1.1)	
Any-grade NEs	27 (30.7)	
Grade ≥ 3 NEs	8 (9.1)	
Prolonged cytopenias[h]	35 (39.8)	
Grade ≥ 3 infections	13 (14.8)	

[a]Includes patients who received liso-cel (DL1 + DL2) who had PET-positive disease per IRC at baseline; [b]Includes patients in the efficacy set; patients in ongoing response who died due to COVID-19 were censored in this analysis; [c]Includes all patients who received liso-cel (DL1 + DL2); [d]TEAE period was defined as the time from initiation of liso-cel administration through study Day 90; [e]Related to liso-cel and LDC; [f]Unrelated to liso-cel or LDC; [g]Related to liso-cel; [h]Defined as any grade ≥ 3 laboratory result of decreased hemoglobin, decreased neutrophil count, and decreased platelet count at Day 29.

CRS, cytokine release syndrome; DL1, dose level 1; DL2, dose level 2; DOR, duration of response; IRC, independent review committee; LDC, lymphodepleting chemotherapy; liso-cel, lisocabtagene maraleucel; NE, neurological event; NR, not reached; TEAE, treatment-emergent adverse event.

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LBA4 | TRANSCEND FL: PHASE 2 STUDY RESULTS OF LISOCABTAGENE MARALEUCEL (LISO-CEL) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL)

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Introduction: Pts with R/R indolent NHL (iNHL), particularly those with high-risk features, have poor outcomes. TRANSCEND FL (NCT04245839), a global, phase 2, single-arm, multicohort, pivotal study assessed efficacy and safety of the anti-CD19 CAR T cell therapy liso-cel in pts with R/R iNHL. We report primary analysis results in pts with R/R FL, with safety in all liso-cel–treated pts (i.e., second-line or later [2L+] pts; safety set) and efficacy focused on pts in third line or later (3L+).

Methods: Eligible pts with R/R FL included 3L+ pts and second-line (2L) pts with disease progression within 24 mo (POD24) of diagnosis and/or modified Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria. All pts received ≥1 prior combination systemic therapy, including an anti-CD20 antibody and an alkylator. Pts received liso-cel (100×10^6 CAR^+ T cells) after lymphodepleting chemotherapy. Bridging therapy was allowed. The primary endpoint was ORR per independent review committee (IRC) by PET/CT using Lugano 2014 criteria. Secondary endpoints included CR rate, duration of response (DOR), PFS, OS, safety, and PK. Pharmacodynamics (PD) were exploratory.

Results: At data cutoff (January 27, 2023), of 139 leukapheresed pts, 130 (94%) received liso-cel, 5 received nonconforming product, and 124 (89%) were efficacy evaluable (EE) per IRC. In pts with 3L+ FL, median (range) age was 62 y (23–80), 89% had Ann Arbor stage III/IV disease, and 57% were high-risk per FL International Prognostic Index. Forty-three percent of pts had POD24, 53% met GELF criteria, and 64% were double refractory to anti-CD20 antibody and an alkylator. Median (range) prior lines of therapy was 3 (2–10). Median (range) follow-up was 18.9 mo (0.3–28.2). In EE pts with 3L+ FL (n = 101), the primary endpoint of ORR was met at 97.0% (95% CI, 91.6–99.4; one-sided $P < 0.0001$; Table). CR rate was 94.1% (95% CI, 87.5–97.8; one-sided $P < 0.0001$). With a median follow-up of 16.6 mo and 17.5 mo, respectively, median DOR and PFS were not reached; 12-mo DOR and PFS were 81.9% and 80.7%, respectively. ORR, CR rate, DOR, and PFS were similar in EE pts with 2L+ FL. In the safety set (2L+ FL, n = 130), the most common grade (gr) ≥3 treatment-emergent adverse events (TEAE) were cytopenias; neutropenia was most frequent (65%). One TEAE death due to gr 5 macrophage activation syndrome occurred. Cytokine release syndrome (CRS) occurred in 58% of pts (gr 3, 1%; no gr 4–5) and neurological events (NE) in 15% (gr 3, 2%; no gr 4–5; Table). Prolonged cytopenia (gr ≥3 laboratory values at Day 29) occurred in 22% of pts and gr ≥3 infection in 5%. PK/PD data will be presented.

Conclusions: In pts with R/R FL, liso-cel demonstrated clinically meaningful benefit, with high response rates that were durable, and a favorable safety profile, with low rates of gr ≥3 TEAEs of CRS/NEs, prolonged cytopenia, and infection.

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Conflicts of interests pertinent to the abstract

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Table. Summary of efficacy and safety

Efficacy endpoints	3L+ FL EE pts (n = 101)
ORR, n (%)	98 (97.0)
(95% CI; one-sided *P* value)	(91.6–99.4; <0.0001)
CR rate, n (%)	95 (94.1)
(95% CI, one-sided *P* value)	(87.5–97.8; <0.0001)
PR, n (%)	3 (3.0)
Stable disease, n (%)	1 (1.0)
Progressive disease, n (%)	1 (1.0)
Not evaluable, n (%)	1 (1.0)
DOR, median (95% CI)	NR (18.0–NR)
Continued response at 12 mo, % (SE)	81.9 (3.986)
PFS, median (95% CI)	NR (18.96–NR)
PFS rate at 12 mo, % (SE)	80.7 (3.989)
Safety	**Liso-cel–treated pts (2L+ FL; safety set) (n = 130)**
AEs of special interest, n (%)	
Any-grade CRS[a]	75 (58)
Grade 1	55 (42)
Grade 2	19 (15)
Grade 3	1 (1)
Grade 4 or 5	0
Any-grade NEs[b]	20 (15)
Grade 1	15 (12)
Grade 2	2 (2)
Grade 3	3 (2)
Grade 4 or 5	0
Prolonged cytopenia[c]	29 (22)
Grade ≥ 3 infection	7 (5)

[a]CRS was graded based on Lee 2014 criteria; [b]NEs were defined as investigator-identified AEs related to liso-cel and were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0; [c]Defined as grade ≥ 3 laboratory abnormalities of neutropenia, anemia, or thrombocytopenia on Day 29.
2L+, second line or later; 3L+, third line or later; CRS, cytokine release syndrome; DOR, duration of response; EE, efficacy evaluable; FL, follicular lymphoma; liso-cel, lisocabtagene maraleucel; NE, neurological event; NR, not reached; SE, standard error.

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LBA5 | BRECADD IS NON-INFERIOR TO EBEACOPP IN PATIENTS WITH ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA: EFFICACY RESULTS OF THE GHSG PHASE III HD21 TRIAL

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Introduction: Individualized, PET2-guided first-line treatment of patients with advanced-stage classical Hodgkin Lymphoma (AS-cHL) with eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) achieves outstanding survival outcomes, but also causes relevant treatment-related morbidity (TRMB). We hypothesized that remodeling the eBEACOPP regimen with brentuximab vedotin (BV) could decrease TRMB while maintaining its high efficacy. Here, we report the results of the HD21 study regarding non-inferiority of BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) as compared to eBEACOPP in terms of progression-free survival (PFS).

Methods: This international open-label phase III trial included adult patients aged ≤60 with AS-cHL. Patients were randomized in a 1:1 ratio to PET2-guided 4–6 cycles of either eBEACOPP or BrECADD. PET2 and PFS events were assessed by blinded panel review. Non-inferiority of the primary efficacy endpoint PFS was defined as an absolute difference <6% at 5 years corresponding to a hazard ratio (HR) of BrECADD versus eBEACOPP <1.69. For this interim analysis at 36 months follow-up, O'Brien-Fleming method with Lan-DeMets alpha-spending function and the actual information fraction was used to calculate the significance level and HR bound for non-inferiority in the intention-to-treat (ITT) analysis set. 100 PFS events were available, resulting in a HR bound of 1.02 and a corresponding alpha level of 0.0108. The trial was registered at clinicaltrials.gov (NCT02661503) and conducted according to ICH-GCP guidelines.

Results: We enrolled 1,500 patients from 9 countries and 233 trial sites between July 2016 and August 2020. The ITT population comprised 1,482 patients, 740 in the eBEACOPP arm and 742 in the BrECADD arm. 44% were female, median age was 34 y (range 18–61), 47% were at high-risk (international prognostic index ≥3), baseline characteristics were well balanced between treatment arms. 59% of patients received 4 and 41% received 6 cycles of therapy. Median follow-up was 40 months. 3-year PFS was 92.3% for eBEACOPP and 94.9% for BrECADD, the corresponding point estimate for the HR was 0.63 (99% CI 0.37–1.07) and thus below the pre-specified bound. Progression or early relapse of HL ≤1 year was documented for 37 patients in the eBEACOPP arm (5%) and 16 patients in the BrECADD arm (2.2%). 3-year overall survival was 98.5% in both groups.

Conclusion: This interim analysis of the GHSG HD21 trial fully establishes non-inferiority of BrECADD compared to eBEACOPP. Importantly, we observed a relevant reduction in early PFS events with BrECADD resulting in a 3-year PFS rate of 94.9%. This mature and unparalleled PFS rate suggests that individualized treatment with PET2-directed BrECADD is currently the most effective therapy for adult patients with AS-cHL.

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Keyword: Hodgkin lymphoma

Conflicts of interests pertinent to the abstract

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009 | THE HUMAN BRAIN MICROENVIRONMENT OF PRIMARY CNS LYMPHOMA: HUMAN PLURIPOTENT STEM CELLS-DERIVED BRAIN MODELS

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The brain microenvironment deeply differs from the microenvironment of any other organ. The brain is, in fact, characterized by distinct metabolic conditions and immune environment, and it is composed of unique cell types such as neurons and cells of the glia, like astrocytes and microglia. Increasing evidence suggests that the brain microenvironment plays an important role in the pathogenesis of brain tumors and metastases. However, how the human brain niche interacts with and is eventually remodeled by primary central nervous system diffuse large B-cell lymphoma (PCNSL) is still a matter of investigation.
The recent advance of human pluripotent stem cells (hPSC)-based technologies offers the opportunity to virtually derive any cell type of the human body and organ-specific organoids. The hPSC-derived organoids are self-assembled 3D structures composed of lineage-specific cells and faithfully recapitulate some aspects of the in vivo tissue. We have now developed an hPSC-derived brain organoid model characterized by high cellular diversity and maturation, which allows the study of PCNSL adaption and growth in the human brain microenvironment.

Keyword: CNS lymphoma

No conflicts of interests pertinent to the abstract.

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