Hematological Oncology

15th International Conference on Malignant Lymphoma
Palazzo dei Congressi, Lugano, Switzerland
18–22 June, 2019

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. 37 Suppl. 2 June 2019
15th International Conference on Malignant Lymphoma

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WILEY

15th International Conference on Malignant Lymphoma Palazzo dei Congressi, Lugano (Switzerland) 18 - 22 June, 2019

Organized by the Foundation for the Institute of Oncology Research (IOR) in cooperation with the American Association for Cancer Research (AACR)

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Live educational activities occurring outside of Canada, recognised by the UEMS-EACCME® for ECMEC® credits are deemed to be Accredited Group Learning Activities (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada.

The meeting is accredited with 25 ESMO-MORA cat.1 points.

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Wilhelm Wössmann, Hamburg (Germany)

Weili Zhao, Shangai (China)

CONFERENCE SECRETARIAT AND LOCAL ORGANISATION

Cristiana Brentan, Orietta Lugli, Chiara Saporiti

Bellinzona (Switzerland)

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IBSA Foundation for Scientific Research

International Extranodal Lymphoma Study Group - IELSG
International Lymphoma Radiation Oncology Group - ILROG
Kompetenznetz Maligne Lymphome e.V. – KML
Leukemia & Lymphoma Society - LLS
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Saudi Society of Blood & Marrow Transplantation - SS-BMT
Swiss Cancer League
Swiss Cancer Research Foundation
Ticino Tourism
Union for China Lymphoma Investigators – UCLI
Università della Svizzera Italiana - USI

15-ICML REVIEWERS' LIST

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SAVE THE DATE: **16-ICML** – 16th International Conference on Malignant Lymphoma

Lugano, Switzerland

June 15 -19, 2021

WILEY

15-ICML - 15th INTERNATIONAL CONFERENCE ON MALIGNANT LYMPHOMA

Lugano, Switzerland–June 18-22, 2019

www.lymphcon.ch

SCIENTIFIC PROGRAM (as of May 15, 2019)

Tuesday, June 18, 2019

08:30–17:10 Auditorium (USI Università)	**CLOSED WORKSHOP - BRIDGING LIQUID BIOPSY INTO MANAGEMENT OF LYMPHOMA PATIENTS: DEVELOPMENT OF FRAMEWORKS FOR CLINICAL RESEARCH AND RECOMMENDATIONS FOR CLINICAL PRACTICE** Co-chairs: D. Rossi, Bellinzona (Switzerland), W.H. Wilson, Bethesda, MD (USA) and E. Zucca, Bellinzona (Switzerland) Organized in co-operation with the American Association for Cancer Research–AACR and the European School of Oncology–ESO and with the endorsement of the Leukemia & Lymphoma Society - LLS **by invitation only**
15:00–17:15 Aula Magna (USI Università)	**WORKSHOP–NEW GUIDELINES FROM THE INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP - ILROG** Organized in collaboration with the International Lymphoma Radiation Oncology Group - ILROG **open to all 15-ICML attendees**
	PART 1–NEW GUIDELINES FROM ILROG Chair: L. Specht, Copenhagen (Denmark)
15:00	RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA A. Ng, Boston, MA (USA)
15:15	SOLITARY PLASMACYTOMA AND MULTIPLE MYELOMA R. Tsang, Toronto (Canada)
15:30	IMAGING IN RADIATION THERAPY FOR LYMPHOMA G. Mikhaeel, London (UK)
15:45	PROTON THERAPY FOR MEDIASTINAL LYMPHOMAS B.S. Dabaja, Houston, TX (USA)
16:00	DISCUSSION
16:15	**COFFEE BREAK** *inside Aula Magna (USI Università), for attendees*
	PART 2 – PANEL DISCUSSION Led by J. Plastaras, Philadelphia, PA (USA)
16:30	FUTURE GUIDELINES TO BE DEVELOPED; ISSUES TO BE CONSIDERED IN ILROG GUIDELINES
16:50	HOW TO DISSEMINATE AND USE ILROG GUIDELINES

Wednesday, June 19, 2019

08:30–09:15	Article Nr	**"MEET THE PROFESSOR" SESSIONS** 🎬 *5 parallel sessions*
Room A	EB09	MULTIPLE MYELOMA: EVERY YEAR A NEW STANDARD? S.V. Rajkumar, Rochester, MN (USA) *repeated on Thursday, June 20, in Room B*

(Continues)

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Room B	EB10	THE MODERN APPROACH TO MANTLE CELL LYMPHOMA S. Rule, Plymouth (UK) *repeated on Thursday, June 20, in Room A*
Cinema Corso	EB07	MANAGING THE TOXICITIES OF CAR T-CELL THERAPY S.S. Neelapu, Houston, TX (USA) *repeated on Friday, June 21, in Auditorium (USI Università)*
Auditorium (USI Università)	EB01	PCNSL, A CURABLE DISEASE T.T. Batchelor, Boston, MA (USA) *repeated on Thursday, June 20, in Cinema Corso*
Aula Magna (USI Università)	EB12	WHAT WE SHOULD KNOW ABOUT NK/T-CELL LYMPHOMAS W. Zhao, Shanghai (China) *offered only once*
09:00–12:00 Marquee		**POSTER SESSION SET UP**
09:30–10:15		*5 parallel sessions*
Room A	EB02	DOUBLE HIT LYMPHOMA, SO WHAT? A. Davies, Southampton (UK) *repeated on Friday, June 21, in Room B*
Room B	EB05	HOW TO APPROACH CLL IN CLINICAL PRACTICE M. Hallek, Cologne (Germany) *repeated on Friday, June 21, in Room A*
Cinema Corso	EB11	LIQUID BIOPSY IN NON-HODGKIN'S LYMPHOMA W.H. Wilson, Bethesda, MD (USA) *repeated on Thursday, June 20, in Auditorium (USI Università)*
Auditorium (USI Università)	EB06	CUTANEOUS LYMPHOMAS W. Kempf, Zurich (Switzerland) *repeated on Friday, June 21, in Cinema Corso*
Aula Magna (USI Università)	EB03	BREAST IMPLANT ASSOCIATED ALCL AND OTHER RARE T-CELL LYMPHOMAS L. de Leval, Lausanne (Switzerland) *offered only once*
10:15–10:35 Marquee, Cinema Corso and USI Università		**COFFEE BREAK**
10:35–12:00		**EDUCATIONAL SYMPOSIA** 🎬 *2 parallel sessions*
Room A, Cinema Corso, Auditorium and Aula Magna (USI Università)		**TREATING HODGKIN LYMPHOMA IN THE NEW MILLENNIUM** Chair: A. Engert, Cologne (Germany)
	EB13	OPTIONS FOR FIRST LINE THERAPY OF HODGKIN LYMPHOMA P.W.M. Johnson, Southampton (UK)
	EB14	RELAPSED AND REFRACTORY DISEASE A.S. LaCasce, Boston, MA (USA)
	EB15	TREATMENT OF ELDERLY HODGKIN LYMPHOMA PATIENTS A. Engert, Cologne (Germany)
Room B and Marquee		**NEW DRUGS FOR NON-HODGKIN LYMPHOMA: BEYOND CHEMOTHERAPY** Chair: G. Salles, Lyon (France)
	EB16	CAR T CELL THERAPY: FULL SPEED AHEAD R.J. Brentjens, New York, NY (USA)
	EB17	NEW DRUGS FOR OLD TARGETS G. Salles, Lyon (France)
	EB18	NEW DRUGS FOR NEW TARGETS A. Younes, New York, NY (USA)

12:00–17:00 Marquee	Abstract Nr	**POSTER SESSION**
	136-159	BIOLOGY AND PATHOLOGY
	160-169	CLL
	170-183	INDOLENT LYMPHOMAS
	184-191	MANTLE CELL LYMPHOMAS
	192-206	AGGRESSIVE LYMPHOMAS
	207-217	EXTRANODAL LYMPHOMAS
	218-233	PTCL AND NK/T CELL LYMPHOMAS
	234-245	HODGKIN LYMPHOMAS
	246-262	IMMUNOTHERAPY
	263-285	NOVEL TREATMENTS
12:00–13:00 Marquee		**LUNCH TIME AND POSTER VIEWING**
13:00–14:00 Room A, B, Marquee, Cinema Corso, Auditorium and Aula Magna (USI Università)		**OPENING OF THE CONFERENCE** 🎬 WELCOME AND INTRODUCTORY REMARKS F. Cavalli, Bellinzona (Switzerland) **HENRY KAPLAN MEMORIAL LECTURE AND SAN SALVATORE FOUNDATION PRIZE**🎬 Introduction to San Salvatore Foundation: S. Coduri, Lugano (Switzerland) Laudatio: R. Stahel, Zurich (Switzerland)
	001	NEXT GENERATION CAR T CELLS FOR LYMPHOMA AND BEYOND C.H. June, Philadelphia, PA (USA)
14:00–15:25 Room A, B, Marquee, Cinema Corso, Auditorium and Aula Magna (USI Università)		**PLENARY SESSION** Co-chairs: J.O. Armitage, Omaha, NE (USA) and F. Cavalli, Bellinzona (Switzerland)
14:00	004	IDENTIFYING MUTATIONS ENRICHED IN RELAPSED-REFRACTORY DLBCL TO DERIVE GENETIC FACTORS UNDERLYING TREATMENT RESISTANCE C. Rushton, Burnaby, B. C (Canada)
14:15	005	ROBUST: FIRST REPORT OF PHASE III RANDOMIZED STUDY OF LENALIDOMIDE/R-CHOP (R2-CHOP) VS PLACEBO/R-CHOP IN PREVIOUSLY UNTREATED ABC-TYPE DIFFUSE LARGE B-CELL LYMPHOMA U. Vitolo, Turin (Italy)
14:30	006	ADDITION OF LENALIDOMIDE TO R-CHOP (R2CHOP) IMPROVES OUTCOMES IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): FIRST REPORT OF ECOG-ACRIN1412 A RANDOMIZED PHASE 2 US INTERGROUP STUDY OF R2CHOP VS R-CHOP G.S. Nowakowski, Rochester, MN (USA)
14:45		Discussant for presentations 004, 005 and 006: M.A. Shipp, Boston, MA (USA)
15:00	007	IBRUTINIB VERSUS PLACEBO IN PATIENTS WITH ASYMPTOMATIC, TREATMENT-NAÏVE EARLY STAGE CLL: PRIMARY ENDPOINT RESULTS OF THE PHASE 3 DOUBLE-BLIND RANDOMIZED CLL12 TRIAL P. Langerbeins, Cologne (Germany)
15:15		Discussant for presentation 007: S.M. O'Brien, Irvine, CA (USA)
15:25–15:50 Marquee		**COFFEE BREAK**
15:50–16:50 Room A, B, Marquee, Cinema Corso, Auditorium and Aula Magna (USI Università)		**AACR-ICML JOINT SESSION - THE ROLE OF NON-CLINICAL MODELS AS BRIDGES TO EARLY CLINICAL TRIALS** Co-chairs: M. Foti, Philadelphia, PA (USA) and B. Nadel, Marseille (France)
15:50	008	DESIGNER ORGANOIDS FOR MODELING EPIGENETICS, SIGNALING, AND THERAPIES IN LYMPHOMA A. Singh, New York, NY (USA)

16:10	009	MOUSE PDX AS NON-CLINICAL MODELS FOR LYMPHOMA A. Louissaint, Boston, MA (USA)
16:30	010	ADVANCING OUR UNDERSTANDING AND TREATMENT OF LYMPHOMA WITH SPONTANEOUS CANINE MODELS L. Aresu, Turin (Italy)
17:05–18:05		**"FOCUS ON …" SESSIONS** *5 parallel sessions*
Room A		**MANTLE CELL LYMPHOMA** Chair: J.P. Leonard, New York, NY (USA)
17:05	011	COMBINATION OF IBRUTINIB WITH RITUXIMAB (IR) IS HIGHLY EFFECTIVE IN PREVIOUSLY UNTREATED ELDERLY (>65 YEARS) PATIENTS (PTS) WITH MANTLE CELL LYMPHOMA (MCL)–PHASE II TRIAL P. Jain, Houston, TX (USA)
17:15	012	IBRUTINIB WITH RITUXIMAB (IR) AND SHORT COURSE R-HYPERCVAD/MTX IS VERY EFFICACIOUS IN PREVIOUSLY UNTREATED YOUNG PTS WITH MANTLE CELL LYMPHOMA (MCL) M. Wang, Houston, TX (USA)
17:25	013	AUTOLOGOUS STEM CELL TRANSPLANTATION IN FIRST REMISSION SIGNIFICANTLY PROLONGS PROGRESSION-FREE AND OVERALL SURVIVAL IN MANTLE CELL LYMPHOMA A. Zoellner, Munich (Germany)
17:35	014	OBINUTUZUMAB PLUS DHAP FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) PLUS OBINUTUZUMAB MAINTENANCE PROVIDES A HIGH MRD RESPONSE RATE IN UNTREATED MCL PATIENTS, RESULTS OF LYMA-101 TRIAL, A LYSA GROUP STUDY S. Le Gouill, Nantes (France)
17:45	015	ZANUBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA Y. Song, Beijing (China)
17:55	016	OUTCOMES IN FIRST RELAPSED-REFRACTORY YOUNGER PATIENTS WITH MANTLE CELL LYMPHOMA: RESULTS FROM THE MANTLE-FIRST STUDY C. Visco, Verona (Italy)
Room B		**PET IMAGING** Chair: B.D. Cheson, Washington, D.C. (USA)
17:05	017	A GENE EXPRESSION-BASED SCORE TO PREDICT INTERIM PET POSITIVITY IN HODGKIN LYMPHOMA PATIENTS TREATED WITH ABVD B. Donati, Reggio Emilia (Italy)
17:15	018	PERSISTENT MEDIASTINAL POSITRON EMISSION TOMOGRAPHY (PET)-POSITIVITY AFTER FRONTLINE THERAPY FOR HODGKIN LYMPHOMA IS BEST MANAGED BY CLOSE OBSERVATION M. Novo, Rochester, MN (USA)
17:25	019	HIGH TOTAL METABOLIC TUMOR VOLUME AT BASELINE ALLOWS TO DISCRIMINATE FOR SURVIVAL PATIENTS IN RESPONSE AFTER R-CHOP: AN ANCILLARY ANALYSIS OF THE REMARC STUDY L. Vercellino, Paris (France)
17:35	020	BASELINE TOTAL METABOLIC TUMOUR VOLUME IS HIGHLY PROGNOSTIC FOR REFRACTORINESS TO IMMUNOCHEMOTHERAPY IN DLBCL: AN ANALYSIS OF THE PHASE 3 GOYA TRIAL M. Trněný, Prague (Czech Republic)
17:45	021	RADIOMICS INCREASE THE PROGNOSTIC VALUE OF CLINICAL AND PET RISK FACTORS IN DLBCL: RESULTS FROM THE PHASE 3 GOYA STUDY S. Chauvie, Cuneo (Italy)
17:55	022	PROGNOSTIC VALUE OF PRE-TREATMENT PET SCAN IN PATIENTS WITH FOLLICULAR LYMPHOMA RECEIVING FRONTLINE THERAPY P. Strati, Houston, TX (USA)

Cinema Corso		**PEDIATRIC LYMPHOMA** Chair: W. Wössmann, Hamburg (Germany)
17:05	023	NON-HODGKIN LYMPHOMA IN ADOLESCENT AND YOUNG ADULTS - A NATIONAL PROSPECTIVE POPULATION-BASED STUDY R. Carr, London (UK)
17:15	024	INCLUSION OF A PEDIATRIC PERSPECTIVE INTO RECOMMENDATIONS FOR THE INITIAL EVALUATION AND STAGING OF HODGKIN LYMPHOMA: A CALL TO ACTION FROM THE INTERNATIONAL SEARCH WORKING GROUP J. Flerlage, Memphis, TN (USA)
17:25	025	SAFETY AND RESPONSE AFTER 2 CYCLES OF BRENTUXIMAB VEDOTIN SUBSTITUTING VINCRISTINE IN THE OEPA/COPDAC REGIMEN FOR HIGH RISK PEDIATRIC HODGKIN LYMPHOMA (HL) J. Flerlage, Memphis, TN (USA)
17:35	026	RESPONSE-ADAPTED TREATMENT WITH NIVOLUMAB AND BRENTUXIMAB VEDOTIN IN YOUNG PATIENTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA: CHECKMATE 744 SUBGROUP ANALYSES K.M. Kelly, Buffalo, NY (USA)
17:45	027	IBRUTINIB + CHEMOIMMUNOTHERAPY (CIT) FOR RELAPSED/REFRACTORY MATURE B-CELL NON-HODGKIN LYMPHOMA (B-NHL) IN CHILDREN (SPARKLE TRIAL): INITIAL SAFETY, PK, AND EFFICACY A. Burke, Cambridge (UK)
17:55	028	CHIMERIC ANTIGEN RECEPTOR T-CELLS (CAR-T) FOR REFRACTORY AND RELAPSED BURKITT'S LYMPHOMA, EARLY RESPONSE IN PEDIATRIC PATIENTS W.Q. Zhang, Beijing (China)
Auditorium (USI Università)		**RESULTS FROM SINGLE AGENT TRIALS** Chair: C. Thieblemont, Paris (France)
17:05	029	PHASE 2 STUDY OF ACALABRUTINIB IN IBRUTINIB-INTOLERANT PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA K.A. Rogers, Columbus, OH (USA)
17:15	030	RAPID AND DURABLE RESPONSES WITH THE SYK/JAK INHIBITOR CERDULATINIB IN A PHASE 2 STUDY IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA—ALONE OR IN COMBINATION WITH RITUXIMAB S.D. Smith, Seattle, WA (USA)
17:25	031	A PHASE 2B STUDY OF SELINEXOR IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) N. Kalakonda, Liverpool (UK)
17:35	032	TIPIFARNIB IN RELAPSED OR REFRACTORY ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA (AITL) AND CXCL12+ PERIPHERAL T-CELL LYMPHOMA (PTCL): PRELIMINARY RESULTS FROM A PHASE 2 STUDY T.E. Witzig, Rochester, MN (USA)
17:45	033	DUVELISIB, AN ORAL DUAL PI3K-δ,γ INHIBITOR, EFFICACY AND SAFETY IN PATIENTS WITH RELAPSED OR REFRACTORY (RR) PERIPHERAL T-CELL LYMPHOMA: RATIONALE FOR THE PHASE 2 PRIMO TRIAL S.M. Horwitz, New York, NY (USA)
17:55	034	EFFICACY OF MOGAMULIZUMAB IN PREVIOUSLY TREATED PATIENTS WITH LESS ADVANCED MYCOSIS FUNGOIDES: RESULTS FROM THE MAVORIC STUDY J. Scarisbrick, Birmingham (UK)
Aula Magna (USI Università)		**ONGOING TRIALS** Chair: J.M. Vose, Omaha, NE (USA)
17:05	OT01	NCRI PETREA TRIAL: A PHASE 3 EVALUATION OF PET-GUIDED, RESPONSE-ADAPTED THERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED, ADVANCED-STAGE, HIGH-TUMOUR-BURDEN FOLLICULAR LYMPHOMA A.R. Pettitt, Liverpool (UK)

17:15	OT02	POLARIX: A PHASE 3 STUDY OF POLATUZUMAB VEDOTIN (POLA) PLUS R-CHP VERSUS R-CHOP IN PATIENTS (PTS) WITH UNTREATED DLBCL H. Tilly, Rouen (France)
17:25	OT03	PHASE III RANDOMIZED STUDY OF ENZASTAURIN/R-CHOP VS PLACEBO/R-CHOP IN FRONTLINE HIGH RISK DIFFUSE LARGE B CELL LYMPHOMA PATIENTS WITH GENOMIC BIOMARKER DGM1 (ENGINE STUDY) Y. Xie, Beijing (China)
17:35	OT04	THE DIAL STUDY (DUAL IMMUNOMODULATION IN AGGRESSIVE LYMPHOMA): RANDOMIZED PHASE 2 TRIAL OF VARLILUMAB PLUS NIVOLUMAB IN RELAPSED/REFRACTORY AGGRESSIVE B-CELL LYMPHOMAS J.C. Villasboas, Rochester, MN (USA)
17:45	OT05	ACCEPT: A PHASE IB/II COMBINATION OF ACALABRUTINIB WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE AND PREDNISOLONE (R-CHOP) FOR PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) T. Cummin, Southampton (UK)
17:55	OT06	TELLOMAK: T-CELL LYMPHOMA ANTI-KIR3DL2 THERAPY: AN OPEN LABEL, MULTI-COHORT, MULTI-CENTER, INTERNATIONAL PHASE II STUDY EVALUATING THE EFFICACY AND SAFETY OF IPH4102 ALONE OR IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS WITH ADVANCED T-CELL LYMPHOMA P. Porcu, Philadelphia, PA (USA)

Thursday, June 20, 2019

08:00–08:45		**MEET THE PROFESSOR SESSIONS** 🎬 *5 parallel sessions*
Room A	EB10	THE MODERN APPROACH TO MANTLE CELL LYMPHOMA S. Rule, Plymouth (UK)
Room B	EB09	MULTIPLE MYELOMA: EVERY YEAR A NEW STANDARD? S.V. Rajkumar, Rochester, MN (USA)
Cinema Corso	EB01	PCNSL, A CURABLE DISEASE T.T. Batchelor, Boston, MA (USA)
Auditorium (USI Università)	EB11	LIQUID BIOPSY IN NON-HODGKIN'S LYMPHOMA W.H. Wilson, Bethesda, MD (USA)
Aula Magna (USI Università)	EB04	NEW TREATMENT OPTIONS IN HAIRY CELL LEUKEMIA WITH FOCUS ON BRAF INHIBITORS B. Falini, Perugia (Italy) *offered only once*
09:00–17.00 Marquee		**POSTER SESSION**
09:00–10:30		**"CASE DISCUSSION" SESSIONS: Spain vs Texas (USA)** *4 parallel sessions*
Room A		**DLBCL** Chair: L.H. Sehn, Vancouver, B.C. (Canada) Discussants: E. Giné Soca, Barcelona vs J.R. Westin, Houston
Cinema Corso		**HODGKIN LYMPHOMA** Chair: A.S. LaCasce, Boston, MA (USA) Discussants: A.M. Sureda Balari, Barcelona vs H.J. Lee, Houston
Auditorium (USI Università)		**RADIOTHERAPY FOR LYMPHOMAS** Chair: L. Specht, Copenhagen (Denmark) Discussants: T. Illidge, Manchester (UK) vs B.S. Dabaja, Houston
Aula Magna (USI Università)		**DIFFICULT PATHOLOGICAL CASES** Chair: M. Ghielmini, Bellinzona (Switzerland) Presenters: E. Campo, Barcelona (Spain), S. Dirnhofer, Basel (Switzerland) and P. Gaulard, Paris (France) Discussants: A. Lopez-Guillermo, Barcelona vs R. Hagemeister, Houston

09:00–10:30 Room B and Marquee	Abstract Nr	**SESSION 1 – DLBCL: BIOLOGY** Co-chairs: R. Dalla-Favera, New York, NY (USA) and R. Küppers, Essen (Germany)
09:00	035	AN AUTOCHTHONOUS MOUSE MODEL OF MYD88 P.L265P- AND BCL2-DRIVEN DIFFUSE LARGE B CELL LYMPHOMA G. Knittel, Cologne (Germany)
09:15	036	CRYPTIC MYC AND BCL2 REARRANGEMENTS ARE AMONG A RANGE OF GENETIC MECHANISMS UNDERLYING THE DOUBLE HIT SIGNATURE IN NON-DOUBLE HIT DIFFUSE LARGE B-CELL LYMPHOMA L.K. Hilton, Burnaby, B.C. (Canada)
09:30	037	FUNCTIONAL CHARACTERIZATION OF NFKBIZ 3′ UTR MUTATIONS IN DIFFUSE LARGE B-CELL LYMPHOMA S.E. Arthur, Burnaby, B.C. (Canada)
09:45	038	THE TRANSCRIPTION FACTOR FLI1 SUSTAINS RELEVANT BIOLOGICAL PATHWAYS AND DRIVES ONCOGENES THAT PROMOTE CELL GROWTH IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) G. Sartori, Bellinzona (Switzerland)
10:00	039	TRANSCRIPTIONAL AND GENOMIC INTRA-TUMOR HETEROGENEITY DRIVES SUBCLONE SPECIFIC DRUG RESPONSES IN DIFFUSE LARGE B CELL LYMPHOMA T. Roider, Heildelberg (Germany)
10:15	040	THE NONCODING RNA GECPAR IS INVOLVED IN WNT SIGNALING AND HAS TUMOR-SUPPRESSOR ACTIVITY IN DIFFUSE LARGE B CELL LYMPHOMA S. Napoli, Bellinzona (Switzerland)
10:30–11:00 Marquee, Cinema Corso and USI Università		**COFFEE BREAK**
11:00–12:00 Room A, B, Marquee, Cinema Corso, Auditorium and Aula Magna (USI Università)		**SESSION 2 – DLBCL: CLINICAL DATA** Co-chairs: M. Trněný, Prague (Czech Republic) and W. Zhao, Shanghai (China)
11:00	041	INTEGRATION BETWEEN METABOLIC TUMOUR VOLUME AND METABOLIC HETEROGENEITY PREDICTS OUTCOME OF DLBCL LYMPHOMA PATIENTS IN THE SAKK 38/07 STUDY COHORT L. Ceriani, Bellinzona (Switzerland)
11:15	042	SMART START: RITUXIMAB, LENALIDOMIDE, AND IBRUTINIB ALONE PRIOR TO COMBINATION WITH CHEMOTHERAPY FOR PATIENTS WITH NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA J.R. Westin, Houston, TX (USA)
11:30	043	RITUXIMAB MAINTENANCE FOR PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA IN FIRST COMPLETE REMISSION: RESULTS FROM A RANDOMIZED HOVON-NORDIC LYMPHOMA GROUP PHASE III STUDY P. Lugtenburg, Rotterdam (Netherlands)
11:45	044	IMPAIRED IMMUNE HEALTH IN SURVIVORS OF DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): A LARGE POPULATION-BASED STUDY T. Shree, Stanford, CA (USA)
12:00–13:00 Marquee		**LUNCH TIME AND POSTER VIEWING** *from 12:30 to 13:00 authors in front of their poster for discussion with attendees*
12:00–13:00 Room E		**15-ICML PRESS CONFERENCE**
13:00–13:45 Room A, B, Marquee, Cinema Corso and Aula Magna (USI Università)		**GIANNI BONADONNA MEMORIAL LECTURE** 🎬 *sponsored by the American Association for Cancer Research–AACR* Laudatio: M.A. Shipp, Boston, MA (USA)
	002	PRECISION EPIGENETIC THERAPY FOR B-CELL LYMPHOMA A.M. Melnick, New York, NY (USA)

13:45–15:15
Room A, B, Marquee,
  Cinema Corso,
  Auditorium and Aula
  Magna (USI Università)
		SESSION 3 – CLL
		Co-chairs: J.F. Seymour, Melbourne (Australia) and M. Hallek, Cologne (Germany)

13:45	045	INTERNATIONAL PROGNOSTIC SCORE FOR EARLY STAGE CHRONIC LYMPHOCYTIC LEUKEMIA (IPS-A) A. Condoluci, Bellinzona (Switzerland)

14:00	046	FIXED-DURATION VENETOCLAX PLUS OBINUTUZUMAB IMPROVES PFS AND MINIMAL
		  RESIDUAL DISEASE NEGATIVITY IN PATIENTS WITH PREVIOUSLY UNTREATED CLL AND
		  COMORBIDITIES
		K. Fischer, Cologne (Germany)

14:15	047	GENETIC MARKERS AND OUTCOME IN THE CLL14 TRIAL OF THE GCLLSG COMPARING
		  FRONT LINE OBINUTUZUMAB PLUS CHLORABMUCIL OR VENETOCLAX IN PATIENTS WITH
		  COMORBIDITY
		E. Tausch, Ulm (Germany) Best abstract submitted by a young investigator / travel grant recipient

14:30	048	ACALABRUTINIB VS RITUXIMAB PLUS IDELALISIB (IR) OR BENDAMUSTINE (BR) BY
		  INVESTIGATOR CHOICE IN RELAPSED/REFRACTORY (R/R) CHRONIC LYMPHOCYTIC
		  LEUKEMIA: PHASE 3 ASCEND STUDY
		P. Ghia, Milan (Italy)

14:45	049	ZANUBRUTINIB FOR PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA W. Xu, Nanjing (China)

15:00	050	A PHASE 2 STUDY TO ASSESS THE SAFETY AND EFFICACY OF UMBRALISIB IN PATIENTS WITH
		  CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WHO ARE INTOLERANT TO PRIOR BTK OR PI3K
		  DELTA INHIBITOR THERAPY
		A.R. Mato, New York, NY (USA)

15:15–15:40 Marquee		**COFFEE BREAK**
15:40–16:55		2 parallel sessions
Room A, Cinema Corso Auditorium and Aula Magna (USI Università)		**SESSION 4 – TREATMENT WITH NOVEL ANTIBODIES** Co-chairs: D.G. Maloney, Seattle, WA (USA) and P.L. Zinzani, Bologna (Italy)

15:40	051	THE FIRST-IN-CLASS ANTI-CD47 ANTIBODY HU5F9-G4 + RITUXIMAB INDUCES DURABLE
		  RESPONSES IN RELAPSED/REFRACTORY DLBCL AND INDOLENT LYMPHOMA: INTERIM
		  PHASE 1B/2 RESULTS
		R.H. Advani, Stanford, CA (USA)

15:55	052	CLINICAL ACTIVITY OF REGN1979, AN ANTI-CD20 X ANTI-CD3 BISPECIFIC ANTIBODY (AB) IN
		  PATIENTS (PTS) WITH (W/) RELAPSED/REFRACTORY (R/R) B-CELL NON-HODGKIN
		  LYMPHOMA (B-NHL)
		M.S. Topp, Würzburg (Germany)

16:10	053	CD20-TCB (RG6026), A NOVEL "2:1" FORMAT T-CELL-ENGAGING BISPECIFIC ANTIBODY,
		  INDUCES COMPLETE REMISSIONS IN RELAPSED/REFRACTORY B-CELL NON-HODGKIN'S
		  LYMPHOMA
		M.J. Dickinson, Melbourne (Australia)

16:25	054	ANALYSIS OF EFFICACY AND SAFETY OF LONCASTUXIMAB TESIRINE (ADCT-402) BY
		  DEMOGRAPHIC AND CLINICAL CHARACTERISTICS IN RELAPSED/REFRACTORY DIFFUSE
		  LARGE B-CELL LYMPHOMA
		J. Radford, Manchester (UK)

16:40	055	ANALYSIS OF CLINICAL DETERMINANTS DRIVING SAFETY AND EFFICACY OF
		  CAMIDANLUMAB TESIRINE (ADCT-301, CAMI) IN RELAPSED/REFRACTORY (R/R) CLASSICAL
		  HODGKIN LYMPHOMA (CHL)
		G. Collins, Oxford (UK)

15:40–16:55 Room B and Marquee		**SESSION 5 – T-CELL LYMPHOMAS** Co-chairs: S. Luminari, Reggio Emilia (Italy) and K.J. Savage, Vancouver, B.C. (Canada)
15:40	056	RISK OF BREAST IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL) IN A COHORT OF 3546 WOMEN PROSPECTIVELY FOLLOWED AFTER RECEIVING TEXTURED BREAST IMPLANTS. P. Ghione, New York, NY (USA)
15:55	057	AUTOLOGOUS STEM CELL TRANSPLANTATION AS PART OF FIRST-LINE THERAPY IN PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA: A MULTICENTER GELTAMO/FIL STUDY M. Lopez-Parra, Salamanca (Spain)
16:10	058	FIRST-LINE THERAPY OF T-CELL LYMPHOMA: ALLOGENEIC OR AUTOLOGOUS TRANSPLANTATION FOR CONSOLIDATION - FINAL RESULTS OF THE AATT STUDY O. Tournilhac, Clermont-Ferrand (France)
16:25	059	TREATMENT BENEFIT ASSOCIATING WITH NON-ANTHRACYCLINE CHEMOTHERAPY IN EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE S. Qi, Beijing (China)
16:40	060	SINTILIMAB FOR RELAPSED/REFRACTORY (R/R) EXTRANODAL NK/T CELL LYMPHOMA (ENKTL): A MULTICENTER, SINGLE-ARM, PHASE 2 TRIAL (ORIENT-4) R. Tao, Shanghai (China)
17:05–18:05		**"FOCUS ON …" SESSIONS** *5 parallel sessions*
Room A		**CLL AND MORE** Chair: D. Rossi, Bellinzona (Switzerland)
17:05	061	FIVE-YEAR FOLLOW-UP OF FIRST-LINE IBRUTINIB FOR TREATMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA//SMALL LYMPHOCYTIC LYMPHOMA A. Tedeschi, Milan (Italy)
17:15	062	HIGH EFFICACY OF VENETOCLAX PLUS OBINUTUZUMAB IN PATIENTS WITH COMPLEX KARYOTYPE (CKT) AND CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A PROSPECTIVE ANALYSIS FROM THE CLL14 TRIAL O. Al-Sawaf, Cologne (Germany)
17:25	063	IMPACT OF MAJOR GENOMIC ALTERATIONS ON OUTCOME OF RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS RECEIVING VENETOCLAX PLUS RITUXIMAB IN THE PHASE 3 MURANO STUDY J. Wu, San Francisco, CA (USA)
17:35	064	AN UNDETECTABLE PB MRD STATUS SHOULD BE THE THERAPEUTIC GOAL WITH VENETOCLAX THERAPY IN RELAPSED/REFRACTORY CLL S. Handunnetti, Melbourne (Australia)
17:45	065	TRANSCEND CLL 004: MINIMAL RESIDUAL DISEASE AFTER LISOCABTAGENE MARALEUCEL IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA T. Siddiqi, Duarte, CA (USA)
17:55	066	THE BRAF INHIBITOR VEMURAFENIB PLUS RITUXIMAB PRODUCES A HIGH RATE OF DEEP AND DURABLE RESPONSES IN RELAPSED/REFRACTORY HAIRY CELL LEUKEMIA: UPDATED RESULTS OF A PHASE-2 TRIAL E. Tiacci, Perugia (Italy)
Room B		**CHEMOTHERAPY-FREE STRATEGIES** Chair: J.W. Friedberg, Rochester, NY (USA)
17:05	067	PREDICTIVE VALUE OF POD24 VALIDATION IN FOLLICULAR LYMPHOMA PATIENTS INITIALLY TREATED WITH CHEMOTHERAPY-FREE REGIMENS IN A POOLED ANALYSIS OF THREE RANDOMIZED TRIALS OF THE SWISS GROUP FOR CLINICAL CANCER RESEARCH (SAKK) A. Moccia, Bellinzona (Switzerland)
17:15	068	EFFICACY AND SAFETY OF OBINUTUZUMAB + LENALIDOMIDE + ATEZOLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA: PRIMARY ANALYSIS OF A PHASE 1B/2 TRIAL F. Morschhauser, Lille (France)

17:25	069	AUGMENT PHASE III STUDY: LENALIDOMIDE/RITUXIMAB (R2) IMPROVED EFFICACY OVER RITUXIMAB/PLACEBO IN RELAPSED/REFRACTORY FOLLICULAR PATIENTS IRRESPECTIVE OF POD24 STATUS J.P. Leonard, New York, NY (USA)
17:35	070	INTERIM ANALYSIS OF PHASE IIIB MAGNIFY STUDY OF INDUCTION R2 FOLLOWED BY MAINTENANCE IN PATIENTS WITH RELAPSED/REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA J. Sharman, Eugene, OR (USA)
17:45	071	RITUXIMAB PLUS LENALIDOMIDE IS AS EFFECTIVE AS IMMUNOCHEMOTHERAPY IN THE ERADICATION OF MOLECULAR DISEASE IN UNTREATED FOLLICULAR LYMPHOMA: RELEVANCE LYSA ANCILLARY STUDY M.H. Delfau-Larue, Creteil (France)
17:55	072	SAKK 35/15: A PHASE I TRIAL OF OBINUTUZUMAB IN COMBINATION WITH VENETOCLAX IN PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA PATIENTS. A. Stathis, Bellinzona (Switzerland)
Cinema Corso		**NON-CLINICAL AND EARLY CLINICAL DATA WITH NEW COMBINATIONS** Chair: A. Davies, Southampton (UK)
17:05	073	PHASE I/II STUDY OF UMBRALISIB (TGR-1202) IN COMBINATION WITH UBLITUXIMAB (TG-1101) AND PEMBROLIZUMAB IN PATIENTS WITH REL/REF CLL AND RICHTER'S TRANSFORMATION A.R. Mato, New York, NY (USA)
17:15	074	PEMBROLIZUMAB WITH RCHOP IN PREVIOUSLY UNTREATED DIFFUSE LARGE B-CELL AND GRADE 3B FOLLICULAR LYMPHOMA: FINAL RESULTS OF A PHASE I TRIAL S.D. Smith, Seattle, WA (USA)
17:25	075	ZANUBRUTINIB PLUS OBINUTUZUMAB IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL) OR RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL) C.S. Tam, Melbourne (Australia)
17:35	076	A PHASE I/II TRIAL OF IBRUTINIB, INTRATUMORAL CPG AND LOCAL RADIATION IN PATIENTS WITH LOW-GRADE B-CELL LYMPHOMA: INTERIM CLINICAL AND CORRELATIVE RESULTS T. Shree, Stanford, CA (USA)
17:45	077	EXTENDED FOLLOW-UP OF A PHASE I TRIAL OF IPILIMUMAB, NIVOLUMAB AND BRENTUXIMAB VEDOTIN IN RELAPSED HODGKIN LYMPHOMA: A TRIAL OF THE ECOG-ACRIN RESEARCH GROUP (E4412) C. Diefenbach, New York, NY (USA)
17:55	078	HIGH EXPRESSION OF BCL-2 AND BCL-XL IN DIFFUSE LARGE B-CELL LYMPHOMA CONFER POOR PROGNOSIS BUT MAY BE REVERSIBLE BY COMBINED INHIBITION WITH BET INHIBITORS AND BH3 MIMETICS. T.E. Cummin, Southampton (UK)
Auditorium (USI Università)		**NON-CLINICAL NEW DRUGS** Chair: L. Pasqualucci, New York, NY (USA)
17:05	079	FIRST-IN-CLASS HAT ACTIVATOR HIGHLY SYNERGISTIC WITH PAN-HDAC INHIBITOR ROMIDEPSIN LEADING TO PROFOUND HISTONE ACETYLATION CYTOTOXICITY Y. Liu, New York, NY (USA)
17:15	080	COPANLISIB AND VOLASERTIB OVERCOME IBRUTINIB-VENETOCLAX RESISTANCE VIA TARGETING PI3K-AKT SIGNALING AND G2/M CELL CYCLE TRANSITION IN MANTLE CELL LYMPHOMA R. Zhang, Houston, TX (USA)
17:25	081	THE LANDSCAPE OF DRUG PERTUBATION EFFECTS IN LEUKEMIA AND LYMPHOMA T. Zenz, Zurich (Switzerland)
17:35	082	DISCOVERY OF A NOVEL, POTENTIAL FIRST-IN-CLASS MALT1 PROTEASE INHIBITOR FOR THE TREATMENT OF B CELL LYMPHOMAS U. Philippar, Bersee (Belgium)

17:45	083	KYM-001, A FIRST-IN-CLASS ORAL IRAK4 PROTEIN DEGRADER, INDUCES TUMOR REGRESSION IN XENOGRAFT MODELS OF MYD88-MUTANT ABC DLBCL ALONE AND IN COMBINATION WITH BTK INHIBITION J. Kelleher, Cambridge, MA (USA)
17:55	084	THE ANTIBODY-DRUG CONJUGATE (ADC) LONCASTUXIMAB TESIRINE (ADCT-402) TARGETING CD19 SHOWS STRONG in vitro ANTI-LYMPHOMA ACTIVITY BOTH AS SINGLE AGENTS AND IN COMBINATION C. Tarantelli, Bellinzona (Switzerland)
Aula Magna (USI Università)		**HIGH RISK LARGE B-CELL LYMPHOMAS** Chair: L.H. Sehn, Vancouver, B.C. (Canada)
17:05	085	EBV+ CNS LYMPHOMAS HAVE A DISTINCTIVE TUMOR MICROENVIRONMENT AND GENETIC PROFILE, WHICH IS AMENABLE TO COMBINATION 3RD PARTY EBV-SPECIFIC CTL AND IBRUTINIB THERAPY M.K. Gandhi, Brisbane (Australia)
17:15	086	YOUNG HIGH RISK PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA INCLUDING BCL-2/MYC DOUBLE HIT LYMPHOMAS BENEFIT FROM DOSE-DENSE IMMUNOCHEMOTHERAPY WITH EARLY CNS PROPHYLAXIS S. Leppä, Helsinki (Finland)
17:25	087	SAFETY AND EFFICACY OF THE PD-L1 INHIBITOR DURVALUMAB WITH R-CHOP OR R2-CHOP IN SUBJECTS WITH PREVIOUSLY UNTREATED, HIGH-RISK DLBCL G.S. Nowakowski, Rochester, MN (USA)
17:35	088	INITIAL RESULTS OF A MULTICENTER PHASE 2 STUDY OF VENETOCLAX IN COMBINATION WITH DOSE-ADJUSTED R-EPOCH FOR PATIENTS WITH RICHTER'S SYNDROME (CRC-043) M.S. Davids, Boston, MA (USA)
17:45	089	IMPROVED OUTCOMES IN PATIENTS (PTS) WITH BCL2-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) TREATED WITH VENETOCLAX (VEN) PLUS R-CHOP: RESULTS FROM THE PHASE 2 CAVALLI STUDY F. Morschhauser, Lille (France)
17:55	090	CD19-DIRECTED CAR T CELL THERAPY (CTL019) FOR RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL AND FOLLICULAR LYMPHOMAS: FOUR YEAR OUTCOMES E.A. Chong, Philadelphia, PA (USA)

Friday, June 21, 2019

08:00–08:45		**MEET THE PROFESSOR SESSIONS** 🎬 *5 parallel sessions*
Room A	EB05	HOW TO APPROACH CLL IN CLINICAL PRACTICE M. Hallek, Cologne (Germany)
Room B	EB02	DOUBLE HIT LYMPHOMA, SO WHAT? A. Davies, Southampton (UK)
Cinema Corso	EB06	CUTANEOUS LYMPHOMAS W. Kempf, Zurich (Switzerland)
Auditorium (USI Università)	EB07	MANAGING THE TOXICITIES OF CAR T-CELL THERAPY S.S. Neelapu, Houston, TX (USA)
Aula Magna (USI Università)	EB08	RARE B CELL LYMPHOMAS IN CHILDREN AND ADOLESCENTS L. Quintanilla-Martinez de Fend, Tübingen (Germany) and W. Wössmann, Hamburg (Germany) *offered only once*
09:00–18:30 Marquee		**POSTER SESSION**
09:00–10:30		**"CASE DISCUSSION" SESSIONS: Spain vs Texas (USA)** *3 parallel sessions*
Room A		**FL/INDOLENT LYMPHOMA** Chair: S. Rule, Plymouth (UK) Discussants: M. Provencio Pulla, Madrid vs L.J. Nastoupil, Houston

Cinema Corso		**CLL** Chair: S.M. O'Brien, Irvine, CA (USA) Discussants: J. Delgado, Barcelona vs P.A. Thompson, Houston
Aula Magna (USI Università)		**PTCL** Chair: K.J. Savage, Vancouver, B.C. (Canada) Discussants: A. Martín, Salamanca vs N.H. Fowler, Houston
09:00–10:30 Room B and Marquee		**SESSION 6 – LYMPHOMA PATHOLOGY** Co-chairs: K. Ohshima, Kurume (Japan) and E. Campo, Barcelona (Spain)
09:00	091	DIAGNOSIS AND CLASSIFICATION ASSISTANCE FROM LYMPHOMA MICROSCOPIC IMAGES USING DEEP LEARNING P. Brousset, Toulouse (France)
09:15	092	INTEGRATING TUMOR- AND MICROENVIRONMENT-REFLECTING GENES IN A UNIQUE AND ROUTINE-APPLICABLE ASSAY FOR ACCURATE RISK PREDICTION IN DLBCL. S.A. Pileri, Milan (Italy)
09:30	093	CONCORDANCE BETWEEN IMMUNOHISTOCHEMISTRY AND GENE EXPRESSION PROFILING SUBTYPING FOR DIFFUSE LARGE B-CELL LYMPHOMA IN THE PHASE 3 PHOENIX TRIAL S. Balasubramanian, San Diego CA (USA)
09:45	094	LONGITUDINAL ANALYSES OF DIAGNOSTIC-RELAPSE BIOPSIES OF DIFFUSE LARGE B CELL LYMPHOMA SUGGEST THAT RELAPSE IS MEDIATED BY DISTINCT MECHANISMS IN ABC AND GCB LYMPHOMA S. Araf, London (UK)
10:00	095	DEFINING BURKITT-LIKE LYMPHOMA WITH 11Q ABERRATION IN A SPECIALISED UK HAEMATOPATHOLOGY DIAGNOSTIC SERVICE S. Barrans, Leeds (UK)
10:15	096	GENOME WIDE-ANALYSIS OF T(14;18)-NEGATIVE FOLLICULAR LYMPHOMA L. Quintanilla-Martinez de Fend, Tübingen (Germany)
09:00–12:00 Auditorium (USI Università)		**WORKSHOP – CONTEMPORARY LYMPHOMA TREATMENT: RADIATION THERAPY ISSUES** Organized in collaboration with the International Lymphoma Radiation Oncology Group - ILROG **open to all 15-ICML attendees** **Part 1: FRACTIONATION ISSUES IN RADIOTHERAPY OF LYMPHOMAS** Chair: M.K. Gospodarowicz, Toronto, ON (Canada)
09:00		DOSE PER FRACTION, RESPONSE, LATE EFFECTS RELATIONSHIP IN LYMPHOMAS R. Hoppe, Stanford, CA (USA)
09:20		OPTIMAL DOSE FRACTIONATION FOR INDOLENT AND AGGRESSIVE LYMPHOMAS P. Hoskin, London and Manchester (UK)
09:40		OPTIMAL DOSE FRACTIONATION IN HODGKIN LYMPHOMAS C. Baues, Cologne (Germany)
10:00–10:25		**COFFEE BREAK** *inside Auditorium (USI Università), for attendees*
10:25		**Part 2: RADIOTHERAPY IN THE ELDERLY LYMPHOMA PATIENT** LYMPHOMA IN THE ELDERLY - SCOPE OF THE PROBLEMS I. Glimelius, Uppsala (Sweden)
10:45		RADIOTHERAPY & LYMPHOMA IN THE ELDERLY: INDOLENT LYMPHOMAS U. Ricardi, Turin (Italy)
11:00		RADIOTHERAPY & LYMPHOMA IN THE ELDERLY: AGGRESSIVE LYMPHOMA J. Yahalom, New York, NY (USA)
11:15		RADIOTHERAPY & LYMPHOMA IN THE ELDERLY: HODGKIN LYMPHOMA L. Specht, Copenhagen (Denmark)
11:30		RADIOTHERAPY & LYMPHOMA IN THE ELDERLY: LATE EFFECTS D. Hodgson, Toronto, ON (Canada)
11:45		QUESTIONS
10:30–11:00 Marquee, Cinema Corso and USI Università		**COFFEE BREAK**

11:00–12:00 Room A, B, Marquee, Cinema Corso and Aula Magna (USI Università)		**SESSION 7 – HODGKIN LYMPHOMA** Co-chairs: R.H. Advani, Stanford, CA (USA) and T.A. Lister, London (UK)
11:00	097	STAGE I-II NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA IN THE MODERN ERA: A MULTI-INSTITUTIONAL EXPERIENCE OF ADULT PATIENTS BY ILROG M.S. Binkley, Stanford, CA (USA)
11:15	098	NIVOLUMAB PLUS DOXORUBICIN, VINBLASTINE AND DACARBAZINE FOR NEWLY DIAGNOSED ADVANCED-STAGE CLASSICAL HODGKIN LYMPHOMA: CHECKMATE 205 COHORT D 2-YEAR FOLLOW-UP S. Ansell, Rochester, MN (USA)
11:30	099	CONSOLIDATION RADIOTHERAPY COULD BE OMITTED IN ADVANCED HODGKIN LYMPHOMA WITH LARGE NODAL MASS IN COMPLETE METABOLIC RESPONSE AFTER ABVD. FINAL ANALYSIS OF THE RANDOMIZED HD0607 TRIAL A. Gallamini, Nice (France)
11:45	100	COST-EFFECTIVENESS AND COST-UTILITY ANALYSIS OF MULTIPLE TREATMENT STRATEGIES USING ABVD AND/OR BEACOPP IN THE TREATMENT OF ADVANCED-STAGE HODGKIN LYMPHOMA A. Prica, Toronto, ON (Canada)
12:00–13:00 Marquee		**LUNCH TIME AND POSTER VIEWING** *from 12:30 to 13:00 authors in front of their poster for discussion with attendees*
13:00–13:45 Room A, B, Marquee, Cinema Corso and Aula Magna (USI Università)		**JOHN ULTMANN MEMORIAL LECTURE** 🎬 *sponsored by the European School of Oncology–ESO* Laudatio: J.M. Vose, Omaha, NE (USA)
	003	THIRTY YEARS OF T-CELL LYMPHOMAS P. Gaulard, Créteil (France)
13:45–15:00		*4 parallel sessions*
Room A and Cinema Corso		**SESSION 8 – FOLLICULAR LYMPHOMA** Co-chairs: B.S. Kahl, St. Louis, MO (USA) and M. Herold, Erfurt (Germany)
13:45	101	PROGNOSTIC IMPLICATIONS OF THE MICROENVIRONMENT IN FOLLICULAR LYMPHOMA UNDER RITUXIMAB AND RITUXIMAB+LENALIDOMIDE THERAPY; A TRANSLATIONAL STUDY OF THE SAKK35/10 TRIAL S. Dirnhofer, Basel (Switzerland)
14:00	102	DECIPHERING THE CONTRIBUTION OF MACROPHAGES TO FOLLICULAR LYMPHOMA PATHOGENESIS: NEW INSIGHTS INTO THERAPY P. Perez Galan, Barcelona (Spain)
14:15	103	IMPACT OF PET IMAGING AND HISTOLOGIC TRANSFORMATION ON THE PROGNOSIS OF EARLY DISEASE PROGRESSION IN FOLLICULAR LYMPHOMA C.L. Batlevi, New York, NY (USA)
14:30	104	RESPONSE ORIENTED MAINTENANCE THERAPY IN ADVANCED FOLLICULAR LYMPHOMA. RESULTS OF THE INTERIM ANALYSIS OF THE FOLL12 TRIAL CONDUCTED BY THE FONDAZIONE ITALIANA LINFOMI M. Federico, Modena (Italy)
14:45	105	INTERIM UPDATE FROM A PHASE 2 MULTICENTER STUDY OF TAZEMETOSTAT, AN EZH2 INHIBITOR, IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA F. Morschhauser, Lille (France)
Room B and Marquee		**SESSION 9 - EXTRANODAL LYMPHOMAS** Co-chairs: M.K. Gospodarowicz, Toronto, ON (Canada) and E. Zucca, Bellinzona (Switzerland)
13:45	106	INTEGRATIVE GENOMIC ANALYSIS IDENTIFIES KEY PATHOGENIC CONCEPTS IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA A. Mottok, Ulm (Germany)

14:00	107	OUTCOME OF PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA IN THE RITUXIMAB ERA: IMPACT OF A PET-GUIDED APPROACH A. Hayden, Vancouver, B.C. (Canada)
14:15	108	NIVOLUMAB COMBINED WITH BRENTUXIMAB VEDOTIN FOR RELAPSED/REFRACTORY PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA: EFFICACY AND SAFETY FROM THE PHASE 2 CHECKMATE 436 STUDY P.L. Zinzani, Bologna (Italy)
14:30	109	R-CHOP PRECEDED BY ENGINEERED TUMOR NECROSIS FACTOR (TNF) IN RELAPSED OR REFRACTORY PRIMARY DIFFUSE LARGE B-CELL LYMPHOMA OF THE CNS (rPCNSL): FINAL RESULTS OF THE INGRID TRIAL A.J. Ferreri, Milan (Italy)
14:45	110	POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD) AFTER SOLID ORGAN TRANSPLANT (SOT): SURVIVAL AND PROGNOSTICATION AMONG 570 PATIENTS (PTS) TREATED IN THE MODERN ERA D. Jagadeesh, Cleveland, OH (USA)
14:15–17:30 Auditorium (USI Università)		**IBSA FOUNDATION SPECIAL FORUM - REVOLUTIONARY THERAPIES FOR CANCER** Chairmen: F. Cavalli, Bellinzona (Switzerland) and A. Alimonti, Bellinzona (Switzerland) Organized by IBSA Foundation for Scientific Research **Open to all 15-ICML attendees, appreciated pre-registration at** www.ibsafoundation.org **(free session)**
14:15		WELCOME AND INTRODUCTION S. Misiti, IBSA Foundation and A. Alimonti, IBSA Foundation Scientific Board
14:30		mTOR SIGNALING IN GROWTH AND METABOLISM M. Hall, Basel (Switzerland)
15:00		INNATE IMMUNITY, INFLAMMATION AND CANCER: FROM BENCH TO BEDSIDE A. Mantovani, Milan (Italy), London (UK)
15:30		BUILDING NEXT GENERATION CAR T CELLS C.H. June, Philadelphia, PA (USA)
16:00		FROM MOLECULAR ADDICTION TO IMMUNE ACTIVATION: REINVENTING THERAPIES FOR CANCER S. Peters, Lausanne (Switzerland)
14:15–17:15 Aula Magna (USI Università)		**UCLI-ICML JOINT SESSION–NEW DATA ON T-CELL AND OTHER LYMPHOMAS** Honorary Presidents: F. Cavalli, Bellinzona (Switzerland) and J. Ma, Harbin (China) Executive Presidents: W.J. Chng, Singapore (Singapore), J. M. Vose, Omaha, NE (USA), J. Zhu, Beijing (China)
14:20	111	20-YEAR SURVIVAL DATA ANALYSIS OF PTCL PATIENTS IN PEKING UNIVERSITY CANCER HOSPITAL Y. Song, Beijing (China)
14:45	112	DEVELOPING IMMUNOEPIGENETIC PLATFORMS FOR PTCL: LEVERAGING A LOGIC FOR PD1/PDL-1 INHIBITORS O.A. O'Connor, New York, NY (USA)
15:10	113	CLINICAL OUTCOME OF AN PROSPECTIVE, MULTICENTRE, RANDOMIZED, PHASE III NON-INFERIORITY CLINICAL TRIAL FOR PATIENTS WITH EXTRANODAL NK/T CELL LYMPHOMA TREATED BY P-GEMOX OR ASPAMETDEX H. Huang, Guangzhou (China)
15:35–15:55		**COFFEE BREAK** *inside Aula Magna (USI Università), for attendees*
15:55	114	NEW DATA IN THE MOLECULAR PATHOLOGY OF T CELL LYMPHOMAS L. de Leval, Lausanne (Switzerland)
16:20	115	DIFFUSE LARGE B-CELL LYMPHOMA: USING IMMUNE BIOMARKERS TO DEFINE NOVEL THERAPIES W. Zhao, Shanghai (China)
16:45	116	THE RELEVANCE OF OBSERVATIONAL REGISTRIES: THE CASE OF T CELL LYMPHOMA PROJECTS 1.0 AND 2.0 M. Federico, Modena (Italy)

15:00–15:30 Marquee		**COFFEE BREAK**
15:30–15:45 Room A, B, Marquee and Cinema Corso		**REPORT OF THE 15-ICML WORKSHOP** Co-chairs: S.S. Neelapu, Houston, TX (USA) and G. Salles, Lyon (France) BRIDGING LIQUID BIOPSY INTO MANAGEMENT OF LYMPHOMA PATIENTS: DEVELOPMENT OF FRAMEWORKS FOR CLINICAL RESEARCH AND RECOMMENDATIONS FOR CLINICAL PRACTICE W.H. Wilson, Bethesda, MD (USA)
15:45–17:15 Room A, B, Marquee and Cinema Corso		**SESSION 10 – ADVANCES IN CAR T-CELL TREATMENT** Co-chairs: S.S. Neelapu, Houston, TX (USA) and G. Salles, Lyon (France)
15:45	117	NOVEL BAFF-R CAR T-CELL THERAPY FOR CD19 ANTIGEN-LOSS RELAPSED B CELL TUMORS L.W. Kwak, Duarte, CA (USA)
16:00	118	PHASE I CLINICAL TRIAL OF CD19-TARGETED 19-28Z/4-1BBL "ARMORED" CAR T CELLS IN PATIENTS WITH RELAPSED OR REFRACTORY NHL AND CLL INCLUDING RICHTER TRANSFORMATION C.L. Batlevi, New York, NY (USA)
16:15	119	CD30-CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS FOR THERAPY OF HODGKIN LYMPHOMA (HL) C.A. Ramos, Houston, TX (USA)
16:30	120	DURABLE RESPONSES AFTER CD19-TARGETED CAR-T CELL IMMUNOTHERAPY WITH CONCURRENT IBRUTINIB FOR CLL AFTER PRIOR IBRUTINIB FAILURE J. Gauthier, Seattle, WA (USA)
16:45	121	HIGH RATE OF DURABLE COMPLETE REMISSION IN FOLLICULAR LYMPHOMA AFTER CD19 CAR-T CELL IMMUNOTHERAPY A.V. Hirayama, Seattle, WA (USA)
17:00	122	SAFETY OF LISOCABTAGENE MARALEUCEL GIVEN WITH DURVALUMAB IN PATIENTS WITH RELAPSED/REFRACTORY AGGRESSIVE B-CELL NON HODGKIN LYMPHOMA: FIRST RESULTS FROM THE PLATFORM STUDY T. Siddiqi, Duarte, CA (USA)
17:15–17:35 Room A, B, Marquee and Cinema Corso		**SPECIAL LECTURE** Chair: F. Cavalli, Bellinzona (Switzerland)
	123	THE HIGH COST OF CANCER DRUGS: WHAT CAN WE DO? S.V. Rajkumar, Rochester, MN (USA)
17:35–18:30 Marquee		**FAREWELL APERO**

Saturday, June 22, 2019

08:30–10:30 Auditorium (USI Università)	**ESO–ESMIT Educational Session - PET-CT IN LYMPHOMA** Chair: A.T. Lister, London (UK) Organized by the European School of Oncology–ESO and the European School of Multimodality Imaging & Therapy–ESMIT **Open to all 15-ICML attendees**
08:30	HOW TO INTERPRET PET-CT SCANS IN LYMPHOMAS: VISUAL AND FUNCTIONAL EVALUATION M. Meignan, Creteil (France)
08:50	PET-BASED CLINICAL DECISIONS: WHERE DO WE STAND AND WHERE WE MAY GO P.W.M. Johnson, Southampton (UK)
09:20	THE LUGANO CLASSIFICATION 5 YEARS AFTER: SHOULD WE CHANGE ANYTHING? B.D. Cheson, Washington, D.C. (USA)
09:40	CHALLENGING CASES FROM THE ONCOLOGY INSTITUTE OF SOUTHERN SWITZERLAND Presented by E. Zucca, Bellinzona (Switzerland) and L. Ceriani, Bellinzona (Switzerland) Discussants: A.T. Lister, London (UK) and all faculty

08:30–10:00		**SESSION 11 – NEW DRUG COMBINATIONS**
Room A and B		Co-chairs: A. Younes, New York, NY (USA) and M. Dreyling, Munich (Germany)
08:30	124	PRIMARY ANALYSIS RESULTS OF THE SINGLE-ARM PHASE II STUDY OF MOR208 PLUS LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (L-MIND) G. Salles, Lyon (France)
08:45	125	BET INHIBITOR RG6146, VENETOCLAX, AND RITUXIMAB IS A HIGHLY ACTIVE REGIMEN IN RELAPSED/REFRACTORY (R/R) DLBCL: INITIAL REPORT OF PHASE 1B SAFETY, BIOMARKER, AND RESPONSE DATA M. Dickinson, Melbourne (Australia)
09:00	126	POLATUZUMAB VEDOTIN (POLA) + OBINUTUZUMAB (G) + LENALIDOMIDE (LEN) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL): PHASE IB/II INTERIM ANALYSIS A. McMillan, Nottingham (UK)
09:15	127	THE PI3KΔ INHIBITOR ME-401 ± RITUXIMAB IN RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL), CHRONIC LYMPHOCYTIC LEUKEMIA (CLL), AND SMALL LYMPHOCYTIC LYMPHOMA (SLL) A.D. Zelenetz, New York, NY (USA)
09:30	128	INVESTIGATING SAFETY AND PRELIMINARY EFFICACY OF AFM13 PLUS PEMBROLIZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA AFTER BRENTUXIMAB VEDOTIN FAILURE S.M. Ansell, Rochester, MN (USA)
09:45	129	TARGETING THE PERIPHERAL T-CELL LYMPHOMA (PTCL) EPIGENOME WITH ORAL 5-AZACYTIDINE AND ROMIDEPSIN: RESULTS AND CLINICAL-MOLECULAR CORRELATIONS FROM A PHASE 2 STUDY L. Falchi, New York, NY (USA)
10:15–11:15 Room A and B		**"FOCUS ON" SESSION - INDOLENT NON-FOLLICULAR LYMPHOMA** Chair: G.S. Nowakowski, Rochester, MN (USA)
10:15	130	EARLY PROGRESSION OF DISEASE (POD24) PREDICTS SHORTER SURVIVAL IN MALT LYMPHOMA PATIENTS RECEIVING SYSTEMIC TREATMENT A. Conconi, Ponderano (Italy)
10:25	131	INTRALESIONAL RITUXIMAB SUPPLEMENTED WITH AUTOLOGOUS SERUM IN RELAPSED CD20+ INDOLENT LYMPHOMAS OF THE CONJUNCTIVA: ACTIVITY AND SAFETY RESULTS OF THE "IRIS" TRIAL A.J. Ferreri, Milan (Italy)
10:35	132	MULTI-OMICS LANDSCAPE OF SPLENIC MARGINAL ZONE LYMPHOMA (SMZL) - INTERIM ANALYSIS OF IELSG46 STUDY A. Bruscaggin, Bellinzona (Switzerland)
10:45	133	UMBRALISIB MONOTHERAPY DEMONSTRATES EFFICACY AND SAFETY IN PATIENTS WITH RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA: A MULTICENTER, OPEN-LABEL, REGISTRATION DIRECTED PHASE 2 STUDY P.L. Zinzani, Bologna (Italy)
10:55	134	IBRUTINIB FOR THE TREATMENT OF BING-NEEL SYNDROME: A RETROSPECTIVE, MULTICENTER STUDY J. Castillo, Boston, MA (USA)
11:05	135	IBRUTINIB MONOTHERAPY PRODUCES LONG-TERM DISEASE CONTROL IN PREVIOUSLY TREATED WALDENSTROM'S MACROGLOBULINEMIA: FINAL REPORT OF THE PIVOTAL TRIAL (NCT01614821) S.P. Treon, Boston, MA (USA)
11:15–11:40 Room A and B		**15-ICML HIGHLIGHTS** 🎬 "TAKE HOME MESSAGES" J.W. Friedberg, Rochester, NY (USA)

11:40–11:50	CLOSURE AND FAREWELL F. Cavalli, Bellinzona (Switzerland)
13:30–18:00 Room B	**IV INTERNATIONAL WORKSHOP ON CANINE LYMPHOMA - HOW TO STAGE CANINE LYMPHOMA IN 2019** Co-chairs: L. Aresu, Turin (Italy), S. Comazzi, Milan (Italy), F. Guscetti, Zurich (Switzerland) and L. Marconato, Bologna (Italy) Organized by the European Canine Lymphoma Network **open to all 15-ICML attendees**

🎬 **This icon denotes presentations that will be audio- and video-recorded and available online, only for 15-ICML attendees, starting from July 2019, thanks to an unrestricted grant.**

SUPPLEMENT ARTICLE

WILEY

SATELLITE SYMPOSIUM PROGRAM AND AGENDA
(as of May 15, 2019)

Tuesday, June 18, 2019

13:30–15:00	*2 parallel symposia*
Room B I	**KITE, A GILEAD COMPANY** **CAR T: FROM BED TO BENCH AND BACK AGAIN** Chair: C. Roddie, London (UK) The journey of CAR T therapy from apheresis to processing and back for infusion is complex with many considerations including logistics and GMP-compliance requirements. Furthermore, there are challenges associated with scalability including the ability to increase manufacturing capacity without compromising quality. This symposium will discuss many of the key considerations associated with manufacturing CAR T therapies and explore potential methods to overcome them including automation. This will help ensure successful and timely delivery of CAR T to as many patients as possible. Use of non-conforming or out of specification products in the clinic will also be discussed.
	INTRODUCTION C. Roddie, London (UK)
	OVERVIEW OF DEVELOPMENT JOURNEY: FROM BENCH TO BEDSIDE J. Rossi (United States)
	FROM PATIENT TO COMMERCIAL PRODUCTION: APHERESIS TO SAMPLE SHIPPING C. Roddie, London (UK)
	FROM SAMPLE RECEIPT TO CAR T PRODUCT C. Shen and L. van de Wiel (The Netherlands)
	PRODUCT RELEASE TESTS: HELPING ENSURE PATIENT SAFETY AND GUARANTEEING QUALITY C. Chabannon, Marseilles (France)
	SCALING CAR T FOR A GMP STANDARD PRODUCT C. Roddie, London (UK)
Room B II	**PFIZER ONCOLOGY** **RITUXIMAB BIOSIMILAR: AN OPPORTUNITY TO FOSTER INNOVATION IN LYMPHOMA TREATMENT** Chair: J. Sharman, Eugene, OR (USA) Rituximab based therapies is in many instances the standard-of-care approach for patients with FL, DLBCL and CLL. In some patients Chemo-free Rituximab combination therapy may be the most appropriate. However, the increase cost of biologics could potentially be a limiting factor to improve patient's outcomes world-wide. The utilization of Rituximab Biosimilar may offer the opportunity to upgrade patient access to expensive treatments. In addition, given the landscape of the Biosimilars field, rigorous and well-designed RWE Biosimilar studies are critical to address data gaps and obtain coverage upon evidence generation. The adoption of Rituximab Biosimilar may help to meet high medical needs while maintaining affordability.
13:30	WELCOME AND INTRODUCTION J. Sharman, Eugene, OR (USA)
13:40	BIOSIMILAR: "DO BIOSIMILARS HAVE SIMILAR SAFETY PROFILE AND EFFICACY"? CURRENT PERSPECTIVE J. Goncalves, Lisboa (Portugal)
14:00	REAL WORD EVIDENCE IN BIOSIMILARS. DECISION MAKING IN THE REAL-WORLD A. Mato, New York, NY (USA)
14:20	RITUXIMAB BIOSIMILAR IN FOLLICULAR LYMPHOMA. EARLY USE OF RITUXIMAB J. Sharman, Eugene, OR (USA)
14:40	PANEL DISCUSSION All
16:00–17:30	*3 parallel symposia*

Room A	**NOVARTIS ONCOLOGY** **MAXIMIZING CLINICAL BENEFIT IN LYMPHOMAS: EXPLORING THE UTILITY OF CAR-T CELL THERAPY** Chair: U. Jäger, Vienna (Austria) In the satellite symposium "Maximizing Clinical Benefit in Lymphomas: Exploring the Utility of CAR-T Cell Therapy," Dr. Ulrich Jäger (chair) and additional faculty will lead an interactive discussion regarding the role of CAR-T cell therapy in lymphomas. Key themes addressed will include defining the diffuse large B-cell lymphoma continuum of care and best practices for adverse event management; in addition, the potential future utility of CAR-T cell therapy in non-Hodgkin lymphoma –including combination partners, use in earlier lines of therapy, and role for pediatric patients– will be covered.
16:00–16:05	INTRODUCTIONS AND OPENING REMARKS U. Jäger, Vienna (Austria)
16:05–16:25	DEFINING THE UTILITY OF CAR-T CELL THERAPY IN THE DLBCL CONTINUUM OF CARE U. Jäger, Vienna (Austria)
16:25–16:45	EXPLORING ADDITIONAL ROLES FOR CAR-T CELL THERAPY IN NHL A. Sureda, Barcelona (Spain)
16:45–17:00	RATIONALE AND FUTURE DIRECTIONS FOR CAR-T CELL THERAPY IN PEDIATRIC NHL K. Curran, New York, NY (USA)
17:00–17:15	PRACTICAL CONSIDERATIONS FOR TOXICITY MANAGEMENT WITH CAR-T CELL THERAPY S. Schuster, Philadelphia, PA (USA)
17 :15–17:25	PANEL DISCUSSION AND Q&A All
17:25–17:30	CLOSING REMARKS U. Jäger, Vienna (Austria)
Room B I	**BRISTOL-MYERS SQUIBB** **RATIONALE: RESEARCH AND NEW THERAPEUTIC APPROACHES–I-O NOVEL AGENTS ADVANCING LYMPHOMA EXPECTATIONS** Chair: P.L. Zinzani, Bologna (Italy) This symposium, sponsored by Bristol-Myers Squibb, describes recent advances in treating patients with lymphoma using immuno-oncology (I-O) agents and the utilization of biomarkers to further understand the underlying disease biology and inform novel targeting strategies. Following an introduction to I-O clinical trial advances and ongoing investigations, there will be a discussion of recent key data in salvage and maintenance settings and their potential impact on post-transplant treatment. The final presentation will focus on the potential of biomarkers in lymphoma to inform future clinical trials. A question-and-answer session will provide an opportunity for the participants to interact with the faculty experts.
16:00–16:05	WELCOME AND INTRODUCTIONS P.L. Zinzani, Bologna (Italy)
16:05–16:25	ONGOING IMMUNO-ONCOLOGY EXPLORATIONS IN LYMPHOMA P.L. Zinzani, Bologna (Italy)
16:25–16:45	OPTIMIZING PERI-TRANSPLANT THERAPY WITH IMMUNO-ONCOLOGY A. Herrera, Duarte, CA (USA)
16:45–17:05	BIOMARKER DISCOVERY IN LYMPHOMA B. Chapuy, Göttingen (Germany)
17:05–17:25	OPEN DISCUSSION WITH THE EXPERTS All
17:25–17:30	CLOSING REMARKS P.L. Zinzani, Bologna (Italy)
Room B II	**KITE, A GILEAD COMPANY** **CAR T THERAPY: A CLOSER LOOK AT THE SCIENCE BEHIND THE CELLS** Chair: M. Topp, Würzburg (Germany) The science surrounding CAR T response and safety profiles is still emerging. During this highly interactive symposium, factors involved in these outcomes including biomarkers of response to treatment as well as the potential underlying mechanisms for common toxicities will be discussed. This symposium will also look at future developments and see how outcomes for patients may be improved with CAR T technologies including third generation-, dual antigen specific-CARs and TRUCKs. We encourage you to take the opportunity to ask our experts questions and learn more about the scientific advancements for these novel therapies for patients treated with CAR T.
	INTRODUCTION AND OVERVIEW M. Topp, Würzburg (Germany)

	INTEGRATING KEY TRANSLATIONAL FINDINGS WITH PATIENT OUTCOMES C. Bonini, Milan (Italy)
	UNDERSTANDING FACTORS LEADING TO NON-RESPONSES M. Topp, Würzburg (Germany)
	Q&A AND PANEL DISCUSSION All
	THE FUTURE OF CAR T THERAPY K. Peggs, London (UK)
	Q&A AND PANEL DISCUSSION All
18:30–20:00	*4 parallel symposia*
Room A	**ROCHE** **ANTIBODY THERAPIES FOR PATIENTS WITH DLBCL: WHAT DOES THE FUTURE HOLD?** Chair: L.H. Sehn, Vancouver B.C. (Canada) While many patients with diffuse large B-cell lymphoma (DLBCL) can be cured with current front-line therapy, a significant proportion relapse or are refractory to treatment. High-dose chemotherapy and stem-cell transplantation are possible for some of these patients, but many are ineligible due to co-morbidities or disease refractory to chemotherapy; these patients face a dismal outcome. An international faculty of experts will discuss treatment and management of both front-line and relapsed/refractory DLBCL, with a focus on novel antibody therapies. Join us to examine how the DLBCL landscape may evolve in the near future as new data and treatment options become available.
18 :30–18:35	INTRODUCTION L.H. Sehn, Vancouver B.C. (Canada)
18 :35–18:45	WHAT OPTIONS DO OUR PATIENTS HAVE FOR FIRST-LINE TREATMENT? A. Lopez Guillermo, Barcelona (Spain)
18:45–18:55	WHAT'S NEXT FOR PATIENTS WHO RELAPSE OR ARE REFRACTORY TO TREATMENT? M.J. Matasar, New York, NY (USA)
18:55–19:10	CAN NOVEL ANTIBODY THERAPIES IMPROVE OUTCOMES FOR PATIENTS WITH R/R DLBCL? F. Morschhauser, Lille (France)
19:10–19:25	POLATUZUMAB VEDOTIN: CLINICAL DATA IN R/R DLBCL L.H. Sehn, Vancouver B.C. (Canada)
19 :25-19:40	WHAT MIGHT THE FUTURE HOLD FOR DLBCL TREATMENT STRATEGIES? A. McMillan, Nottingham (UK)
19:40–19:55	PANEL DISCUSSION All
19:55–20:00	CLOSING REMARKS L.H. Sehn, Vancouver B.C. (Canada)
Room B I	**BAYER** **PRECISION MEDICINE IN MALIGNANT LYMPHOMA: IS IT A REALITY?** Chair: M. Ghielmini, Bellinzona (Switzerland) Precision medicine has traditionally been a personalized approach to the treatment of solid tumors with the advent of biomarker-driven strategies. However, when it comes to the treatment of malignant lymphoma, is precision medicine a reality? Join the esteemed faculty Dr. Michele Ghielmini, Dr. Margaret Shipp, Dr. Louis Staudt, and Professor Martin Dreyling in their invigorating exploration of genetic heterogeneity in aggressive lymphoma, clinical exploration of precision medicine in DLBCL, and enrichment strategies in indolent lymphoma with the aim of uncovering whether precision medicine is a reality in malignant lymphoma.
	WELCOME AND OPENING REMARKS M. Ghielmini, Bellinzona (Switzerland)
	GENETIC HETEROGENEITY IN AGGRESSIVE LYMPHOMA AND POTENTIAL THERAPEUTIC IMPLICATIONS M.A. Shipp, Boston, MA (USA)
	CLINICAL EXPLORATION OF PRECISION MEDICINE IN DLBCL L.M. Staudt, Bethesda, MD (USA)
	PATIENT ENRICHMENT STRATEGIES AND THERAPY SELECTION IN MALIGNANT LYMPHOMAS M. Dreyling, Munich (Germany)
	PANEL DISCUSSION/Q&A Chair: M. Ghielmini, Bellinzona (Switzerland)

Room B II	**TAKEDA ONCOLOGY** **ON THE FRONTLINE: MANAGING PATIENTS WITH CD30+ HL AND PTCL** Chair: M. Hutchings, Copenhagen (Denmark) This satellite symposium supported by Takeda Oncology aims to highlight the current treatment landscape and recent developments in frontline CD30+ HL and PTCL. The latest data from studies in frontline CD30+ HL and PTCL will be discussed, as well as challenges and management strategies for patients in these settings. This symposium will be highly interactive with opportunities for the audience to tailor the topic of discussion during each presentation. There will also be a dedicated question and answer session to enable open interaction between the participants and the faculty.
18:30–18:35	WELCOME AND INTRODUCTION M. Hutchings, Copenhagen (Denmark)
18:35–18:55	TAILOR-THE-TOPIC: HL DISCUSSIONS M. Hutchings, Copenhagen (Denmark)
18:55–19:15	THE LATEST RESULTS IN THE MANAGEMENT OF FRONTLINE CD30+ HL J.M. Connors, Vancouver BC (Canada)
19:15–19:35	CURRENT LANDSCAPE AND RECENT DEVELOPMENTS IN THE FRONTLINE MANAGEMENT OF CD30+ PTCL S.M. Horwitz, New York, NY (USA)
19:35–19:55	PANEL Q&A Faculty, facilitated by M. Hutchings, Copenhagen (Denmark)
19:55–20:00	SUMMARY AND CLOSE M. Hutchings, Copenhagen (Denmark)
Auditorium, **USI Università**	**LYMPHOMA HUB** **NEW CHEMOTHERAPY-FREE APPROACHES FOR THE TREATMENT OF LYMPHOID MALIGNANCES** Chair and co-chair: G. Salles, Lyon (France) and A. Younes, New York, NY (USA) This symposium brings together an international panel of experts who will discuss the novel chemotherapy-free treatment approaches for lymphoid malignancies. Presentations will focus on diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and chronic lymphocytic lymphoma, navigating the rapidly evolving treatment landscapes. The new chemotherapy-free treatment options will be explored alongside the current standards of care. Each presentation will be followed by a question and answer session to allow for discussion with the expert panel. Come and join the debate on whether it is possible to switch to the chemotherapy-free agents. For more information visit: https://icml.lymphomahub.com/en
18:30–18:35	OBJECTIVES AND INTRODUCTIONS G. Salles, Lyon (France)
18:35-18:45	DLBCL–CHEMOTHERAPY-FREE REGIMENS: PROS AND CONS U. Jäger, Vienna (Austria)
18:45 –18:55	ROUND TABLE ON DLBCL All
18:55 –19:05	FL–CHEMOTHERAPY-FREE REGIMENS: PROS AND CONS N.H. Fowler, Houston, TX (USA)
19:05 –19:15	ROUND TABLE ON FL All
19:15–19:25	MCL–CHEMOTHERAPY-FREE REGIMENS: PROS AND CONS S. Rule, Plymouth (UK)
19:25 –19:35	ROUND TABLE ON MCL All
19:35–19:45	CLL–CHEMOTHERAPY-FREE REGIMENS: PROS AND CONS M. Hallek, Cologne (Germany)
19:45–19:55	ROUND TABLE ON CLL All
19:55–20:00	MEETING CONCLUSION A. Younes, New York, NY (USA)

Wednesday, June 19, 2019

18:30–20:00	*3 parallel symposia*
Room A	**JANSSEN PHARMACEUTICAL COMPANIES OF JOHNSON & JOHNSON** **CHALLENGING THE STANDARDS OF CARE IN THE MANAGEMENT IN B-CELL LYMPHOMAS** Co-chairs: C. Buske, Ulm (Germany) and S. Rule, Plymouth (UK) Therapeutic advances in lymphoma have been made over many decades. A deeper understanding of disease pathogenesis guided the development of targeted therapies for patients with MCL and WM. Consequently, providing tolerable and curative therapies to many lymphoma patients is now possible. However, some specific challenges still remain, including limited investigations into rare lymphoma subtypes and using backbone chemotherapy regimens for initial therapy. Our faculty will discuss studies challenging current standards of care and the potential to improve patient outcomes in various B-cell lymphomas.
18:30-18:40	WELCOME AND INTRODUCTION C. Buske, Ulm (Germany)
18:40-19:00	HOW ARE TARGETED THERAPIES IMPACTING THE MANAGEMENT OF PATIENTS WITH MANTLE CELL LYMPHOMA (MCL)? S. Rule, Plymouth (UK)
19:00–19:20	CAN WE IMPROVE ON R-CHOP FOR PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)? G. Lenz, Münster (Germany)
19:20–19:40	DOES CHEMOTHERAPY STILL HAVE A ROLE IN WALDENSTRÖM'S MACROGLOBULINEMIA (WM)? S.P. Treon, Boston, MA (USA)
19:40–20:00	PANEL DISCUSSION AND CLOSING REMARKS C. Buske, Ulm (Germany) and all
Room B	**MEDSCAPE EDUCATION** **CHALLENGING CURRENT PARADIGMS IN CLL: TIME AND TREATMENT** *Supported by an independent educational grant from AbbVie* Chair: P. Hillmen, Leeds (UK) The concept of time-limited therapy is not new; chemotherapy regimens are of fixed duration. However, recent years have seen the emergence of therapies, such as Bruton tyrosine kinase (BTK) inhibitors, which require continuous treatment. In contrast, B-cell lymphoma 2 (Bcl-2)-inhibitor combinations have been developed as 2-year and 1-year fixed-duration therapies, offering new time-limited treatment options. Furthermore, both approaches are–or will potentially be–approved in both front-line and relapse settings, challenging both initial treatment selection and sequencing decisions. This symposium explores the current and emerging treatment paths for patients with treatment-naive chronic lymphocytic leukemia (CLL) and the impact of initial choices on treatment options in relapse.
18:30–18:40	WELCOME AND INTRODUCTION P. Hillmen, Leeds (United Kingdom)
18:40-19:00	NOVEL CONCEPTS IN CLL PRACTICE P. Hillmen, Leeds (United Kingdom)
19:00-19:20	CURRENT AND EMERGING PARADIGMS: TIME-LIMITED THERAPY B. Eichhorst, Cologne (Germany)
19:20-19:40	CURRENT AND EMERGING PARADIGMS: CHRONIC THERAPY M. Davids, Boston, MA (USA)
19:40-20:00	CHALLENGES IN PRACTICE: INITIAL TREATMENT SELECTION AND SEQUENCING THERAPY Panel and Audience Debate
Auditorium, USI Università	**SANDOZ ONCOLOGY** **VARIABILITY OF BIOLOGICS AND ITS IMPACT ON BIOSIMILAR DEVELOPMENT** Chair: P. Cornes, Bristol (UK) Biologics are highly complex to manufacture and their immunogenicity, tolerability, and efficacy profiles can be affected by significant manufacturing process changes. As such, manufacturing changes must be carefully monitored at every step, in order to ensure the correct product identity throughout the lifecycle. Biosimilars are developed using highly sensitive analytical methods and tailored clinical programs. The advent of biosimilars allowed for a much more detailed analysis of batch-to-batch variability and manufacturing shifts of reference medicines. Recently, some shifts in quality attributes of reference medicines have been reported by biosimilar manufacturers. The faculty will discuss the potential impact of biologic variability on clinical outcomes and biosimilar development. (References available on request)
18:30–18:45	THE REGULATORY PERSPECTIVE H. Schellekens, Utrecht (The Netherlands)

18:45–19:00	THE ANALYTICAL PERSPECTIVE M. Schiestl, Kundl (Austria)
19:00–19:15	THE CLINICIAN'S PERSPECTIVE W. Jurczak, Krakow (Poland)
19:15–19:30	THE PATIENT PERSPECTIVE P. Cornes, Bristol (UK)
19:30–20:00	DEBATE AND Q&A All faculty

Thursday, June 20, 2019

18:30–20:00	*2 parallel symposia*
Room A	**CELGENE** **INDIVIDUALIZING TREATMENT AND EMERGING THERAPIES IN B-CELL MALIGNANCIES** Chair: U. Vitolo, Turin (Italy) Recent clinical developments are transforming the treatment of indolent and aggressive B-cell malignancies. Chemotherapy-free therapies are altering the therapeutic landscape of both frontline and relapsed/refractory follicular lymphoma. Additionally, frontline treatment of diffuse large B-cell lymphoma is becoming increasingly individualized with a focus on selecting optimal therapies according to cell of origin. Meanwhile, the emergence of CAR T therapies for the treatment of various non-Hodgkin lymphomas and chronic lymphocytic leukemias have the potential to shift treatment paradigms entirely. Key emerging data in B-cell malignancies will be highlighted and discussed by experts in the field.
18:30-18:35	WELCOME AND INTRODUCTIONS U. Vitolo, Turin (Italy)
18:35-18:55	TREATMENT IN THE CHEMOTHERAPY-FREE ERA IN FRONT-LINE AND RELAPSED AND REFRACTORY FOLLICULAR LYMPHOMA J.P. Leonard, New York, NY (USA)
18:55-19:15	OPTIMIZING FRONTLINE DLBCL TREATMENT: THE ROLE OF CELL OF ORIGIN U. Vitolo, Turin (Italy)
19:15-19:35	EMERGING ROLE OF CAR T THERAPIES IN THE TREATMENT OF NHL AND CLL D.G. Maloney, Seattle, WA (USA)
19:35–20:00	CLOSING AND Q&A U. Vitolo, Turin (Italy) and All
Room B	**MORPHOSYS** **SURVIVAL, SAFETY, SIMPLICITY: TRANSFORMING TREATMENT SEQUENCING IN DLBCL** Co-chairs: B.D. Cheson, Washington DC (USA) and G. Salles, Lyon (France) Join us for this interactive symposium as we explore DLBCL treatment approaches: the progress made, remaining challenges, and the potential future of the treatment landscape. With an emphasis on the patient journey, we will seek to understand the issues faced beyond the first-line treatment setting, and hear expert insights to navigate real-world treatment decision-making challenges. In addition, through advances in DLBCL disease understanding, we will provide perspectives on how novel treatment approaches may be utilized to achieve new treatment strategies for patients who experience relapsed or refractory DLBCL.
18:30–18:35	WELCOME AND INTRODUCTION Co-chairs: B.D. Cheson, Washington DC (USA) and G. Salles, Lyon (France)
18:35–18:45	DLBCL TREATMENT LANDSCAPE: CURRENT PERSPECTIVE G.S. Nowakowski, Rochester, MN (USA)
18:45–19:00	THE PATIENT JOURNEY: TREATMENT DECISION MAKING IN REAL-WORLD PRACTICE J.R. Westin, Houston, TX (USA)
19:00–19:10	PANEL DISCUSSION All
19:10–19:25	THE FUTURE FOR DLBCL: TRANSFORMING OUR APPROACHES AND TREATMENT SEQUENCING? A. Davies, Southampton (UK)
19:25-19:40	TARGETING CD19: A NOVEL ANTIBODY STRATEGY G. Salles, Lyon (France)

19:40–19:55	PANEL DISCUSSION All
19:55–20:00	SUMMARY AND CLOSE B.D. Cheson, Washington DC (USA)

Friday, June 21, 2019

Room A 18:30–19:30	**ONCOLOGY INSTITUTE OF SOUTHERN SWITZERLAND–IOSI** **"THE BIG DEBATE: POINT COUNTER POINT"** **ARE NEW EXPENSIVE ANTI-LYMPHOMA DRUGS WORTH THE MONEY?** Chair: M. Ghielmini, Bellinzona (Switzerland) *Supported by Gilead Sciences who provided funding.* Often targeted therapy, immunotherapy and CAR-T cells are registered at high price for indications for which they have at most demonstrated an increase in PFS and not in OS. The Big Debate, organized by the Oncology Institute of Southern Switzerland (IOSI) has become a tradition, and this year will discuss this issue. In three short debates, 6 distinguished speakers (10 minutes each) will argue, for three different classes of drugs, if the results of new and expensive treatment do or not justify their very high costs.
	BCR PATHWAY INHIBITORS Yes: M. Dreyling, Munich (Germany) vs No: A. Davies, Southampton (UK)
	IMID'S Yes: S. Rule, Plymouth (UK) vs No: G. Salles, Lyon (France)
	CART-T CELLS Yes: A. Sureda, Barcelona (Spain) vs No: L.H. Sehn, Vancouver B.C. (Canada)

WILEY

ORAL PRESENTATIONS

KEYNOTE LECTURES

001
NEXT GENERATION CAR T CELLS FOR LYMPHOMA AND BEYOND

C.H. June

Perelman School of Medicine, University of Pennsylvania, Center for Cellular Immunotherapies, Philadelphia, PA, United States

Engineered T cells that encode transgenic T cell receptors (TCR) or chimeric antigen receptors (CAR) are increasingly being tested is a new modality for cancer immunotherapy. In this presentation we will review emerging patterns of efficacy and toxicity after adoptive cell transfer (ACT), with a focus on blood cancers. Striking efficacy has been observed in acute and chronic B cell leukemia and lymphoma. More unexpectedly, strong antitumor effects are being observed in multiple trials in patients with advanced refractory and relapsed myeloma. In some cases, toxicity has been predicted in preclinical models. In other cases, toxicity was only uncovered after results from Phase 1 clinical trial results were in hand. Onset of toxicity can be immediately observed following infusion of cells or maybe delayed. Toxicity usually occurs coincident with peak (Cmax) levels of adoptively transferred cells. Today with more than 1,000 patients having been infused with genetically engineered human T cells, genotoxicity has not been reported. To date, the induction of irAE appears to be less than with checkpoint therapies, although more experience with ACT is required to determine the ultimate incidence of autoimmune toxicities.

Keywords: T-cell receptor (TCR).

Disclosures: June, C: Research Funding: *Parker Institute for Cancer Immunotherapy, NIH/NCI, Tmunity Therapeutics.*

002
PRECISION EPIGENETIC THERAPY FOR B-CELL LYMPHOMA

A. Melnick

Medicine, Weill Cornell Medical College, New York City, United States

Mutation in epigenetic modifier genes is one of the hallmarks of lymphomas such as DLBCL and FL. Invariable the genes mutated play critical roles in the B-cells during the germinal center response and their mutation results in aberrant retention of germinal center features. Somatic mutations of EZH2 result in enzymatic gain of function leading to aberrant silencing of bivalent promoters affecting genes involved in B-cell terminal differentiation and cell cycle checkpoints. CREBBP and EP300 are tumor suppressors in B-cell lymphomas. Loss of function of these genes drives lymphomagenesis through aberrant silencing of gene enhancers linked to antigen presentation and germinal center exit programs. Notably mutations in CREBBP and EZH2 result in loss of immune surveillance due to epigenetic silencing of MHC class II and MHC class I proteins. Loss of function mutations of the histone methyltransferase KMT2D disrupts enhancer monomethylation of H3K4, resulting in attenuated response to extracellular signals derived from T-cells such as CD40. Loss of function mutations of TET2 occur in ~10% of patients with DLBCL and drive transformation of B-cells due to reduction of enhancer DNA hydroxymethylation, which results in their loss of function. The principle biological effect of TET2 loss of function in the cell of origin is to block differentiation, which results in their eventual malignant transformation. We have identified specific epigenetic therapies that antagonize the effects of each of these mutations and can be used as precision therapy for these patients as well as adjuvants to immunotherapies by restoring the ability of T-cells to recognize lymphoma cells.

Keywords: B-cell lymphoma; diffuse large B-cell lymphoma (DLBCL); EZH2.

Disclosures: Melnick, A: Employment Leadership Position: *Janssen Biotech*; Consultant Advisory Role: *Consultant*; Stock Ownership: *None*; Honoraria: *N/A*; Research Funding: *Yes, Research Support.*

003
THIRTY YEARS OF T-CELL LYMPHOMAS

P. Gaulard

Pathology, Hôpital Henri Mondor, Creteil, France

Peripheral T-cell lymphomas (PTCLs) are characterized by a usually aggressive clinical course. Owing to their rarity and diversity, most PTCLs remain a diagnostic issue and a therapeutic challenge. However, these last 30 years have been a major break in the field of PTCL. From morphologically based classification, the first PTCL entities started to be recognized in the 1980s. Since then, the concept that malignant lymphomas relate to a cell of origin together with the recognition of new recurrent genetic alterations led to the delineation of

around 30 distinct clinicopathological PTCL entities in the current WHO classification.

Follicular helper T cells (TFH) appear as the cell counterpart of a major proportion of PTCL worldwide, including angio-immunoblastic T-cell lymphoma and other nodal lymphomas with a TFH phenotype; the later disclose a rather homogeneous mutational landscape which recapitulates a multi-step oncogenic process associating epigenetic deregulation (*TET2 +/- DNMT3A*mutations, often at early stages), and second hit mutations affecting the T-cell receptor signaling pathway (*RHOA*,..). This oncogenic model has been confirmed in mouse models and opens the field for using emerging epigenetic- or signaling-modulating therapies. Among anaplastic large cell lymphoma (ALCL), those with ALK rearrangement constitute the best-delineated entity. ALK-negative ALCLs appear genetically heterogeneous with translocation-associated subsets (DUSP22, TP63,...) found in both systemic and cutaneous types. DUSP22-rearranged ALK-negative ALCL likely constitutes a unique category with a distinct signature and a good outcome. Except for DUSP22-rearranged ALCL, a constitutive activation of STAT3 is shared by ALK-positive and ALK-negative ALCLs, including the newly described usually indolent breast implant-associated ALCL. Lymphomas derived from cells of the innate immune system affect preferentially extranodal sites, which are continuously exposed to various antigens. Chronic immunosuppression and genetic background may also play a role. There is evidence of plasticity in terms of cellular derivation (NK, Tγδ,Tαβ) within a single entity. Most of these tumors also harbor a combination of mutations affecting different classes of epigenetic modifyers, and mutation-induced activation of the JAK-STAT pathway which may serve as potential therapeutic targets. While most of these proliferations are highly malignant, some more indolent forms have been identified, arising in the skin or the GI tract. Despite significant progress in the understanding of PTCLs, 20-30% of PTCL patients remain "unspecified", a basket category which may contain emerging (GATA3 or T-bet) subtypes.

Most PTCL probably harbor distinct therapeutic vulnerabilities supporting the need for biologically-oriented therapeutic strategies to improve patient's outcome.

Keywords: peripheral T-cell lymphomas (PTCL).

Disclosures: GAULARD, P: Consultant Advisory Role: *Takeda*; Honoraria: *Takeda, Roche*; Research Funding: *Takeda, Celgene, Innate Pharma.*

PLENARY SESSION

004
IDENTIFYING MUTATIONS ENRICHED IN RELAPSED-REFRACTORY DLBCL TO DERIVE GENETIC FACTORS UNDERLYING TREATMENT RESISTANCE

C. Rushton[1] | M. Alcaide[1] | M. Cheung[1] | N. Thomas[1] | S. Arthur[1] | N. Michaud[2] | S. Daigle[2] | J. Davidson[1] | K. Bushell[1] | S. Yu[1] | M. Jain[3] | L. Shepherd[4] | M. Crump[3] | K. Mann[5] | J. Kuruvilla[3] | S. Assouline[6] | N. Johnson[5] | D.W. Scott[7] | R.D. Morin[1]

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Introduction: Diffuse Large B-cell Lymphoma (DLBCL) the most common subtype of Non-Hodgkin Lymphoma and is characterized by genetic and clinical heterogeneity. In relapsed/refractory DLBCL (rrDLBCL) cases, where frontline treatment is unsuccessful, patient prognosis is extremely poor, with 2-year overall survival of 20-40%. While numerous treatments are under investigation to improve patient outcomes, their success has been limited as the genetic mechanisms underpinning treatment resistance are largely unknown. Identifying genomic alterations associated with relapse may open new treatment avenues and allow the stratification of patients into subgroups based upon relevant mutations.

Methods: We have collected samples from 134 patients enrolled in three clinical trials (LY17, Obinituzumab-GDP, QCROC2) exploring candidate treatment options for rrDLBCL. For each patient enrolled, blood plasma samples were collected prior to and at several time points following candidate treatment. A combination of exome sequencing and target panel sequencing of lymphoma-associated genes was performed on cell-free DNA extracted from plasma samples and tissue biopsies (where available) obtained upon trial enrollment (relapse). Somatic mutations were identified using Strelka2, and clonal population structure was inferred using PyClone. Mutation prevalence was compared to a large unselected cohort of diagnostic DLBCLs to identify genes enriched for mutations.

Results: Patients with rrDLBCL were enriched for mutations in 5 genes; *TP53* (Q=6.74x10^{-5}), *IL4R* (Q=0.00391), *HVCN1*(Q=0.0729), *RB1* (Q=0.0127) and *MS4A1* (Q=0.0522), with *TP53* mutations previously associated with rrDLBCL. Mutations in *IL4R*may lead to constitutively active JAK/STAT signalling and inferior overall survival in DLBCL. *HVCN1* encodes a voltage-gated proton channel which modulates the B-Cell Receptor (BCR), and truncated *HVCN1* isoforms have been shown to enhance BCR signaling. *MS4A1* encodes CD20, the target of the monoclonal antibody Rituximab, a cornerstone of frontline DLBCL treatment. In several patients, clonal subpopulations with *MS4A1* mutations underwent clonal selection following treatment. These mutations are predicted to either truncate CD20, or destabilize a common transmembrane helix, with 4/15 patients containing mutations affecting Tyrosine 86. We also observed recurrent in-frame

deletions targeting S1680 of *CREBBP*, and although *CREBBP* mutations are associated with treatment resistance in other cancers, the functional effect of this deletion has not been characterized.

Conclusions: DLBCL patients with mutations in relapse-enriched genes are at a higher risk of treatment failure. Mutations in these genes, specifically hotspot deletions, may have power as biomarkers to identify patients at a high risk of relapse and could inform on the mechanism of acquired resistance to components of R-CHOP.

Keywords: CD20; diffuse large B-cell lymphoma (DLBCL); R-CHOP.

Disclosures: Michaud, N: Employment Leadership Position: *Epizyme.*
Daigle, S: Employment Leadership Position: *Epizyme.*

005

ROBUST: First report of phase III randomized study of lenalidomide/R-CHOP (R²-CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma

U. Vitolo[1] | T.E. Witzig[2] | R.D. Gascoyne[3] |
D.W. Scott[3] | Q. Zhang[4] | W. Jurczak[5] |
M. Özcan[6] | X. Hong[7] | J. Zhu[8] | J. Jin[9] |
D. Belada[10] | J.M. Bergua[11] | F. Piazza[12] |
H. Mócikova[13] | A.L. Molinari[14] | D.H. Yoon[15] |
F. Cavallo[16] | M. Tani[17] | K. Izutsu[18] | K. Kato[19] |
M. Czuczman[20] | S. Hersey[20] | A. Kilcoyne[20] |
J. Russo[20] | K. Hudak[20] | J. Zhang[20] |
A. Chiappella[1] | G.S. Nowakowski[2] | on behalf of the ROBUST study investigators

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Introduction: The activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) continues to convey inferior survival despite efforts to enhance outcomes with novel R-CHOP combinations. Phase II studies have suggested that the addition of the immunomodulatory agent lenalidomide to R-CHOP could ameliorate the poor prognostic effect of the ABC phenotype and improve treatment outcome in this subgroup of patients.

Methods: The global phase III ROBUST trial (NCT02285062) is the first to compare lenalidomide/R-CHOP (R²-CHOP) vs placebo/R-CHOP in previously untreated, prospectively selected, CD20+ ABC-type DLBCL. Patients included adults with Ann Arbor stage II-IV disease, IPI score ≥ 2, and ECOG PS ≤ 2. Confirmation of histology and cell-of-origin type were prospectively analyzed from formalin-fixed, paraffin-embedded excisional/surgical or core needle biopsy samples by central pathology using the NanoString Lymphoma Subtyping Test (LST), based on the Lymph2Cx GEP assay (Scott, *Blood* 2014). ABC-DLBCL patients were stratified by IPI score (2 vs ≥ 3), bulky disease (< 7 vs ≥ 7 cm) and age (< 65 vs ≥ 65 y), and randomized 1:1 to

R²-CHOP vs Placebo/R-CHOP
HR = 0.85 (95% CI, 0.63-1.14)
$P = 0.29$

No. of patients at risk								
R²-CHOP	285	221	178	162	119	57	10	0
Placebo/R-CHOP	285	229	187	173	111	55	10	3	0
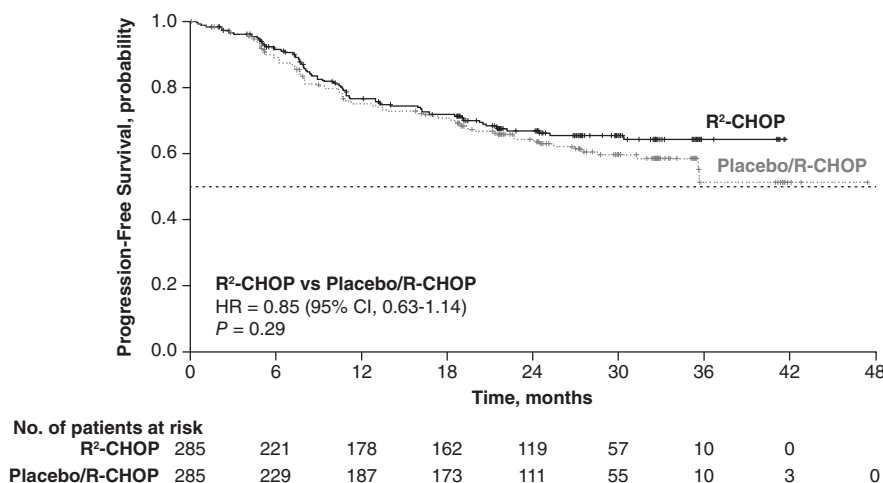
lenalidomide PO 15 mg/d, d1-14/21 + standard R-CHOP21 vs placebo/R-CHOP21 for 6 cycles, with 2 additional, optional doses of rituximab per local practice. The primary endpoint was progression-free survival (PFS) assessed by independent central radiology per 2014 NHL IWG criteria, and defined as time from randomization to PD or death from any cause.

Results: A total of 570 ABC-DLBCL patients met eligibility criteria and were enrolled in ROBUST (n = 285 per arm). Baseline demographics were similar between arms, with a median age for all patients of 65 y (52% ≥ 65 y), 42% IPI 2 score/58% IPI ≥ 3 score, 88% stage III/IV disease, and 34% bulky disease. The primary endpoint of PFS was not met with an HR = 0.85 (95% CI, 0.63-1.14) and P = 0.29; median PFS was not reached for either arm (**Figure**). Positive PFS trends favoring R^2-CHOP over placebo/R-CHOP were observed with disease stage III/IV (HR = 0.81 [95% CI, 0.60-1.10]) and IPI score ≥ 3 (HR = 0.74 [95% CI, 0.53-1.05]). Median EFS was not reached for either arm (HR = 1.04; 95% CI, 0.80-1.34; P = 0.73). At a median follow-up of 27.1 mo (range, 0-47) for survivors, 2-y OS was 79% for R^2-CHOP and 80% for placebo/R-CHOP (medians not reached). ORR was 91% for both arms, with 69% vs 65% CR for R^2-CHOP vs placebo/R-CHOP, respectively. 74% R^2-CHOP and 84% placebo/R-CHOP patients completed 6 cycles of treatment; AEs (mainly neutropenia) were the most common reason for treatment discontinuation. The most common grade 3/4 AEs (≥ 10%) for R^2-CHOP vs placebo/R-CHOP were neutropenia (60% vs 48%), anemia (22% vs 14%), thrombocytopenia (17% vs 11%), leukopenia (14% vs 15%), febrile neutropenia (14% vs 9%), and lymphopenia (11% vs 8%).

Conclusions: Overall, the ROBUST study did not meet the primary endpoint of PFS for R^2-CHOP vs placebo/R-CHOP in previously untreated patients with ABC-DLBCL, although a positive trend favoring R^2-CHOP has been observed in advanced stage and higher risk patients. The safety profile of R^2-CHOP was consistent with those of individual medicines, and no new safety signals were identified with the combination.

006

ADDITION OF LENALIDOMIDE TO R-CHOP (R2CHOP) IMPROVES OUTCOMES IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): FIRST REPORT OF ECOG-ACRIN1412 A RANDOMIZED PHASE 2 US INTERGROUP STUDY OF R2CHOP VS R-CHOP

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Introduction: Lenalidomide has single-agent activity in relapsed DLBCL. Single arm phase I/II trials of lenalidomide with RCHOP (R2CHOP) for untreated DLBCL have shown the regimen to be safe with promising activity, particularly in the activated B-cell-like (ABC) subtype. ECOG-ACRIN trial 1412 (E1412) is a randomized phase II study comparing R2CHOP vs R-CHOP in previously untreated DLBCL.

Methods: Eligible patients were ≥ 18 years, with pathlogically confirmed DLBCL regardless of COO, stage II bulky-IV disease, IPI ≥ 2, ECOG PS ≤ 2 and measurable disease. Patients were randomized 1:1 and stratified by International Prognostic Index (2/3 vs 4/5) and age (<60 vs ≥ 60 y) to lenalidomide PO 25 mg/d, d1-10 q21d + standard RCHOP21 vs RCHOP21 for 6 cycles. Paraffin-embedded tumor tissue from the initial biopsy were analyzed using the NanoString Lymph2Cx GEP assay allowing for outcome analysis in ABC DLBCL. The primary endpoint was progression-free survival (PFS). With anticipated 289 evaluable patients (102 ABC-DLBCL), the study was designed to have 89% power at one-sided 0.1 significance level with 89 PFS events for testing in all patients, and 81% power at one-sided 0.125 significance level with 40 PFS events in ABC DLBCL. Secondary endpoints included response rate and overall survival (OS). Kaplan Meier method was used to estimate PFS and OS, stratified log-rank test and Cox model were used to compare between arms and estimate hazard ratios (HR).

Results: 349 patients were enrolled between 8/2013 to 1/2017; 280 patients (145 R2CHOP, 135 RCHOP) were evaluable (ineligibility was primarily due to central pathology exclusion or lack of diagnostic material for central review); 94 were ABC-DLBCL; 122 GCB-DLBCL and 18 Unclassfied. Baseline patient characteristics are balanced between arms, median age 66 (range 24-92); 61% male; 88% white; 70% stage IV; 34%, 43% and 24% IPI 2, 3 and 4/5, respectively. Toxicity was as expected with R-CHOP; significantly different rates of grade ≥3 adverse events between arms were: diarrhea (6% vs. 0.6% of patients, p=0.005), febrile neutropenia (25% vs. 12% of patients, p=0.003), and thrombocytopenia (36% vs. 12% of patients, p<.0001) in R2CHOP vs R-CHOP arm, respectively. 86% and 85% patients completed 6 cycles of therapy in R2CHOP and RCHOP arms respectively. The overall and complete response rates were 92% and 67% in R-CHOP and 97% (p=0.12) and 72% (p=0.44) in R2-CHOP arm, respectively. With a median follow-up was 2.4 years; R2CHOP was

All patients
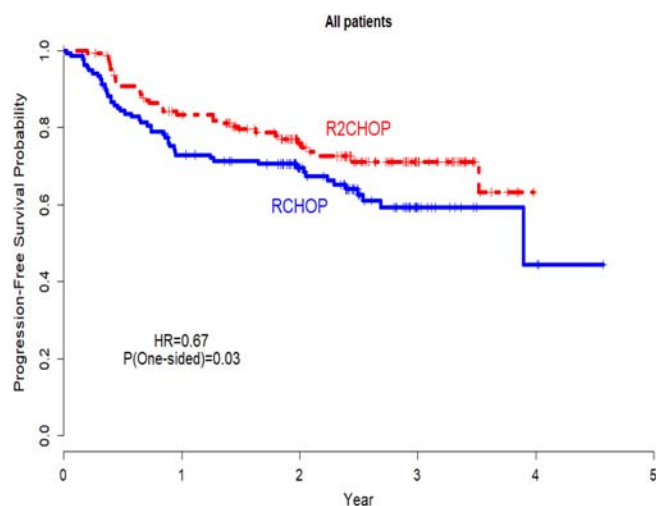
associated with a 33% reduction in risk of progression or death vs RCHOP, HR 0.67 (95% CI 0.44- 1.03), p (one-sided) =0.03 (Figure). The 2-year overall survival was 87% and 80%, respectively. Based on COO, PFS HR for R2CHOP was: 0.68 for ABC, p=0.15, 0.86 for GCB, 0.83 for Unclassified and 0.61 for unknown cases.

Conclusion: The addition of lenalidomide to R-CHOP (R2CHOP) in this phase II study improved PFS in newly diagnosed DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL); gene expression profile (GEP); immunochemotherapy.

Disclores: Nowakowski, G: *Celgene consultancy (personally uncompensated) and research support; MorphoSys consultancy (personally uncompensated), research support, Bayer: consultancy (personally uncompensated) and research support, Curis: research support, Roche: Research support, Genentech: Research support, NanoStrings Technologies: research support.* **Scott, DW:** *Named inventor on a patent licensed to NanoString Technologies [Institution], Research funding: Janssen, Roche/Genentech, NanoString Technologies, Consulting: Janssen, Travel: Celgene.* **Macon, R:** *Celgene research support.* **Leonard, JP:** *Consulting: Sutro, Bayer, Gilead, AstraZeneca, Celgene, Merck, Morphosys, Beigene, Nordic Nanovector, Roche/Genentech, ADC Therapeutics, Sandoz, Karyopharm, Miltenyi, Akcea Therapeutics.* **Kostakoglu, L:** *Roche/Gentech: Research support.* **Kahl, BS:** *Consulting: Celgene, Genentech, Roche, AbbVie, Pharmacyclics, Astra Zeneca.* **Witzig, TE:** *Research support: Celgene, Spectrum, Acerta, Consulting (personally uncompensated): Incyte, Seattle Genetics, Abbvie, Morphosys, Spectrum, Celgene. Consulting personaly compensated: Immune Design, Karyopharm.*

007

IBRUTINIB VERSUS PLACEBO IN PATIENTS WITH ASYMPTOMATIC, TREATMENT-NAÏVE EARLY STAGE CLL: PRIMARY ENDPOINT RESULTS OF THE PHASE 3 DOUBLE-BLIND RANDOMIZED CLL12 TRIAL

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Introduction: So far, treatment of asymptomatic, early stage CLL patients has not been proven beneficial. Ibrutinib is a BTK inhibitor with impressive clinical efficacy in advanced or relapsed CLL. Therefore we wished to evaluate whether ibrutinib prolongs event-free survival (EFS) in early stage CLL patients with increased risk of progression.

Methods: Asymptomatic Binet A patients were stratified according to a recently developed score (Pflug et al., Blood 2014). Patients with intermediate, high and very high risk were randomized 1:1 to receive ibrutinib 420 mg per day or placebo. EFS was defined as time from randomization until occurrence of *active* disease according to iwCLL guidelines, new CLL treatment or death. Secondary endpoints progression free survival (PFS) and time to next treatment (TTNT) were defined as time from randomization until progression/death (PFS) or until the date of initiation of subsequent treatment for CLL (TTNT). Survival will be analyzed later with 60% (N=28) of the required events being reported. Patients with low risk (N=152) were allocated to an observational arm and were not included in primary endpoint analysis.

Results: A total of 182 or 181 patients were assigned to receive ibrutinib or placebo, respectively. At median observation time of 31 months EFS was not reached in the ibrutinib arm and was 47.8 months in the placebo arm (HR 0.25; 95%CI, 0.14 to 0.43; P<0.0001; **Figure 1**). Similarly PFS was not reached for ibrutinib and 14.8 months with placebo (HR 0.18; 95%CI, 0.12 to 0.27). TTNT was longer in the ibrutinib arm (HR 0.21; 095%CI, 0.11 to 0.39).

Figure 1: Event-free survival (intention to treat population)

	total	events	N	%
Ibrutinib	182	18	164	90.1
Placebo	181	55	126	69.9
...	363	73	290	79.9

P median$_{EFS}$ 47.8 vs. NR

P value <0.000; HR 0.248
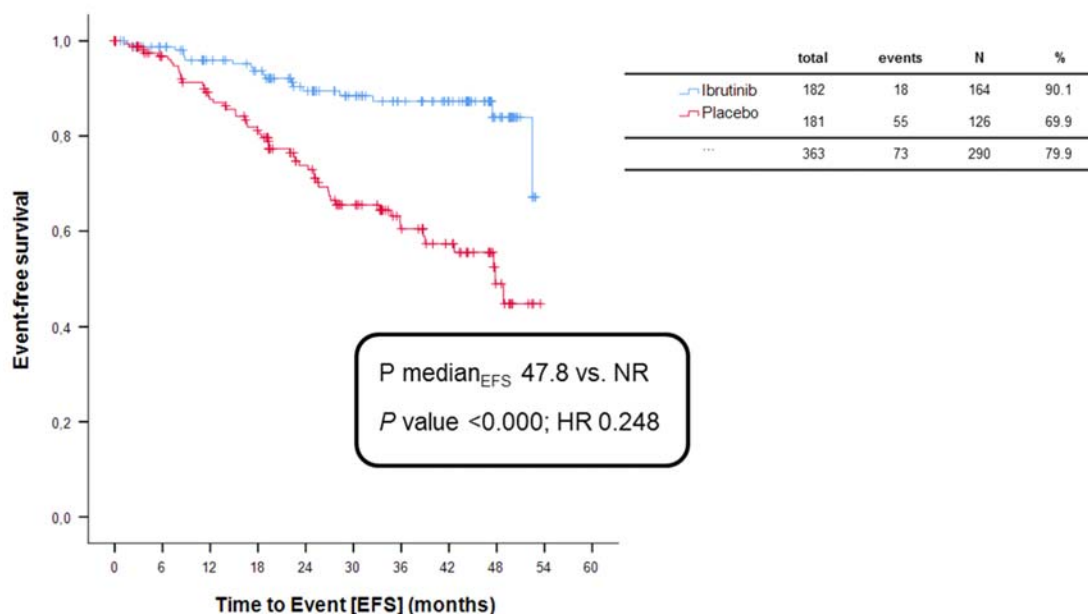
TABLE 1　(S)AEs of particular interest: *number of patients* (*percent*). [3 patients of the placebo-arm received 1 cycle (28 days) of ibrutinib]

	ibrutinib n=185	placebo n=178	*P*-value
Any (S)AE of particular interest	106 (57.3)	71 (39.9)	0.001
Diarrhea	**58 (31.4)**	**44 (24.7)**	n.s.
• CTC 1-2	56 (30.2)	39 (21.9)	
• CTC 3-4	2 (1.1)	5 (2.8)	
Bleeding	**51 (27.6)**	**17 (9.6)**	0.000
• CTC 1-2	45 (24.3)	15 (8.4)	
• CTC 3-4	6 (3.2)	2 (1.2)	
Atrial fibrillation	**33 (17.8)**	**13 (7.3)**	0.003
• CTC 1-2	21 (11.3)	10 (5.6)	
• CTC 3-4	11 (6.5)	3 (1.7)	
Hypertensive disorders	**18 (9.7)**	**7 (3.9)**	0.04
• CTC 1-2	15 (8.1)	4 (2.3)	
• CTC 3-4	3 (1.6)	3 (1.7)	

EFS, PFS and TTNT improvement was consistent across all risk groups analyzed, except for very high risk patients due to small numbers (N=8). At cut-off, 6 and 5 deaths were documented in the ibrutinib and placebo arm, respectively. There was no significant difference in non-serious and serious adverse events (SAE) in ibrutinib and placebo treated patients respectively (82.7 vs. 84.3%). SAEs were reported in 34.6 and 34.8% of ibrutinib and placebo treated patients respectively; most common SAEs were infections (11.4 vs. 11.8%), neoplasms (5.9 vs. 10.7%) and cardiac disorders (8.6 vs. 6.7%). AEs of particular interest were mostly of CTC-grade 1-2 and significantly more frequent in ibrutinib treated patients (**Table 1**).

Conclusions: The results of this study allow to conclude that ibrutinib significantly improves EFS, PFS and TTNT in patients with treatment-naïve early stage CLL when compared to placebo. There were no significant differences in adverse events between both study arms.

Disclosures: Langerbeins, P: Consultant Advisory Role: *Sunesis*; Honoraria: *Janssen, Abbvie*; Research Funding: *Janssen*. **Cramer, P:** Consultant Advisory Role: *Janssen, Novartis*; Honoraria: *Roche, Janssen*; Research Funding: *Roche, Gilead, GlaxoSmithKline/ Novartis, Janssen*. **Al-Sawaf, O:** Honoraria: *Roche, Gilead, Abbvie, Janssen*; Research Funding: *Beigene*. **von Tresckow, J:** Honoraria: *Roche, AbbVie, Janssen*; Research Funding: *Roche, Janssen*. **Fink, A:** Honoraria: *Roche*; Research Funding: *Celgene*. **Wendtner, C:** Consultant Advisory Role: *AbbVie, Roche, Genentech, Gilead, Novartis, Janssen*; Honoraria: *AbbVie, Roche, Genentech, Gilead, Novartis, Janssen*; Research Funding: *AbbVie, Roche, Genentech, Gilead, Novartis, Janssen*. **Fischer, K:** Other Remuneration: *travel grants by Roche*. **Stilgenbauer, S:** Consultant Advisory Role: *AbbVie, Amgen, AstraZeneca, Celgene, Gilead, GSK, Hoffmann La-Roche, Janssen, Novartis*; Honoraria: *AbbVie, Amgen, AstraZeneca, Celgene, Gilead, GSK, Hoffmann La-Roche, Janssen, Novartis*; Research Funding: *AbbVie, Amgen, AstraZeneca, Celgene, Gilead, GSK, Hoffmann La-Roche, Janssen, Novartis*. **Eichhorst, B:** Consultant Advisory Role: *Janssen, Gilead, Roche, Abbvie, Novartis, Celgene*; Honoraria: *Roche, Novartis, Gilead, Janssen, Abbvie, Celgene*; Research Funding: *Roche, Janssen, Abbvie, Gilead*. **Hallek, M:** Consultant Advisory Role: *Roche Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Boehringer*; Honoraria: *Roche Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Boehringer*;

AACR-ICML JOINT SESSION - THE ROLE OF NON-CLINICAL MODELS AS BRIDGES TO EARLY CLINICAL TRIALS

008
DESIGNER ORGANOIDS FOR MODELING EPIGENETICS, SIGNALING, AND THERAPIES IN LYMPHOMA

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Diffuse Large B cell lymphoma (DLBCL) is the most common lymphoma with significant molecular heterogeneity within morphologically indistinguishable tumors of the lymph node. Two subtypes of DLBCL have remarkably poor clinical outcomes: the recently defined extranodal class of activated B cell-like (ABC)-DLBCL and the epigenetic class of germinal center B cell (GCB)-DLBCL (1, 2). The mechanism through which DLBCLs, and potentially other lymphomas, are resistant to current therapies are unknown but may be linked to the particular spectrum of somatic mutations in these tumors, which are in concert with complex growth signals provided by the malignant lymph node tumor microenvironment (Ly-TME). Many of the hallmark ABC-DLBCL mutations result in constitutive activation of protein components of B cell receptor (BCR) and Toll-like receptor (TLR) pathways in these malignant immune cells. Hence these pathways are emerging as a source of therapeutic targets for the treatment of ABC-DLBCLs. However, to date, existing BCR pathway inhibitors such as those targeting Bruton's tyrosine kinase are active in a limited subset of patients and only for a short duration, the causes of which are unknown. The substantial differences in response rates and response duration between ABC-DLBCL patients reflect the variable dependencies on BCR and TLR signaling and/or differential regulation by the Ly-TME. Unfortunately, we do not understand the impact of Ly-TME on cooperative, feed-back, and bypass signaling pathways in ABC-DLBCLs and, consequently, on the efficacy of inhibitors and/or agonists to adequately suppress these networks. A major limitation in the field has been the lack of an experimental therapeutics platform that recapitulates human cell and extracellular matrix components of Ly-TME, fluid characteristics and tissue stiffness that regulate DLBCL signaling, and also could model BCR-Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) paracaspase and TLR signaling cross-talk. In this talk, we will discuss the discoveries enabled by designer lymphoid organoids and on-chip technologies in understanding the epigenetic switches such as enhancer of zeste homolog 2 (EZH2) and components of the B Cell receptor signaling pathway that have emerged as key therapeutic targets in DLBCLs (3-6). We will also discuss the ongoing development of a more accurate 3D on-chip model and test the cooperative signaling between BCR-MALT1-TLR as well as the therapeutic efficacy of select inhibitors alone or in combination with other drugs.

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Keywords: B-cell receptor (BCR); EZH2; Mucosa-Associated Lymphoid Tissue (MALT).

009
MOUSE PDX AS NON-CLINICAL MODELS FOR LYMPHOMA

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Lymphomas represent nearly 70 distinct diseases with unique clinical presentations, therapeutic responses and underlying biology. There is a pressing shortage of publicly available cell line and *in vivo* models of nearly all of these diseases, which has severely hampered efforts to understand and target their biology. Most *in vivo* models of lymphoma are genetically-engineered mouse models, which often don't faithfully recapitulate human disease. To address this issue, we have established a repository of patient-derived xenografts (PDX) of lymphomas by engrafting human tumors into immunodeficient NOD/Scid/IL2rgnull mice with or without an MHC Class 1 deficiency (to prevent graft versus host disease). Blood and bone marrow specimens involved with tumor were injected by tail vein injection. Lymph node and extranodal biopsy specimens were implanted under the renal capsule as a 1x1x2mm tumor seed, which maintains the *in situ* microarchitecture.

The PDXs have been extensively characterized by immunohistochemistry (IHC), flow cytometry, transcriptome sequencing and targeted DNA sequencing. These studies have demonstrated retention of key architectural, cellular, and molecular features of the primary tumors. Flow cytometric analysis of patient tumors and their respective xenografts revealed highly concordant patterns of surface marker expression. IHC of murine tissues confirmed retention of tumor immunophenotypes, architecture, and even tissue tropism in the PDXs. The genetic characterization of the PDX models using a targeted DNA sequencing approach showed a mutational profile that clearly matched primary lymphoma samples and significantly expands the current repertoire of available pre-clinical models.

These models represent a unique opportunity to interrogate biology and perform preclinical studies with *in vivo* models. We have utilized models extensively to interrogate chemical, antibody and other therapeutic manipulations. The lymphomas, along with a spectrum of PDXs from other hematologic malignancies, are available through the online portal PRoXe (Public Repository of Xenografts) at http://www.proxe.org.

010
ADVANCING OUR UNDERSTANDING AND TREATMENT OF LYMPHOMA WITH SPONTANEOUS CANINE MODELS

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Lymphoma is one of the most frequently diagnosed malignances in dog and represents the most widely investigated tumor in veterinary medical oncology. Knowledge on the diagnosis, molecular biology, genetics and epigenetics has grown substantially in the recent years. Within the different lymphoma subtypes, canine diffuse large B-cell lymphoma (DLBCL) resembles in many elements the human counterpart, including frequency, molecular abnormalities and similar therapeutic responses to chemotherapy. But, many others aspects are still scarcely known and a complete characterization becomes fundamental when including dogs with DLBCL in clinical trials to test new molecules.

In the NGS era researchers have attempted to fill this gap and to accurately describe canine lymphoma model in a similar fashion to rodent models. This presentation is intended to provide an overview of the main ground-breaking investigations in canine B-cell lymphoma that have been published in the last decade. In three large-scale studies of gene expression profiling, similarities between canine DLBCL and human activated B cell-like DLBCL subtype were found both by DNA-microarray and RNA-seq. NF-kB activation by two pathways, named MyD88-dependent signaling pathway through several Toll-like receptors and Bruton's tyrosine kinase pathway were highlighted in this subtype. Also, functional relevance of

NF-kB activation in dogs with DLBCL was tested using NEMO-binding domain peptide in two clinical trials and the compound resulted safe and blocked NF-kB activity. Few years before treatment with Ibrutinib was found effective in dogs with B-cell lymphoma, however no information about cell of origin was available for these dogs. Interestingly, a peculiar MYC deregulation via the LIN28B/Let-7 axis was identified in canine DLBCL and LIN28B resulted the most upregulated gene both in vivo and in vitro, opening new scenario both for treatment of this tumor in dog and the relevance of this disease as model when testing compounds targeting this pathway.

Moreover, advantages and pitfalls when using dogs with B-cell lymphoma in preclinical experiments for human drug development will be considered in this lecture. To date, drug development pipelines follows common strategy with preclinical testing in cell lines and in mice, PK/PD testing in large animals such as experimental Beagle dogs, and then phase I–III testing in human clinical trials. The inclusion of dogs with lymphomas as part of preclinical testing or in parallel with human trials would be a serious advantage both in data analysis and if results are positive for the expansion to the veterinary market of the new drug. Limitations are also present, including that dogs are from private owners and some toxicities may be species-specific.

In future, we expect an increasing number of clinical trials including data from dogs with DLBCL, but also a detailed pathological and molecular classification of the tumors should be always requested to avoid biases related to the heterogeneity of the disease.

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FOCUS ON... SESSION: MANTLE CELL LYMPHOMA

011

COMBINATION OF IBRUTINIB WITH RITUXIMAB (IR) IS HIGHLY EFFECTIVE IN PREVIOUSLY UNTREATED ELDERLY (>65 YEARS) PATIENTS (PTS) WITH MANTLE CELL LYMPHOMA (MCL) – PHASE II TRIAL

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Introduction: We reported the efficacy of ibrutinib with rituximab (IR) combination in relapsed MCL. Here we present the first efficacy/safety analysis of single center, phase II clinical trial of IR combination in untreated elderly pts with MCL.

Methods: Previously untreated elderly (>65 years) MCL pts (n=42) were enrolled in this study (NCT01880567). Pts with Ki-67% ≥ 50% and blastoid/pleomorphic histology were excluded. Pts received IR combination - ibrutinib 560 mg orally daily for 28 days (one cycle) continued until disease progression or discontinued for any reason. Rituximab was given on days 1, 8, 15 and 22 +/- 1 day by intravenous infusion (IV) at a fixed dose of 375 mg/m^2 (cycle 1), followed by rituximab on day 1 of every cycle starting in cycles 3 – 8. Following cycle 8, rituximab was given on day 1 of every other cycle for up to 2 years. The primary objective was to assess the safety and the efficacy. Among evaluable samples, minimal residual disease (MRD) by flow cytometry at best response and other molecular studies for clonal evolution at various time points were performed.

Results: The median age was 71 years (range 65-84), ECOG PS was (0/1) in 41 (98%) pts, 20% had high risk MIPI score, Ki-67% was low (<30%) in 30 (73%) and high (≥30-50%) in 11 (27%) pts, and 10% had complex karyotype. Median number of IR cycles was 19 (1-43). Best overall response (ORR) was 95% (69% CR, 26% PR, 5% stable disease). Median number of IR cycles to reach CR 4 (2-31). Thirty two patients had PET- based response assessment and all had CR (100%). MRD

TABLE 1 Summary of response and outcomes

Best Response*	CR	PR	SD	ORR
IR combination	69%	26%	5%	95%
#MRD negative at best response	65%			
Survival outcomes (months; range/95%CI)				
Median follow up (range)	24 (6-42)			
Median PFS (range)	Not reached			
Median OS (range)	Not reached			

ORR overall response, CR complete response, PR partial response, SD is stable disease, * 4 patients discontinued treatment within first 3 cycles for grade 3 adverse events and one is on study and started treatment 2 months ago, # 37 pts were evaluable at best response for MRD

negative CR by flow cytometry was 65%. Overall, the median follow up was 24 months (6-42). Median PFS and OS were not reached. Among pts with low and high Ki-67%, median PFS was (not reached; p=0.28) and OS (not reached; p=0.02). Median duration on study was 19 months (range 1-39). Overall, 4 pts progressed (2 transformed to blastoid MCL) on study after taking IR for 4, 9, 13 and 32 months. Two pts died. At the time of last follow up, 24 pts remained on study and 18 (43%) discontinued therapy. Dose reduction was performed in 23 (55%) pts for various reasons. Most frequent grade 3-4 toxicities were 17% myalgias, 14% fatigue, 12% shortness of breath, 9% neutropenia and 5% new onset atrial fibrillation.

Conclusions: IR combination in elderly pts with MCL as a frontline treatment was very effective and safe. This strategy provides an excellent frontline alternate to chemotherapy in elderly pts with MCL.

Keywords: ibrutinib; mantle cell lymphoma (MCL).

Disclosures: Wang, M: Consultant Advisory Role: *Pharmacyclics and Janssen.*

012

IBRUTINIB WITH RITUXIMAB (IR) AND SHORT COURSE R-HYPERCVAD/MTX IS VERY EFFICACIOUS IN PREVIOUSLY UNTREATED YOUNG PTS WITH MANTLE CELL LYMPHOMA (MCL)

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Introduction: Ibrutinib with rituximab (IR) combination induces durable responses in relapsed MCL. This is a single institution phase II trial of IR with short course (4 cycles) of R-HCVAD/R-MTX consolidation as frontline therapy in MCL.

Methods: Previously untreated young (≤65 years) MCL pts (n=50) were included. The study was registered with a ClinicalTrials.gov identifier number NCT02427620. Pts received IR induction (part-A), until they achieved complete remission (CR) up to a maximum of 12 cycles, followed by only 4 cycles of R-HCVAD/R-MTX (part-B). None of the patients received stem cell transplant or maintenance. The primary objective was to assess response rates after part-A. Among evaluable samples, minimal residual disease (MRD) by flow cytometry at best response, clonal evolution using circulating tumor DNA (ctDNA) at various time points, baseline somatic mutations and baseline gene expression profile (GEP) was performed.

Results: Overall, the median follow up was 36 months (10-42). Forty nine percent had high Ki-67 (≥30%), 72% had low risk MIPI score, one pt had *TP53* mutation and 2 pts had aggressive MCL (one blastoid and one pleomorphic). Median number of cycles on IR was 6 (2-12). Overall response (ORR) on part-A of therapy was 100% (90% CR and 10% PR) and at the time of last follow up after completion of part A and part B, ORR was 100% (All CR). MRD negative CR rate assessed by bone marrow flow cytometry performed at best response at any phase of treatment was 91%. Overall, the median PFS and OS were not reached (3 year 89% and 100% respectively). Four pts had progressed after 17, 24, 34, 35 months of treatment (3 pts had Ki-67% ≥ 30% and one was blastoid MCL). None of the pts died. Grade 3-4 toxicities on part A were 4% myelosuppression and 8% each with fatigue, myalgia and rashes. GEP was done in 18 pts (2 PR, 16 CR on part A). Pts in PR had higher expression of *HES1* while those in CR had significantly higher expression of *CTLA4* and *ITK* genes compared to those in PR. Targeted DNA sequencing was done in 18 pts at baseline, one pt with PR had *NSD2*, *KMT2C* and another pt had *TP53* mutations and had CR.

Conclusions: IR followed by short course R-HCVAD/R-MTX as frontline treatment induced durable and profound remissions in young MCL pts. This strategy demonstrated excellent efficacy and safety and minimized the exposure to chemotherapy.

Keywords: hyper-CVAD; ibrutinib; mantle cell lymphoma (MCL).

Disclosures: Wang, M: Consultant Advisory Role: *Janssen, AstraZeneca, MoreHealth, Pulse Biosciences, AxImmune, Celgene, Juno Therapeutics, Pharmacyclics, IO Biotech, BioInvent*; Stock Ownership: *MoreHealth*; Honoraria: *Janssen, Dava Oncology, OMI, PeerView Institute for Medical Education (PVI)*; Research Funding: *Janssen,*

Table-1 Summary of response and outcomes

Best Response	CR	PR	ORR
Part A	90%	10%	100%
Part B*	100%	-	100%
#MRD negative at best response	91%		
Survival outcomes (months; range/95%CI)			
Median follow up (range)	36 (10-42)		
Median PFS (range)	Not reached		
Median OS (range)	Not reached		

ORR overall response, CR complete response, PR partial response, *2 pts did not take part B and one patient was not evaluable for response, # 43 pts were evaluable at best response for MRD

AstraZeneca, Acerta Pharma, Juno Therapeutics, Kite Pharma, BeiGene, Novartis, Celgene, BioInvent, Karus, Oncternal, Amgen.

013
AUTOLOGOUS STEM CELL TRANSPLANTATION IN FIRST REMISSION SIGNIFICANTLY PROLONGS PROGRESSION-FREE AND OVERALL SURVIVAL IN MANTLE CELL LYMPHOMA

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Introduction: We report here the long term efficacy results (median follow up of 14 years) of the first randomized trial of the European MCL network which compared consolidation with myeloablative Radiochemotherapy followed by autologous stem cell transplantation (ASCT) to α-interferon maintenance (IFN) in first remission.

Methods: First results have been published previously (Dreyling et al., Blood 2005). In summary, between September 1996 and March 2004, 269 patients 65 years of age or younger from 129 institutions were randomized to either ASCT or IFN after induction with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP), without or with Rituximab (R), or Mitoxantrone-Chlorambucil-Prednisone. R-CHOP was used in 32% of 232 patients with confirmed MCL.

Results: After a median follow-up of 14 years, 93 patients in the ASCT arm and 81 patients in the IFN arm, respectively, were evaluable for the intention to treat analysis of progression-free survival (PFS) and overall survival (OS) after responding to induction treatment. Clinical characteristics were comparable in both treatment groups with a

Figure 1: Description of progression-free (top) and overall survival (bottom) in remission from end of induction by treatment arm (random assignment) in European MCL 1
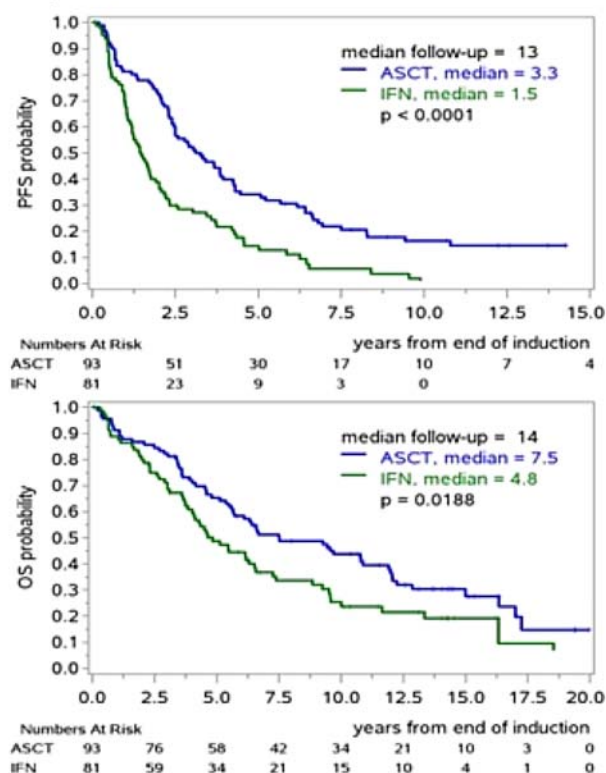
median age of 55 years (34-65), 82% stage IV and 73% low, 20% intermediate, and 7% high risk according to Mantle cell lymphoma international prognostic index (MIPI). In patients receiving ASCT, the median PFS was 3.3 years, in patients receiving IFN the median PFS was 1.5 years (p < 0.0001). Furthermore, the median OS was significantly prolonged in patients receiving ASCT (7.5 years) than in patients receiving IFN (4.8 years) (p = 0.019). Adjusting for MIPI score and use of R-Chemotherapy, the hazard ratios for ASCT versus (vs.) IFN were 0.50 (95% CI, 0.36-69) for PFS and 0.66 (0.46-0.95) for OS. Cox regression analyses were performed to evaluate the differential effects of ASCT vs. IFN on PFS and OS according to induction treatment with R-Chemotherapy vs. Chemotherapy alone, adjusting for MIPI score. For patients treated without Rituximab the PFS hazard ratio for ASCT (n = 52) vs. IFN (n = 54) was 0.40 (0.26-0.61), in comparison to 0.72 (0.42-1.24) for patients treated with Rituximab (ASCT n = 41, IFN n = 27). For OS the hazard ratio for ASCT vs. IFN was 0.52 (0.33-0.82) for patients treated without Rituximab and 1.05 (0.55-1.99) for patients treated with Rituximab.

Conclusion: After a prolonged median follow up of 14 years the mature results of our trial confirm a significantly prolonged PFS and OS after ASCT in first remission of mantle cell lymphoma. However, there was only a non-significant trend for PFS and no difference in OS in the subset of patients treated with a Rituximab-containing induction therapy, potentially due to the reduced statistical power of this subgroup analysis. In the current study generation, the substitution of ASCT by the BTK inhibitor Ibrutinib is evaluated.

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OBINUTUZUMAB PLUS DHAP FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) PLUS OBINUTUZUMAB MAINTENANCE PROVIDES A HIGH MRD RESPONSE RATE IN UNTREATED MCL PATIENTS. RESULTS OF LYMA-101 TRIAL, A LYSA GROUP STUDY

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Introduction: Achievement of prolonged minimal residual disease (MRD) negativity after both induction and ASCT is a strong independent prognostic marker in mantle cell lymphoma (MCL). A high-dose aracytine- (HA) and salt platinum-containing (P) chemotherapy regimen with Rituximab followed by autologous stem cell transplantation (ASCT) consolidation plus 3 years Rituximab maintenance is considered as a standard of care for untreated younger patients with MCL (Le Gouill et al. NEJM 2017). Obinutuzumab is a glycoengineered, type II, anti-CD20 monoclonal antibody designed to improve the antibody-dependent cell mediated cytotoxicity compared to Rituximab. in vitro experiments suggest that Obinutuzumab may provide better anti-MCL activity (Chiron et al., Blood 2016) than Rituximab but no in vivo data are available regarding Obinutuzumab in naive MCL patients.

Methods: The LYMA-101 study is a prospective and open phase II trial testing the effect of Obitunuzumab in untreated MCL patients under 66 years of age and eligible for intensive therapy. Induction consisted of 4 cycles of Obinutuzumab-DHAP (O-DHAP) before consolidation with ASCT (BEAM conditioning plus Obinutuzumab)

followed by Obinutuzumab maintenance for 3 years then Obinutuzumab on-demand for MRD positive patients. The LYMA-101 primary objective was the MRD negativity rate after 4 cycles of O-DHAP. MRD in the BM was assessed by IGH clonospecific or bcl1-JH PCR, and quantification with a sensitivity of at least 10^{-4} was reach by dd-PCR following Euro-MRD lymphoma group recommendations. We hypothesized that O-DHAP would be considered as an effective induction chemotherapy regimen if MRD negativity was ≥ 70%. We calculated that a minimum of 83 patients should be included (α risk of 0.05 and β of 0.20 one-sided test).

Results: We enrolled 86 patients between Nov 2016 and May 2018. One patient withdrew consent before starting treatment. Sixty-three patients (73.3%) were male and median age was 55.5 years (32-65). MIPI and MIPI-b risk scores were low in 47 (54.7%) and 9 (10.5%) cases, intermediate in 24 (27.9%) and 38 (44.2%) cases and high in 14 (16.3%) and 21 (24.4%) cases. Fifteen patients (17.4%) presented with a blastoid variant. At the time of analysis, median FU was 14 months (3.8-24.4). Twelve patients out of 85 were not evaluable for MRD, essentially due to purely nodal disease and no detectable MCL clone in PB or BM. Among the 73 MRD-informative patients, 62 reached MRD negativity in the BM (84.9%) while 6 were MRD positive after O-DHAP. The remaining 5 patients were not evaluated because 4 stopped treatment during induction due to AEs and one progressed then died. 72 patients underwent ASCT and 68 started Obinutuzumab maintenance. Twelve patients stopped treatment before ASCT (including disease progression in 2 cases and AE in 7 cases), 3 before maintenance (2 because of AE, one died during ASCT), and 9 during maintenance (including disease progression in one case, death in another, AE in 4 cases or other malignancies in 2 cases). In the whole population (n=85), 3 patients progressed, three died. At one year, PFS is 93.4% (IC95%, 84.7-97.2) and OS is 96% (IC95%, 88.1-98.7).

Conclusion: The Lyma-101 trial successfully achieved its primary end-point (84.9% of MRD BM negativity after induction) and demonstrates the high efficacy of O-DHAP as induction chemotherapy regimen before ASCT with an unprecedented high level of MRD negativity, which predict better PFS and OS. Longer FU is needed to evaluate patient outcome after O-DHAP/ASCT/Obinutuzumab on-demand maintenance. However, both PFS and OS are highly encouraging at one year.

Keywords: mantle cell lymphoma (MCL); minimal residual disease (MRD); obinutuzumab.

Disclosures: Le Gouill, S: Consultant Advisory Role: *Roche Genentech*; Honoraria: *Roche Genentech*; Research Funding: *Roche Genentech*.

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ZANUBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

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Introduction: Zanubrutinib is a selective and irreversible BTK inhibitor that has demonstrated potent inhibition of BTK in prior studies, with minimal, off-target inhibition of other kinases. We present updated safety and efficacy results from a phase 2 study of zanubrutinib in patients with R/R MCL.

Methods: In this single-arm, multicenter phase 2 study (ClinicalTrials.gov NCT03206970), oral zanubrutinib (160 mg BID) was given to R/R MCL patients until disease progression (PD) or unacceptable toxicity. Primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC) according to the 2014 Lugano Classification. Secondary endpoints included progression-free survival (PFS), time to response (TTR), duration of response (DOR), investigator-assessed ORR, and safety.

Results: As of September 16, 2018, 86 R/R MCL patients were enrolled at 13 centers in China. Patient characteristics are summarized in the table. The median study follow-up was 13.9 months (range, 0.3-18.5 months) with treatment discontinuation in 29 (33.7%) patients, primarily due to PD (19 [22.1%]) and AE

Table. Patient Characteristics, Efficacy, and Safety

Patient Characteristics	N = 86
Median age, y (range)	60.5 (34-75)
Sex, n (%)	
Male	67 (77.9)
Female	19 (22.1)
Time since first diagnosis of MCL (months)	30.1 (3.1-102.4)
Median no. of prior lines of therapy (range)	2 (1-4)
Bulky disease, n (%)	
>10 cm	7 (8.1)
>5 cm	37 (43.0)
Blastic variant form of MCL, n (%)	12 (14.0)
Stage IV disease, n (%)	64 (74.4)
Intermediate/high-risk per MIPI-b, n (%)	72 (83.7)
Efficacy (Best Response)[b]	**N = 85[a]**
Overall response rate, n (%); (95% CI)	72 (84.7); (75.3, 91.6)
Complete response, n (%)	65 (76.5)
Partial response, n (%)	7 (8.2)
Stable disease, n (%)	1 (1.2)
Progressive disease, n (%)	8 (9.4)
Discontinued prior to first response assessment, n (%)	4 (4.7)
Safety, n (%)	**N = 86**
Any TEAE	83 (96.5)
Any grade ≥3 TEAE	34 (39.5)
TEAE leading to zanubrutinib discontinuation	9 (10.5)
Grade 5 TEAE	5 (5.8)

[a]One patient was not evaluable for response due to a lack of central pathologic confirmation of MCL.
[b]IRC-assessed efficacy will be reported later.
MIPI-b, Mantle Cell International Prognostic Index-biologic

(8 [9.3%]). In 85 efficacy evaluable patients, investigator-assessed ORR was 84.7%, and 65 (76.5%) patients achieved complete response. The median DOR was 14.0 months (range, 2.32-14.0 months). The median PFS was 16.7 months (range 0.0+ to 16.7+ months). The ORR was generally consistent across subgroups analyzed (MIPI [Mantle Cell International Prognostic Index], previous therapy, blastoid variant, etc). The most common (≥15%) treatment-emergent AEs (TEAEs) included decreased neutrophil count (41.9%), rash (33.7%), upper respiratory tract infection (33.7%), decreased white blood cell (WBC) count (26.7%), decreased platelet count (25.6%), hypokalemia (16.3%), and diarrhea (15.1%). Grade 3 TEAEs reported in >2 patients included decreased neutrophil count (16.3%), decreased WBC count, anemia, lung infection (each 5.8%), decreased platelet count (4.7%), and hypertension (3.5%). The most frequent hemorrhage events were hematuria and petechiae/purpura/contusion (4.7% each, grade 1/2). Major hemorrhage (serious or grade 3 bleeding or central nervous system bleeding of any grade) was reported in 2 patients (2.3%). No cases of atrial fibrillation/flutter, second primary malignancies or tumor lysis syndrome were reported. TEAEs leading to treatment discontinuation in nine (10.5%) patients included infection, lung infection, pneumonia, upper gastrointestinal hemorrhage, road traffic accident, cerebral hemorrhage, interstitial lung disease (n=1 each), and decreased platelet count (n=2).

Conclusions: Updated results of this study further substantiated the high activity of zanubrutinib resulting in a high rate of durable response in R/R MCL. The safety profile was consistent with previous reports of zanubrutinib treatment.

Keywords: BTK inhibitors; mantle cell lymphoma (MCL); zanubrutinib.

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OUTCOMES IN FIRST RELAPSED-REFRACTORY YOUNGER PATIENTS WITH MANTLE CELL LYMPHOMA: RESULTS FROM THE MANTLE-FIRST STUDY

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Median PFS (months): ibrutinib 24±14; R-BAC 25±6; R-B 12±1; other regimens 7±2.
P=0.11 between R-BAC and R-B; p=0.07 between ibrutinib and R-B;
p=0.86 between ibrutinib and R-BAC; p=0.001 between ibrutinib and other regimens;
p=0.06 between R-B and other regimens; p=0.0002 between R-BAC and other regimens.

Introduction: Patients with mantle cell lymphoma (MCL) that fail induction treatment represent a difficult-to-treat population with poor outcome, where no standard therapy exists. There is a paucity of large-scale data in relapsed or refractory (r/r) MCL.

Methods: MANTLE-FIRST, an international, retrospective study, evaluated outcomes in patients with MCL who had progressive disease or first relapse when treated upfront with high dose cytarabine (HDAC), followed by autologous stem cell transplantation if appropriate. Response rates, overall survival (OS), and progression-free survival (PFS) were estimated from the time of initiation of salvage therapy. The previously defined threshold of 24 months since MCL initial diagnosis was used to define patients as having early- or late- first relapse or progression (POD).

Results: Overall, 258 patients with r/r MCL were included, with a median follow-up from time of relapse or progression of 38 months (range 1-122). Second line regimens consisted of rituximab bendamustine (R-B) in 22%, rituximab, bendamustine, cytarabine (R-BAC) in 29%, ibrutinib in 18%, and other regimens in 31%. Overall response rate was higher in ibrutinib and R-BAC treated patients (79% for both), as compared to R-B (62%), or other regimens (30%). Complete response (CR) were significantly higher in patients treated with R-BAC (63%) than with R-B (43%, p=0.02), ibrutinib (34%, p=0.002), or other approaches (22%, p<0.0001). Median OS and PFS for all patients were 34±5 and 13±8 months, respectively. PFS curves according to second line therapy are shown in **Figure 1**. For patients with early-POD (n=126), outcomes were consistently poor, irrespectively of administered second line therapy (median OS 10±1 months), unless for those receiving allogeneic transplant (n=27, median OS 63±24 months). Ibrutinib was associated with longer PFS and OS (10±1 and 30±13, respectively), compared to immunochemotherapy (6±2 and 12±2 months, p=0.09 and p=0.08). For patients with late-POD (n=132), median OS was 74±9 months, and PFS was 34±5. Ibrutinib (not reached), R-BAC (not reached) and R-B (73±21) had similar significant OS advantage, compared to other regimens (41±11, p=0.03). Ibrutinib and R-BAC had similar PFS of 52±18 and 53±22 months, respectively, while R-B was associated with shorter PFS of 31±3 months, although not statistically significant, and other regimens with median PFS of 13±1 months (p<0.0001). At multivariate analysis, factors significantly and independently associated to a reduction of the risk of death were achievement of CR after second line regimens (HR 0,19), allogeneic transplant (HR 0,40), ibrutinib second line therapy (HR 0,47) and late-POD (HR 0,49).

Conclusions: MANTLE-FIRST is the largest patient-level pooled retrospective analysis to characterize survival for a population of HDAC treated first r/r MCL. Time to POD confirmed its importance for treatment decisions, with allo-transplant being the only curative option in early-POD. Ibrutinib second line was associated with OS advantage, while R-BAC induced higher CR rate and similar PFS.

Keywords: Bendamustine; ibrutinib; mantle cell lymphoma (MCL).

FOCUS ON... SESSION: PET IMAGING

017

A GENE EXPRESSION-BASED SCORE TO PREDICT INTERIM PET POSITIVITY IN HODGKIN LYMPHOMA PATIENTS TREATED WITH ABVD

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Introduction: Response-adapted therapy through the use of FDG-PET after 2 cycles of ABVD (interim PET-iPET) is an effective strategy in Hodgkin's Lymphoma (HL). However, this approach may cause 2 months of suboptimal treatment. The objective of this study was to use gene-expression profiling to build and validate a model to predict iPET positivity (iPET+).

Methods: Consecutive untreated patients (pts) with stage I-IV HL with available diagnostic tumor sample who underwent iPET after two cycles of ABVD were identified from the Reggio Emilia Hematology unit and used to define the training set. A validation set was identified from the hematology unit in Firenze using the same criteria. Expression of 770 immune related genes was analyzed by digital expression profiling (Nanostring Technology). Conventional clinical and laboratory parameters were collected. iPET was centrally reviewed according to the five-point Deauville scale (5PS), and was used as primary study endpoint. Clinical events were used as secondary endpoint and included treatment change for iPET+ cases and relapse/progression for other cases. An iPET+ predictive model was derived by multivariate regression analysis and assessed in a validation set.

Results: A training set of 121 and a validation set of 113 pts were identified, with 23 iPET+ cases in each group. Median age of the training cohort was 38 years (18 to 75); 63 (52.1%), 19 (15.7%) and 39 (32.2%) had stage I-II, III and IV respectively. iPET+ HLs have a distinctive transcriptional profile at diagnosis that discriminate these lesions from iPET-. A list of 13 genes was found significantly associated with iPET+. This signature comprises two functionally distinct, stromal-related nodes. Lymph mono-ratio (LMR) was also associated

to iPET+. In the training cohort a 5-gene and LMR integrated score predicted interim iPET+ (AUC0.88 95%CI, 0.80-0.96). Model score was used to divide the training cohort into quartiles showing that the vast majority of iPET+ patients segregated within Q4[th] (Q4[th] -76.2%, Q3[th] -9.5%, Q2[th] -14.2% and Q1[th] -0%). Model performance was confirmed in the validation set (AUC0.67 95%, 0.47-0.84). Furthermore, score-based quartile separation in this cohort, confirmed the preferential distribution of iPET+ pts within Q4[th]. Merging the training and validation set, 34 events were identified out of 172 pts (16 pts who underwent therapy escalation after iPET+ and 18 with relapse). iPET score was higher in pts with event vs those without event. Correlation of iPET score with pts survival was not informative because the adoption of intensified therapies in iPET+ cases (46% of iPET+) likely corrected the higher risk of progression in these pts.

Conclusions: In HL interim metabolic response measured with PET after 2 ABVD cycles is associated with a genetic signature and can be predicted applying an integrated gene-based model on the diagnostic biopsy.

Keywords: ABVD; gene expression profile (GEP); Hodgkin lymphoma (HL).

018

PERSISTENT MEDIASTINAL POSITRON EMISSION TOMOGRAPHY (PET)-POSITIVITY AFTER FRONTLINE THERAPY FOR HODGKIN LYMPHOMA IS BEST MANAGED BY CLOSE OBSERVATION

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Introduction: Residual FDG PET uptake in the mediastinum after frontline therapy for classical Hodgkin lymphoma (cHL) is a challenging situation as it is difficult to distinguish between persistent disease and inflammatory changes post treatment. Thus, we analyzed the practice patterns at a single institution to determine how often a biopsy of the site was informative, and whether it influenced patient management and outcome.

Methods: We retrospectively reviewed all cHL treated at the Hematology Department of Mayo Clinic in Rochester MN between January 2003 and December 2018. Cases with a mediastinal mass at diagnosis (largest diameter ≥5 cm) and isolated PET-positivity at that site after standard frontline therapy were included into the study. Clinical approach adopted and outcomes were analyzed and an independent radiological review of PET images was performed.

Results: Among 1060 cHL evaluated, 37 were eligible for the study. A mediastinal biopsy was performed in 19/37 cases (group 1): 9/19
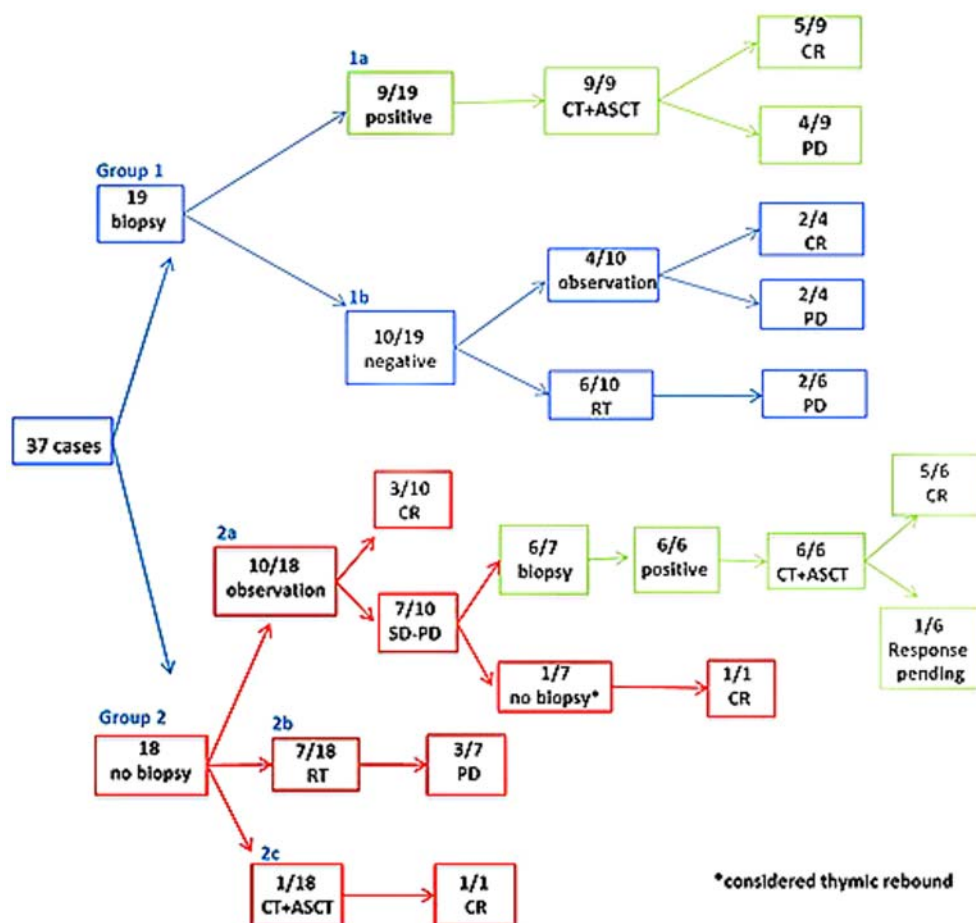
Figure 1. flow chart with summarized clinical approaches.

(47%) were positive for cHL and all underwent salvage chemotherapy followed by autologous stem cell transplant (CT+ASCT) (group 1a). Among biopsy-negative cases (group 1b), 4/10 were observed and 6/10 received radiotherapy (RT) consolidation. Among the non-biopsied cases (group 2), 10/18 were observed (group 2a), 7/18 received RT (group 2b), and 1/18 underwent CT+ASCT (group 2c). Patients of group 2a had a repeat PET scan after a median time of 13 weeks (range 4-35) and then only 7/10 showed persistent FDG uptake or progression disease. 6/6 biopsies performed at this time were positive and all cases received CT+ASCT. No biopsy was done in 1/7 case considered to be thymic rebound. Among patients of group 1a, 2a and 2c receiving CT-ASCT, complete remission (CR) was obtained in 11/16 (69%); 8/13 (61%) patients from group 1b or 2b receiving consolidative RT remained in CR; 2/4 cases observed after a negative biopsy subsequently progressed; 3/10 cases of group 2a converted to PET negativity and remained in CR. (Fig 1) With a median follow up of 38.4 months, no survival difference between groups 1 and 2 was observed.

On radiological review of 34/37 patients at the end of therapy, Deauville scores (DS) of the PET images were as follows: 3 cases DS2, 4 DS3, 12 DS4, 12 DS5, 3 thymic rebound (DSX). The rate of relapse was 1/3 (33%) for DS2, 1/4 (25%) for DS3, 4/12 (33%) for DS4, 10/12 (83%) for DS5 and 1/3 (33%) for DSX.

Conclusions: Within the limitations of this small retrospective cohort, biopsy of post-treatment persistent mediastinal PET-positivity in cHL patients is positive in less than half the cases and DS was relatively unhelpful in selecting patients with potentially refractory disease. We conclude that adopting a "wait-and-see" strategy with a repeat PET scan reassessment 8-12 weeks later increases the likelihood that the subsequent biopsy will be positive without compromising the outcome and may be the preferred approach.

Keywords: classical Hodgkin lymphoma (cHL); Deauville's criteria; F-18-fluorodeoxyglucose (FDG).

019

HIGH TOTAL METABOLIC TUMOR VOLUME AT BASELINE ALLOWS TO DISCRIMINATE FOR SURVIVAL PATIENTS IN RESPONSE AFTER R-CHOP: AN ANCILLARY ANALYSIS OF THE REMARC STUDY

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Introduction: High total metabolic tumor volume (TMTV) measured on 18F-FDG PET/CT before R-CHOP has been shown to be significantly associated with inferior progression-free survival (PFS) and overall survival (OS) in patients with diffuse large B-cell lymphoma. The REMARC study (NCT01122472) showed a significantly better progression-free survival (PFS) in 650 patients responding to R-CHOP treated with maintenance therapy with lenalidomide (LEN) versus placebo (PBO), but no difference in OS was observed. The aim was to analyze the prognostic impact of baseline TMTV together with biological profile.

Methods: TMTV was computed on baseline PET/CT using the 41% SUVmax method. The optimal TMTV cut-off for PFS and OS was determined by Receiver Operating Curve and X-tile analyses and confirmed by a training validation method. A subset of patients (n = 192) was classified as GCB or non-GCB profile, and with MYC or BCL2 by FISH. Survival was estimated using Kaplan Meier (KM) curves. Analyses were performed on the evaluable population (n=301/650) and each arm, with 146 pts on PBO and 155 pts on LEN.

Results: Clinical characteristics were similar to the overall population. After a median 5 years follow-up, 4y-PFS was 73% and 4y-OS was 85%. Median baseline TMTV was 238 cm^3 (Q1-Q3;78,523). The optimal TMTV cut-off was 220 cm^3 for PFS and OS. Patients with TMTV >220 vs ≤220 cm^3 presented with worse ECOG performance status (ECOG ≥2: 21% vs 11.5%, p=0.029), higher Ann Arbor stage (stage III-IV: 94% vs 87%, p=0.043), more extra-nodal sites (>1: 63.5% vs 39%, p<0.001), more frequently elevated LDH (74% vs 45%, p<0.001), higher IPI (IPI 3-5: 85% vs 58%, p=10^{-3}), and higher aaIPI (score 2-3: 74% vs 40%, p=10^{-3}). In all evaluated patients, a significant impact of TMTV was observed for PFS (p=2.10^{-4}) and OS (p=10^{-4}). Patients with high TMTV>220 vs low TMTV≤220, had a 4-year PFS of 56% vs 82% and OS of 74% vs 92% respectively. This prognostic impact of a high baseline TMTV on PFS (HR=2.2; 95% CI, 1.4-3.5) and OS (HR=3.2; 95% CI, 1.5-6.6) was maintained in both PBO and LEN arms. As demonstrated in the original report, GCB/nonGCB profile had no significant impact on PFS and OS, regardless of TMTV. BCL2 impacted PFS and could be stratified by TMTV. MYC had no impact on PFS and OS. In multivariate analysis, baseline TMTV was the most powerful parameter associated with inferior PFS and OS, compared to aaIPI and treatment arm.

Conclusion: TMTV measured on baseline PET/CT is the strongest prognosticator of outcome in DLBCL, even in patients in responding after R-CHOP. High TMTV at baseline was significantly associated with inferior PFS and OS in patients receiving either PBO or LEN.

Keywords: diffuse large B-cell lymphoma (DLBCL); positron emission tomography (PET).

020
BASELINE TOTAL METABOLIC TUMOUR VOLUME IS HIGHLY PROGNOSTIC FOR REFRACTORINESS TO IMMUNOCHEMOTHERAPY IN DLBCL: AN ANALYSIS OF THE PHASE 3 GOYA TRIAL

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Introduction: The prognosis for patients (pts) with diffuse large B-cell lymphoma (DLBCL) refractory to treatment with standard frontline rituximab (R)-based immunochemotherapy is poor, and there are currently no clinical tools to identify these pts. This exploratory analysis investigated primary refractoriness in previously untreated pts with DLBCL from the phase 3 GOYA trial (NCT01287741).

Table. Baseline patient and disease characteristics and their association with primary refractoriness in a univariate analysis

Characteristic*	At baseline		Association with primary refractoriness (p-value)
	Overall population (n=1418)	Primary refractory patients (n=113)	
Treatment arm			0.1304
R-CHOP	712 (50.2)	63 (55.8)	
Ann Arbor stage			0.0176
III/IV	1076 (75.9)	95 (84.1)	
IPI risk category			0.0092
High	220 (15.5)	23 (20.4)	
Median SPD, mm² (range)	4425 (0–510000)	5968.05 (240–47104)	0.0120
Bulky disease (≥7.5 cm)	523 (37.0)	51 (45.1)	0.0231
Extranodal involvement	952 (67.1)	79 (69.9)	0.0067
Elevated LDH	816 (57.7)	80 (71.4)	0.0016
Hb <LLN	736 (52.5)	69 (61.1)	0.0193
TMTV†			0.0093
Q1 (1–103 mL)	283 (21.9)	18 (15.9)	
Q2 (102–336 mL)	283 (21.9)	14 (12.4)	
Q3 (336–842 mL)	284 (22.0)	18 (15.9)	
Q4 (841–8282 mL)	284 (22.0)	33 (29.2)	
Missing	158 (12.2)	30 (26.6)	
Time since diagnosis			0.0234
<1 month	895 (63.4)	76 (67.3)	
CD4+ T cell (CD3+ CD4+) count	-	-	0.1114
NK cell (CD16+ CD56+) count	-	-	0.0405

*All characteristics n (%) unless otherwise specified; †In the GOYA intent-to-treat population, n=1292
Hb, haemoglobin; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LLN, lower limit of normal; NK, natural killer; R, rituximab; SPD, sum of the product of diameters of up to 6 target lesions; TMTV, total metabolic tumour volume

Methods: Pts were randomised 1:1 to receive either obinutuzumab (G)- or R-CHOP (G 1000 mg cycle [C]1 day [D]1, 8 and 15, and C2–8 D1; R 375 mg/m² C1–8 D1; CHOP 6 or 8 cycles every 21 days). Primary refractory pts were defined as those with no metabolic response or progressive metabolic disease (PMD) at end of treatment (EOT) by Independent Review Committee using Lugano PET criteria, or progression (PD)/death due to PD before EOT by investigator. The association between baseline characteristics and primary refractoriness was analysed using univariate Cox regression; significant covariates (p≤0.15, Wald test) were assessed via multivariate analysis using backward elimination (significance cut-off p<0.05).

Results: Of 1418 pts in GOYA, 113 (8.0%) were identified as primary refractory (median age 61 years; 54% male). At baseline, more primary refractory pts presented with unfavourable disease characteristics versus the overall GOYA population (**Table**). Median overall survival (OS) was 14 months for primary refractory pts, with a 2-year OS of <30% versus 83.9% (G-CHOP) and 83.6% (R-CHOP) in the overall GOYA population. In a univariate analysis, multiple baseline covariates were significantly associated with primary refractoriness (p≤0.15; **Table**); tumour metabolic total volume (TMTV) remained the only independent adverse prognostic factor in multivariate analysis (p=0.0094). Across the 4 TMTV quartiles (Q), the proportion of primary refractory pts (33/284; 11.6%) found in Q4 was almost twice that in the other quartiles (18/283 [6.4%] in Q1, 4.9% [14/283] in Q2, 6.3% [18/286] in Q3), and a receiver operating characteristics analysis identified a TMTV >523.8 mL as the optimal cut-off for identification of primary refractory pts.

Conclusions: TMTV was the only independent prognostic factor for primary refractoriness in previously untreated pts with DLBCL, suggesting that responsiveness to immunochemotherapy is associated with tumour burden. Considering TMTV as a prognostic factor may assist in the identification of high-risk pts who may benefit from an alternative therapeutic strategy.

Disclosures: Trněný, M: Consultant Advisory Role: *Takeda, Bristol-Myers Squibb, Incyte, Abbvie, Amgen, Roche, Gilead Sciences, Janssen, Celgene, MorphoSys*; Honoraria: *Janssen, Gilead Sciences, Takeda, Bristol-Myers Squibb, Amgen, Abbvie, Roche, MorphoSys, Incyte*; Other Remuneration: *Expenses: Gilead Sciences, Takeda, Bristol-Myers Squibb, Roche, Janssen,*

021
RADIOMICS INCREASE THE PROGNOSTIC VALUE OF CLINICAL AND PET RISK FACTORS IN DLBCL: RESULTS FROM THE PHASE 3 GOYA STUDY

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Introduction: We investigated whether quantitative image texture analysis that measures tumour heterogeneity, i.e. radiomics, improves the prognostic value of baseline ^{18}F-fluorodeoxyglucose (FDG)-PET using PET/CT imaging data from the phase 3 GOYA trial (NCT01287741) of obinutuzumab (G) versus rituximab (R) plus CHOP in patients (pts) with previously untreated diffuse large B-cell lymphoma (DLBCL).

Figure. PFS probability over time according to IPI and radiomics feature 'GTSDM AC'.
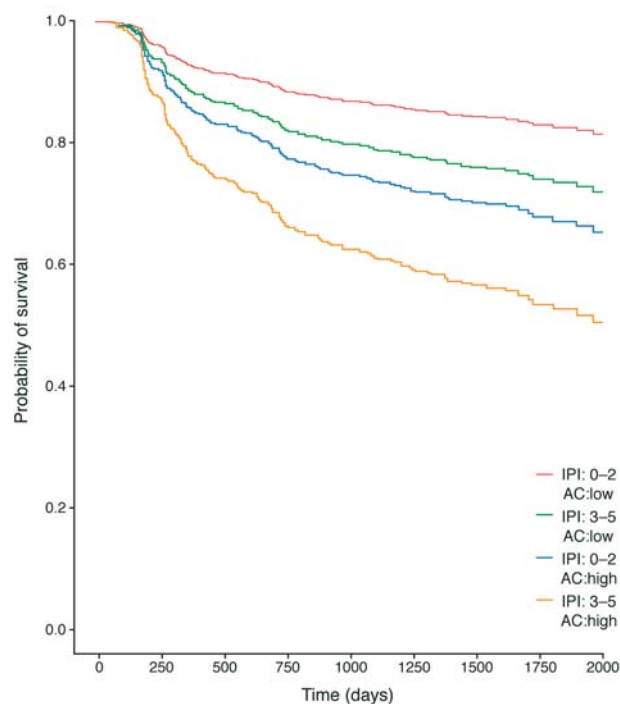
AC, autocorrelation; GTSDM, grey-tone spatial dependence matrix; IPI, International Prognostic Index; PFS, progression-free survival

Methods: GOYA enrolled 1418 pts from 207 centres. Pts were randomized to receive either G (1000 mg) or R (375 mg/m^2) every 21 days for 8 cycles, plus CHOP chemotherapy every 21 days for 6–8 cycles. A total of 1334 pts had a baseline FDG-PET scan with detectable lesions. Centrally analysed image data with annotated regions of interest (ROIs) were transferred to the Cuneo imaging core laboratory. The 42 Haralick radiomic image texture features (ITFs) were computed using the PET oncology radiomics test suite (PORTS) for lesions >5 mL. Random Forest analysis for survival data was applied to select the most important clinical, standardised uptake value, and ITF prognostic variables. The selected variables were then inserted into Cox models to predict progression-free survival (PFS).

Results: A total of 1085 radiomics-evaluable pts with 9307 lesions were analysed. Random Forest analysis identified the following important variables: International Prognostic Index (IPI), cell-of-origin (COO), Ann-Arbor stage, age, bone marrow involvement, total metabolic tumour volume (TMTV), and several ITFs (histogram skewness and energy, grey-tone spatial dependence matrix entropy, correlation, autocorrelation [AC], difference entropy, cluster shade, and low grey-level zone length matrix [GLZSM] emphasis). The accuracy of the Cox model for predicting PFS during a follow-up of 75 months was 0.61 with clinical variables only, 0.62 with the addition of TMTV, and 0.67 with the addition of ITFs. On multivariate analysis, statistically significant variables were IPI ≥3 (hazard ratio [HR] 1.6, p=0.004), non-germinal centre B-cell COO (HR 1.5, p=0.004), >median TMTV (HR 1.2, p=0.0004), AC ≥1100 (HR 1.7, p<0.001), difference entropy (HR 1.3, p=0.03), and GLZSM emphasis (HR 0.6, p=0.03). The radiomics AC feature shows improved

discrimination of PFS probability compared to IPI risk category (Figure). Preliminary analyses suggest that several ITF variables, e.g. AC, identified different 3-year PFS for pts treated with R-CHOP (51%, 95% confidence interval [CI] 33%–79%) versus those treated with G-CHOP (79%, 95% CI 68%–92%).

Conclusions: A prediction model based on quantitative image texture analysis by radiomics signatures increased the prognostic value of risk prediction of DLBCL patients at baseline. Further analyses with different algorithms are underway to improve the predictive value of radiomics and to develop an effective nomogram to stratify DLBCL pts by risk prior to first-line treatment.

022
PROGNOSTIC VALUE OF PRE-TREATMENT PET SCAN IN PATIENTS WITH FOLLICULAR LYMPHOMA RECEIVING FRONTLINE THERAPY

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Background: Positron emission tomography (PET) is recommended in follicular lymphoma (FL) for initial staging, evaluation of potential transformation, and response assessment. The prognostic value of pre-treatment PET scan in previously untreated FL patients has not been adequately explored.

Methods: We performed a single-institution retrospective analysis of patients with advanced stage low grade FL, without histological evidence of transformation, treated with frontline rituximab-based therapy at MD Anderson Cancer Center between 08/2001 and 04/2014, and analyzed the prognostic significance of maximum standardized uptake value (SUV_{max}) calculated from pre-treatment PET scan.

Results: Three-hundred and forty-six patients were included in the study and median pre-treatment SUV_{max} was 11 (range, 1.5-42). Among multiple single unit increments of SUV_{max}, a value of >18 (observed in 52 [15%] patients) showed the strongest association with progression-free survival (PFS)(hazard ratio [HR] 1.5, 95% confidence interval (CI) 0.95-2.3, p=0.08), and was selected as cut-off for further analysis. On univariate analysis, factors associated with SUV_{max} > 18 were male sex (67% vs 52%, p=0.05), elevated β2-microglobulin (65% vs 47%, p=0.02), elevated LDH (37% vs 13%, p<0.001), presence of B symptoms (35% vs 14%, p=0.01), and largest lymph node $\geq$ 6 cm (64% vs 30%, p<0.001). On multivariate analysis, largest lymph node $\geq$ 6 cm was the only factor maintaining its association with SUV_{max} > 18 (odds ratio [OR] 2.7, 95% CI 1.3-5.3, p=0.006). One-hundred and fifty-one (44%) patients were treated with frontline R-CHOP, and 195 (56%) with other therapies, including BR in 55 (16%) patients, R2 in 63 (18%), RFND in 24 (7%), and single agent rituximab in 53 (15%) patients. Two-hundred and thirty-two (65%) patients received maintenance rituximab and 114 (33%) were observed after completion of frontline therapy. While no differences in use of maintenance therapy were observed between the 2 groups (75% vs 67%, p=0.20), a significantly higher proportion of patients with baseline pre-treatment SUVmax 18 was treated with R-CHOP (75% vs 38%, p<0.001). SUV_{max} > 18 significantly associated with a lower CR rate among patients treated with non-R-CHOP regimens (45% vs 92%)(p<0.001) but not among patients treated with R-CHOP (p=1). SUV_{max} > 18 associated with significantly shorter PFS among patients treated with non-R-CHOP regimens (77 months vs not reached, p=0.02), but not among patients treated with R-CHOP (p=0.73) (Figure). SUV_{max} > 18 associated with shorter overall survival (OS) both in patients
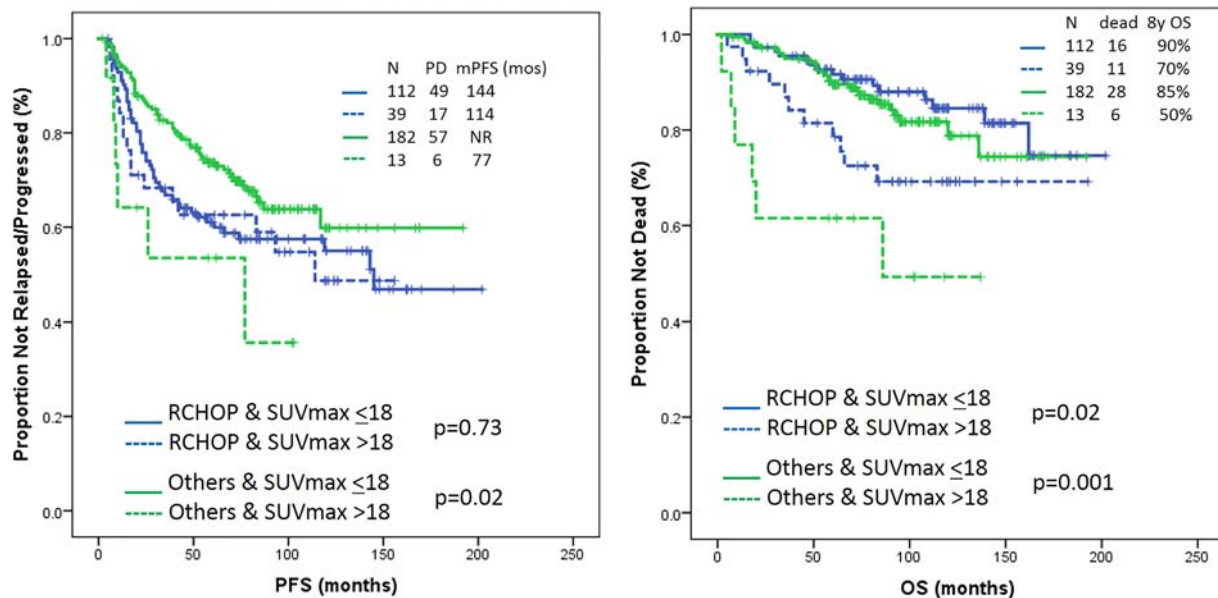
treated with R-CHOP (15 year OS 70% vs 75%, p=0.02) and non-R-CHOP regimens (15 year OS 50% vs 75%, p=0.001) (Figure).

Conclusions: In conclusion, pre-treatment SUV_{max} has prognostic value in patients with advanced stage FL receiving rituximab-based therapies, as it may suggest undiagnosed transformation and/or a more aggressive biology. Evaluation in prospective studies is needed to further confirm these findings.

Keywords: follicular lymphoma (FL); positron emission tomography (PET); R-CHOP.

FOCUS ON... SESSION: PEDIATRIC LYMPHOMA

023
NON-HODGKIN LYMPHOMA IN ADOLESCENT AND YOUNG ADULTS - A NATIONAL PROSPECTIVE POPULATION-BASED STUDY

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Introduction: Non-Hodgkin Lymphoma (NHL) is common but poorly understood in adolescents and young adults (AYA). English Cancer Registry records of NHL diagnosed 2008 to 2013 found patients aged 15-23y had 2y survivals, including all NHL types, 10% lower than younger children and 7% less than adults aged 24-30y. Inferior survival was most marked for diffuse large B-cell lymphoma (DLBCL) and Burkitt's lymphoma (BL). The reasons for these poor outcomes are unclear, particularly as AYA with NHL are infrequently recruited into clinical trials. The study purpose is to document the frequency of NHL subtypes, treatments and outcomes in AYA aged 15y to 29y, diagnosed in England and Wales during 4 years, January 2015 to December 2018, to understand the reasons for treatment failure.

Methods: The study records patient demographic and clinical data from two sources to create 2 separate, but overlapping cohorts. Cohort 1 is a whole population cohort based on information in the English Cancer Registry which includes patient demographics, diagnosis, where treated and updated vital status. It does not record treatment or response. Cohort 2 comprises consented patients treated at regional cancer centres in England and Wales. This cohort has record of diagnosis detail, staging, all treatments, response, survival to 2y from diagnosis, and notified of mortality to 5y.

Results: Cohort 1 shows an annual incidence of 250 new cases of NHL diagnosed in AYA annually, with approximately 125 cases aged 15 – 24y and 125 aged 25 – 29y. The most frequent population-based diagnoses being proportionally: DLBCL 38%, BL 15%, Primary Mediastinal NHL 8%, Follicular NHL 7%. We report here mortality rates for the 265 consented patients (cohort 2) with reported outcomes and median follow up of 24 months. There are 167 patients aged 15-24y and 98 patients 25-29y. Overall 14% have died. The highest mortality, in order of frequency: Hepato-splenic T-cell NHL 4/4 (100%), Peripheral T-cell 2/3 (66%), T-Lymphoblastic 4/7 (57%), BL 11/34 (32%), non-GC DLBCL 10/64 (16%), Alk+ ALCL 2/17 (12%), post-transplant LPD 2/17 (12%). Mortality is greater in the 25 – 29y patient group, but early death more frequent in 15 – 24y olds; 7 patients are recorded as dying within 24h of hospital admission.

Conclusions: This preliminary analysis highlights the poor prognosis of T-cell NHL at this age. More surprising is the 32% deaths in Burkitt's

lymphoma, a disease with excellent outcome in younger children. It is worrying that 7 patients have died soon after presentation, perhaps highlighting the consequences of delayed diagnosis at this age.

024

INCLUSION OF A PEDIATRIC PERSPECTIVE INTO RECOMMENDATIONS FOR THE INITIAL EVALUATION AND STAGING OF HODGKIN LYMPHOMA: A CALL TO ACTION FROM THE INTERNATIONAL SEARCH WORKING GROUP

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Introduction: Initial evaluation and staging of patients with Hodgkin lymphoma (HL) provides the foundation for formulation of a risk-adapted treatment plan. The Ann Arbor staging system at first, and later the Cotswolds modifications criteria, have helped classify patients into risk groups according to the distribution and number of anatomic sites of disease. As imaging has evolved over the years fewer invasive measures (laparotomy with splenectomy or bone marrow biopsies) are required to determine involved sites. However, radiologic advances have created new challenges as they allow for volumetric measurements of disease; factors such as "bulk" disease are now prognostic and part of staging. Further refinements to the staging of patients with HL are needed to allow for improved prognostication and assignment to risk groups. While the treatment regimens for pediatric Hodgkin lymphoma have somewhat differed from that of adults with a goal to minimize late-effects and specific cumulative drug dosages for this young and surviving population, the staging is the same as for adults.

Methods: The International SEARCH (Staging, Evaluation and Response Criteria Harmonization) for CAYAHL (Childhood, Adolescent and Young Adult Hodgkin Lymphoma) group is comprised of representatives from the Children's Oncology Group, European Network for Pediatric HL, St. Jude-Stanford-Dana-Farber consortium, and the Asociación de Hemato-Oncología Pediátrica de Centro América to facilitate the interpretation and comparison of clinical studies worldwide. As we look ahead to potential changes in the staging of HL, we feel it is important to ensure pediatric representation from the SEARCH for CAYAHL group. Given that adolescent and young adult patients are a known peak age range for HL and shared between the adult and pediatric groups, the more unified the staging remains across all age ranges, the better patient outcomes can be compared between trials and inform decision-making. In an era where positron emission tomography scans are the standard for initial staging work up, many new strategies such as the utilization of total metabolic tumor volume, may provide an improved methodology for staging.

Conclusion: As the field of HL moves forward, initial staging is an evolving process. Despite differences in the treatment of pediatric and adult patients with HL there is a need to ensure consistency in the staging between the groups. The SEARCH for CAYAHL working group has representation from all major pediatric consortia and should work together with colleagues from the adult groups towards a common goal and vision for the establishment of new staging criteria.

025

SAFETY AND RESPONSE AFTER 2 CYCLES OF BRENTUXIMAB VEDOTIN SUBSTITUTING VINCRISTINE IN THE OEPA/COPDAC REGIMEN FOR HIGH RISK PEDIATRIC HODGKIN LYMPHOMA (HL)

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Introduction: This study regimen is based on theGPOH-HD 2002 study that demonstrated 5-year EFS and OS of 87% and 95% respectively with 6 cycles OEPA/COPDAC and 20-30 Gy IFRT. The subsequent EuroNet-C1 study showed that 30% of high-risk patients achieved an adequate response (AR) after 2 cycles of OEPA and could forgo radiation therapy. To explore if radiation could be reduced further, this study substituted Brentuximab vedotin (Bv) for vincristine in the regimen.

Methods: Children≤ 18 years of age, newly diagnosed with stage IIB, IIIB, and IV classical Hodgkin lymphoma were treated with Bv substituting vincristine (AEPA/CAPDac) and 25 Gy ISRT only to areas not in CR at early response evaluation (CR: >75% anatomic response - product of 2 perpendicular diameters of lesions by CT and Deauville Score (DS) < 4 on PET). Objectives: To evaluate the safety of AEPA/CAPDac and the efficacy, defined as the number of patients achieving AR when retrospectively applying the Euro-Net C1 criteria (AR: residual tumor volume ≤50% [CT/MRI] and DS < 3 in lesions ≥ 2 cm and DS < 2 in smaller lesions) following 2 cycles of AEPA.

Results: 77 patients were enrolled in this multi-institutional trial between 8/2013 and 2/2018 (table). Therapy was well-tolerated with most common adverse events being leukopenia and excessive weight gain. Peripheral neuropathy was rarely reported (mostly grade 2; 3 grade 3). Events included one cardiac death (arrhythmia associated to pancarditis) during therapy and one disease progression in an originally involved site (now disease free > 4 years after retrieval therapy). The first 32 enrolled patients were available for post-hoc EuroNet-C1 response assessment. The proportion of patients achieving AR following AEPA (x2) using the EuroNet-C1 criteria did not differ from that observed after OEPA (x2) in EuroNet C1, TG3 28% versus 30% (90% CI [16; 44]).

Conclusions: AEPA/CAPDac is very well tolerated without substantial neurotoxicity. Substitution of vincristine with Bv did not reduce the proportion of individuals receiving radiation compared to EuroNet-C1 trial; however, radiating only sites of inadequate response (less than 1 out of 5 sites) rather than all sites of initial disease reduces the number of sites treated. Additional follow-up is required to determine the sustainability of disease free and overall survival. This is a PI initiated trial, sponsored by Seattle Genetics Inc.

Keywords: brentuximab vedotin; Hodgkin lymphoma (HL).

Disclosures: Metzger, M: Research Funding: *Seattle Genetics.*

TABLE 1 Patient characteristics

Characteristic	N (%)
Total 77 patients	
Gender	
Female	39 (51)
Male	38 (49)
Age at diagnosis in yrs	
Median (range)	16.2 (6.0 -18.99)
Race	
White	51 (66)
Black	16 (21)
Asian	4 (5)
Other	6 (8)
Histology	
Nodular sclerosing	59 (77)
Lymphocyte rich	4 (5)
Mixed cellularity	3 (4)
Classical NOS	11 (14)
Stages	
IIB	13 (17)
IIIB	19 (25)
IVA	12 (16)
IVB	33 (43)

026

RESPONSE-ADAPTED TREATMENT WITH NIVOLUMAB AND BRENTUXIMAB VEDOTIN IN YOUNG PATIENTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA: CHECKMATE 744 SUBGROUP ANALYSES

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Introduction: New strategies for first salvage therapy (tx) are required for young patients (pts) with relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) to improve cure rates and long-term safety, particularly in pts with primary refractory cHL. In adult R/R cHL, first salvage with nivolumab + brentuximab vedotin (BV) resulted in 82% objective response rate (ORR) with 61% complete metabolic response (CMR). CheckMate 744 (NCT02927769) is an ongoing phase 2 study evaluating a risk-stratified, response-adapted approach using nivolumab, BV, and bendamustine (benda) in children, adolescents, and young adults with R/R cHL. In the standard-risk cohort, the regimen was well tolerated and resulted in high CMR rates prior to consolidation with high-dose chemotherapy (HDCT)/autologous transplantation (auto-HCT). Here, we evaluate this approach in primary refractory pts, and in pediatric pts (aged < 18 y) in CheckMate 744, focusing on the nivolumab + BV induction (IND) phase.

Methods: Pts aged 5–30 y, after 1 prior tx without auto-HCT were eligible. Risk stratification was based on disease stage at diagnosis, time to relapse, B symptoms or extranodal disease at relapse, extensive disease with radiation tx (RT) contraindicated at relapse, or relapse in a prior RT field. In the standard-risk (R2) cohort, pts received 4 IND cycles with nivolumab + BV. Tumors were assessed every 2 cycles by investigators and blinded independent central review (BICR) per Lugano 2014 criteria. Pts who achieved CMR any time after cycle 4 proceeded to HDCT/auto-HCT consolidation. Pts with suboptimal response after IND received 2–4 cycles of BV + benda intensification (INT). Primary endpoint was CMR rate per BICR any time before consolidation. Efficacy and safety in primary refractory pts, and in pts aged < 18 y were post hoc analyses.

Results: 44 pts were treated in the R2 cohort. At baseline, median age was 16 y; 31 pts (70%) were aged < 18 y and 24 (55%) had primary refractory disease. Median follow-up was 43 wk overall and 47 wk in pts aged < 18 y. Ten pts aged < 18 y entered INT; of these, only 2 received 4 INT cycles. CMR rates and ORR per BICR after IND and any time prior to consolidation for primary refractory pts and pts aged < 18 y are shown in the **Table**. Overall, 12/44 pts (27%) experienced a grade (G) 3–4 tx-related adverse event (TRAE). Among pts aged < 18 y, 10/31 (32%) experienced a G3–4 TRAE, most commonly neutropenia (2/31 pts; 6%); no deaths or TRAEs led to discontinuation. Tx-related immune-mediated AEs were all G1–2, and were maculopapular rash, hypersensitivity, and infusion-related reaction (1 pt each).

Conclusions: Response-adapted tx with nivolumab + BV achieved high CMR rates after 4 IND cycles in primary refractory pts with cHL. In pediatric pts with a standard risk of relapse, IND with nivolumab + BV, followed by BV + benda INT for suboptimal response, demonstrated high CMR rates and favorable safety prior to consolidation.

Keywords: brentuximab vedotin; classical Hodgkin lymphoma (cHL); nivolumab.

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IBRUTINIB + CHEMOIMMUNOTHERAPY (CIT) FOR RELAPSED/REFRACTORY MATURE B-CELL NON-HODGKIN LYMPHOMA (B-NHL) IN CHILDREN (SPARKLE TRIAL): INITIAL SAFETY, PK, AND EFFICACY

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Table. CMR rates and ORR in primary refractory patients and in pediatric patients (aged <18 y) per BICR

n (%)	Overall (n=44)	Primary refractory (n=24)	Pediatric (aged <18 y) (n=31)
After nivolumab + BV induction			
CMR	26 (59)	15 (63)	18 (58)
ORR	36 (82)	19 (79)	25 (81)
Any time prior to consolidation			
CMR	38 (86)	20 (83)	27 (87)

Figure. Ibrutinib Exposures With 240-440 mg/m² Doses. Box/whisker plots of estimated AUC on PK occasions by cycle and day for each dose for (A) AUC$_\tau$ (estimated AUC of 24-hour dosing interval) and (B) AUC$_\infty$ (dose*F/CL; predicted AUC at steady state). Solid line represents median, box represents 25/75%, and whiskers represent 10/90% confidence interval. (C) AUC$_\tau$ vs age and (D) AUC$_\tau$ vs body surface area (BSA). Lines represent individual patients, color represents dose, and symbol represents PK occasion.
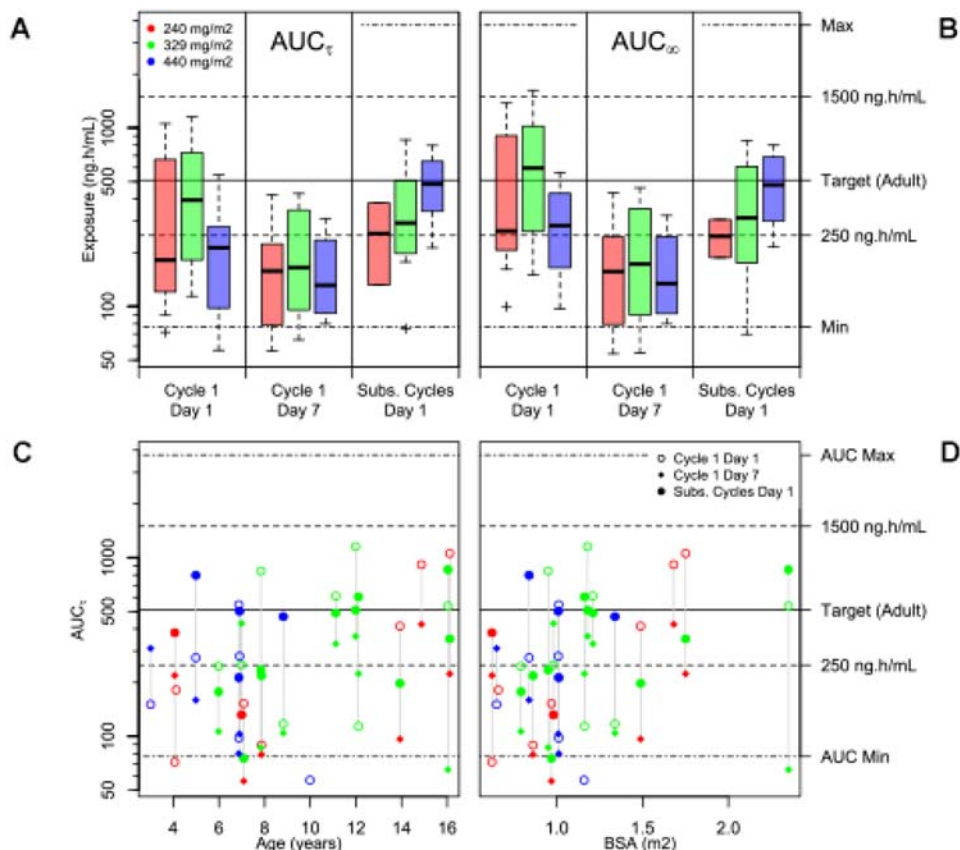
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Introduction: The survival of children with relapsed/refractory (R/R) B-NHL is < 40%. Ibrutinib (ibr), a BTK inhibitor indicated for adult B-cell malignancies, has shown significant preclinical activity in Burkitt lymphoma (BL). We report results from the run-in phase of an ongoing phase 3 trial of ibr + CIT in pediatric R/R mature B-NHL.

Methods: SPARKLE (NCT02703272) is a 2-part, randomized, open-label trial assessing the safety and efficacy of ibr + rituximab, ifosfamide, carboplatin, etoposide (RICE), and dexamethasone (D) or R, vincristine, idarubicin, C, I (RVICI), and D CIT vs CIT alone in pediatric R/R mature B-NHL. Part 1 is a safety/PK run-in in ~ 24 planned patients (pts) aged 1 to < 18 years (yrs) treated with ibr up to 440 mg/m²/day (max 560 mg/day for 28-day cycles) by oral suspension/capsule + 3 cycles of RICE or RVICI. Ibr was initiated at 240 mg/m² and escalated if no safety concerns. Ibr exposure (area under concentration-time curve [AUC]), safety, and preliminary efficacy were assessed. In Part 2, additional pts are randomized to ibr + CIT or CIT alone.

Results: As of Dec 7, 2018, 21 pts had received ≥ 1 dose of ibr (11 ibr + RICE; 10 ibr + RVICI): 13 had BL, 2 Burkitt-like lymphoma, 3 diffuse large B-cell lymphoma (DLBCL), 2 primary mediastinal BCL, and 1 high-grade BCL. Median age was 8 (range, 3-17) yrs. 33.3% of pts had > 1 prior line of therapy. In the ibr + RICE and ibr + RVICI arms, respectively, median cycle number (range) was 3 (1-4) and 2 (1-4), and median ibr relative dose intensity was 66.3% and 43.4%. AUCs (n = 20) were within target range (250-1500 ng.h/mL) in the 12-17 yr age group (n = 6), supporting the 329 mg/m² dose. AUCs at this dose were lower than expected in younger pts (n = 14), prompting an increase to 440 mg/m². No AUC value was > 1500 ng.h/mL (Figure). 3 pts completed treatment (tx), 1 remains on study, and 17 discontinued early (5 death; 3 progression [PD]; 1 investigator decision; 8 HSCT).

All pts had ≥ 1 tx-emergent adverse event (TEAE) grade (gr) ≥ 3 (18 tx [ibr or RICE/RVICI] related), with hematologic, gastrointestinal, and infectious events being most common (≥ 50%); 19 had a serious AE (all gr ≥ 3; 7 tx related); no TEAEs led to discontinuation. 5 pts (2 ibr + RICE, 3 ibr + RVICI) had a major hemorrhage event (all gr 3/4); 2 events were possibly related to ibr. 13 pts died: 4 from sepsis (1 ibr

+ RICE, 3 ibr + RVICI), 9 from PD (3 ibr + RICE, 6 ibr + RVICI). Overall response rate was 57.1% (12/21) in all pts (7 complete, 5 partial responses): 72.7% (8/11) with ibr + RICE and 40% (4/10) with ibr + RVICI. Median event-free survival was not reached with ibr + RICE and was 2.4 months with ibr + RVICI.

Conclusions: These results support continued assessment of ibr + RICE/RVICI in this poor prognosis pediatric population. Safety is consistent with known profiles of the drugs in the combination regimens. Part 2 is ongoing, assessing the efficacy of the combination with ibr at 440 mg/m2 and 329 mg/m2 in pts aged < 12 and ≥ 12 yrs, respectively.

Keywords: ibrutinib; immunochemotherapy; non-Hodgkin lymphoma (NHL).

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CHIMERIC ANTIGEN RECEPTOR T-CELLS (CAR-T) FOR REFRACTORY AND RELAPSED BURKITT'S LYMPHOMA: EARLY RESPONSE IN PEDIATRIC PATIENTS

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Introduction: Pediatric patients with relapsed or refractory Burkitt's lymphoma (BL) present as a major challenge due to their poor outcomes despite use of high-intensity chemotherapy and anti-CD20 monoclonal antibody (mAb). CAR-T has shown efficacy in treating refractory or relapsed leukemia and Non-Hodgkin Lymphoma in adult patients. The aim of our study is to assess the safety and efficacy of CAR-T in the treatment of refractory or relapsed BL in pediatric patients.

Methods: Patients with refractory/relapsed BL were enrolled to clinical trial (ChiCTR18000144) during January 2018-January 2019. The inclusion criteria were: 1) No complete remission (CR) after at least 5 courses of standard chemotherapy plus anti-CD20 mAb; or 2) No partial remission (PR) or showing progression after 2 courses of second-line chemotherapy; and 3) High expression of at least one B cells markers (CD19/CD20/CD22) examined by immunohistochemistry. The highest expressed marker was chosen for the first round CAR-T target. The therapeutic doses of CAR-T range from $1 \times 10^{\check{}}6$ to $3 \times 10^{\check{}}6$ per kilogram of body weight each course. The CAR-T cell numbers and cytokines were measured weekly. Tumor responses were evaluated at day 30 and day 60 post infusion and every two months thereafter.

Results: Five refractory or relapsed BL patients, aged 6 to 10 years with a median age of 8 years, were enrolled, 4 males (80%) and 1 female (20%) according to St Jude's staging at the initial diagnosis: 3 cases (60%) in stage III, 2 cases (40%) in stage IV, 1 case of CNS invasion (20%), 1 case of bone marrow invasion (20%). They all failed initial intense chemotherapy and anti-CD20 mAb treatment (Table 1). They were then treated with 1 to 3 rounds of CAR-T (Table 2). Patients were monitored for CAR-T side effects: fever, gastro-intestine discomfort, rash, capillary leak syndrome, Immuno-pneumonia, tremor, hypotension, immunocytopenia, abnormal coagulation, liver dysfunction. One patient (20%) was diagnosed of cytokine-release syndrome (CRS) grading I and the other four grading III(80%). All subjects recovered fully after active symptomatic and supportive treatment including application of glucocorticoids in CRS grading III, but no patient required Tombuzumab. There were no death events (Table 2). Three subjects (60%) achieved CR by one round of CD19 CAR-T cell therapy, while two subjects (40%) achieved PR with first round of CD19 CAR-T treatment and achieved CR with subsequent CD22 or CD22 and CD20 CAR-T. The overall response rate (OR) was 100% with a median follow up 249 days, range 62-382 days, last follow up date January 30, 2019. (Table 3). Currently, all patients were in event-free survival.

Conclusion: CD19/CD20/CD22-CAR-T therapy showed a robust efficacy in pediatric patients with refractory and relapsed BL and the toxicity profiles were moderate and could be well controlled.

Keywords: Burkitt lymphoma (BL); CD19; CD22.

TABLE 1 Clinical characteristics of enrolled patients

NO.	Onset age (Y)	Relapsed/ refractory	Stage	Risk group	Chemotherapy (courses)	Rituximab (courses)	Radiotherapy
01	6	refractory	III	C1	7	6	no
02	8	refractory	III	C1	5	5	no
03	9	refractory	IV	C1	6	6	no
04	9	relapsed	III	C1	9	5	yes
05	10	relapsed	IV	C2	8	7	no

TABLE 2 CRS in enrolled patients

CRS	01	02	03	04	05
High fever	+	+	+	+	+
Fatigue, myalgia, joint pain, loss of appetite, etc.	+	+	+	+	+
Cough	+	+	-	+	+
Dyspnea	+	+	-	-	-
pulmonary exudative changes	+	+	+	-	+
Nausea, vomiting, diarrhea, abdominal pain, etc.	-	-	+	-	-
Stomatitis	-	-	-	-	+
Rash, itching	+	+	-	-	-
Hypotension	-	-	+	-	-
Arrhythmia, bradycardia, tachycardia	-	-	-	-	-
Oliguria, gross hematuria, foamy urine	-	-	-	-	-
Creatinine and urea nitrogen increase	-	-	-	-	-
Liver damage	+	+	+	-	+
Coagulopathy	+	+	+	+	+
Capillary leak syndrome	-	-	-	-	+
Tremor	-	-	+	-	-
Application of glucocorticoid	+	+	+	-	+
Application of tombuzumab	-	-	-	-	-
CRS grading	III	III	III	I	III

TABLE 3 Efficacy evaluation

NO.	Tumor site before CAR-T	Tumor size before CAR-T(cm^3)	Pathological reexamination	CAR-T (courses)	CAR-T target	efficacy	Time to CR (days)	Current state	Continuous remission time (days)
01	abdominal	10.5×7.5×5.7 7.2×5.9×6.0	No	2	CD19	PR			
					CD22	CR	76	EFS	306
02	abdominal	7.1*6.0*11	yes	1	CD19	CR	30	EFS	214
03	neck	3.5*3.5	no	3	CD19	PR			
		5.0*3.5	yes		CD22	PR			
		2.0×1.0	yes		CD20	CR	186	EFS	128
04	abdominal	7.2*2.3*6.3	yes	1	CD19	CR	30	EFS	96
05	Gums	7.0*3.4*3.5	no	1	CD19	CR	to be evaluated	EFS	to be evaluated

FOCUS ON... SESSION: RESULTS FROM SINGLE AGENT TRIALS

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PHASE 2 STUDY OF ACALABRUTINIB IN IBRUTINIB-INTOLERANT PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

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TABLE 1

	N=60
Overall response rate (≥ PRL), n (%)	46 (77)
95% CI	64, 87
CR	1 (2)
PR	42 (70)
PRL	3 (5)
Median PFS	Not reached
21-month PFS rate, % (95% CI)	76 (61, 86)

Abbreviations: CR, complete response; PFS, progression-free survival; PR, partial response; PRL, partial response with lymphocytosis.

Background: In patients with chronic lymphocytic leukemia (CLL) treated with the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, intolerance was the most common reason for discontinuation (50% to 63%; Mato AR, et al. *Haematologica.* 2018). This Phase 2 trial evaluated acalabrutinib, a highly selective, potent, covalent BTK inhibitor, in ibrutinib-intolerant patients with relapsed/refractory CLL.

Methods: Patients with relapsed/refractory CLL (≥1 prior therapy) who discontinued ibrutinib due to Grade 3/4 adverse events or persistent/recurrent Grade 2 adverse events and had progressive disease after ibrutinib discontinuation were eligible. Acalabrutinib was given orally at 100 mg twice daily in 28-day cycles until progressive disease or unacceptable toxicity. The primary endpoint was overall response rate.

Results: Sixty patients were treated. The median age was 70 years (range, 43 to 88). Patient characteristics included bulky disease ≥5 cm (33%), Rai stage III/IV (47%), del17p (28%), del11q (23%), and unmutated *IGHV* (79%). Fifty-two of 55 patients (95%) with available baseline samples were wild type for *BTK* and *PLCG2*. The median number of prior therapies was 2 (range, 1 to 10). The median duration of prior ibrutinib therapy was 6 months (range, <1 to 55); common adverse events that led to ibrutinib discontinuation were atrial fibrillation/flutter (25%), diarrhea (12%), arthralgia (10%), and rash (12%). At a median follow-up of 19 months (range, 1 to 31), 67% of patients remain on acalabrutinib; discontinuations were mostly due to progressive disease (13%) and adverse events (10%; pneumonia [n=2], diarrhea, headache, ascites, arthralgia, subdural hematoma [all n=1]). Efficacy outcomes are in the **Table**. Common adverse events (any grade) were diarrhea (48%), headache (40%), contusion (35%), and dizziness (32%). Serious adverse events (≥2 patients) were pneumonia (10%), anemia (3%), and syncope (3%). Atrial fibrillation occurred in 3 patients (5%; all Grade 1/2) and major hemorrhage in 2 (3%; Grade 3 hematuria and Grade 2 subdural hematoma). Grade 5 adverse events were pneumonia (n=2), bronchopulmonary aspergillosis (n=1), and ventricular fibrillation (n=1); all were considered not related to treatment.

Conclusions: Acalabrutinib is tolerable and effective in ibrutinib-intolerant patients, providing a viable strategy for continuing BTK inhibitor therapy.

Keywords: BTK inhibitors.

030
RAPID AND DURABLE RESPONSES WITH THE SYK/JAK INHIBITOR CERDULATINIB IN A PHASE 2 STUDY IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA—ALONE OR IN COMBINATION WITH RITUXIMAB

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Background: Despite recent advances, follicular lymphoma (FL) remains incurable for most patients (pts). Relapsed/refractory (r/r) FL is associated with decremental treatment responses, accumulating toxicity, and poor survival among early failures of 1st line chemo-immunotherapy. Underscored by the recent approvals of idelalisib, copanlisib, and duvelisib, targeting B-cell receptor (BCR) signaling produces ORR of ~50% in r/r pts; however, new agents with a better therapeutic index over long-term administration are needed.

SYK is a key regulator of BCR signaling (upstream of BTK and PI3K), and its inhibition results in clinical activity in FL. Compared with unaffected nodes, lymph nodes from FL pts have greater numbers of follicular helper T cells that express high levels of IL-4, which may support the tumor via the JAK1/3 pathway.

Cerdulatinib, an oral, reversible inhibitor of SYK and JAK kinases (JAK1, JAK3, TYK2), previously reported a ~45% ORR in r/r FL as a single agent. Xenograft studies suggest cerdulatinib may combine with rituximab to enhance antitumor activity. We report updated results from a Ph2a study of single-agent cerdulatinib and initial results in combination with rituximab in r/r FL.

Methods: This Ph2a study confirmed the safety and efficacy of cerdulatinib 30 mg BID in r/r B- and T-cell lymphoma pts. Dose reductions were permitted to 15 mg BID. Response was assessed by Lugano criteria.

Results: As of Jan 2019, enrollment was 40 pts in the single-agent cohort and 11 in the rituximab combination cohort. Median (range) age was 64 (42-81) and median prior therapies was 3 (1-8). Fifty (98%) pts had prior anti-CD20 therapy, and 8 (16%) had prior PI3K or BTK inhibitors. The most common AEs of any grade were diarrhea (47%), nausea (37%), lipase increase (29%), and amylase increase (22%). Grade 3+ AEs in ≥5% pts were lipase increase (24%), diarrhea (12%), amylase increase (10%), nausea (8%), hypertension (8%), and neutropenia (6%). Grade 3+ infections occurred in 6 (12%) pts. One pt had grade 5 multi-organ failure potentially related to study drug. Amylase and lipase increases generally were not associated with abdominal pain or pancreatitis. The safety profile appeared similar in both cohorts.

The ORR was 46% as a single agent (5 CRs, 13 PRs in 40 pts) and 67% in the combination cohort (4/6 PRs; 2 pts with SD had a >40% reduction in tumor volume at 1st re-scan). Responses typically occurred after 2 cycles and were durable in the single-agent cohort, with 10 pts on drug for >1 year. Enrollment in the combination cohort is ongoing. Updated safety and efficacy will be presented.

Conclusion: The recommended cerdulatinib Ph2 dose of 30 mg BID was tolerable and efficacious in heavily pretreated r/r FL. The cerdulatinib + rituximab combination appears to be well tolerated, with tumor reductions in all evaluable pts. The safety profile and unique MOA of cerdulatinib support further combination studies in FL.

Keywords: follicular lymphoma (FL); JAK/STAT; SYK.

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A PHASE 2B STUDY OF SELINEXOR IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Introduction: Patients (pts) with R/R DLBCL who have received at least 2 lines of therapy, including pts who have progressed post stem cell transplantation (SCT) or who are not candidates for SCT, have limited treatment options. Active novel therapies with different mechanisms of actions are needed to improve the survival of these pts. Selinexor, a selective oral XPO1 inhibitor, leads to nuclear accumulation and activation of tumor suppressor proteins (e.g., p53, p21, and IkB), and reductions in c-Myc and Bcl-2 oncogenes. Single agent selinexor in heavily treated DLBCL demonstrated an overall response rate (ORR) of 25.6% with complete response (CR) in 9.3%, in a phase 1 study. To confirm these findings, a phase 2b study of selinexor was initiated.
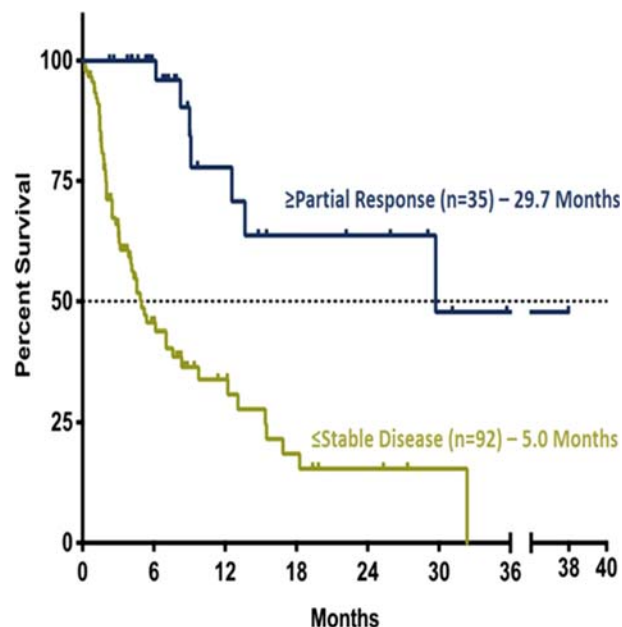
Methods: This is a multicenter, open-label study in pts with R/R DLBCL who have received 2-5 lines of prior therapy. Pts may have progressed post SCT or are not candidates for SCT. Pts were stratified by subtype (germinal center B-cell [GCB] or non-GCB) and treated with 60 mg selinexor twice weekly per 28-day cycle. The primary endpoint was ORR. Secondary endpoints included duration of response (DOR) and assessment of safety. Disease response was assessed by an Independent Central Radiological Review (ICRR), using the Lugano Classification.

Results: 129 pts were enrolled (76 M, 53 F). Median age was 67 years (54% of pts >65 years). Median number of prior therapies was 2 (range 1-6), 34% of pts received ≥3 prior therapies, and 31% of pts had prior SCT. Two pts did not meet eligibility requirements and were excluded from the analysis. Treatment-related serious adverse events (SAEs) were reported in 21% of pts. The most frequently reported treatment-related AEs (Grades 3, 4) included: nausea (6%, 0%), thrombocytopenia (24%, 13%), fatigue (9%, 0%), anorexia (3%, 0%), and anemia (13%, 1%). Of the 85.8% pts who discontinued treatment, the majority were due to progressive disease and 9.3% were due to AEs. The ICRR determined ORR was 27.6% (14 CRs and 21 partial responses). The ORR was 32.2% for GCB and 20.6% for non-GCB subtypes. Median time to response was 57 days (range 47-115 days) and the median DOR was 8.4 months; pts with a CR had a median DOR of 13.4 months. Median progression free survival was 3.6 months. The median overall survival (OS) was 9.1 months. Median OS in pts ≥partial response was 29.7 months which was significantly longer than the 5.0 months observed in pts ≤stable disease (p<0.0001) [Figure 1].

Conclusion: Single agent, oral selinexor demonstrated deep and durable responses in R/R DLBCL (ORR of 27.6% and DOR of 8.4 months). No new safety signals were identified; AEs were managed with dose modification and/or supportive care. Clinical benefit was observed across both GCB and non-GCB subtypes. These results underscore the potential of selinexor as a novel therapy for R/R DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL).

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TIPIFARNIB IN RELAPSED OR REFRACTORY ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA (AITL) AND CXCL12+ PERIPHERAL T-CELL LYMPHOMA (PTCL): PRELIMINARY RESULTS FROM A PHASE 2 STUDY

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Introduction: Tipifarnib is a potent and selective inhibitor of the enzyme farnesyltransferase (FT). CXCL12 is a chemokine that is essential for T cell homing to lymphoid organs and the bone marrow, and for the maintenance of immune cell progenitors. Tipifarnib has previously been shown to modulate the CXCL12 pathway and to drive clinical activity in CXCL12-expressing T cell lymphomas.

Methods: This Phase 2 study (NCT02464228) is a multi-institutional, single-arm, open-label trial initially designed as a two-stage (11+7 pts) study to determine the efficacy, safety and biomarkers of tipifarnib in pts with relapsed/refractory (R/R) PTCL. Based on initial findings, the study was amended to include a cohort of AITL (n=12) and PTCL (n=12) with the CXCL12 rs2839695 A/A genotype (CXCL12+ cohort). Pts received tipifarnib 300 mg orally twice daily on days 1-21 of 28-day treatment cycles. The primary endpoint is overall response rate (ORR). Ancillary studies are ongoing to investigate the prognostic value of CXCL12 expression in pts who received standard of care treatment.

Results: As of 20 February 2019, 43 PTCL pts (20 AITL, 21 PTCL-NOS, 1 ALK- ALCL, 1 gamma-delta TCL) have been treated with tipifarnib, 19 pts in stages 1 and 2, and 24 pts in the ongoing AITL histology and CXCL12 cohort. Median number of prior treatment regimens was 3; 19 pts had a prior stem cell transplant. All pts had at least 1 treatment-emergent adverse event (TEAE); 39 (90%) had at least 1 drug-related TEAE and 12 (28%) at least 1 drug related SAE. The most frequently observed drug-related TEAEs of Grade >3 occurring in >10% of pts were blood and lymphatic system disorders, including neutropenia (44%), thrombocytopenia (37%), leukopenia (28%), anemia (21%) and febrile neutropenia (21%). There have been 14 deaths on study; none were related to study drug. Of 18 evaluable pts enrolled in Stages 1 and 2 of the trial, 3 partial responses (PR), 2 of them in pts with AITL histology, and 4 best responses of stable disease (SD) were observed. In the AITL cohort (11 evaluable pts), a 45% ORR and 73% clinical benefit rate (CBR; 3 CR, 2 PR and 3 SD) was observed. In the CXCL12+ cohort (n=3 evaluable pts), 1 PR and 2 SD have been observed, with 4 pts pending cycle 2 response evaluation. CXCL12 expression correlated with favorable outcome to tipifarnib treatment. Pre-treatment high CXCL12 expression had 90% sensitivity and 93% specificity to identify pts who experienced CR/PR/SD on study in a preliminary analysis of 24 pts. The prognosis of CXCL12 was retrospectively investigated in 73 pts who received standard of care therapy (AITL N=50, PTCL NOS=23). A trend for poor prognosis (22 vs 40 months median OS from diagnosis, HR=1.8, p=0.09) was observed in the high CXCL12 subset using the cut-off point that predicted clinical benefit under tipifarnib therapy.

Conclusion: Preliminary activity of tipifarnib was observed in PTCL pts, particularly in those with tumors of AITL histology and high CXCL12 expression and enrollment in the CXCL12+ cohort continues.

Keywords: angioimmunoblastic T-cell lymphoma (AITL); peripheral T-cell lymphomas (PTCL).

Disclosures: Witzig, T: Research Funding: *Study Investigator for KO-TIP-002 (Kura Oncology).* **Sokol, L:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **Kim, W:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **Foss, F:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **Jacobsen, E:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **de la Cruz Vincente, F:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **Caballero, D:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **Advani, R:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **Roncero Vidal, J:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **Marin-Niebla, A:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **Rodriguez Izquierdo, A:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **de Ona Navarrete, R:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **Terol, M:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **Domingo-Domenech, E:** Research Funding: *Investigator for KO-TIP-002 (Kura Oncology Sponsored Clinical Study).* **Rodriguez, M:** Research Funding: *Kura Oncology.* **Piris, M:** Research Funding: *Kura Oncology.* **Bolognese, J:** Consultant Advisory Role: *Kura Oncology.* **Janes, M:** Consultant Advisory Role: *Kura Oncology.* **Burrows, F:** Employment Leadership Position: *Kura Oncology;* Stock Ownership: *Kura Oncology.* **Kessler, L:** Employment Leadership Position: *Kura Oncology;* Stock Ownership: *Kura Oncology.* **Mishra, V:** Employment Leadership Position: *Kura Oncology;* Stock Ownership: *Kura Oncology.* **Curry, R:** Employment Leadership Position: *Kura Oncology;* Stock Ownership: *Kura Oncology.* **Kurman, M:** Employment Leadership Position: *Kura Oncology;* Stock Ownership: *Kura Oncology.* **Scholz, C:** Employment Leadership Position: *Kura Oncology;* Stock Ownership: *Kura Oncology.* **Gualberto, A:** Employment Leadership Position: *Kura Oncology;* Stock Ownership: *Kura Oncology.*

033

Duvelisib, an oral dual PI3K-δ,γ inhibitor, efficacy and safety in patients with relapsed or refractory (RR) peripheral T-cell lymphoma: rationale for the phase 2 PRIMO trial

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Background: RR PTCL is associated with a poor prognosis, with most therapies inducing responses in <30% of pts and median progression-free survival (PFS) <4 mo. Phosphoinositide-3-kinase (PI3K) pathway has a role in survival and proliferation of malignant T cells, as well as T-cell receptor and cytokine signaling in nonmalignant T cells. Duvelisib (DUV), an oral dual PI3K-δ-γ inhibitor, exhibited potent activity against T-cell lymphoma (TCL) cell lines in vitro and reprogrammed tumor-associated macrophages from the immunosuppressive M2-like phenotype to the inflammatory M1-like phenotype (Horwitz, *Blood* 2018). DUV monotherapy 25 mg BID is FDA approved for the treatment of RR CLL/SLL in pts who have received ≥2 lines of prior therapy and RR follicular lymphoma in pts who have received ≥2 lines of prior systemic therapy. The optimal dose of DUV in TCL is undefined. Here we summarize the safety and activity of DUV in pts with RR PTCL from 2 phase 1 studies that support the rationale for the ongoing phase 2 PRIMO study (NCT03372057).

Methods: In the initial phase 1 study (NCT 01476657), pts with RR PTCL received DUV until progression or intolerance, as part of a dose-escalation phase. In a separate phase 1 study (NCT02783625), pts with RR PTCL received DUV 25 mg or 75 mg BID as monotherapy for 1 mo as a lead-in to a combination regimen with either romidepsin (R) or bortezomib (B).

Results: A total of 29 pts with RR PTCL received DUV in the phase 1 studies. Among pts who received the DUV 75-mg dose as monotherapy or lead-in therapy before R, the ORR was 54% and 44%, with CR rates of 15% to 22%, respectively (Table). Notably, ORR was 57% among pts receiving lower dose of DUV (25 mg BID) as lead-in therapy before B. Pts receiving DUV as lead-in had a response at the end of cycle 1. In the phase 1 escalation study, response to DUV typically occurred by the first assessment (cycle 2) and was observed across a spectrum of PTCL subtypes. Two pts who attained a CR and PR, respectively, in the phase 1 escalation study completed >1 year of DUV treatment (Horwitz, *Blood* 2018). The preliminary safety profile of DUV in pts with PTCL was considered reasonable and consistent with previous reports.

Conclusions: DUV 25 or 75 mg BID demonstrated encouraging clinical activity and an acceptable safety profile in RR PTCL, a population in need of new and effective therapies. The ongoing phase 2 PRIMO study dose optimization phase will identify the optimal regimen of DUV monotherapy in RR PTCL and characterize the efficacy and tolerability of DUV in ≈100 pts.

Disclosures: Horwitz, S: Consultant or Advisory Role: *ADCT Therapeutics, Aileron, Forty-Seven, Infinity/Verastem, Kyowa-Hakka-Kirin,*

TABLE 1 DUV Efficacy in RR PTCL in Phase 1 Studies

	Phase 1 study DUV monotherapy (NCT 01476657)	Phase 1 study DUV monotherapy lead-in before a combination regimen (NCT02783625)	
	DUV 75 mg (n=13)	DUV 75 mg BID monotherapy 1 month lead-in before R (n=9)	DUV 25 mg BID monotherapy 1 month lead-in before B (n=7)
ORR (CR + PR), n (%)	7 (54)	4 (44)	4 (57)
Best overall response, n (%)			
CR	2 (15)	2 (22)	2 (29)
PR	5 (38)	2 (22)	2 (29)

034

EFFICACY OF MOGAMULIZUMAB IN PREVIOUSLY TREATED PATIENTS WITH LESS ADVANCED MYCOSIS FUNGOIDES: RESULTS FROM THE MAVORIC STUDY

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Introduction: In the MAVORIC Phase 3 study, patients (pts) with previously treated mycosis fungoides (MF)/Sezary syndrome (SS) stage IB-IVB who received mogamulizumab (MOGA; Poteligeo®) had significantly prolonged progression-free survival (7.7 vs 3.1 months; P<0.0001) and greater overall response rates (ORR) compared to pts on vorinostat (VORI) (Kim YH, et al. Lancet Oncol 2018). Less advanced MF (stage IB/IIA) is a chronic skin malignancy that can involve blood and nodes and may require many lines of systemic therapy over the disease course with a reduced quality of life. This post-hoc analysis specifically examined efficacy and safety of the recently approved MOGA in stage IB/IIA MF pts.

Methods: In MAVORIC, stage IB-IVB MF/SS pts (n=372) who were treated with ≥1 prior systemic therapy were randomized to MOGA or oral VORI. In the post-hoc analysis, time to next treatment (TTNT) was defined as time to any therapy excluding topical steroids or focal radiation treatment. ORR was based on global composite response in 4 disease compartments – skin, blood, lymph nodes, and viscera – achieved at 2 consecutive visits at least 8 weeks apart. Individual compartment responses were also assessed.

Results: A total of 85 pts with stage IB/IIA MF were included (MOGA, IB n=15, IIA n=21; VORI, IB n=27, IIA n=22). Overall, 79% (33/42) of IB pts and 84% (36/43) of IIA pts had received ≥2 prior systemic therapies, and 24% (10/42) of IB pts and 28% (12/43) of IIA pts had received ≥6 prior systemic therapies. Median TTNT with MOGA in IB pts was 11.5 months (mo) (95% CI, 1.4,16.0) compared to 3.1 mo (95% CI, 2.7, 5.3) with VORI; in IIA pts, median TTNT was 10.1 mo (95% CI, 5.5, 12.6) and 4.9 mo (95% CI, 2.4, 8.0), respectively. ORR in IB pts receiving MOGA and VORI was 20% (3/15) and 18.5% (5/27), respectively; ORR in IIA was 19% (4/21) and 0% (0/22), respectively. With respect to stage IB and IIA, compartmental response rates with MOGA were: skin (20% [3/15], 38% [8/21]), blood (0% [0/2], 75% [6/8]), and lymph node (0% [0/0], 15% [3/20]), respectively. Adverse events were generally manageable and consistent with the ITT population.

Conclusions: This post-hoc analysis of TTNT, ORR, and compartmental response in stage IB/IIA demonstrates meaningful clinical benefit with MOGA in early stage MF pts previously treated with systemic therapies despite MAVORIC not being powered to determine treatment effect by disease stage.

Sponsor: Kyowa Kirin.

Keywords: cutaneous T-cell lymphoma (CTCL); monoclonal antibodies (MoAb); mycosis fungoides (MF).

Disclosures: Scarisbrick, J: Consultant Advisory Role: *4SC, Innate, Kyowa Kirin, Mallinckrodt, Takeda*; Honoraria: *4SC, Kyowa Kirin, Mallinckrodt, Takeda*; Research Funding: *Kyowa Kirin, Takeda*. **Geskin, L:** Consultant Advisory Role: *Actelion, Kyowa Kirin, Mallinckrodt, Soligenix*; Research Funding: *Helsinn, Kyowa Kirin, Mallinckrodt, Merck*; Other Remuneration: *Travel, Kyowa Kirin*. **Bagot, M:** Consultant Advisory Role: *Innate, Kyowa Kirin, miRagen*; Stock Ownership: *Innate*; Other Remuneration: *Patent, Innate*. **Fisher, D:** Consultant Advisory Role: *Genetech, Gilead Sciences*. **Elmets, C:** Consultant Advisory Role: *Leo*; Stock Ownership: *Aevi Genomic*; Research Funding: *Elorac, Kyowa Kirin, Soligenix*; Other Remuneration: *Travel, Soligenix*. **Duvic, M:** Consultant Advisory Role: *Kyowa Kirin*; Research Funding: *Seattle Genetics*; Other Remuneration: *Travel, Kyowa Kirin*. **Beylot-Barry, M:** Consultant Advisory Role: *Takeda*; Honoraria: *Celgene, Takeda*; Research Funding: *Roche*. **Kim, E:** Consultant Advisory Role: *Actelion, Galderma, Seattle Genetics*; Research Funding: *Actelion, Galderma, Kyowa Kirin, Medimmune, Soligenix*; Other Remuneration: *Travel, Actelion, Galderma, Soligenix*. **Moriya, J:** Employment Leadership Position: *Kyowa Kirin*. **Leoni, M:** Employment Leadership Position: *Kyowa Kirin*. **Zinzani, P:** Consultant Advisory Role: *EusaPharma, Merck Sharp & Dohme, Sanofi, Verastem*; Honoraria: *Bristol-Myers Squibb, Celgene, Celltrion, Gilead, Jansen, Merck Sharp & Dohme, Roche, Servier*; Other Remuneration: *Speaker. Bristol-Myers Squibb, Celgene, Celltrion, Gilead, Jansen, Merck Sharp & Dohme, Roche, Servier, Verastem*.

FOCUS ON... SESSION: ONGOING TRIALS

OT01
NCRI PETREA TRIAL: A PHASE 3 EVALUATION OF PET-GUIDED, RESPONSE-ADAPTED THERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED, ADVANCED-STAGE, HIGH-TUMOUR-BURDEN FOLLICULAR LYMPHOMA

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Introduction: Frontline treatment for advanced stage, high tumour burden follicular lymphoma (FL) usually consists of 6-8 cycles of chemotherapy combined with the CD20 antibody rituximab (R) or GA101/obinutuzumab (G). The PRIMA trial showed that R maintenance following R+chemo induction improves PFS but also increases toxicity with no OS advantage. The separation of PFS curves suggests that its main effect is to delay relapse in the minority of patients destined to progress within the first 2-3 years. The GALLIUM trial showed that replacing R with G further improves PFS but also increases toxicity and likewise has no OS advantage.

FDG PET-CT (PET) imaging has emerged as a powerful predictor of both PFS and OS following frontline R/G+chemo induction in FL. Most patients who achieve a complete metabolic response (CMR, Deauville 1-3) experience prolonged remissions irrespective of anti-CD20 maintenance whereas those who remain PET +ve (Deauville 4-5) have an increased probability of early disease progression. We therefore hypothesised that the PFS benefit of maintenance is largely confined to anatomical responders who remain PET +ve and is of limited magnitude in those who achieve a CMR. The PETReA trial was developed to test this hypothesis and also to investigate treatment intensification in the PET +ve population by adding lenalidomide to anti-CD20 maintenance. The combination of lenalidomide plus R is highly effective in FL, being superior to R in the relapsed/refractory setting and non-inferior to R+chemo in the frontline setting. Encouraging phase II data have also been obtained with lenalidomide plus G.

Methods: PETReA is a non-blinded, phase 3 randomised controlled trial for patients with previously untreated (excepting local
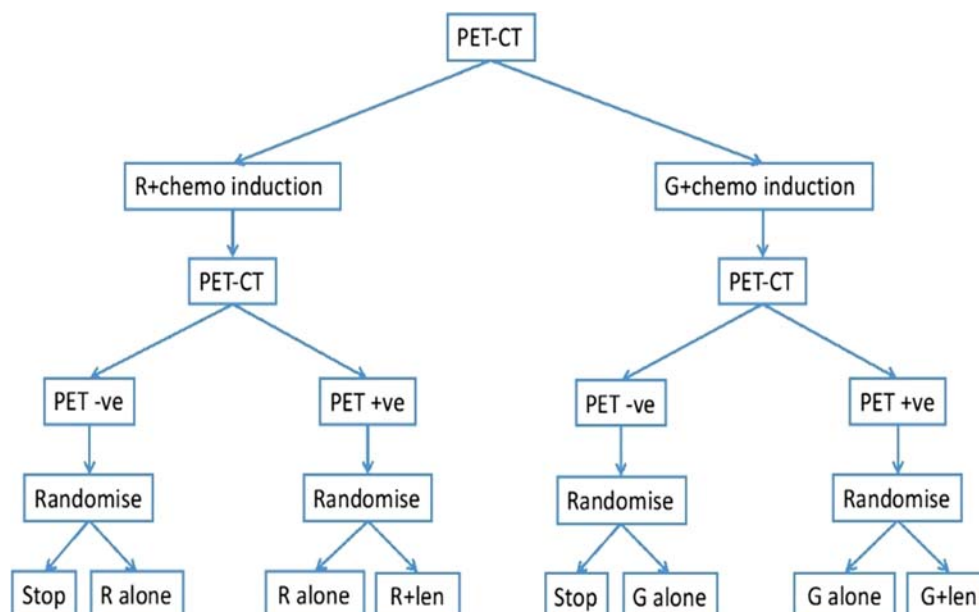
radiotherapy), advanced-stage FL (grade 1, 2, 3a) meeting the GELF criteria for starting treatment. Patients receive R+chemo with the option of CVP, CHOP or bendamustine. Anatomical responders are grouped based on post-induction PET status: those who achieve a CMR (Deauville 1-3) are randomised 1:1 to R maintenance (8 weekly for 12 doses) versus no further treatment, whereas those who remain PET +ve (Deauville 4-5) are randomised 1:1 to R maintenance with or without lenalidomide. The primary endpoint is PFS with secondary endpoints including OS, toxicity, quality of life, conversion to PET negativity (PET +ve group only) and response to induction therapy. The study opened in the UK in May 2018 and Australia in February 2019 and is recruiting at the expected rate.

A protocol amended is being planned to allow G as an alternative to R. In the revised design, which aims to recruit ~1000 patients from ~100 centres over 4.5 years, R- and G-treated patients will be analysed initially as a single cohort and as separate cohorts once sufficient events have accumulated. PETReA is the first trial in FL to stratify patients for separate questions based on post-induction PET status.

Keywords: follicular lymphoma (FL); positron emission tomography (PET).

OT02
POLARIX: A PHASE 3 STUDY OF POLATUZUMAB VEDOTIN (POLA) PLUS R-CHP VERSUS R-CHOP IN PATIENTS (PTS) WITH UNTREATED DLBCL

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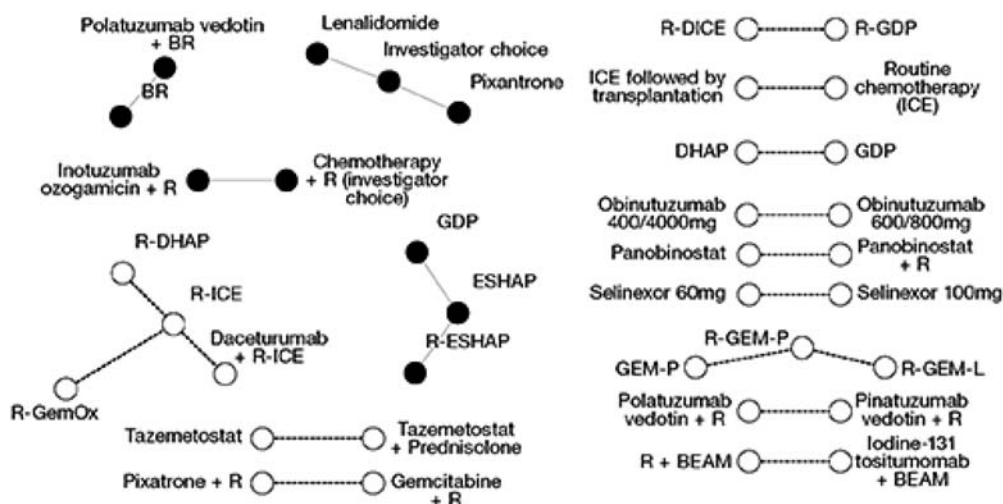
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Background: Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) remains the standard of care in pts with previously untreated diffuse large B-cell lymphoma (DLBCL) but outcomes remain poor in pts with high-risk disease. Pola is an antibody–drug conjugate targeting CD79b; it delivers the antimitotic agent monomethyl auristatin E. Addition of pola to bendamustine and R in pts with transplant-ineligible DLBCL resulted in improved OS (Sehn et al, 2018). In front-line treatment of DLBCL, pola is being evaluated as a replacement for vincristine within the R-CHOP regimen. In a phase Ib/II study in pts with higher risk DLBCL, pola + R-CHP demonstrated promising efficacy and a safety profile similar to that observed in the R-CHOP arm of the GOYA study (Tilly et al, 2017; Vitolo et al, 2017). The phase 3 POLARIX study investigates pola + R-CHP in untreated DLBCL.

Methods: POLARIX (NCT03274492) is an ongoing, international, randomised, double-blind, active-placebo-controlled, phase 3 study in pts with previously untreated DLBCL. Pts aged 18–80 years with CD20-positive DLBCL (including DLBCL not otherwise specified, GCB, and ABC subtypes), ECOG performance status 0–2, and IPI score 2–5, are stratified by IPI score (2 vs 3–5), bulky disease and geographical region and randomised (1:1). Pts receive 6 cycles of either: pola 1.8 mg/kg on Day 1 plus R-CHP (standard dosing schedule) plus vincristine placebo; or pola placebo plus R-CHOP (standard dosing schedule). R monotherapy is administered in cycles 7 and 8 (both arms). PET-CT and CT scans are obtained at screening, after 4 cycles (planned interim assessment), and 6–8 weeks after end of study treatment. Follow-up will continue for 5 years after treatment.

Primary endpoint: investigator-assessed progression-free survival (PFS; Lugano classification).

Secondary endpoints: independent review committee-assessed PET-CT complete response rate at end of treatment, event-free survival, 2-year PFS rate, and overall survival.

Enrolment began Nov 2017. This trial is currently recruiting, and plans to enrol 875 patients in 24 countries.

Disclosures: Tilly, H: Consultant Advisory Role: *Karyopharm, Janssen, Roche*; Honoraria: *BMS, Servier*; Other Remuneration: *Roche (travel, accommodation and expenses)*. **Flowers, C:** Consultant Advisory Role: *AbbVie, AstraZeneca, Bayer, BeiGene, Celgene (unpaid), Denovo Biopharma, Genentech, Inc./Roche (unpaid), Gilead, OptumRx, Karyopharm, Pharmacyclics/Janssen, Spectrum*; Research Funding: *AbbVie, Acerta, BeiGene, Celgene, Gilead, Genentech, Inc./Roche, Janssen Pharmaceutical, Millennium/Takeda, Pharmacyclics, TG Therapeutics*. **Friedberg, J:** Consultant Advisory Role: *Bayer, Astellas Pharma*; Research Funding: *Seattle Genetics, Kite Pharma*; Other Remuneration: *Roche (travel, accommodation and expenses); patent on bone marrow microenvironment signals*. **Herbaux, C:** Honoraria: *Roche, Janssen-Cilag, AbbVie*; Research Funding: *Takeda*; Other Remuneration: *Janssen-Cilag, AbbVie, Roche (travel, accommodation and expenses)*. **Morschhauser, F:** Consultant Advisory Role: *Gilead*; Honoraria: *Celgene, Roche, Janssen, Bristol-Myers Squibb, Servier, Epizyme*. **Sehn, L:** Consultant Advisory Role: *Celgene, AbbVie, Seattle Genetics, TG Therapeutics, Janssen, Amgen, Roche/Genentech, Inc., Gilead Sciences, Lundbeck, Amgen, Apobiologix, Karyopharm Therapeutics, Kite Pharma, Merck, Takeda, Teva, AstraZeneca, Acerta Pharma, MorphoSys*; Honoraria:

OT03

PHASE III RANDOMIZED STUDY OF ENZASTAURIN/R-CHOP VS PLACEBO/R-CHOP IN FRONTLINE HIGH RISK DIFFUSE LARGE B CELL LYMPHOMA PATIENTS WITH GENOMIC BIOMARKER DGM1 (ENGINE STUDY)

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Introduction: Progress in genome technology allows analysis of previously completed trials to identify patient subgroups potentially benefiting from therapy. Enzastaurin is a potent inhibitor of protein kinase C beta (PKC-ß) and suppresses the phosphoinositide 3-kinase (PI3K)/AKT pathway. The safety and efficacy of enzastaurin has been tested in more than 60 clinical trials including 2 major studies in DLBCL: (1) PRELUDE (A phase III maintenance trial of enzastaurin vs Placebo, N=758) (*Crump, 2016*), and (2) S028 (A randomized phase II study of enzastaurin/R-CHOP vs R-CHOP in frontline intermediate/high-risk DLBCL, N=101) (*Hainsworth, 2016*). DNA samples extracted from blood of patients from PRELUDE were retrospectively genotyped using whole genome SNP arrays. From the genome wide screening a novel genetic biomarker, DGM1, was identified showing high correlation with response to enzastaurin treatment (*Luo, ASH 2018*). Importantly, these findings were replicated in the phase II S028 study. In the S028 study the hazard ratio (HR) for OS in high-risk (IPI $\geq$ 3) DGM1 positive (+) patients who received Enzastaurin/R-CHOP was 0.28 (0.1-0.81) when compared to subjects who received R-CHOP, a benefit favoring enzastaurin (p=0.018). These data suggest that addition of enzastaurin to R-CHOP may significantly improve outcome in frontline high-risk DGM1 (+) DLBCL. The ENGINE study was initiated to validate this finding in a prospective study.

Methods: This is a randomized, double-blind, placebo-controlled phase III Trial. Adult patients must have untreated historically confirmed CD20+ DLBCL and IPI $\geq$ 3. Patients are randomized 1:1 to enzastaurin/R-CHOP or placebo/R-CHOP for six 21-day cycles during combination phase. Randomization is stratified by IPI score: 3 vs. 4, 5, and by region. Each subject's treatment assignment will be unblinded after response assessment at the end of the combination phase. Subjects randomized to the investigational arm who have a complete or partial response will have the option to continue in the single agent phase to receive enzastaurin at 500 mg/day for up to 2 additional years. The study intends to enroll approximately 235 patients with primary endpoint of OS in DGM1 (+) patients. Secondary endpoint includes CR, ORR and safety. The study is ongoing with 53 sites open in the US and China. As of 22 Feb 2019, 78 patients have been randomized. Clinical trial information: NCT03263026.

Keywords: diffuse large B-cell lymphoma (DLBCL).

OT04

THE DIAL STUDY (DUAL IMMUNOMODULATION IN AGGRESSIVE LYMPHOMA): RANDOMIZED PHASE 2 TRIAL OF VARLILUMAB PLUS NIVOLUMAB IN RELAPSED/REFRACTORY AGGRESSIVE B-CELL LYMPHOMAS

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Introduction: The DIAL study is testing the efficacy of dual immuno-modulation in patients with advanced B cell non-Hodgkin lymphoma (B-NHL). Developed by the Cancer Therapy Evaluation Program (CTEP), the trial combines the use of a programmed cell death protein 1 (PD-1) inhibitor (nivolumab) with an agonist of the CD27 receptor (varlilumab) in a randomized phase 2 design. CD27, a co-stimulatory receptor, regulates T cell activation through interaction with CD70. T cell exhaustion plays a major role in immune evasion in B-NHL. Combining varlilumab and PD-1 inhibition is highly effective in a murine model of lymphoma, and varlilumab also demonstrates direct anti-tumoral activity in xenograft models of human lymphoma cell lines via antibody-dependent cell-mediated cytotoxicity. Phase 1 data supports the safety and tolerability of single-agent varlilumab in advanced hematologic malignancies. We hypothesize that CD27 activation synergizes with PD-1 inhibition resulting in a superior anti-lymphoma effect compared to PD-1 blockade alone. The study will also evaluate the effect of these agents on tumor and immune cells using IHC, mass cytometry (CyTOF), imaging mass cytometry (IMC), multiplex ELISA, and whole exome sequencing (WES).

Methods: The trial is open to participation for patients with a diagnosis of an aggressive B-cell non-Hodgkin lymphoma (B-NHL) that is recurrent or refractory to standard therapy. Standard inclusion criteria and prior treatment with at least 2 lines of standard therapy are required. Prior autologous stem cell transplant and/or chimeric antigen receptor (CAR) T cell therapy is allowed. Patients with active CNS disease are excluded. Eligible patients will be randomized to treatment with single-agent nivolumab (group 1) or dual immunotherapy with nivolumab and varlilumab. Group 1 is allowed to cross-over at the time of progression. Nivolumab will be administered intravenously (IV) every 2 weeks (240 mg) for 4 months followed by monthly dosing (480 mg) thereafter. Varlilumab will be given IV every 4 weeks (3 mg/kg). Response assessment will be done by PET-CT scan every 12 weeks. Primary outcome is overall response rate (ORR) according to the LYRIC criteria. The trial will enroll 48 patients per arm, allowing 80% power to detect at least 20% increase in ORR in the experimental arm (group 2) assuming a 25% ORR in the control arm (group 1). The trial is registered (NCT03038672) and open to participation to members of the Experimental Therapeutics Clinical Trials Network (ETCTN) and Early Drug Development Opportunity Program (EDDOP).

OT05
ACCEPT: A PHASE IB/II COMBINATION OF ACALABRUTINIB WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE AND PREDNISOLONE (R-CHOP) FOR PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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T. Maishman[1] | **A. Schuh[2]** | **L. Lopez Pascua[2]** |
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Background: R-CHOP remains the standard of care in DLBCL yet many patients (pts.) either fail to respond or relapse after having achieved an initial remission. Dysregulation of B Cell receptor (BCR) signalling is well recognised in non-germinal centre (non-GC) DLBCL. In the phase III PHOENIX study, the addition of the Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib (I) to R-CHOP (R-CHOP-I) did not improve the outcome of the study population with non-GC DLBCL although R-CHOP-I treated pts. aged less than 60 years had a significantly improved progression free survival (PFS) and overall survival (OS) compared to those receiving R-CHOP. In pts. aged over 60 years, the addition of I increased toxicity and compromised the delivery of R-CHOP. Acalabrutinib (A) is a second generation BTKi, with enhanced kinase selectivity and potential for better efficacy and tolerability over first-generation inhibitors. There is a strong rationale to combine this targeted agent with R-CHOP in untreated *de novo*DLBCL to understand its safety profile and efficacy.

Method: Eligible patients are treatment naive with histologically confirmed DLBCL. During cycle 1 whole transcriptome analysis will be performed to determine cell of origin (COO). All will receive 6 cycles of R-CHOP therapy on a standard 21-day schedule, with the addition of A in cycles 2-6. Subsequently a continuation phase of A only, for 2 cycles of 28 days will be administered. The primary objective of the phase Ib is to establish a recommended phase II dose of A in

combination with R-CHOP (modified classical 6+6 design). Phase II is to assess overall response rate activity of the combination and ascertain additional safety information. Secondary endpoints include duration of response, PFS and OS and their relation to the COO, and BTK receptor occupancy in PBMCs and tumour measured by a drug analogue ELISA. The effect of acalabrutinib on antibody-directed cellular cytotoxicity mediated by rituximab will be measured *in vitro* during treatment. To date 22 (12 in dose escalation) of a planned 28 pts. have been recruited. In the phase Ib the maximal administered dose of A (100mg bd) with R-CHOP demonstrated no safety concerns beyond those seen with R-CHOP alone. In dose expansion, regardless of age, there has been no compromise in the delivery of full dose R-CHOP when given in combination with A. With anticipated full recruitment before 06/19, safety data, with $_{CT}$DNA dynamics will be presented.

The trial is coordinated by the CRUK Southampton Clinical Trials Unit. This is an investigator initiated study that has been granted free access to investigational medicinal product, trial management and translational study support through a grant from Acerta Pharma B.V. (IST-LY-801) and has endorsement from Cancer Research UK (CRUKDE/16/006). Trial registration: ISRCTN11965217 NCT03571308

Keywords: acalabrutinib; diffuse large B-cell lymphoma (DLBCL); R-CHOP.

OT06

TELLOMAK: T-CELL LYMPHOMA ANTI-KIR3DL2 THERAPY: AN OPEN LABEL, MULTI-COHORT, MULTI-CENTER, INTERNATIONAL PHASE II STUDY EVALUATING THE EFFICACY AND SAFETY OF IPH4102 ALONE OR IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS WITH ADVANCED T-CELL LYMPHOMA

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Background: KIR3DL2 is a killer immunoglobulin-like receptor that is expressed by tumor cells across different subtypes of T-cell lymphomas (> 85% of Sézary Syndrome (SS), ~50% of mycosis fungoides (MF), and ~50% in peripheral T-cell lymphomas (PTCL)). IPH4102 is a humanized first-in-class anti-KIR3DL2 monoclonal antibody designed to deplete KIR3DL2-expressing cells via antibody-dependent cell-cytotoxicity (ADCC) and phagocytosis. A first-in-human study including 44 patients with relapsed/refractory cutaneous T-cell lymphoma (CTCL) showed that the drug is safe and has very robust clinical activity. The majority of the patients enrolled had relapsed/refractory SS (n=35). In this population, IPH4102 produced an overall response rate (ORR) of 42.9%, and median progression free survival (PFS) of ~1 year leading to FDA fast track designation in January 2019. IPH4102 has not been previously investigated in PTCL. Preclinical studies have shown that gemcitabine and oxaliplatin can upregulate KIR3DL2 expression on T-cell lymphoma cell lines. Furthermore, IPH4102 anti-tumor activity was enhanced *in-vitro* by each of these chemotherapy agents, and even more by the combination.

Methods: This is an open-label, multi-cohort, multi-center, international phase II trial. Patients will be allocated to one of five cohorts: Cohort 1: SS, Cohorts 2&3: MF stratified according to KIR3DL2 expression, Cohorts 4&5: PTCL stratified according to KIR3DL2 expression. In the SS and MF cohorts, patients should have received ≥2 prior systemic therapies and have no evidence of large cell transformation as detected centrally. In the SS cohort, prior treatment with mogamulizumab is required. In the PTCL cohorts, only patients with PTCL-NOS, AITL and ALCL who have received ≥ 1 line of prior systemic therapy are eligible. All patients will undergo KIR3DL2 testing at baseline in a central laboratory. In the SS and MF cohorts, IPH4102 will be administered as single agent at a flat dose of 750mg weekly x 4 weeks, every 2 weeks x 20 weeks (10 doses), then every 4 weeks. In the PTCL cohorts, IPH4102 will be administered using the same schedule in combination with gemcitabine and oxaliplatin (GEMOX), which will be administered every 2 weeks for a maximum of 8 cycles. In all cohorts, IPH4102 treatment will continue until progression or unacceptable toxicity. The primary endpoint is overall response, evaluated using the International Consensus Criteria for MF/SS and the Lugano Criteria for PTCL. Secondary endpoints include safety, other efficacy endpoints, and biomarker analyses. Each cohort has a separate design and dedicated statistical analysis plan. A biomarker-stratified design is applied in cohorts 2-5 using a Simon 2-stage design to inform on the activity of assigned treatment according to KIR3DL2 expression. In total, approximately 140-260 patients will be recruited across 30-40 sites in the US and Europe.

SESSION 1 - DLBCL: BIOLOGY

035
AN AUTOCHTHONOUS MOUSE MODEL OF MyD88 p.L265P- AND BCL2-DRIVEN DIFFUSE LARGE B CELL LYMPHOMA

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Background: There are several recurrent mutations in DLBCL leading to the constitutive activation of NF-kB, frequently by activating the BCR and TLR pathways (mostly via mutations in *CD79B* and *MyD88*, respectively), or by the loss of a negative feedback loop mediated by the loss of *TNFAIP3*.

Methods: Here, we aimed to investigate the role of the p.L265P mutation in lymphomagenesis. We generated a novel mouse model in which Cre-mediated recombination leads to the conditional expression of *Myd88* p.L252P (the orthologue of the human *MyD88* p.L265P mutation) from the endogenous locus. We combined this *Myd88* allele (abbr. M) with a *BCL2* overexpression allele (abbr. B) and both alleles were activated with *CD19:Cre* (abbr. C). The effects of these mutations were carefully characterised *in vivo*. Additionally, we have generated a conditional *Cd79b*p.Y195H allele and model the loss of *Tnfaip3* by using a previously published *floxed* allele.

Results: MBC animals showed elevated levels of self-reactive antibodies. Immunization experiments revealed that *Myd88* p.L252P and *BCL2* overexpression cooperate in generating exaggerated antibody responses to exogenous antigen. Ultimately, these animals develop clonal tumors which resemble features of ABC DLBCL histologically and transcriptionally. They were exquisitely sensitive to inhibition of BCL2 *in vitro* and *in vivo*. MBC tumors expressed PD-L1 at elevated levels compared to *Eμ:Myc* driven lesions. Anti-PD1 antibody treatment had a stabilizing effect on tumor growth and resulted in a survival benefit. We are currently investigating the effects of *Cd79b* p.Y195H expression and loss of *Tnfaip3* and initial comparative results will be shown.

Conclusion: Taken together, we established a *Myd88* p.L252P driven mouse model for B cell lymphoma which shares many features with human ABC DLBCL. These tumors are sensitive to inhibition of BCL2 by ABT-199 and respond to immune checkpoint blockade by anti-PD1 treatment, suggesting these treatments as potential new strategies in the therapy of a subset of DLBCL patients. Additionally, we are extending our spectrum of modelled genetic alterations recurrent in DLBCL by the use of a novel conditional *Cd79b* p.Y195H and a previously published *Tnfaip3* flox allele.

036
CRYPTIC *MYC* AND *BCL2* REARRANGEMENTS ARE AMONG A RANGE OF GENETIC MECHANISMS UNDERLYING THE DOUBLE HIT SIGNATURE IN NON-DOUBLE HIT DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBL-DH/TH) has poor outcome after standard therapy. We recently described a gene expression signature (DHITsig) that was characteristic for HGBL-DH/TH with *BCL2* rearrangement (Ennishi *et al. J Clin Oncol* 2019). Interestingly, while this signature identified 27% of GCB diffuse large B-cell lymphoma (DLBCL) as DHITsig positive, only half of these tumors harbored both *MYC* and *BCL2* rearrangements detected by FISH. Here, through whole genome sequencing (WGS), we sought to identify potential mechanisms for expression of DHITsig, including aberrant *MYC* and *BCL2* expression, in non-HGBL-DH/TH-*BCL2* tumors.
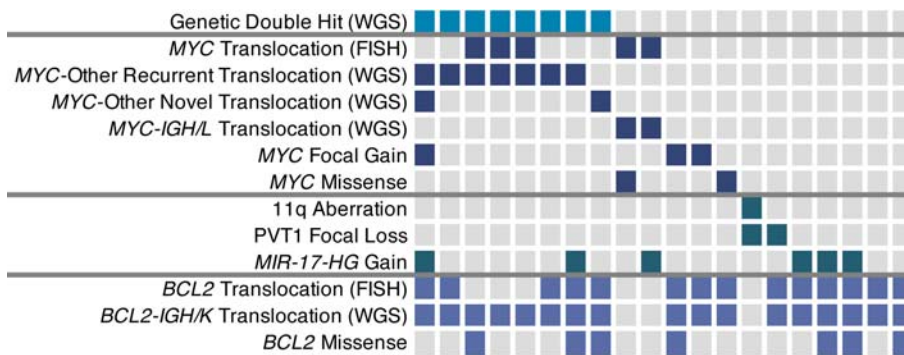
Methods: We performed WGS on 20 DHITsig-pos tumors from Ennishi *et al* that lack rearrangements of *MYC*, *BCL2*, or both. Of these, 18 cases lack a matched normal and were analyzed for somatic SNVs and indels using a combination of Strelka2 and Mutect2, using the GnomAD database to filter germline variants based on population allele fraction. Structural variants and copy number alterations were identified using Manta and Control-FREEC, respectively.

Results: Our analysis identified *MYC* or *BCL2* rearrangements that were cryptic to breakapart FISH assays, revealing that 40% of these apparently non-HGBL-DH/TH-*BCL2* tumors had, in fact, a "genetic double hit" (Figure 1). These *MYC* rearrangements involved recurrent non-*IG* partner loci *ZCCHC7*, *RFTN1*, or *CD96*. Although the breakpoints for two of these translocations were outside of the locus interrogated by FISH, the remainder involved small insertions of either the *MYC* gene or enhancer regions. Three tumors had focal copy number gains of *MYC*, including one with a double minute, and six tumors harbored gains of *MIR-17-HG*, a regulator of *MYC* expression. Similarly, rearrangements involving *BCL2* that were cryptic to breakapart FISH were identified in three tumors, including the insertion of an IGK enhancer element into the *BCL2* locus. In the only case lacking both *BCL2* and *MYC* translocations, the 11q alteration associated with *MYC*-negative high-grade lymphomas was found. Finally, several focal deletions were found affecting the promoter region around TSS1 of the lncRNA *PVT1* gene, telomeric of *MYC*. This locus has recently been found to contain a boundary element that insulates *MYC* from the actions of downstream enhancers.

Conclusions: Genetic mechanisms for the membership of apparently non-HGBL-DH/TH-*BCL2* tumors to the DHITsig-pos subtype of DLBCL were revealed in 90% of tumors. These mechanisms included *MYC* and *BCL2* rearrangements cryptic to FISH assays, copy number aberrations, and focal deletion of *PVT1*. This study further supports the notion that DHITsig identifies a new biological entity within DLBCL and highlights the limitations of FISH assays in the detection of genetic mechanisms of aberrant *MYC* and *BCL2* expression.

Keywords: diffuse large B-cell lymphoma (DLBCL); gene expression profile (GEP); high-grade B-cell lymphoma with or without rearrangement of MYC and BCL2 and/or BCL6.

037
FUNCTIONAL CHARACTERIZATION OF *NFKBIZ* 3′ UTR MUTATIONS IN DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: The activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) is characterized by activation of NF-kB signaling and an increased risk of mortality. Recurrent somatic mutations affecting genes such as *MYD88*, *CD79A/B* and *TNFAIP3* have been shown to constitutively activate the NF-kB pathway through B-cell receptor signaling in ABC DLBCL; however, there still remain cases with no known genetic basis for this pathway activation (Arthur *et al. Nat Com* 2018). We recently published a meta-analysis of DLBCL genome and targeted sequencing data identifying non-coding mutations. We described novel mutations affection the 3′ untranslated region (UTR) of *NFKBIZ* in 18% of ABC DLBCLs. Overall, *NFKBIZ* is mutated (amplifications and UTR mutations) in 34% of ABC DLBCLs. These *NFKBIZ* mutations are mutually exclusive with *MYD88* mutations, implicating them in activation of the NF-kB signaling pathway. *NFKBIZ* encodes the IkB-ζ protein, which interacts with NF-kB transcription factors and is thought to regulate canonical NF-kB signaling. We hypothesized that these mutations affect the ability of regulatory mechanisms to target this transcript for degradation through disruption of UTR secondary structures. This leads to enhanced mRNA stability and elevated protein levels and represents a novel mechanism of promoting NF-kB signaling in ABC DLBCL.

Methods: *NFKBIZ* 3′ UTR mutations were introduced in a DLBCL cell line using CRISPR-Cas9. *NFKBIZ* mRNA and protein levels were evaluated using custom designed droplet digital PCR assays and western blot. RNA-sequencing was performed on mutant and wild-type (WT) cell lines to identify genes up-regulated by IkB-ζ. A competitive growth assay with WT and CRISPR mutant lines was set up to assess whether UTR mutations provide a growth advantage in culture. The pool composition was determined by DNA sequencing and comparison of WT and mutant DNA sequences.

Results: Introduction of *NFKBIZ* mutations into DLBCL cell lines confirmed that UTR deletions lead to increased levels of mRNA and protein. Stimulation with LPS revealed that mRNA levels stay elevated for longer in mutant lines. *NFKBIZ* UTR deletions also give DLBCL cells a selective growth advantage over WT when grown together in culture. RNA-sequencing of mutant and WT lines revealed possible transcriptional targets of IkB-ζ, including *TNFRSF14B*, *HCK*, *GNAZ*, *BATF* and *CD274*. These targets are either involved in activation of NF-kB signaling, associated with decreased survival in other lymphomas or potential new drug targets in *NFKBIZ* mutant DLBCL.

Conclusions: This work highlights the role of *NFKBIZ* and 3′ UTR mutations in driving ABC DLBCL. We demonstrate that these UTR mutations can lead to over-expression of *NFKBIZ* and activate potentially novel drug targets in ABC DLBCL. These findings contribute to a better understanding of the genetic basis of DLBCL, which is necessary to guide personalized therapeutic strategies.

Keywords: activated B-cell-like (ABC); molecular genetics; NF-kB.

038

THE TRANSCRIPTION FACTOR FLI1 SUSTAINS RELEVANT BIOLOGICAL PATHWAYS AND DRIVES ONCOGENES THAT PROMOTE CELL GROWTH IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Introduction: Gains affecting chromosome 11, often in its integrity, are recurrent events in lymphomas. Our group identified and functionally characterized an 11q24.3 gain occurring in 25% of diffuse large B-cell lymphoma (DLBCL) cases and associated with the overexpression of two ETS transcription factors, ETS1 and FLI1 (Blood 2013). Here, we have focused on the latter to identify the network of FLI1 regulated genes in DLBCL.

Methods: We interrogated the specific transcriptome orchestrated by FLI1 using ChIP-Seq paired with transcriptome analysis (RNA-Seq) after FLI1 silencing (siRNA). Sequencing was performed using the NextSeq 500 (Illumina). Detection of peaks was carried out using HOMER (v2.6), differential expressed genes were identified using a moderated t-test (limma R-package) and functional annotation was done by Gene Set Enrichment Analysis (GSEA, Broad Institute).

Results: ChIP-Seq on four DLBCL cell lines, two derived from activated B cell-like (ABC) subtype (HBL1 and U2932) and two from germinal center B-cell (GCB) subtype (OCI-Ly1 and VAL), identified 17.574 FLI1 binding sites. The majority of peaks mapped in promoter regions of annotated genes (37%), followed by distal intergenic regions (22%), intronic regions other than first intron (21%) and others regions like first intron, 5' or 3' UTR and exons (20%). Integration of the identified binding sites with RNA-Seq from FLI1 genetically silenced DLBCL cell lines allowed the identification of putative FLI1 direct targets. The FLI1 negatively regulated genes included tumor suppressors genes involved in negative regulation of cell cycle and p53 cascade. Among the FLI1 positively regulated targets we found genes annotated for immune response, MYC targets and B cell receptor, TNF-alpha and IL2 signaling pathways. Of note, direct targets of FLI1 overlapped with those genes regulated by ETS1, the other transcription factor including co-gained in DLBCL (Priebe et al, ICML 2017), suggesting a functional convergence within the ETS family. FLI1 positively regulated targets included *MYC*, *CXCR5*, *CD40*, *LCK*, *ICAM1*, *CD79A*, *CD19*, *BTK*, *PIK3CD*, *PRKACD*, *NFBK1/2*, *FAIM3*, *BTG2*, *TRAF1/4/5* and *IL2RA/G*. Conversely, *BCOR*, *SAP30*, *EZR*, *CDKN1B*, *E2F7*, *TFDP2* and *BARD1* were among the negatively regulated. Importantly, the majority of the FLI1 positively regulated targets overlapped with those genes positively correlated with FLI1 in DLBCL clinical specimens (GSE10846, n=414). Finally, we took advantage of genome-wide CRISPR-CAS9 screening of DLBCL cell lines performed by Reddy et al. 2017 (EGAS00001002606) to identify *PRKX*, *RASGRP1*, *ATG9a*, *ASB2*, *DDX21*, *TAF1* and *AATF* as FLI1-regulated driver genes in DLBCL.

Conclusions: We reported that FLI1 directly regulates a network of biologically crucial genes and processes in DLBCL. Further studies based on FLI1 itself or some of its targets might provide the rational for novel therapeutic approaches.

Keywords: B-cell receptor (BCR); diffuse large B-cell lymphoma (DLBCL); MYC.

039

TRANSCRIPTIONAL AND GENOMIC INTRA-TUMOR HETEROGENEITY DRIVES SUBCLONE SPECIFIC DRUG RESPONSES IN DIFFUSE LARGE B CELL LYMPHOMA

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Figure 1. Study outline
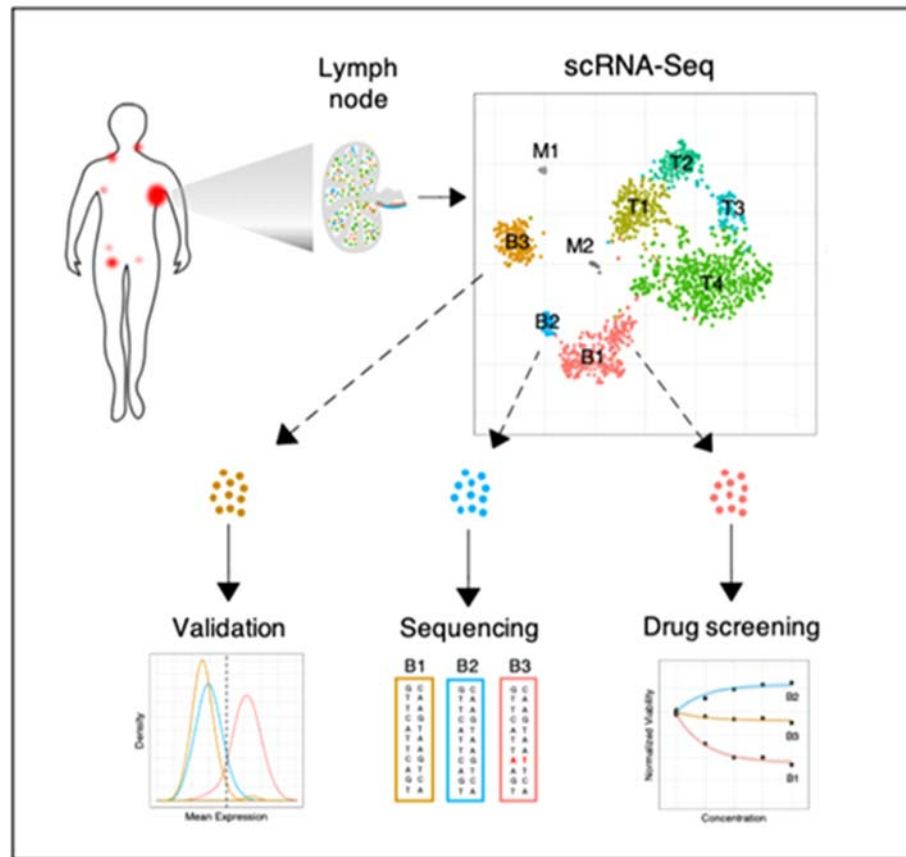
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Introduction: Little is known about intra-tumor heterogeneity of lymphoma and their complex disease-specific lymph node (LN) microenvironment.

Methods: To address this gap of knowledge we characterized follicular lymphoma, diffuse large B cell lymphoma (DLBCL) and reactive LN biopsies by comprehensive immunophenotyping (29 markers, n=40) and single cell RNA sequencing (scRNA-Seq, n=7). We used state-of-the-art clustering algorithms to identify malignant subclones and separated them by fluorescence-activated cell sorting (FACS). We further characterized these subclones by whole-genome sequencing (WGS) and extensive drug response profiling (64 drugs at 5 concentrations, Figure 1).

Results: We sequenced a total of 17,210 malignant B cells and 7,165 non-malignant bystander cells. Non-malignant cell subsets were distinguished based on expression profiles of established marker genes, and malignant B cells were identified based on exclusive expression of either κ or λ light chain genes. Frequencies of B and T cells calculated based on scRNA-Seq highly correlated with frequencies of B and T cells calculated based on FACS analysis (r=0.97) or immunohistochemistry analysis of corresponding paraffin sections (r=0.95). These results suggested that our approach portrays a representative picture of each tumor and its microenvironment.

We further characterized non-malignant cell populations and identified, apart from well-described T cell subsets, a distinct T helper cell population with an exhaustion gene expression profile. Unsupervised clustering of all non-malignant cells from 7 LN biopsies grouped non-malignant cells by cell subtype rather than by sample origin. In contrast, frequencies of each T cell subset were highly variable across LN biopsies. These results suggested that expression profiles and functional states of T cell subsets were comparable across multiple LN, while each lymphoma conditions its own LN microenvironment by the abundance of different infiltrating T cells.

Next, we characterized malignant B cells of individual DLBCL patients and identified distinct subclones with unique gene expression profiles. We took advantage of differentially expressed surface markers (such as CD48, CD32, CD62L) and successfully sorted viable tumor cell subclones by FACS. We could demonstrate that lymphoma subclones of the same LN exhibited a strikingly different drug response profile. To understand differential drug responses, we performed WGS of each

subclone separately. A detailed comparison of gene mutation and copy number profiles between subclones of the same LN will be presented.

Conclusions: Together, our results uncover the complex cellular and clonal substructure of malignant B cell lymphomas. For the first time, our research links scRNA expression profiles of aggressive lymphoma subclones with distinct drug response, gene mutation and copy number profiles.

Keywords: diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); molecular genetics.

040

THE NONCODING RNA GECPAR IS INVOLVED IN WNT SIGNALING AND HAS TUMOR-SUPPRESSOR ACTIVITY IN DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: Enhancers are cell-type specific regulatory DNA regions which play a key role in differentiation and development. Most active enhancers are transcribed in enhancer RNAs that can regulate transcription of relevant target genes by means of *in cis* but also *in trans* action. They stabilize contact between distal genomic regions and mediate interaction between DNA and master transcription factors. Here, we characterized an enhancer RNA that we called GECPAR (GErminal Center Proliferative Adapter RNA) in diffuse large B cell lymphoma (DLBCL).

Methods: GECPAR expression was characterized in 22 DLBCL cell lines and in a dataset of DLBCL clinical specimens and normal samples from different development stages of B cell. Direct genomic target sequences of GECPAR were determined by CHART-seq experiment and then validated at RNA level after GECPAR silencing in DLBCL cell lines. GECPAR associated signature was identified by gene set enrichment analysis and then confirmed by RNA expression correlation in RNA-seq performed on DLBCL patients. Antiproliferative activity of GECPAR was shown by proliferation assay after GECPAR silencing.

Results: Transcribed in the super-enhancer of POU2AF1, a key gene for the regulation of germinal center reaction, GECPAR is an enhancer RNA that we found typically expressed in normal centroblasts but less abundant in GCB-DLBCL and even lower in ABC-DLBCL. This molecule is able to regulate transcription of other genes by *in trans* activity as demonstrated performing CHART-seq experiments. In two DLBCL

cell lines, we identified a list of direct target genes of GECPAR, which we confirmed to be correlated to GECPAR expression also in a RNA-seq dataset of 32 DLBCL patients. Gene set enrichment analysis performed on GECPAR direct targets highlighted its function as transcriptional modulator of genes involved in proliferation and differentiation, including negative regulators of Wnt pathway. Accordingly to this observation, we showed that GECPAR silencing enhanced the proliferation rate of two DLBCL cell lines. Even if the exact mechanism of action of GECPAR is still to be fully elucidated, it appeared to exert its regulatory role through the antagonism with FOXJ2, a transcription factor that we showed to co-localize at the same DNA binding sites with GECPAR. GECPAR and FOXJ2 seem to counteract favoring transcription transactivation by LEF1, the main mediator of Wnt pathway activation. As final evidence of GECPAR role in Wnt pathway inhibition, in ABC-DLBCL cell lines (n=4) the response to treatment with the tankyrase inhibitor AZ6102 resulting in Wnt pathway blockade, correlated to GECPAR expression (p=0.03 R=0.97).

Conclusions: GECPAR is an enhancer RNA regulating proliferation in germinal center B cells and has a tumor suppressor activity in DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL); epigenetics; Wnt.

SESSION 2 – DLBCL: CLINICAL DATA

041

INTEGRATION BETWEEN METABOLIC TUMOUR VOLUME AND METABOLIC HETEROGENEITY PREDICTS OUTCOME OF DLBCL LYMPHOMA PATIENTS IN THE SAKK 38/07 STUDY COHORT

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Introduction: Recent studies suggest that the metabolic tumor volume (MTV) assessed in baseline (18) F-fluorodeoxyglucose (18FDG) positron emission tomography/computed tomography (PET/CT) images may predict the prognosis of patients with DLBCL. The present study was aimed at assessing the ability of the baseline functional PET parameters

Kaplan-Meier estimates of progression free survival (PFS)
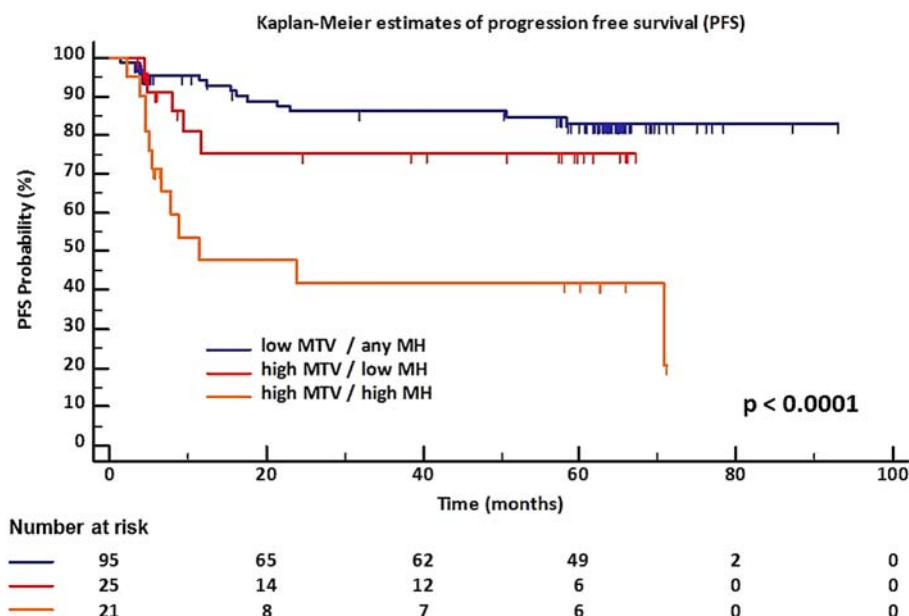
considered alone or in association in predicting the efficacy of conventional immunochemotherapy treatment administered every 14 (R-CHOP14) or 21 days (R-CHOP21) in two cohorts (testing and validation sets) of DLBCL patients. Here, we report results of the testing set.

Methods: The testing set included 141 DLBCL patients treated with R-CHOP14 in the prospective SAKK38/07 study with available baseline PET/CT data. The lymphoma lesions were segmented by a fixed threshold algorithm, with a 2.5 SUVmax value as cut-off to estimate the metabolic tumor volume (MTV). Maximum standardized uptake value (SUVmax), and total lesion glycolysis (TLG) were estimated. MH was also measured using the area under the curve of cumulative SUV-volume histogram (AUC-CSH). The optimal MTV cut off values to discriminate subgroups with different progression free (PFS) and overall survival (OS) have been defined by ROC curves analysis. Cell of origin was determined by immunohistochemistry (Hans algorithm).

Results: After a median follow-up of 63 months, 30 progressions and 23 deaths were recorded. Among quantitative PET parameters baseline MTV was the most powerful predictor of outcome (Cox model $p < 0.001$ for PFS and OS). At 5 years, PFS was 83% for patients with low MTV vs. 59% for those with high MTV (log-rank test, $p=0.0005$). OS was 91% vs. 64%, respectively (log-rank test, $p=0.0001$). High MTV values predicted shorter PFS only in patients with non-germinal center B (GCB) subtype (n = 84) but not in patients with GCB subtype (n = 29) (log-rank test p = 0.006 vs. 0.7). In patients with high MTV, the presence of high MH increased the prognostic discrimination and the combined analysis of MTV and MH demonstrated that increased values of these two parameters might be used to identify patients with different risk of progression (Figure 1). Patients with both high MTV and high MH had a 5-years PFS of 42%, while those with both low MTV and low MH had a 5-year PFS of 83% (log-rank $p < 0.0001$).

Conclusions: Baseline MTV is a powerful predictor of clinical outcomes in patients with DLBCL treated with R-CHOP. High MTV values predict a worse response to treatment especially in patients with non-GCB subtype. A prognostic model based on the combination of MTV and MH may allow the early identification of patients at high risk of disease progression following conventional treatment. The validation of these results in an independent retrospective cohort of patients treated with R-CHOP21 is ongoing and full data will be presented.

Keywords: diffuse large B-cell lymphoma (DLBCL); positron emission tomography (PET); R-CHOP.

042
SMART START: RITUXIMAB, LENALIDOMIDE, AND IBRUTINIB ALONE PRIOR TO COMBINATION WITH CHEMOTHERAPY FOR PATIENTS WITH NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA

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Background: The non-germinal center (non-GCB) subtype of Diffuse Large B-cell Lymphoma (DLBCL) is associated with inferior outcomes with standard therapies. The BTK inhibitor ibrutinib (I) and

immunomodulatory agent lenalidomide (L) have promising activity in non-GCB DLBCL as single agents, and result in synthetic lethality in non-GCB DLBCL models when combined. In relapsed non-GCB DLBCL, rituximab (R), L and I result in overall response rate (ORR) of 55% (Ramchandren, ASH 2018). We conducted an investigator initiated, single-arm, open-label, phase 2 study (NCT02636322) of RLI alone and then with chemotherapy in newly diagnosed non-GCB DLBCL patients, and report the final results of the RLI lead in.

Methods: Adult patients with newly diagnosed non-GCB DLBCL, determined by the Hans method, with adequate organ function and performance status were eligible. The primary objectives were to determine (1A) the ORR of two cycles of RLI as initial therapy, and (1B) the complete response rate (CRR) after 6 cycles of chemotherapy combined with RLI. All patients were treated with rituximab 375 mg/m2 IV day 1, ibrutinib 560 mg po daily, and lenalidomide 25 mg po days 1-10 of 21 day cycles for 2 cycles, followed by 6 additional cycles of RLI with chemotherapy (CHOP or EPOCH per treating MD choice). Responses were assessed with PET/CT as per the Lugano criteria. Growth factors, venous thromboembolism prophylaxis, and pneumocystis pneumonia prophylaxis were required for all patients.

Results: The protocol accrued 60 patients from May 2016 – February 2019, with 52 patients evaluable for disease response (2 withdrew consent prior to restaging, 6 pending restaging prior to abstract deadline). The median age was 64 years (range: 30-83), 28% were >= 70 years, and 50% were female. Half the patients had poor risk IPI, 61% had advanced stage, and 71% had a Ki-67 of >= 80%. One patient had a fatal fungal infection (CNS aspergillosis) attributed to high dose corticosteroids for symptom control during screening and with RLI, leading to prohibition of corticosteroids during the RLI only cycles with no further fungal infections identified. The ORR for 2 cycles of RLI alone was 84.6% (n = 44), and the CRR was 38.5% (n = 20). One patient refused to proceed with the pre-planned chemotherapy after achieving a CR with 2 cycles of RLI, and remains relapse free with no additional therapy 18 months later. Preliminary results demonstrate a CRR of 100% for the full therapy (RLI for 2 cycles, RLI-chemo for 6 cycles), with updates to be presented at the meeting.

Conclusions: The Smart Start trial demonstrates the chemotherapy-free combination of rituximab 375 mg/m2, ibrutinib 560 mg, and lenalidomide 25mg is highly effective in patients with newly diagnosed non-GCB DLBCL. Further studies are planned with other novel agents and with fewer cycles of chemotherapy consolidation for patients achieving a CR with RLI alone.

Keywords: activated B-cell-like (ABC); BTK inhibitors; IMiDs.

Disclosures: Westin, J: Consultant Advisory Role: *Celgene, Janssen, Novartis, Kite, Juno, Genentech.*

043

RITUXIMAB MAINTENANCE FOR PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA IN FIRST COMPLETE REMISSION: RESULTS FROM A RANDOMIZED HOVON-NORDIC LYMPHOMA GROUP PHASE III STUDY

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Introduction: This randomized phase III trial assessed whether intensification of rituximab (R) during the first 4 cycles of R-CHOP can improve outcome of diffuse large B-cell lymphoma (DLBCL) patients compared with standard R-CHOP. Patients in complete remission (CR) after induction treatment were randomized between rituximab maintenance and observation. Intensification of rituximab was not more effective than standard R-CHOP, showing same CR-rates and progression free survival after induction (ASCO 2016 # 7504). Here, we report the results of the second randomization for rituximab maintenance therapy.

Methods: Patients in CR after R-CHOP were randomized between 24 months of rituximab maintenance 375 mg/m^2 intravenous every 8 weeks (n = 199) or observation (n = 199). CT scans were performed at 6, 12, 18 and 24 months in both arms. The primary endpoint was disease free survival (DFS) from maintenance randomization. Secondary endpoints were overall survival (OS) and adverse events (AEs). (www.trialregister.nl NTR1014)

Results: Median age was 65 years (range 31-80), 48% were 66 years or older and 49% were male. The majority of patients (54%) had a high-intermediate or high aa-IPI score. After a median follow-up of 79.9 months (maximum 125.7 months), the 5-year DFS rate was 79% for rituximab maintenance versus 74% for observation. This difference was not statistically significant, with a hazard ratio of 0.83 (95% confidence interval 0.57-1.19, *p*=0.31, adjusted for age and aa-IPI).

The secondary endpoint OS was also not significantly different (85% versus 83% at 5 years). No clinical subgroup benefited from rituximab maintenance. Toxicity was mild. Among patients who received rituximab maintenance CTCAE grade 3 and 4 AEs were reported in 17% and 6% of patients, respectively. Infection was the most frequent AE, a grade 3 infection occurred in 6% of patients. Neutropenia was seen in 1% (grade 3) and 3% (grade 4) of patients.

Conclusions: Rituximab maintenance therapy provides no additional benefit for DLBCL patients in first CR after R-CHOP.

Keywords: diffuse large B-cell lymphoma (DLBCL); R-CHOP; rituximab.

044
IMPAIRED IMMUNE HEALTH IN SURVIVORS OF DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): A LARGE POPULATION-BASED STUDY

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Introduction: Improved outcomes in Diffuse Large B-cell Lymphoma (DLBCL) have led to a growing number of survivors. Treatments for DLBCL and the disease itself affect the immune system, yet little is known about the immune health of survivors. We investigated whether DLBCL survivors have altered risk of developing autoimmune or infectious conditions during survivorship.

Methods: This retrospective cohort study compared 21,690 DLBCL survivors to survivor cohorts of breast, prostate, head and neck cancer, and melanoma in the California Cancer Registry (CCR). We linked records from the CCR to a statewide database recording diagnoses from inpatient and certain outpatient encounters to investigate the incidence of 43 pre-specified autoimmune conditions, immune

	vs. Breast	vs. Prostate	vs. Head & Neck	vs. Melanoma
Specific Immune Deficiency	8.41	13.25	7.00	8.65
CNS Infections	2.97	4.05	1.67	3.29
Hematologic Autoimmune Conditions	2.50	3.10	1.91	3.06
Other/ General Infection Codes	1.42	2.52	1.49	2.88
Gastrointestinal and Kidney Autoimmune Conditions	1.92	2.25	1.76	2.00
Gastrointestinal and Hepatic Infections	1.42	2.09	1.39	1.90
Respiratory/Chest Infections	1.55	2.02	0.86	2.20
Eye & Ear Infections	1.68	1.90	0.76	1.79
Diffuse AIDs	1.32	1.64	1.21	1.47
AID of Skin, Bone, and Joints	1.54	1.25	1.19	1.38
Cardiac Infections	1.82	2.00		1.91
Infections, Coded by Pathogen	1.48	1.97		2.05
Genitourinary Infections	1.28	1.35		1.56
Skin and bone infections	1.39	1.78	0.76	
Vasculitides	2.10			1.56
AIDs of the Endocrine System	1.60			1.94
Neurologic Autoimmune Conditions	2.03		1.61	
Oral Infections			0.10	

Figure 1. Incidence rate ratios for 18 categories of immune-related conditions (autoimmune diseases, immune deficiencies, and infectious diseases) for Diffuse Large B-cell Lymphoma (DLBCL) survivors compared to survivors of either breast, prostate, head and neck cancer, or melanoma. Only results reaching significance (confidence intervals not crossing 1) are shown. Color scale is logarithmic (log10) with green shading for categories of diagnoses found more commonly in DLBCL survivors and pink and red shading for categories of diagnoses found more commonly in the comparator cohort. "vs.", *versus*. CNS, central nervous system. AID, autoimmune disease.

deficiencies and infections, occurring between 1-10 years after cancer diagnosis. If an observed condition had also been recorded prior to or within 1 year of cancer diagnosis, it was excluded. We used multivariable Poisson regression models adjusted for age, sex, race/ethnicity and year of diagnosis, to estimate incidence rate ratios (IRRs) for each condition comparing DLBCL survivors to each of the other cohorts. We also estimated the cumulative incidence of selected conditions over 10 years, accounting for death as a competing risk. We performed sensitivity analyses excluding patients with stem cell transplant (SCT), limiting comparison to a cohort that had uniformly received systemic chemotherapy, and restricting the analysis to a later survivorship period (years 5-10). Finally, we expanded the analysis to encompass 595 diagnosis codes for infections, autoimmune disease and immunodeficiencies, grouped into 18 clinical categories.

Results: Survivor cohorts were similar with regard to frequency of healthcare encounters and median follow-up time [5.7-8.3 years]. DLBCL survivors had a significantly higher incidence of many immune-related conditions, including humoral deficiency [IRRs 13.5-18.3], autoimmune anemia [IRRs 7.4-13.4], and Sicca syndrome [IRRs 2.8-8.6]), which have been associated with DLBCL previously but here were observed with new onset during survivorship. DLBCL survivors also had elevated rates of infections, notably fungal pneumonias [IRRs 3.9-11.3], viral pneumonias [IRRs 3.9-6.6], and meningitis [IRRs 3.0-5.0]. Sensitivity analyses produced similar results. Finally, a broader assessment of infections, autoimmune diseases and immunodeficiencies grouped by clinical category found widely increased risk among DLBCL survivors (Figure 1).

Conclusion: These findings, from a large, population-based cohort, show that immune-related conditions in DLBCL survivors are wide-ranging, and increased risk for these conditions is long-lasting. These data highlight a need to understand the mechanisms of immune dysfunction and to define predictors of clinical risk among DLBCL survivors.

Keywords: diffuse large B-cell lymphoma (DLBCL); immune system; immunosuppression.

SESSION 3 – CLL

045
INTERNATIONAL PROGNOSTIC SCORE FOR EARLY STAGE CHRONIC LYMPHOCYTIC LEUKEMIA (IPS-A)

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Introduction: Most patients with chronic lymphocytic leukemia (CLL) are diagnosed in early, Binet stage A disease. Although as a whole stage A patients have good prognosis, the individual outcome is heterogeneous and can be estimated only after a period of observation. Upfront definition of the risk of treatment can be used to plan a risk-tailored active surveillance, counsel patients about their likely outcome, and design clinical trials. We aimed at developing an IPS-A for time-to-first-treatment (TTFT) prognostication in stage A CLL patients.

Methods: We performed an analysis using individual patient data from 10 Binet A CLL cohorts initially managed with observation, for a total of 4106 patients. The adjusted association between variables and TTFT was estimated by Cox regression. Backward elimination was used to derive the final model, and variables resulting non-significant in more than half of the validation cohorts were excluded from the model. We assigned a weighted risk score to each factor of the final model based on the regression parameters. The prognostic score was then defined as the sum of single-risk parameters. We identified different risk groups based on recursive partitioning. Discrimination capacity of the model was assessed through c-index.

Results: By multivariate analysis in the stage A training cohort (University of Eastern Piedmont cohort, n=358) 3 out of 19 variables independently associated with TTFT, namely: lymphocyte count >15 G/L (HR=2.6), palpable lymph nodes (HR=2.7), and unmutated IGHV genes (HR=3.1). Using weighted grading, a score of 1 was assigned to each variable. By recursive partitioning, patients were segregated into three risk categories according: low- (score 0), intermediate- (score 1), and high-risk (score 2-3) with significantly different probability of need of therapy (c-index 0.74). The trained IPS-A was consistently
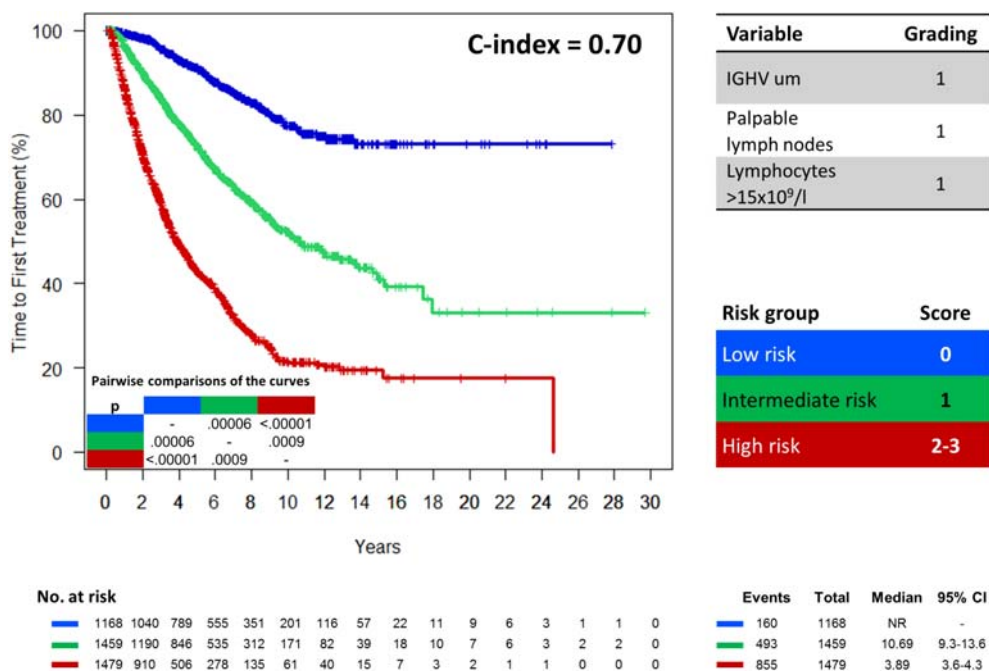
Fig.1

validated and the 3 risk groups were reproduced in 9 stage A series, including clinical trials (CLL1, n=547, c-index 0.71; CLL7, n=339, c-index 0.73; O-CLL1, n=312, c-index 0.67), institutional (MDACC, n=1225, c-index 0.66; Barcelona, n=355, c-index 0.75; Brno, n=269, c-index 0.69; Sapienza University, n=250, c-index 0.70; Southampton, n=227, c-index 0.75), and population based-series (SCAN, n=224, c-index 0.70). By compiling the training and validation series to narrow the confidence interval of the estimates, among low risk patients median TTFT was not reached and at 10 years 77% of patients were treatment free. Among intermediate-risk patients, median TTFT was 10.69 years (95% CI 9.31-13.60). Among high-risk patients, median TTFT was 3.89 years (95% CI 3.56-4.30) (Fig. 1).

Conclusions: Among stage A CLL initially managed with active surveillance, the IPS-A allows to inform upfront patients, physicians and researchers about the likelihood of disease progression.

Keywords: chronic lymphocytic leukemia (CLL); prognostic indices.

046

FIXED-DURATION VENETOCLAX PLUS OBINUTUZUMAB IMPROVES PFS AND MINIMAL RESIDUAL DISEASE NEGATIVITY IN PATIENTS WITH PREVIOUSLY UNTREATED CLL AND COMORBIDITIES

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TABLE 1 MRD levels in PB by NGS 3 months after treatment completion

All pts (ITT) N	ClbG 216	VenG 216
MRD level, n (%)		
$<10^{-6}$	9 (4.2)	67 (31.0)
$\geq 10^{-6}$ and $<10^{-5}$	33 (15.3)	75 (34.7)
$\geq 10^{-5}$ and $<10^{-4}$	32 (14.8)	26 (12.0)
$\geq 10^{-4}$ and $<10^{-2}$	50 (23.1)	13 (6.0)
$\geq 10^{-2}$	62 (28.7)	10 (4.6)
No sample/not evaluable	30 (13.9)	25 (11.6)

Figure 1a: Investigator-assessed progression-free survival

Venetoclax-obinutuzumab
88.2% still event-free 24 months
after randomization

Chlorambucil-obinutuzumab
64.1% still event-free 24 months
after randomization

HR 0.35, 95% CI 0.23−0.53
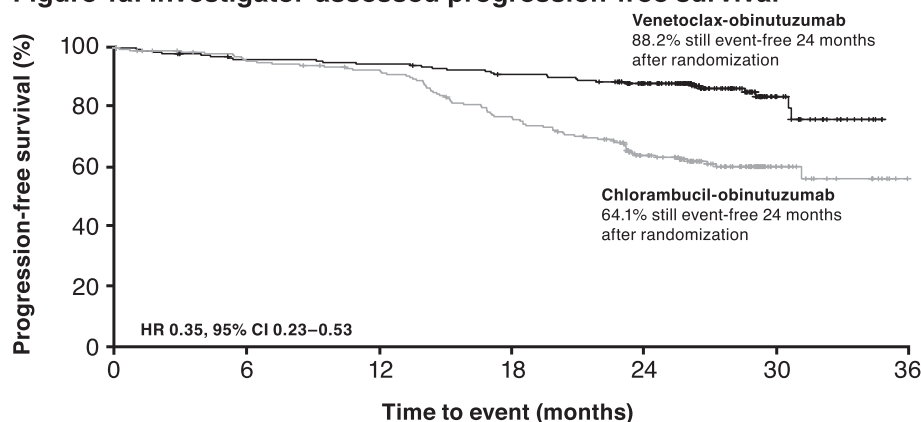
Figure 1b: Duration of MRD negativity after treatment completion

Venetoclax-obinutuzumab
81.2% still MRD negative 12 months
after completion of treatment

Chlorambucil-obinutuzumab
27.3% still MRD negative 12 months
after completion of treatment

Median time off-treatment: 19 months

HR for MRD conversion 0.19, 95% CI 0.12−0.30
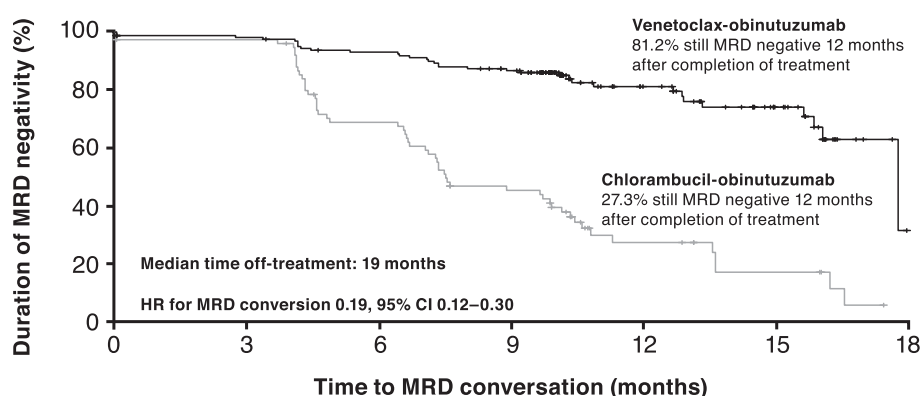
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Introduction: The multinational, open-label, phase 3 CLL14 trial (NCT02242942) compared fixed-duration targeted venetoclax plus obinutuzumab (VenG) treatment with chlorambucil-obinutuzumab (ClbG) treatment in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities. We present endpoint analyses with particular emphasis on progression-free survival (PFS) and minimal residual disease (MRD)-negativity.

Methods: Pts with a CIRS score >6 and/or an estimated creatinine clearance <70 mL/min were randomized 1:1 to receive equal duration treatment with 12 cycles of standard Clb or Ven 400 mg daily in combination with G for the first 6 cycles. The primary endpoint was PFS. MRD-negativity in peripheral blood (PB) or bone marrow (BM) 3 months after treatment completion was a key secondary endpoint. MRD was analyzed serially from Cycle 4 every 3 months by an allele-specific oligonucleotide polymerase chain reaction assay (ASO-

PCR; cut-off, 10^{-4}) and by next generation sequencing (NGS; cut-offs, 10^{-4}, 10^{-5}, 10^{-6}).

Results: 432 pts were enrolled (216 in each treatment group; intent-to-treat population). Median age, total CIRS score, and CrCl at baseline were 72 years, 8, and 66.4 mL/min respectively. After 29 months' median follow-up, superior PFS was observed with VenG vs ClbG (**Figure 1a**). Median PFS was not reached in either group: at Month 24, PFS rates were 88% with VenG and 64% with ClbG (hazard ratio [HR] 0.35; 95% confidence interval [CI] 0.23–0.53; P<0.0001). MRD-negativity by ASO-PCR was significantly higher with VenG vs ClbG in both PB (76% vs 35% [P<0.0001]) and BM (57% vs 17% [P<0.0001]) 3 months after treatment completion. Overall, 75% of VenG MRD-negative pts in PB were also MRD-negative in BM vs 49% in the ClbG group. Landmark analysis for this timepoint by PB MRD status showed that MRD-negativity was associated with longer PFS. MRD-negativity rates were more sustainable with VenG: 81% (VenG) vs 27% (ClbG) of pts were MRD-negative 12 months after treatment completion (**Figure 1b**). MRD-negativity rates by NGS confirmed these results; 78% (VenG) vs 34% (ClbG) of pts had MRD-negative status at $<10^{-4}$, 35% vs 15% at $\geq 10^{-6}$–$<10^{-5}$ and 31% vs 4% at $<10^{-6}$, respectively.

Conclusions: Fixed-duration VenG induced deep, high ($<10^{-4}$ in 3/4 of pts and $<10^{-6}$ in 1/3 of pts), and long lasting MRD-negativity rates (with a low rate of conversion to MRD-positive status 1 year after treatment) in previously untreated pts with CLL and comorbidities, translating into improved PFS.

This abstract has been previously submitted in part to ASCO 2019 and EHA 2019.

Keywords: chronic lymphocytic leukemia (CLL); obinutuzumab; venetoclax.

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047

GENETIC MARKERS AND OUTCOME IN THE CLL14 TRIAL OF THE GCLLSG COMPARING FRONT LINE OBINUTUZUMAB PLUS CHLORABMUCIL OR VENETOCLAX IN PATIENTS WITH COMORBIDITY

Best abstract submitted by a young investigator / travel grant recipient

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Introduction: Genomic aberrations, IGHV mutation status and mutations in genes such as *TP53* are established prognostic factors in CLL in the context of chemoimmunotherapy. Their role is less-well established when using chemo-free regimens such as obinutuzumab (GA-101) plus venetoclax (Ven-G).

Methods: We assessed the incidence and impact of genomic aberrations via FISH, mutations in 13 genes via NGS and IGHV status in the phase 3 CLL14 trial comparing G-Clb vs. Ven-G in patients with CIRS>6 or creatinine clearance < 70 ml/min. Of the intention to treat population (n=432) FISH/IGHV/NGS was assessable in 418/408/421 cases.

Results: The incidence of genomic aberrations considering the hierarchical model were del(17p) 7%, del(11q) 18%, +(12q) 18% and del (13q) 35%. IGHV was unmutated in 61% of patients. The incidence of gene mutations was *NOTCH1* 23%, *SF3B1* 16%, *ATM* 13%, *TP53* 10%, *XPO1* 6%, *RPS15* 5%, *POT1* 5%, *BRAF* 4%, *BIRC3* 4%, *NFKBIE* 4%, *EGR2* 4%, *MYD88* 2% and *FBXW7* 1%. High coincidence was found for del(17p) and *TP53*^{mut}. Overall response rate (ORR) to G-Clb was lower with del(17p), del(11q) *TP53*^{mut}, *ATM*^{mut} and *BIRC3*^{mut}. None of the parameters impaired ORR to Ven-G.

At a median follow-up of 29 months, there were 107 events for PFS and 37 for OS in the intention to treat population. Del(17p) was the only genomic abnormality with impact on PFS in G-Clb (HR 4.6, p<0.001) and Ven-G (HR 4.4, p=0.001; Fig 1a). Similarly, *TP53* mutations affected PFS in both treatment arms (G-Clb HR 2.7, p=0.001; Ven-G HR 3.1, p=0.01). None of the other evaluated factors affected Ven-G efficacy, while for G-Clb del(11q) (HR 2.3, p=0.002), *BIRC3* (HR 4.0, p=0.001), *NOTCH1* (HR 1.8, p=0.03) and IGHV^{unmut} (HR 3.4, p<0.001) were adverse factors.

Ven-G was superior to G-Clb regarding PFS in most genetic subgroups including del(17p), del(11q), *TP53*^{mut}, *NOTCH1*^{mut}, *SF3B1*^{mut} and *ATM*^{mut}. Regarding IGHV, only patients with unmutated status had a significant PFS benefit from Ven-G in comparison to G-Clb (IGHV^{unmut} HR 0.2, p<0.001; IGHV^{mut} HR 0.6, p=0.29; Fig 1b). Multivariable testing for interaction between treatment and IGHV status was significant (p=0.03) indicating IGHV^{unmut} as a predictive factor for increased benefit from Ven-G. OS was lower with del(17p) in both treatment arms (G-Clb: HR 11.0, p<0.001; Ven-G: HR 3.4, p=0.03) and with *TP53*^{mut}, *BRAF*^{mut} and IGHV^{unmut} in the G-Clb arm (HR 5.5, p=0.002; HR 6.6, p<0.01; HR 5.4, p=0.03), while none of the other factors were significantly associated with OS.

Conclusion: Prognostic value of genomic aberrations, IGHV and gene mutations were confirmed for G-Clb, while with Ven-G only del(17p) and *TP53*^{mut} were associated with short PFS and only del(17p) with short OS. IGHV^{unmut} was identified as a predictive factor identifying a group of patients with particular benefit from Ven-G.

Keywords: chronic lymphocytic leukemia (CLL); prognostic indices; venetoclax.

1a PFS — Ven-G, no del(17p); Ven-G, del(17p); G-Clb, no del(17p); G-Clb, del(17p)

1b PFS — Ven-G, IGHV mutated; Ven-G, IGHV unmutated; G-Clb, IGHV mutated; G-Clb, IGHV unmutated

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Acalabrutinib vs Rituximab Plus Idelalisib (IdR) or Bendamustine (BR) by Investigator Choice in Relapsed/Refractory (RR) Chronic Lymphocytic Leukemia: Phase 3 ASCEND Study

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Background: Acalabrutinib is a highly selective, potent, covalent Bruton tyrosine kinase inhibitor that has shown clinical benefit in patients (pts) with RR CLL. In this randomized, global, multicenter, open-label Phase 3 study, the efficacy and safety of acalabrutinib monotherapy were evaluated vs the investigator's choice of IdR or BR in RR CLL (NCT02970318).

Methods: Eligible pts with RR CLL were randomized 1:1 to 100 mg oral acalabrutinib BID until progression vs IdR (150 mg oral Id BID combined with ≤8 IV infusions of R [375 or 500 mg/m^2]), or BR (70 mg/m^2 IV B on Day 1 and 2 of each cycle combined with R [375 or 500 mg/m^2 IV] on Day 1 of each 28-d cycle for ≤6 cycles). Stratification was by del(17p) status (y vs n), ECOG status (0-1 vs 2), and prior therapy lines (1-3 vs ≥4). The primary endpoint was progression-free survival (PFS) assessed by independent review committee (IRC). Secondary endpoints included overall survival (OS), overall response rate (ORR; by IRC), and safety. Pts with confirmed progression on IdR/BR could cross over to receive acalabrutinib monotherapy.

Results: 310 pts were randomized to acalabrutinib (n=155) or IdR/BR (n=155 [IdR, n=119; BR, n=36]); median age was 67 y (range, 32-90); 16% had del(17p); 27% had del(11q); 42% had Rai stage III/IV CLL. Median (range) no. of prior therapies was 1 (1-8) for acalabrutinib and 2 (1-10) for IdR/BR. Discontinuation due to AEs occurred in 11% of pts on acalabrutinib vs 49% Id, 12% R in IdR, 11% B and 17% R in BR. At a median follow-up of 16.1 mo, acalabrutinib significantly prolonged IRC-assessed PFS vs IdR/BR (median NR vs 16.5 mo; HR 0.31, 95% CI 0.20-0.49, P<.0001; **Figure**). PFS rates at 12 mo were 88% with acalabrutinib and 68% with IdR/BR; improvement was seen across subgroups, including del(17p), *TP53* mutation and Rai stage.

ORR by IRC was similar with acalabrutinib vs IdR/BR (81% vs 75%; p<.22). 12-mo OS rates were 94% and 91% (with 15 and 18 deaths) for acalabrutinib and IdR/BR, respectively. 23% of IdR/BR pts crossed over to acalabrutinib monotherapy.

All-grade AEs (≥15%) with acalabrutinib were headache (22%), neutropenia (19%), diarrhea (18%), anemia and cough (15% each); with IdR, diarrhea (47%), neutropenia (45%), pyrexia (18%) and cough (15%); with BR, neutropenia (34%), infusion-related reaction and fatigue (23% each), nausea (20%) and pyrexia (17%). Grade ≥3 AEs (≥5%) with acalabrutinib were neutropenia (16%), anemia (12%) and pneumonia (5%); with IdR (≥15%), neutropenia (40%) and diarrhea (24%); with BR (≥5%), neutropenia (31%), anemia (9%) and constipation (6%).

AEs of interest were atrial fibrillation (5.2% of pts on acalabrutinib vs 3.3% on IdR/BR), bleeding AEs (26% vs 7.2%; including major

Acalabrutinib vs IdR/BR
HR 0.31 (95% CI, 0.20-0.49)
P<.0001

+ Censored

Number at Risk																							
Acalabrutinib	155	153	153	149	147	146	145	143	143	139	139	137	118	116	73	61	60	25	21	21	1	1	1	0
IdR/BR	155	150	150	146	144	142	136	130	129	112	105	101	82	77	56	44	39	18	10	8	0			
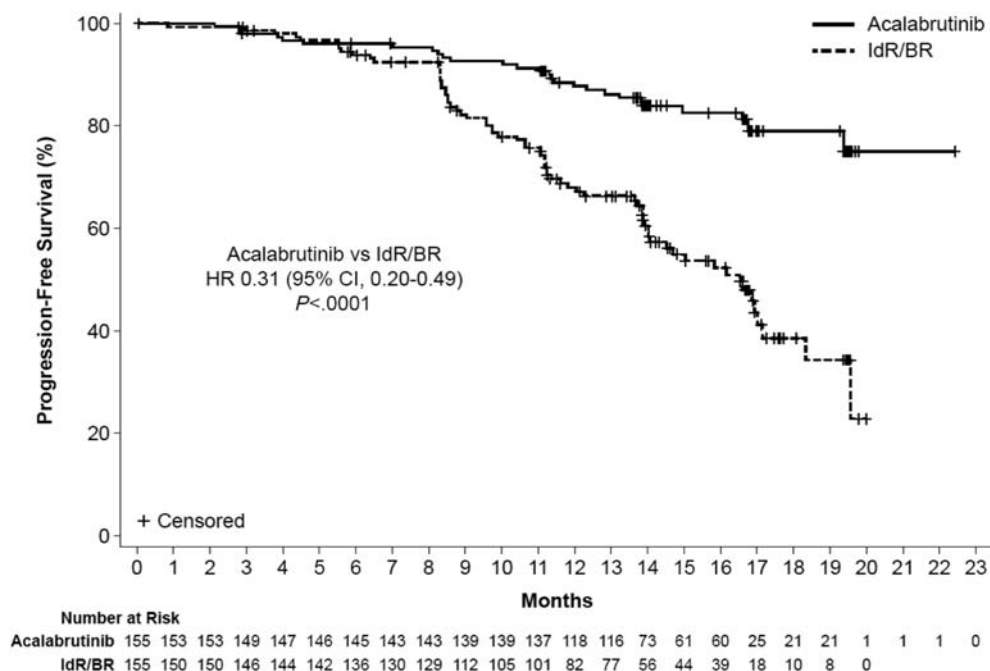
hemorrhage [1.9% vs 2.6%]), Grade ≥3 infections (15% vs 24%) and 2nd primary malignancies (excluding NMSC; 6.5% vs 2.6%).

Conclusion: Acalabrutinib monotherapy significantly improved PFS with a more tolerable safety profile vs IdR/BR in pts with RR CLL.

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ZANUBRUTINIB FOR PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: Zanubrutinib is a selective and irreversible BTK inhibitor that has demonstrated potent inhibition of BTK preclinically, with minimal, off-target inhibition of other kinases. Complete and sustained BTK occupancy in both blood and lymph node biopsies from patients treated with zanubrutinib at 160 mg twice daily (BID) was observed in a phase 1 clinical trial.

Methods: In this single-arm, multicenter phase 2 study (ClinicalTrials.gov NCT03206918), zanubrutinib was given by mouth, 160 mg BID to patients with relapsed or refractory CLL/SLL until disease progression (PD) or unacceptable toxicity. Efficacy endpoints were assessed by independent review (IRC) in accordance with IWCLL guidelines (IWCLL, 2008) or the Lugano Classification (Cheson, 2014) for CLL and SLL, respectively.

Results: As of 14 December 2018, 91 pts (82 with CLL; 9 with SLL) were enrolled and treated at 11 centers in China. Baseline disease characteristics are summarized in the table. Median follow-up was 15.1 mo (range, 0.8-21.2 mo) with treatment discontinuation in 16 (17.6%) pts (8 due to AEs, 7 due to PD, and 1 due to pt withdrawal). A total of 83 pts (91.2%, 95% CI: 83.4, 91.6) achieved a best response of partial response with lymphocytosis (PR-L) or better according to investigators' assessment. Patients with del(17p) or TP53 mutation achieved a high

Baseline Disease Characteristics	N=91
Median age, y (range)	61.0 (35-87)
Male, n (%)	52 (57.1)
Binet stage B or C (CLL pts), n (%)	77 (93.9)
Stage IV (SLL pts), n (%)	7 (77.8)
Del(17p), n (%)	17 (18.7)
TP53 mutation, n (%)	20 (22.0)
Del(17p) or TP53 mutation, n (%)	22 (24.2)
Del(13q), n (%)	41 (45.1)
Del(11q), n (%)	20 (22)
Trisomy 12, n (%)	21 (23.1)
IGHV unmutated, n (%)	51 (56.0)
Lines of prior therapy, median (range)	1 (1-9)
Efficacy[a]	
Complete response (CR), n (%)	4 (4.4)
Nodular partial response (nPR), n (%)	2 (2.2)
Partial response (PR), n (%)	60 (65.9)
Partial response with lymphocytosis (PR-L), n (%)	17 (18.7)
Stable disease (SD), n (%)	4 (4.4)
Progressive disease (PD), n (%)	1 (1.1)
Discontinued prior to 1st assessment, n (%)	3 (3.3)
Safety	
Any TEAE, n (%)	91 (100)
Serious AE, n (%)	30 (33.0)
AE leading to treatment discontinuation, n (%)	8 (8.8)
AE leading to death[b], n (%)	3 (3.3)

Common Adverse Event	Any Grade	Grade ≥3
Neutrophil count decreased, n (%)	62 (68.1)	40 (44.0)
Upper respiratory tract infection, n (%)	41 (45.1)	9 (9.9)
Purpura, n (%)	31 (34.1)	0 (0)
Platelet count decreased, n (%)	30 (33.0)	8 (8.8)
Haematuria, n (%)	27 (29.7)	0 (0)
Anaemia, n (%)	25 (27.5)	8 (8.8)
Hypokalaemia, n (%)	23 (25.3)	6 (6.6)

[a] Best response as assessed by the investigator. IRC-assessed efficacy outcomes are on-going and will be presented.
[b] One of the patients with primary reason of death due to PD also reported a fatal AE of multiple organ dysfunction syndrome.

ORR (95.5%). Median time for achieving first response was 2.79 mo (range, 2.6-5.6 mo) among responders. Estimated PFS rate at 12 months was 80.9% (95% CI: 67, 89). The most frequently reported AEs are summarized in the table below. Major hemorrhage was reported in 2 patients (Gr 3, gastrointestinal hemorrhage and Gr 2 intracranial hemorrhage), which led to discontinuation of zanubrutinib. Four (4.4%) pts died within 30 days of their last dose of study drug, 2 due to PD and 2 due to AEs (pulmonary infection; cardiopulmonary failure).

Conclusions: Zanubrutinib was generally well-tolerated and resulted in a high response rate, including in patients with del(17p) or TP53 mutation.

Keywords: BTK inhibitors; chronic lymphocytic leukemia (CLL); zanubrutinib.

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A PHASE 2 STUDY TO ASSESS THE SAFETY AND EFFICACY OF UMBRALISIB IN

PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WHO ARE INTOLERANT TO PRIOR BTK OR PI3K DELTA INHIBITOR THERAPY

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Introduction: Although kinase inhibitor (KI) therapies are generally well tolerated, intolerance is the most common reason for discontinuation (~50% discontinuations; Mato et al 2017). Therefore, patients (pts) who discontinue a KI due to intolerance represent an unmet medical need. Umbralisib (TGR-1202, Umbra) is a novel, highly-specific PI3Kδ inhibitor which is active and well tolerated in pts with CLL. This phase 2 trial evaluates the safety/efficacy of Umbra in CLL pts who are intolerant to prior BTK or PI3Kδ inhibitor therapy.

Methods: KI intolerant is defined as: ≥ 1 GR 3 or ≥ 2 GR 2 non-heme tox, ≥ 1 GR 3 neutropenia with infection or fever, and/or ≥ 1 GR 4 heme tox leading to KI discontinuation. Prior KI must be discontinued for ≥ 14 days without CLL progression. Pts must start Umbra within 12 mos of prior KI. All pts treated with Umbra (800 mg oral daily) until progression, toxicity, or study conclusion. Primary endpoint is progression-free

Figure 1: PFS

Figure 1
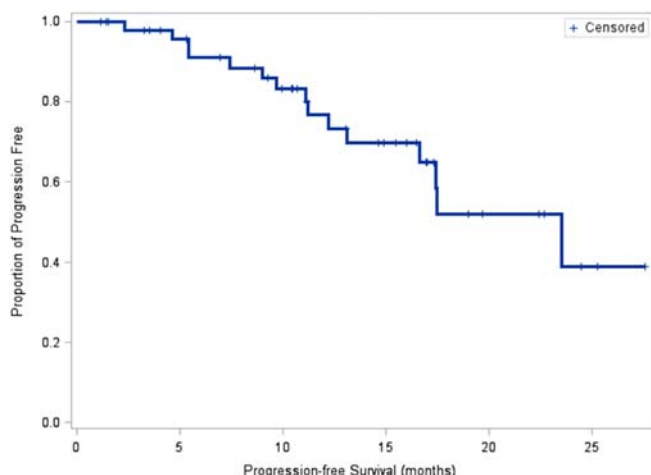
survival (PFS). Secondary endpoints include time to treatment failure as compared to prior KI therapy and characterization of Umbra safety profile. Peripheral blood samples are being collected for correlative analyses to identify markers associated with KI intolerance.

Results: 51 pts were enrolled (44 BTK & 7 PI3Kδ intolerant). Baseline demographics include: med age 70 yrs (range 48-96), med prior therapies 2 (1-7), del17p and/or TP53 (24%), del11q (18%), IGHV unmutated (57%), BTK mut or PLCg2 mut (8%). 76% required tx within 6 mos of prior KI discontinuation. Most common AEs leading to prior KI discontinuation were: rash (14 events), arthralgia, A-Fib/Cardiac, (9 events each), diarrhea/colitis, bleeding/hemorrhage (6 events each). 50 pts were evaluable for efficacy. Median PFS is 23.5 mos (95% CI 16.6-not estimable, Fig 1). As of the cut-off date, 58% of pts have been on Umbra for a longer duration than their prior KI. Most common (≥ 5%) GR ≥3 AEs while on Umbra (all causality) were: neutropenia (14%), thrombocytopenia (10%), diarrhea (8%), hypophosphatemia, pneumonia (6% each). Six pts (12%) discontinued Umbra due to an AE (pneumonitis (2), pneumonia, rash, dermatitis, pancreatitis). Four pts had recurrence of an AE that led to prior KI intolerance, however 3/4 recurrences did not result in dose-modification. No prior PI3K treated patients (n = 7) had a recurrence of AE that led to PI3K discontinuation including the 3 pts with colitis. Four pts (8%) had dose reductions (headache, hematologic, AST/ALT and colitis) and were successfully re-challenged.

Conclusion: Umbralisib is safe and effective in a KI intolerant CLL population. These are the first prospective data to confirm that switching from KI to Umbra can result in durable, well tolerated responses. From a therapy sequencing perspective, these data suggest use of an alternate KI is a reasonable strategy prior to class switch to a BCL-2 inhibitor. Pre-umbralisib dosing samples are being analyzed for CYP-3A4 polymorphisms.

Keywords: BTK inhibitors; chronic lymphocytic leukemia (CLL); PI3K/AKT/mTOR.

SESSION 4 – TREATMENT WITH NOVEL ANTIBODIES

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THE FIRST-IN-CLASS ANTI-CD47 ANTIBODY HU5F9-G4 + RITUXIMAB INDUCES DURABLE RESPONSES IN RELAPSED/REFRACTORY DLBCL AND INDOLENT LYMPHOMA: INTERIM PHASE 1B/2 RESULTS

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Introduction: Hu5F9-G4 (5F9) is a first-in-class IgG4 antibody targeting CD47, a macrophage immune checkpoint and "don't eat me" signal on cancers leading to phagocytosis of tumor cells. Pre-clinically,

5F9 synergizes with rituximab to eliminate lymphoma by enhancing antibody-dependent cellular phagocytosis. 5F9+rituximab had encouraging safety/efficacy in a Phase (Ph)1b dose escalation cohort in relapsed/refractory (r/r) DLBCL and FL patients that were rituximab-refractory (Advani et al., NEJM 2018). We report on extended follow up of this Ph1b cohort and preliminary Ph2 data.

Methods: The Ph2 enrolled: 1) DLBCL: primary refractory or r/r to ≥ 2 prior therapies, ineligible for CAR-T therapy; and 2) indolent lymphoma (FL/MZL) r/r to ≥ 2 prior therapies. A 5F9 priming dose was used to mitigate on-target anemia; followed by weekly or Q2 week maintenance doses. Based on a potential dose-response seen in Ph1b, 5F9 maintenance doses of 30 and 45 mg/kg were tested with rituximab.

Results: 100 patients (63 DLBCL, 35 FL, 2 MZL) have been treated in both Ph1b+2 cohorts. Median age (range) was 66 years (21-88) with 3 median prior therapies (range 1-10). 84% were rituximab-refractory and 72% refractory to their last therapy. 5F9+rituximab was well-tolerated at 5F9 doses up to 45 mg/kg with no maximum tolerated dose reached or significant dose-dependent toxicities. Treatment-related AEs (TRAEs) in >10% of patients included infusion reactions (38%), headache (34%), chills (30%), fatigue (30%), anemia (27%), nausea (24%), pyrexia (23%) vomiting (13%), and back pain (11%). The majority were G1/2 with 7% or lower being G3/4, except G3 anemia (15%) which was an expected transient first-dose effect. Treatment discontinuation from TRAEs occurred in only 4% of patients. As of Feb 2019, for Ph1b patients dosed from 10-30 mg/kg (n=22), at a median follow up of 12 months (DLBCL) and 18 months (FL), the median duration of response had not been reached (DLBCL range: 2.4 – 20+ months; FL range: 6.2 – 22.6+ months), including some durable CRs for > 20 months. Of 100 patients enrolled, 75 patients were efficacy evaluable, 8 were not, and 17 had first assessment pending. Pooled data from Ph1b+2 efficacy evaluable patients (n=75) show an objective response rate (ORR) and CR rate of 49% and 21%, respectively. In indolent lymphoma (n=28 FL, 1 MZL), the ORR and CR rate was 66% and 24%, respectively. In DLBCL (n=46), the ORR/CR rate was 39/20%. Median time to response for responding patients was rapid at 1.8 months. The ORR for patients treated with 30 mg/kg 5F9 (n=59) was 47% and at 45 mg/kg was 71% in a limited number (n=7). Accrual is ongoing and additional data at the 45 mg/kg dose will be presented.

Conclusions: 5F9+rituximab is a novel immunotherapy blocking a key macrophage/cancer checkpoint. It is well tolerated with rapid and durable responses observed in heavily pre-treated DLBCL and indolent lymphoma patients. Ph2 enrollment is ongoing (NCT02953509). Funded by Forty Seven and the Leukemia and Lymphoma Society.

Keywords: diffuse large B-cell lymphoma (DLBCL); indolent lymphoma; macrophages.

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CLINICAL ACTIVITY OF REGN1979, AN ANTI-CD20 X ANTI-CD3 BISPECIFIC ANTIBODY (AB) IN PATIENTS (PTS) WITH (W/) RELAPSED/REFRACTORY (R/R) B-CELL NON-HODGKIN LYMPHOMA (B-NHL)

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Introduction: REGN1979 (R1979) is an anti-CD20 x anti-CD3 bispecific IgG4 Ab. We report updated results of a Phase 1 trial of R1979 in pts

Table. Best overall response according to Cheson 2007 criteria[1]

	R/R FL Gr 1–3a*			R/R DLBCL				Other R/R B-NHL (MCL, MZL, FL Gr 3b, FL unknown/ungraded, WM)			
	<5 mg (n=7)	≥5–≤12 mg (n=5)	≥18–≤40 mg (n=5)	<5 mg (n=15)	≥5–≤12 mg (n=11)	≥18–≤40 mg (n=11)	80 mg (n=2)	<5 mg (n=5)	≥5–≤12 mg (n=3)	≥18–≤40 mg (n=4)	80 mg (n=3)
Overall response rate (ORR), n (%)	1 (14.3)	5 (100)	5 (100)	3 (20.0)	2 (18.2)	6 (54.5)	2 (100)	2 (40.0)	1 (33.3)	3 (75.0)	2 (66.7)
Complete response (CR), n (%)	1 (14.3)	4 (80.0)	4 (80.0)	0	1 (9.1)	2 (18.2)	2 (100)	0	0	2 (50.0)	1 (33.3)
Partial response (PR), n (%)	0	1 (20.0)	1 (20.0)	3 (20.0)	1 (9.1)	4 (36.4)	0	2 (40.0)	1 (33.3)	1 (25.0)	1 (33.3)
Duration of follow-up, median (range) weeks	22.1 (8.1–51.3)	59.1 (31.3–63.4)	29.0 (11.1–52.6)	6.9 (3.1–52.3)	10.7 (3.1–59.3)	17.1 (2.4–59.6)	9.4 (5.4–13.3)	5.3 (5.0–44.1)	8.1 (4.3–58.6)	30.1 (4.1–39.3)	10.9 (4.3–15.3)

* Patients were not treated with 80 mg dose in this subtype.

Figure. Best response per Cheson 2007 criteria[1] in target lesions from baseline in patients with R/R FL Gr 1–3a and DLBCL treated with REGN1979 ≥5 mg
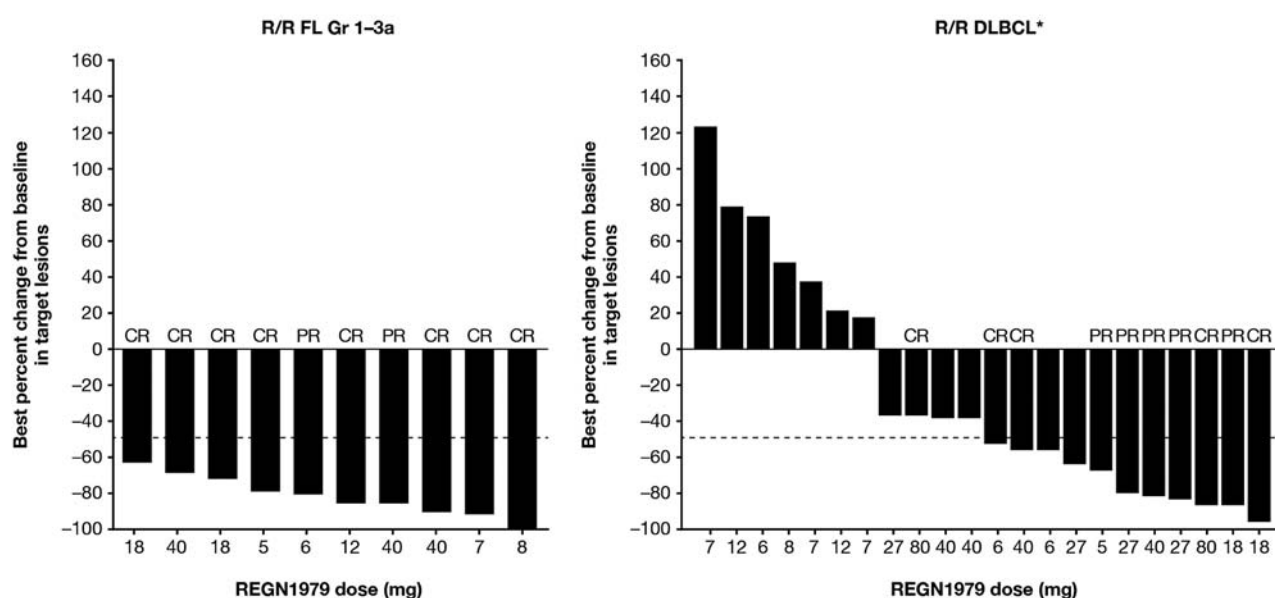
*Two patients discontinued prior to the first on-treatment disease assessment.
CR, complete response; PR, partial response.
[1]Cheson BD. *Hematol Oncol Clin North Am.* 2007;21:841–854.

w/ R/R B-NHL previously treated w/ anti-CD20 Ab therapy. Primary objectives are to determine safety, tolerability, and occurrence of dose limiting toxicities (DLTs). Other objectives are to assess antitumor activity, pharmacokinetics (PK), and pharmacodynamics.

Methods: Eligible pts w/ R/R B-NHL must have received ≥1 prior CD20-directed Ab therapy. Treatment (tx) consists of 12 weekly intravenous doses of R1979 followed by every 2-week dosing for 12 doses (total of 36 weeks).

Results: As of Dec 6, 2018, 71 pts (diffuse large cell B-cell lymphoma [DLBCL] [n=39], follicular lymphoma [FL] grade [Gr] 1-3a [n=17], other [mantle cell lymphoma {MCL}, marginal zone lymphoma {MZL}, FL grade 3b, FL unknown/ungraded, or Waldenstrom macroglobulinemia {WM} [n=15]) were treated w/ R1979 0.03–80 mg and received a median of 9 doses (range 1–24). Ten pts remain on tx; 15 completed tx; 46 discontinued early (29 due to progressive disease [PD]).

No pts w/ B-NHL experienced a DLT. Most common tx-emergent adverse events (AEs) were pyrexia (n=56), chills (n=38), cytokine release syndrome (CRS; n=37, w/4 experiencing Gr ≥3). The severity of CRS symptoms declined through optimized pre-medication even w/ R1979 dose escalation. Most common Gr ≥3 AEs were decreased neutrophils/neutropenia (n=14), decreased lymphocytes/lymphopenia (n=14), anemia (n=12). No seizure and/or encephalopathy was reported. No neurological event required tx termination. Four pts discontinued due to AEs: Gr 3 hemolysis; Gr 3 fatigue; Gr 3 pneumonia; and Gr 3 neck abscess (1 each). Nine pts died on study: PD (n=6), gastric perforation (n=1), cardiac arrest (n=1), lung infection (n=1).

Tx w/ R1979 at doses ≥5 mg has shown marked efficacy in R/R FL Gr 1–3a (ORR: 100% [10/10 OR; 8/10 CR; 2/10 PR]), while increasing efficacy is observed in pts w/ R/R DLBCL (and other B-NHL subtypes) as the dose is further increased (Table and Figure); of note, in patients

with R/R DLBCL, 2/11 (18%) had responses at doses between 5-12 mg, 6/11 (55%) had responses at doses between 18-40 mg, and 2/2 (100%) had responses at the 80 mg dose, with both of these latter being CRs. Elevated levels of serum cytokines were observed w/ dosing; however, no correlation was observed w/ clinical efficacy. Immunohistological analysis of malignant lymph node tissue demonstrated that pts w/ high and low CD20 achieved clinical response. Relapse among responders was seen w/ either maintenance or loss of CD20 expression, suggesting antigen-dependent and independent disease escape mechanisms.

Conclusions: R1979 was well tolerated in pts w/ R/R B-NHL. No DLTs and no significant neurological toxicity were observed. Tx w/ R1979 showed impressive efficacy w/ 100% ORR in R/R FL starting at doses ≥5 mg. More resistant tumors such as R/R DLBCL are showing benefit w/ increasing doses. Based on these efficacy findings, a Phase 2 study in R/R FL Gr 1-3a, R/R DLBCL, and other R/R B-NHL subtypes is planned.

Keywords: CD20; CD3; non-Hodgkin lymphoma (NHL).

053
CD20-TCB (RG6026), A NOVEL "2:1" FORMAT T-CELL-ENGAGING BISPECIFIC ANTIBODY, INDUCES COMPLETE

REMISSIONS IN RELAPSED/REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA

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Introduction: CD20-TCB (RG6026) is a T-cell-engaging bispecific antibody with a novel "2:1" molecular format which preclinically showed greater avidity for CD20 antigen, combinability with other anti-CD20 antibodies, and greater efficacy as compared to other CD20-CD3 bispecific formats. NP30179 is an ongoing multicenter phase I dose escalation trial investigating the safety, tolerability, pharmacokinetics (PK), biomarkers and antitumor activity of CD20-TCB.

Methods: Patients receive escalating doses of CD20-TCB as intravenous infusions guided by a model implementing a Bayesian CRM method with overdose control. To reduce the risk of cytokine release syndrome (CRS), a single dose of obinutuzumab as pretreatment (Gpt) is administered seven days prior to CD20-TCB to debulk B cells in peripheral blood and normal tissues (Bacac et al Clin Canc Res 2018). Updated data at clinically-relevant doses of 600 µg and above are reported.

Results: As of February 13th 2019 a total of 87 pts with r/r aggressive (a)NHL (DLBCL/PMBCL/trFL/Richter´s transformation; n=79) and r/r FL (n=8) received CD20-TCB doses ranging from 600 µg to 25mg in a Q2W or Q3W schedule. Median age was 61 years (range 22-84),

median prior lines of therapy was 3 (range 1-13), and 86% pts were refractory to prior therapy. CRS (according to the criteria by Lee et al. Blood 2014) occurred in 45 patients (23% G1, 24% G2, 3% G3, 1% G4). At the highest dose cohort (25 mg) $\geq$G3 CRS occurred in 3/8 pts at cycle 1, thereby preventing further dose escalation. One patient in the 25 mg cohort died of upper GI bleeding after an episode of severe CRS. All other CRS events were manageable and resolved, and patients were retreated without delay at the same dose at cycle 2, where only one additional CRS event was seen (G1).

In the efficacy evaluable pts (n=84) the ORR and CR rate by investigator assessment (Lugano 2014 criteria) in aNHL (n=76) was 46% and 29%, and in FL (n=8) 63% and 50%, respectively. In the highest dose cohorts (10-25 mg) the ORR and CR rate in aNHL (n=38) was 55% and 37% indicating a dose-response relationship. CR was usually achieved at the first or second response assessments (C3 or C6) although in 4 aNHL pts late conversion from PR or SD to CR was observed at cycle 12. A patient with FL initially dosed at 15 µg who had progressed was retreated at 10 mg, achieving CR. After a median follow up of 3.8 months all but 2 CRs are still ongoing. Responses were seen across NHL subtypes and across prognostic factors such as disease burden, prior lines of therapy, and refractoriness to prior therapy. CD20-TCB exposure and receptor occupancy increased dose-dependently across the investigated dose range. No anti-drug-antibodies have been found. Mode of action was demonstrated by rapid and sustained T cell activation in peripheral blood and tumor biopsies.

Conclusions: CD20-TCB is a novel 2:1 format T-cell-engaging bispecific antibody which displays highly promising clinical activity in heavily-pretreated NHL.

Keywords: B-cell lymphoma; CD20; immune system.

Disclosures: Dickinson, M: Consultant Advisory Role: *Roche*; Honoraria: *Roche.* **Morschhauser, F:** Consultant Advisory Role: *Advisory role for Celgene, Roche, BMS, Gilead, Epizyme, Verasteem*; Honoraria: *Novartis, Janssen, Abbvie.* **Iacoboni, G:** Honoraria: *Celgene, Novartis, Roche.* **Carlo-Stella, C:** Consultant Advisory Role: *Sanofi, ADC Therapeutics, Servier France, Roche*; Honoraria: *BMS, MSD, Novartis, Janssen.* **Sureda, A:** Other Remuneration: *Travel Grants from Roche.* **Salles, G:** Consultant Advisory Role: *Abbvie, Celgene, Gilead, Epizyme, Janssen, Karyopharm, Kite, Merck, Morphosys, Novartis, Roche, Servier, Takeda*; Honoraria: *Abbvie, Amgen, BMS, Celgene, Gilead, Epizyme, Janssen, Karyopharm, Kite, Merck, Morphosys, Novartis, Roche, Servier, Takeda.* **Martinez, J:** Honoraria: *Novartis, Celgene, BMS, Jansen*; Research Funding: *Novartis, Celgene, BMS, Jansen.* **Crump, M:** Consultant Advisory Role: *Roche Canada, Servier, Kyte/Gilead.* **Thomas, D:** Employment Leadership Position: *Roche*; Stock Ownership: *Roche.* **Morcos, P:** Employment Leadership Position: *Roche*; Stock Ownership: *Roche.* **Ferlini, C:** Employment Leadership Position: *Roche*; Stock Ownership: *Roche.* **Broeske, A:** Employment Leadership Position: *Roche.* **Bacac, M:** Employment Leadership Position: *Roche*; Stock Ownership: *Roche.* **Dimier, N:** Employment Leadership Position: *Roche*; Stock Ownership: *Roche.* **Umaña, P:** Employment Leadership Position: *Roche*; Stock Ownership: *Roche.* **Moore, T:** Employment Leadership Position: *Yes*; Stock Ownership: *Yes.* **Weisser, M:** Employment Leadership Position: *Roche*; Stock Ownership: *Yes.* **Hutchings, M:** Consultant Advisory Role: *Takeda, Roche, Celgene*; Honoraria: *Takeda, Roche, Celgene, Janssen*; Research Funding: *Takeda, Roche, Novartis, Celgene.*

054

ANALYSIS OF EFFICACY AND SAFETY OF LONCASTUXIMAB TESIRINE (ADCT-402) BY DEMOGRAPHIC AND CLINICAL CHARACTERISTICS IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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TABLE 1 Overall response to loncastuximab tesirine by selected demographic and clinical characteristics in patients with R/R DLBCL

Factor	Group	Dose (≥120 µg/kg) % (responders/total)
Age, y	<65	33.3 (23/69)
	65–74	52.8 (19/36)
	≥75	59.1 (13/22)
Sex	Male	42.1 (32/76)
	Female	45.1 (23/51)
Country	Italy	40.9 (9/22)
	UK	36.7 (11/30)
	US	46.7 (35/75)
Bulky disease	Absent	46.8 (51/109)
	Present	22.2 (4/18)
Double-/Triple-hit	Absent	47.6 (50/105)
	Present	22.7 (5/22)
Transformed	No	39.6 (38/96)
	Yes	54.8 (17/31)
ECOG performance status	0	48.4 (15/31)
	1	43.0 (34/79)
	2	26.7 (4/15)
	3*	100.0 (2/2)
Response to first line therapy	Relapsed	53.1 (43/81)
	Refractory	23.1 (6/26)
Response to most recent therapy	Relapsed	59.1 (26/44)
	Refractory	35.1 (26/74)
Number of prior therapies	≤3 lines	43.8 (35/80)
	>3 lines	42.6 (20/47)

*Patients with ECOG performance status 3 were not eligible for the study.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; R/R, relapsed/refractory; y, year.

Figure 1: Duration of response to loncastuximab tesirine (≥120 μg/kg) by response to (A) first-line therapy and (B) most recent therapy in patients with DLBCL
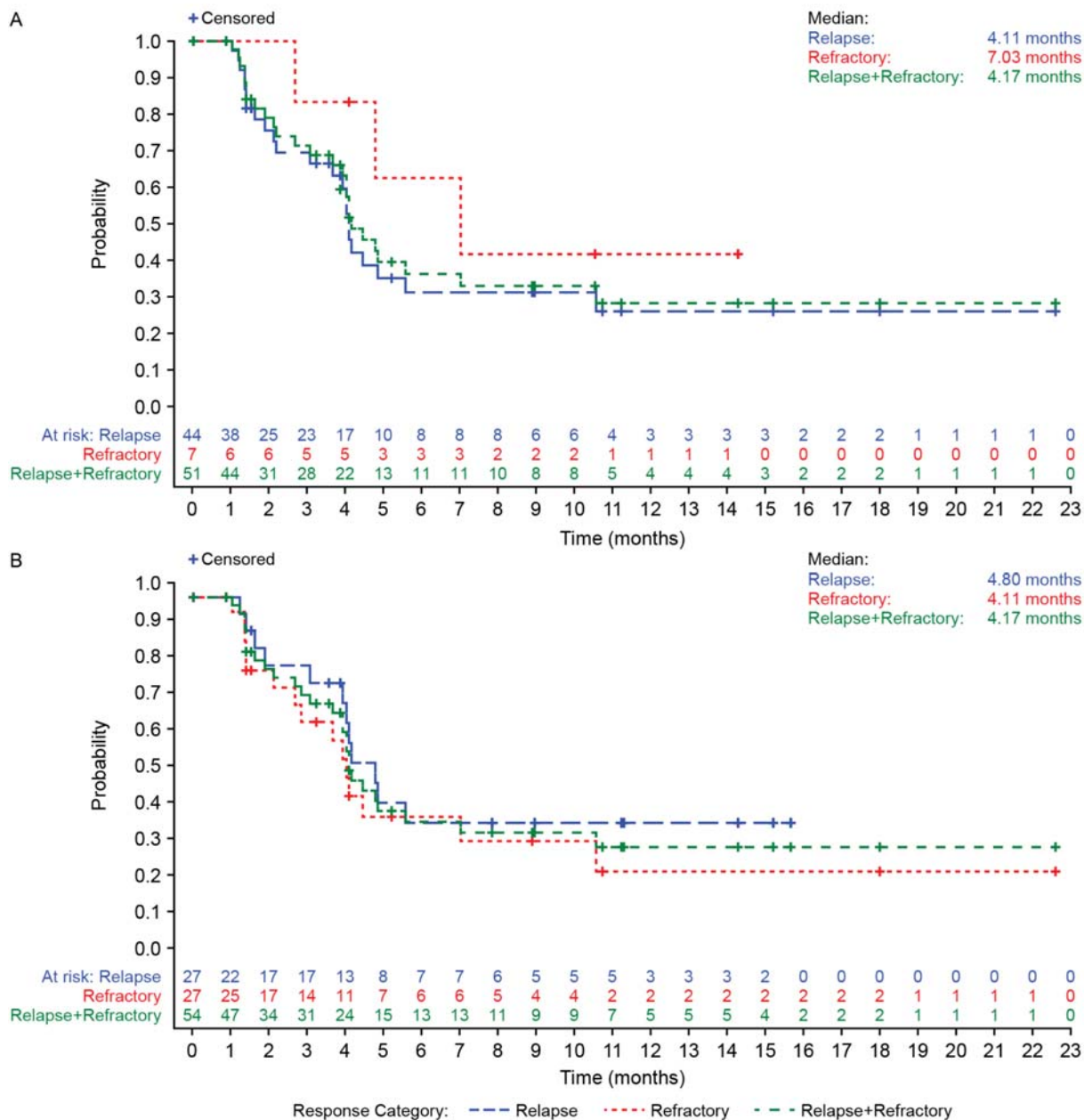
DLBCL, diffuse large B-cell lymphoma.

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Introduction: Diffuse large B-cell lymphoma (DLBCL) accounts for approximately one-third of non-Hodgkin lymphomas (NHL) and expresses CD19, a B-cell marker. Loncastuximab tesirine (Lonca)

comprises a humanized anti-CD19 antibody conjugated to a potent pyrrolobenzodiazepine dimer toxin. A first-in-human study of Lonca in patients (pts) with relapsed/refractory (R/R) B-cell NHL demonstrated encouraging and durable single-agent antitumor activity and manageable toxicity at doses ≥120 µg/kg in pts with R/R DLBCL. Here we present subgroup analyses of response in R/R DLBCL.

Methods: Pts ≥18 years of age with R/R B-cell NHL were enrolled in this phase 1 study (NCT02669017). Analyses of treatment-emergent adverse events (TEAE), overall response rate (ORR) by demographic and clinical characteristics, and duration of response (DoR) by response to prior therapy were performed in pts with DLBCL receiving ≥120 µg/kg Lonca.

Results: As of data cutoff (October 16, 2018), 129 pts with DLBCL had received Lonca at ≥120 µg/kg; 129 and 127 pts were evaluable for safety and efficacy, respectively.

The most common TEAEs, regardless of relationship to Lonca, were fatigue (42.6%), peripheral edema (34.1%), and nausea (34.1%). The most common grade ≥3 TEAEs were hematological abnormalities (neutrophil count decreased [38.0%]; platelet count decreased [27.1%]; anemia [11.6%]) and increased gamma-glutamyltransferase (20.2%). The TEAE profile was comparable between age groups.

ORR in pts with DLBCL was 43.3%. Subgroup analyses of ORR are presented in **Table 1**. Older pts had higher ORR than younger pts (≥75 years: 59.1%; 65–74 years: 52.8%; <65 years: 33.3%). Pts with transformed disease had higher ORR than those with de novo DLBCL (54.8% vs 39.6%).

Pts who responded to first-line therapy had higher ORR than primary refractory pts (53.1% vs 23.1%), as did pts who responded to their most recent therapy (59.1% vs 35.1% for refractory pts). Median DoR was longer for primary refractory pts than relapsed pts (7.03 vs 4.11 months; **Figure 1**), and comparable for pts refractory to the most recent therapy vs relapsed (4.11 vs 4.80 months). Further details will be presented at the meeting.

Conclusions: Lonca at ≥120 µg/kg has substantial antitumor activity in patients with R/R DLBCL. In subgroup analyses, older pts and those with transformed or primary refractory disease had particularly encouraging responses.

Study sponsor: ADC Therapeutics

Keywords: diffuse large B-cell lymphoma (DLBCL); immuno-conjugates; non-Hodgkin lymphoma (NHL).

055

ANALYSIS OF CLINICAL DETERMINANTS DRIVING SAFETY AND EFFICACY OF CAMIDANLUMAB TESIRINE (ADCT-301, CAMI) IN RELAPSED/REFRACTORY (R/R) CLASSICAL HODGKIN LYMPHOMA (CHL)

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Introduction: Cami is a humanized anti-CD25 antibody conjugated to a potent pyrrolobenzodiazepine dimer toxin with impressive activity in a phase 1 trial (NCT02432235) in heavily pretreated patients (pts) with cHL. Cami's immunological mode of action may have synergistic efficacy with checkpoint inhibitors (CHPi) and could underlie autoimmune toxicities observed in this trial, such as Guillain-Barré Syndrome (GBS)/radiculopathy. Here we report subgroup analyses to identify

TABLE 1 ORR by selected demographic and clinical characteristics in 45 µg/kg dose-expansion cohort

Characteristic	Subgroups	45 µg/kg cohort (N=37)	
		ORR n/N, % (95% CI)	CR n/N, %
Overall	-	32/37, 86.5 (71.2–95.5)	16/37, 43.2
Age, y	≤55	25/28, 89.3 (71.8–97.7)	12/28, 42.9
	>55	7/9, 77.8 (40.0–97.2)	4/9, 44.4
Sex	Female	12/14, 85.7 (57.2–98.2)	6/14, 42.9
	Male	20/23, 87.0 (66.4–97.2)	10/23, 43.5
Disease stage at study entry	I–II	12/14, 85.7 (57.2–98.2)	6/14, 42.9
	III	8/8, 100.0 (63.1–100.0)	5/8, 62.5
	IV	12/15, 80.0 (51.9–95.7)	5/15, 33.3
Number of prior therapies	<4	6/6, 100.0 (ND)	3/6, 50.0
	≥4	26/31, 83.9 (ND)	13/31, 41.9
Response to first-line systemic anticancer therapy	Refractory[a]	11/13, 84.6 (54.6–98.1)	5/13, 38.5
	Relapsed[b]	21/24, 87.5 (67.6–97.3)	11/24, 45.8
Response to most recent prior systemic anticancer therapy	Refractory[a]	22/25, 88.0 (68.8–97.5)	9/25, 36.0
	Relapsed[b]	8/10, 80.0 (44.4–97.5)	6/10, 60.0
Prior CHPi[c]	≤4 months	14/15, 93.3 (68.1–99.8)	6/15, 40.0
	>4 months	6/8, 75.0 (34.9–96.8)	3/8, 37.5
	None	9/11, 81.8 (48.2–97.7)	6/11, 54.5
	Timing unknown[d]	3/3, 100.0 (29.2–100.0)	1/3, 33.3

[a]Stable or progressive disease to first-line/most recent therapy.
[b]Partial response or CR to first-line/mos recent therapy.
[c]Time between last CHPi and first Cami dose.
[d]Patients who received CHPi but timing information was missing.
Abbreviations: CHPi, checkpoint inhibitor; CI, confidence interval; CR, complete response; ND, not determined; ORR, overall response rate; y, year.

Figure 1: Probability of objective response vs C_{max} in patients with cHL receiving Cami
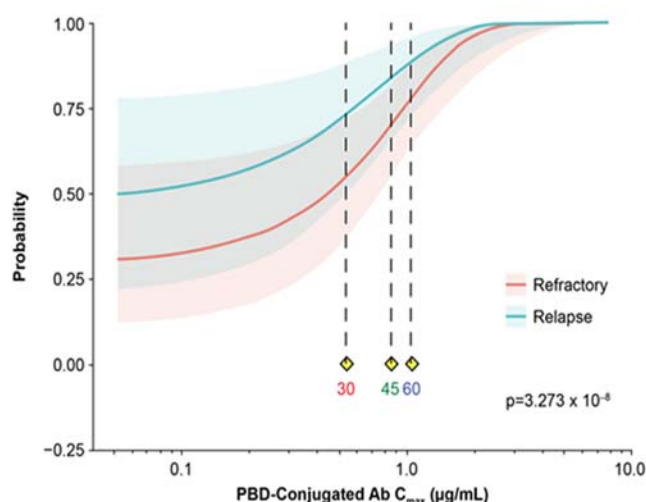
Graphics depict mean and 95% confidence intervals of predicted probabilities. Colored numbers denote the dose (µg/kg) groups administered; yellow diamonds and vertical dotted lines denote the median respective exposures. P-value is overall significance of model with predictors compared to intercept alone.
Ab, antibody; cHL, classical Hodgkin lymphoma; C_{max}, concentration maximum; PBD, pyrrolobenzodiazepine.

clinical determinants of antitumor activity, safety, and pharmacokinetic (PK) exposure-response relationships.

Methods: R/R cHL pts aged ≥18 years were treated with 5–300 µg/kg Cami every 3 weeks, including dose expansion at 30 and 45 µg/kg. Analyses of response and treatment-emergent adverse events (TEAE) were performed using descriptive statistics. Peak (C_{max}) and average (C_{avg}) concentrations of conjugated antibody in serum were determined using a population PK model and associated with objective response using logistic regression.

Results: Overall response rate (ORR) was 73.1% in the study population and 86.5% at 45 µg/kg (n=37; 43.2% complete response). **Table 1** presents subgroup analyses of response at 45 µg/kg. Of note, 3 pts improved from partial to complete response after permanent treatment discontinuation.

In PK modeling, a significant association of C_{max} to objective response was observed for the typical pt (p=3.273 x 10^{-8}; **Figure 1**); mean predicted probability of Cami response was 0.84 for pts who responded to their most recent therapy vs 0.70 for refractory pts.

Autoimmune and neurologic TEAE profiles were comparable between pts with differing prior CHPi exposure. The 5 reported cases of GBS/radiculopathy did not appear related to prior CHPi (≤4 mo: 1 pt [4%]; >4 mo: 1 pt [7%]; none: 2 pts [10%]; 1 pt [20%] who received CHPi but timing information was missing).

Updated results will be presented, including response data for the ongoing 30 µg/kg cohort.

Conclusions: A difference in Cami response was seen between relapsed vs refractory pts in PK modeling, but response rates were

high across all subgroups, suggesting robust antitumor activity across the R/R cHL population. There was a trend for increased ORR in pts with recent prior CHPi exposure, <4 prior therapies, and Stage III cHL. Increased ORR in pts with recent prior CHPi could suggest a possible immunological interaction between Cami and prior CHPi, but it did not appear to increase autoimmune and neurologic TEAEs.

Study sponsor: ADC Therapeutics

Keywords: Hodgkin lymphoma (HL); immunochemotherapy; immunoconjugates.

SESSION 5 – T-CELL LYMPHOMAS

056
RISK OF BREAST IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL) IN A COHORT OF 3546 WOMEN PROSPECTIVELY FOLLOWED AFTER RECEIVING TEXTURED BREAST IMPLANTS

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Background: Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is a rare subtype of T-cell lymphoma, developing in in the fluid or capsule surrounding breast implants, primarily or exclusively in those with textured surfaces. Several prior series have estimated the risk of BIA- ALCL at 1/6920 -1/3800 women in retrospectively defined cohorts (from diagnosed cases within national or pathology databases), approximating the population at risk from sales records or other estimates (Sirinvasa 2017; Loch-Wilkinson 2017; de Boer 2018).

Methods: A prospective cohort study was conducted in the population that underwent breast reconstruction by a single surgeon at Memorial Sloan Kettering Cancer Center (MSKCC) from April 1993 to December 2017. Patients had long-term follow-up, and events related to implants were prospectively recorded. We identified all cases of BIA-ALCL by cross-checking data from internal clinical records, pathology records, and outside reports. Incidence rate per person-years and cumulative incidence when accounting for competing risk were calculated. 134 women who received smooth-surface implants were excluded from the analysis, since these implants have not been associated with BIA-ALCL.

Subdistribution of developing BIA-ALCL
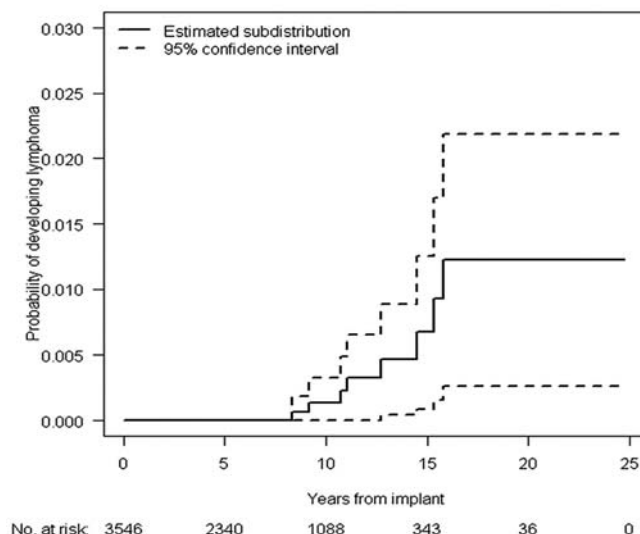
Years since implant	Cumulative risk of developing BIA-ALCL
5	0.0
10	$1.4*10^{-3}$
15	$6.7*10^{-3}$
20	$1.2*10^{-2}$

TABLE 1

	Reason for reconstruction	Years of exposure	Presentation of BIA-ALCL
Case 1	R – DCIS L – prophylactic mastectomy	11.1	Peri-prosthetic fluid collection
Case 2	R - DCIS L - stage I Ca	12.7	Peri-prosthetic fluid collection
Case 3	R - invasive tubular Ca L - invasive lobular Ca	8.3	Peri-prosthetic fluid collection
Case 4	R – ductal hyperplasia L – invasive ductal Ca	14.4	Peri-prosthetic fluid collection
Case 5	R – prophylactic mastectomy L – DCIS	15.7	Breast mass + LN
Case 6	R - invasive ductal Ca L - prophylactic mastectomy	10.5	Internal mammarian lymphadenopathy
Case 7	R – infiltrating lobular ca L – prophylactic mastectomy	9.2	Peri-prosthetic fluid collection in the context of breast Ca relapse
Case 8	R – DCIS L – prophylactic mastectomy	11.3	Peri-prosthetic fluid collection

Results: From 1993 to 2017, 3546 patients underwent 6023 breast reconstructions using textured surface implants. All reconstructions were performed by a single surgeon (PGC) on patients enrolled in this study. To identify BIA-ALCL occurrence, clinical and pathological data were assessed from a prospective database. Median follow-up was 7 years (range, 3 days - 24.7 years). Eight women developed ALCL after a median exposure of 11.2 years (range, 8.3-15.8 years). Overall risk of BIA-ALCL in this cohort was 0.294 cases per 1000 person-years (1/443 women).

Conclusions: This study, evaluating the risk of women with textured breast implants from a prospective database with long-term follow-up, demonstrated that the incidence rate of BIA-ALCL may be higher than previously reported. These results can help inform implant choice for women undergoing breast reconstruction.

Keywords: anaplastic large cell lymphoma (ALCL); extranodal lymphomas; T-cell lymphoma (TCL).

057
AUTOLOGOUS STEM CELL TRANSPLANTATION AS PART OF FIRST-LINE THERAPY IN PATIENTS WITH

PERIPHERAL T-CELL LYMPHOMA: A MULTICENTER GELTAMO/FIL STUDY

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Introduction: The role of autologous stem cell transplantation (ASCT) after first-line chemotherapy in patients with peripheral T-cell lymphomas (PTCL) is controversial. The main objective of our study is to analyse the progression-free survival (PFS) and overall survival (OS) of patients with PTCL who underwent ASCT in complete remission (CR) after first-line chemotherapy, compared to a control group with similar characteristics who did not undergo ASCT as part of first-line.

Methods: This is a retrospective study performed in 44 hospitals from GELTAMO and FIL groups. Inclusion criteria were: i) Histological diagnosis of PTCL between 2001 and 2010; ii) patients deemed fit for

TABLE 1 Patient characteristics

Characteristics	Cases (transplanted patients) N (%)	Controls (non-transplanted patients) N (%)
Age, median (range)	50 (18-70)	50 (19-67)
Sex, male	64 (59%)	62 (60%)
ECOG performance status <2	24 (22%)	15 (15%)
B Symptoms	55 (51%)	41 (42%)
Ann Arbor Stage III-IV*	88 (84%)	56 (55%)
IPI ≥ 3*	54 (55%)	29 (30%)
PIT≥ 3*	40 (39%)	23 (24%)
Histology*		
Angioimmunoblastic T-cell lymphoma	32 (29%)	16 (15%)
Peripheral T-cell lymphoma, NOS	40 (37%)	30 (29%)
Peripheral T-cell lymphoma, lymphoepiteliod variant	2 (2%)	-
ALCL, T/null cell, ALK+, primary systemic type	4 (4%)	27 (26%)
ALCL, T/null cell, ALK-, primary systemic type	19 (17%)	21 (20%)
Enteropathy type T-cell lymphoma	5 (5%)	4 (4%)
Hepatoesplenic T-cell lymphoma	4 (4%)	1 (1%)
NK/T-cell lymphoma, nasal type (not localized)	4 (4%)	2 (2%)
Primary cutaneous gamma-delta	1 (1%)	-
First-line treatment		
CHOP/CHOP-like	83 (76%)	89 (86%)
CHOEP/CHOEP-like	25 (23%)	12 (12%)
Others	1 (1%)	2 (2%)

*p < 0.05

Abbreviations: ALCL, anaplastic large-cell lymphoma; ECOG, Eastern cooperative Oncology Group; IPI, International Prognostic Index; PIT, Prognostic Index for Peripheral T cell Lymphoma.

Figure 1. Overall survival of transplanted patients (continuous line) and non-transplanted patients (dashed line) after excluding ALCL ALK+ cases

ASCT were: medical decision (N=84), poor performance status (N=10), patient decision (N=7) and other reasons (N=2). The baseline clinicopathologic characteristics of the patients are listed in table 1. The histologic subtypes were different between groups: angioimmunoblastic T-cell lymphoma and PTCL-NOS were more frequent in the transplant group, whereas anaplastic large cell lymphoma (ALCL), ALK+ was more frequent in the control group. More patients in the transplant group had adverse prognostic factors (table 1). First-line treatment was similar in both groups. With a median follow up of 73.9 months, no significant differences in survival were observed between cases and controls in the overall series. However, after excluding ALCL ALK+ cases, the PFS (65% vs 44% at 5 years, p=0,012) and OS (74% versus 65% at 5 years, p=0,046, figure 1) were significantly better in the patients who underwent ASCT. The PFS advantage in favour of ASCT was independent of IPI or type of first-line chemotherapy in the Cox multivariate analysis (HR 1.62, 95% CI 1.03-2.54, p=0.35).

Conclusion: Our results indicate that ASCT in 1st CR improves the survival of patients with PTCL other than ALK+ anaplastic large-cell lymphoma. These results should be confirmed in a prospective randomized study. A propensity score matching analysis is planned.

Keywords: autologous stem cell transplantation (ASCT); peripheral T-cell lymphomas (PTCL).

ASCT at the time of diagnosis; and iii) partial remission (PR) or CR after anthracycline-based first-line treatment. A landmark analysis was performed, with time zero defined as the time at which the assessment after the first-line was carried out.

Results: 286 patients were registered. For this analysis, we have only considered 212 patients who were in CR or uncertain CR after first-line chemotherapy. A total of 109 patients underwent ASCT (cases) and 103 did not (controls). The causes for not receiving

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FIRST-LINE THERAPY OF T-CELL LYMPHOMA: ALLOGENEIC OR AUTOLOGOUS TRANSPLANTATION FOR CONSOLIDATION - FINAL RESULTS OF THE AATT STUDY

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Background: In patients (pts) with peripheral T-cell lymphoma (PTCL) results of first-line therapy remain poor; guidelines recommend consolidation with autologous transplantation (autoSCT) in transplant-eligible pts. AATT (**A**utologous or **A**llogeneic**T**ransplantation in **T**-cell lymphoma) sought to improve first-line therapy and compared alloSCT with autoSCT.

Methods: This was a prospective randomized trial comparing autoSCT with alloSCT in younger pts (18-60 yrs) with newly diagnosed PTCL who had achieved CR, PR, or SD after 4 courses of CHOEP and 1 course of DHAP. Pts were to receive BEAM followed by autoSCT or myeloablative conditioning (fludarabine, busulfan, cyclophosphamide) followed by alloSCT from a matched related or unrelated donor. Primary endpoint was 3-year event-free survival (EFS). The study was stopped prematurely after a pre-planned interim analysis (JCO 33, 2015, suppl 8507a)

Results: 103 pts randomized upfront to autoSCT (n = 54) or alloSCT (n = 49) formed the full analysis set. Median age was 50 years, 63% were male. 36 pts (35%) could not proceed to transplantation mostly due to early progression. Median observation time for EFS was 42 months. 3-year EFS and overall survival (OS) did not significantly differ between alloSCT and autoSCT (EFS: 43% (95% CI29-57%) vs. 38% (25-52%), p = 0.58, OS: 57% (43-71%) vs. 70% (57-82%)(p = 0.41). Comparing pts who actually received autoSCT (n = 41) or alloSCT (n = 26) EFS, PFS, and OS also showed no significant difference. No patient relapsed but eight pts (31%) died of treatment-related mortality (TRM) after alloSCT compared to 13 relapses (36%) but no TRM observed after autoSCT. Comparison of pts with aaIPI 2/3 vs. 0/1 showed significant differences for all endpoints.

Conclusions: AlloSCT or autoSCT given to consolidate response in pts with PTCL showed no significant survival differences. While exerting a strong GvL-effect alloSCT resulted in substantial TRM. For younger pts with PTCL autoSCT remains the preferred consolidation, in particular, because pts relapsing after autoSCT can be successfully salvaged with alloSCT.

Keywords: allogeneic stem cell transplant (alloSCT); autologous stem cell transplantation (ASCT); T-cell lymphoma (TCL).

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TREATMENT BENEFIT ASSOCIATING WITH NON-ANTHRACYCLINE CHEMOTHERAPY IN EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

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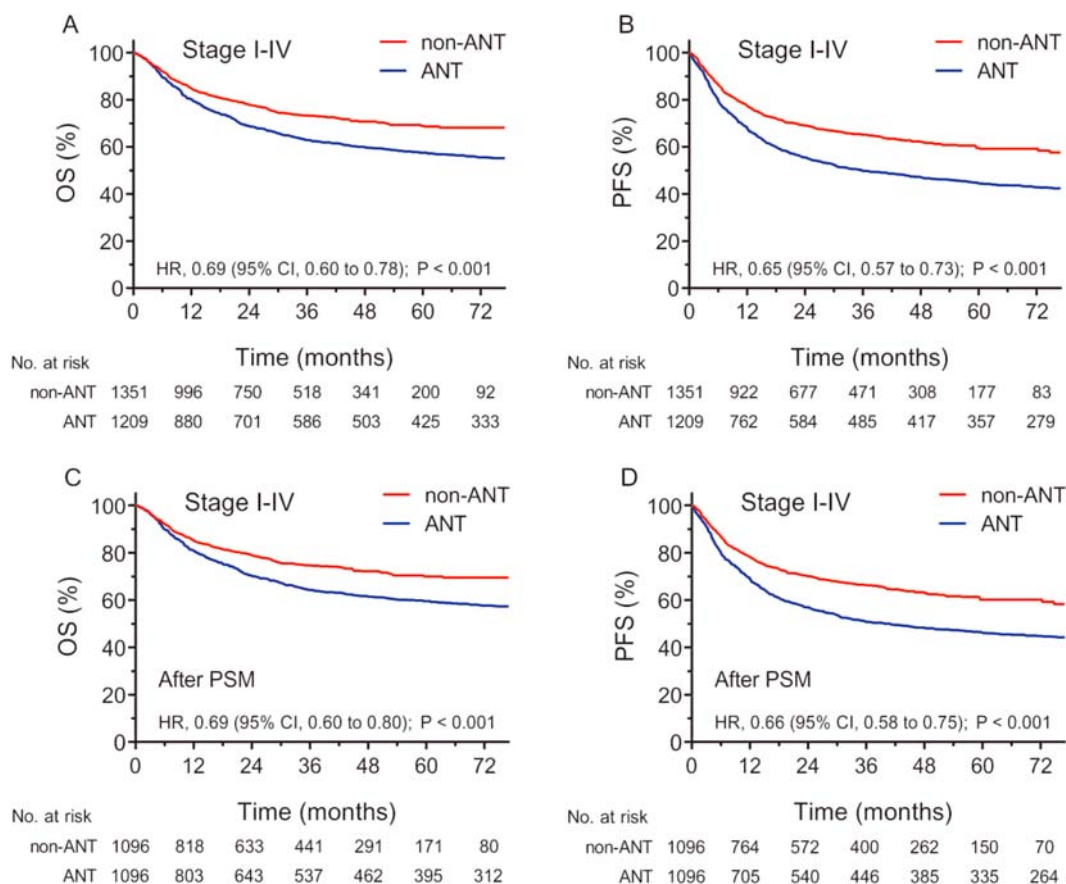
Non-ANT chemotherapy associated with prolonged OS(HR, 0.69; 95%CI 0.60-0.78; *P*<.001; Fig. A) and PFS (HR, 0.65; 95%CI 0.57-0.73; P<.001 Fig. B) comparing to ANT chemotherapy. After PSM, the OS (HR, 0.69; 95% CI, 0.60-0.80; *P*<.001, Fig. C) and PFS advantage (HR, 0.66; 95% CI, 0.58 -0.75; *P*<.001, Fig. D) still remained statistically significant.

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Introduction: The recommended non-anthracycline (non-ANT) chemotherapy on treating Extranodal NK/T-cell lymphoma, nasal type (ENKL) is based on evidences of single-arm phase I/II studies and retrospective series with limited cases and short-term follow-ups. The current study was to investigate treatment benefit of non-ANT chemotherapy in comparison to anthracycline (ANT) chemotherapy in a large-scaled cohort.

Methods: Patients consecutively diagnosed with ENKL and treated with chemotherapy with/without radiotherapy between 2000 and 2015 from 20 Chinese institutes were retrospectively analyzed. Association of short-term response and long-term survival with chemotherapy categories were evaluated.

Results: 2560 cases were enrolled, 87% had stage I-II disease, and median age was 43. The proportion of non-ANT chemotherapy increased notably through 2005 to 2012. Demographic and disease characteristics showed great similarities across chemotherapy subgroups. Non-ANT chemotherapy associated with increased response comparing to ANT regimen (CR, 40 vs. 28%; PR, 43 vs.37 %, P<0.05). With a median follow-up of 4 years, overall survival (OS) and progression free survival (PFS) were significantly better favoring non-ANT chemotherapy in the entire cohort (5-year OS, 68.9% vs 57.5%, P < 0.001; 5-year PFS, 59.5% vs 44.5%, P < 0.001), localized disease (5-year OS, 73.3% vs 60.9%, P < 0.001; 5-year PFS, 64.0% vs 47.6%, P < 0.001), advanced disease (OS, 39.8% vs 29.9%, P = 0.013; PFS, 30.1% vs 18.8%, P = 0.003), and each risk subgroups, respectively. The survival benefit remained consistent after adjustments with multivariate analysis and propensity score matching analysis. Gemcitabine + L-Asparaginase combination showed promising treatment outcomes, especially for advanced disease.

Conclusions: Non-ANT chemotherapy constituted the mainstay of chemotherapy in ENKL treatment. The application of non-ANT chemotherapy associated improved response and survival comparing to ANT chemotherapy.

Keywords: anthracycline; L-asparaginase; T-cell lymphoma (TCL).

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SINTILIMAB FOR RELAPSED/REFRACTORY (R/R) EXTRANODAL NK/T CELL

LYMPHOMA (ENKTL): A MULTICENTER, SINGLE-ARM, PHASE 2 TRIAL (ORIENT-4)

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Introduction: ENKTL account for more than 20% of the peripheral T-cell lymphoma in Asia. Patients with r/r ENKTL have a poor prognosis after failing an L-asparaginase based regimen, and the median overall survival is less than 6 months. The overexpression of PD-L1 induced by EBV infection is a potential mechanism for ENKTL to avert immune surveillance, and recent studies of PD-1 antibodies in pts with r/r ENKTL have demonstrated potential efficacy. Sintilimab, a fully human anti-PD-1 monoclonal antibody, has a safety profile consistent with other approved PD-1 antibodies and was approved for r/r classical Hodgkin lymphoma in China in 2018. This multicenter, single-arm, phase 2 study aims to validate the efficacy and safety of sintilimab monotherapy in patients with r/r ENKTL in China.

Methods: Patients with pathologically confirmed relapsed or refractory ENKTL were enrolled. Sintilimab was given 200 mg IV Q3W, until PD, death, unacceptable toxicity, or withdrawal from the study. Treatment beyond PD is allowed. Tumor response evaluation was performed by both PET-CT and CT/MRI with contrast. The primary endpoint was objective response rate based on LUGANO 2014 criteria. Data cut-off date for this analysis was Feb 2, 2019.

Results: From Aug 31, 2017 to Feb 7, 2018, a total of 28 patients were enrolled: 60.7% (17/28) male and the median age was 37 (range: 19~65) yr. Sixty-eight percent (19/28) of patients were stage IV and 89.3% (25/28) were ECOG PS ≥ 1. All patients had failed an L-asparaginase based regimen, the median lines of previous therapy were 3 (range: 1~13), 78.6% (22/28) patients received prior radiotherapy and 7.1% (2/28) had failed HSCT. Median duration of therapy was 14.04 (range: 1.4~17.3) months and 19 patients are still receiving sintilimab. Sixty-eight percent (19/28, 95%CI: 47.6%~84.1%) of patients achieved response (CR+PR), including 4 pts who experienced PD prior to having a response. DCR was 85.7% (24/28), including 5 pts who experienced PD before SD or response. The 1-year OS rate was 82.1% and the median OS has not been reached. Most TRAEs were G1~2 (67.9%) and no patients discontinued treatment due to AEs. The most common TRAE was decreased lymphocyte count (46.4%, 13/28) and 84.6% were grade 1~2. SAEs occurred in 21.4%

of patients and none were related to sintilimab. No patients died from AEs.

Conclusions: ORIENT-4 is the first multicenter and prospective study validating efficacy of PD-1 antibody in ENKTL and with results. Sintilimab is effective and well tolerated in r/r ENKTL and could be a promising treatment option for these patients. Early disease progression observed by PET scan in this study could be pseudo-progression as it did not correlate with poor outcome, which warrants further investigation. Clinical trial information: NCT03228836

Keywords: monoclonal antibodies (MoAb); PD-1; peripheral T-cell lymphomas (PTCL).

Disclosures: Xu, L: Employment Leadership Position: *Innovent Biologics (Suzhou) Co. Ltd.* **Zhou, H:** Employment Leadership Position: *Innovent Biologics (Suzhou) Co. Ltd.*

FOCUS ON... SESSION: CLL AND MORE

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FIVE-YEAR FOLLOW-UP OF FIRST-LINE IBRUTINIB FOR TREATMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA//SMALL LYMPHOCYTIC LYMPHOMA

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Introduction: Ibrutinib (ibr) is a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase (BTK) approved in the EU and other regions to treat chronic lymphocytic leukemia (CLL). The phase 3 RESONATE-2 study compares the efficacy and safety of first-line ibr vs chlorambucil (chl) in older patients (pts) with CLL/small lymphocytic lymphoma (SLL). There is a critical clinical need for long-term efficacy and safety data for ibr, which is given as continuous therapy.

Methods: RESONATE-2 is a phase 3, randomized, open-label, international study (PCYC-1115/1116; NCT01722487, NCT01724346). Pts with previously untreated CLL/SLL without 17p deletion and ≥65 y old (N=269) were randomized 1:1 to continuous ibr 420 mg once daily or chl 0.5–0.8 mg/kg for up to 12 cycles. Efficacy was assessed by investigator per International Workshop on Chronic Lymphocytic Leukemia 2008 criteria with modification during long-term follow-up. Prevalence rates for adverse events (AE) are reported.

Results: Baseline characteristics were well balanced between ibr and chl arms. After a median follow-up of 60 mo (range 0.1–66 mo), superior progression-free survival (PFS) was sustained for ibr vs chl (hazard ratio [HR] 0.15 [95% CI 0.10–0.22]). PFS estimates at 5 y were 70% for ibr vs 12% for chl. Ibr improved PFS compared to chl in pts with unmutated immunoglobulin heavy chain variable region (*IGHV*; HR 0.11 [95% CI 0.06–0.19]), 11q deletion (HR 0.03 [95% CI 0.01–0.11]), and the high-risk genomics subgroup (unmutated *IGHV*, 11q deletion, and/or *TP53* mutation; HR 0.08 [95% CI 0.05–0.15]). Ibr also resulted in improved overall survival (OS) vs chl; 83% vs 68% at 5 y, even with 57% of pts crossing over from chl to ibr after progression. With ibr, overall response rate, including partial response with lymphocytosis, for ibr was 92%. The complete response (CR)/CR with incomplete marrow recovery (CRi) rate increased to 30% at 60 mo from 11% at primary analysis (18 mo). Common grade ≥3 AEs included neutropenia (13%), pneumonia (12%), hypertension (8%), anemia (7%), hyponatremia (6%), atrial fibrillation (5%), and cataract (5%), with rates of most events decreasing over time. Dose reductions due to grade ≥3 AEs decreased over time and discontinuation rates due to AEs remained stable over time. After ibr discontinuation, pts responded to subsequent CLL therapies, such as chemoimmunotherapy and alternate kinase inhibitors. Ibr maintains benefit in 58% of pts who remained on therapy.

Conclusions: Single-agent ibr sustained superior PFS and OS compared to chl, including for pts with high-risk genomic features, in the longest follow-up to date from a phase 3 study of first-line BTK-directed therapy. After up to 66 mo follow-up, responses to ibr improved over time with almost three-fold more pts achieving CR/CRi with long-term

Progression-free survival with single-agent ibrutinib versus chlorambucil in first-line CLL/SLL

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HIGH EFFICACY OF VENETOCLAX PLUS OBINUTUZUMAB IN PATIENTS WITH COMPLEX KARYOTYPE (CKT) AND CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A PROSPECTIVE ANALYSIS FROM THE CLL14 TRIAL

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Introduction: CKT (≥3 chromosomal aberrations) is associated with poor prognosis in CLL. In the CLL14 trial, treatment-naïve, elderly, unfit CLL patients (pts) received chlorambucil plus obinutuzumab (ClbG, n=216) or venetoclax plus obinutuzumab (VenG, n=216) for 12 cycles. After median follow-up of 29 months (mo), longer progression-free survival (PFS), and higher overall response rate (ORR) and rate of minimal residual disease (MRD) negativity were seen with VenG vs ClbG. Here, we present a prospective evaluation of CKT in CLL pts treated with a fixed-duration, chemotherapy-free regimen of VenG.
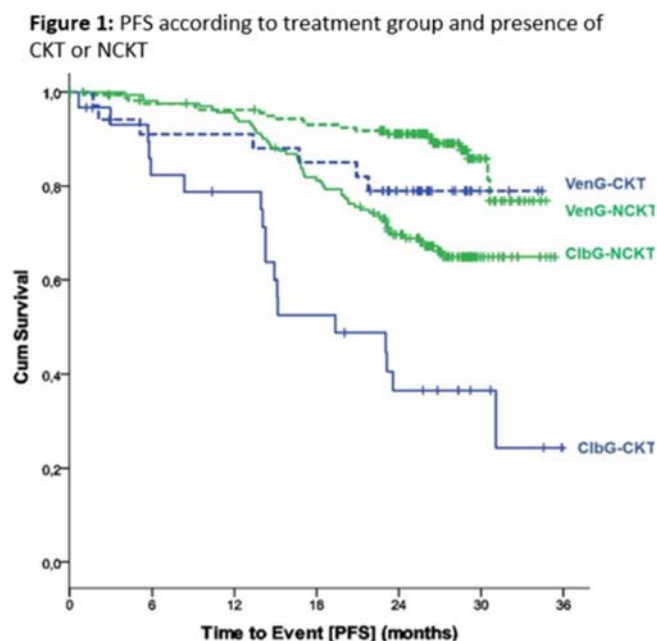
Methods: Metaphase spreads were produced after IL-2/CpG-stimulation and analyzed according to ISCN 2013. ORR, PFS, overall survival (OS) and MRD rates were evaluated according to presence of CKT alone and in combination with *TP53*aberrations. PFS and OS were estimated using the Kaplan–Meier method. Survival times were compared using non-stratified log-rank tests. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression modelling.

Results: Chromosome analysis was performed successfully in 397/432 (92%) randomized pts. CKT and non-CKT (NCKT) were found in 34 (17%) and 166 (83%) VenG pts, respectively, and 30 (15%) and 167 (85%) ClbG pts, respectively. Del(17p)/*TP53*mut was detected in 11/34 (32%) VenG CKT pts and in 9/29 (31%) ClbG CKT pts. Most pts with CKT were graded as high or very high risk according to the CLL-International Prognostic Index (CLL-IPI; 79% and 82%, respectively). In the VenG arm, ORR was 82% in CKT and 87% in NCKT pts; MRD negativity rate 3 mo after treatment completion in peripheral blood (PB) was 79% vs 77%, respectively, and in bone marrow (BM) 59% and 58%, respectively. No difference in PFS **(Figure 1)** or OS was seen between CKT and NCKT pts (median not reached [NR]; HR 1.909 [95% CI 0.806–4.520] and HR 1.511 [95% CI 0.496–4.600], respectively).

For ClbG, ORR was 50% in CKT and 78% in NCKT pts; MRD negativity rate was lower in CKT vs NCKT pts, in PB (20% vs 40%, respectively) and BM (0% vs 22%, respectively). Median PFS was 19 mo in ClbG CKT pts and NR in NCKT pts (HR 2.790 [95% CI 1.631–4.772], p<0.001). OS was significantly shorter in CKT vs NCKT pts (median NR; HR 3.736 [95% CI 1.357–10.287], p=0.006).

In CKT pts, presence of del(17p)/*TP53*mut did not significantly alter PFS compared with pts without del(17p)/*TP53*mut in the VenG (HR 1.419 [95% CI 0.317–6.353]) or ClbG groups (HR 2.103 [95% CI 0.795–5.567]).

Conclusion: CKT, which can be observed frequently in older, treatment-naïve CLL pts, correlates with CLL-IPI high/very high risk, although 2/3 of these pts do not show *TP53* aberrations. CKT is associated with shorter PFS and OS in pts treated with ClbG, including pts without *TP53* aberrations. VenG can overcome this adverse risk. These data support the importance of chromosome analysis before frontline therapy, and the value of VenG in CLL CKT pts.

Figure 1: PFS according to treatment group and presence of CKT or NCKT

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IMPACT OF MAJOR GENOMIC ALTERATIONS ON OUTCOME OF RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS RECEIVING VENETOCLAX PLUS RITUXIMAB IN THE PHASE 3 MURANO STUDY

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Introduction: We reported superior efficacy for venetoclax + rituximab (VenR) vs bendamustine + rituximab (BR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) in the MURANO study (NCT02005471), with significant progression-free survival (PFS) benefit and sustained undetectable minimal residual disease (uMRD), irrespective of historical risk factors for poor response. This analysis explores the clinical impact on outcome of major somatic mutations and cytogenetic high-risk features in patients (pts) treated with VenR and BR in MURANO.

Methods: Whole exome sequencing (WES) and analysis of genomic complexity (aGC; defined as having ≥3 or ≥5 genetic aberrations) by high-density array-comparative genomic hybridization were performed on baseline DNA specimens, available from 313/389 enrolled pts. Kaplan–Meier estimates and Cox proportional-hazards models were used to analyze PFS. uMRD was defined as <1 CLL cell in 10,000 leukocytes in peripheral blood (PB).

Results: At least one of the 9 mutated driver genes examined was identified in 234/313 (74.8%) pts from both arms; clonal mutations of *ATM* occurred in 30.7% of pts, *TP53* in 24.9%, *SF3B1* in 22.0%, *NOTCH1* in 13.7%, *BRAF* in 8.3%, *BIRC3* in 8.0%, and *NRAS/KRAS/MYD88* in 1.6% each. After 36.0 months' median follow-up, a PFS benefit was observed consistently with VenR over BR across mutated (mut) and wildtype (WT) subgroups for *ATM*, *TP53*, *SF3B1*, *NOTCH1* (**Figure 1**) and *BIRC3*. Median PFS for VenR was not reached in *TP53*mut or WT pts, compared with medians of 12.2 months (mo; hazard ratio [HR] 0.11, 95% confidence interval [CI] 0.055–0.24) and 21.6 mo (HR 0.16, 95% CI 0.098–0.25), respectively, for BR. Within treatment arms, inferior PFS was observed with both VenR and BR for *TP53*mut pts, but only with VenR for *NOTCH1*mut pts (interaction p=0.007). Two-year PFS with VenR was 76% for *NOTCH1*mut pts vs 89% for WT. Negative impact on PFS in *NOTCH1*mut VenR pts was confirmed by multivariate analysis (MVA) with IGHV, del(17p)/*TP53*, B2M, stage, and age as covariates (HR 0.54, 95% CI 0.22–1.30). Higher rates of disease progression were seen in *NOTCH1*mut (47.1%) vs WT (13.9%) pts treated with VenR, but not BR (69.2% vs 70.8%, respectively).

The PB uMRD rate was lower in *NOTCH1*mut pts (23.5% vs 49.3% in WT pts) at the end of Ven treatment visit. Prevalence of all CLL key mutated genes will be presented. Assessments of aGC are ongoing and impact on clinical outcomes will also be shown.

Conclusions: We assessed the mutational landscape of R/R CLL by WES and confirmed prior mutation frequency reports. Superior PFS benefit was observed for VenR vs BR in all clinical and molecular subgroups assessed, including the key CLL driver mutations reported here. *NOTCH1* mutations may define a new high-risk pt subgroup for VenR. To address the biological basis of the findings, MVA, further validation in larger cohorts and deep sequencing for subclones are needed.

Acknowledgment: Venetoclax is being developed in collaboration between Genentech and AbbVie. Genentech and AbbVie provided

Figure 1: Kaplan-Meier plots of investigator-assessed PFS according to *NOTCH1, SF3B1, ATM,* and *TP53* MUT vs WT subgroups
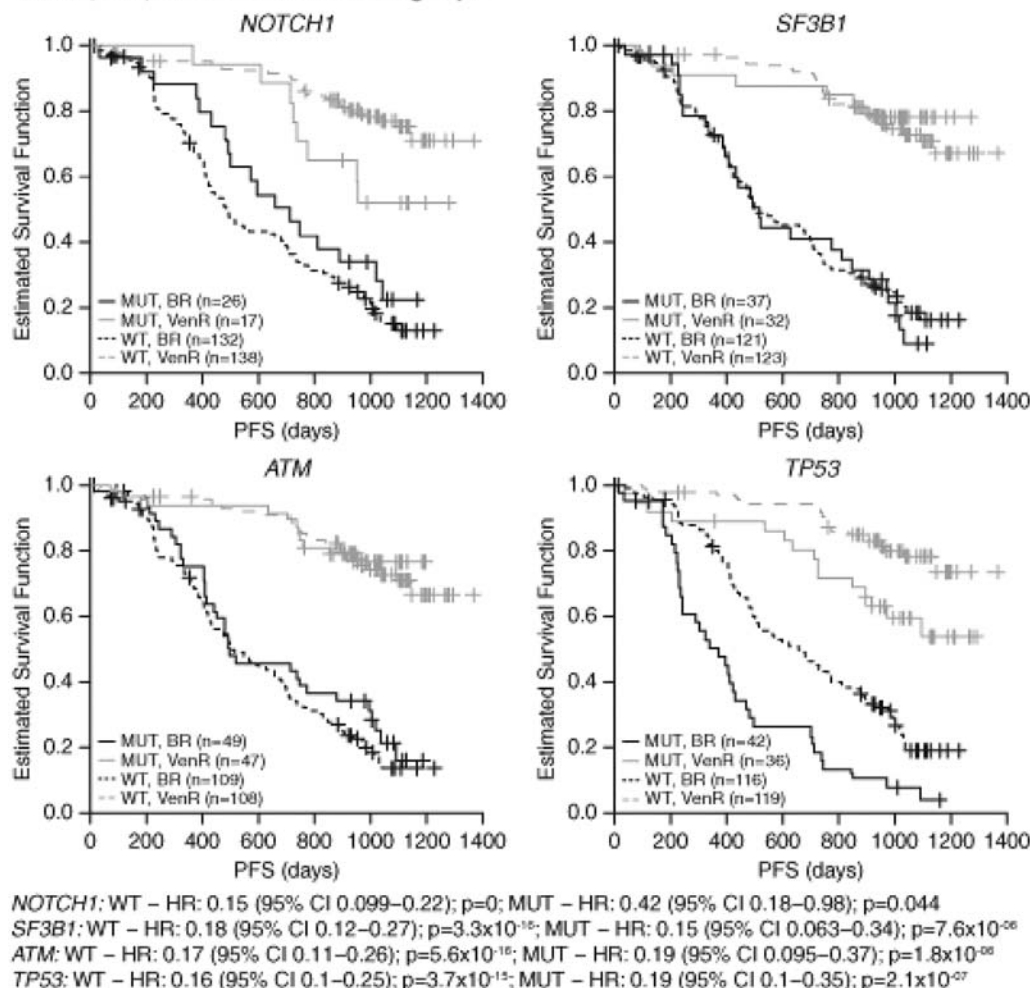
NOTCH1

| MUT, BR (n=26)
| MUT, VenR (n=17)
| WT, BR (n=132)
| WT, VenR (n=138)

SF3B1

| MUT, BR (n=37)
| MUT, VenR (n=32)
| WT, BR (n=121)
| WT, VenR (n=123)

ATM

| MUT, BR (n=49)
| MUT, VenR (n=47)
| WT, BR (n=109)
| WT, VenR (n=108)

TP53

| MUT, BR (n=42)
| MUT, VenR (n=36)
| WT, BR (n=116)
| WT, VenR (n=119)

NOTCH1: WT – HR: 0.15 (95% CI 0.099–0.22); p=0; MUT – HR: 0.42 (95% CI 0.18–0.98); p=0.044
SF3B1: WT – HR: 0.18 (95% CI 0.12–0.27); p=3.3×10⁻¹⁵; MUT – HR: 0.15 (95% CI 0.063–0.34); p=7.6×10⁻⁶
ATM: WT – HR: 0.17 (95% CI 0.11–0.26); p=5.6×10⁻¹⁶; MUT – HR: 0.19 (95% CI 0.095–0.37); p=1.8×10⁻⁶
TP53: WT – HR: 0.16 (95% CI 0.1–0.25); p=3.7×10⁻¹⁵; MUT – HR: 0.19 (95% CI 0.1–0.35); p=2.1×10⁻⁷

Disclosures: Wu, J: Employment Leadership Position: *Genentech/Roche*; Stock Ownership: *Genentech/Roche*; Other Remuneration: *Expenses: Genentech/Roche*. **Bolen, C:** Employment Leadership Position: *Genentech/Roche*; Stock Ownership: *Genentech/Roche*. **Seymour, J:** Consultant Advisory Role: *Abbvie, Acerta, Celgene, Janssen, Roche, Takeda*; Honoraria: *AbbVie, Roche*; Research Funding: *AbbVie, Celgene, Janssen, Roche*; Other Remuneration: *Expert Testimony: Roche; Expenses: Abbvie; Review activities: Celgene*. **Hillmen, P:** Consultant Advisory Role: *Abbvie, Janssen*; Honoraria: *Abbvie, Janssen, Roche*; Research Funding: *Abbvie, Janssen, Roche (all Institution only)*; Other Remuneration: *Travel, Accommodations, expenses: Janssen, Abbvie*. **Eichhorst, B:** Consultant Advisory Role: *AbbVie, Roche*; Honoraria: *AbbVie, Roche*; Research Funding:

AbbVie, Roche; Other Remuneration: *Travel, accommodations, expenses: AbbVie, Roche; Speakers' bureau: AbbVie, Roche*. **Eldering, E:** Research Funding: *Celgene, Roche, Gilead*. **Kipps, T:** Employment Leadership Position: *UC, San Diego Health, Moores Cancer Center*; Consultant Advisory Role: *AbbVie, Genentech/Roche, Gilead, Pharmacyclics, Celgene*; Honoraria: *Gilead, AbbVie, Pharmacyclics, Janssen, Verastem*; Research Funding: *AbbVie, Genentech/Roche, Pharmacyclics, Oncternal*; Other Remuneration: *Speakers' bureau/Advisory committee: AbbVie, Pharmacyclics, Janssen, Verastem*. **Langerak, A:** Consultant Advisory Role: *AbbVie*; Research Funding: *Roche-Genentech, Gilead*. **Mellink, C:** Research Funding: *The cytogenetics laboratory (AMC) receives research funding from Roche to perform the microarray analysis*. **van der Kevie-Kersemaekers, A:** Research Funding: *The cytogenetics laboratory (AMC) receives research funding from Roche to perform the microarray analysis*. **Owen, C:** Honoraria: *AbbVie, Roche, AstraZeneca, Janssen, Gilead, Teva*. **Chyla, B:** Employment Leadership Position: *AbbVie*; Stock Ownership: *AbbVie*. **Punnoose, E:** Employment Leadership Position: *Genentech, Member of the Roche Group*; Stock Ownership: *Genentech, Member of the Roche Group*; Other Remuneration: *Patents, Royalties, other intellectual property: Genentech,*

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AN UNDETECTABLE PB MRD STATUS SHOULD BE THE THERAPEUTIC GOAL WITH VENETOCLAX THERAPY IN RELAPSED/ REFRACTORY CLL

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Introduction: BCL2 inhibitor venetoclax (Ven) is highly active in relapsed/refractory CLL. Attainment of undetectable minimal residual disease (uMRD; $<10^{-4}$), especially in bone marrow (BM), strongly predicted progression free survival when analyzed after short term follow up (Seymour 2017). We aimed to determine:

1. Correlation between peripheral blood (PB) and BM MRD assessment
2. Association between uMRD in PB and BM with MRD recrudescence and time to progression (TTP)
3. Time to uMRD attainment
4. Factors associated with uMRD attainment

Methods: 62 CLL patients treated with continuous Ven were serially monitored for MRD in PB and BM, using flow cytometry by ERIC methodology. Patients who came off Ven, including some in deep remission, were censored at time of cessation. Baseline factors assessed included variables in *Table 1*. Kaplan Meier and univariate analyses were done with significance set at $P<0.05$.

Results: Of 17 patients with PB uMRD and paired BM samples, 14 (82%) had confirmed uMRD in BM (*Fig 1a*).

1. Patients who achieved PB uMRD had prognosis at least as favorable as patients who achieved BM uMRD with respect to time to
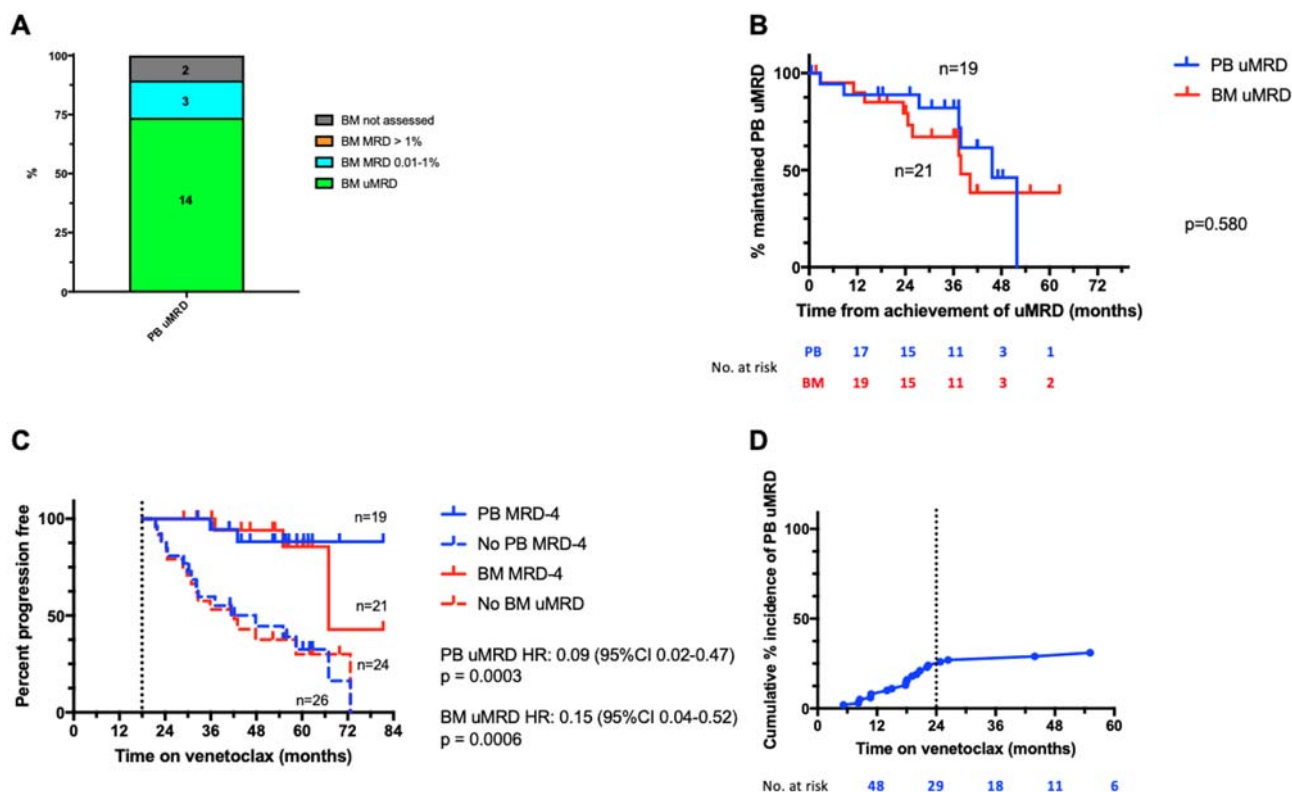
Figure 1: A) MRD in paired BM in patients who achieved PB uMRD. B) Time to uMRD recrudescence in PB stratified by time from uMRD achievement in PB v BM. C) Time to iwCLL progression stratified by achievement of uMRD in PB v BM. Patients who progressed / came off Ven before median time to uMRD achievement (18 months for PB and BM uMRD) were excluded in landmark analysis. D) Cumulative incidence of PB uMRD v Time on Ven.

TABLE 1 Baseline characteristics & association with uMRD in PB

Variable		N=	PB uMRD N= (%)	Fisher's Exact P value
Age ≥ 65	Y	38	11 (29%)	0.781
	N	24	8 (33%)	
≥ Prior Lines of Therapy	Y	25	6 (24%)	0.410
	N	37	13 (35%)	
Fludarabine Refractory	Y	30	7 (23%)	0.277
	N	32	12 (38%)	
Bulky Disease	Y	28	9 (32%)	1.000
	N	34	10 (29%)	
Rituximab Combination Therapy	Y	14	6 (43%)	0.327
	N	48	13 (27%)	
Dose ≥400mg	Y	46	17 (37%)	0.114
	N	16	2 (13%)	
Del(17p) and / or *TP53* Mutation	Y	33	6 (18%)	**0.015**
	N	21	11 (52%)	
Complex Karyotype	Y	14	1 (7%)	**0.023**
	N	21	10 (48%)	
Prior navitoclax	Y	9	0 (0%)	**0.047**
	N	53	19 (36%)	

MRD recrudescence and TTP (*Fig 1b & c*). Median time to MRD recrudescence after uMRD attainment in PB was 46 months (*Fig 1b*).

2. Of 62 patients, 19 achieved PB uMRD (31%). 2 patients had PB uMRD confirmed after 4-5 years without prior MRD tests. Excluding them, median time to PB uMRD was 18 (range 5-26) months and 90% of PB uMRD attainment occurred by 24 months (*Fig 1d*). Median follow up from Ven start for 43 patients who did not achieve PB uMRD was 25 (range 4-73) months.

3. Baseline TP53 dysfunction, complex karyotype and prior navitoclax were associated with lower likelihood of PB uMRD (*Table 1*).

Conclusions: PB uMRD commonly correlates with BM uMRD in CLL patients treated with Ven, and serves as an equivalent predictor of long term outcome. Patients who have not achieved PB uMRD by 24 months are unlikely to do so. This group is enriched for *TP53* dysfunction and complex karyotype. While patients achieving uMRD have prolonged TTP, CLL eventually recrudesces, supporting a drive to time-limited combination therapy.

Keywords: chronic lymphocytic leukemia (CLL); minimal residual disease (MRD); venetoclax.

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TRANSCEND CLL 004: MINIMAL RESIDUAL DISEASE AFTER LISOCABTAGENE MARALEUCEL IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

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Introduction: Eradication of minimal residual disease (MRD) in patients with chronic lymphocytic leukemia (CLL) may be necessary for deep and durable responses. We assessed safety, pharmacokinetics, and efficacy of lisocabtagene maraleucel (liso-cel; JCAR017), an investigational, anti-CD19 chimeric antigen receptor (CAR) T cell product administered as a defined composition of CD4+/CD8+ CAR T cells, in the ongoing phase 1/2 TRANSCEND CLL 004 study.

Methods: Eligible patients had CLL/small lymphocytic lymphoma (SLL), received ≥2 prior lines of therapy (including Bruton's tyrosine

kinase inhibitors [BTKi] unless medically contraindicated), and had Eastern Cooperative Oncology Group performance status of ≤1. After lymphodepleting chemotherapy, patients received liso-cel infusion at either dose level 1 (50×10^6 total CAR+ T cells) or dose level 2 (100×10^6 total CAR+ T cells). Patients were monitored for dose-limiting toxicities (DLTs). Response was assessed by International Workshop on CLL 2008 criteria. MRD was assessed by flow cytometry in blood (sensitivity, 10^{-4}) and by Next-Generation Sequencing in bone marrow (BM; sensitivity, 10^{-6}).

Results: At the data cutoff, 16 patients had received liso-cel; 6 at dose level 1 and 10 at dose level 2. 75% of the patients had high-risk features (TP53 mutation, complex karyotype, del17p), all had received prior ibrutinib, and 50% had received prior venetoclax. Median number of prior lines of therapy was 4.5 (range, 2–11). There was 1 DLT of grade 4 hypertension, which occurred at at dose level 2. The most common grade 3/4 treatment-emergent adverse events were cytopenias (thrombocytopenia, 75%; anemia, 69%; neutropenia, 63%; leukopenia, 56%). One patient had grade 3 cytokine release syndrome (CRS); 3 patients had grade 3 neurological events (NE). Best overall response rate (ORR) in 15 evaluable patients was 87% (13/15). Seven patients (47%) achieved complete remission with/without complete blood count recovery (CR/CRi). ORR at 6 mo was 83% (5/6). Undetectable MRD in blood was achieved in 10/15 patients (67%) by day 30, and in 7/8 patients (88%) in BM. MRD-negative CRs were seen in patients who had failed both BTKi and venetoclax. Median time to peak blood CAR-T cell level was 16 days (range 4–30).

Conclusions: In this study of heavily pretreated patients with standard- and high-risk CLL/SLL and previous ibrutinib treatment, liso-cel–related toxicities of CRS and NE were manageable and grade 3 or higher events were limited. Patients rapidly achieved CR/CRi and undetectable MRD. The phase 2 component of the study is currently enrolling patients for treatment at dose level 2. Additional follow-up will be presented.

Keywords: CD19; chronic lymphocytic leukemia (CLL); T-cells.

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THE BRAF INHIBITOR VEMURAFENIB PLUS RITUXIMAB PRODUCES A HIGH RATE OF DEEP AND DURABLE RESPONSES IN RELAPSED/REFRACTORY HAIRY CELL LEUKEMIA: UPDATED RESULTS OF A PHASE-2 TRIAL

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Introduction: Up to 50% of hairy cell leukemia (HCL) patients relapse after purine analogs. We identified the BRAF-V600E kinase mutation as the genetic cause of HCL (Tiacci et al., NEJM 2011). We documented, in 26 relapsed/refractory patients treated with the oral BRAF inhibitor vemurafenib for a median of 16 weeks, 96% of overall responses (including 35% complete remissions - CR), obtained after a median of 8 weeks (Tiacci et al., NEJM 2015). However, residual bone marrow (BM) HCL cells persisted even in CR cases (5-10% cells) and the median relapse-free survival in all responding patients was 9 months.

FIG. 1A

B

C
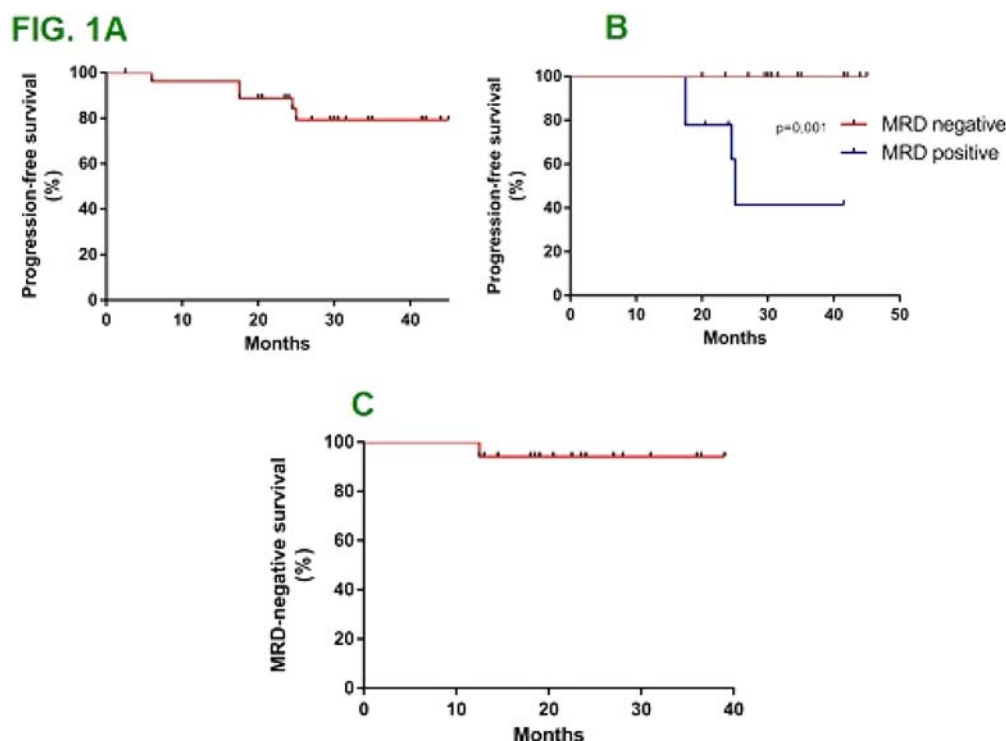
Since HCL strongly expresses CD20, rituximab could improve the efficacy of BRAF inhibition by targeting leukemic cells resistant to vemurafenib.

Methods: In this academic, phase-2, single-center trial (EudraCT 2014-003046-27), relapsed/refractory HCL patients received vemurafenib (960 mg b.i.d.) for 8 weeks and concomitant rituximab (375 mg/m^2 i.v.) every 2 weeks. Rituximab was then given as consolidation 4 times every 2 weeks post-vemurafenib.

Results: We enrolled 31 patients (median age: 59 years) with a median of 3 previous therapies. Toxicity was mostly of grade 1-2, without myelosuppression, and overlapped that of either drug when used alone.

Strikingly, a CR was achieved by 26/27 (96%) evaluable cases, including 2 with delayed platelet recovery and 2 with incomplete resolution of splenomegaly who nonetheless remain in otherwise CR at 22.5 and 25 months post-treatment. The 26 CR cases, all previously treated with purine analogs, also included some patients previously refractory to rituximab (n=5) and/or who had relapsed after a prior BRAF inhibitor (n=7; 5 obtained a PR and 2 a CR after the BRAF inhibitor). Notably, a CR was obtained after just 4 weeks of vemurafenib and two doses of rituximab in 15/24 evaluable patients (63%). Measurable residual disease (MRD) by allele-specific PCR (sensitivity: 0.05% BRAF-V600E alleles) was absent in the BM of 17/26 (65%) patients; in 8/17 cases (47%), MRD clearing was obtained before rituximab consolidation.

Progression-free survival (PFS) in 29 evaluable cases was 83% at a median of 29.5 months (range: 2-45) (Fig. 1A). Progressions (n=5) always occurred in MRD-positive cases, including 3/5 whose immediate prior treatment was a BRAF inhibitor (leading to PR in all 3 cases).

Indeed, PFS was significantly longer in the 17 MRD-negative CR cases (100% at a median of 30.5 months) than in the 9 MRD-positive CR cases (44% at a median of 24.5 months) (p=0.001; Fig. 1B). In subsequent BM evaluations, 16/17 (94%) CR patients maintained a MRD-negative status at a median of 22.5 months (range 12.5-36.5) (Fig. 1C).

Conclusions: Vemurafenib plus rituximab is a brief, safe and non-myelotoxic regimen inducing MRD-negative durable responses in most relapsed/refractory HCL patients. Randomized testing against the chemotherapy-based standard of care in the frontline setting is warranted.

Keywords: BRAF; hairy cell leukemia; minimal residual disease (MRD).
Disclosures: Tiacci, E: Research Funding: *Roche.*

FOCUS ON... SESSION: CHEMOTHERAPY-FREE STRATEGIES

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PREDICTIVE VALUE OF POD24 VALIDATION IN FOLLICULAR LYMPHOMA PATIENTS INITIALLY TREATED WITH CHEMOTHERAPY-FREE REGIMENS IN A POOLED ANALYSIS OF THREE RANDOMIZED TRIALS OF THE SWISS GROUP FOR CLINICAL CANCER RESEARCH (SAKK).

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Introduction: It is well established that follicular lymphoma (FL) patients
who have progression of disease within 24 months (POD24) from
frontline immunochemotherapy have worse overall survival (OS) and
thus constitute a high-risk population (Casulo et al. J Clin Oncol
33:2516-2522, 2015; Jurinovic et al., Blood 128:1112-1120, 2016).
Thus far, however only one report from the Nordic Lymphoma Group
(NLG) has shown, without an independent validation cohort, that this
endpoint can be useful also to predict the long term survival of patients
receiving systemic treatment with chemotherapy-free regimens
(Lockmer et al. J Clin Oncol 36:3315-3323, 2018).

In the present study, we sought to confirm that early progression after
first-line treatment is affecting OS also in patients initially treated with
immunotherapy only.

Methods: In order to determine whether POD24 is associated with
inferior OS, we analyzed a pooled dataset of three randomized trials
including FL patients with advanced and symptomatic disease con-
ducted between 1998 and 2016 by the Swiss Group for Clinical Can-
cer Research (SAKK), namely the SAKK35/98 and 35/03 studies,
which evaluated different durations of rituximab therapy, and the
SAKK 35/10 study, which compared rituximab monotherapy versus
rituximab plus lenalidomide in the front-line therapy. OS was calcu-
lated from disease progression in patients with POD24 and from
24 months after the start of treatment in the reference group of those
without POD24.

Results: A total number of 521 FL patients were enrolled in the
three SAKK studies, 333 of them had no prior systemic treatment
(64 in the SAKK 35/98, 115 in the SAKK 35/03 and all 154 in the
SAKK 35/10 studies, respectively) and received front-line therapy
with Rituximab alone (n=256) or in combination with lenalidomide
(n=77). We excluded 1 patient from the analysis who died without
progression within 24 months and 14 other patients who were
lost to follow-up without progression within 24 months from
treatment start. Hence, the final cohort of this study comprised
318 evaluable patients. POD24 was observed in 85 of 318 (27%
[95%-CI: 22, 32]) patients initially treated without chemotherapy.
Patients with POD24 showed a trend towards more advanced dis-
ease at presentation than the reference group without POD 24:
stage IV (55% vs 43%), B-symptoms (26% vs 17%), bulky disease
(44% vs 35%), but the differences did not reach the statistical sig-
nificance. In patients with early POD, median age was 59 years,
42 patients were male (49%) and 43 female (51%), and 20 had ele-
vated LDH (24%). In the reference group of patients without
POD24, median age was also 59 years, 97 patients were male
(42%) and 136 female (58%), and 48 had elevated LDH (21%).
Figure 1 shows the Kaplan-Meier estimates of survival according
to POD24. Median survival was not reached in either of the treat-
ment groups. The patients experiencing POD24 had 5- and
10-year OS rates of 69% and 59%, respectively, while in the refer-
ence group the 5- and 10-year OS rates were 92% and 77% (HR =
3.12 [1.73, 5.65]; log-rank P < 0.0001). In a multivariable Cox
model POD24 predicted poor survival (P=0.0355) across all stud-
ies irrespectively of LDH value, presence of B-symptoms or
advanced stage. FLIPI score and beta2-microglobulin values were
available only in the SAKK 35/10 study and could not be included
in the model.

Conclusions: We provided the first validation in an independent
cohort of the recent observation that POD24 retains its prognostic
validity in patients treated without chemotherapy and may represent
a useful endpoint for the future evaluation of novel chemotherapy-
free strategies.

Keywords: follicular lymphoma (FL); rituximab.

Kaplan-Meier survival estimates

at risk

233	200	150	131	124	118	109	93	80	27	13
85	71	60	50	33	24	20	17	13	10	2
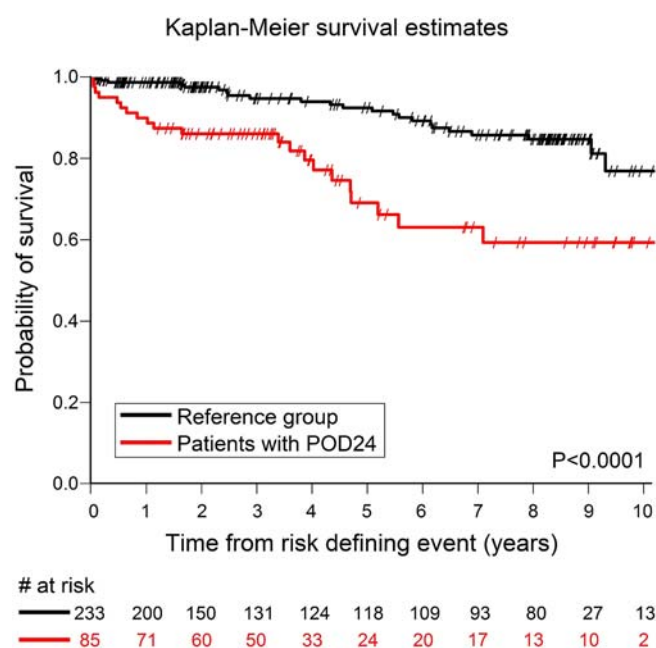
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EFFICACY AND SAFETY OF OBINUTUZUMAB + LENALIDOMIDE + ATEZOLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA: PRIMARY ANALYSIS OF A PHASE 1B/2 TRIAL

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Introduction: In the phase 2 GALEN study, induction and maintenance with obinutuzumab (GA101; G) plus lenalidomide (LEN) demonstrated favourable activity and tolerable safety in patients (pts) with relapsed/refractory (R/R) follicular lymphoma (FL). G plus atezolizumab (atezo) has also demonstrated activity in this setting. We present primary efficacy and safety data from a phase 1b/2 study (BO29562; NCT02631577) evaluating induction and maintenance with G-LEN-atezo in pts with R/R FL.

Methods: BO29562 is an open-label, multicentre study. All pts had received ≥1 prior anti-CD20-containing chemoimmunotherapy regimen. An initial 3+3 dose-escalation phase to define the phase 2 LEN dose was followed by an expansion phase. Pts received induction with six 28-day cycles (C) of: G 1000 mg IV on day (D) 1, 8, and 15 of C1 and D1 of C2–6; LEN 15/20 mg (dose escalation) or 20 mg (expansion) PO on D1–21 of C1–6; and atezo 840 mg IV on D1 and 15 of C2–6. Responders received maintenance for 24 months (G 1000 mg D1 every 2 months; LEN 10 mg D1–21 months 1–12; atezo 840 mg D1–2 every month). The primary endpoint was complete response (CR) by PET-CT assessed by Independent Review Committee (IRC; modified Lugano 2014 criteria) at end of induction (EOI). Minimal residual disease (MRD) was evaluated at EOI (10^{-5} sensitivity) using the Adaptive ImmunoSEQ® NGS platform (v2).

Results: At the time of the primary analysis (23 October 2018), 38 pts (LEN 15 mg, n=4; 20 mg, n=34) had enrolled and entered induction. Baseline characteristics were: median age, 61.5 years; male, 50.0%; Ann Arbor Stage III–IV, 78.9%; FLIPI high-risk (≥3), 26.3%; bulky disease (≥7cm), 15.8%; ≥2 prior lines of therapy, 47.4%; refractory to last line of prior regimen, 44.7%; and refractory to last line of anti-CD20 treatment, 28.9%. In the primary efficacy population (LEN 20 mg, n=32), CR rate at EOI was 71.9% (double-refractory pts [n=12], 66.7%). Most pts who received maintenance had durable clinical responses (median duration of response not yet reached [n=32]; **Figure**). At baseline, 22/28 MRD-evaluable pts had a circulating clone detected. Of these, 21 were MRD-evaluable at

Figure. Duration of response* by investigator assessment (n=32; median observation time 14.5 months [range 0.6–32.1 months])
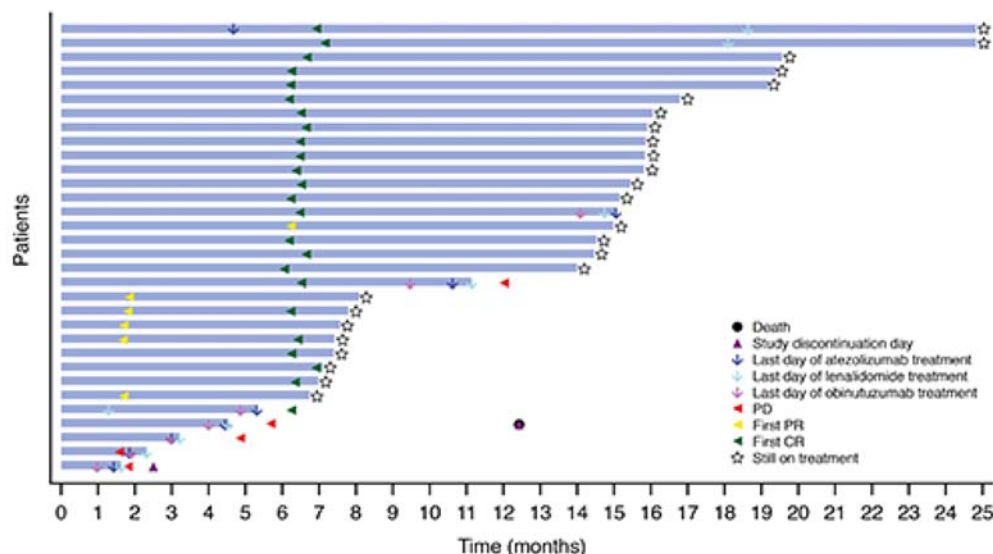
*Defined as the time from first PR or CR based on PET/CT to PD or death from any cause
CT, computerized tomography; CR, complete response; PET, positron emission tomography; PD, progressive disease; PR, partial response

EOI; 16 (76.2%) were MRD-negative (CR, n=15; partial response, n=1). The proportion of pts receiving >90% dose intensity during induction (n=34) and maintenance (n=27), respectively, was: G, 91.2% and 100%; LEN, 76.5% and 70.4%; and atezo, 71.9% and 85.2%. All treated pts had ≥1 adverse event (AE), 28 (73.6%) pts had a grade 3–4 AE, 12 (31.6%) had a serious AE, and 9 (23.7%) had an AE that led to discontinuation of any drug (induction, n=6; maintenance, n=3).

Conclusions: CR rate at EOI for the chemo-free regimen G-LEN-atezo is comparable with currently available treatment options in this indication and higher than with historical controls, with durable activity. The overall safety and tolerability profile is consistent with the known profiles for the individual drugs and for G-LEN.

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AUGMENT PHASE III STUDY: LENALIDOMIDE/RITUXIMAB (R[2]) IMPROVED EFFICACY OVER

RITUXIMAB/PLACEBO IN RELAPSED/REFRACTORY FOLLICULAR PATIENTS IRRESPECTIVE OF POD24 STATUS

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Introduction: Relapse within 2 years of initial chemoimmunotherapy (ie, POD24) in follicular lymphoma (FL) patients has been associated with less favorable prognosis and survival (Casulo et al. *Blood.* 2019). The objective of this analysis was to examine the potential impact of POD24 in FL patients receiving lenalidomide/rituximab (R[2]) vs rituximab/placebo (R/placebo) from the phase III AUGMENT study.

Methods: Patients with FL grade 1-3a were relapsed/refractory (R/R) after ≥ 1 prior systemic therapy, but were not refractory to rituximab. Treatment arms included R[2] (lenalidomide PO 20 mg/day [d], d1-21/28 X12 cycles plus rituximab IV 375 mg/m^{2} given cycle 1, d1, 8, 15, 22 and d1, cycles 2-5) and R/placebo (treated on the same schedule). Progression-free survival (PFS) was the primary endpoint, evaluated by 2007 IWG (without PET). For the AUGMENT study, POD24 was defined post-hoc as progression or relapse within 2 years of initial antilymphoma treatment, which included immuno- and/or chemotherapy.

TABLE 1 Efficacy of R^2 vs R/placebo by POD24 Status in Patients With R/R Follicular Lymphoma

	R^2			R/Placebo		
	All FL Patients (n = 147)	POD24 (n = 56)	No POD24 (n = 89)	All FL Patients (n = 148)	POD24 (n = 57)	No POD24 (n = 89)
Median PFS, mo (95% CI)	39.4 (23.1-NR)	30.4 (16.8-NR)	39.4 (22.9-NR)	13.9 (11.2-16.0)	13.8 (6.7-16.9)	13.9 (11.2-16.6)
ORR, %	80	80	80	55	51	58
CR, %	35	30	37	20	18	21

Results: As of 22June2018, 295 FL grade 1-3a patients had been randomized 1:1 to R^2 (n=147) and R/placebo (n=148). Median age was 62 years (range, 26-88), 74% of patients had Ann Arbor stage III/IV disease, 34% high FLIPI score, 84% had received prior rituximab, and 53% prior antilymphoma treatment within 2 years of enrollment. Of these FL patients, 56 (38%) R^2 and 57 (39%) R/placebo patients were identified as POD24 (ie, relapsing/progressing within 2 years of initial treatment). For all FL patients and subgroups based on POD24 status, median PFS was improved in the R^2 vs R/placebo arm (Table). For patients with POD24, HR was 0.41 (95% CI, 0.24-0.68) and for patients with no POD24, HR was 0.43 (95% CI, 0.28-0.65), both groups favoring the R^2 arm. Best overall response rates (ORR) and complete responses (CR) were similar within each arm in all FL patients and with or without POD24 (Table). Treatment with R^2 (vs R/placebo) reduced the risk of relapse/progression by 59% in patients with POD24, and improved both ORR and CR. Similar outcomes were observed for patients who relapsed within 2 years from diagnosis (data not shown).

Conclusions: R^2 demonstrated superior efficacy over R/placebo in patients with FL grade 1-3a, including those with POD24, patients who have historically been associated with worse outcomes.

Keywords: follicular lymphoma (FL); lenalidomide; rituximab.

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INTERIM ANALYSIS OF PHASE IIIB MAGNIFY STUDY OF INDUCTION R^2 FOLLOWED BY MAINTENANCE IN PATIENTS WITH RELAPSED/REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA

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TABLE 1 Efficacy for induction R^2 in R/R iNHL

	ORR, %	CR, %	Median TTR, mo (range)	Median DOR, mo (95% CI)*	Median PFS, mo (95% CI)*
Overall	73	45	2.7 (1.6-12.0)	36.8 (35.8-NR)	36.0 (26.5-NR)
By histology					
FL gr 1-3a	74	46	2.8 (1.6-12.0)	NR (27.7-NR)	30.2 (23.0-NR)
MZL	65	38	2.7 (1.9-11.1)	35.8 (NR-NR)	38.4 (26.5-38.4)
Rituximab-refractory status					
Yes	63	40	2.8 (1.6-12.0)	35.8 (19.2-NR)	18.1 (15.5-26.5)
No	78	47	2.7 (1.6-11.6)	NR (36.8-NR)	NR (36.0-NR)

*If patients were already in maintenance at data cutoff, then response assessments also contributed to DOR and PFS.

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Introduction: The lack of standard treatment approaches for relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL), along with a less than 1 y median progression-free survival (PFS) with PI3K inhibitors in this setting, indicate an unmet need in these patients. The immunomodulatory agent lenalidomide enhances the activity of rituximab when used in combination (R^2). Recent phase III results reported from the AUGMENT study show a median PFS of 39.4 mo in patients with R/R iNHL patients (Leonard. ASH 2018:445).

Methods: MAGNIFY is a multicenter, non-registrational phase IIIb trial in patients with R/R follicular lymphoma (FL) grade 1-3a and marginal zone lymphoma (MZL), and was designed to determine the optimal duration of lenalidomide (NCT01996865). R^2 treatment includes lenalidomide 20 mg/d, d1-21/28 plus rituximab 375 mg/m^2/wk cycle 1 and q8wk cycles 3+ given for 12 cycles. This induction phase is followed by 1:1 randomization to continued R^2 vs rituximab maintenance in patients with stable disease or better. These analyses examine the interim primary endpoint of overall response rate (ORR; 1999 IWG) for induction R^2. Efficacy-evaluable patients include those receiving ≥ 1 treatment with available baseline and post-baseline assessments.

Results: 370 enrolled patients included 80% FL grade 1-3a and 20% MZL with a median age of 66 y, 83% stage III/IV disease, and a median of 2 prior therapies (95% prior rituximab-containing). At a median 16.7 mo follow-up, the ORR was 73% and complete response (CR) was 45% (Table). ORR and CR showed similar efficacy results by histology. The overall median time to response (TTR) was 2.7 mo, median duration of response (DOR) was 36.8 mo, and median progression-free survival (PFS) was 36.0 mo. Based on rituximab-refractory status at baseline, patients who were rituximab-refractory and non-refractory had a respective ORR of 63% and 78%, CR of 40% and 47%, and median PFS 18.1 mo vs not reached. Of 370 randomized patients, 142 (38%) have entered the maintenance phase. The most common all-grade adverse events were 48% fatigue, 40% neutropenia, 35% diarrhea, 30% nausea, and 29% constipation. The most common grade 3/4 adverse event was neutropenia at 34%, whereas all other grade 3/4 adverse events were < 6%.

Conclusions: R^2 therapy is an active treatment regimen in patients with R/R FL grade 1-3a and MZL, including patients who were refractory to rituximab, and with a tolerable safety profile.

Keywords: indolent lymphoma; lenalidomide; rituximab.

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RITUXIMAB PLUS LENALIDOMIDE IS AS EFFECTIVE AS IMMUNOCHEMOTHERAPY IN THE ERADICATION OF MOLECULAR DISEASE IN UNTREATED FOLLICULAR LYMPHOMA: RELEVANCE LYSA ANCILLARY STUDY

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Introduction: Molecular response (MR) after first-line immunochemotherapy in patients (pts) with follicular lymphoma (FL) is considered as a valuable surrogate endpoint of patient outcome. RELEVANCE is the first phase III trial comparing the chemo-free regimen R2 vs R-Chemo followed by R maintenance in previously untreated pts with FL. The objective of the minimal residual disease (MRD) analysis was to determine the ability of a chemo free regiment to eradicate the MRD.

Methods: The MRD study in RELEVANCE was performed in 45 LYSA participating centers. Diagnostic peripheral blood (PB) and bone marrow (BM) samples were screened by the t(14;18) biomed 2 PCR (Evans 2007) in the 440 included pts. In t(14;18) (+) pts, MRD was quantified by ddPCR (Delfau-Larue, 2018) (ratio tumor cells /analyzed cells, with a sensitivity of at least 10^{-4}) in PB and BM at baseline, at week 24 (W24) (end of induction in R-chemo arm), and at W120 (end of maintenance in both arms). Factors associated (p<0.10) with (+) MRD at W24 were integrated in a backward stepwise logistic regression model. Survival was calculated using Kaplan-Meier estimates.

Results: A t(14;18) translocation was detectable in 222 pts before treatment. Compared to all LYSA pts enrolled in RELEVANCE, pts with MRD analyses presented more frequently with BM involvement (62% vs 48% p=.003), Ann Arbor stage III-IV (96% vs 90%, p=.004) and higher FLIPI score (FLIPI 2-5 91% versus 83%, p=.002). No

PFS according to MRD (bone marrow) at 24 weeks
With Number of Subjects at Risk and 95% Confidence Limits

+ Censored
Logrank p=0.0110

1: Negative
2: Positive or Positive(<10E-5)

	No. of Subjects	Event	Censored	Median Survival (95%CL)
Negative	103	17.5 % (18)	82.5 % (85)	Not reached
Positive or Positive(<10E-5)	30	33.3 % (10)	66.7 % (20)	Not reached (34.9 ; NA)
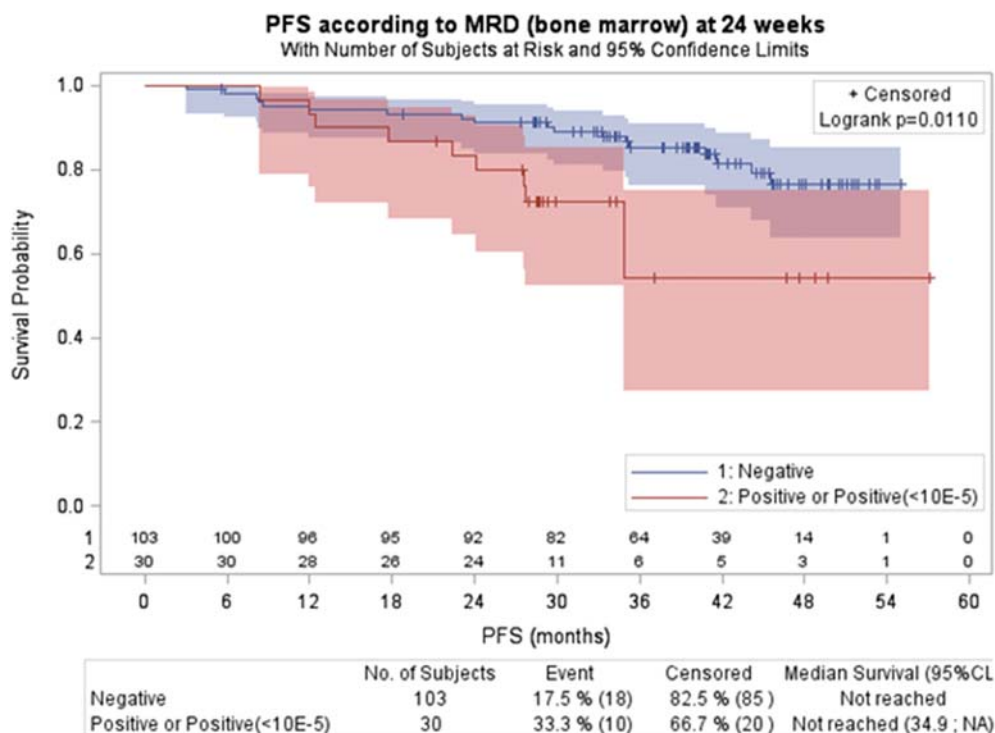
significant difference was observed in term of treatment arm (55% in R-chemo vs 49% in R²). At diagnosis, 213/220 PB and 136/139 BM samples were (+) with a median of 0.0058 and 0.021 respectively. At W24, 98% and 78% of those pts have reached MR in PB and BM respectively. The MRD positivity in BM at W24 was significantly (p=.02) more frequently observed in pts receiving R-chemo (32% vs 15%), in those with beta2m ≥ 3 mg/L (55% vs 34%, p=.05), and in those with higher levels of molecular disease before treatment (median value ten times higher in pts with (+) MRD (PB=0.056 and BM=0.16) than in pts with (-) MRD (PB=0.0056 and BM=0.016), p= 0.03 and p=0.02 respectively). Multivariate analysis results showed that only R-Chemo arm (OR=3.4, p=.008) and beta2m ≥ 3 mg/L (OR=3.1, p=.014) were factors independently associated with an increased risk of MRD (+) in BM at W24. Achievement of MRD negativity at W24 in BM was significantly associated with an improved PFS (p=.011) (3-year PFS 85.3% vs 54.4% for pts with (+) MRD (figure). At W120 in pts with persisting clinical response, only 2/166 pts were MRD (+) in PB, and 11/99 in BM. Longer follow up is needed to evaluate the prognostic value of those positive samples.

Conclusions: In agreement with the clinical results of RELEVANCE trial, our results show that an immunomodulatory induction treatment in first line FL can achieves high rate of MR in both blood and bone marrow; Achieving a complete MR at the end of induction was predicting a more favorable PFS.

Keywords: follicular lymphoma (FL); lenalidomide; minimal residual disease (MRD).

Disclosures: Delfau-Larue, M: Research Funding: *Celgene.* **Maisonneuve, H:** Other Remuneration: *personal fees from Roche and Celgene outside the submitted work.* **Casasnovas, O:** Consultant Advisory Role: *Advisory Board (Celgene, Roche, Takeda, BMS, MSD, Gilead, Janssen);* Research Funding: *Takeda, Gilead, Roche.* **Haioun, C:** Other Remuneration: *personal fees from Celgene and Roche during the conduct of the study.* **Tilly, H:** Other Remuneration: *personal fees from Celgene.* **Cartron, G:** Other Remuneration: *personal fees for consultancy and honoraria from Roche and Celgene.* **Salles, G:** Other Remuneration: *grants and personal fees from Celgene and Roche.* **Morschhauser, F:** Other Remuneration: *personal fees for advisory boards and scientific lectures from Celgene and Roche.*

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SAKK 35/15: A PHASE I TRIAL OF OBINUTUZUMAB IN COMBINATION WITH VENETOCLAX IN PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA PATIENTS

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Introduction: The anti-CD20 monoclonal antibody obinutuzumab and the bcl-2 inhibitor venetoclax are both active in different lymphoma subtypes. SAKK 35/15 is an open label phase I trial, which is being conducted by the Swiss Group for Clinical Cancer Research (SAKK) and the German Low Grade Lymphoma Study Group (GLSG)/German Lymphoma Alliance (GLA) and aims to determine the recommended phase II dose (RP2D), toxicity profile and preliminary activity of obinutuzumab in combination with venetoclax in previously untreated advanced stage follicular lymphoma (FL) patients (pts).

Methods: Pts with grade 1 to 3A FL, untreated and in need of systemic therapy were eligible. Two dose levels are being evaluated in a 3+3 design with an expansion cohort at the RP2D. DL1 consists of venetoclax 600mg once daily (OD) and DL2 of venetoclax 800mg OD, continuously for six 28-day (d) cycles, starting on cycle 1 d 2. In both DLs pts receive obinutuzumab 1000mg on d 1,8,15 of cycle 1 and on d 1 of cycles 2-6. Following cycle 6, pts on partial or complete remission (PR or CR) continue maintenance treatment with single agent obinutuzumab 1000mg every two months for up to 2 years.

Results: The study completed its accrual with 25 pts enrolled (3 in DL1 and 22 in DL2). Demographics: median age 55 (range 30–78), F: M = 12:13, ECOG 0:1:2 = 21:3:1 pts, stage II:III: IV= 2:10:13 pts, FLIPI score low:intermediate:high=5:10:10 pts, reason for start of systemic therapy B symptoms:bulky disease:clinical progression:symptomatic disease=10:10:13:19 pts. Among 22 pts completing cycle 1, only one patient treated at DL2 had a dose limiting toxicity consisting of grade (G) 4 thrombocytopenia after the first obinutuzumab infusion. Three pts have not completed cycle 1 yet. Thus far, adverse events (AE) of G ≥3, of at least possible attribution to study treatment, were neutropenia (2 pts, both G4), thrombocytopenia (2 pts, 1 G3 and 1 G4), and one pt each for anemia (G3), febrile neutropenia (G3), fatigue (G3), AST increase (G3), ALT increase (G3), lymphopenia (G3) and

pneumonitis (G3). AEs were all manageable and no toxic deaths were seen. The median relative dose intensity (proportion of administered doses relative to planned doses) was 100% for both drugs. Eleven pts are currently receiving combination therapy and 10 are on maintenance, while 4 pts discontinued treatment, 3 for progressive disease (2 under combination therapy and one during maintenance) and one for AEs (thrombocytopenia G4, ALT increase G3 and pneumonitis G3). Eleven pts are evaluable for response at 6 months, 10 were evaluated by PET-CT and one by CT only. Five achieved CR (45%; 95% CI, 17-77%), 4 PR (36%; 95% CI, 11-69%) and 2 pts had progressive disease, for an overall response rate (ORR) at 6 months of 82% (95% CI, 48-98%).

Conclusions: This is the first study to assess obinutuzumab plus venetoclax in untreated advanced FL in need of systemic therapy. The two drugs could be safely combined and may represent a valuable chemotherapy-free regimen. The RP2D is venetoclax 800mg OD continuously for 6 cycles starting on d 2 of cycle 1 in combination with obinutuzumab 1000mg on d 1,8,15 of cycle 1 and on d 1 of cycles 2-6, followed by obinutuzumab maintenance for up to two years. Preliminary data show promising activity and updated results will be presented.

Keywords: follicular lymphoma (FL); obinutuzumab; venetoclax.

Disclosures: Stathis, A: Research Funding: *Roche*; Other Remuneration: *Travel support Abbvie.* **Mey, U:** Consultant Advisory Role: *Roche*; Honoraria: *Roche.* **Schmidt, C:** Research Funding: *Roche.* **Hess, D:** Stock Ownership: *Roche.* **Moccia, A:** Consultant Advisory Role: *Roche.* **Unterhalt, M:** Research Funding: *Roche.* **Rossi, D:** Honoraria: *Roche.* **Zucca, E:** Consultant Advisory Role: *Roche*; Research Funding: *Roche.* **Hiddemann, W:** Honoraria: *Roche*; Research Funding: *Roche.*

FOCUS ON… SESSION: NON-CLINICAL AND EARLY CLINICAL DATA

073
PHASE I/II STUDY OF UMBRALISIB (TGR-1202) IN COMBINATION WITH UBLITUXIMAB (TG-1101) AND PEMBROLIZUMAB IN PATIENTS WITH REL/REF CLL AND RICHTER'S TRANSFORMATION

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Introduction: Preclinical data suggest that PD-1 mediates immune evasion in CLL, however clinical data indicate that pembrolizumab (pembro) monotherapy is ineffective in r/r CLL patients (pts) (0% ORR; Ding, BLOOD 2017). We hypothesized synergistic activity with PD-1 + PI3K blockade. Umbralisib (Umbra), is a PI3Kδ inhibitor with unique effect on CK1ε. We conducted a Ph 1 (3+3 design) study to assess the safety and activity of Umbra with the anti-CD20 mAb ublituximab (UTX) and pembro in r/r CLL and RT - the first reported triple combination of a PD-1 inhibitor + PI3Kδi + anti-CD20 mAb.

Methods: Treatment for CLL: Induction: Umbra (800mg daily) + UTX (900mg 3 out of 4 wks) for two 28-day cycles (Cy). Consolidation (Cy3-6): Pembro (dose level 1=100mg, dose level 2=200mg) every 3 wks + Umbra 800mg daily + UTX (900mg in Cy4 & 6). Maintenance: Cy≥6, Umbra 800 mg daily. For RT pts, all study drugs started in Cy1: Umbra 800 mg daily + UTX 900 mg Cy1 (D1, 8, 15), D1 Cy2-4, Cy7 and q3 cycles thereafter + pembro D3 of Cy1 and D2 of Cy2-4. Primary endpoint safety; secondary efficacy. Peripheral blood and/or BM was obtained for correlates at screening, Cy2, & Cy6.

Figure 1: Time on Study

Results: 18 pts treated to date: 11 CLL (5 at 100 mg pembro / 6 at 200 mg pembro) and 7 with RT (4 at 100 mg pembro / 3 at 200 mg). Demographics: M/F (12/6), med age 69.5 yrs (range 53-81), med prior tx 2 (1-9) (for RT, med prior was 5, all ibrutinib refractory), 83% refractory to immediate prior tx. 13/14 BTK exposed pts were refractory. 61% were high risk (del17p, del11q, TP53 mut, Notch1 mut or complex karyotype). AE's (all causality) were manageable. Grade 3/4 AE's included neutropenia (n=6, 33%), ALT/AST increase (n=3, 17%), and thrombocytopenia (n=3, 17%). One DLT occurred at 200 mg dose level (ALT/AST elevation). MTD not reached. No increase in expected Gr≥ 3 PI3Kδ-associated toxicities noted (1 pneumonitis, no colitis events). ORR was 91% for CLL pts, with 7/11 pts progression free at median f/u of 24.8 mos, including one CLL pt off all therapy for 32+ mos. ORR was 83% in BTK refractory pts (5/6); notably 80% of BTK refractory CLL pts achieved a response to Umbra + UTX (U2) induction alone prior to the addition of pembro. 5/7 RT pts were available for efficacy (1 ineligible, 1 too early to evaluate): 2 CR, 1 SD (40%↓) and 2 PD. RT CRs were durable (20+ mos and 12 mos, each); both were ibrutinib refractory, had 7 (including SCT) and 8 prior lines respectively, and one had failed CAR-T. Fig 1 is a Swimmer Plot of time on study. Correlative studies demonstrated relative retention of Tregs.

Conclusion: The triple combination of umbralisib + ublituximab + pembrolizumab was well-tolerated. Responses were durable in BTK refractory, high risk pts, including two CRs in RT pts. Data suggests that time-limited therapy could be possible. Enrollment is ongoing in both the CLL and RT cohorts and an amendment is planned to evaluate the triplet combination of U2 + TG-1501 (PD-L1 mAb).

Keywords: chronic lymphocytic leukemia (CLL); Richter's syndrome (RS).

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PEMBROLIZUMAB WITH RCHOP IN PREVIOUSLY UNTREATED DIFFUSE LARGE B-CELL AND GRADE 3B FOLLICULAR

LYMPHOMA: FINAL RESULTS OF A PHASE I TRIAL

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Background: Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) is standard first-line therapy diffuse large B-cell lymphoma (DLBCL). The anti-PD-1 antibody pembrolizumab (P) shows limited efficacy in relapsed DLBCL, but the first-line setting may represent a better opportunity for PD-1 inhibition. We report final results testing the safety of P+RCHOP in aggressive B-NHL.

Methods: Adults with previously untreated DLBCL, transformed lymphoma and grade 3 B follicular lymphoma were eligible. P was given at 200 mg IV q 3 weeks x 6 doses, with standard RCHOP x 6 q 3 weeks. A sample size of 30 permitted estimation of the rate of clinically relevant toxicity (assumed 40% with RCHOP alone) with a 95% CI of 23-57%. Response rates (Lugano criteria), event-free survival (EFS), overall survival (OS) and progression-free survival (PFS) were secondary endpoints. End of treatment (EOT) PR with negative biopsy, or repeat PET converting to Deauville 1-3, were scored as CR. PDL1 expression was analyzed using the 22c3 antibody.

Results: From March 2016- August 2018, 30 pts were enrolled and treated (Table 1). Grade 3-5 clinically significant AE's occurred in

TABLE 1 Pt Characteristics (N=30)

Median age (range)	62 (22-78)
Gender female	11/30
Histology	DLBCL NOS: 24 EBV+ DLBCL: 2 TCHRLBL: 1 Grade 3B FL: 3
Composite DLBCL/FL	5/30
Non-GCB by IHC	11/26 (excluding TCHRLBL, grade 3B FL)
IPI: Low (0-1), Low-int (2), High-int (3), High (4-5)	8, 9, 11, 2
NCCN IPI: Low (0-1), Low-int (2-3), High-int (4-5), High (≥6)	2, 12, 16, 0
Double expressor	6/18 tested
Double hit	1 (grade 3b composite w/low-grade FL)

Progression Free Survival
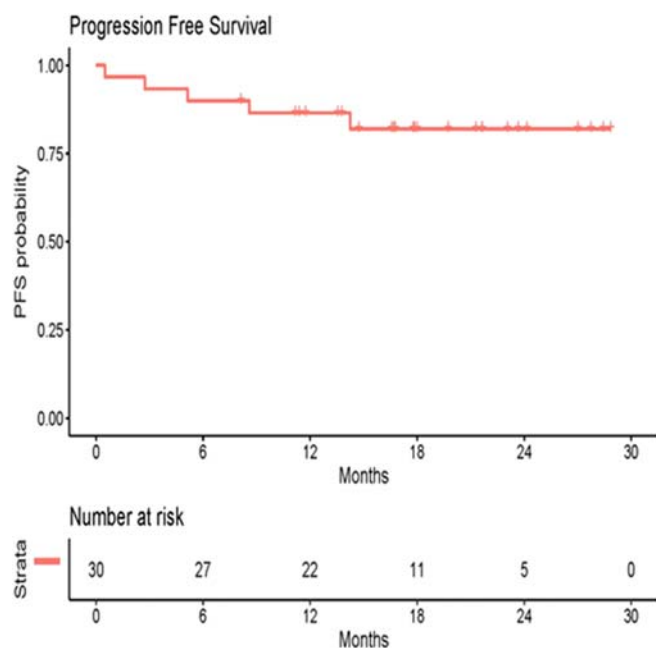
14 pts (14/30, 46%) and 18 SAE's occurred in 12 pts (12/30, 40%). Four immune-related adverse events (IRAE) occurred: grade 3 rash, grade 1 hyperthyroidism, grade 2 colitis, and grade 3 pneumonitis (in a 78 y.o. with a history of tobacco use and COPD). One pt. died during cycle 1 from bleed of gastric DLBCL, despite inpatient management, and was not assessed for response or dose intensity.

Anthracycline relative dose intensity was 94.7%. 26/29 received all planned P. ORR in 29 assessable pts was 93%: 24 CR (83%), 3 PR (19%) and 2 SD/PD (7%). 19 pts had PET- CR on EOT assessment; 3 had initial PR but a negative biopsy, and 2 had PR converted to CR with repeat PET. Among 8 pts with residual FDG-avid lesions on EOT PET, only 1 relapse occurred.

At 16 months follow-up, four relapses and 2 deaths occurred, with PFS/OS of 82/97% at 18 months (Figure 1). In 22 tested pts to date, 55% had PDL-1 tumor cell ≥ 30%, and PDL H-score (a weighted average) was 0 in 3 pts, 1-99 in 9 pts, and 100 or more in 10 pts. PFS was inferior in PDL1 H score 0 pts (p<.001) and IPI 3-5 pts (p=.07), but no different in GCB vs non-GCB.

Conclusions: P + RCHOP did not show toxicity beyond what is expected with RCHOP, and was associated with a high CR rate in this trial. FDG avid lesions in pts with PR were commonly false positives. Significant PDL-1 tumor staining was seen in most pts tested, and appears to predict PFS; final PDL-1 results will be presented. Our data supports further comparative study of P+RCHOP in DLBCL.

Keywords: chemotherapy; diffuse large B-cell lymphoma (DLBCL); Pembrolizumab.

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ZANUBRUTINIB PLUS OBINUTUZUMAB IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL) OR RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL)

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Introduction: Bruton Tyrosine Kinase (BTK) plays a critical role in B cell receptor (BCR) signaling. Zanubrutinib is a selective and irreversible BTK inhibitor that has demonstrated potent inhibition of BTK preclinically, with minimal inhibition of other kinases; it has minimal effect on interleukin-2 inducible tyrosine kinase (ITK) and does not inhibit ITK-mediated rituximab-induced antibody-mediated cytotoxicity. **Methods:** This is a phase 1b study of the combination of zanubrutinib with obinutuzumab in patients with B-cell malignancies. Eligible

TABLE 1

	37 CLL (n=37) / SLL (n=8) (20 TN & 25 RR) n = 45	R/R FL n = 36
Demographics		
Median (range) age, y	68 (38, 82)	59 (34, 86)
Median (range) prior therapies	1 (0, 4)	2 (1, 9)
Safety, n (%)		
Grade ≥3 AEs	32 (71)	18 (50)
Serious AEs	22 (49)	12 (33)
AEs leading to zanubrutinib discontinuation	2 (4)	2 (6)
Fatal AEs	1 (2)	0
Efficacy (Evaluable)	**n = 45**	**n = 36**
Median (range) follow-up, mo	25 (8, 34)	18 (2, 34)
ORR, n/N (%)	43/45 (96) CLL: 15/15 TN, 20/22 RR SLL: 5/5 TN, 3/3 RR	26/36 (72)
Best response		
CR	12 (27) CLL: 5/15 TN, 6/22 RR SLL: 1/5 TN, 0/3 RR	13 (36)
PR	31 (69)	13 (36)
Stable disease	2 (4)	5 (14)
Progressive disease	0	5 (14)

patients had ECOG status of 0-2, neutrophil count >1000/μL, platelets >40,000/μL, adequate renal and hepatic function and no significant cardiac disease. Growth factors, transfusion and anticoagulation were allowed. The primary efficacy endpoint was objective response using 2007 International Working Group criteria.

Results: As of 16Nov2018, enrollment was complete with 45 CLL/SLL patients (20 treatment-naïve [TN] and 25 R/R) and 36 R/R FL patients. Median follow-up was 25.5 mo (range: 7.9-33.5) for CLL/SLL and 17.8 mo (range: 2.3-33.8) for R/R FL. One fatal adverse event (AE) occurred: squamous cell carcinoma in a CLL patient with prior squamous cell carcinoma. Serious AEs were reported in 22 (49%) CLL/SLL and 12 (33%) R/R FL patients. Common (>20%) any-grade AEs reported in CLL/SLL patients were upper respiratory tract infection (URTI; 49%), neutropenia (42%), contusion (33%), diarrhea (27%), cough (27%), fatigue (27%), and pyrexia (22%); and in FL patients were URTI (39%), contusion (28%), fatigue (25%), and cough (22%). AEs lead to zanubrutinib discontinuation in 2 (4%) CLL/SLL (disseminated cryptococcusand squamous cell carcinoma) and 2 (6%) R/R FL patients (lethargy, ascites). There were no AEs of atrial fibrillation. All patients completed baseline and ≥1 response assessment. Overall response rates [complete response+partial response] were 96% in CLL/SLL (100% for TN, 92% for R/R) and 72% in R/R FL. There were 6 CRs in patients with TN CLL/SLL, 6 in R/R CLL/SLL and 13 in R/R FL.

Conclusions: The combination of zanubrutinib plus obinutuzumab was generally well tolerated and active in patients with CLL/SLL and R/R FL. Few patients discontinued due to AEs. A Phase 2 trial comparing zanubrutinib plus obinutuzumab against obinutuzumab alone in R/R FL is ongoing.

Keywords: B-cell receptor inhibitors; chronic lymphocytic leukemia (CLL); follicular lymphoma (FL).

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A PHASE I/II TRIAL OF IBRUTINIB, INTRATUMORAL CPG AND LOCAL RADIATION IN PATIENTS WITH LOW-GRADE B-CELL LYMPHOMA: INTERIM CLINICAL AND CORRELATIVE RESULTS

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Introduction: Local treatment with intratumoral CpG (a toll-like receptor 9 agonist) and low-dose radiation can elicit antitumor immune
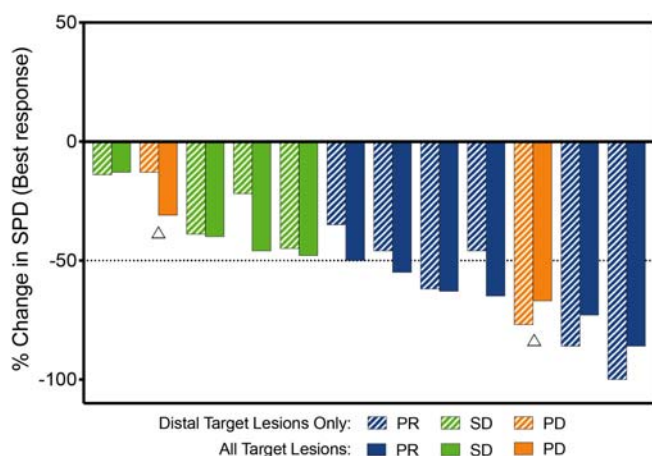
Figure 1. Waterfall plot depicting percent change in sum of product diameters (SPD) from baseline to best overall response for each evaluable patient. Bars are colored by best overall response and shaded by inclusion (solid bars) or exclusion (hashed bars) of the injected site in the SPD. PR, partial response. SD, stable disease. PD, progressive disease. △ Both patients with progressive disease as best response met criteria for progression other than a 50% increase in SPD (one had a new site of disease and the other had progression at one target lesion).

responses and global tumor reduction in patients with low-grade lymphoma (Frank, *Cancer Discov*, 2018). Ibrutinib compromises B-cell survival by inhibiting Bruton's tyrosine kinase, but also modulates T-cells by inhibiting interleukin-2-inducible T-cell kinase. In a mouse model of lymphoma, ibrutinib plus intratumoral CpG was curative of systemic disease, an effect that was T-cell dependent (Sagiv-Barfi, *Blood*, 2015). Thus, we initiated a phase I/II clinical trial combining oral ibrutinib, intratumoral CpG and local low-dose radiation in adults with recurrent low-grade lymphoma (NCT02927964).

Methods: Enrolled patients received intratumoral injections of CpG (SD-101, 3mg) weekly for 5 doses, starting on the second day of a 2-day course of local radiation (4Gy) to the same site. Daily oral ibrutinib (560mg) began on day 9. Treatment-emergent adverse events (AEs), ibrutinib dose modifications and adherence were recorded at every visit. Revised Lugano criteria were used to assess response to therapy, based on CT scans at 3, 6, 12, 18, and 24 months. Fine needle aspirates (FNAs) were obtained from CpG-injected and non-injected tumor sites pre- and post-treatment and analyzed by flow cytometry and single-cell RNA sequencing (scRNAseq). When available, viably preserved tumor and peripheral blood cells were used for *in vitro* immune response assays.

Results: As of January 2nd, 2019, 13 patients have been treated, with a median follow-up of 7.7 months. AEs are consistent with known effects of ibrutinib and of CpG with no unexpected AEs to suggest synergistic toxicity. There were no grade 4 or 5 events. AEs led to ibrutinib dose reduction or discontinuation in 3 patients. At the time of analysis, 6 of 12 evaluable patients had achieved a partial response (50% ORR) and 3 of them had achieved greater than 50% reduction in distal tumor burden (Figure 1). Eight of 12 patients had experienced at least a 30% reduction in distal tumor burden. Flow cytometry revealed decreased T follicular helper cells and increased CD4 and/or CD8 effector T-cells, CD137+ activated T-cells, and NK cells in

CpG-injected tumors. Abscopal immune effects in distant non-injected lesions included an increase in Granzyme B+ CD8 T-cells, most prominent after the addition of ibrutinib. scRNAseq data showed significant transcriptional shifts in tumor cells and in tumor-infiltrating T-cells, including signatures of interferon response. Finally, *in vitro* assays showed tumor-specific immune responses in peripheral blood T-cells of all 6 evaluable patients.

Conclusion: Early data suggest that the combination of oral ibrutinib, intratumoral CpG, and local low-dose radiation is safe and can generate systemic antitumor immune responses and systemic tumor shrinkage in low-grade lymphoma.

Keywords: ibrutinib; immunochemotherapy; indolent lymphoma.

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EXTENDED FOLLOW-UP OF A PHASE I TRIAL OF IPILIMUMAB, NIVOLUMAB AND BRENTUXIMAB VEDOTIN IN RELAPSED HODGKIN LYMPHOMA: A TRIAL OF THE ECOG-ACRIN RESEARCH GROUP (E4412)

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Background: Relapsed/refractory (R/R) Hodgkin lymphoma (HL) remains a significant clinical problem. We hypothesized that activating the immune microenvironment, and concurrently targeting tumor cells with brentuximab vedotin (B) could overcome tumor resistance. Here we report the extended follow-up for all patients treated on Phase 1 of E4412 with the combinations of B (1.2 or 1.8 mg/kg), nivolumab (N) 3mg/kg and ipilimumab (I) (1 or 3mg).

Figure 1: PFS and OS
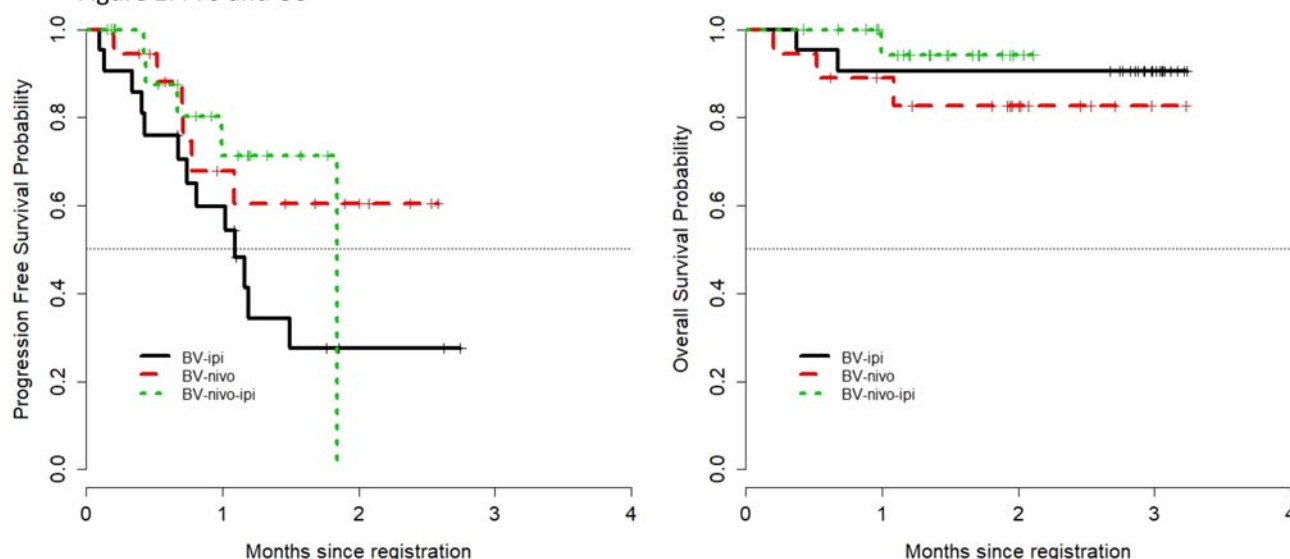
Methods: Patients with confirmed R/R HL were enrolled sequentially in cohorts of B-I (n=21), B-N (n=18), and B-N-I (n=22). Schedule was: B-N q 21 days for 16 cycles and N an additional 12 months; I q 3 weeks for 4 cycles and then q 3 months (B-I), or every 12 weeks for up to 24 months (B-N-I). Dose limiting toxicity (DLT) was defined within the first cycle of therapy.

Results: As of 3/1/2019, 64 patients were enrolled of which 61 were eligible, 3 were ineligible due to prior treatment or laboratory values. The median age was 33; median prior therapies 2 (excluding SCT) across all cohorts, range: 1-9 (B-I), 1-6 (B-N), and 1-5 (B-N-I). Twenty-five patients (40%) had prior SCT: 9 (B-I), 7 (B-N), and 9 (B-N-I). Seven patients: 3 (B-I), 4 (B-N) and 1 (B-N-I) had prior BV.

Safety: All enrolled patients are evaluable for safety. There were 2 grade 5 pneumonitis deaths, one each in B-N and B-N-I. There were 5 DLTs: pneumonitis and typhlitis (B-N), and one each grade 4 diabetic ketoacidosis and hyperglycemia, transient grade 3 AST elevation, and post AlloSCT grade 4 GVHD (B-N-I). Significant grade 3 AEs included rash (12%), and colitis, gastritis, pancreatitis, and arthritis each in 1 patient. Common toxicities considered at least possibly related to drug, included: fatigue (28%), transaminitis (36%), rash predominantly with B-I (25%) versus 8% combined B-N, and B-N-I, peripheral neuropathy (53%) and diarrhea (43%), primarily grade 1-2.

Response: Five patients: (1 each B-I, B-N, and 3 B-N-I) were unevaluable for response. For the entire cohort the ORR/CR is 76%/57% (B-I), 88%/61% (B-N), and 82%/73% (B-N-I). For patients with at least 2 cycles of therapy and one imaging time point the ORR/CR is 80%/60%, 94%/64%, and 95%/84% for B-I, B-N and B-N-I respectively. With a median follow-up of 2.98 years, 2 years, and 1.35 years the 1 year PFS is 60%, 68%, and 72% for B-I, B-N and B-N-I respectively The median OS has not been reached for any of the arms (Figure 1).

Conclusion: All combinations were well tolerated, with mainly grade 1-2 immune toxicities, however deaths secondary to pneumonitis were noted in N containing cohorts. The ORR and CR rate in the N containing cohorts is superior to that of B-I doublet; the CR of B-N-I is higher than both doublet combinations and some patients have durable responses. It remains to be seen if a higher CR rate will eventually translate into more durable response rates. The ongoing randomized phase 2 study (E4412) is comparing the B-N doublet to the B-N-I triplet (NCT01896999).

Keywords: brentuximab vedotin; Hodgkin lymphoma (HL); nivolumab.

078

HIGH EXPRESSION OF BCL-2 AND BCL-XL IN DIFFUSE LARGE B-CELL LYMPHOMA CONFER POOR PROGNOSIS BUT MAY BE REVERSIBLE BY COMBINED INHIBITION WITH BET INHIBITORS AND BH3 MIMETICS.

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Introduction: Double-hit lymphoma (DHL) and double-expressor (DE) Diffuse Large B cell Lymphoma (DLBCL) are both characterised by dysregulation of MYC and BCL-2, and associated with worse

survival following treatment with current standard of care (R-CHOP). Novel approaches capable of improving response for these sub-groups are therefore urgently needed. Surprisingly, venetoclax, a BH3-mimetic that potently inhibits BCL-2, has limited activity in this disease. We therefore sought to understand the expression and potential prognostic relevance of all anti-apoptotic BCL-2 family members, not just BCL-2, in DLBCL and how these might be overcome with new therapeutic approaches. To this end we investigated a novel BET inhibitor (BETi), PLX2853, and its combination with the BH3-mimetics, venetoclax (BCL-2) and WEHI-539 (BCL-xL).

Methods: We analysed the relationship between survival and expression of BCL-2 family mRNA using the Whole Genome-DASL array from 928 patients from the REMoDL-B trial. E-myc lymphoma cell lines (LCLs) and DLBCL cell lines (CL) (4 GCB, 3 ABC) were utilised to dissect potential mechanisms of cell death following exposure to BETi and BH3-mimetics. Techniques employed included qPCR, western blot, immunoprecipitation, retroviral transduction, flow cytometry and *in-vivo* mouse studies.

Results: We identified differential mRNA expression patterns of anti-apoptotic BCL-2 family members in DLBCL subtypes. These had prognostic relevance: specifically, across sub-types high *BCL-2* conferred poor response to R-CHOP, whilst in GCB DLBCL high *BCL-xL* was associated with worse survival.

In Eμ-myc LCLs, a novel BETi developed by structure-based design, PLX2853, induced cell death at lower concentrations than other agents of its class. Cell death was mediated by upregulation of the pro-apoptotic protein, BIM, associated with downregulation of the suppressive *miR-17~92*.

When Eμ-myc LCLs were transduced to overexpress BCL-2 or BCL-xL, reflecting the situation in DLBCL they became resistant to PLX2853. Similar resistance to BETi was seen in human DLBCL CLs. E-myc LCLs overexpressing BCL-2 or BCL-xL could be resensitised to BETi through combination with venetoclax or WEHI-539, respectively, and this was associated with priming of anti-apoptotic proteins with BIM.

In GCB DLBCL CLs, BIM upregulation in response to PLX2853 was identified. The combination of PLX2853 and venetoclax produced synergistic increases in cell death, resulting in reduced tumour growth and enhanced survival in NSG mice bearing DLBCL xenografts.

Conclusion: We identified a varied landscape of expression of anti-apoptotic BCL-2 proteins in DLBCL and highlighted the contribution of high BCL-xL expression to treatment resistance in DLBCL. High expression of anti-apoptotic BCL-2 family members also provides resistance to BETi. However, this could be overcome by use of specific BH3-mimetics targeting the relevant pro-survival BCL-2 member, involving mitochondrial priming.

Keywords: "double-hit" lymphomas; BCL2; venetoclax.

FOCUS ON... SESSION: NON-CLINICAL NEW DRUGS

079
FIRST-IN-CLASS HAT ACTIVATOR HIGHLY SYNERGISTIC WITH PAN-HDAC INHIBITOR ROMIDEPSIN LEADING TO PROFOUND HISTONE ACETYLATION CYTOTOXICITY

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Introduction: Inactivating mutations of the histone acetyltransferase (HAT) coding genes, EP300 and CREBBP, present in ~40% of germinal center (GC) derived lymphomas. Mutations are monoallelic, suggesting that their activity may be restored if the wildtype allele's function can be enhanced.

Methods: Starting from parent compound CTPB, a library of 70 HAT modulating analogues was synthesized. The cytotoxic effects were evaluated by cell TiterGlo. Functional effects on the acetylation of histone was measured by immunoblot in cell free assays. Histone acetylation was measured in cells following histone extract and immunoblot or mass spectrometry. P53 acetylation was measured by immunoblot. Binding of lead HAT compound YF2 to p300 was determined by recording ^{1}H-^{15}N HSQC NMR spectra of recombinant ^{15}N-enriched p300-bromodomain. Synergy was calculated by Excess over Bliss (EOB>10 =synergy). SCID-beige mice were xenografted with SUDHL6 and treated with either vehicle, YF2 40mg/kg, romidepsin 2mg/kg or the combination. Mice were evaluated for tumor volume by caliper. Survival was determined using the Kaplan Meier method.

Results: The IC50 of 29 compounds ranged from 3.6-43.2 μM in 4 DLCBL cell lines. Four compounds demonstrated significant dose

dependent increase in acH3K27 (EC50 9.4 ± 3.1 - 152.7 ± 0.8 nM) and acH3K18 (EC50 83.4 ± 1.3 - 269.9 ± 0.8 nM). YF2 was chosen as the lead compound because it demonstrated functional effect on acetylation and selective cytotoxicity in EP300 mutated verses WT cell lines (medium IC50 5 μM and 19 μM respectively, p<0.0005). In cells, YF2 induced acetylation of H3K27 6-fold and p53 5-fold. YF2 induced acH3K27 in mouse lymphoma tissue 2-fold. The IC50 of YF2 ranged from 5.9 to 25 μM in DLBCL lines (N=11) and 4.4 to 14 μM in TCL lines (N=6). YF2 induced cytotoxicity in 3 primary patient samples including a FL patient (CREBBP and p53 mutated). The addition of YF2 induced numerous chemical shift perturbations throughout the ^{1}H-^{15}N HSQC NMR spectrum of ^{15}N-enriched p300-bromodomain indicating binding.

The combination of YF2 and romidepsin demonstrated strong synergism in 8 out of 11 DLBCL cell lines (6/6 EP300 mut, 2/5 wt, EOB=48) and 2 out of 4 TCL lines (EP300 wt, EOB=28). The combination led to enhanced acetylation in multiple histone marks compared to single agents. In mice, the combination of YF2 and romidepsin was well tolerated with no weight loss. Single agent treatment with YF2 or romidepsin led to equivalent tumor growth delay and the combination was superior. Mice treated with the combination demonstrated a significant prolonged survival.

Conclusions: YF2 induces HAT-mediated acH3K27 and Acp53. It demonstrates selective cytotoxicity in EP300-mutated DLBCL and strong synergy with romidepsin in DLBCL and TCL. The combination demonstrated significant tumor growth delay in mice suggesting a potential precision medicine opportunity for patients harboring HAT mutations.

Keywords: diffuse large B-cell lymphoma (DLBCL); epigenetics.

080

COPANLISIB AND VOLASERTIB OVERCOME IBRUTINIB-VENETOCLAX RESISTANCE VIA TARGETING PI3K-AKT SIGNALING AND G2/M CELL CYCLE TRANSITION IN MANTLE CELL LYMPHOMA

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Background: Mantle cell lymphoma (MCL) is an aggressive and incurable non-Hodgkin lymphoma (NHL). Bruton's tyrosine kinase (BTK) and anti-apoptotic proteins, including BCL2, promote MCL survival and progression. BTK inhibitor ibrutinib and BCL2 inhibitor venetoclax alone or in combination have proven to be effective treatment options for MCL. However, mono- and dual resistance frequently develops, necessitating the development of new therapies to overcome primary and acquired ibrutinib and venetoclax resistance in MCL.

Methods: Cell viability, cell apoptosis and cell cycle arrest assays were conducted to investigate the *in vitro* efficacies of copanlisib and
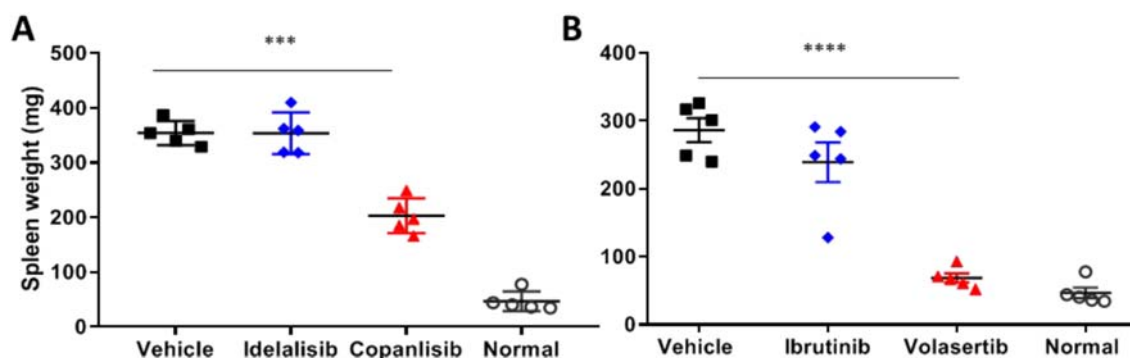
Figure 1. Copanlisib and volasertib overcome ibrutinib-venetoclax dual-resistance in orthotopic MCL PDX models. An orthotopic PDX model was established using a primary MCL sample from a patient with ibrutinib-venetoclax dual resistance. The PDX cells were isolated and injected intravenously into NSG mice and allowed to engraft for 4 four weeks. The mice were administrated with single agents copanlisib at 6 mg/kg/2d, idelalisib at 50 mg/kg/2d, or vehicle (A), or ibrutinib at 50 mg/kg/d, volasertib at 10 mg/kg/week, or vehicle (B) for 4 weeks. At the end of experiments, spleen weight was measured and plotted. Spleen weight of normal NSG mice was also included (A-B). ***, p<0.001; ****, P<0.0001.

volasertib alone or in combination. Western blotting was conducted to investigate the signaling pathways altered upon drug treatment. An orthotoppic PDX model was established from a MCL patient with dual resistance to ibrutinib-venetoclax. Single agent copanlisib at 6 mg/kg/2d, idelalisib at 50 mg/kg/2d, ibrutinib at 50 mg/kg/d, volasertib at 10 mg/kg/week, or vehicle control, were administrated in mice carrying the orthotopic PDX model to assess their *in vivo* efficacies.

Results: Our data revealed that PI3K-AKT signaling closely associated with ibrutinib resistance, venetoclax resistance and dual resistance. Constitutive PI3K-AKT-mTOR signaling overcomes the G2/M cell cycle checkpoint and promote continuous cell proliferation in tumor cells. All four isoforms of PI3K, α, β, γ and δ are expressed in all the MCL cell lines tested. Unlike idelalisib, a PI3Kδ-specific inhibitor, copanlisib is a pan-PI3K inhibitor, which targets all PI3K isoforms, and was approved by FDA to treat follicular lymphoma. Compared to idelalisib, copanlisib is more potent in targeting MCL cells *in vitro* with IC50 at a nanomolar range. Copanlisib significantly inhibited *in vivo* tumor growth of an ibrutinib-venetoclax dual-resistant PDX model (**Fig. 1A**). PLK1, a central player in regulating G2/M transition, acts upstream of PI3K/AKT signaling via phosphorylating PTEN to cause a tumor-promoting metabolic state. Volasertib, a specific PLK1 inhibitor, is under a phase III clinical trial for patients with Acute Myeloid Leukemia. Volasertib dramatically arrested MCL tumor cells at G2/M phase, which leads to cell apoptosis at a low nanomolar range. Volasertib at 10mg/kg/week significantly inhibited *in vivo* tumor growth of the ibrutinib-venetoclax dual -resistant PDX model (**Fig. 1B**). More interestingly, the combination of copanlisib and volasertib induced synergistic effect in ibrutinib-resistant, venetoclax-resistant, and ibrutinib-venetoclax dual resistant cell lines. Detailed mechanism of the observed synergy is still under investigation *in vitro* and *in vivo*.

Conclusion: Copanlisib and Volasertib are potent agents in targeting MCL cells *in vitro* and *in vivo*, and have great potential to overcome ibrutinib and venetoclax resistance in MCL.

Keywords: BCL2; mantle cell lymphoma (MCL); PI3K/AKT/mTOR.

081
THE LANDSCAPE OF DRUG PERTURBATION EFFECTS IN LEUKEMIA AND LYMPHOMA

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Introduction: As new generations of targeted therapies emerge, the functional relationships of mutations to tumor phenotypes or drug response remain largely unknown. Here, we measured ex vivo sensitivity of 710 tumor samples from 18 blood cancers to 63 drugs alongside genome, transcriptome, and DNA methylome analysis to understand determinants of drug response. We also included sequential samples from CLL over the disease course.

Methods: Compounds were pre-diluted in dimethylsulfoxide and cryopreserved primary cells were cultured in RPMI 1640 medium containing 10% human AB serum and seeded on top of the drugs at a final concentration of 1×10^6 cells/ml in a 384 well format. After 48h (37°C, 5% CO_2), cell viability was determined by luminescence measurement (EnVision Plate Reader, PerkinElmer) using an ATP assay (CellTiter-Glo, Promega). Raw data were processed using a data analysis pipeline (R/Bioconductor package cellHTS2) which enabled visualisation of data. Accuracy and reproducibility were confirmed with technical (n=9; $R^2 > 0.9$) and biological replicates ($R^2 = 0.7-0.9$). In total 710 blood samples were screened on this platform. 347 samples were obtained from 141 patients at different clinical time points were used for longitudinal investigation.

Results: To obtain a global overview of drug response, we used hierarchical clustering and T-SNE of all patients and found that disease and genotypes show differential drug response. IGHV status, trisomy 12 and individual gene mutations were associated with drug response to multiple drugs (n>10). p53 mutation was associated with decreased response to *in vitro* treatment with Cytarabine, Fludarabine and Nutlin-3a (n=321; 2μM; p<0.05). We identified drugs with disease specific response for individual lymphomas including T-PLL. The analysis of sequential samples showed stable drug response over time in most patients but also revealed that a subset of patients who underwent *in vivo* treatment with Idelalisib or Ibrutinib (n=16) showed changes in *in vitro* sensitivity to several small molecule inhibitors. BCR inhibitor therapy led to higher sensitivity to bromodomain inhibitor OTX015 and less sensitivity to heat shock protein 90 inhibitors Ganetespib and Onalespib (all 2μM; p<0,05) in line with activity of HSP inhibitors mediated through BCR targeting.

Conclusion: Ex-vivo high-throughput drug screening discovers entity/genotype-specific vulnerabilities. BCR inhibitors lead to alteration of drug sensitivity pattern which can be assessed and may form the basis for optimized combination treatment. Our data of drug response profiles and Omics characterization will provide a unique tool to query molecular determinants of response and thus provide hypothesis for clinical trials.

Keywords: B-cell receptor inhibitors; chronic lymphocytic leukemia (CLL); non-Hodgkin lymphoma (NHL).

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DISCOVERY OF A NOVEL, POTENTIAL FIRST-IN-CLASS MALT1 PROTEASE INHIBITOR FOR THE TREATMENT OF B CELL LYMPHOMAS

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Introduction: Constitutive activation of the classical nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) pathway is a clear driver of B-cell lymphomas, especially the aggressive activated B-cell (ABC) subtype of diffuse large B-cell lymphoma (DLBCL). Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) is a key mediator of the classical NF-κB signaling pathway downstream of B-cell and T-cell receptor. MALT1 possesses 2 functions: a scaffolding function to recruit NF-κB signaling proteins and a protease function to cleave and inactivate inhibitors of the NF-κB signaling pathway.

Methods: Using a high-throughput screen followed by iterative structure-activity relationship (SAR) analyses, a lead MALT1 inhibitor was identified. The lead compound was evaluated using biochemical, in vitro cellular, in vivo tumor efficacy and safety models.

Results: The lead compound is a potent, selective, allosteric inhibitor of MALT1 protease activity as measured by biochemical assays, downstream cellular cytokine readouts (IL 6/10) or direct MALT1 substrate cleavage (RelB, BCL10). The compound inhibits proliferation of activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL) cell lines bearing CD79b or CARD11 mutations as well as models mimicking resistance to covalent Bruton's Tyrosine Kinase (BTK) inhibitors.

Furthermore, combination effects were observed in CD79b-mutant cellular ABC-DLBCL models when the lead MALT1 inhibitor was combined with a BTK inhibitor. The lead MALT1 inhibitor leads to potent in vivo pharmacodynamic shutdown in CD79b- as well as CARD11-mutant ABC-DLBCL models as measured by serum IL10 or uncleaved BCL10 levels in tumors. The lead MALT1 inhibitor exhibits potent tumor growth inhibition in two human DLBCL xenograft models, OCI-Ly3 and OCI-Ly10.

To address the role of MALT1 inhibition in T cells, primary human T cells derived from normal healthy volunteers were treated with the lead MALT1 inhibitor in vitro. Dose dependent inhibition of the generation of T_{regs} ($CD4^+CD25^+FoxP3^+$) following CD3/28 stimulation was observed upon treatment with the lead MALT1 inhibitor suggesting a potential immune modulatory role of MALT1 inhibition.

Conclusions: Phase 1 clinical trials assessing the safety and efficacy of the lead MALT1 inhibitor are planned to initiate in 2019. This MALT1 inhibitor is a combination partner for BTK inhibitors and a promising treatment option for BTKi-resistant tumors with demonstrated preclinical activity in CARD11 mutant tumors. In addition to ABC-DLBCL, a MALT1 inhibitor is a promising treatment option for patients with CLL, MCL, WM and FL whose tumors have been shown to be sensitive to inhibition of BTK. MALT lymphomas, characterized by MALT1 and BCL10 translocations, represent another attractive target for MALT1 inhibition.

Keywords: BTK inhibitors; diffuse large B-cell lymphoma (DLBCL); MALT1.

083

KYM-001, A FIRST-IN-CLASS ORAL IRAK4 PROTEIN DEGRADER, INDUCES TUMOR REGRESSION IN XENOGRAFT MODELS OF MYD88-MUTANT ABC DLBCL ALONE AND IN COMBINATION WITH BTK INHIBITION

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Introduction: ABC DLBCL comprises approximately 45% of DLBCL and has a worse outcome with R-CHOP chemotherapy compared to GCB DLBCL. Activating mutations in MYD88 occur in 30-40% of ABC DLBCL; L265P, the most prevalent MYD88 mutation, causes constitutive assembly and activation of the Myddosome. IRAK4 kinase and scaffolding functions are essential for full signaling through the Myddosome to NFκB and MAPK pathways. Kymera Therapeutics is using a chemical knockdown strategy to develop heterobifunctional small molecule IRAK4 degraders, exemplified by KYM-001, for the treatment of MYD88-driven B cell malignancies.

Methods: IRAK4 in human PBMC, ABC DLBCL cell lines and tumor xenografts was quantified by immunoassays or targeted mass spectrometry. Cell viability and cell cycle were monitored by flow cytometry. Tumor xenograft studies were conducted by implanting human ABC DLBCL lines into immunocompromised mouse strains.

Results: KYM-001 led to potent E3 ligase-dependent degradation of IRAK4. Notably, KYM-001 more effectively inhibited TLR-activated Myddosome signaling compared to IRAK4 kinase inhibitors in human whole blood. Degradation was highly selective for IRAK4 vs >10,000 other detected proteins in the MYD88 L265P mutant ABC DLBCL line OCI-LY10. IRAK4 degradation by KYM-001 resulted in cell cycle inhibition and apoptosis within 72 h in MYD88-mutant ABC DLBCL.

Since mutations in MYD88 frequently co-occur with CD79 mutations in B-cell malignancies, we investigated the potential for combined activity of IRAK4 degradation with BTK or PI3Kδ inhibition. In the OCI-LY10 and TMD8 cell lines, which have activating mutations in both MYD88 and CD79B, BTK inhibition with ibrutinib or PI3Kδ inhibition with umbralisib both synergized with KYM-001 to induce cell death *in vitro*.

Oral dosing of KYM-001 showed dose-dependent antitumor activity in several mouse xenograft models of human MYD88-mutant ABC DLBCL at tolerated doses and schedules. In the OCI-LY10 model, tumor regression was associated with >80% degradation of IRAK4, establishing the pharmacodynamic effect required for maximal efficacy. Combination of KYM-001 with ibrutinib drove tumor regression in both OCI-LY10 and TMD8 at suboptimal doses of each agent. Hypothesis-driven combination studies with umbralisib and other drugs with activity in DLBCL, including lenalidomide, are in progress in MYD88-mutant DLBCL xenograft models.

Conclusions: KYM-001 is a first-in-class, potent, selective and orally active IRAK4 degrader that causes tumor regression in MYD88-mutant ABC-DLBCL models. Degradation of IRAK4 removes both the kinase and scaffolding functions of IRAK4, and may be superior to kinase inhibition alone. These data support clinical development of IRAK4 degraders as a promising new therapeutic opportunity for MYD88-driven lymphoma, both alone and in combination with inhibitors of complementary pathways.

Keywords: B-cell lymphoma; MYD88.

084

THE ANTIBODY-DRUG CONJUGATE (ADC) LONCASTUXIMAB TESIRINE (ADCT-402) TARGETING CD19 SHOWS STRONG *IN VITRO* ANTI-LYMPHOMA ACTIVITY BOTH AS SINGLE AGENTS AND IN COMBINATION

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Introduction: Loncastuximab tesirine (ADCT-402) is an anti-CD19 antibody-drug conjugate (ADC) conjugated via a protease cleavable linker to SG3199, a highly cytotoxic DNA minor groove cross-linking pyrrolobenzodiazepine dimer (PMID 29298756). ADCT-402 is in phase 2 as single agent for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) (NCT03589469) and in phase 1 in different combinations (NCT03684694 and NCT03685344). Here, we further assessed its preclinical activity as single agent and in combination with approved drugs in lymphoma cell lines.

Methods: MTT proliferation assay and IC50 calculation on cell lines exposed (96h) to increasing ADCT-402 concentrations. Pearson correlation (r): calculated for IC50s vs cell surface CD19 expression levels (absolute fluorescence quantitation with Quantum Simply Cellular microspheres; non-absolute, data from PMID 29298756) and vs RNA levels (Illumina HT-12 arrays and HTG EdgeSeq Oncology Biomarker Panel data from PMID 29066507). Synergy at 96h was assessed by Chou-Talalay combination index (CI) (synergism CI<0.9, additive CI=0.9-1.1, antagonism/no benefit CI> 1.1) on 2 activated B cell like (ABC) DLBCL (OCI-LY-3, TMD8) and 2 germinal center (GCB) DLBCL (VAL, WSU-DLCL2).

Results: Median ADCT-402 IC50 was 4 pM (95%C.I, 2-10 pM) in 48 B-cell lymphoma lines, and, as expected based on CD19 expression pattern, over 800 times higher in 9 T-cell lymphoma lines (3.5 nM; 95%C.I, 0.8-11 nM).

Focusing on B-cell lymphomas, ADCT-402 in vitro activity was correlated with its target expression measured both at cell surface protein level [(absolute quantitation, n=40, r -0.37 P 0.02; non-absolute quantitation, n=42, -0.48, P 0.001] and RNA level [(arrays, n=39, -0.69 P <0.001; HTG, n=31, -0.73 P 0.001]. In DLBCL, the presence of BCL2 and MYC translocations or TP53inactivation did not affect the sensitivity to ADCT-402.

ADCT-402 was then combined in GCB- and ABC- DLBCL cell lines with the BCL2 inhibitor venetoclax, the PIK3delta inhibitor idelalisib, the PIK3 inhibitor copanlisib, the proteasome inhibitor bortezomib (ABC only), the BTK inhibitor ibrutinib (ABC only), the chemotherapy agent bendamustine and with the PARP inhibitor olaparib. Synergism in all cell lines was achieved combining ADCT-402 with venetoclax and with idelalisib and in all but OCI-LY-3 with bendamustine. Synergism was observed in half of the cell lines tested with copanlisib (OCI-LY-3, VAL), ibrutinib, and olaparib (VAL, WSU-DLCL2). No advantage was seen adding bortezomib and lenalidomide to the ADCT-402 in the two ABC DLBCL (TMD8, OCI-LY-3).

Conclusion: The strong single agent in vitro anti-lymphoma activity of ADCT-402 correlated with its target expression and supports the currently on-going clinical studies in relapsed/refractory DLBCL. The novel combination data provide rational for further clinical development.

Keywords: CD19; diffuse large B-cell lymphoma (DLBCL); venetoclax.

FOCUS ON... SESSION: HIGH RISK LARGE B-CELL LYMPHOMAS

085
EBV+ CNS LYMPHOMAS HAVE A DISTINCTIVE TUMOR MICROENVIRONMENT AND GENETIC PROFILE, WHICH IS AMENABLE TO COMBINATION 3RD PARTY EBV-SPECIFIC CTL AND IBRUTINIB THERAPY

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Introduction: Primary CNS Lymphomas (PCNSL) with DLBCL histology in the immunosuppressed, e.g. after HIV (HIV+ PCNSL) or organ
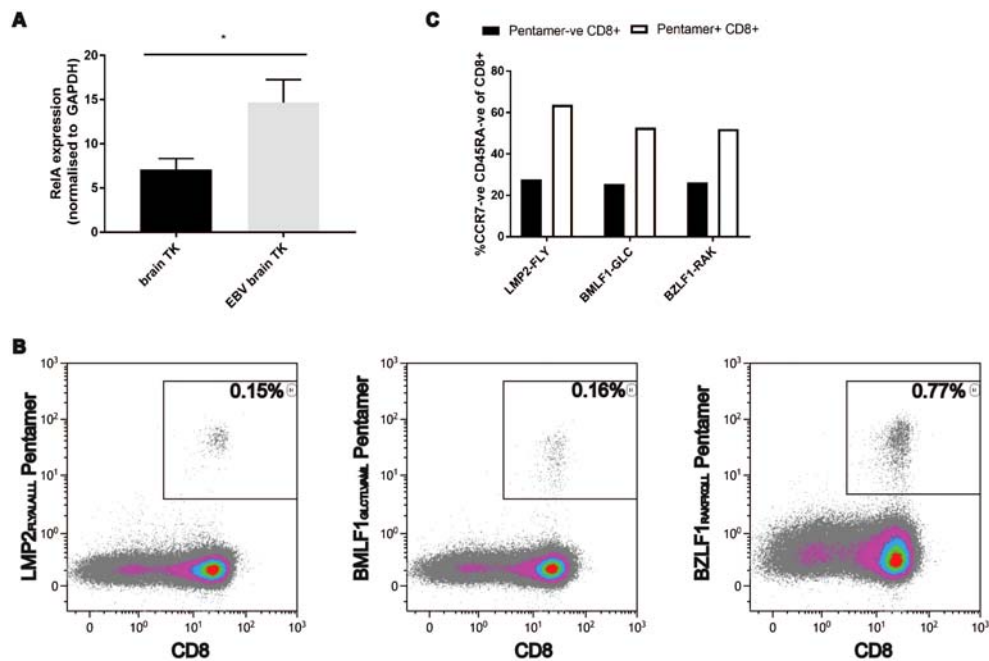
Fig 1. (A) NFκB signalling is significantly upregulated in a PCNSL line (brain TK) infected with EBV compared to the non-EBV infected brain TK (p<0.05). Data represent 3 independent experiments. **(B)** CD8 T cells specific to the EBV antigens present in the PCNSL tissue (LMP2-FLY, BMLF1-GLC and BZLF1-RAK) were detected in CD3+ CD8+ T cells in PBMC taken 1-2 hours post CTL infusion. Shown are representative FACS plots from a patient receiving 3rd Party CTL (matched for A2 and B8) for which the latent antigen LMP2-FLY and lytic antigens BMLF1-GLC and BZLF1-RAK were present at 3.7%, 11.7% and 12.9% of IFNγ+ CD3+ T cells, respectively, in the CTL product. **(C)** EBV antigen specific CD8 T cells were enriched in an effector memory phenotype (CCR7-ve CD45RA-ve) compared to the non-antigen specific CD8 T cells.

transplant (EBV+ PCNSL-PTLD: where anti-PD-1 is contraindicated), are characterized by dismal outcome and almost universal EBV positivity. However, incidence is low, biopsy material limited and immunogenetic characterization minimal. We provide detailed data (308 patients) comparing the genetic landscape and tumor microenvironment (TME) of EBV+ PCNSL-PTLD (22); HIV+ PCNSL (24); EBV- PCNSL (41); EBV- systemic (sy) DLBCL (199) and EBV+ syPTLD (22), which led to implementation of a rationally designed combination therapy.

Methods: Targeted sequencing, CNV analysis, nanoString (for immune checkpoints and effectors, and macrophage gene expression) and *in vitro* assays were used. Based on the findings, a novel regimen was administered to patients' refractory to or unsuitable for frontline therapy. Sequential imaging, pharmacokinetic (PK) and T cell assays were performed.

Results: Mutational burden was much lower in EBV+ lymphomas than EBV- lymphomas (p<0.0001). Notably, genetic aberrations in BCR-NFB were rarely observed in EBV+ PCNSL-PTLD and HIV+ PCNSL, and (unlike EBV- PCNSL) in these patients, *HLAI/II copy number loss was largely absent*. Mutations in CARD11 (which confers ibrutinib resistance) were also rare in EBV+ PCNSL-PTLD and HIV+ PCNSL. By nanoString analysis, EBV+ PCNSL-PTLD expressed higher levels of the immunosuppressive 'M2' macrophage marker CD163 and LAG3 and PD-L1/L2 (p<0.001), and high levels of EBV protein LMP1 (known to upregulate PD-L1/L2 and NFB). *In vitro* co-incubation experiments showed a PCNSL line upregulated CD163+ PD-L1/L2+ M2 polarized monocyte/macrophages relative to a systemic DLBCL line (≥7-fold, p<0.001), and EBV infection of a PCNSL line enhanced NFB activity (Fig 1A). Three immunosuppressed patients (2 frontline, 1 refractory, ages 30-70yrs) with EBV+ lymphoma (2 PCNSL, 1 CNS + systemic) were treated with ibrutinib (starting dose 560mg) and 3rd party partially HLA matched EBV specific CTL. PK confirmed therapeutic CSF levels, including a patient on haemodialysis. CD8 T cells specific for EBV antigens present in PCNSL were detectable post infusion and had an effector memory phenotype (Fig 1B-C). Microchimerism post infusion was confirmed by ultra-sensitive ddPCR. Toxicity was manageable and all 3 are alive (2CR, 1PR).

Conclusion: EBV+ CNSL in the immunosuppressed, have a tolerogenic TME with intact antigen presentation and expression of viral antigens, upregulated NFB signalling and absent CARD11 mutations. Results support combination strategies that cross the Blood Brain Barrier, to block NFB driven oncogenesis (ibrutinib), reconstitute EBV specific T cell immunity (3rd Party EBV specific CTL) and expand the TCR repertoire (ibrutinib). Findings led to an ALLG phase 1 clinical trial (ACTRN12618001541291).

086

YOUNG HIGH RISK PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA INCLUDING *BCL-2/MYC* DOUBLE HIT LYMPHOMAS BENEFIT FROM DOSE-DENSE IMMUNOCHEMOTHERAPY WITH EARLY CNS PROPHYLAXIS

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Introduction: Survival of patients with high-risk diffuse large B-cell lymphoma (DLBCL) is suboptimal, and the risk of central nervous system (CNS) progression is relatively high. We aimed to assess, whether a dose-dense immunochemotherapy approachwith early systemic CNS prophylaxis improves outcome and reduces the incidence of CNS events.

Methods: We conducted a Nordic Lymphoma Group phase II (NLG-LBC-05) trial during 2011-2014 in patients aged 18–64 years with untreated DLBCL including *BCL-2/MYC* double hit lymphomas, and an age-adjusted international prognostic index (aaIPI) 2-3 or site specific risk factors for CNS recurrence. Treatment consisted of two courses of high-dose methotrexate (HD-Mtx) in combination with biweekly rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP-14), followed by four courses of R-CHOP-14 with etoposide (R-CHOEP-14) and one course of high dose cytarabine with R (R-HD-AraC). In addition, liposomal AraC was administered intrathecally at courses 1, 3 and 5. Our co-primary endpoints were failure free survival and CNS progression rates.

Results: Of 143 enrolled patients, 139 patients were eligible with a median age of 56 (range 20-64). The majority of the patients had advanced stage (92%), elevated LDH (91%), more than one extranodal site, (67%) and B-symptoms (63%). Four (2.9%) patients developed AML/MDS. Treatment related death occurred in five (3.6%) patients. Of the 119 patients who underwent PET-CT, 91 (77%) achieved a metabolic CR, and 19 of 35 patients (21%) with CT-based CRu/PR were in metabolic CR according to PET-CT. Only one out of 15 biopsies (9%) from the PET+ lesions contained vital lymphoma.

At five years of median follow-up, failure free survival (FFS), overall survival (OS) and CNS progression rates were 74%, 84% and 2.3%, respectively. Deauville score 5, but not 4 at the end of treatment was associated with increased risk of progression and death. Treatment reduced the risk of progression compared to our previous NLG-LBC-04 trial, where systemic CNS prophylaxis was given after six courses of biweekly R-CHOEP (HR=0.493; 95% CI 0.312-0.780, p=0.003), and overcame the adverse impact of aaIPI3 and *BCL-2/MYC* double hit lymphomas on survival.

Conclusion: The results are encouraging with favorable survival rates, low toxic death rate and low number of CNS events.

Keywords: "double-hit" lymphomas; CNS prophylaxis; diffuse large B-cell lymphoma (DLBCL).

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SAFETY AND EFFICACY OF THE PD-L1 INHIBITOR DURVALUMAB WITH R-CHOP OR R²-CHOP IN SUBJECTS WITH PREVIOUSLY UNTREATED, HIGH-RISK DLBCL

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Introduction: We report the results of a phase 2, open-label study
(NCT03003520) of durvalumab (durva) in combination with R-CHOP
or R^2-CHOP (R-CHOP + lenalidomide) in previously untreated, high-
risk diffuse large B-cell lymphoma (DLBCL).

Methods: Subjects (≥18 years; ECOG 0–2) with previously untreated,
high/high-intermediate risk DLBCL (IPI ≥3/NCCN-IPI ≥4) were strati-
fied to durva + R-CHOP (Arm A, GCB DLBCL) or R^2-CHOP for 6–8
cycles (Arm B, ABC DLBCL) based on cell of origin identified by gene
expression followed by durva consolidation up to month 12 from start
of induction. After the US Food and Drug Administration placed clini-
cal holds on trials that include combination therapy with checkpoint
inhibitors and immunomodulatory agents, the study was revised to
include both ABC and GCB in Arm A (durva + R-CHOP). The primary
endpoint was complete response rate at the end of induction; second-
ary endpoints were rate of subjects continuing to consolidation,
safety, and response in biological subgroups.

Results: A total of 46 subjects were treated (safety; A/B, n=43/3);
median age, 62/66 y; male, 61%/67%; ECOG 2, 19%/33%; Ann Arbor
stage IV, 79%/33%; bulky disease: 49%/67%; double/triple-hit lym-
phoma, 30%/33%. As of Aug 2, 2018, 30/3 (A/B) had completed
induction therapy, and 19 subjects (A) were ongoing. Complete
response rate (95% confidence interval) at end of induction was
(A) 54% (37%–71%) and (B) 67% (9%–99%); 68%/67% (A/B) contin-
ued to consolidation therapy and were progression-free at month 12.
The safety profile was as expected for the components of the combi-
nation regimen with no new safety signals identified. Frequent
treatment-emergent adverse events (TEAEs; ≥25%; A+B) included
fatigue (61%), neutropenia (52%), peripheral sensory neuropathy
(50%), nausea (46%), diarrhea (28%); constipation, decreased appetite,
insomnia, pyrexia (24% each); and alopecia, dizziness, dyspnea, head-
ache, stomatitis (22% each). Grade 3/4 TEAEs occurred in 84%/100%
of subjects (A/B), and 3 subjects (2/1) died with no death related to
study treatment. Follow-up for efficacy and safety is ongoing.

Conclusions: Durva + R-CHOP combination therapy has an accept-
able safety profile and demonstrates encouraging response rates in
subjects with high-risk DLBCL including double-hit lymphoma.

Keywords: diffuse large B-cell lymphoma (DLBCL); PD-1L; R-CHOP.

088

INITIAL RESULTS OF A MULTICENTER PHASE 2 STUDY OF VENETOCLAX IN COMBINATION WITH DOSE-ADJUSTED R-EPOCH FOR PATIENTS WITH RICHTER'S SYNDROME (CRC-043)

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Introduction: Despite recent advances in CLL, the outcomes for Richter's Syndrome (RS) remain dismal. Complete response (CR) is observed only in about 20% of RS patients (pts) who receive chemoimmunotherapy such as dose-adjusted (da)-R-EPOCH, with short PFS/OS of <6 mo (Rogers et al., 2018). The oral Bcl-2 inhibitor venetoclax (ven) had a 43% response rate in RS (Davids et al., 2017). Here, we report for the first time on an ongoing study of ven + da-R-EPOCH in RS.

Methods: This is a single-arm, phase 2, investigator sponsored trial of ven + da-R-EPOCH for RS (NCT03054896) open in the CLL Research Consortium (CRC) at 3 US sites. We treated CLL pts with biopsy-confirmed DLBCL transformation with R-EPOCH for 1 cycle, then after count recovery with accelerated inpatient daily ven ramp-up (20/50/100/200/400 mg), then ven + da-R-EPOCH for up to 5 additional 21d cycles (ven 400 mg qd, d1-10 of each cycle). Responders then received alloHCT or daily ven 400 mg qd maintenance in 28d cycles. Response by Lugano criteria with PET/CT, toxicity by CTCAE v4.03.
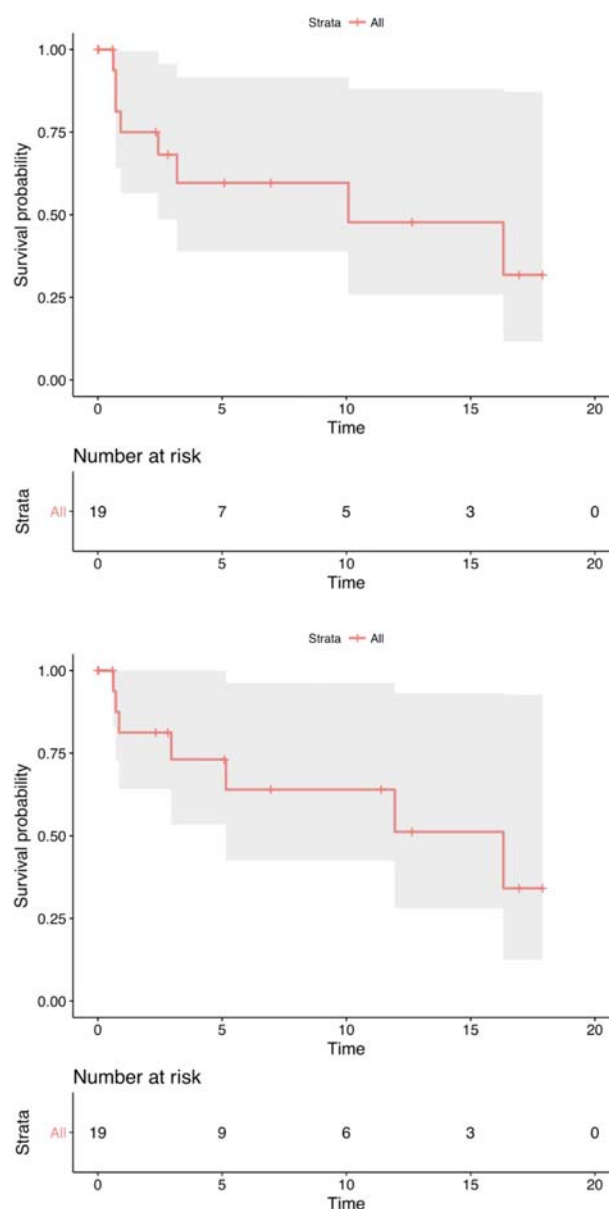
Results: As of 21 Feb 2019, 20 pts have been treated. Median age: 63 yrs (range 50-77), 33% del(17p), 43% complex karyotype, and 29% and 10% TP53 and NOTCH1 mutation, respectively. Median # prior CLL treatments 2 (range 0-5, prior ibrutinib (n=8), idelalisib (n=2), and ven (n=2); 5 pts no prior treatment). Median # ven + da-R-EPOCH cycles in this ongoing study is 3.5 (range 1-6), including 5 pts who recently enrolled. 4 pts had dose de-escalation of R-EPOCH and 1 pt had dose escalation. ≥Gr 3 heme toxicity included: neutropenia (45%), anemia (35%), thrombocytopenia (25%). ≥Gr 3 non-heme toxicities in ≥15% of pts: febrile neutropenia (20%), hypocalcemia and hypophosphatemia (15% each). No TLS occurred with daily ven ramp-up after 1 cycle of R-EPOCH. Infectious complications: 3 pts with sepsis during C1 of R-EPOCH (prior to starting ven) and 1 pt each with influenza A and norovirus while on combination therapy. 7 pts died, including 4 due to disease progression (2 during C1 before ven), and 1 each due to sepsis, sudden death, and GVHD post-alloHCT. 8 pts are not evaluable for efficacy of the combination (3 are still in C1, 4 had toxicity in C1 and never started ven, 1 pt withdrew in C1). Of the 12 evaluable pts who have started combination therapy, 9 responded (ORR 75%); 8/12 (67%) had CR, all of whom also had undetectable bone marrow MRD for CLL. 5 pts went to alloHCT, with pts still in CR now up to 1.5 yrs post-alloHCT. With a median follow-up of 3 mo (range 0-17.9), median PFS is 10 mo (Fig 1A), median OS is 16.3 mo (Fig 1B).

Conclusions: Our initial data suggest that ven + da-R-EPOCH is a feasible regimen to treat RS. Expected toxicities from intensive chemoimmunotherapy were seen, without significant additional toxicity from ven, including no TLS with daily ven ramp-up. The 67% CR and PFS/OS of 10/16.3 mo are favorable in the context of historical results. Accrual is ongoing, and updated results will be presented.

Keywords: DA-R-EPOCH; Richter's syndrome (RS); venetoclax.

089

IMPROVED OUTCOMES IN PATIENTS (PTS) WITH BCL2-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) TREATED WITH VENETOCLAX (VEN) PLUS R-CHOP:

RESULTS FROM THE PHASE 2 CAVALLI STUDY

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Introduction: BCL2 and BCL2 plus MYC overexpression, and coexisting *BCL2* and *MYC* translocation (double-hit [DH]) are associated with poor outcomes in DLBCL. Ven, a highly selective BCL2

Figure: PFS in the overall population and BCL2 IHC+ pts
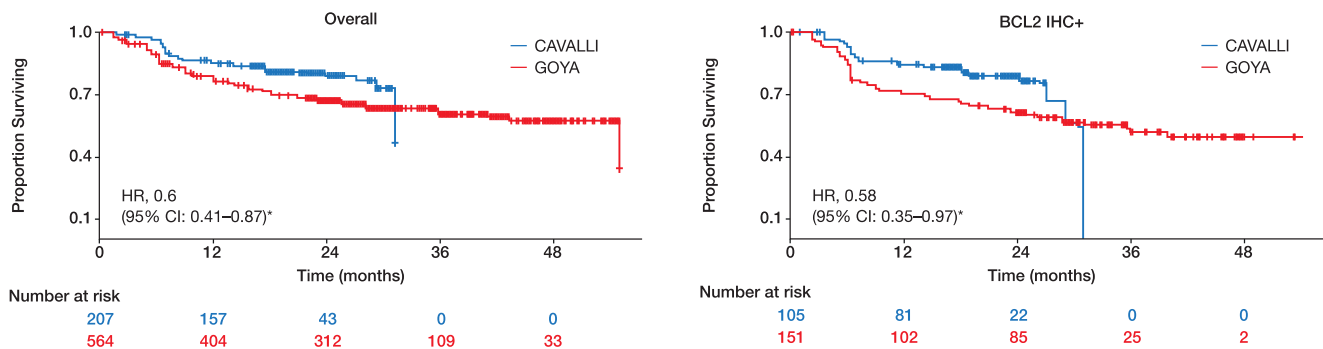
Median follow-up: CAVALLI, 22.3 months (data cut-off, Jul 13, 2018); GOYA, 29.6 months (data cut-off, Apr 29, 2016). *Covariates: age, sex, ECOG PS, BMI, IPI (high vs non-high), bulky disease (>7.5cm), disease stage (IV vs I-III), LDH, COO

Table: PET-CR at EOT across biomarker subgroups in CAVALLI and GOYA

| Pts | PET-CR rate | | | | Delta CR, |
| | CAVALLI | | GOYA | | |
	%	N	%	N	% (95% CI)
All	69	208	63	564	6 (0–13)
BCL2 IHC+	65	105	60	151	5 (0–14)
DE	67	81	61	124	6 (0–18)
BCL2 FISH+	70	40	48	59	23 (7–39)
DH	71	7	25	8	46 (37–56)

DE, double-expressor

inhibitor, may enhance the current standard regimen of rituximab (R) +CHOP chemotherapy. Phase (Ph) 1b of CAVALLI (NCT02055820) established Ven 800 mg on Days (D) 1–4, Cycle (C) 1 and D1–10, C2 –8 as the recommended Ph 2 dose combined with R-CHOP in first-line (1L) DLBCL. We report safety, efficacy and biomarker analyses of CAVALLI Ph2 (data cut-off, July 13 2018).

Methods: Eligible pts were ≥18 yrs old with 1L DLBCL, ECOG performance status ≤2 and IPI score 2–5. Oral Ven 800 mg was given on D1–4, C1 and D1–10, C2–8 combined with R (8 Cs) and CHOP (6–8 Cs); 21-day Cs. Primary endpoint was PET-complete response (CR) at end of treatment (EOT; modified Lugano criteria 2014). Secondary endpoints were PFS, OS and safety. The R-CHOP control arm of GOYA (564 pts, IPI 2–5) was used as a historical control. Factors affecting completion of 8 treatment Cs were assessed using multivariate analysis (MVA). Time-to-event endpoints were compared using adjusted Cox regression. Biomarker analyses included BCL2 and MYC immunohistochemistry (IHC), *BCL2 and MYC* translocations by fluorescence *in situ* hybridization (FISH) and cell of origin (COO) by NanoString.

Results: Of 211 pts enrolled in CAVALLI, 208 received any treatment and were analyzed for efficacy and safety. Baseline characteristics for CAVALLI vs GOYA were similar, but more Ann Arbor Stage IV (65% vs 47%) and BCL2 IHC+ (58% vs 49%) pts enrolled in CAVALLI. In the overall population, EOT PET-CR rates were similar (CAVALLI, 69%; GOYA, 63%), while PET-CR rates were higher in CAVALLI for *BCL2* FISH+ and DH pts (**Table**). PFS was improved in the overall and BCL2 IHC+ populations vs GOYA (**Figure**); PFS benefit in BCL2 IHC+ pts was observed across ABC and GCB COO subtypes. There was also evidence of OS benefit vs GOYA; HR 0.7, 95% CI 0.43–1.1 (overall), HR 0.7, 95% CI 0.35–1.2 (BCL2 IHC+). Grade

3–4 AEs occurred in 86% of pts in CAVALLI vs 66% in GOYA, mainly cytopenia, febrile neutropenia (FN) and infection. A trend towards lower neutropenia and FN/infection incidence was seen in pts receiving G-CSF prophylaxis. On MVA, age <60 yrs was the only factor to predict completion of 8 treatment Cs (p=0.002). There were 4 fatal AEs (2%) in CAVALLI vs 30 (5%) in GOYA, but follow-up was longer in GOYA (29.6 vs 22.3 months). The high AE rate in CAVALLI led to dose interruptions/discontinuations; 61% of pts received >90% relative dose intensity (RDI) of Ven; 73% received >90% RDI for cyclophosphamide and doxorubicin. The RDI of chemotherapy was similar in GOYA.

Conclusions: Adding Ven to R-CHOP improved efficacy in BCL2 IHC+ 1L DLBCL pts versus matched GOYA controls. A higher rate of cytopenia, FN and infection was observed in CAVALLI vs GOYA; however, there was no increase in risk of death and the RDI of chemotherapy was similar.

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CD19-DIRECTED CAR T CELL THERAPY (CTL019) FOR RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL AND FOLLICULAR LYMPHOMAS: FOUR YEAR OUTCOMES

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Introduction: Anti-CD19 chimeric antigen receptor-modified T cell therapy (CAR T) is indicated for diffuse large B-cell, high grade B-cell, transformed follicular and primary mediastinal B-cell lymphomas. To date, the longest reported median follow-up is 19 months (mo) for tisagenlecleucel (Schuster et al., Blood 2018) and 24 mo for axicabtagene ciloleucel (Locke et al., Lancet Oncol 2019). We previously reported two-year follow-up for 28 patients (pts) who received CTL019 (Schuster et al., NEJM 2017). We now report our four-year experience with CAR T (CTL019, now tisagenlecleucel).
Methods: We enrolled pts with relapsed/refractory CD19+ diffuse large B cell lymphoma (DLBCL) or follicular lymphoma (FL) from February 2014 to September 2017 on a single institution trial of CTL019. Eligible pts had no curative treatment options, prognosis of <2 years survival, and less than complete response to last therapy. Pts underwent leukapheresis, bridging therapy at the investigator's discretion, then lymphodepleting therapy followed by a single dose of 1e8 to 5e8 CTL019 cells. Outcomes were analyzed as of February 25, 2019.
Results: Median follow-up is now 49 mos. 49 pts, 24 with DLBCL and 15 with FL, were enrolled. Median age at enrollment was 56 years (range: 25 – 77) and 41% were women. The median number of prior therapies was 5 (range: 2-10). Median ECOG PS was 1 (range: 0-1). 78% had advanced stage lymphoma at enrollment. 38 pts received the protocol-specified dose of CTL019. 46% of DLBCL pts and 71% of FL pts had a complete response (CR). For DLBCL, median progression free survival (PFS) is 5.8 mo (95%CI: 1.6 mo-NE), median overall survival (OS) 22.2 mo (95%CI: 10.9-45.6mo). For FL, median PFS is 32.4 mo (95%CI: 3.5 mo-NE), median OS was not reached (95%CI: 27.2mo-NE). For responding patients with DLBCL or FL, median response duration (RD) was not reached at 49 mo follow-up (DLBCL RD, 95%CI: 3.2 mo-NE; FL RD, 95%CI: 9.5 mo-NE). The patient with the longest follow-up remains in remission from DLBCL (double-hit) at 60 mo after CTL019. Of 21 pts in CR, only 6 received IVIG for recurrent or severe infections and 2 pts developed late myelodysplasia.

Response Duration

DLBCL ----- FL
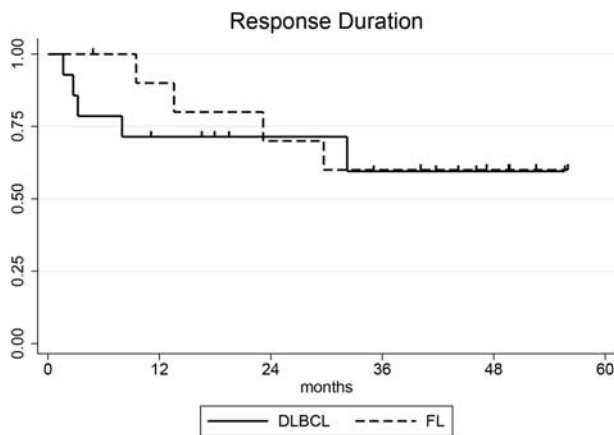
Four patients relapsed more than 12 months from CTL019 infusion (PFS: 16.3 mo, 26.2 mo, 32.4 mo, 35.2 mo). At the time of these late relapses, CAR T cells persisted by quantitative PCR and there was no loss of CD19 expression by tumor cells.

Conclusions: At a median follow-up over four years, we demonstrate that a single infusion of CTL019 provides durable remissions in pts with relapsed/refractory DLBCL and FL. This is the longest follow-up for CTL019 therapy for relapsed/refractory B-cell lymphomas reported to date.

Keywords: diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); T-cells.

SESSION 6 – LYMPHOMA PATHOLOGY

091
DIAGNOSIS AND CLASSIFICATION ASSISTANCE FROM LYMPHOMA MICROSCOPIC IMAGES USING DEEP LEARNING

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The microscopic diagnosis of lymphoma remains challenging. Recent data from our group within the French (nationwide) Lymphopath network shows that 20% of diagnoses are inaccurate, with direct impact on patient care[1]. Another difficulty is the subclassification of lymphoma subtypes to predict therapeutic response and clinical behaviour. For these, molecular techniques, not affordable for all pathology departments, have become critical. Currently, automated solutions that could help with diagnostic decisions or histological grading are lacking, and it is unreasonable to expect pathologists to be experts on rare tumours if they only see a few cases per year. Digital microscopy offers unique features which are not available in conventional optical microscopy[2] and allows automated image analysis and quantification by using computer vision and, in particular, deep learning (DL) approaches[3]. Using DL on digital slides we tried to address two questions: 1) Can we train deep neural network (CNN) to distinguish follicular lymphoma (FL) from either follicular hyperplasia or other small B-cell lymphoma subtypes on hematoxylin-eosin stained lymph node digital slides? 2) Can CNN separate germinal center from non germinal center diffuse large B-cell lymphoma (DLBCL) the same way? Patch extraction or patch coordinated extraction was carried with different architectures (Residual Net, GoogleNet, VG-GNet) of whole slides images. A home designed neural network classification was also performed on 125x125pixel non-overlapping tiles of a whole slide image extracted at very low resolution (pyramid level 5 ó 7,68μm/pixel). The latter classifier was a fairly simple CNN architecture. It stacked three blocks of Convolution-MaxPooling with respectively 32, 64 and 128 filters, followed by two 1024-unit fully connected layers. Output of the network is a 2-unit layer with softmax activation to produce class probabilities. As to the diagnosis of FL, the accuracy of our method is superior to that of non expert pathologists, with an average area under the curve (AUC) of 0.95. Furthermore, we trained CNNs to predict GC and non GC phenotype of DLBCL previously determined with Hans' algorithm with an average AUC of 0.882. Our models were validated on independent series of biopsies (training, testing and validation sets) and provide quite similar accuracy irrespective of the architecture we used. These findings strongly suggest that DL models, even on very simple CNNs, can assist pathologists in the diagnosis and subclassification of lymphoma as recently shown is subsets of lung cancers[3].

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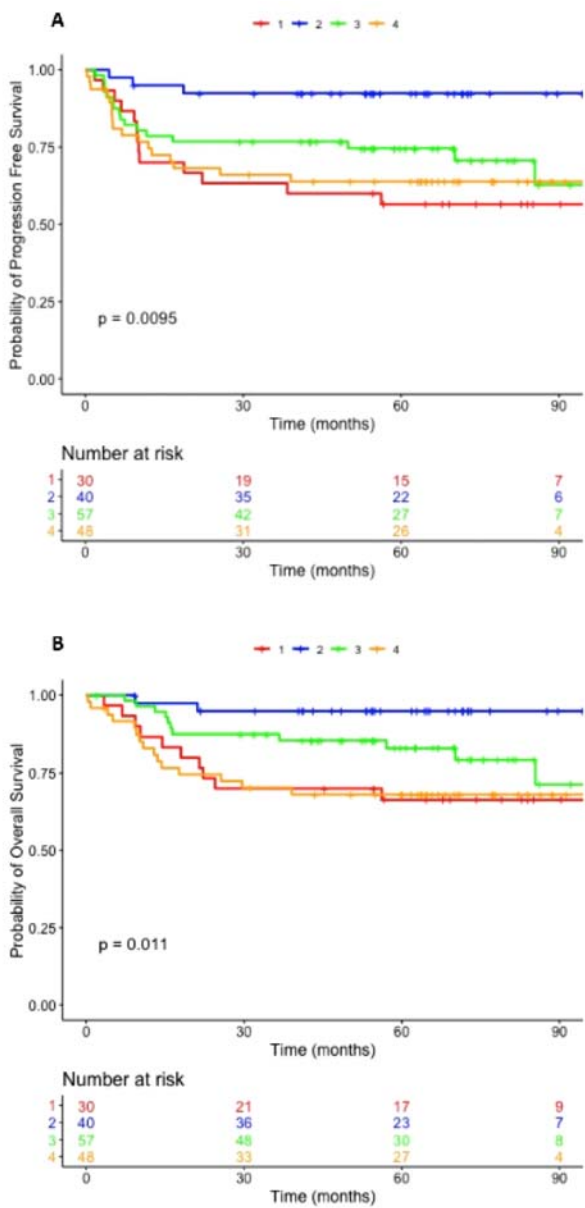
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Keywords: diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL).

092
INTEGRATING TUMOR- AND MICROENVIRONMENT-REFLECTING GENES IN A UNIQUE AND ROUTINE-APPLICABLE ASSAY FOR ACCURATE RISK PREDICTION IN DLBCL

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C

Progression Free Survival

Variable p-value		N	HR
Clusters Reference	2	40	
0.003	1	30	6.35 (1.89, 23.35)
0.026	3	57	4.06 (1.18, 13.97)
0.008	4	48	5.28 (1.54, 18.11)
IPI Reference	Intermediate-High	28	
0.208	High	47	1.47 (0.81, 2.68)

D

Overall Survival

Variable p-value		N	HR
Clusters Reference	2	40	
0.01	1	30	7.37 (1.61, 33.66)
0.09	3	57	3.73 (0.83, 16.89)
0.01	4	48	6.59 (1.50, 28.99)
IPI Reference	Intermediate-High	28	
0.07	High	47	1.84 (0.94, 3.57)

Legend to the Figure

Figure 1 - Prognostic subgroups of DLBCL based on integration of COO + TME gene expression. Kaplan–Meier curves of PFS (A) and OS (B) and show that patients in clusters 1 and 4 have significantly shorter OS and PFS than those in cluster 2 and 3. Tables report data of multivariate analysis for PFS (C) and OS (D), adjusted for clusters and IPI.

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Introduction: Sequencing studies identified mutational drivers in diffuse large B cell lymphoma (DLBCL), capturing outcome difference in previously unrecognized patient subsets. However, the lack of routine-applicable genomic approaches limits translation of such information to the clinic. Currently, molecular prognostication consists in cell of origin (COO) determination by the Lymph2Cx NanoString assay. We recently developed two independent prognostic signatures incorporating genes reflecting the COO, the activation of pivotal oncogenic pathways, and the composition of tumor microenvironment (TME). We aimed this study at examining the prognostic strength of a model combining the performance of each signature and developing a comprehensive NanoString assay rapidly transferable to the clinic for prognostic purposes.

Methods: The expression of the genes was measured by the NanoString nCounter Analysis System using customized probes for 73 genes, including 15 COO genes, 6 additional oncogenic genes (MYC, BCL-2, NFKBIA, PIK3CA, PTEN, STAT3), 47 TME genes, and 5 housekeeping genes. The analysis was performed on 175 newly diagnosed, nodal DLBCL, homogeneously selected from the RHDS0305 and DLCL04 trials. Patients had comparable clinical features and double-hit cases were excluded. Heatmaps, Kaplan–Meier survival estimator, tree-based survival model, and P values were produced by 'R' statistical software. Long-rank test was used to compare overall survival (OS) and progression-free survival (PFS) among groups. Multivariate analysis was constructed through the Cox proportional hazards regression model.

Results: Based on the expression of the COO and oncogenic genes, a tree-based survival model stratified patients into subgroups showing significantly different survival, with MYC, BCL-2 and NFKBIA holding additional prognostic power based on their high (H) or low (L) expression. The TME panel identified a lower gene expression cluster (C3) with significantly worse survival than those at intermediate (C2) and higher expression (C1). Integration of COO-, TME-, and MYC/BCL-2/NFKBIA-based data produced a new survival risk categorization of DLBCL. The high-risk category, showing the worst outcomes, includes ABC/H/C1-2-3, ABC/L/C3 and GCB/H/C3 cases; the intermediate-risk category comprises ABC/L/C2, GCB/H or L/C1 and UN/H or L/C1 or C3 cases; whereas the low-risk category contains GCB/H or L/C2, GCB/L/C3, UN/H/C1 or C2 and UN/L/C2 or C3 cases, with longer survival. An unsupervised clustering analysis was also performed based on the expression of the entire 74-gene panel and stratified cases into four clusters with significantly different OS (p=0.011) and PFS (p=0.009). In particular, cluster 1 and 4 showed significantly worse survival than cluster 2 and 3 (Figure 1), and a multivariate Cox analysis indicated that the prognostic performance of the panel overcomes the IPI score. Finally, such model was also validated "in silico" using a gene expression profiling dataset (GSE10846 and GSE98588) relative to a cohort of 146 DLBCL patients uniformly selected according to R-CHOP treatment.

Conclusions: This study supports the idea that DLBCL heterogeneity involves both tumor and TME, resulting in diverse transcriptional subtypes with distinct outcomes and, putatively, diverse biology. Our integrative analysis prompts the development of a new survival categorization outperforming current prognostic risk-assessment. Moreover, the applicability of a unique Nanostring-based assay to routine biopsies may facilitate the stratification of patients at diagnosis and their inclusion in future trials exploring novel therapeutic approaches.

Keywords: diffuse large B-cell lymphoma (DLBCL); gene expression profile (GEP); prognostic indices.

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CONCORDANCE BETWEEN IMMUNOHISTOCHEMISTRY AND GENE EXPRESSION PROFILING SUBTYPING FOR DIFFUSE LARGE B-CELL LYMPHOMA IN THE PHASE 3 PHOENIX TRIAL

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Introduction: Diffuse large B-cell lymphoma (DLBCL) can be classified based on cell-of-origin (COO) into germinal center B-cell–like (GCB), activated B-cell–like (ABC), and unclassified (UNC) subtypes by gene expression profiling (GEP), and GCB and non-GCB subtypes by immunohistochemistry (IHC). In the phase 3 PHOENIX trial (NCT01855750) that enrolled untreated patients (pts) with non-GCB DLBCL by IHC, ibrutinib (ibr) + R-CHOP did not improve event-free survival (EFS) vs placebo (pbo) + R-CHOP in the intent-to-treat (ITT,

Figure. (A) Number of Calls by IHC or GEP; (B) Overall, Non-GCB, and GCB Concordance (%); (C) EFS in ABC and GCB DLBCL in Patients < 60 Years

A

		All Patients		Age < 60 Years		Age ≥ 60 Years	
		EdgeSeq COO GEP					
		GCB	Non-GCB	GCB	Non-GCB	GCB	Non-GCB
Hans-based IHC	GCB	119	75	68	32	51	43
	Non-GCB	182	735	91	279	91	456

B

C

	p Value	HR	95% CI
ABC	0.0348	0.561	0.326-0.967
GCB	0.4119	0.644	0.223-1.858

Legend: ABC pbo + R-CHOP; GCB pbo + R-CHOP; ABC ibr + R-CHOP; GCB ibr + R-CHOP

Patients at risk

	0	10	20	30	40	50
ABC pbo + R-CHOP	115	84	76	49	16	0
GCB pbo + R-CHOP	40	33	33	22	5	0
ABC ibr + R-CHOP	90	72	63	43	14	0
GCB ibr + R-CHOP	30	26	24	12	5	0

non-GCB by IHC) or ABC (by GEP) populations; however, an increase in EFS and overall survival with ibr was seen in pts < 60 years (yrs), but not in pts ≥ 60 yrs due to increased toxicity in elderly pts. This work aimed to determine the concordance between IHC and GEP for DLBCL subtyping and outcomes related to subtypes.

Methods: Baseline paraffin-embedded, formalin-fixed tissue samples were used to confirm non-GCB DLBCL by Hans-based IHC (Dako pharmDx™ kit) at a central laboratory. Available tumor samples were retrospectively analyzed for ABC subtype by GEP (HTG EdgeSeq DLBCL COO Assay). The concordance was evaluated by comparing non-GCB calls by IHC with ABC + UNC by GEP or GCB calls between IHC and GEP. Survival outcomes were compared between GEP subtypes in each arm and across study arms.

Results: In all screened pts, 1111/1336 (83.2%) samples also provided evaluable GEP results; the concordance between GEP and IHC was 80.2% for non-GCB and 61.3% for GCB calls, resulting in an overall concordance of 76.9% (Figure), with 73.7% of non-GCB samples (by IHC) being identified as ABC by GEP. In pts < 60 yrs (n = 506), the concordance for non-GCB, GCB, and overall was 76.1%, 67.6%, and 74.3% respectively. In 747 evaluable samples from 838 enrolled non-GCB pts, 75.9% were ABC by GEP; 17.2% were GCB and 6.8% UNC.

In both ITT and age < 60 yrs populations, EFS rate in GCB DLBCL by GEP was higher vs ABC in either arm, although the difference was not statistically significant and even smaller in the ibr arm. When comparing the two arms in the ITT population, EFS was similar between arms regardless of COO. In pts < 60 yrs, EFS was better with the addition of ibr to R-CHOP in ABC pts (HR 0.56 [95% CI, 0.33-0.98]; p = 0.0348; Figure); the difference between arms was not statistically significant in GCB (HR 0.64 [95% CI, 0.22-1.86; p = 0.4119) or UNC (HR 1.12 [95% CI, 0.22-5.97]) subtypes as numbers were small.

Conclusions: The overall concordance between non-GCB by Hans-based IHC and GEP using the EdgeSeq DLBCL COO Assay was 74-77% in the ITT population and age-related subgroups, even with centralized testing. Although only 75.9% of enrolled pts were the ABC subtype, the addition of ibr improved outcomes in pts < 60 yrs in both IHC-based non-GCB or GEP-based ABC DLBCL.

Keywords: gene expression profile (GEP); ibrutinib; immunohistochemistry (IHC).

Disclosures: Balasubramanian, S: Employment Leadership Position: *Janssen, Pharmacyclics*; Stock Ownership: *Pharmacyclics, Johnson & Johnson, Gilead Sciences, Celgene, Vertex, AbbVie.* **Wang, S:** Employment Leadership Position: *Janssen*; Stock Ownership: *Janssen.* **Major,**

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LONGITUDINAL ANALYSES OF DIAGNOSTIC-RELAPSE BIOPSIES OF DIFFUSE LARGE B CELL LYMPHOMA SUGGEST THAT RELAPSE IS MEDIATED BY DISTINCT MECHANISMS IN ABC AND GCB LYMPHOMA

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Introduction: Although diffuse large B cell lymphoma (DLBCL) can be cured using immuno-chemotherapy, 40% of patients experience relapse or refractory disease. Large-scale profiling studies have mainly focused on DLBCL at diagnosis with a limited number of longitudinal studies and no compelling biomarkers linked to relapse identified. To address this, we utilized a multifaceted approach integrating transcriptomic and intratumoral T-cell repertoire analyses in paired diagnostic/relapse tumors to enable identification of signaling pathways and microenvironmental changes underlying disease relapse.

Methods: We retrospectively collected archival paired diagnostic/relapse tumor biopsies from 38 *de novo* DLBCL patients (stage I-IV, 38-89 years old) treated with rituximab-based immuno-chemotherapy. We performed gene expression profiling (GEP) and T-cell repertoire analysis using the Ion AmpliSeq Transcriptome Kit and TCR-β sequencing (immunoSEQ), respectively. Cell-of-origin (COO) classification was performed by the Lymph2Cx assay on NanoString to distinguish activated B-cell-like (ABC) and germinal center B-cell-like (GCB) subtypes.

Results: COO remained stable from diagnosis to relapse in >90% of pairs. In examples where we observed a switch in COO between diagnosis/relapse, targeted-seq analysis revealed some shared mutations suggesting that relapse tumors originated from a common ancestral clone. Our global GEP of 17 ABC-ABC and 11 GCB-GCB pairs identified 163 and 136 genes that were differentially expressed in ABC and GCB relapse tumors relative to their matched diagnostic biopsies respectively, with minimal overlap. Gene set enrichment analysis showed that ABC and GCB relapses are potentially mediated via different mechanisms, with tumor growth and proliferation signatures enriched in ABC relapse, compared with adaptive immunity-related signatures accompanying GCB progression. In parallel, we assessed the dynamics of the T-cell repertoire in paired biopsies observing a

reduction in T-cell fraction upon relapse that was most pronounced in ABC pairs and was positively correlated with changes in CD8^{+} T cells. Furthermore, we noted a decrease in T-cell clonal diversity that was independent of COO at relapse with evidence for significant T-cell specific clonal expansion.

Conclusions: The nature of the biological mechanisms responsible for DLBCL relapse has remained fairly elusive that may be inherent to the diagnostic tumor or acquired/enriched at disease relapse. Gene expression profiling of a series of DLBCL tumor pairs, resolved changes in gene expression that support distinct mechanisms of lymphoma relapse, based on a patient's COO, that parallel changes in the overall T-cell composition of the tumor microenvironment.

Keywords: diffuse large B-cell lymphoma (DLBCL); gene expression profile (GEP); T-cells.

Disclosures: Korfi, K: Consultant Advisory Role: *Roche.* **Rule, S:** Consultant Advisory Role: *Celgene, Sunesis, Astrazeneca, Napp, Pharmacyclics, TG Therapeutics, Kite, Gilead, Roche, Janssen;* Honoraria: *Celgene, Sunesis, Astrazeneca, Pharmacyclics, TG Therapeutics, Gilead, Roche, Janssen;* Research Funding: *Roche, Janssen;* Other Remuneration: *Roche, Janssen.* **Davies, A:** Consultant Advisory Role: *Roche, Kite, Celgene, Acerta Pharma, MorphoSys, BioInvent;* Honoraria: *Roche, Celgene, Kite, Janssen;* Research Funding: *Roche, Acerta Pharma, Celgene, Gilead, Karyopharm, GSK;* Other Remuneration: *Roche, Celgene.* **Gribben, J:** Honoraria: *Janssen, Acerta, Celgene;* Research Funding: *Janssen, Acerta, Celgene.* **Johnson, P:** Consultant Advisory Role: *Janssen;* Honoraria: *Bristol-Myers Squibb, Takeda, Novartis, Celgene, Janssen, Epizyme, Boeringher Ingelheim, Kite, Genmab, Incyte;* Research Funding: *Janssen, Epizyme.* **Fitzgibbon, J:** Consultant Advisory Role: *Epizyme;* Honoraria: *Gilead;* Research Funding: *Epizyme.*

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DEFINING BURKITT-LIKE LYMPHOMA WITH 11Q ABERRATION IN A SPECIALISED UK HAEMATOPATHOLOGY DIAGNOSTIC SERVICE

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Introduction: A subset of aggressive lymphomas that have similar clinicopathological features to sporadic Burkitt lymphoma (BL), lack the hallmark *MYC* gene rearrangement that typifies BL, and are characterised by deregulation of genes on 11q[1]. Burkitt-like lymphoma with 11q aberration (BLL-11q) is a provisional entity in the 2016 WHO classification of lymphoid malignancies[2], but its demonstration in routine practice has been limited because copy number variation using SNPa, the technique originally used to describe the abnormality, is not widely implemented for FFPE, and FISH probes to detect the simultaneous gain/loss of 11q23/11q24 are not widely available. Furthermore, there is little consensus how to treat these patients, although good outcomes based on BL-directed therapies have been reported[3].

Methods: We retrospectively identified potential patients with 11q aberration from the HMRN population[4] and REMoDL-B trial (ISRCTN51837425) based on their reported gene expression profile (GEP)[1] using existing Illumina WG-DASL data. FISH probes were designed to cover the minimally gained and deleted regions on 11q using Cytocell MyProbes®, and these were validated against known positive cases[2]. Of cases identified by GEP, 7/14 had an 11q aberration using FISH. In 2017 we incorporated this FISH assay into routine practice; testing samples with morphologic and immunophenotypic features that were similar to BL, but where *MYC* rearrangement was lacking, we identified a further 5/36 patients.

Results: In line with previous reports[3,5], BLL-11q was found to be molecularly and phenotypically distinct from BL; all cases investigated to date using targeted Sanger sequencing lacked ID3/TCF3 mutations (6/6) that are associated with BL[6], and the majority had molecular high grade (MHG)[7] GEP (5/7) and most expressed LMO2 (3/5). This is in contrast to BL (n=138), which had high levels of ID3 (50/126) and TCF3 mutations (14/124), mostly lacked LMO2 (20/27), but also showed MHG GEP (51/65). Double hit lymphomas (DHL) had low incidence of TCF3/ID3 mutations (5/45), were mostly MHG (12/19) and mostly expressed LMO2 (6/7).

All patients treated with BL directed therapies (3/3) are alive with a median follow-up of 5 (0.4-7.6) years. Of those who received R-CHOP (n=4) or RB-CHOP (n=3), one relapsed after 8 months, one elderly patient died (10 months), and 5 remain in complete remission with a median follow-up of 2.7 (1.1-7.5) years.

Conclusions: These findings suggest that not all BLL-11q patients require high dose therapy, supporting the hypothesis that their biological features are more similar to DLBCL than BL. Further investigation into the molecular landscape of these patients is underway. Taken with data from the other molecular subgroups (DHL/MHG) this will direct standardised treatment decision making in routine practice, and help define when alternative therapies are warranted.

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GENOME WIDE-ANALYSIS OF T(14;18)-NEGATIVE FOLLICULAR LYMPHOMA

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Introduction: Follicular lymphoma (FL) represents about 20% of adult non-Hodgkin lymphomas (NHL) in Western countries. About 90% of FL carries the t(14;18)(q32;q21) translocation resulting in BCL2 over-expression. FL lacking the t(14;18) translocation and BCL2 protein expression are less well characterized and their pathogenesis remains largely unknown. The aim of this study was to genetically characterize a group of bona-fide t(14;18)-negative FL.

Methods: We analyzed 44 t(14;18)-negative, BCL2 protein negative, nodal FL cases grade 1-3A. PCR IGH clonality and FISH analysis for *BCL2, BCL6* and IGH breaks were performed. The NGS analysis was based on a custom AmpliSeq panel (*TNFRSF14, KMT2D, EP300, MEF2B, FOXO1, GNA13, HIST1H1B-E, CREBBP, EZH2, TNFAIP3, STAT6, SOCS1, XPO1, NOTCH2, MYD88, MAP2K1* and *NOTCH2 [3`UTR]*). The Ion Torrent sequencing platform was used. Copy number analyses were performed using the Oncoscan FFPE assay. Gains and losses and copy number neutral loss of heterozygosity (CNN-LOH) regions were evaluated and visually inspected using Nexus Bio-discovery version 9.0 software.

Results: All cases were IGH monoclonal and lacked a *BCL2* translocation by FISH analysis. *BCL6* translocation was identified in 7 cases (7/41; 17%). The genome-wide analysis showed that the 44 cases could be divided into 3 clusters based on their genetic changes. In the

Cluster 1
Some diffuse growth pattern
Mainly female
Mainly Inguinal presentation
CREBBP mut-16p CNNLOH
TNFRSF14 mut-1p CNNLOH
STAT6 mut

Cluster 2
Follicular growth pattern
Mainly female
Some inguinal presentation
CREBBP, TNFRSF14 and STAT6 mut
No 1p/ 16p CNNLOH

Cluster 3
Follicular growth pattern
Both male/female
No inguinal presentation
Lack of CREBBP mut
1p/ 16p deletion

first cluster there were 15 cases characterized by 1p and/or 16p CNN-LOH (100%). *CREBBP* and *STAT6* were the most frequently mutated genes (67%), followed by *TNFRSF14* (62%). Clinically, there was a female predominance (12/15; 80%), and inguinal presentation (10/15; 67%) with a frequent diffuse growth pattern (6/15; 40%). The second cluster comprised 14 cases without 1p or 16p CNN-LOH but 5 cases showed 1p deletion. *CREBBP* was the most frequently mutated gene (77%) followed by *STAT6* (57%), *KMT2D* (50%), *TNFRSF14* (43%) and *EZH2* (36%) mutations. Clinically, there was a female predominance (9/14; 64%), some inguinal presentation (6/13; 46%) but diffuse growth pattern was rare (3 cases). In the third cluster there were 15 cases characterized by low number of genetic alterations. *CREBBP* was not mutated and CNN-LOH was not identified. Clinically, no sex predilection and rare inguinal presentation was observed. The *BCL6* translocated cases were equally distributed among the three groups.

Conclusions: *BCL2*-negative FLs are genetically and clinically a heterogeneous disease. Three different genetic profiles were identified that correlated with some clinical features. Groups 1 and 2 had in common the frequent occurrence of *STAT6* and CREBBP mutations; however, they differed in the extent of 1p and 16p CNN-LOH and deletions. Group 3 showed low mutational level and different clinical features. *MAP2K1* mutations were not identified in any of the cases indicating that *BCL2*-negative FL and pediatric-type FL are two different entities.

Keywords: follicular lymphoma (FL).

SESSION 7 – HODGKIN LYMPHOMA

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STAGE I-II NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA IN THE MODERN ERA: A MULTI-INSTITUTIONAL EXPERIENCE OF ADULT PATIENTS BY ILROG

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Introduction: Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an uncommon subtype of HL; the optimal management of stage I-II remains undefined.

Methods: We conducted a multi-center retrospective study including patients (pts) ≥16 years (yr) with CD20+ stage I-II NLPHL diagnosed from 1995-2018. Management included observation after excision, single agent rituximab (R), chemotherapy (CT), radiation therapy (RT), and combined modality therapy (CMT=RT+systemic therapy). Primary outcomes were progression-free survival (PFS, by clinical, radiographic or pathologic progression) and overall survival (OS). Outcomes were measured with the Kaplan-Meier method with uni- and multivariable analyses (MVA) conducted with Cox regression.

Results: We identified 437 pts with stage I-II NLPHL with median age 38 yr (range, 16-90) and median follow up of 5 yr (interquartile range=2.0-8.2). The majority were male (n=307 [70%]), had stage I (n=241 [55%]), ECOG 0-1 (n=366 [84%]), and were staged by PET-CT (n=295 [68%]). The 5-yr PFS and OS were 86.7% and 97.6%, respectively. 5-yr PFS by treatment were: 89.7% for RT (n=199 [46%], median dose 36 Gy), 92.5% for CMT (n=160 [37%]), 69.9% for CT

At risk				
CMT	160	77	31	9	2
RT	199	93	42	15	3
CT	37	10	3	1	0
R	12	2	1	0	0
Obs	29	6	2	0	0
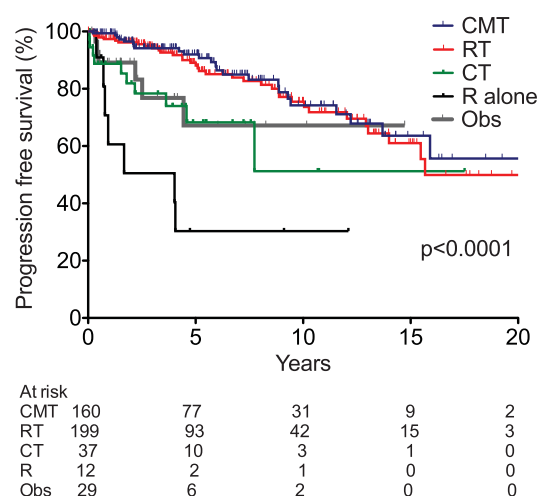
(n=37 [8%]), 92.9% for observation (n=29 [7%]), and 33.3% for R (n=12 [3%]). CT only regimens were ABVD (n=27, 3 with R), R-CHOP (n=9), and R-COMP (n=1). CMT systemic therapies were ABVD (n=116, 19 with R), R-CHOP (n=24), R (n=15), MOPP (n=3), BEACOPPesc (n=1), and CVP (n=1). On univariable analysis, stage II (p=0.008), age (continuous, p=0.004), R alone (p=0.0005), and omission of RT (p=0.0001) were associated with worse PFS. There was no difference in PFS for pts with stage II NLPHL who received RT vs CMT (p=0.88). For RT alone group, RT volume (extended-field n=28 [14%], involved-field n=114 [57%], involved-site n=51 [26%], unknown n=6 [3%]) was not associated with PFS (p=0.77). On MVA, age (p=0.02) and omission of RT (p=0.002) remained associated with worse PFS. After adjusting for age and stage, treatment type was not associated with OS. A subset had immunoarchitectural pattern (IAP) available (n=206, 47.1%), and those with variant pattern (C-F n=43) had significantly worse PFS (p=0.03). 5-yr PFS for pts with IAP C-F receiving CMT (n=18) vs. RT (n=14), was 100% vs 78.6%, respectively (p=0.18). 14 pts (3.2%) experienced large cell transformation. 16 pts (3.7%) had a second cancer: n=14 outside RT field, n=2 within RT field (5 and 10-yr post-RT), n=2 no RT.

Conclusions: OS for pts with stage I-II NLPHL is excellent and did not differ based on treatment after adjusting for age and stage. There was no PFS benefit for pts with stage II NLPHL receiving CMT over RT alone although there was a suggestion that pts with IAP C-F may benefit from CMT. PFS was superior among pts who received RT as a component of initial therapy.

Keywords: nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).

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NIVOLUMAB PLUS DOXORUBICIN, VINBLASTINE AND DACARBAZINE FOR NEWLY DIAGNOSED ADVANCED-STAGE CLASSICAL HODGKIN LYMPHOMA: CHECKMATE 205 COHORT D 2-YEAR FOLLOW-UP

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Introduction: Up to 30% of patients (pts) with advanced-stage (AS) classical Hodgkin lymphoma (cHL) are not cured by current front-line therapies (Tx). High expression of programmed death-1 (PD-1) ligands in these pts, associated with frequent genetic alterations at chromosome 9p24.1 in Hodgkin Reed–Sternberg cells, supports the investigation of front-line PD-1 blockade in cHL. Promising activity and acceptable safety were reported in newly diagnosed pts with AS cHL treated with nivolumab, an anti–PD-1 immune checkpoint inhibitor monoclonal antibody, followed by nivolumab plus doxorubicin, vinblastine and dacarbazine (N-AVD) at a 9-mo follow-up of CheckMate 205 Cohort D (NCT02181738). Here, we report the efficacy and safety of this cohort in a 2-y extended follow-up, including Deauville assessment of tumor response.

Methods: Pts ≥ 18 y of age with newly diagnosed AS cHL (stage IIB with unfavorable risk factors, III, or IV) received 4 doses of nivolumab monotherapy (240 mg IV every 2 weeks) followed by N-AVD combination Tx for 6 cycles (12 doses). Primary endpoint was safety; secondary endpoints included complete remission (CR) rate per independent review committee (IRC) at end of study Tx (EOT) using 2007 International Working Group criteria. Complete metabolic response (CMR) was defined as a Deauville score of ≤ 3 (PET negative) in a post hoc analysis

PFS per investigator

12 mo: 86%
18 mo: 86%
21 mo: 83%

Patients at risk: 51 49 48 47 41 39 38 36
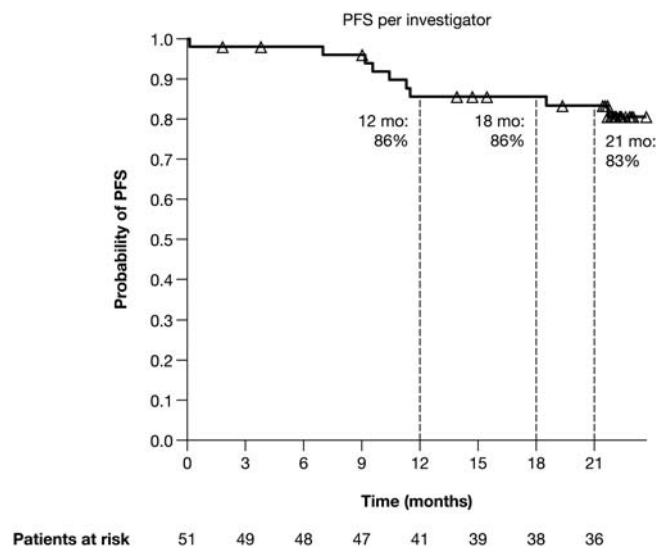
by IRC. Overall survival (OS) and modified progression-free survival (mPFS; time to progression, death, or subsequent Tx) were exploratory endpoints. PFS was a post hoc analysis.

Results: Fifty-one pts were treated (median age 37 y); minimum follow-up was 24.4 mo at data cut-off. Other baseline characteristics have been previously described (Ramchandren R et al. EHA 2018). Monotherapy was completed by 49/51 (96%) pts, combination Tx by 45/50 (90%); 48 pts entered follow-up. After 2 combination cycles, CR rate was 51% per IRC (71% CMR) and 71% per investigator; at EOT, CR rate was 69% (75% CMR) per IRC and 80% per investigator. At 21 mo, mPFS rate per investigator was 80% (95% CI, 66–89) and PFS rate per investigator was 83% (95% CI, 69–91; **Figure**). Overall, 30 (59%) pts experienced grade (G) 3–4 TRAEs, most commonly neutropenia in 21 (41%). The most common G 3–4 immune-mediated AE was hepatitis (2 pts, 4%). No G 5 TRAEs occurred ≤ 30 d from last dose; 2 deaths were reported during the extended follow-up: 1 pt (aged 68 y) died 38 d after last dose due to study drug toxicity; another (aged 85 y) died 451 d after last dose due to disease progression.

Conclusions: With extended follow-up, nivolumab followed by N-AVD demonstrated a 21-mo PFS rate of 83% per investigator, a high metabolic response rate with 75% CMR at EOT per IRC, with no new safety signals. Incorporation of Deauville assessment improved the concordance of CR between IRC- and investigator-assessed responses. Nivolumab followed by N-AVD provides a promising alternative Tx option in newly diagnosed AS cHL.

Keywords: classical Hodgkin lymphoma (cHL); nivolumab; PD-1.

Disclosures: Ansell, S: Honoraria: *WebMD, Research to Practice*; Research Funding: *Affimed Therapeutics (Inst), Bristol-Myers Squibb (Inst), Merck (Inst), Regeneron (Inst), Seattle Genetics (Inst), Trillium Therapeutics (Inst), Pfizer (Inst)*. **Ramchandren, R:** Consultant Advisory Role: *Bristol-Myers Squibb, Seattle Genetics*; Research Funding: *Merck, Pharmacyclics, Janssen*. **Domingo-Domènech, E:** Honoraria: *Bristol-Myers Squibb, Takeda*; Other Remuneration: *Travel, Accommodations, Expenses: Bristol-Myers Squibb, Roche, Takeda*. **Rueda, A:** Consultant Advisory Role: *Bristol-Myers Squibb, Merck, MSD, Novartis, Roche, Takeda*; Honoraria: *Bristol-Myers Squibb, Merck, MSD, Roche*. **Trněný, M:** Consultant Advisory Role: *AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Gilead Sciences, Incyte, Janssen, MorphoSys, Roche, Takeda*; Honoraria: *AbbVie, Amgen, Bristol-Myers Squibb, Gilead Sciences, Incyte, Janssen, MorphoSys, Roche, Takeda*; Other Remuneration: *Travel, Accommodations, Expenses: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Roche, Takeda*. **Feldman, T:** Consultant Advisory Role: *Bristol-Myers Squibb, Seattle Genetics*; Honoraria: *Takeda*; Research Funding: *Portola (Inst), Seattle Genetics (Inst)*; Other Remuneration: *Celgene, Pharmacyclics, Seattle Genetics, KITE, Johnson and Johnson, Janssen*. **Lee, H:** Employment Leadership Position: *MD Anderson Cancer Center*; Consultant Advisory Role: *Bristol-Myers Squibb*; Honoraria: *Bristol-Myers Squibb*; Research Funding: *Bristol-Myers Squibb, Celgene, Oncternal*. **Provencio, M:** Consultant Advisory Role: *AbbVie, Bristol-Myers Squibb, Merck Sharp & Dohme, Takeda, Roche, Novartis, Pfizer*; Honoraria: *Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Boerhinger*; Research Funding: *Roche, Boerhinger, Bristol-Myers Squibb*. **Cohen, J:** Consultant Advisory Role: *AbbVie, Celgene, Genentech, Pharmacyclics, Seattle Genetics*; Research Funding: *American Society of Hematology, Bristol-Myers Squibb, Lam Therapeutics, Lymphoma Research Foundation, Novartis, Seattle Genetics, Takeda, Unum Therapeutics*. **Savage, K:** Consultant Advisory Role: *AbbVie, Bristol-Myers Squibb, Merck, Seattle Genetics, Servier, Verastem*; Honoraria: *Bristol-Myers Squibb, Merck, Seattle Genetics, Takeda*; Research Funding: *Roche (Inst)*. **Willenbacher, W:** Consultant Advisory Role: *Bristol-Myers Squibb, Takeda*; Honoraria: *Bristol-Myers Squibb, Takeda*; Research Funding: *Bristol-Myers Squibb, Takeda*. **Sumbul, A:** Employment Leadership Position: *Bristol-Myers Squibb*. **Sacchi, M:** Employment Leadership Position: *Bristol-Myers Squibb*. **Armand, P:** Consultant Advisory Role: *Affimed Therapeutics, Bristol-Myers Squibb, Infinity Pharmaceuticals, Merck, Pfizer, Adaptive*; Research Funding: *Affimed Therapeutics (Inst), Bristol-Myers Squibb (Inst), Merck (Inst), Otsuka (Inst), Pfizer (Inst), Roche (Inst), Sequenta (Inst), Sigma Tau (Inst), Tensha Therapeutics (Inst), Adaptive (inst)*; Other Remuneration: *Travel, Accommodations, Expenses: Genmab*.

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CONSOLIDATION RADIOTHERAPY COULD BE OMITTED IN ADVANCED HODGKIN LYMPHOMA WITH LARGE NODAL MASS IN COMPLETE METABOLIC RESPONSE AFTER ABVD. FINAL ANALYSIS OF THE RANDOMIZED HD0607 TRIAL

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N at risk

	0	1	2	3	4	5	6	7	8	9	10
NFT	148	143	136	133	116	94	62	38	16	5	
RT	148	144	141	136	121	101	66	49	24	9	3
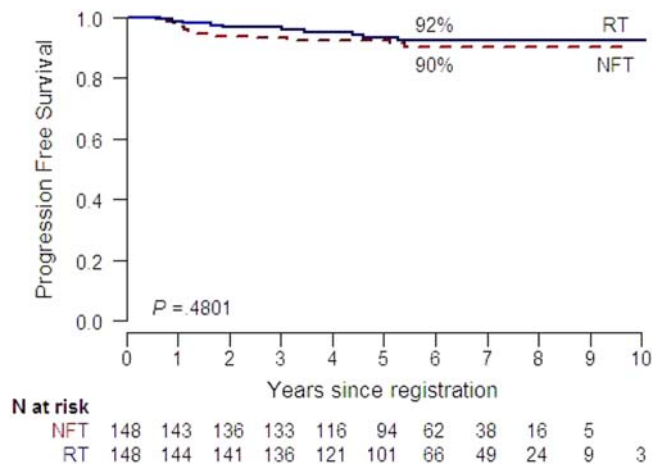
Introduction: Consolidation Radiotherapy (cRT) was originally proposed for ABVD-treated advanced stage Hodgkin Lymphoma (aHL) presenting with bulky or a residual mass (RM) after ABVD. However, very few published data exist on the role of cRT on RM in patients (pts) with a negative end-of treatment PET (EoT-PET) after ABVD.

Methods: In the HD0607 clinical trial (Gallamini JCO 2018) aHL pts (stage IIB-IVB) were treated with 2 ABVD courses, followed by an interim PET (PET-2). PET-2 positive pts were randomized to 4 BEACOPP escalated + 4 BEACOPP baseline cycles ± rituximab before each cycle. PET-2 negative pts were treated with 4 more ABVD and a EoT-PET was performed afterwards. PET-2 and EoT-PET negative pts were randomized to either cRT on the sites where a large nodal mass (LNM) was detected at baseline, or no further therapy (NFT). LNM was defined as single or a conglomerated nodal mass with the largest diameter ≥ 5 cm in baseline CT.

Results: After ABVD, 47/630 (7%) PET2 negative pts with a positive EoT-PET, 27/630 off study pts for disease progression or consent withdrawal and 260 pts without LNM were not suitable for the random, while 296 were randomized to cRT (148) or NFT (148). In this pts cohort the largest diameter of LNM was 5-7 cm in101 (34%) 8-10 cm in 96 (32%), while a classical bulky (diameter >10 cm) was detected in 99 (33%) pts. Prognostic factors, age, sex, stage, IPS, Performance status, extra-nodal sites, bulky disease were well balanced between the two cohorts. In pts presenting with one (265) or more (31) LNM, the most common nodal region was mediastinum (82%), followed by cervical (14%), abdominal (6%) or axillary (3%) regions. A post-ABVD RM was detected in 260 (88%) of 296 pts presenting with a LNM and in 92/99 pts with classical bulky. The median dose of RT was 30.6 (24.0-113.6) Gy, by involved field (88%) involved node (1%) or involved site (11%) technique. After a median follow-up of 5.9 (0.5-10) years the 6-year PFS for RT versus NFT in an intention to treat analysis was 92% (95% CI, 88-97%) versus 90% (95% CI, 85-95%) p = .48 (Figure) and a 6-year OS 99% (95% CI, 97-100%) versus 98% (95% CI, 96-100%), respectively. When the analysis was limited to patients with a classical bulky lesion, the 6-year PFS was 89% (95% CI, 81-99%) for consolidation RT and 86% (95% CI, 77-96%) for NFT (p = .53). The 6-year PFS of the 260 non-randomized pts without

LNM at baseline, was 92% (95% CI, 88-95%). When the analysis was limited to those with RM, the relapse rate of patients treated or not with cRT was 7% versus 9%, with a 6-year PFS of 93% (95% CI, 88 to 97%) versus 89% (95% CI, 84% to 95%) (P = .41).

Conclusions: cRT could be safely omitted in aHL pts presenting with a LNM and both a negative PET-2 and EoT-PET, irrespective from the LNM size. As in more than 80% of the pts the site of LNM at baseline was in mediastinum, this could translate in a significant reduction of late-onset treatment related mortality for secondary tumours and coronary arterial disease.

Keywords: ABVD; classical Hodgkin lymphoma (cHL); positron emission tomography (PET).

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COST-EFFECTIVENESS AND COST-UTILITY ANALYSIS OF MULTIPLE TREATMENT STRATEGIES USING ABVD AND/OR BEACOPP IN THE TREATMENT OF ADVANCED-STAGE HODGKIN LYMPHOMA

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Background: There remains clinical equipoise over the best initial treatment strategy for advanced-stage Hodgkin lymphoma. Recent PET-adapted trials (RATHL, HD18, AHL2011) have tried to balance the trade-off that occurs with an inferior progression-free survival in the ABVD strategy, but higher rates of hematologic toxicity, infertility, and second malignancy in the BEACOPP strategy. The overall lifetime cost of each strategy remains unknown, especially costs which incorporate therapies for relapsed disease including brentuximab consolidation after autologous stem cell transplant and palliative therapy with nivolumab, and associated health state utilities.

Methods: We developed a Markov decision analytic model to compare the life expectancy, quality-adjusted life expectancy (QALYs), and direct costs with varying upfront treatment regimens for a

TABLE 1 20-year life expectancy, quality adjusted life years (QALYs) and direct costs for multiple initial treatment strategies for advanced-stage Hodgkin lymphoma

Regimen	Life expectancy	QALYs	Direct costs
ABVD	12.5 years	12.1 years	$94,152
BEACOPP (including HD18)	14.2 years	12.8 years	$72,203
RATHL	14.5 years	13.2 years	$59,247
Echelon-1 (A-AVD)	13.8 years	12.7 years	$165,294
AHL2011	14.9 years	13.4 years	$58,136
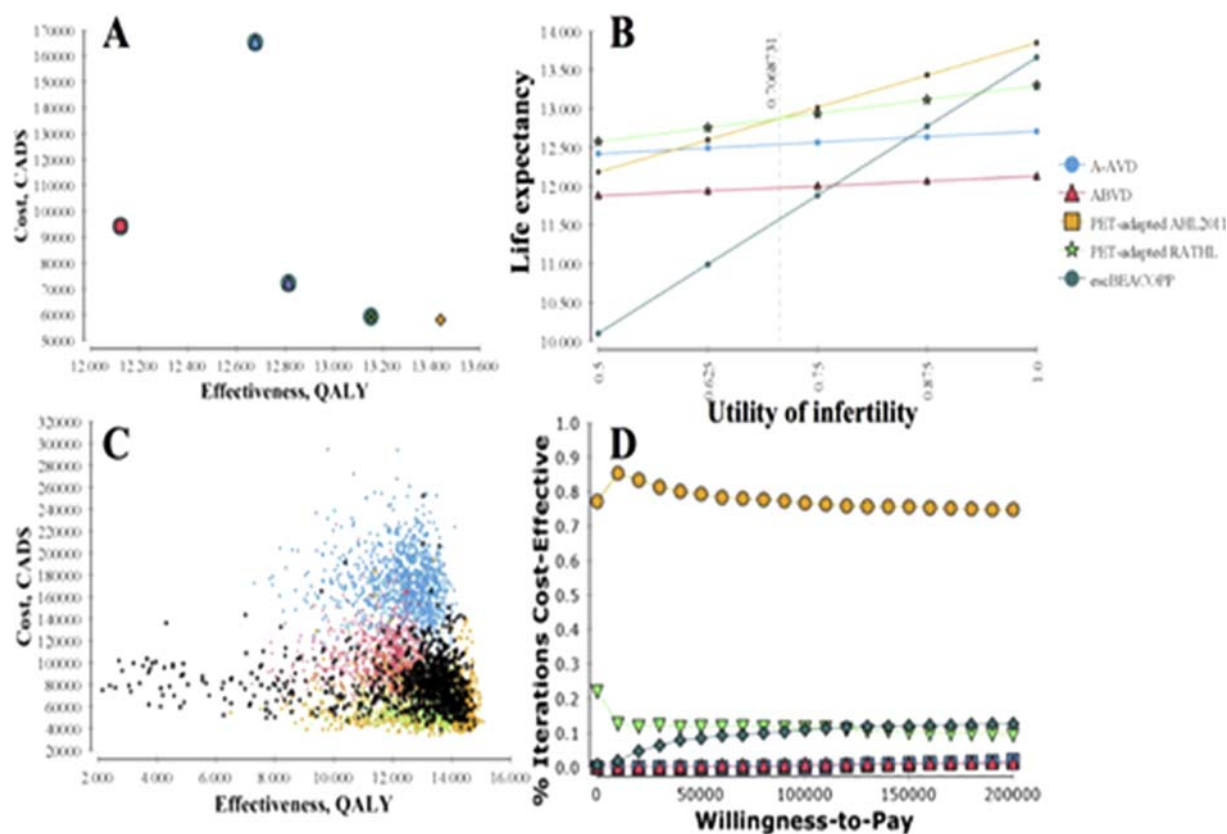
hypothetical cohort of transplant-eligible patients with newly-diagnosed advanced-stage Hodgkin lymphoma. A 20-year time horizon was used. Baseline probability estimates and utilities were derived from a systematic review of published studies (i.e. HD2000, Viviani, EORTC, HD15, HD18, RATHL, AHL2011, Echelon-1). A Canadian public health payer's perspective was considered and costs are presented in 2018 Canadian dollars. All costs and benefits were discounted by 1.5%. Sensitivity analyses were performed for key variables.

Results: See Table 1 for results of the 20-year model. In the base-case analysis, the AHL2011 protocol was associated with both cost-savings and improved quality-adjusted outcomes over all other treatment strategies (Figure 1A). Sensitivity analyses demonstrated that the model was robust to key variables including probability of treatment-related mortality, probability of death from secondary malignancy, and probability of infertility secondary to BEACOPP. The threshold utility of infertility was found to be 0.71 (Figure 1B). Probabilistic sensitivity analyses (10,000 simulations) were performed (Figure 1C). For the WTP threshold of $100,000, AHL2011 was the dominant strategy 73% of the time (Figure 1D).

Conclusions: The preferred treatment strategy for patients with newly diagnosed advanced-stage Hodgkin lymphoma is the AHL2011 PET-adapted regimen. This strategy maximizes life expectancy, quality-adjusted life years, and is the most cost-effective strategy, accounting for increased rates of hematologic toxicity, secondary malignancy, and infertility caused by exposure to at least 2 cycles of BEACOPP.

SESSION 8 – FOLLICULAR LYMPHOMA

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PROGNOSTIC IMPLICATIONS OF THE MICROENVIRONMENT IN FOLLICULAR LYMPHOMA UNDER RITUXIMAB AND RITUXIMAB+LENALIDOMIDE THERAPY. A TRANSLATIONAL STUDY OF THE SAKK35/10 TRIAL

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Treatment group Rituximab — PD1 below cut-off / PD1 above cut-off

Treatment group Rituximab+Lenalidomide — PD1 below cut-off0 / PD1 above cut-off

Treatment group Rituximab — GATA3 below cut-off / GATA3 above cut-off

Treatment group Rituximab+Lenalidomide — GATA3 below cut-off / GATA3 above cut-off
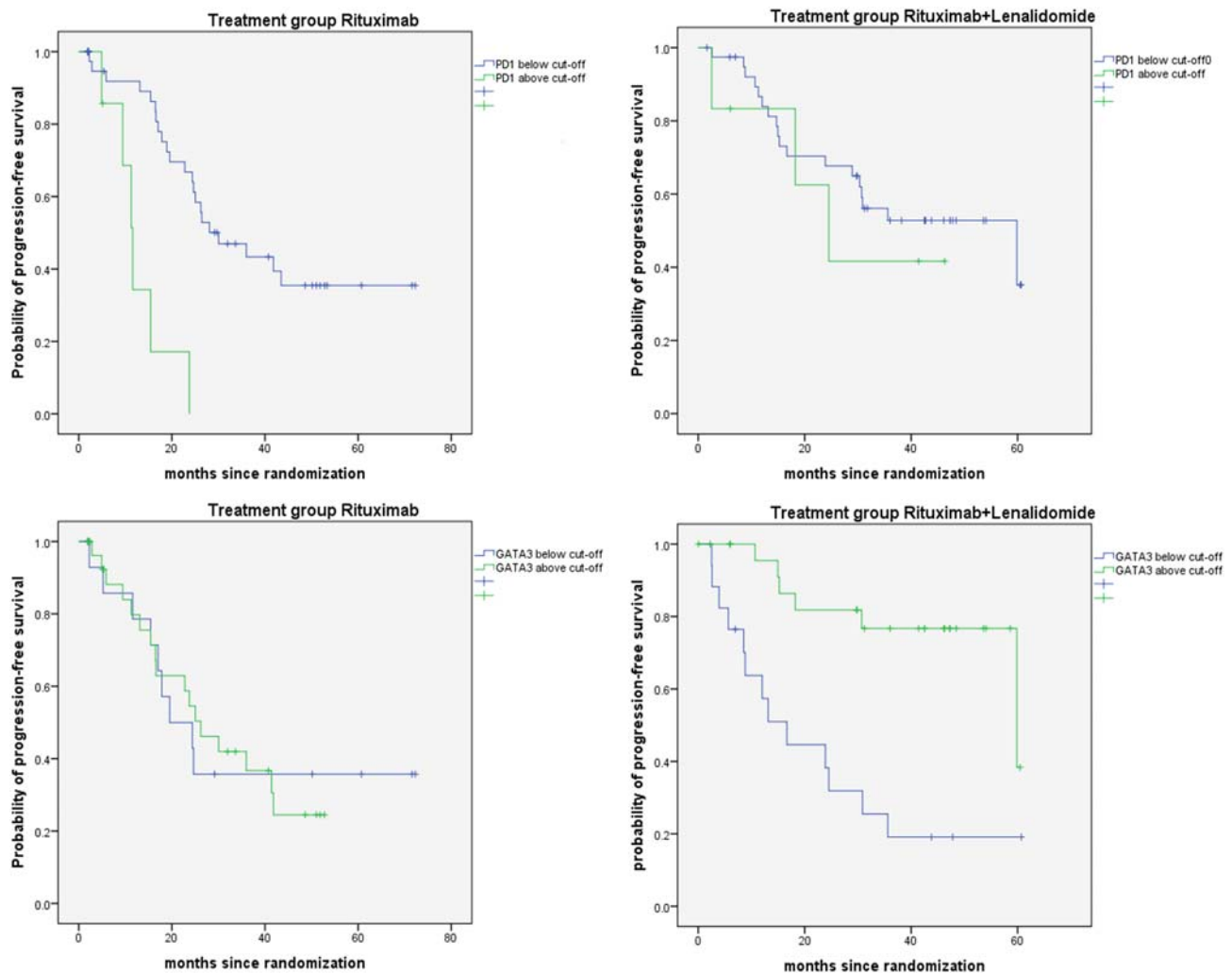
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Introduction: Follicular lymphoma (FL) constitutes a significant disease proportion of lymphomas and is prone to relapsing after therapy. Lately, new therapeutic approaches beyond conventional chemotherapy have emerged focusing on the interplay between lymphoma cells and the surrounding reactive cells of the microenvironment.

Methods: Here we report the immunophenotypic investigation of the microenvironment of a clinically well characterized cohort (study SAKK35/10) including 135 evaluable treatment naïve FL patients in need of treatment, who have been treated with either rituximab (R) only or a combination of rituximab and the immunomodulatory drug lenalidomide (R/R).

Results: After initial large-scale phenotypic (BCL2, CD3, CD4, CD5, CD8, CD21, CD68, CD163, Cereblon, c-MYC, FoxP3, GATA3, Granzyme B, PD1, PDL1, Perforin, pSTAT5, t-BET, TIA1) analysis of 34 tissue-microarrayed biopsies focusing on prognostic impact, several promising markers for T-cell subgroups were selected for further evaluation of the whole cohort of 135 patients. High ratio of CD4- to CD8-positive T cells (p=0.009) and an increased amount of PD1-positive T-cells (p=0.007) were associated with inferior progression free survival (PFS) in the whole cohort. These findings remained significant in the multivariate statistical analysis taking into consideration FLIPI and stage of the disease. Interestingly, the prognostic impact of PD1-positive T-cells and the CD4/CD8 ratio was lost in the subgroup treated with lenalidomide. In the latter group, high amounts of GATA3-positive TH2-equivalents was associated with better PFS (p<0.001) and also overall survival (p=0.030), see also the attached figure for survival curves related to PD1- and GATA3 positive T-cells of the two treatment groups.

Conclusions: Based on data from this prospective clinical trial on FL, we identified tumor microenvironmental characteristics which may allow prognostic stratification with respect to immuno- and combined

immuno- and immunomodulatory therapy. Our analysis implicates that lenalidomide might help to overcome the adverse prognostic implication of higher amounts of regulatory T cells in the microenvironment of follicular lymphoma and that it may have particularly favorable effects in cases with higher amounts of TH2-equivalents as demonstrated by GATA3-positive T-cells. Additional analysis by gene expression profiling of the microenvironment may further contribute to a better understanding of this so far still underestimated component of follicular lymphoma.

Keywords: follicular lymphoma (FL); immunohistochemistry (IHC); lenalidomide.

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DECIPHERING THE CONTRIBUTION OF MACROPHAGES TO FOLLICULAR LYMPHOMA PATHOGENESIS: NEW INSIGHTS INTO THERAPY

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Introduction: Follicular Lymphoma (FL) represents the paradigm of a lymphoid neoplasia depending on microenvironment. Early studies by gene expression profiling (GEP) in FL tumor biopsies found that those cases enriched in certain genes expressed mainly in macrophages and Follicular Dendritic Cells (FDC) showed an inferior outcome (Dave et al, NEJM 2004). In the current study we have analyzed the three-way crosstalk of FL-FDC-M2, the correlation of CSF1-R expression, the M-CSF receptor essential for macrophage differentiation, with FL clinical data, and explored the potential antitumor effect of FL-M2 disruption using a specific CSF1-R inhibitor in combination with anti-B cell therapies.

Figure 1
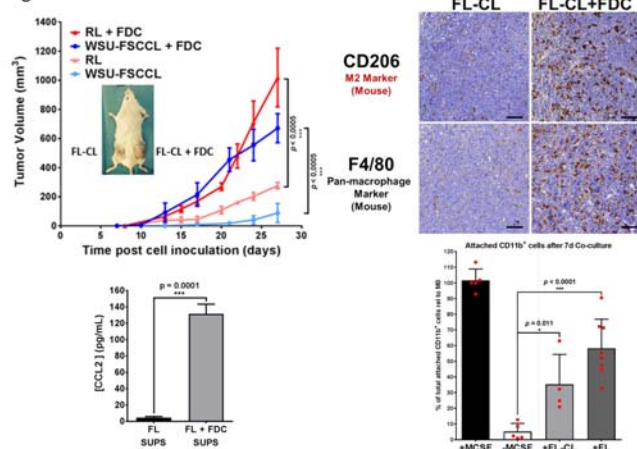
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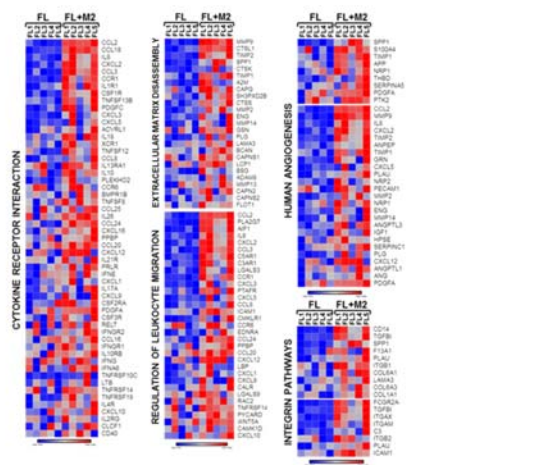
Figure 3
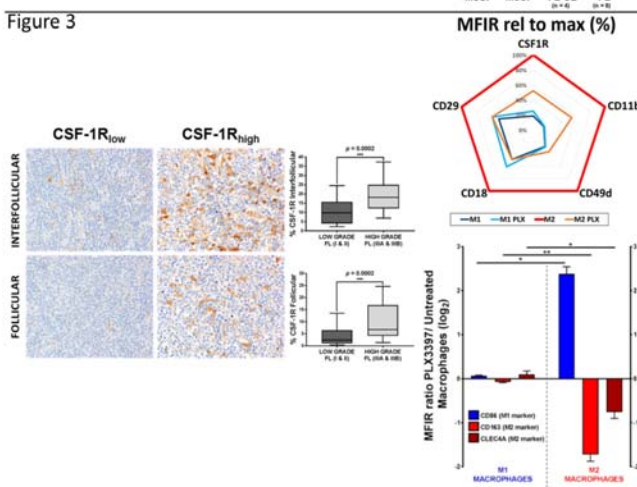
Figure 4
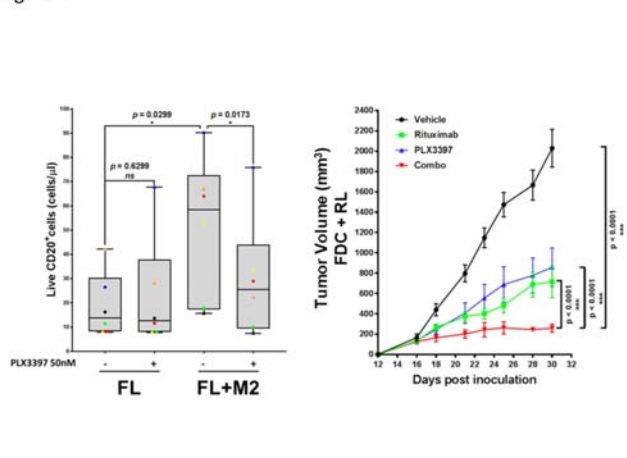
Methods: Primary FL cells (n=5) were co-culture (48h) with M2 macrophages at 4:1 ratio, generated from peripheral blood monocytes of healthy donors (100ng/mL M-CSF). Purified B cells (CD20 beads, Miltenyi) were subjected to GEP using HG-U219 microarray (Affymetrix). Data mining analysis was done with GSEA software. IHC analysis of CSF1-R and CD163 expression were performed in FFPE of FL patients (grade 0-2 (n=59) grade 3a-3b (n=28)). *In vivo* FL-FDC mouse model was generated by sc inoculation of the FL cell lines RL or WSU-FSCCL w/wo the FDC non-immortalized cell line HK in SCID mice.

Results: *In vivo*, FDC significantly increased FL cell lines tumorigenicity (p<0.001), being these FL-FDC co-xenografts highly infiltrated with mouse M2 macrophages (CD206+). Remarkably, macrophage depletion (liposomal clodronate) significantly (p< 0.001) decreased tumor growth, supporting the contribution of macrophages to FL progression. Cell culture supernatants from FL-FDC co-cultures were enriched in pro-angiogenic factors and in the macrophage-attractant CCL2, favoring *in vitro* monocyte recruitment to the tumor. Moreover, primary cultures of FL cells induce monocyte differentiation towards M2-like macrophages (Fig.1). FL viability was significantly increased in FL-M2 co-cultures, and gene sets related to migration, adhesion and invasion were enriched in FL cells (Fig.2). Interestingly, in FL tumor biopsies, while the well-established M2 maker CD163 did not correlate with FL clinical parameters, CSF1-R expression correlated with the histological grade. The CSF1-R inhibitor Pexidartinib (PLX3397) changed M2 integrin profile decreasing their adhesion, and switching the M2 macrophage polarization towards a M1 phenotype (Fig.3). PLX3397 hampers the *in vitro* pro-survival effect provided by M2 to FL primary cells. *In vivo*, the simultaneous targeting of FL tumor cells with anti-CD20 Rituximab and Macrophages with PLX3397, led to a cooperative and significant reduction of tumor growth (Fig.4).

Conclusions: In summary, these results support the role of M2 macrophages in FL pathogenesis and suggest that therapies manipulating FL-M2 crosstalk may be a new strategy, especially in combination with anti-B cell therapies.

Keywords: dendritic cells; follicular lymphoma (FL); macrophages.

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IMPACT OF PET IMAGING AND HISTOLOGIC TRANSFORMATION ON THE PROGNOSIS OF EARLY DISEASE PROGRESSION IN FOLLICULAR LYMPHOMA

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Introduction: The ability of progression-free survival status within the first 24 months (PFS24) to predict adverse overall survival (OS) in follicular lymphoma (FL) patients were reported in patients whose pre-treatment imaging modality was unknown. Since 2-[^{18}F] Flouro-2-deoxyglucose positron emission tomography (PET) based staging more accurately identifies disease sites and de novo transformation, we investigated the impact of pre-treatment PET staging on the prognostic value of PFS24.

Methods: We retrospectively evaluated treatment outcomes in 1,053 patients with grade 1-3A FL diagnosed and managed at Memorial Sloan Kettering Cancer Center from 1998 to 2009. We identified 238 patients with stage II-IV grade 1-3A FL initially treated with R-CHOP chemotherapy to analyze the impact of PFS24 on OS, 84 patients with pretreatment CT, 154 patients with pretreatment PET. Histological transformations to DLBCL at time of relapse were biopsy confirmed. An independent cohort of 161 FL patients, 114 patients with pretreatment CT, and 47 patients with pretreatment PET, treated with R-CHOP between 2006-2010 in the FOLL05 clinical trial was used for validation. We applied both event defining and landmark analyses to risk stratify patients based on early progression status. We used a competing risk analysis to understand the association between early progression and transformation.

Results: For patients not achieving PFS24 in an event defining analysis, the 10-year OS was 67.1% for PET-based pretreatment imaging and 43.2% for CT-based imaging (**Figure A**). In the validation cohort, the 5-year OS of patients not achieving PFS24 was 54% in CT-imaged patients and 100% in PET-imaged patients (**Figure B**). Using a landmark analysis at 24 months, the 10-year OS for patients not achieving PFS24 was 76% for PET-imaged and 47% for CT-imaged patients, with similar results in the validation cohort. In a competing risk model, we compared the risk of transformation and the risk of death attributed to transformation. Patients who achieve PFS24 with no progression have a 3.4% risk of transformation at 3 years (**Figure C**). The risk of death from transformation for patients who achieve PFS24 is <1% at 3 years. The risk of transformation in patients with early progression within 1 year is 42.4% at 3 years with risk of death from transformation being 18.6% at 3 years.

A MSKCC (R-CHOP)

CT plus PET (n=238) — PFS24 achiever, n=179; PFS24 failure, n=59 — Log-rank p<0.001

CT (n=84) — PFS24 achiever, n=64; PFS24 failure, n=20 — Log-rank p<0.001

PET (n=154) — PFS24 achiever, n=115; PFS24 failure, n=39 — Log-rank p=0.002

B FOLL05 (R-CHOP)

CT plus PET (n=161) — PFS24 achiever, n=117; PFS24 failure, n=44 — Log-rank p<0.001

CT (n=114) — PFS24 achiever, n=83; PFS24 failure, n=31 — Log-rank p<0.001

PET (n=47) — PFS24 achiever, n=34; PFS24 failure, n=13 — Log-rank p=0.857

C

- Risk of death w/o tFL, progression within 1 yr
- Risk of death w/o tFL, progression between 1-2 yr
- Risk of death w/o tFL, PFS24 achiever
- Risk of tFL, progression within 1 yr
- Risk of tFL, progression between 1-2 yr
- Risk of tFL, PFS24 achiever

Conclusion: Our study provides evidence that in the modern era of PET-based staging, PFS24 may not be a robust surrogate endpoint for OS. The improved outcomes in PET-staged patients with early progression may be associated with identification and exclusion of patients with transformed disease at time of therapy. Patients with early progression are at risk for early death. In contrast, patients with early progression and no evidence of transformation have an extended OS, suggesting aggressive upfront therapies may not be warranted in these patients.

Keywords: follicular lymphoma (FL).

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RESPONSE ORIENTED MAINTENANCE THERAPY IN ADVANCED FOLLICULAR LYMPHOMA. RESULTS OF THE INTERIM ANALYSIS OF THE FOLL12 TRIAL CONDUCTED BY THE FONDAZIONE ITALIANA LINFOMI.

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Introduction: Rituximab maintenance after frontline R+chemo prolongs remissions and is a widely adopted treatment option for patients with follicular lymphoma (FL). Moreover, metabolic and molecular response assessed with FDG-PET and MRD have been confirmed as strong predictors of patients' survival thus suggesting the benefit of a response adapted maintenance strategy as post induction therapy.

Methods: FOLL12 is a multicenter, randomized, phase III, non inferiority study comparing standard vs response adapted maintenance in patients with stage II-IV, previously untreated, intermediate-high risk FL according to FLIPI2, requiring therapeutic intervention. All patients received induction immunochemotherapy (ICT) with 6 cycles of R-CHOP or 6 cycles of R-bendamustine both followed by 2 additional doses of rituximab. After induction ICT, patients in the standard arm were treated with bimonthly rituximab doses for up to two years. Patients in the experimental arm were managed according to centrally reviewed metabolic and molecular response (i.e. Complete metabolic and molecular response: no therapy; Complete metabolic response without molecular response: 4 weekly rituximab doses; Lack of metabolic response (Deauville score 4-5): radioimmunotherapy with ibritumomab tiuxetan followed by standard rituximab maintenance). Primary study endpoint was 3 years progression free survival (PFS) by intention to treat. A sample size of 770 evaluable patients was planned assuming a reference of 3yr PFS at 70% with a non inferiority margin of 7% between arms.

Results: A total of 790 eligible patients were randomized to standard (394 patients) or experimental (396 patients) arm. Groups were well balanced according to patient characteristics and response rates. At the end of induction therapy 88% of cases resulted PET- and 91% MRD-. After a median follow-up of 37 months (range 1-71), the 3-year overall survival (OS) and PFS were 96% and 76%, respectively.

An interim analysis, planned at the occurrence of 70% events, was anticipated at the occurrence of 50% of events and submitted to the external data safety monitoring committee (DSMC). The analysis showed that response oriented experimental arm resulted significantly inferior to the standard maintenance arm in terms of PFS (estimated 3-year PFS, 68% vs. 84%; hazard ratio for PFS, 2.05 [95% CI 1.50-2.81; P < 0.0001]). The DSMC considered unlikely that longer follow-up could modify the results and was favorable in publishing these data.

Conclusions: In patients with intermediate-high risk FL according to FLIPI2 and requiring systemic therapy, omission of R-maintenance resulted in a significantly lower 3-year PFS, despite the attainment of a post-induction complete metabolic response.

Keywords: follicular lymphoma (FL); minimal residual disease (MRD); positron emission tomography (PET).

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INTERIM UPDATE FROM A PHASE 2 MULTICENTER STUDY OF TAZEMETOSTAT, AN EZH2 INHIBITOR, IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA

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Introduction: Relapsed or refractory (R/R) follicular lymphoma (FL) remains an area of unmet medical need and treatments with novel mechanisms of action are desirable. The histone methyltransferase EZH2 is an important regulator of the germinal center (GC) reaction that is involved in preventing terminal differentiation of GC B-cells. *EZH2* activating mutations are present in ~20% of FL patients (pts) and are postulated to be oncogenic drivers. Tazemetostat, a selective, oral EZH2 inhibitor has shown antitumor activity in a phase 1/2 study that included non-Hodgkin lymphoma pts with mutant (MT) or wild-type (WT) *EZH2*tumors, providing rationale for further investigation.

Methods: This open-label, multicenter, phase 2 study of tazemetostat enrolled pts with either MT or WT *EZH2* R/R diffuse large B-cell lymphoma or FL (Grade 1-3b). Key inclusion criteria included: age ≥18 years, ≥2 prior treatment regimens, and measurable disease. Tumor tissue was analyzed for *EZH2* hot spot activating mutations (Y646X, A682G, A692V) using a **cobas®** EZH2 Mutation Test (Roche Molecular Systems, investigational use only). Tazemetostat 800 mg was administered orally, twice daily. Response was assessed every 8 weeks using 2007 IWG-NHL criteria. The primary endpoint was ORR (CR + PR). Secondary endpoints included PFS and safety/tolerability. Efficacy and safety were analyzed for the *EZH2* MT and *EZH2* WT groups.

Results: As of February 1, 2019, interim data were summarized from 95 FL pts (41 *EZH2* MT and 54 *EZH2* WT). The overall median age was 61 years, and median prior lines of therapy was 2 (range: 0-11) in the *EZH2* MT group and 3 (range: 1-8) in the *EZH2* WT group. Median follow-up times, ORR, median duration of response for 92 response evaluable patients in both *EZH2* MT and WT groups are highlighted in the table. Response duration was greater than 24 weeks in 83% of pts, and 50% of pts had a response duration greater than 1 year. Treatment-emergent adverse events (TEAEs) leading to dose reductions occurred in 8% of pts and study drug discontinuation due to TEAEs occurred in 9% of FL pts. The overall safety profile was similar to what has been previously reported. Grade ≥3 treatment-related TEAEs were reported in 18% of pts; no Grade 5 AEs were reported.

Conclusion: Tazemetostat 800 mg BID appears to be generally well tolerated with observed meaningful clinical activity and durability of response in pts with R/R FL. ORR was pronounced in pts with EZH2 activating mutations. Late onset responses have been reported on tazemetostat. Given the consistently favorable safety and low rates of discontinuation due to TEAEs, these encouraging phase 2 data demonstrate that EZH2 inhibition may be an important and effective therapeutic target in FL.

Keywords: follicular lymphoma (FL); germinal center B cell-like (GCB).

	EZH2 MT group (n= 39 evaluable)	EZH2 WT group (n= 53 evaluable)
Objective response rate, % (95% CI)	74 (57.9, 87.0)	34 (21.5, 48.3)
Complete response, %	10	6
Partial response, %	64	28
Stable disease, %	26	30
Progressive disease, %	0	28
Progression-free survival, weeks (95% CI)	60.0 (46.7, 83.9)	24.6 (15.1, 47.9)
Median duration of response, weeks (95% CI)	40 (22.3, NE)	56 (31.7, NE)
Median follow-up, weeks (min, max)	64 (5-161 weeks)	107 (1–178 weeks)

CI, confidence interval; MT, mutant; NE, not estimable; WT, wild type

SESSION 9 – EXTRANODAL LYMPHOMAS

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INTEGRATIVE GENOMIC ANALYSIS IDENTIFIES KEY PATHOGENIC CONCEPTS IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

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Introduction: Primary mediastinal large B-cell lymphoma (PMBCL) is recognized as a distinct entity in the current WHO classification, accounting for 2-3% of non-Hodgkin lymphomas. Molecular studies have provided evidence that PMBCL can be distinguished from diffuse large B-cell lymphoma (DLBCL) and highlighted a strong relationship between PMBCL and classical Hodgkin lymphoma (cHL). There is cumulative evidence to support that correct classification is important for patient risk stratification and therapeutic decision making. We aimed to comprehensively describe genetic alterations and perturbed pathways in molecularly defined PMBCL, as targeted sequencing studies in the past have focused on a limited number of genetic lesions involved in disease pathogenesis.

Methods: We performed whole-exome sequencing of 95 centrally reviewed PMBCL cases, using the SureSelect Human All Exon V6 +UTR baits (Agilent) followed by massively parallel sequencing. For 21 cases paired germline DNA was available. Somatic SNV/indel variants were identified using the intersection of predictions by VarScan, Strelka and MuTect, and annotated with SnpEff. We inform on oncogenic driver genes as identified by MutSigCV and recurrent copy number alterations utilizing CNVkit and GISTIC. For 69 patients global gene expression profiling performed on the DASL platform (Illumina) was available and 90 cases have been molecularly classified using the Lymph3Cx assay. The impact of somatic mutations on gene expression was assessed using xseq.

Results: Tumor and normal samples were sequenced to an average coverage of 115X. Analysis of somatic alterations in tumor-normal pairs yielded 50 putative driver genes recurrently mutated in PMBCL. Besides mutations in the JAK-STAT (*SOCS1, STAT6, IL4R, PTPN1*) and NFkB-pathway (*TNFAIP3, NFKBIE, TRAF3*), we provide additional evidence of the importance of immune evasion in this disease (*CIITA, CD58, B2M*) and identified the IRF-pathway as a putative novel hallmark. As expected, the most significant regions of copy number gain predicted by GISTIC were located on 9p (72%). The most frequent regions of loss were mapped to 10q, 8p, 1p, and 7p. PMBCL driver genes, with the exception of *EZH2*, were significantly more frequently mutated in comparison to DLBCL, whereas only three genes were significantly different between PMBCL and cHL.

Conclusions: Here we identified candidate driver genes with clear evidence of somatic mutations in PMBCL, the majority being distinct from DLBCL. We observed an enrichment of somatic mutations affecting genes involved in the JAK-STAT- and NFkB-pathway, and propose that the IRF-pathway is critically involved in PMBCL pathogenesis.

Keywords: molecular genetics; primary mediastinal large B-cell lymphoma (PMLBCL).

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OUTCOME OF PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA IN THE RITUXIMAB ERA: IMPACT OF A PET-GUIDED APPROACH

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Background: Primary mediastinal large B-cell lymphoma (PMBCL) is a rare subtype of lymphoma which typically presents in females with a bulky anterior mediastinal mass. Patients (pts) are treated with chemo-immunotherapy ± consolidative radiotherapy (CRT). Herein, we reviewed outcomes of PMBCL pts treated at BC Cancer in the rituximab era and the impact of a PET-adapted approach.

Methods: The BC Cancer Lymphoid Cancer Database was used to identify pts >16 years (y) of age with newly diagnosed PMBCL based on the WHO classification who were treated with chemotherapy + rituximab. Prior to the availability of FDG-PET scan at end of treatment (EOT) in July 2005, all pts were recommended to receive R-

Figure 1

OS and TTP by Deauville

5 y TTP
D1-3,DX - 90%
D4 - 94%
D5 - 33%
P<0.0001

5 y OS
D1-3, DX - 97%
D4 - 100%
D5 - 67%
P=0.002

Number at risk

TTP D1-3,X	73	63	48	37	24	15
TTP D4	18	17	12	10	7	5
TTP D5	12	5	5	4	3	1
OS D1-3,X	73	66	52	40	26	16
OS D4	18	18	12	10	7	5
OS D5	12	9	7	4	3	1
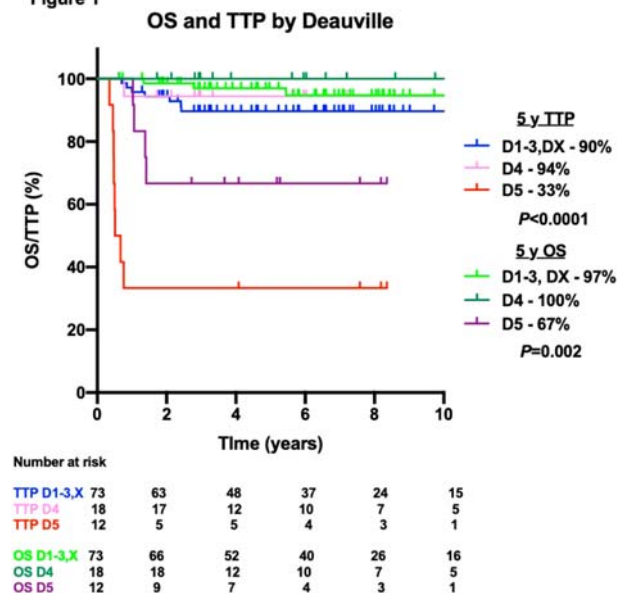
CHOP and CRT (RT era, n=50). Since the availability of an EOT PET (PET era, n=109), only pts with a positive EOT PET (PETpos) were recommended to have CRT. Before 2014, PET scans were interpreted based on the International Harmonization Project (IHP) and after 2014 the Deauville (D) criteria (D1-3, DX = PETneg). IHP era PET scans were retrospectively reclassified using D criteria.

Results: 159 pts with PMBCL were identified with a median follow up of 7.9 y (range 0.7 – 16.7 y) and the following characteristics: median age 36 y (range 19-84); 57% female; 70% bulky $\geq$10cm; 40% pleural/pericardial effusion; 37% extranodal sites >1; 43% B symptoms; 72% elevated LDH; 63% stage I/II. Pts received R-CHOP (n=149), R-CHOP/R-ICE (n=8) or DAEPOCH-R (n=2). 70 pts (44%) received CRT, 78% (n=39) in the RT era (2001-2005) and 28% (n=31) in the PET era (>2005). The 5y time to progression (TTP) and overall survival (OS) for the entire cohort were 80% and 89%, respectively. In a treatment era comparison, there was no difference in TTP (78% vs 81%, P=0.74) and OS (86% vs 91%, P=0.26) for pts treated in the RT vs PET era, respectively, with only one pt in the PET era not having a PET scan due to disease progression. 113 pts had an EOT PET which included 10 pts who had a self-pay PET: PETneg n= 71 (63%), of which 1% (n=1) received CRT; PETpos n=42(37%), of which 79% (n=33) received CRT. For all 113 pts treated with a PET guided approach, the 5 y TTP and OS were 83% and 94% respectively. For PETneg and PETpos cases, the 5 y TTP were 88% vs 74% (P=0.03) and 5 y OS were 97% vs 88% (P=0.78), respectively.

All centrally performed PET scans pre-2014 (n=59) were reassigned by D criteria for a total of 103 D assigned cases; 71% PETneg; 29% PETpos. The 5 y TTP and OS for PETneg by D were 90% and 97%, respectively. For PETpos cases, outcomes were inferior for D5 (n=12) vs D4 (n=18): 5y TTP 33% vs 94% (P<0.0001); 5 y OS 67% vs 100% (P=0.002).

Conclusions: Overall outcomes of PMBCL pts primarily treated with R-CHOP are favourable with a 5 y OS of 89%. Changing to a PET-adapted approached has reduced the use of CRT by over 60% without compromising cure rates. EOT PETneg scan is associated with excellent outcomes with 90% cure rate using modern D criteria. In contrast, D5 have a very poor outcome and may benefit from alternate treatment approaches.

Keywords: positron emission tomography (PET); primary mediastinal large B-cell lymphoma (PMLBCL); R-CHOP.

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NIVOLUMAB COMBINED WITH BRENTUXIMAB VEDOTIN FOR RELAPSED/REFRACTORY PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA: EFFICACY AND SAFETY FROM THE PHASE 2 CHECKMATE 436 STUDY

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Introduction: Primary mediastinal B-cell lymphoma (PMBL) is a rare but aggressive non-Hodgkin lymphoma (NHL) with poor outcomes in relapsed/refractory (R/R) patients. Increased programmed death-1 (PD-1) ligand and weak CD30 expression are characteristics of PMBL. PD-1 blockade and CD30-targeted therapy alone have demonstrated overall response rates (ORRs) of 41% and 13%, respectively, in R/R PMBL. Nivolumab, a fully human IgG4 anti–PD-1 immune checkpoint inhibitor monoclonal antibody, and brentuximab vedotin (BV), an anti-CD30 antibody–drug conjugate, may have synergistic activities in R/R PMBL.

Methods: CheckMate 436 (NCT02581631) is an open-label, phase 1/2 study of nivolumab + BV to treat CD30+ NHLs. This expansion cohort enrolled patients with confirmed PMBL and R/R disease after either high-dose conditioning chemotherapy and autologous hematopoietic cell transplantation (auto-HCT) or ≥ 2 prior multi-agent chemotherapy regimens if ineligible for auto-HCT. Patients received nivolumab (240 mg IV) and BV (1.8 mg/kg IV, pre-specified dose modifications allowed) every 3 weeks until disease progression or unacceptable toxicity. Primary endpoints were investigator-assessed ORR per the Lugano 2014 criteria, and safety.

Results: 30 patients were treated with nivolumab + BV and included in this primary analysis. At baseline, median (min, max) age was 35.5 (19, 83) years; patients had received a median (min, max) of 2 (2, 5) prior systemic therapies and 4 (13%) had received prior auto-HCT. With a median follow-up of 11.1 months, ORR (95% CI) was 73% (54–88), with 11 patients (37%) achieving complete remission (CR);

13 (52%) of the 25 evaluable patients had a best reduction in target lesion of > 50% (**Figure**). At data cutoff, 3 of the 22 responders had progressed or died before starting subsequent therapy; median duration of response has not been reached. Treatment-related AEs (TRAEs) were reported in 25 (83%) patients. The most frequently reported TRAEs were neutropenia (30%), peripheral neuropathy (27%), peripheral sensory neuropathy, thrombocytopenia, rash, and hyperthyroidism (13% each). Grade 3–4 TRAEs were reported in 16 (53%) patients, including 9 (30%) with neutropenia, 3 (10%) each with thrombocytopenia or peripheral neuropathy, 2 (7%) with decreased neutrophil count, and 1 (3%) each with hypersensitivity, colitis, rash, maculopapular rash, or immune-mediated hepatitis. Four patients (13%) had treatment-related serious AEs; 2 of them had grade 3–4 colitis, maculopapular rash, or immune-mediated hepatitis.

Conclusions: In patients with R/R PMBL, nivolumab + BV demonstrated a high investigator-assessed ORR of 73%, with 37% CR. TRAEs were consistent with the safety profiles of nivolumab and BV treatment alone. The combination of nivolumab + BV may be synergistic and is active in patients with R/R PMBL.

Keywords: brentuximab vedotin; nivolumab; primary mediastinal large B-cell lymphoma (PMLBCL).

Figure. Best change from baseline in target lesion by best overall response[a]

□ Complete remission
▨ Partial remission
▤ Stable disease
■ Progressive disease

Best reduction from baseline in target lesion (%)[b]

Evaluable patients (n = 25)
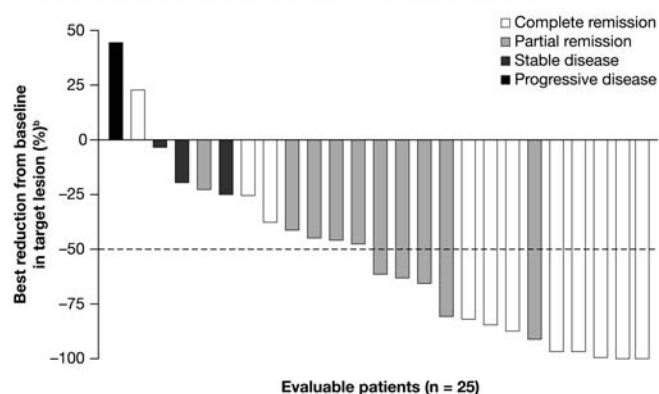
[a]Per Lugano 2014 criteria incorporating FDG-PET scan.
[b]Sum of the product of the diameters, based on CT scan.

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R-CHOP PRECEDED BY ENGINEERED TUMOR NECROSIS FACTOR (TNF) IN RELAPSED OR REFRACTORY PRIMARY DIFFUSE LARGE B-CELL LYMPHOMA OF THE CNS (rPCNSL): FINAL RESULTS OF THE INGRID TRIAL

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Background: Patients (pts) with PCNSL are usually treated with high-dose methotrexate-based combinations that are not currently used in other DLBCL and require hospitalization and extensive expertise to manage toxicity. The use of R-CHOP could overcome these difficulties, but CNS availability of related drugs is poor. TNF induces blood-brain barrier (BBB) permeabilization and enhances CNS access of anticancer drugs. Coupling TNF with NGR, a peptide that targets CD13+ tumor vessels, improves its biological effects. Thus, we tested the hypothesis that this conjugate (NGR-hTNF) can break the BBB, thereby improving CNS access and activity of R-CHOP in pts with rPCNSL enrolled in a phase II trial (NCT03536039). Herein, we report results of activity, safety and BBB permeabilization.

Methods: HIV-neg adults with PCNSL failed after methotrexate-based chemo and measurable disease were enrolled and treated with 6 courses of R-CHOP21 preceded by NGR-hTNF (0.8 μg/m^2). Overall response rate (ORR) was the primary endpoint. The two-stage Simon Minimax design was used; sample size estimated to demonstrate an improvement from 30% ORR to 50% was 28 pts. NGR-hTNF/RCHOP would be declared active if ≥12 responses were recorded. Secondary endpoints regarded changes induced by NGR-hTNF in vessel permeability, assessed by Dynamic Contrast Enhanced MRI (DCE-MRI) and 99mTc-DTPA-SPECT, and in anticancer drug levels in CSF and plasma, and CD13 expression on diagnostic tumor samples.

Results: 28 pts (median age 58 yo, range 26-78; 14 males) were enrolled; 21 (75%) pts had intermediate-high IELSG score. Pts were heavily pretreated: 25 had received ASCT, WBRT or both; 15 had refractory disease.

NGR-hTNF/RCHOP was active: the predetermined activity threshold (≥12 responses) was achieved, with confirmed tumor response in 21 pts (75%; 95%CI= 59-91), which was complete in 11. At a median follow-up of 12 (4-20) months, 8 pts remain relapse free and 9 are alive. Treatment was well tolerated; toxicities were quickly solved without dose reductions or interruptions. G4 toxicities were neutropenia (44% of courses), thrombocytopenia (20%), anemia (2%), and FN (1%). 15 SAE were recorded in 13 pts: seizures (3), DVT (2), infections (5), syncope (2), constipation, FN, and LVEF reduction. There were 7 g1-2 TNF infusion reactions.

DCE-MRI and SPECT studies showed an increase of vascular permeability after NGR-hTNF infusion in tumor and perilesional areas. Specificity of this effect was suggested also by CD13 expression in all tumor samples, and by absence of changes in CSF/plasma drug levels after NGR-hTNF infusion.

Conclusions: NGR-hTNF/RCHOP is active and safe in pts with rPCNSL. CD13, the target of TNF, was expressed in tumor tissue and, consistently, NGR-hTNF enhanced vascular permeability specifically in tumor and perilesional areas. This innovative approach deserves to be addressed as first-line treatment in PCNSL pts.

Keywords: primary CNS lymphoma (PCNSL) R-CHOP

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POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD) AFTER SOLID ORGAN TRANSPLANT (SOT): SURVIVAL AND PROGNOSTICATION AMONG 570 PATIENTS (PTS) TREATED IN THE MODERN ERA

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Background: PTLDs are rare, aggressive and clinically heterogeneous diseases that may arise in the setting of immunosuppression following SOT. There remains an absence of a standard frontline treatment approach in the real world setting. We conducted a comprehensive multicenter retrospective study to analyze disease characteristics and outcomes of post-SOT PTLD in the modern era.

Methods: Data on newly diagnosed pts age ≥18 years (yrs) with SOT-related PTLD from 2000-2017 were analyzed from 10 academic institutions under IRB approval. Detailed patient and disease characteristics were summarized. Survival endpoints estimated by Kaplan-Meier method and compared by log rank test.

Results: We identified 570 PTLD pts with median age of 54 yrs (range, 18-82 yrs) at diagnosis. The majority of pts were male (67%), caucasian (79%), and had stage III-IV disease (67%) at diagnosis. Median time from SOT to PTLD was 61 months (range 0.23-1318). SOT type was renal (35%), liver (19%), lung (18%), heart (13%), intestine & pancreas (1% each), other/missing (1%) and 66 pts (12%) had multiple SOT (11% having 2 organs transplanted, 1% 3 organs). 53% had EBV positive tumor. A minority had graft involvement or rejection (19% each) at the time of diagnosis. For therapy, most pts (85%) underwent reduction in immunosuppression (RIS). For 1st line treatment, rituximab (R)-based therapy was given in 65% (R monotherapy 35% and R+chemotherapy 30%); 8% received chemotherapy without R and 27% received RIS alone. Response to 1st line therapy was: complete response (CR) 59% and partial response (PR) 12% yielding an overall response rate of 71% with 8% stable disease and 21% of pts had primary refractory disease. With 41-month median follow-up, the estimated 5 yr relapse free survival (RFS) and overall survival (OS) rates for all pts were 65% and 71%, respectively. The median OS and RFS were 185 and 181 months respectively. 23% relapsed after 1st line therapy. Outcomes varied significantly by SOT type, with cardiac and lung pts having the worst 5-yr RFS [95% CI] (49% [34, 71] and 58% [44, 77], respectively; P=0.09) and 5 yr OS [95% CI] (63% [51, 79] and 59% [48, 72], respectively, P< 0.0001. Achievement of CR vs PR to 1st line therapy by month 3 after diagnosis was strongly associated with RFS (5 yr RFS 69% [95% CI 63, 76] vs 44% [95% CI 31, 64], P< 0.0001). Furthermore, CR vs non-CR to 1st line therapy was associated with significantly improved OS (5 yr OS 85% [80, 90] vs 70% [62, 80], respectively, P< 0.0001).

Conclusions: These data represent the largest cohort of SOT-related PTLD pts reported to date. Collectively, pts with lung and heart SOT-related PTLD had significantly inferior OS and depth of response to 1st line therapy was a critical determinant for long-term RFS and OS. Our data demonstrates improved outcomes in pts with newly diagnosed PTLD treated in the era of novel agents.

Keywords: post-transplant lymphoproliferative disorders (PTLDs); PTLD.

Disclosures: Venugopal, P: Consultant Advisory Role: *AbbVie and Bayer.* **Fenske, T:** Consultant Advisory Role: *Genentech.*

UCLI-ICML JOINT SESSION – NEW DATA ON T-CELL AND OTHER LYMPHOMAS

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20-YEAR SURVIVAL DATA ANALYSIS OF PTCL PATIENTS IN PEKING UNIVERSITY CANCER HOSPITAL

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Introduction: During the past 20 years, nearly 3500 NHL patients were treated in Peking University Cancer Hospital (PUCH). Among of them, the 5-y OS of B-NHL cases improved significantly, from 50% (before 2000) to 66% (after 2010), but unfortunately the 5-y OS of PTCLs patients was never satisfied. Several frontline regimens were tried, and HDT/ASCT was given to selected newly diagnosed or R/R PTCLs patients. We evaluated the regimens and HDT/ASCT in patients who had complete medical records in PUCH.

Methods: 116 newly diagnosed PTCL patients received CHOP (n=46), CHOPE (n=46) or CHOPE/G (n=24, CHOPE alternating with gemcitabine-based regimen) at PUCH from 2009 to 2017 were analyzed. 83 cases (71.6%) were male. The median age was 57.5 years old. The subtypes included AITL (49.1%), ALK–ALCL (21.6%), PTCL NOS (21.6%), 6 cases of EATL, 2 of hepatosplenic γδT-cell lymphoma and 1 of SPTCL. 77.6% patients were at stage III/IV, 35.3% were with IPI 3-5.

79 patients received HDT/ASCT. The subtypes included ALCL (40.5%), advanced-stage or R/R NKTCL (26.6%), AITL (n=14), PTCL-NOS (n=10), SPTCL-αβ (n=1), SPTCL-γδ (n=1). 47 patients received HDT/ASCT as first-line consolidation (38 cases in CR1, 9 in PR1); 32 cases received HDT/ASCT after salvage chemotherapy (10 cases in CR2, 12 in PR2, 10 in SD/PD). The conditioning regimens included 47 cases with CBV, 10 with BEAC, 20 with BEAM. 2 NKTCL cases received TBI plus HD-CTX.

Results: For 116 newly diagnosed PTCL patients, the ORRs of CHOP, CHOPE and CHOPE/G regimens were 82.6%, 76.1% and 75.0%, with CR rates of 32.6%, 56.5% and 45.7%, respectively. With a median follow-up time of 35.5 months, the 3-y PFS of CHOP, CHOPE and CHOPE/G were 19.9%, 29.9% and 5.3%; the 3-y OS were 37.0%, 47.0% and 56.3%, respectively. CHOPE regimen showed a significantly higher CR rate (p = 0.021) and more favorable OS (p = 0.046). CHOPE/G regimen did not improve the ORR, CR or OS as compared with either CHOP or CHOPE regimen, with a significantly poorer PFS compared with CHOPE regimen (p = 0.029). Anemia and thrombocytopenia occurred most frequently in CHOPE/G regimen.

As for 79 patients who received HDT/ASCT in PUCH, at a median follow-up time of 23.6 months, the 2-y PFS and 2-y OS were 75.2%

and 83.6%, respectively. Patients in CR1 (2-y PFS 85.8%, 2-y OS 94.2%) were superior to others in survival. Patients with CR2 had no advantage in survival as compared with those with PR1 (2-y PFS: 43.8% vs. 76.2%; 2-y OS: 72.9% vs. 77.1%). Response status and LDH level before HDT/ASCT were highly predictive for PFS. Subgroup analysis revealed that patients with AITL benefited mostly from HDT/ASCT in survival, the survival rates (2-y PFS 74.3%, 2-y OS 94.9%) were superior to any other subtypes. NKTCL patients who received HDT/ASCT in CR1 also benefited from HDT/ASCT.

Conclusions: According to our experiences, CHOPE regimen improved the efficacy and survival of PTCLs in front-line; addition of gemcitabine resulted in more adverse events without benefit of survival. Patients with AITL and advanced-stage NKTCL who achieved CR after first-line therapy should be recommended to receive HDT/ASCT.

Keywords: autologous stem cell transplantation (ASCT); chemotherapy; peripheral T-cell lymphomas (PTCL).

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DEVELOPING IMMUNOEPIGENETIC PLATFORMS FOR PERIPHERAL T-CELL LYMPHOMA: LEVERAGING A LOGIC FOR PD1/PDL-1 INHIBITORS

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The peripheral T-cell malignancies represent a group of rare and highly heterogonous diseases, widely regarded as being marginally sensitive to conventional cytotoxic chemotherapy. Over the last several years, gene expression profiling has revealed the ability to classify discrete sub-types of PTCL with greater precision, though has not produced any tangible leads regarding unique pathogenetic targets that might form the basis for a new rational therapeutic approach. What has emerged over the past decade is the growing sense the PTCL may represent the protypical 'epigenetic' disease.

This is based on the following:

1. the PTCL are the only disease for which there are 4 histone deacetylase (HDAC) inhibitors approved as single agents;
2. recent genetic analyses have confirmed recurring mutations in TET2, IDH2 and DNMT3, mutations that collectively conspire to produce global genome wide methylation;
3. genetically manipulated murine models have consistently demonstrated that RhoG17V mutations in combination with TET2 mutations can produce spontaneous PTCL closely resembling angioimmunoblastic T-cell lymphoma (AITL); and finally
4. recent preclinical and clinical data have demonstrated potent synergy between drugs targeting the PTCL epigenome, with combinations of HDAC inhibitors plus hypomethylating agents, PI3K

inhibitors and pralatrexate producing compelling activity in patients with heavily treated disease. For example, combinations of pralatrexate and romidepsin have demonstrated overall response rates (ORR) in B-cell lymphoma and T-cell lymphoma patients of 33% and 71% respectively, with all complete remissions (CR) being seen among the patients with PTCL. A second doublet of romidepsin and oral 5-azacytidine has produced an ORR of 11% and 75% in patients with B- and T-cell lymphoma respectively, with all CR being seen among patients with PTCL. Additionally, among the patients with AITL, all have attained a complete remission. Importantly, progression free survival (PFS) is statistically superior among patients with PTCL compared to those with B-cell disease.

No obvious correlation with underlying TET2, IDH2, DNMT3 or RHOA mutations has been found thus far.

These data confirm the findings in the preclinical studies, suggesting these unique, non - chemotherapy based combinations exhibit a selectivity in one lineage of lymphoma over another.

These novel : novel doublet experiences have created an opportunity to potentially 'redesign' treatment platforms for PTCL not predicated on conventional cytotoxic therapy. Biologically, it is clear that combinations of HDAC inhibitors and hypomethylating agents appear to modulate a host of genes involved in immunomodulatory signaling pathways, including cancer testes antigens, PD-1/PDL-1, gamma-interferon, TBET, as well as expression of endoretroviral elements. These immunological sequelae following exposure to a host a various epigenetic targeted drugs creates a natural logical for considering integration of rationally targeted biologicals such as the checkpoint inhibitors durvalumab (PDL-1) or pemborlizumab (PD-1). Albeit early, these studies are demonstrating that these novel immunoepigenetic based platforms have the potential to produce lineage selective activity, perhaps independent of the TET2 status, with time to event metrics that appear superior to what is being seen with the B-cell malignancies. We will share the evolving biological rational and early preclinical and clinical experience which warrants further study of these potentially paradigm changing approaches.

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CLINICAL OUTCOME OF AN PROSPECTIVE, MULTICENTRE, RANDOMIZED, PHASE III NON-INFERIORITY CLINICAL TRIAL FOR PATIENTS WITH EXTRANODAL NK/T CELL LYMPHOMA TREATED BY P-GEMOX OR AspaMetDex

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Intruduction: Extranodal natural killer/T-cell lymphoma (ENKTL) is an uncommon, aggressive form of non-Hodgkin's lymphoma. Optimal therapeutic strategies have not been fully defined yet. Nasal NK/T-cell lymphomas present mostly with stage I/II disease. For stage I/II nasal lymphoma, a combination of chemotherapy and radiotherapy yields good results. Concomitant chemoradiotherapy and sequential chemotherapy and radiotherapy have similar response rates and survivals. For stage III/IV nasal, nonnasal, and disseminated ENKTL, systemic chemotherapy is indicated. Conventional anthracycline-based regimens are ineffective. Regimens containing L-asparaginase are most effective. Both AspaMetDex and P-Gemox is recommended as major effective combined chemotherapy regimen by NCCN guideline. Therefore, we try to evaluate the efficacy and toxicity for P-Gemox plus thalidomide and AspaMetDex followed by extensive involved field radiotherapy (EIFRT) as first-line treatment for newly diagnosed stage I/II patients and as salvage regimen for newly diagnosed stage III/IV or relapsed/refractory ENKTL in this clinical study.
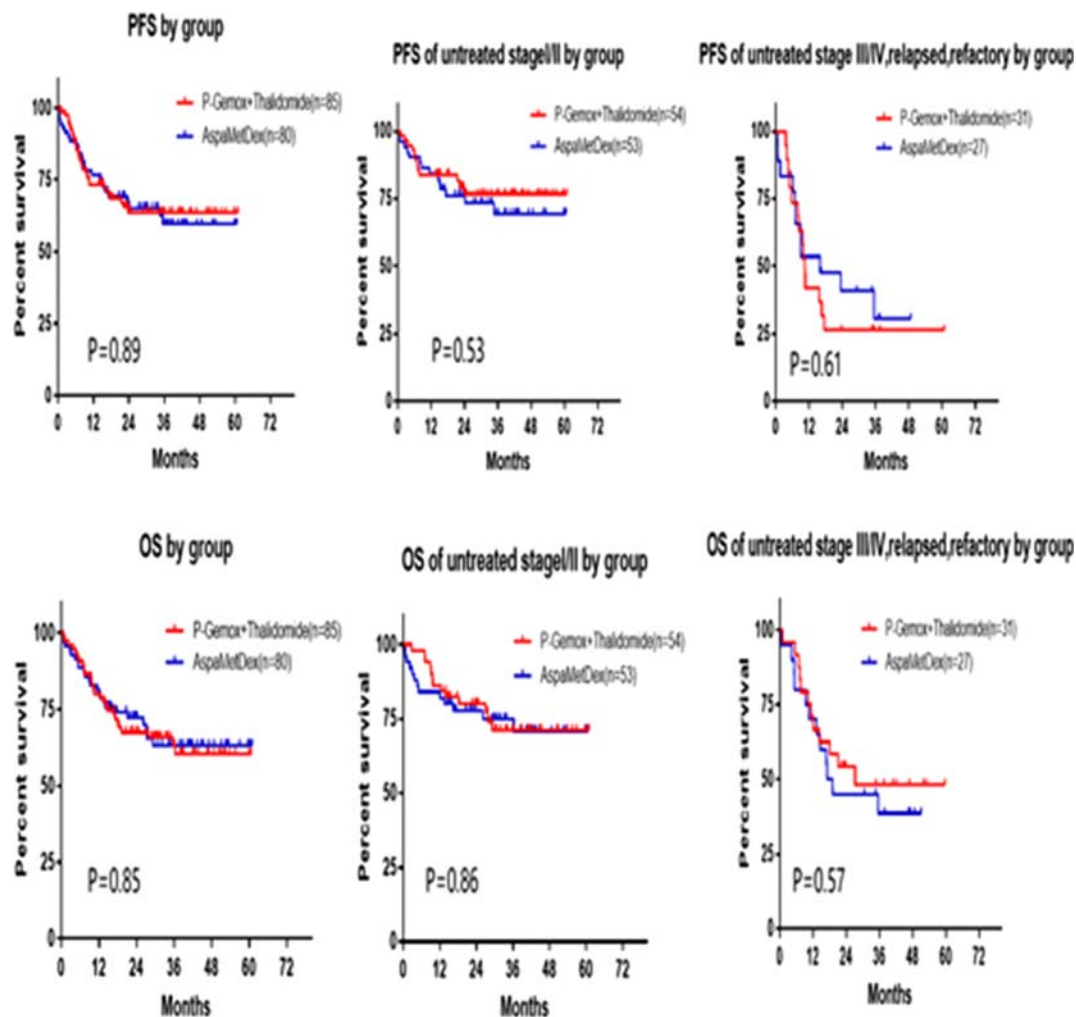
Methods: We initiated the prospective, multicentre, randomized, phase III, non-inferiority clinical trial at 12 centers in China at March 2014. Patients were randomly assigned to receive either P-Gemox+thalidomide regimen (**Group A:** Pegaspargase 2000U/m^2; im d1, Gemcitabine 1000mg/m^2; iv drip, d1, d8. Oxaliplatin 130mg/m^2; ivdrip, d1, thalidomide 100mg/d po, for one year.) or AspaMetDex regimen (**Group B:** Pegaspargase 2000U/m^2; im, d1, Methotrexate 3000mg/ m^2; civ 6-hour d1, calcium folinate 30mg iv, q6h, until reach safe serum MTX concentration, Dexamethasone 40mg/d ivdrip, d1-4.). For newly diagnosed stage I/II patients, both regimens were repeated every three weeks for a maximum four cycles as induction chemotherapy and followed by EIFRT at the dosage of 56Gy in 28 fractions over 4 weeks. Primary EIFRT was delivered using 6-MeV linear accelerator using 3-dimensional conformal treatment planning. For newly diagnosed stage III/IV or relapsed/refractory ENKTL, the regimens were repeated every three weeks for a maximum six cycles. Patients underwent autologous hematopoietic stem cell transplantation (ASCT) as consolidation if they achieved response (CR or PR). The primary endpoint was progression-free survival (PFS), with a non-inferiority margin of 15%.

Results: Between March 2014 and March 2018, 165 patients were randomly assigned. 85 patients to Group A, 80 patients to Group B. 156 patients were evaluable for response. Investigator-assessed overall response at the end of induction was 88.2% in the Group A and 75.0% in the Group B. Complete remission (CR) rate were 60.0% and 55.0%. Among 107 newly diagnosed stage I/II patients, 54 patients were assigned to Group A (52 assessed), and 53 to Group B (47 assessed). Overall response during induction in Group A and B was similar in both groups, were 64.8% and 64.2%. 58 newly diagnosed stage III/IV or relapsed refractory patients were enrolled. 31 patients were assigned to Group A (30 assessed), and 27 to Group B. The efficacy rate of Group A was higher than that of Group B. Overall response rate were 87.1% and 66.6%, respectively. At median follow-up of 24.6 (1.0-60.9) months, 3-year progression-free survival (PFS) and overall survival (OS) of whole cohort were 61.4% and 63.4%. PFS and OS rate of Group A were similar to Group B (Figure 1). Group B was better tolerated than Group A, with lower rates of agranulocytosis, thrombocytopenia and infections. While anemia, hyperbilirubinemia, edema, and increased BUN/Cr were more common in Group B. Three patients died of treatment related toxicity only in Group B. Two patients died of severe acute renal failure and sepsis at the first cycle, and one patient died of sepsis at the third cycle.

Conclusion: Induction chemotherapy of both P-Gemox+Thalidomide and AspaMetDex regimen followed by EIFRT yielded promising efficacy for patients with stage I/II ENKTL. There is little difference in response and survival between the two regimens. For advanced or relapsed patients, both regimen showed unsatisfied survival outcome. Meanwhile, P-Gemox+ Thalidomide was less toxic with more convenient administration in outpatients' clinics in comparison to AspaMetDex. (ClinicalTrials.gov, NCT 2085655).

Disclosures: No relevant conflicts of interest to declare.

Figure 1. OS and PFS in ENKTCL treated with P-Gemox+Thalidomide or AspaMetDex

Keywords: chemotherapy; extranodal lymphomas.

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NEW DATA IN THE MOLECULAR PATHOLOGY OF T-CELL LYMPHOMAS

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Peripheral T-cell lymphomas (PTCL) represent diverse and aggressive malignancies. Findings derived from high-throughput transcriptomic and genomic studies have shed light onto the complex molecular features of these rare diseases, and provided the grounds to a better understanding of their pathogenesis and a more comprehensive classification, already in part reflected in the 2017 WHO classification of lymphoid tumors.

The genetic alterations in PTCL target multiple pathways. Highly recurrent mutations occur in different classes of epigenetic modifiers mostly involved in DNA or histone methylation, in T-cell receptor and co-receptors signaling pathways, and in components or regulators of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. There is established or presumed evidence that the resulting functional deregulations represent pathogenic mechanisms contributing to induce or maintain some attributes of the malignant phenotype. Although a few variants are characteristic of certain entities, for example $RHOA^{G17V}$ highly prevalent in angioimmunoblastic T-cell lymphoma, no novel disease-defining mutation has been found, there is major overlap in the mutational landscapes of different entities, and ALK-positive anaplastic large-cell lymphoma (ALCL) essentially remains the only PTCL defined by a specific genomic rearrangement.

Immune evasion has also emerged as another oncogenic mechanism in PTCLs. Increasing interest has developed regarding the PD-1/PDL-1 axis in lymphoid malignancies. PD-L1 is expressed at variable frequencies in different PTCLs, suggesting that PD-1 blockade may represent an efficient an efficient therapy in some patients; however, because PD-1 has been demonstrated to act as a tumor suppressor which is inactivated in a fraction of T-cell lymphomas, PD-1 checkpoint inhibition may also potentially lead to unwanted effects.

Nodal lymphomas of follicular helper T cell derivation represent the largest group of PTCL; pathological and experimental evidence suggest a multistep oncogenic process starting with epigenetic deregulation acquired in hematopoietic cells, and secondary mutations targeting T cells. In group of anaplastic large cell lymphomas, breast implant-associated cases represent a new indolent ALK-negative entity characterized by recurrent mutations in *STAT3* and *JAK1*, without evidence of *DUSP22* rearrangements. The GATA3 (TH2) and TBX2 (TH1) subgroups of PTCL-not otherwise specified defined by specific molecular signatures, are associated with different copy abnormalities and oncogenic pathways, indicating distinct oncogenic evolution.

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DIFFUSE LARGE B-CELL LYMPHOMA: USING IMMUNE BIOMARKERS TO DEFINE NOVEL THERAPIES

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Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous type of non-Hodgkin's lymphoma varied from clinical, pathological, immunophenotypic, molecular and prognostic features. According to gene expression profiling, DLBCL can be distinguished to three subtypes, germinal center B-like (GCB), activated B-cell like (ABC) and primary mediastinal B-cell lymphoma (PMBL) subtypes, the latter two referred as non-GCB subtype. As a more practical method, classification of GCB and non-GCB subtype is mostly detected by immunohistochemistry study of CD10, BCL6, MUM1. Nowadays, growing studies have applied system biology techniques to determine multiomic heterogeneity and to accomplish molecular classification in DLBCL.

The immunotherapy of cancer has also made significant progress in the past decade. Improved understanding of cancer immunology increases insights into the mechanism of tumor response to immune cells, elucidating the therapeutic role of immunity in cancer and fueling an expanding array of new therapeutic agents. Evaluation of the effectiveness of immunotherapy involves various immune cells within peripheral blood or tumor, including monocytes, lymphocytes, myeloid-derived suppressor cells (MDSC), as well as inflammatory factors and cytokines, etc. In DLBCL, lymphocyte-monocyte ratio (LMR) and cytokines like sIL-2R, IL-6, IL-8, IL-10, and TNF-a are significantly associated with clinical outcome. From 1114 patients with non-Hodgkin's lymphoma, we develop a nomogram for OS prediction, including lactate dehydrogenase (LDH), LMR, sIL-2R, and TNF-a. Moreover, MDSC is a group of immune cells from the myeloid lineage, including granulocyte-like (G-MDSC) and monocytic (M-MDSC). MDSC has negative correlation with T cells and increased M-MDSC is related to poor disease outcome in DLBCL.

Addition of immunoregulatory agents to R-CHOP proves efficient in treating high-risk DLBCL patients. Lenalidomide, an oral immunomodulatory agent, has shown activity in DLBCL. A phase III randomized study revealed that lenalidomide maintenance for 24 months after obtaining a CR or PR to R-CHOP significantly prolonged PFS in elderly patients with DLBCL. Atezolizumab is a humanized anti-programmed death-ligand 1 (PD-L1) antibody. Another phase I/II open-label study enrolled advanced DLBCL patients. Among 40 evaluable patients for response, 31 patients (77.5%) had a CR and 4 patients (10%) had a PR. Together, immune dysregulation plays an important role on disease progression and may become potential therapeutic targets. Further mechanism study is helpful for the identification of biological subsets sensitive to immunotherapy and eventually to realize precision treatment in DLBCL.

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THE T CELL PROJECT 2.0: THE MORE WE REGISTER, THE MORE WE LEARN

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Peripheral T-cell lymphomas (PTCLs) encompass a biologically and clinically heterogeneous group of rare neoplasms arising from mature T cells of post-thymic origin at different stage of differentiation. PTCLs account for 10-15% of all lymphoproliferative disorders in Western countries and usually exhibit a poor prognosis, with a 5-year-survival <50%.

Due to its rarity and the heterogeneity of subtypes, large, prospective, and randomized trials comparing different treatment approaches are still lacking. First-line therapy usually consists of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) +/- Etoposide. In recent years, early consolidation with high dose chemotherapy and stem cell rescue has been adopted in many Institutions, with promising results.

In any case, the risk of relapse remains quite high and relapsed or refractory patients have been shown to have a very dismal outcome. For those patients in need of salvage therapy, current data confirm the unmet need for better treatment. However, a trend towards greater response and survival in those treated with single agents, while maintaining the ability to bridge to transplantation, is emerging.

In 2006 we started the T-cell Project (TCP), a prospective registry of patients with PTCL. Many lessons come from this project: 1) the risk of incorrect diagnostic classification is high, with the consequence need to find reliable tools, specific markers and objective criteria to improve accuracy in the routinely diagnostic work-up for these entities; 2) the outcome of PTCL continues to be dismal in the majority of cases and no improvement was found in OS in the majority of subtypes, compared to older series; 3) treatment remains challenging and new therapies are welcome. Moreover, this project allowed to build a new prognostic model for patients with PCTL-NOS, based on advanced stage, poor ECOG-PS, low serum albumin level and elevated absolute neutrophil counts.

Recently, several new findings have contributed to further understanding of biological, clinical, and therapeutic aspects of PTCLs. Thus, the International T-cell non-Hodgkin's Lymphoma Study Group recently launched the T-cell Project 2.0, being again a prospective, longitudinal, international, observational study of patients with PTCLs. This study adapts to changes made in diagnosis, classification, staging and response evaluation, in order to have a contemporary, real-time

understanding of the evolving landscape of T-cell lymphoma biology and treatment, together with the application of contemporary technologies to further identify of new therapeutic targets. A final accrual of 1,000 cases has been planned. At present, 60 Institutions from 18 different countries already joined the project. So far, 151 patients have been registered by 25 active sites, 34% of whom with diagnosis of PTCL-NOS.

Keywords: T-cell lymphoma (TCL).

SESSION 10 – ADVANCES IN CAR T-CELL TREATMENT

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Novel BAFF-R CAR T-cell Therapy for CD19 Antigen-loss Relapsed B Cell Tumors

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Introduction: Chimeric antigen receptor (CAR) T cells against CD19 have shown great potential in treatment of B cell malignancies. However, tumor relapse from antigen loss can limit efficacy. B-cell activating factor-receptor (BAFF-R), a tumor necrosis factor receptor superfamily protein (TNFRSF13C), is another potential B-cell specific target of B cell malignancies. BAFF-R is an especially interesting alternative to CD19 as BAFF-R signaling is a driver of B-cell survival, which may limit the capacity of clonal B-cell tumors to escape therapy by down-regulation of antigen expression. However, while the BAFF/BAFF-R axis has been successfully targeted for autoimmune diseases, the promise for cancer therapy has not yet been fulfilled.

Methods and Results: A humanized, single-chain variable fragment (scFv) derivative of an anti-human BAFF-R antibody (Qin et al. Clin Can Res 2018;24:1114-1123) was engineered onto a second generation CAR construct containing 4-1BB costimulatory and CD3ζ intracellular signaling domains. BAFF-R-CAR T cells demonstrated cytotoxicity against human lymphoma and acute lymphocytic leukemia (ALL) lines. Adoptively transferred BAFF-R-CAR T cells eradicated 10-day pre-established tumor xenografts after a single treatment and were superior to CD19-CAR T cells (not shown) and retained efficacy against xenografts deficient in CD19 expression, including one primary patient-derived xenograft (PDX). Specifically, we modeled disease relapse due to the loss of CD19 by generating CRISPR CD19 gene knock-out of the ALL (Nalm-6) cell line and a gRNA-silenced CD19 gene knock-down of an ALL PDX. We confirmed the absence of CD19 and presence BAFF-R expression, which was unaffected, on the resulting cell lines by surface staining (Fig. 1A). Using transduced CD8 T_N cells, we found that CD19-CAR T cells demonstrated cytotoxicity only against wild-type tumor cells, while BAFF-R-CAR T cells maintained significant cytotoxicity against both wild-type and CD19-negative tumors in vitro (Fig. 1B). The therapeutic efficacy of BAFF-R-CAR T cells was tested against human ALL Nalm-6-CD19 deficient xenografts established in NSG mice following IV tumor challenge on day 0 with luciferase-expressing cells. A single dose of 2.5 x 10^6 CD4 T_N + 10^6 CD8 T_N BAFF-R- or CD19-CAR T cells/mouse infused IV on day 11 post tumor implantation completely eliminated established Nalm-6-CD19KO ALL tumors and conferred long-term survival. In contrast, treatment with PBS or identical mixtures of CD19-CAR T cells or non-transduced T cells from the same donor were associated with progressive tumor growth and 100% mortality by Day 60 (Fig. 1C).

Finally, four relapsed, antigen loss primary ALLs obtained after CD19-directed therapy retained BAFF-R expression and activated BAFF-R-, but not CD19-CAR T cells. Specifically, cell surface staining demonstrated CD19 and BAFF-R expression in tumors obtained prior to CD19-targeted therapy. However, post-treatment samples exhibited clear down-regulation of CD19, while retaining positive BAFF-R expression (Fig. 1D, samples from a single representative patient shown). The ability of the primary tumor samples to activate either CD19- or BAFF-R-CAR T cells was determined by expression of the degranulation marker CD107a on the CAR T cells. Cryopreserved ALL samples were co-cultured with BAFF-R or CD19 CAR-T cells derived from the same healthy donor in the presence of anti-CD107a antibody for 6 h. Non-transduced T cells (non-CAR) from the same donor were used as a negative control. Activation of CD19-CAR T cells by all four CD19-negative post-blinatumomab therapy tumors was significantly reduced, compared with BAFF-R-CAR T cells and with corresponding available CD19-positive pre-therapy tumors, while BAFF-R-CAR T cells were equally activated by pre- and post-CD19-targeted therapy tumors (Fig.1E-F). We observed similar trends for both CD19- and BAFF-R-CAR T cell activation by pre- and post-CD19-targeted therapy tumors, as measured by specific intracellular CAR T-cell TNF-α and IFN-γ production (not shown).

Conclusion: Taken together, our data suggest that BAFF-R is amenable to CAR T-cell therapy and that targeting it may add to existing alternative strategies to overcome relapse from CD19 antigen loss, such as CD22 CAR T cells. Future strategies combining dual targeting of CD19 and BAFF-R may also be effective.

Keywords: B-cell lymphoma; CD19.
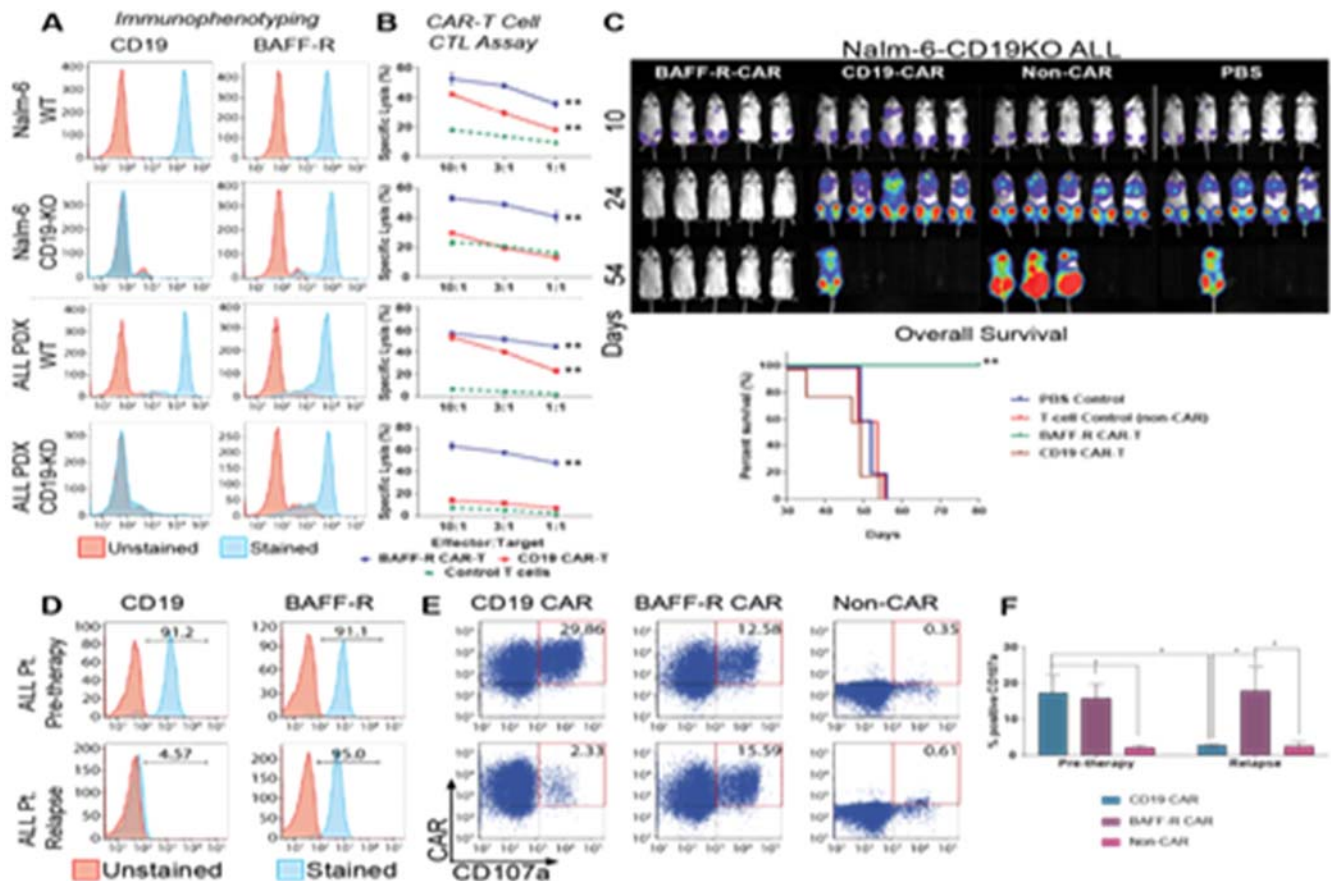
Figure 1. Activity of BAFF-R CAR Ts against CD19-negative human ALL lines and primary CD19 antigen-loss human ALL escape variants. A) FACS histograms of CD19 and BAFF-R expression on wildtype (WT) and corresponding KO/KD tumors. **B)** Cytotoxicity of corresponding tumor targets shown as the mean ± s.d. of triplicate samples. **C)** Bioluminescence images of groups of NSG mice as indicated and Kaplan-Meier plots of overall survival at 80 days. **P<0.001 compared with controls. **D)** Expression of CD19 and BAFF-R in tumor samples from a representative ALL patient pre- or post-relapse following CD19 bi-specific antibody treatment. **E)** Representative and **F)** combined degranulation data from all patients for CAR T cells following coculture of patient ALL samples with BAFF-R- or CD19-CAR T cells, mean ± SEM (*P<0.05 with Mann-Whitney analysis).

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PHASE I CLINICAL TRIAL OF CD19-TARGETED 19-28Z/4-1BBL "ARMORED" CAR T CELLS IN PATIENTS WITH RELAPSED OR REFRACTORY NHL AND CLL INCLUDING RICHTER TRANSFORMATION

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Introduction: CD19-specific second generation chimeric antigen receptor (CAR) T cell therapy with either CD28 or 41BB co-stimulatory domain demonstrate complete remission (CR) rates of 30-50% in relapsed/refractory (R/R) NHL and 20-30% in CLL. Concurrent expression of 4-1BBL in a CD19 CAR T cell enhances T cell proliferation, IL-2 secretion, and cytolytic activity of CAR T cells in the inhibitory tumor microenvironment (Zhao Z et al. Cancer Cell 2015). We report the outcomes of adult patients (pts) with NHL and CLL treated with escalating doses of autologous 19-28z/4-1BBL+ CAR T cells (NCT03085173).

Swim Plot

Legend: ▨ DLBCL GCB ■ DLBCL Non-GCB ■ CLL ■ Richter ■ Indolent Lymphoma ■ ALL ▲ CR ■ PR ● SD ✗ POD ■ VGPR

Y-axis: Subjects on Study Drugs (1–27)
X-axis: Months (0–19)
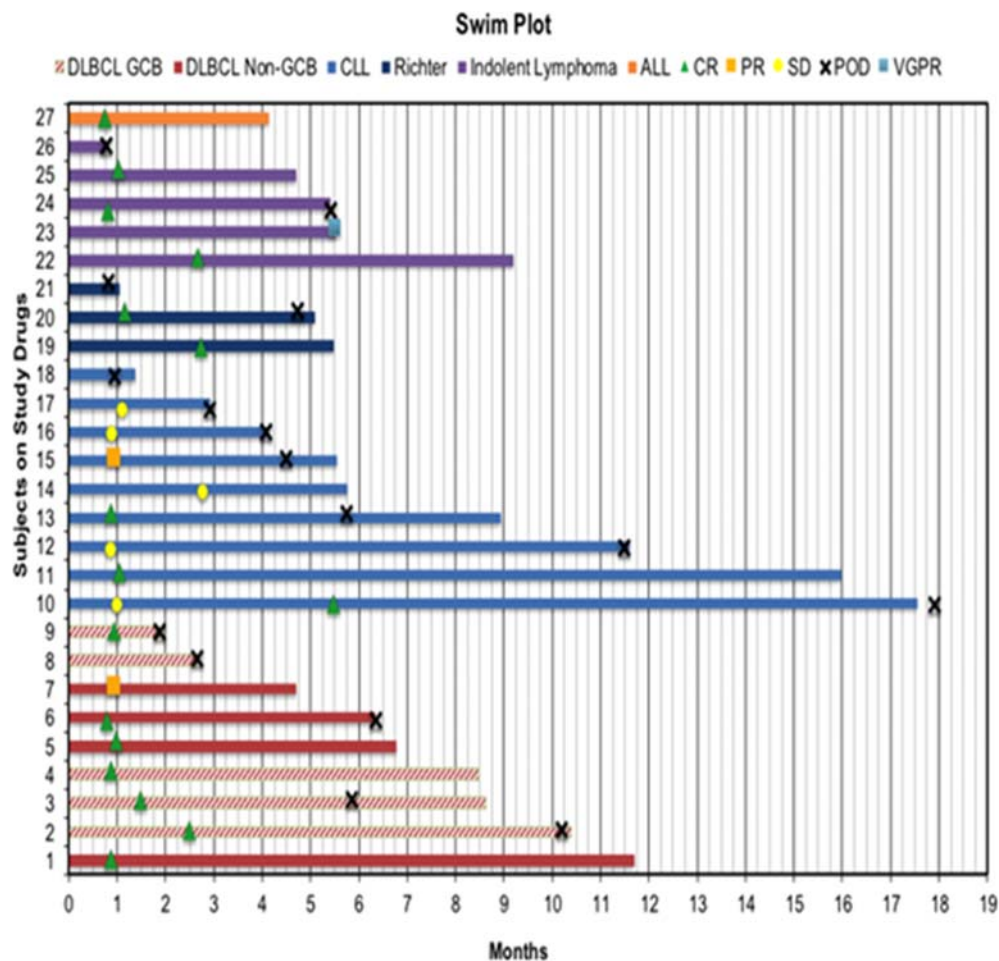
Methods: Pts with R/R NHL (DLBCL, follicular lymphoma (FL), transformed FL (tFL), Waldenström's macroglobulinemia (WM)) and CLL including Richter's transformation were eligible. Pts received conditioning chemotherapy with cyclophosphamide (Cy) alone or combined with fludarabine (Flu) followed by escalating doses of CAR T cells. For DLBCL pts, R-GemOx was the preferred bridging chemotherapy. CAR T cells were administered at dose level (DL) 1 (1×10^5 cells/kg), DL2 (3×10^5 cells/kg), DL3 (1×10^6 cells/kg), and DL4 (3×10^6 cells/kg). The primary and secondary objectives of the study was to evaluate safety of autologous 19-28z/4-1BBL CAR T cells and assess overall response rate.

Results: 28 pts were enrolled with R/R CLL (n=9), de novo R/R DLBCL (n=6), tFL (n=3), FL and WM (n=5), Richter's transformation (n=4), and B-ALL (n=1). Median age of the pts was 70 (range, 53-81), and median number of prior treatments was 5 (range, 2-17). No dose-limiting toxicity (DLT) was observed. All 28 pts are at least 2 weeks from T cell infusion and evaluable for toxicity. Cytokine release syndrome (CRS) was observed in 11 pt (39.3%), one patient with a grade 3 event. Neurotoxicity was observed in 11 pts (39.3%), grade 1-2 in 8 pts and grade 3 in 3 pts. Twenty-seven patients were evaluable for response; one patient was not evaluable because of progressive multifocal leukoencephalopathy attributed to prior therapy, which developed within 1 month after CAR T cell therapy. Responses were observed at all DL. Three patients received multiple infusion of CAR T cells with response from first infusion considered evaluable. Sixteen of 27 pts (59%) achieved a CR, including 7/9 (78%) pts with DLBCL, 3/4 (75%) pts with FL, 3/9 (33%) pts with CLL, 2/3 (67%) pts with Richter's transformation, and one pt with B-ALL. The pt with WM achieved a VGPR. With a median follow-up of 169 days (24-534 days), 8 pts (29%) remain in CR. Peak CAR T cell expansion occurred at a median of 9 days after CAR T cell infusion (range, 2-82). CAR T cell detection beyond 160 days noted.

Conclusions: Treatment with 19-28z/4-1BBL armored CAR T cells is safe with no severe CRS. Grade 3 neurotoxicity was noted in 3 pt (11%) with no case of cerebral edema. The overall CR rate is 57% with 8 patients remaining in CR at the time of this report. Future studies are warranted to develop and improve on existing CAR T cell therapies.

Keywords: CD19; non-Hodgkin lymphoma (NHL); T-cells.

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CD30-CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS FOR THERAPY OF HODGKIN LYMPHOMA (HL)

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Almost all HL and some NHL express the CD30 antigen, and monoclonal antibodies (mAb) targeting CD30 (e.g. brentuximab) produce objective antitumor responses. However, mAb have limited biodistribution and their benefits may be short-lived. We therefore expressed the antigen binding domain of a CD30 mAb as part of a chimeric antigen receptor (CAR) on T cells, coupled to the CD28 and ζ chain endodomains. We have previously published results of a phase 1 study of autologous CD30.CAR-T cells (CD30.CARTs) infused in patients with relapsed/refractory CD30^{+} HL or NHL without preceding cytoreductive chemotherapy (Ramos *et al.*, J Clin Invest 2017). Of 6 patients with relapsed active HL, 1 entered complete remission (CR) that has lasted more than 3 years, and 3 had transient stable disease. We have now incorporated cytoreductive chemotherapy (cyclophosphamide and fludarabine) prior to CD30.CAR T infusion to discover if we can enhance the in vivo expansion and anti-tumor activity of these CD30.CARTs (RELY-30, NCT02917083). Our preliminary results suggest a substantial improvement in efficacy.

We have manufactured CD30.CARTs for 23 patients using retroviral transduction. Cell products comprise >98% T cells with a final transduction efficiency of 97.6%±1.8%. Fourteen HL patients, all of whom had disease relapse or progression after a median of 5 treatment regimens (which included brentuximab in 11 and a PD-1 mAb in 13 patients), have received a single infusion of these CD30.CARTs under the RELY-30 trial. Three patients have been treated on dose level (DL) 1 (2×10^7 CD30.CAR$^+$ T cells/m^2), 6 on DL2 (1×10^8) and 5 on DL3 (2×10^8). All patients received preceding lymphodepleting chemotherapy (cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days). CART infusions were associated with grade 1 cytokine release syndrome in 6 of the patients, and a transient maculopapular rash in 10 of the patients, starting approximately one week after administration. The molecular signal from CARTs, assessed by Q-PCR in peripheral blood, peaked at 1-2 weeks following infusion, but dropped progressively after 4 weeks and decreased to the limit of detection by 6 months. The signal level was dose dependent, with a peak average of 7,132, 14,326, and 34,433 copies/mg DNA in patients treated on DL1, DL2 and DL3, respectively; expansion was 523, 77 and 41-fold higher, respectively, than patients receiving the same CD30.CART dose without prior cytoreduction in our previous trial.

Twelve patients have been evaluated at 6 weeks after infusion. Seven have had a CR lasting up to >15 months, 1 had a partial response, and 4 had disease progression. In 2 patients who relapsed after CR and were re-biopsied, immunohistochemistry evidenced persistent tumor expression of CD30. Hence, infusion of CD30.CARTs after cytoreductive chemotherapy is well tolerated at the doses used. Inclusion of cytoreduction pre-infusion substantially improves CD30.CART expansion and appears associated with superior anti-tumor activity in relapsed patients.

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Durable responses after CD19-targeted CAR-T cell immunotherapy with concurrent ibrutinib for CLL after prior ibrutinib failure

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Introduction: We previously reported that CD19-targeted chimeric antigen receptor-engineered T (CD19 CAR-T) cells could lead to durable responses in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) patients (pts) who had previously failed ibrutinib therapy. Since pre-clinical studies showed that ibrutinib might improve CAR-T cell anti-tumor efficacy and reduce cytokine release syndrome (CRS), we carried out a pilot study to evaluate the safety and efficacy of CD19 CAR-T cells with concurrent ibrutinib administration.

Methods: We treated pts in a pilot cohort of a phase I/II trial (NCT01865617) to evaluate the concurrent administration of ibrutinib with infusion of a defined composition of 2×10^5 or 2×10^6/kg CD4$^+$ and CD8$^+$ CD19 CAR-T cells after lymphodepletion chemotherapy in pts with R/R CLL. Ibrutinib (420mg/day) was scheduled from at least 2 weeks before leukapheresis through at least 3 months (m) after CAR-T cell infusion.

Results: Nineteen high risk CLL pts were included in this study. The median number of prior therapies was 5 (range: 1-10), and 17 pts (89%) had high risk cytogenetics (17p deletion and/or complex karyotype and/or 11q abnormalities). All pts had failed treatment with ibrutinib prior to study entry. Fourteen pts (74%) developed CRS (grade 1, n=6, 32%; grade 2, n=8, 42%). Despite robust expansion of CAR-T cells in blood (median peak: 159,157 transgene copies/μg DNA), we did not observe grade ≥ 3 CRS (Lee 2014 criteria). Five pts

A iwCLL response at day 28 — CR/PR — Other

B iwCLL response at day 28 — CR/PR — Other

C Marrow MRD by IGH sequencing — Negative — Positive

D Marrow MRD by IGH sequencing — Negative — Positive
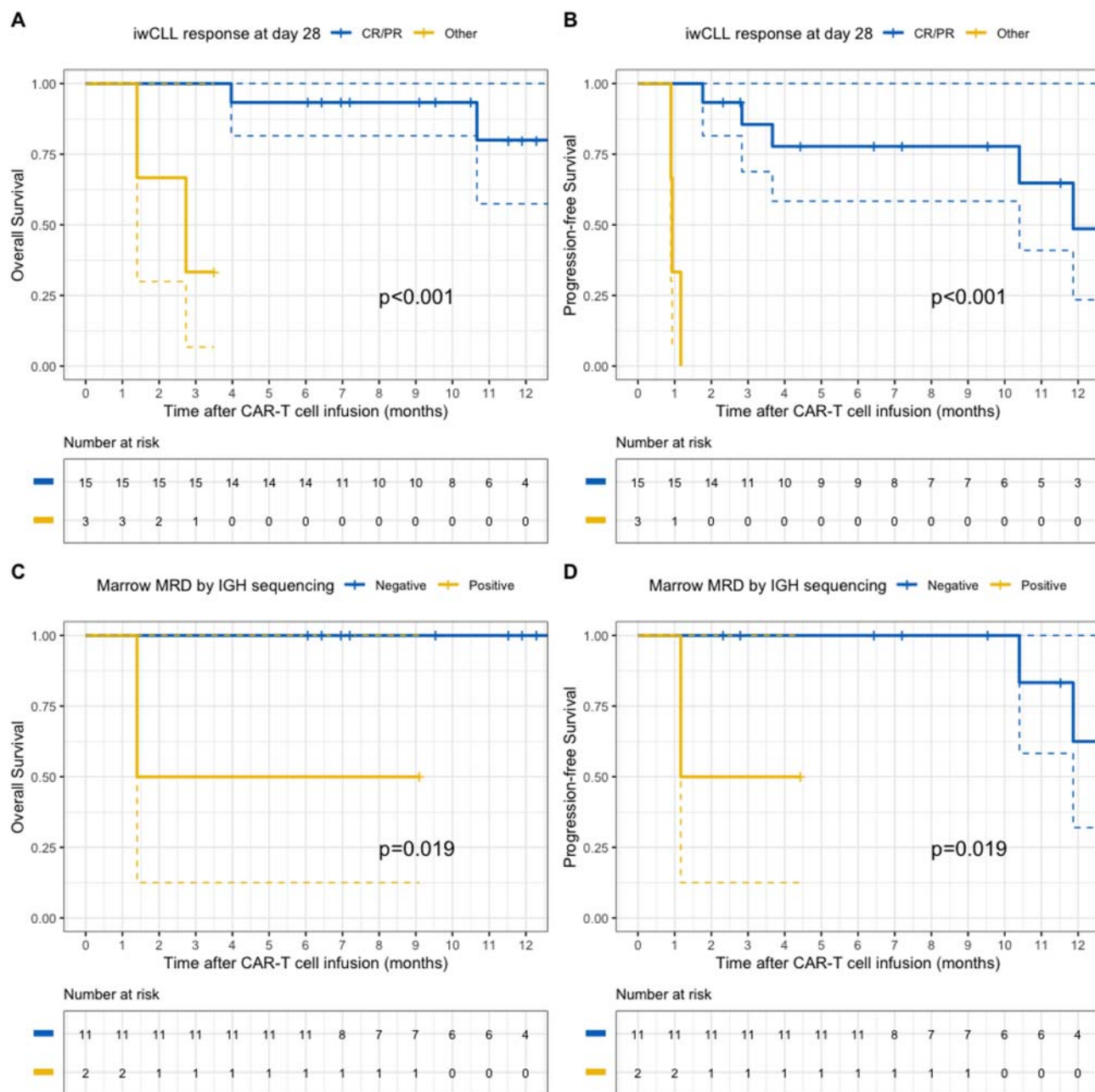
Abbreviations: CAR, chimeric antigen receptor; CR, complete response; PR, partial response; iwCLL, international workshop chronic lymphocytic leukemia; MRD, minimal residual disease. P values per logrank test.

developed neurotoxicity (grade 3, n=5, 26%, CTCAE 4.03 criteria). Eighteen pts were evaluable for response at restaging 4 weeks after CAR-T cell infusion (one patient died from a presumed ibrutinib-induced cardiac arrhythmia during grade 2 CRS). Fifteen pts (83%) responded (CRi or PR) by iwCLL criteria (CRi, n=4, 22%; PR, n=11, 61%). Ten of 14 pts (71%) with nodal disease by CT achieved CR or PR by iwCLL CT criteria. We observed elimination of marrow disease by multi-parameter flow cytometry in 13 pts (72%) and 11 (61%) had no residual malignant clone by IGH sequencing. In responders by iwCLL criteria (n=15) the 1-year probabilities of OS and PFS were 80% (95% CI: 57-100) and 49% (95% CI: 23-100), respectively (median follow-up: 11m; Figure A-B). In pts who achieved MRD-negative marrow response by IGH sequencing (n=11), the 1-year probabilities of OS and PFS were 100% (95% CI: 12-100) and 62% (95% CI: 32-100), respectively (Figure C-D); 9 of 11 pts (82%) without MRD by IGH sequencing were free of disease at last follow-up (median follow-up: 9.5m). Bayesian comparisons showed the concurrent administration of ibrutinib was associated with higher probabilities of IGH-negative marrow response and lower probabilities of grade ≥ 3 CRS, compared to pts treated with CD19 CAR-T cells alone.

Conclusions: In conclusion, CD19 CAR-T cell therapy with concurrent ibrutinib for R/R CLL was feasible and led to high rates of durable responses, without ≥ grade 3 CRS.

Keywords: chronic lymphocytic leukemia (CLL); ibrutinib; immune system.

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HIGH RATE OF DURABLE COMPLETE REMISSION IN FOLLICULAR LYMPHOMA AFTER CD19 CAR-T CELL IMMUNOTHERAPY

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Introduction: Patients (pts) with follicular lymphoma with early relapse after initial chemoimmunotherapy have limited survival, as do those who fail multiple regimens or develop histologic transformation to large cell non-Hodgkin lymphoma (NHL). Initial responses after CD19-directed chimeric antigen receptor (CAR)-modified T (CAR-T) cell immunotherapy in pts with follicular lymphoma have been reported; however, the incidence and durability of responses in pts with follicular lymphoma without transformation (FL) or with histologic transformation (tFL) have not been established.

Methods: We conducted a phase 1/2 clinical trial (NCT01865617) of CD19 CAR-T cell immunotherapy in adults with relapsed/refractory (R/R) CD19+ B-cell malignancies. Best responses were reported
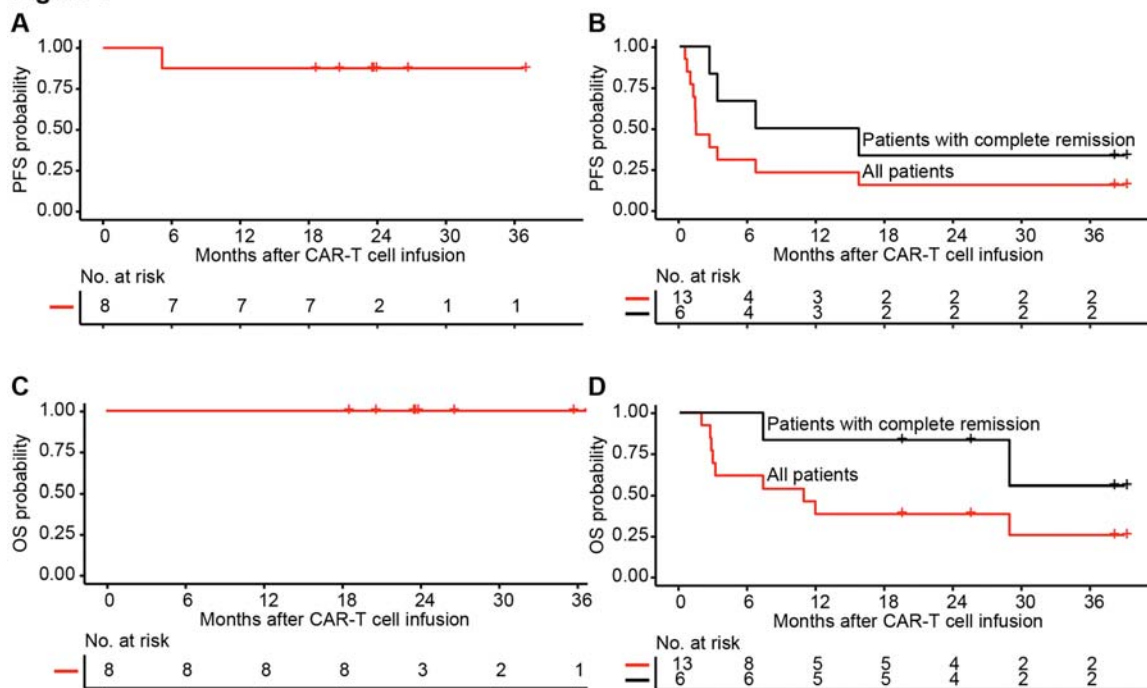
Figure 1. Progression-free (PFS) and overall survival (OS) in patients with follicular lymphoma after CD19 CAR-T cell immunotherapy. Kaplan-Meier estimates of PFS (**A-B**) and OS (**C-D**) in patients with follicular lymphoma (**A-C**) and transformed follicular lymphoma (**B-D**) who achieved complete remission (black) and in all patients (red). The numbers of patients at risk at 6-month intervals are indicated.

according to the Lugano criteria. Fisher's exact and Wilcoxon rank-sum tests were used to compare categorical and non-categorical variables, respectively.

Results: Twenty-one pts who received cyclophosphamide and fludarabine lymphodepletion followed by 2×10^6 CD19 CAR-T cells/kg are included in this study. Eight pts (38%) had FL and 13 (62%) had tFL. The FL pts had received a median of 4 prior therapies (range, 2-7); all had failed chemoimmunotherapy with an anti-CD20 antibody and alkylating agents; 75% had progressive disease after the last therapy; and 50% had failed prior autologous (n=3) or allogeneic (n=1) hematopoietic cell transplantation. Before lymphodepletion, 75% had stage III or IV disease; 62% had extranodal involvement; and 75% had intermediate or high FLIPI score. Seven of 8 pts with FL achieved complete remission (CR, 88%; 95% CI, 47-99) after CAR-T cells. The median time to CR was 29 days (range, 27-42), and all who achieved CR remained in remission without additional therapy (median follow-up, 24 months). Despite high-risk disease, durable CR was observed in most FL pts, indicating this therapy should be further investigated in larger studies.

For the 13 pts with tFL, the best overall response without additional therapy was 46% (95% CI, 20-74), with all responding pts achieving CR. For tFL pts who achieved CR, the median progression-free survival (PFS) was 11.2 months (95% CI, 3.3-NR; median follow-up 38 months). The median PFS for all pts with tFL was 1.4 months (95% CI, 1.2-NR) [Figure 1]. Pts with FL and tFL had comparable baseline and treatment characteristics; however, more tFL pts had elevated lactate dehydrogenase (LDH; FL vs tFL, 13% vs 69%, P = .02) and fewer had bone marrow involvement (50% vs 15%, P = .15). No significant differences were observed between FL and tFL pts in peak CAR-T cell counts in blood, or the incidence and severity of cytokine release syndrome (CRS) or neurotoxicity (NT). No severe (grade ≥3) CRS or NT were observed.

Conclusions: CD19 CAR-T cell immunotherapy is highly effective in adults with clinically aggressive R/R FL, with durable CR in a high proportion of FL pts.

Keywords: CD19; follicular lymphoma (FL); T-cells.

Disclosures: Hirayama, A: Honoraria: *DAVA Oncology.* **Hay, K:** Consultant Advisory Role: *Celgene.* **Vakil, A:** Stock Ownership: *Nektar Therapeutics.* **Riddell, S:** Consultant Advisory Role: *Adaptive Biotechnologies, Cell Medica, Juno Therapeutics, a Celgene/Bristol-Myers Squibb company, and NOHLA*; Stock Ownership: *Celgene*; Research Funding: *Juno Therapeutics, a Celgene/Bristol-Myers Squibb company.* **Maloney, D:** Honoraria: *Janssen Scientific Affairs, Seattle Genetics, and Roche/Genentech*; Research Funding: *GlaxoSmithKline, and Juno Therapeutics, a Celgene/Bristol-Myers Squibb company.* **Turtle, C:** Consultant Advisory Role: *Caribou Biosciences, Eureka Therapeutics, Precision Biosciences, Aptevo, Humanigen, Juno Therapeutics, a Celgene/Bristol-Myers Squibb company, Kite, a Gilead Company, Nektar Therapeutics, and Novartis*; Stock Ownership: *Caribou Biosciences, Eureka Therapeutics, and Precision Biosciences*; Research Funding: *Juno Therapeutics, a Celgene/Bristol-Myers Squibb company, and Nektar Therapeutics.*

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SAFETY OF LISOCABTAGENE MARALEUCEL GIVEN WITH DURVALUMAB IN PATIENTS WITH RELAPSED/REFRACTORY AGGRESSIVE B-CELL NON HODGKIN LYMPHOMA: FIRST RESULTS FROM THE PLATFORM STUDY

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Introduction: In the ongoing TRANSCEND NHL 001 study (NCT02631044), lisocabtagene maraleucel (liso-cel; JCAR017), an investigational, anti-CD19 chimeric antigen receptor (CAR) T cell product administered as a defined composition of CD4+/CD8+ CAR T cells, has shown high response rates and a low incidence of severe cytokine release syndrome (CRS) and neurological events (NE) in patients (pts) with relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL) (Abramson et al, ASCO 2018). Immune system modifiers may further enhance the response and response durability seen with anti-CD19 CAR T cell therapy. The ongoing multiarm, parallel cohort, phase 1/2 PLATFORM study evaluates liso-cel in combination with immune system modifiers in pts with R/R non-Hodgkin lymphoma (NHL). We report preliminary data from the dose escalation part of Arm A, combining liso-cel with the anti-PD-L1 antibody, durvalumab.

Methods: Eligible pts had R/R B-cell NHL, ≥2 prior lines of therapy, and ECOG PS ≤1. Pts received lymphodepletion with fludarabine and cyclophosphamide for 3 days before liso-cel was given at 1 of 2 dose levels (DL): DL1 = 50×10^6 or DL2 = 100×10^6 CAR+ T cells. Durvalumab was given as an IV infusion from day 29 at a total dose of 1500 mg/4 weeks for up to 12 months. Efficacy was assessed per the Lugano Classification.

Results: At data cutoff, 18 pts were enrolled (DL1 n=9; DL2 n=9). 15 pts (DL1 n=8; DL2 n=7) received liso-cel; 11 pts (DL1 n=8; DL2 n=3) completed at least one durvalumab total dose of 1500

mg/4 weeks (2 pts are awaiting treatment; 1 pt no longer met the eligibility criteria; 1 pt died of sepsis). Among the 11 pts, 7 were male; the age ranged from 53 to 78 years. Ten pts had DLBCL; 1 patient had follicular lymphoma grade 3B. Treatment-emergent adverse events included fever, CRS, and NEs (all grade ≤2), cytopenia, and fatigue related to liso-cel (n=7 pts); and hemolytic anemia, fatigue, and rash related to durvalumab (n=3 pts). Two pts had grade ≥3 related events (neutropenic fever and cytopenia) after durvalumab treatment. No CRS occurred after durvalumab infusion. One pt died of acute respiratory failure after disease progression. No dose-limiting toxicities were observed. The best overall response rate was 91% (10/11); 64% of pts (7/11) achieved a complete response (CR). Among the first 6 pts who received durvalumab, 3 pts showed increased CAR T cells at day 85 compared with pre-durvalumab levels on day 29. One pt maintained CAR T cells near peak expansion levels until day 85 and achieved CR at month 6.

Conclusions: Based on preliminary results, the combination of liso-cel with durvalumab has an acceptable safety profile. No CRS was observed after initiation of durvalumab. Preliminary data suggest CAR T cells persist and/or increase with combination treatment, warranting further clinical evaluation. Updated data will be presented.

Keywords: CD19; diffuse large B-cell lymphoma (DLBCL); PD-1L.

Disclosures: Siddiqi, T: Consultant Advisory Role: *AstraZeneca, Juno, Pharmacyclics, BeiGene*; Research Funding: *Dr. Siddiqi's institution received research funding from Juno, Celgene, Kite, BeiGene, Oncternal Therapeutics, TG therapeutics, Acerta Pharma, Pharmacyclics*; Other Remuneration: *Speaker for Pharmacyclics, Janssen, Seattle Genetics. Travel, Accommodations, Expenses: Juno.* **Abramson, J:** Consultant Advisory Role: *Gilead Sciences, Seattle Genetics, Celgene Novartis, Amgen, Juno Therapeutics, Karyopharm, Verastem, Bayer, Abbvie, Janssen, Merck, Kite Pharma Genentech, EMD Serono*; Research Funding: *Seattle Genetics, Celgene, Genentech, Juno therapeutics, AI therapeutics.* **Lee, H:** Research Funding: *Celgene.* **Schuster, S:** Consultant Advisory Role: *Celgene, Novartis, Merck, Genentech, Nordic Nanovector, Gilead*; Research Funding: *Dr. Schuster's institution received research funding from Novartis, Celgene, Merck, Genentech.* **Hasskarl, J:** Employment Leadership Position: *Celgene International*; Stock Ownership: *Celgene.* **Montheard, S:** Employment Leadership Position: *Celgene.* **Dell Aringa, J:** Employment Leadership Position: *Celgene.* **Thompson, E:** Employment Leadership Position: *Celgene*; Stock Ownership: *Celgene.* **Ananthakrishnan, R:** Employment Leadership Position: *Celgene.* **Lunning, M:** Consultant Advisory Role: *AbbVie, Bayer, Celgene, Genentech, Gilead Sciences, Inc, Janssen/Pharmacyclics, Juno Therapeutics, Kite, Novartis, Portola, Sanofi-Genzyme, Seattle Genetics, Spectrum, TG Therapeutics, Verastem*; Research Funding: *Dr. Lunning's institution received research funding from Celgene, Curis, Janssen Scientific Affairs, LLC, Juno Therapeutics, miRagen, Pharmacyclics, TG Therapeutics.*

SPECIAL LECTURE

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THE HIGH COST OF CANCER DRUGS: WHAT CAN WE DO?

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The cost of cancer drugs is a major problem for patients around the world. Globally, over $110 billion is spent on the cost of cancer drugs. Each cancer drug introduced in 2017 in the United States was priced at $100,000 per year or more. The average price was in excess of $150, 000 per year. More aggravating is that despite high launch prices, prices of new drugs continue to increase with time in the United States at a rate much higher than inflation. This is not sustainable.

Pharmaceutical companies usually argue that the high costs are related to cost of drug development, the value provided by new drugs, market forces, and the need to sustain future innovation. But, there are many problems with these assertions. The ability to command a high price for a drug with borderline benefit, encourages the development of closely related low risk drugs rather than truly novel drugs that can have major impact.

The high cost of cancer drugs worldwide is likely related to many factors including: a vulnerable population that is willing to pay high amounts for access to live-saving drugs, monopoly, patent ever-greening, cumbersome processes for biosimilar and generic approval, and the influence of pharmaceutical company lobbying on elected officials. In addition, there are problems unique to the United States that impact prices worldwide. High among them is the inability of the largest purchaser, Medicare, to negotiate directly for low prices with pharmaceutical companies.

Potential solutions include, patent reform, value based pricing, reciprocal approval of generics and bio-similars among countries, legalization of personal importation of prescription drugs, and compulsory licensing. In addition, physician groups should create strong national and international practice guidelines that take price into account. Physicians should also discuss affordability with their patients when prescribing drugs, and choose the most cost-effective option. Finally, oncologists should advocate for policy changes individually and collectively.

Keywords: Hodgkin lymphoma (HL).

SESSION 11 – NEW DRUGS COMBINATIONS

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PRIMARY ANALYSIS RESULTS OF THE SINGLE-ARM PHASE II STUDY OF MOR208 PLUS LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (L-MIND)

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Introduction: CD19 is an important target for the treatment of B-cell malignancies, including relapsed or refractory diffuse large B-cell lymphoma (R-R DLBCL). MOR208, an Fc-enhanced, humanized, anti-CD19 monoclonal antibody, has shown single agent activity in patients (pts) with R-R B-cell lymphoma (Jurczak et al, 2018). MOR208 combined with lenalidomide (LEN) demonstrated synergistic activity in preclinical models, which formed the basis for the single-arm phase II L-MIND study (Salles et al, ASH 2018).

Methods: Patients with R/R DLBCL, ineligible for autologous stem cell transplantation, who had received up to 3 prior lines of therapy, including at least one anti-CD20 therapy, and had adequate organ function were eligible. Treatment comprised up to 12, 28-day (d) cycles (C) of MOR208, 12 mg/kg IV, q1w C1–3 (loading dose on d4 of C1), and q2w C4–12 plus LEN 25 mg PO d1–21, C1–12. Pts progression-free after C12 received MOR208 q2w until progression. The primary endpoint was independent review committee (IRC)-assessed overall response rate (ORR) as per Cheson 2007 criteria. Secondary endpoints included investigator (INV)-assessed ORR, as well as overall survival (OS), progression-free survival (PFS), duration of response (DoR), and safety.

Results: As of June 5, 2018, recruitment was complete (n=81 pts). At baseline, median age was 72 years (range 41–87), median number of prior therapies was 2 (range 1–4), 23% of pts had early relapse (≤12 months from initial diagnosis), 40% were rituximab-refractory (no response or progression during or within 6 months of a prior rituximab therapy), 42% were refractory to their last therapy, and 52% had an International Prognostic Index (IPI) of 3–5. MOR208 plus LEN therapy was well tolerated, and 58 (72%) pts stayed on a LEN dose of ≥20 mg/day. The most common grade ≥3 treatment-emergent adverse events were neutropenia in 43% of pts, thrombocytopenia in 17%, febrile neutropenia in 12%, anemia in 9%, leukopenia in 7%, and hypokalemia in 6% of pts. Investigator (INV)-assessed complete response (CR) and partial response rates were 33% and 25%, respectively; as a result, ORR was 58% (n=81). IRC-assessed ORR and CR rates were 54% and 32%, respectively (n=76). At a median follow-up of 12 months, the INV-assessed median PFS, OS and DoR (intention-to-treat analysis) were 16.2 months (95% CI: 6.3 months–NR), not reached (95% CI: 18.6 months–NR), and not reached (95% CI: NR–NR), respectively. Thirty-seven (46%) pts were ongoing in the study.

Conclusions: The combination of MOR208 and LEN was well tolerated and has shown encouraging activity and long lasting responses in pts with R-R DLBCL, who have poor prognosis and urgently need effective therapies. Primary analysis results of the study with a recent cut-off (November 30, 2018) and a longer follow-up will be presented at this conference.

Keywords: CD19; diffuse large B-cell lymphoma (DLBCL); lenalidomide.

Disclosures: Salles, G: Consultant Advisory Role: *Roche/Genentech, Gilead Sciences, Janssen, Celgene, Novartis, Merck, Pfizer, Acerta Pharma, Kite Pharma, SERVIER, MorphoSys, and Epizyme*; Honoraria: *Roche/Genentech, Amgen, Janssen, Celgene, SERVIER, Gilead Sciences, Novartis, Abbvie, Merck, Takeda, and MorphoSys*. **González Barca, E:** Consultant Advisory Role: *Celltrion, Janssen, Gilead Sciences, Sandoz, and Kowa*; Other Remuneration: *Fees for participation in a speakers' bureau from Janssen, Abbvie, Takeda, and Roche; travel, accommodations and expenses from Abbvie, Janssen, and Roche*. **Jurczak, W:** Consultant Advisory Role: *AstraZeneca, Gilead Sciences, Sandoz-Novartis, Roche, and MorphoSys*; Research Funding: *MorphoSys, Roche, Sandoz-Novartis, Celltrion, Celgene, and Janssen*. **Gaidano, G:** Consultant Advisory Role: *Abbvie, Janssen, MorphoSys, and Sunesis Pharmaceuticals*; Honoraria: *Abbvie, Janssen, MorphoSys, and Sunesis Pharmaceuticals*; Other Remuneration: *Fees for participation in a speakers' bureau from*

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BET INHIBITOR RG6146, VENETOCLAX, AND RITUXIMAB IS A HIGHLY ACTIVE REGIMEN IN RELAPSED/REFRACTORY (R/R) DLBCL: INITIAL REPORT OF PHASE 1B SAFETY, BIOMARKER, AND RESPONSE DATA

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Introduction: Outcomes of patients (pts) with R/R DLBCL are inferior after standard R-CHOP chemotherapy, and a significant proportion of patients has concurrent expression or rearrangements of MYC and BCL2. Bromodomain and extra-terminal (BET) proteins are transcriptional activators for multiple oncogenic processes in DLBCL, including MYC, BCL2, E2F, and toll-like receptor signaling. Results from monotherapy trials inhibiting BET by RG6146 (B)[1] or BCL2 by venetoclax (V)[2] demonstrated single agent activity in DLBCL pts (ORR: 15% and 18%, respectively). The combination B+V+rituximab (R) demonstrates enhanced activity in preclinical models of DLBCL. We report results of an ongoing phase 1b study in R/R DLBCL (NCT03255096).

Fig. 1: *Summary of overall best response and duration on study (PET-CT Lugano Classification)**
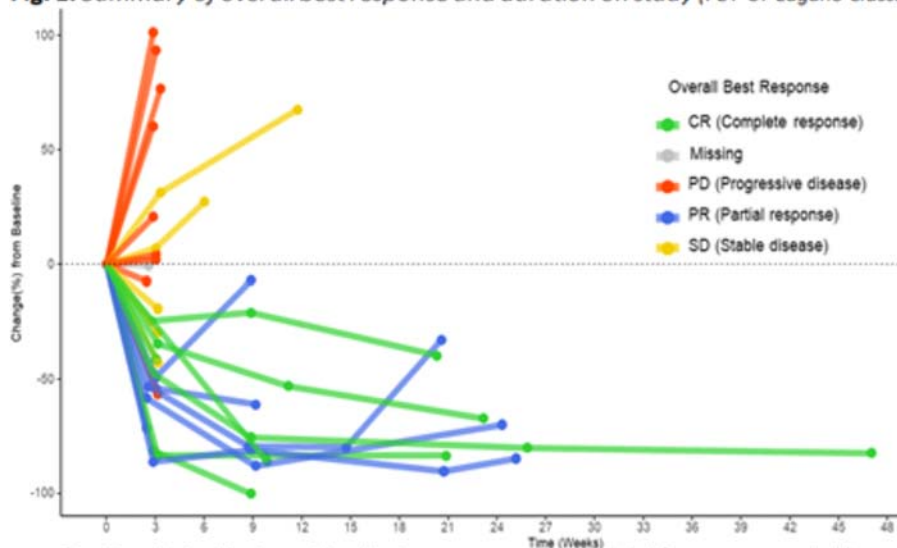
* n=28; patients without a post baseline tumor assessment are excluded from response-evaluable population

Methods: Pts with R/R DLBCL, including transformed follicular lymphoma (tFL), with at least 1 prior regimen which included an anti-CD20 agent were eligible. Other key criteria: ECOG ≤2, ineligible or R/R to ASCT, prior CAR-T cell or bispecific antibodies treatment was allowed. A 3 + 3 escalation design was used, initially B [(0.30, 0.45, or 0.65 mg/kg/d s.c. (14 d/3 wk cycle)] + V (400, 600, or 800 mg/d/3 wk cycle) to determine doublet maximum tolerated dose (MTD); R was added (375 mg/m2 x 3d cycle 1; then d1 cycle 2+) in later cohorts. Primary endpoint was safety [DLT, MTD, recommended dose (RD)] and secondary endpoints were PK, biomarker, and preliminary efficacy assessments (modified Lugano criteria; investigator assessed).

Results: 36 pts were treated from 8/2017 to 2/2019. Median age 68 (28-81) years, 17M:19F, stage IV 26 (72%), median prior regimens 3 (1-6), prior CAR-T or bispecifics 6 (17%). Baseline biomarker data (26 pts): COO GCB in 18/26 (69%); MYC+BCL2 wt disease (58%), 1 pt had MYC and 7 pts had BCL2 translocations.

Safety: Doublet MTD was determined as 0.65 mg/kg B + 600 mg V and triplet expansion is near completion to confirm 0.45 mg/kg B + 600 mg V + 375 mg/m2 R as MTD/RD. Pts received a median of 3 (1-11) cycles. Higher rates of Grade (G) 3/4 AEs (%): thrombocytopenia (+6.9), anemia (+11.2), neutropenia (+2.3) and diarrhea (+3.1) relative to V monotherapy were observed and expected. DLTs include G3 febrile neutropenia, G4 diarrhea and hypomagnesemia for B+V; and G3 hyperbilirubinemia, G4 diarrhea for B+V+R. PK: Data for B are similar to B monotherapy with approximately dose proportional increases in exposure with increasing dose and ~2-fold accumulation. Activity: ORR (28 evaluable pts) is 46%, with 25% CR; median DOR is 5 mo (0.5-11 mo) (Figure 1). Responses were seen in all cohorts and all molecular subtypes.

Conclusions: RG6146, venetoclax, and rituximab is a tolerable, highly active regimen [46% ORR (25% CR)] with durable responses in R/R DLBCL and tFL. These results suggest the regimen is a valuable treatment option for heavily-pretreated R/R DLBCL patients.

1. P. Caimi, ICML, abstr. 274, 2017

2. MS Davids, J Clin Oncol, 2017

Keywords: BCL2; bromodomains; diffuse large B-cell lymphoma (DLBCL).

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POLATUZUMAB VEDOTIN (POLA) + OBINUTUZUMAB (G) + LENALIDOMIDE (LEN) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL): PHASE IB/II INTERIM ANALYSIS

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Introduction: Pola-G-Len may enhance anti-tumor immune response in R/R FL. We report a pre-planned interim analysis of the safety/efficacy of induction and maintenance with Pola-G-Len in pts with R/R FL in a phase Ib/II study (NCT02600897).

Methods: Pts received induction treatment with 6x 28-day (D) cycles (C) of: G 1000mg IV (C1: D1, D8, D15; C2–6: D1); Pola 1.4mg/kg or 1.8mg/kg dose escalation (DE) or recommended phase 2 dose (RP2D; expansion) IV (D1); and Len 10–20mg (DE) or RP2D (expansion) PO (D1–21). Pts with complete response (CR)/partial response (PR)/stable disease (SD) at the end of induction (EOI) received G 1000mg (D1 every 2mo, for 24mo), and Len (10mg, D1–21 monthly, 12mo). Primary endpoints were C1 dose-limiting toxicities (DLTs), safety/tolerability, CR rate at EOI (modified Lugano criteria).

Results At the interim data cut-off (6 July 2018), 52 pts were enrolled: 9 discontinued the study (adverse events [AE], n=3; death due to PD, n=4; pt withdrawal, n=1; other, n=1). At baseline, the median pt age was 62 (range 32–87) years; 60% were male; 58% had FLIPI score 3–5; 79% had received ≥2 prior therapy lines; 50% were refractory to their last treatment; 17% had bulky disease (≥7cm). Two DLTs were reported in the cohort receiving Pola 1.8mg/kg + Len 10mg during the DE period (Gr 4 lipase/amylase elevation; asymptomatic, resolved with supportive care; Gr 3 thrombocytopenia leading to a delay in the initiation of cycle 2). Gr ≥3 AEs were experienced by 75% of pts: neutropenia (46%), thrombocytopenia (17%), anemia (12%) and infections (12%) were the most common AEs. Len dose reduction or interruption occurred in 31% and 52% of pts, respectively. One Gr 5 AE was reported (septic shock after PD in pt receiving subsequent therapy). The RP2D was determined as Pola 1.4mg/kg + Len 20mg. Preliminary efficacy data suggest high activity, with an independent review committee-assessed Modified Lugano response rate of 89% and a CR rate of 67% (**Table**). Median progression-free survival was not reached (median follow-up duration 8.95 mo in the efficacy-evaluable population).

Conclusions The safety profile of Pola-G-Len is consistent with known profiles of the individual drugs. Response rates at EOI with Pola-G-Len are promising, with high CR compared with available R/R FL treatments.

TABLE 1 Responses at end of induction (efficacy-evaluable population; recommended phase II dose; N=18)

Best overall response, n (%)	Modified Lugano 2014		Lugano 2014	
	INV	IRC	INV	IRC
Objective response rate	16 (89)	16 (89)	16 (89)	16 (89)
CR	11 (61)[1]	12 (67)[2]	14 (78)	14 (78)
PR	5 (28)	4 (22)	2 (11)	2 (11)
SD	1 (6)	1 (6)	1 (6)	1 (6)
PD	0	0	0	0
Missing/unevaluable	1 (6)[3]	1 (6)[3]	1 (6)[3]	1 (6)[3]

[1]3 pts and [2]2 pts downgraded from CR to PR with Modified Lugano due to missing bone marrow biopsy; [3]1 pt had PR by CT (interim scan) but no PET at EOI performed before SCT.
Abbreviations: CR, complete response; EOI, end of induction; INV, investigator assessment; IRC, independent review committee assessment; PD, progressive disease; PR, partial response; SD, stable disease.

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THE PI3Kδ INHIBITOR ME-401 ± RITUXIMAB IN RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL), CHRONIC LYMPHOCYTIC LEUKEMIA (CLL), AND SMALL LYMPHOCYTIC LYMPHOMA (SLL)

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Background: ME-401, a potent and selective oral PI3kδ inhibitor, is being evaluated in a Phase 1b study in patients (pts) with R/R B-cell malignancies (NCT02914938). 70 pts were treated as of January 2019 and we report here results in pts with FL and CLL/SLL.

Methods: Adult pts with ECOG performance status ≤2, no prior PI3K therapy, and progression of disease (POD) after ≥1 prior therapy were initially enrolled in a dose escalation phase (60-180 mg) then in 60 mg expansion cohorts as monotherapy or in combination with rituximab (375 mg/m² x 8 doses in 6 months). ME-401 was given initially on a daily continuous schedule (CS) until POD or unacceptable toxicity. Patients on CS were switched to an intermittent schedule (IS) on days 1-7 of a 28-day cycle in Cycle 3 (n = 20) or in Cycles ≥4 (n = 18) of CS. Toxicity on CS was managed by switch to IS and POD on IS was managed by switch to CS.

Results: 61 pts, 48 with FL and 13 with CLL/SLL received ME-401 alone (n = 48) or with rituximab (n = 13). Median age 65 yrs. (range: 38-81), median prior therapies 2 (range: 1-10), 33 pts had ≥2 prior therapies, and 25 FL pts were POD24. In CLL/SLL pts, IgVH was unmutated in 7, mutated in 2, and not evaluated in 4. 39 pts (64%) remain on therapy with a median follow-up of 12.3 months (range: 1.6-25.1) and 22 pts discontinued: 9 POD, 5 adverse events (AEs), 5 withdrew consent, and 3 were referred to stem cell transplant in CR. Delayed (i.e., Cycle >2) grade 3 immune related AEs (irAEs), primarily diarrhea/colitis and rash, were reported in 13/41 pts (31.7%) on CS and 2/20 pts (10%) who had switched to IS in Cycle 3, with irAEs noted 15 and 18 days after switch to IS. 6 pts with grade 3 irAEs had a drug holiday and corticosteroid therapy then resumed ME-401 on IS without recurrence of the irAE. Objective responses were achieved in 33/43 evaluable FL pts (77%) and 11/11 evaluable CLL/SLL pts (100%). In FL,

TABLE 1

Dosing Schedule	No. of Pts	No. (%) of irAEs	No. Efficacy Evaluable Pts	No. (%) CR+PR
CS or CS → IS in Cycles ≥4	41	13 (31.7%)	34	28 (82%)
CS → IS in Cycle 3	20	2 (10%)	20	16 (80%)

response rate was 77% with ME-401 alone (including 29% CR by Lugano criteria), 78% with ME-401 plus rituximab, 91% in POD24, and 75% in pts who had ≥2 prior therapies. Of 38 pts switched to IS, 33 (87%) remain on therapy (median: 14.5 months), 26 on IS and 7 who switched back to CS due to POD on IS, 3 pts discontinued due to persistent POD after switch to CS, and 2 pts withdrew.

Conclusions: ME-401 achieves a high rate of durable responses in R/R FL and CLL/SLL. IS appears to reduce the incidence of irAEs and maintain responses. POD on IS can be successfully retreated by reverting to CS. A global study is enrolling pts with R/R FL randomized to ME-401 by IS or CS after 2 cycles of CS, with switch to IS for irAEs and switch to CS if POD on IS (NCT03768505).

Keywords: chronic lymphocytic leukemia (CLL); follicular lymphoma (FL); PI3K/AKT/mTOR.

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INVESTIGATING SAFETY AND PRELIMINARY EFFICACY OF AFM13 PLUS PEMBROLIZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA AFTER BRENTUXIMAB VEDOTIN FAILURE

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Background: AFM13 is a bispecific, tetravalent NK cell-engaging antibody construct binding to CD30 on Hodgkin Lymphoma (HL) cells and CD16A on NK cells [1]. Pembrolizumab is a PD-1 blocking antibody that induces high response rates in patients (pts) with relapsed or refractory HL (RRHL) [2]. AFM13 has shown clinical activity in pts with RRHL in a Phase 1 study [3]. Preclinical data of the combination of AFM13 with PD-1 inhibition suggest synergism [4].

Methods: This Phase 1b dose escalation/extension study is evaluating the safety, tolerability and preliminary efficacy of the combination of AFM13 with pembrolizumab as salvage therapy after failure of standard therapies including brentuximab vedotin (BV) in pts with HL (NCT02665650). Pts receive escalating doses of AFM13 in combination with pembrolizumab following the classical 3+3 design. Response assessment is performed every 12 weeks by PET/CT according to the Lugano Classification [5]. Data as of February 12, 2019 are presented.

Results: All thirty pts have been enrolled. The median age is 34 years (18-73), with a median of 4 (3-7) prior lines of therapy. All pts have failed standard treatments including BV and 43% had BV as their latest therapy. Thirty seven percent have undergone prior autologous stem cell transplantation. Twelve pts were enrolled into the dose escalation cohorts and 18 into the Extension Cohort. All 30 pts completed the dose limiting toxicity (DLT) observation period. No DLTs occurred in Cohorts 1/2, one DLT occurred in Cohort 3 (missed ≥25% of AFM13 during the DLT period) and one DLT occurred in the Extension Cohort (Grade (G)4 infusion-related reaction (IRR)). Adverse Events were mainly G1/G2 and included IRRs (87%), rash (30%), nausea (23%), pyrexia (23%), and diarrhea (20%). G3/4 AEs included IRRs (13%), elevated aspartate aminotransferase (3%), gastritis (3%), hypotension (3%), nausea (3%), neutropenia (3%), and vomiting (3%). Included in the efficacy analysis were the best response from all 30 patients. The best overall response rate (ORR) and complete response (CR) rate for pts treated at the dose and schedule chosen for expansion (n=24; Cohort 3 and Extension Cohort) were 88% and 46% by independent assessment. Investigator assessment resulted in an ORR of 88% and CR rate of 42% for these pts. Estimated 6-month PFS rate at the highest treated dose level was 77%. Longer term follow up results will be presented at the meeting.

Conclusions: The combination of AFM13 and pembrolizumab is well-tolerated with most AEs mild to moderate in nature. The ORR of 88% compares favorably to the historical data of pembrolizumab in a similar RRHL population, with the CR rates of 42% and 46% by local and independent assessment, respectively, approximately doubling that of pembrolizumab (CR rates 22-25%) [2].

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TARGETING THE PERIPHERAL T-CELL LYMPHOMA (PTCL) EPIGENOME WITH ORAL 5-AZACYTIDINE AND ROMIDEPSIN: RESULTS AND CLINICAL-MOLECULAR CORRELATIONS FROM A PHASE 2 STUDY

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Introduction: PTCL exhibit pervasive dysfunction of epigenetic operations. This may be a targetable vulnerability, as demonstrated by the single-agent activity of histone deacetylase inhibitors (HDACi) and hypomethylating agents (HMA). We previously showed marked synergism between HDACi and HMA in T-cell lymphoma lines, accompanied by the modulation of >900 unique genes with the combination, but not the single agents. In a recently completed phase-1 study we observed encouraging activity of combined oral 5-azacytidine (AZA)

and romidepsin (ROMI) in T-cell lymphoma patients. Here, we report the first analysis of the phase-2 portion of that study.

Methods: Patients with newly diagnosed (ND) or relapsed/refractory (R/R) PTCL were eligible for enrollment. The recommended phase-2 dose from the phase-1 trial was AZA 300 mg daily days 1-14 and ROMI 14 mg/ms days 8, 15, 22 every 35 days. The primary objective was overall response rate (ORR). Other endpoints were progression-free survival (PFS) and duration of response (DOR). We performed targeted next-generation sequencing (NGS) of pre-treatment tumor samples to correlate epigenetic gene mutations and response.

Results: Among 25 enrolled patients the median age was 63 years [42-88] and the M:F ratio was 14:11. 11 patients were ND and 14 were R/R, with a median of 2 prior therapies [1-6], 17 patients had AITL or PTCL-TFH, 3 PTCL-NOS, and 4 other subtypes (1 each of ALCL, ATLL, EATL, and ENKTL).

19 patients are evaluable for response and 5 are pending evaluation (complete data will be presented). The ORR was 68% (13/19), including 42% complete responses (CR) (8/19). Among 8 evaluable ND patients the ORR and CR were 75% and 37%, respectively, while among 11 R/R patients these were 64% and 45%, respectively. Notably, among 11 evaluable patients with AITL (9) or PTCL-TFH (2), 10 responded, and 6 achieved a CR.

23 patients are evaluable for toxicity. The most frequent hematologic G3-4 AE were thrombocytopenia (39%) and neutropenia (39%). The most frequent non-hematologic G3-4 AE included lung infection (17%) and febrile neutropenia (13%). Other common G1-2 toxicities included anemia, diarrhea, fatigue, nausea, and vomiting. No patients discontinued therapy due to AE. At a median follow-up of 5.8 months [0.3-23.1], the median DOR has not been reached (1.8-20.0+ months) and the median PFS for the entire population, ND and R/R patients is 7.9 months, 7.9 months, and not reached, respectively. Two patients have died, one due to progressive disease, one due to unknown cause.

Pre-treatment tumor samples are available for 17 patients, 13 of whom are evaluable for response: all patients had at least one mutation in an epigenetic gene. Importantly, 9/10 patients with a TET2 mutation responded, whereas only 1 of 3 patients with wild-type TET2 responded.

Conclusions: The AZA-ROMI combination is well tolerated and highly active in PTCL patients, particularly AITL or PTCL-TFH. TET2 mutations may portend a higher likelihood of response. Sequencing data from the entire study population will be presented (NCT01998035).

Keywords: epigenetics; peripheral T-cell lymphomas (PTCL); romidepsin (RD).

FOCUS ON... SESSION: INDOLENT NON-FOLLICULAR LYMPHOMA

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EARLY PROGRESSION OF DISEASE (POD24) PREDICTS SHORTER SURVIVAL IN MALT LYMPHOMA PATIENTS RECEIVING SYSTEMIC TREATMENT

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Introduction. Progression of disease within two years from the start of therapy (POD24) is linked with poor outcome in follicular lymphoma who received first-line systemic therapy[1]. In the present study, we sought to understand whether early progression after first-line treatment is affecting overall survival (OS) also in extranodal marginal zone B-cell lymphomas of MALT type (EMZL).

Methods. We analyzed the dataset of the IELSG19 clinical trial[2] (training set) to determine whether POD24 is associated with inferior OS. The study population included 401 EMZL patients (131 randomly assigned to chlorambucil treatment, 138 to rituximab and 132 to chlorambucil plus rituximab). Reproducibility was analyzed in an independent validation set (generated from the larger validation cohort of the MALT-IPI study[3]) which comprised 287 patients with adequate treatment and follow-up data, who received systemic treatment (chemotherapy, immunotherapy or both). In both, training and validation sets, we excluded from the analysis patients who died without progression within 24 months and those who were lost to follow-up without progression within 24 months from treatment start. Overall survival was calculated from disease progression in patients with POD24 and from 24 months after the start of treatment in those without POD24 (reference group).

Results. POD24 was observed in 69 of 401 patients of the IELSG19 study. The reference group comprises 315 patients with no relapse or death during the first 24 months since 17 patients were excluded

Testing set
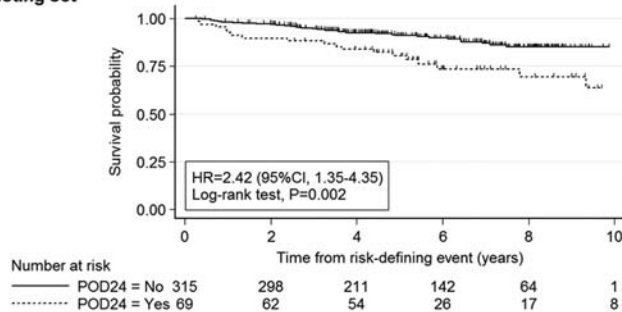
Validation set
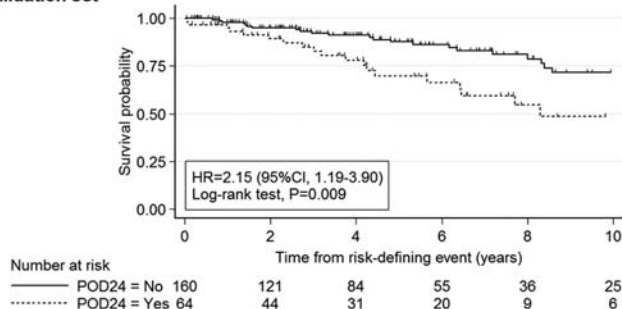
from the analysis (8 dead without POD within 24 months and 9 followed up for less than 24 months from treatment start). For the 69 patients (18%) with early POD, median age was 62 years, 32 patients were male and 26 had gastric localization. The 10-year OS rate was 64% in the POD24 group and 85% in the reference group (HR= 2.42, 95%CI, 1.35-4.35; log-rank P=0.002). Patients in the early-POD group were more likely to have high-risk MALT-IPI scores than those in the reference group (P=0.013). The prognostic impact of POD24 was confirmed in the validation set, in which POD24 was observed in 64 patients out of 224 evaluable patients (63 patients were excluded: 9 dead without POD within 24 months and 54 followed up for less than 24 months from treatment start) with 10-year OS rate of 48% in the POD24 group and 71% in the reference group (HR of 2.15, 95% CI, 1.19 to 3.90; log-rank P=0.009).

Conclusions. In patients with EMZL who received front-line systemic treatment, POD24 is associated with poorer survival and may represent a useful endpoint in future prospective clinical trials.

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Keywords: extranodal lymphomas; extranodal marginal zone lymphoma of MALT type; prognostic indices.

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INTRALESIONAL RITUXIMAB SUPPLEMENTED WITH AUTOLOGOUS SERUM IN RELAPSED CD20+ INDOLENT LYMPHOMAS OF THE CONJUNCTIVA: ACTIVITY AND SAFETY RESULTS OF THE "IRIS" TRIAL

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Background: Most lymphomas primarily arising in the conjunctiva exhibit indolent behavior, with rare cases of systemic dissemination and symptomatic disease. Conventional chemo-, radio- and immune-therapy are associated with good disease control rates; however, the excellent prognosis of this lymphoma seems to suggest that less invasive and safer therapies should be preferred. Intravenous rituximab is well tolerated, but responses are usually short lived. Topic and intralesional therapies may play a role in the management of conjunctival lymphomas, but experience is limited to a few pts treated with intralesional interferon. Herein, we report a monoinstitutional phase II trial addressing safety and activity of intralesional rituximab supplemented by autologous serum in pts with CD20+ indolent lymphomas of the conjunctiva (NCT01514344 – IRIS trial).

Methods: Adults with relapsed/refractory CD20+ indolent lymphoma (MZL, FL, SLL, lymphoplasmacytic lymphoma) limited to the conjunctiva (mono- or bilateral disease), and measurable disease were registered and treated with intralesional injections of 10-20 mg of undiluted rituximab (1-2 ml) combined with local anesthetic. Pts received four weekly doses followed by six monthly injections. Toxicity was assessed before each rituximab dose, and objective response was assessed after weekly doses and at the end of the therapeutic program by photographs of the lesions. 500 microL of autologous serum were added to rituximab in pts who did not achieved at least partial response (PR). Safety was the primary endpoint; response rate and antitumor effect of the addition of autologous serum were secondary endpoints.

Results: 20 pts (median age 63 – range 30-81; 12 females) were registered; all pts had MZL, 4 pts had HBV/HCV infection, no pt had increased LDH serum levels. Treatment tolerability was excellent: there were no interruptions or delay due to toxicity; only 3 pts experience mild local effects like edema and bleeding. 11 pts achieved tumor regression after the 4 weekly doses, whereas 9 pts required autologous serum. Response at the end of the whole treatment was complete in 10 pts and partial in 2, with an ORR of 63% (95%CI: 42-84%). At a median follow-up of 3 years (range 7-73), 12 pts remain relapse-free; relapse occurred in the contralateral eye in 2 pts, with a 3-year local disease control rate of 63 ±11%, and a 3-year PFS of 60 ±12%. Interestingly, 3 failed pts were retreated with intralesional rituximab and autologous serum achieving a further response that lasted 12, 25+ and 32+ months, respectively. All pts are alive.

Conclusions: Intralesional rituximab is a safe and active treatment in pts with conjunctival indolent lymphoma. The addition of autologous serum is associated with improved response in some cases.

Retreatment of local relapses can result in a second long-lasting response.

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MULTI-OMICS LANDSCAPE OF SPLENIC MARGINAL ZONE LYMPHOMA (SMZL) - INTERIM ANALYSIS OF IELSG46 STUDY

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Introduction: Splenic marginal zone lymphoma (SMZL) is heterogeneous at the morphological, biological and clinical level, suggesting the existence of includes still unveiled subtypes. According to the 2016 WHO classification, discovery of new entities or subtypes within heterogeneous tumors should be based using a multiparametric approach, encompassing tumor histopathology, genetics, immunophenotype and clinical course.

Methods: The IELSG46 study (NCT02945319) is the largest repository of clinical data and spleen samples from SMZL patients, and has the statistical power to resolve tumor subgroups within this lymphoma. Mutations were identified by CAPP-seq of tumor genomic DNA, copy number aberrations (CNA) by sequencing reads-based GATK4-CNV, IGHV rearrangements by LymphoTrack®, gene expression profiling (GEP) by mRNA-seq.

Results: Overall, the genetic-immunogenetic profile of the study cohort (n=382) was consistent with prior unselected SMZL series, reported by us in previous findings by our and other groups. Genes recurrently mutated in >10% SMZL were *KLF2*, *NOTCH2*, *KMT2D*, *TNFAIP3* and *NOTCH1*. Deletion 7q occurred in 24% SMZL and IGHV1-2*04 was used in 30% SMZL. Machine learning approaches applied to multiple layers of "big" data led to the discovery of unexpected molecular clusters (MC) in SMZL, each associated with distinct clinical outcome (Fig.1A). MC1 (NF-κB pathway) and MC2 (NOTCH pathway), driven by *KLF2* and *NOTCH2* mutations respectively, were enriched in IGHV1-2*04 gene usage and 7q deletion. MC3 was defined by epigenetic mutated genes and was enriched in *KMT2D* mutations. MC4 was enriched in *TP53* and *ATM* mutations, and in 17p deletions. SMZL patients showed an overall 26% decrease in survival at 15 years compared to the matched general population. Among molecular clusters, only MC1 and MC2 showed a lower relative survival compared to the general population, indicating a significant impact of the disease on MC1 and MC2 patients' life expectancy. Transcriptome profiling of 55 tumor samples led to the discovery of 3 molecular phenotypes (MP) in SMZL. MP1 showed an inflammatory response signature, MP2 a B-cell receptor signaling signature, and MP3 that lacked of both these signatures (Fig.1B).

Conclusions: Genetic analysis of a large cohort of SMZLs cases identified four molecular subtypes characterized by unique deregulated genetic pathways, clinical outcome and potentially a molecular phenotype. These results can provide the basis for proposing the

Fig. 1
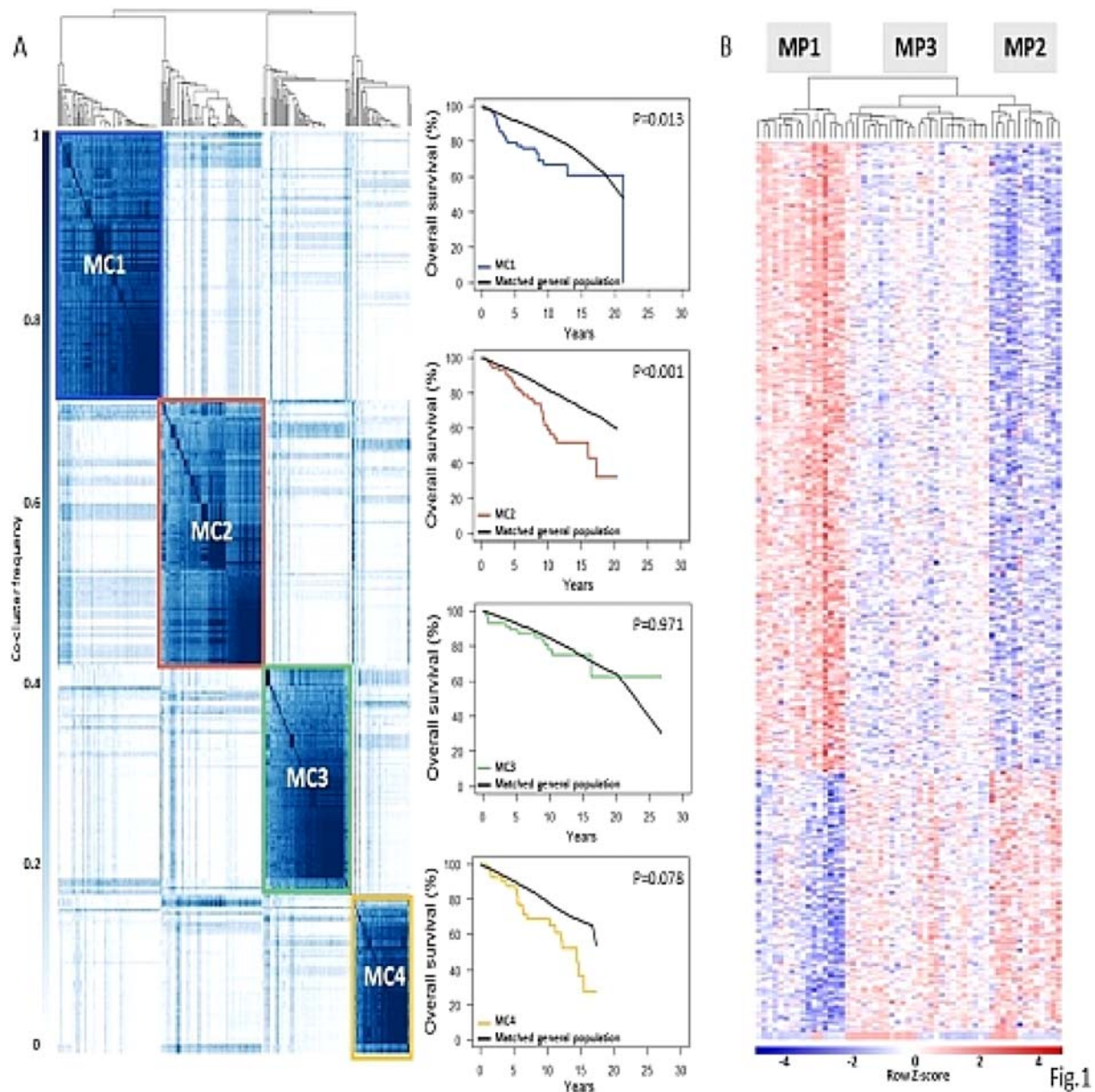
classification of SMZL into provisional molecular subtypes, that may lead to a conceptual edifice for developing precision therapies for SMZL patients.

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UMBRALISIB MONOTHERAPY DEMONSTRATES EFFICACY AND SAFETY IN PATIENTS WITH RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA: A MULTICENTER, OPEN-LABEL, REGISTRATION DIRECTED PHASE 2 STUDY

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Introduction: Rituximab (RTX) alone or in combination with chemotherapy has substantially improved treatment outcomes for patients (pts) with marginal zone lymphoma (MZL), but relapse is common and not all pts are acceptable candidates for, or respond to, current salvage therapies. Umbralisib is a novel, next-generation PI3K-delta inhibitor with unique inhibition of casein kinase-1ε (CK1ε) and, compared to earlier generation PI3K-delta inhibitors, exhibits a differentiated tolerability profile with reduced rates of immune-mediated toxicity (Burris et al, 2018). This registration-directed study evaluates the efficacy and safety of umbralisib in pts with relapsed/refractory (R/R) MZL.

Methods: Pts had histologically confirmed MZL, ECOG PS ≤2, and had previously received ≥1 prior therapy including at least one CD20 monoclonal antibody (mAb)-containing regimen. All pts received umbralisib 800 mg orally once daily until progression or unacceptable toxicity. The primary study endpoint was overall response rate (ORR) as assessed by an independent review committee (IRC) according to 2007 IWG criteria. ORR by investigator assessment is reported here, and ORR by IRC is forthcoming. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), and safety.

Results: Sixty-nine pts were enrolled; we report on the first 38 who are eligible for at least 6 months (mos) of follow-up as of the data cutoff date. Disease status for the 38 pts: extranodal (n=23), nodal (n=8), and splenic (n=7). Median age was 67 years (range, 34-81). Median number of prior systemic therapies was 2 (range, 1-5). Seven pts (18%) had received monotherapy RTX only, and 26 (68%) had received at least one CD20 mAb-containing chemoimmunotherapy. As of the cut-off date, the median follow-up was 9.6 mos. Per investigator assessment, ORR was 55% (4 CRs and 17 PRs), 29% of pts (n=11) had stable disease (SD) of which 6 of these SD pts remain on study with durations ranging from 7-12+ mos. The clinical benefit rate (CR+PR+SD) was 84%, and 91% of pts with at least 1 post-baseline assessment experienced tumor reductions. The median time to initial response was 2.7 mos, while the median DOR was not reached (95% CI: 8.4-not reached). The 12-month PFS was 71%. The most common (≥20%) adverse events (AE) of any grade included: diarrhea (45%), nausea (29%), fatigue (26%), headache (26%), cough (24%), and decreased appetite (21%). The most common Grade 3/4 events were neutropenia (8%), febrile neutropenia (5%), and diarrhea (5%). As of the cutoff date, 16 pts discontinued treatment (PD: 18%; AEs: 8%; pt decision: 8%; physician decision: 8%) and 58% continue treatment.

Conclusions: PI3K-delta inhibition with single-agent umbralisib is active and well tolerated in pts with R/R MZL, achieving durable responses with chemotherapy-free therapy.

Keywords: marginal zone lymphoma (MZL); non-Hodgkin lymphoma (NHL); PI3K/AKT/mTOR.

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IBRUTINIB FOR THE TREATMENT OF BING-NEEL SYNDROME: A RETROSPECTIVE, MULTICENTER STUDY

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3-year EFS rate: 69% (95% CI 48-84%)

Number at risk
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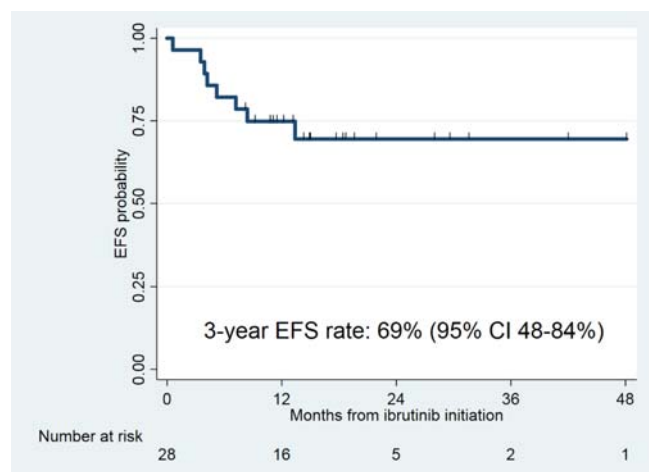
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Background: The oral BTK inhibitor ibrutinib is the only approved therapy for patients with symptomatic Waldenström macroglobulinemia (WM). Bing-Neel syndrome (BNS) is a rare complication of WM that results from infiltration of malignant lymphoplasmacytic cells into the central nervous system (CNS) causing neurological deficits. Treatment options in patients with BNS are limited to agents with CNS penetration. Furthermore, patients with BNS are excluded from WM clinical trials.

Methods: We performed a multicenter retrospective study evaluating the efficacy of ibrutinib in patients with BNS. The diagnosis of BNS was established in patients with a clinicopathological diagnosis of WM by radiological and/or cytological evidence of CNS involvement by WM. Ibrutinib was given orally at doses of 420-560 mg PO once daily until disease progression or intolerable toxicity. Response was assessed using criteria from the 8th International Workshop for WM. Events were defined as disease progression, death from disease progression and stopping ibrutinib due to ibrutinib-related toxicity. The time to event was estimated using the Kaplan-Meier method. Adverse events were assessed according to the Common Toxicity Criteria version 4.03.

Results: Twenty-eight patients were included in our study. The median age at BNS diagnosis was 65 years. Ibrutinib was the first line of treatment for BNS in 39% of patients. Ibrutinib was administered orally at a dose of 560 and 420 mg once daily in 46% and 54% of patients, respectively. Symptomatic and radiologic improvements were seen in 85% and 60% of patients within 3 months of therapy, respectively. At best response, 85% of patients had improvement or resolution of BNS

symptoms, 83% had improvement or resolution of radiologic abnormalities, and 47% had cleared the disease in the cerebrospinal fluid (CSF). With a median follow-up time of 20 months, 12 patients have stopped ibrutinib. Of these, 8 were considered related events; 3 patients had disease progression, 3 patients had ibrutinib-related toxicity and 2 patients died of disease progression. The other 4 unrelated events included death due to unrelated causes (n=2), myelodysplasia (n=1) and receiving allogeneic transplantation (n=1). The median EFS was not yet reached. The 3-year EFS rate was 69% (95% CI 48-84%) (Figure). Thirteen patients (45%) had a reported adverse event. Grade 4 adverse events included neutropenia (n=1). Grade 3 adverse events included pneumonia (n=2), muscle cramps (n=1), bleeding (n=1), atrial fibrillation (n=1), and ventricular tachycardia (n=1).

Conclusion: Ibrutinib monotherapy can induce durable responses with acceptable toxicity in patients with BNS. Despite symptomatic and radiological improvements in the majority of patients, half of the patients can have persistence of disease in the CSF, and this should not represent treatment failure.

Keywords: BTK inhibitors; ibrutinib; Waldenström's macroglobulinemia (WM).

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IBRUTINIB MONOTHERAPY PRODUCES LONG-TERM DISEASE CONTROL IN PREVIOUSLY TREATED WALDENSTROM'S MACROGLOBULINEMIA. FINAL REPORT OF THE PIVOTAL TRIAL (NCT01614821).

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MYD88 mutations are present in $\geq$95% of WM patients and trigger malignant cell survival through BTK and HCK, both ibrutinib targets. CXCR4 mutations are found in 30-40% of WM patients and confer in vitro drug resistance. We therefore investigated the activity of ibrutinib in previously treated WM patients. The initial findings showed that ibrutinib was highly active, and supported FDA and EMA drug approval in WM (Treon et al, NEJM 2015). Herein, we provide a long-term follow-up of this study that included impact of MYD88 and CXCR4 mutation status on long-term progression-free survival. Sixty-three symptomatic WM patients with a median of 2 (range 1-9) prior therapies, including 40% refractory were enrolled. Ibrutinib was

initiated at 420 mg a day, and dose de-escalation for toxicity permitted. The median time on ibrutinib was 46 months. Improvements in categorical responses occurred with prolonged treatment, with overall ($\geq$ minor response) and major ($\geq$ partial response) response rates of 90.4% and 77.7%, respectively. At best response, median serum IgM level declined from 3,520 to 821 mg/dL (p<0.0001), bone marrow involvement declined from 60% to 20% (p<0.0001), and hemoglobin level rose from 10.5 to 14.2 g/dL (p<0.0001). Response attainment including the impact of MYD88 and CXCR4 mutation status on responses is shown in **Table 1.**

Adverse events (Grade $\geq$2) in $\geq$5% of patients during active follow-up were: neutropenia (22%); thrombocytopenia (14%), pneumonia (9%); GERD (8%); hypertension (8%); anemia (6%); and skin infection (5%). Seven patients (11%) had an atrial arrhythmia at a median of 4 (range 0-33 months), and 6 continued ibrutinib following medical management of arrhythmia. The findings confirm that ibrutinib is highly active, and produces long-term responses in previously treated WM. Prolonged ibrutinib therapy is associated with deeper responses, including VGPR. Response activity, time to major response, and PFS are impacted by MYD88 and CXCR4 mutation status.

Keywords: ibrutinib; Waldenström's macroglobulinemia (WM).

	All Patients* (n=63)	MYD88^MUT CXCR4^WT (n=36)	MYD88^MUT CXCR4^Mut (n=22)	MYD88^WT CXCR4^WT (n=4)	P-value
Overall Responses (%)	90.4	100	86.4	50.0	<0.001
Major Responses (%)	77.7	97.2	63.6	0	<0.001
VGPR (%)	28.6	44.4	9.1	0	<0.001
Median Time to Minor Response or better (months)	1.0 (range 1.0-22.5)	1.0 (range 1.0-15)	1.0 (range 1.0-22.5)	1.0	0.10
Median Time to Major Response (months)	2.0 (range 1.0-49)	2.0 (range 1.0-49)	6.0 (range 1.0-40)	N/A	0.05

*One patient had MYD88 mutation, but no CXCR4 mutation determination, and had stable disease.

Figure 1 shows the Kaplan Meier curves for progression free survival (PFS) for all study participants **(A)**, and by MYD88 and CXCR4 mutation status **(B)**. The 5-year PFS for all patients was 54%. For patients with MYD88^Mut CXCR4^WT, the median PFS was not reached (5-year PFS 71%). For patients with MYD88^Mut CXCR4^Mut, median PFS was 42 months (5-year PFS 34%), and 54 months (5-year PFS 39%) if transformation for two patients attributed to prior nucleoside analogue exposure was not counted as ibrutinib-related progression. For those with MYD88^WT disease, the median PFS was 5 months (Log-rank p<0.001 for 3-way comparison). The 5-year overall survival for all patients was 87%.

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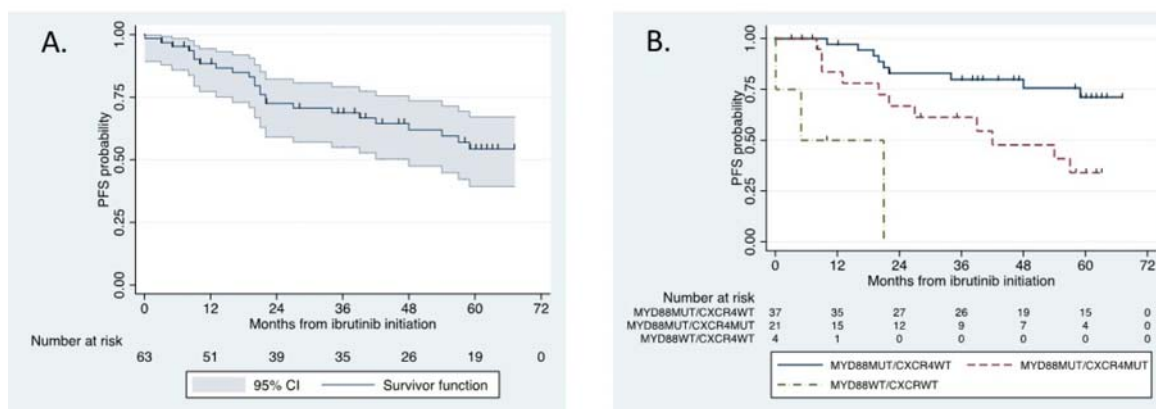
POSTER PRESENTATIONS

BIOLOGY AND PATHOLOGY

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ONE-YEAR REAL-LIFE TARGETED NEXT GENERATION SEQUENCING FOR LYMPHOMA DIAGNOSIS: STUDY OF PATIENTS FROM THE FRENCH LYMPHOMA NETWORK IN RHÔNE-ALPES

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Introduction: During last years, NGS studies, performed on patient cohorts, provided new insights into genomic characterization of lymphoma landscape. However, to date, the impact of NGS data on the daily diagnosis practice has not been reported yet. We reported here the clinical impact of targeted next generation sequencing (TNGS) in lymphoma diagnosis after expert histological review in Rhône-Alpes (France).

Materials and Methods: In France, difficult lymphoma diagnoses are systematically reviewed, in real time, by histological experts through the Lymphopath Network. To increase diagnosis accuracy, we used a TNGS approach to identify pathogenic genomic variants that could be helpful in lymphoma diagnosis. From 12/2017 to 12/2018, we performed TNGS on tumour biopsy (FFPE or frozen) samples from primary CNS lymphomas and lymphoma of difficult diagnosis, that were histologically reviewed in Lyon Pathology Department. Because a difficult diagnosis implies a doubt between several entities, benign conditions were classified with the lymphoma they were suspect of. We used a panel of 46 genes, chosen after an extensive literature review of NGS lymphoma studies. Impact of TNGS data on histological diagnosis was classified as follows: confirms diagnosis; changes diagnosis; does not help. The term concordance was defined as the addition of "confirms" and "does not help". To evaluate the potential impact on patient care, modifications into the final diagnosis were divided into major and minor changes according to the ESMO guidelines.

Results: Among the 230 patients and after expert histological reviewing, 20 (8.6%) were suspected of primary CNS lymphoma (PCNSL), 47 (20.3%) of large B-cell lymphoma (LBCL), 90 (38.7%) of small B-cell lymphoma (SBCL), 6 (2.6%) of Hodgkin lymphoma (HL), 56 (23.9%) of TFH T-cell lymphoma and 12 (5.7%) of non-TFH T-cell lymphoma. After TNGS, the overall concordance rate was 85.3%, from 76.9% in non-TFH T-cell lymphoma to 100% in PCNSL and HL. TNGS confirmed the histological diagnosis in 122 cases (53%), changed the diagnosis in 33 cases (14.3%) and did not bring any help in 75 cases (32.6%, from 10% in PCNSL to 100% in HL). Modifications between initial and final diagnosis had an impact on patient care for 11.3% of cases (26/230). Diagnosis modifications occurred in all types of lymphoma except PCNSL and HL, and the highest modification rate was in TFH and in non-TFH T-cell lymphoma, 21.8% and 23.1%, respectively. In about 2/3rd (65,4%) of the cases of changes, reclassification of the lymphoma subtype had a direct therapeutic impact, whereas only 12.1% of the changes were a reclassification between benign and malignant.

Conclusions: This study highlights that TNGS may directly contribute to a more accurate diagnosis in lymphoma patients and improve their clinical management in routine. One current limitation is the lack of sensitivity of TNGS in lymphoma with low tumour infiltration.

Keywords: B-cell lymphoma; molecular genetics; T-cell lymphoma (TCL).

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MUTATIONAL LANDSCAPE OF DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) AT DIAGNOSIS AND AT PROGRESSION ASSESSED BY CIRCULATING TUMOR DNA ANALYSIS

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Introduction: Previous studies have highlighted the potential of circulating tumor DNA (ctDNA) to determine the mutational profile of DLBCL, and assess the molecular changes over time and the genetic mechanisms of resistance. In addition, the quantity of ctDNA could also predict the response and outcome of the patients. The aim of this study was to analyze the mutational profile at diagnosis and its dynamics after frontline treatment and in the refractory/relapse settings.

Methods: We included 65 patients (M/F 32/33, median age 64 years) diagnosed with DLBCL in a single institution between 2016 and 2018 according to the WHO criteria. All patients were treated with chemo-immunotherapy. After initial treatment, 47 patients achieved CR, 4 PR, 7 were refractory and in 7 cases the response was not evaluable. Samples were obtained both at diagnosis and at relapse/progression in refractory/relapsed patients. Tumor genomic DNA (gDNA) was isolated from formalin-fixed paraffin-embedded (FFPE) diagnostic tissue biopsies and at relapse when available. A panel of 115 genes was amplified using a hybridization capture based protocol from 10-30 ng of ctDNA and 150 ng of gDNA (SureSelectXT-Agilent Technologies) and sequenced in a MiSeq instrument (Illumina).

Results: ctDNA was obtained from all patients at diagnosis (median of 34 ng; range: 10-1507 ng) and from 12 refractory/relapsed cases. At least one mutation could be detected in 88% of the cases. Median number of mutations per sample was 6 (0-21 mutations). The genes most frequently mutated at diagnosis in plasma samples were *KMT2D, TP53, MYD88, TNFRSF14, PIM1, CREBBP, BCL2* and *EP300*. In 38 cases, paired FFPE samples were available as detailed in the figure. Sensitivity of ctDNA to detect tumor mutations at baseline FFPE samples was 75% (95%IC: 69.5-80.5). Of note, most of the cases in which mutations were not detected in the ctDNA had a primary extranodal origin. In the 12 cases with a ctDNA sample at diagnosis and at progression, 5 cases showed the same mutational profile, whereas in 6 cases a change in the number of mutated genes was observed (3 cases had fewer mutations; 3 cases

had new mutations) and in one case no mutations were detected at relapse. In addition, selection of minor subclonal mutations was observed in 2 cases. Patients with high pretreatment ctDNA levels (>3 log hGE/mL) had a worse PFS and OS than those with low levels (18-month PFS 24 vs 77%; 18-month OS 58 vs 94%; p<0.004).

Conclusions: ctDNA shows a good correlation with the information obtained in the tumor. Therefore it could be a valuable tool to assess the mutational profile both at diagnosis and at relapse. Pretreatment ctDNA levels have an impact on outcome.

Keywords: diffuse large B-cell lymphoma (DLBCL); molecular genetics.

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TARGETED GENOTYPING OF CIRCULATING TUMOR DNA FOR CLASSICAL HODGKIN LYMPHOMA MONITORING: A PROSPECTIVE STUDY

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Introduction: The relevance of circulating tumor DNA (ctDNA) analysis as a liquid biopsy and minimal residual disease tool in the management of classical Hodgkin Lymphoma (cHL) patients was demonstrated in retrospective settings and remains to be confirmed.

Methods: We developed a targeted Next-Generation sequencing (NGS) panel for fast analysis (AmpliSeq® technology) of nine commonly mutated genes in biopsy and ctDNA of cHL patients. We then conducted a prospective trial to assess ctDNA follow up at diagnosis and after 2 cycles of chemotherapy (C2). A dedicated bioinformatics pipeline to optimize detections of variants with low rates and minimize artefactual misinterpretations was built. Sixty cHL patients treated by first line conventional chemotherapy (BEACOPPescalated [21.3%], ABVD/ABVD-like [73.5%] and other regimens [5.2%, for elderly patients] were included in this non-interventional study (NCT02815137).

Results: Median age of the patients was 33.5 years (range 20-86) with a predominance of male patients, scleronodular subtype and ECOG 0-1 (53.3%, 70% and 88.3%, respectively). Variants were
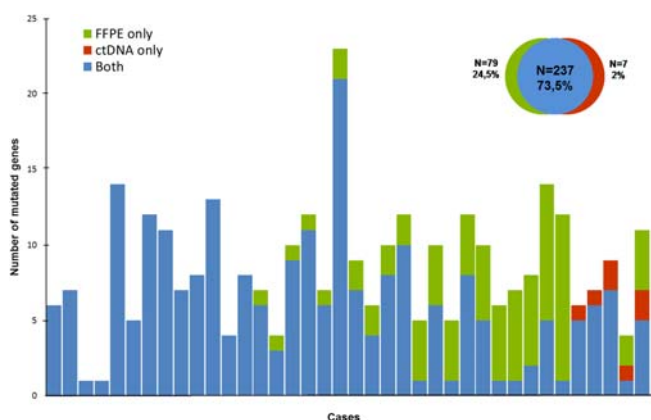
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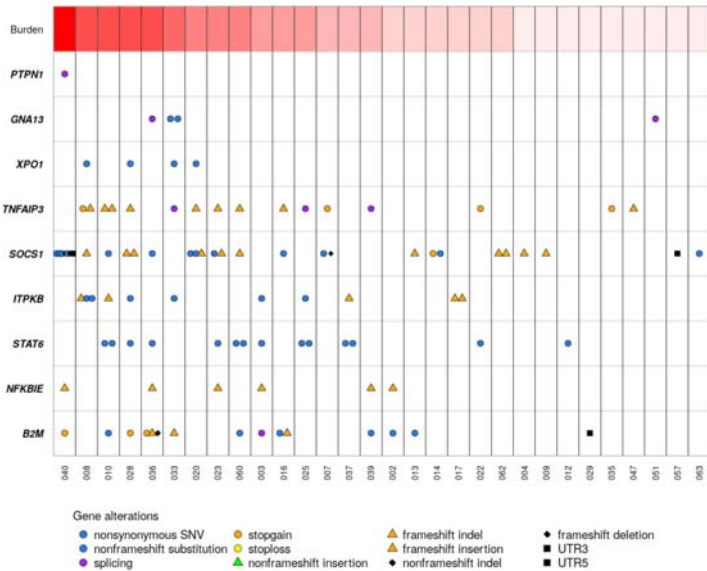
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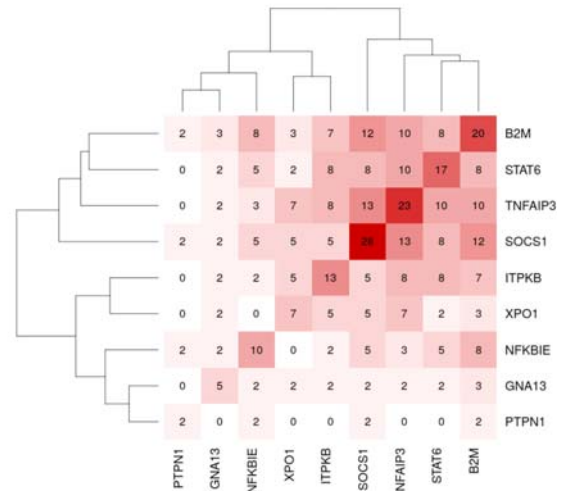
identified in 33 (55%) patients, precisely in 16/30 (53.3%) and 30/60 (50%) of available biopsy and ctDNA samples respectively. Concordance between genetic profiles of biopsy and ctDNA was accurate for 22/30 patients (73.3%). Mutations of *NFKBIE*, *TNFAIP3*, *STAT6*, *PTPN1*, *B2M*, *XPO1*, *ITPKB*, *GNA13* and *SOCS1* were found in 11.7% (mean number of variants by sample [range]: 1 [0-1]), 25% (1.1 [0-2]), 21.7% (1.4 [0-2]), 1.7% (1 [0-1]), 25% (1.3 [0-3]), 6.7% (1 [0-1]), 15% (1.4 [0-3]), 5% (1.3 [0-2]) and 31.7% (1.8 [0-7]) of all patients, respectively. Unsupervised hierarchical clustering was performed among the 9 genes to represent the association of alterations (See **Figure 1**).

Higher level of [ctDNA] at diagnosis was associated with adverse characteristics: age ≥45 years, presence of anemia (hemoglobin <10.5g/dl), albuminemia <40g/l, sedimentation rate ≥50mm, stage III-IV, lymphocytes count <0.6 G/L, presence of B symptoms, International prognostic Index ≥3, elevated LDH. The *ITPKB* and *B2M* mutated patients displayed more disseminated disease (≥ 4 median nodal areas versus [vs] 3 for non-mutated patients, p = 0.005) and *XPO1* mutations were associated with female sex (p = 0.042). Median VAF were higher in ctDNA than in biopsy (3.23% vs 2.15%, p = 0.023) and there was a moderate correlation between higher metabolic tumor volume (MTV) and higher [ctDNA] (r = 0.36, p = 0.005).

Regarding early therapeutic response, 45 patients (83%, NA = 6) had a negative positron emission tomography (PET) after C2 (Deauville Score 1-3). Mean of DeltaSUVmax after C2 was -78.8%. We analyzed ctDNA after C2 for 45 patients (70%). A rapid clearance of ctDNA in all cases was observed after C2.

Conclusions: Variants detection in ctDNA is suitable to depict the genetic features of cHL at diagnosis and may help to assess early treatment response, in complement to PET. [ctDNA] level and genotype are correlated with clinical characteristics and presentation.

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ANALYSIS OF CIRCULATING TUMOR DNA (ctDNA) IN CEREBROSPINAL FLUID DETECTS THE PRESENCE OF CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT IN B-CELL LYMPHOMAS

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Introduction: Central nervous system (CNS) involvement in B-cell malignancies is associated with frequent relapses and poor prognosis. Recently, the presence of circulating tumor DNA (ctDNA) in plasma has been correlated with treatment response and outcome in B-cell malignancies. In brain tumors, cerebrospinal fluid (CSF) ctDNA better represents the tumoral mutational profile than plasma. Against this background, we hypothesized that in CNS lymphomas (CNSL), ctDNA

Figure 1: Analysis of ctDNA in CSF and plasma in patients with restricted CNS disease and changes in ctDNA during treatment.
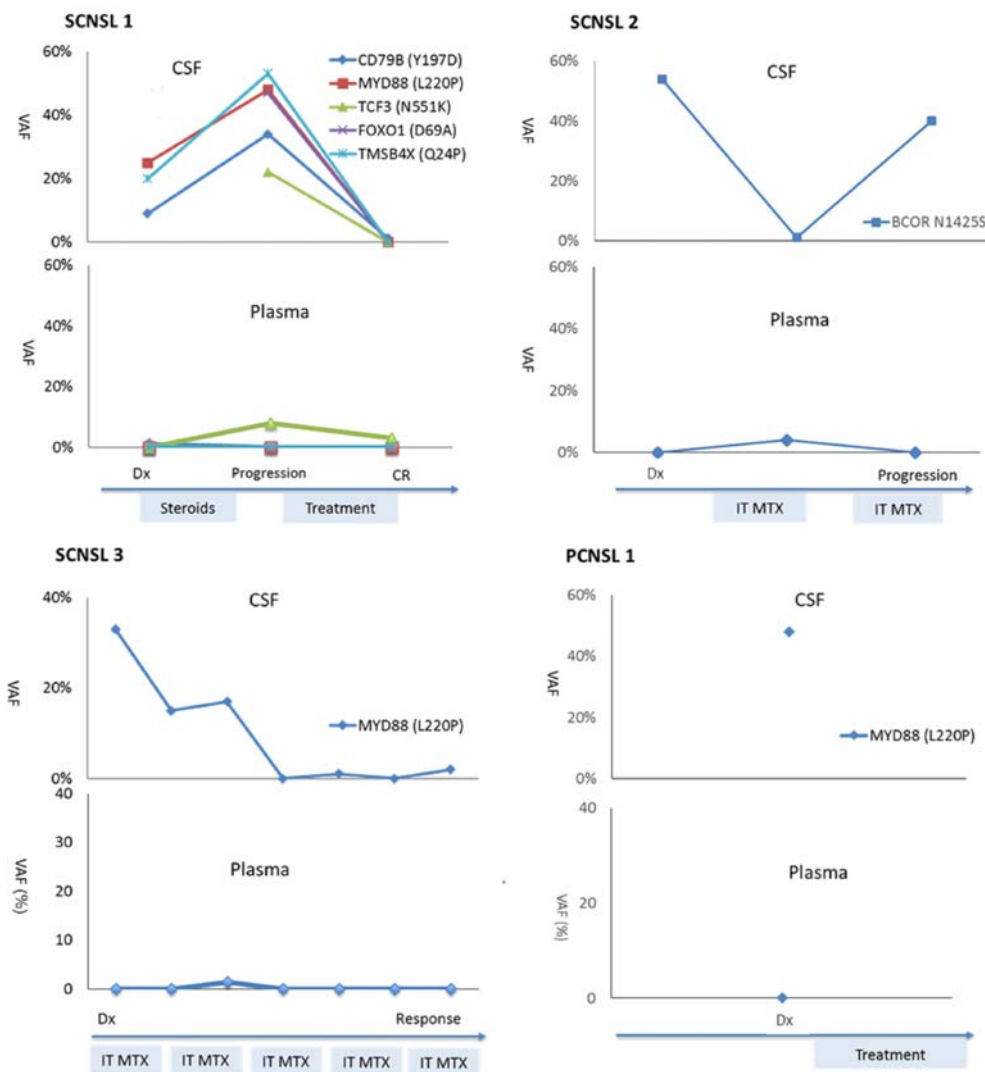
analysis in CSF could be useful to detect the disease and to appraise the response to treatment. Furthermore, CSF ctDNA could help to detect occult leptomeningeal (LM) disease.

Methods: Fifteen patients diagnosed with the following conditions were included: primary CNSL (PCNSL), n = 1; secondary CNSL (SCNSL), n = 3; systemic diffuse large B cell lymphoma (DLBCL) with risk factor for CNS relapse, n = 9; and Burkitt lymphoma (BL), n = 2. CSF and plasma were collected before treatment in all patients and sequentially in 11. Tumors were sequenced using whole exome sequencing (n = 6) or a next generation sequencing panel (n = 11) to identify at least 1 somatic mutation. Two patients had a *MYD88* mutation previously identified by Sanger sequencing. We next designed personalized droplet-digital PCR assays for each mutation. Conventional cytology (CC) and flow cytometry (FC) were performed in all CSF samples.

Results: We detected ctDNA in the CSF from all patients with CNSL (PCNSL, n = 1; SCNSL, n = 3). In these 4 cases with restricted CNS disease, the variant allele frequencies (VAFs) in CSF were higher than in plasma. Moreover, in patients with sequential samples (n = 3) we

observed that VAFs of CSF ctDNA decreased with response to therapy while increased with disease progression (Figure 1). Finally, in these 4 patients, LM disease was detected by FC in 3 patients and undetected by FC or CC in 1 patient. As per systemic lymphoma, 11 patients without detectable LM disease (negative CC and FC) and risk factors for CNS relapse (DLBCL, n = 9; BL, n = 2) were included. Interestingly, we detected CSF ctDNA in 2 cases, with similar VAFs in CSF and plasma. In the first patient, the CSF ctDNA disappeared after the first cycle of therapy and no CNS relapse has been observed to date (follow-up 15 months), while the other one died shortly after treatment due to progression. In the remaining 9 cases in whom CSF ctDNA was not detected, no CNS relapse was observed after a median follow-up of 18 months. Notably, in 7 out of these 9 cases ctDNA was found in plasma, these levels of ctDNA decreasing after treatment in all patients with PET response (n = 5).

Conclusions: In this study, we demonstrated that the presence of ctDNA in CSF of patients with CNSL correlates with tumor burden. In addition, we showed that in patients with CNS involvement, CSF

ctDNA could be a very sensitive method in assessing the tumor burden at diagnosis and the response to treatment.

Keywords: diffuse large B-cell lymphoma (DLBCL); primary CNS lymphoma (PCNSL).

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MOLECULAR ANALYSES AND AN INNOVATIVE DIAGNOSTIC ALGORITHM IN *MYC*-NEGATIVE BURKITT-LIKE LYMPHOMA WITH 11Q ABERRATION: A SINGLE INSTITUTION EXPERIENCE

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Burkitt-like lymphoma with 11q aberration (BLL,11q) is a new entity of a germinal center (GCB)-derived, highly aggressive B-cell lymphoma. Clinically and pathomorphologically, BLL,11q resembles Burkitt lymphoma (BL), but it lacks *MYC* rearrangements and presents proximal gains and distal losses in chromosome 11. In the updated 2017 WHO classification, BLL,11q has been recognized as a provisional entity. BLL,11q could be promoted to definite lymphomas but for this purpose it is necessary to publish as many new cases as possible, and more molecular studies are expected to add to an understanding and managing of this very rare malignancy.

Still, the recognition of BLL,11q entity is clinically relevant because a favorable outcome is observed after BL-directed therapy. Unfortunately, the routine diagnosis of BLL,11q is difficult, and BLL,11q is often misdiagnosed by histopathology and due to the lack of *MYC* rearrangement it is inappropriately treated. To the best of our knowledge, we have so far published the largest cohort of BLL,11q and of BL cases carrying both *MYC* rearrangement and 11 aberration. Our initial RT-qPCR-based miRNA studies showed similarities of BLL,11q (n = 12) to BL

(n = 34), but not to DLBCL (n = 49) in miR-155, miR-21 and mir-26a expression Next, a detailed immunohistochemical and flow cytometry analysis of 10 BLL,11q and 23 *MYC*-positive BL cases revealed similarities along with subtle but essential differences in BLL,11q and BL immunophenotypes.

We also correlated the occurrence of bulky tumors in BLL,11q with amplification of the 11q23.3 region, where *KMT2A* is located. Most recently, by next generation sequencing of 10 BL and 7 BLL,11q, we identified 49 microRNAs and 2572 mRNA transcripts differentially expressed between BL and BLL,11q. Accumulating data show significant differences between sporadic BL and BLL,11q in mRNA and microRNA profiles, and point to different chromosomal and mutational profiles of BLL,11q from BL, and additionally from other aggressive GCB-lymphomas. Thus, BLL,11q seems indeed to be a molecularly distinct category. Still, BLL,11q patients, if treated with BL-directed regimen, have a relapse-free outcome similar to BL patients.

We proposed an original and practical flow cytometry- and immunohistochemistry-based diagnostic algorithm for the differential diagnosis of BLL,11q vs. BL and other aggressive lymphomas which enables BLL,11q diagnosis within 1.5 hours following fine needle aspiration biopsy procedure.

Keywords: Burkitt lymphoma (BL); fine-needle aspirate (FNA); flow cytometry.

Disclosures: Rymkiewicz, G: Other Remuneration: *Roche, fee, travel expenses.*

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HIGH RISK OF ADVERSE EVENTS AFTER AUTOLOGOUS STEM-CELL TRANSPLANTATION IN LYMPHOMA PATIENTS WITH DNA REPAIR PATHWAY MUTATIONS: A NATION-WIDE COHORT STUDY

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Cum. incidence of admission to intensive care

Figure 1
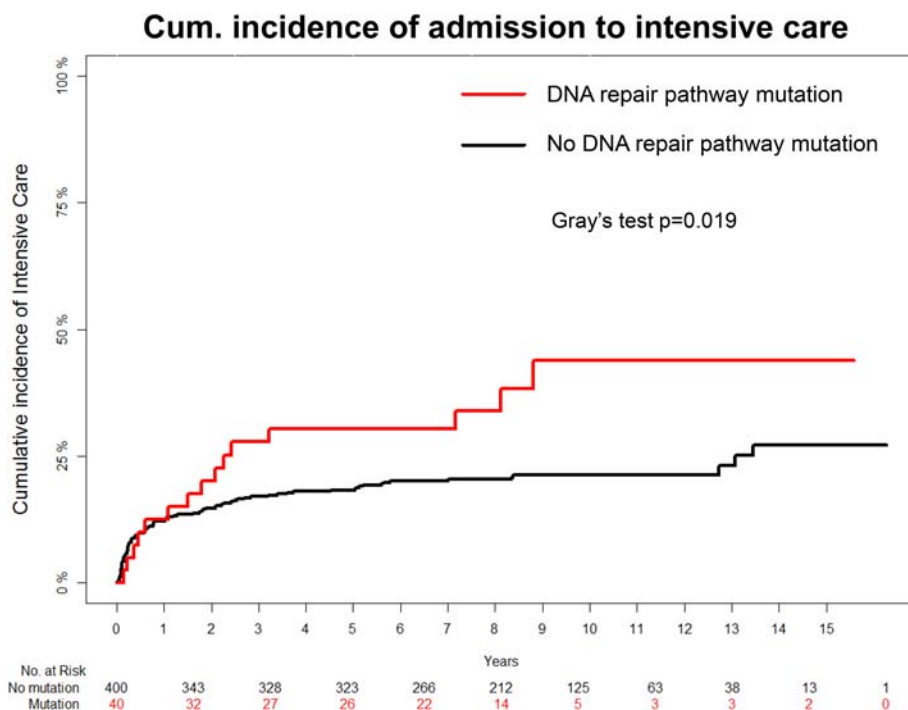
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Introduction: It is estimated that at least 30% of patients with lymphoma die within five years after autologous stem-cell transplantation (ASCT). A substantial fraction of patients succumb to therapy-related side effects. Identifying patients not suited for ASCT has so far been challenging, but clonal hematopoiesis (CHIP) mutations in peripheral blood and/or bone marrow has in single-center studies been proposed as markers of vulnerability. We performed a national population-based analysis of CHIP in lymphoma patients undergoing ASCT to investigate this.

Methods: Patients in Denmark with a lymphoma diagnosis (both Non-Hodgkin and Hodgkin lymphoma) and a registered autologous stem cell sample harvested at Danish transplant centers between January 1, 2000 and July 1, 2012 were included. We performed targeted next generation sequencing (NGS) of autologous stem cell harvest material with a panel covering 21 of the most commonly mutated genes in clonal hematopoiesis. To allow accurate mutation calling unique molecular identifiers (UMI's) were employed and a median coverage of 5832X was obtained.

We retrieved prospective clinical data from five independent nation-wide registries covering death, relapse, severe infections (sepsis and invasive fungal infection), secondary malignancies, days in hospital, use of transfusion products (red blood cell and platelets), and intensive care admission.

Results: A total of 892 patients were identified; 565 patients fit inclusion criteria and were sequenced. The median follow-up was 9.1 years (IQR 7.0–10.3). Of these, 440 patients were intended for immediate ASCT, 121 patients had stem cells harvested as part of a 'rainy day strategy', and 4 patients had unknown infusion status. CHIP mutations were identified in 112 patients (25.5%) intended for immediate ASCT. These mutations were, in contrast to findings in single-center studies, not associated with a significant inferior overall survival after adjusting for age, sex, and line of therapy (hazard ratio [HR] 1.36, 95%CI 0.93–1.99, p = 0.11). However, patients with mutations in DNA repair pathway genes (*PPM1D*, *TP53*, *BRCC3*, and *RAD21*; 9.1% of patients in the cohort) had a significant independent inferior overall survival (adjusted HR 2.37, 95%CI 1.44–3.90, p<0.0001). In addition, patients with DNA repair pathway mutations had a significant higher incidence of admission to intensive care (p = 0.019; **Figure 1**), a significant higher incidence of therapy-related leukemia (p = 0.0018), and a non-significant higher incidence of severe infections (p = 0.061). We also found that these patients had a significantly increased number of days in hospital following ASCT (p = 0.0025).

Conclusions: This nation-wide population-based study show that patients with lymphoma who carry clonal hematopoiesis mutations in genes of the DNA repair pathway (*PPM1D*, *TP53*, *BRCC3*, and *RAD21*) have a significant independent inferior overall survival (p<0.0001) and an increased risk of several adverse events after ASCT.

Keywords: autologous stem cell transplantation (ASCT); clonal hematopoiesis; non-Hodgkin lymphoma (NHL).

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EZH2 GAIN-OF-FUNCTION MUTATIONS ARE NOT ASSOCIATED WITH MORE FAVORABLE PROGNOSIS IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA (FL): A PRELIMINARY ANALYSIS ON 590 PATIENTS

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Background: Tazemetostat, a selective, oral inhibitor of the histone methyltransferase EZH2, has shown antitumor activity in FL. Gain-of-function (GOF) mutations in *EZH2* are found in 20–25% of FL tumors. Mutant (MT) *EZH2* is widely considered an oncogenic driver of FL. Some studies suggest GOF *EZH2* mutations provide a prognostic benefit in the frontline setting (1L) in FL patients (pts) treated with immunochemotherapy (ICT). However, the impact of MT *EZH2* on clinical outcomes in relapsed/refractory (R/R) FL pts receiving systemic anticancer therapy beyond frontline ICT is unknown. We present interim results from a multicenter study evaluating the impact of *EZH2* activating mutations on FL pt outcomes.

Methods: Retrospective data on therapy types and clinical outcomes are being collected from 5 academic sites. Available data from 3 sites (Barts Cancer Institute, Institute Gustave Roussy, Semmelweis University) were analyzed to determine and compare clinical outcome parameters with regard to *EZH2* mutation. Best overall response rate (ORR), per best judgment of the treating physician, was compared by *EZH2* status and stratified by line of therapy using Cochran-Mantel-Haenszel chi-square test. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method and compared by the logrank test. Tumor tissues, collected primarily at time of diagnosis, were analyzed for activating *EZH2* mutations (Y646X, A682G, A692V) via various approaches, including next generation sequencing, digital droplet PCR (BioRad) and the **cobas**® EZH2 Mutation Test (Roche Molecular Systems).

Results: Data from 590 pts with *EZH2* MT (n = 140) or wild-type (WT; n = 450) FL treated with systemic anticancer therapy between 1972–2017 were analysed. *EZH2* activating mutation frequency was 24%. In 1L, 43% of pts received ICT. In second line (2L) and beyond, 65–80% of pts received chemotherapy and 14–20% received ICT. Median follow-up from diagnosis was 10.5y (95% CI, 9.7–11.5). No significant differences in ORR between MT and WT *EZH2* cohorts were found in 1L, 2L, or third line and beyond (3L+). In the combined dataset, ORR for MT and WT *EZH2* cases in 1L were 89% and 87%, respectively (P = 0.493), 73% and 73%, respectively (P = 0.996) in 2L, and 82% and 80%, respectively (P = 0.647) in 3L+. There were no significant differences (P>0.05) in PFS between R/R FL pts with MT and WT *EZH2* for any line of therapy. In addition, OS was not significantly different for pts with and without *EZH2* mutations (median OS 12.7 vs 16.6y; P = 0.464; Figure).

Conclusion: No differences were observed in ORR or PFS by line of therapy in R/R FL pts with MT or WT *EZH2*. Similarly, MT *EZH2* was not associated with significantly longer OS. Findings suggest that MT *EZH2* is not a positive prognostic factor and clinical activity observed in pts with R/R FL treated with standard of care agents or tazemetostat is likely due to the drugs' mechanism of action.

Keywords: EZH2; follicular lymphoma (FL).

Overall Survival

Mutant type	140	80	48	23	15	7	1	1	0
Wild Type	450	277	169	95	48	29	8	1	0
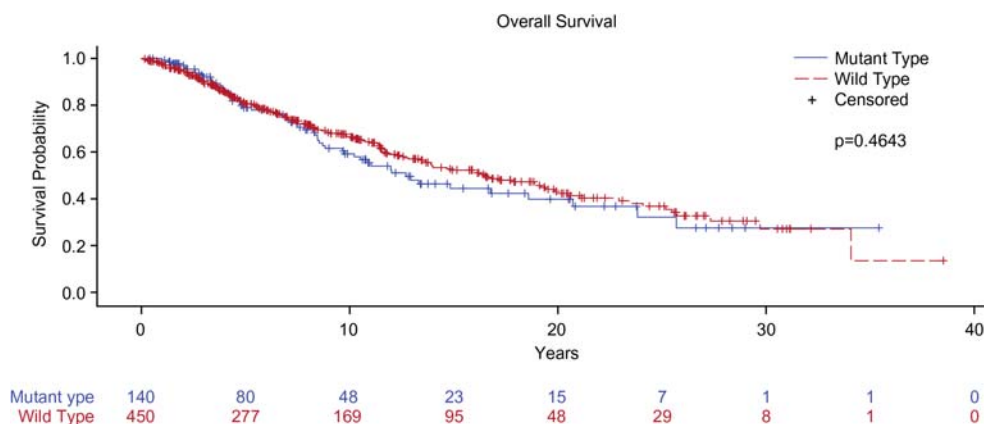
Disclosures: Michot, J: Consultant Advisory Role: *Abbvie, Aduro, Agios, Amgen, Argen-x, Astex, AstraZeneca, Aveo pharmaceuticals, Bayer, Beigene, Blueprint, BMS, Boeringer Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, Gamamabs, Genentech, Gortec, GSK, H3 biomedecine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, Medimmune, Menarini, Merus, MSD, Nanobiotix, Nektar Therapeutics, Novartis, Octimet, Oncoethix, Oncopeptides AB, Orion, Pfizer, Pharmamar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro, Xencor*; Honoraria: *Bristol-Myers Squibb, AstraZeneca, Janssen*; Other Remuneration: *AstraZeneca, Roche, Novartis, Gilead, Celgene, Bristol-Myers Squibb.* **Vose, J:** Honoraria: *Novartis, Abbvie, Epizyme, Roche, Legend Pharmaceuticals, Kyopharm, Sandoz, Vaniam Group, Janssen/Pharmacyclics, Kite Pharma, Acerta/Astra-Zeneca, Nordic Nanovector, Verastem*; Research Funding: *Amgen, Acerta Pharma, Astra-Zeneca, Bristol – Myers Squibb, Celgene, Incyte Corp., Kite Pharma, Merck, Novartis, Seattle Genetics, Inc.*; **Younes, A:** Consultant Advisory Role: *BMS, Incyte, Janssen, Genentech and Merck*; Honoraria: *Genentech, Merck, Takeda, Incyte, BMS, AbbVie*; Research Funding: *Novartis, J&J, Curis, Roche, BMS*; **Ribrag, V:** Consultant Advisory Role: *Epizyme, Servier, Nanostring, Gilead, Pharmamar, BMS, MSD, Incyte, Roche, Infinity*; Honoraria: *ESAI*; Research Funding: *Epizyme, ArgenX*; **Fitzgibbon, J:** Consultant Advisory Role: *Epizyme, Gilead, Roche*; Research Funding: *Epizyme*; **Yang, J:** Employment Leadership Position: *Epizyme, Inc*; Stock Ownership: *Epizyme, Inc*; **Agarwal, S:** Employment Leadership Position: *Epizyme, Inc*; Stock Ownership: *Epizyme, Inc*; **Newberry, K:** Employment Leadership Position: *Epizyme, Inc*; Stock Ownership: *Epizyme, Inc*; **Michaud, N:** Employment Leadership Position: *Epizyme, Inc*; Stock Ownership: *Epizyme, Inc.*

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TREATMENT-DEPENDENCE OF HIGH-RISK GENE EXPRESSION SIGNATURES IN *DE NOVO* FOLLICULAR LYMPHOMA

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Background: *De novo* follicular lymphoma (FL) is an indolent disease with good prognosis, but some patients (pts) with FL who relapse early (progression within 24 months) have significantly worse outcomes (Casulo and Barr. Blood 2019). We evaluated the performance and treatment-dependence of two high-risk FL models in pts with FL treated in the Phase III GALLIUM trial (NCT01332968).

Methods: Enrolled pts (age ≥18 years with previously untreated advanced-stage FL) were randomised to receive either obinutuzumab (G)- or rituximab (R)-based immunochemotherapy plus maintenance. The chemotherapy arm (CHOP, CVP, or bendamustine [benda]) was selected by each study centre (33%; 10%; 57%, respectively). Pt samples with available tumour tissue (n = 274) were profiled by RNASeq; normalised counts were combined using either the published weights (23-gene signature model) or principal component analysis (six-gene T-effector signature) (Huet et al. Lancet Oncol 2018; Bolen et al. Blood Adv 2017). High-risk pts were defined as the top 25th (23-gene signature) or top 75th (T-effector signature) percentile in order to align with Huet et al. (2018) prevalence. P-values were calculated using Cox-proportional-hazards (PH) after controlling for treatment arm, sex, FL International Prognostic Index (FLIPI), and geographic region.

Results: In 274 evaluable FL pts, the 23-gene signature high-risk group was not significantly associated with progression-free survival (PFS; p = 0.97). However, the 23-gene signature appeared to capture high-risk biology in pts treated with CHOP/CVP (PFS hazard ratio [HR]: 2.40 [range: 1.19—4.85]; p = 0.015; **Figure 1A**). Pts defined by the 23-gene signature as high risk performed better than low-risk pts in the benda cohort (PFS HR: 0.43 [range: 0.20—0.92]; p = 0.031), with similar trends in the R-benda (PFS HR: 0.54 [range: 0.22—1.3]; p = 0.18) and G-benda (PFS HR: 0.3 [range: 0.06—1.3]; p = 0.11) arms, representing a highly significant chemotherapy-dependent interaction (interaction p<0.001). None of the individual 23 signature genes were consistently prognostic in both treatment regimens. Significant chemotherapy dependence was observed for *ABCB1, SEMA4B, FOXO1, PRDM15, AFF3, ALDH2,* and *KIAA0040* (interaction p<0.05), suggesting that benda may overcome some of the high-risk biology connected with cell cycle or cell migration. A different treatment dependence was also seen in other prognostic signatures, including the T-effector signature (interaction p = 0.001), where a subset of pts defined as low risk with CHOP/CVP treatment captured high-risk biology among pts treated with a benda backbone (PFS HR: 0.48 [range: 0.27—0.85]; p = 0.012; **Figure 1B**).

Conclusions: We identified a significant chemotherapy-dependent interaction for two high-risk signatures in *de novo* FL, highlighting the challenges of building high-risk signatures for pts independent of treatment.

This abstract has been previously submitted to EHA 2019.
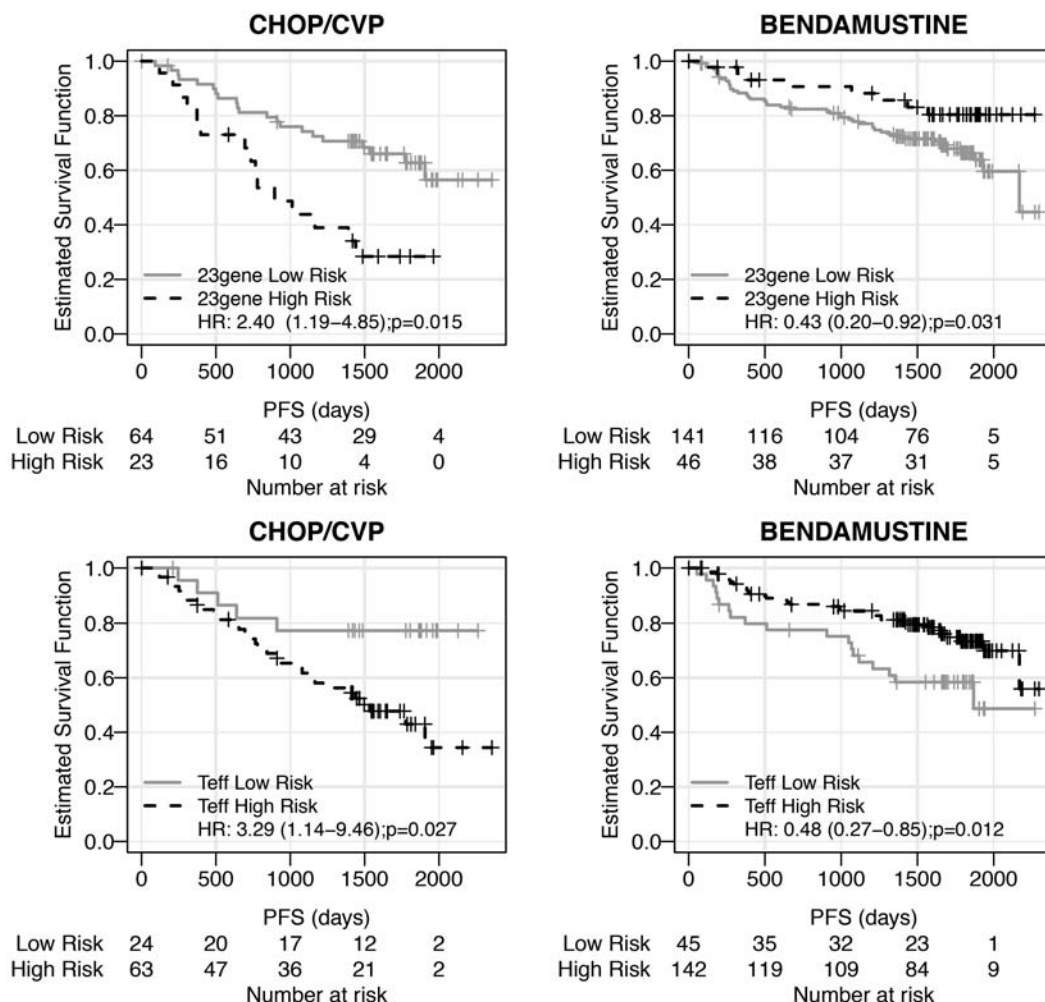
Figure 1. Progression-free survival split by (A) 23-gene signature or (B) T-effector signature is shown for CHOP/CVP-treated FL patients or bendamustine- treated FL patients. Hazard ratios and p-values were calculated using Cox-proportional hazards, after adjusting for treatment arm, sex, FLIPI, and geographic region. (Teff: T-effector signature)

Keywords: follicular lymphoma (FL); gene expression profile (GEP); obinutuzumab.

Disclosures: Bolen, C: Employment Leadership Position: *Genentech/Roche*; Stock Ownership: *Genentech/Roche*. **Hiddemann, W:** Consultant Advisory Role: *Roche, Janssen, Helsinn*; Honoraria: *Roche, Celgene, Janssen*; Research Funding: *Roche, Janssen, Bayer*; Other Remuneration: *Expenses: Janssen, Roche*. **Marcus, R:** Consultant Advisory Role: *Gilead*; Honoraria: *Roche*; Other Remuneration: *Speakers' Bureau: Roche*; *Expert Testimony: Gilead*; *Expenses: Takeda*. **Herold, M:** Consultant Advisory Role: *Janssen*; Honoraria: *Roche, Janssen, Gilead, Celgene*; Research Funding: *Roche*. **Salles, G:** Consultant Advisory Role: *Abbvie, Celgene, Gilead, Epizyme, Janssen, Karyopharm, Kite, Merck, Morphosys, Novartis, Roche, Servier, Takeda*; Honoraria: *Abbvie, Amgen, BMS, Celgene, Gilead, Epizyme, Janssen, Karyopharm, Kite, Merck, Morphosys, Novartis, Roche, Servier, Takeda*. **Mattiello, F:** Employment Leadership Position: *Roche*. **Nielsen, T:** Employment Leadership Position: *Roche*; Stock Ownership: *Roche*. **Mir, F:** Employment Leadership Position: *Roche*. **Venstrom, J:** Employment Leadership Position: *Genentech*. **Oestergaard, M:**

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PERSONALIZED PREDICTION IN DLBCL ENABLED BY FUNCTIONAL MOUSE GENOMICS

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Introduction: Major efforts have been undertaken to determine novel molecular subgroups in diffuse large B-cell lymphoma (DLBCL). Despite

their tremendous biological insights, these static "at diagnosis" classifications cannot anticipate complex response conditions such as therapy-induced senescence (TIS), and have not yet affected the clinical standard of care. A syngeneic, immune-competent mouse lymphoma model that reproduces key molecular features of human DLBCL might be instrumental to dynamically explore genetic determinants of drug responsiveness. Here, we focus on TIS in treatment outcome of mouse lymphoma models and patients diagnosed with DLBCL.

Methods: Gene expression-profiled primary Eμ-*myc* transgenic lymphomas were exposed to genotoxic therapy *in vivo*, and subsequently monitored in a clinical trial-like design. Lymphoma senescence capability was studied *in vivo* by loss- and gain-of-function genetics. Large publicly available DLBCL transcriptome datasets co-annotated with the individual patient outcome to an R-CHOP-like induction therapy were used for cross-species analyses.

Results: We found the Eμ-*myc* lymphoma platform to closely recapitulate established DLBCL subtypes related to cell-of-origin (*i.e.* GCB/ABC) and distinct DLBCL biologies (*i.e.* comprehensive consensus clusters). Mechanistically, we identified in mouse lymphomas lysine 9-trimethlyated histone H3 (H3K9me3) with its modifying writer/eraser activities as a central TIS relay. Moreover, the H3K9me3 mark predicted superior treatment outcome: mice bearing lymphomas with engineered loss of the H3K9me3-essential methyltransferase Suv39h1 presented with shorter PFS and OS, as observed in mice harboring genetically non-engineered lymphomas with low endogenous H3K9me3 expression. Importantly, machine-learning retrieved a 22-gene signature characterizing non-engineered lymphomas (*i.e.* with intact Suv39h1 alleles) as being Suv39h1-proficient-like or -deficient-like, termed "SUVAR-ness" in reminiscence of "BRCA-ness" used to describe a BRCA1/2-mutant-like status in the absence of BRCA mutations. Strikingly, a humanized version of this SUVAR-ness classifier identified DLBCL patients with superior PFS and OS already in baseline transcriptome profiles, and further marked the recently reported best-outcome Chapuy/Shipp clusters C0, C1 and C4 as SUVAR-ness/senescence capacity-enriched.

Conclusions: Functional *in vivo*-dissection of cellular senescence in mice – virtually impossible in human DLBCL material – unveiled its profound impact on long-term lymphoma control. Our work highlights the power of tractable transgenic mouse models with and without defined genetic lesions to predict individual outcome of DLBCL patients, and to further inform lesion- and state-based treatment decisions in personalized cancer precision medicine.

Keywords: diffuse large B-cell lymphoma (DLBCL); induction treatment; mouse models.

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SAMD14/NEURABIN-I AS BCR-ANTIGENS OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Introduction: Primary central nervous system lymphoma represents a distinct subgroup of DLBCL with exclusive manifestation in the CNS, which is therefore challenging to treat. PCNSL often harbour mutations in the BCR pathway and have overrepresented IGVH4-34. Polyreactive, low affinity BCRs have been reported recently for PCNSL.

Methods: To address the role of chronic antigenic stimulation in primary central nervous system lymphoma, we searched for autoantigens by expression cloning of PCNSL B-cell receptors (BCRs) and subsequent screening for antigens in the spectrum of self antigens and antigens of infectious origin. Identified antigens were verified by immunoassays and analyzed for immunogenic differences in respective cases by sequencing and proteomic means. ABC type DLBCL cell lines transfected to express recombinant PCNSL BCRs were used as modell for PCNSL and the effects of addition of SAMD14/neurabin-I on BCR activation and cell proliferation were studied. Moreover targeting PCNSL BCRs was investigated as a proof of principle by using an immunotoxin comprising the common BCR binding epitope of neurabin-I conjugated to a truncated form of *Pseudomonas Exotoxin A* by cytotoxcity and apoptosis assays.

Results: Sterile α-motif domain containing protein 14 (SAMD14) and neural tissue-specific F-actin binding protein I (neurabin-I) were identified as autoantigenic targets of the BCRs from 8/12 PCNSLs. Neurabin-I contains a SAM domain with high homology to SAMD14. In the respective cases, SAMD14 and neurabin-I were atypically hyper-N-glycosylated (SAMD14 at ASN339 and neurabin-I at ASN1277), explaining their immunogenicity. PCNSL-patients had SAMD14/Neurabin-I autoantibodies in relevant titres. Addition of SAMD14 and/or neurabin-I induced BCR pathway activation and proliferation of

aggressive lymphoma cell lines transfected with SAMD14-/ neurabin-I-reactive BCRs. Moreover, the BCR binding epitope of neurabin-I conjugated to truncated *Pseudomonas exotoxin A* killed lymphoma cells expressing the respective BCRs.

Conclusion: Our results support the role of chronic antigenic stimulation by speicific and posttranslationally modified autoantigens in the pathogenesis of a subgroup of PCNSL. Studies on the frequency of hyper-N-glyocsylated SAMD14/neurabin-I isoforms and of SAMD14/neurabin-I autoantibodies in prospectively collected sera of patients from PCNSL rials are necessary to better determine the "real" proportion of the SAMD14/neurabin-I-reactive subgroup in PCNSL. Finally, different therapeutic concepts for this subgroup will be presented.

Keywords: B-cell receptor (BCR); immunoglobulins (Ig); primary CNS lymphoma (PCNSL).

Disclosures: Thurner, L: Consultant Advisory Role: *MERCK*; Other Remuneration: *Travel Funding to Meeting: JANSSEN.*

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POPULATION-BASED OUTCOMES IN LARGE B-CELL LYMPHOMA BY WHO SUBTYPE: FINDINGS FROM THE UK'S HAEMATOLOGICAL MALIGNANCY RESEARCH NETWORK

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Introduction: Distinct morphologic, molecular and immunophenotypic variants of large B-cell lymphoma are well recognised, but information on their outcomes in the general (non-trial) patient populations is scarce. With centralised diagnostics at HMDS, Leeds and a unified clinical network covering a catchment population of ~4 million, the UK's population-based Haematological Malignancy Research Network (www.hmrn.org) was established to provide timely real-world data to answer such questions; and the findings are reported here.

Methods: All 3,357 patients newly diagnosed 2004-16 with de novo DLBCL were followed-up until January 2019 (median 7.5 years); and demographic, prognostic, treatment and outcome data were analysed.

Results: Median diagnostic age was 70.3 yrs, 52.7% of patients were male and 29.1% had a high IPI. DLBCL NOS predominated (87%); but clinical and demographic factors varied significantly with subtype (Table 1), as did survival (Figure 1). Patients with primary CNS DLBCL had the poorest OS (median 6 months); median survival for those with primary cutaneous DLBCL, leg type (PCLBCL) (5.6 years) was similar to DLBCL NOS (5.4 yrs), but patients with T-cell/histiocyte-rich DLBCL had better outcomes, approaching those of PMBL. DLBCL NOS patients (n = 874/2919) were further stratified by their cell-of-origin (assigned using gene-expression profiling); median OS for GCB and ABC subtypes was 8.9 and 2.5 years respectively; the latter increased to 5.5 years when adjusted for age.

Most patients were treated with intensive chemotherapy (80.3%, 94.6% received rituximab immunotherapy); the remainder received non-intensive chemotherapy, radiotherapy only, or supportive/palliative care. Of the 80% of patients who responded to first line therapy, 25% subsequently relapsed; this was highest in primary CNS DLBCL (67.4%). Around 20% of patients received second line therapy, either because of refractory disease or due to relapse; median survival in these patients was 6 months.

Conclusions: Our findings confirm the heterogeneity of DLBCL, the improved survival in patients with PCLBCL in the rituximab era and continued poor outcomes for plasmablastic lymphoma. Within DLBCL NOS, the distinct cell-of origin differences highlight the importance of molecular profiling in the study and therapy of this disease. Future trials aimed at improving outcomes for patients need to take account of both molecular and histological subtypes and focus on the unmet need of those with a poor prognosis.

TABLE 1

	N (%)	Median Age (years)	Male %	High IPI %	Intensive Chemotherapy %	Response %	Relapse %
Total	3357 (100)	70.3	52.7	29.1	80.3	79.4	24.2
DLBCL, NOS	2919 (87.0)	71.0	51.1	30.5	79.8	80.1	23.9
Primary CNS (CNS DLBCL)	118 (3.5)	65.2	55.1	30.8	75.4	48.3	67.4
Primary testicular	96 (2.9)	71.4	100.0	13.8	89.6	88.4	21.5
Primary mediastinal (PMBL)	79 (2.4)	41.4	46.8	8.5	96.2	89.5	5.9
T-cell/histiocyte-rich (THRLCBL)	74 (2.2)	64.4	59.5	23.6	87.8	76.9	13.7
Plasmablastic (PBL)	38 (1.1)	68.1	60.5	25.9	68.4	61.5	56.3
Primary cutaneous, leg type (PCLBCL)	25 (0.7)	78.9	32.0	11.1	64.0	93.8	40.0
Intravascular	8 (0.2)	74.6	62.5	80.0	75.0	100	33.3

Figure 1: Overall survival by large cell lymphoma subtype

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REFINEMENT OF MUM1 EXPRESSION THRESHOLD FOR DOUBLE POSITIVE CD10+ MUM1+ DIFFUSE LARGE B CELL LYMPHOMA ALLOWS A BETTER CELL OF ORIGIN CLASSIFICATION FOR GCB SUBTYPE

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The cell-of-origin (COO) determination of diffuse large B cell lymphoma (DLBCL) into germinal center B-cell like (GCB) and activated B-cell like (ABC) by immunohistochemistry based on the most commonly used Hans' algorithm, has at most 86% (Meyer et al, JCO, 2011) to 91% of concordance (Petrella et al, Annals Oncol, 2017) compared with the gold standard gene-expression profiling approach. Among those discrepancies, the algorithm is giving to CD10 positivity a priority over MUM1 for assigning GCB subtype, whatever the level of expression of MUM1 above 30%. Indeed, a substantial number of cases featuring a double positive (DP) CD10+ MUM1+ phenotype are classified as GCB according to Hans' algorithm whereas ABC on gene expression profiling.

The aim of this study was to evaluate whether the expression level of MUM1 assessed by immunohistochemistry could predict the molecular classification of DP in GCB or ABC. For that purpose, we used 2 independent cohorts of patients: one with 1608 DLBCLs from LYSA trials (GHEDI Cohort, GAINED, REMARC, RT3), the other with 255 DLBCLs treated in Nantes University Hospital (CHU Nantes) between 2006 and 2016. One hundred twenty two and 22 DP DLBCLs respectively were identified in these 2 cohorts, representing

TABLE 1 Threshold selection among evaluable patients (excluding unclassified DLBCLs, n=73)

Cut-Off (%)	Predicted Probabilities	True Positive (GC correctly identified)	True Negative (ABC correctly identified)	False Positive (ABC identified as GC)	False Negative (GC identified as ABC)	Sensitivity	Specificity
30	0.92	10 (14.49%)	24 (34.78%)	0	35 (50.72%)	0.222	1
40	0.88	14 (20.29%)	24 (34.78%)	0	31 (44.93%)	0.311	1
50	0.82	19 (27.54%)	23 (33.33%)	1 (1.45%)	26 (37.68%)	0.422	0.958
60	0.76	22 (31.88%)	21 (30.43%)	3 (4.35%)	23 (33.33%)	0.488	0.875
70	0.68	25 (36.23%)	18 (26.09%)	6 (8.70%)	20 (28.99%)	0.556	0.75
80	0.56	34 (49.28%)	13 (18.84%)	11 (15.94%)	11 (15.94%)	0.756	0.542
90	0.46	40 (57.97%)	6 (8.70%)	18 (26.09%)	5 (7.25%)	0.889	0.25
100	0.34	45 (65.22%)	0	24 (34.78%)	0	1	0

8% of DLBCLs. RNA extracted from FFPE tissues was available for 91 DP DLBCLs, tested for gene expression profiling by the RT-MLPA assay, a sensitive method validated on archival paraffin-embedded formalin-fixed (FFPE) tissues for the GCB/ABC classification (Bobee et al, J Mol Diagn, 2017). The level of MUM1 expression by 10% increments was evaluated on those 91 cases by three pathologists on multihead microscope. Among the 81 DP DLBCLs with available results (5 failures, 2 DLBCL EBV+ and 3 PMBL) for GCB/ABC classification by RT-MLPA, 48 cases (59.2%) were classified in GCB molecular subtype, 25 (30.8%) in ABC and 8 were unclassified (9.8%).

In order to correctly identify GCB molecular DP DLBCLs based on Hans' algorithm, depending on MUM1+ tumor cells, we tested different MUM1 thresholds (Table 1). A MUM1 threshold ≤ 50% correctly identified 19/48 molecular GCB and misclassified only 1 ABC (specificity 95%), while higher thresholds could not reliably identify GCB or ABC DLBCL.

Overall, our study clearly demonstrates that Hans' algorithm cannot be used to accurately identify molecular GCB and ABC DLBCL within the DP CD10+MUM1+ except when MUM1+ tumor cells do not exceed 50%. This new threshold could be included in the Hans' algorithm to identify GCB DLBCLs among DP DLBCLs. Above this threshold, targeted gene expression tests should be used to correctly classify these subgroups of DLBCLs for COO.

Keywords: diffuse large B-cell lymphoma (DLBCL).

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REDUCED *BCL2* EXPRESSION SUGGESTS ALTERNATIVE SURVIVAL MECHANISMS IN HIV(+) DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) OF GERMINAL CENTER ORIGIN

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Introduction: DLBCL is more aggressive in HIV infected individuals compared to the general population. RNAseq studies showed DLBCL to be comprised of two key Cell of Origin (COO) subtypes with distinct survival profiles post therapy; namely GCB (germinal center B-cell like) and ABC (activated B-cell like). The Lymph2Cx clinical diagnostic assay for COO subtyping was recently developed for use with FFPE tissues. To date, accurate investigation of HIV related DLBCL by COO has not been done. In this study we examined the genomic and transcriptional differences between HIV(+) and HIV(-) GCB-DLBCL, defined using the Lymph2Cx assay, to better understand the molecular mechanisms underlying the enhanced aggressive nature of HIV related DLBCL.

Methods: A total of 40 cases, including 19 HIV(+) GCB-DLBCL cases from the AIDS Cancer Specimen Resource Network (https://acsr.ucsf.edu/) and 21 HIV(-) GCB DLBCL institutional cases were included in this study. H&Es were reviewed by a hematopathologist to validate diagnosis and determine tumor content. Samples were macro-dissected up to minimal tumor content by area of ≥60%. Two 10 μm FFPE sections per sample were DNA/RNA extracted. DNA was used for copy number variant (CNV) analysis using Agilent array CGH. Protein expression was assessed by IHC. RNA was used to perform COO subtyping using the Lymph2Cx assay, and gene expression profiling (GEP) using the NanoString Pan-Cancer Pathways panel.

Results: Significant differences were observed between the HIV(+) and HIV(-) GCB-DLBCL cohorts. Although CNV analysis revealed both cohorts to be predominately diploid at the *BCL2* locus, when aberrations did occur, they were exclusively losses/deletions in the HIV(+) cohort and exclusively gains/amplifications in the HIV(-) cohort. These results were highly concordant with BCL2 protein expression; where those with losses/deletions had low BCL2 expression, while those with gains/amplifications had high BCL2 expression. Overall, the HIV(+) cohort had significantly reduced *BCL2* expression at both the transcriptional (p<0.001) and protein level (p = 0.0194). Intriguingly, the HIV(+) cohort was also found to be significantly more proliferative by Ki67 staining (p = 0.008), with significantly reduced gene expression of cell cycle inhibitors (*CDKN1A*, *CDKN1B*, p≤0.025). In fact an inverse relationship was found between the proliferation marker Ki67 and BCL2 by IHC in samples with *BCL2* gene aberrations. Reduced expression of key pro-apoptotic *BCL2*-genes (*BAX*, *BIM*, *BMF*, *PUMA*) was also observed in the HIV(+) cohort (p≤0.027).

Conclusions: BCL2 is a known negative prognostic marker in DLBCL. Reduced expression of BCL2 and of other pro-apoptotic *BCL2* family genes in HIV(+) DLBCL, as well as cell cycle inhibitors, suggests a reduced dependence on the pro-survival effects of BCL2 and a switch to a mechanism that depends on preventing cycle inhibition and the induction of apoptosis.

Keywords: BCL2; diffuse large B-cell lymphoma (DLBCL); human immunodeficiency virus (HIV).

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SINGLE CELL LEVEL ANALYSIS OF MYC/ BCL2/ BCL6 CO-EXPRESSION IN DIFFUSE LARGE B-CELL LYMPHOMA THROUGH MULTIPLEXED QUANTITATIVE IMMUNOFLUORESCENCE

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Introduction: MYC, BCL2 and BCL6 are commonly used markers for immunohistochemistry of DLBCL, providing prognostic information for outcome. Co-expression of MYC and BCL2 in particular constitute a subgroup of "double expressor lymphomas" with a distinct clinical outcome. However, it is not known if MYC and BCL2/BCL6 co-expression occurs in the same cell or in different cells within the tumour, as traditional immunohistochemical approaches are limited by the number of markers that can be simultaneously assessed within formalin-fixed paraffin embedded (FFPE) samples. In this study we have used multiplexed quantitative immunofluorescence (qIF) to concurrently study MYC and BCL2/BCL6 expression in DLBCL.

Methods: 130 cases of DLBCL, treated with R-CHOP chemo-immunotherapy and annotated clinical data (n = 90) were included in this study. The samples were arrayed on a Tissue Microarray (TMA). Multiplexed immunofluorescence for MYC/ BCL2/ BCL6/ Ki67 and CD20 was performed on single TMA slides using the sequential OPAL-TSA method. The slides were imaged using the Vectra 3 system, and unmixed to yield monochrome single colour images of each marker. The relative intensity of each marker per cell was then quantified using the InFORM software. Further statistical analyses were performed using graphpad prism and R.

Results: qIF was able to simultaneously measure MYC, BCL2, BCL6 and KI67 in CD20 positive cells within a single DLBCL TMA slide. Only a subset of cells within the population expressed multiple markers concurrently. A probability-based co-localization algorithm shows that MYC and BCL2 co-localize largely along a probabilistic pattern, while MYC-BCL6 and KI67 co-localize more often than predicted by probability alone. Unsupervised clustering of cases based on single markers and multiple co-localization values yielded 4 distinct subsets of DLBCL with variable clinical outcomes.

Conclusion: Multiplexed qIF demonstrates that only a subset of cells within a MYC-BCL2 "double expressor" lymphoma actually demonstrate colocalization at the single cell level, unlike with MYC-BCL6-KI67. The difference between MYC-BCL2 and MYC-BCL6 co-expression in terms of clinical outcome may therefore be a reflection of increased clonal heterogeneity within the tumour for cells expressing these oncogenes.

Keywords: BCL2; diffuse large B-cell lymphoma (DLBCL); MYC.

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CLINICAL SIGNIFICANCE OF T-CELL EXHAUSTION IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Tumor microenvironment (TME) and limited immune surveillance play important role in lymphoma pathogenesis and survival. Immune checkpoint receptors, such as programmed cell death-1 (PD1), lymphocyte-activation gene-3 (LAG3) and T-cell immunoglobulin and mucin domain-3 (TIM3), mediate signals leading to T-cell exhaustion and immune escape. Here, we have characterized the immunological profiles of diffuse large B-cell lymphoma (DLBCL) and associated the findings with outcome.

Methods: Gene expression analysis was conducted for 81 DLBCL samples utilizing the NanoString platform with a 770-gene PanCancer Immune panel. Multiplex immunohistochemistry (mIHC) with digital image analysis was used to characterize the T-cell phenotypes, including cytotoxic T-cells (CD8, GrB, OX40, Ki67), exhausted T-cells (CD3, CD4, CD8, PD1, TIM3, LAG3), Tregs and Th1 effector cells (CD3, CD4, FOXP3, TBET) of a total of 225 DLCBL samples. The findings were associated with patient demographics and survival and clinical significance validated in an independent patient cohort.

Results: We observed a high degree of heterogeneity in transcriptome level among the DLBCL samples. Correlation matrix analysis identified gene expression signatures with highly correlating genes. The main signatures contained genes for cytolytic factors and immune checkpoint molecules (*GZMB*, *PRF1*, *IFNG*, *TIM3*, *LAG3*) and T-cells (*CD3*, *CD2*, *CD28*), together entitled as a T-cell signature, macrophages (*CD68*, *CD163*), B-cells (*MS4A1*, *CD19*, *CD79A/B*), and extracellular matrix (*FN1*, *ITGA1/5/6*, *VEGFA*). None of the gene expression signatures as such were associated with survival. However, immuno-phenotyping of the distinct T-cell subsets with mIHC revealed that a high proportion of exhausted T-cells (TIM3+ and/or LAG3+) was associated with unfavorable survival in a cohort of 51 young high risk DLBCL patients treated in a Nordic phase II (NLG-LBC-05) trial with dose-dense immunochemotherapy and systemic CNS prophylaxis (5-year OS 73% *vs.* 96%, p = 0.022 and 5-year PFS 74% *vs.* 93%, p = 0.064). In contrast, the number of cytotoxic T cells, Tregs or Th1 effector cells did not correlate with outcome. The adverse prognostic impact of exhausted T-cells on survival was validated in an independent cohort of 137 DLBCL patients treated with immunochemotherapy

(5-year OS 66% *vs.* 79%, p = 0.029 and 5-year PFS 60% *vs.* 76%, p = 0.035).

Conclusions: Our results demonstrate that the molecular immunological profile of DLBCL is heterogenic and that putative markers of T-cell exhaustion associate with unfavorable survival in patients with DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL); immunophenotype; T-cells.

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THE INFLUENCE OF TUMOR IMMUNE MICROENVIRONMENT AND TUMOR IMMUNITY ON THE PATHOGENESIS, TREATMENT AND PROGNOSIS OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

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Introduction: PTLD is a heterogeneous group of abnormal lymphoid proliferations occurring in the immunosuppressed recipients of solid organ transplant (SOT) or bone marrow transplant. Epstein-Barr virus infection is considered as one of the major risk factors of PTLD. Although the relationship between PTLD pathogenesis and tumor immune microenvironment (TIME) is still unclear, it is well known that the PD-1/PD-L1 pathway and regulatory T cells attenuate anti-tumor response of cytotoxic T lymphocytes (CTLs) in other tumors. We have recently shown that PD-L1 expression is associated with poor prognosis in DLBCL and ATLL. Furthermore, reduction of immunosuppressants (RIS) and/or rituximab (RTX) are considered as the first-line therapy in PTLD patients, although it is not clear which group of patients responds to RIS/RTX. The aim of this study is to elucidate the influence of TIME on the pathogenesis, treatment, and prognosis of PTLD.

Methods: We retrospectively analyzed 26 consecutive patients with PTLD who were diagnosed and treated at our institution between 2006 and 2016. We examined FFPE samples using immunohistochemistry and in situ hybridization. Degree of immunosuppression was classified into three groups, strong: use of three or more immunosuppressants or high calcineurin inhibitor (cyclosporine > 200 ng/mL or tacrolimus > 8 ng/mL), none: no use of immunosuppressants, and intermediate: moderate use of immunosuppressants.

Results: The median age was 43 years, 61% patients received SOT, median time from transplant to PTLD development was 12 months, and 70% patients were DLBCL type. Patients who developed PTLD soon after transplantation had significantly more PD-1+ tumor infiltrating lymphocytes (TILs) (p = 0.0039) (Fig. 1). Furthermore, most of them were positive for EBER. In EBER negative patients, a large number of PD-1+ TILs were observed. Multivariate analysis with the number of PD-1+ TILs and EBER positivity showed that high number of PD-1+ TILs remained a significant factor for early-onset of PTLD in all patients and in DLBCL type patients (p = 0.0012 and p = 0.0030, respectively). Among 18 patients who received RIS/RTX for the first line treatment, overall response rate (ORR) was lower in the patients received strong immunosuppressants than in those received intermediate and no immunosuppressants (22% vs. 100% and 100%, respectively; p = 0.0029). Similar results were also found in 12 DLBCL type patients (p = 0.0073). Time to progression (TTP) was relatively less in the patients with FoxP3+ TILs and significantly less in DLBCL type patients with FoxP3+ TILs (p = 0.069 and p = 0.011, respectively).

Conclusions: This study revealed that high number of PD-1+ TILs was an important factor responsible for early-onset PTLD; strongly immunosuppressed patients exhibited lower ORR in RIS/RTX therapy, and

Fig. 1 Association of the number of PD-1+ TILs with PTLD onset
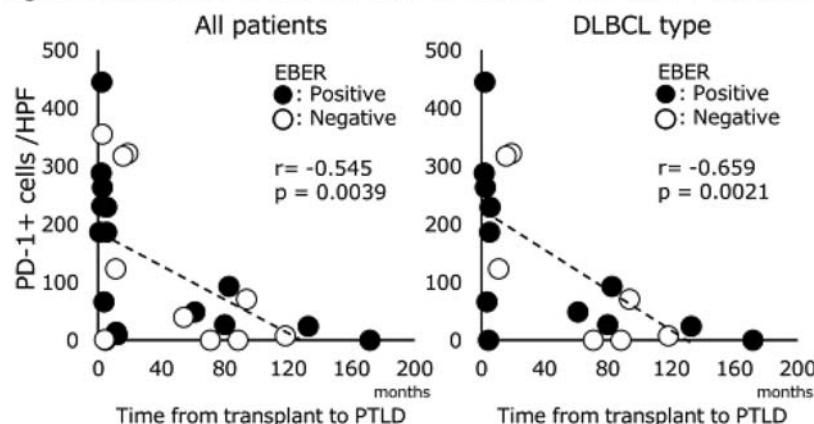
DLBCL type patients with FoxP3+ TILs exhibited significantly less TTP. These results suggested that TIME plays a vital role in pathogenesis, treatment, and prognosis of PTLD.

Keywords: post-transplant lymphoproliferative disorders (PTLDs).

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JAK-STAT PATHWAY AND EPIGENETIC REGULATORS ARE CRITICAL PLAYERS IN BI-ALCL PATHOGENESIS?

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Background: Breast Implant-associated anaplastic large cell lymphoma (BI-ALCL) is a rare T-cell lymphoma arising in association with breast implant, particularly those with textured surfaces. We recently identified two histopathological BI-ALCL subtypes: in-situ and tumor-type which correlated with the seroma vs tumor mass clinical presentation, respectively. Although genetic events involving the JAK/STAT pathway have been reported and the putative role of local chronic inflammation has been suspected, BI-ALCL pathogenesis remains elusive. To further explore potential molecular mechanisms involved in the pathobiology of these two distinct BI-ALCL subtypes, we performed a genomic characterization of 34 such cases.

Patient and Methods: Fifty-four BI-ALCL patients have been diagnosed through the Lymphopath network and registered in the Lymphoma Study Association Registry from 2010 to 2018. A total of 34 BI-ALCL samples have been analyzed by whole exome sequencing (WES) (n = 22 paired tumor/ germline DNA) and/or targeted next generation sequencing (NGS) (n = 24), across 406 genes to validate the findings. The average depth of sequencing was 300x for WES and 500x for targeted NGS.

Results: Fifty nine percent of cases (20/34) showed mutations in at least one member of the JAK/STAT signaling pathway. STAT3(38%) and JAK1 (18%) were the most mutated genes whereas STAT5B (n = 1) and the negative regulators SOCS3 (n = 2), SOCS1 (n = 1) and PTPN1 (n = 1) were seldom mutated. Fifteen percent of cases harbored simultaneous mutations in two genes of this pathway. STAT3 mutations were more frequent in tumor-type than in-situ BI-ALCL (p = 0.0078). Recurrent mutations in epigenetic modifiers were seen in 70% of cases with KMT2C (26%), CHD2 (15%), CREBBP (15%) and KMT2D (9%) being the most frequently mutated genes. Loss of function mutations in TP53 (12%) have also been identified. Genomic alterations in genes involved in lymphocytes development such as EOMES and in PI3K-AKT and MAP cascades were also seen in 23.5%, 12% and 9% BI-ALCL cases, respectively. In addition, CNV analysis in 8 cases identified recurrent deletions on chromosomes 8q, 15p and 20. Furthermore, by this approach additional alterations in SOCS3 (2/8), SOCS1 (1/8), PTPN1 (6/8) and STAT5B (3/8) as well as LOH in several epigenetic regulators such as TET2 (3/8) and HDAC8 (2/8) were seen.

Conclusions: This large series strongly reinforce the hypothesis that dysregulation of cytokine receptor signaling caused by recurrent mutations in the JAK/STAT pathway is a key event in BI-ALCL pathogenesis. Furthermore, our observation of frequent mutations in chromatin remodeling genes highlights the importance of epigenome and provides new insights into the complexity of BI-ALCL oncogenesis.

Keywords: anaplastic large cell lymphoma (ALCL); epigenetics; JAK/STAT.

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SPECIFIC GENETIC ALTERATIONS CHARACTERIZE SEROMA- AND TUMOR-TYPE BREAST-IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL) AS A DISTINCT DISEASE ENTITY

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Background: Breast Implant-Associated Anaplastic Large Cell lymphoma (BIA-ALCL) is a distinctive clinical subtype in the family of ALCL. In most patients, BIA-ALCL remains confined to the periprosthetic seroma space (seroma-BIA-ALCL), while a mass in the capsule or breast tissue is seen in approximately 20% (tumor-BIA-ALCL). Seroma-BIA-ALCL can be adequately treated with explantation and capsulectomy resulting in 5 year survival of ≥ 90%. In tumor-BIA-ALCL systemic chemotherapy is required, and in rare cases, women may die of disseminated disease. As we previously showed in a population-based study, women with breast implants have a more than 400 times increased risk to develop breastALCL than women without breast implants with a life-time risk of 1:7000.

Data on molecular tumor characteristics for BIA-ALCL is limited and largely refer to activation of the JAK-STAT signaling pathway by mutations and other mechanisms, presumably epigenetic and regulatory factors. The common ALCL-related translocations have alos been convincingly demonstrated to be absent. No specific molecular characteristics that distinguish BIA-ALCL from other subtypes of ALCL have been identified.

Methods: From the Dutch BIA-ALCL cohort of all BIA-ALCL cases diagnosed in the Netherlands between 1990 to 2017 (n = 50), we selected BIA-ALCL tumor (n = 16) and seroma (n = 19) FFPE samples of 29 patients. We performed shallow whole genome sequencing (sNGS) in these samples and in 7 cases with not-implant-associated ALCL in the breast to identify copy number aberrations (CNAs). Whole Exome Sequencing (WES) was performed for 4 tumor-BIA-ALCL and 3 seroma-BIA-ALCL cases with normal germline tissue available.

Results: Copy number losses of chromosomes 20, 2p and 15q were found at significantly higher frequency in BIA-ALCL compared to nodal- and cutaneous-type ALCL. The most frequent aberration for both seroma-BIA-ALCL and tumor-BIA-ALCL, loss of a 3Mb chromosomal region 20q13.12-q.13.13 was found in 19/29 (65.5%) patients with a minimal common lost region spanning 20q13.12-q12.2. A considerably higher genome instability level was observed for seroma-BIA-ALCL compared to tumor-BIA-ALCL with features of complex subclonality. A significant higher frequency of loss at chromosomes 4, 8p and 15q in seroma-BIA-ALCL was seen. We observed an overall high mutational load in tumor-BIA-ALCL, while mutational load in seroma-BIA-ALCL was low. The majority of recurrent mutations were identified in the IL6-JAK1-STAT3 pathway as previously reported.

Conclusions: Chromosome 20 loss distinguishes BIA-ALCL from other ALCL subtypes, providing a distinctive differential diagnostic parameter. Progression from seroma-BIA-ALCL to tumor-BIA-ALCL may be mediated by a pool of subclones driven by retention of chromosome 4q, 8p and 15q, while upon progression to tumor-BIA-ALCL the process becomes dominantly mutation-driven.

Keywords: anaplastic large cell lymphoma (ALCL); deep sequencing; extranodal lymphomas.

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WHOLE GENOME SEQUENCING REVEALS POTENTIAL THERAPEUTIC STRATEGY FOR MEITL

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Introduction: Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) is a rare malignancy accounting for majority of intestinal T-cell lymphoma in Asia. METIL are highly aggressive malignancy with a dismal overall survival while there currently is no effective treatment for this disease. However, the rarity of MEITL poses challenges in trying to improve clinical outcome with clinical trials. Therefore, there is an urgent need to establish a well-characterized and clinical relevant MEITL *in vitro* and *in vivo* model to decipher the biological meaning of genetic alterations, and to exploring the potential therapeutic targets.

Methods: Whole-genome sequencing (WGS) was performed on four MEITL tumors and corresponding blood samples. All sequencing reads were aligned with BWA-MEM. Somatic short-variants were called by Strelka2 and annotated by Annovar. Somatic structural rearrangements were called by MantaSV and annotated by AnnotSV. Simultaneously, a subcutaneous and orthotropic patient derived xenograft (PDX) model was also established. The PDX model was fully characterized histologically and genetically up to 6 passages. The cytotoxic/cytostatic effect of drugs targeting frequent METIL mutations was evaluated *in vitro* and *in vivo*.

Results: WGS analysis showed that somatic short-variant calling called out an 1.52 variants per Mb. A total of 338 non-silent protein-coding mutations were predicted, and recurrent oncogenic mutations were validated in *CREBBP*, *STAT5B*, *SETD2*, *GNAI2* and *JAK3*. Mutational spectrum analysis revealed clock signature to be the dominant signature within our cohort. Somatic structural rearrangement analysis revealed clustered structural breakpoints to the locality of *MYC*. The histological analysis demonstrated high similarity in the overall immunomorphologic features between the primary tumour and PDX tumors: all the PDX tumors were CD3+CD4-CD8+CD56+ and extensive nuclear expression of MATK. Sanger sequencing rediscovered

83 out of 86 somatic mutations in the 6th passage of our xenografts, suggesting that the generated PDX tumors were genetically stable. Moreover, WES results showed that the clonal architecture in primary tumor was also well preserved in the PDX tumors. We observed the PDX model by chance bearded the most frequent MEITL related driver mutations, including STAT5B, SETD2, CERBBP and which are all targetable with inhibitors, i.e., pimozide, AZD1775 and romidepsin. The *in vitro* and *in vivo* experiments demonstrated a wide range of sensitivities to these three inhibitors. The most effective inhibitor is romidepsin (*In vitro* IC$_{50}$: 13nM; *In vivo*, 1mg/kg once per week), which has been approved by FDA for the CTCL treatment. The QPOP analysis results further showed that romidepsin had great synergistic effect with pimozide (CI: 0.45).

Conclusions: These results showed that the key driver mutations in METIL are targetable and the combined targeted therapy might achieve a higher efficacy for MEITL treatment.

Keywords: enteropathy associated T-cell lymphoma (EATL); JAK/STAT; romidepsin (RD).

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WHOLE-GENOME SEQUENCING REVEALS IMMUNOTHERAPEUTIC OPTIONS FOR NATURAL-KILLER/T CELL LYMPHOMA PATIENTS

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Introduction: Natural-killer/T cell lymphoma (NKTL) is an uncommon and aggressive malignancy with a predilection for Asian, Mexican and South American populations. Currently, no published studies have used whole-genome sequencing (WGS) to study NKTL. With the aim of exploring the NKTL tumor genomes for actionable pathways, we used WGS to study the somatic genomic landscape of NKTL.

Methods:

Study Design: Patients were diagnosed with NKTL according to the 2008 World Health Organization classification with cytotoxic, CD3ε+ and EBER+ phenotypes. All subjects in this study provided written informed consent.

Somatic analysis: All analysis was based on the human reference genome hs37d5. Alignment was performed by BWA-MEM. Somatic short-variant calling and annotation were done by Strelka2 and wAnnovar, respectively. Somatic copy number analysis was performed by CNVkit. Somatic structural analysis and annotation were performed by MantaSV and AnnotSV. Somatic mutational signatures analysis were performed with Non-negative factorization package.

Results: An average of 39 (range: 1 – 80) somatic non-silent protein-coding variants per sample was identified. Our bioinformatics analysis has also reidentified recurrent non-silent short variants in *TP53*, *DDX3X*, *STAT3*, *FAT4* and *JAK3*. These observations suggest similar pathology between previously studied cohorts and our study cohorts.

Non-negative factorization also defined 4 robust mutational signatures, including 'COSMIC Signature 5' that has been reported in many cancer types, APOBEC 'COSMIC Signature 2', Oxidative Stress 'COSMIC Signature 18' and *MUTYH*-associated 'COSMIC Signature 17'. A predominant mutational signature to represent each sample and 'COSMIC Signature 5' was found to dominate NKTL samples (n = 21) as compared the other mutational signatures.

Somatic structural rearrangements analysis found frequent disruptions (n = 8, 25%) to the 3'UTR of *PD-L1* and not of the *PD-L2* gene. *PD-L1* was found to be more frequently altered than other known commonly mutated genes such as *DDX3X*, *STAT3*, and *JAK3* as reported in other studies. This makes *PD-L1* the most frequent mutated gene in NKTL.

We have previously reported the association of *PD-L1* SR with durable response to PD-1 blockade therapy in relapsed/refractory NKTL patients. However, the extent of treatment effect and the mechanisms of response/resistance to PD-1 blockade in the treated patients still remains to be elucidated. To summarize, this study reveals that a large proportion of NKTL patients could very well benefit from PD-1 blockade therapy.

Conclusion: We reported the whole-genome mutational profiles of NKTL patients using WGS data, which uncovered a large extent of genomic alterations in immune checkpoint related genes.

Keywords: non-Hodgkin lymphoma (NHL); PD-1.

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KIR3DL2 MUTATION MAY DEFINE A HIGH RATE OF RESPONSE OF AITL TO TIPIFARNIB

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Introduction: We have previously shown that Angioimmunoblastic T-cell Lymphoma (AITL) overexpresses CXCL12 and that patients (pts) with CXCL12-overexpressing T-lymphomas, including AITL, experience a high rate of response to the farnesyltransferase inhibitor tipifarnib (50% ORR, 90% clinical benefit rate, Witzig ASH 2018). Killer-cell immunoglobulin-like receptors (KIRs) are transmembrane glycoproteins expressed in NK and T cells that play regulatory functions, including roles in the regulation of chemokine/cytokine release (KIR3DL2) and angiogenesis (KIR2DL4). KIRs may be activatory (KIR-DS) or inhibitory (KIR-DL), interact with HLA and other ligands through extracellular D1-D3 loops, and signal intracellularly through ITAM (KIR-DS) or ITIM (KIR-DL) motifs.

Methods: Twenty-seven pretreatment biopsies from pts with relapsed or refractory peripheral T-cell lymphomas enrolled in a multi-institutional, single-arm, open-label, phase 2 study of tipifarnib were investigated using next generation whole exome sequencing and single nucleotide variations (SNVs) analyzed according to the primary study endpoint of objective response. Tumor CXCL12 and CXCR4 expression were determined by RNA Seq. Pts had received at least one prior cytotoxic systemic therapy, were ≥18 years old, and with performance status of 0–2. Clinical trial information: NCT02464228.

Results: A high rate of inhibitory KIR mutation (SNV of expected maximal population frequency <1%) was observed in the 11 AITL pts. The most notable mutations were found in the ITIM2 of KIR3DL1 and KIR2DL3 (3 subjects) and in the vicinity of the ITIM1 and CK2 phosphorylation sites of KIR2DL3 and KIR3DL2 (5 subjects). The latter mutations were associated with higher CXCL12/CXCR4 expression ratio (~3 fold) and susceptibility to response to tipifarnib. Two complete responses (CR), 2 partial responses and one disease stabilization (80% ORR) were observed in 5 AITL subjects carrying Q386E KIR3DL2. One additional CR was observed in 1 of 4 PTCL NOS pts with Q386E KIR3DL2. Nine of 27 PTCL samples (33%) carried Q386E. An additional 11 samples from tipifarnib treated pts and the overall incidence of KIR-DL mutation in PTCL and other lymphomas are being investigated.

Conclusions: The high rate of inhibitory KIR mutation in AITL may contribute to the understanding of the hypervascularity and inflammatory phenotype of these tumors. The association of KIR3DL2 mutation with objective response may provide a robust method for the selection or stratification of AITL and other lymphoma pts who could benefit from tipifarnib therapy.

Keywords: angioimmunoblastic T-cell lymphoma (AITL); chemokines; peripheral T-cell lymphomas (PTCL).

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KIR3DL2 IS EXPRESSED IN PERIPHERAL T-CELL LYMPHOMAS AND MAY BE A THERAPEUTIC TARGET

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Introduction: KIR3DL2, a killer immunoglobulin-like receptor normally expressed by a subset of natural killer (NK) cells and a minority of CD4+ and CD8+ T lymphocytes, is aberrantly expressed in cutaneous T-cell lymphomas (CTCL), particularly in Sézary Syndrome (SS)[1]. IPH4102, a monoclonal antibody directed against KIR3DL2, demonstrated *in-vitro* antitumor activity and has shown beneficial clinical activity in a phase 1 dose-escalation plus expansion cohort study in relapsed advanced CTCL patients (NCT02593045)[2,3].

Methods: Our cohort included a total of 91 peripheral TCL (PTCL) patients. NK receptors expression was assessed by immunohistochemistry (IHC) on frozen biopsies (n = 49), and by flow-cytometry
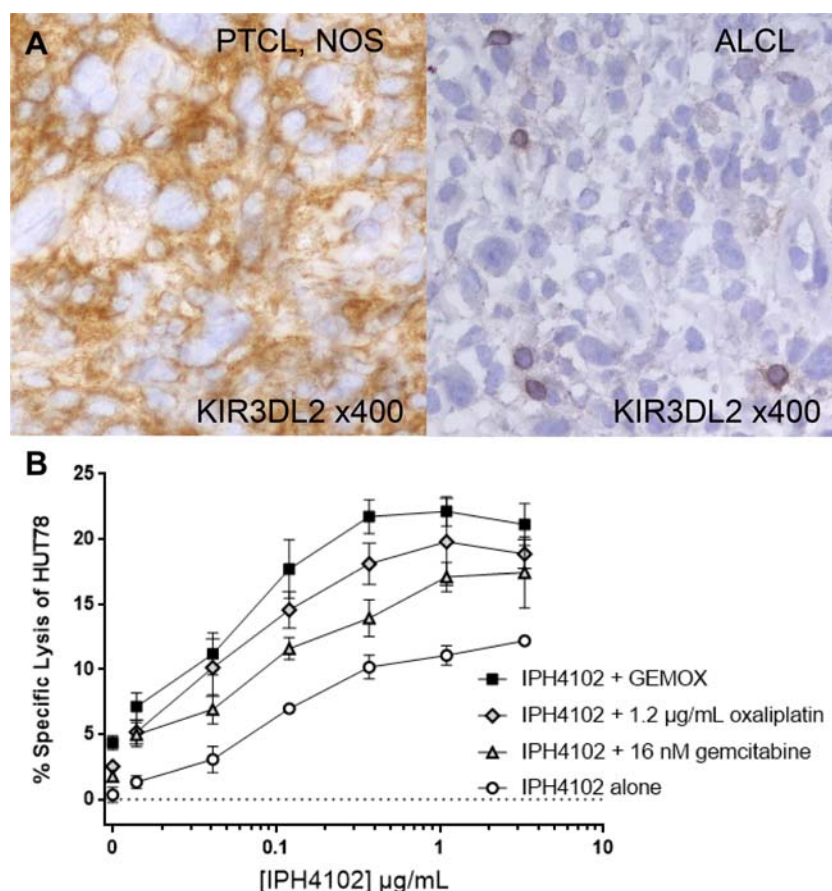
(n = 42) on peripheral blood samples (n = 12) and lymph node/tumor tissue (n = 30). *Ex-vivo* antibody dependent cell cytotoxicity (ADCC) assays are currently being performed on sorted primary KIR3DL2-positive PTCL cells with IPH4102. Finally, IPH4102 and gemcitabine plus oxaliplatin (GemOx), a combination chemotherapy regimen commonly used in relapsed PTCL, was studied *in-vitro*.

Results: Overall, irrespective of the staining technique, KIR3DL2 expression was evidenced in 41/91 (45%) of PTCL patients. More precisely, KIR3DL2 was expressed on 7/20 (35%) PTCL-not otherwise specified (NOS), 9/25 (36%) angioimmunoblastic TCL (AITL), 8/14 (57%) anaplastic large-cell lymphomas (ALCL), 5/11 (45%) enteropathy-associated TCL (EATL), 5/11 (45%) NK/T-cell lymphomas, 0/2 hepatosplenic TCL and 7/8 (88%) T-cell large granular lymphocyte leukemias (T-LGL). By IHC, within all PTCL categories, > 5% of lymphoid cells were KIR3DL2-positive in 22 out of 49 cases (45 %). High expression (> 50% KIR3DL2-positive lymphoid cells) was found in 11 (22 %) patients (**figure 1A**). In addition, by flow cytometry, KIR3DL2 was expressed on tumor cells compared to isotype control in 18/42 PTCL (43%). Incubation of T-cell lymphoma cell lines with GemOx enhances baseline KIR3DL2 expression. *In-vitro*, IPH4102 ADCC against KIR3DL2-positive tumor T-cell lines is increased by GemOx (**figure 1B**).

Conclusion: KIR3DL2 is expressed in multiple PTCL subtypes including the most frequent like PTCL-NOS, AITL and ALCL, but also the rarer EATL, NK/T-cell lymphomas and T-LGL. IPH4102 and GemOx combination improves anti-tumor activity against KIR3DL2-positive T-cell line *in-vitro*. The benefit of targeting KIR3DL2 by IPH4102 in combination with GemOx will be further investigated in relapsed PTCL patients in the Tellomak Phase 2 study.

Keywords: monoclonal antibodies (MoAb); peripheral T-cell lymphomas (PTCL).

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A PTCL GENE SIGNATURE CAPTURING STROMAL AND NEOPLASTIC DATA STRATIFIES PTCL/NOS AND AITL INTO DIFFERENT GROUPS WITH VARIABLE SURVIVAL PROBABILITY

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Introduction: Peripheral T-cell lymphoma, NOS (PTCL-NOS) and
angioimmunoblastic T-cell lymphoma (AITL) are aggressive lymphoma
types with a low survival probability, where prognostic models are
mainly base on clinical data at diagnosis or proliferation rate of the
neoplastic cells.

We hypothesized that gene profiles from diagnostic samples could be
used to define prognostic risk groups to identify patients with differ-
ent survival probabilities.

Methods: PTCL-NOS and AITL (n. 96 with high quality RNA) samples
treated with chemotherapy were profiled for a 216 genes custom T-
cell lymphoma CodeSet, using the NanoString platform. The analysis
was designed for including genes expressed by the different compo-
nents of the stroma and neoplastic cells, together with genes known
to be therapeutic targets.

Genes associated with overall survival (OS) were identified using Cox
regression, followed by generation of risk scores and development of
a assay to stratify patients into risk groups associated with OS. Co-
regulated genes were investigated for identifying the best prognostic
marker.

Results: Regression and clustering analysis defined a 10-genes
PTCL Gene Signature and two risk groups with different OS [haz-
ard ratio (HR) 5.77; 95% CI 2.23-14.95; p = 0.002]. The median OS
of high- and low-risk groups were 47 [95% confidence interval
(CI) of 13.80 and 80.20 months] and 17 months [95% CI: 9.93
months and 24.07], respectively. These risk groups were indepen-
dent of the IPI.

The PTCL gene signature includes genes expressed by both neoplas-
tic and stromal cells (endothelium, macrophages, immunoregulatory
cells, cytokines, oncogenes) and was valid for both PTCL-NOS
and AITL.

Conclusions: These results suggest that gene expression - based risk
groups, capturing data from both the stroma and the neoplastic cells,
can independently predict survival in PTCL/NOS and AITL.
This signature may help to stratify these patients for different thera-
peutic strategies in future clinical trials.
Keywords: gene expression profile (GEP); peripheral T-cell lymphomas
(PTCL).

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MULTICENTRIC MFI30 STUDY: STANDARDIZATION OF CD30 EXPRESSION BY FLOW CYTOMETRY IN NON-HODGKIN LYMPHOMA

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Introduction: The Brentuximab vedotin (BV), an anti-CD30 monoclo-
nal antibody (Ab) conjugated to chemotherapy, has shown its efficacy
in Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL)
that typically expressed the CD30. However, the response to BV is
difficult to correlate to CD30 expression analyzed by immunohisto-
chemistry (IHC) which only allows the count of high positive cells. The
objective of this multicentric study is to standardize and evaluate
CD30 expression by flow cytometry (FCM) in malignant T and B-cell
proliferation.
Material and methods: Among 18 centers participating to the first
step of standardization, 12 included cases (n = 155): 5 ALCL, 70 B-
NHL including 64 DLBCL, 80 malignant T-cell proliferations (24 Sezary,
26 PTCL-NOS, 14 T-PLL, 8 AITL, 2 EATL, 6 T / NK-LGL) from various
samples (74 bloods, 43 lymph node suspensions, 10 bone marrows,
28 others) (www.mfi30.fr). BD Biosciences (BD, n = 9) or Beckman
Coulter (BC, n = 9) cytometers are used with the Euroflow strategy.
Abs recognizing different CD30 epitopes are tested: BerH83 (BD),
HRS4 (BC) and AC10 (Ancell) which recognizes the same epitope as

| Negative group n=109 | Discordant group n=19 | Dim group n=16 | Positive group n=11 |

× Ancell clone   △ BD clone   ● BC clone   (+)=IHC CD30+   (-)=IHC CD30-   (ND)=IHC CD30 not determined
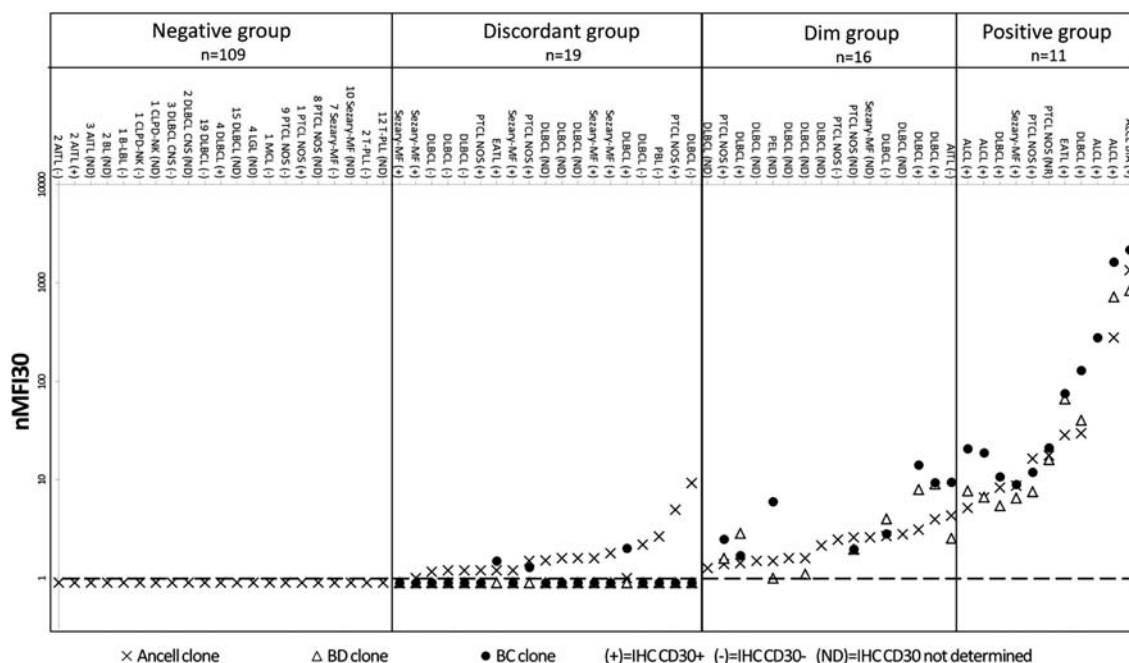
BV. The mean fluorescence intensity (MFI) of CD30 is normalized in % compared to CD4 (nMFI30). Abs BC and BD are tested if only nMFI30> 1% with Ab Ancell. In 85 cases IHC has been also realized with the clone BerH2 (Dako).

Results: FCM results has allowed to define 4 groups (Fig): a high positive group (n = 11) with nMFI30> 5% with the 3 Abs tested; a dim positive group (n = 16) with nMFI30 between 1 and 5% with the 3 Abs tested; a discordant group (n = 19) with nMFI30> 1% with Ab Ancell and <1% with another Ab; a negative group (n = 109) with nMFI30 <1% with Ab Ancell. When tested, IHC is positive in all cases of high positive group (10), in 4 out of 7 in the dim positive group, 10 out of 16 in the discordant group, and in 7 out of 52 in the negative group (2 AITL, 1 PTCL-NOS and 4 DLBCL). This last discordance could be explained by CD30 expression of non-tumoral cells present in microenvironment or by intracytoplasmic staining. 10/38 DLBCL are positive by IHC (26%) and 21/64 (33%) are in positive or discordant groups by FCM. 6/13 Sezary are positive by IHC (46%) and 7/24 (29%) are in positive or discordant groups by FCM. All ALCL are positive by both techniques. All T-PLLs, DLBCL-CNS and LGL are negative.

Conclusion Multicenter standardization of CD30 is achievable by FCM, using in particular the AC10 and making it therefore a powerful tool for clinical trials to extend the treatment of BV to various NHL.

Keywords: brentuximab vedotin; flow cytometry; non-Hodgkin lymphoma (NHL).

Disclosures: BASEGGIO, L: Consultant Advisory Role: *consultant role*; Honoraria: *yes*. **Debliquis, A:** Consultant Advisory Role: *consultant*; Honoraria: *yes*. **Jacob, M:** Consultant Advisory Role: *consultant*; Honoraria: *yes*. **Drenou, B:** Consultant Advisory Role: *consultant*; Honoraria: *yes*.

CLL

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SURVIVAL CONTINUES TO INCREASE IN CHRONIC LYMPHOCYTIC LEUKEMIA: A POPULATION-BASED ANALYSIS AMONG 20,324 PATIENTS DIAGNOSED IN THE NETHERLANDS BETWEEN 1989 AND 2015

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Introduction: The treatment landscape in chronic lymphocytic leukemia (CLL) rapidly evolved since the last decade with improvements in supportive care and the advent of anti-CD20 agents, kinase inhibitors, and anti-apoptotic agents. At present, it is largely unknown how these advances impacted survival of patients with CLL at the population level. The aim of this nationwide, population-study was to assess trends in long-term excess mortality (EM) among patients with CLL diagnosed during a 27-year period in the Netherlands.

Figure 1 Relative survival per diagnostic period and age group

Figure 1 Relative survival per diagnostic period and age group
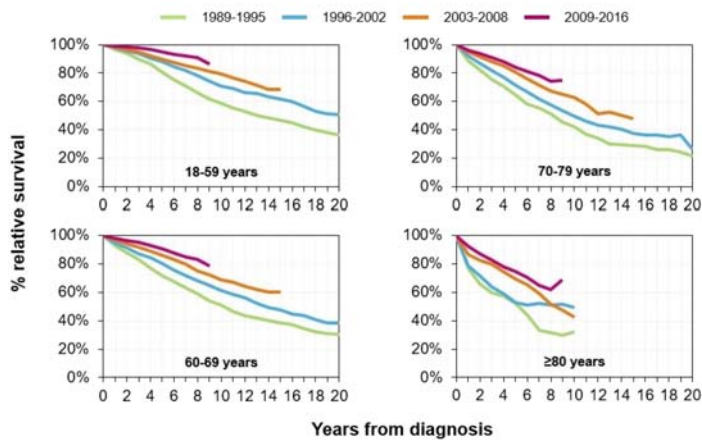
Table 1 EMR during the first 10 years after CLL diagnosis

Covariate	EMR[a]	95% CI		P[b]
Period of diagnosis				
1989-1995	2.04	1.86 -	2.23	<0.001
1996-2002	1.45	1.32 -	1.58	<0.001
2003-2008	1	(reference)		
2009-2016	0.65	0.58 -	0.74	<0.001
Sex				
Male	1	(reference)		
Female	0.66	0.61 -	0.71	<0.001
Age at diagnosis, years				
18-59	1	(reference)		
60-69	1.43	1.30 -	1.58	<0.001
70-79	2.08	1.89 -	2.29	<0.001
≥80	3.90	3.47 -	4.38	<0.001
Previous malignancy				
No	1	(reference)		
Yes	1.80	1.64 -	1.96	<0.001

Abbreviations: EMR, excess mortality ratio.
[a]All covariates are simultaneously adjusted.
[b]P-values are compared with the reference category.

Methods: We selected all 20,324 patients with CLL diagnosed between 1989-2016 (median age 69 years; range 21-101 years; 61% males; 11% with a prior malignancy) from the Netherlands Cancer Registry, with follow-up for survival through January, 2018. Patients were categorized into four periods (1989-1995, 1996-2002, 2003-2008, and 2009-2016) and four age groups (18-59, 60-69, 70-79, and ≥80 years). Age-standardized incidence rates (ASRs) were calculated per 100,000 person-years and standardized according to the European standard population. Relative survival (RS) was calculated as a measure of disease-specific survival. Multivariable evaluation of RS was performed using Poisson regression with adjustment for period of diagnosis, sex, age at diagnosis, and a prior malignancy before CLL diagnosis.

Results: The annual ASR of CLL initially increased gradually since 1989; however, the overall incidence pattern subsequently stabilized at around 4.0 to 4.5 as from 2003. The overall ASR was consistently higher among males than females throughout the entire study period (5.0 vs. 2.6 in 1989-2015). Patients across the four age groups experienced continued EM, as compared to the general population during all periods studies. Nevertheless, RS improved with each period for all 4 age groups (Figure 1). More specifically, 5-year RS was 80%, 71%, 64%, and 52% in 1989-1995 for the 4 age groups, as compared with 94%, 90%, 84%, and 75% in 2009-2015 (P<0.001 for all comparisons). The multivariable analysis confirmed an improvement of survival over time, with an EM ratio (EMR) of 2.04 (P<0.001) in 1989-1995, 1.45 (P<0.001) in 1996-2002, and 0.65 (P<0.001) in 2009-2015, as compared with 2003-2008. Furthermore, females had lower EM, as compared to males (EMR, 0.66; P<0.001), whereas patients with a prior malignancy had higher EM, as compared with patients without a prior malignancy (EMR, 1.80; P<0.001) (Table 1). Subgroup analyses confirmed the consistency of the abovementioned associations across the four age groups, with the exception that females and males age ≥80 had comparable EM (EMR, 0.99; P = 0.906).

Conclusion: In this large, nationwide, population-based study, 5- and 10-year RS improved over time among patients with CLL across all age groups. Advances in supportive care, ameliorated management, and the advent of novel agents might have accounted for the improvement. As kinase inhibitors and anti-apoptotic agents have been introduced recently for routine use, EM will hopefully improve even more in the next decade.

Keywords: chronic lymphocytic leukemia (CLL).

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PROTEOMICS MARKERS PROGNOSTIC FOR OUTCOME OF CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS UNDER TREATMENT: RESULTS FROM THE HOVON-109 STUDY

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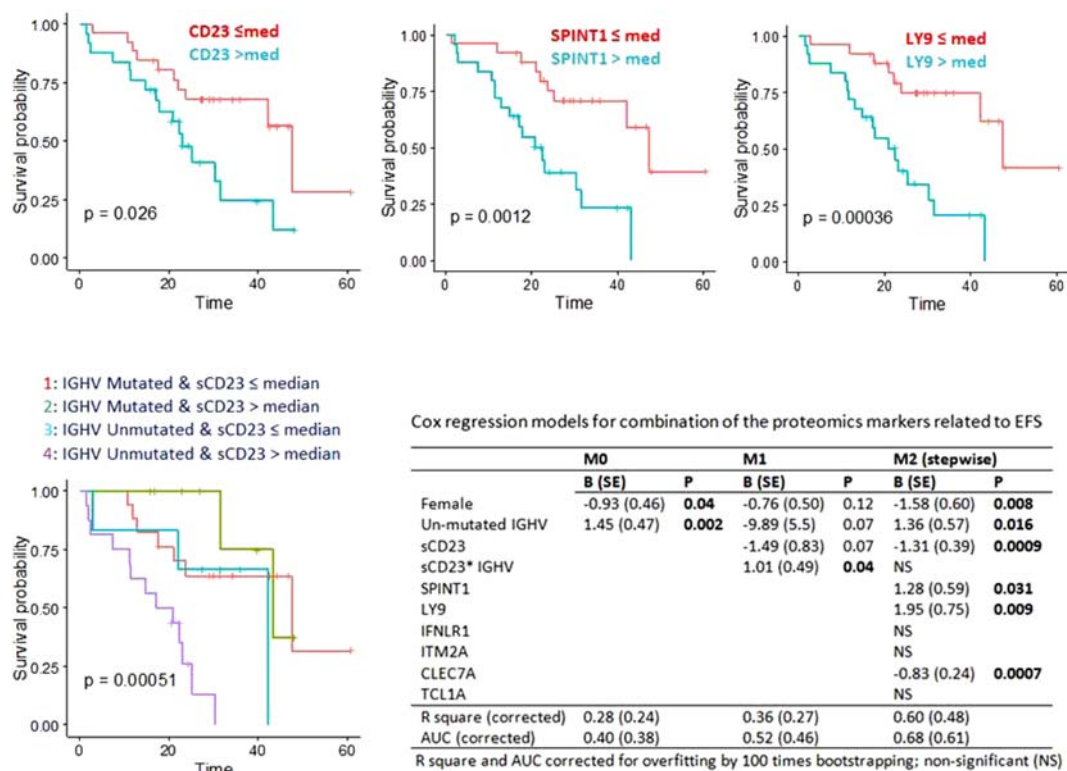
Introduction: Chronic lymphocytic leukemia (CLL) follows a highly variable clinical course. In recent years, several molecular and cellular markers have been explored and correlated with disease aggressiveness in order to enable risk group stratification. However, since many CLL cases show discordant prognostic factors, the identification of new parameters able to relate disease stage and clinical outcome is important to further improve treatment efficacy. Therefore, the aim of our study was to examine the prognostic ability of a) known proteomics markers measured pre-treatment and b) to search for new proteomics markers that might be related to treatment response.

Methods: Samples of CLL patients treated with chlorambucil, rituximab and lenalidomide within the HOVON-109 trials were collected. Fifty-one of 63 patients had an available sample at baseline and were included in our study. Serum samples were analyzed for 360 proteomics markers using a multiplex proximity extension assay (Olink Bioscience, Uppsala, Sweden). Kaplan-Meier curves and Cox proportional hazards models were used for testing independent and additive effects of the markers for event-free survival (EFS; time from registration to induction failure, progression or death from any cause, whichever comes first).

Results: Fifty-one patients were included (59% males; mean age 71 years). Median EFS was 23 months (26 events). Female and IGHV mutated patients showed longer EFS, as compared to male and unmutated patients. No significant survival effects were seen for β2-microglobulin levels, Rai stage, or well-defined chromosomal aberrations. Among B-cell activation markers, the sCD23 level was associated with EFS in univariate ($\beta = 0.45$, $p = 0.04$) and adjusted models ($\beta = -1.49$, $p = 0.07$). Patients with high (i.e. above median) sCD23 levels had a shorter EFS, as compared to those with low levels (**Fig 1**). There was a significant interaction between sCD23 and IGHV mutational status ($\beta = 1.01$, $P = 0.04$), as unmutated IGHV patients with high sCD23 levels had the shortest EFS (**Fig 1**). Low levels (i.e. equal to or below median) of SPINT1 and LY9 levels were correlated with a significantly longer survival. Added prognostic value of the potential proteomics markers compared with a basic model including gender and IGHV status was evaluated, showing a significant independent effect on EFS for especially sCD23, SPINT1, and LY9 (**Fig 1**). Several other evaluated proteomics markers were significantly associated with EFS in univariate and adjusted models, albeit, none remained significant after multiple testing correction.

Conclusion: Our study suggests a possible prognostic role for sCD23 (probably released from activated B-cells), LY9 (probably from CD4^{+}T helper cells), and SPINT1 (a potent inhibitor specific for HGF activator) in CLL patients in this clinical trial. Further studies are required to validate these results.

Keywords: chemokines; chronic lymphocytic leukemia (CLL); cytokines.

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Acalabrutinib With Obinutuzumab in Treatment-Naive and Relapsed/Refractory Chronic Lymphocytic Leukemia: 3-Year Follow-Up

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Background: Acalabrutinib is a highly selective, potent, covalent Bruton tyrosine kinase inhibitor. This Phase 1b/2 trial evaluated acalabrutinib with the CD20 antibody obinutuzumab in patients with treatment-naive or relapsed/refractory chronic lymphocytic leukemia (CLL).

Methods: Patients with treatment-naive or relapsed/refractory (≥1 prior therapy) CLL were eligible. In 28-day cycles, acalabrutinib was given orally at 100 mg twice daily or 200 mg once daily (n = 15; all switched to 100 mg twice daily) until progressive disease; obinutuzumab was given in standard fashion for 6 cycles starting with Cycle 2. The primary endpoints were overall response rate and safety. Minimal residual disease (MRD) was assessed using flow cytometry (sensitivity 10^{-4}).

Results: Nineteen treatment-naive and 26 relapsed/refractory patients were treated. The median age of all patients was 61 years (range, 42 to 76). Patient characteristics, disposition, efficacy, and MRD data are in the **Table**. Common adverse events (any grade) were upper respiratory tract infection (71%), increased weight (71%), maculopapular rash (67%), cough (64%), diarrhea (62%), headache (56%), nausea (53%), arthralgia (51%), and dizziness (47%). Common Grade 3/4 adverse events were decreased neutrophil count (24%), syncope (11%), decreased platelet count, increased weight, and cellulitis (9% each). There were 2 (4%) Grade 3 bleeding events (hematuria, muscle hemorrhage) and 1 (2%) Grade 3 atrial fibrillation event.

Conclusions: Acalabrutinib plus obinutuzumab was well tolerated and yielded high response rates that were durable and deepened over time in treatment-naive and relapsed/refractory patients with CLL.

Keywords: BTK inhibitors; CD20; minimal residual disease (MRD).

TABLE 1

	Treatment naive (n = 19)	Relapsed/refractory (n = 26)
Percent of patients		
Lymph nodes ≥5 cm	53	50
del17p	22[a]	19
del11q	28[a]	35
Complex karyotype	42	56
IGHV unmutated	53[b]	65
Follow-up, median (range), mo	36 (1-42)	39 (20-46)
Discontinued, n (%)	2 (11)	7 (27)
Adverse event	1 (5)	4 (15)
Richter transformation	1 (5)	2 (8)
Death	0	1 (4)[c]
Overall response rate (≥ PR), %	95	92
95% CI	74, 100	75, 99
CR, n (%)	6 (32)	2 (8)
PR, n (%)	12 (63)	22 (85)
Median time to CR (range), mo	18 (6-32)	13 (10-16)
Median time to ≥ PR (range), mo	3 (3-3)	3 (3-21)
Median DOR	NR	NR
33-mo DOR rate, % (95% CI)	94 (67, 99)	91 (68, 98)[d]
Median PFS	NR	NR
36-mo PFS rate, % (95% CI)	94 (67, 99)	73 (34, 91)[e]
MRD− in bone marrow Cycle 12 Day 1, n (%)	5 (26)[f]	4 (15)

Abbreviations: CR, complete response; DOR, duration of response; MRD, minimal residual disease; NR, not reached; PFS, progression-free survival; PR, partial response.
[a]1 or [b] 2 patients missing data.
[c]Due to progressive disease.
[d]39-mo rate.
[e]42-mo rate.
[f]Includes 3/6 patients in CR.

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IBRUTINIB DECREASES OBINUTUZUMAB-INDUCED SECRETION OF CYTOKINES ASSOCIATED WITH INFUSION-RELATED REACTIONS IN PATIENTS WITH CLL: ANALYSIS FROM THE ILLUMINATE STUDY

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Introduction: Infusion-related reactions (IRRs) are potentially serious complications resulting from release of inflammatory cytokines in response to administration of certain drugs, including obinutuzumab (G), an anti-CD20 antibody (Freeman, *Blood*2015). In the phase 3 iLLUMINATE study of first-line ibrutinib-G (ibr-G) vs chlorambucil-G (clb-G) in patients (pts) with chronic lymphocytic leukemia (CLL), IRRs were decreased with ibr-G vs clb-G (any grade: 25% vs 58%; grade ≥3 or serious: 3% vs 9%) (Moreno, *Lancet Oncol* 2019). As IRR results from the release of inflammatory cytokines, we prospectively analyzed cytokines thought to be associated with IRRs in pts from iLLUMINATE to evaluate the impact of ibr on secretion of cytokines following G infusion.

Methods: Pts with previously untreated CLL/small lymphocytic lymphoma were randomized to ibr-G or clb-G. Ibr or clb was given approximately 30-120 min before the first G infusion. Plasma samples were collected at 4 timepoints (before ibr/clb, immediately before G infusion, and 2h and 4h post-G infusion) on day 1. Cytokines evaluated were IFNγ, IL6, IL8, IL10, IL18, MCP1, MIP1α, MIP1β, and TNFα. Changes from baseline (immediately before G infusion) to post-G infusion peak cytokine levels were compared between arms and between pts with vs without IRRs using Wilcoxon rank sum test. A 2-sided P value of <0.05 was considered significant with no adjustments for multiplicity.

Results: Of 229 randomized pts, 95 pts on ibr-G (15 with IRR; 80 without IRR) and 88 pts on clb-G (45 with IRR; 43 without IRR) had cytokine data and were included in the analysis population. Baseline characteristics were similar between arms, except for lower platelets in ibr-G pts and higher baseline MCP1 levels in clb-G pts. As expected, all cytokine levels increased after infusion of G. Analysis of cytokine levels by treatment arm (ibr-G vs clb-G), irrespective of IRR occurrence, revealed that the median increase in cytokines was lower in ibr-G vs clb-G pts for all cytokines ($P<0.01$) except MIP1β (Figure). When analyzing pts with and without IRR, the median increase in post-G peak from baseline was greater in pts with vs without IRR for all cytokines ($P<0.001$) except MIP1β. Analysis of cytokine levels in pts with and without IRR within each treatment arm showed that IL6 and IL8 elevations were associated with IRRs in both treatment arms. In ibr-G arm, pts with IRR had increases in post-G levels of IL6, IL8, IL18, MCP1, MIP1α, and TNFα ($P<0.04$); in clb-G arm, pts with IRR had increases in IFNγ, IL6, IL8, and IL10 ($P<0.03$). Among the pts with IRR, ibr-G pts had lower post-G increases in IL6, IL8, IL10, and MCP1 levels ($P<0.04$) than clb-G pts.

Conclusions: These data demonstrate that ibr suppresses G-induced increases in multiple cytokines related to IRRs and suggest that the reduction in IRR events in ibr-treated pts is the result of a reduction in the release of inflammatory cytokines.

Keywords: cytokines; ibrutinib; obinutuzumab.

Figure. Median change in cytokine levels from baseline to post-G peak by treatment arm.
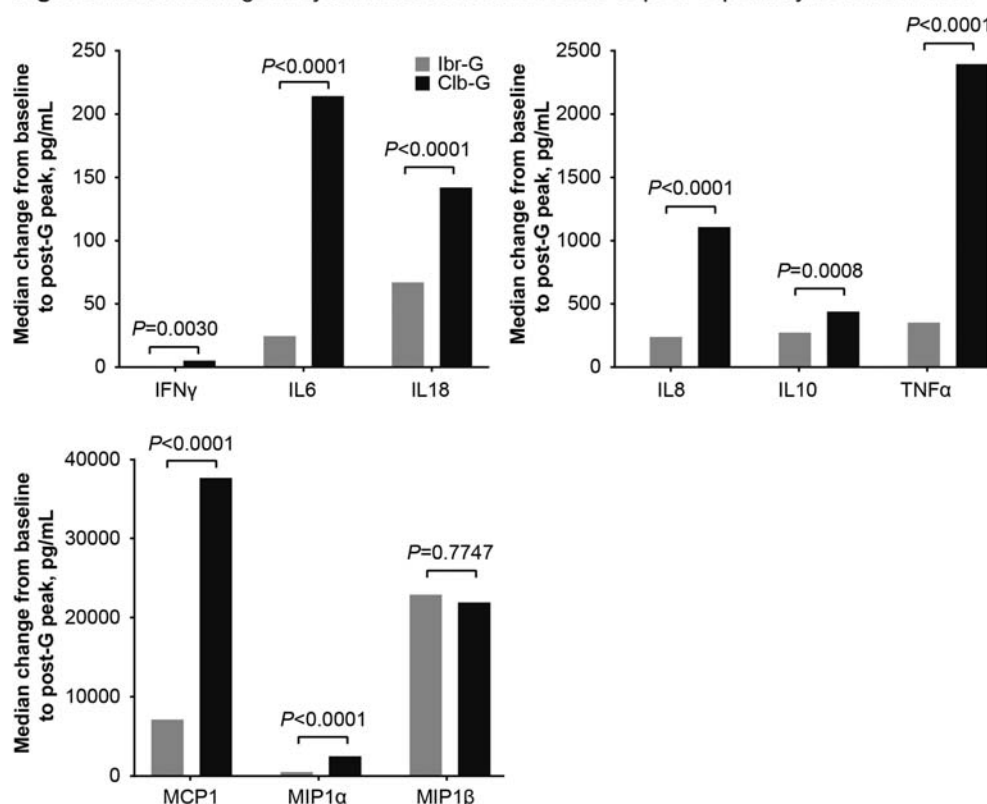
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HYPERTENSION (HTN) IN PATIENTS (PTS) TREATED WITH IBRUTINIB (IBR) FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Introduction: HTN is the most common grade ≥ 3 Ibr-associated adverse event (AE) in trials (26%) (O'Brien, Blood 2015). Meta-analysis of trials suggests a 2.8-fold increased risk of HTN for pts treated with Ibr (Caldeira, PLOS ONE 2019). In practice, data on incidence, management, and long term cardiovascular (CV) consequences of Ibr-associated HTN are limited. As Ibr is administered continuously and HTN incidence is cumulative, this toxicity is understudied.

Methods: Multicenter, retrospective study of CLL pts treated with 420 mg Ibr for at least 6 months. We collected baseline CV comorbidities, CV medications (meds), blood pressure (BP) measurements prior to Ibr initiation and following exposure at specific times in a 12-month period, and adjustments to CV meds. Incident HTN is defined as BP > 140/90 mmHg, and worsening BP as sustained rise in SBP or DBP ≥ 3 mmHg over baseline.

Results: We identified 247 Ibr treated CLL pts. Pre-Ibr CV comorbidities included: HTN (43%), hyperlipidemia (35%), diabetes (16%), coronary artery disease (CAD; 9.7%), valvular heart disease (2.8%), atrial fibrillation (Afib; 4.5%), stroke (2.8%), and smoking history (42%). At least one anti-HTN med was used in 51% prior to Ibr initiation (median number of meds 1). Median BP prior to Ibr was 127/71 mmHg (range 92-174/48-95) and median pulse 75 bpm (range 27-110). Median peak BP following Ibr was significantly elevated (153/80 mmHg range 105-218/53-121, p<0.0001). Median time to peak BP was 6 months (range 0-35 months). Figure 1 depicts median systolic BP at baseline and 1, 3, 6, 9, and 12 months following Ibr initiation. During the observation period, 36% and 84% experienced new HTN or worsening of existing HTN respectively. 19.8% of pts required initiation of at least one new anti-HTN med, and 4.7% required increased dose of a pre-Ibr anti-HTN med. Of the 49 pts who required BP management, 86% started 1 new agent, and 14% started ≥2 new

Figure 1. Systolic blood pressure prior to Ibrutinib exposure and at sequential time points following Ibrutinib exposure.

SYSTOLIC BLOOD PRESSURE OVER TIME

☐ BASELINE ☐ 1 Month ☐ 3 Months ☐ 6 Months ☐ 9 Months ☐ 12 Months
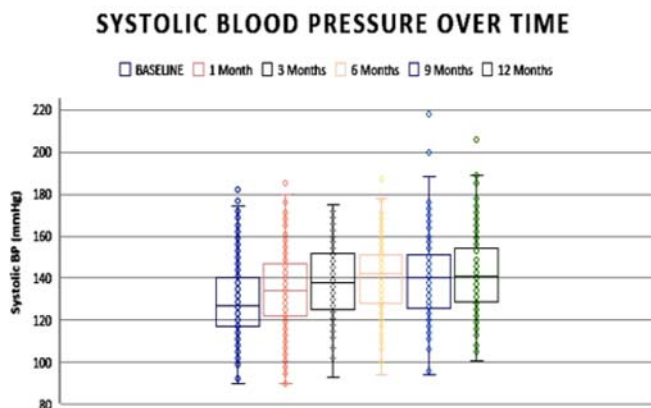
agents. The most common new classes of agents were beta blockers (32%), angiotensin receptor blockers (21%), diuretics (19%), calcium channel blockers (14%), and angiotensin converting enzyme inhibitors (14%). 6.4% experienced new onset Afib, 1.6% had CAD. Preexisting CV comorbidities, smoking history, and diabetes were not predictive of HTN development in univariate analyses.

Conclusion: HTN is a pervasive AE of Ibr affecting pts with and without baseline HTN or CV conditions. Physiologically, systolic BP appears to be more significantly affected than diastolic BP. While these data demonstrate 20% of pts adjust anti-HTN meds or start new ones, it is not known how effective current management is at controlling HTN or preventing long term vascular events. In addition, we demonstrate that the proportion of pts initiating new anti-HTN meds is significantly lower than those experiencing new/worsening HTN, identifying an opportunity for care optimization in partnership with cardio-oncology.

Keywords: BTK inhibitors; chronic lymphocytic leukemia (CLL); ibrutinib.

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AN IMPROVED BENEFIT-RISK PROFILE OF DUVELISIB IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA WHO RECEIVED 2 OR MORE PRIOR THERAPIES

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Introduction: Despite effective frontline therapies, many patients (pts) with CLL or SLL eventually relapse and require additional therapies to control their disease. Duvelisib (DUV), a first-in-class oral dual PI3K-δ,γ inhibitor, was approved by the FDA for the treatment of relapsed or refractory CLL or SLL after ≥2 prior therapies. Here we present the efficacy and safety of DUV in pts who had received ≥2 prior therapies in the phase 3 DUO trial (NCT02004522).

Methods: Pts were randomized 1:1 to oral DUV 25 mg BID or IV ofatumumab (OFA) 300 mg once, then 2000 mg for 12 doses total. The primary endpoint was PFS as assessed by a blinded IRC.

Results: Of the 319 total pts randomized, 191 had received ≥2 prior therapies (93 DUV; 98 OFA). In this population, the median number of prior therapies was 3 (range, 2-10). DUV was superior to OFA across all efficacy endpoints (Table). AEs occurring in >25% of pts who received DUV (all grade; grade ≥3) were diarrhea/colitis (58%; 24%), neutropenia (40%; 38%), pyrexia (33%; 2%), upper respiratory infection (30%; 0%), pneumonia (29%; 22%), and fatigue (26%; 3%). Many AEs were successfully managed through dose modifications, with dose reductions occurring in 28% of pts and dose interruptions occurring in 74% of pts who received DUV; diarrhea/colitis (10%) and neutropenia (5%) were the most common AEs leading to dose reduction. 22 pts (23%) discontinued DUV due to a related AE; diarrhea/colitis (n = 8), pneumonia (n = 3), and pneumonitis (n = 2) were the only treatment-related events leading to discontinuation in >1 pt. 11 pts (12%) treated with DUV experienced a fatal AE. The only fatal events to occur in >1 pt were hemorrhagic stroke (n = 2) and staphylococcal pneumonia (n = 2). AEs with OFA were similar to those previously reported.

TABLE 1 Efficacy in Pts With CLL/SLL Who Had Received ≥2 Prior Therapies

Endpoint	DUV N = 95	OFA N = 101
PFS, median, months	16.4[a]	9.1
95% CI	12.0-20.5	7.9-10.7
Hazard ratio (95% CI)	0.4 (0.27-0.59)	
ORR, %	78.9[a,b]	38.6
95% CI	70.7-87.1	29.1-48.1
Odds ratio (95% CI)	7.28 (3.61-14.67)	
CR	0	0
PR	77.9	38.6
PRwL	1.1	0
LNRR, %	88.4[a]	13.9
95% CI	82.0-94.9	7.1-20.6

[a]Statistically significant (*P*<.0001).
[b]Includes CR, CRi, PR, and PRwL per iwCLL/revised IWG criteria.

Conclusions: DUV monotherapy had a manageable safety profile and demonstrated significantly improved clinical outcomes over OFA in CLL/SLL pts who had received ≥2 prior therapies, a population in need of additional targeted therapies.

Keywords: chronic lymphocytic leukemia (CLL); Duvelisib; PI3K/AKT/mTOR.

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EFFECT OF DOSE MODIFICATIONS ON RESPONSE TO DUVELISIB IN PATIENTS WITH RELAPSED/REFRACTORY CLL/SLL IN THE DUO TRIAL

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Introduction: Duvelisib (DUV), a first-in-class oral dual PI3K-δ,γ inhibitor, is approved for treatment of relapsed/refractory (R/R) CLL/SLL after ≥ 2 prior therapies. In the phase 3 DUO trial, DUV 25 mg BID significantly improved efficacy vs ofatumumab (OFA; mPFS, 13.3 vs 9.9 mo; HR, 0.52 [$P < .0001$]; ORR, 74% vs 45% [$P < .0001$]) in pts with R/R CLL/SLL (Flinn et al. *Blood* 2018). Treatment-emergent AEs (TEAEs) of special interest (AESIs) such as infections, diarrhea, colitis, neutropenia, rash, ALT/AST elevation, and pneumonitis, were moderate and manageable with early intervention and dose modification. We examined dose-modification patterns and their impact on response to DUV in the DUO trial.

Methods: TEAEs were assessed according to the NCI CTCAE v4.03. Dose interruptions (DI) or reductions (DR) to 15, 10, or 5 mg BID were permitted per study protocol to manage TEAEs. Responses were assessed by an independent review committee before and after dose modifications and were analyzed using descriptive statistics.

Results: Among 158 DUV-treated pts, median duration of DUV exposure was 11.6 mo (vs 5.3 mo, OFA). DI and DR occurred in 80% (126/158) and 27% (43/158) of pts, respectively. The most common cause of DI was diarrhea (23%), followed by neutropenia (12%) and pneumonia or colitis (11% each). Among responders (n = 118), median time to first response on DUV was 1.9 mo and estimated median duration of response was 11.1 mo. Median time to first DI was 3.9 mo and median duration of DI was 15 d (range, 1-133 d). Response to DUV was improved or maintained in most pts evaluated for response who had ≥ 1 DI for > 1 wk (84% [42/50]) or > 2 wk (82% [31/38]) followed by ≥ 3 wk on DUV. In a landmark analysis, median PFS was similar in pts with DI and those without DI for > 1 wk (17.8 vs 16.3 mo) or > 2 wk (17.8 vs 16.3 mo) within the first 3 mo. The median time to DR after CR/PR was 5.6 mo (n = 25) and median duration was 3.4 mo. Median time to onset across AESIs after starting DUV ranged from 2.2 to 4.3 mo; median time to resolution was within 4 wk across AESIs. Proportions of pts experiencing AESIs were stable or decreased over time after 3-6 mo: 0-3 mo, 64% (101/158); > 3-6 mo, 63% (86/137); > 6-9 mo, 47% (54/114); > 9-12 mo, 52% (52/100), and seldom led to discontinuation of DUV (≤ 10%).

Conclusions: DI/DR can contribute to the effective management of TEAEs with DUV. These findings suggest that DI of > 1-2 weeks or more do not appear to significantly impact response to DUV or PFS.

Keywords: chronic lymphocytic leukemia (CLL); PI3K/AKT/mTOR; small lymphocytic lymphoma (SLL).

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PATTERNS OF DUVELISIB-INDUCED LYMPHOCYTOSIS IN PATIENTS WITH R/R CLL OR SLL INCLUDING THOSE WITH HIGH-RISK FACTORS TREATED IN THE DUO TRIAL

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Background: Although lymphocytosis is a defining feature of chronic lymphocytic leukemia (CLL), it is also recognized as a class effect of treatment with B-cell receptor pathway inhibitors. Duvelisib (DUV) is a first-in-class, oral, dual PI3K-δ,γ inhibitor approved for the treatment of pts with relapsed/refractory (R/R) CLL or small lymphocytic lymphoma (SLL) who have received ≥2 prior therapies (Flinn et al. ICHM 2019). In the phase 3 multicenter DUO trial, DUV 25 mg twice daily (BID) showed a significant improvement in efficacy vs ofatumumab (mPFS, 13.3 vs 9.9 mo; HR, 0.5 [*P*<.0001]; ORR, 74% vs 45% [*P*<.0001]) with a manageable safety profile (Flinn et al. *Blood*. 2018). In preclinical studies using CLL cells from pts transferred into mice, dual PI3K-δ,γ inhibition was more effective than PI3K-δ inhibition alone in reducing CLL cell burden (Chen et al. ASH 2018). Herein we aim to characterize the pattern of DUV-related lymphocytosis in the DUO trial.

Methods: Lymphocytosis was defined as an absolute lymphocyte count (ALC) of ≥5×10^9/L and a ≥50% increase of ALC from baseline (BL). ALC measured by local laboratories to determine peak ALC, median time to 50% reduction from BL ALC, and median time to onset (TTO) and resolution (TTR) of lymphocytosis. Median TTR was defined as ALC at or below the BL value or ALC of <5×10^9/L, whichever occurred first. Data were summarized using descriptive statistics, including medians for continuous variables and proportions for discrete variables.

Results: Of 158 pts treated with DUV, 78% experienced lymphocytosis. Median ALC at BL was 41.1×10^9/L (range, 0.2-381.7). Median TTO of lymphocytosis was 1 wk across all pts, including high-risk pts. Median TTR of lymphocytosis (<5×10^9/L or BL) was 14 wk (Figure; solid arrow), with a 50% reduction from BL ALC at 21 wk (Figure, dashed arrow). Similar results were observed regardless of high-risk status: del(17p)/*TP53* (n = 48 [30%]), 14 wk; del(11q) (n = 38 [24%]), 18 wk; bulky disease (n = 74 [47%]), 11 wk; unmutated *IGHV* (n = 110 [70%]), 13 wk. Rapid shrinkage of lymph nodes was noted, with 86% of pts achieving lymph node response. Among pts who achieved a response with DUV at first or second assessment, 78% and 86%, respectively, experienced lymphocytosis; median TTR of lymphocytosis in these pts was 12 and 18 wk, respectively. Prolonged lymphocytosis (for >12 mo) occurred in 12 pts (8%). The ORR in pts with prolonged lymphocytosis was 83%. Of note, the median PFS was similar among pts with and those without prolonged lymphocytosis (22.1 mo [95% CI, 12.9-27.6]) vs [24 mo [95% CI, 20.5-NE], respectively).

Conclusion: DUV monotherapy induces rapid and transient lymphocytosis temporally associated with a reduction in lymphadenopathy in pts with R/R CLL/SLL. Notably, DUV resulted in a deep and prolonged resolution of lymphocytosis to >50% below BL. The pattern of lymphocytosis in high-risk pts was similar to that in the general pt population.

Keywords: chronic lymphocytic leukemia (CLL); Duvelisib; PI3K/AKT/mTOR.

Note: The upper CI for ALC at 24 months exceeds 125%

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BRIEF CO-ADMINISTRATION OF IDELALISIB MAY IMPROVE THE LONG-TERM EFFICACY OF FRONTLINE CHEMOIMMUNOTHERAPY IN CHRONIC LYMPHOCYTIC LEUKAEMIA: 3-YEAR FOLLOW-UP FROM THE RIALTO TRIAL

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Introduction: The Phase 3 RIAltO trial opened in December 2011 to compare ofatumumab plus chlorambucil (O+C) with ofatumumab plus bendamustine (O+B) in patients with previously untreated chronic lymphocytic leukaemia (CLL) considered unfit for FCR (fludarabine, cyclophosphamide, rituximab). The protocol was amended in September 2014 to investigate the addition of idelalisib (first-in-class inhibitor of the p110δ isoform of phosphoinositol-3 kinase) or placebo. However, all idelalisib/placebo treatment was withdrawn from the trial in March 2016 following safety analysis of idelalisib registration studies and recommendations from Gilead Sciences Ltd and regulatory authorities. Here, we present an updated ad-hoc analysis of the cohort of patients in RIAltO who received idelalisib or placebo.

Numbers at risk

Idelalisib	73	64	62	60	54	50	38	22	5
Placebo	72	68	63	53	44	39	26	14	3
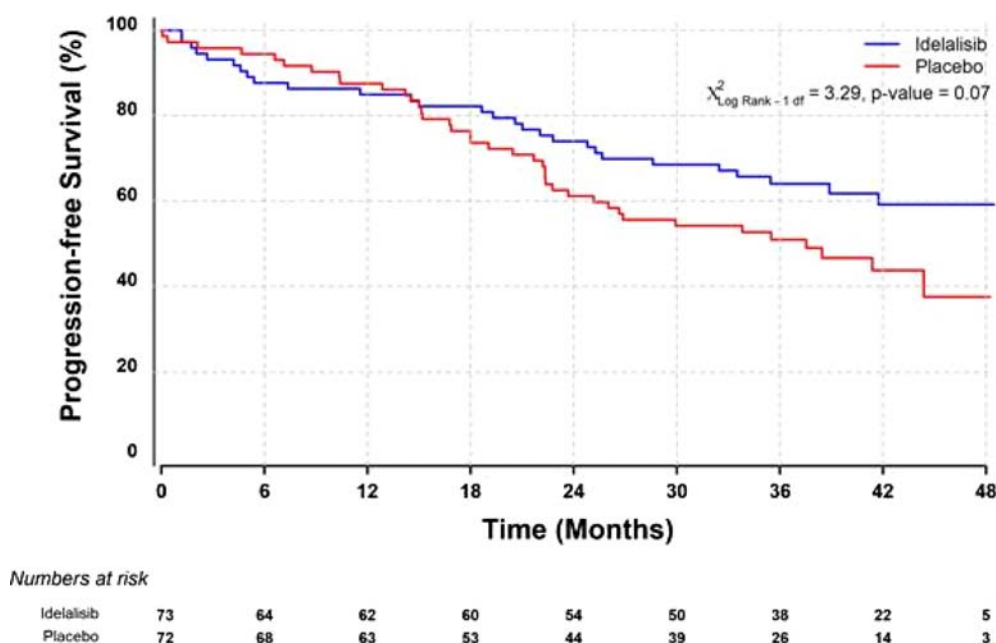
Methods: Patients were eligible for inclusion if they had previously untreated CLL requiring treatment by NCI/IWCLL criteria, were considered unfit for FCR and did not have any contraindications to the study drugs. Consenting patients underwent an unblinded 1:1 randomisation to ofatumumab (300mg iv day 1 and 1000mg iv day 8 of cycle 1; 1000mg iv day 1 of cycle 2 onwards) plus either chlorambucil (10mg/m^2 day 1-7, repeated every 28 days for 3-12 cycles) or bendamustine (70mg/m^2 iv day 1-2 for 3-6 cycles) and a double-blinded 1:1 randomisation to concurrently administered placebo or idelalisib (150mg bd for up to 3 years). Co-trimoxazole prophylaxis was recommended. Study drugs were discontinued in the event of disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). The mandatory post-treatment reporting period for serious adverse events (SAEs) was 6 months for grade ≥3 infections and 28 days for other events.

Results: 145 patients received idelalisib (73) or placebo (72), the two arms being well balanced for age, gender, stage, co-morbidity, performance status and chemotherapy allocation. The median idelalisib exposure time was 3.3 months (IQR 1.2-7.3 months). As of January 2019, SAEs were reported in 79% of idelalisib-treated patients (87 grade 3-4 and 9 grade 5) compared to 50% of the placebo arm (38 grade 3-4 and 6 grade 5). The frequency of SAEs in the idelalisib arm was similar in both chemotherapy groups. After a median follow-up of 41.7 months (IQR 36.2-45.4 months), 28 PFS events have been reported in the idelalisib arm compared with 39 in the placebo arm (P = 0.070, log-rank test), while 10 and 16 deaths have been observed in the idelalisib and placebo arms, respectively (P = 0.218, log-rank test). Although 6-month mortality in the idelalisib arm was twice that of the placebo arm, only 2 deaths have been reported beyond 6 months in the idelalisib arm compared with 12 in the placebo arm.

Conclusions: The early toxicity associated with the addition of idelalisib to frontline chemoimmunotherapy in CLL appears to be offset by improved long-term efficacy.

Keywords: chronic lymphocytic leukemia (CLL); idelalisib; ofatumumab.

Disclosures: Pettitt, A: Research Funding: *Celgene, Chugai, Gilead, GSK/Novartis, Roche, Verastem*; Other Remuneration: *Celgene, Gilead*. **Kalakonda, N:** Research Funding: *Celgene*. **Schuh, A:** Consultant Advisory Role: *Gilead, Abbvie, Janssen, Roche*; Honoraria: *Gilead, Abbvie, Janssen, Roche*; Research Funding: *Gilead and Janssen*. **Duncombe, A:** Honoraria: *Abbvie, Novartis, Gilead, Janssen*. **Paneesha, S:** Honoraria: *Speaker Fee Janssen, Gilead, Abbvie*. **Fox, C:** Consultant Advisory Role: *Abbvie, Adienne, Celgene, Gilead, Janssen, Roche, Takeda, Sunesis, Atarabio*; Honoraria: *Abbvie, Adienne, Celgene, Gilead, Janssen, Roche, Takeda, Sunesis, Atarabio*; Research Funding: *Abbvie, Adienne, Gilead, Roche*. **Hamblin, M:** Honoraria: *Roche*. **Hillmen, P:** Honoraria: *Janssen, Abbvie, Roche*; Research Funding: *Janssen, Pharmacyclics, Abbvie, Roche, Gilead*.

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UNMAINTAINED REMISSION AFTER DISCONTINUATION OF KINASE INHIBITOR TREATEMENT IN CHRONIC LYMPHOCYTIC LEUKEMIA: AN OBSERVATIONAL COHORT

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Introduction: Kinase inhibitors (KI) rapidly changed treatment paradigms in CLL and ibrutinib currently enters clinical standards in previously untreated patients. Thus, the prevailing "treat-until-progression" concept will lead to very long treatment durations or a need for drug cessation. However, explored stopping rules largely rely on MRD negativity, rarely achieved with KI. Outcomes in lineages after KI are reported mostly on patients that received immediate salvage treatment. However, in real-life experiences a large proportion of discontinuations of KI in CLL treatment happen due to toxicity and patient decisions rather than progression and often happen in meaningful clinical remission due to the KI, but without achieving MRD negativity. Their fate in a treatment-free observation setting is unknown.

Methods: We here report a first real-world cohort of CLL patients that had received ibrutinib or idelalisib in different lines of treatment, that had achieved measurable response, suffered toxicities or made decisions to stop therapy and remained in unmaintained (i.e. untreated) observation after discontinuing the kinase inhibitor. Retrospective analyses from chart review in 7 academic centres were performed.

Results: We report on 54 patients, treated with either ibrutinib (n = 29) or idelalisib (n = 25). Median age was 74 years at the start of the novel drug and the median number of treatments prior to KI was 1 (range 0 to 6). The median duration on KI was 8 months before stopping due to toxicity (n = 49) or patient's decision (n = 5). Expectedly, the most important toxicities leading to drug cessation were cardiac events, infection and bleeding for ibrutinib and gastrointestinal events, as well as skin and hepatic toxicity for idelalisib. FISH cytogenetics were available in 51 and mutation states in 42 patients. Twenty patients had del17p and 13 had del11q. Eleven patients stopped treatment in CR and 43 achieved PR. Median PFS after treatment cessation was 9.4 months, median TTNT was 12 months and OS was 62% at a median observation time of 27 months. PFS and TTNT at 2a were 19 and 27%, respectively. No differences were observed between the two drugs in PFS and TTNT, but the idelalisib cohort had a significantly better OS (median n.r. vs 20 mo, p = .002) in our cohort. PFS, TTNT and OS were not significantly different by FISH risk, while unmutated IgVH predicted earlier progression, but not OS. Despite low numbers in some groups, the type of toxicity had no apparent large effect on outcome. While the line of treatment did not affect PFS or OS, achievement of CR showed better PFS, but not OS.

Conclusion: Treatment cessation in CR or PR after kinase inhibitor treatment is associated with limited median PFS, but some patients experience prolonged treatment free intervals. Exploratory analyses point to clinical response quality and mutational state as predictors of PFS. OS from stop of kinase inhibitor was respectable for this elderly cohort, suggesting available salvage options.

Keywords: chronic lymphocytic leukemia (CLL); ibrutinib; idelalisib.

Disclosures: Egle, A: Consultant Advisory Role: *Janssen, Gilead*; Honoraria: *Janssen, Gilead.* **Jäger, U:** Consultant Advisory Role: *Janssen and Gilead*; Honoraria: *Janssen and Gilead*; Research Funding: *Janssen and Gilead.* **Nösslinger, T:** Consultant Advisory Role: *Janssen and Gilead*; Honoraria: *Janssen and Gilead.*

INDOLENT LYMPHOMAS

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LONG TERM FOLLOW-UP OF FoRT: A PHASE 3 MULTI-CENTER PROSPECTIVE RANDOMIZED TRIAL OF RADIATION THERAPY FOR FOLLICULAR AND MARGINAL ZONE LYMPHOMA

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Introduction: The FoRT trial was a prospective multi-center non-inferiority study designed to compare 24 Gy in 12 fractions with 4 Gy in 2 fractions. The initial analysis with a median follow-up of 26 months, showed that 24Gy resulted in significantly better local progression free survival than 4Gy. This data has now been updated with a median follow up of 73.8 months.

Methods: Patients requiring local radiation therapy for FL with either palliative or radical intent were eligible, and patients with marginal zone lymphoma (MZL) were also included later in the study. The primary endpoint was time to local progression, with overall survival, quality of life and toxicity as secondary endpoints.

Results: A total of 614 treatment sites in 548 patients were randomized. 299 were randomized to receive 24 Gy and 315 to 4 Gy. Median age was 66 years (25-95); 86.3% were diagnosed with FL and the remainder MZL. Treatment intent was curative in 40% and palliative in 60%. Stage at randomisation was: stage I (42.6%), stage II (17.6%), stage III (18.1%), stage IV (10.4%), stage unknown (10.9%). FLIPI index was: low (49.5%), intermediate (24.9%), high (15.6%), missing (9.9%).
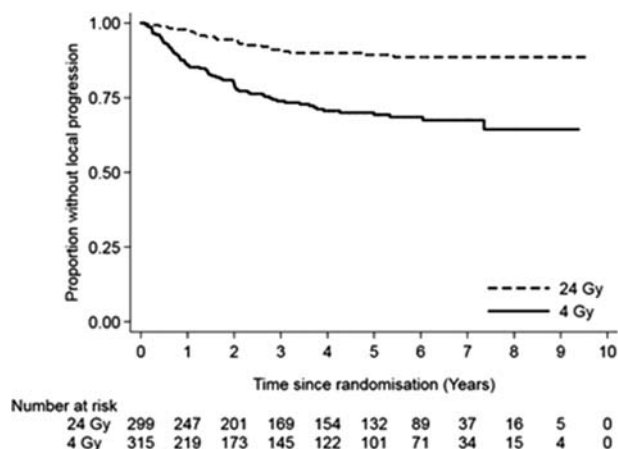
24.6% had received previous radiation therapy and 33.7% previous chemotherapy.

With a median follow up of 73.8 months the local progression free survival at 3 years was 90.9% after 24Gy and 74.6% after 4Gy; the corresponding rates at 5 years are 89.9% after 24Gy and 74.4% after 4Gy; at the median follow up of 73.8 months the rates are 89.3% and 68% (Hazard ratio (HR): 3.46 (95% CI: 2.25 – 5.33, p<0.001)- see figure below.

There remains no difference in overall survival (HR: 1.03 (0.74 – 1.43, p = 0.86). Median time to local progression has not been reached but for patients who had local progression these occurred at a median time of 19.3 months (range: 1.3 – 65.0) for sites treated with 24 Gy and 11.7 months (range: 0.9 – 88.3) for sites treated with 4Gy. In the subgroup treated with curative intent there were 5/119 relapses after 24Gy and 29/129 after 4Gy: HR: 5.80 (2.25 – 14.99) p<0.0001.

Conclusions: Whilst 4 Gy in 2 fractions can be effective in the palliative setting, it is significantly inferior to 24 Gy in 12 fractions. This difference is maintained with long term follow up and is greatest in patients treated with radical intent. 24Gy in 12 fractions should remain the schedule of choice for curative radiation therapy in follicular or marginal zone lymphoma.

Keywords: follicular lymphoma (FL); indolent lymphoma; marginal zone lymphoma (MZL).

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SYSTEMIC THERAPY AFTER RADIATION THERAPY IN STAGE I-II FOLLICULAR LYMPHOMA: FINAL RESULTS OF AN INTERNATIONAL RANDOMIZED TRIAL TROG 99.03

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Aim: The first analysis of the TROG 99.03 randomized controlled trial of curative-intent involved-field radiotherapy (IFRT) with or without systemic therapy reported improved progression–free survival (PFS) by the addition of systemic therapy, especially with rituximab. We present the final analysis of that study.

Patients and Methods: Patients from Australia, New Zealand and Canada with stage I-II FL of grade 1, 2 or 3a were enrolled after CT scans and bone marrow biopsies. Patients were randomized to either; Arm A: 30Gy IFRT alone or Arm B: IFRT followed by 6 cycles of cyclophosphamide 1000 mg/m^2 IV D1, vincristine 1.4 mg/m^2 D1 and prednisolone 50mg/m^2 D1-5 (CVP), stratified by center, stage, age and use of PET staging (which was not mandatory). A protocol amendment in 2006 added Rituximab 375 mg/m^2 D1 to arm B (R-CVP).

Results: Between February 2000 and July 2012, 150 patients were recruited: 75 per arm: 44 arm B patients were allocated CVP and 31 R-CVP. Median age was 57 (range 30-79) years, 52% were male, 75% had stage 1 and 48% were PET-staged. Only 8% had an extranodal site (ENS). Median potential follow-up was 11.3 years for this analysis. PFS remained significantly superior for arm B (IFRT + systemic therapy) compared to arm A [HR 0.60 (0.37-0.98); p = 0.043]. At 10 years PFS was 60% for arm B and 43% for arm A. Patients who received R-CVP had substantially superior PFS compared to those who received IFRT alone or with CVP (no rituximab) (83.1% (se = 6.9%) vs 50.4%% (se = 4.8%) at 8 years, P = 0.013). In univariable analysis, patients with ENS (p = 0.041), fewer involved nodal regions (p = 0.018) and PET staging (p = 0.086) had improved PFS. When analysis of PFS was confined to 72 PET-staged patients the difference between arms A and B increased (HR 0.38 P = 0.027), whereas analysis confined to 78 non-PET staged patients showed weak evidence of a difference between arms (HR 0.78, P = 0.42). More deaths (Figure) occurred in arm A (13 versus 6), with 10-year overall survival rates of 95.3% (se = 2.7%) and 84.4% (se = 4.9%) for arms B and A respectively (HR 0.45, p = 0.11). One possible and 5 definite transformations to aggressive lymphoma occurred in arm B versus 11 in arm A.

Conclusion: Treatment with 6 cycles of CVP or R-CVP after IFRT significantly improved PFS compared to IFRT alone, especially for rituximab-treated patients. Improved PFS was most evident in PET staged patients. More deaths and transformations to high grade lymphoma were observed with IFRT alone and, with more than 10-years of follow-up, OS favors combined modality therapy (P = 0.11).

Keywords: follicular lymphoma (FL); positron emission tomography (PET); rituximab.

PFS by arm: PET-staged patients (adjusted)

PFS by arm: non-PET-staged patients (adjusted)

Overall survival by arm (unadjusted)
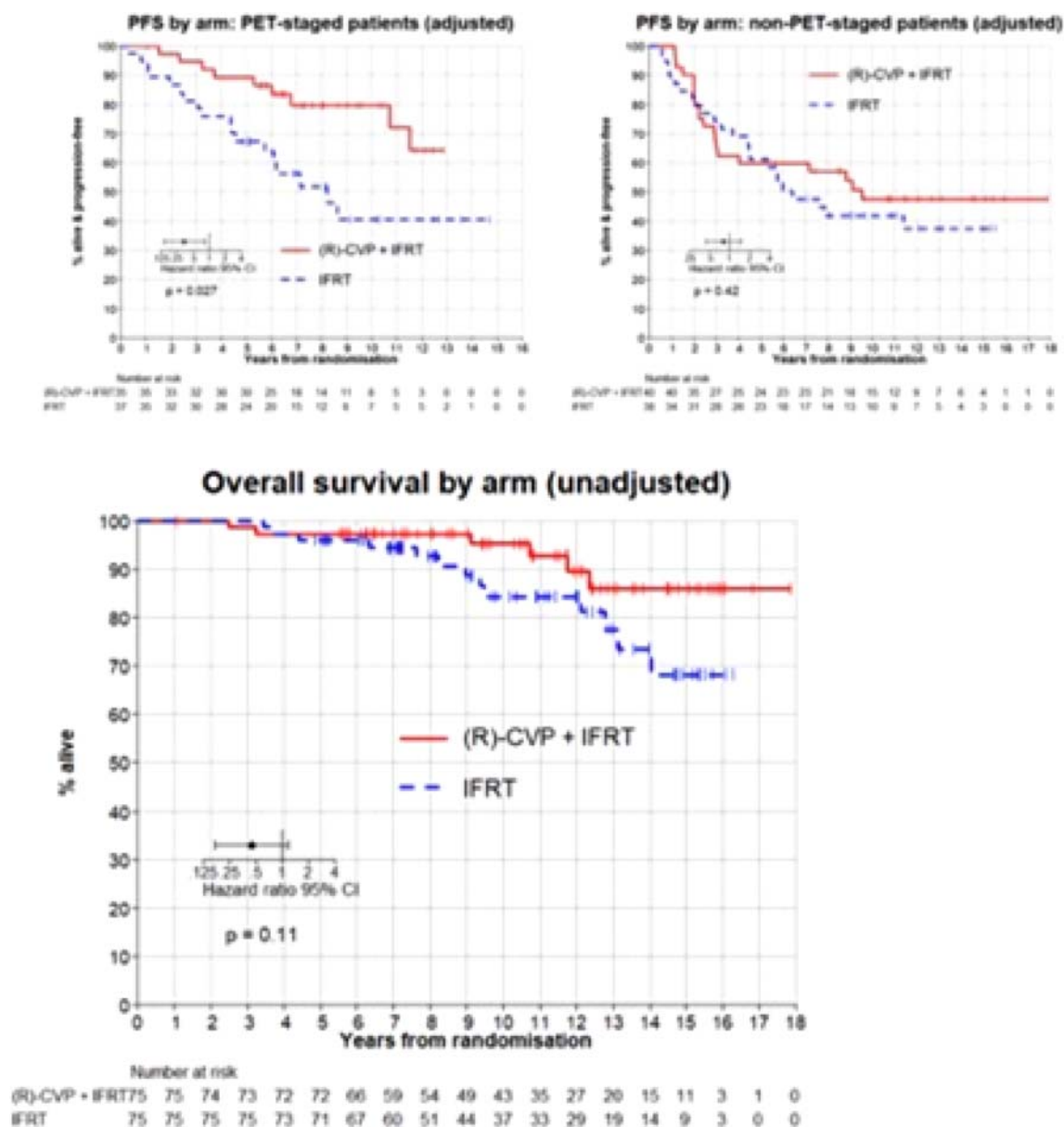
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RESULTS OF A MULTICENTER PHASE2 TRIAL OF INVOLVED FIELD RADIOTHERAPY ALONE FOR LOCALIZED NON-GASTRIC MARGINAL ZONE LYMPHOMA: TROG 05.02

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Introduction: We conducted the first prospective phase 2 multicenter clinical trial to assess the long term efficacy and safety of radiotherapy for localized non-gastric marginal zone lymphoma (MZL) and documented the prevalence of autoantibodies, autoimmune events and *Helicobacter Pylori* (HP) infection in this population.

Methods: Eligible patients had untreated stage I or II, or paired-organ confined, non-gastric marginal zone lymphoma. Mandatory investigations included CT and bone marrow aspirate and trephine, autoantibody panel and HP evaluation. FDG-PET was optional. Involved-field or site, conventionally-fractionated radiotherapy was delivered to 30-30.6 Gy, except for orbital MZL which received 24-25 Gy.

Results: Six centres enrolled 70 patients. Two patients were ineligible after registration: 68 patients commenced protocol treatment. Median

Number at risk

| 68 | 61 | 58 | 53 | 39 | 30 | 21 | 13 | 7 | 5 | 0 |
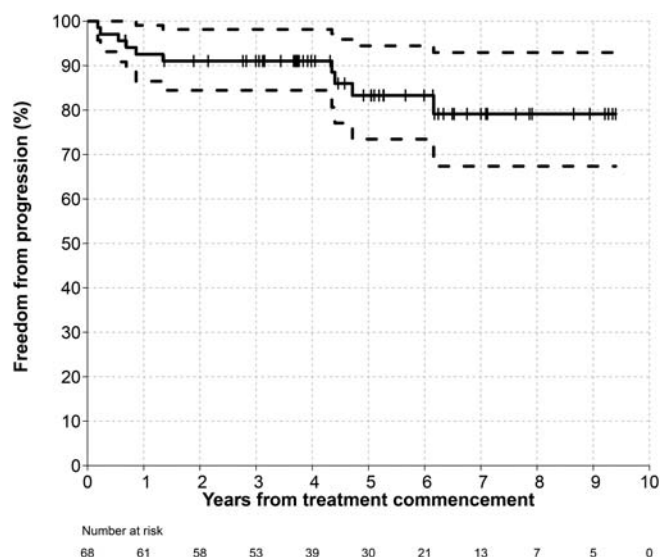
age was 59 (range: 23-84) and 31 (46%) were male. Stage was I n = 55, II n = 9 and IV n = 4. Sites were orbital n = 18, conjunctiva n = 13, lacrimal n = 8, skin n = 8, primary nodal n = 8, salivary n = 7, muscle n = 3 and 15 other extranodal sites with single cases of each. Four patients (6%) had paired organ (salivary or orbital) MZL. Fourteen (21%) were PET-staged. Median follow-up was 5 years (range 0.7 – 9.4). At 7 years, freedom from progression and overall survival were 79% (95% CI: 67-93) (Figure) and 95% (95% CI: 89-100) respectively. One transformation to diffuse large B cell lymphoma occurred. There was one lymphoma-related death and 2 in-field failures (after 25 and 30 Gy respectively). Out-of-field relapse sites were skin (n = 2) duodenum, stomach, paravertebral muscle and conjunctiva. No patient with paired organ disease relapsed. Acute toxicity $\geq$ grade 3 occurred in 7 cases. Apart from cataracts (n = 18), there were 6 late grade 3 adverse events. Two grade 4 late events (nephrotic syndrome and catheter thrombosis) and two second malignancies were not treatment-related. Autoantibodies or auto-immune events were detected in 26 of 68 (38%) patients. HP infection was detected (and treated) in 15 of 63 patients tested (24%). Neither autoimmunity or HP was detected in 27/68 (40%) patients.

Conclusions: Most patients with localized non-gastric MZL had either evidence of autoimmunity or HP infection or both and RT was a highly effective treatment associated with low toxicity and excellent survival.

Keywords: extranodal marginal zone lymphoma of MALT type; Helicobacter pylori; marginal zone lymphoma (MZL).

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OUTCOMES OF 180 PATIENTS WITH INDOLENT LYMPHOMAS TREATED WITH VERY LOW DOSE (4 GY) RADIATION THERAPY ALONE

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Introduction: Follicular lymphoma (FL) and marginal zone lymphoma (MZL) are highly radiosensitive and often respond to very low dose radiation therapy (VLDRT). We investigated the outcomes of patients treated with 4 Gy from a large, contemporary, real world cohort, and a subset of potentially curable (PC) patients with early stage disease and no prior therapy before VLDRT.

Methods: We analyzed 221 treated sites from 180 consecutive adult patients (Table 1) with FL or MZL who were treated with VLDRT of 2 Gy x 2 fractions between 2006 and 2019 at our center. Initial overall response rate (ORR) was defined as complete response (CR) or partial response (PR) using Lugano radiographic or clinical criteria at 2 months post-RT. Stable disease (SD) or progressive disease (PD) at 2 months post-RT were considered local failure (LF). Freedom from local failure (FFLF) was defined as time from VLDRT to LF. Patients were censored at the start of a subsequent line of therapy if the VLDRT-treated site had not progressed. Event-free survival (EFS) was calculated per patient from VLDRT to LF or distant PD. FFLF and EFS were estimated using Kaplan-Meier and compared using log-rank.

Results: Initial ORR for all sites was 90% (CR: 66%, PR: 24%); 10% (n = 23) were initially nonresponding (SD: 6%, PD: 4%). Ten sites with initial PR/SD/PD received additional RT (median: 30 Gy) within 6 months of VLDRT and had subsequent CR (n = 5), PR (n = 4), and PD (n = 1). With median follow-up of 21 months, 2-year FFLF was 73%. Initial response to VLDRT was prognostic since the 2-year FFLF for sites with CR (n = 146) was significantly better than those with PR (n = 52) (90% vs. 66%, p<0.001). There was improved 2-year FFLF for nodal vs. extranodal disease (63% vs. 82%, p = 0.02) but not for previously untreated vs. relapsed/refractory (76% vs. 72%, p = 0.4) or early vs. advanced stage sites (73% vs. 73%, p = 0.4).

In the subset of PC patients (n = 48), median follow-up was 11 months with a 1-year EFS of 78%. The majority of PD (n = 11) were distant (73%). Diffuse large B cell lymphoma transformation after VLDRT was rare in the PC (n = 0) and overall (n = 7, 4%) cohort; all were diagnosed out of the VLDRT field.

Conclusions: Overall, patients with FL and MZL treated with only 4 Gy have excellent initial ORR. Early evaluation following VLDRT identifies nonresponders who may benefit from additional RT and spares many patients from higher doses of RT with durable local control. Our analysis of PC patients suggests that VLDRT does not compromise the standard RT curative approach.

Keywords: follicular lymphoma (FL); indolent lymphoma; marginal zone lymphoma (MZL).

TABLE 1 Characteristics of patients and sites treated with 4 Gy

Per patient (n = 180)	Characteristics	n	(%)
	Sex		
	Female	86	(48)
	Age at VLDRT (years)		
	Median	67	
	Range	27-92	
Per lesion (n = 221)	Characteristics	n	(%)
	Histology		
	FL	137	(62)
	MZL	65	(29)
	Mixed FL and MZL	19	(9)
	Type		
	Extranodal	133	(60)
	Nodal	79	(36)
	Mixed	9	(4)
	Stage at VLDRT		
	I-II	145	(66)
	Prior treatment		
	No	71	(32)

Abbreviations: VLDRT, very low dose radiation therapy; FL, follicular lymphoma; MZL, marginal zone lymphoma.

Figure 1. Freedom from local failure estimates for sites treated with 4 Gy, stratified by early stage (I-II) vs. advanced stage (III-IV) (A), and initial complete response (CR) vs. partial response (PR) at 2 months follow-up (B).

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CLONAL B-CELL LYMPHOCYTOSIS OF MARGINAL ZONE ORIGIN (CBL-MZ): DESCRIPTION OF MAIN CLINICAL

FEATURES, DISEASE EVOLUTION AND OUTCOME IN A SERIES OF 100 PATIENTS

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Introduction: CBL-MZ has been recognized in WHO classification as a provisional entity. In the present analysis we describe CBL-MZ patients' (pts) characteristics, disease evolution and prognostic factors for outcome after a long follow-up.

Methods: Pts were selected based on the presence of circulating CD5-clonal B-cells with MZ features, without B-symptoms, no evidence of disease elsewhere than the bone marrow (BM), and no cytopenias.

Results: 100 consecutive pts were analyzed. The median age was 70y (33-90). Referral reasons: incidental lymphocytosis (77%) or paraproteinemia (13%) or inverted differential (10%). Median # of absolute lymphocyte counts (ALCs) and circulating CBL were 6780/μL (1000-150.000) and 3447/μl (185-145.000), respectively. Elevated LDH and paraproteinemia were found in 10% and 38%, respectively. All but one pts presented BM infiltration by small lymphoid cells (median 30%) with an intrasinusoidal pattern in 1/3 of pts. Immunophenotyping revealed positivity for CD23, CD11c and CD38 in 31%, 43% and 11%, respectively. MYD-88 was positive in 9/84 (11%). The presence of paraprotein was significantly associated with MYD-88 positivity (p<0.0001), lower ALCs (p = 0.002) and CBL (p = 0.001) counts, higher frequency of CD38 expression (p = 0.03) and lymphoplasmacytic differentiation in the BM (p = 0.001). The degree of BM infiltration was associated with the level of ALCs (p = 0.003). At a median follow-up time of 42.3 mos, 30 pts progressed but only 10 required treatment. Progression included: worsening lymphocytosis (17%), cytopenias (4%), splenomegaly (5%), nodal MZL (1%) and increase in paraprotein levels (3%). Therefore, five patterns of disease evolution were recognized (Figure).
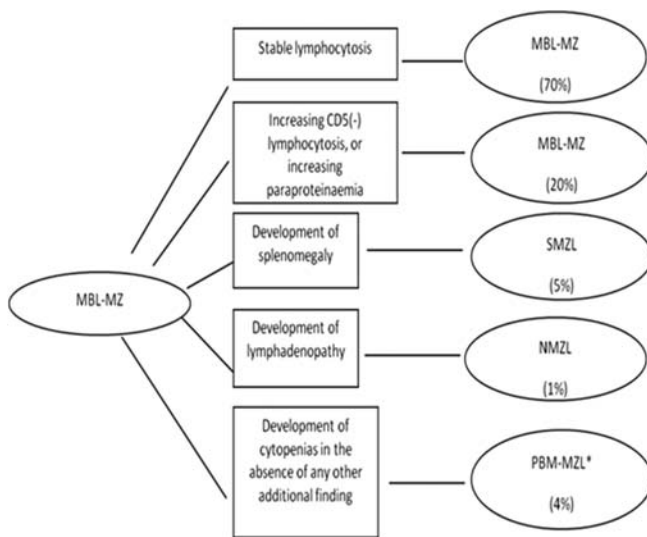
*Primary bone marrow marginal zone lymphoma

Figure. Pattern of progression - clinical evolution of MBL-MZ patients

Treatment was delivered due to cytopenias in 7 pts, symptomatic paraprotein in 1 and bulky splenomegaly in 2. Seven deaths were recorded, one disease related. The median OS was not reached; 5-y time to treatment (TTT) was 91%, and the median time to progression (TTP) 95.6 mos. By univariate analysis ALC ≥median (6780/μL), p = 0.014, CD38+, p = 0.006 and elevated LDH, p<0.0001 were significantly associated with TTP. These factors remained significant at multivariate analysis. We constructed a prognostic model for TTP stratifying pts into 3 risk groups: low-risk - 0 risk factors; intermediate - ALC≥median; high-risk – any of the 2 remaining risk factors or ≥2 factors. Median TTP was 159, 96 and 49 months, for the low-, intermediate and high-risk groups, respectively (p<0.0001). This model was prognostic of TTT, as well, though at a lower level of significance (p = 0.03).

Summary/Conclusion: CBL-MZ remain stable in the majority of pts. Progressive disease requiring treatment occurs rarely and it is usually associated with worsening cytopenias. Progression to SMZL was evident in 5%. A prognostic model for TTP using 3 factors was developed: ALCs, LDH and CD38 expression, needing further validation.

Keywords: marginal zone lymphoma (MZL); monoclonal B-cell lymphocytosis (MBL).

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FIRST APPLICATION OF MINIMAL RESIDUAL DISEASE ANALYSIS IN SPLENIC MARGINAL ZONE LYMPHOMA TRIALS: PRELIMINARY RESULTS FROM BRISMA/IELSG36 PHASE II STUDY

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Introduction: Although often managed as an indolent disease, splenic marginal zone lymphoma (SMZL) can achieve complete clinical remission if treated with modern chemo-immunotherapy. It might be worthy to assess minimal residual disease (MRD) in SMZL, both to assess the prognosis and evaluate the efficacy of new compounds.

Methods: The BRISMA/IELSG36 trial is an international, phase II study (NCT02853370) designed by the Fondazione Italiana Linfomi (FIL) and the French LYmphoma Study Association (LYSA) to evaluate the efficacy of bendamustine and rituximab for six cycles (BR). [Iannitto, BJH 2018]. Between 2013-2014, 56 SMZL patients were enrolled. Bone marrow (BM) and peripheral blood (PB) samples were collected at baseline, after 3 BR (interim), after the last BR (EOT) cycle, respectively and during follow-up (1, 3 and 5 years) for MRD purposes. All patients provided written informed consent in accordance
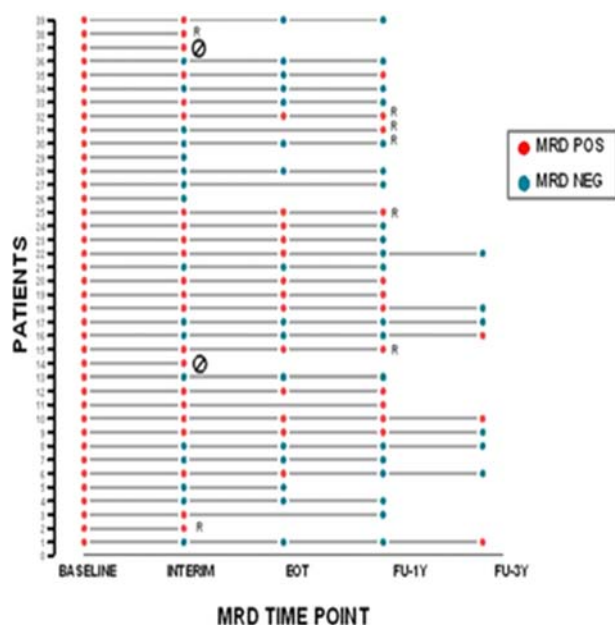
Figure 1. MRD analysis plot for BRISMA/IELSG 36 trial.
R: relapse/refractory, ⊘ out for patient withdraw

with Helsinki's declaration. MRD was assessed both on BM and PB samples by droplet digital PCR, employing IGH-directed ASO primers. [Drandi, JMD 2015]

Results: 54/56 patientshad at least 1 FU sample available for MRD analysis. A molecular marker was found in 43/54 (80%) cases: hereby, MRD results are reported for 39 patients. Median tumor burden at baseline was 1.45E-01 (range 1 - 2.67E-03) on BM and 4.04xE-01 (1 - 5.60E-03) on PB. MRD negativization rates were 47% at interim (BM: 13/32; PB: 21/36), 54% at EOT (BM: 10/23; PB: 18/22) and 61% after one year (BM: 14/22; PB: 19/29), Figure 1. Median tumor burden shrinkage was 4 logs both at interim and at EOT in BM (2.67E-05) and reached the negativity in PB (1.00xE-08). Three different trends of MRD kinetics were described: A) persistent MRD negativity (n = 16, 41%); B) persistent MRD positivity (n = 12, 31%); C) alternating MRD (n = 11, 28%). Only 6 relapses (based on Cheson 1999 criteria) were recorded so far, 5 of which being in the groups B and C. The median FU is currently 32 months: accordingly many relapses are expected. Three MRD recurrences were detected, so far, that might herald future clinical relapses.

Conclusion: This is the first application of MRD in a prospective trial for SMZL, with an overall good feasibility. The MRD trends highlighted the activity of BR in this disease and accurately described the response/relapse patterns. Moreover, MRD recurrences detected during FU might herald late relapse. Therefore, our preliminary results suggest that MRD analysis needs further development in SMZL.

Keywords: Bendamustine; minimal residual disease (MRD); splenic marginal zone lymphoma (SMZL).

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RITUXIMAB ALONE (R) VERSUS RITUXIMAB PLUS BENDAMUSTINE (BR) FOR SPLENIC (SMZL) AND NODAL MARGINAL ZONE LYMPHOMA (NMZL)

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Background: SMZL and NMZL, rare lymphomas diagnosed at median age of 69, are increasingly treated with BR as 1st line therapy, despite limited histology-specific experience and uncertain risk/benefit ratio of BR over R monotherapy in these indolent subtypes. We compared outcomes of R and BR using causal inference methods in population-based data from Medicare beneficiaries.

Methods: Using Medicare claims linked to cancer registry (SEER) data from 19 areas of the United States covering about 34% of the population, we identified patients with SMZL/NMZL age ≥65 who received 1st line R or BR between 2009 and 2016. We used a propensity score to balance patient and disease characteristics (including histology, stage, B symptoms, prior splenectomy, anemia, transfusions, hospitalizations, comorbidities, and performance status) between treatment arms. In the resulting pseudo-randomized cohort we then compared time to treatment failure (TTF, defined 2nd line chemotherapy, splenectomy, hospice enrollment, or death), overall survival (OS), risk of major toxicities (hospitalization, transfusions), and Medicare spending.

Results: Among 958 eligible patients (median age 77 years, 54% women, 34% SMZL and 66% NMZL), proportion receiving BR (n = 235; 23%) increased from 8% in 2009 to 32% in 2016. BR was used less frequently among patients with age over 70 years, with SMZL, with stage IA lymphoma, and in those treated >3 months from diagnosis. Median TTF for the entire cohort was 4.5 years, and median OS was 5.7 years. In pseudo-randomized cohort balanced with regard to patient and disease characteristics, we did not observe any significant difference between BR and R for either TTF or OS, but toxicities were significantly higher with BR (**Table**). There was no evidence of a differential effect of the regimens between NMZL and SMZL (interaction *P* = 0.62 for TTF and 0.96 for OS). Adjusted costs of care were higher for BR than R ($84,003 vs. $53,048, *P*< .001). A sensitivity analysis for potential unobserved confounding showed that over 50% of BR patients would need to have an unrecorded risk factor doubling their mortality to explain the lack of survival benefit of BR over R.

Conclusions: Among older patients with SMZL and NMZL, BR offers no OS or TTF benefit over single-agent R, while it increases hospitalizations, need for transfusions, and costs. Without a formal randomized study (which has not been conducted), single-agent R may offer a

TABLE 1

Outcome	BR	R	Risk ratio	95% CI	P
TTF at 3y	65%	62%	1.04	0.80-1.36	0.78
OS at 3y	69%	71%	1.15	0.86-1.54	0.35
Anemia	55%	38%	1.46	1.23-1.73	<0.0001
Transfusion	22%	9%	2.50	1.65-3.78	<0.0001
Hospitalization	37%	26%	1.45	1.14-1.84	0.0028

Fig. 1. OS of patients treated with single-agent R or with BR as first-line regimen for SMZL or NMZL
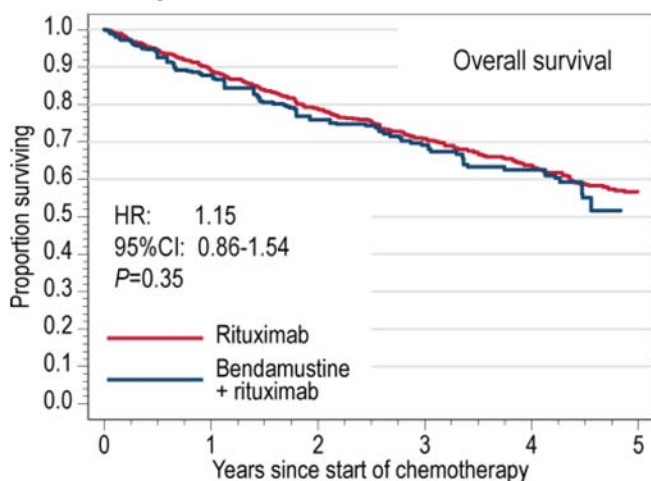
better risk/benefit ratio as first-line therapy for older patients with these indolent lymphomas.

Keywords: Bendamustine; nodal marginal zone lymphoma (NMZL); splenic marginal zone lymphoma (SMZL).

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POST HOC ANALYSES OF PATIENTS WITH RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA WHO RECEIVED LENALIDOMIDE PLUS RITUXIMAB (R[2]) VS RITUXIMAB/PLACEBO (AUGMENT)

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Introduction: Initial AUGMENT study results in R/R FL grade 1-3a and MZL patients showed significantly improved PFS for lenalidomide plus rituximab (R[2]) over R/placebo overall and in subgroups, with the exception of the MZL histology. Given the small MZL sample size, post hoc analyses of baseline characteristics and univariate/multivariate analyses of PFS were further examined.

Methods: The AUGMENT phase III study randomized patients 1:1 to R[2] (lenalidomide PO 20 mg/d, d1-21/28 X12 cycles (c) plus rituximab IV 375 mg/m^{2}/wk c1 and d1 c2-5) or rituximab-placebo (R/placebo; same dosing schedule). The primary endpoint PFS was evaluated by 2007 IWG (without PET). Post hoc Cox regression models evaluated univariate analysis of one risk factor and multivariate analyses for treatment arm and significant risk factors ($P<0.05$) from the univariate analyses.

Results: Of 358 overall patients, 63 (18%) were MZL, including n = 14/16 MALT, n = 9/6 splenic, and n = 8/10 nodal MZL subtypes for R[2] and R/placebo arms, respectively. Numerical differences for R[2] vs R-placebo, respectively, were ECOG PS 0 (55% vs 72%), age (≥65 y: 68% vs 59%; ≥70 y: 42% vs 38%), refractory to last regimen (13% vs 3%), Ann Arbor stage IV (65% vs 41%), high-risk MALT-IPI (50% vs 19%), elevated LDH (29% vs 19%), B symptoms (13% vs 3%), and high tumor burden per GELF (65% vs 56%). For MZL patients receiving R[2] vs R/placebo, respectively, neutropenia (47% vs 16%), pneumonia (3% vs 13%), and leukopenia (10% vs 0) were the most common grade 3/4 AEs. 5 total deaths occurred in the R[2] arm (most associated with PD; 2 early deaths occurred at 3 and 13 days post-randomization [1 patient before receiving R[2] and 1 patient 2 days after initiating treatment]) and 2 in the R/placebo arm. Despite worse prognostic features, best response was higher, but not statistically significant, with R[2] (vs R/placebo): ORR = 65% vs 44% and CR = 29% vs 13%. Median

TABLE 1 Cox Proportional Hazard Model for PFS (IRC) in MZL Patients (ITT)

Variable	Univariate Model			Final Multivariate Model		
	HR	95% CI	P Value	HR	95% CI	P Value
Treatment (R^2 vs R/placebo)	1.001	(0.471, 2.125)	0.998	0.509	(0.202, 1.284)	0.153
Age (≥ 70 vs < 70 y)	2.083	(0.936, 4.634)	0.072			
Sex (male vs female)	1.990	(0.939, 4.216)	0.072			
Ann Arbor stage (IV vs I/II/III)	2.746	(1.205, 6.258)	0.016	2.436	(0.998, 5.947)	0.051
FLIPI (high vs low/medium)	1.775	(0.841, 3.745)	0.132			
ECOG (1-2 vs 0)	1.228	(0.562, 2.685)	0.607			
LDH (elevated vs not elevated)	2.348	(1.096, 5.031)	0.028	2.792	(1.131, 6.897)	0.026
B symptom (yes vs no)	0.931	(0.220, 3.941)	0.923			
High tumor burden (yes vs no)	1.465	(0.662, 3.244)	0.346			
Chemoresistant (yes vs no)	0.493	(0.067, 3.644)	0.488			
Unfit for chemotherapy (yes vs no)*	2.377	(1.043, 5.416)	0.039	2.086	(0.892, 4.876)	0.090

*Defined as age ≥ 70 y, or if 60-69 y and CrCl < 60 mL/min or ECOG PS ≥ 2.

PFS for MZL was 20.2 mo R^2 vs 25.2 mo R/placebo (HR = 1.00; 95% CI, 0.47-2.13; P = 1.0). Univariate analyses identified several prognostic factors for MZL patients ($P<0.05$): Ann Arbor stage IV, elevated LDH, and unfit for chemotherapy (Table). Multivariate analyses of PFS showed an adjusted HR of 0.51 (95% CI, 0.20-1.28) favoring R^2, similar to the overall PFS HR (HR = 0.46; 95% CI, 0.34-0.63).

Conclusions: Overall, these additional analyses in MZL patients suggest that the PFS results were negatively impacted by baseline prognostic factor imbalances and more aggressive disease in the R^2 over R/placebo arm.

Keywords: lenalidomide; marginal zone lymphoma (MZL); rituximab.

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AUGMENT: RELAPSED/REFRACTORY INDOLENT NHL PATIENTS WERE MORE SENSITIVE TO NEXT TREATMENT FOLLOWING LENALIDOMIDE/RITUXIMAB (R^2) THAN RITUXIMAB/PLACEBO

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Introduction: Indolent NHL patients need more effective and tolerable therapies to improve remission times with subsequent lines of therapy. The combination of lenalidomide + rituximab (R^2) has shown improved efficacy in firstline and relapsed/refractory (R/R) B-cell lymphoma. The objective here was to evaluate the sensitivity of patients to their next treatment following R^2 or rituximab (R)/placebo.

Methods: The multicenter, global phase III AUGMENT study enrolled patients with R/R FL gr 1-3a and MZL after ≥ 1 prior systemic therapy (but were not rituximab refractory). Patients were randomized 1:1 to R^2 (lenalidomide PO 20 mg/d, d1-21/28 X12 cycles (c) + rituximab [R] IV 375 mg/m^2/wk, c1, d1, 8, 15, 22 and c2-5, d1) and R/placebo (same dosing schedule). Progression-free survival (PFS; primary endpoint) and response were per 2007 IWG criteria (without PET). Time to next antilymphoma/chemotherapy treatment (TTNLT/TTNCT) was defined as time from randomization to date of the next antilymphoma/chemotherapy treatment. Per regulatory guidance, PFS2 was defined as time from randomization to first PD or death from any cause after next antilymphoma treatment, or initiation of a third antilymphoma treatment.

Results: A total of 358 patients (n = 178 R^2; n = 180 R/placebo) were enrolled, including 82% FL grade 1-3a and 18% MZL. Patients had a median age of 63 y, 34% with FLIPI score ≥ 3, and a median of 1 (range, 1-12) prior systemic therapy (84% receiving prior rituximab). The primary endpoint of PFS was met showing superiority for R^2 over R/placebo (median PFS: 39.4 vs 14.1 mo; HR = 0.46; P < 0.0001). As of 22June2018, the medians for TTNLT, TTNCT, and PFS2 were not reached for R^2, and were significantly longer than R/placebo with hazard ratios of 0.54 (95% CI, 0.38-0.78), 0.50 (95% CI, 0.32-0.78), and 0.52 (95% CI, 0.32-0.82), respectively. There were 49/178 (28%) R^2 and 80/180 (44%) R/placebo patients who received a next antilymphoma therapy; their subsequent responses to next treatment were generally higher with R^2 (57% ORR; 31% CR) than R/placebo (36% ORR; 16% CR; Table).

Conclusions: For patients with R/R FL gr 1-3a and MZL, R^2 showed prolonged time to subsequent treatment, which was associated with longer PFS2 compared with R/placebo, thus enabling greater responses to next therapy. Interestingly, patients were generally more sensitive to subsequent therapy after R^2 than R/placebo, hypothetically due to the impact of longer disease control, allowing for re-emergence of sensitivity to therapy other than rituximab or R^2.

Keywords: indolent lymphoma; lenalidomide; rituximab.

TABLE 1 Response to next treatment after R^2 and R/placebo

Treatment (R^2 n, R/placebo n)	Response after R^2		Response after R/placebo	
	ORR, %	CR, %	ORR, %	CR, %
Single agent chemo (n = 8, 14)	63	38	36	21
Other R-Chemo combo (n = 7, 11)	43	29	64	18
Other (n = 9, 10)	44	22	40	30
Combo chemo (n = 2, 15)	0	0	27	0
Single agent targeted therapy (n = 7, 8)	43	14	13	0
R-Benda (n = 5, 10)	100	40	40	30
R monotherapy (n = 3, 4)	67	67	25	0
O-Chemo (n = 3, 3)	100	67	67	33
R-CHOP (n = 3, 2)	67	33	0	0
Combo targeted therapies (n = 2, 3)	50	0	33	33

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EFFICACY AND SAFETY OF PROLONGED MAINTENANCE WITH SUBCUTANEOUS RITUXIMAB IN PATIENTS WITH RELAPSED OR REFRACTORY INDOLENT NHL: RESULTS OF THE PHASE III MABCUTE STUDY

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Background: Rituximab (R)-chemotherapy (chemo) induction plus R maintenance (maint) is an established treatment for indolent NHL (iNHL), but the optimum duration of R maint is unknown. A subcutaneous (SC) form of R (R-SC) is now available. MabCute (NCT01461928) is a randomised Phase III trial evaluating the efficacy and safety of prolonged R-SC maint after standard R-SC-based induction and maint in relapsed or refractory (R/R) iNHL pts. We report the primary analysis.

Methods: Eligible pts were aged ≥18 years with R/R CD20+ follicular lymphoma (grade [Gr] 1, 2 or 3a) or other iNHL. Pts received 8 cycles (Cs) of R (375mg/m^2 IV in C1 then 1400mg SC in Cs 2–8) in combination with 6–8 Cs of chemo as induction. Responders (CR/PR) then received a 2 year maint comprising 12 Cs of 1400mg R-SC every 8 weeks. Responding pts (CR/PR) were randomised 1:1 to prolonged R-SC maint or observation (observ) until PD. The primary endpoint was PFS from randomisation (PFS$_{rand}$) in all randomised pts (ITT$_{rand}$). Sample size calculation assumed a median PFS$_{rand}$ of 38 months (mo) in the R-SC arm and 23 mo in the observ arm. On this basis, 129 PFS$_{rand}$ events were needed to achieve 80% power for the log-rank test at a significance level of 5%. To observe this number of

Table 1: Patient and disease characteristics in the randomised patient groups

Characteristic	Maintenance (n=138)	Observation (n=138)
Median age, years (range)	64 (26–89)	65 (34–86)
Male, n (%)	74 (53.6)	68 (49.3)
Ann Arbor stage IV, n (%)	88/134 (65.7)	78/135 (57.8)
Bone marrow involvement, n (%)	60 (43.5)	59 (42.8)
FL, n (%)	73 (52.9)	77 (55.8)
FLIPI low / intermediate / high, %	34.2 / 30.1 / 35.6	36.4 / 35.1 / 28.6
Median duration of disease, months (range)	65.0 (4–303)	62.4 (4–275)

Figure 1: Kaplan-Meier curve of PFS_{rand} in the ITT_{rand} population

	N	Censored	PFS_{rand} events	Median (95% CI)
Maintenance	138	119	19	NR (NR, NR)
Observation	138	111	27	NR (39.75, NR)

No. of patients at risk

Maintenance	138	132	131	126	124	120	115	113	105	99	96	80	69	60	44	36	23	12	11	7	4	2	0	0
Observation	138	133	129	126	124	119	115	112	99	97	92	81	69	55	41	32	22	16	12	7	4	2	2	0
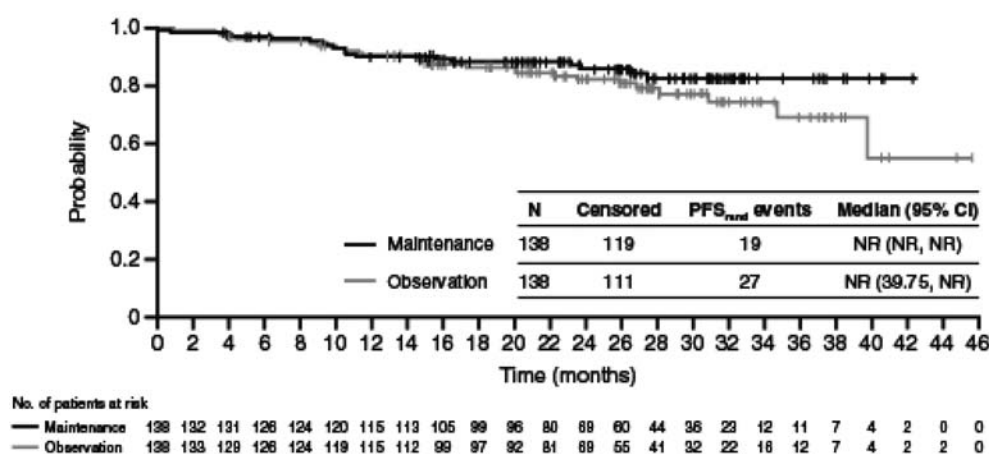
events, approximately 300 pts were needed and followed for ≥15 mo. In the observ arm, Gr 1 and 2 AEs were collected until 28 days after the last R administration, leading to an imbalance in AE collection between the arms. End of study was the time when all randomised pts had been followed for ≥15 mo, or earlier if at least 129 PFS events had been observed.

Results: Of 693 pts who entered induction, 276 were randomised to prolonged maint or observ (n = 138 in both arms). Pt and disease characteristics were generally well balanced (**Table**). A total of 46 PFS_{rand} events were observed (19 in maint and 27 in observ), corresponding to 36% of the 129 events needed to achieve 80% power. Median PFS_{rand} was not reached in either arm (**Figure**) and the difference in PFS_{rand} between the two treatment arms was not statistically significant (p = 0.410, stratified log rank test). At end of study, 10 pts in the maint group and 8 pts in the observ group had died. Median OS was not reached. Gr >3 AEs (34.8% vs 29.0%) and serious AEs (22.5% vs 23.2%) were reported with a similar frequency in the maint and observ arms, respectively. Common (≥2%) Gr ≥3 AEs were: neutropenia (8.7% vs 5.8%); pneumonia (5.1% vs 2.9%); decreased neutrophil count (2.2% vs 0%); and hypertension (2.2% vs 0%). The most common serious AE was pneumonia (5.8% vs 2.9%). Five pts (3.6%) in each arm died due to an AE. ORR (CR/PR) at end of induction (EOI) was 84.7%, and 77 of 357 pts with a PR at EOI achieved a CR by end of initial maint (conversion rate: 21.6%).

Conclusions: MabCute was unable to fully address the primary study endpoint of PFS_{rand} due to the limited number of events observed. The safety profile of R-SC during prolonged maint was consistent with the known profile of R-SC.

Disclosures: Rule, S: Consultant Advisory Role: *Janssen, Astra-Zeneca, Roche, Sunesis, Pharmacyclics, Celgene, Celltrion, Kite*; Research Funding: *Janssen*; Other Remuneration: *Janssen*. **Barreto, W:** Employment Leadership Position: *Bloods Bank Ribeirão Preto - University of São Paulo*; Consultant Advisory Role: *Director*. **Briones, J:** Consultant Advisory Role: *Takeda, Jansen, Celgene, Gilead*; Honoraria: *Roche, Takeda, Celgene, Novartis, Gilead*; Research Funding: *Roche*; Other

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OUTCOMES AFTER EARLY TRANSFORMATION (tPOD24) VS. EARLY FOLLICULAR LYMPHOMA PROGRESSION (fPOD24) IN FOLLICULAR LYMPHOMA TREATED WITH FRONTLINE IMMUNOCHEMOTHERAPY

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Introduction: Early events within 24 months (e.g. EFS24, POD24) after initiation of frontline immunochemotherapy (IC) are associated with poor survival in follicular lymphoma (FL). The incidence and outcomes of early transformation compared to early progression of FL remain understudied. We now examine the types of early events and subsequent outcomes by event type in IC treated FL.

Methods: Patients prospectively enrolled in the University of Iowa/Mayo Clinic SPORE MER between 2002-2015 with FL grade 1-3A and treated with frontline R-CVP, R-CHOP, and R-bendamustine IC were included. Early event was defined as progression, re-treatment, or death within 24 months of start of IC. Early-events were classified into biopsy proven transformation (tPOD24), biopsy proven FL progression (fPOD24), progression without biopsy (oPOD24), and death without progression or retreatment. Early event frequencies were determined via cumulative incidence. Overall survival (OS) from POD24 was defined as date of progression until death. Validation was performed in patients with grade 1-2 FL treated with R-CVP, R-CHOP, or R-bendamustine enrolled in the Danish LYFO from 2006-2017.

Results: 439 patients treated with IC at diagnosis in the MER were evaluated with 28% receiving R-CVP, 44% R-CHOP and 28% B-R based IC. Median age was 59 years (range 23-86), 55% were male, 26% were grade 3A, and FLIPI was high in 35%. Early event rate at 24 months was 6.5% tPOD24, 8.2% fPOD24, 6.3% oPOD24, and 3.3% early deaths, Table. OS after tPOD24 (OS5 = 27%, ref) was inferior to fPOD24 (5-year OS = 54%, HR = 0.36; 95% CI: 0.19-0.70) and oPOD24 (5-year OS = 44%, HR = 0.51; 95% CI: 0.26-1.00), Figure.

630 patients were evaluated in the Danish LYFO cohort with 46% receiving R-CVP, 29% R-CHOP and 25% B-R based IC. Median age was 65 years (range 29-90), 52% were male, and FLIPI was high in 46%. Early event rate was 3.0% tPOD24, 8.0% fPOD24, 2.6% oPOD24, and 5.2% early deaths, Table. OS after tPOD24 (OS5 = 31%, ref) was inferior to fPOD24 (5-year OS = 61%, HR = 0.45; 95% CI: 0.22-0.89), and similar to oPOD24 (5-year OS = 30%, HR = 0.86; 95% CI: 0.39-1.92), Figure.

TABLE 1

Cohort	MER	MER	MER	MER	LFYO	LYFO	LYFO	LYFO
Therapy	R-CVP	R-CHOP	B-R	Total	R-CVP	R-CHOP	B-R	Total
N Initiating Therapy	123	192	124	439	288	184	158	630
Achieve EFS24 Rate	73.6%	77.3%	75.4%	75.7%	77.7%	82.8%	86.9%	81.2%
tPOD24 Rate	2.5%	5.8%	11.7%	6.5%	4.2%	1.1%	2.6%	3.0%
fPOD24 Rate	9.1%	11.1%	2.6%	8.2%	9.1%	10.6%	2.8%	8.0%
oPOD24 Rate	12.3%	4.2%	3.5%	6.3%	3.8%	1.7%	0.9%	2.6%
Early Death Rate	2.5%	1.6%	6.8%	3.3%	5.2%	3.8%	6.8%	5.2%

MER OS After POD24

LYFO OS After POD24
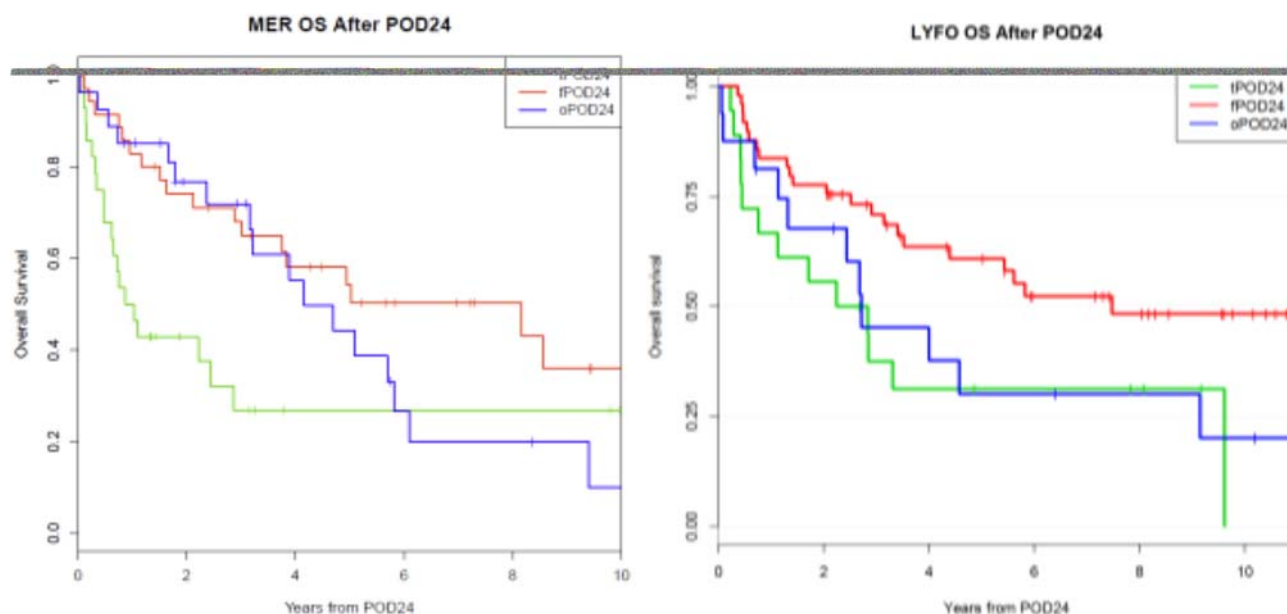
Conclusions: Follicular lymphoma progression is more common than transformation in biopsy-proven early events of IC-treated FL. OS is poor after both tPOD24 and fPOD24 and both represent an unmet clinical need. These histology specific results have implications for clinical trial development and interpretation. Biopsy of early progression in IC-treated FL is necessary for 2nd line management and prognostication.

Keywords: follicular lymphoma (FL).

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HEALTH-RELATED QUALITY OF LIFE (HRQoL) IN RELAPSED/REFRACTORY (R/R) INDOLENT NHL IN THE PHASE 3 AUGMENT TRIAL OF RITUXIMAB (R) PLUS LENALIDOMIDE (R[2]) VERSUS R PLUS PLACEBO

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Introduction: In the AUGMENT study (NCT01938001), median progression-free survival (PFS) for patients (pts) treated with R[2] was 39.4 months vs 14.1 months for pts treated with R-placebo (PBO) (P < 0.0001) in 358 pts with R/R indolent NHL [Leonard, 2019]. The effect of R[2] vs R-PBO on HRQoL, an exploratory endpoint, is presented here.

Methods: HRQoL data were collected using the EORTC QLQ-C30 and EQ-5D-3L questionnaires. The QLQ-C30 global health status/QoL (GHS/QoL) domain score was the prespecified primary

TABLE 1 QLQ-C30 completion rates

Visit	Definition of denominator	R^2 n/N (%)	R-PBO n/N (%)	P value
Screening	ITT population	174/178 (97.8)	177/180 (98.3)	0.723
C4D1	Received ≥ 1 dose at or after C4	158/163 (96.9)	165/169 (97.6)	0.747
C7D1	Received ≥ 1 dose at or after C7	140/148 (94.6)	140/148 (94.6)	1.000
C10D1	Received ≥ 1 dose at or after C10	121/131 (92.4)	106/119 (89.1)	0.390
TC (C12)	Received ≥ 11 doses at C12 and progression-free at C13D1	113/119 (95.0)	86/92 (93.5)	0.767
FU1 (6 months post-TC/TD)	QoL visit recorded during FU period or alive and progression-free for ≥ 24 weeks after last dose	121/137 (88.3)	90/103 (87.4)	0.844
FU2 (12 months post-TC/TD)	QoL visit recorded during respective FU period or alive and progression-free for ≥ 24 weeks after last FU visit	103/115 (89.6)	70/85 (82.4)	0.149
FU3 (18 months post-TC/TD)		84/95 (88.4)	45/57 (78.9)	0.160
FU4 (24 months post-TC/TD)		60/74 (81.1)	31/39 (79.5)	1.000
FU5 (30 months post-TC/TD)		49/60 (81.7)	24/27 (88.9)	0.535
FU6 (36 months post-TC/TD)		36/45 (80.0)	20/20 (100)	0.048
FU7 (42 months post-TC/TD)		24/26 (92.3)	15/17 (88.2)	1.000
FU8 (48 months post-TC/TD)		18/19 (94.7)	12/13 (92.3)	1.000
FU9 (54 months post-TC/TD)		13/14 (92.9)	7/7 (100)	1.000
FU10 (60 months post-TC/TD)		5/6 (83.3)	6/6 (100)	1.000
FU11 (66 months post-TC/TD)		2/2 (100)	1/1 (100)	1.000
TD	Received < 12 doses at C12	42/57 (73.7)	75/88 (85.2)	0.131

Abbreviations: C, cycle; D, day; FU, follow-up; ITT, intention to treat; QoL, quality of life; R, rituximab; R^2, rituximab + lenalidomide; R-PBO, R + placebo; TC, treatment completion; TD, treatment discontinuation.

outcome. Mean QLQ-C30 changes from baseline were compared within and between treatment arms using ANCOVA tests. The proportion of pts with clinically meaningful deterioration in HRQoL over time and time to deterioration were determined using mixed-model repeated-measure analysis and Cox regression analysis, respectively.

Results: 338 pts completed the baseline QLQ-C30 questionnaire and ≥ 1 post-baseline measurement (HRQoL evaluable population). Baseline characteristics were generally similar between arms. Median age was 61.6 years and 161 pts (48%) were male (R^2: 41%; R-PBO: 54%). QLQ-C30 completion rates did not differ between arms and remained > 70%, although the number of responders decreased over time (Table). Mean QLQ-C30 baseline scores across all domains did not

differ between arms. No clinically meaningful changes in GHS/QoL within or between arms were seen across post-baseline measurements (Figure). Changes in other domains were observed during treatment: clinically meaningful worsening diarrhea for R-PBO, worsening fatigue, appetite loss, constipation, diarrhea, and overall health status (based on EQ-5D VAS) for R^2; these scores returned to baseline levels after treatment completion. Median time to deterioration was not statistically significant between pts receiving R^2 and R-PBO (P = 0.16). HRQoL changes over time were not associated with disease histology, response status, or presence of grade 3–4 adverse events (AEs).

Conclusions: HRQoL was maintained over time in the R^2 arm of the AUGMENT study and no clinically meaningful difference in HRQoL

Figure. Cross-sectional assessment of GHS/QoL changes from baseline
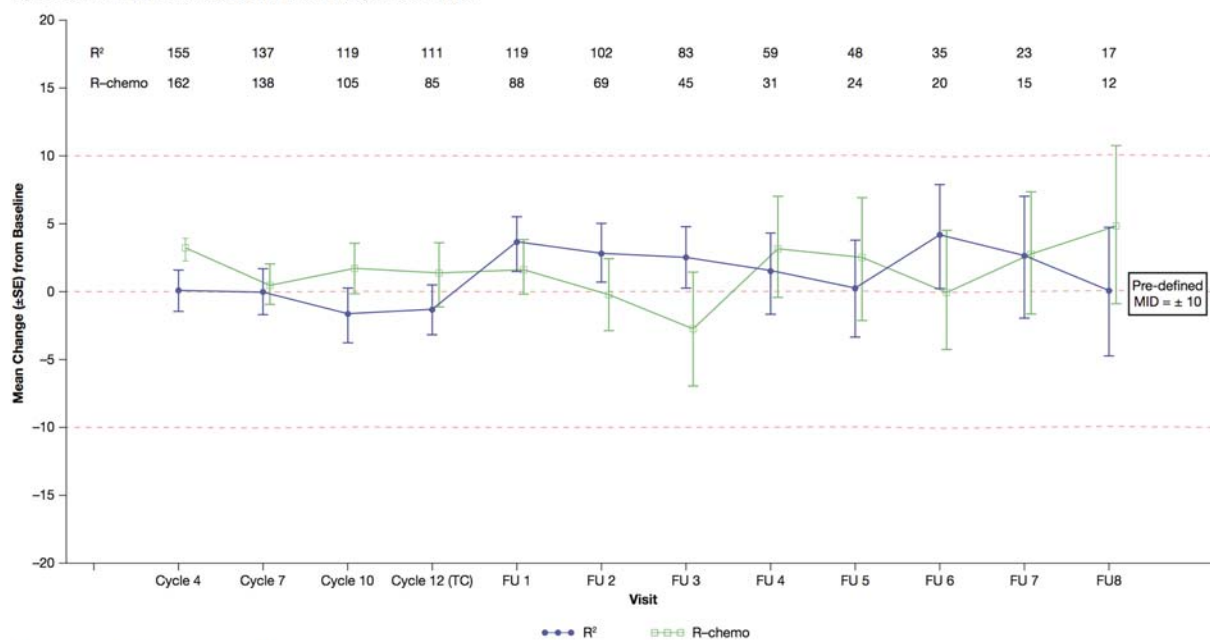
FU, follow-up; MID, minimally important difference; TC, treatment completion.

was observed between treatment arms. AEs had little effect on HRQoL and improved after treatment was completed or stopped. Adding lenalidomide to R significantly extended PFS without compromising HRQoL. Post-progression HRQoL was not included in the analysis. Therefore, potential worsening of HRQoL due to disease and treatment after progression and the impact of fewer or delayed progressions with R^2 were not captured.

Keywords: lenalidomide; non-Hodgkin lymphoma (NHL); rituximab.

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WhiMSICAL (WALDENSTRÖM'S MACROGLOBULINEMIA STUDY INVOLVING CArt-wheeL): A GLOBAL PATIENT-DERIVED DATA REGISTRY MAPPING TREATMENT AND QUALITY OF LIFE

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Introduction: Patient-derived data and reported outcomes (PROs) can increase breadth of knowledge in rare cancers like Waldenström's Macroglobulinemia (WM). This study utilised www.cart-wheel.org, an ethically approved online rare cancer database for patient-derived data, to develop a continuously expanding dataset for hypothesis generation around WM.

Methods: An ethically approved WM-specific extension to the www.cart-wheel.org questionnaire was developed by clinician and patient investigators. Patients complete consent online and enter their symptom, pathology and treatment data. Recruitment strategies driven by the International Waldenström's Macroglobulinemia Foundation investigators utilised multiple social media platforms. Inclusion of the EORTC QLQ C30 quality of life (QoL) questionnaire went live in October 2018, with targeted recruitment messaging sent out in February 2019.

Results: 355 patients from 17 countries have been recruited, predominantly from USA (48%) and male (62%). Median age at diagnosis was 61 years (24-83), median IgM 27.4 g/L (IQR 13.1-40.3 g/L, n = 130) and median hemoglobin 112 g/L (IQR 97-128 g/L, n = 134). Fatigue was the most common symptom listed at diagnosis (44%). Using the Impact of Event Scale for symptoms of posttraumatic stress disorder (PTSD) related to cancer, the mean score was 5.8 (no stress = 0, maximal stress = 24, n = 305), with 29 (10%) scoring $\geq$13 (PPV 94% for PTSD, Thoresen et al, 2010). 41 unique first line therapeutic combinations were documented by 238 patients. Median time from diagnosis to first treatment for USA patients was 50 days (IQR 15-423, n = 104) vs Rest of World (ROW) 170 days (IQR 22-775, n = 120) (p = 0.06). Of the 213 therapies listed by USA patients (n = 108), 59 (28%) were reported as accessed by government or public program and 8 (4%) via clinical trials, whereas among ROW patients (n = 113), 122/225 (54%) were government/public program accessed and 31/225 (14%) via clinical trials (p = 0.0001 and p = 0.0002, respectively). 156 patients responded to the QoL questions within 3 weeks from targeted messaging. Raw scores for overall health (Q29) and overall quality of life (Q30), ranging from 1: very poor to 7: excellent, demonstrated means of 5.1 and 5.8, respectively. Respondents who received BTK inhibitors (BTKi, n = 33) had comparable Q29 and Q30 scores compared to those who received non-BTKi treatment (n = 84): Q29 means 5.8 vs 5.5, Q30 6.1 vs 5.7 (p = 0.2 and p = 0.13, respectively). This was despite median 2 (IQR 1-4) lines of treatment in the BTKi group compared to median 1 (IQR 1-2) in the non-BTKi group.

Conclusions: WhiMSICAL is a robust global patient-derived data platform providing insight into patient symptoms, diversity of therapies and QoL. Further recruitment (Project 1000) and ongoing data entry will increase its utility. As it grows, WhiMSICAL has the potential to map real-world PROs to treatments and provide a scientific and ethically approved portal for patients' voices globally.

Keywords: BTK inhibitors; Waldenström's macroglobulinemia (WM).

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PATIENT-REPORTED OUTCOMES (PROs) IN WALDENSTRÖM MACROGLOBULINEMIA (WM) PATIENTS TREATED WITH IBRUTINIB-RITUXIMAB IN THE INNOVATE STUDY

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TABLE 1 Patients with clinically meaningful improvement in PROs

Patients, %	IR (n=75)	R (n=75)	P
FACIT-F[a]	69	57	0.13
FACT-An TS[b]	73	59	0.06
FACT-An AS[c]	64	48	0.05
EQ-VAS[b]	49	55	0.54
EQ-US[d]	43	36	0.37

[a]Increase of ≥3 points.
[b]Increase of ≥7 points.
[c]Increase of ≥6 points.
[d]Increase of ≥0.08 points.

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Introduction: Anemia and fatigue are known to impair quality of life in patients with WM. Ibrutinib, a first-in-class, once-daily inhibitor of BTK, is approved in the EU for the treatment of WM after ≥1 prior therapy or as first-line therapy in patients unsuitable for chemo-immunotherapy. In the US, ibrutinib is approved for the treatment of WM as a single agent or in combination with rituximab. In patients with rituximab-refractory WM, single-agent ibrutinib induced clinically meaningful improvements in PROs (Trotman, EHA 2017). In the iNNOVATE study, the combination of ibrutinib and rituximab (IR) produced higher rates of sustained hemoglobin improvement and clinically meaningful improvements in PROs when compared with placebo-rituximab (R) (Dimopoulos NEJM 2018). Here, we report a more detailed analysis of PROs from iNNOVATE.

Methods: Patients with symptomatic WM requiring therapy were randomized to once-daily oral ibrutinib (420 mg) or placebo; both groups were given rituximab (375 mg/m² /week IV at weeks 1–4 and 17–20). PRO measures included FACIT-Fatigue (FACIT-F), FACT-An total score (TS) and anemia subscale score (AS), and the visual analog scale (EQ-VAS) and utility score (EQ-US) of EQ-5D-5L (© EuroQol Research Foundation. EQ-5D™ is a trademark of the EuroQol Research Foundation).

Results: A total of 150 patients were randomized with 75 patients in each arm. Across both arms, the most common reasons for

Figure: Proportion of Patients With Clinically Meaningful Improvement in PROs Over Time
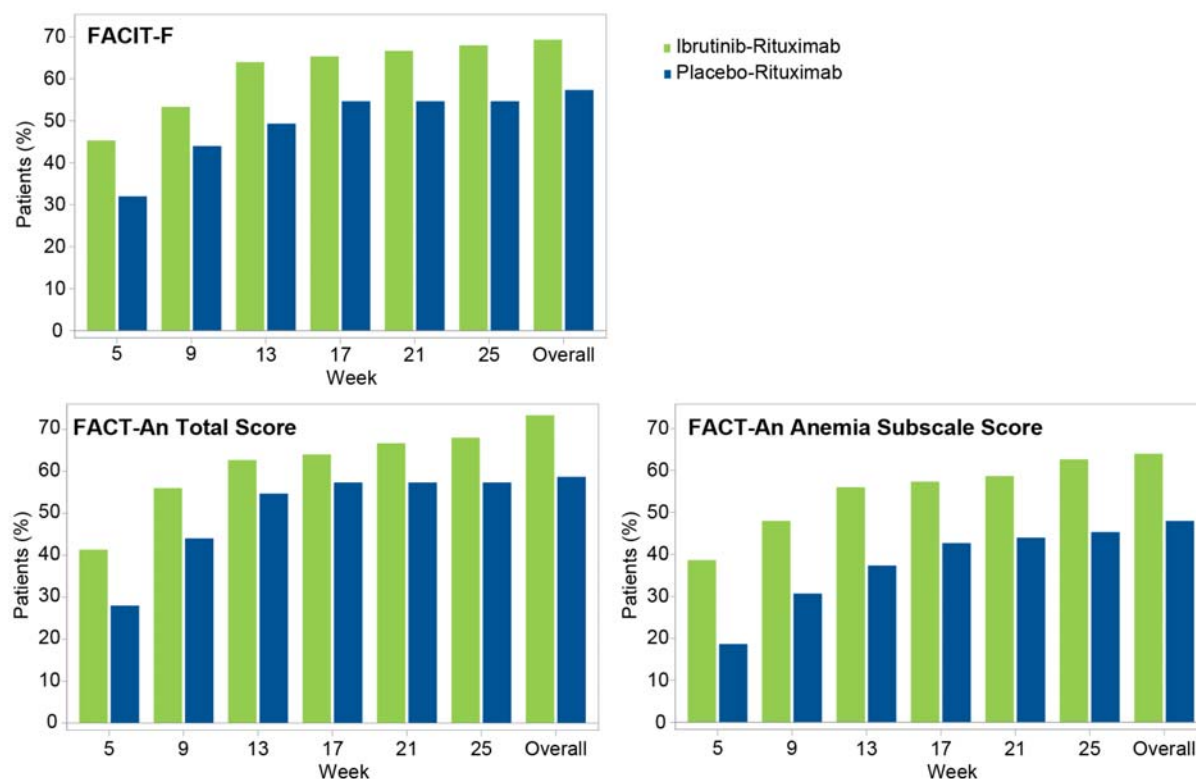
initiating therapy were fatigue (61%), constitutional symptoms (32%), and anemia (32%). Baseline PRO scores were comparable in both arms. At the interim analysis (median follow-up, 26.5 months), a greater proportion of patients showed clinically meaningful improvements in FACIT-F, TS, and AS with IR than R (Table and Figure). The median time to improvement was about 1-2 months in both arms. At week 25, the Pearson correlation coefficients for changes in hemoglobin levels with IR vs changes in FACIT-F, TS, and AS were 0.28, 0.29, and 0.26, respectively; no meaningful correlations were observed for R. The correlation coefficients for changes in IgM levels for IR vs changes in FACIT-F, TS, AS, and EQ-VAS were -0.32, -0.33, -0.35, and -0.26, respectively, and for R vs changes in FACIT-F and TS were 0.29 and 0.35, respectively.

Conclusions: Clinical response and improvements in anemia with IR are consistent with more patients showing clinically meaningful improvements in PROs vs R. Changes in IgM were also found to correlate with improvements in PROs.

Keywords: ibrutinib; rituximab; Waldenström's macroglobulinemia (WM).

Disclosures: Tedeschi, A: Consultant Advisory Role: *AbbVie, Gilead, Janssen SpA, and Sunesis*; Other Remuneration: *Speakers' bureau for Janssen*. **Dimopoulos, M:** Consultant Advisory Role: *Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis and Takeda*; Honoraria: *Amgen, Bristol-Myers Squibb, Celgene, Janssen and Takeda*. **Trotman, J:** Research Funding: *Pharmacyclics LLC, an AbbVie Company*. **García-Sanz, R:** Consultant Advisory Role: *Bristol-Myers Squibb and Takeda*; Honoraria: *Amgen, Janssen, and Takeda*; Research Funding: *Gilead and Incyte, and institution research funding from Amgen and Janssen*; Other Remuneration: *Patents, royalties, or other intellectual property for IVS (Biomed 2 - Euroclonality); travel expenses from Janssen and Takeda*. **Macdonald, D:** Consultant Advisory Role: *Janssen*; Honoraria: *AbbVie, Gilead, Roche and Teva*. **Heffner, L:** Consultant Advisory Role: *Pharmacyclics LLC, an AbbVie Company*; Research Funding: *Amgen, ADC Therapeutics, Biotest, Genentech, Gilead, Idera, Kite, Micromet, Pfizer, and Pharmacyclics LLC, an AbbVie Company*; Other Remuneration: *Travel expenses from Pharmacyclics LLC, an AbbVie Company*. **Tam, C:** Honoraria: *Janssen, and Pharmacyclics LLC, an AbbVie Company*; Research Funding: *Janssen*. **Varettoni, M:** Consultant Advisory Role: *Janssen and Roche*; Other Remuneration: *Travel expenses from Gilead and Janssen*. **Palomba, M:** Consultant Advisory Role: *Celgene, Merck, and Pharmacyclics LLC, an AbbVie Company*; Honoraria: *Juno and Seres*; Other Remuneration: *Patents, royalties, or other intellectual property for Juno and Seres*. **Matous, J:** Consultant Advisory Role: *Celgene*; Other Remuneration: *Speakers' bureau for Celgene*. **Shustik, C:** Consultant Advisory Role: *Amgen, Celgene, and Takeda*. **Kastritis, E:** Consultant Advisory Role: *Amgen, Genesis Pharma, Janssen, Prothena and Takeda*; Honoraria: *Amgen and Takeda*; Other Remuneration: *Travel expenses from Janssen and Takeda*. **Treon, S:** Consultant Advisory Role: *Janssen and Pharmacyclics LLC, an AbbVie Company*; Research Funding: *Pharmacyclics LLC, an AbbVie Company*; Other Remuneration: *Expert testimony for Johnson & Johnson; travel expenses from Janssen and*

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MANTLE CELL LYMPHOMAS

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CLINICO-BIOLOGICAL CHARACTERISTICS AND TREATMENT OUTCOMES FOR AGRESSIVE MANTLE CELL LYMPHOMA PATIENTS INCLUDED IN CLINICAL TRIALS. A LYSA STUDY

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Introduction: Aggressive Mantle Cell Lymphoma (A-MCL), including blastoid and pleomorphic variants, is a rare morphological subtype of MCL with a more adverse prognosis. Few data are available in the literature focusing specifically on this rare subtype of MCL. The aim of our study was to perform a retrospective analysis of all

A-MCL from the LYSA cohort included in clinical trials in order to compare their clinico-biological characteristics and outcomes to classical variants.

Methods: Individual data from patients enrolled in 5 studies were analysed, respectively RiPAD+C (Houot R. et al, Ann Oncol 2011), RiBVD (Gressin R. et al, Haematologica 2018), MCL Younger (Hermine O. et al, Lancet 2016), MCL Elderly (Kluin-Nelemans H.C. et al, NEJM 2012) and LYMA (Le Gouill S. et al, NEJM 2017) trials. A centralized pathological review of all cases was performed at the time of inclusion in each clinical trial, but an additional central review, according to 2017 WHO classification, was specifically achieved by expert pathologists from the LYSA for all A-MCL. Univariate analysis of Progression-Free Survival (PFS) and Overall Survival (OS) were performed and a stratified multivariate Cox model was used to assess the correlation between histologic subtypes and outcomes.

Results: Data from 773 patients were collected, 59 with an A-MCL (53 pleomorphic and 6 blastoid) and 714 with a classical form. The two cohorts were similar in age (median: 61.2 y; range: 27-83), ECOG status, B symptoms, extra-nodal involvement, MIPI risk group (low: 39%; intermediate: 30%; high: 31%) and haematological parameters. A-MCL patients differed significantly in Ann Arbor stage (stage III-IV: 86% in A-MCL vs 96%, p = 0.002), bulky disease (31% in A-MCL vs 19%, p = 0.040), LDH level (LDH > normal limit: 63% in A-MCL vs 40% p<0.001) and Ki67 (Ki67 > 30%: 87% in A-MCL vs 29%, p<0.001). With a median follow up of 60 months, univariate PFS was significantly lower for A-MCL with a median of 28 mo (95% CI = 15-NR) vs 59 mo (95% CI = 54-72) for classical variants (p = 0.048). Univariate OS was also significantly lower for A-MCL patients with a median of 65 mo (95% CI: 29-NR) vs 109 mo (95% CI: 94-NR) (p = 0.005). In multivariate analysis stratified by studies, A-MCL subtype (HR (95% CI) for PFS 1.50 (1.03-2.19), OS 1.82 (1.21-2.74)) elevated LDH level (PFS 1.62 (1.3-2.03), OS 1.79 (1.36-2.35)) and intermediate/high MIPI scores (intermediate MIPI: PFS 1.64 (1.21-2.22), OS 1.82 (1.24-2.67); high MIPI: PFS 2.71 (1.96-3.74), OS 3.56 (2.4-5.29)) were significantly associated with a worse PFS and OS.

Conclusion: This study describes one of the largest cohorts of well-characterized A-MCL patients included in clinical trials. All A-MCL were strictly classified according to the 2017 WHO classification. A-MCL variant was associated with high LDH level, Ki67 > 30% and bulky disease. PFS and OS were significantly lower for A-MCL compared to classical form.

Keywords: mantle cell lymphoma (MCL).

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COMPREHENSIVE ANALYSIS OF PROGNOSTIC FACTORS, OUTCOMES AND MUTATION PROFILE IN PATIENTS WITH AGGRESSIVE HISTOLOGY (BLASTOID/PLEOMORPHIC) OR

TRANSFORMED MANTLE CELL LYMPHOMA

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Introduction: Analysis of clinical, molecular features and prognostic factors in aggressive histology MCL (AH-MCL; blastoid or pleomorphic) is not described. AH-MCL can be [de novo (*dn*MCL) or transformed from classic morphology (t-MCL)].

Methods: We reviewed 183 pts with AH-MCL (108 were *dn*-MCL and 75 were t-MCL). Overall, 152 were blastoid and 31 pleomorphic. Pt characteristics were collected at the time of diagnosis in *dn*MCL and at transformation. Overall survival (OS) - time of initial diagnosis of AH-MCL to death/last follow-up and failure free survival (FFS) - time of starting first-line treatment of AH-MCL to treatment discontinuation. Whole-exome sequencing (WES) with SureSelect Human All Exon V6 was performed from biopsy samples from 44 pts (*dn*MCL = 32, t-MCL = 12).

Results: Median follow up after diagnosis of AH-MCL was 19.6 months (0.1-168). Clinical features of AH-MCL were - 20% B symptoms, 6% had ECOG PS (3-4), CNS involvement in 4%, 19% with GI involvement, 67% with marrow involvement and 27% had leukemic phase. The median Ki-67% was 70% (10-100), complex karyotype 13%, LDH > ULN in 45%, Sox-11 positive in 81%, median β2M of 2.9 mg/dL. Pts with t-MCL were distinct from *dn*MCL in having significantly higher median age, poor PS, lower WBC count, lower marrow involvement and lower rate of achieving CR with first line treatments. All pts with t-MCL had prior treatment for MCL before transformation with median lines of prior therapy 2 (range 1-8). The median OS after diagnosis of AH-MCL was 33 months (48 and 14 months for *dn*MCL and t-MCL respectively; p = 0.001; **Figure-1A-B**). Univariate and multivariate (MVA) analyses were performed. Recursive partitioning analysis revealed that Ki-67% ≥50% **(Fig. 1C)**, LDH ≥1519, β2M ≥ 4, hemoglobin <14 and platelet count <63,000 had increased risk of death. In MVA, factors significantly associated with inferior OS in AH-MCL were age (>72 yrs), t-MCL category, Ki-67% ≥50%, ECOG-PS (1-4 compared to 0). Presence of t-MCL, high Ki-67%, CNS involvement were predictive of inferior FFS. Pts who received ibrutinib based or R-HCVAD based therapies had lower hazard ratio for FFS. Subset analysis of blastoid vs pleomorphic MCL did not reveal any significant

Figure 1 (A-E) Survival of patients with aggressive histology MCL (AH- Blastoid or pleomorphic) – overall, by MCL category (denovo AH vs transformed MCL) and Ki-67%. D) Failure free survival by type of first line treatment at diagnosis of AH-MCL. E) Oncoprint showing the somatic mutations identified by whole exome sequencing by Ki-67% in AH-MCL (High n=32; Ki-67 ≥50%) and (Low n=10: Ki-67 <50%).
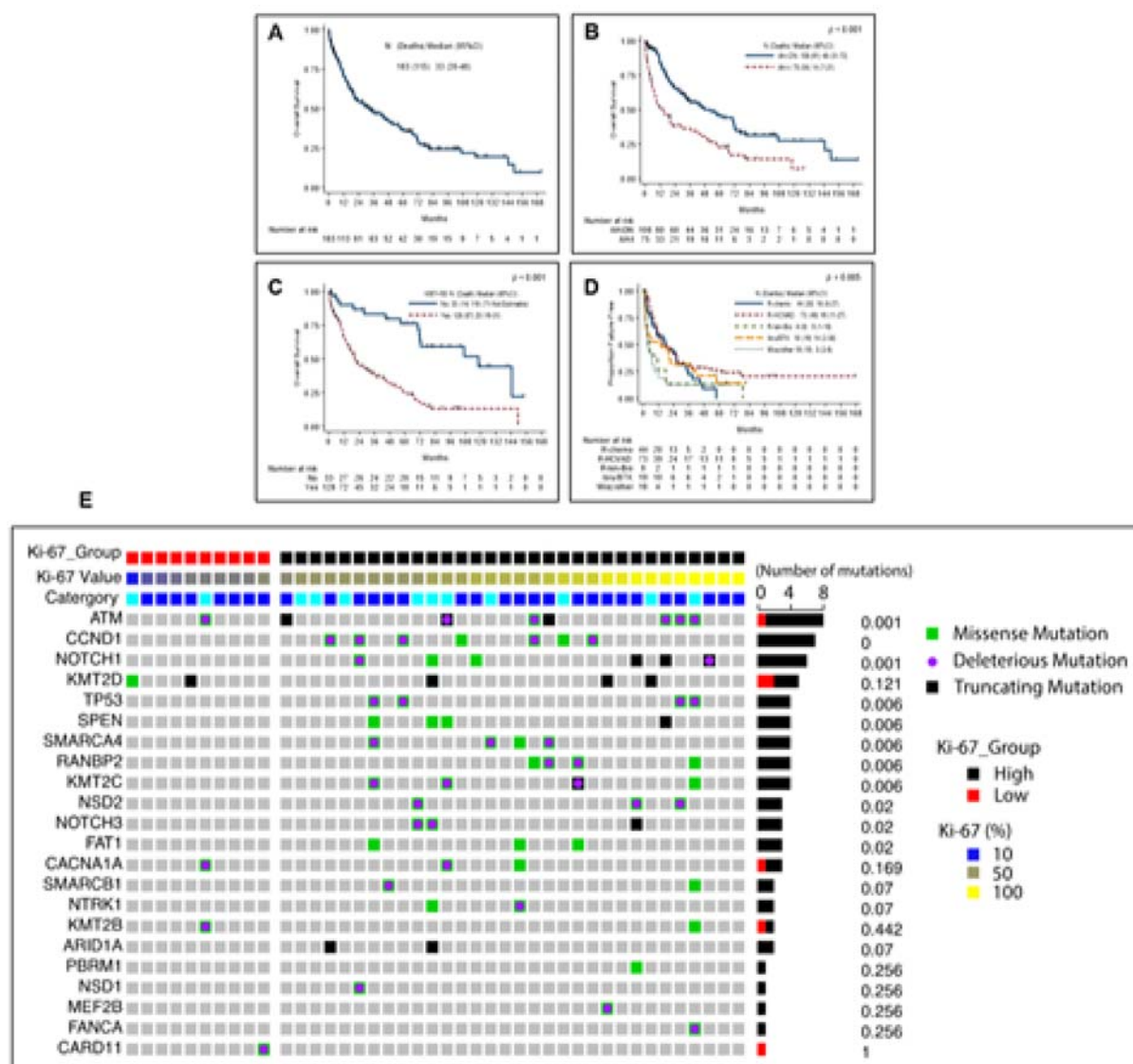
difference in clinical features of survival but FFS was inferior in pleomorphic category.

Frequently mutated genes in AH-MCL were *ATM*, *CCND1*, *NOTCH1*, *KMT2D*, *KMT2C*, *TP53*, *SPEN*, *SMARCA4* and *NSD2*. There was no statistically significant difference in the mutation profile of *dn*MCL vs t-MCL. Significant differences in the mutation burden between pts with high Ki-67 (≥50%) and those with low Ki-67%, were noted - *ATM* (p = 0.001), *CCND1* (p<0.001), *NOTCH1*(p = 0.001), *TP53* (p = 0.006), *SMARCA4* (p = 0.006), *NSD2* (p = 0.02), *NOTCH3* (p = 0.02) **Figure-1E**.

Conclusions: We have shown that pts with AH-MCL with t-MCL and/or Ki-67% ≥ 50% are a very high risk category of MCL. Further analysis are ongoing and will be reported.

Keywords: mantle cell lymphoma (MCL).

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EVOLUTION OF CLONAL HEMATOPOIESIS IN MANTLE CELL LYMPHOMA PATIENTS BEFORE, DURING, AND AFTER INDUCTION CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION

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Evolution of clonal hematopoiesis clones in MCL patients
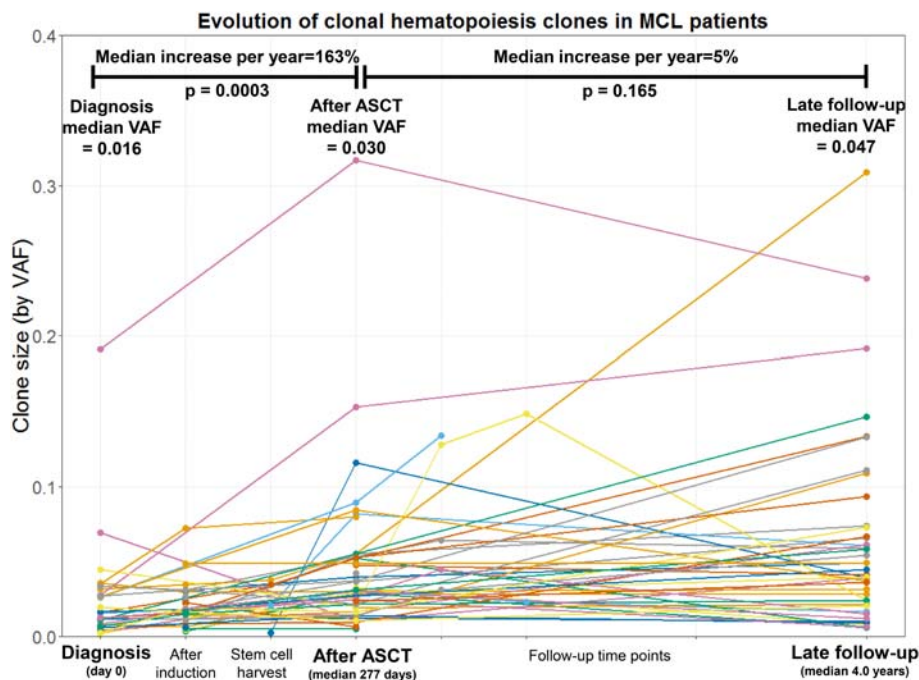
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Introduction: Patients with lymphoma often carry somatic mutations in their hematopoietic stem cells, also called clonal hematopoiesis (CH). These mutations can be detected in both peripheral blood (PB) and bone marrow (BM), and increase the risk of later therapy-related malignancy (Takahashi et al., Lancet Oncology 2017). It is unknown how CH clones evolve during and after treatment for lymphoma. The clinical impact is also unclear.

We therefore investigated CH in consecutive samples from a cohort of homogeneously treated mantle cell lymphoma (MCL) patients with available minimal residual lymphoma-disease (MRD) status and long-term follow-up.

Methods: Newly diagnosed patients with MCL were enrolled in the two Nordic trials, MCL2 and MCL3, and treated with six alternating cycles of R-CHOP and R-HD-AraC followed by high-dose chemotherapy (BEAM/BEAC) and autologous stem cell transplant (ASCT). From 148 patients with available MRD status, we retrieved samples (BM and/or PB) before treatment, during induction chemotherapy and ASCT, and in the follow-up period (median 4.0 years after ASCT). CH was investigated by targeted next-generation sequencing with the use of unique molecular identifiers allowing deep sequencing.

A total of 378 consecutive samples were analyzed. Patients were screened for mutations down to a variant allele frequency (VAF) cut-off of 0.01 in MRD negative samples (n = 148) taken shortly after ASCT. Identified mutations were tracked with deep sequencing (down to 0.001 VAF) in samples before chemotherapy, during induction treatment as well as in follow-up samples.

Results: In 148 MCL patients with samples taken after ASCT (all MRD negative) we identified 63 CH mutations in 51 patients (34%, median VAF 0.033). The mutated genes were mainly DNMT3A (n = 51), TET2 (n = 6), PPM1D (n = 5), TP53 (n = 4), and ASXL1 (n = 4). Of these mutations, 30 were also identified before administration of chemotherapy with VAF ranging from 0.0019 to 0.414 (**Figure 1**). After induction chemotherapy, high-dose chemotherapy, and ASCT the size of the CH clones had grown significantly with a median increase of 129.3% (IQR = 6.8%–245.7%, paired samples Wilcoxon test p = 0.0003). This amounted to a 162.7% median increase per year. In the follow-up period after ASCT, with no pressure from chemotherapy, the mutations did not continue to increase in size (5.0% median increase per year, [IQR = -7.6%–59.4%], paired samples Wilcoxon test p = 0.165). CH was in this cohort of first line treated MCL patients not associated with an inferior overall survival (HR 0.98, 95%CI 0.52–1.80). Analysis of other outcomes are ongoing and will be presented at the meeting.

Conclusions: The pressure of induction chemotherapy and ASCT significantly increased the size of CH clones. Many were detectable already at diagnosis at very low frequencies. However, after end of chemotherapy, the mutated clones became stable and ceased to grow. CH was not associated with an inferior survival in MCL patients treated with immunochemotherapy and ASCT in first line.

Keywords: clonal hematopoiesis; mantle cell lymphoma (MCL); R-CHOP.

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MAGNIFY PHASE IIIB INTERIM ANALYSIS: FIRST REPORT OF INDUCTION R^2 FOLLOWED BY MAINTENANCE IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

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Introduction: The combination of lenalidomide + rituximab (R^2) has demonstrated efficacy comparable to standard chemoimmunotherapy regimens in the frontline setting, and improved efficacy compared to rituximab monotherapy in the relapsed/refractory (R/R) setting among patients with indolent B-cell NHL. The multicenter, non-registrational phase IIIb MAGNIFY trial enrolled patients with R/R follicular, marginal zone, and mantle cell lymphomas (NCT01996865). This evaluation focuses on MCL patients, an aggressive though uncommon form of NHL, to determine the optimal duration of induction and maintenance therapy.

TABLE 1 Efficacy for induction R^2 in evaluable R/R MCL patients

	ORR, %	CR, %	Median TTR, mo (range)	Median DOR, mo (95% CI)*	Median PFS, mo (95% CI)*
All MCL patients	54	38	2.9 (2.4-9.9)	27.4 (14.6-31.6)	10.6 (5.5-30.9)
R-refractory status					
Yes	31	31	2.8 (2.7-6.6)	31.6 (NR-NR)	5.3 (2.3-34.3)
No	63	40	2.9 (2.4-9.9)	27.4 (5.9-NR)	14.7 (5.7-30.9)

*If patients were already in maintenance at data cutoff, then response assessments also contributed to DOR and PFS.

Methods: R^2 treatment includes lenalidomide 20 mg/d, d1-21/28 + rituximab 375 mg/m^2/wk cycle 1 and q8wk cycles 3+ for 12 cycles of induction followed by 1:1 randomization to continued R^2 vs rituximab maintenance in patients with stable disease or better. Rituximab refractory was defined as a best response of progressive/stable disease to rituximab-containing treatment or partial/complete response for < 6 mo following the last dose of rituximab. These analyses evaluate the interim primary endpoint of ORR by 1999 IWG criteria for induction R^2 in efficacy-evaluable MCL patients receiving ≥ 1 treatment and with baseline/post-baseline assessments, including those who were rituximab refractory.

Results: Seventy MCL patients were enrolled with a median age of 69.5 y (range, 51-88), 90% stage III/IV disease, 43% bulky disease, and 100% had received prior rituximab-containing therapy. At a median follow-up of 14.6 mo, efficacy-evaluable MCL patients showed a 54% ORR and 38% CR (Table). Median TTR was 2.9 mo, median DOR was 27.4 mo, and median PFS was 10.6 mo. Seventeen of 70 patients have been randomized and entered maintenance. The most common all-grade adverse events (AEs; ≥ 20%) were 45% neutropenia, 40% fatigue, 24% constipation, 24% dyspnea, 22% anemia, 21% diarrhea, and 21% nausea. Grade 3/4 neutropenia was 39%; all other grade 3/4 AEs were ≤ 10%.

Conclusions: This first report of patients with R/R MCL from the MAGNIFY study showed that R^2 therapy is active with a tolerable safety profile, including improving activity among patients considered sensitive to prior rituximab.

Keywords: lenalidomide; mantle cell lymphoma (MCL); rituximab.

Disclosures: Sharman, J: Employment Leadership Position: *US Oncology*; Consultant Advisory Role: *Pharmacyclics, Celgene, TG Therapeutics, Genentech, Abbvie, Acerta Pharma/Astra Zeneca*; Research Funding: *(all institutional) Pharmacyclics, Genentech, Celgene, Acerta Pharma, Gilead Sciences, Seattle Genetics, TG Therapeutics, Merck, Takeda*; Other Remuneration: *Expert Testimony: Gilead Sciences*. **Coleman, M:** Consultant Advisory Role: *Medaptive Health*; Stock Ownership: *Medaptive Health*; Research Funding: *Medaptive Health*; Other Remuneration: *Speakers' Bureau: Medaptive Health*. **Yacoub, A:** Consultant Advisory Role: *Medadaptive*; Other Remuneration: *Speakers' Bureau: Medaptive Health*. **Melear, J:** Employment Leadership Position: *Medaptive Health*. **Fanning, S:** Consultant Advisory Role: *Medaptive Health*; Stock Ownership: *Medaptive Health*; Other Remuneration: *Speakers' Bureau: Medaptive Health*. **Kolibaba, K:** Employment Leadership Position: *Compass Oncology*; Consultant Advisory Role: *Gilead Sciences*; Honoraria: *TG Therapeutics*; Research Funding: *(all institutional) Acerta, Celgene, Cell Therapeutics, Genentech/Roche, Gilead Sciences, Janssen, Pharmacyclics, Novartis, Seattle Genetics, TG Therapeutics*; Other Remuneration: *Travel: TG Therapeutics*. **Lansigan, F:** Consultant Advisory Role: *Spectrum*; Research Funding: *Spectrum*. **Li, J:** Employment Leadership Position: *Celgene*; Stock Ownership: *Celgene, Medaptive*. **Llorente, M:** Employment Leadership Position: *Celgene*; Stock Ownership: *Celgene, Medaptive*. **Rummel, M:** Consultant Advisory Role: *Medadaptive*; Honoraria: *Medadaptive*; Research Funding: *Medadaptive*; Other

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EARLY PROGRESSION OF MANTLE CELL LYMPHOMA DEPICTS A HIGH-RISK DISEASE WITH POOR RESPONSE TO SUBSEQUENT THERAPIES AND A DISMAL OUTCOME

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Introduction: The prognosis of mantle cell lymphoma (MCL) has improved in recent years due to intensified frontline therapy. However, the disease remains very heterogeneous, and the only potential cure is allogeneic stem cell transplant (allo-SCT). After relapse, prognosis is generally poor and there is no consensus about therapy.

Methods: We conducted a retrospective cohort study of all 149 patients with progression/relapse of disease (POD) after initial treatment in the Nordic MCL trials, MCL2 and MCL3 - both representing intensive cytarabine-containing frontline regimens followed by auto-SCT.

Results: Median time from diagnosis to POD was 36 months (range 1-164), and median OS and PFS after POD (OS-2 and PFS-2) were 22 and 12 months, respectively. Median follow-up from POD was 85 months.

As previously shown (Visco et al, BJH, 2018), time to POD was highly prognostic. Patients with early POD (TTP <24 months, n = 49), showed a median OS-2 of 6.6 months compared to 46 months for patients with late relapses (p<0.001, HR: 3.2 (95% CI 2.2-4.8)). Likewise, PFS-2 was 3.6 and 18 months, respectively (p<0.001, HR: 3.5 (2.2-5.5)). Early POD was associated with MIPI high-risk (p = 0.08), Ki-67>30% (p = 0.007) and TP53-mutations (p<0.001).

Data on later lines of therapy was available for 114 (2nd line), 65 (3rd line) and 34 patients (4th line). Treatment responses gradually decreased. After 2nd, 3rd, and 4th line, respectively, 73% (CR 44%), 63% (CR 37%) and 46% (CR 24%) responded to therapy, and TTP decreased from 11.5, through 6.7, to 2.9 months. Furthermore, patients with early POD after frontline therapy, responded significantly worse to all succeeding lines of therapy (2nd line: p<0.001, 3rd line: p = 0.04, and 4th line: p = 0.02, Figure 1). Not surprisingly, shorter duration from previous line of therapy in general was associated with significantly poorer TTP (p<0.001).

Allo-SCT was performed in 25 patients. Median PFS from allo-SCT was 34 months; however, again patients with early POD (n = 3) showed significantly inferior outcomes (3.6 vs. 35 months, p<0.001, HR 11.8 (2.6-54)). Seven (28%) patients remained alive in CR after a median of 72 months from the allo-SCT.

Comparing different regimens, R-bendamustine seemed superior to other combination chemo-immunotherapies (2nd line: HR 0.46 (0.25-0.86); 3rd line: 0.26, (0.08-0.80); 4th line: 0.15, (0.03-0.7); however, when adjusting for duration from last line of therapy, this became insignificant.

Ibrutinib was administered at only 7 occasions. Despite the low number, these patients showed prolonged responses, even when adjusting for duration from last line of therapy (HR = 0.076, (0.01-0.55).

Conclusions: We present data of patients who experienced POD after initial treatment in the Nordic trials, MCL2 and MCL3. We confirm the significance of time to POD as both a prognostic and predictive marker. Allo-SCT did not seem to omit this difference, but data on newer targeted agents for early progressors is much needed. R-bendamustine was superior to other more intensive combination chemo-immunotherapies, but in general, it seemed to have been administered in less aggressive states of disease.

Keywords: autologous stem cell transplantation (ASCT); mantle cell lymphoma (MCL).
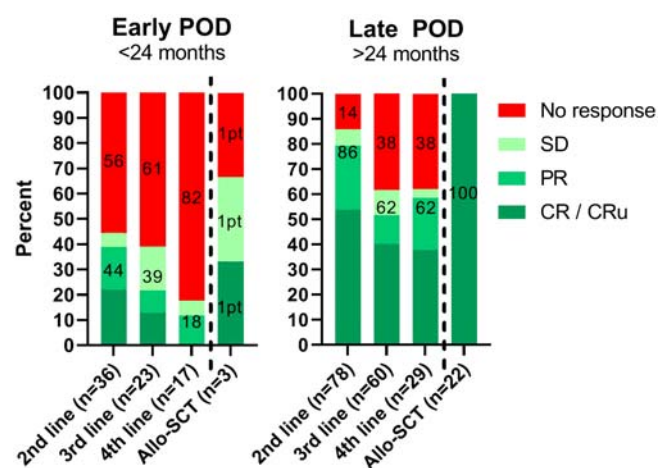
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THE EFFICACY OF IBRUTINIB IN PATIENTS WITH RELAPSED MANTLE CELL LYMPHOMA AFTER FIRST LINE INTENSIVE CHEMO-IMMUNOTHERAPY AND ASCT – A RETROSPECTIVE STUDY FROM THE LWP-EBMT

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Introduction: Current first line therapy for fit patients with mantle cell lymphoma (MCL) is cytarabine and chemo-immunotherapy induction followed by an autologous stem cell transplant (ASCT). Responses are excellent but there is a continuous pattern of relapse. Ibrutinib is an effective therapy for relapsed MCL, but there is no published data of its efficacy in the post ASCT setting.

Methods: This was a retrospective analysis of the EBMT registry. Inclusion criteria:- patients with MCL ≥18 years old, 1st line therapy containing cytarabine and rituximab, ASCT in first CR/PR between 2009 and 2016, received ibrutinib for first relapse after ASCT.

Results: 66 patients were included (Table 1). Relapse occurred at a median of 25 months (range 15-33) after ASCT and ibrutinib was started at a median of 30 days after relapse (range 10-54). Overall response rate (ORR) was 74% [32 (48%) CR, 18 (27%) PR]. The median duration of response from the start of ibrutinib was

16 months (range 2-40); 22, 15 and 2 months for those achieving CR, PR, SD respectively. The median duration of ibrutinib therapy was 5 months (range 0.2-39). At last follow-up, 23 (35%) patients remain on ibrutinib. In 16 patients ibrutinib was stopped because of a subsequent SCT, in 13 because of relapse and in 5 due to toxicity (cytopenia, infection, tachycardia, hepatitis and poor tolerance, 1 case each). In 9 cases ibrutinib was stopped due to other/unknown reasons. 21 patients (33%) relapsed post ibrutinib (in 8 cases ibrutinib had been stopped for second SCT or toxicity), at a median of 12 months (range 1-34), of whom 17 (81%) received further therapy.

TABLE 1 Patient characteristics

Patient characteristics		n (%)
Age (years)	Median (range)	59 (39-73)
Sex	Male	59 (89)
	Female	7 (11)
MIPI score at diagnosis	High	15 (27)
	Intermediate	22 (33)
	Low	19 (34)
	Unknown	10 (15)
Stage at diagnosis	III	9 (14)
	IV	56 (85)
	Unknown	1 (2)
Induction chemoimmunotherapy	Rituximab containing	66 (100)
	HD cytarabine containing	66 (100)
	CHOP like	30 (45)
	CHOP/DHAP alternating	15 (23)
	DHAP	7 (11)
	R-AraC alone	6 (9)
	Oxaliplatin based	5 (8)
	Other	3 (5)
Lines of therapy to achieve CR/PR pre ASCT	Median (range)	1 (1-3)
Response pre ASCT	CR	43 (65)
	PR	23 (35)
Time from diagnosis to ASCT (months)	Median (range)	7 (3-70)
Conditioning for ASCT	BEAM	48 (73)
	LEAM	7 (11)
	FEAM	4 (6)
	Other	7 (11)
TBI conditioning for ASCT		2 (3)
Engrafted post ASCT		66 (100)
Response at 100 days post ASCT	CR	54 (82)
	PR	12 (18)

Twenty-three patients (38%; 16 in CR/PR after ibrutinib only) had a subsequent SCT. 22 patients had an alloSCT (11 MUD, 5 MSD, 6 mismatch related) with reduced intensity conditioning in 19, and 1 patient had a 2nd ASCT. Acute GvHD occurred in 50% of the patients and chronic in 50% (extensive in 3). With a median follow up of 17 months post alloSCT, 18 (63%) are in remission.

With a median follow-up of 22 months after starting ibrutinib, 49 patients are alive, with 35 (71%) in CR and 4 (8%) in PR. Causes of death were MCL in 14 cases (82%), alloSCT toxicity in 2 patients and unknown in 1 case. 2-year OS after starting ibrutinib was 72% (69% for alloSCT patients) and 2-year PFS 62%.

Conclusion: Although ibrutinib results in a high ORR, the median response duration is 16 months, suggesting that consolidative alloSCT should be considered in fit patients with an available donor. Ibrutinib does not seem to increase the toxicity of alloSCT.

Keywords: autologous stem cell transplantation (ASCT); ibrutinib; mantle cell lymphoma (MCL).

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IBRUTINIB COMPARED TO STANDARD CHEMOTHERAPY FOR CENTRAL NERVOUS SYSTEM RECURRENCE OF MANTLE CELL LYMPHOMA

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Background: Central nervous system (CNS) relapse of Mantle Cell Lymphoma (MCL) is a rare condition for which a standard of care has not been identified. Responses to conventional treatment for CNS-MCL are poor and prognosis is dismal, with median survival of less than 6 months. Ibrutinib is approved for relapsed/refractory MCL; small series demonstrated its efficacy on CNS localization thanks to the capability to cross the blood-brain barrier.

Methods: We retrospectively analyzed a multi-center series of consecutive patients (pts) with CNS relapse of systemic MCL with the aim to evaluate outcome of pts treated with ibrutinib compared to pts treated with a standard chemotherapy (CT) and previously described in the MANTLE-FIRST study. Overall survival (OS) and progression-free survival (PFS) were estimated from the time of initiation of therapy for CNS-MCL.

Results: The entire series consisted of 31 pts: 16 pts (52%) received conventional CT (standard cohort), while 15 pts (48%) received ibrutinib monotherapy (ibrutinib cohort). Median age was 54 years (range: 39-70) in the standard cohort and 60 years (range: 54-76) in the ibrutinib cohort. Blastoid variant was diagnosed in 6 pts in the standard and in 5 pts in the ibrutinib cohort. A ki-67 value was available in 12 pts in the standard cohort (≥30% in these cases), while in the ibrutinib cohort ki-67 was available in 8 pts (≥30% in 5 pts, 62%). MIPI score was high in 46% and 73% of pts in standard and ibrutinib cohort. Upfront treatment for systemic MCL included high-dose cytarabine and autologous stem cell transplantation in 100% and 68% in the standard cohort and in 80% and 33% in the ibrutinib cohort. Median number of therapies for MCL before CNS recurrence was 1 in the standard and 2 (range: 1-3) in the ibrutinib cohort. In the standard cohort, treatment for CNS relapse consisted of rituximab plus high-dose methotrexate in 5 pts (33%), bendamustine in 6 pts (37%),
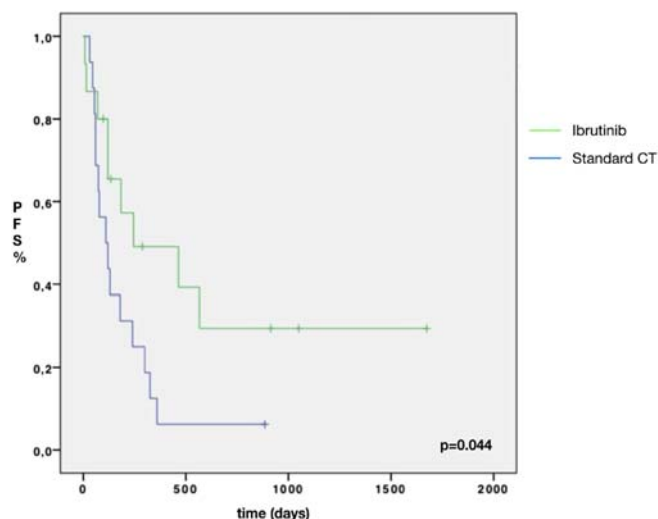
Fig1: Progression free survival in patients treated with standard CT compared with patients treated wit ibrituinib

ifosfamide in 2 pts (12%) and other regimens in 3 pts (18%). Pts treated with ibrutinib received 560 mg p.o. daily. Intratechal CT was added in 5 pts (31%) and 7 pts (47%) in standard and ibrutinib cohort. Radiotherapy was delivered to 3 pts, all in the standard cohort, in one case as consolidation and in 2 cases as salvage. With a median follow-up of 10.4 months, the 1-year PFS and OS of the entire study population are 24% and 46%. A statistically significant difference in 1-year PFS was observed in favor of ibrutinib versus standard CT (49% vs 6%, p = 0.044). The difference in 1-year OS in favor of ibrutinib versus standard CT did not reach statistical significance (57% vs 37%, p = 0.097). In the standard cohort only one pt is alive after allogeneic transplantation.

Conclusion: In this study, ibrutinib monotherapy appears to be effective for CNS-MCL; with the usual limitations of a retrospective analysis, our data show a benefit in PFS for CNS-MCL pts treated with ibrutinib in comparison to standard chemoimmunotherapy.

Keywords: ibrutinib; mantle cell lymphoma (MCL); salvage treatment.

Disclosures: Rusconi, C: Research Funding: *Celgene, Takeda (advisory board), Roche, Celgene*; Other Remuneration: *Takeda, Roche.*

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UPDATED SAFETY AND EFFICACY DATA IN THE PHASE 1 TRIAL OF PATIENTS WITH MANTLE CELL LYMPHOMA (MCL) TREATED WITH BRUTON TYROSINE KINASE (BTK) INHIBITOR ZANUBRUTINIB (BGB-3111)

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Introduction: Zanubrutinib, an investigational BTK inhibitor, has demonstrated greater selectivity for BTK vs other TEC- and EGFR-family kinases in biochemical assays and shown favorable PK/PD properties in preclinical studies. In phase 1 testing, high plasma concentrations were achieved, resulting in complete and sustained 24-hour BTK inhibition in blood and lymph nodes in patients (pts) treated at 160 mg twice daily (bid; Tam. *Blood* 2016;128:642). Here, we present updated safety and efficacy data from pts with MCL.

Methods: This is a global, phase 1 study investigating zanubrutinib in pts with B-cell malignancies with indication-specific expansion cohorts. In the expansion phase, enrolled pts received zanubrutinib 320 mg daily or 160 mg bid (the RP2D). Treatment emergent adverse events (TEAEs) were summarized according to NCI CTCAE v4.03 and responses were assessed by CT scans as per Lugano Classification (Cheson. *J Clin Oncol* 2014;32:3059).

Results: As of 16 Sep 2018, 48 MCL pts were enrolled: 37 relapsed/refractory (R/R) and 11 treatment-naïve (TN) (**Table**). Of the 48 pts, 45 were evaluable for efficacy; 3 were not efficacy evaluable as they had not yet reached the first 12-week efficacy assessment. Median follow-up for efficacy evaluable pts was 16.0 mo (range, 1.6–38.2). Twenty-six pts discontinued treatment (16 due to progressive disease [PD]; 10 due to TEAEs including peripheral edema, small cell lung cancer, renal hematoma, ANCA-positive vasculitis with acute kidney injury, subdural hematoma, and myelodysplastic syndrome, pneumonia (2 pts), congestive cardiac failure, thalamic infarction). Five pts died due to TEAEs (1 pneumonia, 1 congestive cardiac failure, 1 thalamic infarction, and 2 sepsis/septic shock), none of which were assessed by investigator as related to zanubrutinib. Most common TEAEs of any cause (≥15% of pts) included diarrhea (35%), petechiae/purpura/contusion (31%), upper respiratory tract infection (27%), fatigue (25%), constipation (21%), rash (19%), back pain (17%), headache (17%) and peripheral edema (17%). Overall response rate (ORR) for TN, R/R and overall was 87.5% (7/8), 86.5% (32/37) and 86.7% (39/45) respectively (**Table**). Responses were based on computed tomography scans for most pts, as positron-emission tomography was not required. Median progression-free survival was 15.4 mo (**Table**).

Conclusions: Zanubrutinib monotherapy was shown to be well tolerated and highly active in pts with MCL, with high ORR and rate of CR.

Keywords: BTK inhibitors; mantle cell lymphoma (MCL).

Disclosures: Tam, C: Honoraria: *Beigene, Janssen, AbbVie, Novartis*; Research Funding: *Janssen and AbbVie.* **Wang, M:** Consultant Advisory Role: *BioInvent; IO Biotech; Celgene; Juno Therapeutics; Janssen; Pharmacyclics; AstraZeneca; MoreHealth; Pulse BioSciences; AxImmune*; Stock Ownership: *MoreHealth*; Honoraria: *Janssen; Dava Oncology; OMI; PeerView Institute for Medical Education (PVI)*; Research Funding: *Janssen; AstraZeneca; Acerta Pharma; Kite Pharma; Juno Therapeutics; BeiGene; Novartis; Celgene; BioInvent; Karus; Oncternal; Amgen*; Other Remuneration: *Travel, Accommodations, Expenses: Janssen; AstraZeneca; Dava Oncology; OMI.* **Simpson, D:** Honoraria: *Celgene, Janssen, Abbvie, Roche*; Research Funding: *Amgen, Pharmacyclics, Acerta, Beigene, Celgene, BMS, Roche, Sanofi, GSK*; Other Remuneration: *Travel, Accommodations, Expenses: Janssen, Celgene.* **Opat, S:** Consultant Advisory Role: *Roche, Janssen, Abbvie, Celgene, Takeda, Merck, Gilead, Mundipharma*; Honoraria: *Roche, Janssen, Abbvie, Celgene, Takeda, Merck, Gilead, Mundipharma*; Research Funding: *BeiGene, Roche, Janssen,*

TABLE 1 Patient Characteristics, Safety, and Efficacy

Patient characteristics	N = 48		
Median (range) age, y	71 (42–90)		
ECOG PS, n (%)			
0	20 (41.7)		
1	22 (45.8)		
2	6 (12.5)		
Stage at study entry, n (%)			
Stage I	3 (6.3)		
Stage II	1 (2.1)		
Stage III	4 (8.3)		
Stage IV	40 (83.3)		
MIPI, n (%)			
Low risk	12 (25.0)		
Intermediate risk	18 (37.5)		
High risk	18 (37.5)		
Disease status, n (%)			
Treatment-naïve	11 (22.9)		
Relapsed/refractory	37 (77.1)		
Median (range) no. of prior therapies	1 (1–4)		
Median (range) follow-up, mo	15.1 (0.6–38.2)		
Bulky disease >10 cm, n (%)	3 (6.3)		
Safety, n (%)	**N = 48**		
Any AE	47 (97.9)		
Grade ≥3 AEs	28 (58.3)		
Serious AEs	19 (39.6)		
AEs leading to zanubrutinib discontinuation	11 (22.9)		
AEs leading to death	5 (10.4)		
Efficacy			
Best response per investigator (n)	**TN (n=8)**	**R/R (n=37)**	**Overall (n=45)**
Overall response rate, n (%); 95% CI	7 (87.5); 47.3, 99.7	32 (86.5); 71.2, 95.5	39 (86.7); 73.2, 94.9
Complete response, n (%)	3 (37.5)	11 (29.7)	14 (31.1)
Partial response, n (%)	4 (50.0)	21 (56.8)	25 (55.6)
Stable disease, n (%)	0 (0.0)	2 (5.4)	2 (4.4)
Progressive disease, n (%)	1 (12.5)	3 (8.1)	4 (8.9)
Median follow up (min, max)	8.6 (1.6, 25.0)	17.1 (1.9, 38.2)	16.0 (1.6, 38.2)
Duration of response (mo)	**R/R (n=32)**		**Overall (n=39)**
Follow up, median (min, max)[a]	14.7 (0.0, 28.2)	14.3 (0.0, 28.2)	
Median (95% CI)[b]	14.7 (10.6, 18.5)	14.7 (10.6, 18.5)	

Abbreviations: AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; CI, confidence interval.
[a]Follow-up time is estimated by the reverse Kaplan-Meier method.
[b]Median is estimated by Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.

AGGRESSIVE LYMPHOMAS

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THE CLINICAL COURSE OF DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) OVER TIME: A MULTISTATE SURVIVAL ANALYSIS USING META-DATA FROM 13 FIRST-LINE RANDOMIZED TRIALS

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Introduction: The Surrogate Endpoints for Aggressive Lymphoma (SEAL) collaboration established a meta-database integrating individual patient data from 13 first-line randomized clinical trials on previously untreated diffuse large B-cell lymphoma (DLBCL). This meta-database provides an opportunity to investigate the impact of clinical factors and treatment response on DLBCL-specific and other causes of death following initial therapy to define new opportunities for trials and improve survivorship.

Methods: Using the SEAL database, we studied DLBCL outcomes for patients receiving anthracycline-based chemotherapy with/without added rituximab (R-Chemo) in a multistate survival analysis model having the model states "Alive with No Progression of Disease (PoD) after Treatment (TX)", "Alive after PoD", "Death from DLBCL", and "Death from Other Causes" (top Figure). The Aalen-Johansen estimator was used to calculate the likelihood of being in each model state and project the course of DLBCL over time (bottom Figure).

Results: We identified 7,911 DLBCL patients (Figure) with median age 62 (range 18-92) years, 62.1% stage III/IV, 64.7% IPI ≥ 2, including 5,108 treated with R-Chemo. Following initial TX for all patients (or with R- Chemo), 2- and 5-year DLBCL-specific death rate were 7.5% (5.9%) and 8.8% (7.0%) for patients age < 40 at initial TX, 8.9% (7.2%) and 12.8% (10.6%) for age 40-60, 10.4% (9.8%) and 15.2% (14.6%) for age 60-70, and 12.8% (12.5%) and 18.3% (17.6%) for age ≥ 70. Death rates at 2- and 5-year from all other causes were 2.3% (2.1%) and 3.5% (3.8%) for age < 40, 4% (3.1%) and 6.5% (5.1%) for age 40-60, 5.1% (4.8%) and 9.4% (7.9%) for age 60-70, and 11.3% (12.3%) and 18.3% (20.0%) for age ≥ 70. Following R- Chemo (n = 5,108), 2-year PoD rates were 12.3% for patients achieving CR, 24.1% for PR, and 28.4% for SD; 2- and 5- year DLBCL-specific mortality rates were 4.6% and 8.7% for CR, 11.8% and 18.6% for PR, 20.3% and 25.6% for SD, and 69.1% and 71.2% for PD. These rates were similar for "non R-Chemo" regimens. International Prognostic Index (IPI) affected the 2- and 5-year DLBCL-specific mortality rates, which were 4.8% and 8% for IPI = 0 or 1, 7.8% and 11.9% for IPI = 2, 13.3% and 18.6% for IPI = 3, and 24.4% and 29.7% for IPI = 4 or 5 in the whole SEAL population (n = 7,911).
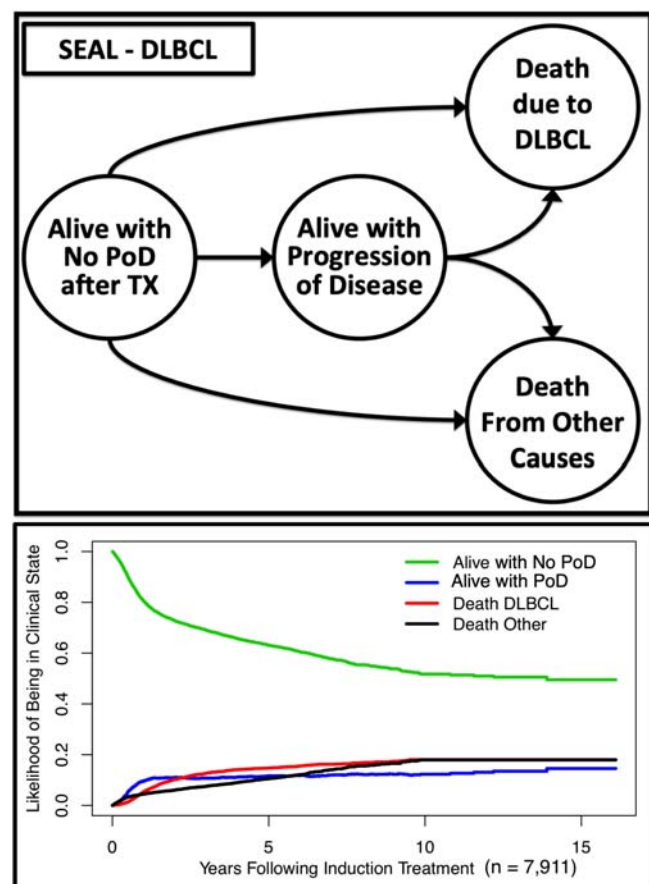
Conclusion: In young DLBCL patients, lymphoma was the predominant cause of death despite its relatively low 5-year mortality rate, which was still > 2 times higher than other-causes of death. On the contrary, DLBCL- and other causes-related death risk were both high in older (age ≥ 70) patients and became equivalent 5 years following initial TX. High IPI scores increased the DLBCL-specific death risk up to 8 times. Response to initial TX was critical, where patients who had PD had extremely high rates of DLBCL-associated death. Cox models will be used to identify predictors and quantify their impact on the rate/time of critical clinical events.

Keywords: diffuse large B-cell lymphoma (DLBCL); immunochemotherapy; R-CHOP.

Disclosures: Poeschel, V: Consultant Advisory Role: *Spekers's bureau: Hexal*; Other Remuneration: *Travel, accomodations, expenses: Abbvie, Amgen, Roche.*

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COMPARISON OF CLINICAL SCORING SYSTEMS IN AGGRESSIVE B-CELL LYMPHOMAS (BCL): AN INDIVIDUAL PATIENT-LEVEL ANALYSIS ACROSS INTERNATIONAL TRIAL

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Background: In 2010, we reported that the standard IPI developed in the pre-rituximab era remains valid also for DLBCL patients (pts) treated with R(ituximab) plus CHOP (Ziepert et al., JCO 2010; 28: 2373) This study included 1,062 pts with aggressive B-cell lymphoma treated with R-CHOP-14, R-CHOP-21, or dose-escalated R-MegaCHOEP. Here we studied a much larger group of DLBCL pts treated with R-CHOP or variants and compared IPI, R-IPI, and NCCN-IPI to determine which scoring system best identifies subgroups with favorable and poor outcomes that might be well treated with R-CHOP (low-risk) or might benefit most from new approaches (high-risk group).

Methods: Individual pt data from 7 multicenter trials (1998-2009) of pts with BCL (86% DLBCL) treated front-line with R-CHOP (or variant) were analyzed to determine whether IPI, R-IPI, or NCCN-IPI best discriminated overall survival (OS). The concordance index (c-index) from a proportional hazards model, stratifying on trial and induction therapy, quantified predictive accuracy of each scoring system.

Results: 2561 pts (median age 63 yrs, 56% male) were classified into IPI, R-IPI, and NCCN-IPI risk groups (Table). With a median follow-up of 5 yrs, NCCN-IPI had the greatest absolute difference in OS estimates between the highest and lowest risk groups at 1, 3, and 5 yrs, and best discriminated OS (c-index = 0.631, Table).

Conclusions: In an independent and large cohort of pts, NCCN-IPI performed best in risk-stratifying pts with BCL, readily distinguishing pts at high and low risk for treatment failure using clinical parameters (5-yr OS between 48 and 92%). Improvement over the simpler IPI was moderate, and IPI may remain a valuable alternative. Pts with low NCCN-IPI have quite favorable survival outcomes and there is little space for further improvement. Work integrating molecular features of the tumor into the (NCCN-) IPI is in progress to better characterize a high risk group where targeted novel approaches are needed most.

Keywords: diffuse large B-cell lymphoma (DLBCL).

Disclosures: Schmitz, N: Consultant Advisory Role: *Riemser, Takeda, Janssen, Gilead, Novartis*; Stock Ownership: *Celgene*; Honoraria: *Riemser, Takeda, Janssen, Gilead, Novartis.*

TABLE 1

Scoring System	N (%)	% Alive			c-index
		1-yr	3-yr	5-yr	
IPI					0.621
Low	818 (32)	97	90	87	
Low-intermediate	609 (24)	91	83	77	
High-intermediate	609 (24)	86	73	66	
High	525 (20)	75	60	54	
R-IPI					0.589
Very good	195 (8)	98	93	93	
Good	1232 (48)	94	86	81	
Poor	1134 (44)	81	67	61	
NCCN-IPI					0.631
Low	303 (12)	98	92	92	
Low-intermediate	1057 (41)	95	88	83	
High-intermediate	945 (37)	84	70	63	
High	256 (10)	66	54	48	

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THE ELDERLY PROJECT BY THE FONDAZIONE ITALIANA LINFOMI: A PROSPECTIVE COMPREHENSIVE GERIATRIC ASSESSMENT (CGA) OF 1353 ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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TABLE 1 Simplified Comprehensive Geriatric Assessment (sCGA)

	FIT	UNFIT	FRAIL
ADL	6	5*	≤4*
IADL	8	7-6*	≤5*
CIRS-G	0 of score 3-4 <5 of score 2	0 of score 3-4 5-8 of score 2	≥ 1 of score 3-4 > 8 of score 2
Age	-	≥ 80 FIT	≥ 80 UNFIT

*Residual Functions

Figure 1: Overall Survival by geriatric groups

	n	36 months OS%	HR (95CI)	p
FIT	488	74 (CI95 68-80)	1.00	
UNFIT	296	68 (CI95 59-76)	1.37 (1.02-1.83)	0.038
FRAIL	374	47 (CI95 40-54)	2.74 (2.13-3.51)	<0.001
			FRAIL vs UNFIT 2.00 (1.53-2.62)	<0.001

at risk

FIT	488	444	387	308	242	176	116	62	25	3	0
UNFIT	296	266	228	185	140	100	59	36	16	6	0
FRAIL	374	281	210	154	121	98	70	37	22	4	0

Introduction: Treatment choice in elderly patients (pts) with Diffuse Large B-Cell Lymphoma (DLBCL) is challenging. A simplified CGA (sCGA) based on ADL (Activity of Daily Living), IADL (Instrumental ADL) and CIRS-G (Comorbidity Index Rating Scale for Geriatrics) scales has demonstrated to be better than clinical judgement to stratify pts.

To confirm the impact of sCGA, we conducted a prospective observational study on the outcome of a large series of elderly pts with DLBCL.

Methods: Pts were enrolled if ≥65 years, with an untreated de novo DLBCL. sCGA was available at a web based platform that classified pts as FIT (F), UNFIT (U), and FRAIL (FR), as shown in Table 1. According to anthracycline doses treatment was classified as curative (≥70%), intermediate (<70%) or palliative (no anthracycline). Primary study endpoint was Overall Survival (OS).

Results: Form December 2013 to December 2017, 1353 pts have been registered by 37 centres and 1207 were eligible. Median age was 76 years (65-94), 68% had stage III-IV, and 55% had an IPI ≥3; 500 (42%), 304 (25%), and 403 (33%) were classified as F, U and FR, respectively.

A significant difference among groups was observed in the rate of B symptoms (F 22%, U 27%, FR 31%; p = 0.01), ECOG PS >1 (F 8%, U 15%, FR 38%; p<0.001), anemia (F 34%, U 40%, FR 54%; p<0.001), and IPI ≥3 (F 50%; U 56%; FR 63%; p<0.001).

Data on treatment were available in 1164 pts: curative in 89%, 53%, and 36% of F, U, and FR pts, respectively; intermediate in 10%, 39%, and 31%, palliative in <1%, 8%, and 33% of pts.

With a median follow up of 29 months (1-59) 3y-OS was 64%; according to sCGA the OS was significantly different in the three geriatric groups (Fig. 1).

F pts had a significant better 3y-OS when treated with a curative approach in comparison with intermediate (77% vs 57%, p = 0.003); the use of a curative vs intermediate approach did not affect the outcome of U and FR pts (U: 72% vs 67%, p = 0.257; FR: 63% vs 54%, p = 0.364).

The use of palliative approach had a negative impact in all groups.

Conclusion: This large prospective observational study on unselected elderly DLBCL pts shows that sCGA is a useful tool to identify three groups of pts with significant different outcome.

Our results confirm that curative treatment (R-CHOP or like) is the standard of care in F pts.

In U and FR pts, the intermediate approach improves outcome compared to palliation and is superimposable with curative treatment. FR group warrants further characterization to better define the risk/benefit ratio of treatment.

Keywords: diffuse large B-cell lymphoma (DLBCL); elderly; non-Hodgkin lymphoma (NHL).

PET–CR Hazard Ratios for PFS By Study Characteristic

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PET-CR AS A SURROGATE FOR SURVIVAL OUTCOMES IN DLBCL: A LITERATURE BASED META-ANALYSIS

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Introduction: Previous studies have reported an association between end of treatment PET results and clinical outcomes, such as overall survival (OS), progression free survival (PFS) and event free survival (EFS), in patients with diffuse large B-cell lymphoma (DLBCL) who received standard first-line chemoimmunotherapy. The development of PET-CR as a novel endpoint may expedite and shorten the duration of clinical development. We conducted a prospectively designed individual-level and literature-based meta-analysis to address the use of PET-CR as a possible surrogate end point for drug registration in DLBCL. This work was funded by Genentech/Roche.

Methods: We conducted a literature search for studies reporting long-term survival outcomes by PET-CR status in DLBCL patients who had previously untreated DLBCL. We augmented the literature studies with previously unpublished patient-level datasets from prospective phase II and III studies (GOYA (NCT01287741), GATHER (NCT01414855), MAYO (NCT00670358). All analyses were pre-specified. We took a Bayesian meta-analytic, random-effects approach, comparing the hazard ratio (HR) for PET-CR versus non-PET-CR within and across all studies. We derived hazard ratios and their 95% confidence intervals for long-term survival outcomes by PET-CR status overall and within subgroups defined by study characteristics. We considered progression-free survival (PFS) type endpoints as well as overall survival (OS).

Results: We identified 21 studies involving a total of 3960 patients. Of these studies, 18 were from the literature (2464 patients) and 3 were patient-level datasets (1496 patients). In 20/21 studies patients underwent R-CHOP or R-CHOP-like therapies. The other study considered chemotherapy. The overall mean PET-CR rate was 78% and the HR for achieving a PET-CR versus non-CR was 0.16 (95% CI = 0.11, 0.23) for PFS and 0.16 (95% CI = 0.11, 0.25) for OS. The figure shows the modeled HRs and 95% credible intervals for PFS for the overall primary analysis as well as by study characteristic. The predictability of PET-CR was consistent across all study characteristics considered. It was also consistent across all 21 studies, recognizing the limitations of small sample sizes in some studies.

Conclusions: Our results support the use of end of therapy PET-CR as a surrogate for PFS and OS in clinical trials that are evaluating experimental therapies. This has the potential for bringing new and effective therapies to patients more quickly.

Keywords: diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL); positron emission tomography (PET).

Disclosures: Berry, D: Employment Leadership Position: *I am co-owner of Berry Consultants, LLC, a company that provides statistical design and analysis services to pharmaceutical companies (including Genentech/Roche), medical device companies, U.S. NIH cooperative groups, patient advocacy groups, and international consortia.*; Consultant

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CLINICAL CHARACTERISTICS AND OUTCOMES OF STAGE I DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) IN THE RITUXIMAB-ERA

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TABLE 1

	Extranodal n=224 (%)	Nodal n=117 (%)
Median age (range)	61 (20-87)	58 (28-88)
Sex, male	111 (50)	58 (50)
ECOG <2	216 (96)	116 (99)
Bulky (>7cm)	21 (11)	11 (9)
High LDH (n=317)	48 (23)	21 (20)
Treatment		
R-CHOP 3-4	29 (13)	23 (20)
R-CHOP 3-4 + RT	100 (47)	46 (44)
R-CHOP 6	48 (21)	20 (17)
R-CHOP 6 + RT	51 (23)	5 (4)
Radiotherapy	147 (66)	74 (63)

Introduction: Diffuse large B-cell lymphoma (DLBCL) presents as stage I in 15-20% of patients and with extranodal (EN) involvement in 50%. Based on recent studies, 4 cycles of immunochemotherapy may be an option for low-risk risk patients with negative interim PET/CT. However, the optimal treatment and outcome of EN stage I DLBCL are poorly described. This study aimed to analyze the characteristics and outcome of stage I DLBCL in the rituximab era.

Methods: We reviewed all newly diagnosed patients with DLBCL at Memorial Sloan Kettering Cancer Center from 2001-2015 treated with frontline rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (RCHOP) or RCHOP-like regimens. All patients underwent staging with PET/CT and bone marrow biopsy. Primary central nervous system (CNS) lymphoma and transformed indolent lymphoma were excluded. We compared survival using a multinomial propensity score weighted analysis across treatment groups adjusted for age, gender, IPI, bulky, nodal and cell of origin.

Results: We identified 1986 patients treated with frontline RCHOP-like regimens. Among them, 341 had stage I DLBCL: EN stage I in 224 (66%) and nodal in 117 (34%). The most common EN sites were bone 21%, n=47; stomach 19%, n = 42; testicle 9%, n = 20; intestine 8%, n = 19 and breast 8%, n = 18. Germinal-center was the most frequent phenotype by Hans criteria: 60% EN, 72% nodal. Complete response rate was 99% in EN and 98% in nodal, confirmed by PET/CT in 93% of patients. Twenty-three (7%) patients relapsed, 8% EN and 5% nodal. Median time to relapse was 36 m and 37 m, respectively. Sixteen patients (62%) relapsed as a localized disease, 5 at the initial site. The most common sites at relapse were the CNS, (27%, n = 7; initial site: 2 testicle, 2 breast, 3 nodal) and the lymph nodes (27%, n = 7). With a median follow-up of 5.6 y, EN patients had a worse outcome than nodal [10-y disease-free survival (DFS) 73% EN vs. 91% nodal (p = 0.003); 10-y overall survival (OS) of 74% EN vs. 94% nodal (p = 0.003) (figure 1)]. In the EN group, patients who received radiotherapy (RT) had better outcome than those who did not [10y DFS

DFS / OS survival probability plots. Number at-risk tables below each plot. Legend: Extranodal, Nodal. X-axis: Years since diagnosis.
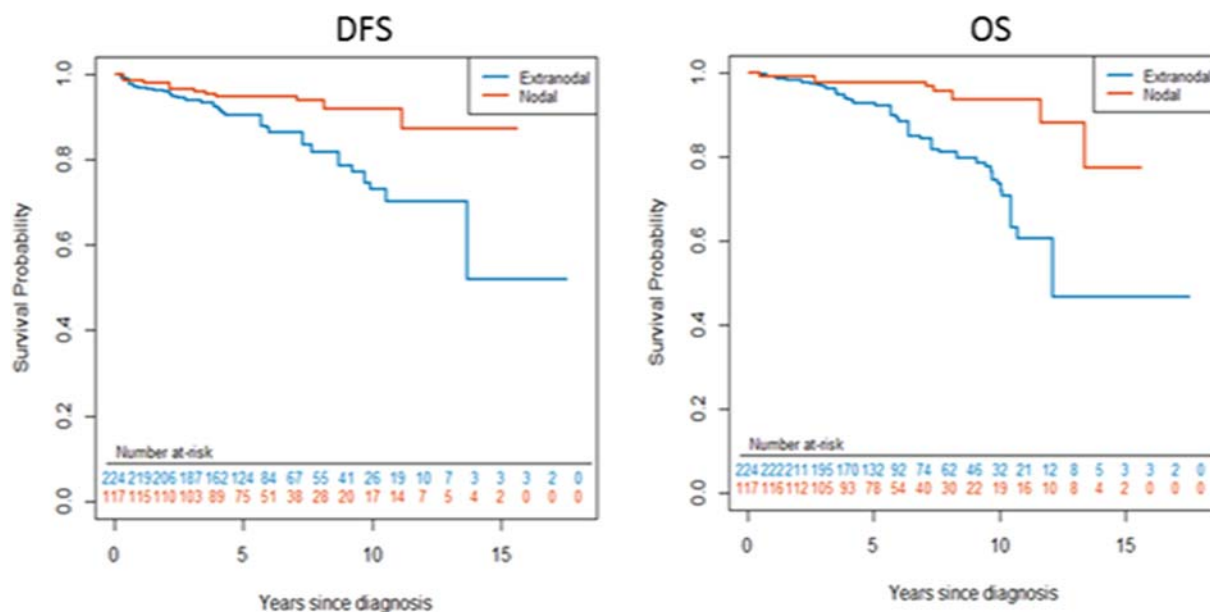
78% RT vs. 72% no RT (p = 0.047); 10y OS 77% RT vs. 72% no RT (p = 0.002)].

Conclusions: Patients with stage I DLBCL and EN disease have a worse outcome than those with nodal involvement. Late relapses are common, including CNS relapses, requiring prolonged surveillance. Patients with EN stage I DLBCL may benefit from RT consolidation and is deserving of further study.

Keywords: diffuse large B-cell lymphoma (DLBCL); extranodal lymphomas; R-CHOP.

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POPULATION-BASED STUDY ON DIFFERENT REGIMENS OF R-CHOP IN PATIENTS WITH NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA IN THE NETHERLANDS SUPPORTS THE USE OF 6 CYCLES OF R-CHOP21

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Introduction: Randomized clinical trials (RCTs) showed similar efficacy between R-CHOP14 and R-CHOP21 regimens, and less toxicity with 6 v 8 cycles of R-CHOP when applied as first-line treatment among elderly (>60 years) DLBCL patients. Likewise, both 6x R-CHOP14 plus two cycles of rituximab (2R) and 8x R-CHOP21 result in comparable efficacy in patients 18-80 years. However, it is unknown whether the interval of 6x R-CHOP can be extended to 21 days especially among younger patients with advanced-stage DLBCL. Unfortunately, this question is unlikely to be addressed in future RCTs. In this regard, population-based studies can lend support to address unanswered hypotheses.

The aims of this population-based study among newly diagnosed DLBCL patients were two-fold. First, we sought to confirm results of RCTs on the effectiveness of R-CHOP21 v R-CHOP14, irrespective of the number of cycles (analysis A) and 6x v 8x R-CHOP, irrespective of dose density (analysis B). Secondly, we specifically assessed in patients aged 18-64 years whether 6x R-CHOP21±2R is equally effective as other R-CHOP regimens (analysis C).

Methods: We selected all patients aged ≥18 years diagnosed with advanced-stage DLBCL (stages II-IV) between 2004-2010 from the Dutch Population-based HAematological Registry for Observational Studies (PHAROS) and between 2014-2015 from the nationwide Netherlands Cancer Registry (NCR). Of note, the use of 2R after 6x R-CHOP was not uniformly registered in PHAROS. The primary endpoint was overall survival (OS) in age groups: 18-64, 65-74, and ≥75 years. Multivariable evaluation of OS was applied using Cox regression to account for some imbalances between treatment groups.

Results: The cohort for analysis A included 2,338 patients who received ≥1 cycle of R-CHOP outside the setting of a RCT, of whom 637 (27%) received R-CHOP14 and 1,701 (73%) R-CHOP21. Recipients of R-CHOP21, as compared to recipients of R-CHOP14, were older (median age, 68 v 61 years; P<0.001) and more often had an IPI of ≥3 (47% v 38%; P<0.001). The adjusted risk of mortality was similar between both groups across all age groups (Fig 1A for patients <65 years).

(A) 18-64 years

	Adjusted HR	95% CI	P
R-CHOP21	1	Ref	
R-CHOP14	0.80	0.57-1.11	0.181

No. at risk

R-CHOP21 643	574	526	332	132
R-CHOP14 383	340	314	277	215

(B) 18-64 years

	Adjusted HR	95% CI	P
6x R-CHOP	1	Ref	
8x R-CHOP	0.69	0.47-1.01	0.057

No. at risk

6x R-CHOP 224	206	191	128	73
8x R-CHOP 673	640	595	437	245

(C) 18-64 years

	Adjusted HR	95% CI	P
6x R-CHOP21	1.55	0.93-2.57	0.091
8x R-CHOP21	1	Ref	
6x R-CHOP14	1.10	0.62-1.94	0.747
8x R-CHOP14	0.82	0.50-1.32	0.414

No. at risk

6x R-CHOP21 116	107	99	53	23
8x R-CHOP21 437	417	386	247	91
6x R-CHOP14 108	99	92	75	50
8x R-CHOP14 236	223	209	190	154

For analysis B, 1,887 (80%) of 2,338 patients were included who received 6x (45%) or 8x (55%) R-CHOP. Recipients of 6 cycles, as compared to recipients of 8 cycles, were older (median age, 71 *v* 61 years; P<0.001), whereas IPI score distribution was not significantly different (P = 0.099). The adjusted risk of mortality was similar between both groups across all age groups (Fig 1B for patients <65 years).

Lastly, for analysis C, 897 (48%) of 1,887 patients were included, of whom most received 8x R-CHOP21 (49%) followed by 8x R-CHOP14 (26%), 6x R-CHOP21 (13%), and 6x R-CHOP14 (12%). Recipients of 6 R-CHOP21±2R, as compared to recipients of other regimens, were not older (median age, 55 *v* 55 years; P = 0.602), but had slightly less often an IPI of ≥3 (24% *v* 27%; P = 0.004). The adjusted risk of mortality was similar between 6xR-CHOP21±2R and the other regimens (Fig 1C).

Conclusion: Our population-based analyses add support to the notion from several RCTs that R-CHOP21 and R-CHOP14, and 6x and 8x R-CHOP are equally effective. Furthermore, 6x R-CHOP21±2R was found to be equally effective compared to all other regimens in all age groups. Therefore, 6xR-CHOP21 (±2R) should be considered the preferred first-line regimen for all patients with advanced-stage DLBCL. The question whether 2R after 6x CHOP21 can be omitted without compromising efficacy remains a topic for future studies.

Keywords: diffuse large B-cell lymphoma (DLBCL); R-CHOP.

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PET-DRIVEN RADIOTHERAPY IN PATIENTS WITH LOW RISK DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): THE DLCL10 MULTICENTER PHASE 2 TRIAL BY FONDAZIONE ITALIANA LINFOMI (FIL)

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Background: Historically, in DLBCL bulky sites at diagnosis are irradiated after rituximab-chemotherapy (R-CT), whereas residual uptake area (RUA) at other sites are considered as failure. As PET negativity is mandatory to define complete remission (CR), some groups postulated that PET-neg areas after R-CT do not need consolidation RT.

Aims: To assess the role of RT in PET-neg and in PET-pos low-risk DLBCL patients after R-CT

Methods: The DLCL10 protocol was a phase II study of patients (pts) > = 18 years with low risk DLBCL according to the MiNT trial, (aa IPI 0 and bulky, aa IPI 1 +/- bulky) conducted in 19 FIL centers. Pts were treated with 6 courses of RCHOP and final response was evaluated with FDG-PET. Both pre and post treatment PET scans were centrally reviewed through the Widen web platform by a panel of 5 nuclear medicine experts. Positive scans were those centrally classified with Deauville score 3-4-5 by the first 2 concordant reviewers. Pts with one UA received RT, 36 Gy involved-field, regardless of bulky disease at onset, while those with multiple RUA were shifted to salvage systemic therapy. Primary aim was to obtain a 2-year PFS of at least 85% for post R-CT PET-neg pts. Secondary endpoints were OS and response.

Results: From January 2012 to December 2017, 115 consecutive pts were enrolled, and 109 were evaluable. Median age 58 years (47-65); M:F 60/49; DLBCL de novo 90%, aa IPI 0 15, aa IPI 1 94 (20 with bulky mass); RCHOP-14 /RCHOP-21 72/37. Median follow-up was 36 months and 6 pts died (2 lymphoma, 3 toxicitiy, 1 unknown). A total of 105 pts completed the R-CT program, while four were discontinuated for lymphoma progression (1), toxicity (2, both died) and unknown cause (1). At end of treatment, 83 patients had PET-neg, whereas 17 had single RUA and received RT. In PET-neg patients, PFS was 90.6% (95% CI 81.1-95.4) at 2 years and 88.7% (95% CI

78.4-94.3) at 3 years. After RT, 15 pts reached CR, one PR and one was not evaluable. None of them relapsed. Thus, all patients with positive focal RUA after R-CT were cured with IF RT. Concerning the 35 pts with bulky disease, 20 reached PET-neg and 15 had single RUA after R-CT and were thus irradiated (1 PD). There were two relapses in the PET-neg/not irradiated group, but only one in previously bulky site. In the PET-pos /RT group no relapse occurred. In the total population, 3-year PFS and OS are 85.1% (95%, CI 76.4-89.3) and 94% (95%, CI 87.3-97.7), respectively.

Conclusion: Our data suggest that irradiating only sites of unique PET RUA, regardless of bulky at onset, can be considered as a reasonable strategy for low risk DLBCL pts. In cases with bulky disease, PET-driven RT allowed RT sparing in approximately half of patients. Moreover, consolidation RT in those with focal residual PET positivity, guaranteed excellent prognosis (17/17 cured) and could be recommended as a valid option.

Keywords: diffuse large B-cell lymphoma (DLBCL); positron emission tomography (PET).

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SAFETY 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 strategy for very elderly patients (pts) with Diffuse Large B Cell Lymphoma (DLBCL) remains controversial. R-mini-CHOP has been shown to be tolerable, albeit with limited

Table: ARTD and ARDI (n=69)

Based on 6 cycles of I-R-mini-CHOP	Median ARTD % (IQR)	Median ARDI % (IQR)	Mean ARTD % (SD)	Mean ARDI % (SD)
Entire regimen	96.5 (80.2, 100.1)	96.8 (88.4, 100.4)	85.2 (30.3)	94.5 (15.6)
Rituximab alone	99.9 (87.1, 103.5)	99.6 (94.3, 104.0)	88.4 (27.5)	97.8 (9.9)
Chemotherapy (mini-CHOP) alone	96.5 (80.2, 100.1)	98.2 (91.9, 100.8)	85.2 (30.3)	96.7 (15.6)
Cyclophosphamide & doxorubicin combined	99.1 (82.6, 100.8)	99.1 (94.0, 100.9)	85.6 (26.3)	95.6 (9.2)
Ibrutinib alone	87.3 (55.6, 100.0)	92.9 (73.4, 100.0)	74.1 (33.5)	75.4 (56.2)

efficacy. Ibrutinib (BTK inhibitor) has suggested efficacy in combination with R-CHOP in younger pts, but with significant toxicity limiting the ability to complete therapy in pts ³60 yrs. We present deliverability results from this prospective Phase II study of ibrutinib, rituximab and mini-CHOP in pts ≥75yrs with newly diagnosed DLBCL.

Methods: Pts received six 21 day cycles of ibrutinib 560mg daily and R-mini-CHOP (Rituximab 375mg/m^2, cyclophosphamide 400mg/m^2, doxorubicin 25mg/m^2, vincristine 1mg on day 1 & prednisone 40mg/m^2 or 100mg/d x 5) followed by an additional two 21 day cycles of rituximab + ibrutinib (or high dose methotrexate for CNS prophylaxis). Deliverability is measured using Average Relative Total Dose (ARTD) [Average delivered dose of the chemotherapy regimen as a % of the target dose] and Average Relative Dose Intensity (ARDI)[Average delivered dose of the chemotherapy regimen per unit time (week) as a % of the target dose intensity].

Results: 80 pts were recruited between Nov 2015 & Dec 2018. Of the first 70 to complete therapy by the data cut-off 14 Feb 2019, one died prior to commencing therapy. Median age was 81yrs (75-95); 51% female, 81% stage III/IV and 64% IPI 3-5. The ARTD & ARDI data are presented in the Table. Most patients received 6 cycles (75%; 52/69), with 14% (10/69) receiving <4. Treatment was discontinued in 23 pts (33%) due to: progressive disease 5/69 (7%), ibrutinib toxicity 4/69 (6%), consent withdrawal 4/69 (6%), intercurrent illness 3/69 (4%), R-mini-CHOP toxicity 2/69 (3%), other reasons 2/69 (3%), and death 2/69 (3%). Most patients 63/69 (91%) experienced an adverse event (AE), and 67% experienced a serious AE (SAE): one SAE in 15/69 (22%), 2 in 8/69 (12%) and ≥3 in 23/69(33%). The most common SAEs were infection (26 events, 24 ≥Gd 3), atrial fibrillation (8 events, 5 ≥Gd 3), febrile neutropenia (6 events, 6 ≥Gd 3). Of AEs of special interest, diarrhoea occurred in 38/69 (55% pts; 6 ≥Gd 3), atrial fibrillation in 12/69 (17%, 4 ≥Gd 3), and two pts had major bleeding (Gd 3, Gd 5). At a median follow-up of 12.7 months (IQR 5.0-22.1) there were 18/69 (26%) deaths, mostly due to lymphoma (11/69, 16%), and infection (3/69, 4%).

Conclusions: In this very elderly cohort the majority of pts were able to complete 6 cycles of R-mini-CHOP, maintaining a high ARDI and

ARTD of both immunochemotherapy and ibrutinib, with notable but expected toxicity. Despite limited follow-up, there remains a high rate of early progression and death, undermining the potential of this combination to improve overall survival over the use of R-mini-CHOP in very elderly patients with DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL); elderly; ibrutinib.

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PROSPECTIVE MULTICENTER REGISTRY FOR SECONDARY CNS INVOLVEMENT IN MALIGNANT LYMPHOMA: AN UPDATE WITH DATA FROM 181 PATIENTS

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Introduction: Secondary central nervous system involvement of lymphoma (SCNSL) is a rare (<5%) complication of systemic disease. The prognosis of SCNSL is considered to be poor with median overall survival (OS) of less than 6 months. The optimal management for SCNSL is yet to be defined.

Methods: Since 2011, a prospective multicenter international registry for SCNSL is being conducted. Patients with secondary CNS involvement of indolent or aggressive Non-Hodgkin lymphoma (NHL, confirmed histologically or cytologically) with or without systemic involvement at the time point of CNS involvement are eligible. Since July 2011, 232 patients were included. Here, we present data of the first 181 patients with April 2018 as data cutoff.

Results: Median age was 63 years (range, 23-86 years). 31 patients (17%) had CNS involvement at initial diagnosis and 150 (83%) at relapse. Out of these 150 patients 66 (44%) had simultaneous systemic disease. In 180 patients with available data, 151 (84%) had aggressive B-/T-cell NHL and 29 (16%) indolent NHL. Localisation of CNS lymphoma was brain parenchyma in 103 patients (57%), meninges in 43 (24%), spinal cord in 2 (1%) and a combined manifestation in 33 patients (18%). First-line therapy (defined as therapy at diagnosis at CNS involvement) was given to 177 of the 180 patients. 83 (46%) received a combined systemic and intrathecal chemotherapy, 72 (40%) systemic therapy alone, 3 (2%) radiotherapy (RT) alone, 14 (8%) a combination of RT and systemic and/or intrathecal therapy, 2 (1%) intrathecal therapy alone and 3 patients (2%) palliative treatment or best supportive care only. Systemic chemotherapy was high-dose methotrexate-based in 139 patients (79%) and high-dose cytarabin-based in 100 (56%). Systemic rituximab was given to 111 patients (63%). Regarding all 181 patients, median progression-free survival (PFS) was 7.9 months (95% CI 6.1-9.7), and median OS 14.5 months (95% CI 8.1-21.0). As consolidation therapy within the first-line regimen, 56 patients (32%) received high-dose chemotherapy followed by autologous stem-cell transplantation (HD-ASCT). In the HD-ASCT group, median PFS was 13.2 (95% CI 1.4-25) months and median OS was 30 months.

Conclusions: We here report a large series of patients prospectively registered to analyse therapeutic approaches for SCNSL. The data suggest that intensive systemic (immune-) chemotherapy may improve the outcome of SCNSL patients as compared to historical controls, particularly if HD-ASCT can be applied.

Keywords: B-cell lymphoma.

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LONG-TERM EFFICACY AND SAFETY OF LENALIDOMIDE MAINTENANCE IN PATIENTS WITH RELAPSED DIFFUSE LARGE B-CELL LYMPHOMA WHO ARE NOT ELIGIBLE FOR AUTOLOGOUS TRANSPLANTATION (ASCT)

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Background: A multicentre phase II trial showed that lenalidomide (LENA) maintenance was well tolerated and improved outcome in pts with chemosensitive relapse of DLBCL not eligible for or relapsed after ASCT (NCT00799513). However, late side effects and events remained undefined as median follow-up was only 25 months and LENA was ongoing in 41% of pts at time of report. Herein, we report results of the trial after LENA completion in all pts and a median follow-up of 5 years.

Methods: HIV-neg pts with *de novo* or transformed DLBCL responsive to conventional salvage therapy were registered and treated with LENA 25 mg/day for 21/28 days, until lymphoma progression or unacceptable toxicity. A protocol amendment in 2015 allowed physicians to interrupt LENA after a minimum duration of 2 ys. Primary endpoint was 1-yr PFS. Simon's two-stage optimal design was used. To demonstrate a 1-yr PFS improvement from 30% to 50%, 47 pts were needed. Maintenance would be considered effective if ≥19 pts were progression-free at 1 yr. Cell of origin was assessed by NanoString Technology and Hans algorithm.

Results: Between 3/2009 and 12/2015, 48 pts were recruited; 46 were assessable (median age 72 ys; range 34-86); 36 pts had *de novo* DLBCL; most pts had unfavourable features, with an IPI ≥2 in 38 (83%) pts. Salvage therapy before LENA contained high doses of cytarabine or ifosfamide in two-thirds of cases; response at trial registration was complete in 26 pts and partial in 20.

LENA was well tolerated after an average of 16 courses/pt (range 3-82); 16 pts received LENA for ≥2 years. 3 pts died of toxicity during maintenance (intestinal infarction, meningitis and sudden death) and 2 died due to myelodysplastic syndrome at 31 and 62 months. LENA was interrupted due to toxicity in other 6 pts, and 25 required dose reduction (transient in 21), mostly due to neutropenia and rash. With the exception of neutropenia, g4 toxicities occurred in <1% of courses. Infections were rare and well controlled with oral antibiotics.

After 1 year from registration, 31 pts were progression free, which was significantly higher than the pre-determined efficacy threshold (n≥19). At a median follow-up of 5 years and a median observation period from LENA completion of 35 (8-101) months, 22 pts remain relapse-free, with a 1- and 5-yr PFS of 67 ± 7% and 48 ± 7%, respectively. The duration of response to LENA was longer than response to prior treatment in 30 (65%) pts, and benefit was observed both in *de novo* and transformed DLBCL, and in GCB and nonGCB subtypes. 27 (59%) pts are alive, with a 1- and 5-yr OS of 80 ± 6% and 58 ± 7%, respectively.

Conclusions: These long-term results soundly promote the use of LENA maintenance in pts with chemosensitive relapse of DLBCL not eligible for or failed after ASCT. LENA was well tolerated in this elderly population, even among pts treated for ≥2 ys. Further investigations on immunomodulatory drugs as maintenance in these high-risk pts are warranted.

Keywords: diffuse large B-cell lymphoma (DLBCL); elderly; lenalidomide.

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ESTIMATION OF LONG-TERM SURVIVAL WITH POLATUZUMAB VEDOTIN PLUS BENDAMUSTINE AND RITUXIMAB FOR PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (R/R DLBCL)

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Background: To inform payers/HTA organisations regarding estimated survival benefits when all events have not occurred, statistical methods are used to model projected clinical benefits/costs of new interventions. We estimated overall survival (OS) benefit associated with polatuzumab vedotin (pola) + bendamustine (B) + rituximab (R) vs BR alone in patients (pts) with R/R DLBCL.

Methods: Data from a Ph2 randomised controlled trial (RCT; GO29365; NCT02257567; Sehn et al, ASH 2018) of pola-BR vs BR in pts with R/R DLBCL were used (N = 80; follow up 27.6 months [mo]). Most disease progression events occurred ≤12 mo from treatment initiation, after which fewer events were observed, causing Kaplan–Meier estimates of progression-free survival (PFS) and OS to plateau (Fig. A). A mixture model was therefore explored alongside standard parametric survival models (Fig. B). Mixture models combine two processes: (1) OS for pts who died from the disease; (2) OS for long-term survivors (LTS; pts who had not died from their disease, informed by life tables given pts' age/gender/nationality). The mixture model was fitted to the RCT data; from this, the proportion of LTS is estimated. We explored two survival models for each treatment arm: OS (Bansal et al. MDM 2019) and OS informed by PFS. Mean OS was estimated by the area under the curve. Two datasets were used to validate the predictions: (1) pooled Ph2 pola-BR (N = 40) and Ph1b pola-BR data (N = 6; max. follow up 45.9 mo); (2) a Ph2 trial (NCT01691898; ROMULUS; Morschhauser et al. ASH 2014) of pola-R (R/R DLBCL; N = 39; max. follow up 49.5 mo).

Results: Estimated mean OS (assuming a Weibull distribution) was between 1.9 yrs (parametric model) and 4.7 yrs (mixture model) for pola-BR, vs 0.8 yrs for BR (both models). When modelled, most pts who died from their disease died within ~2 yrs; those who did not, could be considered LTS. Fig. B shows the mixture model extrapolations (purple/green dashed lines). From these extrapolations, the proportion of LTS was derived: when modelled using PFS, the estimated proportion of LTS was 21% (95% CI 16–27%) for pola-BR vs 0% (95% CI 0–2%) for BR; when estimated using Ph2 OS data, the predicted proportion of LTS was 38% for pola-BR (95% CI 31–42%) vs 9% for BR (95% CI 1–21%). Survival predictions were in line with those from the pooled GO29365 dataset (Fig. B solid lines) and ROMULUS (not shown). Of the extrapolation methods tested, mixture model predictions were best aligned with pooled pola-BR survival data over parametric survival analysis. Sensitivity analysis showed that censoring (at time of initiation) pts who had received stem-cell transplant/chimeric antigen receptor T-cell therapy had no impact on the estimates, suggesting the effects were due to pola-BR and not subsequent therapy.

Conclusion: These models suggest that pola-BR is associated with a 4-year increase in life-years and at least a fourfold increase in the proportion of LTS vs BR alone.

Figure: (A) GO29365 Ph2 survival data (N=40 per arm) and parametric extrapolations;
(B) Comparison of pola-BR extrapolation models and pooled Ph1b/2 GO29365 data (N=46)
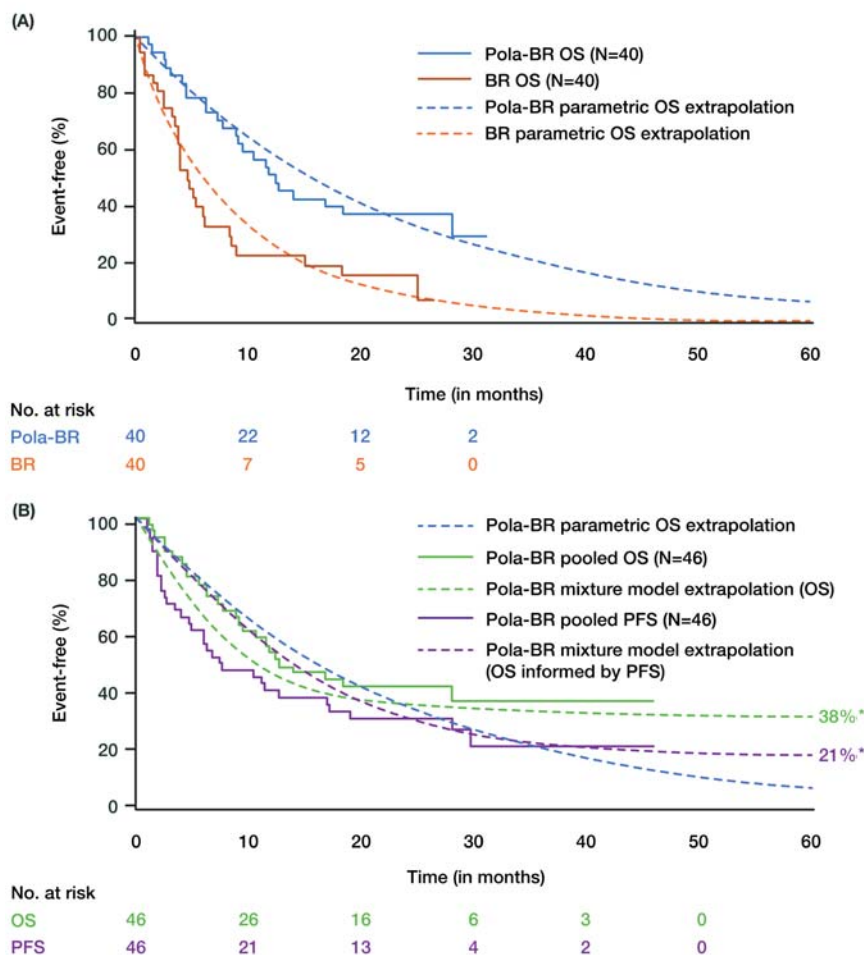
*Estimations of LTS proportions are in line with plateaus shown in the mixture models, these do not directly refer to a particular time point on the curve

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LENALIDOMIDE PLUS R-GDP (R2-GDP) IN RELAPSED/REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA. PRELIMINARY RESULTS OF THE R2-GDP-GOTEL TRIAL

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Introduction: Lenalidomide is an immunomodulatory drug that can reverse rituximab refractoriness in lymphoma patients (pts). We conducted an open label multicenter phase 2 trial testing the synergism of a combination of lenalidomide and rituximab (R2) plus GDP schedule (R2-GDP) in Relapsed/Refractory Diffuse Large B Cell Lymphoma (R/R DLBCL) pts, not suitable for autologous stem cell transplant (ASCT).

Methods: Patients > 18 years of age with R/R DLBCL, ECOG performance status 0-2, adequate organ function, having received previously at least 1 prior therapy including rituximab, and not candidates for ASCT were eligible. Treatment consisted in an induction phase up to a maximum of 6 cycles with lenalidomide 10 mg administered po days 1-14, rituximab 375 mg/m2 iv day 1, cisplatin 60 mg/m2 iv day 1, gemcitabine 750 mg/m2 iv d1 and 8 and dexamethasone 20 mg d1-3. Pts without disease progression (DP) entered into a maintenance phase with lenalidomide (LEN) 10 mg, or last LEN dose received in the induction phase, d1-21 in cycles every 28 days. Primary endpoint was overall response rate (ORR) by investigator assessment. Secondary endpoints included disease free survival (DFS), event free survival (EFS), median overall survival (OS), safety and response by cell of origin (COO), type of DLBCL (double-triple hit, double expressors) and other microenvironment and genomic biomarkers.

Results: 79 pts with R/R DLBCL were enrolled between April 2015 and September 2018. Median age was 71 years, 48,7% women. Primary refractory DLBCL in 31 cases (39,2%). 76 pts were considered for efficacy in the intention to treat (ITT) analysis and 78 for safety. With a median follow-up of 13 months at the time of cut-off (December 2018), ORR was 59,21% with 31,58% complete responses (CR) and 27,63% partial responses (PR). In the primary refractory population ORR was 45,16% with 22,58% CR and 22,58% PR. Median event free survival (EFS) was 12,0 months (7,8-16,1 months). Most common grade 3/4 (G3/4) events were thrombocytopenia (60,26%), neutropenia (56,1%) and anemia (26,92%). Febrile neutropenia occurred in 14,10% pts. Most frequent non-hematologic G3/4 events were asthenia (16,67%), respiratory infection (6,41%) and hypocalcemia (5,13%). There were 4 toxic deaths related to the R2-GDP schedule.

Conclusions: LEN with Rituximab and GDP (R2-GDP schedule) is feasible and highly active in R/R DLBCL. Results in the primary refractory DLBCL population are particularly appealing. Analysis of COO and immune and genomic biomarkers are pending to ascertain if there are subpopulations that may obtain greater benefit with this combination.

Keywords: diffuse large B-cell lymphoma (DLBCL); gemcitabine; lenalidomide.

Disclosures: de la Cruz-Merino, L: Research Funding: *Celgene.*

TABLE 1

Response status	R/R DLBCL	Primary Refractory DLBCL
ORR	59,21%	45,16%
CR	31,58%	22,58%
PR	27,63%	22,58%
SD	9,21%	12,90%
PD	31,58%	41,94%

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MSKCC EARLY EXPERIENCE USING RADIOTHERAPY AS A BRIDGING STRATEGY FOR RELAPSED DIFFUSE LARGE B CELL LYMPHOMA BEFORE CD19 CAR T THERAPY

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Patient	Age at RT	Diagnosis	Original stage	Prior therapies	Staging prior to RT bridging	Irradiated sites	RT dose (Gy)	RT fractions	In field response after RT bridge	CAR product	CRS	Neurotox	Day +30 response	Day +90 response
1	66	DLBCL - CD5+	IV	4	IV	R leg	20	5	PMR	JCAR017			PMR (near CMR)	PD
2	77	DLBCL - CD5+	IV	4	bulky IV	Right sciatic nerve and pelvis	20	5	PMR	EGFRt/19-28z/4-1BBL "Armored"	Grade 1	Grade 3	CMR	PD
3	69	DLBCL - ABC (tFL)	IIIA	2	III	Bilateral neck	33	11	PMR	JCAR017			CMR	CMR
4	61	DLBCL - GC	I*	2	IIA	Right groin	46.8	26	PD	AxiCel	Grade 1	Grade 1	CMR	CMR
5	34	DLBCL - EBV+	IVB*	3	IV	Left iliac bone and sacrum	20	5	PMR	AxiCel	Grade 2	Grade 3**	CMR	CMR
6	54	DLBCL - GC	IV	2	IV	1. R wrist 2. R femur 3. R femur	1.27 2-3.30	1.9 2-3.10	PMR	AxiCel	Grade 3	Grade 3	CMR	
7†	72	DLBCL - GC (tFL)	IV*	8	IV	L abdomen	20	5	PMR	JCAR017				
8†	48	DLBCL - GC (tFL)	IV	5	IV	Larynx	20	5	SD	AxiCel	Grade 1			
9†	72	DLBCL - GC	IV	1	IV	L scapula and soft tissue	20	5		tisagen-lecleucel				
10†	39	DLBCL - ABC	II	2	III	Right neck	30	20 (BID)		AxiCel				
11†	55	DLBCL - ABC	IIIS*	2	I	Spleen	30	20 (BID)		AxiCel				

Figure: Cohort details of patients who received RT bridge therapy prior to CD19 CAR T. Abbreviations: ABC – reflects non-germinal center histology by Hans algorithm; GC – germinal center histology by Hans algorithm; tFL – suspected transformed follicular lymphoma; PMR – partial metabolic response; SD – stable disease, PD – progressive disease; AxiCel – axicabtagene ciloleucel; CRS – cytokine release syndrome. For original stage, * reflects primary refractory. ** Patient developed severe, generalized cord edema and lower extremity paresis that ultimately improved with rehabilitation, this was felt to be potentially attributable to prior checkpoint inhibitor exposure along with RT. †Patient currently undergoing or recently completed treatment and updated results will be presented at ICML Meeting.

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Introduction: CD19-targeted chimeric antigen receptor T cell (CAR T) therapies have remarkable overall response rates (ORR) for relapsed diffuse large B cell lymphoma (DLBCL). There is strong rationale to use a radiotherapy (RT) bridge during cellular manufacturing including palliation, local control and cytoreduction with limited count impact. Recent data from our institution suggests RT may also augment an immune response and sensitize antigen negative cells to CAR-mediated death. This series details our early experience using RT conditioning.

Methods: 11 patients (median age 61 years) with DLBCL (n = 8) or transformed follicular lymphoma (n = 3) were analyzed. Overall, patients had a median of 2 prior therapies (range 1-8) including 3 with auto transplant, 3 with distant RT and 1 with CAR T infusion. Several CAR products were used, including axicabtagene ciloleucel (n = 6), JCAR017 (n = 3, per NCT02631044), tisagenlecleucel (n = 1) and EGFRt/19-28z/4-1BBL "armored" CAR (n = 1, per NCT03085173). Most patients began RT (n = 8) post apheresis with median duration between RT and CAR infusion of 20d (range 13-80). The most common RT regimen (n = 6) was 20 Gy in 5 fractions (range 20-47 Gy) but 2 received our pre-transplant regimen of 30 Gy in 20 BID fractions. None received concurrent chemotherapy with RT but one had a cycle post RT and pre CAR. All had cy/flu lymphodepletion. PET response was evaluated by Lugano criteria.

Results: 2 patients (18%) had limited stage PET avid disease at RT and were treated comprehensively pre-CAR. The remaining 9 were advanced stage, and were treated palliatively to limited sites. Irradiated sites included the neck (n = 4), pelvis/groin (n = 3), intra-abdominal (n = 2) and extremity (n = 2). Most (n = 9) had intensity modulated RT. RT fields were large (median planning treatment volume of 887 cc, range 163-1641). Post RT PET interpretation was challenging given a short interval since RT completion (median 11d) but of 8 evaluable patients, many (n = 6, 75%) had partial response (PR). Though locally controlled, most (n = 7, 88%) had out of field progressive disease (PD) pre CAR. Of 7 evaluable patients post CAR T, no severe adverse events in the RT field were noted, 5 had cytokine release syndrome (n = 1 grade 3) and 4 had neuro-toxicity (n = 3 grade 3). At day 30, ORR was 100%; of 6 evaluable patients, 5 had complete metabolic response (CMR) and 1 had near CMR. Of the 5 evaluable patients at day 90, 3 (60%) had continued CMR and the other 2 (40%) had PD and subsequently died from DLBCL. One relapsed at 95d post armored CAR both in and out of the RT field, and the other relapsed at 64d post JCAR017 primarily out of field.

Conclusions: Use of RT as a CAR T bridging strategy is feasible and associated with excellent pre CAR local control and initial post CAR ORR in a cohort of heavily pre-treated DLBCL patients. We observed moderate serious CAR toxicity that did not appear to be clearly

augmented by RT. Future efforts should clarify the optimal RT timing/dose and assess the potential for incremental immunogenicity with combined therapy.

Keywords: diffuse large B-cell lymphoma (DLBCL); immune system; salvage treatment.

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HIGHLY FAVORABLE OUTCOMES WITH RT FOLLOWED BY ASCT IN LOW/LOW-INTERMEDIATE SECONDARY AGE ADJUSTED IPI REL/REF DLBCL PATIENTS REFRACTORY TO SALVAGE CHEMOTHERAPY

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Introduction: For patients with relapsed or primary refractory (rel/ref) diffuse large B-cell lymphoma (DLBCL) who respond to salvage chemotherapy (ST), high-dose chemotherapy and autologous stem cell transplantation (ASCT) is considered standard of care. Patients with refractory disease to ST, defined as stable disease (SD) or progressive disease (PD), by functional imaging are ineligible for ASCT, and have a dismal prognosis. In practice, we have attempted to salvage these patients with radiation therapy (RT) to residual sites of active disease prior to consolidative ASCT. The outcome of this unique combined modality therapy has not been previously reported.

Methods: We retrospectively reviewed all patients with rel/ref DLBCL who received ST followed by RT and ASCT between the years of 2000 and 2017 at a single center. Only patients with SD or PD as defined by Deauville 5 on the 5-point scale after ST and who had at least 1 year of follow-up were included in this analysis. Survival functions were estimated by the Kaplan-Meier method and compared using a log-rank test.

Results: Thirty-six patients, 12 with rel and 24 with ref disease, with a median age of 43 years (range: 18-66 years) were analyzed. Twenty-three patients had DLBCL while 13 had primary mediastinal B-cell lymphoma (PMBCL). The secondary age-adjusted International Prognostic Index (sAAIPI) for this cohort was as follows: 0 (n = 10), 1 (n = 21), 2 (n = 4), and 3 (n = 1). All patients received ST with subsequent functional imaging showing SD (n = 32) and PD (n = 4) and then went on to receive RT to the sites of disease. Median RT dose was 39.6Gy (range: 30-54Gy). Six patients also received TBI as part of their conditioning regimen prior to ASCT.

With median follow up of 4.0 years (range: 1.0-12.3 years) for survivors, 4-year relapse-free survival (RFS) was 76% and 4-year overall survival (OS) was 80%. There was no significant difference in 4-year RFS for rel versus ref disease (80% v 75%, p = 0.59) nor for DLBCL versus PMBCL (68% v 92%, p = 0.12). By sAAIPI score, 4-year RFS was 80% for a score of 0, 90% for a score of 1, and 0% for scores of 2 and 3. Patients with low- and low-intermediate risk sAAIPI scores of 0 and 1 had improved RFS as compared to patients with sAAIPI scores of 2 and 3 (87% v 0%, p<0.0001).

Conclusions: Patients with chemorefractory rel/ref DLBCL who have had minimal or no response to systemic salvage therapy may benefit from salvage RT to the residual PET-avid disease followed by ASCT, particularly if their sAAIPI score is ≤ 1. The outcome of this retrospective cohort is markedly superior to outcomes described in the literature for this high-risk population and represents a promising treatment paradigm to be further explored. We suggest there may be a role for sequencing this salvage paradigm prior to CAR T-cell therapy.

Keywords: autologous stem cell transplantation (ASCT); diffuse large B-cell lymphoma (DLBCL); salvage treatment.

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POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER IN PATIENTS WITH LYMPHOMA AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introduction: Post-transplant lymphoproliferative disorder (PTLD) is a life-threatening complication after hematopoietic stem cell transplantation (HSCT). PTLD represents a heterogeneous group of abnormal lymphoid proliferations and is generally associated with Epstein-Barr virus infection. Several risk factors for PTLD have been reported, but no studies regarding risk factors in patients with lymphoma have been conducted to date.

Methods: In the national Japanese transplant registry database, 5,270 patients with lymphoma and 34,922 patients with other diseases underwent allogeneic HSCT between 1990 and 2015. Data for these patients were used for analysis. The most common primary disease in patients with other diseases was acute myeloid leukemia or myelodysplastic syndrome (N = 20,472), followed by acute lymphoblastic leukemia (N = 6,808) and chronic myeloid leukemia or myeloproliferative disorder (N = 2,827).

Results: The median age was 47 years (range, 16 to 88) for lymphoma patients and 45 years (range, 16 to 85) for those with other diseases. A total of 31 lymphoma patients and 236 patients with other diseases developed PTLD. The probability of PTLD 2 years after HSCT was 0.77% with a median onset of 217 days (range, 48 to 2,210) for lymphoma patients and 0.80% with a median onset of 127 days (range, 15 to 6,356) for those with other diseases. No difference in the probability of PTLD was found between patients with lymphoma and those with other diseases ($P = 0.98$). In the univariate analysis, the significant factors associated with PTLD development in lymphoma patients were the year of HSCT, donor type, graft-versus-host disease prophylaxis, use of antithymocyte globulin (ATG) in the conditioning regimen, and use of rituximab before HSCT. Among these factors, the year of HSCT (hazard ratio (HR) = 5.6, $P = 0.01$), ATG use (HR = 4.5, $P = 0.004$), and rituximab use (HR = 0.32, $P = 0.01$) were identified as significant variables by multivariate analysis. The probability of PTLD at 1 year was 0.23% for patients who received rituximab but not ATG, 0.74% for those who did not receive either rituximab or ATG, 1.25% for those who received both rituximab and ATG, and 3.99% for those who received only ATG (Figure). The patients who received both ATG and rituximab had a trend of lower probability of PTLD than those who received only ATG (HR = 0.24, $P = 0.08$). Regarding lymphoma subtypes, patients with mature B cell lymphoma had the lowest incidence of PTLD.

Conclusion: Rituximab use before HSCT significantly reduced the risk of PTLD in patients with lymphoma. As patients who receive ATG have a high risk of developing PTLD, adding rituximab to ATG in the conditioning regimen is a good candidate strategy to reduce the risk of PTLD.

Keywords: allogeneic stem cell transplant (alloSCT); post-transplant lymphoproliferative disorders (PTLDs); rituximab.

Probability of PTLD

EXTRANODAL LYMPHOMAS

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DEPTH OF REMISSION FOLLOWING FIRST LINE HP-ERADICATION IS AN INDEPENDENT PROGNOSTIC FACTOR IN GASTRIC MALT LYMPHOMA

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Patients with gastric MALT lymphoma responding to initial HP-eradication have an excellent outcome, and no further oncological therapy is recommended even in the presence of residual disease after antibiotic therapy due to excellent long term prognosis. However, no long term data exist on the influence of initial depth of remission (i.e. CR versus residual disease after response) on PFS in such patients.

In view of this, we have retrospectively analysed the course of patients with gastric MALT lymphoma following initial treatment with focus on HP-eradication. In total, 137 patients with gastric MALT lymphoma (70 f / 67 m) were treated at our institution: 66% had stage I, 23% stage II while the remaining patients had disseminated disease. The MALT-IPI was 0 in 61%, 1 in 33%, 2 in 5% and 3 in 1% of cases.

Out of those patients, 69% were found positive for HP, while 31% were negative by means of histology, breath test and serology. Consequently, 70% were given antibiotics for first line therapy, 24% systemic therapy and 4% local therapy; 4 patients were only watched and were excluded from this analysis. Response was assessed based on histology as defined in the GELA-criteria for no change, responding residual disease (rRD) and probable minimal residual disease (pMRD) as well as complete remission (CR) based on regular follow up biopsies every 3 months for the first two years after therapy and every 6 months afterwards. The median follow-up was 56 months for our cohort. In total, 67% responded to first line therapy as assessed by histology according to the GELA-criteria (48% CR, 19% PR including rRD and pMRD) as judged by best outcome, while 30% had stable disease/no change. Overall, the median PFS for all responders was 68 months and significantly better than for patients with stable disease/no change at 17 months (p < 0.01); furthermore, patients achieving CR had a significantly longer PFS at 95 months versus 29 months for the PR group (p = 0.01); and all differences remained significant after correction for MALT-IPI. Also among the subgroup of HP-positive patients undergoing eradication for first line therapy, the difference between CR and PR remained significant for PFS at 109 months vs 28 months (p = 0.02). However, in terms of overall survival, no difference between CR and PR after initial therapy could be demonstrated.

These data suggest that patients with gastric MALT lymphoma achieving a CR after initial therapy, especially HP-eradication have a significantly longer PFS than patients with residual disease after initial response. In view of these results, patients with PR should probably be followed more closely than after CR.

__Keywords:__ extranodal marginal zone lymphoma of MALT type.

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^{90}Y-IBRITUMOMAB TIUXETAN IN PATIENTS WITH EXTRA-NODAL MARGINAL ZONE B-CELL LYMPHOMA OF MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT LYMPHOMA) – THE ZENO STUDY

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__Introduction:__ Currently, no standard treatments are available for extra-nodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma), which appears to be a radiosensitive tumor. ^{90}Y-ibritumomab tiuxetan (YIT) delivers targeted radiotherapy in specific MALT localizations, avoiding the exposure of other tissues and consequent organ toxicities.

__Methods:__ The aim of this phase II trial was to evaluate the efficacy of a single course of YIT in generating clinical responses in patients with MALT lymphoma in first line or with relapsed/refractory disease. The radioimmunotherapy treatment plan consisted of an initial infusion of rituximab on day 1, then repeated on day 8, immediately followed by a weight-based dose of YIT.

__Results:__ Seventeen patients were enrolled and 16 were evaluable for efficacy analysis as 1 patient refused to undergo YIT due to a drug infusion reaction after the first administration of rituximab. Four out of 16 patients were previously untreated. For the other 12 patients, the median duration of the last response was 13 months. All but 2 (IE,

__TABLE 1__

	Baseline	Nadir (range)	Days from Baseline to nadir
Absolute neutrophil count, cells/mm^3	3400 (1500-6000)	700 (210-2950)	36 (19-52)
Platelets, cells x10^3/mm^3	216 (118-338)	159 (89-121)	33 (19-38)
Hemoglobin, g/dL	13.6 (9.9-16.2)	11.9 (8.8-13.0)	39 (19-56)

intraorbital) presented with a stage IV disease. At 3 months after YIT 10 complete responses (CR, 62.5%), 5 partial responses (PR) and 1 stable disease were observed, leading to an overall response rate of 94%. With a median follow up of 1 year, only 4 patients relapsed (3 from CR and 1 PR). Seven patients are in continuous CR with a median duration of response of 18 months. Adverse events after YIT were only hematologic and transient. The severity of hematologic toxicities (expressed as the lowest, i.e. nadir, concentration of granulocytes, platelets, and hemoglobin reached after radioimmunotherapy) are reported in the table. Grade 3 to 4 thrombocytopenia and neutropenia occurred in 7 patients (43.8%). Four patients (25.0%) received G-CSF; no patients received transfusions.

Conclusions: YIT represents a highly effective and tolerable treatment option for MALT lymphoma, both in first-line and in relapsed/refractory disease setting.

Keywords: extranodal marginal zone lymphoma of MALT type; radio-immunotherapy (RIT).

Disclosures: Zinzani, P: Consultant Advisory Role: *Verastem, MSD, EUSAPHARMA, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, Immune Designa, Celgene, Portola, Roche, Kyowa Kirin.*

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TRANSFORMED MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMAS: A SINGLE INSTITUTION RETROSPECTIVE STUDY INCLUDING PCR-BASED CLONALITY ANALYSIS

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Background: The natural course of mucosa-associated lymphoid tissue (MALT) lymphoma is favorable but histological transformation (HT) to diffuse large B-cell lymphoma (DLBCL) may occur in a small proportion of patients and drastically worsen prognosis. However, only little is known about clonal lymphomagenesis and disease behavior in these patients.

Patients and methods: Given the lack of consistent data on clinico-pathological features and clonal relationship of patients with MALT lymphoma and HT, we have systematically analyzed 379 patients (32% gastric, 68% extragastric; median follow-up 52 months) diagnosed at the Medical University of Vienna 1999 - 2017 for HT, and reassessed tissues of identified patients by PCR-based clonality analysis of both, indolent and aggressive lymphoma.

Results: HT was documented in 12/379 patients (3.2%) and occurred at a median time of 22 months (range; 6-202 months) after initial diagnosis of MALT lymphoma. Development of HT was significantly associated with presence of lymph node- (p<0.001) and bone marrow involvement (p = 0.029). By PCR-based clonality analysis, we detected a clear-cut clonal relationship of MALT lymphoma and DLBCL in 8 of 11 analyzed cases proving that the large majority of DLBCL following MALT lymphoma are clonally-related and constitute a real transformation. Interestingly, HT occurred within the first 2.5 years after diagnosis in patients with clonal relationship, whereas time to aggressive lymphoma was longer in patients identified as clonally-unrelated (most likely secondary) lymphoma (82–202 months), suggesting that HT is an early event in this disease. Survival of patients with HT was poor with 6/12 dying at 1.5-33 months after transformation, however, patients with localized gastric transformation had a superior outcome with only 1/6 dying due to progression of lymphoma.

Conclusion: These data show clearly that the large majority of DLBCL following MALT lymphoma are clonally-related and constitute a real transformation of indolent to aggressive lymphoma. With the exception of localized gastric transformation, however, prognosis is poor in patients with HT.

Keywords: extranodal lymphomas; extranodal marginal zone lymphoma of MALT type; indolent lymphoma.

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INCIDENCE AND TREATMENT OUTCOMES OF PATIENTS WITH TRANSFORMED MARGINAL ZONE LYMPHOMA TREATED WITH RCHOP-LIKE REGIMENS

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Introduction: Transformed marginal zone lymphoma (tMZL) is frequently included among diffuse large B cell lymphoma (DLBCL) cases and is treated in a similar manner. We aimed to define the prevalence of tMZL and compare treatment outcomes to those of patients with non-transformed DLBCL treated with RCHOP-like regimens.

TABLE 1 Baseline tMZL cohort and matching characteristics

	tMZL	non-GCB (matched)	p value
	80	240	
Age	64.5 [35;91]	68.0 [23;94]	0.2
Sex (F)	47 (59%)	121 (50%)	0.3
ECOG >=2	7 (9%)	22 (9%)	1.0
Stage			
I-II	21 (26%)	67 (28%)	0.9
III	14 (18%)	45 (19%)	
IV	45 (56%)	128 (53%)	
Elevated LDH	42 (53%)	126 (53%)	0.9
Treatment regimen			
R-CHOP	65 (81%)	196 (82%)	0.8
R-CHOP/RICE	5 (6%)	11 (5%)	
R-EPOCH	10 (13%)	33 (14%)	

Methods: We included all cases of DLBCL who were treated with RCHOP/RCHOP-like regimens at Memorial Sloan Kettering Cancer Center between 2001 and 2015. Among these we identified all patients with a pathology-confirmed diagnosis of MZL prior-to or at-the time of presentation with DLBCL, divided into treatment-naïve and those who received systemic immunotherapy or chemotherapy prior to transformation. PFS was defined as the time from initiation of RCHOP until progression or death from any cause. We also conducted an event free survival analysis (EFS), excluding progression as indolent MZL not requiring systemic chemotherapy. Survival was compared to all DLBCL cases (data not shown), and to a cohort of non-germinal-center DLBCL matched on age, stage, LDH, ECOG, and treatment regimen, excluding transformed histologies.

Results: We identified 1986 patients with newly diagnosed DLBCL treated with frontline RCHOP, of whom 63 (3.2%) had treatment-naïve tMZL. Of these 23 (37%) had pre-existing MZL (median time to transformation 33m). An additional 17 patients treated with RCHOP at the time of transformation, but with prior systemic therapy for MZL, were analyzed as a separate group (tMZL-Chemo). Fifty-four had ENMZL (68%), 16 (20%) nodal and 10 (13%) splenic. tMZL patients were matched with 240 non-GCB DLBCL cases (table 1). With a median follow-up of 76m from initiation of RCHOP, patients with tMZL had a trend towards a higher rate of progression (7yPFS of 44% for tMZL vs. 60% for DLBCL, p = 0.09). However, EFS, which excluded progressions as indolent MZL not requiring systemic chemotherapy, was similar (7yEFS 59% tMZL vs. 60% DLBCL, p = 0.64). Patients with tMZL who had received prior systemic rituximab or chemotherapy had a worse PFS and EFS (7yPFS 15% 7yEFS 35%, p<0.0001 vs. DLBCL). OS was similar between the groups (7yOS 72% tMZL vs. 68% DLBCL vs. 53% MZL-Chemo, p = 0.2) (figure 1).

Conclusions: tMZL represents 3% of newly diagnosed DLBCL cases and has a similar overall survival compared with non-transformed DLBCL non-GCB. To the best of our knowledge this is the largest tMZL cohort to be reported and the first to evaluate the prevalence and natural course of tMZL as compared to DLBCL.
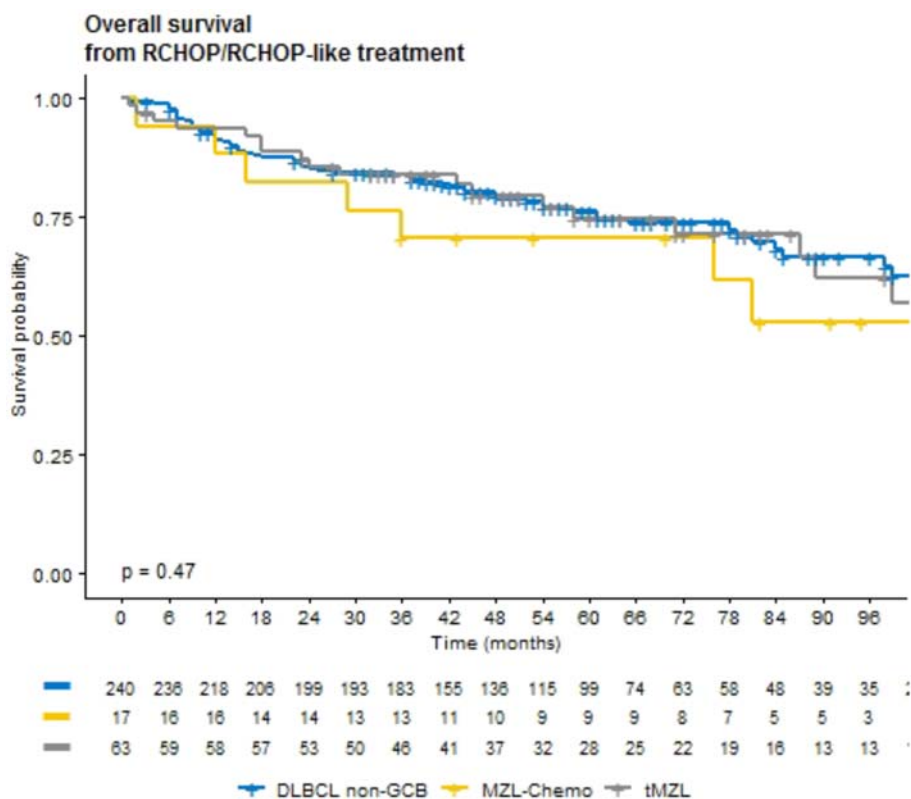
Overall survival from RCHOP/RCHOP-like treatment

	240	236	218	206	199	193	183	155	136	115	99	74	63	58	48	39	35
	17	16	16	14	14	13	13	11	10	9	9	9	8	7	5	5	3
	63	59	58	57	53	50	46	41	37	32	28	25	22	19	16	13	13

DLBCL non-GCB — MZL-Chemo — tMZL

p = 0.47

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ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA PATIENTS RELAPSING AFTER HIGH DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION: DATA FROM THE JAPAN SOCIETY FOR HEMATOPOIETIC CELL TRANSPLANTATION (JSHCT) REGISTRY

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Introduction: The outcome of primary mediastinal large B-cell lymphoma (PMBL) has been significantly improved by the addition of rituximab to CHOP-like or dose adjusted EPOCH. And high dose chemotherapy with autologous stem cell transplantation (HDT/ASCT) has been reported to be effective for relapsed or refractory (rel/ref) PMBL patients. However, PMBL patients relapsing after HDT/ASCT have few options of cure.

Methods: We have retrospectively analyzed the detailed records on allogeneic hematopoietic stem cell transplantation (AlloSCT) in PMBL patients relapsing after HDT/ASCT in the JSHCT registry. The objectives were to determine overall survival (OS), relapse rate, progression-free survival (PFS), non-relapse mortality (NRM) and GVHD rate following AlloSCT.

Results: Between 2004 and 2016, 23 PMBL patients relapsing after HDT/ASCT underwent AlloSCT. The median patient age was 33 years (range, 21 to 63 years). The median time from diagnosis to AlloSCT and HDT/ASCT to AlloSCT were 23 months (range, 11 to 168) and 11 months (range, 3 to 120), respectively. Disease status at AlloSCT were CR (or CRu) for 2 patients(pts), PR for 6 pts and refractory for 15 pts. Five, 4 or 7 pts received transplants from matched related, mismatched related or matched unrelated donors, respectively. Seven pts had cord blood transplantation. Myeloablative conditioning regimen was used in 7 pts, whereas reduced intensity regimen was used in 16 pts. Two out of 6 pts in PR prior AlloSCT and 6 out of 15 pts in refractory prior AlloSCT achieved CR following AlloSCT. Grade II-IV acute GVHD occurred in 11 pts and chronic GVHD occurred in 3 pts. After a median follow-up of 3.1 years among surviving patients, the estimated 3-year OS and PFS were 48.8% (95% CI, 26.3-68.1%) and 32.6% (95% CI, 14.2-52.6%), respectively. The 1-year relapse rate was 46.3% (95% CI, 24.9-65.2%), whereas NRM was 17.3% at 100 days. Patients in CR after AlloSCT had significantly better OS and PFS (P = 0.001 and P<0.001, respectively)

Conclusions: AlloSCT may provide durable response even in the chemo-refractory patients with PMBL relapsing after HDT/ASCT. The remission status after AlloSCT correlated with a prolonged OS and PFS.

Keywords: allogeneic stem cell transplant (alloSCT); primary mediastinal large B-cell lymphoma (PMLBCL).

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PROGNOSTIC FACTORS (PFs) IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL) TREATED WITH RITUXIMAB-CHOP (RCHOP) ± RADIOTHERAPY (RT)

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TABLE 1

FFP: Multivariate Analysis				LSS: Multivariate Analysis			
Factor	HR	95% CI	p-value	Factor	HR	95% CI	p-value
E/IV	2.52	1.50-4.23	<0.001	E/IV	2.71	1.26-5.86	0.011
LDH ≥2x	1.68	1.00-2.82	0.05	Bulk	4.40	1.32-14.64	0.016
FFP: Prognostic Models				**LSS: Prognostic Models**			
Factors (#)	Pts [# (%)]	5-year FFP	p-value	Factors (#)	Pts [# (%)]	5-year LSS	p-value
Model 1: E/IV and LDH ≥2x				**Model 1: E/IV and LDH ≥2x**			
0	151 (48%)	89.5%		0	151 (48%)	96.4%	
1	121 (39%)	72.9%	<0.0001	1	121 (39%)	83.6%	0.0014
2	41 (13%)	62.0%		2	41 (13%)	80.8%	
Model 2: E/IV and Bulk				**Model 2: E/IV and Bulk**			
0	74 (26%)	88.7%		0	74 (26%)	98.6%	
1	134 (47%)	81.2%	0.0009	1	134 (47%)	90.8%	0.0002
2	78 (27%)	64.5%		2	78 (27%)	76.6%	

HR = Hazard Ratio; 95% CI = 95% Confidence Intervals; E/IV = any extranodal involvement

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Introduction: RCHOP provides satisfactory results in PMLBCL, minimizing failure rates, but PFs have not been sufficiently evaluated, since only 2 moderately-sized studies have appeared so far including 96 and 123 patients (pts) from British Columbia and Japan, respectively. In the presence of R-da-EPOCH, a potentially better but also more toxic regimen compared to RCHOP, a reliable prognostic classification of PMLBCL is urgently needed, in order to define subgroups of pts at high- or very low-risk for treatment failure and death.

Aims: The identification of PFs for the outcome of pts with PMLBCL treated with RCHOP±RT.

Methods: 325 pts with PMLBCL ≤65 years old were treated with RCHOP±RT (usually 6-8 cycles) in a multicenter setting in Greece and Cyprus. The following potential PFs were evaluated: Age (median 32; range 16-65), gender (female 65%), B-symptoms (32%), stage III/IV (14%), infradiaphragmatic disease (10%), any extranodal involvement (E/IV, 37%), any serositis (45%), bulky disease (≥10 cm; 63%), performance status (PS) ≥2 (14%), LDH levels (elevated 83%; ≥2x, 27%), anemia (38%), leukocytosis ≥10x10^9/L (26%), ESR ≥50 mm/h (39%), albumin <4 g/dL (46%), age-adjusted IPI (aaIPI; ≥2 in 22%).

Results: At amedian follow-up of 64 months (2-198), 68 failures and 34 deaths were recorded (including 2 unrelated deaths) for a 5-yearfreedom from progression (FFP) of78% and both 5-year overall survival (OS) and lymphoma specific survival (LSS) of 89%. The aaIPI was moderately predictive with 5-year FFP of 82% vs. 71% for aaIPI 0-1 vs 2-3 (p = 0.04). On univariate analysis, extranodal involvement (E/IV), bulky disease, and low albumin were significantly associated with both inferior FFP and LSS, infradiaphragmatic disease and LDH ≥2x only with FFP, while any serositis and anemia only with LSS. The results of multivariate analysis and the respective prognostic models are shown in the table.

Conclusions: In the largest pt series with PMLBCL reported so far, RCHOP±RT provided long-term disease control and LSS rates of 78% and 89%. The combination of any extranodal involvement (E/IV) with either bulky disease or LDH ≥2x defined high-risk subgroups (13-27% of pts) with ~20-23% mortality. More importantly, their absence defined subgroups comprising ~1/4 or 1/2 of the pts, with 10-11% risk of failure and only 1.5% or 3.5% 5-year mortality, who might not benefit from intensified treatment as R-da-EPOCH.

Keywords: primary mediastinal large B-cell lymphoma (PMLBCL); prognostic indices.

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IS IT RADIOTHERAPY NECESSARY FOR PRIMARY MEDIASTINAL B-CELL LYMPHOMA (PMBL) PATIENTS ACHIEVING PET NEGATIVITY AFTER IMMUNOCHEMOTHERAPY?

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Introduction: Primary mediastinal B-cell lymphoma (PMBL) has specific clinical and biological characteristics. The current standard of therapy is based on immunochemotherapy which means rituximab and anthracycline based chemotherapy (R-CHT), either CHOP, CHOEP or DA-EPOCH or more intensive chemotherapy. Radiotherapy (RT) consolidation has been a standard especially in pre PET era. Although the RT has started to be skipped now in situation of complete metabolic response after R-CHT, there is lack of data to answer this question. Primary objective of this analysis is to compare PFS and OS of PMBL patients who achieved PET negative response after R-CHT according to RT.

Methods: Patients (pts) with confirmed diagnosis of PMBL observed in NiHiL project (NCT03199066) were included. Pts have to be treated with R-CHT and PET/CT has to be performed at the end of the immunochemotherapy. Response criteria according to Cheson 2007 were used. Only pts who achieved PET negativity could be included for primary analysis. The indication of RT was based on center/physician decision. PFS and OS were calculated since the time of dg.

Results: Altogether 190 PMBL pts diagnosed between 6/2002 and 8/2017 fulfilled the inclusion criteria and were included. The age median was 36 years (range 18-78) with slight female predominance (56.8%). The localized stage I-II was observed in 69.5%; low or low-intermed IPI in 79.5% pts. All patients received R-CHT (CHOP 57.9%, DA-EPOCH or CHOEP 8.9%, intensive regimens 32.6% and 1pt received ICE as primary CHT). High dose therapy and ASCT as part of the induction was performed in 27.9% pts. At the end of R-CHT (including ASCT) 136 (71.6%) pts. achieved PET negative remission (PET-neg), 43 (22.6%) were PET positive (PET-pos) and the finding was inconclusive (PET-un) for 11 (5.8%) pts. Median follow up was 4.5 years. OS probability at 5y was 89.4% vs 80.0% vs 70.0% for PET-neg vs PET-un vs PET-pos resp. (p = 0.002). Out of 136 PET-neg pts the radiotherapy was used in 54 (39.0%) and 83 (61.0%) were observed (OBS). There was insignificant trend for better PFS probability at 5y for RT group (95.5%) vs OBS group (85.4%) with 3.85 times increased risk for progression or death in OBS arm (HR 3.86; 95%CI; 0.96-8.77; p = 0.0585). There was insignificant trend for better 5y OS probability for RT group (97.6%) vs OBS group (90.2%) with 4.7 times increased risk of death in OBS arm (HR 4.71; 95%CI; 0.77-13.02; p = 0.1098).

Conclusion: The radiotherapy use in PMBL patients who achieve PET negativity at the end of immunochemotherapy remains controversial. Our observational analysis failed to show statistically significant benefit of radiotherapy, however from the clinical point of view, the numeric difference 10% and 7.5% resp. in 5 years progression free survival and overall survival probability resp. could be viewed as the important one esp. when therapy de-escalation is discussed. The results of randomized IELSG-37 study (NCT01599559) could bring more information in the future.

Keywords: positron emission tomography (PET); primary mediastinal large B-cell lymphoma (PMLBCL).

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PD-1 INHIBITOR PLUS CHEMOTHERAPY IN RELAPSED/REFRACTORY PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL) WITH AGGRESSIVE BULKY DISEASE

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Background: Primary mediastinal large B-cell lymphoma (PMLBCL) is an aggressive type of diffuse large B-cell lymphoma (DLBCL) and represents a molecular signature reminiscent of classical Hodgkin's lymphoma (cHL). The frontline therapy is very effective in PMBCL, but relapsed/refractory PMLBCL (rrPMLBCL) generally has limited treatment options and dismal prognosis. Monotherapy of PD-1 inhibitor was reported to induce an effective clinical response and was approved for the treatment of patients with rrPMLBCL by FDA in 2018. However, PD-1 inhibitor is not recommended for treatment of rrPMLBCL patients with life-threatening tumor burden (bulky disease) who require urgent cytoreductive therapy. We aimed to develop a salvage therapy for patients with aggressive bulky disease.

Methods: This ongoing trial is enrolling patients with rrPMLBCL who have bulky disease (minimum measurement must be >5 cm in the longest diameter) with aggressive phenotype, rapid progression and fatal prediction. All patients have been heavily treated with rituximab-containing regimens, and have relapsed or refractory disease after ≥ 2 lines of prior therapy. Enrolled patients received GVD chemotherapy regimen (Gemcitabine, Vinorelbine and Doxorubicin, day 1) plus PD-1 antibody SHR-1210 (4 mg/kg, day 2) every 3 weeks. Treatment

duration was up to completion of 12 cycles or until progressive disease (PD) or unacceptable adverse events (AEs) occurred or upon patient request to discontinue therapy. Safety was assessed by CTCAEv4.0 in the population consisted of all patients who received ≥ 1 dose of study drug. Clinical response was evaluated by computed tomography (CT) every two cycles and by positron emission tomography-computed tomography (PET-CT) every 4 cycles using International Working Group (IWG) Response Criteria. Peripheral blood samples were collected before every cycle and tumors were biopsied prior to initiation of therapy for relevant biomarker analysis. The primary end points were safety/tolerability and objective response rate (ORR). Key secondary end points were complete response rate (CRR), progression-free survival (PFS) and overall survival (OS).

Interim Results: At the analysis cutoff date (March 10, 2019), 29 rrPMLBCL patients were enrolled: median age 30 years (range: 16 - 45), 52% female (15/29), median 3 lines of prior therapy (range: 2 - 6), median 6 cycles of rituximab-containing regimens (range: 2 - 10), median aaIPI score 2 (range: 1 - 4). Median follow-up duration was 11.8 mos (range: 6.2 - 19.9). 26 patients had completed the first efficacy assessment: 12 CR, 7 PR, 3 SD and 4 PD; ORR 73% and CRR 46%. median PFS and OS were not reached, and all responders were still alive at data cutoff.

ClinicalTrials.gov (NCT03346642)

Keywords: chemotherapy; PD-1; primary mediastinal large B-cell lymphoma (PMLBCL).

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TEMOZOLOMIDE IN RELAPSE/REFRACTORY PRIMARY VITREO-RETINAL LYMPHOMA (R/R PVRL): A SIMPLE, CHEAP, EFFECTIVE AND WELL TOLERATED TREATMENT. RESULT OF THE LARGEST STUDY ON R/R PVRL, FROM THE LOC NETWORK

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Background: Primary vitreoretinal lymphoma (PVRL) is a very rare subset of non Hodgkin lymphoma. The main adverse evolution is central-nervous system localization which arise in more than 1/3 of

Progression free survival

Time from Temozolomide initiation

Patient at risk
21 15 9 6 6 5 5 4 3
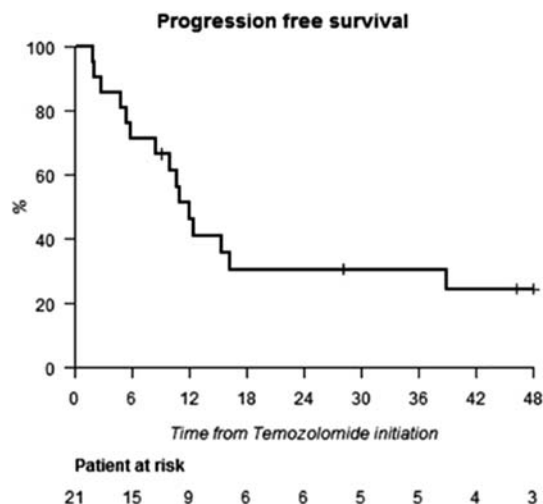
patients at 4 years. Publications in this field are very limited and no consensus or recommendations exist. Temozolomide is used in first line gliobastoma and has been described effective in some cases of CNS lymphoma.

Purpose: To evaluate the efficacy and safety of temozolomide for the treatment of relapsed or refractory (R/R) primary vitreoretinal lymphoma or as front-line therapy in patients not eligible for intensive treatment.

Patients and methods: From March 2008 to January 2018, immunocompetent adults with R/R PVRL or patients not eligible for intensive treatment were treated with oral temozolomide (TMZ) monotherapy at a dose of 150 or 200 mg/m^2 for 5 days a month every 4 weeks.

Results: Twenty-one patients were treated. Two patients received TMZ as first-line therapy, two patients had undergone autologous stem cell transplantation (ASCT) prior to treatment with TMZ, one patient had relapsed after treatment with lenalidomide and two other patients had relapsed after treatment with ibrutinib. Median age was 75 years (range: 35-90) and median follow-up was 42 months. Overall response rate was 81%: 15 patients (71%) achieved complete remission and two (10%) had a partial response. The median duration of response was 10.9 months (range: 3-109) and median progression-free survival was 12 months [95%CI: 8-NR]. TMZ was well tolerated and there was no unexpected toxicity.

Conclusion: TMZ is an attractive therapeutic option in patients with R/R PVRL or as front-line therapy in patients not eligible for intensive treatment, with a high response rates and good tolerance, even in patients who have become resistant to treatment with ibrutinib, lenalidomide or ASCT. In economic terms, this treatment is far less expensive than other new medications.

Keywords: B-cell lymphoma; primary CNS lymphoma (PCNSL); temozolomide.

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CLINICAL FEATURES, TREATMENT AND OUTCOME OF NEUROLYMPHOMATOSIS: SINGLE INSTITUTION EXPERIENCE

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Introduction: Neurolymphomatosis (NL) is a highly rare disorder defined as infiltration of peripheral nervous system by a lympho-proliferative neoplasm, both presented as the first manifestation of the malignancy (primary NL) or as a site of disease progression or relapse (secondary NL). Clinical features of NL and best approach are still widely unknown.

Methods: We retrospectively reviewed clinical records of all histologi-cally confirmed-NL, diagnosed and treated at the Hematology Depart-ment of Mayo Clinic in Rochester MN between January 2002 and December 2018.

Results: Over a 16-year period 40 patients were diagnosed with NL. Primary and secondary NL were 18 (45%) and 22 (55%) respec-tively, with a median age of 60.5 years (range 37-83) and male sex 24/40 (60%). The majority had B-cell lymphomas (39/40 patients): 27/40 (60%) with diffuse large B-cell lymphoma (DLBCL) and only 1 case of T-cell lymphoma. The affected structures included peripheral nerves in 16/40 cases, spinal nerves (12/40), neural plexus (14/40), cranial nerves (4/40), cauda equine (6/40); multiple sites were involved in 13/40. 4/40 cases had brain involvement and cerebrospi-nal fluid (CSF) was positive in 7/29. NL clinical manifestations included muscular weakness (33/40 patients), sensory deficit (32/40), pain (28/40) and autonomic dysfunction (3/40). Magnetic resonance imaging (MRI) detected neural abnormalities in 35/36 cases (97%), CT imaging identified disease in 3/8 (37%) and FDG-PET scan was posi-tive in 22/31 (71%); electromyography showed some grade of neu-ropathy in 28/29 cases. Treatment included systemic chemotherapy in 38/40 patients, containing high dose methotrexate (HD-MTX) in 26/40(65%) and rituximab in 20/40 (50%); 11/39 (28%) patients underwent consolidative autologous stem cell transplant; 4/40 received consolidative radiotherapy (RT) and 1/40 was managed with RT alone; intrathecal chemotherapy was infused in 1/40 cases; one patient with solely great auricular nerve NL involvement was cured with surgery only. Treatment efficacy evaluated by imaging and clini-cal improvement consisted with an overall response rate of 73% (27/37) with a 51% (19/37) rate of complete remission (CR); the rates of CR reached with HD-MTX regimens and other systemic treatments were 56% (13/24) and 42% (5/13) respectively. The median overall survival (OS) was 137.8 months with a 48-months OS 73%. A trend of longer survival rate for primary NL, although no statistically
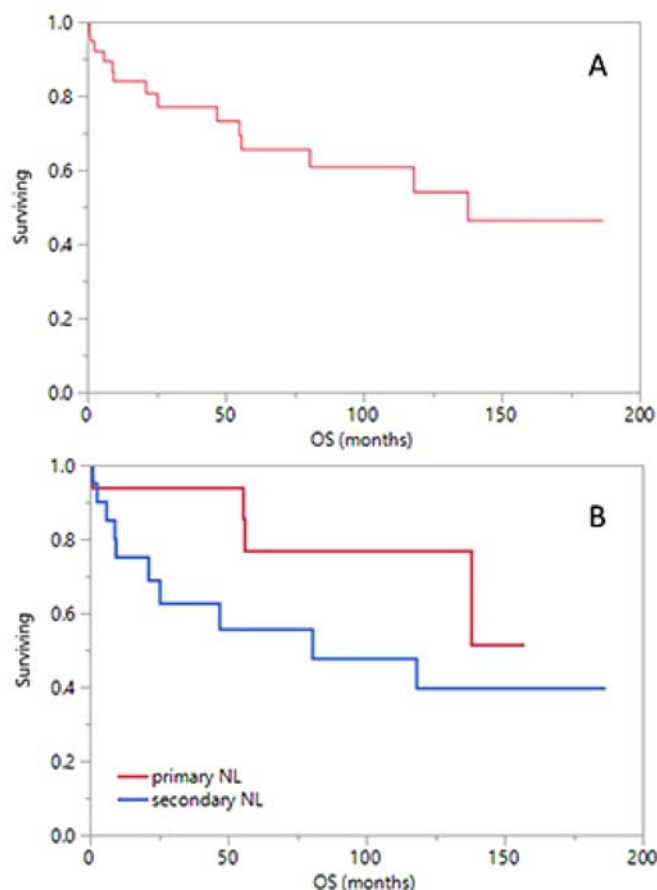
Figure 1. Kaplan-Meier Curves of Overall survival (OS) of global population (median OS 137.8 months; 40 patients) (A), and patients with either primary NL (median OS not reached; 18 patients) or secondary NL (median OS 80.7 months; 22 patients) (B). Median Follow-up 45.1 months.

significance, was observed, with a 48-month OS of 94% vs 56% for secondary NL (p 0.134). (Figure 1)

Conclusions: In our retrospective cohort of NL, DLBCL represent the predominant histologic subtype; MRI appeared to be the most accurate radiological tool to detect relevant neural disease; primary NL showed a trend of better prognosis with high rates of prolonged survival; HD-MTX - containing regimens are associated with higher rates of deep response.

Keywords: extranodal lymphomas; immunochemotherapy; non-Hodgkin lymphoma (NHL).

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BICENTRIC PILOT STUDY ON AGE-ADAPTED HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT IN NEWLY DIAGNOSED PRIMARY CNS LYMPHOMA PATIENTS > 65 YEARS - MARiTA TRIAL

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Introduction: Intensive chemo(immuno)therapy followed by high-dose chemotherapy and autologous stem cell transplantation (HCT-ASCT) is widely regarded standard treatment for younger patients with primary central nervous system lymphoma (PCNSL). Although elderly PCNSL patients are able to tolerate intensive systemic therapy, such approaches are often only offered to patients younger than 65-70 years. However, similar to experience in myeloma and systemic lymphoma, it has been shown that a selected subgroup of elderly patients is eligible for HCT-ASCT (Schorb et al. BMT 2017). The rationale of this study is to prospectively determine efficacy and safety of HCT-ASCT in elderly PCNSL patients.

Methods: This is a prospective, single-arm, pilot study conducted at two German centers (DRKS 00008900). Main eligibility criteria included newly diagnosed PCNSL, immunocompetency, age > 65 years, ECOG PS ≤ 2, and adequate organ function. Induction treatment consisted of 2 cycles (21 days): methotrexate 3.5 mg/m² (day 1), cytarabine 2 g/m² twice daily (days 2 and 3) and rituximab 375 mg/m² before and after each chemotherapy; stem cell harvest after 1st cycle. Subsequent consolidation with HCT-ASCT included: Busulfan 3.2 mg/kg on day -7 and -6, thiotepa 5 mg/kg/d on day -5 and -4 and reinfusion of stem cells on day 0. Main endpoints included toxicity, lymphoma response, progression free survival (PFS) and overall survival (OS).

Results: Fourteen patients were included between Dec 2015, and Sept 2017. Median age and Karnofsky performance score were 73 years (range 69-79 years) and 80% (range 30-90%), respectively. 13 of 14 patients responded to induction treatment (2 with complete remission (CR), 11 with partial remission (PR), 1 patient with premature end of treatment was not evaluable and considered not responding). 13 of 14 patients commenced HCT-ASCT; 30 days after HCT-ASCT 12/13 patients achieved CR and 1/13 PR. No treatment related deaths were recorded. After a median follow-up of 30 months, one patient developed progressive disease 9 months after HCT-ASCT and died due to lymphoma progression later on. All other patients are in complete remission. Respective 2-year PFS and OS rates were 92% (95% CI 79% to 100%) and 89% (95% CI 71% - 100%).

Conclusions: In selected elderly PCNSL patients age-adapted induction treatment followed by HCT-ASCT with thiotepa and busulfan is safe and effective. Further details will be presented at the meeting. A phase II study in Germany (MARTA trial, DRKS 00011932) is currently investigating this approach in a multicenter setting.

Keywords: autologous stem cell transplantation (ASCT); elderly; primary CNS lymphoma (PCNSL).

PTCL AND NK/T CELL LYMPHOMAS

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MEMBRANE EXPRESSION OF NK RECEPTOR KIR3DL2 CONTRIBUTES TO DELINEATE THE ACUTE-TYPE AND IS A THERAPEUTIC TARGET IN ADULT T-CELL LEUKEMIA/LYMPHOMA

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Introduction: Adult T-cell leukemia/lymphoma (ATL) is a lymphoid neoplasm of CD4+ T lymphocytes caused by the human T-cell leukemia virus type I (HTLV-1), which is classified into 4 clinical subtypes (ie, smoldering, chronic, acute, and lymphoma). Natural killer receptors (NKRs) were previously identified on T-cell lymphoma.

Methods: NKRs expression was assessed by flow-cytometry and immunohistochemistry on peripheral blood samples (n = 55) and biopsies (n = 21) obtained from 50 ATL patients. Array-based analysis of genomic DNA methylation patterns of *KIR3DL2* promoter was assessed. To explore the role of HTLV-1 on KIR3DL2 expression, KIR3DL2 and *TAX* mRNA expressions were assessed on primary ATL cells and on activated CD4+ T cells that were infected with HTLV-1 *in-vitro*. *Ex-vivo* autologous antibody dependent cell cytotoxicity (ADCC) was performed on sorted primary ATL cells with IPH4102, a monoclonal anti-KIR3DL2 antibody that has shown robust clinical activity in Phase I in patients with relapsed Sézary Syndrome (NCT02593045).

Results: KIR3DL2 was the only detected NKR, mainly expressed on acute- compared to lymphoma- and chronic-types ATL (28/30 vs. 2/8 and 2/12 respectively; p = 0.001). KIR3DL2 expression correlated with the demethylation status in its promoter, and treatment by 5-Aza increased its expression from a positive basal state. *TAX* mRNA and KIR3DL2 expressions were correlated on primary ATL cells. HTLV-1 infection triggered KIR3DL2 protein expression by CD4+ cells. However, Tax alone is not sufficient to induce *KIR3DL2* mRNA expression. Treatment with IPH4102 can selectively kill human KIR3DL2+ primary ATL cells *ex-vivo* through ADCC with autologous NK cells.

Conclusion: KIR3DL2 expression is mainly associated with acute-type ATL, the most frequent subtype with the poorest prognosis. Induction of *KIR3DL2* gene transcription may be triggered by HTLV-1 infection followed by transcription maintenance due to DNA hypomethylation of the gene promoter. The benefit of targeting KIR3DL2 by IPH4102 should be further investigated in ATL patients.

Keywords: human T-lymphotropic virus (HTLV); monoclonal antibodies (MoAb); peripheral T-cell lymphomas (PTCL).

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PD-1 BLOCKADE IN A FRENCH SERIES OF 13 RELAPSED / REFRACTORY NK/T-CELL LYMPHOMA PATIENTS

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Introduction: Extranodal Natural killer/T-cell lymphoma, nasal type (ENKTCL) is a rare and aggressive subtype of peripheral T cell lymphoma strongly associated with Epstein-Barr virus. The use of Asparaginase in the last ten years has significantly improved the prognosis of this lymphoma. Although 60% of these patients are now cured with this regimen even while relapsing, some are however primary refractory or relapse early. NK/T lymphomagenesis is characterized by immune resistance with inefficient immune response directed against EBV-positive tumor cells. The PD-1 (programmed cell death protein 1) / PD-L1 (programmed cell death protein ligand 1) axis is thought to play a role in this process by averting effector T-cell targeting. PD-1/PD-L1 blockade represents therefore a relevant therapeutic strategy in relapsed/ refractory ENKTCL patients and has already demonstrated efficacy in very few cases.

Methods: We report here the outcome of 13 ENKTCL patients treated with PD-1 inhibitors between March 2017 and August 2018. All patients presented with relapsed or refractory lymphoma failing Asparaginase regimens. Four out of these patients have been treated in the frame of the AcSé Pembrolizumab UNICANCER Immunotherapy Group protocol.

Results: Median age was 44 years (range, 20-73) and sex ratio (M/F) was 1.6. Five patients presented at diagnosis with localized disease and 8 had advanced-stage disease. PINK score was low in 2, intermediate in 7 and high in 4 patients. All patients have been previously treated by at least one line of chemotherapy containing Asparaginase. In most cases (12/13), patients have received pembroluzimab as PD-1 inhibitor and a median of 5 (range, 1-14) cycles were administered. Four patients (31%) have responded to pembroluzimab durably (3 complete response and one partial response) with a median follow

up of 12.5 months (range, 7.7-19). One patient achieved partial response but relapsed, 7 patients (53%) progressed and one was unevaluable. Progression-free survival and overall survival at 12 months were 39% and 46% respectively. Treatment-related adverse events of grade ≥3 were observed in 3 patients (cytopenia in 2 cases and cytokine release syndrome in one case).

PD-L1 immunohistochemical data are currently available in 4 patients (1 complete response, 1 partial response and 2 progressions). In all patients, no PD-L1 expression was detected in ENKTCL cells, suggesting that response to anti-PD1 antibodies is not correlated to PD-L1 expression in the tumor.

Conclusions: To our knowledge, this is the largest reported series of ENKTCL patients treated with PD-1 inhibitors. Our findings indicate that PD-1 blockade represents a potent strategy for a subset of relapsed/refractory ENKTCL patients failing Asparaginase regimens. However, further immunohistochemical and molecular studies are warranted to identify predictive biomarkers of response to immune checkpoints inhibitors in order to improve patient selection.

Keywords: non-Hodgkin lymphoma (NHL); PD-1; Pembrolizumab.

Disclosures: Salles, G: Honoraria: *from BMS and Merck to participate to advisory boards and symposiums.*

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A PROSPECTIVE PHASE II STUDY OF PEGASPARGASE-COEP PLUS RADIOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED EXTRA-NODAL NK/T-CELL LYMPHOMA

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Introduction: The optimal first-line treatment for extra-nodal NK/T-cell lymphoma (ENKTL) has not been well-defined. This study aimed to evaluate the efficacy and safety of pegaspargase, cyclophosphamide, vincristine, etoposide and prednisone (COEPL) regimen combined with radiotherapy for patients with newly diagnosed ENKTL.

Methods: Our study is a prospective, open-label clinical trial. Patients with newly diagnosed ENKTL and an ECOG performance status of 0 to 2 were eligible for enrollment. For patients with stage I/II nasal type ENKTL, treatment included 2-3 cycles of induction COEPL (cyclophosphamide 750mg/m^2 day 1; vincristine 1.4mg/m^2 day 1; etoposide 60mg/m^2 days 1-3; prednisone 100mg days 1-5; pegaspargase 2500IUmg/m^2 day 2, every 21 days) followed by concurrent chemoradiotherapy (e.g. RT ≥50Gy with concurrent 1-2 cycles of LOP regimen: pegaspargase, vincristine and prednisone every 14-21 days, with the same doses as described above), then by 1-2 cycles of COEPL regimen as consolidation. For patients with stage III/IV or extra-nasal ENKTL, treatment included 6 cycles of COEPL regimen with or without radiotherapy to local sites, and autologous stem cell transplantation was given in selected patients.

Results: A total of 80 patients were enrolled. The median age was 41 years (range, 15-76 years). Sixteen patients (20%) had stage III/IV disease, 6 (8%) presented with extra-nasal ENKTL, and 10 (12.5%) had a PINK score ≥2. Complete response and overall response rates were 75.0% and 87.0%, respectively. With a median follow-up of 41.4 months (range 2.7-76.2 months), the 3-year progression-free survival (PFS) and overall survival (OS) rates were 71.3% (95%CI 61.1-81.5%) and 73.3% (95%CI 63.1-83.5%), respectively. For patients with stage I/II nasal type ENKTL (n = 62), the 3-year PFS and OS were 78.1% and 81.2%, respectively. For patients with stage III/IV or extra-nasal ENKTL (n = 18), 3-year PFS and OS were 48.1% and 45.7%, respectively. Major grade 3-4 adverse events were anemia (21.3%), leucopenia (18.8%), neutropenia (13.8%), thrombocytopenia (7.6%) and transaminase elevation (3.8%). No treatment-related death was observed.

Conclusions: Pegaspargase-COEP chemotherapy in combination with radiotherapy is highly effective and safe for patients with newly diagnosed ENKTL.

Keywords: chemotherapy; T-cell lymphoma (TCL).

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A PROSPECTIVE STUDY OF MRI AND PET/CT-GUIDED THERAPY FOR IMPROVING SURVIVAL IN UPPER AERODIGESTIVE TRACT NATURAL KILLER/T-CELL LYMPHOMA, NASAL TYPE

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TABLE 1 HN-MRI could revise the initial clinical stages in patients undergoing PET/CT According to the Ann Arbor and TNM Staging Systems

PET/CT[a]	PET/CT-MRI[b]				P value
	I	II	III	IV	
AA Staging[c]					
I	14	8	0	0	0.011
II	0	46	0	1	
III	0	0	0	0	
IV	0	0	0	2	
TNM Staging[d]					
I	25	2	5	0	0.019
II	0	2	3	0	
III	0	0	26	0	
IV	0	0	0	8	

a, PET/CT, [18F]-Fluorodeoxyglucose positron emission tomography/computed tomography; b, PET/CT-MRI, [18F]-Fluorodeoxyglucose positron emission tomography/computed tomography combined with magnetic resonance imaging; c, AA Stage, Ann Arbor staging; d, TNM Staging (American Joint Committee on Cancer for Nasopharyngeal Carcinoma, 8th edition, 2017).
Survival of patients undergoing HN-MRI with PET/CT were significantly better than that of patients undergoing PET/CT alone

Introduction: Radiotherapy is extremely important in extranodal natural killer/T-cell lymphoma (ENKTL). [18F]-Fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) is a routine pretreatment imaging technique used in ENKTL, while magnetic resonance imaging (MRI) plays a key role in head and neck (HN) cancer. The purpose of this study was to investigate the value of pretreatment HN-MRI and PET/CT-guided therapy in improving survival in upper aerodigestive tract ENKTL (UADT-ENKTL).

Methods: We prospectively conducted a single center study on untreated patients with pathologically diagnosed UADT-ENKTL. Patients undergoing PET/CT with/without HN-MRI were decided by clinicians for staging and restaging. The patients were treated with L-asparaginase/Pegaspargase and non-anthracycline-based chemotherapy with intensity-modulated radiation therapy (IMRT).

Results: We enrolled 171 patients (median age, 44 years; range, 18-75 years; 118 (69%) males) from April 2011 to March 2018. Overall, 71 patients underwent PET/CT and HN-MRI (PET/CT-MRI) and 100 patients underwent PET/CT alone. HN-MRI upgraded the clinical stages in 8 patients (8/71) undergoing PET/CT based on the Ann Arbor staging system and in 10 patients (10/71) based on the TNM staging system by detecting additional local lesions ($P = 0.011$ and $P = 0.019$, respectively).With a median follow-up of 54 months, the 5-year overall survival (OS), local recurrence-free survival (LRFS) and progression-free survival (PFS) rates were 72.7%, 68.6% and 68.2%, respectively, for all patients. The 5-year LRFS rate was 100% in the PET/CT-MRI group and 64.3% in the PET/CT group ($P<0.001$). Similarly, the 5-year OS and PFS were longer in the PET/CT-MRI group than in the PET/CT group (84.5% vs. 67.8% and 78.3% vs. 65.6%; $P = 0.04$ and $P = 0.03$, respectively).
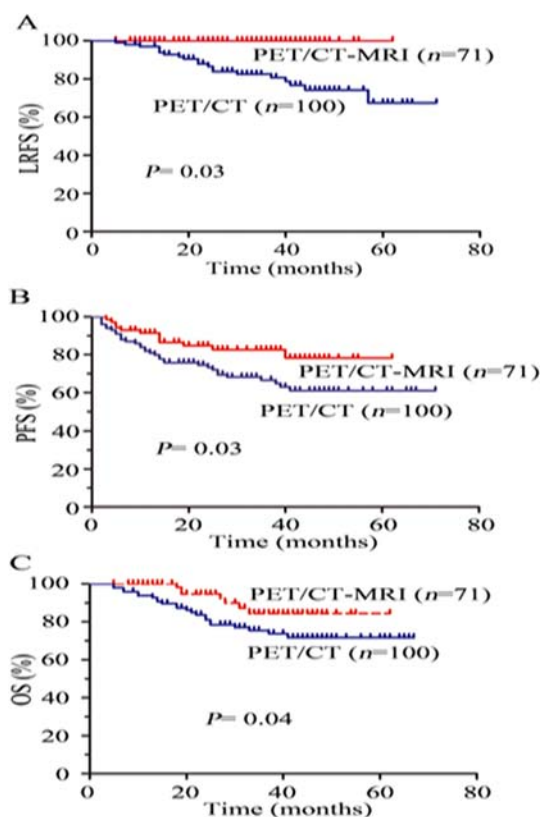
Conclusions: HN-MRI and PET/CT-guided therapy could assist in decreasing local recurrence, which improved prognosis in UADT-ENKTL patients. Therefore, HN-MRI and PET/CT should be incorporated into routine pretreatment imaging examinations in patients with UADT-ENKTL.

Keywords: magnetic resonance imaging (MRI); non-Hodgkin lymphoma (NHL); positron emission tomography (PET).

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CLINICAL OUTCOMES AND DIAGNOSIS-TO-TREATMENT INTERVAL IN PATIENTS WITH NK/T-CELL LYMPHOMA: 7-YEAR FOLLOW-UP OF THE NKEA STUDY

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Introduction: Our recent retrospective study (NKEA Part A) revealed the treatments and outcomes of 358 patients (pts) with extranodal NK/T-cell lymphoma, nasal type (ENKL) diagnosed between 2000 and 2013 at 31 institutes in Japan (Yamaguchi M, et al. JCO 2017). The study also demonstrated that the baseline clinical features, efficacy, and toxicity of pts who received RT-DeVIC in clinical practice were comparable to those of pts enrolled in a clinical trial of RT-DeVIC (JCOG0211) and that the incidence of 2nd malignancies was 5% at a median (med.) follow-up (f/u) of 5.6 years (yrs). A recent study demonstrated that the diagnosis-to-treatment interval (DTI) was shorter in pts in clinical practice (med., 15 days) than in those enrolled in clinical trials (med., 23 days) and was strongly associated with clinical factors and outcomes in diffuse large B-cell lymphoma (DLBCL) (Maurer MJ, et al. JCO 2018). The aim of the present analysis was to update data on the efficacy and toxicity of RT-DeVIC and to determine the relationship between DTI and survival in ENKL.

Methods: Data on survival, late toxicity, and DTI of our NKEA Part A dataset were collected as of Feb 20, 2019. According to the original report for DTI, the date of diagnosis used to calculate DTI was defined as the biopsy date from the first biopsy specimen containing lymphoma.

Results: Data on the survival of 313 pts were updated and included in the analysis. The med. f/u period was 7.9 yrs. The 5-yr OS and PFS were respectively 56% and 48% in the whole cohort and 66% and 58% in pts with localized disease. In pts with localized ENKL who received RT-DeVIC in clinical practice (n = 140), the 5-yr OS and PFS were 71% and 64%, respectively. OS events after 5 yrs from diagnosis included 2 events of ENKL, 4 events of 2nd malignancy, and 6 events of other diseases. Late toxicity was manageable in most pts. Ten (7.1%) pts experienced 2nd malignancies. Of those, 7 were men and were > 60 yrs of age. The remaining 3 pts were women and had been heavily treated for relapsed ENKL. Data on DTI were obtained from 298 pts. The med. DTI was 25 days (0-163) in the whole cohort, 27 days (0-163) in pts with localized disease, and 19 days (0-79) in pts with advanced disease. In pts with localized ENKL who received RT-DeVIC, the DTI was 27 days in 130 pts in clinical practice and 30 days in 10 pts who were enrolled in the clinical trial. Shorter DTI grouped by week was not associated with shorter OS and PFS in pts with localized ENKL (P = 0.23 and 0.30, respectively) in contrast to those with advanced ENKL (P = 0.001 and 0.072, respectively).

Conclusions: Our 7-yr f/u analysis provided an update on survival in pts with ENKL and confirmed the efficacy and safety of RT-DeVIC. The incidence of 2nd malignancies (7.1% at 7.9 yrs) did not increase compared to the results of our previous analysis. DTI in pts with localized ENKL was long and its impact on survival was relatively small, supporting the feasibility of future clinical trials for localized ENKL.

Keywords: extranodal lymphomas.

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CLINICOPATHOLOGICAL DIFFERENCES OF NODAL PTCL WITH TFH PHENOTYPE FROM AITL AND PTCL, NOS, AND DETECTION OF PROGNOSTIC MARKER OF NODAL PTCL WITH TFH PHENOTYPE

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Introduction: In the revised 4th edition of WHO classification (2017), nodal peripheral T-cell lymphoma with Tfh phenotype (PTCL with Tfh-phenotype) has been listed as lymphoma derived from T follicular helper (Tfh) cells as well as angioimmunoblastic T-cell lymphoma (AITL) apart from peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS). Few researches have investigated the clinicopathological differences among these diseases, and prognostic marker of PTCL with Tfh.

Methods: We reviewed 166 cases of peripheral T-cell lymphoma diagnosed at Kurume University. Cases with FDC meshwork and high endothelial venules in the stroma were classified as AITL (n = 45). PTCL with Tfh-phenotype (n = 63) were CD4-positive and exhibited two or more positive TFH markers including CD10, PD-1, bcl6, CXCL13, ICOS, SAP, CXCR5, c-Maf and CD200. Remaining cases were classified as PTCL, NOS (n = 58). Chi-squared test, Fisher's two-sided exact test, and Mann-Whitney Test were performed to determine the statistical association of clinicopathological features. Overall survival curves are shown by Kaplan-Meier method, and Log-lank test is used for comparison.

Results: There are no significant differences in clinical findings of PTCL with Tfh-phenotype comparison with AITL and PTCL, NOS including age, sex, Ann Arbor stage, B-symptom, splenomegaly, hepatomegaly, PS, IPI, extra nodal involvement, bone marrow infiltration, hemolytic anemia, circulating tumor cells in blood, white blood cell counts, neutrophil counts, lymphocyte counts, hemoglobin, platelets, elevated LDH, hypergammaglobulinemia, hypercalcemia, elevated CRP, and OS curves. In morphological features, PTCL with Tfh-phenotype had lower value of infiltration of plasma cells (P = 0.018)

TABLE 1 Pathological findings of AITL, PTCL with Tfh-phenotype, and PTCL, NOS

Pathological features	AITL(n=45)	AITL vs PTCL with Tfh-phenotype (p-value)	PTCL with Tfh-phenotype(n=63)	PTCL with Tfh-phenotype vs PTCL, NOS (p-value)	PTCL, NOS (n=58)
Polymorphic infiltrate neutro (count/10HPF), average/median [range]	0.3/0 [0-1]	0.054	6.0/3.0 [0-25]	0.111	30.0/0.5 [0-464]
Polymorphic infiltrate eosino (count/10HPF), average/median [range]	261.0/267.0 [8-508]	0.140	132.0/7.0 [0-1200]	**0.037**	42.2/0 [0-907]
Polymorphic infiltrate plasma (count/10HPF), average/median [range]	109.6/40.0 [14-275]	**0.018**	19.3/5.5 [0-205]	0.651	55.8/1.5 [0-456]
High endothelial venules (count/10HPF), average/median [range]	58.6/57.0 [57-62]	0.093	38.5/35.5 [6-116]	0.496	31.2/21.5 [7-82]
Clear cell (%), average/median [range]	53.3/60.0 [30-70]	0.574	40.6/40.0 [0-90]	0.370	30.9/25 [0-90]
EBER potive cells in surrounding cells	48.9 (%)	0.535	42.9 (%)	0.431	50.0 (%)
Tumor cell size, Large	66.7 (%)	0.252	31.3 (%)	0.735	40.9 (%)
Tfh markers					
PD-1	71.1 (%)	**0.003**	42.9 (%)	**<0.0001**	8.6 (%)
CXCL13	15.6 (%)	**0.026**	3.2 (%)	1.000	1.7 (%)
CD10	15.6 (%)	**0.032**	3.2 (%)	0.497	0 (%)
Bcl-6	75.6 (%)	0.316	66.7 (%)	**<0.0001**	12.1 (%)
ICOS	75.6 (%)	**0.001**	44.4 (%)	**<0.0001**	10.3 (%)
SAP	31.1 (%)	0.808	33.3 (%)	0.002	8.6 (%)
CXCR5	6.7 (%)	0.424	11.1 (%)	0.063	1.7 (%)
c-Maf	60.0 (%)	0.108	74.6 (%)	**<0.0001**	29.3 (%)
CD200	42.2 (%)	0.428	49.2 (%)	0.066	32.8 (%)

than AITL, and higher value of that of eosinophils (P = 0.037). In analysis of Tfh markers, many kinds of Tfh markers in PTCL with Tfh-phenotype are less observed than AITL and more than PTCL, NOS. Among clinicopathological features of PTCL with Tfh-phenotype, cases with PS≥2 (P = 0.001), elevated CRP (P = 0.020), and bcl6-negative (P = 0.008) showed significantly poorer OS curve, respectively.

Conclusions: PTCL with Tfh-phenotype should be considered clinicopathologically as disease entity distributed between AITL and PTCL, NOS. Prognostic markers might be useful for stratification of clinical strategy. More investigation including genomic abnormalities and mRNA expression would be desired to confirm the results of this study.

Keywords: angioimmunoblastic T-cell lymphoma (AITL); peripheral T-cell lymphomas (PTCL); prognostic indices.

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EVENT FREE SURVIVAL AT 12 MONTHS AND 24 MONTHS AS PREDICTORS FOR OUTCOME OF SYSTEMIC PERIPHERAL T CELL LYMPHOMA: ANALYSIS OF NATIONWIDE THAI LYMPHOMA STUDY GROUP

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Figure 1: Kaplan Meier Survival Curve A) EFS and OS of entire cohort B) OS from treatment initiation stratified by EFS12 C) OS from landmark 12 months timepoint stratified by EFS12 D) OS from landmark 24 months timepoint stratified by EFS24
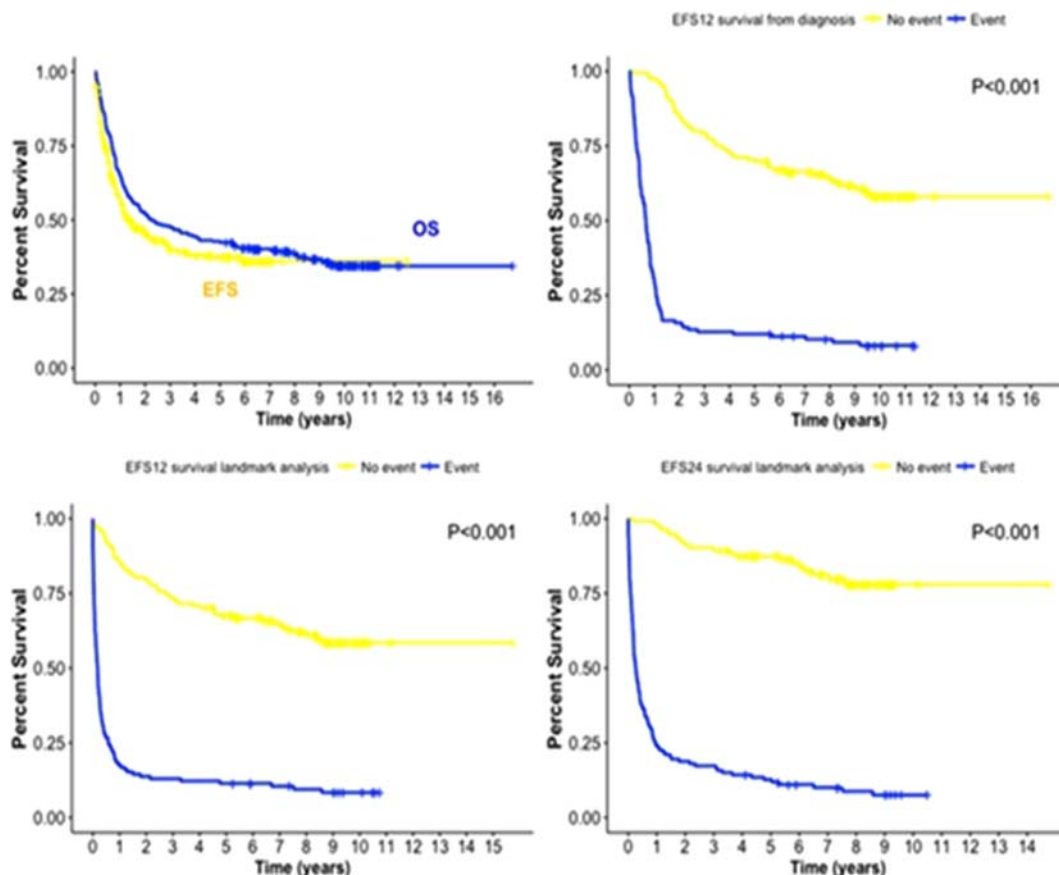
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Background: Peripheral T cell lymphoma (PTCL) is relatively uncommon compared to B cell lymphoma, however, it generally carries worse prognosis. Treatment failure and early relapse are major dilemma of PTCL. Identification of high-risk patients using various tools may better refine long-term prognosis of PTCL patients. There were data indicating event free survival (EFS) at 12 months (EFS12) and 24 months (EFS24) as strong surrogate predictors for disease-related outcomes in many B-cell lymphoma. However, the implication of such surrogate end-points has been limited in PTCL. Herein, we explored EFS12 and EFS24 as tools to stratify survival outcome in PTCL patients.

Methods: Thai Lymphoma Study Group is the nationwide collaborative effort composing of 13 major medical centers in Thailand. The registry prospectively enrolled newly diagnosed lymphoma patients between 2006 and 2014. Here, we focused on systemic PTCL treated with chemotherapy and had adequate follow-up data. EFS was defined as time between primary treatment to relapse, re-treatment, or death from any causes. EFS12 and EFS24 were binary endpoints defined as whether developing events at 12 and 24 months after treatment initiation. Overall survival (OS) was defined as time from a specific timepoints either diagnosis or EFS12 to death. Logistic regression model was used to evaluate associations between clinical characteristics and EFS12/EFS24. Cox regression with EFS12/EFS24 as a time-dependent covariate was applied to evaluate the association between EFS12 and OS.

Results: Of 353 PTCL, 292 (83%) received multiagent chemotherapy. Median age at diagnosis was 49 years (IQR 36-60 years). Median EFS and OS of patients who received treatment were 16.3 and 27.7 months (CI 95% 12.6-28.3 and 18.8-50.4 months respectively). A total of 138 patients (47.1%) developed an event within 12 months after treatment initiation (failed to achieve EFS12). Patients who failed to achieve EFS12 had higher proportion of impaired performance status, high IPI, and presence of B symptoms. After a median follow-up of 53.7 months, Patients who achieved EFS12 had superior OS compared to patients who failed to achieve EFS12 (5-years OS after treatment initiation 70.5% vs 12%, HR 7.0, p<0.001). Landmark analysis confirmed the association between EFS12 and OS after 12 months timepoint (5-years OS after EFS12 67.5% vs 11.5%, HR 6.45, p<0.001). Similar results were seen with patients who achieved EFS24 for both survival after treatment initiation and after 24 months timepoint (Figure 1).

Conclusion: EFS12 and EFS24 are strong surrogate endpoints for treatment outcomes in PTCLs.

Keywords: peripheral T-cell lymphomas (PTCL); prognostic indices; T-cell lymphoma (TCL).

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BONE MARROW INVOLVEMENT, BUT NO BLOOD INVOLVEMENT, IMPAIRS SURVIVAL IN ANGIOIMMUNOBLASTIC T CELL LYMPHOMA: AN ANCILLARY STUDY OF THE REVAIL TRIAL

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Introduction: Angioimmunoblastic T-cell lymphoma (AITL) is the most frequent peripheral T-cell lymphoma. Treatment with CHOP has limited efficacy. In the recent analysis of the REVAIL study, a phase 2 trial assessing the combination of Lenalidomide and CHOP in previously untreated patients with AITL, the mutational landscape (i.e TET2, DNMT3A, IDH2 or RHOA) has limited impact on survival (Lemonnier, Safar et al. ASH 2018), making important to find alternative methods to predict the prognosis of AITL patients.

Methods: The 72 patients included in REVAIL study with a centrally confirmed diagnosis of AITL are analyzed. Bone marrow involvement (BMI) was determined locally on BM trephine biopsy. Fresh blood samples were centrally collected for flow cytometry and DGGE PCR analyses aiming at detecting circulating neoplastic T cells by aberrant immunophenotype or a monoclonal TCR rearrangement. Total metabolic tumor volume (TMTV) was measured on baseline PET CT as previously reported (PMID: 28864629).
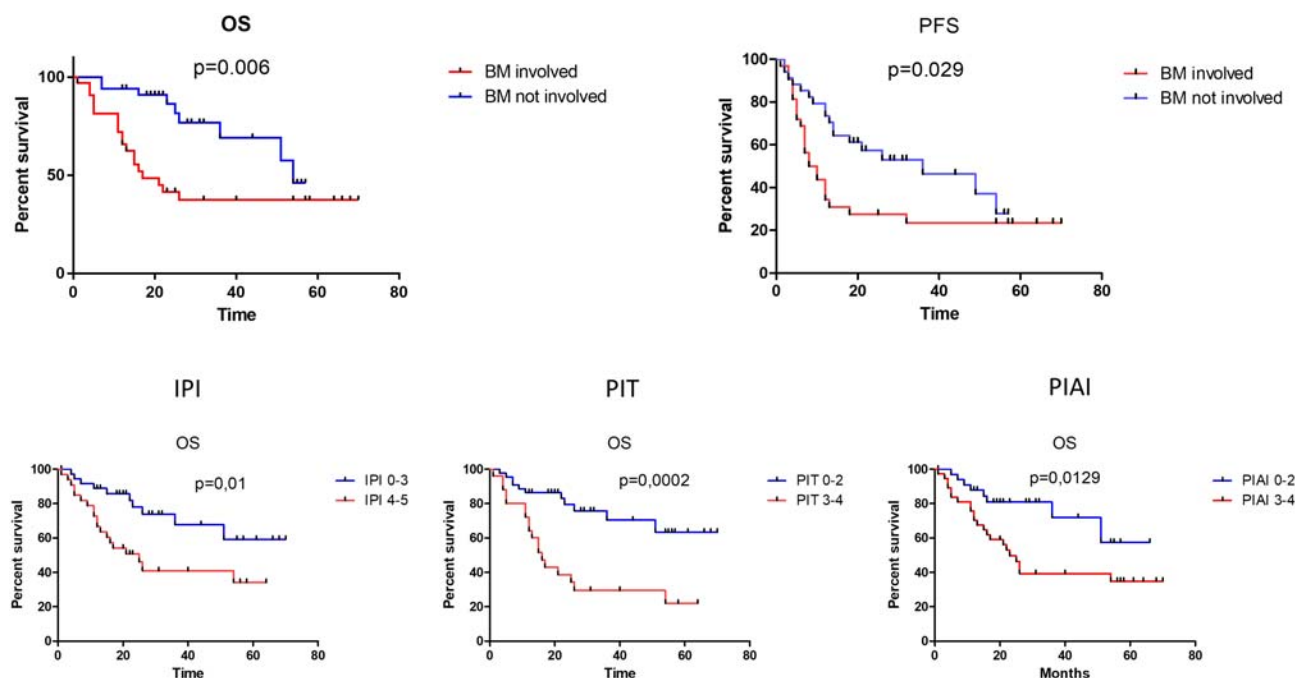
Results: At inclusion, 33/67 (49%) patients had a BMI. No difference in median age, performance status or presence of B symptoms was observed between patients with or without BMI. However, IPI was higher in patients with BMI (60% of patients with BMI vs 30% of patients without BMI had IPI 4-5, p = 0.02). Although the complete metabolic response rate was similar in patients with or without BMI [13/33 (39%) vs 18/34 (53%) (p = 0.33)], BMI was associated to poorer outcome, as the median progression-free survival (PFS) was 9 months versus 36 months (p = 0.029) and the median overall survival (OS) was 17 vs 54 months (p = 0.006) in patients with or without BMI, respectively. We thus compared the relevance of three prognostic models [International prognosis index, Prognostic Index for Peripheral T-Cell Lymphoma (PIT), and Prognostic Index for AITL] used in T-cell lymphomas. As shown in the figure, PIT, which includes BMI as a prognostic factor, gave the best discrimination between high-risk and low-risk patients with a 2yr OS of 38% for PIT 3-4 and 79% for PIT 0-2. Flow cytometry identified abnormal circulating cells in 30/51 (59%) patients, and DGGE PCR identified a circulating clonal population in 39/59 (66%) patients. However, the presence of circulating cells identified by flow cytometry or PCR had no impact on survival and was not correlated with the presence of BMI. We also observed that lymphomas with BMI had a higher percentage of neoplastic T cells in the tumor and higher TMTV. Mutational analysis revealed that BMI was present in 12/13 (92%) IDH2-mutated samples and in 19/47 (40%) IDH2 unmutated samples (p = 0.001).

Conclusion: In this prospective series of homogeneously treated AITL patients, BMI had a pejorative impact on survival. In contrary to B-cell lymphomas, detection of circulating lymphoma cells does not correlate with BMI and had no prognostic impact. BMI is associated with specific features, such as the presence of IDH2 mutations.

Keywords: angioimmunoblastic T-cell lymphoma (AITL); prognostic indices.

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COMBINATION OF CHIDAMIDE WITH CHOEP REGIMEN IN PREVIOUSLY UNTREATED PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA: A PROSPECTIVE, MULTICENTER, SINGLE-ARM, PHASE 1B/2 TRIAL

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A PFS: intent-to-treat analysis

OS: intent-to-treat analysis

B PFS: PTCL subtypes

OS: PTCL subtypes
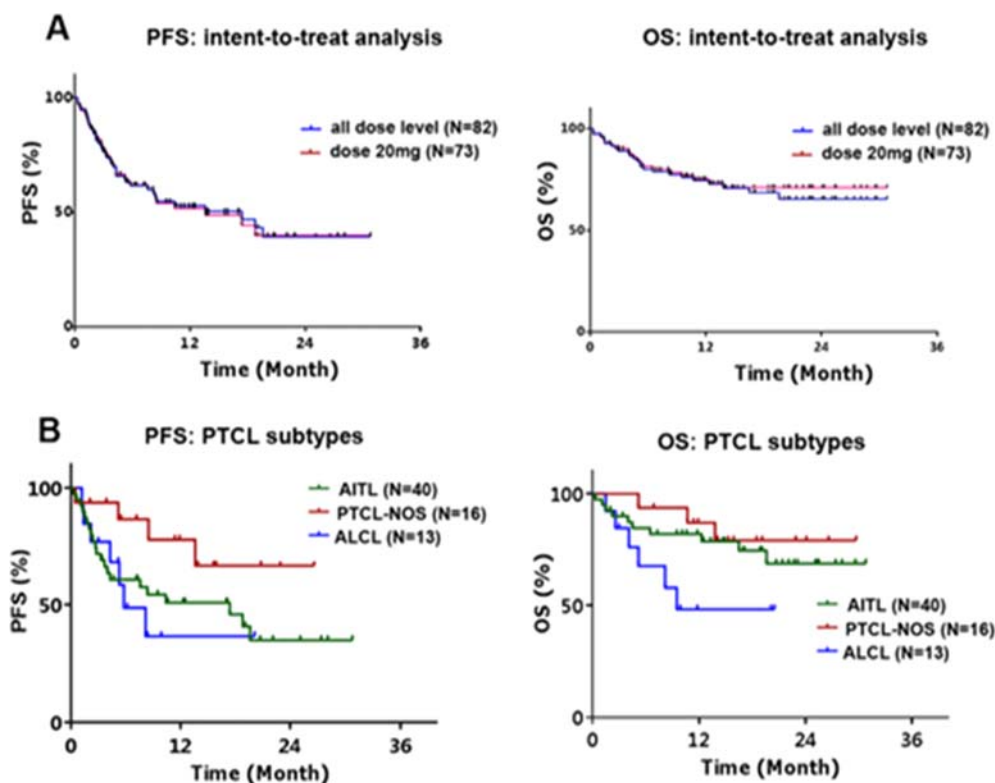
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Introduction: The aim of this study was to assess the safety and efficacy of the histone deacetylase (HDAC) inhibitor chidamide together with the cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP) regimen (Chi-CHOEP) in previously untreated peripheral T-cell lymphoma (PTCL) patients.

Methods: This was a prospective, multicenter, single-arm, open-label, phase 1b/2 clinical trial. The sample comprised patients with untreated PTCL. The study consisted of dose-escalation (phase 1b) and expansion (phase 2) phases. Patients received up to six cycles of CHOEP with chidamide. In the phase 1b study, a dose-escalation scheme was evaluated, and three dose levels of chidamide were tested. In the phase 2 study, the cohort of patients who received the recommended dose of chidamide plus CHOEP was extended. The primary endpoint was the recommended dose of chidamide plus CHOEP. Secondary endpoints included progression-free survival (PFS), overall survival (OS), overall response rate (ORR), complete response (CR) rate, and the incidence of adverse events (AEs).

Results: A total of 82 patients from across China were enrolled in the study between Mar 2016 and Dec 2017. A chidamide dose of 20 mg biw was recommended for phase 2. In the intent-to-treat analysis of response to Chi-CHOEP, the ORR was 68.3% with a CR rate of 43.9% for chidamide across all dose levels (N = 82). After the median follow-up time of 12.7 months (range 0.3-30.8 months), 1-year PFS was 52.9% and 1-year OS was 74.5%. For PTCL not otherwise specified (PTCL-NOS) patients (N = 16), 1-year PFS was 77.9% and 1-year OS was 87.1%. Chi-CHOEP was generally well tolerated. The most common toxicities were leucopenia (84.1%), anemia (80.5%), neutropenia (75.6%), and nausea/vomiting (59.8%). No reactivation of Epstein–Barr virus (EBV) or Hepatitis B virus (HBV) was observed.

Conclusion: Chi-CHOEP is an effective novel regimen for untreated PTCL. It exhibits superiority in survival and among a subpopulation of PTCL-NOS patients compared with historical control data. This regimen requires further investigation in a phase 3 randomized trial.

Keywords: epigenetics; histone deacetylase inhibitors; peripheral T-cell lymphomas (PTCL).

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PHASE I/II STUDY OF CHOEP PLUS LENALIDOMIDE AS INITIAL THERAPY FOR PATIENTS WITH STAGE II-IV PERIPHERAL T-CELL LYMPHOMA: PHASE II RESULTS

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Introduction: CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) is a common upfront regimen for peripheral T-cell lymphoma (PTCL). Lenalidomide (len) is an immunomodulatory agent with 22% single agent response rate in relapsed and refractory PTCL. Here we report the phase II results of len-CHOEP including consolidation outcomes of those proceeding to len maintenance or autologous stem cell transplantation (ASCT).

Methods: Eligible patients (pts) had newly diagnosed PTCL with adequate hematologic and organ function. Based on phase I results 10 mg of len was deemed the recommended phase II dose. CHOEP was administered at standard doses with len given on days 1-10 of 21-day cycle for 6 planned cycles. Pts received thromboprophylaxis and growth factor support. The primary endpoint was complete response (CR) by PET/CT after 6 cycles. Secondary endpoints included toxicity, overall response rate (ORR), progression free survival (PFS), 2-year PFS, and overall survival (OS). Pts who had CR or partial response (PR) at the end of therapy had the option of len maintenance (10 mg/day for 21 out of 28 days) for 1-year or consolidative ASCT without len maintenance.

Results: 39 pts with PTCL-NOS (n = 19), ALK negative ALCL (n = 4) and AITL (n = 16) enrolled into the phase II portion. Median age was 63 years (range 24-79) and 20 were male. Stage III/IV was seen in 89%. Prognosis by international prognostic index was 0-1 (15%), 2 (41%), and 3-5 (44%). 29 (75%) pts completed all 6 cycles. One pt was re-classified as Hodgkin lymphoma post completion of len-CHOEP and is included in toxicity analysis. Reasons for discontinuing len-CHOEP early were toxicity (n = 7) and progressive disease (PD; n = 5). The primary endpoint of CR by an intent to treat (ITT) analysis was 48% (19/40; 95CI—33-64%) with an ORR of 69%. Responding pts (CR/PR; n = 30) proceeded either to an ASCT (n = 16), len maintenance (n = 10) or neither (investigator/pts preference; n = 1). At a median follow up of 18 months (range: 2-30 months), the 1-year estimated PFS and OS is 67% [95% CI: 50-79%] and 90% [95%CI: 73-96%] respectively. There is no difference in 1-year PFS by PTCL subtype or between the len maintenance or ASCT. There were 5 grade (G) 5 events including PD (n = 1), secondary malignancy (n = 1; AML), sepsis (n = 2), and cardiac arrest (n = 1). Serious or recurrent adverse events (SAEs or AEs; G 3-4) of interest occurring during any cycle included 38% febrile neutropenia despite mandated GCSF use, 43% anemia, 45% thrombocytopenia (without report of G 3-4 bleeding or bruising despite ASA use), and 8% diarrhea.

Conclusions: The phase II portion of the study in an ITT population noted a modest 48% CR rate and a high discontinuation rate due to AEs or SAEs. The utility of post initial therapy strategy (len maintenance vs ASCT) continue to be monitored for PFS and OS in this limited cohort. Improving frontline outcomes for pts with PTCL remains an unmet need.

Keywords: peripheral T-cell lymphomas (PTCL).

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RESPONSE TO A+CHP BY CD30 EXPRESSION IN THE ECHELON-2 TRIAL

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TABLE 1 Response by CD30 expression

	CD30	Pts, n	CR, n (%)	PR, n (%)
AITL	CD30 >median	14	8 (57)	1 (7)
	CD30 ≤ median	15	8 (53)	3 (20)
	CD30=10%	8	5 (63)	0
PTCL-NOS	CD30 >median	14	8 (57)	2 (14)
	CD30 ≤median	14	10 (71)	2 (14)
	CD30=10%	6	4 (67)	2 (33)

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Introduction: Brentuximab vedotin (BV) is an antibody-drug conjugate that targets CD30. The ECHELON-2 (E-2) study demonstrated significantly longer progression-free (P = 0.0110) and overall survival (P = 0.0244) with BV plus cyclophosphamide, doxorubicin, and prednisone (A+CHP) versus CHOP in frontline treatment of patients (pts) with CD30+ peripheral T-cell lymphoma (PTCL). Complete remission (CR) rate (A+CHP 68%; CHOP 56%; P = 0.0066) and objective response rate (ORR) (A+CHP 83%; CHOP 72%; P = 0.0032) were also significantly increased. Expression of CD30 is universal in systemic anaplastic large-cell lymphoma (sALCL) but variable among non-sALCL subtypes. As ORR is a direct measure of antitumor activity, we examined response to A+CHP by CD30 expression.

Methods: Pts with CD30+ (≥10% by local review) PTCL were included in E-2. Eligible histologies included ALK+ sALCL (IPI ≥2), ALK− sALCL,

PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), adult T-cell leukemia/lymphoma, enteropathy-associated T-cell lymphoma, and hepatosplenic T-cell lymphoma. We analyzed the relationship between CD30 expression (IHC Ber H2 antibody) above and below the median (median CD30 = 18% PTCL-NOS; 25% AITL) and CR rate, ORR, and duration of CR (DOCR) in pts with AITL and PTCL-NOS treated with A+CHP.

Results: Most (26/29, 90%) AITL pts had CD30 expression between 10% and 30%. PTCL-NOS pts were more evenly distributed across levels of CD30 expression ranging from 10% to 100%. CD30 levels were neither predictive of response (Table) nor significantly associated with DOCR in pts with AITL (P = 0.30) or PTCL-NOS (P = 0.90) (log-rank test).

Conclusions: CD30 expression above vs below median (or at 10%) did not predict response to A+CHP in E-2 non-ALCL subtypes, as responses were seen across CD30 levels. This may be due to intra- and inter-tumoral heterogeneity of CD30 expression, limitations of IHC, the nature of CD30 on the cell surface, and multiple mechanisms of action of BV. Further evaluation of the expression-response relationship in PTCL pts with CD30 <10% is warranted.

Keywords: brentuximab vedotin; CD30; peripheral T-cell lymphomas (PTCL).

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ANAPLASTIC LARGE CELL LYMPHOMA, ALK-NEGATIVE: ANALYSIS OF 235 CASES COLLECTED BY THE T-CELL PROJECT

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Introduction: Anaplastic Large Cell Lymphoma, ALK-Negative(ALCL, ALK-) is an aggressive lymphoid neoplasm of T/null-cell lineage with strong expression of CD30, which represent 5.5% of all PTCL and NKTCL, with a unique ethnic and geographical distribution. ALCL, ALK- displays a poorer outcome compared to ALK-positive, with a 5-year OS of 49% and 70%, respectively. This study aims to provide accurate and update information on prognostic factors, therapy, and outcomes of ALK- ALCL registered in the T-Cell Project.

Methods: Eligible patients (pts) with the first diagnosis of aggressive, mature PTCLs were prospectively registered at a dedicated website and baseline demographic, clinical and laboratory data, as well as therapy details and outcome data were collected.

Results: From Sept 2006 to Feb 2018, a diagnosis of ALCL, ALK- was reported in 235 cases out of 1553 validated cases registered by 77 sites from 14 countries worldwide. The median age at diagnosis was 54 (range, 18-89) years with male predominance (61%). Stage III-IV disease was identified in 71% pts, bulky and bone marrow involvement were uncommon. Therapy was administered according to treating physician's standard practice. Out of 205 patients for which we have available data about treatment, in 9% were addressed to consolidating post-transplant chemotherapy.

The overall response rate was 77% with 57% of patients achieving complete remission. After a median follow-up of 55 (95% CI, 36-75) months, the PFS was 41 (95% CI, 17-62) months, the 3-year and 5-year PFS rates were 47% and 39%, respectively. The median OS was 55 (95% CI, 36-75) months, 3-year and 5-year OS rates were 60% (95CI 48-72) and 49% (95CI35-59), respectively. International Prognostic Index (IPI) and the Prognostic Index for T-cell Lymphomas (PIT) were both predictive of clinical outcomes. Treatment with anthracycline and etoposide vs. anthracycline-only containing regimens was associated with a better OS(3 and 5-year OS 56% and 44% vs 76% and 69%, respectively, (P = 0.05), but not PFS 3 and 5 year PFS 47% (95CI 32-59) and 39 % (95CI 29-48) vs. 65% (95CI 32-87) and 50% (95CI 36-89) respectively (P = 0.186).

In the multivariate analysis the presence of B symptoms (P = 0.008), elevated LDH rate (P = 0.001), ECOG-PS >2 (P = 0.001) and PTL<150x10^9(P = 0.05), were significant for OS. The presence of B symptoms (p = 0.02), elevated LDH (P = 0.001) and ECOG-PS>2 (P = 0.001) maintained their adverse prognostic value for PFS.

Conclusions: ALCL, ALK- remains a difficult T cell lymphoma to be cured. Combinations regimens that include both etoposide and anthracycline might improve outcomes. In this large prospective

cohort study, we observed an outcome comparable with a previous report from the retrospective International Lymphoma Project. The study underscores the urgent need for designing new treatment platforms for ALCL, ALK-, and establishes a benchmark for future prospective clinical trials.

Keywords: anaplastic large cell lymphoma (ALCL); prognostic indices; T-cell lymphoma (TCL).

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INCREASED RISK OF SECOND PRIMARY HEMATOLOGIC AND SOLID MALIGNANCIES IN PATIENTS WITH MYCOSIS FUNGOIDES: IMPACT ON OVERALL SURVIVAL IN SEER REGISTRY

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Background: Mycosis fungoides (MF) is a rare, generally indolent non-Hodgkin T-cell lymphoma of the skin. It has previously been associated with increased risk of second hematologic malignancies but association with second solid malignancies has not been well characterized.

Methods: We studied a large population of patients diagnosed with MF from 2000-2015 in the 18 population-based United States cancer registries of the Surveillance, Epidemiology, and End Results Program (SEER-18) to assess the risk of developing a second primary hematologic or solid malignancy. Relative risks were estimated using the standardized incidence ratios (SIR). Overall survival (OS) was assessed by Cox proportional hazards analysis.

Results: In the SEER-18 cohort, of 6742 patients, there were 511 (7.5%) second cancer events (SIR 10.15, 95% confidence interval [CI], 9.29-11.07). These included 184 (36.0%) hematologic malignancies (SIR 39.71, 95% CI, 34.05-46.05) and 327 (64.0%) solid tumor malignancies (SIR 7.33, 95% CI, 6.56-8.17). Patients with MF were at substantially increased risk for non-Hodgkin (SIR 66.65, 95% CI, 56.06-78.65) and Hodgkin lymphoma (SIR 105.26, 95% CI, 54.39-183.87). MF patients were also at higher risk of melanoma (SIR 9.00, 95% CI, 5.5-13.9), lung (SIR 8.34, 95% CI, 6.4-10.6), female breast (SIR 11.28, 95% CI, 8.29-15.00), prostate (SIR 5.65, 95% CI, 4.3-7.28), bladder (SIR 4.35, CI 2.38-7.3), colon (SIR 6.99, CI 4.9-9.68) and renal (SIR 3.26 CI, 1.33-8.87) cancers. Females with MF were at higher risk (SIR 13.95, 95% CI 12.09-16.02) than males (SIR 8.62, 95% CI, 7.69-12.09) of being diagnosed with second malignancies (*p*<0.05). All ethnic groups showed a statistically significant elevation in SIR with Non-Hispanic white patients having the lowest SIR (9.13, 95% CI, 8.22-10.11). There was no significant difference in the incidence of second malignancy based on MF stage
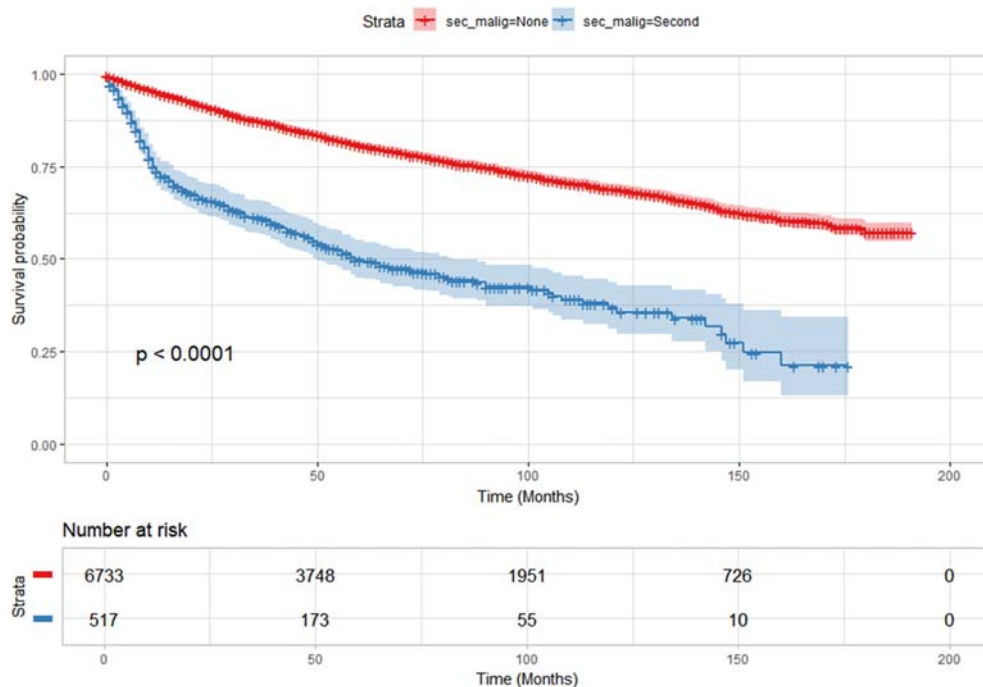
(p = 0.17 for stage IA-IIA vs. stage IIB+). Second malignancy was associated with worse overall survival (Figure) in the Cox proportionate hazards ratio model, the hazard ratio (HR) for patients with vs. those without second malignancy was 2.72 (95% CI, 2.37-3.12, p<0.001) after adjustment for age (p<0.001), ethnicity (p<0.001), and stage (p<0.001) of disease.

Conclusions: Patients with MF are at increased risk of developing second hematologic and solid malignancies which in turn leads to poor survival. These findings warrant careful screening for signs and symptoms of second malignancies in patients with MF.

Keywords: cutaneous T-cell lymphoma (CTCL); mycosis fungoides (MF).

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TIME TO NEXT TREATMENT IN PATIENTS WITH PREVIOUSLY TREATED CUTANEOUS T-CELL LYMPHOMA (CTCL) RECEIVING MOGAMULIZUMAB OR VORINOSTAT: A POST-HOC ANALYSIS OF THE MAVORIC STUDY

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Introduction: CTCL is a rare group of NHL of T-cell origin, characterized by relapsing/remitting behavior and progressive resistance to treatments, with a reported median time to next treatment (TTNT; mostly systemic therapies, total skin radiation, excludes localized treatments, topical steroids) in mycosis fungoides (MF) and Sézary syndrome (SS) of 5.4 months (mo) (Hughes CF, et al. Blood, 2015). The phase 3 MAVORIC study demonstrated mogamulizumab (MOGA; Poteligeo®), a novel anti-CCR4 monoclonal antibody, was superior to vorinostat (VORI) in progression-free survival (median 7.7 vs 3.1 mo, P<0.0001) and confirmed overall response rates (28% vs 4.8%, P<0.0001) in previously treated patients with MF/SS (Kim YH, et al. Lancet Oncol 2018). In MF/SS-CTCL with a chronic course where patients suffer life-quality issues, the duration of clinical benefit of treatments, as reflected by TTNT, is an important clinically meaningful endpoint. This post-hoc analysis examines TTNT to further explore the patient clinical experience.

Methods: Patients with MF/SS (n = 372) who were treated with ≥1 prior systemic therapy were randomized 1:1 to receive MOGA (1.0 mg/kg, administered once weekly for the first 28-day cycle, then on Days 1 and 15 of subsequent cycles) or oral VORI (400 mg daily). Patients on VORI were permitted to crossover to MOGA upon approval (e.g., disease progression or intolerable toxicity). TTNT was defined as time to any significant therapy (systemic treatment, total skin radiation, or psoralen-UVA therapy). The length of TTNT was assessed overall and by disease stage grouping (IB/II and III/IV) and disease type (MF and SS).

Results: Median TTNT for the full ITT population was longer with MOGA at 11 mo (95% CI, 8.8-12.6) compared to VORI at 3.5 mo and consistently longer for MOGA vs VORI across disease stage grouping or by disease type (Table). In subjects who crossed over to MOGA, median TTNT was 10 months (95% CI: 8.0-12.6).

Conclusions: TTNT in MF/SS represents an additional measure of clinical benefit and disease control in patients who may have progressed based on strict protocol definitions of progression. This post hoc analysis showing a prolonged TTNT across disease stages and types supports a clinical benefit for MF and SS patients who receive MOGA.

Sponsor: Kyowa Kirin.

Keywords: cutaneous T-cell lymphoma (CTCL); mycosis fungoides (MF); Sezary syndrome.

Disclosures: Kim, Y: Consultant Advisory Role: *Kyowa Kirin*; Research Funding: *Kyowa Kirin*. **Ortiz-Romero, P:** Consultant

TABLE 1   TTNT, Overall and By Disease Stage and Type

Median TTNT (mo), 95% CI	N	MOGA	N	VORI	P-value (stratified log-rank)
Intent-to-treat population	186	11.0 (8.8-12.6)	186	3.5 (3.1-4.3)	<0.0001
Stage IB/II	68	7.0 (4.9-10.1)	72	3.3 (2.8-4.9)	0.0664
Stage III/IV	118	12.9 (10.6-16.7)	114	3.5 (2.8-4.7)	<0.0001
MF	105	8.8 (6.1-11.5)	99	4.1 (3.1-5.2)	0.0038
SS	81	12.9 (10.7-16.7)	87	3.3 (2.6-3.8)	<0.0001

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FINAL DATA FROM THE PHASE 3 ALCANZA STUDY: BRENTUXIMAB VEDOTIN (BV) VS PHYSICIAN'S CHOICE (PC) IN PATIENTS (PTS) WITH CD30-POSITIVE (CD30+) CUTANEOUS T-CELL LYMPHOMA (CTCL)

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TABLE 1 Subsequent anti-cancer therapy (intent-to-treat population)

	BV n=64	PC n=64
Pts with ≥1 subsequent anti-cancer therapy, n (%)	50 (78)	48 (75)
Type of therapy, n (%)*		
Skin-directed therapy	26 (52)	30 (63)
Radiotherapy	15 (30)	20 (42)
Phototherapy	13 (26)	13 (27)
Topical steroids	3 (6)	6 (13)
Other	0	0
Topical chemotherapy	0	0
Topical retinoids	0	0
Systemic therapy	44 (88)	45 (94)
Chemotherapy	34 (68)	27 (56)
Other	28 (56)	23 (48)
Methotrexate	14 (28)	10 (21)
BV	12 (24)	33 (69)
Immunotherapy	12 (24)	9 (19)
Other	9 (18)	5 (10)
Bexarotene	6 (12)	6 (13)
Histone deacetylase inhibitor	6 (12)	4 (8)
Non-topical retinoids	3 (6)	0
Photopheresis	1 (2)	1 (2)
Denileukin diftitox	0	0
Other/Unknown	1 (2)	4 (8)

*Percentages are based on the number of patients with ≥1 subsequent anti-cancer therapy in the intent-to-treat population in each arm.
Abbreviations: BV, brentuximab vedotin; PC, physician's choice; pts, patients.

Figure. PFS per IRF (intent-to-treat population; median follow-up: 36.8 months)
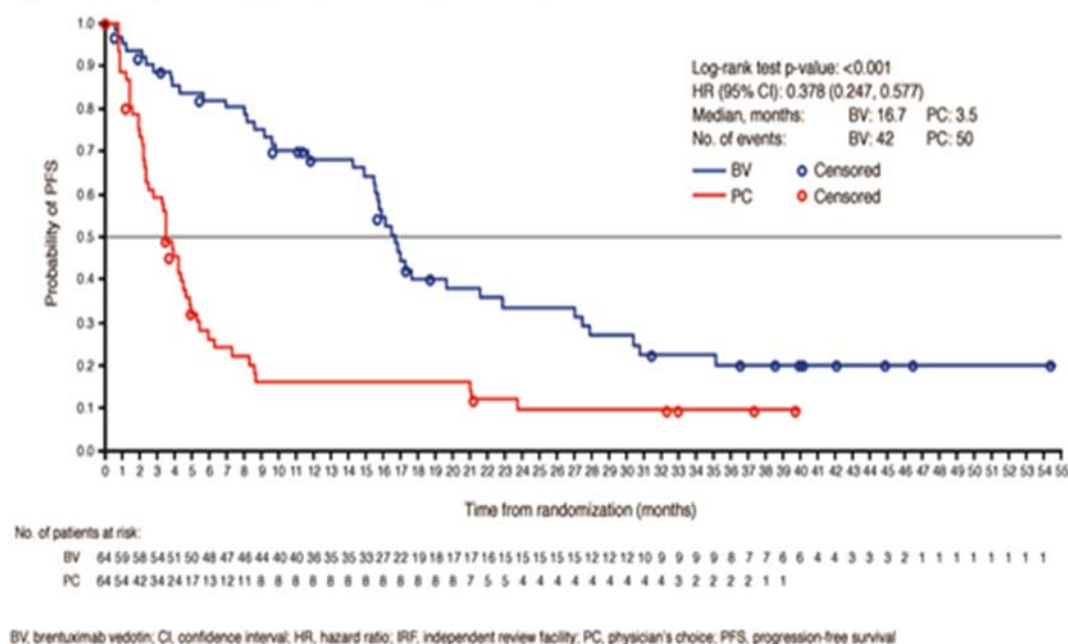
Log-rank test p-value: <0.001
HR (95% CI): 0.378 (0.247, 0.577)

	BV: 16.7	PC: 3.5
Median, months:		
No. of events:	BV: 42	PC: 50

— BV   ○ Censored
— PC   ○ Censored

No. of patients at risk:
BV 64 59 58 54 51 50 48 47 46 44 40 36 35 35 33 27 22 19 18 17 17 16 15 15 15 15 12 12 12 10 9 9 9 9 8 7 7 6 6 4 4 3 3 3 2 1 1 1 1 1 1 1 1
PC 64 54 42 34 24 17 13 12 11 8 8 8 8 8 8 8 8 8 8 8 7 5 5 4 4 4 4 4 4 4 3 2 2 2 2 1 1

BV, brentuximab vedotin; CI, confidence interval; HR, hazard ratio; IRF, independent review facility; PC, physician's choice; PFS, progression-free survival

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Introduction: The original ALCANZA analysis (median follow-up: 22.9 months; Prince et al, *Lancet*, 2017; NCT01578499) showed significant improvements in rate of objective response lasting ≥4 months (ORR4) and progression-free survival (PFS) with BV vs PC (methotrexate or bexarotene) for the treatment of CD30+ CTCL. We report final ALCANZA results (data cut-off: 28 Sep 2018; median follow-up for overall survival [OS]: 45.9 months).

Methods: Adults with previously treated CD30+ mycosis fungoides (MF; including transformed MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL) were randomized 1:1 to BV or PC. Detailed methods have been published previously.

Results: The intent-to-treat population comprised 128 pts (MF = 97; pcALCL = 31). Final results demonstrate improved efficacy with BV vs PC: ORR4 per independent review facility (IRF), 54.7% vs 12.5% (P<0.001); ORR4 per investigator, 59.4% vs 7.8% (P<0.001); CR rate per IRF, 17.2% vs 1.6% (P = 0.002). Median PFS was 16.7 months in the BV arm vs 3.5 months with PC (P<0.001; **Figure**). In the BV and PC arms, 78% and 75% of pts had received subsequent antineoplastic therapy, respectively. Median time to next therapy (TTNT) was significantly longer with BV vs PC (14.2 vs 5.6 months;

HR, 0.269; 95% CI: 0.171, 0.424; p<0.001). In the BV arm, the probability of pts not requiring subsequent antineoplastic therapy was 65.5% at 1 year and 23.6% at 2 years. Types of subsequent anti-cancer therapy are shown in the **Table**; 24% of pts were retreated with BV, and 69% received BV after PC. There were 23 deaths in the BV arm and 25 in the PC arm (HR: 0.745; 95% CI: 0.421, 1.318; P = 0.310; ALCANZA was not powered to evaluate OS). Peripheral neuropathy (PN) is a known toxicity with BV. 44/66 pts (67%) treated with BV (safety population) experienced a PN event (standardised MedDRA query); most events were Grade (G) 1 (18/44) or 2 (20/44), and there were 6 G3 and no G4 events. Final results show that 86% (38/44) of pts with PN events in the BV arm had complete resolution (26/44) or improvement (by at least 1 grade; 12/44) of all PN events, compared with 82% (36/44) in the original analysis; ongoing PN was G1/2 in 15/3 pts (no pts had ongoing G3/4 PN), compared with G1/2 in 17/5 pts in the original analysis.

Conclusions: Final analyses from ALCANZA confirm improved, durable responses and longer PFS with BV vs PC in CD30+ CTCL. BV demonstrated extended TTNT vs PC, suggesting that durable BV responses were clinically meaningful. PN is ongoing in 27% (18/66) of pts treated with BV, but is all G1/2.

Keywords: brentuximab vedotin; CD30; cutaneous T-cell lymphoma (CTCL).

Disclosures: Horwitz, S: Consultant Advisory Role: *ADCT Therapeutics, Aileron, Forty-Seven, Infinity/Verastem, Kyowa-Hakka-Kirin, Millennium Pharmaceuticals Inc, Seattle Genetics, Affimed, Angimmune, Beigene, Corvus, Innate Pharma, Kura, Merck, Miragen, Mundipharma, Portola, Syros Pharmaceutical*; Research Funding: *ADCT Therapeutics, Aileron, Forty-Seven, Infinity/Verastem, Kyowa-Hakka-Kirin, Millennium*

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CLINICAL AND BIOLOGICAL PREDICTORS OF OUTCOME IN LARGE GRANULAR LYMPHOCYTE LEUKEMIA: A SINGLE CENTER EXPERIENCE OF 205 PATIENTS

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Introduction: Large Granular Lymphocyte Leukemia (LGLL) is a rare chronic lymphoproliferative disorder characterized by the expansion of LGLs. Among LGLL, according to the phenotype, a CD3+ T-LGLL and a CD3- Chronic Lymphoproliferative disorder of Natural Killer cells (CLPD-NK) are recognized. Moreover, according to the T cell receptor rearrangement, the $T\alpha\beta$ and $T\gamma\delta$ subsets can be identified. LGLL is a heterogeneous disease with some patients being asymptomatic and other developing cytopenias. The etiology is unknown but a constitutive activation of JAK/STAT pathway is involved in LGL proliferation, supported by the evidence of somatic *STAT3* and *STAT5b* mutations in approximately 40% of patients.

The aim of this study is to analyse clinical and biological features of a large cohort of LGLL patients to identify prognostic markers affecting patients' outcome.

Methods: From 1992 to 2018, clinical and biological data of 205 patients affected by LGLL have been collected. *STAT3* exon 21 mutation and *STAT5b* exon 16-18 mutation analyses were performed by Sanger sequencing.

Results: Median age at diagnosis was 58 years. By phenotype, 129/205 (62.9%) patients were affected by $T\alpha\beta$ LGLL, 23/205 (11.2%) by $T\gamma\delta$ LGLL, and 36/205 (17.6%) by CLPD-NK. Moreover, 17 patients (8.3%) were characterized by a bi-phenotypical variant, identified by a concomitant T/NK or $T\alpha\beta/T\gamma\delta$ clone. According to CD4 and CD8 expression, $T\alpha\beta$ LGLL was further classified in CD4-/CD8+ LGLL (CD8+ T-LGLL, 84/205, 41%) and CD4+/CD8$^{dim/neg}$ LGLL (CD4+ T-LGLL, 45/205, 21.9%).

Neutropenia (Absolute Neutrophil's Count, ANC<1,500/mm^3) was the most relevant feature (78/205, 38%), severe neutropenia (ANC<500/mm^3) being present in 20.5% of patients. Anemia (Hb<120 g/L, 27/205, 13.2%), severe anemia (Hb<90g/L, 20/205, 9.8%) and thrombocytopenia (PLTs <100.000/mm^3, 12/205, 4.8%) were less recurring.

DNA samples of 166 and 152 patients were available for *STAT3* and *STAT5b* mutations analysis, respectively. *STAT3* mutations were detected in 47 patients (28.3%), with a higher frequency in CD8+ Tαβ LGLL towards Tγδ LGLL (60% vs 25%, p = 0.0232) and CLPD-NK (60% vs 5.8%, p<0.0001). At variance, *STAT5b* mutations were found in 15 patients (9.8%), in 12 case were CD4+ Tαβ LGLL and in 3 cases were Tγδ LGLL.

With a median follow up of 8 years, median overall survival (OS) of our cohort was not reached. Major features associated to reduced OS were ANC<500/mm^3 (267 months vs not reached, p = 0.0297), severe anemia (144 months vs not reached, p<0.0001), treatment requirement (214 vs not reached, p = 0.0011) and presence of *STAT3* mutations (267 months vs not reached, p = 0.0113).

Conclusion: Our results confirmed the remarkable heterogeneity of LGLL. We identified clinical and biological features associated to reduced OS in LGLL patients and, for the first time, we demonstrated the dismal impact of *STAT3* mutations in patients' survival, suggesting that this marker should be regarded as a potential target of therapy.

Keywords: immunophenotype; non-Hodgkin lymphoma (NHL).

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CLINICAL CHARACTERISTICS AND OUTCOME OF PATIENTS WITH HODGKIN'S LYMPHOMA OLDER THAN 60 YEARS TREATED IN SWITZERLAND OVER THE LAST 17 YEARS

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Introduction: Approximately 20% of Hodgkin lymphoma (HL) patients (pts) are older than 60 years at diagnosis. Despite the fact that HL remains a highly curable disease, this particular group of pts tends to have a less favorable outcome than their younger counterparts. This is mainly related to the increased toxicity resulting in higher treatment-related mortality and insufficient dosing of the drugs applied.

Methods: We conducted a population-based, retrospective analysis which aimed to investigate patient characteristics, treatment strategies and outcome of pts with HL older than 60 years of age, treated between 2000 and 2017, in 15 Centers across Switzerland.

Results: We identified 249 pts with the following characteristics: Median age at diagnosis 71 years (range: 60-94), 123 pts 60-70 years, 89 pts 71 – 80 years, 37 pts > 80 years. 158 (63.5%) male, 191 (81.7%) Performance Status (PS) 0-1, Charlson Comorbidity Index (CCI) low (2-4 points) in 42 (16.9%) pts and high (> 4 points) in 205 (82.3%) pts. 121 (49%) pts with stage I/II ; 126 (51%) with stage III/IV and the following histologies: 238 (96%) classical HL, 11 (4%) nodular lymphocyte predominant HL. Treatment was performed as follows: radiotherapy (RT) only in 11 (4%) pts; chemotherapy followed by RT in 79 (32%) pts, chemotherapy only 142 (57%) pts; 221 pts received systemic therapy with: ABVD 117 (53 %); BEACOPPesc. 8 (4.0 %), other chemotherapy combinations or single agent 57 (25 %), antibody drug conjugate one pt; 12 (5.0 %) pts received best supportive care, in 5 (2%) pts information was missing. Haematological
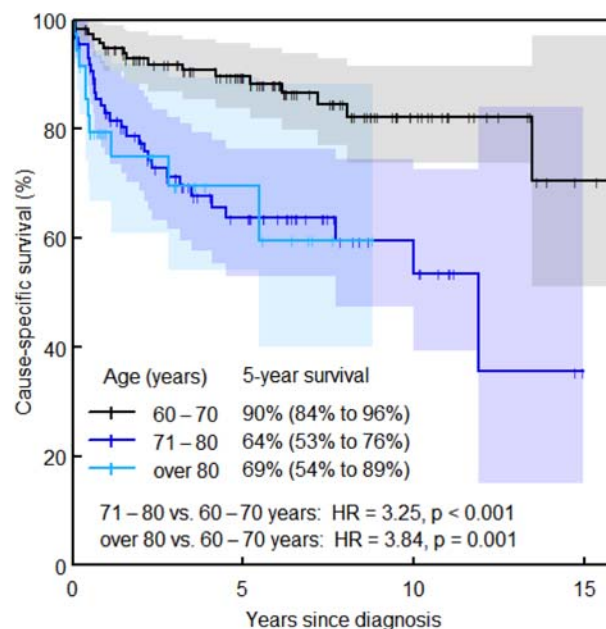
toxicity ≥G2 was observed in 111 (42.7%) pts, 65 (25%) pts presented with infections and 44 (17%) pts with febrile neutropenia.

Bleomycin lung-toxicity (BLT) was documented in 25 (18%) pts: 6 (4 %) pts had mild toxicity (radiologic changes only), 12 (9%) pts had severe toxicity (leading to hospitalization), in 7 (5%) pts severity was unknown.

In 58 (24%) pts treatment was discontinued prematurely due to toxicity. 171 (68.7%) pts achieved complete remission, 30 (12%) partial response. 58 (23%) pts relapsed/progressed after first line treatment. 25 (23%) pts died of HL and 15 (14%) of treatment toxicity. With a median follow-up of 4.1 years (range: 0.05 - 17.95) for the whole study population, progression-free survival (PFS) at 2 and 5 years was 81% and 72% respectively, cause-specific survival (CSS) at 2 and 5 years was 85% and 78%, respectively. CSS for pts 71-80 years vs 60-70 years; HR = 3.25, p<0.001 and > 80 years vs 60-70 years; HR 3.84, p = 0.001.

Conclusion: Cause-specific survival of unselected, elderly HL pts > 71 years decreased significantly in comparison to those 60 to 70 years. Toxicities appeared to be relevant, in particular infections and BLT. Bleomycin needs to be used with extreme caution in this particular group of patients. New treatment strategies with a low toxicity profile are clearly needed, in particular for frail pts and pts older than 70 years.

Keywords: elderly; Hodgkin lymphoma (HL).

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EXPLORATORY BIOMARKER ANALYSIS IN THE PH 3 ECHELON-1 STUDY: WORSE OUTCOME WITH ABVD IN PATIENTS WITH ELEVATED BASELINE LEVELS OF SCD30 AND TARC

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Introduction: Soluble (s)CD30 and thymus and activation-regulated chemokine (TARC) are established prognostic biomarkers in Hodgkin lymphoma (HL): higher baseline serum levels are associated with poorer survival outcomes. Elevated sCD30 and TARC levels are also associated with established poor prognostic factors in HL, e.g. Stage IV disease, higher International Prognostic Score (IPS), and extranodal involvement (ENI). The phase 3 ECHELON-1 study compared front-line brentuximab vedotin (a CD30-directed antibody-drug conjugate) plus doxorubicin, vinblastine, and dacarbazine (A+AVD) vs ABVD in patients (pts) with advanced classical HL (cHL). A+AVD demonstrated superior modified progression-free survival (modified PFS) vs ABVD (HR = 0.77 [95% CI 0.60–0.98]; p = 0.035; 2-yr mPFS 82.1% vs 77.2%. An exploratory ad-hoc biomarker analysis evaluated mPFS according to baseline sCD30 and TARC levels.

Methods: Serum samples were collected from 1334 pts with Stage III (36%) or IV (64%) cHL during the screening period and analyzed using validated assays for sCD30 (Covance Labs) and TARC (ICON Labs). mPFS (defined as time to progression, death, or evidence of noncomplete response followed by subsequent anticancer therapy) per independent review facility (IRF) was analyzed according to baseline sCD30 and TARC levels; the association of biomarker levels with treatment outcomes along with other potential predictive factors was explored in a multivariate Cox model.

Results: For the ad-hoc sCD30 analysis, pts were dichotomized around the median sCD30 baseline level (207.9 ng/mL). Pts in the A+AVD arm performed similarly regardless of baseline sCD30 level, with a 2-yr mPFS of 80.7% (sCD30 >median) and 82.7% (sCD30 ≤median). However, a decrease in effectiveness of ABVD was observed in pts with sCD30 >median with a 2-yr mPFS of 68.9% [sCD30 >median] and 85.7% [sCD30 ≤median]). A mPFS benefit in

favor of A+AVD vs ABVD was observed in pts with sCD30 >median (HR (95% CI) = 0.600 (0.428-0.841)) . Multivariate Cox analysis with the interaction between treatment group and sCD30 level showed an increased risk of experiencing an mPFS event with ABVD and sCD30 >median (interaction p = 0.025) when adjusted by other prognostic factors (Ann Arbor stage, IPS and ENI). Similar trends were observed with the exploratory ad-hoc TARC analysis. No new safety signals were reported in subgroups with elevated sCD30 or TARC levels.

Conclusions: Preliminary adhoc analysis indicates that ABVD treated patients do not perform as well with elevated baseline sCD30 and TARC levels. A+AVD treated patients perform well regardless of levels of these poor prognostic markers. Prospective studies need to be conducted in order to further validate these findings. If validated, these biomarkers may help identify patient populations that could benefit from more effectively targeted therapy.

Keywords: ABVD; brentuximab vedotin; classical Hodgkin lymphoma (cHL).

Disclosures: Radford, J: Consultant Advisory Role: *Millennium Pharmaceuticals Inc, ADC Therapeutics, BMS, Novartis*; Stock Ownership: *GSK, AstraZeneca (spouse)*; Honoraria: *Millennium Pharmaceuticals Inc, Seattle Genetics, Novartis, BMS*; Research Funding: *Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited*. **Connors, J:** Consultant Advisory Role: *Seattle Genetics, Millennium Pharmaceuticals Inc*; Honoraria: *Seattle Genetics, Millennium Pharmaceuticals Inc*; Research Funding: *Seattle Genetics*. **Younes, A:** Consultant Advisory Role: *BMS, Incyte, Janssen, Genentech, Merck*; Honoraria: *Genentech, Merck, Millennium Pharmaceuticals Inc, Incyte, BMS, AbbVie*; Research Funding: *Novartis, J&J, Curis, Roche, BMS*. **Ansell, S:** Research Funding: *BMS, Seattle Genetics, Trillium, Affimed, Pfizer, LAM Therapeutics, Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited*. **Kim, W:** Research Funding: *Roche, Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, J&J, Mundupharma, Kyowa-kirin, Celltrion, DongaN*. **Flinn, I:** Consultant Advisory Role: *Abbvie, Seattle Genetics, TG Therapeutics, Verastem*; Research Funding: *Abbvie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Calithera Biosciences, Celgene, Constellation Pharmaceuticals, Curis, FORMA Therapeutics, Forty Seven, Genentech, Gilead Sciences, Incyte, Infinity Pharmaceuticals, Janssen, Juno Therapeutics, Karyopharm Therapeutics, Kite Pharma, Merck, MorphoSys AG, Novartis, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Roche, Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Teva, TG Therapeutics, Trillium Therapeutics, Unum Therapeutics, Verastem*. **Pettengell, R:** Consultant Advisory Role: *CTI Life Sciences Ltd, Immune Design, Pfizer, Roche Ltd, Servier, Millennium Pharmaceuticals Inc, TEVA*; Honoraria: *CTI Life Sciences Ltd, Immune Design, Pfizer, Roche Ltd, Servier, Millennium Pharmaceuticals Inc, TEVA*. **Onsum, M:** Employment Leadership Position: *Seattle Genetics*; Stock Ownership: *Seattle Genetics*. **Josephson, N:** Employment Leadership Position: *Seattle Genetics, Inc.*; Stock Ownership: *Seattle Genetics, Inc.*. **Kuroda, S:** Employment Leadership Position: *Takeda Pharmaceutical Company Limited*. **Liu, R:** Employment Leadership Position: *Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited*. **Miao, H:** Employment Leadership Position: *Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited*. **Gautam, A:** Employment Leadership Position: *Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited*; Stock Ownership: *Takeda Pharmaceutical Company Limited*. **Trepicchio, W:** Employment Leadership Position: *Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited*. **Sureda, A:** Consultant Advisory Role: *Millennium Pharmaceuticals Inc, BMS, Gilead, Novartis*; Honoraria: *Millennium Pharmaceuticals Inc, BMS, MSD, Gilead, Novartis, Jannssen, Celgene, Sanofi, Roche*.

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DOSE DENSE ABVD (DD-ABVD) AS FIRST LINE THERAPY IN EARLY-STAGE UNFAVORABLE HODGKIN LYMPHOMA (HD): RESULTS OF A PHASE II, PROSPECTIVE STUDY BY FONDAZIONE ITALIANA LINFOMI

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Four cycles of ABVD followed by 30Gy involved site radiotherapy (ISRT) is the standard of care in unfavourable classical Hodgkin lymphoma (HL). Since dose-density might represent an important factor to achieve complete remission and longterm survival, we designed a trial to evaluate dose-dense ABVD (ddABVD) in ptients (pts) with early unfavourable HL. This prospective, multicentric, phase 2 study enrolled pts aged 18–70 years with newly diagnosed cHL, unfavourable stage I or II (EORTC criteria). Stage IIB bulky were excluded.

Aims of the study were feasibility, safety and efficacy of ddABVD. DdABVD consists of Doxorubicin, Bleomycin, Vinblastine and Dacarbazine used at the same doses of conventional ABVD but is administered on days 1 and 8 every 3 weeks instead of days 1 and 15 every 4 weeks. In the absence of progressive disease (PD) or unacceptable toxicity, 4 cycles of ddABVD followed by ISRT were administered. Interim PET was mandatory after 2 courses (PET2). Pts experiencing PD were shifted to second-line therapy. Feasibility and activity of ddABVD were the primary endpoints of the study. By design, the study was considered feasible if ≤5 out of 52 pts required a dose reduction below 85% of the planned dose. The percentage of PET2 negativity was chosen as the parameter to evaluate its activity.

Between Feb 2012 and Jun 2015, 96 pts were enrolled and evaluated. The feasibility endpoint was achieved with only 4 out of 52 pts requiring a dose reduction greater than 15%. The mean dose intensity in the 96 pts who started ddABVD treatment was 93.7% with only 3 pts unable to complete ddABVD due to toxicity. The activity analysis was performed in all 96 pts. PET-2 was available for 92/96 (95.8%) pts: 79 were PET2 negative (85.9%) and 13 PET2 positive (14.1%). In 4 pts PET2 wasn't performed (3 logistic reasons, 1 switched to standard ABVD due to a SAE at cycle 1). Considering the global outcome of the 96 pts who received at least 1 ddABVD course: 90 pts achieved CR (93.8%), 1 PR (1%), 4 PD (4.2%) and 1 (1%) was without a known disease assessment. With a median followup of 39.9 months (2.1- 57.6), median PFS and OS were not reached, at 24 months PFS and OS were 91.5% and 97.9%. No statistically significant differences were observed for PET2 negative and PET2 pts for both 2 years PFS (94.9% vs 84.6%, p:0.260) and OS (98.7% vs 100% a, p:0.560). Most frequent toxicities were haematological. The infection rate was low (infection 8.3% and febrile neutropenia 6.25%); no patient developed cardiac toxicity until now. There was 1 toxic death after cycle 4; 3 pts were discontinued due to toxicity and were switched to standard ABVD or AVD. The study demonstrates the feasibility of ddABVD in early unfavourable cHL which also allows a reduction in overall treatment duration without a significant increase in toxicity. The dose-dense strategy translated in excellent outcome in term of CR rate, PFS, OS with a low rate of PR at 2 years. DdABVD deserves further comparison with conventional ABVD.

Keywords: ABVD; chemotherapy; Hodgkin lymphoma (HL).

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BRENTUXIMAB-VEDOTIN AND BENDAMUSTINE IS A FEASIBLE AND EFFECTIVE DRUG COMBINATION AS FIRST-LINE TREATMENT OF HODGKIN LYMPHOMA IN THE ELDERLY (HALO TRIAL)

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Background: Hodgkin Lymphoma (HL) in the elderly is a challenge as standard ABVD failed to achieve long-term disease control as in adults. Bendamustine (Be), and Brentuximab Vedotin (BV), are well-tolerated and effective drugs in relapsing HL, but only preliminary data exist with this combination in 1st line treatment of elderly HL (Evens AM 2018).

Pts and methods: A prospective multicenter phase I/II study (HALO study NCT n°02467946) was launched to assess the safety and efficacy of Be given at 90 mg/m2/D1D2 combined with BV at 1.2 mg/kg D1 repeated Q3W for 6 cycles, in 1st line therapy for advanced-stage (IIB-IV) HL patients (pts) aged 60-80 years. A non-decisional FDG-PET after the 2nd cycle (PET-2) was done and assessed using the Lugano criteria. Pts with Progressive Metabolic Disease (PMD) at any time underwent salvage therapy. The study was split up in a phase 1 (12 pts) for feasibility and a phase 2 (48 pts) for efficacy assessment. Secondary endpoint was the efficacy (3-Y PFS and OS) of the regimen

Results: The 60 pts required for the study design were enrolled, but only 42 with complete dataset are valuable for analysis. For this group, the mean age was 70 years (62-79), M/F ratio 28/14 and performance status 0 in 19 or 1-2 in 23. Histology was: HL classic NOS 8, nodular sclerosis 24, mixed cellularity 6, and lymphocyte rich 4. Mean Hb value was 12.2 g/dl, WBC 9.63 x 10^3/μl, Albumin 36.8 g/l, LDH elevated in 14. The stage was II in 8, III in 13 and IV in 21 pts. B-symptoms were present in 29/42; 16 had no extranodal sites (ENS), 26 ≥1 ENS. IPS was 0-1 in 2, 2-3 in 22, > 3 in 18. Pts frailty was high, as geriatric ADL and IADL functional tests showed

the highest score (6 and 8) in 35 (83%) and 33 (78%) of pts., respectively. The most frequent comorbidity was arterial hypertension (19%) and diabetes (6%). PET-2 was positive in 6/39 pts, with a Deauville score of 4 in 5 and 5 in 1 patient. 12/39 did not complete the treatment for toxicity (6), progression (5) or investigator decision (1). 125 grade 3-4 toxicities were recorded: lymphopenia (56%), neutropenia (19%), CMV reactivation (2.4%), febrile neutropenia (2.4%), rash/infusion reaction (3.2%). Five pts died of recurrent HL (2), CMV reactivation (2) and stomach cancer (1). In an intention to treat analysis 39 pts are evaluable for response: 27 (69%) were in CR. After a median FU of 16.2 (12.2-26.6) months 17 pts experienced a treatment failure: 3 for progression during treatment and 12 for progression or relapse 94-670 days after treatment end. The 2y OS and PFS rate in intention to treat were 85% (95% CI 72-100) and 47% (95% CI 31-71) and in per protocol analysis 100% and 75% (95%CI 58-97), respectively.

Conclusion: The present analysis, though conducted in 2/3 of enrolled patients showed that Be-BV is an effective regimen in the real life of elderly HL, when delivered according to the schedule. The toxicity of this treatment could be improved by a more strict prophylaxis of CMV infections.

Keywords: Bendamustine; brentuximab vedotin; Hodgkin lymphoma (HL).

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PET-ADAPTED NIVOLUMAB +/- ICE AS INITIAL SALVAGE THERAPY IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA

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Introduction: Nivolumab (nivo) is an anti-PD-1 antibody that restores effective anti-tumor immune responses and is tolerable and effective in patients (pts) with relapsed/refractory (RR) Hodgkin lymphoma (HL). Nivo combined with brentuximab vedotin (BV) as initial salvage therapy yields high response rates and favorable progression-free survival as a bridge to autologous stem cell transplantation (ASCT) in pts with RR HL. With the frontline approval of BV, it is necessary to evaluate the role of nivo as salvage therapy separate from BV. We report the preliminary results of a phase 2 trial evaluating PET-adapted nivo +/- ICE chemotherapy as initial salvage treatment in RR HL prior to ASCT.

Methods: In this prospective, multicenter trial, pts with biopsy-proven RR HL after frontline therapy received 3 mg/kg nivo every 2 weeks for up to 6 cycles. PET-CT was performed after cycle 3 and cycle 6. After cycle 6, pts in CR proceeded to ASCT while pts not in CR received nivo + ICE (NICE) for 2 cycles. The primary endpoint was complete response rate according to 2014 Lugano classification.

Results: 28 pts were evaluable for toxicity; 26 were evaluable for response. 68% were male, median age 35 years, 46% were primary refractory; at baseline, 50% had stage III-IV, 43% had B symptoms, and 68% had bulky disease (> 5cm). 22 pts received nivo alone and 6 pts received nivo/NICE. 25 pts completed therapy, 1 pt discontinued early in CR to undergo ASCT, 2 pts discontinued nivo early due to adverse events (AE, 1 pt = Gr 4 altered mental status, 1 pt = Gr 2 pneumonitis). Nivo-related AEs were consistent with known AE profile, rash (21%, all grade 1) was the most common AE and only 1 pt had grade 3-4 AEs (1 HIV+ pt with Gr 4 altered mental status and Gr 3 tumor lysis syndrome). In pts who received NICE, the most common AEs were nausea and vomiting (50%, all Gr 1) and the only Gr 3-4 event was Gr 4 neutropenia in one pt.

25 out of 26 evaluable pts (96%) responded to nivo, with a best CR rate of 81% (21/26). 3 pts who initially responded to nivo (1 CR, 2 PR) had progressive disease at the end of 6 cycles. At the end of nivo, the CR rate was 77% (20/26) and overall response rate was 85% (22/26). 6 pts were treated with NICE and 5 achieved CR (83%). Overall, at the end of protocol therapy (nivo or nivo/NICE), 96% (25/26) of evaluable pts were in CR. 22 pts proceeded to ASCT directly after protocol therapy and 3 pts in CR refused ASCT. One pt with PR after NICE subsequently responded to additional salvage therapy and is proceeding to ASCT. In pts who proceeded to ASCT, a median of 2 stem cell collections were required, a median of 4.8×10^6 CD34+ cells/kg (range 3.12 – 16.23) were collected, and the median time to neutrophil and platelet engraftment were 11 and 13 days, respectively. All transplanted pts remain in CR with median follow-up time of 5 months (range, 0-19mo).

Conclusion: PET-adapted Nivo followed by NICE is a well-tolerated and highly effective first salvage regimen in pts with RR HL that merits further exploration.

AFH and RC contributed equally

Keywords: Hodgkin lymphoma (HL); ICE; nivolumab.

Disclosures: Herrera, A: Consultant Advisory Role: *Bristol-Myers Squibb, Genentech, Merck, Adaptive Biotechnologies and Kite Pharma/Gilead*; Research Funding: *Bristol-Myers Squibb, Genentech, Immune Design, AstraZeneca, Merck, Seattle Genetics and Kite Pharma, Gilead Sciences.*

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TRANSCRIPTIONAL NETWORKS ASSOCIATED WITH TREATMENT FAILURE IN ADVANCED-STAGE HODGKIN LYMPHOMA: DATA FROM THE RATHL TRIAL (CRUK/07/033)

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Introduction: First line treatment of advanced-stage Hodgkin lymphoma produces high response rates but fails in up to 20%, with disease progression or relapse. Interim PET imaging is used for guiding treatment adaptation. However, in the RATHL trial[1], 15% of patients with interim negative PET experienced subsequent disease relapse, indicating a need to improve upon the current approach. We performed next generation RNA sequencing on a selected cohort within the RATHL trial, to identify transcriptional networks associated with treatment failure. These analyses serve to study the mechanisms of chemotherapy resistance in Hodgkin lymphoma and yield gene sets which might improve upon the negative predictive value of interim PET.

Methods: Whole transcriptome profiling was performed on RNA derived from diagnostic FFPE samples. The cases selected were divided into 2 groups; group one, patients who experienced disease relapse, progression or death within 2 years of trial registration (interim PET neg (n = 21) vs PET pos (n = 11)), and group two, patients who continued to be in complete remission at 2 years (n = 38). Both cohorts were standardised in histology subtype, age, stage, bulk, performance status and B symptoms. Unsupervised consensus gene co-expression network analysis was used to identify features associated with chemotherapy response.

Results: After RNA sequencing data pre-processing and outlier removal, a measure of topological overlap (TO) was calculated separately for the two groups, based on pairwise correlations between 12,209 expressed genes. The TO between each gene pair was then set to parallel minimum. Within this consensus dissimilarity matrix, 57 modules were identified by unsupervised clustering. These modules were highly enriched for genes associated with immune and non-immune cells (e.g. T-helper cells, macrophages and lymphatic endothelial cells) as well as biological response pathways (e.g. endothelial-mesenchymal transition and angiogenesis). Conventional differential expression analysis indicated that treatment failure was associated with increased extracellular matrix components and myeloid lineage genes. To gain an insight into how these changes might confer chemotherapy resistance, we constructed eigengene networks between co-expressed modules for each group. This analysis indicated that aberrant lymphatic vessel growth and development were associated with treatment failure, driven by a network of paracrine signals between eosinophils, M2 macrophages and endothelial cells.

Conclusions: Our findings indicate that protective signals arising from the stromal microenvironment, centered on a CXCL9-CXCR3 axis, confer chemotherapy resistance and suggest targeted therapies may be useful in this context.

Reference

[1]Johnson P et al. Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma. NEJM 2016;374:2419-29.

Keywords: classical Hodgkin lymphoma (cHL); gene expression profile (GEP); macrophages.

Disclosures: Lim, S: Consultant Advisory Role: *Celldex Therapeutics*; Honoraria: *Gilead*; Research Funding: *Celldex Therapeutics, Bioinvent, Incyte*; Other Remuneration: *Takeda, BMS*. **Burton, C:** Consultant Advisory Role: *Roche, Takeda, BMS, Celgene*; Honoraria: *Roche, Takeda, BMS*; Other Remuneration: *Roche, Takeda*. **Barrans, S:** Other Remuneration: *HTG molecular*. **Johnson, P:** Consultant Advisory Role: *Janssen*; Honoraria: *Bristol-Myers Squibb, Takeda, Novartis, Celgene, Janssen, Epizyme, Boeringher Ingelheim, Kite, Genmab, Incyte*; Research Funding: *Janssen, Epizyme*.

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OUTCOME AND TREATMENT OF RELAPSING EARLY PET NEGATIVE PATIENTS INCLUDED IN THE EORTC/LYSA/FIL H10 TRIAL ON STAGES I/II HODGKIN LYMPHOMA

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Background: The final results of the randomized EORTC/LYSA/FIL H10 trial showed that early PET negative patients have an excellent

TABLE 1. Demographic, disease and treatment characteristics in relapsing patients

	Initial treatment received		All	p-value
	CT N=66	CMT N=28	N=94	
Sex, Female	25 (37.9%)	14 (50.0%)	39 (41.5%)	0.36
Median Age	31.2	30.4	31.2	0.85
Prognostic factors				0.005
Favourable	30 (45.5%)	4 (14.3%)	34 (36.2%)	
Unfavourable	36 (54.5%)	24 (85.7%)	60 (63.8%)	
Ann Arbor clinical stage				0.25
I	15 (22.7%)	3 (10.7%)	18 (19.1%)	
II	51 (77.3%)	25 (89.3%)	76 (80.9%)	
Histologically documented Hodgkins Lymphoma (HL)				0.87
Lym Depl	1 (1.5%)	0 (0.0%)	1 (1.1%)	
Mix Cell	11 (16.7%)	4 (14.3%)	15 (16.0%)	
Nod Lym Predom	2 (3.0%)	0 (0.0%)	2 (2.1%)	
Nod Scler	48 (72.7%)	24 (85.7%)	72 (76.6%)	
Unclass	3 (4.5%)	0 (0.0%)	3 (3.2%)	
Other	1 (1.5%)	0 (0.0%)	1 (1.1%)	
Median number of nodal areas	2.0	2.5	2.0	0.15
Bulky mediastinum, Yes	23 (34.8%)	10 (35.7%)	33 (35.1%)	0.99
B symptoms, Yes	21 (31.8%)	13 (46.4%)	34 (36.2%)	0.24
WHO performance status (0-4)				0.095
0	57 (86.4%)	19 (67.9%)	76 (80.9%)	
1	7 (10.6%)	8 (28.6%)	15 (16.0%)	
2	2 (3.0%)	1 (3.6%)	3 (3.2%)	
Median ESR	26.0	54.5	37.0	<0.001
Number of salvage treatment lines				0.74
1	47 (71.2%)	22 (78.6%)	69 (73.4%)	
2	6 (9%)	3 (10.7%)	9 (9.6%)	
≥3	12 (18.2%)	3 (10.7%)	15 (16%)	
Unknown	1 (1.6%)	0 (0%)	1 (1%)	
Type of salvage treatment				0.012
ASCT	41 (63.1%)	25 (89.3%)	66 (71.0%)	
CT and/or RT	24 (36.9%)	3 (10.7%)	27 (29.0%)	
Unknown				
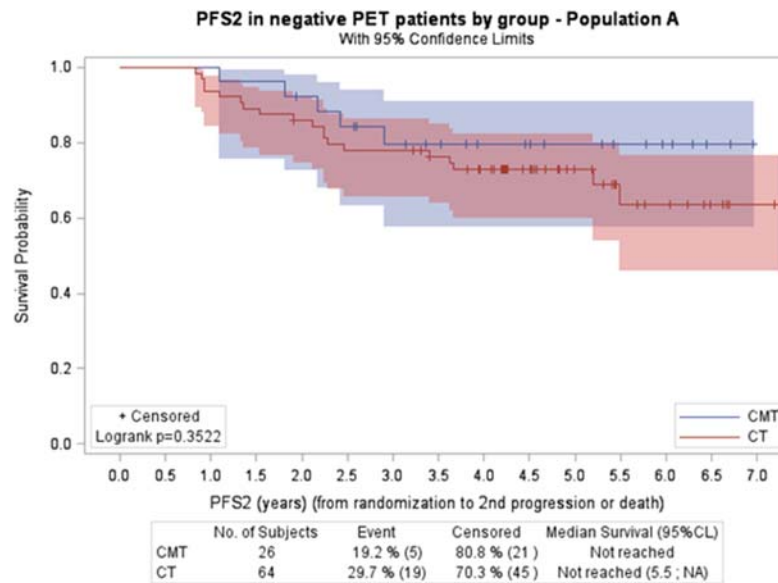
Figure 1: PFS2 in PET2 negative patients by initial treatment: blue line represents group initially treated by CMT and red line, group initially treated by CT.

outcome with combined modality therapy (CMT) or chemotherapy (CT) only, although relapses occurred in both treatment arms. We analyzed the type of salvage treatment and outcome of these relapsing patients.

Methods: In the H10 trial, previously untreated patients, 15-70 years old, with classical supradiaphragmatic stage I-II HL, both favorable (F) and unfavorable (U) according to EORTC/LYSA criteria, were eligible. The primary protocol treatment for earlyPET (after 2xABVD) negative patients consisted of: in F patients, 3xABVD+involved-node radiotherapy (INRT) or 4xABVD; in U patients 4xABVD+INRT or 6xABVD. In 2010, the H10 trial was amended since more early relapses occurred in the CT arm of the trial and from that moment on, all early PETnegative patients received CMT. All earlyPET negative patients who relapsed were included in the current analysis and grouped in the CMT or CT group, dependent of the actually delivered primary treatment. The type of salvage treatment was left to the discretion of the investigator. Second progression/relapse (PFS2) was defined as the time from randomization to objective tumor progression on next-line treatment or death from any cause.

Results: Ninety-four earlyPET negative patients relapsed, 28 of those after initial CMT and 66 after CT. Their demographic and disease characteristics are described in table 1. In CMT, almost all relapses occurred in the U group whereas in CT relapses both in F and in U. Regarding salvage treatment, 69 patients received 1 line of treatment, 9 received 2 lines and 15 received 3 lines or more; for one patient, this information is missing. Overall, 66 (71%) patients received autologous stem cell transplantation (ASCT) and 29% received CT and/or RT. After CMT, the first salvage treatment was ASCT in 25/28 patients, while after CT the ASCT was first line salvage in 41/66. Overall, relapsed patients had a similar number of treatment lines whether they were initially treated with CMT or CT, but the type of treatment differed significantly with more ASCT in the CMT group (89.3% vs 63.1%, p = 0.012). There was no significant difference in OS or PFS2 between relapsing patients treated initially with CMT or CT: 3y-OS of 89% (95% CI: 69.7-96.3) vs 93.9% (95% CI: 84.6-97.7 resp.) and PFS2 (3y-PFS2 of 79.6 (95% CI:57.5-91) vs 78% (95% CI:65.7-86.3, resp.). The 3y-PFS2 and OS of patients undergoing ASCT was 62.8% and 93.9% and the 3-y PFS and OS of patients treated with CT and/or RT only was 88.9% and 88.6% respectively.

Conclusion: The outcome of earlyPET negative patients relapsing after first line treatment is good, irrespective of initial treatment with CMT or CT. More patient received ASCT as first line salvage in the CMT group. The PFS2 and OS were comparable in patient treated with initial CMT and CT.

Keywords: Hodgkin lymphoma (HL).

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FIRST SALVAGE TREATMENT WITH BENDAMUSTINE AND BRENTUXIMAB VEDOTIN IN HODGKIN LYMPHOMA: A PHASE 2 STUDY OF FIL ONLUS

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Introduction: Effective salvage options inducing high complete metabolic response (CMR) rates without significant toxicity are needed for Hodgkin lymphoma (HL) patients failing induction treatment and who are candidate to autologous stem cell transplantation (ASCT). Brentuximab vedotin (BV) and bendamustine are monotherapies both active in the relapsed/refractory setting and their combination (the BBV regimen) possibly enhances their activity.

Methods: A single-arm multicenter phase 2 study investigating the efficacy and safety of BBV as first salvage therapy in 40 patients with relapsed/refractory HL was conducted. Intravenous bendamustine was administered at the dose of 90 mg/m^2 (day 1 and 2) and BV at the standard dose of 1.8 mg/kg (day 1) every 21 days, for 2-6 cycles. Patients with at least disease stability could mobilize peripheral blood stem cells (PBSC) and proceed to ASCT.

Results: Thirty-eight patients were evaluable for efficacy: 30 (78.9%) had a CMR and 2 (5.3%) a partial response, leading to an overall response rate (ORR) of 84.2%. The ORR in the primary refractory subset was 75.0%, among relapsed patients it was 94.4%. Thirty-five patients could mobilize PBSC and 33 underwent ASCT. At a median follow-up of 23 months, the estimated 3-year overall survival and progression-free survival are 88.1% and 67.3%. During therapy, only 3 grade IV cases of neutropenia occurred and resolved within a week. No grade 4 extra-hematologic toxicities were reported; skin reactions were however rather frequent and involved 26 patients overall.

Conclusions: These results suggest that the BBV regimen exhibits promising efficacy and a manageable toxicity in a challenging subpopulation of HL patients.

Keywords: Bendamustine; brentuximab vedotin; Hodgkin lymphoma (HL).

Disclosures: Zinzani, P: Consultant Advisory Role: *Verastem, MSD, EUSAPHARMA, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, Immune Designa, Celgene, Portola, Roche, Kyowa Kirin.*

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PHASE 1B KEYNOTE-013 STUDY OF PEMBROLIZUMAB IN PATIENTS WITH CLASSIC HODGKIN LYMPHOMA AFTER BRENTUXIMAB VEDOTIN FAILURE: RESULTS OF >4 YEARS OF FOLLOW-UP

TABLE 1

	Total Population N=31	ASCT Unsuccessful/Received BV After ASCT n=16	ASCT-Ineligible/Received BV n=8	ASCT Unsuccessful/Received BV Before ASCT n=7
Objective response (CR +PR), % (95% CI)	58 (39-76)	69 (41-89)	38 (9-76)	57 (18-90)
Complete remission (CR), %	19	19	25	14
Partial remission (PR), %	39	50	13	43
Stable disease, %	23	19	38	14
Progressive disease, %	19	13	25	29

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Introduction: Programmed death-1 (PD-1) inhibitors are an effective treatment option for patients (pts) with relapsed/refractory classic Hodgkin lymphoma (cHL). The multicohort phase 1b KEYNOTE-013 study (NCT01953692) of the PD-1 inhibitor pembrolizumab (pembro) in pts with hematologic malignancies included cHL as an independent expansion cohort. To better understand the durability of responses in this patient population, we present long-term follow-up results for the cHL cohort.

Methods: Pts with cHL who experienced relapse after, were ineligible for or refused autologous stem cell transplantation (ASCT) and whose disease progressed after brentuximab vedotin (BV) therapy were enrolled. Pts received pembro IV 10 mg/kg every 2 weeks for up to 2 years or until confirmed progression or unacceptable toxicity. Primary end points were safety and complete remission rate (CRR) per central review. Secondary end points were overall response rate (ORR) duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Data cutoff was September 28, 2018.

Results: Among enrolled patients (N = 31), median follow-up was 52.8 mo (range, 7.0-57.6).The median number of lines of prior therapy was 5 (range, 2-15), and in 74% of pts, prior ASCT was ineffective. At analysis, 81% of pts had discontinued, primarily because of progression (48%), and 19% of pts had completed treatment. CRR was 19% and partial remission was 39%; ORR was 58% (18/31) (Table). Median DOR was not reached (Figure). Seven patients had a response duration ≥12 mo; 2 patients had a response duration ≥36 mo. Median PFS was 11.4 mo (95% CI, 4.9-27.8); 24-mo PFS rate was 30% (Figure). Median OS was not reached; 24-mo and 36-mo OS rates were 87% and 81%, respectively. Among pts refractory to (n = 11) and not refractory to (n = 20) first treatment, CRR was 27% and 15% respectively; ORR was 55% and 60%. By transplant status and BV status at baseline, ORR was 69% among pts who received BV after ASCT failure, 57% among pts with failed ASCT and BV before ASCT and 38%

Kaplan-Meier Estimate of Duration of Response by Central Review

Kaplan-Meier Estimate of Progression-Free Survival by Central Review
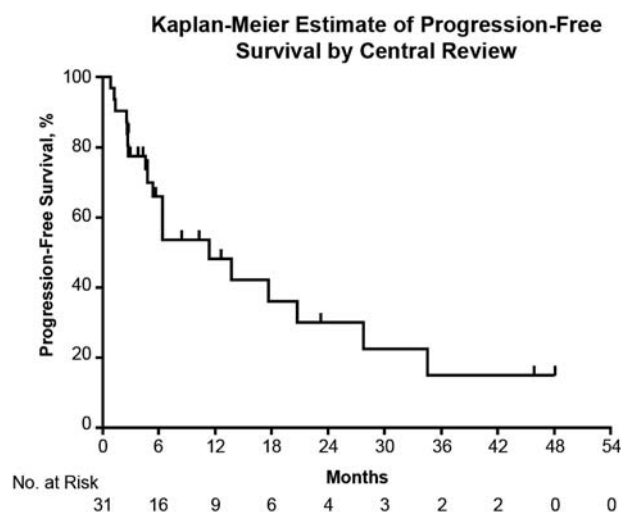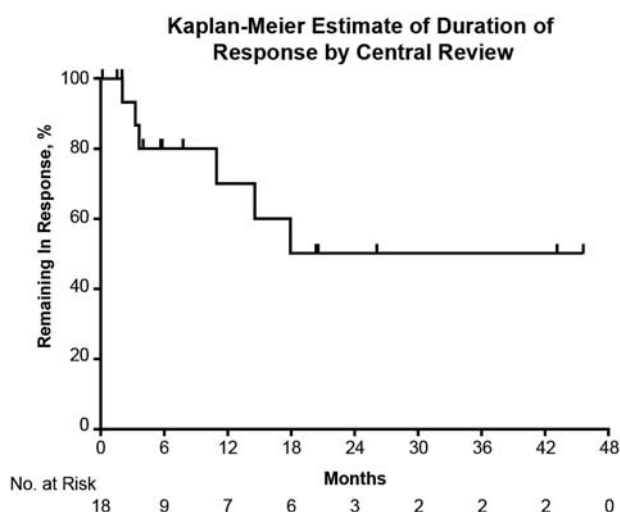
among pts who received BV and were ineligible for ASCT (Table). Overall, 22 pts (71%) experienced treatment-related adverse events (TRAEs), with diarrhea (23%) the most common; 6 pts (19%) experienced grade 3-5 TRAEs.

Conclusions: After a median follow-up of >4 years, some heavily pretreated pts for whom BV therapy was ineffective maintained long-term response with single-agent pembro. The safety profile of pembro was tolerable and as expected.

Keywords: Hodgkin lymphoma (HL); PD-1; Pembrolizumab.

Disclosures: Zinzani, P: Consultant Advisory Role: *Verastem, MSD, Eusapharma, Sanofi, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, Immune Design, Celgene, Portola, Roche, Kyowa Kirin*; Other Remuneration: *Speaker's Bureau: Verastem, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, MSD, Immune Design, Celgene, Portola, Roche, Eusapharma, Kyowa Kirin.* **Armand, P:** Employment Leadership Position: *Merck & Co., Inc., Bristol Myers Squibb Pharmaceuticals, Infinity Pharmaceuticals*; Consultant Advisory Role: *Merck & Co., Bristol Myers Squibb Pharmaceuticals, Infinity Pharmaceuticals*; Research Funding: *Merck & Co., Bristol Myers Squibb Pharmaceuticals, Pfizer, Inc, Affimed, Roche, Serventa, Otsuka, Sigma-Tau*; Other Remuneration: *Travel fees, gifts, and others: Bristol Myers Squibb Pharmaceuticals, Merck & Co..* **Ribrag, V:** Employment Leadership Position: *Gilead, Infinity, Bristol Myers Squibb Pharmaceuticals, Laboratoires Servier, NanoString Technologies, Incyte Corporation*; Consultant Advisory Role: *Gilead, Infinity, Bristol Myers Squibb Pharmaceuticals, Laboratoires Servier, NanoString Technologies, Incyte Corporation*; Research Funding: *Amgen*; Other Remuneration: *Travel fees, gifts, and others: Roche, Bristol Myers Squibb Pharmaceuticals.* **Kuruvilla, J:** Consultant Advisory Role: *Merck*; Other Remuneration: *Payment for lectures including service on speaker's bureau: Merck.* **Zhu, Y:** Employment Leadership Position: *Merck.* **Farooqui, M:** Employment Leadership Position: *Merck & Co., Inc.*; Stock Ownership: *Merck & Co., Inc.* **Nahar, A:** Employment Leadership Position: *Merck & Co., Inc.* **Moskowitz, C:** Employment Leadership Position: *Celgene, Genentech, Merck & Co., Seattle Genetics Inc.*; Consultant Advisory Role: *Celgene, Genentech, Merck & Co., Seattle Genetics Inc.*; Research Funding: *Pharmacyclics, Genentech, Merck & Co., Seattle Genetics Inc.*

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CHECKPOINT INHIBITION BEFORE HAPLOIDENTICAL TRANSPLANTATION IN RELAPSED OR REFRACTORY HODGKIN LYMPHOMA PATIENTS IS ASSOCIATED WITH HIGHER PFS WITHOUT INCREASED TOXICITIES

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Background: Immune checkpoint inhibitors (CPI) before allogeneic stem cell transplantation (SCT) could enhance allogeneic T-cell responses, increasing both the graft-versus-tumor effect and the incidence of immune complications.

Methods: We retrospectively analyzed the outcome of 52 consecutive HL patients undergoing haploidentical (haplo)-SCT with post-transplant cyclophosphamide as Graft Versus Host Disease (GVHD) prophylaxis between 2014 and 2018. The aim of this study was to

Patient characteristics	No CPI treatment (n=24)	CPI treatment (n= 28)	p
Age at transplant	31 (9-64)	29 (20-61)	
Prior autologous	22 (92%)	20 (71%)	0.58
Prior lines of therapy	4 (2-8)	6 (3-9)	**0.0006**
Disease status at SCT:			
- CR	17 (71%)	18 (64%)	
- PR	5 (21%)	8 (29%)	0.9
- SD	1 (4%)	-	
- PD	1 (4%)	2 (7%)	
Stem cells source			
Bone marrow	5 (21%)	10 (36%)	0.35
Peripheral blood stem cells	19 (79%)	18 (64%)	
Conditioning regimen			
Non mieloablative	18 (75%)	19 (68%)	0.74
Reduced intensity	6 (25%)	9 (32%)	
HCT-CI			
0-1	4 (17%)	11 (39%)	
2-3	17 (71%)	17 (61%)	0.40
4-5	3 (12%)	-	
Median follow-up (months)	26.9 (6.5-55.1)	23.7 (10.3-43.1)	0.076

compare the outcome of 28 patients who received CPI before haplo-SCT to 24 patients who underwent haplo-SCT without prior CPI. Patients' characteristics are listed in Table 1. The two cohorts were similar in their main pre-transplant characteristics, except for the CPI group who received more line therapy.

Results: After a median follow-up of 26 months (range 7.5-55), taking into account all the patients, the 6-mounths cumulative incidence (CI) of aGVHD grade 2-4 was 33% (95% CI, 20-45), whereas the 2-year CI of moderate to severe cGVHD was 11.5% (95% CI, 4-24). The 1-year CI of NRM was 10% (95% CI, 8-31) and the 2-year CI of relapse was 13% (95% CI, 5-25). The 2-year OS and PFS were 78% (95% CI, 62-88) and 69.5% (95% CI, 52-82), respectively. In univariate analysis, prior use of CPI had no effect on either acute or chronic GVHD. The 6-month CI of grade 2-4 aGVHD was 39% (95% CI, 21-57) in the CPI group and 25% (95% CI, 10-44) in the non-CPI group (p = 0.23), while the 2-year CI of moderate to severe cGVHD was 16% (95% CI, 3-39) and 9% (95% CI, 1-26), respectively (p = 0.67). The 2-year CI of relapse in the CPI group was only 4% (95% CI, 0-16) versus 22% (95% CI, 8-41) (p = 0.08) in the non-CPI group. A significantly higher 2-year PFS was observed in the CPI group (89% (95% CI, 70-96) vs 54% (95% CI, 31-72), p = 0.029)). No differences were observed in OS and NRM between the two cohorts, the 2-year OS was 88% (95% CI, 66-96) in the CPI group vs 71% in the non-CPI group (95% CI, 47-86) (p = 0.30), and the 2-year CI of NRM was 10% (95% CI, 4-27) vs 24% (95% CI, 8-44) (p = 0.26) respectively. Based on the other pre-transplant characteristics, only a correlation between disease status at SCT and OS was found: the 2-year OS was 84% (95% CI, 61-94) in CR patients, 73% (95% CI, 35-91) in PR patients and 50% (95% CI, 6-85) in PD/SD patients (p = 0.04). In multivariate analysis, disease status other than CR had a negative impact on OS (hazard ratio (HR) 6.18 (95% CI, 1.13-33, 72) for PR and HR 14 (95% CI, 199-98.29) for PD/SD). Treatment with checkpoint inhibitors before SCT was an independent protective factor for PFS (HR 0 .23 (95% CI, 0.05-0.92)).

Conclusions: CPI as a bridge to haplo-SCT significantly improve the PFS in relapse/refractory HL, lowering the relapse rate. Pre-treatment with CPI did not enhance the toxicity. However, the main limitation of our study lies in the small number of patients; further studies are warranted to extend our findings.

Keywords: allogeneic stem cell transplant (alloSCT); Hodgkin lymphoma (HL); nivolumab.

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HOW TO SELECT DONOR, STEM CELL SOURCE, AND CONDITIONING REGIMEN FOR HAPLOIDENTICAL TRANSPLANTS WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE FOR LYMPHOMA: A REPORT OF THE EBMT LWP

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Introduction: Allogeneic stem cell transplantation (SCT) is potentially curative for patients with lymphoma, particularly those who progress after autologous SCT. For patients with no identical donor a haploidentical transplant (haploSCT) with post-transplant cyclophosphamide (ptCy) is becoming a major alternative. However, multiple haploidentical donors are often available and the identification of the best donor, as well as the adequate stem cell source and conditioning becomes a dilemma.

Methods: We used a large sample from the European Society for Blood and Marrow Transplantation registry. We identified 474 adults

TABLE 1

Lymphoma subtype	2-year PFS	2-year OS
Hodgkin	57%	72%
Follicular	56%	56%
Mantle cell	52%	61%
Diffuse large B cell	35%	35%
Peripheral T cell	54%	62%

(65% males; median age: 41 years) with Hodgkin lymphoma (HL; 240), peripheral T-cell lymphoma (PTCL; 88), diffuse large B-cell lymphoma (DLBCL; 77), mantle cell lymphoma (MCL; 40) or follicular lymphoma (FL; 29), who received a haploSCT with ptCy between 2010 and 2016.

Results: The median follow-up of alive patients was 32 months. The 2-year progression free survival (PFS) and overall survival (OS) for each lymphoma subtype are shown in Table 1. On multivariate analysis, acute GVHD (aGVHD) grade 2-4 was higher when using sibling donors (HR = 1.9 p = 0.01) whereas grade 3-4 was higher when using peripheral stem cells (HR = 4.5 p = 0.001) or CMV donor negative/recipient positive status (HR = 5.3 p = 0.04). Chronic GVHD was higher in male patients (HR = 1.7 p = 0.03) or those in partial response (PR) at SCT (HR = 1.7 p = 0.03) and lower with male donors (HR = 0.6 p = 0.02). Non-relapse mortality was lower in PTCL (HR = 0.4 p = 0.02) but higher in patients with refractory disease (HR = 2.2 p = 0.006), older patients (HR = 1.2 p = 0.02), a CMV donor positive /recipient positive status (HR = 2 p = 0.04), or the use of a reduced intensity conditioning other than "Baltimore" (HR = 1.7 p = 0.04). PFS and OS were lower for patients in PR (HR = 1.8 p = 0.001; and 1,6 p = 0.01, respectively), in refractory disease (HR = 3.3 p = 0.001; and 2.9 p = 0.001, respectively), or a CMV donor positive /recipient positive status (HR = 1.7 p = 0.01 for both), whereas a diagnosis of FL or HL positively affected PFS (HR = 04 p = 0.02; and 0.5 p = 0.001, respectively), and a diagnosis of PTCL improved PFS and OS (HR = 0.6 p = 0.02; and 0.5 p = 0.005 respectively). No other donor characteristics (age, gender, relationship to recipient, HLA mismatch, ABO incompatibility, or prior pregnancies) affected PFS or OS.

Conclusion: PFS and OS are mostly influenced by disease status and lymphoma subtype, supporting the use of any haploidentical family member as a donor.

Keywords: allogeneic stem cell transplant (alloSCT).

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IMPACT OF CLASS II HLA MISMATCH ON CLINICAL OUTCOMES IN HODGKIN LYMPHOMA PATIENTS RECEIVING HAPLOIDENTICAL STEM CELL TRANSPLANTATION (HAPLO-SCT) WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE (PT-CY)

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Introduction: In Hodgkin lymphoma (HL) patients unmanipulated Haplo-SCT with PT-Cy seems to induce a stronger graft versus lymphoma effect than conventional donors. Usually, HLA class II molecules are expressed infrequently on Hodgkin Reed-Sternberg cells, but their expression is a predictor of favorable outcome after immunotherapy with anti-PD-1 antibodies. This is a retrospective study aiming to evaluate the impact of class II HLA mismatch, both in graft versus host (GVH) and host versus graft (HVG) direction, between donor and recipient, after haplo-SCT in HL.

Methods: Donors and recipients were typed using the DNA method (sequence specific oligonucleotide and sequence based typing) for HLA-A, -B, -C, -DRB1, -DQ, at a high resolution level, as defined by European federation for immunogenetics standards. Class II HLA mismatch in the GVH direction was defined as the presence of host antigens or alleles not shared by the donor. HLA mismatch in the HVG direction was defined as the presence of donor antigens or alleles not shared by the host.

Patients were conditioned with nonmyeloablative or reduced intensity conditioning regimens, infused with bone marrow or peripheral blood stem cells, and graft versus host disease (GVHD) prophylaxis was PT-CY (at day +3 and +4), cyclosporine A/tacrolimus, and MMF (both from day +5).

Results: From March 2010 and March 2018, we retrospectively analyzed 85 patients in 2 institutions. 24 donor/recipient pairs had a class II mismatch: 17 in GVH direction and 7 in HVG direction. We evaluated the main clinical outcomes according to the presence of class II HLA mismatch in any direction. Comparing pairs with class II mismatch to pairs without, the CI of Grade 2-4 acute GVHD and Grade 3-4 acute GVHD was 8 % and 0% (p = 0.02) vs 33% and 5 % (p = 0.272), respectively. The CI of cGVHD was 0 % vs 9 % (p = 0.16). The 1-year relapse incidence was 13% and 26% (p = 0.176) and the 1-year NRM was 15 % and 20% (p = 0.489) The 2-year PFS was 73% vs 54 % (p = 0.081) and the 2-year OS was 80% and 67 %(p = 0.125), The 1-year graft-relapse-free survival (GRFS) was 73% vs 44 % (P = 0.012), respectively. In the multivariate analysis, the class II mismatch significantly reduce the risk of acute GVHD (HR 0.19, CI95 0.04 - 0.81, p = 0.025) and improve the GRFS (HR 0.27, CI95 0.11-0.68, p = 0.005). However, even if not statistically different probably due the low number of patients, the presence of mismatch improve the relapse incidence (HR 0.33, CI95 0.07-1.50, p = 0.15), PFS (HR 0.44, CI95 0.18-1.08, p = 0.07) and OS (HR 0.50, CI95 0.18-1.35, p = 0.17).

Conclusions: This study suggests that in HL patients treated with haplo-SCT with PT-Cy, a class II HLA mismatch, in GVH or HVG direction, can induce a strong anti-tumoral effect and protect from GVHD, translating in a high GRFS. These data should be analyzed in more patients, and if confirmed, this difference could be help in the donor selection.

IMMUNOTHERAPY

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REAL-WORLD RESULTS ON CD19 CAR T-CELL FOR 60 FRENCH PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA INCLUDED IN A TEMPORARY AUTHORIZATION FOR USE PROGRAM

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Background: Autologous anti-CD19 chimeric antigen receptor (CD19 CAR) T-cell therapy demonstrated significant clinical benefit and a manageable safety profile for patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), with 6-month ORR at 41-47% and CR at 32-41% in the 3 pivotal clinical trials (ZUMA1, TRANSCEND, JUNO), leading to a rapid approval in third line R/R DLBCL in Europe and USA. Since April 2018 in France, a cohort patient program (called ATU) allowed to use the CD19 CAR T-cells, Axicabtagene and Tisagenlecleucel, for patients with DLBCL, primary mediastinal B-cell lymphomas (PMBL) and transformed FL (tFL), recurrent or refractory after > 2 systemic therapy lines; CNS excluded.

Methods: We performed a retrospective analysis of the patients treated with Axicabtagene or Tisagenlecleucel between April 2018 and Feb 2019 in the 5 authorized centres. The eligibility criteria were confirmed based on age, comorbidities, LVEF > 45%, no pericarditis or cardiogram abnormality, clearance > 60 mL/min, ALT/AST < 2.5 N, total bilirubin < 1.5 mg/dL, no pleural effusion, SpO2 > 92% without oxygen, lymphocytes > 100/μL, no rapid progressive disease (compressive mass, PS > 2 or rapid increase of LDH), no active neurological disease, no auto-immune disease. The final decision was validated by a local multidisciplinary tumor board.

Results: A total of 60 patients have been selected for a treatment with Yescarta (30) or Kymriah (30). 73% of the patients were referred. Median age was 52 (range 18 -77). 11 (18%) pts were over 65 years old. 67% were male. By histology, patients presented with DLBCL (n = 42), PMBL (n = 8), trFL (n = 9), and transformed marginal zone lymphoma (n = 1). 68% were primary refractory defined as progressive or stable disease as the best response to the most recent chemotherapy regimen or disease progression or relapse within 12 months after autologous stem cell transplantation (ASCT). Median number of prior lines was 3 (range 2 to 9) and 18 (30%) pts had a prior ASCT. Only one leukapheresis was necessary, except for 4 patients who required 2-4 leukapheresis. At time of analysis, 45 patients have been reinfused. 5 patients died before reinfusion, 3 because progressive disease and 2 because of infections. The median time duration between the ATU validation and receipt of the CD19 CAR T-cells was 47.5 days (range 30-190 days). During this time, all patients except 4 (93%) received a bridging therapy. The median time between the receipt of the cells and their infusion was 6 days (range 1 to 20 days). Data regarding efficacy and tolerance will be further analysed.

Conclusion: The time elapsed between ATU validation and CAR T-cell reception remains substantial and a bridging therapy was necessary for almost all patients. The LYSA group and the CALYM institute (www.calym.org) are organizing a national registration program for these patients with clinical and biological data collection.

Keywords: diffuse large B-cell lymphoma (DLBCL).

Disclosures: Thieblemont, C: Consultant Advisory Role: Gilead, Roche, Novartis, Janssen, Takeda, Bayer, Kyte.

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SAFETY AND PRELIMINARY EFFICACY IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA RECEIVING LISOCABTAGENE MARALEUCEL IN TRANSCEND NHL 001

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Introduction: Most patients with mantle cell lymphoma (MCL) relapse after first-line immunochemotherapy, with poor responses to salvage therapy. We report initial dose-finding results from patients with relapsed/refractory MCL treated with lisocabtagene maraleucel (liso-cel; JCAR017), an investigational, anti-CD19 chimeric antigen receptor (CAR) T cell product administered as a defined composition of CD4+/CD8+ CAR T cells, in the ongoing phase 1 TRANSCEND study.

Methods: Eligible patients had confirmed MCL (cyclin D1 expression, t[11;14]) with relapsed/refractory disease after ≥1 prior lines of therapy. After lymphodepleting chemotherapy, liso-cel was administered at 1 of 2 dose levels: dose level 1 (50×10^6 total CAR+ T cells) or dose level 2 (100×10^6 total CAR+ T cells).

Results: At data cutoff, 9 patients (n = 6 at dose level 1 and n = 3 at dose level 2) had received liso-cel. The median (range) age was 66 (58–78) years; 7 patients were male. Histologies included blastoid (n = 3) and pleiomorphic (n = 1) variants. Eight patients had documented Ki67 >30% (40%–80%); 1 patient had *TP53* mutation. Patients had received a median of 5 (3–7) prior therapies; 3 patients had received prior hematopoietic stem cell transplant. All 9 patients had prior ibrutinib; 4 had a best response of progressive disease on ibrutinib. Six of 9 patients (67%) received bridging chemotherapy. Four of 9 patients (44%) had serious treatment-emergent adverse events (TEAEs). Five of 9 patients (56%) had grade 3/4 TEAEs, primarily anemia, neutropenia, and hypophosphatemia (22% each). Three of 9 patients (33%) had cytokine release syndrome (CRS); all were grade 1. Median time to CRS onset was 6 (2–7) days; median time to resolution was 6 (2–6) days. One patient received tocilizumab and corticosteroids. There were no neurological events. Four patients died, all in dose level 1 (3 from disease progression; 1 after receiving a new anticancer therapy post liso-cel). Overall response rate was 78% (7/9 patients; 4/6 in dose level 1, median follow-up 12.4 [95% CI: 9.2–12.4] mo; 3/3 in dose level 2, median follow-up 1.4 [95% CI: 1.0–1.4] mo). Two patients in dose level 1 maintained a durable complete response until last follow-up (day 281 and 378, respectively). Median time to peak CAR+ T cell expansion: 9.5 (9–10) days at dose level 1 and 17.5 (10–27) days at dose level 2.

Conclusions: In this phase 1 study in patients with relapsed/refractory MCL, liso-cel treatment showed tolerable toxicity and had clinical activity. Updated data for dose level 2 and longer follow-up will be presented.

Keywords: CD19; mantle cell lymphoma (MCL); T-cells.

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OUTCOMES OF PATIENTS ≥ 65 YEARS OF AGE IN ZUMA-1, A PIVOTAL PHASE 1/2 STUDY OF AXICABTAGENE CILOLEUCEL (AXI-CEL) IN REFRACTORY LARGE B CELL LYMPHOMA

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Background: Axi-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy approved in the European Union and the United States for the treatment of patients with relapsed or refractory large B cell lymphoma with ≥ 2 prior systemic therapies. In the 2-year follow-up of ZUMA-1, the objective response rate was 83% with a complete response rate of 58%, and 39% of patients were in ongoing response (Locke et al. *Lancet Oncol.* 2019). Here, we report efficacy and safety outcomes by age.

Methods: Eligible patients with refractory large B cell lymphoma underwent leukapheresis and conditioning chemotherapy followed by a target dose of 2×10^6 anti-CD19 CAR T cells/kg. The Phase 2 primary endpoint was investigator-assessed objective response rate. Additional key endpoints were adverse events, overall survival, and levels of CAR gene-marked cells in peripheral blood. Efficacy was evaluated for Phase 2 patients; safety was evaluated for all treated patients (Phases 1 and 2). Patients were analyzed by age ≥ 65 years vs < 65 years.

Results: As of August 11, 2018, 108 patients were treated. Patients aged ≥ 65 years (n = 27) vs < 65 years (n = 81) had a median age of 69 years vs 55 years, respectively, and were 81% vs 63% male; 70% vs 36% had an International Prognostic Index score of 3-4, 59% vs 57% had an Eastern Cooperative Oncology Group performance status of 1, 67% vs 72% had ≥ 3 prior therapies, and median tumor burdens were 3790 mm^2 vs 3574 mm^2. Median follow-up was 27.1 months for Phase 2 patients (n = 101). The objective response rate for patients ≥ 65 years (n = 24) and < 65 years (n = 77) was 92% and 81% (complete response rate, 75% and 53%), respectively, with ongoing responses in 42% and 38% of patients (ongoing complete response, 42% and 35%). The 24-month overall survival rate was 54% for patients ≥ 65 years and 49% for patients < 65 years. Most patients experienced Grade ≥ 3 adverse events (100% of patients ≥ 65 years; 98% of patients < 65 years), and 4% of each group (1/27 patients ≥ 65 years and 3/81 patients < 65 years) died due to adverse events as previously reported. Grade ≥ 3 neurologic events and cytokine release syndrome occurred in 44% vs 28% and 7% vs 12% of patients ≥ 65 years vs < 65 years, respectively. CAR T cell expansion by peak level (43 vs 35 cells/μL) or area under the curve (562 vs 448 days × cells/μL) was similar in patients ≥ 65 years vs < 65 years, respectively.

Conclusions: The 2-year follow-up of ZUMA-1 demonstrates that axi-cel can induce high rates of durable responses with a manageable safety profile for patients ≥ and < 65 years. Axi-cel offers substantial clinical benefit for older patients with refractory large B cell lymphoma who otherwise have limited treatment options.

Keywords: CD19; non-Hodgkin lymphoma (NHL).

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SAFETY AND EFFICACY OF AXICABTAGENE CILOLEUCEL (AXI-CEL) IN OLDER PATIENTS: RESULTS FROM THE US LYMPHOMA CAR-T CONSORTIUM

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Introduction: Axi-cel, an autologous anti-CD19 CAR T-cell therapy, induced an overall response rate (ORR) of 83% and complete response (CR) rate of 58% in patients with refractory large B-cell lymphoma on the pivotal ZUMA-1 study. At a median follow-up of 27.1 mo, 39% of the patients remain in remission (Neelapu et al. N Eng J Med 2017; Locke et al, Lancet Oncol 2019). Here, we present retrospective analysis of safety and efficacy outcomes in older patients treated with axi-cel in the post-approval setting from a 17-center US Lymphoma CAR-T Consortium.

Methods: Patients with relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, or transformed follicular lymphoma, received axi-cel infusion following conditioning with cyclophosphamide and fludarabine. Bridging therapy was allowed. Cytokine release syndrome (CRS) was graded by Lee criteria and neurotoxicity (CAR-related encephalopathy syndrome or CRES) was graded according to CTCAE or CARTOX system.

Results: Of 300 apheresed patients, 206 (69%) were <65 years (yrs) and 94 (31%) were ≥65 yrs. Baseline characteristics such as gender, ECOG performance status, stage, number of prior lines of therapy, prior autologous transplant, refractory status, and bridging therapy usage were comparable between the two groups but patients ≥65 yrs had higher IPI (IPI 3-5: 77% vs. 44%, P<0.001). Of the apheresed patients, 14 (7%) patients <65 yrs and 10 (11%) patients ≥65 yrs did not receive axi-cel. Overall, 274 patients (191 <65 vs. 83 ≥65) were evaluable for safety and 272 patients (190 <65 vs. 82 ≥65) were evaluable for efficacy. Of the axi-cel-treated patients, best ORR through day 90 was comparable between the two groups (82% for all patients; 82% <65 vs. 84% ≥65, P = 0.61) but CR rate was higher in patients ≥65 yrs (57% for all patients; 51% <65 vs. 71% ≥65, P<0.01). Median follow-up for all patients was 5.9 months. Estimated median PFS (7.4 mo <65 vs. 9.2 mo ≥65, P = 0.83) and OS (18.7 mo <65 vs. not assessable ≥65, P = 0.99) were comparable between the two groups.

Incidence and severity of CRS was comparable in both groups (all CRS grades: 91% <65 vs. 92% ≥65; grade ≥3 CRS: 7% in both groups). There was a trend towards higher incidence of CRES in older patients (all CRES grades: 65% <65 vs. 78% ≥65, P = 0.08) but grade ≥3 CRES was comparable (31% <65 vs. 35% ≥65, P = 0.53). There were two axi-cel-related deaths, one in each group. The use of tocilizumab and corticosteroids were not significantly different between the two groups. Median hospitalization period was 14 days in both groups and ICU admission rate was 32% in both groups.

These safety and efficacy results had similar pattern when patients were grouped based on age cut-off of 60 or 70 yrs.

Conclusions: Our results suggest that the safety and efficacy of axi-cel are largely comparable between younger and older patients with the exception of CR rate, which was higher in older patients.

Keywords: CD19; diffuse large B-cell lymphoma (DLBCL); elderly.

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PRELIMINARY RESULTS OF EARLIER STEROID USE WITH AXICABTAGENE CILOLEUCEL (AXI-CEL) IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B CELL LYMPHOMA

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Background: Axi-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy approved in the EU and US for patients with relapsed/refractory large B cell lymphoma with ≥ 2 prior systemic therapies. In the 2-year follow-up of ZUMA-1, the objective response rate was 83% with a complete response rate of 58%. Grade ≥ 3 cytokine release syndrome (CRS) and neurologic events (NE) occurred in 11% and 32% of patients, respectively; 26% of patients received steroids, and 43% received tocilizumab (Locke et al. *Lancet Oncol.* 2019). A safety expansion cohort was added to evaluate the effect of earlier steroid use on the rates of these adverse events (AEs).

Methods: Eligible patients with relapsed/refractory large B cell lymphoma were leukapheresed and received conditioning chemotherapy followed by a target dose of 2×10^6 anti-CD19 CAR T cells/kg. Patients in this cohort received early steroid intervention starting at Grade 1 NE and at Grade 1 CRS when no improvement was observed after 3 days of supportive care. The primary endpoint for this cohort was incidence and severity of CRS and NE.

Results: As of September 14, 2018, 21 of 40 planned patients received axi-cel with a minimum follow-up of 1 month (median, 2.6 months). The median age was 63 years (range, 36 – 73), 67% were male, 81% had disease stage III-IV, 76% were relapsed/refractory to ≥ second-line therapy, and 10% had relapsed post-autologous stem cell transplantation. Seventy-six percent of patients received steroids and 81% received tocilizumab. Most patients (81%) had Grade ≥ 3 AEs, most commonly neutrophil count decreased (33%), anemia (29%), and pyrexia (24%). Grade ≥ 3 NE occurred in 10% of patients; the most common symptoms were somnolence (10%) and confusional state (10%). Grade 1 and 2 NE occurred in 38% and 5% of patients, respectively. No patient had Grade ≥ 3 CRS; 33% of patients had Grade 1 CRS and 67% had Grade 2. There were no deaths due to AEs; 1 patient died due to disease progression. The objective response rate per investigator assessment was 76% with 48% of patients achieving a complete response. Pharmacokinetic data will be presented.

Conclusions: Early use of steroids may help in managing severe CRS and NE by potentially reducing their incidence in patients treated with CAR T cell therapy without affecting response rates. Optimizing AE management may help to further improve the benefit:risk profile of CAR T cell therapy.

Keywords: CD19; non-Hodgkin lymphoma (NHL).

Disclosures: Topp, M: Consultant Advisory Role: *Kite, a Gilead Company; Amgen; Roche; Regeneron.* **Wermke, M:** Consultant Advisory Role: *Bristol-Myers Squibb, Merck, Kite, a Gilead Company, and Novartis*; Honoraria: *Bristol-Myers Squibb, Merck, Roche, and Novartis*; Other Remuneration: *travel expenses from AstraZeneca and Bristol-Myers Squibb.* **Lugtenburg, P:** Consultant Advisory Role: *Takeda, Servier, Roche, Bristol-Myers Squibb, Celgene, Sandoz, and Genmab*; Research Funding: *Takeda and Servier.* **Minnema, M:** Consultant Advisory Role: *Servier, Takeda, Amgen, Janssen-Cilag*; Research Funding: *Celgene*; Other Remuneration: *travel expenses from Roche and Amgen.* **Song, K:** Honoraria: *Celgene, Janssen, Amgen, Novartis, Takeda*; Research Funding: *Celgene.* **Thieblemont, C:** Honoraria: *Celgene, Abbvie, Bayer, Janssen, Roche, Incyte*; Research Funding: *Roche.* **Jiang, Y:** Employment Leadership Position: *Kite, a Gilead Company*; Stock Ownership: *Gilead Sciences.* **Plaks, V:** Employment Leadership Position: *Kite, a Gilead Company.* **Kerber, A:** Employment Leadership Position: *Kite, a Gilead Company.* **Kersten, M:** Consultant Advisory Role: *Kite, a Gilead Company*; Honoraria: *Kite, a Gilead Company*; Other Remuneration: *travel expenses from Kite, a Gilead Company.*

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PHASE 1 STUDY OF ANTICD19 CAR-T CELLS WITH TNFα TRANSMEMBRANE DOMAIN AND 41BB, CD3ζ COSTIMULATORY DOMAINS. RESPONSES IN SUBJECTS WITH RAPIDLY PROGRESSIVE LYMPHOMA

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Introduction: AntiCD19 CAR-T cells have shown encouraging anti-lymphoma activity. Decreased time from apheresis to CAR-T infusion can make this therapy available to patients (pts) with rapid disease progression. We present the interim results of a phase I clinical trial using on-site CAR-T manufacture for treatment of relapsed / refractory (r/r) B cell non Hodgkin lymphoma (NHL).

Methods: Adult pts with r/r CD19+ B cell lymphomas who failed ≥ 2 lines of therapy were enrolled. Autologous T cells were transduced with a lentiviral vector (Lentigen Technology, Inc, LTG1563) encoding an antiCD19 binding motif, CD8 linker, tumor necrosis receptor superfamily 19 (TNFRS19) transmembrane region, and 4-lBB/CD3ζ intracellular signaling domains. GMP-compliant manufacture was done using CliniMACS Prodigy, in a 12-day culture. Dose levels were 0.5, 1 and 2×10^6 CAR-T cells/kg. Lymphodepletion was done with cyclophosphamide (60mg/kg x 1) and fludarabine ($25mg/m^2$/d x 3).

Results: As of March 15, 2019, 7 pts (4 women, 3 men) were enrolled. Median age was 60y [range 43-69]. Diagnoses include DLBCL (n = 3) PMBCL, follicular lymphoma (FL), transformed FL, and transformed lymphoplasmacytic lymphoma; with a median of 4 previous treatments. All pts were refractory to the prior line of therapy and 6 had symptomatic bulky disease at the time of lymphocyte collection.

CAR-T cell product manufacture was successful in all pts. Mean transduction rate was 44% [range 29-57]. CAR-T cell doses were 0.5×10^6/kg (n = 3) and 1×10^6/kg (n = 4). Median apheresis to infusion time was 13 days [range 13–20], 5 products were infused fresh. CAR-T persistence peaked in peripheral blood MNCs between days 14-21, all evaluable subjects had persistent CAR-Ts on day 30.

Cytokine release syndrome was observed in 5 pts. Grade 1 – 2 (Lee) was observed in 4 pts; whereas 1 pt died as a consequence of CRS in the context of bulky disease. Pharmacologic interventions for CRS included tocilizumab (n = 4), siltuximab (n = 2) and steroids (n = 1). One pt presented grade 4 CRES (CARTOX-10) with resolution after steroids. Among 6 pts evaluable for response, 4 have achieved complete response. One pt did not respond and died and 1 subject died secondary to CRS. After a median follow up 3.5 months all responding pts are alive and 1 relapsed 6 months after treatment.

Conclusions: In this ongoing phase 1 study, second generation antiCD19 CAR-T cells with TNFRS19 transmembrane domain and 4-lBB/CD3z have clinical activity against refractory lymphomas. The response rates observed so far indicate that antiCD19 CAR-T cell therapy is active in patients with rapidly progressive disease. The presence of bulky disease is associated with high risk of CRS, and debulking strategies prior to CAR-T cell therapy or lower doses should be considered. The short manufacture time achieved by local CAR-T cell manufacture with the CliniMACS Prodigy enables treatment of a very high risk NHL population.

Keywords: B-cell lymphoma; CD19; T-cells.

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CD19/CD20-REDIRECTED BISPECIFIC CAR T CELL TREATMENT IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN LYMPHOMA

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Background: Patients with relapsed or refractory non-Hodgkin lymphoma (NHL) have a dismal prognosis. CART therapy targeting CD19 and CD20 achieves outstanding clinical responsiveness in B-cell malignancies, in B-NHL, the target CD19- or CD20-modified CAR-T cell therapy achieved a 41-54% complete remission rate, but the variability of single-target antigens in tumor cell leads to therapeutic resistance and relapse. We have previously constructed eight bispecific, tandem CD19/CD20 CAR structures and screened the optimal CAR structure with robust antitumor activity. Base on this, we performed aphase I trial to assess the safety and efficacy of CD19 and CD20 bispecific CAR T cells to patients with refractory or relapsed CD20 or CD19 positive B-cell lymphoma.

Methods: Adult (≥18 years) patients with pathologically confirmed diagnose of CD20+ or CD19+ NHL and active relapsed or refractory disease were eligible. The patients underwent cytoreductive chemotherapy for tumor debulking and lymphocyte-depletion between days -7 to -2 before T cell infusion. Patients received bispecific CAR T cell dose from 1.5 to 8×10^6/kg. The level of the CAR gene was detected by Real-time PCR, and the CAR T cell in peripheral blood or in tumor site was detected by flow cytometry and RNAscope. Clinical responses were assessed according to the recommendations of the International Workshop NHL Response Criteria. Toxicity and adverse events were graded using the National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0. Disease staging using computed tomography (CT) and positron emission tomography (PET) scans was performed at the time of study entry. CT was repeated during follow up

every two months (first year), every six months (years 2–3) and yearly thereafter. A FDG-PET study was performed at six weeks after treatment in all patients.

Results: Forty-twopatients were enrolled, and 36 patients has completed a three-month assessment. The current overall objective response rate was 34 of 36 (94.4%) with 29 complete remissions (CRs) and 5 partial remissions (PRs). no severe toxicity was observed. Twenty-seven patients occurred Cytokine release syndrome (CRS). This clinical trial is ongoing (www.clinicaltrials.org as NCT03097770).

Keywords: B-cell lymphoma; CD19; CD20.

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CYTOKINE RELEASE SYNDROME AND NEUROTOXICITY BY BASELINE TUMOR BURDEN IN ADULTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH TISAGENLECLEUCEL

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Introduction: Autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel has demonstrated efficacy with favorable benefit-risk profile in adults with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) in the JULIET trial. CAR T-cell therapy is associated with cytokine release syndrome (CRS) and neurotoxicity (NT). This post-hoc analysis described safety profiles among tisagenlecleucel-treated adults with r/r DLBCL, stratified by baseline tumor burden.

Methods: CRS and NT events observed in JULIET were graded with approaches common to CAR T-cell therapy (CRS: Penn, Lee; NT: Common Terminology Criteria for Adverse Events v4.03 [CTCAE], modified CAR-T Related Encephalopathy Syndrome [mCRES]). Penn grades were reported prospectively per trial protocol; Lee, mCRES and CTCAE grades were obtained via expert consensus grading (ASH 2018: #4190; #4183). JULIET patients (pts) were stratified by baseline tumor burden, defined by active tumor volume (TV; <100 vs ≥100 mL per PET scan) or presence of bulky

disease (BD; any single tumor mass >10 cm in CT-determined, longitudinal diameter). Demographics, disease characteristics, medical history, CRS and NT grades were summarized and compared between subgroups.

Results: Of 111 JULIET pts infused with tisagenlecleucel as of Dec 8, 2017, TV was assessed in 95 pts, divided into two subgroups: <100 mL (n = 60), ≥100 mL (n = 35). Overall, pts were similar in demographics and medical history; with one exception, BD pts (N = 9) had no prior HSCT (0.0% vs 52.9%, p<0.01). The rates of any CRS grade were similar (<100 vs ≥100 mL: 50.0% vs 68.6% per Lee; 51.7% vs 68.6% per Penn). Higher TV was associated with CRS grade≥3 (Lee: 11.7% vs 31.4%; Penn: 13.3% vs 34.3%, both p<.05). Of 64 pts with CRS, baseline TV was available for 55 (<100 mL n = 31; ≥100 mL n = 24); a higher number of pts with TV > 100 mL had CRS within 3 days post infusion (35.5% vs 87.5%, p<.001) and experienced high fever (>38.6°C) due to CRS (83.9% vs 100.0%, p<.05). CRS duration, tocilizumab administration and corticosteroid use were similar between subgroups. With CTCAE grading, NT grades were similar between subgroups; with mCRES grading; high TV pts had higher NT rates compared with low TV group (any grade: 11.7% vs 31.4%, p<.05) and grade 3 or 4 NT (8.3% vs 22.9%, p<.05). No Grade 5 CRS or NT were observed. BD pts had higher grade 3 and 4 CRS rates per Lee (13.7% vs 55.6%, p<.01).

Conclusions: This JULIET post-hoc analysis observed differences in CRS and NT grades among pts with low vs high baseline tumor burden according to BD or TV and indicates an association between tumor burden and higher rates of CRS grade 3 and 4 by both Penn and Lee scales. There was a correlation between BD and NT grade 3 and 4 per mCRES; but the trend was not observed with CTCAE grading. These findings may help guide clinical care of r/r DLBCL pts with BD and/or high TV receiving tisagenlecleucel.

Keywords: diffuse large B-cell lymphoma (DLBCL).

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CORRELATIVE ANALYSES OF CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL EVENTS IN TISAGENLECLEUCEL-TREATED RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS

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Background: Tisagenlecleucel (anti-CD19 CAR-T cell therapy) has shown durable responses and a manageable safety profile in adult patients (pts) with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). We report a 24 mo clinical update and correlative analyses between cytokine release syndrome (CRS)/neurological events (NE) and inflammatory/lab analyte markers.

Methods: JULIET (NCT02445248) is a single-arm, pivotal, phase 2 trial of tisagenlecleucel in adult pts with r/r DLBCL. The primary endpoint was overall response rate (ORR: complete [CR] + partial response). Peak (within 1 mo of infusion) serum cytokine levels/lab parameters were correlated with rate/grade (gr) of CRS (by Penn) and NE (by CTCAE v4.03) within 8 wk of infusion.

Results: As of 11 Dec 2018, 115 pts were infused (99 evaluable for efficacy). ORR remained 54% (95% CI: 43, 64), CR rate was 40%, and median duration of response was not reached (NR; 95% CI: 10, –) at a max follow-up of almost 24 mo from onset of response. Of 31 pts with CR at 6 mo, 3 relapsed between 6-12 mo and 1 relapsed beyond 12 mo. Median overall survival for all 115 pts was 10.3 mo (NR for pts in CR). Severe (gr 3/4) CRS and NE occurred in 23% and 11%, respectively. 83% of pts with any gr NE also had CRS; 62% of pts with severe NE had severe CRS. Median time to onset of CRS and NE was 3 and 6 d, respectively. Peak cytokine levels within 1 mo of infusion were increased in pts with CRS/NE and the trend was more noticeable in pts with severe CRS and severe NE. Higher CRP, ferritin, interferon- (IFNG), IL2, IL6, and IL10 were observed in pts with severe CRS; severe NE showed similar trends of a lesser degree, except for IFNG. In pts with CRS, cytokines peaked on d 6-9, with early increase of IL2, IL6, and IFNG in the first 2 d post-infusion with severe CRS. Low platelet count, elevated lactate dehydrogenase, and below-normal albumin levels were seen after lymphodepleting chemotherapy; these trends continued post-infusion in pts with severe CRS. As CRS progressed, hepatic and kidney dysfunction-related analytes trended toward an increase, peaking 2 wk post-infusion in pts with

TABLE 1 Number of patients with coincidence of CRS and NE in the JULIET trial

	N = 115	Any Grade NE (n = 23/115)	Grade 3/4 NE (n = 13/115)
No CRS	49	4	3
Grade 1/2 CRS	40	6	2
Grade 3 CRS	17	6	2
Grade 4 CRS	9	7	6
Any Grade CRS	66	19	10

Figure 1A. Peak serum cytokine levels within 1 mo of infusion by CRS gr (N = 115)

No CRS (n = 49) Grade 1/2 (n = 40) Grade 3 (n = 17) Grade 4 (n = 9)
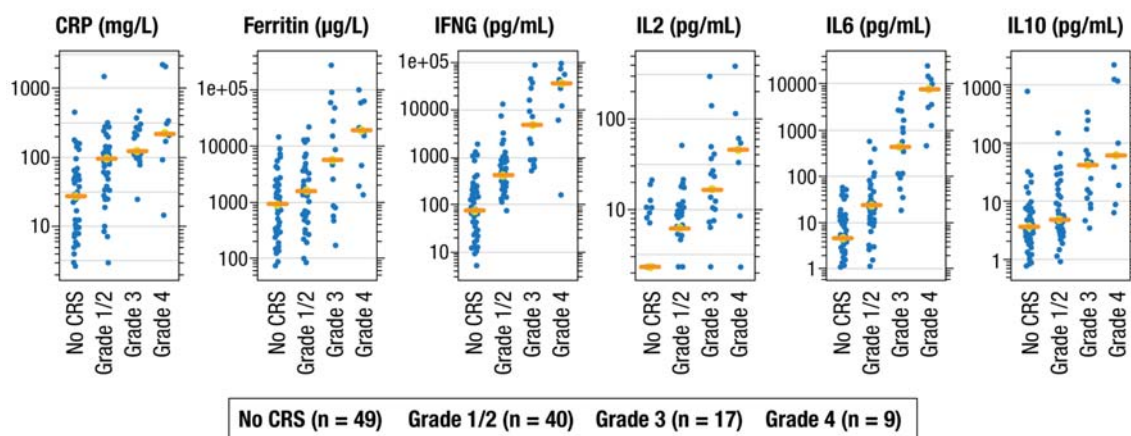
Figure 1B. Peak serum cytokine levels within 1 mo of infusion by NE gr (N = 115)

No NE (n = 92) Grade 1/2 (n = 10) Grade 3/4 (n = 13)
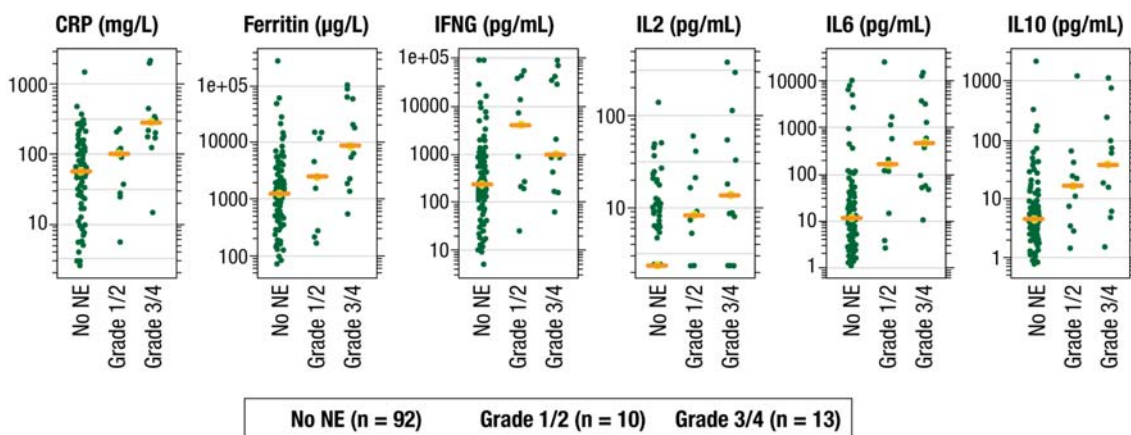
severe CRS. Additional univariate/multivariate analyses using pts' disease and clinical characteristics in an attempt to predict CRS/NE severity are ongoing.

Conclusions: With almost 24 mo max follow-up, tisagenlecleucel continued to demonstrate durable efficacy. Severe NE appeared to correlate with severe CRS. Trends in peak levels of several markers were noted with severe CRS and – to a lesser extent – severe NE.

Keywords: CD19; cytokines; diffuse large B-cell lymphoma (DLBCL).

Disclosures: Bachanova, V: Consultant Advisory Role: *Novartis*; Research Funding: *GAMIDA Cell, UNUM, Novartis, GT Biopharm.* **Westin, J:** Consultant Advisory Role: *Novartis, Kite Pharma, Juno, Celgene, Janssen, Genentech.* **Tam, C:** Honoraria: *Novartis.* **Borchmann, P:** Honoraria: *Novartis.* **Jaeger, U:** Honoraria: *AbbVie, Bioverativ, Celgene, Gilead, Janssen, MSD, Novartis, Roche, Takeda Millenium, Amgen, AOP Orphan, BMS, Sandoz*; Research Funding: *Bioverativ, Celgene, Gilead, Janssen, MSD, Novartis, Roche*; Other Remuneration: *AbbVie, Celgene, Gilead, Janssen, MAD, Novartis, Roche, Takeda Millenium, Amgen, AOP Orphan, BMS, Sandoz.* **McGuirk, J:** Honoraria: *Kite Pharma*; Research Funding: *Novartis, Kite Pharma, Fresenius Biotech,*

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MANAGING CYTOKINE RELEASE SYNDROME (CRS) AND NEUROTOXICITY WITH STEP-UP DOSING OF MOSUNETUZUMAB IN RELAPSED/REFRACTORY (R/R) B-CELL NON-HODGKIN LYMPHOMA (NHL)

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Introduction: T-cell directed therapies (e.g., CAR-T, blinatumomab) are associated with significant risk of Grade (Gr) ≥3 neurotoxicity and CRS/infusion-related reaction (IRR). Mosunetuzumab is a CD20/CD3 bispecific antibody that directs T-cells to engage and eliminate malignant B-cells. We report safety results from an ongoing Phase 1/1b study (NCT02500407) of mosunetuzumab in patients (pts) with R/R B-cell NHL.

Methods: Pts received ascending doses on Day 1, Day 8, and Day 15 of Cycle 1 (step-up dosing), then a fixed dose on Day 1 of every 21-day cycle thereafter, up to a maximum of 17 cycles. Primary outcome measures included safety and efficacy.

Results: As of October 23, 2018, 114 pts who received step-up dosing of mosunetuzumab were evaluable for safety (**Table**). The majority of adverse events (AE) occurred during Cycle 1 and 2. Neurologic AEs (NAE), defined from Nervous System or Psychiatric System Organ Classes, were mostly low grade, transient (median duration 4 days) and reversible; most common ones were headache (14%) and

TABLE 1 Safety

Pts, n (%)	n=114 [Max dose: 20 mg]
≥1 AE	109 (96)
Gr ≥3 AEs; drug-related	68 (60); 33 (29)
Serious AE*; drug-related	34 (30), 15 (13)
NAE	50 (44)
Gr 1–2	46 (40)
Gr 3	4 (4)
CRS/IRR	29 (25)
Gr 1–2	28 (25)
Gr 3	1 (1)

*excluding progressive disease

dizziness (8%). Gr ≥3 NAEs occurred in 4 pts (4%) with only 1 treatment-related event (hepatic encephalopathy). CRS/IRR was reported in 25% of pts, with only 1 Gr 3 event. Most common CRS symptoms were pyrexia (86%), chills (38%), and tachycardia and headache (14% each). There were no Gr 5 events related to CRS or NAEs. No apparent dose toxicity relationship was observed with step-up dosing in these pts, despite escalation of the Cycle 1 Day 15 dose to 20 mg, consistent with observed peak IL-6 levels after a low Cycle 1 Day 1 dose. In these pts, objective responses were observed in 24/73 (33%; complete response [CR], 13 [18%]) aggressive NHL and 17/32 (53%; CR, 10 [31%]) indolent NHL pts.

Conclusions: Step-up dosing has enabled continued dose escalation of mosunetuzumab with no apparent increases in toxicity, exhibiting a promising risk-benefit profile.

Keywords: CD20; CD3; non-Hodgkin lymphoma (NHL).

Disclosures: Sehn, L: Consultant Advisory Role: *AbbVie, Amgen, Roche/Genentech, Inc., Apobiologix, AstraZeneca, Acerta, Celgene, Gilead, Janssen, Kite, Karyopharm, Lundbeck, Merck, MorphoSys, Seattle Genetics, Teva, Takeda, TG Therapeutics*; Honoraria: */Genentech, Inc., Apobiologix, AstraZeneca, Acerta, Celgene, Gilead, Janssen, Kite, Karyopharm, Lundbeck, Merck, MorphoSys, Seattle Genetics, Teva, Takeda, TG Therapeutics*; Research Funding: *Roche/Genentech, Inc.* **Assouline, S:** Employment Leadership Position: *No*; Consultant Advisory Role: *Yes. 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CLINICAL IMPLICATIONS OF CYTOPENIAS BEYOND DAY 30 AFTER AXI-CEL THERAPY IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA

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Introduction: Cytopenia lasting beyond 30 days has been observed after CAR T cell therapy. Here, we describe the hematopoietic recovery and immune reconstitution following axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory large B-cell lymphoma.

Methods: Patients with available complete blood counts 30 days after axi-cel infusion were eligible for the analysis. Significant cytopenia was defined as any grade 3 or greater hematological toxicity (absolute neutrophil count < 1×10^9/L, hemoglobin < 8 g/dL, platelet count < 50×10^9/L).

Results: Of 31 patients treated on ZUMA-1 (N = 24) and ZUMA-9 (N = 7) trials at our institution, grade $\geq$3 cytopenias were observed in 15 (48%) patients at day 30 (d30), represented by neutropenia in 9 (29%), anemia in 5 (16%), and thrombocytopenia in 13 (42%). Baseline (d-5) characteristics associated with d30 grade $\geq$3 cytopenia on univariate analysis were ECOG performance status >0 (60% vs 19%, p = 0.03) and >3 prior therapies (67% vs 25%, p = 0.03). A trend for association with previous autologous stem cell transplant (93% vs 44%, p = 0.07) and higher baseline ferritin levels (2025 ng/mL vs 450 ng/mL, p = 0.08) was observed. While on study, patients with d30 grade $\geq$3 cytopenia had a significantly higher need for intravenous immunoglobulins (Ig)(67% vs 25%, p = 0.03) and platelet transfusion (73% vs 25%, p = 0.01). No significant association was observed between d30 grade $\geq$3 cytopenia and subsequent grade $\geq$3 infections (27% vs 31%, p = 1), need for growth factor support (both 100%, p = 1), red blood cell transfusions (87% vs 63%, p = 0.22) or diagnosis of myelodysplastic syndromes (20% vs 1%, p = 0.33). Fifty-nine infectious complications were observed during the study, and the etiology was viral in 16 (27%) cases, bacterial in 7 (12%), fungal in 4 (7%); no organism was isolated in 32 (54%) patients.

No significant association was observed between d30 grade $\geq$ 3 cytopenia and overall response rate (93% vs 81%, p = 0.60) or complete remission rate (53% vs 50%, p = 1).

At a median follow-up of 2.7 years, a higher 3-year progression-free survival was observed for patients with d30 grade $\geq$3 cytopenia (63% vs 35%, p = 0.18)(Figure 1A).

Among patients with ongoing response at most recent follow-up, resolution of grade $\geq$3 cytopenia was observed in 75% of patients at 1 year and 86% at 2 years; recovery in CD4, CD8, CD56, CD19, and IgG was observed in 63%, 100%, 100%, 29%, and 58% of patients at 1 year, and 86%, 100%, 100%, 25% and 50% of patients at 2 years. Among patients with d30 cytopenia, a strongly significant and positive correlation was observed between platelet count and CD56 count (r = +0.64, p<0.001) (Figure 1B).

Conclusions. Grade $\geq$ 3 cytopenias are common after axi-cel therapy, but resolve in most patients by 1 year. Recovery of CD4 T cells appears to be delayed beyond 1 year in 1/3 of the patients, highlighting the need for prolonged prophylaxis for opportunistic infections. The effect of CAR T cells on the bone marrow microenvironment warrants further investigation.

Keywords: autologous stem cell transplantation (ASCT); diffuse large B-cell lymphoma (DLBCL); immune system.
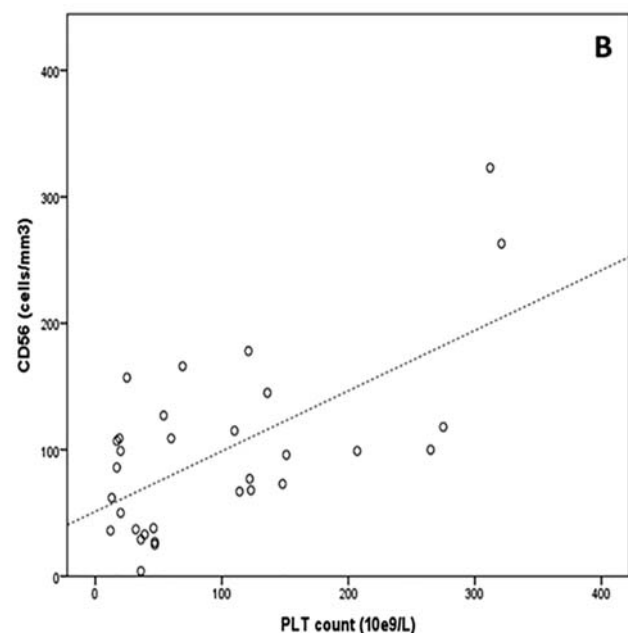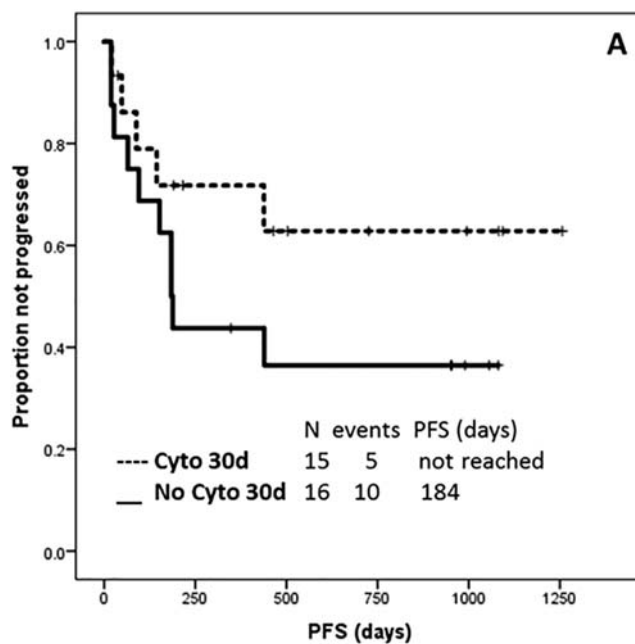
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COMPREHENSIVE REPORT OF ANTI-CD19 CHIMERIC ANTIGEN RECEPTOR T-CELLS (CAR-T) ASSOCIATED NON RELAPSE MORTALITY (CART-NRM) FROM FAERS

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Background: CAR-T cells targeting CD19 positive B-cells have improved outcomes for relapsed/refractory non-Hodgkin lymphoma (NHL) and B-cell acute lymphoblastic leukemia (B-ALL). CAR-T emergent toxicities for FDA approved therapies leading to non-progression related death have been reported in the pivotal studies. However, they are underreported and there remains a need to obtain a comprehensive report of NRM emergent with anti-CD19 CAR-T.

Methods: We retrospectively searched FDA adverse events reporting system (FAERS) for all adverse events (AE) related to "Tisagenlecleucel(T)" and "Axicabtagene ciloleucel(AC)" reported from 2013-2018. FAERS contains AEs from clinical trials and standard of care patients. All cases with the outcome of death were analyzed.

Results: Total numbers of anti-CD19 CAR-T pts reported were 636, out of which 288 cases received "T" and 348 received "AC". Out of total 129 total deaths, 95 died due to non-disease progression. Patient characteristics are summarized in Table 1. CART-NRM for entire cohort was 15%; 21% for "T" and 10% for "AC". Major toxicities reported include CRS, hematological, cardiovascular, neurological and infectious. Difference in mortality is likely related to different patient population, diagnoses and the CAR-T construct.

Conclusion: CART-NRM remains considerably high at 15%. Our analysis highlights the major toxicities and informs the potential opportunities for interventions to reduce mortality. We will present updated data with comparative analysis of published clinical studies at the upcoming ICML Meeting in Lugano.

Keywords: B-cell lymphoma; diffuse large B-cell lymphoma (DLBCL).

TABLE 1 Analysis of cases of anti-CD19 CAR-T NRM

Total Deaths (n=95)	Tisangenlecleucel (n=61)	Axicabtagene ciloleucel (n=34)
Median age	21 years (3-78 years; n=57)	64 years (13-71 years; n=21)
Number of patients ≤18 years	26 (median-age 7.5 years)	1 (13 years)
Number of patients >18 years	31 (median-age 48 years)	20 (median-age 64 years)
Unknown age of patients	4	13
Sex		
Male	33	12
Female	25	17
Unknown	3	5
Indications		
ALL	31	2
NHL	13	23
Chronic lymphocytic leukemia	2	0
Unknown	15	9
Non Relapse Mortality*		
Cytokine release syndrome(CRS)	14 (23%)	18 (53%)
Hematological	28 (46%)	9 (26%)
Cardiovascular	29 (47%)	14 (41%)
Neurological	28 (46%)	19 (56%)
Renal	25 (41%)	3 (9%)
Gastrointestinal	17 (28%)	9 (26%)
Respiratory	20 (32%)	8 (23%)
Infectious	34 (56%)	15 (44%)
Hepatic	4 (6%)	3 (9%)
Median time to AEs	7 days	5 days

*Overlapping toxicities

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SAFETY OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT IN ADULTS AFTER CD19 TARGETED CHIMERIC ANTIGEN RECEPTOR-MODIFIED T-CELL (CAR-T) THERAPY

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Introduction: Allogeneic hematopoietic cell transplant (allo-HCT) is offered to selected patients (pts) after chimeric antigen receptor-modified T-cell (CAR-T) therapy. Lymphodepletion and CAR-T therapy have immunosuppressive and immunomodulatory effects that could alter the safety profile of subsequent allo-HCT.

Methods: We reviewed our institutional experience with adult pts who received an allo-HCT after prior CD19 CAR-T and focused on post allo-HCT toxicities. Cox proportional hazard models were used

to study association between clinical factors and overall survival and non-relapse mortality (NRM).

Results: We identified 32 pts (ALL = 19; NHL/CLL = 13). Median age at allo-HCT was 46 years (23-74). The median time from CAR-T to allo-HCT was 72 days in ALL and 122 days in NHL/CLL pts. Nine pts (28%) had 2 CAR-T infusions. After first CAR-T, 22 pts (69%) had CRS (grade 3, 6%) and 15 (47%) developed NT (grade 3, 19%). After second CAR-T, 3 pts (33%) had CRS and 2 (22%) had NT (grade 4: 1). All ALL pts were in complete remission and all NHL/CLL patients had active disease at the time of allo-HCT. Myeloablative conditioning (MAC) was used in 59% of pts (74% of ALL; 39% of NHL/CLL). Graft sources were matched unrelated (53%), matched related (16%), umbilical cord blood (16%), haploidentical (9.5%), and mismatched-unrelated (6%). Nineteen pts (59 %) had HCT-CI ≥ 2. All pts had neutrophil recovery (median 18.5 days to 1000/mm^3) and all but 3 had platelet recovery (median 14 days to 70,000/mm^3). Three pts (9%) developed thrombotic microangiopathy. Grade 3-4 acute GVHD occurred in 8 (25%) pts and 5 (16%) pts developed chronic GVHD. Within 100 days after allo-HCT, 3 pts (9.4%) developed CMV disease (all gastrointestinal). Other viral infections included HSV-1 stomatitis (n = 1), parainfluenza (n = 2) and RSV pneumonia (n = 1), adenovirus hepatitis (n = 1). Six pts (18%) had invasive fungal infections (3 with documented aspergillosis). One patient had vitreous toxoplasmosis. Eleven pts (34%) had bacterial infections. Other complications included: renal (16.5%); pulmonary (12.5%), cardiac (6%), hepatic (3%), neurologic (3%). Six ALL pts (31%) died due to: disease (n = 2), aspergillosis pneumonia (n = 1), sepsis (n = 1), GVHD (n = 1), and idiopathic pulmonary syndrome (n = 1). Six NHL/CLL pts (46%) died due to: disease (n = 2), GVHD (n = 2), pulmonary emboli (n = 1) and fungal infection (n = 1). The NRM rate at 100-day and 1-year was 16% and 21% for ALL pts and 15% and 33% for NHL/CLL pts. In ALL pts, earlier (less than 80 days) utilization of allo-HCT after CAR-T was associated with improved survival [HR 4.01, 95% CI: (1.14-14.0) ; p = 0.03]. In NHL/CLL pts, MAC was associated with higher mortality [HR 3.83 (0.91-16.6); p = 0.06].

Conclusions: Toxicities did not exceed the expected incidences in this high-risk population. The data provide a platform for the design of larger studies to address the role of allo-HCT after CAR-T immunotherapy.

Keywords: allogeneic stem cell transplant (alloSCT); T-cells.

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CLINICAL AND BIOLOGICAL EVALUATION OF THE NOVEL CD30/CD16A TETRAVALENT BISPECIFIC ANTIBODY (AFM13) IN RELAPSED OR REFRACTORY CD30-POSITIVE LYMPHOMA WITH CUTANEOUS PRESENTATION: A BIOMARKER PHASE IB/IIA STUDY (NCT03192202)

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Introduction: Natural Killer cells (NKC) play an important role in tumor immune-surveillance. AFM13 is a CD30/CD16A targeting high affinity bispecific tetravalent antibody that engages and activates NKC. This study evaluates AFM13 clinical and immunological activity. It examines the immunologic changes in the tumor and peripheral blood (PB) as a function of the dose and method of administration of AFM13 over time.

Methods: Subjects with relapsed or refractory CD30 expressing lymphoma with cutaneous involvement were recruited into 3 cohorts: 1.5 mg/kg IV weekly, 7 mg/kg IV weekly and 7 mg/kg continuous intravenous infusion (CIVI) over 5 days weekly. Each cohort consisted of 3 patients. Subjects received 8 weeks of therapy each cycle. Response assessment was performed on week 11 of each cycle by mSWAT,

TABLE 1 Clinical results displayed by cohort, disease, toxicity and response

Cohort	Disease	Toxicity	Response
1.5 mg/kg IV weekly	Systemic Anaplastic Large Cell Lymphoma-ALK negative	No AE	PR
	Transformed Mycosis Fungoides	No AE	POD
	Cutaneous anaplastic large cell lymphoma	Rash (G4) Skin infection (G3)	CR
7 mg/kg IV weekly	Mycosis Fungoides	IRR (G1)	SD
	Transformed Mycosis Fungoides	IRR (G1)	SD
	Transformed Mycosis Fungoides	Skin infection (G3) IRR (G1)	Not assessed
7 mg/kg CIVI over 5 days weekly	Transformed Mycosis Fungoides	No AE	PR
	Systemic Anaplastic Large Cell Lymphoma-ALK negative	No AE	PR
	Mycosis Fungoides	No AE	POD

photography, PET imaging and PB flow cytometry. A 2nd cycle was administered if there was no progression. Subjects underwent skin biopsies and PB immunologic studies as follows: pretreatment, day 5, week 4 and week 8 of therapy. Biopsies were analyzed and evaluated by a pathologist and IHC image analyzer. PB samples were analyzed by flow cytometry.

Results: Nine subjects were accrued. Age 37-79 years, 3 of 9 where white and 6 of 9 were men. The median number of prior therapies was 4 (1-11) and 2 patients had progressed on brentuximab vedotin. The disease etiologies, treatment emergent toxicities and response by cohort are presented in table 1. An objective response rate of 44% was observed in the study.

In the PB, flow cytometry revealed a decrease in circulating NKC (CD56+ CD3-, CD56+ CD16+ and NKp46+) during therapy with post therapy recovery. The activation marker CD69 on NKC increased in responders (R) compared to non-responders (NR).

Figure 1:

a) Increase in the expression of the activation marker CD69 on NK cells from responders compared to non-responders
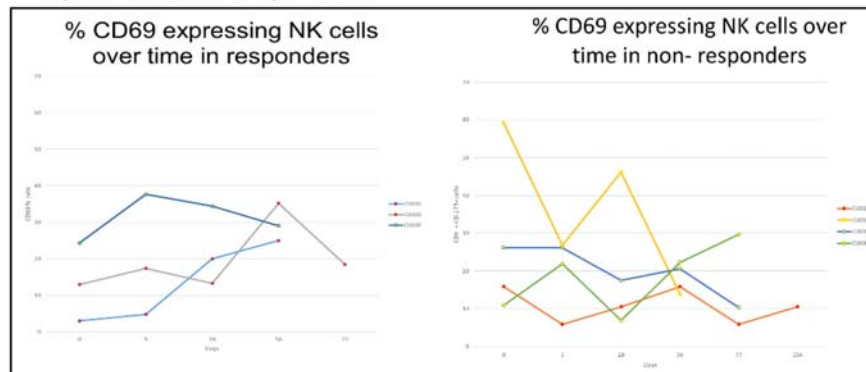
b) Increase in % of CD56 in total cells over time in responders vs. non-responders
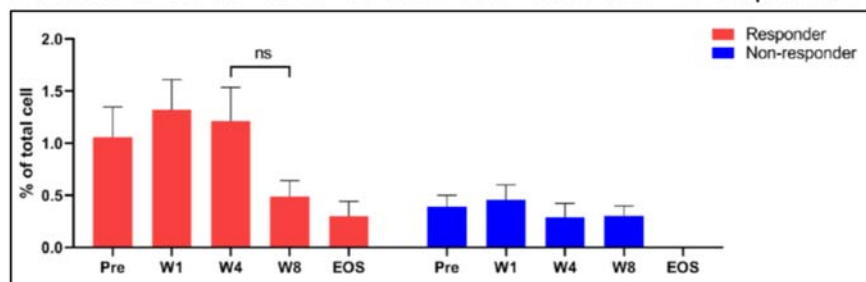
Similarly, tumor biopsies in R showed increased infiltration and activation of CD56+ NKC as opposed to NR (Figure 1). NKC cytotoxicity through the expression of Granzyme B was seen in R vs NR. Flow quantitation of circulating CD4+ CD25+ T cells (Tregs) shows a decrease in R vs. NR.

Conclusions: AFM13 demonstrated a high ORR of 44 % among a population of heavily pretreated patients with a CD30 positive lymphoproliferative T-cell malignancy. AFM 13 exhibited activity post brentuximab vedotin failure. In addition, biological changes in NKC infiltration and activation in the PB and tissue biopsy correlate with response. This data is the first to demonstrate the therapeutic advantages of this bispecific, and the first to correlate changes in NKC as a function of dose and schedule.

Keywords: anaplastic large cell lymphoma (ALCL); CD30; cutaneous T-cell lymphoma (CTCL).

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IPILIMUMAB PLUS LENALIDOMIDE FOR TREATMENT OF RELAPSED DISEASE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION (AlloSCT) IN PATIENTS (PTS) WITH LYMPHOID MALIGNANCIES

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Purpose: Treatment of relapsed lymphoma after alloSCT requires novel strategies. Clinical trials using ipilimumab in this setting have disappointing results. Based on its immunomodulatory properties, we hypothesized that lenalidomide can harness the immune effect of ipilimumab to combat lymphomas.

Experimental design: Patients with lymphoma or chronic lymphocytic leukemia (CLL) who relapsed after alloSCT, with no active graft-versus-host disease (GVHD) were eligible. Treatment consisted of 8 total cycles of lenalidomide 10 mg PO daily for 21 days (cycles 1,3, 5 and 7) alternating with ipilimumab 3 mg/kg IV on day 1 (Cycles 2, 4, 6 and 8).

Results: Eleven pts were enrolled. Median age was 55 yrs (range, 44-66). Histologies included [Follicular (n = 2), CLL (n = 3), Mantle cell (n = 2), diffuse large b-cell (n = 3; 2 of whom were Double-hit), and T-cell anaplastic lymphoma (n = 1)]. The median number of therapies excluding the alloSCT was 3 (range 2-7). Two failed a prior autologous

SCT, one had 2 prior alloSCT, and three failed prior donor lymphocyte infusions. Two pts relapsed within 3 months of their alloSCT prior to enrollment on study. One pt was taken off study after cycle 1 of lenalidomide due to flare of previously diagnosed liver and skin GVHD. Another pt developed skin chronic GVHD after cycle 4 which precluded treatment with the pre-planned 8 cycles. No other cases of GVHD were noted. Overall response rate was 73%. Five (45%) pts had a complete response (four of which were durable at 14+, 32+, 33 + and 34+ months (including one CLL pt who failed prior ibrutinib, idelalisib, venetoclax and CAR-T), and 3 (27%) had partial response (PR). With a median follow-up time of 30.8 months (range, 3–45.1 months), 9 (82%) patients remain alive. One PR pt died secondary to cardiac complications after an elective surgery; and 1 died of progression.

Immune monitoring: We conducted multiparametric flow cytometric analyses of PBMCs before and after treatment. We previously identified an increase in the number of inducible costimulatory (ICOS) +CD4+ T cells as a pharmacodynamic biomarker for ipilimumab-based therapy. In the present trial, we observed a statistically significant increase in the number of ICOS$^+$CD4$^+$FoxP3$^-$ T cells number with a notable increase after the first cycle of lenalidomide and a further increase after the first dose of ipilimumab, suggesting an additive effect to these 2 agents when combined together (P = 0.007). We also found a higher frequency of CD4+ICOS+PD-1+ and CD8+PD+1 T effector cells in the responders at baseline when compared to non-responding pts. In contrast, the non-responders had a higher frequency of CD4+GATA3+ T effector memory cells at baseline.

Conclusions: These results demonstrate promising durable responses in pts with lymphoid malignancies who relapsed after alloSCT. Future analysis in a bigger cohort would help validate these findings.

Keywords: immune system; non-Hodgkin lymphoma (NHL).

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DONOR LYMPHOCYTE INFUSIONS INDUCE DURABLE RESPONSES IN PATIENTS WITH FOLLICULAR, MANTLE AND T CELL LYMPHOMAS RELAPSING AFTER AN ALLOSCT. AN EBMT-LWP STUDY

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Introduction: Donor lymphocyte infusions (DLI) can be employed to treat relapsed lymphoma following allogeneic stem cell transplantation (alloSCT) and provide the most direct evidence for the graft versus lymphoma effect. Given the paucity of data describing the efficacy of DLIs in NHL relapsing after alloSCT we have conducted an extensive analysis from the EBMT database.

Methods: 118 patients [follicular lymphoma (FL) n = 28, diffuse large B cell lymphoma (DLBCL) n = 28, T cell lymphoma (TCL) n = 52 and mantle cell lymphoma (MCL) n = 10] who received DLI as the only treatment for clinical relapse post alloSCT were identified on the EBMT database. The median age at alloSCT was 50 (18-73) years. There were 37 female and 81 male patients who underwent an alloSCT with reduced intensity (n = 90) or myeloablative conditioning (n = 28) from matched sibling (n = 63), unrelated (n = 47) or mismatched family (n = 8) donors. 85 were T cell depleted with CAMPATH or ATG. The median time from alloSCT to relapse was 3.8 months (18 days-67 months).

Results: Patients received a median of 1 (range 1-19) DLIs at a median starting dose of 1.5 x106 CD3/kg (0.01-120x106 CD3/kg) at a median of 152 days (18-2136) post alloSCT. The median time from relapse to the first DLI was 35 days (0-168). The best response achieved in 102 evaluable patients was CR in 56 and PR in 10, whereas 13 patients had stable disease and 23 progressed. The median duration of response was 36 months (range 1-168). When analysed according to histology the overall response rate (ORR=CR +PR) for FL was 88% (CR 77%), DLBCL 41% (32% CR), TCL 60% (53% CR) and MCL 86% (CR 71%). The median duration of responses for FL, DLBCL, TCL and MCL were 30 (range 2-150), 38 (4-76), 37 (range 1-168) and 50 months (13-116), respectively. With a median follow up of 77 months after the 1st DLI, 36 (31%) patients remain in complete remission, 29 (25%) without any further therapy. 37 patients (35%) received additional antilymphoma therapy after the DLI. Of 20 patients with FL achieving a CR post DLI, 13 (65%) remain in remission without further therapy at a median of 74 months. Of 24 patients with TCL that achieved a CR with DLI, 20 (83%) remain in remission without any further therapy at a median of 95 months. Following the DLI 43 (36%) patients developed aGVHD (6 grade I, 13 grade II, 11 grade III, 9 grade IV, 4 grade unknown) and 33 (28%) developed cGVHD (11 limited, 20 extensive, 2 unknown). Following the first DLI the cumulative incidence of relapse was 31% (CI 22-41) at 4 years. The 4-year PFS after 1st DLI was 39% (CI 30-50) and the OS, 44% (CI 35-54).

Conclusions: DLI monotherapy can induce significant ORR in patients with NHL which are most impressive in FL and MCL. Although the ORR was not so high in patients with TCL, those who achieved a CR post DLI have an excellent chance of long-term remission. In contrast, in DLBCL DLI as single treatment provides only limited benefit. Acute and chronic GVHD remains a significant complication of DLI.

Keywords: allogeneic stem cell transplant (alloSCT).

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INTRANODAL TREATMENT WITH IFNα-DENDRITIC CELLS AND RITUXIMAB INDUCES SYSTEMIC CLINICAL RESPONSE AND ENDOGENOUS VACCINATION AGAINST FOLLICULAR LYMPHOMA: FINAL RESULT OF A PHASE I STUDY

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Purpose: This study was aimed at evaluating the feasibility, safety, immunological and clinical responses in patients with Follicular lymphoma (FL) treated with monocyte-derived dendritic cells generated in the presence of interferon-alpha and GM-CSF (IFN-DC) in combination with low doses of Rituximab (R).

Experimental design: Firstly, we analyzed *in vitro* and *in vivo* the immunological properties of IFN-DC against FL. Thus, we performed a phase I trial in 8 refractory and relapsed FL patients based on sequential intranodal injections of low-dose of R and unloaded IFN-DC and report the safety, clinical and immunological results of the enrolled patients.

Results: Preclinical studies indicated that IFN-DC can synergize with R leading to increased cytotoxicity and T cell tumor infiltration. The clinical evaluation showed that the combined treatment was totally safe. The overall response rate was 50%, PET-negative complete response rate 37% and remission is still ongoing in 2/4 of responding patients (median follow- up 26 months, range 11-47). Notably, following the combined therapy all patients showed induction/enhancement of T cell responses by CD107 degranulation or IFN-g ELISPOT assay against patient-specific tumor IGHV sequences.

Conclusions: These results represent the proof-of-principle on the effectiveness of unloaded IFN-DC in inducing durable clinical responses and promoting induction of tumor specific peripheral T cells, thus suggesting the occurrence of an effective endogenous antitumor vaccination. The overall findings indicate that some unique properties of IFN-DC can be successfully exploited to induce/enhance antitumor responses, thus representing a valuable antitumor strategy for novel and more effective combination therapies in cancer patients.

Translational relevance: The development of protocols of *in situ* cancer immunotherapy aimed at inducing an endogenous vaccination is currently regarded as a practical and promising antitumor strategy, with potential advantages with respect to the use of defined tumor antigens for inducing a broader antitumor immunity, potentially targeting also neoantigens emerging during tumor progression and therapies. This study represents the first evidence on the safety and clinical effectiveness of IFN-DC, a unique type of DC rapidly generated from monocytes under simple GMP conditions and endowed with special immunostimulatory properties. Combined with low doses of intranodal injection of R, IFN-DC induced clinical response in cancer patients and promoted the induction of tumor specific T cells. All this implies the occurrence of an endogenous antitumor vaccination possibly resulting in clinical response. The findings suggest that IFN-DC are a good candidate for a selective clinical use in combination therapies in cancer patients

Keywords: dendritic cells; follicular lymphoma (FL); immune system.

NOVEL TREATMENTS

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COPANLISIB SYNERGIES WITH CONVENTIONAL AND TARGETED AGENTS INCLUDING VENETOCLAX IN PRECLINICAL MODELS OF B- AND T-CELL LYMPHOMAS

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Introduction: Copanlisib has shown activity in lymphomas, but the number of patients achieving complete remission is relatively low, a problem shared by many targeted agents. We performed a pharmacological screening to identify active combinations.

Methods: We tested copanlisib as single agent and in combination with other molecules in cell lines derived from mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) and T cell lymphomas (T-NHLs). Synergism was evaluated with Chou-Talalay combination index, as previously done (Tarantelli et al, CCR 2018).

Results: Copanlisib showed an *in vitro* dose-dependent antitumor activity in the vast majority of the models with a median IC50 of 75 nM (95% C.I., 21-160 nM). The drug was active both in B- (n = 17) and T-NHLs (n = 9), but the latter were less sensitive (285 vs 22 nM, P = 0.0002). The *in vitro* activity was confirmed using the human JeKo-1 MCL xenograft model.

We evaluated 16 combination partners, including rituximab (B-NHL), crizotinib and brentuximab vedotin (T-NHLs), lenalidomide, bendamustine, agents targeting AKT1/2, BCL2, BET, BTK, CDKs (pan, CDK4/6, CDK9), HDAC, JAK1/2, MALT1, and the proteasome. In B-NHLs, copanlisib/venetoclax were the most beneficial (14 synergism, 2 additive), and the 4th best in T-NHLs (5 synergism, 1 additive). The combination led to increased apoptosis, as shown by a dose-dependent increased PARP cleavage in 3 MZL, and 1 MCL cell lines and by a reduction of cell viability in 2 MCL primary cells. In MZL (SSK41) and MCL (Jeko1) 24h exposure to copanlisib determined a dose-dependent down-regulation of pAKT and anti-apoptotic proteins (BCL-XL in the MZL and of MCL1 in the MCL). These changes were maintained in cells exposed to the combination, but not after venetoclax alone. An *in vivo* experiment using the SSK41 MZL cell line validated the beneficial effect of this combination and also of copanlisib/lenalidomide (*in vitro* beneficial in 12/17 B- and 4/9 T-NHL). In T-NHLs, benefit was observed in all ALCL-ALK+ with

copanlisib/crizotinib (3/4 synergisms). All but one of the non ALCL-ALK+ cell lines achieved a synergism with copanlisib/ruxolitinib. Copanlisib/brentuximab vedotin was synergistic in the non ALCL-ALK + and Sezary Syndrome cell lines.

Transcriptome analysis identified the PIM1 and PIM2 kinases and the anti-apoptotic gene MCL1 as up-regulated in the MZL cell line HAIR-M exposed to copanlisib (5nM, for 4, 8 and 12h). Thus, we tested combinations with the PIM inhibitor AZD1208 and the MCL1 inhibitor MIK665 (S63845) in 3 MCL and 3 MZL cell lines. Both combinations were synergistic in the HAIR-M and beneficial in additional 5/5 and 3/5 cell lines, respectively.

Conclusions: Our study identified a series of active copanlisib-containing combinations and provided the rational for the design of the new SAKK 66/18 phase I study exploring copanlisib plus venetoclax in relapsed/refractory B-cell lymphomas.

Keywords: marginal zone lymphoma (MZL); PI3K/AKT/mTOR; venetoclax.

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MECHANISMS OF SECONDARY RESISTANCE TO IDELALISIB IN MARGINAL ZONE LYMPHOMA

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Background: PI3Kδ-inhibitor (i) idelalisib (IDEL) is currently used to treat indolent lymphomas including marginal zone lymphoma (MZL).

However, a subset of patients relapses due to acquired resistance. A better understanding of resistance mechanisms could help to design improved therapies. With this aim, we generated MZL cell lines resistant to IDEL.

Materials and Methods: Cells were kept under IDEL(IC90) until acquisition of resistance (RES) or with no drug (parental, PAR). Stable resistance was confirmed by MTT assay after 2-weeks of drug-free culture. Multi-drug resistance phenotype was ruled out. Cells underwent transcriptome profiling (RNA-Seq), lipidomics profiling, pharmacological screening (348 compounds), and immunophenotypic analysis.

Results: The RES models, with 5-10 fold times higher IC50s than PAR counterparts, derived from VL51 and Karpas1718 presented different mechanisms of resistance to IDEL, although both involved secreted molecules since conditioned media conferred resistance to IDEL in the PAR cells. Lipidomics analyses revealed increased levels of specific triacylglycerols and glycerophosphocholines with lower cardiolipins and sphingomyelins levels in RES-VL51, and up-regulated of some triacylglycerols and repressed levels for specific glycerophosphocholines in the RES-K1718.

Comparing RES vs PAR, there was an enrichment at transcriptomic level in IL6-STAT3, chemokines and PDGFRA signatures for the RES-VL51, paired with increased p-AKT and p-BTK levels. In particular, there was an over-expression of IL6, PDGFRA and CXCR4. In accordance, addition of a CXCR4-i overcame resistance. Furthermore, targeting IL6 or PDGFRA with siRNAs partially reverted the resistance, and the effect was stronger when both genes were silenced. Finally, the pharmacologic screening showed anti-proliferation activity of a PDGFR-i in the RES.

In the RES-K1718 model, there was enrichment for proliferation signatures and growth factors. HB-EGF and ERBB4 were among the most up-regulated transcripts and their involvement in the resistance mechanisms were studied. First, recombinant HB-EGF stimulation was able to induce resistance to IDEL and also to the BTK-i ibrutinib in both PAR lines. Second, RES-K1718 recovered sensitivity to IDEL upon combination with a pan ERBB-i and with ibrutinib, tested due to its reported ERBB inhibition capacity.

Conclusions: We created two distinct novel models derived from MZL of secondary resistance to the PI3Kδ-i idelalisib. These models, driven by different biologic processes, will help in clarifying mechanisms of resistance to the drug and to evaluate alternative therapeutic approaches. Indeed, we already identified potential active treatments that might overcome resistance to IDEL and are worth of further investigations.

Keywords: idelalisib; marginal zone lymphoma (MZL).

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A SELECTIVE AND COVALENT INHIBITOR OF ITK BLOCKS TCR SIGNALING, INHIBITS PROLIFERATION OF HUMAN SÉZARY CELLS IN VITRO, AND INDUCES TUMOR REGRESSION IN DOGS WITH T-CELL LYMPHOMA

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Introduction: ITK is a tyrosine kinase involved in T-cell receptor (TCR) signaling and differentiation of naïve T cells. ITK is closely related to RLK, a kinase of redundant function that is expressed in cytotoxic T cells and Th1 but not Th2 cells. Studies in knockout mice indicate that selective inhibition of ITK will inhibit Th2 differentiation and allow normal T cell immunity. ITK is widely expressed in T cell malignancies and signaling is associated with poor survival in peripheral T cell lymphoma (PTCL). Copy number gain of the ITK gene is often seen in PTCL and ITK is frequently overexpressed in cutaneous T‑cell lymphoma (CTCL). Therefore, selective inhibition of ITK may be a new treatment strategy. Here we describe CPI-818, a compound designed to bind covalently and selectively to the CYS-442 residue of ITK.

Methods: Human PBMC, T cell lines and Sézary cells were stimulated in vitro with anti CD3/CD28 with or without CPI-818. TCR signaling and proliferation were evaluated by flow cytometry and western blots. Mice were treated with CPI-818 and effects on immune cell subsets, humoral and cellular immune response were evaluated. Th skewing in mice was determined using an ovalbumin vaccine adoptive transfer model. Companion dogs with TCL were treated with CPI-818 at 20mg P.O. BID and evaluated for safety and tumor response.

Results: CPI-818 inhibits kinase activity with IC_{50} values of 2.3nM, 430nM and 850nM for ITK, RLK and BTK, respectively. In a wider survey of 468 human kinases, CPI-818 (1μM) was highly selective for ITK. CPI-818 inhibited anti-CD3/28 induced phosphorylation of ERK and PLCγ1 in PBMC and inhibited IL-2 secretion in stimulated Jurkat T cells (75 nM). in vitro proliferation of human Sézary cells was inhibited with 200nM of CPI-818, a concentration that did not affect the proliferation of autologous normal T cells. Anti CD3/28-induced Th2 cytokine production in Sézary cells was also inhibited by CPI-818. in vivo studies showed no changes in blood counts or T, B, NK cell subsets in lymphoid organs of mice given CPI-818 for 28 days. Neither primary nor secondary antibody responses nor CD4 T cell responses to KLH antigen were inhibited. Spleen cells from treated mice demonstrated an increase in the ratio of IFNγ/IL-4 cells indicative of Th1 skewing. Three dogs with T-cell lymphoma; 1 PTCL and 2 CTCL were treated with CPI-818 for 2-20 weeks. Treatment was well tolerated with no dose limiting toxicities and no changes in lymphocyte counts. One complete (CTCL, 5 months duration) and two partial responses were observed.

Conclusions: CPI-818 blocks TCR signaling and T cell activation and also affects T cell differentiation with a biasing to Th1 cells. There are preferential anti-proliferative effects in Sézary cells compared to autologous normal T cells. The demonstration of safety and clinical activity in dogs with T-cell lymphoma support recently initiated clinical trials in patients with TCL.

Keywords: T-cell lymphoma (TCL); T-cell receptor (TCR).

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NUCLEAR EXPORT INHIBITION ENHANCES THE ACTIVITY OF R-CHOP IN NON-HODGKIN'S LYMPHOMA

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Introduction: The nuclear exporter protein exportin-1 (XPO1) regulates the activity of tumor suppressor proteins (TSPs) via compartmentalization within the nucleus. XPO1 over-expression in cancer including Non-Hodgkin's Lymphoma (NHL) leads to increased nuclear export of TSPs and their functional inactivation and often correlates with poor prognosis. Single agent oral selinexor has demonstrated an ORR of 29.6% in patients with RR DLBCL with durable responses > 8 months. R-CHOP is highly active in NHL, however fails to sufficiently activate TSPs due to high XPO1 activity. This makes the enhancement of R-CHOP sensitivity through XPO1 inhibition and nuclear retention of TSPs a viable therapeutic strategy for NHL. Earlier, we had demonstrated that targeting XPO1 by Selective Inhibitor of Nuclear Export (SINE) compounds (selinexor and analogs) resulted in anti-tumor activity in patient-derived lymphoma cell lines and NHL xenograft models.

Methods: Using several assays for cytotoxicity and apoptosis analysis, molecular assays and CRISPR/Cas9 genome editing for specificity, we evaluate the anti-tumor activity of SINE compounds with R-CHOP

in vitro, in vivo and in a Phase Ib/II clinical trial (NCT03147885) in NHL patients. Eight NHL patients were administered R-CHOP every 3 weeks (Rituximab 375 mg/m^2 IV day 1; Cyclophosphamide 750 mg/m^2 IV day 1; Doxorubicin 50 mg/m^2 IV day 1; Vincristine 2 mg IVP day 1 and Prednisone 100 mg days 1-5) along with selinexor 60 mg PO weekly. Peripheral blood from patients treated with the combination was obtained for RNA-Seq, RT-PCR and protein analyses.

Results: SINE compounds synergized with CHOP in vitro (CI<1). Selinexor-R-CHOP and next generation analog altanexor-R-CHOP combination treatment resulted in statistically significant enhancement of survival of a systemic (disseminated) NHL model. The superior cytotoxicity was consistent with enhanced nuclear retention of different TSPs consistent with the suppression of pro-survival markers and activation of pro-apoptotic molecules in the combination treatment. Using CRISPR/Cas9 genome editing we discovered an R-CHOP priming mechanism in which XPO1 inhibition leads to the enhancement of CD20 through cancer cell selective activation of p-ERK. In blood biopsies from the selinexor-R-CHOP trail patients a statistically significant down-regulation of XPO1 and 9 pro-survival markers were uniformly captured in RNA-seq, mRNA and protein analysis and corroborated the in vitro and in vivo data. Immunostaining of the NHL patient biopsies were in line with the molecular results and showed nuclear retention of TSPs.

Conclusion: Selinexor plus R-CHOP demonstrates strong anti-tumor activity in established and patient derived NHL models. We are broadening the characterization of this combination regimen in patient biopsies from our ongoing trial. We anticipate that our results will bring forward a novel and effective treatment regimen for NHL.

Keywords: B-cell lymphoma; non-Hodgkin lymphoma (NHL); R-CHOP.

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REVERSAL OF IMMUNE TOLERANCE AND INCREASED SURVIVAL AFTER XPO1 AND BTK INHIBITION IN MOUSE MODELS OF PRIMARY CNS LYMPHOMA (PCNSL)

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Introduction: On the grounds of frequent deregulated chronic BCR signaling in PCNSLs, targeting the BCR pathway is emerging as a promising therapeutic avenue for these poor-prognostic patients. Unfortunately, responses to the inhibition of BCR signaling with ibrutinib are scarce and short-lasting. Of note, inhibition of the XPO-1 activity with selinexor has been shown to impede BCR and NF-kB signaling, while having excellent brain penetrance. Herein, we studied the activity of selinexor alone or in combination with ibrutinib in preclinical mouse models of PCNSL.

Methods: Proliferation and survival analysis in DLBCL cell lines were performed by MTS and Annexin V-propidium iodide assays. Orthotopic xenograft models were established by the injection of ABC-DLBCL cells transfected with luciferase or patient-derived PCNSL cells into the brain parenchyma of athymic mice. Tumor growth was monitored by bioluminescence. Immunohistochemical (IHC) detection was performed using human anti-CD20, human anti-Ki-67 and mouse anti-F4/80 antibodies. Changes in the proportion of M1/M2 macrophages and in the expression of immune checkpoints were studied by flow cytometry.

Results: Firstly, we observed that in vitro sensitivity to selinexor was independent of the cell of origin, but that a strong synergy with ibrutinib occurred mainly in ABC-DLBCL cells. Accordingly, after treating the OCI-Ly10 (ABC origin) bearing mice with 5mg/kg selinexor or vehicle three times a week, it was found that selinexor significantly blocked tumoral growth prolonging mice survival (median: 48 days vs. 34 days). Next, for the purpose of evaluating potential synergy between ibrutinib and selinexor, PCNSL mice were distributed in four groups: selinexor (5mg/kg twice a week), ibrutinib (25mg/kg daily), combination of both or vehicle. Although tumoral growth was blocked by all treatments, the combination of both drugs significantly increased survival compared to monotherapies. Further analysis of the innate immune microenvironment by flow cytometry and IHC showed that PCNSLs were infiltrated by macrophages, particularly by pro-tumoral M2 expressing PD1 and SIRPα. Notably, the treatment with the combination of drugs increased the proportion of inflammatory M1 macrophages, while the remaining M2 macrophages expressed lower levels of the immune checkpoints PD1 and SIRPα.

Conclusions: Our results show that selinexor blocks PCNSL tumor growth and prolongs survival, while its combination with ibrutinib further increases survival. Additionally, we show that PCNSL in mice is infiltrated by tumor-promoting PD1$^+$ and SIRPα$^+$ M2 macrophages. Treatment with both drugs favors an anti-tumoral immune response by shifting polarization toward anti-tumoral M1. These observations provide pre-clinical evidence for the development of selinexor as a new therapeutic option for PCNSL.

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THE FIRST-IN-CLASS ETS INHIBITOR TK-216 INTERFERES WITH ETS TRANSCRIPTION FACTORS AND SYNERGIZE WITH LENALIDOMIDE IN LYMPHOMA

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Background: Altered expression levels of members of the ETS-transcription factors are often observed in lymphomas. TK-216, clinical derivative of YK-4-279, is the first-in-class inhibitor of the Ets family of transcription factors. Here, we characterized TK-216 and YK-4-279 for their anti-lymphoma activity and mechanism of action in lymphomas.

Methods: Cells were exposed to YK-4-279 or TK-216 alone or combined with other compounds; cell proliferation was measured with MTT; synergy calculated with the Chou-Talalay combination index. in vivo studies were done in NOD-SCID mice. RNA and proteins changes were analyzed using standard techniques.

Results: YK-4-279 and TK-216 demonstrated an anti-tumor activity across over 50 lymphoma cell lines. The anti-tumor activity was confirmed in a DLBCL xenograft model (TMD8). Compared with control group, mice treated with TK-216 or YK-4-279 clearly presented a reduction in tumor growth (P<0.01). We then combined YK-4-279 or TK-216 in vitro with 5 anti-lymphoma agents (ibrutinib, idelalisib, birabresib, venetoclax and lenalidomide) in 2 ABC (OCI-LY-10, TMD8) and 2 GCB (Karpas422, SU-DHL-4) DLBCL cell lines. The biggest benefits were achieved in the combination with venetoclax and lenalidomide. Since lenalidomide is known to act in ABC DLBCL via the IRF4-SPIB axis, we firstly confirmed the synergism also in vivo in the OCI-LY-10 xenograft model and then we evaluated the contribution of SPIB in the synergism between TK-216 and lenalidomide. Reduction in SPIB protein level was observed with both compounds as single agents but with a more pronounced effect in the combination. Co-IP experiments also demonstrated that TK-216 decreased the binding of SPIB to RHA and DDX5 in ABC-DLBCLs and of SPI1 to the same helicases in GCB-DLBCLs, as reported for EWS-FLI1 fusion protein and the two helicases in Ewing Sarcoma.

Finally, we investigated the effect of TK-216 treatment on transcriptome changes. Gene expression profiling on U2932 ABC DLBCL cell lines exposed 8 hrs to the TK-216 demonstrated that transcripts upregulated by TK-216 were enriched of genes repressed by IRF4 and SPIB, while genes downregulated by lenalidomide or positively regulated by IRF4 and SPIB were present in the transcripts downregulated by the compound. After 18 hrs of treatment with TK-216, the transcriptome changes were more similar to what reported for RNA helicase A knockdown, indicating the interference with SPIB as an early event.

Conclusions: In ABC DLBCL, YK-4-279 and its clinical derivative TK-216 synergize with lenalidomide, both in vitro and in vivo, interfering with SPIB. TK-216 shows a promiscuous activity on ETS factors interfering between helicases and two different ETS factors: SPIB and SPI1. A clinical trial for DLBCL patients is being designed.

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THE NOVEL BISPECIFIC CD47-CD19 ANTIBODY TG-1801 POTENTIATES THE ACTIVITY OF UBLITUXIMAB-UMBRALISIB (U2) DRUG COMBINATION IN PRECLINICAL MODELS OF B-NHL

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Umbralisib is an orally available PI3Kδ inhibitor that has demonstrated activity in preclinical models and primary B-cell non-Hodgkin lymphoma (B-NHL) cells, and in patients with B-cell malignancies. The doublet of umbralisib used in combination with the

glycoengineered anti-CD20 mAb ublituximab ("U2" regimen), provides a non-chemotherapy backbone regimen on which novel multidrug combinations are being explored. TG-1801 is a novel, bispecific antibody currently in Phase 1 that selectively targets CD47 on CD19+ B-cells, sparing red blood cells or platelets, and blocking the CD47-SIRPα macrophage checkpoint on mature B cells. Here we show that activity of the U2 combination in B-NHL cell lines co-cultured with bone marrow-derived stromal cells, M2-polarized primary macrophages, and primary circulating PBMCs, is mainly associated with a decrease of anti-inflammatory cytokines genes (IL-6, IL-10, IL-1RA). In addition, upregulation of pro-inflammatory IL-2, accompanied by a 2-fold increase of M2-dependent antibody-dependent cell phagocytosis (ADCP), is also observed. Notably, when U2 is combined with TG-1801, this 2-fold increase in ADCP is doubled up to 4-fold increase. Moreover, the activated antibody-dependent cell death (ADCC) observed with TG-1801 alone (4.1-fold above control) becomes increased (7.2-fold above control) when combined with ublituximab, whereas umbralisib alone does not affect ADCC. RNA-seq analysis further reveals that U2 treatment is mainly associated with modulation of redox processes in B-NHL co-cultures (NES = -0.57, p = 0.016). Although TG-1801 single agent does not significantly affect B cell transcriptome, combination with U2 provokes the down-regulation of genes associated with cell architecture homeostasis, including cellular membranes (NES = -0.57, p = 0.006), cytoskeleton (NES = -0.51, p = 0.046), and cell proliferation (NES = -0.44, p = 0.018). *In vivo*, treatment with ublituximab alone (5mg/kg, qw) displays a tumor growth inhibition (TGI) of 88%, with 3/8 mice harboring a barely palpable tumor, while treatment with umbralisib alone (150mg/kg, bid) shows a TGI of 50%, with 2/8 mice lacking detectable tumors. TG-1801 (5mg/kg, qw) exhibits a 76% TGI with 1/8 tumor free-mouse. Most importantly, the combination of TG-1801 with umbralisib alone, ublituximab alone, and U2 achieves TGI of 85%, 93% and 93% respectively, and 35 days after the last dose 3/8 mice remain tumor-free in the triple combo groups, *versus* only 1/8 mouse in the TG-1801 group. Interestingly, this superior anti-tumor effect of the TG-1801-based combinations is associated with a higher infiltration of mouse macrophages within the tumors, as assessed by F4/80 IHC labeling. In conclusion, the results presented herein set the preclinical rationale for a combination strategy of the novel CD47-CD19 antibody TG-1801 with other B-cell targeted drugs, particularly umbralisib and ublituximab, in B-NHL.

Keywords: antibody-dependent cytotoxicity (ADC); non-Hodgkin lymphoma (NHL); PI3K/AKT/mTOR.

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THE ANTI-CD25 ANTIBODY-DRUG CONJUGATE CAMIDANLUMAB TESIRINE (ADCT-301) PRESENTS A STRONG PRECLINICAL ACTIVITY BOTH AS SINGLE AGENT AND IN COMBINATION IN LYMPHOMA CELL LINES

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Introduction: Camidanlumab tesirine (ADCT-301) is an anti-CD25 antibody-drug conjugate (ADC) conjugated via a protease cleavable linker to SG3199, a highly cytotoxic DNA minor groove cross-linking pyrrolobenzodiazepine dimer (Flynn et al. *Mol Cancer Ther* 2016). ADCT-301 is currently in phase I as single agent in relapsed/refractory lymphomas (NCT02432235), advanced solid tumors (NCT03621982) and just concluded in acute myeloid leukemia (NCT02588092). We assessed its preclinical activity as single agent in 57 lymphoma cell lines and in combination with selected drugs in T cell lymphomas-derived cell lines.

Methods: Cell lines were exposed to increasing concentrations of ADCT-301 for 96h followed by MTT proliferation assay. CD25 expression was measured both at cell surface level via fluorescence quantitation (Quantum Simply Cellular microspheres) and at RNA level (Illumina HT-12 arrays and HTG EdgeSeq Oncology Biomarker Panel). Combination studies of increasing doses of ADCT-301 and increasing doses of additional drugs were assessed by MTT proliferation assay over 96h in FE-PD, Karpas-299, KI-JK and MAC1 cell lines. Chou-Talalay method was used to calculate median combination index (CI) (synergism CI<0.9, additive CI = 0.9-1.1, antagonism/no benefit CI> 1.1).

Results: ADCT-301 presented much stronger activity in T (n = 9, median IC50 = 4 pM; 95% C.I., 1.6pM-0.9nM) than B cell lymphomas (n = 48, 0.7 nM; 95% C.I., 0.4-2.6 nM) (P = 0.047). *In vitro* activity was highly correlated with CD25 expression both at cell surface level (n = 53, Pearson r = -0.50, P = 0.0001) and RNA level (n = 53, Pearson r = -0.52, P<0.0001). CD25 was also more highly expressed in T than B cell lymphoma (P<0.0001), in agreement with the IC50s differences, and the correlation was still maintained within the subgroups (T cell lymphomas, Pearson r = -0.90, P = 0.0021; B cell lymphomas; Pearson r = -0.3, P = 0.05).

Based on the higher activity in T-cell lymphomas, ADCT-301-containing combinations were evaluated in 4 cell lines derived from peripheral T cell lymphoma not otherwise specified (n = 1), ALK-pos (n = 2) or ALK-neg (n = 1) anaplastic large cell lymphoma (ALCL).

ADCT-301 plus the mTOR inhibitor everolimus showed synergism in 4/4 cell lines. Combinations with the PI3K inhibitor copanlisib, the BCL2 inhibitor venetoclax and the HDAC inhibitor vorinostat were synergistic in all but one cell line. The combination with pralatrexate was synergistic in 2/2 ALK-pos ALCL cell lines. The addition of bortezomib or romidepsin led to synergism in 2/4 cell lines. Finally, the combinations with bendamustine and with 5-azacytidine achieved synergism in 1 out 4 cell lines (ALK+ALCL Karpas-299).

Conclusion: The strong single agent anti-lymphoma activity and the observed *in vitro* synergisms with targeted agents support the current ADCT-301 clinical development and identify potential combination partners for future clinical studies.

Keywords: histone deacetylase inhibitors; pralatrexate; venetoclax.

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PRELIMINARY RESULTS OF A PHASE 1 DOSE ESCALATION STUDY OF THE FIRST-IN-CLASS ANTI-CD74 ANTIBODY DRUG CONJUGATE (ADC), STRO-001, IN ADVANCED B-CELL MALIGNANCIES

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Background: CD74 is expressed on B cells throughout differentiation and is an attractive target for treatment of MM and NHL. Sutro's cell-free protein synthesis and site-specific conjugation platform technologies were used to generate STRO-001, a novel CD74-targeting ADC. STRO-001 contains a potent maytansinoid warhead conjugated to two specific sites (DAR of 2) using a stable non-cleavable linker. This first-in-human Phase 1, open-label, multicenter, dose escalation study was designed to evaluate the safety, tolerability, and preliminary anti-tumor activity of STRO-001 in adults with B-cell malignancies.

Methods: Patients with advanced, relapsed/refractory MM and NHL are eligible for enrollment. STRO-001 is administered as a 60-minute IV infusion on Days 1 and 15 of a 28-day cycle until disease progression or dose-limiting toxicity (DLT). Two cohorts, one for MM and one for NHL patients, with an initial accelerated dose titration design (N of 1) are being enrolled and analyzed independently with 3+3 dose escalation being triggered by pre-specified safety events.

Results: 14 patients (7 MM and 7 NHL), have been treated at 7 dose levels: .05, .075, .15, .27, .43, .65 and .91 mg/kg. 4 females and 10 males have been treated to date. Median age is 67 (r 21-82). Median ECOG performance - 1 (r 0-2). Median number of prior systemic therapies is 5 (range 2-12). Based on a related, grade 2 non-hematologic adverse event (fever, chills, vomiting), the 3+3 dose escalation design was triggered at the 0.91 mg/kg dose level in the NHL cohort. Median number of STRO-001 doses administered is 4 (r 1-12). 11 patients have completed at least one cycle (two doses) of STRO-001 and are evaluable for safety and for dose escalation recommendation. The most common grade 1-2 TRAEs are fatigue, nausea, chills and infusion reaction occurring in 2 out of 11 patients. One patient with localized recurrence of DLBCL achieved a complete response (CR) after 2 cycles and progressed with new sites of disease after 12 doses (6 cycles). 3 patients remain on treatment and dose escalation is ongoing. Preliminary PK analysis showed maximum serum concentrations of ADC (0.39-8.2 μg/mL) and total antibody (0.41-9.1 μg/mL) increased after single IV doses of STRO-001 (0.05-0.65 mg/kg). The terminal phase half-life estimated for total antibody in 3 patients ranged 37-47 hours. There is no evidence of anti-STRO-001 antibodies.

Conclusions: STRO-001 is the first ADC generated with novel cell-free protein synthesis technology and site-specific conjugation to be tested in the clinic. STRO-001 has been well-tolerated, and the absence of immunogenicity is encouraging. No ocular toxicity or DLTs have been observed and MTD has not been reached. Preliminary anti-tumor activity (CR) has been observed in a patient with recurrent DLBCL. The study continues to enroll patients in dose escalation. with single patient MM cohorts and 3+3 NHL cohorts. This study is registered with clinicaltrials.gov identifier NCT03424603.

Keywords: B-cell lymphoma; multiple myeloma (MM); non-Hodgkin lymphoma (NHL).

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LONG-TERM OUTCOME OF PATIENTS WITH RELAPSED/REFRACTORY B-CELL NON- HODGKIN LYMPHOMA TREATED WITH BISPECIFIC ANTIBODY BLINATUMOMAB IN A PHASE I TRIAL

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Introduction: Treatment of relapsed/refractory (rr) Non-Hodgkin´s lymphoma of B-cell type (B-NHL) is still challenging and new and more effective therapies are urgently warranted. Blinatumomab, a first-in-class bispecific T-cell engager (BiTE®) antibody construct, engages CD3+ cytotoxic T cells, resulting in T-cell expansion and lysis of CD19 + B cells. In a prior phase I study, blinatumomab treatment resulted in an overall response rate (ORR) of 69% and 55% in diffuse large B-cell lymphoma (DLBCL), respectively for patients treated at MTD 60 μg/m²/d. The clinically most relevant side effects are neurological symptoms and cytokine release syndrome. Based on this study we here present first single-center, long-term follow-up data on 38 patients with r/r B-NHL after treatment with blinatumomab.

Methods: Patients with rr B-NHL who participated in the phase I MT103-104 trial (NCT00274742) and were treated with blinatumomab at the trial site Wuerzburg were eligible for long-term follow-up analysis. Kaplan-Meier estimates for progression free survival (PFS) probability were calculated from first infusion to relapse or death. Patients without an event were censored at last follow-up. This study was conducted in accordance with the Declaration of Helsinki.

Results: Median OS after for all 38 patients was 4.2 years, median OS of patients treated at target dose of 60 μg/m²/day was 5.4 years, whereas patients, who did not receive the target dose, achieved a median OS of 1.0 year. Median PFS in the responders' group was 3.2 years (95% CI: 0.0-6.7 years), in the non-responders´ group 32.1 days (95% CI: 23.0-41.0 days). Patients at target dose had a median PFS of 1.5 years (95% CI: 7.2 months-2.3years), in contrast to
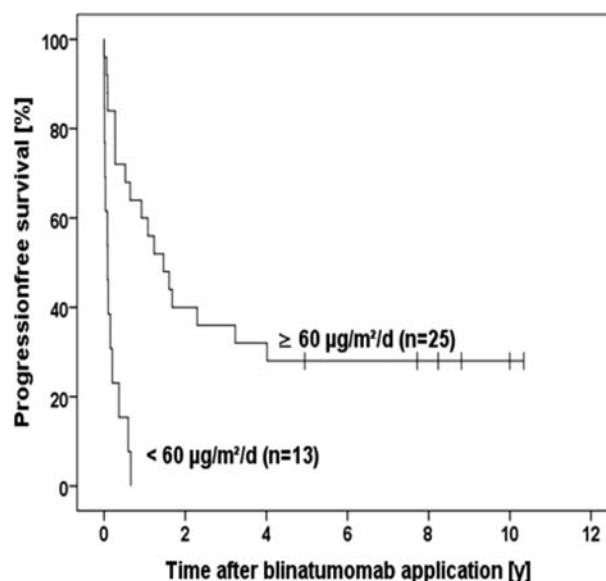
patients treated below target dose who had a PFS of 1.1 months (95% CI: 5.0 days-1.9 months; Fig. 1). At a median follow up of 4.15 years 6 patients treated at target dose were still alive and treatment-free, whereas the 13 patients treated at lower dose levels have progressed.

Conclusion: Here we provide first evidence that blinatumomab has the potential to induce sustained long-term remissions in patients with rr B-NHL. Prerequisite for durable remission is treatment at the effective dose of 60 μg/m²/day. Treatment with Blinatumomab in rr B-NHL is efficient.

Keywords: B-cell lymphoma; CD19; CD3.

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A FIRST-IN-HUMAN TRIAL OF THE NOVEL MULTI-ACTION THERAPY TINOSTAMUSTINE (EDO-S101) IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) HODGKIN LYMPHOMA (HL)

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Introduction: Although 70–80% of patients with advanced HL are cured by first-line therapy, the management of primary refractory disease and post-transplant recurrence remains an area of high unmet medical need, even in the era of brentuximab vedotin (BV) and immune checkpoint inhibitors (CPI). The alkylating histone deacetylase inhibitor tinostamustine is a novel multi-action therapy that improves drug access to DNA strands, breaks them and counteracts damage repair. Preclinical data have shown antitumour efficacy of tinostamustine in HL cells, including some alkylator-resistant cell lines.

Methods: Here we report findings from the dose-escalation stage of a Phase I first-in-human study to evaluate the safety and pharmacokinetics, and to determine the maximum tolerated dose (MTD), optimal infusion time and recommended Phase II dose (RP2D) of tinostamustine in patients with R/R haematological malignancies, including HL (NCT02576496). A standard 3+3 design was used; the first cohort receiving 40mg/m² iv tinostamustine over 1 hour. Four ascending cohorts to a maximum dose of 120mg/m², and shorter infusion times were also explored. Dose-limiting toxicities (DLT) were defined as: any Grade (G) 3 or 4 non-haematological toxicity; nausea,

vomiting or diarrhoea ≥10 days; G4 neutropenia or thrombocytopenia ≥7 days; any ≥G2 toxicity for >3 weeks; and any toxicity resulting in a delay of the next dose administration (Cycle 2 Day 1 ≥14).

Results: Ten heavily pre-treated (3–7 previous lines) HL patients were enrolled and received 40–120mg/m² tinostamustine over 60 minutes. The MTD was determined to be 100mg/m², and recommended infusion time confirmed as 60 minutes. The principal G3/4 toxicities observed were haematological, including thrombocytopenia, neutropenia, and lymphopenia with incidence increasing with increasing dose. Efficacy signals were observed, with only 2/10 patients experiencing disease progression (PD); 1 complete (CR) and 5 partial responses (PR) were recorded plus 2 patients with stable disease. Notably, a patient with primary refractory disease who had never achieved a response despite previous chemoradiotherapy, BV and CPIs, and had never been auto-transplanted due to PD, obtained a CR of 8 months. This patient was consolidated by haplo-transplant, is GvHD-free >20 months after last tinostamustine and remains in CR as of March 2019.

Conclusions: Administration of tinostamustine on Day 1 in a 21-day cycle was well tolerated with signals of efficacy in patients with HL. The RP2D for tinostamustine in HL, depending on patient platelet count at treatment initiation, was determined as 80mg/m² for those with >100 x 10⁹/l platelets, and 100mg/m² for those with ≥200 x 10⁹/l platelets. This will be applied in the second phase of this study, where patients will be recruited into one of five different cohorts, including HL.

Funding: Mundipharma EDO GmbH

Keywords: Hodgkin lymphoma (HL).

Disclosures: Zinzani, P: Consultant Advisory Role: *Verastem, MSD, Eusapharma, Sanofi*; Honoraria: *Verastem, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, MSD, Immune Design, Celgene, Portola, Roche, Eusapharma, Kyowa Kirin*. **Hilgier, K:** Consultant Advisory Role: *Mundipharma EDO*. **Remmy, D:** Employment Leadership Position: *Mundipharma EDO*. **Mehrling, T:** Employment Leadership Position: *Mundipharma EDO*.

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PHASE 2 STUDY OF PARSACLISIB (INCB050465) FOR RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) (CITADEL-202)

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Introduction: Parsaclisib, a potent, highly selective, next-generation PI3Kδ inhibitor, showed preliminary efficacy as monotherapy for relapsed or refractory non-Hodgkin lymphoma, including DLBCL (Abstract 410, ASH 2017), in a phase 1/2 study. This phase 2 study further assessed parsaclisib in patients with relapsed or refractory DLBCL (NCT02998476).

Methods: Patients enrolled into 2 groups (A, Bruton tyrosine kinase [BTK] inhibitor naïve; B, BTK inhibitor experienced) and received oral parsaclisib 20 mg once daily (QD) for 8 weeks, then 20 mg once weekly (QW). In a planned interim futility analysis conducted in the first 40 patients treated in Group A, if ≤13 (≤32.5%) responded by an independent review committee assessment, Group A was to be terminated.

Results: At data cutoff (22 Jun 2018), 60 patients (Group A, n = 55; Group B, n = 5) were treated (median age, 71 years [range, 36–94]; men, 63.3%; ≥3 prior systemic therapies, 60%).

At the planned interim analysis in Group A, the objective response rate (ORR; by positron emission tomography) was 25% (10/40 patients; 5 complete metabolic response [CMR], 5 partial metabolic response [PMR]); the futility boundary was crossed. At data cutoff, ORR in Group A was 25.5% (14/55 patients; 8 CMR, 6 PMR); median progression-free survival was 2.2 mo (95% CI: 2.0–4.1); median duration of response was 4.5 mo (95% CI: 2.1–5.1). Objective responses were observed in germinal center B-cell (GCB) and non-GCB subtypes. ORR in Group B was 20% (1/5 patients; 1 CMR).

The most common non-hematologic treatment-emergent adverse events (TEAEs) occurring in >10% of all patients (all grade [Gr]; Gr 3/4) were rash events (21.7%; 1.7%), colitis/diarrhea events (16.7%; 5.0%), nausea (16.7%; 0%), cough (15%; 0%), and pyrexia (15%; 8.3%). Gr 3/4 aspartate aminotransferase and alanine aminotransferase elevations occurred in 5.0% and 1.7% of patients, respectively; Gr 3/4 neutropenia and anemia occurred in 5.0% of patients each. The most frequent (>5%) serious TEAEs were pyrexia (8.3%), general physical health deterioration (6.7%), and hypercalcemia (6.7%). TEAEs led to therapy discontinuation in 7 patients (2 treatment-related), dose interruption in 20 patients (10 treatment-related), and dose reduction in 3 patients (all treatment-related). Median duration of therapy was 57.5 days (range, 11–318).

Conclusion: Parsaclisib monotherapy using a QD followed by QW dosing regimen was well tolerated with no new safety signals reported. Further evaluation of parsaclisib in all subtypes of DLBCL is ongoing in a combination study (NCT03424122).

Keywords: diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL); PI3K/AKT/mTOR.

Disclosures: Belada, D: Research Funding: *Celgene.* **Fay, K:** Research Funding: *Incyte.* **Casasnovas, R:** Consultant Advisory Role: *Roche, Takeda, Gilead, AbbVie, Bristol-Myers Squibb, Merck, Karyopharm*; Research Funding: *Roche, Gilead, and Takeda.* **Lee, H:** Consultant Advisory Role: *MSD and Janssen.* **Mehta, A:** Consultant Advisory Role: *Spectrum, Celgene, Kite, BMS*; Research Funding: *Incyte, Roche, Merck, BMS, Epizyme, Seattle Genetics*; Other Remuneration: *Gilead, Astra Zeneca, Kite, Spectrum, Kyowa Kirin.* **Munoz, J:** Consultant Advisory Role: *Pharmacyclics/Janssen, Bayer, Gilead/Kite, Pfizer, Juno/Celgene, and Bristol-Myers Squib*; Other Remuneration: *Gilead/Kite, Bayer, Pharmacyclics/Janssen, and AstraZeneca.* **Corrado, C:** Employment Leadership Position: *Incyte Corporation*; Stock Ownership: *Incyte Corporation.* **DeMarini, D:** Employment Leadership Position: *Incyte Corporation*; Stock Ownership: *Incyte Corporation.* **Zhao, W:** Employment Leadership Position: *Incyte Corporation*; Stock Ownership: *Incyte Corporation.* **Chen, X:** Employment Leadership Position: *Incyte Corporation*; Stock Ownership: *Incyte Corporation.* **Coleman, M:** Consultant Advisory Role: *Gilead, Bayer, Celgene*; Stock Ownership: *Kite Pharmaceuticals*; Research Funding: *Incyte, Gilead, Merck, Bayer, Celgene*; Other Remuneration: *Gilead, Bayer, Celgene, Pharmacyclics.*

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ACALABRUTINIB PLUS PEMBROLIZUMAB IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: A PHASE 1/2 STUDY

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TABLE 1

	All (N=61)
Overall response rate, n (%) [95% CI]	16 (26) [19, 39]
Best response, n (%)	
Complete response	4 (7)
Partial response	12 (20)
Stable disease	18 (30)
Progressive disease	22 (36)
Other[a]	5 (8)
Duration of response, median (95% CI), mo	6.9 (2.3, not estimable)
Progression-free survival, median (95% CI), mo	1.9 (1.6, 3.7)

[a]Due to death (progressive disease, abdominal abscess [n=1 each]), clinical progressive disease (n=1), and withdrawal due to adverse events (thrombocytopenia, altered mental status [n=1 each]).

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Background: Acalabrutinib, a highly selective, potent, covalent Bruton tyrosine kinase inhibitor, has a 24% overall response rate as a single agent in relapsed/refractory diffuse large B-cell lymphomas (DLBCL). Pembrolizumab targets PD-1, an immune checkpoint that limits anti-cancer responses. Pembrolizumab showed responses in patients with Richter transformation who failed ibrutinib and can augment acalabrutinib activity in vitro. This study assessed acalabrutinib plus pembrolizumab in relapsed/refractory DLBCL.

Methods: Patients with DLBCL, ≥1 prior chemoimmunotherapy and no prior allogeneic transplant received oral acalabrutinib 100 mg twice daily until progressive disease plus pembrolizumab 200 mg/kg intravenously every 3 weeks for up to 2 years. Germinal center B-cell (GCB) vs non-GCB subtype was assessed by immunohistochemistry. Primary endpoint was safety.

Results: Sixty-one patients (30 GCB; 31 non-GCB) were accrued, with a median age of 67 years (range, 30 to 85) and a median of 3 (range, 1 to 8) prior therapies; 1 patient had prior autologous transplant. The most common grade 3/4 adverse events were neutropenia (15%) and anemia (11%). Grade 5 adverse events were respiratory failure (n = 3), sepsis, septic shock, and abdominal abscess (n = 1 each). All-grade atrial fibrillation was 5% (n = 3), and major hemorrhage (≥ Grade 3) was 11% (4 gastrointestinal, 1 pulmonary, 1 epistaxis, 1 hematuria). Grade 3/4 immune-mediated events were elevated alanine amino-transferase (n = 4), pneumonitis (n = 2), and colitis (n = 1). The overall response rate was 26% (**Table**) and was similar in GCB (27%) and non-GCB (26%) tumors. The median time on study was 5.2 months (0.4 to 30.4+). Acalabrutinib/pembrolizumab discontinuations were due to progressive disease (62%/56%) and adverse events (15%/26%). As of June 2018, 10 patients remain on study; 6 on active therapy and 7 without progressive disease.

Conclusions: Acalabrutinib plus pembrolizumab was well tolerated, with meaningful activity and some exceptional responders (>24 months) in these relapsed/refractory DLBCL patients. Randomized trials of the combination vs single agent are needed.

Keywords: acalabrutinib; diffuse large B-cell lymphoma (DLBCL); Pembrolizumab.

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ANTITUMOR ACTIVITY OF PEMBROLIZUMAB PLUS DINACICLIB IN PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA: THE PHASE 1B KEYNOTE-155 STUDY

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Introduction: KEYNOTE-155 (NCT02684617) evaluated the anti-tumor activity of pembrolizumab (pembro) plus dinaciclib in patients (pts) with relapsed/refractory (rr) CLL, MM, and DLBCL. Here we present data from an interim analysis of safety and efficacy in pts with rrDLBCL.

Methods: In this phase 1b, two-part, non-randomized, open-label study, pts with rrDLBCL who received ≥2 prior therapies were enrolled into a dose-evaluation phase (two 21-day [d] cycles of pembro 200 mg [d1] and dinaciclib 7 mg/m^2 [d1], 10 mg/m^2 [d8] in cycle 1 and 14 mg/m^2 [d1, d8] from cycle 2 onwards). The DLBCL expansion cohort was opened for the signal-detection phase (≥30 patients) if ≤4 pts had dose-limiting toxicities (DLTs) during dose-evaluation. Treatment continued up to 35 cycles or until progression (PD) or unacceptable toxicity. Response was assessed every 3 cycles for DLBCL (Revised Response Criteria for Malignant Lymphoma 2007). Pts who discontinued before PD were followed Q12W until PD, new anticancer treatment, or death. The primary endpoint was safety and tolerability. Secondary endpoints included ORR by investigator, DOR, PFS, and OS. Efficacy and safety were assessed in all pts who received ≥1 dose of pembrolizumab or dinaciclib.

Results: As of Apr 25, 2018, 38 pts with rrDLBCL were enrolled and treated. Median age was 64.5 years (range, 39-85), 22 (58%) pts had ECOG PS 1, and 22 (58%) had ≥3 prior therapies. After median follow-up of 2.79 mo (range, 1.5-6.8), 36 (95%) pts discontinued treatment: 21 (55%) PD, 12 (32%) by physician decision (10 [26%] clinical progression, 1[3%] logistics, 1 [3%] new therapy), 2 (5%) pt decision, and 1 (3%) AE. Median time on treatment was 51d (range, 1-471). Among 12 pts in all disease cohorts enrolled in the dose-evaluation phase, DLTs occurred in 1 of 6 (17%) evaluable pts (grade 4 thrombocytopenia) with rrDLBCL. Of 38 pts with rrDLBCL, 24 (63%) had a treatment-related AE. Common treatment-related AEs were decreased platelets (21%), lymphopenia (16%), nausea (13%), anemia (13%), diarrhea (13%), and pyrexia (13%). 12 (32%) pts had a grade 3-4 treatment-related AE. Common grade 3-4 treatment-related AEs were lymphopenia (13%), decreased neutrophils (11%), decreased platelets (8%), leukopenia (8%), and laboratory TLS (5%). There was no clinical TLS and no treatment-related deaths. ORR was 18% (95% CI, 8-34) (3 CR and 4 PR) and median DOR was 4.9 mo (range, 2.1-13.8); 2 pts were on treatment at data cutoff. With 36 (95%) events, median PFS was 2.1 mo (95% CI, 2-3) with 6-mo and 12-mo PFS of 13% and 8%, respectively. 19 (50%) pts died, with median OS of 9.8 mo (95% CI, 3 to not reached), and 12-mo OS of 43%.

Conclusion: Despite limited overall response, the observed CRs and durability (up to 13 mo) provide proof of concept for activity of this combination in rrDLBCL and rationale for further studies to define optimal dosing of dinaciclib, given the brevity of CDK9 inhibition observed in preclinical models.

Keywords: diffuse large B-cell lymphoma (DLBCL); PD-1L; Pembrolizumab.

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SAFETY AND EFFICACY OF VENETOCLAX COMBINED WITH RITUXIMAB, IFOSFAMIDE, CARBOPLATIN AND ETOPOSIDE (VICER) FOR TREATMENT OF RELAPSED DLBCL: FINAL RESULTS FROM THE PHASE 1 TRIAL

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Introduction: Diffuse large B cell lymphoma (DLBCL) patients (pts) with refractory or relapsed (r/r) disease after front line chemo-immunotherapy have poor survival. Overall response rates (ORR) to second line, platinum – containing regimens is approximately 50%, and complete response (CR) rates are 30 – 40%. Only 40% of patients proceed to an autologous stem cell transplant (ASCT). We conducted a phase I trial evaluating the combination of venetoclax (VEN) with RICE (rituximab, ifosfamide, carboplatin and etoposide) (VICER). We have reported the adverse event profile of this combination, with common but manageable hematologic toxicity and rare laboratory tumor lysis. The recommended phase 2 dose of VEN is 800mg/d. We present the final results of this phase I trial and outcomes of patients proceeding to ASCT.

Methods: Patients (≥18 years of age) with r/r DLBCL who failed one or two lines of therapy were enrolled. VEN was given orally on days 1 – 10 of each 21 – day cycle x 3 cycles. Dose escalation was conducted according to a 3+3 design, with 3 dose levels (400, 600 and 800mg). RICE was given at standard dose and schedule on days 1 –

TABLE 1 Baseline characteristics

Patient Characteristic	
Gender, n (%)	
Female	4 (22)
Male	14 (78)
Age, years, median (range)	55.5 (27 – 78)
Disease refractory to prior chemotherapy, n (%)	6 (46)
Bulky disease at enrollment	6 (33)
Involvement of > 1 extranodal site	2 (15)
Secondary IPI	
Low (0 – 1)	12 (67)
High (≥ 2)	6 (33)
Cell of origin, n (%)	
GCB	10 (42)
Non – GCB	8 (58)
Molecular abnormalities, n (%)	
Double hit lymphoma	4 (22)
Double expressor lymphoma*	4 (22)

Abbreviations: GCB, germinal center B cell; IPI, International Prognostic Index.
*Does not include double hit subjects (all had positive IHC for MYC and BCL2)

3. All pts received tumor lysis prevention during cycle 1 and pegfilgrastim after every cycle.

Results: 18 pts enrolled and completed follow up (table 1). All pts received rituximab and anthracycline containing first line therapy, 4 patients had failed a second line of therapy and 6 had refractory disease (table 1). Fourteen pts (78%) achieved CR and 2 (11%) achieved a partial response (ORR = 89%). Two pts did not respond.

Successful stem cell collection was done in 14/16 responding pts. The median CD34 cell dose collected was 3.71 CD34+ cells/kg. Both pts with mobilization failure were older than 70 years and declined a second collection. All 14 subjects undergoing ASCT had hematopoietic engraftment. After a median follow up of 12 months, 5 pts have relapsed, including one subject who did not undergo ASCT. 1 – year PFS for intention to treat (ITT) cohort is 55%. 4 patients have died, including 2 pts without response to VICER and 2 patients relapsed after ASCT. One – year OS for the ITT cohort is 71%. Among patients undergoing ASCT, 1 – year PFS and OS were 62% and 77%, respectively.

Conclusions: This phase I trial of VICER has shown the combination is safe and active in r/r DLBCL, including high risk pts, achieving CR in 78%, with a high transplant rate (78%). The observed PFS and OS appear superior to those of comparable pts treated with R-ICE alone and those reported with other second line regimens. A phase II study of VICER will open to enrollment in mid-2019.

Keywords: diffuse large B-cell lymphoma (DLBCL); venetoclax.

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FEASIBILITY AND BENEFIT OF MOLECULARLY-INFORMED ENROLLMENT INTO EARLY PHASE CLINICAL TRIALS FOR PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Patients with relapsed or refractory diffuse large B cell lymphoma (r/r DLBCL) often do poorly with conventional salvage chemotherapy regimens. Next-generation sequencing (NGS) panels can identify recurrent molecular abnormalities, which can help to orient patient's treatement (pts) for potential molecularly oriented therapies or appropriated clinical trials with investigational targeted therapies. We aimed to evaluate whether orientating pts with r/r DLBCL through tumor genotyping is associated with a better outcome.

Methods: From 2013 to 2018, all pts with r/r DLBCL having molecular tumor portrait before enrollment in early clinical trials (eaCTs) for r/r DLBCL were analyzed for clinical and histomolecular characteristics, tumor response, progression-free survival (PFS) duration of response and overall survival. The main objective was to evaluate the feasibility and potential benefit of using tumor genotyping for orientating enrollment in eaCTs. Molecular Screening methods included immunohistochemistry and next-generation sequencing. All pts gave their written consent for the study.

Results: Sixty-two pts with r/r DLBCL had tumor molecular portraits. At the time of tumor molecular portrait, the median age was 69 years (range 26-77), median of previous line of therapies was 2 (range 1-9) and 14 pts (23%) had prior auto stem-cell transplant. Fifteen out of the 62 pts (24%) were molecularly oriented (MO) in eaCTs. Identification of potentially actionable targets was found in 30/62 (48%) of pts, of whom 15/30 (50%) received a molecularly-informed therapy. Beyond molecular portrait, fifty pts were enrolled in eaCTs (15 pts were MO and 35 were non-MO oriented) and 12 pts were not enrolled in eaCTs. The MO-oriented group of pts included the following therapeutic targets: *CD79A/B* or *MYD88* (n = 10 pts), *EZH2* or *ARIDI1A* (n = 3 pts), *MYC* (n = 1 pt) and *BRAF* (n = 1 pt). The overall responses rate was 60% (6 PR and 3 CR) in MO group *versus* 20% (5 PR and 2 CR) in non-MO group (p = 0.01). The median of PFS in MO and non-MO groups were 2.2 months and 1.9 months, respectively (p = 0.23; HR = 0.69 [CI95:0.38-1.26]). The median duration of response in MO and non-MO groups were 10.9 and 9.3 months, respectively (p = 0.78; HR = 0.76 [CI95: 0.26-2.18]. The mean PF2/PF1 ratio in MO and non-MO groups were 2.34 [CI95: 0.27-4.41] and 1.67 [CI:0.53-2.81], respectively (p = 0.093; HR = 0.61 [CI95: 0.33-1.14]. The median overall survival in MO and non-MO groups were 8.9 and 7.7 months, respectively (p = 0.34; HR = 0.69 [CI95: 0.33-1.47]).

Conclusions: Molecularly oriented treatments of recurrent diffuse large B-cell lymphoma were associated with higher responses rates. A subset of patients with recurrent or refractory diffuse large B-cell lymphoma may benefit from incorporation of tumor genotyping to guide their enrollment in clinical trials. Accelerating the use of prospective genomics tumor molecular portraits may increase the chances for a precision medicine for recurrent diffuse large B-cell lymphoma.

Keywords: epigenetics; EZH2; high-grade B-cell lymphoma with or without rearrangement of MYC and BCL2 and/or BCL6.

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SAFETY AND EARLY DATA FROM A PHASE II TRIAL OF PEMBROLIZUMAB (PEM) AND ENTINOSTAT (ENT) IN RELAPSED AND REFRACTORY (R/R) HODGKIN LYMPHOMA (HL) AND FOLLICULAR LYMPHOMA (FL)

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Introduction: Histone deacetylase (HDAC) inhibitors have single agent activity in HL and FL, and may enhance antigen-specific immune recognition in cancer in addition to modulating programmed cell death (PD)-1 expression. In preclinical studies, the combination of HDAC inhibitors and anti-PD-1 antibodies acts synergistically against various tumor models in mice. Accordingly, we investigated the safety and efficacy of the novel combination of the HDAC inhibitor ENT and the PD-1-blocking antibody PEM in patients with R/R FL or HL.

Methods: Patients with R/R HL or FL were eligible for this trial. Prior use of anti-PD-1 or HDAC inhibitor was allowed if there had been clinical benefit and this was not the most recent therapy. Patients received ENT 5-7 mg orally once weekly and PEM 200 mg intravenously once every three weeks. Tumor assessment was evaluated using the RECIL criteria. The primary objective is overall response rate (ORR) and 12-month progression-free survival (PFS).

Results: At data cutoff on 2/7/19, 12 patients (5 HL, 7 FL) have been enrolled. Median age was 60 (26-81). Median number of prior therapies was 3 (2-11) and 3 (2-4) in HL and FL, respectively.

With median duration of follow-up of 145 (33-288) days, 4 patients are currently receiving treatment on study, 3 patients have discontinued treatment due to toxicity, 3 due to disease progression, and 2 to proceed to consolidation with transplant or radiation. Out of
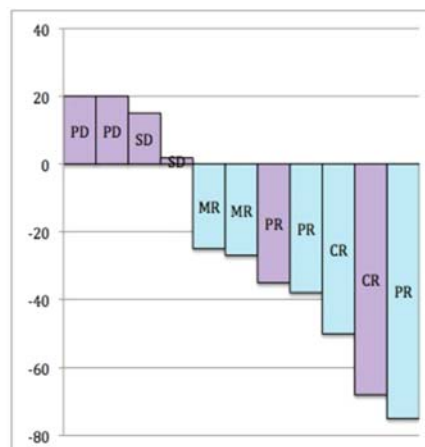
Waterfall plot depicting best responses (% change) in 11 evaluable patients by RECIL criteria. Tumor size assessment was not available for the two patients with PD. The patient with the greatest tumor reduction in size did not have complete resolution of metabolic activity and thus was classified as a PR.
PD – Progressive disease, SD – Stable disease, MR – Minor response, PR – Partial response, CR – Complete response, **Purple bars**– FL, **Blue bars** – HL

11 evaluable patients, there was a 64% ORR across both disease types (100% and 33% ORR in the HL and FL groups, respectively). There was one complete response (CR) in each group, including one patient with FL who had relapsed after CAR T cell therapy. A patient with HL who had previously received both PEM and ENT as monotherapy achieved a partial response (PR). Median duration of response in both groups was 172 (69-209) days.

All patients experienced at least one adverse event (AE). 8/12 (67%) had grade 3 or higher adverse events (AE), which were mainly hematologic compared to non-hematologic (58% vs 8%), including neutropenia (50%), thrombocytopenia (25%), and anemia (17%). Two patients who experienced serious adverse events (SAEs) due to pericarditis and the hemophagocytic lymphohistiocytosis (HLH) syndrome and one patient with grade 3 bullous dermatitis were taken off study. ENT was dose-reduced in 5 patients and was held temporarily without dose-reduction in 4 patients. The median duration on treatment was 112 (27-288) days.

Results from previously performed targeted next-generation sequencing of lymph node biopsies were available for 8 patients. All (100%) had at least one mutation in epigenetic-modulating genes and 5/8 (63%) had at least one mutation in histone acetyltransferase-encoding genes. There was no association between mutation status and response rate.

Conclusions: Early results from this ongoing phase II clinical trial suggest that the combination of PEM and ENT is safe with encouraging responses in the study population, especially in those with HL.

Keywords: epigenetics; Hodgkin lymphoma (HL); PD-1.

Disclosures: Younes, A: Honoraria: *Merck.*

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SAFETY AND EFFICACY OF ATEZOLIZUMAB, OBINUTUZUMAB AND VENETOCLAX COMBINATION FOR RELAPSED/REFRACTORY NON-HODGKIN LYMPHOMAS: RESULTS FROM THE SAFETY-RUN OF A LYSA STUDY

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Introduction: Despite major advances introduced by immunochemotherapy, relapse and refractory B-lymphomas (R/R NHLs) treatment remains challenging. Atezolizumab and obinutuzumab are monoclonal antibodies acting respectively to inhibit T-lymphocyte exhaustion or by inducing lymphoma cells cytotoxicity, whereas venetoclax is a small molecule inhibiting BCL-2. Combining tumor-targeted therapies with agents that enhance anti-tumor immunity represents an attractive treatment paradigm. The LYSA conducts a multicenter phase II trial (NCT03276468) evaluating the efficacy and safety of the chemotherapy-free combination of atezolizumab, obinutuzumab and venetoclax in R/R NHLs. We present safety and early response data of the patients included in the safety-run.

Methods: Patients ≥18 years with biopsy-confirmed R/R NHL (DLBCL or FL) who failed at least one line of therapy (rituximab and anthracycline containing regimen) were eligible. An initial safety-run was performed to assess this novel therapeutic combination. Obinutuzumab was given IV at the dose of 1000 g on day (D) 1, 8 and 15 of cycle (C) 1 and on D1 from C2 to C8 every 3 weeks. Atezolizumab was given IV, 1200 g every 3 weeks, started at D2 of C1, then administered at D2 of each cycle for 24 cycles. Venetoclax was given orally at 800 mg/D at full dose, started on D8C1 for 24 cycles. The primary endpoint of the safety-run was to evaluate the safety of this combination. Before entering in the main study, the safety-run had to include at least 12 patients treated at least 6 weeks (2 cycles).

Results: A total of 13 patients were enrolled in the safety-run between Feb and Apr 2018: 9 were DLBCL and 4 FL. Median age was 61.7 years [39-77]. With a median follow up of 4.4 months [3.5-5.1], and during the 4 first cycles of treatment, hematologic toxicity was the most common AE, with G≥3 neutropenia (7 [54%] pts) and G≥3 thrombocytopenia (4 [31%] pts). No patient experienced febrile neutropenia. The most common non-hematologic all-grade AE were infections (6 [46%] pts), back pain (3 [23%] pts), diarrhea (2 [15%] pts) and IRR (2 [15%] pts). All these non-hematologic AE were G1 or 2, except one G3 lung infection. No tumor lysis syndrome was observed. Four patients (3 DLBCL and 1 FL) have permanently discontinued study treatment, all of them due to progression. At intermediate analysis (after C4), 12 patients were evaluable for response: 3 (25%, 3 DLBCL) achieved complete metabolic response (CMR) and 5 (42%, 3 FL and 2 DLBCL) achieved partial metabolic response (PMR). The Overall Metabolic Response Rate (OMRR) was 67% (8 out of 12). A pseudo-progression was observed retrospectively in one FL patient. He was in tumoral metabolic progression at C4, and has showed a CMR at C8.

Conclusion: The atezolizumab, obinutuzumab and venetoclax combination appears to be well tolerated. The Data and Safety Monitoring Board decided to add primary prophylaxis of neutropenia. The OMRR of 67% is encouraging for a chemo-free regimen in R/R NHLs. Treatment and follow-up of these patients are currently ongoing and updated data will be presented at the congress.

Keywords: B-cell lymphoma; immune system; venetoclax.

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PHASE 1B STUDY OF ViPOR (VENETOCLAX, IBRUTINIB, PREDNISONE, OBINUTUZUMAB, LENALIDOMIDE) IN RELAPSED/REFRACTORY B-CELL LYMPHOMA: SAFETY, EFFICACY AND MOLECULAR ANALYSIS

Figure 1

A. Change in Tumor Burden
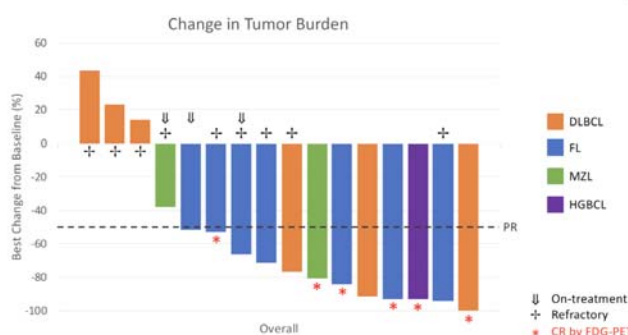
B. Response Characteristics
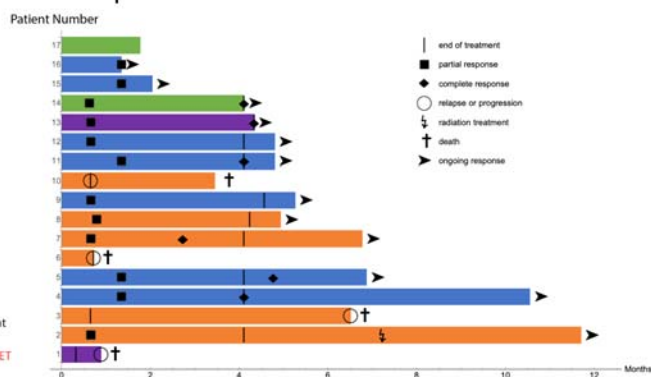
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M.D. Miljkovic[1] | C.A. Portell[3] | R.J. Farah[4] |
A.M. Juanitez[1] | L.L. Chou[1] | S.M. Steinberg[5] |
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Introduction: Aggressive B-cell lymphomas can be cured with chemo-immunotherapy; however, those who fail primary therapy and indolent lymphomas are rarely curable. Novel targeted therapies can disrupt key survival pathways in lymphoma such as BCL2 (venetoclax), BTK (ibrutinib), and NFκB (lenalidomide). These agents are active as monotherapy but do not induce deep responses and require continuous therapy. Also, genetically defined subtypes of lymphoma that best respond to these targeted therapies are undefined. We hypothesized that combining synergistic agents that target unique survival pathways will leverage efficacy and time-limited, cyclic dosing will limit toxicities.

Methods: Relapsed/refractory B-cell lymphoma pts, excluding MCL and CLL/SLL, with adequate organ function were eligible. A 3+3 design was used to determine the MTD of 4 DLs of venetoclax (200mg, 400mg, 600mg, 800mg) PO D2-14 (starts cycle 2 for DL1) in combination with fixed-dose ibrutinib 560mg PO D1-14, prednisone 100mg PO D1-7, obinutuzumab 1000mg IV D1-2, and lenalidomide (Revlimid®) 15mg PO D1-14. Aggressive and indolent expansion cohorts were included at the MTD. Max. 6 cycles of ViPOR q21 days was given unless PD or unacceptable AE. TLS prophylaxis was given to all pts and VTE prophylaxis and G-CSF use was per investigator discretion. Pre-treatment biopsies were obtained and analyzed for WES, RNA-sequencing, and CNAs. Baseline CT, PET and BM was performed with CT scans after cycles 1, 2, 4, and 6 and PET after cycle 6 or at time of suspected CR.

Results: 17 pts were enrolled in the dose-escalation cohort (DL1-8, DL2-3, DL3-3, DL4-3). Subtypes included FL (7), DLBCL (6), HGBCL (2), and MZL (2). Median (range) of prior therapies was 2 (1-6) and 10 (59%) pts were refractory to last therapy. A single DLT of G3 intracranial hemorrhage (ICH) occurred at DL1 with concomitant enoxaparin. The MTD was not identified and a dose of 800mg for venetoclax was used in expansion. G3/4 heme AEs (%pts/%cycles) included neutropenia (56%/27%), thrombocytopenia (25%/17%), and anemia (19%/4%). G3/4 non-heme AEs (%pts) included diarrhea (13%), edema, a.fib, ICH, and hypophosphatemia (6% each). SAEs (%pts) included fever (25%), thromboembolic event (13%), and ICH (6%). Of 14 pts off-therapy (10 completed, 1 PD, 3 AE), 13 are evaluable for response with an ORR of 77% (10/13) and 46% (6/13) CR. In 16 evaluable pts overall, 81% (13/16) had tumor reduction (Fig.1A). All responses are on-going with a median DOR of 4.8m (Fig.1B). One DLBCL pt with PR received XRT and 1 FL pt with PR had transformation and is proceeding to CAR-T.

Conclusions: ViPOR demonstrates rapid responses including CR in refractory lymphoma pts. No TLS or unexpected toxicities were observed and hematologic AEs, mainly neutropenia, were most common. Updated response durability and molecular correlates of response will be presented at the meeting.

Keywords: ibrutinib; lenalidomide; venetoclax.

Disclosures: Farah, R: Consultant Advisory Role: *Celgene advisory board*; Other Remuneration: *Celgene speaker bureau*.

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RESULTS FROM THE SAFETY RUN-IN PERIOD OF THE SYMPATICO STUDY EVALUATING IBRUTINIB IN COMBINATION WITH VENETOCLAX IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

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Introduction: Ibrutinib (ibr), a once-daily Bruton tyrosine kinase inhibitor, is indicated in the US and EU for treatment of relapsed/refractory (R/R) mantle cell lymphoma (MCL). Combining ibr with venetoclax (ven; B-cell lymphoma-2 inhibitor) has shown synergistic activity in preclinical and early phase clinical studies (Portell *Blood* 2014; Tam *NEJM* 2018). SYMPATICO (PCYC-1143; NCT03112174), an ongoing phase 3 study, is evaluating the efficacy and safety of concurrent ibr + ven (I+V) in patients (pts) with R/R MCL. A safety run-in (SRI) period is included per protocol to determine whether concurrent I+V is tolerable or if a 1-mo ibr lead-in is needed.

Methods: SYMPATICO has an open-label SRI and double-blind randomized period. In the SRI, pts received ibr 560 mg QD plus ven starting at 20, then 50, 100, 200, 400 mg QD in weekly dose ramp-up over 5 wks to a final dose of 400 mg QD. After SRI, pts were randomized 1:1 to I+V or ibr + placebo (pbo); ven or pbo is to be discontinued after 24 mo and ibr continued until progressive disease (PD) or unacceptable toxicity. Primary endpoints for SRI are frequency of tumor lysis syndrome (TLS) and dose-limiting toxicities (DLTs; grade [G] ≥3 non-TLS adverse events [AEs] possibly related to ibr and/or ven observed during the ≥5-wk DLT assessment period). Pts at high baseline TLS risk had ≥1 lesion >10 cm or ≥1 lesion >5 cm with circulating lymphocytes >25000 cells/mm^3 and/or creatinine clearance (CrCl) <60 mL/min. Pts not meeting high risk criteria were classified as low risk for TLS.

Results: 21 pts with R/R MCL were enrolled in SRI (low risk, n = 6; high risk, n = 15). Median age was 67 yrs (range, 53–84) and median prior therapies was 2 (range, 1–4); 8 pts had ≥1 lesion >10 cm, no pt had ≥1 lesion >5 cm with circulating lymphocytes >25000 cells/mm^3, and 9 pts had CrCl <60 mL/min at baseline. One high-risk pt with a Wk 1, D 1 WBC of 111.89 x 10^9/L had laboratory TLS for 5 d; no clinical TLS events occurred. In total, 3 pts had DLTs (high risk, n = 3; low risk, n = 0): G4 neutropenia, G4 infection; and G3 atrial fibrillation and G3 hypotension. Treatment-emergent AEs occurred in all pts, with G3/4 events in 12 pts (high risk, n = 10; low risk, n = 2). The most common AEs were diarrhea (n = 15; high risk, n = 10; low risk, n = 5) and fatigue (n = 11; high risk, n = 6; low risk, n = 5); 1 death occurred ≤30 d after last dose (12 d) due to retroperitoneal hemorrhage and was unrelated to ibr or ven in a low risk pt with PD and MCL in the spleen. Two deaths occurred in high risk pts >30 d after the last dose due to MCL.

Conclusions: In the SRI of SYMPATICO that evaluated concurrent I +V, 1 laboratory TLS event occurred in a pt at high risk for TLS. No clinical TLS events occurred. DLTs were infrequent and observed in 3/21 pts. Based on these data, concurrent I+V was recommended per protocol for pts at low and high risk for TLS. The ongoing phase 3 randomized period is evaluating the efficacy (primary endpoint: PFS) and safety of I+V vs ibr + pbo in pts with R/R MCL.

Keywords: ibrutinib; mantle cell lymphoma (MCL); venetoclax.

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PHASE I STUDY OF ROMIDEPSIN AND LIPOSOMAL DOXORUBICIN IN RELAPSED OR REFRACTORY T-CELL LYMPHOMA

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Introduction: Romidepsin and liposomal doxorubicin have single-agent activity in cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL). In pre-clinical studies using lymphoma cell lines, we demonstrated that romidepsin had strong synergistic effects in combination with doxorubicin. The aim of this study is to determine the safety and feasibility of the combination of romidepsin and liposomal doxorubicin in patients with relapsed/refractory CTCL and PTCL.

Patients and Methods: This is a phase I study that employed a standard "3+3" dose-escalation design with a dose-expansion cohort to evaluate safety, maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and clinical activity of romidepsin in combination with liposomal doxorubicin. Patients with relapsed/refractory 1) CTCL (stage IB-IVB MF or SS) after $\geq$ 1 prior systemic therapy or $\geq$ 2 prior skin-directed therapies, or 2) PTCL of any stage or subtype after $\geq$ 1 prior systemic therapy, are eligible. The primary endpoint is to identify the MTD of romidepsin in combination with liposomal doxorubicin. The secondary endpoints included overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). Patients were treated with liposomal doxorubicin 20 mg/m^2 on day 1 and romidepsin at four dose levels (8, 10, 12 and 14 mg/m^2) on days 1, 8 and 15, every 28 days, until 2 cycles beyond best response, 8 cycles, disease progression, or intolerability; whichever comes first. Response was determined by using the International Working Group and International Society for CTCL consensus criteria for PTCL and CTCL, respectively.

Results: Twenty-three patients (11 CTCL, 12 PTCL) were enrolled and received at least 1 dose of study drugs. Three DLTs occurred: grade 4 nonfebrile neutropenia lasting > 7 days in 1 PTCL patient, grade 3 thrombocytopenia lasting > 7 days in 2 PTCL patients. The MTD of romidepsin was determined to be 12 mg/m^2. There was a higher incidence of grade 3/4 treatment-related hematologic AEs in the PTCL vs. the CTCL cohort. The most frequent non-hematologic AEs were nausea (48%), fatigue (43%), vomiting (35%), and anorexia (30%).

Disease response was evaluable in 20 (10 CTCL, 10 PTCL) patients, with a ORR of 70% (1 CR, 6 PR, 2 SD, 1 PD) in the CTCL cohort and 20% (2 CR, 8 PD) in the PTCL cohort. The median reduction in mSWAT score was 81% in CTCL patients. After a median follow-up of 17.8 months, median PFS was 7.4 months for the CTCL cohort and 2 months for the PTCL cohort. Median OS was not reached for the CTCL cohort and 7.8 months for the PTCL cohort.

Conclusions: The combination of romidepsin and liposomal doxorubicin has an acceptable toxicity profile at an MTD of 12 mg/m^2 for romidepsin with mostly grade 1/2 fatigue and GI-related toxicities. The combination has promising activity in CTCL and merits further investigation.

Keywords: T-cell lymphoma (TCL).

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A PHASE 1B/2 STUDY OF ORAL NANATINOSTAT (N) AND VALGANCICLOVIR (VG) IN SUBJECTS WITH EPSTEIN-BARR VIRUS (EBV)-ASSOCIATED LYMPHOMAS

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Introduction: Nanatinostat (N; VRx-3996) is a Class I-selective oral hydroxamate histone deacetylase (HDAC) inhibitor active against HDAC1-3, but not HDAC6. N induces the expression of EBV thymidine kinase (BXLF1) and protein kinase (BGLF4) in EBV-positive lymphomas models. This study examines if N sensitizes tumors to antivirals (i.e., VG) and impacts EBV-induced T-cell exhaustion.

Methods: The study employs a 3+3 design with expansion in patients (pts) with relapsed/refractory EBV+ lymphomas. (determined by EBER-ISH). Objectives: Maximal Tolerated Dose (MTD), Recommended Phase 2 Dose (RP2D), and efficacy. Primary endpoint: safety. Secondary endpoints: PK, response rate. Exploratory endpoints: PBMC histone H3 acetylation (Ac), quantitative plasma EBV DNA (pEBVd), and immune biomarkers. Responses: investigator-assessed and centrally-reviewed by Lugano Classification.

Results: As of 07-Mar-2019, 18 pts (5F/13M, median age 60 yrs [19-79]) were enrolled with a median of 2.5 prior therapies and various lymphoma subtypes including anaplastic large cell (1), AITL (2), Gray Zone (1), DLBCL (6), Hodgkin's (2), lymphoplasmacytic (2), peripheral T-cell (4). Cohort 1 (C1: N 10 mg BID/VG 900 mg BID) exceeded MTD (DLTs: leukopenia, neutropenia and thrombocytopenia). PK demonstrated ~2-fold higher N exposure compared to a prior Phase I study. VG levels were consistent with published data. Doses were reduced in Cohort 2 (C2: N 5 mg BID/VG 450 mg BID) with no DLTs observed to date and 2 active pts. Most non-hematologic treatment-related AEs (TRAEs) were G1-2. G3+ TRAEs were largely hematologic (neutropenia, leukopenia, thrombocytopenia). Increases in creatinine occurred early and responded to reductions in VG. 7 pts are evaluable for response (2 CR (DLBCL[in C1], AITL[in C1]), 2 PR (peripheral T-cell[C2] and DLBCL[C2]), 2 SD (Hodgkin's[C1], DLBCL[C1]), and 1 PD (Gray Zone[C1]) with all 7 patients showing reduction in PET avidity (range 9.7 – 100% reduction compared to liver update) as demonstrated in the figure. 8 pts had detectable baseline pEBVd with 7 demonstrating a reduction (median -54% [17 to -83%]). PBMC H3Ac levels, multi-cytokine expression panel and functional assessments in CD8 T cells are in progress.

Conclusion: N+VG appears well-tolerated at 5 mg and 450 mg BID, respectively with hematologic DLTs in the initial higher dose cohort. Responses are observed at all dose levels, in both B and T-cell lymphomas, with reductions in pEBVd levels and preliminary evidence of changes in T cell functionality. A RP2D will be defined prior to dose expansion. NCT03397706.

Keywords: epigenetics; Epstein-Barr virus (EBV); histone deacetylase inhibitors.

Best Response by PET
(Normalized/corrected to liver SUV)

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IMPROVEMENT OF RITUXIMAB ADMINISTRATION BY PREMEDICATION WITH RUPATADINE, MONTELUKAST AND THEIR COMBINATION

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Background: Rituximab is associated with frequent infusion reactions, in particular during the first administration. They carry significant burden to both patients and health care providers. Standard pre-medications (SP) do not prevent reactions sufficiently. Montelukast (M) and Rupatadine (R) are used for symptomatic treatment of chronic urticarial and allergic rhinitis. Their impact on Rituximab infusion is unknown. We assessed whether addition of M, R and their combination (M+R) improves Rituximab delivery, infusion/rate and decreases rate, severity of reactions and cost of administration

Methods: Adult patients with lymphoproliferative disorders (LPD) treated at our cancer center between Jan 2018 to Jan 2019 with Rituximab-containing regiments were evaluated. Our study was limited to the initial Rituximab infusion. Patients received either SP with diphenhydramine/acetaminophen and additional M, R or M+R combination. Comparative analysis of infusion time/rate, severity of infusion reactions, number of rescue medications and cost of Rituximab infusions among groups was performed using one-way ANOVA with Tukey post-hoc or chi-square. The study was approved by our institutional REB

Results: Patients received either: 1) standard pre-medications (SP); 2) SP + Montelukast 10 mg, 12h and 30 min prior to infusion (M); 3 SP + Rupatadine (R) 10 mg; 12 h prior to infusion or 4) both (SP+M+R) given as the same schedule. Patient characteristics and therapy are shown in Table 1.

Compared to SP, the M, R and M+R groups had greater improvement in Rituximab delivery. Mean infusion time was 305 [range 235-441] min. in SP, 254 [105-390] in M, 265 [193-350] in R and 229 [196-342] in M+R groups, (p = 0.0001). Mean Rituximab delivery rate (mg/min) was 2.40 [1.78-3.23] (SP), 3.10 [2.12-6.67] (M), 2.85 [2.10-3.88] (R), and 3.12 [2.4-3.69] in M+R group. Infusion reactions occurred in 92% in SP vs. 38, 45, 31% in M, R and M+R groups (p = 0.0001). Median reaction grade was 2 in SP, 1 (M), 0 (R and M+R). Median number of rescue medications was 3 [0-10] in SP vs 0 [0-7]

TABLE 1 Patient characteristics and therapy received

	Standard Premedications	Montelukast	Rupatadine	Monteleukast + Rupatadine
Number of patients	26	21	20	26
Age: median [min, max]	67 [45-87]	73 [35-91]	65 [51-88]	72 [50-86]
Male (%)	46	71	75	81
Hx of allergy (%)	39	33	50	31
LPD: pts (%)				
Diffuse Large B-Cell Lymphoma	6 (23)	3 (14)	5 (20)	8 (31)
Follicular Lymphoma	9 (31)	2 (10)	5 (20)	5 (19)
Chronic Lymphocytic Leukemia	4 (16)	4 (19)	5 (20)	2 (8)
Other indolent Non-Hodgkin Lymphoma	7 (27)	12 (57)	5 (20)	11 (42)
Advance stage/bulky (%)	65	76	85	70
Tx naive	96	86	80	93
Chemotherapy regimen:				
RCHOP	8 (31)	5 (24)	6 (30)	10 (39)
BR	15 (58)	9 (43)	6 (30)	10 (39)
FCR	2 (8)	2 (10)	5 (25)	2 (8)
Other	1 (4)	5 (24)	3 (15)	4 (14)
Rituximab dose (mg): Mean [min-max]	727 [600-1000]	750 [550-1000]	740 [550-950]	762 [550-1000]

Abbreviations: LPD, lymphoproliferative disorders; DLBCL, Diffuse Large B-Cell Lymphoma; FL, Follicular Lymphoma; CLL, Chronic Lymphocytic Leukemia; iNHL, indolent Non-Hodgkin Lymphoma; RCHOP, Rituximab/Cyclophosphamide/ Doxorubicin/Oncovin/Prednisone; BR, Bendamustine/Rituximab; FCR, Fludarabine/Cyclophosphamide/Rituximab.

in M, R and M+R groups. Cost of rescue medications (US$) was 41 [0-63] in SP group, 11 [0-50] (M), 17 [0-63] (R), 7 [0-58] (M+R) groups (p < 0.0001). Mean nursing cost (US$) per patient infusion was calculated as 269 [207-388] in SP vs 222 [92-343] (M), 233 [170-308] (R), 202 [174-301] (M+R) group.

Summary/Conclusion: Addition of Montelukast, Rupatadine, and particularly Montelukast+Rupatadine combination significantly shortened Rituximab infusion time, decreased the rate and severity of infusion reactions, and lowered total cost of Rituximab administration

Keywords: B-cell lymphoma; chemotherapy; rituximab.

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BIOLOGY AND PATHOLOGY

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MULTI-OMICS APPROACHES TO UNDERSTAND GASTRIC MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) LYMPHOMA

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Gastric Mucosa-Associated Lymphoid Tissue (MALT) lymphoma is one of non-Hodgkin lymphoma that occurs in digestive tracts. The main risk factor for gastric MALT lymphoma is *Helicobacter pylori (Hp)* infection. Pathogenesis of *Hp* encompasses four steps: 1) entrance into host and tolerance against acidic environment; 2) motility and chemotaxis; 3) interaction between adhesion-receptors and colonization, and 4) release of toxins and damage to the host. Up until now, the pathogenic mechanism diverging from the bacterial infection to lymphomagenesis is largely unknown. We aim to characterize the carcinogenic mechanism of *Hp*-associated MALT lymphoma using multi-omics data analysis.

Gastric tissues of both tumor and adjacent normal were collected from gastric MALT lymphoma patients. Matched saliva samples from each donor were also collected. Whole exome sequencing (WES) data was generated using gastric lesion tissues and saliva samples whereas whole transcriptome sequencing (WTS) data was generated using gastric lesion and adjacent normal tissues. For WTS analysis (18 tumor and 5 normal samples), we aligned raw data, quantified the gene expression, and explored both significant genes and pathways using negative binomial GLM fitting and their function using GO ontologies. For WES analysis, we aligned raw data, performed variant calling, and detected a list of genes with somatic mutations (12 pairs).

Based on the comparison of expressed genes between tumor and normal samples from MALT lymphoma patients, biological pathways associated with diverse immune responses were converged when filtered using classical Fisher's test on the GO ontologies of markedly regulated genes. The immune-associated pathways include leukocyte/lymphocyte activation, immune response-regulating cell
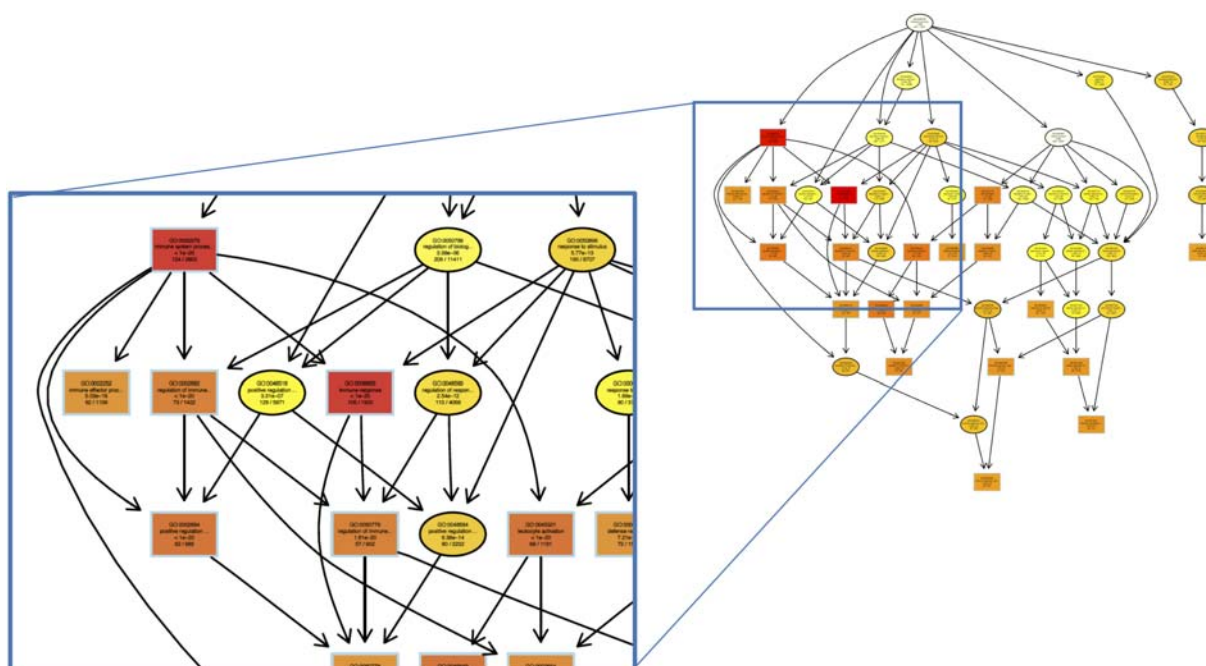
Figure 1. **Significant GO ontologies for enriched genes in rectangular boxes**

surface receptor signaling pathway, and regulation of immune system processes. In addition, both complement *C3* and adenosine deaminase (*ADA*) genes were upregulated in tumor gastric tissues. *IFI30* gene encoded by Gamma-interferon-inducible lysosomal thiol reductase (GILT) whose function is closely associated with bacterial activities was also upregulated in the tumor tissue. WES data revealed that two recurrent missense mutations (K169R and N175S) of *CDC27* were found in ~20% of MALT lymphoma patients.

Upregulated expression of complement *C3* gene in tumor tissues suggests that the defense mechanisms of innate immunity have been activated due to the bacterial infection. Upregulated *ADA* agrees on the findings from previous studies showing higher ADA activities in *Hp*-infected patients. Upregulation of *IFI30* in tumor tissues supports evidence of enhanced bacterial hemolysis and bacterial replication/infection activities. On top of that, repeatedly observed mutations in a cell cycle-associated gene, *CDC27*, may have a role to play in cell growth inhibition.

Keywords: Helicobacter pylori; immune system; Mucosa-Associated Lymphoid Tissue (MALT).

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THE ROLE OF DUSP22 (DUAL SPECIFICITY PHOSPHATASE 22) GENE EXPRESSION IN THE PROGNOSIS OF LOW GRADE LYMPHOMAS

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Introduction: Dual specificity phosphatase 22 (DUSP22) is a novel phosphatase and has been demonstrated to be a cancer suppressor gene associated with various biological and pathological processes. Prognostic role of DUP22 expression in cases with ALK (-) anaplastic large cell lymphoma has been demonstrated but little is known about DUSP22 expression and its prognostic value in other lymphomas. Here clinical/prognostic importance of DUSP22 expression has been determined in cases with indolent lymphomas including follicular lymphomas, marginal zone lymphomas and chronic lymphocytic leukemia. The aim of this study to evaluate the prognostic importance of DUSP22 expression in low grade lymphomas according to clinical and demographic variables.

Methods and patients: Fluorescence in situ hybridization (FISH) was performed 3 micron sections of formalin-fixed, paraffin-embedded tissue. IRF4/DUSP22 (Cytotest, USA) break-apart FISH probe kit was used for rearrangement detection. Slides were analyzed using standard fluorescence microscopy techniques. 100 cell nuclei without overlapping were counted on each slide. The cutoff value for IRF4/DUSP22 was accepted %15. Eighty four cases with indolent lymphoma were evaluated for DUSP22 expression. The signal could not be detceted in 8 cases and of the total 76 cases with indolent lymphoma were

Survival Functions
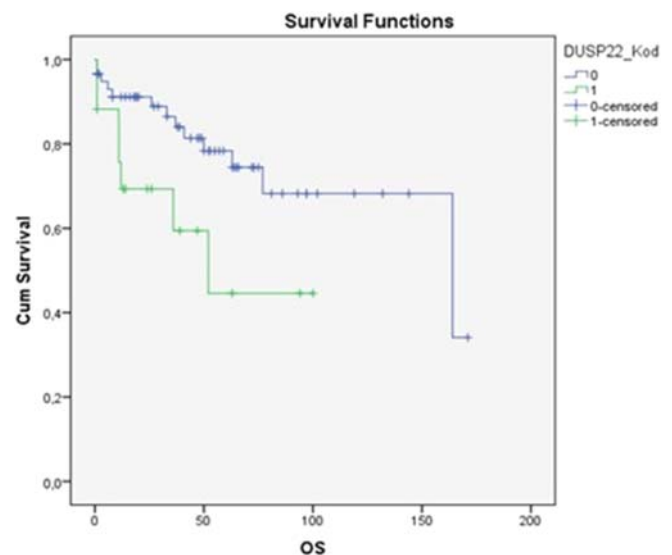
evaluated for DUSP22 expression. Female/male ratio was 31/45. Fifteen cases had stage I disease, 8 had stage II, 18 had stage III and 26 had stage IV disease. Thirty nine had follicular lymphoma (FL), 30 had marginal zone lymphoma (MZL) and 7 had chronic lymphocytic leukemia (CLL). Among FL, 5 had grade I, 10 cases had grade II, 24 had grade III disease: 13 had grade IIIA-11 had grade IIIB. Among MZL 4 had nodal and 26 had extranodal MZL. Complete response was achieved in 42 cases and partial response in 11 cases; 8 cases did not respond to treatment. During this analysis 43 cases was living without disease, 12 cases was living with disease and 21 cases died.

Results: DUSP22 expression was detected in 17 cases (22.3%). Expression was detected 4 of 31 women and 13 of 45 men. DUSP22 expression was detected 10 of 39 cases with FL, 6 of 30 cases with MZL and 1 of 7 cases with CLL. Among grade I cases. The mean OS was found to be longer in cases without DUSP22 compared to cases with DUSP22 expression (126 vs 58 months p:0.036) (Figure 1). However no significant differences were found between the cases with and without DUSP22 expression according to mean of event-free survival (EFS) (58 vs 82 months p:0.717). The OS was found to be longer in DUSP22 (-) females than males (157 vs 104 months p: 0.018). In univariate analysis, OS was found to be longer in cases with early stage disease (p:0.0001) and in females (p:0.009). Sex (OR:3.5, %95CI:1.0-12.1, p:0.046), stage (OR:8.0, %95CI:1.736.7, p:0.008) and DUSP22 expression (OR:3.4, %95CI:1.2-9.3, p:0.018) were found to be independent prognostic factors according to Cox regression analysis.

Conclusions: Little is known about the functional roles of DUPS22 and the underlying mechanisms. The silencing of DUSP22 in peripheral T cell lymphomas especially in ALK (-) anaplastic large cell lymphoma suggest that this gene is a candidate tumor suppressor gene and its inactivation may contribute to the pathogenesis of peripheral T cell lymphoma subtypes. Some studies showed that of the 20-30% of ALK(-) anaplastic large cell lymphomas have chromosomal rearrangements of DUSP22. DUSP22 rearranged cases with ALK (-) subtype have favorable outcomes similar to ALK (+) anaplastic large cell lymphoma. There is no sufficient data about the clinical and/or prognostic significance of DUSP22 rearrengement in other

lymphomas. We found poor outcome in cases with DUSP22 expression. How can we define this controversy? It is known that DUSP22 regulates MAPK signal transduction but the effect of DUSP22 on MAPKs is controversial. Since there have been several conflicting reports regarding its substrate specificity. One report showed that DUSP22 dephosphorylates ERK2 in vitro, while other studies showed that DUSP22 enhances JNK activation but not p38 and ERK2. Therefore, further studies are required to clarify the physiological role of DUSP22. We found poor overall survival in cases with DUSP22 expression and we need further studies about the prognostic significance of DUSP22 expression in indolent lymphomas.

Keywords: non-Hodgkin lymphoma (NHL); prognostic indices.

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GENE MUTATIONS AND SITES OF INVOLVEMENT IN DUODENAL-TYPE FOLLICULAR LYMPHOMA

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Background: Duodenal-type follicular lymphoma (DTFL) is a rare variant of FL characterized by duodenal involvement and favorable prognosis. A clinicogenetic risk model m7-FLIPI was originally proposed for the prognostication of nodal FL. There are few studies analyzing the m7-FLIPI score and gene mutations according to the sites of involvement in patients with DTFL.

Methods: This study included 11 patients with DTFL diagnosed according to the 2017 WHO classification between 2005 and 2016 at Mie University Hospital. Five patients with involvement of mesenteric lymph nodes were excluded in total 16 patients. Intestinal involvement was examined by double-balloon endoscopy and/or capsule endoscopes in addition to esophagogastroduodenoscopy and colonoscopy in all the patients. Genomic DNA was examined using the AmpliSeq Comprehensive Cancer Panel investigating the exonic regions of 409 genes and direct sequencing of MEF2 (exon 2 to 3).

Results: The median age was 59 years (42-84) and 6 patients were women. Sites of lymphomatous involvement were as follows: second part of the duodenum, 100% of the patients; third part of the duodenum, 82%; first part of the duodenum, 0%; jejunum, 72%; ileum, 36%; colon, 9%; stomach, 0%. Lymphoma cells by all the patients were positive for CD20, CD10, and BCL2 by immunohistochemistry. The t (14;18) translocation was confirmed in 10 of the cases by FISH. All

the patients were alive at follow up (median 5.7 years). The mutation frequencies of genes regarding m7-FLIPI were as follows: EP300, 36%; FOXO1, 0%; CREBBP, 64%; ARID1A, 45%; and EZH2, 36%. The CARD11 mutation was identified in 55% of the cases, whereas none of cases had the MEF2B mutation. One hundred percent of the patients were classified in the low risk group with the m7-FLIPI model. KMT2D was mutated in 45% of the cases. Of note, KMT2C mutation was detected in 64% of the cases. MYC, TP53 and MYD88 were not mutated in any of the cases. All 3 cases without the involvement of both ileum and jejunum had the NOTCH2 mutation.

Conclusions: Our results suggest that the m7-FLIPI model was valid with DHFL patients in this cohort. The incidence of KMT2C was higher compared with that of the other lymphoma subtypes (1-13%). KMT2C and NOTCH2 mutations may be associated with the diversity in the sites of intestinal involvement in DTFL.

Keywords: follicular lymphoma (FL).

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PREVALENCE OF EPSTEIN BARR VIRUS IN FOLICULAR LYMPHOMA AND PROGNOSTIC VALUE OF FOXP1 AND P53 BIOMARKERS IN A MEXICAN POPULATION
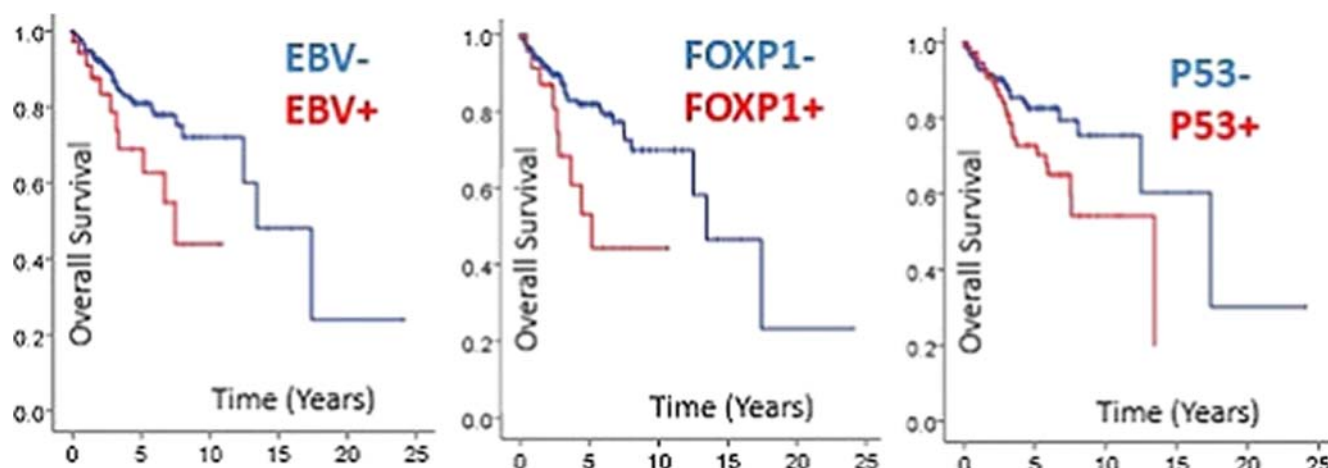
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Introduction: Follicular lymphoma (FL) is the second most frequent neoplasm in B cells. Epstein Barr Virus (EBV) causes a latent infection in B-lymphocytes with transformation capacity; however in FL there is just one previous publication that documented 2.6% of prevalence and there are no studies in Latin America. Other factors related to worse overall survival (OS) are P53 mutations and the transcription factor FOXP1, who is down-regulated in presence of EZH2 mutations. In search of prognostic biomarkers for LF, and in the absence of molecular tests for TP53 and EZH2, we wanted to determine the prognostic value of FOXP1 and P53, as well as the association between EBV and LF in a Mexican population.

Methods: We conducted an observational, descriptive, analytical and retrospective study including cases with lymph node diagnosis of LF. We obtained clinical data from the electronic records and reviewed the slides selecting the representative area of the neoplasia for tissue microarrays (TMA), *in situ* hybridization (EBER-ISH) and immunohistochemical markers. The statistical analysis was performed using Kaplan-Meier curves, Log-rank test and Cox regression using IBM SPSS version 25.

Results: We analyzed 228 patients, with a median OS of 13.4 years; 16% of the cases were EBV+. We found association in EBV+ patients to low hemoglobin ≤12mg/L (p = 0.014) and albumin ≤4g / dL (p = 0.009) levels. EBV+ patients had shorter OS than the EBV- (7 vs. 13 years, p = 0.029). EBV+ combinations with Ki67 ≥ 40% and histological grade 3 were associated with OS of 3.6 and 3.2 years respectively (p = 0.052, p = 0.017). Concurrent expression of EBV+, FOXP1 ≥ 10% and Ki67 ≥ 40% reduces OS to 2.9 years (p = 0.004). P53 expression ≥ 1% was positive in 100% of EBV+ cases (p = 0.021) while p53 ≥ 20% was positive in 31% of them (p = 0.067). FOXP1 expression ≥ 85% was negatively associated with OS (p = 0.010) and relapse-free survival (RFS) (p = 0.051), as was p53 ≥ 10% (p = 0.035). FOXP1 ≥ 10% concurrent with EBV+ decreases OS to 6.7 years (p = 0.014). Multivariate analyses for OS confirmed FOXP1 ≥ 85% as independent prognostic factor.

Conclusions: The LF/EBV+ association has a high prevalence in Mexico with a significant prognostic value for OS. FOXP1 expression ≥ 85%, but not at 10% was an independent factor of poor prognosis. P53 had an impact on OS at a cut-off value of 10%, independently of EBV status. Those LF/EBV+ patients with concurrent Ki67 expression (≥ 40%) and histological grade 3 exhibited worse prognosis. We consider of particular importance to identify relevant prognostic factors in the Mexican population. These biomarkers should be both reproducible and accessible to our diagnostic capabilities allowing the development of better therapeutic strategies for high-risk EBV+ LF cases.

Keywords: Epstein-Barr virus (EBV); follicular lymphoma (FL).

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INCREASED *CCND1* FISH SIGNALS ARE ASSOCIATED WITH WORSE PROGNOSIS IN MANTLE CELL LYMPHOMA

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Background: Mantle cell lymphoma (MCL) is a heterogeneous disease still lacking reliable prognostic factors. A recurrent feature of this disease is however the t(11;14) translocation, yielding an increased production of Cyclin D1 through activation by the IGH promoter. In a previous study based on a controlled randomized trial (LyMA study, #113303; presented at ASH 2017 and currently submitted) we observed that large gains on chromosome 11, identified by single nucleotide polymorphisms (SNP), in a region always including the *CCND1* locus encoding for cyclin D1, were related to a worse prognosis. In this series of 94 lymph node biopsies, this anomaly was observed in 7 patients who displayed a significantly worse outcome (p=0.004)

Aims: Here we examined a real-life cohort of MCL patients who benefited from fluorescence *in situ hybridization* (FISH), to assess whether chromosome 11 gains indeed impacted outcome.

Methods: All patients intensively treated between 1995 and 2018 with an assessment of *CCND1* gains by FISH analysis were included. Fifty-one patients were consolidated with an autograft similar to that applied in the LyMA trial. Patients with FISH results suggestive of tetraploidy were considered separately. Outcomes were established as the delay between the initiation of the first line treatment and first relapse, death or last news.

Results: A cohort of 65 MCL patients was included with a median age of 58 years old (range 34-74) and a M/F ratio of 2,1. Seventeen patients displayed a significant signal suggesting *CCND1* or fusion gain. FISH signals were interpreted as normal wild type chromosome, fusion signals and extraneous (supernumerary) signals. When considering patients with extra *CCND1* or fusion signals, compared with patients with an expected classical translocation signal, a significantly worse outcome was observed in terms of progression free survival (PFS) with respective medians of 30 vs 116 months (HR=2.4[1.0-5.7];p=0.05). Moreover, when removing patients likely to present tetraploidy (i.e. double translocation load associated with whole genome increase), the significance of these gains reached a significance of p=0.02 (25 vs 116 months; HR=3.2[1.2-8.7]).

Conclusions: Although the t(11;14) translocation is an undisputed hallmark of MCL diagnosis, in an integrated approach of morphological and immunophenotypic features, closer examination of FISH signals could provide an additional prognosis factor, as suggested by SNP analysis but not systematically requiring it.

Keywords: B-cell lymphoma; fluorescence in situ hybridization (FISH); mantle cell lymphoma (MCL).

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QUANTIFYING SOMATIC HYPERMUTATION RATES AND IDENTIFYING IMMUNOGLOBULIN HEAVY CHAIN STEREOTYPES IN MANTLE CELL LYMPHOMA THROUGH NEXT-GENERATION SEQUENCING

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Introduction and aim of study: Mantle cell lymphoma (MCL) is a distinct subtype of non-Hodgkin lymphoma, and the mechanism of its development is still not fully elucidated. Most of mantle cell lymphoma did not undergo germinal center reaction such as somatic hypermutation. Interestingly, prior immunoglobulin sequencing has noted that there are several stereotypes of V(D)J recombination, hypothesizing that these stereotypes might result from unknown biased selection. This study took advantage of next generation sequencing (NGS) to characterize the detail of recombined VDJ sequences in mantle cell lymphoma in comparison of other lymphoma subtypes.

Patient and method: In this single-institute retrospective study, 112 patients (male: 90 vs. female: 22) were diagnosed as having MCL between 2006 and 2018. The median age at diagnosis was 62 years old. The Ann Arbor staging at diagnosis was mostly stage 4 (81.1 %), and the blastoid variant comprised of 13.4 %. Among them, 15 patients' lymphoma specimens were analyzed through Lympho-Track®Dx IGH/IGK assay coupled with Illumina MiSeq sequencer to characterize the post-recombine immunoglobulin sequences. As control, 53 patients with other lymphoma subtypes including diffuse large B cell lymphoma, follicular lymphoma, MALToma, Hodgkin lymphoma and other lymphoproliferative disorders were analyzed with the same platform.

Results: In line with the prior notion that mantle cell lymphoma developed independent of somatic hypermutation in the germinal center, the mutation rate of V gene in mantle cell lymphoma is much lower than other lymphoma subtypes (median: 1.32% vs. 7.27%, p<0.001, Figure 1). VH3-21 was the most prominent stereotype in mantle cell lymphoma (53.3%). Through conceptual translation for the recombined VDJ sequences in three reading frames, an 87-amino-acid peptide domain was obtained via alignment at the carboxyl terminal for comparison. Interestingly, a 10-amino-acid motif, which is hydroxyl and amine group-rich, differed strikingly between MCL and other lymphoma subtypes. Seven out of 10 amino acids in this motif were significantly enriched in mantle cell lymphoma (Figure 2).

Conclusion: VDJ recombination of immunoglobulin heavy chain in mantle cell lymphoma of this study underwent the lower somatic hypermutation rate compared with other lymphoma subtypes. The predominant stereotype involved VH3-21. A hydroxyl- and amine-rich motif was identified as mantle cell lymphoma-specific peptide. Implications of this motif in three dimension and its relationship with potential antigens warrant further investigation.

Keywords: immunoglobulins (Ig); mantle cell lymphoma (MCL); molecular genetics.

Figure 1.

Figure 2.

P value	0.02	0.027	0.023	NS	NS	0.006	0.023	0.047	0.043	NS
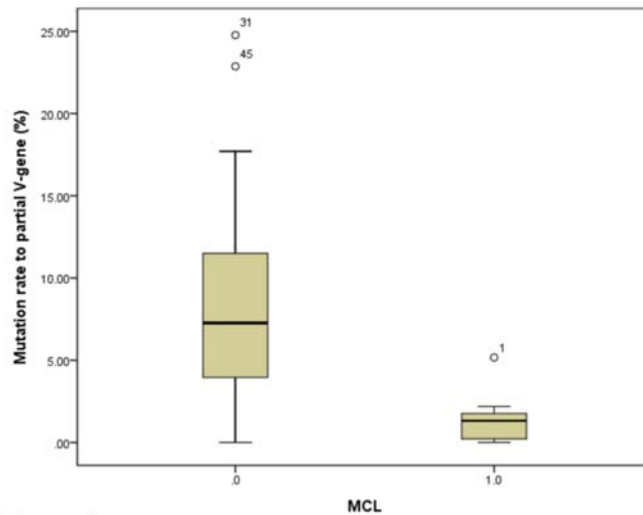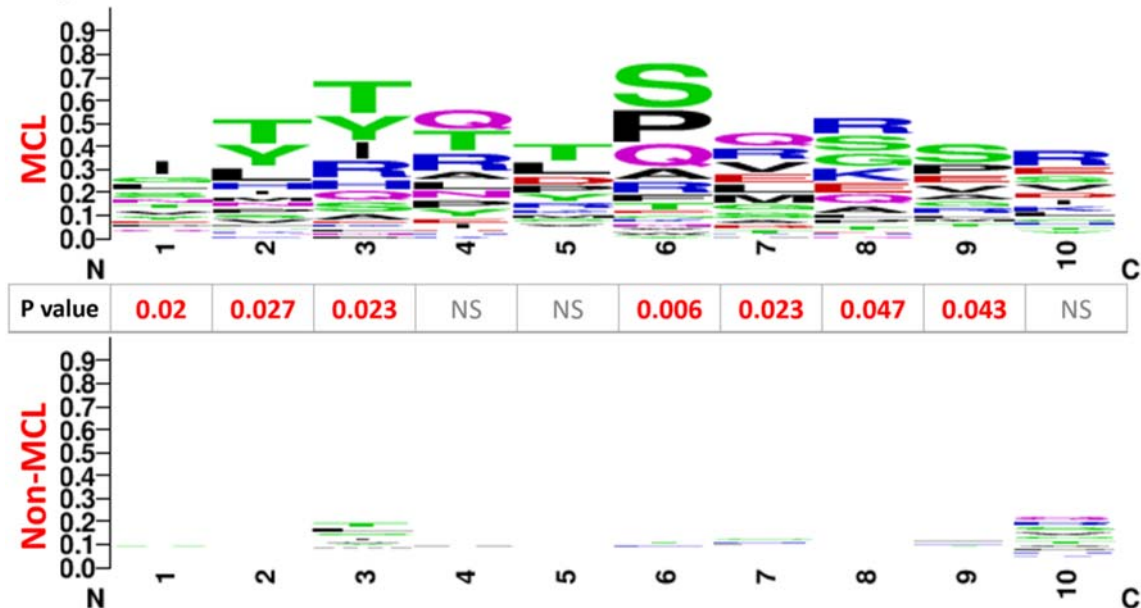
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THE IMMUNE MICROENVIRONMENT AS A PROGNOSTIC TOOL FOR MCL PATIENTS

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Introduction: Breakthroughs in immunotherapy and targeted drugs have provided increased survival among patients with mantle cell lymphoma (MCL) but companion diagnostic tools remain to be developed.

Median overall survival (OS) was until recently 3-5 years but novel strategies such as the Nordic MCL2/MCL3 regiments combining high dose cytarabine with Rituximab and autologous stem cell transplantation (ASCT) have improved life-expectancy to more than 12 years for younger fit patients. Although promising, it is still not possible to stratify patients into different treatment protocols based on diagnostic markers. The molecular diversity has been explored but so far *TP53* mutational status and Ki-67 expression are the only validated markers associated to poor treatment response. Based on the success of incorporating anti-CD20 antibodies and ASCT to MCL treatment, the role of an effective immune response has been pin-pointed. In this study, we aim to identify prognostic markers for patients treated within the Nordic MCL2/3 protocol with the long-term goal of developing validated predictive tools.

Methods: The data set combines clinicopathological information, *TP53* mutational status and FFPE samples (total n=98;

Immunohistochemistry (IHC) n=52; Gene expression (GEX) n=72). The median follow-up time is 9 years. Tissue microarrays were stained with p53 and c-myc to distinguish classical MCL from more aggressive variants. Immune infiltration was accessed by staining with CD3, CD4, CD8, CD20, CD25, FoxP3 and PD1 antibodies. IHC results were digitally scored with HALO software (Indica Labs). Optimal cut-off points for immune cell numbers were selected using the maximally selected chi-square method (maxχ^2). GEX was performed with Gene ST 1.0 arrays (Applied Biosystems) and analyzed with Qlucore Omics Explorer (Qlucore AB).

Results: Preliminary results showed that the percentage of CD4+ cells is negatively correlated with progression free survival (PFS) ($p<0.05$) in linear Cox model analysis. After dichotomization with maxχ^2 method, high infiltration of CD4, CD3 and CD8 cells was negatively correlated with PFS ($p<0.05$) and CD4, CD8 and FoxP3 high infiltration was associated to a worse OS. Efforts to expand the cohort by inclusion of material from additional MCL2/3 clinical sites are ongoing.

Conclusions: Immunotherapy is an effective therapy against many cancers and immune infiltration has been proved to be an important indicator of response to therapy. Efforts to validate these findings and develop companion diagnostic test are of major importance. Our findings show that MCL tumor immune-microenvironment, with particular emphasis on the CD4+ population, is prognostic for patients treated with combinatorial protocols, including anti-CD20 treatment and ASCT. Further studies to classify T cell subsets are warranted to further refine the understanding of the molecular events associated with response to therapy.

Keywords: immune system; immunochemotherapy; mantle cell lymphoma (MCL).

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MUTATION OF *PIM1* GENE IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA INHIBITS CELL DEATH THROUGH CHANGE IN SUBCELLULAR LOCALIZATION OF Pim-1 AND INCREASE OF BAD PHOSPHORYLATION

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Backgrounds: In a study of Next Generation Sequencing in primary central nervous system lymphoma (PCNSL), we have previously reported several mutations of high frequency, in comparison with systemic diffuse large B cell lymphoma (DLBCL)s. Consequences of these specific mutations in PCNSL are unknown. In this study, we have analyzed the functional consequence of mutations in the *PIM1* gene, observed in 100% of PCNSL patients, which encodes a serine/threonine kinase and is known to drive tumorigenesis in several malignancies.

Methods: Four most frequent mutations of *PIM1* in PCNSL, *S77N*, *K115N*, *P216S*, *L275F*, were chosen from our previous study, and each mutant was generated by site directed mutagenesis in *PIM1* cDNA cloned in an expression vector. Resulting vectors were transiently transfected into human cancer cell lines. Cell death of the cells expressing each mutant was evaluated by dye-exclusion method under treatment of chemotherapeutic agents. Alteration of molecular signaling was evaluated by immunoblotting.

Results: Among the four mutants, increased phosphorylation of BCL-2 associated death promoter (BAD) at Ser112, which is a phosphorylation target of Pim-1, was observed by expression of *K115N* mutant compared with wild type *PIM1* in Nagai and Hela cells expressing endogeneous BAD. Decreased cell death under campthothecin treatment was also observed in *K115N* mutant expressing Nagai cells compared with wild type *PIM1*-expressed cells. Moreover, we observed a significant shift in subcellular localization of Pim-1 carrying *K115N* mutant; from the nucleus, main sublocalization for wild type Pim-1, into the cytosol determined by immunocytochemistry and immunoblotting of nuclear and cytosolic fraction of the cells.

Discussion: It is suggested that *PIM1 K115N* mutant may drive chemoresistance through increased BAD phosphorylation that suppresses cell death compared with wild-type *PIM1* through modification of its subcellular localization.

Keywords: B-cell lymphoma; primary CNS lymphoma (PCNSL).

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CLINICALLY INDOLENT PRIMARY HHV8-NEGATIVE EFFUSION-BASED LYMPHOMA IS CHARACTERIZED BY COMPLEX GENOMIC ALTERATIONS WITH AGGRESSIVE FEATURES

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Human herpesvirus 8-negative effusion-based lymphoma (HHV8-negative EBL) is a distinct lymphoma entity related to fluid overload states caused by underlying medical conditions such as cardiac failure or renal insuffciency. Due to a phenotypical resemblance with secondary effusion of diffuse large B-cell lymphoma (DLBCL), HHV8-negative EBL is easily misdiagnosed. However, in contrast to DLBCL, HHV8-negative EBL follows a mild clinical course that is largely determined by comorbidity and high age at diagnosis, underpinning the importance to differentiate between the two entities.

From the files of the Dept of Pathology, AmsterdamUMC/VUMC, we retrospecively identified 11 cases of HHV8-negative EBL. All patients presented with isolated pleural (n=10) or pericardial effusion (n=1).
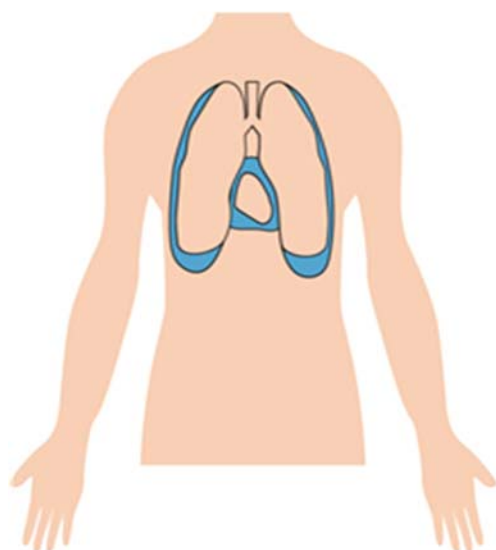
1. Mature B-cell phenotype

HHV8-negative
Effusion Based Lymphoma

HHV8-
CD20+
CD79a+
CD138-
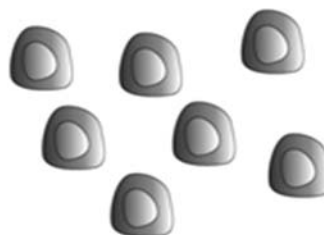
2. Aggressive genomic features

Mutation
Translocation
Copy number loss
Copy number gain
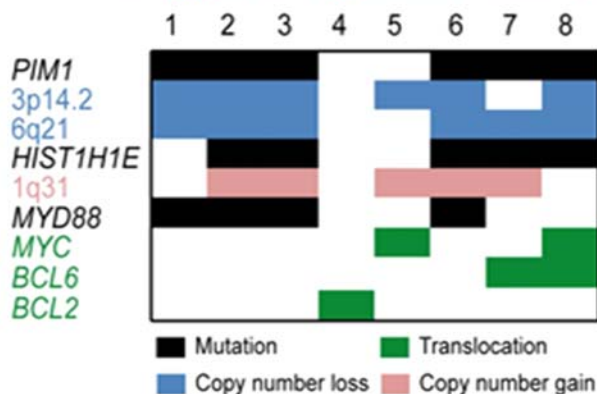
3. Indolent clinical behavior

Age at presentation ranged from 60-92 years (median 85 years). All cases, except one, showed a mature B-cell immunophenotype (CD20, CD79a positive), one case showed plasmacytic differentiation (CD138 positive). All were EBER negative, 9/10 showed a non-GCB phenotype and 1/10 a GCB-phenotype (Hans/Tally alogorithms).

We performed extensive genomic profiling using a custom-made all-in-one assay (NimbleGen EZ SeqCap) to determine genome wide copy number alterations, mutations (369 genes) and translocations (12 target regions) on 8 HHV8-negative EBL cases. A mean number of 33.6 copy number gains and losses per case were found, with recurrent focal deletions of chromosome 3p14.2 and 6q21 in 6/8 cases, encompassing tumor supressor genes *FHIT* and *PRDM1*, respectively. We observed a high rate of mutations across genes frequently involved in DLBCL, including patterns of somatic hypermutation (*PIM1, KLHL1, BCL2*). The most abundant hotspot mutation was found in *MYD88L265P* (3/8 cases). In addition, 5/8 cases had one or more translocations, involving *MYC* (n=2), *BCL2* (n=1), *BCL6* (n=2), *TP63* (n=1), *EXOC2* (n=1) and *KMT2D* (n=1), with Ig and non-Ig partners, of which one *MYC/BCL6* double hit context.

We conclude that HHV8-negative EBL is characterized by heterogeneous genomic features with frequent mutations, copy number aberrations and translocations, similar to aggressive B-cell lymphomas, but despite this follows an indolent clinical course.

Keywords: diffuse large B-cell lymphoma (DLBCL); elderly; molecular genetics.

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GENOTYPING PRIMARY MEDIASTINAL B-CELL LYMPHOMA (PMBCL) BY MEANS OF CIRCULATING TUMOR DNA ANALYSIS

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Introduction: Primary mediastinal B-cell lymphoma (PMBCL) is a rare subtype of non-Hodgkin lymphoma that predominantly occurs in adolescents and young adults. Biologically, PMBCL shares many similarities with classical Hodgkin lymphoma, including constitutive activation of the JAK-STAT and NF-kB pathways. High-throughput sequencing of circulating tumor DNA (ctDNA) in peripheral blood has emerged as a noninvasive approach in different types of neoplasms and it could be helpful in PMBCL when a biopsy specimen of the tumor is not available for molecular analysis. The aim of this study

Recurrent mutated genes in ctDNA at diagnosis
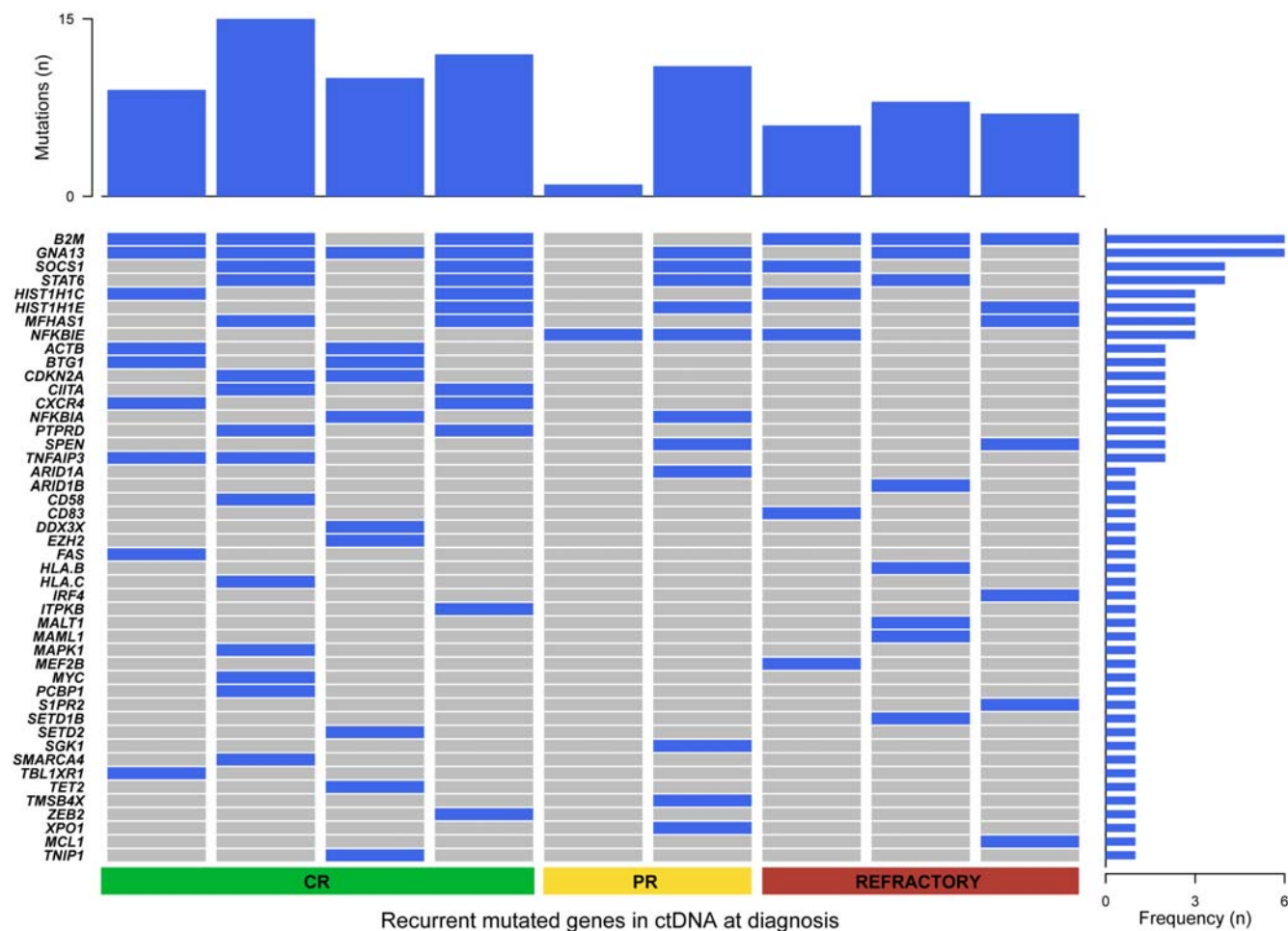
was to analyze the mutational profile at diagnosis and in the refractory/relapse settings in PMBCL patients using ctDNA and to compare, when available, with genotyping from tissue biopsy DNA.

Methods: We included 9 patients (M/F 4/5, median age 29 years) diagnosed with PMBCL in a single institution between 2015 and 2018 according to the WHO criteria. All patients were treated with chemoimmunotherapy. After initial treatment, 4 patients achieved complete remission (CR), 2 partial response (PR), 3 were refractory. Samples were obtained both at diagnosis and at progression. Tumor genomic DNA (gDNA) was isolated from formalin-fixed paraffin-embedded (FFPE) diagnostic tissue biopsies. A panel of 115 genes was amplified using a hybridization capture based protocol from 10-30 ng of ctDNA and 150 ng of gDNA (SureSelectXT-Agilent Technologies) and sequenced in a MiSeq instrument (Illumina).

Results: ctDNA was obtained from all patients at diagnosis and from 4/5 patients in PR or who were refractory after treatment. Median amount of ctDNA at diagnosis was 46 ng (range: 10-74 ng). In all the cases, at least one mutation could be detected, with a median of 10 mutations per sample (range 1-22 mutations). In 4 of the 5 cases with simultaneous tissue and peripheral blood samples, a similar number of mutations was detected with the same genes involved. The genes most frequently mutated at diagnosis were *B2M, GNA13, SOCS1, STAT6, HIST1H1C, HIST1H1E,* *MFHAS1, NFKBIE* (figure). In 3 of the 4 cases with a ctDNA sample at diagnosis and at progression, changes in the allelic frequency of the mutations could be observed, whereas in the remaining case no mutation at progression could be detected. Of note, none of the 3 patients with *NFKBIE* mutation achieved a CR after first line treatment.

Conclusions: ctDNA could be used instead of tumor DNA to assess mutational landscape in patients with PMBCL.

Keywords: molecular genetics; primary mediastinal large B-cell lymphoma (PMLBCL).

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ABNORMALITIES IN MICRORNA EXPRESSION SIGNATURE CAN CONTRIBUTE TO THE GENOME INSTABILITY AND FAILURE OF DNA REPAIR MECHANISMS IN CASE OF DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Genome instability and high mutation rate are typical features of diffuse large B-cell lymphoma (DLBCL), facilitating the rapid tumor evolution and acquisition of therapy resistance. This research aims to identify in what way the shifts in microRNA (miRNA) expression pattern can contribute to the DNA damage and genome instability.

Methods: MiRNA targets within gene transcripts were predicted *in silico* using the TargetScan software.

Results: MiRNAs miR-17, miR-18, miR-19, miR-20, miR-21, miR-29, miR-92, miR-106, miR-144, miR-146, miR-155, miR-221/222, miR-363, miR-500 and miR-574, hyperexpression of which is essential for DLBCL cells, can target transcripts of genes encoding many DNA repair enzymes as well as other DNA damage response proteins that are key elements of all DNA repair systems – base excision repair (*UNG, SMUG1, MBD4, TDG, OGG1, NTHL1, NEIL1/2, APEX1, LIG3, APLF*), direct reversal of damages (*ALKBH3*), repair of DNA-topoisomerase crosslinks (*TDP1/2*), mismatch excision repair (*MSH2/3, MLH1/3*), nucleotide excision repair (*RAD23B, DDB1, RPA1/3, ERCC2, GTF2H1/2/3/5, CCNH, ERCC1/4/6/8, UVSSA*), homologous recombination (*RAD50/51/52, RAD51B/D,XRCC2, RAD54B, MRE11A, NBS1, RBBP8, EME1, GEN1*) and non-homologous end-joining (*XRCC6, PRKDC, LIG4, DCLRE1C, NHEJ1*). Targets of the up-regulated miRNAs are also revealed in transcripts of genes encoding ATM kinase and Fanconi anemia proteins (*FANCA/C/D2/E/F/G/I/M, BRCA2, BRIP1, RAD51C, BTBD12, FAAP20*).

In addition, down-regulation of miRNA miR-150 can contribute to the aberrant reactivation and hyperexpression of *AICDA* gene, encoding cytidine deaminase AID, because its transcript carries targets of this miRNA. Also, down-regulation of anti-onco-miRNAs (e.g. miR-15/16, miR-34, miR-145 and miR-150) allows overexpression of genes encoding the factors NF-kB, SP1, HoxC4, TCF3, Stat6, Id2/3, which are *AICDA* transcription activators. On the contrary, tumors have indolent course if AID cannot be reactivated. For instance, MALToma cells hyperexpress miRNA miR-150, high conservative binding sites of which are revealed in transcript of *AICDA* gene. It can be assumed, that AID can cause even the target damage (endogenous gene knock-out) of tumor suppressor genes (incl. genes of anti-onco-miRNAs) in result of mutations in single-stranded R-loop that arises from DNA duplex during the transcription.

Conclusions: MiRNAs, hyperexpression of which is essential for abnormal proliferation and surviving of DLBCL cells, silence also genes encoding DNA repair enzymes as well as other key elements of the DNA damage response network. Therefore, shifts in miRNA signature can contribute to increase of genomic instability and mutation rate, leading on the whole to oncogene abnormalities and damage of tumor suppressor genes. This process underlies the tumor evolution as well as drug resistance acquisition.

Keywords: diffuse large B-cell lymphoma (DLBCL); microRNA.

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COMPARISON OF OUTCOMES BETWEEN PATIENTS WITH *MYC* REARRANGED DLBCL

AND DOUBLE/ TRIPLE HIT HIGH-GRADE B CELL LYMPHOMA: A PAN-LONDON RETROSPECTIVE REVIEW

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Introduction: Diffuse large B cell lymphoma (DLBCL) is a clinically heterogeneous disease. Increasing emphasis is being placed on the prognostic impact of tumour biology to identify groups at highest risk of treatment failure. Chromosomal rearrangements enhancing the activity of the *MYC* proto-oncogene (*MYCr*) have been linked to adverse outcomes although some studies suggest that cases harbouring additional translocations affecting BCL2, BCL6 or both, have the worst outcomes. There is currently no consensus on the management of *MYC*r, 'double-hit' (DH) and 'triple-hit' (TH) cases. Retrospective data suggests that whilst treatment intensification is associated with an improved PFS, it does not translate to an improved overall survival (OS). Moreover recent evidence suggests that the *MYC* translocation partner may be important in prognostication. We aimed to capture the trends in current management of patients with these high risk alterations in a pan-London retrospective study.

Methods: DLBCL patients with *MYC*r, DH or TH were identified at 9 London centres. Demographics, cytogenetics, treatment and outcomes were obtained from patient records and anonymised data was submitted for analysis. OS was defined as survival from date of diagnosis until death, censored at last follow-up. Median OS and follow-up time were calculated using the Kaplan Meier (KM) and reverse KM

Figure

(a) OS by rearrangements

MYCr, n=47
DH/TH, n=48

p= 0.2

(b) OS by rearrangements in patients less than 70 years

MYCr, n=36
DH/TH, n=37

p= 0.02
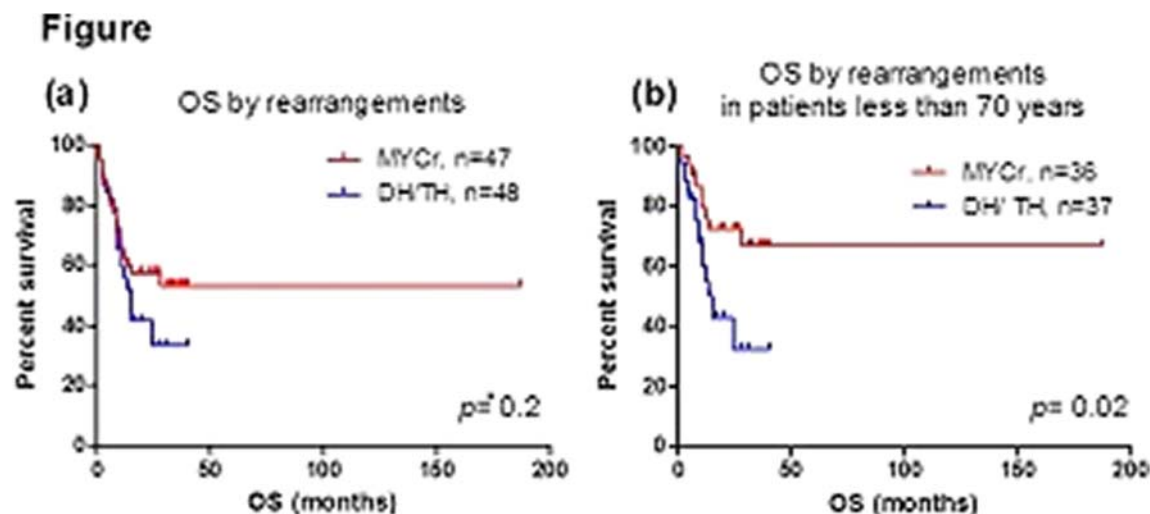
method respectively. Log-rank test was used to assess differences in median OS.

Results: 101 patients (pts) have been evaluated to date. *MYC* rearrangement was the sole abnormality in 51 cases. 34 had DH (22 with BCL2 and 12 BCL6 rearrangement) and 16 TH. Median age was 65 yrs (Range 18-93). IPI was evaluable in 95 cases (0-2 in 28 and 3-5 in 67 pts). There was no significant difference in median age or IPI comparing sole MYCr cases to DH/ TH cases. Of the 101 pts, 27 (17 *MYCr*, 10 DH/TH) received either R-CODOX M/ R-IVAC or DA R-EPOCH. A further 53 pts received R-CHOP or similar regimens with an equal split between *MYCr* and DH/TH cases. The remaining had alternative treatments and a minority received only palliation.

With a median follow-up of 25 months, the median OS for pts with *MYCr* was not reached (NR) versus 15 months for pts with DH/ TH, p= 0.2 (Figure 1a). In pts under 70 years, median OS for pts with DH/ TH (n=36) was 13 months versus NR in the *MYCr* pts (n=33), p=0.02 (Figure 1b). In these younger pts with DH/ TH OS was 13 months in pts who received R-CHOP like chemotherapy (n= 23) and 15 months in those who had R-CODOX M/ R-IVAC or DA R-EPOCH (n=10).

Conclusions: Patients with DH/TH lymphomas in our cohort had a dismal outcome irrespective of age and IPI emphasizing the need for newer treatment strategies. The data shows a trend towards better outcome in patients with sole *MYC*r compared to those with DH/TH. This difference is striking in patients under 70, with a significantly better outcome in favour of those with sole *MYC*r. Data collection is ongoing to investigate the outcomes according to *MYC* translocation partner.

Keywords: "double-hit" lymphomas; MYC.

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CLINICAL SIGNIFICANCE AND OUTCOMES IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) HARBORING EXTRA COPIES [EC] AND/OR TRANSLOCATIONS [TL] OF MYC, BCL2, AND BCL6

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Introduction: Patients with DLBCL and "double hit" cytogenetics (MYC plus BCL2 and/or BCL6 translocations) have been shown to have inferior outcomes and appear to do better with first-line intensive chemotherapy regimens such as R-EPOCH compared to R-CHOP. In contrast, the clinical significance of EC of these genes is unknown. The current retrospective study investigates clinical characteristics and outcomes of DLBCL patients with 5 different cytogenetic profiles.

Methods: The study population consisted of adult patients diagnosed with DLBCL between 2001-2015 and available FISH reports, who were then categorized into the following groups: 1) MYC EC+ BCL2/6 EC (DEC), 2) MYC EC +BCL2/6 TL (EC), 3) MYC TL+BCL2/6 TL (DHL), 4) MYC TL+BCL2/6 EC (TL) and 5) Normal FISH (NL). To be eligible for inclusion, all were treated with rituximab and anthracycline-based chemotherapy and had at least 12 months of follow-up. Patients with a history of prior indolent lymphomas were excluded. EC was defined by ≥10% of nuclei in the FISH report. The primary objective was 2-year progression-free survival (PFS) and secondary objectives were complete remission rate (CRR), event-free survival (EFS) and overall survival (OS). In addition, outcomes based on type of induction (R-CHOP-based regimens vs intensive therapy) and number of ECs (1-2 versus ≥3) were analyzed (excluding NL).

Results: Out of 267 patients with available FISH reports, 98 were categorized into the 5 designated groups with 5-35 patients in each. Patients with DHL were most likely to have high IPI score, GCB-subtype, and be treated with intensive therapy. Relevant clinical outcomes are presented in **Table 1**. Across all groups, the CRR ranged from 74% (DHL) to 100% (EC, TL). Only DHL was found to be significantly associated with worse

PFS curves with X-Axis representing time from treatment initiation (months). Fig 1A (Top): PFS of 5 cytogenetic groups of interest. Black line represents remaining 169 uncategorized patients as reference. Fig 1B (Bottom): PFS of 4 groups categorized by type of induction therapy and by DHL vs non-DHL status.
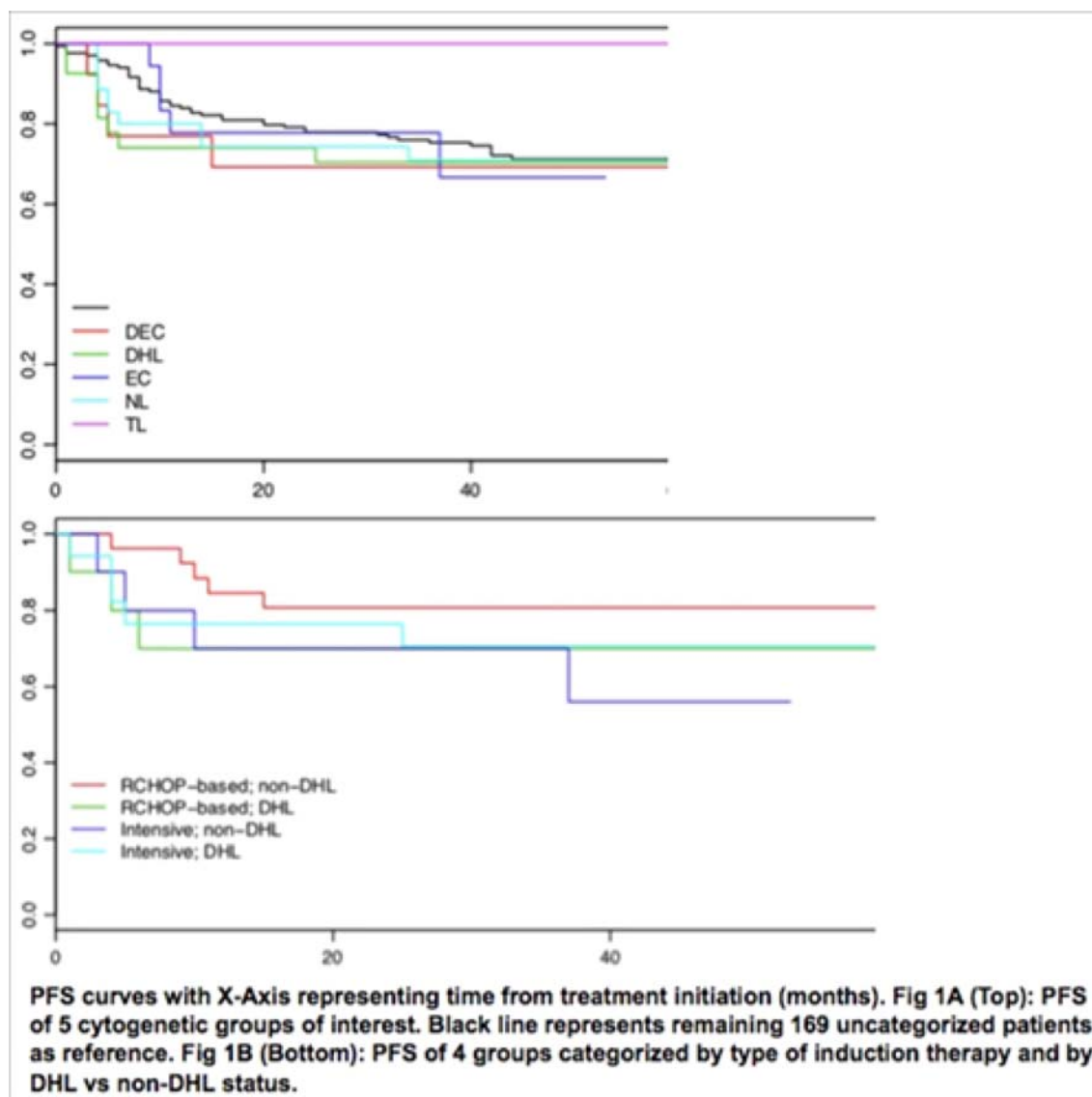
CRR (p=0.031). 2-yr PFS ranged from 69% (DEC) to 100% (TL). There was no significant difference in PFS (p=1.0), OS (p=0.5), or EFS (p=0.9) between groups by log-rank analysis (**Fig 1A**). Use of intensive vs R-CHOP-based therapies resulted in 2-yr PFS of 77% vs 70% in the DHL group and 70% vs 81% in a pooled non-DHL group. However, differences in survival curves were not significantly significant in either DHL (PFS, p=0.9; OS, p=0.7; EFS, p=0.7) or non-DHL groups (PFS, p=0.2; OS,

p=0.09; EFS, p=0.3). (**Fig 1B**). Lastly, there was no association between number of ECs (1-2 versus ≥3) and outcomes.

Conclusions: A retrospective analysis of 5 different cytogenetic profiles of uncertain clinical significance in DLBCL only revealed an association between DHL and inferior CRR rate.

Keywords: "double-hit" lymphomas; cytogenetics; diffuse large B-cell lymphoma (DLBCL).

TABLE 1

	DEC	EC	DHL	TL	NL	p
Total Number	13 (4.9%)	18 (6.7%)	27 (10%)	5 (1.8%)	35 (13%)	
CR	11 (85%)	18 (100%)	20 (74%)	5 (100%)	29 (83%)	0.031
SD or PD	1 (7.7%)	0 (0%)	6 (22%)	0 (0%)	5 (14%)	0.007
Relapse	2 (15%)	3 (17%)	1 (3.7%)	1 (20%)	3 (8.6%)	NS
2-yr EFS	69%	82%	77%	100%	74%	NS
2-yr PFS	69%	78%	74%	100%	74%	NS
2-yr OS	77%	89%	78%	100%	79%	NS

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CLINICAL, IMMUNOPHENOTYPIC AND GENETIC CHARACTERISTICS OF AGGRESSIVE (NON-BURKITT) B-CELL LYMPHOMA IN A REAL LIFE COHORT

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is an aggressive and heterogeneous disease characterized by recurrent genetic alterations. Several adverse prognostic factors are well known as International Prognostic Index (IPI) parameters or *MYC* and *BCL2* and/or *BCL6* gene rearrangements (High-Grade B-cell Lymphoma double/triple hit, HGBL-DH/TH, according to the 2016 WHO classification). Other factors are controversial as previous history of indolent lymphoma, cell of origin (COO), co-expression of MYC and BCL2 proteins (double expresser (DE) status), *MYC* partner gene if rearranged. The aim of this study is to describe a « real life » cohort of patients treated in our institution for aggressive (non-Burkitt) B-cell lymphoma and to evaluate the prognostic impact of phenotypic and genetic alterations.

Methods: We collected clinical and histological characteristics of patients uniformly treated between January 2009 and June 2017 with rituximab R-CHOP/CHOP-like chemotherapy. Treatment was reinforced with high dose methotrexate in case of central nervous system (CNS) localization or HGBL subtype. All tumor samples were analysed for MYC and BCL2 protein expression by immunohistochemistry. *BCL2*, *BCL6* and *MYC* break were analysed by Interphase Fluorescence In Situ Hybridization (FISH) with breakapart probe. When *MYC* was rearranged *MYC* partner gene was analysed with double fusion probes (MYC/IgH, MYC/IgL, MYC/IgK).

Results: 242 patients were studied. Baseline characteristics were: median age: 61 y (18-88), IPI 3-5: 49.6%, CNS localization: 6.6%. With a median follow-up of 4.4 years, 5y-OS and 5y-PFS were 72% (66.0-78.5) and 65% (58.5-71.3), respectively. Histological diagnoses were DLBCL-NOS: 57%, transformed DLBCL: 26%, HGBL: 7.9%, PMBL: 4.1% and others: 5%. Using Hans algorithm, 48.8% were classified as germinal center (GC), 47.9% as non-GC, 3.3% could not be evaluated and 38% were DE. *MYC* rearrangement was detected in 36 cases (14.9%) with an immunoglobulin partner gene (IgH, IgL or IgK) in 24 (77.4%) of 31 evaluable cases. *BCL2* and *BCL6* rearrangement were observed in 45 cases (18.6%) and 62 (25.6%) cases respectively. Fifteen cases were HGBL DH/TH including 7 DH MYC/BCL2, 5 DH MYC/BCL6 and 3 TH MYC/BCL2/BCL6. Four cases were HGBL-NOS. IPI score 3-5 (p<0.0001) and HGBL (p=0.03) were significantly associated with inferior OS. IPI score 3-5 (p<0.0001), DE status (p=0.03), *MYC*-R (p=0.05) and *BCL2*-R (p=0.0014) were significantly associated with inferior PFS. Previous indolent lymphoma, COO and MYC partner gene had no impact on OS or PFS.

Conclusions: This monocentric study in a large cohort of aggressive B-cell lymphoma patients treated in real life conditions confirms previous reports on the negative prognostic impact of DE status, *MYC* and *BCL2* translocations and HGBL subtype. These genetic and immuno-histological characteristics should have implications in the design and interpretation of future clinical trials.

Keywords: "double-hit" lymphomas; diffuse large B-cell lymphoma (DLBCL); fluorescence in situ hybridization (FISH).

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REAL-WORLD PROGNOSTIC IMPACT OF BCL2 AND MYC EXPRESSION AND TRANSLOCATION AMONG DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS TREATED WITH FIRST-LINE R-CHOP

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Introduction: Patients with diffuse large B-cell lymphoma (DLBCL) and overexpression of both BCL2 and MYC proteins (double-expressor; DE) or translocations of both *MYC* and *BCL2* genes (double-hit; DH) have inferior outcomes. Given heterogeneity of testing across laboratories, we investigated outcomes of DE and DH patients

TABLE 1 Univariate Cox proportional-hazards model analyses comparing OS and TTNT among DLBCL patients treated with 1L R-CHOP according to BCL2 and MYC status

		OS			TTNT		
	N	Deaths	HR (95% CI)	p	Events	HR (95% CI)	p
Assessed by FISH							
DH Status							
Non-DH*	644	126	1.00 (ref)		186	1.00 (ref)	
DH	44	18	3.22 (1.96, 5.29)	<0.0001	23	2.75 (1.78, 4.24)	<0.0001
BCL2 Translocation							
Negative	570	114	1.00 (ref)		163	1.00 (ref)	
Positive	198	42	1.13 (0.79, 1.61)	0.50	70	1.39 (1.05, 1.84)	0.02
MYC Translocation							
Negative	761	136	1.00 (ref)		206	1.00 (ref)	
Positive	101	41	3.19 (2.24, 4.55)	<0.0001	52	2.74 (2.02, 3.72)	<0.0001
Assessed by IHC							
DE Status							
Non-DE†	251	33	1.00 (ref)		50	1.00 (ref)	
DE	232	46	1.51 (0.96, 2.36)	0.07	79	1.87 (1.31, 2.66)	0.001
BCL2 Expression							
Negative	396	70	1.00 (ref)		83	1.00 (ref)	
Positive	1429	317	1.33 (1.03, 1.72)	0.03	466	1.71 (2.16, 1.36)	<0.0001
MYC Expression							
Negative	203	28	1.00 (ref)		43	1.00 (ref)	
Positive	317	55	1.23 (0.78, 1.94)	0.38	95	1.48 (1.03, 2.12)	0.03

*Non-DH includes those who were either *BCL2*+/*MYC*−, *BCL2*−/*MYC*+, or *BCL2*−/*MYC*−, tested via FISH. Those who were unknown for either *BCL2* or *MYC* translocation were not included in the DH and non-DH classification.

†Non-DE includes those who were either BCL2+/MYC−, BCL2−/MYC+, or BCL2−/MYC−, tested via IHC. Those who were unknown for either BCL2 or MYC expression were not included in the DE and non-DE classification.

tested in the real world and treated with first-line (1L) standard-of-care immuno-chemotherapy: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). If outcomes reflect those in large multi-center trials by central testing, local laboratories may provide reliable and rapid diagnosis, and allow faster trial enrollment and treatment.

Methods: We identified DLBCL patients treated with 1L R-CHOP in the Flatiron Health electronic health record (EHR)-derived database with BCL2/MYC expression by immunohistochemistry (IHC) and cytogenetic data by fluorescence in situ hybridization (FISH), based on values extracted by Flatiron Health (2011–18). Due to nonstandard reporting, no standard cutoff was used to assign IHC positivity. Univariate Cox proportional-hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for overall survival (OS) and time to next treatment (TTNT).

Results: Of 483 patients with both BCL2 and MYC expression available, 232 (48%) were DE. Of 688 patients with both *BCL2* and *MYC* translocation available, 44 (6%) were DH, similar to prior findings. Inferior OS and TTNT were observed among DH and DE patients, and those with high BCL2 expression and *MYC* translocation. Inferior TTNT was observed among patients with high MYC expression and *BCL2* translocation. Multivariate analyses will be presented.

Conclusions: BCL2 expression and *MYC* translocation had strong prognostic ability in this population. Despite missing data inherent to EHRs, and varied testing methods used in practice, DE and DH patients had worse prognosis than non-DE and non-DH patients, comparable with results from single-center trials. This demonstrates a robustness of BCL2 and MYC biomarkers to identify high-risk 1L DLBCL patients. Improving technical, interpretive, and reporting accuracy would further strengthen confidence in these markers.

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DIFFUSE LARGE B-CELL LYMPHOMA SURVIVAL PROGNOSTICATION, A COMPARATIVE ANALYSIS OF CELL OF ORIGIN VS. MYC/BCL2 EXPRESSION

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Introduction: Multiple conflicting prognostic markers have been proposed for R-CHOP treated diffuse large B-cell lymphoma (DLBCL) cases. Aggressive behaviour has been shown to be associated with ABC-like phenotype, Double Hit (DH) or Double Expression (DE) phenotype, CD5 expression and other molecular or immunohistochemical markers.

Methods: Here we have analyzed the survival probability in a series of chemoimmunotherapy-treated 100 DLBCL cases comparing COO vs. MYC/BCL2 gene expression vs. the expression of other prognostic markers such as CD30, PDL1, CD5, p53 and Ki67, using a NanoString custom assay that includes COO and other 7 genes. Data have been also correlated with immunohistochemical and other cytogenetic studies.

Univariable and multivariable Cox proportional hazard regression models were used to evaluate the proposed prognostic factors. For Kaplan Meier analysis the continuous series were divided taken into account the median value and quartiles of the series.

Results: Double Expression (DE) (MYC/BCL2) was found in 26 cases and related with a shorter time to progression (TTP) (HR: 1.95, P<0.05). COO analysis identified 53 cases as GC-type; 27 as ABC-type and 19 unclassified. ABC-phenotype was associated with shorter overall survival (OS) (HR:2.5; p<0.05).

Association between ABC and DE identified 11 cases with double expression and ABC-phenotype, with a HR: 2.82, n<0.05.

Clinical variables integrated into the IPI were significantly associated with both TTP and OS.

All the three parameters were basically independent prognostic markers. When associated, multivariate analysis allowed to integrate IPI, DE and COO into a single model, identifying an integrated risk score for each sample that stratifies the series into four groups from risk quartiles (0.50, 0.74 and 1.56) with very strong differences in TTP and DSS. The relapse probabilities at 36 months for the risk groups created were 0.90, 0.67, 0.43 and 0.35 from down risk to high risk, while the OS probabilities at 36 months were 0.96, 0.71, 0.64 and 0.52.

Conclusions: DE (MYC/BCL2), COO and IPI are independent prognostic markers in CHOP-R treated DLBCL cases. An integrated risk score identified quartiles with significant differences in OS, TTP and DSS, and could eventually be used for selecting risk-stratified therapeutic strategies.

Keywords: "double-hit" lymphomas; activated B-cell-like (ABC); diffuse large B-cell lymphoma (DLBCL).

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A NEW PROPOSAL FOR IDENTIFICATION OF DOUBLE-HIT DIFFUSE LARGE B-CELL LYMPHOMA BASED ON THE PREDOMINANCE OF DOUBLE HITS INVOLVING BCL6 REARRANGEMENT IN TAIWAN

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No.	FISH			IHC					Phenotype
	MYC	BCL2	BCL6	MYC	BCL-2	BCL-6	CD10	MUM1	
1.	+	~	+	+	+	+	~	~	GCB
2.	+	+	+	+	~	+	~	~	GCB
3.	+	~	+	+	~	~	~	+	non-GCB
4.	+	~	+	~	~	+	+	~	GCB
5.	+	+	~	~	+	~	+	~	GCB
6.	+	+	~	NA	NA	NA	NA	NA	
7.	+	+	~	+	+	+	+	~	GCB
8.	+	~	+	~	+	~	~	+	non-GCB
9.	+	~	+	+	~	~	~	+	non-GCB
10.	+	~	+	+	+	+	+	+	GCB
11.	+	~	+	~	+	+	~	+	non-GCB
12.	+	~	+	~	+	+	~	+	non-GCB

Table 1

Figure 1
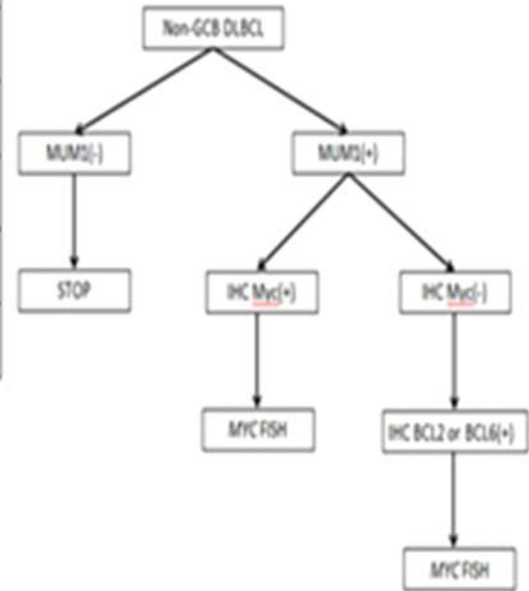
Figure 2

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of the non-Hodgkin's lymphoma all over the world and it is extremely heterogeneous both clinically and pathologically. Concurrent *MYC* and *BCL2/BCL6* translocation, the so-called double hits (DH) has been identified as an important reverse prognostic factor in DLBCL. For BCL2-rearranged DH DLBCL, it has been believed that double expression of Myc and BCL2 detected by the immunohistochemical(IHC) stains with a GCB phenotype is the most important surrogate to screen DH. Chang and his colleagues have published a manuscript to describe the immunophenotypic and genetic characteristics of DLBCL in Taiwan in 2016. In their study, *BCL6*, rather than *BCL2*, rearrangement seemed predominant in DH DLBCL although only 3 patients were identified. *BCL6*-rearranged DH DLBCL has been less discussed because of its minority in the Western countries. The frequency and predominant rearrangement type of DH DLBCL in Taiwan should be explored.

Aims: We aim to establish the predominance of *BCL6* rearrangement in DH DLBCL and figure out the phenotypes and the status of Myc, BCL2 and BCL6 expression in DH DLBCL in Taiwan. Finally, we correlate DH with their IHC features to propose a flow chart to screen DH DLBCL.

Results: Among the 154 patients, 25 of them had *MYC* translocation (16.2%). Of the 25 *MYC*-rearranged patients, concurrent *BCL2* or *BCL6* translocation were detected in 12 patients. Two-thirds of them (8 patients) had simultaneous *MYC* and *BCL6* translocation while the other 3 were MYC- and *BCL2*-rearranged (Figure 1). We had one patient with concurrent *MYC, BCL2 and BCL6* translocation, the so-called triple hits (TH). Taken together, 75% of DH (including TH) DLBCL patients had *BCL6* rearrangement and therefore we confirmed the predominance of *BCL6* rearrangement in Taiwan. Among

DH (including TH) DLBCL patients, one did not have enough residual tissue to confirm his phenotype and consequently, only 11 can be further analyzed. Only 6 out of 11 (54.5%) has Myc overexpression in the IHC stains. Among BCL6-rearranged DH (including TH) DLBCL patients, only 3 out of 9 (33.3%) has concurrent over-expression of Myc and BCL6 in the IHC stains (Table 1) and conse-quently, simultaneous overexpression of Myc and BCL6 proteins was not a good surrogate to screen *BCL6*-rearranged DH DLBCL. Similarly, only one-third has concurrent overexpression of Myc and BCL2 proteins in the *BCL2*-rearranged counterpart. Five patients (55.6%) were non-germinal center B-cell (non-GCB) phenotype in 9 *BCL6*-rearranged DH(including TH) patients, indicating the screen-ing of DH with *BCL6* rearrangement should include the non-GCB phenotype of DLBCL.

As a result, we propose an IHC flow chart to screen DH for GCB and non-GCB DLBCL, respectively. For GCB DLBCL, we would like to test MUM1 first. If it is positive, we will do *MYC* FISH directly. If not, fur-ther BCL6 IHC stain is mandatory. For patients with positive BCL6, *MYC* FISH will be done to screen DH (Figure 2). Among non-GCB DLBCL, MUM1 test is still our first step. For MUM1-positive non-GCB DLBCL, Myc IHC stain is the next gate keeper. If Myc IHC is pos-itive, we will do *MYC*FISH directly. If not, FISH will only be done in patients with positive either BCL2 or BCL6 protein (Figure 3). According to the flow charts, we can find 10 patients with DH DLBCL and the detection rate is 90.9%. Furthermore, we can detect DH DLCBL with either *BCL2* or *BCL6* rearrangement presented with either GCB or non-GCB phenotype.

Conclusions: 1. The majority (75%) of DH (including TH) DLBCL in Taiwan had *BCL6* rearrangement and it was quite different from data of the Western countries.

2. More than half (55.6%) of BCL6-rearranged DH (including TH) DLBCL were non-GCB phenotype, indicating the screening of DH with *BCL6* rearrangement should include the non-GCB phenotype of DLBCL in Taiwan.

3. The screening of *BCL6*-rearranged DH DLBCL was mandatory in Taiwan.

4. According to our flow charts, we can detect DH DLCBL with either *BCL2* or *BCL6* rearrangement, presented with either GCB or non-GCB phenotype with a detection rate of 90.9%.

Keywords: BCL2; BCL6; MYC.

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OUTCOME OF PATIENTS WITH C-MYC REARRANGED DIFFUSE LARGE B CELL LYMPHOMA ASSOCIATED OR NOT WITH BCL2 AND/OR BCL6 REARRANGEMENT: A MULTICENTRIC AND RETROSPECTIVE STUDY

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Introduction: Myc rearrangement plays an important role in diffuse large B cell lymphoma (DLBCL). It is often associated with Bcl2 and/or Bcl6 rearrangements, known as double or triple hit lymphoma (DH/TH) and seems to have a bad outcome after standard immunochemotherapy treatments. Some more intensive regimens have been associated with better outcomes, but to date, there is no consensus for a standard of care. We evaluated the impact of first-line treatment on the outcome of newly diagnosed DLBCL patients with C-myc alone or in combination with Bcl2 and/or Bcl6 rearrangements.

Methods: It is a retrospective and multicenter study of C-myc rearranged DLBCL patients who were treated between 2012 and 2017 in 3 European centers. Patients received different induction reg-imens with or without front-line transplant (auto or allo SCT). Clinical and biological characteristics of the patients were analyzed, as well as the type of chemotherapy, the response rate and the survival. All the patients had a PET-CT at baseline and for response evaluation.

Results: Sixty-three patients were included. Median age was 60 (26,8 - 86) with 71% of male. All patients had a DLBCL with C-myc rearrangement by FISH. C-myc was associated with Bcl2 (23 patients (38%)), Bcl6 (13 pts (21%) or both (6 pts (10%). AA stage was ≥ 3 in 56 patients and 46/58 patients had an IPI ≥ 2. Chemotherapy regi-mens consisted in R-CHOP (47 pts), R-Da-EPOCH or Burkitt-like regi-mens (16 pts). 8 pts received an auto-SCT and 2 pts an alloSCT . The overall response rate (complete and partial response) after front line therapy was 60,6%, (CR=52,4%). Twenty-four pts had a refractory dis-ease. After a median follow-up of 26.3 months (0.3-68.5) the progres-sion free survival and overall survival were 48% and 63% respectively. PFS and OS were 32% / 53%, 59% / 70%, and 60% / 60% for patients with isolated C-myc, DH and TH respectively. After R-CHOP, PFS and OS were 46% and 61,9% respectively. After intensive chemotherapy and SCT, PFS and OS were 60% and 66,7% respectively.

Conclusion: In this retrospective but multicenter study, we confirm that DLBCL pts with C-myc alone or associated with Bcl2 and/or Bcl6 rearrangement have a poor outcome after R-CHOP. In the absence of a randomized trial with a large number of patients, it is difficult to con-clude on the best chemotherapy regimen.

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DIGITAL SPATIAL PROFILING OF IMMUNE MARKERS IN R-CHOP TREATED DIFFUSE LARGE B-CELL LYMPHOMA REVEALS A DOMINANT PROGNOSTIC SIGNIFICANCE OF M2 MACROPHAGE INFILTRATION

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Introduction: Understanding the relative prognostic significance of distinct immune infiltrates in the micro-environment of Diffuse Large B-Cell Lymphoma (DLBCL) is essential to appropriately develop immunotherapy for front line treatment. Traditional immunohisto-chemical approaches are limited by the number of markers that can be simultaneously assessed within formalin-fixed paraffin embedded (FFPE) samples of DLBCL. In this study, we have used a novel technology- Digital Spatial Profiling (DSP) by Nanostring, to study the immune contexture of DLBCL samples through a customized panel of 36 antibodies to markers of immunological significance covering sub-populations of lymphocytes, macrophages and key immune checkpoints.

Methods: 81 cases of DLBCL, treated with R-CHOP chemo-immunotherapy and with at least 3 months of follow up were included in this study. The samples were arrayed on a Tissue Microarray (TMA). The antibodies in the panel were conjugated to proprietary oligonucleotide sequences (barcodes), and simultaneously applied to a single TMA slide. Regions of interest (ROI) were selected using a PAX5/CD20 fluorescent counterstain. Barcoded antibodies were digitally quantified, and normalized for area of the ROI. The prognostic significance of each immunological marker for Progression Free Survival (PFS) and Overall Survival (OS) was then evaluated using both univariate and multivariate models. The TMA was also evaluated for PDL1 expression using quantitative immunofluorescence (qIF) (OPAL-Vectra), which was compared to PDL1 estimation in the Nanostring immune panel.
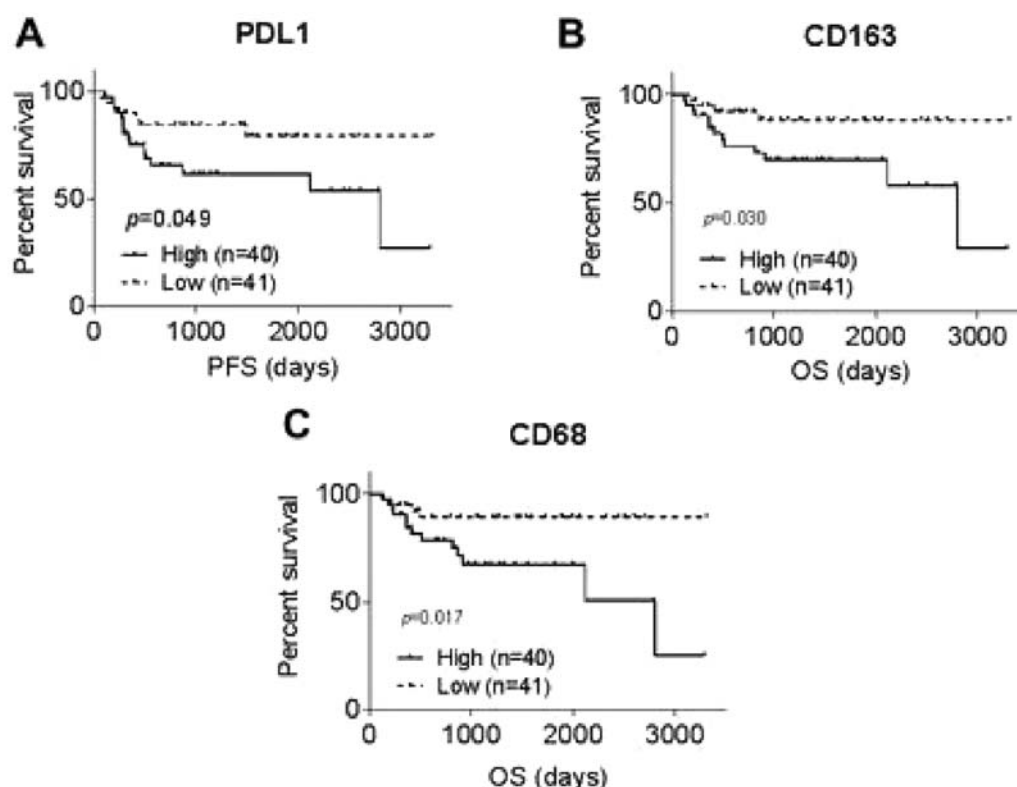
Figure 1. A, Kaplan-Meier plots for PFS stratified according to median PDL1 DSP score. B, OS analysis according to CD163 DSP score. C, OS analysis according to CD68 DSP score. Log-rank test.

Results: PDL1 estimation by the qIF assay and the DSP assay showed concordance (r=0.50, p< 0.001) and PDL1 DSP score was a statistically significant predictive marker for PFS in multivariate analysis (HR 2.6, 95% CI 1.1-6.5, p=0.035)- Figure 1A. Among the markers in the Nanostring immune panel, tumour infiltration by M2 macrophages (CD163 and CD68) showed the highest negative prognostic value for OS and was independently statistically significant on multivariate analysis that included IPI score and cell-of-origin data (CD163 HR 3.5, 95% CI 1.1-10.8, p=0.029; CD68 HR 4.4, 95% CI 1.4-13.6, p=0.012)- Figure 1B/C. Other markers including those of T-cell infiltration and non-PDL1 immune checkpoints on tumour cells did not approach statistical significance.

Conclusion: Highly multiplexed immune profiling demonstrates the relative significance of PDL1 expression and M2 macrophage infiltration towards survival of R-CHOP treated DLBCL. These findings suggest possible value in strategies incorporating PDL1 inhibition with therapeutics targeting tumour promoting macrophages, to enhance first line responses to R-CHOP in DLBCL. The Nanostring DSP assay is an FFPE-compatible method for immune profiling in DLBCL, of potential applicability to the analysis of clinical trial samples.

Keywords: diffuse large B-cell lymphoma (DLBCL); immunophenotype; macrophages.

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A2aR AS ONE OF NOVEL IMMUNE CHECKPOINTS, AND TUMOR-INFILTRATING LYMPHOCYTES IN DIFFUSE LARGE B‑CELL LYMPHOMA
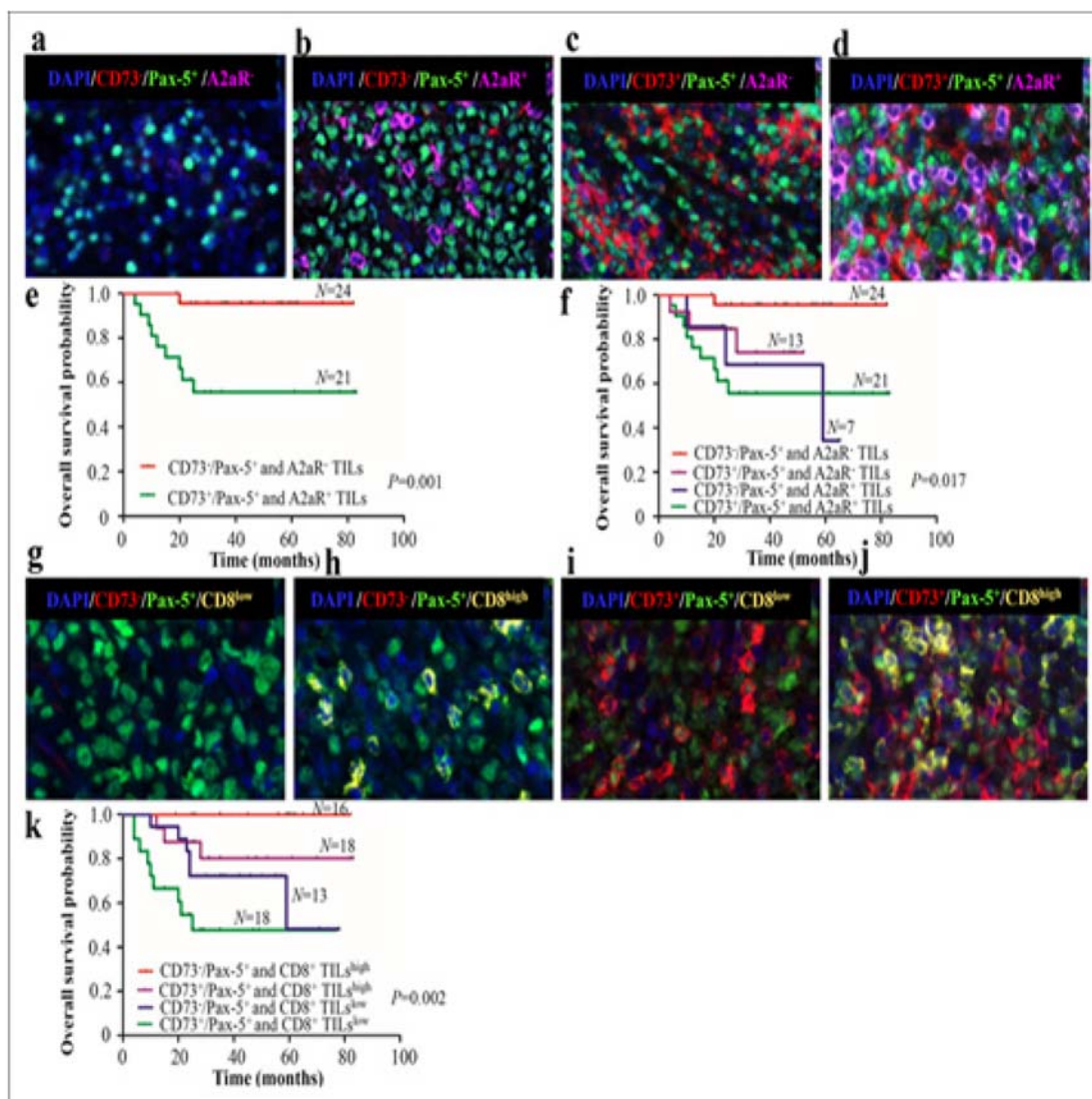
Figure 1. Localization of CD73 on tumor cells, A2aR+ TILs and CD8+ TILs, and their associations with survival in DLBCL.

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Introduction: CD73/A2a adenosine receptor (A2aR) adenosine signaling has been identified as one of the most attractive immunosuppressive pathways, as it dampens T cell-mediated immune responses and promotes tumor immune escape. Thus, A2aR is a novel immune checkpoint. Several anti-CD73 or anti-A2aR antibodies are being evaluated in different types of malignancies in clinical trials. However, the expression characteristics and clinical significance of the CD73/A2aR adenosine immunosuppressive axis, as well as tumor-infiltrating lymphocytes (TILs) in DLBCL remain unclear.

Methods: Multiplexed immunofluorescence staining, and a professionally and automatically assessed computer-assisted platform were applied to localize and quantify the different markers from the DLBCL tumor and microenvironment cells. Gene expression status was also analyzed according to the microarray data. The associations among marker expression patterns or their correlations with clinicopathological characteristics were estimated with the χ^2 test and two-tailed Spearman analyses.

Results: CD73 expression on DLBCL tumor cells, rather than the total protein and gene levels of CD73, was associated with survival of DLBCL patients. Patients with CD73$^+$/Pax-5$^+$ (median survival, 57.8 months; 95% CI, 46.4-69.3) experienced significantly poorer outcomes than those with CD73$^-$/Pax-5$^+$ (median survival, 73.5 months; 95% CI, 65.9-81.2). Additionally, A2aR expression on both total TILs and CD8$^+$ TILs was correlated with survival of DLBCL patients. Patients with A2aR$^+$ TILs(median survival, 53.3 months; 95% CI, 40.6-66.0) had a significantly shorter survival time than patients with A2aR$^-$ TILs (median survival, 74.5 months; 95% CI, 67.5-81.5). Spearman's rank test showed that CD73 expression on DLBCL tumor cells was positively correlated with A2aR expression on TILs (R=0.395, p = 0.001). We further found that DLBCL patients could be more precisely stratified through the combination of CD73 tumor cell expression and A2aR TILs expression, and patients with CD73$^+$/Pax-5$^+$ and A2aR$^+$ TILs experienced the worst outcome. We also revealed that DLBCL patients with CD73$^+$/Pax-5$^+$ and low CD8$^+$ TILs or low absolute lymphocyte counts had unfavorable outcomes.

Conclusions: Our findings uncovered that DLBCL patients with CD73$^+$ on tumor cells as well as A2aR$^+$ on TILs or low CD8$^+$TILs exhibited inferior survival, supporting potential combination strategies using CD73/A2aR immunosuppressive blockades as treatment options for DLBCL patients.

Keywords: diffuse large B-cell lymphoma (DLBCL); immunosuppression.

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MORPHOLOGICAL EVALUATION OF THE IMMUNE PROFILE IN A SERIES OF DIFFUSE LARGE B CELLS LYMPHOMA IN TISSUE MICROARRAYS: PRELIMINARY RESULTS

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Introduction: Immunotherapy with checkpoint inhibitors is emerging as a promising new option of antitumor treatment in solid tumor but also in lymphomas. The tumoral microenvironment is regarded as playing a pronostic role and may be correlated to the good therapeutic response to checkpoint inhibitors in Hodgkin lymphoma.

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma. 60% of DLBCL patients are cured using standard chemotherapy (R-CHOP). However, 30–40% of DLBCL patients will develop relapse or have refractory disease that cannot be cured with the standard R-CHOP therapy or will suffer of adverse and toxic chemotherapy effects, indicating the need for more effective therapies for patient subsets. The establishment of predictors of treatment response and the understanding of the immunomodulationhave become a priority. Therefore, the purpose of this study is to assess the morphological immune profile by density of known immune key players, taking into account the immunecheckpoints.

Methods: A series of 189 consecutive DLBCL cases (68 female age from 20 to 94 years old with a mediane of 76 years old and 121 male, age from 20 to 92 years old, with a mediane of 66 years old, with biopsies carried out between 2010 and 2016 is investigated. Tissue microarray (TMA) samples have been collected in paraffin embedded tumor tissue. They were immunostained with cytotoxic and immune modulators antibodies, first of all with CD8 and PDL1, antibodies. A software dedicated to TMA morphometric analysis with virtual slides ("ExploraNova"; La Rochelle, France) already developped as been used, allowing to study the density of the immunostained cells.

Results: this study evidence an inverse correlation between the density of CD8 immunostained cells and the age, (Pearson: r= -0,23; p: 0,01). There was a non significant tendance of correlation between the age, and the density of PDL1 heavely immunostained lymphocytes cells (Pearson, r= -0,16, p: 0,053). But no significant correlation was found between age and the density or relative area of faint PDL1 immunostained non lymphocytes mononuclear cells (Pearson, r= 0,12, p: 0,147 and r= -0,05, p: 0,536, respectively).

Conclusions: In accordance to the progressive alterations to the immune system associated with increased mortality in the very elderly, we demonstrated the loss of cytotoxic response in the

Linear reg. of T CD8 density
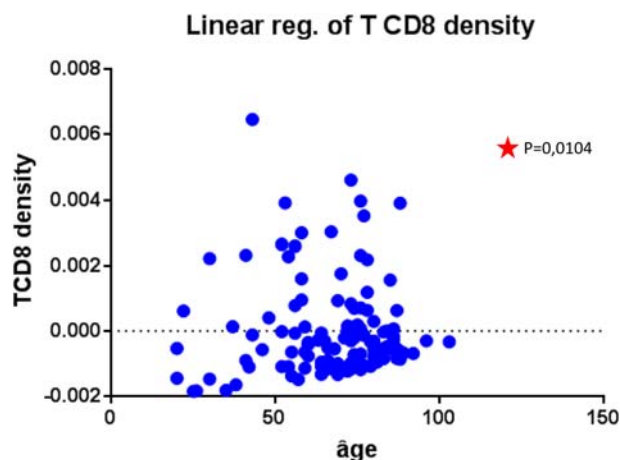
microenvironement of DLBCL, related to the age. The blockade of PDL1 immunecheckpoint seems less clearly correlated to age, according to the cells on which it is expressed.

These preliminary results evidenced the variable spectrum of the immune response in DLBCL and the need to investigate thoroughly the different parameters of the microenvironnement according to clinical, morphological and biological parameters, with the advent of new therapeutic paradigms.

Keywords: diffuse large B-cell lymphoma (DLBCL); immune system; immunohistochemistry (IHC).

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EPSTEIN–BARR VIRUS-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA FEATURES DISRUPTED ANTIGEN CAPTURE/PRESENTATION AND HIJACKED T-CELL SUPPRESSION

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Background: B-cells can function as antigen presenting cells by presenting antigens captured by the B-cell receptor (BCR) on Class II Major Histocompatibility Complex (MHCII) to T-cells. In addition, B-cells can also maintain immune homeostasis by expressing PD-L1 and suppress T-cell activity. Epstein-Barr virus (EBV) infection can disrupt B-cell function and lead to B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL). Here we show that EBV-positive DLBCL (EBV+ DLBCL) has decreased BCR and MHCII expression, but over-expressed PD-L1, which may lead to immune evasion.

Design: An EBV+ DLBCL cohort (n=30) and an EBV-negative DLBCL control cohort (n=83) were established. Immunostaining of PD-L1,

MHCII, MHCII Transactivator (CIITA) and pBTK were performed on automated stainer. H-score was used to denote the results of staining of PD-L1 and pBTK. Break apart and deletion of *CIITA* locus was studied by fluorescent *in situ* hybridization. Surface immunoglobulin mean fluorescent insensitivity (MFI) was detected by flow cytometry to demonstrate the level of BCR.

Results: EBV+ DLBCL showed significantly lower expression of CIITA and MHCII compared to EBV-negative DLBCL. Genetic aberrations involving *CIITA* were also more common in EBV+ DLBCL, with 23% break apart events and 6% deletion events, compared to 2% break apart and 0% deletion in EBV-negative DLBCL. In addition to the loss of antigen presenting molecules, the antigen capturing receptor, BCR, was also down-regulated in EBV+ DLBCL. Accordingly, BCR signaling was also significantly decreased in EBV+ DLBCL as denoted by the respective pBTK levels. Finally, EBV+ DLBCL showed over expression of the T-cell inhibitory ligand, PD-L1.

Conclusions: Antigen capture and presentation system were disrupted, and T-cell inhibitory molecule was hijacked in EBV+ DLBCL, which may contribute to immune escape in this high risk disease. Therapies targeting these aberrations may improve the outcome of patients with EBV+ DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL); Epstein-Barr virus (EBV).

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LATENT MEMBRANE PROTEIN 2A (LMP2A) MIMICS B-CELL RECEPTOR SIGNALING AND PROMOTES IMMUNE ESCAPE IN EPSTEIN-BARR VIRUS (EBV)-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Background: EBV+ DLBCL is an aggressive malignancy that is largely resistant to current therapeutic regimens. LMP2A is expressed during different latency stages of EBV-infected B cells in which it triggers activation of cytoplasmic protein tyrosine kinases. Early studies have revealed that an immunoreceptor tyrosine-based activation motif in the cytoplasmic N-terminus of LMP2A can trigger a transient increase of the cytosolic Ca^{2+} concentration similar to that observed in activated B cells. Meanwhile, tumor cells often express PD-L1 in EBV+ DLBCL, providing a possible mechanism for immune escape. We thus explored the correlations between LMP2A expression, B-cell receptor (BCR) signaling, and PD-L1 expression in EBV+ DLBCL.

Design: Two cohorts of DLBCL cases, respectively EBV-positive (n=28) and EBV-negative (n=32), were selected. LMP2A, PD-L1 and
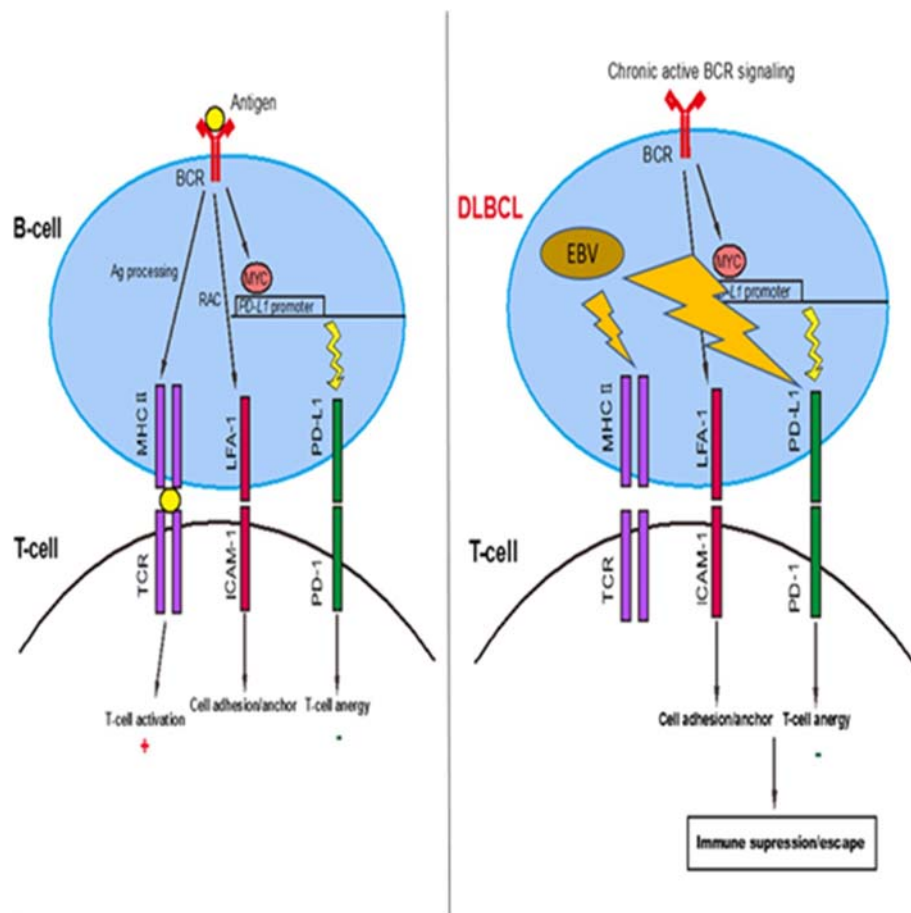
the BCR signaling-related molecule, phosphorylated form of SYK (pSYK), were immunohistochemically evaluated on formalin-fixed, paraffin-embedded tumor tissues. The expression status of LMP2A, pSYK and BCR were further validated by a flow cytometry analysis using fresh tissues from 3 EBV-positive and 5 EBV-negative DLBCL patients.

Results: The EBV-positive cases, with a median age of 61yrs, were more frequently associated with a high-risk IPI score and a non-GCB phenotype (P=0.029). Compared with EBV-negative ones, patients with EBV-positive tumors showed a worse response to the RCHOP therapy and a shorter median survival (P = 0.041). Twenty-one EBV-positive cases (75 %) expressed LMP2A, whereas none of the EBV-negative cohort expressed this protein. The expression level of pSYK was significantly lower (P = 0.0313) in EBV+ DLBCL cases than those EBV-negative ones, and the pSYK level correlated negatively with LMP2A level (P = 0.119). The expression level of PD-L1 was significantly higher (P = 0.042) in EBV+ DLBCL, which correlated positively with the LMP2A level (P=0.184). Flow cytometry confirmed the LMP2A expression in EBV+ DLBCL, which correlated with a down-regulated BCR and pSYK expression.

Conclusions: EBV+ DLBCL seems to feature an inactive BCR signaling, which may be related to the expression of LMP2A. Besides, LMP2A may function and promote the PD-L1 expression. These findings indicate that targeting immune checkpoints including PD-1/PD-L1 instead of BCR signaling molecules seems to be more reasonable and promising for the treatment of EBV+ DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL); Epstein-Barr virus (EBV).

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PROGNOSTIC IMPACT OF TUMOR-ASSOCIATED MACROPHAGES, LYMPHOCYTE-TO-MONOCYTE AND NEUTROPHIL-TO-LYMPHOCYTE RATIO IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS

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Introduction: diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of non-Hodgkin lymphomas (NHLs). Standard chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) is able to cure a significant proportion of patients; however, 30% of total cases experience relapse or have refractory disease. The international prognostic index (IPI) represents the most useful prognostic score, but it is exclusively based on clinical parameters. Previous studies showed the microenvironment has a prognostic influence in DLBCL cases; among its cellular components, tumor-associated macrophages (TAM) surely play a leading role. TAM can be classified into 2 distinct types, M1 (anti-tumor activity) and M2 (pro-tumor activity). Another prognostic factor could be represented by lymphopenia, measured as lymphocyte-to-monocyte and neutrophil-to-lymphocyte ratio (LMR and NLR), that reflects a reduced host systemic immunity.

Methods: in this study we would like to evaluate the prognostic impact of total TAM, M1 and M2 subtypes, LMR and NLR in newly diagnosed DLBCL patients. The primary objective is represented by progression-free survival (PFS). Secondary objectives are complete remission (CR) rate and overall survival (OS). We have retrospectively analyzed a cohort of 37 consecutive newly diagnosed DLBCL patients, treated between 2009 and 2013. Out of 37 patients, 28/37 (75.6%) received R-CHOP or CHOP-like regimens, 9/37 (24.4%) were treated with less intensive therapies. Treatment response was assessed according to 2007 revised criteria. Immunohistochemistry stainings were performed on paraffin-embedded sections with antibodies against CD68 (PG-M1 clone, 1:50, Dako) and CD163 (1:200, Novocastra-Leica). We have evaluated total TAM (CD68+ and CD163+) and different subtypes (CD68+, CD163+, CD68+/CD163+). We have divided our cohort in 2 categories as previously published by Steidl and colleagues; score 1-2 represented the group with low expression, while score 3 represented the group with high expression. TAM with the expression of both CD68 and CD 163 were considered as M2. For LMR and NLR we used previouly published cut-off of 2.71 and 2.81, respectively.

Results: CR rate was 70.3% (26/37 cases), 11 cases did not achieve an adequate response (5 PR, 4 SD, 2 PD). We did not report a significant correlation between total TAM, CD68+ TAM, CD163+ TAM, CD68+/CD163+ TAM, LMR, NLR and CR. We observed an association between lower expression of M2 TAM, higher expression of CD68+ TAM and improved PFS and OS, even if it did not reach a statistical significance.

Conclusion: our study suggests TAM CD68+ and especially M2 TAM could have a prognostic role for DLBCL cases receiving R-CHOP; the lack of statistical significance could be due to the small sample size. Multicenter prospective studies are needed to compare and standardize all the different available scoring methods, with the aim to perform in the future TAM evaluation at diagnosis in daily clinical practice.

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THE SIGNIFICANCE OF PD-L1 AND PD1 RECEPTORS EXPRESSION IN PATIENTS WITH DIFFUSE B-CELL LARGE-CELL LYMPHOMA

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Introduction: The treatment response of patients with diffuse B-cell large-cell lymphoma (DLBCL) depend on clinical and immunohistochemical parameters as during of diagnostics as a therapy. Such as the promising prognostic markers may be the expression of PD-L1 and PD1 receptors on tumor cells.

Material and methods: 35 patients in age from 42 to 83 years (the median was 62 years) with DLBCL have been included in analysis. All patients received 6 cycles of induction R-CHOP therapy. The period of observation was from 1 to 110 months (the median - 20 months). For PD-L1 and PD1, staining in more than 5% of tumor cells was estimated as positive expression.

Results: The positive expression of PD-L1 and PD1 was detected in 7 (20.0%) and 17 patients (51.0%) accordingly. There were no significantly age differences between groups of patients with positive and negative expression of PD-L1 (Wilcoxon rank test, p=0.2) and PD-1 (Wilcoxon rank test, p=0.29). In the group with positive PD-L1 expression all of patients (100%) had a non-GCB subtype according to the Hans algorithm. Among patients with negative PD-L1expression the GCB subtype was detected in 8 (33%), and the non-GCB subtype in 16 (67%). So there were no statistically significant differences (Fisher test, p = 0.146). In the group with positive PD-1 expression 4 (29%) patients had a GCB subtype and 10 (71%) – a non-GCB subtype of DLBCL. In negative PD-1 expression group the GCB subtype was detected in 4 (27%) and non-GCB – in 11 (63%) patients (Fisher test, p=0.146). Also we did not find statistically significantly associations between PD-L1 or PD1 positive expression and risk-groups by International Prognostic Index (Fisher test, p=0.94 [PD-L1 – IPI], p=0.54 [PD-1 – IPI]). The median of progressive-free survival (PFS) in patients with positive PD1 expression was 13 months and was not achieved in negative expression group (Hazard Ratio=1.4, 95% CI 0.4–4.84, p=0.6). In patients with

positive PD-L1 expression PFS was 100%, but in group with negative PD-L1 expression the median of PFS was 13 months (Log-rank test, p=0.6)

Conclusion: We did not find any significantly associations between PD-L1 and PD1 receptors expression on tumor cells and other known clinical and immunohistochemical parameters in patients with DLBCL as also as PFS. Maybe it is result of small sample of patients included in analysis. Further research work can show final conclusions.

Keywords: diffuse large B-cell lymphoma (DLBCL); PD-1; PD-1L.

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CLINICAL PRESENTATION AND MOLECULAR CHARACTERISTICS OF CUTANEOUS DLBCL

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Introduction: DLBCL with cutaneous manifestation shows a highly heterogeneous clinical course. We aimed to characterize molecular and clinical differences helping to assess the patient's individual risk and potential treatment options.

Methods: We identified 24 patients with cutaneous DLBCL treated at our center, 15 patients with leg-type DLBCL (LT-DLBCL) and 9 patients with cutaneous DLBCL at other anatomic sites (DLBCL-OS). Targeted sequencing was conducted for *CD79B,MYD88, CARD11* and *BTK*. Besides routine markers, we further analyzed CD30, PD-1/ PD-L1 expression and aberrations of 9p24.1.

Results: Age at diagnosis was 48 years in DLBCL-OS vs. 81 years in LT-DLBCL (p=0.001) (range 22-94 years). 92% of cases from both entities were classified as non-GCB based on the Hans Classifier. DLBCL-OS showed manifestations on the head and back, but no other region. LT-DLBCL had a higher median ki67-index with 82% vs. 67% (p=0.007). Further, 66.6% of LT-DLBCL patients had *MYD88* mutations, compared to 25% of DLBCL-OS patients. 75% of *CD79B* mutations were observed in LT-DLBCL along with the only *BTK* mutation. No *CARD11* mutations were observed in the whole cohort. Patients received a median of 2 (0-7) treatment regimen showing a highly heterogeneous response to last therapy. Patients with DLBCL-OS showed a complete remission (CR) in 89% of cases, with only 11% being refractory. LT-DLBCL showed a CR in 45%, partial remission in 9%, stable disease in 9% and refractory disease in 37%. Median overall survival (OS) was significantly different for both subtypes with LT-DLBCL patients showing a much shorter OS compared to patients

with DLBCL-OS (21 months vs. not reached, p=0.01). 77% of DLBCL-OS patients were alive at last observation.

We further evaluated markers pointing to alternative treatment options. CD20 was expressed in all cases. While PD-L1 was negative in 89% of cases and no amplification of 9p24.1 was detected, 44% of cases showed positive staining for PD1 (5-90%). CD30 expression is reported in approximately 15-30% of DLBCL, with predominance in the non-GCB subtype, but was not observed in analyzed cases of our cohort. Distinct mutational profiles in DLBCL were reported to indicate BCR pathway addiction and potential sensitivity towards ibrutinib. 43% of cases with *MYD88* mutation showed an accompanying *CD79B* mutation and in one case a *BTK* mutation. 27% exhibited a *CD79B* wild type together with a *MYD88* mutation, previously associated with BCR independence. Patients exposed to ibrutinib (n=3) showed variable responses including 2 CR, with one lasting till date.

Conclusion: LT-DLBCL presents at older age and shows a poor clinical course, in contrast to DLBCL-OS. *MYD88* mutations are frequent in LT-DLBCL. Mutational profiles and ibrutinib response were in line with previous models for sensitivity to BCR inhibition. CD30 negativity does not advocate the use of brentuximab vedotin as salvage treatment option in this setting.

Keywords: B-cell receptor (BCR); diffuse large B-cell lymphoma (DLBCL); molecular genetics.

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EVALUATION OF BONE MARROW INFILTRATION BY MULTIDIMENSIONAL FLOW CYTOMETRY IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: SUB-STUDY OF A PHASE 2 GELTAMO CLINICAL TRIAL

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TABLE 1 Prognostic impact of bone marrow infiltration by multidimensional flow cytometry

	n	CR (%)	p	ORR (%)	p	3-y PFS (%)	p	3-y OS (%)	p
Concordant	6	50		83		17		33	
Discordant	14	57		93		37		57	
Not infiltrated	34	71	0,29	83	0,39	51	0,28	74	0,16

Abbreviations: CR, complete remission rate; MFC, multidimensional flow cytometry; OS, overall survival; PFS, progression-free survival.

Introduction: Multidimensional flow cytometry (MFC) has not yet shown a high clinical value in patients with diffuse large B-cell lymphoma (DLBCL), probably due to the phenotypic heterogeneity of these lymphomas. In the present study, we have evaluated bone marrow (BM) infiltration in patients with DLBCL using MFC with the following objectives: 1) evaluating its prognostic impact compared to other techniques such as histology or PET; 2) determine the specific phenotypic pattern of the tumor cell of each patient for subsequent follow-up of minimal residual disease (MRD) after treatment.

Methods: We centrally evaluated BM samples from patients included in the multicenter randomized phase 2 clinical trial GEL-R-COMP-2013 (EudraCT: 2013-001065-17), that compares R-CHOP versus R-COMP in patients with newly diagnosed DLBCL or follicular lymphoma (FL) grade 3b. High resolution (8 colors) and high sensitivity (more than 1 million cells analyzed) direct immunofluorescence techniques were used, following the protocols defined by EuroFlow. An automatic analysis was carried out in addition to the manual analysis, using the Compass III tool, available in the Infinicyt analysis software (Cytognos, S.L.).

Results: From a total of 91 patients included in the clinical trial, 54 participated in the present study (48 DLBCL and 6 FL grade 3b). The median age was 75 years (61-86). BM infiltration was detected by MFC in 20 patients (37%) at diagnosis and 0 out of 13 at post-treatment evaluation. Regarding the phenotypic characterization, concordant BM infiltration by DLBCL was detected in only 6 cases. In contrast, discordant infiltration was detected in 14 (70%) patients, with a very heterogeneous phenotype: 3 low grade FL, 2 chronic lymphocytic leukemia, 5 marginal zone lymphoma and 4 small cell lymphoma with non-specific phenotype. Molecular studies showed monoclonal rearrangements in 14 out of 17 (82.3%) samples tested. Preliminary analysis of the prognostic impact of BM infiltration by MFC is shown in Table 1. The presence of concordant BM infiltration

Image 1: Prognostic impact of bone marrow infiltration by MFC and R-IPI
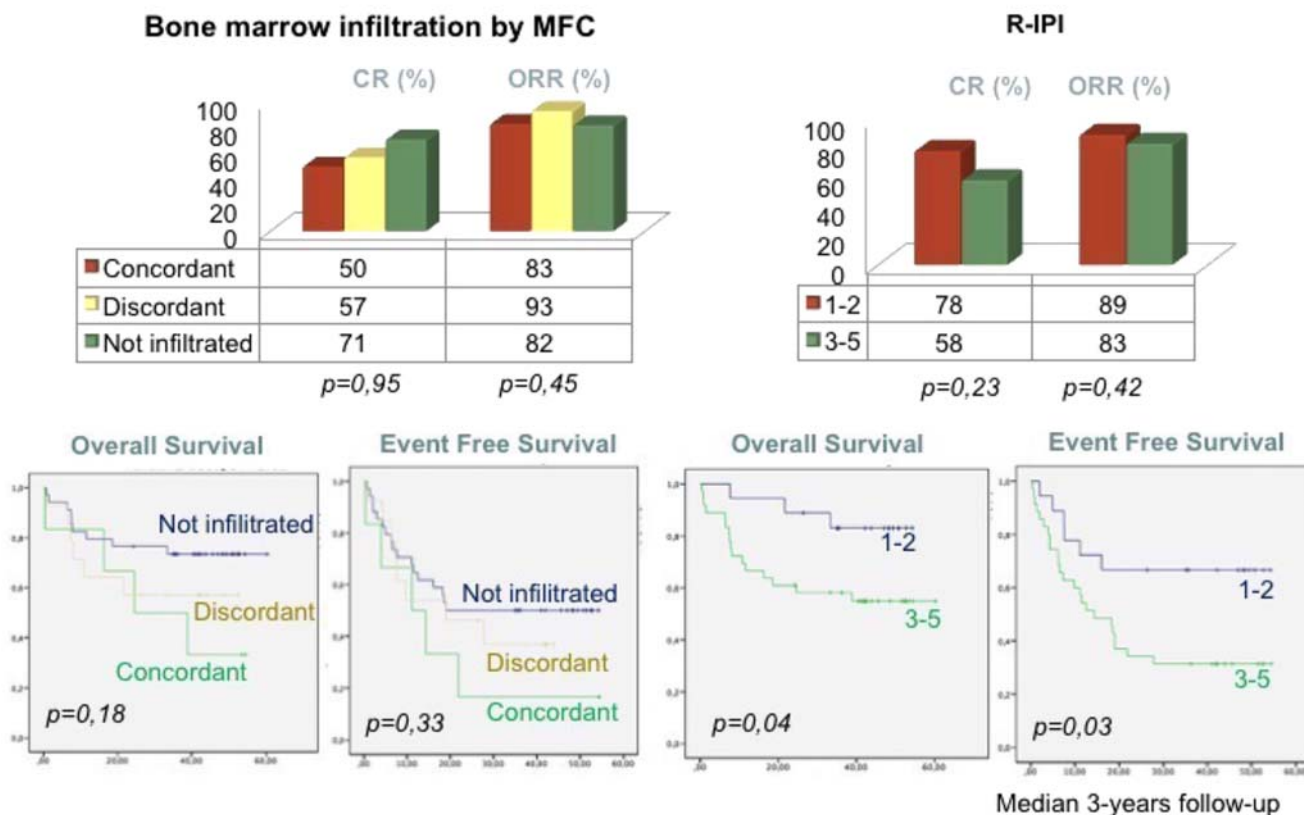
was associated with worse survival, although the differences were not statistically significant, possibly due to the low number of cases. On the other hand, discordant BM infiltration had no significant prognostic influence.

Conclusions: High resolution MFC allowed the detection of small clonal populations in BM in a very high proportion of patients with newly diagnosed DLBCL. In most cases, infiltration was discordant with tumor histology and, apparently, had no prognostic relevance. MRD was not detected in any of the cases. We plan to correlate MFC findings with those of histology and PET, also centrally reviewed, as well as to perform molecular studies on lymph node and BM samples to assess their clonal relationship.

Keywords: diffuse large B-cell lymphoma (DLBCL); flow cytometry.

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ACTIVATION OF THE AhR/ARNT PATHWAY IS ASSOCIATED WITH OUTCOME OF DLBCL PATIENTS AFTER TREATED WITH RITUXIMAB

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Introduction: As DLBCL is genetically and clinically heterogeneous, there is an increasing interest in identifying patients who gain the maximum benefit from rituximab. However, a few molecular markers have been characterized so far. Here, we sought to identify potential biomarkers that might predict outcome after rituximab.

Methods: Using the R2 Platform, a data-mining analysis was performed to sort out the genes correlated with CR to rituximab. An IHC analysis was then carried out to examine expression of these genes in biopsies of DLBCL patients who had received frontline rituximab-based regimens, as well as its relationship with PFS and OS.

Results: The data-mining analysis revealed two genes (*AhR, SPARCL1*) that were the most significantly expressed in DLBCL patients who achieved CR after rituximab, compared to those who had PD. While *SPARCL1* is a secreted soluble protein related to DLBCL microenvironment, we thus focused on *AhR*, a member of the PAS superfamily of transcription factors involved in sensing environmental signals such as hypoxia (HIF-1α, HIF-2α, HIF-3α), and its partner *ARNT* encoding HIF-1ß (the regulatory subunit of the HIF complexes). In a cohort of 93 DLBCL patients (extranodal excluded), IHC showed high nuclear

expression (>60%) of *AhR* and *ARNT* in 68% and 81% cases, respectively. With cut-off of 80% (for both genes), *ARNT* expression was significantly related to male, increased LDH level, and high IPI score (>2), but *AhR* was not. Interestingly, both of them were positively associated with expression of BCL-6 and Ki67, and *ARNT* also with MUM-1, but not BCL-2, CD10, and MYC. *AhR*expression was markedly associated with shorter PFS (HR=0.458 [0.169-0.920], P=0.034), while a similar trend was observed for *ARNT* although not significantly (HR=0.650 [0.314-1.359], P=0.260). Of note, the high level of *AhR*, rather than *ARNT*, was able to override the favorable effect of CR on PFS (P=0.652 vs P=0.002), as well as the adverse influence of high IPI score although to a lesser extent (P=0.075 vs P=0.027), but likely not on OS. In the subgroups, the unfavorable role of *AhR* was observed exclusively in GCB (P=0.044), rather than non-GCB (P=0.139). BCL-2, a marker for poor prognosis in DLBCL, no more predicted worse PFS in patients with high *AhR* (P=0.650 vs P=0.036), arguing that *AhR* expression might impair the value of BCL-2 for risk stratification. But this phenomenon was not observed in the case of *ARNT*. However, both PFS (78.6%) and OS (64.3%) of patients with high BCL-2 but low *ARNT* were obviously longer than the median PFS and OS of those with both high Bcl-2 and *ARNT*, suggesting a BCL-2-independent prognostic role of *ARNT*. Median OS for virtually all (sub)groups was not reached yet.

Conclusions: Together, these findings argue that the AhR/ARNT pathway is constitutively activated in DLBCL, suggesting a novel signal that might drive DLBCL. However, *AhR*, other than *ARNT*, might play important role in outcome prediction after rituximab, likely by interacting with other prognostic factors.

Keywords: diffuse large B-cell lymphoma (DLBCL); prognostic indices; rituximab.

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GENETIC PREDISPOSITION OF FAMILIAL HODGKIN LYMPHOMA

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Introduction: Hodgkin lymphoma (HL) is a B-cell lymphoproliferative neoplasms that affects 2.7 individuals per 100,000/yr. Risk factors include EBV infection, especially in the context of acquired or innate immunodeficiency. Despite evidence that genetic predisposition plays

an important role in a subset of HL, there is a dearth of functionally validated disease-causative genes.

Methods: We aim to identify germline genetic "drivers" of HL by applying Whole Exome Sequencing (WES) to rare, familial HL samples, followed by functional validation of prioritized candidate genes with rare, potentially pathogenic variants that co-segregate with disease within families.

Results: A pilot study on 20 affected individuals from 10 families identified between 24 and 96 such altered genes per family, 23 of which were identified in more than one. Intriguingly, they include several proteins that regulate mitosis and mitotic checkpoints, suggesting this may be an important pathway in disease. Variants in the top two of these candidate genes -(i) one involved in the first step of glycolysis and (ii) the other a cell-cycle regulated E3-ubiquitin ligase- were in vitro tested for their effects on protein function and showed a loss of function. We are further expanding the WES on an additional series of 18 families to confirm the recurrence of altered genes in familial HL and to look for somatic-second hit locally eliminating the wild-type allele, according to the classical paradigm for tumor-suppressor gene.

Conclusions: Rather than limiting ourselves to identifying a set of genes that cause disease in a few families each, we propose to use pathway-analysis to identify shared molecular disease mechanisms.

(*Nisha Limaye and Hélène A. Poirel: Equal contribution)

Keywords: Hodgkin lymphoma (HL); molecular genetics.

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'NOT SO CLASSICAL': A STUDY OF THE IMMUNOPROFILE IN CLASSICAL HODGKIN LYMPHOMA, AN EXPERIENCE FROM A REFERRAL CENTER

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Introduction: According to WHO classification, Classical Hodgkin Lymphoma (CHL) expresses CD15 and CD30 antigens in majority of cases, and CD20 in a small subset of cases. Expression of CD20 may affect the patients' prognosis, relapse, and refractoriness to the therapy. We come across a subset of cases of CHL in our lymphoma consultation cases that exhibit a lack of the 'positive' diagnostic marker CD15 and express CD20 in the Hodgkin and Reed-Sternberg (HRS) cells. This observation has important prognostic implication, based on the western studies from the more developed world, and furthermore prompted us for a systematic evaluation of the immunoprofile of South-East Asian CHL patients and to compare those with the Western data.

Methods: In this retrospective analysis, 111 cases of CHL diagnosed over a period of six months were studied. Demographics, clinical details, histopathological (including unusual morphologic patterns),

and immunohistochemical (IHC) parameters were recorded. The diagnoses were made according to the 2016 WHO classification of lymphoid neoplasms. The cases were further subtyped. The IHC panel included CD45, CD15, CD30, CD3, CD20, PAX5, ALK1, and EBV (LMP-1) in all cases and MUM1, CD21, EMA, PD1, OCT2, BOB.1, and BCL6, in a subset of cases, wherever necessary. A case was designated CD20+, if >10% of HRS cells were strongly positive.

Results: The cases of CHL fit into 'textbook phenotype' (WHO 2016 update) of CD15+, CD30+, CD20- in 54% cases. HRS cells were positive for CD30 in all, CD15 in 56%, PAX5 in 96%, CD20 in 18% cases and EBV (LMP1) in 58.3% cases. In majority of instances, morphology and an initial panel of CD3, CD20, CD15, CD30, CD45, and PAX5 were sufficient for diagnosis. When IHC pattern discordance was noted or mimics of CHL were in the differential diagnostic consideration, additional markers supported the diagnosis of CHL.

Conclusions:

1. Our study results broaden the understanding of the demographic, histopathologic, and IHC characteristics of CHL cases.

2. The second peak of bimodal distribution occurs two decades earlier as compared to those of the western population in majority cases in our cohort.

3. 56% of our cases expressed CD15 that is lower than the reported positivity rates (75% to 85%).

4. Significant CD20 positivity in HRS cells as seen in our cohort can create diagnostic dilemma. However, CD45 negativity in the presence of weak to barely perceptible PAX5 and moderate to strong expression for EBV aid in arriving at a diagnosis of CHL.

5. Future directions: The management of CHL is essentially based on radiotherapy and chemotherapy, due to lack of information about the clinical outcomes with anti-CD20 antibody therapy or combined drug therapy using a classic regimen. The prognostic impact of lack of CD15 and positive CD20 expression in the cases of CHL requires further research and clinical follow-up studies in a larger cohort of patient to assess the role of CD20 in the pathophysiology and progression of CHL.

Keywords: CD20; classical Hodgkin lymphoma (cHL); immunohisto-chemistry (IHC).

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PRE-T CELL RECEPTOR SIGNALING DRIVES LEUKEMOGENESIS AND IS A THERAPEUTIC TARGET IN T CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive lymphoid neoplasm that results from the malignant transformation of T-cell progenitors. The biology of T-ALL is strongly influenced by its developmental origins. For example, mutations in *NOTCH1*, a critical regulator

of thymocyte development, are found in approximately 60% of patient tumors. Less is known, however, about the extent to which other determinants of thymocyte development participate in the leukemogenesis of T-ALL. Using a thymus transplantation-based, spontaneous mouse model of T-ALL, we found that multiple β-selection checkpoint factors were upregulated in leukemic T cells, including Ptcra, a subunit of the pre-T cell receptor (pre-TCR) complex. Genetic ablation of *Ptcra* in the mouse model dramatically reduced the occurrence of T-ALL. In human T-ALL cell lines, CRISPR/Cas9 knockout of *PTCRA* reduced in vitro proliferative capacity and the ability to form tumors in vivo. Analysis of clinical T-ALL datasets and patient samples demonstrated that *PTCRA* is highly and specifically expressed in leukemic T cells but not in normal, mature T cells, suggesting an appropriate therapeutic window for targeted therapy in T-ALL. Cumulatively, our findings highlight an important role for pre-TCR signaling in driving and sustaining T-ALL and support the further evaluation of PTCRA-directed therapies in T-ALL.

Keywords: Notch pathway; T-cells.

Disclosures: Kuhnert, F: Employment Leadership Position: *Regeneron Pharmaceuticals Inc.*

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THE EVALUATION OF THE CLINICOPATHOLOGIC CHARACTERISTICS OF T-CELL NON-HODGKIN'S LYMPHOMA: THE SINGLE CENTER EXPERIENCE

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Aim: T-cell lymphoma is a subgroup of non-Hodgkin's lymphoma with different morphological, immunological and clinical features that constitute approximately 10-15% of all lymphomas. In this study, we aimed to evaluate the clinical stages, histopathological diagnosis, treatment and response of T cell lymphoma patients in Hacettepe University Department of Hematology.

Method: 62 T cell lymphoma patients who followed between 2002 and 2018 in Hacettepe University Faculty of Medicine Department of Hematology were included in the study. Patients were evaluated retrospectively with imaging studies and pathological reports and classified according to the National Comprehensive Cancer Network (NCCN Guidelines Version 4.18) classification. Overall survival was analysed by evaluating the treatments which the patients were taken and response of the treatment.

Results: The number of patients diagnosed with T-cell lymphoma (n = 62) were 8% of all lymphoma cases followed in our department at this period. Of the 62 patients enrolled in the study, 8% were stage I, 17% were stage II, 29% were stage III and 46% were stage IV according to Ann Arbor staging. 9 patients with anaplastic type,

4 angioimmunoblastic type, 3 extranodal NK / T cell lymphoma nasal type, 4 enteropathy related T cell lymphoma, 2 follicular type, 6 hepatosplenic type, 10 T cell large granular lymphocytic leukemia (T-LGL) and 22 unclassifiable peripheral T cell lymphoma. Sixty patients (96.7%) were treated. 52 patients out of T-LGL, 18 (34.6%) received CHOEP chemotherapy as the firstline therapy and 27 (51.9%) received CHOP chemotherapy however, hematopoietic stem cell transplantation was performed in 18 of 52 patients (34.6%). Complete remission was achieved in 63.2% of the patients who received CHOP chemotherapy and this rate was 72% in CHOEP chemotherapy (p: 0.23). The median survival of patients who underwent hematopoietic stem cell transplantation (98.5 months) was higher than the patients who did not (71.8 months) but the difference was not statistically significant (p = 0.160). Median overall survival was 126.7 months [1 - 168.5 months], 5-year survival was 64.3% and 3-year survival was 74% in the whole study group. The group having the lowest overall survival was hepatosplenic T-cell lymphoma whose survival was 18.9 [1 - 89.3] months. It was significantly lower than the other groups (p = 0.020). In cox regression analysis, non-response to initial therapy was an independent prognostic factor for overall survival (OR = 11.6, p = 0.001).

Conclusion: T-cell lymphoma is a type of non-hodgkin lymphomas, consisting of several subgroups with different pathologies and different clinical features. Pathology and clinical difference inevitably affect treatment and prognosis. Each case of T cell lymphoma should be approached by considering these differences.

Keywords: R-CHEOP; R-CHOP; T-cell lymphoma (TCL).

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POTENTIAL METABOLITES WITH DIAGNOSTIC VALUE IN PLASMA FOR ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA BY LC-MS BASED UNTARGETED METABONOMICS STUDY

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Introduction: Angioimmunoblastic T-cell lymphoma (AITL) is an uncommon subtype of mature peripheral T-cell lymphoma (PTCL). And its characteristics is not fully understood. Because it is a rare form of lymphoma, there is difficulty in diagnosis based on current traditional method. Metabolic reprogramming is a major cancer hallmark, which provides cancer cells with vital energy and metabolites. Mass spectrometry-based metabolomics has emerged as an informative technique for profiling metabolic features associated with cancers. This study aims to discover metabolites with potential diagnostic value in plasma of AITL patient.

Methods: Plasma was collected from 27 patients newly diagnosed with AITL in Zhejiang Cancer Hospital and 30 age- and gender- matched healthy controls. An aliquot of 50 μL plama was added with 150 μL of chilled acetonitrile, vortexed and centrifuged. the supernatant was dried, reconstituted for metabolomics. Mass spectrometry analysis was performed on a UPLC coupled with a Q Exactive Orbitrap mass spectrometer. "XCMS" and "MetaX" were used to analyze LC-MS data. Significant features were selected as candidate for identification by matching their MS and MS/MS data with online databases HMDB and METLIN.

Results: Eighteen altered metabolites (choline, betaine, L-leucine, creatine, 2-butyl-1H-benzimidazole, hypoxanthine, methionine sulfoximine, L-carnitine, 2-hydroxycinnamic acid, L-tyrosine, D-tryptophan, indoleacrylic acid, lysoPC(P-18:0), 5-aminopentanoic acid, uric acid, sucrose, L-lactic) were indentified (VIP value>1, p<0.05) in AITL patient plasma. The altered metabolites contributed to different metabolic pathways including glycine, serine and threonine metabolism (P=0.003), glycerophospholipid metabolism (P=0.024), Phenylalanine metabolism (P=.030).

Conclusion: This study revealed metabolic reprogram and potential diagnostic metabolites in plasma for AITL, and gave more metabolic information for carcinogenesis of AITL.

Keywords: angioimmunoblastic T-cell lymphoma (AITL).

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PROGNOSTIC SIGNIFICANCE OF PD-L1 AND PHOSPHORYLATED ERK EXPRESSION IN T-CELL LYMPHOMA: PD-1/PD-L1 AXIS ACTIVATES INTRACELLULAR ERK SIGNALING IN TUMOR CELLS
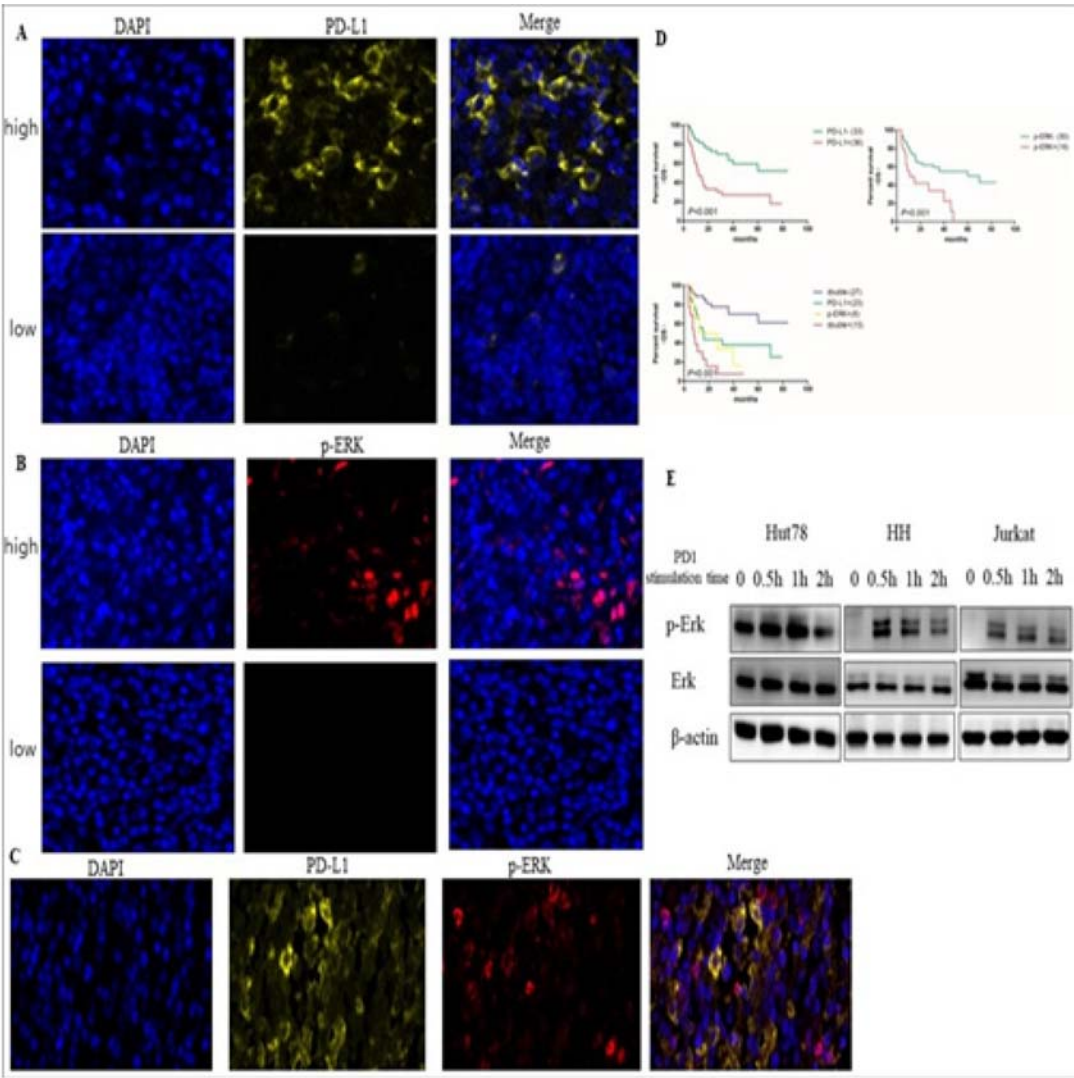
Fig.1. Expression of PD-L1, p-ERK, overall survival, and PD-1/PD-L1 binding directly activates the intracellular ERK1/2 oncogene signaling in T-cell lymphoma.

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Introduction: Programmed death ligand-1 (PD-L1) engages with PD-1, which leads to an exhaustion of antitumor T-cell responses. PD-L1 is a type I transmembrane protein with 290 amino acids, including immunoglobulin V-like and C-like domain. Structural analysis also shows that there is a protein kinase c (PKC) on PD-L1 cytoplasmic domain, suggesting that it may be involved in the activation of intracellular signal transduction. The purpose of this study was to investigate the prognostic significance of PD-L1 and phosphorylated ERK (p-ERK), and their interactions in T-cell lymphoma (TCL).

Methods: Multiplexed immunofluorescence staining was performed to visualize the expression of PD-L1 and p-ERK using the Opal immunostaining. Flow cytometry was used to quantify the membrane PD-L1 (mPD-L1) expression on TCL cell lines. Total PD-L1 expression in TCL cell lines, and the level of ERK and p-ERK were measured using western blotting. The associations among PD-L1, p-ERK expression and clinicopathological characteristics were estimated with two-tailed Spearman analyses. Kaplan-Meier analyses were used to compare survival curves.

Results: We found that the expression rate of PD-L1 and p-ERK were 52% and 28% in TCL cases, respectively. Spearman test showed that PD-L1 expression was correlated with stage (R=0.217, P=0.037), and p-ERK expression was correlated with stage (R=0.283, P=0.009), IPI score (R=0.321, P=0.004) and subtype (R=0.211, P=0.041). Meanwhile, PD-L1 expression was positively correlated with p-ERK expression (R=0.200, P=0.049). Survival analysis showed that TCL patients with PD-L1 and p-ERK positivity had significantly poorer outcome than those with their negativity (P=0.008 and P<0.001), respectively, and those patients with co-expression of PD-L1 and p-ERK had the worst OS (P<0.001). In three TCL cell lines with PD-L1 expression, we further found that the expression of p-ERK was upregulated after stimulation of PD-1, suggesting that ERK signaling was activated.

Conclusions: Our findings demonstrated that PD-1/PD-L1 axis activated intracellular ERK signaling in tumor cells, and PD-L1, p-ERK or their combination were potential biomarkers to predict prognosis for TCL patients.

Keywords: ERK; PD-1; T-cell lymphoma (TCL).

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COMPREHENSIVE IMMUNOHISTOCHEMICAL ANALYSIS OF IMMUNE CHECKPOINT MOLECULES IN ADULT T-CELL LEUKEMIA/LYMPHOMA

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Introduction: Adult T-cell leukemia/lymphoma (ATLL) is an aggressive hematopoietic malignancy with poor prognosis. As immune checkpoint inhibitors have improved the clinical outcome of some refractory tumors, understanding their role in ATLL is of interest. We previously reported that programmed cell death ligand 1 (PD-L1) expression on neoplastic and/or microenvironmental stromal cells could predict prognosis of ATLL. However, other immune checkpoint molecules have not been well studied in ATLL. We performed comprehensive immunohistochemical analysis of immune checkpoint molecules in ATLL and examined the clinical outcome.

Methods: Formalin-fixed, paraffin-embedded biopsy samples from 71 ATLL patients were reviewed. Immunohistochemistry was performed on a DAKO autostainer with the following antibodies: PD-L1, CD134, CD134L, CD137, CD137L, Galectin-9, Tim-3, CTLA-4, LAG-3, CD80, CD86, PD-L2, GITR, GITRL, and PD-1. Neoplastic expression of immune checkpoints was considered positive at ≥30% positive neoplastic cells, and microenvironmental expression was defined as positive in patients with ≥10 positive stromal cells per high power field.

Results: Immune checkpoint molecules were variably expressed on ATLL neoplastic and/or stromal cells. Neoplastic PD-1, CD134, galectin-9, GITRL, and PD-L1 expression was nearly mutually exclusive, suggesting that immune checkpoint pathways differ in patients.

TABLE 1 Prognostic factors affecting the DSS of ATLL patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
miPD-L1^{+}	0.4209 (0.2165-0.8310)	0.0134*	0.2541 (0.1077-0.5766)	0.0011*
miCD134L^{+}	0.4090 (0.1525-0.9238)	0.0303*	0.2815 (0.0782-0.8333)	0.0207*
nGalectin-9^{+}	3.2327 (1.1847-7.5349)	0.0244*	3.7671 (1.2946-9.6958)	0.0172*
Age (>70)	3.0763 (1.5750-6.1601)	0.0001*	4.5924 (2.1352-10.3178)	<0.0001*
JCOG-PI (high)	1.8401 (0.9038-3.6389)	0.0911	1.4582 (0.6681-3.1094)	0.3366
Ann Arbor Stage (III or IV)	1.0509 (0.4967-2.6114)	0.9058	0.9710 (0.3711-3.0010)	0.9557
eleated LDH	1.7837 (0.7943-4.7616)	0.1703	1.7862 (0.7113-5.2146)	0.2265

Patients with microenvironmental PD-L1 (miPD-L1$^+$) or CD134L (miCD134L$^+$) expression showed significantly better disease-specific survival (DSS) than that in miPD-L1$^-$ or miCD134L$^-$ groups (P = 0.00807 and 0.0407, respectively). Conversely, patients with neoplastic galectin-9 expression (nGalectn-9$^+$) had significantly inferior DSS than nGalectin-9$^-$ patients (P = 0.0072,). Univariate and multivariate analyses with clinical prognostic factors identified miPD-L1, miCD134, and nGalectin-9 expression and age (>70 y) as significant prognostic factors.

Conclusions: This is the first comprehensive analysis of ATLL immune checkpoint molecules. Our results may provide information on new therapeutic strategies in ATLL.

Keywords: human T-lymphotropic virus (HTLV); immunohistochemistry (IHC); PD-1L.

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SAFETY AND EFFICACY OF ULTRASOUND-GUIDED COARSE NEEDLE BIOPSY IN THE DIAGNOSIS OF SUSPECTED LYMPHOMA

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Background: Accurate lymph node staging and sampling through biopsy is critical for diagnosis and accurate staging of lymphoma patients. The current study aims to investigate the safety and value of standardized a minimally-invasive Ultrasound-guided Core Needle Biopsy (UGCNB) in patients with suspicion of lymphoma.

Methods: UGCSB was performed in 367 patients suspected of lymphoma from January 2017 to July 2018. Biopsies were performed using 16-G or 18-G needle collecting At least 2 and up to four 4 tissue samples were collected. All needle adequate biopsies (at least two connected tissue longer than 0.5 cm) were formalin-fixed, paraffin-embedded, and hematoxylin–eosin (HE) stained according to regular protocol.

Results: Out of 367 patients underwent UGCNB, there were 58 patients (16%) diagnosed with lymphoma, 107 patients (29%) diagnosed with metastatic cancer, 99 cases (27%) with benign tumour, and 103 cases (28%) with unclear diagnosis. Out of the 58 patients diagnosed with lymphoma, there were 23 cases of Diffuse large B-cell lymphoma (DLBCL), NOS, 9 cases of (Follicular lymphoma, 7 cases of Classic Hodgkin lymphoma, 6 cases of small lymphocytic lymphoma, 3 cases of Mantle cell lymphoma, 2 cases of Angioimmunoblastic T-cell lymphoma, and 2 cases of Peripheral T-cell lymphoma, NOS. There were also 1 case each of Anaplastic large cell lymphoma, Plasma cell myeloma, Plasmablastic lymphoma Nodal marginal zone

lymphoma, and T-lymphoblastic leukaemia/lymphoma. Up until February 28, 2019 no patients of 99 patients diagnosed as benign tumour have been diagnosed with lymphoma.

Conclusion: The current study demonstrates that standardized UGCNB is a safe and effective method of diagnosing lymphoma. Our protocol help optimizes the sampling procedure and preserves the minimally-invasive nature of the protocol. Further studies using UGCNB in combination with molecular diagnostic tools such as immunohistochemistry and/or in-situ hybridization could provide even more diagnostic information.

Keywords: fine-needle aspirate (FNA); non-Hodgkin lymphoma (NHL).

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IMAGE-GUIDED CORE BIOPSY IS SAFE AND EFFECTIVE FOR THE DIAGNOSIS OF LYMPHOMA

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Introduction: Excisional biopsy (EB) from nodal or extranodal sites is the standard technique to reach an accurate histological classification and to establish the definitive diagnosis of lymphomas. Advances in knowledge in flow cytometry, genetics and molecular analyses, image-guided core biopsy (IGCB) could be an alternative to EB in most cases.

Methods: In this study, we compare the safety and efficacy for the diagnosis of lymphoma between image-guided core biopsy (IGCB) and

TABLE 1

	Image-guided core biopsy (IGCB)	Excisional biopsy	P
Age (years, median)	66 (19-93)	58 (10-87)	0.026
Tree or more comorbidities	72 (80.9%)	30 (60%)	0.007
Interval between suspicion and biopsy (days, median)	9 (0-119)	23 (5-109)	<0.0001
Time from diagnosis to treatment (median)	14 (0-364)	27 (4-436)	0.029
Complications (n° of patients)	Haemorrhage (1)	Severe pain that needed morphine treatment (1) Delayed healing process (1)	

excisional biopsy in 117 patients who have suspicious radiological findings of lymphoma and 32 hematology patients with a possible recurrence.

149 consecutive lymphoma patients diagnosed between January 2016 and December 2017 were analysed in this study. IGCB was carried out in 89 patients. Among them, ultrasonic-guided IGCB was performed in 45 patients and CT-guided IGCB in 44. EB was performed in 50 patients. The efficacy and safety of both techniques were analysed by standard statistical methods.

Results: Nodal localization was mediastinal or abdominal (non-palpable) in 47 IGCB-diagnosed patients (52.8%), but only in 7 EB-diagnosed patients (14%). IGCB-analysed patients were older and had more comorbidities. Compared with EB, the diagnosis was faster and the treatment was initiated sooner in IGCB-analysed patients (table 1). Sample enough to be sent to pathology exam was obtained by IGCB in 89 patients (100%), to flow cytometry in 86 (96.6%), and to genetic analysis in 84 (94.4%). There was a complete concordance (100%) among the results obtained by flow cytometry, genetic and molecular analyses in those patients diagnosed by excisional biopsy, but only in 81 IGCB-diagnosed patients (91%). In 4 of those non concordant cases, the definitive diagnosis was further established by EB. The rate of complications was low with both techniques and no statistical differences were observed.

Conclusions: IGCB is an effective and safe alternative to EB for lymphoma diagnosis. Compared with EB, IGCB may be even less risky for older patients that have associated comorbidities. Another advantage of image is that non palpable lymph nodes can be visualized and biopsied. IGCB is also faster, since avoids the waiting list for surgery, and allows starting the treatment sooner. Inconclusive diagnoses using IGCG were infrequent. In those ambiguous cases, EB may be used to definitely diagnose the patients.

Keywords: flow cytometry.

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VALIDATION OF REAL-TIME MULTIPLEX LIGATION PROBE AMPLIFICATION (RT-MLPA) TO ANALYZE LYMPHOMA TRANSCRIPTOME FROM FORMALIN-FIXED PARAFFIN EMBEDDED SAMPLES

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Introduction: Real-time multiplex ligation probe amplification (RT-MLPA) is a new technique allowing for the concomitant amplification of several RNA from various tissues. It uses gene-specific probes targeting regions supposed to be close together on RNA molecules such as fusion transcripts but also normally coded exons. In the latter case, it can provide a precise idea of the landscape of gene expression in a given condition. Recent data have suggested that it may also be applied to poor-quality RNA extracted from formalin fixed paraffin embedded biopsies. This could allow to investigate for new markers in lymphomas.

Methods: With the aim of applying this methodology to lymph nodes from patients with mantle cell lymphoma (MCL), we first tested its feasibility on 7 MCL cell lines. The latter were obtained from the American Tissue Cell Collection (ATCC), Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ), graciously provided by Pr Chen Kiang or derived locally from patients. A panel of oligonucleotides was designed targeting RNA from *CCND1*, *SOX11*, Ki-67 and genes of the TP53 pathway. According to the principle of RT-MLPA, these oligonucleotides, tagged with size markers, were mixed with extracted RNA previously retrotranscripted in cDNA. After a time allowing for potential hybridization, ligase was added to link adjacent probes. Denaturation then removed the initial cDNA and ligated probes were amplified by PCR. The amplicons were then analyzed by capillary electrophoresis (3500XL). Hybridized probes yielded a size-specific signal and the height of each peak was proportional to the amount of RNA initially present in the preparation. In parallel, 6 of the cell lines were tested in gene expression profiling (GEP) (n=6) or sequenced by RNA-Seq (Illumina, n=3). Finally, RT-MLPA was also applied to 16 MCL FFPE lymph node samples and compared to 17 from diffuse large B-cell lymphomas (DLBCL).

Results: An expected high signal for *CCND1*, and significant levels of Ki67, were obtained in all cell lines while 6 had variable levels of *SOX11*. All results satisfactorily compared to RNA Seq and GEP data of the same cell lines. Exploration of the *TP53* pathway disclosed a highly heterogeneous pattern among cell lines. Signals were interpretable in all RNA samples from FFPE lymph nodes but one, disclosing also between-patient heterogeneity. However, of interest, significantly different patterns were observed between MCL and DLBCL, with an overexpression of the TP53 pathway in the latter.

Conclusion: This work confirms the feasibility of the RT-MLPA technique to properly detect and semi-quantify MCL-related transcripts. The method was validated on representative MCL cell-lines. Its application to FFPE samples was demonstrated to be also feasible. This paves the way to further investigations of the transcriptome of lymphomas.

Keywords: diffuse large B-cell lymphoma (DLBCL); expression arrays; mantle cell lymphoma (MCL).

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CeVi: A UNIQUE CRYOPRESERVED HUMAN VIABLE CELL COLLECTION FROM LYMPHOMA PATIENTS, A CALYM INITIATIVE TO ACCELERATE INNOVATION AND ITS TRANSFER TO LYMPHOMA FIELD

TABLE 1

CeVi_Collection samples a March 2019									
Subtypes						**Origin**			
		Cases	%	Vials			Cases	%	Vials
B-NHL	Follicular Lymphoma	309	19.6	1143		**Nodes**	801	50.9	3355
	Diffuse Large B-cell Lymphoma	203	12.9	690		**Blood**	407	25.9	1313
	Marginal Zone Lymphoma	197	12.5	835		**Spleen**	154	9.8	716
	Mantle Cell Lymphoma	131	8.3	518		**Marrow**	133	8.5	453
	Other B NHLs*	234	14.9	1044		**Tonsil**	54	3.4	314
T-NHL		85	5.4	275		**Others**	24	1.5	94
Hodgkin Lymphoma		160	10.2	586		**TOTAL**	1573	100	6245
Others**		14	0.9	78					
Non Tumoral		240	15.3	1076					
TOTAL		**1573**	100	**6245**					

* e.g. Waldenström, lymphocytic lymphoma, …
** e.g. Castelman, post-transplant lymphoma diseases
NHL: Non Hodgkin lymphoma
CeVi collection comprises a median 10M viable cells/vial (SD = 4.2), with a median 4 vials/sample. All samples are clinically and biologically annotated. Dry pellets and plasma are available for 70% and 12% cases, respectively. 180 lymph nodes are paired with PBMC +/- BM.

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Introduction: Lymphomas are among the most heterogeneous diseases. Over 80 subtypes have been defined on the basis of clinical, morphological, phenotypical, genetic and molecular criteria. Today, the fine functional characterization of tumors within their microenvironment appears highly recommended, but remains poorly addressed due to the lack of comprehensive viable cell collections.
Here, the CALYM Carnot Institute* reports the generation of a unique and comprehensive collection of viable cells from over 1000 clinically annotated patient samples.
*LYSA, LYSARC & 13 top French academic labs www.calym.org

Materiel and Methods

- CeVi collection is built around 6 CeVi platforms supported by local Biological Resource Centers under CALYM's umbrella
- CeVi collects lymph nodes (LN), peripheral blood (PBMC), bone marrow (BM) and other lymphoma proliferation sites (e.g. spleen)
- Both, sample processing and storage are standardized & certified NF S96-900 (French QA policy), CeVi management is certified ISO 9001
- All viable cell samples are annotated, after anonymization, with clinical and biological data (authorized by French data protection authority, CNIL)
- Informed consent is available and validated by *ad hoc* ethical committee
- Sample requests are evaluated by a steering committee and granted based on scientific interest and sample subtype rarity.

Results: Since 2013, CeVi has collected a total of 1616 samples (6658 vials) from 1297 patients, and more than 1573 samples (>6200 vials) are available. All classic and rarer lymphoma subtypes have been collected in routine practice (Table1).

Cession of CeVi samples is open for both academic researchers and private partnerships (request: partnering@calym.org). CeVi contributed to CALYM research programs and led to 4 publications in rank A journals. Two major industrial partnerships, currently under CDA, will be disclosed in 2019.

Conclusions: The generation of a comprehensive collection of lymphoma viable cells is feasible and valuable.

CeVi is a unique human lymphoma viable cell collection from LN, BM and PBMC, clinically and biologically annotated. The collection comprises a critical number of samples with a steady in/out flow, allowing academic and industrial partnerships. CeVi is connected to LYSA/LYSARC databases, including REALYSA real life study, and others projects such as the Lymphoma Data Hub linked to Artificial Intelligence & machine learning.

Keywords: B-cell lymphoma; Hodgkin lymphoma (HL); T-cell lymphoma (TCL).

Disclosures: NADEL, B: Honoraria: *Amgen, Celgene, Gilead, Sanofi*; Research Funding: *MedImmune, Roche*. **BASEGGIO, L:** Consultant Advisory Role: *TAKEDA*; Research Funding: *TAKEDA*. **CARTRON, G:** Consultant Advisory Role: *Roche, Celgene*; Honoraria: *Sanofi, Gilead, Jansen, Roche*. **FEST, T:** Research Funding: *Roche*.

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EPIDEMIOLOGY REVIEW OF LYMPHOMA IN A SINGLE INSTITUTION IN MALAYSIA

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Introduction: The subtype distribution of lymphoma reveals diverse geographic and ethnic variations. There is limited information available in regards to the epidemiologic distribution and survival outcome of lymphoma in the South East Asia regions. In this study, we report a single institutional data of patients with lymphoma in Malaysia.

Methods: We obtained data of patients diagnosed with lymphoma treated by the adult haematology unit between 1996 and 2018 from the hospital's electronic medical record. The diagnosis were retrieved from the pathology report and then grouped into non Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Demographic data of age, gender, ethnicity and histopathology (HP) pattern were collected. Only patients who had a minimum of 5 years follow up were analysed for survival outcome.

Results: A total of 708 cased were identified. The median age of the patients was 55.5 years (range, 14-89 years). The male-to-female ratio was 1.1:1. Majority were of Chinese ethnic origin (52.5%) followed by Malay (34.9%) and Indian (10.6%). 84.7% were diagnosed with NHL and 15.3% were HL. Among the NHL diagnosis, 72.5% were B cell in

origin of which the two leading HP subtypes were diffuse large B-cell lymphoma (DLBCL) (71.7%) and follicular lymphoma (FL) (7.8%). T cell lymphoma constitutes 6.1% of NHL. With a median follow-up duration of 80.75 months, the overall survival (OS) of HL was significantly better than that of patients with NHL (88.4% vs 70.2%, P =0.001). Patient age below 60 years had better OS than older age group (79.7% vs 63.3%, P=0.000). The main cause of death from the available retrieved record were lymphoma related (42.7%).

Conclusions: The HP subtypes of lymphoma in Malaysia are similar to what was reported in the Asia regions where HL remains relatively uncommon when compared to the western population. The frequency of FL is uncommon and T cell lymphoma is comparable to what was also reported in other western countries. Compared to other Asian countries, it appeared that the prevalence of DLBCL and HL in Malaysia is higher. The overall survival rates are comparable to other countries. The major cause of death remained as disease related.

Keywords: diffuse large B-cell lymphoma (DLBCL); Hodgkin lymphoma (HL); non-Hodgkin lymphoma (NHL).

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HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY OF MALIGNANT LYMPHOMAS

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Introduction: The morphologic classification of lymphomas in the field of hematopathology includes different techniques such as immunohistochemistry and genotypic studies in order to appropriately classify and subclassify these entities according to the WHO Classification; so, the patients can receive the best treatment.

Objective: The study with immunohistochemical technique was to classify the different anatomopathological entities of these neoplastic lymphoid processes.

Material and Methods: We studied 1813 biopsies of different sites diagnosed such as malignant lymphomas at the Pathology Department of the National Oncology Institute, Havana City, Cuba, from the period of 2007 to 2018 with a panel of different antibodies for

hematolymphoid processes employing the technique of immunohisto-chemistry in paraffin blocks. The manual and automated immunohis-tochemical staining were used. The visualization systems included the Polymer Detection System and the ultraview Universal DAB Detection Kit.

Results: The Non-Hodgkin´s B Cell Lymphomas were the most frequent immunophenotypic type (1303 cases)(71,86%).The B Cell Lymphomas CD20 positive were 1184 cases (65,03%).The most frequent histopathological type was the Diffuse Large B Cell Lymphomas (649 cases)(35,79%).The Peripheral T Cell Lymphomas (76 cases) and Anaplastic Large Cell Lymphomas (61 cases) were the most principal types diagnosed in the group of Non-Hodgkin´s T Cell Lymphomas (137 cases in total)(7,55%).The extranodal location were 868 cases (47,87%) and the Head and Neck location was the most common site diagnosed in this group (180 cases) (20,73%).

Conclusion: The study demonstrated the different histologic types, locationand frequencies of the lymphomas in our daily work of a period of time of 12 years in the Immunohistochemistry Laboratory at the Pathology Department.

Keywords: anaplastic large cell lymphoma (ALCL); diffuse large B-cell lymphoma (DLBCL); peripheral T-cell lymphomas (PTCL).

CLL

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PTBP1 REGULATES ALTERNATIVE SPLICING OF APOPTOTIC PROTEIN: IMPLICATIONS IN CLL AND IBRUTINIB RESISTANCE

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Introduction: Ibrutinib, an oral, selective inhibitor of Bruton's tyrosine kinase (BTK), dramatically improved Progression-free survival (PFS) and Overall survival (OS) compared with immunochemotherapy in CLL both in first line and relapsed/refractory patients. However, some patients did progress on ibrutinib with dismal outcome. The underlying mechanism remains to be investigated beyond evolving of BTK and/or PLCg2 mutation, the dysfunction of apoptotic protein and mitochondrial apoptotic dependencies may be involved in ibrutinib resistance. PTBP1 (Polypyrimidine tract binding protein 1), a splicing factor, was found to be necessary for B cell selection in germinal centers. Knocking out PTBP1 in B cell resulted in impaired BCR-mediated B-cell activation and antibody production. Here, we investigate the regulation of PTBP1 on alternative splicing of apoptotic protein and its implications in CLL and ibrutinib resistance.

Methods: Eighty-one CLL patients and 5 healthy controls were enrolled in this study from January 2010 to May 2018. The PTBP1 mRNA expression was measured by real-time polymerase chain reaction (RT-PCR) and Western-blot. We analyzed the PTBP1 expression with established CLL prognostic factors such as p53 and IGHV mutation status, and treatment to first treatment (TTFT). Resistant MEC-1 cell line was established by intermittently incubating with ibrutinib at a low concentration for short intervals and then gradually increased to 2-fold of IC50 value. Cells were allowed to recover every time after washing off the drug. RT-PCR was performed for both long and short
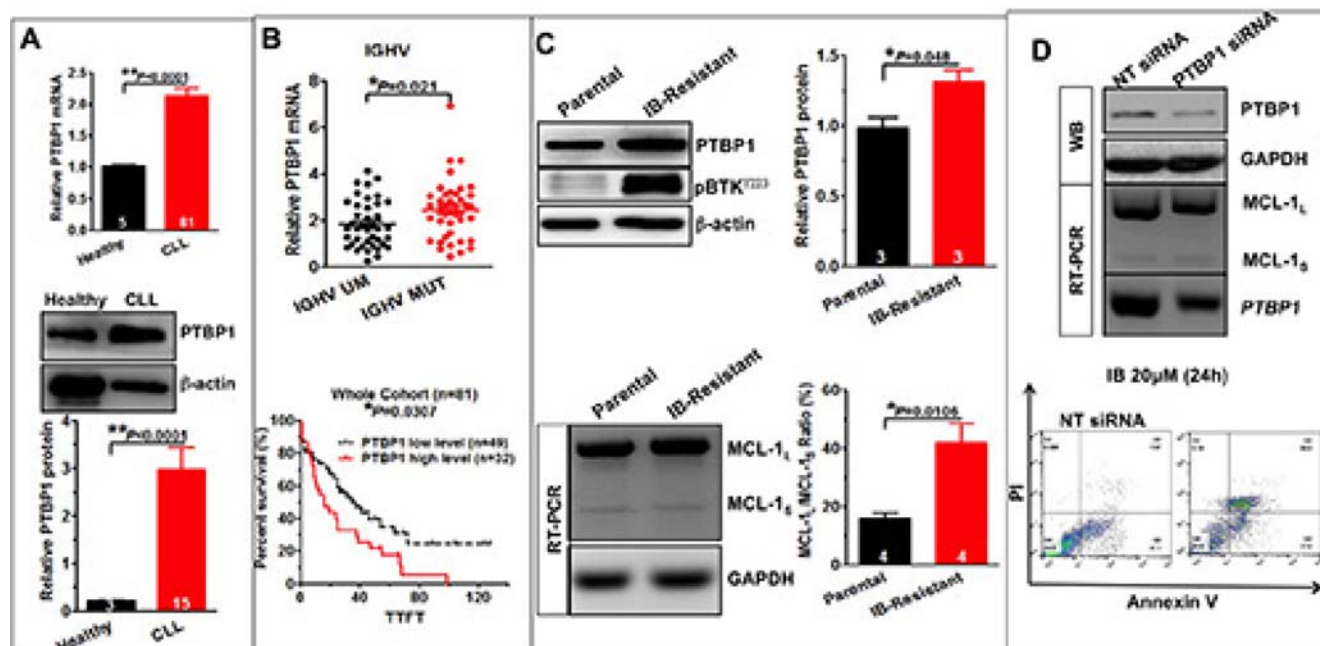
isoform of MCL-1 by using specific primer in both parent and resistant cell lines and paired ibrutinb resistant patients primary cells. Resistant MEC-1 cell line was cultured in RPMI 1640 without ibrutinib for 48hrs before transfection, siRNA targeting with PTBP1 mRNA and non-targeting siRNA were transfected into cells by using lipofectamine 3000. The transfection efficiency was verified by Western blot after 24 h and ibrutinib was added into resistant cell line. Apoptosis was then analyzed using flow cytometry (FCM) after 24 hrs. Receiver operating characteristic curve (ROC) and area under the ROC curve (AUC) were established to verify the best cut-off value in differentiating the high or low expression of PTBP1 mRNA. Time-to-first-treatment (TTFT) interval was defined as interval from diagnosis to first treatment. All statistical analyses were performed using the SPSS software program.

Results: The expression of PTBP1 in CLL primary patients was significantly increased than 5 healthy donors ($p < 0.01$)(A). Patients with IGHV-mutated had higher level of PTBP1 as compared with patients with IGHV-unmutated ($p < 0.05$). Furthermore, Higher level of PTBP1 was associated with shorter TTFT in whole cohort, also in IGHV-mutated and unmutated subgroup ($p < 0.05$)(B). We further demonstrated that PTBP1 was aberrant expressed in ibrutinib resistant MEC-1 cell line or ibrutinib resistant primary patients' samples, as compared with parent cell line or patients' baseline samples. We also found the dysregulation of alternative splicing of MCL-1 in ibrutinib resistant models, presented with increased anti-apoptotic MCL-1$_L$ and decreased pro-apoptotic MCL-1$_S$(C). Moreover, knocking down of PTBP1 sensitized CLL to ibrutinib via switching alternative splicing of MCL-1 to its pro-apoptotic isform MCL-1$_S$(D).

Conclusions: The splicing factor PTBP1 is involved in the pathogenesis of CLL. Its aberrant expression may lead to the dysregulation of alternative splicing of MCL-1, resulted in increased MCL-1$_{L/s}$ ratio. PTBP1 can be as a promising target for the treatment of CLL patients progressed on ibrutinib.

Keywords: chronic lymphocytic leukemia (CLL); ibrutinib.

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EBV-MIR-BHRF1-1 TARGETS P53 GENE: POTENTIAL ROLE IN EPSTEIN-BARR VIRUS ASSOCIATED CHRONIC LYMPHOCYTIC LEUKEMIA

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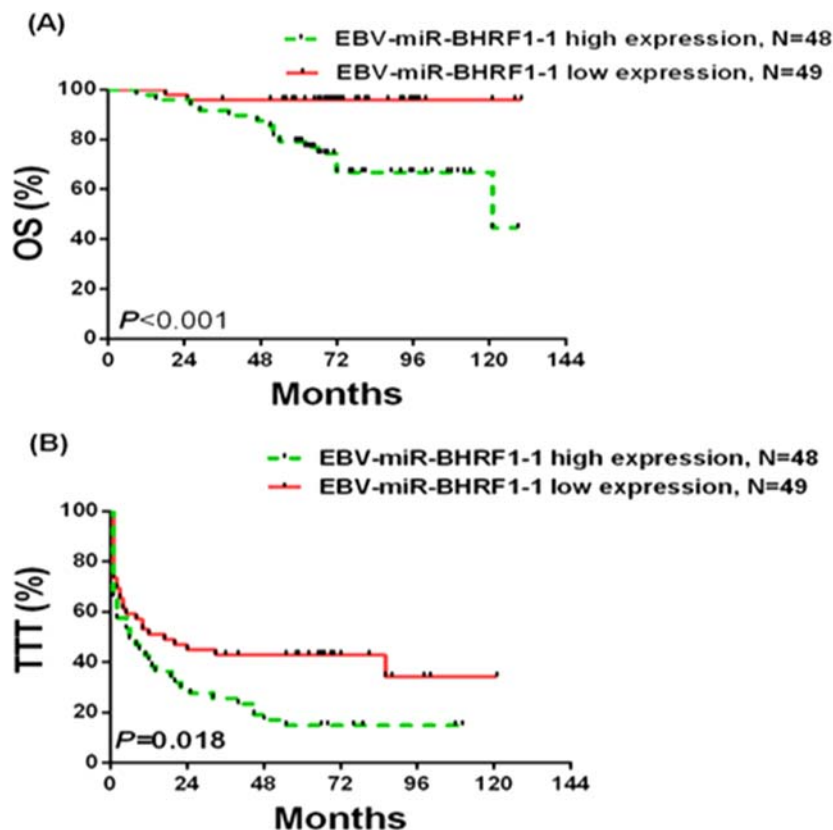
Figure 1. Time to treatment (TTT) and overall survival (OS) curve of 97 patients with CLL based on EBV-mir-BHRF1-1 by Kaplan-Meier estimation. Low group value is below the cut-off value (0.0012), and high group above the cut-off value.

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Introduction: Epstein-Barr virus (EBV) was the first virus shown to encode viral microRNAs (miRNAs). To date, 44 mature miRNAs of EBV were classified into two clusters (BHRF1 cluster and BART cluster). Our previous study showed that nearly 10.0% of newly-diagnosed chronic lymphocytic leukemia (CLL) patients had high level of EBV-DNA viral load in whole blood. Furthermore, a positive blood EBV-DNA test at diagnosis was significantly associated with inferior time-to-treatment (TTT) and overall survival (OS) in CLL patients. p53 gene has a vital role in the disease-progress, clone evolution and drug-resistance for CLL patients. Until now, no therapies can fully overcome the inferior prognosis caused by p53 aberration even in the era of the emerging of so many molecular targeted drugs such as BTK inhibitor and Bcl-2 inhibitors. One of the members of the BHRF1 miRNAs, EBV-miR-BHRF1-1, was found to bind to the 3'UTR of p53, suggesting that p53 may be a target of EBV-miR-BHRF1-1. These findings provide one of the potential mechanisms by which EBV can promote CLL development through its miRNA functions.

Methods: Quantitative reverse transcription–PCR (qRT–PCR) and western blotting were used to quantify EBV-miR-BHRF1-1 and p53 expression in cultured CLL and to validate the role of EBV-miR-BHRF1-1 targeting p53.

Results: p53 aberration was associated with higher expression level of EBV-miR-BHRF1-1 ($P<0.001$) which was also an independent prognostic marker for overall survival (OS) ($P=0.028$; HR 5.335 [1.193, 23.846]) in 97 newly-diagnosed CLL patients after adjusted with CLL-international prognostic index (CLL-IPI) (**Figure 1**). In this study, we identified EBV-miR-BHRF1-1 as a viral miRNA regulator of p53. EBV-miR-BHRF1-1 repressed luciferase reporter activity by specific interaction with the seed region within the p53 3' untranslated region. Discordance of p53 messenger RNA and protein expression was associated with high EBV-miR-BHRF1-1 levels in CLL patients and cell lines. EBV-miR-BHRF1-1 inhibition upregulated p53 protein expression, induced cell cycle arrest and apoptosis and decreased cell proliferation in cell lines. EBV-miR-BHRF1-1 mimics downregulated p53 protein expression, decreased cell cycle arrest and apoptosis, and induced cell proliferation in cell lines.

Conclusions: The interaction between EBV-miR-BHRF1-1 and p53 may be one of the mechanisms by which EBV-miR-BHRF1-1 promotes EBV-positive CLL. Our results support the potential of EBV-miR-BHRF1-1 as a therapeutic target in EBV-associated CLL with p53 gene aberration.

Keywords: chronic lymphocytic leukemia (CLL); Epstein-Barr virus (EBV); P53.

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THE tRNA-DERIVED RNA FRAGMENTS (tRFs) BEARING THE GLYCINE ANTICODONS GCC AND CCC AS EMERGING MOLECULAR BIOMARKERS OF

UNFAVORABLE PROGNOSIS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: This original research study evaluated, for the first time, the prognostic potential of internal tRNA-derived RNA fragments (tRFs) bearing the Glycine anticodons GCC (i-tRF-GlyGCC) and CCC (i-tRF-GlyCCC) as novel molecular biomarkers in chronic lymphocytic leukemia (CLL).

Methods: Peripheral blood mononuclear cells (PBMCs) from 91 CLL patients and 43 non-leukemic blood donors were evaluated. Cell immunophenotyping showed that most PBMCs isolated from patients' blood samples were leukemic B cells. The mutational status of the immunoglobulin heavy chain variable (*IGHV*) region was specified using Sanger sequencing. Total RNA was extracted from PBMCs and *in vitro* polyadenylated using *Escherichia coli* poly(A) polymerase, prior to first-strand cDNA synthesis with an oligo-dT–adaptor primer, using MMLV transcriptase. This reaction was optimized, so as to exclude reverse transcription of complete tRNA molecules. Subsequently, a real-time quantitative polymerase chain reaction (qPCR) method was developed for the quantification of particular tRNA fragments and applied in all samples. The small nucleolar RNAs *RNU43* and *RNU48* were used as reference genes, to normalize tRF expression.

Results: The results show that i-tRF-GlyCCC was downregulated in PBMCs (mostly leukemic B cells) of CLL patients, compared to PBMCs of non-leukemic controls. On the other hand, no significant differences in i-tRF-GlyGCC levels were observed. An optimal cutoff value for each tRF was first defined by statistical analysis. The expression status of each tRF was then compared with other established prognostic factors, in terms of overall survival (OS). In Kaplan-Meier OS analysis of the entire cohort of patients, positive i-tRF-GlyGCC and/or i-tRF-GlyCCC expression proved to be a significant predictor of reduced OS ($P≤0.001$). Univariate Cox regression analysis for OS revealed a statistically significant hazard ratio (HR) of 3.40 for i-tRF-GlyGCC–positive CLL patients (HR=3.40, 95% CI=1.61-7.18 $P=0.001$). Bootstrapping Cox in regression analysis enhanced these results. ($P<0.001$). Moreover, i-tRF-GlyCCC–positive expression was associated with inferior OS of CLL patients (HR=3.95, 95% CI=1.60-9.74, $P=0.003$, Bootstrap $P<0.001$). Multivariate Cox regression analysis revealed that the prognostic value of i-tRF-GlyGCC and i-tRF-GlyCCC is independent of other prognostic factors in CLL, including Binet and/or Rai stage, CD38 expression, and *IGHV* mutational status.

Conclusions: To the best of our knowledge, this study shows, for the first time, that internal tRFs bearing the Glycine anticodons GCC and

CCC (namely: i-tRF-GlyGCC and i-tRF-GlyCCC) could be considered as emerging, molecular prognostic biomarkers in CLL.

Keywords: chronic lymphocytic leukemia (CLL).

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RESULTS OF MUTATIONAL STATUS OF IMMUNOGLOBULIN HEAVY-CHAIN VARIABLE GENES ANALYSIS IN A COHORT OF PATIENTS WITH B-CLL. A SINGLE CENTRE EXPERIENCE

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Background: The mutational status of the variable region of the Immunoglobulin heavy-chain (IGHV) gene is one of the most robust prognostic markers in Chronic Lymphocytic Leukemia (CLL), allowing the identification of 2 groups with different clinical behavior. Those with no or few somatic mutations (unmutated CLL, UM-CLL) with a more aggressive course of their disease, and those with a heavier load of mutations (mutated, M-CLL), with a more indolent disease. European Research Initiative on CLL (ERIC) has defined clear guidelines for Immunoglobulin gene sequence analysis.

Materials and Methods: Patients with CLL in our institution were studied for productive IGHV rearrangements and its mutational status. There were no exclusion criteria for the analysis of this prognostic marker. IGHV-D-J gene rearrangements and mutational status were analyzed between 6/2016 and 2/2019. Nucleic acid used was genomic DNA (gDNA) and ERIC guidelines were followed. High molecular weight DNA was isolated from all patients and amplified using forward Leader primers combined with JH reverse consensus primer. In those cases, in which leader primers were unsuccessful at providing a product that could be sequenced, VH FR1 primers were used. Direct bidirectional sequencing was performed and Stereotype B cell receptors were analyzed.

Results: From 150 samples received and analyzed, 138 productive IGHV-IGHD-IGHJ rearrangements were identified, 12 patients had insufficient leukemic cells for the analysis. Of 138 patients 54 (39%) were UM-CLL and 84 (61%) were M-CLL. Within this last group, 12 were considered "borderline" M-CLL. The most frequent IGHV family in this series was IGHV3, followed by IGHV4 and IGHV1. Double rearrangements were detected in 16 of the cases. Stereotype B cell receptors were found in 16 patients.

Conclusion: These results show a slightly higher incidence on M-CLL than the published data. We believe this is due to a high proportion of asymptomatic patients with no need of treatment, in this cohort. The most frequent used IGHV family was IGHV-3 while IGHV4 and IGHV1 were in second and third place, respectively. The frequency of Stereotyped BcRs was lower from those observed in western countries cohorts. These results support previous published experience in other Latin American countries. Longer follow up will be necessary to determine the impact of this molecular factor in the clinical behavior of this group of patients.

Keywords: gene rearrangement; immunoglobulins (Ig).

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CHANGES IN CONCENTRATION OF SERUM FREE LIGHT CHAINS OF IMMUNOGLOBULINS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AS A FACTOR FOR EVALUATING CHEMOTHERAPY EFFECTIVENESS

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Goals: To evaluate effectiveness of chemotherapy in patients with chronic lymphocytic leukemia (CLL) by measuring changes in concentrations of serum free light chains of immunoglobulins (sFLC) and light chain (LC) expression on circulating B-lymphocytes of peripheral blood (PB).

Material and methods: 10 patients with newly diagnosed CLL were recruited for this study. Concentrations of sFLC were measured by Freelite^{TM} method (The Binding Site, UK). Immunophenotyping of PB lymphocytes was performed by 4 color flow cytofluorometry (BD FACSCalibur, USA). All patients received FCR-therapy (Rituximab 375 mg/m2, i.v.; Fludarabine 25 mg/m2, i.v.; Cyclophosphamide 250 mg/m2, i.v.). The cycle was repeated every 4 weeks. Disease stage and chemotherapy effectiveness were evaluated by IWCLL 2008 criteria. 5 patients had stage II, 5-stage IV Rai. Standard clinical tests, measurements of sFLC concentrations and LC expression on PB B-lymphocytes were performed at the time of diagnosis, before and after chemotherapy cycle. Patients received 6 FCR cycles.

Results and Discussion: At presentation 6 of 10 patients had monoclonal increase of sFLC, whereas 4 patients did not demonstrate monoclonal changes in sFLC concentrations. Changes in sFLC concentrations, κ/λ-ratio of LC expression on PB circulating B-lymphocytes, absolute blood lymphocytosis and a clinical response to therapy were analysed. A decrease in serum concentrations of tumor sFLC was achieved on average up to 63,1% (35,0% -83,3%). It correlated with normalization of sFLC κ/λ ratio (normal range 0,4-0,69). Complete remission (CR)-2 patients; partial remission (PR)-2 patients. In those 4 cases, κ/λ ratio of LC on membrane of PB lymphocytes was normalized, and absolute lymphocytosis was approaching the normal range. In the remaining 2 of 6 patients, no decrease in tumor sFLC

concentration was observed, whereas κ/λ ratio of LC on PB B-cell lymphocyte was normalized, no absolute lymphocytosis was present, and a clinical improvement was noted. Therefore, sFLC has higher sensitivity in determining residual disease compared with standard treatment evaluation criteria. sFLC κ/λ ratio normalization can serve as an additional criterion for antitumor therapy effectiveness due to visualization of minimal residual disease in CLL patients. In 4 of 10 patients with no initial sFLC clonal changes 1 patient had CR, and 3-PR. In above 4 patients increases in sFLC secretion were polyclonal and reflected the state of normal antibody-producing cells. 1 patient had concentrations of both κ and λ sFLC on the low range, which indicated a humoral deficit.

Conclusion: Changes in sFLC concentrations and their κ/λ ratio can serve as a high-sensitivity criterion for evaluating chemotherapy effectiveness in patients with CLL.

Keywords: chemotherapy; chronic lymphocytic leukemia (CLL); minimal residual disease (MRD).

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FOXP1, PD-1 AND PD-L1 ARE SIGNIFICANTLY UPREGULATED IN LYMPHOCYTES FROM CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS COMPARED TO AGE-MATCHED HEALTHY DONORS

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Background: Age-associated immunodeficiencies increase the probability of developing malignant hemopathies including chronic lymphocytic leukemia (CLL). One reason could be due to the accumulation of genetic/epigenetic changes leading to deregulation of transcriptional programs in lymphocytes. The transcription factor FOXP1 is a key regulator of B cell development and abnormally expressed in B cell malignancies. We investigated the significance of FOXP1 and inhibitory immune checkpoint (PD-1, PD-L1 and TIM-3) expression in the major lymphocyte subsets from CLL patients (pts) to investigate their contribution to a malignant/exhaustion phenotype.

Population and methods: Peripheral blood mononuclear cells were isolated from 101 individuals [40 untreated CLL; 60 healthy donors (HD)]. T and B cells were purified by magnetic bead isolation or FACS sorting. FOXP1, PD-1, PD-L1 and TIM3 transcripts were quantified using RT-qPCR. Nuclear labeling of FOXP1 followed the labelling of membrane markers and data was acquired by flow cytometry. The prognostic value of FOXP1 expression in purified CD19^{+} leukemic B cells was analyzed retrospectively in a cohort of 184 CLL pts and correlated with clinical parameters.

Results: FOXP1 gene/protein expression in CD4^{+}, CD8^{+} T cells and leukemic B cells was significantly higher in untreated CLL pts compared to age-matched HDs. Analysis of FOXP1 gene expression in our retrospective CLL cohort confirmed increased expression in the leukemic-B cells. Higher FOXP1 expression was correlated with worse overall survival of CLL patients in this cohort (p=0.0165). There was no correlation between FOXP1 and Binet stages or IGHV mutation status. PD-1 and TIM-3 expression on T cells and PD-L1 expression on B cells was analyzed to determine whether an exhausted phenotype was associated with CLL and aging. These data reveal that PD-1 (transcripts/protein) is significantly upregulated on CD4^{+}/CD8^{+} T cells in the older vs younger HD groups and further increased on T cells from CLL pts in comparison with age-matched HD. High PD-L1 expression (transcripts) was significantly correlated with increased age in HD B cells, and again further increased in the leukemic-B cells. A trend toward an inverse correlation between FOXP1 and PD-1 was observed in CD4^{+}/CD8^{+} T cells. TIM-3 expression (transcripts/protein) in T cells was very low in our CLL cohort.

Conclusions: We show that FOXP1 is significantly upregulated on T and B cells from CLL patients with its higher expression associated with worse overall survival. Higher PD-1 and PD-L1 expression on T and B cells from older HD, which is even more pronounced on CLL patients, suggests that impaired immune functions may in part be due to the inhibitory immune checkpoint expression. Current investigations are examining the role of FOXP1 in T and B cell functionality and immune checkpoint molecule expression with age.

Keywords: chronic lymphocytic leukemia (CLL); PD-1; PD-1L.

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THE IMPACTS OF ZANUBRUTINIB ON IMMUNE CELLS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

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Introduction: Ibrutinib, a first-generation Bruton tyrosine kinase (BTK) inhibitor, could improve immunity of relapsed or refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) patients. Whether zanubrutinib, a second-generation BTK inhibitor, has similar effects as ibrutinib remains to be determined.

Methods: Dynamics of number and immunophenotype of immune cells during zanubrutinib treatment in 25 R/R CLL/SLL patients were examined by flow cytometry and blood routine tests.

Results: The expression intensity of programmed cell death protein 1 (PD-1) on total CD4^{+}, total CD8^{+} and T helper cells, and cytotoxic T lymphocyte-associated antigen-4 on total CD4^{+} (*P*=0.010) and regulatory T cells (*P*<0.05) reduced after treatment (*P*<0.05). There were significant differences in expression intensity of CD19 (*P*<0.01), C-X-C chemokine receptor type 5 (CXCR5) (*P*<0.01) and CD49d (*P*<0.05) on B cells before and after treatment. Down-regulation of PD-1 on T cells and CXCR5 and CD19 on B cells were observed in nearly all patients after zanubrutinib treatment. The number of B cells and programmed death-ligand 1 expression down-regulated, especially in the young, CLL, normal spleen, normal β2-macroglobulin (β2-MG), abnormal lactate dehydrogenase (LDH) and normal *tumor protein 53* subgroups, while CD49d expression tended to decrease in the male, old, CLL, splenomegaly, abnormal β2-MG and abnormal LDH subgroups after zanubrutinib treatment.

Conclusions: These findings suggest that zanubrutinib can regulate immunity primarily by improving T cell exhaustion, inhibiting suppressor cells and disrupting CLL cells migration through down-regulation of adhesion/homing receptors. Furthermore, favorable changes in cell number and immunophenotype were preferably observed in patients without adverse prognostic factors.

Keywords: BTK inhibitors; chronic lymphocytic leukemia (CLL); immunophenotype.

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REAL WORLD OUTCOMES OF OBINUTUZUMAB MONOTHERAPY IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: Obinutuzumab (OBI) is approved for use in combination with chlorambucil for patients (pts) with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in both frontline and relapsed/refractory (r/r) settings. OBI has been successfully evaluated as a single agent without significant loss of efficacy (Gay ND, Leuk. Lymphoma 2018). We performed an analysis of all CLL/SLL pts treated with OBI monotherapy at our institution to assess efficacy and safety in any line of therapy.

Methods: We conducted a retrospective cohort study of all adult pts who received OBI monotherapy for CLL at the University of Pennsylvania between 2/2013 and 2/2019. Demographics, duration of therapy, reason for discontinuation, overall response, survival, and toxicities were examined. The primary endpoints were progression-free survival (PFS; defined as time from OBI start to disease progression or regimen change, death due to CLL or last-follow-up in remission), and overall survival using the Kaplan-Meier method.

Results: We identified 40 pts with CLL/SLL for this analysis. Median age of start was 70 years, Rai stage 2 (35% $\geq$3), and ECOG performance status 1. Most pts were rituximab naïve (58%) and 20% were rituximab refractory. Frontline use was seen in 53% of pts received OBI frontline and 47% were treated for r/r disease. 9 pts were documented with progression and 4 patients met indication for subsequent therapy. At this time, 7 pts are receiving active OBI treatment. 55% of pts followed the package insert recommended schedule of OBI administration. Overall response rate was 90% (10% CR). The median PFS and OS for the entire cohort was 11.5 and 16.5 months respectively.

At least 1 adverse events (AEs) occurred in 90% of pts. AEs included infusion related reactions (63%), thrombocytopenia (43%), infection (23%), neutropenia (15%), diarrhea (10%), neutropenic fever (8%). All pts with infusion reactions experienced symptoms on the first dose (92% grade 2; 8% grade 3), with 6 pts experiencing more than one infusion reaction in the first cycle. One patient stopped therapy after experiencing a severe grade 3 infusion reaction. One patient had an opportunistic infection (*Rhizopus* sp.).

Conclusions: We describe our experience using OBI as monotherapy. AEs, while expected and manageable, were observed frequently in our

Progression Free Survival

Overall Survival
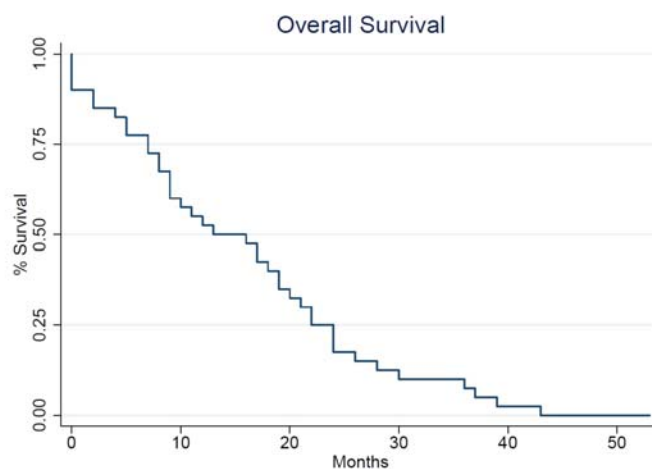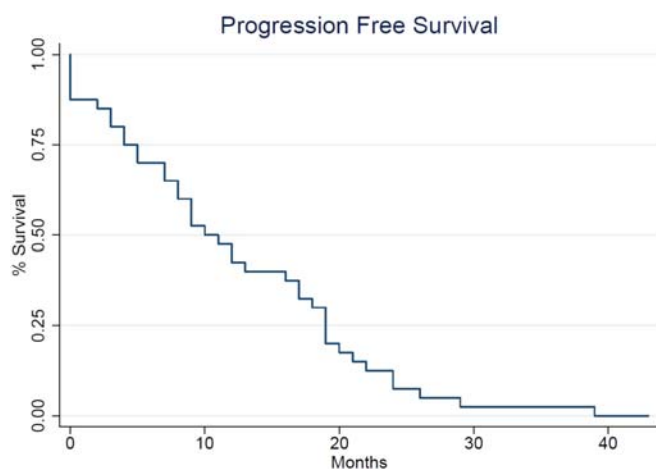
cohort, suggesting potential overlap with immunodeficiency seen with CLL/SLL pts. Most surprisingly is the high rate of infusion related reactions; however, these were mainly confined to grade 2 reactions and grade 3 reactions were much lower than in the CLL11 trial (Goede V, NEJM 2014). While PFS is shorter compared to CLL11, this reflects both pts not completing therapy, as well as including pts in the r/r setting. Regardless, OBI remains an effective and well tolerated agent in both frontline and r/r pts with CLL/SLL who may not be eligible for other therapies.

Keywords: chronic lymphocytic leukemia (CLL); obinutuzumab.

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ROLE OF CHLORAMBUCIL IN COMBINATION OR NOT WITH ANTI-CD20 AS FRONTLINE THERAPY IN CHRONIC LYMPHOCYTIC LEUKEMIA IN "REAL LIFE"

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Introduction: Recently, different studies have shown superiority of ibrutinib in progression-free survival (PFS) over chlorambucil or chlorambucil in combination anti-CD20 in the treatment of chronic lymphocytic leukemia (CLL) in first line. Some guidelines consider that the role of chlorambucil is obsolete. However, despite superiority in PFS, no benefit in overall survival (OS) has been observed. Moreover, anti-CD20 chlorambucil combination has been used in population with comorbidities in which life expectancy, either by age or comorbidities, is short. Therefore, the benefit of ibrutinib in this

TABLE 1 General characteristics of the patients

TOTAL PATIENTS	n=20
Sex (M/F)	80/20
CIRS ≥6	15 (75%)
Binet C	7 (35%)
FISH:	
13q-	8 (40%)
+12	4 (20%)
11q-	1 (in combination with 13q-)
17p-	0
No aberrations	1 (5%)
Not done	7 (35%)
First line therapy:	
- Clorambucil (Cl)	2 (10%)
- Rituximab + Cl	11 (55%)
- Obinotuzumab + Cl	7 (35%)
DEAD PATIENTS	n=10
Desease statys at time of dead:	
- Active	5 (50%)
- In progresssion	2 (20%)
- Complete remission	3 (30%)

population is controversial, in addition to an exponential increase in drug cost.

Aims: Analyze characteristics and the evolution of patients diagnosed of CLL treated with chlorambucil in monotherapy or in combination with antiCD20 in first line, in real life.

Methods: A retrospective study of patients with CLL in University Hospital of Alava, between January 2012-2019, whose frontline therapy is chlorambucil in monotherapy or in combination with antiCD20. Comorbidities were assessed using the CIRS scale (Cumulative Illness Rating Scale for Geriatrics), and time to next treatment (TTNT), OS and disease status at the time of death were also recorded.

Results: 16 men and 4 women were included, with a median age of 81 years (75-86) and a median CIRS score of 7 (2-15), additional characteristics are shown in table 1. With a median follow-up of 35 months, the PFS was 30 months, while the median TTNT was 40 months and OS was 59 months (figure 1). It should be noted that 7 of the 10 patients died without receiving a second line therapy, although 70% of them had active disease at the time of death. The cause of death were: infections (3), pulmonary thromboembolism (1), sudden death (1), progression to acute leukemia (1) and uncontrolled primary immune thrombocytopenia and hemolityc anemia.

Conclusions: In our setting, CLL patients requiring treatment with Chlorambucil +/- antiCD20 are older and have more comorbidities than patients reported in the published clinical trials. 70% of patients died without requiring a second line therapy. Therefore, in terms of therapeutic efficiency and also regarding pharmaco-economy, chlorambucil-antiCD20 continues to be a valid alternative in unfit patients.

Figure 1.

OVERALL SURVIVAL

Median OS: 59,03 months
10 dead
10 alive

PROGRESSION FREE SURVIVAL

Median PFS: 30 months

TIME TO NEXT TREATMENT

Median TTNT: 40 months
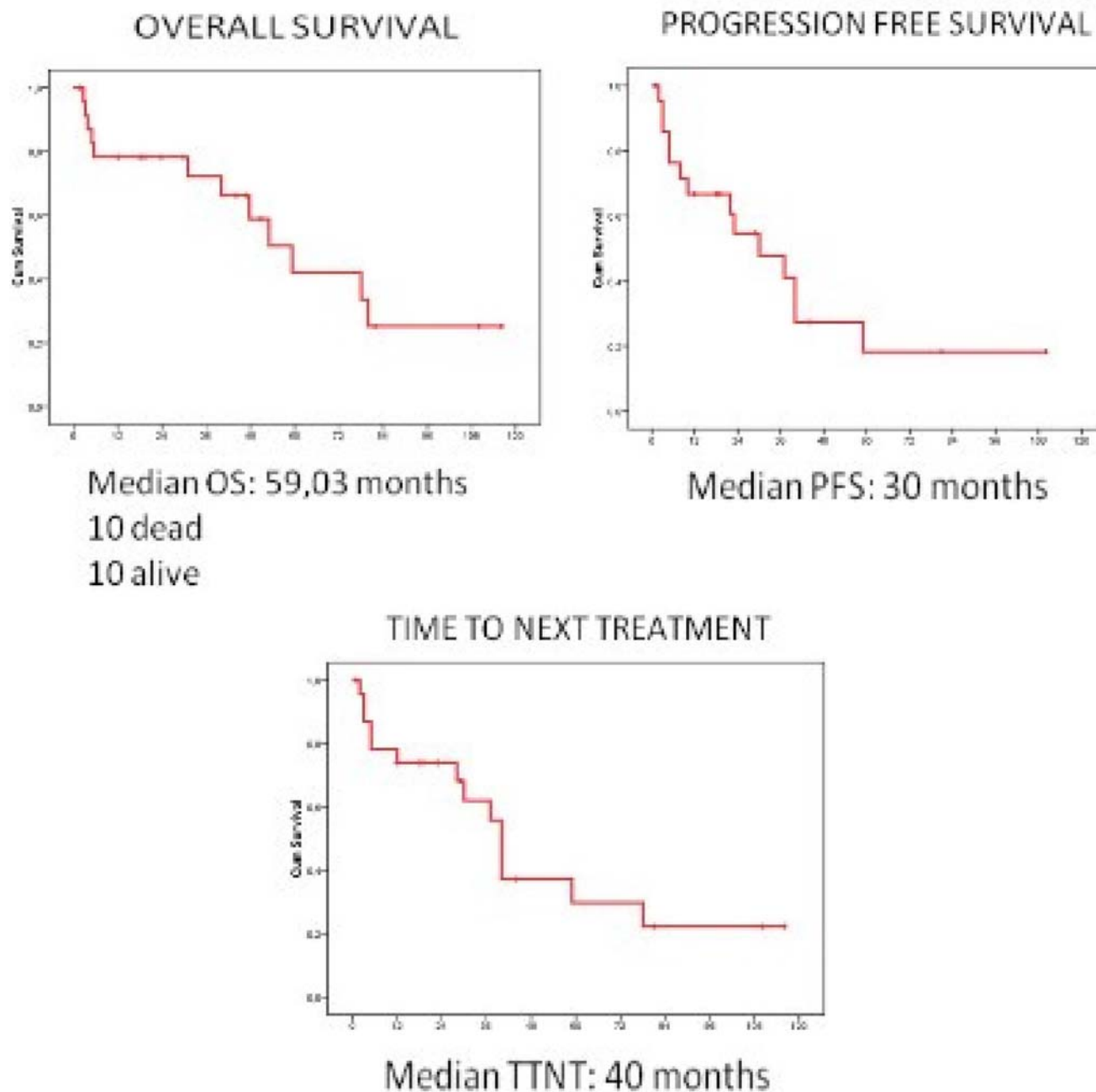
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A PHASE II TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF THE COMBINATION OF OBINUTUZUMAB BENDAMUSTINE TREATMENT IN PATIENTS WITH RELAPSED /REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

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Figure 1. Progression free survival (A), overall survival (B), response duration (C) and time to re-treatment (D).
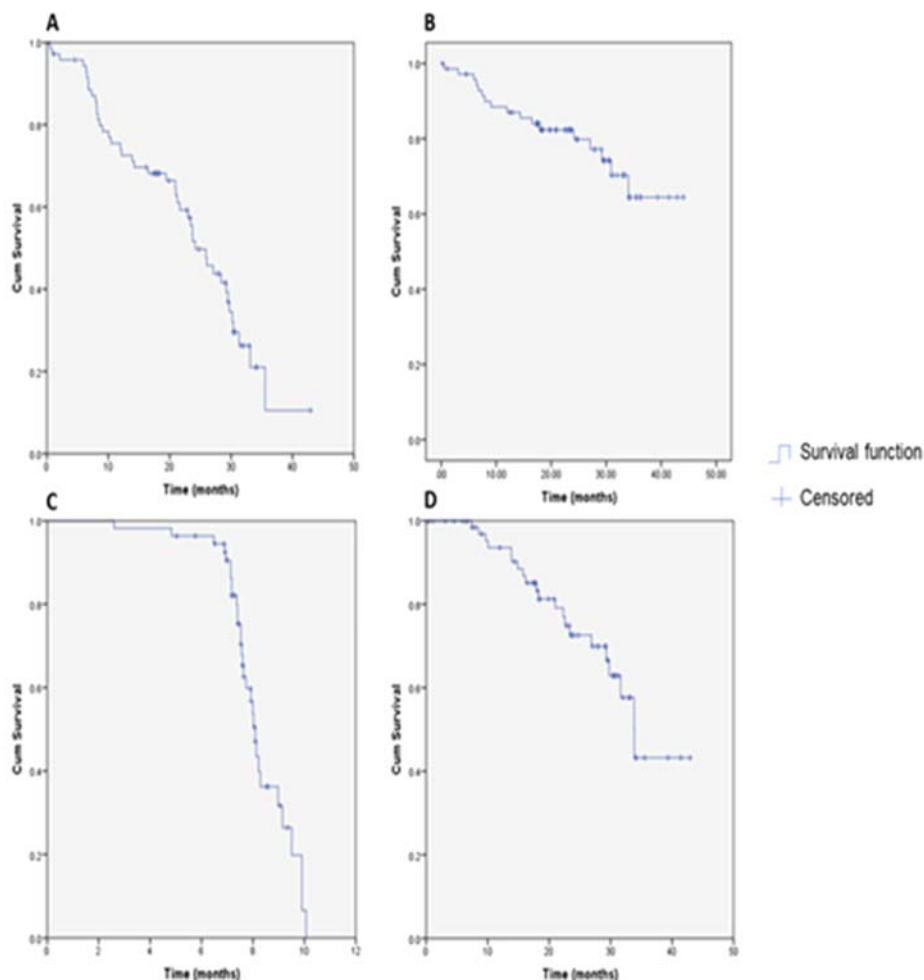
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Introduction and objective: The use of combined rituximab(R)-bendamustine(B) has shown to be effective in terms of overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) in pts with relapsed/refractory (R/R) CLL. Based on the enhanced in vitro and in vivo anti-CLL activity of obinutuzumab (Obi) compared to R, we designed this study to evaluate the efficacy of Obi with B in patients (pts) with R/R CLL.

Methods: Between April 2014 and April 2017, 72 adult pts with R/R CD20+ CLL and active disease were included in this prospective, multicenter, non-comparative, phase II study. Pts received up to six-28-day cycles of treatment: intravenous (IV) infusion of Obi (1000 mg) on Days 1, 8, and 15 of Cycle 1 and on Day 1 of subsequent cycles, and B (70 mg/m2) by IV infusion on days 2 and 3 of Cycle 1 and on

Days 1 and 2 of subsequent cycles. The primary endpoint was ORR; secondary endpoints: best response rate, OS and PFS, response duration (RD) and minimal residual disease (MRD) rate (flow cytometry; sensitivity: 1 CLL cell in 10^{-4} leucocytes). We present the results of an interim analysis at 17 months of last Obi-B cycle with the data cut-off date of 22nd March 2018.

Results: Pts were mostly male (66.7%), with a median age of 67.9 years and ECOG 0 in 62.5% of them. RAI clinical stage was 0-II in 52.7% pts and III-IV in 47.3% pts. Expression of CD38 (>30%), CD49D (>20%), ZAP-70 (>20%) was seen in 15.3%, 55.6%, and 39.4% of pts respectively, and IGHV unmutated in 75.0% of pts. Genetic abnormalities detected were: del13q(43.1%), trisomy 12(19.4%), del11q/ATMmutation(43.1%), del17p/p53mutation (26.4%), mutations of BIRC3(2.8%), SF3B1(8.3%) and NOTCH1 (20.8%). Out of 72 enrolled pts, 80.6% and 79.2% completed 6 cycles of treatment with Obi and B respectively. Median treatment duration was 4.9 months and discontinuation rates due to adverse events were 16.7% (Obi) and 18.1% (B). Obi and B doses were modified in 75% and 54.2% of pts, respectively. ORR was 76.4 % (CR 27.8%, CRi 8.3% and PR 40.3%), PD (4.2%) and SD (8.3%). After a median follow-up of 23.6 months, median RD and PFS (Fig 1.) were 8.1 and 24.1 months, respectively and median OS was not reached. PFS and OS (Fig. 1) were significantly higher (p<0.001) in pts with negative MRD, mutated IGHV and no p53 aberrations in peripheral blood. Median time to re-treatment was 33.9 months. 64 pts (88.9%) presented at least 1 toxicity, being the most common grade 3/4 neutropenia (52.8%) and thrombocytopenia (20.9%). Two deaths occurred due to toxicities (acute myeloid leukemia and septic shock).

Conclusions: This preliminary analysis anticipates that the combination of obinutuzumab with bendamustine is feasible, effective and well-tolerated in relapsed/refractory CLL. Achievement of MRD negativity in peripheral blood correlates with a longer PFS and OS regardless of clinical response and cytogenetic abnormalities.

Keywords: Bendamustine; chronic lymphocytic leukemia (CLL); obinutuzumab.

Disclosures: García-Marco, J: Consultant Advisory Role: *Mundipharma, Glaxo, AbbVie, Roche, Gilead and Janssen and research support from Hoffman-La Roche and Janssen.* **Baltasar Tello, P:** Consultant Advisory Role: *AbbVie, Roche, Gilead and Janssen.* **Ríos Herranz, E:** Consultant Advisory Role: *Janssen*; Honoraria: *Roche, Janssen y Abbvie.* **Terol Castera, M:** Consultant Advisory Role: *AbbVie*; Honoraria: *Takeda, AbbVie, Roche and Janssen*; Research Funding: *Roche and Janssen.* **Champ, D:** Employment Leadership Position: *Roche Farma S.A.* **Puerta Puerta, J:** Consultant Advisory Role: *Roche, AbbVie and Janssen.*

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SECOND CANCER INCIDENCE IN CLL PATIENTS RECEIVING BTK INHIBITORS

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Background: Patients (pts) with chronic lymphocytic leukemia (CLL) suffer morbidity and mortality from CLL and increased risk for second primary neoplasia (SPN). BTK inhibitors (BTKi) are highly effective for the treatment of CLL and are associated with partial restoration of immune function with ongoing treatment. The impact of BTKi on the risk for and patterns of SPN is yet to be characterized.

Methods: CLL pts treated with ibrutinib or acalabrutinib at our center were identified retrospectively. Baseline and outcome data were collected including incidence of Richter's transformation (RT), nonmelanoma skin cancer (NMSC), and SPN.

Standard incidence ratio (SIR) with 95% confidence intervals (CI) were calculated using expected incidence rates from the Surveillance, Epidemiology, and End Results Program (SEER), assuming a Poisson distribution for the observed incidence. Cumulative incidence rate (CIR) of SPN (excluding RT and NMSC) was calculated from BTKi start date to the diagnosis of SPN; death was a competing risk and pts without event were censored at last follow-up. SPN was correlated with baseline data using the Fine-Gray model.

Results: 691 pts were included; the median age was 64 years, median prior lines of treatment was 2 (20% treatment-naïve, 66% with prior chemo-immunotherapy), and 56% were never smokers. At a median follow-up of 44 months, 68 pts (10%) were diagnosed with SPN (SIR 2.4, CI 1.9-3.0) including 13 lung (SIR 3.2, CI 1.7-5.5), 9 melanoma (SIR 6.9, CI 3.1-13), 9 prostate (SIR 1.4, CI 0.6-2.6), 7 bladder (SIR 5.2, CI 2.1-10.6), 4 breast (SIR 1.7, CI 0.5-4.5), and 3 kidney cancers (SIR 2.9, CI 0.6-8.5). CIR of SPN at 3 year was 7.6% (Table). Smoking (hazard ratio (HR) 2.9, CI 1.7-5.0, p<.01) and low baseline CD8 count (HR 0.9 for 2-fold increase, CI 0.8-0.9, p<.01) were associated with higher incidence of SPN. RT was diagnosed in 58 pts (8%) and NMSC in 138 pts (20%). 179 pts had died with 3 year overall survival of 79% (CI 76-82); the most common causes of death were CLL/RT (57%) and SPN (13%).

Conclusions: The incidence of SPN in pts treated with BTKi for CLL is increased relative to the general population. With a 5 year CIR of NMSC and SPN of 23% and 12% respectively, these data support consideration of intensive cancer screening for CLL pts receiving BTKi.

Keywords: BTK inhibitors; chronic lymphocytic leukemia (CLL).

Disclosures: Owen, D: Consultant Advisory Role: *Astra Zeneca, L&M Policy Research*; Research Funding: *Bristol-Myers Squibb, Merck Sharp & Dohme, Genentech/Roche, Palobiofarma.* **Bertino, E:** Consultant Advisory Role: *Boehringer Ingelheim.* **Rogers, K:** Consultant

TABLE 1 CIR of Second Cancers

	NMSC % (95% CI)	Other SPN (95% CI)
1 year	7.5 (5.8-9.7)	2.1 (1.2-3.4)
3 year	15.6 (12.8-18.5)	7.6 (5.7-9.9)
5 year	23.0 (19.2-27.1)	11.5 (8.7-14.8)

Figure: Cumulative Incidence of Second Cancer

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ANTICOAGULANT THERAPY IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA RECEIVING IBRUTINIB

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Introduction: The use of new oral anticoagulants (NOAC) in patients with chronic lymphocytic leukemia (CLL) is a difficult task due to the high risk of hemorrhagic complications in these patients associated with the course of CLL. The use of highly effective targeted therapy with ibrutinib (Ib), which affects platelet function, creates an additional risk of bleeding. It is important to assess the use of NOAC in CLL patients receiving Ib, taking into account the frequency and severity of hemorrhagic manifestations, the need to cancel, reduce the dose and replace with another NOAC.

Methods: We have examined and observed in the dynamics of 197 patients with CLL who received Ib from 5 to 56 months at a dose of 420 mg per day as 1, 2, 3, and 4 lines of CLL therapy. We included patients with CLL aged 32 to 91 years (66.0 (59.0-72.0) years), of which 70 women aged 39 to 83 years (64.0 (54.0-71.0) years) and 127 men aged from 32 to 91 years (66.0 (60.0-72.0) years). All occurring hemorrhagic manifestations were evaluated in patients receiving Ib and NOAC, taking into account the glomerular filtration rate (GFR) and the level of platelets.

Results: The need for NOAC occurred in patients with CLL and atrial fibrillation (AF) (n = 34). Rivaroxaban (n = 16), dabigatran (n = 6), apixaban (n = 12) were prescribed. Hemorrhagic manifestations were observed in 53.6% of patients receiving NOAC and Ib. They were hematomas (n = 12), petechiae (n = 3), nasal (n = 4) and gingival (n = 2) bleedings, hemorrhage into the anterior chamber of the eye (n = 1), gross hematuria (n = 3). A combination of several hemorrhagic manifestations was observed in 40% of CLL patients receiving NOAC. In 4 patients who received rivaroxaban in a dose of 20 mg it was changed to the minimum effective dose of apixaban 2, 5 mg twice a day, due to the development of recurrent nasal bleeding, gross hematuria, large recurrent hematomas. NOAC (rivaroxaban 20 mg per day) was canceled in 6 patients due to the development of thrombocytopenia (less than $100 * 10^9$ / l). In 1 patient, the cancellation of NOAC was due to recurrent gross hematuria, developed on rivaroxaban 20 mg and 15 mg per day and apixaban 2, 5 mg twice a day. We did not reveal significant differences in platelet count indices in groups of patients with and without hemorrhages. In

12 patients receiving rivaroxaban 20 mg once a day (n = 6), dabigatran 150 mg twice a day (n = 2), apixaban 5 mg twice a day (n = 4) for periods ranging from 9 to 25 months with Ib therapy no hemorrhagic manifestations have been observed.

Conclusions: Hemorrhagic manifestations occurring in CLL patients receiving NOAC and Ib treatment were not life-threatening, in most cases did not require the abolition of NOAC and a dose reduction of Ib. The development of thrombocytopenia was the main reason for the abolition of NOAC in patients with CLL.

Keywords: chronic lymphocytic leukemia (CLL); ibrutinib.

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IBRUTINIB ABOVE 79 YEARS OLD FOR CHRONIC LYMPHOCYTIC LEUKEMIA: IMPORTANT TOXICITIES

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Introduction: Ibrutinib, covalent inhibitor of bruton tyrosine kinase, is approved for the treatment of 1L and R/R Chronic Lymphocytic Leukemia (CLL). Older patients are more likely to suffer from comorbidities putatively compromising both tolerance and outcomes, but were mostly not represented in pivotal registration trials.

Methods: We sought to determine efficacy and tolerance of ibrutinib in a series of 350 cases, including 92 patients over 79y with 1L or R/R CLL, with at least one year of clinical follow-up, in eight French Centers. We studied overall survival (OS), rate of patients on-therapy at 1 year, and causes of death/drug withdrawal. We next compared these result to patients receiving ibrutinib for a Waldenstrom macroglobulinemia (WM) or mantle cell lymphoma (MCL) aged 79+ years.

Results: 92 patients with CLL were included, with a FU of 12-50 months, median age was 81 y, 68% were males, median number of previous lines was 2, and 55% presented del17p/mutated TP53 status. At the last FU, 53% of patients had stopped ibrutinib (vs 38% in the <79y population), including 60% during the first year. We noticed that 50% of patients needed a dose reduction to manage toxicities. Reasons for permanent drug discontinuations were: toxicities (66%), disease progression (28%), and secondary cancer (6%). Out of 35 deaths, main causes were toxicities (58%, including infection (18 patients) and cardiovascular events (2 patients)), followed by disease progression (34%) and secondary cancer (5%).

These toxicity/OS outcomes are similar to a series of patients with similar age receiving ibrutinib for other lymphoma entities. 37 patients with lymphoma (6 WM, 31 MCL) were included, median age was 83y. As is CLL we observed ibrutinib discontinuation in 67% of patient (half during the first year). Out of 24 deaths, main causes were also toxicities (13 patients) and disease progression (11 patients).

KM curves showed that patients >82y had a statistically inferior median OS of 18 months, and that median OS of <79y versus 79-82y were comparable.

Conclusions: In very elderly patients (> 79y) from our retrospective cohort, tolerance profile of ibrutinib precluded long term exposure. Only 50% of patients are treated more than one year, and therefore this drug did not meaningfully impact OS above 82y. Comprehensive geriatric assessment should be performed to evaluate life expectancy before initiating ibrutinib.

Keywords: chronic lymphocytic leukemia (CLL); elderly; ibrutinib.

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USING BTK INHIBITORS FOR CHRONIC LYMPHOCYTIC LEUKEMIA: ONLINE EDUCATION SIGNIFICANTLY IMPROVED THE KNOWLEDGE AND COMPETENCE OF HEMATOLOGISTS/ONCOLOGISTS

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Introduction: Chronic lymphocytic leukemia (CLL), a type of non-Hodgkin lymphoma, is the most common type of leukemia in adults and can be indolent or aggressive in nature. Hematologists/oncologists (hem/oncs) need to be competent treating this disease in order to optimize patient outcomes. The goal of this initiative was to determine if online education could improve hem/onc knowledge and competence using BTK inhibitors (BTKi) to treat CLL.

Methods: The format was an online continuing medical education (CME)-certified activity consisting of a 30-minute video in which 2 expert faculty discussed use of BTKi in CLL. Evidence-based educational feedback was provided following each response. Three multiple-choice competence questions and 1 self-efficacy question were selected from the set of intra-activity questions to be repeated immediately after activity participation. Questions assessed the impact of the education with a repeated pairs pre-assessment/post-assessment study design where each participant served as his/her own control. A chi-square test was used to identify differences between pre- and post-assessment responses. P values were calculated; those < 0.05 were considered statistically significant. The activity launched online Sept 24, 2018 and data were collected through Mar 15, 2019.

Results: Results are for those who have completed the pre- and post-assessment questions during the study period (n = 109 hem/oncs).

Upon completion of the activity, an improvement from pre- to post-assessment was observed in the hem/oncs ability to:

- Determine which patients with relapsed/refractory (R/R) CLL would candidates for acalabrutinib (45% vs 73%, $P < .001$)
- Recognize the typical presentation of treatment-related adverse effects (TRAEs) with ibrutinib (41% vs 63%, $P < 0.001$)
- Identify the timeframe that BTK and PCLG2 mutations can become detectable before onset of clinical relapse in patients with CLL receiving ibrutinib (55% vs 77%, $P < 0.001$)
- Report greater confidence incorporating BTKi in the treatment of patients with B-cell malignancies (total average confidence shift: increase of 15.7%)

Conclusions: This online, interactive, CME-certified educational activity led to statistically significant improvements in the knowledge of hem/oncs about TRAEs of BTKi and the relationship of mutations that can precede clinical relapse. Additionally, a statistically significant gain in competence was seen with hem/oncs ability to select patients with R/R CLL who would be candidates for acalabrutinib. The education also increased hem/onc confidence incorporating BTKi into the treatment of patients with B-cell malignancies. The results indicate that unique educational methodologies and platforms, which are available on-demand, can be effective tools for advancing clinical decision making. Additional studies are needed to assess whether improved aptitude translates to improved performance during clinical practice.

Keywords: acalabrutinib; chronic lymphocytic leukemia (CLL); ibrutinib.

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IDELALISIB PLUS ANTI-CD20 USED SECOND LINE SHOWS IMPROVED PFS AND COMPARABLE SAFETY COMPARED TO LATER LINE THERAPY OF RELAPSED CLL

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Introduction: Idelalisib (IDELA) is a first-in-class PI3Kδ inhibitor approved for use in combination with rituximab or ofatumumab for patients with relapsed or refractory chronic lymphocytic leukemia (R/R CLL). Increased incidence of serious adverse events (AEs) observed in the treatment naïve setting has produced a prevailing view that early line use of IDELA may also lead to inferior clinical outcomes. To address this question, we evaluated the clinical benefit: risk balance for IDELA in early vs. later lines of use in the relapsed setting.

Methods: Using clinical outcomes data collected in Gilead-sponsored trials of patients with R/R CLL treated with IDELA + α-CD20 (N=110, Furman et al., N. Engl. J. Med. 2014 and N=173, Jones et al., Lancet Haematol. 2017), we retrospectively compared the overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and AE profile for patients previously treated with 1 prior regimen (IDELA given in the second line setting, 2L), 2 prior regimens (3L), or ≥3 prior regimens (≥4L). PFS and OS were estimated using the Kaplan-Meier method and groups were compared using a log-rank test. The incidence of AEs was compared using the Kruskal Wallis test.

Results: Among 283 patients treated with IDELA + α-CD20, 49 (17.3%) received IDELA 2L, 69 (24.4%) received it 3L, and 165 (58.3%) received it ≥4L. Patient characteristics were similar except that patients in the ≥4L group presented with Rai stage III/IV disease more frequently compared to the 2L and 3L groups (70.3% vs. 61.3% and 57.9%, respectively). ORR was similar irrespective of the number of prior regimens (85.7% for the 2L group, 73.9% for the 3L group, and 80% for the ≥4L group, p=0.2866); however, PFS and OS were longer in the 2L group compared to the 3L and ≥4L groups (median PFS= 31.5 months, 16.6 months, and 17.3 months, respectively, [Figure 1] and median OS=47.4 months, not reached (NR), and 34.6 months, respectively). No statistically significant difference was observed across treatment setting groups in the incidence of key treatment-emergent AEs, including cough, diarrhea, infection, transaminitis, and colitis.

Conclusion: These analyses indicate that patients with R/R CLL experience comparable or improved efficacy and have a similar safety profile when IDELA + α-CD20 regimens are used 2nd line compared to later lines, after chemo-immunotherapeutic regimens. Longer PFS and OS for patients treated with IDELA in the 2L may reflect shorter time since diagnosis, lower stage disease, or less disease resistance, but also suggest that the efficacy benefit is greater and may better offset potential toxicity in this patient sub-group. These findings support the use of IDELA + α-CD20 in the 2L+ setting for patients with R/R CLL following chemo-immunotherapy.

Keywords: chronic lymphocytic leukemia (CLL); idelalisib; PI3K/AKT/mTOR.

Disclosures: Brown, J: Consultant Advisory Role: *Abbvie, Acerta, Beigene, Genentech/Roche, Gilead, Juno/Celgene, Kite, Loxo, Novartis, Pfizer, Pharmacyclics, Sunesis, TG Therapeutics, Verastem*; Honoraria: *Janssen and Teva*; Research Funding: *Gilead, Loxo, Sun and Verastem*; Other Remuneration: *Morphosys and Invectys*. **Chan, R:** Employment Leadership Position: *Gilead*; Stock Ownership: *Gilead*. **Xing, G:** Employment Leadership Position: *Gilead*; Stock Ownership: *Gilead*. **Bhargava, P:** Employment Leadership Position: *Gilead*; Stock Ownership: *Gilead*. **Ruzicka, B:** Employment Leadership Position: *Gilead*; Stock Ownership: *Gilead*. **O'Brien, S:** Consultant Advisory Role: *Amgen, Astellas, Celgene, GlaxoSmithKline, Janssen Oncology, Aptose Biosciences Inc., Vaniam Group LLC, AbbVie, Alexion, Gilead, Pharmacyclics, TG*
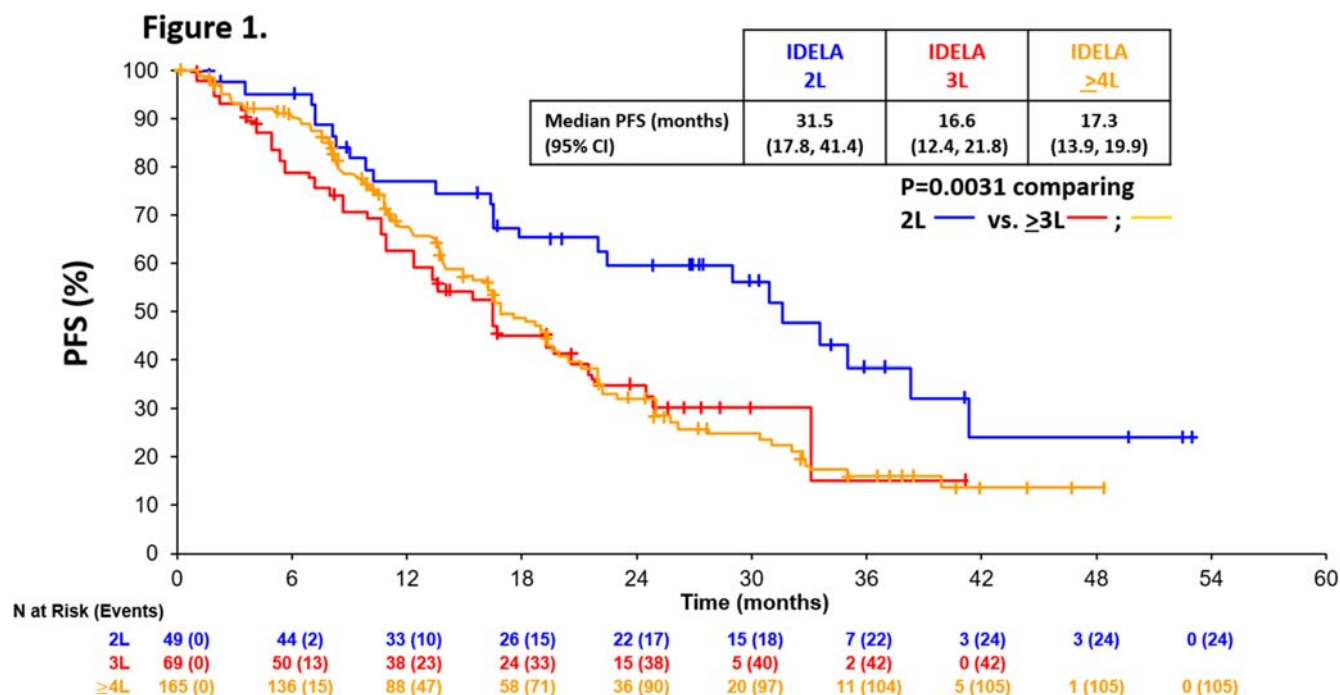
Figure 1.

	IDELA 2L	IDELA 3L	IDELA ≥4L
Median PFS (months) (95% CI)	31.5 (17.8, 41.4)	16.6 (12.4, 21.8)	17.3 (13.9, 19.9)

P=0.0031 comparing
2L ——— vs. ≥3L ——— ; ———

N at Risk (Events)

2L	49 (0)	44 (2)	33 (10)	26 (15)	22 (17)	15 (18)	7 (22)	3 (24)	3 (24)	0 (24)
3L	69 (0)	50 (13)	38 (23)	24 (33)	15 (38)	5 (40)	2 (42)	0 (42)		
≥4L	165 (0)	136 (15)	88 (47)	58 (71)	36 (90)	20 (97)	11 (104)	5 (105)	1 (105)	0 (105)

INDOLENT LYMPHOMA

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CLINICAL OUTCOMES OF PATIENTS WITH INTERMEDIATE-TO-HIGH-RISK FOLLICULAR LYMPHOMA (FL) IN THE GALLIUM PHASE III STUDY

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Introduction: Patients (pts) with a Follicular Lymphoma International Prognostic Index (FLIPI) score of ≥2 represent a subgroup of intermediate-to-high-risk pts in need of better treatment options. We conducted a retrospective analysis to evaluate the clinical outcomes of these pts from the Phase III GALLIUM study (NCT01332968).

Methods: Pts (age ≥18 years; advanced disease [stage III/IV or stage II with tumour diameter ≥7cm], ECOG performance status 0–2) with previously untreated FL were randomised to receive either rituximab (R; 375 mg/m² on Day [D] 1 of each cycle) or obinutuzumab (G; 1,000 mg on D1, D8, and D15 of Cycle 1 and D1 of subsequent cycles) in combination with chemotherapy (CHOP, CVP, or bendamustine at the discretion of the investigator site), followed by maintenance with the same antibody for a maximum of 2 years (or until progression of disease [PD]) in pts who achieved at least a partial response at the end of induction therapy. The endpoints of interest for this *ad-hoc* analysis in the intermediate-to-high-risk FLIPI ≥2 subgroup were investigator-assessed progression-free survival (PFS), overall survival (OS), proportion of patients free of new anti-lymphoma treatment at 4 years, and PD within 24 months (POD24).

Results: As of April 2018 (median follow-up of 4.75 years), in the ITT population (n=1202), the estimated PFS hazard ratio (HR) stratified by FLIPI and chemotherapy backbone was 0.73 (95% CI: 0.59–0.90). The treatment effect on PFS appeared to be different between pts with FLIPI <2 and FLIPI ≥2 (interaction test: p=0.02). PFS markedly improved in the FLIPI ≥2 pts (n=952) treated with G-chemo vs R-chemo (HR=0.65 [95% CI: 0.52–0.82]) (**Figure**). The 4-year OS rate was 91.8% with G-chemo vs 88.7% with R-chemo (HR=0.78 [95% CI: 0.53–1.16]). The proportion of FLIPI ≥2 pts who were free of new anti-lymphoma treatment at 4 years was 81.8% with G-chemo vs 71.2% with R-chemo (HR=0.62 [95% CI: 0.47–0.81]). Fewer POD24 events occurred in FLIPI ≥2 pts treated with G-chemo (43/474; cumulative incidence rate [CIR]: 9.6%]) vs pts treated with R-chemo (85/476; CIR: 18.7%) with a 1-HR based risk reduction of 52.9% (95% CI: 31.9–67.4). The risk of mortality (number of deaths/100 patient-years) following a POD24 event was similar in both arms (17.7 [95%

Figure. PFS (investigator assessed) in FLIPI ≥2 intermediate-to-high-risk pts

— G-chemo (N=474)   — R-chemo (N=476)   + Censored

	FLIPI ≥2 intermediate-to-high-risk pts	
	R-chemo (n=476)*	G-chemo (n=474)*
4-year PFS rate,% (95% CI)	64.4 (59.9–68.9)	78.2 (74.3–82.1)
HR (95% CI)	0.65 (0.52–0.82)	

*Efficacy-evaluable population

Number at risk

R-chemo 476	362	292	97	0
G-chemo 474	399	337	96	0
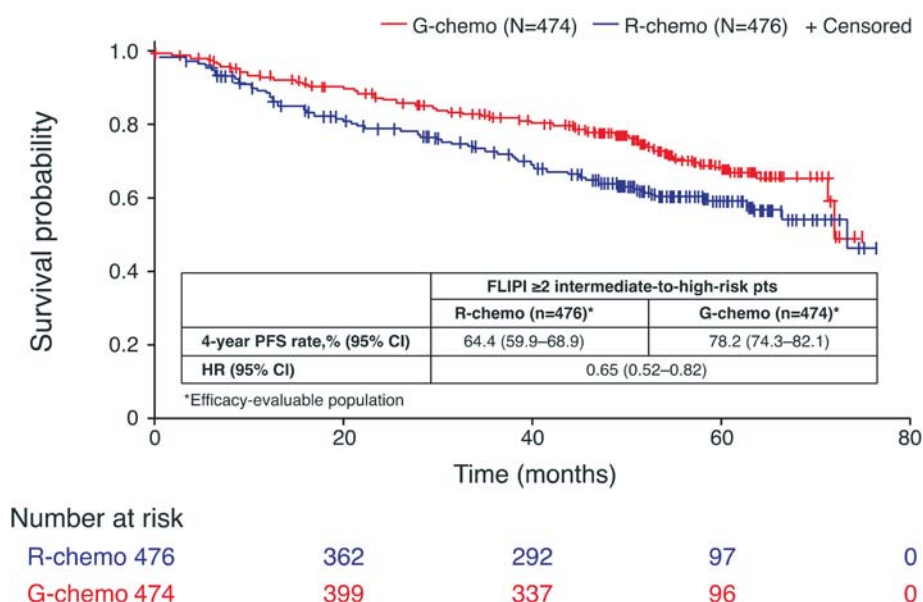
CI, confidence interval; FLIPI, Follicular Lymphoma International Prognostic Index; G-chemo, obinutuzumab plus chemotherapy; HR, hazard ratio; PFS, progression-free survival; pts, patients; R-chemo, rituximab plus chemotherapy

CI: 11.5–27.4] vs 17.7 [95% CI: 12.8–24.3], respectively). More FLIPI ≥2 pts experienced Grade ≥3 adverse events [AEs] with G-chemo (79.9%) vs R-chemo (73.1%); the most common was Grade ≥3 infection, which occurred in 20.8% vs 18.9% of pts, respectively. The number of Grade 5 AEs were similar between the G-chemo arm (19 [4.1%]) vs R-chemo (22 [4.6%]).

Conclusion: These data suggest that pts with FLIPI ≥2 have a better risk-benefit profile with G-chemo vs R-chemo, than those with FLIPI <2.

Disclosures: Launonen, A: Employment Leadership Position: *F. Hoffman La-Roche Ltd*; Stock Ownership: *Novartis*; Other Remuneration: *Partner works as a manager at Novartis*. **Casulo, C:** Honoraria: *Gilead*; Research Funding: *Celgene*; Other Remuneration: *Expenses: Roche, Gilead*. **Pott, C:** Consultant Advisory Role: *Roche, Genetech*; Honoraria: *Roche, Genetech*; Research Funding: *Roche, Genetech*; Other Remuneration: *Speakers' Bureau: Roche; Expenses: Roche*. **Rusconi, C:** Consultant Advisory Role: *Takeda, Roche, Celgene, Jannsen*; Research Funding: *Celgene*; Other Remuneration: *Expenses: Takeda, Roche*. **Hernandez, J:** Employment Leadership Position: *F. Hoffman La-Roche Ltd*. **Davies, A:** Consultant Advisory Role: *Roche, Kite, Celgene, Acerta Pharma, MorphoSys, BioInvent*; Honoraria: *Roche, Celgene, Kite,*

Janssen; Research Funding: *Roche, Acerta Pharma, Celgene, Gilead, Karyopharma, GSK*; Other Remuneration: *Sponsorship to attend conferences: Roche, Celgene*; Expert Testimony: *Roche*.

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EFFICACY AND SAFETY IN HIGH-RISK RELAPSED OR REFRACTORY INDOLENT FOLLICULAR LYMPHOMA PATIENTS TREATED WITH COPANLISIB

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Introduction: Patients (pts) with follicular lymphoma (FL) who have progression of disease within 24 months of first-line immunochemotherapy (POD24) have worse overall survival (OS). The Phase II CHRONOS-1 study in pts with relapsed or refractory indolent B-cell lymphoma showed durable responses with the intravenous pan-class I phosphatidylinositol 3-kinase inhibitor copanlisib. We explore the outcomes with copanlisib in pts with POD24 in the subset of pts with FL.

Methods: Pts with histologically confirmed FL relapsed after or refractory to ≥2 prior lines of treatment, including rituximab and an alkylating agent or regimen (eg R-CHOP), were eligible for the subset analysis. Copanlisib 60 mg was given as a 1-hour infusion on days 1, 8 and 15 of a 28-day cycle. The primary efficacy endpoint was objective response rate per independent assessment after ≥4 cycles. Secondary endpoints included progression-free survival (PFS) and OS. Adverse events (AEs) were reported using MedDRA (v.20.1).

Results: 104 pts with FL were treated, with 102 evaluable for POD24: 66.7% with POD <24 months [POD<24] and 33.3% with POD ≥24 months [POD≥24]. R-CHOP was the most common first-line treatment and accounted for 39.7% of pts with POD<24 and 38.2% of pts with POD≥24. The median time from first-line treatment to first POD was 12.0 months in pts with POD<24 and 34.1 months in pts with POD≥24. The median number of lines of prior therapy for both groups was 3.

Responses were similar in both groups (Table), with complete responses exceeding 20% in the POD<24 groups. Median PFS was 11.3 months (range 0-44.2) in pts with POD<24 and 10.8 months (0-35.8) in pts with POD≥24; median OS was 38.3 and 31.0 months, respectively. Results were similar in the FL pts previously treated with R-CHOP (Table).

The median duration of safety follow-up was 7.0 months in pts with POD<24 and 4.7 months in pts with POD≥24. Overall, grade (G) 3 treatment-related AEs were reported in 48.1% of pts, and G4 in 26.0%. Treatment-related serious AEs occurred in 29.8% of pts (15.4% G3; 7.7% G4). There were 3 treatment-related G5 events.

Conclusions: This exploratory analysis from the CHRONOS-1 study in relapsed or refractory indolent FL pts having received 2 or more prior lines of therapy demonstrated robust responses in pts with high-risk disease as evidenced by POD24 status on first-line treatment. These

TABLE 1 Response evaluation in FL patients by independent assessment

	FL patients			
	Overall (N=102)		R-CHOP subgroup (N=40)	
n (%)	POD<24 (n=68)	POD≥24 (n=34)	POD<24 (n=27)	POD≥24 (n=13)
Complete response	15 (22.1)	6 (17.7)	8 (29.6)	1 (7.7)
Partial response	26 (38.2)	14 (41.2)	8 (29.6)	6 (46.2)
Stable disease (SD)	21 (30.9)	11 (32.4)	10 (37.0)	6 (46.2)
Unconfirmed early SD	1 (1.5)	0	NA	NA
Progressive disease	0	2 (5.9)	0	0
NA/NE	5 (7.4)	1 (2.9)	1 (3.7)	0
Objective response rate	41 (60.3)	20 (58.8)	16 (59.3)	7 (53.9)

Abbreviations: NA, not available; NE, not evaluable.

results support exploration of copanlisib in combination with chemo-immunotherapy in earlier lines of treatment (NCT02367040; NCT02626455).

Keywords: follicular lymphoma (FL); PI3K/AKT/mTOR.

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SAFETY ANALYSIS OF PATIENTS WITH A MEDICAL HISTORY OF RESPIRATORY DISORDERS TREATED WITH COPANLISIB FROM THE CHRONOS-1 STUDY IN RELAPSED OR REFRACTORY INDOLENT B-CELL LYMPHOMA

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Introduction: ESMO guidelines for patients with relapsed follicular lymphoma (FL) state that treatment of patients in the relapsed setting with the phosphatidylinositol 3-kinase (PI3K) inhibitor idelalisib may have increased mortality risk due to pulmonary morbidity, including atypical pneumonias and pneumonitis, such that prophylaxis is strongly recommended (Dreyling et al. Ann Oncol 2016). The intravenous intermittently administered pan-class I PI3K inhibitor copanlisib was approved by the FDA in 2017 for treatment of relapsed FL with no black box warnings or recommendation for prophylaxis for opportunistic infections. We sought to examine whether patients with a medical history of respiratory disorders from the CHRONOS-1 trial in patients with relapsed or refractory indolent non-Hodgkin lymphoma (iNHL) treated with copanlisib had higher rates of respiratory-related adverse events (AEs).

Methods: Patients with histologically confirmed iNHL who relapsed after or were refractory to ≥2 prior lines of treatment, including rituximab and an alkylating agent or regimen (eg R-CHOP), were eligible for this subset analysis. Copanlisib 60 mg was given as a 1-hour infusion on an intermittent schedule (days 1, 8 and 15 of a 28-day cycle). Prophylaxis for opportunistic infections was not required. AEs were reported using MedDRA (v.20.1).

Results: 142 patients with iNHL were treated, of whom 39 had medical histories of respiratory disorders and 103 did not; 46% and 56%, respectively, were non-smokers. The median duration of treatment was 4.8 months (range 0.5-32.7) and 6.2 months (range 0.2-44.2), respectively. The objective tumour responses per independent assessments were similar: 59.0% and 61.2%, respectively. The incidence of respiratory-related AEs was similar across the two groups (Table). There were 3 grade 5 AEs attributed to the study drug, including 1 lung infection in a patient with a history of bronchiectasis and 1 respiratory failure in a patient with multifactorial etiology, including pre-existing chronic obstructive pulmonary disease.

Conclusions: This exploratory analysis in patients with relapsed or refractory iNHL treated with copanlisib demonstrated a low overall incidence and no difference in incidence or severity of respiratory-related AEs in patients based on medical histories of respiratory disorders. These results are further evidence of the favourable safety profile of copanlisib and support the use of intermittent intravenous dosing in this setting.

Keywords: non-Hodgkin lymphoma (NHL); PI3K/AKT/mTOR.

TABLE 1 Respiratory-related treatment-emergent AEs (TEAEs)

TEAEs (all grade/G3/G4)	History of respiratory disorders (n=39)	No history of respiratory disorders (n=103)
Pneumonia	10.3%/5.1%/0%	15.5%/10.7%/1.9%
Upper respiratory tract infection	12.8%/0%/0%	15.5%/1.9%/0%
Lung infection	7.7%/2.6%/0%	2.9%/0%/0%
*Pneumocystis jirovecii*pneumonia	2.6%/2.6%/0%	1.0%/0%/1.0%
Dyspnoea	7.7%/2.6%/0%	8.7%/2.9%/0%
Pneumonitis	7.7%/0%/0%	5.8%/1.9%/0%
AE grouping – lower respiratory tract infection	30.8%/7.7%/0%	27.2%/11.7%/1.9%
AE grouping – non‑infectious pneumonitis	7.7%/0%/0%	8.7%/3.9%/0%
AE grouping – respiratory tract infections	53.8%/10.3%/0%	41.7%/12.6%/1.9%

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A PHASE II TRIAL OF RITUXIMAB/LENALIDOMIDE FOLLOWED BY LENALIDOMIDE MAINTENANCE IN UNTREATED AND RELAPSED INDOLENT LYMPHOMA: LONG TERM FOLLOW UP AND CORRELATIVE ANALYSIS

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Introduction: Lenalidomide is a potent immunomodulator that has demonstrated activity in a broad spectrum of lymphoma subtypes. The combination of lenalidomide and rituximab has been shown to be effective in patients with previously untreated and relapsed or refractory (R/R) indolent non-Hodgkin lymphoma (NHL). Here, we report long term follow up of a phase II trial assessing efficacy and correlative analysis for lenalidomide plus rituximab followed by indefinite lenalidomide maintenance in patients with advanced stage untreated and R/R indolent NHL.

Methods: We conducted a phase II, open-label trial involving patients with advanced stage previously untreated and R/R indolent NHL.

Overall Survival and Time to Progression for Patients with Indolent Lymphoma

A. Survival among Untreated Indolent Lymphoma Patients

Overall Survival (n=27)
Median (95% CI): Not Reached

Progression Free Survival (n=27)
Median (95% CI): 64.6 months (20.4, 94.0)

B. Survival among Relapsed/Refractory Indolent Lymphoma Patients

Overall Survival (n=28)
Median (95% CI): Not Reached

Progression Free Survival (n=28)
Median (95% CI): 12.0 months (1.8, 9.2)
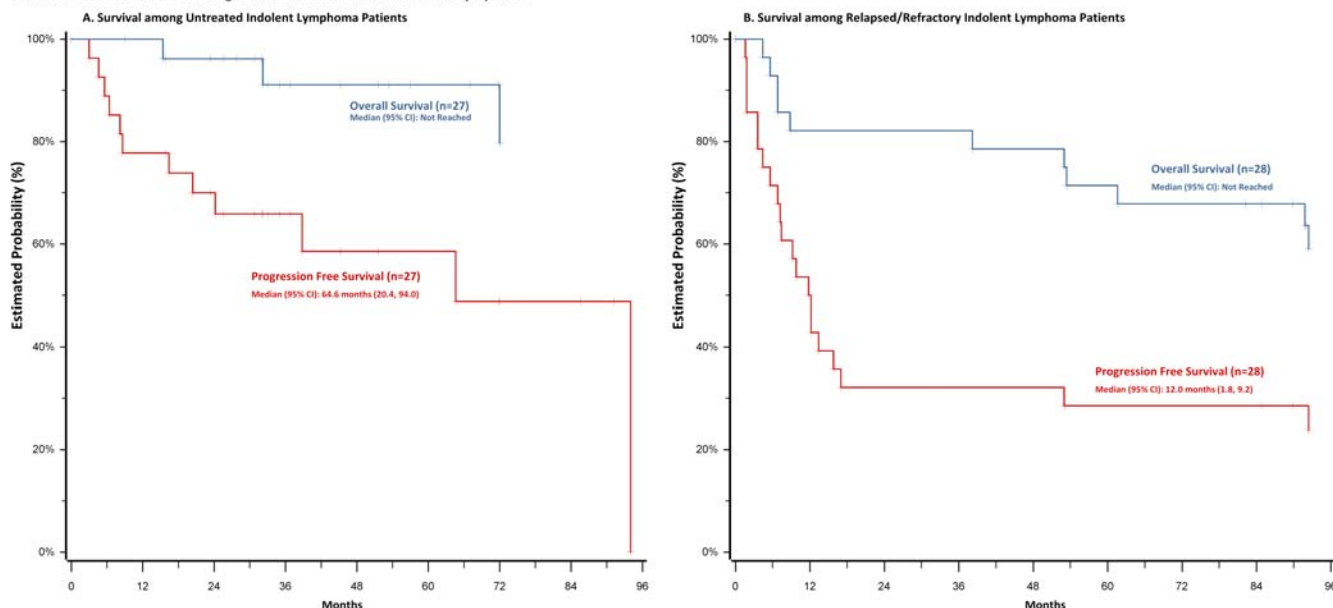
Patients received oral lenalidomide 20 mg daily on days 1-21 of a 28-day cycle and intravenous rituximab 375 mg/m2 weekly for 4 or 8 doses starting day 15 of cycle 1 followed by lenalidomide maintenance until progression or toxicity. The primary endpoint was best overall response rate (ORR). Secondary endpoints included progression free survival (PFS), time to next therapy (TTNT), overall survival (OS) and safety.

Correlative analysis included serum cytokine levels (IFN-γ, GM-CSF, CXCL-10, IL-2, TNF-α, IL-6, IL-10, IL-1, IL-8 and IL-12) and immune cellular subset analysis (B cell, cytotoxic T cell, T cell) at baseline, days 15, 30, 60, 120 of treatment and at treatment discontinuation. Unpaired student's t test was used to assess correlation with response.

Results: A total of 60 patients were enrolled (30 untreated and 30 R/R). Median follow-up was 52 months (range 9.2 to 97 months) for the previously untreated group and 113 months (range 4.3 to 129 months) for the R/R group. The ORR was 89% and 75%, respectively. Median progression-free survival was 64.6 months (95% CI, 20.4 to 94) and 12 months (95% CI, 6.8 to 17), respectively. The 9 R/R patients who achieved complete remission remained in continuous remission on lenalidomide maintenance for 16 to 126 months. In patients with disease progression, median time to next therapy was not reached in the untreated group and 15.6 months (95% CI, 7.6 to 40.2) in the R/R group. Median overall survival was not reached in both groups. Most common grade ¾ adverse events were neutropenia (55%), lymphopenia (45%), fatigue (23%) and hyponatremia (9%). Increased cytokine, INF-γ, IL-2, CXCL-10 and GM-CSF levels on day 15 correlated with response. Increased T cell, cytotoxic T cell and decreased B cell levels on day 30 also correlated with response.

Conclusions: Rituximab plus lenalidomide followed by lenalidomide maintenance is effective and associated with acceptable toxicity in patients with both previously untreated and R/R advanced stage indolent NHL. This regimen produces durable remissions, even in previously treated patients, with some lasting greater than 10 years. Increased INF-γ, IL-2, CXCL-10, GM-CSF, T cells and decreased B cell levels correlated with response.

Keywords: indolent lymphoma; lenalidomide.

Disclosures: Tuscano, J: Honoraria: *Celgene*; Research Funding: *Celgene*.

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GRADE 3A FOLLICULAR LYMPHOMA CAN BE EFFECTIVELY CONTROLLED WITH VERY LOW DOSE RADIATION THERAPY

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Introduction: Very low dose radiotherapy (4Gy; VLDRT) has been demonstrated as an effective treatment for low-grade (1-2) follicular lymphoma (FL) and offers the advantage of a shorter course and better side effect profile compared to full dose RT regimens (24 Gy). Whether this treatment can be applied to higher grade (3A) FL remains an open question and is generally not recommended. We reviewed outcomes of a pilot cohort of patients with grade 3A FL treated with VLDRT.

Methods: We analyzed 9 consecutive patients (78% female) with median age of 70 years (range 52-92) who received 2 Gy x 2 fractions for grade 3A FL between 2010-2018. Post treatment response at the first follow-up after VLDRT (median 1.9 months) was analyzed by CT and PET if available using the Lugano criteria. Freedom from local failure (FFLF) was analyzed per treated field and defined as time from VLDRT to LF. For FFLF, patients were censored at the start of a subsequent line of therapy if the VLDRT-treated site had not yet progressed. Freedom from distant failure (DF) was analyzed per patient. FFLF and FFDF were analyzed using Kaplan-Meier.

Results: The cohort was heterogeneous and reflective of the diverse utility of RT for treating indolent lymphomas. Two (22%) received VLDRT palliatively for newly diagnosed disease, 3 (33%) were treated for progressive disease after initial observation (range 19-87 months) and the remaining 4 (44%) had relapsed/refractory disease and all received 3 prior lines of therapy. All were PET staged before VLDRT with roughly equal distribution of early stage (n=5, 56%) and advanced stage (n=4, 44%). Four (44%) received VLDRT to exclusively nodal sites, 3 (33%) to exclusively extranodal sites and 2 (22%) to mixed nodal/extranodal. The median maximum diameter of a treated lesion was 3.1 cm (range 1.9-5.0) and median maximum pre-treatment SUV on PET was 8.0 (range 5.6-15.6). Despite heterogeneity, overall response rate at the first post-treatment visit was 100% (complete response, CR: 6, partial response, PR: 3). With median follow-up of 27 months post VLDRT, there was only 1 in-field LF at 6.3 months which corresponds to a 1-year FFLF of 86%. Overall, there were 3 DF, corresponding to a 1-year FFDF of 74%. Two of these patients received additional RT and systemic therapy whereas the third was observed. Only one patient had transformation to diffuse large B cell lymphoma (DLBCL). There was 1 non-disease related death in a patient alive with FL.

Conclusions: This is, to our knowledge, the first reported series of patients with high grade FL treated with VLDRT. Our data suggests that grade 3A FL behaves similarly to low grade disease, demonstrating outstanding radiographic responses and local control to only 4 Gy.

These findings support an expanded evaluation of VLDRT in patients with higher-grade FL.

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CONSOLIDATION THERAPY USING ^{90}Y-IBRITUMOMAB TIUXETAN AFTER BENDAMUSTINE AND RITUXIMAB FOR RELAPSED FOLLICULAR LYMPHOMA; A MULTICENTER, PHASE II STUDY (BRiZ2012)

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Introduction: The role of consolidation therapy with ^{90}Y-ibritumomab tiuxetan (^{90}YIT) for patients with relapsed follicular lymphoma (FL) who receive re-induction immunochemotherapy has not been established. Therefore, we conducted a multicenter prospective phase II trial evaluating the efficacy and toxicities of bendamustine and rituximab (BR) followed by ^{90}YIT for patients with relapsed FL.

Methods: This study included patients who had biopsy-proven, relapsed FL (Grade 1/2 or 3a); one or two prior therapies; age of 20–74 years; ECOG performance status of 0–2; measurable lesion(s); no severe organ dysfunction; 3 months or longer life expectancy; and written informed consent. BR consisted of rituximab (375 mg/m^2, day 1) and bendamustine (90 mg/m^2, day 2 and 3), and repeated every 4 weeks up to 4–6 cycles. As the consolidation therapy, 14.8 MBq/kg of ^{90}YIT was administered to patients who achieved complete response (CR) or partial response after BR therapy. The primary endpoint was 2-year progression-free survival (PFS) after the consolidation with ^{90}YIT. The secondary endpoints were response rates after BR therapy, response rates after consolidation with ^{90}YIT, 2-year overall survival (OS) rate after the consolidation with ^{90}YIT, and toxicities.

Results: A total of 30 patients were registered between 2013 and 2015. Of these patients, 6 were excluded from the study because of pathological diagnoses other than FL in the central review (n = 3), unmet criteria (n = 2), and the other advanced cancer found (n = 1), respectively. Thus, 24 patients with a median 60 years of age (range 47–74 years) and a median of 6.7 years (range 1.6–14.8 years) of duration from the initial diagnosis were evaluated. Among them, R-CHOP based chemotherapy was the most common initial treatment (92%). The FLIPI2 score at the time of registration was high in 3, intermediate in 7, and low in 14 patients, respectively. After re-induction treatment with BR, 22 patients (92%) ultimately received consolidation with ^{90}YIT, resulting in an overall response rate of 95% and a CR rate of 91%, respectively. Within the 2-year observation period, 10 patients relapsed and 3 of them had a histological transformation to diffuse large B-cell lymphoma. Severe non-hematological toxicities were rare and no treatment-related mortality was observed. Within the observation period, one patient died of disease progression. Second primary malignancies were not observed. Consequently, the 2-year PFS and OS rates after the consolidation were 58%, and 94%, respectively.
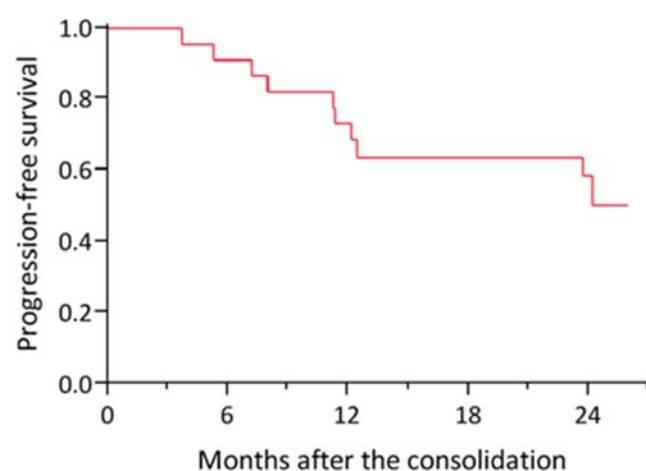
Conclusions: Consolidation therapy with ^{90}YIT after BR re-induction therapy was feasible in patients with relapsed FL. Clinical efficacy was comparable, but the long-term effect should be further investigated. *Trial protocol number: UMIN000008793, release date: 03. September 2012*

Keywords: 90-yttrium; follicular lymphoma (FL); radio-immunotherapy (RIT).

Disclosures: Kanno, M: Research Funding: *NPO-ACRO (Advanced Clinical Research Organization).*

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INTERIM ANALYSIS OF CENTRAL REVIEW OF END-OF-THERAPY PET IN FOLL12 TRIAL FOR FOLLICULAR LYMPHOMA

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Introduction: WIDEN® platform, is a tool that allows the management of medical images through the internet network in multicenter trials. WIDEN® platform is currently used in FOLL12 trial for ^{18}F-FDG PET/CT (PET) images exchange and reviewing. The aim of the current study is: to assess (1) the feasibility and effectiveness of WIDEN® platform in PET image management and (2) the agreement among the PET reviewers.

Methods: FOLL12 trial (EUDRACT NUMBER 2012-003170-60) is an ongoing multicenter, phase III, randomized study to evaluate the efficacy of a response-adapted strategy to define the role of maintenance treatment after standard chemoimmunotherapy in patients with advanced-stage Follicular Lymphoma. PET scans are performed at staging and after induction therapy (EoT-PET). In the experimental arm EoT-PET and minimal residual disease (MRD) persistence are key points for selecting patients for maintenance therapy vs observation. Upon EoT-PET upload on WIDEN® by the local site, the image quality is checked automatically for required standard fitting and an email alert is sent to reviewers (LG, AV, AF, SP, FF, GS) to urge the PET revision. The reviewer has 120 hours (5 days) to review EoT-PET from receipt of email alert and to upload the review form on WIDEN®. EoT-PET scans were compared to baseline PET scan and reviewed according to a Blinded Independent Central Review (BICR) modality using the Deauville Score. The first three concordant revisions in terms of negativity (Score 1-3) or positivity (Score 4-5) adjudicate the final result to the EoT-PET.

Results: At the time of writing, 762 baseline and 733 EoT anonymized PET have been uploaded on WIDEN® by the local sites. The median time for PET uploading was 1.3 minutes. Reviewers downloaded 733 pairs of baseline and EoT-PET; the median time for the download was 1.5 minutes. Currently, 733 EoT PET have been reviewed by Nuclear Medicine Reviewers according to BICR. The median time duration of review, calculated as the number of hours elapsed from the alert to the review submission, was 76h. The percentage of reviews done by the single reviewer that concurred to the final results (the first three concordant) were 89%, 68%, 71%, 81%, 78% and 37% for reviewer 1,2,3,4,5 and 6 respectively. The concordance between pairs of reviewers with respect to binary reporting (positive vs. negative) measured with the Cohen k for the 15 combinations of the 6 reviewers was 0.58. The overall concordance between reviewers with respect to binary reporting (positive vs. negative) measured using the Krippendorf alpha-coefficient was 0.62.

Conclusions: WIDEN® platform is an efficient tool for image exchange in multicentre trials allowing fast downloading and uploading PET scans by common HTTPS internet based protocol. The concordance among the reviewers in term of positivity/negativity was good confirming the reliability of the BICR for PET studies in multi-center clinical trials.

Keywords: follicular lymphoma (FL); positron emission tomography (PET).

Disclosures: Luminari, S: Consultant Advisory Role: *Roche, Celgene, Gilead, Sandoz.* **Gallamini, A:** Consultant Advisory Role: *Takeda, Roche;* Honoraria: *Takeda, Roche.* **Federico, M:** Honoraria: *Jannsen, Gilead, Astra Zenca, Takeda, Roche, Sandoz.* **Chauvie, S:** Employment Leadership Position: *Co-Founder of Dixit srl, spin-off of University of Torino and INFN;* Honoraria: *IAEA, CONSIP and Sirtex;* Research Funding: *Grants from La Roche, Takeda, Fondazione Cassa di Risparmio di Cuneo and AIRC;* Other Remuneration: *travel/accommodation from GE Healthcare, Philips Medical System, Sirtex, BTG, Terumo.*

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CLINICAL SIGNIFICANCE OF UPTAKE VALUE ON F18-FDG PET/CT AND HISTOLOGICAL GRADE IN 164 PATIENTS WITH FOLLICULAR LYMPHOMA INCLUDING TRANSFORMATION – A SINGLE CENTER RETROSPECTIVE STUDY

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Introduction: Follicular lymphoma is the most common indolent non-Hodgkin lymphoma, but has heterogeneous clinical behavior. PET-CT scan has the central role of determining of clinical staging and its five-point Deauville scale to grade response has been widely accepted in the management of follicular lymphoma. PET-CT scan also plays a significant role of predicting transformation of follicular lymphoma by considering high uptake of standardized uptake value (SUV). However, the SUV cut-off values distinguishing transformation are not determined and are different in each study, and clinical significance of SUV value on FDG PET/CT is not considered in detail yet.

Methods: We retrospectively analyzed 275 patients who were diagnosed as follicular lymphoma including transformed form in our hospital between January 2008 and November 2018. One patient had also been diagnosed as rectal cancer as well as follicular lymphoma, aso we excluded this patient from our study.

Results: We first investigated the relationship between histological grade and SUV value on FDG PET/CT. One hundred and ninety-eight biopsies were conducted at the same time of PET-CT. The median SUVmax value was 6.6 (range, 0-34.1) in FL grade 1 patients (n=89), 7.4 (0-23.9) in FL grade 2 patients (n=59), 12.1 (4.6-26.5) in FL grade 3a patients (n=33), and 14.8 (6.5-34.4) in FL grade 3b (n=17) (p<0.01).

We then analyzed clinical impact of SUVmax value on follicular lymphoma grade 1-3a. Patients with follicular lymphoma grade 3b, or lack of information were excluded, so we finally analyzed 164 patients. Median follow-up of survivors was 47.5 (0.4-10989) months. The median age at diagnosis was 62 (31-90) years. Ninety patients were male. Thirty-two patients were diagnosed as duodenum follicular lymphoma. Ninety-four patients were advanced clinical stage (III/IV). Using FLIPI2 score, 32 patients (20%) were in the low risk group, 105 (64%) in the intermediate group, and 27 (16%) in the high risk group. Thirty-six patients had high tumor burdens defined by GELF criteria. The median SUVmax value was 7.5 (range, 0-34.1). As first line treatment strategy, 83 patients (51%) received watch and wait strategy, 38 (23%) received R-CHOP, 3 patients (2%) received R-CVP, 14 (9%) received R-Benda, 20 (12%) received RIT, and 6 (4%) received others. High uptake value (SUV max ≥ 10 vs. SUV max < 10) correlated with high tumor burden (p<0.01), but did not affect OS and time to next treatment (97.3% vs. 98.9% in 5-year OS (p=0.79), 54.6% vs. 72.3% in time to next treatment (p=0.07)).

Conclusion: Uptake value of SUVmax correlated with histological grade of follicular lymphoma and high tumor burden, but did not affect OS and TTT after first line treatment therapy.

Keywords: F-18-fluorodeoxyglucose (FDG); follicular lymphoma (FL); positron emission tomography (PET).

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FOLLICULAR LYMPHOMA: PRE-TREATMENT TEP/CT SCAN TEXTURE PARAMETERS AS PREDICTIVE BIOMARKERS OF PROGRESSION FREE SURVIVAL AND TIME TO NEXT TREATMENT

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Purpose: To determine whether texture analysis features on pre-treatment non-enhanced computed tomography (CT) images derived from FDG-TEP-CT scan can predict progression free survival (PFS), time to next treatment (TTNT) and overall survival (OS) in patients with follicular lymphoma treated with immuno-chemotherapy and maintenance.

Materials and Methods: This institutional-approved retrospective study included 72 patients with follicular lymphoma. Texture analysis of 360 lesions was performed on CT scanners obtained within one month before treatment. Mean grey-level, entropy, kurtosis, skewness, and standard deviation values were derived from the pixel distribution histogram before and after spatial filtration at different anatomic scales (SSF), ranging from fine to coarse. Lasso penalized Cox regression analyses were performed to identify independent predictors of PFS, TTNT and OS. FLIPI score and T-MTV were tested as well.

Results: Median PFS, TTNT and OS were 1304 days (range 63-3294), 1392 days (range 63-3294) and 1572 days (range 111-3528) respectively.

Kurtosis at zero texture scale (SSF=0; HR (CI 95%) = 1.25 (1.05, 1.48), p=0.012), skewness at fine texture scale (SSF=2; HR (CI 95%) = 3.43 (1.03, 11.48), p=0.045), sexe (HR (CI 95%) = 4.996 (1.77, 14,13), p=0.002) and performans status (HR (CI 95%) = 6.86 (1.83, 25.65), p=0.004) were independent predictors of PFS. Kurtosis at zero texture scale (SSF=0; HR (CI 95%) = 1.28 (1.05, 1.54), p=0.012), skewness at fine texture scale (SSF=2; HR (CI 95%) = 4.94 (1.03, 17.81), p=0.045), sexe (HR (CI 95%) = 4.59 (1.66, 12.70), p=0.003) and performans status (HR (CI 95%) = 6.05 (1.48,

24.75), p=0.012) were independent predictors of TTNT. Sexe (HR (CI 95%) = 19.00 (1.66, 217.82), p=0.018) and FLIPI score (HR (CI 95%) = 6.43 (1.35, 30.66), p=0.019) were independent predictors of OS.

Conclusion: Pretreatment TEP scan texture analysis-derived tumour kurtosis and skewness may act as predictive biomarkers of PFS and TTNT in patients with follicular lymphoma treated with immunochemotherapy and maintenance.

Keywords: follicular lymphoma (FL); immunochemotherapy.

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THE ROLE OF SURVEILLANCE COMPUTED TOMOGRAPHY IN PATIENTS WITH FOLLICULAR LYMPHOMA

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Introduction: Surveillance computed tomography (sCT) has been performed in patients with lymphoma as a follow-up procedure after initial therapy. Several studies have demonstrated the lack of benefit of routine sCT in patients with curable subtypes such as diffuse large B-cell lymphoma and Hodgkin lymphoma. However, few studies have evaluated the clinical benefit of sCT in patients with incurable subtypes such as follicular lymphoma (FL).

Methods: We retrospectively reviewed the medical records of patients with FL grade 1-3a who achieved complete response (CR) or CR unconfirmed (CR/CRu) with first-line treatment between 2000 and 2016 at our institution. In accordance with the practice policy at our institution, patients had generally undergone sCT at 6-month intervals for the first 5 years, then at least annually before relapse. In patients who experienced first relapse, we examined the clinical characteristics at relapse and the prognosis after relapse according to the method of relapse detection.

Results: Of the 248 patients with FL who achieved first CR/CRu following initial therapy, 109 experienced relapse of FL with a median follow-up of 11 years, and 100 were evaluated in this study (Fig. 1). Among 100 patients, 61 relapses were detected by sCT (sCT group) and 39 were detected by clinical signs, including patient-reported symptoms, physical findings, and blood abnormalities (clinical signs group). There were no significant differences in patient characteristics at relapse between the two groups, except for a higher incidence of extranodal involvement in the clinical signs group. Histological transformation (HT) at relapse was confirmed in 8.2% of the sCT group and 7.7% of the clinical signs group by rebiopsy, with no significant difference. The proportion of patients who had received cytotoxic treatments after relapse was 50.8% in the sCT group and 64.1% in the clinical signs group, with no significant difference. The two groups also showed no significant difference in the time from relapse to the next cytotoxic treatment. Moreover, there was no significant difference between the two groups in overall survival from relapse.

sCT is thought to facilitate early detection of relapse only in cases of deep lesions such as mesenteric or retroperitoneal lymph nodes that would not be identified without imaging modalities. In this study, 54.1% of patients in the sCT group and 15.4% of those in the clinical signs group had only deep lesions at relapse.

Conclusion: Our results showed that the sCT and clinical signs group exhibited no significant differences in patient characteristics at relapse, incidence of HT, proportion of patients receiving next cytotoxic treatment, time to next cytotoxic treatment, and survival from relapse. In addition, the percentage of patients in the sCT group who had only deep lesions at relapse was higher than that in the clinical signs group.

Keywords: follicular lymphoma (FL).

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PATTERNS OF CHANGE IN TREATMENT, SURVIVAL, HISTOLOGICAL TRANSFORMATION, AND SECONDARY MALIGNANCIES OF FOLLICULAR LYMPHOMA OVER THE LAST 4 DECADES: A SINGLE CENTER EXPERIENCE

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Fig1. Flow diagram of patients in this study

TABLE 1

Characteristic	Entire cohort (N=727)	Decade 1 (1980-1989) (N=79)	Decade 2 (1990-1999) (N=163)	Decade 3 (2000-2009) (N=254)	Decade 4 (2010-2017) (N=231)	P value
Age (median)	57	54	54	57	61	<0.001
Male sex (%)	47	58	44	46	46	NS
Histologic grade 1 or 2 (%)	84	NA	89	83	83	NS
Performance status, ECOG ≥2 (%)	9	21	11	6	7	<0.001
Ann Arbor stage IV (%)	60	57	62	59	62	NS
Elevated LDH (%)	19	25	22	19	17	NS
High-risk FLIPI (%)	25	30	27	17	29	0.009
Initial watch & wait strategy (%)	15	3	3	13	30	<0.001
Rituximab-containing frontline regimen (%)	54	0	0	69	99	<0.001
CR/Cru rate (%)	65	45	53	74	70	<0.001
5-year PFS (%)	48	40	27	57	61	<0.001
5-year OS (%)	81	77	74	83	86	<0.001
5-yearrisk of HT (%)	8	8	10	5	8	NS
5-yearrisk of SM (%)	6	2	6	7	5	NS
Death due to progression (%)	54	61	66	42	45	0.023

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Introduction: Follicular lymphoma (FL), the most frequent type of indolent non-Hodgkin lymphoma, exhibits a long survival but a pattern of continuous relapses. With the advent of immunotherapy, both progression-free (PFS) and overall survival (OS) have improved significantly, but early progression and histologic transformation (HT) still confer a much poorer prognosis. However, few single-center series have been published describing the changes in outcomes of FL patients over the last decades.

Methods: 727 patients (338 M / 389 F; median age: 57 years) diagnosed with grade 1-3a FL at Hospital Clínic of Barcelona between 1980 and 2017 were categorized into 4 groups according to the decade (D) of diagnosis: D1, 1980-1989; D2, 1990-1999; D3, 2000-2009; and D4, 2010-2017. Baseline and follow-up characteristics were assessed retrospectively and compared among decades.

Results: Baseline characteristics, treatment modalities, response, survival, rate of HT and secondary malignancies (SM), and causes of death are detailed in the Table and plotted in the Figure. Median follow-up for the entire series was 7.6 years. Initial features were not significantly different across decades, except for the more advanced age at diagnosis in D4 and worse performance status in D1. An initial watch & wait strategy was adopted more frequently in D3 and D4. Rituximab was not part of the frontline regimen in D1 and D2, while it became an essential part of treatment in D3 and D4. A steady increase in the rate of complete responses was seen over the decades. The median PFS for treated patients was 4.6 years, and 10-year PFS was 35%, with a significant increase over time. Eighty-one patients experienced HT, and no significant differences were found in the risk of HT over the decades. Hematological malignancies were the most frequent type of secondary neoplasm (20%), and the risk of SM remained stable over time. Median OS for the entire cohort was 17.6 years, and the 10-year OS rate was 65%, with a significant increase in OS over the decades. When analyzing the causes of death over the decades, we saw a reduction in the percentage of patients dying due to FL progression.

Conclusions: Over the past 4 decades, presumably due to advances in therapy and supportive care, significant improvements have been seen in the response rate, PFS, OS, and the proportion of patients dying due to FL. The risk of HT and SM have essentially remained unchanged.

Keywords: follicular lymphoma (FL); rituximab.
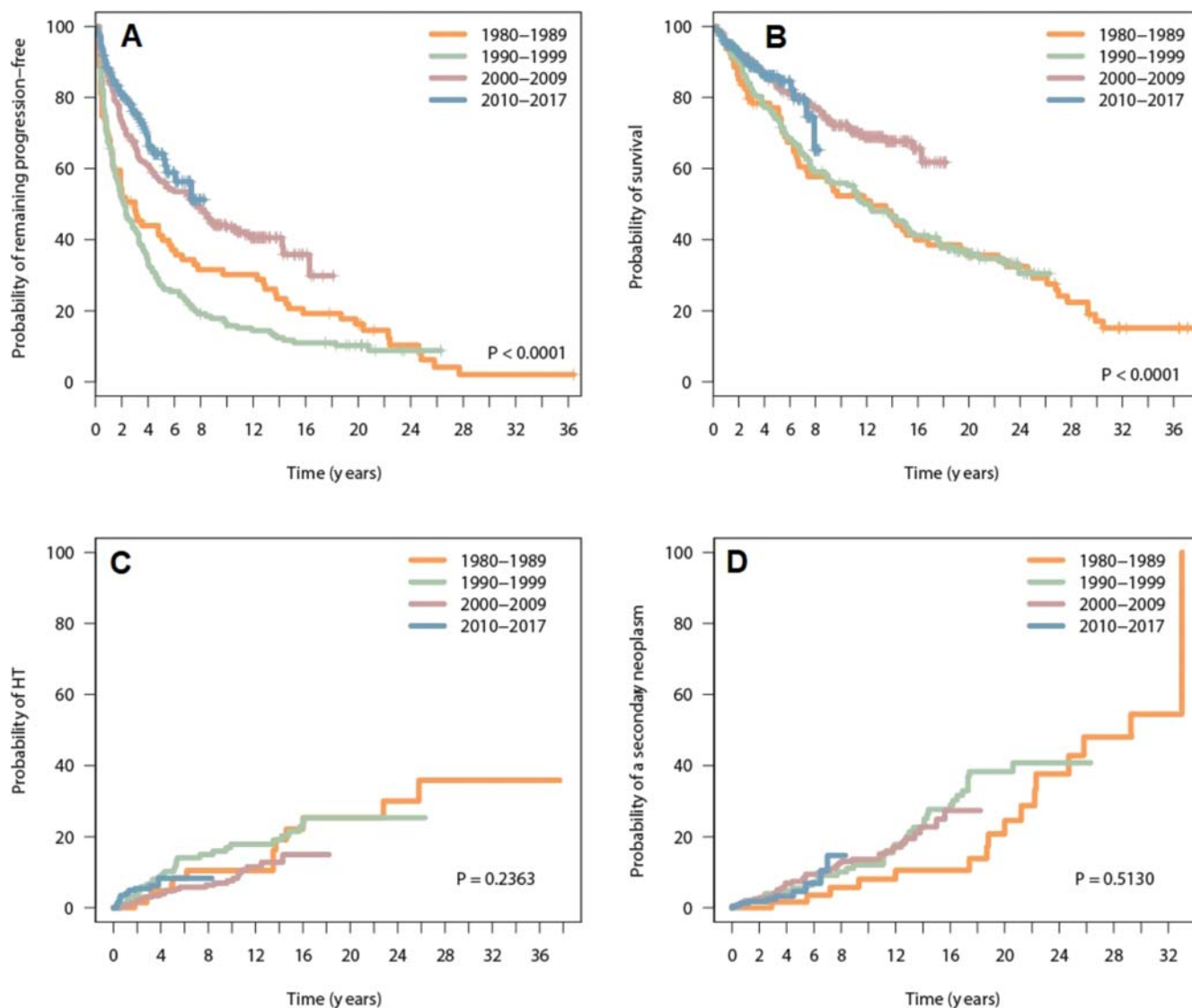
Figure. (A) PFS. (B) OS. (C) Risk of HT. (D) Risk of SM. All curves are plotted according to the decade of diagnosis.

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CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH RELAPSED FOLLICULAR LYMPHOMA FOLLOWING RETREATMENT WITH SECOND-LINE RITUXIMAB-CONTAINING CHEMOTHERAPY

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Background: The prognosis of follicular lymphoma (FL) is considered favorable with rituximab-containing first-line chemotherapy (R-CHEMO1). However, many patients will eventually require second line therapy, for which there is no current standard. Generally, patients receive a second course of rituximab-containing chemotherapy (R-CHEMO2) even though there are no prospective trials backing this approach.

Methods: We did a retrospective study of consecutive patients from 6 Canadian centres treated with R-CHEMO2 for relapsed biopsy-proven grade 1-3A FL initially treated with R-CHEMO1 ± maintenance rituximab (MR), and excluded transformed FL and second line radiotherapy or chemotherapy alone.

Results: 129 patients with FL, 48% female, were included. R-CHEMO1 was R-CVP in 95 (74%), R-CHOP in 29 (23%), BR in 4 (3%), and FR in one patient. 73 (57%) received MR1. 49 (38%) patients progressed within 24 months of R-CHEMO1 (POD24), with a median time from start of R-CHEMO1 to start of R-CHEMO2 of 36 months (range 2-145). At start of R-CHEMO2, the median year was 2011 (range 2004-2017), the median age was 60 (range 22-82). 80% had stage III/IV, 44% high-risk FLIPI, 39% high LDH. R-CHEMO2 included 40 (31%) BR, 19 (15%) R-CHOP, 19 (15%) R-CVP, 17 (13%) FR, 17 (13%) platinum-containing, and 17 (13%) other regimens. Overall response rate was 80%, complete response 37%. 40 (31%) patients received autologous stem cell transplantation (ASCT), 34 (26%) received MR2, and 5 received radiotherapy.

With a median follow-up of 5.2 years (range 1.1-13.3) after R-CHEMO2, 56 (43%) patients progressed (PROG2). 20 were biopsied (7 DLBCL, 13 FL) and 36 were not (34 had indolent behavior). Median PFS2 was 6.4 years (95% CI 3.0-9.9) and 5-year PFS2 was 54% (95% CI 53-55). 31 (24%) patients progressed within 6 months of R-CHEMO2 or MR2. Age >60 (HR 1.75, 95% CI 1.04-2.95, p=0.036), ASCT (HR 0.26, 95% CI 0.13-0.53, p<0.001), and CR to R-CHEMO2 (HR 0.22, 95% CI 0.11-0.44, p<0.001) were associated with PFS2. Median OS2 was not reached and 5-year OS2 was 81% (95% CI 80-82). 27 patients died at the time of last follow up including 20 from lymphoma. Elevated LDH (HR 3.22, 95% CI 1.42-7.28, p=0.005), high FLIPI (HR 5.13, 95% CI 2.04-12.86, p<0.001), ASCT (HR 0.19, 95% CI 0.06-0.64, p=0.007) and CR to R-CHEMO2 (HR 0.31, 95% CI 0.11-0.89, p=0.029) were associated with OS2.

Third line therapy was given to 53/56 patients with PROG2: 35 received R-CHEMO3, 3 ASCT, 9 allogeneic SCT, and many received novel/experimental agents. The median time to third line therapy was 1.5 years (range 0.13-8.1). 5-year OS3 of 57% (95% CI 55-59) did not differ according to indolent vs. aggressive behavior (p=0.306).

Conclusions: Relapsed FL after R-CHEMO1 can be successfully treated with R-CHEMO2 and lead to prolonged PFS2 and freedom from third-line treatment. Age <60, ASCT, and achieving CR are associated with improved PFS2. Outcomes at progression after R-CHEMO2 are less favorable, highlighting the need for other therapies in these patients.

Keywords: follicular lymphoma (FL); rituximab.

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PREDICTIVE VALUE OF PRIMA-PROGNOSTIC INDEX (PRIMA-PI) IN FIRST RELAPSE OF FOLLICULAR LYMPHOMA

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Introduction: The FLIPI (Follicular Lymphoma International Prognostic Index) is most commonly used prognostic index in follicular lymphoma (FL). Recently a new simple prognostic score (PRIMA-PI), based on bone marrow involvement and serum beta2 microglobulin was proposed for patients (pts) treated with immunochemotherapy (Bachy E. et al, Blood 2018). Predictive value of this score in setting of relapsed disease hasn´t been tested.

Aim: To evaluate PRIMA-PI in prediction of secondary overall survival (sOS) and progression free survival (sPFS) and to compare this index with FLIPI in first relapse of FL.

Methods: This retrospective analysis is a part of an observational clinical study NiHiL (GovTrial No NCT03199066). 436 pts in first relapse of FL grade 1-3a after first line treatment including rituximab (R) or obinutuzumab (G) were identified. Of these, 199 pts with full data set required for PRIMA-PI available were included into the analysis. sPFS and sOS were calculated from the time of first relapse.

Median age at the time of relapse was 61 years (range 30-86), 58% were females, 63% had clinical stage III-IV, 46% had elevated LDH, 12% had performance status ECOG ≥2, median time from initial diagnosis to first relapse was 32.2 months (range 3.7-148.1), 38% has progressed within 24 months of first line treatment. First line treatment was mainly R-CHOP/G-CHOP/R-CHOP-like regimen (78%) or R-CVP (12%). In relapse R, G or ofatumumab were used in 84% of pts, 31% were treated with platinum based regimen, high dose chemotherapy with autologous stem cell transplant was performed in 20% of pts. Local radiotherapy was used in 5% and watch and wait strategy in 11% of pts. Median follow up from date of relapse was 5.5 years.

Results: Secondary PRIMA-PI at the time of first relapse was low in 133/199 (66.8%), intermediate in 27/199 (13.6%) and high in 39/199 (19.6%) pts. Secondary FLIPI score was low in 58/199 (29.1%), intermediate in 53/199 (26.6%), high in 59/199 (29.6%) and unknown in 29/199 (14.6%) pts. 5-year-sPFS and sOS in PRIMA-PI low/intermediate/high group (Fig 1a) was 42.2% vs. 39.8% vs. 23.1% (p=0.0067) and 74.8% vs. 81.0% vs. 49.1% respectively (p=0.0023). 5-year-sPFS and sOS in FLIPI low/intermediate/high group (Fig 1b) was 50.4% vs. 32.5% vs. 32.2% (p=0.0136) and 83.8% vs. 66.1% vs. 62.4% respectively (p=0.0274).

Conclusions: PRIMA-PI maintains its prognostic value for predicting both sPFS and sOS in first relapse of FL. Particularly high risk PRIMA-PI is associated with significantly worse prognosis. However, at least

Fig. 1a

PFS by PRIMA-PI
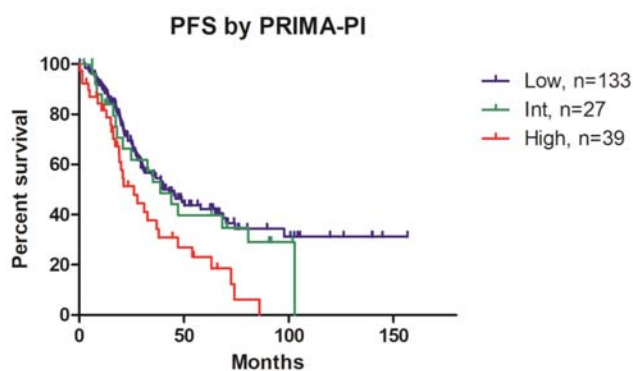
5y-PFS	Low	Int	High	p
	42.2%	39.8%	23.1%	0.0067

OS by PRIMA-PI

5y-OS	Low	Int	High	p
	74.8%	81.0%	49.1%	0.0023

Fig. 1b

PFS by FLIPI

5y-PFS	Low	Int	High	p
	50.4%	32.5%	32.2%	0.0136

OS by FLIPI
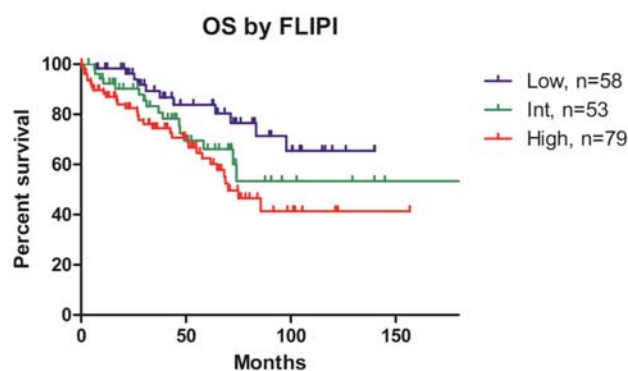
5y-OS	Low	Int	High	p
	83.8%	66.1%	62.4%	0.0274

in our cohort, the index hasn´t divided pts proportionally (67% of pts with low risk), furthermore, survival curves of low and intermediate risk groups seem to overlap. FLIPI was also predictive for both sPFS and sOS, especially low risk FLIPI was associated with long sOS.

Keywords: follicular lymphoma (FL); prognostic indices.

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COPANLISIB TREATMENT OF PATIENTS WITH RELAPSED OR REFRACTORY MARGINAL ZONE LYMPHOMA

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Introduction: Marginal zone lymphoma (MZL) is an indolent B-cell malignancy, comprising >10% of non-Hodgkin lymphomas. In 2017, the FDA approved the BTK inhibitor ibrutinib for treatment of patients with relapsed/refractory MZL based on outcomes from a study of 60 patients, wherein an objective response rate (ORR) of 48% (3% complete responses [CR]) and a median progression-free survival (PFS) of 14.2 months were reported (Noy et al. Blood 2017). We report here on the results from 23 heavily pretreated patients with relapsed or refractory MZL from the Phase II CHRONOS-1 study (NCT01660451; Part B) with the pan-class I phosphatidylinositol 3-kinase inhibitor copanlisib.

Methods: Patients enrolled in the CHRONOS-1 trial with histologically confirmed MZL relapsed after or refractory to ≥2 prior lines of treatment, including rituximab and an alkylating agent, were included in the subset analysis. Copanlisib 60 mg was administered via a 1-hour infusion on days 1, 8 and 15 of a 28-day cycle. Treatment continued until progression or unacceptable toxicity. The primary efficacy endpoint was ORR after ≥4 cycles, per independent assessment (Cheson et al. J Clin Oncol 2007). Secondary efficacy endpoints included duration of response (DoR), PFS and overall survival (OS). AEs were reported using MedDRA (v.19.1). The last patient was enrolled in February 2016. The initial data cut-off was June 2016; the long-term follow-up is based on a data cut-off of February 2018.

Results: The 23 MZL patients enrolled included 15 (65%) nodal MZL and 4 each (17%) with mucosa-associated lymphoid tissue (MALT) lymphoma and splenic MZL. Median age was 69 years (range 39-81). Patients had a median of 3 (range 2-9) prior lines of therapy; 48% were refractory to the last regimen and 44% were refractory to the last rituximab regimen.

As of February 2018, patients received a median of 5.8 cycles of treatment, with a median treatment duration of 23 weeks (range 1-191). Objective responses by independent assessment were observed in 18 patients (ORR 78%) and CRs in 3 patients (13%); ORRs were 50% (2/4 patients) in MALT MZL, 87% (13/15 patients) in nodal MZL and 75% (3/4 patients) in splenic MZL. Overall median DoR was 17.4 months (range 0-37.6). Median PFS was 24.2 months (range 0-41.1) and median OS was not reached, with an estimated 83% alive at 2 years. The most common treatment-emergent AEs (TEAEs; all grade/grade 3+) for the total MZL population were fatigue (52.2%/13.0%), hyperglycaemia (52.2%/43.5%) and diarrhoea (47.8%/13.0% grade 3). Laboratory toxicities of interest were principally grade 1, including increased AST (31.8% all grade/22.7% grade 1) and increased ALT (27.3%/13.6%). No grade 5 TEAEs were reported.

Conclusions: MZL patients with 2 or more lines of prior therapy treated with copanlisib had durable responses and PFS exceeding previous benchmarks.

Keywords: marginal zone lymphoma (MZL); PI3K/AKT/mTOR.

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CHARACTERIZATION OF DUVELISIB IN PATIENTS WITH REFRACTORY MARGINAL ZONE LYMPHOMA: DATA FROM THE PHASE 2 DYNAMO TRIAL

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Introduction: Duvelisib (DUV), a first-in-class oral dual phosphoinositide 3-kinase-δ,γ inhibitor, was approved by the US FDA for the treatment of relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after ≥ 2 prior therapies and for follicular lymphoma (FL) after ≥ 2 prior systemic therapies. DYNAMO is a phase 2 trial that evaluated the safety and efficacy of DUV monotherapy in a double-refractory iNHL population (NCT01882803; Flinn *J Clin Oncol* 2019), which included patients (pts) with marginal zone lymphoma (MZL). Here, we characterize the efficacy and safety of DUV for patients with MZL from the DYNAMO trial.

Methods: DYNAMO was an open-label, single-arm trial in pts with FL, CLL/SLL, or MZL whose disease was double refractory to rituximab (monotherapy or as part of a combination regimen) and to chemotherapy or radioimmunotherapy. Pts received DUV 25 mg BID in 28-day treatment cycles until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) as assessed by an independent review committee (IRC) per revised International Working Group (IWG) criteria. Secondary endpoints included duration of response, progression-free survival (PFS), overall survival, time to response, adverse events (AEs), and other safety parameters. *Pneumocystis jiroveci* prophylaxis was mandated for all pts.

Results: Of the 129 pts in the DYNAMO study, 18 (14%) were pts with MZL histology, of which 50% were of extranodal subtype, 22.2% nodal subtype, and 27.8% splenic subtype. Median age was 67 years (range, 61-77 years), and 72% (n = 13) were male. Median number of prior regimens was 2 (range, 1-8 prior), and 67% (n = 12) were refractory to ≥ 2 regimens. Median exposure to DUV was 8.35 months (range, 0.9-31.3 months).

The ORR per IRC was 39% (7 pts; 95% CI, 17.3%-64.3%), including 1 CR (ORR by subtype: 0% extranodal, 75% nodal, 80% splenic). Median time to response was 3.7 months. As of the data cutoff (18May2018) the median duration of response had not been reached. With a median follow-up of 31.2 months, the median PFS by IRC was 15.5 months (95% CI, 3.6-27.8 months).

AEs were mostly gr 1/2. Most common gr ≥ 3 AEs (> 15%) were neutropenia (28%) and diarrhea (17%). 33% of pts discontinued DUV due to an AE, including 3 who were in PR at the time of discontinuation. Follow-up imaging is not available for 1 pt, but the other 2 had sustained responses of > 1 year as of most recent imaging after treatment discontinuation. There was 1 gr 5 non-PD related AE of pancolitis (classified as potentially related to DUV).

Conclusions: DUV monotherapy demonstrated clinically meaningful antitumor activity in pts with MZL. DUV had a manageable safety profile, consistent with previous reports. These preliminary findings suggest that DUV represents a promising treatment option that warrants further investigation in pts with double-refractory MZL for whom limited treatment options exist.

Keywords: Duvelisib; marginal zone lymphoma (MZL); PI3K/AKT/mTOR.

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A PROGNOSTIC SCORE FOR TRANSFORMED WALDENSTRÖM MACROGLOBULINEMIA

TABLE 1

Entire cohort (n = 133)	
Median age (years)	64 (range, 32-86)
Sex male/female (ratio)	75/58 (1.3/1)
Prior MGUS history	20 (15%)
WM characteristics (concurrent WM and HT excluded) (n = 116)	
Serum IgM level (g/L)	17.7 (range, 1.4-66.7)
IPSS score (n = 76)	
0-1	31 (41%)
2	30 (39%)
≥ 3	15 (20%)
Median number of regimens	1 (range, 0-9)
Therapies (n = 98)	
Chlorambucil	43 (44%)
Fludarabine-based regimens	41 (42%)
Bendamustine +/- rituximab	19 (19%)
CHOP +/- rituximab	17 (17%)
Bortezomib-based regimens	15 (15%)
RCD	14 (14%)
Ibrutinib	5 (5%)
Autologous stem-cell transplantation	4 (3%)
Rituximab (alone or in combination)	67 (50%)
HT characteristics (n = 133)	
Median age (years)	68 (range, 33-89)
PS (0-1/≥ 2)	59/48 (55%/45%)
B symptoms	56 (47%)
Extranodal involvement	111 (86%)
Serum IgM level (g/L)	6.9 (range, 0-66.6)
Absolute neutrophils (x 10^9/L)	4.1 (range, 0.2-20.2)
Absolute lymphocytes (x 10^9/L)	0.9 (range, 0.1-56)
Hemoglobin (g/L)	104 (range, 46-155)
Platelets (x 10^9/L)	172 (range, 9-610)
Elevated LDH	85 (72%)
Albumin level < 3.5 g/dL	62 (56%)
Stage III or IV	96 (86%)
IPI score (n = 99)	
Low risk (0-1)	8 (8%)
Low-intermediate risk (2)	17 (17%)
High-intermediate risk (3)	33 (33%)
High risk (4-5)	41 (41%)
Median number of lines	1 (range, 0-5)
Therapies (n = 127)	
CHOP-like regimen +/- rituximab	102 (80%)
DHAP +/- rituximab	10 (8%)
GEMOX +/- rituximab	3 (4%)
Rituximab-containing regimen	110 (87%)
Autologous stem-cell transplantation	20 (16%)
Allogeneic stem-cell transplantation	6 (5%)

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Introduction: Transformation of Waldenström macroglobulinemia (WM) into diffuse large B-cell lymphoma is a rare complication usually associated with a poor but heterogeneous prognosis. Factors predicting survival in this setting are unknown. The objective of this study was to develop a prognostic index for overall survival in transformed WM patients.

Methods: We developed the scoring system from a cohort of 133 patients with transformed WM treated between 1995 and 2017 in French centers (n = 80), Dana-Farber Cancer Institute (Boston, n = 36), UCLH (London, n = 13) and Nieuwegein (Netherlands, n = 4). Clinical and biological characteristics were retrospectively collected. Multivariate analyses using cox proportional hazard model were performed to investigate the factors independently associated with 2-year overall survival and a risk score was created. Internal validation was performed.

Results: At the time of transformation, the median age was 68 years (range, 33-89) and the median time from WM diagnosis to histological transformation (HT) was 4.3 years [95% confidence interval (CI), 1.1–8.7]. The median number of therapies received for WM was 1 (0-9), including half of the patients receiving rituximab. At HT, patients presented with high-risk features. Extranodal involvement was found in 86% of patients and elevated LDH in 72%. First-line treatment for transformation consisted of R-CHOP-like regimen in 80% of patients. The median OS was 19 months (95% CI, 12-31) for the entire cohort. In univariate analysis, variables that predicted shorter 2-year OS were ≥ 1 previous treatment for WM ($p = 0.02$), prior rituximab exposure ($p = 0.01$), time to transformation ≥ 5 years ($p = 0.006$), elevated LDH ($p = 0.003$), B symptoms ($p = 0.02$) and platelet count < 100 x 10^9/l ($p = 0.007$). By multivariate analysis, three independent prognostic factors were identified: elevated LDH ($p = 0.003$; HR 3.6, 95% CI, 1.53-8.5), platelet count < 100 x 10^9/l ($p = 0.03$; HR 1.8, 95% CI, 1.04-3.19) and ≥ 1 previous treatment for WM ($p = 0.04$; HR 2, 95% CI, 1.04-3.94). Three risk groups were defined: low risk (0-1 point, 24% of patients), intermediate risk (2-3 points,
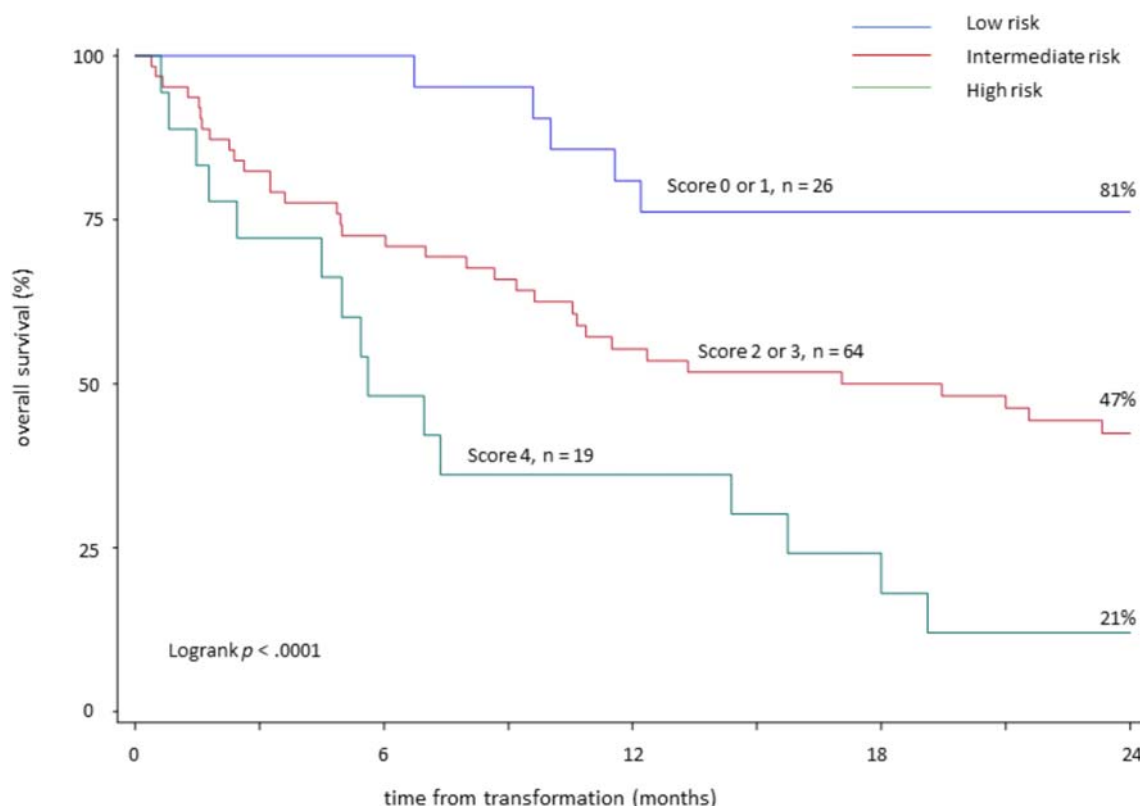
59% of patients) and poor risk (4 points, 17% of patients). Two-year OS rates were 81%, 47%, and 21%, respectively ($p < 0.0001$) (figure).

Conclusion: This easy-to-compute scoring index may allow the identification of groups of transformed WM patients with different outcomes and could be used for improving treatment choices.

Keywords: diffuse large B-cell lymphoma (DLBCL); prognostic indices; Waldenström's macroglobulinemia (WM).

MANTLE CELL

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SERUM BIOMARKERS ARE ASSOCIATED WITH TREATMENT RESPONSE IN RELAPSED MANTLE CELL LYMPHOMA

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Introduction: Recent advances in therapeutic strategies have provided novel treatment regimens for MCL, that until recently, was associated with dismal prognosis of 3-5 yrs median overall survival. However, strategies to guide patient stratification are still lacking in both diagnostic and relapsed setting. Non-invasive methods based on liquid biopsies would facilitate the continuous sampling of patients over time and identification of companion diagnostic biomarkers is warranted. For this purpose, we have used an antibody-based platform to identify serum proteins in relapsed patients that are homogenously treated as per the Nordic MCL6 clinical trial (Philemon). We hypothesize that, the platform can identify if the immune status at treatment start can influence the response to combinatorial immune-directed therapies. We also intend to study how treatment can influence the immune status across time.

Methods: Sequential serum samples from 44 patients treated with Lenalidomide, Ibrutinib and Rituximab (Philemon trial) were processed on the IMMRay™ platform (Immunovia). We processed serum samples from 4 time-points; at baseline and 12, 24 and 36 weeks of treatment which corresponds to cycle 4, 7 and 10, of the trial. The platform, allows the analysis of 380 different epitopes among approximately 150 unique proteins. It focuses on soluble immune-related proteins such as cytokines, chemokines and complement factors, as well as, several cancer-related markers. In brief, antibody fragments are produced and printed on a solid support. Samples are biotinylated and detected using a fluorescent marker after hybridization to the array. Spot recognition and raw data processing was performed using standard operating procedure according to the IMMRay guidelines (Immunovia). Normalization and further bioinformatic and biostatistical analysis were performed using standard tools which includes R, Qlucore and SIMCA; and several other in-house built softwares developed in conjunction to the experimental platform.

Results: Preliminary results using COX regression analysis shows that, at baseline, a signature of approximately 6-8 relevant proteins are associated with PFS. Further investigations are needed to validate this in an independent cohort of patients. Current investigations aim to identify if additional prognostic and biological information related to the treatment can be derived by comparing samples at baseline, cycle 4 and beyond.

Conclusion: We have showed that prognostic information can be derived from serum samples collected from relapsed MCL patients. To our knowledge, this is the first time that an antibody-based array is used as a tool to assess the possibility of developing serum-based signatures useful for treatment selection in relapsed MCL patients.

Keywords: B-cell lymphoma; immune system; mantle cell lymphoma (MCL).

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HIGH VIRAL LOADS OF CIRCULATING EPSTEIN-BARR VIRUS DNA COPY NUMBER IN PERIPHERAL BLOOD IS ASSOCIATED WITH INFERIOR PROGNOSIS IN PATIENTS WITH MANTLE CELL LYMPHOMA

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Introduction: Mantle cell lymphoma (MCL) is a distinct subtype of B cell non-Hodgkin lymphoma. No research has yet documented to investigate the prognostic implications of Epstein-Barr virus (EBV) infection in MCL. The objective of this study was to examine whether EBV DNA load may influence the heterogeneity in the course of the disease in MCL patients.

Methods: Eighty-eight MCL patients were retrospectively enrolled in the study. EBV DNA load was detected by real-time quantitative PCR for quantification. The univariate and multivariate Cox proportional hazards models were established for the estimation of prognostic factors.

Results: Twenty-seven patients were detected positive for EBV DNA ad the median virus titer was 1.72×10^4 copies/mL (range, 8.20×10^2 to 4.14×10^5 copies/mL). With a median follow-up of 39 months (range, 9 to 120 months), patients in EBV DNA-positive group
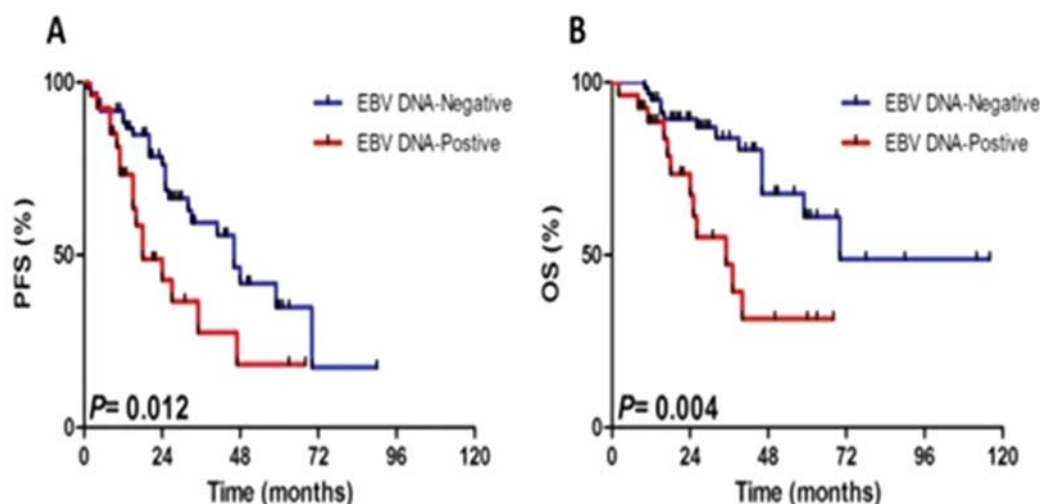
Figure 1. Progressive-free survival (PFS) and overall survival (OS) for 88 patients with the analysis of pretreatment Epstein-Barr virus (EBV) DNA status.

displayed unfavorable progression-free survival (PFS) (P=0.012) and overall survival (OS) (P=0.004) than patients in EBV DNA-negative group (Figure 1). Multivariate Cox regression analysis revealed that EBV DNA-positivity was independent risk factor for both PFS (HR, 2.04; 95% CI, 1.07 to 3.92; P=0.031) and OS (HR, 2.68; 95% CI, 1.20 to 6.00; P=0.016). Reduction in EBV copies was significantly associated with therapy-response.

Conclusion: Circulating EBV DNA load in whole blood proved to be a significant predictor of prognosis in patients with MCL, which needs further validation in large-scale clinical studies.

Keywords: Epstein-Barr virus (EBV); mantle cell lymphoma (MCL); prognostic indices.

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OBINUTUZUMAB THERAPY IN PATIENTS WITH MARGINAL ZONE AND MANTLE CELL LYMPHOMA

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Introduction: Obinutuzumab (OBI) is FDA approved in chronic lymphocytic leukemia and follicular lymphoma, with favorable efficacy profiles noted in both settings. While there was a small subpopulation of marginal zone lymphoma (MZL) and mantle cell lymphoma patients (pts) in the GAUSS trial and GADOLIN/GAUGUIN trials respectively, there is little clinical experience in using OBI in these patient populations outside the context of a clinical trial. We describe a real world experience of OBI use in MZL and MCL pts off clinical trial.

Methods: We conducted a retrospective cohort study of all adult pts who received OBI for MZL and MCL at the University of Pennsylvania between 2/2013 and 2/2019. Demographics, duration of therapy, reason for discontinuation, overall response, survival, and toxicities were examined. The primary endpoints were progression-free survival (PFS; defined as time from OBI start to disease progression or regimen change, death due to MZL/MCL or last-follow-up in remission), and overall survival using the Kaplan-Meier method. All other analyses were descriptive.

Results: We identified a total of 10 pts for the entire cohort, 6 with MZL and 4 with MCL. The median age at start of OBI was 64 years (Range 50-92). 80% of pts were stage 4, had a median of 2 prior therapies (1 MZL patient treated frontline), median ECOG status 0, and one MZL patient had an MYD88 mutation. One patient was rituximab naïve, but 70% were rituximab refractory. The median number of cycles administered of OBI was 7 (Range 1-31) respectively. 50% of pts received OBI in combination, 3 pts with bendamustine, 1 with chlorambucil, and 1 with ibrutinib. Overall response rate was 90% (10% CR). Median PFS and OS were 11.5 and 13.5 months respectively. Two pts progressed following OBI therapy; one patient with MZL who subsequently was treated with ibrutinib and one with MCL subsequently treated with venetoclax.

50% of pts experienced at least one Adverse event(AE). AEs included: Infusion related reactions (40%), thrombocytopenia (40%), diarrhea (30%), neutropenia (20%), infection (10%). Three pts were on growth factor during OBI administration. One patient discontinued therapy secondarily to an infusion related reaction.

Conclusions: OBI therapy was well tolerated in our cohort of MZL and MCL pts. We observed a high ORR and durable PFS and OS opportunity. Only two pts experienced progression following OBI therapy, both of whom are currently controlled with novel oral agents. The AE profile of OBI was well tolerated, with toxicities consistent with current package labeling. Additional clinical trials and/or pooled data from retrospective observational studies will help confirm OBI therapy's durable efficacy benefit for pts with MZL and low-risk MCL.

Keywords: mantle cell lymphoma (MCL); marginal zone lymphoma (MZL); obinutuzumab.

Progression Free Survival

Overall Survival

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MAINTENANCE RITUXIMAB IS ASSOCIATED WITH IMPROVED OVERALL SURVIVAL IN MANTLE CELL LYMPHOMA PATIENTS RESPONDING TO INDUCTION THERAPY WITH BENDAMUSTINE + RITUXIMAB (BR)

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Introduction: Bendamustine + rituximab (BR) is frequently utilized as initial treatment for patients (pts) with mantle cell lymphoma (MCL). Following induction BR, the role of maintenance rituximab (MR) is controversial and practice patterns vary. MR improves overall survival (OS) in younger pts following autologous stem cell transplantation (ASCT) and in older pts following R-CHOP. However, a preliminary analysis of the randomized phase 3 MAINTAIN study revealed neither a progression-free survival (PFS) nor OS benefit for MR versus observation for MCL pts (Rummel, ASCO 2016). We evaluated the impact of MR following BR in a non-trial population.

Methods: We reviewed outcomes for MCL pts treated with frontline BR at 12 U.S. medical centers from 2011 - 2017. After BR, pts were treated with or without MR based on individual physician/patient preferences. We compared baseline pt characteristics using chi-squared test, Fisher's exact tests, or ANOVA. Descriptive statistics, comparisons, and OS using the Kaplan-Meier method were first stratified by response status as determined by the treating site (complete response (CR) only, partial response (PR) only, and CR/PR), and were then evaluated for pts who did not receive ASCT in first remission.

Results: 206 pts were treated with frontline BR. 73% achieved CR 73%, 16%, PR, 2% stable disease 9% and progressive disease. Among these who did not undergo consolidation ASCT, 114 pts achieved a CR (n=91) or PR (n=23) to BR and had available data regarding MR. The median age was 70 (range 50 – 89) years and 65% were male. 68 pts (60%) received MR and 46 (40%) received no maintenance. Baseline MIPI score was low (11%), intermediate (39%), or high
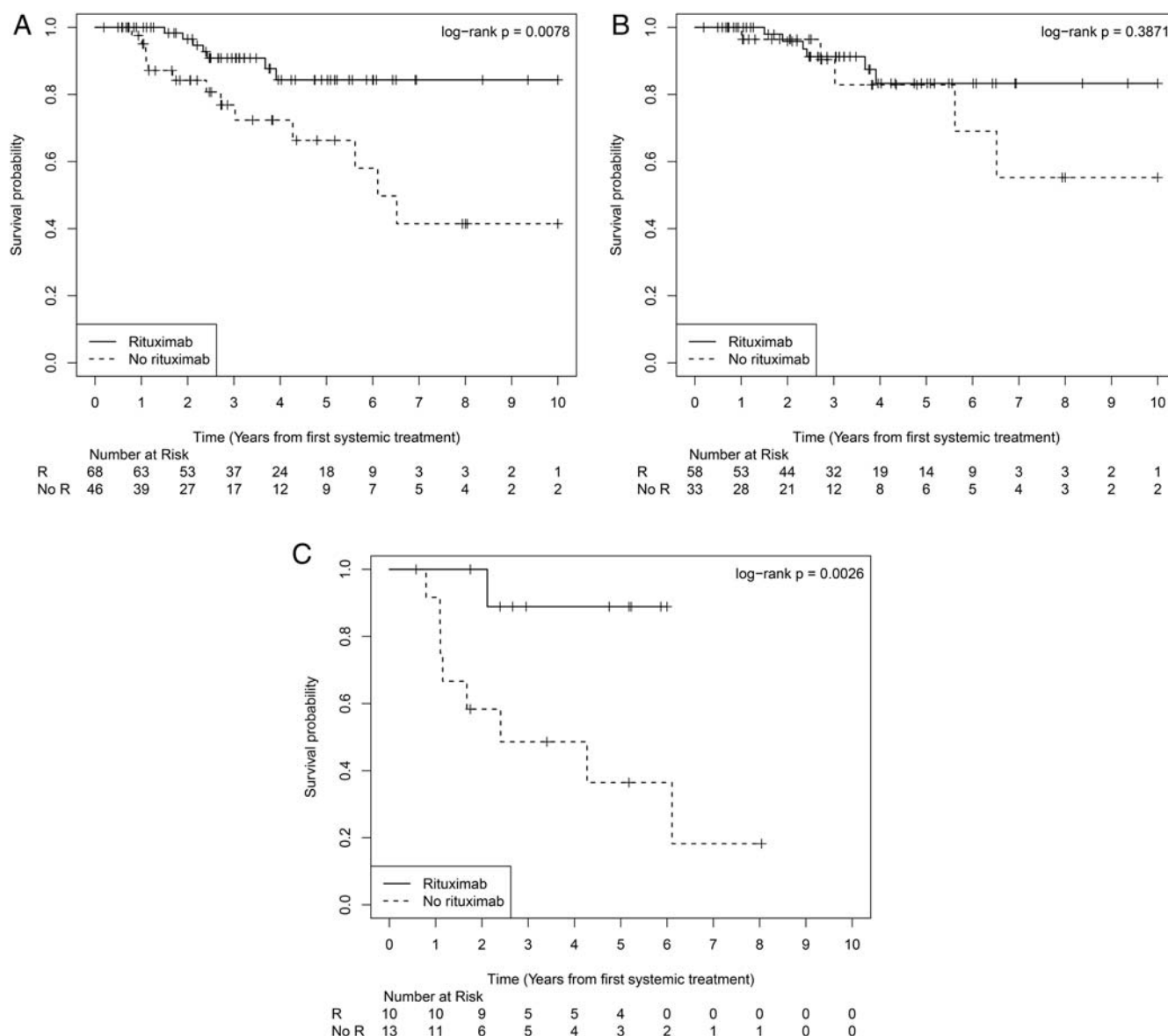
Figure: Outcomes of pts treated with BR without consolidation ASCT, followed by MR vs. no maintenance. Panel A: OS for pts in CR or PR; Panel B, OS for patients in CR; Panel C, OS for patients in PR.

(50%) among 88 patients with available data and did not differ between treatment cohorts. With a median follow up of 2.9 years, median OS was not reached for pts who received MR vs. 6.1 years for those who received no maintenance (Figure Panel A, P = 0.008). Use of MR vs. no maintenance was associated with a significant improvement in OS for pts in PR at the end of induction therapy (Figure Panel B, median not reached vs. 2.4 years, P = 0.0226), but there was no statistically significant OS difference for pts in CR (Figure Panel C, median not reached vs. 11.5 years, P = 0.387).

Conclusions: Contrary to the prospective MAINTAIN randomized study, in this multi-center retrospective analysis, MR was associated with an improvement in OS in pts receiving frontline BR without consolidative ASCT, with benefit primarily for pts in PR after induction therapy. Because patient selection may have influenced outcomes,
additional prospective data are needed to clarify the possibility of an OS benefit to RM after BR and to further delineate the possibility of differential benefit of RM based on depth of response to frontline BR.

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MANTLE CELL LYMPHOMA: TWO REFERENCE CENTER'S RESULTS

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Introduction: Mantle cell lymphoma (MCL) is a B-cell neoplasm with CCND1[t(11;14)(q13;q32), cyclin D1] translocation (1). In the guidelines recommend various treatment recommendation based on the age, performance status (fitnes status), comorbities (2). In this retrospective study, we have sought out to analyze the clinical characteristic features and evaluate prognostic factors on the survival of 78 MCL patients.

Methods: This is a retrospective study. We analyzed patients' information who applied two reference center Hacettepe University and Ondokuz Mayıs University, Hematology Department between January 2001 and September 2018. Categorical and continuous data were expressed as ratio (%) and median (range) and they were compared by Chi-square and Mann Whitney U tests, respectively. The primary endpoint of study was overall survival and disease free survival. Parameters related to survival were investigated by cox regression univariate and multivariate analyses.

Results: The median age of patients was 62 years (34-86 years). 78.2% of patients were male. For initial therapy, only one patient had no chemotherapy because of age and poor general status. The other treatment choices were 42.3% RCHOP, 26.9% R-Bendamustin, 9% HyperCVAD, 7.7% RCHOP/RDHAP alternating. Only 13 patients
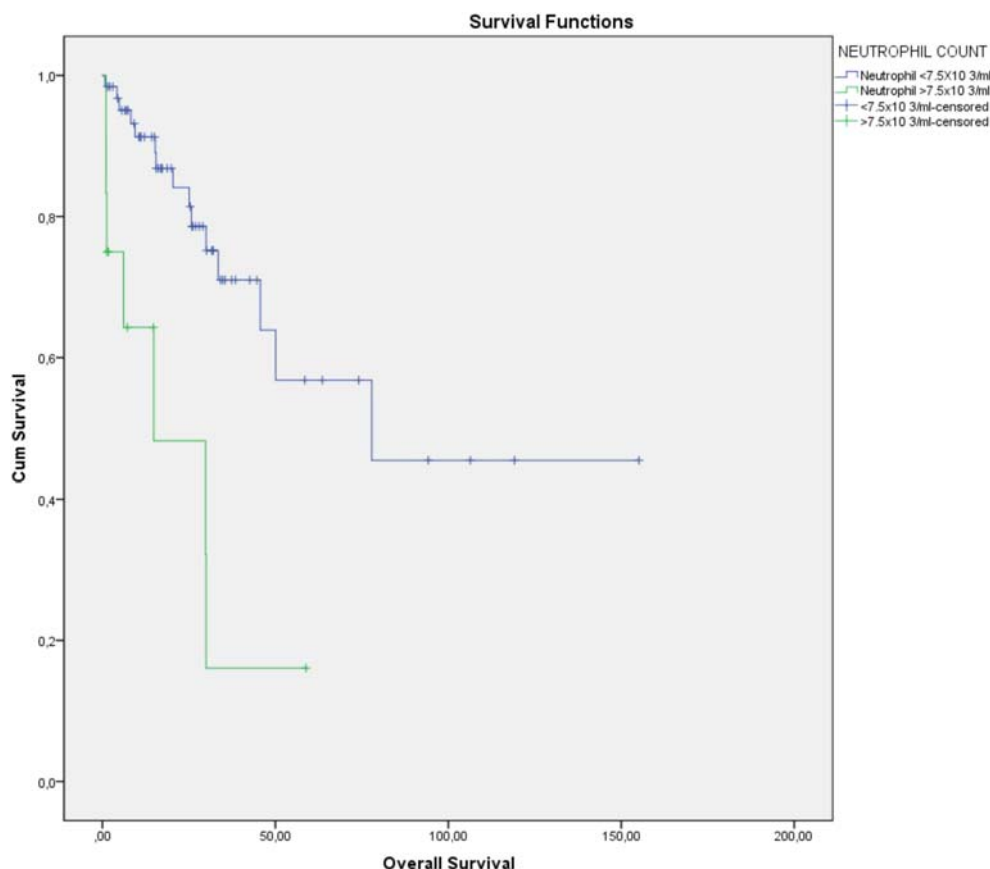
Figure 1. Overall Survival According to Neutrophil Count Groups.

underwent ASCT. Median overall survival (OS) duration was 77.8 months (53.8-101.8). Median disease-free survival (DFS) duration was 20.6 months (14.2-26.9), for the whole MCL group. The univariate analysis showed that MIPI and neutrophil count was effecting the OS (p=0.047 and p=0.001). The multi-variate analyses showed that the neutrophil count at diagnosis was independent prognostic risk factor (p=0.005) for OS. The univariate and multi-variate analysis showed that age <65 effect was prominent DFS(p=0.074).

Conclusions: Mantle cell lymphoma (MCL) one of Non-Hodgkin's lymphomas has a poor prognosis (3). The median OS duration is somewhat prolonged in the last years with new treatment approaches but MCL is still an incurable disease. Herein, we have reported two referral centers of MCL results. Similarly in the literature, the neutrophil count was independent prognostic risk factor for OS.

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Keywords: mantle cell lymphoma (MCL); non-Hodgkin lymphoma (NHL); prognostic indices.

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OUTCOMES FOR PATIENTS WITH MANTLE CELL LYMPHOMA EXPERIENCING FRONTLINE TREATMENT FAILURE: A MULTICENTER RETROSPECTIVE STUDY

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Background: Early progression (EP) after intensive initial treatment (tx) for mantle cell lymphoma (MCL) is associated with inferior overall survival (OS; Dietrich Ann Oncol 2014), but its impact after less intensive tx and the appropriate management of patients with EP is not understood. We examined outcomes for MCL pts with EP stratified by tx intensity and described the impact of 2nd line tx selection on progression free survival (PFS) after EP.

Methods: We reviewed clinical data and examined outcomes for MCL pts treated between 2000 and 2017 at 12 centers with EP defined by progression of disease within 1 year (y) of tx initiation. OS was defined as time from 1st progression to death or last follow-up for pts with EP. Post-EP PFS was defined from 1st progression to either 2nd progression or death or last follow-up. OS and PFS were estimated using the Kaplan-Meier method and compared using log rank test. Intensive tx was defined as receipt of high dose cytarabine and/or autologous transplant in 1st remission. Patient characteristics were compared across intensive and less intensive tx using ANOVA.

Results: Of 1119 pts treated at the centers, 473 experienced progression and 153 had EP. Median follow-up after initial progression was 1.3 y for patients with EP. Baseline characteristics for pts with EP included median age 65 y, 72% male, Ki67 > 30% in 62% (52/83 with available data), complex karyotype in 27% (12/44 with available data), MIPI risk score high in 49% and intermediate in 26%. Frontline tx was intensive in 33%. Pts receiving intensive frontline tx were younger; median age 59 vs 67 y (p<0.001). Second line salvage tx was known for 111 pts with EP; salvage tx included BTK inhibitor (BTKi; single agent 19% and in combination 9%), bendamustine (benda) based chemoimmunotherapy (CIT) in 13%, other salvage CIT in 33%, lenalidomide and/or bortezomib (len/bortez) in 16%, and other tx (6%), with 3% of pts receiving no salvage tx. Twenty-four pts underwent allogeneic transplant at any time after progression. Median PFS was 1.4 y (95% confidence interval (CI) 0.8-2.4). No salvage tx was associated with superior PFS (p=0.38); median PFS for single agent BTKi was 1.2 y (CI 0.5-2.9), for benda was 0.7 y (C.I. 0.3-1.7), for len/bortez was 0.4 y (CI 0.3-3.3), and for other CIT was 2.3 y (CI 0.5-not reached). PFS after EP did not differ between intensive

Figure:

Overall Survival All Patients with Early Progression

Kaplan-Meier Plot

Overall Survival: Early Progression Intensive vs Less Intensive Therapy

Kaplan-Meier Plot
With Number of Subjects at Risk
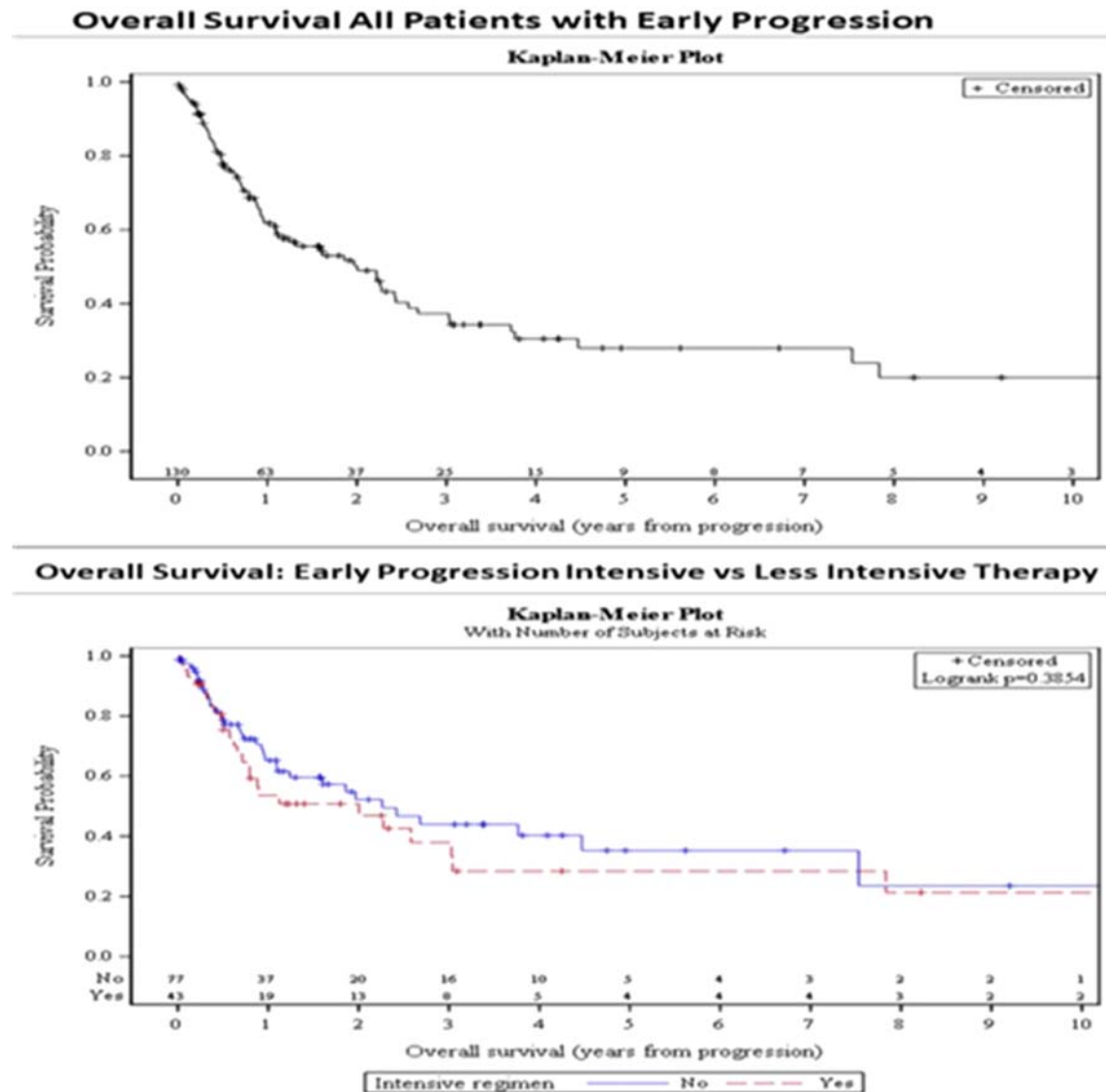
and less intensive frontline tx; median PFS 0.8 vs 1.2 y (p=0.056). The median OS for pts with EP was 2.0 y (CI 1.1-2.6), with no difference between intensive vs less intensive frontline tx (2.3 vs 2.0 y, p=0.39).

Conclusions: Relapse of MCL within one y of frontline tx is associated with very poor outcomes for all pts regardless frontline tx and post-EP PFS was poor for all current 2nd txs. MCL pts experiencing EP represent an unmet medical need and a target population for novel approaches.

Keywords: mantle cell lymphoma (MCL); salvage treatment.

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ONLINE EDUCATION SIGNIFICANTLY IMPROVED THE COMPETENCE OF HEMATOLOGISTS/ONCOLOGISTS AND NURSES REGARDING THE USE OF BTK INHIBITORS FOR MANTLE CELL LYMPHOMA

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Introduction: Mantle cell lymphoma (MCL) is an aggressive, rare, form of non-Hodgkin lymphoma. Due to the rarity of MCL, it is important that hematologists/oncologists (hem/oncs) and nurses are competent utilizing treatments in order to optimize patient outcomes. The goal of this initiative was to determine if online education could improve hem/onc and nurse clinical knowledge and competence using BTK inhibitors (BTKi) to treat MCL.

Methods: The format was an online continuing medical education (CME)-certified text-based activity composed of 2 patient cases with interactive questions. Evidence-based educational feedback was provided following each response. Three multiple-choice competence questions and 1 self-efficacy question were selected from the set of intra-activity questions to be repeated immediately after activity participation. Questions assessed the impact of the education with a repeated pairs pre-assessment/post-assessment study design where each participant served as his/her own control. A chi-square test was used to identify differences between pre- and post-assessment responses. P values were calculated; those < 0.05 were considered statistically significant. The activity launched online September 20, 2018 and data were collected through March 15, 2019.

Results: Results are for those who have completed the pre- and post-assessment questions during the study period (n = 166 hem/onc; n = 363 nurses). Upon completion of the activity, an improvement from pre- to post-assessment was observed in the hem/oncs and nurse's ability to:

- Determine when a BTK inhibitor would be appropriate for a patient with relapsed MCL (hem/oncs: 84% vs 93%, P < .05; nurses: 58% vs 72%, P < .001)
- Differentiate between first and second generation BTKi (hem/oncs: 48% vs 93%, P < 0.001; nurses: 28% vs 53%, P < .001)
- Manage treatment-related adverse events (TRAEs) for patients receiving BTKi (hem/oncs: 59% vs 95%, P < 0.001; nurses: 31% vs 78%, P < .001)

- Report greater confidence incorporating BTKi in the treatment of patients with B-cell malignancies (total average confidence shift; hem/oncs: increase of 17.3%; nurses: increase 18.3%)

Conclusions: This online, interactive, case-based CME-certified educational activity led to statistically significant improvements in the knowledge and clinical competence of hem/oncs and nurses regarding selection of patients with MCL to receive BTKi, the differences between first and second generation BTKi, and management of TRAEs for patients receiving BTKi. The results indicate that unique educational methodologies and platforms, which are available on-demand, can be effective tools for advancing clinical decision making. Additional studies are needed to assess whether improved aptitude translates to improved performance during clinical practice.

Keywords: acalabrutinib; ibrutinib; mantle cell lymphoma (MCL).

AGGRESSIVE LYMPHOMA

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VERY EARLY FDG PET/CT SCAN MAY PREDICT OUTCOMES IN RELAPSED OR REFRACTORY DLBCL PATIENTS TREATED WITH SALVAGE THERAPY

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Background: Standard therapy for first relapsed Diffuse Large B-cell Lymphoma (DLBCL) is platinum-based chemotherapy (PBC) and autologous stem cell transplant (AutoSCT), however only half of patients respond. To date, there are no patient or tumor factors that are predictive for response. Early identification of lack of response could allow for alternative therapy selection, avoidance of toxic and futile therapy, and potentially impact clinical outcomes. Positron emission tomography–computed tomography (PET-CT) is commonly utilized to assess response after two cycles of PBC, but the utility at earlier time points remains unknown. We conducted an investigator initiated pilot study (NCT02405078) of PET-CT on day 4 and day 21 of therapy for patients with relapsed DLBCL in comparison with standard time points, along with paired collection of blood for circulating tumor (ct) DNA analysis.

Methods: Adult patients with relapsed DLBCL who were eligible for PBC and AutoSCT were eligible. Therapy was selected by the treating physician and not restricted per protocol. The primary objectives were

to evaluate the ability of early PET-CT to predict response to standard immunochemotherapy, in comparison with PET-CT at standard time points and with blood based detection of a ctDNA. Patients underwent standard ^{18}F-fluorodeoxyglucose (FDG) PET-CT during screening and at the conclusion of 2 cycles of PBC per standard clinical practice, and research FDG PET-CT on day 4 and day 21 of cycle 1 of PBC. Treating physicians were not blinded to the research PET-CT results, but were encouraged to manage the patients per standard practice.

Results: The protocol has accrued 28 patients from February 2016 to March 2019. The median age was 62 years (range: 25-82), and 36% were female. 61% had poor risk IPI, 71% had advanced stage. 24 patients had a PET-CT on day 4 (4 missing due to patient status factors and logistical issues). The response rates on day 4 were: complete response 21% (CR, n=5), partial response 33% (PR, n=8), stable disease 37.5% (SD, n=9), and progressive disease 8% (n=2). Among the 5 patients with CR on day 4, all had CR at the end of therapy and have not relapsed. Among the 8 patients with PR on day 4, 2 achieved a CR at the end of therapy and 6 had progressive disease. Among the 11 patients with SD or PD on day 4, 2 patients achieved a PR but both had eventual relapse and all others had PD at end of therapy. Additional data from day 21 PET-CT and ctDNA testing may be presented at the meeting.

Conclusions: Our pilot study suggests that very early FDG PET-CT may be able to predict for end of therapy response in patients with relapsed DLBCL. Patients who achieve less than a complete response on day 4 of salvage chemotherapy have a high probability of therapeutic failure and could be considered for alternative therapeutic options. The limitations of our study include small patient numbers, heterogeneity of therapy, and availability of PET-CT at very early time points off study.

Keywords: diffuse large B-cell lymphoma (DLBCL); positron emission tomography (PET); prognostic indices.

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PROGNOSTIC VALUE OF BASELINE FDG PET PARAMETERS IN HIGH RISK DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS

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Introduction: In treatment of diffuse large cell lymphoma (DLBCL) PET/CT is currently used as interim risk stratification and response evaluation. Here, a high risk cohort of patients included in a Nordic multi-centre study was analysed to evaluate possible associations between baseline FDG-PET parameters and patient outcome.

Methods: Patients with available baseline PET/CT were included for study. Patients were treated with dose-dense chemo-immunotherapy, and data on overall survival (OS) and progression-free survival (PFS) were available for all patients. The following PET parameters were derived for each lesion: Standardized uptake value (SUV) max, metabolic tumour volume (MTV) and total lesion glycolysis (TLG). Total MTV and TLG values (tMTV and tTLG) were evaluated as possible predictors of outcome. Each variable was divided at the median and high vs. low values were entered into Cox regression. Analyses were adjusted for age and international prognostic index (IPI) score.

Results: Fifty-one patients were included for study. Median age was 52 years and 29 % were female. Median follow-up time was 42 months (5-66). During follow-up, nine patients died, and ten patients relapsed. Median baseline values (range) for tMTV, SUVmax and tTLG were 567.0 (3.1 – 13505.9), 20.5 (5.1-79.0) and 4615.3 (15.3– 46393.3), respectively.

In adjusted analyses, tMTVwas significantly associated with both increased mortality (HR 5.2, 1.1-11.3-, p=0.037) and relapse or death (HR 4.7, 1.0-10.4, p=0.046). No significant associations were seen for SUVmax or tTLG.

Conclusion: Baseline tMTV could be a promising marker for risk stratification at baseline. However, this is a small study sample of high risk DLBCL patients, and results must be interpreted with caution. A larger study of baseline parameters and outcome seems warranted.

Keywords: B-cell lymphoma; positron emission tomography (PET); prognostic indices.

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C-REACTIVE PROTEIN-TO-ALBUMIN RATIO IS AN INDEPENDENT POOR PROGNOSIS AND IMPROVING NCCN-IPI SCORE IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA: A CLINICAL ANALYSIS OF 414 CASES

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Introduction: In recent years, increasing evidences have validated that cancer-associated systemic inflammation and malnutrition had exact prognostic impact on the majority of patients with malignancies. Numerous circulating inflammatory and nutritive indicators have been proposed as prognostic indicators for malignant tumors including
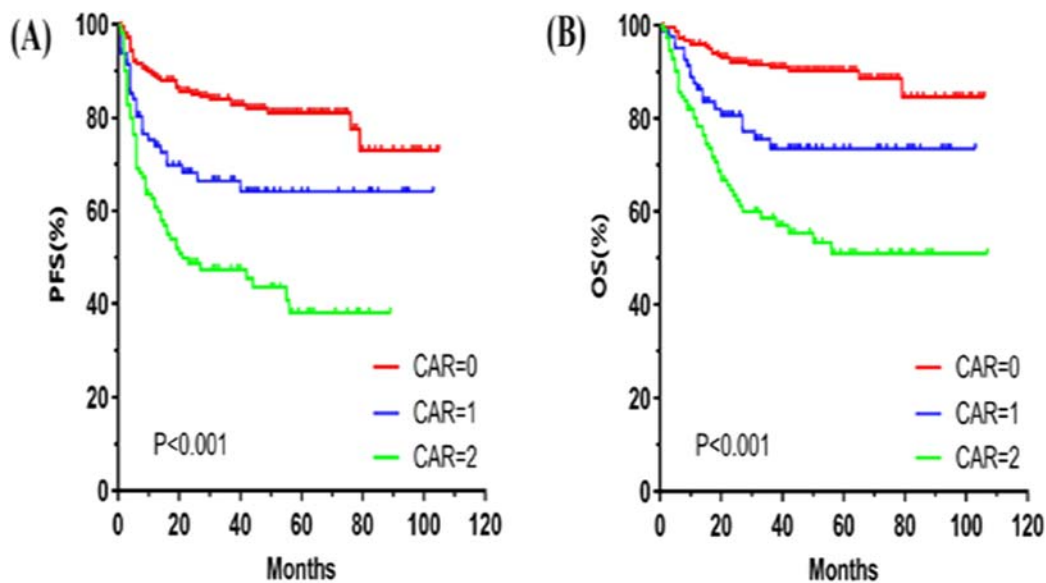
Figure 1. Time to treatment (TTT) and overall survival (OS) curve of 97 patients with CLL based on EBV-mir-BHRF1-1 by Kaplan-Meier estimation. Low group value is below the cut-off value (0.0012), and high group above the cut-off value.

DLBCL. Among them, the Glasgow Prognostic Score (GPS), the modified Glasgow Prognostic Score (mGPS) are novel inflammatory indicators which consist of C-reactive protein (CRP) and albumin (ALB) and reflect both the systematic inflammatory response and nutritional status. Recently, the ratio of CRP-to-ALB (CAR) has been identified as another serum-based inflammatory indicator and several studies have reported that the CAR is significantly related to prognosis in various types of cancers.

Methods: Four hundred and fourteen newly-diagnosed DLBCL patients were enrolled in the retrospective study. The univariate and multivariate Cox proportional hazards models were established for the estimation of prognostic factors. Receiver-operator characteristic (ROC) curves and the corresponding areas under the curve (AUC) were calculated to predicted probability of variables.

Results: With a median follow-up of 40 months (range, 0 to 105 months), patients with higher CAR displayed unfavorable progression-free survival (PFS) ($P<0.001$) and overall survival (OS) ($P<0.001$) (**Figure 1**). Multivariate Cox regression analysis validated that CAR was independent risk factor for both PFS (HR, 1.548; 95% CI, 1.224 to 1.958; $P<0.001$) and OS (HR, 1.763; 95% CI, 1.291 to 2.335; $P<0.001$). It was demonstrated that CAR + NCCN-IPI had a superior prognostic significance than NCCN-IPI alone ($P=0.0028$ for PFS, $P=0.0011$ for OS)

Conclusions: The pre-existing high CRP-to-ALB ratio was an independent prognostic factor for PFS and OS. Synchronously, adding the criterion of high CAR evidently improved the prognostic capacity of the National Comprehensive Cancer Network -International Prognostic Index (NCCN-IPI) for predicting PFS and OS in DLBCL.

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RELATIONSHIP BETWEEN SOCIOECONOMIC FACTORS AND DELAY IN DIAGNOSIS AND INITIAL TREATMENT IN PATIENTS WITH DIFUSSE LARGE B CELL LYMPHOMA (DLBCL). DO THESE FACTORS IMPACT ON THE RESPONSE RATE? RESULTS OF A MULTICENTRIC ARGENTINIAN STUDY

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Introduction: Immunochemotherapy (ICT) with R-CHOP (or R-CHOP-like) is the standard of care for patients (pts) diagnosed with DLBCL. Due to the aggressiveness of these lymphomas and their potential curability treated with the standard of care, treatment should be initiated without delay.

Objectives: To define the impact generated by the delay in the different diagnostic-therapeutic stages, from the onset of symptoms to the administration of ICT, on therapeutic response rates in a series of pts diagnosed with DLBCL from various institutions from Argentina (public and private). We focused our analysis on the reasons of delay and their relationship with socioeconomic factors.

Patients and methods: We designed a multicentric, descriptive, retrospective study in which patients diagnosed with DLBCL between 2/2004 and 4/2015 in the participating institutions were registered. Variables of interest were: date of beginning of the symptoms, 1st consultation, date of anatomopathological diagnosis, beginning and end of treatment. All causes of identified delay on the process of diagnosis and treatment were recorded. The place of residence, educational level, health care coverage, availability of rituximab (R) in 1st cycle and response rate, completed the studied variables.

Results: 278 pts were recorded (Male/female ratio: 1.007/1). Median age was 54 years old (19-88 years). The interval between symptoms onset and 1st consultation was variable (258 pts): <3 months: 65.11%; 3-6 months: 24.03%; 6-12 months: 7.36%, and more 1 year: 3.48%. The delay was not related to social coverage or educational level, but related to psychological factors: reluctance to consultation in the majority of pts (probably negation).

Clinical presentation: ECOG PS: 75% of pts had scores 0-1, only 3% had ECOG:4. 49% of pts had advanced disease (Ann-Arbor III-IV); 18.54% were stage I. Bulky disease was present in 21.08%, and 46% of pts had B symptoms. Extranodal (EN) compromise was present in 55.3% (141/255pts: EN 1: 87.23%; EN 2: 11.34%; EN 3: 1.41%). LDH was increased in the half of pts. Distribution by IPI score was: low: (0-1): 49.09%, Int/low (2): 25.45%, Int/high (3): 16.72% and High (4-5): 8.72%. 55.09 % of pts had social security, 21.50% private medicine and 23.39% had public health system assistance. 12.33% of pts came from rural areas and 11.03% were foreigners (neighbor countries). The 26.25% had university education, 36.25% completed high-school, 36.87% primary and 0.62% were illiterate.

The interval between diagnosis and onset of ICT (data from 252 pts) was 1 month in 37.3%; 1-3 months: 21.82% and,≥ 4 months: 5.55% of pts (delay was due to staging process and variable access to ICT).

There were no delays in the availability of chemotherapy drugs, but the 27.34% (73/267) did not receive R in 1st cycle due to lack of access. 10.11% received R for advancement from the institution. Only in 62% of pts (167/267) R was available from the 1st cycle by the health coverage.

The response rate among the 250 pts treated and evaluable was: 75.60% CR, 12.40% PR, 1.60 % SD and 10.40% PD. Surprisingly there was no correlation between CR rate and delay to the 1st consultation (p=0.31), as well as CR rate and the interval between diagnosis and time to ICT onset (probably due to the low number of cases). Not receiving R from the 1st cycle of ICT was inversely correlated to CR rate (p=0.0063), although these patients completed all doses of rituximab.

Discussion: Argentina has a very heterogeneous health system (public, social security and prepaid medicine). The availability of chemotherapeutic drugs is guaranteed by law, but there are differences and delays in the access to high-cost drugs, depending on the payers. Our patients population receive attention in public and private hospitals with different funding sources and access to high cost medication, such as monoclonal antibodies. To emphasize this aspect, our results show that the only variable with impact in the response rate was the fact of not receiving R from the 1st treatment cycle.

Conclusion: A prompt beginning ofICT is essential to obtain CR in pts diagnosed with DLBCL. An unacceptable proportion of our DLBCL pts (30%) receive the ICT with some degree of delay, which decreases their chances of achieving CR.

Keywords: diffuse large B-cell lymphoma (DLBCL); R-CHOP.

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PROGNOSTIC VALUE OF THE INTERVAL BETWEEN RELAPSE AND THERAPY INITIATION IN DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS. ANALYSIS FROM THE CZECH LYMPHOMA STUDY GROUP DATABASE

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Introduction: Patients with relapsed/progressed diffuse large B-cell lymphoma (rDLBCL) survive globally with median 12 months since relapse and majority of deaths is attributed to lymphoma. There is urgent need of efficient therapy for rDLBCL, but clinical trials cannot find efficient therapy up to now. Regardless the selection bias of inclusion/exclusion criteria in clinical trials, time to therapy initiation seems to be a critical point for the trial enrollment.

Methods: As a data source for this retrospective analysis, the CLSG (Czech Lymphoma Study Group; Govtrial NT 03199066) database was used. Patients with the first relapse/progression of DLBCL (initial diagnosis 2000-2017) and without CNS involvement were included. The date of relapse was defined as the first documented manifestation (clinical symptoms, radiological finding or the date of biopsy confirming DLBCL). According to time between diagnosis of relapse and start of therapy, patients were divided into three subgroups: 1) <7 days, 2) 7-21 days, and 3) ≥21 days, and the comparison of overall survival (OS) was carried out.

Results: Totally, 587 patients with DLBCL relapsed with median 12.8 months (range; 1.6 to 152.3) since diagnosis, 304/587 (51.8%) were males, median age was 67 yrs (range 22-95) at the relapse, 351/587 (49.9%) patients had stage III/ IV, bone infiltration was found in 51/587 (8.7%) cases. B-symptoms appeared in 140/587 (23.9%) cases, ECOG>2 showed 61/587 (10.4%) and bulky disease (≥7.5cm) 129/587 (22%) patients. LDH>norm was present in 387/587 (65.9%) cases. First line systemic therapy was administered in 98% patients, the most frequent chemotherapy backbone was CHOP (70%), anti-CD20 was given to 84% patients (including 99% of rituximab). The therapy of rDLBCL was based on systemic immuno/chemotherapy in 81.9% of patients (40% platinum-based regimen).

Median time between diagnosis of rDLBCL and therapy start was 20 days (1-851 days), 136 pts (23.2%) initiated therapy in <7 days, 166 (28.2%) pts between 7-21days, and 285 (48.6%) ≥21 days. Shorter interval between relapse and treatment was associated with shorter 5-year OS (17.4% vs. 20.5% vs. 42.2%; p<0.001). Subgroups with time to therapy intervals <7 days vs. ≥ 21 days

showed significant differences in clinical and laboratory parameters: B-symptoms (32.8% vs. 18.6%; p.015), limited stage I/ II (31.1% vs. 44.6%; p.031), ECOG ≥3 (19.7% vs. 5%; p.001), bulky disease ≥ 7.5cm (40.2% vs. 19.6%; p.001), elevated LDH (80.8% vs. 58.9%; p.002).

Conclusions: The short time between relapse/progression and therapy initiation in rDLBCL is associated with significantly shorter OS and mirrors real clinical behavior of DLBCL represented by worse clinical and laboratory parameters. Unfortunately, this high-risk proportion of patients requiring urgent therapy (< 7 days; 23%) usually fails to enter into majority of clinical trials.

Keywords: diffuse large B-cell lymphoma (DLBCL); immunochemotherapy; prognostic indices.

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SHORT DIAGNOSIS-TO-TREATMENT INTERVAL IS ASSOCIATED WITH HIGH RISK AND POOR OUTCOMES IN DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Recent evidence has demonstrated associations between adverse risk characteristics and survival outcomes in diffuse large B-cell lymphoma (DLBCL) patients with a shorter diagnosis-to-treatment interval (DTI) (Maurer et al, 2018). The imperative for exigent therapy in aggressive DLBCL presentations may select against the recruitment of such patients to clinical trials and introduce significant bias. We sought to confirm the relationship between DTI and risk status and to compare cohorts of patients receiving standard therapy versus a clinical trial as initial treatment.

Methods: Treatment and outcome data were collected for patients with newly diagnosed DLBCL (as per WHO criteria) treated at our institution either with standard therapy or an upfront clinical trial. Associations between DTI and clinical characteristics and outcomes were investigated. Overall survival (OS) and progression free survival (PFS) were modelled using Cox regression. Differences in patient and disease characteristics were analysed with the Mann-Whitney U test or Chi-square test.

Results: 455 patients receiving non-trial therapy with reliably determined DTI were identified. An additional 21 patients received upfront treatment on a clinical trial. The median DTI of the non-trial treatment group was 14 days, compared to 20 days for the clinical trial group (p=0.031). 1 patient was treated on a clinical trial within 7 days of diagnosis (5%) vs 122 (26.8%) patients receiving non-trial treatment. Patients with a DTI of >7 days demonstrated superior OS, HR 1.555 [95%CI:

1.085-2.227], p=0.016, and PFS, HR 1.564 [95%CI: 1.15-2.129], p=0.004. DTI of ≤7 days was significantly associated with several established markers of poor prognosis in DLBCL, including elevated lactate dehydrogenase (p<0.001), and advanced Ann Arbor stage (III or IV) p=0.034. Other poor prognostic markers such as the revised international prognostic (RIPI) score, cell of origin, Eastern Cooperative Group (ECOG) score ≥2, age >60 years and presence of 'B' symptoms did not show significant associations with a DTI ≤7 days. In comparing the non-trial and trial groups, no statistically significant difference between the aforementioned characteristics was present.

Conclusion: These findings confirm that patients requiring emergent treatment for DLBCL experience inferior OS and PFS and are more likely to have elevated LDH and advanced stage disease. The significantly higher median DTI in clinical trial participants suggests these patients are not representative of the general DLBCL cohort. Our findings raise further concerns for significant selection bias against poor risk patients treated on upfront clinical trials in DLBCL. Further work is needed to evaluate the extent of this bias and strategies to ensure patients requiring emergent treatment are included in future clinical trials is essential

Keywords: diffuse large B-cell lymphoma (DLBCL); prognostic indices.

Disclosures: Gilbertson, M: Honoraria: *Roche.*

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A RETROSPECTIVE ANALYSIS OF REAL-WORLD OUTCOMES OF CHINESE ELDER PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)

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Background: Elderly patients with diffuse large B-cell lymphoma (DLBCL) have a worse prognosis compared to the younger population, however, this group is often precluded from clinical trials and population-based studies, optimal treatment strategy for the old patients with DLBCL remains controversial. Here, we describe a Chinese real-world experience of management of elderly DLBCL patients.

Methods: Consecutive DLBCL patients aged ≥ 60 were included in this single-center, retrospective analysis. The standard regimens included 3-4 cycles (early stage disease) or 6 cycles (advanced) of R-CHOP like regimens (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) followed by two rituximab doses in fit patients; R-miniCHOP for unfit and R-CE(etoposide)OP for frail elder patients. The primary endpoint was progression-free survival (PFS).

TABLE 1 Baseline characteristics for 349 patients with diffuse large B-cell lymphoma (DLBCL) aged <70 years and ≥70 years

	60-69 years	≥70 years	All	p-value
Number	204 (58.5)	145 (41.5)	349	
Male (%)	108 (53)	78 (54)	186 (53)	0.875
Extranodal sites				0.799
0/1	153 (75)	107 (74)	260 (74)	
>1	51 (25)	38 (26)	89 (26)	
Ann Arbor Stage				0.380
I-II	125 (61)	88 (61)	213 (61)	
III-IV	79 (39)	57 (39)	136 (39)	
B-symptoms				0.961
Yes	37 (18)	26 (18)	63 (18)	
No	167 (82)	119 (82)	286 (82)	
ECOG performance status				<0.001
0-1	158 (77)	87 (60)	245 (70)	
2-4	46 (23)	58 (40)	104 (30)	
LDH				0.878
Normal	101 (50)	73 (50)	174 (50)	
Elevated	103 (50)	72 (50)	175 (50)	
IPI				0.065
0-1	72 (35)	37 (25)	109 (31)	
2-3	98 (48)	72 (50)	170 (49)	
4-5	34 (17)	36 (25)	70 (20)	
Treatment				0.112
Chemo only	79 (38.7)	59 (40.7)	138	
Chemo +Rituximab	113 (55.4)	75 (51.7)	188	
Others	12 (5.9)	11 (7.6)	23	

Abbreviations: LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index.

Results: From June 2006 to December 2012, 349 eligible patients were included, in which 204 patients were aged <70 years. 326 patients received chemotherapy or chemo-immunotherapy with rituximab. With a median follow up of 82 months, the 5-year PFS and OS were 45.8% and 51.9%, respectively. Significant difference was seen between patients < 70 years and those ≥70 years in terms of PFS (51.0% vs 38.6%, p=0.030) and OS (58.3% vs 42.8%, p=0.007). Patients with early-stage disease (Ann Arbor Stage I/II) had better 5-year PFS (60.1% vs 23.5%, p<0.001) and OS (65.3% vs 30.9%, p<0.001) than patients with advanced disease stage (Ann Arbor Stage III/IV). In addition, regimen including rituximab significantly improved the survival than chemotherapy alone (5-year PFS: 37.3% vs 64.0%, p<0.001; 5-year OS: 44.5% vs 69.3%, p<0.001), especially in patients ≥70 years, which almost doubled 5-year PFS and OS (5-year PFS:

Figure 1 Overall survival (A) and Progression-free survival (B) for elderly patients with DLBCL
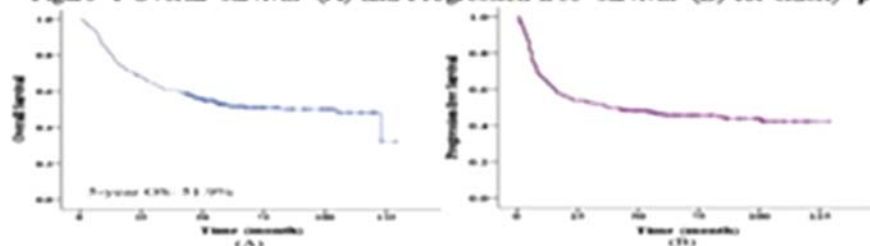
Figure 2 Overall survival (A) and Progression-free survival (B) for elderly patients with DLBCL according to age group
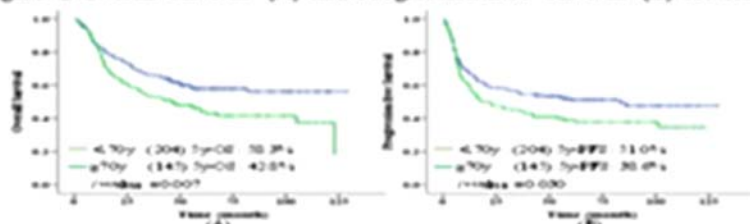
Figure 3 Overall survival (A) and Progression-free survival (B) for elderly patients according to Ann Arbor Stage.
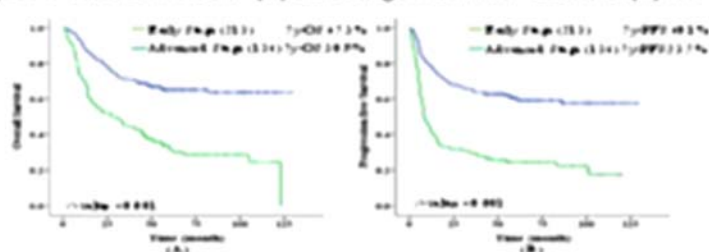
Figure 4 Overall survival (A) and Progression-free survival (B) for 134 elderly patients ≥70y according to therapy.
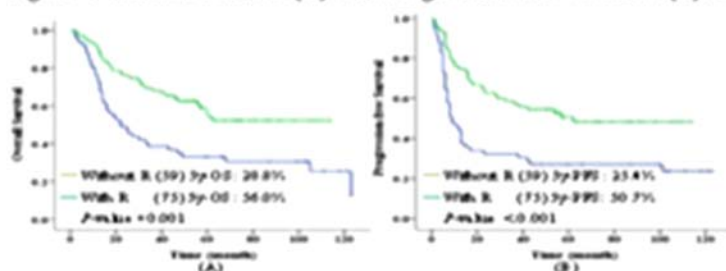
Figure 5 Overall survival (A) and Progression-free survival (B) for elderly patients with N-DLBCL and EX-DLBCL
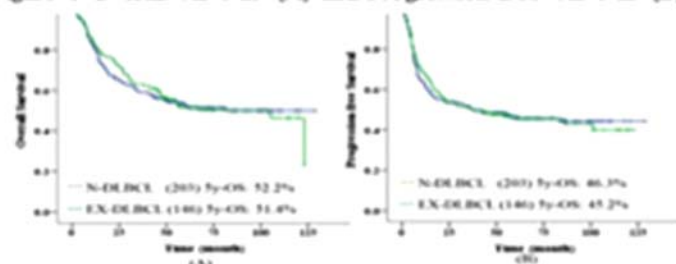
25.4% vs 50.7%, p<0.001; 5-year OS: 28.8% vs 56.0%, p<0.001) (Figure 3).

Conclusions: Older age (≥70 years) and advanced disease stage (Ann Arbor Stage III/IV) are associated with poor PFS and OS in Chinese elder DLBCL patients. The addition of rituximab significantly improves the survival, especially in patients aged ≥70 years. These findings underscore the importance of personalized evaluation and treatment in elder patients with DLBCL.

Keywords: B-cell lymphoma; diffuse large B-cell lymphoma (DLBCL); elderly.

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HYPOGAMMAGLOBULINEMIA AND HYPOCOMPLEMENTEMIA AS STRONG PROGNOSTIC FACTORS IN NEWLY DIAGNOSED DIFFUSE LARGE B CELL LYMPHOMA
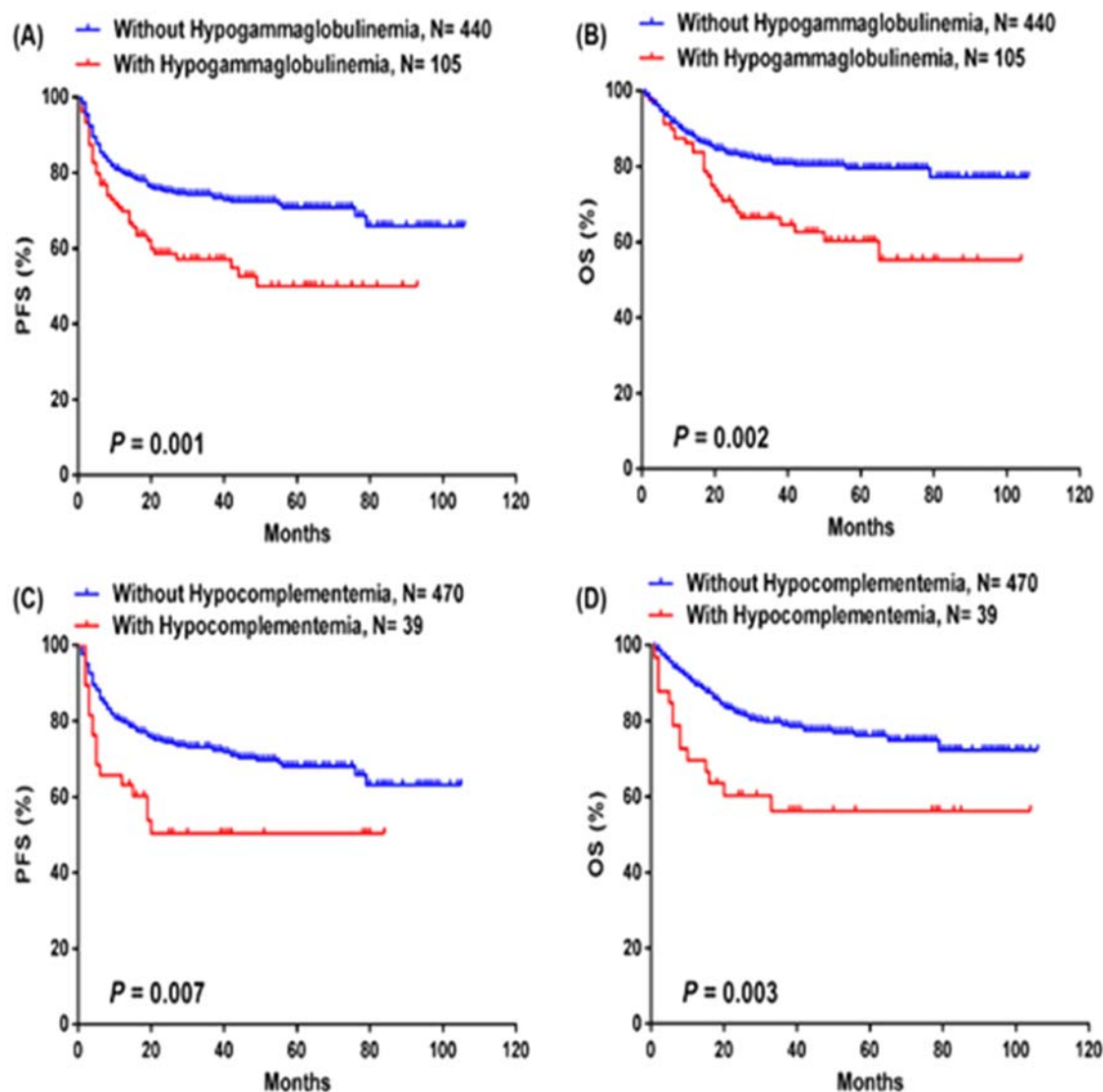
Figure 1. Progression-free survival according to hypogammaglobulinemia (A) and hypocomplementemia (B); overall survival according to hypogammaglobulinemia (C) and hypocomplementemia (D)

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Introduction: Diffuse large B cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL) in all over the world, occupied almost 31% in all NHL. In our study, we analyzed the serum immunoglobulin and complement levels of newly diagnosed DLBCL patients in our hospital in order to evaluate their prognostic value and want to build a new prognostic model.

Methods: Five hundred and fifty-three newly diagnosed DLBCL patients between May 2009 and May 2018 were included in the study. The relationship between hypogammaglobulinemia, hypocomplementemia at diagnosis and progression-free survival (PFS), overall survival (OS) were performed by univariate and multivariate regression analyses.

Results: In our study, 105 of 534 (19.7%) DLBCL patients had hypogammaglobulinemia, and 39 of 509 (7.7%) patients had hypocomplementemia. The patients with hypogammaglobulinemia displayed unfavorable PFS (*P*=0.001) and OS (*P*=0.002) and hypocomplementemia had the same inferior PFS (*P*=0.007) and OS (*P*=0.003) than patients in normal complement level (**Figure 1**). In addition, we defined a new prognostic system called immunization cumulative prognostic score (ICPS), based on the hazard ratio (HR) of hypogammaglobulinemia (2.048; 95% CI: 1.341–3.126) and hypocomplementemia (2.356; 95% CI 1.339–4.147) for OS. Multivariate

Cox regression analysis revealed that ICPS was independent risk factor for both PFS (HR 1.493; 95% CI: 1.052–2.120; P=0.025) and OS (HR 1.688; 95% CI: 1.101–2.589; P=0.016). And the ICPS + IPI may have a superior predictive effect on prognosis in newly diagnosed DLBCL patients (P =0.037 for OS, P =0.016 for PFS).

Conclusions: Both hypogammaglobulinemia and hypocomplementemia at diagnosis had poor prognosis to PFS and OS. New prognostic system ICPS+IPI could be more sensitive to predict survival in newly diagnosed DLBCL patients.

Keywords: diffuse large B-cell lymphoma (DLBCL); prognostic indices.

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AGE IS NOT IMPORTANT IN FIT ELDERLY PATIENTS WITH AGGRESSIVE LYMPHOMA

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Introduction: High-dose chemotherapy followed by autologous hematopoietic cell transplantation (auto HSCT) is an effective salvage therapy for patients with relapsed chemosensitive non-Hodgkin's lymphoma (NHL). Retrospective analyses suggest that the benefit of HDT extends to elderly patients with NHL, which is an important finding considering that the median age at diagnosis is 67 years (range: 65-74) for NHL in United States, using 2010-2014 US SEER data. We aimed to define the efficacy and toxicity of auto HSCT in patients >60 years with NHL.

Methods: From January 2005 through January 2019, data from 29 patients (M/F: 21/8; median age: 63 years) with aggressive NHL above 60 years of age who were eligible for auto HSCT according to geriatric assessment (GA) were evaluated. All these data were obtained from the Ankara University Faculty of Medicine, Department of Hematology and Bone Marrow Transplant Unit. Their diagnosis were as following; 17 diffuse large B cell lymphoma (primary refractory or relapsed disease), 8 mantle cell lymphoma (first complete remission), 2 follicular lymphoma, 1 anaplastic large cell lymphoma and 1 peripheral t cell lymphoma. We compared the toxicity profile and outcome between the research group: patient aged 60 years and above and the control group: patient <60 years.

Results: All of the patients were stage III or IV at diagnosis; 13 out of 29 elderly patients had active disease at the time of auto HSCT. The median follow-up was 14.1 months (range, 1-60 mos). Prior to transplantation majority (79.3 %) of the elderly patients received BEAM protocol as conditioning treatment. Bone marrow stem cell was used in only 1 patient None of the patient had mobilization failure, the median peripheral CD34 level was 4.75 x10^6/kg. Twenty-one percent of the patients experienced ≥ grade 2 mucositis and 76 % of the patients had microbiology-documented infection. Fifty-four percent of the patients had diarrhea with median duration of 8 days (range, 5-20 days). Renal toxicity was occurred in 7 (27%) patients while hepatic toxicity in 3 (12.5 %) patients. Median time to neutrophil recovery was 10 days (range, 8-18 days) and platelet recovery 11 days (range, 10-32 days). Overall response was obtained from all patients (23% CR). At the time of data collection, 4 patients (15%) of patients' ≥ 60 years have deceased. Relapse (n=3) was the main course of death. The probability of 4-year progression free survival (PFS) and estimated overall survival (OS) in elderly patients were 37.5 % and 78.1 %, respectively.

Conclusions: Based on this single center study, auto-HSCT is safe and efficacious in the treatment of elderly lymphoma patients. We emphasize the need for further research in order to determine the risk-benefit threshold for HSCT based on age coupled with comorbidity and fragility.

Keywords: autologous stem cell transplantation (ASCT); elderly; non-Hodgkin lymphoma (NHL).

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PRE-TREATMENT HEMOGLOBIN AND OUTCOME IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH ANTHRACYCLINE CONTAINING CHEMOTHERAPY

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Hemoglobin (Hgb) concentration at diagnosis is associated with outcome in cancer. We estimated the prognostic impact of pre-treatment Hgb in a nationwide cohort of DLBCL and validated our findings in an independent cohort from the US. We included patients from the Danish Lymphoma Registry (LYFO; N = 3,499) and from the Molecular Epidemiology Resource (MER; N = 1,225), Mayo Clinic and University of Iowa. Four sex-specific Hgb groups were defined: below transfusion threshold, from transfusion threshold to below

Table 2. Crude and adjusted HRs for OS according to Hgb for both LYFO and MER

Hgb (LYFO)	OS 5-year			OS Unadjusted		OS Multivariable			EFS 5-year		EFS Multivariable	
	N	%	95% CI	HR	95% CI	N	HR	95% CI	%	95% CI	HR	95% CI
>149/>134‡	755	79	71 - 82	1.00	Ref.	739	1.00	Ref.	73	70 - 76	1.00	Ref.
134-149/118-134†	1,132	71	68 - 73	1.52	1.26 - 1.85	1,103	1.23	1.01 - 1.49	64	61 - 67	1.19	1.01 - 1.42
98-133/98-117†	1,246	54	51 - 57	2.74	2.29 - 3.27	1,211	1.51	1.25 - 1.83	49	46 - 52	1.46	1.23 - 1.73
<98	366	37	32 - 42	4.51	3.67 - 5.55	355	2.05	1.65 - 2.56	33	28 - 37	1.96	1.60 - 2.41
Hgb (MER)												
>145/>135‡	322	84	80 - 88	1.00	Ref.	322	1.00	Ref.	73	68 - 78	1.00	Ref.
135-144/120-134†	285	75	70 - 80	1.54	1.12 - 2.12	285	1.43	1.03 - 1.97	64	59 - 70	1.30	0.99 - 1.70
99-134/99-119†	482	65	60 - 69	2.31	1.75 - 3.06	482	1.53	1.14 - 2.05	51	47 - 56	1.32	1.03 - 1.68
<99	136	63	55 - 73	2.48	1.72 - 3.57	136	1.27	0.86 - 1.86	45	37 - 56	1.33	0.97 - 1.83

§ Adjusted for NCCN-IPI, sex, comorbidity, and rituximab treatment, ‡ Hgb cut off value for men/Hgb cut off value for women,
† Hgb range for men/Hgb range for women
Hgb; pre-treatment hemoglobin. OS; overall survival. ref; reference. HRs; hazard rate ratios
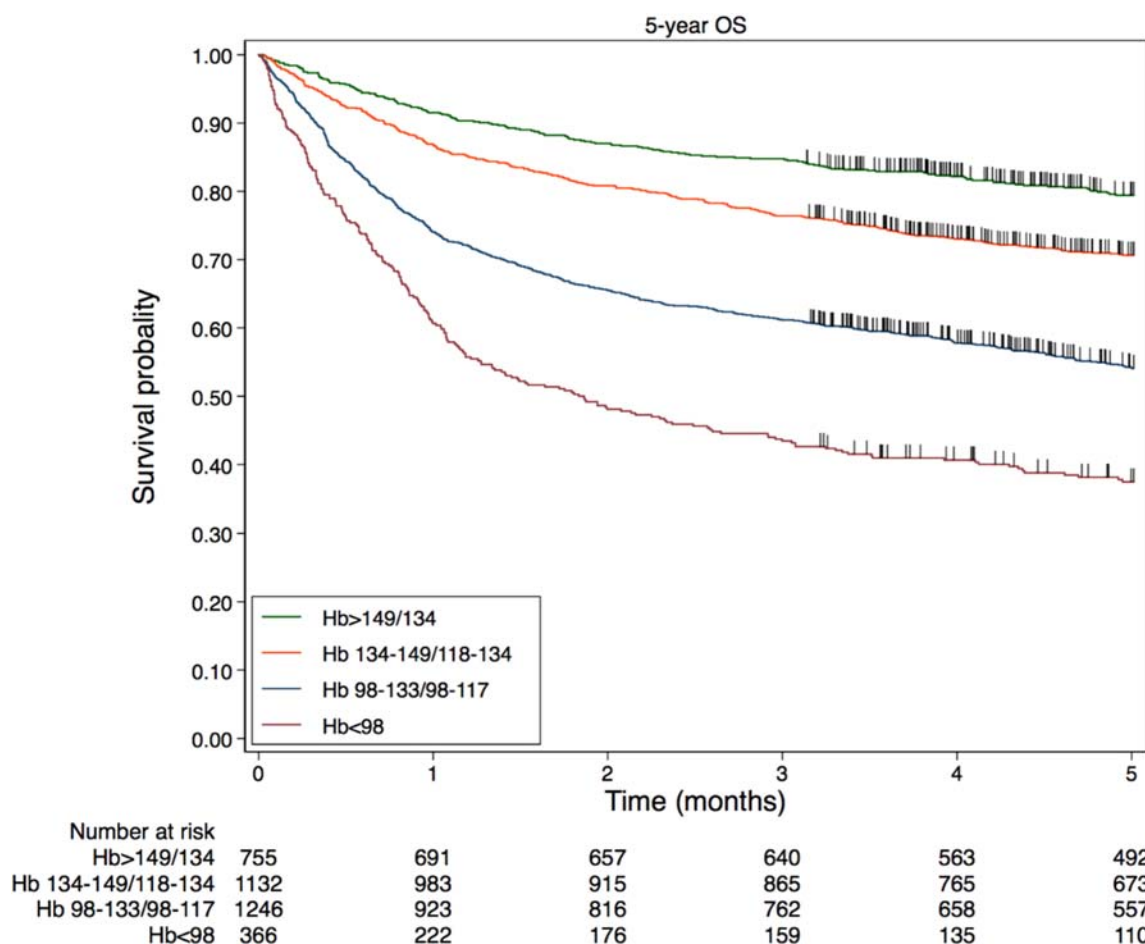
lower limit of normal, from lower limit of normal to the population mean, and above the mean. We used multivariable Cox regression to estimate hazard ratios (HR) and 95% confidence intervals for overall (OS) and event-free survival (EFS), adjusting for sex, NCCN-IPI, comorbidity, and rituximab treatment. Approximately half of the patients had Hgb levels below the lower limit of normal. Compared to patients with Hgb levels above the mean, an inferior OS was observed for patients (LYFO) with Hgb levels in the normal range but below the mean (HR=1.23), below lower limit of normal (HR=1.49), and below transfusion limit (HR=2.03). These findings were replicated in the MER. Based on multivariable analysis, lower pre-treatment Hgb, even within the normal range but below the mean, added

prognostic information to established risk factors such as comorbidity and NCCN-IPI.

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REAL LIFE DATA ABOUT CHARACTERISTICS, STANDARD TREATMENT AND OUTCOMES IN BRAZILIAN ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA – A SINGLE CENTER ANALYSIS

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is common lymphoma in elderly patients. Unfortunately, it is not possible to prescribe standard classic regimen RCHOP for all. Although, attenuated regimen is suggested for patients older than 80 years old, sometimes is necessary to reduce dose in patients between 60-80 years old due to fragility and other comorbidities. In addition, we do not have data from real life practice in elderly Brazilian patients with DLCBL. We aimed to investigate patients aged over 60 years old with DLBCL treated in a single Brazilian private health service about use of full dose RCHOP and outcomes.

Methods: A retrospective observational single center study was conducted to investigate clinical characteristics, frequency of standard RCHOP and outcomes in patients with DLCBL older than 60 years old treated in our institution between January 2007 to July 2017. Data were collected by eletronic medical records. It was excluded patient with AIDS related lymphoma.

Results: Fifty-eight patients were analyzed. Median age was 74.2 (range 60.4-88.2) years. Female gender represented 41(70.7%). Twenty-three (57.5%) of forty patients that were possible to evaluated had an International prognostic index score 2-3. Full dose RCHOP was prescribed in 28 (48.2%) cases and 5 (8.6%) did not receive any treatment. Patients older than 80 years old represented 15 (25.9%) and this subgroup was not treated with full dose RCHOP. Patients younger than 65 years old and patients aged between 65 and 80 years old received standard RCHOP 13 (100%) and 15/30(50%), respectively. Complete response (CR) of 53 treated patients was obtained in 37 (69.8%). CR in patients younger than 65, 65-80, and older than 80 years old were: 9(69.2%), 21(70%) and 7(46.6%), p > 0.05. Overall survival (OS) and Progression free survival (PFS) in 2 years was 81.8% and 65.3%, respectively. OS in 2 years in patients older than 80 years and patients aged between 60 and 80 years old were: 64.3% x 87.6%, p=0.018 and PFS in 2 years 64.3% x 66.5%, p > 0.05, respectively.

Conclusion: Therefore, it was evidenced patients aged between 65 and 80 years old were considered frail to receive standard full dose RCHOP and patients older than 80 years old presented poor outcomes.

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PREVALENCE AND CLINICAL SIGNIFICANCE OF HYPERCALCEMIA AT DIAGNOSIS IN DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: The reported prevalence of hypercalcemia in non-Hodgkin's lymphoma is 1.3% to 7.4%, while the prevalence of hypercalcemia in diffuse large B cell lymphoma (DLBCL) at diagnosis is unknown. Hypercalcemia in patients with cancer has been associated with a poor prognosis. However, it is unknown whether hypercalcemia per se contributes to the poor outcome or whether hypercalcemia is a biomarker for an underlying aggressive biological feature. The

Overall survival

Progression free survival
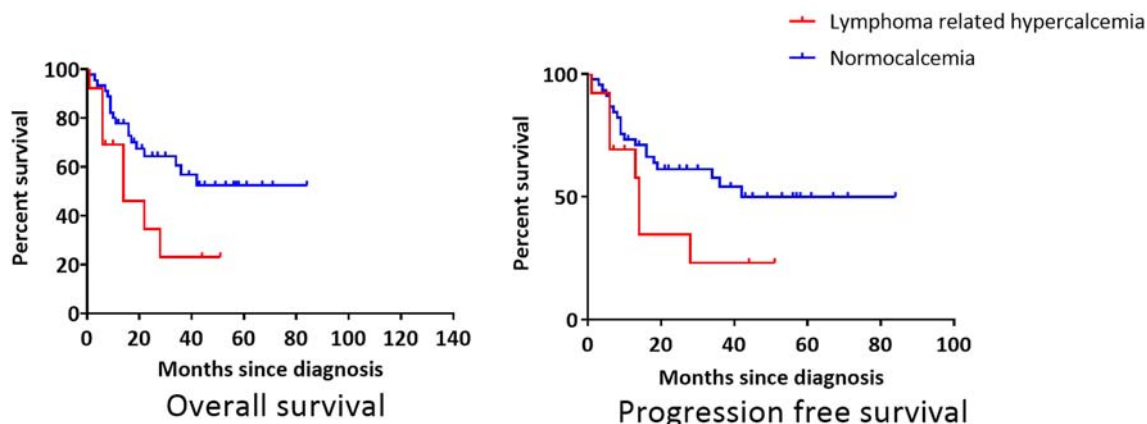
outcome of DLBCL patients with primary hyperparathyroidism (PHPT)-related hypercalcemia compared to lymphoma related hypercalcemia may help clarify this question.

In this study we determine the prevalence of hypercalcemia among newly diagnosed patients with DLBCL and compare the clinical features and outcomes of patients with and without hypercalcemia. We also evaluate the effect of hypercalcemia etiology on outcome.

Patients and methods: We performed a retrospective case-control study of patients at two academic medical centers with newly-diagnosed DLBCL, between 2010 & 2016. Patients with a corrected calcium levels above 10.5mg/dl [{4-albumin(g/dl)} x 0.8+calcium (mg/dl)] at diagnosis comprised the study cohort. Age and sex-matched DLBCL patients with normal calcium levels at diagnosis served as controls.

Results: Among 250 newly diagnosed patients with DLBCL 46 (18%) had hypercalcemia at the time of diagnosis. Median age was 72 years (31-89), and 60% were males.

Patients with hypercalcemia presented with more advanced stage disease (85% vs 65%), and had higher levels of LDH (median 736 vs 669u/l) compared to patients with normal calcium levels.

The overall response rate (ORR) and complete remission (CR) were similar among hypercalcemic and normocalcemic patients (ORR: 74% vs 83%, P = 0.312, CR: 72% vs 72%). These comparable response rates translated in to similar rates of PFS and OS.

We then stratified patients with hypercalcemia and available PTH levels (27/46) into two groups: those with PHPT-related hypercalcemia (PTH>= 20pg/ml, 44%, n=12/27) and those with lymphoma-related hypercalcemia (PTH< 20pg/ml, 56% 15/27). Patients with lymphoma related hypercalcemia were older, had more advanced stage, higher IPI, higher levels of LDH compared to PHPT-related hypercalcemia. These adverse features were translated to shorter PFS (median 13 months vs 86 months, p=0.016) and OS (median 14 months vs not reached, p=0.016) in patients with lymphoma related hypercalcemia. Patients with lymphoma related hypercalcemia also had shorter PFS (median 13 vs 42 months, p=0.027) and OS (median 14 months vs not reached, p=0.011) compared to patients with normal calcium levels.

Conclusion: The findings suggest that in newly diagnosed patients with DLBCL, hypercalcemia is frequent and that lymphoma-related but not PHPT-related hypercalcemia is associated with adverse prognostic factors and adverse clinical outcomes in DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL).

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THE CRITERIA OF INTERIM THERAPY CHANGE FOR PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: INTERIM ΔSPD LESS THAN 80% VS. 50%

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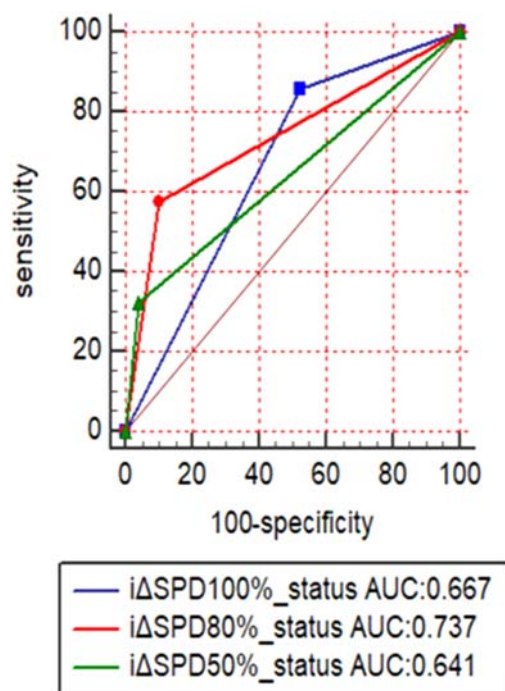
Figure 1. Time-dependent ROC curve analysis for three iΔSPD cut-off values.

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Introduction: Interim response assessment is performed to identify patients whose disease has not responded to or has progressed on induction therapy. The Lugano Response Criteria has been widely used for response assessment for DLBCL. Patients with interim reduction percentage of the sum of the products of the greatest perpendicular diameters for multiple lesions (iΔSPD) between baseline and interim contrast-enhanced computed tomographic (CECT) less than 50% are regarded as non-sensitive to induction therapy and may benefit from a therapy change. However, there is no consensus on the criteria for early therapy change during interim response assessment yet. Here we compared the prognostic value of three iΔSPD cut-off values: 50%, 80% and 100%.

Methods: Two hundred and sixty-five newly-diagnosed DLBCL patients with baseline and interim CECT available were enrolled in the retrospective study.

Results: The optimal cut-off value of iΔSPD calculated by X-tile was 80%, which yielded the highest difference in OS. The iΔSPD=100% group had significantly superior PFS than 80%≤iΔSPD<100% group (P=0.009), while OS only showed a trend of statistical significance (P=0.07) (Figure 1). A trend for statistical significance (P=0.089) for OS was observed in 50%≤iΔSPD<80% group compared with iΔSPD<50%

group while no statistical significance (P=0.247) for PFS were observed between them. The 50%≤i∆SPD<80% group had significantly inferior PFS and OS than 80%≤i∆SPD<100% group (both P<0.001). Compared with 50% and 100%, 80% had the intermediate sensitivity and specificity (57.75% and 86.69% for OS, 48.98% and 92.22% for PFS, respectively), but the maximal Youden Index (0.4744 for OS, 0.4120 for PFS, respectively) (Table) and the maximal areas under the curve (0.737 [0.680, 0.789] for OS). PPV and NPV of 80% cut-off value were 78.69% and 75.49% for PFS, respectively, while 67.21% and 85.29% for OS, respectively. If the status of PFS and OS were considered as "gold standard", 80% was the only cut-off value consistent with PFS (kappa=0.447) and OS (kappa=0.497) status. Cox regression analysis also revealed that i∆SPD<80% could independently predict an inferior OS and PFS (both P<0.001) while neither i∆SPD<50% nor i∆SPD=100% could.

Conclusions: i∆SPD with cut-off value 80% is an independent predictor of PFS and OS for patients with DLBCL. During interim response assessment, patients with i∆SPD<80% should change to a more efficient therapy.

Keywords: diffuse large B-cell lymphoma (DLBCL); positron emission tomography (PET).

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TREATMENT PATHWAYS OF DIFFUSE LARGE B-CELL LYMPHOMA IN GERMAN CLAIMS DATA

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Introduction: Routine sick fund claims data provide a meaningful and reliable base for the in- and outpatient treatment landscape. Real world data (RWD) from Germany was used to describe treatment patterns for Diffuse Large B-cell Lymphoma (DLBCL), the most frequent non-Hodgkin lymphoma type in adults.

Methods: Claims data from several sick funds of 4.8 million insured were analyzed. Diagnosis of non-follicular Lymphoma (ICD-10 C83) was confirmed in 2,178 patients, DLBCL (ICD-10 C83.3) in 819 patients. The analysis was age- and gender-adjusted, observational period was 2014 and 2015. Treatments were analyzed for hospitalization and medication based on ATC code, Pharma Central Number and coded diagnoses (per ICD). In a second claims cohort analysis from different sick funds, treatment patterns and pathways for 189 DLBCL patients identified 2013-2016, were investigated over time course.

Results: In the first [second] claims cohort, mean age of DLBCL patients was 60.3 [66.5] years, with two peaks at 50-54 and 70-74 years. Total yearly costs for patients with DLBCL averaged 25,048 [63,771] EUR versus 1,259 EUR in healthy insured. Per year, mean 3.2 [3.5] hospitalizations with an average of 31.5 [34.5] hospital days were observed. During the observation period less than half of the patients received an oncological treatment, which is supported by published cure rates after first line treatment of approx. 60%, but also includes a share of patients not receiving further treatment anymore. Only few patients received a therapy modality by stem cell transplantation or radiation. Most frequent pharmacological first line treatments were Rituximab (RTX) + CHOP (57%, respectively 56%) in both claims analyses and RTX in combination with Bendamustine (8%, respectively 7%), which is in accordance with German medical guidelines. The second claims cohort confirmed most results –except significantly higher costs. In both analyses consistently 84% of patients did not receive further therapies after a first line DLBCL treatment during the limited observation period.

Conclusions: Despite limitations in sick fund claims analyses, these provide a reasonable database for rare diseases. Results from two different sources were well in agreement. They allow standard treatment pathway and longitudinal analyses. However, some relapses may not be identified in the limited observation period of two [maximum four] years. All DLBCL patients frequently required hospitalization and generated significant costs. A high unmet medical need exists for treatments other than palliative care, especially for a tolerable and effective outpatient therapy in elderly relapsed / refractory DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL).

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TREATMENT OUTCOMES OF INVOLVED-FIELD RADIOTHERAPY IN ELDERLY PATIENTS WITH HIGH-GRADE OR RECURRENT NON-HODGKIN LYMPHOMA

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Purpose: This study was designed to evaluate the usefulness and efficacy of involved-field radiotherapy (IFRT) in elderly patients with high grade or recurrent non-hodgkin lymphoma (NHL).

Materials: We analyzed the treatment outcomes of 14 patients who had received IFRT between January 2014 and August 2018. IFRT was defined as the involved-site radiotherapy with/without adjacent nodal-station irradiation (ANI) to high risk areas. The median age of study population was 75 (range, 65-83) years and 7 (50%) patients were male.

Tumor histology was diffuse large B-cell lymphoma in 10 (71.4%), NK/T-cell lymphoma, nasal type in 2 (14.3%), high-grade follicular lymphoma in 1 (7.1%) and recurrent nodal marginal zone lymphoma in 1 (7.1%) patient, respectively. The treatment sites were neck/nasal cavity in 9 (64.3%), neck/abdomen in 1 (7.1%), chest in 1 (7.1%), axilla in 1 (7.1%), neck/chest in 1 (7.1%) and abdomen/pelvis in 1 (7.1%), respectively. ANI was selectively accomplished in 7 patients with neck and axilla origins. The ECOG performance status was 0 in 1 (7.1%), 1 in 10 (71.4%) and 2 in 3 (21.4%) patients, respectively. The majority of the patients (n=10, 71.4%) had aging-related multiple comorbidities.

Results: The median follow-up duration was 11 (range, 2.2-56.2) months and 4 (28.6%) patients were dead at the time of this analysis. A total of 10 (71.4%) patients had received upfront chemotherapy before IFRT. Among 8 patients who had received IFRT as a consolidation treatment after chemotherapy, 7 (87.5%) patients maintained major responses during follow-up. One patient experienced both infield and outfield disease progression after initial partial response following IFRT. Among the remaining 6 patients who had received IFRT as a curative or salvage aim, 5 (83.3%) patients achieved major infield responses. One and 2 patients experienced infield and outfield progression, respectively. Major causes of death and worsening of general condition were pulmonary infection and aging-related illness. In 4 dead patients, the median survival duration after IFRT was 3.2 (range, 2.2-12.3) months. There was 6 (42.9%) long-term (≥ 1 year) survivors after IFRT and their median survival duration was 31.2 (range, 14.4-56.2) months.

Conclusions: IFRT was efficacious and well tolerated in elderly high grade or recurrent NHL patients. Although durable response and long-term survival was achieved in medically healthy population, watchful management is necessary to avoid deaths from cancer-unrelated causes.

Keywords: diffuse large B-cell lymphoma (DLBCL); elderly; non-Hodgkin lymphoma (NHL).

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OUTCOME AFTER SALVAGE RADIOTHERAPY TO FDG-PET/CT AVID DISEASE POST CHEMOTHERAPY IN ADVANCED STAGE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Introduction: Most patients with Diffuse Large B Cell Lymphoma (DLBCL) present with advanced stage disease and are treated with multi-agent chemotherapy. Despite this some patients will not be in

TABLE 1

Patient characteristics	N (22)	%
Deauville score 1-3 pre radiotherapy	10	45
Deauville score 4-5 pre radiotherapy	12	55
Primary DLBCL	19	86
Relapsed DLBCL	3	14
MYC,BCL2,BCL6 status		
Double hit	1	5
Negative	13	59
Unknown	8	36

For the entire group local control at 2 years was 81 %.(DS 1-3 90% Vs. DS 4-5 75%). Cancer specific survival at 2 years was 64 % (DS 1-3 80% Vs. DS 4-5 50%). Overall survival at 2 years was 59 % (DS 1-3 80 % Vs. DS 4-5 41% P value 0.044) (Fig 1)

remission at the end of chemotherapy. Some patients can be salvaged with high dose chemotherapy, but many are not medically fit for treatment escalation or, despite treatment escalation will remain with residual disease. For these patients salvage radiotherapy alone may be offered.

Method: We carried out a single centre retrospective review of patients with advanced stage DLBCL treated with salvage radiotherapy alone for PET avid disease after undergoing curative intent chemotherapy. Patients underwent curative intent consolidative radiotherapy to all sites of FDG PET/CT avid disease. Further testing for a double or triple hit was attempted using Fluorescent In Situ Hybridisation testing (FISH)

Results: Twenty two patients were treated between 2010 and 2016. The median age was 71 (range 35-81). All patients received at least 30 Gy in 15 fractions with a median dose of 36 Gy in 18 fractions (range 30 Gy-40 Gy)

Of the 13 patients with a FISH confirmed non double/triple hit DLBCL the two year local control, cancer specific survival and overall survival respectively were 92 %, 75% and 69 %. Seven from this group

Fig 1. Overall survival
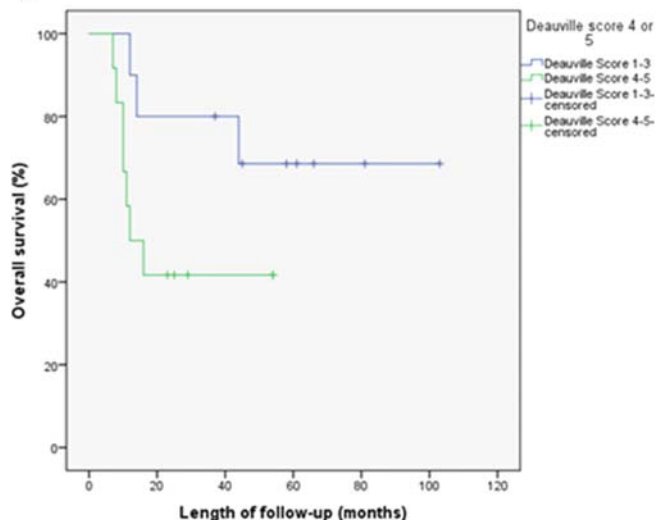
were treated for residual DS 4-5 disease. The two year local control, cancer specific survival and overall survival respectively were 86%, 71% and 57%.

Conclusion: A trend for an improvement in all outcomes was found for patients treated with a DS of 1-3, compared to a DS of 4-5. Given the excellent outcomes in the DS 1-3 patients avoidance of radiotherapy may be appropriate. Some patients with a post-chemotherapy DS of 4-5 can be successfully salvaged with radiotherapy alone. This appeared to especially be the case for non double/triple hit DLBCL.

Keywords: "double-hit" lymphomas; Deauville's criteria; diffuse large B-cell lymphoma (DLBCL).

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R-CHOP VS. R-CHOP+X FOR NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. Despite advances in the understanding of the pathophysiology and molecular biology of DLBCL, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has remained standard of care for first-line treatment for almost two decades. However, treatment outcomes are still suboptimal, and approximately 40% of patients have refractory disease or relapse. Recent prospective studies have examined the addition of various drugs to R-CHOP (termed R-CHOP+ X) to improve outcomes.

Our aim was to compare the efficacy and safety of R-CHOP vs. R-CHOP +X for first line treatment for DLBCL.

Methods: Systematic review and meta-analysis of randomized controlled trials including patients with DLBCL, comparing first line treatment with R-CHOP to R-CHOP+X (i.e. R-CHOP with the addition of another single drug). The Cochrane Library, MEDLINE, conference proceedings and references were searched until January 2019. Two reviewers appraised the quality of trials and extracted data. Primary outcome was overall survival (OS). Secondary outcomes included overall response rate (ORR), complete response (CR) rate, disease control and safety.

Results: Our search yielded five trials conducted between the years 2010 and 2018, including 2020 patients (one abstract, and four published in peer review journals). Median age of patients ranged between 50 to 65 years. The added drug was bortezomib in two trials; gemcitabine, bevacizumab and ibrutinib - each drug in one trial. Three trials included only patients with non-GCB DLBCL while two trials did not have this restriction.

There was no difference in OS between the R-CHOP+X and R-CHOP arms, HR 0.96, [95% confidence interval (CI) 0.74-1.25, I^2=0, 1134 patients, 3 trials].

ORR was higher in the R-CHOP arm *vs.* RCHOP+X, RR 0.93 [95% CI 0.9-0.97, I^2=33%, 1974 patients, 5 trials]. There was no significant difference in CR rates between the two groups, RR 0.95 [95% CI 0.88-1.02, I^2=34%, 1976 patients, 5 trials]. Disease control did not differ between the two arms, HR 0.99 [95% CI 0.84-1.16, I^2=0].

Regarding safety, three trials (N=1200) reported serious adverse events. These adverse events were significantly more common in the R-CHOP+X group, RR 1.42 [95% CI 1.24-1.64. I^2=55%]. In addition, grade III/IV thrombocytopenia was significantly higher in the R-CHOP +X arm, RR=6.66 [95% CI 1.59-27.84, I^2=70%]. There was no difference in grade III/IV anemia and neutropenia between the arms.

Conclusions: The addition of an extra drug to the conventional first line R-CHOP regimen in patients with DLBCL did not improve response rates, disease control or OS. Moreover, R-CHOP+X was associated with an increased risk for serious and grade III/IV adverse events. R-CHOP still remains the "gold standard" of treatment for DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL); R-CHOP.

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A SYSTEMATIC REVIEW OF THE CLINICAL EFFICACY OF TREATMENTS IN RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (R/R DLBCL)

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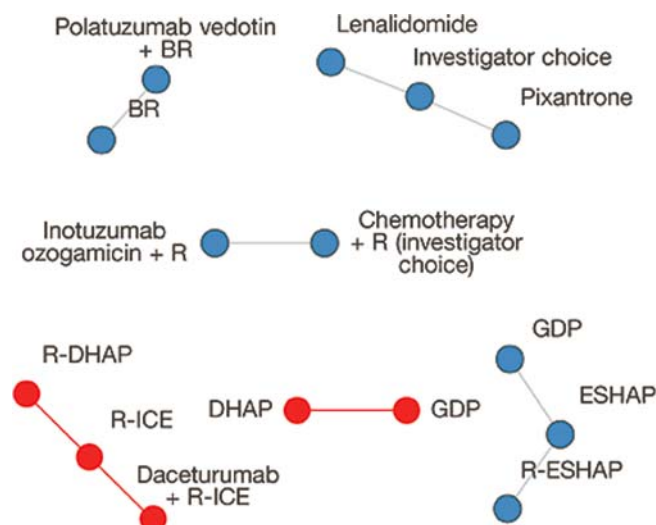
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Background: Despite improvements in DLBCL treatment, outcomes for patients with R/R DLBCL remain poor. This systematic literature review (SLR) aimed to summarise current clinical evidence for treatment of patients with stem-cell transplant (SCT) ineligible R/R DLBCL. A secondary objective was to assess the possibility of completing an indirect treatment comparison (ITC) or network meta-analysis (NMA).
Methods: Databases were searched in September 2018 (Embase®, MEDLINE®, The Cochrane Library) and November 2018 (ASH 2018 abstracts). Only studies of patients with SCT-ineligible R/R DLBCL were included, per pre-defined eligibility criteria. Identified studies were evaluated in a network-building exercise to identify whether a connected network of evidence could be constructed. To explore a broader evidence base, evidence not meeting the study criteria was evaluated in a *post-hoc* network-building exercise.
Results: The SLR identified 36 studies of patients with R/R DLBCL (90 publications); of these, 19 studies (53 publications) met the eligibility criteria. Six of the 19 studies were randomised controlled trials (RCTs [**Figure**]), and 13 were prospective, observational or single-arm trials. A further three RCTs not meeting the eligibility criteria were identified (**Figure**). Thirteen included studies had a sample size <60. Across studies, baseline median patient ages ranged from 54–74 years; the proportion of patients with Ann-Arbor stage III–IV disease ranged from 48%–90%; three studies had >65% male patients. All studies reported objective and complete response rates; additional endpoints included median progression-free survival (PFS; 11 studies, range 2.6–17.1 months), overall survival (OS; 11 studies, range 5–22.2 months), safety, and discontinuation. The IWG 1999-NHL guidelines were used by 10/19 studies. As response criteria and PFS definitions varied between studies, cross-study comparisons were limited. Construction of a connected network of evidence was not possible using data from RCTs or the broader *post-hoc* analysis (**Figure**). Thus, conducting an NMA was deemed unfeasible.
Conclusions: This SLR provides a summary of currently published evidence on treatments for patients with R/R DLBCL. Only nine of 36 identified studies were RCTs, preventing completion of an ITC or NMA. This SLR highlights the paucity of published RCTs to establish the comparative efficacy of R/R DLBCL treatments, and demonstrates a lack of standard of care in this setting.
Figure: Network-building analysis of evidence in 9 RCTs
Treatments: BR=bendamustine, rituximab; **DHAP**=dexamethasone, cytarabine, cisplatin; **ESHAP**=etoposide, methylprednisolone, cytarabine, cisplatin; **GDP**=cisplatin, dexamethasone, gemcitabine; **ICE**=ifosfamide, carboplatin, etoposide; **R**=rituximab. Single-arm studies not shown.
Blue lines: RCTs meeting the SLR criteria (SCT ineligible)
Red lines: RCTs not meeting the SLR criteria
This abstract was previously submitted to EHA 2019.
Keywords: B-cell lymphoma; diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL).
Disclosures: Vander Velde, N: Employment Leadership Position: *Tulane University & Southeast Louisiana Veterans Affairs Health Care System*; Other Remuneration: *Co-author (unpaid) on abstracts in lymphoma and urothelial CA: studies funded by Roche.* **Thuresson, P:** Employment Leadership Position: *Roche.* **Harvey*, R:** Employment Leadership Position: *Was an employee at DRG Abacus during the time the work was undertaken.* **Gupta, P:** Employment Leadership Position: *Decision Resources Group.* **Qayum**, N:** Employment Leadership Position: *Roche.*

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EXCELLENT OUTCOMES USING RITUXIMAB, GEMCITABINE, CYCLOPHOSPHAMIDE, VINCRISTINE, PREDNISOLONE (R-GCVP) IN PATIENTS WITH DLBCL AND CARDIAC COMORBIDITIES

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Introduction: Diffuse large B cell lymphoma (DLBCL) is the most common type of Non-Hodgkin lymphoma with a median age of presentation > 65 years. The gold standard induction regimen is anthracycline based. However, there are patients (pts) who cannot tolerate anthracyclines due to cardiac comorbidities. A unique phase II trial (Fields et al, JCO 2014) investigated the substitution of anthracycline with Gemcitabine (Gem), administered on D1 and D8 (Gem dose750-mg/m2 in Cycle (C)1, escalating to 875mg/m2 in C2 and 1000mg/m2 in C3) in a 3 weekly R-GCVP regimen with encouraging results; overall

TABLE 1 Patient characteristics

Variable	Characteristic	N (%)
Sex	Male	57 (70%)
Ann Arbor stage	I-II	25 (30%)
	III-IV	56 (69%)
	Unknown	1 (1%)
IPI	0-1	11 (14%)
	2	19 (23%)
	3	23 (28%)
	4 – 5	29 (35%)
ECOG PS	0-1	55 (67%)
	2	17 (21%)
	3-4	10 (12%)
B symptoms	Present	32 (39%)
Age	< 60	8 (10%)
	61-79	54 (66%)
	>80	20 (24%)

Comorbidities		
	LVEF<50 (n=28)	LVEF≥50 (n=44)
IHD + 2 cardiac risk factors	15	14
Cardiac risk factors +1	6	8
Single Cardiac risk factor	2	12
Other	3	5
Nil	2	2

response rate (ORR) 61.3%, 2 year Progression Free Survival (PFS) 49.8% and overall survival (OS) 55.8%.

Methods: We retrospectively analysed outcomes for 82 pts with de novo DLBCL deemed unsuitable for anthracycline regimens from 5 large UK academic centres. Data were collected via pt records on age, sex, histology, stage, international prognostic index (IPI) score, performance status, ORR, cardiac risk factor comorbidities, left

Figure 1: Overall Survival for patients ≥80 vs patients < 80

ventricular ejection fraction (LVEF) and detailed analysis of the Gem dosage schedule. OS was calculated from diagnosis to the death, PFS from diagnosis until first progression or death. Both were censored at the last day of follow up for pts without events. Statistical analysis was performed using STATA v15.1.

Results: The median age was 72y (range 41-92);pt characteristics are shown in Table 1. 28/72 (39%) pts recorded an LVEF >50%, and 44/72 (61%) pts LVEF ≤ 50%. Cardiac risk factors that were present included: ischaemic heart disease (n= 30), hypertension (n=29) and conduction disorders (n=25).The median number of cycles administered was 5 (range 1-6): 33 (40%) pts received 6 cycles, 10 (12%) pts 5 cycles, 11(13%) pts 4 cycles, 9 (12%) pts 3 cycles, 6 (7%) pts 2 cycles, and 6 (7%) pts 1 cycle. Twenty pts escalated to a Gem dose of 1000mg/m2 on C3D1, 10/20 pts maintained the 1000mg/m2 dose in C4D1, 3/20 in C5D1 and 3/20 in C6D1. 23 (27%) pts received involved field radiotherapy. 71 (84%) pts had end of treatment imaging. ORR was 74% (58.5% CR + 15.8% PR) for the whole cohort of 82 pts. The median follow up was 34m (5.2 – 88.4). The median PFS was 48m with 3 year PFS: 64.2% (52.1 – 74.0). The median OS was 54m with 3 year OS: 66.4% (54.3 – 76.0). 3-year PFS for ≥80 year group: 47.1% (21.3 – 69.4) and 3-year OS: 46.8% (21.0 – 69.1) (Figure 1).

Conclusions: The R-GCVP regimen achieved responses and survival rates comparable to those in the UK multicentre phase 2 study, confirming efficacy in pts with DLBCL and multiple cardiac comorbidities in a real world clinical setting.

Keywords: diffuse large B-cell lymphoma (DLBCL); elderly; gemcitabine.

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FIRST-LINE THERAPY OF ELDERLY PATIENTS WITH DLBCL-A COMPARISON OF STUDY PATIENTS TREATED WITH R-CHOP ON THE RICOVER-60 TRIAL AND PATIENTS TREATED WITH R-CYCLOPHOSPHAMIDE, EPIRUBICIN, VINDESINE, PREDNISONE (R-EpiVDSP) AT PEKING UNIVERSITY

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Introduction: R-CHOP is the standard first-line therapy for patients with diffuse large B-cell lymphoma (DLBCL). Alternative chemotherapy regimens have been proposed to increase efficacy (e.g. R-ACVBP) or decrease toxicity e.g. R-CE(Etoposide)OP, with conflicting results.
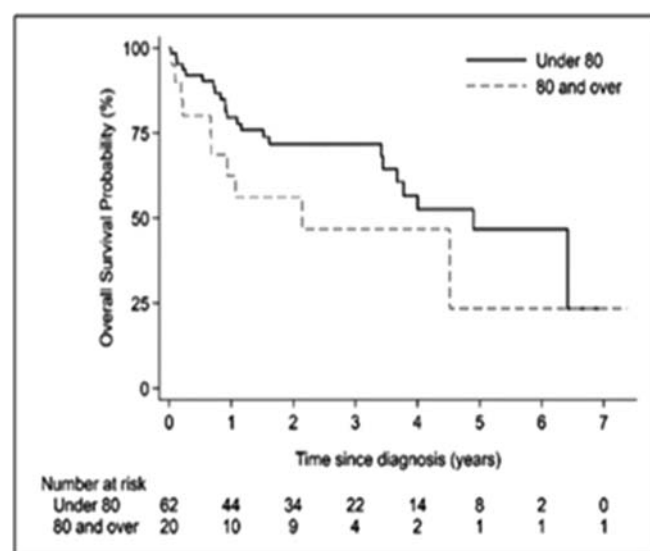
We analyzed how the R-CEpiVDSP regimen frequently used in China performs in comparison to R-CHOP.

Methods: We analyzed the outcome of consecutive DLBCL patients (pts) aged 61-80 years treated between May 2009 and April 2018 at People`s hospital, a tertiary referral center in Beijing, China. These pts received first-line therapy with rituximab (375 mg/ m2), cyclophosphamide (750 mg/m2), epirubicin (60 mg/ m2) instead of doxorubicin, vindesine (2 mg/m2) instead of vincristine, and prednisone (100mg, days 1-5). Pts diagnosed in early stages I-II received six, pts in advanced stages III-IV received 8 courses of such therapy. In order to compare outcomes progression-free survival (PFS) and overall survival (OS) curves were generated and compared to those DLBCL patients treated with 6 (stages I-II) or 8 (stages III-IV) courses of R-CHOP within the RICOVER-60 trial (Pfreundschuh et al. Lancet Oncology 2008; 9: 105-16)) of the German High-grade Lymphoma Study Group (DSHNHL) using the log-rank test; multivariate Cox models adjusting for IPI factors were calculated.

Results: 58 pts (59% male, median age 70 years) from People`s Hospital, Peking University, and 243 pts (54% male, median age 69 years) were included in this analysis. Major clinical characteristics including distribution of IPI score (IPI>2 was detected in 41% of RICOVER-60 pts and 48% of Chinese pts) did not significantly differ between both cohorts (p=0.308) except for ECOG >1 pts who were seen more frequently in the RICOVER-60 trial. Three-year-PFS was 66% (95%CI 54-79%) for pts treated with R-CEpiVDSP and 73% (95%CI 67-78%) for pts treated with R-CHOP-14 (p=0.659). OS also did not significantly differ (79% vs. 77%) (p=0.764). No significant differences were seen for pts with low or higher IPI score or any other IPI subgroup. PFS and OS (R-CEpiVDSP vs. R-CHOP) adjusted for IPI factors showed no significant differences, with HR=1.1 for PFS and 0.9 for OS.

Discussion: No significant differences in PFS or OS were found between pts treated with 6 (8) x R-CEpiVDSP in China or 6 (8) x R-CHOP-14 administered to elderly pts within the RICOVER-60 trial. Both regimens gave favorable results given the age and frequency of patients with IPI >2. In elderly pts with preexisting cardiac disease or neuropathy the R-CEpiVDSP regimen represents a valuable alternative to R-CHOP with comparable efficacy and potentially less cardiac and neurological toxicity.

Keywords: diffuse large B-cell lymphoma (DLBCL); R-CHOP.

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LENALIDOMIDE AND RITUXIMAB (ReRi) AS FRONT LINE THERAPY OF ELDERLY FRAIL PATIENTS WITH DIFFUSE LARGE B-CELLS LYMPHOMA. FIRST PLANNED INTERIM ANALYSIS OF A PHASE II STUDY OF THE FONDAZIONE ITALIANA LINFOMI (FIL)

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Introduction: Treatment of Diffuse Large B cell lymphoma (DLBCL) in the elderly population is challenging as many patients (pts) are not eligible to receive standard curative therapy, due to comorbid conditions and to a higher susceptibility to the side effects of standard anthracycline containing regimens.

Among currently available active drugs, Lenalidomide has been used in the setting of relapsed/refractory DLBCL both as monotherapy and in combination with rituximab, showing a good activity and an acceptable safety profile.

We started a prospective, multicenter, single arm, phase II trial to demonstrate activity and safety of lenalidomide + rituximab combination in elderly (≥ 70 years) untreated pts with DLBCL who were prospectively defined as frail according to a simplified comprehensive geriatric assessment (CGA).

Patients and methods: Pts were eligible if they were previously untreated DLBCL patients, older than 69 years and defined as frail according to CGA.

The treatment consisted of a 28-day cycle (R2) combining oral Lenalidomide (20 mg/m2/d on days 1 to 21) and i.v. Rituximab (375 mg/m2 on day 1); a maximum number of 6 cycles was planned; response assessment was performed after cycles 4 and 6. At the end of the 6th cycle, patients with partial or complete response continued treatment with Lenalidomide 10mg/d on days 1 to 21 every 28 days, until cycle 12 or unacceptable toxicity. Final response was evaluated within 28 days after the last study drug administration. Primary study endpoint was Overall Response Rate (ORR) after 6 R2 cycles, defined according to Lugano 2014 criteria; co-primary endpoint was the rate of extra-hematological toxicity with CTCAE grade >2 and of death for any cause during the treatment.

The study was planned according to a two stage Simon design. A total of 68 pts had to be enrolled to complete the study: 23 pts were

required in the first stage. Second stage could be activated with at least 12 patients showing a Partial or Complete Response (PR/CR) in stage I. According to the Ray and Rai method less than 15/23 adverse events were also required for the safety coprimary endpoint.

Results: From January 2017 to December 2017, 24 newly diagnosed frail DLBCL were enrolled in 8 Italian centers. Median age was 83 years (range 76-89) and 79% had stage III/IV; 42% of pts were male, and 44%, had elevated LDH. All pts were confirmed eligible and started R2 treatment. The planned 6 courses of R2 were completed in 13 pts (54%). The median number of R2 cycles was 4.6. Treatment was discontinued in 11 pts for the following reasons: lymphoma progression in 4 cases, malignancy in 2, extra-hematological toxicities in 2 cases, consent withdrawal and investigator choice after 4 cycles in CR in 1 case each. Response assessment after 6 R2 cycles showed 12 pts in CR, that was higher than the inferior limit of 11 required by the Simon optimal design.

Regarding safety coprimary endpoint 13 events were reported including 9 extra-hematological toxicities > grade 2 CTCAE (3 cardiovascular and 6 respiratory events, all resolved) and 4 deaths (2 patients due visceral arterial ischemia and 2 due infectious disease). The rate of adverse events was lower than the superior limit of 15 allowed the first stage of the study, according to Ray and Rai method.

Conclusions: The results of the planned interim analysis of our study confirmed the initial efficacy and safety hypotheses of R2 combination in untreated elderly pts with DLBCL. Since August 2018 the enrollment in the stage II of the trial has been resumed and it is currently ongoing. Treatment of elderly frail DLBCL pts with R2 holds promise in terms of both ORR and safety.

Keywords: diffuse large B-cell lymphoma (DLBCL); elderly; lenalidomide.

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REAL-WORLD BENDAMUSTINE USE IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (R/R DLBCL)

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Introduction: Bendamustine is approved for the treatment of indolent lymphomas. However, bendamustine has been studied and used off-label in DLBCL, where it has been shown to have anti-tumour activity and is well tolerated relative to combination chemotherapy. This study describes real-world usage patterns of bendamustine in combination with rituximab (R-Benda) for the management of R/R DLBCL.

TABLE 1 R-Benda utilisation in R/R DLBCL

Treatment received	Line of therapy			
	2L (N=993)	3L (N=386)	4L (N=166)	5L (N=70)
R-Benda, n (%)	77 (7.8)	14 (3.6)	5 (3.0)	1 (1.4)
Other (most common) regimens, n (%)				
CODOX-M	22 (2.2)	3 (0.8)	1 (0.6)	-
DA-EPOCH	21 (2.1)	6 (1.6)	-	2 (2.9)
GemOx	62 (6.2)	56 (14.5)	19 (11.4)	3 (4.3)
R monotherapy	17 (1.7)	11 (2.8)	2 (1.2)	2 (2.9)
R-CHOP	68 (6.8)	9 (2.3)	2 (1.2)	-
R-ICE	227 (22.9)	29 (7.5)	4 (2.4)	3 (4.3)

Abbreviations: CODOX-M, cyclophosphamide, cytarabine, vincristine, doxorubicin, methotrexate; DA-EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; GemOx, gemcitabine, oxaliplatin; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-ICE, rituximab, ifosfamide, carboplatin, etoposide.

Methods: This is a retrospective cohort study using Flatiron Health's data on patients with DLBCL diagnosed from 2011 through 2018 at any of 265 cancer clinics in the United States. We included patients with at least one prior line of therapy who initiated treatment within 90 days of their diagnosis.

Results: We identified 993 patients receiving second-line (2L) treatment or beyond who were treated between 2011 and 2018 for R/R DLBCL. R-Benda was received by 97 (9.8%) patients in the overall cohort. The proportion of patients receiving R-Benda ranged from 7.8% in 2L to 1.4% in 5L (**Table**).

The median age of patients receiving R-Benda was 75 years (interquartile range 68–79); 90% of patients were 60 years or older. R-Benda was the second-most common regimen in 2L and the third-most common in 3L. The most common regimen in 2L (and second-most common in 3L) was R-ICE (typically given to prepare patients for transplant). Patients refractory to their last prior line of therapy accounted for 40% of the R-Benda-treated population. For patients who received R-Benda, the median duration of follow up was 7.3 months and the median time to next treatment was 6 months. A dose of 90mg/m^2 bendamustine in combination with R was prescribed to 70/97 (72%) patients.

Conclusion: Treatment patterns in patients with R/R DLBCL vary widely with few regimens accounting for more than a small proportion of treated patients. R-Benda was among the more commonly used regimens in a cohort of unselected patients. Most patients who received R-Benda were older, which suggests the regimen may be favoured in the elderly, transplant-ineligible population. The majority of patients received 90mg/m^2 of bendamustine.

Keywords: Bendamustine; diffuse large B-cell lymphoma (DLBCL).

Disclosures: Herrera, A: Consultant Advisory Role: *Bristol-Myers Squibb, Genentech, Inc., Merck, Adaptive Biotechnologies, Kite*; Research

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RITUXIMAB PLUS GEMCITABINE AND OXALIPLATIN (R-GemOx) IN REFRACTORY/RELAPSED (R/R) DLBCL. A REAL LIFE STUDY IN PATIENTS INELIGIBLE FOR AUTOLOGOUS TRANSPLANTATION

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Introduction: There is no standard treatment of refractory or relapsed (R/R) patients (pts) with DLBCL ineligible for stem cell autologous transplantation (ASCT). However, R-GemOx is widely used in these circumstances. We here report the results of a retrospective analysis of a cohort of patient treated in two academic centers in France. The main objectives were to evaluate the activity and safety profile of this regimen in a large series of R/R DLBCL pts in a real life setting.

Methods: Patients selected had to have de novo or transformed DLBCL, R/R after at least one line of treatment containing doxorubicin and rituximab, to be ineligible for ASCT and to have received at least one cycle of R-GEMOX. Rituximab 375 mg/m2 was administered on D1, gemcitabine 1000 mg/m2 on D2 and oxaliplatin 100 mg/m2 on D2 as previously described (Mounier N. et al. Haematologica. 2013;98:1726–31.). Cycles were given every 2 weeks and 8 cycles were planned if at least a partial response (PR) was obtained after 4 cycles.

Results: Between May 2002 and May 2017, 196 pts were treated. Baseline characteristics were: median age: 72 y (range, 24-89), international prognostic index (IPI) 3-5: 63%, refractory state to last treatment (tx): 42%, history of indolent lymphoma: 45%, prior ASCT: 16%. The median number of previous line was 1 (range 1-7) with 112 pts having received R-GemOx in second line. One hundred and thirty-six pts received at least 4 cycles, and 61 completed 8 cycles. After 4 cycles, the overall response rate (ORR) according to IWC (Cheson 1999 or 2007) was 54 % and the complete response (CR) rate was 23 %. At the end of treatment, the ORR and CR rates were 38 % and 33 %, respectively. With a median follow-up of 22 months, median (m) progression-free survival (PFS) and overall survival (OS) were 5 and 10 months (mo), respectively. mOS was significantly longer in case of prior history of indolent lymphoma (21 vs 8 mo, p < 0.001), age<75y (16 v 7mo, p < 0.001), IPI <3 (p < 0.001), non-refractory status to last treatment (18 v 7mo, p < 0.001). The mOS of patients who attained a CR was 40 mo. Among pts who were treated with R-GemOx in second line, the CR rate was similar (32%), the same factors influenced the OS and duration of a first remission longer than 12 months was a favorable factor (p=0.006). The most common toxicities during treatment were hematological and manageable. Grade 3-4 toxicities occurred in 23% of pts. Grade 1-2 peripheral neuropathy related to oxaliplatin was observed in 26%.

Conclusion: This real life study of R/R DLBCL, confirms the activity and a safety of R-GemOx. This combination represents a possible platform to be combined with targeted therapies as it is currently proposed with nivolumab in the NIVEAU trial (NCT03366272). However, facing this very high unmet medical need, development of new approaches including CAR T-cells should also be considered in this patient population.

Keywords: diffuse large B-cell lymphoma (DLBCL); gemcitabine.

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DURABILITY OF COMPLETE RESPONSE AFTER BLINATUMOMAB THERAPY FOR REFRACTORY/RELAPSED AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMA

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Introduction: Achieving durable response in patients with relapsed/refractory (R/R) aggressive B-cell lymphoma (B-NHL) is challenging. Blinatumomab, a bispecific T-cell engager (BiTE®) immunotherapy targeting CD19-expressing cancer cells, has shown promising

Table. Results

Complete Responders (CR)	NCT01741792 (n = 4)	NCT02910063 (n = 9)	Pooled (n = 13)
KM time to event, mo			
Median (95% CI)	NE (5.9, NE)	NE (2.5, NE)	NE (5.9, NE)
Range	5.9, 24.0	0.3, 10.5	0.3, 24.0
Events, n (%)	2 (50.0)	1 (11.1)	3 (23.1)
Relapse	2 (50.0)	1 (11.1)	3 (23.1)
Death from any cause	0 (0.0)	0 (0.0)	0 (0.0)
Censored, n (%)	2 (50.0)	8 (88.9)	10 (76.9)
Alive without relapse	2 (50.0)	8 (88.9)	10 (76.9)
Median follow up, mo	23.7	8.8	9.1

NE, not estimable.

efficacy in patients with R/R aggressive B-NHL. We report the durability of complete response (DOCR) in patients treated with blinatumomab.

Methods: The DOCR in patients with R/R aggressive B-NHL responding to blinatumomab was assessed using data from two phase 2 studies (study 1 [N=25], NCT01741792; study 2 [N=41], NCT02910063) in patients with R/R aggressive B-NHL. Complete response (CR) was assessed using Cheson (study 1) and Lugano (study 2) criteria. Time-to-event variables were analyzed using the Kaplan-Meier (KM) method.

Results: Baseline patient characteristics in the pooled analysis were: median age 59 years (range, 41–77); 54% men; 54% treatment refractory; median 2 lines of prior therapy (range, 1–7); and 15% with prior autologous hematopoietic stem cell transplant. Of 25 patients treated with blinatumomab in study 1, 4 (16%) evaluable patients achieved CR. Of 41 patients treated with blinatumomab in study 2, 9 (22%) achieved CR. Median DOCR was not reached (Table). At a median follow-up of 9.1 months in the pooled analysis, 3 patients (23%) had relapsed (study 1, n=2 [50%]; study 2, n=1 [11%]). At 12 and 18 months, the KM probability of maintaining CR in the pooled analysis was 53.0% (95% confidence interval [CI], 8.5, 85.0).

Conclusions: For patients with R/R aggressive B-NHL who received blinatumomab, a durable response is possible. Longer-term follow up is needed to fully characterize the durability of complete response to blinatumomab.

Disclosures: Viardot, A: Consultant Advisory Role: *Roche, BMS, Amgen, Kite/Gilead, Pfizer*; Honoraria: *Roche, BMS, Amgen, Kite/Gilead, Pfizer*; Other Remuneration: *travel fees received from Roche, Celgene, BMS, Abbvie, Kite/Gilead.* **Hess, G:** Consultant Advisory Role: *Roche, Janssen, Celgene, Gilead, Servier, Abbvie*; Research Funding: *Roche, Servier, Celgene*; Other Remuneration: *Speakers' bureau: Janssen.* **Bargou, R:** Honoraria: *Amgen, Cellex, GEMoAB, Molecular Partners, Novartis*; Other Remuneration: *Patent/royalties: Amgen.* **Morley, N:** Consultant Advisory Role: *Amgen, Roche*; Honoraria: *Amgen, Janssen*; Other Remuneration: *Speakers' bureau: Amgen.* **Gritti, G:** Consultant Advisory Role: *Autolus*; Other Remuneration: *Travel fees received from Roche, Takeda, and Gilead.* **Iskander, K:** Employment Leadership Position: *Amgen*; Stock Ownership: *Amgen.* **Cohan, D:** Employment Leadership Position: *Amgen*; Stock Ownership: *Amgen.* **Zhang, A:** Employment Leadership Position: *Amgen*; Stock Ownership: *Amgen.* **Franklin, J:** Employment Leadership Position: *Amgen*; Stock Ownership: *Amgen.* **Coyle, L:** Consultant Advisory Role: *Amgen.*

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THE RITUXIMAB MAINTENANCE THERAPY IMPROVES PROGNOSIS OF TRANSFORMED DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: Diffuse large B-cell lymphoma (DLBCL) with follicular lymphoma (FL) component at diagnosis has been considered as one of transformed DLBCLs. The prognosis of transformed DLBCL has improved by use of rituximab-contained therapy as same as de-novo DLBCL. However, it is still unclear whether transformed DLBCL can obtain identical outcomes compared to de-novo DLBCL. Furthermore, there are few reports about the effects of rituximab maintenance therapy for transformed DLBCL. We retrospectively analyzed the difference of clinical features and outcomes between transformed DLBCL and de-novo DLBCL and the efficacy of rituximab maintenance therapy for transformed DLBCL.

Methods: We studied patients with newly diagnosed as transformed DLBCL or de-novo DLBCL from March 2005 to October 2017 in our institution. The pathological diagnosis was performed based on morphological and immunohistochemical analyses. Transformed DLBCL

was defined in our study as a coexistence with components of FL and DLBCL in the same biopsied tissue at diagnosis. PET-CT scan was used to evaluate the stage at the diagnosis and the response after therapy. The statistical analysis of characteristics of patients were performed by Fisher's exact test. The survivals were calculated by the Kaplan Meier method, and statistical analysis were performed by log rank test. The various factors affecting OS and PFS were evaluated using Cox proportional hazard model.

Results: We analyzed patients with 51 transformed DLBCL and 532 de-novo DLBCL. Almost all patients were treated with R-CHOP chemotherapy in both groups. Among transformed DLBCL patients, 19 patients received rituximab maintenance therapy for two years after achieving good PR or more by induction therapy. In the comparison of patients' characteristics, the rate of advanced stage (58.8% vs 33.8%, P=0.001), bone marrow invasion (13.7% vs 5.3%, P=0.025), and GCB subtype (80.0% vs 55.0%, P=0.001) were significantly higher in transformed DLBCL compared to de-novo DLBCL. The median follow-up time was 71 months (range 3-160 months). 5-year PFS was significantly lower in transformed DLBCL than de-novo DLBCL (67.3% and 78.2%, respectively, P=0.0155), however there was no significant difference in 5-year OS (93.5% and 84.9%, respectively, P=0.31). With regard to patients with transformed DLBCL, there was significant difference between the group with rituximab maintenance therapy and the group without maintenance in 5-year OS (100% and 89.7%, respectively, P=0.0306) and 5-year PFS (94.7% and 51.4%, respectively, P=0.0046).

Discussion and Conclusion: Our data showed that transformed DLBCL had similar OS compared with de-novo DLBCL under R-CHOP therapy. Shorter PFS in patients without rituximab maintenance might be affected by the indolent component in transformed DLBCL. Our data suggested that rituximab maintenance therapy can control those components and improve outcomes of transformed DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); rituximab.

Disclosures: Mishima, Y: Consultant Advisory Role: *Chugai-Roche Pharmaceuticals Co LTD.* **Nishimura, N:** Consultant Advisory Role: *Chugai-Roche Pharmaceuticals Co LTD.* **Yokoyama, M:** Consultant Advisory Role: *Chugai-Roche Pharmaceuticals Co LTD.* **Terui, Y:** Honoraria: *Bristol-Myers Squibb, Celgene, Janssen, Novartis Pharma and Takeda Pharmaceutical Co LTD.*

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INTENSIVE IMMUNOCHEMOTHERAPY (R-CHOEP) VS HIGH-DOSE IMMUNOCHEMOTHERAPY (R-MegaCHOEP) IN YOUNG PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMA: A 10-YEAR LONG-TERM FOLLOW-UP

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Introduction: In 2012, we were first to report the results of a randomized trial comparing high-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT) to aggressive conventional chemotherapy (R-CHOEP-14) as first-line therapy in young high-risk patients (pts) with aggressive B-cell lymphoma (Schmitz et al., Lancet Oncology 2012; 13, 1250-1259). We and others demonstrated that HDT/ASCT does not confer a survival advantage in the rituximab era. Here, we present the 10-year follow-up of the R-MegaCHOEP trial including data on secondary neoplasms and molecular profiles.

Methods: In the randomized, prospective phase III R-MegaCHOEP trial younger pts aged 18-60 years with newly diagnosed, high-risk (aaIPI 2-3) aggressive B-cell lymphoma were included. 130 pts received 8 cycles of CHOEP-14 plus Rituximab; 132 pts were treated with 4 cycles of high-dose therapy necessitating repetitive ASCT (MegaCHOEP-21) with Rituximab. Primary endpoint was event free survival (EFS). This follow-up report includes molecular data based on immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) for MYC (IHC: 31/92 positive, FISH: 14/103 positive), BCL2 (IHC: 65/89 positive, FISH: 23/111 positive) and BCL6 (IHC: 52/86 positive, FISH: 34/110 positive) and data on cell of origin (COO) classification according to the Lymph2CX assay (GCB: 53/88; ABC: 24/88; unclassified: 11/88).

Results: After a median observation time of 111 months, EFS at 10 years was 57% (95% CI 47-67%) in the R-CHOEP14- vs. 51% in the R-MegaCHOEP-arm (42-61%) (hazard ratio 1.3, 95% CI 0.9-1.8, p=0.228), OS after 10 years was 72% (63-81%) vs. 66% (57-76%) respectively (p=0.249). In total, 12% of pts died due to lymphoma (30 pts), 9% therapy-related (23 pts), 3% of secondary neoplasia

(8 pts) and 2% due to concomitant disease (5 pts). The frequency of secondary malignancies was comparable in both arms (9% vs. 8%) and despite extremely high doses of etoposide (total dose 4g/m^2 in R-MegaCHOEP) we observed 2 cases of AML and 1 case of MDS per arm only. With regard to molecular characterization, we were unable to detect a significant benefit for HDT/ASCT when taking into account COO or expression- and translocation-status of MYC, BCL2, and BCL6 although the number of double-/triple-hit (n=14) and double-expressor (n=22) lymphomas was limited.

Conclusions: This 10-year long-term follow-up of the R-MegaCHOEP trial confirms the encouraging outcome of young high-risk pts following aggressive conventional chemotherapy with 8 x R-CHOEP14. HDT/ASCT still does not confer any survival benefit including pts with poor-risk molecular characteristics. Solid tumors occurred at comparable frequencies in both treatment arms while the addition of etoposide to CHOP, even at very high doses, does not seem to increase the incidence of secondary AML/MDS.

Supported by Deutsche Krebshilfe.

Keywords: diffuse large B-cell lymphoma (DLBCL); high-dose therapy (HDT).

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TREATMENT OF HIGH RISK AGGRESSIVE B CELL LYMPHOMAS WITH DA EPOCH R– THE AUSTRIAN EXPERIENCE

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Introduction: Promising results in patients suffering from Burkitt`s lymphoma (BL) and primary mediastinal B cell lymphoma (PMBCL) treated with DA EPOCH R have been reported. Additionally DA EPOCH R seems to be an option in first line treatment in high risk aggressive B cell lymphoma (HR BCL) in phase II trials.

PFS 2a, DEL, n=22
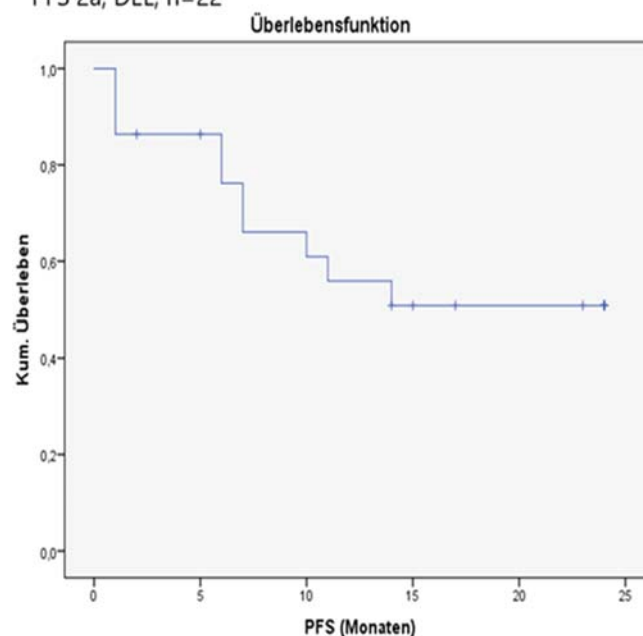
In our centres HR BCL - defined as DLBCL NOS with double protein expression (DEL) and/or high/ high-intermediate risk NCCN IPI, high grade B cell lymphoma with myc and bcl 2and/or bcl 6 rearrangements and high grade B cell lymphoma NOS - BL and PMBCL are treated with DA EPOCH R.

Methods: we performed a retrospective analysis of toxicity and efficacy in DA EPOCH R treated patients.

Results: So far 71 previously untreated patients with a median age of 52 years (range 18 – 89) have been treated with a total of 375 cycles of DA EPOCH R: 41 HR BCL, 18 PMBCL, and12 BL.

Dose escalation according to hematological toxicity was possible in 53 (77%) patients – but only in 7 (33%) of 21 patients ≥ 65 years. 29 (62%) of 48 patients aged <below 65 years received at least dose level 3 (144% dose intensity). Due to peripheral sensory neuropathy, vincristine had to be dose reduced in 37% of all cycles. Other CTCAE grade III/IV non-hematological toxicities were infrequent and manageable.

After a median follow up of 21,5 months overall survival (OS) rate is 80% and PFS 60% for all 71 patients. OS and PFS rates are 90% and 92% in BL, 92% and 93% in PMBCL, respectively.

In 41 HR BCL patients OS is 73% and PFS is 44% after a median follow up of 22 month, 2 years PFS is 58%. 2 years PFS for 22 patients in the subgroup of DEL is 51% (figure below), 2 years PFS in 10 patients with high risk NCCN IPI is 50%.

Conclusion: Despite limited data, DA EPOCH R is a feasible treatment with acceptable toxicity and a promising response rate. Dose escalation is age dependent. Excellent response rates to DA EPOCH R in BL and PMBCL are confirmed. As presented by Bartlett et al at ASH 2016 DA EPOCH R can not be recommended for standard risk DLBCL, but might be an valuable option for high risk aggressive BCL and can challenge more toxic regimens like R ACVBP or R Hyper CVAD.

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A PHASE II STUDY OF LENALIDOMIDE AND RITUXIMAB (R²) COMBINATION IN PATIENTS WITH HIGH-RISK REFRACTORY/RELAPSED DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Patients with refractory/relapsed (R/R) diffuse B-cell lymphoma (DLBCL) have a poor prognosis after traditional chemotherapy salvage regimens. Refractory patients and early relapses (<12 months) are particularly refractory to chemotherapy. Lenalidomide (L) is an immunomodulatory drug with pleiotropic antineoplastic effects. There are numerous studies of L and Rituximab (R) combination (R²) in patients with R/R DLBCL, resulting in a 28% to 41% objective response rate, depending on the status of disease. Herein, we report mature data for safety and efficacy of R² in high-risk R/R DLBCL.

Methods: Eligible patient's age ³18 years had CD20+ B-cell R/R DLBCL. Cell of origin (COO) was assessed at time of entry in the study. High-risk patients were defined as refractory or relapsing within 12 months, ³ 3 prior therapy lines, high international prognostic index (IPI) at relapse, histological transformation (HT), and non-germinal center (non-GC) COO signature. L was given orally at 25 mg/day (d) from d1 to d21, for a 28-d cycles, and R at 375 mg/m2 at d8. Treatment was planned for 12 cycles, and was interrupted in case of progression or unacceptable toxicity. Primary objective was response rate. Secondary objectives were progression-free survival (PFS) and overall survival (OS).

Results: From 10/2013 to 10/2017, 34 patients were included in the study of whom 32 were evaluable for both toxicity and efficacy. Median age was 69 years (range 40-86), with 22/32 (69%) of patients > 60 years, 21/32 (66%) were male, and 22/32 (69%) had stage III/IV disease. Twenty-six of 32 patients (81%) were considered as high-risk R/R DLBCL: refractory 4, ³ 3 prior therapy lines 12, High IPI 24, HT 15, non-GC 10. The median number of prior anticancer therapies was 2 (1-4), and 30/32 (94%) received ³ 2 lines. The median number of L cycles was 2 (1-12) and 8/32 (25%) received less than 2 cycles. Median total dose of L was 1050 mg (300-6200). Toxicity was mainly haematological and the

most common (³10% of patients) grade 3-4 treatment-emergent adverse events consisted in neutropenia and thrombocytopenia. Treatment was interrupted in 27/32 (84%) patients due to progression of disease. Only 4 patients experienced an objective response (12.5%) with 2 complete responses (6%). With a median follow-up of 22.6 months ([9.6-54.8], 95% confidence interval), 1-year PFS and OS were 8% [2%-21%] and 44% [25%-61%] respectively. At the last follow-up, 18/32 (56%) patients were dead all from lymphoma.

Conclusions: Our data of the R² regimen in R/R DLBCL were comparable in terms of tolerance to those reported in the literature. However, response and survival rates were very low when compared to previous reports of the combination. This could be due to our population features as the majority of patients in this series could be classified as high-risk R/R. Alternative options should be offered in these situations.

Keywords: diffuse large B-cell lymphoma (DLBCL); lenalidomide.

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DA-EPOCH-R VERSUS R-CHOP IN HIGH RISK DLBCL PATIENTS: ANALYSIS OF THE CZECH LYMPHOMA STUDY GROUP (CLSG)

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Introduction: The prognosis of younger (≤ 70 years) patients (pts) with diffuse large B-cell lymphoma (DLBCL) at high risk (aa-IPI score 2-3) after R-CHOP chemotherapy is suboptimal. Intensification with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) plus rituximab (DA-EPOCH-R) in unselected patients with DLBCL has not resulted in increased efficacy according to CALGB/Alliance 50303 trial (Wilson et al., ASH 2016). However, the role of DA-EPOCH-R as a regimen for untreated younger patients with high risk DLBCL excluding those with primary mediastinal large B-cell lymphoma (PMBL) remains controversial.

Methods: Between 10/2013 and 12/2017, a total of 37 pts with newly diagnosed high risk DLBCL (excluding PMBL) pts treated with

TABLE 1 Baseline characteristics of patients treated with DA-EPOCH-R (n=37)

	N	%
Age, years (median, range)	56 (20-70)	
≥60 years	12	32
Females	12	32
Age-adjusted IPI score		
High-intermediate/High	25/12	68/32
Ann Arbor stage		
II/III/IV	2/5/30	5/14/81
Presence of B symptoms	18	47
Performance status (ECOG)		
0-1/2/3-4	19/13/5	51/35/14
Extranodal involvement	36	97
Bulky disease >5.0 cm	20	54
LDH level>ULN	35	95
B2M >ULN	20	61
Bone marrow (involved)	13	35
DEL	7	26
DHL/THL	3	12
Cell of origin (Hans)		
GC/Non-GC/Not evaluable	19/10/8	51/27/22
CD5 positivity	1	3

B2M beta-2-microglobulin, DHL double hit lymphoma; THL triple hit lymphoma, DEL double expressor lymphoma, GCB germinal center B-cell lymphomas, ULN upper limit of normal, LDH lactate dehydrogenase

Fig 1. Kaplan-Meier plot for: (A) PFS for DA-EPOCH-R vs. R-CHOP; and (B) OS for DA-EPOCH-R vs. R-CHOP

DA-EPOCH-R were registered in the Observational Epidemiological and Clinical Study registry NIHIL (govTrial no: NCT03199066). Basic characteristics are summarized in Table 1. The clinical outcomes of DA-EPOCH-R cohort were compared to 117 pts treated with R-CHOP regimen from 2 centres where intensification approach is not introduced. We performed 1:1 matched-pair analysis including these criteria: aaIPI, age and performance status.

Results: Median age was 56 years (range: 20–70). Median number of administered DA-EPOCH-R cycles was 6 (range, 1-6). Dose escalation to 3rd dose level or above was feasible in 68% pts. The overall response/complete remissions were achieved in 92%/78% pts. At a median follow up of 2.3 years, the median overall survival (OS) and progression-free survival (PFS) had not been reached; estimated 3-year PFS and OS were 70% and 85%, respectively. Predictors of short PFS in univariate analysis were the presence of B symptoms (p=0.006) and increased beta-2-microglobulin level (p=0.034). Serious (CTCAE grade III/IV) infections occurred in 21.6% of pts. 11% pts developed other serious non-hematologic toxicity. No significant differences in PFS and OS were observed between DA-EPOCH-R vs. R-CHOP in the matched-pair analysis (Fig. 1). Estimated 3-year PFS and OS of pts treated with R-CHOP were 66% and 70%, respectively.

Conclusion: The DA-EPOCH-R is an active and feasible treatment for high risk DLBCL pts. According to our data, DA-EPOCH-R did not improve PFS or OS compared to standard R-CHOP treatment.

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UPFRONT AHSCT IN NON HODGKIN LYMPHOMA-BETTER OUTCOME?

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Background: High dose therapy (HDT) followed by autologous hematopoietic stem cell transplantation (AHSCT) is recognized as a standard of care for relapsed/refractory Non-Hodgkin Lymphoma (NHL). There are many studies which have demonstrated improved disease free survival(DFS) and overall survival(OS) with AHSCT in these patients. There have been also several studies which reported better outcome in patients with high risk NHL who had upfront AHSCT.

Aims: This study aims to determine if upfront AHSCT do improve patients' clinical outcome.

Methods: This is a retrospective study where patients who had undergone AHSCT from October 1997 to September 2017 in 2 hospitals in Malaysia were included. Patients' demographic data and clinical information were collected. The risk groups were categorized into 2 groups via the International Prognostic Index (IPI); whereby IPI score of 0-2 were defined as low risk and IPI score of 3-5 were considered as high risk.

Results: A total of 148 patients (male: female 92:56) were included. Majority of patients had B cell lymphoma (85.1%). The median age at diagnosis was 46 (ranges from 15 – 69) years. The median period of diagnosis to AHSCT was 9.5 (range 2-112) months. Majority of patients (88.5%) were transplanted in complete remission (CR) and the remaining (11.5%) in partial remission (PR). 68% of patients were categorized as low risk and 32% patients were categorized as high risk. The transplant related mortality (TRM) was 3.4%. The overall survival (OS) and event free survival (EFS) at 3 years were 70.1% and 62.6% respectively. Patients who were transplanted in first CR had significantly better OS and EFS, p value of <0.0001. The TRM of 3.4% is similar to what was reported in other centres internationally.

Summary/Conclusion: The significantly better clinical outcome of patients transplanted in first CR may suggest that upfront AHSCT is feasible and may improve outcomes. However, further studies would be required to confirm this finding.

Keywords: autologous stem cell transplantation (ASCT); high-dose therapy (HDT); non-Hodgkin lymphoma (NHL).

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OUTCOME OF PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMA WHO FAILED TO PROCEED TO OR RELAPSED AFTER HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

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Background: Patients with high-risk or relapsed aggressive lymphoma are usually treated with high dose chemotherapy (HDT) and autologous hematopoietic cell transplantation (auto-HCT).

Aim: We evaluated patients who were referred to auto-HCT and who failed to proceed to or relapsed after auto-HCT.

Methods: We evaluated data from 101 consecutive patients with aggressive B-cell lymphoma: DLBCL (n= 86) and PMBL (n=15), who were planned for HDT and auto-HCT at our institution between 2012 and 2017 including 45 female and 56 male, median age (range) of 49 (20-69), clinical stage III/IV in 85 (85%) pts.

Results: After first-line treatment, CR and PR was achieved in 51 (50%) and 43 (43%), respectively. Twenty three patients (23%) were not eligible for transplant: 7 pts failed stem cell mobilization, and 16 patients progressed before transplantation. 78 pts underwent HDT and auto-HCT: 21 pts in the first remission, and 57 pts after a median of 2 (2-4) lines of treatment. At transplant, 46 (60%) and 31 (40%) patients were in CR, and PR, respectively. Relapse after transplant occurred in 30 (38%) patients including 6 pts in first remission and 24 pts in subsequent remission (p=0.24), and 12 (26%) pts in CR and 18 (58%) in PR (56%) (p=0.003). The HR for progression in pts with response less than CR was 2.89 (95%CI: 1.51, 6.66) compared to pts with CR at transplant. With a median (range) PFS of 20 months (0-79), 1-year PFS was 66% (95%CI: 56%, 76%). Median (range) PFS for patients who relapsed post-transplant was 3 (0-40) months. With a median (range) follow up of 21 (0-79) months, 1- year OS for all transplanted patients was 69% (95%CI: 59%, 79%). Median (range) OS for pts who relapsed after auto-HCT was 6 (0-40) months. Conclusion: Around 20% of patients with high-risk or relapsed aggressive B-cell lymphoma were not able to proceed to HDT/auto-HCT, and around 40% of those who did, progressed after transplantation. Non-CR at transplant increased the risk of progression after transplantation. Taken together, 60% of patients with aggressive B-cell lymphoma referred to HDT/auto-HCT at our institution might be candidates for novel therapies.

Keywords: diffuse large B-cell lymphoma (DLBCL); high-dose therapy (HDT).

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R-IVAC SALVAGE THERAPY IN RELAPSED AND REFRACTORY DLBCL

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TABLE 1

Characteristic	N = 27
Age (median, range)	51.8 (30.4-65.8)
Male gender	73%
ECOG	
0-1	21
>2	6
Ann Arbor Stage median	2.5
I-II	12 (44%)
III-IV	15 (56%)
>1 Extranodal sites	8 (30%)
Bulky disease	11 (41%)
R-IPI	
0	6
1-2	11
>3	10
Prior lines of therapy (median, range)	1 (1-2)
Time to relapse:	
<12 months or refractory disease	22 (82%)
>12 months	5 (18%)

Introduction: Despite advances in novel therapy for diffuse large B-cell lymphoma (DLBCL), salvage chemotherapy prior to autologous stem cell transplant (HSCT) remains the standard approach at relapse. However, there is no consensus salvage regimen and practice varies considerably. Refractory DLBCL or short remission duration cases have particularly poor outcomes (Gisselbrecht, 2010). R-IVAC is an infusional protocol incorporating etoposide (60mg/m^2 Day 1-5), ifosfamide (1.5g/m^2 Day 1-5), cytarabine (2g/m^2 BD Day 1-2) in addition to Rituximab (375mg/m^2).

Methods: We retrospectively analysed 27 patients treated at two teaching hospitals to determine the safety and efficacy of R-IVAC for relapsed DLBCL. Disease response was assessed by PET (Lugano 2014 criteria).

Results: Patient characteristics are summarised in Table 1. 13 patients (48%) were refractory to their previous therapy and 9 patients (33%) had relapsed in <12 months. 70% of patients received 2 cycles of treatment (range 1-3) and 92.5% received rituximab with IVAC.

In 26 evaluable patients, the overall response rate (ORR) was 54% (42% complete response, 12% partial response). In patients with disease relapsing after >12 months, the ORR was 100%, versus 43% in relapses <12months or refractory disease. 21 patients were referred for HSCT, and 10 (37%) patients proceeded (9 autograft, 1 allograft). Stem cell mobilisation succeeded in 90% of patients. 2 patients declined HSCT, 8 did not proceed due to inadequate disease control.

With a median duration of follow-up in surviving patients of 30 months, 2-year progression-free survival (PFS) of the whole cohort was 25% and 2-year overall survival (OS) was 32%. Patients who responded achieved 2-year PFS of 53% and OS of 62%. In HSCT recipients, 2-year PFS and OS were 44% and 66%.

Hematologic toxicity was considerable with grade 3/4 neutropenia and thrombocytopenia in 92.5% and 100% patients respectively. 25 patients experienced febrile neutropenia, but only 1 patient died of treatment-related toxicity. The mean hospital length of stay per cycle was 15.6 days. 18 patients required an unplanned admission.

Conclusion: R-IVAC demonstrated significant therapeutic efficacy and manageable toxicity in a cohort overwhelmingly composed of refractory or early relapse DLBCL, perhaps suggesting therapy intensification to be effective in refractory disease. Judicious patient selection is required given the rate of toxicity.

Keywords: diffuse large B-cell lymphoma (DLBCL); salvage treatment.

Disclosures: Opat, S: Consultant Advisory Role: *Roche, Janssen, Celgene, Takeda, Novartis, Abbvie, Gilead, Bristol-Myers Squibb, Merck, Sanofi, Mundipharma*; Honoraria: *Roche, Janssen, Celgene, Takeda, Novartis, Abbvie, Gilead, Mundipharma*; Research Funding: *Roche, Janssen, Celgene, Takeda, Novartis, Abbvie, GIlead, Beigene, Merck*; Other Remuneration: *Roche, Bristol-Myers Squibb*. **Gregory, G:** Consultant Advisory Role: *Roche*; Honoraria: *Roche*; Other Remuneration: *Roche*. **Gilbertson, M:** Honoraria: *Roche*.

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OFATUMUMAB WITH IVAC FOR DLBCL PATIENTS WHO FAILED R-CHOP AND WERE NOT CANDIDATES FOR HIGH-DOSE THERAPY AND ASCT - PHASE 2 TRIAL OF THE POLISH LYMPHOMA RESEARCH GROUP (PLRG-8)

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Introduction: Second or subsequent line chemotherapy for DLBCL patients who relapse or progress after R-CHOP induction treatment involve different cytotoxic agents but there is no alternative to anti-CD20 antibody rituximab available. In addition, rituximab is not reimbursed for recurrent DLBCL in Poland. We hypothesized that a combination of ofatumumab – type II anti-CD20 antibody with different mechanism of action than rituximab, with dose-intensive chemotherapy IVAC (ifosfamide, etoposide, and cytarabine) will be active in relapsed/refractory DLBCL patients who are not candidates for high-dose chemotherapy and autologous hematopoietic cell transplantation (ASCT).

Methods: Patients with DLBCL not suitable for ASCT who progressed on or relapsed after R-CHOP treatment were eligible. Patients received O-IVAC regimen (ofatumumab + IVAC) that was dose-modified for age ≥ 60. Primary endpoint was objective response rate (ORR = CR + PR, CR complete remission, PR partial remission). Secondary endpoints were: progression-free survival (PFS), event-free survival (EFS), overall survival (OS), safety and tolerability. The minimum patient follow-up was 1 year after treatment completion. The baseline ECOG performance status, age, systemic (B) symptoms, Ann Arbor stage, number of prior salvage therapies and time since last therapy (TSLT) were analyzed as potential prognostic factors. The PLRG-8 study is registered with ClinicalTrials.gov at NCT01481272. The study was supported by the research grant from GSK/Novartis (OMB114361).

Results: Between November 2011 and May 2016, 77 eligible patients were enrolled in the study, received at least one cycle of O-IVAC and were included in the final analysis. The average age was 56,8 (+/-13,6) yrs, ≥60 yrs– 50,6%, male – 57,1%, ECOG 1-2 – 61%, ≥3 – 39%, systemic symptoms – 48,1%, Ann Arbor stage 1-2/3-4 – 22,1%/77,9%, number of prior salvage therapies ≥1 – 58,5%. The ORR was 51.9% (95% CI: 40.7%, 63.1%) with 10% CR (n=8). The presence of systemic symptoms was the only statistically significant (p=0.031) factor for ORR with the odds ratio of 2.77 (95% CI: 1.10, 6.98). Treatment related mortality was 15.5%. 1-year PFS, and EFS were 61% (95% CI: 49.8%, 72.2%) each, and 1-year OS was 84.4% (95% CI: 76.1%, 92.5%). Estimated 5-year OS was 30.6% (95% CI: 20%; 41.2%). ECOG score and TSLT were statistically significant factors for survival endpoints. Age was significant for OS, and the number of therapy lines - for PFS and EFS. The most frequent adverse events were hematological.

Conclusions: O-IVAC regimen was an active salvage regimen for DLBCL patients who failed R-CHOP induction treatment with ORR rate of 51% and estimated 5-year OS of 30%. This outcome compares favorably to the outcome reported in Scholar-1 study (Blood 2017; 130: 1800) with ORR of 26%, and 2-year OS of 20%. Further clinical evaluation of the O-IVAC regimen is justified.

Keywords: diffuse large B-cell lymphoma (DLBCL); ofatumumab; salvage treatment.

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EFFICIENCY AND SAFETY OF STEM CELL MOBILIZATION FOLLOWING GDP SALVAGE IN PATIENTS WITH RELAPSED OR REFRACTORY LYMPHOMA

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Background: High-dose chemotherapy and autologous stem cell transplant (ASCT) remains a key treatment strategy in patients (pts) with relapsed/refractory (R/R) aggressive lymphoma. After CCTG study LY.12 (*Crump, et al, JCO 2014*) established gemcitabine, dexamethasone and cisplatin (GDP) as standard salvage chemotherapy regimen at our centre, we replaced our previous mobilization strategy using cyclophosphamide + etoposide (CE) with PBSC collection using GDP. The aim of this study was to compare the efficiency, resource use and ASCT outcomes of PBSC mobilisation with GDP to CE.

Methods: All pts undergoing PBSC mobilization following salvage GDP for R/R lymphoma from 1/2012 to 8/2018 were included in this analysis. CE comprised C 2 g/m^2 d1, E 200mg/m^2 d 1-3 + GCSF 10µg/kg d4-12, with apheresis planned d13. For collection following GDP, GCSF was added 10µg/kg d9-14, apheresis starting d15. Leukapheresis started when the blood CD34 count was >10 cells/µl (target $\geq$5 x 10^6 CD34 cells/kg). From May 2014 plerixafor 24 µg/kg was added to GCSF for slow or inadequate mobilization. Primary outcomes were PB CD34 count on planned day of apheresis and total CD34 cell yield. Secondary outcomes included number of apheresis days, febrile neutropenia after mobilisation, engraftment, hospital stay, transfusions, PFS and OS.

Results: A total of 339 pts underwent PBSC mobilisation, 210 following GDP and 129 after CE. Pts in GDP group had more delays from planned to actual day of collection (mean 0.7 vs 0.4 days, p=0.006) and required more days of apheresis (mean, 1.7 vs 1.5 days, p = 0.001). The percentage of GDP pts collected on planned day of harvest and who required only one day of apheresis were 71% and 50%, versus 84% and 69% respectively after CE. In multi-variable analysis, CE led to both higher PB CD34 count on planned day of harvest and higher total CD34 yield (both p<0.001), despite a higher rate of plerixafor use in the GDP group (36/210 vs y/129). When considering a target CD34 yield ≥5x10^6/kg there was no difference between mobilization regimens (p=0.66). Similarly, on multivariable analysis, febrile neutropenia during mobilization, days to engraftment, ASCT admission duration and platelet transfusions did not differ between the two strategies; pts mobilized with CE required more RBC transfusion during ASCT (p=0.04). Prior BM involvement and plerixafor use were independent predictors for longer engraftment (p=0.013 and p=0.007 respectively), irrespective of regimen and CD34 yield. In multi-variable Cox analyses, disease status at time of ASCT was the main predictor of PFS and OS.

Conclusions: CE+GCSF appears to be a more efficient mobilization method than GDP+GCSF with regard to number and timing of leukapheresis in pts undergoing GDP salvage for R/R lymphoma; however this did not translate to significant differences in engraftment or length of hospital admission.

Keywords: autologous stem cell transplantation (ASCT); gemcitabine; salvage treatment.

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ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IMPACTS ON IMMUNE EVASIVE MECHANISMS IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA – A SINGLE CENTER EXPERIENCE

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Introduction: Allogeneic hematopoietic cell transplantation (allo-HCT) produces durable remission in a subset of relapse/refractory (r/r) DLBCL. Chemoresistance, remission status, age, comorbidities, and performance status are known predictors of outcomes from previous single center and registry studies. However, it remains unclear whether the graft-versus-lymphoma effect through allo-HCT could overcome established immune evasive mechanisms deployed by r/r DLBCL including MHC downregulation, TP53 overexpression, or c-myc overexpression.

Methods: We retrospectively reviewed 114 patients who had undergone first allo-HCT for r/r DLBCL at our institution from 2000 to 2018. We examined the association of clinical, disease, and transplant characteristics with outcomes post-allo-HCT. We explored pathological correlations between MHC downregulation and TP53 or c-myc overexpression using immunohistochemistry and transplant outcomes. Standard COX proportional hazard model statistical analysis was performed.

Results: One hundred fourteen patients were included in the analysis and their baseline characteristics were summarized in Table 1. With median follow-up of 4.1 years (range 0.8-17.5) for survivors, the 4-year overall survival (OS) and progression-free survival (PFS) is 53% (95% CI 43-63) and 43% (95% CI 34-52), respectively (Figure 1). The 2-year cumulative incidence of relapse and non-relapse mortality is 24% (95% CI 16-32) and 28% (95% CI 20-37), respectively (Figure 2). In multivariate analysis, only transformed disease was borderline significantly associated with improved OS (HR 0.58, 95% CI 0.32-1.06, p=0.077); while Deauville score 4-5 (HR 1.71, 95% CI 0.95-3.07, p=0.072) and prior ASCT (HR 1.76, 95% CI 0.94-3.28, p=0.077) were borderline significantly associated with inferior PFS. Thirty-eight patients had available tumor specimen prior to allo-HCT, and 16 of them had MHC downregulation (either class I or II), 11 of them had TP53 overexpression (≥30%), and 8 of them had c-myc overexpression (>40%). There was no difference in either OS or PFS among patients with or without these immune evasive mechanisms.

Conclusions: We demonstrate here that allo-HCT for r/r DLBCL could achieve favorable long-term survival in nearly half of heavily pretreated patients. Allo-HCT might overcome several established lymphoma immune evasive mechanisms in the subset of patients with available pathologic samples, although our dataset is limited in statistical power toward this analysis. While requiring confirmation from a larger study, our data supports expanded consideration of allo-HCT for r/r DLBCL.

Keywords: allogeneic stem cell transplant (alloSCT); diffuse large B-cell lymphoma (DLBCL); immune system.

Table 1. Baseline Characteristics

	N (%)
Number of patients	114
Patient age, years (median, range)	53.9 (18.8-78.7)
Female Gender	33 (29)
Disease status by PET-CT (Deauville score)	
1-3	55 (56)
4-5	44 (44)
Missing information	15
Pre-transplant ISRT	
No	97 (85)
Yes	17 (15)
Previous Lines of Therapy	
1-2	35 (31)
3 or more	79 (69)
Chemosensitivity	
No	27 (24)
Yes	87 (76)
ATG/Campath	
No	81 (71)
Yes	33 (29)
Prior ASCT	
No	83 (73)
Yes	31 (27)
Transformed from Indolent Lymphoma	
No	60 (53)
Yes	54 (47)
Karnofsky Performance Score (KPS)	
≥90	60 (55)
<90	50 (45)
Missing information	4
HCT-CI	
0-2	61 (54)
≥3	52 (46)
Missing information	1
Donor HLA-match	
Matched	78 (68)
Mismatched	36 (32)
Conditioning Intensity	
Myeloablative	23 (20)
NMA/RIC	91 (80)
GVHD Prophylaxis	
Conventional	91 (80)
CD34+ selected	13 (11)
PT-Cy	10 (9)

Figure 1. K-M Survival

No. at risk					
OS	114	61	37	24	17	10
PFS	114	49	29	20	15	10
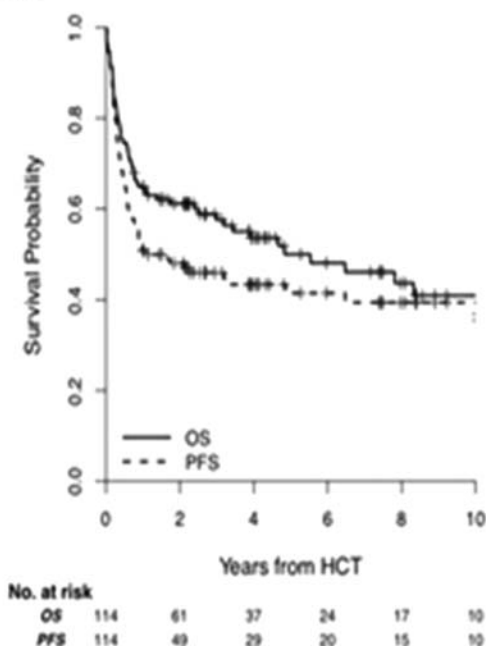
Figure 2. Cumulative Incidence
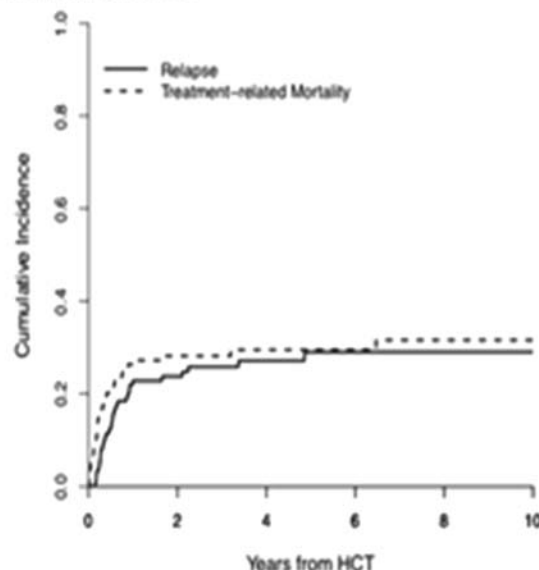
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ANTIVIRAL THERAPY AND IMMUNOCHEMOTHERAPY IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) WITH HEPATITIS C (HCV)

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Currently the association between hepatitis C virus and DLBCL widely accepted. The result of evidence from epidemiological and clinical studies carried out in the last decades. The majority of studies are

related to antiviral therapy (AT) consisting of interferon (IFN) and ribavirin (RBV). New antiviral regimes without interferon allowed to obtain a high percentage of cure of patients from viral infection. There were limited data about efficacy of the new direct-acting antiviral agents (DAAs) in the treatment of patients DLBCL+HCV.

The research objective is to analyze clinical, laboratory, morphological parameters and treatment results in patients with DLBCL+HCV who received DAA together with chemotherapy.

Our study included 16 patients with DLBCL+HCV, who received DAA and immunohypotherapy (R-CHOP) from 2016 to 2019 at National Medical Research Center of Oncology named after N. N. Blokhin and Russian National Research Medical University named after N.I. Pirogov. The median age of patients was 48 years (32-75). Man/woman ratio of was 10/6. All 16 patients had III-IV stages. B-symptoms were present in 50% (8) of patients. Bulk disease occurred in 62%(10) of patients. Histological variants: 3 patients had GCB type DLCBCL, 13 patients - non-GCB type DLBCL. Spleen lesion was present in 37%(6) patients, bone marrow - in 31% (5) of patients, liver lesion - in 37%(6) of patients. Hb≤14,0g/dl were found in 37%(6) and platelets ≤100x10^9/l in 25%(4) of patients. Before the treatment: increase level of LDH ≥450 IU/l was in 81%(13) of patients, ALT ≥40 IU/l - in 100%(16) of patients, AST ≥40 IU/l - in 85%(14) of patients, GGTP ≥ 35IU/l in 44%(7) of patients, and albumin ≤35g/l in 37%(6) of patients. HCV RNA were detect in blood of all patients. In all patients the viral RNA was more then 1.6x10^6 IU/l. The 1st genotype of the virus was found in 63%(10) of patients.

Before immunochemotherapy all patients received DAA therapy, according on the virus genotype. After 30 days of DAA therapy virology remission obtained in 94%(15) of patients. The level of ALT≤40 IU/l decreased at 81%(13) patients, AST ≤40 IU/l-62%(10) patients. DAA conducted during 4-6 months together with immunochemotherapy.

The total response (ORR) of R-CHOP+DAA therapy was 50%. The 2-year survival without progression of the disease (PFS) was 25%. Median follow-up was 24 months. 56% of patients had a relapse of lymphoma. Median of OS was 20 months. Median DFS was 11 months.

Conclusion: DAAs therapy makes it possible to complete the therapy program without complications for all patients with DLBCL + HCV. Safety, rapidity and efficacy of DAA in obtaining a virological response, as well as a good profile of tolerance DAA therapy can be used in combination with chemotherapy.

Keywords: diffuse large B-cell lymphoma (DLBCL) hepatitis C

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HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION COMPARED WITH HLA-MATCHED STEM CELL TRANSPLANTATION FOR REFRACTORY OR RELAPSED AGGRESSIVE NON-HODGKIN LYMPHOMA

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Objective: To examine the efficacy of haploidentical stem-cell transplantation (haplo-SCT) for patients with refractory relapsed(R/R) aggressive non-Hodgkin lymphoma (NHL) by comparing with those who contemporaneously receiving HLA-matched SCT in myeloablative conditioning settings.

Methods: One hundred and fifty-one patients who had undergone haplo-SCT (n=81) or HLA-matched SCT (n=70, sibling or unrelated) in our center between January 2006 and December2018 were enrolled. A median age at alloSCT was 30(5-59) years old. All patients received a myeloablative conditioning (MAC) consisting of total body irradiation (12 Gy) combined cyclophosphamide or busulphan plus cyclophosphamide, and followed by infusion of granulocyte-colony stimulating factor–primed bone marrow (G-BM) and/or peripheral blood stem cells without in vitro T cell depletion. In the case of haplo-SCT and HLA-matched unrelated donor for SCT, the GVHD prophylaxis consisted of antithymocyte globulin, cyclosporine A, mycophenolate mofetil and a short course of methotrexate. The clinical effect, hematopoietic reconstitution, and transplant-related complications were retrospective analyzed.

Results: One hundred and forty-five (96%) patients engrafted with a median time to neutrophil and platelet recovery of 12 and 15 days, respectively. At a median follow-up of 20 months, 72 of 151 patients were alive (48%) and 57 (38%) were dead (34 disease recurrence, 23 transplantation-related mortality (TRM)). Between the haplo-SCT and HLA-matched SCT group, the corresponding progress free survival (PFS) rate was 60.5% and 54.3% (P = .938), respectively; and

Image:
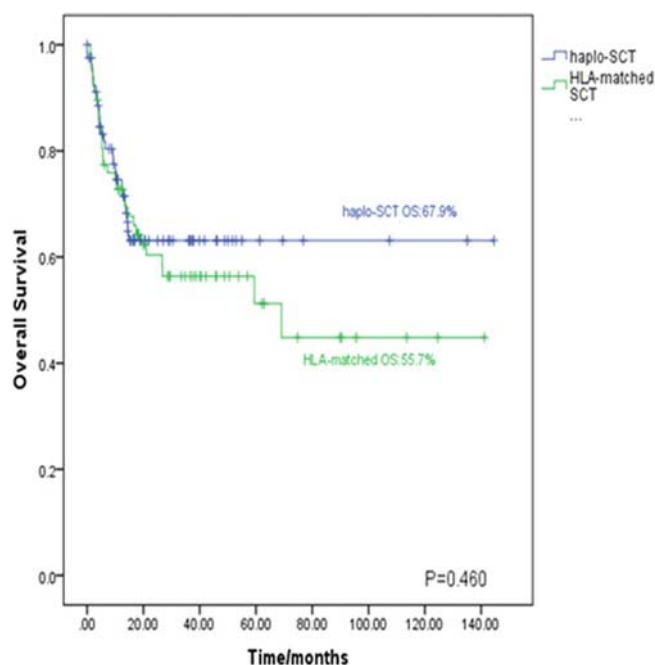
overall survival (OS) rate were 67.9% and 55.7% (P = .460), respectively. The cumulative incidences of relapse (RI) were 23.5% and 21.5% (P = .482), and those of NRM were 20.0 % and 28.2% (P = .44), respectively. And cumulative incidences of chronic GVHD were 42.3% and 39.6%(P=0.46), respectively. These data showed no difference in every major HSCT endpoint between two groups. Multivariate analysis suggested that occurrence of grade III-IV aGVHD had a significant worse outcome, primary chemorefractory was the strongest factors for relapse.

Conclusion: Our results indicate that the outcomes of haplo-SCT are equivalent to HLA-matched SCT, and that MAC followed by haplo-SCT can be an acceptable and feasible alternative for patients with R/R NHL who having no access to a HLA-matched donor.

Keywords: allogeneic stem cell transplant (alloSCT); B-cell lymphoma; T-cell lymphoma (TCL).

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A NATIONAL RETROSPECTIVE ANALYSIS OF CLINICAL OUTCOMES FOLLOWING ALLOGENEIC TRANSPLANTATION FOR HIGH GRADE B-CELL LYMPHOMA (HGBL)

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Introduction: Patients with either primary refractory or relapsed/refractory High Grade B-Cell Lymphoma have a poor outcome with convention therapy as illustrated by the Scholar 1 Study (Crump et al.). High-Grade B-Cell Lymphoma with *MYC* and *BCL-2*and/or *BCL-6* rearrangements, often referred to as Double Hit Lymphoma (DHL) also have a poor outcome with a published overall survival (OS) of 23.3% to 58% (Niitsu et al, Johnson et al). More recently novel therapies such as CAR-T therapy have shown the potential to improve outcomes in these patients (Schuster et al). These patients were considered for allogeneic transplantation from 2007 to 2017 and we performed a retrospective analysis of the outcomes, prior to the introduction of a CAR-T program.

Methods: Consecutive patients transplanted for HGBL between 2007-2017 in the EBMT database were included. Data collected included age, sex, pathology subtype (HGBL (including subtypes), Transformed follicular lymphoma (tFL), DHL), disease status at SCT, conditioning (myeloablative vs reduced intensity), engraftment, day 100 outcome, development of graft versus host disease

(GvHD), Non-relapse mortality (NRM), OS and eligibility for CAR-T therapy.

Results: Fifty patients (29M, 21F) with a median age 47 at diagnosis and 50 at SCT were included. The subtypes included were HGBL (n=29), tFL (n=11) and DHL (n=10). Indications for SCT were: primary refractory (n=17), relapse <12 months after primary treatment (n=12), previous Autologous-SCT (n=10) and DHL (n=11). The median lines of therapy was 4 (range 1 to 6). Conditioning used was myeloablative (n= 23) or reduced intensity (n= 27). The day 100 mortality was 8% (progressive disease 4%, NRM 4%) with a OS of 56% and mortality due to progressive disease 22% and NRM 16%. 23 patients were eligible for a licensed CAR-T product. Disease subtype influenced outcome with an OS for primary refractory HGBL, relapsed HGBL, tFL and DHL respectively of 53%, 58%, 57% and 89%. Disease status at time of SCT significantly influenced outcome with a OS of 74% for patients in PET negative remission at time of SCT vs 36% for patients with PET positive disease.

Conclusion: In this retrospective analysis patients with high risk HGBL had an overall survival of 56%. The most common cause of mortality was relapsed disease. Patients with PET negative remission at time of transplant have a good outcome with an OS of 74%. In our cohort patients with DHL have a particularly good outcome; it is likely some of these patients with a non-immunoglobulin gene associated MYC translocation could be managed more conservatively based on recent evidence (ASH Sehn). This analysis will provide a baseline outcome in the national transplant centre in a challenging disease cohort prior to the introduction of a CAR-T program.

Keywords: allogeneic stem cell transplant (alloSCT); diffuse large B-cell lymphoma (DLBCL); high-grade B-cell lymphoma with or without rearrangement of MYC and BCL2 and/or BCL6.

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THE ADDITION AT DAY 9 OF HD-MTX TO THE (DA)-EPOCH SCHEME WITH OR WITHOUT RITUXIMAB IS AN EFFECTIVE REGIMEN IN UNTREATED ADVANCED STAGE HIGH RISK LYMPHOMA: A FEASIBILITY STUDY

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DA-EPOCH is an infusional regimen designed to improve the response rate in highly proliferative tumors by prolonging cell exposure to low concentrations of chemotherapeutic agents. It was demonstrated as effective regimen in both T and B cell high grade lymphomas with an elevated proliferative index. Moreover, the

addition of Rituximab is currently the standard of care in any B cell lymphoma treatment strategy. Previous studies have shown that high dose methotrexate (HD-MTX) therapy is better than intrathecal MTX administration to prevent CNS relapse, but so far few data are available that explore the feasibility of combination therapy including HD-MTX and DA-EPOCH with or without Rituximab. Our pilot study reported the result of the above combination therapy in a series of high risk advanced stage lymphoma patients (pts).

Five patients were enrolled in this feasibility study: 3 pts were affected by Diffuse Large B Cell Lymphoma (DLBCL) no GC type, 1 pt had a diagnosis of Primary Mediastinal Diffuse Large B Cell Lymphoma (PMDLBCL) and 1 pt had an ALK+ Anaplastic Large Cell Lymphoma (ALCL). All pts showed a stage IV disease with $\geq$ 2 extranodal sites, high LDH level, a very high proliferation index evaluated by Ki67 (median 90%, range 60-100%) and intermediate/high IPI score (3). High risk of CNS relapse was present in all pts because of type of extranodal sites (gut, bone, liver, heart, mediastinum, pancreas) and for high proliferation rate. The combination therapy included classical DA-EPOCH-R scheme with exception of Rituximab in ALCL with the addition of high dose (3.5 g/m^2) Methotrexate at day 9 after urine alkalinization and hydration. All patients were scheduled to receive a total of 6 courses of therapy including 4 courses of the classic DA-EPOCH scheme and 2 combined therapy cycles. G-CSF prophylaxis was administered to all patients starting on day +9 and day +12 in the case of DA-EPOCH or combination therapy, respectively. The aim of the study was to evaluate the impact of adding HD-MTX to DA-EPOCH on the time between DA-EPOCH- (R) cycles. Secondary endpoints were response rate, PFS, toxicity, and CNS relapse rate.

After a total of 9 courses administered of combination therapy, no delay in DA-EPOCH-(R) schedule of 21 days was observed. All patients showed a very favorable toxicity profile with only G3 neutropenia without infectious complications and G2 hepatotoxicity with elevations in transaminases. Three out of 5 pts completed the treatment strategy obtaining a CR and are now in follow-up, while the others are still on treatment. No CNS relapse were observed.

Our preliminary results showed the feasibility of the combination therapy DA-EPOCH-R/HD-MTX with satisfactory results on controlling very aggressive disease. However, only prospective trials can define the optimum scheduling of this regimen and the possibility to use as standard therapy in very aggressive lymphomas with high risk of CNS relapse.

Keywords: DA-R-EPOCH; high-dose methotrexate; non-Hodgkin lymphoma (NHL).

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DIFFUSE LARGE B CELL LYMPHOMA WITH SECONDARY CENTRAL NERVOUS SYSTEM INVOLVEMENT: CAN MRI PATTERN HELP PREDICTING OUTCOME?

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Purpose: To assess the prognostic significance of baseline neuroimaging for patients with secondary central nervous system (CNS) diffuse large B-cell lymphoma (DLBCL).

Methods: After obtaining institutional review board approval, we reviewed 44 patients between 2006-2016. Patient's clinical and treatment-related factors were examined. An experienced neuro-radiologist and radiation oncologist reviewed baseline imaging studies and grouped them into three cohorts: leptomeningeal disease (LMD), corpus callosum/basal ganglia (CCBG), or intraparenchymal disease (IPD).

Results: Median age was 55 years (range 23-83); 68% were male (n=30). Germinal center histology in 12 of 44 patients. Of the 44 patients, 3 had CNS involvement at presentation and 41 had CNS disease at relapse. Majority (75%) received R-CHOP (rituximab, cyclophosphamide, Adriamycin, vincristine, and prednisone) as front-line chemotherapy, 21 presented with LMD, 13 with IPD, and 10 with CCBG. Cerebrospinal fluid (CSF) evaluation was performed in 42 patients with cytopathologic evidence of CSF involvement in 20 patients (12/21 LMD (2 unknown), 2/13 with IPD, and 6/10 CCGB). Extra-nodal disease systemic disease at presentation was seen in 14/21 with LMD, 0/13 of IPD, 3/10 CCGB. Prior to administering RT, 30 patients (68%) were given CNS-directed chemotherapy. Whole brain RT (WB) in 42 patients with a median dose of 30 Gy (range 19-30); 13 received boost to the gross disease, median of 9 Gy (range 5-20). At a median follow up of 31 months from RT (range 1-120), 35 patients died. The cause of death was secondary to CNS DBLCL in 14, disease progression outside of the CNS in 16 and unknown in 6. Median survival for the entire cohort was 7 months. Median survival for LMD patients was 9 months with 4/21 patients alive at 20, 33, 87, and 120 months; most patients died from progression of distant disease (11/21). Median survival for IPD patients was 10 months with 5/10 patients alive at 99, 95, 48, 31 and 25 months, and, interestingly, as opposed to those with LMD (9/21 distant disease), all 5 patients died secondary to CNS disease. On the other hand, the median survival for patients with CCGB was only 5 months with only 1/10 surviving to 72 months. All nine patients died secondary to progression of disease both distant and in CNS in less than 8 months.

Conclusions:

1- The best survival was observed in patients with IPD, who seemed to derive the greatest benefit from radiation, in stark contrast to those with disease in the perivascular/corpus callosum area who all died except one.

Corpus callosum/basal ganglia
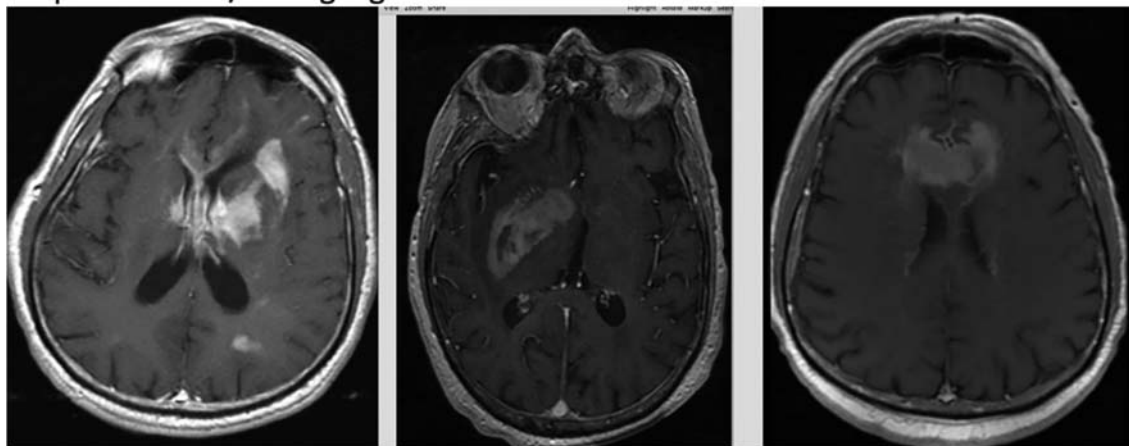
Intraparenchymal disease
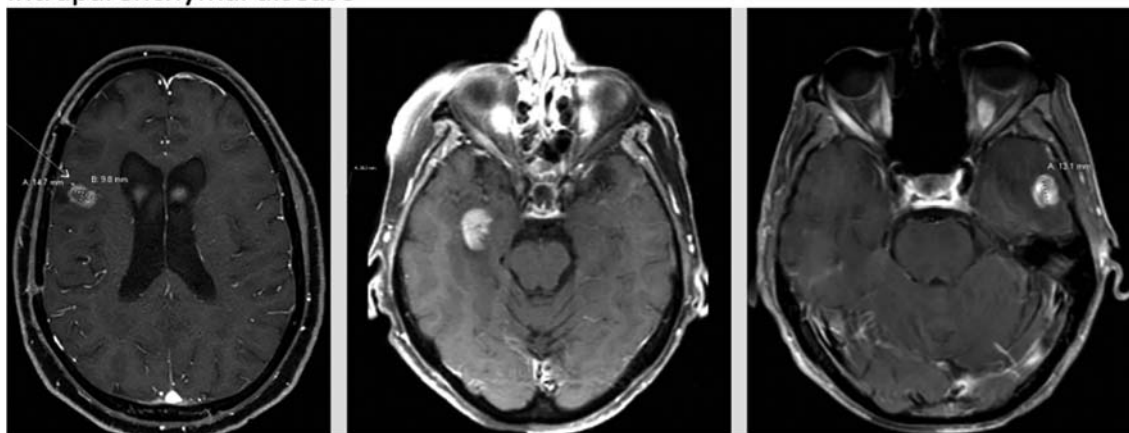
Leptomeningeal disease
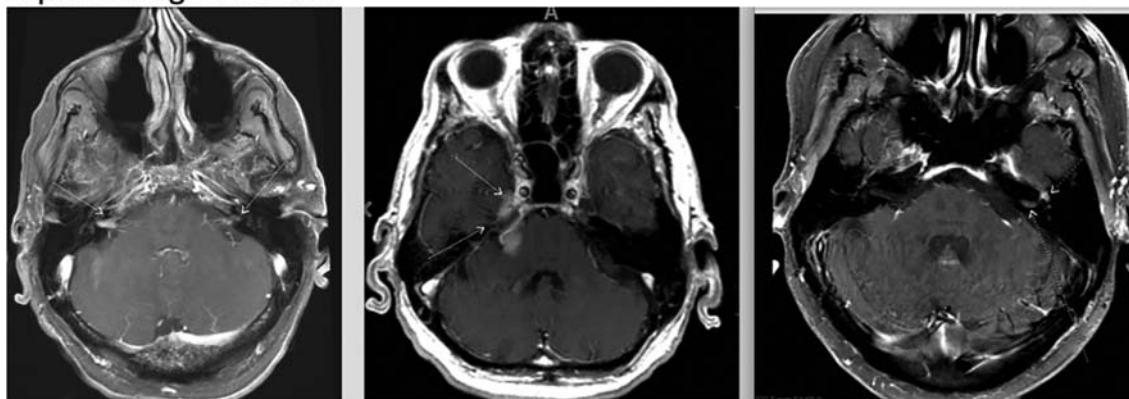
2-It also appears that local control, perhaps with radiation, is of prime importance for patients with IPD as all causes of death were secondary to disease in the brain.

3-Patients with LMD can enjoy long term survival if distant disease in under control thus comprehensive radiation might be worth attempting in selected cases.

Keywords: germinal center (GC); non-Hodgkin lymphoma (NHL); whole brain radiotherapy (WBRT).

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TOLERABILITY OF HIGH DOSE INTRAVENOUS METHOTREXATE FOR CNS PROPHYLAXIS INTERCALATED WITH R-CHOP – A SINGLE CENTRE RETROSPECTIVE ANALYSIS

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Introduction: Central nervous system (CNS) relapse in diffuse large B cell lymphoma (DLBCL) is rare but is associated with poor outcomes. The majority of CNS relapses in DLBCL occur in the brain parenchyma and are therefore unlikely to be prevented by intrathecal prophylaxis. There is increasing evidence to support use of high dose intravenous methotrexate (HDMTX) as a prophylactic regimen in selected high-risk patients. As most CNS relapses occur early in the disease course, ideally prophylaxis should be delivered as early as possible. There remains concern that HD MTX carries a risk of toxicity, especially renal, which could result in delays to systemic chemotherapy if delivered in an intercalated fashion. We performed a single centre, retrospective analysis of 45 patients who received HDMTX intercalated with R-CHOP chemotherapy with a focus on toxicity rates and subsequent delays in systemic therapy.

Methods: 45 consecutive patients receiving HDMTX as CNS prophylaxis alongside R-CHOP chemotherapy for HIV negative DLBCL between 2012-2018 were identified and medical records analysed for toxicity rates, timing of chemotherapy cycles and evidence of CNS relapse. 60% were male (n=27) and median age was 60 years (range 37y–80y). The majority (78%) had stage IV disease and the median CNS IPI was 3, with 31% (n=14) falling in the high risk (4-6) CNS IPI group. Patients with known CNS disease at presentation were excluded. Local guidelines stipulated that 2 cycles of HDMTX at 3g/m2 should be delivered at day 14 following the R-CHOP courses 2 and 3.

Results: 73% (n=33) received at least 2 cycles of MTX. Reasons for only delivering 1 cycle of MTX in 12 patients were patient fitness/frailty (n=7), renal toxicity (n=2) and mucositis (n=3). 5 (11%) patients experienced renal toxicity according to CTCAE definitions (3 = grade 2, 2 = grade 3). All patients had recovery of renal function without the need for invasive intervention. Mucositis occurred in 13 (29%) patients (grading not recorded). Hepatotoxicity was seen in 2/45 (4%) patients. 80 cycles of HD MTX were delivered in total. Neutrophil count on the scheduled day of subsequent RCHOP chemotherapy was >1.0 in 73/80 (91%) cycles. 5/45 (11%) patients experienced a delay of subsequent R-CHOP chemotherapy (7 or more days) directly attributable to methotrexate. 3/45 (7%) of patients suffered CNS relapse with median follow up of 32 months – all relapses were parenchymal and 2/3 had only received 1 cycle HDMTX.

Discussion: This retrospective analysis demonstrates that HDMTX can be delivered intercalated with R-CHOP chemotherapy with acceptable rates of toxicity and few delays in systemic chemotherapy. The rate of renal toxicity was low and was reversible in all patients. Although the numbers are small, the rate of CNS relapse (7%) was low in this selected, high-risk group. Careful assessment of patient fitness is required prior to consideration of HDMTX, but the median age of 60 years in our study suggests that age alone should not be a barrier to delivering this treatment.

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SANDOZ RITUXIMAB FOR TREATMENT OF DIFFUSE LARGE B-CELL LYMPHOMA: INTERIM SAFETY RESULTS OF THE NON-INTERVENTIONAL, OBSERVATIONAL, MULTICENTER, OPEN-LABEL REFLECT STUDY

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Introduction: Sandoz rituximab (SDZ-RTX) is approved in Europe for all indications of reference rituximab. Approval was based on the totality of evidence for biosimilarity, including: extensive physico-chemical and structural data; preclinical and clinical pharmacokinetic, pharmacodynamic, and immunogenicity data; and also clinical trials, including a Phase III confirmatory study in patients (pts) with follicular lymphoma. REFLECT, a real-world study of SDZ-RTX as curative therapy for treatment-naïve CD20^{+} diffuse large B-cell lymphoma (DLBCL), is the first biosimilar rituximab post-approval study in DLBCL.

Methods: The study includes pts aged ≥18 years with CD20^{+} DLBCL, eligible for rituximab and cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP). Exclusion criteria include any prior DLBCL treatment or contraindication to rituximab. R-CHOP is administered according to product label. The primary endpoint is complete response rate at the end of treatment. Secondary endpoints include: overall response rate; 12-month progression-free survival; quality of life; and adverse events (AEs). Data are collected at baseline and every study visit for 12 months (efficacy) and ≥30 days after last SDZ-RTX dose (safety). No imputation for missing data is planned; endpoints are summarized descriptively.

Results: In an interim analysis (cut off: Sep 6, 2018; recruitment approx. 50% complete), the full analysis set comprised 80 pts: 38 males (47.5%) and 42 females (52.5%), with median age of 68.5 years; 70% of pts were aged ≥60 years. In total, 6 pts have discontinued. Most pts had little or no restriction in daily activities; >80% had an ECOG score of 0 (34%) or 1 (50%). Baseline disease characteristics are reported in the Table. Most pts had early stage (I–IIB: 64%), low to intermediate risk disease (IPI score 0–2: 61%). B-symptoms were reported in 15 pts (19%).

A summary of safety is reported in the Table. AEs were reported in 53 pts (66%), serious AEs were reported in 19 pts (24%), and

TABLE 1 Summary of baseline disease characteristics and safety

n (%)	All patients N=80	
Disease stage		
I	26 (32.5)	
IIA	17 (21.3)	
IIB	8 (10.0)	
III	17 (21.3)	
IV	10 (12.5)	
Not available	1 (1.3)	
Missing	1 (1.3)	
International Prognostic Index (IPI) score		
0	7 (8.8)	
1	22 (27.5)	
2	20 (25.0)	
3	14 (17.5)	
4	4 (5.0)	
Missing	13 (16.3)	
Extranodal infiltration		
Extranodal infiltration	40 (50.0)	
Bulky disease	9 (11.3)	
Spleen involvement	2 (2.5)	
Unknown	8 (10.0)	
Not available	20 (25.0)	
Missing	1 (1.3)	
Safety	**All**	**Treatment-related**
AE	53 (66.3)	13 (16.3)
Serious AE	19 (23.8)	2 (2.5)
AE leading to discontinuation	6 (7.5)	1 (1.3)
AE leading to dose interruption	6 (7.5)	2 (2.5)
Death	0	–

treatment-related AEs were reported in 13 pts (16%). The most frequent AEs were polyneuropathy (n=10, 13%), anemia (n=8, 10%), and fatigue (n=8, 10%).

Conclusions: Interim baseline data are as expected for treatment-naïve pts with CD20$^+$ DLBCL; safety results are as expected for rituximab-based treatment. The study is ongoing. Biosimilar rituximab has the potential to provide savings for healthcare systems, broaden pt access to rituximab-based chemotherapy, and support the sustainability of cancer care.

Keywords: diffuse large B-cell lymphoma (DLBCL); monoclonal antibodies (MoAb); rituximab.

Disclosures: Welslau, M: Consultant Advisory Role: *Sandoz.* **Marschner, N:** Consultant Advisory Role: *Sandoz*; Stock Ownership: *iOMEDICO (contract research organization that runs the REFLECT study).* **Otremba, B:** Consultant Advisory Role: *Sandoz.* **Topaly, J:** Consultant Advisory Role: *AbbVie, BMS, Hexal, Janssen, MSD, and Roche*; Other Remuneration: *Travel Grants: AbbVie, BMS, Hexal/Sandoz, Gilead, Ipsen, Janssen and Sanofi.* **Bittencourt da Silva, L:** Employment Leadership Position: *Sandoz Group, a Novartis Division.*

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REAL WORLD EFFECTIVENESS AND SAFETY OF CT-P10 IN DIFFUSE LARGE B-CELL LYMPHOMA: INTERIM RESULTS FROM A EUROPEAN NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY

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Introduction: In February 2017, CT-P10 became the first biosimilar of rituximab to be approved in Europe for treatment of rheumatic diseases and specific blood cancers including non-Hodgkin's lymphoma (NHL). Diffuse large B-cell lymphoma (DLBCL) is the commonest type of NHL, representing an estimated 40-58% of cases (Sant et al, 2010). The aim of the current study was to evaluate the real world clinical effectiveness and safety of CT-P10 in patients with DLBCL in Europe.

Methods: This non-interventional post-authorisation safety study is in progress in five European countries (France, Germany, Italy, Spain and the United Kingdom [UK]), and involves collection of data from the medical records of consenting adult patients with DLBCL who were treated with CT-P10 as part of their routine clinical care. Effectiveness and safety data are being collected for an observation

Figure 1: Best responses to CT-P10 during the observation period
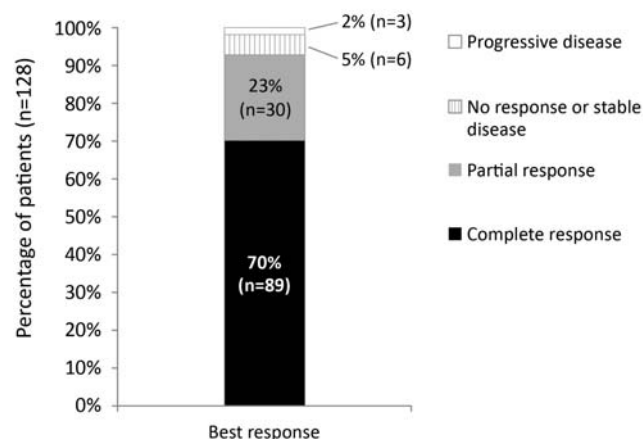
period of 30 months after the index date (date of CT-P10 initiation) or until death, if sooner. The primary objective is to describe the effectiveness of CT-P10 (overall survival, progression free survival, CT-P10 responses), with secondary objectives to describe the safety profile and CT-P10 treatment pathways. Response to CT-P10 is as documented by the local investigator. Here we report interim results (patients' baseline characteristics and preliminary response/safety data), based on a data cut on 18 January 2019. Where n is less than the total number of patients, data were missing.

Results: The interim analysis includes 151 patients enrolled from sites in the UK and Spain, with a median 8.9 months (interquartile range [IQR] 6.1–12.6) post-index observation at the cut-off. Patients are receiving CT-P10 as a first-line (n=138, 91%), second-line (n=9, 6%) or third-line (n=4, 3%) DLBCL treatment. Ninety-five (63%) patients are male. Other patient characteristics at index: median age 70.9 years (IQR 61.5–76.0) (n=149); median disease duration 20 days (IQR 10.5–41.0) (n=147); Eastern Cooperative Oncology Group performance status (n=98): 0 (n=45, 46%), 1 (n=36, 37%), 2 (n=11, 11%), 3 (n=4, 4%) or 4 (n=2, 2%); Ann Arbor stage (n=77): I (n=8, 10%), II (n=9, 11%), III (n=18, 21%), IV (n=40, 48%) or other (n=2, 2%; recorded as 'at least stage II'). Best responses to CT-P10 (evaluable in n=128) are shown in Fig. 1. Safety of CT-P10 was evaluable in 128 patients, of whom 118 (92%) experienced adverse events (AEs) during the observation period (732 AEs recorded in total, including infusion-related reactions), 77 (60%) had AEs of grade 3 and above and 11 (9%) discontinued CT-P10 due to AEs.

Conclusions: Early results from this ongoing study suggest that a high proportion of patients with DLBCL treated with CT-P10 in the real world achieve complete or partial responses, similar to the response rates reported previously for reference rituximab (Horvat et al, 2017). Continued recruitment and extended follow-up will enable more comprehensive analyses of CT-P10 effectiveness and safety.

Keywords: diffuse large B-cell lymphoma (DLBCL); rituximab.

Disclosures: Zinzani, P: Consultant Advisory Role: *Verastem, MSD, Eusapharma and Sanofi;* Honoraria: *Verastem, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, MSD, Immune Design, Celgene, Portola, Roche, Eusapharma and Kyowa Kirin.* **Kang, H:** Employment Leadership Position: *Celltrion Healthcare.* **Kim, S:** Employment Leadership Position: *Celltrion Healthcare.* **Lee, Y:** Employment Leadership Position: *Celltrion Healthcare.*

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A PROSPECTIVE REGISTRY STUDY OF PEG-G-CSF PROPHYLAXIS FOR PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (CISL 1403)

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Background: Febrile neutropenia (FN) is the most important side effect of chemotherapy in diffuse large B cell lymphoma (DLBCL) causing not only treatment-related morbidity but also suboptimal chemotherapy delivery. Prophylactic use of granulocyte colony

TABLE 1 Patients characteristics

Characteristics	This cohort (N=992)	PROCESS cohort (N=487)	P value
Age-years			0.019
median	62	59	
range	19-86	20-89	
Gender			0.855
M	56.5%	56.7%	
F	43.5%	43.3%	
ECOG			0.734
0,1	91.3%	88.6%	
≥2	8.7%	11.4%	
Stage			
1,2	48.7%	48.9%	
3,4	51.3%	51.1%	0.494
Extranodal involvement			0.358
0 or 1	62.8%	65.3%	
≥2	37.2%	34.7%	
LDH elevation			0.229
Yes	52.6%	48%	
no	47.4%	52%	
IPI			0.091
0 or 1	36.6%	44.1%	
2	25.9%	20.5%	
3	20.7%	19.5%	
4 or 5	16.8%	15.9%	
Albumin			0.521
≥3.5mg/dl	74.8%	76.1%	
<3.5mg/dl	25.2%	23.9%	

TABLE 2 Febrile neutropenia with Peg-G-CSF prophylaxis

Characteristics	Giraffe B	Process	P value
Neutropenia (grade4)			
patients	28.8%	69.1%	<0.001
cycles	11.7%	44.4%	<0.001
FN			
patients	13.4%	23.7%	<0.001
cycles	4.2%	16.2%	<0.001
TRM	3.1%	5.5%	0.032
infection-related	1.6%	4.5%	0.001

FN: febrile neutropenia
TRM: treatment-related mortality within 6months

in the analysis. Base-line characteristics were summarized in Table 1. Median age at diagnosis was 62 (19-86) with a predominance of males (56.5%). Most patients had extranodal involvement (90.2%) and 369 patients (37.2%) had two or more extra-nodal involvements. The most common extranodal involvement sites were stomach (15.6%), bone (12.3%), intestine (9.7%) and lung (7.6%). All clinical characteristics were well- matched between the two cohorts other than age at diagnosis. Grade 4 neutropenia was developed in 286 patients (28.8%) with an overall incidence of 11.7% in the cycles and FN developed in 133 (13.4%) patients with an overall incidence of 4.2%, which were significantly lower in this cohort (Neutropenia 11.7% vs. 38.1% p=0.000; FN 13.4% vs 23.7% p=0.000) (Table 2.). Forty-seven patients (35.9%) had multiple episodes of FN. Most patients (80.4%) experienced the first episode of FN within three cycles. Treatment-related mortality (TRM) was significantly lower in this cohort (3.1% vs. 5.5%, p=0.032), mainly due to the low incidence of early infection-related death (1.6% vs. 4.5%, p=0.0001) (Table 2). In this cohort, 765 (77.1%) patients completed 6 cycles of R-CHOP therapy. Dose delays more than 3days and 5days were less common (18.1% vs. 23.7%, p=0.000; 12.0% vs 18.3% p=0.000) with Peg-G-CSF prophylaxis compared to the PROCESS cohort (Table 3). Dose reductions more than 20% in delivery of cyclophosphamide and doxorubicin happened in 13.3%

TABLE 3 Delivery of R-CHOP with prophylactic Peg-G-CSF

Chemotherapy	This cohort (n=992)	Process cohort (n=487)	P value
Completion of 6 cycles			
Dose delay	77.1%	75.1%	0.401
>3 days	18.1%	23.7%	<0.001
>5 days	12.0%	16.5%	<0.001
Dose reduction >20%	13.3%	15.0.%	0.046
cyclophosphamide	19.5%	15.5%	<0.000
doxorubicin	73.2%	70.9%	0.039
*ARDI ≥80%			

*ARDI: average relative dose intensity - ARDI was calculated by averaging the delivered RDIs of cyclophosphamide and doxorubicin

stimulating factor (G-CSF) or pegylated G-CSF (Peg-G-CSF) is known to reduce the incidence of both neutropenia and FN. We conducted a prospective registry study to evaluate prophylactic effect of Peg-G-CSF in DLBCL patients treated with R-CHOP regimen (ClinicalTrials.gov Identifier: NCT02474550).

Patients and Method: Since January 1st 2015, after written informed consent, patients receiving R-CHOP therapy with curative intent were registered and prospectively monitored. All patients were pathologically confirmed with DLBCL according to World Health Organization Classification 2008. Prophylactic Peg-G-CSF (pegfilgrastim 6mg) was administered 24 hours after R-CHOP chemotherapy subcutaneously. The incidence of neutropenia and neutropenic fever were studied. Febrile neutropenia (FN) is defined as an oral temperature >38.5°C or two consecutive readings of >38.0°C for 2h and an absolute neutrophil count <0.5 × 10^9/l, or expected to fall below 0.5 × 10^9/l. We compared the outcomes of the cohort with those of the PROCESS cohort*. This analysis was performed as of December 11st 2018.

Results: A total of 5357 cycles in 992 patients of this cohort and 2581cycles in 487 patients from the PROCESS cohort were included

TABLE 4 Incidence of febrile neutropenia according to clinical characteristics

Characteristics	N (%)	P value
Age		<0.001
≤65	45/566 (8.0)	
>65	88/426 (20.7)	
Gender		0.037
male	64/560 (11.4)	
female	69/432 (16.0)	
BM involvement		0.415
no	121/882 (13.7)	
yes	12/110 (10.9)	
Ann arbor Stage		0.011
I to III	75/656 (11.4)	
IV	58/336 (17.3)	
LDH		0.668
normal	63/451 (14.0)	
elevated	68/541 (12.6)	
ECOG Performance		<0.001
0 or 1	105/906 (11.6)	
≥2	28/86 (32.6)	
Extranodal involvement		0.497
0 or 1	80/623 (12.8)	
≥2	53/369 (14.4)	
Albumin		<0.001
<3.5mg/dl	57/249 (22.8)	
≥3.5mg/dl	80/740 (10.8)	
ANC at diagnosis		0.224
<1500	2/19 (10.5)	
≥1500	132/973 (13.6)	

and 19.5% of the cycles, respectively. Overall, more patients received ≥80% ARDI (average relative dose intensity, cyclophosphamide and doxorubicin) with a prophylactic use of Peg-G-CSF (73.2% vs. 70.9%, p=0.039). Among pretreatment clinical characteristics analyzed, age over 65, female gender, ECOG performance status 2 or higher, stage IV, and albumin level less than 3.5mg/dl were related with the development of FN (Table 4.). Multivariate analysis showed that age, gender, ECOG PS and albumin level were significantly related to FN (Table 5).

Conclusion: Prophylactic use of Peg-G-CSF reduced the incidence of neutropenia and FN significantly in patients with DLBCL receiving R-CHOP therapy when compared to the control cohort, which resulted in the reduction of early infection-related deaths. In addition, Peg-GCSF support significantly improved dose-delay and ARDI. However, the patients who were elderly, female gender, with poor performance status and low albumin level still had high incidence of FN.

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TABLE 5 Multivariate analysis of risk factors for febrile neutropenia

Characteristics	Odds ratio	95% CI	P value
Age >65	2.618	1.757-3.903	<0.001
Female Gender	1.573	1.068-2.316	0.022
ECOG PS ≥2	3.447	2.025-5.857	<0.001
Stage IV	1.126	0.744-1.702	0.575
Albumin <3.5mg/dl	3.021	1.992-4.584	<0.001

*The PROCESS Cohort

Keywords: diffuse large B-cell lymphoma (DLBCL); fever; G-CSF.

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CLINICAL OBSERVATION OF METRONOMIC CHEMOTHERAPY COMBINED WITH CLEARING HEAT AND DETOXICATING TRADITIONAL CHINESE MEDICINE IN THE TREATMENT OF REFRACTORY AND RELAPSED ELDERLY LYMPHOMA

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Objective: The elderly patients with malignant lymphoma had poor response to standard chemotherapy, high relapse rate after remission, short survival time and poor quality of life. Guidelines recommended salvage therapy for patients with relapsed and refractory lymphomas, while the elderly cannot tolerate high-dose chemotherapy and hematopoietic stem cell transplantation, a new protocol suitable for this population has been under discussion. Studies have shown that low-dose metronomic chemotherapy has a unique therapeutic effect in the treatment of mouse malignant tumors. Our previous clinical observations have shown that it can induce remission, improve the quality of life and prolong survival in some patients. Traditional Chinese Medicine believes that the elderly patients with lymphoma often have congenital deficiency of kidney essence, resulting in deficiency of vital qi, viscera, meridians, yin and yang, qi and blood disorder, To recover the feelings of six sexual feelings or warm heat evil, so that the evil influence into the viscera and bone marrow, resulting in the stagnation of

Qi and blood stasis, phlegm and blood stasis are intertwined. According to the theory of "Wei Qi Ying Xue" from the "Fu Qi Qi Ying Xue" to treat and detoxify.

Metronomic chemotherapy has good tolerance and prolongation of survival in the treatment of malignant tumor. Modern pharmacological studies have found that many Chinese herbs for clearing away heat and detoxification could inhibit the proliferation of lymphoma cells, inhibit angiogenesis and regulate immune function. Fully accord with the concept of metronomic chemotherapy, the combination of Qingrejiedu decoction and oral chemotherapy is a new combination of metronomic chemotherapy. In order to verify the efficacy of low-dose continuous oral chemotherapy combined with Qingrejiedu decoction, we made a preliminary attempt for the treatment of elderly lymphoma with refractory or recurrence.

Methods: Sixty-three cases of refractory or relapsed non-Hodgkin's lymphoma were treated with metronomic chemotherapy combined with Qingrejiedu decoction and Qingrejiedu decoction, and were treated with Qingrejiedu decoction and metronomic chemotherapy. Aged 66 to 93 years, median age 74 years, male 37 cases, female 26 cases. According to the Chinese medicine diagnosis, 3 cases of deficiency of qi and blood were classified according to syndrome differentiation, There were 37 cases of deficiency of liver and kidney yin and 23 cases of deficiency of spleen and kidney. They were treated with traditional Chinese medicine based on dialectical treatment. Patients were treated with selective low-dose dexamethasone, thalidomide, Lenalidomide, methotrexate or etoposide according to their condition and economic condition. The median follow-up was 15 months and 46 patients survived with a total survival rate of 73%. Seventeen patients died, of which 15 were disease progression; One patient died of lung infection. Another died of sudden cardiac death. Metronomic chemotherapy combined with heat-clearing and detoxifying Chinese herbs showed mild side effects, such as mild leukopenia, mild asthenia, mild diarrhea or constipation, which were the main side effects of grade I. The quality of life has improved markedly.

Conclusion: Heat-clearing and detoxifying Chinese herbs combined with metronomic chemotherapy is a simple and effective method for treatment, It is a well-tolerated and effective method to improve the quality of life, which is suitable for outpatient treatment and follow-up. It is helpful to improve the prognosis, improve the quality of life, prolong the survival and lighten the economic burden of the patients by treating the patients with refractory lymphoma in the elderly.

Keywords: non-Hodgkin lymphoma (NHL); salvage treatment.

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OUTCOME OF CHILDREN AND ADOLESCENTS WITH LYMPHOBLASTIC LYMPHOMA TREATED WITH THE EORTC 58951 PROTOCOL

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Introduction: Lymphoblastic lymphoma (LBL) are the second most commun subtype of non-hodgkin lymphoma (NHL) in children and adolescents. The aim of this study was to characterize the clinical course of children and adolescents with LBL treated in our department.

Patients and Methods: This is a retrospective study concerning patients aged 25 years or younger with LBL admitted between January 2009 and August 2018 in the hematology department of Hedi Chaker Hospital of Sfax, Tunisia. Patients were treated according to the EORTC protocol used for pediatric acute lymphoblastic leucemia. Diagnosis was based on biopsy of tumor for all patients. We analyzed in our study complete remission, relapse, death and the event free survival (EFS: using Kaplan-Meier method).

Results: We collected 12 children and adolescents with LBL. The median age at diagnosis was 8 years (range, 2- 23 years). There was a predominance of males. LBL had T-cell type in 10 patients (83%). The most common primary manifestation in T-cell LBL was mediastinal involvement, in 9 patients (90%). Testicular involvment was the manifestation in 2 patients with precursor B-LBL. A cutaneous tumor was the initial manifestation in one patient with B-LBL. Seven patients (58%) had advanced disease (Stage III or IV) at diagnosis. Eleven patients (92%) achieved complete clinical remission and one patient was not evaluable (died at day 14 of induction course). After a median follow-up of 69 months, 8 patients (67%) were alive in first complete remission. Four children (33%) died, one of them soon after admission and three after relapsing. At 5 years of follow up, EFS was 72%.

Conclusion: LBL comprise approximately 30% of the NHL that occur in children and young adults. In the literature, the most frequent phenotype was T (85 - 90%) similar to in our study. During the last decades, several systematic clinical trials contributed to the controlled optimization of treatment. Using acute lymphoblastic leukemia type treatment regimen to treat children with LBL was an important development in the treatment with EFS can be achieved 75-90%. Our findings confirm the favorable prognosis of children with LBL with an intensive chemotherapy regimen derived from ALL therapy.

Keywords: non-Hodgkin lymphoma (NHL).

EXTRANODAL LYMPHOMA

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FIRST LINE SYSTEMIC TREATMENT IN MUCOSA-ASSOCIATED LYMPHOID TISSUE
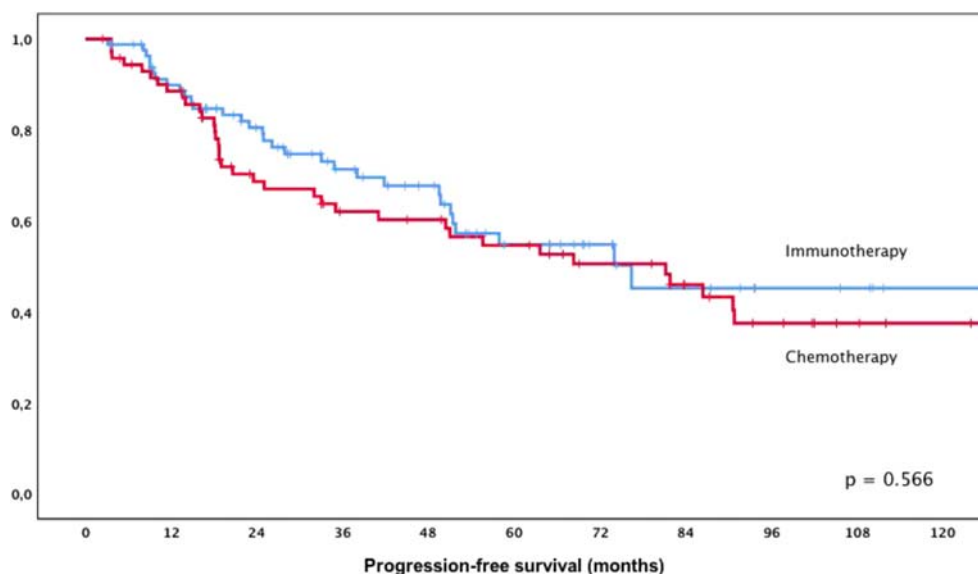
(MALT) LYMPHOMA NOT ELIGIBLE FOR H. PYLORI ERADICATION – DO WE NEED CHEMOTHERAPY?

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Background: There is still no clear therapeutic algorithm for MALT lymphoma patients beyond H. pylori eradication and while recent data on chemotherapy based regimens +/- rituximab (R) have potentially set new standards for patients in need of systemic treatment, it appears of interest to investigate also chemotherapy-free strategies.

Methods: We have retrospectively assessed all patients with histologically verified MALT lymphoma treated at the Medical University Vienna 1999-2019, and identified patients receiving first line systemic treatment defined as either chemotherapy (=classical cytostatic agents +/- R) or immunotherapy (=immunomodulatory agents or anti-CD20 antibodies). Primary endpoint was comparison of progression-free survival (PFS) following chemo- and immunotherapy.

Results: A total of 159 patients received upfront systemic treatment (median age 65 years, female-male ratio 1.3) with the median follow-up being 66 months (IQR 33-101). Naturally, the majority of patients had extragastric disease (80%) but we identified also 32 patients (20%) with H. pylori negative gastric lymphoma treated with systemic therapy. At initial diagnosis, 64% had stage I/IIE and 36% disseminated disease (IIIE/IV) and MALT-IPI predicted low risk in 39%, intermediate risk in 46% and high risk in 15% of cases. Looking at the type of first line systemic treatment and outcome, 46% (74/159) received chemotherapy-based regimens and 54% (85/159) immunotherapy including IMiDs lenalidomide/ thalidomide (36%), anti-CD20 monotherapy rituximab/ ofatumumab (27%), macrolides clarithromycin/ azithromycin (27%) and proteasome inhibitor bortezomib (9%). Median estimated PFS after first line treatment for the entire collective was 76 months (95% CI 50-102) and while the overall response rate (90% vs 68%, p<0.01) and the complete remission rate (75% vs 43%, p<0.01) was significantly higher in the chemotherapy group, there was no difference in PFS between the chemotherapy (median 81 months, 95% CI 47-115) and the immunotherapy cohort (median 76 months, 95% CI 50-103) (p=0.57), suggesting comparable efficacy in terms of long-term outcome. Interestingly, there was a non-significant trend towards a decrease in relapse rates for immunotherapy, consequently resulting in a tendentially lower number of patients in need of second line treatment (39% vs 50%, p=0.15).

Conclusion: Our data show higher response rates with chemotherapy compared to immunotherapy, but this did not translate into a superior PFS. Thus, given the biological background of MALT lymphoma being a disease highly depend on the microenvironment and in view of the favorable toxicity profile particularly of novel immunotherapeutic approaches such as IMiDs and macrolides, we suggest that chemo-free systemic treatment is active and should be further investigated in clinical trials.

Keywords: extranodal marginal zone lymphoma of MALT type; immunochemotherapy; indolent lymphoma.

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PRIMARY BREAST DIFFUSE LARGE B-CELL LYMPHOMA. CLINICAL FEATURES AND

OUTCOME IN 55 PATIENTS. POLISH LYMPHOMA RESEARCH GROUP STUDY

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Primary breast diffuse large B-cell lymphoma (PB-DLBCL) is a rare subtype of aggressive large B cell lymphoma (DLBCL). Here we describe pathological and clinical feature, adverse factors of outcome in PB-DLBCL patients (pts) treated over fifteen-year period. Methods: We retrospectively collected data on PB-DLBCL patients diagnosed between 2002–2017 at seven oncology centers from the Polish Lymphoma Research Group. Results: Fifty-five female with a diagnosis of PB-DLBCL were identified. Median age (range) was 62 (17- 90), 13 pts (24%) were 75 or older. On review of orginal biopsy material we found 2 cases of high grade B lymphoma, one case of Burkitt lymphoma, two cases anaplastic large cell lymphoma, and 50 cases DLBCL including 4 cases of CD5+ DLBCL. Bulky disease was present in 28 pts (50%), 44 pts (80%) had low/low-intermediate IPI score. Rituximab and CHOP was given to 46 patients (80%) and the rest of patients received CHOP alone, 11 pts (20%) received intrathecal CNS prophylaxis. Adjuvant radiotherapy was applied in 13 (25%) patients. In 52 pts evaluable for response post first-line therapy the overall response rate was 88% and complete remission rate was 73%. After a median (range) follow up of 30 (1-186) months, median progression free survival (PFS) and overall survival (OS) for entire group were 25 and 30 months, respectively. 2-year PFS and 2- year OS were 62% (95%C.I. 48%, 76%), and 75% (95%C.I. 64%, 86%). In patients who received rituximab, 2 year PFS was 75% (95%C.I. 61%, 89%) (p=NS) and 2 year OS was 84% (95%C.I. 73%, 95%) (p=0.09). High-intermediate/high IPI score increased the risk of death with the HR of 3.35 [95%C.I (1.34-8.14), p<0.01] and the risk of progression with HR of 3.57 [95%C.I (1.52-8.22), p<0.01] compared to low/low-intermediate IPI. No other adverse factors for OS or PFS were found. After initial treatment, 18 (32%) patients subsequently progressed or relapsed: 8 pts (14%) in the ipsilateral breast, 8 pts (14%) in CNS, and 4 pts had disseminated disease. Median time to relapse was 9 months with range 1- 186 months, the 5-year cumulative risk of CNS relapse was 12,7% with median time to CNS relapse 7 months. Primary breast diffuse large B cell lymphoma is a rare disease with a substantial risk of secondary CNS involvement and progression to ipsilateral breast and other extranodal sites. High-intermediate/high IPI score was the only adverse factor which increased the risk of death and the risk of progression.

Keywords: B-cell lymphoma; extranodal lymphomas.

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IMMUNOCHEMORADIOTHERAPY OR IMMUNOCHEMOTHERAPY ONLY IN PATIENTS WITH EXTRANONAL DIFFUSE LARGE B-CELL LYMPHOMA OF STOMACH

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Introduction: Radiation therapy (RT) is an effective method for treating indolent lymphomas of the stomach (Yahalom, 2006), but the results proving its role in patients with extranodal diffuse large B-cell lymphoma with predominant lesions of the stomach during chemoradiation treatment are few and conflictive (Metijharissi et al., 2017, Mehmood, 2017).

The purpose of the study: is to evaluate the effectiveness of immunochemoradiotherapy (ICT + RT) compared with only ICT in patients with extranodal diffuse large B-cell lymphoma of the stomach.

Methods: The study included 66 primary patients aged 25-90 years (mean age - 59 years), who received and completed in the period 2006-2017. ICT + RT (26 patients) or ICT only (40 patients). Of these, men - 32; women - 34; Stage I - 6, II - 30; III - 3; IV - 27. The average observation period of the group - 45 months. 63 patients received 4-8 cycles of ICT R-CHOP-21, 3 patients - DA-EPOCH-R. RT was performed after ICT at doses of 30-40 Gy for the entire volume of the stomach and in perigastric lymph nodes. In 10 patients before treatment, 3 weeks after ICT (20 patients) and 4 weeks after RT (15 patients), a full body PET scan with 18F-FDG was performed. The groups were comparable in terms of the main prognostic factors for the IPI criteria. Patients, who received surgical treatment were not included into the study. Five patients from the ICT group with a lack

of efficacy of R-CHOP-21 were treated with 2 therapy lines, 1 - the third line of therapy.

Results: A complete response after R-CHOP-21 was established in 48 of 66 (73%) patients. After subsequent RT in all 26 patients of the group of ICT + RT, complete remission was achieved in terms from 7 to 93 months. (average - 50 months.). In the group of ICT only, 5 patients died (4 of them in stage IV), including 4 from the underlying disease advance, 1 - from relapse in the central nervous system. The average follow-up period for this group was 42 months, the deceased patients — 10 months. The overall 5-year survival rate of the combined treatment group is 100%, ICT is 72%. In patients with PET positive results after PCT after irradiation, the metabolic activity of the tumour was not detected.

Conclusion: ICT+RT is the optimal method of treating patients with extranodal aggressive lymphoma with gastric lesions.

Keywords: diffuse large B-cell lymphoma (DLBCL); extranodal lymphomas.

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INCIDENTAL RADIATION TO THE SPLEEN AFTER TREATING GASTRIC LYMPHOMA WITH RADICAL RADIOTHERAPY – SHOULD WE RECOMMEND PROPHYLACTIC IMMUNISATION AND AN OAR DOSE CONSTRAINT?

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Introduction: Radiotherapy (RT) is an effective treatment for gastric lymphoma, the majority of which is low grade Mucosa-Associated Lymphoid Tumour (MALT) subtype. In view of its close proximity to the stomach, the spleen receives a significant dose of radiation which can affect its subsequent function. This leads to the potential for increased risk of infection, which could be life-threatening. We therefore reviewed doses to the spleen, and aim to calculate a RT dose constraint for the spleen as an organ at risk (OAR).

Methods: A retrospective analysis was performed of 15 patients (pts) with gastric MALT and 1 with DLBCL who received radical RT from 2012 to 2018 at our centre. Doses to the spleen were analysed to evaluate the effect of radiation dose in relation to lymphocyte count and infection rates.

Splenic Dose Volume Histogram (DVH) parameters were reported as mean splenic dose (MSD), maximum splenic dose (MxSD) and V5, V20 and V30 for the spleen.

Lymphopenia was defined as absolute lymphocyte count (ALC) <1.5 and infection was defined as any infection noted within hospital records.

Results: 14 pts received 30Gy in 20 fractions and 2 pts received 24Gy in 12 fractions. Median MSD 19Gy (range 14-27) and Median MxSD

32Gy (26-34). Median V5 91.5% (63.6-100), Median V20 52.3% (30.6-94) and Median V30 23.6% (6.1-59.2).

All pts regardless of lymphocyte count before RT were found to be lymphopenic in the first 2 years (yrs) following treatment. Beyond 2 yrs, return to normal lymphocyte count was variable. However, between yrs 2 and 4 post RT, 50% had lymphopenia, then from yr 5 onwards all lymphocyte counts were normal.

Conclusion: There appears to be no direct correlation between MSD, MxSD, V5, V20, V30 and rates of lymphopenia but all patients became lymphopenic for the first 2 years following RT. Therefore, minimising dose to the spleen should be achievable to limit long term reduced function of this important organ, and prophylactic immunisations should be considered to protect these pts against potentially life-threatening infections.

Discussion: RT can reduce the function of the spleen after gastric irradiation for lymphoma (and for solid tumours). Routinely, the spleen has not been considered an important OAR. However, our data shows that lymphopenia occurs in all patients for the first 2 yrs following RT, and can continue for several more yrs, leaving pts at risk of infection.

To prevent infection, in the UK, we would recommend immunisation for at least 2 yrs after receiving RT with the following vaccines: seasonal Influenza, Pneumococcal, Haemophilus influenza type B, Meningococcal C, Meningococcal ACWY conjugate and Meningococcal B.

Introducing a formal OAR dose constraint would be useful for clinicians treating upper abdominal organs with RT. As we were able to achieve a MSD of 14Gy, we would suggest 15Gy as a starting point. This could then be used to gather further data and relate to levels of lymphopenia and infection with a prospective audit.

Keywords: extranodal marginal zone lymphoma of MALT type.

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PROGNOSTIC IMPACT OF PD-L1 EXPRESSION, DOUBLE EXPRESSOR LYMPHOMA, AND PROGRESSION OF DISEASE WITHIN 24 MONTHS IN PRIMARY GASTROINTESTINAL DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is heterogeneous and the most common gastrointestinal lymphoma, accounting
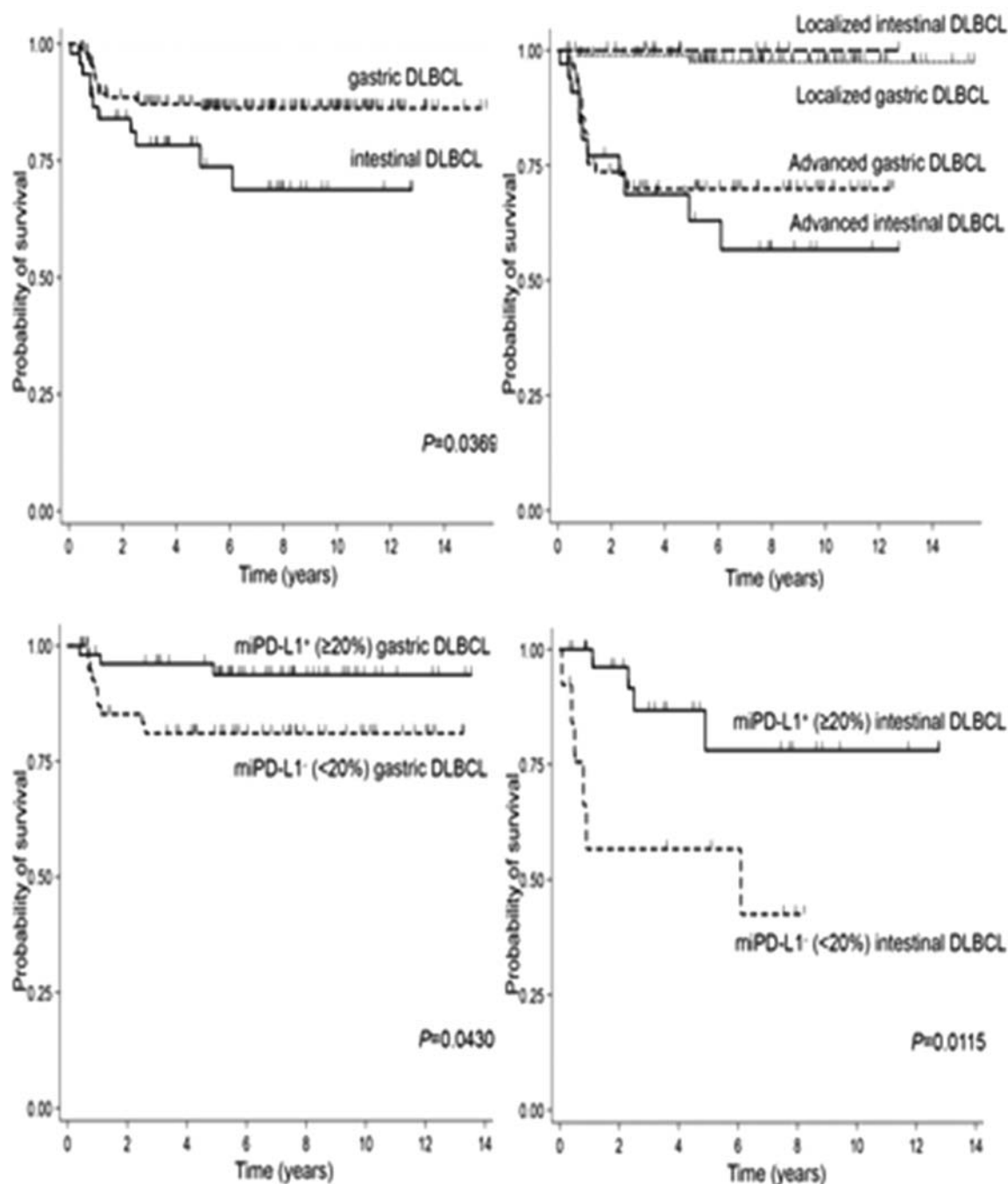
for 39%-58%. The prognostic/predictive indicators and treatment strategies among patients with gastric and intestinal DLBCL (giDLBCL) still remain controversial beyond their anatomical sites. We investigated the clinical utility of newly emerging prognostic/predictive indicators in patients with giDLBCL with an emphasis on PD-L1 immunostain of neoplastic and non-neoplastic immune cells, double expressor lymphoma (DEL) with co-expression of MYC and BCL2, and progression of disease within 24 months (POD24) after diagnosis.

Methods: This retrospective study included 302 patients with primary gastric (n=243) and intestinal DLBCL (n=59) between 1995 and 2018. Survival analyses were performed among patients treated with rituximab-containing chemotherapy.

Results: Compared to gastric DLBCL, intestinal DLBCL had a significantly higher rate of perforation (11% vs. 0.4%, P<0.001) and advanced Lugano stage (71% vs. 46%, P=0.001). Neoplastic PD-L1 expression on tumor cells (≥5%) was detected in only three of 183 cases with early relapse and/or aggressive clinical course. PD-L1 expression on microenvironment immune cells (≥20%, miPD-L1) was observed in 35 (64%) and 61 (48%) gastric and intestinal cases examined, respectively, with a statistically marginal difference (P=0.054). A total of 205 (69%) patients received rituximab-containing chemotherapy, most frequently R-CHOP. The intestinal group had significantly worse overall survival (OS) compared to the gastric group (P=0.0369). Notably, the curves delineated by localized or advanced Lugano stage

almost overlapped beyond their anatomical sites. The miPD-L1-positive cases showed significantly better OS compared to the negative cases in both gastric and intestinal DLBCL (P=0.0430 and P=0.0115). DEL was found in 11 gastric (9%) and 6 intestinal cases (12%), with significantly worse OS than the others in each anatomical group (P=0.0012 and P=0.0008, respectively). Among patients with complete remission, 21 (16%) of 134 gastric and 6 (17%) of 36 intestinal DLBCL patients had recurrence. Differences in survival, calculated from recurrence, were significant between gastric DLBCL patients with and without POD24 (P=0.0427), but did not work in prognostic delineation of intestinal cases (P=0.563). Multivariate analysis revealed that advanced Lugano stage (P<0.001), DEL (P<0.001), and miPD-L1 negativity (<20%, P=0.027), but not intestinal site (P=0.171), were significant prognostic factors for OS of giDLBCL.

Conclusion: The anatomical site of disease did not influence outcome in giDLBCL in the rituximab era. Lugano stage, PD-L1 expression on microenvironment immune cells, and MYC/BCL2 co-expression provide therapeutic guidance for patients with giDLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL); PD-1L; rituximab.

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IMPACT OF DIFFERENT TYPES OF ANTIVIRAL THERAPY ON PROGNOSIS OF HEPATITIS C VIRUS POSITIVE MARGINAL ZONE LYMPHOMAS

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Background: The association between hepatitis C virus (HCV) and marginal-zone lymphomas (MZL) is now widely accepted, as a result of evidence from epidemiological and therapeutic studies carried out in the last decades. The large number of studies demonstrated that antiviral therapy (AT) is an active therapeutic option in the patients with HCV-positive MZL. The use of AT, consisted of interferon (IFN) and ribavirin (RBV), at any time during the life of these patients (pts) is able to induce high anti-tumor response rate and associated with improved outcome. There were limited data about efficacy of the new direct-acting antiviral agents (DAAs) in the treatment of pts HCV+ MZL.

Aims: The purpose of our study is evaluated clinical feature and outcomes of HCV+ MZL patients depending on the availability and type of antiviral treatment.

Methods: We retrospectively selected 64 pts affected by MZL and infected by HCV, defined as HCV-RNA positivity, and who were treated since 2005-2018 in N.N. Blokhin National Cancer Research Center. The median age was 50 years (31-75), 59% were male, 55 pts (86%) had advanced stages, B-symptoms were revealed in 14 pts (22%). The distribution of MZL subtypes were as follows: nodal 13 (20%), extranodal MALT 11 (17%), splenic 21 (33%), disseminated MZL 19 (30%) pts. Depending on the treatment, the patients were stratified into three groups (G): 26 (41%) pts did not receive any kinds of antiviral therapy (G1), 27 (42%) pts were treated with IFN-based antiviral regimen (G2), the 11 (17%) pts (G3) receive direct antiviral agents (sofosbuvir-based regimen). The most common anti-tumor treatment regimen in the G1 was the R-CHOP\R-CVP (21 out of 26 pts).

Results: The overall response rate (ORR) were comparable in all three groups (87% vs 82% vs 73% respectively, p=ns). In contrast, the duration of response was significantly higher in the groups of pts receiving antiviral therapy, estimated 3-year progression-free survival (PFS) were 38% (G1) vs 67% (G2) vs 58% (G3) respectively (p=0, 03). In median follow-up was 36 months, 24 (38%) pts had relapse. Most relapses developed in pts (63%) receiving systemic antitumor therapy without any kind of antiviral therapy.

Conclusion: Antiviral therapy is a preferential first-line option in patients with HCV-associated MZL. Because of DAAs' safety, rapidity, and efficacy in obtaining a virologic response, as well as good tolerance profile, DAA therapy should be preferred to IFN-based antiviral treatment. Our preliminary data suggest a similar activity of IFN-based and INF-free regimen in HCV+ MZL, but limited number of pts and length of follow-up provide a strong rational background for a larger prospective series to determine precisely the impact of AT in HCV-infected patients with MZL.

Keywords: hepatitis C; non-Hodgkin lymphoma (NHL).
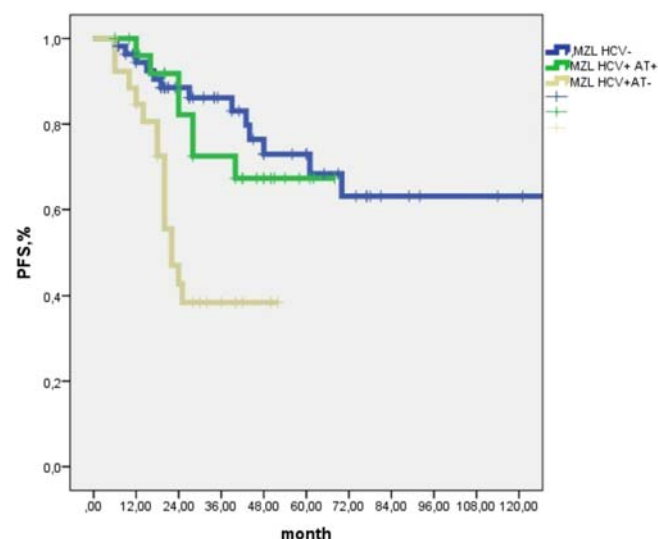
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PRIMARY PANCREATIC LYMPHOMA: CLINICAL PRESENTATION, DIAGNOSIS, TREATMENT AND OUTCOME IN A MULTICENTRIC ITALIAN EXPERIENCE

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Introduction: Primary Pancreatic Lymphoma (PPL) is a very rare disease, representing only 0.1% of lymphomas and 0.2% of pancreatic tumors. PPL presentation is variable and may overlap the onset of other neoplastic or inflammatory pancreatic diseases, often resulting in diagnostic difficulties. Due to the limited number of PPL study series, standardized diagnostic and therapeutic protocols are currently lacking.

Methods: Diagnostic criteria for PPL were established according to the "Fourth WHO Classification of digestive tumors". Clinical and treatment data of patients diagnosed with PPL between 2005 and 2018 were retrieved from medical record databases of 7 Italian Hematology Units. Overall survival (OS) and progression free survival (PFS) were calculated according the Kaplan Meier test and compared by the log-rank test.

Results: Overall 37 patients were affected by PPL. Clinical manifestations at diagnosis are summarized in the table. Most patients (83%) had a high grade B cell histotype. Fifty nine % of patients were first line treated with chemotherapy, 21% with chemo + radiotherapy, 10% with surgery + chemotherapy, 3% with surgery and 7% did not received any treatment. With a median follow up of 37.5 months the 2 year OS is 59% while the 2 year PFS is 45%. Provided the relatively low number of cases, patients with low grade lymphomas and a good risk Revised International Prognostic Index (R-IPI) had better median OS (not reached vs 26 months and not reached vs 8 months, p=0.31 and 0.001) and PFS (not reached vs 108 months and 108 vs 8 months, p=0.095 and 0.01) as compared to the others. There were no differences in OS and PFS beetween chemotherapy or chemo-radiotherapy treatments (p=0.8 and 0.33) while patients who underwent debulking surgery (alone or + chemotherapy) had a significant worse OS as compared to those treated with chemotherapy alone (median not reached vs 6 months, p=0.033). Importantly 3/28 (10.7%) patients with high grade PPL experienced a central nervous system (CNS) relapse of disease.

Conclusions: PPL represents a rare and difficult-to-recognize disease with symptoms and pancreatic gland localization superimposable to those of pancreatic ductal adenocarcinoma. Most PPL are high grade non Hodgkin lymphoma. According to our study biopsy should be the preferred diagnostic method since debulking surgery was associated

TABLE 1

CHARACTERISTICS		n (%)
Median age (years)		56 (15-79)
M/F		22/15
ECOG>2		6 (17%)
Presenting symptoms		
	Abdominal pain	20 (55%)
	Jaundice	17 (47%)
	B symptoms	11 (30%)
Laboratory values		
	LDH > upper limits	14 (40%)
	Pancreatic amylase > upper limits	16 (52%)
	CA 19-9 > 25 U/L	6 (24%)
Diagnostic method		
	Percutaneous biopsy	16 (43%)
	Endoscopic biopsy	14 (38%)
	Surgical biopsy	4 (11%)
	Debulking surgery	3 (8%)
Pancreatic location		
	Head	25 (70%)
	Body and Tail	11 (30%)
Mean diameter, mm (range)		83 (20-180)
Histology		
	DLBCL	19 (51%)
	High grade B cell lymphoma NOS	10 (27%)
	Follicular lymphoma	4 (11%)
	Hodgkin lymphoma	2 (5%)
	PTCL	1 (3%)
	Burkitt lymphoma	1 (3%)
Clinicale stage		
	I-II	17 (48%)
	III-IV	19 (52%)
Type of treatment		
	Surgery	1 (3%)
	Surgery + Chemotherapy	3 (10%)
	Chemotherapy	17 (59%)
	Chemotherapy + Radiotherapy	6 (21%)
	No treatment	2 (7%)

with a worse OS. The high CNS relapse rate suggests that patients with high grade PPL should receive CNS directed prophylaxis.

Keywords: extranodal lymphomas.

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SEQUENTIAL CHEMOTHERAPY/RADIOTHERAPY WAS SUPERIOR TO SANDWICH THERAPY FOR PRIMARY EARLY-STAGE DLBCL OF WALDEYER'S RING

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Introduction: Waldeyer's ring (WR) consists of lymphoid tissue located in the pharyngeal and tubal tonsils, which are at the pharynx to the back of the oral cavity and the base of the tongue, as well as in the palatine and lingual tonsils. Diffuse large B-cell lymphoma of Waldeyer's ring (WR-DLBCL) is an extremely rare malignancy, and radiotherapy (RT) can improve survival for early-stage WR-DLBCL patients. However, the superiority of sequential chemotherapy/radiotherapy (CT+RT) and sandwich therapy (ST) remains unclear.

Methods: Eighty-two primary early-stage WR-DLBCL patients treated with CT+RT, ST or chemotherapy (CT) alone were enrolled. Treatment response and patient survival were evaluated. The clinicopathological parameters impacting PFS or OS were analysed by univariate analyses. The Kaplan-Meier test was used to analyse survival.
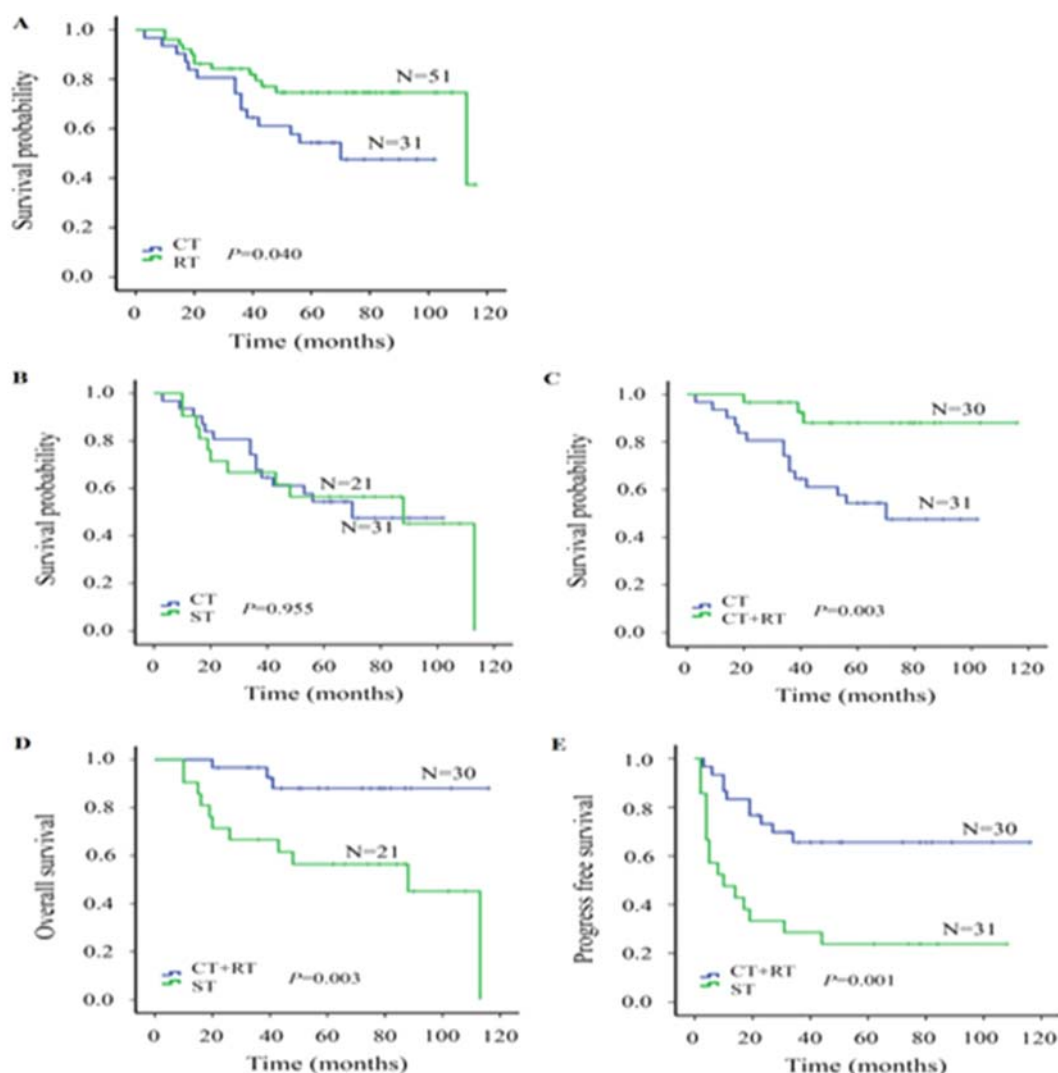
Fig.1. Kaplan-Meier curves of primary early-stage WR-DLBCL patients treated with CT and RT (A, OS curves), CT and ST (B, OS curves), CT and CT+RT (C, OS curves), CT+RT and ST (D, OS curves), and CT+RT and ST (E, PFS curves)

Independent prognostic factors for PFS and OS were further studied using multivariate analyses.

Results: The ORR of patients treated with CT+RT and ST were 100% and 95.2% respectively, which were higher than the ORR of patients treated with CT alone (100% vs 90.3% and 95.2% vs 90.3%). Complete response of patients treated with CT+RT tended to be better than that of patients treated with ST (70.0% vs 61.9%). Importantly, patients treated with CT+RT could maintain the higher CR rate than those treated with ST (73% vs 33.3%) and those treated with CT alone (73% vs 45.2%) during the long follow-up. Patients treated with CT+RT but not ST had significantly superior OS (P=0.003) to the survival of patients treated with CT alone. Patients treated with CT+RT experienced better outcomes than those treated with ST did (5-year PFS, 47.4% vs 23.8%, P=0.049; 5-year OS, 83.3% vs 50.0%, P=0.032). The univariate analysis showed that CT+RT treatment regimen was significantly associated with better survival.

Conclusions: CT+RT was superior to ST and improved the survival for primary early-stage WR-DLBCL patients.

Keywords: chemotherapy; diffuse large B-cell lymphoma (DLBCL); radioimmunotherapy (RIT).

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PRIMARY THYMIC MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA: 7 CLINICAL CASES REPORT AND A REVIEW OF THE LITERATURE

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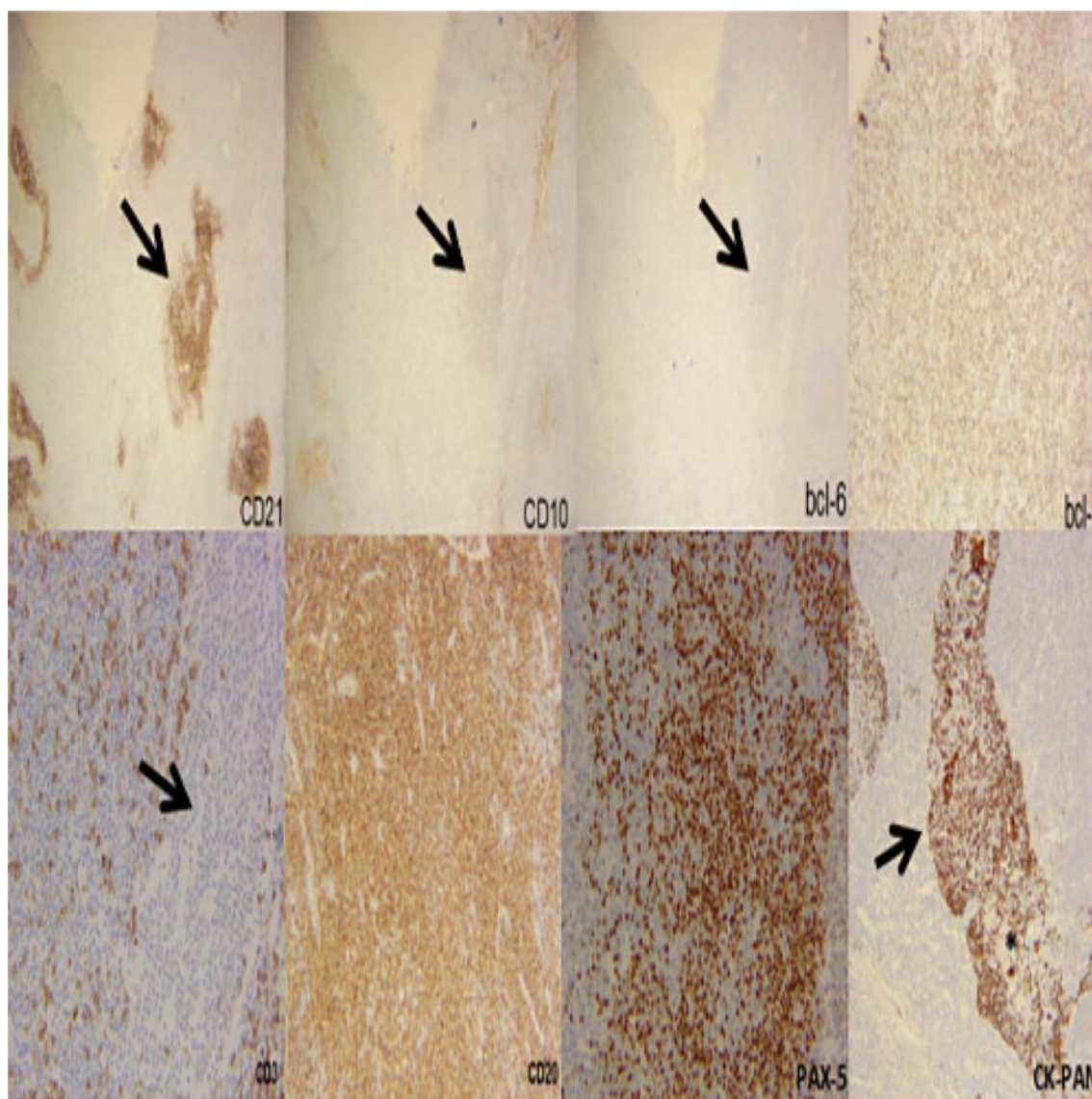
Figure 1. Pathological features of thymic MALT lymphoma

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Introduction: Mucosa-associated lymphoid tissue (MALT) lymphoma is one kind of non-Hodgkin lymphomas (NHL), accounts for 7% to 8%. MALT lymphoma is an indolent, organophilic lymphoma that can nearly occur at any epithelial tissues and mucosal sites. The predilection sites of MALT lymphoma are gastrointestinal tract, salivary glands, lungs and other organs. Studies have shown that MALT lymphoma is associated with chronic inflammation and antigenic stimulation, including chronic infection of pathogens and autoimmune disease. Primary thymus MALT lymphoma is rare. Only 92 cases have been reported over the past 27 years, and only 15 cases reported from China before. Here we introduce 7 cases of primary thymic MALT lymphoma found in the First Affiliated Hospital of Nanjing Medical University, and takes a review of the literature.

Methods: We analyze 7 cases of primary thymic MALT lymphoma in the First Affiliated Hospital of Nanjing Medical University from December 2017 to February 2019. We evaluate the clinical features, laboratory test results, PET-CT scans, pathological specimen stained by hematoxylin–eosin (HE) or immunohistochemistry, etc (**Figure 1**). The median follow-up of 7 cases is 8 months (range 1 to 15 months).

Results: primary thymic MALT lymphoma is a kind of indolent small lymphocytic lymphoma, appears mostly in Asian women and is often accompanied with AID. SS is the most common AID. Both contrast-enhanced CT and other imaging findings before surgery and pathological specimen after surgery can see mass with smooth boundary, containing cystic cavities of different sizes and numbers. We can also observe a wide range of small to medium-sized lymphocytes, with increased plasma cells surrounding small blood vessels. Primary thymic MALT lymphoma is lack of API2-MALT1 fusion gene. All cases only received "watch and wait" approach after surgery. Up to now, none of them had recurrence, and their quality of life was no different from normal people.

Conclusions: When clinicians meet female patient with thymic solid-cystic or cystic mass, together with AID, especially SS, and without any symptom of myasthenia gravis, we should take primary thymic MALT lymphoma into consideration.

Keywords: Mucosa-Associated Lymphoid Tissue (MALT); positron emission tomography (PET); thyroid function.

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FIRST-LINE ADJUVANT RADIOTHERAPY IMPROVES PFS IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA - A RETROSPECTIVE ANALYSIS OF 102 PATIENTS FROM A SINGLE CENTER

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Introduction: The cure rate of primary mediastinal large B-cell lymphoma (PMBL) in the rituximab era is about 80-90%, using CHOP-like or more intensive induction regimens (e.g. DA-EPOCH-R). The use of consolidative radiotherapy (RT) varies among centers, mostly being a standard of care until now. PMBL typically affects young population, with a female predominancy. Therefore, there are concerns about a long-term toxicity of RT, including secondary breast and lung cancer and heart failure. On the other hand, RT could improve the local disease control and maybe reduce the relapse rate. Prospective trials for this rare disease are sparse and the role of radiotherapy (RT) in the consolidation of remission remains unclear.

Methods: We have retrospectively analyzed data of 102 patients (pts) with newly diagnosed PMBL treated in our center between 2001-2017, with a median follow-up 6.8 years (range 0.1 – 17.7). The induction regimen was predominantly CHOP-like chemotherapy (94%) plus rituximab (94%). Disease status was assessed after 6 cycles of induction chemotherapy, using PET-CT and the Cheson 2007 criteria. The eventual consolidation with radiotherapy depended individually on the physician decision only.

Results: Median age was 35 years (women: men = 1.1:1). B symptoms were present at 54% of pts, elevated LDH in 90% and ECOG 2-4 in 27% cases; the most of pts had aaIPI 1 (51%). Five-year overall survival (OS) and progression-free survival (PFS) of the entire group were 86% and 80%, with 16 relapses and 8 deaths. After induction chemotherapy, the response was evaluated in 94 pts, 75% of them achieved complete remission (CR), 15% partial remission (PR), and 9/94 (10%) had a stable disease or progression (SD/PD). The SD/PD pts had poor outcome with only 30% OS at 5 years. The role of radiotherapy was analyzed in 71 pts with CR, where 40 of them (56%) received radiotherapy (RT+ group) on mediastinum or residual mass (the dose 36-44 Gy), and 31 (44%) were observed without RT. We have found statistically significant difference in PFS in favor of subgroup with radiotherapy (5-year PFS 97% vs. 80%, p=0.03). There were only 2 relapses in the RT+ group, compared to 6 relapses in pts without RT, but this effect was not projected into OS (5-year OS 95% in RT+ vs. 90% in observation cohort, p= n.s.).

Conclusions: Our retrospective and non-randomized data evaluating the role of radiotherapy in the first-line consolidation show that patients reaching PET negative CR after R-CHOP induction displayed lower relapse rate and better PFS, but these facts do not impact the overall survival. These results should be confirmed in a larger prospective randomized trial.

Keywords: primary mediastinal large B-cell lymphoma (PMLBCL).

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PREDICTIVE VALUE OF END-OF-TREATMENT POSITRON EMISSION TOMOGRAPHY SCAN AFTER DA-EPOCH-R IN PRIMARY MEDIASTINAL B-CELL LYMPHOMA. REAL-LIFE EXPERIENCE

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Figure 1

Figure 1. PFS and OS Kaplan-Meier curves comparing PET NEGATIVE and PET POSITIVE groups.
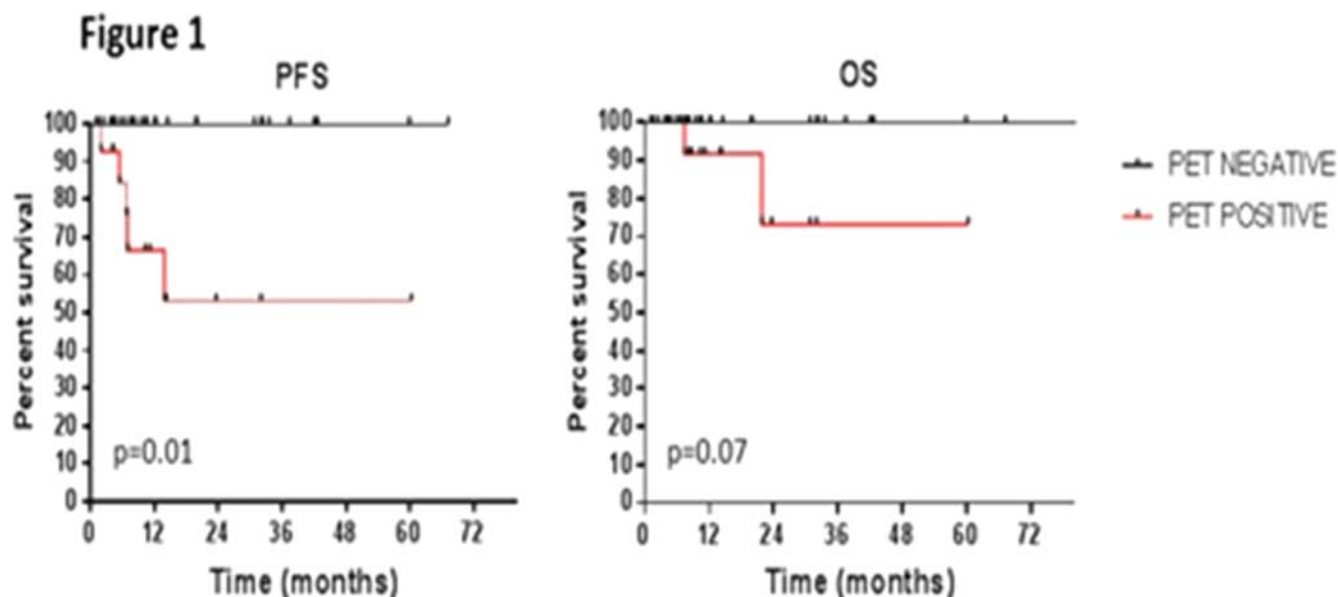
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Background: In recent years DA-EPOCH-R has been shown to be very effective in primary mediastinal B-cell lymphoma (PMBCL), and available data suggest that this regimen could obviate the need of consolidative radiotherapy (RT). However, the available evidence is based on a limited number of studies, and the large scale applicability of these data needs to be confirmed. In this study, we report the data of a real-life experience with R-DA-EPOCH-R regimen.

Methods: Between 2013 and 2018, 44 patients (pts) affected by PMBCL were treated with 6 cycles DA-EPOCH-R + 2 additional Rituximab infusions at 2 italian institutions. Median age at initial diagnosis was 36 years (range 18-55), 29 pts were female (female/male ratio=1.8/1). Histology was centrally reviewed. Positron emission tomography (PET) scans were performed at least 1 month after last Rituximab infusion. 26 pts had stage I-II, 18 pts stage III-IV. All but one pts had bulky disease at diagnosis.

Results: All pts evaluable for response (n=40) completed the planned treatment, which is still ongoing in 4 pts (all pts completed ≥ 4 cycles). 30 pts (68%) experienced grade III-IV hematological toxicities. 4 pts (9%) had febrile neutropenia. Prophylactic G-CSF was given to all pts. Among patients who completed treatment, end of treatment positron emission tomography (EOT-PET) scan was negative (Deauville score 1-3) in 28 patients (70%) and positive (Deauville 4-5) in 12 pts (30%). 15 pts (37%) underwent consolidative RT, 8 of them were in complete remission (CR) after R-DA-EPOCH (these pts were enrolled in a randomized trial). Four-year estimated overall survival (OS) and progression free survival (PFS) rates of the whole cohort were 87% (2 events) and 84% (5 events) respectively. Serial EOT-PET scans were performed in 5 patients, receiving 10 scans. None of the EOT-PET positive pts evaluated with serial PET scans progressed. A negative EOT-PET scan translated in a 100% PFS and OS rate, with no relapses observed after a median follow-up of 12 months (range 4-60). Among pts with positive EOT-PET scans, 4-year estimated PFS rate was 53% (p<0.01 vs PET negative), and 4-year estimated OS rate was 73% (p=0.07 vs PET negative), with all relapses/progressions occurring within 6 months from therapy completion (Figure 1). Only 8 of 28 EOT-PET negative pts (28%) received consolidative RT, which was given to 7 of 12 EOT-PET positive pts.

Conclusions: These data confirm a very high negative predictive value of EOT-PET in PMBCL treated with DA-EPOCH-R, with no patient relapsing after a negative EOT-PET, irrespective of consolidative radiotherapy (which was given in a minority of pts). Serial final PET scans could reduce unnecessary radiotherapy in a fraction of EOT-PET positive pts. These data support the use of DA-EPOCH-R in PMBCL, confirming that this regimen enalbles to spare radiotherapy in the majority of patients in real-life.

Keywords: DA-R-EPOCH; Deauville's criteria; primary mediastinal large B-cell lymphoma (PMLBCL).

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THE ROLE OF RITUXIMAB IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL): A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: For primary central nervous system lymphoma (PCNSL) a high-dose methotrexate (HD-MTX)-based combination chemotherapy with or without whole-brain radiotherapy (WBRT) has been the preferred front-line treatment since 2000, although no consensus exists for the most effective chemotherapy regimen until now. Now rituximab plus combination chemotherapy is also frequently used for these patients. In this study, we evaluated the survival benefit of addition of rituximab to HD-MTX-based combination chemotherapy for the patients with primary central nervous system lymphoma (PCNSL) by a systematic review with meta-analysis of clinical studies.

Methods: We searched the electronic databases, MEDLINE, EMBASE, COCHRANE, Web of Science, and SCOPUS to retrieve clinical studies evaluating benefit of rituximab on the patients with PCNSL. A total of 5 articles were included into qualitative systematic review. Two of them were used to conduct qualitative meta-analysis. Hazards ratios (HRs) with 95% confidence intervals (CIs) were pooled across studies using a random-effects model.

Results: The 5 finally selected studies compared the OS between R+ group and control group. The OS was reported by median months of PFS, HR with 95% CI, or percent of OS for 2 years Three of the 5 studies reported overall survival (OS) by median month, in which OS was longer in the R+ group (rituximab add-on group) than in the control group. The other two studies presented OS as HR with 95% CI; the HRs between R + group and control group were 0.63 (95% CI, 0.42-1.02), and 0.73 (95% CI, 0.35-1.52). The risk of heterogeneity was very low between the 2 studies: Q-value = 0.859, p = 0.354; I^2 = 0.000. When we combined the 2 studies with a fixed effect model, the pooling estimate of HR was 0.604 with 95% CI of 0.413 to 0.883 (p < 0.01).

Conclusions: This study suggests that the addition of rituximab to HD-MTX-based combination chemotherapy could prolong OS as well as PFS. The meta-analysis on PFS suggests that there was no significant heterogeneity between the studies.

Keywords: methotrexate (MTX); primary CNS lymphoma (PCNSL); rituximab.

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TREATMENT OF BING NEEL SYNDROME: USING A SLEDGEHAMMER TO CRACK A NUT?

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Introduction: Bing Neel syndrome (BNS) is a rare complication of Waldenström's Macroglobulinaemia (WM) comprising direct infiltration of the CNS by lymphoplasmacytic lymphoma. Asymptomatic patients need active surveillance; symptomatic patients require treatment. Systemic and intrathecal chemo/immune therapy and BTK inhibitors are effective, but their optimum deployment remains unclear.

Methods: Data from 30 WM and 2 MZL patients with CNS involvement were extracted from the Rory Morrison Registry for WM; 5 with DLCBL histology were excluded. Diagnostic data are presented separately. Responses are reported as per Minnema et al. (2017).

Results: 27 patients with BNS were evaluated (16 female, 11 male). Median age at WM/MZL diagnosis was 62 (36 – 71) and BNS diagnosis was 68 (53 – 74). A median of 1 prior line of therapy was given for WM (range 0 – 7).

First line therapies for BNS: MATRix in 14 (54%) [4 cycles in 6, 3 cycles in 1, 2 cycles in 6 and 1 ongoing]; IDARAM in 6 (23%) [4 cycles in 2; 2 and 3 cycles in one each and 1 cycle in 2]; HD MTX +/- R +/- ARA-C was given in 3 (12%); IT MTX following systemic chemo in 1 (4%); Ibrutinib 1 (4%) and Fludarabine-R 1 (4%). The majority (74%) showed a partial response, with CR in 4 (15%).

In 9 (45%) patients, treatment was consolidated for different reasons (to limit toxicity, to deepen response): Rituximab in 3 (30%); Ibrutinib in 3 (30%); ASCT in 2 (20%); IT MTX in 2 (20%) and IT Rituximab in 1 (10%). Three patients (12%) had no response and 2 (8%) progressed through first line therapy; 2 (8%) patients are inassessible due to ongoing therapy.

Relapse occurred in 5 patients at a median time of 17 months (3 – 81); 4 (80%) patients received second line therapy all achieving a response (including 1 CR). Median overall survival from BNS diagnosis was not reached; 7/27 (30%) of patients have died; 3/7 (43%) from disease progression, 1/7 (14%) from sepsis during treatment, 1/7 (14%) treatment-unrelated, 1/7 (14%) unknown (likely disease progression). Of the 7 who died; median age at death 69 (55 – 74); median survival from diagnosis of WM/MZL 122 months (6 – 232); median survival from BNS diagnosis 3 months (0 – 13).

Conclusions: Our results suggest that the use of adapted intensive regimens +/- consolidation with Rituximab or BTK Inhibitor induces a prolonged remission with limited toxicity. Further investigation including a prospective multicentred clinical trial is required to help elucidate optimum treatment in BNS.

Keywords: BTK inhibitors; lymphoplasmacytic lymphoma (LPL); Waldenström's macroglobulinemia (WM).

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BING NEEL SYNDROME: FIRST SUSPECT, THEN PROVE - A ROLE FOR CSF IgM ANALYSIS?

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Introduction: Bing Neel syndrome (BNS) is a rare complication of Waldenström's Macroglobulinaemia (WM) comprising infiltration of the central nervous system by lymphoplasmacytic lymphoma. Clinical presentation is heterogeneous and the diagnosis rests on abnormal neurological, radiological and cerebrospinal fluid (CSF) / cellular features.

Methods: Data from patients seen in our Neurohaematology Clinic were extracted from the Rory Morrison Registry for WM. From a total of 30 WM and 2 MZL patients with CNS involvement, 5 with high grade transformation to DLCBL were excluded here.

Results: 27 patients with BNS were characterised; female 16, male 11. Median age at WM/MZL diagnosis was 61 (36 – 71) and at BNS diagnosis was 68 (53 – 74). Median time from WM/MZL to BNS diagnosis was 31 months (0 – 222); median time from first symptoms to BNS diagnosis 2 months (0 – 69). A median of 1 line (range 0 – 7) of therapy was given for WM/MZL.

Clinical presentation was heterogeneous: motor weakness 48%; paraesthesia 44%; visual disturbance 33%; cognitive decline 30%; ataxia 30%; headache 19 %; psychiatric 11%; seizures 11%. 74% patients had an MRI with contrast prior to diagnosis, of which 80% had diffuse involvement (93% leptomeningeal, 7% perivascular) and 45% had tumoral disease (33% localised, 66% multifocal; 85% had brain and 50% spinal).

At BNS diagnosis CSF analysis was usually abnormal (12/18 patients). The median white cell count 13.5/µl (range 0 – 434) and red cell count 5.5/µl (1 – 3000) and flow cytometry frequently uninformative; MYD88 L265P was seen in the CSF of 4 patients. 15 patients underwent detailed analysis of CSF IgM, IgG and Albumin at diagnosis. Mean CSF IgM was 19.8mg/L (0.57-310), CSF IgG 85mg/L (13 – 297) and CSF Albumin 1262mg/L (155 – 4950); mean IgM CSF: serum ratio was 4.9 (0.04 – 35.91; normal <0.04) and IgM index (IgM ratio corrected for albumin) 0.2 (0.002 – 0.79), normal <0.045.

The combination of elevated CSF IgM and elevated Serum IgM was evaluated in 15 cases of BNS vs 20 other clonal haematological disorders. This has an 86.7% sensitivity, 75% specificity, 72.2% PPV and 88.2% NPV (c^2(1)= 13.04, p<0.001) for the detection of BNS, which in combination with other features is diagnostically useful, but seldom measured.

Conclusions: Our study confirms the significant heterogeneity in clinical presentation of BNS, radiological findings and relationship to WM disease, emphasising the need for robust diagnostic tools. The optimum treatment approach remains to be elucidated.

Keywords: lymphoplasmacytic lymphoma (LPL); Waldenström's macroglobulinemia (WM).

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A PROSPECTIVE STUDY ON THE CIRCULATION AND CENTRAL NERVOUS SYSTEM AFTERPRIMARY CENTRAL NERVOUS SYSTEM B CELL LYMPHOMATREATMENT WITH RITUXIMAB

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Introduction: The use of Rituximab for the treatment of primary central nervous system lymphoma(PCNSL) is controversial, whether the Rituximab permeability of blood-brain-barrier(BBB) can be improved by craniotomy is unknown.

Methods: ImmunocompetentPCNSL patients newly diagnosed via craniotomy or stereotactic biopsy were enrolled and received Rituximab (375 mg/m^2, Q3w) treatment. Systemicnon-Hodgkin's B cell lymphoma (systemic-B-NHL) patients without CNS involvement as the control group. The trough concentrations of Rituximab (C_{RTX}) and CD19 levels in cerebrospinal fluid (CSF) and plasma were analyzed by ELISA and flow cytometry methods during each treatment cycle. The efficacy and adverse effects were recorded. Trial registration: ChiCTR1900021415.

Results: From December 2016 to February 2018, 23 PCNSL and 12 systemic-B-NHL patients were enrolled. The $C_{RTX-CSF}$in craniotomy PCNSL group (0.2430[0.0606, 0.5198]µg/ml) was significantly higher than those in stereotactic-PCNSL group (0.0846[0.0235, 0.1178]µg/ml, P=0.000) and systemic-B-NHL group (0.1058[0.0764, 0.1431]µg/ml, P=0.000). The BBB penetrabilityof RTX in craniotomy PCNSL group (1.15%[0.92%, 2.03%]) was nearly four times that in stereotactic-PCNSL group (0.40%[0.28%, 0.54%], P=0.000) and three times that in systemic-B-NHL group (0.49%[0.26%, 0.61%], P=0.000). No significant differences in the $C_{RTX-CSF}$or BBB penetrability of RTX were observedbetween stereotactic-PCNSL and systemic-B-NHL groups. The time for CSF CD19 cell clearance in craniotomy PCNSL patients tended to be reduced compared with stereotactic-PCNSL patients. The CR and ORR rates of craniotomy PCNSL patients were 30% higher than those of stereotactic-PCNSL patients.

Conclusions: The BBB penetrability of RTXand the CSF $C_{RTX}$are significantly improved in PCNSL patients diagnosed via craniotomy. Rituximab could be recommended for routine use in craniotomy PCNSL patients.

Keywords: CD20; rituximab.

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FRONTLINE THERAPY RESULTS IN UNSELECTED PRIMARY CNS LYMPHOMA PATIENTS WITHOUT CONSOLIDATION HD
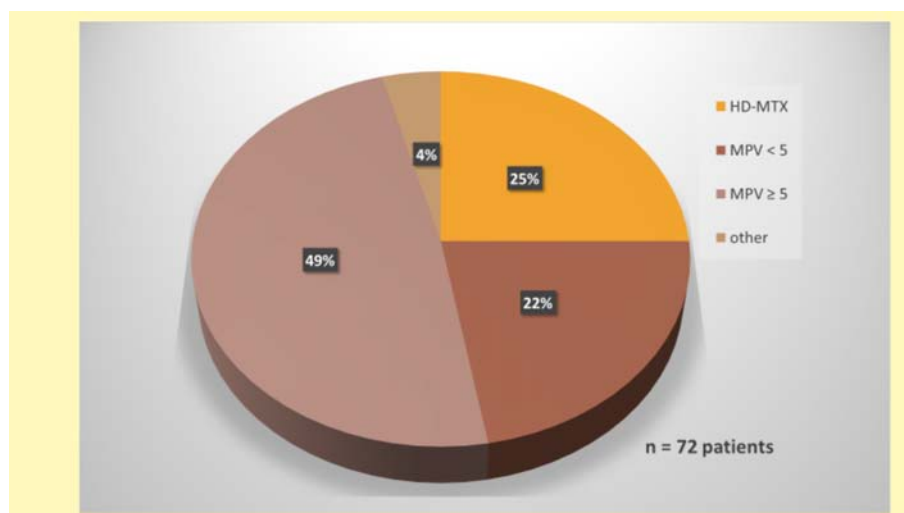
CHEMOTHERAPY FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION

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Introduction: Therapy results from large prospective clinical trials in primary CNS lymphoma (PCNSL) are influenced by restrictive inclusion and exclusion criteria. Herein we present frontline therapy results in unselected patients with PCNSL based on retrospective analysis from single center database over the past 17 years, when consolidation high-dose chemotherapy with autologous stem cell transplantation (ASCT) was not a standard therapeutic approach.

Methods: Between 2000 and 2017 we register 79 patients with newly diagnosed PCNSL, median age 64 years (31 – 84). Frontline regimen for patients ≤ 70 years was 5-7x MPV +/- rituximab. Consolidation therapy conceded 2 cycles of cytarabine for selected patients in complete remission instead whole brain radiation therapy (WB RT) up to 45 Gy. None of the patients had consolidation HD chemotherapy with ASCT.

Results: Chemotherapy was administered to 72 patients (91 %), in 71 % (51 pts.) MPV regimen +/- rituximab. The rest of the patients had single agent methotrexate or cytarabine or WB RT. Only 35 patients completed at least 5 cycles of MPV-based chemotherapy, the others failed to complete because of unacceptable toxicity or progressive disease. Median OS in the whole unselected cohort was 38 months, 2-year PFS was 40 % and median PFS 14 months. Response rates were evaluated only in the subgroup of 35 patients who completed at least 5 MPV-based chemotherapy. Median age was 57 years (31 - 70), ORR was 80 %, progression was seen in 5 patients (14%), 2 were unable to assess. In this subgroup of relatively fit patients 2-year PFS was 45 % and 2-year OS was 55 %. 10 patients in CR after frontline therapy did not undergo WB RT consolidation, but received 2 courses of single agent cytarabine instead. 5 of them reached durable remission and in the other 5 late relapses occured with median PFS 31 months (12-72).

Conclusion: R-MPV frontline therapy for PCNSL patients is widely used and considered as relatively effective with expected and manageable toxicity profile. But significant portion of patients is unsuitable for this regimen, mainly because of age and poor condition. Despite limited data from our single center database, only about 2/3 of all of the newly diagnosed PCNSL patients were fit for MPV-based chemotherapy and only 2/3 of them completed at least 5 cycles, that means nearly 50 % of all of the new cases. Compared to results from prospective clinical trials, long term survival data in this subgroup of relatively fit patients consolidated without HD-chemotherapy and ASCT are worse. Consolidation therapy with single agent cytarabine instead WB RT was administered as an option for selected patients in complete remission to avoid delayed neurotoxicity. Despite some long term remissions, late relapses were frequent after cytarabine consolidation, and so this approach cannot be recommended. Clinical factors that could predict recurrences in this subgroup were not identified, but the number of patients is too small for appropriate evaluation.

Keywords: autologous stem cell transplantation (ASCT); primary CNS lymphoma (PCNSL).

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IMPACT OF SURGERY TYPE ON THE OVERALL SURVIVAL TIME OF PATIENTS WITH PRIMARY BRAIN LYMPHOMA

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Introduction: The primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma (NHL) without any symptoms of

systemic disease. They constitute about 3% of the primary central nervous system (CNS) tumors and about 1% of all NHL. They are diagnosed in patients of all ages, most often in men between 60 and 70 years of age. Histologically, they form a very homogeneous group of lymphomas. The most common (> 95%) are diffuse B-cell large lymhomas (DLBCL) expressing CD20, CD19 and CD79a antigens, which are non-germinal B-cell like (non-GCB). The aim of the study was to assess the significance of neurosurgical procedure scope (total resection, partial resection, biopsy) on overall survival (OS) and progression free time (PFS).

Methods: A retrospective study included 50 patients with PCNSL. There were 22 (44%) women and 28 (56%) men, aged 20-87 (mean age 62). Functional status of every patient was assessed using the Karnofsky scale, neurological examination and magnetic resonance imaging (MRI) of the head were performed. The final diagnosis was based on histopathological examination of tissue material obtained during a stereotactic biopsy or total / partial tumor resection.

Results: The most frequently diagnosed histopathological type of primary brain lymphoma was DLBCL (46/92%). In the majority of patients, PCNSL was located in the hemispheres of the brain (28/56%) and the corpus callosum (10/20%). Biopsy was performed in 26 (52%), partial resection in 6 (12%) and complete resection in 18 (36%) patients. In the entire study group, median overall survival was 16 months (0-108 months), while progression-free survival was 7.5 months (0-98 months). There was no statistically significant relationship between OS and PFS and the type of neurosurgical procedure performed (total resection, partial resection, biopsy) and the number and location of lymphoma tumors.

Conclusions: The lack of significant impact of complete tumor resection on OS and PFS in patients with PCNSL indicates the justifiability of performing it only in a selected group of patients, singled out on the basis of the neurological status and the location of lesions in the CNS.

Keywords: primary CNS lymphoma (PCNSL).

PTCL AND NK/T CELL LYMPHOMAS

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PRE-TREATMENT SERUM ALBUMIN LEVEL AS A MEANS OF IMPROVING PROGNOSTIC MODELS IN PERIPHERAL T-CELL LYMPHOMAS: A STUDY FROM THE LATIN AMERICAN GROUP OF LYMPHOMAS (GELL)

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Introduction: Peripheral T-cell lymphomas (PTCL) are heterogeneous and aggressive malignancies recognized by the 2016 WHO classification. The goal of this study is to evaluate the prognostic role of pre-treatment serum albumin level (PAL) in aggressive PTCL subtypeS in a cohort of patients from Peru, Argentina, Chile, and Colombia.

Methods: Patients with PTCL treated between January 1991 and December 2017 were analyzed. Diagnosis of PTCL was based on histological findings. Overall survival (OS) curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Uni and multivariate logistic and Cox regression analyses were performed.

Results: 425 patients with PTCL met inclusion criteria; 48% were peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS),38% were adult T-cell leukemia/lymphoma (ATLL) and 18% where others (ie. anaplastic, angioimmunoblastic, NK/T cell, enteropathy-associated and hepatosplenic lymphoma). The median follow-up was 3.5 years. 54% were younger than 60 years, and 55% were men. An ECOG ≥1 was seen in 48%, B symptoms in 65%, clinical stage III-IV in 75%, and high LDH level in 55% of the patients. PAL was <3.5 g/dl in 56% of the patients. 52% were classified as high/high-intermediate IPI score (31% and 21%, respectively), and 61% as high/high-intermediate PIT score (28% and 33%, respectively).75% of patients received systemic therapy (25% best supportive care).

The IPI score and PIT score were useful to discriminate the highest risk group. High/high-intermediate had worse survival than low/low-

median OS of 3.5 years, PIT-alb 1 with 1 year and PIT-alb 2 with 0.4 years. The PIT-alb 1 had worse survival than PIT-alb 0 (HR 2.08, 95% CI 1.30-3.33, p=0.002), and PIT-alb 2 had worse survival than PIT-alb 0 (HR 3.38, 95% CI, 2.13-5.38, p<0.001).

Conclusions: The PAL<3.5 g/dl could add prognostic value and improve the already known prognostic models IPI and PIT scores in PTCL. These findings warrant validation in prospective studies.

Keywords: prognostic indices; T-cell lymphoma (TCL).

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OUTCOME OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN FIRST COMPLETE REMISSION IN PATIENTS WITH LOW-RISK PERIPHERAL T-CELL LYMPHOMAS (PTCLs)

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Introduction: Patients with peripheral T cell lymphomas (PTCLs) generally have a poor prognosis with conventional chemotherapy. Consolidation with autologous stem cell transplantation is an option for patients with PTCL. However, whether prospective or retrospective studies on the timing of autologous stem cell transplantation remains controversial. We cannot determine whether autologous stem cell transplantation is necessary in patients with PTCL achieving first complete remission (CR1) following induction chemotherapy, especially in

intermediate IPI score (HR 2.92, 95%CI, 2.13-4.01, p<0.001); and high/high-intermediate had worse survival than low-low intermediate PIT score (HR 2.63, 95% CI, 1.88-3.68, p<0.001). In the multivariate analysis, the ATLL group had worse survival than PTCL-NOS (HR 1.82, 95% CI, 1.32-2.50, p<0.001). PAL<3.5 had poor survival than PAL>3.5 (HR 1.82, 95% CI, 1.33-2.48, p<0.001). The median OS at 5 years was 1.5 years with Albumin >3.5 and 0.6 years with Albumin <3.5.

When combining PAL<3.5 g/dl and IPI score (IPI-alb), patients were stratified in 3 risk categories: IPI-alb 0 with a median OS of 3.5 years, IPI-alb 1 with 1 year and IPI-alb 2 with 0.4 years. The IPI-alb 1 had worse survival than IPI-alb 0 (HR 2.13,95% CI 1.38-3.28, p=0.001), and IPI-alb 2 had worse survival than IPI-alb 0 (HR 3.73, 95% CI, 2.43-5.71, p<0.001). When we combine PAL<3.5 g/dl and PIT score (PIT-alb), were also stratified in 3 risk categories: PIT-alb 0 with a

Fig 1. Progression free survival(PFS) stratified by consolidative strategy. K-M PFS plots for patients who underwent ASCT in CR1 following induction regimens versus patients who underwent observation and waiting during CR1(*P*=0.723).

patients with low-risk group. Therefore, we compare prognosis of low-risk patients who underwent ASCT in CR1 following induction regimens and patients who underwent observation and waiting during CR1.

Methods: We completed a retrospective analysis for low-risk PTCL patients who underwent either observation or up-front ASCT during CR1 in our center between 1/1/2007 and 12/31/2018. In our study, patients with PTCL age ≤65 years (median age, 52 years) and IPI score 0-1 were included. Histologic subtypes include PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma a(AITL) and anaplastic lymphoma kinase-negative large cell lymphoma (ALK-negative ALCL). In addition, patients with cutaneous T cell lymphoma and anaplastic lymphoma kinase-positive large cell lymphoma (ALK-positive ALCL) were excluded. The probabilities of PFS was calculated by the Kaplan-Meier method and compared by a log-rank test. The estimated lymphoma of relapse was calculated using cumulative incidence.

Results: In our center, 42 patients met all inclusion and exclusion criteria. And 29 patients underwent observation and waiting in CR1, 13 patients underwent consolidative ASCT. In low-risk patients of PTCL, with a median follow-up of 22 months, estimated 2-year PFS and 5-year PFS in the observation group were 57.4% and 46.0%, respectively. Among ASCT recipients, the 2-year and 5-year PFS were 67.7% and 54.2%, respectively. When considering incidence of disease relapse, the 1-year cumulative incidence of relapse in the observation and ASCT groups was 20.3% and 32.3%, respectively. However, there were no difference between observation and ASCT groups.

Conclusion: In conclusion, for low-risk PTCL patients achieving CR1 following induction therapy, consolidative ASCT does not extend progression-free survival compared to observation. We favor proceeding to observe and wait because of high toxic of hematopoietic stem cell transplantation.

Keywords: autologous stem cell transplantation (ASCT); peripheral T-cell lymphomas (PTCL).

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OUTCOMES IN THE TREATMENT OF PATIENTS WITH T-CELL NON-HODGKIN'S LYMPHOMAS. THE EXPERIENCE OF SINGLE INSTITUTION

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T-cell non-Hodgkin lymphomas (NHL) are uncommon neoplasms that account for only 10-15% of all NHL. Every year in Cuba are diagnosed around 850 new cases of NHL, 12% of them are classified as T-cell NHL. A descriptive and retrospective study was performed to characterize patients with T-cell non-Hodgkin lymphoma diagnosed and treated at the National Institute of Oncology and Radiobiology (INOR), in the period from 2008 to 2016.

Between 2008 and 2016, 557 NHL received primary treatment at INOR, 56 of them (10.1%) were diagnosed as T-Cell NHL. A median age at diagnosed was 57 years. Most frequent histologic subtypes were Peripheral T-Cell Lymphoma NOS (26.8%), Anaplastic Large Cell Lymphoma (23.2%) Cutaneous Anaplastic Large Cell Lymphoma (16.0%) and Primary Cutaneous T-cell Lymphoma (14.3%). Most of the patients were diagnosed in advanced stage III-IV (57.6%), and 40.4% had extranodal involvement. The more frequent treatment modality was chemotherapy (64.3%) followed by the combination of chemotherapy with radiotherapy (26.8%). Most of patients were treated with CHOP/like regimens. High response rates were achieved with the combination treatment (86.7%). The 5 years overall survival was 29.5% for all patients, and 36.4% for patients who received treatment (n=52). The 5 years overall survival (OS) rate was better for patients with low-low-intermediate IPI (45.0%); cutaneous T-Cell Lymphoma subtype (65.0%); Ann Arbor stage I-II (68.8% p=0.021); treated with combined modality (77.9% p=0.003), and with CHOEP regimen (63.3% p=0.031); and patients who achieved completed response after primary treatment (66.3% p=0.001).

This is the first report from a series of T-Cell NHL treated at INOR. Outcomes in the treatment were similar to data reported internationally. A better characterization of the lymphoma subtypes could let identified subgroups of patients with better prognosis.

Keywords: non-Hodgkin lymphoma (NHL); peripheral T-cell lymphomas (PTCL); T-cell lymphoma (TCL).

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T-CELL LYMPHOMA IN THE ELDERLY PATIENTS. WHO IS YOUNG, OLD, AND ELDERLY?

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TABLE 1

	Age at diagnosis					Log rank p-value
	< 60 years (n = 435)	60– <65 (n = 140)	65–<70 (n = 111)	70–<75 (n = 101)	≥ 75 years (n = 119)	
Median OS (95% CI)	9.8 yrs (-)	2.6 yrs (1.3–3.9)	2.2 yrs (1.3–3.2)	2.2 yrs (1.0–3.5)	1.3 yrs (0.8–1.9)	< 0.001
Median PFS (95% CI)	3.7 yrs (1.5–5.9)	1.0 yrs (0.7–1.3)	1.4 yrs (0.5–2.3)	1.0 yrs (0.6–1.4)	0.8 yrs (0.6–1.1)	< 0.001

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Introduction: Ageing of lymphoma population becomes the medical problem with growing proportion of patients > 60 years. Moreover, the term "elderly" is vague comprising people old between 61 to more than 100 years. We decided to analyze prognosis of the T-cell lymphoma patients >60yrs and different age subgroups within this cohort.

Methods: We used CLSG (Czech Lymphoma Study Group) database (Govtrial NT 03199066) for the retrospective analysis, where the cohorts of patients were compared according to their age at diagnosis (<60 yrs, 60-<65, 65-<70, 70-<75, and ≥ 75 yrs), in terms of baseline parameters, treatment and survival.

Results: In total, 906 patients with new systemic T-cell lymphoma diagnosed 1999-2015 were identified, including 471 (52%) pts >60 years, 140 (15%) pts between 60 and <65yrs, 111 (12%) pts between 65-<70yrs, 101 (11%) pts between 70-<75yrs and 119 (13%) pts ≥75 yrs. With the age increases proportion of ECOG 3-4 (9.6% vs. 11.7% vs. 12.7% vs. 15% vs. 21.8%), and especially in cohort ≥75yrs decreases frequency of B-symptoms (44.5% vs. 55.2% vs. 51.4% vs. 54.5% vs. 36.3%). Proportion of sex, stage, bone marrow infiltration, bulky disease, and extranodal involvement were similar across age-groups.

Systemic chemotherapy was administered in 83.4% vs. 87.1% vs. 84.7% vs. 86.1% and 63% pts, including CHOP like therapy in 36% vs. 55% vs. 47% vs. 57% vs. 29%, CHOEP was given in 18% vs. 13% vs. 13% vs. 2% vs. 2%, and more intensive regimens were administered in 18% vs. 10% vs. 1% vs. 0% vs. 0%. In the 1st-line, auto-SCT was performed in 16.3% vs. 13.6% vs. 1.8% vs. 0% vs. 0% pts, but alotransplants in 1.4% pts <60yrs only.

Overall survival (OS) differs significantly among cohorts with median 9.8 vs. 2.2 vs. 2.2 vs. 2.6 vs. 1.3 yrs (Table; p<0.001). Further, we analyzed survival according to IPI in three cohorts (<60yrs vs. 60-<75yrs vs. ≥75 yrs). Survival differences remained significant in the IPI low

Figure
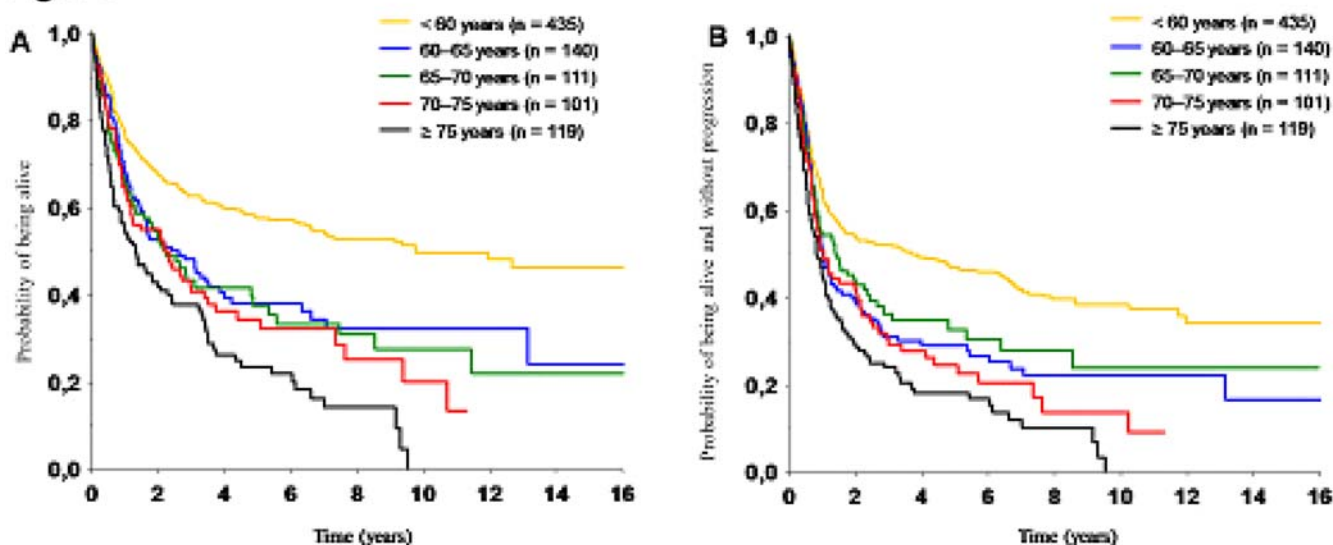
risk patients with median not reached for group <60yrs, 11.4yrs (95% CI; 5.6-17.3) for age 60-<75yrs and 3.4yrs (95% CI; 0.6-6.3) for patients ≥75yrs (p<0.001). For higher IPI groups, there were no significant differences in OS and PFS among age-cohorts.

Conclusions: There is evident that elderly T-cell lymphoma patients (>60yrs) represent heterogenous population, where we can recognise the patients aged 60- <75yrs who share similar clinical characteristics and similar outcomes and patients ≥75 yrs with significantly worse prognosis. Interestingly, the cohort of patients 60- <75 yrs has similar survival regardless difference in the therapy intensity.

Keywords: elderly; peripheral T-cell lymphomas (PTCL); prognostic indices.

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RANDOMIZED PHASE II STUDY OF CHOP VS. FRACTIONATED ICED IN TRANSPLANT-ELIGIBLE PATIENTS WITH PREVIOUSLY UNTREATED PERIPHERAL T-CELL LYMPHOMA: INTERIM RESULTS OF CISL1504

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Introduction: The induction chemotherapy followed by autologous stem cell transplantation (ASCT) is a current widely used treatment strategy for patients with previously untreated peripheral T-cell lymphoma (PTCL). However, it is still not clear whether anthracycline-

TABLE 1

	CHOP	Fractionated ICED	
	n = 40 (%)	n = 41 (%)	p
Characteristics at diagnosis			
Age, median (range)	55.9 years (27-64)	55.9 years (29-64)	0.561
Histologic subtype			0.483
PTCL-NOS	19 (48)	16 (39)	
AITL	16 (40)	15 (37)	
ALK-negative ALCL	2 (5)	6 (15)	
EATL	2 (5)	3 (7)	
Others	1 (2)	1 (2)	
Gender			0.413
Male	26 (65)	23 (56)	
Female	14 (35)	18 (44)	
Stage			0.212
I/II	2/7 (23)	1/3 (10)	
III/IV	18/13 (77)	15/22 (90)	
Bone marrow involvement			0.107
Presence	9 (23)	16 (39)	
Absence	31 (77)	25 (61)	
IPI risk			0.424
Low	9 (23)	9 (22)	
Low-Intermediate	18 (45)	13 (32)	
High-intermediate	6 (15)	12 (29)	
High	7 (17)	7 (17)	
Treatment outcomes			
Response to induction therapy			0.639
Complete response	18 (45)	23 (56)	
Partial response	6 (15)	6 (15)	
Stable disease	0	1 (2)	
Progressive disease	13 (33)	8 (20)	
Not evaluated	3 (7)	3 (7)	
Completion of planned ASCT			0.456
Completed	20 (50)	21 (51)	
Failed to complete	18 (45)	15 (37)	
Ongoing	2 (5)	5 (12)	
Relapse or progression or death			0.904
Occurred	22 (55)	22 (54)	
Absence of event	18 (45)	19 (46)	
Survival status			0.860
Alive	29 (72)	29 (71)	
Dead	11 (28)	12 (29)	
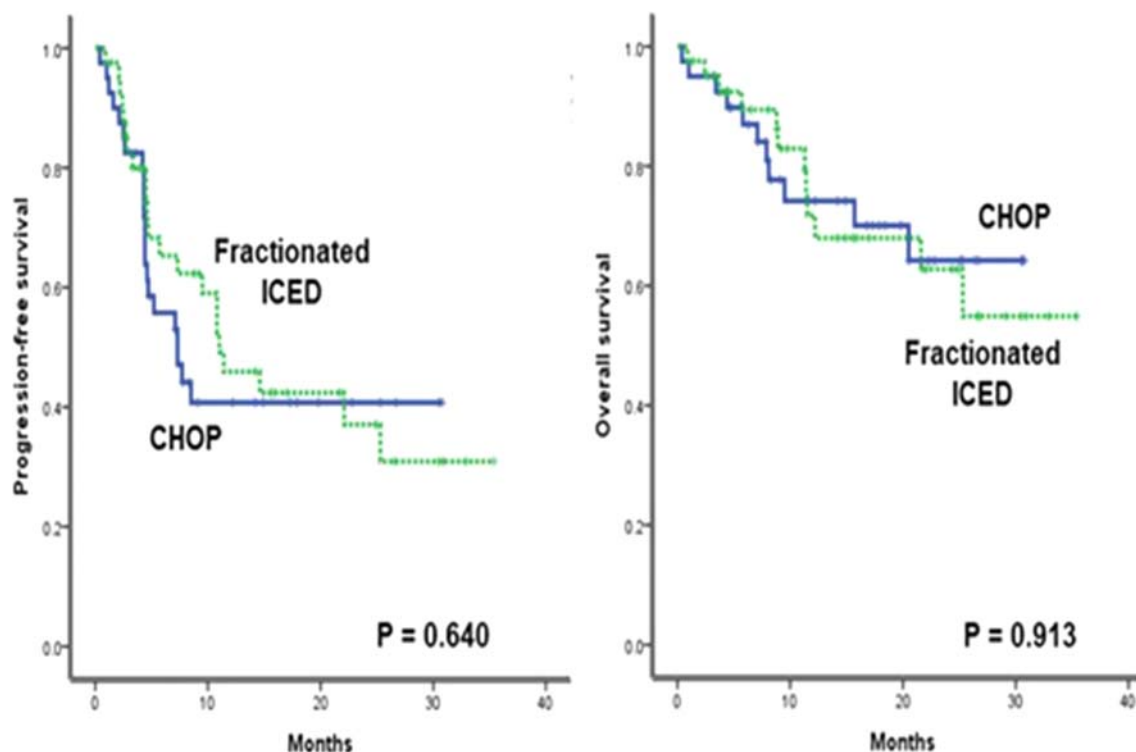
based chemotherapies such as CHOP could be a standard induction therapy for PTCL. Thus, we conducted a randomized phase II study to compare the efficacy of CHOP with a non-anthracycline-based chemotherapy regimen, fractionated ICED in transplant-eligible patients with PTCL (NCT02445404).

Methods: Patients are randomized at a 1:1 ratio to receive either CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone: n=69) or fractionated ICED (ifosfamide, carboplatin, etoposide, dexamethasone: n=69) every 3 weeks for 6 cycles. After the 6th cycle, patients achieving complete or partial response undergo high-dose chemotherapy (Bu-Cy-Etoposide) followed by ASCT. The randomization is done by histologic subtype and International Prognostic Index. The primary endpoint is progression-free survival (PFS), and secondary endpoints include overall survival (OS) and overall response rate (ORR). The interim analysis is planned after 41 cumulative events occur. If interim analysis shows less than 0.017 of P-value, the study will be terminated after declaring fractionated ICED is better than CHOP. If P-value is between 0.017 and 0.686, the study will continue to proceed.

Results: The interim analysis was performed after 44 events occurred, and the outcomes of 81 patients were analyzed (CHOP: n=40; Fractionated ICED: n=41). All patients had 2 or less than 2 of ECOG performance, and their characteristics at diagnosis was not significantly different (Table 1). PTCL-NOS (n=35) and AITL (n=31) accounted for 81% of patients. The complete response rate of ICED (23/41, 56%) was higher than CHOP (18/40, 45%), thus, the ORR of ICED (29/41, 71%) was higher than that of CHOP (24/40, 60%). The planned ASCT was done in a half of patients in each arm. At a median follow-up of

17.9 months (95% Confidence Interval [CI]: 13.4-22.4), the median PFS of ICED was 11.0 months (95% CI: 5.8-16.1), and it was not significantly different from that of CHOP (7.3 months; 95% CI: 3.8-10.7). There was no significant difference of OS between two arms, either (Figure 1).

Conclusions: The interim results did not show significant difference between CHOP and fractionated ICED. This study will be continued until the planned number of patients based on the study protocol.

Keywords: autologous stem cell transplantation (ASCT); induction treatment; peripheral T-cell lymphomas (PTCL).

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A PHASE II STUDY OF THP (PIRARUBICIN)-COP THERAPY IN PATIENTS WITH NEWLY DIAGNOSED ADVANCED PTCL: THP-3 STUDY OF JAPAN HEMATOPOIETIC MALIGNANCY CLINICAL STUDY GROUP

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Introduction: Although a randomized phase III study demonstrated superiority of brentuximab vedotin (BV) with CHP than CHOP alone in patients with newly diagnosed CD30+ peripheral T-cell lymphoma (PTCL) in progression-free survival (PFS) and overall survival (OS), it has not yet been established whether CHP is the most appropriate chemotherapy combined with BV. And, CHOP is still a de fact standard of care in newly diagnosed CD30-negative (neg) PTCL. Thus, new treatment regimen or strategy has been awaited since the outcome of patients (pts) with CD30-neg PTCL treated with CHOP is still poor. Pirarubicin (THP) is, an anthracycline drug, which is not affected by the multidrug resistance mediating p-glycoprotein, and is less cardiotoxic than doxorubicin. THP exhibits activity against some doxorubicin-resistant cell lines. A multicenter phase II study was conducted to evaluate the efficacy and toxicity of THP-COP (pirarubicin, cyclophosphamide, vincristine and prednisolone) therapy in newly diagnosed PTCL by Japan Hematopoietic Malignancy Clinical Study Group.

Methods: Eligibility criteria were as follows; newly diagnosed PTCL including PTCL-not otherwise specified (NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T-cell lymphoma (AITL); clinical stage of bulky II, III or IV; aged 20 to 79 years (yrs); PS 0-2 by ECOG's scale. THP-COP {doxorubicin is replaced with pirarubicin (50mg/m^2 on Day1) in CHOP} was delivered every 3 weeks up to 8 cycles in younger pts less than 69 years, and 6 cycles in elderly pts aged 70 to 79 yrs. The primary endpoint was complete response rate (%CR) including unconfirmed CR (CRu). The planned sample size was 40 pts, which provided at least 80% power with the expected %CR of 55%, threshold of 35%, and a one-sided α of 5%.

Results: From October 2007 to December 2012, 41 pts with a median age of 63 (21-77) yrs were enrolled. The numbers of pts with PTCL-NOS, AITL and ALCL was 21 (51%), 14 (34%) and 6 (15%), respectively. The number of stage II bulky, III and IV was 2 (5%), 22 (54%) and 17 (41%), respectively. 44 % were International Prognostic Index high/intermediate or high risk. The %CR including %CRu and overall response rate were 51.2% (90% CI; 37.4-64.9) which met the primary endpoint, and 70.7% (95% CI; 54.5-83.9), respectively. The PFS (Figure) and OS at 3 years (3-year PFS and 3-year OS) were 43.5% (95% CI; 27.5-58.4) and 62.9% (95% CI; 43.3-77.4), respectively. Most common Grade 4 toxicities were hematologic: %Grade 4 neutropenia and thrombocytopenia were 80.5% and 9.8%, respectively. Cardiac adverse events were observed in 2 patients with Grade 1 arrhythmia. No secondary malignancies were observed.

Conclusions: In pts with untreated advanced PTCL including PTCL-NOS, AITL and ALCL, THP-COP demonstrated high efficacy with durable PFS and OS and acceptable toxicity profiles. Further large-scaled randomized study to compare with CHOP is warranted.

Keywords: chemotherapy; peripheral T-cell lymphomas (PTCL).

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PROGRESSION FREE SURVIVAL AT 12 MONTHS AFTER FIRST-LINE THERAPY IS ASSOCIATED WITH FAVOURABLE OUTCOMES AFTER FIRST RELAPSE/PROGRESSION IN PERIPHERAL T-CELL LYMPHOMA

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Introduction: Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of aggressive lymphomas accounting for 5-15% of non-Hodgkin lymphomas. Survival outcomes of PTCL after relapse/progression are poorly understood. We analyzed the survival outcomes of PTCL after first progression/relapse, and report on newly identified prognostic factors for relapse/refractory PTCL (RR-PTCL).

Methods: We identified 83 patients with newly diagnosed PTCL, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL) between 2005-2017 in our institution. We then analyzed 48 cases with either disease progression or relapse after first line therapy (PTCL-NOS n=33, AITL n=10, ALK- ALCL n=4, ALK+ ALCL n=1). Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method, and further compared by subtypes. Moreover, the ROC approach was used to determine the cut-off in discriminating between patient outcomes, then OS and PFS were compared. Additionally, possible prognostic factors were compared by log rank test. Variables that remained significant in univariate analysis were incorporated in multivariate analysis using the Cox proportional hazard regression model to further investigate independent prognostic factors.

Results: 54 patients (65%) experienced progression/relapse after first line therapy. After excluding those who did not receive salvage treatment at our institution, we analyzed the remaining 48 cases of RR-PTCL. A majority of patients were treated with ICE (45.8%) or GDP (20.9%). Other treatment included DHAP (4.2%), mogamulizumab (4.2%), pralatrexate (2.1%), and romidepsin (2.1%) among others (20.9%). The overall response rate (ORR) and complete remission (CR) rates were 27.7% and 51.1%, respectively, with median OS of 14 months (95% CI: 9-27 months) and PFS of 4 months (95% CI: 2-8months). No significant difference was observed among subtypes. Patients with PFS of at least 12 months before relapse/progression had significantly longer PFS and seemingly longer OS (Figure 1). Multivariate analysis revealed that presence of B-symptoms (HR: 6.20 95% CI: 2.30-16.72, P<.001) was significantly associated with inferior OS, whereas achieving CR or partial remission (PR) from salvage therapy was associated with superior OS (HR 0.41, 95% CI 0.19-0.89, P=.002). CR or PR after first line therapy (HR 0.30, 95% CI:0.14-0.64, P=.001) as well as after second line therapy (HR 0.28, 95% CI:0.14-0.55, P<.001) were identified to be predictive of better PFS.

Conclusions: Prognosis of RR-PTCL remains poor. Achieving PFS at 12 months after first line therapy was associated with significantly superior survival after first relapse/progression. Response (CR or PR) to therapy could serve as proxy for longer OS as well as PFS, and achieving CR or PR from previous therapy was also associated with better PFS.

Keywords: anaplastic large cell lymphoma (ALCL); angioimmunoblastic T-cell lymphoma (AITL); peripheral T-cell lymphomas (PTCL).

Disclosures: Yokoyama, M: Consultant Advisory Role: *Chugai-Roche Pharmaceuticals Co LTD.* **Nishimura, N:** Consultant Advisory Role: *Chugai-Roche Pharmaceuticals Co LTD.* **Mishima, Y:** Consultant Advisory Role: *Chugai-Roche Pharmaceuticals Co LTD.* **Terui, Y:** Honoraria: *Bristol-Myers Squibb, Celgene, Janssen, Novartis Pharma and Takeda Pharmaceutical Co LTD.*
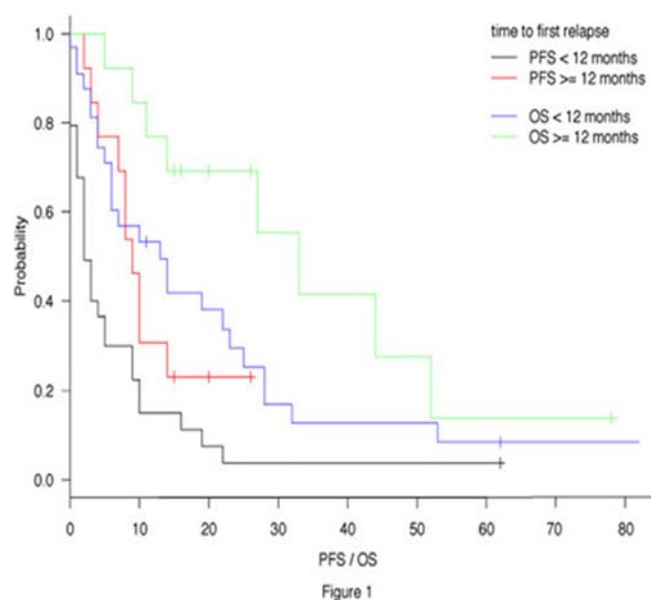
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RESPONSE TO BRENTUXIMAB VEDOTIN BY CD30 EXPRESSION: RESULTS FROM FIVE TRIALS IN PTCL, CTCL, AND B-CELL LYMPHOMAS

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Figure 1

TABLE 1 ORR by CD30 expression, n/N (%)

	Study	CD30≥10%	CD30<10%	CD30=0
PTCL	SGN35-012	10/22 (45)	4/12 (33)	2/6 (33)
	35-IST-030*	NA	4/6 (67)	1/2 (50)
CTCL (MF)	ALCANZA	20/28 (71)	12/22 (55)	NA
	35-IST-001	11/20 (55)	11/20 (55)	NA
	35-IST-002	12/15 (80)	9/17 (53)	NA
B-cell lymphoma	SGN35-012	17/47 (37)	24/66 (36)	17/50 (34)

NA=not applicable

*interim analysis of non-registrational study

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Introduction: Brentuximab vedotin (BV), an antibody-drug conjugate targeting CD30, has been evaluated in multiple trials in patients (pts) with peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL), or B-cell lymphoma. We examined the ability of CD30 expression level to predict response to BV across these patient populations.

Methods: Data were integrated from 275 pts with PTCL, CTCL, and B-cell lymphoma treated with BV from 5 prospective clinical trials. Study SGN35-012 evaluated BV plus rituximab or BV monotherapy in pts with relapsed/refractory non-Hodgkin lymphoma. The ALCANZA study compared BV to physician's choice of methotrexate or bexarotene in pts with mycosis fungoides (MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL). Three investigator-sponsored trials evaluated BV monotherapy in pts with relapsed PTCL, MF, and pcALCL (35-IST-030, 35-IST-001, 35-IST-002). Exploratory analyses were conducted to examine the relationship between CD30 expression and objective response rate (ORR) for pts with CD30 expression ≥10%, <10%, or undetectable (0%) by IHC (malignant cells or lymphoid infiltrate; local review).

Results: 143 pts had tumors with CD30 <10%, including 58/143 with undetectable CD30. Activity with BV was observed at all levels of CD30 expression, including CD30=0 (Table). Analysis of the interaction between CD30 and duration of response is ongoing and will be shown in the presentation.

Conclusions: CD30 expression levels ≥10%, <10%, or undetectable did not predict response to BV in a range of CD30-expressing lymphomas: Clinical responses occurred in pts with CD30 low and CD30 undetectable lymphomas. Limitations of IHC, the dynamic nature and heterogeneity of cell-surface CD30 expression, and multiple mechanisms of action of BV may all contribute to this observation.

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A PHASE II TRIAL OF BRENTUXIMAB VEDOTIN (BV) AND LENALIDOMIDE (LEN)

IN RELAPSED AND REFRACTORY (R/R) CUTANEOUS (CTCL) AND PERIPHERAL (PTCL) T-CELL LYMPHOMAS: PRELIMINARY RESULTS OF A PHASE II TRIAL

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Background: Patients with r/r tumor stage CTCL and/or PTCL have a poor prognosis. BV is currently FDA approved for CD30 positive CTCL and anaplastic large cell lymphoma (ALCL) with single agent activity in additional PTCL subtypes. Len also has single agent activity in patients with r/r CTCL/PTCL. The safety of the combination was established in a phase I trial in patients with r/r diffuse large B-cell lymphoma which defined the dose for this single-center, open label phase II trial of the combination in r/r CTCL/PTCL

Methods: Patients with ≥ 1 line of systemic therapy, at least stage IB (for CTCL), and no prior progression on BV were eligible. Treatment consisted of BV 1.2 mg/kg IV and Len 20 mg PO daily q3 weeks for a maximum 16 cycles. After 7 patients were treated, we reduced Len to 10 mg given safety/tolerability concerns. Responses are assessed by the ISCL/EORTC Global response criteria (for CTCL) and Cheson year criteria (for PTCL). The effect of treatment on quality of life (QOL) is assessed by Skindex-16.

Results: As of March 12, 2019, 14 subjects were accrued to the trial; 10 with mycosis fungoides, 2 with Sezary syndrome, 1 with CD30+ lymphoproliferative disorder, and 1 with systemic ALK-ve ALCL. Median age was 60 (49-74) years and 79% were males. For patients with CTCL, 2 (15%) had stage IB, 7 (54%) IIB, and 4 (31%) had stage IVA disease with median baseline modified Severity Weighted Assessment Tool (mSWAT) of 65 (4.4-190). Median CD30+ positivity by visual immunohistochemistry was 7.5% (1-75) and 6 (43%) patients had large cell transformation. Median number of prior therapies was 5.5 (1-9). Grade 3 adverse events (AEs) were reported in 8/14 (57%) patients; including neutropenia (4), thrombocytopenia (1), bronchitis (1), dyspnea (1), abdominal pain (1), vertigo (1), DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome (1), urinary tract infection (1), and tumor flare (2). All AEs were possibly related to Len and recovered with no sequelae. No new or worsening neuropathy was reported. Median number of cycles received was 3.5 (1-13). Best response in 12 evaluable patients, who completed ≥ 2 cycles of treatment, included complete response=2 (17%), partial response=3 (25%), and stable disease=7 (58%) with overall response rate of 38%. Currently 10/14 patients discontinued treatment due to progression (5), grade 3 thrombocytopenia (1), DRESS syndrome (1), tumor flare (2), and abdominal pain (1). On an earlier analysis of Skindex-16 scores, 4/6 (66%) evaluable patients with CTCL had >50% reduction in their Skindex-16 scores after 2 cycles of treatment.

Conclusion: These results demonstrate that BV + Len is safe, has clinical activity in a heavily pre-treated patient population, with a potential to positively impact QOL in patients with T-cell lymphomas. Len doses >10 mg daily are poorly tolerated in CTCL patients because of tumor flare. Recruitment of both CTCL and PTCL patients for this trial is ongoing.

Keywords: cutaneous T-cell lymphoma (CTCL); peripheral T-cell lymphomas (PTCL).

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SURVIVAL BENEFIT WITH NOVEL AGENTS IN PATIENTS WITH RELAPSED OR REFRACTORY PERIPHERAL T-CELL LYMPHOMAS (PTCL): THE COLUMBIA UNIVERSITY EXPERIENCE

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Introduction: Peripheral T-cell lymphomas (PTCL) are a group of rare and heterogeneous diseases characterized by an unfavorable prognosis. Conventional chemotherapy (CT) is only marginally effective as derived from the management of aggressive B-cell lymphomas. Patients often relapse, and available FDA-approved novel agents (NA) for these patients include pralatrexate and histone deacetylase inhibitors (HDACI). In these analyses, we aim to determine if NA improve outcomes in our cohort of patients.

TABLE 1 Patient Characteristics

Subtype	Count (%)	Median Age, years (range)	Median OS, years (95% CI)
Adult T-Cell Leukemia Lymphoma (ATLL)	18 (16)	46 (15-72)	2.53 (0.81-5.25)
ALK+ ALCL	8 (7)	24 (2-61)	NR (0.83-NR)
ALK- ALCL	10 (9)	63 (44-76)	7.38 (0.46-NR)
Angioimmunoblastic T-Cell Lymphoma (AITL)	33 (29)	56 (28-88)	2.94 (1.3-9.96)
PTCL not otherwise specified (NOS)	24 (21)	46 (19-76)	3.6 (1.29-12.79)
Other	19 (17)	50 (8-82)	2.32 (0.91-11.2)
TOTAL	**112**	**57 (2-90)**	**3.3 (2.26-6.75)**

Figure 1. The survival curves for patients who achieved CR (line 1) to second line novel agents compared to those who did not (line 0), p=0.0033.
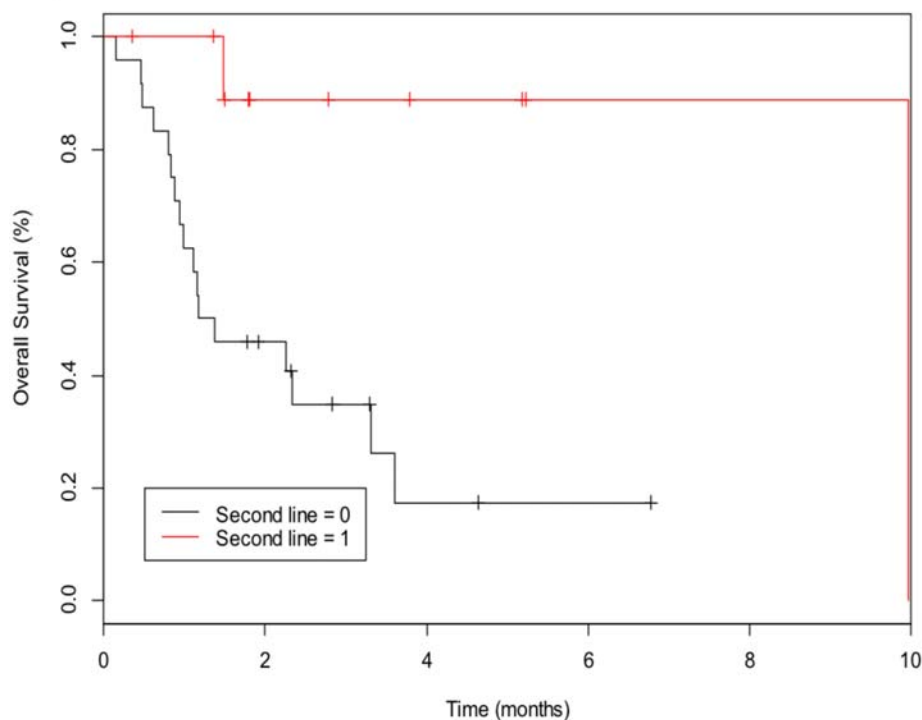
Methods: Research was conducted in accordance with the Institutional Review Board at New York Presbyterian Hospital - Columbia University Medical Center. From 1994 to 2018, 112 patients with PTCL were treated and included in the analysis. Overall survival (OS) was calculated from the time of diagnosis to death from any cause. Kaplan-Meier curves were generated and compared based on the log-rank test. Cox proportional hazard models were used to investigate the association by adjusting for age, gender, diagnosis, and the type of treatments. The analysis was done in SAS version 9.4.

Results: Table 1 summarizes the subtypes of PTCL, median age, and median OS. First line therapies mostly consisted of CT such as CHOP, CHOEP, and EPOCH. Patients who did not achieve a complete remission (CR) with first line CT were at increased risk of death (HR 4.6, p<0.0001). This remained true after excluding anaplastic large cell lymphoma (ALCL), which has a better prognosis (HR 4.0, p=0.0001). Second and third line therapies included platinum- and gemcitabine-based CT, clinical trials, and novel agents. Importantly, patients who did not achieve a CR with second line novel agents had increased risk of death compared to those who achieved CR (HR 11, p=0.019) as shown in Figure 1. Patients who did not undergo autologous or allogeneic stem cell transplant (ASCT) had increased risk of death (HR 1.2, p=0.0058), and this impact was stronger after removing patients with ALCL from analysis (HR 2.5, p=0.016).

Conclusions: Our data is consistent with historical data, where ALK+ ALCL did better compared to other subtypes of PTCL. Patients who received NA as second line therapy after relapse and achieved CR had a survival benefit. Novel agents can be efficacious in a the relapsed/refractory population with limited treatment options. We are currently finding new ways to combine NA upfront to shift the paradigm in the treatment of these heterogeneous diseases.

Keywords: histone deacetylase inhibitors; pralatrexate; T-cell lymphoma (TCL).

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TREATMENT OF RELAPSED AND REFRACTORY T-CELL LYMPHOMAS: FIRST PAVLOV STATE MEDICAL UNIVERSITY OF SAINT-PETERSBURG EXPERIENCE

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Introduction: T-cell lymphomas represent rare and heterogeneous group of aggressive non Hodgkin lymphomas. There are currently no standards for the treatment of relapsed/refractory T-cell lymphomas (r/r PTCL). A number of novel therapy approaches are aimed for improvement of outcomes in patients with r/r PTCL. This report summarizes the First Pavlov State Medical University experience in the treatment of patients with T-cell lymphomas.

Methods: We analyzed data of 34 patients with r/r PTCL eligible for stem cells transplantation treated in First Saint-Petersburg state medical University from 2005 to 2018. Among them n8 with anaplastic large cell lymphoma (ALK+), n3 with anaplastic large cell lymphoma (ALK-), n4 with angioimmunoblastic T-cell lymphoma, n5 with hepatosplenic T-cell lymphoma, n1 with $\gamma\delta$ T cell lymphoma and n13 with PTCL not otherwise specified (PTCL-NOS). The median age was 46 years (range 11 – 73 years).

Median time from initial diagnosis to relapse or progression after primary therapy was 6.7 months (1,8-41). Among all patients n18 (53%) had a primary chemoresistant disease, while the rest n14 (47%) had a relapse after initial treatment. All patients received at least one line of salvage chemotherapy. The treatment was tailored according to biological factors presented in patients. In 7 patients with CD30+ PTCL the brentuximab vedotine was used. One patient with ALK+ anaplastic lymphoma received ALK inhibitor crizotinib. One patient with $\gamma\delta$ TCL and PD-L1 hyperexpression was treatment with nivolumab. Responses were consolidated with hematopoietic stem cells transplantation. Overall 16 patients undergo SCT: high dose chemotherapy with autologous stem cells transplantation was performed in 10 patients, 11 patients underwent allogeneic hematopoietic stem cells transplantation (among them 5 patients with relapses after auto-SCT).

Results: At the time of analysis, 25 patients remain alive. The median follow up of alive patients was 29 months (1,5-101 mo). The median overall survival was not reached and 2-year survival rate was 82%. The disease status at the last follow up was CR in 15 patients, PR in 3 patients and PD in 16. Among factors significantly associated with adverse prognosis was lower ECOG performance status at the time of diagnosis (p=0,03). Patients that had undergo salvage SCT showed significantly better disease status at the moment of last follow up: 12/16 (75%) were in CR, versus 3/18 (17%) in patients who did not undergo SCT. No difference was found in OS between relapsed and primary refractory patients (p=0,73).

Conclusions: The results of analysis show that introduction of novel agents and consolidation with high dose chemotherapy and auto-SCT or allo-SCT in selected cases may improve outcomes in patients with relapsed and refractory peripheral T-cell lymphomas. Brentuximab based regimens may be successfully used as a bridge therapy before stem cells transplantation.

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ANALYSIS OF PUBLISHED TREATMENT OPTIONS FOR RELAPSED OR REFRACTORY (R/R) PERIPHERAL T–CELL LYMPHOMA (PTCL): AN EVIDENCE BASED DECISION MAKING APPROACH

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Introduction: PTCL are rare diseases with a poor prognosis. Front line therapy achieves CR in 30% to 60% and OS of 25%. Patients with R/R disease have an even worse prognosis. There is no consensus on the management of R/R disease because evidence supporting most treatment approaches is modest. Many approaches are often not supported by literature, and categorizations regarding efficacy and toxicity without attention to details are ignored. Treatments that have achieved regulatory approval with stringent independent assessment of pathology and response are viewed as less established, or equivalent to smaller published experiences. In the effort to take a critical and comprehensive evidence-based approach to available standards in R/R PTCL we developed an objective scoring system for all types of studies published in the literature (eg randomized phase 3, case match control, phase 2, phase 1, case reports and small series) to aid decision-making based on an assessment of all the available data.

Methods: We performed an extensive review on PubMed of the clinical trials published in the literature that included patients with R/R PTCL. We proposed a rigorous scoring system based on a survey from nearly 100 authorities in the field to assess the scientific impact of each study based on the agreed study characteristics, including type of study (ie, randomized phase 3, case match control analysis, phase 2 weighted based on number of PTCL patients [> 100 vs < 100 patients], phase 1 with > 5 or < 5 PTCL patients enrolled, and retrospective) weighted based on percent of PTCL patients included; weighting for inclusion of central pathology or response review; weighting for detailed reporting of study metrics (ORR, CR, DoR, PFS). The scoring system included a penalty of -0.5 each for ORR, DoR, or PFS not being reported and -0.2 for omitting previous lines of therapy. Studies that ranked 0 or below

were all grouped under the minimum score of 0. The proposed scoring system was evaluated by a panel of experts belonging to different academic institutions in three different continents, actively involved in T-cell lymphoma clinical research. The scoring system was modified accordingly based on recommendations made by 2 or more of the panel members.

Results: We identified 58 publications between 2004 and 2018. The scoring system spanned from 0 to 9. Only 12 of the 58 studies had a score above 5; 15 of 58 had a score between 1 - 5; remaining publications scored 0 - 1.

Conclusion: Our analysis suggests practice patterns are based on studies with low priority scores, and underweight robust clinical experiences. This analysis aims to produce an evidenced based approach for R/R PTCL.

Keywords: chemotherapy; peripheral T-cell lymphomas (PTCL).

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AGGRESSIVE NK CELL LEUKEMIA: CLONALITY, CLINICAL AND GENETIC FEATURES

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Introduction: Aggressive natural killer cell leukemia (ANKL) is an extraordinary rare aggressive malignancy of NK cells, but is relatively common in Asian. The accurate diagnosis of ANKL remains a great challenge. This study intends to describe the clonality, clinical and genetic features of ANKL and guide the diagnosis of this disease.

Methods: A total of 45 consecutive newly diagnosed ANKL patients were recruited from the First Affiliated Hospital of Nanjing Medical University, and clinical data were collected. Cytological morphology, flow cytometric analysis including killer cell immunoglobulin-like receptors (KIR), karyotypic analysis and molecular biology tests were used to diagnose and assess the monotypic clonality of NK cells. Survival analyses were done to verify the prognostic predictors of ANKL.

Results: All patients were adults, with a median age of 39 years (range 8-80 years) and a male: female ratio 1.4:1 (Table 1). B symptoms and fever were noted in all patients. Splenomegaly (91.1%) and hemophagocytic lymphohistiocytosis (HLH) (80.0%) were also

TABLE 1 Clinical and biological characteristics of 45 patients with ANKL

Characteristics	Number of Patients	%
Gender		
Male	26	57.8
Female	19	42.2
Performance status (ECOG)		
0-2	22	48.9
3-4	23	51.1
LDH>250U/L	43	95.6
β2-MG>3.0mg/L (n=28)	26	92.9
Lymphocytosis	9	20.0
Neutropenia	20	44.4
Anemia	24	53.3
Thrombocytopenia	37	82.2
Initial presentation		
Fever	45	100
Hepatomegaly	21	46.7
Splenomegaly	41	91.1
Hemophagocytic lymphohistiocytosis	36	80.0
Pleural effusion/ascites	24	53.3
EBV-DNA>5000copies/ml (n=38)	34	89.5

common. Most patients (34/38) were confirmed with EBV infection. Immunophenotyping of the ANKL cells were typically positive for CD2 and CD3, and CD7, CD16 and CD56 were positive for 66.7%, 52.9% and 87.8%, respectively. Either monotypic (n=8) or complete lack (n=20) of KIR expression was observed in 28 ANKL patients (Figure 1). Highly complex karyotypes were detected in five cases. No patient had clonal rearrangement of the T-cell receptor gene, and only one patient had *STAT3* mutation. Median overall survival of ANKL patients was 27 days. HLH ($P<0.001$), pleural effusion/ascites ($P=0.003$), absolute lymphocyte count $\leq 4.0\times10^9$/L ($P<0.001$), neutropenia ($P=0.001$), thrombocytopenia ($P=0.009$), positive EBV-DNA ($P=0.036$), positive CD56 ($P=0.035$), and performance status >2 ($P<0.001$) were identified as unfavorable factors of early death.

Conclusions: Our findings suggest that ANKL is a highly aggressive leukemia with high mortality. Detection of immunophenotyping and KIR may have important diagnostic value. More studies are needed to obtain a better understanding of the pathogenesis of this disease.

Complete lack of KIR antigens was observed in ANKL patient 20. The expression of KIR was evaluated by gating on the total population of CD3^{−} and CD56^{+} NK cells.

Keywords: Epstein-Barr virus (EBV); non-Hodgkin lymphoma (NHL).

Figure 1. Representative tetramer staining of ANKL by FCM analysis
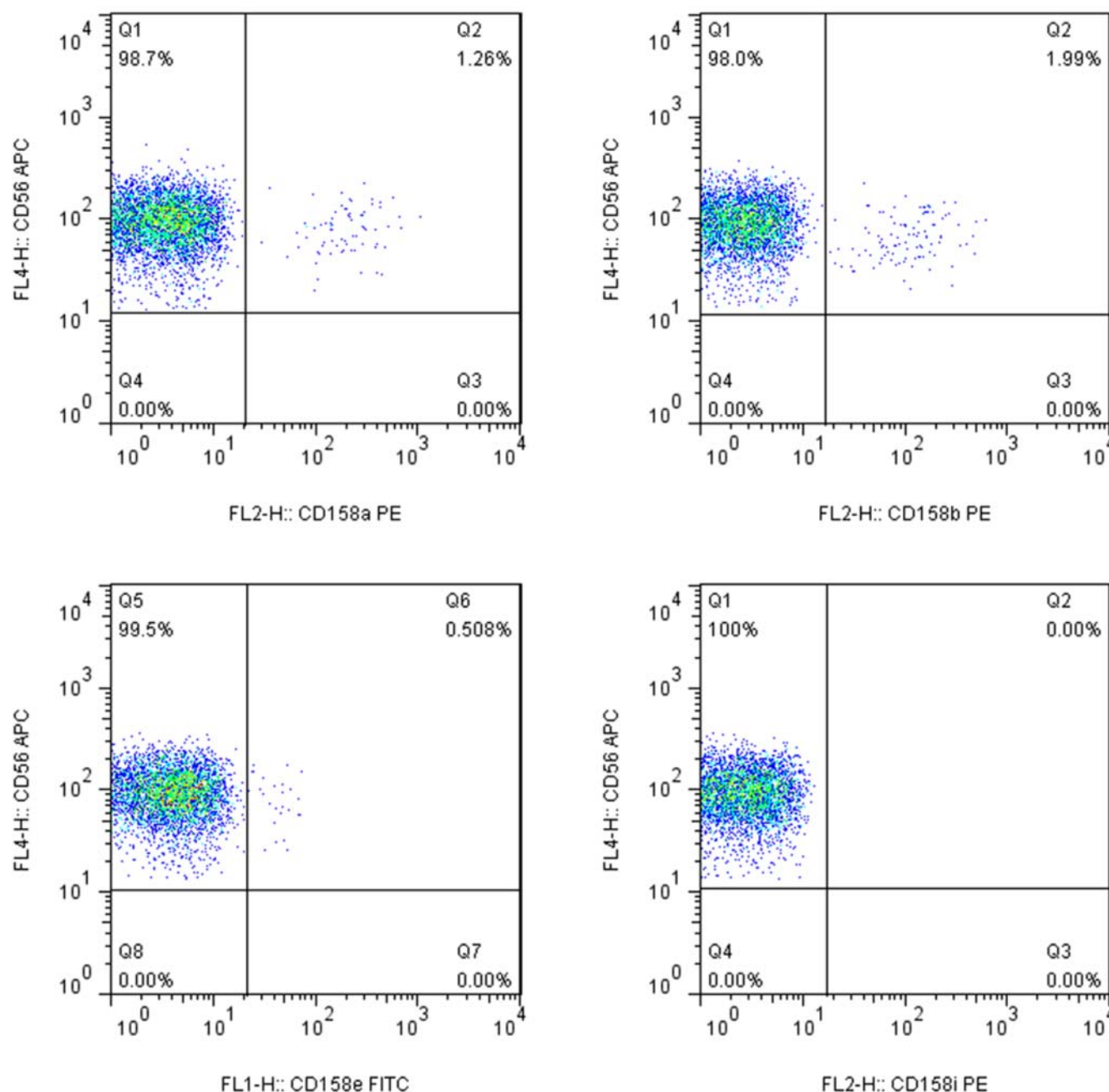
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CLINICAL OUTCOMES IN PATIENTS WITH EPSTEIN-BARR VIRUS (EBV)-POSITIVE NON-B CELL LYMPHOMA AT THE OHIO STATE UNIVERSITY JAMES COMPREHENSIVE CANCER CENTER (OSU JAMES CCC)

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Background: EBV+ lymphomas, including extranodal NK/T-cell lymphoma (ENKTL), and EBV+ peripheral T cell lymphoma (PTCL) are rare, aggressive forms of non-Hodgkin lymphoma. EBV exhibits a restricted tropism for infecting naïve B lymphocytes; consequently, its oncogenic activity is most frequently associated with B cell lymphomagenesis. Given the rarity of EBV+ non-B cell lymphomas, there are no evidence-based treatment guidelines available. Here we

TABLE 1 Patient Characteristics

Demographics	n/N (range or %)
Female	15/28 (54%)
Median age	58 (37-84)
Median ECOG	1 (0-3)
Diagnosis	**n/N (range or %)**
ENKTL	10/28 (36%)
PTCL AITL	9/28 (32%)
PTCL NOS	8/28 (29%)
Adult T cell leukemia/lymphoma	1/28 (4%)
Disease characteristics	**n/N (range or %)**
Median IPI	3 (1-5)
Stage III-IV	17/25 (58%)
LDH elevated	22/28 (79%)
Beta-2-microglobulin elevated	9/13 (69%)
Bone marrow involvement	7/24 (29%)
Peripheral blood involvement	5/20 (25%)
EBV viral load detectable	14/25 (56%)
First line treatment	**n/N (range or %)**
CHOP w/wo rituximab	7/28 (25%)
EPOCH	6/28 (21%)
SMILE (for ENKTL only)	7/28 (25%)
GELOX or GEMOX (for ENKTL only)	3/28 (1%)
Other systemic treatment	5/28 (14%)
Radiation therapy (Stage I-II only)	5/28 (18%)
Response to first line treatment	**n/N (%)**
CR	15/25 (60%)
PR	7/25 (28%)
No response	3/25 (12%)

report an analysis of clinical outcomes and prognostic factors of EBV+ non-B-cell lymphoma at OSU James CCC.

Methods: Data were collected by retrospective chart review and all diagnoses were established by a hematopathologist with investigator review. Univariate probabilities of overall survival (OS) and progression-free survival (PFS) were estimated utilizing the Kaplan-Meier method using IBM SPSS v 24.0. The log-rank test was utilized to assess for differences between groups in regard to OS and PFS.

Results: 28 patients, with a median follow-up time of 18 months, were treated for EBV+ non-B cell in 2014-2018. 10/28 (36%) had ENKTL and 17/28 (61%) had PTCL with 1 Adult T-cell lymphoma. Details of the patient demographics, disease characteristics and details of first-line therapy are listed in Table 1. OS for the entire cohort was 80% and 46% at 1 and 3 years. At 1 and 3 years, OS for PTCL was 80% and 41%, and 56% for ENKTL. Patients received a median of 2 lines of therapy. Response rate to frontline therapy was 88%, with 60% CR. OS was improved for patients who achieved a CR to first-line therapy (79% vs 33%) at 1 year and 66% vs 11% at 3 years, (p=0.004), Statistical significance was maintained within the ENKTL and PTCL disease cohorts. PFS for the entire patient cohort was 73%

and 27% at 1 and 3 years. PFS for ENKTL was 56% at 1 and 3 years, and PFS for PTCL was 59% and 16% at 1 and 3 years. PFS was improved in patients with IPI score of 1-2 vs 3-4 (PFS 75% vs 33% at 1 year, p=0.044). There was no significant association of sex, age, stage, EBV viral load, LDH elevation, absolute CD4 or CD8 counts and bone marrow involvement with either OS or PFS.

Conclusions: EBV-associated ENKTL and PTCL have similar OS and PFS rates with EBV+ PTCL outcomes similar to previously reported 5-year OS international PTCL consortium) expected for patients with PTCL. Sensitivity of EBV+ non B-cell lymphomas to chemotherapy and attainment of CR to first line of therapy was critical to achieving longer OS duration irrespective of disease type. Novel treatment approaches for patients with these rare histologic subtypes of lymphoma is clearly needed.

Keywords: Epstein-Barr virus (EBV); extranodal lymphomas; peripheral T-cell lymphomas (PTCL).

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TREATMENT AND OUTCOMES OF PATIENTS WITH NK/T-CELL LYMPHOMA TREATED WITH MODIFIED (m)SMILE AND INTENSITY-MODULATED RADIOTHERAPY (IMRT), A SINGLE CENTER EXPERIENCE

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Introduction: Extranodal NK/T cell lymphoma (ENKTL) is a rare subtype of lymphoma, poorly responsive to anthracycline-based chemotherapy. Treatment and prognosis are largely driven by stage, and the PINK and PINK-E scores appear to further refine it. Outcomes for patients with ENKTL have improved with L-asparaginase containing regimens into combined modality approaches. Based on the reported efficacy of SMILE (Yamaguchi, Cancer Sci, 2008), in 2009, we adopted a modified (m)SMILE (dexamethasone, methotrexate, ifosfamide, peg-asparaginase, etoposide) regimen given every 3 weeks, followed by

Localized (Nasal cavity only treatment)
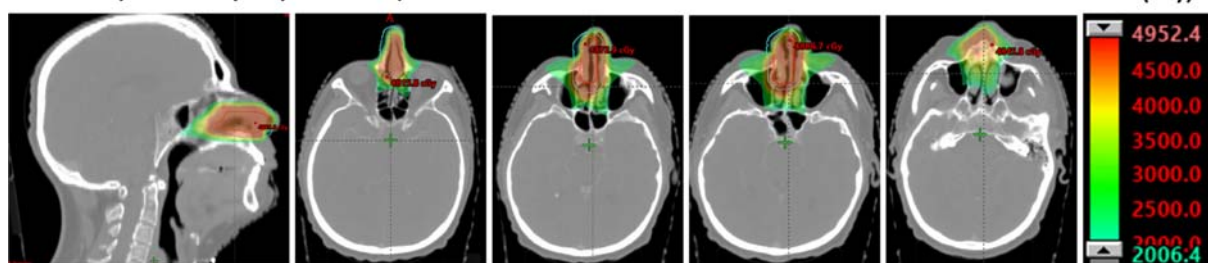
Locally advanced (Nasal cavity, nasopharynx and paranasal sinus treatment)
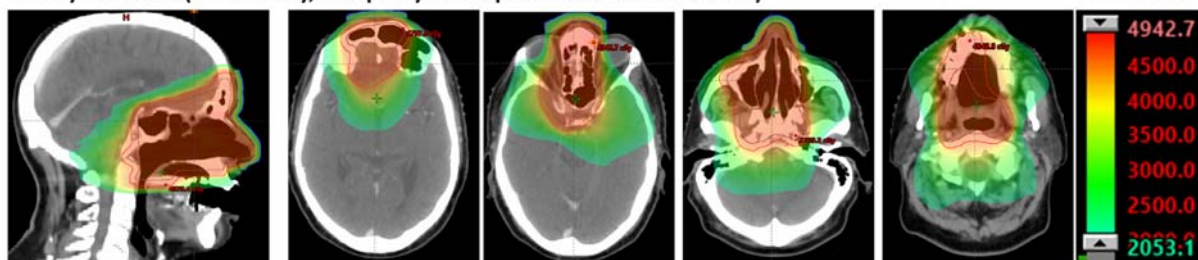
radiotherapy (RT) as our standard approach. Main differences from the SMILE are: I) shorter course of chemotherapy, II) the use of peg-asparaginase (most common dose was 1500 U/m2), and III) lower dose and Intensity-Modulated Radiotherapy (IMRT) consolidation.

Methods: We retrospectively analyzed 28 patients with ENKTL treated at our institution with mSMILE from 10/2009–3/2019. Early-stage patients were planned to receive 2 cycles of mSMILE+IMRT, advanced stage 3-4 cycles of mSMILE+/-IMRT. We collected patient characteristics and estimated survival with the Kaplan-Meier method.

Results: Patient characteristics were: age median 52y (24-69); female 53%; Asian 25%, other races 75%. Response post mSMILE was 93% (26/28, CR 68%) and response post IMRT was 95% (23/24, CR 87.5%). After a median follow-up of 31 months (range 5-105) 17 patients are alive (61%). Among early-stage patients (IE)/low PINK-E (n=13), overall survival (OS) was 100% at the median follow up, and progression-free survival (PFS) was 92%. However, there were two subsequent events: one death due to relapse and one death from unrelated causes in remission. Intermediate and high-risk stage/PINK-E patients fared similarly, with an OS of 43% and a PFS of 33.3% at the median follow-up. Four pts (14%) had chemotherapy dose reductions, 9 pts (32%) experienced G3-4 non-hematologic toxicity, all pts had hematologic toxicity, for 21/28 (75%) G3-4. Twenty-four pts, (86%) received RT as part of their treatment course. 22/24 received IMRT consolidation post 1-2 mSMILE 16 with receiving 4500 cGy. Of these 22, 2 pts received IMRT consolidation composite with total body irradiation conditioning for allo-transplant to total doses of 3947 cGy. An example of IMRT field design is shown in the figure.

Discussion: In 28 patients treated at MSKCC for newly diagnosed ENKTL with mSMILE+/-IMRT, we confirmed the overall high response rate with mSMILE. This is a highly active albeit aggressive approach with good results in patients with early-stage/favorable risk disease for whom the PFS and OS were excellent. However,

outcomes remain inadequate for those with more extensive disease or higher risk factors. For these patients, the recent identification of new agents including pembrolizumab and daratumumab raise the possibility of novel regimens or approaches.

Keywords: extranodal lymphomas; L-asparaginase; T-cell lymphoma (TCL).

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EXTRANODAL NATURAL KILLER (NK)/T-CELL LYMPHOMA, NASAL TYPE – CASE REPORT AND REVIEW OF CZECH LYMPHOMA STUDY GROUP (CLSG) DATABASE

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Introduction: Nasal NK/T-cell lymphomas (ENKL) show a geographic predilection for Asian and South American populations (incidences

with 5.2 and 3%), and are uncommon in other countries (incidences with just 0.3% in North American and European countries). The prognosis for patients (pts) with advanced or refractory ENKL is extremely poor. The role of allogeneic transplantation (alloSCT) has been explored in a few small retrospective studies, which almost exclusively were comprised of Asian patients. Here, we describe the case report of pt with refractory ENKL successfully treated with haploidentical transplantation (haploSCT) and provide the analysis of ENKL in Caucasian pts using the observational database of the Czech Lymphoma Study Group (CLSG).

Case report: A 35-year-old woman was referred to our department with 6 years history of autoimmune granulomatosis (repeated biopsy from mouth), last biopsy from the right vestibule diagnosed ENKL. PET CT scan showed involvement of gingiva, face and one mediastinal lymph node. Pt was treated with 4 cycles of chemotherapy (CHOEP), after the initial improvement the progression of ENKL on the tongue was histologically verified. Salvage chemotherapy DHAP was started with subsequent progression after the first cycle. The 3rd line chemotherapy DeViC (2 cycles) was administered only with a partial transient effect and early recurrence of lymphoma infiltration. Radiotherapy of soft facial tissues was performed with complete regression of infiltrates. However early after the radiotherapy 2 new FDG accumulating lesions in spleen were detected. Early haploSCT was performed (donor haploidentical brother, reduced intensity conditioning). 1 year after the haploSCT pt is alive in complete remission of ENKL.

Further we analyzed the group of pts with ENKL from CLSG database. 40 adult (≥18 years) pts with ENKL were reported to the CLSG database between 1999 and 2018. The median age at the time of diagnosis was 52 years (range: 21–86); 62% were male and 74% had ECOG 0-1. Therapy was known for 37 pts; 18 (49%) received only chemotherapy (mostly CHOP and CHOEP), 2 (5%) radiation alone, and 17 (46%) received combined radiation and chemotherapy. 19 pts (52%) responded after the first line treatment; 16 pts (43%) achieved CR and 3 pts (8%) PR, 6 pts. (16%) were not evaluable and 12 pts (32%) had primary progressive disease. 10-years probability of OS of the whole group was 38%, RFS 27%. 7 pts from progressive disease group received second line chemotherapy with subsequent further progression, 1 pt underwent alloSCT and achieved complete remission. Except for the patient after alloSCT all pts died from disease progression.

Discussion: alloSCT should be considered for high-risk or advanced-stage patients in remission or relapsed/refractory ENKL. However, reports of alloSCT for ENKL are limited because of the rarity of the disease. GovTrial Number: NCT03199066.

Keywords: allogeneic stem cell transplant (alloSCT); extranodal lymphomas; reduced-intensity conditioning regimen (RIC).

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ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PATIENTS WITH AGGRESSIVE NATURAL KILLER CELL LEUKEMIA: A NATIONWIDE MULTICENTER ANALYSIS IN JAPAN

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Introduction: Aggressive natural killer cell leukemia (ANKL) is a rare leukemic form of mature natural killer cell neoplasm that is closely associated with Epstein-Barr virus. ANKL presents a fulminant clinical course, resulting in a poor prognosis. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently the only curative treatment, but the long-term outcomes after allo-HSCT remain unclear.

Methods: Using the national Japanese transplant registry database, the outcomes of 59 ANKL patients who underwent first allo-HSCT between 1997 and 2016 were analyzed.

Results: The median patient age was 37 years (range, 9 to 66), and males accounted for 68%. The median time from diagnosis to allo-HSCT was 3.7 months (range, 1.1 to 13.9). Twenty-nine patients received stem cells from cord blood (CB), 18 received them from peripheral blood (PB) and 12 received them from bone marrow (BM). Two patients had a prior history of autologous HSCT. Twenty-one patients (36%) had complete response (CR), and 7 (12%) had partial response (PR), but 31 (52%) were not responding at the time of allo-HSCT. Forty-four patients received myeloablative conditioning and 15 received non-myeloablative conditioning. Thirty-two patients received tacrolimus-based graft-versus-host disease (GVHD) prophylaxis, including 1 with additional post-transplant cyclophosphamide as part of haploidentical HSCT, whereas 26 received cyclosporin-based prophylaxis. The median overall survival (OS) and relapse-free survival were 3.9 months and 2.6 months, respectively. The median cumulative incidences of relapse and non-relapse mortality were 1.5 months and 2.2 months, respectively. The probability of OS was significantly

Overall Survival
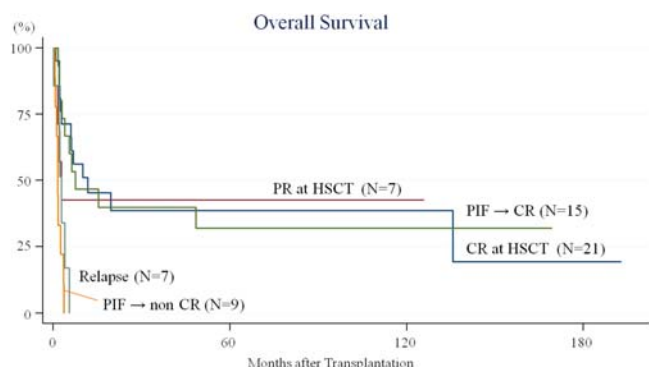
higher for patients in CR or PR at allo-HSCT than for those without a response (40.6% vs 16.1% at 5 years after HSCT, P = 0.046). Among the 24 patients with primary induction failure at allo-HSCT, 15 achieved CR after allo-HSCT. The prognosis of these 15 patients was almost equivalent to that of those who received allo-HSCT in CR or PR, as shown in the Figure (P = 0.95). Regarding the stem cell source, the probability of OS was significantly higher for patients who received stem cells from CB than for those who received them from PB or BM (P = 0.04). The time from diagnosis to allo-HSCT was not different based on the stem cell sources (median CB 3.3 months, PB 3.7 months, and BM 4.1 months; P = 0.31). Patients who developed acute GVHD grade 1/2 had a significantly better prognosis than those with grade 3/4 or without GVHD (P < 0.001). At last follow-up, 42 patients (71%) had died. The most common cause of death was primary disease (62%).

Conclusion: Although patients with ANKL have a poor prognosis, allo-HSCT can induce stable remission even for patients with primary induction failure at HSCT. CB is a good alternative stem cell source, which enables timely allo-HSCT for this rapidly progressive disease.

Keywords: allogeneic stem cell transplant (alloSCT); Epstein-Barr virus (EBV); T-cell lymphoma (TCL).

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UPDATED ANALYSIS OF GENETIC SEQUENCING OF NORTH AMERICAN ATLL

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ATLL (Adult T cell Leukemia Lymphoma) is an aggressive leukemia caused by HTLV-1 virus and is inherently resistant to chemotherapy. A recent whole genome/exome sequencing of 81 Japanese ATL cases identified alterations that overlap with the HTLV1 Tax interactome and are highly enriched for T cell receptor-NF-kB signaling, and T cell trafficking (Kataoka, Nagata et al. 2015). We showed that ATL in Caribbean patients carries a poor prognosis, has distinctive clinical and genomic features with more epigenetic mutations and less TCR mutations when compared to the Japanese cohort (Zell, Assal et al. 2016). Here we report the updated results of 35 patients in the Carribean cohort (Shah U et al, 2018 and additional results).

Targeted exon sequencing was performed on 35 North American ATLL patients and classified by the Shimoyama criteria. 45.7% (n=16) were acute, 42.9% (n=15) were lymphomatous and 11.4% (n=4) were chronic/smoldering ATLL with an average of 4.92 and 3.75 identified mutations per sample in acute and chronic cases respectively. Genes most commonly mutated in North American ATLL were TP53 (8/35, 23%), FAT1 (8/35, 23%), EP300 (7/35, 20%), NOTCH1 (8/35, 23%), APC (5/35, 15%), TBL1XR1 (5/35, 14%). 54% (19/35) of the cases carry mutations in the epigenetic and histone modifying genes, including EP300, TET2, EZH2, MED12, PBRM1, DNMT3A, KMT2A, HIST1H1E, SPEN, IDH1, SMARCB1 and ASXL1. Comparison with the germline profiles demonstrated that the majority of epigenetic and TP53 mutations were somatic in nature while FAT1 alterations originated from the germline. Frequency of TCR pathway mutations was high in the Japanese cohort but was conspicuously low in our cohort (e.g., CARD11 was mutated at 11.4 vs 23.8% in the two cohorts) while tumor suppressor mutations like TP53 were also higher at 23% (vs 13.6% in the Japanese) in our cohort.

In summary, there is a higher rate of epigenetic mutations, lower rate of TCR pathway genes such as CARD11 in our cohort. Some of the differences might be due to the lower percentage of chronic/smoldering cases in our cohort. In the cohort from France, with African and Caribbean patients, 50% of patients had epigenetic mutations, which was considerably higher than the Japanese cohort (22.2%) and similar to our cohort (Marcais et al ASH 2018 abstract 2841). The impact of these epigenetic mutations on the development and clinical characteristics of ATLL merits further investigation and may provide a basis for epigenetic based therapies in ATLL.

Keywords: human T-lymphotropic virus (HTLV); molecular genetics; T-cell lymphoma (TCL).
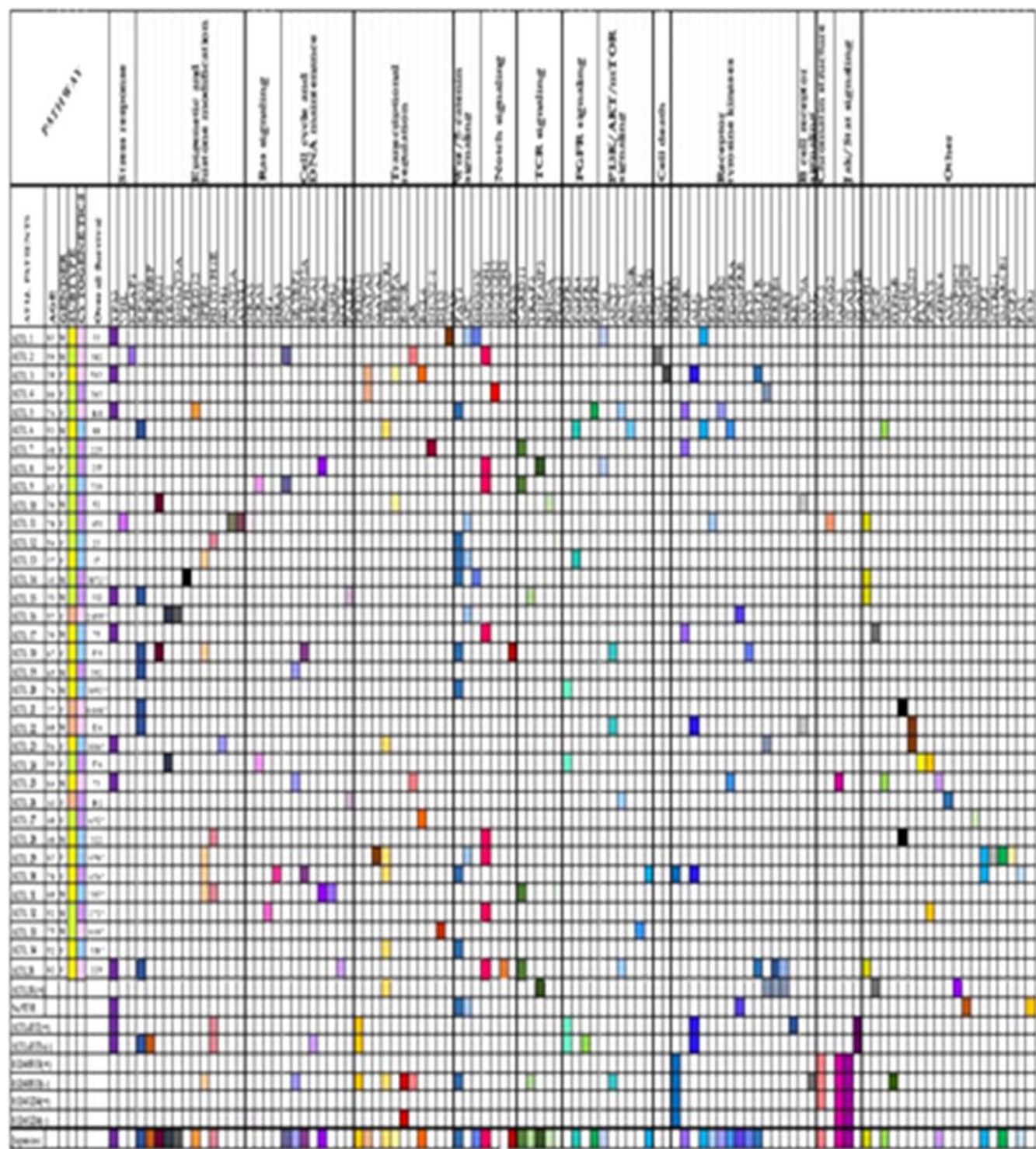
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CLINICAL OUTCOMES OF PATIENTS WITH T-CELL LARGE GRANULAR LYMPHOCYTIC LEUKEMIA (T-LGLL) AT THE OHIO STATE UNIVERSITY JAMES COMPREHENSIVE CANCER CENTER (OSU JAMES-CCC)

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TABLE 1 Patient Characteristics

Characteristic	N=60 (%)
Sex	
Male	29 (48)
Female	31 (52)
Presenting Cytopenia	
Neutropenia (ANC <1500/mm³)	11 (18)
Anemia (HgB <12 g/dL)	17 (28)
Both	13 (22)
Neither[+]	15 (25)
Unknown	4 (7)
LGL Count: CD3CD8+ (at Diagnosis)	N = 52
< 1500	25 (48)
≥ 1500	27 (52)
LDH at Diagnosis (190 = U/L Normal)	N = 50
≤ 190	28 (56)
> 190	22 (44)
Splenomegaly	N=58
Yes	16 (27)
No	42 (43)
Associated Autoimmune Disease	
Rheumatoid Arthritis (RA)	16 (27)
Autoimmune other than RA	6 (10)
None	38 (63)
Additional Hematologic Malignancy[*]	
Pure Red Cell Aplasia	3 (5)
Myelodysplasia	2 (3)
Lymphoma	5 (8)
Evolving Myeloma	1 (2)
1st Line Treatment	
None	11 (18)
Methotrexate	30 (52)
Cyclosporine	8 (13)
Other	10 (17)
2nd Line Treatment	N=24
Cyclophosphamide	10 (42)
Methotrexate	8 (33)
Cyclosporine	3 (13)
Other (Splenectomy, Pentostatin, BNZ-1)	3 (13)
3rd Line or Greater Treatment	N=13
Alemtuzumab	3 (23)
Cyclosporine	3 (23)
Other	7 (54)

*At any time during T-LGL course; +Noted as a lymphocytosis; or incidental

Introduction: T-LGLL is a rare, incurable disorder characterized by clonal proliferation of CD3+CD8+ T-cells that can result in severe neutropenia, anemia and even death. Given the rarity of this disease, there is limited clinical data describing the course of the disease and prognostic factors for survival to guide treatment approaches.

Methods: This study was conducted at the OSU James-CCC with IRB approval. All patients with a diagnosis of T-LGLL at OSU prior to 1 October 2018 were included. T-LGL was defined by 2016 WHO criteria: a monoclonal T-cell receptor and CD3+CD8+ population on flow cytometry of at least 500 cells/mm³. All pathology was reviewed by the investigators. Response rates were determined utilizing the criteria from the ECOG 5998 study. Univariate probabilities of overall survival (OS) were estimated utilizing the Kaplan-Meier method using IBM SPSS v 24.0. The log-rank test was utilized to assess for differences between groups for OS.

Results: 60 patients, with median age of 64 years (range 30-87) were included in the analysis (Table). With a median follow-up time of 28 months, OS at 1, 3, 5, and 10 years was 94%, 82%, 72%, and 66%. There was a trend toward improved 5-year OS in patients with rheumatoid arthritis (RA) vs those without (88% vs 66%; p=0.138). Women had improved OS at 4 years when compared to men (87% vs 66%; p=.081), and there was a trend towards worse OS at 3-years for patients with LDH > 190 U/L (72% vs 86%; p=.139). There was no impact of age, cytopenia, lymphocyte count, concomitant hematologic malignancy or autoimmune disease, degree of anemia or neutropenia at diagnosis on OS.

Eighty-percent (48/60) patients received first line treatment; with 63% receiving methotrexate (MTX). Overall response rate (ORR) to frontline MTX was 37%: 3 CR (10%) 8 PR (27%). Of 43 evaluable patients, the ORR to all frontline therapy was 16/43=37% (30% PR, 7% CR). Twenty-four (40%) of patients received a second line treatment. Ten received cyclophosphamide (Cy), with 8/10 having received prior MTX. The ORR for 6 patients with prior MTX treatment who received Cy was 75%. ORR in 24 evaluable patients for all second line therapies was 54% (9 PR, 4 CR). 13 patients received a third line or greater treatment, with the ORR 54%.

Conclusion: In this large analysis of patients with T-LGLL, we observed impaired long-term survival, with worse OS in patients with high LDH or male sex. ORR to current agents at any stage of treatment is limited, with ORR around 40-50%, highlighting the need for novel therapeutics in this rare disease.

Keywords: T-cell lymphoma (TCL); T-cell receptor (TCR); T-cells.

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THE COMBINATION OF VENETOCLAX AND IBRUTINIB IS EFFECTIVE IN RELAPSED/REFRACTORY T-PROLYMPHOCYTIC LEUKEMIA AND INFLUENCES BCL-2-FAMILY MEMBER DEPENDENCIES

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Introduction: T-cell prolymphocytic leukemia (T-PLL) is a rare and
aggressive T-lymphoid malignancy with poor response to current
treatment strategies associated with short survival. We recently dem-
onstrated single agent activity of venetoclax in relapsed/refractory
(r/r) T-PLL. As a next step, we set out to identify combination partners
of venetoclax to overcome single-agent resistance mechanisms.

Methods: We applied next-generation functional testing of primary T-
PLL cells from seven patients in a combinatorial screen to identify
combination partners for venetoclax with 14 agents including
ibrutinib, idelalisib, 5-azacytidine, 6-mercaptopurine, bendamustine,
bortezomib, and cisplatin. Two late stage r/r-PLL patients were
treated with the best scoring combination. BH3 profiling was per-
formed on patient samples on treatment, and serum levels of drugs
were determined using mass spectrometry.

Results: A pairwise combination screen of venetoclax on primary T-
PLL cells with candidate small molecule inhibitors revealed synergistic
action of venetoclax with ibrutinib, idelalisib, and 5-azacytidine,
whereas cisplatin antagonized the effect of venetoclax across all
patient samples tested. (Fig 1a) Two patients with T-PLL relapsed
after at least two treatment lines including alemtuzumab were treated
with the combination of venetoclax and ibrutinib, resulting in signifi-
cant clinical responses with substantial decreases in leukocytosis,
LDH and B2M, as well as substantial clinical improvement (Fig 1b).
One patient had to stop treatment due to an infectious complication,
andthe response of the second patient is still ongoing. BH3 profiling
indicated that venetoclax serum levels above 1µg/ml enhanced overall
apoptotic priming, and ibrutinib increased cellular dependency on
BCL-2, suggesting a complementary effect of the two drugs
mechanistically.

Conclusion: Our early data suggest the possibility of a benefit to the
venetoclax + ibrutinib combination in r/r-T-PLL. Ibrutinib may
enhance the sensitivity of T-PLL cells to venetoclax by selectively
increased BCL-2 dependency. These results provide the basis for an
upcoming clinical trial testing the efficacy of combination venetoclax
and ibrutinib in a larger cohort of r/r T-PLL patients.

Keywords: apoptosis; BTK inhibitors; T-cell lymphoma (TCL).
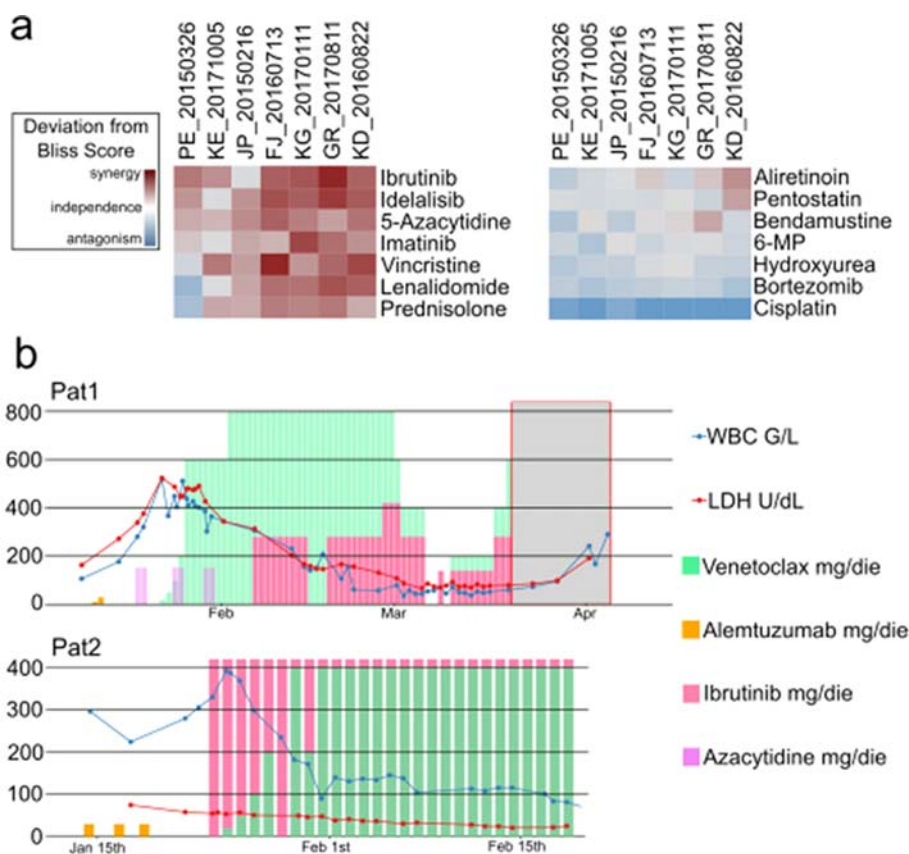
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ADULT T-CELL LEUKEMIA/LYMPHOMA: EPIDEMIOLOGY, CLINICAL FEATURES AND OUTCOME OF A CARIBBEAN COHORT FROM GUADELOUPE

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Introduction: Adult T-cell Leukemia/Lymphoma (ATLL) is a rare mature T-cell malignancy first described in Japan in 1977. The causative agent of ATLL has been identified as the Human T cell Lymphotropic Virus type 1 (HTLV- 1) which is endemic in Japan, Caribbean area, South America and parts of sub-Saharan Africa. ATLL is an unfrequent and subsequently unknown in Europa, in opposite to the French overseas departments of the caribbean area. The aim of this study is to report and describe ATLL in the lesser Antilles at the modern area of zidovudine and interferon treatment.

Methods: We identified ATLL patients diagnosed in our institution between 2014 and 2018. Charts were reviewed to report clinicopathologic features, treatment patterns and outcomes. ATLL diagnosis is based for all patients on the presence of a clonal T cells proliferation along with positivity for HTLV-1 serology.

Results: Among 309 patients positive for HTLV-1 in the 5 years period, 24 developed an ATLL (7.76%). The median age at presentation is 59 years (27-92). The sex ratio M/F was 11/13. Based on the Shimoyama classification, 14 patients (58,9%) had acute subtype, 9 (37,5%) had lymphomatous and 1 (4,1%) chronic disease. 22/24 had lymphadenopathy or deep tumoral syndrom at diagnosis whereas 2 patients presented splenomegaly. LDH was elevated in 23 patients. Hypercalcemia was present in half of the cases. Lymphocytosis was present in 7 patients and typical flower cells in 14 cases. Circulating lymphocyte phenotyping, performed for 19 patients, showed clonal T-cells in 15 cases. Two third of the available karyotype were complex.

Most of the patients (n=22) received first-line treatment, whereas 2 quickly passed away before initiating any specific medication. As first line, 11 patients were treated by zidovudine and pegylated interferon, 10 patients received a polychemotherapy only or associated with zidovudine and peg-interferon and one received steroid only. Among the 15 patients with relapse or refractory diseases, 6 were able to receive a second line treatment. One patient benefits from haploidentical bone marrow transplantation. Five patients are still alive at last follow-up. Among them, 4 are still treated with interferon and zidovudine. Mean overall survival is 10.1 months. Among the 18 death with available data: 10 were related to ATLL progression and 8 to infections or acute respiratory distress syndrome.

Conclusion: We report the first description of ATLL in Guadeloupe island with young patients and dominance of acute and lymphomatous ATLL subtypes. Shimoyama classification requires a very low blood cell count (<1%) for lymphomatous category. Cytologic detection of flower cells needs trained biologists and can be improved by immunophenotyping which might be worthly introduced in this classification. Despite large and early use of zidovudine and interferon, with or without chemotherapy, ATLL remains a very poor prognostic disease. Innovative therapies are still needed.

Keywords: human T-lymphotropic virus (HTLV); interferon (INF); T-cell lymphoma (TCL).

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PUVA AND INTERFERON α2b COMBINED THERAPY FOR PATIENTS WITH MYCOSIS FUNGOIDES: A SEVEN-YEAR RETROSPECTIVE STUDY IN RUSSIA

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Introduction: Cutaneous T-Cell Lymphomas (CTCLs) are characterized by proliferation and accumulation of malignant monoclonal T lymphocytes or Natural Killer cells in the skin, which may also sequentially involve lymph nodes, internal organs and bone marrow. There are still only a limited number of controlled studies to support treatment decisions for MF patients with therapy being frequently determined by institutional experience and availability.

The aim of our survey was to investigate the efficacy and tolerability of combined PUVA and IFN-α2b therapy in patients with different stages of MF, refractory to first line treatment with PUVA.

Methods: We observed 31 patients with MF. The diagnoses were verified with histological, immunohictochemical methods and molecular analysis. The following combined IFN-α2b - PUVA treatment protocol was used: IFN-α2b was administered at a dose of 3 MU three times weekly. The dose was increased according to patient's tolerance up to

6 MU three times weekly. For PUVA therapy, 0.8 mg/kg oral 8-methoxypsoralen was given 1.5 hours before UVA radiation, three times a week with gradually increasing dose of 0.5-1.0 J/cm2 in every 2 sessions starting from a dose of 0.5-2 J/cm2 depending on skin phototype. Treatment toxicity was graded according to World Health Organization (WHO) criteria.

Results: In terms of the stage of the disease, patients were distributed as follows: IB – 3 (10%), IIA – 7 (23%), IIB – 6 (19%), IIIA – 4 (12%), IIIB – 3 (10%), IVA – 3 (10%), IVB – 5 (16%). The mean total IFN-α2b dose was 275 MU (range 171-576 MU). Conversely, the median PUVA sessions for the entire group of patients was 81 with the median joules/cm2 being 177.13 (range 127-204 joules/ cm2) and the median combination treatment period being 189 days (range 133–254 days).

The overall response rate was 93%, including complete response (CR) (73%) and partial response (PR) (20%). CR was found in 100% stage IIB-IIIA group respect 0% in stage IIIB-IV, P<0.05; the CR rate was in line with the mean CR percentage reported in previous studies (76.5%). Patients with early stage disease had a 2-year progression free survival of 100% vs. 82% for the advanced stage group (P<0.001). In our study, combined treatment showed a 2- and 5-year progression free survival (PFS) of 90% and 43%, respectively; obviously, patients with early stage disease had a superior 2-year PFS respect to the advanced stage group (100% vs 82%) (P < 0.001).

Conclusion: IFN-α2b + PUVA combined treatment seemed to be an efficacious therapy option for MF patients refractory to PUVA ± topical corticosteroids, presenting also a convenient tolerability profile, especially in patients with IB-IIB stage. This combined therapy protocol showed to be effective in both early and advanced MF disease stage, even if significantly better outcomes were observed for early stage disease.

Keywords: interferon (INF); mycosis fungoides (MF); phototherapy.

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SURVIVAL AMONG A PATIENT COHORT OF RELAPSED/REFRACTORY MYCOSIS FUNGOIDES IN FRANCE, GERMANY, ITALY, SPAIN AND THE UNITED KINGDOM

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Introduction: Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma (CTCL) wherein those with advanced stage have a poor prognosis, severe skin manifestations, blood and/or lymph node involvement, and compromised survival. The aim of this study was to describe patient clinical characteristics, management and survival in MF patients who were refractory or had relapsed after a first systemic therapy across 5 European countries.

Methods: A retrospective multicenter chart review study was conducted at 19 European sites. Patient data were pseudonymized following both central & local Ethics Committees approval. Inclusion criteria allowed patients to enrol if they had a first diagnosis of MF and proved to be relapsed/refractory (R/R) prior to 1-Jan-2016 after a first course of systemic therapy. Overall survival (OS) was estimated from the date of R/R (defined here as index date) using Kaplan-Meier estimates.

Results: This analysis included 69 R/R MF patients with a median follow-up of 3.9 (range: 0.1-16.9) years from the index date. The median age at index date was 60.0 (range: 22-84) years. After R/R 68 (98.6%) patients received further treatment including systemic therapies in routine practice (91.2%), allogeneic stem-cell transplant (1.5%) and treatment within a clinical trial (7.3%). At treatment initiation following R/R, the majority of patients had advanced stage, i.e. IIB-IVB (64.3%) as per the International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer. At index date 45 patients (66.2%) had one or more new lymphoma lesions, mostly associated with MF subtype but other new subtypes were observed in a small number of patients. The presence of large cell transformation was detected in 12.5% at index date. In total 72.1% of patients became refractory or relapsed again at end of therapy in R/R, with a median time to next R/R of 15.8 (range: 0.6-174.6) months. In total, 27 deaths (39.1%) were observed during the study, with a median age at death of 65 (range: 50-85) years. The majority of patients (74.1%) died from CTCL, CTCL complications, or toxicity from treatment of CTCL. The estimated median OS was 11.5 years (95% CI: 6.5 – not reached [NR]) from time of R/R in this MF population (Figure). There were some differences in trends in OS according to treatment received for R/R, with single and combination chemotherapies having an estimated median OS of 6.5 years (95% CI: 2.25 – NR) compared to NR (95% CI: 12.1 – NR) for the other systemic therapies (i.e. retinoids, methotrexate, interferon and photopheresis).

Conclusions: This analysis from an observational study in treated R/R MF who previously received one systemic therapy estimates median OS at 12 years. The high rate of relapse suggests that the clinical burden of R/R MF is significant in Europe, and in this context recently approved targeted therapies have the potential of improving outcomes

Keywords: chemotherapy; cutaneous T-cell lymphoma (CTCL); mycosis fungoides (MF).
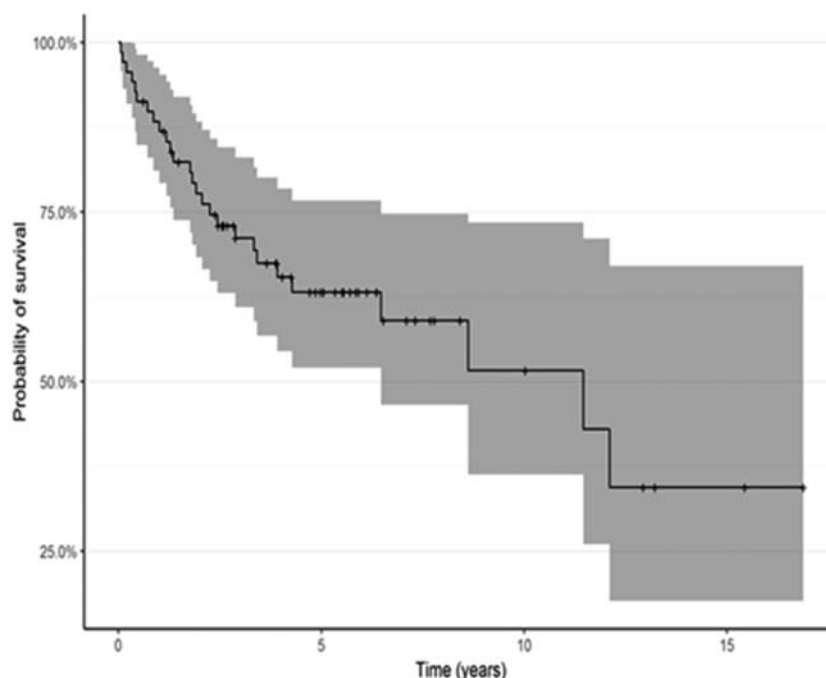
Figure: Kaplan Meier curve for OS from time of R/R

Legend: Grey area represents the 95% CI. + represents censored data

HODGKIN LYMPHOMAS

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TREATMENT PATTERNS, CLINICAL OUTCOMES, AND BIOMARKER EVALUATION IN CLASSICAL HODGKIN LYMPHOMA: A PROSPECTIVE OBSERVATIONAL STUDY IN US ONCOLOGY PRACTICES

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Introduction: Classical Hodgkin lymphoma (cHL) is highly curable with frontline multi-agent chemotherapy (CTx) +/- radiotherapy, but standard-of-care treatment (Tx) for relapsed/refractory (R/R) cHL fails in ~50% of patients (pts). The programmed death-1 (PD-1) inhibitors nivolumab and pembrolizumab have expanded Tx options in cHL. Thus, it would be beneficial to understand current Tx patterns and identify pts who are likely to be refractory to conventional Tx early in the disease course.

Methods: This is an ongoing, prospective, observational study (NCT02856646) at ~80 US oncology practices with a target enrollment of 500 pts and a planned follow-up of ≤ 5 y. Eligible pts were ≥ 18 y with histologically confirmed cHL, beginning any line of Tx. Index therapy was defined as Tx received at or within 2 wk of enrollment. Blood and tissue samples were collected for biomarker analysis, including PD-1 ligand (PD-L1) expression on Hodgkin Reed–Sternberg (HRS) cells/tumor microenvironment (TME), and quantification of CD68+ tumor-associated macrophages.

Results: At data cutoff, 266 pts were enrolled; median (range) age was 38 (18–90) y, 56% were male, and 82% white. In all, 260 (98%) pts received CTx, 5 (2%) immunotherapy (IO), and 1 stem cell transplantation as index Tx. 216 (81%) pts were Tx naive at study enrollment and

Figure. Percentage of PD-L1+ HRS cells (A) and percentage of CD68+ cells (B) by disease stage among pts receiving frontline Tx

CR. Defining predictors of outcomes to conventional Tx and immunotherapies using biomarkers may ultimately result in developing more effective and less toxic Tx algorithms.

Keywords: chemotherapy; Hodgkin lymphoma (HL); nivolumab.

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PRELIMINARY RESULTS OF A QUALITY CONTROL STUDY ON INVOLVED NODE RADIOTHERAPY IN THE EORTC/LYSA/FIL H10 TRIAL ON STAGES I/II HODGKIN LYMPHOMA

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received frontline Tx as index Tx; 50 (19%) pts had R/R disease. Frontline index Tx consisted of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) for 89% of pts; of evaluable pts, complete response (CR) was achieved in 70% and partial response (PR) in 16%. Among pts with R/R cHL, the most common index CTx were ICE (ifosfamide, carboplatin, etoposide; n = 19, 45%) and brentuximab vedotin (n = 15, 36%), and the most common index immunotherapy was nivolumab (n = 4, 80%); of evaluable pts, CR was achieved in 57% and PR in 14%. In total, 15 pts (6%) received IO during the study (as index or non-index Tx). Tx-related adverse events occurred in 83% of all pts, including 5 deaths. Analysis of toxicity patterns is ongoing. Currently, 196 pts have data available for biomarker analyses. Among frontline-treated pts (n = 158), increased CD68+ tumor-associated macrophages in TME correlated with advanced-stage disease ($P < 0.001$); increased PD-L1 expression in HRS cells showed a trend correlating with advanced-stage disease (**Figure**). Pts with CR after frontline Tx tended to have fewer CD68+ cells in the TME, but no difference in the percentage of PD-L1+ HRS cells or tumor-associated immune cells. Enrollment is ongoing and additional outcomes–biomarker association analyses will be presented.

Conclusions: Initial data from this study suggest that up to 30% of pts treated with conventional frontline CTx regimens did not achieve

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Introduction: Recently, the final results of EORTC/LYSA/FIL H10 trial on early Positron Emission Tomography (PET) response–adapted treatment in stage I and II Hodgkin Lymphoma were published. In this trial a new radiotherapy concept was introduced: Involved Node Radiotherapy (INRT). The aim of the current study was to evaluate the quality of INRT in a large multicenter trial in a representative sample of patients.

Methods: Approximately 70% of 1950 patients enrolled in H10 were treated with INRT. The aim of this retrospective and descriptive study was to evaluate INRT in a representative sample (~10% of all irradiated patients). To obtain a representative sample, sampling was stratified by study group, year of treatment, size of treatment center, treatment arm and it was done proportional to the size of the strata. Because of the retrospective data collection difficulties with retrieval of the data was anticipated for 1/3 of the patients. The sample was completed with all patients with known recurrences to enable future evaluation of pattern of relapse in relation to the field. A feasibility questionnaire was mailed to centers from which cases were sampled.

The VODCA (Visualisation and Organisation of Data for Cancer Analysis) software, was used to perform the quality control. Most important items that were scored for each case were radiotherapy principle, delineation and coverage of the target volume and applied technique and -dose. Each case was reviewed by 2 reviewers and in case of disagreement an adjudicator was invited to review the case, in order to come to a conclusion.

Results: The sample consisted of 219 patients. The feasibility questionnaire showed that centers indicated that uploading the data would be possible for 134 cases. Data collection was, however, hampered by changes in radiology and treatment planning systems during the running period of the trial, significantly more than anticipated. Currently, data were retrieved for 52 patients. Preliminary review results are available for 34 patients. All evaluated patients were treated according to the INRT principle. Approximately 80% of cases were treated according to the protocol. Major deviations were mostly caused by definite or likely misses in target volume delineation.

Conclusions: The preliminary results of the current analysis show that principle of INRT was applied to all patients evaluated. Approximately 80% of the patients were treated according to the protocol, which is in line with results from other study groups. In future trials, either prospective quality assurance of radiotherapy will be done or data will be collected prospectively to enable quality control. The preliminary results should be interpreted with caution because of the number of patients evaluated and because of the potential bias as the currently available data may not be representative for all patients irradiated in the H10 trial.

Keywords: Hodgkin lymphoma (HL).

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CLINICAL OUTCOMES ASSOCIATED WITH THE TREATMENT OF NEWLY DIAGNOSED STAGE IV CLASSICAL HODGKIN LYMPHOMA IN PRACTICE SETTINGS IN FRANCE, GERMANY AND THE UNITED KINGDOM

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Introduction: Classical Hodgkin lymphoma (cHL) is a hematologic malignancy with poor prognosis for advanced-stage patients who do not respond well to first line (1L) therapy. 1L treatment patterns for cHL are well-known. However, clinical outcomes associated with 1L treatments in a community setting have not been routinely assessed. This study examines clinical outcomes associated with commonly used 1L systemic regimens used to treat Stage IV cHL in France (FRA), Germany (DE), and the United Kingdom (UK) in a community setting.

Methods: Hematologists and oncologists (N=47) from FRA, DE, and the UK retrospectively identified patients diagnosed with Stage IV cHL and treated with 1L systemic therapy: doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD); doxorubicin, vinblastine, and dacarbazine (AVD); dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP$_{escalated}$); BEACOPP. Descriptive statistics examined patient demographics and 1L systemic regimens. Bivariate analyses (chi-square) compared second line (2L) treatment patterns by 1L systemic regimen. Unadjusted progression-free survival (PFS) was assessed with Kaplan Meier curves and PFS by 1L systemic regimen was compared with a log-rank test. Disease progression was defined as the occurrence of progression, relapse, 2L treatment, or death.

Results: Patients in 1L (N=78) were administered ABVD (57.7%), AVD (10.3%), BEACOPP$_{escalated}$ (24.4%), or BEACOPP (7.6%). Mean (SD) age at initial diagnosis for the aggregate patient sample was 49.5 (16.1) years, which was mostly male (71.8%) and distributed across FRA (30.8%), DE (26.9%), and the UK (42.3%). Outcomes and 2L treatment patterns are presented in **Table 1.** Median follow-up was 25.5 months (range: 14.0-80.3 months). Unadjusted PFS by 1L systemic regimen is presented in **Figure 1.** Median (95% CI) PFS was 32 months (16-43 months) for 1L ABVD patients, 13 months (0-not

TABLE 1 2L treatment patterns and clinical outcomes by 1L systemic regimen

		1L Systemic Regimen			
	Aggregate (N=78)	ABVD (N=45)	AVD (N=8)	BEACOPP (N=6)	BEACOPP escalated (N=19)
Median (95% CI) Unadjusted PFS					
12-Month PFS	69.2% (59.0 - 79.5)	73.3% (60.4 - 86.2)	50.0% (15.3 - 84.7)	66.7% (28.9 - 100)	68.4% (47.5 - 89.3)
24-month PFS	52.4% (40.3 - 64.4)	58.4% (42.6 - 74.2)	16.7% (0.0 - 45.7)	44.4% (0.9 - 88.0)	54.7% (30.9 - 78.6)
2L Treatment Modality					
Systemic therapy only	24.4%	28.9%	25.0%	16.7%	15.8%
ASCT only	0.0%	0.0%	0.0%	0.0%	0.0%
Radiation therapy only	1.3%	2.2%	0.0%	0.0%	0.0%
Radiation therapy only as consolidation for 1L	1.3%	0.0%	0.0%	0.0%	5.3%
Radiation and systemic therapy	5.1%	0.0%	37.5%	16.7%	0.0%
ASCT and systemic therapy	7.7%	6.7%	0.0%	16.7%	10.5%
Radiation, ASCT, and systemic therapy	1.3%	0.0%	0.0%	16.7%	0.0%
No 2L treatment	58.9%	62.2%	37.5%	33.2%	68.4%

Note. No patients were deceased at the time these data were collected. 2L treatment modality differed by 1L systemic regimen in chi-square test, p=0.001. PFS: progression-free survival; CI: confidence interval; 1L: first line therapy; 2L: second line therapy; ASCT stem cell transplant; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD: doxorubicin, vinbalastine, and dacarbazine; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone.

estimable) for 1L AVD patients, not estimable for 1L BEACOPP$_{escalated}$ patients, and 17 months (7-37 months) for 1L BEACOPP patients.

Conclusions: These findings demonstrate that treatment outcomes in the clinical practice setting with commonly used treatment regimens may be different than those observed in clinical trials. These findings underscore the unmet medical need in patients with cHL and the importance of novel treatment regimens.

Keywords: chemotherapy; classical Hodgkin lymphoma (cHL).

Figure 1. Unadjusted PFS by 1L systemic regimen

Product-limit Survival Estimate
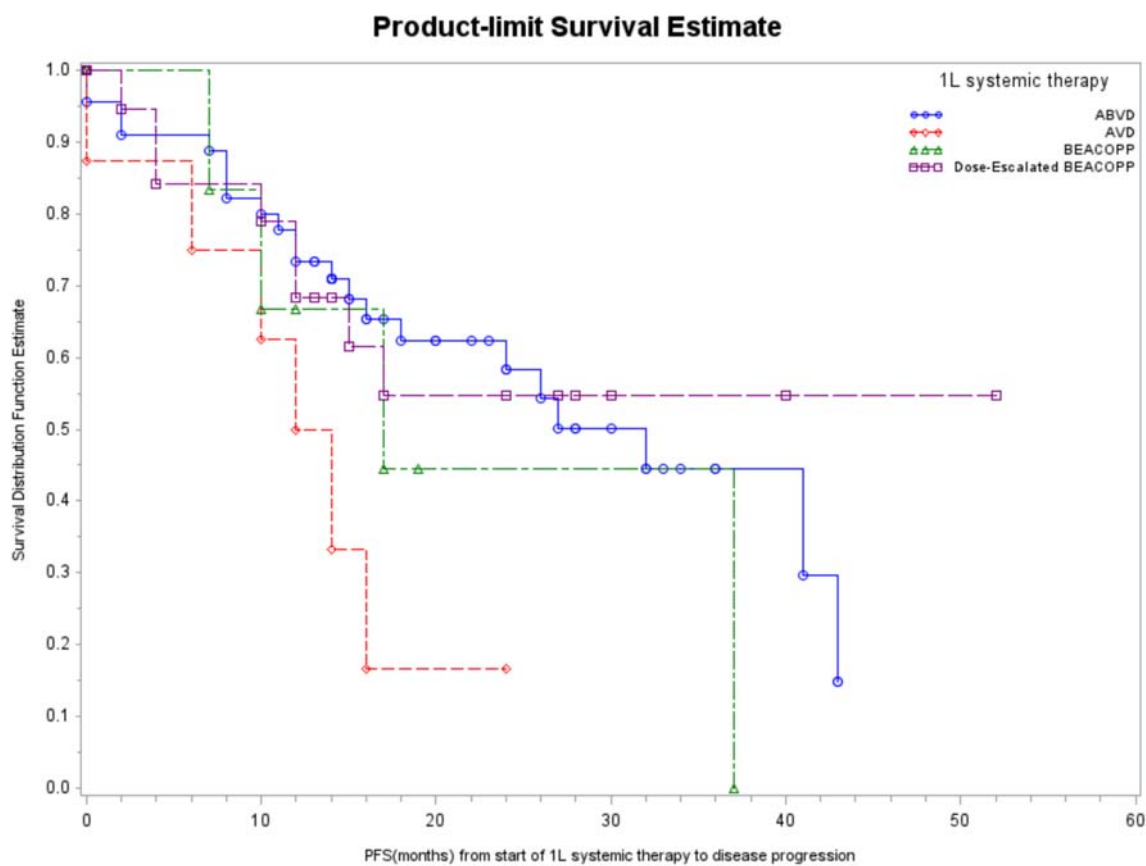
Note. There is no significant difference of Kaplan-Meier survival time among 1L therapy groups, Log-rank p=0.138. PFS: progression-free survival; 1L: first line therapy; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD: doxorubicin, vinblastine, and dacarbazine; BEACOPP: dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone.

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MODIFICATION OF ESCALATED BEACOPP WITH DACARBAZINE / PROCARBAZINE SUBSTITUTION REDUCES RED CELL TRANSFUSION REQUIREMENTS AND MAY SHORTEN TIME TO MENSTRUAL PERIOD RECOVERY

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Introduction: It is increasingly common practice to modify escalated BEACOPP (eBPP) by removing oral procarbazine and replacing with intravenous dacarbazine (250mg/m2 D2-3), hoping to reduce haematopoietic stem cell and gonadal toxicity. However, published data on the so-called 'escalated BEACOPDac (eBPDac)' regimen are limited.
Methods: We collected retrospective data from 14 UK and Ireland centres that offer this protocol for first line advanced stage Hodgkin

Lymphoma, and compared outcomes with matched patients treated with eBPP at 4 UK centres.

Results: From 2009, 103 patients were managed first line with either eBPP (n=51) or eBPDac (n=52) with median follow-up 37 months for eBPP and 10.4 months for eBPDac patients. Patients were well matched with no significant differences in age (median: 25), sex, stage (stage 3/4: 82%) and international prognostic score (IPS3+:71%).

More patients treated with eBPDac received only 4 cycles of treatment (54% vs 10%; p=0.0007) reflecting recent HD18 trial data (1). In total, 74% patients achieved iPET Deauville score 2 or 3 and 98% patients achieved PET negative remission by end of treatment. Of eBPDac patients, 78% achieved iPET Deauville 2 or 3 which was statistically similar to the eBPP cohort (68%; p=0.344) and matched the 76% iPET D2/3 reported in HD18 (1). Of 103 patients, 102 are alive and 99 continue in first remission. Two eBPP patients have relapsed at 13 and 41 months. One eBPDac patient had primary refractory disease and one eBPDac patient died with bowel perforation.

Toxicity was compared over the first 4 cycles. There was no difference in day 8 ALT between the two regimens although the mean day 8 neutrophil count was lower in eBPDac than eBPP patients (1.82 vs 2.35; p=0.056; G-CSF given day 9). There was a trend to fewer non-elective days of in-patient care for eBPDac compared with eBPP (mean: 2.8 vs 6.06; p=0.13), and eBPDac patients received fewer red cell transfusions during cycles 1 to 4 compared with eBPP patients (Mean 2.06 units vs 4.42 units; p=0.0009). Women aged < 35 with > 6 months post chemotherapy follow-up had a similar rate of return of menstrual cycles (eBPP: 20/21; eBPDac: 11/12), although eBPDac patients appeared to restart menstruation earlier post chemotherapy completion (mean: 3.91 months vs 8.65 months, p=0.0002). However, this could also reflect the higher mean chemotherapy cycle number completed by the eBPP women (5.86 vs 4.67; p=0.0005). The use of monthly Goserelin to suppress ovulation varied between centres.

Conclusions: Accepting the limitations of a retrospective study, we suggest that substituting dacarbazine for procarbazine is unlikely to compromise the efficacy of eBPP and may have some toxicity benefits. As it is highly unlikely that this single drug substitution will ever be tested in a prospective trial, publishing real-world data from eBPDac patients is important.

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Keywords: BEACOPP; dacarbazine; Hodgkin lymphoma (HL).

Disclosures: Follows, G: Consultant Advisory Role: *BMS, Takeda, Abbvie, Roche, Janssen, Celgene.* **Osborne, W:** Consultant Advisory Role: *Roche, Takeda, Servier, Gilead, MSD*; Honoraria: *Roche, Takeda, Pfizer*; Other Remuneration: *Novartis.* **Ardeshna, K:** Consultant Advisory Role: *Takeda, Roche, Celgene, ADC therapeutics.* **McKay, P:** Consultant Advisory Role: *BMS, Takeda, Roche, Janssen, Celgene*; Other Remuneration: *Lecture fees, support to attend conferences: Takeda, Janssen, Abvie, Gilead.* **Nagumantry, S:** Honoraria: *Abbvie, Takeda*; Other Remuneration: *Lecturing: Alexion, Takeda.* **Shah, N:** Consultant Advisory Role: *Abbvie, Janssen.* **Uttenthal, B:** Honoraria: *Roche, Takeda, Jazz.*

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UPDATED SAFETY AND EFFICACY RESULTS OF «HLMoscow 1-3» STUDY FOR THE 147 UNTREATED PATIENTS WITH ADVANCED CLASSICAL HODGKIN LYMPHOMA

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Introduction: Standard of care advanced stages classical Hodgkin lymphoma (cHL) remains a problem to the discussion over the past decades. The ABVD is the well tolerant regimen but causes prolonged remissions in approximately 70% of patients. The BEACOPP is effective in more than 85% of patients (pts) but associated with a high frequency of early and late adverse events and toxicity. In order to reduce the long-term effects of treatment, we initiated a protocol «HLMoscow 1-3» based on 8 cycles of the BEACOPP-14. We omitted bleomycin because of pulmonary toxicity, increased the dose of doxorubicin to 50 mg\m2 and reduced the number of cycles from 8 to 6.

Aims: The purpose of our study was to achieve the highest cure rate with the least reduce the early and late toxicity. We aimed to assess the value of early-interim fluorodeoxyglucose (FDG)-PET scan after two cycles of EA(50)COPP-14 as a predictor of treatment outcome in cHL.

Methods: In 2009-2017, 147 pts with advanced stages cHL received treatment in the N.N. Blokhin Cancer Research Center under the protocol «HLMoscow 1-3»: 6 cycles of EA(50)COPP-14 + radiation therapy (RT) for residual mass > 2.5 cm. The median age was 28 years (17-50), 57% were female, B-symptoms were revealed in 69 pts (47%). Consolidation radiotherapy was given to 79 (54%) pts. Interim FDG-PET after 2 cycles (PET2) was performed in 87 (59%) pts. Interim PET images were scored according to the 5-point «Deauville score». Scores ≤3 on the PET2 were considered as negative and scores 4-5 were considered as positive.

Results: The median follow-up was 36 months. The efficacy of the protocol was high, estimated 4-year progression-free survival (PFS) was 86 ±4%, overall survival (OS) – 95 ±2,6%. More than 90% of pts received 6 cycles EA(50)COPP-14 without dose reduction. The most frequent advance events III-IV grades were neutropenia (88%), anemia (24%), infection (27,4%), but thrombocytopenia was rare (3,8%). The second tumors were diagnosed in 3 (2,04%) pts. Complete metabolic response (CMR) after 2 cycles had 74 pts (85%), PET2-positive were 13 (15%). CMR is a powerful prognostic and predictor factor for the favorable outcome of pts with cHL: 4-year PFS was 95 ± 2.5% in PET2-negative and 67 ± 17.1% in PET2-positive patients (p = 0.03).

Conclusions: The intensive EACOPP-14±RT program showed durable and early response with expected and slight toxicity for pts with advanced stage cHL. Interim FDG-PET is a strong and independent predictor of PFS in cHL and may help risk-adapted treatment strategies by selecting pts for less intensive treatment (omitted radiotherapy for PET2-negative pts)

Keywords: BEACOPP; classical Hodgkin lymphoma (cHL).

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POOLED RESULTS OF THREE ANNUAL COHORTS FROM AN OBSERVATIONAL PROSPECTIVE STUDY DESCRIBING BRENTUXIMAB VEDOTIN USE IN ROUTINE PRACTICE IN FRANCE FOR HODGKIN LYMPHOMA: INTERIM ANALYSIS

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Introduction: Use of brentuximab vedotin (BV) in clinical practice has not been widely described as in clinical trial.

Methods: A national observational prospective study designed to evaluate the use of brentuximab vedotin (BV) for the treatment of Hodgkin lymphoma (HL) in routine practice. Patients receiving BV are registered in annual independent cohorts since 2015 and until 2018 at participating centers. We report here the pooled results of the 2015, 2016 and 2017 cohorts. The primary objective was to describe the use of BV therapy outside of clinical trials; Secondary objectives were to report response rate according to Cheson 2007, survival and safety.

Results: From January 2015 to December 2017, 45 sites registered 405 patients of which 396 were evaluable. 265 patients (67%) have been treated for HL, 127 (32 %) for non-Hodgkin lymphoma and 4 for others. HL Patients had been diagnosed at a median of 1 year before BV initiation. They received at any time and modalities chemotherapy for 258 patients (97%), radiotherapy in 58 patients (22%), monoclonal antibodies in 16 patients (6%) and others in 4 patients (1, 5%). For chemotherapy, ABVD was given in 61% of cases and BEACOPPesc in 27% of the cases. The median number of previous treatment lines before BV was 2 (range 0-9): 72 (27%) patients received BV in second line, 131 (49%) in third line and 56 (21%) beyond the third line. Six (2%) unfit patients with comorbidities received BV as part of first-line treatment. At BV initiation, median age was 39 (18-90) years: 62 (23%) patients were ≥ 60 years; 63% were male; Ann Arbor stage was III-IV in 65%; performance status was 0-1 in 89%; and B symptoms were present in 26%. BV was initiated mainly for relapse/progression in 150 (57%) and refractory in 70 (26%) patients.

The main indication for the second line treatment with BV was failure of the frontline treatment (83%), with intent of transplantation after BV in 171 (65%) patients (autologous in 141 patients, allogeneic in 30 patients). BV was used in monotherapy in 34% of HL patients or in combination with chemotherapy in 66% (mainly bendamustine or GVD regimen). The median number of BV cycles was 4 for all HL patients (IQR 3 - 6) and for patients who received BV+chemotherapy (IQR 3 -6). The overall response rate was 59% for all HL patients treated with BV; 115 (43%) patients proceeded to transplantation BV consolidation accounted for 7% of cases 104 of 265 (39%) patients discontinued BV and median time from initiation to discontinuation was 8 months if planned by physicians, 4 months for adverse events, 3 months for autologous transplantation, 4 months for allogeneic transplantation and 4 months if due to progression.

Conclusions: In the pooled data of the 2015, 2016 and 2017 cohorts of a French national observational study, BV was mainly prescribed after a median of 2 previous lines of treatment, often in combination with chemotherapy 66%, for a median of 4 cycles and as a bridge to transplantation in eligible patients.

Keywords: autologous stem cell transplantation (ASCT); brentuximab vedotin; Hodgkin lymphoma (HL).

Disclosures: Sibon, D: Consultant Advisory Role: *Takeda.* **Coulibaly, C:** Employment Leadership Position: *Takeda.* **Casasnovas, O:** Consultant Advisory Role: *Takeda.* **Bouabdallah, R:** Consultant Advisory Role: *Takeda.* **Brice, P:** Consultant Advisory Role: *Takeda.*

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BRENTUXIMAB VEDOTIN SALVAGE FOLLOWED BY CONSOLIDATION POST AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN HIGH RISK RELAPSED REFRACTORY HODGKIN LYMPHOMA

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Introduction: Brentuximab vedotin (Bv) improves PFS post autologous HCT in high risk relapsed/refractory classical Hodgkin Lymphoma (r/r

PFS In Recipients of Bv based Salvage Followed by Post HCT Bv Consolidation

Overall Survival In Recipients of Bv based Salvage Followed by Post HCT Bv Consolidation
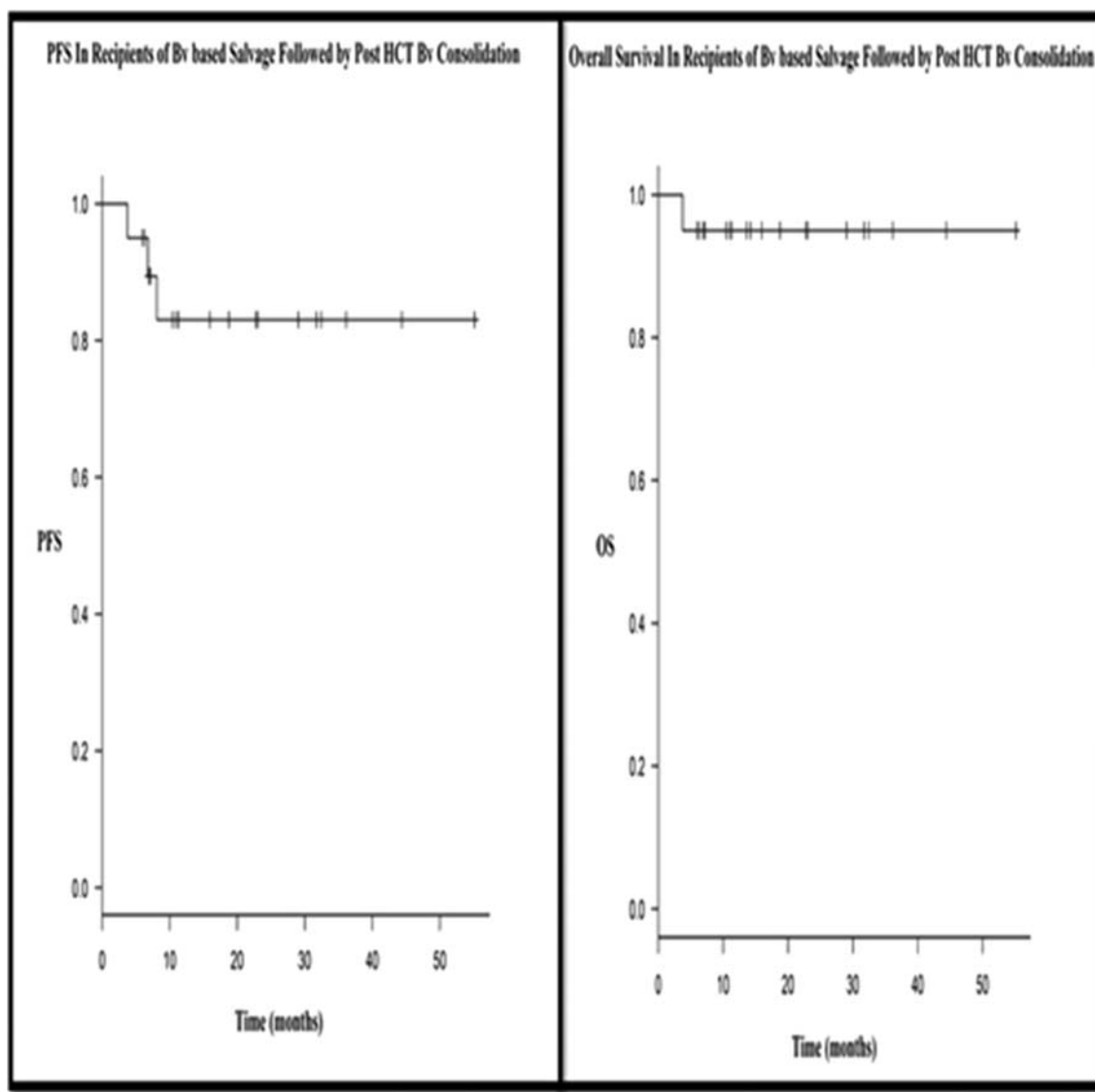
cHL). Furthermore, chemoimmunotherapy salvage with Bv results in a higher rate of complete metabolic response (CMR) compared with chemotherapy alone as shown by multiple groups. Attainment of such CMR status prior to HCT is highly predictive of prolonged remissions.

Aim: To examine the outcome of Bv containing salvage followed by consolidation in high risk r/r cHL. Primary endpoint was overall response rate (ORR) including rate of CMR. Secondary endpoint was 2-year PFS and overall survival (OS).

Methods: Pts with high risk r/r cHL whom were candidates for curative HCT were identified and all records were retrieved retrospectively after IRB approval. High risk r/r cHL was defined as patients with primary refractory disease, relapse within 12 months of front line therapy or relapse with extranodal disease. Patients received Bv with salvage at 1.8 mg/kg on day 1 of each cycle. Post-HCT Bv consolidation was given starting day 30-45 at 1.8 mg/kg every 3 weeks for up to 16 cycles. Response assessment was done in accordance with the Lugano criteria including the definition of CMR as deauville score ≤

3. OS and PFS were computed using Kaplan-Meir method with log ranks test.

Results: A total of 20 patients were identified and all records were retrospectively collected. Baseline characteristics were as follows; 11 (55%) male with median age at HCT of 22 years. 12 (60%) had refractory disease with median time to relapse following front line therapy of 3.7 months. Bv was given with IGEV in 14 (70%), ESHAP in 4 (20%) and Bendamustine in 2 (10%). The ORR was 100% and all patients had evidence of partial response or better. Furthermore,14 (70%) of patients achieved CMR status pre-HCT.

A total of 19 patients were collected during salvage with GCSF while the remaining patient was mobilized with GCSF alone. Median CD34 $x10^6$/kg collected was 12.75 (2.51-42.5) and the median time to ANC and platelet engraftment was 12 (9-15) and 16 (11-20) days, respectively. Post HCT, all patients received Bv consolidation with a median number of doses of 12 (3-16). Observed adverse events on Bv consolidation were; grade 3 neutropenia in 9 (45%) requiring GCSF support

in all and dose reduction in 6 (30%), neuropathy grades 1-3 in 2 patients (15%), 3 (15%) and 1 (5%) leading to early discontinuation of planned consolidation in 4 (20%). Neuropathy resolved or improved in all cases. A total of 2 patients relapsed, both while on Bv consolidation. Median follow up was 15.4 months (3.8-56) with estimated 2-year PFS and OS of 83% and 95%, respectively as shown in table 2 and figure 1 A-B.

Conclusion: Use of Bv containing salvage followed by post-HCT consolidation resulted in excellent outcomes in high risk r/r cHL and did not impact stem cell mobilization. Adverse events were common but manageable. Longer follow up and further validation of these observations are warranted.

Keywords: brentuximab vedotin; classical Hodgkin lymphoma (cHL); Deauville's criteria.

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BRENTUXIMAB VEDOTIN PRIOR TO ALLOGENEIC STEM CELL TRANSPLANTATION IN HODGKIN'S LYMPHOMAS: A RETROSPECTIVE EXPERIENCE BY THE RETE EMATOLOGICA PUGLIESE (REP)

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Allogeneic SCT is an effective treatment modality for HL patients suffering relapse or progression after autologous SCT. However, the success of this treatment modality is largely dependent on the tumour being sensitive to salvage therapy before transplantation This study reports a retrospective multicentre experience of the Rete Ematologica Pugliese (REP) over the past 16 years, aiming to compare the patient characteristics and outcomes of 21 BV pre-treated patients to 51 patients who received reduced-intensity conditioning (RIC) allogeneic SCT without prior BV.

72 patients with cHL who received allogeneic SCT were retrospectively studied. Prior use of BV had no effect on either engraftment or on the incidence and severity of acute graft versus host disease (GVHD). Indeed, there was a lower incidence of chronic GVHD in the BV group, with a 43% cumulative incidence at 3 years versus 47% in the no BV group, although this was not statistically significant.

Despite the low incidence of chronic GVHD, we did not observe a worse survival in the BV-treated group: 3-year progression-free survival (PFS) was 53%, 3-year overall survival (OS) was 62%, 3-year non relapse mortality (NRM) was 19%. In the no-BV group the 3-year PFS was 33%, 3-year OS was 44%, 3-year NRM was 16%.

In patients who were chemorefractory at the time of transplant, we found a statistically significant difference in PFS between the BV and no BV group (51% vs. 10% - p=0.029).

In conclusion, patients allografted for HL after prior exposure to BV do not have a superior outcome after allogeneic SCT. However, chemorefractory patients pretreated with BV prior to transplant have a better survival, implying that BV can improve the outlook after allogeneic SCT. The decrease in chronic GVHD is an interesting finding that needs to be further studied in the allogeneic SCT setting, also for diseases other than HL.

Keywords: allogeneic stem cell transplant (alloSCT); brentuximab vedotin; classical Hodgkin lymphoma (cHL).

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COMBINATION OF NIVOLUMAB AND BENDAMUSTINE IN PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA

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Introduction: Immune checkpoints inhibitors therapy had shown significant activity in patients with relapsed or refractory classical Hodgkin lymphoma (r/r cHL). However, disease relapse or progression is observed in the majority of patients. One potential approach to enhance the effect of anti-PD1 therapy is a combination with chemotherapy. Bendamustine is a bifunctional alkylating agent with antimetabolite properties that had demonstrated activity for the treatment of r/r cHL and therefore may be the candidate drug for a combined regimen.

The aim of this analysis was to evaluate the safety and the efficacy of nivolumab (nivo) and bendamustine (benda) combination in patients with relapsed r/r cHL.

Methods: This analysis included 41 adult patients (26 m/15 f) with a median age of 31 years (21-62). The median number of previous therapy lines was 6 (3-11). Among all patients, 38/41 (93%) had received nivo in monotherapy with the median number of infusions 18 (4-27), and one patient received 12 infusions of pembrolizumab. The previous treatment also included auto-HSCT in 18/41 (44%) of patients, 21/41 (51%) had prior treatment with brentuximab vedotine, 23/41 (56%) had prior treatment with benda. According to LYRIC criteria, the status of the patients at the moment of nivo/benda combination was disease progression (PD) in 54%, indeterminate response (IR) in 27%, stable disease (SD) in 10%, partial response (PR) 10%. Patients were treated in a 28-day cycle for up to 3 cycles. Benda (90 mg/m2) was infused on day 1,2 and nivo (3 mg/kg) on day 1 of the cycle.

Toxicity was graded according to the NCI CTCAE (version 4.03). After treatment completion, the responses were evaluated by PET-CT scan and assessed by investigators using LYRIC criteria.

Results: Median follow-up time was 21 months (range; 4–28) from the start of combined treatment. The objective response rate among all treated patients was 80 % with the 44% CR rate; 5 (12%) patients had an IR and 1 patient - SD. The PD was the best response in 2 patients. Median OS was not reached, 39/41 (95%) of patients were alive at the time of analysis. Median PFS was 10 mo (7-12) with 32% of patients alive and free of disease progression. Twelve patients undergo allo-HSCT. Adverse events (AE) during treatment were observed in 36 (88%) of patients. The most common AE were fatigue (76%), nausea (66%), pruritus (37%), headache (37%). Grade 3-4 adverse events included 2 cases of leucopenia and thrombocytopenia, uveitis, colitis, pneumonia, infusion reaction in 1 case each. All cases of immune related AE resolved completely after treatment with glucocorticosteroids.

Conclusions: This analysis shows that nivo and benda combination have promising activity in the treatment of r/r cHL with a manageable toxicity profile. The combination showed efficacy despite the previous failure of the benda containing regimens or immune checkpoint inhibitors therapy. Nivo/benda combination may be used as the bridge therapy for allo-HSCT in selected patients with r/r cHL.

Keywords: classical Hodgkin lymphoma (cHL); PD-1; salvage treatment.

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RESPONSE TO NIVOLUMAB AS ≥3rd LINE THERAPY IN PTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN'S LYMPHOMA (CHL) AND ITS IMPACT ON QUALITY OF LIFE IN RESPONDERS AND NONRESPONDERS

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The goal of treatment of relapsed/refractory (r/r) cHL is to achieve long-term disease control with limited toxicity and complications of therapy and to improve patients' quality of life (QoL). We aimed to study response rates in pts with r/r cHL receiving nivolumab (Nivo) as ≥3nd treatment and to analyse QoL changes in responders and non-responders.

Pts with r/r cHL who received Nivo 3 mg/kg q2w till disease progression, intolerance/toxicity of Nivo or refusal were included in the study. Treatment response was assessed using CT/PET-CT in accordance with LYRIC criteria for response assessment of malignant lymphomas to immunotherapy. Safety was assessed in accordance with NCI CTCAE v. 4.03. For QoL assessment pts filled out RAND SF-36 and EQ-5D questionnaires, for symptom assessment – CSP-Lym 41-1w questionnaire; the data were analyzed at baseline, at 3 and at 6 mos after Nivo treatment start. Pts who achieved complete/partial response (CR/PR) were considered as responders (Rs), pts with disease progression (DP) – non-responders (nRs). For longitudinal QoL analysis paired t-test, Wilcoxon test and χ2 test were used.

In total, 101 pts cHL were involved in the study: median age – 31 y.o., range 19-62, 52% males. All the pts received 2-10 previous treatment lines; 90 out of 101 pts received Nivo as part of a named patient program. At the time of diagnosis 63.4% pts had advanced stage (III–IV), 61.4% - primary chemotherapy resistance. Median follow-up – 25 mos (3-31). Adverse events (AEs) were reported in 87.1% pts (severe AEs of 3-4 grades –18.8%). At 3 mos of treatment response was registered in 51%pts (20.5% – CR, 30.8% – PR); 45% pts progressed and 4% had disease stabilization. Rs and nRs groups were similar by age and gender (p>0.05). Baseline QoL was dramatically worsened for all SF-36 scales in both groups. All the pts experienced symptoms before Nivo treatment start; >50% pts had moderate-to-severe symptoms. During 6 mos of Nivo treatment significant QoL improvement by almost all SF-36 scales was revealed both in Rs and nRs (p<0.05). Positive QoL changes were more pronounced in Rs, however QoL scales improved significantly in nRs as well. EQ VAS significantly improved during treatment in both groups: 59.5 before treatment vs 81.1 at 6 mos in Rs, 57.4 vs 76.2 in nRs, consequently (p≤0.001). The severity of the vast majority of symptoms (28/41) significantly decreased during 6 mos of treatment both in Rs and in nRs (p<0.05).

The results obtained in this observational study demonstrate that r/r cHL pts exhibit good response and tolerability to Nivo as monotherapy as well as experience dramatic QoL improvement and significant decrease of symptom burden. Nivo treatment is accompanied with QoL improvement and decrease of symptom burden both in responders and non-responders.

Keywords: Hodgkin lymphoma (HL); nivolumab.

Disclosures: Ionova, T: Research Funding: *Principal Investigator BMS study.*

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REAL-WORLD HEALTHCARE RESOURCE UTILIZATION (HRU) OF CLASSICAL HODGKIN LYMPHOMA (cHL) PATIENTS (PTS) TREATED WITH ANTI-PD1 CHECKPOINT INHIBITORS IN THE UNITED STATES (US)

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Introduction: cHL pts with relapsed/refractory (RR) disease who relapse after or are ineligible for autologous stem cell transplantation have a poor prognosis. Recently, the anti-PD1 monoclonal antibodies nivolumab (nivo) and pembrolizumab (pembro) were approved by the FDA (May 2016 and March 2017, respectively) as treatment options for RR cHL pts.

Objective: This study aims to describe real-world patient characteristics and HRU (hospitalizations and outpatient [OP] visits) among pts with RR cHL receiving pembro or nivo in the US.

Methods: A retrospective database analysis was conducted using Symphony Health's Patient Integrated Dataverse® (07/2014–06/2018). The date of the first dispensing or administration of pembro or nivo was termed the index date. Pts with ≥12 months of clinical activity prior to the index date, ≥1 hospitalization or ≥2 OP encounters with an ICD-9/10-CM diagnosis of cHL prior to the index date, no diagnosis of nodular lymphocyte-predominant HL, and ≥18 years of age were included. Baseline characteristics were assessed in the 12 months prior to the index date. HRU was evaluated over the follow-up period, from the index date to the end of clinical activity or data availability. Crude rates of hospitalizations and OP visits were expressed as rate per person per year (PPPY) to account for varying durations of observation across pts. Mean and median hospital length of stay (LOS) were reported.

Results: Among cHL pts, 92 received pembro and 225 received nivo. The mean age was 59 and 53 years among those treated with pembro and nivo, of whom 40% and 44% were female, respectively. Corresponding median (IQR) follow-up periods were 214 (92–325) and 249 (126–443) days. Mean baseline Quan-Charlson comorbidity index score for pembro and nivo pts was 4.9 and 4.0; 18% and 14% had depressive disorders, and 16% and 8% had substance-related/addictive disorders, respectively. Of pembro pts, 7% had received nivo and 26% brentuximab vedotin (BV). Of nivo pts, none had received pembro, 40% BV, and 2% ibrutinib. Pembro and nivo pts had an average of 1.5 and 1.4 all-cause hospitalizations during the baseline period, respectively, while the corresponding rate of all-cause hospitalizations during follow-up was 0.9 and 1.3 PPPY with an associated mean [median] LOS of 3.1 [1.5] and 4.2 [2] days (Figure). The rate of all-cause OP visits during follow-up was 36.4 and 35.5 PPPY for pembro and nivo pts, respectively. The rate of cHL-related hospitalizations during follow-up was 0.1 and 0.4 PPPY for pembro and nivo pts, respectively, with an associated mean [median] LOS of 4.7 [1] and 7.4 [4] days.

Figure. Hospitalizations During Follow-up in cHL Patients Receiving Pembrolizumab or Nivolumab
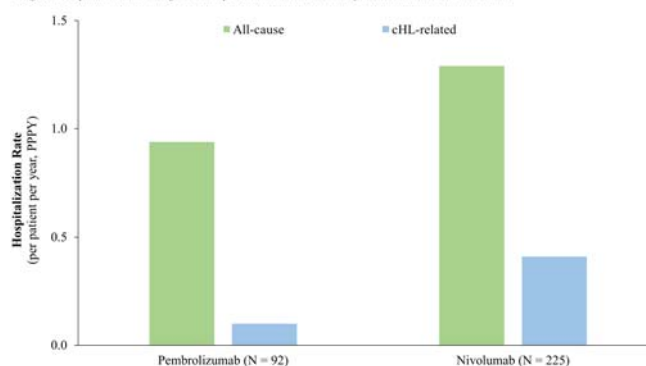
Conclusion: This real-world descriptive study attempts to provide an early assessment of pembro and nivo user profiles and HRU since their market approval in the US. cHL pts treated with pembro are found to be older at treatment initiation, with greater comorbidity burden and baseline hospitalization rates than the nivo group.

Keywords: classical Hodgkin lymphoma (cHL); nivolumab; Pembrolizumab.

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RETREATMENT WITH NIVOLUMAB IN PATIENTS WITH R/R CLASSICAL HODGKIN LYMPHOMA AFTER DISCONTINUATION OF THE THERAPY WITH IMMUNE CHECKPOINT INHIBITORS

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Introduction: Immune checkpoint inhibitors (ICI) may allow to achieve a durable remission in patients with resistant or refractory (r/r) classical Hodgkin lymphoma. The population of patients who discontinued therapy due to various causes is increasing. In case of relapse after

the ICI treatment the optimal treatment is not yet defined. One of the possible options is the retreatment of the patient with ICI. To date there is lack of information regarding the retreatment of patients with relapse after ICI cessation. Our aim was to determine the effectiveness of nivolumab therapy in patients with r/r Hodgkin lymphoma with relapse of disease after achievement of complete remission with ICI and cessation of therapy.

Methods: This analysis included 20 patients (5 male/15 female) with median age 32 (20-47) years with r/r classical Hodgkin lymphoma who were treated with nivolumab (3 mg/kg every 14 days) and achieved CR. After nivolumab therapy was stopped the patients received no other treatment before the disease progression. Response was assessed by positron-emission tomography/computed tomography (PET/CT) using LYRIC criteria every 3 month. After relapse of disease the patients were retreated with nivolumab monotherapy or in combination with chemotherapy. Median follow-up after the retreatment initiation was 10 (6-14) months.

Results: In 20 patients previously treated with nivolumab the median number of cycles was 25 (18-30). CR was achieved after median of 6 (6-18) cycles. The median duration of therapy after CR achievement was 7 (1-15) months. Median follow-up after therapy discontinuation was 23 (13-24) months. At the time of analysis, all patients were alive. Eight (40%) out of 20 patients relapsed after therapy discontinuation. In 4 out of 8 patients relapse was confirmed by biopsy. Median time before the relapse was 11 (5-20) month. All patients had undergone the retreatment with nivolumab: 7 were treated with monotherapy and 1- in combination with chemotherapy. Doses of nivolumab were 3 mg/kg in 5 patients, 1,5; 1,0 and 0,5 mg/kg in one patient each. Six patients were evaluated for response: CR (n=3), PR (n=1), indeterminate response type 2 (n=2). The best response was achieved after median of 6 (6-12) cycles.

It is worth noting that 3 patients had adverse events after retreatment with nivolumab. Two of these patients did not have any complications during initial nivolumab treatment. Adverse events included pyrexia, thrombocytopenia and pneumonitis. In last case therapy was discontinued before resolution of complication, but the patient achieved the complete remission before therapy cessation.

Conclusions. This analysis demonstrates that patients with relapse after nivolumab discontinuation sustained sensitivity to nivolumab and achieved a response during retreatment with nivolumab monotherapy or with chemotherapy combination. Further research is needed to determine response rate and durability of response.

Keywords: classical Hodgkin lymphoma (cHL); nivolumab; PD-1.

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RETROSPECTIVE COHORT STUDY TO ASSESS THE PROGNOSTIC VALUE OF BASELINE NECROSIS ON PET-CT IMAGING IN HODGKIN LYMPHOMA

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Background: Identifying prognostic markers at diagnosis is essential to determine optimal tailored therapy for patients. The presence of necrosis has been shown to be associated with inferior outcomes in patients with diffuse large B cell lymphoma. This retrospective cohort study assesses whether necrosis at baseline correlates with clinical outcomes in patients with Hodgkin lymphoma.

Methods: All available baseline PET-CT scans of patients diagnosed with Hodgkin lymphoma between January 2015 and December 2016 at a large UK teaching hospital were reviewed for evidence of tumour necrosis by a consultant radionuclide radiologist with a specialist interest in lymphoma. Potential necrosis identified on PET-CT was then confirmed visually and quantitatively on alternative imaging. The presence or absence of necrosis was correlated with prognostic markers (Total Metabolic Volume (TMV), Total Lesion Glycolysis (TLG) International Prognostic Index (IPI) (Hasenclever Index)) and response assessment (metabolic response, current remission status, relapse outcome and mortality).

Results: Fifty three patients' PET-CT scans were reviewed in total. Ten patients were confirmed to have necrosis on both PET-CT and alternative imaging. The presence of necrosis was associated with increased total mortality (40%) vs no necrosis (16%); Kaplan Meier survival analysis demonstrated a significant difference between the necrosis cohort compared with the no necrosis cohort using the log rank test (p = 0.042). The presence of necrosis did not correlate with other prognostic markers (TMV, TLG or IPI).

Conclusion: The presence of necrosis on baseline PET-CT scan in patients receiving frontline treatment for Hodgkin lymphoma significantly correlates with increased patient mortality. Tumour necrosis did not significantly correlate with other prognostic markers. Identifying high risk patients at diagnosis is important. The current UK practice of delivering more intensive frontline therapy to patients with a high IPI is suboptimal and intensifying treatment after a positive interim PET scan is also associated with poor outcomes. Robust prognostic markers at diagnosis are a priority for the management of patients with Hodgkin Lymphoma. This study has identified a new independent prognostic marker in Hodgkin Lymphoma and prospective clinical trials are required.

Keywords: Hodgkin lymphoma (HL); positron emission tomography (PET).

Disclosures: Osborne, W: Consultant Advisory Role: *Roche, Takeda, Servier, Gilead, MSD*; Honoraria: *Roche, Takeda, Pfizer*; Other Remuneration: *Novartis.* **Petrides, G:** Honoraria: *Takeda and GE Healthcare.*

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PROGNOSTIC VALUE OF PRE-TRANSPLANT PET/CT IN HODGKIN LYMPHOMA

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Background and aim: Autologous stem cell transplant (ASCT) is the standard of treatment in patients with refractory/relapsed Hodgkin lymphoma (HL). Several adverse prognostic factors at relapse are known (stage, anaemia, B signs, Karnofsky score, early relapse etc.) to predict the outcome after ASCT. We analyzed the prognostic value of pre- transplant PET/CT retrospectively.

Methods: Between January 1, 2007 and December 31, 2018 pre-transplantation [18]FDG-PET/CT scans of Hodgkin-lymphoma patients were performed. Deauville criteria were used for evaluation of PET/CT scans. Positive PET scans were defined, if Deauville score was 4 or 5. We analyzed the effect of PET/CT results for survival (overall-, relapse- and event free), and investigated differences between PET positive and PET negative groups. Statistical analysis was performed using IBM SPSS 25 programme.

Results: Sixty-two Hodgkin-lymphoma patients (33 men and 29 women) had PET/CT scan before AHSCT. Median age at the time of AHSCT was 35 (19-65) years. Median follow up time was 55.4 (0-175) months. There were 49 (79%) PET negative and 13 (21%) PET positive patients. Five-year overall survival rate was 80% in PET-group, and 46.2 % in PET+ group (p<0.042). Five-year relapse-free and event-free survival rate for negative and positive groups were 85.5% and 43.5% (p<0.012), and 70.3% and 30.8% (p<0.006). There were 6 relapse and 9 deaths (3 due to HL) in PET- group, and 5 relapse and 6 deaths (due to HL) in PET+ group. Twenty-five of 49 patients in the PET- group got only one type of salvage treatment (DHAP) before AHSCT, against 2 of 13 patients in PET+ group (p=0.046). Patients who acquired PET negative status after DHAP therapy only, had no relapse. Patients who were treated with 2 or more lines of salvage therapy and acquired PET negative status after these treatments, has no significantly better relapse-free survival, than patients who remained PET positive.

Conclusion: Clinical routine use of PET/CT before AHSCT is highly suggested based on our investigation. PET- patients have significantly better OS, PFS and EFS. PET negative status attends better prognosis, if it is reached with first salvage treatment.

Keywords: autologous stem cell transplantation (ASCT); Hodgkin lymphoma (HL); positron emission tomography (PET).

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MORBIDITY AND MORTALITY IN LONG-TERM SURVIVORS OF HODGKIN LYMPHOMA: A SINGLE CENTER EXPERIENCE

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Since the introduction of modern radiotherapy and combination chemotherapy, Hodgkin lymphoma (HL) has become a highly curable malignancy with 5-year survival rates of more than 80%. However, the life expectancy and quality of life of HL survivors are reduced by the occurrence of late adverse treatment effects.

This retrospective study was focused on 96 patients with newly diagnosed HL treated at the University Hospital of Bari (Italy) between 2005 and 2008.

Median age at diagnosis was 35 years (range 15-83), 33 pts (34%) presented advanced stage (III-IV), 43 (45%) bulky disease, 45 (47%) presented B symptoms, 26 (27%) extranodal disease.

First line chemotherapy was ABVD in all the patients. The median number of chemotherapy lines was 1 (1-5), 49 patients (51%) had undergone radiotherapy

At the end of treatment, 75 patients (78%) were in CR, and 24 patients (25%) in PR; 18 patients (24%) relapsed after a median follow-up of 54 months (range: 12 – 62 months); 20 (21%) underwent autologous hematopoietic stem cells transplantation, 3 (3%) allogeneic stem cell transplantation.

After a median follow-up of 12 years, 83 patients (86%) remain alive and 13 (14%) have died (4 of A second neoplasia, 1 of infection, 8 of the disease). The 10-year Kaplan-Meier survival estimates were 84%. Three women were pregnant and 3 healthy children were born. The most prevalent chronic conditions At last follow-up were: overweight/obesity (65%), elevated fasting glucose (38%), high total cholesterol (34%), and hypertension (25%).

Results of this study offer indications about how long after the initial treatment the excess deaths from causes other than Hodgkin's disease begin to occur. However, challenges remain in establishing the optimal time to begin screening for potential late complications and in developing better surveillance guidelines. Further work is also needed to identify risk factors that may predict specific late effects.

Keywords: Hodgkin lymphoma (HL).

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COGNITIVE IMPAIRMENT AFTER 6 AND 12 MONTHS OF HODGKIN LYMPHOMA TREATMENT

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Introduction: Chemotherapy-related cognitive impairment (CRCI) occurs after chemotherapy and other cancer treatments in 17-75% of patients in all age groups and with various malignancies and significantly worsens their quality of life. Certain drugs, such as bleomycin, penetrating the blood-brain barrier may have direct toxic effects on the brain and its functions. The aim of the study is to elucidate the influence of Hodgkin lymphoma and its treatment on neurocognitive performance (sustained attention, short-term, long-term memory and working memory, verbal and cognitive fluency).

Methods: Overall 28 pts (46% female) were tested: mean age of 36,5 years and mean years of education of 14,1. Pts received 2 cycles of ABVD + 20GyISRT (initial stages), 2 cycles of BEACOPP escalated combined with 2 cycles of ABVD +30Gy ISRT (intermediate stages) and 6 cycles of BEACOPP escalated ± 30GyRT (advanced stages).

Cognitive functions were evaluated by neurocognitive testing battery covering all domains of the International Cognition and Cancer Task Force (ICCTF; Wefel et al., 2011) recommendations for cancer patients: the Hopkins verbal learning test revised, the trail making test A-B, Stroop test, Controlled oral word association, Verbal fluency task, Rey-Osterrieth complex figure, and WAIS-III (Digit span, Comprehension, Picture arrangement, Digit symbol - coding, Logical memory, Letter-number sequencing test) and Continous Performance Test (CPT). The data were collected before treatment, 6 and 12 months after the initiation of the first-line treatment.

Results: Statistical analyses looked at the cognitive performance measured with neurocognitive testing battery covering all domains of the International Cognition and Cancer Task Force (ICCTF; Wefel et al., 2011) recommendations for cancer patients. The results show that in the majority of the test methods, the performance of the repeated measurements was improved in patients with Hodgkin lymphoma. These findings could be interpreted as a practice effect. However, the prolongation of reaction time in CPT after 6 months of treatment did not improve during 6 months period after chemotherapy (1 year after diagnosis). [HJ1]

Conclusion: Our data indicate that a) the reaction time could represent the most sensitive domain within chemotherapy-related cognitive impairment, and b) this parameter does not normalize during 6 month post-chemotherapy period.

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IMPACT OF AUTOIMMUNE CYTOPENIAS ON THE CLINICAL COURSE AND SURVIVAL OF HODGKIN LYMPHOMA

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Background: Autoimmune cytopenias (AICP), namely autoimmune hemolytic anemia (AIHA) and autoimmune thrombocytopenia (AITP) often complicate the course of malignant lymphomas. The incidence and clinical significance of AICPs associated with Hodgkin lymphoma (HL) have not been thoroughly defined. Our aim was to retrospectively assess the incidence, clinical features and response to treatment of HL-associated autoimmune phenomena.

Methods: Five hundred and sixty-five HL patients were diagnosed and treated at the University of Debrecen between 1990 and 2017. We compared the clinicopathological characteristics of HL patients developing AICPs with those who had no clinical evidence of autoimmune events. We considered an AICP to be a disease-defining event if it led to diagnosis or revealed disease progression, relapse or secondary malignancy. Statistical analysis was performed using Fisher's exact test.

Results: We identified 8 cases of AIHA and 8 cases of AITP among 14 patients altogether, one of them presented with Evans syndrome. Two AICPs preceded the diagnosis of HL, 2 of them developed simultaneously with the disease and 11 AICPs occurred during follow-up after first line therapy. During more than 5000 person-years of follow-up, the incidence of AICPs in HL patients was 2,8%. Eighty-one percent of AICPs required treatment, 77% of these patients responded well to intravenous steroid. Treatment of the underlying lymphoma with ABVD combination chemotherapy resulted in the effective control of both the underlying disease and the immune condition, in most cases, where AICPs were identified at the presentation of HL. Almost half of the AICPs (46%) were disease-defining events: 5 cases led to the diagnosis of HL or indicated relapse and 2 events revealed secondary malignancies. AICPs were more frequently observed in patients with advanced stage disease at initial diagnosis (p<0.004). The association of HL and AICPs had no effect on long-term overall- (OS) and progression-free survival, however, short-term (1 year) mortality of HL patients experiencing AICPs was significantly elevated (p<0.022) compared to the majority of patients, who did not have AICPs. Also, the OS rate of HL patients with AICPs at initial diagnosis was significantly lower (p=0.033) compared to patients developing AICPs during follow-up.

Conclusions: While AICPs are rare complications of HL, these events can imply clinical significance. Those HL patients who experienced AICPs had a particular disease-related profile. These cytopenias show a good response to steroid treatment. This large series of consecutive, unselected patients demonstrate that the association of HL and AICPs may increase short-term mortality. Our results emphasize the importance of taking into consideration the possibility of an underlying hematological malignancy in newly diagnosed AIHA/AITP cases.

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RELAPSED AND REFRACTORY NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA (NLPHL): A US ANALYSIS FROM MD ANDERSON CANCER CENTER

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Introduction: The clinical course and optimal treatment of patients with relapsed or refractory NLPHL is not clearly defined.

Methods: We retrospectively analyzed the characteristics and outcomes of patients with relapsed or refractory NLPHL, without histological evidence of transformation at time of first relapse, followed at MDACC between 12/1972 and 12/2018.

Results: Forty patients were included in the analysis. At time of initial diagnosis, median age was 34 (range, 15-85), 27 (67%) were male, and 20 (50%) had advanced stage. Frontline regimen consisted of chemotherapy (variably combined with rituximab and/or radiotherapy [XRT]) in 24 (60%) patients (ABVD in 16 patients, CHOP in 6 patients, and NOVP in 2 patients), rituximab (with or without XRT) in 4 (10%) and XRT in 12 (30%). Two (5%) patients were primary refractory, 9 (23%) relapsed within 1 year, and median PFS after frontline treatment (PFS-1) was 45 months (95% CI, 5-85 months).

Thirty-nine patients received 2nd line therapy (and 1 was observed): chemotherapy in 16 (40%) patients (including ABVD in 4, CHOP in 8, and ICE in 4, variably combined with rituximab), biological therapy in 14 (35%)(including rituximab in 11, brentuximab vedotin in 2 and lenalidomide in 1), XRT in 6 (15%), and high-dose chemotherapy followed by autologous stem cell transplant (ASCT) in 3 (8%). The median PFS after 2nd line therapy (PFS-2) was 85 months (95% CI, 1-218 months) with 15 (38%) patients relapsing or progressing. No difference in PFS-2 was observed based on treatment type (p=0.49) (Figure), but a trend for longer PFS-2 was observed for those receiving biological therapy (p=0.13).

Subsequent relapse/progression was observed in 10/15 (67%) patients receiving 3rd line therapy, 2/10 (20%) patients receiving 4th line therapy, both patients receiving 5th line therapy, and 1/2 patients receiving 6th line therapy. Median number of relapses/progressions was 1 (range, 1-5): 1 in 24 patients, 2 in 6 patients, and $\geq$3 in 10 patients.

Four (10%) patients transformed (after a median of 69 months) and 6 (15%) received ASCT. A significantly higher transformation rate was observed among patients treated with 2nd line chemotherapy (21% vs 0, p=0.02) and those receiving ASCT (50% vs 3%, p=0.008).
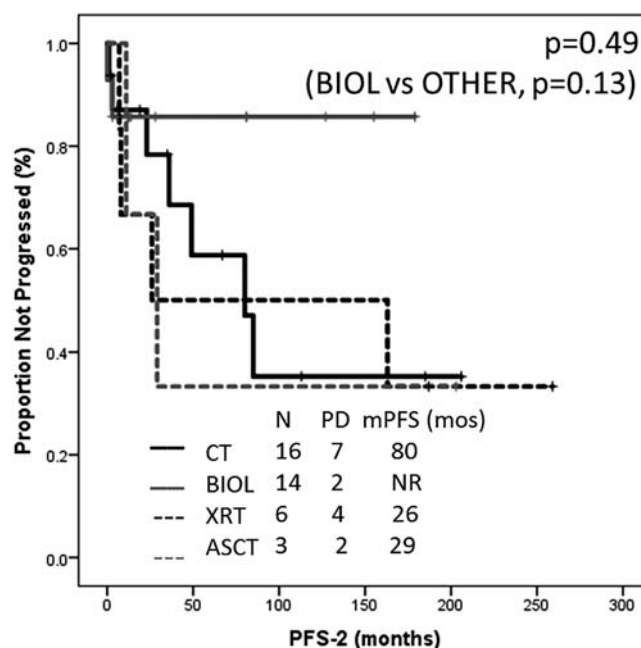
After a median follow up from time of first relapse/progression of 44 months (95% CI, 22-67 months), 5 (13%) patients died (3 of disease progression, 1 of ASCT-related infection), median OS-2 was not reached, and 5-year OS-2 was 88%. On univariate analysis, the only factor associated with longer OS-2 was absence of transformation (not reached vs 90 months, p=0.002); a trend for longer OS-2 was observed for patients relapsing beyond 1 year of frontline therapy (p=0.18) and patients not receiving ASCT (p=0.11).

Conclusions: Patients with relapsed or refractory NLPHL have overall a good prognosis and may not need aggressive treatment.

Keywords: nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL); salvage treatment.

IMMUNOTHERAPY

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CASE SERIES OF NIVOLUMAB TREATMENT IN PATIENTS WITH RELAPSED/REFRACTORY HIV-RELATED LYMPHOMAS

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Table 1.

Pts	Ds	Age	HIV load	CD4+ cells/mcl	cART	Nivo	N of nivo	Response	Followed therapy	Outcome	Follow up
1	HL	33	<40	140	+	mono 40 [1]	10	CR	Auto-HSCT	Remission;	Alive; 499 days
2	HL	41	<40	45	+	BeGe	12	PR	Continued	Relapse; 485 days	Alive; 506 days
3	HL	36	<40	362	+	mono 40 [1]	10	PR	Continued	Remission;	Alive; 528 days
4	HL	40	<40	490	+	BeGe	7	CR	Auto-HSCT	Remission;	Alive; 427 days
5	DLBCL	33	3381	410	-	BeGeR [2]	2	PD	-	Progression;	Died; 45 days
6	DLBCL	38	<40	473	+	BeGeR [2]	7	CR	Auto-HSCT	Relapse; 266 days	Alive; 397 days
7	PBL	37	<40	340	+	IGB	2	PR	Continued	Remission (clinical)	Alive, 27 days

Pts – patients, Ds – diagnose, HL – Hodgkin lymphoma, DLBCL – diffuse large B-cell lymphoma, PBL- plasmablastic lymphoma, BeGeR – bendamustine, gemcitabine, rituximab, IGB - ifosfamide, gemcitabine, bortezomib; Nivo – nivolumab, CR – complete remission, PR – partial remission, PD – progression disease, auto-HSCT – autologous hematopoietic stem cell transplantation

Introduction: Nivolumab (nivo) is a salvage option in relapsed/refractory (r/r) HL and NHL. Patients with HIV-related lymphoma may benefit not only anticancer activity of nivo, but also from its potential anti-HIV effect [1]. Just a few cases of HIV-related lymphoma treated with nivo were reported [2,3]. We describe a case series of r/r HIV-related lymphoma receiving nivo in Raisa Gorbacheva Institute of Children Oncology, Hematology and Transplantation (CIC 725).

Materials and methods: Seven male patients with r/r HIV-related lymphoma were treated with nivo in 2017-2019. The primary end point was response to therapy. Secondary end points were toxicity, relapse incidence and overall survival (OS) at 12 months after first nivo infusion. CTCAE v4.03 for the toxicity analyse and immune-related adverse effects have been used. LYRIC criteria for assessing FDG-PET/CT were applied.

Results: The underlying diseases of observed patients were: HL n=4 (57%), diffuse large B-cell lymphoma (DLBCL) n=2 (28,6%) and one with plasmablastic lymphoma (PBL). Median number of prior lines of therapy was 2 (range, 2-3). Relapse after ASCT was treated in one patient. Four patients received nivo as a bridge to ASCT; two patients didn't proceed to ASCT. Two patients received nivo as monotherapy, 4 patients in combination with bendamustine and gemcitabine, one in combination with ifosfamide, gemcitabine and bortezomib. The median dose of nivo was 1 mg/kg (range, 0,5-1,5 mg/kg), number of nivo doses – 7 (range, 2-12). The median number of CD4+ was 382 c/mcl (range, 45-490); 86% patients were on cART. Only 5 patients were available for estimating response, one – died before PET/CT was performed from the progression of the diseases, one just has started therapy (clinical response). Overall response rate was 83,3%. Two – partial remission by PET/CT, three (60%) patients had complete metabolic responses. Severe toxicity according to CTCAE of nivo and an immune-related adverse effect was not registered. Relapse of the underlying disease was diagnosed in 2 patients, time to progression were 485 and 266 days. OS at 12 months for the patients with HIV from the time of using nivo was 85,7%. Patient who didn't receive cART died from undetermined cause. Summary of patients are presented on table 1.

Conclusions: Overall response rate to nivolumab in patients with HIV-related lymphomas was 83,3% and 60% of them had complete metabolic remission. One-year overall survival was 85,7%. Severe ttoxicity and immune-related adverse effects were not registered. Our preliminary data provide that nivolumab is safety treatment option for HIV-infected patients with relapsed/refractory lymphomas. Further research is needed to clarify the efficacy of nivolumab as for HIV as lymphomas in this cohort of patients.

Keywords: human immunodeficiency virus (HIV); immunochemotherapy; non-Hodgkin lymphoma (NHL).

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INFECTIOUS COMPLICATIONS OF NIVOLUMAB THERAPY IN RELAPSED/REFRACTORY HODGKIN'S LYMPHOMA

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Introduction: The clinical development of checkpoint inhibitor-based immunotherapy has ushered in an exciting era of anticancer therapy. Despite of many reports on anti PD-1 antibody therapy for the treatment of Hodgkin's lymphoma (HL), risk of infection among patients receiving nivolumab is still unknown. We are the first to present the real-life data on infection complications in large cohort of r/r HL after nivolumab (nivo) therapy.

Methods: Between 2016 and 2018 years 112 patients with r/r HL were observed and treated with nivo (3 mg/kg) in CIC 725. The median age was 31 y.o. (13 -62 years). The median number of nivo courses received was 20 (range, 1-30). 18 patients underwent allo-HSCT after therapy of nivo. The median follow-up period was 1,4 years (1 month-2,6 year). Outcome analysis considered events at one year after first nivo administration and were censored at the date of allo-HSCT or auto-HSCT. Infections were identified by reviewing patient clinical, laboratory data and imaging studies. All patients had a standard anti-infective prophylaxis and treatment according to the international guidelines.

Results: During salvage treatment with nivo of r/r HL in 11 (10%) patients were documented infection episodes (n=16): bacterial infections – 37,5% (n=6), invasive fungal diseases (IFD) – 25% (n=4) and

viruses – 37,5% (n=6). The median time to infection episodes was 98 days (12-365) after first nivo administration. Incidence of bacterial infections in study cohort was 5,3% (n=6). Two patients developed pneumonia, others met in one: sinusitis, meningitis cause by Listeria meningitis, colitis and gonitis. Incidence of viral infections was 5,3% (n=6): pneumonia associated with HHP-6 and CMV in 50% and generalized infections in 50% caused by HSV-1,2 and HHV-6. Invasive fungal diseases were diagnosed in 3,6% patients (n=4). The main etiology agent was Aspergillus spp. in 50%. Primary chemoresistant disease before nivo therapy was the only risk factor of infection complications during treatment of r/r HL (p=0,029). Overall survival (OS) at 1 year after first nivo administration in study cohort was 96,5%. The only one death was attributed to infection, patient died due to sepsis unknown etiology.

Conclusion: Incidence of infectious complications in r/r HL treated with nivolumab was 10% with the median time of onset – 98 days. Etiology of infectious complications presented by bacterial infections –37,5%, invasive fungal diseases – 25% and viruses – 37,5%. Primary chemoresistance was a risk factor for infection complications. Wherewith infections could be managed successfully and carry favorable prognosis.

Keywords: Hodgkin lymphoma (HL); immunochemotherapy; nivolumab.

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TREATMENT OF RELAPSED/REFRACTORY AGGRESSIVE NON-HODGKIN LYMPHOMA (NHL) WITH LISOCABTAGENE MARALEUCEL IN THE OUTPATIENT SETTING: RESULTS FROM TWO PHASE 2 TRIALS

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Introduction: Chimeric antigen receptor (CAR) T cell therapy has generally been limited to inpatient administration at university medical centers. Among US patients (pts) treated for relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), about 80% receive

treatment at nonuniversity medical centers where outpatient therapy is often at a distinct site from hospitalization for adverse event management. In the ongoing TRANSCEND NHL 001 study in R/R DLBCL, lisocabtagene maraleucel (liso-cel, JCAR017), an investigational, anti-CD19 CAR T cell product administered at a precise dose of CD4+/CD8+ CAR T cells, showed high overall response rates with a favorable safety profile (Abramson et al, ASCO 2018). Late onset and low rates of all grade and severe cytokine release syndrome (CRS) and neurological events (NE) support outpatient treatment with hospital admission at the first sign of fever. We report on 2 newly initiated open-label, phase 2 trials that allow outpatient treatment, assessing the safety and efficacy of liso-cel either as third-line therapy (OUTREACH; NCT03744676) or in second-line, transplant noneligible pts (PILOT; NCT03483103).

Methods: In both trials, eligible pts had R/R aggressive B-cell NHL, adequate organ function, and prior systemic chemoimmunotherapy (OUTREACH: ≥2 prior lines of therapy and ECOG PS ≤1; PILOT: 1 prior line of therapy and deemed ineligible for autologous hematopoietic stem cell transplantation based on ECOG PS, organ function, and/or age). Liso-cel was administered at 100×10^6 total CAR+ T cells after lymphodepletion (LD) with fludarabine/cyclophosphamide. Both trials allowed outpatient treatment at nonuniversity (OUTREACH) or at both university and nonuniversity medical centers (PILOT). Outpatient treatment required pts to have a caregiver, safety monitoring education, and to stay close to the site of care. All sites were required to have a multidisciplinary CAR T cell team identified and standard operating procedures for outpatient administration and monitoring in place.

Results: At data cutoff, 15 pts were leukapheresed (OUTREACH n=7; PILOT n=8). Age ranged from 60–79 years; 11 pts were female. 13 pts had DLBCL NOS, 2 had DLBCL transformed from indolent lymphoma. 7 pts had LD followed by liso-cel infusion, including 3 outpatients. The remaining 8 pts are awaiting liso-cel treatment. Among the 4 pts with 30 days of follow-up, no CRS, NE, or febrile neutropenia were reported. There were no grade ≥3 nonhematologic treatment-emergent adverse events (TEAEs), grade 5 TEAEs, or ICU admissions. Objective responses were observed in 4/4 pts (1 complete remission; 3 partial remissions). Updated enrollment, incidence of toxicity, intervention for CRS/NE and hospitalizations with longer follow-up data will be presented.

Conclusions: In these ongoing phase 2 studies in R/R NHL, pts were successfully treated with liso-cel in the outpatient setting.

Keywords: B-cell lymphoma; CD19; non-Hodgkin lymphoma (NHL).

Disclosures: Sehgal, A: Research Funding: *Juno/Celgene, Kite/Gilead, Merck.* **Hildebrandt, G:** Consultant Advisory Role: *Pfizer, Kite Pharma, Incyte, JAZZ Pharmaceuticals*; Stock Ownership: *Sangamo Bioscience, Juno Therapeutics, Kite Pharma, Novartis, Insys Therapeutics, Abbvie, GW Pharmaceuticals, Cardinal Health, Immunomedics, Endocyte, Clovis Oncology, Cellectis, Aetna, CVS Health, Celgene, Bluebird Bio, Bristol-Myers Squibb / Medarex, crispr therapeutics, IDEXX laboratories, Johnson & Johnson, Pfizer, Procter & Gamble, Vertex, JAZZ Pharmaceuticals*; Research Funding: *Takeda, JAZZ Pharmaceuticals, Pharmacyclics*; Other Remuneration: *Travel, expenses, accommodation: Kite Pharma, Incyte,*

Pfizer, Falk Foundation, JAZZ Pharmaceuticals, Astellas Pharma. **Trede, N:** Employment Leadership Position: *Celgene*; Stock Ownership: *Celgene.* **Kostic, A:** Employment Leadership Position: *Celgene*; Stock Ownership: *Celgene.* **Wang, L:** Employment Leadership Position: *Celgene Corporation*; Stock Ownership: *Celgene Corporation.* **Lymp, J:** Employment Leadership Position: *Celgene*; Stock Ownership: *Celgene.* **Bachier, C:** Honoraria: *Sanofi.*

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CORRELATION OF CIRCULATING EPSTEIN-BARR VIRUS-TARGETED CYTOTOXIC T LYMPHOCYTE PRECURSORS (EBV-CTLp) AND CLINICAL RESPONSE FOLLOWING TABELECLEUCEL (TAB-CEL) INFUSION IN PATIENTS WITH EBV-DRIVEN DISEASE

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Background: EBV is implicated in a variety of diseases. Tab-cel is an investigational off-the-shelf, allogeneic T-cell immunotherapy utilizing endogenous T cell receptors targeting EBV antigens. We hypothesized the clinical activity of tab-cel is mediated by expansion and persistence of EBV-specific T cells. Therefore, we quantified circulating EBV- CTLp after tab-cel administration and examined the correlation between expansion and clinical response.

Methods: Samples from 10 patients with EBV+ post-transplant lymphoproliferative disease (PTLD) and other EBV-associated diseases enrolled in an multicenter expanded access protocol (EAP) study (NCT02822495) were analyzed. To evaluate CTLp frequencies, limited dilution analysis was performed on samples taken at baseline and day 34 post 1st tab-cel dose (end cycle 1). The day 34 persistence of circulating EBV-CTLp from best overall response to initial tab-cel product was tested using the two-tailed Mann-Whitney test. Changes in inflammatory cytokines were also measured.

Results: Responders represented in this sampling (n=6; 2 PR and 4 CR) showed a median 5.8-fold increase in circulating CTLp between baseline and day 34 (range: 0.8 to 133-fold). Five of 6 responders showed an increase in EBV-CTLp at day 34 of > 3.8-fold while 1 pt showed no change in CTLp (0.8-fold change). In contrast, the 4 non-responders (3 SD; 1 PD) showed a median 0.3-fold decrease in EBV-

CTLp from baseline (range: 1.2 to 0.02-fold; ns). Cumulative analyses revealed a statistically significant correlation between the fold-change of circulating CTLp at day 34 and clinical response (p=0.038) which did not appear to correlate with the type of the EBV-associated disease. Inflammatory cytokines showed no meaningful change from baseline. The safety profile remains consistent with previously reported data.

Conclusions: These data support the correlation of clinical activity of tab-cel with the expansion and persistence of EBV-specific T-cells at day 34 post-treatment, as well as the use of circulating CTLp as a biomarker for response in clinical studies.

Keywords: Epstein-Barr virus (EBV); PTLD; T-cells.

Disclosures: Aftab, B: Employment Leadership Position: *Atara Biotherpeutics*; Consultant Advisory Role: *none*; Stock Ownership: *Atara Biotherapeutics*; Honoraria: *none*; Research Funding: *none*; Other Remuneration: *none*. **Munson, D:** Employment Leadership Position: *Atara Biotherapeutics*; Stock Ownership: *Atara Biotherapeutics*. **Rasor, K:** Employment Leadership Position: *Atara Biotherapeutics*; Stock Ownership: *Atara Biotherapeutics*. **Foubert, P:** Employment Leadership Position: *Atara Biotherapeutics*; Stock Ownership: *Atara Biotherapeutics*. **Tsai, D:** Employment Leadership Position: *Loxo Oncology*; Consultant Advisory Role: *Bristol Myers, Novartis*; Stock Ownership: *Loxo Oncology*; Honoraria: *Atara Biotherapeutics*. **van Besien, K:** Stock Ownership: *Hemogenyx*. **Sun, Y:** Employment Leadership Position: *Atara Biotherapeutics*; Stock Ownership: *Atara Biotherapeutics*. **Hiremath, M:** Employment Leadership Position: *Atara Biotherapeutics*; Stock Ownership: *Atara Biotherapeutics*. **Navarrow, W:** Employment Leadership Position: *Atara Biotherapeutics*; Stock Ownership: *Atara Biotherapeutics, Bluebird, GE, Pfizer*.

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THE ROLES OF PET/CT IN PREDICTING THE PROGNOSIS OF CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY TREATED PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: Chimeric antigen receptor T cell (CAR-T) therapy is an effective treatment for relapsed or refractory (r/r) diffuse large B cell lymphoma (DLBCL) patients. Positron emission tomography/computed tomography (PET-CT) played an important role in DLBCL in the era of chemoimmunotherapy, while its value in CAR-T therapy remained undetermined.

Methods: In this study, we retrospectively explored the role of PET-CT in 13 r/r DLBCL patients who were receiving CAR-T therapy.

Parameters reflecting tumor metabolic burden, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), were measured before and after CAR-T treatment. These trials were registered at www. clinicaltrials.gov as #NCT02976857 and #NCT03598179.

Results: Patients with larger baseline MTV or longer sum of longest diameters had shorter overall survival (OS) than those with low tumor burden. Patients who achieved complete response (CR), partial response (PR) and minor response determined by response evaluation criteria in lymphoma (RECIL) at 12 weeks had superior progression-free survival and OS than those with no response. In addition, we found that 2 patients with residual masses classified as PR by contrast-enhanced CT had complete metabolic response by PET-CT imaging. In general, in r/r DLBCL patients, PET-CT at baseline and at 12 weeks after CAR-T therapy could predict the prognosis, while early PET-CT at 4 weeks failed to predict long-term outcomes. CR rate was higher when detected by PET-CT than contrast-enhanced CT.

Conclusions: Therefore, PET-CT showed great value in prognosis assessment and response evaluation in CAR-T-treated r/r DLBCL patients.

Keywords: diffuse large B-cell lymphoma (DLBCL); positron emission tomography (PET).

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BASELINE CLINICAL AND PET-CT TUMOR BURDEN PARAMETERS DO NOT PREDICT OUTCOME OF RELAPSE/REFRACTORY AGGRESSIVE B CELL LYMPHOMA PATIENTS TREATED WITH ANTI-CD19 CAR T-CELLS

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Background: Phase II trials have suggested that anti-CD19 CAR T-cell therapy can induce durable responses in around 40% of patients (pts) with relapse/refractory (R/R) aggressive B cell lymphomas (aBCL). We

initiated a single center program in which pts with R/R aBCL were treated with locally produced anti-CD19 CAR T-cells. Eligibility of the pts enrolled reflected a real world setting.

Aim: To evaluate the safety, efficacy, and clinical/PET-CT imaging parameters associated with survival outcomes.

Methods: Pts with R/R aBCL and adequate organ function were eligible. The approach used autologous T-cells expressing anti-CD19 CAR construct with CD28 co-stimulatory domain. Treatment included lymphodepletion with fludarabine and cyclophosphamide followed by infusion of fresh 1×10^6 CAR T-cells after 9-10 days of culture. Baseline PET-CT scans, which were done within maximum 2 weeks before CAR T-cell treatment, were analyzed for total lesion glycolysis (TLG) and total metabolic tumor volume, using a segmentation algorithm of 41%SUVmax (TMTV41%).

Results: Between November 2016 and January 2019, 30 pts with R/R aBCL were included: 25 with diffuse large B cell lymphoma (6 of them were transformed), 3 with primary mediastinal lymphoma and 2 with Burkitt lymphoma. 23 pts were male. Median age was 45 (range 19-66). Median number of prior therapies was 3 (range 2-6). 27 pts (90%) were refractory to their last therapy. 13 (43%) had a prior stem cell transplantation (SCT) (11 – auto, 1 – allo, 1 – auto and allo). The overall response rate was 57% (27% CR). With a median follow-up of 5.1 month (1.2-26.5) median overall and progression free survival (PFS) were 20.7 and 3.7 months, respectively. The estimated PFS at 18 months for the entire cohort was 25%, and 44% among the 17 pts who had an objective response. 11 patients deceased, 9 of them due to disease progression and 2 from transplant related toxicity. No deaths were attributed to CAR T-cell therapy. Cytokine release syndrome occurred in 22 pts (73%), but was severe in only one. 11 pts (37%) experienced neurotoxicity, in 6 (20%) it was grade 3 or 4. Toxicities related to CAR T-cell therapy did not predict survival outcomes. Median baseline TMTV and TLG were 76 (7-1357) and 717 (19-8460), respectively. None of these PET-CT measurements and other baseline patient and disease characteristics, including CRP and stage, predicted OS or PFS. AlloSCT was performed after CAR T-cell therapy in 13/30 patients (43%). Severe acute GVHD and sinusoidal obstruction syndrome were identified in 2/13 patients (15%), each.

Conclusion: This prospective analysis of a single center cohort of mostly refractory aBCL pts treated with in-house produced anti-CD19 CAR T-cell therapy suggests that long-term responses may be achieved, particularly in pts who had an objective response. None of the clinical and PET-CT parameters that indicate tumor burden predicted long term survival.

Keywords: non-Hodgkin lymphoma (NHL); positron emission tomography (PET); T-cells.

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INTRAVENOUS IMMUNOGLOBULIN THERAPY USE IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE

B-CELL LYMPHOMA TREATED WITH TISAGENLECLEUCEL IN THE JULIET TRIAL

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Background: Tisagenlecleucel is an anti-CD19 chimeric antigen receptor (CAR)-T cell therapy that has demonstrated durable responses and

Box plot of immunoglobulin levels over time by IVIG use (yes vs no)
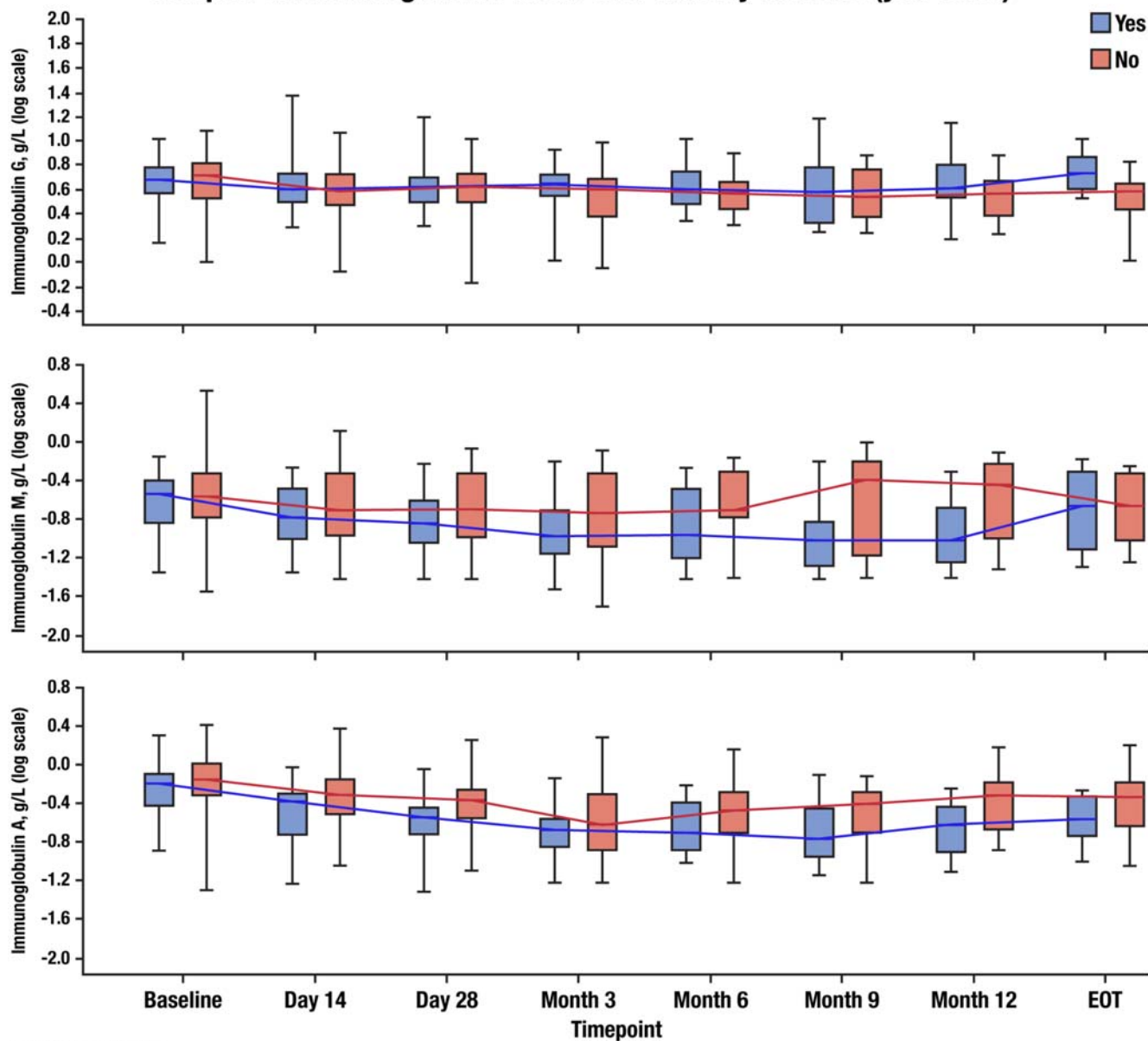
No. of obersvations

	Baseline	Day 14	Day 28	Month 3	Month 6	Month 9	Month 12	EOT
Yes	34	31	29	21	16	15	14	12
No	69	64	60	30	17	11	12	18

a manageable safety profile in adult patients (pts) with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). Intravenous immunoglobulin (IVIG) is commonly used to manage hypogammaglobulinemia following stem cell transplant; hypogammaglobulinemia can also be a consequence of CD19+ B-cell depletion by anti-CD19 CAR-T cell therapy. We report use of IVIG and clinical outcomes for JULIET study pts.

Methods: JULIET is a single-arm, pivotal, phase 2 trial of tisagenlecleucel in adult pts with r/r DLBCL. IgG, IgM, and IgA at baseline; d 14, 28; mo 3, 6, 9, 12; and end of follow-up, together with IVIG use and clinical outcomes, were evaluated. Hypogammaglobulinemia was defined as IgG <4 g/L.

Results: At data cutoff (21 May 2018; median follow-up: 19 mo), hypogammaglobulinemia was observed in 68 of 115 pts (59%) following tisagenlecleucel infusion. Among 75 pts with IgG ≥4 g/L prior to tisagenlecleucel, 37 (49%) subsequently developed hypogammaglobulinemia, with a median duration of 70 d (range: 0-726) and median onset of 14 d (range: 14-376). CAR-T transgene levels (copies/μg DNA) were comparable between pts with or without hypogammaglobulinemia at all timepoints after infusion. Immunoglobulin recovery in the overall population according to IVIG use is summarized in the **Figure**. Thirty-eight of 115 pts (33%) received IVIG following tisagenlecleucel infusion; 25 of 38 pts received IVIG in the presence of hypogammaglobulinemia, while 13 received IVIG with levels of IgG ≥4 g/L. Nine of 115 pts (7.8%) received IVIG before infusion. Median start of IVIG was 55 d after tisagenlecleucel infusion (range: 5-555). IVIG use in responders vs nonresponders to tisagenlecleucel was 38.3% vs 27.3%, respectively. Within 8 weeks of

tisagenlecleucel infusion, the frequency of grade 3-4 infections was similar between pts who received IVIG (n=8/38, 21%) and those who did not (n=14/77, 18%); however, at later timepoints (>8 wk to ≤1 yr and >1yr), the frequency of grade 3-4 infections was higher in pts receiving IVIG (n=11/35 [31%] and n=3/20 [15%], respectively) vs those who did not (n=7/65 [11%] and n=0/21 [0%], respectively). IgG levels in pts receiving and not receiving IVIG supplementation were comparable over time.

Conclusions: Approximately one third of pts received IVIG following tisagenlecleucel infusion; use of IVIG was driven by local institutional practice, with heterogeneity in terms of indication, frequency, and duration of treatment. Although our study was not powered to address this question, no clear pattern associating IVIG use with patient characteristics and conditions was observed. Further research is needed to develop guidance for IVIG use following CAR-T infusion in pts with r/r DLBCL.

Clinical trial information: NCT02445248.

Keywords: CD19; diffuse large B-cell lymphoma (DLBCL); hypogammaglobulinemia.

Disclosures: Jaeger, U: Honoraria: *AbbVie, Bioverativ, Celgene, Gilead, Janssen, MSD, Novartis, Roche, Takeda Millenium, Amgen, AOP Orphan, BMS, Sandoz*; Research Funding: *Bioverativ, Celgene, Gilead, Janssen, MSD, Novartis, Roche*; Other Remuneration: *AbbVie, Celgene, Gilead, Janssen, MSD, Novartis, Roche, Takeda Millenium, Amgen, AOP Orphan, BMS, Sandoz*. **Tam, C:** Honoraria: *Novartis*. **McGuirk, J:** Honoraria: *Kite Pharma*; Research Funding: *Novartis, Kite Pharma, Fresenius Biotech, Astellas Pharma, Bellicum Pharmaceuticals, Gamida Cell, Pluristem Ltd.* **Holte, H:** Consultant Advisory Role: *Novartis*; Honoraria: *Novartis*. **Waller, E:** Employment Leadership Position: *Cambium Medical Technologies*; Consultant Advisory Role: *Kalyera, Novartis*; Stock Ownership: *Cerus Corporation, Chimerix*; Honoraria: *Cambium Medical Technologies, Kalytera, Novartis*; Research Funding: *Celldex, Novartis, Pharmacyclics*; Other Remuneration: *Pharmacyclics*. **Jaglowski, S:** Consultant Advisory Role: *Kite Pharma, Juno*; Research Funding: *Novartis*. **Andreadis, C:** Honoraria: *Novartis, Genentech, Seattle Genetics, Gilead, Astellas*; Research Funding: *Novartis, Cellerant Therapeutics, Incyte, Pharmacyclics, Amgen, Genentech*. **Fleury, I:** Honoraria: *Gilead, Novartis, Roche, Seattle Genetics, Janssen, AbbVie*. **Teshima, T:** Honoraria: *Novartis*; Research Funding: *Novartis*. **Mielke, S:** Consultant Advisory Role: *Celgene, KIADIS Pharma, Miltenyi Biotec, DGHO, EHA*. **Salles, G:** Consultant Advisory Role: *Novartis*; Honoraria: *Novartis*. **Ho, P:** Other Remuneration: *Novartis, Celgene, La Jolla Pharmaceuticals*. **Izutsu, K:** Honoraria: *Novartis, Eisal, Kyowa Hakko Kirin, MSD, Takeda, Janssen, Bristol Myers Squib, Dainihon Sumitomo, Mundipharma, Nihon Mediphysics, Chugai, AstraZeneca, AbbVie, Bayer, Ono, Celgene*; Research Funding: *Novartis, Elsai, MSD, Takeda, Janssen, Mundipharma, Chugai, AbbVie, Bayer, Ono, Gilead, Zenyaku, Celgene, Solasia, Symbio, Astellas, Amgen, Diichi Sankyo*. **Schuster, S:** Honoraria: *Celgene, Genentech, Merck, Pharmacyclics, Novartis, Nordic Nanovector, Acerta, Pfizer, Gilead*; Research Funding: *Celgene, Genentech, Merck, Pharmacyclics, Novartis, Gilead*. **Bachanova, V:** Research Funding: *GAMIDA Cell, UNUM, Novartis, GT Biopharm*. **Maziarz, R:** Consultant Advisory Role: *Novartis,*

Incyte, Juno Therapeutics; Honoraria: *Novartis, Incyte, Juno Therapeutics, Kite Therapeutics*; Other Remuneration: *Athersys, Inc.* **Van Besien, K:** Research Funding: *Novartis*. **Kersten, M:** Consultant Advisory Role: *Roche, Celgene, Takeda, Novartis, Kite, BMS*; Honoraria: *Roche, Celgene, Takeda, Novartis, Kite*; Research Funding: *Roche, Celgene, Takeda*. **Wagner-Johnston, N:** Honoraria: *JUNO, ADC Therapeutics, Janssen*; Research Funding: *Merck, Novartis, Celgene, Astex*. **Corradini, P:** Consultant Advisory Role: *Celgene, AbbVie, Amgen, Daiichi Sankyo, Gilead, Janssen, KiowaKirin, Novartis, Roche, Sanofi, Servier, Takeda*. **Tiwari, R:** Employment Leadership Position: *Novartis*. **Forcina, A:** Employment Leadership Position: *Novartis*. **Pacaud, L:** Employment Leadership Position: *Novartis*. **Bishop, M:** Employment Leadership Position: *United Healthcare*; Consultant Advisory Role: *Celgene, Juneau Therapeutics, Novartis*; Honoraria: *Celgene, Juneau Therapeutics, Novartis*.

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MDS AS A CAUSE FOR PROLONGED HEMATOLOGIC TOXICITY AFTER TREATMENT WITH CD19 TARGETED CAR-T CELL THERAPY IN PATIENTS WITH RELAPSED REFRACTORY LYMPHOMA

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Introduction: The advent of adoptive cellular therapy utilizing autologous T cells expressing chimeric antigen receptors (CAR-T) against CD19 has revolutionized relapsed and refractory B cell lymphoma treatment. CAR-T cell therapy, however, is not without toxicity. Other than cytokine release syndrome and neurotoxicity, hematologic toxicity occurs commonly as well. Grade 3 and above prolonged neutropenia and thrombocytopenia (longer than 4 weeks since T cell infusion) was seen in 15 to 40% and 18 to 40% of patients treated with CD19 CAR T cells in clinical trials respectively. The exact mechanism underlying the pathogenesis of prolonged hematologic toxicity in CAR-T cell therapy is not well understood. Interestingly, we identified four cases of prolonged cytopenias after CAR-T cell therapy due to the presence of myelodysplastic syndrome in patients receiving this treatment for relapsed refractory B cell lymphoma.

Methods: We performed a retrospective review of four patients with relapsed refractory aggressive B cell lymphoma treated at our institution with CD19 directed autologous CAR-T cells.

Results: Median age was 74 (range: 57-76). Two patients had GCB type, 2 had non-GCB type DLBCL. The median number of lines of therapy prior to CAR-T cell therapy was 5. All four patients had prior autologous stem cell transplantation. Median time to MDS diagnosis from CAR T infusion was 3 months (range: 2 to 3). One patient developed MDS after additional chemotherapy was given for relapsed disease. One patient had evidence of a dysplastic clone prior to CAR-T

cell therapy. The remaining two patients did not have evidence of MDS until immediately after CAR-T cell therapy. Two patients developed severe CRS requiring tocilizumab and corticosteroids. One patient showed partial response to CAR-T cell therapy, while three others achieved CR, two of which have since relapsed.

Discussion: We identified four patients with prolonged hematologic toxicity after CAR-T cell therapy due to MDS. These patients have multiple risk factors for the development of MDS including advanced age, and heavy pretreatment. In fact, one patient had evidence of MDS prior to CAR-T cell therapy, underscoring the potential benefit of providing CAR-T cell therapy earlier in the course of treatment. In addition, our findings suggest that a bone marrow study should be performed in patients with prolonged cytopenias post CAR T cell therapy. It is not clear if there is any direct contribution of CAR T cells and the resulting immune system disturbance to the development of MDS. Long term follow up of all patients receiving CAR T cell therapy is therefore crucial to assessment true incidence of MDS and establish association.

Keywords: B-cell lymphoma; CD19.

Disclosures: Herrera, A: Consultant Advisory Role: *Gilead.* **Siddiqi, T:** Consultant Advisory Role: *Juno Therapeutics.* **Budde, E:** Consultant Advisory Role: *Gilead.*

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CAR T-CELLS ARE ARRIVING. IS ALLOGENEIC TRANSPLANT AN OBSOLETE APPROACH FOR DE NOVO/TRANSFORMED DLBCL IN THE CAR T-CELLS ERA? LONG-TERM FOLLOW-UP OF A SINGLE CENTRE UNIT

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Background: Allogeneic stem-cell transplant (allo-SCT) has been a curative option in patients younger than 65-70 years with diffuse large B-cell lymphoma (DLBCL) - de novo or transformed from previous indolent B-cell lymphoma - relapsing or non-candidates to standard salvage therapy including autologous stem-cell transplant (auto-SCT). Due to complications, this approach is offered to only a few patients according to registry data. Moreover, many patients did not reach the transplant due to refractory disease. On august 2018, two chimeric antigen receptor (CAR) T-cells anti-CD19 (Yescarta® and Kymriah®) were approved by the European regulatory agency in de novo and transformed DLBCL patients refractory to at least two chemotherapy lines, based on the results of two Phase II trials reporting a best response of 58% and 40% at 12 months (Chow et al., Blood 2018). Unfortunately, CAR T-cells are not yet a realistic option for patients in centres in Spain. Whether allo-SCT should still be offered to these patients is an opening question.

Methods: From 130 patients with non-Hodgkin lymphoma out of 1000 patients transplanted in our Unit between 1995 and 2018,
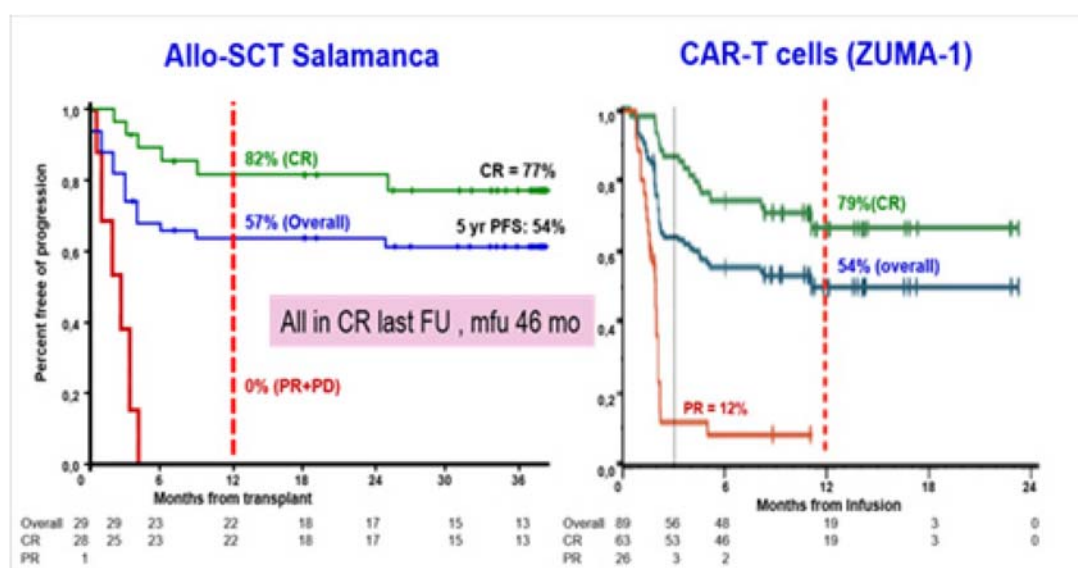
Figure 1. Duration of response in R/R-DLBCL by best response, A) allo-SCT Salamanca B) CAR T-cells (ZUMA-1).

40 have been included in this analysis; of them, 23 had a de novo DLBCL and 17 a transformed lymphoma.

Results: Median age was 53 (20-66), 85% have received more than three lines of chemotherapy including auto-SCT (70%); 47% were refractory to first-line, and in 64% duration of response after auto-SCT were lower than 12 months. After transplant, complete response (CR) at 100 days was 67.5%, and 82% of the patients remain in CR at 12 months. With a median follow-up of 46 months, 5-year progression-free survival (PFS) and overall survival (OS) were 54% and 48% respectively (Figure 1A). In our series, refractoriness at the time of the transplant was associated with a poorer prognosis, with only two out of nine refractory patients being long term survivors. Although similar results were reported in the ZUMA-1 trial with the best response of 55% CR retained in 79% of them at 12 months, we have to point it out that follow up is much shorter, 15.4 months (Figure 1B).

Conclusions: Although very few patients with de novo or transformed DLBCL are offering an allo-SCT (4% of all allo-SCT in our Unit), this is a curative option in chemosensitive patients, and with more mature data and longer follow-up than with CAR T-cell therapy; for these reasons and due to the difficulties still remaining of offering CAR T-cells to these patients, allo-SCT should still be offer to them. Moreover, almost all patients have now available donor, better graft-versus-host disease prophylaxis will decrease TRM and morbidity, and new therapies will make more patients in sensitive disease before allo-SCT. Therefore, allo-SCT and CAR T-cells are strategies to be discussed in every young patient with available donor.

Keywords: allogeneic stem cell transplant (alloSCT); diffuse large B-cell lymphoma (DLBCL).

TABLE 1 Adverse events and serious events in the maintenance and follow-up phases

Event	N(%)	
Any grade	219 (100)	
Grade 0	141 (64.4)	
Grade 1	46 (21.0)	
Grade 2	25 (11.4)	
Grade ≥3	5 (2.3)	
UK	2 (0.9)	
TRM-related AE,n(%)	**Any grade**	**Grade≥3**
All	29 (100)	3 (100)
Diarrhea	4 (13.8)	0 (0)
Neutropenia	3 (10.3)	3 (100)
Infection	6 (20.6)	0 (0)
Arthralgia	7 (24.1)	0 (0)
Asthenia	4 (13.8)	0 (0)
Erytema	1 (3.4)	0 (0)
Anxiety/depression	1 (3.4)	0 (0)
Pyrexia	1 (3.4)	0 (0)
Paresthesia	1 (3.4)	0 (0)
Anorexia	1 (3.4)	0 (0)
SAE,n(%)	**8 (3.7)**	
TRM-relationship, n(%)	Yes	No
All	0 (0)	8 (100)
Urosepsis	0 (0)	2 (25.0)
Prostatitis	0 (0)	3 (37.5)
Female sterilization	0 (0)	1 (12.5)
AMI	0 (0)	1 (12.5)
Prostatectomy	0 (0)	1 (12.5)

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RESULTS OF PHASE II STUDY OF COMBINED IMMUNOTHERAPY WITH RITUXIMAB PLUS LYMPHOKINE-ACTIVATED KILLER CELLS AS MAINTENANCE IN FOLLICULAR LYMPHOMA PATIENTS

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Introduction: Anti-CD20 monoclonal antibodies (mAbs) have shown promise infollicular lymphoma (FL) as post-induction therapy by enhancing antibody-dependent cellular cytotoxicity (ADCC). However, cytotoxic effector cells are reduced in FL patients receiving this treatment. We hypothesized that administration of *ex vivo*expanded lymphokine-activated killer (LAK) cells to FL remission patients is safe and improves the efficacy of concomitantly administered anti-CD20 mAbs.

Methods: This is a multicenter open, prospective, phase II, single-arm study to assess safety and efficacy of *ex vivo*expanded LAK cells in 20 FL remission patients following 24-months bimonthly rituximab maintenance therapy. Peripheral blood cells (PBC) were withdrawn in odd rituximab cycles to isolate mononuclear cells and stimulate them with interleukin-2 for 8 weeks, after which > 5 x 10^8 LAK cells were injected. Cell phenotypes were determined by flow cytometry, and cytotoxic activities of LAK cells were tested against appropriate targets. Patients were followed up for the subsequent 5 years.

FIGURE . Progression free survival. The Kaplan-Meier estimation of progression free survival of patients during the period comprising 24-months maintenance with rituximab/LAK cells and a subsequent 59.4 (43.8-70.9)-months [median (IQR)] follow-up phase is shown.

Number at risk

20 20 19 19 19 18 17 16 16 15 14 13 9 7 6 1
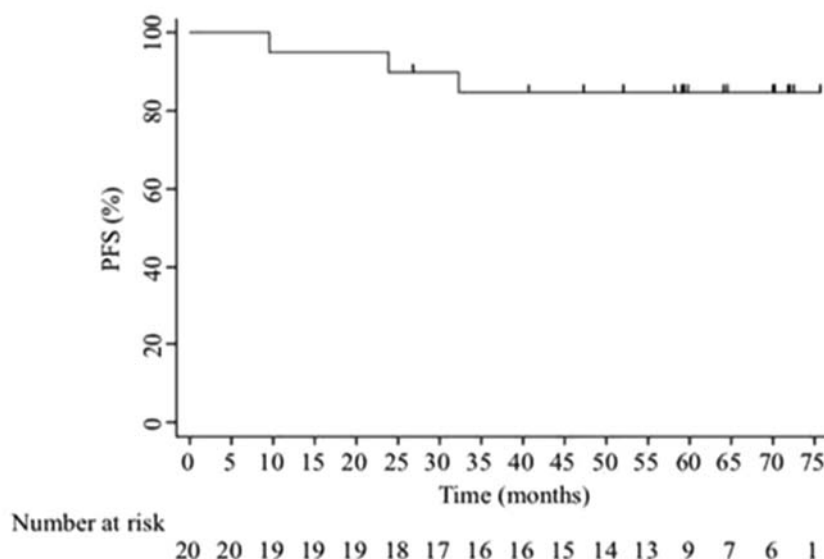
Results: At the end of maintenance, PBC phenotype had not changed markedly. *In vitro* NK, LAK and ADCC activities of isolated mononuclear cells increased significantly after rhIL-2 stimulation in all cycles, and ADCC activity was always significantly enhanced in the presence of rituximab. No patients discontinued treatment. There were no treatment-related serious adverse events (table). 3 patients had progressed by the end of follow up. After a median follow-up of 59.4 (interquartile range, 43.8 to 70.9) months, 85% of patients remained free of progression (figure). No deaths occurred. Quality-of-life seems to improve throughout the study.

Conclusion: Post-induction concomitant LAK cells and rituximab seems safe at long term. The observed efficacy warrants larger studies to confirm their usefulness in delaying FL disease progression.

Keywords: fine-needle aspirate (FNA); follicular lymphoma (FL).

NOVEL TREATMENTS

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UMBRALISIB AND CARFILZOMIB POTENTLY INHIBIT CAP DEPENDENT TRANSLATION IN LYMPHOMA

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Introduction: Umbralisib (TGR-1202) is an investigational drug developed to target the delta isoform of phosphoinositide 3-kinase (PI3Kδ), and is recently found by our group to inhibit casein kinase 1 epsilon (CK1ε)[1]. In the clinic, umbralisib demonstrates a clinical activity in indolent lymphoma that is comparable to idelalisib, the first-in-class PI3Kδ inhibitor; importantly, umbralisib appears to lack the frequent and troubling autoimmune toxicities associated with idelalisib, according to our recent publication[2]. While combining idelalisib and lenalidomide has resulted in mortality, umbralisib and lenalidomide is reported to be well tolerated. These results suggest that umbralisib may be uniquely qualified as a safe partner for combination with various drugs to improve the outcome of DLBCL. Carfilzomib is a proteasome inhibitor approved for multiple myeloma. Interestingly, our previous results demonstrate that umbralisib and carfilzomib synergistically induce apoptosis in DLBCL cells, which is correlated with potent inhibition of phosphorylation of the eukaryotic translation initiation factor 4E (eIF4E) binding protein 1 (4E-BP1), and downregulation of c-Myc dependent genes. The objective of this study is to further decipher the mechanism underlying the synergy of umbralisib and carfilzomib.

Methods: (1) Cell lines included those of DLBCL and mantle cell lymphoma (MCL). (2) Cell signaling in translational regulation. Western blot was performed to study the following signaling regulators of translation: 4E-BP1, p70S6K, RPS6, eIF4E, and eIF4B. (3) Assembly of eIF4F was studied using the 7-methyl GTP pulldown assay. (4) Polysome profiling. Mono- and poly-risobomes were isolated by ultracentrifugation of cell

lysates a sucrose gradient, and detected by measuring OD260nm. (5) RNA-seq. The abundance of gene transcripts was determined by RNA sequencing, using the Illumina HiSeq 2500 platform. (6) Proteomic studies were performed using data independent analysis (DIA) Liquid chromatography–mass spectrometry (LC/MS). (7) Data analysis. Omics data were analyzed by gene set enrichment analysis (GSEA) and Virtual Inference of Protein-activity by Enriched Regulon (VIPER) analysis.

Results: Umbralisib and carfilzomib in combination, but not the single agents, inhibited phosphorylation of 4E-BP1 in DLBCL and MCL cells. The combination potently inhibited assembly of eIF4F, inhibited polysomes, and selectively downregulated target genes in the following signatures: c-Myc, E2F, G2M checkpoint, and DNA repair. More than 5,000 proteins were detected by LC/MS, and about 400 proteins were significantly decreased. The proteins downregulated were enriched with transcription factors and proteins involved in chromosome/DNA modification. These results suggest that umbralisib and carfilzomib synergistically inhibit cap dependent translation of tumor promoting genes, and represent a promising treatment for lymphoma.

Keywords: diffuse large B-cell lymphoma (DLBCL); mantle cell lymphoma (MCL); MYC.

Disclosures: Pal, I: Research Funding: *Research funding from TG Therapeutics and Amgen.*

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POTENTIAL THERAPEUTIC ADVANTAGE FOR DUVELISIB IN MANTLE CELL LYMPHOMA: PI3Kδ AND OVEREXPRESSED PI3Kγ IN LYMPHOMA CELLS HAVE SPECIALIZED FUNCTIONAL ROLES

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Introduction: Mantle cell lymphoma (MCL) is a rare B-cell non-Hodgkin lymphoma (NHL) that is aggressive and incurable with existing therapies, presenting a significant unmet clinical need. New treatment strategies that are based upon functional understanding of distinctive features associated with the malignant cells of this disease are required.

Methods: Tissue microarrays from B-cell NHLs were analysed by immunohistochemistry and RNAScope for the expression of PI3Kγ. The function of PI3Kγ in MCL was examined using MAVER-1 and JEKO-1 cells and in malignant lymphocytes from patients with MCL. We examined the effects of specific inhibitors of PI3Kα (A66), PI3Kγ (CZC24832), and PI3Kδ (idelalisib) and a dual PI3Kδ/γ inhibitor (duvelisib) on the migration and proliferation of MCL cells.

Results: We found that a distinctive feature of primary MCL cells is the elevated expression of PI3Kγ relative to that in other B-cell malignancies (Figure below). Our preliminary data provide compelling hints that high levels of PI3Kγ in MCL cells resident in tissues correlate with poor disease outcome. The functional role of PI3Kγ in MCL cells was differentiated from that of PI3Kδ: CZC24832 and duvelisib inhibited CCL21-induced migration of PI3Kγ-positive MAVER-1 and primary MCL cells but had no effect on PI3Kγ-negative JEKO-1 cells. Interestingly, duvelisib was more effective than CZC24832 in these assays, particularly with respect to migration of primary MCL cells. In contrast, specific inhibition of PI3Kδ with idelalisib did not affect CCL21-induced migration of the MCL cells used in this study, but did block BCR-induced signalling and its effects. These data suggest that when PI3Kγ is aberrantly expressed by MCL cells, these cells become reliant on this PI3K isoform for chemokine-induced migration and tissue residency. Thus, duvelisib may have a therapeutic advantage in

Figure. Comparison of PI3Kγ immunohistochemical staining scores (= staining intensity x proportion of positive cells) in SLL/CLL (n = 13), DLBCL (n = 15), FL (n = 10), MCL (n = 17), and MZL (n = 7).
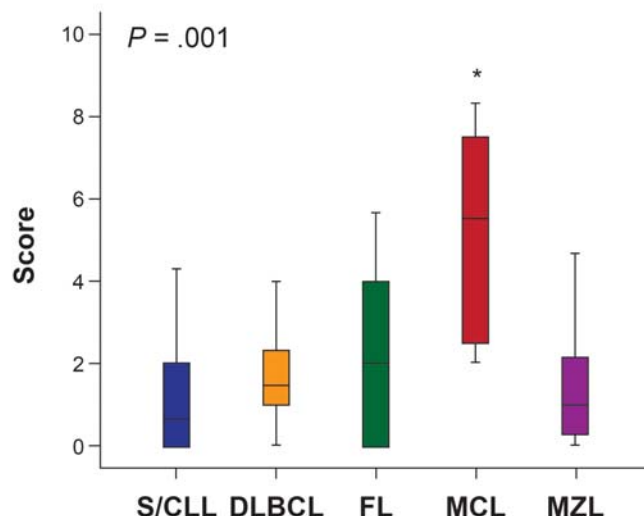
MCL by restricting entry and retention of malignant cells within the mantle zone. Further functional analysis showed that inhibition of PI3Kγ with duvelisib and CZC24836 inhibited proliferation of MAVER-1 but not JEKO-1 cells, whereas specific inhibition of PI3Kδ had no effect on cell division in either cell type.

Conclusions: These results suggest a functional role of PI3Kγ in MCL cells such that aberrant expression of PI3Kγ by the malignant cells of MCL rewires these cells to promote migration and proliferation. Considering the importance of chemokine- and BCR-induced signals in MCL pathobiology, duvelisib, as a dual inhibitor of PI3Kδ and PI3Kγ, may be particularly effective in the treatment of this disease. These data support clinical trials of duvelisib in patients with MCL.

Keywords: Duvelisib; mantle cell lymphoma (MCL); PI3K/AKT/mTOR.

Disclosures: Till, K: Research Funding: *Verastem Inc.* **Weaver, D:** Employment Leadership Position: *Verastem Oncology*; Consultant Advisory Role: *FemtoDx, Nanogen Therapeutics*; Stock Ownership: *Verastem Oncology, FemtoDx, Nanogen Therapeutics.* **Pachter, J:** Employment Leadership Position: *Verastem Oncology*; Stock Ownership: *Verastem Oncology.* **Pettitt, A:** Research Funding: *Verastem Oncology, Celgene, Chugai, Gilead, GSK/Novartis, Roche*; Other Remuneration: *Celgene, Gilead.* **Slupsky, J:** Research Funding: *Verastem Oncology.*

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COMBINATION OF IRAK4 (CA-4948) AND BTK (VECABRUTINIB) INHIBITORS SHOW SUPERIOR EFFICACY IN PRECLINICAL MODELS OF ABC DLBCL TUMORS CONTAINING *MYD88*-L265P MUTATIONS

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Introduction: NF-κB signaling is required for proliferation and survival of activated B cell-like diffuse large B cell lymphoma cells (ABC DLBCL). Alterations in the upstream toll-like receptor (TLR) and B-cell receptor (BCR) signaling pathways contribute to constitutive NF-κB activity. In particular, activating mutations in *MYD88* in the TLR pathway and *CD79A/B, TNFAIP3* and *CARD11* in the BCR pathways are prevalent, and alterations in both TLR and BCR pathways co-occur frequently in ABC DLBCL tumors (Ngo *et al* 2011, Schmitz *et al* 2018, Chapuy *et al* 2018). Thus, a combination strategy whereby inhibiting key enzymes in both pathways may be required for effective drug treatment. Potential targets include the MYD88 proximal IRAK4 kinase in the TLR pathway and the well validated BTK kinase in the BCR pathway. We are developing an IRAK4 kinase inhibitor, CA-4948, as a therapeutic agent for cancers with dysregulated MYD88/IRAK4 signaling. We previously demonstrated that CA-4948 exhibits

PD and antitumor activity in *in vitro* and *in vivo* models with *MYD88* alterations. Vecabrutinib is a selective, reversible, noncovalent BTK inhibitor that has shown potent activity in vitro against both wild type and C481S-mutated BTK, the most common mutation associated with resistance to ibrutinib. In the present study, the efficacy of CA-4948 in combination with vecabrutinib was studied in *in vivo* preclinical ABC DLBCL tumor models.

Methods: Two human ABC DLBCL subcutaneous tumor xenograft models in immunodeficient mice were evaluated. OCI-Ly10 (ap-1) is an ABC DLBCL, *MYD88*-L265P, *CD79A* mutant cell line. LY0257 is an ABC DLBCL, *MYD88*-L265P, *BCL6* translocation patient-derived xenograft (PDX) tumor (CrownBio). CA-4948 was dosed orally at 75 mg/kg BID and vecabrutinib was dosed orally at 50 mg/kg BID, either as single agent or in combination. The control group was dosed BID with the two respective drug vehicles. Efficacy was determined by measurement of tumor volumes and calculated as percent tumor growth inhibition (%TGI) relative to the vehicle control group.

Results: In both tumor models, significant superior efficacy was observed with CA-4948 plus vecabrutinib combination treatment compared to single agent alone treatment (p≤0.001). In the OCI-Ly10 (ap-1) model, CA-4948, vecabrutinib, and combination treatments showed 28%, 42%, and 97% TGI, respectively, after 21 days of treatment. The combination group had a 2% mean body weight loss. In the LY0275 model, CA-4948, vecabrutinib, and combination treatments showed 25%, 56%, and 85% TGI, respectively, with no body weight loss, after 19 days of treatment.

Conclusion: These results demonstrate that targeting both TLR/MYD88 and BCR signaling pathways may be an effective therapeutic strategy in ABC DLBCL. The combination of the IRAK4 inhibitor CA-4948 and vecabrutinib, a noncovalent BTK inhibitor, merits further investigation clinically in R/R NHL subtypes.

Keywords: BTK inhibitors; diffuse large B-cell lymphoma (DLBCL); MYD88.

Disclosures: Booher, R: Employment Leadership Position: *Curis, Inc.*; Stock Ownership: *Curis, Inc.* **Borek, M:** Employment Leadership Position: *Curis, Inc.*; Stock Ownership: *Curis, Inc.* **DellaRocca, S:** Employment Leadership Position: *Curis, Inc.*; Stock Ownership: *Curis, Inc.* **Samson, M:** Employment Leadership Position: *Curis, Inc.*; Stock Ownership: *Curis, Inc.* **Fox, J:** Employment Leadership Position: *Sunesis Pharmaceuticals*; Stock Ownership: *Sunesis Pharmaceuticals.* **Taverna, P:** Employment Leadership Position: *Sunesis Pharmaceuticals*; Stock Ownership: *Sunesis Pharmaceuticals.*

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SIMULTANEOUS BET/CREBBP/EP300 TARGETING APPROACH COMPARED TO SINGLE BET OR CREBBP/EP300 INHIBITION IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Background: Lymphoma cells have frequent deregulation of their epigenome. The Bromodomain (BRD) and Extra-Terminal domain (BET) proteins are key regulators of the transcription process. The acetyltransferases cyclic AMP response element binding protein (CREB)-binding protein (CBP) and the E1A interacting protein of 300 kDa (EP300) are highly homologous BRD-containing transcriptional co-activators and are often mutated in diffuse large B cell lymphoma (DLBCL). Targeting the individual classes of proteins is a new therapeutic approach, as shown especially by BET inhibitors with both preclinical and early clinical anti-lymphoma activity. NEO2734 and NEO1132 are novel oral dual inhibitors of BET and CREBBP/EP300 proteins. Here, we present data exploring their anti-tumor activity in DLBCL models.

Methods: Lymphoma cell lines were exposed to increasing doses of compounds for 72h. Cell proliferation was measured with the MTT assay.

Results: Twenty-seven DLBCL cell lines were exposed to NEO2734 and NEO1132. NEO2734 showed anti-tumor activity with a median IC50 of 157 nM (95% C.I., 135-214), while NEO1132 showed a lower activity compared, with a median IC50 of 400nM (95% C.I., 316-622). For both compounds, cell lines derived from activated B-cell–like (ABC) DLBCL (n.=8) were more sensitive than the ones derived from germinal center B-cell (GCB) DLBCL (n.=19) ($P < 0.05$). All the cell lines were also exposed to a BET inhibitor (birabresib, OTX015) and to a CREBBP/EP300 inhibitor (CBP30). The median IC50 values of the 2 molecules were 237 nM (95% C.I., 171-344) and 5.5 μM (95% C.I., 4.2-8.3 μM) respectively. The 4 compounds presented a similar pattern of anti-proliferative activity across all the cell lines ($p < 0.001$) (NEO2734 vs NEO1132, r = 0.99; NEO2734 vs birabresib: r =0.97; NEO2734 vs CBP30, r = 0.87; birabresib vs CBP30, r = 0.85) but with different degrees of IC50. NEO2734 was more potent ($P < 0.05$) than birabresib, CBP30 and NEO1132. The higher activity of NEO2734 compared to NEO1132 could be explained by its superior potency in binding CREBBP and EP300. Cell cycle demonstrates that NEO2734 has a cytotoxic activity in 4 out of 5 cell lines tested (3 ABC and 2 GCB-DLBCL) and a slightly higher activity than birabresib in 2 cell lines. Transcriptome profiling on 2 GCB- and 2 ABC-DLBCLs treated for 6h with NEO2734 or birabresib highlighted a very similar effect of the two compounds (r= 0.90, $P < 0.001$), but also highlighted changes specifically induced by the dual inhibitor.

Conclusions: The novel dual BET and CREBBP/EP300 inhibitors NEO2734 and NEO1132 showed robust *in vitro* anti-tumor activity in DLBCL cell lines. Transcriptome changes and antiproliferative activity demonstrated both some overlap between NEO2734 and birabresib but also distinct features of the dual inhibition approach.

Keywords: bromodomains; diffuse large B-cell lymphoma (DLBCL); epigenetics.

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EG-011 IS A NOVEL SMALL MOLECULE WITH *IN VITRO* AND *IN VIVO* ANTI-TUMOR ACTIVITY AGAINST LYMPHOMA

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Introduction: Despite the improvements, still too many patients die for their lymphomas and novel compounds are needed. We present a new small molecule, EG-011 (PCT/EP2018/057678), with *in vitro* and *in vivo* anti-cancer activity in lymphoma models.

Methods: Lymphoma and solid tumor cell lines were exposed to a large range of concentrations of EG-011 as single agent for 72h, followed by MTT proliferation assay and IC50 calculation. Cell viability of twelve acute lymphoblastic leukemia (ALL) primary patient cells from different high-risk subgroups (VNN2+, E2A-HLF, refractory T and IKZF plus) co-culture with marrow–derived MSCs were assayed after 72h of incubation with EG-011 and controls. Apoptosis assay was measured with annexin V by FACS. Xenografts were established s.c. into the left flanks of female NOD-SCID mice; treatment (200 mg/kg, i.p. 5 days per week) started with already established tumors. Combinations were evaluated with Chou-Talalay combination index (CI): synergism (<0.9), additive (0.9-1.1), antagonism/no benefit (> 1.1) after 72 hr treatments.

Results: EG-011 presented a median IC50 of 2.25 mM in 62 lymphoma cell lines (95% C.I. 1-5μM). A higher activity was observed in a group of 21 cell lines that had a median IC50 of 250 nM (95% C.I. 40-600 nM). Among these there were 11 germinal center B cell (GCB) diffuse large B cell lymphomas (DLBCL) (sensitive n=11/21, resistant n=9/41, $P < 0.05$), 4 mantle cell lymphoma (MCL) (sensitive n=4/21, resistant n=6/41, P n.s.), 3 marginal zone lymphoma (sensitive n=3/21, resistant n=2/41, P n.s.). EG-011 did not show any anti-

effect of PTL on immuno-phenotypically defined leukemic stem cells (LSCs) and normal hematopoietic stem cells (HSCs). Because NFκB is constitutively active in LSC, and PTL is a potent inhibitor for it, we also investigated the expression of activated NFκB (NFκBp65) in selected samples.

Method: Forty ALL samples and 24 normal bone marrow and cord blood samples were included in this study after obtaining informed consent. The mononuclear cells from ALL and normal samples were isolated using density gradient separation. ALL samples were sorted into 4 LSC populations (CD34+CD38-CD19+, CD34+CD38+CD19+, CD34+CD38-CD19-, and CD34-CD38-CD19-). Unsorted and sorted cells were cultured with different PTL concentrations for 24, 48 and 72 hours. Post-culture cell viability was assessed using 7ADD in a flow cytometry-based test. Normal unsorted marrow and cord blood samples were tested under similar conditions. In addition, colony forming unit assay (CFU) was carried out with normal samples to assess the effect of PTL on HSCs. In selected ALL and normal samples the expression of NFκB was assessed using PE labeled anti-NFκB p65 antibody.

Results: In ALL, LSCs form heterogeneous compartments with different percentages of the four LSC populations. This heterogeneity extended across and within cytogenetically classified groups of cases. There was no significant effect of PTL on the viability of normal cells at concentrations of ≤ 50μM; but at 25 μM and 10 μM after 24 and 72 hours respectively it affected the ability of HSCs to form colonies. For ALL-LSCs PTL was significantly toxic at 10 μM and most cases, with the exception of those with +3 karyotype abnormality and CD34-CD38- CD19- LSCs with t(9;22), showed >50% cell-death at 25μM PTL concentration. The CD34+, CD38+, CD19+ LSCs showed significantly higher sensitivity compared to other sub-populations. ALL cases with limited response to PTL expressed significantly higher levels of pNFκB p65 as compared to PTL-sensitive cases.

Conclusion: The study concluded that LSCs are heterogeneous within and between cytogenetically classified groups of ALL. Overall, CD34+ CD38- CD19+ and CD34+ CD38- CD19 cells are the predominant LSC populations in B-ALL. PTL has a differential effect on normal HSCs versus ALL cells at lower concentrations in vitro; cord blood HSCs are more resistant than marrow cells. PTL also has a differential effect on LSC subpopulations. PTL sensitivity/resistance in ALL is related to the level of activated NFκB expression in these cells.

Keywords: apoptosis; NF-kB.

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IH2 INHIBITION ENHANCES PROTEASOME INHIBITOR RESPONSIVENESS IN HEMATOLOGICAL MALIGNANCIES

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The ubiquitin-proteasome pathway plays a crucial role in protein processing and degradation, and it regulates critical cellular functions. Proteasome inhibitors (PIs) are extensively used for the therapy of multiple myeloma (MM) and mantle-cell lymphoma (MCL). However, patients continuously relapse or are intrinsically resistant to this class of drugs. We have previously identified isocitrate dehydrogenase 2 (IDH2) as a synthetic lethal target that synergizes with the PI carfilzomib (CFZ). Here, we demonstrate that combinations of FDA approved PIs with a pharmacological IDH2 inhibitor (AGI-6780) trigger synergistic cytotoxicity in MM, MCL, Burkitt's lymphoma, and diffuse large B-cell lymphoma cell lines. CFZ/AGI-6780 treatment increases death of primary CD138+ cells from MM patients and exhibits a favorable cytotoxicity profile towards peripheral blood mononuclear cells and bone marrow-derived stromal cells. Mechanistically, CFZ/AGI-6780 combination significantly decreases tricarboxylic acid (TCA) cycle activity and ATP levels, as a consequence of enhanced IDH2 enzymatic inhibition. Specifically, CFZ treatment reduces the expression of nicotinamide phosphoribosyltransferase (NAMPT), thus limiting IDH2 activation through the NAD+-dependent deacetylase SIRT3. Consistently, combinations of CFZ with either NAMPT or SIRT3 inhibitors impair IDH2 activity and increase MM cell death. Finally, we demonstrate that inducible IDH2 knockdown enhances the therapeutic efficacy of CFZ in subcutaneous and systemic xenograft models of MM, resulting in inhibition of tumor progression, bone marrow disease, and extended survival. Taken together, these findings indicate that NAMPT/SIRT3/IDH2 pathway inhibition enhances the therapeutic efficacy of PIs, thus providing compelling evidence for treatments with lower and less toxic doses and broadening the application of PIs to other malignancies. Our preclinical studies, therefore, provide the rationale for the development of novel IDH2 inhibitors directed against wild-type IDH2.

Keywords: B-cell lymphoma; multiple myeloma (MM); proteasome.

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PRE-CLINICAL ANTI-TUMOR ACTIVITY OF A RAPIDLY-SYNTHESIZED MONOCLONAL ANTIBODY TARGETING B-CELL RECEPTOR POSITIVE LYMPHOMA

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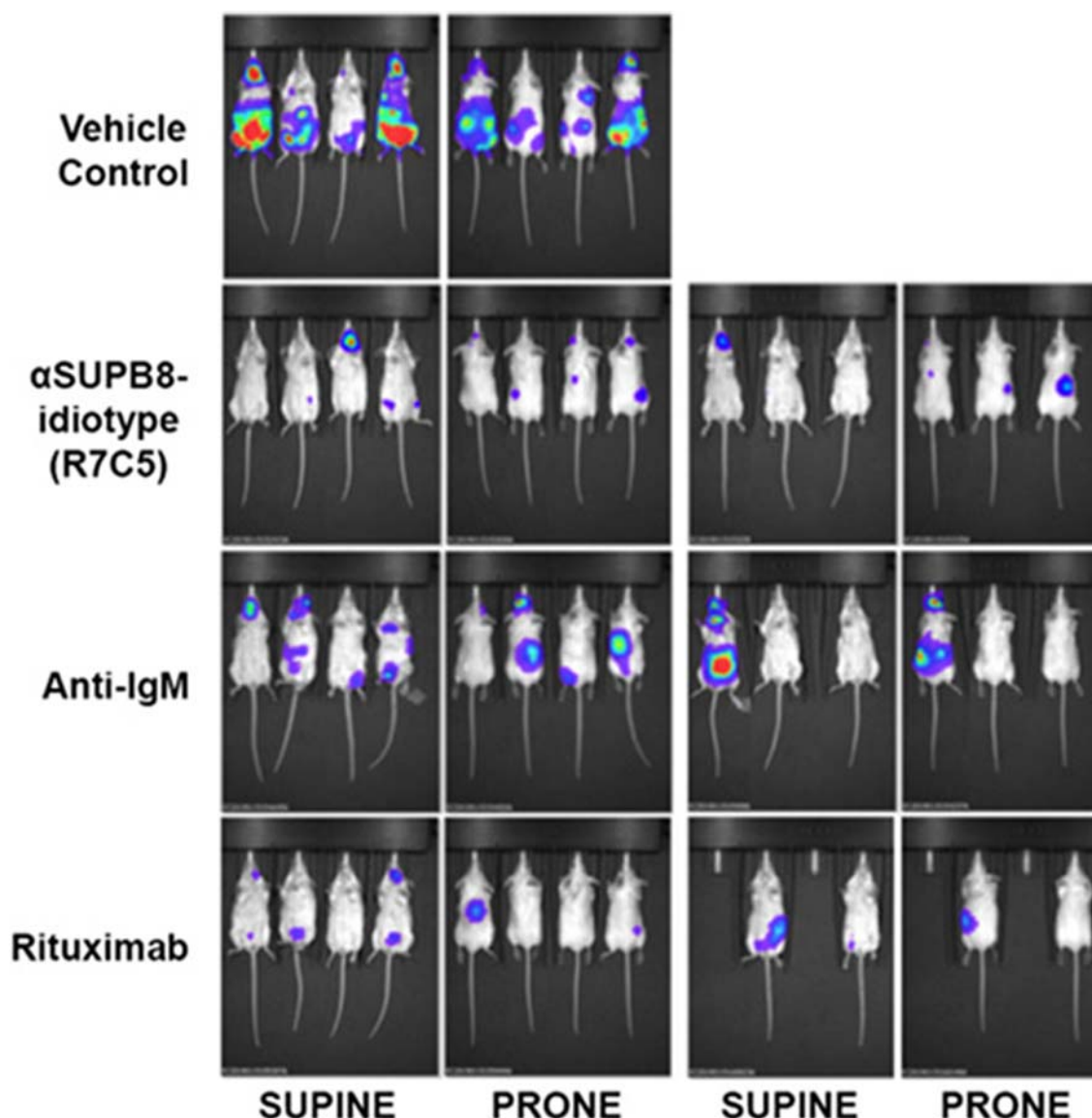
Background: The B-cell receptor (BCR) idiotype represents an attractive immunotherapy target for many non-Hodgkin B cell lymphomas (NHL). The BCR expressed on cancerous cells is unique and clonal, and drives tumor proliferation and survival via its downstream signaling pathways. Here, we report the rapid discovery and characterization of an anti-idiotype (anti-id) monoclonal antibody that demonstrates *in vitro* cell killing and tumor growth inhibition in a xenograft model of NHL.

Methods: We sequenced the BCRs from the human B cell malignancy-derived cell lines SUPB8, Raji, Ramos, Mec1, DOHH2 and NALM6, and expressed their respective idiotype for screening using a high-diversity phage display library containing stability- and manufacturability-optimized collection of human donor-derived scFvs. scFv candidates with high binding affinity and predicted manufacturability were reformatted into human IgG1s and characterized for binding affinity, target selectivity, *in vitro* tumor killing, and *in vivo* tumor growth inhibition.

Results: For each of the cell lines, 4 rounds of panning against recombinant BCR idiotype baits consistently yielded hundreds of scFv binders with low nM to low μM binding affinity in under a week. We further characterized 298 high-affinity anti-SUPB8 scFv clones. By flow cytometry, 63 unique scFv clones achieved specific to non-specific labeling ratio (SUBB8:PBMC lymphocyte/monocyte) of >10-fold (expected ratio = 1), with 3 clones achieving selectivity ratio of >40-fold. Reformatting improved affinity and avidity and directly produced IgG1 candidates with single-digit nanomolar binding affinity. We observed diminished viability in cultured SUPB8 cells co-incubated with anti-SUPB8 IgG1 clone R7C5 (affinity = 19nM; selectivity ratio = 87.2) as early as 24 hours after antibody addition. In CB17-scid mice inoculated with 2e6 SUPB8 GFP+/Luc+ cells (i.v.) on day 0, treatment with R7C5 (50μg/mouse/day i.p. from day 6 to 13; n=8/treatment) achieved tumor burden reduction on par or superior in effectiveness to treatment with anti-IgM antibody or rituximab by day 36 (Figure). Finally, R7C5 showed no appreciable off-target

binding activity when tested against all 5,300 proteins in the human surfaceome.

Conclusion: Our proof-of-concept study demonstrates that, using a pre-optimized high-diversity library, anti-id antibodies highly selective for malignant B cells can be obtained in weeks, thus making feasible a truly personalized antibody therapeutic that can be manufactured on demand and delivered in approximately 60 days, with substantial acceleration possible. By sparing healthy B cells from undesired pharmacological effect, anti-id therapy may offer meaningful safety and efficacy improvements over existing treatment options.

Keywords: B-cell lymphoma; B-cell receptor (BCR); monoclonal antibodies (MoAb).

Disclosures: Santos, C: Employment Leadership Position: *Yes*; Stock Ownership: *Yes*.

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THIRD GENERATION CAR T-CELL THERAPY UTILISING TOLL LIKE RECEPTOR 2 CO-STIMULATION

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Introduction: Licensed second-generation Chimeric Antigen Receptor (CAR) T-cells directed against CD19 have produced excellent response rates in relapsed or refractory (r/r) B-cell non-Hodgkin Lymphomas (B-NHL), but fewer than 50% of patients remain progression free of disease 12 months after therapy, presenting a need for CAR T-cell therapies exhibiting improved long-term responses.

Human T-cells expressing a third-generation anti-CD19 CAR incorporating a Toll Like Receptor 2 (TLR2) Toll/interleukin-1 receptor (TIR) co-stimulatory domain alongside CD28 exhibit improved cytotoxicity against CD19$^+$ target cells both *in vitro* and in xenograft models *in vivo*, compared to second-generation CAR T-cells using the CD28 co-stimulatory domain alone in work carried out in Guangzhou, China. Furthermore, activity against solid CD19$^+$ B-cell tumours in xenograft models and efficacy observed in patients with extramedullary B-cell Acute Lymphoblastic Leukaemia (B-ALL) in preliminary results from a Phase 1 Clinical Trial, provides rationale to assess the role of this co-stimulatory domain in B-NHL.

Methods: A self-inactivating, third generation lentiviral (LV) vector encoding a third-generation CAR incorporating the TLR2 TIR alongside CD28 and CD3ζ was manufactured in GMP laboratories at the Malaghan Institute of Medical Research under license from Wellington Zhaotai Therapies Ltd (WZTL). Peripheral blood leukocytes were obtained by leukapheresis, and T-cells immunomagnetically enriched and stimulated. Purified T-cells were transduced using the LV vector,

then expanded *ex vivo* to produce WZTL-002, third-generation anti-CD19 CAR T-cells incorporating CD28 and TLR2 co-stimulatory domains.

Results: Cytotoxicity of WZTL-002 was assessed *in vitro*. WZTL-002 generated from healthy donors demonstrated potent cytotoxicity against CD19$^+$, but not against CD19$^-$, K562 target cells. Both an inhibitor of TLR2 dimerisation, ortho-vanillin, and a peptide inhibitor of MYD88 dimerisation, but not their respective control compounds, led to reduced activity of WZTL-002 in the presence of CD19$^+$ target cells, consistent with co-stimulatory activity of the TLR2 domain.

Conclusion: Our findings support the utility of the TLR2 TIR co-stimulatory domain within WZTL-002, a new third generation CAR. A phase I Trial of WZTL-002 for the treatment of r/r B-NHL is planned.

Keywords: B-cell lymphoma; CD19; immune system.

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SAFETY AND CLINICAL ACTIVITY OF ATEZOLIZUMAB IN COMBINATION WITH TAZEMETOSTAT IN RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: PRIMARY ANALYSIS OF A PHASE 1B STUDY

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Introduction: Despite recent treatment advances, patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) have a poor prognosis. Here we present the primary analysis of GO29383 (NCT02220842), a phase 1b study evaluating atezolizumab (atezo), an anti-programmed death-ligand 1 (PD-L1) antibody, plus tazemetostat, an EZH2 inhibitor, in pts with R/R DLBCL.

Methods: Eligible pts had CD20+ R/R DLBCL, with ≥2 measurable nodal lesions >1.5 cm and ≥2 prior lines of therapy. Primary endpoints were safety and tolerability. Pts received tazemetostat (800 mg bid) on days (D) 1–21 and atezo (1200 mg IV) on D1 of each 21-day cycle until unacceptable toxicity or disease progression (PD) occurred. Tumour response was assessed by PET-CT or CT (Lugano 2014

Figure 1. Tumour burden over time (days) by change in SPD from baseline (%)

CMR, complete molecular response; NE, not evaluable; PMD, progressive molecular disease; PMR, partial molecular response; SMD, stable molecular disease; SPD, sum of the products of diameters
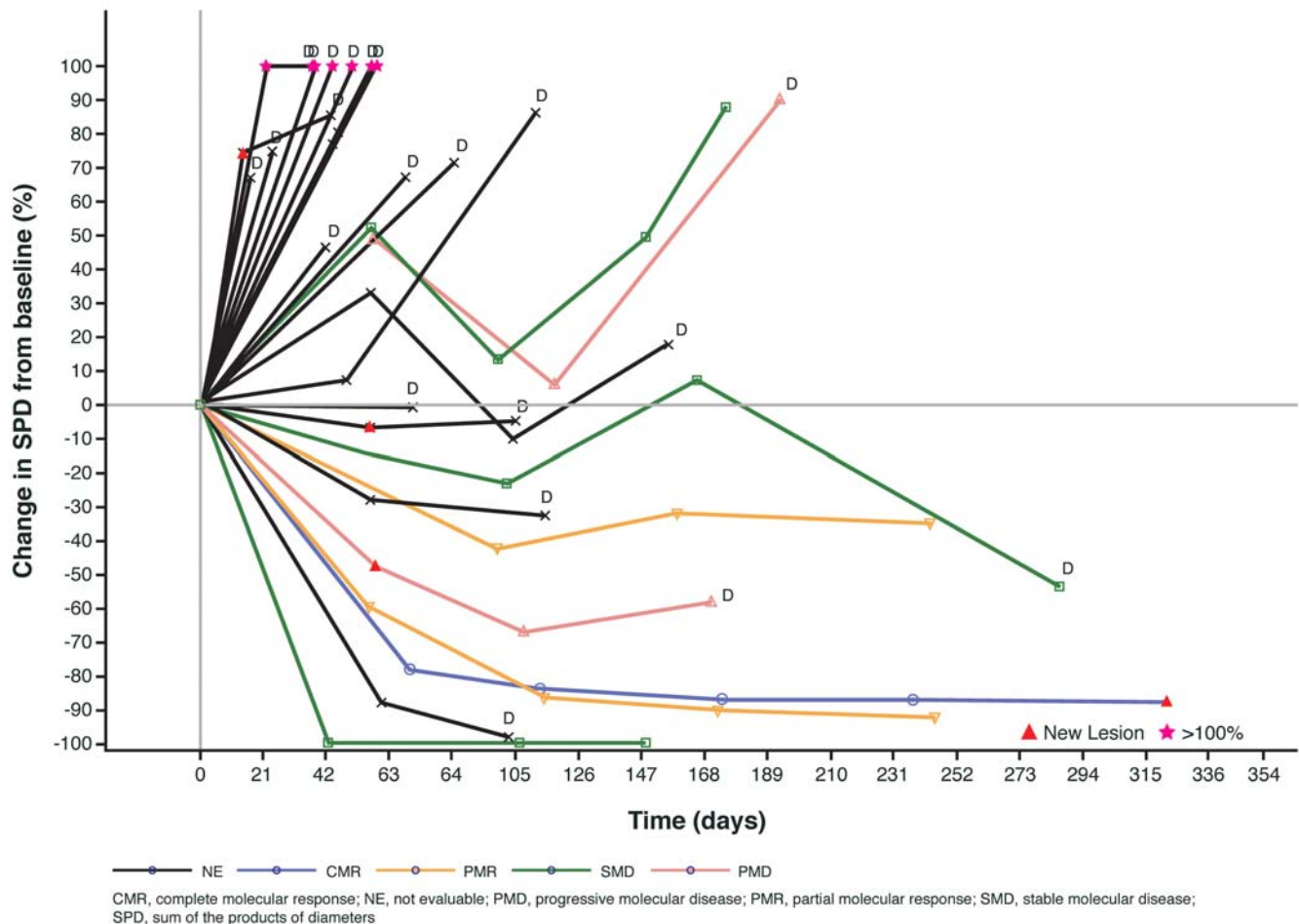
criteria). PD-L1 (SP263), FOXP3 and CD8+ expression were studied by immunohistochemistry; EZH2 gene mutation was analysed using the FoundationOne Heme platform. T-effector signature was studied using RNAseq.

Results: At the data cut-off (28 Aug 2018), 43 pts had enrolled. Median age was 62 years (range 26–86), 32 (74%) pts were male and 40 (93%) had an ECOG status of 0–1. The majority (81%) were refractory to their last treatment (refractory to anti-CD20 therapy, 44%). All enrolled pts received ≥1 dose of study drug; at the data cut-off, 19 (44%) had discontinued study treatment (death, n=17; withdrawal by subject, n=2). Median duration of treatment was 1.4 months (atezo) and 2.1 months (tazemetostat). Forty-one (95%) pts experienced ≥1 adverse event (AE); the most common treatment-emergent AEs were anaemia (26%) and fatigue (23%). Grade ≥3 AEs were experienced by 20 (47%) pts and 15 (35%) had a serious AE (most common: anaemia [12%], neutropenia [9%], thrombocytopenia [9%]). AEs leading to discontinuation of either study drug occurred in 6 (14%) pts (atezo, n=3; tazemetostat, n=3). Two grade 5 AEs occurred: sepsis, deemed unrelated to treatment; and hyponatraemia, related to both study treatments. Tumour burden is described in **Figure 1**. Median progression-free survival was 1.9 months (95% CI 1.8, 2.8). Best

overall response rate was 16% (complete response [CR], n=2 [5%]; partial response [PR], n=5 [12%]). Eight (19%) pts had stable disease; 19 (44%) had PD. EZH2 mutation was identified in 5/29 (17%) pts (3 pts with a Y646N or Y680L mutation achieved a response [CR, n=1; PR, n=2]; in the remaining 2 pts [Y646N and Y646C mutation], PD occurred before clinical assessment). Correlation between response or tumour shrinkage and T-effector signature as well as baseline PD-L1, FOXP3 and CD8+ expression will be presented.

Conclusions: The safety profile of atezo in combination with tazemetostat was tolerable and no new safety signals were identified. Three pts with EZH2 mutation showed response; however, the combination did not demonstrate promising efficacy in pts with R/R DLBCL and no further studies with this combination are planned.

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A PHASE IIA STUDY EVALUATING THE SAFETY AND TOLERABILITY OF UMBRALISIB AND IBRUTINIB IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Relapsed or refractory (rel/ref) diffuse large B-cell lymphoma (DLBCL) remains an unmet medical need. Umbralisib (UMB) a dual PI3K delta/CK-1ε inhibitor and Ibrutinib (IBR) a Bruton's Tyrosine kinase (BTK) inhibitor have activity in DLBCL. Pre-clinical data demonstrated synergistic activity of UMB-IBR against DLBCL cell lines. We report the complete results of a phase IIa study.

Methods: Eligible patients (pts) had rel/ref DLBCL with adequate hematologic and organ function. UMB was dosed at 800 mg daily in AM and IBR 560 mg daily in PM. Treatment stratification was performed on a 1:1:1 design to Cohort A (UMB), B (IBR), or C (UMB+IBR). In cohorts A/B the combination was initiated at day 8. A cycle was 28 days. The primary endpoint was monitoring for cumulative toxicity events (CTEs) occurring during cycles 1-4. Stopping rules for CTEs and efficacy were employed. Secondary endpoints included overall response rate (ORR), complete response (CR) rate, partial response (PR) rate, progression-free survival (PFS), time to response (TTR), and duration of response (DOR).

Results: 13 pts with rel/ref DLBCL were enrolled. Median age was 71 years (range 27-81) and 9 were male. Median number of prior therapies was 2 [range 1-7]. 62% were refractory to last therapy. DLBCL subtypes were GCB in 7 and non-GCB in 6 pts. Cohorts A (n=1) and B (n=1) included pts that consented to optional biopsies. Cohort C (n=11) included the first 3 pts enrolled into the study and those thereafter that did not consent to optional biopsies. Two CTEs were seen: G3 rash and G3 C. diff diarrhea. No CTEs occurred during cycle 1. Notable serious or recurrent adverse events (SAEs or AEs) of interest occurring across all cycles regardless of attribution included elevated AST/ALT 0% G 3-4 (all G 31%), nausea 15% G 3-4 (all G 54%), and diarrhea 15% G 3-4 (all G 31%). One patient in CR was taken off study in recurrent C. diff infection despite dose reductions. The ORR of the UBR-IBR regimen was 31% with 3 PRs and 1 CR. The median PFS was 3 months [95 % CI 0.85, 3.4].

Conclusion: UMB-IBR was well tolerated with only 2 CTEs and limited AEs. The evaluation of CTEs was limited by the PD in many pts seen prior to 4 cycles of therapy. The ORR of the UMB-IBR was 31% surpassing the pre-planned efficacy stopping rule. However given the limited durability in responding patients and difficulty in obtaining biopsies for planned correlative analyses, this study was closed.

Keywords: diffuse large B-cell lymphoma (DLBCL).

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PHASE 1/2 TRIAL OF ANTI-PD-LIGAND 1 (DURVALUMAB) +/- LENALIDOMIDE IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA: PRELIMINARY RESULTS OF PHASE 1 AND CORRELATIVE STUDIES

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Background: T cells in CTCL are functionally exhausted and are characterized by the expression of immune inhibitory molecules such as PD1 and PD-L1 (Cancer Immunol Res 6; 2018). These findings justify the evaluation of immune checkpoint inhibition to reverse T cell exhaustion in CTCL. We initiated a phase 1/2 clinical trial of lenalidomide and durvalumab to determine the safety and efficacy of this regimen. Durvalumab is a human monoclonal antibody with high affinity and selectivity for PD-L1, targeting exhausted T cells and distinct cells within their environment. Lenalidomide, an oral IMiD and analog of thalidomide, has previously shown activity in CTCL (Blood 123; 2014). Durvalumab may restore an anti-tumor immune response, and the combination of durvalumab and lenalidomide may enhance immune checkpoint blockade-induced immune responses.

Methods: A Phase 1 portion is ongoing to evaluate the safety and tolerability of the durvalumab and lenalidomide combination. Pts are enrolled in sequential cohorts to receive durvalumab (fixed dose at 1500 mg) and dose escalation of lenalidomide (cohort 1 = 10 mg; cohort 2 = 15 mg; cohort 3 = 20 mg) to characterize safety, efficacy and antitumor activity. Serial skin and blood samples were collected to assess the impact on the tumor microenvironment using single molecule super-resolution microscopy and multiplex imaging.

Results: Nine pts (7 males/2 females, age 29–59 y) with refractory/advanced CTCL, clinical stages IB (1), IIA (3), IIB (3), IIIA (1), and aggressive epidermotropic CD8+ CTCL (1) have been enrolled. Duration time on treatment was 3 to 18+ months. Seven pts showed improvement of skin disease, with 2 pts achieving PR plus >90% improvement of skin disease by mSWAT. Three pts developed PD. No DLTs or serious AEs were observed. The most frequently reported AEs were fatigue (n=6), skin pain (n=4), chills (n=4), anemia (n=3), and leukopenia (3). All treatment-related AEs were Grade 1/ 2 in severity. One grade 3 rash occurred in one patient. Using multispectral microscopy, we analyzed expression panels of several checkpoints (PD1, PD-L1 & ICOS) on baseline skin bx. Detectable levels of PD-L1 but low levels of ICOS are observed in responding pts vs. high PD-L1 and ICOS levels in non-responders. Quantitative super-resolution microscopy detected nanoscale clusters of PD1 in T cells from responders vs. no clustering in non-responders.

Conclusions: Durvalumab/lenalidomide has significant clinical activity in refractory/advanced CTCL, which will be formally evaluated in the Phase 2 portion. Responses were durable and ongoing, and treatment was well tolerated. Dose escalation is up to lenalidomide 20 mg daily. Our preliminary results from pts on trial demonstrated that immune signatures on skin biopsies at baseline may be predictive of response to checkpoint blockade and yield insights into mechanisms of therapeutic resistance.

Keywords: cutaneous T-cell lymphoma (CTCL); immunomodulators (IMIDs); PD-1L.

Disclosures: Querfeld, C: Consultant Advisory Role: *MiRagen, Medivir, Bioniz, Actelion, Kyowa Kirin*; Research Funding: *Celgene*. **Rosen, S:** Consultant Advisory Role: *Novartis Pharmaceuticals Corp; Pepromene Bio, Inc; Exicure; Apobiologix/Apotex Inc, Seattle Genetics; NeoGenomics; Aileron Therapeutics, Inc*; Honoraria: *Celgene; Global Education Group and Paradigm*.

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PHASE 1/2A CLINICAL TRIALS OF BI-1206, A MONOCLONAL ANTIBODY TO FCΓRIIB, ADMINISTERED AS A SINGLE AGENT OR IN COMBINATION WITH RITUXIMAB IN SUBJECTS WITH B-CELL MALIGNANCIES

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Introduction: BI-1206 is a fully-human anti-FcγRIIB antagonistic antibody that is thought to work by enhancing the activity and overcoming resistance to anti-CD20 antibody treatments (Roghanian et al., 2015).

Methods: BI-1206 is currently being tested in two parallel Phase 1/2a clinical trials CRUKD/16/001 and 17-BI-1206-02, in the UK and the US/EU respectively.

CRUKD/16/001 includes patients with FcγRIIB-positive B cell malignancy. The phase 1 comprises a dose escalation to determine the maximum tolerated dose or maximum administered dose, and recommended phase 2 dose (RP2D) of BI-1206, in two parallel arms: 1) BI-1206 administered as a single agent. 2) BI-1206 administered in combination with rituximab (not open to recruitment yet). The phase 2a is an expansion phase using the RP2D from each arm.

17-BI-1206-02 includes the indolent B-cell non-Hodgkin lymphoma (NHL) forms of follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma (MCL) and evaluates the safety and tolerability of BI-1206 in combination with rituximab. Phase 1 is a dose escalation for selection of the RP2D. Phase 2a is an expansion cohort at the RP2D.

In both trials, subjects in each phase receive one cycle of induction therapy. BI-1206 and rituximab (375 mg/m^2) are administered as intravenous infusions once weekly for a period of 4 weeks.

Subjects who show clinical benefit are eligible to continue onto maintenance therapy (Q8W).

The pharmacokinetic (PK) is assessed by measuring the blood serum concentrations of BI-1206 and rituximab. Pharmacodynamic analysis (PD) includes B cell depletion, FcγRIIB expression and BI-1206 receptor occupancy (RO).

Results: In CRUKD/16/001 twelve patients have received BI-1206 single agent therapy with up to 4 weekly doses of 100 mg. In 17-BI-1206-02, five patients have received up to 4 weekly doses of 100 mg BI-1206 in combination with rituximab.

PK/PD analysis is available for patients administered with BI-1206 in the dose range 0.4–100 mg. The PK parameters were calculated by non-compartmental analysis. The C$_{max}$ and exposure increased with the dose. A one-compartment elimination profile of BI-1206 could be observed. RO is dose proportionate and anticipated to yield high levels of receptor blockade at clinically relevant doses of BI-1206. Decrease in clearance and supra-proportional increase in exposure indicates that target-mediated drug disposition did not seem to be overcome yet. Interestingly, PD analysis showed a loss of peripheral B cells, including circulating MCL cells during the initial week of induction therapy of BI-1206 in combination with rituximab.

Conclusions: BI-1206 is a first-in-class therapeutic approach that utilizes a unique mechanism of action, circumventing anti-CD20 mAb internalization by FcγRIIB and thereby it may enhance the therapeutic activity. We report on the first data from our ongoing phase 1/2a clinical trials where BI-1206 is given as single agent and/or in combination with rituximab.

Keywords: B-cell lymphoma; mantle cell lymphoma (MCL); rituximab.

Disclosures: Karlsson, I: Employment Leadership Position: *BioInvent International AB.* **Järås, K:** Employment Leadership Position: *BioInvent International AB*; Stock Ownership: *BioInvent International AB.* **Gramming, E:** Stock Ownership: *BioInvent International AB.* **Lindell Andersson, M:** Employment Leadership Position: *BioInvent International AB.* **Mårtensson, L:** Employment Leadership Position: *BioInvent International AB*; Stock Ownership: *BioInvent International AB.* **Teige, I:** Employment Leadership Position: *BioInvent International AB*; Stock Ownership: *BioInvent International AB.* **Dyer, M:** Research Funding: *BioInvent International AB.* **Jerkeman, M:** Research Funding: *Celgene, Janssen, Abbvie and Gilead.* **Frendéus, B:** Employment Leadership Position: *BioInvent International AB*; Stock Ownership: *BioInvent International AB.* **McAllister, A:** Employment Leadership Position: *BioInvent International AB*; Stock Ownership: *BioInvent International AB.* **Davies, A:** Consultant Advisory Role: *Roche, Kite, Celgene, Acerta Pharma, MorphoSys, BioInvent*; Honoraria: *Roche, Celgene, Kite, Janssen*;

Research Funding: *Roche, Acerta Pharma, Celgene, Gilead, Karyopharma, GSK,*; Other Remuneration: *sponsorship to attend conferences: Roche, Celgene; Expert Testimony: Roche.*

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A PHASE 2 CLINICAL TRIAL OF RITUXIMAB AND β-GLUCAN PGG IN RELAPSED/REFRACTORY INDOLENT B-CELL NON-HODGKIN LYMPHOMA

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Introduction: Rituximab (R) as a single agent is effective in indolent B-NHL (iB-NHL), but response rates and durability fall in relapsed/refractory (r/r) disease. Resistance is in part due to variable complement activation. Imprime PGG (IPGG) is a yeast-derived β-glucan that, when complexed with anti-β-glucan antibodies (ABA) and opsonized by iC3b, activates innate immune cells through CR3. Combining IPGG with R, then, may improve responses in r/r iB-NHL through complement-dependent cytotoxicity (CDC).

Methods: Twenty-five patients with iB-NHL were enrolled on this study from Dec 2014-July 2018. IPGG (4mg/kg) and R (375mg/m^2) were given IV qwk x4. CT scans were done at 10wks and at 6 and 12m. No maintenance was given. The primary endpoint was overall response rate (ORR). Secondary endpoints included progression free survival (PFS) and duration of response (DOR). Assuming an ORR of 30% for R alone (GAUSS study), an ORR of 44% (11/25) was considered promising. Immunopharmacodynamic (IPD) analyses, such as cytokine and ABA levels, and assessment of IPGG binding to, and the immunophenotype of, innate immune cells, was done pre- and post-therapy.

Results: Patient characteristics will be presented. The majority had follicular lymphoma (64%). Over 1/3 had R-refractory disease. Median number of prior therapies was 2 (range 1-5). The ORR was 46% (11/24), with one CR. Median DOR was 12m and mPFS was 14m (Fig1 A,B). There was no association between response and histology, FLIPI, number of prior therapies, time from last therapy, or prior response to R. Prior response to R did not predict for DOR or PFS; patients treated in ≥4th line had an inferior PFS (7m vs NR, p=0.028). Treatment was well tolerated, with only 1 grade 3 toxicity (neutropenia); all others were grade 1/2 with infusion reactions, fatigue, and arthalgias most common. Increased levels of MCP-1, MIP-1b, MIP-1a, IP-10, and IL1-RA were seen after therapy, and IPGG binding to neutrophils and monocytes was detected, as was an increase in CD16+
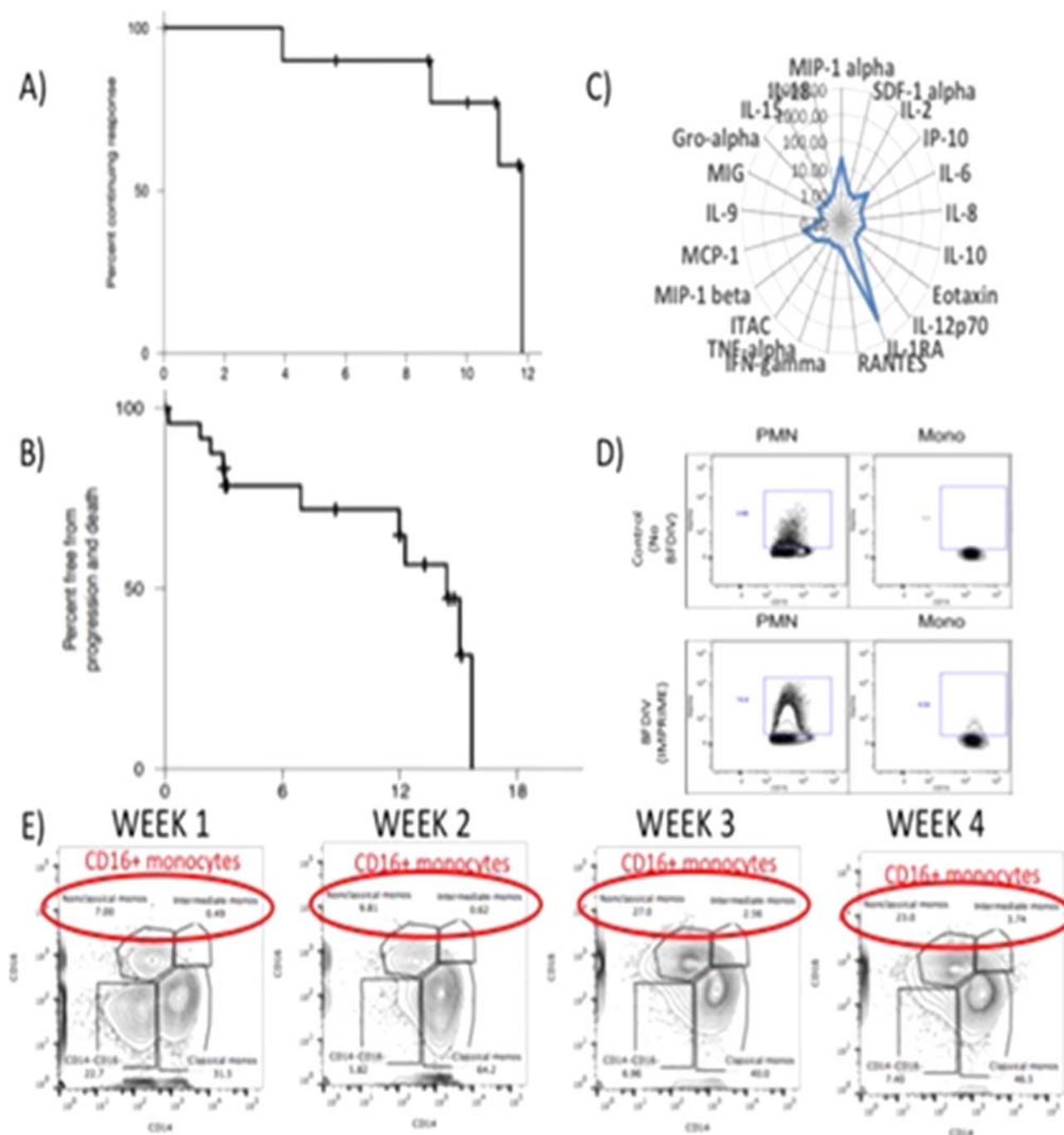
Figure 1. Duration of response (A) and progression-free survival curves (B). Examples of post-treatment cytokine changes (C), IPGG binding to myeloid cells (D), and increasing CD16 expression in monocytes (E) following treatment in representative individual patients.

monocytes, which are known for enhanced cytotoxicity as well as M1-polarizing functions (Fig1C-E). The relationship between ABA status and response is being investigated.

Conclusions: R-IPGG is well tolerated with a promising ORR of 46% in a r/r population. Importantly, treatment with R-IPGG resulted in a cytokine profile that is associated with M1-macrophage polarization and enhanced antigen presentation, and resultant expansion and activation of tumor infiltrating T cells. These IPD responses are not only important for the immune effector mechanisms required for combination with antitumor antibodies, like R, but also for the activity of immune checkpoint inhibitors. IPGG has been combined with pembrolizumab in solid tumors (NCT02981303), and pre- and on-treatment biopsies demonstrate increased M1-macrophage and activated T-cell tumor infiltration. These data support a trial exploring the

triplet combination of R-IPGG with checkpoint inhibition in r/r indolent B-NHL.

Keywords: B-cell lymphoma; complement-dependent cytotoxicity (CDC); immunoconjugates.

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TREATMENT EMERGENT ADVERSE EVENTS VARY WITH DIFFERENT PI3K INHIBITORS

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Introduction: Idelalisib (IDELA) and duvelisib (DUVA), both oral agents, and copanlisib (COPA), an IV agent, are PI3K inhibitors approved as monotherapy for relapsed / refractory (R/R) follicular lymphoma (FL). IDELA and DUVA are also listed in the National Comprehensive Cancer Network (NCCN) guidelines as monotherapy for R/R CLL. We compared safety profiles for IDELA vs. COPA and IDELA vs. DUVA and evaluated the effect of preexisting conditions on IDELA-induced TEAEs.

Methods: Using the Safety Analysis Set (SAS) for IDELA-treated patients (pts) with R/R iNHL (median duration of treatment [mDoT] 27 weeks [wks]) and TEAEs reported for COPA-treated pts with FL and other hematologic malignancies (Aliqopa® USPI, mDoT 22 wks, Dreyling *et al.*, J. Clin. Oncol. 2017 mDoT 22 wks, Dreyling *et al.*, Blood. 2017 mDoT 26 wks) or the SAS for IDELA-treated pts with R/R iNHL or CLL (mDOT 28.1 wks) and TEAEs reported for DUVA-treated pts with hematologic malignancies (Copiktra™ USPI, mDOT 39.1 wks), we compared all grade (aGr), grade 3/4 (Gr3/4, for IDELA vs. COPA) or grade ≥ 3 (Gr≥ 3, for IDELA vs. DUVA) TEAEs and the effect of preexisting comorbidities on selected IDELA-mediated AEs.

Comparisons are reported as estimate difference in proportions with p-values based on Fisher's exact test.

Results: IDELA-treated pts demonstrated significantly increased aGr and Gr3/4 AST and ALT elevation and diarrhea compared to COPA-treated pts. In contrast, COPA-treated pts showed significantly increased aGr and Gr3/4 hyperglycemia and hypertension relative to IDELA (Table 1A). IDELA-treated pts experienced significantly more Gr≥ 3, but not aGr, AST and ALT elevation than DUVA-treated pts. DUVA-treated pts experienced significantly higher aGr and Gr≥ 3 diarrhea + colitis, lower respiratory tract infection, anemia, and neutropenia; aGr mucositis, musculoskeletal pain, and thrombocytopenia; and Gr≥ 3 rash and fatigue than IDELA-treated pts (Table 1B).

We evaluated the effect of co-morbidities in IDELA-treated patients on emergence of Gr3/4 or Gr≥ 3 TEAEs observed more commonly in COPA- or DUVA-treated pts, respectively. IDELA-treated pts with pre-existing diabetes mellitus experienced more Gr3/4 hyperglycemia; however, pre-existing hypertension had no impact on aGr or Gr3/4 hypertension seen with IDELA. Concomitant systemic steroids also did not increase hyperglycemia or hypertension in IDELA-treated pts. A predisposition to diarrhea did not increase the incidence of diarrhea + colitis and a history of rash did not increase rash in IDELA-treated pts.

Conclusion: Although the approved PI3Kδ inhibitors may be perceived to be associated with synonymous AE profiles, this intra-class comparison highlights specific AE risks associated with each compound. Drug exposure differences and major limitations of cross-trial comparisons should be noted.

Keywords: chronic lymphocytic leukemia (CLL); follicular lymphoma (FL); PI3K/AKT/mTOR.

Table 1A. Treatment Emergent AEs or Lab Abnormalities in IDELA- vs. COPA-Treated Patients.

IDELA mDOT = 27 wks COPA mDOT = 22 – 26 wks TEAE or Lab Abnormality	All Grade (aGr)			Grade 3/4 (Gr3/4)		
	IDELA N=163 n (%)	COPA N=142 or 168 n (%)	P-Value	IDELA N=163 n (%)	COPA N=142 or 168 n (%)	P-Value
Colitis	7 (4.3)	1 (0.7)	0.0719	4 (2.5)	1 (0.7)	0.3769
Diarrhea	77 (47.2)	60 (35.7)	0.0347	22 (13.5)	8 (4.8)	0.0068
Fatigue	51 (31.3)	37 (26.1)	0.3753	2 (1.2)	3 (2.1)	0.6667
Hyperglycemia	11 (6.7)	90 (53.6)	<.0001	2 (1.2)	66 (39.3)	<.0001
Hypertension	9 (5.5)	59 (35.1)	<.0001	2 (1.2)	46 (27.4)	<.0001
Infection (multiple preferred terms)	24 (14.7)	35 (20.8)	0.1539	17 (10.4)	23 (13.7)	0.4018
Nausea	51 (31.3)	43 (25.6)	0.2737	3 (1.8)	1 (0.6)	0.3653
Neutropenia (including febrile neutropenia)	44 (27)	53 (31.5)	0.3987	35 (21.5)	42 (25)	0.5156
Pneumonitis	7 (4.3)	11 (7.7)	0.2297	4 (2.5)	2 (1.4)	0.6889
Pyrexia	54 (33.1)	38 (26.8)	0.2608	4 (2.5)	6 (4.2)	0.5228
Rash (including exfoliative skin reactions)	35 (21.5)	26 (15.5)	0.2017	4 (2.5)	3 (1.8)	0.7200
Thrombocytopenia	28 (17.2)	20 (14.1)	0.5293	8 (4.9)	7 (4.9)	1.0000
Increased ALT (lab parameter)	85 (52.1)	32 (22.7)	<.0001	29 (17.8)	2 (1.4)	<.0001
Increased AST (lab parameter)	71 (43.6)	39 (27.7)	0.0042	21 (12.9)	2 (1.4)	0.0001

Table 1B. Treatment Emergent AEs or Lab Abnormalities in IDELA- vs. DUVA-Treated Patients.

IDELA mDOT = 28.1 wks DUVA mDOT = 39.1 wks TEAE or Lab Abnormality	All Grade (aGr)			Grade ≥3 (Gr≥3)		
	IDELA N=261 n (%)	DUVA N=442 n (%)	P-Value	IDELA N=261 n (%)	DUVA N=442 n (%)	P-Value
Anemia (lab parameter)	84 (32.2)	198 (44.8)	0.0011	13 (5.0)	66 (14.9)	<.0001
Arthralgia	17 (6.5)	46 (10.4)	0.1004	0	1 (0.2)	1.0000
Constipation	27 (10.3)	57 (12.9)	0.3377	0	1 (0.2)	1.0000
Cough	80 (30.7)	111 (25.1)	0.1115	4 (1.5)	2 (0.5)	0.2019
Diarrhea or colitis	109 (41.8)	222 (50.2)	0.0347	30 (11.5)	101 (22.9)	0.0002
Dyspnea	36 (13.8)	52 (11.8)	0.4793	7 (2.7)	8 (1.8)	0.4325
Fatigue	88 (33.7)	126 (28.5)	0.1503	5 (1.9)	22 (5.0)	0.0433
Lower respiratory tract infection	4 (1.5)	46 (10.4)	<.0001	1 (0.4)	11 (2.5)	0.0381
Mucositis	0	61 (13.8)	<.0001	0	6 (1.4)	0.0897
Musculoskeletal pain	10 (3.8)	90 (20.4)	<.0001	1 (0.4)	6 (1.4)	0.2681
Nausea	68 (26.1)	104 (23.5)	0.4683	3 (1.1)	4 (0.9)	0.7146
Neutropenia (lab parameter)	138 (52.9)	276 (62.4)	0.0140	74 (28.4)	184 (41.6)	0.0005
Pneumonia (multiple preferred terms)	47 (18.0)	91 (20.6)	0.4328	41 (15.7)	67 (15.2)	0.9138
Pneumonitis	10 (3.8)	22 (5.0)	0.5761	6 (2.3)	NA*	N/A**
Rash (multiple preferred terms)	70 (26.8)	136 (30.8)	0.3035	8 (3.1)	41 (9.3)	0.0019
Thrombocytopenia (lab parameter)	75 (28.7)	170 (38.5)	0.0089	27 (10.3)	65 (14.7)	0.1059
Increased ALT (lab parameter)	114 (43.7)	177 (40)	0.3834	41 (15.7)	34 (7.7)	0.0014
Increased AST (lab parameter)	108 (41.4)	163 (36.9)	0.2616	32 (12.3)	24 (5.4)	0.0022

*NA = not available; **N/A = not applicable.

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BRENTUXIMAB VEDOTIN POPULATION PHARMACOKINETIC (POPPK) MODELLING IN ADULT AND PAEDIATRIC PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) HEMATOLOGIC MALIGNANCIES

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Introduction: Prior PK analyses of brentuximab vedotin PK in paediatric pts with R/R hematologic malignancies found a trend for decreased area under the curve (AUC) for antibody-drug conjugate (ADC) in low body-weight pts receiving the adult brentuximab vedotin dose (1.8 mg/kg Q3W). POPPK analyses utilizing data from paediatric
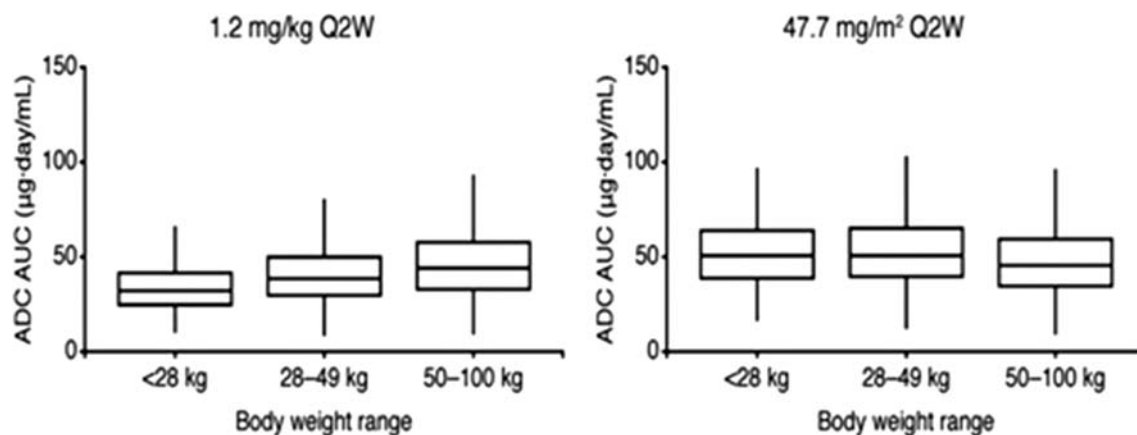
(NCT01492088) and adult studies (NCT00412282) were performed to quantify sources of variability, including body size effects, on ADC and monomethyl auristatin E (MMAE) PK in paediatric pts with classical Hodgkin lymphoma (cHL).

Methods: POPPK base-models were based on previously reported models. A full model was developed including all statistically-relevant prespecified covariate effects; a final model was chosen by retaining only the significant covariate effects (p<0.001). Model parameters were estimated using NONMEM (v7.3). The final model was used to simulate mg/kg or body surface area (BSA)-based dosing scenarios in paediatric pts to inform selection of posology that provides exposures matching those achieved in adults with weight-based (mg/kg) dosing.

Results: Data were collected from 84 pts with a median age of 25.7 years (range 7–87, 34 of whom [40.5%] were aged <18 years), median weight of 67 kg (range 21–154), and median BSA of 1.8 m^2 (range 0.86–2.8). ADC PK was described by a linear 3-compartment model with zero-order input and first-order elimination. In covariate analyses, BSA was the best predictor of body size effects on ADC PK, and was a strong predictor of clearance (CL), V_1, and V_3; anti-drug antibodies were predictors of ADC CL.

POPPK simulations of 1.8 mg/kg Q3W dosing found lower AUC values in small/moderate body weight paediatric pts (<28 kg/ 28–49 kg) compared with larger paediatric/adult pts (50–100 kg). Dosing at 71.5 mg/m^2 had comparable AUC values across all body weight ranges and a similar AUC to the reference scenario of 1.8 mg/kg dosing in the 50–100 kg group.

Simulations of low dose Q2W BV dosing (1.2 mg/kg and 47.7 mg/m^2), found similar results to the adult Q3W 1.8 mg/kg regimen. These results provide a hypothesis to further evaluate the relative performance of BSA-based vs weight-based dosing as an approach to minimize inter-patient variability in pediatric PK. AUC distributions with BSA-based dosing at 47.7 mg/m^2 across the weight ranges (including the <28 kg group) were similar to those achieved in the adult weight range (50–100 kg) with body weight-based dosing at 1.2 mg/kg (Figure). POPPK results for MMAE will be presented.

Conclusions: ADC POPPK results support the evaluation of a BSA-based dosing regimen (48 mg/m^2 Q2W) as an alternative dosing option in a phase 1/2 study to evaluate frontline A+AVD efficacy and safety in paediatric cHL pts (NCT02979522). Model-informed approaches to pediatric oncology drug development enable dose selection aimed at minimizing inter-pt variability during clinical evaluation of safety and efficacy.

Keywords: anaplastic large cell lymphoma (ALCL); brentuximab vedotin; classical Hodgkin lymphoma (cHL).

Disclosures: Suri, A: Employment Leadership Position: *Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.* **Mould, D:** Consultant Advisory Role: *Diane R Mould was a paid consultant.* **Song, G:** Employment Leadership Position: *Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.* **Kinley, J:** Employment Leadership Position: *Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.* **Venkatakrishnan, K:** Employment Leadership Position: *Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.*

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EXCEPTIONAL RESPONSE OF REFRACTORY ATLL WITH MDM4 AMPLIFICATION TO NOVEL STAPLED PEPTIDE DUAL MDM4/2 INHIBITOR

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Adult T cell leukemia lymphoma is an aggressive T cell leukemia caused by HTLV-1, which is resistant to most conventional chemotherapies during relapse. Herein we report the successful treatment of a chemo-refractory ATLL patient with a novel stapled peptide, ALRN-
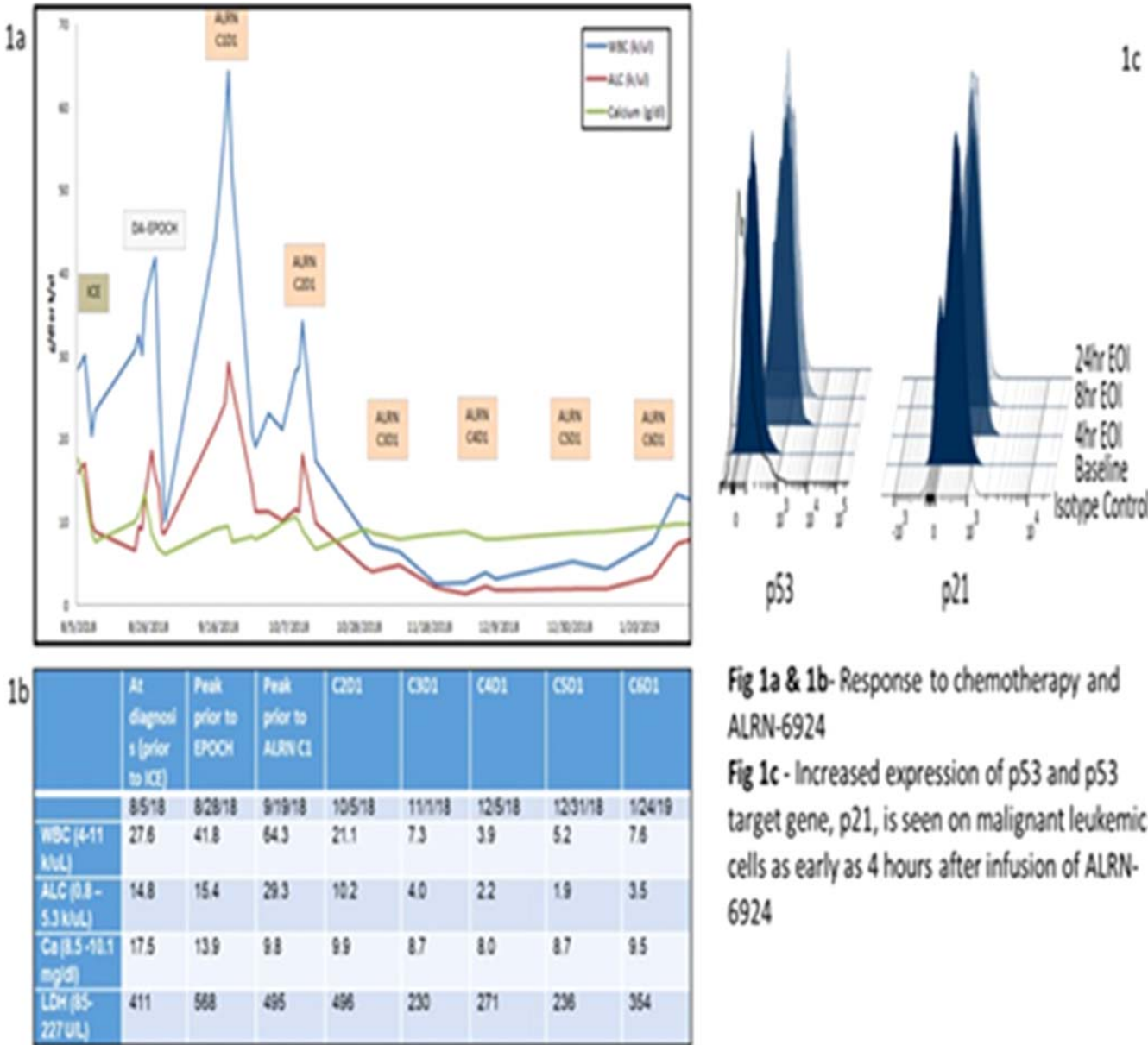
Fig 1a & 1b - Response to chemotherapy and ALRN-6924

Fig 1c - Increased expression of p53 and p53 target gene, p21, is seen on malignant leukemic cells as early as 4 hours after infusion of ALRN-6924

6924 that inhibits MDM4 and MDM2 and restores the function of p53 on a Phase 1 clinical trial [NCT02264613]. The stapled peptide is a small molecule comprised of the α-helical portion of p53 stabilized by a hydrocarbon cross-linker retaining the molecular target specificity of the underlying peptide with minimal off target effects.

A 52 yr old female presenting with tiredness, weight loss, hypercalcemia (17.5 mg/dl), high LDH (411 u/l) and lymphocytosis (14.8 k/ul) was diagnosed with acute ATLL based on a lymph node biopsy and peripheral blood flow cytometry. She was initially diagnosed with T cell lymphoma in 1995 (further details unknown) and underwent 5 cycles of CHOP. She received a cadaveric renal transplant for IgA nephropathy in 2016 and her immunosuppression was promptly decreased upon diagnosis. She was treated with polychemotherapy-ICE on 8/8/18, EPOCH on 8/31/18 with only a transient clinical response, and the disease progressed within 15 days (Fig 1a, 1b).

Targeted NGS showed wild type P53 and FISH showed MDM4 amplifications.

She was enrolled in the NCT02264613 clinical trial and started on ALRN 6924 on 9/19/18 and within 2 cycles, her hypercalcemia and lymphocytosis resolved. Response assessment after 4 cycles found her in a PR by revised ATLL criteria and IWG criteria.

Pharmacodynamic studies performed during drug treatment showed significant upregulation of p53 one day after ALRN-6924 infusion in this patient's leukemia cells (Fig. 1c). We also observed activation of the p53 target gene p21 in the patient's leukemia cells post infusion, demonstrating functional activation of p53 in vivo.

Several aspects are unique to this case. We found MDM4 amplifications (copy number=3) by FISH in this case, accounting for functional inactivation of the p53 gene, thus providing a possible explanation for the chemo-refractory nature of this patient's leukemia. The

remarkable response to single-agent therapy with ALRN-6924, a stapled dual MDM4/MDM2-inhibiting peptide, suggests particularly impressive efficacy of this novel targeted therapy for MDM4-amplified cases, and implies clinically detectable cytogenetic MDM4 amplifications as a possible biomarker to guide future use and patient selection.

Keywords: human T-lymphotropic virus (HTLV); P53; T-cell lymphoma (TCL).

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PRELIMINARY RESULTS OF ASTX660, A NOVEL NON-PEPTIDOMIMETIC cIAP1/2 AND XIAP ANTAGONIST, IN RELAPSED/REFRACTORY PERIPHERAL T-CELL LYMPHOMA AND CUTANEOUS T CELL LYMPHOMA

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Background: ASTX660 is an oral, novel nonpeptidomimetic, small-molecule antagonist of cellular/X-linked inhibitors of apoptosis proteins (cIAP1/2 and XIAP). ASTX660 is currently being evaluated in a first-in-human phase 1–2 study in patients (pts) with advanced solid tumors and lymphoma (ClinicalTrials.gov NCT02503423). In the phase 1 part of the study, the recommended phase 2 dose (RP2D) was identified with a favorable safety profile and initial evidence of clinical activity in a pt with mycoses fungoides (Mita et al, presented at the AACR-NCI-EORTC Conference 2017, abs #A091). Herein we report preliminary efficacy and safety data from the relapsed/refractory (r/r) peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL) Phase 2 cohorts.

Methods: Pts receive treatment with ASXT660 at the RP2D 180mg/day on Days 1 to 7, and 15 to 22 in a 28-day cycle. The primary endpoint is response rate as assessed by the investigator according to either the Lugano criteria (PTCL) or Global Assessment (CTCL). Adverse events (AEs) are assessed per CTCAE V4.03.

Results: As of 15 January 2019, 16 PTCL pts and 13 CTCL pts have received ASTX660. Pt characteristics: median (range) age: PTCL: 59 (39-81) years and CTCL: 57 (23-75) years; median prior therapies: PTCL: 3 (1-7) and CTCL: 3 (1-9). In the PTCL cohort the ORR is 28% (4/14); 2 pts have yet to reach their first assessment. Three responding pts remain on study drug for 7-10 months. Responses have been observed in pts with AITL and PTCL-NOS. In the CTCL cohort the global response is 25% (3/12); 1 pt has yet to reach their first assessment. Two responding pts remain on study drug for 4-6 months. Responses have been seen in pts with large cell transformation, sezary syndrome and visceral metastases. Among all pts, the most common related AEs of any grade (≥ 15%) were lipase elevation (38%), amylase elevation (34%), ALT elevation (28%), elevation (24%) and rash (24%). Related AEs ≥ Grade 3 occurring in ≥3 pts were rash (n=5) and lipase elevation (n=4). Accrual continues; updated efficacy and safety data will be presented at the meeting.

Conclusion: In ongoing Phase 2 cohorts ASTX660 has shown activity against PTCL and CTCL with manageable safety profile. These early data support continued development of ASXT660 for the treatment of r/r PTCL and CTCL. Correlative studies are aimed at identifying predictors of response.

Keywords: cutaneous T-cell lymphoma (CTCL); peripheral T-cell lymphomas (PTCL); XIAP.

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DECITABINE PLUS R-CHOP IN PATIENTS WITH NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA: INTERIM RESULTS OF A PHASE I/II STUDY

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Background: Diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of non-Hodgkin lymphoma and is heterogeneous in clinical, immunophenotypic and genetic features. Approximately 30-40% of the patients eventually experience disease progression or relapse upon R-CHOP treatment, particularly in the intermediate and high risk group. The benefit of high-dose chemotherapy combined with autologous stem cell transplantation as first-line consolidation therapy remains controversial. Novel agents in combination with R-CHOP need to be investigated to improve clinical outcome in this subset of DLBCL patients.

Abnormal DNA methylation can be observed in DLBCL patients. Aberrant DNA hypermethylation of tumor suppressor genes can result in transcriptional silencing and thus contributing to resistance to chemotherapy. Low doses of DNA methyltransferase inhibitor (DNMTI) can induce DNA demethylation and cell death with minimal DNA damage in susceptible DLBCL cells, and restore responsiveness to doxorubicin in chemotherapy-resistant DLBCL cells. Therefore, we conducted a phase I/II study to evaluate safety, tolerability and efficacy of decitabine in combination with R-CHOP in patients with newly diagnosed DLBCL (NCT02951728).

Methods: Patients with newly diagnosed DLBCL, aged 15-75 years, Eastern Cooperative Oncology Group (ECOG) score of 0-2, and International prognostic index (IPI) ≥ 2 were included. The primary objective of phase I study was to determine the maximum tolerated dose (MTD) of decitabine with a standard R-CHOP regimen. Patients received decitabine 10 mg/m^2, 15 mg/m^2 or 20 mg/m^2 on days 1-5, followed by standard dose of R-CHOP on days 6-11, every 28 days for a total of 6 cycles. Safety of the recommended phase II dose was then assessed in a dose-expansion population.

Results: From December 2016 to November 2018, a total of 58 patients were enrolled (phase I: 8, phase II: 50). Median age was 55.5 years (range, 25-74) and 79% of patients had IPI ≥ 3. The MTD of decitabine was 10 mg/m^2. The most common grade ≥ 3 toxicities were hematological adverse events (AEs), including neutropenia (grade 3: 46%, grade 4: 74%), thrombocytopenia (grade 3: 24%, grade 4: 17%), anemia (grade 3: 33%). Grade ≥ 3 neutropenia most frequently occurred during the first cycle with a short duration, median 4 days (range, 3-6). Granulocyte-colony stimulating factor prophylaxis was given from the second cycle. Grade 3 infection and dosage modification occurred predominantly in elderly patients. No major non-hematological AEs were observed. There was no death related with AEs. To date, 35 patients have completed treatment and were valuable for response evaluation. Thirty patients (86%) received a response, of which 26 received complete response and 4 received partial response. After a median follow-up of 12 months (range, 6-27), 25 patients were still in remission.

Conclusion: Decitabine is well tolerated when added to R-CHOP, and could improve responses in patients with DLBCL.

Keywords: dacarbazine; diffuse large B-cell lymphoma (DLBCL); immunochemotherapy.

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PHASE I DOSE-ESCALATION STUDY OF VENETOCLAX PLUS BEAM FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) FOR CHEMORESISTANT, RELAPSED/REFRACTORY, OR HIGH-RISK NON-HODGKIN'S LYMPHOMA (NHL); PRELIMINARY RESULTS

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D. Benson | **Y. Efebera** | **A. Rosko** | **S. Ayyappan** |
N. Grieselhuber | **S. Vasu** | **K. Larkin** | **N. Epperla** |
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Autologous stem cell transplant (ASCT) using carmustine, etoposide, cytarabine, and melphalan (BEAM) is standard treatment for patients with chemosensitive, relapsed, non-Hodgkin's lymphoma (NHL). Rational approaches to patients who relapse post-ASCT remains an unmet need. Venetoclax is an oral BCL-2 inhibitor that has significant single-agent and combination activity in r/r NHL. In this trial, we aim to test the safety of the combination of venetoclax plus BEAM followed by ASCT. We hypothesize that venetoclax will help overcome the chemoresistance of these tumors and decrease post-ASCT relapse.

We designed an open-label, single-center, phase I trial (NCT03583424) of venetoclax in combination with BEAM and ASCT for patients with r/r or high-risk NHL. Venetoclax is administered for 10 days at three dose levels (400, 800, 1200 mg) using a brief ramp-up schedule (Table 1). Accrual is planned in a standard 3+3 fashion to establish the maximum tolerated dose (MTD) of venetoclax with a

TABLE 1

D -17	D -16	D -15	D -14	D -13	D -12	D -11
Allopurinol	Mobilization and collection					
D -10	**D -9**	**D -8**	**D -7**	**D -6**	**D -5**	**D -4**
Venetoclax* 100 mg PO	Venetoclax 200 mg PO	Venetoclax 400 mg PO	Venetoclax+per dosing cohort Coh 1 = 400 Coh 2 = 800 Coh 3 = 1200	Venetoclax per dosing cohort BCNU 300 mg/m2	Venetoclax Etoposide 100 mg/m2 IV bid Cytarabine 100 mg/m2 IV bid	Venetoclax Etoposide 100 mg/m2 IV bid Cytarabine 100 mg/m2 IV bid
D -3	**D -2**	**D -1**	**D 0**			
Venetoclax Etoposide 100 mg/m2 IV bid Cytarabine 100 mg/m2 IV bid	Venetoclax Etoposide 100 mg/m2 IV bid Cytarabine 100 mg/m2 IV bid	Venetoclax Melphalan 140 mg/m2	Stem cell Infusion			

planned 10 patient expansion at the MTD. Inclusion criteria consists of adult, fit patients with B and T-cell NHL refractory after upfront induction therapy, in partial remission after induction therapy, with progression after salvage requiring ≥ 3 lines of therapy, or relapsed within 1 year of induction. Patients with chronic lymphocytic leukemia and central nervous system involvement by lymphoma are excluded. Toxicities were graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03 until BEAM regimen starts and then using the Bearman scale (for regimen-related toxicity) after.

Cohort 1 has fully accrued with 3 patients with r/r diffuse large B-cell lymphoma. All are males with median age of 64 (55-69) years. All 3 patients fully engrafted and were discharged home; with median time to neutrophil and platelet engraftment of 10 (11-13) and 12 (10-14) days respectively. Safety data for cohort 1 is presented in Table 2. After starting BEAM, only one patient experience grade 1 stomatitis, diarrhea and liver toxicity by the Bearman scale. We have not observed any tumor lysis syndrome. One patient developed pneumonia and respiratory failure (G3) after engraftment and hospital

TABLE 2 Demographics and safety data for cohort 1 (D-17 to D-6)

Adverse Event CTCAE	Grade 1-2
Anemia	3
Platelet count decreased	3
Hyperglycemia	3
Alkaline phosphatase increased	2
Lymphocyte count decreased	1
Back pain	1
Cough	1
Fatigue	1
Hypercalcemia	1
Abdominal pain	1
Alanine aminotransferase increased	1
Nausea	1
Peripheral sensory neuropathy	1

discharge but he had an underlying obstructive airway disease and he fully recovered. We are currently enrolling patients on cohort 2.

Keywords: autologous stem cell transplantation (ASCT); non-Hodgkin lymphoma (NHL); venetoclax.

MISCELLANEA

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EBV LEAVES ITS MARK: NEW EVIDENCE OF <<HIT AND RUN>> HYPOTHESIS IN B-CELL LYMPHOMAS FROM NON-CONVENTIONAL METHODS

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Introduction: Epstein-Barr virus (EBV) infection is a common feature of B cell lymphoproliferative disorders, including Burkitt lymphoma (BL) and diffuse large B cell lymphoma (DLBCL), with a frequency ranging from 10% to 100% in endemic BL cases. The role of EBV to B-cell lymphomas pathogenesis is largely unknown. EBV might be associated with all BL cases, including those diagnosed as EBV negative by routine methods [immunohistochemistry – IHC and EBV-encoded RNAs (EBER) in situ hybridization – ISH] thanks to a mechanism of hit-and-run. To escape the immune system, the viral genome is progressively lost from the host human cell.

Aim: The aim of this study was to identify the presence of EBV in a series of "EBV negative" B-cell lymphomas by applying conventional

(IHC and EBER-ISH) and non-conventional methods (EBV viral load measurement; EBV-encoded miRNAs detection, RNAscope assay).

Material and methods: We investigated a total of 179 cases: 16 BL, 34 DLBCL, 50 FL, 44 cHL, 10 T-LL, 20 HCL, 5 MCL. We performed EBER-ISH in all samples and then we screened by RT-qPCR targeting regions of EBV genome: BamH1 W and EBNA-1.

Results: We diagnosed 10 EBER-positive and 6 EBER-negative BL, 4 EBER-positive and 30 EBER-negative DLBCL, 47 EBER-negative FL and 3 EBER-positive, 12 EBER-positive and 32 EBER-negative HL. By qPCR, all cases reported a significant presence of the virus in 6/6 of BL, 11/30 DLBCL, 3/47 FL and 16/32 of HL cases, demonstrating EBV infection also in those samples diagnosed as "EBV negative". An higher viral loads in BL-EBER negative compared with the DLBCL, FL, HL EBER-negative cases was detected. The presence of the virus was also assessed and confirmed by the expression of EBV-encoded miRNAs (BART9-5p, BART10-3p, BART19-3p). In addition, we performed the RNAscope assay for targeting EBNA1 mRNA molecule and identify which cells were EBV positive. The positive staining was observed in few tumour cells of all lymphomas found to be EBV-positive by qPCR. Finally, considering the ability of EBV to manipulate the cellular epigenome that result in stable and heritable alterations, we studied the methylation status of *MGMT*, *E-cadherine* known to be significant hypermethylated by the virus. The level of methylation in EBER-negative samples but qPCR positive was higher in respect to EBER-negative cases where both genes were hypomethylated.

Conclusions: Though our findings do not represent a definitive proof of EBV presence inside the neoplastic cells, they highlight for the first time the possibility that EBV might contribute to the development of more cancers than simply those remaining viral genome-positive. Whether confirmed on a larger cohort of cases and different tumor types, the current study may support the rationale for strengthening the effort toward EBV vaccines that could potentially prevent the development of EBV-associated neoplasms independently of the presence or absence of viral genomes in the neoplastic cells, thus affecting the worldwide epidemiology of lymphomas.

Keywords: B-cell lymphoma; Epstein-Barr virus (EBV).

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SINGLE-CENTER ANALYSIS OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD) OUTCOMES WITH EPSTEIN BARR VIRUS (EBV) ASSESSMENTS

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Background: EBV is associated with the majority of cases of PTLD, a serious complication after solid organ and hematopoietic stem cell transplantation. EBV serum viral loads have been used to identify those at risk of this disease in EBV-positive cases. We aimed to characterize the clinical presentation, pathologic diagnosis and prognostic implications of EBV viral load and its response to treatment.

Methods: This is a retrospective observational study approved by IRB including all organ transplant patients with histologic diagnosis of PTLD between 2000 and 2018 at Loma Linda University Medical Center. Data wascollected by chart review. Kaplan-Meier survival estimates were used to determine primary outcomes of overall survival and progression-free survival.

Results: 68 patients (41 male, 27 female) were identified who developed PTLD following solid organ transplantation (22 kidney, 37 heart, 6 liver, 3 multi-organ). Median time from transplant to PTLD diagnosis was longest among neonatal transplants 12.0 years versus 3.76 in pediatric and 6.43 in adult transplantations. EBER positive histology was observed in 93% (39/42) of pediatric population versus 52% (12/23) of the adult population. During treatment 16 (23%) experienced acute rejection with 5 (7%) graft losses. The largest subset, monomorphic diffuse large B-cell lymphoma (n = 34), had a median overall survival of 15.1 years. M-DLBCL with high levels of EBV copy load > 10,000 IU/mL had a trend toward worse overall survival of 9.0 versus 15.1 years in < 10,000 IU/mL (HR 2.74, p = 0.14). Treatment resulted in complete serologic EBV copy load response in 15/19 and a trend toward improved overall survival with a median OS not yet reached versus 13.7 years in incomplete responders (HR 0.76, p = 0.76).

Conclusions: Our study introduces the hypothesis that initial EBV viral loads and treatment response may have prognostic importance. The characteristics, pathologic diagnosis, and treatment response for this cohort of patients will be presented.

Keywords: post-transplant lymphoproliferative disorders (PTLDs).

TABLE 1

Histology		All	Pediatrics	Adults
Histology	Polymorphic	15	13	2
	M-DLBCL	33	15	18
	HL	7	4	3
	M-Burkitt's	4	4	0
Antiviral Used	Yes	57	38	19
	No	9	3	6
M-DLBCL Treatment	Rituximab	16	12	4
	Rituximab + Chemotherapy	15	4	11

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A RETRO-PROSPECTIVE STUDY IN HIV+ PATIENTS AFFECTED BY LYMPHOMA: THE MUSTHAL MULTICENTER EXPERIENCE IN NORTHERN ITALY

Figure 1
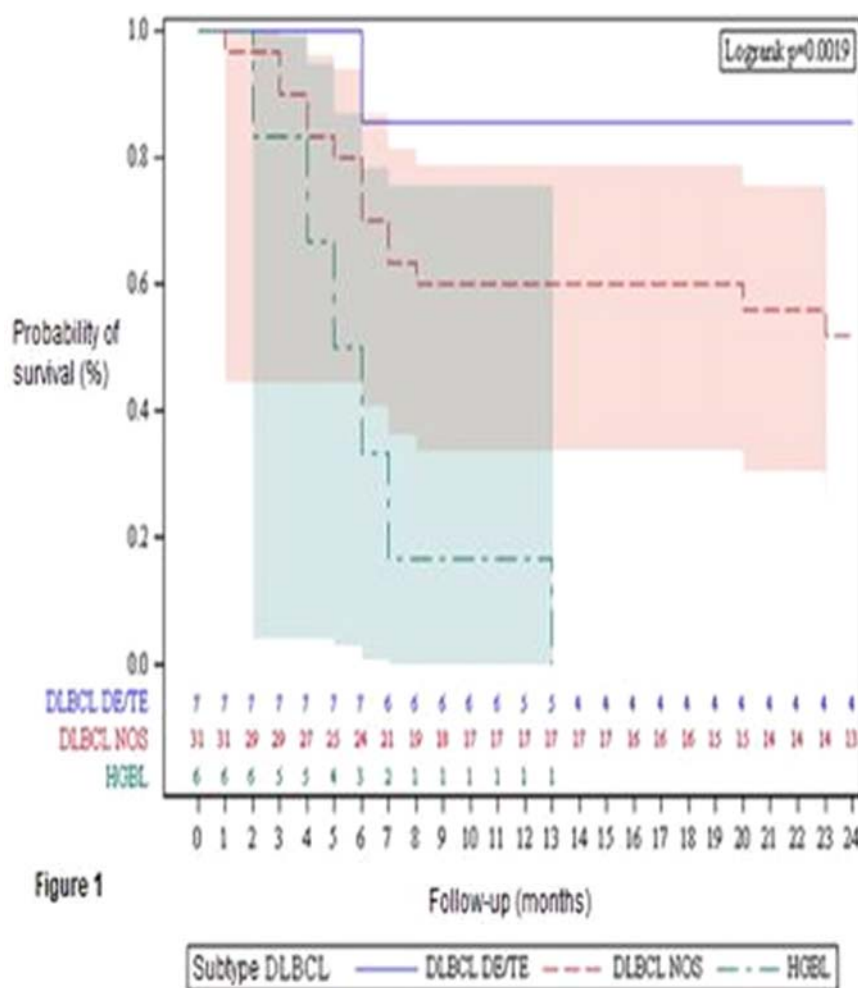
24-months OS of different DLBCL subtypes according to cytogenetic and immunohistochemical features

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Introduction: HIV+ people carry a higher risk of developing lymphomas. Combined antiretroviral therapy (cART) improves survival, but HIV+ patients (pts) with lymphoma are still considered poorly treatable. Our aim was to describe biopathological features of a cohort of HIV+ pts affected by lymphoma and their clinical implications.

Methods: we conducted a retrospective and prospective multicentre study collecting clinical and immunovirological data in HIV+ pts affected by non-Hodgkin lymphoma (NHL) from 2003 and 2017 in six centres in Northern Italy, to evaluate overall (OS) and progression-free survivals (PFS). We collected biopathological data in 50 NHLs to better define the differences in term of outcome among diffuse large B-cell lymphomas (DLBCL) not otherwise specified (NOS), DLBCL

double/triple expressors (DE/TE) and high grade B-cell lymphomas (HGBL). Differences in survival were tested with χ^2 or Mann-Withney tests. OS was estimated by Kaplan Meyer. Hazard ratios (HR) for mortality for each biopathological subtype were corrected for IPI score and T CD4+ lymphocyte count (CD4+) at diagnosis.

Results: 127 pts were enrolled: 86 DLBCL, 18 Burkitt lymphomas (BL), 6 primary central nervous system lymphomas (PCNSL), 11 plasmablastic lymphomas (PBL), 3 primary effusive lymphomas (PEL) and 3 anaplastic large T-cell lymphoma (ALCL). Median age was 48.9 years. 30% of the pts were on cART at NHL diagnosis. The burden of disease was usually high at diagnosis. 80/127pts received R-CHOP and 40/127 pts R-DA-EPOCH or more intensive regimens. Median follow up is 28 months. 2-years OS and PFS were 69.3% and 61.3%, respectively. No differences in OS among different lymphoma subtypes were noted. We observed 33 progressions and 3 relapses after 1° line treatment (36/127, 28.3%). Factors significantly associated with a worse survival in multivariate analysis were Age, high IPI score and CD4+ < 200/µl at diagnosis. Pts with CD4+ < 200 cells/µl at diagnosis had a significantly higher HR for lymphoma-related deaths, especially those with a low disease burden (HR 4,136 if IPI ≤ 3). The use of cART at diagnosis had no impact on OS. The 50 pts screened for biopathological features resulted in 36 DLBCL NOS, 8 DLBCL DE/TE and 6 HGBL. HGBL showed a particularly high risk of poor response and early mortality as 6/6 pts died within 13 months, despite aggressive treatment schedules (Figure 1).

Conclusions: Usual lymphoma prognostic scores were found to be reliable in our cohort of HIV+ pts; an independent effect of CD4+ at diagnosis on NHL survival was noted. Biopathological analyses should be standardised to find rapidly HGBL-affected pts also in HIV+ population, as the response to chemotherapy seems to be poor. The majority of pts who progressed after first line of therapy died without receiving autologous bone marrow transplant. We advocate the possibility to create new studies and treatment protocols in these pts.

Keywords: high-grade B-cell lymphoma with or without rearrangement of MYC and BCL2 and/or BCL6; human immunodeficiency virus (HIV).

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CHEMOTHERAPY IN HIV-POSITIVE PATIENTS WITH NON-HODGKIN LYMPHOMA: A SINGLE INSTITUTION RETROSPECTIVE STUDY

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Background: HIV-positive (HIV+) patients (pts) have a 25-fold higher risk of developing non-Hodgkin's lymphomas (NHL). Two independent prognostic factors influence the incidence and prognosis of HIV+ pts: highly active antiretroviral therapy (HAART) and the CD4+ lymphocyte (CD4+) count.

The diagnosis of NHL can occur simultaneously with the diagnosis of HIV infection (naive patients) or after the diagnosis of HIV infection and during HAART (experience-patients).

Our aim is to compare the characteristics, the response to treatment and the survival of the NHL treated with first line chemotherapy, between naive patients and experience-patients.

Methods: This is a single institution retrospective cohort study conducted in Ospedale Luigi Sacco Milan, Italy. We selected pts aged >18 years with diagnosis of HIV infection and NHL from January 2007 to January 2017. We included HIV+ on HAART treated with first line R-CHOP-like chemotherapy regimens.

Differences between naïve and experience-pts were assessed using Chi-square, Fisher's exact or Wilcoxon Rank-sum test. Overall survival (OS), progression-free survival (PFS) and response rate (RR) were compared across groups using the log-rank test or Cox regression model.

Results: We enrolled 46 HIV+ pts: 11 naive-pts and 35 experience-pts (exp-pts). No difference was observed in median age at diagnosis (49 vs 48 ys p=0.40), sex (male 72.7% vs 85.7 p=0.37), characteristic histological types PEL, PSNCL, BL, PBL (p=0.13).

Naïve-pts had higher stage at diagnosis (stage IV 90.9% vs 41.2% p=0.05). No difference was observed in frequency of B symptoms (40% vs 41% p=0.99), bulky masses (18.2% vs 20.6% p=0.99), ≥ 2 extranodal sites (45.5% vs 40% p=0.61), CNS involvement (44.4% vs 38.2% p=0.99), AIDS-defing diseases (44.4% vs 28.6% p=0.43) HCV/HBV infection (p=0.08/0.99). Naive-pts were more likely to be in advanced aaIPI (intermediate-high risk: 90.0% vs 58.1% p = 0.11). As expected at NHL diagnosis naïve-pts had lower median CD4 + count (102 vs 222/mcl p=0.05).

During R-CHOP-like chemotherapy naïve-pts developed more frequently infectious toxicity (50% vs 10.7% p=0.02).

During a median (IQR 2-44) follow-up of 12 months no difference was observed in RR (CR 60% vs 62.5% p=0.85), median OS (67 mts vs 69.4 mts p=0.3) and PFS (p=0.8).

Conclusions: CD4+ count is the independent prognostic factor with the greatest influence on OS [exp vs naïve-pts: OS HR 0.83 (95% CI); OS/CD4+ HR 1.80 (95% CI)]. Our study supports the role of immediate start of HAART in combination with chemotherapy in naive patients. A compromised immune status in HIV+ pts does not require modification of chemotherapy schedule; therefore naive-pts should be treated with standard chemotherapy regimens.

Keywords: diffuse large B-cell lymphoma (DLBCL); human immunodeficiency virus (HIV).

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DOSE-ADJUSTED EPOCH FOR LYMPHOMA-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A STONE TWO BIRDS
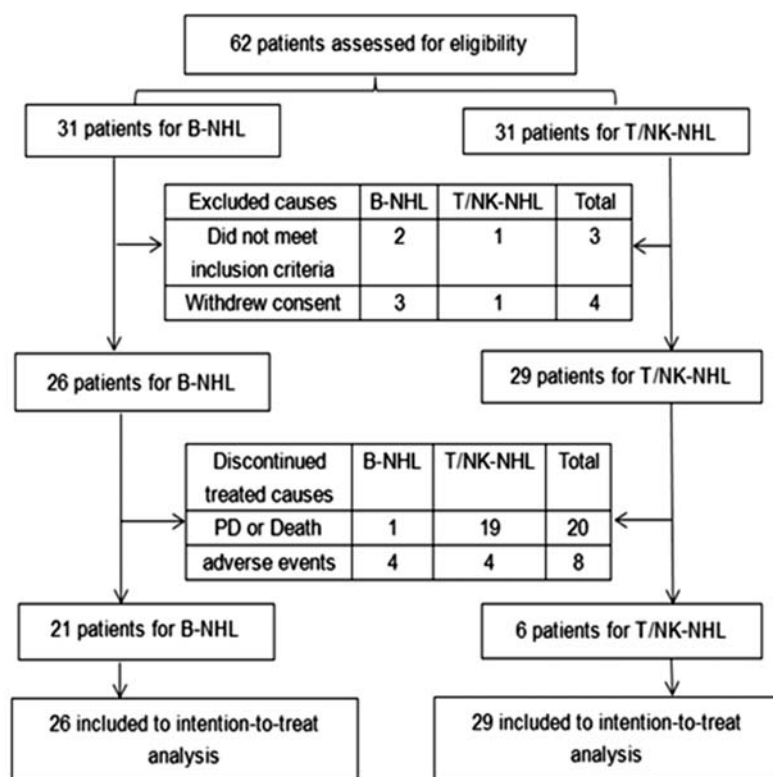
Figure 1. Trial profile (abreviations: HLH=hemophagocytic lymphohistiocytosis; NHL=non-Hodgkin's lymphoma; NK=natural killer; PD=progressive disease)

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Purpose: Lymphoma-associated hemophagocytic lymphohistiocytosis (LA-HLH) has a high fatality rate and the worst outcome. The major cause of LA-HLH is aggressive non-Hodgkin's lymphoma (NHL), especially T/NKT cell lymphomas. Until now, there is no recommended therapeutic schedule for this fatal disease. Dose-adjusted (DA) EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) shows effective activity in patients with aggressive NHL, which also contains the critical drugs for HLH of HLH-94/04. The investigators therefore developed DA-EPOCH regimen to treat non-Hodgkin's lymphoma with hemophagocytic lymphohistiocytosis and assess its clinical outcome including safety and efficacy.

Methods: We did a single-arm, open-label, phase 2 clinical trial in previously untreated patients diagnosed as NHL with HLH (NCT01818908). We planned for B-NHL patients with HLH to receive six cycles of the DA-EPOCH-R regimen while for T/NK-NHL patients with HLH to receive six cycles of the DA-EPOCH regimen. Also, after achieving more than partial response (PR) after six cycles of DA-EPOCH±R regimen, autologous stem cell transplantation (ASCT) for B-NHL or allogeneic stem cell transplantation (allo-SCT) for T/NK-NHL was followed as consolidation therapies. The DA-EPOCH±R regimen included etoposide (50 mg/m^2), vincristine (0.4 mg/m^2), and doxorubicin (10 mg/m^2) at daily doses by continuous intravenous infusion over 96 hours (days 1–4); cyclophosphamide (750 mg/m^2, intravenous bolus, day 5), prednisone (60 mg/m^2 bid, days 1–5) with or without rituximab (375 mg/m^2, day 0). The cycle was repeated every 3 weeks. The primary endpoint was the overall response rate (ORR).

Results: We enrolled 26 B-NHL and 29 T/NK-NHL patients between March, 2013 and Dec, 2015 (**Figure 1**). The median cycle was six (range 1-6) for all B-NHL patients and three (range 1-6) for T/NK-NHL patients. The overall response rate was 80.7% for B-NHL while only 13.8% for T/NK-NHL. With a median follow-up of 52 months (35-75 months) for B-NHL with HLH, 5-year progression-free survival (PFS) and overall survival (OS) was 56.7 ± 9.9% and 73.1 ± 8.7%. B-NHL patients who received ASCT (12 patients) have significantly superior PFS (*P*<0.001) and OS (*P*=0.033) than patients not (9 patients). For the T/NK-NHL with HLH, 6-month PFS and OS rate was 10.3 ± 5.7% and 24.1 ± 7.9%. Grade 3/4 neutropenia toxicities occurred on 43.9% of all cycles.

Conclusions: DA-EPOCH-R regimen as front-line treatment followed by ASCT as consolidation treatment demonstrates a highly effective and safe strategy for B-NHL patients with HLH while DA-EPOCH cannot improve outcomes for T/NK-NHL patients with HLH.

Keywords: DA-R-EPOCH; histiocytes; non-Hodgkin lymphoma (NHL).

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A VALIDATION, WITH NEW CLINICAL APPLICABILITY, OF A CLINICAL-GENETIC RISK MODEL THAT PREDICTS THROMBOSIS WITH HIGH SENSITIVITY IN PATIENTS WITH LYMPHOMA

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The incidence of venous thromboembolic events (VTE) in patients with lymphoma is estimated around 10%, increasing the morbidity and mortality for this group of patients. Khorana scale has been developed to assess VTE risk in cancer patient but it is not useful for lymphoma patients. Recently, a new risk score has been developed to predict VTE in this specific population (Throly). Likewise, the incorporation of genetic variables into a VTE risk model improved VTE risk assessment in solid tumors (TiC-ONCO). In this context, the aim of our study was to evaluate if the same approach of TiC-ONCO is applicable to patients with lymphoma.

Between 2014 and 2018, 254 lymphomas were diagnosed in our center, 33 of them presented VTE. The F5 rs6025, F5 rs4524, F13 rs5985, SERPINA10 rs2232698, in addition to clinical variables (immobilization, tumor type, Ann Arbor score, mediastinum extension, and personal thrombotic history) were significant associated to VTE risk and used to build the TiC-ONCO-associated Lymphoma score (TiC-Lympho). The Khorana, ThroLy and TiC-Lympho scores were compared through predictive value and area under the curve (AUC). We observed a cumulative incidence of VTE of 9% (Fig.1). The results of sensitivity, specificity, predictive value and AUC of the Khorana, Throly, and TiC-Lympho are shown in Table 1 and Table 2.

Our results demonstrated that the incorporation of genetic-clinical data to assess VTE risk it is not only valid to solid tumors, but it is also relevant in lymphoma. In fact, it is the first time that this approach has been applied to haematological patients. It is noteworthy that the predictive capacity for VTE in lymphoma patients of our score far exceeds that obtained by the Khorana and Throly scores. Therefore, TiC-Lympho will allow us to categorize lymphoma patients adequately at diagnosis and offering an individualized thromboprofilaxis.

Keywords: immunochemotherapy; non-Hodgkin lymphoma (NHL); prognostic indices.

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NEUTROPHIL TO LYMPHOCYTE RATIO, PLATELET TO LYMPHOCYTE RATIO, AND RISK OF THROMBOEMBOLISM IN PATIENTS WITH LYMPHOMA RECEIVING CHEMOTHERAPY

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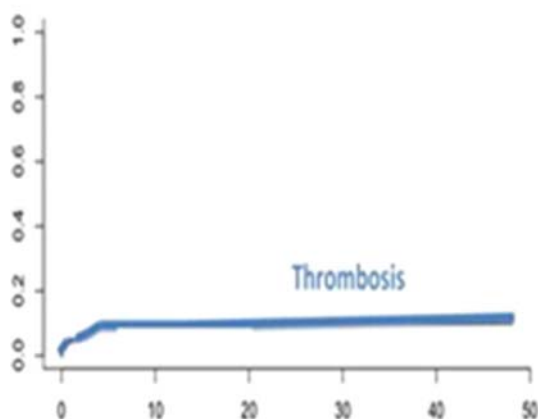
Figure 1. Cumulate incidence of Thrombosis

Table 1

Score	Sensitivity	Specificity	PPV	NPV
Tic-Lympho	93,55	54,49	23,36	97,98
Khorana	35,48	71,79	16,60	84,41
Throly	45,16	64,74	50	86,63

Table 2

Score	AUC	(95% CI)	p
Tic-Lympho	0,783	(0,721-0,837)	<0,0001
Khorana	0,503	(0,431-0,574)	0,902
Throly	0,579	(0,50-0,648)	0,0319

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Introduction: Thromboembolism (TE) is common and one of major causes of morbidity and mortality in patients with malignancy. The neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) are biomarkers for systemic inflammation. Principal advantage of NLR and PLR is their modest computability from complete blood count (CBC). Several publications showed predictive strength of high NRL for development of venous thromboembolism (VTE) in cancer patients receiving chemotherapy. However, the prognostic values of the NLR and PLR in patients with lymphoma have not been elucidated. We aimed to investigate the association between NLR, PLR and future risk of TE, in a prospective cohort of lymphoma patients receiving chemotherapy.

Methods: A total of 484 patients who were diagnosed with lymphoma (including non-Hodgkin and Hodgkin lymphoma; excluding chronic lymphocytic leukemia/small lymphocytic lymphoma) at the Clinic for Hematology, Clinical Centre of Serbia, were prospectively included in the study. Data for newly diagnosed and relapsed patients who had completed a minimum of one chemotherapy cycle were collected for all venous and arterial TE events from time of diagnosis to 3 months after the last cycle of therapy. NLR and PLR were calculated according to the CBC. TE was diagnosed objectively based on radiographic studies, clinical examination, and laboratory evaluation. Logistic regression analysis and ROC curve were performed to assess the association of NLR and PLR with TE.

Results: The mean patients' age was 53 years (range, 18–89 years); 52.3% were males. Most patients were newly diagnosed and had advanced stage disease: Ann Arbor stage III 21.1% and stage IV, 42.5%. A total of 242 patients (50.0%) had high-grade NHL; 137 (28.3%) had low-grade NHL; 84 (17.4%) had HL; 21 (4.3%) had other forms. 35 (7.2%) patients developed thromboembolic events. There were 30 patients with venous TE (6.2%), and 6 with arterial TE (1.2%), while one patient had both. NLR and PLR were significantly higher in TE patients compared to patients without TE (p=0.001 and p=0.002, respectively). The NLR was positively associated with PLR (p<0.001). A positive NLR was considered 3.1 or higher, while a positive PLR was a ratio of 10 or more. The ROC curve analysis demonstrated acceptable specificity and sensitivity of NLR and PLR in predicting TE. NLR and PLR were found to be prognostic factors for the TE in lymphoma patients (relative risk [RR] = 4.1, 95% confidence interval [CI] = 1.9-8.7, p<0.001 and RR=2.9, 95% CI =1.3-6.3, p=0.008, respectively). In multivariate model NLR was found to be independent prognostic factors for the TE (RR=4.5, 95% CI=2.1-9.9, p<0.001).

Conclusion: The NLR and PLR demonstrated significant powerfulness in prediction of future risk of TE in lymphoma patients. Simplicity, effectiveness, modesty and practicability qualify these new tools for routine TE prognostic assessment.

Keywords: chemotherapy; immunochemotherapy; prognostic indices.

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CLINICAL OUTCOMES FROM VENETOCLAX BASED THERAPY IN PATIENTS WITH RELAPSED/REFRACTORY B-CELL LYMPHOMAS

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Background: B-cell non-Hodgkin lymphomas (B-NHL) are frequently characterised by deregulation of the B-cell leukaemia/lymphoma-2 (BCL2) family of anti-apoptotic proteins. Venetoclax is a BCL2-specific inhibitor approved for chronic lymphocytic leukemia (CLL), with activity in other B-cell malignancies in small cohorts. Venetoclax has been available for patients (pts) with relapsed/refractory B-NHL via the Abbvie compassionate access scheme or as off label treatment, however data regarding effectiveness in this setting are scarce.

Methods: We performed a multicentre, international, retrospective study of the clinical outcomes and safety of pts with B-NHL (excluding CLL) who received venetoclax either as monotherapy or as combination treatment in Australia or Denmark between 7/2016 and 12/2018.

Results: The baseline characteristics of the 24 eligible pts are summarised in the table (Figure 1a). Target daily dose varied from 400-1200mg and was reached in 77%. Among all pts, the objective response rate (ORR) was 35%, clinical benefit rate (SD/PR/CR) 65% and CR rate 8%; one patient each with MCL and transformed follicular lymphoma. The Waldenstrom macroglobulinaemia patient

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Patient characteristics, n=24	
Characteristic	Study patient cohort, n (%)
Sex	
Male	14 (58%)
Female	10 (42%)
Median age (years) at starting Venetoclax (range)	64 (46-78)
Diagnosis	
Mantle cell lymphoma	12 (50%)
Diffuse large B cell lymphoma	5 (22%)
Transformed follicular lymphoma	2 (8%)
Richter's transformation of CLL	2 (8%)
Follicular lymphoma	1 (4%)
Waldenstrom macroglobulinaemia	1 (4%)
Unspecified	1 (4%)
TP53 mutated or 17p deleted	5/9 (56%)
MCL	3/5
Richter's transformation of CLL	2/5
ECOG performance status	
0-1	14/19 (74%)
2-4	5/19 (26%)
Unknown	5/19 (26%)
B symptoms	11/22 (50%)
Ann Arbor Stage	
I-II	1/21 (5%)
III-IV	20/21 (95%)
Median no. of prior therapies (range)	4 (1-7)
Prior Autologous stem cell transplant	7/24 (29%)
Prior BTK inhibitor therapy	14/24 (58%)
Best response to most recent prior therapy	11 (46%)
PD	4 (17%)
SD	9 (37%)
PR/VGPR/CR	
Concurrent systemic therapy	8 (33%)
Ibrutinib	4
Rituximab	1
Steroids/other	3
Concurrent radiotherapy	6 (25%)
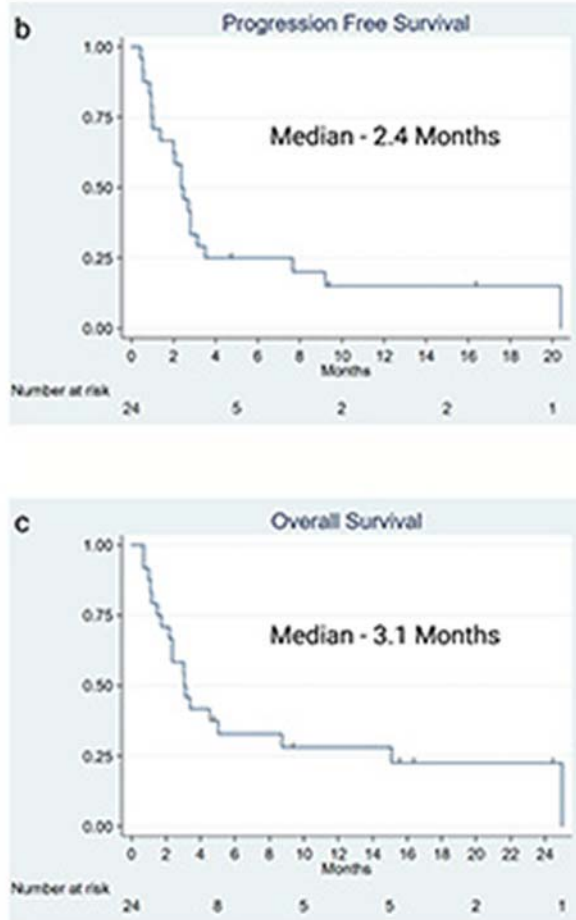
Figure 1.
a) Patient baseline and treatment characteristics
b) Progression free survival (all patients)
c) Overall survival (all patients)

achieved a MR with monotherapy, improving to a PR when cyclophosphamide and dexamethasone were subsequently added. The ORR was 50% and 27% for pts treated with venetoclax combined with additional systemic therapy and monotherapy respectively. The ORR was 42% in MCL (ORR 66%, n=2 in those receiving combination treatment, and ORR 33%, n=3 in BTK inhibitor refractory pts) and 0% in DLBCL. 1/5 patients bearing TP53 aberrations (n=5 [MCL n=3, Richter's n=2]) had a response (PR). Median time on venetoclax, PFS and OS for all pts were 2.7, 2.4 and 3.1 months respectively (Figure 1b,c). 5 pts had a PFS >6 months (maximum 20.4 months), and 6 pts (25%) were alive at last follow-up, with 4 (17%) remaining on venetoclax. 75% (n=3) of these received concurrent therapy (ibrutinib n=2) and 25% (n=1) received monotherapy. Causes of death included progressive lymphoma (78%, n=14) and infection (11%, n=2). 10 (50%) discontinued therapy due to PD and 4 (20%) due to adverse events. The most frequent grade 3/4 adverse events were neutropenia(35%, n=6), febrile neutropenia(18%, n=3), tumour lysis syndrome (laboratory 33%, n=8 [MCL n=6, DLBCL n=1, Richter's n=1], clinical 8%, n=2 [MCL n=2]), thrombocytopenia (17%, n=4) infection (12%, n=3) and anaemia (8%, n=2), and diarrhoea (4%, n=1)

Conclusions: In a heavily pre-treated population of pts with various B-NHL, venetoclax resulted in modest activity and an adverse event profile similar to published trials. Response rates were numerically higher in patients receiving concurrent systemic therapy, suggesting potential synergy, especially with ibrutinib. Venetoclax had limited activity in the low numbers of pts with MCL refractory to BTK inhibitors, and minimal activity in DLBCL and pts with TP53 aberrations.

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INCREASED CYTOMEGALOVIRUS (CMV) REACTIVATION IN PATIENTS TREATED WITH BENDAMUSTINE BASED REGIMEN IS CORRELATE WITH DRAMATICAL REDUCTION OF CD4+ T LYMPHOCITES

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Bendamustine (BENDA) alone or in combination with other drugs is being increasingly used in the treatment of chronic lymphocytic leukaemia (CLL), non-Hodgkin lymphomas (NHL), and multiple myeloma (MM) due to its safety and efficacy. Variable infection rates both in BENDA monotherapy and in BENDA-containing regimens have been documented, while it is reported that CD4+ lymphocytes are severely reduced during BENDA therapy, that their recovery is impaired and that CD4+ lymphopenia persists for a long time after the end of BENDA administrations.

Since January 2017 we started monitoring levels of CD4+ lymphocytes of patients undergoing to a treatment with schedules BENDA based. At today 51 consecutive patients, 15 female and 36 male with median age of 70 old years (range 40-88 years), had at least one CD4+ lymphocytes detection. All the patients had a B-NHL diagnosis. 34 patients were treated with BENDA plus Rituximab (R-BENDA), while 17 with BENDA plus Rituximab plus Dexamethasone (RD-BENDA).

In 41 new patients, our measurements started before the beginning of BENDA courses, with a median of basal CD4+ lymphocytes of 617 cells/mm3 (range 154-1278 cells/mm3). After 2/3 BENDA courses, it dropped to 42 cells/mm3 (range 0-118 cells/mm3). (P value <0.004)

30 patients are evaluable on their last planned BENDA course (4 to 6 courses). Their median of CD4+ lymphocytes was 53 cells/mm3 (range 15-160 cells/mm3).

25 patients are evaluable after 3 months from the end of the therapy. Their median of CD4+ lymphocytes was 94 cells/mm3 (range 41-288 cells/mm3).

After 6 months, CD4+ lymphopenia is still present in 15 evaluable patients. Their median of CD4+ lymphocytes was 186 cells/mm3 (range 114-399 cells/mm3). In 15 (30%) patients we have documentedthe reactivation of CMV virus; 7 in the group RD-Benda and 8 in the group R-Benda (41% and 23% of treated patients).

This single-center study provides further evidence that BENDA regimens for lymphoproliferative diseases are associated with a deep reduction of CD4+ lymphocytes which persists even after 6 months off-therapy and requires an adequate monitoring and prophylaxis to avoid infections.

Keywords: Bendamustine; CD4.

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OFF-LABEL USE IN LYMPHOMA PATIENTS IN SWITZERLAND

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Background: Off-label use (OLU) of drugs in haematology/oncology is increasing, however, little is known on the frequency of OLU in lymphoma therapy and whether it is more common than for solid tumors. It is also unclear how often requested OLU is actually reimbursed by health insurers.

Methods: We conducted a cross-sectional study using information from routinely collected health data. We included all patients treated for a malignant disease between January 2015 and July 2018 in the Department of Medical Oncology of the University Hospital Basel and manually screened their electronic patient records. For all patients, for which at least one request for OLU reimbursement was issued, we extracted information on patient demographics, disease characteristics, treatment history and correspondence with the health insurer. We defined OLU as intentional drug use outside of the Swissmedic label. Main outcomes were the drug type and approval/rejection of an OLU request. We used descriptive statistics to investigate the prevalence of OLU for lymphoma therapy compared to solid tumors and to determine whether health insurers more often reimburse intended OLU for lymphoma compared to solid tumors.

Results: We screened health care records of 1865 patients. 159 (8.5%) had a lymphoma and 1706 (91.5%) a solid tumor. Among lymphoma patients, OLU requests are more prevalent than among patients with a solid tumor (30 of 159 requests [18.9 %] versus 214 of 1706 requests [12.5%]). Preliminary results show that top three lymphomas with OLU requests were follicular lymphoma (N=7), diffuse large B-cell lymphoma (DLBCL, N=7) and primary central nervous system lymphoma (PCNSL, N=4). Most frequently requested drugs were rituximab (N=18), obinutuzumab (N=4) and thiotepa (N=4). There was more intended

OLU in first line treatment of lymphoma than for solid tumors (23 of 30 [76.7%] versus 125 of 214 [58.4%]). Requests for OLU for lymphoma patients were less frequently rejected by health insurers (3 of 30 [10.0%] versus 64 of 214 [29.9%]). In two cases, OLU of the same drug and the same lymphoma therapy indication was approved by one health insurer for reimbursement but rejected by another.

Conclusion: In Switzerland, off-label use seems to be more frequent in lymphoma patients than in patients with solid tumors. Their chances for reimbursement of OLU also seem to be higher. However, reimbursement decisions seem to be inconsistent, which reflects intransparency of the current decision making process on OLU reimbursement requests by health insurers. Reasons for these differences remain to be elucidated and further data will be presented at the meeting.

Keywords: chemotherapy; non-Hodgkin lymphoma (NHL).

Figure 1: Best responses to CT-P10 during the observation period

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CT-P10 RAPID INFUSION IN PATIENTS WITH NON-HODGKIN'S LYMPHOMA OR CHRONIC LYMPHOCYTIC LEUKAEMIA: INTERIM RESULTS FROM A NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY

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Introduction: CT-P10 is the first rituximab biosimilar approved in Europe for treatment of rheumatic diseases and specific blood cancers including non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL). To minimise the risk of infusion-related reactions (IRRs), the recommended rituximab administration protocol is a slow initial infusion rate with gradual up-titration; however, rapid infusion protocols are now used widely for second and subsequent infusions in patients with no serious complications from their first infusion. A recent meta analysis (Polwart, 2017) reported an IRR rate of 8.8% for rapidly infused rituximab; there are limited data for CT-P10. This study aimed to evaluate the safety and effectiveness of rapidly infused CT-P10 in patients with NHL or CLL in a real world setting.

Methods: This non-interventional post-authorisation safety study is ongoing in 4 European countries (United Kingdom [UK], Spain, France, Italy) and involves collection of data from the medical records of consenting adult patients with NHL or CLL who received rapidly infused CT-P10 (i.e. total infusion time ≤90 minutes) during routine care. Index date (day 1): date of first rapid CT-P10 infusion, given in the second or a subsequent cycle. Safety and effectiveness data are collected for 6 months post-index (or to death, if sooner). Primary outcome: incidence of IRRs on day 1 or 2 post-index. Response to CT-P10 is as documented by the local investigator. Interim results are based on a data cut on 18 Jan 2019. Where n is less than the total number of patients, data were missing.
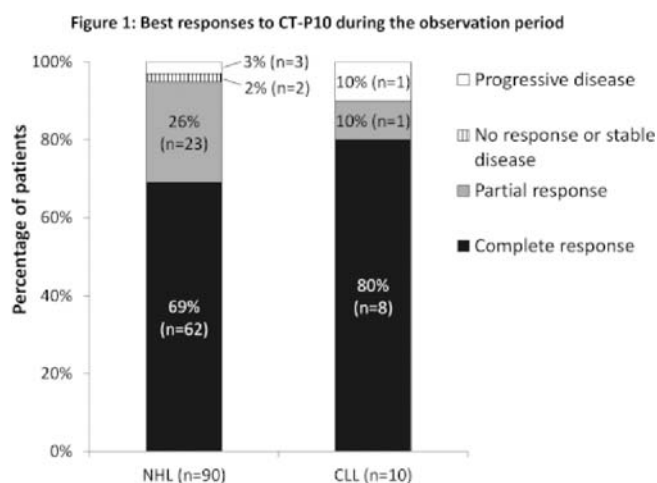
Results: The interim analysis includes 110 patients enrolled from the UK and Spain. 98 patients (90%) have NHL (68 [62%] diffuse large B-cell lymphoma, 30 [28%] follicular lymphoma) and 11 (10%) have CLL (n=1 diagnosis missing). Other patient characteristics at index: 66 (60%) male; median age 68 years (interquartile range [IQR] 59–74) (n=109); median disease duration 0.2 years (IQR 0.1–0.3) (n=109); 22 (20%) patients with prior NHL/CLL treatment (n=109); Eastern Cooperative Oncology Group performance status (n=71): 0 (n=34, 48%), 1 (n=27, 38%), 2 (n=3, 8%), 3 (n=6, 8%) or 4 (n=1, 1%); Ann Arbor stage for NHL (n=52): I (n=4, 8%), II (n=5, 10%), III (n=7, 13%) or IV (n=36, 69%); Binet stage for CLL (n=7): A (n=4, 57%), B (n=1, 14%) or C (n=2, 29%). 8/106 patients with data available (8%) had IRRs recorded on day 1 or 2 post-index. Ten IRRs were reported (fatigue [n=3], oropharyngeal pain, vomiting, nausea, rash, headache, generalized oedema, peripheral oedema [all n=1]), of which 8 were grade 1 (mild), 1 was grade 2 (moderate) and 1 was grade 3 (severe [oropharyngeal pain during cycle 2, unlikely to be related to CT-P10 according to local investigator opinion]). Best responses to CT-P10 during the observation period are shown in Fig. 1.

Conclusions: This is the first multi-country study to investigate the safety and effectiveness of rapidly infused CT-P10 in a real world setting. Early results suggest that the IRR rate for rapidly infused CT-P10 is similar to rates previously reported for reference rituximab.

Keywords: chronic lymphocytic leukemia (CLL); non-Hodgkin lymphoma (NHL); rituximab.

Disclosures: kang, H: Employment Leadership Position: *Celltrion Healthcare.* **Kim, S:** Employment Leadership Position: *Celltrion*

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PATIENT-REPORTED EXPERIENCE AND PREFERENCES WITH TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL), DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) AND FOLLICULAR LYMPHOMA (FL)

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Background: Patients (pts) are now receiving treatment for CLL, DLBCL and FL via multiple modes of administration. There is little quantitative evidence on pts' experiences and preferences regarding these modes of administration.

Methods: We developed a survey to understand pt experiences, preferences and factors that contribute to treatment decision making. The survey was designed through consultation with medical experts, pt advocacy organisations and research team members. Concept elicitation and cognitive pretesting were conducted with pts to inform the survey content. Pt-reported information was quantified via Likert options that measured aspects of a pts most recent treatment. Additionally, pt preferences for subcutaneous (SC) injection and intravenous (IV) infusion were measured through direct assessment with a hypothetical choice between the two and modelled using a logit model.

Results: The survey was completed by 424 pts who were associated with The Leukemia & Lymphoma Society and/or the Lymphoma Research Foundation (309 pts with CLL, 59 pts with DLBCL and 69 pts with FL). Respondents had a mean age of 66 (range: 22–95) and 51% were female; 68% (n=290) had prior or current experience with oral anti-cancer therapies, 81% with IV therapies (n=342) and 10% with SC therapies (n=41). Among pts currently receiving oral, IV or SC therapy, 6% (13/227) on oral, 41% (29/70) on IV and 0% (0/6) on SC reported that it was very difficult/difficult to go about their daily activities on the day they received medication. Most pts currently taking oral (85%) or SC (100%) therapies indicated that they were not at all bothered by the amount of time it took to receive their medicines. However, 49% of pts currently receiving IV therapy indicated that they were bothered (slightly/moderately/very/extremely) by the amount of time. Logit model results suggested that being female, having higher education and having prior SC experience were associated with preferring SC over IV administration in the hypothetical preference question, while prior IV experience was associated with a preference for IV administration. Among pts who indicated that they had received both IV infusion and SC injection treatments (n=36), a majority (61%) preferred SC administration.

Conclusions: Evaluations of pt preferences and priorities are increasingly important as pts are enabled to take more active roles in decision-making for their treatment pathways and as novel therapies are developed. We identified pt demographics and information that may be predictive of preferences for certain treatment modalities. The resulting data can be used for education of the clinical community in a landscape that includes several new therapies.

Employment Leadership Position: *Full-time salaried employee of Research Triangle Institute d/b/a RTI Health Solutions, an independent research institute, which was retained by Genentech to conduct the study that is the subject of this abstract. There is no connection between an RTI employee's compensation and the projects on which they work. Information about projects with other clients is confidential.*; Research Funding: *Full-time salaried employee of Research Triangle Institute d/b/a RTI Health Solutions, an independent research institute, which was retained by Genentech to conduct the study that is the subject of this abstract. There is no connection between an RTI employee's compensation and the projects on which they work. Information about projects with other clients is confidential.* **Comenencia-Ortíz, E**: Employment Leadership Position: *Roche, Genentech*; Stock Ownership: *Roche, Genentech*; Other Remuneration: *Employment by a for-profit health care company that funded any part of this research: Genentech.* **Masaquel, A**: Employment Leadership Position: *Genentech, Inc.*; Stock Ownership: *Roche*. **Ravelo, A**: Employment Leadership Position: *Genentech*; Stock Ownership: *Genentech*.

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REAL-WORLD ASSESSMENT OF PRACTICE EFFICIENCY WITH THE INTRODUCTION OF SUBCUTANEOUS RITUXIMAB

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Introduction: Rituximab (R), available as an intravenous (IV; R-IV) infusion or subcutaneous (SC; R-SC) injection, is used in the treatment of follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukaemia (CLL). This study evaluated real-world practice efficiency changes associated with the adoption of R-SC by studying differences in chair time by route of administration.

Methods: We conducted a retrospective analysis of practice care delivery measures before and after adoption of R-SC at Memorial Sloan Kettering Cancer Center (MSKCC). Data for patients (pts) with FL, DLBCL or CLL receiving R-based therapy from September 2016 to September 2018 were extracted from the electronic medical record. A linear mixed effect multivariate model with random intercept was used to analyse the association between treatment type (R-IV vs R-SC) and chair time (defined as the difference in pt room-in and room-out times) in the year prior to and following R-SC adoption at MSKCC. Model covariates included treatment time and location, therapy type (monotherapy vs combination) and pt demographics. Given the prolonged infusion time, pts' first dose of R-IV was excluded from the analysis.

Results: Data were collected during 6744 visits (3018 visits prior to R-SC adoption and 3726 after) for 1503 pts receiving R. Pts receiving R-IV combination therapy had a mean chair time of 203 minutes (min); overall, R-SC injection reduced chair time by a mean of 92 min (p<0.001 vs R-IV). Monotherapy, regardless of route, reduced chair time by a mean of 30 min (p<0.001) compared with combination therapy, and mean chair time was further reduced by 39 min (p<0.001) for R-SC pts receiving monotherapy. Reductions in chair time increased over time following initial adoption of R-SC (p=0.042), and were greater at the lymphoma-specific site than multispecialty oncology infusion centres (p<0.001).

Conclusions: Adoption of R-SC results in substantial time savings for both the pt and health system as measured by reduced chair time and improved pt throughput. Given increasing constraints on infusion chair space, increased utilisation of R-SC may improve practice efficiency and pt access to care.

Disclosures: Matasar, M: Consultant Advisory Role: *Genentech, Bayer, Merck, Juno Therapeutics, Roche, Teva, Rocket Medical, Seattle Genetics*; Stock Ownership: *Merck*; Honoraria: *Genentech, Roche, GlaxoSmithKline, Bayer, Pharmacyclics, Janssen, Seattle Genetics*; Research Funding: *Genentech, Roche, GlaxSmithKline, Bayer, Pharmacyclics, Janssen, Rocket Medical, Seattle Genetics*; Other Remuneration: *Genentech, Roche, Seattle Genetics, Bayer*. **Shapouri, S:** Employment Leadership Position: *Genentech, Inc.*; Stock Ownership: *Roche*. **Ravelo, A:** Employment Leadership Position: *Genentech, Inc.*; Stock Ownership: *Genentech, Inc.* **To, T:** Employment Leadership Position: *Genentech, Inc.*; Stock Ownership: *Genentech, Inc.* **Dawson, K:** Employment Leadership Position: *Genentech, Inc.*; Stock Ownership: *Roche/Genentech, Inc.*

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GRANISETRON TRANSDERMAL DELIVERY SYSTEM USE IN LYMPHOPROLIFERATIVE DISEASE: A SINGLE CENTER EXPERIENCE

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Background: Chemotherapy induced nausea and vomiting (CINV) represents a major impairment of quality of life in patients who undergo to a single-day and multi-day chemotherapy leading to a lower

adherence to further chemotherapies. The prevention of acute (0-24 h) and delayed (25-120 h) CINV associated with moderately emetogenic chemotherapy (MEC-AC based) and highly emetogenic chemotherapy (HEC) recommented by international guidelines (MASCC, NCCN, ASCO) consists in a combination of corticosteroids (i.e. dexametasone), type 3 serotonine receptor antagonist (5HT3Ra) and neurokinin-1 receptor antagonist (NK1Ra). Granisetron Transdermal Delivery System (GTDS) was developed as 5HT3Ra for CINV prophylaxis over 7 days.

Methods: In this retrospective non comparative single center experience a total 19 outpatients were observed from Nov 2016 to March 2019: 13 pt were female and 6 were male, median age of pts in treatment was 52 yrs (range: 26-69). 5 Pts with cHodgkin Lymphoma, 2 pts Marginal Zone Lymphoma, 3 Mantle Cell Lymphoma, 2 Primary Mediastinal Large Cell Lymphoma, 2 pts Follicolar Lymphoma, 4 pts with Diffuse Large B Cell Lymphoma. GTDS was used as second line therapy after Ondansetron iv in MEC (Bendamustine, CHOP) and in HEC (Cisplatin-based CHT) instead was used as third line after palonosetron i.v. and Netupitant-Palonosetron p.o. in Dacarbazine based CHT. A multiday CHT (range: 2-4 days) was administered in 6/19 pts. A single dose patch granisetron was administered a day before CHT for 7 days continuously. The complete remission consists in complete control (CC) of acute and delayed CINV (no vomiting/retching, no nausea, no other rescue medication).The tolerability was evaluated true reported adverse events and laboratory data as AST, ALT, creatinine and potassium.

Results: GTDS was safe and no dizziness, headache or severe constipation were observed. CC was observed in 83% (5/6) of symptomatic pts during acute CINV and 81% (13/16) of pts with delayed CINV. DTDS failed in 19% (3/16) of pts with delayed CINV and other medications such as metoclopramide, promazine and aprepitant were administered. A good control of delayed CINV was evidenced in multi-day CHT's pts. No significant increase of AST and ALT were observed and mild hyperkaliemia was reported only 2/19 pts.

Conclusion: The GTDS provides effective, well tolerated control of CINV associated with MEC or HEC in one or multi day chemotherapy.

Keywords: ABVD; classical Hodgkin lymphoma (cHL); diffuse B-cell lymphoma (DLBCL).

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FUNCTIONAL PREDICTORS OF CHEMOTHERAPY TOXICITY IN ELDERLY LYMPHOMA PATIENTS – A PROSPECTIVE PILOT STUDY

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Introduction: Treatment of lymphoma often includes curative intent chemotherapy. In older patients, oncologists often rely on their clinical impression and the patient's age to make treatment decisions. More objective measures may be more accurate and reproducible in predicting chemotherapy eligibility and toxicity.

Methods: This is a single centre pilot feasibility study in patients ≥70 yrs with lymphoma, planned for systemic chemotherapy. Patients completed geriatric tools (eg. Hurria and CRASH questionnaires, gait speed test and grip strength, CSHA Frailty Scale) and physical tests were repeated with each cycle. Sarcopenia at the L3 level was measured on baseline and follow-up CT scans. Primary outcomes were feasibility, with correlation between chemotherapy toxicity and geriatric tools, as the main 2ry outcomes.

Results: 30 patients were enrolled, with a median age of 77 yrs (range 69-90) and 59% being male. The treating diagnosis was DLBCL in most (59%). Chemotherapy treatments most commonly included RCHOP (59%). The chemotherapy was dose reduced from the start in 8 patients (28%), and in 3 pts during tx (10%). Using the Hurria score, 18 pts (60%) were intermediate and 5 (17%) high risk for chemotherapy toxicity. Similarly, CRASH identified 11 (38%) as medium-low, 15 (50%) as medium-high and 2 (7%) as high risk. The Hurria tool on median took 2 min (1-5 min) vs. 20 min (5-30min) for the CRASH score. Sixteen pts (53%) experienced CTCAE grade 3-5 toxicity. The most common gr ≥3 AE was febrile neutropenia (4 pts). Dose delays occurred in 9 pts (31%) and 5 pts (17%) required hospitalization. 2-yr OS was 73%. The CSHA frailty score, grip strength and sarcopenia worsened throughout treatment and had not recovered by the 1 mo visit post-treatment (Figure 1). On univariate analysis, only the CSHA frailty score and Hurria risk score were associated with Grade 3 or higher events (Tables 1). On

TABLE 1 Probability of ≥gr3 AEs

UV	OR(95%CI)	p-value
Hurria		
Low (0-5)	Ref	
High (10-19)	7.77 (1.01,59.8)	**0.048**
Int (6-9)	5.58 (0.835,37.3)	0.07
CSHA frailty	2.53 (1.60,3.99)	**<0.001**
Grip Strength (lbs)	0.98 (0.95,1.03)	0.607
Sarcopenia	0.69 (0.06,6.94)	0.75
MV	**OR(95%CI)**	**p-value**
Hurria		
Low (0-5)	Ref	
High (10-19)	0.898 (0.076,10.5)	0.932
Int (6-9)	5.20 (0.759,35.6)	0.093
CSHA	2.81 (1.76,4.37)	<0.001

Figure 1

a. CSHA Frailty scores
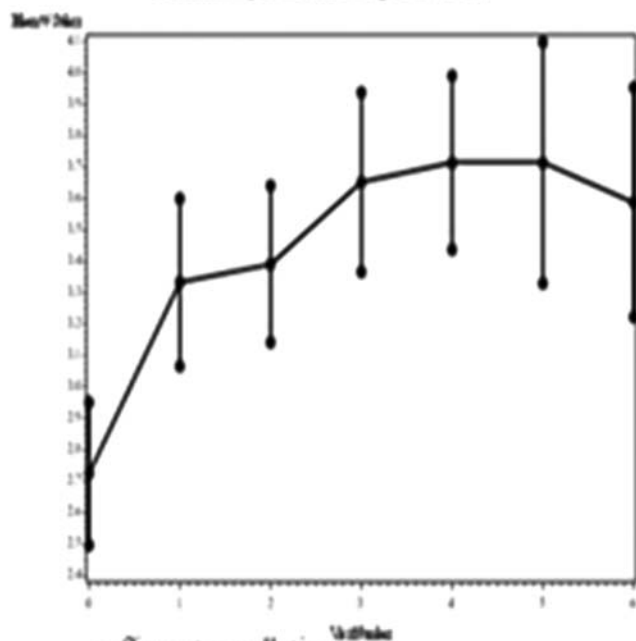
b. Grip strength scores
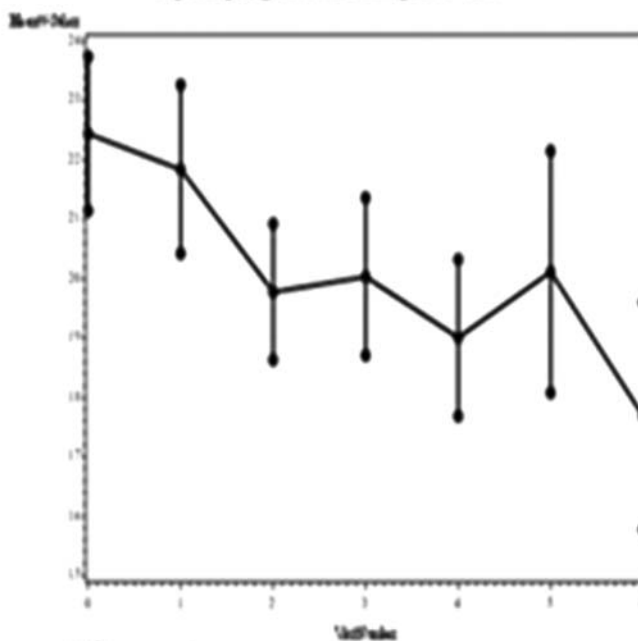
c. Six meter walk times
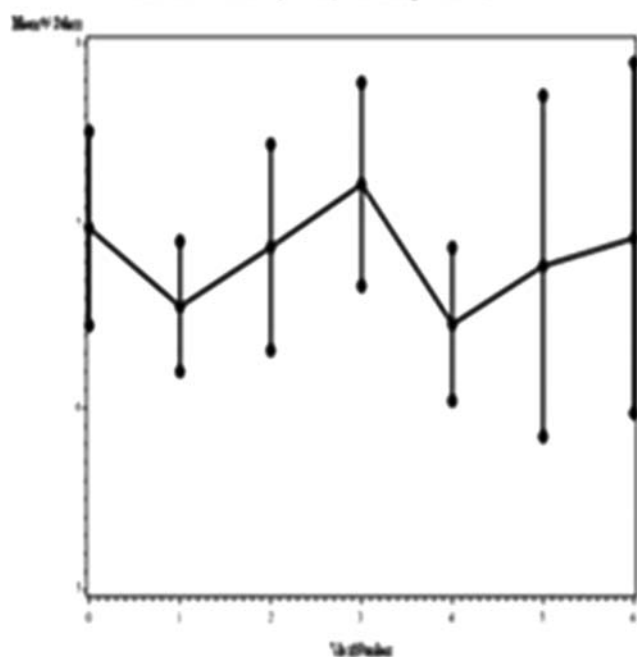
d. Sarcopenia
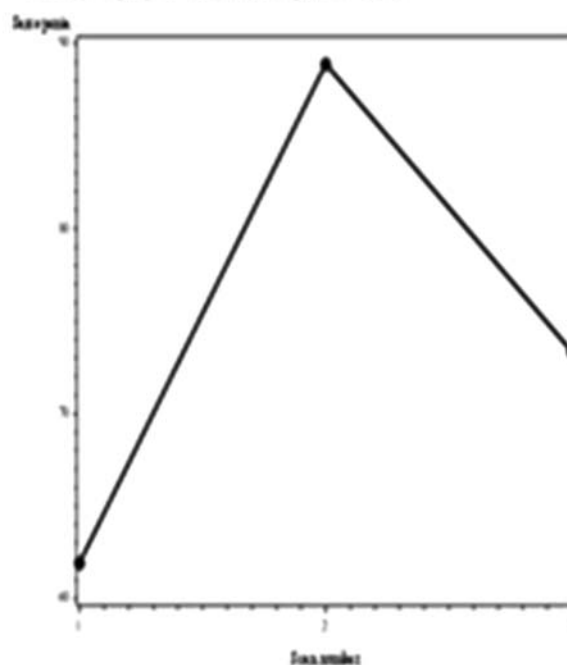
multivariate analysis, the CSHA Frailty score and Hurria risk score retained significance for any AE, but only CSHA frailty for gr. 3 or higher events.

Conclusions: Older patients can be treated with full-dose systemic chemotherapy, but the rate of toxicity is high. The Hurria tool, which is much shorter to administer and seems to predict toxicity. The CSHA Frailty is the most robust predictor of chemotherapy toxicity, and is a very simple measure to administer. We plan routine measurement of these simple tools in all lymphoma patients at our centre.

Keywords: elderly; non-Hodgkin lymphoma (NHL).

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IS THERE A ROLE OF RESPIRATORY TRAINING IN THE SUPPORTIVE CARE OF LYMPHOMA PATIENTS? - SINGLE CENTRE PROSPECTIVE TRIAL

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Introduction: Better outcome of lymphoma patients calls for improvement in the field of supportive care for the survivors who often struggle with long time side effects of intensive treatment. Fatigue and physical activity intolerance interfering with daily activities remain the most common issue. Physical training improves physical fitness, not only by increasing muscle mass and cardiovascular capacity but - more importantly it restores sympathovagal (SV) balance.

However, not all patients can participate in training. Based on data of disabled cardiological and neurological patients benefits of respiratory training using a pressure threshold device to increase inspiratory and expiratory muscle strength are known. Improvement of respiratory parameters decreases the number of infections and improve quality of life. Moreover, breathing is closely related to SV system. In our pilot project, we analysed feasibility and potential impact of respiratory training on lymphoma survivors.

Methods: 11 patients were enrolled (9 Hodgkin lymphoma, 2 Non-Hodgkin), 1 to 3 months after the end of intensive systemic chemotherapy (eBEACOPP or R-CHOP), all in complete remission. We measured the breathing muscle strength using Micro RPM device. The set of additional tests contained: BMI, body composition (the body composition (InBody 203©), aerobic capacity (cycle spiro-ergometry, Lode excalibur©), sympathovagal balance (DiANS PF 8©), and muscle strength (hand grip and leg flexor and extensor test). The respiratory training was performed with Threshold IMT/PEP device. The resistance level was individually set by a physiotherapist based on the patients´ initial parameters. Patients were provided by a training lesson and video instruction course with recommended exercises and breathing techniques and subsequently were checked regularly online and every month in person. The resistance was gradually increased up to 30% if tolerated. All above mentioned functional tests were repeated after 8 weeks of training.

Results: We observed statistically significant improvement only MIP (maximum inspiratory pressure; p.0153), other parameters - MEP (maximum expiratory pressure; p.28), and FVC (forced vital capacity; p.15) were also improved, though not significantly. The training was well tolerated, no infections occurred. On the other hand, the respiratory training did not affect BMI, body composition, muscle strength, and cardiovascular fitness or SV balance.

Conclusion: Respiratory training led to respiratory parameters improvement of lymphoma survivors, we also proved its feasibility and safety in our patients. Nevertheless, there was no impact on SV balance or physical fitness. We can conclude, that respiratory training cannot replace the physical exercise in lymphoma patients in remission. On the other hand, improvement of respiratory function can be more beneficial for inpatients, especially embedded to avoid respiratory complications.

Keywords: immune system; performance status.

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A CROSS-SECTIONAL STUDY EXAMINING HOW KNOWLEDGE OF LYMPHOMA SUBTYPE AFFECTS THE PATIENT EXPERIENCE

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Introduction: When first diagnosed, many lymphoma patients are told they have non-Hodgkin Lymphoma (NHL). NHL is not a disease, it is a series of 80+ subtypes, each requiring different diagnostic evaluation and treatment approaches. Over one-third of patients are not told their subtype. It is critical that patients be informed on their subtype so they can better understand their diagnosis and treatment options, and more effectively source relevant, case-appropriate information. To examine how knowledge of subtype affects the patient experience, the Lymphoma Coalition (LC) used the 2018 Global Patient Survey (GPS) on Lymphomas and CLL.

Methods: The 2018 LC GPS was available in 19 languages and was hosted on a third-party portal from January-March 2018. Globally, 6631 participants took part (70+ countries). Raw data was entered, merged, and cleaned in IBM SPSS v21. For this analysis, two subpopulations were defined and compared. Patients who were informed of their subtype at diagnosis (n=4215) were compared against those who were not/not sure (n=2361) using cross-tabulations and chi-square tests (p=0.05).

Results: Subtype knowledge was correlated with how informed patients felt: 41% of patients who were informed of their subtype reported having an adequate level of information overall, compared to only 22% of patients who were not informed/not sure. Additionally, 28% of patients who were informed of their subtype reported receiving enough information at their diagnosis meeting, compared to only 16% of patients who were not informed/not sure.

Importantly, the impact of knowledge of subtype was reflected in
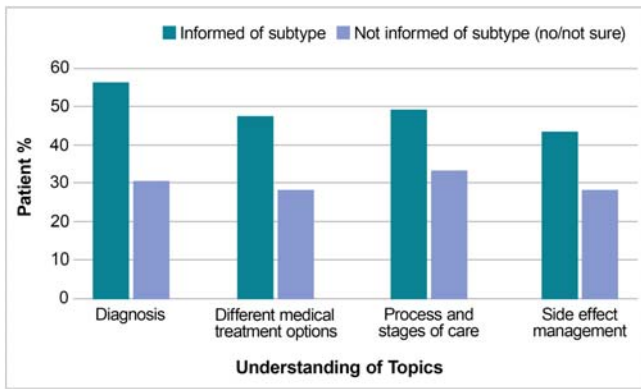
Figure 1. Patient's understanding after diagnosis meeting based on knowledge of subtype

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patient's understanding of the medical aspects of their lymphoma. Patients who were informed of their subtype reported a greater understanding of all topics surrounding diagnosis and care following their diagnosis meeting (figure 1).

Additionally, patients informed of their subtype reported improved communication with the doctor across key categories. Compared to those who were not informed/not sure, patients who were informed of their subtype felt more confident voicing their concerns to the doctor (59% vs 47%, respectively), sought clarification on things they did not understand more frequently (80% vs 70%), and brought forward questions about side effects more frequently (82% vs 74%).

Conclusions: Being informed of subtype at diagnosis was correlated with more self-reported positive healthcare experiences; those informed reported bettered management of their healthcare through improved understanding and communication. Informing patients of their subtype is the best way to ensure they understand their diagnosis and care and are sourcing the right information, which can translate positively across their experience.

Keywords: B-cell lymphoma; non-Hodgkin lymphoma (NHL); T-cell lymphoma (TCL).

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REDUCED SEXUAL FUNCTION IN LONG-TERM MALE LYMPHOMA SURVIVORS AFTER HIGH DOSE THERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION

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Introduction: Autologous stem cell transplantation (ASCT) is associated with long-term effects. However, less is known about sexual health. Our primary aim was to explore sexual health among male long-term lymphoma survivors after ASCT and compare the results to normative controls. Our secondary aim was to investigate the

Figure: Odds Ratio and 95% Confidence Interval for sexual problems among ASCT lymphoma survivors compared with controls

BSFI caseness*	OR [95% CI]
SEXUAL DRIVE	2.99 [1.98-4.51]
ERECTILE FUNCTION	3.57 [2.33-5.45]
EJACULATORY FUNCTION	3.91 [2.48-6.17]
SUM OF DRIVE, ERECTION, EJACULATION	5.54 [3.18-9.66]
SEXUAL SATISFACTION	2.94 [1.95-4.45]
OVERALL SEXUAL PROBLEM	3.04 [2.03-4.56]

<----- Decreased risk survivors -------- ---------- Increased risk survivors ----------->

ODDS RATIO AND [95% CONFIDENCE INTERVALS]

TABLE 1 Associations between sexual outcomes and population characteristics

	Total BSFI unstandardized coefficient β [95% Confidence Intervals]	Overall satisfaction unstandardized coefficient β [95% Confidence Intervals]
Age at survey, in 10 years	**-4.16 [-5.45, -2.87]**	**-0.27 [-0.43, -0.11]**
Chronic fatigue		**-0.46 [-0.87, -0.05]**
Anxiety caseness	**-5.11 [-9.33, -0.90]**	**-0.67 [-1.21, -0.14]**
Cardiovascular risk or disease		
None	0 Ref.	
Risk (body mass index >30, smoking, hypertension, or hypercholesterolemia)	0.58 [-2.80, 3.95]	
Diabetes type 1 or 2	-3.14 [-8.87, 2.60]	
Cardiovascular disease (transitory ischemic attack, stroke, angina pectoris or myocardial infarction)	**-5.68 [-10.6, -0.75]**	
Sedentary	**-4.19 [-7.09, -1.28]**	

associations between sexual health and study group characteristics, somatic and psychological comorbidity.

Methods: A national cross-sectional study was conducted from 2012 to 2014 among ASCT lymphoma survivors treated during 1987-2008. In the present study, 67% of eligible men (n=161) with valid questionnaire data were included in analyses. Age-matched controls (1:3) were drawn from a Norwegian normative sample. Brief Sexual Function Inventory (BSFI) was used to asses sexual function domains (drive, erection, ejaculation, problem) and overall sexual satisfaction. Based on the functional items a sum score, total BSFI score, was calculated. Sexual problem caseness was defined based on predetermined cut-off values for BSFI domain scores. Age-adjusted and multivariable linear and logistic regression analyses were used to investigate the associations between survivors´ characteristics and BSFI outcomes.

Results: Survivors had significantly lower scores on all BSFI domains, compared with controls (all p-values <0.001). Greatest clinical relevance was found regarding erectile and ejaculatory function were the effect sizes were -0.61 and -0.75, respectively. The most prevalent sexual problems among survivors were lack of drive (44%), and erectile dysfunction (53%). Survivors had increased risk for all problems compared with controls (Figure). Among the survivors, we found significant associations between total BSFI score and increasing age, anxiety, cardiovascular disease and physical inactivity in multivariable models. In addition, a lower sexual satisfaction was related to increasing age, chronic fatigue and anxiety (Table).

Conclusions: Sexual functions were reduced and sexual problems more frequent among survivors compared with controls. The associations with age, anxiety, cardiovascular disease and physical inactivity illustrate the multifaceted interactions on sexual health. In order to acknowledge the importance of sexual health in life beyond cancer, and to initiate treatment it is pertinent that doctors assess patients sexual health pre- and during treatment and at follow-ups.

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QUALITY OF LIFE AND CAREGIVER BURDEN IN MULTIPLE MYELOMA AND LYMPHOMA PATIENTS UNDERGOING OUTPATIENT AUTOLOGOUS STEM CELL TRANSPLANTATION VERSUS INPATIENT TRANSPLANTATION

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Introduction: The outpatient setting has now become a standard alternative to the traditional inpatient approach for autologous stem cell transplantation (ASCT) for multiple myeloma and lymphoma. Outpatient ASCT involves family/friends assuming round-the-clock caregiving responsibilities, and though it is perceived as potentially providing superior patient quality of life (QOL), supporting evidence is limited. Furthermore, little is known about caregiver QOL and lost opportunity costs for caregivers (i.e., wages/travel time). Our objectives were to compare QOL of patients, and their caregivers, in the inpatient versus outpatient settings, and to delineate costs associated with caregiving.

Methods: Patients completed 4 questionnaires (FACT-BMT, FACT-Fatigue, EQ5D, and distress impact thermometer) at 5 timepoints during their ASCT: D0 (baseline), D+7, D+14, D+28, and D+100. Caregivers completed 3 questionnaires (C-QOLC, distress impact, and financial impact), as well as a caregiver financial burden questionnaire (C-SAFE), at the same timepoints.

Results: In total, 52 patients and 51 caregivers were enrolled (21 inpatients/31 outpatients). Patients' median age was 57 (range: 18-70), and 67% were male. Majority of caregivers were spouses (73%). In the overall patient population, FACT-BMT scores significantly declined at D+7, then increased to above-baseline by D+100, which is indicative of greater QOL. FACT-Fatigue worsened significantly at D+7, then improved to lower than baseline at D+100. Additionally, EQ5D scores (imaginable health status) significantly declined at D+7 and D+14, then increased to above baseline at D+100 (albeit p>0.05). QOL scores were not significantly different when comparing inpatients vs. outpatients, though general trends existed for less deterioration in QOL in inpatients. Caregiver QOL scores were consistently higher for

TABLE 1 Changes in QOL scores from baseline (D0) in the overall patient population

	FACTBMT	FACTF	EQ5D	CQOLC	Global p value
D+7	-13.21 (5.59) p=0.014	-9.46 (2.66) p=0.00053	-21.99 (5.53) p=0.00012	11.17 (6.02) p=0.067	0.00
D+14	-7.76 (6.09) p=0.20	-5.98 (93.07) p=0.053	-13.84 (6.23) p=0.028	12.09 (8.68) p=0.17	0.00
D+28	3.16 (5.77) p=0.58	-5.43 (2.91) p=0.064	-5.2 (5.91) p=0.38	12.44 (6.3) p=0.051	0.00
D+100	16.36 (5.92) p=0.0065	6.75 (2.98) p=0.025	1.56 (6.05) p=0.08	21.26 (6.64) p=0.0019	0.00

Figure 1. Serial trends in QOL scores, comparing inpatients (red) versus outpatient (blue)
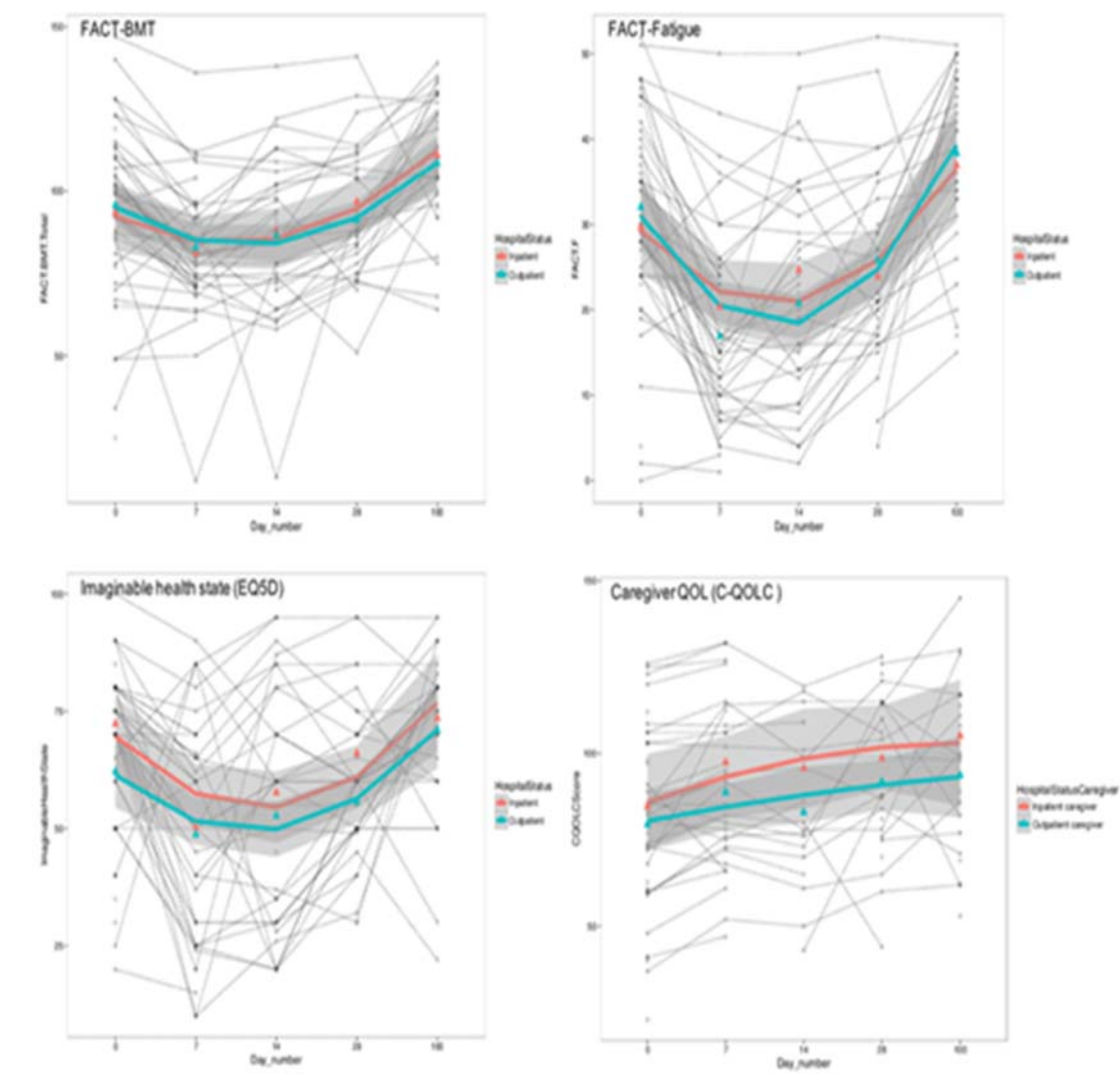
inpatients, though not statistically significant. Average lost opportunity costs for caregivers was $4195 CAD per caregiver.

Conclusions: There was significant deterioration of various aspects of QOL in the overall population. Inpatient caregivers report better QOL than outpatients, though sample size limits further analyses.

Keywords: autologous stem cell transplantation (ASCT).

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SYMPATHOVAGAL IMBALANCE IN LYMPHOMA PATIENTS CAN BE RESTORED

BY PHYSICAL TRAINING - SINGLE CENTRE PROSPECTIVE TRIAL

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Introduction: Despite significantly improved survival of lymphoma patients in the last decades, many remain physically unfit years after their successful treatment. Major complaints include dyspnoe, fatigue and physical activity intolerance which are in concordance with impaired sympathovagal (SV) balance. The predominance of sympathicus is a sign of autonomic nervous system neuropathy caused by the lymphoma itself, as well as combined cytotoxic therapy. SV imbalance is an independent negative prognostic factor for morbidity and mortality, especially due to cardiovascular diseases and metabolic syndrome. Data from cardiological and neurological trials prove the aerobic physical activity as a strong tool to reset the SV balance. The primary aim of this prospective project was to analyze the impact of systemic treatment on parameters of fitness, and to evaluate the efficacy of the supervised training on the lymphoma population comparing to matched controls.

Methods: Between 2012 and 2016, 101 patients with Hodgkin (n=23) and Non-hodgkin lymphomas (n=78) were enrolled in the project. After systemic therapy (RCHOP or BEACOPP), the patients who achieved remission, were geographically randomized into training (n=40) or observation group (n=61). The 3-month supervised training program consisted of combined aerobic and anaerobic training (60mins, 3 times/ week). The following parameters were measured in all patients: body mass index (BMI), the body composition (InBody 203©), aerobic capacity (cycle spiroergometry, Lode excalibur©), sympathovagal balance (DiANS PF 8©), and muscle strength (hand grip tests and leg flexor and extensor test). The evaluation was performed at 3 time points: 1) before start of the therapy (n=19), 2) after the treatment (in remission) (n=65), 3) and after either training or observation 3-6 months since last therapy (n=45).

Results: During the treatment, a significant deterioration of SV balance was observed (total score= TS: -1,08 ± 1,86 vs. -1,96 ± 1,57, p= 0.04), whereas other parameters (aerobic capacity p=0.18 and muscle strength p=0.84, body composition p=0.58) changed insignificantly. In the training group, a significant improvement of aerobic capacity (98,33 ± 16,7 vs. 112,2± 17,4, p 0.001) as well as SV balance (TS -2,27 ± 1,70 vs. -2,27 ± 1,70, p 0.02) was observed. In the control group, no improvement in fitness parameters was observed; the only difference was BMI increase (p 0.01) but without improvement of muscle mass. The adherence to the training program was 80%, no adverse events were reported.

Conclusion: Our trial proved that physical training in lymphoma survivors is safe, feasible and effective. It significantly improves cardiovascular fitness and leads to SV balance restoration which might play a major role in life quality, relapse/non-relapse morbidity and mortality.

Keywords: BEACOPP; performance status; R-CHOP.

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LYMPHOMA TREATMENT REGIMES AND THEIR IMPACT ON BEHAVIOUR AND COGNITION IN AN ANIMAL MODEL

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Introduction: Chemotherapy-induced cognitive impairment is defined as clinically and statistically important decrease of cognitive functions often related to chemotherapy. The study focused on neurobiological substrate of chemobrain adapted to an animal model.

Methods: Chemotherapeutics have been used according human lymphoma therapies in all phases comprising combinations of drugs: adriamycin, bleomycin, cyclophosphamide, dacarbazine, etoposide, vincristine and prednisone. Weight loss up to 4% was a limiting factor of drug dose used in Wistar rats. Rats were subjected to behavioral testing prior, immediately after, and in 3 months delay to administration of the chemotherapy. At these intervals, blood, and nerve tissue were collected and then immune-histological and neuro-chemical analysis was performed. The battery of behavioral tests comprised of: open field, elevated plus maze, social behavior test, and cognitive tests of the Y-maze.

Results: Our behavioral outcomes indicated for a combination of motivation deficit and cognitive impairment after chemotherapy. It should not be neglected that rats generally have lower locomotor activity after post-treatment. This finding could also suggest a "sickness behavior" effect which is less pronounced with much time span after treatment. Lack of habituation indicates for learning and memory problems. We have also measured transient changes in blood cells counts, namely white blood cells (WBC), after ABVD, CHOP chemotherapy. Similarly in both regimes, drugs administration dropped number of WBC up to 30%, which did not fully return to the number before treatment. BEACOPP therapies decreased counts of lymphocytes, which have returned to beginning levels after delay. Immunohistological analysis pointed at a clear decrease in the number of newly emerging neurons in the dentate gyrus. In addition to changes in the number of neurons, there were also differences in morphology of neurons. Following chemotherapy a relatively high percentage of

cells exhibited abnormal orientation and poor or totally absent arborization.

Conclusions: Overall, we have introduced the novel animal model of neurobiological substrate of chemobrain induced by the application of selected chemotherapeutic regimens. This model can be useful to study neuroprotective and precognitive drugs.

Keywords: chemotherapy; Hodgkin lymphoma (HL); non-Hodgkin lymphoma (NHL).

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PROSPECTIVE STUDY OF 3T WHOLE BODY DIFFUSION WEIGHTED MAGNETIC RESONANCE (WB DWI MRI) COMPARED TO PET IN STAGING AND ASSESSMENT OF TREATMENT RESPONSE IN FDG AVID LYMPHOMAS

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Introduction: PET is considered the gold standard for staging and evaluation of treatment response in FDG avid Lymphoma. 3T WB-DWI-MRI may represent an option for detection and better characterisation of tumoral lesions without use of FDG or iodated/paramagnetic contrast medium. We compared 3T WB-DWI-MRI with PET in the evaluation of Hodgkin lymphoma (HL) and Diffuse large cell lymphoma patients (DLBCL).

Methods: From may 2016, 25 patients (14 cases of HL and 11 cases of DLBCL) were diagnosed at our institution. PET and 3T WB-DWI-MRI was perfomed at diagnosis and post treatment for a total of 118 nodal sites and 21 extranodal valued sites. DWI imaging was obtained with multi shot sequences (thickness 4 mm) multi-b (b-value: 0, 150, 1000) and ADC cut off value 1.2 for functional evaluation. Morphological images were obtained by using sequences fast spin-echo short time inversion recovery (STIR with thickness 4mm) and Turbo spin-echo (T2-TSE with thickness 4mm) and sequnces T1-FAST-Field-echo (T1-FFE) in and out – phase (thickness 4mm). MRI were compared with PET imaging performed at the same time and assessed blind by radiologist and *Nuclear Medicine* physician.

Results: The 3T WB-DWI-MRI and PET results were concordant at the diagnosis after evaluation of 118 nodal site and 21 extra nodal site with Cohen's Kappa coefficient showed agreement to be excellent (K = 0.82 and 0.84 respectively). When performed after treatment the two methods were not concordant due to the greater sensitivity and specificity of the RMI (high positive and negative predictive value. In 5/25 cases of nodal site and in 2/16 cases of extra nodal site after chemotherapy MRI and PET results were discordant and PET failed complete remission finding (doubts residues after therapy not confirmed at subsequent follow-up).

Conclusions: These data suggest that 3T WB-DWI-MRI can be considered a sensitive and specific method for assessing treatment response in Lymphoma without the use of ionising radiation or administration of F-18 Flurodeoxyglucose.

In this population, MRI appears to obtain a better definition of the response after chemotherapy especially in mediastinal, hepatic, waldeyer ring and bone sites.

Further studies are needed to evaluate the optimum ADC values in assessing treatment response in a more large number of patients.

Keywords: diffuse large B-cell lymphoma (DLBCL); Hodgkin lymphoma (HL); positron emission tomography (PET).

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ABSCOPAL REGRESSION OF LYMPHOMA AT DISTANT SITES AFTER LOCAL RADIOTHERAPY, DETECTED BY POSITRON EMISSION TOMOGRAPHY IN SIX CASES

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Introduction: "Abscopal" regression of untreated lymphoma outside radiotherapy (RT) treatment volumes, in the absence of any other therapeutic intervention, is rarely reported. An immune mechanism is likely and results of clinical trials combining RT and immunotherapy are awaited.

Methods: We investigated PET-detected abscopal regressions of lymphoma at a comprehensive cancer center.

Results: Eight cases were identified and 6 were well-documented on FDG-PET imaging as follows:

1: Male age 54, follicular lymphoma (FL), relapsed after immunochemotherapy, demonstrated abscopal regression of mediastinal disease, following further RT (30 Gy in 15 fractions) to a neck mass (persistent after very low dose RT to 4 Gy in 2 fractions).

2: Male age 38 with multiply relapsed advanced FL had a complete metabolic response (CMR) of all local and systemic disease, after 4 Gy in 2 fractions to large skin lesion. He relapsed after allogeneic stem cell transplantion but with an ongoing CMR to donor lymphocyte infusion and RT.

3: Female age 67 with untreated advanced FL and severe comorbidities demonstrated both local CMR to 4 Gy in 2 fractions to a 10cm abdominal mass and ongoing complete abscopal regression of mediastinal lymphoma.

4: Female age 67 with severe comorbidities, untreated CLL and biopsy proven Richter's transformation to DLBCL in the right breast and painful iliac node. With no systemic therapy, 30 Gy in 10 fractions to pelvis achieved CMR in both pelvis and untreated breast. Circulating lymphocytes reduced from 40 x10^9/L to 3.4. She later developed progressive disease and died with DLBCL.

5: Female age 58, after decades of multiply-relapsed Hodgkin lymphoma received a re-irradiation to 30 Gy in 15 fractions to bone lesion with complete symptomatic response and abscopal CMR in other distant bone lesions. After subsequent relapse she attained ongoing CMR lasting >3 years on nivolumab.

6: Female age 75 with multiply relapsed advanced mantle cell lymphoma had 2 Gy x 2 to lower limb disease with complete local CMR and abscopal regression of all measurable systemic disease. She remained free of symptomatic progression for 2 years.

Conclusions: Abscopal regression of lymphoma was detected by FDG-PET scanning in 6 cases. It was associated with subsequent durable responses to immunotherapy in 2 cases, it followed a second course of radiotherapy to persistent lesions in 2 and it required only 4 Gy in 2 cases. A better understanding of the biology and frequency of this phenomenon may be of considerable value, both because of its intrinsic therapeutic impact and potential synergy with immunotherapy.

Keywords: follicular lymphoma (FL); Hodgkin lymphoma (HL); immune system.

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ABERRANT HYPEREDITING OF MYELOMA TRANSCRIPTOME BY ADAR1 CONFERS ONCOGENICITY AND IS A MARKER OF POOR PROGNOSIS

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Background: While alterations at the DNA level have been extensively studied in multiple myeloma (MM), the genomic changes including mutations, indels and translocations cannot yet fully explain all the biological and molecular abnormalities in MM. Recent years have shown that abnormalities at the RNA levels harbour biological importance in cancers. Our recent work published in Blood indicated that the aberrancy of the landscape in MM transcriptome has a role in disease pathogenesis. We reported that ADAR1-mediated-RNA-editing is of biological and clinical relevance in MM.

Methods: We analysed several publicly available MM datasets, including CoMMpass RNA-seq dataset from the MMRF. We also performed a systematic high throughput RNA-sequencing on normal plasma cells and some primary patient samples (n=17) to identify the ADAR1 expression trend. For the elucidation of ADAR1 protein expression, immunofluorescence was conducted on patient's tissue microarray (n=200). The functional importance of ADAR1 and NEIL1 editing was determined with cell viability, cell cycle and colony formation assays.

Results: Our analyses on gene expression microarray datasets, RNA-seq datasets and TMA revealed that ADAR1 was overexpressed in MM; its expression gradually increased along the disease progression route (Normal to MGUS to SMM to MM to Relapsed) and was higher in the high-risk disease subtypes, namely the 4p16 and MAF- translocation groups, signifying the role of ADAR1 in disease progression and in conferring disease aggressiveness. Critically, relative to the normal CD138+ cells, MM transcriptome was found to be aberrantly hyperedited and the global editing events was closely correlated with ADAR1 expression. Manipulation of ADAR1 expression conferred differential level of A-to-G editing, indicating that ADAR1 is a critical player of editing in MM. Notably, multivariate analysis revealed that ADAR1 was a prognostic factor independent of 1q21 amplification. ADAR1 level could also influence patients' responsiveness to different treatment regimes. Physiologically, our functional assays established ADAR1 as oncogenic, acting in an editing-dependent manner. In addition, we identified NEIL1 (base-excision repair gene) as an essential and a ubiquitously edited ADAR1 target in MM. The recoded NEIL1 protein showed defective oxidative damage repair capacity and gain-of-function properties.

Conclusion: These data unravelled novel insights into MM molecular pathogenesis at the RNA level.

Keywords: bortezomib; epigenetics; multiple myeloma (MM).

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AUTOLOGOUS STEM CELL TRANSPLANT WITH HIGH DOSE MELPHALAN PREPARATIVE REGIMEN IS SAFE AND EFFECTIVE FOR ELDERLY MULTIPLE MYELOMA PATIENTS IN THE ERA OF TRIPLE INDUCTION THERAPY

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Conclusions: Our data shows that in the era of triple induction therapy ASCT with high dose MEL conditioning is safe in transplant eligible MM patients ≥ 65 years of age and provides similar outcomes as seen in younger patients. The response to first line treatment significantly influences PFS after ASCT with satisfactory outcomes for patients with CR and VGPR. However, the reduction of the dose of melphalan in conditioning to 100 mg/m^2 is associated with shorter PFS.

Keywords: autologous stem cell transplantation (ASCT); elderly; multiple myeloma (MM).

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THE USE MODIFIED RISK STRATIFICATION mSMART 3.0 IN REAL CLINIC PRACTICE IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

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Introduction: Autologous stem cell transplantation (ASCT) is commonly used in treatment of patients over 65 years of age with multiple myeloma (MM), however the safety and efficacy of this procedure in the era of new agents is controversial.

Methods: We conducted a retrospective review of newly diagnosed MM patients treated with triple induction therapy who underwent first ASCT between 2012 and 2018 to evaluate the outcomes across different age groups. The purpose of this retrospective study was to compare the 100-day non-relapse mortality, progression-free survival (PFS) and overall survival (OS) in elderly MM patients (≥ 65 years) with younger patients in the era of triple induction therapy.

Results: A total of 162 patients were analysed and categorized by age into group A (28 to 55 y; n=46), B (56 to 64 y; n= 87) and C (65 to 71 y; n=29). The patients received triple combination therapy based on bortezomib (45%) or a combination of cyclophosphamide, thalidomide and dexamethasone (55%) as first line treatment prior to ASCT. The compared groups did not differ significantly in terms of gender, ECOG performance status, HCT-specific comorbidity index (HCT-CI), and disease status at ASCT. Melphalan (MEL) at a dose of 200 mg/m^2 was used as preparative regimen in 83% of younger patients in group A, 79% of patients in group B, and 59% of the elderly in group C. The dose of 140 mg/m^2 was used in 13%, 15% and 30% of patients in group A, B and C, respectively. The remaining patients received 100 mg/m^2 of MEL (4%, 5% and 11%). The dose of MEL was reduced due to HCT-CI >2 or age, at the physician's discretion. In the whole study group there were no transplant related deaths within the first 100 days of ASCT. After the median follow-up of 24 months (range, 3-84 months) for survivors, the estimated OS at 36 months was 79%, 83% and 83% for patients in group A, B and C, respectively (p=0.96). The respective 3-year PFS was 53%, 45% and 58% (p= 0.51). In univariate and multivariate analysis the adverse factors associated with shorter PFS were response to first line treatment worse than very good partial remission (HR 2.09, 95%CI 1.15-3.90; p=0.015) and the dose of MEL lower than 140 mg/m^2 (HR 5.99, 95%CI 2.32-16.70, p=0.0002)

Background: Studies over the past decade, have greatly improved our understanding of the molecular basis of multiple myeloma and mechanisms of disease progression. Metaphase cytogenetics and fluorescence in situ hybridization (FISH) help us to identify the most frequent genetic abnormalities. The division of patients into various risk groups based on the chromosomal markers is being utilized by many centers for select and optimize of therapeutic strategy. However, such molecular risk-stratification systems are repeatedly updated in accordance with the emergence of new information about the prognostic impact of anomalies. The role of complex karyotype and combination of genetic abnormalities remains unclear. Aims: to estimate the incidence of genetic abnormalities and their impact on overall and progression-free survival in patients with newly diagnosed multiple myeloma (NDMM).

Methods: The study included 159 patients (median age 63 years, range 28 - 83; male: female ratio – 1:1.37) with NDMM. Metaphase cytogenetics on bone marrow samples was done by standard GTG-method. FISH analyses were performed according to the manufacturer's protocol for detection primary IgH translocations, 13q (13q14/13q34) deletion, 1p32/1q21 amplification/deletion, P53/cen 17 deletion (MetaSystems DNA probes). We additional searched the t (4;14), t(6;14), t(11;14), t(14;16) and t(14;20) in patients with IgH translocation. All patient was treated by bortezomib-based programs (VD, CVD, VMP, PAD).

Results: The frequency of genetic abnormalities in NDMM patients was 49% (78/159). IgH translocation was detected in 26.4% (42/159)

patients: t(11;14) – 16.3% (26/159), t(4;14) – 5.0% (8/159); TP53/del17p – 5.6% (9/159); 1p32/1q21 amp/del – 12% (19/159); hypodiploidy – 3.1% (5/159); hyperdiploidy – 1.25% (2/159); del5q – 0,6% (1/159); other – not found. Combination two aberrations was discovered in 11.9% (19/159) patients, complex abnormalities ($\geq$3 aberrations) – in 4.4% (7/159) patients.

The median OS in "two aberration" and "complex abnormalities" groups were lower than in standard-risk mSMART 3.0 (normal, t(11;14), hypodiploidy, hyperdiploidy and other): 49 months, 37 months and not reached, respectively (p=.02). The median PFS for these groups was 12 months, 11 months and 30 months, respectively (p=0.004). We modified high-risk mSMART 3.0 by adding "two aberration" and "complex abnormalities" groups on based the OS and PFS results.

The median OS in standard-risk mSMART 3.0 was not reached, in high-risk mSMART 3.0[mod] – 50 months; 5-years OS was 65% and 38%, respectively (p=0.01). The median PFS was 58 and 29 months, respectively (p=.02).

Conclusion: Combination two aberrations and complex abnormalities are unfavorable prognostic markers. The median OS and PFS was higher in standard-risk than high-risk patients mSMART 3.0[mod]. It can be useful for update risk stratification in future.

Keywords: chromosomal translocations; fluorescence in situ hybridization (FISH); multiple myeloma (MM).

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OUTCOME OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN MULTIPLE

MYELOMA; EXPERIENCE FROM A SINGLE CENTER IN SAUDI ARABIA

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Introduction: Autologous stem cell transplantation (ASCT) prolongs progression free survival (PFS) in newly diagnosed multiple myeloma (MM) patients in the era of novel therapy. However, the outcome of MM patients from the Middle East and North Africa (MENA) is much less known due to the paucity of SCT centers.

Methods: This is a retrospective analysis of all MM patients that underwent ASCT at our center. All data were retrieved from electronic medical records. Baseline patient characteristics, disease and treatment related variables were reported using descriptive statistics (frequency, median and percentage). Estimates of overall survival (OS) and PFS were computed using Kaplan-Meier method. The treatment protocol includes induction phase with bortezomib based triplet regimen such as VCD or VRD followed by stem cell mobilization. This was followed by melphalan conditioning 200 or 140 mg / m^2.

Results:

Figure 1A: PFS Post HCT in MM

Figure 1B: OS Post HCT in MM

Cumulative Proportion Surviving (Kaplan-Meier)

A: <u>Baseline Characteristics.</u> A total of 60 patients were identified and males represented 65% of the cohort. The median age was 53 years (31-70). ISS stage I, II and III were 25, 27 and 45% respectively. Disease subtype was IgG kappa or lambda in 45%, light chain kappa or lambda in 28%, IgA kappa or lambda in 18% and others in 9%. Normal cytogenetic was seen in 57% while the remaining comprised of hyperdiploidy in 22%, complex cytogenetic in 12%, t (11:14) in 6% and 1.5% with trisomy 3 and no cytogenetic result available in the remaining 1.5%. Disease status pre-HCT was stringent complete response (sCR) in 21/60 (35%) patients, complete response (CR) in 17/60 (28%) patient, very good partial response (VGPR) in 10/60 (17%) patient, partial response (PR) in 11/60 (18%) patient and in 1/60 (2%) patient no documentation was available.

B: <u>Post ASCT Outcome.</u> The median duration for absolute neutrophil count (ANC) and platelet engraftment was 13 and 14 days respectively. Primary graft failure was observed in one patient (1.7%) leading to transplant related mortality. Evaluable response by day 100 was available in 55 patients and were; sCR 26/55 (47%) patient, CR 17/55 (31%) patient, VGPR 11/55 patient (20%) and disease progression (DP) in 1/55 (2%) patient. Median follow up was 828 days (18-2790). Estimates of PFS at 100 days, 1 year and 5 years were 98.3%, 84.5% and 43.1% respectively while corresponding OS was 98.3%, 94.3% and 70.5% respectively (Fig 1A/B). PFS and OS for combined high risk and non-high risk MM patients at 3 years from CIBMTR were 43% and 78.5% respectively.

Conclusion: We observed comparable post ASCT outcome in our emerging transplant center compared with well-established centers worldwide. Given that AHCT remains underutilized in the MENA region, reporting of such data highlights that increased access to such therapy will be of great value to the region.

Keywords: IMiDs; peripheral blood stem cell (PBSC).

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THE ROLE OF AUTOLOGOUS STEM CELL TRANSPLANTATION AND TUMOR LOAD IN MULTIPLE MYELOMA

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Background: Multiple myeloma remains an incurable disease despite the emergence of new drugs. The search of optimal therapeutic strategy to increase life expectancy and remission in patients with this disease is continues. This is facilitated to the achievement of the maximum possible response and eradication of residual tumor load. Existing recommendations for the treatment of multiple myeloma approve the use of autologous stem cell transplantation (autoSCT) to improve disease control.

Aims: To determine the impact of autologous stem cell transplantation on efficiency of treatment and tumor load in patients with multiple myeloma.

Methods. The study included 89 patients with MM (median age 58 years, male/female – 1.12:1). The induction therapy with Bortezomib-based regimens (VD, CVD, VMP, PAD) was used in 62/89 (69.6%) patients, Immunomodulator-based regimens (Thal+D, RD, VRD, PomD) – in 22/89 (24.8%), chemotherapy – in 4/89 (5.6%). High dose therapy (Mel200) and autoSCT is carried out in 64/89 (71.9%)

patients. The efficiency of therapy was evaluated according to IMWG criteria. Tumor load was determined by multicolor flow cytometry (5-colors): 79 patients – after 4-6 courses of induction therapy, 39 patients – after autoSCT; 29 patients – tumor load was performed in dynamics (before and after autoSCT).

Results. The sex, age, the variant induction antimyeloma therapy did not affect on response rate and tumor load. CR was achieved in 28/89 (31.4%) before AutoSCT and 50/89 (56.2%) after AutoSCT (p>.05). However, high dose therapy (Mel200) and AutoSCT has increased the possibility of achieving complete response in dynamics: before AutoSCT in 5/29 (17.2%), after AutoSCT – in 13/29 (44.8%) (p<.05).

Tumor load after 4-6 courses of induction therapy (n=79) was 0.28 ±0.34 for CR+sCR, 1.65±2.66 for VGPR, 2.10±2.53 for PR.Tumor load after HDT (Mel200) and AutoSCT (n=39) was 0.06±0.07 for CR+sCR, 0.15±0.46 for VGPR, 0.17±0.22 for PR.

The effect of autoSCT on PFS in 39 patients. The median PFS was 97 months in the group "tumor load after autoSCT <0.01%", 70 months – in the group "tumor load without autoSCT <0.01%", 50 months – in the group "tumor load after autoSCT >0.01%" and 25 months – in the group "tumor load without autoSCT >0.01%"(p=.006).

Examination of tumor load in the dynamics in 29 patients showed that autoSCT reduces the level of tumor load (before autoSCT = 2.27 ±0.20, after autoSCT – 0.14±0.01). Tumor load <0.01% after autoSCT was detected more often than before autoSCT (14/29 and 5/29 patients, respectively) (p<.05).

Conclusions. AutoSCT increase the efficiency of therapy, reduce tumor load and increase the duration of progression free survival in patients with multiple myeloma.

Keywords: autologous stem cell transplantation (ASCT); minimal residual disease (MRD); multiple myeloma (MM).

WILEY

ONGOING TRIALS

OT07
A PHASE 3 STUDY OF ACALABRUTINIB PLUS BENDAMUSTINE AND RITUXIMAB IN ELDERLY (AGED ≥65 Years) TREATMENT-NAIVE PATIENTS WITH MANTLE CELL LYMPHOMA

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Background: Mantle cell lymphoma is an aggressive B-cell non-Hodgkin lymphoma that remains incurable with current therapies, including standard first-line bendamustine and rituximab. There is a medical need for novel strategies to improve disease control in elderly patients with mantle cell lymphoma. Acalabrutinib is a highly selective, potent, covalent Bruton tyrosine kinase inhibitor with minimal off-target activities. For patients with relapsed/refractory mantle cell lymphoma, acalabrutinib demonstrated an overall response rate of 81%, with 40% of patients achieving a complete response (*Lancet*.2018;391:659). Taken together, combining acalabrutinib with bendamustine and rituximab in treatment-naive patients with mantle cell lymphomamay improve disease control and is being explored in an ongoing, global, phase 3 study ACE-LY-308 (NCT02972840).

Methods: ACE-LY-308 is a phase 3, randomized, double-blind study with approximately 250 sites. Patients must be aged ≥65 years, have treatment-naive mantle cell lymphoma, and not be intended for stem cell transplant. Patients are excluded for history of central nervous system lymphoma or significant cardiovascular disease (asymptomatic or controlled atrial fibrillation allowed) or if they require treatment with proton-pump inhibitors, warfarin or equivalent vitamin K antagonists, or strong CYP3A inhibitors/inducers. Approximately 546 patients will be randomized 1:1 to receive oral acalabrutinib 100 mg twice daily or placebo twice daily plus 6 cycles of bendamustine (90 mg/m^2 on days 1 and 2) and rituximab (375 mg/m^2 on day 1 of each 28-day cycle). Patients achieving partial or complete responses will receive maintenance rituximab every 2 cycles for up to 12 additional doses plus acalabrutinib or placebo. Patients will be treated until progressive disease or unacceptable toxicity. Patients assigned to placebo who have progressive disease on-study can cross-over to receive acalabrutinib until second disease progression. The primary endpoint is independent review committee-assessed progression-free survival per the Lugano Classification. Secondary endpoints include overall response rate (≥partial response), duration of response, time to response, overall survival, and safety. Exploratory endpoints include pharmacokinetic and pharmacodynamic assessments, minimal residual disease, patient-reported outcomes, and medical resource utilization. The study opened for enrollment in February 2017. Accrual is ongoing.

Keywords: acalabrutinib; mantle cell lymphoma (MCL); rituximab.

Disclosures: Wang, M: Consultant Advisory Role: *AstraZeneca, Janssen, and MoreHealth; Board of Directors or advisory committees for Celgene and Janssen*; Honoraria: *Acerta Pharma, Celgene, Dava Oncology, Janssen, and Pharmacyclics*; Research Funding: *Acerta Pharma, AstraZeneca, Celgene, Janssen, Kite Pharma, Juno, Novartis, and Pharmacyclics.* **Belada, D:** Consultant Advisory Role: *Gilead Sciences, Roche, Takeda*; Research Funding: *Takeda*; Other Remuneration: *Gilead Sciences, Roche.* **Cheah, C:** Consultant Advisory Role: *Roche, Janssen,*

OT08
ARGO: A RANDOMISED PHASE II STUDY OF ATEZOLIZUMAB WITH RITUXIMAB, GEMCITABINE AND OXALIPLATIN IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA WHO ARE NOT CANDIDATES FOR HIGH-DOSE THERAPY

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Introduction: Relapsed and refractory (R/R) diffuse large B-cell lymphoma (DLBCL) patients (pts.) have poor outcomes with only 20-30% alive at 3 years. A large proportion of pts. are not fit enough for high-dose therapy (HDT) and autologous stem cell transplantation (SCT) following salvage immunochemotherapy. Whilst a significant number progress prior to reaching SCT. This is an area of unmet need in older pts. who may not tolerate HDT followed by SCT. Novel approaches are urgently needed, specifically requiring incorporation of promising agents to improve existing regimens for populations that are not candidates for HDT plus SCT.

Checkpoint inhibitors have revolutionised treatment for several solid tumours and induce frequent responses in Hodgkin lymphoma. Single agent anti-PD-1 monoclonal antibodies (mAbs) have produced responses in DLBCL. Atezolizumab (Atezo) is a mAb that enhances T-cell directed cytotoxicity by targeting PD-L1 in the tumour microenvironment and on malignant cells. Rituximab, gemcitabine and oxaliplatin (R-GemOx) has demonstrated efficacy with acceptable toxicity in R/R DLBCL.

Method: ARGO is an open-label randomised phase II trial with 3:1 randomisation, stratified by relapsed and refractory patients. Patients in the experimental arm receive 1 cycle of R-GemOx (given every 14 days) followed by 5 cycles of this regimen plus 840mg atezo IV, followed by 8 21-day cycles of 840mg single agent atezo as maintenance. This will be compared with a control arm treated with R-GemOx for 6 cycles. Rituximab is delivered subcutaneously from cycle 2. The study utilises a Case and Morgan 2-stage phase II design (p0=25%, p1=40%, a= 10%, b=90%) requiring 112 participants.

The primary objective is to document durable anti-tumour activity of R-GemOx-Atezo, assessed by progression free survival at 1 year. Secondary objectives are to determine safety, response rate and overall survival rates. Comprehensive translational components are supported by the Bloodwise funded Precision Medicine for Aggressive Lymphoma consortium and include characterising: PD-1, PD-L1 and PD-L2 expression in the tumour (using FISH, immunohistochemistry, and gene expression) and on peripheral blood T-lymphocytes, gene expression signatures (including cell of origin), mutation profile by NGS, T-cell repertoire and dynamic changes in circulating tumour DNA.

The trial opened recruitment in May 2018 and is scheduled to complete recruitment in March 2020. To date 24 pts. have been randomised. It is an investigator initiated study co-ordinated by the Cancer Research UK (CRUK) Southampton Clinical Trials unit and sponsored by University Hospitals Southampton NHS Foundation Trust. It is funded by a grant from F. Hoffman-La Roche (M030090) and endorsed by CRUK, Clinical Research Committee (CRUKE/16/028).

Trial registration ISRCTN11965217

Keywords: diffuse large B-cell lymphoma (DLBCL); immunochemotherapy.

OT09
A PIVOTAL, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, TWO-ARM, PHASE 2 STUDY OF ME-401 INVESTIGATING TWO DOSING SCHEDULES IN PATIENTS WITH FOLLICULAR LYMPHOMA (FL) AFTER FAILURE OF TWO OR MORE PRIOR SYSTEMIC THERAPIES

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Background: ME-401, a potent and selective oral PI3kδ inhibitor, has demonstrated very high and durable objective response rates (ORR) in both FL and CLL/SL; 76% in 38 patients with relapsed/refractory (R/R) FL and 100% in 12 patients with CLL/SLL (Soumerai 2018, Zelenetz 2018). A continuous dosing schedule resulted in delayed (>cycle 2) grade 3 adverse events of diarrhea and skin rash in ~1/3 of patients, likely related to on-target effects on T-regs resulting in immune-mediated toxicity. Based on the half-life of ME-401 (~26 hours) and the reported kinetics of T-reg regeneration (~10 days) we developed a rational 'intermittent' dosing schedule of 7 daily doses/28-day cycle after 2 cycles of continuous daily dosing. We hypothesized that such a schedule would provide 10-12 days of effective PI3kδ inhibition followed by washout and sufficient time for T-reg recovery. Preliminary evaluation of this novel schedule resulted in a decrease in delayed Grade 3 immune-related adverse events (irAE's) from 34% to 11%. To define the optimal balance of safety and efficacy of ME-401 in refractory R/R FL, we designed this phase 2 study evaluating 2 dosing schedules.

Methods: This is a study of ME-401 in patients with FL after failure of ≥2 prior systemic therapies and will enroll 150 patients. Group A will receive 60mg QD on a continuous schedule until disease progression (PD) or toxicity. Group B will receive 60mg QD on a continuous schedule for 2 cycles then QD for the first 7 days of each subsequent cycle. In this group PD will trigger dose modification to the continuous schedule. Subjects who develop grade ≥2 irAE in A or B will trigger dose modification to open label intermittent schedule. The primary objectives are ORR using Lugano Response Criteria, as determined by an Independent Response Review Committee, and tolerability defined as the rate of AE's requiring dose modification or study drug discontinuation. A correlative study will evaluate the effects of ME-401 on T-cell subsets, cytokines and chemokines. The study opened to enrollment in December 2018 with approximately 80 global sites planned. (NCT03768505)

OT10
PHASE II FIL-PTCL13 STUDY OF ROMIDEPSIN-CHOEP FOLLOWED BY HIGH-DOSE CHEMOTHERAPY AND TRANSPLANTATION IN UNTREATED PERIPHERAL T-CELL LYMPHOMAS

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Introduction: Peripheral T-cell lymphomas (PTCL), with the exception of anaplastic ALK-positive subtype, have a poor prognosis, when treated with standard CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). The introduction of etoposide (CHOEP) and the consolidation in responsive patients with autologous stem cell transplantation (autoSCT), represents the most common therapeutic option, in patients younger than 65 years. However, 25-30% of patients do not reach the transplant because of primary refractory or early progressive disease. To increase the response rate pre-autoSCT, we designed the phase I-II FIL-PTCL13 study (NCT02223208), aimed to define the maximum tolerated dose of romidepsin, a histone-deacetilase non-cross resistant agent, in combination with CHOEP (Ro-CHOEP) followed by high-dose chemotherapy and autoSCT. The phase I part of the study was conducted, according to continual reassessment method, from September 2014 to July 2017, and 21 patients were enrolled. Eight dose limiting toxicities were reported; the observed toxicity was 26.1% (95% Credibility Interval: 10.1%-46.3%) and prompted to define 14 mg/ms the recommended dose of romidepsin in addition to CHOEP. On September 2017, the phase II part of the trial was opened.

Methods: Inclusion criteria are: stage II-IV patients aged 18-65, with newly diagnosis of PTCL including PTCL-NOS, angioimmunoblastic, ALK negative anaplastic lymphoma; no central nervous system disease; normal organ function; no active infections. Treatment scheme includes an induction phase with 6 courses of Ro-CHOEP every 21 days (romidepsin at the dose of 14 mg/ms on day 1 and 8 of each cycle). Patients in complete (CR) or partial (PR) response after induction, will continue with one cycle of DHAP (cisplatin, citarabine, desamethasone) followed by stem cell harvest. Patients in CR after the 6 Ro-CHOEP will proceed to autoSCT; patients in PR with an available HLA-matched donor, will undergo alloSCT upfront. The primary end-point of the phase II part of the study is progression free survival at 18 months (18m-PFS). Secondary endpoints are: overall response rate and CR (defined according to the Lugano Classification 2014 response criteria), after 6 Ro-CHOEP and after SCT; event free survival, overall survival, any grade III or higher toxicities, treatment-related mortality defined as any death that was not attributable to the lymphoma, and incidence of acute or chronic graft versus host disease in allografted patients. Exploratory endpoint is the evaluation of response biomarkers (GATA3, TBX21, CDKN2A, PTEN). According to the Case and Morgan 2-stage design, to demonstrate an absolute improvement from 55% to 70% of the 18m-PFS, (alpha, 1-tail=0.05; beta=0.10), the target accrual is 110 patients, with the interim analysis planned when the first 75 patients have been enrolled. At now, 60 patients have been enrolled, 57 of which treated at the maximum tolerated dose of romidepsin.

Keywords: autologous stem cell transplantation (ASCT); peripheral T-cell lymphomas (PTCL); romidepsin (RD).

Disclosures: Chiappella, A: Consultant Advisory Role: *advisory board: Celgene, Janssen*; Honoraria: *lecture fee: Amgen, Celgene, Janssen, Nanostring, Roche, Servier, Teva*; Research Funding: *Romidepsin was provided free by Celgene in PTCL13 study*.

OT11
A MULTICENTER, OPEN LABEL, UNCONTROLLED, PHASE II TRIAL EVALUATING SAFETY AND EFFICACY OF VENETOCLAX, ATEZOLIZUMAB ANDOBINUTUZUMAB IN RICHTER TRANSFORMATION FROM CLL

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Introduction: Diffuse large B-cell (DLBCL) transformation from chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), Richter Syndrome (RS), has poor prognosis. Venetoclax, Bcl-2 inhibitor, has shown activity either in DLBCL and DLBCL-type RS. Atezolizumab is a humanized immunoglobulin monoclonal antibody (MoAb) targeting PD-L1 on tumor-infiltrating immune cells or tumor cells and prevents interaction with the PD-1 receptor and B7.1. Obinutuzumab, anti CD-20 MoAb compared to rituximab, presents a greater antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and direct cell death. Preliminary data of atezolizumab alone or in combination with obinutuzumab showed to be safe and promising in heavily pretreated DLBCL. We present a phase II trial evaluating safety and efficacy of venetoclax, atezolizumab, obinutuzumab combination in RS.

Methods: Eligible pts are: ≥18 years, ECOG PS ≤2, diagnosis of DLBCL RS from CLL/SLL. Exclusion criteria: pretreated RS, prior therapy with venetoclax or atezolizumab, CNS involvement, history of autoimmune disease. The study consists of 2 phases. In the run-in phase 9 pts will be enrolled in three cohorts of 3 subjects each. If no more than 1 pt in each of the 3 groups experiences during the first 3 cycles: treatment-related death or grade 4 non-infective/non-hematologic adverse event; the expansion phase will follow enrolling up to 31 pts. Treatment consists of 35 cycles with: obinutuzumab (1000 mg C1-8), atezolizumab (1200 mg C1-18), venetoclax (400 mg/d C1-35). Primary endpoint of the study is safety and tolerability for the run-in phase; efficacy (overall response, complete remissions, response duration, progression free and overall survival) for the expansion phase. Safety and efficacy are also secondary endpoints of each phase. Exploratory consists of MRD monitored by flow cytometry and ultra-deep NGS of disease markers; correlation between outcome and disease biomarkers. EUDRACT 2018-005028-40.

Keywords: chronic lymphocytic leukemia (CLL); Richter's syndrome (RS); venetoclax.

OT12
BIANCA: A PHASE 2 STUDY OF THE SAFETY AND EFFICACY OF TISAGENLECLEUCEL IN PEDIATRIC PATIENTS WITH RELAPSED/REFRACTORY MATURE B-CELL NON-HODGKIN LYMPHOMA

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Background: Pediatric patients with relapsed/refractory mature B-cell non-Hodgkin lymphoma (r/r B-NHL) have very poor prognosis and limited clinical benefit from available salvage therapies. Tisagenlecleucel is an anti-CD19 chimeric antigen receptor-T cell (CAR-T) therapy that was approved for the treatment of pediatric patients with r/r B-cell acute lymphoblastic leukemia in 2017 (Maude et al. *NEJM.* 2018) and adult patients with r/r diffuse large B-cell lymphoma (DLBCL) in 2018 (Schuster et al. *NEJM.* 2018) in the United States, and for the treatment of the same patient populations in 2018 in Europe. Very limited experience exists in collecting, producing, and treating pediatric B-NHL patients with CAR-T therapies. Here we introduce BIANCA (NCT03610724), a phase 2 trial investigating the safety and efficacy of tisagenlecleucel in pediatric patients with r/r B-NHL. This will be the first international multicenter trial to assess the feasibility and efficacy of an FDA/EMA-approved CAR-T cell therapy with centralized manufacturing in pediatric r/r NHL.

Methods: BIANCA is a phase 2, single-arm, multicenter, open label trial of tisagenlecleucel in pediatric patients with CD19+ r/r B-NHL (including Burkitt lymphoma, DLBCL, primary mediastinal B-cell lymphoma, gray zone lymphoma, and follicular lymphoma). Eligible

patients must be <18 years of age, weight ≥6 kg, and have confirmed B-NHL relapsed or refractory to ≥1 prior lines of therapy. Karnofsky (age ≥16 years) or Lansky (age <16 years) performance status must be ≥60. Patients must not have active central nervous system disease involvement before infusion or prior treatment with any anti-CD19 or gene therapy. Prior therapy can include systemic therapies and allogeneic or autologous hematopoietic stem cell transplant (HSCT) provided it occurred >3 months prior to screening. The primary endpoint of this study is overall response rate by International Pediatric NHL Response Criteria and Lugano 2014 criteria. Secondary outcomes include duration of response, event-free survival, relapse-free survival, progression-free survival, overall survival, pharmacokinetics, immunogenicity, frequency of post-tisagenlecleucel SCT, and biomarkers. Estimated enrollment for this study is 35 patients (at least 26 infused and evaluable).

Clinical trial information: NCT03610724.

Keywords: CD19; non-Hodgkin lymphoma (NHL).

Disclosures: Burkhardt, B: Research Funding: *Celgene, Roche.* **Maude, S:** Honoraria: *Novartis, Kite Pharamceuticals.* **Phillips, C:** Honoraria: *Novartis.* **Diaz de Heredia Rubio, C:** Honoraria: *Novartis.* **Laetsch, T:** Consultant Advisory Role: *Novartis, Loxo Oncology, Eli Lilly, Bayer*; Research Funding: *Novartis, Pfizer.* **Curran, K:** Consultant Advisory Role: *Novartis, Juno Therapeutics.* **Newsome, S:** Employment Leadership Position: *Novartis.* **Murray, N:** Employment Leadership Position: *Novartis.* **Pacaud, L:** Employment Leadership Position: *Novartis.* **Buechner, J:** Honoraria: *Novartis*; Research Funding: *Novartis.*

OT13
ELARA: A PHASE 2 TRIAL INVESTIGATING THE EFFICACY AND SAFETY OF TISAGENLECLEUCEL IN ADULT PATIENTS WITH REFRACTORY/RELAPSED FOLLICULAR LYMPHOMA

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Background: Tisagenlecleucel is an anti-CD19 chimeric antigen receptor-T cell (CAR-T) therapy that was approved in 2017 for the treatment of pediatric and young adult patients up to 25 years of age with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (Maude et al. *NEJM.* 2018), as well as for the treatment of adult patients with r/r diffuse large B-cell lymphoma in 2018 (Schuster et al. *NEJM.* 2018). Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma in the Western hemisphere, with limited treatment options in patients refractory to or relapsing after standard therapies. In a phase 2a study of patients with r/r CD19+ lymphomas, 10 of 14 (71%) patients with r/r FL treated with tisagenlecleucel achieved a durable complete remission at a median follow-up of 28.6 months (Schuster et al. *NEJM.* 2017). Here we introduce ELARA (NCT03568461), a phase 2 study evaluating the efficacy and safety of tisagenlecleucel in patients with r/r FL.

Methods: ELARA is a phase 2, single-arm, multicenter, open label trial. Eligible patients must be ≥18 years of age, have radiographically measurable grade 1, 2, or 3A FL that is refractory to a second or later line of systemic therapy (including an anti-CD20 antibody and an alkylator), or relapsed within 6 months after completion of a second or later line of systemic therapy, or relapsed during anti-CD20 antibody maintenance (following ≥2 lines of therapy as above) or within 6 months after maintenance completion, or relapsed after autologous hematopoietic stem cell transplant (HSCT). Patients with central nervous system involvement, or those who received prior anti-CD19 therapy, gene therapy, adoptive T-cell therapy, or allogeneic HSCT are not eligible. The primary endpoint of this study is complete response rate based on Lugano classification response criteria. Secondary outcomes include overall response rate, duration of response, overall survival, cellular kinetics, immunogenicity, safety, and patient-reported outcomes. Estimated enrollment for this study is 113 patients. The study is currently open to patient enrollment.

Clinical trial information: NCT03568461.

Keywords: CD19; follicular lymphoma (FL).

Disclosures: Dickinson, M: Consultant Advisory Role: *Novartis*; Honoraria: *Novartis.* **Popplewell, L:** Honoraria: *Pfizer, Roche, Spectrum.* **Ho, P:** Consultant Advisory Role: *Takeda*; Other Remuneration: *Novartis, Celgene, La Jolla Pharmaceuticals.* **Teshima, T:** Honoraria: *Novartis*; Research Funding: *Novartis.* **Dreyling, M:** Consultant Advisory Role: *Acerta, Bayer, Celgene, Gilead, Janssen, Novartis, Roche, Sandoz*; Honoraria: *Bayer, Celgene, Gilead, Janssen, Mundipharma, Roche*; Other Remuneration: *Celgene, Janssen, Roche, Takeda.* **Schuster, S:** Honoraria: *Celegene, Genentech, Merck, Pharmacyclics, Novartis, Nordic Nanovector, Acerta, Pfizer, Gilead*; Research Funding: *Celgene,*

OT14

PORTIA: A PHASE 1B STUDY EVALUATING SAFETY AND EFFICACY OF TISAGENLECLEUCEL AND PEMBROLIZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Tisagenlecleucel is an anti-CD19 chimeric antigen receptor-T cell therapy approved for pediatric patients with r/r B-cell acute lymphoblastic leukemia in 2017 (Maude et al. *NEJM.* 2018) and adult patients with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) in 2018 (Schuster et al. *NEJM.* 2018). The JULIET trial showed efficacy and safety of tisagenlecleucel in r/r DLBCL; subgroup analyses suggested an association between PD-1/PD-L1 interaction and lack of response (Agoulnik et al. EHA. 2018). Pembrolizumab after tisagenlecleucel has shown clinical activity in r/r DLBCL (Chong et al. *Blood.* 2017). We introduce PORTIA, a trial investigating safety and efficacy of tisagenlecleucel plus pembrolizumab in r/r DLBCL.

Methods: PORTIA is a phase 1b, multicenter, open-label, dose-timing and dose-expansion trial. Optimal timing of pembrolizumab administration will be based on the estimation of probability of dose-limiting toxicities (DLTs). A 2-parameter Bayesian Logistic Regression Method guided by the Escalation with Overdose Control principle will guide dose-timing selection together with review of accumulating safety and cellular kinetic data. Eligible patients must be ≥18 years old and have a confirmed diagnosis of r/r DLBCL with measurable disease and no active central nervous system disease; received ≥2 prior lines of therapy, including anti-CD20 and anthracycline-based chemotherapy, relapsing to or not eligible for autologous stem cell transplant (SCT); ECOG performance status must be 0 or 1. Patients treated with prior allogeneic SCT or anti-CD3, anti-CD19, or checkpoint inhibitor therapy are excluded. Primary endpoints are the proportion of patients receiving pembrolizumab per protocol schedule, the incidence of DLTs in the dose-timing selection phase, and overall response rate in the dose-expansion phase. Secondary outcomes include duration of response, progression-free survival, overall survival, safety, cellular kinetics, and immunogenicity. Estimated enrollment is 8-12 patients in the dose-timing and 12-16 patients in the dose-expansion phase. Dose-timing selection is currently ongoing. The first cohort of 4 patients receiving pembrolizumab at day 15 after tisagenlecleucel infusion has been completed.

OT15

MULTI-CENTER PHASE II STUDY OF ORAL AZACITIDINE (CC-486) PLUS CHOP AS INITIAL TREATMENT FOR PERIPHERAL T-CELL LYMPHOMA

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Introduction: Peripheral T-cell lymphomas (PTCL) are an uncommon and heterogeneous group of non-Hodgkin lymphomas with divergent cells of origin and mechanisms of lymphomagenesis. Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy, the most commonly prescribed initial treatment for systemic PTCL, provides suboptimal complete remission rates and response duration in the majority of non-ALCL patients. Emerging genetic studies have shown recurrent mutations affecting TET2, DNMT3A, IDH2 and RHOA in PTCL subtypes, particularly in nodal peripheral T-cell lymphoma with T-follicular helper phenotype (PTCL-TFH) such as angioimmunoblastic T-cell lymphoma. The association of aberrant DNA methylation with PTCL lymphomagenesis provides rationale for clinical application of hypomethylating agents. Azacitidine is an epigenetic modifier of DNA methylation by inhibition of DNA methyltransferase at low doses. In human PTCL patients, treatment with 5-azacitidine produced sustained responses (ORR 75%, CR/Cru 50%) in R/R AITL in a retrospective cohort study (Lemonnier et al. Blood 2018;132:2305). The feasibility of combining CHOP chemotherapy with azacitidine has been evaluated in 2 phase 1 studies in B-cell lymphoma, one with injectable 5-azaticidine (Clozel et al. Cancer Discov 2013;3:1002), the other with oral azacitidine (CC-486) (Martin et al. Blood 2017;130:192). We initiated a multi-center phase 2 study in 5/2018 to evaluate the efficacy and safety of chemo-sensitization with oral azacitidine (CC-486) in combination with CHOP for initial treatment of PTCL (ClinicalTrials.gov - NCT03542266).

Methods: This exploratory phase 2 study prioritizes enrollment of nodal TCL with TFH phenotype (PTCL-TFH). Additional eligible subtypes include PTCL/NOS and ATLL. Subjects receive standard dose CHOP on day 1 of each cycle for a total of 6 cycles. Priming with oral azacitidine (CC-486) at 300 mg daily is administered for 7 days prior to CHOP cycle 1 initiation, and for 14 days (days 8-21) before CHOP cycles 2-6. Supportive care includes mandatory G-CSF and recommended prophylaxis against PCP and VZV. The primary endpoint is CR per 2014 IWG criteria. Secondary endpoints include ORR, safety and survival. The study has a sample size of 20, and follows two-stage minimax design for primary efficacy analysis. Correlative biomarker studies are prospectively planned to assess changes in genome-wide methylation, gene expression and immune profile in response to DNMT inhibitor. The study is actively enrolling patients at Weill Cornell Medicine, with additional 3 US sites due to open in the 2nd quarter of 2019.

Keywords: angioimmunoblastic T-cell lymphoma (AITL); epigenetics; peripheral T-cell lymphomas (PTCL).

OT16
DOSE FINDING STUDY TO ASSESS SAFETY, PK AND EFFICACY OF FIMEPINOSTAT (CUDC-907) WITH VENETOCLAX OR RITUXIMAB PLUS BENDAMUSTINE IN PATIENTS WITH RELAPSED/REFRACTORY LYMPHOMA

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Background: The 2016 WHO reclassification of lymphoid tumors distinguishes double-hit (DHL) and triple-hit (THL) lymphomas as clinically important subtypes, now classified as high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements. Double-expressor lymphoma with MYC and BCL2 protein over-expression without rearrangement (included within DLBCL-NOS) also has prognostic importance. This reclassification highlights the dismal outcomes for patients with tumors harboring MYC and/or BCL2 alterations. Currently, there are no approved therapies that target MYC. Fimepinostat (F) is an investigational small-molecule dual inhibitor of PI3Ks and HDACs. F inhibited both PI3K and HDAC in non-clinical studies and substantially reduced MYC protein levels. PI3K and HDAC were also inhibited by F in patients. F demonstrated synergistic anti-tumor effects with venetoclax (V) in DHL and DEL models *in vitro* and

TABLE

Arm	Cohort: Dose/Schedule
F + V	1: F 30 mg daily, 5/2 + V 400 mg QD
	2: F 60 mg daily, 5/2 + V 400 mg QD
	3: F 60 mg daily, 5/2 + V 800 mg QD
F + B + R	1: F 30 mg daily, 5/2 + B 90 mg/m^2 Day 1,2 + R 375 mg/m^2 Day 1
	2: F 60 mg daily, 5/2 + B 90 mg/m^2 Day 1,2 + R 375 mg/m^2 Day 1
	3: F 60 mg daily, 5/2 + B 120 mg/m^2 Day 1,2 + R 375 mg/m^2 Day 1

in vivo. In clinical studies, F as monotherapy or in combination with rituximab (R) was well tolerated with a favorable safety profile in patients with R/R lymphoma, and resulted in robust and durable objective response rates (ORR) in patients with R/R MYC-altered DLBCL.

Methods: CUDC-907-101 is a Phase 1/2, multi-center, dose-finding study that was recently amended to study F in combination with V, or F with R plus bendamustine (B) in pts with R/R lymphoma, including DLBCL or HGBL with MYC and BCL2 alterations. The primary objectives are to determine the MTD, safety and tolerability of each combination, and to assess preliminary efficacy, as measured by ORR and DOR. Pts must be R/R to ≥1 prior regimen, have measurable disease (Lugano criteria), and have archived or fresh tumor tissue. Approximately 12 pts (dose escalation; 3+3 design) and 30 pts (dose expansion) will be enrolled into each combination arm. Clinical trial: **NCT01742988**.

Keywords: "double-hit" lymphomas; high-grade B-cell lymphoma with or without rearrangement of MYC and BCL2 and/or BCL6; MYC.

Disclosures: Younes, A: Consultant Advisory Role: *BMS, Incyte, Janssen, Genentech and Merck;* Honoraria: *Genentech, Merck, Takeda, Incyte, BMS, AbbVie;* Research Funding: *Novartis, Johnson & Johnson, Curis, Roche, BMS.*

OT17
SOLAR: A PHASE 2, GLOBAL, RANDOMIZED, ACTIVE COMPARATOR STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF COBOMARSEN IN SUBJECTS WITH MYCOSIS FUNGOIDES (MF)

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Introduction: Mycosis fungoides (MF, the most prevalent subtype of peripheral T-cell lymphomas, is characterized by proliferation of atypical T lymphocytes in the skin, forming patches, plaques, or nodular tumors. The goal of treatment is to minimize morbidity and limit disease progression; however, most therapies have significant side effects which limit their chronic use.

Cobomarsen is an inhibitor of microRNA-155, which is elevated and plays an important role in the proliferation and survival of malignant cancer cells in MF. In vitro, cobomarsen reduces proliferation and increases apoptosis in lymphoma cells. A Phase I clinical trial of cobomarsen in MF showed improvement in skin disease in 92% of subjects, with a durable response lasting at least 4 months in 77% of those achieving a PR (ORR4 based on mSWAT). The mean duration of response was 276 days and no significant side effects were attributed to cobomarsen.

Methods: MRG106-11-201 or SOLAR is a randomized, controlled, open-label study to assess the efficacy and safety of cobomarsen in patients with MF. The active comparator is vorinostat, an HDAC inhibitor approved in the US for the treatment of MF. The trial is currently recruiting subjects with a target of 126 subjects (63 per arm). Eligible subjects must have MF Stage IB-IIIB with a minimum mSWAT score of 10, B0-1, N0-1, no visceral involvement, and no large cell transformation. Prior treatment with an HDAC inhibitor is prohibited. Stratification will be performed based on age and LDH level at diagnosis. The primary endpoint is the proportion of subjects achieving ORR4 using composite global response criteria; secondary endpoints include progression free survival, patient reported outcomes, time to progression, time to next treatment, and overall survival. Subjects will receive weekly cobomarsen 282 mg IV infusions or daily 400 mg oral vorinostat. Assessments include changes in skin lesion severity, disease-associated symptoms and quality of life, as well as the length of time that the subject's disease remains stable or improved. Safety and tolerability will include assessment of the frequency and severity of side effects, as well as laboratory and ECG changes. Treatment will continue until the subject becomes intolerant, develops clinically significant side effects, progresses, or the trial is terminated.

Subjects assigned to receive vorinostat who experience confirmed disease progression during their participation in this study may have the option to enroll in a single arm study of cobomarsen (MRG106-11-203 or PRISM), if they meet the entry criteria for that study.

ClinicalTrials.gov Identifier: NCT03713320

Keywords: cutaneous T-cell lymphoma (CTCL); microRNA; mycosis fungoides (MF).

Disclosures: James, A: Employment Leadership Position: *Director, Clinical Operations, miRagen Therapeutics;* Stock Ownership: *miRagen Therapeutics, Array Biopharma;* **Ruckman, J:** Employment Leadership Position: *Director, Regulatory Affairs, miRagen Therapeutics;* Stock Ownership: *miRagen Therapeutics;* **Pestano, L:** Employment Leadership Position: *Senior Director, Translational Science, miRagen Therapeutics; Immediate Family Member - Biodesix;* Stock Ownership: *miRagen, Sanofi Pasteur, Cascadian Therapeutics, Biodesix;* Research Funding: *miRagen, Servier;* **Hopkins, R:** Employment Leadership Position: *miRagen Therapeutics;* Stock Ownership: *miRagen Therapeutics;* **Rodgers, R:** Employment Leadership Position: *miRagen Therapeutics;* Stock Ownership: *miRagen*

SOLAR: A Phase 2, Global, Randomized, Active Comparator Study to Investigate the Efficacy and Safety of cobomarsen in Subjects with Mycosis Fungoides

Primary Endpoint
- Overall Response Rate of Four Months (ORR4) Using Global Response Criteria

Key Secondary Endpoint
- Progression-Free Survival

Additional Secondary Endpoints
- Patient Reported Outcomes (Skindex-29, Pruritus, Pain)

Participating Countries
- Europe (Austria, Belgium, France, Germany, Italy, Netherlands, Spain, United Kingdom)
- North America (Canada, United States)
- Australia

OT18
A PHASE 1/1B DOSE-ESCALATION TRIAL EVALUATING CPI-818, AN ORAL INTERLEUKIN-2-INDUCIBLE T-CELL KINASE INHIBITOR, IN PATIENTS WITH RELAPSED/REFRACTORY T-CELL LYMPHOMA

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Background: Interleukin-2-Inducible T-Cell Kinase (ITK) is a Tec-family, non-receptor tyrosine kinase expressed in T cells that plays a key role in T-cell receptor (TCR) signaling, which is required for development of T-cells. In T-cell lymphoproliferative disorders, expression of the TCR and its downstream signaling components are maintained, which suggests that malignant cells may exploit this growth and survival pathway to their advantage. Professional antigen-presenting cells abundant in the lymphoma microenvironment may provide antigen to drive TCR signaling through ITK, which is expressed in a variety of T-cell lymphomas including PTCL, CTCL, ALCL, and in a subgroup of T-lymphoblastic leukemia/lymphoma. CPI-818 is a first-in-class, irreversible, covalent-binding ITK inhibitor with a high degree of selectivity for ITK. By inhibiting ITK, CPI-818 blocks signaling pathways that are essential to inflammatory responses and has shown to inhibit tumor growth in animal models. To test this clinically, a phase 1/1b dose-escalation trial of CPI-818 is initiated in subjects with relapsed/refractory T-cell lymphoma.

Methods: The trial will include patients with various types of T-cell lymphoma (PTCL and CTCL) who have progressed on, refractory to, relapsed, or intolerant to at least 2 standard therapies; age ≥18 yo; have ECOG status 0-1; adequate organ function; and without any other condition that would contraindicate the use of the investigational product. Dose Escalation with 3 + 3 (+ optional 3) design will consist of up to 6 ascending dose levels (100,200, 400, 600, 900, and 1200 mg BID) of CPI-818. In the Dose Expansion phase, there will be 4 disease-specific expansion cohorts (AITL, PTCL-NOS, CTCL and other T-cell lymphoma), and each cohort may enroll up to a maximum of 28 subjects/cohort based on a 2-stage expansion design- Figure.

The objectives of the study are to evaluate the safety and tolerability of CPI-818; establish the maximum tolerated dose or the maximum administered dose of CPI-818; evaluate pharmacokinetics and pharmacodynamics of CPI-818 in humans; assess the anti-tumor activity of CPI-818 and identify potential biomarker signals. Study schema in the figure.

Approximately 151 subjects will be enrolled at approximately 35 sites in the US, South Korea, and Australia.

Figure: Study Schema
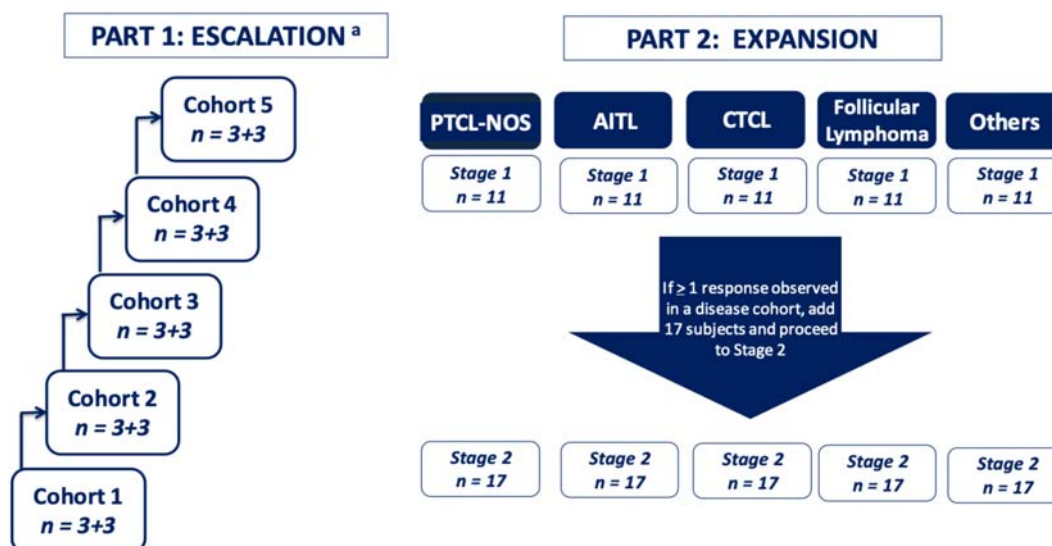
Others: Other types of T-cell lymphoma (NK/T-cell lymphoma, enteropathy associated T-cell lymphoma, hepatosplenic T-cell lymphoma, anaplastic large cell lymphoma, ATL)

Keywords: cutaneous T-cell lymphoma (CTCL); peripheral T-cell lymphomas (PTCL); T-cell lymphoma (TCL).

Disclosures: Mobasher, M: Employment Leadership Position: *Chief Medical Officer.*

OT19
ONGOING PHASE 1B/2 TRIALS OF MOSUNETUZUMAB INVESTIGATING NOVEL TREATMENT REGIMENS FOR PATIENTS WITH B-CELL NON-HODGKIN LYMPHOMA (NHL)

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Background: There is an unmet need for more effective and less toxic treatments for patients (pts) with B-cell NHL. Mosunetuzumab is a CD20/CD3 bispecific antibody that directs T-cells to engage and eliminate CD20+ B-cells. Interim results from a phase 1/1b study show that mosunetuzumab-monotherapy (M) is clinically active with a manageable safety profile in pts with relapsed/refractory (R/R) NHL (Budde et al. ASH 2018). Here we present 3 ongoing phase 1b/2 studies in NHL with mosunetuzumab (**Table**), 2 in novel combinations, and 1 as monotherapy consolidation after first-line (1L) immunochemotherapy or initial 1L therapy in elderly/unfit pts.

Methods: Two randomised, open-label, multicentre combination studies are being conducted to compare the following regimens across B-cell

TABLE Study details

Phase 1b/2 study	Key inclusion criteria	Regimen(s)	Target number of pts
NCT03677141 GO40515	Phase 1b: R/R B-cell NHL Phase 2: 1L DLBCL ECOG PS ≤2 Age ≥18 years	M + CHOP M + CHP-pola R + CHP-pola	110–160
NCT03671018 GO40516	R/R B-cell NHL ECOG PS ≤2 Age ≥18 years	M + pola M-monotherapy R + bendamustine-pola [DLBCL/transformed follicular lymphoma] or obinutuzumab + bendamustine followed by obinutuzumab maintenance or R-CHOP/CVP [follicular lymphoma]	249–282
NCT03677154 GO40554	DLBCL ECOG PS ≤2 Group A: age ≥18 years; best response of PR to 1L immunochemotherapy Group B: age ≥80 or 60–79 years + unfit for full-dose chemotherapy	M-monotherapy	40–60

NHL: mosunetuzumab + cyclophosphamide, doxorubicin, vincristine and prednisone (M-CHOP); mosunetuzumab + cyclophosphamide, doxorubicin, and prednisone (M-CHP) + polatuzumab vedotin (M-CHP-pola); or rituximab-CHP-pola in 1L diffuse large B-cell lymphoma (DLBCL); M-pola compared with M-monotherapy, or immunochemotherapy in R/R NHL. A third study is evaluating M-monotherapy in DLBCL pts, either as consolidation after partial response (PR) to 1L immunochemotherapy or as 1L therapy in pts unfit for full-dose chemotherapy. Safety and efficacy data from these studies will further define the role of mosunetuzumab in the treatment of B-cell NHL.

Disclosures: Budde, L: Consultant Advisory Role: *Gilead, Genentech, AstraZeneca*; Research Funding: *Mustang Therapeutics, Merck & Co, Amgen*; Other Remuneration: *Gilead, AstraZeneca (speakers' bureau)*. **Babu, S:** Employment Leadership Position: *Fort Wayne Medical Oncology & Hematology*; Consultant Advisory Role: *Bristol-Myers Squibb, Alexion Pharmaceuticals*; Stock Ownership: *Fort Wayne Medical Oncology & Hematology, Lutheran Hospital*; Honoraria: *Bristol-Myers Squibb, Alexion Pharmaceuticals, Lilly, Bayer, AstraZeneca*; Research Funding: *Bristol-Myers Squibb, Novartis, Genentech, Inc./Roche, AstraZeneca/MedImmune, HERON, Janssen Oncology, Amgen, Incyte, TG Therapeutics, Seattle Genetics, AbbVie, Lilly, Alexion Pharmaceuticals, Merck, Novartis*; Other Remuneration: *Alexion Pharmaceuticals (speakers' bureau); Bristol-Myers Squibb, Alexion Pharmaceuticals, Lilly (travel, accommodation and expenses)*. **Lossos, I:** Consultant Advisory Role: *Seattle Genetics, Janssen Scientific*. **Alderuccio, J:** Consultant Advisory

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OT20
A PHASE 1/2 STUDY OF MT-3724 TO EVALUATE SAFETY, PHARMACODYNAMICS AND EFFICACY OF MT-3724 FOR THE TREATMENT OF PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin's Lymphoma accounting for approximately 30-40 percent of NHL cases. Approximately 40% of all newly diagnosed DLBCL subjects develop either refractory or relapsed DLBCL and represent a population with unmet need for new therapeutic strategies to achieve or regain disease remission.

Because of the ubiquity and persistence of CD20 expression in B-cell malignancies, there is strong rationale to develop novel mechanisms of action (MOA) targeting CD20. However, CD20's non-internalizing nature has impeded the development of novel MOAs against this target.

MT-3724 is an engineered toxin body (ETB) comprised of a single chain variable fragment (scFv) genetically fused to Shiga-like toxin A subunit (SLTA). MT-3724 binds CD20 and induces its own internalization; once internalized, MT-3724 is cytotoxic through the novel mechanism of ribosomal inactivation. MT-3724 has been shown to specifically bind and kill CD20+ malignant human B-cells *in vitro* and in *in vivo* animal models.

As a direct-kill immunotoxin directed against CD20, MT-3724 has achieved malignant cell lysis in patients with refractory or relapsed NHL regardless of the biologic variations of malignant B-cells or the patient's immune status. Thus, MT-3724 could avoid, mitigate or delay the emergence of resistance to anti-CD20 MAb therapy.

Methods: MT 3724 is being evaluated as both monotherapy (NCT02361346) and in combination with either a chemotherapy combination (gemcitabine/oxaliplatin) or an immunomodulatory agent (lenalidomide). Adult patients with histologically confirmed, relapsed or refractory DLBCL who have received prior therapy are eligible.

Patients must have serum rituximab levels <500 ng/mL before the start of treatment to allow adequate binding of MT-3724 and have at least one tumor lesion at screening that is measurable according to the revised Lugano criteria [Cheson 2014, 2016]. Patients receive MT-3724 IV infusions over 1 hour on Days 1, 3, 5, 8, 10 and 12 of a 21-day treatment cycle for the first two cycles and then weekly. Combination therapy will be administered per a usual schedule.

The primary endpoint is objective response rate (ORR) by the revised Lugano Classification for Lymphoma adjusted according to LYRIC assessed by independent, blinded central review. Secondary endpoints include safety, progression-free survival, investigator-assessed ORR and DOR, and overall survival as well as PK, PD, ADA and QOL. Accrual is ongoing.

Keywords: diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL).

OT21
A FIRST-IN-HUMAN STUDY OF A HALF-LIFE EXTENDED CD19-TARGETING BiTE IN RELAPSED/REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA, MANTLE CELL LYMPHOMA OR FOLLICULAR LYMPHOMA

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Introduction: AMG 562 is a half-life extended (HLE) CD19-targeting BiTE® antibody construct being developed to treat patients with diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and follicular lymphoma (FL). BiTE®immunotherapy engages the patients' own T cells to potentially eliminate detectable cancer. Adults with relapsed/refractory (R/R) DLBCL treated with blinatumomab, a canonical BiTE® immunotherapy also targeting CD19, have shown durable complete responses. Compared with canonical BiTE® immunotherapy like blinatumomab, the HLE BiTE® construct has an added single-

chain fragment crystallizable (scFc) fragment to prolong its half-life. Preclinical models have demonstrated pharmacodynamic activity by demonstrating hallmarks of BiTE® activity and robust B-cell depletion.

Methods: This first-in-human, multicenter, nonrandomized, open-label, phase 1 study with sequential dose exploration willevaluate the safety and tolerability of AMG 562 in adults with R/R DLBCL, MCL, or FL. Target enrollment is 85 subjects. At 18 sites in the US, Canada, Belgium, Germany, South Korea, and Japan, approximately 30 subjects will be enrolled in the dose escalation cohorts (DECs) and up to 55 additional subjects will be enrolled in the dose expansion cohort. Dose escalation is guided by a two-parameter Bayesian logistic regression model. Clinical activity of AMG 562 in the expansion cohort will be examined in R/R DLBCL using a Bayesian predictive probability design.

Patients with ECOG status ≤2 will be eligible with disease refractory to first or later treatment or in 3rd or greater relapse. Adults with DLBCL with transformed disease are eligible and prior autologous transplantation is allowed. Patients with prior CD19-targeted treatment or current central nervous system involvement are excluded. The DECs will estimate the maximum tolerated dose (MTD), safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of AMG 562. At completion of the DECs, additional subjects will be enrolled in a dose expansion cohort. A final estimate of the MTD and recommended phase 2 dose will be evaluated and confirmed utilizing all subjects evaluable for dose-limiting toxicity.

Results: As of March 1, 2019, 1 subject is enrolled and has completed 1 cycle of AMG 562 at the lowest investigational dose level.

Conclusion: This study will identify initial safety, PK, and efficacy profile of the HLE BiTE® AMG 562 in adults with R/R DLBCL, MCL, and FL.

This is an Amgen-sponsored study.

Keywords: CD19; diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL).

OT22
AN ONGOING PHASE 1/1B TRIAL INVESTIGATING NOVEL TREATMENT REGIMENS WITH MOSUNETUZUMAB IN RELAPSED/REFRACTORY B-CELL NON-HODGKIN LYMPHOMA

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TABLE Patient enrolment

Group	No. of patients (enrolled as of January 25, 2019)	
	Dose-escalation	Dose-expansion*
D: mosunetuzumab (SC)	10 enrolled	R/R DLBCL/tFL; FL; MCL Target = 60
E: mosunetuzumab (IV) + atezolizumab	17 enrolled	R/R DLBCL/tFL; FL; MCL Target = 180

*Dose-expansion is also ongoing for Group B

Background: Mosunetuzumab is a novel CD20/CD3 bispecific antibody that directs T-cells to engage and eliminate malignant B-cells. Interim results from an ongoing, open-label, multicentre, phase 1/1b study (NCT02500407; GO29781) indicate that mosunetuzumab monotherapy administered intravenously (IV) induces durable complete responses with favourable safety in patients with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) (Budde et al. ASH 2018). We report details of 2 other ongoing dose-escalation groups from this study: Group D assesses mosunetuzumab administered subcutaneously (SC) as an approach intended to minimize cytokine-driven toxicities; Group E combines mosunetuzumab and atezolizumab for potentially enhanced clinical efficacy with the addition of immune checkpoint blockade. Dose-expansion cohorts in patients with R/R diffuse large B-cell lymphoma (DLBCL)/transformed follicular lymphoma (tFL), follicular lymphoma (FL), and mantle cell lymphoma (MCL) are ongoing.

Methods: Patients with R/R NHL (age ≥18 years; ECOG performance status of 0 or 1) in Group D receive a fixed dose of mosunetuzumab SC on Day 1 of each 21-day cycle, up to a maximum of 17 cycles; patients in Group E receive ascending doses of mosunetuzumab IV on Day 1, Day 8 and Day 15 of Cycle 1 (step-up dosing), then from Cycle 2 onwards, a fixed dose on Day 1 of every 21-day cycle with concurrent administration of atezolizumab (1200 mg IV), up to a maximum of 17 cycles. Primary outcome measures are maximum tolerated dose (MTD) based on dose-limiting toxicities, tolerability, pharmacokinetics and best objective response. Dose-expansion cohorts are enrolling patients with R/R DLBCL/tFL, FL, or MCL and patients will receive doses of mosunetuzumab up to the MTD. Details of patient enrolment for the dose-escalation and dose-expansion cohorts are provided (**Table**).

Disclosures: Kim, W: Research Funding: *Roche, Takeda, Eisai, Mundipharma, Pfizer, Celtrion, Kyowa-Kirin, J&J.* **Assouline, S:** Consultant Advisory Role: *Pfizer, Roche*; Other Remuneration: *Pfizer, Janssen (speakers' bureau); Roche (travel, accommodation and expenses)*. **Bartlett, N:** Consultant Advisory Role: *Pfizer, Seattle Genetics, ADC Therapeutics*; Research Funding: *Seattle Genetics, Genentech, Inc., Kite Pharma, Merck, Bristol-Myers Squibb, Celgene, Immune Design, Forty Seven, Affirmed Therapeutics, Janssen, Pharmacyclics, Millennium, Gilead Sciences*. **Bosch, F:** Consultant Advisory Role: *Roche, Janssen, Celgene, AbbVie, Novartis, Gilead*; Honoraria: *Roche, Janssen, Celgene, AbbVie, Novartis, Gilead*; Research Funding: *Roche, Janssen, Celgene, AbbVie, Novartis, Gilead, Sobi, Bayer*; Other Remuneration: *Roche, Janssen, Celgene, AbbVie, Novartis, Gilead (speakers' bureau)*. **Budde, L:** Consultant Advisory Role: *Gilead, Genentech, Astrazeneca*; Research Funding: *Mustang Therapeutics, Merck & Co, Amgen*; Other Remuneration: *Gilead, Astrazeneca (speakers' bureau)*. **Cheah, C:** Consultant Advisory Role: *Roche, Janssen, Takeda, MSD, Gilead, Bristol Myers Squibb, AstraZeneca*; Honoraria: *Roche, Janssen, Takeda, MSD, Gilead, Bristol Myers Squibb, AstraZeneca*; Research Funding: *Celgene, Roche, AbbVie*; Other Remuneration: *Roche, Amgen (travel, accommodation and expenses)*. **Gregory, G:** Consultant Advisory Role: *Gilead*; Honoraria: *Roche*; Research Funding: *BeiGene, AbbVie, Janssen, Merck*; Other Remuneration: *Roche (speakers' bureau and, travel, accommodation and expenses)*. **Hong, J:** Consultant Advisory Role: *Takeda, Roche*; Honoraria: *Takeda, Roche, Janssen, Celgene, Mundipharma, Celtrion, Eisai*; Research Funding: *Janssen, Boryung Pharmaceutical*. **Marlton, P:** Consultant Advisory Role: *Roche, Janssen-Cilag, Novartis, Amgen, Pfizer, Takeda, AbbVie*; Honoraria: *Roche, Janssen-Cilag, AbbVie, Novartis, Pfizer, Amgen, Takeda*; Other Remuneration: *Janssen-Cilag (speakers' bureau); Roche, Takeda (travel, accommodation and expenses)*. **Matasar, M:** Consultant Advisory Role: *Genentech, Bayer, Merck, Juno Therapeutics, Roche, Teva, Rocket Medical, Seattle Genetics*; Stock Ownership: *Merck*; Honoraria: *Genentech, Roche, Bayer, Pharmacyclics, Janssen, Seattle Genetics*; Research Funding: *Genentech, Roche, Bayer, Pharmacyclics, Janssen, Seattle Genetics*; Other Remuneration: *Genentech, Roche, Seattle Genetics, Bayer (travel, accommodation and expenses)*. **Nastoupil, L:** Honoraria: *Celgene, Genentech, Inc., Gilead, Janssen, Novartis, Spectrum, TG Therapeutics*; Research Funding: *Celgene, Genentech, Inc., Janssen, Merck, TG Therapeutics*. **Panizo, C:** Consultant Advisory Role: *Bristol-Myers Squibb, Kyowa Kirin*; Other Remuneration: *Roche Pharma (speakers' bureau, and travel, accommodation and expenses), Janssen (speakers' bureau)*. **Sehn, L:** Consultant Advisory Role: *AbbVie, Amgen, Roche/Genentech, Apobiologix, AstraZeneca, Acerta, Celgene, Gilead, Janssen, Kite, Karyopharm, Lundbeck, Merck, MorphoSys, Seattle Genetics, Teva, Takeda, TG Therapeutics*; Honoraria: *AbbVie, Amgen, Roche/Genentech, Apobiologix, AstraZeneca, Acerta, Celgene, Gilead, Janssen, Kite, Karyopharm, Lundbeck, Merck, MorphoSys, Seattle Genetics, Teva, Takeda, TG Therapeutics*; Research Funding: *Roche/Genentech, Inc.* **Tzachanis, D:** Consultant Advisory Role: *Jazz*; Other Remuneration: *Takeda (speakers' bureau)*. **Chu, W:** Employment Leadership Position: *Genentech, Inc.*; Stock Ownership: *Roche*. **Hernandez, M:** Employment Leadership Position: *Genentech, Inc.*; Stock Ownership: *Genentech, Inc.* **Kwan, A:** Employment Leadership Position: *Genentech, Inc./Roche*; Stock Ownership: *Genentech, Inc./Roche*. **Li, C:** Employment Leadership Position: *Genentech, Inc.*; Stock Ownership: *Roche*. **Sison, I:** Employment Leadership Position: *Genentech, Inc.*; Stock Ownership: *Genentech, Inc.* **Wei, M:** Employment Leadership Position: *Genentech, Inc.*; Stock Ownership: *Roche*. **Yin, S:** Employment Leadership Position: *Genentech, Inc.*; Stock Ownership: *Genentech, Inc.*; Other Remuneration: *Genentech, Inc. (travel, accommodation and expenses)*. **Yousefi, K:** Employment Leadership Position: *Roche*; Other Remuneration: *Roche (travel, accommodation and expenses)*. **Yoon, S:** Consultant Advisory Role: *Novartis, AbbVie, Amgen, Celgene, Roche*; Research Funding: *Roche*.

OT23
SPIReL: PHASE 2 STUDY DPX-SURVIVAC WITH INTERMITTENT LOW DOSE CYCLOPHOSPHAMIDE AND PEMBROLIZUMAB IN PATIENTS WITH RECURRENT/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Patients with relapsed diffuse large B cell lymphoma (DLBCL) who have failed autologous stem cell transplant (ASCT), or are ASCT ineligible, have few effective options and a poor prognosis. Chimeric antigen receptor (CAR) T cell is a new treatment option; however, its use is limited due to significant toxicities and financial cost.

Survivin, an inhibitor of apoptosis, is overexpressed in up to 60% of relapsed refractory DLBCL. DPX-Survivac, a novel T cell activating therapy, elicits a cytotoxic T cell response to tumor cells expressing survivin. Pembrolizumab 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). Low dose intermittent cyclophosphamide is used for its immunomodulator effect. Pre-clinical studies have demonstrated synergistic activity with this drug combination in control of tumor growth with resultant improved survival (Weir,GM et al., J Immunother Cancer. 2016 Oct 18;4:68).

Methods: This is a Phase 2 non-randomized, open label, efficacy and safety study. Study participants will receive two initial doses of 0.5 mL of DPX-Survivac 21 days apart and up to six 0.1 mL subsequent doses every two months. Intermittent low dose cyclophosphamide will be taken (50mg BID oral) for a rotating schedule of 7 days on followed by 7 days off. Pembrolizumab 200 mg will be administered every 3 weeks. Study participants continue active therapy for up to one year or until disease progression, whichever occurs first. Patients are eligible if they have DLBCL, including double hit lymphoma, with confirmed survivin expression. They must have recurrent disease post ASCT or are ineligible for ASCT.

The primary endpoint is to document the objective response rate to this treatment combination, using the modified Cheson criteria, in patients with recurrent, survivin-expressing DLBCL. Secondary endpoints include duration of response, immune-related response, and safety. Exploratory endpoints include; T cell response by antigen-specific ELISpot assay, tumour immune cell infiltration by multiplex immunohistochemistry and gene expression assay using the nCounter ®PanCancer Immune Profiling panel (Nanostring Technologies).

Up to 25 patients will be enrolled in this national, multi-centre study, over 36 months. Preliminary data will be available on enrolled participants. Trial design is shown below.

Keywords: diffuse large B-cell lymphoma (DLBCL); immunochemotherapy; Pembrolizumab.

Disclosures: Berinstein, N: Honoraria: *received honoraria from Merck for ad hoc ad boards.* **Stewart, D:** Honoraria: *received honoraria from Merck for ad hoc ad boards.*

OT24
PHASE IB/II STUDY OF IBRUTINIB AND VENETOCLAX IN RELAPSED AND REFRACTORY FOLLICULAR LYMPHOMA

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Background: Despite high response rates to front-line chemo-immunotherapy, patients with follicular lymphoma (FL) inevitably
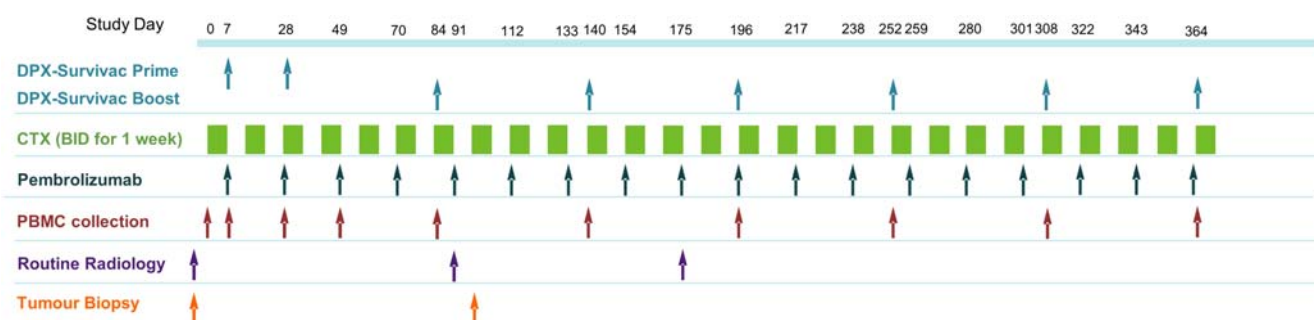
relapse and further treatment options are necessary. The BTK inhibitor, ibrutinib, has demonstrated an overall response rate (ORR) of 21% and median duration of response of 19 months in relapsed/refractory disease (Gopal A, et al. JCO 2018). Venetoclax, a selective inhibitor of the pro-survival BCL-2 protein, has demonstrated an ORR of 38% and median PFS of 11 months in previously treated FL (David M, et al. JCO 2017). Preclinical data have shown synergy with these agents in B-cell non-Hodgkin lymphoma cell lines (Kuo H, et al. Mol Cancer Ther. 2017) Based on these observations, we proposed the first clinical trial to evaluate the combination of a BTK inhibitor and a BCL-2 inhibitor in FL. Correlative studies include next-generation sequencing, assessment of BCL-2 family member proteins, and tissue co-culture models to assess mechanisms of resistance.

Methods: This phase Ib/II study in relapsed/refractory FL is being conducted at Lombardi Comprehensive Cancer Center, John Theurer Cancer Center, and Seattle Cancer Care Alliance. Eligibility criteria include WHO grade 1-3a FL, at least 1 prior systemic therapy, measurable disease warranting therapy by standard criteria, ECOG performance status <2, and adequate marrow, hepatic, and renal function. All FLIPI risk groups are eligible. The primary and secondary objectives in the phase I portion are to determine the recommended phase II doses and pharmacokinetics of ibrutinib and venetoclax when administered together in FL. The primary and secondary objectives in the phase II portion are efficacy and safety, respectively. Patients will be enrolled in a standard phase I 3+3 design at a starting dose level (DL) of ibrutinib 420 mg daily and venetoclax 400 mg daily (DL0). The highest dose level is DL3: ibrutinib 560 mg daily and venetoclax 800 mg daily. Patients will receive the combination until progression or unacceptable toxicity. Once the maximum tolerated dose is determined, there will be a 17-patient phase II study for a maximum of 41 patients. To date, 8 patients have been enrolled. Clinical trial information: NCT02956382.

Keywords: follicular lymphoma (FL); ibrutinib; venetoclax.

OT25
A WINDOW STUDY OF IXAZOMIB IN UNTREATED B-NHL

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Background: Standard initial treatment of indolent B-cell non-Hodgkin lymphoma (iB-NHL) includes intravenous or subcutaneous treatment requiring regular infusion center appointments. These can be burdensome, especially for patients living remotely from a cancer care facility. Furthermore, most patients with iB-NHL will have survival comparable to age matched controls. Thus, therapies that are sufficiently effective and minimally toxic while being maximally convenient are sought. Ixazomib, an orally bioavailable proteasome inhibitor, showed promising activity in a single study that included a small number of patients with relapsed/refractory iB-NHL (Assouline et al., 2014). As the maximum activity of a therapy is typically in the treatment-naïve setting, we designed a frontline "window" study to assess the potential ceiling of activity of ixazomib monotherapy in iB-NHL.

Methods: This single-arm, open-label investigator-initiated phase II trial (NCT 02339922) is being conducted at the University of Washington / Fred Hutch Cancer Research Center. Patients must have a diagnosis of one of the following iB-NHL: follicular lymphoma, marginal zone lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia / small lymphocytic lymphoma, or Waldenstrom's macroglobulinemia / lymphoplasmacytic lymphoma. Additional eligibility criteria include a clinical indication for treatment, an Eastern Cooperative Oncology Group performance status of ≤2, and having received no prior standard systemic anti-neoplastic treatment except in cases of mucosa-associated marginal zone lymphoma relapsed after or refractory to antibiotics.

Ixazomib is administered at 4 mg orally once a week on consecutive 28-day cycles until disease progression or unacceptable toxicity. The window period closes after 6 cycles, with four doses of weekly rituximab added during the 7th cycle. Ixazomib continues concurrently with rituximab and thereafter. Addition of rituximab is included to assure that all patients receive a standard therapy as part of their initial treatment.

The primary endpoint is investigator-assessed response rate performed every 2 cycles. The null hypothesis that the true response rate is ≤40% will be tested against the alternative hypothesis that the true response rate is ≥60% with a type I error rate of 8% and a power of 85%, requiring an overall response rate of ≥19 of 36 to conclude promising efficacy. Secondary endpoints include duration of response, progression free survival, time to next treatment, and safety / tolerability. Tumor tissue is being collected for gene expression profiling using the NanoString platform and immunohistochemical evaluation of molecular pathways associated with proteasome inhibition. The study is supported by Takeda Oncology.

Keywords: non-Hodgkin lymphoma (NHL).

OT26
ONGOING STUDY OF OBINUTUZUMAB SHORT DURATION INFUSION IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA

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Introduction: In the Phase III GALLIUM study, obinutuzumab (G) in combination with chemotherapy (G-chemo) demonstrated improved progression-free survival (PFS) and a similar tolerability profile compared with rituximab (R)-chemo, the current standard of care for first-line treatment of follicular lymphoma (FL). Administration of G can take about 4 hours using an infusion-related reaction (IRR) risk-reduction strategy. Shorter infusion times would improve convenience by yielding substantial time savings for patients (pts) and benefiting outpatient infusion facilities. Previous studies with R have led to the development of a 90-minute short duration infusion (SDi), which is now widely used if the first dose of R is well tolerated. Results of the Phase II GATHER study, in pts with previously untreated advanced diffuse large B-cell lymphoma (DLBCL) (Sharman et al. Leuk Lymphoma 2018) and the Phase II GATS study in Japanese pts with previously untreated non-Hodgkin Lymphoma (NHL) (Ohmachi et al. Jpn J Clin Oncol 2018) indicated that G can be safely administered as a 90-minute SDi, after the initial cycle. Here we report GAZELLE (NCT03817853; MO40597), an ongoing Phase IV study investigating the safety of G administered as a 90-minute SDi in pts with previously untreated advanced FL, who have received G-chemo at the standard infusion rate without experiencing a Grade (Gr) 3 or 4 IRR.

Methods: Pts with CD20-positive, previously untreated stage III or IV FL, or stage II bulky disease (GELF criteria for initiating

Figure. GAZELLE study design

C, cycle; CR, complete response; D, day; G-chemo, obinutuzumab plus chemotherapy; Gr, grade; IRR, infusion-related reaction; PD, progressive disease; PR, partial response; SD, stable disease; SDi, short duration infusion; SoC, standard of care
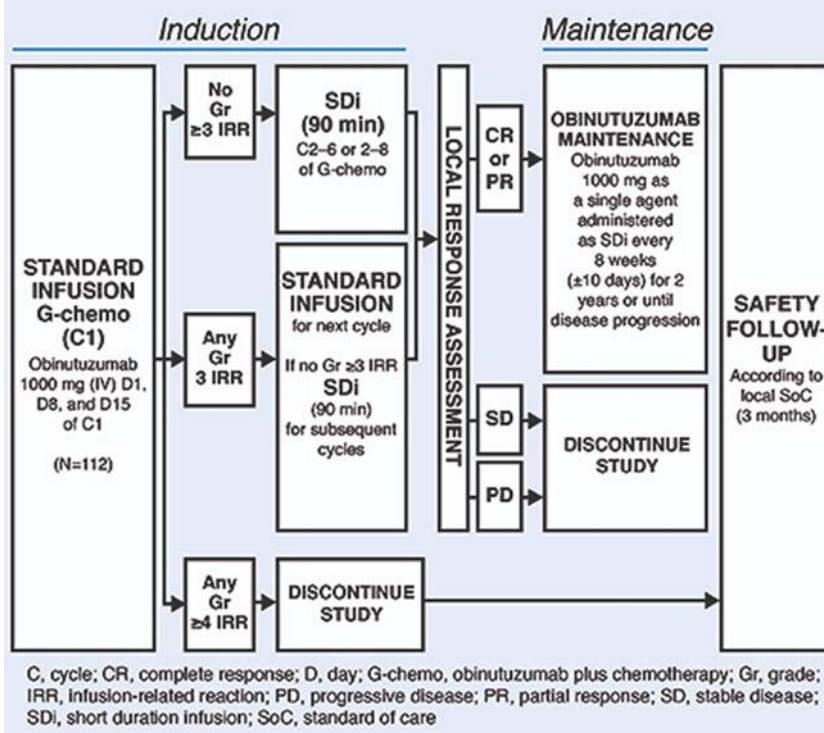
treatment, ECOG PS 0–2, life expectancy ≥12 months) will receive G (1000 mg) intravenously on Day (D) 1, D8, and D15 of cycle (C) 1, and on D1 of subsequent cycles (**Figure**). The standard infusion rate will be administered in C1, starting on D1 at 50 mg/hour, then increase by 50 mg/hour every 30 minutes to a maximum of 400 mg/hour. If no IRR or a Gr 1 IRR occurs, C1D8 (and subsequently C1D15) will start at 100 mg/hour, then increase by 100 mg/hour every 30 minutes to a maximum of 400 mg/hour. If a Gr 2–3 IRR occurs during C1D1 or C1D8, the next infusion (C1D8 or C1D15, respectively) will be administered at the same rate as C1D1. If no Gr ≥3 IRR occurs in C1, all subsequent infusions will be administered via a faster 90-minute SDi; 100 mg/hour for 30 minutes, then 900 mg/hour for 60 minutes. If a Gr 3 IRR occurs during any SDi administration, the next dose of G will be administered at the standard infusion rate. The investigator will decide if the pt can restart with the SDi. The primary endpoint is incidence of Gr ≥3 IRRs during C2 in pts who had previously received G at the standard infusion rate during C1 without experiencing a Gr ≥3 IRR. Secondary safety endpoints include adverse events, time to IRRs, type and duration of Gr ≥3 IRRs and duration of G administration by cycle. Secondary efficacy endpoints include overall response rate, PFS, overall survival and complete response at 30 months. It is estimated that 112 pts will be enrolled.

OT27
THE CANNABINOID STUDY – 01: INVESTIGATING THE EFFECTS OF CANNABINOIDS IN INDOLENT LEUKEMIC B-CELL LYMPHOMA

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Introduction: The endocannabinoid system has been suggested as a possible target for cancer treatment. Case-reports have suggested that cannabinoids could have an effect on certain difficult to treat patients with acute lymphoblastic leukemia (Sing, Y and Bali, C. *Case Rep Oncol* 2013). Agonists to the cannabinoid receptor-1 and cannabinoid receptor-2 (CB1; CB2) have been showed to induce cell-death of overexpressing lymphoid cell lines (Gustafsson, K. et al. *Int J Cancer* 2008). CB1 is most commonly found in the central nervous system where as CB2 is found in the peripheral nervous system and in lymphocytes and myeloid cells (Bouaboula, M. et al. *Eur J Biochem* 1993). In this study we aim to investigate how a controlled amount of cannabinoids affects malign and benign white blood cells (WBCs) in vivo by administering an oral mucosal spray containing both the CB1/CB2-agonist tetrahydrocannabinol (THC) and the partial CB1-antagonist cannabidiol (CBD).

Methods: We are including patients into an open-label, non-randomized clinical study (EudraCT 2014-005553-39) which have been approved by the regional ethics board and the Swedish Medical Products Agency. The patients included have indolent, non-symptomatic leukemic B-cell lymphoma, (mostly chronic lymphocytic leukemia). The first part of the study has identified a maximum tolerated dose with respect to side effects. Further inclusion of patients is now ongoing.

Patients are given a single dose of the oral spray mix of THC and CBD at 9 in the morning and sampled at 0, 1, 2, 4, 6, 24, and 168 hours. We investigate if THC and cannabidiol might affect white blood cell subsets, particularly if this single dose might reduce leukemic cell numbers, and, if so, by what mechanism. By also sampling the patients on a separate day (prior to the cannabinoid exposure) at the same hours, we control for any confounding natural circadian variations in blood leukocyte subset levels. Further analyses include standard clinical chemistry measurements, THC- and CBD-concentrations in plasma/urine/saliva/exhaled air, flow cytometry of lymphocyte subsets, analysis of cannabinoid receptors mRNA expression by quantitative polymerase chain reaction (qPCR), in vitro assays of the effect of cannabinoids on ex vivo isolated lymphoma cells (cell death, cell proliferation, cell migration) as well as cytokine analyses.

So far 23 patients have been included. Adverse events have been manageable (no grade 3-4 events) and all patients have been able to return home in the afternoon. We plan to end inclusion of patients in the summer of 2019.

Keywords: B-cell lymphoma; chronic lymphocytic leukemia (CLL); indolent lymphoma.

OT28
A PILOT TRIAL OF ADRIAMYCIN, PEMBROLIZUMAB, VINBLASTINE AND DACARBAZINE (APVD) FOR PATIENTS WITH UNTREATED CLASSICAL HODGKIN LYMPHOMA

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Background: ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) forms the backbone of frontline management of classical Hodgkin lymphoma (CHL) in North America regardless of stage. Expected cure rates with upfront therapy approach 75% in advanced stage, and 85-90% in early stage. A novel regimen incorporating brentuximab vedotin sought to improve upon ABVD in untreated advanced stage CHL patients. While it demonstrated a modest modified PFS benefit, it was associated with notable toxicities including higher rates of neuropathy and infection. PD1 inhibition is highly effective in relapsed/refractory CHL, leading to the FDA approval of nivolumab and pembrolizumab in this setting. The first-line setting may represent the ideal time for a PD1 inhibitor, with relatively intact host immunity and coexistence of malignant cells and T cells in the microenvironment. Using a proven chemotherapy backbone, we designed a trial adding pembrolizumab to AVD chemotherapy for untreated CHL (NCT03331341).

Methods: We designed a non-randomized, single arm pilot study combining pembrolizumab with AVD in untreated CHL of any stage. Eligibility requires ECOG 0-1, adequate organ function, and measurable disease. The trial intends to enroll 30 patients. AVD is given at standard doses on days 1 and 15 of a 28 day cycle. Pembrolizumab (200 mg IV) is given starting cycle 1 day 1 and every 21 days thereafter (cycle 1 day 22, cycle 2 day 15 etc.). The primary objective is to estimate the safety of delivering 2 cycles of APVD. The study will be determined a success if >85% of subjects are able to complete 2 cycles of therapy without a dose delay >3 weeks. Operationally, the stopping rule will be activated if the lower limit of the 95% confidence interval of toxicity crosses 15%. Thus, the trial would stop if 4/10, 7/20, 8/25, or 9/30 had a dose delay of >3 weeks due to toxicity. The secondary objective is to estimate the FDG-PET2 negative (Deauville score 1-3) after 2 cycles of APVD. Exploratory objectives include overall and progression free survival, predictive capacity of PET2 after APVD, and analysis of ctDNA. After PET2 response assessment, subjects may continue APVD for up to 6 total cycles, or pursue treatment deemed appropriate for their stage/risk factors (including alternate systemic therapy or radiotherapy) at investigator discretion.

Keywords: chemotherapy; Hodgkin lymphoma (HL); Pembrolizumab.

OT29
EVITA: PHASE I/II STUDY OF EVEROLIMUS PLUS ITACITINIB IN RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA

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Introduction: There is an unmet need for patients (pts) with relapsed/refractory classical Hodgkin lymphoma (cHL) who failed or cannot tolerate immune check point inhibitors and brentuximab vedotin (BV). Biology of cHL is characterized by scant Hodgkin Reed Sternberg cells (HRS) within a pro-inflammatory tumor microenvironment (TME). Both HRS and TME are rich with therapeutic targets. One of those is Akt which is constitutively activated in cHL-derived cell lines and its downstream effectors include mTOR substrates. Other promising targets in cHL are components of JAK/STAT pathway as genetic alterations in multiple genes (including STAT3, STAT5B, JAK1, JAK2, PTPN1) have been demonstrated in cHL. In pre-clinical studies, co-treatment of mTOR and JAK inhibitors resulted in synergistic activity against the proliferation of JAK mutated cell lines. Everolimus (oral inhibitor of mTOR) is clinically active in cHL with overall response rate (ORR) 40%, but low complete response rate (CR) of 5%. Ruxolitinib (oral JAK1/2 inhibitor) monotherapy produced only modest responses in cHL. Itacitinib adipate is another oral JAK inhibitor with potent selectivity for JAK1, but limited data in cHL. Itacitinib also inhibits STAT protein phosphorylation and pro-inflammatory cytokines including IL-6 which is expressed on HRS/TME and its expression has been associated with B symptoms. To our knowledge, no clinical studies

have been done with concurrent mTOR/JAK inhibition in cHL. We hypothesize that targeting multiple pathways in HRS/TME using combination of everolimus and itacitinib will result in deeper disease control compared to everolimus monotherapy.

Methods: An open-label, single-group study of everolimus in combination with itacitinib is currently opened at the University of Pennsylvania. Eligible pts must have relapsed/refractory cHL after at least 2 prior systemic therapies and must have relapsed after or be ineligible for autologous stem cell transplant. They also must have progressed after treatment with, be intolerant to, or are not a candidate for BV and pembrolizumab/nivolumab. Phase I will evaluate the safety and tolerability of the combination using a standard 3 + 3 design with dose-escalation or de-escalation. The starting dose of everolimus is 5 mg daily and of itacitinib is 300 mg daily with treatment planned for 2 years or until progression/intolerance. Phase II will evaluate the efficacy of the combination in cHL as demonstrated by CR (the null hypothesis is set at CR rate of 5%). Secondary objectives include progression free/overall survival, ORR, duration of response. Exploratory analyses include impact on quality of life/B symptoms. Ancillary studies exploring tumor biology/biomarkers are planned. Since opening in January 2019, 2 pts have been enrolled. The goal is to enroll 23 pts over a period of 3 years.

Keywords: Hodgkin lymphoma (HL); JAK/STAT; mTor inhibitors.

Disclosures: Nasta, S: Research Funding: *Incyte.*

OT30
UK: NATIONAL COHORT STUDY INVESTIGATING MAJOR LATE EFFECTS OF HODGKIN LYMPHOMA TREATMENTS ON BEHALF OF THE ENGLAND & WALES HODGKIN LYMPHOMA FOLLOW-UP GROUP

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Background: Dramatic improvement in Hodgkin Lymphoma (HL) survival rates over recent decades is one of the greatest success stories in modern Oncology. However it has come at a significant cost: treatment-related toxicity. These issues are epitomised in female HL patients treated at young ages, who have many decades to accumulate late effect burden, and are additionally susceptible to sex-specific outcomes such as breast cancer and premature menopause. In 2003, a national cohort comprising all young women (under <36 years) treated for HL with radiotherapy above the diaphragm in England and Wales since 1960 was established (5,000 women). This quantified the significantly raised risks of breast cancer, particularly those treated with high dose radiotherapy to the breast around menarche. Increased risk of other second malignancies and mortality are also known to be serious consequences of HL treatments. It is hoped de-intensification of treatments will attenuate risk of these long-term effects but this has not yet been definitively demonstrated. These outcomes have been studied in relation to treatment largely in those treated in childhood or in smaller populations than our UK cohort. We have expanded this cohort to include women treated more recently, until 2010, and to encompass all treatment types, to investigate risk factors for the most severe long term effects of HL treatments, and whether risks have diminished over time.

Methods: 10,000 women diagnosed with HL under 36 years have been identified from English and Welsh Cancer Registries from the 1960-2010 with >99% complete follow up for mortality until 2018 and are in the process of linking to causes of death. We are currently obtaining treatment and second cancer information for each patient from NHS hospital records across the country. We have achieved this for 7,000 patients so far. We have also obtained linked second cancers from national cancer registrations. Once complete, this will be the much the largest cohort of its kind worldwide, to enable high power analyses of risk factors for a range of serious late effects in Hodgkin Lymphoma.

Keywords: Hodgkin lymphoma (HL).

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