

ORAL PRESENTATIONS

KEY NOTE LECTURES

1 HENRY KAPLAN MEMORIAL LECTURE: “IMMUNOTHERAPY COMES OF AGE TO TREAT LYMPHOMAS”

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Introduction: The advent of Monoclonal Antibodies, first made by the method of Kohler and Milstein, ushered in a new era of treatment for cancer. Originally, the targets for antibodies were on the tumor. More recently, additional targets on the host immune system “Checkpoints” have entered our therapeutic tool kit.

Methods: The first target was the idiotype of the B cell tumor surface immunoglobulin. This required a new antibody custom-made product for each patient. Later, an antibody against the CD20 molecule, originally described by Nadler and Scholssman, was substituted because it was a single product for all patients, even though it is present on all normal mature B cells as well as lymphoma cells.

Results: Rituximab and a number of new versions of antibodies against CD20 are included in the standard of care for patients with B cell lymphoma. New targets are emerging and new forms of monoclonal antibodies that bind to two different targets or that carry drugs are in widespread testing. A special version of an engineered T cell that carries a receptor incorporating the recognition unit of an antibody against CD19 (CAR-T cells) is the latest and most exciting of these engineered therapies. But, once again this is a patient-specific, customized therapy. Antibodies against the host immune system (i.e. PD1) are rapidly changing the field of cancer treatment and especially of Hodgkin's Disease, where durable response rates in excess of 80% have been observed, even in relapsed/refractory patients.

Conclusions: Immunotherapy is now one of the mainstays of treatment for lymphoma. The field is moving rapidly and we can anticipate even newer versions of immune system therapies and combinations with existing targeted and cytotoxic therapies in the future.

Keywords: immune system.

2 GIANNI BONADONNA MEMORIAL LECTURE: “GENETIC SIGNATURES AND TARGETABLE PATHWAYS IN LYMPHOID MALIGNANCIES”

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Genetic signatures of lymphoid malignancies identify key signaling and survival pathways and associated therapeutic vulnerabilities. Increasing evidence suggests that specific lymphoid malignancies utilize genetic bases of immune evasion to limit recognition and avoid attack. We previously identified near-universal copy number alternations (CNA) of 9p24.1/CD274(PD-L1)/ PDCD1LG2(PD-L2) and associated increased expression of the two PD-1 ligands in classical Hodgkin lymphoma (cHL) and a related lymphoid malignancy, primary mediastinal large B-cell lymphoma (MLBCL). In these lymphomas, the extended 9p24.1 amplicon also includes JAK2, of note because JAK/STAT signaling further induces PD-1 ligand transcription. These observations defined 9p24.1 gain as a genetic alteration that increased the gene dosage of the PD-1 ligands and their induction via JAK/STAT signaling in specific lymphoid malignancies. In additional studies, PD-1 and PD-L2 were also infrequently identified as chromosomal translocation partners in cHL and MLBCL.

PD-1 signaling triggers the dephosphorylation of proximal components of the T-cell receptor complex and inhibition of T-cell activation and proliferation, termed “T-cell exhaustion.” The genetic bases for enhanced PD-1 ligand expression in cHL and MLBCL prompted clinical evaluation of PD-1 blockade in these diseases. In patients with relapsed/refractory cHL, pilot and registration trials of two different PD-1 blocking antibodies, nivolumab and pembrolizumab, revealed response rates of ~70% with many long-term remissions. In patients with relapsed/refractory MLBCL, a pilot study of PD-1 blockade revealed a response rate of ~40%; a national/international follow up trial is ongoing. These data established that lymphoid malignancies with genetic bases of increased PD-1 ligand expression are very sensitive to PD-1 blockade, prompting the development of clinical trials at earlier stages of treatment.

More recently, we have identified two additional large cell lymphoma subtypes with frequent 9p24.1 alterations - primary central nervous system lymphoma (PCNSL) and primary testicular lymphoma (PTL). In patients with relapsed/refractory PCNSL and PTL, pilot studies of PD-1 blockade with nivolumab revealed a high response rate and long-term remissions and a national/international phase II trial is ongoing.

Important questions include the precise mechanisms of response and resistance to PD-1 blockade in specific lymphoid malignancies and the optimal way to utilize this promising treatment strategy at earlier

timepoints in treatment. The data also prompt speculation regarding additional targetable genetic bases of immune evasion in other lymphoid malignancies.

3 JOHN ULTMANN MEMORIAL LECTURE: “GENOMES IN TRANSIT: WHAT MULTI-OMICS CAN TELL US ON LYMPHOMAS”

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Since the first detection of recurrent chromosomal aberrations in malignant lymphomas back in the 1970s a wealth of data has been accumulated showing that lymphoma cells differ from their normal counterparts on the various levels of cellular information. Despite being limited by the resolution, throughput and costs of the analyses the pioneering cytogenetic, molecular cytogenetic as well as targeted molecular and RNA expression analyses unraveled important information on lymphoma biology and clinical behavior. The data obtained by these technologies have been fundamental for the present classification of lymphomas.

The recent years have seen dramatic technological developments allowing the comprehensive profiling of malignant lymphomas on various OMICs levels. Considering cellular information encoded in nucleic acids high throughput sequencing technologies now enable the in-depth investigation of the whole genome as well as the various layers of the epigenome and transcriptome with a base-pair resolution. Nevertheless, the integrated analysis of these multiple layers of nucleic acid information is still at its beginning. In this context it is important to recognize, that information encoded in nucleic acids is in many aspects “fluent”: genomic information transits from DNA via epigenomic regulation and expression patterns of RNA to its ultimate function. Moreover, during tumor evolution the information at all these levels transits from the germline state via driving changes to complex aberration patterns. Additionally, the information transits from mother to daughter cells which in turn receive further information from environmental factors. Thus, “a” lymphoma is indeed an ecosystem with multiple interacting levels of informational dysregulation which unlikely is comprehensively described by targeted re-sequencing on DNA level or transcriptional profiling alone.

Thanks to the interdisciplinary cooperation of clinicians, pathologists, geneticists and bioinformaticians within the interdisciplinary German-wide MMML-network we have profiled meanwhile more than 250 germinal-center B-cell derived by sequencing and more than 800 B-cell lymphomas by array-based means for genomic, expression and methylation changes. This lecture will give examples on the strategies aiming at integrating these complementary levels of nucleic-acid-based OMICs data as well as novel insights into the biology of lymphomas provided by such integrative analyses.

Keywords: epigenetics.

PLENARY SESSION

4 INTERIM REPORT FROM A PHASE 2 MULTICENTER STUDY OF TAZEMETOSTAT, AN EZH2 INHIBITOR, IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN LYMPHOMAS

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Background: New treatments with novel mechanisms of action are needed for patients with relapsed/refractory (R/R) DLBCL and FL. Because tumor cells may depend on the histone methyltransferase EZH2 to perpetuate a less-differentiated state, and activating mutations may be oncogenic drivers, tazemetostat, a potent, selective EZH2 inhibitor was developed. Tazemetostat shows antitumor activity in preclinical models and in a phase 1 study in patients (pts) with mutated or wild-type (wt) EZH2 tumours. This open-label, multicentre phase 2 study enrolled pts with either mutated or wt EZH2 R/R DLBCL or FL to determine efficacy and safety in 6 separate cohorts.

Methods: Tazemetostat 800 mg is administered po BID. Tumour tissue is analysed prospectively to guide cohort assignment based on EZH2 hot spot activating mutations (Y646X, A682G, A692V) using a **cobas**® EZH2 Mutation Test (Roche Molecular Systems, in development). A 62-gene panel is used to assess tissue DNA and circulating tumour

DNA (ctDNA) for biomarkers of tazemetostat sensitivity. Key inclusion criteria include: ≥ 18 yrs old; ≥ 2 prior treatment regimens; measurable disease; and adequate organ function. The primary endpoint is overall response rate (ORR). Secondary endpoints include progression-free survival and safety/tolerability. Enrolment for monotherapy has been completed in 3 cohorts with wt EZH2 and is ongoing in 2 cohorts of mutant EZH2. Enrolment for a tazemetostat combination with prednisolone in wt EZH2 DLBCL was recently initiated.

Results: As of Feb. 28, 2017, interim safety data are summarized from 165 DLBCL or FL pts with documented tazemetostat dosing. Grade-3 treatment-emergent adverse events related to tazemetostat were reported in 18% of pts. The most common ($>10\%$) adverse events across all grades were: nausea; thrombocytopenia; cough; diarrhoea; fatigue; and asthenia. Interim efficacy results are summarized from 149 pts (median: 3 prior therapies) and exclude ongoing pts who lack an on-study tumor assessment. The ORR (CR + PR) was 40% in pts with DLBCL with EZH2 mutations ($N = 10$), 18% in pts with DLBCL with wt EZH2 ($N = 85$), 63% in FL pts with EZH2 mutations ($N = 8$), and 28% in FL pts with wt EZH2 ($N = 46$). In the cohorts of EZH2 mutant FL and EZH2 wt FL, 38% and 30% of pts, respectively, remained on study with stable disease. Safety and efficacy data will be further updated at the conference. The genetic analysis of tumor biomarkers will be reported separately.

Conclusion: This phase 2 interim assessment shows preliminary clinical activity of tazemetostat with a favourable safety profile in pts with R/R DLBCL and FL, with preferential benefit in pts whose tumours bear activating EZH2 mutations. Pts continue to be followed for tazemetostat treatment outcomes in light of previously reported observations that the onset of clinical response may be delayed and evolve over time from SD to PR and from PR to CR.

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

5 CRISPR-CAS9 GENETIC SCREENS UNCOVER a B CELL RECEPTOR-MYD88 SUPERPATHWAY 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) frequently relies on signaling from the B cell receptor (BCR) and mutant isoforms of MYD88 to maintain oncogenic levels of NF- κ B activity essential to its survival. These pathways are commonly mutated in ABC DLBCL. A recent clinical trial of ibrutinib, an inhibitor of the BCR proximal kinase BTK, in relapsed/refractory DLBCL patients reported exceptional responses in ABC DLBCL patients co-expressing mutations in both MYD88 and CD79B. These clinical data suggested the BCR and MYD88 signaling pathways may be functional coupled.

Methods: We performed genome-wide CRISPR-Cas9-based lethality (dropout) screens in 8 DLBCL lines to discover modulators of BCR signaling that are required for cell viability or proliferation. Essential genes were subjected to further genetic, biochemical and image analysis, including the proximity ligation assay (PLA) to visualize protein-protein interactions *in situ*.

Results: Our CRISPR screens identified TLR9 as the only MYD88 binding receptor required in MYD88-mutant ABC cell lines. Surprisingly, this requirement was limited to ABC models that relied on both the MYD88 L265P mutant isoform and chronic active BCR signaling, leading us to explore a link between chronic active BCR signaling and TLR9. We found that TLR9 and IgM co-immunoprecipitate in ABC lines. Moreover, the association between TLR9 and MYD88 L265P is dependent upon active BCR signaling. Using the PLA, we visualized BCR and TLR9 association with each other in Lamp1+ endolysosomes. To advance these findings, we fused the MYD88 L265P isoform to BioID2, a promiscuous biotin ligase that will attach biotin on neighboring proteins. When this construct was expressed in ABC DLBCLs, we unexpectedly observed that MYD88 was in close association with CARD11 and MALT1, components of the CBM adapter complex that is assembled downstream of the BCR. Employing the PLA, we show that endogenous MYD88 interacts with all members of the CBM complex in ABC lines, and that these interactions were dependent on the BCR and TLR9. Finally, we visualized MYD88 signaling in cells expressing the MYD88-L265P-BioID2 construct. We observed MYD88 signaling in large-scale complexes juxtaposed to Lamp1+ vesicles. These complexes contained active NF- κ B signaling and were disrupted by BTK inhibition with ibrutinib.

Conclusions: We demonstrate that TLR9 and IgM facilitate the assembly of a superpathway of signaling adapters including MYD88 and the CBM complex on endolysosomal membranes to cooperatively drive oncogenic activation of NF- κ B in ABC DLBCL. These supercomplexes apparently create a hyperaddiction phenotype given the frequent responses to ibrutinib in ABC tumors that harbor CD79B and MYD88 L265P mutations.

Keywords: B-cell receptor (BCR); diffuse large B-cell lymphoma (DLBCL); MYD88.

6 BENDAMUSTINE (B), FOLLOWED BY OBINUTUZUMAB (G) AND VENETOCLAX (a) IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): CLL2-BAG TRIAL OF THE GERMAN CLL STUDY GROUP (GCLLSG)

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Introduction: The prospective, open-label, multicenter phase-II CLL2-BAG trial is based on the theoretical “sequential triple-T” concept [Hallek M., Blood 2013; 122(23): 3723-34] of a tailored and targeted treatment aiming for total eradication of minimal residual disease (MRD). It investigates a sequential treatment with a bendamustine (B) debulking, followed by obinutuzumab (G) and venetoclax (A) as induction and maintenance therapy in an all-comer population of physically fit and unfit, treatment-naïve (TN) and relapsed/refractory (R/R) CLL pts.

Methods: Pts with an absolute lymphocyte count $\geq 25,000/\mu\text{l}$ and/or lymph nodes ≥ 5 cm received 2 cycles of B as debulking (70 mg/m² d1&2 q28 days), unless contraindicated. In the induction G (1000 mg) was administered 3 times in cycle 1 (days 1/2, 8 & 15) and every 4 weeks in cycles 2-6. A was added in cycle 2 with a dose ramp-up (to 400 mg daily) over 5 weeks and several safety precautions. In the

maintenance therapy, daily intake of A was continued and G administered every 3 months until achievement of a MRD-negative complete response or for up to 24 months.

The primary endpoint is the overall response rate (ORR) at the end of induction therapy; secondary endpoints include MRD evaluations, safety and survival parameters. This primary endpoint analysis is based on uncleaned data, the final analysis will be presented at the meeting.

Results: Between May 2015 and January 2016, 66 pts were enrolled; 3 pts with <2 induction cycles were excluded from the analysis as predefined by protocol (2 R/R pts died of a sepsis and 1 TN pt discontinued due to toxicity). 34 pts were TN and 29 had R/R CLL (median number of prior therapies: 2, range: 1-8). Median age was 59 (28-77) years, the median CIRS score was 2 (0-14). 11 of 59 pts (19%) had a del(17p) and 14 (24%) had a del(11q); 45 of 61 (74%) had an unmutated IGHV status. 45 pts (71%) received B debulking, 18 (29%) pts immediately started with the induction. 60 pts completed 6 induction cycles with G and A. With an ORR of 97% at the end of induction, the primary endpoint was met: all TN (100%) and all but two of the R/R pts (93%) responded. According to investigator assessment, 6 pts had a CR/CRi, 19 pts an unconfirmed clinical CR/CRi and 36 pts a PR. MRD negativity ($<10^{-4}$ by flow cytometry) in peripheral blood (pB) was achieved in 56 pts (89%); MRD assessment from bone marrow was available in 8 pts and were

	all patients (n=63)	treatment-naïve (n=34)	relapsed/refractory (n=29)
Total number of SAEs	83	22	61
- SAEs related to study treatment	69	19	50
Time point of occurrence [1 missing]			
- Debulking	12	9	3
- Induction	63	10	53
- Maintenance	4	2	2
- Follow-up	3	-	3
Severity			
- CTC grade I/II	16	7	9
- CTC grade III/IV	66	15	51
- CTC grade V	1	-	1
Outcome [1 missing]			
- resolved	74	20	54
- resolved with sequelae	2	1	1
- persisting	5	1	4
- fatal	1	-	1
Infections			
- Pneumonia	9	-	9
- other respiratory tract infections [incl. bronchitis, sinusitis]	6	1	5
- Skin infections [incl. 1 herpes zoster]	2	1	1
- Urinary tract	1	-	1
- other [incl. 2 CMV oesophagitis & 1 viral hepatitis]	9	2	7
Febrile Neutropenia	6	2	4
Pyrexia	4	2	2
Neutropenia	7	1	6
Thrombocytopenia	4	-	4
Hemolysis	1	-	1
Infusion related reactions	6	2	4
Cytokine release syndrome	1	1	-
Tumor lysis syndromes	5	2	3
Cardiovascular events			
- myocardial infarction, acute coronary syndrome	5	3	2
- hypertensive crisis	1	-	1
Secondary primary malignancies			
- skin cancer [incl. 1 melanoma, 3 squamous cell and 1 basal cell carcinoma]	5	-	5
- bladder and prostate cancer (1 each)	2	2	-
- pleural effusion related to CLL	1	1	-

all negative. As of January, 9th 2017, 83 serious adverse events (SAEs) were reported in 37 pts, including 69 SAEs (83%) related to study treatment. 66 SAEs (80%) were CTC^o3-4 and 1 had a fatal outcome (sepsis in 4th induction cycle). Most SAEs occurred in the R/R cohort and during the induction phase (see table). 5 laboratory TLS occurred in 5 patients (1 during bendamustine debulking, 1 in induction cycle 1 with obinutuzumab, 2 in cycle 3 and 1 in cycle 4 with obinutuzumab and venetoclax).

Conclusion: This sequential treatment of B debulking, followed by G and A was very efficacious with an ORR of 97% and a MRD negativity rate of 89% in pB at the end of induction phase. No unexpected toxicities and no clinical TLS were reported.

Keywords: ABT-199; chronic lymphocytic leukemia (CLL); obinutuzumab.

AACR-ICML JOINT SESSION: CANCER IMMUNOTHERAPY

7

GLOBAL PIVOTAL PHASE 2 TRIAL OF THE CD19-TARGETED THERAPY CTL019 IN ADULT PATIENTS WITH RELAPSED OR REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)—AN INTERIM ANALYSIS

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Introduction: CTL019 is an investigational chimeric antigen receptor (CAR) T-cell therapy with a high rate of durable complete responses (CRs) and a manageable safety profile in a previously reported single-center trial in adult patients (pts) with R/R DLBCL.

Methods: Results of a planned interim analysis of a single-arm, open-label, multicenter, global phase 2 trial of CTL019 in pts \geq 18 y with R/R DLBCL (JULIET;NCT02445248) are reported. Industry-manufactured CAR T cells were provided to pts at 27 centers on 4 continents using a global supply chain. Pts had received \geq 2 lines of chemotherapy and had disease progression after or were ineligible for autologous stem cell transplant (autoSCT). Autologous T cells were transduced with a lentiviral vector encoding an anti-CD19 CAR, expanded, cryopreserved, shipped, and infused at study sites. The primary endpoint (centrally reviewed by an independent review committee) was best overall response rate (ORR: CR + partial response [PR]). **Results:** 141 pts were enrolled. Following restaging, bridging therapy, and lymphodepleting chemotherapy (fludarabine 25 mg/m²/cyclophosphamide 250 mg/m²/day \times 3 days or bendamustine 90 mg/m²/day \times 2 days), 85 pts received a single dose of CTL019 transduced cells (median, 3.1×10^8 [range, 0.1 - 6.0×10^8] cells). Median time from infusion to data cutoff (December 2016) was 3.7 mo. Median age was 56 y (range, 24-75) and median prior lines of antineoplastic therapy was 3 (range, 2-7). 51% of pts had prior autoSCT. Among 51 pts with \geq 3 mo follow-up or earlier discontinuation, best ORR was 59% (95% CI, 44%-72%) with 43% CR and 16% PR; the primary endpoint was met. CR and PR rates at 3 mo were 37% and 8%, respectively. All pts in CR at 3 mo remained in CR at data cutoff. Efficacy was observed across prognostic subgroups. Median duration of response was not reached. CTL019 was detectable in peripheral blood by quantitative PCR for up to 355 days in responders. Cytokine release syndrome (CRS) was graded using the UPenn scale and managed by a protocol-specific algorithm. CRS occurred in 57% of infused pts (17% grade 3; 9% grade 4); no CRS-associated deaths occurred. 16% of pts received tocilizumab for CRS management. 13% of pts had grade 3/4 neurologic adverse events (AEs), managed with supportive care; no cerebral edema was reported. Grade 3/4 cytopenias lasting $>$ 28 days and grade 3/4 febrile neutropenia occurred in 21% and 14% of pts, respectively. 3 pts died from disease progression within 30 days of infusion. No deaths were attributed to CTL019.

Conclusions: This planned interim analysis of a global study of CTL019 in adults with R/R DLBCL confirms the high response rates and durable CRs observed in the previous single-center experience. Centralized manufacturing was feasible. AEs were effectively and reproducibly managed by appropriately trained investigators.

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

8 AXICABTAGENE CILOLEUCEL (AXI-CEL; KTE-C19) IN PATIENTS WITH REFRACTORY AGGRESSIVE NON-HODGKIN LYMPHOMAS (NHL): PRIMARY RESULTS OF THE PIVOTAL TRIAL ZUMA-1

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Introduction: Outcomes for pts with refractory aggressive NHL are poor with current therapies (Crump, ASCO 2016). Results from the interim analysis of ($n = 62$) of ZUMA-1, the 1st multicenter trial of an anti-CD19 chimeric antigen receptor (CAR) T cell, axi-cel, in refractory aggressive NHL, showed an objective response rate (ORR) of 79% (complete response [CR] 52%; *Blood*2016;128:LBA-6). Here we present results from the primary analysis of ZUMA-1.

Methods: Pts received a target dose of 2×10^6 anti-CD19 CAR T cells/kg after low-dose conditioning with cy/flu. Eligible pts (≥ 18 y) had diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL) or transformed follicular lymphoma (TFL); an ECOG performance status (PS) 0-1; and refractory disease (progressive or stable disease as best response to last prior therapy, or relapsed ≤ 12 m of autologous stem cell transplant [ASCT]). The primary endpoint for this analysis was ORR in the combined DLBCL, PMBCL, and TFL population. Key secondary endpoints were duration of response (DOR), overall survival (OS), and frequency of adverse events (AEs). The primary analysis was triggered when 92 pts had at least 6 m of follow-up.

Results: As of January 27, 2017, 111 pts from 22 institutions were enrolled; 101 pts (91%) received axi-cel. Median age was 58 y (range, 23-76), 67% male, 85% stage III-IV, 47% IPI 3-4, 77% refractory to ≥ 2 nd line of therapy, and 21% relapsed ≤ 12 m of ASCT. Axi-cel was

successfully manufactured in 110/111 (99%) pts with an average turnaround time from apheresis to the clinical site of 17 d.

With an ORR of 82% ($n = 92$; $P < .0001$) the study met the primary endpoint. The ORR in the mITT analysis set of 101 pts was 82% (CR 54%, PR 28%), and was consistent across key covariates including disease subtype, refractory status, stage, and IPI score. At a median follow up of 8.7 m, 44% of pts were in response and 39% were in CR. The median DOR was 8.2 m overall and not reached for pts who achieved a CR. Median OS was not reached; 80% of pts remained alive at 6 m. The most common Gr ≥ 3 treatment-emergent AEs were neutropenia (66%), leukopenia (44%), anemia (43%), febrile neutropenia (31%), and encephalopathy (21%). Gr ≥ 3 cytokine release syndrome (CRS) and neurologic events (NE) occurred in 13% and 28% of pts, respectively. All CRS and all NE resolved except 1 Gr 1 memory impairment. As previously reported, there were 3 Gr 5 AEs (3%). Peak and cumulative CAR T levels post-axi-cel were associated with durable responses.

Conclusions: Axi-cel significantly improved ORR in pts with refractory aggressive NHL. The CR rate was 7-fold higher compared to historical controls (Crump, ASCO 2016) and nearly half the patients have an ongoing response. Axi-cel demonstrated significant clinical benefit with a manageable safety profile in pts lacking curative treatment options.

*Drs Neelapu and Locke contributed equally to this study.

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Keywords: CD19; diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL).

9 WHAT CAN WE LEARN REGARDING IMMUNOTHERAPY FROM MALIGNANT MELANOMA?

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ICB History: Melanoma has been the most important cancer to drive immunotherapy development in the field of solid tumors. Where immune stimulating approaches with cytokines in the 1980's and 1990's lead to approvals of interferon-alpha and interleukin-2, the clinical impact was rather small. Since 2010 immunotherapy has been revolutionized by the concept of breaking tolerance with ICs. It represents a major paradigm shift that marks the beginning of a new era. The impact of the first ICBs, i.e. anti-CTLA-4 (Cytotoxic T Lymphocyte Antigen-4) and anti-PD1 / anti-PDL1 (Programmed death-1 receptor and its ligand PD-L1) is unprecedented.

Advanced Disease: In only 5 years advanced melanoma has been transformed from an incurable disease into a curable disease in over 50% of metastatic patients. We are only at the beginning of discovering its transversal impact throughout oncology. For the treatment of advanced disease approvals were obtained for the immune checkpoint inhibitors ipilimumab (2011), nivolumab (2014), pembrolizumab (2014) and the combination ipilimumab + nivolumab (2015).

Adjuvant Therapy: Ipilimumab is the first checkpoint inhibitor that has also been approved as adjuvant therapy for high risk stage III melanoma (2015). Results regarding adjuvant therapy with either nivolumab or pembrolizumab are expected in 2018.

Combinations: Further developments in the field of melanoma are focused on combination therapies between various immunotherapeutic agents such as vaccines and antibodies, and combination therapies between immunotherapeutic agents with chemotherapeutic or targeted agents, or even radiation therapy.

Transversal Development: Thanks to in particular anti-PD1/anti-PDL1- based immunotherapies and the activity of the combination of anti-PD1/anti-CTLA4 immunotherapy is now developed in a transversal manner across multiple tumor types (a.o lung, head&neck, oesophageal and gastric, liver, MSI-colorectal, MSI-any tumor type, renal, bladder, and Merkel cell cancers and Hodgkin-lymphoma with unprecedented success.

Toxicities: Success however does come at a price, both in terms of side-effects, in particular immune-related adverse events (irAEs), as well in terms of financial toxicity. irAEs come in many forms. With ipilimumab at 10 mg/Kg the most frequent are Gastro-Intestinal (diarrhea, colitis, perforations); Hepatic (grade 3-4 hepatitis in 16%); Endocrinopathies (hypophysitis in up to 16%, grade 3-4 in up to 5%) and hyper/hypothyroiditis; Dermatitis; Arthralgia; Rare but important are neurodegenerative irAEs, Guillain-Barré syndrome, pneumonitis, and myocarditis. Anti-PD1/PDL1 agents are much less toxic in general. The combination of anti-CTLA-4 and anti-PD1/L1 are associated with increased irAEs. Algorithms have been established including administration of high dose corticosteroids and anti-TNF agents. All treatment regimens with ICBs have reported drug-related fatalities range.

Smart Combos: Anti-PD1/PDL1 has become the central drug in all further development strategies to be combined with other ICBs, agonists, cytokines, vaccines, targeted agents, chemotherapeutics and radiotherapy.

10 WHAT CAN WE LEARN REGARDING IMMUNOTHERAPY FROM LUNG CANCER?

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In the past, lung cancer has been considered to be a non-immunogenic tumor and great effort with vaccination trials failed. However, some retrospective analyses of infiltrating immune cells in resected tumor specimens suggested a role of immunity also in this disease. Following the lead of melanoma where CTLA-4 inhibition gave the first evidence of the role of immune checkpoint inhibition, initial studies performed in small cell and non-small cell lung cancer (NSCLC) gave disappointing results. This changed with the introduction of inhibitors of the PD-1 and PD-L1 axis. Here large phase I trials in different cohorts of patients demonstrated a rapid and long lasting anti-tumor activity in a 15-20% of sometimes heavily pretreated patients with NSCLC. This was followed by phase III trials comparing PD-1 or PD-L1 inhibitors with the then standard second line therapy docetaxel. These trials

demonstrated a superior outcome in terms of survival and toxicity and lead to the regulatory approval of nivolumab, pembrolizumab and atezolizumab for second line treatment of NSCLC. The fact the only a proportion of patient seem to have a strong benefit, the well implemented personalized treatment of oncogenic driver NSCLC, as well as the high costs of immunotherapy lead great efforts to identify predictive biomarkers. The initial focus was on the expression of PD-L1 in tumor cells. Laboratory validation, retrospective and prospective clinical validation, and the approval of pembrolizumab for first line therapy in patient with NSCLC expressing PD-L1 in 50% or more of tumor cells has made PD-L1 immunohistochemistry to a – albeit imperfective – but routinely used test. Since, there is emerging data on the use of tumor mutation load and immune signatures as complementary predictive information. The major questions being answered by ongoing clinical trials in advanced NSCLC focus around the use of immunotherapy in first line, either alone in biomarker selected patients or in combination with CTLA-4 blockade or with chemotherapy. In stage III disease, trials are investigation the introduction of immune checkpoint inhibitors with or after chemoradiotherapy. The potential impact of adjuvant single agent immune checkpoint inhibition in resected NSCLC is being examined in phase III trials whereas in second line therapy the focus is on combinatorial treatments. There is a need for the academic community to address clinical questions on the duration of immune therapy and translational research questions on primary or acquired resistance to immunotherapy.

“FOCUS ON...” SESSION: CLASSICAL THERAPIES FOR FOLLICULAR LYMPHOMA

11 OUTCOME OF CURATIVE RADIOTHERAPY FOR LOCALISED FOLLICULAR LYMPHOMA IN THE ERA OF ¹⁸F-FDG PET-CT STAGING: AN INTERNATIONAL COLLABORATIVE STUDY ON BEHALF OF ILROG

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Introduction: Most patients (pts) with follicular lymphoma (FL) present with advanced disease and are generally considered incurable. For the minority with localised disease, radiotherapy (RT) can be curative, with historical series showing a 10 year disease free survival of 40%-50%. PET-CT with ¹⁸F-fluorodeoxyglucose is considered the gold standard imaging technique for staging FL. Compared to CT, upstaging occurs in 10-60% of pts. We evaluated outcomes in pts who underwent definitive RT for stage I-II FL after staging by PET-CT. Our hypothesis was that more accurate staging will lead to better pt selection for treatment (Rx), with consequent improvement in Rx results.

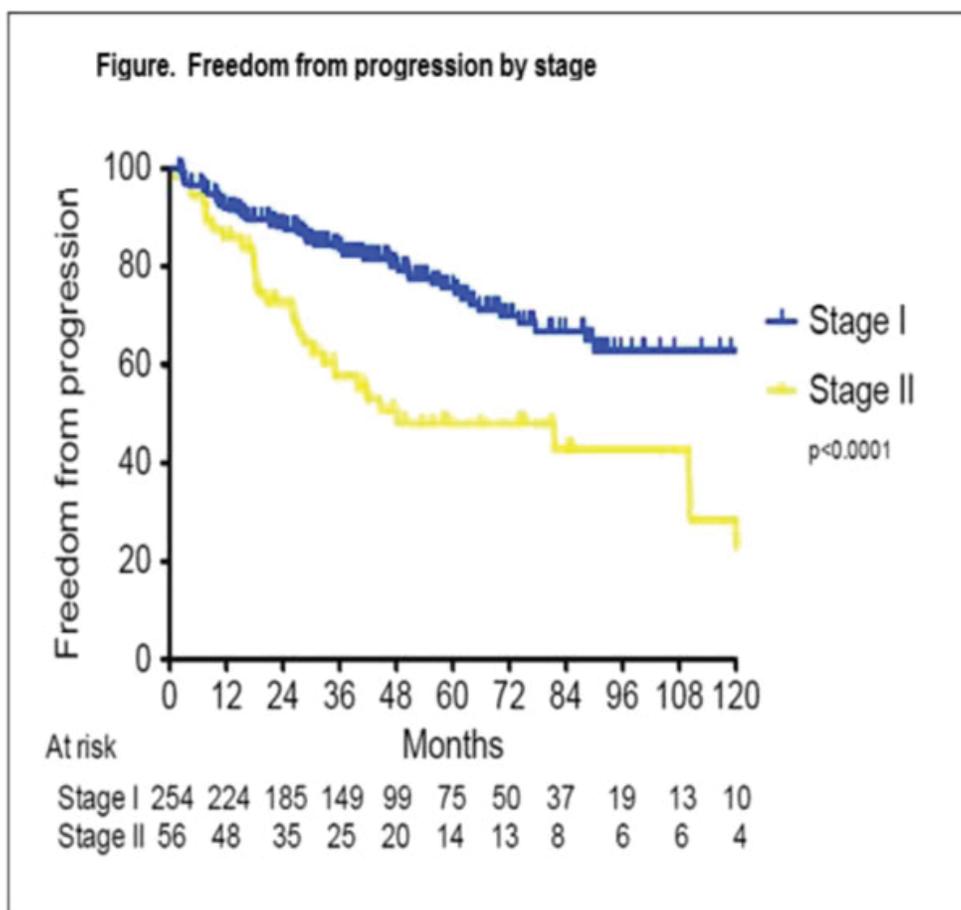
Methods: We conducted a multicentre retrospective study of pts who received RT for stage I-II FL, staged by PET-CT. Eligible pts were ≥ 18 years with grade 1-3A FL. Disease site, maximal bulk, and FL Prognostic Index (FLIPI) were recorded. Additional inclusion criteria were RT dose ≥ 24 Gy, follow up ≥ 3 months, and no prior Rx.

Primary outcomes were local control, freedom from progression (FFP) and overall survival (OS). Secondary outcomes were response rate by PET-CT and toxicity. OS and FFP were estimated with Kaplan-Meier, and uni- and multivariate analyses of prognostic factors performed with Cox Regression.

Results: 310 pts treated from 2000-2016 at 11 centres were eligible for analysis. Pre-treatment characteristics included age (median 58 years, range 20-84), female sex ($n = 160$, 51.6%), stage I disease ($n = 254$, 81.9%), FLIPI score (median 1, range 0-3), B-symptoms ($n = 2$, 0.6%), bulk of disease (median 2.5 cm, range 0.2-10) and extranodal disease ($n = 83$, 26.8%). Median RT dose was 30Gy (range 24-36). Median follow up was 50 months (range 3.2-174.6). 222/310 (71.6%) pts remain disease free. 6 pts have relapsed in field (1.9%) and 2 had marginal recurrences (0.6%). 80 pts (25.8%) relapsed at distant sites, 90.9% of all relapses. 5y FFP and OS were 70.2% and 95.8%. For stage I 5y FFP was 74.3%, vs 48.1% for stage II ($p < 0.0001$) (Figure). There was no significant difference in 5y FFP between nodal and extranodal presentations ($p = 0.23$).

158 (51%) pts had a PET-CT scan post RT. 89.9% achieved complete metabolic response (CMR) (Deauville score 1-3). Failure to achieve CMR was associated with higher risk of progression ($p = 0.03$).

On multivariate analysis of prognostic factors including age, stage, grade, bulk, FLIPI, RT dose, nodal versus extra nodal site, and CMR status; stage II disease (HR = 2.51, 95% CI: 1.53-3.77, $P = 0.0001$) and failure to achieve CMR (HR = 3.11, 95% CI = 1.35-7.16, $P = 0.008$) were significantly associated with worse FFP. Toxicity data were available on



13 RITUXIMAB MAINTENANCE VERSUS OBSERVATION AFTER IMMUNOCHEMOTHERAPY (R-CHOP, R-MCP, R-FCM) IN PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA: A RANDOMISED TRIAL OF GLSG AND OSHO

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Introduction: Despite frequent long lasting remissions to first-line treatment, follicular lymphoma of advanced stages is characterized by recurrent relapses. In the randomized PRIMA trial of the GELA, rituximab maintenance achieved prolonged progression-free survival (PFS) compared with observation in remission after first-line immunochemotherapy (Salles et al., Lancet 2011). The German study groups GLSG and OSHO initiated in 2007 a double randomized trial to investigate the efficacy and safety of rituximab maintenance versus observation in remission after randomly assigned induction treatment.

Methods: Previously untreated patients with Ann Arbor stage II-IV follicular lymphoma in need of therapy and not candidates for autologous stem cell transplantation or curative radiotherapy were randomised to receive 6 cycles of R-CHOP, R-MCP, or R-FCM. Patients responding to induction treatment were subsequently randomised to 2 years rituximab maintenance or

observation, stratified by type of induction treatment, quality of remission, and FLIPI. The trial was initially planned to detect with 95% power a 15% difference in complete remission rates between any of the three induction groups and a PFS hazard ratio of 0.60 by postremission strategy.

Results: Recruitment was stopped in 2011 after the PRIMA results had been published. Median age of the 206 recruited patients was 66 years (range, 24-86), and FLIPI was low in 13%, intermediate in 28%, and high in 60%. A trend towards higher complete remission rates with R-FCM (43% of 58 patients) compared to R-CHOP (23% of 66) and R-MCP (24% of 66) was observed, but the differences were not statistically significant. High and comparable overall response rates were observed after R-CHOP (88%), R-MCP (89%), and R-FCM (91%). In terms of grade 3-4 leukocytopenia and grade 3-4 thrombocytopenia, R-FCM (92%, 17%) was more toxic than R-MCP (88%, 6%) which was more toxic than R-CHOP (63%, 3%); R-CHOP showed more frequent neurological toxicities (40%) compared with R-MCP (14%) and R-FCM (16%). Rituximab maintenance substantially prolonged progression-free survival in comparison to observation in remission (hazard ratio 0.39, $p = 0.0064$). In the rituximab maintenance group, 3-years PFS was 89% (8 PFS events among 65 patients) compared with 69% in the observation group (19 events among 63 patients). With 11 events, no differences in overall survival could be observed for maintenance vs. observation (hazard ratio 1.04, 95% CI 0.32-3.43, $p = 0.95$). Rituximab maintenance was more toxic with regards to leukocytes and the gastro-intestinal tract.

Conclusions: In this randomized trial, 2 years rituximab maintenance was associated with substantially prolonged PFS in comparison to observation after response to first-line immunochemotherapy in follicular lymphoma. Our data represent an independent confirmation of the GELA PRIMA trial results.

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

14 DURABLE BENEFIT OF RITUXIMAB MAINTENANCE POST-AUTOGRAFT IN PATIENTS WITH RELAPSED FOLLICULAR LYMPHOMA: 12-YEAR FOLLOW-UP OF THE EBMT LYMPHOMA WORKING PARTY LYM1 TRIAL

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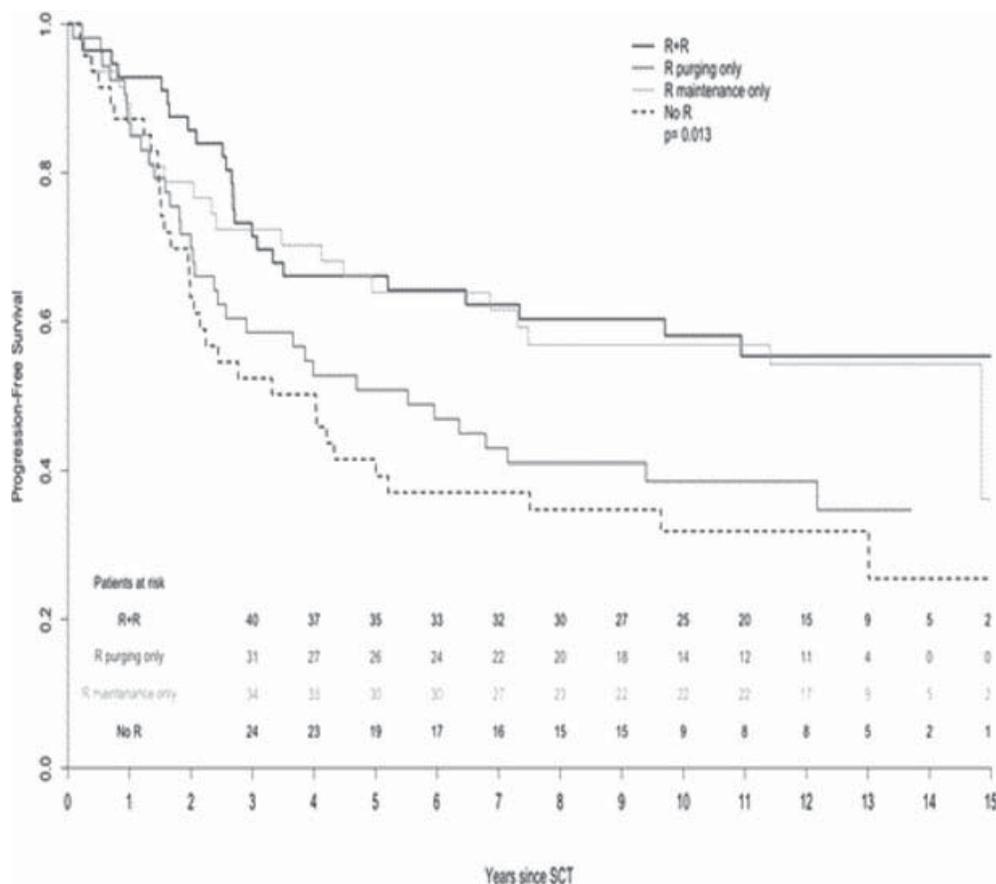
Purpose: To evaluate the long-term effects of in vivo purging with rituximab 375 mg/m² weekly x 4(RP) and maintenance rituximab 375 mg/m² every 2 months for 4 doses (RM) on progression free survival (PFS) in patients with relapsed FL receiving a BEAM autograft (ASCT).

Methods: 280 patients with relapsed FL after complete or very good partial remission after salvage chemotherapy were randomly assigned using a factorial design to rituximab (R) purging (RP; 375 mg/m² once per week for 4 weeks) or observation (NP) before ASCT and to R maintenance (RM; 375 mg/m² once every 2 months for 4 infusions) or observation (NM) (Pettengell et al. JCO 2014): there is thus a group of patients who received no R (neither for purging nor for maintenance) (no R) and a group who received R both for purging and maintenance (RR).

Results: For the 280 randomised patients (pts, intent-to-treat population), the median time from diagnosis to randomisation was 44 months (range 3 - 464), 40% having received two lines and 60%, three lines of prior therapy. 203 pts received an ASCT. With a median follow-up of 12 years (range 10-13), 68 pts remain alive in remission, and 30 are lost to follow-up. RM (with or without RP) continues to significantly improve 10-year PFS compared with NM (with or without RP) [ITT: 53% (range 45-62) v 34% (27-43); post ASCT: 58% (49-68) v 36% (27-47) P = 0.002; Hazard ratio (HR) 95% CI, 0.548 (0.375-0.801)]. A significant improvement in 10-year PFS was observed in pts who received any R [P = 0.015; HR 0.603 (0.399-0.910)]. By treatment arm, 10-year PFS after ASCT (figure) for no R pts was 32% (21-49) compared to 58% (46-73) in RR pts [(P = 0.006; HR 2.102 (1.237 -3.573)]. Non-relapse mortality was not significantly different at 10 years (7% overall) and 12 years (9% overall). Overall survival by ITT at 10 years was 71% (65-76) and after ASCT 75% (69-81) with no significant differences according to treatment sub-groups with patients receiving rituximab at progression post ASCT.

Conclusion: The benefit of R maintenance after ASCT on PFS in patients with chemosensitive relapsed FL is sustained at 12 years, suggesting that RM adds to ASCT-mediated disease eradication and may enhance the curative potential of ASCT, as relapses were rare after 7.5 years. The success of salvage therapies at relapse post ASCT in rituximab naïve patients is reflected in comparable overall survival.

Keywords: autologous stem cell transplantation (ASCT); follicular lymphoma (FL); rituximab.



15 LONG TERM RESULTS OF THE FOLL05 RANDOMIZED STUDY COMPARING R-CVP WITH R-CHOP AND R-FM AS FIRST LINE THERAPY IN PATIENTS WITH ADVANCED STAGE FOLLICULAR LYMPHOMA. A FIL STUDY

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Introduction: The FOLL05 trial compared R-CVP with R-CHOP and R-FM for the initial treatment of patients with advanced stage Follicular Lymphoma (FL). The previous analysis with a median follow-up of 34 months showed that R-CHOP and R-FM were better than R-CVP in terms of 3-year time to treatment failure (TTF), the primary study endpoint, and that R-CHOP had a better risk/benefit ratio compared with R-FM in terms of toxicity. Here we present the long term results analysis of the study.

Methods: Patients were 18-75 years old, with untreated stage II-IV grade 1-3a FL, ECOG performance status of 0-2, and active disease

according to the Italian Society of Hematology guidelines. Five hundred and thirty four patients were randomly assigned to receive 8 cycles of R-CVP, or 6 cycles of R-CHOP + 2R or 6 cycles of R-FM + 2R, 504 of them were evaluable (168, 165, and 171 per arm). Maintenance was not accepted. Study enrollment was completed in September 2010.

Results: The updated median follow-up was 84 months (range 1-119). In the prolonged observation period 68 additional progressions (cumulative = 252) were reported, including 63 new relapses/progressions (cum = 239) and 5 deaths not related to lymphoma progression (cum = 13). The 8-year PFS rate was 48% (95% CI, 43-52), and was 46% (95% CI, 38-54), 57% (95% CI, 49-64) and 59% (95% CI, 51-66) for R-CVP, R-CHOP and R-FM, respectively. HR adjusted for FLIPI2 was 0.74 (95% CI, 0.55-0.99) between R-CHOP vs. R-CVP and 0.68 (95% CI, 0.50-0.92) between R-FM vs. R-CVP. Overall 97, 77, and 73 patients required a second line therapy after R-CVP, R-CHOP and R-FM, respectively ($p = 0.013$). A total of 41 second malignancies (SM) were reported including 9 AML/MDS (1, 3, 5), 5 other hematologic cancers and 27 solid tumors (Gray test $p = 0.076$). Four, 11, and 13 SM were reported in patients without or before lymphoma relapse for R-CVP, R-CHOP and R-FM. Overall 75 patients died (21, 23, 31 in R-CVP, R-CHOP, and R-FM). The 8-years OS rates was 83% (95% CI, 78-86); although the study was not powered to demonstrate differences for OS, the three arms had similar OS rates ($p = 0.243$). Forty six deaths (61%) were due to lymphoma progression, and 29 (39%) due to other causes including 12 deaths due to SM (1,4,7 by arm). The risk of death for lymphoma was comparable between arms ($p = 0.900$), while the risk of death for other causes was higher for R-FM (0.11 at 8-years, compared to 0.02, and 0.06 for R-CVP and R-CHOP; $p = 0.019$).

Conclusions: The long term update of the FOLL05 trial confirms the findings already reported in 2013. Moreover with a longer follow-up we found that patients treated with R-FM had a higher risk of death due to causes unrelated with lymphoma. Although OS was similar among study arms, this result was achieved with an extra 25% need of salvage therapies when R-CVP was administered as initial therapy.

Keywords: follicular lymphoma (FL).

16 CAUSE OF DEATH IN FOLLICULAR LYMPHOMA IN THE RITUXIMAB ERA: A POOLED ANALYSIS OF FRENCH AND US COHORTS

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Introduction: Although the life expectancy of patients with follicular lymphoma (FL pts) has increased, little is known regarding their cause of death (COD) in the current treatment era.

Methods: Two cohorts were pooled of 1643 newly diagnosed pts with de novo FL enrolled since 2001 at Lyon University Hospital [N = 723, median follow-up (FU) 86 m] and the University of Iowa and Mayo Clinic Specialized Program of Research Excellence [SPORE, N = 920, median FU 84 m]. COD was classified as due to lymphoma, treatment-related (TRM, including infection, cardiac and secondary MDS/AML), second cancer, other, or missing.

Results: At a median FU of 85 months for pts still alive, there were 283 (17.2%) deaths. The 10 year overall survival (OS) was comparable in the Lyon (80%) and SPORE (77%) cohorts. Lymphoma (49%) was the most common COD followed by TRM (15%) (7% infection, 4% MDS/AML and 2% cardiac), second cancer (12%), unrelated other causes (12%), and missing (12%). Of the 140 pts who died from lymphoma (median OS of 50 m), 77 (55%) had a transformed disease. In pts <60y, lymphoma was the leading COD (59%), followed by TRM (19%, of whom 50% had an ASCT); in pts ≥60y it was lymphoma (45%), followed by second cancer (15%) and other causes (15%). Pts who were initially observed died less frequently from lymphoma than those initially treated (38% vs 53%, $P = 0.02$). Death due to lymphoma remained the most common cause over follow-up time: <1y (51%), 1-4.9y (50%), 5-9.9y (48%) and >10y (50%). Lymphoma was the principal COD among pts failing to achieve event free survival at 24 m (EFS24, 56%) compared to pts who achieved EFS24 (37%, $P = 0.003$); among pts initially treated with immunochemotherapy, 86% who did not achieve EFS24 died from lymphoma or TRM compared to 59% achieving EFS24 ($P < 0.001$). Transformation occurred in 91 pts and accounted for 85% of the deaths in these cases, while only 33% of the pts without transformation died from lymphoma ($P < 0.001$). Death due to lymphoma after transformation was the leading COD in pts who died within 1y of diagnosis (32%), but this decreased over follow-up time: 1-5y (30%), 5-10y (23%) and >10y (15%). Pts who had a transplant (N = 45, autologous, ASCT) died more frequently from TRM (12/45, 27%) compared to no transplant (30/238, 12%, $P = 0.02$). Among the 24 pts without transformation and treated with an ASCT, 46% (11/24) died from TRM compared to 15% for the 166 pts without transformation and treated without ASCT ($P < 0.001$).

Conclusion: Lymphoma, particularly after transformation, is the leading COD over the first 10 years from diagnosis in newly diagnosed FL pts in the rituximab era: regardless of age, time of progression/transformation, EFS24 achievement, or treatment. TRM, and particularly death after ASCT, is of concern, supporting the development of less toxic therapies.

Keywords: follicular lymphoma (FL).

“FOCUS ON...” SESSION: PET/CT: VISUAL ASSESSMENT AND BEYOND

17 PROGNOSTIC VALUE OF BASELINE TOTAL METABOLIC TUMOR VOLUME (TMTV) FOR

PATIENTS WITH EARLY STAGE HODGKIN LYMPHOMA ENROLLED IN THE STANDARD ARM OF THE H10 (EORTC/LYSA/FIL) TRIAL

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Objective: The outcome of early stage HL is excellent under current treatment, but there is a subset of patients who could benefit from less or more intensive regimen. We investigated in patients with supra diaphragmatic stage I/II HL included in the H10 randomized intergroup trial if TMTV measured on baseline PET scan improve risk stratification.

Methods: Patients from the standard arm (combined modality treatment) of the H10 trial, included by LYSA centers, were eligible if they had baseline PET/CT (not mandatory) available for quantitative PET. Total metabolic tumor volume (TMTV) was computed using 41% SUVmax thresholding method and Total Lesion Glycolysis (TLG) was computed. Optimal cut-off to predict PFS and OS was determined by ROC and X-tile analysis. Multivariate analysis (MVA) were performed using Cox models, testing 1) at baseline, TMTV vs EORTC/LYSA risk factors with p value < 0.05 in univariate analysis ($ESR \geq 30$ with B symptoms or $ESR \geq 50$, bulk defined on M/T ratio ≥ 0.35 , ≥ 4 lymph nodes sites involved) and vs favorable (F)/unfavorable (unF) classification 2) TMTV vs response after two cycles of ABVD (iPET2 positive when Deauville score > 3).

Results: 255 patients were eligible, 101 F and 154 unF with similar characteristics to the entire population. Median age was 31 years;

13% were ≥ 50 year old, 36% had ESR ≥ 30 with B symptoms or ESR ≥ 50 , 31% a bulk and 10% ≥ 4 lymph nodes sites. Median TMTV ($n = 255$) and TLG ($n = 249$) were 67 cm^3 and 332 respectively, with a significant difference between the F (median TMTV/TLG: 48/206) and unF groups (87/419; $p < 0.0001$). With a median follow-up of 55 months, 27 patients progressed and 12 died, leading to 88% and 95% 5-y PFS and OS respectively. TMTV with a cut-off of 147 cm^3 was a strong prognosticator of 5y-PFS (92% for low TMTV vs 71%) and OS (98% vs 82%), ($p < 0.0001$; HR = 5.2/ $p = 0.0001$; HR = 7.3) as was TLG with a cut-off of 495 ($p < 0.0001$; HR = 6.9 / $p = 0.0001$; HR = 10.9). In MVA TMTV and ESR were the only independent risk factors impacting PFS (HR = 3.7, $p = 0.0029$, HR = 3.1, $p = 0.0074$) and OS (HR = 4.1, $p = 0.029$, HR = 6.9 $p = 0.015$). High TMTV was a stronger predictor of poor PFS (HR = 4.0, $p = 0.0004$ and HR = 4.3, $p = 0.018$ respectively) than F/unF and the only independent factor associated with a shorter OS (HR = 4.8, $p = 0.0076$, $p = 0.9$). TMTV and iPET2 are independent predictors for PFS (HR = 4.4, $p = 0.0002$ and HR = 10.7 $p < 0.0001$) and OS (HR = 5.5 $p = 0.0042$ and HR = 10.9, $p = 0.001$). TMTV combining with iPET2 stratifies patients in different risk categories ($p < 0.0001$ for PFS and OS). Particularly, TMTV allows splitting iPET2 negative patients ($n = 234$) in two groups with different outcomes: high TMTV (16%) with a 81% 5y-PFS and a 95% 5y-OS compared to 95% and 98% for low TMTV.

Conclusion: Metabolic tumor burden measured on baseline PET improves identification of patients at risk at staging in early HL compared to standard risk factors. TMTV combined with early PET response further improves risk assessment of PET negative patients.

Keywords: Hodgkin lymphoma (HL); positron emission tomography (PET).

18 BASELINE METABOLIC TUMOR VOLUME IS AN INDEPENDENT PROGNOSTIC FACTOR FOR RELAPSED AND REFRACTORY HODGKIN LYMPHOMA PATIENTS RECEIVING PET-ADAPTED SALVAGE THERAPY WITH BRENTUXIMAB VEDOTIN AND AUGMENTED ICE

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Introduction: Identification of prognostic factors for patients (pts) with relapsed or refractory (rel/ref) Hodgkin lymphoma (HL) is essential for optimizing therapy by designing risk-adapted treatment strategies. In our phase II study of PET-adapted salvage therapy (ST) with brentuximab vedotin (BV) and augmented ICE (augICE) we assessed clinical factors, quantitative PET assessments, and serum cytokine/chemokine values as potential prognostic factors predictive of event free survival (EFS).

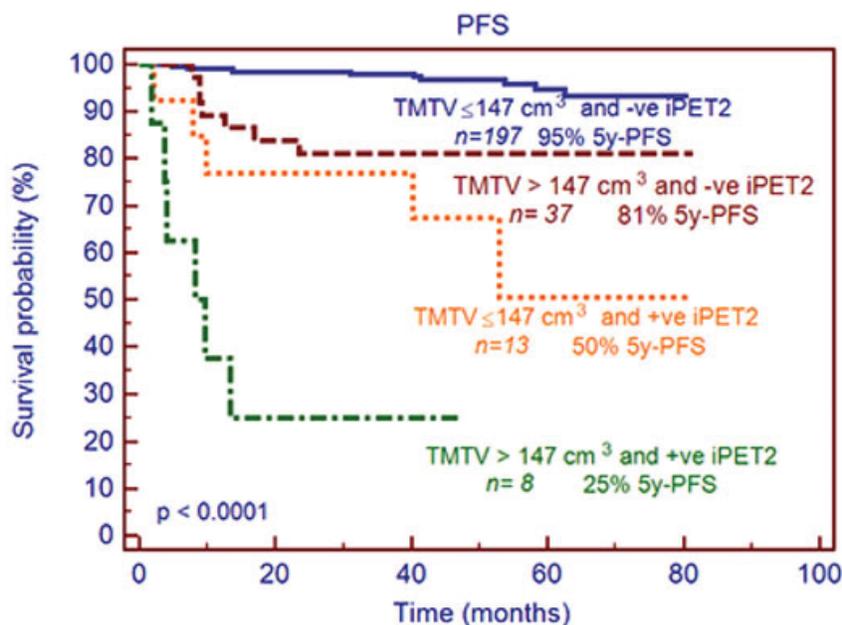
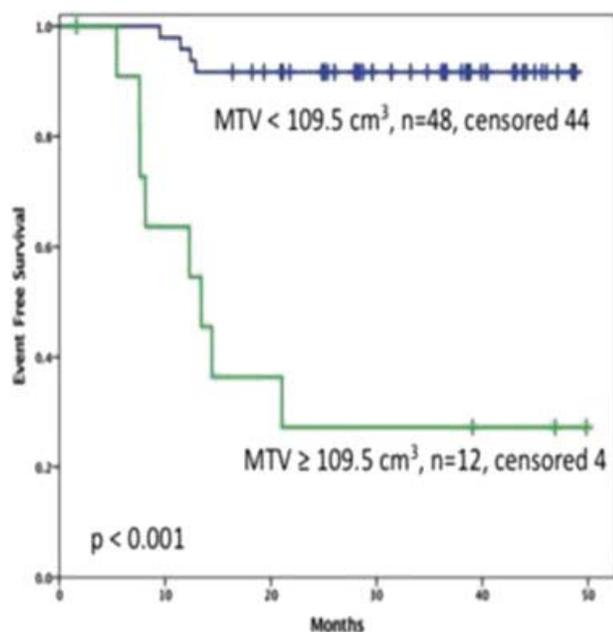


Figure : Kaplan Meier estimates of progression-free survival (PFS) according to TMTV combining with iPET2 positivity (+ve) or negativity (-ve)

Methods: Transplant eligible pts with rel/ref HL following 1 line of therapy were eligible. Pts received 2 (cohort 1) or 3 (cohort 2) cycles of weekly BV (1.2 mg/kg days 1, 8, 15 of 28 day cycles); PET-negative pts proceeded directly to autologous stem cell transplant (ASCT) while PET-positive pts received augICE before ASCT. Serum cytokines and chemokines (TARC, IL-6, IL-10, TNF- α , IFN- γ) were measured at baseline and after BV. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were measured at baseline, after BV and after augICE.

Results: 65 pts enrolled (45 cohort 1, 20 cohort 2), including 34 (52%) females, 29 (45%) with advanced stage disease, 34 (52%) with refractory disease (lack of CR after front-line therapy), 10 (15%) with B symptoms, 24 (37%) with extranodal disease, and 16 (25%) with bulk (any mass > 5 cm). Overall, 18 of 65 (28%) pts achieved complete response (defined as Deauville ≤ 2) following BV. 19 pts (18 with Deauville 2 response and 1 with Deauville 3 response after BV) proceeded directly to ASCT. Among the other 46 pts, 1 was lost to follow-up; 45 received augICE chemotherapy of which 31 (69%) achieved CR. Overall, 49 (75%) of 65 pts achieved complete response and 64 pts proceeded to ASCT. 3-year overall survival and EFS were 95% and 82%. Factors predictive for EFS by univariate analysis included age over 45 years ($p = 0.016$), refractory disease ($p = 0.033$), B-symptoms ($p = 0.032$), advanced stage at relapse ($p = 0.011$), as well as baseline MTV, TARC, and TLG (all $p < 0.001$). Factors that remained prognostic by multivariate analysis were MTV ($p < 0.001$, HR 54, 95% CI 9-319) and refractory disease ($p = 0.001$, HR 82, 95% CI 6.1-1107). The optimal cut-off for baseline MTV, determined by a grid search of log-rank test p values, was 109.5 cm^3 . Using this cutoff, the 3-year EFS for pts with low ($n = 48$) and high ($n = 12$) MTV was 92% and 27% respectively ($p < 0.001$) (Figure).

Conclusion: In this phase II study of PET-adapted ST with BV and augICE for rel/ref HL, baseline MTV and refractory disease were independent prognostic factors for EFS. Additional studies are needed to confirm the prognostic significance and optimal cutoff for MTV in rel/ref disease. Future studies should optimize efficacy and tolerability of ST by stratifying pts according to risk factors such as baseline MTV.



Keywords: brentuximab vedotin; Hodgkin lymphoma (HL); positron emission tomography (PET).

19 CAN BASELINE PET-CT FEATURES PREDICT OUTCOMES IN ADVANCED HODGKIN LYMPHOMA? A PROSPECTIVE EVALUATION OF UK PATIENTS IN THE RATHL TRIAL (CRUK/07/033).

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Introduction: PET-CT after 2 ABVD (PET2) was used to guide treatment in advanced Hodgkin Lymphoma (HL) in the RATHL trial. Patients (pts) with PET2 negative (-) scans were randomised to continue ABVD or AVD; pts with PET2 positive (+) scans were escalated to BEACOPP. This study aim was to evaluate whether baseline PET features of metabolic tumour volume (MTV), total lesion glycolysis (TLG) and number of extranodal sites could predict prognosis and PET2 response.

Methods: Baseline total MTV and TLG and MTV and TLG of the bulk-iest lesion (bulk) were measured in the first 100 pts using i) standardised uptake value (SUV) ≥ 2.5 , ii) uptake $\geq 140\%$ of mean liver uptake iii) $\geq 41\%$ of maximum tumour SUV. Baseline total/bulk MTV and TLG using SUV ≥ 2.5 and extranodal sites were measured in all UK pts ($n = 848$).

Results: MTV/TLG using SUV ≥ 2.5 and TLG compared to liver were associated with PFS and progression or death from HL (HL event) in the first 100 pts but the 41% method was not. MTV/TLG were then measured using SUV ≥ 2.5 in all UK pts, split into training and validation sets of 571 and 277. Pts with PET2+ scans had significantly higher total and bulk MTV and TLG than pts with PET2- scans; all $p < 0.0002$. Cox and logistic regression were used to assess association of MTV/TLG and other baseline factors with PFS and HL events by 3 yr. In univariable analysis (UV) age, stage, B-symptoms and TLG (total and bulk) were associated with PFS, but MTV and PET extranodal sites were not. Age, B-symptoms and total TLG were significant in multivariable (MV) analysis.

Stage, B-symptoms and TLG (total and bulk) were associated with increased risk of a HL event by 3y in UV analysis but total TLG was the only significant variable in the stepwise selected MV model.

A threshold of 3318 g (optimal by Youden's index) was used to divide pts into high and low total TLG groups. HL event rate at 3y was 12.8% for all pts with low TLG vs. 23.9% for all pts with high TLG; HR 2.2 (95%CI: 1.5-3.4), $p < 0.001$. After a negative PET2, the rate of

progression or death from HL was 21.5% vs 10.9% for high and low TLG respectively at 3y. The groups diverged further at 5y with rate of HL events of 31.0% and 13.1% for high and low TLG. Similar results were obtained in the validation set, suggesting that the threshold derived from the training set was reliable.

Conclusion: In advanced HL, baseline TLG and MTV are significantly associated with PET2 response. TLG is a strong independent risk factor for prognosis, and may be useful for selecting patients likely to benefit from more intensive earlier therapy. A MV model including TLG may assess risk better than current clinical parameters but further work is needed. Such a model may be especially useful in pts with negative PET2 scans, in whom the overall 3 yr-PFS of 85% was lower than anticipated.

Keywords: Hodgkin lymphoma (HL); positron emission tomography (PET).

20 CLINICAL CHARACTERISTICS OF PATIENTS WITH NEGATIVE INTERIM-PET AND POSITIVE FINAL PET: DATA FROM THE PROSPECTIVE PET-ORIENTED HD0801 STUDY BY FONDAZIONE ITALIANA LINFOMI (FIL)

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Introduction: Interim-PET (i-PET) has shown an high prognostic impact in the definition of ABVD efficacy in advanced stage Hodgkin Lymphoma (HL). Patients with positive i-PET had a worst prognosis in comparison with those with negative i-PET. These data were reproduced in real life clinical setting and in a large series of prospective PET oriented studies. From these studies was pointed out an intriguing issue regarding patients with i-PET negative but with a positive results at the end of therapy (PET6 positive). This group of

patients represent without doubt the failure of functional imaging in selecting chemosensitive versus not chemosensitive patients.

Aim: The aim of this analysis was to identify, in a prospective PET oriented study supported by FIL (HD0801), those PET6 positive patients defining the clinical characteristics in order to identify earlier patients with i-PET negative but with an high probability of negative evolution that means progression of the disease.

Methods: HD0801 study was a multicenter prospective PET oriented study involving patients with advanced stage HL treated with ABVD. Patients performed PET at staging after two cycles of ABVD (i-PET) and at the end of therapy (PET6) to define response to therapy.

Results: Between September 2008 and April 2013, 520 patients were enrolled and 512 performed i-PET. Four hundred and nine were i-PET negative and continued ABVD, 16 patients interrupted therapy before end of therapy, 3 of these due to disease progression; the remaining 393 patients performed, after 6 ABVD, final PET to define response to therapy (PET6). In 355 PET6 was negative and in 38 patients it was positive confirming a progression of the disease. In summary patients with progressive disease after negative i-PET were 41: 38 (PET6 positive) and 3 progressed between i-PET and PET6. None of the analyzed clinical characteristics were significantly different between 355 PET6 negative and 41 PET6 positive a part for LDH value at diagnosis either in univariate or in multivariate analysis: Odds Ratio (OR) 2.33 (1.15 to 4.7). The only factor predicting OS in the group of patients with i-PET negative was the positive results of PET6 with an OR 83.74 (12.75 to 557.64). The OS from PET6 at 24 and 36 months was 99% and 98% for PET6 negative patients and 91% and 78% for PET6 positive patients.

Conclusions: Patients with negative i-PET but with a positive PET at the end of therapy had a very bad prognosis even in comparison with i-PET positive patients salvaged with intensification of therapy. From our study only LDH value at diagnosis was associated with a significant probability to have a positive PET6, none of the other clinical characteristics were associated with this result. Probably biological and pathological markers could be associated with i-PET to increase the predictive power but in particular to reduce the false negative i-PET.

Keywords: Hodgkin lymphoma (HL); positron emission tomography (PET).

21 PROGNOSTIC VALUE OF PET-CT AFTER FIRST-LINE IMMUNOCHEMOTHERAPY FOR FOLLICULAR LYMPHOMA IN THE PHASE III GALLIUM STUDY

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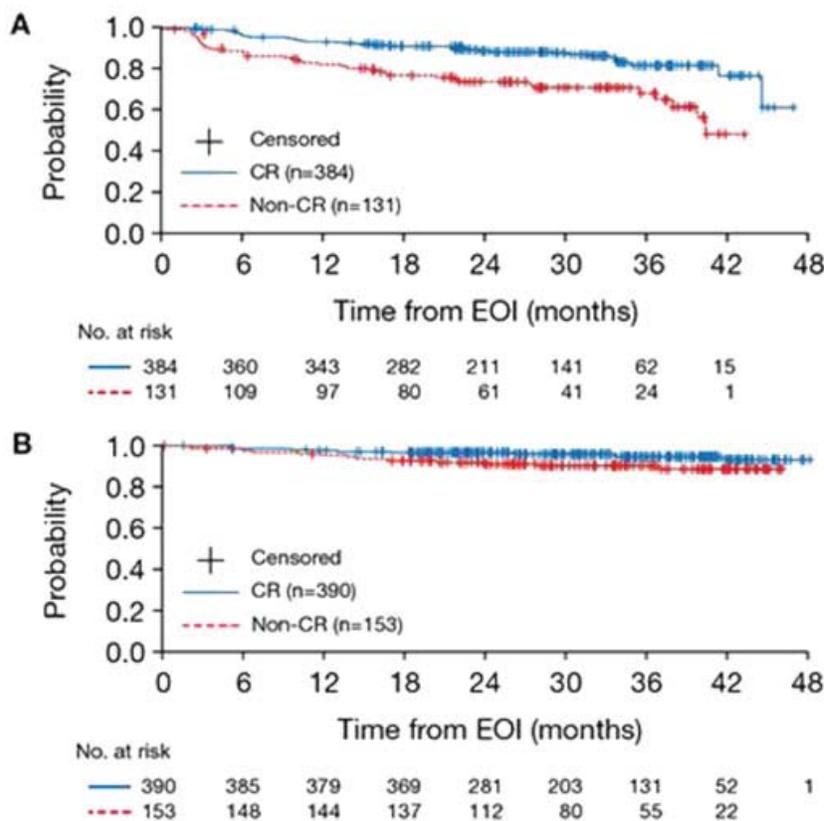
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Introduction: The prognostic value of ¹⁸F-FDG PET-CT (PET) response assessment after first-line (1 L) immunochemotherapy for advanced-stage symptomatic follicular lymphoma (FL) has been reported in several smaller trials. We evaluated the prognostic value of PET complete remission (PET-CR) status for the large FL patient (pt) cohort enrolled in the prospective Phase III GALLIUM study (NCT01332968; Marcus 2016).

Methods: 1202 pts with previously untreated FL (ITT population) were randomised 1:1 to receive induction therapy comprising chemotherapy plus 1000 mg obinutuzumab (G; D1, 8, 15 C1 then D1 subsequent cycles) or 375 mg/m² rituximab (R; D1 each cycle), for 8 x 21-day cycles (CHOP, CVP) or 6 x 28-day cycles (bendamustine). PET scans, introduced after an early protocol amendment (July 2011), were taken at baseline and end of induction (EOI) visits and assessed by the investigator (INV) and an independent review committee (IRC) comprising two radiologists, with a third adjudicator; final response was determined by a clinician. Response was assessed by CT and PET plus bone marrow biopsy, applying the revised International Working Group (IWG) criteria (Cheson 2007, Juweid 2007). EOI PET-CR status was compared with pt characteristics, CT-based response, PFS and OS.

Results: Of 609 pts with a baseline PET scan, 595 had detectable lesions, and 535 also had an evaluable PET at EOI. Baseline disease and demographic characteristics were similar in the PET-evaluable and non-PET populations. Pts with non-available (n = 52) and non-evaluable (n = 8) scans were considered as non-responders; these pts and those who progressed prior to EOI were excluded from landmark PFS analyses. At EOI 390/595 (65.5%) pts had achieved a PET-CR according to IRC, comprising 212/297 (71.4%) G-chemo pts and 178/298 (59.7%) R-chemo pts. After a median follow-up of 34.5 months, EOI PET-CR status was highly prognostic of both PFS (PET-CR vs PET-non CR: HR 0.39; 95% CI 0.25-0.60; p < 0.0001)

Figure. Landmark (from EOI) Kaplan-Meier curves of A) PFS* (N=515) and B) OS† (N=543) for PET-CR vs PET-non CR status at EOI according to IRC assessment



*Patients who died or progressed (had CT-based PD assessment) before or at EOI were excluded; †Patients who died before or at EOI were excluded.

and OS (HR 0.41; 95% CI 0.19–0.86; $p = 0.018$; see Figure). 2.5-year PFS from EOI was 87.6% (95% CI 83.5–90.8) for PET-CR pts compared with 70.9% (95% CI 61.3–78.6) for PET-non CR pts; corresponding OS was 96.6% (95% CI 94.1–98.1) vs 90.9% (95% CI 84.7–94.6). IRC PET status was prognostic in both G- and R-treated populations. Concordance between INV and IRC evaluation was 68.6%.

Conclusions: This large prospective analysis confirms that PET status after 1 L immunochemotherapy, applying IWG 2007 criteria, is an early prognostic factor for PFS and OS in FL. Further analyses, including PET assessment by the INV, according to treatment arm, and IRC review applying a ≥ 4 point cut-off on the recommended 5-point scale for response assessment (Barrington 2014) will be presented. Pooled analyses of these and other data with longer follow-up may determine PET response as a reliable surrogate for PFS and OS, providing a platform for study of response-adapted therapy.

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

22 FDG-PET AS A BIOMARKER OF RESPONSE IN DLBCL: THE HOVON 84 STUDY EXPERIENCE

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Introduction: The HOVON 84 study, an international randomized clinical trial, was conducted between 2007 and 2012 (EudraCT number 2006-005174-42). 574 previously untreated eligible patients with CD-20 positive DLBCL were randomized between standard R-CHOP14 and early intensification of rituximab in the first 4 cycles (R2-CHOP14). Rituximab intensification did not improve the complete remission rate, progression-free survival (PFS) and overall survival (OS). No clinical subgroup benefited from rituximab intensification (P.J. Lugtenburg et al., oral presentation at ASCO 2016 and EHA 2016). In this trial interim FDG-PET scans were performed after 4 cycles (I-PET, without treatment modifications) and at end of therapy (EoT-PET). Our aim was to assess the predictive value of I-PET on PFS in DLBCL.

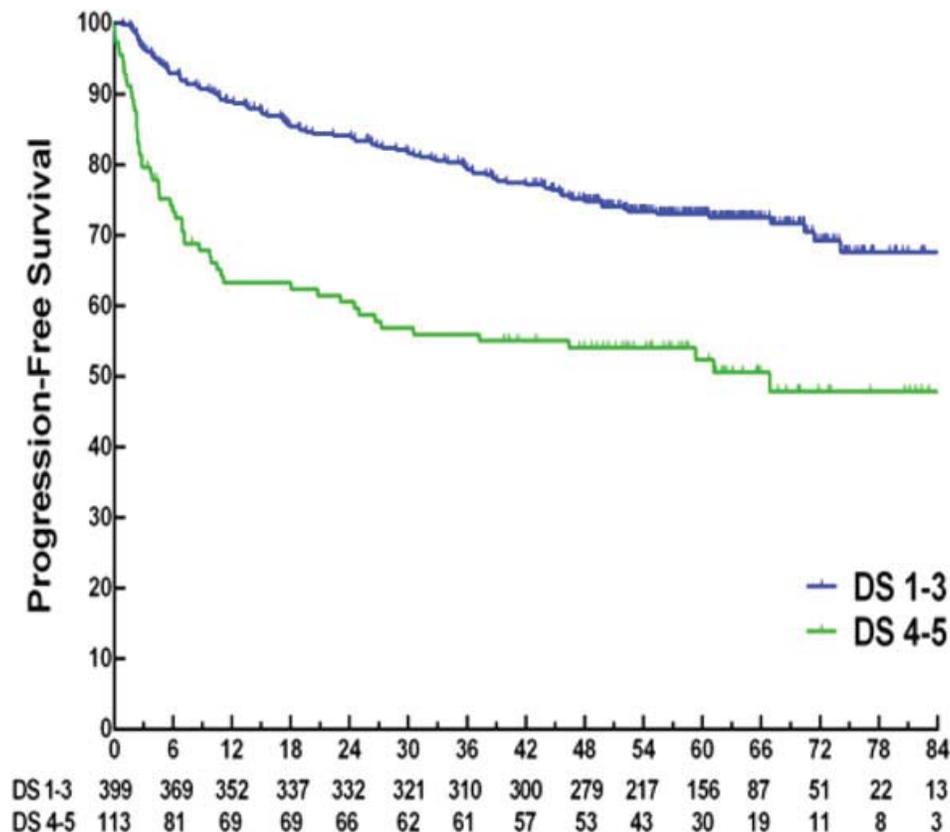


Figure 1. Kaplan-Meier curve of I-PET for PFS in DLBCL patients. I-PET negative (DS 1-3) patients are indicated in blue and I-PET positive (DS 4-5) patients are indicated in green.

Methods: I-PET and EoT-PET scans were centrally reviewed using the Deauville 5-point scale (DS), blinded to clinical outcome. DS 1-3 was regarded as negative and DS 4-5 as positive in both I-PET and EoT-PET. PFS for I-PET or EoT-PET was defined as time from I-PET or EoT-PET scan respectively, to disease progression, relapse or death from any cause. Kaplan-Meier (KM) analyses, log rank test and univariate hazard ratio (HR) calculations were performed for PFS. 2x2 contingency tables with PFS at 2 years after I-PET or EoT-PET were constructed, to calculate positive predictive values (PPV) and negative predictive values (NPV).

Results: A total of 512 I-PET scans and 496 EoT-PET scans were reviewed. 113 patients (22%) had a positive I-PET and 79 patients (16%) had a positive EoT-PET. After a median follow-up of 61 (interquartile range 53-68) months in progression-free patients the estimated 2-year PFS was 61% (95% CI 51-70) for I-PET positive and 84% (95% CI 81-88) for I-PET negative patients ($P < 0.001$) with a univariate HR of 2.3 (95% CI 1.7-3.2). EoT-PET positive patients' estimated 2-year PFS was 46% (95% CI 34-57) versus 86% (95% CI 83-90) for EoT-PET negative patients ($P < 0.001$) with a univariate HR of 4.1 (95% CI 2.8-5.8). Corresponding PPV and NPV values were 40% (95% CI 31-49) and 84% (95% CI 80-87) for I-PET and 56% (95% CI 45-66) and 86% (95% CI 83-89) for EoT-PET respectively.

Conclusions: In this prospective multicentre study, I-PET after 4 cycles R-CHOP14 discriminates between good and bad responders. However, switching to other therapies based on I-PET after 4 cycles might not be recommended, unless predictive values can be improved. Future research should focus on the added value of quantitative PET methods.

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

“FOCUS ON...” SESSION: CLINICO-PATHOLOGICAL CORRELATIONS

23 NON-MEDIASTINAL CASES OF GREY ZONE LYMPHOMA: A PATHOLOGICAL AND

CLINICAL SERIES OF 17 CASES FROM THE LYSA

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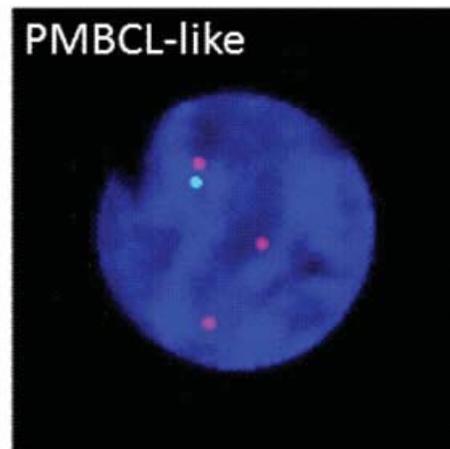
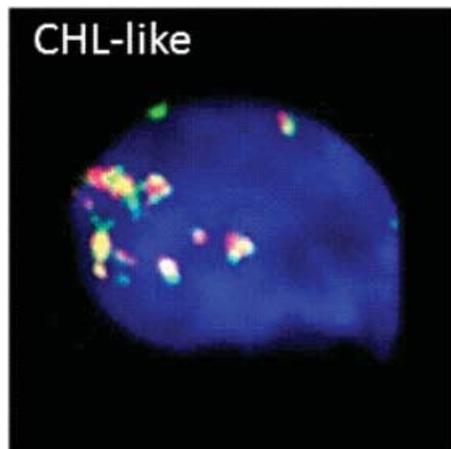
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Introduction: Mediastinal grey zone lymphomas (MGZL) present an intermediate morphology between classical Hodgkin lymphoma (CHL) and primary mediastinal large B cell lymphoma (PMBCL). Cases without mediastinal involvement or non-MGZL (NMGZL) have been described, but their classification remains controversial. The aim of this study was to describe their clinico-pathological characteristics.

Methods: Within the LYSA-P and LYMPHOPATH network, we collected a series of GZL centrally reviewed by expert hematopathologists. A total of 135 cases classified as CHL-like ($N = 90$, morphology closer to CHL and an immunophenotype (IP) to PMBCL), PMBCL-like ($N = 45$, morphology closer to PMBCL and an IP to CHL) were collected. Clinical and follow-up data were available for 108 patients (pts): 17 NMGZL (16%) and 91 MGZL. Additional immunohistochemistry, for MAL protein and B cell markers, and fluorescence in situ hybridization using break-apart probes to assess structural alterations of the *CIITA* and *PDL1-2* (Programmed death-ligand) gene loci were performed.

Results: Among the 17 NMGZL, 12 had a CHL-like morphology with various inflammatory backgrounds and a variable degree of fibrosis.



EBV positivity of the malignant cells was found in 3/11 cases (EBER) and 4/9 expressed MAL. The remaining 5 cases presented with a PMBCL-like-morphology with scant fibrosis and an inflammatory background. EBV was found in 1/5 cases, 1/3 expressed MAL, 2/5 did not express CD20. Compared to MGZL, there were no significant differences in subtype distribution (CHL/PMBCL-like) or with regards to EBV positivity ($p = 0.48$ and 0.78 χ^2 test, respectively). *CIITA* break could be observed in 4/10 cases (2/2 PMBCL-like and 2/8 CHL-like). *PDL1/2* abnormalities could be observed in 8/12 NMGZL cases (6/9 CHL-like and 2/3 PMBCL-like, figure 1): 3/12 with a break and 7/12 with a CNV (gain in 3 cases and amplification in 4). *PDL1* expression was observed in 6 cases (1/3 PMBCL-like and 5/7 CHL-like). None of the cases expressed *PDL2*. Regarding the clinical data, the median age was 55 y, significantly older than MGZL cases (34 y, $p = .01$). All the 17 pts with NMGZL had nodal involvement, 9 (53%) a stage III/IV, 7 presented an extra-nodal site (3 with more than extra-nodal 1 site involved): spleen ($n = 5$), bone marrow ($n = 3$), bone ($n = 2$), liver ($n = 3$), lung ($n = 3$). A bulky disease (> 10 cm) was present in 5 pts (31%). The age adjusted IPI score was >1 in 7 pts (41%). Age was the only parameters that significantly differed between NMGZL and MGZL pts. Among the 17 pts, 8 received R-CHOP, 5 an intensified R-CHOP (R-ACVBP), 4 ABVD. CR was reached in 14 pts, 1 of them relapsed at 167 m with a MGZL. Three pts (18%) were primary refractory (progression <1 y). The median EFS was 72 m. Although a trend towards a better outcome could be observed, there were no significant differences in EFS or OS between MGZL and NMGZL ($p = 0.3$ and 0.1 , respectively).

Conclusion: NMGZL should be considered as part of the spectrum of GZL diseases representing almost 1 case out of 6 in this series.

Keywords: Hodgkin lymphoma (HL); primary mediastinal large B-cell lymphoma (PMLBCL).

24 FOXP1 EXPRESSION IS INVERSELY CORRELATED WITH *EZH2* MUTATION STATUS AND PREDICTS POOR FAILURE-FREE SURVIVAL IN FOLLICULAR LYMPHOMA TREATED WITH RITUXIMAB AND CHEMOTHERAPY

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Introduction: Most patients with follicular lymphoma (FL) present with advanced stage disease and are considered incurable with standard immunochemotherapy. FL is a clinically and molecularly highly heterogeneous disease. However, prognostication relies predominantly on clinical tools and there is no consensus strategy for risk-based treatment stratification. We have recently demonstrated that integration of the mutation status of seven genes, including *EZH2* and *MEF2B*, improves risk stratification. In particular, *EZH2* mutations were associated with longer failure-free survival (FFS) in two independent cohorts of patients receiving immunochemotherapy. We aimed to assess whether FOXP1 protein expression, a potential surrogate for unmutated *EZH2*, is useful for predicting prognosis.

Methods: We mined publicly available gene expression datasets to identify potential *EZH2* targets. To assess whether FOXP1 protein expression is associated with FFS, we assembled a training cohort of 142 FL patients treated at the British Columbia Cancer Agency with R-CVP within one year of diagnosis. The validation cohort consisted of 395 patients with advanced stage FL, who received CHOP +/- rituximab within the GLSG1996 ($n = 86$) or GLSG2000 ($n = 309$) trials. Immunohistochemistry (IHC) for FOXP1 was performed on tissue microarrays and expression was independently scored by two hematopathologists in 10% increments. To differentiate cases with high vs. low expression, we chose the cut-off that maximized the log-rank test statistic in the training cohort. The effect of FOXP1 expression on FFS in the validation cohort was estimated using Cox regression analysis.

Results: Across three independent studies, three genes (*FOXP1*, *TCL1A* and *RASGRP2*) were consistently down-regulated in *EZH2* mutated cases. We focused on *FOXP1* as IHC assessment of its protein expression is widely available and has prognostic value in diffuse large B-cell lymphoma. This cut-off was determined to be 10%. Samples from 76 patients (54%) had high FOXP1 expression ($>10\%$) in the training cohort. Five-year FFS rates were 58% vs. 73% for cases with high vs. low FOXP1 expression, respectively ($P = 0.036$). In the validation cohort, 248 patients (63%) had high expression of FOXP1. High FOXP1 expression was associated with significantly shorter FFS in patients treated with R-CHOP (HR 1.95, 95%-CI [1.13-3.38], $P = 0.017$), but not in patients treated with CHOP (HR 1.15, 95%-CI [0.80-1.67], $P = 0.44$). Five-year FFS rates for high vs. low FOXP1 expression were 22% vs. 32% in CHOP-treated patients, and 55% vs. 72% in R-CHOP treated patients, respectively.

Conclusions: We find that *EZH2* mutations are associated with reduced FOXP1 transcriptional levels. FOXP1 protein expression by IHC correlates with shorter FFS in patients receiving immunochemotherapy, both in a retrospective population-based series and in a prospective clinical trial cohort.

Keywords: follicular lymphoma (FL); immunohistochemistry (IHC).

25 ELEVATED EXPRESSION OF LAG3 IS ASSOCIATED WITH POOR OUTCOME IN PATIENTS WITH DLBCL TREATED WITH R-CHOP

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Introduction: Immune checkpoint therapy has revolutionised the treatment of metastatic solid tumours. LAG3 is an immune checkpoint that is highly expressed on a variety of immune cells including a sub-population of 'exhausted' T cells. We have previously demonstrated LAG3 as a marker of tumour-associated T-cells with regulatory function in Hodgkin Lymphoma (Gandhi et al. Blood 2006). Agents targeting this molecule are currently undergoing phase I trials in combination with PD-1 blockade in a number of tumours. We set out to investigate the importance of LAG3 expression in a large DLBCL cohort treated with R-CHOP chemotherapy.

Methods: A population based cohort of 241 patients with DLBCL were tested. Inclusion criteria were use of R-CHOP chemotherapy and tissue availability. LAG3 expression was measured using DMGE (digital multiplex gene expression) by nanoString. Key immune molecules and Cell of Origin (COO) were measured in tandem. Results were compared to protein expression on immunohistochemistry (IHC) and to mutation testing.

Results: LAG3 gene expression was highly correlated with protein expression by IHC ($r = 0.79$, $p < 0.001$). Elevated LAG3 gene expression was associated with inferior 4-year progression free (PFS 47% vs. 80%, $p = 0.003$) and overall survival (OS 62% vs. 82%, $p = 0.003$) compared to patients with low expression of LAG3. In keeping with previous results in Hodgkin Lymphoma, the frequency of the EBV+ DLBCL subtype was enriched in the high LAG3 gene expression group (18% of LAG3 high patients vs. 6.5% of LAG3 low patients, $p = 0.02$). There was no difference between COO or IPI in high/low LAG3 gene expression patient samples. High levels of LAG3 were strongly correlated with other immune checkpoint molecules PD-1 ($r = 0.58$), PD-L1 ($r = 0.6$), PD-L2 ($r = 0.58$), TIM3 ($r = 0.69$) all $p < 0.0001$. LAG3 was strongly correlated with T cell infiltration as assessed by CD4 ($r = 0.53$, $p < 0.0001$) and CD8 ($r = 0.7$, $p < 0.0001$) expression in the tumours. Combined, these results suggest a key role for LAG3 in adaptive resistance by the tumour to immune attack. No patient with high LAG3 gene expression (0/16) had a mutation in B2M compared to 23% of LAG3 low patients (15/50) which is important as B2M mutations may convey resistance to anti-PD1 therapy ($p = 0.03$). Interestingly, the patients with high LAG3 expression could be stratified into two distinct survival groups based on their expression of PD-L1. Co-expression of both checkpoints was associated with inferior survival (5-year OS 44% vs. 83%, $p = 0.011$) compared to patients with low PD-L1 expression (and high LAG3 expression).

Conclusions: LAG3 expression is associated with inferior outcome in patients treated with DLBCL with R-CHOP. Co-expression of LAG3 with PD-L1 predicts for particularly poor prognosis. Therapeutic

modalities that target dual blockade of LAG3 and PD-L1 should be considered in future studies of DLBCL.

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

26 CELL OF ORIGIN COMBINED WITH CNS INTERNATIONAL PROGNOSTIC INDEX IMPROVES IDENTIFICATION OF DLBCL PATIENTS WITH HIGH CNS RELAPSE RISK AFTER INITIAL IMMUNOCHEMOTHERAPY

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Introduction: Central nervous system (CNS) relapse is a rare, and usually fatal, event in diffuse large B-cell lymphoma (DLBCL). Improved identification of patients (pts) with high CNS relapse risk is needed. The CNS International Prognostic Index (CNS IPI, Schmitz JCO 2016), a clinical prognostic model that identifies pts with higher CNS relapse risk, may be improved by integration of biomarkers.

Methods: CNS relapse was analysed in DLBCL pts treated with first-line obinutuzumab (G) or rituximab (R) plus CHOP in the Phase III GOYA study (Vitolo Blood 2016; NCT01287741). Cell-of-origin (COO) was assessed using gene expression profiling (Nanostring Lymphoma Subtyping). Cumulative incidence and time to CNS relapse were estimated with Kaplan-Meier statistics. The impact of variables of interest (CNS IPI score, COO, study stratification factors – number of planned cycles, geographical region) on CNS relapse was assessed using a multivariate (MV) Cox regression model.

Results: Of 1418 pts, 19.7% were categorised by CNS IPI score as low risk (0–1) for CNS relapse, 63.0% as intermediate risk (2–3) and 17.3% as high risk (4–6). After 29.0 mo (range 0.1–56.6) median observation, 40 (2.8%) pts developed CNS relapse (21 G-CHOP; 19 R-CHOP).

Median time to CNS relapse was 8.5 mo (range 0.9–43.5); 2-yr CNS relapse rates were 3.0% overall and 0.8%, 2.1% and 9.3%, for the low, intermediate and high risk CNS IPI subgroups, respectively. COO was available in 933 pts (65.8%). In these pts, 2-yr relapse rates were 1.4%, 2.2% and 10.3% for the low, intermediate and high risk CNS IPI subgroups, respectively (Figure A). Pts with activated B-cell-like (ABC) and unclassified subtypes had significantly higher CNS relapse risk vs the germinal-center B-cell-like subtype (2-yr rates: 6.9%, 4.8% vs 1.5%, respectively). The impact of dual BCL2 and MYC protein expression on CNS relapse risk is being evaluated and will be presented. On MV analysis, CNS IPI score (hazard ratio [HR] 2.06; 95% CI 1.50–2.82, $p < 0.001$) and ABC (HR 4.37; 95% CI 1.84–10.37, $p < 0.001$) or unclassified COO subtypes (HR 3.94; 95% CI 1.45–10.68, $p = 0.007$) were associated with CNS relapse risk. Three risk subgroups were identified according to presence of high CNS IPI score and/or ABC/unclassified COO ($n = 933$): low risk (L-R, no risk factors; $n = 450$, 48.2%); intermediate risk (I-R, 1 risk factor [high CNS IPI or ABC/unclassified COO]; $n = 408$, 43.7%); and high risk (H-R, both risk factors [high CNS IPI and ABC/unclassified COO]; $n = 75$, 8.0%). Two-yr CNS relapse risk was 0.5% (L-R), 4.7% (I-R) and 15.2% (H-R) (Figure B).

Conclusions: CNS IPI score and ABC/unclassified COO subtypes were independent risk factors for CNS relapse in DLBCL in the GOYA study. Combining these factors improved prediction of CNS relapse vs CNS IPI alone and stratified pts into 3 risk groups, including a small but

notable subgroup (8.0%) of pts with a very high risk of CNS relapse (2-yr risk: 15.2%).

Keywords: diffuse large B-cell lymphoma (DLBCL); obinutuzumab; prognostic indices.

27 NKP46 EXPRESSION IS A DIAGNOSTIC AND PROGNOSTIC BIOMARKER IN PRIMARY GASTROINTESTINAL T-CELL LYMPHOPROLIFERATIONS. A CELAC NETWORK STUDY

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Figure A. Risk of CNS relapse by CNS IPI, COO population ($n=933$)

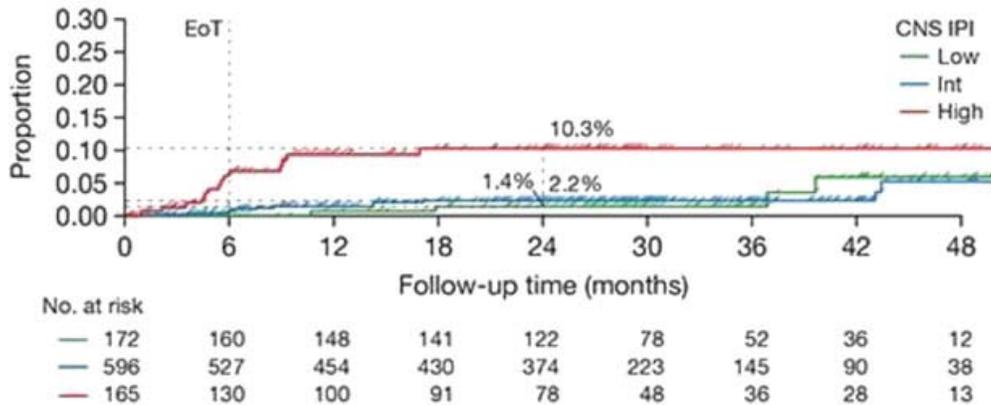
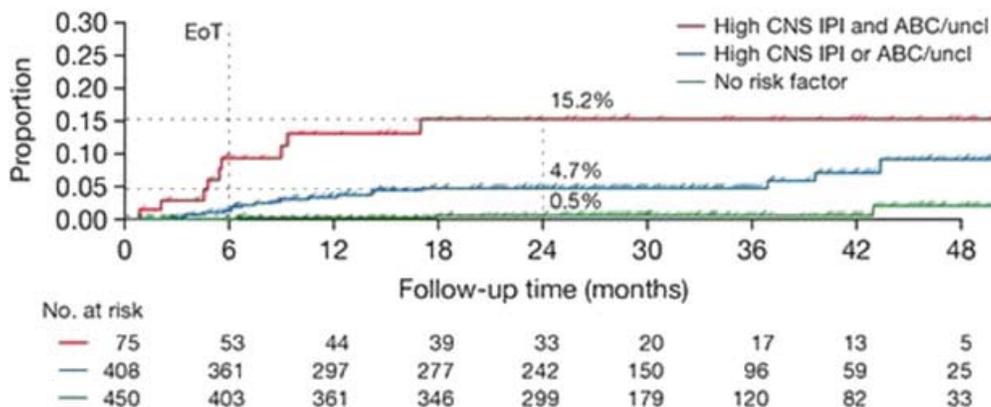


Figure B. Risk of CNS relapse by high CNS IPI and/or ABC/unclassified COO, COO population ($n=933$)



EoT, end of treatment.

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Introduction: Primary gastrointestinal (GI) T-cell lymphoproliferations (T-CL) are heterogeneous entities, which diagnoses are difficult to perform. T-CL include aggressive lymphoma such as enteropathy-associated T-cell lymphoma (EATL) as well as indolent monoclonal lymphoproliferations. Refractory coeliac disease type II (RCDII) is one of the indolent clonal T-CL that complicates coeliac disease (CD) and may evolve toward an overt EATL. The differential diagnosis of RCDII from CD and RCDI is difficult and essentially based on negative expression of sCD3 and CD8 and the presence of a clonal TCR rearrangement. Lymphocytes from RCDII are dependent for survival on IL-15, which reprograms T lymphocytes towards a cytotoxic NK phenotype. We thus studied the expression of NKp46 on a representative panel of GI T-CL to assess its diagnosis and prognosis value.

Methods: Using formalin-fixed paraffin-embedded tissue biopsies, we assessed NKp46 expression by immunohistochemistry (IHC) and investigated its clinical and biologic significance on 177 intestinal, 11 lymph node and 7 other biopsies from 84 CD or RCD patients (RCDI, $n = 20$; RCDII, $n = 40$), 44 GI T-cell lymphoma patients (EATL, $n = 25$; monomorphic epitheliotropic intestinal T-cell lymphoma_MEITL, $n = 4$; indolent T-LPD, $n = 15$), 11 healthy patients and 5 patients with a GI inflammatory environment as controls.

Results: By doing ROC analysis on number of cells expressing NKp46 on GI-TCL we identify that 25 intra-epithelial lymphocyte (IEL) per 100 epithelial cells (EC) clearly separates RCDII from CD and RCDI patients, with a good positive and negative predictive values (100 and 95% respectively). In healthy controls, CD or RCDI patients, NKp46 was only expressed on scattered IEL (median 3%, 0-15). Based on NKp46 expression the overall survival is poor if over 25% of IEL are positive for NKp46 (OS-5 years 96.4% vs. 72.8%, $P = 0.0004$). Among patients with GI T-cell lymphoma, we show that NKp46 was expressed in most of aggressive lymphoma (EATL 80%, $n = 20/25$ and MEITL 100%, $n = 4/4$). On the other hand, NKp46 was never expressed on indolent T-LPD ($n = 0/15$). The NKp46 expression was also associated with a poor prognosis in GI T-cell lymphoma patients (OS-5 years 50.5% vs. 5.4%, $P = 0.0011$).

Conclusion: The NKp46 expression in more than 25 IEL per 100 EC by IHC analysis can easily identify RCDII from CD and RCDI. Furthermore, the NKp46 expression is associated with aggressive forms of GI T-cell lymphoma. Finally, the NKp46 expression was strongly associated with shortened survival. Thus NKp46 provides a new biomarker for both diagnosis and prognosis in GI T-CL.

Keywords: enteropathy associated T-cell lymphoma (EATL); immunohistochemistry (IHC); peripheral T-cell lymphomas (PTCL).

28 ADULT PATIENTS WITH CAEBV-LIKE FEATURES: A DISTINCT SUBTYPE OF EPSTEIN-BARR VIRUS POSITIVE T/NK-CELL LYMPHOPROLIFERATIVE DISORDER

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Background: Chronic active Epstein-Barr virus infection (CAEBV), which is also described as systemic EBV-positive T-cell lymphoproliferative disorder (EBV-T-LPD) of childhood in World Health Organization (WHO) classification of lymphoid neoplasms, is a fatal disease developing exclusively in children and young adults. Recently, EBV-T/natural killer (NK)-LPD with CAEBV-like features in adult patients (adult-onset CAEBV) has been linked to a fever of unknown origin in Asia, as well as worldwide. However, the characteristics of adult-onset CAEBV are poorly recognized, hindering early diagnosis and an improved prognosis. The aim of the present study was to characterize the detailed clinical features of adult-onset CAEBV, in comparison with pediatric-onset patients, in order to explore the early diagnosis of adult-onset CAEBV. **Methods:** A retrospective descriptive epidemiology study of Japanese patients with adult-onset CAEBV ($n = 54$) diagnosed between 2005 and 2015 was conducted. Adult-onset was defined as an estimated age of onset ≥ 15 years. To characterize the clinical features of adult-onset CAEBV, we compared them to those of a pediatric-onset (estimated age of onset < 15 years) infection ($n = 75$). In addition, we compared the prognosis of adult-onset CAEBV with that for 82 patients with extranodal NK/T-cell lymphoma, nasal type (ENKTL).

Results: The median estimated age of onset was 39 years (range: 16–86 years). Compared to that for pediatric-onset patients, adult-onset patients had a significantly decreased incidence of fever ($P = 0.005$), but greater frequency of skin lesions ($P < 0.001$). Moreover, hypersensitivity to mosquito bites and hydroa vacciniforme occurrences were less frequent in patients with adult-onset CAEBV ($P < 0.001$ and $P = 0.0238$, respectively). Thrombocytopenia, high EBV nuclear antigen (EBNA) antibody titer, and presence of hemophagocytic syndrome were associated with a poor prognosis (Log-rank $P = 0.0087$, $P = 0.0236$, and $P = 0.0149$, respectively). Allogeneic hematopoietic stem cell transplantation may improve survival (Log-rank $P = 0.0289$). Compared to that for pediatric-onset CAEBV and ENKTL, adult-onset CAEBV had a poorer prognosis ($P < 0.001$ and $P = 0.0484$, respectively). In multivariate analysis, thrombocytopenia (platelets $< 100 \times 10^9/L$, hazard ratio [HR] 6.157, 95% confidence interval [CI] 2.433–15.58, $P < 0.001$), high EBNA titer (≥ 40 ; HR 2.815, 95%CI 1.225–2.497, $P = 0.0148$), and not receiving HSCT (HR 5.410, 95%CI 1.892–15.47, $P = 0.0016$), were independent poor prognostic factors, respectively.

Conclusions: CAEBV can develop in a wide age-range, with clinical differences between adult-onset and pediatric-onset CAEBV. Adult-onset CAEBV may be one of the most important primary diseases of unknown fever. Adult-onset CAEBV has a very poor prognosis and may be a subtype of EBV-T/NK-LPD. Therefore, an accurate early diagnosis and appropriate treatment strategies are critical for adult patients.

Keywords: Epstein-Barr virus (EBV); T-cell lymphoma (TCL).

“FOCUS ON...” SESSION: NOVEL ANTI-LYMPHOMA DRUGS

29 PHARMACOLOGICAL ACTIVITY OF CB-103 IN HAEMATOLOGICAL MALIGNANCIES – AN ORAL PAN-NOTCH INHIBITOR WITH A NOVEL MODE OF ACTION

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Introduction: NOTCH signalling is critical during embryonic development as well as for the regulation of self-renewing tissues. Aberrant activation of NOTCH signalling in cancer leads to sustained proliferation, escape from apoptosis, loss of differentiation capacity, increased invasion and metastasis and is a negative prognostic factor. Overactivation of the NOTCH pathway due to various genetic lesions (over expressions, mutations, translocations), is a major driver for NOTCH-dependent cancers and resistance to standard of care treatment. Several therapeutic NOTCH inhibitors are currently in clinical testing with a) monoclonal antibodies (mAbs) against NOTCH ligands and receptors and b) gamma-secretase inhibitors (GSIs). However clinical activity and exposure of these in clinical studies were limited due to gastro-intestinal toxicities. In haematological malignancies with constitutive NOTCH activation (gene fusion due to chromosomal translocations or NOTCH mutations), mAbs and GSIs will have very limited clinical benefits. Here we report, discovery and development of a novel orally active small molecule inhibitor (CB-103) of the NOTCH pathway. CB-103 blocks NOTCH signalling by a novel mode of action, directly targeting the NOTCH transcriptional activation complex. We will further present the in vitro and in vivo pharmacological characterization of CB-103.

Methods: Primary pharmacodynamic (PD) studies were conducted to investigate CB-103 in relation to its desired therapeutic effect for treating advanced haematological malignancies as a NOTCH pathway inhibitor. Regarding the PD effect, in vitro studies demonstrated for CB-103 a dose-dependent decrease in NOTCH signalling activation with a unique mechanism compared to GSIs and mAbs. The NOTCH inhibitory potential of CB-103 was further confirmed by downregulation of NOTCH target genes in human T-cell acute lymphoblastic leukaemia (T-ALL), suggesting therapeutic efficacy of CB-103 in the context of T-ALL. In a panel of >120 cell lines of various malignancies CB-103 was active on a subset of 24 cancer cell lines, including different lymphomas. Moreover, CB-103 demonstrated anti-NOTCH activity in the Triple-Negative Breast Cancer (TNBC) HCC1187 cell line, being resistant to GSIs due to a NOTCH2 chromosomal translocation.

Results: We demonstrate that in vitro CB-103 potently inhibits NOTCH signalling in various lymphoma and leukaemia cell lines, and T-ALL blasts derived from relapse/refractory patients. In addition,

CB-103 exhibited anti-tumor efficacy in in vivo models of NOTCH-driven T-ALL using T-ALL cell lines and PDx models.

Conclusions: Toxicology studies have revealed an excellent safety profile in the expected human therapeutic dose range. Clinical development of CB-103 with a first-in-human Phase I/IIA clinical study in advanced HL, selected NHL indications and solid tumours is under preparation.

Keywords: Hodgkin lymphoma (HL); Notch pathway; T-cell lymphoma (TCL).

30 ANTI-TUMOR ACTIVITY OF DARATUMUMAB, A NOVEL HUMAN ANTI CD38 MONOCLONAL ANTIBODY, IN IN VITRO AND IN VIVO MODELS OF B-CELL NON-HODGKIN LYMPHOMA

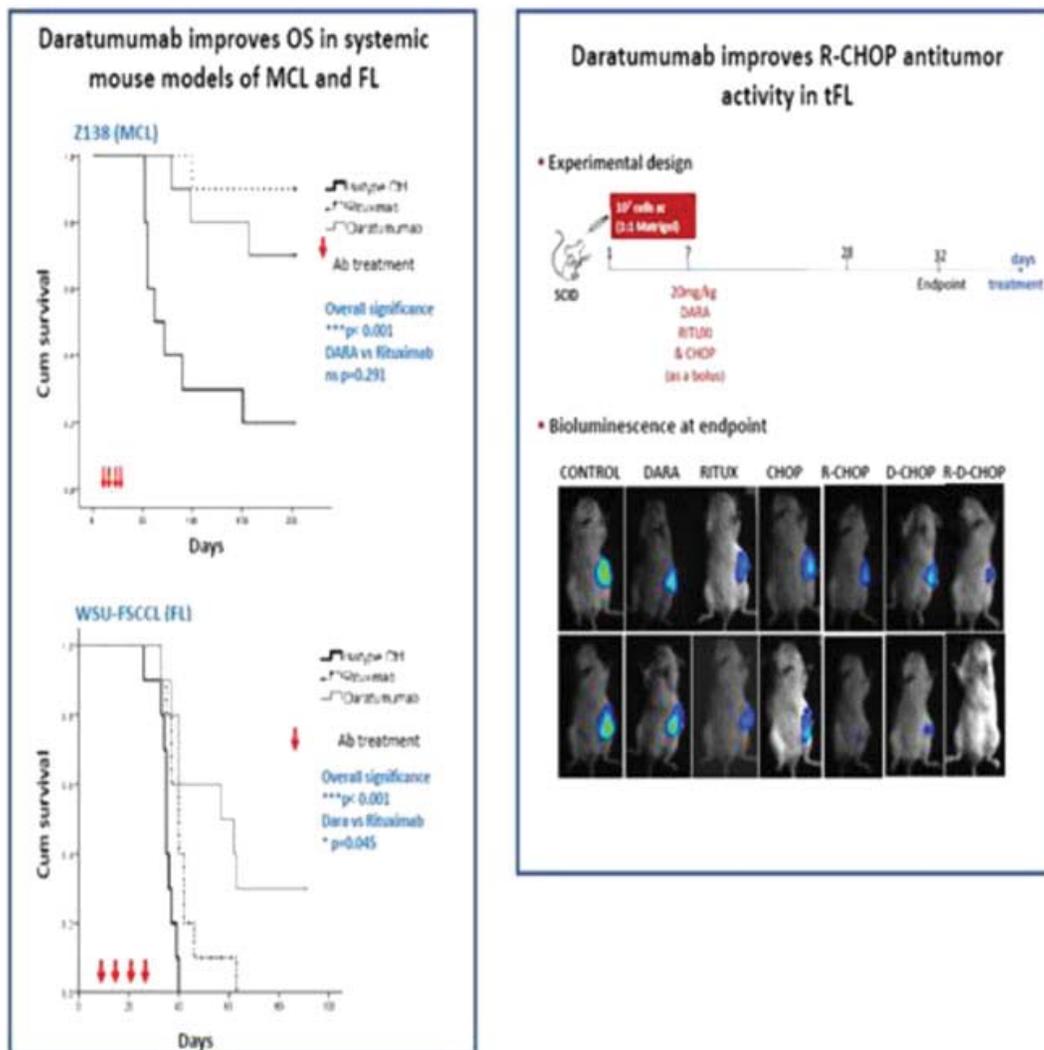
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Introduction: Daratumumab (DARA) is a first-in-class human monoclonal antibody that targets the CD38 epitope, and is approved for the treatment of relapsed/refractory (R/R) multiple myeloma patients. DARA is currently being evaluated in phase 2 clinical trials as monotherapy in patients with R/R Mantle Cell Lymphoma (MCL), Follicular Lymphoma (FL) and Diffuse Large B-Cell Lymphoma. In this study, we have analyzed the in vitro and in vivo activity of DARA in MCL and FL, both as single agent and in combination therapy.

Methods: ADCC, CDC and ADCP activities were assessed by calcein release or flow cytometry. Penetration of DARA was analyzed in a 3D model by Selective Plane Illumination Microscopy (SPIM). Molecules per cell were analyzed by Qifikit and flow cytometry. In vivo activity was assessed in SCID mice following prophylactic (subcutaneous (sc); 3 doses of 10 mg/kg, on alternate weeks) or therapeutic (intravenous (iv); 4 doses 20/10/10/10 mg/kg, once a week) set ups. For combination regimens in FL, sc injected SCID mice were treated following the therapeutic schedule in combination with Rituximab (20/10/10/10 mg/kg, once a week) and/or CHOP (initial unique dose).

Results: DARA(0.0001-1 µg/mL) induced dose -dependent ADCC on MCL (n = 6) and FL (n = 4) cell lines in the presence of PBMCs in vitro. DARA induced significant levels of ADCP at 1 µg/mL on MCL (n = 6) and FL (n = 4) cell lines in the presence of murine macrophages in vitro. However, DARA did not induce significant CDC in any of these models due to high expression of the complement inhibitors CD46, CD55 and CD59, and insufficient number of CD38 molecules per cell. In a 3D



model of FL, SPIM analysis revealed a maximum penetration of DARA at 1 $\mu\text{g}/\text{mL}$ after 48 h of treatment. In vivo, following the prophylactic setting DARA completely prevented the outgrowth of MCL and FL cells in sc tumor xenografts. In the therapeutic set up, DARA significantly increased the overall survival (OS) and reduced organ infiltration of tumor cells both in MCL and FL systemic xenograft models. In addition, the combination of DARA to Rituximab/CHOP regimen in FL resulted in a synergistic reduction of tumor growth.

Conclusions: DARA shows encouraging antitumor activity as a single agent in MCL and FL in in vitro and in vivo models. In addition, DARA contributes to potent therapeutic efficacy in combination with standard therapies. These results warrant further studies of DARA in the clinical setting for these conditions.

Keywords: CD38; follicular lymphoma (FL); mantle cell lymphoma (MCL).

31 A NEW BCL-2 INHIBITOR (S55746/BCL201) AS MONOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY NON-HODGKIN LYMPHOMA:

PRELIMINARY RESULTS OF THE FIRST-IN-HUMAN STUDY

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Introduction: The anti-apoptotic protein BCL-2, overexpressed in many non-Hodgkin lymphoma (NHL) subtypes, is responsible for apoptosis machinery dysregulation and contributes to chemotherapy resistance. S55746/BCL201 is a novel, oral, selective BCL-2 inhibitor.

Methods: S55746/BCL201 monotherapy is currently being tested in an international, first-in-human, open-label, non-randomized, dose-escalation study in patients (pts) ≥ 18 years with relapsed or refractory B-cell NHL including mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), follicular lymphoma (FL), small lymphocytic lymphoma (SLL), and diffuse large B-cell lymphoma (DLBCL). Primary objectives are to evaluate safety and establish the recommended phase 2 dose; secondary objectives include pharmacokinetics (PK), food interaction on PK, pharmacodynamics, and preliminary activity. S55746/BCL201 is administered once daily in fasting pts continuously over 21-day cycles until progressive disease (PD) or unacceptable toxicity. Pts could receive 50 to 2000 mg S55746/BCL201 according to a modified version of the continual reassessment method for dose allocation.

Results: As of 9 March 2017, 37 NHL pts (median age 64 years, range 24-85) were dosed up to 1300 mg with a median duration on treatment of 42 days. NHL subtypes were DLBCL (68%), MCL (16%), FL (8%), and MZL (8%). Median number of prior regimens was 5 (range 2-15). Preliminary PK results showed that exposure increases linearly with some interindividual variability. Most common adverse events (AEs) include asthenia ($n = 6$), vomiting ($n = 6$) and nausea ($n = 5$). The most frequent (≥ 3 pts) grade ≥ 3 AEs were lymphopenia ($n = 4$), anemia ($n = 3$), and disease progression ($n = 3$). AEs possibly related to study drug were reported in 5 pts, the most frequent being nausea ($n = 3$) and asthenia ($n = 2$) all grade 1/2. Causes of death were disease progression ($n = 2$) and pulmonary embolism ($n = 1$). No DLT and no tumor lysis syndrome were reported. In the 35 evaluable pts, 2 DLBCL pts reached partial response [PR] (at 200 and 400 mg) and were treated for 709 and 221 days, respectively, and 1 DLBCL patient reached complete response (CR) at 400 mg. Interestingly, both primary mediastinal B-cell lymphoma pts responded (1 CR and 1 PR). DLBCL pt who reached CR is still being treated after 32 cycles (i.e. 674 days). In FL pts, 1 PR was observed at 100 mg. 36 patients have withdrawn from the study (32 due to PD, 2 AEs, 1 non-medical reason, and 1 protocol deviation). A non-compartmental PK analysis of a food interaction cohort demonstrated that S55746/BCL201 C_{max} and AUC increased by approximately 6-fold with food intake.

Conclusion: S55746/BCL201 monotherapy showed acceptable safety and tolerability, and preliminary evidence of activity across the range of doses explored in various NHL subtypes, most notably DLBCL. Based on PK food interaction results, dose escalation is ongoing with S55746/BCL201 administered with food. Clinical trial information: NCT02920697.

Keywords: apoptosis; BCL2; non-Hodgkin lymphoma (NHL).

32 PHASE I STUDY OF IPH4102, ANTI-KIR3DL2 MAB, IN RELAPSED/REFRACTORY CUTANEOUS T-CELL LYMPHOMAS (CTCL): DOSE-ESCALATION SAFETY, BIOMARKER AND CLINICAL ACTIVITY RESULTS

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Introduction: KIR3DL2 belongs to the killer Ig-like receptor (KIR) family, is expressed on minor subsets of normal NK, CD8 and CD4 T cells and in several subtypes of CTCL. IPH4102 is a first-in-class anti-KIR3DL2 monoclonal antibody that depletes KIR3DL2-expressing cells through antibody-dependent cell-cytotoxicity and phagocytosis. IPH4102 showed potent efficacy in preclinical models.

Method: IPH4102 is currently investigated in a first-in-Human dose finding phase I study (NCT02593045) in systemically pre-treated relapsed or advanced CTCL. An accelerated 3 + 3 design with cohort expansion is employed. The primary objective is to assess safety and tolerability of IPH4102 by identifying the Maximal Tolerated Dose (MTD) or a Recommended Phase 2 Dose (RP2D). The MTD is the highest dose at which 0/3 or 1/6 patient experiences a DLT within 14 days after the first IPH4102 administration. Secondary objectives include PK, immunogenicity and signals of clinical activity by CTCL-specific International Response Criteria. Exploratory biomarkers include KIR3DL2 expression and minimal residual disease in involved disease compartments. Centrally assessed KIR3DL2 expression on malignant cells is required for inclusion. IPH4102 is administered 4 times QW, followed by 10 times Q2W and Q4W thereafter. Patients are treated until progression or unacceptable toxicity. Intra-patient dose escalation is allowed in the dose escalation portion. The MTD/RP2D will be further characterized in CTCL subtype-specific expansion cohorts.

Results: At the date of abstract submission, the 10th dose-level (10 mg/kg) is enrolling. A total of 22 patients have been treated at the 9 first dose levels and are evaluable for safety and clinical activity: 19 SS, 2 MF and 1 "not-otherwise-specified" CD4⁺CTCL. Median age is 72 years (range 47-90). Median number of prior lines of systemic therapies is 4. Median duration of treatment is 201 days (range 43-455). Twenty one patients received escalated doses after their initial 4 weekly doses. No DLT was observed within the first 14 days of treatment and the MTD was not reached yet. Six patients experienced AE \geq grade 3 and none was treatment-related. No IPH4102-related skin rashes or infections have been observed. Best global overall response rate (ORR) is 45% across doses, with 10 partial responses. All but one response are ongoing at the time of data cut-off for the abstract. Best global ORR is 47% in SS patients, reaching 58% responses in blood compartment. Two complete responses were seen in skin and 5 in blood. It is too early to evaluate median duration of response; it will be presented at the conference. Biomarkers are consistent with clinical activity signals.

Conclusions: Preliminary data show excellent tolerability and promising clinical activity in heavily pretreated advanced CTCL

patients. Updated results up to 10 mg/kg will be presented at the meeting.

Keywords: cutaneous T-cell lymphoma (CTCL); monoclonal antibodies (MoAb); Sezary syndrome.

33

A PHASE 1 STUDY OF THE ANTI-CD37 ANTIBODY-DRUG CONJUGATE AGS67E IN ADVANCED LYMPHOID MALIGNANCIES. INTERIM RESULTS

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Background: CD37 is a tetraspanin expressed in most B- and T-cell malignancies in previous tumor profiling studies. AGS67E is an antibody drug conjugate (ADC) composed of a fully human IgG2 antibody targeting CD37 that is conjugated to the microtubule-disrupting agent MMAE through a cleavable linker. CD37 expression is found in: >80% of B and T-cell lymphomas as well as in 100% of Chronic lymphocytic leukemia (CLL) samples tested. Patient-derived xenograft studies demonstrated the efficacy of AGS67E in non-Hodgkin lymphomas (NHLs) and CLL models (Pereira et al., Mol Cancer Ther; 2015).

Methods: The first in human, ongoing, multicenter, phase 1 dose-escalation study is evaluating the safety, PK and anticancer activity of AGS67E given as monotherapy to subjects with relapsed / refractory NHLs and CLL. AGS67E is administered intravenously (IV) once every 3 weeks (Q3 weeks) until disease progression or unacceptable toxicity. The dose escalation first determined the maximum tolerated dose (MTD) of AGS67E without growth factor (GF), followed by the MTD of AGS67E with GF support.

Results: As of Sept 19, 2016, 50 subjects have been treated of which 19 (38%) have a diagnosis of Diffuse Large B-Cell Lymphoma (DLBCL), 7 (14%) Follicular Lymphoma (FL), 4 (8%) Adult T-Cell Lymphoma (CTCL), 4 (8%) Mycosis Fungoides (MF), 3 (6%) Peripheral T-Cell Lymphoma (PTCL), 3 (6%) Transformed Diffuse Large B-Cell Lymphoma (TDLBCL), 2 (4%) Mantle Cell Lymphoma (MCL) and 8 (16%) have other diagnoses. Median age was 63.5 years (range 25 - 85). Subjects received a median number of 3 (1 - 14) prior therapies. The MTD was 0.9 mg/kg without GF; the dose limiting toxicity (DLT) was Gr 4 neutropenia 8 - 15 days after 1st dose. No major non-hematological toxicities have been observed. Eight subjects experienced symptoms of peripheral neuropathy: 5 (Gr 1) and 3 (Gr 2). The MTD with GF was exceeded at 1.8 mg/kg. Responses were noted in subjects dosed at 0.9, 1.2 and 1.5 mg/kg; Specifically, 7 subjects experienced a

complete remission (CR) (4 DLBCL, MALT, FL and primary cutaneous marginal zone lymphoma (PCMZL)) and 4 subjects experienced a partial remission (PR) (prolymphocytic leukemia (PLL), MF, transformed DLBCL and DLBCL). The serum AGS67E concentrations indicated a non-linear PK at ≤ 0.6 mg/kg dose levels. At 1.2 mg/kg, the half-life of AGS67E and free MMAE ranged from 1.59-2.25 and 2.34-3.64 days, respectively.

Conclusions: AGS67E administered Q3 weeks has a favorable safety profile and has demonstrated signs of activity, especially in DLBCL and CTCL. Expansion cohorts are ongoing at the MTD with GF for DLBCL and T-Cell lymphoma.

Keywords: B-cell lymphoma; CD37; T-cell lymphoma (TCL).

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FIRST CLINICAL RESULTS OF ADCT-402, A NOVEL PYRROLOBENZODIAZEPINE-BASED ANTIBODY DRUG CONJUGATE (ADC), IN RELAPSED/REFRACTORY B-CELL LINEAGE NHL

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Introduction: CD19 expression has been demonstrated in many types of NHL, including FL and DLBCL. Pyrrolobenzodiazepine (PBD) is a DNA cross-linking agent. ADCT-402, a humanized antibody directed against human CD19 conjugated to a PBD dimer toxin, has demonstrated potent pre-clinical anti-tumor activity against CD19-expressing B-cell malignancies. Interim results of the first in-human clinical study of ADCT-402 in the difficult-to-treat relapsed/refractory NHL setting are reported here.

Methods: Patients (pts) with recurrent B-cell NHL who had failed or were intolerant to established therapies, or had no other treatment options available, were assigned IV infusions of ADCT-402 every 3 weeks (1 cycle) according to a 3 + 3 dose-escalation study design. No intra-patient dose escalation was allowed. Safety, tolerability, and efficacy were assessed.

Results: As of 3 Feb 2017, 37 pts (23 male, 14 female; median age: 69 years [range 24-85]; median number of previous therapies: 3 [range 1-10]) have been recruited. Diagnoses included DLBCL (n = 22), MCL (n = 7), FL (n = 6) and other B-cell NHL (n = 2). Pts received ADCT-402 doses ranging from 15 to 200 μ g/kg (median cycles: 3 [range 1-11]). Treatment-emergent adverse events (TEAEs) included fatigue (21 [56.8%] pts), peripheral edema (10 [27.0%] pts), and nausea (9 [24.3%] pts). Grade ≥ 3 TEAEs included decreased

neutrophil count (4 [10.8%] pts), increased γ -glutamyltransferase (3 [8.1%] pts), neutropenia (3 [8.1%] pts), and thrombocytopenia (2 [5.4%] pts). TEAEs in 4 (10.8%) pts led to ADCT-402 withdrawal (increased γ -glutamyltransferase; increased blood alkaline phosphatase and γ -glutamyltransferase; fatigue and edema; abdominal pain and myalgia). No DLTs were reported and the MTD was not reached. 15/34 (44.1%) evaluable pts achieved a CR or PR (overall response [OR]), including 9/22 (40.9%) pts with DLBCL. 2/15 pts progressed by data cut-off. One 30 μ g/kg pt continues in CR for

>24wks. Table 1 shows the best OR by dose. 10/17 (58.8%) pts in the ≥ 120 μ g/kg cohort achieved OR, including 7/12 (58.3%) with DLBCL. Figure 1 shows nodal regression. Preliminary PK and anti-drug antibody data will be reported at the meeting.

Conclusions: ADCT-402 demonstrates encouraging single-agent anti-tumor activity and manageable toxicity in recurrent B-cell lineage NHL. At doses >120 μ g/kg, the OR in DLBCL is 58%. Further evaluation in specific NHL subtypes is warranted. A dose expansion in DLBCL is planned. <http://clinicaltrials.gov/show/NCT02669017>

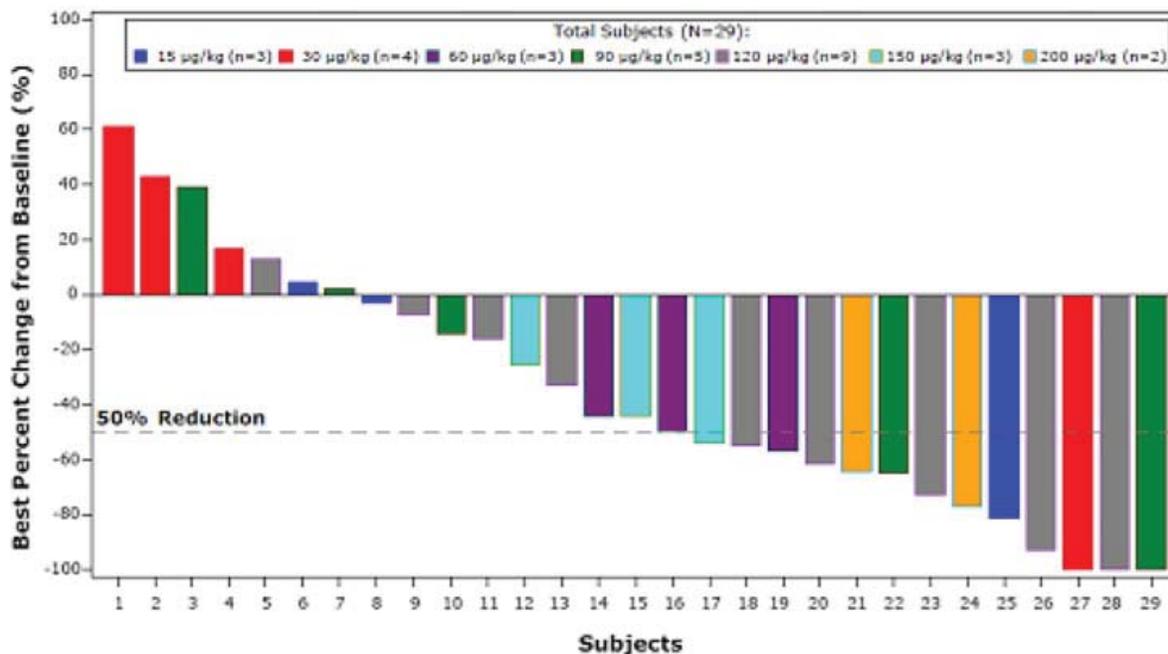
TABLE 1 Best overall responses* at each ADCT-402 dose

Response (n, %)	Dose (μ g/kg)							
	15	30	60	90	120	150	200	≥ 120
All Patients (n=34)								
	4	4	4	5	11	3	3	17
CR	0	1	0	1	2	0	3	5
PR	1	0	1	1	3	2	0	5
SD	1	0	0	3	3	1	0	4
PD	2	3	3	0	3	0	0	3
OR	1 (25.0%)	1 (25.0%)	1 (25.0%)	2 (40.0%)	5 (45.5%)	2 (66.7%)	3 (100%)	10 (58.8%)
DLBCL Sub-Group (n=22)								
	2	3	3	2	9	1	2	12
CR	0	1	0	0	2	0	2	5
PR	0	0	0	1	2	1	0	2
SD	1	0	0	1	3	0	0	3
PD	1	2	3	0	2	0	0	2
OR	0 (0%)	1 (33.3%)	0 (0%)	1 (50.0%)	4 (44.4%)	1 (100%)	2 (100%)	7 (58.3%)

* Best visit response based on the 2014 Lugano Classification Criteria

Key: CR, complete response; OR, overall response (CR+PR); PD, progressive disease; PR, partial response; SD, stable disease

Figure 1: Waterfall plot showing nodal regression (best percentage change from baseline; evaluable pts)



NB: Missing data, n=5 [1xCR, 1xPR, 1xSD, 2xPD]

Keywords: CD19; diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL).

“FOCUS ON...” SESSION: CHEMOTHERAPY-FREE COMBINATIONS

35

FINAL RESULTS OF CALGB 50803 (ALLIANCE): A PHASE 2 TRIAL OF LENALIDOMIDE PLUS RITUXIMAB IN PATIENTS WITH PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA

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Background: In 2008 we initiated a multicenter phase 2 trial of lenalidomide and rituximab in patients (pts) with previously untreated follicular lymphoma (FL) and evaluated whether FcR polymorphisms and changes in circulating pro-angiogenic cell populations were associated with outcomes.

Methods: Pts with untreated FL, grade 1-3a, stage 3-4 or bulky stage 2, FLIPI 0-2, were eligible. Treatment consisted of lenalidomide 20 mg/day on days 1-21 of a 28-day cycle for 12 cycles plus rituximab administered weekly x 4 on cycle 1 and day 1 of cycle 4, 6, 8, and 10. Polymorphisms in FcgR2A and FcgR3A were evaluated. Circulating endothelial cells (CEC), endothelial progenitor cells (EPC), and hematopoietic progenitor cells (HPC) were evaluated pre-treatment and at completion of therapy. The primary endpoint was complete response (CR).

Results: Sixty-five pts started treatment and are included in this analysis. The median age was 53 y (range 32-79); 68% were FLIPI 0-1. Fifty-one pts (78.5%) completed 12 cycles of lenalidomide. Reasons for early termination included adverse events ($n = 6$) and patient refusal ($n = 6$) and disease progression ($n = 2$). Grade 3-4 neutropenia occurred in 21%. Infections occurred in 40%, including grade 3 infections in 9% and one (2%) grade 3 febrile neutropenia. Grade 1-2 and grade 3 fatigue were reported in 51 and 4 pts, respectively. Grade 1-2 and grade 3 rash were noted in 32% and 8% of pts, respectively. Other common adverse events included grade 1-2 diarrhea (38%), grade 1-2 constipation (25%), grade 1-2 nausea (25%), grade 1-2 arthralgia (22%). Grade 1-2 thromboembolic events were reported in 3 pts (5%). Notably, grade 3 tumor lysis syndrome was reported in two patients (3%) and grade 3 serum sickness was reported in one pt (2%). Overall, 62/65 (95%) of patients responded, including 72% CR

(95% CI 60-83%). Mean CECs and HPCs decreased significantly compared to baseline ($p < 0.01$ in both), while EPCs remained stable ($p = 0.88$). There was no association between decrease in CEC/HPC or FcgR2A/FcgR3A polymorphism and CR. Sixteen pts have progressed, including 7 pts with a best response of CR, 8 of 9 patients with a best response of PR, and one with SD. With a median follow-up of 5 years, the 2-year, 3-year, and 4-year PFS were 86%, 81%, and 73%. There was no association between FLIPI and CR rate or PFS. Overall survival is 100%.

Conclusion: In this multicenter phase 2 trial, lenalidomide plus rituximab yielded complete responses in 72% of pts with previously untreated FL, meeting the predefined criteria for a positive study. Seventy percent of all patients remain free from progression at 5 years.

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

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L-MIND: MOR208 COMBINED WITH LENALIDOMIDE (LEN) IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (R-R DLBCL) – A SINGLE-ARM PHASE II STUDY

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Introduction: The Fc-enhanced CD19 antibody MOR208 and the immunomodulatory drug LEN have demonstrated single agent activity in patients with R-R DLBCL. MOR208 and LEN have shown synergy in vitro and in vivo in preclinical lymphoma models. This ongoing phase II study was designed to assess the safety and efficacy of MOR208 plus LEN in patients with R-R DLBCL.

Methods: Patients >18 years of age with R-R DLBCL, ECOG performance status 0-2, adequate organ function, having previously received at least 1 but not more than 3 prior therapies, including at

least 1 CD20-targeting regimen and who are not candidates for autologous stem cell transplant (ASCT), are eligible. Treatment comprises up to 12, 28-day cycles of MOR208 12 mg/kg IV, administered weekly during cycles 1–3 (loading dose day 4 of cycle 1) and every second week during cycles 4–12 plus LEN 25 mg administered po days 1–21 of each cycle. Patients progression-free after 12 cycles receive up to 12 additional cycles of MOR208 12 mg/kg IV, administered every second week. The primary endpoint is the overall response rate (ORR) by central radiology assessment. Secondary endpoints include disease control, duration of response, progression-free and overall survival, safety, and response by cell of origin and other biomarkers. A preplanned safety evaluation was undertaken.

Results: 31 of 80 planned patients were enrolled prior to data cutoff (3 January 2017). Median age was 74 years (range 47–82); 45% of patients received ≥ 2 prior lines of therapy; 23% had rituximab refractory disease; 74% had Ann Arbor stage $\geq III$ disease; 65% had elevated lactate dehydrogenase level, and 52% had a poor revised International Prognostic Index (3–5). The most common treatment-emergent adverse events (any grade/grade ≥ 3 [% patients]) were neutropenia (39/26), anemia (23/0) thrombocytopenia (16/6), infections (26/10) diarrhea (13/0), pyrexia (13/0), and rashes (13/6). Of 26 response evaluable patients (median follow-up 3.3 months), ORR (investigator assessed) was 58% (15 patients), with 7 (27%) complete responses. Median time to response was 1.8 months.

Conclusions: The combination of MOR208 plus LEN is well tolerated and shows promising activity in patients with R-R DLBCL. Accrual and follow-up of patients is ongoing, as are cell of origin and other biomarker analyses.

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

37 A PHASE II LYSA STUDY OF OBINUTUZUMAB COMBINED WITH LENALIDOMIDE FOR RELAPSED OR REFRACTORY FOLLICULAR B-CELL LYMPHOMA

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Background: The combination of rituximab (RTX) and lenalidomide (LEN) has been shown to be synergistic in patients (pts) with previously untreated and relapsed follicular lymphoma (FL). A combination of obinutuzumab (GA), a glycoengineered type II anti-CD20 antibody, with LEN (GALEN) might be even more efficient while retaining a similarly manageable safety profile. We determined the recommended GA + LEN dosing in part IB of this study. Here, we report the results of the Phase II part assessing efficacy and safety of GALEN therapy in a cohort of relapsed/refractory (R/R) FL pts (NCT01582776).

Methods: Eligible pts had a ECOG PS ≤ 2 and previously received at least 1 RTX-containing prior regimen. Induction treatment consisted of LEN 20 mg on d 1–21 of a 28-d cycle for the first cycle and on d 2–22 of a 28-d cycle from cycles 2 to 6. GA 1000 mg was given I.V. on d 8, 15, and 22 of cycle 1 and at D1 of cycles 2 to 6. Responding pts then received maintenance with 12 cycles of LEN at 10 mg on d 2–22 every 28 d for 18 cycles and GA 1000 mg every 8 wk for 12 cycles until progression or unacceptable toxicity. The primary study endpoint was overall response rate (ORR) by investigator assessment at the end of induction according to 1999 IWG criteria. Secondary endpoints included ORR and complete response (CR) according to IWG 2007, progression-free survival (PFS), overall survival (OS) and safety.

Results: 89 pts with WHO FL gr 1–2 (73.2%), 3a (15.5%) or unspecified (11.3%) were enrolled between Jun 2014 and Dec 2015. Median age was 64 y, 62.8% men, 83.7% Ann Arbor stage III–IV, 34.9% with bulky lesions (≥ 5 cm) and 31.0% with elevated LDH. Median time from initial diagnosis was 73.7 mo (range, 12–254) and 27.9% had progressed within 2 years of first-line treatment. Median number of prior regimens was 2 (range, 1–7); 26.7% were refractory to a RTX-containing regimen or last prior therapy. 88 pts were assessable for safety and 86 for efficacy. With a median follow-up of 18.1 mo, 75 pts (87.2%) completed induction and 67 (78%) went on maintenance (ongoing in 45 pts). At the time of cut-off, 19 (22.1%) pts progressed and 10 (11.6%) had died mainly due to FL (6 pts). Response at the end of induction, PFS and OS are summarized in the table.

Most common AEs ($>20\%$ of pts) during induction (% all Gr / % Gr 3/4) were gastrointestinal disorders (76.1/2.3), infections (62.5/6.8), asthenia (52.3/2.3), neutropenia (30.7/28.4), muscle spasms (30.7/0), and cough (20.7/0). Febrile neutropenia occurred in 3.4% pts. AEs of special interest were rash (19.3/0), peripheral neuropathy (17.0/1.1), IRR (14.8, 3.4), venous thrombosis (1.1/0). 6 second primary malignancies were reported in 3 pts (5 basal carcinoma and 1 myelodysplastic syndrome).

Conclusion: Oral LEN plus GA infusion is highly effective in relapsed or refractory FL pts with no unexpected toxicity.

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

TABLE		All pts (N=86)	Early relapse pts (within 24 mo of 1 st treatment line) (N=24)	Refractory pts (N=23)
IWG 1999	ORR, % (95%CI)	80.2 (70.2-88.0)	70.8 (48.9-87.4)	60.9 (38.5-80.3)
	CR/CRu % (95%CI)	39.5 (29.1-50.6)	33.3 (15.6-55.3)	34.8 (16.4-57.3)
IWG 2007	ORR, % (95%CI)	74.4 (63.8-83.2)	66.7 (44.7-84.4)	56.5 (34.5-76.8)
	CR, % (95%CI)	44.2 (33.5-55.3)	54.2 (32.8-74.4)	30.4 (13.2-52.9)
1-year PFS	% (95%CI)	75.5 (64.2-83.7)	74.8 (52.2-87.8)	65.2 (42.3-80.8)
1-year OS	% (95%CI)	88.8(79.5-94.0)	86.9 (64.6-95.6)	71.5 (47.1-86.1)

38 PHASE IB STUDY OF CC-122 IN COMBINATION WITH OBINUTUZUMAB (GA101): RELAPSED OR REFRACTORY (R/R) PATIENTS WITH B-CELL NON-HODGKIN LYMPHOMAS (NHL)

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Introduction: CC-122 is a cereblon modulating agent with promising clinical activity in FL and DLBCL. Preclinically, CC-122 with obinutuzumab has improved activity vs either single agent.

Methods: This phase Ib study (EUDRACT 2014-003333-26; NCT02417285) evaluates CC-122 plus obinutuzumab in patients with CD20+ R/R B-cell NHL. Patients with FL/MZL had ≥ 1 prior regimens, or ≥ 2 regimens \pm ASCT for DLBCL. Oral CC-122 was given (5 of 7d for 28-d cycles in escalating doses until PD or unacceptable toxicity) plus IV obinutuzumab (1000 mg, d2, 8, 15 of c1 and d1 of c2-8). CC-122 active ingredient in capsule formulation (AIC) 1, 2, 3, and 4 mg and formulated capsules (F6) of 3 and 4 mg were evaluated in separate cohorts. Primary endpoints included safety/tolerability, non-tolerated dose (NTD), and maximum tolerated dose. Response was assessed per Cheson 2007 criteria every 2 cycles to c6, every 3 cycles to c12, and every 6 cycles thereafter.

Results: As of January 12, 2017, 34 R/R B-cell NHL patients (18 DLBCL [8 transformed FL], 15 FL, 1 MZL) were enrolled. At study entry, patients had a median age of 60 y (range, 26-81), 68% were male, and 76% had stage III/IV disease. Of the 16 FL/MZL patients, 44% relapsed <12 months following first-line treatment. The median number of prior regimens was 4 (range, 1-11), and 13 (38%) patients had received prior SCT. One patient experienced a dose-limiting toxicity of grade 4 neutropenia (CC-122 AIC 3 mg); no dose was yet an NTD. Median CC-122 duration was 22 wks (range, 3-71), equivalent to 6 cycles (range, 1-18). CC-122 dose reduction occurred in 10 (29%) patients and temporary interruption in 26 (76%), mainly due to AEs. Interruption due to AEs was <1 wk in 56% of patients. The most common grade 3/4 treatment-emergent AEs (TEAEs) were neutropenia (50%) and thrombocytopenia (21%). Fifteen patients (44%) had ≥ 1 serious TEAE, including 2 each of febrile neutropenia (related to CC-122), cytokine release syndrome (related to obinutuzumab), and pneumonia. There were 3 deaths during the study (2 PD; 1 AE). ORR was 59% (26% CR; Table 1). Median time to best response was 57 d (median DOR not reached). In evaluable patients, 6-mo PFS was 63%.

Conclusions: CC-122 plus obinutuzumab was well tolerated with favorable response rates and durable remissions in R/R B-cell NHL. CC-122 ≥ 3 mg with obinutuzumab shows the best response rates to date, with deepened response upon prolonged treatment. Study is ongoing to identify the phase II recommended dose.

Data cutoff was 10Feb2017. *3 patients were not evaluable for efficacy.

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

TABLE 1 Best responses with CC-122 and obinutuzumab in evaluable patients.

Response Status, n (%)	R/R DLBCL*n=18	R/R FL/MZL n=16	All Patients N=34
ORR	8 (44)	12 (75)	20 (59)
CR	3 (17)	6 (38)	9 (26)
PR	5 (28)	6 (38)	11 (32)
SD	4 (22)	3 (19)	7 (21)
PD	3 (17)	1 (6)	4 (12)

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PHASE I/IB DOSE ESCALATION AND EXPANSION OF IBRUTINIB AND BUPARLISIB IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA, MANTLE CELL LYMPHOMA, AND FOLLICULAR LYMPHOMA

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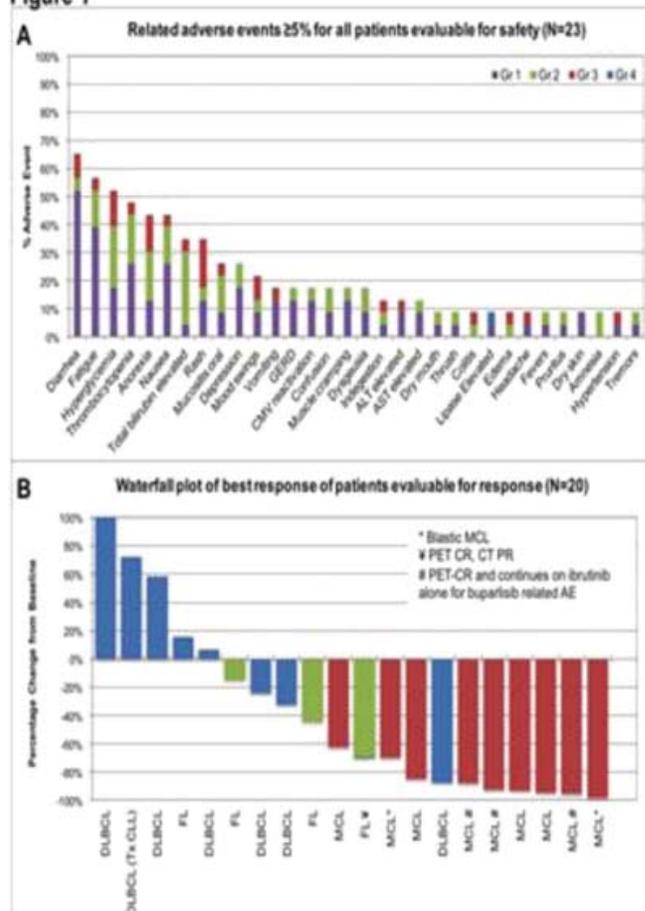
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Introduction: Based on preclinical studies that demonstrated synergism between BTK and PI3K inhibitors in B-cell non-Hodgkin lymphoma, we conducted a phase I/Ib investigator-initiated study of ibrutinib (BTK inhibitor) and buparlisib (pan-PI3K inhibitor) combination in patients (pts) with relapsed or refractory B cell lymphoma.

Methods: Patients (pts) were eligible if they had relapsed/refractory diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL), ECOG ≤ 2 , and adequate organ function. Ibrutinib and buparlisib were given daily by mouth on a 28-day cycle with dose reductions permitted after cycle 1. Tumor response was based on a modified Lugano Classification; with CRs requiring both FDG-PET resolution and \geq PR by CT.

Results: To-date, 25 pts enrolled (DLBCL 10, FL 5, MCL 10) with median prior systemic therapies being 4 for DLBCL (range 1-7), 2 for FL (all had 2 prior regimens), and 1 for MCL (range 1-2). 23 pts completed at least one cycle and were evaluable for toxicity. Pts received escalating doses of once daily ibrutinib and buparlisib in 3 dose levels (ibrutinib 420-560 mg; buparlisib 80-100 mg). Dose level 3 (ibrutinib 560 mg, buparlisib 100 mg) was selected for dose expansion based on 1/6 pt with DLT. Nine patients enrolled on the dose expansion. Four of the first 7 patients enrolled on the dose expansion developed grade 2-3 toxicities requiring dose reductions and/or interruptions, most notably rash and diarrhea. Dose expansions then proceeded at reduced dose level 2 (ibrutinib 560 mg, buparlisib 80 mg) and all patients on buparlisib 100 mg were dose reduced to 80 mg. Adverse events of all grades $\geq 20\%$ related to therapy include diarrhea (65%), fatigue (57%), hyperglycemia (52%), thrombocytopenia (48%), anorexia (43%), nausea (43%), hyperbilirubinemia (35%), rash (35%), depression (26%), mucositis (26%), mood swings (22%) (Figure 1A). Of 23 pt, dose reduction/interruption required for ibrutinib in 11(48%) pt, buparlisib in 14 (61%) pt. All 14 pt treated beyond cycle 3 were able to tolerate subsequent cycles with dose modification as needed for toxicities. Serious adverse events (SAE) related to therapy include: colitis, orthostatic hypotension, cerebrovascular ischemia, rash, diarrhea, fall. One unexpected death from unknown cause occurred in pt on protocol. 20 pts were evaluable for response. The overall response rate (ORR) as follows: DLBCL 14%, FL 25%, MCL 100% (Figure 1B). Targeted sequencing and cell-free DNA analysis is on-going.

Figure 1



Conclusions: Our preliminary results demonstrate that the combination of ibrutinib and buparlisib has a promising clinical activity, especially in pts with MCL. Initial dose expansion of ibrutinib 560 mg, buparlisib 100 mg was associated with excessive toxicity. The study is currently enrolling patients at dose level 2 (ibrutinib 560 mg, buparlisib 80 mg).

Keywords: ibrutinib; non-Hodgkin lymphoma (NHL); PI3K/AKT/mTOR.

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UPDATED RESULTS OF A MULTICENTER PHASE I/IB STUDY OF TGR-1202 IN COMBINATION WITH IBRUTINIB IN PATIENTS WITH RELAPSED OR REFRACTORY MCL OR CLL

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Introduction: The depth and durability of response to ibrutinib in patients (pts) with relapsed/refractory (R/R) MCL and high risk CLL is limited. TGR-1202 is a novel oral PI3K- δ specific inhibitor designed to have less toxicity than other PI3K inhibitors. We hypothesized that combined PI3K/BTK blockade with TGR-1202 and ibrutinib would be tolerable and efficacious in R/R MCL and CLL.

Methods: This is an ongoing phase I/Ib investigator-initiated trial with primary endpoints of recommended phase 2 dose (RP2D) and safety/tolerability. Secondary endpoints include ORR and CR rates, PFS, and OS. Pts receive daily ibrutinib (560 mg MCL, 420 mg CLL) and TGR-1202. TGR-1202 doses from 400 mg to 800 mg were evaluated in a standard 3 + 3 design. Pts continue both drugs until progression or unacceptable toxicity. Eligibility criteria: ≥ 1 prior therapy, ECOG PS ≤ 2 , and adequate hematologic and organ function. Prior PI3K/BTK inhibitors were allowed. Lugano Classification (MCL) and IW-CLL criteria were used to evaluate efficacy.

Results: Thirty-three pts have enrolled on study, including 15 MCL and 18 CLL pts. The median age at enrollment was 67 yrs. (range 48-83). The median number of prior therapies was 3 for MCL (range 2-5, including 4 with prior autoSCT) and 2 for CLL (range 1-6). In CLL pts, del(17p) was present in 4/17 (24%), del (11q) in 7/17 (41%), and unmutated IGHV in 11/17 (65%).

In phase I, no DLTs occurred in either arm, and the RP2D of TGR-1202 for both MCL and CLL was 800 mg. In a combined safety analysis of both arms ($n = 33$), hematologic toxicity included neutropenia (36%, 12% gr3/4), thrombocytopenia (21%, 3% gr3), and anemia (21%, 3% gr3). All grade non-hematologic toxicities in $>10\%$ of pts included: nausea (36%, all gr1/2), fatigue (33%, all gr1/2), diarrhea (33%, all gr1/2), and dizziness (24%, all gr1). Transaminitis (all gr1) was observed in 7/33 (21%) pts. SAEs included 2 pts each with: gr3/4 lipase elevation, gr3 hypophosphatemia, CNS aspergillus infection, and atrial fibrillation, and 1 pt each with: adrenal insufficiency (gr3), influenza A infection (gr4), *C. difficile* infection (gr4), and sudden death of uncertain cause. Two pts had dose reduction of TGR-1202 (dizziness, nausea), and 3 pts had dose-reduction of ibrutinib (atrial fibrillation, palpitations, vitreous hemorrhage). In MCL, with a median time on study of 10.9 mo. (range 1.1-19.8 mo.), the ORR is 85% (11/13), including 1 CR. In CLL, with a median time on study of 11 mo. (range 0.1-23.5 mo.), the ORR is 89% (16/18), with 1 pt achieving iwCLL CR, and 1 pt with radiographic CR. The 1 year PFS and OS for MCL are 37% and 52%, and for CLL both are 94%.

Conclusions: TGR-1202 plus ibrutinib is well-tolerated in pts with R/R MCL and CLL, with no DLTs observed and a RP2D of TGR-1202 800 mg daily. Preliminary efficacy data suggest a high response rate in both diseases. Phase Ib expansion cohorts continue to accrue in this ongoing study (NCT 02268851).

Keywords: chronic lymphocytic leukemia (CLL); ibrutinib; mantle cell lymphoma (MCL).

SESSION 1: LYMPHOMA BIOLOGY

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GB VIRUS-C (GBV-C) INFECTION AND RISK OF LYMPHOMA: A CASE-CONTROL STUDY FROM NORTH AMERICA

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Background: GBV-C is a single-stranded RNA virus belonging to the *Flaviviridae*, and is the most closely related human virus to the Hepatitis C virus. GBV-C is transmitted through parenteral, sexual and perinatal routes and replicates *in vitro* in T and B-lymphocytes. Active infection lasts months to years and viremia can be detected in plasma by real time (RT)-PCR methods. GBV-C viremia has been linked to risk of non-Hodgkin lymphoma in some previous studies, but these have had a limited number of cases. In the largest study conducted to date, we evaluated the association of GBV-C viremia with risk of developing lymphoma, overall and by major subtypes, in the Mayo Clinic Case-Control Study of Lymphoma.

Methods: We used risk factor data and banked plasma samples (stored at -80°C) from 2094 lymphoma cases newly diagnosed from 2002-2009 and 1572 frequency matched controls with no history of lymphoma or leukemia. Plasma samples (blind to case/control status) were tested for GBV-C RNA by RT-PCR, and those with RNA concentrations $<5,000$ genome equivalents/ml were confirmed using RT-PCR again. Unconditional logistic regression model was used to estimate odds ratio (ORs) and 95% confidence intervals (CI), adjusted for age and sex.

Results: The mean age of cases was 61 years, and 58.2% were male, while the mean age of controls was 63 years, and 51.1% were male; 78 (5.0%) controls and 211 (10.1%) cases were GBV-C positive. There was a positive association of GBV-C viremia with risk of lymphoma overall (OR = 2.14; 95% CI 1.63-2.80; $p < 0.0001$), and for all major subtypes except HL and CLL/SLL (Table). Further adjustment for history of hepatitis, transfusion, autoimmune disease, atopy, family history of lymphoma, farming, obesity, smoking, alcohol use, or sun exposure did not confound these results, and results were consistent when excluding plasma samples (38%) collected after initiation of treatment.

Conclusion: GBV-C infection was associated with the overall risk of lymphoma, as well as most of the major NHL subtypes except CLL/SLL and HL, supporting a role for this virus in lymphomagenesis.

Keywords: etiology principles; Hodgkin lymphoma (HL); non-Hodgkin lymphoma (NHL).

TABLE 1 Association of GBV-C infection with NHL overall and NHL subtypes.

	GBV-RNA positivity		
	Total N	N (%)	OR (95% CI)
Control	1572	78 (5.0)	1.00 (reference)
All NHL	2094	211 (10.1)	2.14 (1.63-2.80)
FL	483	70 (14.5)	3.20 (2.27-4.51)
DLBCL	388	38 (9.8)	2.14 (1.64-2.81)
MCL	115	13 (11.3)	2.62 (1.39-4.95)
MZL	184	17 (9.2)	1.98 (1.14-3.43)
TCL	112	12 (10.7)	2.25 (1.18-4.28)
HL	170	13 (7.6)	1.47 (0.76-2.85)
CLL/SLL	400	18 (4.5)	0.90 (0.53-1.53)
Other NHL	242	30 (12.4)	2.71 (1.72-4.27)

42 DRUG PERTURBATION BASED STRATIFICATION OF LYMPHOPROLIFERATIVE DISORDERS

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Background: Mutational landscapes of tumors have been comprehensively mapped, but functional annotation and relation to tumor phenotypes remains largely lacking.

Methods: To understand determinants of drug response, we measured *ex-vivo* sensitivity of 249 blood cancers to 63 drugs alongside genome, transcriptome and DNA methylome analysis.

Results: This dataset, the Primary Blood Cancer Encyclopedia, revealed unexpected disease-specific sensitivities for each studied blood cancer entity (CLL, T-PLL, MCL, FL, AML). Within the largest group comprising $n = 184$ chronic lymphocytic leukemia (CLL) patient samples, response to 61% of drugs was associated with \geq two mutations or cop number alterations. For instance, B-cell receptor (BCR) pathway activity was linked to trisomy 12, an important CLL driver. Drug responses partitioned phenotypic groups, which either relied on BCR signaling or BCR-independent alternative signaling activities. For instance, 15% of CLL were driven by mTOR signaling in a non-BCR dependent manner. These subgroups were characterized by a distinctive mutation-, gene expression- and DNA methylation profile.

The large cohort size empowered us to infer multivariable models for each drug response. We demonstrate that the molecular basis of variable response is multifactorial and can involve multiple layers including gene mutations, gene expression and DNA methylation. We asked which of the 'omic' data types is most important for which class of drugs. For instance, response to chemotherapeutics was predominantly explained by cancer mutations, while response to kinase inhibitors depended on IGHV status, DNA methylation and gene expression patterns. The use of primary patient cells allowed us to assess associations of drug response phenotypes with clinical outcome. For instance, we found that good responses to doxorubicin, fludarabine and nutlin-3 were each predictive of better OS. This effect was only partially explained by *TP53* mutation status, since we found that even within wild type *TP53* CLL, doxorubicin response had predictive value for OS. The independent predictive value of drug response phenotypes was confirmed in multivariable cox regression models using established covariates (age, pre-treatment, trisomy 12, del(11)(q22.3), del(17)(p13), *TP53* mutation, IGHV status) and individual drug responses as continuous variables.

Conclusion: The study shows how phenotypic tumor heterogeneity can be functionally characterized at the level of drug responses, which integrate much more heterogeneous molecular diversity, with implications for biomarker discovery and cancer care.

Keywords: B-cell lymphoma; chronic lymphocytic leukemia (CLL); T-cell lymphoma (TCL).

43 ETS1 POSITIVELY REGULATES FAIM3 IN ACTIVATED B CELL-LIKE (ABC) DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)

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Background: ABC DLBCL is a DLBCL subtype characterized by activation of B-cell receptor signaling (BCR) and the nuclear factor κ B (NF κ B) pathway. The transcriptional factor ETS1 is upregulated in up to 25% of DLBCL (Bonetti, et al. Blood, 2013). Here, we aimed to identify the ETS1 regulated network of genes involved in the pathogenesis of ABC DLBCL.

Methods: Gene expression profiling with the Illumina HumanHT-12 v4 Expression BeadChip arrays was performed on RNA extracted 48 h after electroporation of ABC DLBCL cell lines with ETS1 siRNA or non-targeting siRNA. Differentially expressed genes were identified by linear modelling t-statistics for microarray data using R-package "limma" on ComBat corrected and quantile normalized data and

functional annotation was done by gene set enrichment analysis (GSEA).

Results: Genes downregulated after ETS1 silencing by siRNAs in 5 ABC DLBCL cell lines (TMD8, HBL-1, U2932, OCI-Ly10, SU-DHL-2) belonged to the signaling of BCR (NES 2.45 FDR <0.001), CD40 (NES 2.67 FDR <0.001), and NFkB/TNFA (NES 2.03 FDR 0.01), as well as to inflammatory response (NES 2.14 FDR 0.005) and differentiation (NES 2.5 FDR <0.001). Three candidate genes were selected for further studies according to the following educated guess criteria: i) potential biologic role; and ii) presence of binding sites for ETS factors in their promoter regions. *HCST*, *RGS1* and *FAIM3* were confirmed to be downregulated, by qPCR, also after silencing with shRNA. Their expression in clinical specimens was confirmed in two large series of 181 and 233 DLBCL cases, respectively. *FAIM3* expression was higher in ABC DLBCL cases than germinal center type (GCB) DLBCL in both series ($P < 0.0001$), and a similar pattern was confirmed at protein level in cell lines derived from ABC ($n = 6$) or GCB DLBCL ($n = 8$).

Conclusions: ETS1 positively regulates the expression of fundamental pathways in ABC DLBCL cells, including the BCR signaling. *FAIM3*, which codes for a high affinity IgM FC receptor overexpressed in chronic lymphocytic leukemia, appeared as a novel potential ETS1 transcription target, differentially regulated between ABC and GCB DLBCL, and requires additional investigation.

Keywords: activated B-cell-like (ABC); B-cell receptor (BCR); diffuse large B-cell lymphoma (DLBCL).

44 NOTCH1 MUTATED CHRONIC LYMPHOCYTIC LEUKEMIA CELLS ARE CHARACTERIZED BY A MYC-RELATED OVEREXPRESSION OF NUCLEOPHOSMIN-1 AND RIBOSOME ASSOCIATED COMPONENTS

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Introduction: Stabilizing mutations of *NOTCH1* occur in about 10% of chronic lymphocytic leukemia (CLL) cases at diagnosis, with a higher

frequency in unmutated *IGHV* (*IGHV*-UM), immuno-chemorefractory or advanced disease phase CLL, and have been associated with particularly unfavourable prognosis (Rossi et al., Blood, 2012; Del Poeta et al., Br J Haematol, 2013; Stilgenbauer et al., Blood, 2014). In CLL, *NOTCH1* mutations cause accumulation of the active *NOTCH1* isoform, resulting in a sustained pathway activation. We therefore aimed at identifying molecular/biological features of *NOTCH1* mutated (*NOTCH1*-mut) CLL.

Methods: *NOTCH1* mutations were investigated by NGS. Gene expression profile (GEP) was performed on a one-color 4x44K platform. Validations were performed by QRT-PCR, western blotting, flow cytometry. Cell proliferation was evaluated by CellTrace assay.

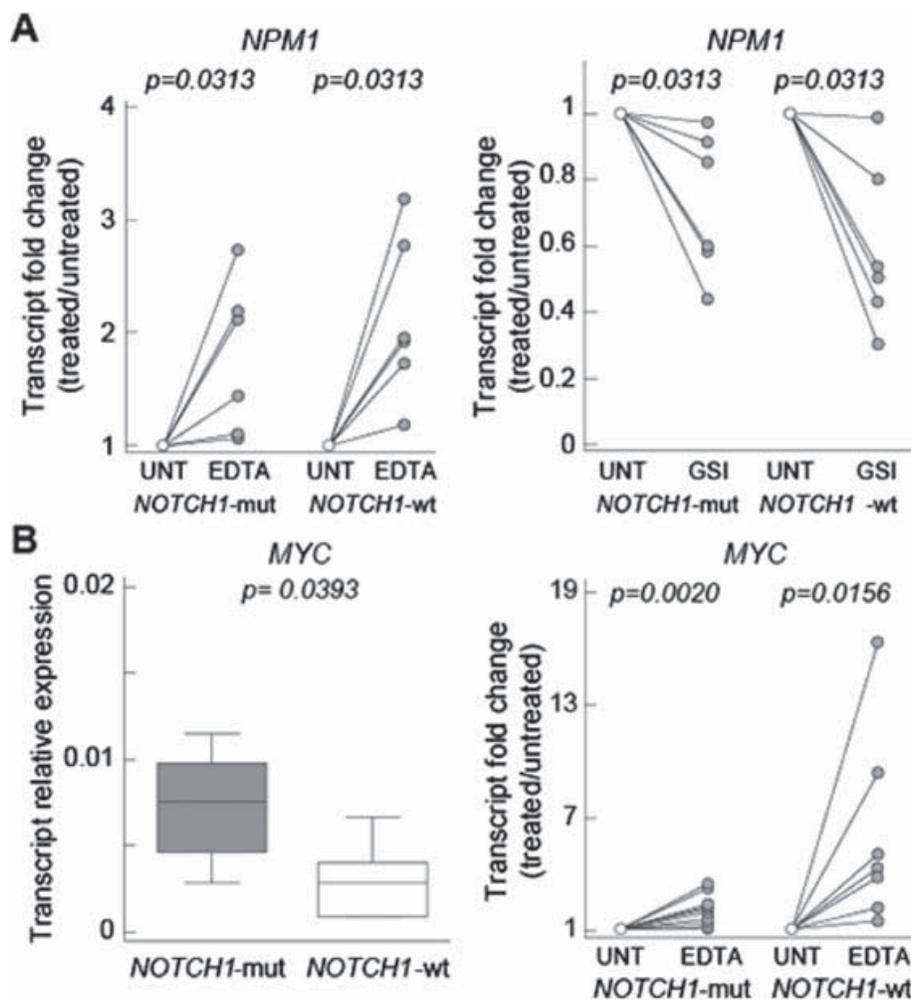
Results: i) A GEP comparing 10 *IGHV*-UM CLL cases (5 *NOTCH1*-mut; 15%-37% of *NOTCH1*-mut alleles) selected nucleophosmin-1 (*NPM1*) and genes codifying for ribosomal proteins (*RNPs*) as up-regulated in *NOTCH1*-mut cases. Results were validated in an independent series of 188 cases (76 *NOTCH1*-mut). ii) Western blotting in 11 CLL cases (5 *NOTCH1*-mut) confirmed a higher *NPM1* protein expression in *NOTCH1*-mut cases, with a direct correlation with *NOTCH1* expression ($r = 0.814$). In *NOTCH1*-mut cases, the *NPM1*^{high} subpopulation, isolated by cell sorting, showed higher mutational load than the *NPM1*^{low} subpopulation. iii) EDTA treatment of 12 CLL cases (6 *NOTCH1*-mut), activated *NOTCH1* signaling, as by *HES1* and *DTX1* induction, and up-regulated *NPM1* and other *RNPs*. The same results were confirmed by co-culture of CLL cells with *JAG1*-expressing M2-10B4 stromal cells. Inhibition of *NOTCH1* signaling by gamma-secretase-inhibitor or by siRNA for *NOTCH1* reduced *NPM1* expression (Figure A). iv) Previous studies identified *MYC* as a direct transcriptional target of *NOTCH1* (Palomero et al., PNAS 2006) and, in turn, a transcriptional activator for *NPM1* and *RNPs*. ChIP assays on MEC1-cells, transfected with exogenous NICD, revealed increased NICD binding to the *MYC* promoter, with higher expression of *MYC*, *NPM1* and *RNPs*. After 48 h culture, *NOTCH1*-mut CLL cells showed increased *MYC* transcript levels than *NOTCH1*-wt cells. *MYC* expression was further increased upon *NOTCH1* activation by EDTA or by stromal co-cultures (Figure B). CpG-ODN/IL-2 treatment, to induce *MYC* overexpression, increased *NPM1* transcript and protein levels in CLL cells, whereas *MYC* silencing by siRNA efficiently reduced *NPM1* expression. v) In turn, *NPM1* silencing by siRNA reduced proliferation rates of both NICD-transfected and control cells.

Conclusions: *NOTCH1* mutations in CLL are associated with the overexpression of *MYC* and *MYC*-related genes involved in protein biosynthesis including *NPM1*, which are allegedly responsible for cell growth and/or proliferation advantages of *NOTCH1*-mut CLL.

Keywords: chronic lymphocytic leukemia (CLL); *MYC*; Notch pathway.

45 ACTIVATION OF RHOA-VAV1 SIGNALING IN ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

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Introduction: Somatic *RHOA* mutations encoding a p.Gly17Val alteration (G17 V *RHOA* mutation) occur in 70% of angioimmunoblastic T-cell lymphoma (AITL). *RHOA*, a small GTPase is converted from the GDP-bound inactive form to the active GTP-bound form by guanine nucleotide exchange factors (GEFs). The G17 V protein lacks GTP binding capacity, suggesting defects in classical *RHOA* signaling; however, mechanisms underlying tumorigenesis remain unknown. *VAV1*

serves as an important mediator of T-cell receptor (TCR) signaling pathway through its GEF-dependent and -independent function.

Methods: The specific binding partner proteins of the G17 V *RHOA* mutant were searched by high throughput screening in Jurkat cells. Targeted deep sequencing of *VAV1* was performed for 126 PTCL samples. Nuclear factor of activated T cell (NFAT) activity in response to TCR stimulation was examined in Jurkat cells transiently transfected with each G17 V *RHOA* and *VAV1* mutant DNA. Whole transcriptome analysis was performed for Jurkat cells inducibly expressing each cDNA in response to TCR stimulation. Expression of phosphorylated *VAV1* was examined by immunostaining for AITL samples.

Results: High throughput screening identified *VAV1* protein as a G17 V *RHOA*-specific binding partner. Targeted deep sequencing and RNA sequencing identified seven *VAV1* alterations out of 85 *RHOA* mutation-negative samples (8.2%), while none of the 41 *RHOA* mutation-positive PTCL samples exhibited *VAV1* alterations (0%). Either G17 V *RHOA* or *VAV1*-STAP2 expression enhanced phosphorylation of *VAV1* at Tyr 174 in Jurkat cells. Phosphorylation was efficiently blocked by the dasatinib treatment. The G17 V *RHOA* and various *VAV1* mutants augmented NFAT reporter activity compared to their WT or mock in Jurkat cells. Moreover, the aberrant reporter activity was also blocked by the dasatinib treatment. Gene set enrichment analysis showed that cytokine and chemokine-related pathways were enriched in Jurkat cells expressing the G17 V *RHOA* compared

to those with WT or mock. Among 12 AITL samples, phosphorylated VAV1 was positive in all 8 AITL samples with *RHOA* or *VAV1* mutations, whereas none of 4 samples without any mutations were stained for phosphorylated VAV1.

Conclusions: The G17 V *RHOA* and *VAV1* mutants both activate TCR pathway through hyper-phosphorylation of VAV1. Our data suggest that the *RHOA-VAV1* axis in AITL may contribute to its clinical features and can be a new therapeutic target.

Keywords: angioimmunoblastic T-cell lymphoma (AITL); T-cell lymphoma (TCL).

46 TARGETABLE FUSIONS OF THE FRK TYROSINE KINASE IN ALK-NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA

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Introduction: Anaplastic large cell lymphoma (ALCL) comprises a group of CD30-positive T-cell non-Hodgkin lymphomas that have unifying pathological features but vary in clinical presentation, genetics, and outcome. About half have rearrangements of the *ALK* tyrosine kinase gene that lead to expression of oncogenic *ALK* fusion proteins, resulting in STAT3 phosphorylation. It has recently become appreciated that *ALK*-negative ALCLs can activate STAT3 signaling through genetic dysregulation of non-*ALK* kinases. Here we identify and describe recurrent rearrangements leading to targetable fusions of the *FRK* tyrosine kinase in *ALK*-negative ALCLs.

Methods: *ALK* status was determined in 30 ALCLs and GEP was performed using Affymetrix gene chips. Molecular signatures were evaluated by supervised and unsupervised clustering and outlier analysis. RNAseq was performed and fusions were detected using SnowShoes. Interphase fluorescence *in situ* hybridization (FISH) was performed in 225 T-cell lymphomas. *In vitro* function was assessed by colony-forming assays in human 293 cells and cell growth and response to tyrosine kinase inhibitors in murine Ba/F3 pro-B cells.

Results: By unsupervised hierarchical analysis, *ALK*-positive ALCLs clustered together and were defined by a gene signature overlapping that reported previously for this disease. Supervised clustering based on this signature showed that a single *ALK*-negative ALCL clustered with *ALK*-positive cases, and could not be segregated on the basis of any gene-set other than *ALK*. Outlier analysis identified the non-*ALK* tyrosine kinase gene *FRK* to be uniquely expressed in this case. RNA-seq on this case identified a *CAPRIN1-FRK* fusion transcript. A novel

breakapart FISH probe validated the *FRK* rearrangement in the index case and identified 5 additional *ALK*-negative ALCLs with *FRK* rearrangements (5.4% frequency among *ALK*-negative ALCLs); FISH was negative in all other T-cell lymphoma subtypes ($p = 0.013$). Lentiviral overexpression of *CAPRIN1-FRK* in 293 cells caused a 2.7-fold increase in colony formation compared to control vector ($p < 0.0001$). In addition, ectopic expression of *CAPRIN1-FRK* in the IL-3-dependent Ba/F3 cell line rescued cells from IL-3 withdrawal. In both cell types, overexpression of *CAPRIN1-FRK* and *NPM-ALK* led to STAT3 phosphorylation. Importantly, the kinase inhibitor, dasatinib, specifically targeted cells expressing *CAPRIN1-FRK* but not *NPM-ALK*.

Conclusions: *FRK* rearrangements are recurrent in T-cell lymphomas and occur exclusively in *ALK*-negative ALCLs. Oncogenic *FRK* fusion proteins represent an alternative kinase-driven mechanism of STAT3 activation in ALCL and can be targeted by the kinase inhibitor dasatinib in experimental models.

Keywords: anaplastic large cell lymphoma (ALCL); chromosomal translocations; JAK/STAT.

SESSION 2: PRIMARY MEDIASTINAL B-CELL LYMPHOMA

47 MOLECULAR CLASSIFICATION OF PRIMARY MEDIASTINAL LARGE B CELL LYMPHOMA USING FORMALIN-FIXED, PARAFFIN-EMBEDDED TISSUE SPECIMENS – AN LLMPP PROJECT

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Introduction: Primary mediastinal large B cell lymphoma (PMBCL) is recognized as a distinct lymphoma entity in the current World Health Organization classification. However, the diagnosis relies on integration of clinical characteristics and presentation since a reliable distinction from diffuse large B cell lymphoma (DLBCL) solely based on morphological or immunophenotypic features can be difficult. Gene expression profiling studies provided evidence that PMBCL can be distinguished from DLBCL on a molecular level and supported a strong relationship between PMBCL and classical Hodgkin lymphoma. Because these studies were performed using snap-frozen tissue, the molecular classification of PMBCL has not penetrated into clinical practice. We sought to develop a robust and accurate molecular assay for the distinction of PMBCL from DLBCL based on gene expression measurements in routinely available formalin-fixed, paraffin-embedded (FFPE) biopsies.

Methods: All cases used in this study were centrally reviewed by a panel of expert hematopathologists in the Lymphoma and Leukemia Molecular Profiling Project consortium. Gene selection was performed using data previously generated on Affymetrix U133 plus 2.0 microarrays and the NanoString platform. The training cohort for the new assay, termed Lymph3Cx, consisted of 68 cases (48 DLBCL and 20 PMBCL); the independent validation cohort comprised 88 PMBCL and 78 DLBCL cases. Cases were required to have a tumor content of $\geq 60\%$ and nucleic acids were extracted from 10 mm FFPE scrolls. Digital gene expression was performed on 200 ng RNA using NanoString technology.

Results: The final Lymph3Cx gene set consisted of 64 probes and included the previously described 20 genes of the Lymph2Cx assay. A probabilistic model accounting for classification error was trained to produce model scores that best distinguished between DLBCL and PMBCL. Cut-points were defined at the 0.1 and 0.9 probability scores. The model, including coefficients and thresholds was then "locked" and applied to the independent validation cohort. The assay yielded gene expression data of sufficient quality in 157/166 cases (94.6%). Among the pathologically-defined PMBCL, 85% were classified as such based on the molecular signature. Ten percent of cases were assigned to the "uncertain" category and 5% showed a molecular signature of DLBCL. Among the pathologically-defined DLBCL cases, 83% were classified as DLBCL by the assay, 14% were "uncertain" and 3% were predicted to be PMBCL.

Conclusion: The newly developed and validated Lymph3Cx assay distinguishes PMBCL and DLBCL based on gene expression signatures and shows high concordance with the pathological classification of an expert hematopathologist panel. Future studies will be needed to determine Lymph3Cx's utility for routine diagnostic purposes and therapeutic decision making.

Keywords: gene expression profile (GEP); primary mediastinal large B-cell lymphoma (PMBCL).

OUTCOME IN PRIMARY MEDIASTINAL B-CELL LYMPHOMA.

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Introduction: Intratumoral heterogeneity can reflect variations in cellularity, angiogenesis, extracellular matrix, or necrosis. High heterogeneity has been associated with treatment failure and poor prognosis in patients with solid cancers and sarcoma. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG PET-CT) has been proposed as a reliable tool to evaluate the metabolic patterns of intratumoral heterogeneity (metabolic heterogeneity, MH). No study to date has investigated MH in lymphomas. This study assessed the prognostic value of MH in primary mediastinal B-cell lymphoma (PMBCL).

Methods: MH was estimated in the PMBCL patients enrolled in the IELSG-26 study. Baseline 18FDG PET-CT scans were evaluable in 103 patients. All were treated with rituximab and doxorubicin-based immunochemotherapy regimens; 93 had consolidation radiotherapy. The mediastinal masses were segmented by a fixed threshold algorithm with a 25% SUVmax cut-off to estimate the metabolic tumor volume (MTV). Maximum standardized uptake value (SUVmax), and total lesion glycolysis (TLG) were also estimated. MH was measured using 2 different methodologies in all patients, namely, the calculation of the SUVmax coefficient of variation (COV) and the estimation of the area under curve of cumulative SUV-volume histogram (AUC-CSH). Higher COV and lower AUC-CSH values correspond to increased MH, respectively. MH cut-off values (COV, > 0.14 for progression and > 0.16 for death; AUC-CSH, ≤ 0.45 for progression and ≤ 0.36 for death) were determined using the receiver operating characteristic (ROC) curve.

Results: The correlation between the two methods was good ($r = -0.73$, $p < .0001$). MH did not show a significant relationship with other quantitative PET-derived parameters (SUVmax, MTV and TLG), with the only exception being a weak ($r = 0.2$) association with MTV when MH was measured as AUC-CSH, however, this correlation disappeared ($r = 0.07$) when MH was measured as COV. Both methodologies generated superimposable results when the impact of MH on treatment outcome was analyzed. At 5 years, overall survival (OS) was 96% for patients with low AUC-CSH heterogeneity vs. 50% for those with high heterogeneity (log-rank test, $p < 0.0001$) while progression-free survival (PFS) was 94% vs. 73%, respectively (log-rank test, $p = 0.0001$). In Cox models including MH, MTV, TLG, and tumor bulk (mediastinal mass > 10 cm), MH was the only predictor of shorter OS ($p = 0.019$), while TLG ($p = 0.0002$) and MH ($p = 0.0002$) retained statistical

48 METABOLIC HETEROGENEITY OF BASELINE 18-FDG PET-CT SCAN PREDICTS

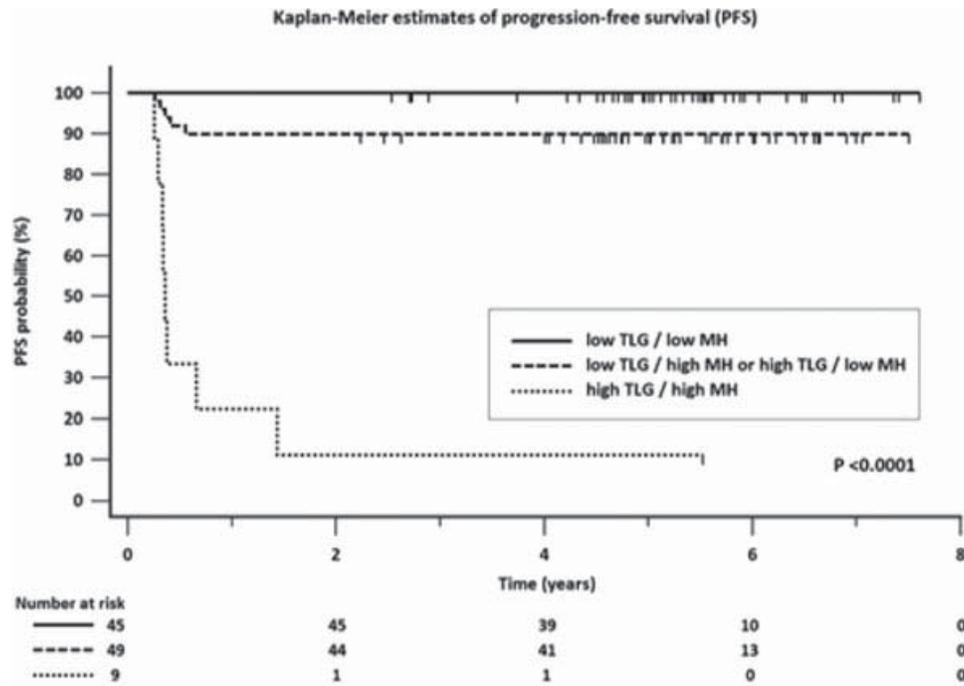


Figure 1. Outcome of 103 patients with PMBCL enrolled in the IELSG-26 study according to the progression risk defined using the combination of MH and TLG values in the baseline 18-FDG PET scan.

significance in PFS analysis. A powerful prognostic model (PPV = 89% and NPV ≥ 90%) based on the combination of MH and TLG at baseline could be built to identify patients with different risk of progression (Figure 1).

Conclusions: MH appears to be a powerful predictor of PMBCL outcomes and warrants further validation as a biomarker. A prognostic model based on TLG and MH may allow the early identification of patients at high risk of disease progression.

Keywords: positron emission tomography (PET); primary mediastinal large B-cell lymphoma (PMBCL); prognostic indices.

49 OUTCOMES OF ADULTS, ADOLESCENTS, AND CHILDREN WITH PRIMARY MEDIASTINAL B-CELL LYMPHOMA TREATED WITH DOSE-ADJUSTED EPOCH-R THERAPY: A MULTICENTER RETROSPECTIVE ANALYSIS

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Introduction: Treatment with dose-adjusted EPOCH chemotherapy and rituximab (DA-EPOCH-R) has become the standard of care for

primary mediastinal B-cell lymphoma (PMBCL) at many institutions despite limited data in the multi-center setting. We report a large, multi-center retrospective analysis of children and adults with PMBCL treated with DA-EPOCH-R to characterize outcomes, specifically assess both pediatric and adult patients, and to evaluate potential prognostic factors.

Methods: 156 patients with PMBCL treated with DA-EPOCH-R across 24 academic medical centers were assessed, including 38 children and 118 adults. All patients received at least one cycle of DA-EPOCH-R. Radiation therapy was administered at the completion of DA-EPOCH-R in 14.7% of patients.

Results: With median follow-up of 22.6 months (range 2.7–101.0 months), the estimated 3-year EFS is 85.9% (95% CI 80.3–91.5) and OS is 95.4% (95% CI 91.8–99.0). Outcomes were similar in pediatric and adult patients. Pediatric patients were more likely to present with bulky mediastinal disease and were more likely to be escalated to at least dose level 4. Thrombotic complications were reported in 28.2% of patients and were more common in pediatric patients (45.9% vs. 22.9%, $p = 0.011$). The sites of thromboses included: upper extremity ($n = 22$), internal jugular vein or superior vena cava ($n = 10$), intracardiac ($n = 5$), pulmonary embolism ($n = 5$), and lower extremity ($n = 2$). Seventy-five percent of patients had a negative FDG-PET scan at the completion of DA-EPOCH-R, defined as Deauville score 1–3. Negative FDG-PET at end-of-therapy was associated with improved EFS (95.4% vs. 54.9%, $p < 0.001$).

Conclusions: Our multicenter data support the use of DA-EPOCH-R for the treatment of PMBCL in children, adolescents, and adults with PMBCL. The high rate of thrombosis suggests that prophylactic anticoagulation should be considered in this setting. Patients with a positive end-of-therapy FDG-PET scan have an inferior outcome and may benefit from augmented or novel therapy.

Keywords: DA-R-EPOCH; primary mediastinal large B-cell lymphoma (PMLBCL).

50 EFFICACY AND SAFETY OF PEMBROLIZUMAB IN RELAPSED/ REFRACTORY PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (RRPMBCL): INTERIM ANALYSIS OF THE KEYNOTE-170 PHASE 2 TRIAL

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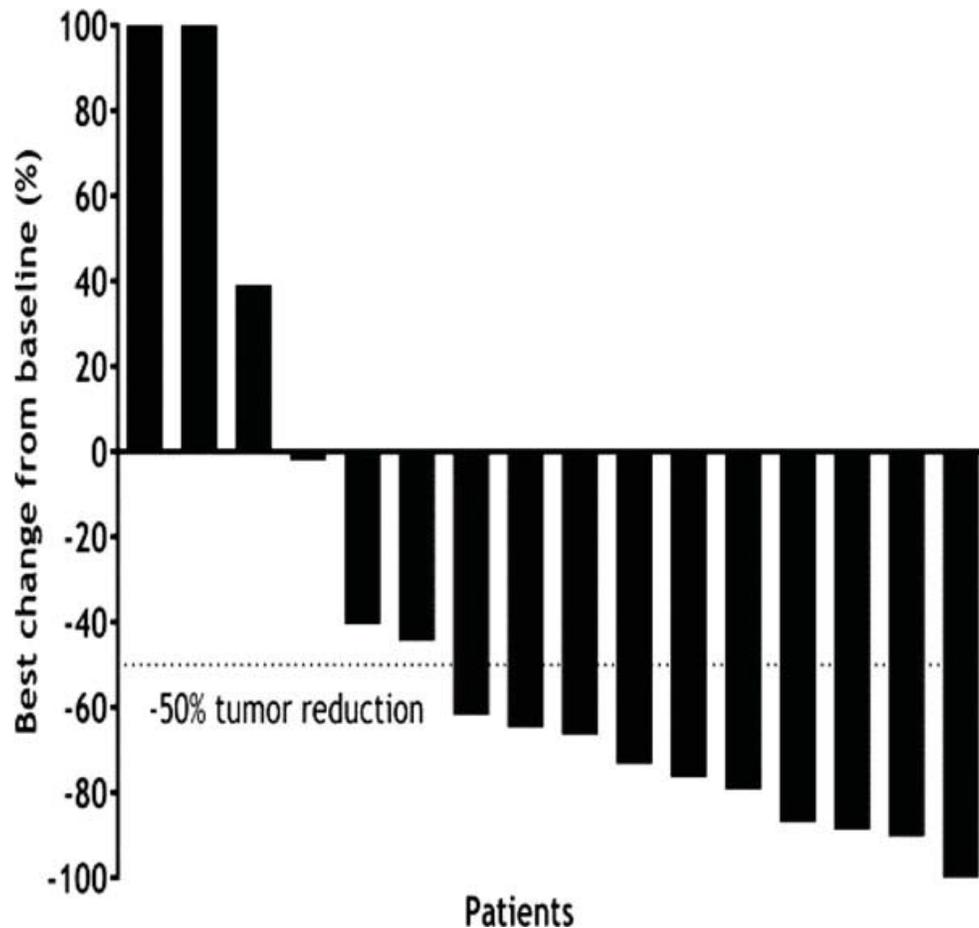
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Introduction: PMBCL frequently harbors genetic abnormalities at the 9p24 locus, resulting in overexpression of the PD-1 ligands PD-L1 and PD-L2. This may serve as an immune evasion mechanism for this tumor type that could be targeted with PD-1 blockade. In a phase 1 clinical trial, the anti-PD-1 antibody pembrolizumab showed promising antitumor activity against rrPMBCL. Here we present interim results from the rrPMBCL cohort of the two-cohort, multicenter, Phase 2 KEYNOTE-170 study (NCT02576990), evaluating safety and efficacy of pembrolizumab in this population.

Methods: This cohort enrolls adult patients with rrPMBCL, who failed or are ineligible for autologous stem cell transplant (auto SCT); patients ineligible for auto SCT must have failed ≥ 2 lines of prior therapy. Patients receive pembrolizumab 200 mg IV every 3 weeks until disease progression, unacceptable toxicity, or completion of 35 treatment cycles. Response is assessed every 12 weeks. Primary end point was objective response rate (ORR) by blinded independent central review (BICR) according to 2007 response criteria. Key secondary end points were ORR by investigator assessment and adverse events (AE).

Results: Patients were enrolled at 14 sites in 9 countries. At the analysis cutoff date (7 December 2016), 33 patients were treated in the rrPMBCL cohort: median age 32 years (range: 20 - 58), 58% female, median 3 lines of prior therapy (range: 1 - 5), 24% with prior radiation, and 70% auto SCT ineligible due to chemorefractory disease. Median follow-up duration was 2.5 mos (range: 0.1 - 9.4); 15 patients discontinued treatment due to progressive disease ($n = 10$), death ($n = 2$), physician decision ($n = 2$), or AE ($n = 1$). At the time of data cut-off, 10 treated patients had not yet reached the first response assessment (none had discontinued). Among the remaining 23 patients, ORR was 35% by BICR and by investigator assessment. By BICR, responses were: 3 complete responses (13%), 5 partial responses (22%), 4 stable disease (17%), 5 progressive disease (22%), and 6 non-evaluable (26%). Median time to response was 2.8 mos (range: 2.4 - 5.5), and all responses were ongoing (range: 0.0 to 5.4 mos) at data cut-off. Among evaluable patients, 81% had target lesion reductions (Figure). Overall, 6/33 patients (18%) experienced serious AEs and 19/33 (58%) experienced drug-related adverse events (DRAEs). Grade 3 DRAEs were neutropenia ($n = 5$ patients), increased hepatic enzymes ($n = 2$), asthenia ($n = 1$), and pneumonia ($n = 1$). One patient had a grade 4 DRAE (neutropenia). There were no drug-related deaths.

Conclusions: In this ongoing global trial, pembrolizumab showed promising antitumor activity and a manageable safety profile in patients



with rrPMBCL (including heavily pretreated patients), similar to results of the Phase 1b KEYNOTE-013 trial. Enrollment is ongoing.

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

SESSION 3: HODGKIN LYMPHOMA

51 RESTORE & TARGET: A CONCEPTUALLY NOVEL TREATMENT APPROACH TO CLASSICAL HODGKIN'S LYMPHOMA

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Introduction: Irrespective of its genomic B-cell origin, classical Hodgkin's lymphoma (cHL) is characterized by the virtual lack of gene products whose expression constitutes the B-cell phenotype. Epigenetic repression of B-cell-specific genes was previously postulated to contribute to the lost B-cell phenotype in cHL. Restoration of the

B-cell phenotype may not only revert a hallmark of cHL but provide a new Achilles' heel by sensitizing cHL to clinically established antibody therapies targeting B-cell surface receptors as well as small compounds interfering with B-cell receptor (BCR) signaling.

Methods: We engineered cHL cell lines to carry a *CD19* reporter, and conducted a high-throughput pharmacological screening with more than 28,000 compounds to identify drugs that promote re-expression of the B-cell phenotype.

Results: We found three chemicals to robustly enhance *CD19* transcription. Since two of them reportedly interfere with epigenetic regulators, we performed chromatin immunoprecipitation assays, showing that these compounds lowered transcriptionally repressive lysine 9-trimethylated histone H3 (H3K9me3) levels at the *CD19* promoter. Inhibition of the H3K9-methyltransferase EHMT2, a possible target structure of these two compounds, by BIX-01294 or shRNA-mediated knockdown resulted in increased *CD19* transcript levels, suggesting that EHMT2 might be involved in repression of the B-cell phenotype in cHL. Furthermore, the anti-leukemic and differentiation-promoting agents arsenic trioxide (ATO) and all-trans retinoic acid (ATRA), both not part of the screened library, were found to reconstitute the silenced B-cell transcriptional program and impair viability of cHL cell lines. In combination with a screening-identified chemical, ATO evoked re-expression of the CD20 surface receptor, which could be therapeutically exploited by enabling CD20 antibody-mediated direct apoptosis and antibody-dependent cellular cytotoxicity of Hodgkin cells. Even more strikingly, restoration of the B-cell phenotype profoundly

sensitized an expanded panel of eight cHL cells towards the B-cell Non-Hodgkin's lymphoma-tailored small compound inhibitors of BCR signaling, ibrutinib and idelalisib, where dramatic death rates were observed after priming with two restore agents. Further investigations, including pre-clinical mouse trials, are currently in progress and will be reported at the meeting.

Conclusions: In essence, we present here a novel "Restore & Target" strategy that builds on the re-expression of a lost tumor cell phenotype in the first place followed by its specific exploration as druggable vulnerability in a subsequent step. Such a strategy would expand the arsenal of treatment options for cHL by a "chemo-free" combination, and might not only be of interest for relapsed or refractory patients.

Keywords: B-cell receptor (BCR); CD20; Hodgkin lymphoma (HL).

52 GENOTYPING OF CLASSICAL HODGKIN LYMPHOMA ON THE LIQUID BIOPSY

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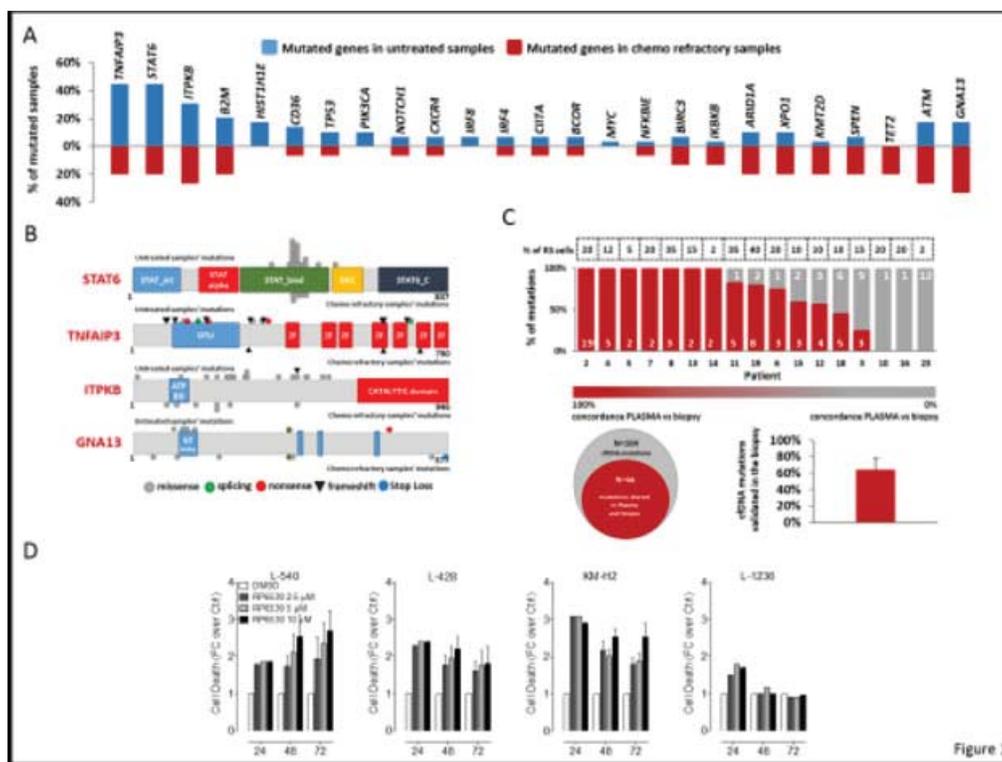
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Introduction: The mutational profile of cHL is poorly characterized, and the genetics of refractory disease is unknown. This study aims at: i) providing the evidence that the mutational profile of cHL can be tracked by using plasma cfDNA; and ii) characterizing the genetics of newly diagnosed cHL and, for comparative purposes, refractory cHL.

Methods: The study includes 29 newly diagnosed and 15 chemorefractory cHL provided with plasma cfDNA and germline gDNA. Paired gDNA from tumor tissue biopsies was available for 17 patients, including 3 cases for which Reed-Sternberg (RS) enriched areas were macrodissected. Plasma cfDNA, normal gDNA and tumor gDNA were subjected to targeted ultra-deep next generation sequencing by using the CAPP-seq strategy and Illumina platforms (sensitivity of 3×10^{-3}).

Results: In newly diagnosed cHL patients, genotyping of plasma cfDNA identified non-synonymous somatic mutations in *STAT6* (45%), *TNFAIP3* (45%), *ITPKB* (31%), *B2M* (21%), *GNA13* (17%) and *XPO1* (10%) among the most recurrent genes. In refractory cHL patients, genotyping of plasma cfDNA identified non-synonymous somatic mutations in *GNA13* (36%), *ITPKB* (29%), *ATM* (29%), *B2M* (21%), *STAT6* (21%), *KMT2D* (21%), *XPO1* (21%), *TET2* (21%) and *TNFAIP3* (14%) (Figure 1A-B). Mutations of *TET2* were enriched in refractory cHL patients compared to newly diagnosed cases, suggesting that they contributed to the chemorefractory phenotype. Consistently, genotyping of longitudinal samples disclosed the acquisition of *TET2* mutations in one refractory patient. By using highly sensitive techniques, most of the mutations discovered in cfDNA were also identified in paired tumor DNA from the tissue biopsy and/or



macrodissected RS cells, thus confirming their tumor origin (Figure 1C). By pathway analysis, the mutational profile pointed to the involvement of PI3K/AKT signaling, cytokines signaling, NF- κ B signaling and immune escape in cHL. *ITPKB* (a negative regulator of PI3K) was specifically mutated in cHL across aggressive B cell lymphomas. In RS cells from wild type cases, the ITPKB protein showed a nucleo-cytoplasmic pattern. Conversely, in RS cells from mutated cases, ITPKB localized only in the cytoplasm, pointing to a functional impact of mutations on the subcellular localization of the protein. Consistent with the involvement of ITPKB in PI3K signaling, the L-1236 cHL cell line, that harbored a truncating mutation of *ITPKB*, was resistant to PI3K inhibitors (RP6530 and AEZS136). Conversely, cHL cell lines harboring a wild type *ITPKB* (L-540, L-428, KM-H2) maintained sensitivity to these compounds (Figure 1D).

Conclusions: This study provides the evidence that cHL can be genotyped by using plasma cfDNA as source of tumor DNA, pointed to a non-overlapping genotype between newly diagnosed and refractory cases, and identified *ITPKB* as a new gene specifically involved in ~30% of cHL patients.

Keywords: Hodgkin lymphoma (HL); molecular genetics; Reed-Sternberg cells.

53 eBEACOPP WITH OR WITHOUT RITUXIMAB IN INTERIM-PET-POSITIVE ADVANCED-STAGE HODGKIN LYMPHOMA: UPDATED RESULTS OF THE INTERNATIONAL, RANDOMIZED PHASE 3 GHSG HD18 TRIAL

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Introduction: FDG-PET (PET-2) after 2 cycles of eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) might be an appropriate tool to guide treatment and predict outcome in patients with advanced-stage HL. In the HD18 trial, we hypothesized that the addition of rituximab to 8 cycles of eBEACOPP could improve the presumably poor progression-free survival (PFS) of PET-2 positive patients. An interim analysis with a median follow-up of 3 years did not show any benefit of this combined immuno-chemotherapy. Here, we report updated results with longer follow-up and the outcome of subsequently enrolled PET-2 positive patients treated with only 6 cycles of eBEACOPP.

Methods: Between May 2008 and July 2014 we recruited patients with newly diagnosed, advanced-stage HL aged 18–60 years. PET-2 was centrally assessed with FDG uptake higher than the mediastinal blood pool defined as positive. Patients with positive PET-2 were randomly assigned to receive six additional cycles of either eBEACOPP or eBEACOPP plus rituximab (R-eBEACOPP). PET-positive residues ≥ 2.5 cm after chemotherapy were irradiated. As result of the previous HD15 study, standard treatment was changed from 8 to 6 cycles in June 2011 and randomization after positive PET-2 was stopped. From there on, all PET-2 positive patients received 6 cycles of eBEACOPP.

Results: We enrolled 2,101 patients. 434 patients with positive PET-2 were randomly assigned to either eBEACOPP ($n = 217$) or R-eBEACOPP ($n = 217$), another 506 PET2-positive patients were assigned to standard treatment with 6xeBEACOPP after June 2011. With a median follow-up of 66 months, estimated 5-year PFS for the randomized comparison was 89.7% (95% CI 85.4–94.0) with 8xeBEACOPP and 88.1% (83.5–92.7) with 8xR-eBEACOPP (log-rank $p = 0.5$). 9 patients (4%) in the 8xeBEACOPP group and 14 (6%) in the 8xR-eBEACOPP group had died; estimated 5-year overall survival was 96.4% (93.8–99.0) with 8xeBEACOPP and 93.9% (90.6–97.3) with 8xR-eBEACOPP (log-rank $p = 0.3$). In patients recruited after June 2011, the estimated 3-year PFS was 92.0% (95% CI 89.3–94.6, median follow-up 36 months) and 3-year overall survival was 98.0% (95% CI 96.7–99.3, median follow-up 37 months) with 6xeBEACOPP.

Conclusions: Updated results confirm that the addition of rituximab to eBEACOPP does not improve the PFS of patients with advanced-stage HL. Importantly, PFS for patients with positive PET-2 is much better than expected and comparable to PET-2-unselected patients treated with eBEACOPP. Thus, PET-2 cannot identify patients at risk for treatment failure in this setting. Importantly, our current analysis shows that this also holds true with the reduced treatment intensity of only 6 cycles of eBEACOPP. We conclude that the high efficacy of the GHSG standard therapy for advanced-stage HL overrides the positive predictive value of PET-2.

Keywords: BEACOPP; Hodgkin lymphoma (HL); rituximab.

54 RESPONSE-ADJUSTED THERAPY FOR ADVANCED HODGKIN LYMPHOMA (RATHL) TRIAL: LONGER FOLLOW UP

CONFIRMS EFFICACY OF DE-ESCALATION AFTER a NEGATIVE INTERIM PET SCAN (CRUK/07/033)

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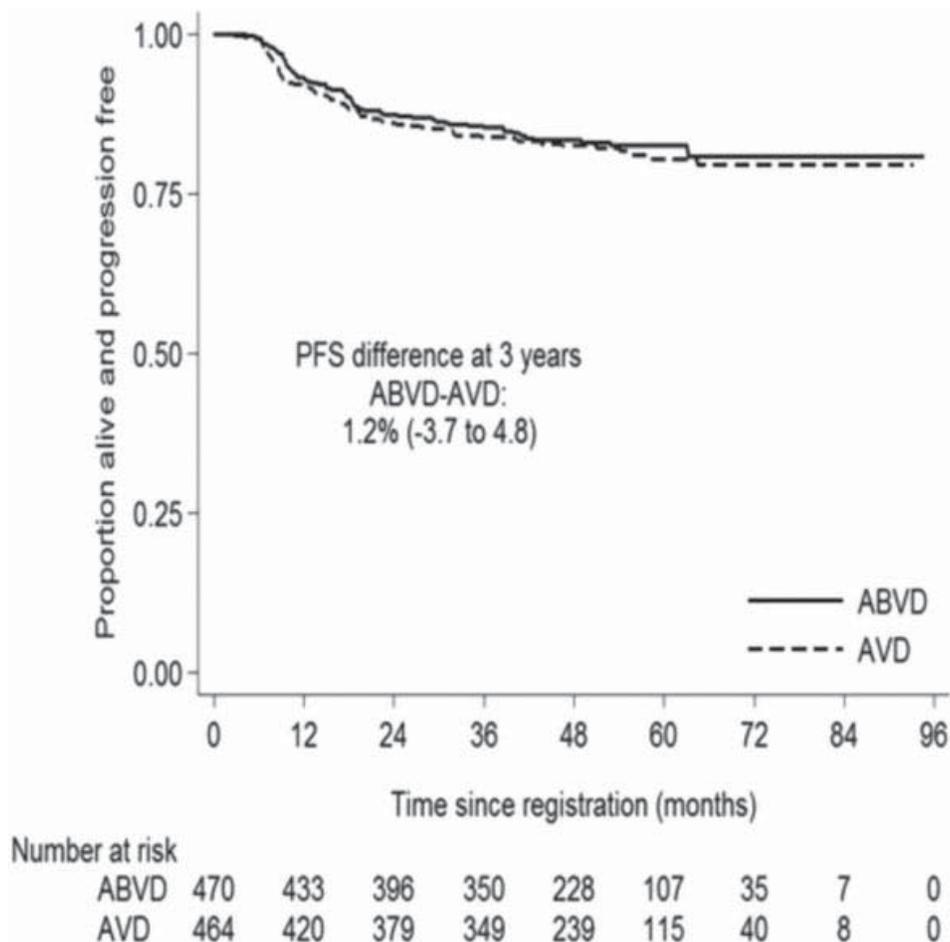
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Introduction: This prospective randomized trial tested whether FDG PET-CT after 2 months of chemotherapy could be used to guide

subsequent treatment for patients with advanced classical Hodgkin lymphoma (HL).

Methods: Adult patients (pts) with newly diagnosed HL (Ann Arbor stages IIB–IV, or IIA with bulk or ≥ 3 involved sites) underwent paired baseline and interim PET-CT scans after 2 cycles of ABVD (PET2). Images were reviewed centrally using the 5-point scale as negative (1–3) or positive (4–5). Pts with negative scans were randomised to ABVD or AVD for 4 more cycles. Pts with positive scans proceeded to intensification with either BEACOPP-14 or escalated BEACOPP. Radiotherapy (RT) was permitted, but not advised for pts with interim negative scans, irrespective of baseline bulk or residual masses.

Results: 1202 eligible pts received treatment. Following a negative PET2, 952 pts were randomised to continue ABVD or AVD. With a median follow-up of 52 months, PFS at 3 years for ABVD was 85.4% (95% CI: 81.9 – 88.4), and for AVD 84.0% (80.3–87.1). The 1.2% difference in 3 yr PFS (95% CI -3.7 - 4.8) now lies within the predefined non-inferiority margin of 5%. There was a similar 5 yr PFS of 82.7% (78.8 – 86.0) and 80.6% (76.2 – 84.2) and OS of 95.3% (93.7 – 97.0) and 95.0% (92.1 – 96.8) for ABVD and AVD respectively. Among 172 pts with a positive PET2, 5 year PFS was 65.7% (57.9 – 72.5) and 5 year OS 85.1% (78.3–89.9%). 197 pts with bulky stage II HL were analysed separately. Eleven patients were not evaluable due to: declined randomisation $n = 2$, death $n = 1$, larceny $n = 1$ and PET scan error $n = 7$. PET2 was negative in 147 (75%): 69 were randomized to ABVD and 7 also received consolidation radiotherapy (RT); 78 received AVD of whom 11 had RT. 3 year PFS was 89% (82.5 – 93.0) with no



significant difference between ABVD and AVD, RT or no RT, presence or absence of a residual mass, or PET score (1-3). The remaining 39 pts with bulky stage II HL and a positive PET2 received BEACOPP. Of the 11 patients receiving RT, there was just 1 progression, despite only 5 reaching conventional CT based CR or CR(u).

Conclusion: With longer follow-up, these RATHL results confirm that the primary study endpoint has been met, reliably excluding a 5% inferior 3 year PFS following de-escalation after a negative interim PET-CT. The omission of bleomycin does not significantly affect PFS or OS in pts with negative PET2. With the caveat that this is a non-randomised subgroup, it appears that in pts with bulky stage II HL, those who achieve a negative PET2 have excellent outcomes without the use of radiotherapy. For those with a positive PET2, escalated therapy with BEACOPP and consolidation RT is effective treatment.

Figure: PFS in randomised PET2 negative patients. Difference at 3 years calculated by applying the hazard ratio (1.08, 95%CI: 0.79 – 1.48) to the 3 year estimate in the AVD arm.

Keywords: ABVD; Hodgkin lymphoma (HL); positron emission tomography (PET).

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BLOCKADE OF THE PD-1 CHECKPOINT WITH ANTI-PD-L1 ANTIBODY AVELUMAB IS SUFFICIENT FOR CLINICAL ACTIVITY IN RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA (CHL)

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Introduction: Classical Hodgkin Lymphoma (cHL) is frequently accompanied by the 9p24.1 amplicon, which contains the PD-L1 and PD-L2 immune checkpoint genes and results in their overexpression. Blockade of PD-1/PD-L1 and PD-1/PD-L2 interactions with anti-PD-1 antibodies is clinically effective; however, it has not been established if blockade of the PD-1/PD-L1 interaction alone is sufficient for therapeutic effect. Avelumab is a fully human IgG1 monoclonal antibody

that selectively binds to PD-L1, leaving the PD-1/PD-L2 interaction intact, thus enabling assessment of the contribution of PD-L2 in the clinical response to PD-1 checkpoint blockade.

Methods: In the phase 1 JAVELIN Hodgkin study (NCT02603419), eligible patients (pts) with histologically confirmed cHL were required to have disease progression following either autologous (auto) or allogeneic (allo) stem cell transplant (SCT), or to be SCT-ineligible. Pts were randomised in equal proportions across 5 avelumab dosing regimens: 70 mg, 350 mg, 500 mg Q2W, 500 mg Q3W, or 10 mg/kg Q2W. Endpoints included safety (NCI CTCAE v4.03) and the objective response rate (ORR) by Response Criteria for Malignant Lymphoma.

Results: As of Feb 9, 2017, 31 pts were randomised and had a median age of 38 years (range 22–81). Five and 8 pts had disease progression following auto-SCT and allo-SCT, respectively; the remaining pts were SCT-ineligible. Pts received a median of 6 cycles (range 1–23) of avelumab to date. In 30 pts analyzed for safety, the most common treatment-related adverse events (TRAEs) of any grade were infusion-related reaction (IRR; 26.7%), nausea (20.0%), rash (20.0%), and fatigue (13.3%). Two pts (6.7%) discontinued treatment due to IRR. Grade ≥ 3 TRAEs occurred in 11 pts (36.7%); there were no treatment-related deaths. Two pts who had received prior allo-SCT developed grade 3 liver graft vs host disease (GVHD), which completely resolved after immunosuppressive therapy and discontinuation of avelumab. ORR across all 31 pts was 54.8% (95% CI 36.0–72.7) with 2 complete responses (CRs; 6.5%) and 15 partial responses (PRs; 48.4%). Responses were observed in all dosing groups (ORR range 14.3%–83.3%). ORR in the 5 post-auto SCT pts was 20.0% (95% CI 0.5–71.6) with 1 PR. ORR in the 8 post-allo SCT pts was 75.0% (95% CI 34.9–96.8) with 1 CR (12.5%) and 5 PRs (62.5%).

Conclusions: Avelumab appears to have clinical activity with an acceptable tolerability profile in pts with heavily pretreated cHL. The ORR was similar to that observed with PD-1 inhibitors, indicating that targeting PD-L2 may not be necessary or sufficient for the therapeutic effect observed following PD-1 checkpoint blockade in cHL. The high ORR observed in the post-allo SCT setting suggests that checkpoint inhibitors may enhance the graft vs lymphoma response; however, more mature data are required to assess the benefit–risk of PD-1 checkpoint blockade regarding GVHD in this setting.

Keywords: classical Hodgkin lymphoma (cHL); Reed-Sternberg cells.

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COMBINED RISK OF SECOND MALIGNANT NEOPLASMS AND CARDIOVASCULAR DISEASE IN LONG-TERM HODGKIN LYMPHOMA SURVIVORS

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Background: Hodgkin lymphoma (HL) survivors are at increased risk of late treatment-related complications, including second malignant neoplasms (SMNs) and cardiovascular diseases (CVDs). Research to date has focused on separate risk estimates for these outcomes. We aimed to examine the combined risk of SMN and CVD, providing more insight into the total burden of morbidity from these severe late effects.

Methods: Our cohort comprised 2,908 5-year HL survivors, treated before age 51 in 1965-2000. CVD endpoints, including coronary heart disease, cardiomyopathy/congestive heart failure, and valvular heart disease (\geq grade 2 according to the CTCAE, vs. 4.0), were assessed through general practitioners. Data on SMNs were obtained from linkage with the Netherlands Cancer Registry. Cumulative incidences of SMN and/or CVD were calculated with death from other causes as competing risk. Treatment-specific risks of developing SMN and/or CVD were quantified using Cox regression. The mean cumulative count (MCC) was calculated as the average number of events per individual in our cohort over a given follow-up period, as an alternative measure of burden from SMN and CVD events.

Results: Median age at HL treatment was 27.3 years. The majority of patients received either radiotherapy (RT) only (27.1%) or RT in combination with chemotherapy (CT; 65.9%). Among patients treated with RT, 24.5% received mantle field irradiation only, 16.2% incomplete mantle field only and 32.7% received (sub)total nodal irradiation. RT was applied using parallel opposed fields. Forty percent of all patients received anthracycline containing CT. After a median follow-up of 22 years, we identified 888 SMNs and 1,045 CVDs. 1247 patients developed \geq 1 event; of those 240 developed both SMN and CVD. After a follow-up of 40 years, at a median attained age of 60 years, the cumulative incidence of SMN or CVD was 67.8% (95%CI: 65.1-70.4) and the cumulative incidence for developing both SMN and CVD was 17.2% (95%CI: 15.0-19.6). Overall, an average of 1.2 events per patient (MCC) over a follow-up period of 40 years was observed. Compared to no or limited RT, both incomplete mantle field and mantle field RT were associated with increased risks of SMN or CVD (HR: 1.9, 95% CI: 1.4-2.5 and HR: 2.6, 95% CI: 2.1-3.4, respectively). Anthracycline-chemotherapy (HR: 1.3, 95%CI: 1.1-1.5) independently increased the risk of SMN or CVD. The 25-year cumulative incidence of SMN or CVD was 28.2% (95% CI, 17.1-40.3) in patients treated with anthracyclines and no or limited RT fields, 37.6% (95% CI, 26.8-48.4) after anthracyclines in combination with incomplete mantle field RT, and 51.4% (95% CI, 42.2-59.8) after mantle field RT without anthracyclines.

Conclusions: HL survivors treated between 1965 and 2000 experience a high disease burden from SMN and CVD during follow-up. Supradiaphragmatic RT increased the risk of developing either SMN or CVD more strongly than anthracyclines.

Keywords: Hodgkin lymphoma (HL).

SESSION 4: TARGETING THE BCR PATHWAYS

57 CLINICAL OUTCOMES AND MOLECULAR CHARACTERIZATION FROM A PHASE II STUDY OF COPANLISIB IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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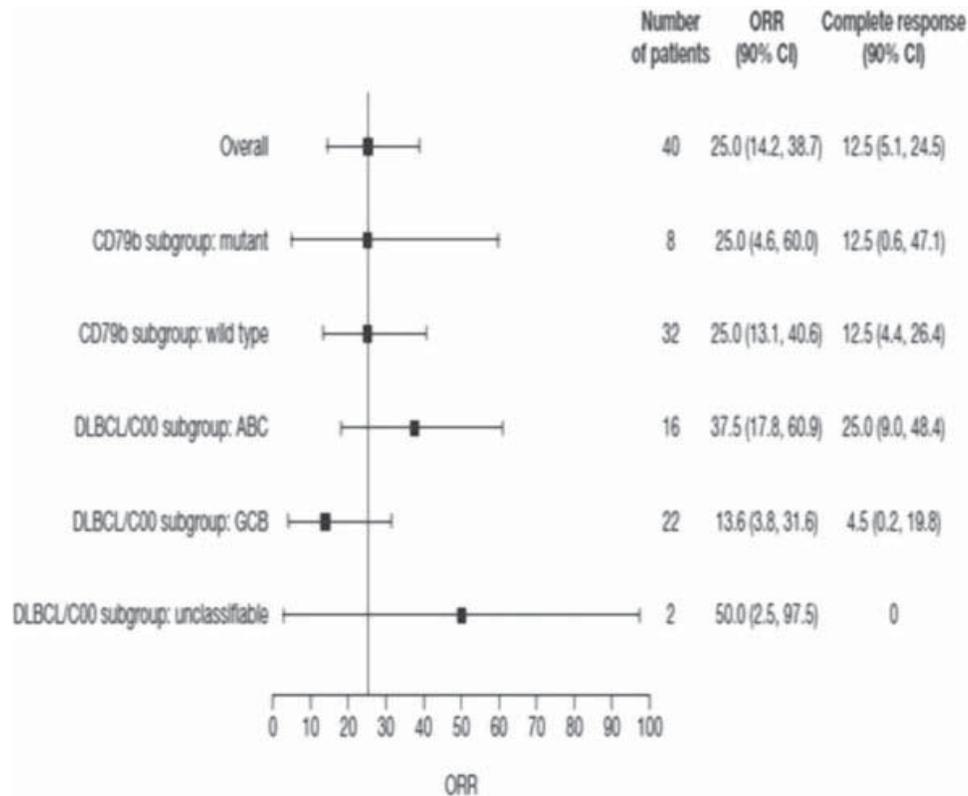
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Introduction: Relapsed/refractory diffuse large B-cell lymphoma (DLBCL) patients are characterized by poor prognosis. Copanlisib is a pan-Class I phosphatidylinositol 3-kinase (PI3K) inhibitor, with modest single-agent activity in unselected DLBCL patients. Here we report the treatment effect of copanlisib in relapsed/refractory DLBCL patients with regards to cell of origin (COO) and molecular biomarker profiles (NCT02391116).

Methods: Patients with relapsed/refractory DLBCL and \geq 1 prior lines of therapy were eligible. Copanlisib (60 mg IV infusion) was administered intermittently on days 1, 8 and 15 of a 28-day cycle. Tumor samples were evaluated for COO, CD79B mutations and >400 genes by next generation sequencing (NGS). The primary endpoint was objective tumor response rate (ORR; per Lugano Classification, 2014) and response by COO and CD79B status.

Results: The full-analysis (FAS) and per-protocol sets (PPS; \geq 3 doses, post-baseline scans and COO/CD79B data) included 67 and 40 patients, respectively. Patients were 58% male, median age 69 (range 25-93), ECOG status 0/1/2 22%/57%/21%, and heavily pretreated (median prior lines = 3, range 1-13). In the PPS, COO (and mutant CD79B status) analysis identified 22 GCB DLBCL (2 mutant), 16 ABC DLBCL (6 mutant), and 2 unclassifiable. The ORR in the FAS was 19% (13 of 67). For patients in the PPS, the ORR was 25% (10 of 40), with 5 complete responses (CR) and 5 partial responses (PR);



stable disease in 12 pts. The ORR was 13.6% with 1 CR in GCB pts and 37.5% with 4 CRs (25%) in ABC patient. Response to copanlisib was 25% in pts with (2/8) and without (8/32) CD79B mutations. Five of 10 ABC DLBCL-wild-typeCD79B patients and one GCB DLBCL-mutantCD79B responded (ongoing >17 cycles). NGS analysis in 54 patients detected 348 mutations; BCL2 (54% of patients), TP53 (41%), BCL6 (30%), MYC (22%), CD79B (19%)/A (6%), MYD88 (19%), TNFAIP3 (17%), CARD11 (13%), and NFKBIA (9%). Response to copanlisib was not significantly different based on mutation status of BCL2 (ORR 17% [4/24] vs 35% [7/20] for mutant and wild-type subsets, respectively), BCL6 (ORR 17% [2/12] vs 28% [9/32]), MYC (ORR 13% [1/8] vs 28% [10/36]), and MYD88 (ORR 25% [2/8] vs 25% [9/36]). With a median of 6 cycles (range 1-29), the most common AEs (% all grade/gr3 + 4) were diarrhea (36/2), nausea (31/2), fatigue (31/3), fever (21/2) and transient hypertension (40/33) and hyperglycemia (34/31). There were 14 grade 5 AEs (none drug-related).

Conclusions: Copanlisib treatment of relapsed/refractory DLBCL patients resulted in encouraging responses, especially in the ABC subtype, with a manageable toxicity. Further study of copanlisib in treatment of DLBCL is warranted.

Keywords: diffuse large B-cell lymphoma (DLBCL); PI3K/AKT/mTOR.

58 DYNAMO: A PHASE 2 STUDY DEMONSTRATING THE CLINICAL ACTIVITY OF DUVELISIB IN PATIENTS WITH DOUBLE-REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA

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Introduction: Duvelisib is an oral, dual inhibitor of PI3K- δ, γ being developed to treat hematologic malignancies.

Methods: DYNAMO is an open-label, single-arm, safety, and efficacy study in patients (pts) with follicular lymphoma (FL), small lymphocytic lymphoma (SLL), or marginal zone lymphoma (MZL), whose disease is double-refractory to rituximab and to chemotherapy or radioimmunotherapy. Pts received duvelisib 25 mg BID in 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint is overall response rate (ORR) as assessed by an independent review committee (IRC) per revised IWG criteria, with significance tested against the null hypothesis that ORR was $\leq 30\%$ per IRC. Secondary endpoints include duration of response (DoR), progression-free survival (PFS), overall survival (OS), time to response (TTR), adverse events (AEs), and changes in safety laboratory values. *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis was mandated for all pts.

Results: 129 pts received duvelisib (FL = 83; SLL = 28; MZL = 18) with a median duration of exposure of 6 mo. (range 0.4 - 24). Median age was 65 years; 68% were male. Median time from last anticancer therapy to first dose of duvelisib was 3.5 months. Pts received a median of 3 prior anticancer regimens (range 1 - 18), and 40% of pts ≥ 4 regimens. 77% had disease refractory to ≥ 2 anticancer regimens and 96% were refractory to their last anticancer regimen.

IRC-assessed ORR was 46% ($p = 0.0001$) (all PRs), and Investigator-assessed ORR was 58% (2 CRs). Median TTR was 1.9 mo. (range 1.4 - 11.7). 83% of pts had reduction in nodal target lesions after treatment with duvelisib. AEs were mostly Gr 1-2. Most common \geq Gr 3 AEs were transient cytopenias (neutropenia [23%], anemia [12%], and thrombocytopenia [10%]), and diarrhoea (15%). 17% of pts discontinued duvelisib due to an AE. Opportunistic infections occurred in $<5\%$ of pts, none fatal, and were: 1 pt with *pneumocystis*; 3 pts with CMV infections. Six pts had an AE with outcome of death.

Conclusions: In DYNAMO, duvelisib met its primary efficacy endpoint for ORR (p -value = 0.0001 against null hypothesis that ORR $\leq 30\%$) in a double-refractory iNHL population, with a 46% ORR, med. DoR 9.9 mo., and 83% with reduction in target lesions. Duvelisib was generally well tolerated, with a manageable safety profile with appropriate risk mitigation. Duvelisib monotherapy has a favorable benefit-risk profile in double-refractory iNHL, and may represent an important treatment option. Mature clinical data will be available at the time of presentation.

Keywords: indolent lymphoma; PI3K/AKT/mTOR; small lymphocytic lymphoma (SLL).

TABLE 1 Efficacy Results per IRC.

	Overall	FL	SLL	MZL
	N=129	N=83	N=28	N=18
ORR, %	46	41	68	33
DoR (mo.), median	9.9	9.2	9.9	NE
PFS *	8.4	8.3	11.3	NE
OS *	18.4	11.1	NE	NE

NE = not estimable

* Median follow-up 11.5 mo.

59 BRUTON'S TYROSINE KINASE (BTK) INHIBITOR BGB-3111 DEMONSTRATES HIGH VERY GOOD PARTIAL RESPONSE (VGPR) RATE IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA (WM)

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Introduction: BTK inhibitors have been shown to be highly active in WM, particularly WM harboring a MYD88 mutation (*MYD88^{MUT}*). BGB-3111 is a potent, specific, and irreversible BTK inhibitor. In primary patient (pt) samples, BGB-3111 demonstrated profound BTK inhibition with minimal inhibition of off-target kinases such as EGFR, ITK, JAK3, HER2, and TEC. In phase 1 testing, high plasma concentrations were safely achieved, resulting in complete, sustained BTK inhibition in blood and lymph nodes.

Methods: This was an open-label, multicenter, dose-finding phase 1 study of BGB-3111 in pts with B-cell malignancies, with indication-specific expansion cohorts. Here, updated safety and efficacy in WM are reported.

Results: As of 31 Dec 2016, 46 pts with WM were enrolled: median 2 prior therapies (range 0-8), median follow-up 8.2 months (1.4-28), 46 evaluable for safety, 41 for efficacy; 5 non-evaluable pts had either baseline IgM <500 mg/dL ($n = 3$) recent plasmapheresis ($n = 1$) or <12 weeks' follow-up ($n = 1$). The most frequent adverse events ($\geq 20\%$, all grade [Gr] 1 or 2) were upper respiratory infection (33%), contusion (28%), and constipation (22%). There were 3 treatment-related serious adverse events (Gr 2 atrial fibrillation [AF], Gr 2 headache, Gr 3 cryptococcal meningitis); in all 3 cases, BGB-3111 was withheld and safely resumed. 3 pts developed AF (one Gr 1, two Gr 2), and 1 developed Gr 3 diarrhea. No serious hemorrhage was reported. The objective response rate was 93% (38/41), with a major response rate of 78% (32/41): VGPR in 39% (16/41) and PR in 39% (16/41). Median time to response was 28 days. Response by *MYD88* and *CXCR4* mutational status, in pts with known status ($n = 32$) is shown in Table 1. In pts with hemoglobin <10 g/dL at

baseline, hemoglobin increased from a median of 8.8 g/dL (7.1-9.8) to 13.8 g/dL (10.7-16.1). IgM decreased from a median of 32.5 g/L (6-88.5) at baseline to 5.4 g/L (0.4-47.8). 16 pts with baseline lymphadenopathy had a median reduction in SPD of 38% (9-81%). 2 pts (both in VGPR) have discontinued BGB-3111 for exacerbation of pre-existing bronchiectasis and prostate adenocarcinoma. The sole

pt with disease progression remains on BGB-3111 with ongoing clinical benefit.

Conclusions: BGB-3111 is well tolerated and highly active in WM. Response depth, especially VGPR rate, and durability appear favorable. A phase 3 study comparing BGB-3111 with ibrutinib in WM is ongoing.

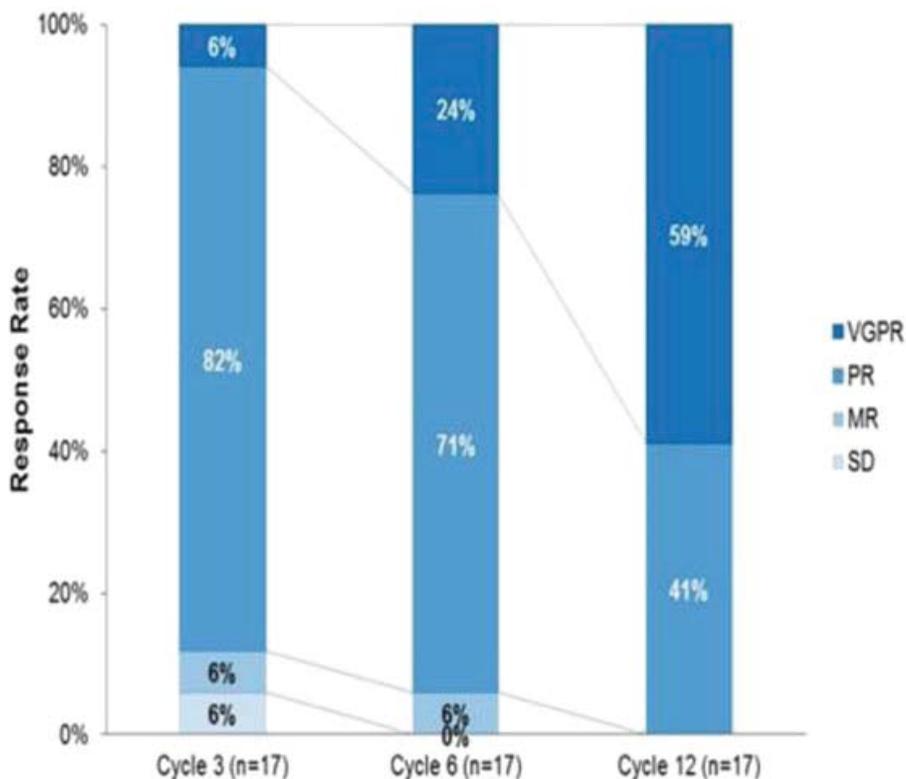
Keywords: BTK; MYD88; Waldenström's macroglobulinemia (WM).

TABLE 1 Best response by follow-up time and mutational status.

Best response by MYD88/CXCR4 mutational status				
	Best response (N=32)	MYD88 ^{L265P} /CXCR4 ^{WT} (N=24)	MYD88 ^{L265P} /CXCR4 ^{MUT} (N=3)	MYD88 ^{WT} /CXCR4 ^{WT} (N=5)
VGPR	11 (34%)	10 (42%)		1 (20%)
PR	12 (38%)	9 (38%)	2 (67%)	1 (20%)
MR	7 (22%)	4 (17%)	1 (33%)	2 (40%)
SD	2 (6.2%)	1 (4.2%)		1 (20%)
Best response by duration of follow up				
	Best response (N=41)	>12 weeks of f/u(N=41)	>24 weeks of f/u(N=28)	>1 yr of f/u(N=17)
VGPR	16 (39%)	2 (4.9%)	4 (14%)	10 (59%)
PR	16 (39%)	25 (61%)	17 (61%)	7 (41%)
MR	6 (14%)	10 (24%)	5 (18%)	0 (0%)
SD	3 (7.3%)	4 (9.8%)	2 (7.1%)	0 (0%)
PD	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ORR	93%	90%	93%	100%
MRR	78%	66%	75%	100%

f/u, follow-up; MR, minor response; MRR, major response rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

Figure 1. Improving depth of response for 17 pts with >1 year of f/u



60 IBRUTINIB IN RELAPSE OR REFRACTORY PRIMARY CNS AND VITREO-RETINAL LYMPHOMA. RESULTS OF THE PRIMARY END-POINT OF THE ILOC PHASE II STUDY FROM THE LYSA AND THE FRENCH LOC NETWORK

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Primary CNS lymphoma (PCNSL) is a diffuse large B-cell lymphoma (DLBCL), predominantly of non-germinal center (non-GC) subtype, with a constitutive activation of the NF- κ B pathway. Mutations in B cell receptor (BCR) pathway (*CD79B*) and mutation of *MYD 88* and *TBL1XR1* play an important role in PCNSL. Ibrutinib is an inhibitor of BCR signaling, with a significant therapeutic activity in relapsed or refractory non-CNS non-GC DLBCL.

This prospective, multicenter, open-label phase II, was designed for immuno-competent patients over 18 with a refractory or relapse of PCNSL or primary vitreo-retinal lymphoma (PVRL) of DLBCL type. The treatment consisted in ibrutinib monotherapy given orally at 560 mg daily until disease progression or unacceptable toxicity. Additional corticosteroids treatment was allowed during the first 4 weeks of treatment in case of a threatening or symptomatic edema. The primary objective of the study was the disease control (DC) rate (CR + CRu + PR + SD) after two months of treatment. Patients were evaluable for response if they received $\geq 90\%$ of the expected dose during the first month of treatment. A total of 35 evaluable patients were required for the final analysis (PO < 10%; P1 hypotheses >30%). Results of the interim analysis were encouraging with a DC achieved in 15/18 patients (83%, IC 95%, [59-96%]) after two months of treatment. NCT02542514.

Between September 2015 and June 2016, 52 patients were recruited in 10 French centers of the French LOC network for PCNSL.

Forty-three patients (24 females; 19 males) are evaluable for response (median age: 70 y, range 52-81). Initial diagnoses were PCNSL ($n = 30$) and PVRL ($n = 13$). Patients were included in the study for a relapse ($n = 31$) or a progressive disease ($n = 12$). At time of inclusion in the study, disease status was PCNSL ($n = 29$) and PVRL or isolated intra-ocular relapse of a PCNSL ($n = 14$). Four patients had a concomitant meningeal involvement. ECOG performance status was 0, 1 and 2 in 11, 22 and 10 patients respectively. All the patients had previously received high-dose methotrexate-based chemotherapy. Six patients had previously received high-dose chemotherapy followed by autologous stem cell transplantation. Patients had received ≥ 2 prior treatments in 25 cases. Twenty-seven patients prematurely interrupted ibrutinib treatment between cycle 2 and cycle 15 (median time: 3 months, range, 0.9-13 months), because of a progressive disease ($n = 22$), toxicity ($n = 1$, grade 3 hyphema), other ($n = 4$). Among the 52 patients included in the study, two patients experienced a pulmonary aspergillosis with a favorable ($n = 1$) and a fatal outcome ($n = 1$). Ibrutinib was detectable in the CSF (> 0.15 ng/ml) in all the samples tested ($n = 26$). Thirteen patients are currently on treatment ≥ 6 months, including 8 patients ≥ 12 months. The analysis of the primary end-point of the 43 evaluable patients is ongoing and results will be presented.

Keywords: ibrutinib; primary CNS lymphoma (PCNSL).

61 TAK-659, AN INVESTIGATIONAL REVERSIBLE DUAL SYK/FLT-3 INHIBITOR, IN PATIENTS WITH LYMPHOMA: UPDATED RESULTS FROM DOSE-ESCALATION AND EXPANSION COHORTS OF A PHASE 1 STUDY

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Introduction: Spleen tyrosine kinase (SYK) is a nonreceptor kinase with a key role in B-cell receptor signaling-driven tumourigenesis and is a key regulator of FMS-like tyrosine kinase 3 (FLT-3). SYK is also involved in CD38 signaling in chronic lymphocytic leukemia (CLL) (Benkisser-Petersen et al. PLoS One 2016:e0169159). TAK-659 selectively inhibits SYK/FLT-3 activity, resulting in inhibition of cell proliferation in vitro and dose-dependent tumor growth inhibition in lymphoma xenograft models. The dose-escalation phase of this study determined 100 mg (daily dose, QD) as the MTD/RP2D of TAK-659 in patients (pts) with advanced solid tumors/lymphoma (Petrich et al. Blood 2015;1262693). Here we report updated data for the lymphoma population from the dose-escalation and expansion cohorts.

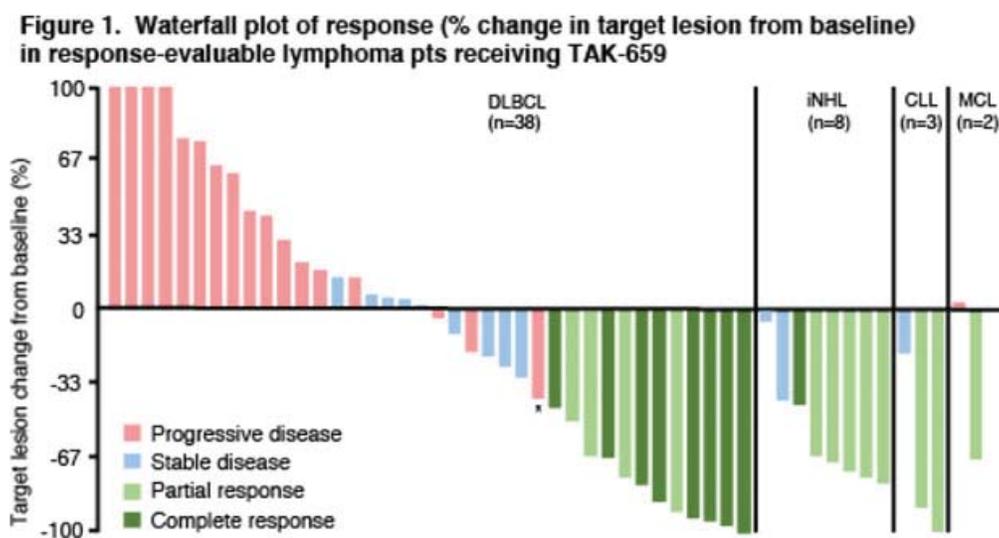
Methods: Adult pts with relapsed and/or refractory lymphoma received oral TAK-659 60–120 mg (escalation) or 100 mg (expansion; including CLL, DLBCL, iNHL, MCL and PTLD) QD in 28-d cycles. Adverse events (AEs) were assessed per NCI-CTCAE v4.03. Plasma and urine PK assessments occurred during C1 in dose escalation. Response was assessed using IWG modified criteria (lymphoma) or IWCLL criteria (CLL) between d22 and d29 (predose) of C2 (both phases), then during C4, C6 and every 3 cycles (escalation), or every even numbered cycle until C12, then every 4 cycles (expansion).

Results: At data cut-off (12 Jan 2017), 77 pts with lymphoma (DLBCL 57; iNHL 11; CLL 5; MCL 3; PTLD 1) received TAK-659 60–120 mg QD (69 pts at 100 mg). Median age was 65 yrs (range 23–84), 52 pts (68%) were male. Pts received a median of 2 (range, 1–31) treatment cycles. Response and outcomes among 57 response-evaluable pts are shown in Table 1 and Figure 1. Of 52 (68%) pts with ≥1 drug-related Gr ≥3 AE, the most common AEs were elevated amylase (25%), hypophosphatemia (18%), neutropenia (16%), elevated blood creatine phosphokinase and elevated lipase (both 12%); enzyme elevations were generally asymptomatic. Of 23 lymphoma pts who died on study, 3 were considered drug-related (respiratory failure, multiorgan failure, and disseminated varicella). TAK-659 was absorbed quickly (median T_{max}: 2 h), with moderate variability (50% CV) in dose-normalized

TABLE 1 Response outcomes in response-evaluable pts[†] receiving TAK-659

	DLBCL (n=44)	iNHL (n=8)	CLL (n=3)	MCL (n=2)
Best response, n (%)CR/PR/CR+PR	8 (18)/4 (9)/12 (27)	1 (13)/5 (63)/6 (75)	0/2 (67)/2 (67)	0/1 (50)/1 (50)
Median treatment duration in responding pts, days (range)	283.5 (53.0–897.0)	185.0 (64–672.0)	NE	NE
Median TTR, days (range)	53.0 (27–168)	58.5 (52–109)	NE	NE
Median DOR, days (range)	160.0 (1–818)	111.5 (1–618)	NE	NE

[†]Response-evaluable patients had received ≥1 dose of study drug, and had sites of measurable diseases at baseline and 1 post-baseline disease assessment. CLL, Chronic Lymphocytic Leukemia; CR, Complete response; DLBCL, Diffuse Large B-cell Lymphoma; DOR, duration of response; iNHL, indolent Non-Hodgkin Lymphoma; MCL, Mantle Cell Lymphoma; NE, Not estimable; PR, Partial response; TTR, time to response



*PD due to new lesion
 CLL: Chronic Lymphocytic Leukemia; DLBCL: Diffuse Large B Cell Lymphoma;
 iNHL: indolent Non-Hodgkin Lymphoma; MCL: Mantle Cell Lymphoma
 Note: Due to missing lesion measures, 6 DLBCL subjects with PD are not included in figure.

AUC_{ss}, mean peak/trough ratio of 4.2, and mean accumulation of 2.1-fold. Renal clearance accounted for 34% of apparent oral clearance.

Conclusions: Our data suggest TAK-659 is generally well-tolerated in lymphoma pts, with evidence of single-agent activity across various lymphoma subtypes. TAK-659 PK profile supports QD dosing. Enrollment of pts with DLBCL, iNHL, CLL, MCL, and PTLD is ongoing, with planned accrual of ~152 pts in the expansion phase.

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

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THE DUAL SYK/JAK INHIBITOR CERDULATINIB DEMONSTRATES RAPID TUMOR RESPONSES IN A PHASE 2 STUDY IN PATIENTS WITH RELAPSED/REFRACTORY B-CELL MALIGNANCIES

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SYK and JAK cooperate to control B cell activation (Coffey et al., 2013) and appear to be relevant to B cell malignancies. IL-4 promotes the survival of CLL cells via up-regulation of MCL1 and BCL_{xL}, protecting cells from death induced by fludarabine and chlorambucil (Steele et al., 2010) and by idelalisib and ibrutinib (Aguilar-Hernandez et al., 2016). Also, unlike ibrutinib, combined SYK/JAK inhibition by cerdulatinib induces apoptosis in 1) primary CLL cells and leads to down-regulation of MCL1 and BCL_{xL} (Blunt et al.), 2) cells from ibrutinib-resistant CLL patients (Guo et al., 2017), and 3) primary DLBCL and DLBCL cell lines with BCR pathway mutations resistant to ibrutinib (Ma et al., 2015). SYK/JAK inhibition may therefore represent a powerful strategy to control B cell malignancies.

A dose escalation study of cerdulatinib in 43 CLL/NHL patients was recently completed (Hamlin et al., EHA Congress 2016). Inhibition of both SYK and JAK by >90% at in peripheral blood was well tolerated. Durable PRs and 1 CR were observed. A concentration-dependent

effect on tumor reduction was seen with more consistent activity with Cminss ≥0.7 μM. 2 G3 DLTs were observed at 45 mg BID (fatigue, pancreatitis). 35 mg BID was identified as the Phase 2 dose based on Phase 1 data and on PK/PD modeling.

A study was initiated in May 2016 to enroll up to 40 patients in each of 4 cohorts; 1) r/r CLL/SLL, 2) r/r indolent NHL, 3) relapsed aggressive NHL, and 4) r/r T-cell lymphoma (recently opened). As of March 15, 2017, 39 patients have been enrolled, 18 with CLL/SLL, 16 with iNHL, and 5 with aNHL. Median age is 69 (51-93) and median number of prior therapies is 3 (1-7). 12 patients had prior BTK, PI3K or BCL-2 inhibitors therapy.

The safety profile has been similar to Phase 1. However, 3 patients at 35 mg BID achieved higher than expected drug concentrations and had SAEs (2 grade 5 infections, 1 G3 pancreatitis). The dose was reduced to 30 mg BID and a PK monitoring and dose reduction strategy has been implemented. To date, this has resulted in a better safety profile without PK outliers. The most common AEs of any grade have been diarrhea (27%), fatigue (27%) and nausea (24%). Grade 3+ AEs occurring in >2 patients are neutropenia (4), and hypertension (4), sepsis (3), lipase increase (3) abdominal pain (3). Lymphocytosis in CLL/SLL is consistently observed following 1 week of therapy. The target PK range has been achieved with an average Cminss of ~0.8 μM. PRs have been seen in all 3 cohorts including 10 of 14 (71%) CLL/SLL and 3 of 6 (50%) FL patients evaluable. Responses typically occurred after 2 cycles of treatment, with 12 of 13 on therapy and 4 patients in response for >6 months. In addition, PRs have been seen in patients who relapsed on ibrutinib (FL, 8+ months) and venetoclax (SLL, 7+ months) therapy. As demonstrated preclinically, we have seen evidence of apoptosis (Annexin V+ B-cells) in 6 CLL patients. Accrual is proceeding; updated PK/PD, safety and efficacy will be presented.

Keywords: apoptosis; JAK/STAT; SYK.

SESSION 5: T-CELL LYMPHOMAS

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GENE EXPRESSION PROFILING USING A RTMLPA ASSAY ALLOWS FOR AN ACCURATE CLASSIFICATION OF PERIPHERAL T-CELL LYMPHOMA AND HIGHLIGHTS NOVEL SUBGROUPS WITHIN PTCLS-NOS

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More than 20 Peripheral T-cell lymphoma (PTCL) entities are recognized in the WHO classification. Their prognosis is usually very poor

and their diagnosis is often challenging for pathologists. Up to 30% of cases thus remain not classifiable (PTCL Not Otherwise Specified, NOS) and there is an important need for alternative diagnostic strategies. Here, we developed a parsimonious GEP assay applicable to a routine diagnostic workflow to differentiate the main PTCL entities and characterize the heterogeneity of PTCL-NOS.

A Reverse Transcriptase-Multiplex Ligation dependant Probe Amplification (RT-MLPA) assay was designed to evaluate the expression of 20 markers. It simultaneously addresses the expression of 18 genes routinely tested by immunohistochemistry (IHC) or selected from GEP studies. It also assesses the EBV infection status (*EBER1*) and the presence of *RHOAG17 V* and *IDH2R172K/T* mutations.

Unsupervised hierarchical clustering of RT-MLPA data from 102 control cases validated the capacity of our assay to identify the main PTCL entities. All Angioimmunoblastic T-cell lymphomas (AITL; $n = 29$), Anaplastic large T-cell lymphomas (ALCL; $n = 23$) ALK+, NK/T-cell lymphomas (NKTCL; $n = 16$), Hepatosplenic T-cell lymphomas (HSTL; $n = 6$) and Adult T-cell Leukemia/Lymphomas (ATLL; $n = 12$) were correctly identified. AITLs classified according to the expression of Tfh markers (*CXCL13*, *CXCR5*, *ICOS*, *BCL6*) and *RHOA* mutations ($n = 18$); NKTCLs according to *EBER1*, *GZMB* and Th1 markers (*TBX21*, *IFN γ*); HSTLs to *CD56*, *GATA3*, *TBX21* and *BCL6*; ALCL ALK+ according to *CD30*, *ALK* and cytotoxic markers (*PRF*, *GZMB*); ATLLs to *ICOS* and Th2 markers (*GATA3*, *CCR4*). Interestingly, ALCL ALK- cases ($n = 16$) divided into two *CD30+* subgroups: one associated with expressions of cytotoxic markers which clustered with ALCL ALK+ cases ($n = 10$), and a second which did not expressed *PRF* and *GZMB* but the two *GATA3* and *CCR4* Th2 markers ($n = 6$). We next developed a support vector machine based predictor combined with a centroid categorization. Applied to a series of 125 PTCL-NOS, this algorithm reclassified 36 Tfh (AITL-like), 6 *CD30/Th2*, 6 ALCL ALK- like, 3 HSTL-like and 5 NKTCL-like PTCLs. After exclusion of these cases, unsupervised clustering analysis identified 17 cytotoxic/Th1 (*GZMB*, *PRF*, *TBX21*, *IFN γ*) cases, 14 Th2 (*GATA3*, *CCR4*) cases and 14 TH2/Tfh (*GATA3*, *CCR4*, *CXCR5*, *ICOS*) cases. Finally, 24 cases (10.5% of the cohort) did not show any recognizable signature.

This study demonstrates the applicability of a robust RT-MLPA classifier for the classification of PTCLs. Its simplicity and its applicability on FFPE samples makes it an attractive alternative to high throughput GEP approaches. In combination with conventional pathological evaluation and IHC, it may participate to improve the classification of PTCLs and the management of these aggressive tumors.

Keywords: gene expression profile (GEP); peripheral T-cell lymphomas (PTCL).

64 CHOP VERSUS GEM-P IN THE FIRST-LINE TREATMENT OF T-CELL LYMPHOMA (PTCL): INITIAL RESULTS OF THE UK NRCI PHASE II RANDOMISED CHEMO-T TRIAL

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Introduction: Outcomes with CHOP in the first-line treatment of PTCL are poor and a superior regimen is required. Gemcitabine is not effluxed by the multidrug resistance gene-1/P glycoprotein (expressed in ~60% of PTCLs) and has demonstrated efficacy in relapsed/refractory PTCL both as a single agent and in combination.

Methods: We conducted a phase II multicenter randomised trial for previously untreated patients ≥ 18 years with bulky stage I-IV PTCL of the following subtypes: PTCL not otherwise specified (PTCL NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL) ALK negative, enteropathy-associated T-cell lymphoma (EATL), and hepatosplenic gamma delta T-cell lymphoma. The trial was funded by Bloodwise. Patients were randomised (stratified by subtype and IPI) to receive either 6 cycles of intravenous (IV) cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² on D1 and oral (PO) prednisolone 100 mg once daily (OD) D1-5 (CHOP) every 21 days (Arm A) or 4 cycles of gemcitabine 1000 mg/m² IV D 1, 8 and 15, cisplatin 100 mg/m² IV on D15 and methylprednisolone 1000 mg (IV/PO) OD on D1-5 (GEM-P) every 28 days (Arm B). The primary endpoint was a comparison of end of treatment (EOT) complete response (CR)/CR unconfirmed (CRu) rates assessed by CT using IWG 1999 criteria. The CR/CRu rate was expected to be 50% in Arm A and increased to 70% in Arm B; 93 patients were required per arm to detect this difference with 80% power and 2-sided alpha of 5%.

Results: From March 2012 to November 2016, 87 patients were accrued from 47 sites (U.K. $n = 46$, Australia $n = 1$). The trial profile is shown in Figure 1. On 22.11.2016 the independent data monitoring committee recommended the trial should close early as the primary endpoint would not be met. Baseline characteristics are shown in

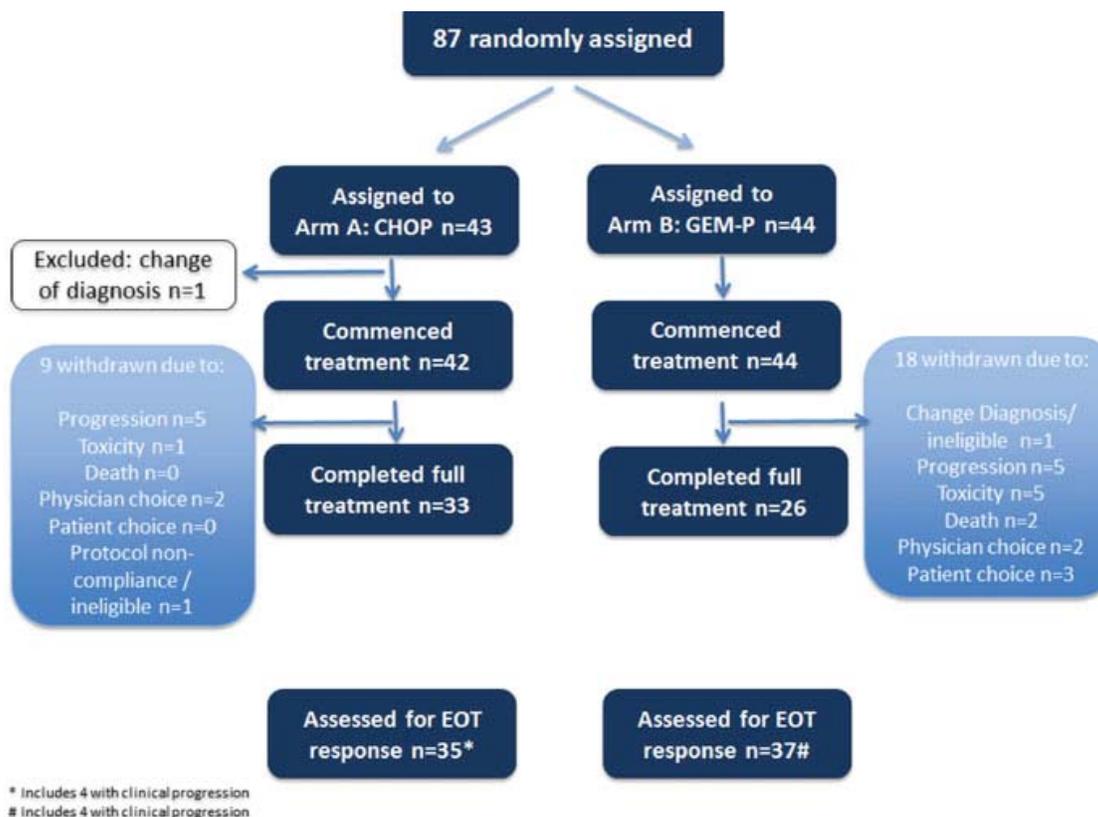


Figure 1: Trial profile

Table 1. EOT response is currently evaluable for $n = 72$, CR/CRu Arm A = 57.1% and Arm B = 43.2% ($p = 0.24$). Overall rates of grade ≥ 3 toxicity were similar between arms, 67.0% vs 73.0% ($p = 0.64$); however

TABLE 1 Baseline characteristics by treatment arm ($n=87$)

Variable	Category	CHOP (Arm A) N=43		GEM-P (Arm B) N=44	
		N	(%)	N	(%)
Gender	Male	30	69.8	32	72.7
	Female	13	30.2	12	27.3
Age (years)	Median (range)	64	26 - 80	61	25 - 76
IPI score	0-1	9	20.9	8	18.2
	2-3	26	58.1	25	56.8
	4-5	8*	20.9	11	25.0
Histology	PTCL NOS	19	44.2	18	40.9
	ALCL ALK-negative	6	14.0	8	18.2
	AITL	17	39.5	17	38.6
	EATL	1	2.3	1	2.3
Stage	I	1	2.3	0	0
	II	8	18.6	3	6.8
	III	16	37.2	16	36.4
	IV	18	41.9	25	56.8
B Symptoms	B	26	60.5	27	61.4
Extra nodal sites	Yes	27	62.8	30	68.2
WHO PS	0	17	39.5	21	47.7
	1	19	44.2	18	40.9
	2	7	16.3	5	11.4

more ≥ 3 grade neutropenia ($p = 0.036$) and febrile neutropenia ($p = 0.03$) were seen in Arm A; while Arm B had more ≥ 3 grade thrombocytopenia ($p = 0.03$). At a median follow-up of 18.1 months, there was no difference in 2-yr overall survival (Arm A = 53.1%, Arm B = 64.7%, $p = 0.56$) or progression-free survival (Arm A = 36.0%, Arm B = 39.0%, $p = 0.81$).

Conclusion: The EOT CR/CRu rate in Arm B (GEM-P) was not superior to Arm A (CHOP), and Arm B was associated with higher rates of study withdrawal. CHOP remains the reference regimen in PTCL.

Keywords: Chemotherapy; gemcitabine; peripheral T-cell lymphomas (PTCL).

65 ROLE OF UP-FRONT AUTOLOGOUS STEM CELL TRANSPLANTATION IN PERIPHERAL T-CELL LYMPHOMAS: A PROPENSITY SCORE MATCHING ANALYSIS OF PATIENTS FROM LYSA CENTERS

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Introduction: Despite years of attempts to improve the prognosis of patients, peripheral T-cell lymphoma (PTCL) remains a therapeutic challenge. Due to the rarity and the heterogeneity of PTCL, no consensus has been achieved regarding the type of first-line treatment. The benefit of autologous stem cell transplant (ASCT) as a consolidation procedure for patient in partial or complete response (PR or CR) is still intensely debated.

Methods: Patient age, disease severity, and induction regimen are known potential confounding factors undermining the formal assessment of ASCT in first-line settings. Moreover, no retrospective study has focused on patients in response after induction, leading to strong bias in favor of the consolidation procedure. In the absence of randomized trials addressing the role of ASCT, we used a Cox proportional hazard model and a propensity score matching approach to correct for sample selection bias between patients allocated or not allocated to ASCT in intention-to-treat. Among 527 patients with peripheral PTCL-NOS, AITL or ALK-ALCL screened from 14 centers in France, Belgium, and Portugal, a final cohort of 269 patients with partial or complete responses after induction was identified and information about treatment allocation was carefully collected before therapy initiation.

Results: With a median follow-up of 5.3 years, the median PFS was 3.7 years, and the median OS was 8.4 years for the entire cohort. At 5 years, PFS was 45.0% (95% confidence interval (CI): 37.8-50.6%), and OS was 60.4% (95% CI: 53.6-66.5%). Patients with ALK-ALCL experienced a slightly longer time to progression compared to patients with PTCL-NOS or AITL, although the difference did not reach significant difference. No OS difference was observed according to histology subtype. Multivariate analysis demonstrated that only remission status (CR vs. PR) at the end of induction was associated with significantly prolonged PFS and OS. In the final matched population of 146 patients, no difference regarding progression-free survival (PFS) or overall survival (OS) was observed ($P = .33$ and $P = .40$). No difference according to the use of up-front ASCT in ITT was further noted when patients with advanced stage disease (III or IV), with aIPI > 1 or reaching a PR only at the end of induction were considered (data not shown).

Conclusion: The present data do not support the use of ASCT for up-front consolidation for patients with PTCL-NOS, AITL or ALK-ALCL with partial or complete response after induction.

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

66 BRENTUXIMAB VEDOTIN VS PHYSICIAN'S CHOICE IN CTCL PATIENTS FROM THE PHASE 3 ALCANZA STUDY: ANALYSIS OF OUTCOMES BY CD30 EXPRESSION

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Introduction: The Phase 3 ALCANZA study showed significant, durable responses with the CD30-directed antibody-drug conjugate brentuximab vedotin (BV) compared with physician's choice (PC) of methotrexate (MTX) or bexarotene (Bex) for CD30-positive (CD30+) cutaneous T cell lymphoma (CTCL). Uniform CD30 expression on neoplastic cells is characteristic of primary cutaneous anaplastic large cell lymphoma (pcALCL), whereas CD30 is variably expressed among other subtypes including mycosis fungoides (MF). We examined the outcomes associated with treatment using BV and MTX / Bex by CD30 expression in patients treated on the ALCANZA study.

Methods: Adults with previously treated CD30+ MF or pcALCL were enrolled. MF patients had ≥ 2 skin biopsies from separate lesions and pcALCL patients had ≥ 1 . Patients were scored CD30+ if ≥ 1 biopsy had $\geq 10\%$ CD30+ lymphoid cells at any intensity above background staining noted by the corresponding negative control, as determined using an investigational Ventana immunohistochemical diagnostic test, assessed centrally. We compared the proportion of MF subgroup patients with objective response lasting ≥ 4 months (ORR4; ALCANZA

TABLE 1

	Brentuximab vedotin	Physician's choice	Difference, % [95% CI]
ORR4, n/N (%)			
CD30 _{min} <10%	9/22 (40.9)	2/21 (9.5)	31.4 [2.8, 58.1]
CD30 _{min} ≥10%	16/28 (57.1)	3/29 (10.3)	46.8 [20.6, 67.0]
Median PFS (months) [95% CI]			Hazard ratio [95% CI]
CD30 _{min} <10%	27.9 [8.6, 27.9]	2.3 [1.6, 3.5]	0.125 [0.044, 0.355]
CD30 _{min} ≥10%	17.2 [9.8, NE]	3.5 [2.1, 4.6]	0.176 [0.072, 0.432]

primary endpoint) and PFS in patients with all biopsies ≥10% CD30+ (CD30_{min} ≥ 10%) vs ≥1 biopsy <10% CD30+ (CD30_{min} < 10%). Patients were randomized 1:1 to BV 1.8 mg/kg IV, Q3W, or PC for up to 16 three-week cycles.

Results: Overall, 125/184 (68%) MF and 44/47 (94%) pcALCL patients were scored as CD30+ at screening evaluation. High inter-lesional variability in CD30 expression was seen in MF patients; 55/125 CD30+ MF patients (44%) had ≥1 biopsy with low (<10%) or undetectable CD30. In total, 100/125 CD30+ MF patients (80%) were eligible and enrolled; 50 per treatment arm. In the BV arm, ORR4 was higher in MF patients with CD30_{min} ≥ 10% vs <10% (57.1% vs 40.9%); median PFS with BV was higher in the CD30_{min} < 10% group (27.9 months) than in the CD30_{min} ≥ 10% group (17.2 months) (Table). ORR4 with BV was greater than PC over all CD30 expression ranges (CD30_{min} < 5%, 38% vs 13%; CD30 ≥ 5–≤20%, 35% vs 10%; CD30 > 20%, 76% vs 7%, respectively).

Conclusions: Notable inter-patient or inter-lesional variability in CD30 expression was seen in MF patients. BV produced highly superior ORR4 and PFS endpoints compared with PC regardless of CD30_{min} expression level.

Keywords: brentuximab vedotin; CD30; cutaneous T-cell lymphoma (CTCL).

67 IMPROVED SURVIVAL OUTCOMES FOR PATIENTS WITH EXTRA-NODAL NK/T LYMPHOMA: DATA FROM 140 PATIENTS PROSPECTIVELY REGISTERED IN THE INTERNATIONAL T-CELL PROJECT

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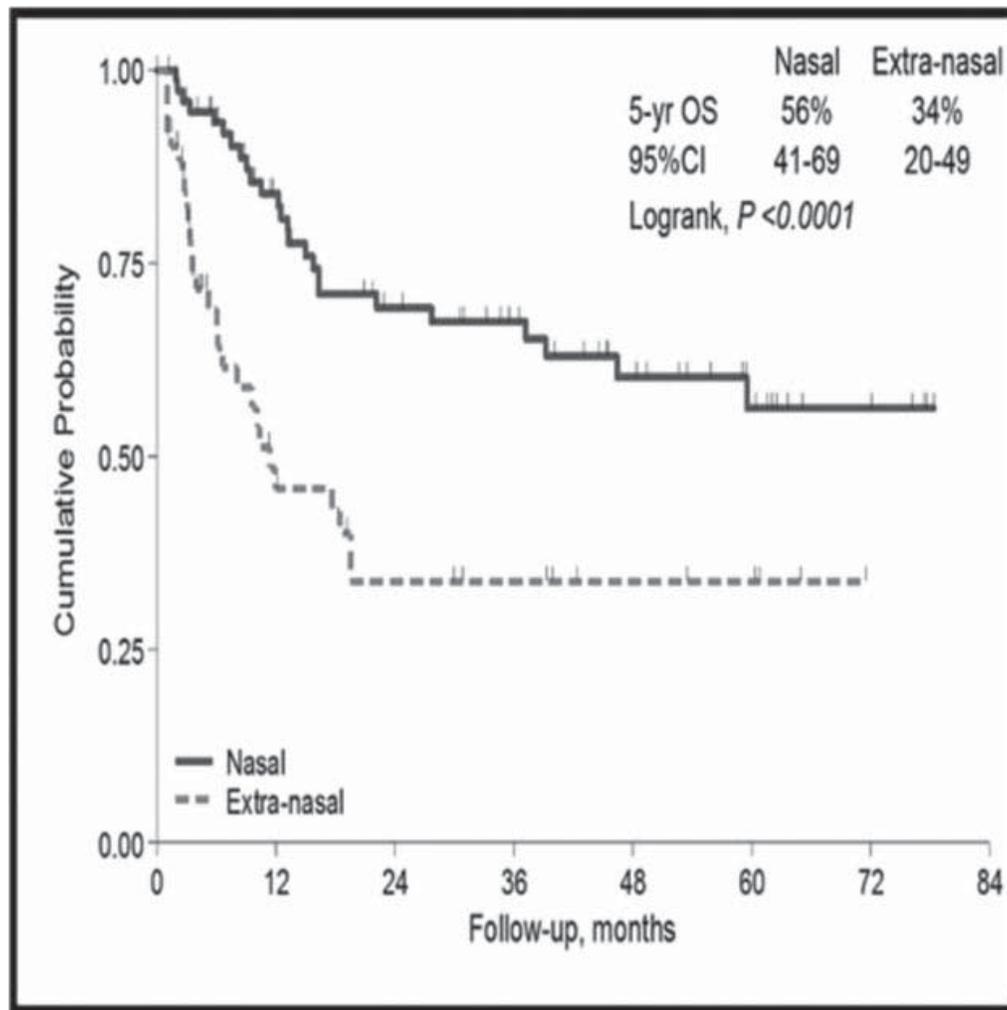
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Introduction: Extra-nodal NK/T cell lymphoma (NKTCL) is a distinct clinicopathological entity characterised by a cytotoxic T or NK cell phenotype and invariable Epstein Barr virus (EBV) infection of the malignant clone. An invasive nasal and upper aero-digestive mass is the dominant clinical presentation, although extra-nasal cases are recognised. Data from the retrospective International T-Cell Lymphoma Project reported poor outcomes for both nasal and extra-nasal NKTCL, with 5-yr OS rates of 40% and 15% respectively (Au *et al.* *Blood* 2009).

Method: The T-Cell Project prospectively registered consecutive patients with newly diagnosed peripheral T cell lymphomas (PTCL) from 74 centres, in 14 countries, across 4 continents from Sep 2006 –Dec 2015. A key aim of this global collaborative project was to more precisely define clinical characteristics and outcome of patients with the less common subtypes of PTCL.

Result: From a total of 1,369 evaluable PTCL cases, 140 (10.2%) were confirmed as NKTCL following international histopathologic panel review. As anticipated, NKTCL cases, as a proportion of all PTCL cases, varied across geographical regions (Asia 28%, South America 9.3%, U.S.A 7.6%, Europe 6.4%). The median age at diagnosis was 52.5 years with a male predominance (66%). Stage III/IV disease was seen in 39% patients, whilst bulky disease >5 cm (7.4%) and BM involvement (9.8%) were uncommon. Data on therapy was available in 111 (79%) patients, of whom 103 (93%) received chemotherapy (CHT) as part of first-line treatment. Sixty-four patients (58%) additionally received concurrent or sequential radiotherapy (RT), whilst 13 patients (11.7%) underwent high-dose therapy as consolidation. Five patients (4.5%) underwent RT only, whilst 3 (2.7%) received palliative care only. Of 103 patients treated with chemotherapy, 41 (40%) received anthracycline-containing regimens whilst 36 (35%) received L-asparaginase-based schedules. With a median follow-up of 39 months,



the median PFS for ($n = 139$) NKTL patients was 33 months (95%CI 7-58) with marked delineation for nasal and extra-nasal cases; 72 months (95%CI 27-118) and 10 months (95%CI 1-20) respectively. For the whole cohort ($n = 140$) the median OS was 46 months, translating to a 5-yr OS of 56% and 34% for nasal and extra-nasal cases respectively ($p < 0.0001$, Figure). Cause of death was most commonly attributable to lymphoma (61%) and infection (15%).

Conclusion: This is the largest prospective international analysis of NKTL to-date, describing notable geographical differences in incidence and treatment approaches. With mature follow-up, we observed significant improvements in both PFS and OS, for both nasal and extra-nasal subgroups, as compared to published outcomes from the previous retrospective International T-Cell Lymphoma Project. The observed improvements in survival outcomes are most likely attributable to the adoption of modern chemotherapy regimens.

Keywords: Epstein-Barr virus (EBV); extranodal lymphomas; T-cell lymphoma (TCL).

68 GAD-M REGIMEN FOR NEWLY DIAGNOSED EXTRANODAL NK/T CELL LYMPHOMA: ANALYSIS OF EFFICACY AND SAFETY FROM PHASE II STUDY (NCT 01991158)

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Introduction: PEG-asparaginase-based chemotherapy regimens have improved the efficacy of extranodal natural killer/T-cell lymphoma (ENKTL). However, the methotrexate was another important drug for ENKTL, which was contained in both SMILE and AspaMetDex regimens. GELOX regimen lost this drug. Therefore, we evaluated the efficacy and safety for methotrexate with gemcitabine, PEG-asparaginase and dexamethasone (GAD-M) regimen in patients with treatment naïve ENKTL in the Phase II Study (NCT 01991158).

Methods: Patients who were newly diagnosed as ENKTL in stage I-IV from 18 to 80 years with ECOG PS of 0 ~ 3 were eligible for enrollment. GAD-M regimen (gemcitabine 1000 mg/m²; ivdrip, d1, d8, PEG-asparaginase 2500 U/m²; im, d1, dexamethasone 20 mg, ivdrip, d1-3, Methotrexate 3000 mg/m²; civ 12-hour, d1) was planned as the protocol treatment. The regimen was repeated every three weeks. For stage I/II patients, 2-4 cycles of GAD-M regimen followed by EIFRT and additional 4-2 cycles. For stage III/IV, GAD-M regimens were repeated for six cycles. The primary endpoint was overall response rate (ORR) after six cycles of GAD-M. Secondary endpoints

were 3-year progression-free survival (PFS), 3-year overall survival (OS), and toxicity. Response was assessed using the revised International Workshop Criteria. Toxicity was graded according to the Common Terminology Criteria for Adverse Events v4.0.

Results: 41 patients were enrolled from Oct 2013 to Aug 2015. 36 patients were evaluable for response. The baseline clinical characteristics were as follows: the median age, 45 years (range: 18–75 years); >60 years, 13.5%; female, 30.6%; ECOG PS >1, 13.9%; stage/II, 86.1%; elevated LDH, 27.8%. After 2 cycles of GAD-M, ORR in all and stage/II were 94.4% (34/36) and 100% (31/31), respectively. CR rate were 50% (18/36) and 54.8% (17/31), respectively. After 6 cycles ORR in all and stage/II were still 94.4% (34/36) and 100% (31/36), respectively. CR rate increased to 83.3% (30/36) and 90.32% (28/31), respectively. At median follow-up of 23.3 months, 3-year PFS was 72.1% (Figure 1A), 3-year OS was 76.3% (Figure 1B). According to the stage, 3-year PFS for stage I/II and III/IV were 77.3% and 40.0%, respectively. 3-year OS were 79.3% and 60.0%, respectively. The most common hematologic adverse event of grade 3/4 was anemia (52.8%). The major non hematologic side effects were hypoalbuminemia (100%), increased transaminases (88.9%) and hyperbilirubinaemia (52.8%). Although grade 1/2 nonhematologic toxicities were frequent during GAD-M treatment. Grade 3/4 toxicities

were few. One patient died of treatment related toxicity, who was 61-year-old man died of electrolyte disorders caused by severe vomiting. Other patients didn't suffer from this adverse event.

Conclusions: These results demonstrate that GAD-M regimen provides a high ORR in newly diagnosed ENKTL, especially for stage/II. GAD-M with EIFRT for ENKTL in stage/II was feasible, although most patients experienced recoverable liver dysfunction and anemia during the protocol treatment.

Keywords: gemcitabine; L-asparaginase; methotrexate (MTX).

“FOCUS ON...” SESSION: TARGETING CD30 IN HODGKIN LYMPHOMA

69 RESULTS OF A PHASE II STUDY OF BRENTUXIMAB VEDOTIN IN THE FIRST LINE TREATMENT OF HODGKIN LYMPHOMA PATIENTS CONSIDERED UNSUITABLE FOR STANDARD CHEMOTHERAPY (BREVITY)

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Introduction: Standard treatment for Hodgkin lymphoma (HL) is poorly tolerated in older patients and results are disappointing. Brentuximab vedotin (BV) is a CD30 targeted antibody-drug conjugate licenced for the treatment of relapsed or refractory HL on the basis of excellent safety and efficacy demonstrated in the pivotal phase 2 clinical trial. BREVITY trial was designed to evaluate the efficacy and tolerability of BV monotherapy in previously untreated patients (pts) with HL unfit for standard treatment due to age, frailty or co-morbidity.

Methods: This response adaptive phase II, Simon 2-stage, single arm study required 30 evaluable pts. Primary outcome was complete metabolic response (CMR, Deauville Score 1–3) by centrally reviewed PET-CT after 4 cycles of BV. Secondary outcomes included PFS, OS, toxicity and comorbidity assessment (CIRS-G). Inclusion criteria were

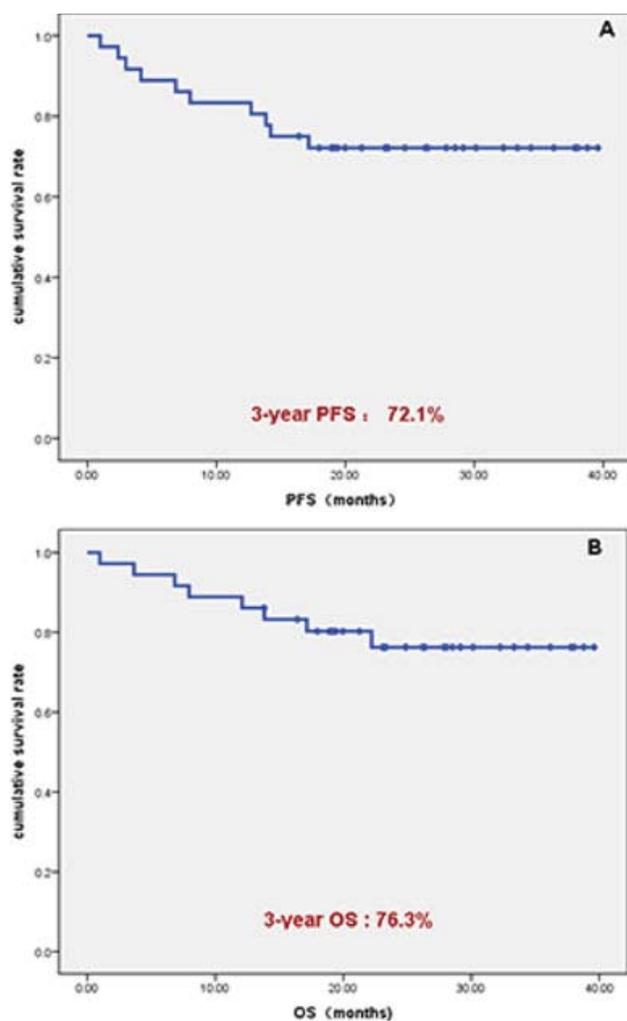


Figure 1: The survival curves of PFS and OS.

TABLE 1

Patient Characteristic	n=38 Median (Range)
Age	76 (59, 90)
CIRS-G Score	3 (0, 7)
No. categories endorsed	1.5 (0, 3)
Severity Total score	6 (0, 11)
	n (%)
Gender	22 (57.9)
Male	16 (42.1)
Female	
Stage	7 (18.4)
Stage 2	13 (34.2)
Stage 3	18 (47.4)
Stage 4	
B symptoms	27 (71.1)
Bulky Disease	5 (13.2)
Extranodal disease	22 (57.9)
ECOG Performance Status	3 (7.9)
0	16 (42.1)
1	11 (28.9)
2	7 (18.4)
3	1 (2.6)
4	

previously untreated HL stage 2 (with B symptoms and/or mediastinal bulk) to stage 4 with cardio-respiratory compromise (at any age), or ECOG PS \leq 3 and considered unfit for standard chemotherapy (in pts \geq 60 yrs). BV dose was 1.8 mg/kg every 3 weeks, reduced to 1.2 mg/kg for toxicity. Pts responding after 4 doses of BV continued to a maximum of 16 cycles if CT/PET-CT every 4 cycles confirmed ongoing response. Pts also underwent exploratory blinded PET-CT after cycle 2.

Results: 38 pts were recruited from Feb 2014-Oct 2015 at 12 UK centres; demographics are shown in Table 1. 35 treated pts were evaluable for toxicity, 31 were evaluable for response. A median of 4 cycles was given (range 1-16). Dose was reduced in 28 cycles across 14 pts due to toxicity and 11 pts stopped treatment due to adverse events (AEs). 716 AEs were reported, 626 (88%) were grade 1/2. 27 (77%) pts had at least one AE \geq grade 3, most commonly infection, myelosuppression or neuropathy. CMR at PET4 was 26% (95% CI 14, 43) and overall objective response was 84% (95%CI: 67, 93). There was a significant correlation of interim PET2 with PET4 (Rho = 0.67, $p < 0.001$) with a CMR rate at PET 2 of 32% (95% CI 17, 52). To date 28 of 31 evaluable pts have progressed and median PFS is 7.4 months (95% CI 5.3, 10.2).

Conclusions: In this study BV monotherapy produced a high overall response rate although the CMR rate after 4 cycles did not meet the pre-specified 40% level, and PFS was short. Toxicity was greater than in the pivotal study in a younger/fitter population and led to treatment termination in some pts. A follow-on study aims to improve CMR and PFS by using a lower dose of BV in combination with other agents.

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

70 BRENTUXIMAB VEDOTIN CONSOLIDATION TO REDUCE RADIATION USE IN PATIENTS WITH LIMITED STAGE NON-BULKY HODGKIN LYMPHOMA: AN UPDATE FROM a PHASE 2 CLINICAL TRIAL

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Background: HL is one of the most common cancer types in young adults. Although approximately 90% of limited stage HL patients are projected to be cured with standard chemotherapy with or without radiation, many do not live their expected life span due to delayed treatment-related complications that include secondary malignancies and cardiovascular disease. Given the risks associated with current therapies for HL, novel treatment strategies are urgently needed to reduce the use of radiation as well as conventional chemotherapy drugs while improving upon current standard of care outcomes.

Methods: In this phase 2 multicenter study, patients with previously untreated limited stage HL received ABVD induction followed by BV consolidation (NCT01578967). The primary objective was to estimate the proportion of patients who achieve PET-negative disease after ABVD followed by BV. The goal was to achieve negative PET and avoid radiation in $>$ 85% of patients. Patients received 2 to 6 cycles of ABVD based on their baseline risk factors and the interim PET scan result. Approximately 6 weeks after induction, 1.8 mg/kg of BV was given every 3 weeks for 6 cycles.

Results: Forty one patients were enrolled from April 2012 through December 2015. Out of 40 evaluable patients, the median age was 29 years (range 19 – 68), and 45% presented with unfavorable disease. Thirty seven out of 40 patients (92.5%) received \leq 4 cycles of ABVD (27.5% received 2 cycles) prior to BV consolidation. One patient received radiation due to disease progression. BV-related grade \geq 3 toxicities included neutropenia (7.5%), peripheral neuropathy (2.5%) and rash (2.5%). There was one death due to sepsis and hepatic failure, a very rare but known complication of BV, and all reported \geq grade 4 toxicities were associated with this event. After 2 cycles of ABVD, 72.5% of patients achieved PET-negative disease (Deauville score $<$ 3), and 37 out 39 evaluable patients (94.9%, CI: 88 – 100%) were PET-negative after the completion of BV. The estimated 2-year progression free (PFS) and overall survival rates were 92% and 97%, respectively, with a median follow up of 22 months. All 37 patients who achieved

TABLE 1 PET results in HL patients who received ABVD followed by BV Consolidation

	Interim-PET2 (n = 40)	Post BV (n = 39)
Deauville 1	13	18
Deauville 2	16	19
Deauville 3	8	1
Deauville \geq 4	3	1

HL, Hodgkin lymphoma; PET, positron emission tomography; HL, Hodgkin lymphoma; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BV, brentuximab vedotin; Interim-PET-2, PET scan after 2 cycles of ABVD; Post BV, PET scan after 6 cycles of BV

PET-negative disease at the end of BV avoided radiation and remain in remission with an estimated 2-year PFS of 100%.

Conclusion: BV demonstrates encouraging safety and clinical activity following ABVD in previously untreated limited stage HL. BV consolidation may reduce the use for radiation therapy and achieve excellent survival outcomes in the majority of patients with limited stage non-bulky HL.

Keywords: brentuximab vedotin; Hodgkin lymphoma (HL); positron emission tomography (PET).

71 RESULTS OF A MULTICENTRE UK-WIDE STUDY EVALUATING THE EFFICACY OF BRENTUXIMAB VEDOTIN IN RELAPSED, REFRACTORY CLASSICAL HODGKIN LYMPHOMA IN THE PRE-TRANSPLANT NAÏVE SETTING

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Introduction: Relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) is associated with a poor outcome once patients (pts) become resistant to traditional chemotherapy and new approaches are needed. Brentuximab vedotin (BV) is a novel anti-CD30 monoclonal antibody conjugated to the antimicrotubule cytotoxic monomethyl auristatin-E. BV has been licenced for use post autologous stem cell transplant (SCT) and in pts who have received 2 prior lines of therapy and unsuitable for SCT. Efficacy data are limited for BV as a 'bridge' to autologous or allogenic SCT.

Methods: We performed a UK-wide retrospective multi-centre study of 99 SCT-naïve R/R cHL to assess the success of incorporating BV pre-SCT. All had previously received ≥ 2 prior chemotherapy lines with curative intent. Pts had all received prior salvage with the initial aim to proceed to potential curative SCT but were not deemed suitable due to failure to induce deep, durable remissions.

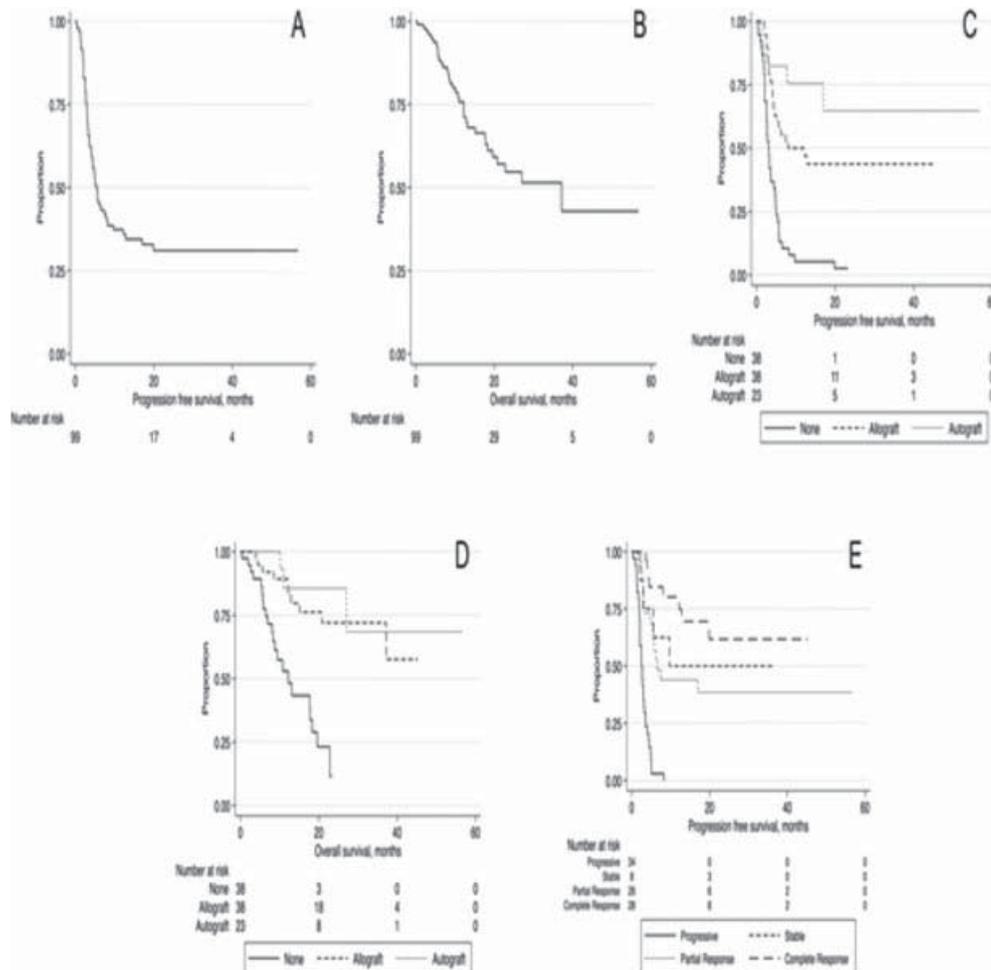


TABLE 1

Characteristics	BV SCT-naive patients (n = 99)
Median age (years) at diagnosis	32 years (range 13-70 years)
Gender	
Male	45 (45%)
Female	54 (55%)
Length of first remission: earliest remission to relapse (n = 66)	Median 6.0 months (range 0.7 - 74.1 months)
Risk factors at relapse	
Haemoglobin (n = 80)	Median 12.2 g/dL (range 6.6 - 15.3 g/dL)
≥ 12	41 (51%)
< 12	39 (49%)
Extranodal disease at first relapse (n = 94)	
Y	44 (47%)
N	50 (53%)
B symptoms at first relapse (n = 88)	
Y	33 (38%)
N	55 (62%)
Ann Arbor stage at first relapse (n = 94)	
1-2	27 (29%)
3-4	67 (71%)
Median time from last treatment to BV (n = 94)	2.5 months (range 0.7 - 34.8 months)
Median time from initial diagnosis to BV (n = 99)	14.5 months (range 4.0 - 190.9 months)
Prior lines of therapy pre-BV (n = 99)	
2	70
3	24
4	5
Median number of prior chemotherapy lines	2 (range 2-4)
Response to BV (n = 96)	
ORR	54 (56%)
CMR / CR / CRu	24 (25%) / 3 (3%) / 1 (1%)
PMR / PR	2 (2%) / 24 (24%)
SD	8 (8%)
PD	34 (35%)
Cycles of BV given	Median 4 (range 1-9)
Treatment pathway summary after receiving	
BV	8 (8%)
No further treatment	15 (15%)
ASCT	19 (19%)
AlloSCT	8 (8%)
Chemotherapy followed by ASCT	19 (19%)
Chemotherapy followed to alloSCT	30 (31%)
Chemotherapy with no SCT	
Abbreviations:	BV: Brentuximab Vedotin ORR: overall response rate P(M)R: partial metabolic response

(Continues)

TABLE 1 (Continued)

Characteristics	BV SCT-naive patients (n = 99)
	C(M)R: complete metabolic response CRu: complete response unconfirmed SD: stable disease PD: progressive disease SCT: stem cell transplantation

Results: Patient characteristics are outlined in the Table. From the start of BV, the median progression-free survival (PFS) for all pts was 5.6 months (95% confidence interval (CI) 4.4 - 12.2 months) and median overall survival (OS) was 37.2 months (95% CI 18.3 months - not reached (NR)) (Figure A & B). The overall response by CT or PET-CT to BV was 56% (complete metabolic response/complete response/complete response unconfirmed (CMR/CR/CRu) 29%; partial metabolic response/partial response (PMR/PR) 27%). 34% had a SCT after BV with no further treatment. 27% required further treatment post-BV pre-SCT. Pts consolidated with either an auto or alloSCT had a superior PFS (Figure C) and OS (Figure D) to those not receiving consolidative SCT ($p < 0.001$ for auto and alloSCT vs. non-SCT for median PFS (auto: NR (95% CI 17.0 months - NR) vs allo: NR (95% CI 5.6 months - NR) vs non-SCT: 3.0 months (95% CI 2.5 - 4.4 months)). The median duration of response for pts entering CR was superior to PR, consistent with prior reports (Figure E). Using multivariate Cox regression, pts with improved performance status and haemoglobin at first relapse had improved PFS from the start of BV. **Conclusion:** We demonstrate that BV has effective activity (ORR 56%) allowing bridge to SCT in a cohort of high risk SCT-naive, predominantly refractory cHL. 34% are consolidated by SCT post-BV (median of 4 cycles) and a further 27% are salvaged to SCT following inadequate BV response. 39% do not reach SCT and have poor outcomes, with PFS of 3.0 months, demonstrating the unmet need to improve outcomes in those unsuitable for SCT.

Keywords: brentuximab vedotin; classical Hodgkin lymphoma (cHL); high-dose therapy (HDT).

72 BRENTUXIMAB VEDOTIN FOR RELAPSED HODGKIN LYMPHOMA AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION: A RETROSPECTIVE STUDY OF THE EBMT LYMPHOMA WORKING PARTY

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Rationale: Brentuximab vedotin (BV) is an anti-CD30 antibody-drug conjugate approved for treatment of relapsed classical Hodgkin lymphoma (HL) after autologous hematopoietic cell transplantation (HCT) or after failing two lines of combination chemotherapy in transplant ineligible patients. Anecdotal reports suggest the efficacy of BV for relapse of HL after allogeneic HCT (allo-HCT). The purpose of this study was to assess safety and efficacy of BV if given as salvage treatment for HL relapse post allo-HCT.

Patients and Methods: We identified 184 adult patients with HL allografted between 2010 and 2014 from a matched related or unrelated donor at EBMT participating centers and who relapsed or progressed after allo-HCT. Median age at diagnosis and at allo-HCT was 27 and 31 years, respectively. Patients were heavily pretreated with a median of 4 lines (1-9) of therapy preallograft. 142 patients (77%) received a prior autologous HCT and 100 patients (54%) received BV prior to allo-HCT. 91 patients (50%) had progressive or active disease at allo-HCT. 43 patients (24%) had a Karnofsky score \leq 80. Median time from allo-HCT to relapse was 7 months (range 3-13). 80 patients received BV as salvage therapy for relapse/progression after allo-HCT (BV group) at a median time of 67 days (range 29-300) after relapse. These patients were compared with 104 patients who did not receive BV salvage after allo-HCT (no-BV group). Median follow-up after relapse of alive patients was 29 months (range 14-38).

Results: Patients in the BV group were younger at the time of HCT (median age: 30 vs 34 years; $p = 0.03$, more likely to receive pre-transplant BV (65% vs 46%; $p = 0.02$), but less likely to receive bone marrow grafts (13 vs 29%; $p = 0.01$). The two groups were comparable in terms of time from diagnosis to allo-HCT, number of prior lines of therapy, recipient gender, performance status and comorbidity at allo-HCT,

disease status at HCT, use of prior autologous HCT, type of donor, type of conditioning received and time from allo-HCT to relapse. Donor lymphocyte infusion (DLI) was administered to 51 (66%) patients in the BV group after a median time from relapse of 71 days (range 16-184) and to 34 patients (33%) in the no-BV group median time from relapse of 41 days (range 19-83). Patients in the BV group received a median of 6 doses of BV for relapse after allo-HCT (range 1-16). Out of 62 evaluable patients in the BV group, 17 patients (27%) achieved complete remission (CR), 26 patients (42%) achieved partial response (PR) and 15 patients (24%) had stable disease (SD). Response to BV post allo-HCT was not affected by whether patients received pre-transplant BV (CR 26%; PR 48%; SD 26%) or not (CR 37%; PR 37%; SD 25%). Despite a longer median follow up for alive patients in the BV group (33 vs 23 months; $p < 0.001$), 34% of them were in CR at last follow up vs 18% only in the no-BV group ($p = 0.003$). Relapse or progression was the main cause of death in 74% of patients in the BV group vs 82% in the no-BV group. Overall, 85 patients developed chronic graft versus host disease (cGVHD), 40 of them before relapse. Among 144 patients with no cGVHD before relapse, 45 patients developed cGVHD after relapse, 22 of them after salvage BV. In univariate analysis, salvage BV had no effect on cGVHD (HR = 0.73; 95%CI: 0.4-1.3; $p = 0.3$), or on 1-year overall survival from relapse post allo-HCT (OS: 76% vs 67%; $p = 0.13$). Similarly, in multivariate analysis, BV salvage had no effect on OS. Older age and poor performance status at time of allo-HCT adversely affected OS.

Conclusion: BV is a safe and effective salvage therapy for patients with HL relapsing or progressing after allo-HCT. Post-transplant BV may synergize with immune interventions such as DLI or checkpoint inhibitors to achieve sustained control of HL recurring after allo-HCT.

Keywords: allogeneic stem cell transplant (alloSCT); brentuximab vedotin; Hodgkin lymphoma (HL).

73 SAFETY AND EFFICACY OF COMBINATION OF BRENTUXIMAB VEDOTIN AND NIVOLUMAB IN RELAPSED / REFRACTORY HODGKIN LYMPHOMA: A TRIAL OF THE ECOG-ACRIN CANCER RESEARCH GROUP (E4412)

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Background: Relapsed/refractory (R/R) Hodgkin lymphoma (HL) remains a significant clinical challenge. We hypothesized that using an immune checkpoint inhibitor to activate the immune cells in the tumor microenvironment, and concurrently targeting tumor cells with the CD30 antibody-drug conjugate brentuximab vedotin (BV) could overcome resistance. E4412 is a Phase 1 ECOG-ACRIN sponsored study of the combinations of BV and ipilimumab (Ipi) and nivolumab (Nivo) in patients with R/R HL. Here we present the updated safety and response data on the full cohort of patients treated with BV + Nivo (Arms D-F).

Methods: Patients with confirmed R/R HL were treated with Nivo 3 mg/kg and BV 1.2 mg/kg (Arm D) or 1.8 mg/kg (Arm E) with a 3 + 3 design, and an expansion cohort (Arm F) of 9 patients. BV and Nivo are given every 21 days for 16 cycles; Nivo may be continued for an additional year. Dose limiting toxicity (DLT) was defined within the first cycle of therapy.

Results: As of 3/10/17 19 patients (1 ineligible) have been treated. Median age was 40, range (21-70); 9 patients were male. Patients were treated with a median of 3 prior therapies. Eight patients had prior SCT; 4 patients had prior BV.

Safety: Nineteen of 19 patients are evaluable for safety. There were 2 significant treatment related adverse events (AEs): 1 patient in Arm E experienced a DLT (pneumonitis grade 3 with grade 3 dyspnea and hypoxia, and typhilitis), and made a full recovery; 1 elderly patient in Arm F had grade 5 pneumonitis occurring in cycle 2. There were no other Grade 4 or 5 AEs; grade 3 AEs were one each: rash, puritis, and neutropenia. The most common grade 1-2 AEs were: transaminitis (9), peripheral sensory neuropathy (8), and rash (6); other grade 1-2

AEs included: diarrhea (4), blurry vision (3), and myalgias (2). One grade 1-2 infusion reaction was noted, this patient was able to receive subsequent therapy with pre-medication.

Response: Response is shown below in Figure 1. Seventeen of 18 eligible patients are evaluable for response, one patient died after cycle 2 and response could not be assessed. The overall response rate (ORR) for the combination was 89%, with a CR rate of 50% (9/18) (95% CI: 26%-74%). There were 2 CRs and 1 PR in patients treated with prior BV. The 6 month PFS is 91% (95% CI: 75-100%), and median OS with a median follow-up of 6 months is not reached.

Conclusion: In this study of the combination of Nivo and BV for R/R HL, therapy was generally well tolerated, however two patients experienced pneumonitis. In a heavily pretreated patient population, the ORR of 89% and CR rate of 50% suggests a deepening of response compared to either therapy alone. Optimization of this strategy is planned with ongoing accrual to cohorts receiving BV + Ipi + Nivo. Data will be updated to include longer term PFS and OS by the time of the meeting.

Keywords: brentuximab vedotin; Hodgkin lymphoma (HL); immune system.

74 INTERIM RESULTS FROM A PHASE 1/2 STUDY OF BRENTUXIMAB VEDOTIN IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

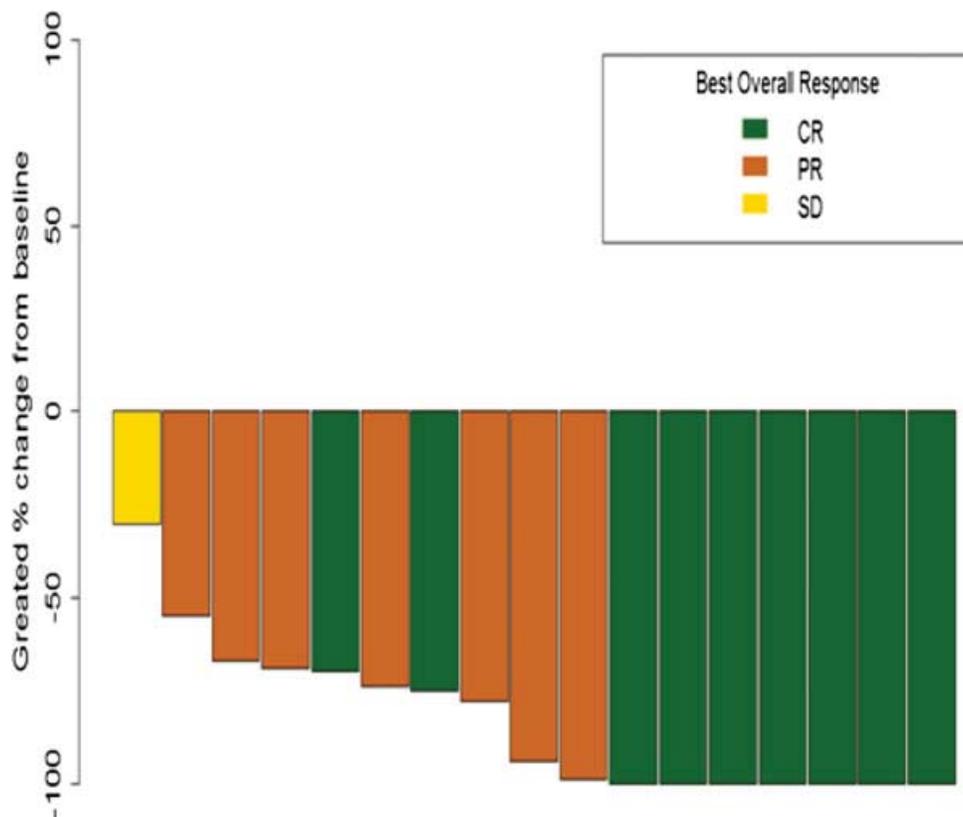


Figure 1: Waterfall Plot.

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Introduction: Brentuximab vedotin (BV) may prime an antitumor immune response through the induction of immunogenic cell death via microtubule disruption of CD30-expressing RS cells in classical Hodgkin lymphoma (HL) (Gardai 2015). Nivolumab (nivo) blocks the programmed death-1 (PD-1) immune checkpoint pathway and restores antitumor immune responses. Both drugs have high single-agent response rates in patients (pts) with relapsed or refractory (RR) HL. In combination, these agents could yield higher complete response (CR) rates prior to autologous stem cell transplant (ASCT) and improved outcomes.

Methods: This phase 1/2 study is ongoing to evaluate the safety and antitumor activity of BV + nivo in pts with RR HL who have failed frontline chemotherapy (NCT02572167). Pts were treated in 21-day cycles for up to 4 cycles. Pts received BV on Cycle 1 Day 1 and nivo on Cycle 1 Day 8. For cycles 2 through 4, BV and nivo were given on Day 1 of each cycle. Following the Cycle 4 response assessment, pts could undergo ASCT. Responses were assessed using the Lugano classification (Cheson 2014).

Results: Of the 62 enrolled pts (52% female, median 36 years), 45% had primary refractory HL. 61 pts received combination treatment (tx): 53 pts completed 4 cycles, 5 pts remain on tx and 4 pts discontinued due to pt decision (2), adverse event (AE,1) and investigator decision (1). Infusion-related reactions (IRRs) occurred in 41%, most frequently during the Cycle 2 BV infusion, and required dose interruptions in 25%. The rate of Gr 3 IRRs was <5%. 60 pts (98%) had tx-emergent AEs prior to ASCT (66% ≤ Gr 2, 28% Gr 3, and 5% Gr 4); Gr 1 nausea (49%) and fatigue (33%) were most frequent. Excluding IRRs, potential immune-related AEs (IrAE) occurred in 72% of pts (66% ≤ Gr 2, 5% Gr 3, 2% Gr 4) with Gr 1 diarrhea (25%) as the most common. Systemic steroids were required in 4 pts (<10%); 1 pt each experienced Gr 4 pneumonitis and colitis, Gr 2 pneumonitis, Gr 3 diarrhea and Gr 2 colitis, and Gr 3 AST elevation. The CR rate was 64%, (55 efficacy evaluable pts; 53% Deauville ≤2, 11% Deauville 3) with an

objective response rate of 85%. 4 pts (7%) had stable disease and 3 pts (5%) progressed on tx. To date, 29 pts have initiated ASCT with a median 4.7×10^6 CD34+ cells/kg collected, and median time to neutrophil and platelet engraftment of 11.5 and 16 days. No unusual post-ASCT toxicities were observed. Observed effects on the immune system, evaluated in peripheral blood, include a decrease in CD30+ T-regulatory cells after Cycle 1 BV while cytotoxic CD8+ T lymphocytes remained stable. With BV + nivo, CD4+ T cells increased, and T-cell receptor sequencing revealed clonal expansion. Serum TARC levels decreased with BV alone, while inflammatory mediators including IFN γ and CXCL10 increased.

Conclusion: Interim data suggest BV + nivo is an active and well-tolerated outpatient therapy. These results support further exploration of this chemotherapy-free regimen for pts with RR HL.

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

“FOCUS ON...” SESSION: NOVEL ANTI-LYMPHOMA STRATEGIES

75 CLARITHROMYCIN AS A “REPURPOSING DRUG” AGAINST LYMPHOMAS: SAFETY AND EFFICACY PROFILES IN 55 PATIENTS WITH EXTRANODAL MARGINAL ZONE LYMPHOMA (EMZL)

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Introduction: Macrolides have been proposed as new anticancer agents. In particular, clarithromycin (K) displays different effects on several pathways, and is active in tumor models. Two phase II trials have demonstrated that K is safe and active in patients (pts) with relapsed/refractory EMZL, but the best administration schedule of this antibiotic as antineoplastic agent remains to be defined. Herein, we report tolerability and efficacy of K monotherapy in a retrospective series of pts with EMZL.

Methods: 55 pts with EMZL and at least one measurable/parametrable lesion treated with single-agent K at two academic institutions were analyzed. Three different administration schedules were used: a 6-month regimen at 500 mg twice a day, every day ($n = 13$); three courses of 500 mg twice a day, days 1-21, every 35 days ($n = 19$); or four courses of 2.000 mg/d, days 1-14, every 21 days ($n = 23$).

Results: Median age of analyzed pts was 65 years (range 30-88), with a M:F ratio of 0.57. EMZL affected a single organ in 40 pts, and was multifocal in 15: the most commonly involved organs were ocular adnexae ($n = 30$), stomach ($n = 9$) and lung ($n = 7$). IPI score was ≥ 2 in 15 patients. A prior history of chronic infection was recorded in 20 pts: HBV/HCV, *H. pylori* and *C. psittaci* in 5 pts each, with multiple

combinations of these micro-organisms in 5. K was the first treatment line in 8 pts, the second in 24, the third in 15, and the 4th-6th in 8. Tolerability was excellent with the three treatment schedules: only 2 pts had G3 toxicity (nausea); the main side effects were G1-2 nausea (17 pts), dysgeusia (7), dizziness (4), headache (3), arthralgia (2), and rash (2). Five pts interrupted treatment due to nausea (3), rash or dysgeusia. Nausea was significantly more common when a daily dose of 2.000 mg was used (52% vs. 25%; $p = 0.03$). Response after K treatment was complete in 13 (24%) pts and partial in 13, with an ORR of 47% (95%CI = 34-60). Responses were more common among pts with gastric MALT lymphoma (7/9 vs. 19/46; $p = 0.04$), but were not associated with prior treatment, IPI and K dose. At a median follow-up of 33 months (range 7-137), 29 pts remain progression-free, with a 3-year PFS of 52% (95%CI = 39-65). Pts with lymphoma refractory to prior treatment and pts with IPI score ≥ 2 had a poorer PFS. Importantly, K dose was not associated with outcome, with a 3-year PFS of 60% and 42% ($p = 0.47$) for pts treated with a daily dose of 1 g and 2 g, respectively. Fifty-two pts are alive, with a 3-year OS of 96% (95%CI = 91-100); causes of death were HCV-related liver failure, stroke and lung cancer.

Conclusions: K is active in pts with EMZL, and exhibits an excellent safety profile when used at a dose of up to 2 g/d for 4-6 months. The recommended daily dose in pts with EMZL is 1 g as it is associated with a lower incidence of nausea and similar efficacy than 2 g/d. A phase II trial (CLEO) addressing the K-lenalidomide combination in EMZL pts is ongoing.

Keywords: marginal zone lymphoma (MZL); Mucosa-Associated Lymphoid Tissue (MALT).

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A PHASE 1 STUDY OF PRALATREXATE PLUS ROMIDEPSIN REVEALS MARKED ACTIVITY IN PATIENTS WITH RELAPSED OR REFRACTORY (R/R) PERIPHERAL T-CELL LYMPHOMA (PTCL)

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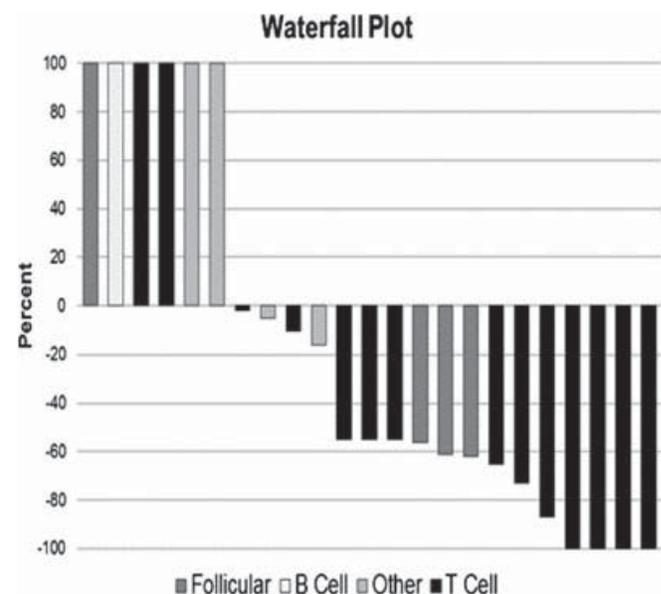
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Introduction: PTCL is a heterogeneous group of lymphomas in which only 25% of patients experience long-term survival. As a single agent in the relapsed setting romidepsin (R) and pralatrexate (P) have response rates of 25-38% and 29-54% respectively across phase I/II studies. Preclinical studies of P + R in models of T-cell lymphoma established strong synergy at doses 50% of the MTD and was well tolerated in mice. Based on these findings, we initiated a Phase I study of P + R in patients with relapsed or refractory lymphoma (NCT01947140), with the plan for a Phase 2 dedicated to PTCL.

Methods: A 3 + 3 dose-escalation design started with P 10 mg/m² and R 12 mg/m² with escalation to P 25 mg/m² and R 14 mg/m². Patients were treated on 1 of 3 dosing schedules (D1, 8, 15 Q28D; D1, 8 Q21D and D1, 15 Q28D). The primary objective was to determine MTD and DLT as a function of schedule; the secondary objectives included ORR (CR + PR), progression free survival (PFS) and duration of response (DOR). Patients enrolled to the Phase 1 study were required to have relapsed lymphoma of any subtype, ECOG PS < 2 , and adequate organ and marrow function. There was no upper limit to the number of prior therapies or transplantation.

Results: 29 patients were enrolled and evaluable for toxicity. Median age was 54 y (23-73) and 62% were male. The median number of prior therapies was 3 (1-16). Histologies included HL/other (N = 4), B-cell (N = 7) and T-cell (N = 18). There were 5 DLTs in cohort 3 (P 15 mg/m² & R 14 mg/m²) over both schedules consisting of 3 Grade 4 thrombocytopenia, 1 Grade 4 pancytopenia and 1 Grade 4 neutropenia. There were 3 DLTs with P 20 mg/m² & R 12 mg/m² given D1, 8 Q21D consisting of 2 Grade 3 oral mucositis and 1 Grade 4 sepsis. The D1, 15 Q28D schedule had no mucositis and resulted in no DLTs at any dose level. The grade 3/4 toxicities reported in $> 5\%$ of patients were: anemia (29%), thrombocytopenia (28%), febrile neutropenia (14%), oral mucositis (14%), hyponatremia (7%), pneumonia (6%), neutropenia (6%) and sepsis (7%). 23 patients were evaluable for response. The ORR in the total, non-PTCL and PTCL populations was 57%; 33%; and 71% respectively. Among PTCL patients 10/14 achieved a response with CR = 4/14 (29%), PR = 6/14 (43%), and 1 stable disease. The mean DOR in all patients was 3.5 m. The OS and PFS in all patients was 13.8 m (95% CI 8.8) and 3.7 m (95% CI 1.4) and in the PTCL population was 12.8 m (95% CI 8.1) and 4.4 m (95% CI 3.5) respectively. First dose PK studies were performed for P and R in 27 patients. A dose of P 25 mg/m² led to a mean AUC_{0-∞} and C_{max} of 6646.6 ng*h/mL and 8373.8 ng/mL, and R 12 mg/m² led to 1378.2 ng/mL and 419.0 ng*h/mL. These values are higher than what was utilized in *in vitro* studies.

Conclusions: Results from the phase I study established that the combination of P + R given on the D1, 15 Q28D schedule is safe and well



tolerated. These data support the lineage specific activity of the P + R combination with a 71% ORR in PTCL. A multicenter Phase II study of P + R is now enrolling patients with PTCL.

Keywords: pralatrexate; romidepsin (RD); T-cell lymphoma (TCL).

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CANADIAN CANCER TRIALS GROUP (CCTG) LY.17: A RANDOMIZED PHASE II STUDY EVALUATING NOVEL SALVAGE THERAPY PRE-AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) IN RELAPSED/REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA (RR-DLBCL) - OUTCOME OF IBRUTINIB + R-GDP

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Introduction: Salvage chemotherapy and ASCT remains the standard of care in patients (pts) with relapsed/refractory (RR) DLBCL. CCTG trial LY.12 established rituximab combined with gemcitabine, dexamethasone and cisplatin (R-GDP) as a standard of care in this population (Crump JCO 2014), with a low incidence of febrile neutropenia (12%) and infection.

Methods: CCTG LY.17 is an ongoing multi-arm randomized phase II “pick a winner” trial evaluating novel salvage therapy and R-GDP in RR-DLBCL pts post rituximab and anthracycline based chemotherapy failure. The first experimental arm evaluated ibrutinib 560 mg PO daily d1-21 with R-GDP (IR-GDP) q3W. Primary endpoint of the study is overall response rate (ORR) after 3 cycles of therapy using CT imaging (FDG-PET response is an exploratory endpoint). According to the protocol futility rule, any treatment arm with an ORR lower than the control arm at the first interim analysis ($n = 16$) is not considered worthy of further testing and enrolment in that arm will cease. After the run-in cohort of the first 5 IR-GDP pts suggested an increased risk of infection, twice weekly blood count monitoring and antimicrobial prophylaxis for opportunistic infection was recommended along with consideration of G-CSF support. This report is the result of the first interim analysis reporting on 30 pts.

Results: Baseline pt characteristics are reported in Table 1. In the IR-GDP arm 11/14 pts received an ibrutinib dose intensity of >90%. The ORR to IR-GDP was 28.6% (CR 0, PR 28.6%, SD 28.6%, PD 14.3%, inevaluable 28.6%). 8 SAEs including 2 grade 5 events (1 sepsis, 1 pneumonia) and 3 grade 3 infectious events were reported in the IR-GDP arm. Median neutrophil and lymphocyte counts were 1.75 (0.9-20.7) and 0.23 (0.15-0.3) at time of onset of infection. The ORR to R-GDP was 50.1% (CR 6.3%, PR 43.8%, SD 12.5%, PD 37.5%, inevaluable 0). Among patients assigned to R-GDP there were no infections grade 3 or higher; there were 4 SAEs and no grade 5 events. At the time of database lock (median f/u 3.5 months, range 0.7-9.2), all

TABLE 1

	ibrutinib-R-GDP	R-GDP	Total
	N=14 (%)	N=16 (%)	N=30 (%)
Age (median, range)	60.5 (42-69)	53.5 (22-74)	57 (22-74)
Gender (M;F)	8:6	7:9	15:15
ECOG PS			
0	4 (28.6)	7 (43.8)	11 (36.7)
1	9 (64.3)	8 (50.0)	17 (56.7)
2	1 (7.1)	1 (6.3)	2 (6.7)
Stage			
I	1 (7.1)	1 (6.3)	2 (6.6)
II	1 (7.1)	5 (31.3)	6 (20.0)
III	3 (21.4)	0 (0.0)	3 (10.0)
IV	9 (64.3)	10 (62.6)	19 (63.4)
rIPI			
0-1	3 (21.4)	6 (37.5)	9 (30.0)
2-5	11 (78.6)	10 (62.6)	19 (63.4)
Primary Refractory	5 (35.7)	6 (37.5)	11 (37.7)
Transformed Disease	2 (14)	5 (31.3)	7 (23.3)
Prior Radiation	3 (21.4)	5 (31.3)	8 (26.7)

patients were off protocol treatment (IR-GDP:R-GDP; death 2:0; AE 1:0, PD prior to completion of protocol therapy 1:4; patient choice 0:1 and treatment complete 10:11) with 19 pts having a progression event (IR-GDP:R-GDP; on treatment 3:3; during follow-up 5:5; death without PD 2:1) and 11 alive without PD (IR-GDP 4, R-GDP 7).

Conclusions: Addition of ibrutinib did not improve the activity of R-GDP and appeared to be associated with increased risk of infection; accrual to this arm has ceased and additional combinations are being explored.

Keywords: diffuse large B-cell lymphoma (DLBCL); ibrutinib; salvage treatment.

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EFFECT OF ADDING IDELALISIB TO FRONTLINE OFATUMUMAB PLUS EITHER CHLORAMBUCIL OR BENDAMUSTINE IN LESS FIT PATIENTS WITH CLL: PRELIMINARY RESULTS FROM THE NCRI RIALTO TRIAL.

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Introduction: The Phase 3 RIAItO 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). A protocol amendment was introduced in September 2014 to investigate the addition of idelalisib (first-in-class inhibitor of the p110 δ isoform of phosphoinositol-3 kinase) or placebo. Review of safety data in January 2016 revealed excessive toxicity due to idelalisib, and recruitment was suspended. 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 a preliminary analysis of the cohort of patients in RIAItO who received idelalisib or placebo.

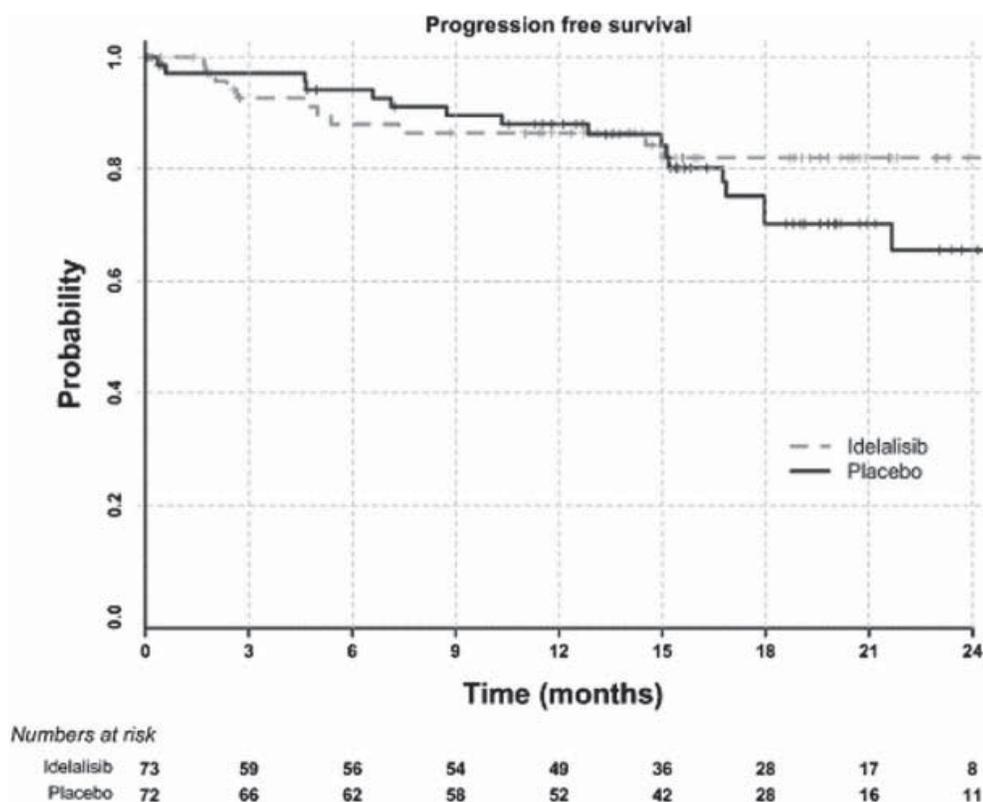
Methods: Patients were eligible for inclusion if they had previously untreated CLL requiring treatment by NCI/IWCLL criteria, were considered unfit for FCR and did not have any contraindications to the

study drugs. Consenting patients underwent an unblinded 1:1 randomisation to ofatumumab (300 mg iv day 1 and 1000 mg iv day 8 of cycle 1; 1000 mg iv day 1 of cycle 2 onwards) plus either chlorambucil (10 mg/m² day 1-7, repeated every 28 days for 3-12 cycles) or bendamustine (70 mg/m² iv day 1-2 for 3-6 cycles) and a double-blinded 1:1 randomisation to concurrently administered placebo or idelalisib (150 mg bd for up to 3 years). Co-trimoxazole prophylaxis was recommended. Study drugs were continued until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). The post-treatment reporting period for serious adverse events (SAEs) was 6 months for grade 3-4 infections and 28 days for other events.

Results: 145 patients received idelalisib (73) or placebo (72), with a median idelalisib exposure time of 2.5 months. As of March 2017, SAEs were reported in 77% of idelalisib-treated patients (81 grade 3-4 and 8 grade 5) compared to 39% in the placebo group (35 grade 3-4 and 2 grade 5). The frequency of SAEs in the idelalisib-treated group was similar in both chemotherapy arms. Grade 5 events in this group included sepsis (1), lung infection (3), febrile neutropenia (2), myocardial infarction (1) and sudden death NOS (1). After a median follow-up of 15 months, 17 PFS events have been observed in the placebo group compared with 11 in the idelalisib group.

Conclusions: In less fit patients with CLL, the addition of idelalisib to frontline O + C or O + B results in an increased rate of grade 3-5 toxicity, much of it due to infection and febrile neutropenia. However, this effect may be offset by a reduction in disease progression. Longer follow-up is required to test this hypothesis.

Keywords: chronic lymphocytic leukemia (CLL); Idelalisib (CAL-101, GS-1101); ofatumumab.



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VENETOCLAX (VEN), BENDAMUSTINE (B) AND RITUXIMAB (R) IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) NON-HODGKIN LYMPHOMA (NHL): FINAL RESULTS OF A PHASE I STUDY

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Introduction: VEN is a potent, selective BCL-2 inhibitor with clinical activity in R/R NHL pts. Preclinical data suggest synergy between VEN and both B and R; together BR is one of the most commonly used regimens in NHL. Final results of a dose finding study of VEN + BR (NCT01594229) are reported.

Methods: This was a Phase 1 dose finding study of VEN + BR in pts ≥ 18 years with R/R NHL and ECOG PS of 0–1. Diffuse large B-cell lymphoma (DLBCL) pts who progressed during/within 2 months (mo) of most recent therapy, and pts with mantle cell lymphoma, were excluded. Dose escalation followed a 3 + 3 design. Oral VEN (50–1200 mg) was given for 3, 7 or 28 consecutive days (d) of each 28d cycle. BR regimen was 6 cycles: B (90 mg/m², IV, 2d/cycle) and R (375 mg/m² IV, 1d/cycle). After completing VEN + BR, pts could continue VEN alone for ≤ 2 years after the date of last subject enrolled (maintenance) in the absence of progression and/or unacceptable toxicity. Primary endpoints included safety, pharmacokinetics, maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D); secondary endpoint was preliminary efficacy. Adverse events (AE) were graded per NCI CTCAE v4.0 and efficacy per 2007 IWG criteria. Data cut-off was Feb 15, 2017.

Results: Between Jun 2012 and Oct 2015 60 pts were enrolled. Median age was 62 (range, 29–90) years; 53% (n = 32) had follicular lymphoma (FL), 37% (n = 22) had DLBCL and 10% (n = 6) had marginal zone lymphoma (MZL). Pts had a median of 3 (1–8) prior therapies. Median time on study was 7.7 (0.13–51.3) mo. Overall, 98% pts had an AE; most frequent (any grade) were nausea, neutropenia (68% each), diarrhea (55%) and thrombocytopenia (52%). Most common Grade 3/4 AEs were neutropenia (60%), and lymphopenia (38%). 24 pts reported serious AEs, with febrile neutropenia (FN) and AEs related to disease progression (8%) the most frequent. 29 pts discontinued the study (PD, n = 16; withdrawn consent, n = 4; AEs, n = 3; other, n = 6); 5 pts died from either disease progression (n = 4) or respiratory failure (n = 1). After early incidents of FN the protocol was revised to incorporate use of G-CSF. MTD was not reached; RP2D for VEN + BR was declared 800 mg continuously. VEN exposure with and without BR was comparable.

The table presents efficacy data.

Conclusions: VEN + BR demonstrated tolerable safety profile at up to 1200 mg continuously, and significant clinical activity; 800 mg VEN continuously is being used in the randomized CONTRALTO study. In pts with indolent lymphoma who received maintenance VEN, durable responses were observed.

Keywords: ABT-199; BCL2; non-Hodgkin lymphoma (NHL).

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POLA-R-CHP: POLATUZUMAB VEDOTIN COMBINED WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, PREDNISONE FOR PATIENTS WITH PREVIOUSLY UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA

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TABLE 1

	FL, (n=32)	MZL, (n=6)	Entire Study Population (including DLBCL, n=60)
ORR, n (%)	24 (75)	6 (100)	39 (65)
CR rate, n (%)	11 (34.4)	3 (50.0)	17 (28.3)
DOR, mo, (median, range)	11.4 (1.2–48.4)	8.9 (1.2–14.9)	8.8 (0.03–48.4)
PFS, mo, (median, range)	9.8 (5.1–50.0)	10.6 (3.8–21.0)	10.7 (95% CI: 4.3–NR)
PFS, mo, (median, 95% CI), maintenance vs no maintenance	Not reached (NR) vs 5.1 (1.5, 10.7)	21.0 (6.5, 21.0) vs 3.8 (-,-)	NR vs 3.5 (1.7, 4.3)
OS, mo, (median, range)	11.6 (1.5–50.0)	10.6 (6.1–22.7)	9.6 (0.9–50.0)

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Introduction: Polatumab vedotin (pola) is an antibody drug conjugate containing the anti-mitotic MMAE targeting CD79b, an antigen expressed ubiquitously in DLBCL. Pola as monotherapy and in combination with anti-CD20 antibodies demonstrated encouraging efficacy in r/r DLBCL (Palanca-Wessels, 2015; Morschhauser, 2014). The initial dose-escalation portion of this multicenter, open-label Ph Ib/II study of pola in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) showed an acceptable safety profile and established a recommended Ph II dose of pola at 1.8 mg/kg (Bartlett, 2015). We report updated safety and efficacy results for the Ph II dose in 45 previously untreated DLBCL patients (pts) (ClinicalTrials.gov NCT01992653).

Methods: Five pts of the dose escalation phase and the 40 pts of the expansion phase were included in this analysis. All had newly diagnosed DLBCL and were treated with pola at 1.8 mg/kg and R-CHP at standard doses every 21 days for 6 or 8 cycles. Investigator assessments for anti-tumor activity were performed according to IWG 2007 following 4 cycles and at the end of study treatment (EOT).

Results: All 45 pts received at least one dose of study drug. The median age was 69 years; 93% were >60 years, 33% ECOG >1, 82% Stage III/IV, and 78% IPI 3-5. Of the 29 pts with cell of origin (COO) status by digital gene expression, 11 (38%) were ABC, 14 (48%) were GCB, while 4 (14%) were unclassified.

Forty patients completed 6 or 8 cycles (23 and 17 pts respectively). All pts experienced at least one AE. Grade (Gr) 3/4 AEs occurred in 58%, and one pt experienced a Gr 5 atrial fibrillation. Gr 3/4 neutropenia and febrile neutropenia (FN) occurred in 27% and 11%. Serious adverse events (SAEs) were reported in 17 pts (38%) including 3 FN, and 2 each of neutropenia, pneumonia, pulmonary embolism and influenza A.

Peripheral neuropathy (PN) occurred in 18 (40%) patients. Among these pts with PN, 12 were Gr 1, 4 were Gr 2, and 2 were Gr 3. All Gr 2/3 PN attributed to pola occurred at C5 or later.

Four pts discontinued pola early for the following reasons: Gr 5 atrial fibrillation (after C2, not attributed to pola by investigator), *E. coli* UTI (C5), worsening essential tremor (C3), PN (C7). During treatment, 6 pts had dose reductions in pola and 1 pt had cyclophosphamide and doxorubicin dose reductions. ORR by PET at EOT was 91%; 78% had a CR and 13% PR. 3 pts progressed and 1 was unevaluable. In the COO determined population, CR was 91% in ABC and 86% in GCB pts. At the data cutoff of November 4, 2016 with a median study duration of 9.5 months, (range 1.3-28 months), only 1 pt had a disease progression in follow up.

Conclusions: Pola at 1.8 mg/kg in combination with R-CHP in 1 L DLBCL has an acceptable safety profile and produced promising

response rates at the end of treatment. The majority of the patients in this trial represented a poor prognosis group by age and IPI. In this context, treatment response to this regimen may warrant further exploration.

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

“FOCUS ON...” SESSION: CLINICO-GENETIC RISK MODELS

81 APPLICATION OF A GENE EXPRESSION-BASED MODEL IN COMBINATION WITH FDG-PET IMAGING TO PREDICT TREATMENT RESPONSE IN ADVANCED HODGKIN LYMPHOMA IN THE RATHL STUDY (CRUK/07/033)

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Introduction: The challenge in classical Hodgkin lymphoma (CHL) is stratifying therapy to maximise success while minimising side effects. Response-adapted therapy using FDG-PET scans after 2 cycles of ABVD (PET2) is an effective strategy, but this approach results in 2 months of suboptimal treatment in those patients (pts) at high risk of treatment failure. We examined whether a previously-described gene expression profiling (GEP) based model performed on RNA from formalin-fixed paraffin-embedded tissue (FFPET) biopsies could be used as a baseline predictor of outcomes.

Methods: RNA was extracted from 315 diagnostic FFPET biopsies from the RATHL trial, a subset representative of the total group of trial pts enrolled. The “26 gene” assay (23 genes of interest, 3 reference genes) was performed on the NanoString platform (NanoString

Technologies, Seattle, WA) as a “locked” biomarker as previously described (Scott et al., *J Clin Oncol* 2013; 31:692-700). The threshold previously described was trained on overall survival (OS) after ABVD. The performance of the assay at predicting PET2 and OS in RATHL was tested using this threshold, then receiver operating characteristic (ROC) analysis was used to assess if a better threshold could be found for our cohort.

Results: 284 patients were analysable as GEP failed in 31 patients. Comparing baseline demographics, the high risk GEP group had an excess of elderly, male and higher disease stage pts. The GEP score was not able to predict PET2 positivity (PET2+); 16 (12.1%) high risk pts and 26 (17.1%) low risk pts were PET2+ (12.5% and 18.3% in the stage III-IV group). Performing ROC analysis using the score as a continuous variable did not suggest a different cut off would perform better (area under the curve: 43.8%). GEP risk was associated with poorer OS in univariable analysis (3 year OS 98% vs 93% for low and high risk, respectively) but this lost significance when adjusted for other baseline factors. The classifier was not prognostic for PFS in any group in RATHL (whole population, PET2- or PET2+).

Conclusions: The GEP based model was not predictive of PET2 response and is not a suitable method for determining escalation of treatment. A higher proportion of patients were assigned to the high risk group in the RATHL trial and OS was higher compared with the original intergroup study, however based on these results, a refined GEP based model with validation across other platforms is required for this modality to be used as a baseline predictor of outcome in CHL.

Keywords: gene expression profile (GEP); Hodgkin lymphoma (HL); positron emission tomography (PET).

82 THE 23-GENE GENE EXPRESSION-BASED ASSAY DOES NOT PREDICT INTERIM PET SCAN RESULTS AFTER ABVD IN ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA IN THE US INTERGROUP S0816 TRIAL

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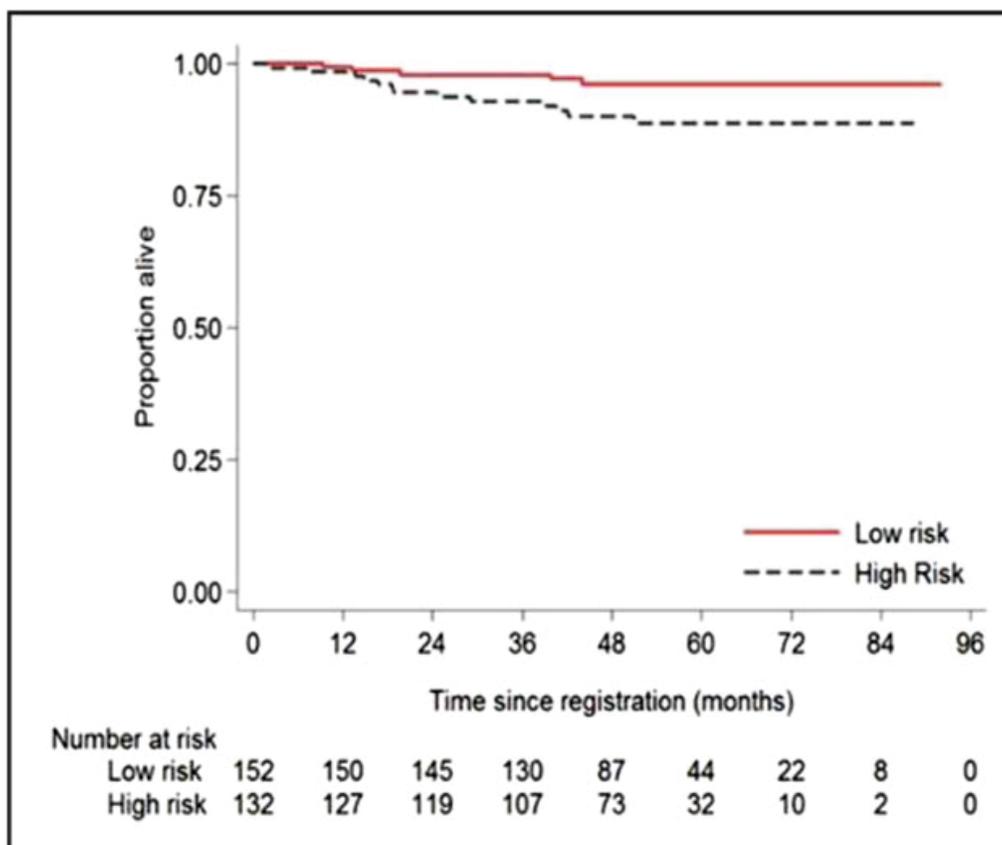


Figure 1: Graph of low and high risk by GEP showing overall survival in all patients.

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Introduction: Recently, we described a 23-gene gene expression-based biomarker that was prognostic for overall survival (OS) in patients (pts) with locally extensive and advanced stage classical Hodgkin lymphoma treated with ABVD chemotherapy (Scott et al. *J Clin Oncol* 2013). The observation that the results of PET scan after 2 cycles (PET2) of ABVD is highly prognostic of progression free survival (PFS) has led to the design of response-adapted trials, where pts with a positive PET2 receive more intensive regimens aiming to improve outcomes. The purpose of this study was to test whether the 23-gene assay could predict PET2 results, allowing rational selective escalation of treatment from the time of diagnosis. The US Intergroup S0816 trial was a response-adapted trial in advanced stage (III and IV) classical Hodgkin lymphoma, with escalation to escBEACOPP where the PET2 was Deauville 4 or 5 (Press et al. *J Clin Oncol* 2016).

Methods: The 23-gene assay was applied to RNA extracted from the formalin-fixed paraffin-embedded (FFPE) diagnostic biopsies of 276 pts from the S0816 trial. Patients were categorized into low- and high-risk groups using previously described assay thresholds. The primary endpoint was the comparison of the proportion of PET2 positive pts in the two risk groups. The secondary endpoint explored whether the risk groups were predictive of PFS in the context of response-adapted treatment.

Results: Adequate gene expression was obtained in 217/276 (79%) biopsies – 119/164 (73%) from archival slides and 98/112 (88%) FFPE blocks. The patient characteristics of the 217 pts were not significantly different from the remainder of the total trial population of 336 pts. 142 (65%) pts were assigned to the low- and 75 (35%) to the high-risk gene expression group. 38 (18%) pts had a positive PET2. The assay did not identify pts at greater risk of PET2 positivity with 21% and 11% of pts having a positive PET2 in the low- and high-risk group, respectively. To test whether this was the result of a suboptimal threshold, we examined the area under the curve (AUC) of the receiver operator characteristic curve. The AUC of 0.41 (95% CI 0.31 – 0.51) demonstrates that the assay is not predictive of PET2 positivity. Furthermore, the assay was not predictive of PFS, with a 2-year PFS of 80% and 84% in the low- and high-risk groups, respectively (log rank $P = 0.65$). There were not sufficient events to test the prognostic power of the assay for OS.

Conclusions: The 23-gene assay, trained on the endpoint of OS, was not predictive of PET2 results. Furthermore, it was not predictive of PFS in this trial of response-adapted treatment. These results provide strong evidence that this assay should not be used for risk stratification where response-adapted therapy is utilized.

Support: National Cancer Institute (NCI), National Clinical Trials Network (NCTN) grants CA180888, CA180819, CA180821, and CA180820; Lymphoma Research Foundation.

Keywords: classical Hodgkin lymphoma (cHL); gene expression profile (GEP); positron emission tomography (PET).

FAILURE IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) TREATED WITH R-CHOP

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Introduction: About 60-70% of DLBCL patients are currently cured with immunochemotherapy. However, patients with early failure (EF), either primary refractory or early progressions, show a dismal outcome independently of standard prognostic factors, including the cell of origin (COO). The aim of the present study was to analyze the genetic profile of EF patients, in order to identify predictive factors of response to R-CHOP and understand mechanisms of resistance.

Methods: We selected 121 patients (65 M/56F; median age, 63 years; median overall survival 9.2 years) diagnosed with *de novo* DLBCL not otherwise specified at GELCAB centers, treated with R-CHOP. Thirty four cases (28%) either primary refractory or relapsed within 12 months were considered EF. Median follow-up for surviving patients was 4.7 yrs. Genomic profiling included targeted next generation sequencing of 106 representative genes, Cytoscan HD arrays and gene expression profiling (GEP). COO was established by gene expression based assays.

Results: Main clinical features predicting EF are detailed in the table. EF cases had more frequently mutations in *KLHL6* and gains in 12q (*CDK4*), 11q (*ETS1*) and 5p (*TERT*). Regarding signaling pathways, alterations in the immune surveillance (*CD58*, *B2M*, *CIITA*), *TP53/CDKN2A* and NOTCH (*NOTCH1&2*, *SGK1* and *FBXW7*) pathways also predicted EF (table). Of note, among GCB cases, those with EF showed more frequently mutations of *KLHL6*, *MYC*, *HIST1H1E* and *SGK1*, and gains in Chr 12. In multivariate analysis only *TP53/CDKN2A* (HR 2.2; $P = .03$) and NOTCH (HR 2.5; $P = .01$) pathways were independently associated with EF. Finally, GEP performed in 41 tumors showed that EF cases had over-representation of pathways related to inflammatory responses mediated by IFN α , IFN γ , IFN-response factors and IL-1, IL6-, IL-8, together with signatures related to leukocyte infiltration.

Conclusions: Different genetic profile aberrations, including alterations in *TP53/CDKN2A* and NOTCH pathways, can predict EF after R-CHOP

83 GENE MUTATIONS AND COPY NUMBER ALTERATIONS (CNA) PREDICT FOR EARLY

TABLE 1

Initial Features	Non Early Failure	Early Failure	P value
Median age	58.6	62.4	NS
Male/Female	45/42	20/14	NS
Advanced Stage	36/87 (41%)	27/34 (79%)	<0.01
Bone marrow infiltration	6/86 (7%)	7/34 (21%)	0.04
Elevated serum LDH	33/83 (40%)	18/33 (55%)	NS
IPI score int-high & high	27/87 (31%)	18/34 (53%)	0.04
COO			
GCB	41/69 (59%)	12/28 (43%)	NS
ABC	28/69 (41%)	16/28 (57%)	
KLHL6 mutation	1/87 (1%)	4/34 (12%)	0.022
Gains of 12q14.1 (CDK4)	12/68 (18%)	11/26 (42%)	0.017
Gains of 5p15.31 (TERT)	10/68 (15%)	10/26 (38%)	0.022
Gains of 11q24.3 (ETS1)	14/68 (21%)	11/26 (42%)	0.04
Gains of 12q15 (MDM2)	14/68 (21%)	11/26 (42%)	0.04
Immune surveillance pathway	36/68 (53%)	21/26 (81%)	0.013
NOTCH pathway	14/87 (16%)	12/34 (35%)	0.021
TP53/CDKN2A pathway	18/70 (26%)	13/26 (50%)	0.024

better than standard prognostic factors, including COO. Further studies are necessary to validate these findings in prospective series.

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

84 KMT2D AND TP53 MUTATIONS PREDICT POOR PFS AND OS IN MANTLE CELL LYMPHOMA RECEIVING HIGH-DOSE THERAPY AND ASCT: THE FONDAZIONE ITALIANA LINFOMI (FIL) MCL0208 PHASE III TRIAL

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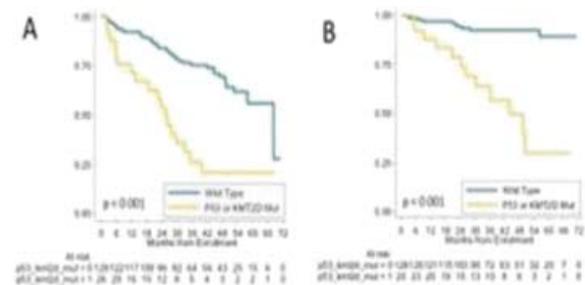


Figure 1: PFS (A) and OS (B) by TP53 and/or KMT2D mutational status

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Introduction: Within the landscape of mutated genes in mantle cell lymphoma (MCL), only TP53 disruption has been so far associated with outcome. Here we present the clinical update of the deep sequencing MCL gene panel analysis in the prospective FIL-MCL0208 phase III trial (NCT02354313, high-dose immunochemotherapy followed by autologous transplantation for untreated, advanced stage <65 years MCL) based on the data from the second interim analysis.

Methods: A targeted resequencing gene panel, including coding exons and splice sites of the ATM, BIRC3, CCND1, KMT2D, TP53, TRAF2, WHSC1, and NOTCH1 genes was analyzed in tumor DNA from baseline bone marrow CD19+ purified MCL cells and, to filter out polymorphisms, in the paired normal genomic DNA (55% of cases) using a TruSeq Custom Amplicon target enrichment system followed by deep next generation sequencing (Illumina, median depth of coverage 2356x). Variants represented in >10% of the alleles were called with VarScan2 with the somatic function when the paired germline DNA was available. For patients lacking germline DNA, a bioinformatics pipeline including a number of stringent filters was applied to protect against the misclassification of polymorphisms as somatic variants. Clinical data were updated at the time of the second interim analysis (January, 2017).

Results: Out of the 300 enrolled patients, 176 were evaluable for mutations. Median follow-up of the cohort was 36 months, and 3-years PFS and OS were 66% and 86%, respectively. Patients not included in the study, due to unavailable tumor DNA (n = 124) showed superimposable clinical features and outcome. Mutations of TP53 (9% of cases) and KMT2D (11% of cases) associated with an increase in the hazard of progression both in univariate analysis as well as after adjusting for MIPI, Ki67 and blastoid variant: HR 3.87 (95% CI 1.64 to 9.13), p < 0.002 and HR 3.66 (95% CI 1.77 to 7.56), p < 0.001, respectively. These results translated into an increase of the hazard of death in both TP53 and KMT2D mutated patients both in univariate analysis as well as adjusting for MIPI, Ki67 and blastoid variant HR 4.26 (95% CI 1.34 to 13.57), p = 0.014 and HR 3.09 (95% CI 1.07 to 8.86), p = 0.036, respectively. On these bases, a survival model was proposed based on the TP53 and KMT2D mutation status: 3-years PFS and OS were 25% and 64% for patients carrying either TP53 or KMT2D

mutations or both vs 75% and 92% for patients without any of these mutations (Figure 1).

Conclusion: The updated clinical results of the FIL-MCL0208 trial show that: i) both *TP53* and *KMT2D* mutations independently associate with shorter PFS and OS in younger MCL patients receiving high-dose therapy; ii) *KMT2D* mutations seem to be as detrimental as *TP53* mutations, at least in terms of PFS; iii) given the negative prognostic impact of these mutations, they might be used to select high-risk patients for novel therapeutic approaches.

Keywords: autologous stem cell transplantation (ASCT); mantle cell lymphoma (MCL); molecular genetics.

85 BASELINE CIRCULATING CELL-FREE DNA LOAD IS RELATED TO, BUT ADDS PROGNOSTIC VALUE TO METABOLIC TUMOR BURDEN MEASURED BY FDG PET/CT IN FOLLICULAR LYMPHOMA

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Introduction: Progression-free survival (PFS) of follicular lymphoma (FL) greatly improved during the last decades, but despite rituximab maintenance relapses still occur. Total metabolic tumor volume (TMTV) computed on baseline FDG-PET was recently shown to have a strong prognosis value independently of FLIPI (Meignan et al., JCO 2016). Circulating cell-free DNA (cfDNA) load correlates with staging and prognosis in Hodgkin and diffuse large B-cell lymphoma but was not explored so far in FL. The aim of our study was to correlate cfDNA with TMTV in FL at diagnosis and to determine their respective prognostic values.

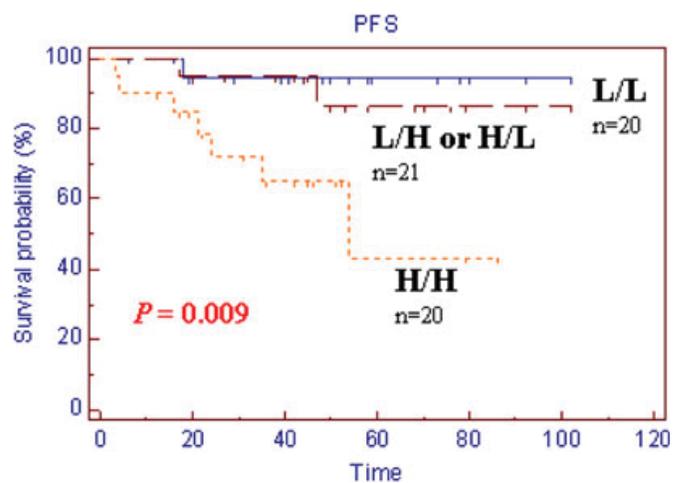
Methods: In 61 consecutive patients with previously untreated FL, baseline PET and plasma sampling were studied. TMTV were calculated according to Meignan et al. Total cfDNA was extracted from plasma, quantified by droplet digital PCR (ddPCR) using ANKRD30B as reference gene and results were expressed as equivalent genome per mL (eqg/mL).

Results: Patient characteristics and first-line treatments are summarized in the Table.

Median TMTV was 392 cm³ (17-7796). CfDNA was detected in all patients, with a median of 2600 eqg/mL (650-410400). A significant correlation was found between TMTV and cfDNA ($R = 0.6$, $p < 0.0001$). With a median follow-up of 47 months, patients with high TMTV (>510 cm³) had a lower 4y-PFS than those with low TMTV (59% [42-75%] vs 84% [75-94%], respectively, $p = 0.0004$).

TABLE 15

	All patients (n=61) n° (%)	TMTV >510cm ³ (n=24/61) n° (%)	CfDNA>2550 (n=37/61) n° (%)
age>60	33 (54)	17 (71%)	23 (62%)
Ann Arbor Stage III-IV	58 (95)	24 (100)	36 (97)
Bone Marrow (+)	39 (65)	21 (87)	26 (72)
LodLIN (cm)>6	19 (31)	8 (33)	13(35)
LDH>NI	13 (21)	6 (25)	10 (27)
B2microglobulin>N1	35 (57)	20 (83)	27 (73)
FLIPI score >2	34 (56)	19 (79)	25(68)
FLIPI2 score>2	28 (47)	18 (75)	23 (64)
First-Line Treatment			
R Chemo	17 (28)	7 (29)	9 (24)
R Chemo +maintenance	29 (48)	9 (37)	16 (43)
Chemo Free	2 (3)		1 (3)
Chemo Free + maintenance	13 (21)	8 (33)	11 (30)



A cfDNA cutoff of >2550 eqg/mL identified patients with lower 4y-PFS (93% vs 73%; HR 6.74 [1.92-23.57]; $p = 0.04$). Patients with both high cfDNA and TMTV values (H/H) had a lower 4y-PFS (65%) than those with discrepant (L/H) or low (L/L) values (86% and 94%, respectively) ($p = 0.009$). After adjusting for maintenance therapy, combined cfDNA and TMTV still identified 3 groups of patients with 72%, 80% and 100% 4y-PFS respectively ($p = 0.06$).

Conclusion: Baseline cfDNA correlates with TMTV in FL and influences patient's outcome. Patients with both high cfDNA and TMTV experienced shorter PFS, even when adjusted for maintenance therapy.

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

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EVALUATION OF CLINICOGENETIC RISK MODELS FOR OUTCOME OF FOLLICULAR LYMPHOMA PATIENTS IN THE PRIMA TRIAL

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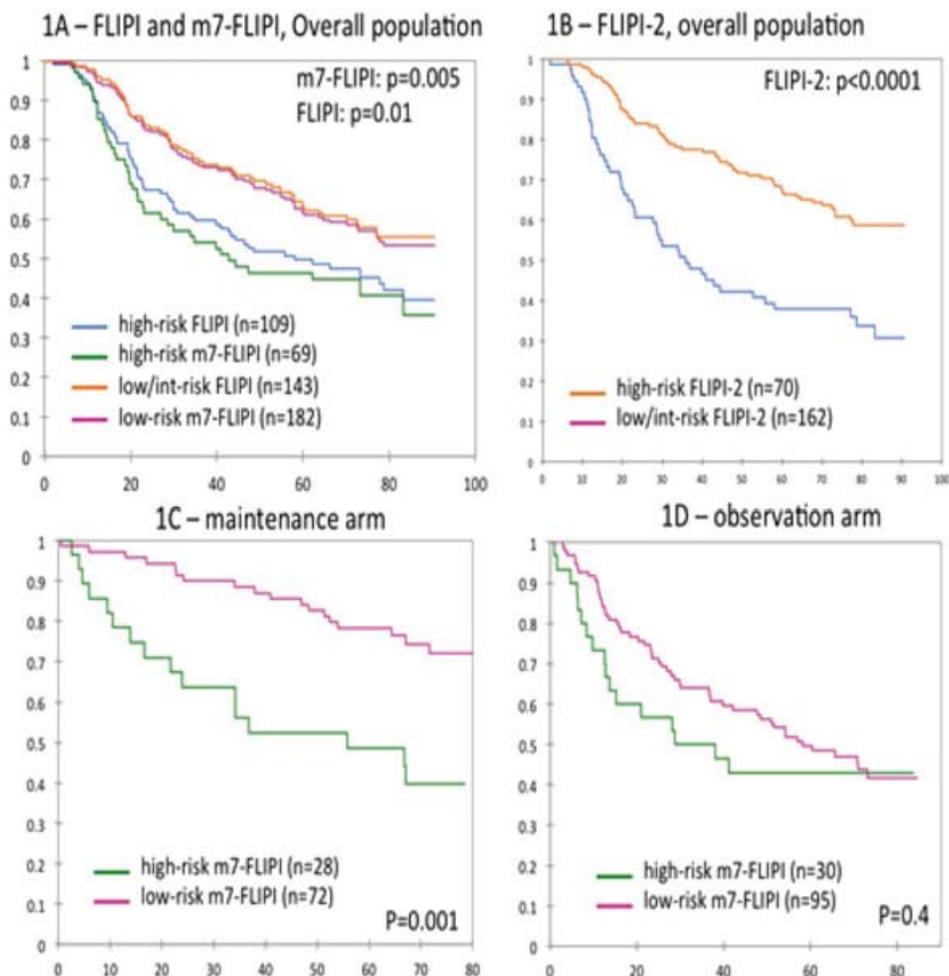
Introduction: Composite scores integrating genes mutation status with the clinical predictor FLIPI have been recently proposed to

improve risk stratification for follicular lymphoma (FL) patients. We evaluated the ability of m7-FLIPI and POD24-PI scores to predict progression free survival (PFS) in a large cohort of patients receiving first-line immunochemotherapy, with or without rituximab maintenance.

Methods: Tumour biopsies were obtained at FL diagnosis from 252 patients from the PRIMA study, either as FFPE tissues ($n = 98$) or fresh-frozen tissues ($n = 154$). After DNA extraction, DNA-targeted sequencing was performed using the Foundation One Heme™ panel. m7-FLIPI and POD24-PI models were applied as originally described.

Results: The frequency of non-silent mutations were similar to those previously reported: CREBBP = 75%, EZH2 = 28%, CARD1 = 19%, ARID1A = 19%, EP300 = 16%, FOXO1 = 16% and MEF2B = 12%. We first evaluated the prognostic value of each gene mutation status separately. While some mutations were associated with a longer (MEF2B, EZH2) or shorter (EP300, CREBBP) PFS as previously described, ARID1A or CARD11 mutations were not associated with patients outcome. Moreover, FOXO1 mutations were associated with a good outcome, in opposite to their prognostic weight in the m7-FLIPI.

The m7-FLIPI and FLIPI scores classified 28% and 43% of patients as high-risk, respectively. m7-FLIPI correlated with PFS ($p = 0.005$; OR = 1.74, 95%CI: 1.00-3.02), slightly outperforming the FLIPI



($p = 0.01$; OR = 1.63, 95%CI: 0.99-2.70), but not the FLIPI-2 ($p < 0.0001$, OR = 2.85, 95%CI: 1.62-5.03) (Figure 1A-B). A high m7-FLIPI score was associated with a shorter PFS in patients randomized in the rituximab maintenance group of PRIMA ($p = 0.001$), but was not prognostic for patients in the observation group (Figure 1C-D).

Progression of the disease within 24 months after diagnosis (POD24) proved to be a strong predictor of overall survival, which led to the proposal of the POD24-PI as a predictor of early progression. In our study, 56 patients (22%) progressed within 2 years. FOXO1 mutations were enriched in the group of patients who did not experience POD24 (19% vs 7%, $p = 0.04$). The m7-FLIPI, POD24-PI, FLIPI-1 and FLIPI-2 scores showed specificity of 77%, 72%, 62% and 76%, respectively, and sensitivity of 46%, 54%, 60% and 53%, respectively, to predict POD24. The m7-FLIPI and FLIPI-2 thus showed the highest specificities, reflecting the prediction of correctly classifying as "low-risk" a patient, but the FLIPI-1 had the highest sensitivity to predict the risk of progression at the critical 2-year endpoint.

Conclusions: We confirmed in a large cohort, using a clinically validated assay, the applicability of composite scores m7-FLIPI and POD24-PI. Nevertheless, these scores showed some limitations, and need further evaluation to better discriminate risk group categories identified with FLIPI-1 or -2 in larger cohorts and in patients treated with other approaches.

Keywords: follicular lymphoma (FL); prognostic indices.

"FOCUS ON..." SESSION: ONGOING TRIALS

Abstracts from OT01 to OT06 can be found in the pertinent section, after the PUBLICATION section.

"FOCUS ON..." SESSION: LYMPHOMA IN THE ELDERLY

87 HIGHER MUTATIONAL BURDEN BUT DOES NOT IMPACT TREATMENT EFFICACY IN FOLLICULAR LYMPHOMA

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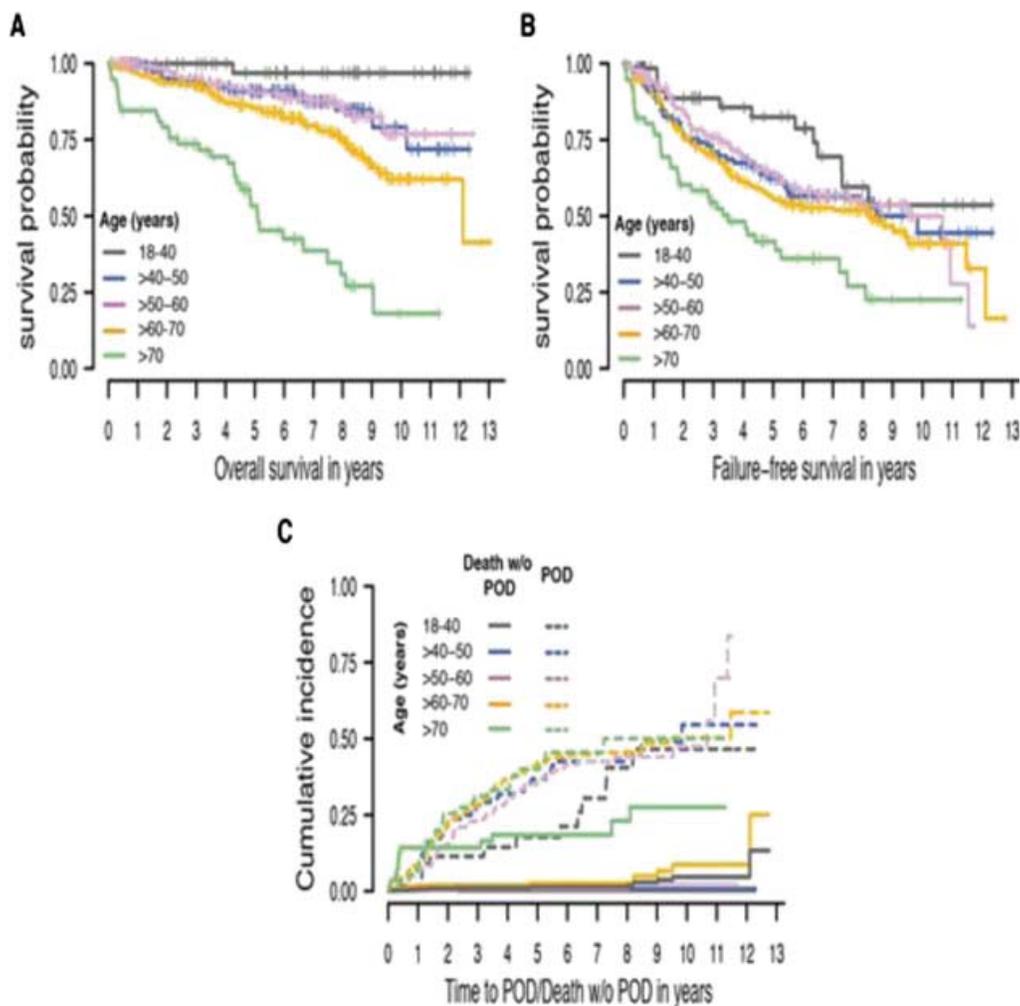
Introduction: Higher age is associated with shorter overall survival (OS) in patients (pts) with follicular lymphoma (FL), and age > 60 years is a component of the FL International Prognostic Index (FLIPI). However, it is unclear whether higher age directly impacts disease biology or treatment efficacy in FL.

Methods: We analyzed 755 pts from the GLSG2000 trial who received R-CHOP for symptomatic, advanced stage FL. Pts who received consolidative autologous stem cell transplantation were censored at time of transplant. Progression of disease (POD) included progressive, relapsed or refractory disease (<PR). Failure-free survival (FFS) events consisted of POD or death. OS and FFS were calculated from treatment initiation. We used Kaplan-Meier curves and Cox proportional hazards regression for survival analyses. We performed competing risk analysis using cumulative incidences of POD and death without prior POD. DNA sequencing data from diagnostic FL biopsies were available from 151 R-CHOP treated pts, and another 107 pts from BCCA who received R-CVP for symptomatic advanced FL. We analyzed mutations in the coding regions of 74 targeted genes.

Results: We categorized GLSG2000 pts into 5 distinct age groups: 65 pts (9%) were 18-40 years (yrs), 163 (22%) >40-50 yrs, 261 (35%) >50-60 yrs, 208 (28%) >60-70 yrs, and 58 (8%) >70 yrs. 5-year OS rates were 97%, 91%, 90%, 85%, and 53% (Figure A); 5-year FFS rates were 82%, 62%, 63%, 55%, and 42% (Figure B), respectively. We used the cohort >50-60 yrs as a reference. Older pts had inferior OS (>60-70 yrs: HR 1.90, 95%-CI [1.15; 3.13], $p = 0.012$; >70 yrs: HR 7.31, 95%-CI [4.25; 12.59], $p < 0.0001$). Significantly inferior FFS was only seen in pts >70 yrs (HR 2.17, 95%-CI [1.45; 3.25], $p = 0.00016$). Competing risk analysis revealed that inferior FFS of pts >70 yrs did not result from increased POD (HR 1.20, 95%-CI [0.75; 1.91], $p = 0.45$), but from higher incidence of death without prior POD (HR 24.81, 95%-CI [5.38; 114.44], $p < 0.0001$; Figure C). Sequencing data of diagnostic FL biopsies from 258 pts showed that the number of gene mutations increased with age (RR 1.14/decade, 95%-CI [1.09; 1.20], $p < 0.0001$). This increase was however caused by silent mutations and mutations predicted to have low functional impact (each $p < 0.0001$), whereas disruptive mutations or mutations predicted to have high functional impact did not significantly increase with age ($p = 0.27$ and $p = 0.16$, respectively). Similarly, the number of mutated genes increased with age (RR 1.12/decade, 95%-CI [1.07; 1.18], $p < 0.0001$), but the fraction of significantly mutated genes (by MutSigCV) decreased from 89% (range 40-100%) in young adults (18-40 yrs) to 74% (range 0-100%, $p = 0.01$) in the oldest cohort (>70 yrs). No single gene mutation was found to be associated with older age after correction for multiple testing.

Conclusions: Our data suggest that older age does not directly impact disease biology and treatment efficacy in FL, and should not be used to guide treatment decisions.

Keywords: follicular lymphoma (FL); molecular genetics; R-CHOP.



88 LOW NK CELL COUNT AT DIAGNOSIS IS ASSOCIATED WITH SHORTER PFS IN ELDERLY PATIENTS WITH DLBCL TREATED WITH RCHOP AND RANDOMIZED FOR LENALIDOMIDE MAINTENANCE: A LYSA STUDY

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Introduction: Natural killer (NK) cells are essential components of immune surveillance against cancers. Several NK activating receptors, including NKp30, NKp46, NKG2D, DNAM-1 have been linked to anti-tumor immunity, and can complement the antibody dependent cytotoxicity (ADCC) mediated by CD16. The addition of Rituximab to CHOP (R-CHOP) has markedly improved the clinical outcomes of elderly diffuse large B cell lymphoma (DLBCL) patients. We have recently shown in the REMARC phase III trial (clinicalTrials.gov NCT01122472) that lenalidomide (LEN) maintenance after response to R-CHOP increase the progression free survival (PFS) when compared to placebo. Given the dominant mechanism of ADCC assumed for R in DLBCL, and the potent immunomodulatory role of LEN, we aimed at analyzing the status and the prognostic value of NK repertoire at diagnosis and at time of LEN administration.

Methods: From 05/2009 to 11/2014, 336 patients enrolled in France in the REMARC study had centralized prospective peripheral blood lymphocyte analyses by flow cytometry (FCM) either at diagnosis ($n = 220$), at randomization ($n = 188$) or both ($n = 73$). Absolute counts of CD4+, CD8+ T cells, B cells, NK cells, and monocytes, were derived directly from the FCM data. According to CD16 and CD56 expression, NK were classified as cytotoxic (16+/56dim), cytokinic (16-/56 bright) and anti-tumoral natural cytotoxic (16-/56 dim) NK cells. For each NK subpopulation, activating receptor expressions cited above were analyzed. Patients were grouped according to their NK subpopulation profile by hierarchical clustering. Associations between NK cell counts and respectively IPI, cell of origin (COO) by both Hans and nanotring, and PFS were assessed.

Results: Similarly to entire REMARC cohort, patients analyzed had median age of 68, a low aalPI for 43% and high for 56%. With median values of 388, 223, and 160 per μl , CD4+ CD8+ and NK cells were within the normal ranges in only half of the patients at diagnosis. Univariate analysis showed that NK cell count $<100/\mu\text{l}$ at diagnosis was not associated with IPI or COO but was significantly associated with a shorter PFS [HR = 2.5 (1.6, 3.8) $P < 0.0001$]. In a Cox model for PFS including IPI, COO (Hans), randomization arm (LEN or observation), NK cell count $<100/\mu\text{l}$ prognostic value was retained (HR = 2.9 (1.6, 5.1) $P < 0.0005$). Clustering of NK subpopulations showed that variation of total NK cell count was mostly associated with variation of the dominant CD16+/CD56dim population expressing activating receptors and identified a patient cluster with depleted count of all subpopulations and poor prognosis.

Conclusion: Low NK cell count at diagnosis is associated with poor clinical outcomes in elderly patients with DLBCL treated with R-CHOP independently of IPI, GCB/nonGCB subtypes and LEN maintenance. Clustering of NK subpopulations allows the identification of a small group of patients with a very unfavorable prognosis.

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

89 CHARACTERISTICS, TREATMENT, AND OUTCOMES OF ≥ 80 YEAR OLD PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) ENROLLED TO PROSPECTIVE TRIALS OF THE GERMAN CLL STUDY GROUP

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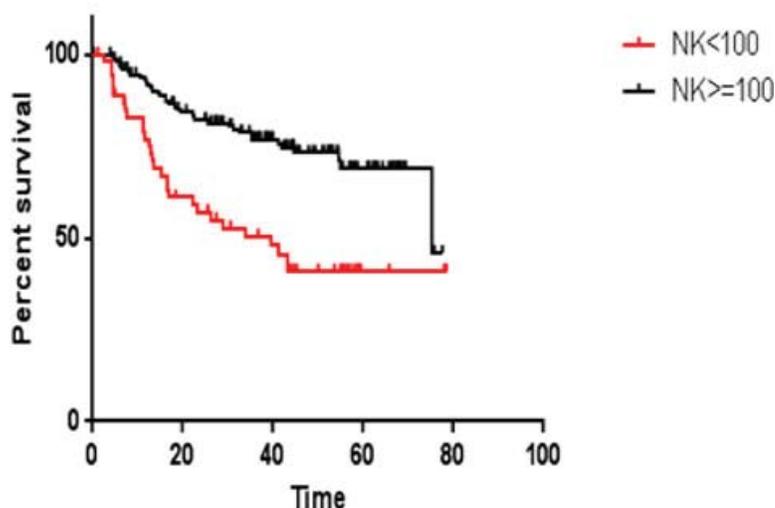
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Introduction: Clinical management of ≥ 80 year old patients (pts) with CLL remains a challenge due to the very limited amount of data currently available for this age segment. Two retrospective studies reported observational data on characteristics, treatment, and outcomes of ≥ 80 year old pts not enrolled in a clinical trial (Bailey et al., Meunier et al.). Comparably little is known about ≥ 80 year old pts who were treated for CLL within clinical trials, however.

Methods: Trial populations of seven clinical trials of the GCLLSG (CLL1, CLL5, CLL7, CLL8, CLL9, CLL10, CLL11; total $N = 3552$) were reviewed and screened for pts ≥ 80 years at frontline treatment. Clinical, laboratory, and genetic data of the identified pts were pooled. Time-to-event data were analysed by Kaplan-Meier methodology. Independent prognostic factors for survival were identified by multivariate analysis using Cox regression modelling with stepwise selection procedures.

Results: Among 3552 reviewed GCLLSG trial participants, 152 were aged ≥ 80 years at initiation of frontline treatment. Pts were identified

Impact of NK cell absolute Value at diagnosis on PFS (DEL PFS)



from CLL11 ($n = 132$), CLL1 ($n = 3$), CLL5 ($n = 1$), CLL7 ($n = 3$), CLL8 ($n = 2$), CLL9 ($n = 9$), and CLL10 ($n = 2$). Median age was 82 years (range 80-90). Concomitant diseases were present in 99% of the pts and median cumulative illness rating scale (CIRS) score was 8 (0-18). Median creatinine clearance was 46 mL/min (range 17-99 mL/min). Distribution of CLL-IPI risk groups was as follows: 6% low, 19% intermediate, 61% high, and 14% very high. Most pts had Binet stage B (36%) or C (43%). Chemoimmunotherapy with chlorambucil plus obinutuzumab (CLB-OB) or chlorambucil plus rituximab (CLB-R) was administered to 61 (40%) and 56 (37%) pts, respectively. Remaining pts received chlorambucil alone (CLB, $n = 19$), fludarabine (F, $n = 10$), F/cyclophosphamide (FC, $n = 1$), FC/rituximab (FCR, $n = 2$), or bendamustine/rituximab (BR, $n = 3$). Rates of grade 3 or 4 neutropenia and infections were 35% and 13%, respectively. Premature treatment discontinuations occurred in 15% of cases and were mostly due to adverse events. The total overall response rate was 92% with 13% complete remissions. Median observation time for all pts was 40.7 months. Median progression-free survival (PFS) and treatment-free survival (TFS) were 17.2 and 32.3 months. A total of 47 pts (31%) received at least one further line of treatment. Median overall survival (OS) was 48.3 months, with adverse events (22%) and progressive CLL (15.8%) being the most frequent causes of death. Standardized mortality ratio was calculated and showed a 1.99 (CI 1.54-2.53) increased risk of death as compared to an age- and sex-matched general population. Independent prognostic factors for OS were 17p deletion and elevated serum thymidine kinase.

Conclusion: Findings suggest that antileukemic therapy (incl. Chemoimmunotherapy) is feasible and efficacious in ≥ 80 year old pts with CLL. However, such pts are still highly underrepresented in clinical trials and even with modern treatment live shorter than age-matched controls of the general population.

Keywords: chronic lymphocytic leukemia (CLL); elderly.

90 UNMET MEDICAL NEEDS IN HODGKIN LYMPHOMA WITH SPECIAL FOCUS ON THE ELDERLY – A POPULATION-BASED STUDY OF PATIENTS DIAGNOSED IN SWEDEN 1973-2014

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Introduction: Major advances in the treatment of Hodgkin lymphoma (HL) have been seen since the 1960s. In younger patients, there has been a relatively stable increase in long-term relative survival (RS) now plateauing at a high level (>0.95). Older HL patients (>50 years), constituting 40-45%, however do significantly worse. Patients aged 65+ are rarely included in clinical trials.

Methods: Using data from the nationwide Swedish Cancer registry, we estimated relative survival ratios (RSRs) for 7,997 HL patients (median age 44 years; age range 2-99; 57% males; 45% aged 50+) diagnosed between 1973 and 2014. We also retrieved information on clinical characteristics for a subset of 1,017 patients aged ≥ 50 years diagnosed 2000-2013.

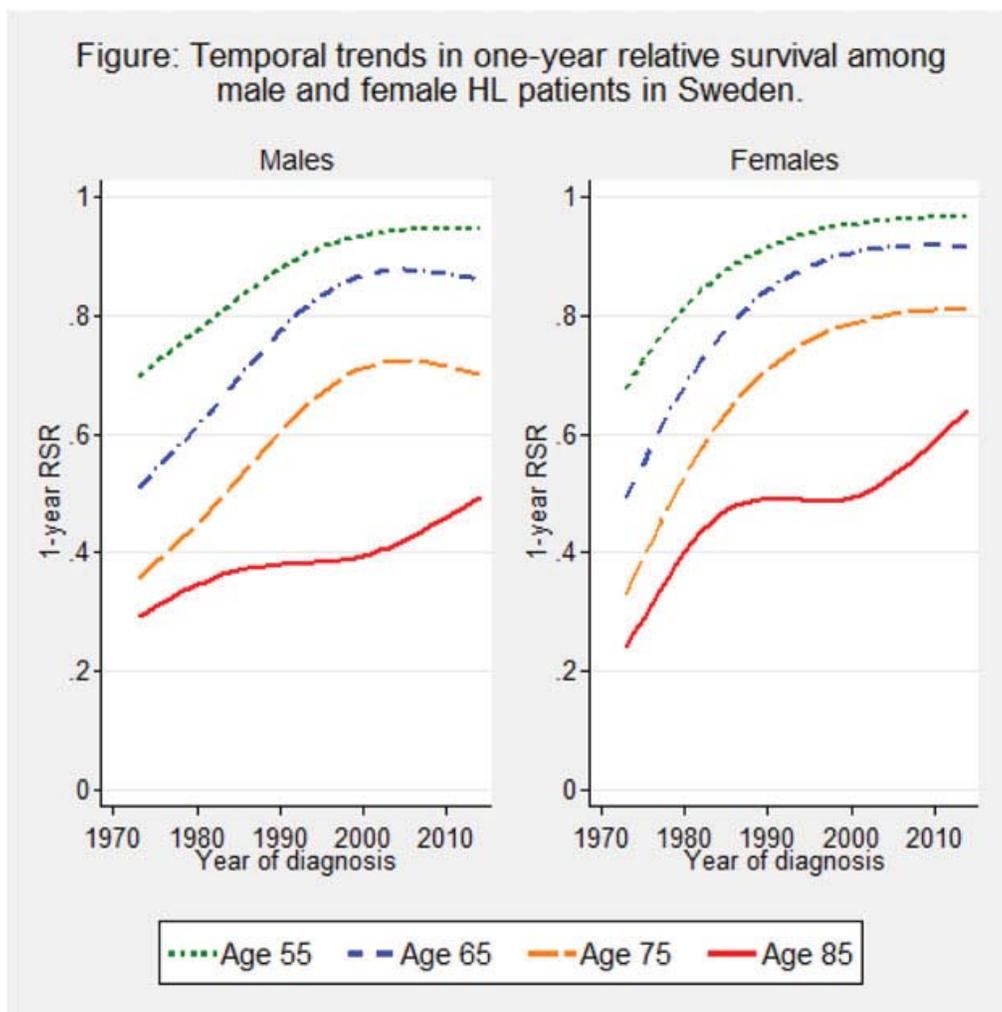
Results: A decline in age-standardized incidence until the mid-1990s was primarily driven by males >50 years. There was, however, evidence of a slight increase in incidence among children and young adults (≤ 34 years). The 1-year RSRs (95% confidence interval; CI) for males aged 55, 65, 75, and 85, diagnosed in 2013, were 0.95 (0.89-0.97), 0.86 (0.81-0.90), 0.70 (0.60-0.79) and 0.49 (0.33-0.63), respectively. The corresponding 1-year RSRs for females were 0.97 (0.92-0.99), 0.92 (0.87-0.95), 0.81 (0.72-0.88) and 0.63 (0.47-0.75), respectively (Figure). Females had significantly better survival than males ($p < 0.001$) in all age groups. Among males, improvement in 1- and 5-year RS from 2000 to 2014 was limited to males aged 85 years. Unexpectedly, no improvements were seen among men aged 55, 65, or 75 years. For females, small improvements were observed in 65- and 75-year-olds, whereas for 85-year-olds the improvements were relatively large. In patients 50 years and older (2000 to 2013) no significant changes in distribution of sex, histopathology, or performance status were observed. However, the proportion of patients with advanced stage (stage IIB-IV) increased from 54% to 63%. This change was mainly explained by more patients diagnosed with stage IV (rising from 17% to 26%). We do not believe the increasing proportion of stage IV is due to increased use of PET-CT staging, since the procedure was not recommended for clinical staging until recently. Of the 407 autografts reported to the EBMT-registry 1973-2014, only 26 (6%) were performed in patients aged ≥ 60 years. None of the 60 reported allografts were performed in patients aged ≥ 60 years.

Conclusions: These results confirm age to be a very strong (if not the strongest) predictor of survival. Older patients constitute a large group with clearly unmet medical needs, with lack of improvement of RSR during the latest years, especially in men. Clinical trials including older patients, novel agents, and management based on accurate risk stratification, will hopefully improve the outlook for older HL patients. The data presented here provide a baseline for outcome comparison prior to the broader introduction of novel targeted drugs.

Keywords: elderly; Hodgkin lymphoma (HL).

91 TREATMENT STRATEGIES AND OUTCOMES IN DIFFUSE LARGE B-CELL LYMPHOMA OF THE ELDERLY: A DANISH POPULATION-BASED COHORT STUDY OF 1,011 PATIENTS

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Introduction: The optimal treatment strategy for elderly patients with diffuse large B-cell lymphoma (DLBCL) remains controversial. Comorbidities and frailty often preclude enrollment in clinical trials and very few population-based studies have addressed outcome of elderly patients in detail. This population-based study investigated treatment strategies and outcomes for DLBCL patients older than 75 years.

Methods: DLBCL patients aged 75 and over diagnosed between 2003 and 2012 were identified using the Danish National Lymphoma Registry (LYFO). Information regarding lymphoma characteristics, treatment, comorbidity and outcome were obtained from LYFO, the Danish

National health registries and medical records. Patients were stratified by age (75-79; 80-84 and ≥ 85 years), comorbidity score, and treatment modality (standard treatment (CHOP or CHOP-like) with or without rituximab, less intensive regimens and palliative treatment).

Results: 1,011 patients were included. Standard treatment was initiated in 64%, ranging from 83% among the 75-79 year olds to 32% among the 85+ year olds. With standard treatment, 5-year overall survival (OS) estimates were 47%, 38% and 26% for the age groups 75-79; 80-84 and ≥ 85 , respectively. Among the 75-79 year olds, OS was superior with standard treatment regardless of comorbidity, although OS benefit associated with standard treatment diminished in patients with high comorbidity scores. Among 85+ year olds OS was equal with standard treatment and less intensive regimens, also in patients with low comorbidity scores. Patients above 80 years had similar OS regardless of intended (R-)CHOP dosing, whereas OS was higher in the 75-79 year olds scheduled for full dose. Patients receiving standard treatment were not hospitalized more than patients receiving less intensive chemotherapy.

Conclusion: Standard treatment is feasible with good outcomes in a large proportion of elderly DLBCL-patients, also outside clinical trials. Candidates for standard treatment must be carefully selected among patients above 80 years, and particular caution is necessary in patients older than 85 years, where even patients without comorbidity might

not benefit from standard treatment. Planned dose reduction seems beneficial in patients older than 80 years.

Figure 1: Overall survival for 1,011 patients with diffuse large b-cell lymphoma (DLBCL) aged 75-79, 80-84, or ≥ 85 years with either none, moderate or high Charlson Comorbidity Index (CCI) score, stratified by treatment modality. Data are population-based and the cohort

TABLE 1 Baseline characteristics for 1,011 patients with diffuse large b-cell lymphoma (DLBCL) aged 75-79, 80-84, or ≥ 85 years. Data are population-based and the cohort comprises all Danish patients older than 74 years with DLBCL diagnosed 2003-2012.

	75-79	80-84	≥ 85	All
Number (%)	403 (100)	367 (100)	241 (100)	1011 (100)
Time trend				
2003-2007	187 (46)	184 (50)	110 (46)	481 (48)
2008-2012	216 (54)	183 (50)	131 (54)	530 (52)
Sex				
Male	192 (48)	188 (51)	136 (56)	516 (51)
Female	211 (52)	179 (49)	105 (44)	495 (49)
Ann Arbor Stage				
1 - Stage I-II	150 (37)	162 (44)	97 (40)	409 (40)
2 - Stage III-IV	244 (61)	186 (51)	119 (49)	549 (54)
Unknown	9 (2)	19 (5)	25 (10)	53 (5)
B-Symptoms				
Yes	180 (45)	144 (39)	101 (42)	425 (42)
No	206 (51)	201 (55)	129 (54)	536 (53)
Unknown	17 (4)	22 (6)	11 (5)	50 (5)
Extranodal disease				
0	135 (33)	144 (39)	82 (34)	361 (36)
1	171 (42)	152 (41)	106 (44)	429 (42)
>1	97 (24)	71 (19)	53 (22)	221 (22)
LDH				
Normal	185 (46)	164 (45)	114 (47)	463 (46)
Elevated	202 (50)	179 (49)	105 (44)	486 (48)
Unknown	16 (4)	24 (7)	22 (9)	62 (6)
ECOG Performance Status				
0-1	281 (70)	251 (68)	150 (62)	682 (67)
2-4	117 (29)	112 (31)	87 (36)	316 (31)
Unknown	5 (1)	4 (1)	4 (2)	13 (1)
IPI				
1	82 (20)	84 (23)	49 (20)	215 (21)
2-3	192 (48)	161 (44)	94 (39)	447 (44)
4-5	100 (25)	81 (22)	56 (23)	237 (23)
Unknown	29 (7)	41 (11)	42 (17)	112 (11)
Co-morbidity (Charlson score)				
None (0)*	160 (40)	158 (43)	100 (41)	418 (41)
Moderate (1-2)	154 (38)	143 (39)	94 (39)	391 (39)
High (3-)	89 (22)	66 (18)	47 (20)	202 (20)
Treatment				
1-Standard	336 (83)	239 (65)	76 (32)	651 (64)
2-Less intensive	36 (9)	62 (17)	45 (19)	143 (14)
3-Palliative	31 (8)	66 (18)	120 (50)	217 (21)

* N = 3 patients are categorized as None due to missing observations in the Danish National Patient Registry.

comprises all Danish patients older than 74 years with DLBCL diagnosed 2003-2012.

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

92 REMARC STUDY: CORRELATION OF LYMPHOMA PD AND DEATH AND HEALTH-RELATED QOL WITH MAINTENANCE LENALIDOMIDE VS PLACEBO IN ELDERLY DLBCL PATIENT RESPONDERS TO R-CHOP

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Introduction: Outcomes are poor in DLBCL patients experiencing relapse; innovative strategies to improve outcomes by minimizing risk of relapse and progressive disease (PD) without impacting health-related quality of life (HRQoL) are needed. REMARC is a multicenter,

randomized phase III trial (NCT01122472) of maintenance lenalidomide (LEN) vs placebo (PBO) in 650 patients responding to R-CHOP, resulting in significantly improved PFS in patients treated with 2 years of LEN maintenance ($P = .01$).

Methods: Relative risks (RR [95% CI]) were calculated on ITT patients to identify treatment effect and pre-treatment variables that have an impact on patient's respective PD/relapse, death with relapse, or death without relapse. Mean change in HRQoL was assessed per the EORTC QLQ-C30 v3.0 questionnaire at randomization (≤ 3 months post induction), cycles 6, 12, 21, end of maintenance (EOM), and 1-year follow-up. The null hypothesis was to observe no difference in Global Health Status (GHS) between treatments and 1-year follow-up (Qs 29-30; primary PRO endpoint). A minimal important difference (MID) of 10 defined the proportion of patients reporting a meaningful difference in QoL.

Results: For the ITT population ($N = 650$), the RR of PD/relapse from DLBCL was lower in the LEN vs PBO arm (RR = 0.67). Irrespective of treatment arm, the risk of death after PD/relapse was associated with elevated aalPI (RR = 1.80), and in patients who died without PD/relapse, increased age ≥ 70 (RR = 5.17). HRQoL evaluable patients ($n = 136$ LEN, $n = 127$ PBO) had similar questionnaire completion rates at baseline: 59% LEN vs 56% PBO. Subscale scores at baseline were generally similar for LEN vs PBO, respectively: 68 vs 72 for GHS, 80 vs 85 for physical functioning and 32 vs 26 for fatigue. There was no change in $MID \pm 10$ from baseline during maintenance in either group

(Figure 1). No significant difference was shown in GHS (improvement, stable, worsening) between LEN and PBO. There was no change in $MID \pm 10$ from baseline at any post-randomization maintenance visit for secondary endpoints of physical functioning or fatigue subscales, nor in a subset of patients experiencing grade 3/4 treatment-emergent neutropenia.

Conclusions: Competing risk analysis confirmed that lenalidomide in maintenance prevents lymphoma progression without increasing toxic death risks. This analysis suggests that patient-reported HRQoL in elderly patients with DLBCL receiving 2 years of maintenance LEN following R-CHOP is not different from patients receiving PBO. HRQoL was maintained despite the higher incidence of grade 3/4 AEs, such as cytopenia, reported in the LEN arm.

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

SESSION 6: LYMPHOMA GENOMICS

93 A SINGLE-CELL BASED MODEL EXPLAINS PATTERNS OF CLONAL EVOLUTION IN PRIMARY AND RELAPSED FOLLICULAR LYMPHOMA

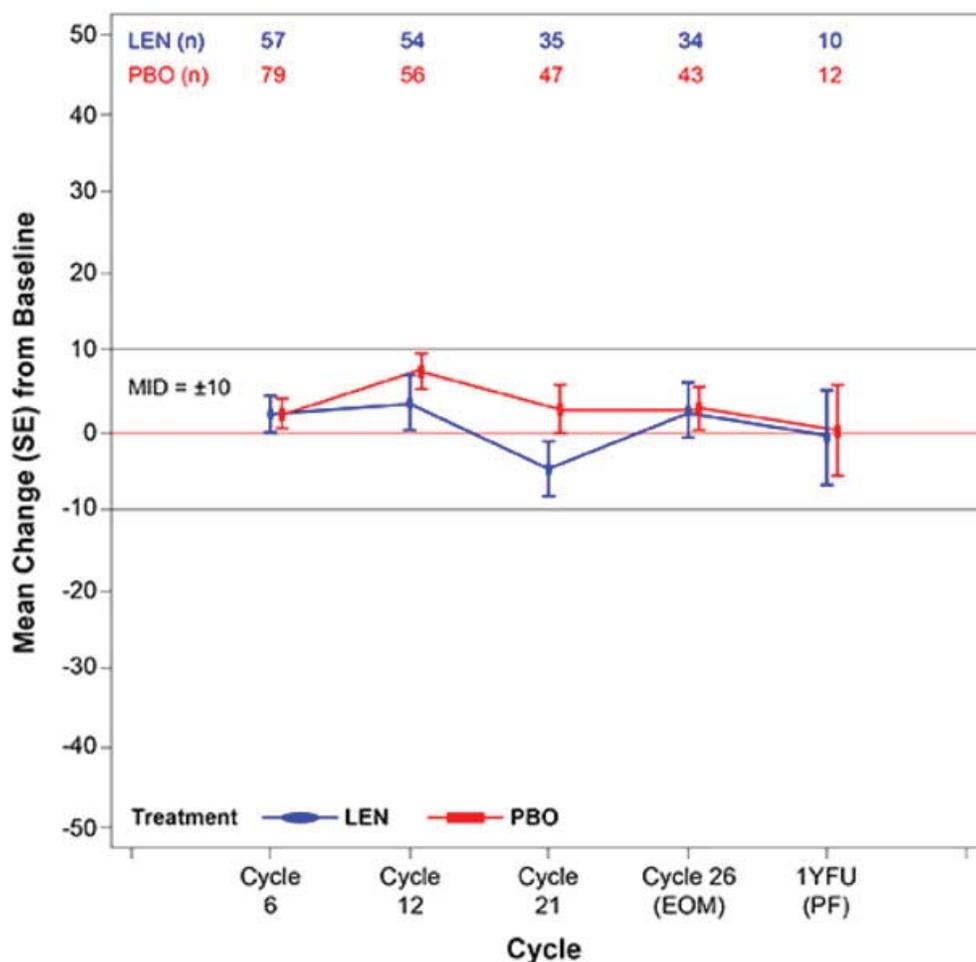


FIGURE 1. Global Health Status.

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Introduction: Germinal centers (GCs) provide signals for B cells to become high affinity antigen-detecting cells. In this process, somatic hypermutation (SHM) in immunoglobulin heavy chain V (IGHV) gene rearrangements and clonal selection play a pivotal role. Follicular lymphoma (FL) represents the prototype of GC B cell-derived lymphomas. Relapses are observed in the majority of patients, in some cases additionally associated with transformation to more aggressive diffuse large B-cell lymphoma. Data of paired primary and relapsed t(14;18) positive FL revealed a large evolutionary heterogeneity, ranging from “divergent evolution” (primary and relapse tumors arise from a common precursor), to “sequential” (relapse sequences emerge out of primary clones) and “no evolution” (shared IGHV sequences in primary and relapse tumors). In order to gain insight into processes underlying clonal evolution and lymphoma relapse, we applied a mathematical modeling approach. We particularly sought to conclusively explain qualitatively different patterns of FL evolution and analyze whether the observed inter-patient heterogeneity is of relevance for clinical decision making.

Methods: We developed a single-cell based mathematical model of physiological GC reaction to study the dynamics of GC expansion and B cell affinity maturation. Furthermore, we applied our model to the situation of FL emergence and relapse. We compared our model results to phylogenetic trees reconstructed from clinical measurements (sequences of IGHV gene rearrangements) of primary and relapse tumor in FL patients [Loeffler et al., *Leukemia* 29(2):456-63, 2015].

Results: We identified a set of parameter changes in single cells (linked to driver mutations), which permit an FL-cell population to take over a normal GC, creating a primary tumor *in silico*. The model is capable of reproducing typical features of FL emergence and relapse. Specifically, the different patterns of evolution observed in FL patients can be fully explained, based on variation of the timepoints of interfollicular cell migration and the absolute number of migrating FL cells. Evolution is stochastic regarding timepoints and number of cells migrating and thus cannot be predicted. As a consequence, different patterns of evolution within the same patient are predicted to be a frequent observation. Importantly, our model predicts complete cessation of SHM after clonal dominance of FL cells within a GC.

Conclusions: We found a comprehensive mathematical model of physiological GC reaction, dynamics of FL emergence and heterogeneity of clonal evolution. Due to the stochasticity of evolution we caution to draw clinically relevant conclusions from evolutionary profiles of tumor cells (e.g., with respect to transformation). Suppression of interfollicular cell migration through lymphatic vessels already in early disease stages might be a therapeutic goal.

Keywords: follicular lymphoma (FL); germinal center (GC); immunoglobulins (Ig).

94 FULL TRANSCRIPTOME SEQUENCING OF SORTED HODGKIN AND REED-STERNBERG CELLS REVEALS PLASMACYTIC DIFFERENTIATION: INSIGHTS INTO MECHANISMS OF ONCOGENESIS AND IMMUNE EVASION

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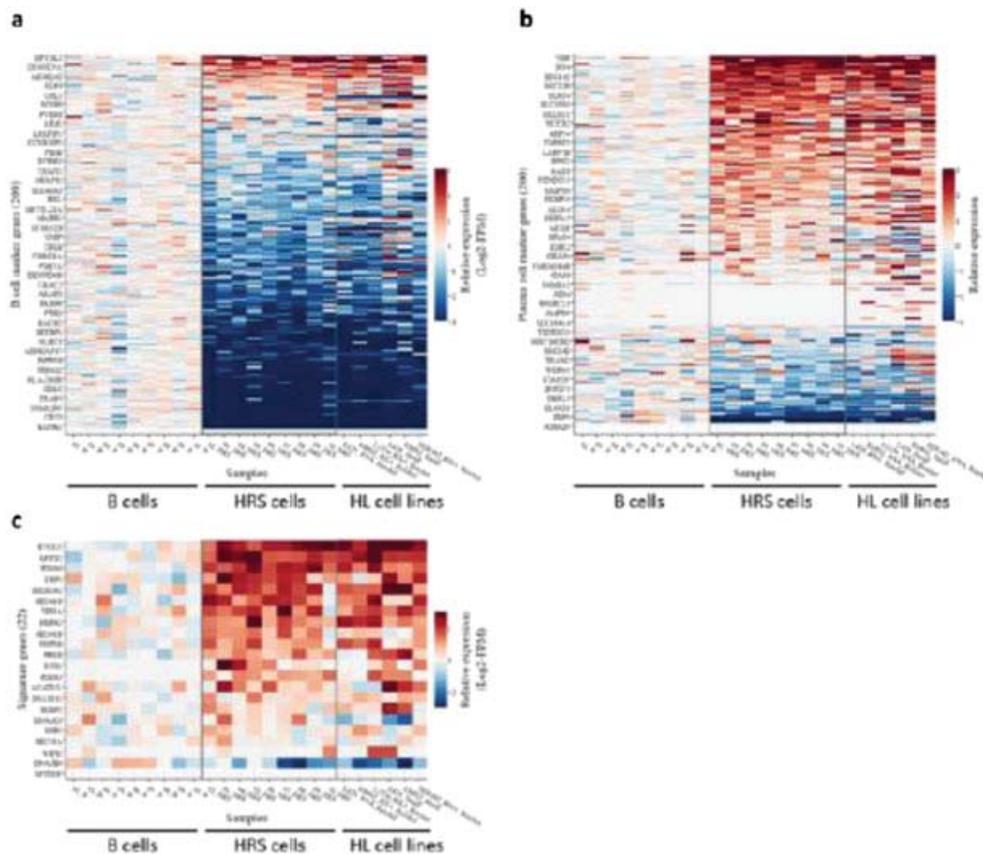
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Introduction: Previous gene expression profiling studies of classical Hodgkin lymphoma (cHL) have been confined to cell lines and micro-dissected HRS cells from tissue biopsies given the difficulty of isolating sparse Hodgkin and Reed-Sternberg (HRS) cells from reactive background tissue. We have previously reported a full exome sequencing of purified HRS cells derived from cell sorting.

Methods: We now used flow cytometric cell sorting and low-input RNA sequencing to generate first full transcriptome data from viable primary HRS cells, along with intratumor B cells. Nine primary cases of cHL and four cell lines were assessed for RNA expression, expressed mutations, cell of origin, signaling pathways, gene fusions and pathogen identification.

Results: HRS cells lines and primary cases showed significant separation by principal component analysis. This was not explained by potential contamination by other cell types. Comparison of HRS cells with normal cellular subsets indicated plasma cell differentiation, suggesting that the cell of origin is more likely a B cell on its way to becoming a plasma cell than the previously thought germinal center B cell. Furthermore we identified unfolded protein response signature strongly upregulated in HRS cells. This signature was shared with plasma cell neoplasms and, to a lesser extent, by activated B cell (ABC) diffuse large B cell lymphoma, but not other B cell lymphoma types (see Figure). Among additional top upregulated genes were those involved in oncogenic processes (HGF/MET, NFkB/apoptosis inhibition), in stem cell differentiation (homeobox genes MEIS1 and PBX1), and many involved in mitotic checkpoints, mitotic spindle formation and DNA repair, explaining the unique nuclear morphology of HRS cells. Down-regulation of both MHC-1 and MHC-2 driven antigen processing and presentation and reduction of expression of NK activating receptors of SLAM family provides mechanisms for tumor immune evasion. Two tumor suppressor genes were underexpressed: BIN1 and TP53INP1. Given the proportion of cHL cases associated with EBV



Signatures of lineage identity in HRS cells. Expression profiles of genes with B cell-specific expression (A), plasma cell-specific expression (B), and belonging to a plasma cell unfolded protein response signature (B) in patient-derived B cells, HRS cells, and HL cell lines.

infection, it has been speculated that other viruses are involved in EBV⁻ cases, but our analysis did not reveal any new viruses.

Conclusions: Transcriptome sequencing of HRS cells provided new insights into cHL pathogenesis, potentially individualized approaches to cHL therapy.

Keywords: classical Hodgkin lymphoma (cHL); gene expression profile (GEP); Reed-Sternberg cells.

95 PROFILING OF DNA METHYLATION IN EPIDEMIOLOGICAL AND CLINICAL SUBGROUPS OF BURKITT LYMPHOMA IN THE FRAMEWORK OF THE MMML: ICGC AND BLUEPRINT CONSORTIA

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Introduction: Burkitt lymphoma (BL) is the most common pediatric mature aggressive B-cell lymphoma. The genetic hallmark of BL is a chromosomal translocation involving the *MYC* oncogene and one of the immunoglobulin loci leading to *MYC* deregulation. Three epidemiologic variants of BL are differentiated: endemic BL (eBL), predominantly occurring in Equatorial Africa and associated with EBV infection, sporadic BL (sBL), occurring in Western countries, and immunodeficiency-associated BL. We studied eBL as well as clinical presentations of sBL encompassing solid BL (solBL) and leukemic BL (leukBL) samples, and *MYC*-positive precursor B-cell acute lymphoblastic leukemia (TdT + BL). Furthermore, we included Burkitt-like lymphoma with 11q aberration (mnBLL). The aim of the present study was to examine the DNA methylome of these BL variants.

Methods: We analyzed the DNA methylation of 116 BL (60 solBL, 10 leukBL, 29 eBL, 15 mnBLL, 2 TdT + BL) using the HumanMethylation450 BeadChip (HM450k) in comparison to 24 diffuse-large B-cell lymphomas (DLBCL) and 30 follicular lymphomas (FL). Most of the cases were recruited in the ICGC MMML-Seq and MMML projects. The eBL were obtained from the NCI Ghana BL project. We included publicly available HM450k data from 93 B-cell populations of various differential stages. Furthermore, we analyzed whole-genome bisulfite sequencing (WGBS) data of 12 solBL and 6 leukBL and compared them to 4 germinal center B-cell populations from healthy donors.

Results: Unsupervised DNA methylation analysis of BL, FL and DLBCL revealed that all BL variants cluster apart from non-BL cases supporting on methylation level all BL samples to be BL variants. Unsupervised comparison of the BL variants separated them in EBV-positive and EBV-negative BL which was mainly driven by a massive hypermethylation of EBV-positive eBL. Applying a newly developed DNA-methylation-based EBV classifier, we were able to predict correctly the EBV status in 12 of 13 cases (92%) with initially unknown status. Comparison of the DNA methylation using HM450k data of solBL and leukBL revealed 218 CpGs to be differentially methylated ($\sigma/\sigma_{\max} = 0.4$, $p < 0.0025$). Using WGBS data of the same samples, 1697 differentially methylated regions (DMR) were identified, most of them being hypomethylated in leukBL. The latter were mostly located in enhancer and polycomb target regions which were enriched for transcription factor binding sites including AP-1/JUND.

Conclusion: In conclusion, we show that all BL variants can be separated from the non-BL based on their DNA methylome. Interestingly, DMRs between solBL and leukBL were mainly located in enhancer and polycomb regions. EBV-positive BL showed a hypermethylated epigenotype in comparison to the other BL variants. Thus, the differences identified by DNA methylation analysis can add to the understanding of the biological differences of the BL variants.

Keywords: Burkitt lymphoma (BL); epigenetics; Epstein-Barr virus (EBV).

FROM ADULT PATIENTS ANALYZED IN THE ICGC MMML-SEQ CONSORTIUM

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Introduction: The ICGC MMML-seq consortium aims at a precise characterization of germinal center derived B-cell lymphomas (gcBCL). Mutational signatures are patterns of single nucleotide variants (SNVs) taking into account the motif context. 30 mutational signatures had previously been extracted from a cross-entity data set, half of which could be attributed to mutational mechanisms. The goal of this work was to identify mutational mechanisms active in gcBCL and link these to B-cell biology.

Methods: Matched tumor normal control pairs of gcBCL (76 diffuse large B-cell lymphomas (DLBCL), 85 follicular lymphomas (FL), 16 FL/DLBCLs, two double hit lymphomas, and one B-cell lymphoma not otherwise specified (B-NOS)) from adult patients were analyzed by whole genome sequencing. SNVs were called with the DKFZ inhouse pipeline. An unsupervised analysis of mutational signatures was performed with non-negative matrix factorization. This analysis was complemented by a supervised analysis of mutational signatures using non-negative least squares and thereby enabling the extraction of enrichment and depletion patterns of the mutational signatures. Clusters at different mutation density were extracted based on intermutation distance.

Results: Clusters of mutations at different levels of mutation density were extracted: Kataegis (rainfalls, high mutation density at single sample level) and Psichales (intermediate mutation density at single sample level). Genomic regions affected by the respective processes recurrently across the cohort were called regions of interest (ROIs).

253 Psychales-ROIs were identified and were enriched in late replicating regions of the genome. 166 Kataegis-ROIs were identified, 42/64/17/4 of which were known targets of aberrant somatic hypermutation (SHM) / were located within the immunoglobulin (IG) loci / overlapped with lymphoma-associated genes / overlapped with cancer genes known from other entities, respectively. Kataegis-ROIs were enriched in early replicating regions of the genome. In an analysis of mutational signatures, 11 known signatures including clocklike signatures (e.g. spontaneous deamination), DNA repair defect signatures, an APOBEC signature and the B-cell specific signature AC9 (attributed to AID and polymerase η) were found. Furthermore, we discovered three new signatures (L1 – L3). L1 was enriched at the IG loci. L2 was specifically enriched in the constant domains of the IGH locus.

Conclusions: L1 and L2 may be interpreted as an imprint of the action of AID on the genome, L2 with a high amount of modulation by altered repair pathways, L1 with a lower amount of modulation. Both L1 and L2 contribute to SHM, whereas class switch recombination (CSR) may be explained with only L1. Kataegis clusters may be classified into two groups, one of which is attributable to aberrant SHM, the other to dysregulated CSR.

Keywords: B-cell lymphoma; germinal center (GC); immunoglobulins (Ig).

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CROSS-PLATFORM VALIDATION OF GENE EXPRESSION PROFILING (GEP) BASED CELL OF ORIGIN (COO) CLASSIFICATION IN A CLINICAL LABORATORY SETTING

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Introduction: Gene expression profiling (GEP) can be used to determine Germinal Centre (GCB) and activated (ABC) B-cell DLBCL. The REMoDL-B trial demonstrated that GEP can be performed in real time on RNA extracted from routine diagnostic formalin-fixed paraffin-embedded (FFPE) biopsies. Patients in the trial were randomised based on their COO classification (DAC classifier; Care et al., PLOS ONE 2013). GEP was performed using Illumina whole genome DASL, but for routine clinical use it is important that this can be replicated using other platforms.

Methods: Affymetrix PrimeView arrays, from the same FFPE-derived RNA as the DASL ($n = 111$), and HTG EdgeSeq DLBCL COO Assay ($n = 164$), either from RNA or directly from FFPE sections, were performed in a subset of cases representative of the REMoDL-B trial population as well as additional cases from other DLBCL cohorts. COO was determined using DAC and the HTG DLBCL COO classifier.

Results: Concordance with DASL/DAC was observed in 85% & 70% of samples using Primeview arrays & HTG EdgeSeq respectively. Where discrepancies between platforms were observed this was predominantly associated with a switch to or from the unclassified (UC) category, with only 1% & 6% of cases switching between ABC/GCB. Furthermore, discrepancies in classification were significantly associated with lower confidence cases. Primeview arrays showed greater concordance with DASL, however both used DAC from the same RNA, and both platforms provide almost whole transcriptome data. In contrast the HTG DLBCL panel consists of 90 genes, and the HTG COO classifier is designed to minimise the proportion of UC samples. Using DAC on data generated from HTG EdgeSeq DLBCL COO panel results in 75% concordance with DASL, despite only 13 of the 20 DAC classifier genes being represented on the HTG panel. An advantage of the HTG platform is that FFPE tissue can be profiled directly from the sections, without the need for RNA extraction. In this study to date, 15 samples have been profiled from spare sections, where there was no tissue remaining for RNA extraction.

Conclusions: This study demonstrates that COO classification of DLBCL using GEP, as advocated by the 2016 revision of the WHO classification of lymphoid neoplasms, is applicable in the routine laboratory and can be consistently applied using different technologies. Affymetrix arrays provide highly comparable results to DASL using DAC classification; however HTG EdgeSeq provides a competitive alternative, especially when biopsy material is limited, with the advantage that RNA extraction is not required. The potential benefit of reducing the numbers of cases placed in the unclassified category with HTG Edge compared to DAC classification needs to be tested in prospective clinical trials.

Keywords: activated B-cell-like (ABC); GCB lymphoma subtype; gene expression profile (GEP).

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THE LANDSCAPE OF SOMATIC MUTATIONS OF PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG-TYPE

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TABLE 1

	Affymetrix PrimeView Arrays			HTG DLBCL COO classifier		
	Concordant	Discordant (UC)	ABC/GCB switch	Concordant	Discordant (UC)	ABC/GCB switch
DASL (n)	94	16	1	114	40	10
DASL %	85	14	1	70	24	6

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Introduction: Primary cutaneous diffuse large B-cell lymphoma leg-type (PCLBCL-LT) is recognized by the World Health Organization (WHO) classification as a rare and aggressive disease accounting for 5 to 10% of primary cutaneous lymphoma. It displays original clinical features occurring mostly in the elderly and preferentially involving

the legs but date the genetic specificities of this entities, as compared to other B-cell aggressive lymphoma is unknown.

Methods: To determine whether the mutational profile of primary cutaneous diffuse large B-cell lymphoma leg-type (PCLBCL-LT) is unique by comparison with other diffuse large B-cell lymphoma (DLBCL) subtypes, we analyzed a total cohort of 28 PCLBCL-LT cases by next generation sequencing with a Lymphopanel designed for DLBCL. We also analyzed 12 pairs of tumor and control DNA samples by whole exome sequencing which led us to perform resequencing of three selected genes not included in the Lymphopanel: *TBL1XR1*, *KLHL6* and *IKZF3*. To pinpoint specificities, comparison with a cohort of DLBCL and Primary central nervous System lymphoma (PCNSL) analyzed by the same targeted panel was performed.

Results: Our study clearly identifies an original mutational landscape of PCLBCL-LT with a very restricted set of highly recurrent mutations (>40%) involving *MYD88* (p.L265P variant), *PIM1* and *CD79B*. Other genes involved in B-cell signaling, NFkB activation or DNA modeling were found altered notably *TBL1XR1* (33%), *MYC* (26%) *CREBBP* (26%) and *IRF4* (21%) or *HIST1H1E*(41%). *MYD88*^{L265P} variant was

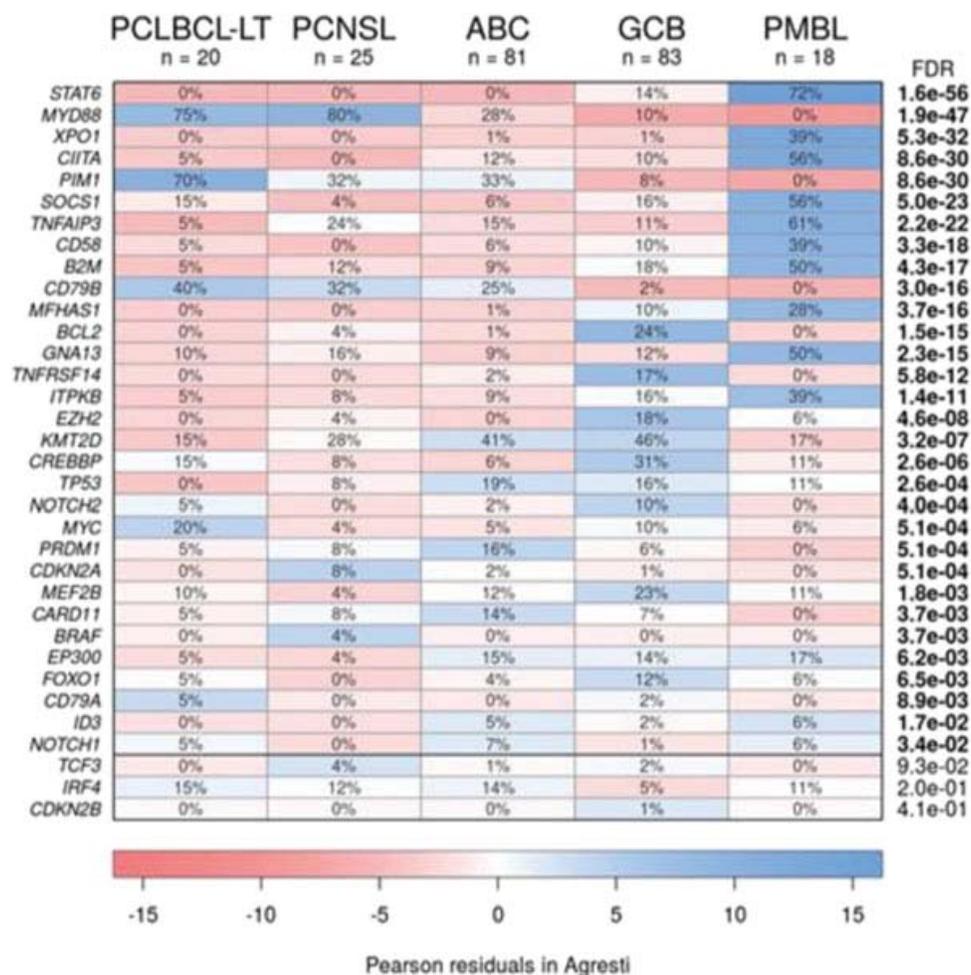


Figure 1. Heat map of mutation frequencies by DLBCL subtypes. Mutation frequencies in each subtype are indicated for each gene of the Lymphopanel. Mutation frequencies per gene and per subtype are shown here as the percentage of the total number of patients. Statistical significance of gene mutation enrichment in a given subtype is indicated in the False Discovery Rate (FDR) column. The horizontal line separates genes with FDR < 0.05, considered as significant, from genes with FDR ≥ 0.05. Bold text indicates FDR values < 0.05. Mutation rates in nodal Activated B-Cell (ABC), primary mediastinal B-cell (PMBL) and germinal center B-cell (GCB) subtypes have been published in Dubois et al. CCR 2016. Mutation rates in primary central nervous system lymphoma (PCNSL) have been obtained by the same methodology.

associated with copy number variations or copy neutral loss of heterozygosity in 60% of cases. The most frequent genetic losses involved *CDKN2A/2B*, *TNFAIP3/A20*, *PRDM1*, *TCF3* and *CIITA*. The high recurrence of specific gene mutations such as *MYD88* and the absence of mutations of *KMT2D* or *FOXO1* are distinct features from nodal DLBCLs of either GC or ABC subtypes. Interestingly PCLBCL-LT exhibits a mutational pattern that is closer to PCNSL than to ABC-type nodal DLBCL but also has distinctive features, such as a very high mutational rate for *PIM1*, a higher rate of *CD79B* mutations and other original mutations such as *CREBBP*, *MYC* and *IRF4* mutations (figure 1). **Conclusion:** This study describes for the first time the genomic landscape of a series of untreated PCLBCL-LT. Our results obtained by WES and targeted sequencing underscore several similarities with ABC-DBCL and more specifically with PCNSL subtypes. On the other hand, we pinpoint specificities that may sustain distinctive clinical features and guide therapeutic strategies according to an individual genetic analysis.

Keywords: activated B-cell-like (ABC); cutaneous B-cell lymphoma (CBCL).

SESSION 7: ADVANCES IN CLL

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INSIDE-OUT VLA-4 INTEGRIN ACTIVATION IS MAINTAINED IN IBRUTINIB-TREATED CHRONIC LYMPHOCYTIC LEUKEMIA EXPRESSING CD49D: CLINICAL RELEVANCE

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Introduction: VLA-4 (CD49d/CD29), a key molecule for microenvironmental interactions in chronic lymphocytic leukemia (CLL), can be

activated via inside-out by BCR triggering in normal B cells. In CLL, nothing has been so far reported regarding these activation mechanisms and their modulation by ibrutinib (IB), a drug known to impair the microenvironmental interactions with consequent shrinkage of tumor masses, and efflux of CLL cells into the blood stream.

Methods: VLA-4 activation was assessed by flow cytometry using conformation sensitive anti-CD29 mAbs (HUTS-21) and LDV-containing VLA-4 ligands, and measured as VLA-4 receptor occupancy (RO) (Chigaev et al. J Biol Chem, 2009). BCR was engaged using goat anti-IgM. In-vitro studies were carried out on purified VLA-4+ CLL cells exposed in-vivo to IB. Clinical assessments of CLL patients treated with IB single agent in the context of name patients program, clinical trials, and real world ($n = 97$) included: kinetics of absolute lymphocyte count (ALC), reduction of lymphadenopathy measured as sum of products of the diameters (SPD), and clinical outcome defined by progression free survival (PFS).

Results: BCR stimulation ($n = 27$) induced VLA-4 activation (mean RO control vs stimulated: 0.40 vs 0.52, $p = 0.0006$), and increased cell adhesion (control vs stimulated: 4.7 vs 7.5; $p = 0.0002$). Comparison of day 30 (t30) in-vivo IB-treated CLL cells with pre-treatment (t0) showed IB-dependent BCR signaling impairment, reduced constitutive VLA-4 activation (mean RO t0 vs t30: 0.40 vs 0.30; $p = 0.02$) and CLL cell adhesion (mean adhesion t0 vs t30: 4.7 vs 2.1; $p = 0.013$), but an unexpected retention of VLA-4 activation upon anti-IgM triggering, with RO values reaching levels similar to those of IB naïve cells (mean RO: 0.49 at t30 vs. 0.52 at t0). From a clinical standpoint, comparison of IB-treated CD49d + versus CD49d- CLL showed: a) lower % ALC change from baseline at day 30 (-4.4% and 126.8%; $p = 0.0002$; Figure 1A), and no typical IB-induced ALC peak; b) minor SPD reduction from baseline at 6 months (70.5% vs 83%; $p = 0.033$) and at 12 months (81.5% vs 92.0%; $p = 0.019$; Figure 1B); c) inferior PFS (median PFS 39.3 months, vs. not reached; $p = 0.004$), even considering the concomitant presence of TP53 disruption (Fig.1CD).

A multivariate Cox regression analysis confirmed the relevance of CD49d, along with TP53 disruption and UM IGHV mutational status, as independent predictor of shorter PFS in IB-treated CLL.

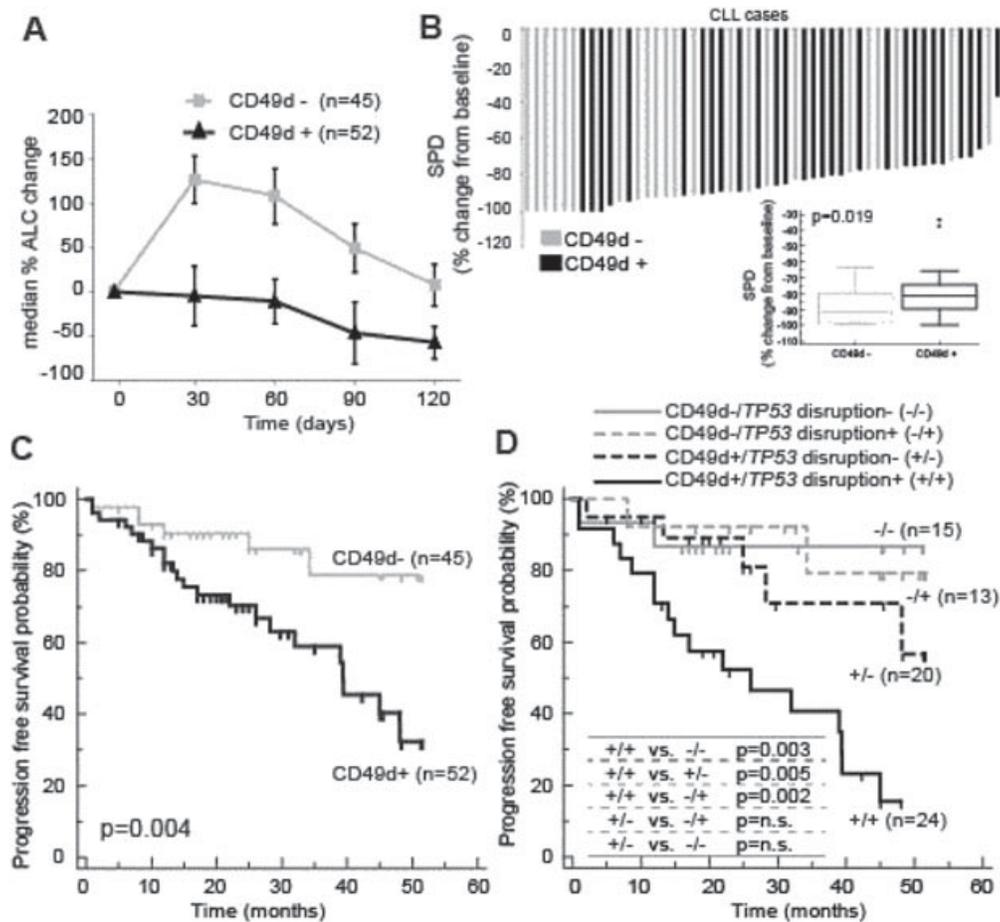
Conclusion: During IB treatment CD49d + CLL cells residing in tissue sites keep receiving BCR-mediated BTK-independent stimuli that, by inducing inside-out VLA-4 activation, result in enhanced cell retention, with consequent reduced lymphocytosis, relatively lower and/or slower nodal response, eventually leading to inferior outcome for CD49d + CLL patients.

Keywords: B-cell receptor (BCR); chronic lymphocytic leukemia (CLL); ibrutinib.

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INTEGRATED ANALYSIS: OUTCOMES OF IBRUTINIB-TREATED PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/ SMALL LYMPHOCYTIC LEUKEMIA (CLL/SLL) WITH HIGH-RISK PROGNOSTIC FACTORS

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Introduction: In phase 3 studies, ibrutinib (ibr) was superior to ofatumumab in relapsed/refractory (R/R) CLL/SLL or chlorambucil in treatment (tx)-naïve (TN) CLL/SLL. Ibr + bendamustine/rituximab (BR) was superior to BR in R/R CLL/SLL. Clinical outcomes of pts in these 3 studies were examined to determine the impact of certain prognostic risk factors other than del17p.

Methods: RESONATE: R/R CLL/SLL, ibr 420 mg/d until progressive disease (PD) or ofatumumab (≤ 24 wk). RESONATE-2: TN CLL/SLL (no del17p) ≥ 65 y, ibr 420 mg/d until PD or chlorambucil (≤ 12 cycles). HELIOS: R/R CLL/SLL (no del17p), BR (≤ 6 cycles) \pm ibr 420 mg/d followed by ibr or placebo until PD. Data from 3 studies ($N = 1238$) were pooled to analyze outcomes with/without genomic risk factors IGHV, del11q, trisomy 12, or complex karyotype (CK). Covariates for

a multivariate analysis (MVA) for progression-free and overall survival (PFS, OS): the 4 genomic risk factors, age, sex, ECOG PS, cytopenias, LDH, bulky disease, and number of prior therapies.

Results: Median follow-up was 21 mo for both ibr- and comparator-tx pts. In each subgroup, PFS, OS, and response rates were higher in ibr- than comparator-tx pts, regardless of these genomic risk factors. By univariate analysis (UVA, Table) in ibr-tx pts, genomic risk factors were not associated with shorter PFS or OS, and del11q was associated with a trend of longer PFS and OS. In comparator-tx pts, unmutated (U)-IGHV, del11q, and CK were associated with shorter PFS, and U-IGHV and CK with shorter OS. By MVA for PFS/OS, in ibr-tx pts (without del17p), only ≥1 prior tx was associated with shorter PFS and OS. Age ≥ 65 and elevated LDH were associated with shorter OS, and del11q with a trend of longer OS. In comparator-tx pts, ≥1 prior tx, U-IGHV, del11q, CK, male sex, and bulky disease ≥5 cm were associated with shorter PFS; CK, male sex, bulky disease ≥5 cm, ECOG PS ≥1 and elevated LDH were associated with shorter OS. Cumulative rates of adverse events were similar in pts with/without genomic factors and reflect a median exposure of 19-20 mo for ibr-tx pts and 5-10 mo for comparator-tx pts.

Conclusions: In UVA and MVA for ibr-tx pts, no clear associations were found for U-IGHV, del11q, trisomy 12, and CK with poor outcomes; del11q associated with trends of longer PFS and OS in UVA, and longer OS in MVA. In comparator-tx pts, U-IGHV, del11q, and

CK associated with shorter PFS, OS, and/or lower response rate. Results suggest that risk factors associated with poor outcomes with chemotherapy have less relevance with ibr.

Keywords: chronic lymphocytic leukemia (CLL); ibrutinib; small lymphocytic lymphoma (SLL).

101 UBLITUXIMAB AND IBRUTINIB FOR PREVIOUSLY TREATED GENETICALLY HIGH-RISK CHRONIC LYMPHOCYTIC LEUKEMIA: RESULTS OF THE GENUINE PHASE 3 STUDY

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TABLE 1 Efficacy Outcomes in Ibrutinib- and Comparator-Treated Patients by Genomic Prognostic Factors (Univariate)

		Ibrutinib-Treated Pts>		Comparator-Treated Pts	
		Present	Absent*	Present	Absent*
PFS	UnmutatedIGHV	24 mo: 78%	24 mo: 81%	24 mo: 10%	24 mo: 32%
		HR 0.93, P=0.78		HR 1.99, P<0.01	
	Del11q	24 mo: 82%	24 mo: 75%	24 mo: 9%	24 mo: 19%
		HR 0.64, P=0.04		HR 1.67, P<0.01	
	Trisomy 12	24 mo: 77%	24 mo: 80%	24 mo: 16%	24 mo: 18%
		HR 1.2, P=0.48		HR 0.86, P=0.27	
	Complex karyotype	24 mo: 76%	24 mo: 79%	24 mo: NE**	24 mo: 20%
		HR 1.15, P=0.65		HR 1.8, P<0.01	
OS	UnmutatedIGHV	30 mo: 88%	30 mo: 89%	30 mo: 76%	30 mo: 87%
		HR 0.95, P=0.86		HR 1.96, P=0.02	
	Del11q	30 mo: 93%	30 mo: 86%	30 mo: 76%	30 mo: 78%
		HR 0.52, P=0.03		HR 1.25, P=0.31	
	Trisomy 12	30 mo: 89%	30 mo: 89%	30 mo: 79%	30 mo: 79%
		HR 0.91, P=0.79		HR 0.72, P=0.26	
	Complex karyotype	30 mo: 84%	30 mo: 90%	30 mo: 69%	30 mo: 81%
		HR 1.53, P=0.25		HR 2.02, P=0.01	
ORR	UnmutatedIGHV	89%	90%	47%	51%
		OR 0.98, P=0.96		OR 0.83, P=0.36	
	Del11q	88%	89%	29%	53%
		OR 0.89, P=0.67		OR 0.36, P<0.01	
	Trisomy 12	86%	90%	51%	44%
		OR 0.71, 0.32		OR 1.29, P=0.26	
	Complex karyotype	87%	89%	19%	48%
		OR 0.86, P=0.71		OR 0.25, P<0.01	
CRR	UnmutatedIGHV	22%	15%	4%	6%
		OR 1.57, P=0.10		OR 0.70, P=0.44	
	Del11q	18%	19%	2%	5%
		OR 0.96, P=0.85		OR 0.36, P=0.09	
	Trisomy 12	25%	16%	5%	3%
		OR 1.8, P=0.03		OR 1.51, P=0.46	
	Complex karyotype	10%	17%	0	3%
		OR 0.51, P=0.13		OR 0.00, P=0.16	

CRR, complete response rate; HR, hazard ratio; NE, not evaluable; OR, odds ratio; ORR, overall response rate.

*For IGHV, indicates mutated IGHV.

**18 mo PFS rate was 8%.

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Introduction: The approval of the BTK inhibitor ibrutinib (IB) has significantly advanced the treatment paradigm for patients (pts) with Chronic Lymphocytic Leukemia (CLL), particularly in pts with high-risk cytogenetics who are traditionally less responsive to chemoimmunotherapy. However, among pts with high-risk CLL defined by interruptions in TP53 (either by mutation or deletion) or loss of chromosome 11q, outcomes remain inferior with ibrutinib monotherapy, particularly in the relapsed/refractory setting (O'Brien ASH 2016). Ublituximab (UTX) is a novel glycoengineered mAb with enhanced antibody dependent cellular cytotoxicity (ADCC) targeting a unique epitope on the CD20 antigen. GENUINE is the first randomized Ph 3 trial conducted assessing the addition of a novel agent to ibrutinib in high-risk rel/ref CLL, and evaluates IB monotherapy vs. UTX + IB.

Methods: Eligible pts with rel/ref CLL and centrally confirmed del17p, del11q, and/or a TP53 mutation were randomized 1:1 to receive IB (420 mg QD) alone or with UTX (900 mg on D1, 8, 15 of Cycle 1, D1 of Cycle 2-6, and Q3 Cycles thereafter). There was no limit on number of prior therapies. Prior IB exposure was excluded. The primary study endpoint was overall response rate (ORR) per iwCLL 2008 criteria, with secondary endpoints including CR rate, MRD negativity, PFS, time to response (TTR) and safety.

Results: 126 pts were randomized at sites in the US and Israel, with 117 pts treated (59 on UTX + IB, 58 on IB alone). Median age 67, median of 3 prior therapies (range 1-8), > 70% of were male. High-risk cytogenetics were relatively balanced between the arms with ~50% having del17p. UTX + IB was well tolerated, with infusion reactions the most prevalent AE (44%, Gr3/4 5%). Neutropenia was comparable with the combination (17%, Gr3/4 7% vs. 10%, Gr3/4 9%), and other AE's were similar or lower with UTX + IB vs. IB alone (all grades), including fatigue (17% vs. 31%), dizziness (12% vs. 21%), contusion (12% vs. 26%), anemia (10% vs. 16%), and myalgia (9% vs. 14%). At median follow-up of 12 months, best ORR per independent radiology and hematology review for UTX + IB was 80% vs. 47% for IB alone ($p < 0.001$). While not powered for secondary endpoints, observed advantages were seen in PFS and radiographic CR rate in the UTX + IB arm. CR and MRD confirmation is ongoing. Median TTR for the combo was 1.97 mos vs. 3.8 mos for IB alone. Both arms have responses pending confirmatory assessments.

Conclusions: The addition of UTX to IB demonstrated a superior response rate compared to IB alone without additional clinically significant toxicity.

Keywords: CD20; chronic lymphocytic leukemia (CLL); ibrutinib.

102 CHEMO-FREE TRIPLET COMBINATION OF TGR-1202, UBLITUXIMAB, AND IBRUTINIB IS WELL TOLERATED AND HIGHLY ACTIVE IN PATIENTS WITH ADVANCED CLL AND NHL.

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Introduction: Novel targeted agents are emerging for B-cell malignancies, but few studies have safely combined these agents. Ublituximab (UTX) is a novel glycoengineered mAb targeting a unique epitope on the CD20 antigen. TGR-1202 is a next generation, once daily, PI3K δ inhibitor, demonstrating a favorable safety profile compared to prior inhibitors, including in long-term follow up (Burris, 2016). This Ph 1 trial evaluates the safety/efficacy of the triplet combination of a novel anti-CD20 mAb + PI3K δ + BTK inhibitor (ibrutinib) in pts with B-cell malignancies.

Methods: Eligible pts had CLL or rel/ref NHL w/o limit to prior therapies, including those ref to prior PI3K δ or BTK inhibitors. UTX dosed on D 1, 8, 15 of C 1, D 1 of C 2-6, and C 9 & 12. TGR-1202 dose escalated (400/600/800 mg QD), ibrutinib dosed at 420 mg (CLL) or 560 mg (NHL), both on C1D1.

Results: 38 pts were enrolled: 20 CLL/SLL and 18 NHL, including 6 follicular (FL), 6 DLBCL, 4 mantle cell (MCL) and 2 marginal zone (MZL). Med age 65 yrs (range 32-85); 29 M/9 F; med prior tx = 3 (range 0-6). 2 pts ref to prior PI3K δ /2 prev treated with ibrutinib (1 ref/1 rel). MTD was not reached. Most common (> 20%) all causality AE's were fatigue (42%), diarrhea (39%), dizziness (34%), nausea (32%), neutropenia, pyrexia, rash, infusion reaction, insomnia (each at 29%), thrombocytopenia, cough (each at 26%), anemia (24%) and sinusitis (21%). GR 3/4 AE's (all causality) were minimal, the only event >10% was neutropenia (16%). ORR amongst 36 evaluable pts was as follows:

Subtype	N	CR	PR	ORR
CLL/SLL	19	3	16	100%
FL/MZL	7	2	4	86%

(Continues)

(Continued)

Subtype	N	CR	PR	ORR
DLBCL	6	0	1	17%
MCL	4	1	3	100%

53% of evaluable CLL pts had high-risk cytogenetics and 4/6 DLBCL pts were non-GCB. One CLL pt (17p/11q del) ref to PI3Kδ and ibrutinib achieved a CR. Med time on study is 10 mos (range 1 – 27 mos). Med DOR not reached (range 3 – 24 mos).

Conclusions: This is the first known triplet combination of an anti-CD20 mAb + PI3Kδ + BTK inhibitor. The combination of UTX, TGR-1202, and ibrutinib has been well tolerated with activity observed across heavily pre-treated and high-risk B-cell malignancies. Expansion cohorts at the highest dose (800 mg TGR-1202 + full dose ibrutinib) are underway. Future trials for the triplet are warranted.

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

103 SAFETY AND ACTIVITY OF THE HIGHLY SPECIFIC BTK INHIBITOR, BGB-3111 PLUS OBINUTUZUMAB IN PATIENTS (PTS) WITH FOLLICULAR LYMPHOMA (FL) AND CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Introduction: BGB-3111 is a potent and irreversible Bruton tyrosine kinase (BTK) inhibitor, designed to minimize off target inhibition of other TEC- and EGFR-family kinases. BGB-3111 has significantly less inhibitory effect against ITK and does not inhibit ITK-mediated rituximab (R)-induced antibody-dependent cell-mediated cytotoxicity (ADCC). BGB-3111 has shown significant activity in a variety of B-cell malignancies, especially CLL/small lymphocytic leukemia (SLL) and Waldenström macroglobulinemia (*Blood* 2016;128:642; *Blood* 2016;128:1216). Obinutuzumab (O) is a second-generation anti-CD20 humanized monoclonal antibody that has increased ADCC activity vs R and is more effective than R when combined with chemotherapy in CLL/SLL and FL. Preliminary results of a phase 1b study of BGB-3111 plus O in pts with CLL/SLL and FL are presented.

Methods: This is an ongoing, open-label, multicenter, phase 1b study of the combination of BGB-3111 and O in pts with B-cell malignancies with indication-specific expansion cohorts. Reported here are interim safety and activity results for the CLL/SLL and FL cohorts.

Results: As of 15 Dec 2016, 40 pts with CLL/SLL (17 pts with treatment-naïve [TN]; 23 pts with relapsed/refractory [R/R]), and 13 pts with FL were enrolled. Demographic and disease characteristics are shown in Table 1. Median follow-up time was 4.1 months for CLL/SLL and 6.2 months for FL. BGB-3111 plus O was well tolerated. No fatal adverse events (AEs) occurred; only 1 AE led to treatment discontinuation (squamous cell carcinoma in a pt with prior squamous cell carcinoma). Serious AEs (SAEs) were reported in 25.0% of CLL/SLL pts and 23.1% of FL pts; there was only 1 SAE related to O (infusion-related reaction) and 1 SAE related to BGB-3111 (pneumonia). There were no AEs of atrial fibrillation. Pts were evaluable for response if they had completed baseline and ≥1 on-treatment response assessment. Objective response rates (complete response [CR] + partial response + partial response with lymphocytosis) were 88.9%, 86.7%, and 81.8% in TN CLL/SLL, R/R CLL/SLL, and R/R FL, respectively, with 3 CRs in R/R CLL/SLL and 5 CRs in FL. Two pts (1 R/R CLL; 1 FL) experienced disease progression; no instances of disease transformation occurred.

Conclusions: BGB-3111 plus O is well tolerated and highly active in CLL/SLL and FL. Most notably, the response rate in FL appears to be higher than that reported with BTK inhibitors or anti-CD20 therapy alone.

	TN CLL/SLL(n=17)	R/R CLL/SLL(n=23)	R/R FL(n=13)
Demographics			
Median (range) age, y	68 (38-82)	68 (51-82)	56 (42-86)
Median no. of prior therapies (range)	0	1 (1-4)	1.5 (1-5)
Safety, n (%)			
Grade ≥3 AE	2 (11.8)	8 (34.8)	3 (23.1)
Serious AE	2 (11.8)	8 (34.8)	3 (23.1)
AEs leading to Rx discontinuation	0	1 (4.3)	0
Fatal AE	0	0	0
Efficacy (Evaluable), Best Response			
Median follow-up, mo	2.8	4.7	6.2
CR, n/N (%)	0	3/15 (20.0)	5/11 (45.5)
PR, n/N (%)	8/9 (88.9)	10/15 (66.7)	4/11 (36.4)
SD, n/N (%)	1/9 (11.1)	1/15 (6.7)	1/11 (9.1)
PD, n/N (%)	0	1/15 (6.7)	1/11 (9.1)

Keywords: BTK; chronic lymphocytic leukemia (CLL); follicular lymphoma (FL).

SESSION 8: FOLLICULAR LYMPHOMA

104 GENE-EXPRESSION PROFILING PREDICTS DISEASE PROGRESSION IN FOLLICULAR LYMPHOMA

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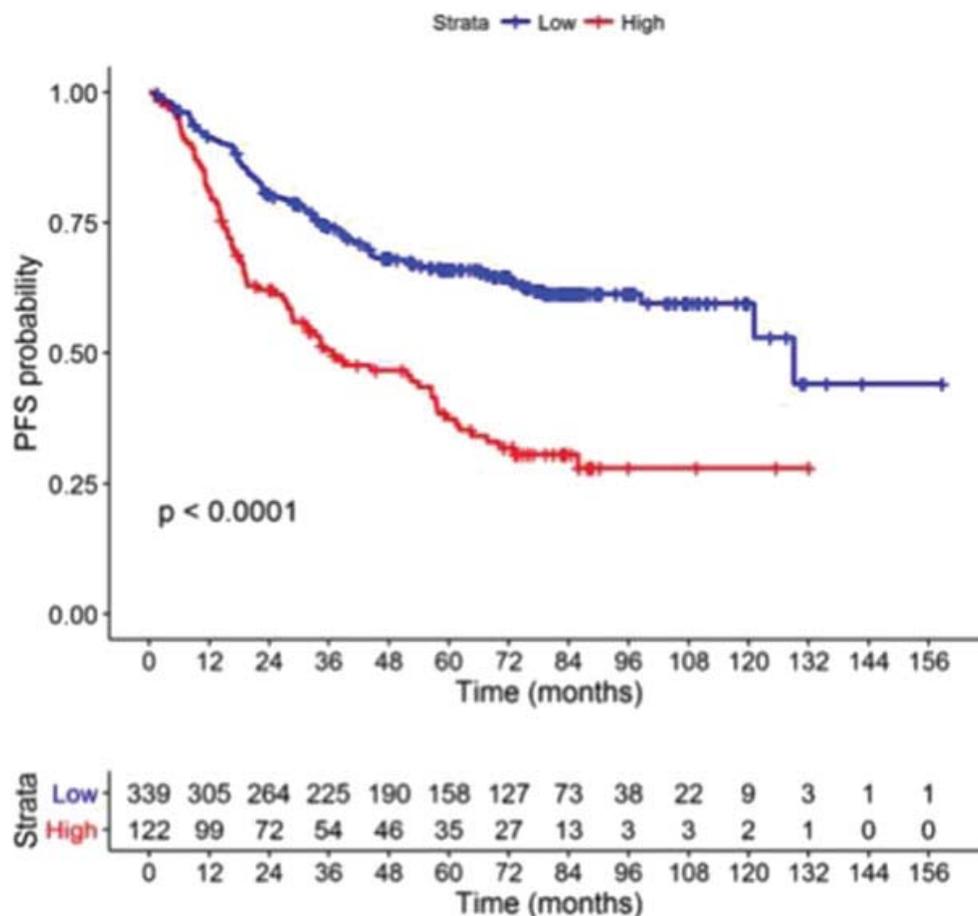
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Introduction: Patients with Follicular Lymphoma (FL) have heterogeneous outcomes. Predictor models able to distinguish, at diagnosis, the patients at high versus low risk of progression are still needed. We developed a gene-expression-based predictor of progression-free survival (PFS) to reliably identify those patients.

Methods: Gene-expression profiling was first performed using Affymetrix U133 Plus 2.0 micro-arrays on fresh frozen tissue (FFT) samples from a training cohort of 149 FL patients enrolled in the international PRIMA trial. A Cox regression analysis identified genes whose expression was associated with PFS. After assessing of the technical replication of expression levels for a selected set of genes between FFT and FFPE samples, a PFS-predictive score was built. The model was further evaluated using NanoString technology in 461 FFPE samples from 3 independent international cohorts: a distinct validation set from the PRIMA trial ($n = 172$), the Mayo Clinic/Iowa SPORE project ($n = 186$) and the Barcelona Hospital Clinic ($n = 103$). All patients were treated by rituximab plus chemotherapy followed by either anti-CD20 maintenance or no maintenance.

All validation cohorts



Results: The expression of 395 genes was associated with the risk of progression. Twenty-three genes reflecting both B-cell biology and tumour microenvironment were retained to build a predictive model. The model identified a population at increased risk of progression in the training cohort ($P < 0.001$).

The locked model was tested in the 3 independent validation cohorts. In the overall validation cohort, 26% of all patients (122/461) were identified as being at high risk of progression. The median PFS was 3.1 and 10.8 years in the high- and low-risk groups, respectively ($p < 0.001$, Figure 1). The risk of lymphoma progression at 2 years was twice higher in the high-risk group (38% versus 19%, $P < 0.001$). In a multivariate analysis, the score predicted PFS independently of anti-CD20 maintenance treatment and of the FLIPI score (Hazard Ratio for the combined cohort, 2.30; 95% CI, 1.72-3.08). In particular, the model stratified patients with high-risk FLIPI into groups with markedly distinct outcome (median PFS of 2.1 vs 6.6 years; log-rank test, $p < 0.001$).

Additional unsupervised analyses of the training cohort expression data confirmed that both tumour cells and microenvironment features impacted FL prognosis. Namely, a centroblast-associated signature had adverse prognostic significance, further strengthening the biological rationale of this model.

Conclusion: Using the largest study evaluating molecular prognostic biomarkers in FL patients, we developed a robust 23-gene expression-based predictor of PFS, applicable to routinely available FFPE biopsies from FL patients at diagnosis. In patients treated initially with rituximab-chemotherapy, this model identifies patients with a high risk of early progression.

Keywords: follicular lymphoma (FL); gene expression profile (GEP); prognostic indices.

105 THE RISK OF TRANSFORMATION OF FOLLICULAR LYMPHOMA “TRANSFORMED” BY RITUXIMAB: THE ARISTOTLE STUDY PROMOTED BY THE EUROPEAN LYMPHOMA INSTITUTE

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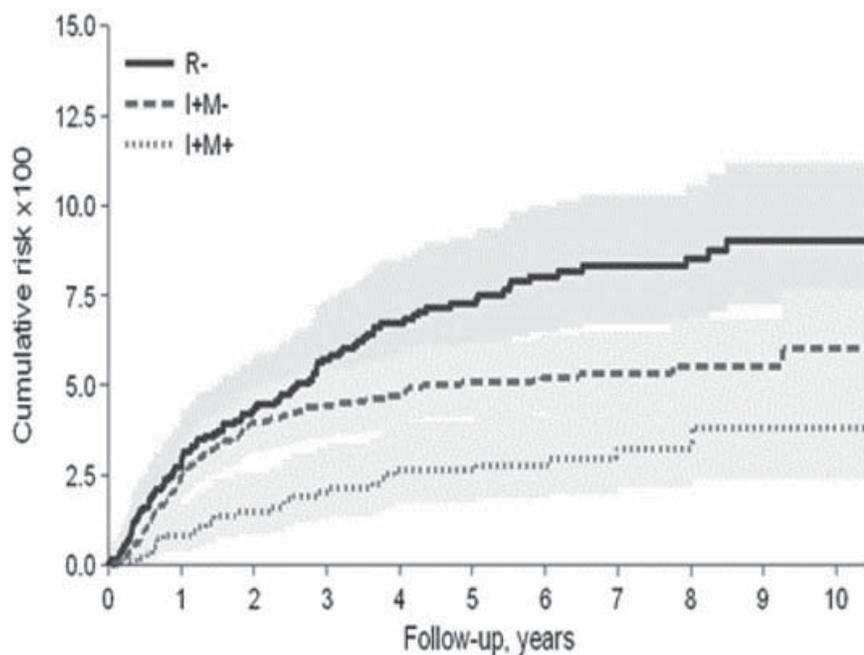
Background: Histologic transformation (HT) is a critical biologic event with profound implications on the natural history and the clinical course of Follicular Lymphoma (FL). Moreover, HT is a very adverse event, with a median post-transformation survival of about 2 years. In most reports the incidence of HT have wavered over the past several decades, due to the adoption of different diagnostic methods, definition of transformation, duration of follow-up, and type of treatment. This study, promoted by ELI and European Hematology Association Lymphoma Group, aims to assess the risk of HT in the immunochemotherapy era, and its outcome.

Methods: Patients included in the Aristotle (Assessing the Risk of Transformation and Outcome of Follicular Lymphoma in the Immunochemotherapy Era) study come from clinical trials or lymphoma registries collected by ten different European Lymphoma Groups. The present study is restricted to cases diagnosed between 1997 and 2013 with biopsy proven HT, as reported by the participating Institutions, and in which transformation was diagnosed as the first event after initial therapy (regardless of whether patients had been managed expectantly at diagnosis or not). Primary endpoints were the cumulative risk of HT and survival after transformation (SAT).

Results: So far 9,172 cases have been referred and 7,342 are assessable for the main endpoint, i.e. the transformation risk. Patient characteristics at time of diagnosis: median age 58 years (2.5-97.5 percentile 33-82); low, intermediate and high risk FLIPI 30%, 34% and 37%, respectively. A total of 4,496 first events (61%) were reported, 767 of whom confirmed by biopsy (18% of events). Overall, 437 of them were classified as HT. Median time to transformation was 19 months (2.5-97.5 percentile 2-116). The cumulative risk of HT was 5.5 (95% CI 5.0-6.1) and 7.2 (95% CI 6.4-8.0), at 5 and 10 years respectively. In 4,468 cases information on the use of Rituximab in induction (I) and maintenance (M) was available. The risk of transformation of the 2,874 cases with lack of data on R use was almost superimposable (7.6 vs 6.3, HR =0.92, 95% CI 0.73-1.15, $p = 0.470$) excluding a selection bias.

The risk of transformation at 10 years was 6.2 (5.4-7.3) for R+, and 9.0 (7.2-11.1) for R-, respectively. Moreover, at 10 years the risk of transformation was 6.0 (95%CI 4.7-7.6) for patients who received R only in Induction (I + M-) and 3.8 (95%CI 2.4-5.9) for patients treated with R in induction and maintenance (I + M+) (Figure 1). After a median

Figure 1. Cumulative risk of biopsy proven HT as first event among patients initially treated without Rituximab (R-) and those receiving Rituximab in induction (I+M-) or in induction and maintenance (I+M+)



R-	1279	1167	1093	1022	946	846	718	596	480	308	247
I+M-	2226	2047	1924	1831	1726	1596	1284	765	415	245	145
I+M+	963	947	915	867	804	747	589	334	174	51	11

follow-up of 55 months (range 1-167) since HT, 248 deaths were recorded, with a SAT of 41% (95% CI 36-46) and 31% (95% CI 25-38) at 5 and 10 years, respectively.

Conclusions: Despite the potential limitation of a retrospective design, the extremely large sample size provides robustness to the study results, which suggest that the risk of HT as first event has been significantly reduced by the introduction of Rituximab.

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

106 PROGNOSTIC MODEL FOR HIGH TUMOR BURDEN FOLLICULAR LYMPHOMA INCLUDING BASELINE TOTAL METABOLIC TUMOR VOLUME AND END INDUCTION PET: A POOLED ANALYSIS FROM LYSA AND FIL TRIALS

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Objective: Identification of patients who progress early after immunochemotherapy is challenging in follicular lymphoma. Among the more recent prognostic imaging markers, end of induction PET (Eoi PET) and total metabolic tumor volume (TMTV) computed on baseline PET show promise, demonstrating better performance than the current prognostic indices for early risk stratification. This study aims to evaluate the added value of a model built on these two imaging biomarkers.

Methods: Patients included in the FOLLICOLL study (pooling from three prospective trials: PRIMA, PETFOLL and FOLL05) were enrolled when they had both baseline PET, allowing the computation of TMTV, and Eoi PET. TMTV was calculated using the 41% SUVmax

thresholding method. 510 cm³ was identified as the optimal cut-off to predict PFS and OS. Eoi PET was reported with a Deauville Score \geq 4 to define positivity. KM curves were obtained, and multivariate analysis performed using a Cox proportional hazard model including TMTV and Eoi PET.

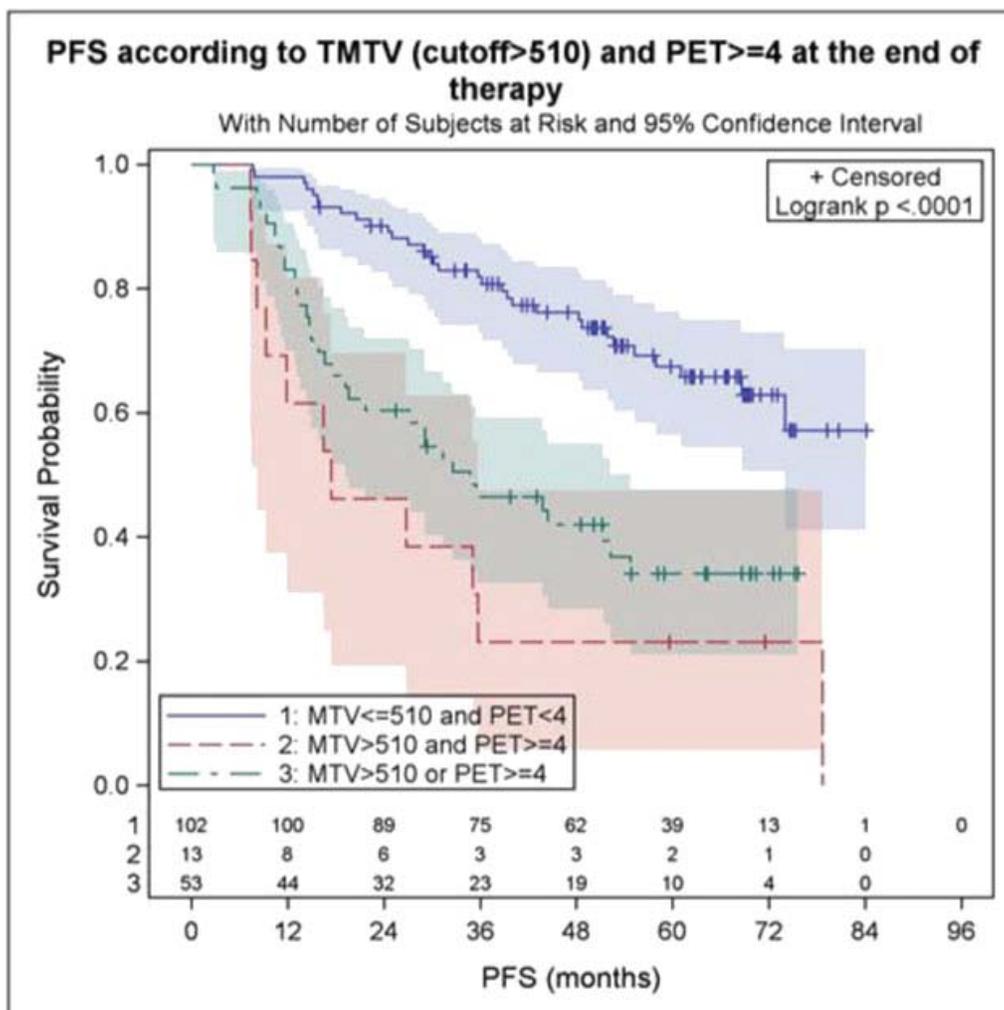
Results: 159 patients were included: median age was 56 years (37% >60). 91% were Ann Arbor stage III/IV, 57% had an involved BMB, 37% a FLIPI score 3-5, and 31% a FLIPI2 score 3-5. 81% had 6 R-CHOP followed by 2 R, 15% R-CVP, and 4% R-FM; 10 patients had maintenance. Median TMTV was 260 cm³ (IQR: 127-554 cm³) and 27.7% patients had a high TMTV (>510cm³). 133 (83.6%) patients had negative Eoi PET. With a median follow up of 64 months, 71 patients progressed and 14 died leading to a 5-y PFS and OS of 54.2% and 91.9% respectively. Patients with a high TMTV had a significantly worse outcome with a 5-year PFS and OS of 31.3% and 83.8% versus 63.2% and 95% for patients with a lower TMTV (HR = 2.8 95%CI (1.7-4.5), $p < 0.001$ for PFS, and HR = 3.9 95%CI (1.3-11.9), $p = 0.0188$ for OS). Similarly patients with positive Eoi PET had a significantly worse outcome with a 5-year PFS and OS of 26.9% and 84% versus 59.6% and 93.3% for patients with negative Eoi PET (HR = 3.2 95%CI (1.9-5.5), $p < 0.001$ for PFS, and HR = 4.4 95%CI (1.5-12.6), $p = 0.0068$ for OS). Multivariable analysis demonstrated that high TMTV and positive Eoi PET were independent prognostic factors of PFS (HR = 2.3, 95%CI (1.4-3.9),

$p = 0.001$ and HR = 2.3, 95%CI (1.3-4.1), $p = 0.0035$ respectively). For OS, only Eoi PET was prognostic: HR = 3.25 95%CI (1.1-9.8), $p = 0.0357$, compared with HR = 2.8 95%CI (0.9-9.0), $p = 0.081$ for TMTV. Combination of TMTV and Eoi PET stratified the population into three groups: patients with no risk factors (negative Eoi PET and low TMTV, $n = 102$) had a 5-year PFS of 67.5% versus 33% (HR = 2.9 95% CI (1.8-4.9), $p < 0.001$) for patients with one risk factor ($n = 44$) and 23.1% (HR = 4.6 95%CI (2.3-9.2), $p > 0.001$) for patients with both risk factors, ($n = 13$), (Figure 1).

Conclusion: The combination of baseline TMTV and Eoi PET identify a subset of patients with follicular lymphoma who have a very high risk of progression within 5 years of treatment.

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

107 IMMUNOCHEMOTHERAPY WITH OBINUTUZUMAB OR RITUXIMAB IN PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA IN THE RANDOMISED PHASE III GALLIUM STUDY: ANALYSIS BY CHEMOTHERAPY REGIMEN



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Introduction: The Phase III GALLIUM study (NCT01332968) showed that obinutuzumab (GA101; G) significantly prolonged PFS in previously untreated follicular lymphoma (FL) pts relative to rituximab (R) when combined with chemotherapy (chemo; CHOP, CVP or bendamustine [B]). Grade 3–5 AEs and SAEs were more common with G-chemo. Updated results for each immunochemotherapy regimen are reported here.

Methods: Pts were aged ≥ 18 years with documented, previously untreated FL (grades 1–3a), advanced disease (stage III/IV or stage II with tumour diameter ≥ 7 cm), ECOG PS 0–2, and requiring treatment according to GELF criteria. Chemo regimen was allocated by centre. Pts were randomised 1:1 (stratified by chemo, FLIPI-1 group and geographical region) to R 375 mg/m² on day (D) 1 of each cycle (C) or G 1000 mg on D1, 8 and 15 of C1 and D1 of C2–8, for 6 or 8 cycles depending on chemo. Pts with CR or PR at end of induction (per Cheson 2007) continued to receive R or G every 2 months for 2 years or until progression. The cut-off date for this analysis was 10 September 2016. All pts gave informed consent.

Results: 1202 FL pts were randomised. Baseline characteristics were generally similar across chemo groups, although B and CVP pts had relatively more comorbidities, e.g. gastrointestinal and vascular disorders, than CHOP pts. After 41.1 months' median follow-up, investigator

Figure. Kaplan-Meier analysis of INV-assessed PFS in FL pts. The study was not powered to show differences between R and G within chemo groups

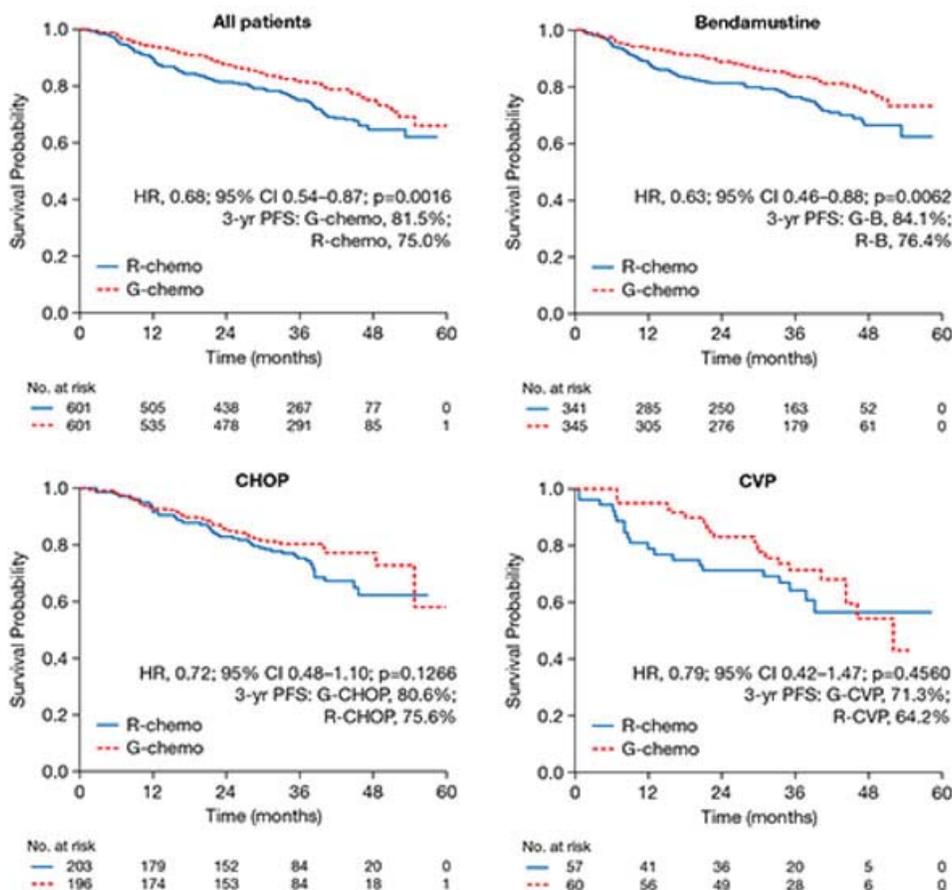


TABLE 1 Safety summary (number [%] of FL pts* with ≥ 1 AE).

	G-B (n=338)	R-B (n=338)	G-CHOP (n=193)	R-CHOP (n=203)	G-CVP (n=61)	R-CVP (n=56)	All G-chemo (n=595)	All R-chemo (n=597)
AEs	338 (100)	331 (97.9)	191 (99.0)	201 (99.0)	61 (100)	56 (100)	593 (99.7)	585 (98.0)
Grade 3–5 AEs	233 (68.9)	228 (67.5)	171 (88.6)	151 (74.4)	42 (68.9)	30 (53.6)	449 (75.5)	409 (68.5)
Neutropenia [†]	100 (29.6)	102 (30.2)	137 (71.0)	111 (54.7)	28 (45.9)	13 (23.2)	265 (44.5)	226 (37.9)
Leucopenia [†]	11 (3.3)	15 (4.4)	39 (20.2)	34 (16.7)	1 (1.6)	1 (1.8)	51 (8.6)	50 (8.4)
Febrile neutropenia [†]	18 (5.3)	13 (3.8)	22 (11.4)	14 (6.9)	2 (3.3)	2 (3.6)	42 (7.1)	29 (4.9)
AEs of special interest by category								
Grade 3–5 infections [‡]	89 (26.3)	66 (19.5)	23 (11.9)	24 (12.4)	8 (13.1)	7 (12.5)	121 (20.3)	98 (16.4)
Second neoplasms [§]	37 (10.9)	23 (6.8)	9 (4.7)	11 (5.4)	1 (1.6)	2 (3.6)	47 (7.9)	36 (6.0%)
SAEs	176 (52.1)	160 (47.3)	76 (39.4)	67 (33.0)	26 (42.6)	19 (33.9)	281 (47.2)	246 (41.2)
Fatal AEs	20 (5.9)	16 (4.7)	3 (1.6)	4 (2.0)	1 (1.6)	1 (1.8)	24 (4.0)	21 (3.5)
AEs causing treatment discontinuation	52 (15.4)	48 (14.2)	32 (16.6)	31 (15.3)	11 (18.0)	9 (16.1)	98 (16.5)	88 (14.7)

*Pts who received ≥ 1 dose of study drug. Three pts received G but no chemo. [†]Occurring in $>10\%$ of pts in any group. [‡]MedDRA System Organ Class 'Infections and Infestations'. [§]Malignant or unspecified tumours occurring >6 months after first study drug intake.

(INV)-assessed PFS remained superior for G-chemo relative to R-chemo (HR, 0.68; 95% CI 0.54–0.87; $p = 0.0016$) with consistent HRs across chemo groups (Figure). HRs for secondary time-to-event endpoints were supportive of the primary analysis. Difference in frequency of grade 3–5 AEs between arms was highest with CHOP and CVP (Table). Rates of second neoplasms and grade 3–5 infections were similar in G and R arms for CHOP and CVP but not for B. In all chemo groups, SAEs were more frequent with G than R, and AEs causing treatment discontinuation and fatal AEs were similar. Reductions in T-cell counts were more pronounced and prolonged in the B group than CHOP or CVP groups.

Conclusions: In treatment-naïve FL pts, PFS was superior with G-chemo relative to R-chemo with consistent effects across chemo regimens. Some differences were seen in safety profiles between chemo regimens, but comparisons may be confounded by the lack of randomisation.

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

108 COPANLISIB IN PATIENTS WITH RELAPSED OR REFRACTORY INDOLENT B-CELL LYMPHOMA (CHRONOS-1)

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Introduction: Treatment options are limited for patients with relapsed/refractory indolent B-cell lymphoma. Copanlisib is an intravenously administered pan-Class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant activity against PI3K- α and PI3K- δ isoforms. We report results from a pivotal phase II study (NCT01660451, part B; CHRONOS 1).

Methods: Patients with indolent B-cell non-Hodgkin lymphoma (follicular [FL], marginal zone [MZL], small lymphocytic and lymphoplasmacytoid/Waldenström macroglobulinemia) and relapsed after, or refractory to, ≥ 2 prior lines of treatment (including both rituximab and an alkylating agent) were eligible. Copanlisib (60 mg, IV) was

intermittently administered on days 1, 8 and 15 of a 28-day cycle. The primary efficacy endpoint was objective tumor response rate (ORR) per independent radiologic review (Cheson et al. 2007). Archival tumor tissues were used for mRNA extraction and gene expression profiling.

Results: The full analysis set comprised 142 treated patients. At the time of analysis, median duration of treatment was 22 weeks (range 1-105); 46 patients remained on treatment. The ORR was 59.2%, including 12.0% complete response (CR) and 47.2% partial response (PR), with 29.6% stable disease and 2.1% progressive disease. In the FL subset ($n = 104$), the ORR was 58.7%, (14.4% CR and 44.2% PR). In the MZL subset ($n = 23$), the ORR was 69.6%, (8.7% CR and 60.9% PR). Tumor shrinkage as best response was observed in 91% of evaluable patients (Figure). The estimated Kaplan-Meier (KM) median duration of response was 687 days (range 0-687). The KM-estimate of median PFS was 340 days (range 0-736). Gene expression analysis based on evaluable archival samples from 71 patients indicated that high expression of PI3K and B-cell receptor gene signatures was associated with response ($p = 0.02$ and $p = 0.04$, respectively). The most common treatment-related AEs (all grade/grade 3+) were transient hyperglycemia (49%/40%) and hypertension (29%/23%). Other AEs included neutropenia (25%/19%), diarrhea (18%/4%), lung infection (14%/11%), pneumonitis (7%/1.4%), and colitis (0.7%/0.7%). There were two non-fatal opportunistic infections. Laboratory

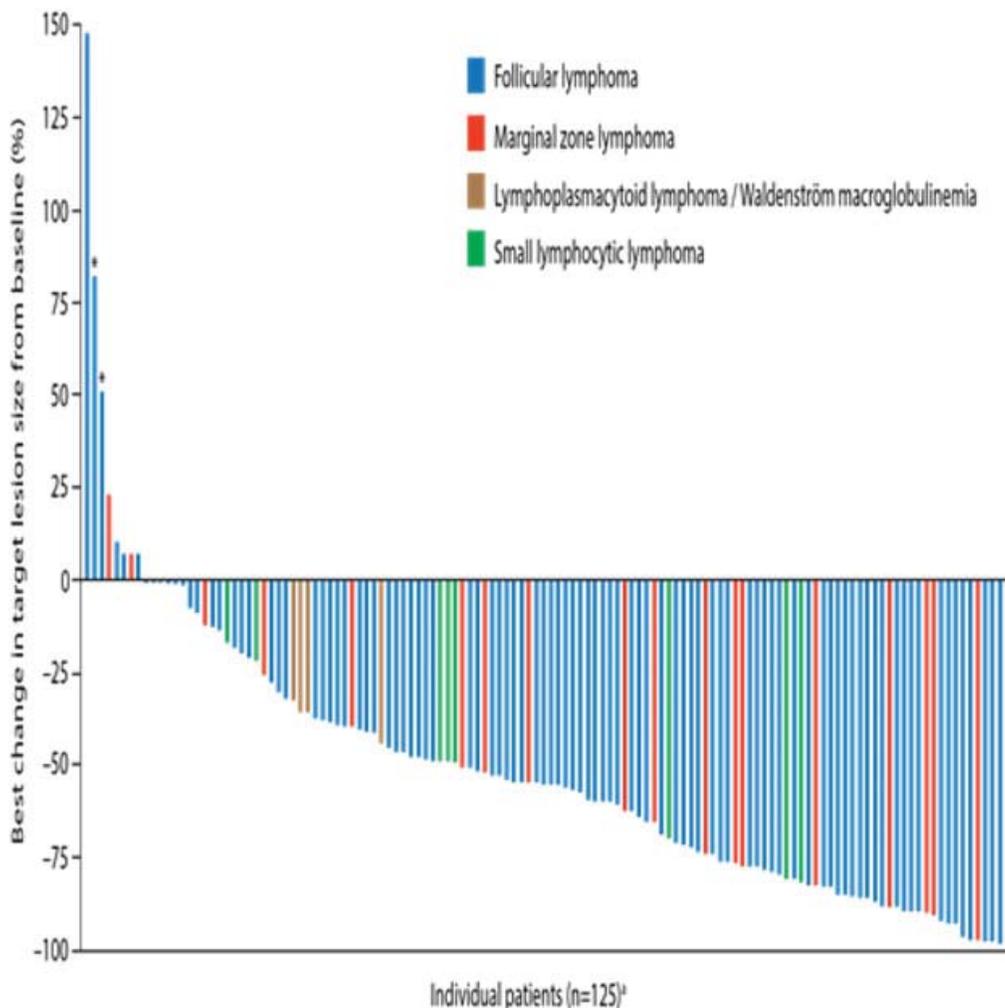
toxicities of interest were principally grade-1, including elevated ALT (23% all-grade/19% grade-1) and AST (28%/25%). There were 6 deaths, with 3 attributed to copanlisib: lung infection, respiratory failure, and a thromboembolic event.

Conclusions: Administration of copanlisib resulted in responses in the majority of patients, with a median duration of response exceeding 22 months. The rate of fatal drug-related events was low; 3 of 142 patients (2.1%). In general the safety profile was distinct and manageable, with low rates of severe hepatic enzymopathy, diarrhea or inflammatory events, and opportunistic infections.

Keywords: non-Hodgkin lymphoma (NHL); PI3K/AKT/mTOR.

109 HIGH RESPONSE RATES WITH PEMBROLIZUMAB IN COMBINATION WITH RITUXIMAB IN PATIENTS WITH RELAPSED FOLLICULAR LYMPHOMA: INTERIM RESULTS OF AN ON OPEN-LABEL, PHASE II STUDY

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Background: Follicular lymphoma (FL) tumors are infiltrated with antitumor T cells, however, their function is impaired by immune checkpoints such as PD-1/PD-ligand pathway. Blocking PD-1 enhances the function of antitumor T cells in FL. In addition, blocking PD-1 on NK cells has been shown to enhance the ADCC effect of NK cells. We reasoned that the combination of pembrolizumab, an anti-PD-1 antibody, and rituximab (R), an anti-CD20 antibody that induces ADCC, is likely to be synergistic through activation of both the innate and adaptive immune systems and result in enhanced clinical activity in FL.

Methods: We evaluated pembrolizumab and R in an open-label, non-randomized, single institution, phase II trial ($N = 30$). Key inclusion criteria included adult (age ≥ 18 years), FL grade 1-3a, ECOG 0-1, in relapse after ≥ 1 prior therapy and R sensitive disease, defined as a complete (CR) or partial response lasting at least 6 months after most recent R-containing therapy. Patients received R (375 mg/m² IV) on days 1, 8, 15, and 22 of cycle 1 and pembrolizumab (200 mg IV) q 3 weeks for up to 16 cycles starting on day 2 of cycle 1. Primary endpoint was overall response rate (ORR).

Results: 27 patients have initiated therapy, median age 65 (range 42-79), 52% male, 76% had intermediate or high risk FLIPI, 56% met GELF criteria. Median prior therapy =1 (range 1-4). Adverse events (AE) regardless of causality were mild, most grade 1-2. Grade 3 AE's included nausea ($N = 2$), infusion reaction ($N = 2$), aseptic meningitis ($N = 1$), pneumonia ($N = 1$). Immune-related AEs included grade 2 diarrhea ($N = 2$), grade 2 pneumonitis ($N = 1$), grade 2 skin rash ($N = 1$). At the pre-planned interim analysis ($N = 15$), ORR was 80%, CR rate was 60%. With a median follow up of 7 months (range 0.5-17), median DOR, PFS, and OS has not been reached. PD-L1 expression was tested in 8 baseline tumor samples using PD-L1 22C3 IHC pharmDx and was detected in histiocytes in all 8 tumors, present in only 1-8% of tumor cells in 5 tumors. Additional biomarker analyses are ongoing.

Conclusions: The combination of pembrolizumab and R is well tolerated in relapsed FL and is associated with high overall and CR rate. These interim results warrant further investigation of this combination in FL.

Keywords: follicular lymphoma (FL); monoclonal antibodies (MoAb); rituximab.

UCLI-ICML SESSION: NATURAL KILLER/T-CELL (NK/T-CELL) LYMPHOMA

110

NON-CANONICAL ROLE OF EZH2 IN NATURAL KILLER / T-CELL LYMPHOMA

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Introduction: The enhancer of zeste homolog 2 (EZH2), is a histone methyltransferase that usually function within the Polycomb Repressor Complex (PRC) 2 and mediate the tri-methylation of the lysine 27 residue on histone 3 (H3K27). The role of enhancer of zeste homolog 2 (EZH2) in cancer is complex and may vary depending on the cellular context. Currently there are no targeted therapies in Natural Killer T-cells Lymphoma (NKTL). The key driver in NKTL has not been fully elucidated. While JAK3 and STAT3 mutations have been found and JAK-STAT pathway activation at the transcriptomic level have been shown, the functional relevance of this pathway and the key downstream mediator of their potential oncogenic activities are not clear. In a series of studies, we first examine the role of EZH2 in NKTL and established a connection between JAK3 and EZH2. The insights from these studies have important implications on therapeutics.

Methods: We use gene expression profiling and microRNA profiling using microarray technology as well as immunohistochemistry on NKTL tissue microarray to examine EZH2 expression and regulation by microRNA. For functional studies, wild-type and mutants with the enzymatic domain of EZH2 deleted we used. Luciferase reporter assay was used to measure the transcriptional effect of both WT and mutant EZH2. Effect of JAK3 on EZH2 was studied using both WT and constitutively active JAK3 mutant. Mass Spectrometry proteomics was employed to identify phosphorylation sites on EZH2.

Results: We found that EZH2 is aberrantly overexpressed in the majority of NKTL. We showed that EZH2 upregulation is mediated by MYC-induced repression of its regulatory microRNAs and EZH2 exerts oncogenic properties in NKTL. Ectopic expression of EZH2 in both primary NK cells and NKTL cell lines leads to a significant growth advantage. Conversely, knock-down of EZH2 in NKTL cell lines results in cell growth inhibition. Intriguingly, ectopic EZH2 mutant deficient for histone methyltransferase activity is also able to confer growth advantage and rescue growth inhibition on endogenous EZH2 depletion in NKTL cells, indicating an oncogenic role of EZH2 independent of its gene-silencing activity. Mechanistically, we show that EZH2 directly promotes the transcription of cyclin D1 and this effect is independent of its enzymatic activity. Furthermore, depletion of EZH2 using a PRC2 inhibitor 3-deazaneplanocin A significantly inhibits growth of NK tumor cells. In addition, we found that phosphorylation of EZH2 at specific residues by JAK3 promotes the dissociation of the PRC2 complex leading to decreased global H3K27me3 levels, while it switches EZH2 to a transcriptional activator, conferring higher proliferative capacity of the affected cells. Gene expression data analysis also suggests that the noncanonical function of EZH2 as a transcriptional activator upregulates a set of genes involved in DNA replication, cell cycle, biosynthesis, stemness, and invasiveness. Consistently, JAK3 inhibitor was able to significantly reduce the growth of NKTL cells, in an EZH2 phosphorylation-dependent manner, whereas various compounds recently developed to inhibit EZH2 methyltransferase activity have no such effect.

Conclusion: Our study uncovers an oncogenic role of EZH2 independent of its methyltransferase activity in NKTL and suggests that targeting EZH2 may have therapeutic usefulness in this lymphoma.

Pharmacological inhibition of JAK3 activity may provide a promising treatment option for NKTL through the novel mechanism of suppressing the non-canonical EZH2 activity in NKTL.

Keywords: EZH2; JAK/STAT; T-cell lymphoma (TCL).

111 EBV-ASSOCIATED NODAL T AND NK-CELL LYMPHOMA SHOWS DISTINCT MOLECULAR SIGNATURE AND COPY NUMBER CHANGES

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Introduction: EBV-positive cytotoxic T- and NK-cell lymphomas (TNKL) occurring in adults are a heterogeneous group of conditions. It is unclear whether there exist unique molecular subtypes associated with distinct clinico-pathologic features.

Method: We performed integrative gene expression profiling (GEP) and copy number aberration (CNA) analyses on 66 cases of TNKL occurring in adults who presented with extranodal and nodal disease and correlated the molecular signature and copy number profile with clinicopathologic features in order to examine if cases with nodal disease at presentation are distinct from their extranodal counterpart. The cases were categorized based on the following features: i) type of disease presentation (extranodal [EN-group] vs nodal [N-group]); ii) absence and presence of nasal involvement; and iii) T- vs NK-cell lineage. Multiplexed immunofluorescence microscopy was utilized to exam co-expression of proteins on tissue microarray.

Results: Three molecular clusters associated with specific CNAs were identified and one cluster was enriched for cases with nodal presentation. The N-group was significantly associated with old age, lack of nasal involvement, CD8+/CD56- immunophenotype, and T-cell lineage compared to EN-group. The molecular signature of N-group is characterized by upregulation of PD-L1 and T-cell related genes, including CD2 and CD8, and downregulation of CD56, consistent with the immunophenotype. Multiplexed immunofluorescence further validated the GEP findings and confirmed a higher CD2 and PD-L1 protein expression in the N-group compared to the EN-group. Interestingly, the N-group is associated with loss of 14q11.2, and since 14q11.2 overlapped the T-Cell Receptor Alpha Constant (TCRA locus), we hypothesized that the loss of 14q11.2 in this group might be an indication of T-cell lineage as focal loss within the TCR locus can be a reflection of physiologic rearrangement of the TCR locus via VDJ recombination. Indeed, our results demonstrated that 14q11.2 loss correlated with T-cell origin, and loss of TCR loci including TCRA, TCRB, TCRG and/or TCRD. We further compared the T-cell signature between the 2 groups and showed a significantly higher expression of the T-cell related genes in N-group compared to EN-group, reinforcing our hypothesis that loss of TCR loci in the former is associated with T-cell lineage and that loss of 14q11.2 may be a potentially useful genetic marker of T-cell lineage.

Conclusion: Our results suggest that TNKL with nodal presentation is distinct and deserved to be classified separately from those with extranodal presentation. In addition, the upregulation of PD-L1 indicates the possibility of anti-PD1 immunotherapy in this distinctive entity.

Keywords: Array-comparative genomic hybridization; gene expression profile (GEP); T-cell lymphoma (TCL).

112 NK/T-CELL LYMPHOMA: WHEN PATIENTS MEET OMICS

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Natural killer/T-cell lymphoma (NKTCL) is a malignant proliferation of CD56+ and cytoCD3+ lymphocytes, which is prevalent in Asian and South American populations. It is characterized by prominent tissue necrosis and aggressive clinical course, with strong association with Epstein-Barr virus (EBV) infection.

The molecular pathogenesis of NKTCL has largely remained elusive. Systemic biology works provide novel insights into the pathogenesis and new biomarkers can be discovered with diagnostic and therapeutic implications. As revealed by comparative genomic hybridization, 6q21 is frequently deleted, thus leading to silencing of the tumor-suppressor genes PRDM1, ATG5, AIM1, FOXO3 and HACE1. Also, NKTCL can be distinguished from normal natural killer cells by gene-expression profiling, which has revealed activation of several oncogenic pathways in NKTCL, including those of NF- κ B, mitogen-activated protein kinase (MAPK) and Janus kinase-signal transducer and activator of transcription (JAK-STAT). To clarify the molecular pathogenesis of NKTCL, we identified somatic gene mutations in 25 patients with NKTCL by whole-exome sequencing and confirmed them in an extended validation group of 80 patients by targeted sequencing. Recurrent mutations were most frequently located in the RNA helicase gene DDX3X (21/105 subjects, 20.0%), tumor suppressors (TP53 and MGA), JAK-STAT pathway molecules (STAT3 and STAT5B) and epigenetic modifiers (MLL2, ARID1A, EP300 and ASXL3). As compared to wild-type protein, DDX3X mutants exhibited decreased RNA-unwinding activity, loss of suppressive effects on cell-cycle progression in natural killer cells and transcriptional activation of NF- κ B and MAPK pathways.

Meanwhile, we detected multiple EBV-related sequences in tumor samples of all subjects. How EBV is involved in pathogenesis of NKTCL? Using viral capture sequencing, we found EBV integrated genes mainly involving protein regulation, cell signaling and cellular process. Clinically, patients with DDX3X mutations presented a poor prognosis. After combining international prognostic index (IPI) score with gene-mutation status, we can further stratify subjects with NKTCL treated with CHOP regimen into three groups with distinct prognoses: a low-risk subgroup (IPI 0-1 and WT DDX3X and WT TP53), an intermediate-risk subgroup (IPI 0-1 and mutated DDX3X and mutated TP53; IPI 2-5 and WT DDX3X and WT TP53) and a high-risk subgroup (IPI 2-5 and mutated DDX3X and mutated TP53).

Although chemotherapy and radiotherapy are able to improve the disease outcome, the prognosis of NKTCL is generally poor, and no targeted therapy is currently available. Recent studies indicated that L-ASP-based regimen, such as SMILE, AspMetDex and P-GEMOX regimen were efficient in treating NKTCL. Using UPLC-QTOFMS, we identified distinct metabolomic profile in NKTCL and suggested that metabolism-targeted agents were key components. On the other hand, novel targeted agents, such as read-through therapy to DDX3X, JAK inhibitors to JAK/STAT pathway, HDACis to epigenetic aberrations, and AKT/mTOR inhibitor, may be promising therapeutic strategies in treating NKTCL. In the future, scientific research on NKTCL should be strengthened in China, focusing on EBV-related pathogenesis, prognostic study in the next-generation sequencing era, as well as genetic abnormalities in relapsed/refractory NKTCL. Meanwhile, multi-center clinical trial should be carried out in Asia-Pacific countries, to further obtain the randomized data of L-ASP-based regimens, to finally realize precision medicine and to make NKTCL a curable disease.

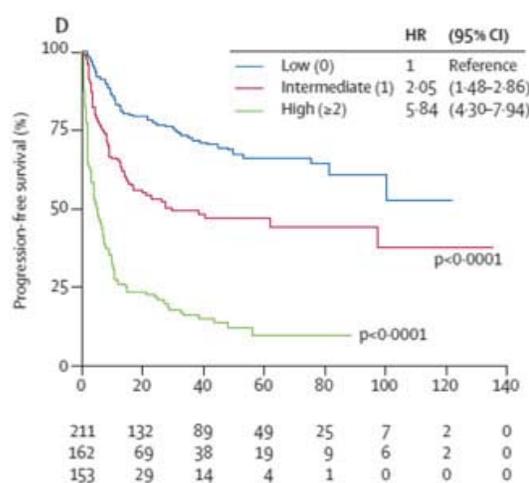
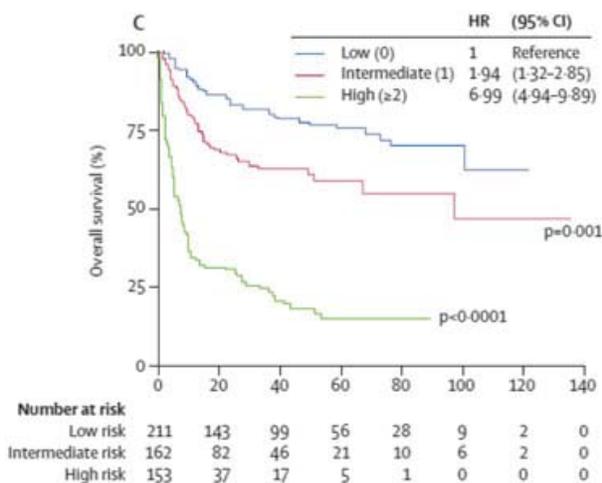
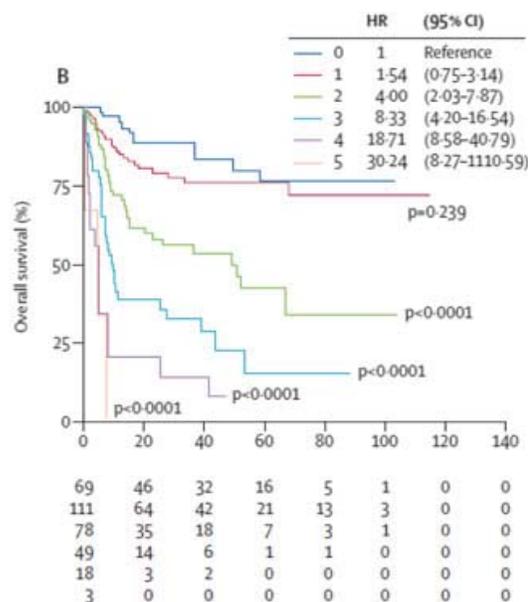
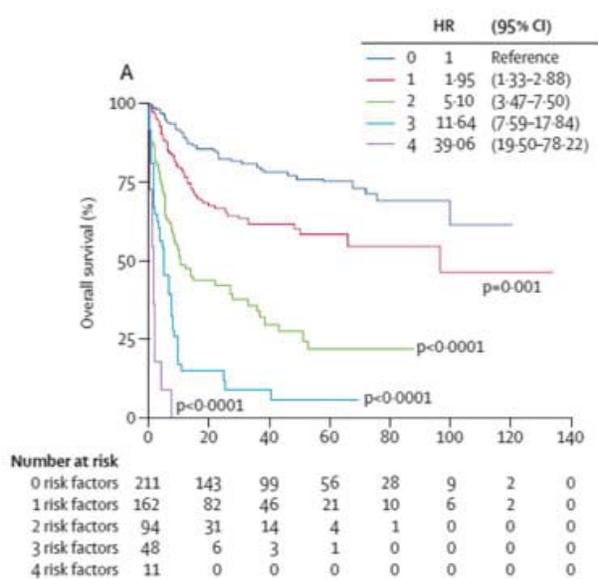
Keywords: L-asparaginase; non-Hodgkin lymphoma (NHL).

113 TREATMENT OF EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE (ENKTL)

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Extranodal NK/T-cell lymphoma (ENKTL) is a rare histopathologic subtype with strong association with Epstein-Barr virus (EBV) infection. In general, the prognosis of ENKTL has been known to be very poor for a long time. Especially, for advanced stage disease, long term survival was less than 10%. However, during last decade the natural history is significantly improved due to recent advances in the treatment. Two big progresses are concurrent chemo-radiation for localized disease and using L-asparaginase containing regimens like SMILE (steroid, ifosfamide, l-asparaginase, and etoposide) or AspaMet-Dex (l-asparaginase, methotrexate and dexamethasone). Therefore, the prognostic model, so called Korean prognostic index (KPI), has limitations to predict outcome. We propose a new prognostic index, the prognostic index for natural killer cell lymphoma (PINK), which includes four independent risk factors: age greater than 60 years, stage III/IV disease, distant lymph-node involvement, and non-nasal type disease. When we added Epstein-Barr virus DNA data to the PINK model (PINK-E). For the relapsed ENKL after current standard treatment, optimal management is not defined yet. Several drugs including brentuximab vedotina, immuncheck point inhibitors are under investigation.



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FIRST-LINE L-ASPARAGINASE-BASED CHEMOTHERAPY PLUS RADIOTHERAPY IS ACTIVE IN STAGE I/II EXTRANODAL NK/T-CELL LYMPHOMA: RESULTS FROM PEKING UNIVERSITY CANCER HOSPITAL

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Introduction: Although most patients diagnosed with extranodal nasal-type natural killer/T-cell lymphoma (NKTCL) have localized disease, the survival outcomes of radiotherapy alone or conventional doxorubicin-based chemotherapy were considered unsatisfactory. This study is retrospectively to investigate the effects and potential survival benefits of L-asparaginase-based chemotherapy and locoregional radiotherapy as first-line treatments in early-staged NKTCL patients.

Methods: From April 2001 to July 2016, a total of 196 pts diagnosed as stage I/II NKTCL were treated in Peking University Cancer Hospital. All patients were confirmed by immunohistochemistry staining according to WHO Classification criteria. Median age was 43 years (range 12 to 81) with 74.0% males ($n = 145$). 84 (42.9%) cases presented with B symptoms, and 17 (8.72%) cases with IPI score ≥ 2 . Among of them, 58 (29.6%) received chemotherapy alone, and 138 (70.4%) received chemotherapy combined with concurrent or sequential locoregional radiotherapy (dosage from 50 to 56Gy) as first-line treatment. Chemoregimens included CHOP-like, CHOP-L (CHOP + L-asparaginase), COEP-L (etoposide instead of doxorubicin), LOP (vincristine, prednisolone, L-asparaginase) or GDP-L (gemcitabine, cisplatin, dexamethasone +L-asparaginase).

Results: After a median follow-up period of 109 months (range, 4-187 months), clinical outcomes of 173 evaluable patients were analyzed. For patients received chemotherapy alone, the complete response (CR) rates of CHOP-like, CHOP-L and COEP-L regimen were 21.1%, 66.7%, 60%, respectively; the overall response rates (ORR) were 47.4%, 86.7%, 60%, respectively. For patients received radiochemotherapy, the CR rates of CHOP-like + RT, CHOP-L + RT and COEP-L + RT were 61.9%, 91.1%, 86.9%, respectively; the ORR were 66.7%, 93.3%, 96.7%, respectively. The one-year progression-free survival (PFS) was only 54.7% in CHOP-like group, while the median PFS in CHOP-L and COEP-L groups had not reached. The PFS were significantly superior in CHOP-L and COEP-L groups as compared to CHOP-like group ($p < 0.001$). But the PFS showed no apparent difference between CHOP-L and COEP-L groups ($p = 0.644$). For patients received chemotherapy alone, the one-year PFS was only 57.1%. However, with the addition of locoregional radiotherapy, the one-year PFS improved to 88.8% ($p = 0.002$).

Conclusions: The data from Peking University Cancer Hospital showed L-asparaginase and locoregional radiotherapy are two essential treatment choices in early-stage NKTCL patients. CHOP-L or COEP-L plus radiotherapy are both promising first-line treatment strategies in this subset of NKTCL.

Keywords: L-asparaginase; peripheral T-cell lymphomas (PTCL).

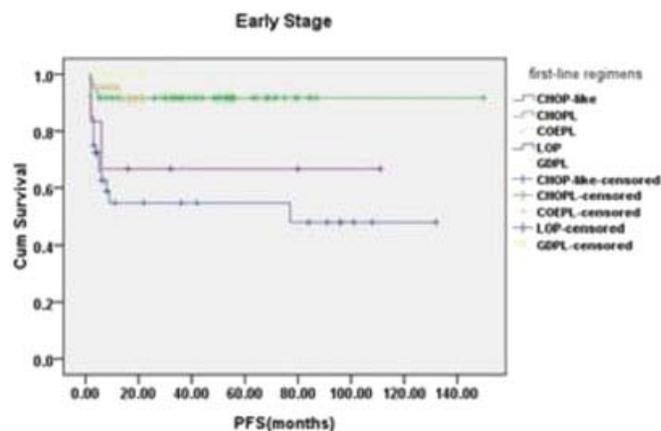
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CURRENT TREATMENT FOR NK/T CELL LYMPHOMA: SUN YAT-SEN UNIVERSITY CANCER CENTER EXPERIENCE, CHINA

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Optimal therapeutic strategies have not been fully defined for NK/TCL yet. SMILE, AspaMetDex and P-Gemox were recommended as major effective chemotherapy regimen by 2016 NCCN guideline. We initiated a prospective, multicenter, randomized, clinical trial in March 2014. And the purpose of this study is to evaluate the efficacy and toxicity between P-Gemox and AspaMetDex for newly diagnosed stage I/II patients as well as stage III/IV or relapsed/refractory NK/TCL. All patients were randomly assigned to receive either P-Gemox + thalidomide regimen (**Group A:** Pegaspargase 2000 U/m²; im d1, Gemcitabine 1000 mg/m²; ivdrip, d1, d8. Oxaliplatin 130 mg/m²; ivdrip, d1, thalidomide 100 mg/d po, for one year) or AspaMetDex regimen (**Group B:** Pegaspargase 2000 U/m²; im, d1, Methotrexate 3000 mg/m²; civ 6-hour, d1, calcium folinate 30 mg iv, q6h, until reached safe serum MTX induction chemotherapy of both regimens were administered and followed by EIFRT. ASCT as consolidation was given to good responders (CR and PR) to two Groups for advanced cases. The results of interim analysis for 110 cases were shown as Table 1. For the patients with early stage (I/II) and advanced stage (III/IV) or relapsed disease, PFS and OS were similar in Group A and Group B. Agranulocytosis, thrombocytopenia, and infections relative were more common in Group B, whereas anemia, hyperbilirubinemia, edema, and increased BUN/Cr were more common in Group B. All 3 patients died of treatment related toxicity in Group B. Therefore, our preliminary results showed both P-Gemox and AspaMetDex yielded promising efficacy for early stage as well as advanced or relapsed NK/TCL, though survival still is unsatisfied for this patients population. Meanwhile,



		Group A P-Gemox/ Thalidomide	Group B AsperMetDex	P value
		+EIFRT N= 27/ 32	+ EIFRT N=27/31	
Stage I/II NK/TCL	ORR (%)	92.6 (25)	88.8(24)	
	CR (%)	88.8 (24)	85.1(23)	
	2-yr PFS(%)	82.9	84.5	0.791
	2-yr OS(%)	95	75.8	0.089
		N= 22/24	N= 20/23	
Stage III/IV or relapsed/refractory NK/TCL	ORR (%)	86.4(19)	70.0(14)	
	CR (%)	50.5(12)	50.0(10)	
	2-yr PFS (%)	43.6	40.5	0.356
	2-yr OS (%)	52.5	48.9	0.935
	Hospitalization (day)	1.9	4.9	<0.01

P-Gemox may be less toxic, and can be used in outpatients clinics. This clinical trial is still ongoing (ClinicalTrials.gov, NCT 2085655).

Furthermore, promising response of single agent, chidamide, a new oral HDAC inhibitor, for the treatment of relapsed or refractory NK/TCL without significant EBV-reactivation was recently observed in SYSUCC. PD/PK of chidamide for different dosage and schedule will be presented.

Table 1: Comparison of effectiveness between two Groups.

EIFRT: Extensive involved field radiotherapy.

Keywords: Epstein-Barr virus (EBV); extranodal lymphomas.

116 MOLECULAR CHARACTERIZATION OF EXTRANODAL NATURAL KILLER (NK)/T-CELL LYMPHOMAS, NASAL TYPE FROM LATIN AMERICA

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Introduction: Extranodal Natural Killer/T (NK/T)-cell lymphoma, nasal type (ENKTCL) is a rare, aggressive type of non-Hodgkin lymphoma associated with Epstein-Barr virus (EBV). This lymphoma is more prevalent in Asians and Native American populations from Mexico and Central and South America. Recent studies from Asia have demonstrated recurrent mutations of various genes in ENKTCL; however, the overlap of mutations found in different studies/populations is rather low. This discrepancy may be due either to the technology used or the genetic background of the population analyzed that might imprint the mutational landscape. Most of the studies, so far, come from China, Japan and Korea and nothing is known about the mutational landscape in ENKTCL cases in Latin American. The aim of this study is to analyze by next generation sequencing (NGS) a large series of ENKTCL from Latin America collected in three National Cancer Institutes (Mexico, Peru and Argentina) using an AmpliSeq Custom Panel including genes recurrently mutated in ENKTCL. This comprehensive genetic analysis aims to understand whether the different molecular results identified are associated with different ethnic backgrounds and how these mutations contribute to the pathogenesis of ENKTCL.

Methods: We analyzed 111 cases (69 from Mexico, 27 from Peru and 15 from Argentina). In all cases H&E stain, CD56 and EBERS in situ hybridization were performed. Tumor DNA was isolated and only cases with DNA quality >300 BP were analyzed by NGS. Genes were selected from previously reported whole exome sequencing data from ENKTCL based on their frequency and potential biological significance. The AmpliSeq Custom Panel included the following genes: *STAT3*, *STAT5B*, *JAK3*, *DDX3X*, *TP53*, *MGA*, *MSN* and *BCOR*. The analysis was performed on the Ion Torrent PGM platform.

Results: In total, 45 cases have been analyzed by NGS (29 from Mexico, 12 from Peru and 4 from Argentina). The mean average read depth of the NGS sequence analysis was 3405 (range 413-6187). 36 mutations were identified in 26 of 45 cases analyzed (58%). Mutations in *STAT3*, *STAT5B* and *JAK3* were identified in 9 (20%), one (2%) and one (2%) cases, respectively. All together, 11 mutations (24%) affected the JAK-STAT pathway. Hotspot mutations G618R, Y640F and D661Y in the SH2 domain of *STAT3* were observed in the majority of the cases whereas the hotspot A573V of the JH2 domain of *JAK3* was identified in one case. The second most frequent mutation was in the transcription co-repressor *BCOR* found in 7 cases (16%). *DDX3X* and *TP53* mutations were detected in 5 (11%) and 4 (9%) cases, respectively. As has been reported, *DDX3X* and *TP53* mutations were mutually exclusive, except for one case. *MGA* mutations were found in 6 cases (13%) and often concurrent with other genes (2 cases each *STAT3* and *BCOR*). *MSN* mutations were identified in 3 cases (7%), 2 of which were concurrent with *STAT3*. From the 26 cases with mutations, 18 cases (69%) had only one mutation, 6 cases had 2 mutations (23%), and 2 cases had 3 mutations (8%). Comparison of the amount of mutated cases among the three Latin American countries revealed that Mexican cases are more frequently mutated compared to Peru and

Argentina (65%, 42% and 50% respectively). *TP53*, *DDX3X* and *MSN* mutations were almost exclusively identified in the Mexican cases. Only one *DDX3X* mutation was present in a Peruvian case. The only *JAK3* mutation identified was in a case from Argentina.

Conclusions: Preliminary results of a large series of ENKTCL cases from Latin America reveal a mutational profile similar to what has been reported in Asian cases, mainly in China, but the frequencies of some genes are different. Mutations leading to abnormal activation of the JAK-STAT3 are highly prevalent in Latin America. *STAT3* mutations found in 20% of the Latin American cases, is the highest prevalence reported of this gene, so far. An interesting finding is that the most frequent mutations – *STAT3*, *BCOR* and *DDX3X* – found in almost half of the cases (21/45 cases) are mutually exclusive, whereas mutations in *MGA* and *MSN* are concurrent either with *STAT3* or *BCOR* mutations. Mutations in *STAT5B* and *JAK3*, in contrast to some reports, were infrequently identified in this series.

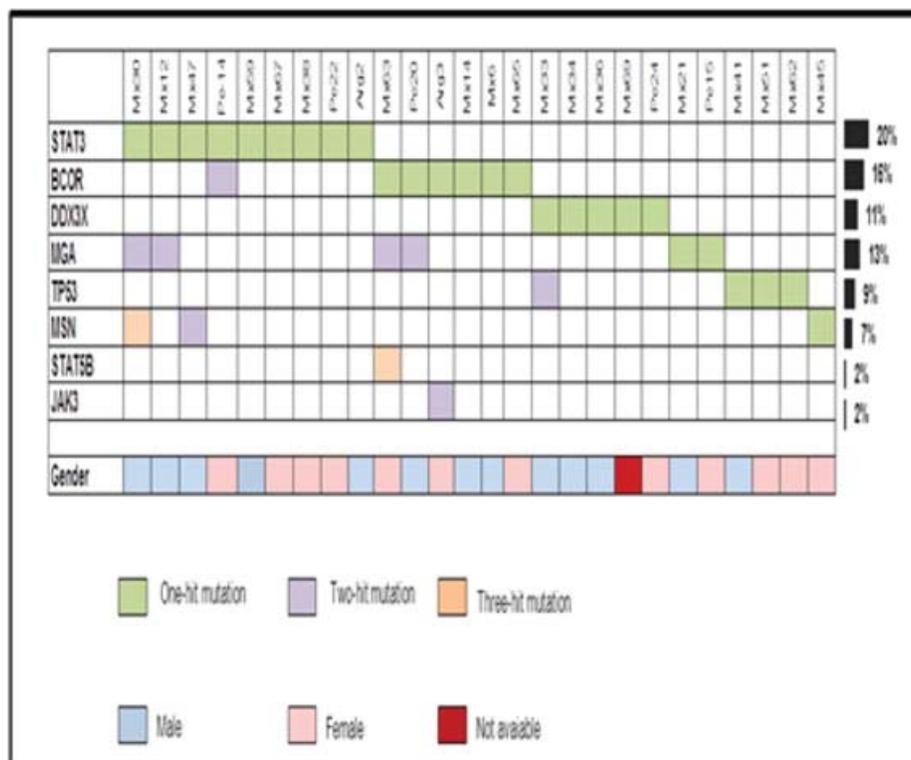
Keywords: Epstein-Barr virus (EBV); non-Hodgkin lymphoma (NHL); T-cell lymphoma (TCL).

117 NK/T-CELL LYMPHOMA, THE FRENCH EXPERIENCE.

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Extra-nodal NK/T-cell lymphoma (ENKTL) is a rare and severe form of lymphoma with a very low incidence in Western countries,



representing 0.4% of lymphoma in France. We have collected a series of 171 patients treated between June 1986 and January 2017 in 33 French and 1 Belgian centres. The clinical presentation is quite similar to the one described in Asian series with 85% of nasal and 15% of extra-nasal forms, 60% of patients with a localized and 40% with a disseminated disease. Median age was 51 (16-85) and 66% of patients were of Caucasian origin with 17% from North Africa and 5% of Asian origin. Eleven among 13 patients tested had a type A EBV strain with in 6/13 a large deletion in the LMP1 gene¹.

Sixty percent of the whole cohort and 95% of patients treated after January 2011 (87 patients) have received an asparaginase (aspa) containing regimen in first line and 72% of second line treatments were aspa based. The estimated median survival of the 171 patients was almost 6 years for the entire cohort with a media follow-up of 2,9 years for living patients (0-27), at 5 years it was 67% for patients with a localized disease and only 23% for patients with a disseminated disease. Our current recommendations for localized disease are to give first 1 cycle of a regimen combining aspa, gemcitabine, methotrexate and dexamethasone (MGAD), then irradiation and then a second course of the same chemotherapy with, since March 2016, a switch from E-coli aspa to Erwinia aspa depending on the aspa activity after the first cycle. For patients with a disseminated disease we use the same association plus oxaliplatin (MOGAD) with the same switch in case of low activity followed, for fit patients, after 3 to 4 cycles, by an autologous (auto) stem cell transplantation (SCT). Among 16 patients with a measure of activity, 9 (56%) had at least one low activity probably due to inhibiting antibodies against aspa. A pegylated form of aspa, that seems to be less immunogenic, should be used in countries where it is possible. Forty-seven patients have been treated with MGAD or MOGAD, with a median follow-up of 1.5 year for living patients. For the 32 patients with a localized form the estimated 2-year survival is 82% and 47% for patients with a disseminated form.

We have done a retrospective study on the merit of auto and allogenic (allo) SCT in 65 patients of this cohort of 171 who have received an allo ($n = 19$) or auto ($n = 46$) SCT. More patients received auto SCT (26/46, 56%) than allo (5/19, 30%) in first remission but other characteristics were similar between the 2 groups. We found no statistical difference between auto and allo groups for complete response (65 and 84%), relapses (52 and 47%) and 4-year survival (52 and 53%).

Finally taking into account the stunning results in a small series using an immune check point inhibitor², some patients in relapse have received anti-PD1 antibodies which should be available soon in France for relapse/refractory patients with ENKTL in a special program authorizing the use of new drugs in rare forms of cancer.

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SESSION 9: AGGRESSIVE LYMPHOMAS

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LONG-TERM SURVIVAL AND LOSS IN EXPECTANCY OF LIFE IN A POPULATION-BASED COHORT OF 7114 PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Survival has improved among patients with diffuse large B-cell lymphoma (DLBCL) following the introduction of anti CD20 antibody treatment, yet one third of the patients experience primary refractory disease or relapse. We aimed to quantify the loss in expectation of life (LEL) due to DLBCL at a population-based level in Sweden.

Methods: DLBCL patients diagnosed 2000-2013 ($N = 7114$, 55% men, 45% women) were identified through the national Swedish Lymphoma Registry (SLR) (population-based coverage >97%). Patients were divided into risk groups based on their age-adjusted International Prognostic Index (aIPI) with age cutoff at 70 years. LEL is the difference between the remaining life years the patients would have had in the absence of DLBCL (obtained from publically available data from Statistics Sweden), and the estimated remaining life years among the patients. LEL was predicted from a flexible parametric model including year and age at diagnosis, risk group (aIPI < 2 or aIPI ≥ 2) and sex, and adjusted for non-proportional hazards. LEL was estimated from the date of diagnosis and among 2-year survivors, at different ages and among men and women separately.

Results: Median age at diagnosis of DLBCL was 70 years (range:18-105 years). The majority of the patients presented with stage III-IV disease (54.8%) and elevated LDH (56.7%), whereas 25.2% had a performance status of 2 or more. In all, 46.4% were classified with aIPI ≥ 2. Median follow-up was 2.9 (range: 0-15) years. In the age groups presented (50, 60, 70 years, Figure 1), the gap in the remaining life expectancy at diagnosis, comparing male patients to the population, decreased substantially with time, especially for patients ≤60 years (Figure 1A-3A). Still, patients diagnosed at the end of the study period are estimated to lose on average 5.5 life years due to DLBCL. Among 2-year survivors, however, there was no evidence of a significant LEL among recently diagnosed patients ≤60 years (Figure 1B-3B). By risk group, evidence of reduced LEL across the study period was most pronounced for patients with aIPI ≥ 2 at ages 50 and 60 years (60 years: LEL 14.5 years (95% CI:13.1-15.9) in 2000; 8.3 years (95% CI 5.5-11.1) in 2013). In older

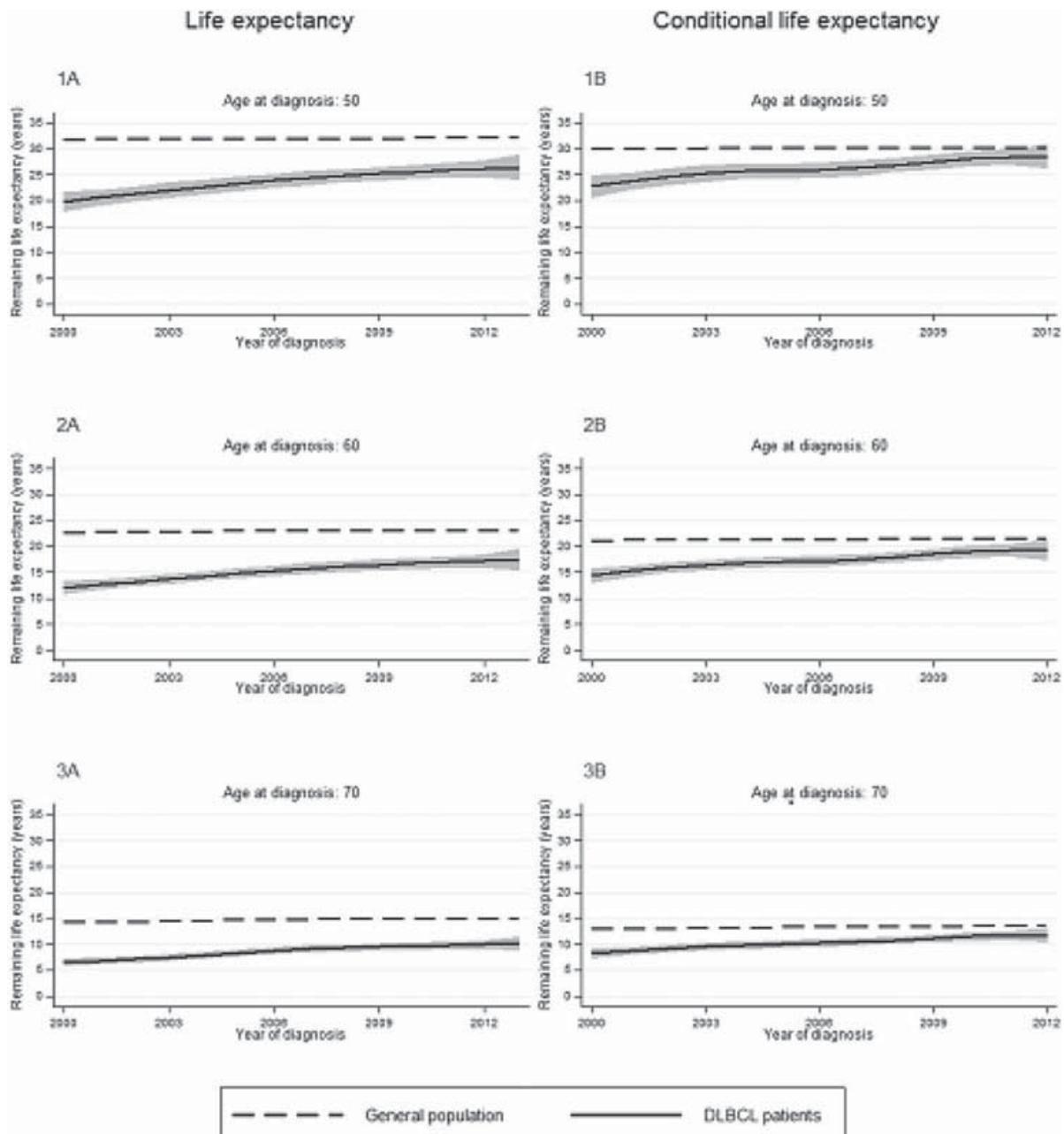
patients (70 years) the estimated LEL at diagnosis was 2.8 years (95% CI:1.7-3.9) for aalPI < 2, and 7.0 (95% CI:5.1-8.8) for aalPI ≥ 2 in 2013. When restricting to 2-year survivors, a small but significant LEL was still observed in both risk groups (aalPI <2: 1.5 years, 95% CI:0.6-2.4, aalPI ≥2: 2.1 years, 95% CI:0.0-4.2). Results for female patients were similar (data not shown).

Conclusions: Using the novel measure LEL, we illustrate the improvement of DLBCL survival over time, and quantify the average loss in recently diagnosed patients to 5.5 years. Despite chemotherapy with anti CD20, a loss of >8 years is still observed among patients ≤60 years with IPI ≥ 2 indicating remaining unmet medical needs in these patients.

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

119 R-CHOP +/-RADIOTHERAPY IN NON-BULKY LIMITED-STAGE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): FINAL RESULTS OF THE PROSPECTIVE RANDOMIZED PHASE III 02-03 TRIAL FROM THE LYSA/GOELAMS

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Introduction: The benefit of radiotherapy (RT) following chemotherapy in limited-stage diffuse large B-cell lymphoma (DLBCL) remains controversial. Before the Rituximab (R) era, randomized trials have reported conflicting results. We conducted a randomized trial in patients with non-bulky (tumor size <7 cm) limited-stage DLBCL to evaluate the benefit of RT following R-CHOP.

Methods: Patients were stratified according to the Miller modified IPI (mIPI) including LDH (normal/elevated), ECOG performance status (0-1/2-3), age (<60/>60 yrs) and disease stage (I/II). The patients received 4 or 6 consecutive cycles of R-CHOP delivered every two weeks, followed or not by RT at 40 Gy delivered 4 weeks after the last R-CHOP cycle. All patients were evaluated by FDG-PETs performed at baseline, after 4 R-CHOP cycles and at the end of treatment. The primary objective of the trial was event-free survival (EFS) from randomization.

Results: The trial randomized 165 patients in the R-CHOP arm and 169 in the R-CHOP + RT arm. Response assessment was performed after the fourth cycle of R-CHOP based on clinical examination, CT-scan and PET. CR was observed in 281 patients (88%) and PR in 38 (12%), without any difference between the two arms. R-CHOP cycles 5 and 6 were delivered to 123 and 118 patients respectively (61/57 in the R-CHOP arm and 62/61 in the R-CHOP + RT arm). According to initial randomization, among the 281 patients in CR following R-CHOP, 144 received RT and 137 did not receive any further treatment. Eight patients declined RT for personal reasons. 27 out of the 38 partial responders received 2 additional cycles of R-CHOP and RT, 5 received 2 additional R-CHOP cycles without RT, and 3 were delivered high dose chemotherapy: complete response was finally documented in 28 cases and the 10 remaining patients were still considered in PR. In an intent to treat analysis, with a median follow-up of 64 months, five-year EFS was not

statistically different between the two arms, with 89% ± 2.9 in the R-CHOP arm vs 92% ± 2.4 in the R-CHOP + RT arm (HR 0.61, 95%CI 0.3 to 1.2, $p = 0.18$). Five-year overall survival was also not different at 92% (95% CI: 89.5-94.5) for patients assigned to R-CHOP alone, and 96% (95% CI: 94.3-97.7) for those assigned to R-CHOP + RT, ($p = ns$).

Conclusion: R-CHOP alone is not inferior to R-CHOP14 followed by RT in patients with non-bulky limited-stage DLBCL. We recommend that these selected patients who reach complete remission based on PET evaluation after 4 or 6 R-CHOP cycles should be spared additional RT, thus avoiding long-term radiation-related toxicity. (ClinicalTrials.gov number, NCT00841945).

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

120 RADIOTHERAPY TO BULKY DISEASE PET-NEGATIVE AFTER IMMUNOCHEMOTHERAPY CAN BE SPARED IN ELDERLY DLBCL PATIENTS: RESULTS OF A PLANNED INTERIM ANALYSIS OF THE FIRST 187 PATIENTS WITH BULKY DISEASE TREATED IN THE OPTIMAL > 60 STUDY OF THE DSHNHL

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Background: Radiotherapy (RT) to bulky sites improves outcome of elderly DLBCL patients [Pfreundschuh et al., Lancet Oncol 2008; 9: 105-116; Held et al., J Clin Oncol 2014; 32:112-1118]. Whether RT can be spared in patients with a PET-negative bulk after R-CHOP was prospectively addressed in OPTIMAL >60. To assure that patients

with bulky disease were not put at risk by this PET-based omission of radiotherapy, a planned interim analysis was performed.

Patients and Methods: 61 to 80 y-old pts. with untreated DLBCL were randomized to 6xCHOP-14 or 6xCHLIP-14 (liposomal instead of conventional vincristine, 2 mg/m² [uncapped]) plus 8 x rituximab 375 mg/m² (R) q 2 wks. or 12xR (days -4,-1,1,4,14,28,42,56,91,126,175, 238). Pts. with bulk (> = 7.5 cm) that remained PET-positive after chemotherapy were assigned to RT (39.6 Gy), while PET-negative bulks were observed.

Results: 187/505 (37%) had bulky disease and were compared to 117/306 (38%) RICOVER-60 pts. (38%) who had received 6xCHOP-14 + 8R. OPTIMAL > 60 pts. were older (70 vs. 68 years) and had more IPI = 3 (33% vs. 29%) and IPI = 4,5 (34% vs. 23%) compared to RICOVER-60. PET was performed in 166/187 OPTIMAL > 60 bulk pts. (reasons for no PET: early death: 5; excessive toxicity: 3; protocol violation: 1, non-compliance: 4, change of diagnosis: 6, others: 2). 80/166 (48%) bulks remained PET-positive and 62/80 (78%) were irradiated (reasons for no RT: progression: 8; medical reasons: 9; negative biopsy: 1), reducing RT from 67/117 (57%) in RICOVER-60 by 42% to 62/187 (33%) in OPTIMAL > 60. Despite the unfavorable demographics, outcome of the 187 bulk pts. in OPTIMAL > 60 was non-inferior to RICOVER-60 in an intention-to-treat analysis, not even in the least intensive of the 4 OPTIMAL > 60 treatment arms consisting of 47 pts. who received 6xCHOP-14 + 8R. 2-year PFS and OS in OPTIMAL > 60 was 79% and 88%, respectively, compared to 75% and 78% of the 117 RICOVER-60 pts. In a multivariable analysis adjusting for the IPI risk factors, the hazard ratio of the OPTIMAL > 60 compared to the RICOVER-60 bulk pts. was 0.7 (95% CI: 0.3; 1.5; *p* = 0.345) for PFS and 0.5 (95% CI: 0.2; 1.3; *p* = 0.154; *p* = 0.154) for OS.

Conclusion: Radiotherapy can be spared in PET-negative bulks, resulting in a 42% reduction of patients who receive radiotherapy without compromising the outcome of these patients. *Supported by Amgen, Roche, Spectrum.*

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

121 DIFFERENTIAL EFFICACY OF BORTEZOMIB IN SUBTYPES OF DIFFUSE LARGE B-CELL LYMPHOMA (DLBL): a PROSPECTIVE RANDOMISED STUDY STRATIFIED BY TRANSCRIPTOME PROFILING: REMODL-B

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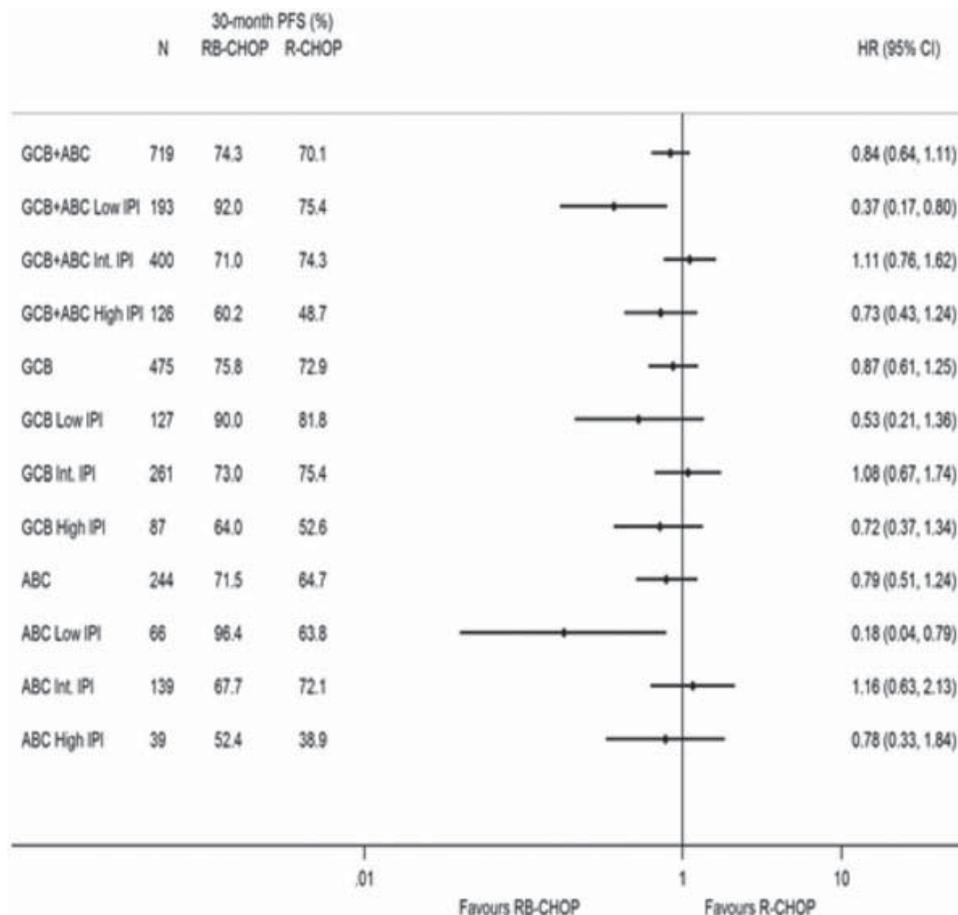
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Background: DLBL subtypes identified by patterns of gene expression correspond to germinal center (GCB) or activated (ABC) B-cells like. The latter demonstrate dysregulation of the NF-KB pathway. Outcomes of treatment with R-CHOP are inferior for ABC DLBL in retrospective series. This study investigated whether adding bortezomib (B), a putative NF-KB inhibitor, can reverse this phenotype.

Methods: The REMODL-B study was a collaboration between the UK NCRI group and the SAKK. Patients (pts) newly diagnosed with DLBL commenced conventional R-CHOP. During the first cycle, whole transcriptome expression profiling (GEP) was performed on formalin-fixed paraffin-embedded tissue by Illumina DASL array. Pts with successful GEP were randomised (1:1) to continue R-CHOP +/- bortezomib (1.3 mg/m² IV or 1.6 mg/m² SC) days 1 + 8 for cycles 2-6. The primary endpoint was progression-free survival for the GCB + ABC population; the study was powered for a 10% benefit in PFS from bortezomib.

Results: Between 6/2011 and 5/2015, 1076 eligible pts were registered. Median age was 64 yrs (20-86); Stage I 2.9%; II 27.5%; III 30.8% and IV 38.8%. The distribution of IPI scores: Low, 25.7%; low int 25.9%; high int. 30.6%, high 17.8%. There was no difference in baseline demographics between arms. Cell of origin results were: GCB *n* = 475 (44.1%); ABC *n* = 244 (22.7%); unclassified (U) *n* = 199 (18.5%); no profile *n* = 158 (14.6%). Mutational frequency of MYD88, PRDM1, CD79B was higher in ABC, whilst mutations in CREBBP, EZH2, DDX3X, FAS and KMT2D were more frequent in GCB. ABC pts were older (median age ABC 67 yrs; GCB 63 yrs; U 63 yrs; *P* < 0.005). Bulk was more common in the GCB (GCB 33.8%; ABC 20.7%; U 27.8%; *P* < 0.001). RB-CHOP was not associated with increased haematological toxicity; Grade ≥ 2 neuropathy occurred in 20.7% RB-CHOP vs 12.5% R-CHOP pts.

There was no difference in PFS in the combined GCB + ABC population between RB-CHOP and R-CHOP; HR = 0.84; *P* = 0.225. PFS at 30 months (PFS30) was 74.3% and 70.1% respectively. Bortezomib did not significantly affect PFS in either the GCB pts HR = 0.87; *P* = 0.458 (PFS30 75.8% vs 72.9%) or ABC pts HR = 0.79; *P* = 0.309 (PFS30 71.5% vs 64.7%). However, pts with low IPI had a significantly better PFS when bortezomib was added to R-CHOP, HR = 0.37; *P* = 0.012. This benefit was seen only in the ABC group. There was no difference in overall survival between arms HR = 0.85 (0.59-1.23); *P* = 0.397. Retrospective application of a Burkitt-like (BL) molecular classifier identified a group of GCB pts (17%) with particularly poor



prognosis. BL pts had a higher mutational burden than other GCB with an excess of c-MYC rearrangements or extra copies (44/61 available). There was a trend towards improved PFS in BL pts treated with bortezomib (HR = 0.56; P = 0.069).

Conclusion: The addition of bortezomib to R-CHOP chemotherapy in DLBL may result in PFS benefit in sub-groups of patients defined by molecular phenotyping. Cancer Research UK E/10/O24.

Keywords: activated B-cell-like (ABC); diffuse large B-cell lymphoma (DLBCL); R-CHOP.

122 PROGNOSTIC IMPACT OF BCL2 AND MYC EXPRESSION AND TRANSLOCATION IN UNTREATED DLBCL: RESULTS FROM THE PHASE III GOYA STUDY

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Introduction: DLBCL pts with tumours co-expressing BCL2 and MYC (dual-expressor, DE) or with dual gene translocations (double-hit, DH) have poor outcomes but prognostic relationships between cell-of-origin (COO) subtype (ABC vs GCB) and BCL2/MYC are unclear. We report predefined exploratory analyses of the prognostic effects of BCL2 positivity (+), MYC+, DE and DH, in relation to COO, in the Phase III GOYA study (NCT01287741).

Methods: Pts with previously untreated DLBCL were randomised 1:1 to receive obinutuzumab or rituximab plus 6 or 8 cycles of CHOP. Using a Ventana investigational-use IHC assay (BCL2 antibody clone, 124; c-MYC, Y69), pretreatment tumour samples were analysed at a central laboratory. Samples stained within the limit of BCL2 (≤ 4 months, 30°C) and MYC (≤ 12 months, 30°C) antigen stability were included in primary analyses; sensitivity analyses included all samples. Scoring algorithm incorporated % of tumour cells stained

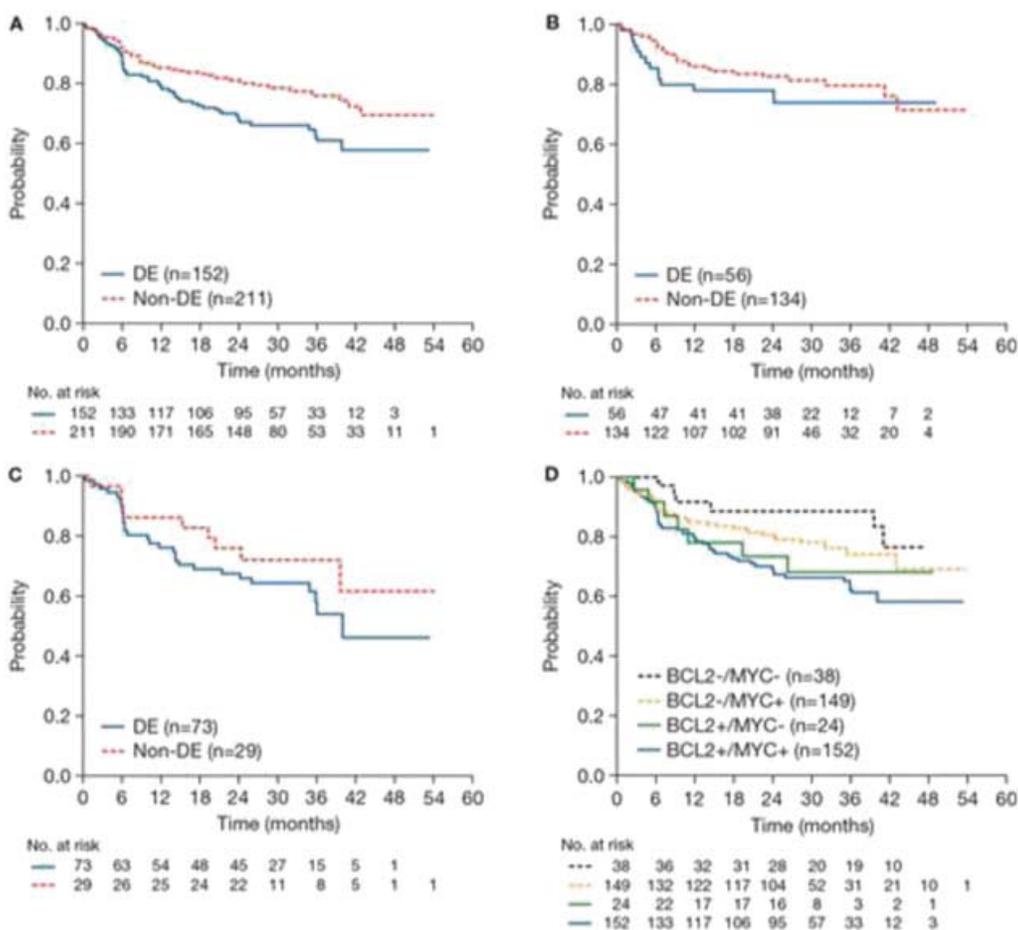
and intensity: BCL2 IHC+, moderate/strong in $\geq 50\%$ of tumour cells; MYC IHC+, $\geq 40\%$ of tumour cells. Vysis LSI Dual Color Break Apart FISH Probes identified BCL2 and MYC translocations: FISH+, $\geq 50\%$. COO classification of RNA extracts used a NanoString Lymphoma Subtyping gene expression assay. Univariate Cox regression analysis of investigator-assessed PFS was performed. Covariates for multivariate analysis were treatment arm (Tx), IPI score, no. of CHOP cycles and COO.

TABLE 1 Prognostic effect of key biomarkers in pts with previously untreated de novo DLBCL*

Biomarker	Status (no. of pts, events)	3-year PFS, % (95% CI)	Univariate analysis HR (95% CI)	Multivariate analysis [†] HR (95% CI)
BCL2 IHC (N=366)	Positive (178; 61)	63 (55–71)	1.77(1.19–2.64)	1.72(1.05–2.82)
	Negative (188; 40)	78 (70–84)		
MYC IHC (N=373)	Positive (309; 90)	68 (62–74)	1.60(0.89–2.86)	1.24(0.65–2.36)
	Negative (64; 13)	81 (69–89)		
BCL2/MYC IHC (N=363)	DE (152; 53)	63 (54–71)	1.69(1.14–2.51)	1.44(0.88–2.35)
	Non-DE (211; 47)	76 (69–82)		
BCL2/MYC FISH (N=560)	DH (20; 8)	55 (29–75)	2.16(1.06–4.42)	2.11(1.03–4.32)
	Non-DH (540; 135)	73 (68–77)		

*Samples from pts in the 2 treatment arms were pooled for these analyses. HR compares positive vs negative for BCL2 IHC and MYC IHC, DE vs non-DE for BCL2/MYC IHC and DH vs non-DH for BCL2/MYC FISH. [†]Multivariate model with treatment arm, IPI score, planned number of CHOP cycles and COO subtype (ABC or GCB) as covariates for each biomarker, except for BCL2/MYC FISH where COO was not included as a covariate (note that no DH patients had ABC subtype). Patients who did not have COO information available or had unclassified COO subtype were excluded from multivariate analyses. Multivariate analysis populations were: BCL2 IHC (N=293: positive, 148; negative, 145; ABC, 102; GCB, 191), MYC IHC (N=298: positive, 245; negative, 53; ABC, 102; GCB, 196), BCL2/MYC IHC (N=292: DE, 129; non-DE, 163; ABC, 102; GCB, 190).

Figure. Kaplan-Meier curves of investigator-assessed PFS according to biomarker status in the following subgroups: comparison of DE vs non-DE pts in the A) total (N=363), B) GCB (N=190) and C) ABC (N=102) populations, and comparison of BCL2 IHC+/- vs MYC IHC+/- pts in the D) total (N=363) population



Results: Baseline characteristics, including IPI score, were similar for biomarker evaluable and ITT populations. Prevalence of BCL2 IHC+, MYC IHC+, DE and DH was 49%, 83%, 42% and 3.6%, respectively. Prevalence by COO: BCL2 IHC+, 75% in ABC and 38% in GCB; MYC IHC+, 95% in ABC and 76% in GCB; DE, 72% in ABC and 29% in GCB; DH, 7% in GCB and 0% in ABC (19/20 DH pts were GCB; 1 unclassified). In univariate analysis, BCL2 IHC+, DE and DH were associated with poorer prognosis (Table). Multivariate analysis confirm the poor prognosis of BCL2 IHC+ pts, independent of Tx, IPI score, no. of CHOP cycles and COO. Context-dependent effects of MYC IHC+ suggest an association with poorer prognosis in BCL2 IHC- pts while BCL2 IHC+ pts drive a suggested prognostic effect in DE pts (Figure). Poor prognosis of DH pts was independent of Tx, IPI score and no. of CHOP cycles, but no. of pts was low.

Conclusions: Robust identification and analysis of biomarker subgroups confirm the prognostic importance of DH and BCL2 IHC+, and demonstrate that the prognostic effect of BCL2 IHC+ is independent of COO in DLBCL pts in the GOYA study.

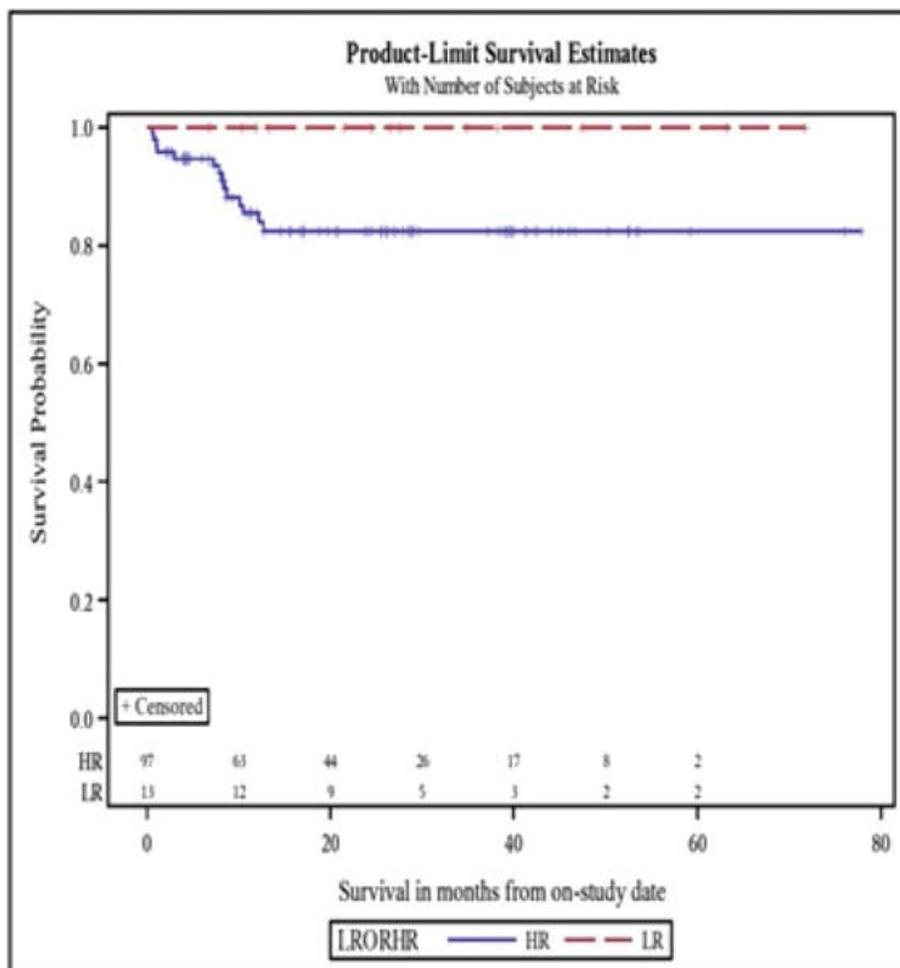
Keywords: "double-hit" lymphomas; BCL2; diffuse large B-cell lymphoma (DLBCL).

123 RISK-ADAPTED THERAPY IN ADULTS WITH BURKITT LYMPHOMA: UPDATED RESULTS OF A MULTICENTER PROSPECTIVE PHASE II STUDY OF DA-EPOCH-R

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Background: Burkitt lymphoma (BL) is an aggressive B-cell lymphoma, which occurs in children and less commonly in adults. Dose-intensive



approaches developed for pediatric leukemia/lymphoma are highly curative, but are poorly tolerated in adults and patients with HIV. A single-center study of 30 patients showed that lower treatment intensity with infusional DA-EPOCH-R was highly curative and well tolerated in adults with sporadic or HIV-associated BL (*N Engl J Med* 2013; 369:1915-1925). To validate these results, we undertook a multicenter study of DA-EPOCH-R in adult BL and investigated if a risk-adapted approach could further reduce treatment toxicity.

Methods: Patients with newly diagnosed BL, age 18 years or older and any HIV status were enrolled at 24 participating sites. Patients were considered low-risk (LR) if they had a normal LDH, ECOG performance status of 0 or 1, stage I or II disease, and no tumor lesion over 7 cm. All other patients were considered high-risk (HR). LR patients received 3 cycles of DA-EPOCH-R without intrathecal treatment. HR patients with negative brain MRI and negative CSF cytology/ flow cytometry received 6 cycles of DA-EPOCH-R with MTX 12 mg IT on days 1 and 5 during cycles 3-6 (8 total doses). HR patients with active CNS disease received 6 cycles of DA-EPOCH-R and concurrent MTX 12 mg IT twice weekly for 2 weeks past negative results (minimum of 4 weeks), followed by MTX 12 mg IT once weekly x 6, and MTX 12 mg IT monthly x 6.

Results: 112 of 116 planned patients have been enrolled; 110 who completed at least 1 cycle of therapy are included in this analysis. Characteristics include median (range) age 48 (19-86) years with 53 (48%) patients aged 50 years or over and 29 (26%) patients aged 60 years or over; male sex 86 (78%); stage III or IV disease 76 (69%); elevated LDH 73 (66%); CNS involvement 11 (10%); HIV positive 29 (26%). The frequency of bone marrow disease is under evaluation. Thirteen (12%) and 97 (88%) patients were classified as LR and HR, respectively. There were 6 deaths in the HR arm not attributed to disease progression/relapse: 2 deaths due to infection, and 1 death each attributed to respiratory failure, second malignancy, myocardial infarction, and unknown. All other reported toxicities were expected toxicities of DA-EPOCH-R. With a median follow-up of 34 months, the progression-free survival (PFS) for all patients beyond 10.2 months is 84.6% (95% CI: 75.6-90.4%); time-to-progression (TTP) is 91.1% (95% CI: 82.8-95.4%) and overall survival is 84.7% (95% CI: 75.4-90.7%). Age (> 40y versus <40y) and HIV status did not impact survival (see table). PFS for LR patients was 100% and 82% for HR patients. Notably, only 1 patient who progressed after DA-EPOCH-R was successfully salvaged and is still alive.

Conclusions: This multicenter study confirms that DA-EPOCH-R is well tolerated and highly effective in adult BL including patients ³ 40 years. Abbreviated treatment with 3 cycles of DA-EPOCH-R is highly effective for LR disease, while the outcome of HR patients compares favorably with more intensive regimens. Further details on outcomes of patients with CNS and BM involvement will be provided at the meeting. Accrual to this study is ongoing with full accrual anticipated this year [NCT01092182]. A randomized study comparing the regimen to standard BL therapy is in progress.

		TTP	PFS	OS
All Patients	N	92%	87%	88%
LR	11	100%	100%	100%
HR	66	91%	85%	86%

(Continues)

(Continued)

		TTP	PFS	OS
p		0.35	0.22	0.24
HIV -	57	96%	88%	90%
HIV +	20	84%	84%	83%
p		0.1	0.66	0.53
Age < 40	35	94%	90%	93%
Age ≥ 40	42	91%	84%	83%
p		0.83	0.45	0.24

SESSION 10: IMMUNOTHERAPIES

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CD27 STIMULATION ENHANCES CD20 MAB THERAPY THROUGH ACTIVATION OF INNATE IMMUNITY

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Introduction: Direct-targeting monoclonal antibodies (mAb) such as anti-CD20 exert their anti-tumor activity through macrophage-mediated antibody-dependent cellular phagocytosis (ADCP). We examined whether the efficacy of anti-CD20 mAb could be augmented by combination with immunomodulatory mAbs against PD-1, CTLA-4, OX40, GITR, and CD27. CD27 is a TNFR superfamily member expressed constitutively on T and NK cells and has been shown to regulate CD8⁺ T-cell priming, cytotoxicity, and memory responses.

Methods: mAb combinations were tested in syngeneic murine B-cell lymphoma models (BCL₁, A31 and Eμ-TCL1) and in a human CD27 transgenic mouse model. We further dissected the mechanism of action of the mAbs using flow cytometry, single-cell RNA sequencing and modified weighted gene co-expression network analysis (WGCNA).

Results: Amongst all the immunomodulatory mAb tested with anti-CD20, only addition of an agonistic mAb against CD27 markedly improved the survival of BCL₁ lymphoma-bearing mice. Single-agent anti-CD20 and anti-CD27 only provided modest survival benefit. When given in combination, 100% of mice survived beyond 100 days. Similar results were observed in A31 and Em-TCL1 B-cell lymphoma models.

We observed profound myeloid cell infiltration in mice treated with anti-CD27, alone and in combination with anti-CD20 mAb. Moreover, tumor-infiltrating macrophages were activated and had increased levels of the activatory Fcγ receptor, FcγRIV. However, CD27 is expressed on NK and T cells, and not myeloid cells. To investigate

the mechanism of myeloid cell infiltration and activation, we performed a chemokine and cytokine microarray and single-cell RNA sequencing. This demonstrated increased levels of NK and T cell-derived CCL3 and CCL4, both known myeloid cell chemo-attractants, as well as increased IFN γ from CD8⁺ T cells. Consistent with involvement of both T and NK cells, depletion of T or NK cells alone did not entirely abrogate combination therapy, but depletion of T and NK cells together, did. To demonstrate that these findings are clinically relevant, the human CD27 mAb, varlilumab was tested in combination with anti-CD20 in the BCL₁ model in a human CD27 transgenic background. Here, as above, the combination was superior to either single agent.

Conclusions: These data demonstrate the therapeutic potential of combining a tumor-targeting mAb with an immune stimulating mAb, through a hitherto, unexpected mechanism of action involving activation of the innate immunity. Here, anti-CD27 indirectly increased the capacity of macrophages to perform anti-CD20-mediated ADCC through T and NK cell activation. Based upon these data, a U.K. multicentre phase II clinical trial examining rituximab and varlilumab in relapsed and/or refractory B-cell lymphoma is being initiated in Spring 2017.

Keywords: B-cell lymphoma; CD20; macrophages.

125 NIVOLUMAB FOR RELAPSED/ REFRACTORY CLASSICAL HODGKIN LYMPHOMA AFTER AUTOLOGOUS TRANSPLANT: FULL RESULTS AFTER EXTENDED FOLLOW-UP OF THE PHASE 2 CHECKMATE 205 TRIAL

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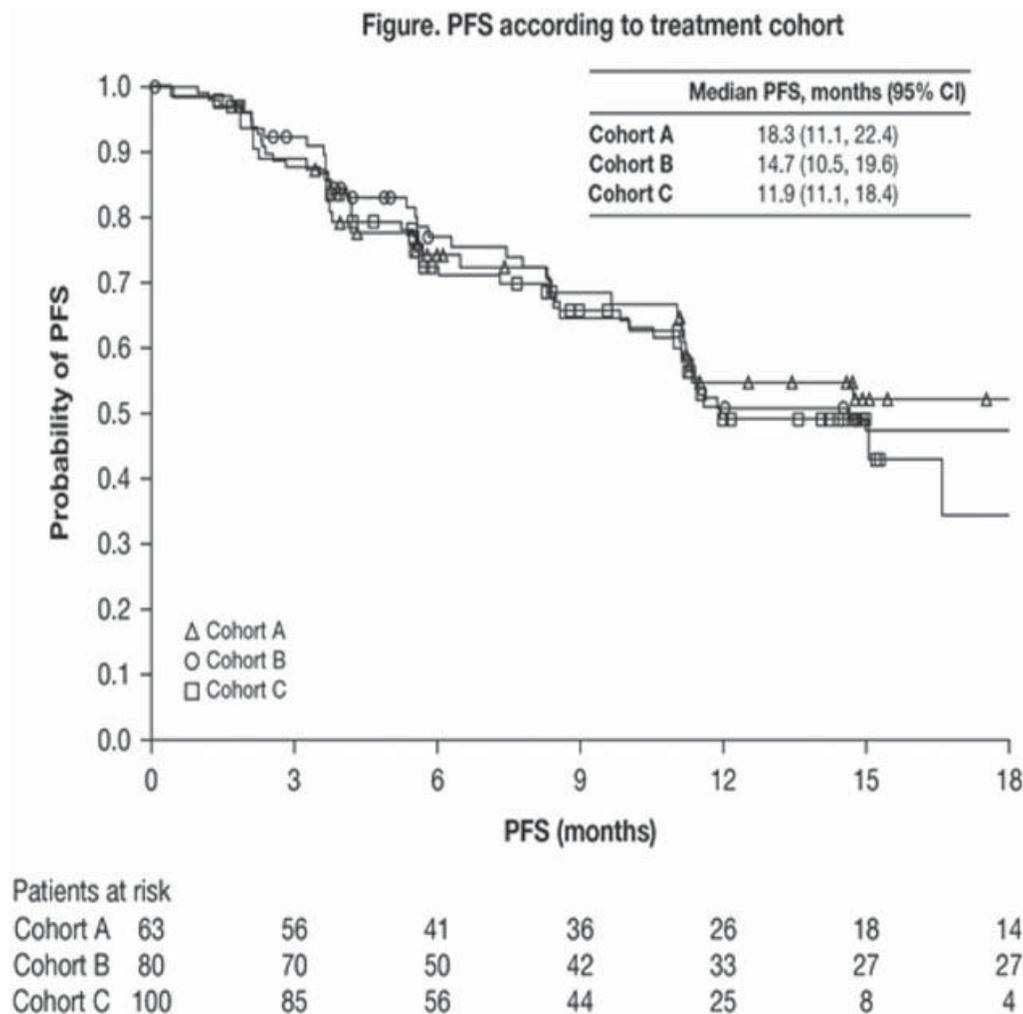
Introduction: Nivolumab (nivo), a programmed death-1 immune checkpoint inhibitor, is indicated for pts with relapsed/refractory classical Hodgkin lymphoma (RR cHL) following autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV). Initial results from the phase 2 CheckMate 205 trial of nivo for RR cHL after ASCT (NCT02181738) demonstrated high objective response rates (ORR), encouraging duration of response (DOR), and an acceptable safety profile (Younes A et al., *Lancet Oncol* 2016). Given limited treatment options post-ASCT, it is key for pts that the therapy offered has high potential for durable remissions. Here we report extended follow-up for all pts with RR cHL after failure of ASCT in CheckMate 205.

Methods: CheckMate 205 enrolled adult pts with RR cHL after ASCT into 1 of 3 cohorts (A: naïve to BV; B: BV only after ASCT; C: BV before and/or after ASCT). All pts received nivo 3 mg/kg q2w until progression or unacceptable toxicity. In Cohort C, pts with complete response (CR) for 1 y were to discontinue nivo and could resume at relapse. Primary endpoint was ORR per IRC. DOR was a secondary endpoint; progression-free survival (PFS), overall survival (OS) and safety were exploratory endpoints.

Results: Of 243 pts treated, 63 were BV-naïve (Cohort A), 80 had BV after ASCT (Cohort B), and 100 had BV before ($n = 33$), after ($n = 58$) or before and after ($n = 9$) ASCT (Cohort C). Median (range) age was 34 (18–72) y; 77% of pts had stage III+ disease at study entry. Fewer BV-naïve pts had ≥ 4 prior lines of therapy (16% vs 69% with prior BV). As of Dec 2016 database lock, median follow-up was 19, 23, and 16 mo for Cohorts A, B, and C, respectively, and 40% of pts remained on treatment. ORR was 65% in BV-naïve pts (Cohort A), 68% in pts with BV after ASCT (Cohort B), and 73% in pts with BV before and/or after ASCT (Cohort C), with CR in 29%, 13%, and 12% of pts, respectively. In BV-naïve pts, median DOR was 20 mo; in BV-treated pts, median DOR was 16 and 15 mo in Cohorts B and C, respectively. For pts with CR, DOR was 20 mo in BV-naïve pts (Cohort A) and ≥ 15 mo in BV-treated pts (Cohorts B and C); for pts with partial response (PR), DOR was 17 and ≥ 11 mo, respectively. PFS by cohort is shown (**Figure**), with extended median PFS observed in all 3 cohorts for pts with CR (≥ 17 mo), PR (≥ 15 mo), and stable disease (≥ 9 mo). Median OS was not reached. The most common drug-related AEs were fatigue (23%), diarrhea (15%), and infusion reactions (IRs; 14%); the most common drug-related serious AEs were IRs (2%) and pneumonitis (1%). To facilitate translation to practice, efficacy results recategorized by sequencing of prior BV will be presented.

Conclusions: Regardless of BV treatment history, high levels of response to nivo were seen across cohorts of pts with RR cHL after ASCT. Notably, with extended follow-up both CRs and PRs remain durable.

Study support: BMS; medical writing support: M Thomas (Caudex).



Keywords: classical Hodgkin lymphoma (cHL); monoclonal antibodies (MoAb).

126 PEMBROLIZUMAB MONOTHERAPY IN PATIENTS WITH PRIMARY REFRACTORY CLASSICAL HODGKIN LYMPHOMA: SUBGROUP ANALYSIS OF THE PHASE 2 KEYNOTE-087 STUDY

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Oncology, Hôpital Saint-Louis, Paris, France; ⁷Division of Molecular & Clinical Cancer Sciences, The University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; ⁸Department of Haematological Cancer, Institut Gustave Roussy, Villejuif, France; ⁹Department of Immunology, Genetics and Pathology, Experimental and Clinical Oncology, Uppsala University, Uppsala, Sweden; ¹⁰Department of Haematology & Bone Marrow Transplantation, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece; ¹¹Department of Hematology & Oncology, Nagoya University Graduate School of Medicine *Current affiliation: Fujita Health University School of Medicine, Toyoake, Japan, Nagoya, Japan; ¹²Department of Internal Medicine, University Hospital Cologne, Cologne, Germany; ¹³Department of Biostatistics, LDS Oncology, Merck & Co., Inc., Kenilworth, USA; ¹⁴Department of Oncology Clinical Development, Merck & Co., Inc., Kenilworth, USA; ¹⁵Department of Hematologic Oncology, Memorial Sloan Kettering Cancer Center, New York, USA

Introduction: Patients (pts) with primary refractory classical Hodgkin lymphoma (cHL) have poorer outcomes compared with those who respond to first-line therapy (Shah et al. *Br J Haematol.* 2016;175:440-447). The PD-1 inhibitor pembrolizumab (pembro) has shown robust antitumor activity (ORR = 69%) and acceptable safety in pts with relapsed or refractory (R/R) cHL in the KEYNOTE-087

study (Chen et al. *J Clin Oncol*. 2017, in press). As the MOA of pembro is fundamentally different from that of chemotherapy, it may also have important activity in the high-risk subset of pts with primary chemorefractory disease. Presented here is efficacy and safety of pembro in the primary refractory subgroup of KEYNOTE-087.

Methods: This phase 2, multicenter, single-arm, multicohort study (NCT02453594) investigated the safety and efficacy of pembro in pts with R/R cHL. Pts received pembro 200 mg IV Q3W. Response was assessed every 12 weeks per 2007 Revised Response Criteria for Malignant Lymphomas. ORR was assessed by blinded independent central review. Here, efficacy and safety were analyzed post hoc in the pt subset with primary refractory cHL (no documented CR with first-line treatment).

Results: Of 210 pts treated, 73 (34.8%) had primary refractory cHL. Median (range) age was 31.0 (18-73) y. Pts received a median (range) of 3.0 (1.0-12.0) prior lines of therapy; 65 (89.0%) had ≥ 3 lines of prior therapy; 63 (86.3%) had received prior brentuximab vedotin. ORR was 79.5% ($n = 58$; 95% CI, 68.4%-88.0%); CR rate was 23.3% ($n = 17$; 95% CI, 14.2%-34.6%), and PR rate was 56.2% ($n = 41$; 95% CI, 44.1%-67.8%). SD rate was 5.5% ($n = 4$; 95% CI, 1.5%-13.4%), and PD rate was 11.0% ($n = 8$; 95% CI, 4.9%-20.5%). Median (range) time to response was 2.8 (2.1-8.8) mo, and median response duration was not reached. At 6 months, the PFS and OS rates were 79.6% and 100%, respectively. At database cutoff of Sept 25, 2016, 30 pts discontinued treatment, mainly because of progressive disease ($n = 10$; 13.7%) and physician decision ($n = 8$; 11.0%). Median (range) duration of follow-up was 10.1 (6.4-14.9) mo.

Treatment-related adverse events (TRAEs) occurred in 46 (63.0%) pts and were consistent with the established safety profile of pembro. 4 pts experienced grade 3 TRAEs, and 2 had grade 4 TRAEs. There were no deaths due to TRAEs. TRAEs led to study discontinuation in 3 pts (myocarditis, cytokine release syndrome, infusion-related reaction, and pneumonitis). Of 59 pts with adequate pretreatment tumor tissue, all were PD-L1⁺; 35 had maximum PD-L1 scores that emphasized staining intensity, histiocytes, and membrane staining. Updated data with additional follow-up will be presented.

Conclusions: Pembro activity in the KEYNOTE-087 pt subgroup with primary refractory disease appeared comparable with that of the overall R/R cHL population. Pembro may be an effective treatment option for pts with primary refractory cHL, who urgently need new treatment options.

Keywords: Hodgkin lymphoma (HL).

127 A PHASE IB STUDY EVALUATING THE SAFETY AND CLINICAL ACTIVITY OF ATEZOLIZUMAB COMBINED WITH OBINUTUZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY NON-HODGKIN LYMPHOMA (NHL)

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Introduction: Outcomes for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL) pts remain poor with modern chemo-immunotherapies. DLBCL and FL may escape immune surveillance partly due to increased PD-L1/PD-1 expression. Atezolizumab (atezo; anti-PD-L1) has shown activity in many cancers, including NHL. Obinutuzumab (obi; anti-CD20) also has activity in NHL. Here we report data from a Ph Ib study to determine if atezo + obi can reinvigorate immunity to enhance antitumor responses in R/R NHL (NCT02220842).

Methods: All pts had measurable disease and ≥ 1 prior chemo-immunotherapy regimen. Primary endpoints were safety and tolerability; secondary endpoints were PK and clinical activity. Pts received obi IV on days 1 (100 mg), 2 (900 mg), 8 and 15 (1000 mg) of Cycle 1. In Cycles 2-8, atezo 1200 mg IV + obi 1000 mg IV were given on day 1 q3w. Maintenance with atezo followed for 6 mo. Response was reported by PET-CT or CT scan using the Lugano 2014 criteria. Biopsies (FL) were collected to assess PD-L1 (SP142 assay), CD8 and MHC1 expression using IHC.

Results: As of Nov 21, 2016, 49 pts (23 DLBCL; 26 FL) were safety evaluable (baseline characteristics in table). Pts were heavily pretreated, with 87% of DLBCL pts refractory to last therapy. 30 pts had ≥ 1 any-grade TEAE. The most common Gr 3-4 TEAEs were pain (8.2%), anemia and neutropenia (6.1% each). AEs led to study drug interruptions in 13 pts. 1 pt had atezo-related AEs leading to treatment discontinuation (Gr 2 diabetes mellitus and pain). Of 17 reported deaths, 15 were due to progression and 2 to unknown causes. At the end of induction assessment (after Cycle 10), 42 pts were efficacy evaluable (treatment characteristics in table). ORR (CR + PR) was 57% for FL and 16% for DLBCL. Most pts with CR/PR had CD8+ T-cell levels above the median. All FL pts with increased tumor-infiltrating CD8+ T cells after atezo + obi had a response; obi alone increased CD8+ T-cell infiltration in 5 of 6 pts. Loss of MHC1 was detected in 2 of 35 evaluable pts (both DLBCL); median MHC1 expression was similar in FL and DLBCL. PD-L1 and MHC1 expression did not correlate with response.

Conclusions: Atezo + obi was well tolerated and exhibited activity in R/R NHL. Biomarker analyses point to a more immune-rich environment in FL and suggest that established mechanisms of immune surveillance for DLBCL alone do not account for differences in activity. Changes in biomarker levels upon treatment demonstrate the dynamic nature of immune functionality biomarkers.

	FL (n=26)	DLBCL (n=23)
Baseline Characteristics		
Age, median (range), years	59.5 (41-83)	69.0 (26-90)
Male, %	61.5	60.9
Prior lines of therapy, median (range)	2.0 (1-7)	2.0 (1-4)
Refractory (relapsed within 6 mo of previous therapy), %	52.2	87.0
Disease burden, median (range), mm ²	3057.4 (620-10145)	2709.2 (598-31400)
Treatment Characteristics		
Duration of therapy, median (range), days	194.5 (23-463)	64.0 (2-491)
Time to onset of response (CT only), median (range), days	83.0 (77-293) (n=15)	201.0 (84-252) (n=5)

Keywords: monoclonal antibodies (MoAb); non-Hodgkin lymphoma (NHL); obinutuzumab.

128 HIGH CR RATES IN RELAPSED/ REFRACTORY (R/R) AGGRESSIVE B-NHL TREATED WITH THE CD19-DIRECTED CAR T CELL PRODUCT JCAR017 (TRANSCEND NHL 001)

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Background: JCAR017 is a second-generation, CD19-directed, 4-1BB CAR T cell product comprising CD8 and CD4 CAR T cells in a 1:1 ratio. A multicenter phase 1 trial of JCAR017 in R/R B-cell NHL (NCT02631044) is underway.

Methods: Patients with R/R DLBCL, PMBCL, FL grade 3B, or MCL and adequate organ function are eligible. There was no minimum ALC

requirement for apheresis; no test expansion was required. Treatment includes lymphodepletion with fludarabine and cyclophosphamide, followed by JCAR017. Multiple dose levels (DLs)/administration schedules of JCAR017 are being evaluated. Study objectives include safety, PK, and antitumor response.

Results: As of November 23, 2016, 28 patients have been treated and are evaluable for safety and efficacy. Nineteen were male, 9 female; 25 DLBCL, 2 MCL, and 1 FL grade 3B. Median age was 63 years (range 37-79), median number of prior therapies was 4 (range 1-8), 23 (82%) were refractory to their last chemotherapy, and 16 (57%) had prior transplant. No severe cytokine release syndrome (sCRS) was observed; 10 patients had grade 1-2 CRS (1 received tocilizumab). Five patients developed neurotoxicity, including 4 grade 3-4; all events resolved in the 4 patients who had adequate follow up. Median onset of CRS and neurotoxicity were 5 and 11 days, respectively. Four deaths after disease progression occurred, none related to JCAR017. In 20 patients treated at DL1 (5×10^7 cells), the RR was 80% with 60% achieving CR. One patient with secondary CNS involvement achieved CR without neurotoxicity. JCAR017 was detected at 3 and 6 months in responding patients, including some who relapsed; higher mean peak levels were detected in patients with durable response at 3 months. Data on patients treated at DL2 (1×10^8 cells), alternative dose schedules, tumor biopsy, and additional biomarkers will be presented.

Conclusions: Treatment with JCAR017 results in high CR rate in patients with heavily pretreated R/R DLBCL. Relapses can occur despite persistence of JCAR017, suggesting tumor immune evasion mechanisms may contribute to relapse. Observed toxicities are manageable and occurred at rates lower than those reported for other CD19-directed CAR T cell products.

Keywords: CD19; diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL).

129 A PHASE I TRIAL OF 19-28Z CAR-T CELLS POST-HIGH DOSE THERAPY AND AUTOLOGOUS TRANSPLANTATION (HDT-ASCT) FOR RELAPSED AND REFRACTORY (R/R) B-CELL NON-HODGKIN LYMPHOMA (B-NHL)

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Introduction: HDT-ASCT is the standard of care for patients with rel/ ref diffuse large B-cell lymphoma (DLBCL). Herein, we report safety and efficacy data on 15 patients of our phase I clinical trial of 19-28z CAR-T post HDT-ASCT for poor-risk r/r aggressive B-NHL (NCT01840566).

Methods: Eligibility for this study includes poor-risk r/r aggressive histology B-NHL chemosensitive to salvage therapy with either: 1) FDG-

TABLE 1 Patient Characteristics.

Patient	Age	Disease	No. lines of prior therapy	Disease at HDT-ASCT	Dose Level	Toxicity	Status Post-HDT-ASCT months (mo, * ongoing CR)
1	34	transformed FL (tFL)	3	PET(+) PR	1	Yes	POD/41 mo
2	68	DLBCL	4	PET(+) PR	1	Yes	CR*/41 mo
3	56	transformed MZL	2	PET(+) PR, BM involved	1	No	POD/12 mo
4	59	tFL/double-hit (DHL)	2	PET(+) PR	2	Yes	CR*/35 mo
5	66	DLBCL	3	PET(+) PR	1	No	CR*/31 mo
6	64	CD5+ DLBCL	2	PET(+) PR	1	No	POD/6 mo
7	65	Burkitt lymphoma	2	PET(+) PR BM involved	1	Yes	POD/2 mo
8	56	DLBCL/DHL	2	PET (+) PR	1	Yes	NRM/1 mo
9	51	DLBCL	2	PET (+) PR	1	No	POD/3 mo
10	61	Blastoid MCL	4	PET CR, BM involved	1	Yes	POD/2 mo
11	75	Richter's	2	PET (+) PR	1	Yes	CR*/21 mo
12	45	tFL	8	PET (+) PR	1	Yes	POD/2 mo
13	61	DLBCL	2	PET (+) PR	1	Yes	POD/3 mo
14	35	DLBCL	3	PET (+) PR	1	No	POD/3 mo
15	68	DLBCL	3	PET (+) PR	1	Yes	POD/14 mo

PET (+) following 2 cycles of salvage therapy or 2) bone marrow involvement of B-NHL at time of r/r disease. T cells were retroviral transduced with anti-CD19 scFV linked to CD28 and CD3 ζ signaling domains. Patients underwent BEAM conditioned HDT-ASCT and 19-28z CAR-T were administered on days +2 and +3.

Results: Fifteen patients with a median age of 61 years (range: 34-75 years) were treated on study, $n = 14$ at dose level (DL) #1 (5×10^6 19-28z CAR-T/kg) and $n = 1$ at DL #2 (1×10^7 CAR-T/kg). See table for full characteristics and status following study treatment. One dose limiting toxicity was observed at both DL #1 and DL #2. Ten of 15 patients experienced toxicity with either grade 2-4 neurotoxicity and/or cytokine-release syndrome (CRS). All study related toxicities were fully reversible with tocilizumab +/- corticosteroids. One death on study was secondary to pulmonary mucormycosis and not attributable to 19-28z CAR-T. Toxicity events were associated with longer persistence of 19-28z CAR-T at a median of 11 days compared to a median 4 days in patients without toxicity ($p = 0.05$). Peak 19-28z CAR-T expansion did not correlate to toxicity. Comprehensive serial serum cytokine analysis revealed upregulation of IFN-gamma ($p < 0.001$) and a trend toward upregulation of IL-10 ($p = 0.07$) were associated with toxicity following 19-28z CAR-T infusion. At a median follow-up for survivors of 31 months, the 2 year progression-free survival (PFS) is 30% (95% CI: 20-70%, Figure 1). There was no observable association between 19-28z CAR-T peak expansion, persistence in days or cytokine changes and PFS. Two of the 10 patients with progression of disease (POD) were CD19 (-) on re-biopsy.

Conclusions: This study established safety of 19-28z CAR-T at 5×10^6 19-28z CAR-T/kg following consolidative HDT-ASCT for poor-risk rel/ref aggressive B-NHL. Persistence of 19-28z CAR-T was associated with toxicity, though not efficacy as measured in PFS. Strategies to enhance durability of response to CAR-T in this setting are in development.

Keywords: autologous stem cell transplantation (ASCT); CD19; diffuse large B-cell lymphoma (DLBCL).

SESSION 11: MANTLE CELL LYMPHOMA

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P53 BUT NOT SOX11 IHC HAS PROGNOSTIC VALUE INDEPENDENT OF MIPI AND KI-67 IN PROSPECTIVE TRIALS OF THE EUROPEAN-MCL NETWORK

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Introduction: Mantle cell lymphoma (MCL) is an aggressive B-cell lymphoma with poor outcome. Currently, prediction of time to treatment failure and overall survival is based on the clinical factors included in the mantle cell lymphoma international prognostic index (MIPI) and proliferation assessed by Ki67 (Hoster, JCO 2016). P53 and SOX11 immunohistochemistry might improve risk stratification.

Methods: All patients were treated in the MCL Younger (*Hermine, Lancet 2016*) and MCL Elderly trials (*Kluin-Nelemans, NEJM 2012*) of the *European MCL Network*. Formalin fixed paraffin embedded (FFPE) diagnostic patients' material was analyzed by SOX11 and P53 immunohistochemistry (IHC) on either tissue microarrays or whole tissue sections. SOX11 was scored as negative (0% positivity), 1 - 10% (low expression) or >10%. P53 was classified as negative (0% positivity), 1 - ≤ 10% (low), >10-50% (intermediate) or >50% (high expression).

Results: For 365 MCL patients FFPE material was available for IHC. No survival difference was observed for patients with and without IHC data available. SOX11 negativity (0%) was detected in 3% ($n = 9$) and low SOX11 expression (1-10%) in 5% ($n = 16$) of patients. In univariate analysis both negative and low SOX11 expression were associated with shorter overall survival. However, in multivariate analyses including MIPI and Ki67 only low SOX11 expression retained significance. SOX11 expression was not significantly associated with time to treatment failure. High, intermediate, low and lack of P53 expression were detected in 16% ($n = 54$), 27% ($n = 95$), 45% ($n = 157$) and 12% ($n = 42$) of samples, respectively. High P53 expression was a strong predictor of inferior OS (Figure 1A) and TTF (Figure 1B) compared to low P53 expression in univariate (OS hazard ratio, HR, 3.0, $p < 0.0001$, TTF HR 2.5, $p < 0.0001$) and multivariate analyses adjusting for MIPI and Ki-67 (OS HR 2.0, $p = 0.010$, TTF HR 1.9, $p = 0.0083$). In contrast, intermediate P53 expression displayed a similar outcome as low P53 expression, whereas lack of P53 expression showed a tendency towards inferior outcome (adjusted OS HR 1.5, $p = 0.18$, adjusted TTF HR 1.4, $p = 0.22$).

Conclusions: In 365 patients treated in prospective trials of the *European MCL Network*, patients with high P53 expression >50% had a shorter time to treatment failure and poor overall survival independent

of both MIPI and Ki-67. Thus we recommend to incorporate P53 IHC in routine diagnostic practice. Future studies should investigate novel therapeutic strategies in these high risk patients.

Keywords: mantle cell lymphoma (MCL); prognostic indices.

131 FIRST-LINE TREATMENT OF INHL OR MCL PATIENTS WITH BR OR R-CHOP/R-CVP: RESULTS OF THE BRIGHT 5-YEAR FOLLOW-UP STUDY

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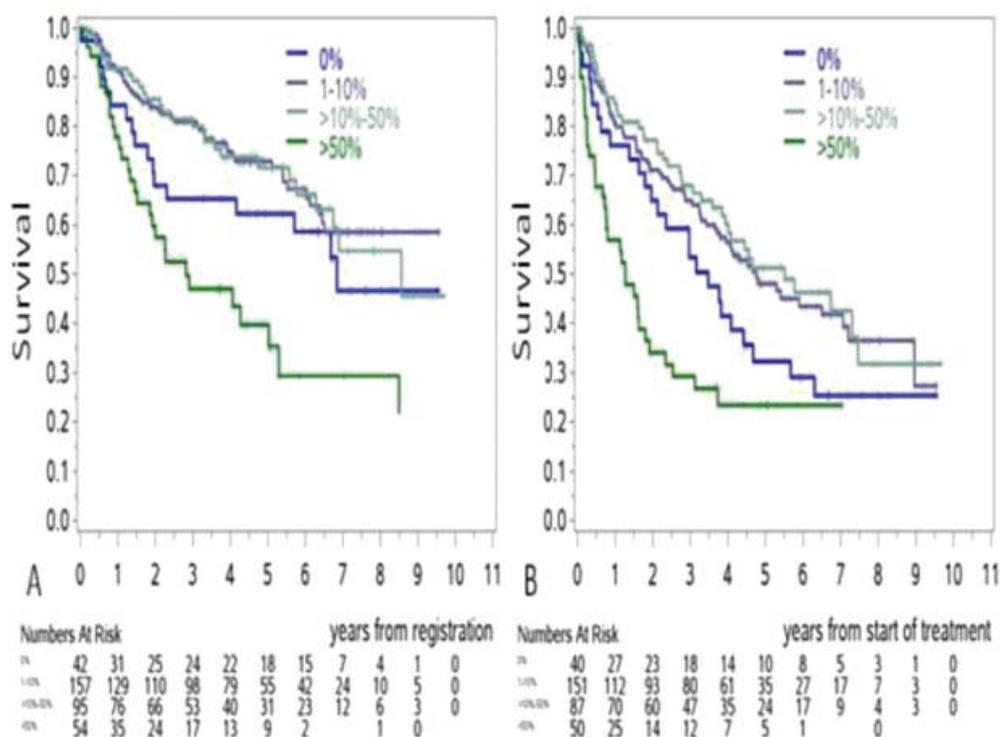
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Figure 1: Prognostic value of p53 IHC score for overall survival (A) and time to treatment failure (B)



Introduction: BRIGHT, a phase 3, open-label, noninferiority study comparing efficacy and safety of bendamustine plus rituximab (BR) vs rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP) in treatment-naive patients with indolent non-Hodgkin lymphoma (iNHL) or mantle cell lymphoma (MCL), showed that the complete response rate for first-line BR was statistically noninferior to R-CHOP/R-CVP (Blood 2014;123:2944-52). Patients were monitored for ≥5 years to assess the overall effect of BR or R-CHOP/R-CVP in a controlled clinical setting. This analysis reports the time-to-event variables of the 5-year follow-up study.

Methods: Patients with iNHL or MCL randomized to 6-8 cycles of BR or R-CHOP/R-CVP underwent complete assessments at end of treatment, then were monitored regularly. Progression-free survival (PFS), event-free survival (EFS), duration of response (DOR), and overall survival (OS) were compared using a stratified log-rank test.

Results: Of 447 randomized patients, 224 received BR, 104 R-CHOP, and 119 R-CVP; 419 entered the follow-up study. The median follow-up time was 65.0 and 64.1 months for BR and R-CHOP/R-CVP, respectively. The 5-year PFS rate was 65.5% (95% confidence interval [CI]: 58.5-71.6) and 55.8% (48.4-62.5), and OS was 81.7% (75.7-86.3) and 85% (79.3-89.3) for BR and R-CHOP/R-CVP, respectively. The hazard ratio (95% CI) for PFS was 0.61 (0.45-0.85; *P* = .0025), EFS 0.63 (0.46-0.84; *P* = .0020), DOR 0.66 (0.47-0.92; *P* = .0134), and OS 1.15 (0.72-1.84; *P* = .5461) comparing BR vs R-CHOP/R-CVP. Similar results were found in iNHL [PFS 0.70 (0.49-1.01; *P* = .0582)] and MCL [PFS 0.40 (0.21-0.75; *P* = .0035)], with the strongest treatment

effect in MCL (Figure). Use of rituximab maintenance was similar, 43% in BR and 45% in R-CHOP/R-CVP. Bendamustine was included as second-line in 27 (36%) of the 75 patients requiring therapy who originally received R-CHOP/R-CVP. Comparable safety profiles with expected adverse events were observed in the follow-up study in BR vs R-CHOP/R-CVP.

Conclusions: The long-term follow-up of the BRIGHT study has confirmed that PFS, EFS, and DOR were significantly better for BR, and OS was not statistically different between BR and R-CHOP/R-CVP. The safety profile was as previously reported.

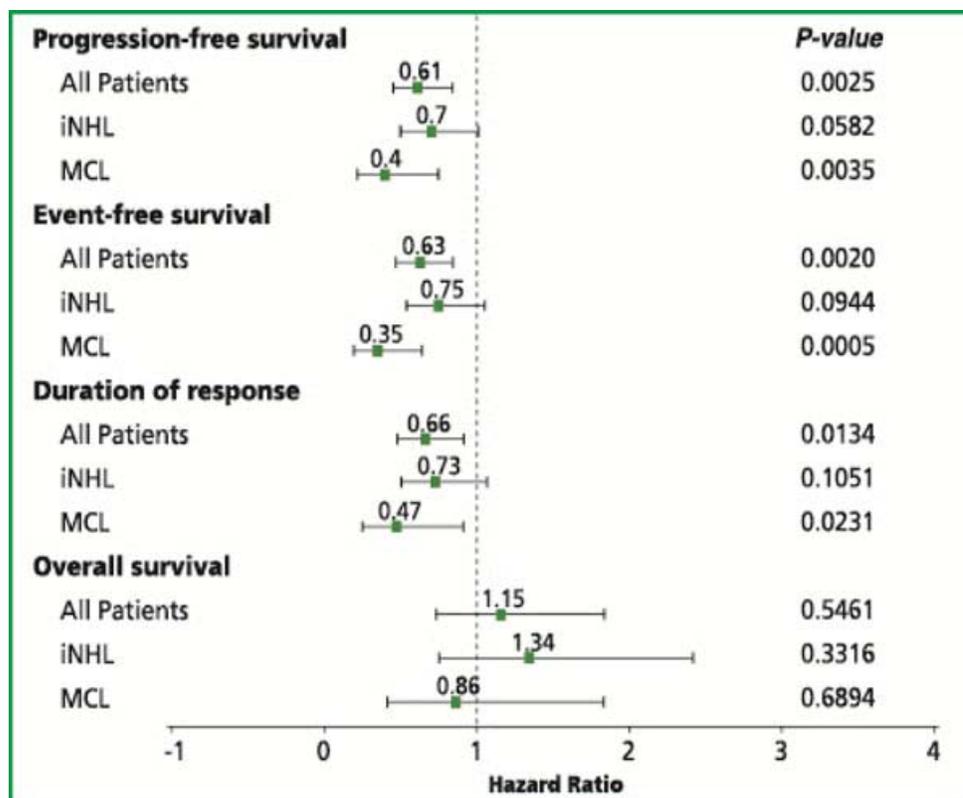
Figure. Hazard ratios of time-to-event variables and their 95% confidence intervals – investigator assessment of randomized patients.

Keywords: bendamustine; mantle cell lymphoma (MCL); non-Hodgkin lymphoma (NHL).

132 FIRST LINE TREATMENT BY THE RIBVD REGIMEN ELICITS HIGH CLINICAL AND MOLECULAR RESPONSE RATES AND PROLONGED SURVIVAL IN ELDERLY MCL PATIENTS; FINAL RESULTS OF A LYSA GROUP TRIAL

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Figure. Hazard ratios of time-to-event variables and their 95% confidence intervals – investigator assessment of randomized patients.



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Introduction: Eight R-CHOP21 cycles followed by rituximab maintenance is considered as the standard first-line treatment for elderly mantle cell lymphoma (MCL) patients. Complete response (CR) and undetectable minimal residual disease (uMRD) rates remain sub-optimal with tR-CHOP regimen (CR rate 30-35%, MR after 8 cycles 67%) and this translates to shorter response duration. Recently VR-CAP, integrating bortezomib to RCHOP has proved superiority to both R-CHOP and the R-BAC regimen (rituximab bendamustine cytarabine) has given also promising results. In this setting, we have explored the association rituximab-bendamustine-bortezomib and dexamethasone in the RiBVD regimen.

Methods: In this prospective phase II study, all patients >65 years old with newly-diagnosed MCL were treated by the RiBVD regimen (inclusion criteria: AA stage II-IV, PS < 3, no active HIV, HBV or HCV infections, no renal or cardiac dysfunction, no diabetes). RiBVD was administered every 4 weeks: rituximab, 375 mg/m² IV on day(D)1; bendamustine at 90 mg/m² IV on D1 and D2; dexamethasone 40 mg IV on D2 and bortezomib 1.3 mg/m² subcutaneously on D1, 4, 8 and 11. Patients received a total of 6 cycles, if they responded (IWG criteria) after 4 cycles. No maintenance was delivered. MRD was centrally evaluated by RQ-PCR using patient specific IGH VDJ targets, and

the FDG-PET response was evaluated visually according to Deauville criteria. The primary objective was to prolong PFS by 6 months (m) compared to the 18 m PFS reported for R-CHOP21. In order to define superiority of the RiBVD, PFS > 65% (H1) was required at 18 m. Treatment failure was considered if PFS at 18 m was 50%. With alpha and beta risks of 5% and 20%, respectively, 69 patients needed to be enrolled. Secondary objectives were to evaluate toxicity, known prognostic indices, response FDG-PET imaging and MRD.

Results: Seventy four patients were enrolled; 80% (n = 58) had high MIPI score. ORR and CR were 84% (n = 62/74) and 75% (n = 56/74), respectively. After 6 cycles, 78% (n = 46/59) were FDG-PET negative; 87% (47/54) and 76% (35/46) had uMRD in blood (PB) and bone marrow (BM), respectively. With a median follow-up of 52 m the primary objective was reached (24 m PFS = 70%). Four years OS was 86.6% for uMRD patients at the end of treatment, compared to 28.6%, detectable MRD patients; p < 0.0001). Neither the MIPI score nor FDG-PET responses were predictive of OS. Toxicities were mainly hematologic with grade 3/4 neutropenia in 51% and thrombopenia in 36%. The principal grade 3/4 extra-hematologic toxicities were fatigue (19%), neuropathy (14%), cardiac (7%) or febrile neutropenia (5%).

Conclusion: The RiBVD regimen is active and well tolerated in MCL patients who are unable or unwilling to receive dose intensive therapy including high risk patients.

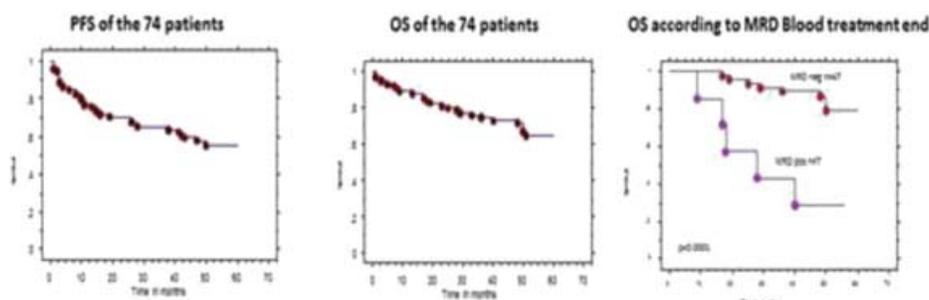
Keywords: bortezomib; mantle cell lymphoma (MCL); minimal residual disease (MRD).

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IBRUTINIB-RITUXIMAB FOLLOWED BY REDUCED CHEMO-IMMUNOTHERAPY CONSOLIDATION IN YOUNG, NEWLY DIAGNOSED MANTLE CELL LYMPHOMA PATIENTS: A WINDOW OF OPPORTUNITY TO REDUCE CHEMO

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Introduction: The ibrutinib-rituximab combination produced durable responses in 88% of relapsed/refractory mantle cell lymphoma (MCL) patients, providing a “Window” of opportunity to use chemotherapy-free induction with ibrutinib-rituximab followed by fewer cycles of chemo-immunotherapy in young, fit patients with newly diagnosed MCL.

Methods: Enrollment began in June 2015 for a Phase II single-center clinical trial consisting of a chemotherapy-free phase of ibrutinib-rituximab treatment (Part 1) until best response, followed by a shortened intense chemo-immunotherapy course (Part 2) among newly diagnosed MCL patients of ≤ 65 years. We previously presented the initial results of this trial with ibrutinib-rituximab and consolidation (Wang et al., ASH 2016). Here, we report updated data with a longer follow-up duration. The primary objective was to evaluate the response rate. Ibrutinib is dosed at 560 mg orally, daily, continuously. Rituximab is dosed at 375 mg/m² IV weekly x 4 during cycle 1 (28 days cycle), then day 1 of cycles 3-12. Intense chemo-immunotherapy consists of rituximab plus cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD); alternating every 28 days with rituximab plus high-dose methotrexate-Ara C. If in complete remission (CR) after ibrutinib-rituximab treatment, only 4 cycles of intense chemo-immunotherapy are given. If the patient is in partial response or progression, and if responding to intensive chemo-immunotherapy, a total of 2 cycles of chemo-immunotherapy therapy are administered beyond achievement of CR.

Results: As of March 3, 2017, 50 patients were evaluable for response. Of the evaluable patients, overall response rate (ORR) to chemotherapy-free therapy alone was 100% (50), with CR in 80% (40) and PR in 20% (10). Thirty-three (33) patients have completed both Parts 1 and 2 and all have achieved CR (i.e., ORR =100%). In Part 1, the most common grade 1-2 non-hematological (non-heme) adverse effects (AEs) were fatigue (50), diarrhea (28), rash (29), myalgia (41), oral mucositis (52), peripheral neuropathy (19), nausea (25), blurred vision (19), edema (23), constipation (18), dry eyes (18), and dizziness (22). Grade 3 non-heme AEs included fatigue (4), nausea (2), infection (3) and dyspnea (2). No grade 4-5 non-heme toxicities were observed in Part 1. Grade 3-4 heme AEs included lymphocytosis (22), thrombocytopenia (13) and leukopenia (15).

TABLE 1 Response rates from the Window Study: a phase II clinical trial.

Response	Chemo-free induction (Part 1), N=50	Chemo-immune consolidation (Part 2), N=33
CR	40 (80%)	33 (100%)
PR	10 (20%)	0 (0%)
ORR	50 (100%)	33 (100%)

Conclusions: These updated data indicate that ibrutinib-rituximab induction in newly diagnosed, young MCL patients was efficacious and well-tolerated, providing a window of opportunity for less chemo-immunotherapy needed for consolidation.

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

134 IBRUTINIB VS TEMSIROLIMUS: THREE-YEAR FOLLOW-UP OF PATIENTS WITH PREVIOUSLY TREATED MANTLE CELL LYMPHOMA FROM THE PHASE 3, INTERNATIONAL, RANDOMIZED, OPEN-LABEL RAY STUDY

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Introduction: Ibrutinib (IBR), a first-in-class, once-daily, oral, covalent inhibitor of Bruton's tyrosine kinase, is highly active in relapsed/refractory (R/R) MCL. The phase 3, randomized, open-label RAY study compared IBR with temsirolimus (TEM) in patients (pts) with R/R MCL and ≥ 1 prior rituximab-containing therapy. At median 20.0 month follow-up, IBR was superior to TEM for independent review committee-assessed progression-free survival (PFS) (HR: 0.43; 95% CI: 0.32-0.58; $p < 0.0001$) (Dreyling et al. Lancet 2016). Here, we present 3-year follow-up results (end of study).

Methods: 280 pts were randomized 1:1 to oral IBR (560 mg once-daily; $n = 139$) or IV TEM (175 mg: days 1, 8, 15 of C1; 75 mg: days 1, 8, 15 of subsequent cycles; $n = 141$) until disease progression/unacceptable toxicity. Long-term efficacy was investigator-assessed.

Results: At a median follow-up of 39 months (mos) for IBR and TEM, respectively, median PFS was 15.6 mos vs 6.2 mos (HR [95% CI], 0.45 [0.35-0.60]; $p < 0.0001$) (Figure 1A); median PFS for pts with only

1 prior line of therapy (LOT) was 25.4 mos (IBR) vs 6.2 mos (TEM) (HR: 0.40; 95% CI: 0.25-0.64) (Figure 1B). Overall response rate (ORR) was 77.0% (IBR) vs 46.8% (TEM); CR rate was 23.0% vs 2.8% ($p < 0.0001$). ORR for pts with 1 prior LOT was 75.4% (IBR) vs 52.0% (TEM); CR rate was 33.3% vs 4.0%. Median duration of response was 23.1 mos (IBR) vs 6.3 mos (TEM). Median time to next treatment was 31.8 mos (IBR) vs 11.6 mos (TEM) (HR [95% CI], 0.33 [0.24-0.46]; $p < 0.0001$). PFS2 was 26.2 mos (IBR) vs 15.4 mos (TEM) (HR [95% CI], 0.67 [0.50-0.90]; $p < 0.0079$). With 39% of pts randomized to TEM crossing over to IBR, median overall survival (OS) was 30.3 mos (IBR) vs 23.5 mos (TEM) (HR: 0.74; 95% CI: 0.54-1.02; $p = 0.0621$) (Figure 1C); median OS for pts with 1 prior LOT was 42.0 mos (IBR) vs 27.0 mos (TEM) (HR: 0.75; 95% CI: 0.43-1.30) (Figure 1D). Median treatment duration was 14.4 mos (IBR) vs 3.0 mos (TEM), with 24% of IBR pts and 0 TEM pts on treatment at study end. Despite differences in exposure, overall frequency of adverse events (AEs) was lower with IBR vs TEM. AEs leading to treatment discontinuation: 17.3% (IBR) vs 31.7% (TEM). Most common treatment-emergent AEs: diarrhea, fatigue, cough (IBR) and thrombocytopenia, anemia, diarrhea (TEM). Grade-3 AEs: 74.8% (IBR) and 87.1% (TEM). Serious AEs: 56.8% (IBR) and 59.7% (TEM).

Conclusions: RAY study 3-year follow-up results are consistent with primary analysis, showing clinically meaningful, statistically significant improvement of PFS for IBR vs TEM, with a strong trend in OS favoring

IBR, despite nearly 40% crossover. Pts who had received IBR after only 1 prior LOT had the most durable and best PFS and OS outcomes, supporting earlier use of IBR in R/R MCL. Significantly longer PFS2 for IBR suggests treatment benefit is maintained after next LOT. No new safety signals were observed. Despite longer exposure, IBR pts experienced fewer grade 3/4 AEs and treatment discontinuations due to AEs.

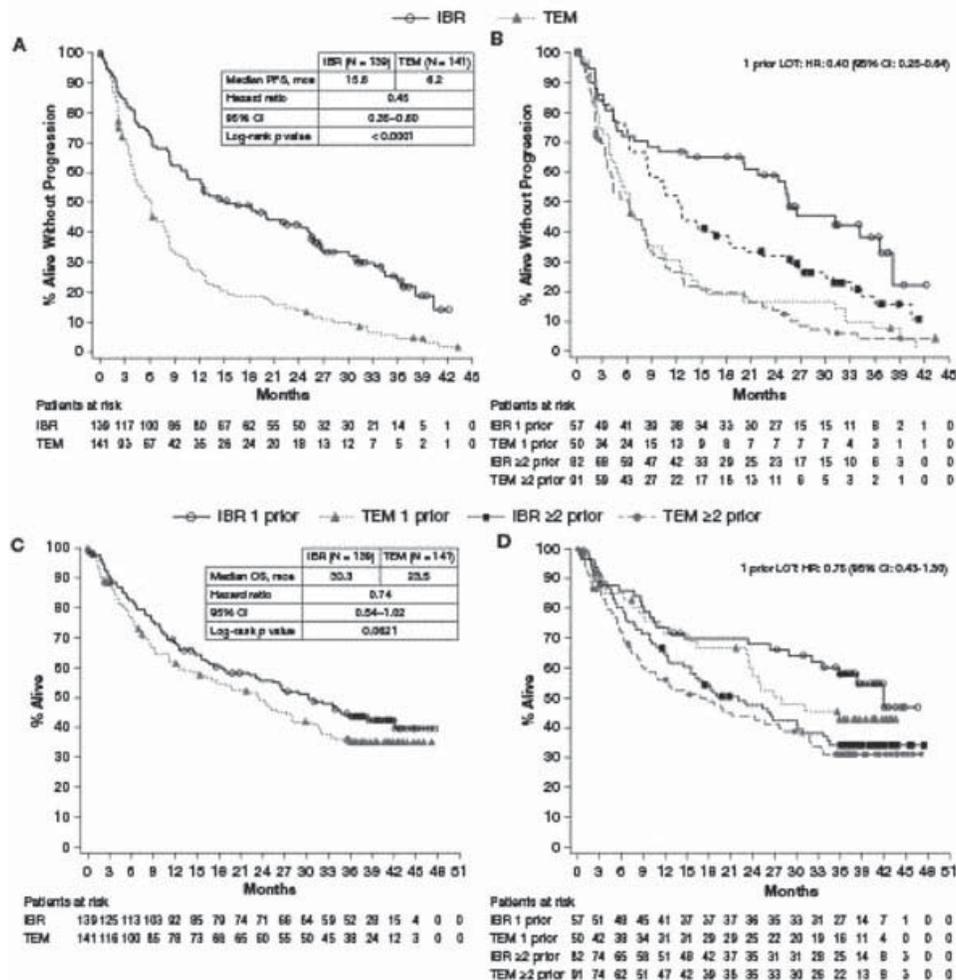
Keywords: ibrutinib; mantle cell lymphoma (MCL); temsirolimus.

135 COMBINATION IBRUTINIB (IBR) AND VENETOCLAX (VEN) FOR THE TREATMENT OF MANTLE CELL LYMPHOMA (MCL): PRIMARY ENDPOINT ASSESSMENT OF THE PHASE 2 AIM STUDY

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Figure 1. PFS (A) and PFS by line of therapy (B) and OS (C) and OS by line of therapy (D).



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Background: Both ibr and ven have activity in relapsed/refractory (R/R) MCL, but complete remissions (CR) are attained in <25% with either. We sought to determine the activity of the combination in an investigator-initiated, phase 2 study.

Methods: Enrolment of 24 patients (pts) with R/R ($n = 23$) or frontline ($n = 1$) MCL completed in 09/16. Pts received 4 weeks of ibr (560 mg/d), followed by introduction of ven (weekly ramp-up to target 400 mg/d). The primary endpoint was CR rate at week 16, as assessed by PET/CT, BMAT, flow & molecular MRD, and endoscopy (if baseline gut involvement). Response was calculated separately with and without knowledge of the PET result by IWG criteria (Cheson JCO 2007), in order to compare with published studies (ibr, 9% CR at wk16; ven, best CR rate 21%).

Results: Median age of pts was 68 (range, 47-81) years. For the R/R pts ($n = 23$), median lines of prior therapy was 2 (1-6), 48% were refractory to last treatment, and 30% had failed previous autologous SCT. As of data cutoff on Jan 11 2017, 18 pts remain on therapy, and 6 stopped treatment due to progressive disease (4), adverse event (1) or unrelated death (1). At week 16, ORR was 71% (63% CR) and 80% of complete responders were flow-cytometry negative in the marrow (sensitivity 10^{-3} to 10^{-4}). Using CT without PET, the comparison responses were CR 42%, CRu 17%, PR 17% (ORR 78%). After a median follow-up of 8.3 (range 1.4-17.7) months, the 8-month estimates of PFS and OS months are 74% and 81%. Adverse events $\geq 20\%$, irrespective of attribution, were fatigue (71%), diarrhea (67%), nausea (50%), URTI (38%), gastro-esophageal reflux (33%), neutropenia (33%), cough (25%) and bruising (21%); with the exception of neutropenia (25% grade 3-4), these were predominantly grade 1-2 in severity. Tumour lysis syndrome occurred in 2 pts with high tumour burden, leading to revision of the protocol ven starting dose from 50 mg, to 20 mg/d.

Conclusion: The combination of ibr and ven was tolerable and achieved CR rate of 63% at week 16 in pts with MCL. The efficacy results compare favorably with historical results, and warrant further phase III investigation.

Keywords: ABT-199; BTK.

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SESSION 12: MARGINAL ZONE LYMPHOMA

136 INTERFERON-FREE ANTIVIRAL TREATMENT IN B-CELL LYMPHOPROLIFERATIVE DISORDERS ASSOCIATED WITH CHRONIC HEPATITIS-C VIRUS INFECTION

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Introduction: Regression of hepatitis C virus (HCV)-associated lymphoproliferative disorders with interferon(IFN)-based antiviral treatment was the strongest evidence for an etiological link between lymphoma and HCV infection (NEJM 2002). To confirm this hypothesis we have recently reported data on IFN-free regimens combining direct-acting antivirals (DAAs) therapy in indolent HCV-positive B-cell non-Hodgkin lymphoma (NHL) (Blood 2016).

Methods: We analyzed virological and lymphoproliferative disease response (LDR) of 97 patients with indolent B-cell non-Hodgkin lymphomas (NHL) or chronic lymphocytic leukemia (CLL) and chronic HCV infection treated with DAAs and their outcome.

Results: Histological distribution was as follows: 69 marginal zone lymphomas (MZL), 6 lymphoplasmacytic lymphomas, 8 follicular lymphomas, 10 CLL/small lymphocytic lymphoma (SLL), 4 low-grade NHL non otherwise specified. All but thirteen patients received a Sofosbuvir-based regimen. Median duration of DAA therapy was 12 weeks (range 4–24 weeks). A sustained virological response at week 12 after finishing DAAs (regarded as cure of HCV) was obtained in 99% of patients; overall LDR rate was 73% including 29 patients (30%) achieving a complete response and 41 (43%), a partial response. After a median follow up of 15 months, 2-year progression-free and overall survival were 70% [95% confidence interval: 49%–83%] and 97% [88–99%], respectively.

Conclusions: DAA therapy induces a high LDR rate in HCV-associated lymphoproliferative disorders and confirms the role of HCV in lymphomagenesis. This chemotherapy-free approach should be considered first-line therapy in patients without need of urgent treatment. Prospective trials are eagerly awaited in this setting.

Keywords: hepatitis C; indolent lymphoma.

137 IMMUNOCHEMOTHERAPY WITH OBINUTUZUMAB OR RITUXIMAB IN A SUBSET OF PATIENTS IN THE RANDOMISED GALLIUM TRIAL WITH PREVIOUSLY UNTREATED MARGINAL ZONE LYMPHOMA (MZL)

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Introduction: Treatment options for advanced MZL include the anti-CD20 antibody rituximab (R) with chemotherapy (chemo). In the randomised Phase III GALLIUM trial (NCT01332968), a preplanned efficacy interim analysis in 1202 previously untreated FL pts demonstrated that obinutuzumab (GA101; G) plus chemo prolonged PFS relative to R-chemo (primary endpoint; Marcus 2016). MZL pts were also enrolled to assess whether treatment effects are consistent with FL

pts; the analysis (cut-off date, 31 January 2016) was not powered to detect PFS differences.

Methods: Pts were aged ≥ 18 yrs with previously untreated MZL (prior antibiotic/antiviral, surgery or radiation allowed), advanced disease (stage III/IV or stage II with tumour diameter ≥ 7 cm), ECOG PS 0–2, and requiring treatment according to the investigator (INV). Chemo regimens (CHOP, CVP or bendamustine [B]) were allocated by pt. Pts were randomised 1:1 (stratified by chemo, IPI group and geographical region) to R 375 mg/m² on day (D) 1 of each cycle (C) or G 1000 mg on D1, 8 and 15 of C1 and D1 of subsequent cycles, for 6 or 8 cycles depending on chemo. Pts with CR or PR at end of induction (EOI; modified Cheson 2007) continued to receive R or G every 2 months for 2 yrs or until progression.

Results: 195 MZL (nodal, 66; extranodal, 61; splenic, 68) pts were randomised: G-chemo (n = 99; median age 63 yrs, 55% male), R-chemo (n = 96, 62 yrs, 46% male). Most pts (83%) were Ann Arbor stage IV at diagnosis; 49% were IPI high risk. At baseline, extranodal involvement, bone marrow involvement, bulky disease and B-symptoms were more common in G-chemo pts. In each arm, 88 pts received all induction cycles; chemo received was B (71% pts), CHOP (16%) and CVP (12%); 56 (G-chemo) and 57 (R-chemo) pts received 2 yrs' maintenance. After 38.4 months' median observation time, there was no clinically relevant difference in INV-assessed PFS between the study arms (HR, 0.82; 95% CL 0.45–1.46; p = 0.49); 3-year PFS rates were 75% in G-chemo pts and 78% in R-chemo pts. HRs for other time-to-event endpoints (including OS) were consistent with the INV-assessed PFS outcome (Table). CR and ORR at EOI were similar for the two arms (Table). More pts in the G-chemo than the R-chemo group had grade 3–5 AEs, SAEs and fatal AEs (Table).

TABLE 1 Summary of efficacy and safety

Efficacy (all randomised MZL pts)		
Parameter	G-chemo (n=99)	R-chemo (n=96)
Median observation time (range), months*	37.0 (0.6–54.4)	40.8 (0.2–52.8)
Number of PFS (INV) events (%)	21 (21.2)	26 (27.1)
HR for PFS (INV), G vs R (95% CL), p-value [†]	0.82 (0.45, 1.46), p=0.49	
HR for other time-to-event endpoints, G vs R (95% CL), p-value[†]		
PFS (IRC) [‡]	0.83 (0.46, 1.51), p=0.55	
Overall survival	0.90 (0.45, 1.81), p=0.78	
Time to new anti-lymphoma treatment	0.85 (0.48, 1.50), p=0.57	
Response at EOI by CT (INV)		
CR, n (%)	16 (16.2)	18 (18.8)
ORR, n (%)	82 (82.8)	78 (81.3)
Safety (all randomised MZL pts who received at least one dose of study drug)[§]		
Number (%) of pts reporting at least one event	G-chemo(n=101)	R-chemo(n=93)
AEs	101 (100)	93 (100)
Grade ≥ 3 AEs	83 (82.2)	72 (77.4)
Neutropenia	46 (45.5)	34 (36.6)
Febrile neutropenia	4 (4.0)	9 (9.7)

(Continues)

TABLE 1 (Continued)

Efficacy (all randomised MZL pts)		
Parameter	G-chemo (n=99)	R-chemo (n=96)
Thrombocytopenia	10 (9.9)	3 (3.2)
Leukopenia	5 (5.0)	8 (8.6)
Infusion-related reactions	8 (7.9)	11 (11.8)
Pneumonia	10 (9.9)	3 (3.2)
Sepsis	5 (5.0)	5 (5.4)
Pyrexia	8 (7.9%)	2 (2.2%)
Dyspnoea	7 (6.9%)	4 (4.3%)
SAEs	65 (64.4)	48 (51.6)
Grade 5 (fatal) AEs	12 (11.9)	6 (6.5)
Infections and Infestations SOC	6 (5.9)	2 (2.2)
AE of special interest (all grades) by category		
Infections**	84 (83.2)	62 (66.7)
Second neoplasms ^{††}	7 (6.9)	8 (8.6)
AEs causing treatment discontinuation	27 (26.7)	19 (20.4)

*From earlier of randomisation date or treatment start date to last date pt known to be alive.

[†]Log rank test, stratified for chemotherapy regimen and IPI risk group.

[‡]Assessed by an independent radiology and oncology review committee (IRC).

[§]Three pts randomised to R-chemo received G (n=2) or no antibody (n=1).

[¶]Grade ≥ 3 AEs with $>5\%$ incidence in either treatment arm.

**All events in MedDRA System Organ Class 'Infections and Infestations'.

^{††}Standardised MedDRA query for malignant or unspecified tumours >6 months after treatment.

Conclusions: The current analysis of this large RCT in previously untreated MZL pts did not show a clinically relevant difference in PFS between arms. G-chemo was associated with a higher frequency of grade 3–5 AEs, SAEs and fatal AEs. Safety by chemo will be presented.

Keywords: marginal zone lymphoma (MZL); obinutuzumab; rituximab.

138 LONG-TERM RESULTS OF THE MULTICENTER PHASE II TRIAL WITH BENDAMUSTINE AND RITUXIMAB AS FIRST LINE TREATMENT FOR PATIENTS WITH MALT LYMPHOMA (MALT-2008-01).

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Background: Optimal treatment of patients with MALT lymphoma with systemic therapy is not established. To date, combinations of Rituximab with Chlorambucil (RChI) or Bendamustine (RB) have demonstrated promising results. We report the long term results of the MALT 2008-01 phase II trial that used the combination of Rituximab and Bendamustine in a response-adapted protocol.

Patients and methods: A prospective multicenter phase II trial (EUDRACT 2008-007725-39) has been carried out in Spain by the GELTAMO group in untreated patients with CD20+ MALT lymphoma requiring systemic therapy. Treatment: Bendamustine (90 mg/m² d1-2) and Rituximab (375 mg/m² d1), every 28 d. Pts received 4 or 6 cycles (if CR or PR after the 3rd cycle, respectively). The aims were: feasibility and security of the combination and outcome. Clinical characteristics: median age 62 years (range, 26-84); 34 (57%) female; Ann Arbor stage: III-IV in 34%; site of disease: stomach 33%, extra-gastric 58% and multifocal 8%.

Results: Sixty pts were enrolled but 3 were subsequently identified ineligible and were not included in the analysis of response and survival. A total of 264 cycles of RB were delivered in the whole population. Number of cycles administered per pt: <4 in 2 (3%), 4 in 44 (73%) and 6 in 14 (23%). Grade 3-4 adverse events in 56 (21%) cycles. At early response assessment after 3 cycles, 43 (75%) achieved CR or uCR and 14 (25%) PR%. At the end of treatment, overall response rate was 100% (CR/uCR: 98%). Presence of t(11;18)(q21;q21) was identified in nine (16%) pts and did not influence response. After a median follow-up of 82 months, 8 events were recorded and EFS at 7 years was 88%. No differences according to the primary site of disease, stage, or number of cycles administered were found. PFS at 7 years was 93% (94% for gastric and 92% for non-gastric). One gastric pt relapsed in the stomach with DLBCL transformation and 4 from non-gastric sites had also relapse (2 with DLBCL transformation and 3 at different site from origin). Three pts have died (2 due to unrelated causes and 1 with transformation to DLBCL and multiple relapses). OS at 7 years was 96%. No myelodysplastic syndrome or acute leukemia occurred, but other neoplasias were observed in 3 pts (1 tongue epidermoid carcinoma, 1 GIST and 1 granular lymphoproliferative disorder of NK-cells). Prophylaxis with cotrimoxazole was done in 39% of cases. During follow-up, 3 pts had opportunistic infections (1 herpes zoster, 1 CMV and 1 lung infection by Nocardia).

Conclusions: The RB combination with a response-adapted schedule in the first line treatment of MALT lymphoma is safe and achieved rapid and sustained long-term responses with 88% EFS and 94% of PFS at 7 years. These long term results with a very brief (4 cycles in

75% of patients) and tolerable treatment are the best obtained to date with rituximab plus chemotherapy.

Keywords: bendamustine; Mucosa-Associated Lymphoid Tissue (MALT); rituximab.

139 PHASE IIIB STUDY OF LENALIDOMIDE PLUS RITUXIMAB FOLLOWED BY MAINTENANCE IN RELAPSED OR REFRACTORY NHL: ANALYSIS OF MARGINAL ZONE LYMPHOMA

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Introduction: Lenalidomide combined with rituximab (R²) has shown synergistic effects in preclinical settings. R² is also clinically active and tolerable non-chemotherapy regimen in untreated and relapsed or refractory (R/R) patients with indolent non-Hodgkin lymphoma (NHL), including marginal zone lymphoma (MZL). The clinical potential of R² supports further study in MZL and its subtypes.

Methods: MAGNIFY (NCT01996865) is a phase IIIB, multicenter, open-label study of R/R NHL patients with grades 1-3b follicular lymphoma (FL; including transformed FL), MZL, and mantle cell lymphoma (MCL). Patients receive 12 cycles of R²(oral lenalidomide 20 mg/d,

d1-21 of a 28-d cycle; intravenous rituximab 375 mg/m², d1, 8, 15, 22 of cycle 1 and d1 of subsequent odd cycles). Following R² induction, those with stable disease or better are randomized 1:1 to maintenance R² (oral lenalidomide 10 mg/d, d1-21 of a 28-d cycle; rituximab 375 mg/m², d1 of every other cycle) or rituximab alone (375 mg/m², d1 of every other cycle). The primary endpoint is progression-free survival (PFS); secondary endpoints include safety, overall survival, and response rates. This analysis focuses on MZL and includes the 3 subtypes: MALT, splenic MZL, and nodal MZL.

Results: As of April 14, 2016, the R/R NHL population (N = 155) was composed of 27 (17%) patients with MZL, including 13 nodal MZL, 8 splenic MZL, and 6 MALT (4 without gastric involvement). The median age of MZL patients was 65 y (range, 46-85), most (81%) with stage III/IV disease at study entry and all with ECOG PS 0-1. Patients with MZL had a median of 1 prior treatment regimen (range, 1-4), with 8 (30%) patients having ≥2. The most common prior therapies were rituximab alone (44%), bendamustine/rituximab (BR; 26%), or R-CHOP-like regimens (26%); 37% were refractory to rituximab, defined as best response of SD/PD to rituximab/R-containing regimen or CR/PR <6 mo after last rituximab dose. The overall response rate (ORR) during induction in 22 evaluable MZL patients was 55% (45% CR/CRu); response assessment was too early with no reported efficacy in non-evaluable patients. Responses by subtype are shown in Table 1. The most common grade 3/4 treatment-emergent adverse events in MZL patients during induction were hematologic, 9 (33%) neutropenia and 3 (11%) thrombocytopenia.

Conclusions: R² induction showed favorable activity and tolerable safety profiles in R/R patients with MZL. Enrollment in MAGNIFY is ongoing.

Keywords: lenalidomide; marginal zone lymphoma (MZL); rituximab.

TABLE 1 Best response in evaluable patients with R/R MZL during R2 induction.

Response status, n (%)	MALT (n=6)	Splenic MZL (n=5)	Nodal MZL (n=11)	Evaluable MZL (N=22)
ORR95% CI	3 (50) 12%-88%	3 (60) 15%-95%	6 (55) 23%-83%	12 (55) 32%-76%
CR/CRu	3 (50)	1 (20)	6 (55)	10 (45)
PR	0	2 (40)	0	2 (9)
SD	3 (50)	2 (40)	4 (36)	9 (41)
PD*	0	0	1 (9)	1 (5)

*Includes PD and/or death prior to response evaluation completion.

POSTER PRESENTATIONS

PATHOLOGY AND BIOLOGY

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WHOLE-EXOME-SEQUENCING OF NODAL MARGINAL ZONE LYMPHOMAS IDENTIFIES RECURRENT MOLECULAR LESIONS IN GENES INVOLVED IN CHROMATIN REMODELLING AND NOTCH SIGNALLING

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Introduction: Nodal marginal zone lymphoma (NMZL) is a rare form of small B-cell lymphoma. NMZL has no disease-defining phenotype, and the diagnostic borders to other small B-cell lymphomas are blurred. NMZL is poorly studied and orphan for molecular diagnostic markers. To better understand the pathogenetic mechanisms involved in NMZL, we aimed to comprehensively characterize the genetic background of NMZL at the single nucleotide variation level.

Methods: Genomic DNA was extracted from frozen biopsies and formalin-fixed paraffin-embedded tumor samples (>70% tumor cell fraction). Sanger sequencing was performed to exclude cases with MYD88 L265P mutation typical for lympho-plasmacytic lymphoma (LPL). Whole-exome-sequencing (WES) of 6 NMZL and 6 paired non-tumor samples was performed to identify novel somatic mutations. Mutated genes discovered by WES were investigated by targeted high throughput sequencing (HTS) on larger collectives of NMZL and B-cell lymphomas.

Results: By means of WES, a total of 655 nonsilent somatic mutations were identified, including 608 point mutations and 47 small insertion/deletion events. On average, samples contained 110 mutations (ranging from 68 to 216 lesions per case). In total, 46 candidate genes affected in at least 2 of the 6 NMZL were identified. Among the recurrently altered genes, we found *CAMK2D*, *EBF1*, *HIST1H1C*, *IGLL5*, *KMT2D*, *KMT2C*, *TET2*, and *TNFRSF14*. Based on genes found to be recurrently mutated in the discovery genomes as well as genes recently reported to be recurrently affected in NMZL (Spina et al., *Blood* 2016), we complemented an existing lymphoma-customized targeted sequencing panel and used it to identify mutations in an

extended screening cohort of 25 NMZL and 40 other small B-cell lymphomas, including LPL, extranodal MZL, and unclassifiable "grey zone" cases with features of both LPL and NMZL. Preliminary results show that among the most frequently affected genes in NMZL were genes encoding for chromatin remodelling and transcriptional regulation pathways, including *KMT2D*, *KMT2C*, *KLF2*, *HIST1H1C*, *CAMK2D*, *EBF1*, and *TET2*. We also noted frequent mutations in the NOTCH signalling pathway, including *NOTCH2*, *SPEN*, *DTX1*, and *CREBBP*.

Conclusions: Collectively, our findings extend the current knowledge on the pathogenetic mechanisms involved in NMZL. We identified somatic mutations potentially helpful for NMZL diagnostics. Together with another recent study on NMZL (Spina et al., *Blood* 2016), our data provide a comprehensive mutation profile for NMZL, which can help discriminating this entity from other morphologically and/or clinically related entities such as LPL and splenic MZL. We further suggest *in silico* pathways that play an important role in NMZL and, therefore, may represent potentially targetable signaling cascades, which could be targeted in novel treatment strategies.

Keywords: deep sequencing; nodal marginal zone lymphoma (NMZL); Notch pathway

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INTEGRATIVE MUTATIONAL ANALYSIS OF PEDIATRIC-TYPE FOLLICULAR LYMPHOMA REVEALS *TNFRSF14* AND *MAP2K1* AS THE MOST FREQUENTLY MUTATED GENES

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Aims: Pediatric-type follicular lymphoma (PTFL) has been recognized as a definite entity in the revised 2016 WHO Classification. Recently, genetic alterations that might be important for its pathogenesis and that disrupt pathways associated with germinal center reaction (*TNFRSF14*, *IRF8*), immune escape (*TNFRSF14*), and anti-apoptosis

(MAP2K1) have been described in different cohorts of PTFL cases. By expanding the genetic analysis of our PTFL cohort for MAP2K1 and IRF8 mutations and performing an integrative analysis, we want to clarify their frequency and correlation with TNFRSF14 mutations and its potential role in the pathogenesis of the disease.

Methods: Molecular analysis of 43 cases previously characterized by targeted sequencing (Ion AmpliSeq Custom Panel) of genes commonly mutated in adult FL and copy number analysis with the Oncoscan array (Schmidt et al., Blood 2016) were analyzed for MAP2K1 and IRF8 mutations by NGS and Sanger sequencing, respectively. The phosphorylated ERK protein (pERK) was analyzed by immunohistochemistry on formalin-fixed paraffin-embedded tissue sections in 12 PTFL cases.

Results: Twenty of 41 PTFL (49%) cases carried MAP2K1 mutations. Mutations were identified mainly in 2 hot spots within exon 2, which encode the negative regulatory region domain of MEK1 protein. MAP2K1 and/or TNFRSF14 mutations were confirmed in 33/43 cases (77%); however, only 8 cases (19%) showed mutations in both genes, whereas most cases had either a TNFRSF14 (13/41; 32%) or a MAP2K1 (12/41; 29%) mutation. Another interesting finding was the different allelic frequencies for MAP2K1 and TNFRSF14 mutated cases (Median \pm SD, 10 ± 8.58 vs 17.75 ± 6.3 ; P value = .046), which suggests that TNFRSF14 mutation occurs first even in cases with concomitant CNN-LOH or deletion of 1p36 locus. Analysis of the downstream targets ERK1/2 revealed good correlation with pERK staining and allelic frequency of MAP2K1 mutation in the evaluable cases. IRF8 mutations at the hotspot p.R66K were found in 15% (6/39) of cases. Interestingly, 4 of the 6 IRF8 mutated cases also showed TNFRSF14 mutations.

Conclusion: This integrative genetic analysis demonstrated that in 88% of PTFL cases, one or several gene mutations were identified. The most frequently mutated genes are TNFRSF14 (51%) followed by MAP2K1 (49%) but in most cases, these 2 mutations occur independently, suggesting that both mutations might play a role in PTFL pathogenesis. Phosphorylation of the MAP2K1 downstream target ERK demonstrates that MAP2K1 mutations are activating mutations, but their exact role in lymphomagenesis still needs to be elucidated. We confirm that IRF8 mutations occur occasionally in PTFL, but are less common than other events. Nevertheless, the similar functions and often co-occurrence of IRF8 and TNFRSF14 mutations suggest that these 2 mutations might cooperate in the pathogenesis of PTFL.

Keywords: ERK; follicular lymphoma (FL); molecular genetics

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DOWN-REGULATION OF MIR-150 AND UP-REGULATION OF ITS TARGET FOXP1 IS ASSOCIATED WITH TRANSFORMATION OF FOLLICULAR LYMPHOMA

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Introduction: We aim to understand the role of microRNAs (miRNAs) in the high-grade transformation of follicular lymphoma (FL) to diffuse large B-cell lymphoma (DLBCL). Recently, a number of genomic aberrations associated with transformed FL (tFL) were described, including frequent aberrations activating MYC proto-oncogene. However, precise molecular mechanisms underlying FL transformation are largely unknown.

Methods: We performed a global expression analysis of 377 miRNAs in paired samples (N = 16) from FL patients before vs after transformation to DLBCL (TLDA miRNA cards; Thermo Fisher Scientific), and additional 85 FL and 12 tFL samples were utilized in further analyses.

Results: The miRNA expression profiling of paired FL-tFL samples (N = 8 pairs) revealed significant changes ($P < .05$, fold change >2.0) of 5 miRNAs. The most striking change was miR-150 down-regulation (~ 4 fold, $P = .01$), which was confirmed in additional cohorts of tFL vs FL. We further analyzed miR-150 expression in a cohort of 85 FL and found significantly lower miR-150 levels in patients with FLIPI score ≥ 3 ($P = .03$), with high proliferation rate of cells (Ki67 $> 20\%$; $P = .003$) and with short survival (N = 85; median, 9.1 y vs not reached; $P = .007$). We have previously shown that miR-150 directly regulates FOXP1 protein in chronic lymphocytic leukemia, and high FOXP1 levels are known to associate with worse prognosis in DLBCL. Therefore, we assessed the association of miR-150 with FOXP1 in FL and found significantly lower miR-150 levels in patients with strong FOXP1 positivity ($>70\%$ cells). Moreover, FOXP1 levels were clearly increased in paired tFL compared to FL. We further examined the association of MYC and miR-150 in FL/tFL and found significantly lower miR-150 levels in MYC-positive FL/tFL vs MYC-negative FL. miR-150 down-modulation ($P < .05$) was also observed in B cells from transgenic mice heterozygous for MYC over-expression (MYC controlled by an Ig-alpha heavy-chain enhancer) in comparison to wild-type animals.

Conclusions: Low-level expression of miR-150 associates with the transformation to DLBCL and shorter survival in FL. Our data suggest that MYC down-modulates miR-150 levels during transformation of FL to DLBCL, and this leads to up-regulation of FOXP1 transcription factor. The increased activity of FOXP1 likely directly contributes to the histological transformation of FL.

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Keywords: follicular lymphoma (FL); microRNA

143 NOVEL MOLECULAR MARKERS FOR MINIMAL RESIDUAL DISEASE (MRD) MONITORING IN MANTLE CELL AND FOLLICULAR LYMPHOMA: THE TARGETED LOCUS AMPLIFICATION (TLA) NGS STRATEGY

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Background: Minimal residual disease (MRD) monitoring by PCR is a strong and standardized predictor of clinical outcome in mantle cell (MCL) and follicular (FL) lymphoma. However, some technical limitations hamper its feasibility in daily clinical routine. First of all, current techniques allow the identification of a molecular marker only in 75% to 80% of MCL and 55% to 60% of FL. All the other cases cannot be

studied for MRD. Next generation sequencing (NGS) might overcome these limitations. The recently developed targeted locus amplification (TLA) technology, that selectively amplifies and sequences entire genes on the basis of the crosslinking of physically proximal DNA loci, was able to identify novel gene fusions in acute lymphoblastic leukemia. Thus, TLA was tested in highly infiltrated MCL and FL baseline samples, with at least one FISH translocation but a molecular marker identification failure, with the aim to increase the rate of success in marker screening for MRD purposes. Moreover, the performances of the newly identified molecular markers were compared to the standardized IGH qPCR approach.

Methods: Genomic DNA was extracted from highly infiltrated (>5%) BM and PB samples of MCL and FL patients, enrolled in prospective clinical trials of the Fondazione Italiana Linfomi (FIL). Libraries for TLA (Cergentis, Utrecht) were prepared using only one couple of antisense primers targeting the IGH-enhancer locus and sequenced on MiSeq platform (Illumina, San Diego). MRD monitoring was carried out by qPCR ASO primers and consensus probes on the breakpoint sequences obtained from TLA NGS. Finally, the efficiency of TLA novel markers to track MRD was compared to MRD data obtained from clonal IGH rearrangements tracked by ASO qPCR, following the EuroMRD guidelines.

Results: TLA was firstly tested on 17 t(11;14)-positive, BCL-1/IGH MTC-negative MCL baseline samples (8 BM and 9 PB): in all cases, a novel BCL-1/IGH breakpoint was identified by NGS. Therefore, additional 5 t(14;18)-positive, BCL-2/IGH MBR/mcr-negative FL BM samples were tested, with again a 100% success rate. In addition, a MBR-positive cell line control sample was correctly sequenced, as well. TLA on cases t(11;14) and t(14;18) negative by FISH or samples with low tumor infiltration (<5%) are currently ongoing. Secondly, ASO primers were designed on the newly identified BCL-1/IGH "minor" breakpoints, and MRD was monitored by qPCR in the first 8 MCL patients: in the 7 cases where also a classical, IGH-based marker was available, and the MRD results were highly comparable between the 2 markers (Figure 1), with overlapping performances ($r^2 = 0,86$). ASO qPCR for all the other MCL and FL cases is ongoing.

Conclusion: The TLA NGS technology allowed to identify a translocation-based, novel molecular marker in FISH-positive MCL and FL baseline samples, where the classical Sanger sequencing failed a marker identification. These new breakpoints can reliably be used for the design of ASO qPCR primers for MRD detection in previously not traceable patients.

Keywords: B-cell lymphoma; gene rearrangement; minimal residual disease (MRD)

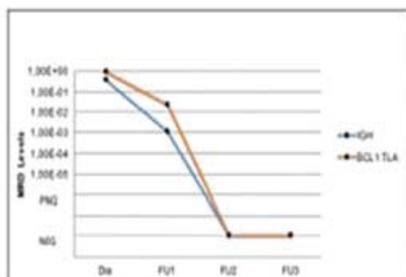


Fig 1. MRD was monitored using IGH rearrangement (blue) and BCL1/IGH translocation (orange). The results showed as the BCL1/IGH sequence obtained by TLA was useful in MRD monitoring as IGH rearrangement detected using classic sequencing techniques. Moreover, in FU1 samples tumour burden detected by TLA BCL1/IGH was higher than IGH results.

144 HOST GENETIC VARIATION IN THE TNF AND NF- κ B PATHWAYS AND PROGNOSIS IN MANTLE CELL LYMPHOMA: AN ANALYSIS OF 2 STUDIES

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Introduction: Mantle cell lymphoma (MCL) is a generally incurable non-Hodgkin lymphoma characterized by the t(11;14) translocation that leads to overexpression of cyclin D1. Multiple genes involved in the tumor necrosis factor (TNF) and nuclear factor- κ B (NF- κ B) pathways have been reported to be up-regulated in MCL. NF- κ B has been shown to be constitutively active in MCL and may play a key role in the growth and survival of MCL cells. We investigated whether host germline variation in the TNF and NF- κ B pathway genes is associated with overall survival (OS) in MCL.

Methods: In a discovery dataset from the NCI-SEER Survival Study, we evaluated the association of 41 candidate genes and 486 tag single nucleotide polymorphisms (SNPs) with OS in 39 MCL patients using a gene-level test. We then attempted to replicate individual SNPs from the top candidate genes ($P \leq .15$) in an independent dataset of 101 MCL patients from the molecular epidemiology resource (MER) of the University of Iowa and Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE). We used Cox proportional hazards regression to evaluate the association of genes (defined by principal components) and SNPs with OS after adjusting for clinical factors and treatment. For SNP associations, we estimated hazard ratios (HRs) and 95% confidence intervals (CI) from Cox regression models.

Results: In the NCI-SEER discovery cohort, 8 genes (*NFKB1L1*, *TNFRSF13B*, *TNFRSF25*, *TRAF5*, *NFKB1*, *RELB*, *IRF4*, *NFKBIA*) were potentially associated with OS ($P \leq .15$). Association of OS was replicated for 3 of these genes at the SNP level in the MER cohort: *TNFRSF25* (rs3138156), *TRAF5* (rs3738199, rs6684874, rs12569232), and *RELB* (rs10424046, rs1560725). We then combined the SNP level data in a meta-analysis of the 2 cohorts. The *TNFRSF25* SNP rs3138156 was associated with inferior survival ($P = .0047$): compared to patients with the AA genotype, those with the AG (HR = 3.04; 95% CI, 1.41-6.56) had inferior OS (no GG genotype was seen in the cohorts). The *TRAF5* SNP rs3738199 was also associated with inferior survival ($P = .00086$): compared to patients with the AA genotype, those with the AG (HR = 1.81; 95% CI, 0.99-3.32) and GG (HR = 4.11; 95% CI, 1.86-9.04) genotypes had inferior OS. Finally, the *RELB* SNP rs10424046 was associated with superior survival ($P = .0062$): compared to the patients with GG genotype, those with the CG (HR = 0.45; 95% CI, 0.25-0.82) and CC (HR = 0.36; 95% CI, 0.17-0.78) genotypes had better OS.

Conclusions: Germline variation in the TNF and NF- κ B pathway genes *TNFRSF25*, *TRAF5*, and *RELB* were associated with OS in MCL after adjustment for clinical and treatment factors. The genetic variation in the TNF and NF- κ B pathway genes may play a role in disease progression and overall survival in MCL. The role of the TNF and NF- κ B

pathways in the pathogenesis of MCL, and targeting these pathways for therapy in MCL, should be further explored.

Keywords: mantle cell lymphoma (MCL); NF- κ B; SNP

145 HIGH PROLIFERATION (MCL35 ASSAY) IS ASSOCIATED WITH INFERIOR OUTCOMES IN PATIENTS TREATED WITH INTENSIVE REGIMENS—A CORRELATIVE STUDY FROM THE CALGB 50403 (ALLIANCE) TRIAL

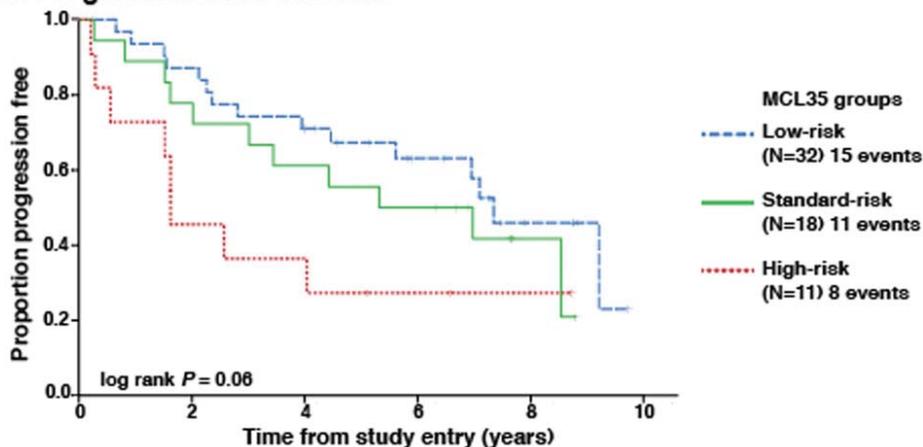
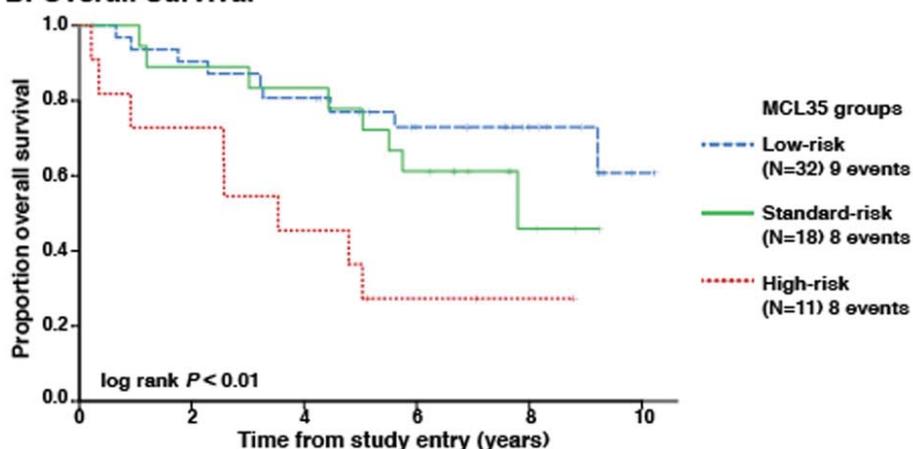
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Introduction: Mantle cell lymphoma (MCL) is an incurable neoplasm that displays heterogeneous outcomes after treatment. One of the most powerful biomarkers in MCL is the “proliferation signature,” first described by the LLMP in 2003. The LLMP developed an assay, the MCL35, that translates this signature into a gene expression-based test on the NanoString platform, applicable to routinely available formalin-fixed paraffin-embedded (FFPE) biopsies. The assay assigned patients (pts) into low-, standard-, and high-risk categories that had significantly different overall survival (OS) after treatment with R-CHOP (Scott et al. *J Clin Oncol* 2017). In that study, a planned subgroup analysis showed that the prognostic power of the assay was maintained in pts where there was an intention to treat with a consolidative autologous stem cell transplant (ASCT) after R-CHOP. Herein, we examined whether this assay remains prognostic in younger pts when modern aggressive treatment was used.

Methods: In an unplanned substudy, the MCL35 assay was run on FFPE-derived RNA from 62 pts with available lymph node biopsies from CALGB 50403—a randomized phase II trial comparing bortezomib consolidation vs maintenance after intensive induction and consolidative ASCT. As outcomes in the 2 arms of the trial were not significantly different, pts enrolled in both arms were pooled for analyses. The primary outcome examined was whether MCL35 categories were associated with different progression free survival (PFS). Secondary endpoints were association of MCL35 categories with OS and association between MCL35 score as a continuous variable and PFS and OS.

Results: Gene expression results of sufficient quality were produced in 61/62 (98%) specimens with 32 (52%), 18 (30%), and 11 (18%) pts assigned to the low-, standard-, and high-risk groups, respectively. PFS across the 3 risk groups was marginally significantly different with

Figure 1: Kaplan Meler curves for PFS and OS**A. Progression Free Survival****B. Overall Survival**

median PFS of 7.3, 6.9, and 1.6 years in the low-, standard-, and high-risk groups, respectively (log rank $P = .06$, Figure 1A). OS was significantly different with median OS of unreached, 7.6 and 3.5 years, respectively (log rank $P < .01$, Figure 1B). For both PFS and OS, outcomes for the low- and standard-risk groups were not significantly different; the high-risk group had inferior outcomes compared with the low-risk group ($P = .02$ for PFS and $P < .01$ for OS). MCL35 score as a continuous variable was associated with both PFS and OS in univariate analysis ($P < .01$).

Conclusions: The recently described MCL35 gene expression-based assay for the proliferation signature in MCL identified groups of younger patients with differing outcomes after treatment with intensive modern regimens. Despite intensive treatment, patients with high proliferation continue to have poor outcomes indicating that novel approaches are needed for this group.

Support: U10CA180821, U10CA180882, Lymphoma Research Foundation.

Keywords: gene expression profile (GEP); mantle cell lymphoma (MCL)

AND INFERIOR OUTCOME IN DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)

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Background: Gene expression profiling (GEP) identifies 2 main DLBCL subtypes based on COO, germinal center type DLBCL (GCB), and activated B cell-like DLBCL (ABC). An upregulation of the transcriptional factor ETS1 occurs in 25% of DLBCL (Bonetti, Testoni et al., Blood 2013). Here, we present the impact of pETS1, a marker for ETS1 activation, in DLBCL cellular models and in clinical specimens.

Patients and Methods: Levels of pETS1, ETS1, ERK, pERK-Tyr204, and IRF4 were analyzed in cell lines derived from ABC (n = 8), GCB (n = 8), and Type 3 (n = 3) DLBCL. p-ETS1 was examined by

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ETS1 PHOSPHORYLATION AT THR38 (pETS1) IS ASSOCIATED WITH CELL OF ORIGIN (COO), CELL CYCLE ACTIVATION,

immunohistochemistry on clinical specimens with available Affymetrix U133plus2.0 GEP: cases were defined as positive if >10% of the neoplastic cells nuclei were pETS1 positive.

Results: pETS1 was detected in ABC, not in GCB cell lines (100% vs 0%, $P < .05$), but also in 2/3 Type 3 (67%). All the cell lines expressed ETS1 and its upstream activator ERK. The ABC marker IRF4 was expressed only in ABC (100%). p-ERK was expressed in 6/8 ABC (75%), 2/3 Type 3 (67%), and 0/8 GCB (0%). pETS1 was present predominantly in the nucleus (5/5), while total ETS1 was in both cytoplasm and nucleus in 4/5, and only in the nucleus in 1/5. To evaluate the mechanisms sustaining pETS1, 2 ABC cell lines (U2932, TMD8) were treated with the PI3K-delta inhibitor idelalisib (1 μ M), the BTK inhibitor ibrutinib (0.5 μ M), and the MEK inhibitor pimasertib (0.5 μ M) with or without anti-IgM. BTK or MEK inhibition decreased pETS1 baseline levels but only MEK inhibition inhibited the IgM stimulation-induced pETS1 increase. PI3K-delta inhibition only lead to a minimal reduction of baseline pETS1 levels. Similar changes were seen for pERK.

To understand the clinical significance of our findings, we assessed pETS1 expression in 315 GEP-classified, RCHOP-treated DLBCL cases from The International DLBCL Rituximab-CHOP Consortium Program Study. pETS1 was more frequent in ABC than in GCB: 79% (123/155) vs 57% (91/160) ($P < .001$). In GCB, pETS1 positivity was associated with inferior progression free survival (PFS) at univariate analysis (P 0.034). The prognostic impact was also maintained in a multivariate analysis including the IPI. No effect on the outcome was seen in ABC. The pETS1 positive GCB ($n = 91$) presented a statistically significant enrichment of gene expression signatures related to cell cycle (mitotic spindle, NES 1.8 FDR 0.003; E2F targets NES 1.7 FDR 0.003; MYC targets NES 1.5 FDR 0.04) when compared to pETS1 negative GCB ($n = 69$).

Conclusions: pETS1 is associated with the ABC phenotype in cell lines and clinical specimens. pETS1 positive GCB are characterized by poor PFS and cell cycle-related gene expression signatures. Pharmacological interventions worth of preclinical investigation for pETS1 DLBCL positive cases could comprise drugs targeting BTK, MEK, and cell cycle.

Keywords: activated B-cell-like (ABC); diffuse large B-cell lymphoma (DLBCL); GCB lymphoma subtype

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DNMT3A-2 EXPRESSION LEVELS CHARACTERISE DIFFUSE LARGE B-CELL LYMPHOMA WITH DISTINCT METHYLATION PATTERNS AND OUTCOME

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Background: DNA methylation changes have been implicated in the pathogenesis of diffuse large B-cell lymphoma (DLBCL), but molecular mechanisms driving aberrant methylation remain largely unknown. Alterations of the DNA methyltransferase DNMT3A are known pathogenetic events in acute leukaemia and T-cell lymphoma, with the short isoform 2 (DNMT3A-2) probably being of particular relevance. The role of DNMT3A in DLBCL has not been investigated yet.

Methods: DNMT3A-2 mRNA expression was derived from Illumina DASL microarray data (ILMN_1654945) of 175 newly diagnosed DLBCL patients from the UK R-CHOP14v21 trial. DNA methylation was analysed in 144/175 cases with Illumina Infinium 450 k arrays using the RnBeads package in R 3.2.3. Differentially methylated regions (DMRs) were analysed on RnBeads tiling level, comparing the highest and lowest DNMT3A-2 expression quartiles.

Results: DNMT3A-2 expression showed significant impact on global DNA methylation, with 27 344 DMRs between the high and low expression groups (false discovery rate < 0.05). In contrast, only 50 DMRs were associated with expression of DNMT3A isoform 3 and 6485 DMRs with cell-of-origin subgroups. We further analysed DNMT3A-2-associated DMRs with at least 15% methylation difference ($n = 3298$), 2806 being hypomethylated (predominantly gene bodies) and 492 hypermethylated (predominantly promoters). Hypomethylated genes were enriched for KEGG cancer- and MAPK-signalling pathways ($P < .0001$), including *MDM2*, *BCL2L1*, *LEF1*, *HDAC1*, and *JAK1*, whereas *WNT7A*, *BMP4*, *DKK3*, *ETV1*, and *WT1* were among hypermethylated genes.

DNMT3A-2 expression was significantly lower in patients with extranodal involvement of >1 sites ($P = .03$) and in cases with *BCL2*-rearrangement ($P = .03$). There was a trend towards lower DNMT3A-2 expression in bulky disease ($P = .09$) and GCB subtypes ($P = .10$). DNMT3A-2 expression correlated with expression of *CREBBP*, *DOT1L*, and *MLL2* (all $P < .05$). No association was observed between DNMT3A-2 expression and *MYC*- and *BCL6*-rearrangements, double-hit-lymphoma, or with patients' age. Patients with higher DNMT3A-2 expression (median) had worse progression-free survival (HR = 2.01; 95% CI, 1.21-3.35; $P = .01$) and a trend towards worse overall survival (HR = 1.72; 95% CI, 0.96-3.10; $P = .07$). We found methylation of 5 sites within the DNMT3A gene to be inversely correlated with DNMT3A-2 expression as a potential mechanism of isoform-specific regulation. Copy number gain of DNMT3A was seen in 9 cases, copy number loss in 3 cases, with no obvious impact on expression of isoform 2. DNMT3A mutational analyses will be provided at the meeting.

Conclusions: DNMT3A-2 expression is associated with global DNA methylation changes and outcome in DLBCL, suggesting a potential role in disease pathogenesis. DNMT3A-2 expression levels might identify clinically meaningful subgroups of DLBCL suitable for epigenetic therapies.

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

148 KRAS AND AGO2 INTERACTION PROMOTE INITIATION OF PLASMABLASTIC LYMPHOMA USING AN IN VIVO MOUSE TRANSPLANT MODEL

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Introduction: The family of Argonaute (Ago) proteins is essential for posttranscriptional gene regulation mediated by the microRNA (miRNA) pathway. Of the 4 mammalian Argonaute proteins, Ago2 is the only member to be found frequently amplified in human cancers, including multiple myeloma. Oncogenic Kras has been previously reported to interact with Ago2 in promotion of tumor progression in solid tumor models. We have investigated whether Ago2 overexpression impacts blood cancers.

Methods: Bone marrow was harvested from KP mice, which harbor a *Kras*^{LSL-G12D} allele as well as “floxed” *Trp53* alleles. These cells were transduced in vitro with a doxycycline-inducible Ago2 construct coexpressing Cre recombinase. The transduced cells were subsequently transplanted via intravenous injection into sublethally irradiated mice and monitored for disease progression.

Results: Approximately 5 months posttransplant, a clinical pathologist confirmed that 100% of the mice (n = 6) with Ago2 overexpressed developed a plasmablastic lymphoma-like (PBL) disease, an aggressive variant of diffuse large B-cell lymphoma. This phenotype was not seen in the doxycycline controls not overexpressing Ago2. Large infiltrates of abnormal lymphocytes were detected in many tissues in the Ago2-overexpressed mice, effacing the architecture of the spleen, lymph nodes, lungs, and many others. These lymphocytes express low levels of B220, CD138 and Mum-1, characteristic of cells undergoing plasmacytic differentiation. These hyperplastic cells display clonal expansion, the presence of mitotic figures and abundant vesicular nuclei, consistent with the histology of high-grade lymphomas. Cell culture experiments demonstrated that Ago2-overexpression is necessary for tumor cell survival, as withdrawal of doxycycline induces massive DNA damage and cell death. This phenotype was found to be dependent on the interaction between Ago2 and Kras and suggests a novel role for Ago2 in a poorly characterized human disease.

Conclusions: Ago2 overexpression is an oncogenic gain-of-function in our novel mouse model producing a highly aggressive B-cell malignancy. In this lymphoma, Ago2 acts cooperatively with Kras to activate downstream signaling pathway, thereby promoting cell proliferation and survival. Patients diagnosed with PBL have a poor survival rate, as standard chemotherapy regimens are ineffective. Thus, establishing a mouse model for PBL could be beneficial to better understanding the genetic and molecular characteristics of the disease and hopefully improve survival outcome.

Keywords: activated B-cell-like (ABC); diffuse large B-cell lymphoma (DLBCL)

149 COMPREHENSIVE EPIGENETIC AND TRANSCRIPTIONAL SURVEY OF THE “IMPRINTOME” IN NORMAL B-Cells AND GERMINAL CENTER DERIVED B-CELL LYMPHOMAS OF THE MMML AND ICGC MMML-SEQ NETWORKS

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Introduction: A subset of genes in the human genome is expressed depending on their parental origin. These so-called “imprinted” genes primarily function in the control of proliferation, fetal development, and cellular differentiation. Inborn errors of imprinting are in part associated with an increased tumor risk. In tumor cells, loss of imprinting can occur on the somatic level, eg, due to uniparental disomy, chromosomal changes, or epigenetic alterations at differentially methylated regions (DMRs) of imprinted loci. We here aimed at characterizing the human “imprintome” in normal B-cells and germinal center (GC) derived B-cell lymphomas.

Methods: We defined the human “imprintome” as all 321 transcription units (TU) known or supposed to be subject to imprinting. Moreover, we investigated all 47 DMRs described to regulate imprinted expression (iDMRs) of these TU. We analysed the expression of the TU using Affymetrix U133A GeneChips in 656 lymphoma and 30 normal GC B-cell samples (gcBC) of the MMML cohort and by RNA sequencing in 196 lymphomas and 5 gcBC samples of the ICGC MMML-Seq cohort. Lymphomas included predominately Burkitt (BL), follicular (FL), and diffuse large B-cell lymphomas (the latter two summarized as non-BL).

Transcriptional profiles were integrated with whole genome bisulfite sequencing (WGBS) data available from a subset of FL and BL (Kretzmer et al., 2015).

Results: Of 64 imprinted TU represented on the array, 31 TU were significantly differentially expressed between BL and non-BL, 16 between BL and gcBC, and 10 between non-BL and gcBC in the MMML cohort. By RNAseq in the ICGC MMML-Seq cohort, 68 TU were differentially expressed between BL and non-BL (overlap with MMML cohort, 24/31 differentially expressed TU), 37 TU between BL and gcBC (overlap, 7/16), and 39 TU between non-BL and gcBC (overlap, 6/10). Using WGBS, we observed in normal gcBC hemi-methylation (mean methylation [0.3, 0.7]) typical for imprinted loci in 43/47 iDMRs. Of the 47 iDMRs, 9 co-occurred with DMRs between BL and gcBC and only one with a DMR between FL and gcBC. Furthermore, 5/47 iDMRs overlap with such DMRs between BL and FL showing significant correlation of DNA hypermethylation and reduced expression in BL.

Conclusions: Transcriptional changes of imprinted genes are common in GC-derived B-cell lymphomas. Nevertheless, the altered transcriptional regulation of imprinted genes seems mostly not to rely on DNA methylation changes of parent-of-origin-specific DMRs.

Keywords: B-cell lymphoma; deep sequencing; epigenetics

150 GENE EXPRESSION PROFILING AND MUTATION ANALYSIS CAN AID TREATMENT DECISION MAKING IN AGGRESSIVE B CELL LYMPHOMA PATIENTS

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Introduction: Accurate distinction between diffuse large B-cell lymphoma (DLBL) and Burkitt lymphoma is critical as both require very different treatments. For those with features between DLBL and Burkitt, the treatment choice is unclear. Many of these have *MYC* rearrangement (*MYC-R*), either as the sole abnormality or "dual/triple hit," with a poor response to standard therapies. We developed a 2-way Burkitt-Like (BL) and DLBL GEP Classifier (BDC) that can dichotomise patients with a BL profile vs non-BL (Sha et al., 2015). The concordance between original pathological diagnosis and the classifier was 92%. Importantly, cases reclassified as BL using the BDC (8%) had an inferior response to RCHOP, and this has been further validated in the recent REMoDL-B trial. A number of genes are genetically altered in Burkitt lymphoma (TCF3, ID3, and CCND3 being the most common, Schmitz et al. 2012); however, the incidence of these mutations by BDC class within the spectrum of high grade B cell (HGB) lymphomas

has not been comprehensively reported. The aim was to assess whether mutational analysis in addition to GEP could improve the diagnostic accuracy of HGB lymphomas compared to using FISH and immunohistochemistry alone.

Methods: Targeted Sanger sequencing (GRCh37/hg19 assembly) of TCF3 (E47) (chr19:1,612,262-1,612,472), ID3 (chr1:23,885,562-23,885,876), and CCND3 (chr6:41,903,628-41,903,822) was performed on DNA from 284 FFPE HGB lymphomas (www.hmrn.org). The BDC was applied to Illumina Whole-Genome DASL data (89 cases with mutation data to date).

Results: Mutations of ID3, TCF3, and CCND3 are predominantly associated with a diagnosis of Burkitt lymphoma and are less frequent in intermediate categories (*MYC-R*, DLBCL, and Dual/Triple Hit) or DLBL (Table). A total of 24 cases had mutation in >1 gene, and all of these had a diagnosis of Burkitt. A similar mutation frequency was seen in patients classified as BL according to BDC (n = 73) (ID3 32%, TCF3 11%, CCND3 21%), and work is underway to fully assess mutations in patients with non-BL GEP.

Conclusions: Targeted sequencing with GEP can be routinely applied to FFPE tissue and can aid clinical decision making. ID3, TCF3, and CCND3 mutations would favour a diagnosis of Burkitt lymphoma in conjunction with other laboratory and clinical parameters. The data highlights significant biological heterogeneity within the specific Burkitt diagnostic category. The inclusion of mutational analysis and GEP in treatment decision making needs to be tested prospectively. Mutation frequency by diagnostic sub-group

	Mutations (n=98)			Normal	Total patients
	ID3	TCF3	CCND3		
Total (%)	41 (14%)	11 (4%)	46 (16%)	211 (74%)	284
Pathological diagnosis					
Burkitt lymphoma	34 (36%)	9 (10%)	31 (33%)	45 (48%)	94
<i>MYC-R</i> DLBL	4 (7%)	0	7 (13%)	44 (80%)	55
DLBL (<i>MYC</i> normal/NK)	3 (2%)	2 (2%)	8 (6%)	122 (90%)	135

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

151 APPLICATION OF CELL-OF-ORIGIN SUBTYPES DETERMINED BY DIGITAL GENE EXPRESSION IN HIV-RELATED DIFFUSE LARGE B-CELL LYMPHOMAS

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Characteristic	GCB N=35	ABC N=11	UNC N=9	P-value (GCB vs. ABC)
MYC rearrangement, N(%)	11/32 (34.4)	0/10 (0)	2/8 (25)	0.030
BCL2 rearrangement, N(%)	2/32 (6.3)	1/10 (10)	1/8 (12.5)	0.568
BCL6 rearrangement, N(%)	7/32 (21.9)	3/10 (30)	4/8 (50)	0.444
Dual-hit, N(%)	1/32 (3.1)	0/10 (0)	2/8 (25)	0.762
CD10, N(%)	16/34 (47.1)	2/11 (18.2)	1/8 (12.5)	0.087
BCL6, N(%)	23/33 (69.7)	4/11 (36.4)	5/8 (62.5)	0.055
MUM1, N(%)	16/33 (48.5)	7/11 (63.6)	6/8 (75)	0.384
CD30, N(%)	4/33 (12.1)	1/11 (9.1)	3/8 (37.5)	0.633
EBER, N(%)	5/33 (15.2)	4/11 (36.4)	2/8 (25)	0.141
BCL2, N(%)	12/31 (38.7)	6/11 (54.5)	4/8 (50)	0.287
MYC, N(%)	12/32 (37.5)	2/11 (18.2)	3/9 (33.3)	0.213
Dual MYC and BCL2 expression, N(%)	6/31 (19.4)	2/11 (18.2)	1/8 (12.5)	0.655

Introduction: Diffuse large B-cell lymphoma (DLBCL) can be divided according to cell-of-origin (COO) in germinal center B-cell-like (GCB) and activated B-cell-like (ABC). Although the importance of COO determined with the Lymph2Cx assay is well established in DLBCL arising in immunocompetent individuals, there are no reports on its use in HIV-infected patients. We aimed to study the characteristics and prognostic impact of COO subtypes in a series of HIV-related DLBCL using the Lymph2Cx assay and to compare the results with those obtained with Hans algorithm.

Methods: A series of 55 patients with the diagnosis of HIV-related DLBCL (N = 48), high-grade B-cell lymphoma (HGBL) with MYC and BCL2 and/or BCL6 rearrangements (N = 3), or HGBL NOS (N = 4) was studied. The following clinical parameters were collected: age, gender, ECOG, extranodal and bulky disease, B-symptoms, Ann-Arbor

stage, LDH and beta2-microglobulin, HCV and HBV serology, history of opportunistic infection and of AIDS-defining illness, onset of combination antiretroviral therapy, CD4-counts, and HIV-loads. IHC and FISH studies were performed on tissue microarrays. RNA was extracted from FFPE samples with RecoverAll kit (Ambion, Carlsbad, CA), and digital GEP was determined with the Lymph2Cx assay (NanoString Technologies, Seattle, WA). Cohen's kappa was calculated to measure the agreement between COO given by Hans algorithm and Lymph2Cx assay.

Results: Allocation of COO subtypes with the Lymph2Cx assay was 63.6% GCB, 20% ABC, and 16.4% unclassified. The only clinical feature significantly associated with a defined COO subtype was B-symptoms (ABC = 81.8% vs GCB = 28.6%, $P = .003$) and detectable HIV-loads tended to be more frequently observed in ABC (90%) than in GCB (58.1%, $P = .066$). Regarding IHC and FISH characteristics (Table 1), MYC rearrangements were only detected in GCB cases and expression of CD10 and BCL6 tended to be associated with GCB. Hans algorithm and Lymph2Cx assay differently assigned COO subtypes ($\kappa = -0.288$, $P = .029$) showing that 44.1% of the GCB cases had a non-GC phenotype according to Hans. The median follow-up of living patients was 8.5 years. Only patients treated with RCHOP were considered in survival analyses (N = 47). COO subtypes had neither impact on OS nor PFS, independently of being determined with Lymph2Cx assay or Hans.

Conclusions: In HIV-related lymphomas, COO subtypes were discordantly assigned with Hans and Lymph2Cx assay and COO subtypes showed no impact on outcomes, independently of the method applied.

Keywords: GCB lymphoma subtype; human immunodeficiency virus (HIV); immunodeficiency-associated lymphomas

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BIODLCL04: THE PROGNOSTIC ROLE OF CELL OF ORIGIN PROFILE, MYC, BCL2, AND TP53 IN UNTREATED POOR-RISK DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: FIL-DLCL04 demonstrated an advantage in failure-free survival (FFS) but not in overall survival (OS) of high dose therapy + autotransplant (R-HDC + ASCT) compared to Rituximab-dose-dense as first line in young diffuse large B-cell lymphoma (DLBCL) at poor risk (Vitolo, ASH 2012). The aim of BIO-DLCL04 was to correlate the cell of origin (COO) and the biomarkers (MYC, BCL2, TP53 Wild Type, mutated) with OS and FFS.

Methods: From 2005 to 2010, 399 DLBCL were enrolled. Central histology revision was mandatory. Cases were classified for COO in germinal center (GC) and nonGC according to Hans' algorithm by immunohistochemistry (IHC) and in GB, activated B-cell (ABC), and

	N of pts	5-year OS, % (95% CI)	HR (95% CI)	aHR (95% CI)	5-year FFS, % (95% CI)	HR (95% CI)	aHR (95% CI)
GC IHC	37	76 (58-86)	1	1	59% (42-73)	1	1
nonGC IHC	57	77 (63-86)	0.93 (0.4-2.18), p.87	0.89 (0.35-2.26), p.813	70% (56-80)	0.64 (0.32-1.28), p.208	0.51 (0.24-1.09), p.081
GC Nano	55	85 (73-92)	1	1	69 (55-80)	1	1
ABC Nano	25	56 (35-73)	3.72 (1.49-9.29), p.005	4.59 (1.55-13.59), p.006	52 (31-69)	1.55 (0.74-3.24), p.249	1.3 (0.56-3.03), p.0.539
UN Nano	15	73 (36-91)	1.34 (0.35-5.03), p.0669	0.88 (0.21-3.58), p.855	77 (43-92)	0.54 (0.16-1.85), p.33	0.33 (0.09-1.22), P.096
MYC-	80	78% (67-86)	1	1	69% (57-78)	1	1
MYC+	8	63% (23-86)	1.75 (0.51-5.99), p.37	1.65 (0.35-7.66), p.524	50% (15-77)	1.8 (0.63-5.19), p.273	2.01 (0.6-6.77), p.258
BCL2-	73	79% (68-87)	1	1	70% (58-79)	1	1
BCL2+	19	68% (43-84)	1.72 (0.67-4.44), p.262	1.65 (0.35-7.66), p.524	53% (29-72)	1.88 (0.87-4.09), p.11	1.48 (0.66-3.32), p.341
TP53 WT	8	81% (70-89)	1	1	73% (61-82)	1	1
TP53 Mut	70	33% (6-66)	4.33 (1.54-12.21), p.006	3.16 (0.81-12.4), p.099	19% (1-53)	3.78 (1.5-9.49), p.005	2.33 (0.77-7.08), p.136

unclassified (UN) by Nanostring. BCL2, MYC, and TP53 anomalies were tested by FISH. OS and FFS were analyzed; a crude hazard ratio (HR) and an adjusted HR (aHR) for age, treatment, gender, aalPI, performance status, and bone marrow involvement were calculated.

Results: Ninety-five DLBCL were analyzed. FFS rates were similar for biomarkers evaluable and FIL-DLCL04 study populations. Only 5 cases were defined as double-hit; due to the small numbers, a separate analysis was not performed. At a median follow-up of 72 months, 5-years OS and FFS for COO by IHC and Nanostring, MYC and BCL2 by FISH and TP53 were reported in Table 1. No significant differences by treatment were observed (data not shown).

Conclusions: In our prospective trial, COO assessed by IHC is not predictive of outcome; Nanostring is able to discriminate 2 groups at different prognosis, GC and ABC. In our series, MYC and BCL2 did not affect OS and FFS. An important role is played by TP53, which represents a factor that impact on OS and FFS. The intensification with R-HDC + ASCT is not able to overcome the dismal prognosis.

Keywords: activated B-cell-like (ABC); diffuse large B-cell lymphoma (DLBCL); P53

LARGE B-CELL LYMPHOMA (DLBL) IN 2 LARGE PROSPECTIVE STUDIES

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PROGNOSTIC SIGNIFICANCE AND CORRELATION TO GENE EXPRESSION PROFILE OF EZH2 MUTATIONS IN DIFFUSE

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Introduction: *EZH2*, a histone methyl transferase subunit of Polycomb repressor complex 2, is frequently mutated in DLBL. Inhibitors of *EZH2* have demonstrated promising responses in early clinical trials. We examined the frequency of *EZH2* mutation in 2 large prospective series of DLBL and correlated this to clinical outcomes in relation to other biological features.

Methods: Patients (pts) received standard immunochemotherapy regimens as first-line treatment for DLBL. Sanger sequencing (SS) focusing on “hotspot” mutation sites in exons 16 and 18 was successful in 1052 of 1097 DLBL samples enrolled in the UK NCRI Molecular Profiling for Lymphoma (MaPLe) study. Next generation sequencing (NGS) using Fluidigm Access Array PCR and Illumina MiSeq was used to profile a separate cohort of 365 pts enrolled in the UK NCRI/ SAKK REMoDL-B trial (NCT01324596) (CRUKE/10/024). In these cases, cell of origin (COO) was determined by gene expression profiling (GEP) using Illumina WG-DASL.

Results: *EZH2* mutations were detected in 9% of DLBL pts (98/1052) by SS and 15% (54/365) by NGS. Ninety-five percent of mutations were at Y646 position in exon 16. *EZH2* mutations were strongly associated with GCB subtype, occurring in 27% of cases (50/185) versus 0/106 in ABC subtype and (4/71) in unclassified subtype ($P < .0001$). Overall, *EZH2* mutations were not significantly associated with age, sex, performance status, stage, or IPI, compared to unmutated GCB DLBL. PFS was similar between *EZH2* mutated and unmutated GCB DLBL subtype: 78.5% vs 80.7% at 30 months, HR 1.06 (95% CI, 0.62-1.81) ($P = .844$). A subset of GCB cases showed Burkitt-like GEP, associated with inferior progression free survival (PFS) HR 2.21 (95% CI, 1.28-7.73) ($P = .012$), among which 11/24, where mutation status was available, had *EZH2* mutations. There was heterogeneity in progression free survival identified by presence or absence of *EZH2* mutations and Burkitt-like gene expression signature.

Conclusions: *EZH2* mutations are significantly associated with the DLBL GCB-subtype and more common in cases identified as Burkitt-like by GEP. Overall outcomes are similar in mutant and wild-type cases when adjusted for COO and IPI, but Burkitt-like cases that carry *EZH2* mutations may be a preferential subset in which to test targeted therapies.

Keywords: diffuse large B-cell lymphoma (DLBCL); *EZH2*; GCB lymphoma subtype

154 PRELIMINARY EVIDENCE OF A MOLECULAR PREDICTOR OF TAZEMETOSTAT RESPONSE, BEYOND *EZH2* MUTATION, IN NHL PATIENTS VIA CHARACTERIZATION OF ARCHIVE TUMOR AND CIRCULATING TUMOR DNA

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Introduction: B-cell malignancies may depend on the histone methyl transferase *EZH2* to perpetuate a less differentiated state, with activating mutations (MT's) of *EZH2* being potential oncogenic drivers. Tazemetostat, a potent, selective *EZH2* inhibitor, is in phase 2 clinical development in relapsed or refractory (RR) NHL. Objective responses were observed in patients (pts) with MT or wild type (WT) *EZH2* tumors in phase 1. The ongoing phase 2 study enrolls pts with MT or WT *EZH2* RR DLBCL or FL to determine efficacy and safety (reported separately). The primary endpoint is overall response rate (ORR). Here, we report results of a molecular analysis of patient tumor material and associations with preliminary response data, including the discovery of a novel candidate molecular predictor of tazemetostat response.

Methods: Archive tumor and/or plasma derived circulating DNA (ctDNA) samples were obtained during screening in the phase 2 trial of tazemetostat in NHL (NCT01897571). Prospectively, archive tumor was analyzed for *EZH2* hot spot MT's Y646X, A682G, and A692V using a *cobas* *EZH2* mutation test (Roche Molecular Systems, in development). Retrospectively, next generation sequencing (NGS) was performed on archive tumor DNA (target coverage of 1500X) and ctDNA (20 000X for somatic MT's and 5000X for structural alterations) to identify somatic MT's, amplifications and translocations in a panel of 62 genes commonly mutated in NHL. Best ORR on January 26, 2017, was used to generate 2 groups, responders (CR + PR n = 25), and nonresponders (PD n = 43). Gene alterations associated with either group were identified using Fischer's exact test, and logistic regression modelling was used to identify multi gene predictors of response.

Results: Regardless of sample type or technology, the concordance rate for detection of *EZH2* status was >95%. NGS and *cobas* testing of archive tumor samples was 100% concordant (n = 92) with 11 *EZH2* MT cases detected. Concordance of *EZH2* status between

archive tumor and ctDNA samples was 97% (n = 125). EZH2 mutation detection rates in archive tumor were 9% in DLBCL and 21% in FL, consistent with previous reports. MT's in EZH2 or MYD88 in WT EZH2 pts were associated with response ($P < .1$) whereas MT's in HIST1H1E or MYC ($P < .08$) were associated with nonresponse. Pts matching a multi gene predictor consisting of WT MYC and/or HIST1H1E but with MT STAT6 and/or MYD88 in archive tumor had ORR = 53% (10/19) whereas pts who did not match this profile had ORR = 16% (12/73) indicating potential for these genes to predict response to tazemetostat.

Conclusions: Molecular genetic profiling of NHL pts identified potential predictors of response beyond EZH2 MT and offered new insights into mechanisms of response in EZH2 WT pts. Plasma-based ctDNA screening may be a viable method to identify NHL pts with EZH2 MT's in the absence of archive tumor samples.

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

155 ARRAY-BASED DNA METHYLOME ANALYSES OF PRIMARY LYMPHOMAS OF THE CENTRAL NERVOUS SYSTEM

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Introduction: Primary lymphomas of the central nervous system (PCNSL) are defined as diffuse large B-cell lymphomas (DLBCL) that are confined to the central nervous system (CNS). Epigenetic studies of PCNSL have mainly focused on DNA methylation profiling and are restricted to limited numbers of genes and/or PCNSL samples. To provide a more global view on this topic, we aimed at extending DNA methylation profiling of PCNSL as compared to systemic DLBCL towards a more genome-wide representation and more extensive series of cases.

Methods: We analyzed the DNA methylation of a total of 26 PCNSL using the Infinium HumanMethylation450 BeadChip Array (Illumina) and contrasted these findings to 79 DLBCL. As controls, we used publicly available DNA methylation data from a total of 50 normal brain samples derived from different regions of the CNS.

Results: Unsupervised cluster analysis of all lymphoma samples entering this study did not separate PCNSL and systemic DLBCL into different clusters. A supervised analysis of the DNA methylation between PCNSL and DLBCL yielded a total of 8279 CpG loci ($\sigma/\sigma_{\max} = 0.4$; $q < 1e-4$). After removal of the "brain signature" and correction of preservation-specific loci, we ended up with a final list of 2226 loci that are differentially methylated between PCNSL and DLBCL. Based on the 457 951 loci entering the analyses, these 2226 CpG represent $<0.5\%$

of the CpGs analysed. Considering a false-discovery rate of $q < 0.05$, this result indicates that PCNSL and DLBCL are strongly similar in their DNA methylation profiles and, if at all, differ only marginally. To address whether these minor, purely statistical differences in DNA methylation between PCNSL and DLBCL translate into biological implications, we further analysed these 2226 loci. First, we performed an unsupervised cluster analysis of the 26 PCNSL for these loci that did not separate them into different groups. Next, we investigated these 2226 loci by evaluating whether they are enriched in functional methylation modules previously described in normal B-cell differentiation. Remarkably, on a global level, they were significantly depleted for those CpGs involved in normal B-cell differentiation indicating that the differentially methylated CpGs are not closely associated to B-cell function. Moreover, the genes linked to the 2226 CpGs are enriched in polycomb targets in stem cells, which is a characteristic feature of CpG DNA methylation signatures linked to cancer and aging in general rather than being specific for a tumor subtype.

Conclusion: In conclusion, the detailed analyses of the 2226 CpGs differentially methylated between PCNSL and DLBCL with regard to biological meaning suggests a rather unspecific cancer effect rather than a specific role in B-cell lymphomagenesis. Hence, our findings support those of our previous study and indicate that the landscape of DNA methylation of PCNSL is similar to DLBCL.

Keywords: diffuse large B-cell lymphoma (DLBCL); epigenetics; primary CNS lymphoma (PCNSL)

156 TUMOR GENOMIC COPY NUMBER ABNORMALITIES ANALYZED BY HIGH RESOLUTION SNP ARRAY IMPACT OUTCOME OF PRIMARY CNS LYMPHOMA: A RETROSPECTIVE ANALYSIS ON 68 PATIENTS

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Introduction: Primary CNS lymphomas (PCNSL) are non-Hodgkin lymphomas involving the brain, the eyes, and meninges with a poor prognosis. The objective of this study is to better understand tumor genomic alterations in a retrospective cohort of 68 PCNSL and correlate them with prognosis.

Methods: This cohort was assembled from 271 consecutive PCNSL treated at Lyon University Hospital between 1984 and 2015 with available frozen brain tumor tissue. The 68 selected PCNSL were diffuse large B-cell lymphoma treated between 2003 and 2015 with a curative intent. All but one patient were treated in first-line therapy with high-dose (HD) methotrexate-based chemotherapy, and 52 patients received HD cytarabine (76%). Tumor DNA from cryopreserved samples was run on a high-resolution single-nucleotide polymorphism Cytoscan HD array (Affymetrix). Data was preprocessed using RawCopy then segmented and called using ASCAT2. Significantly recurrently altered regions were identified by the GISTIC 2.0 algorithm. Clinical parameters were correlated to somatic copy number alterations identified by GISTIC by comparing for each region the patients altered to those not altered using the Log-Rank test for progression free survival (PFS) and overall survival (OS) and Fisher Exact test for other variables. Benjamini Hochberg adjustment was used to correct for the number of peaks tested. This study was supported by the SIRIC LYric Grant INCa-DGOS-4664 and INSERM-ITMO Cancer 2014.

Results: Clinical characteristics were as follows: median age, 71 years (range, 24-87); poor performance status (PS, 2-4) 51%; deep brain involvement, 62%; high LDH level, 46%; high CSF protein, 70%. The IELSG score was 0 to 1 in 18% of the patients, 2 to 3 in 50%, and 4 to 5 in 32%. With a median follow-up of 54.63 months, the 5-year PFS and OS rates were 22% (95%CI, 14-36) and 42% (95%CI,31-56), respectively. The most frequent genomic deletions were 6p21.32 (HLA), 6q21, 8q12.1 (near TOX), 9p21.3 (CDKN2A), 12p13.2 (ETV6), 17p13.1 (TP53 region), and 19p13.11 (near MEF2B). Chromosome 19q13.43 was the most frequent region gained. For survival analyses, genomic deletion 12p13.2 impacted significantly PFS (HR = 6.4; 95% CI, 2.94-13.89; P = 2.89E-6) and OS (HR = 5.03; 95% CI, 2.39-10.59; P = 8.60E-5). The prognosis of the 10 patients representing 15% of the cohort with a focal ETV6 deletion at 12p13.2 had a very poor outcome with a median PFS of 0.14 (0.11-NA) and 1 year (0.68-2.97) for altered and nonaltered groups, respectively (P < .0001). The median OS were

0.17 year (0.12-NA) and 3.45 years (1.48-NA) (P < .0001) for these 2 groups, respectively (Figure).

Conclusions: To our knowledge, this is the largest study that investigates genomic alterations in PCNSL confirming recurrent genomic imbalances at 6p21.32, 6q21, 8q12.1, 9p21.3, 12p13.2, and 19p13. We showed for the first time that ETV6 deletion is significantly associated with shorter PFS and OS.

Keywords: Array-comparative genomic hybridization; primary CNS lymphoma (PCNSL)

157 CHARACTERIZATION OF MEDIASTINAL LYMPHOMAS IN FEMALE SIBLINGS AND IDENTIFICATION OF TIRAP AS A NOVEL LYMPHOMA RISK GENE

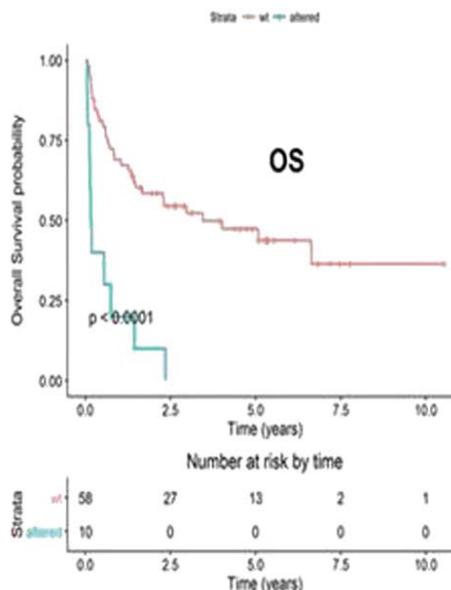
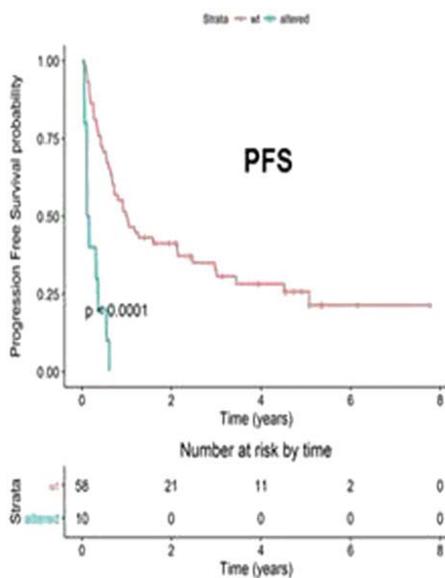
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Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common malignant lymphoma in adults. The vast majority of cases arise sporadically, yet familial clustering is known, suggesting a genetic contribution to disease risk. Familial lymphoma cases are a valuable tool that might identify novel lymphoma risk genes and contribute to a



better understanding of the sporadic cases. Here, we studied a Swiss/Japanese family with 2 female siblings affected by a primary mediastinal B-cell lymphoma (PMBL) and a non-germinal center (GC) DLBCL with features of PMBL, respectively. While the PMBL patient died with primary progressive disease, the non-GC DLBCL patient remains in an ongoing remission.

Methods: We performed whole-exome sequencing (WES) on matched tumor (FFPE tissue) and germline DNA (PBMCs) of the affected siblings and DNA of their family members. Exomes were enriched using the Illumina TruSeq 62 Mb kit, and sequencing was performed on an Illumina HiSeq2000 (2x100bp reads). GATK Haplotype Caller was used to detect germline variants, while somatic alterations were called by Strelka and SomaticSniper. To identify lymphoma susceptibility mutations, we focused on rare, putatively harmful variants with an in silico predicted link with cancer and malignant lymphomas that are present in the affected siblings. Mutations that were present as homozygous in unaffected family members were excluded. In both DLBCLs, genome-wide copy number alterations were analyzed by array comparative genomic hybridization using the Agilent 180 k array.

Results: The somatic mutational landscape of both lymphomas was marked by multiple alterations affecting various components of the JAK-STAT pathway. Consequently, this pathway was constitutively activated as evidenced by high pJAK2 and increased nuclear pSTAT3 and pSTAT6 in lymphoma cells. In addition, we identified molecular features associated with a worse clinical outcome including *TP53* and *B2M* mutations, *MYC* and *REL* gains, *CIITA* translocation, and *PDL1* expression on malignant cells in the sibling with a PMBL that died of primary progressive disease. By WES, we discovered a heterozygous mutation in *TIRAP*, an upstream regulator of NF- κ B, in the germline DNA of both affected siblings and their Japanese mother. We observed increased B-cell proliferation in family members carrying the *TIRAP* R81C variant. B-cell proliferation correlated with *TIRAP* and NF- κ B target gene expression, suggesting enhanced NF- κ B pathway activity in *TIRAP* R81C individuals. Knocking down *TIRAP* reduced both B-cell survival and NF- κ B target gene expression, the latter particularly in *TIRAP* mutated individuals.

Conclusions: Through the identification of an inherited *TIRAP* mutation, we provide evidence for a novel link between genetic alterations affecting components of the NF- κ B pathway and lymphomagenesis.

Keywords: diffuse large B-cell lymphoma (DLBCL); NF- κ B; primary mediastinal large B-cell lymphoma (PMBL)

158 PROGNOSTIC VALUE OF IMMUNOHISTOCHEMICAL MARKERS IN STAGE III/IV CLASSICAL HODGKIN LYMPHOMA TREATED FRONTLINE IN THE LYSA EORTC 20012 RANDOMIZED PROTOCOL

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Introduction: Clinical evolution of classical Hodgkin lymphoma (cHL) cannot be always predicted by clinico-biological or radiological parameters. Given the high treatment-related morbidity of some clinical trials, it should be interesting to get some other prognostic parameters to help to predict cHL patients evolution. Some immunohistochemical (IHC) markers have been already published as prognostic in cHL, but their value is still matter to debate. In the LYSA H3/4 trial that compares patients with stage III to IV cHL in a phase III who were assigned to either doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD, 8 courses) or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escBEACOPP_{x4} and BEACOPP_{x4}) without radiation therapy, we have tested 12 IHC markers in order to determine if some of them could predict different progression free survival (PFS) or overall survival (OS).

Methods: The H3/4 trial includes both high (n = 549) and low risk (n = 150) patients, and we obtained all data for 165 patients (106 high and 59 low risk). CD20, CD3, CD68, CD163, CD117, TIA1, FoxP3, ICOS, CD10, CXL13, PD1, and PDL1 antibodies were performed on Tissue Micro Arrays (TMA) of these 165 cases. Most of these markers were evaluated on the cHL microenvironment by counting the absolute number of cells stained when they were few or the percentage of cells stained on the TMA when they were numerous. For PDL1, we evaluated the number of both microenvironmental cells and Reed-Sternberg (RS) cells stained. These results were compared with the clinical data base of patients. For each variable, different cutoffs were studied on PFS and OS.

Results: Patients characteristics were similar to those of the total population: median age (31 y), male sex (66%), nodular sclerosis histology (83.3%), stage IV (61%), B symptoms (73%), IPS > 2 (66%), bulky disease (26.5%), and bone marrow involvement (16%). Half of the patients received ABVD or escBEACOPP. A total of 82.4% achieved a CR/Cru at the end of treatment. Twenty-three relapsed, and 14 died with a 5-year median follow-up. The IHC study revealed a marked expression of macrophages and lymphocytes markers. None of them was associated with the OS by statistical evaluation. By contrast, we found that a low count of TIA1+ cells in the cHL microenvironment (median=29) and a high number of RS cells PDL1+ (=100) were significantly associated in a multivariate analysis with a worse PFS (TIA1: HR; 95% CI = 5.33; [1.62, 17.52] and PDL1: HR; 95% CI = 5.01; [1.39, 18.05]).

Conclusion: In this large and unselected series of advanced cHL, we do not find prognostic significance of tumor associated macrophages nor

of other lymphoid markers tested in this trial. However, we showed that a low count of TiA+ cells in cHL microenvironment and a high number of RS cells PDL1+ are predictive of a worse PFS.

Keywords: Hodgkin lymphoma (HL); prognostic indices

159 IDENTIFICATION AND CHARACTERISATION OF THE LYMPHOMA- INITIATING CELL (LIC) POPULATION IN AN ALCL MOUSE MODEL

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The constitutively active oncogenic tyrosine kinase NPM-ALK is expressed in 60% of ALCL patients. Immunophenotypic characterization of human ALCLs revealed highly CD30-positive cells of T- or Null-cell-origin. However, the origin of the lymphoma-initiating cell population as well as NPM-ALK signal transduction in course of the disease remains unclear.

In this regard, we established a retroviral murine BM transplantation model resembling human ALCL. Therefore, we use an inducible Cre/loxP system, where NPM-ALK expression is restricted to early T-cells. Lethally irradiated recipient mice were transplanted with BM of Lck-Cre transgenic mice infected with a MSCV-Stop-NPM-ALK-IRES-EGFP construct. With 4 to 5 months, mice developed CD30-positive lymphomas and died from neoplastic T-cell infiltration of lymphatic organs.

Immunophenotypic analysis confirmed T-cell origin of the lymphomas with a heterogeneous compound of all T-cell stages with mainly CD4⁻/CD8⁻ double negative (DN) T-cells including all DN T-cell stages as well as hematopoietic stem cells and lymphatic precursors. Staining of the T-cell subpopulations demonstrated high NPM-ALK expression in immature CD4⁻/CD8⁻ DN T-cells and undifferentiated CD4⁺/CD8⁺ double positive (DP) T-cells with highest expression of proliferation marker Ki67 as well as the activation marker CD30 in the CD4⁻/CD8⁻ DN T-cells. Interestingly, the CD4⁻/CD8⁻ DN lymphoma population expressed aberrantly the T-cell receptor alpha/beta chain, which may allow these early T-cells to establish a systemic lymphoma.

To further identify the LIC population, we performed secondary transplantations with sorted DN and T-cell subpopulations. Indeed, only mice transplanted with DN3 and DN4 lymphoma cells could give rise to secondary lymphomas, whereas sorted DN1, DN2, CD4⁺, CD8⁺ or CD4⁺/CD8⁺ transplanted lymphoma cells failed to established serial lymphomas in recipient mice.

Immunophenotypic analyses of secondary lymphomas caused by transplantation of DN3 and DN4 lymphoma subpopulation

demonstrated CD4⁺/CD8⁺ DP cells as well as single positive CD4⁺ and CD8⁺ cells next to the DN3/DN4 population. However, we were not able to detect redifferentiation of the DN3/DN4 cells to more immature DN1/DN2 lymphoma cells. To substantiate our findings, we performed microarray analyses. Indeed, heatmap analyses revealed wide pattern similarities in the DN3 with DN4 lymphoma subpopulation in contrast to the DN1 and DN2 lymphoma cells. Interestingly, DN3 and DN4 cells show different expression profiles of stemness genes resembling early progenitor cell distribution patterns.

In summary, our results highlight the existence of a lymphoma initiating stem-cell-like population originated within the DN3/DN4 lymphoma cell population in a highly relevant NPM-ALK positive CD30-expressing ALCL mouse model, thereby giving the opportunity to test the eradication of the LIC with established and new therapeutical approaches.

Keywords: anaplastic large cell lymphoma (ALCL); mouse models

160 ONCOGENIC ACTIVATION OF STAT3 PATHWAY DRIVES PD-L1 EXPRESSION IN NATURAL KILLER/T CELL LYMPHOMA

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Introduction: Natural killer/T-cell lymphoma (NKTL) is a rare type of non-Hodgkin lymphoma that occurs more frequently in East Asia and Latin America and is associated with Epstein-Barr virus infection. Recent whole-exome sequencing studies in NKTL have reported recurrent somatic mutations in genes associated with JAK-STAT pathway. We sought to determine the contribution of aberrant JAK-STAT signalling to PD-L1 mediated immune checkpoint evasion in NKTL.

Methods: To determine the prevalence of JAK-STAT pathway alteration in NKTL, we performed targeted sequencing of 188 genes associated with JAK-STAT pathway in 110 NKTL (22 Singapore cases, 79 China cases and 9 cell lines). Single nucleotide variants and microindels were called using FreeBayes and candidate variants annotated using ANNOVAR. Stringent filtering was performed to remove germline variants based on information of dbSNP v137, COSMIC v69 and local germline databases and IGV inspection. Ba/F3 model system was used to test the transformation capacity of identified variants. Cell lines were evaluated for PD-L1 expression by immunoblotting and flow cytometry. Tissue microarrays (TMA) were examined for p-STAT3 and PD-L1 expression by immunohistochemistry.

Results: Recurrent mutations were most frequently located in STAT3 (25/110 cases, 23%) followed by TP53 (13/110 cases, 12%) and JAK3 (9/110 cases, 8%). A total of 17 STAT3 variants were identified including known hotspot mutations (Y604F, S614R, G618R, N647I, D661Y) and novel mutations in the coiled coil (D171N, R278H), DNA-binding (Q344H, D427H, H410R, D566N), and SH2 domains (E616G, E616K, V667L, E696K, A702T, P715L). Characterization of

novel E616K mutant showed that E616K conferred IL3 independent growth to Ba/F3 cells, increased not only p-STAT3 but also PD-L1 expression. Consistent with these findings, PD-L1 was over expressed in cell lines harboring STAT3 mutations and a positive correlation between PD-L1 and p-STAT3 expression was observed in NKTL tumor tissue ($R = 0.51$, $P = .02$).

Conclusions: We characterized a novel-activating STAT3 mutant and demonstrated its ability to drive PD-L1 expression, which may promote tumor evasion from the antitumor immune response. The combination of PD-1/PD-L1 antibodies and STAT3 inhibitors might be a promising and novel therapeutic approach for NKTL in the future.

Keywords: JAK/STAT; non-Hodgkin lymphoma (NHL)

161 SAMHD1 IS FREQUENTLY INVOLVED IN T-CELL PROLYMPHOCYTIC LEUKEMIA (T-PLL) PATHOGENESIS

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Introduction: T-cell prolymphocytic leukemia (T-PLL) is a rare leukemia with an aggressive disease course, characterized by chemotherapy resistance and a short median survival. Inactivating mutations or deletions of ATM and gain-of-function mutations of JAK1/3 and STAT5B are recurrently involved in T-PLL pathogenesis. SAMHD1, encoding a GTP-activated dNTP triphosphohydrolase, has been described as a tumor suppressor gene, which is mutated in about 11% of CLL patients. As previously reported, inactivating mutations occurring in this gene are associated with higher intracellular dNTP levels and mediate most likely chemotherapy resistance.

Methods: CD3+CD4+ tumor cells from peripheral blood samples of 33 T-PLL patients were enriched to a purity of >95% by fluorescence-activated cell sorting (FACS) or magnetic activated cell separation (MACS). We performed single nucleotide polymorphism (SNP) microarray analysis ($n = 10$), next-generation RNA-sequencing ($n = 10$), targeted capture sequencing ($n = 28$), and exome sequencing ($n = 5$). CD3+ cells from 5 healthy donors enriched by MACS were included as controls. Validation of sequencing data was performed on DNA level for 40 candidate genes using a capture approach (Roche, NimbleGen seqcap choice). Selected mutations were validated by direct Sanger sequencing. Next generation sequencing was performed on Illumina HiSeq 2500. SAMHD1 protein levels of T-

PLL samples ($n = 9$) and positive healthy donor cells ($n = 2$) were analysed by Western blot.

Results: We confirmed previously described copy number variations (CNVs) on chromosomes 8, 11, and 22. Additionally, we observed recurrent losses and uniparental disomies (UPDs) on chromosome 20q11 (SAMHD1-including region) in 25% of patients. Sequencing results revealed clonal, nonsynonymous SAMHD1 mutations in further 18% of patients. These mutations matched the typical tumor suppressor gene mutation patterns. A contingency analysis revealed a significant negative association between ATM and SAMHD1 mutations (Fisher's exact test, $P = .02$). Heterozygous nonsynonymous mutations affecting the catalytic Histidine-Aspartate (HD) domain of SAMHD1 as well as homozygous frameshift mutations resulted in a nearly complete loss of the protein. A heterozygous mutation mapping outside any domain and a further UPD on Chr20q resulted in reduced SAMHD1 protein expression. These results point towards a role of SAMHD1 as a potential tumor suppressor in T-PLL, thereby mediating chemotherapy resistance and providing T-PLL cells a further survival benefit next to ATM dysregulation.

Conclusions: Genetic profiling of T-PLL identified novel CNVs and mutations in SAMHD1, supporting its role as a potential tumor suppressor gene and revealing an additional mechanism in the molecular pathogenesis of T-PLL.

Keywords: CD4; T-cells

162 TRANSLOCATIONS INVOLVING CD28 ARE RARE IN PERIPHERAL T-CELL LYMPHOMAS

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Introduction: Peripheral T-cell lymphoma (PTCL) represents a group of aggressive neoplasms of mature T cells with heterogeneous molecular background. Recently, different gene rearrangements fusing CD28 to CTLA4 or ICOS(CTLA4(ex3)_CD28(ex4); CTLA4(ex1)_CD28(ex2); CTLA4(ex2)_CD28(ex4); and ICOS(ex1)_CD28(ex2)) were discovered by RNA sequencing analysis in AITL (angioimmunoblastic T-cell lymphoma), CTCL (cutaneous T-cell lymphoma), or ATLL (adult T-cell leukaemia/lymphoma). While available RNAseq data suggest that these gene fusions are overall rare (2.5%-5% of PTCLs), a high frequency of CTLA4(ex3)_CD28(ex4) fusion was found (38%) in a large series of

AITL, PTCL-NOS, and ENKTCL (extranodal natural killer/T-cell lymphoma) FFPE samples screened by RT-PCR (*Haematologica*, June 2016; 101(6)). Here, we screened by RT-PCR the above described CD28 fusions in 257 frozen diagnostic tumor samples (104 AITL, 25 T-follicular helper-derived [TFH] PTCL, 59 PTCL-NOS, 26 CTCL, 14 ENKTCL, 11 EATL [enteropathy associated T-cell lymphoma], 9 ALK-negative ALCL [anaplastic large cell lymphoma], 6 ATLL, and 3 HSTL [hepatosplenic T-cell lymphoma]) from the Tenomic biobank.

Methods: 500 ng of trizol-extracted and quality-controlled mRNA (bioanalyser) was reverse-transcribed using SuperScript III enzyme and random hexamers. CD28 fusions and beta-actin (internal control, 198 bp) PCR products were analyzed by agarose gel electrophoresis. Three fusions were cloned into expression vector and transduced into HEK293T cells to generate positive controls. All positive samples and a subset of negative samples were cross-validated in 2 different laboratories.

Results: CD28 fusions were detected in 13/257 (5%) cases (8 TFH-derived PTCL, 3 PTCL-NOS, 1 ATLL, and 1 CTCL). Three of these cases harbored 2 different translocations. The most common rearrangement was ICOS(ex1)_CD28(ex2) (11/16 fusions), followed by CTLA4(ex3)_CD28(ex4) (3/16 fusions) while the other two CTLA4 translocations were identified in one patient each. Thus, the prevalence of CTLA4(ex3)_CD28(ex4) fusion (found in one case each of TFH-derived PTCL, PTCL-NOS and CTCL) was 1.2%.

CD28 fusions were found in 8/129 (6.2%) AITL and other TFH-derived PTCLs. All the positive cases harbored ICOS(ex1)_CD28(ex2) rearrangement and one case with a dual rearrangement had an additional CTLA4(ex3)_CD28(ex4) fusion. In a subset of 85 TFH-derived PTCL also explored by targeted deep sequencing analysis, CD28 fusions in 4 patients were mutually exclusive to CD28 mutations. Overall, CD28 alterations in 12/85 (14%) of these patients did not impact OS or PFS. **Conclusion:** Known CD28 translocations with CTLA4 or ICOS are rare events in PTCL (5%) and are most commonly represented by ICOS(ex1)_CD28(ex2) fusion (69%).

Keywords: peripheral T-cell lymphomas (PTCL)

163 INTEGRATIVE ANALYSIS OF FEATURES ASSOCIATED WITH TET2, IDH2, DNMT3A, AND RHOA MUTATIONS IN ANGIOIMMUNOBLASTIC T CELL LYMPHOMA: A LYSA STUDY

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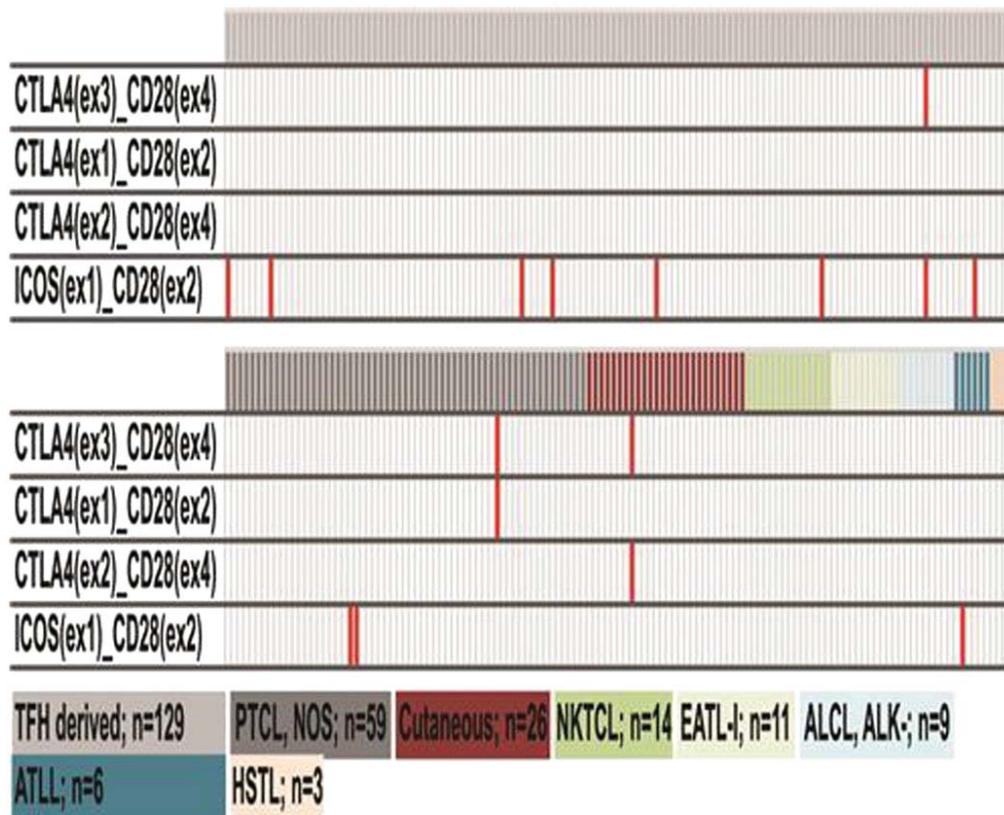


Figure 1. CD28 fusions in 257 PTCL samples. Samples are arranged in columns while fusions are in rows. A red square denotes the presence of a fusion.

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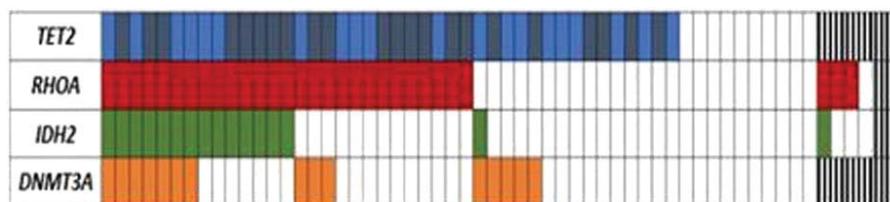
Introduction: Angioimmunoblastic T cell lymphoma (AITL) is the most frequent non-cutaneous peripheral T-cell lymphoma in Western Europe and is associated with a poor prognosis. Mutations in the epigenetic regulators TET2, IDH2, and DNMT3A, as well as in RHOA or in genes involved in the TCR signaling are frequent. However, as molecular studies have been performed so far on retrospective cohorts, with limited clinical and biological annotations, how these mutations correlate with other disease features is unclear.

Methods: Using data from 2 phase II clinical trials, evaluating rituximab CHOP (RAIL, NCT01553786) and lenalidomide CHOP (REVAL,

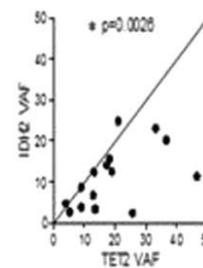
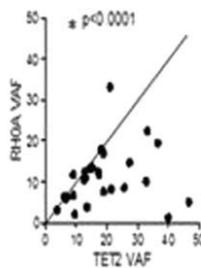
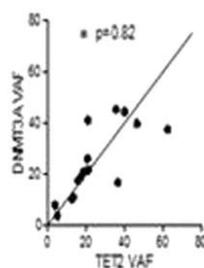
NCT00169156) combinations in untreated AITL, we performed an integrative analysis of clinical, pathological, molecular, and functional imaging parameters.

Results: Fifty-eight patients (RAIL = 16, REVAL = 42) with available monitored clinical data and sequencing data were included in this study. Median age was 69 years, sex ratio was 1/1, and IPI was ≥ 3 in 75% patients (Table). Pathology samples and PET CT were centrally reviewed. TET2, IDH2, DNMT3A, and RHOA sequencing was performed mainly on FFPE samples using the ion PGM (personal genome machine) system, with an in-house gene panel and bioinformatics pipeline. TET2 was mutated in 42/52 patients (81%), with more than one TET2 mutation in 22 patients. RHOA17V was detected in 30/56 (53%) patients, IDH2 mutation in 16/56 (29%), and DNMT3A mutation in 15/52 (27%). TET2 and DNMT3A VAFs were higher than RHOA and IDH2 VAFs, indicating that RHOA and IDH2 mutations could occur later during the oncogenesis (Figure). Using logistic or linear regression, we correlated these sequencing results with various parameters. Presence of TET2 mutation was associated with an age >65 years (OR = 5.0, $P = .03$), an IPI ≥ 3 (OR = 5.8, $P = .02$), and a higher prognostic Index for T-cell lymphoma (PIT) (0.65, $P = .02$) whereas RHOA, IDH2, or DNMT3A mutations did not significantly impact clinical presentation. We found an association between IDH2 mutation and a SUV max $>$ median (OR = 4.2, $P = .06$) and a total metabolic tumor volume $>$ 230 cm³ (OR = 18.18, $P = .009$) in PET CT. RHOA17V appeared to associate with a highly expanded follicular dendritic cell meshwork (OR = 20.2, $P = .008$).

Conclusions: Here, we further expanded the association of TET2 mutation with older age and high IPI in AITL patients. We also observed novel associations between the presence of RHOA or IDH2 mutation with functional imaging data or pathological features, providing new insights on the consequences of these mutations in AITL.



■ ≥ 2 TET2 mutation ■ 1 TET2 mutation ■ RHOA/IDH2/DNMT3A Mutation □ Sequencing failure



* VAF medians are compared with Wilcoxon rank-sum test

	N	Odds ratio[95%CI]			
		TET2 mut	RHOA mut	DNMT3A mut	IDH2 mut
Age>65 years	44/58 (76%)	5.00[1.13;23.079]	1.47[0.42;5.92]	1.28[0.32;6.55]	2.65[0.60;18.67]
IPI (3-5)	43/57 (75%)	5.83[1.29;27.96]	1.41[0.40;5.08]	1.01[0.24;5.25]	2.75[0.63;19.36]
PIT (3-4)	17/50 (35%)	6.00[0.95;117.51]	1.06[0.32;3.05]	2.20[0.56;8.80]	2.92[0.79;11.29]
FDC expansion	26/37 (70%)	4.44[0.78;28.59]	20.25[3.07;407.08]	1.41[0.26;11.11]	-
SUV max> median	21/42 (50%)	1.33[0.30;6.30]	1.21[0.36;4.16]	3.05[0.70;16.36]	4.22 [1.003;22.32]
TMTV total>230cm ³	24/42 (57%)	3.63[0.80;20.05]	1.67[0.48;5.89]	2.04[0.47;10.9]	12.14[1.97;236.86]

Keywords: angioimmunoblastic T-cell lymphoma (AITL); molecular genetics; positron emission tomography (PET)

HODGKIN LYMPHOMA

164 FOCAL SKELETAL 18FFDG UPTAKE CHARACTERIZES A SUBSET OF CLASSICAL HODGKIN LYMPHOMA PATIENTS WITH POOR OUTCOME—A DANISH-SWEDISH STUDY OF 209 NEWLY DIAGNOSED PATIENTS

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Introduction: 18F-fluoro-2-deoxy-D-glucose positron emission tomography/computerized tomography (18F-FDG-PET/CT) is a widely applied tool for the pretherapeutic staging of patients with newly diagnosed classical Hodgkin lymphoma (cHL). In fact, PET imaging has shown its ability to detect the existence of skeletal lesions and increased bone marrow uptake (BMU) in cHL, which were previously not recognizable based on CT technology alone. However, it is still unclear whether diffusely increased pretherapeutic BMU and/or focal skeletal lesions (uni- vs multifocal) represent an adverse prognostic feature in ABVD- or BEACOPP-treated cHL patients. It was therefore our aim to examine the prognostic value of PET/CT-assessed BMU and unifocal or multifocal bone lesions in newly diagnosed cHL patients.

Methods: A total of 209 patients from Aarhus (Denmark) and Uppsala (Sweden) university hospitals (mean age, 42 y; range, 8-83 y) with newly diagnosed cHL were included. BMU was calculated as SUVmax in the vertebral column divided by liver SUVmax. In case of focal skeletal 18F-FDG uptake, patients were subdivided into those having a unifocal skeletal lesion vs those displaying multifocal lesions. For survival analysis, 4 groups were analysed and compared: (1) Patients in

the lower median of BMU with no focal lesions (lowBMU), (2) patients in the higher median of BMU with no focal lesions (highBMU), (3) patients with a single focal bone lesion (unifocal), and (4) patients with multifocal bone lesions (multifocal).

Results: Median BMU was 1.28 (range, 0.52-5.57). Forty patients (19.2%) had either unifocal (N = 20) or multifocal bone lesions (N = 20). With a median follow-up time of 38 months, the 3-year PFS of the different groups was 80% for "lowBMU," 87% for "highBMU," 69% for "unifocal," and 51% for "multifocal" patients. Hence, the presence of bone lesions, regardless of whether unifocal or multifocal, was associated with a significantly inferior PFS (log rank $P = .0001$). No difference in PFS between unifocal and multifocal lesions was observed (log rank $P = .25$). In a multivariate analysis (Cox regression), presence of bone lesions and age were independent predictors of PFS whereas sex, hemoglobin, albumin, and sedimentation rate were not. Notably, the inferior outcome in patients with focal skeletal lesions was observed regardless of whether they had received an ABVD or a BEACOPP based first-line treatment.

Conclusion: Increased BMU at initial staging was not associated with an inferior prognosis, whereas the presence of focal bone lesions, adjusted for known risk factors, was associated with a poor prognosis regardless of whether the lesions were unifocal or multifocal. According to the present results, increased BMU should not be considered a risk factor in cHL, whereas unifocal or multifocal bone lesions should be regarded as equally important predictors of adverse outcome vis à vis of the current therapeutic options.

Keywords: extranodal lymphomas; Hodgkin lymphoma (HL); positron emission tomography (PET)

165 HISTOLOGICAL VERIFICATION OF POSITIVE POSITRON EMISSION TOMOGRAPHY FINDINGS DURING THE FOLLOW-UP OF PATIENTS WITH MEDIASTINAL LYMPHOMA: LARGE EXPERIENCE ON 96 PATIENTS

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Introduction: An important field of application of positron emission tomography (PET) is in the medium and long-term follow-up after complete response of Hodgkin lymphoma (HL) and aggressive non-Hodgkin lymphoma (NHL) with mediastinal involvement at diagnosis. The aim of this study was to verify the reliability of positive PET scans of the mediastinum in following up patients with mediastinal lymphoma, using histological findings as comparison (gold standard).

Methods: From January 2002 to February 2016, 483 patients with mediastinal lymphoma were followed after the end of front-line treatment. Ninety-six patients with a positive PET scan of the mediastinum underwent computed tomography scanning and surgical biopsy.

Results: For 67 HL and 29 NHL, a suspicion of lymphoma relapse was raised based on positive mediastinal PET scanning. Histology confirmed relapse in 63 (48 HL and 15 NHL) of 96 patients (65.6%). In the remaining 33 (34.4%) cases, biopsy revealed: necrotic tissue in 7 patients, fibrosis in 7 patients, thymus in 7 patients, sarcoidosis in 4 patients, tuberculous granulomas in 2 patients, sarcoid-like lymph node granulomatosis in 1 patient, tuberculosis lymph node granulomatosis in 1 patient, reactive inflammation lymph node in 3 patients, and thymoma in 1 patient. The maximum standardized uptake value was significantly higher among patients who had signs of relapse (63 true positive cases) than among those who stayed in remission (33 false positive cases), the median values being 10.30 (range, 3.2-25.0) and 5.0 (range, 2.8-12.6) respectively ($P < .05$).

Conclusions: The analysis on this large series of 96 patients confirms the concept that patients with positive PET in the mediastinum during the follow-up cannot be considered sufficient for final diagnostic purposes considering that at least one third of the patients can present only benign or, anyway, unrelated neoplastic pictures. Histological confirmation can be safely obtained by various biopsy techniques, the choice of which should be made on the basis of the clinical and imaging study findings case by case.

Keywords: positron emission tomography (PET)

166 SAFETY AND EFFICACY ANALYSIS OF ELDERLY PATIENTS TREATED WITHIN THE GATLA HL-05 CLINICAL TRIAL: PET ADAPTED THERAPY AFTER 3 CYCLES OF ABVD FOR ALL STAGES OF HODGKIN LYMPHOMA

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Introduction: Treatment of classical Hodgkin's lymphoma (cHL) in the elderly population remains a challenge. Prevalence of comorbidities, increased toxicity to standard treatments, and the lack of inclusion within clinical trials contribute to this phenomena. Results are often inferior compared to young adults, and there is a paucity of evidence regarding valid treatment approaches. Recently, the GATLA HL-05 protocol has reported the results of a PET/CT-adapted strategy after 3 cycles of ABVD, regardless of stage at presentation and without upper age limit for inclusion¹.

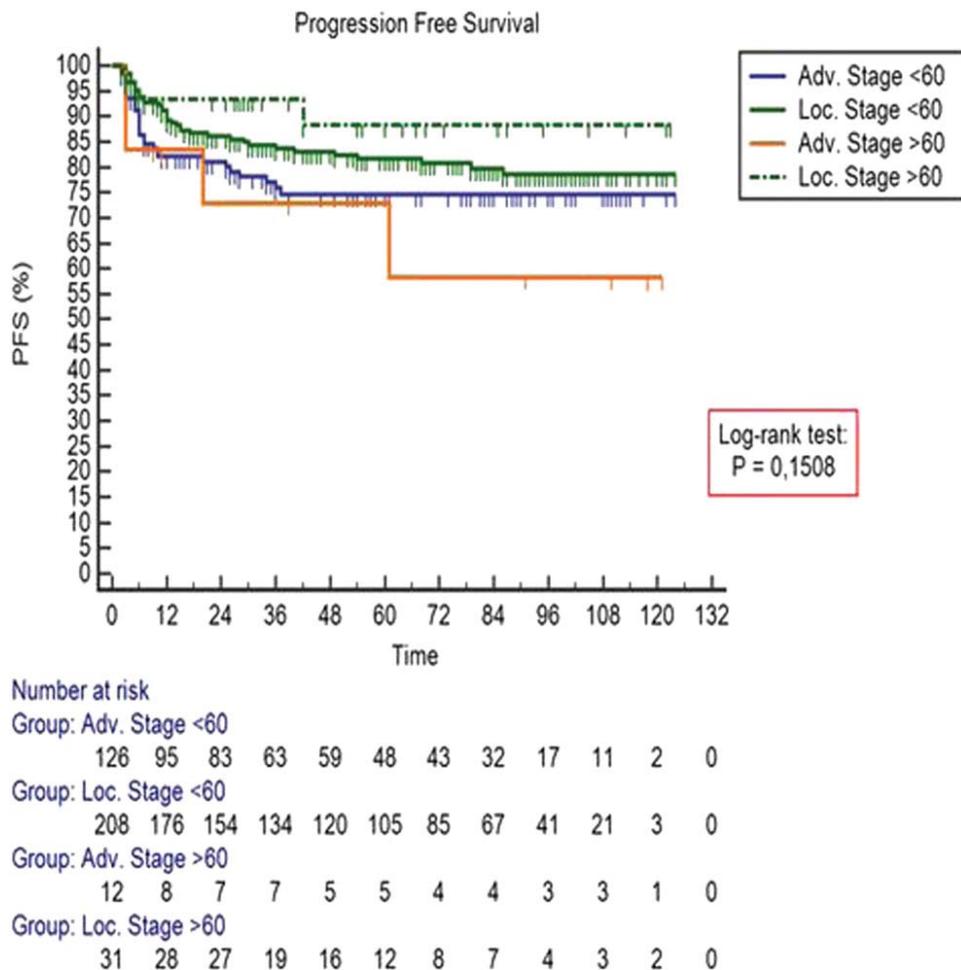
Methods: In order to evaluate the outcome of elderly patients included in this trial, a retrospective analysis was conducted on the HL-05 database. Patients (pts) equal or older than 60 years with a recent diagnosis of cHL and a negative HIV status were considered. Progression-free survival (PFS) was defined as time from treatment to relapse or death from any cause. Overall survival (OS) was defined as time from treatment to death from any cause. Duration of response (DOR) was defined as time from complete remission (CR) to relapse or death. The Kaplan-Meier and Log-rank test method were used for survival curves. The Pearson test was applied for comparison of variables within charts. An α level of 0.05 was regarded as significant.

Results: Of a total 377 pts enrolled within HL-05, 43 met inclusion criteria. With a median age of 66 yeays (range, 60-89 y), 90% had a performance status of 1 to 2. Nodular sclerosis was the most frequent histological subtype (60% of pts), and 72% of pts were early stage (I-II non-bulky disease). These characteristics were similar to the younger cohort. All pts received initial therapy with 3 cycles of ABVD and underwent evaluation with a PET/CT scan: 81% achieved a negative scan (Deauville scores, 1-2). Of the remaining 19% positive scans, 12% were compatible with PR and 7% with PD. No grade III/IV toxicity events or treatment-related deaths were reported. Within a follow-up period of 68 months, median PFS and OS have not yet been reached, and PFS was 88% at 36 months. In comparison to the younger cohort, response rates after 3 and 6 cycles of treatment were statistically similar. Furthermore, there were no significant differences within PFS, OS, and DOR curves. In a multivariate analysis including age, stage, bulky disease, and negative PET/CT after 3 cycles, older age was not a predictive factor related to PFS.

Conclusions: With a PET/CT-adapted therapy after 3 cycles of ABVD for 43 pts older than 60 years, 81% of pts reached a negative scan and thus received no further treatment. These pts had an excellent outcome with a PFS of 88% at 3 years, with no statistically significant differences compared to the younger cohort. The implementation of a PET/CT-guided strategy, regardless of stage at presentation, resulted in a reduced exposition to chemo and radiotherapy and may have contributed to the absence of severe morbidity or treatment-related deaths.

1 Pavlovsky A, Fernandez I, Kurgansky N et al. PET/CT adapted therapy after 3 cycles of ABVD to all stages of Hodgkin Lymphoma: GATLA trial HL-05. Oral Presentation. Abstract S108. EHA 2016 - Copenhagen.

Keywords: elderly; Hodgkin lymphoma (HL); positron emission tomography (PET)



167 ALLOGENEIC TRANSPLANTATION IN HODGKIN'S LYMPHOMA AFTER A FAILED AUTOGRAFT: LONG TERM OUTCOMES AND GRAFT-VERSUS-HOST DISEASE FREE/RELAPSE-FREE SURVIVAL (GRFS)

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Allogeneic stem cell transplantation (alloSCT) is a salvage option for a limited proportion of patients with refractory/relapsed (R/R) Hodgkin's lymphoma (HL). We retrospectively analyzed the outcomes of 62 consecutive patients allografted in a single center with a thiotepa-based reduced intensity conditioning. The aim of this study was to evaluate the long-term overall and progression-free survival (OS and PFS), the graft-versus host disease/relapse free survival (GFRS), and the chronic GVHD-free overall survival (cGVHD-free-OS) in a "real life" clinical setting. GFRS is a rather novel endpoint and is defined as survival without relapse and no acute grade ≥ 3 GVHD or cGVHD requiring treatment;

cGVHD-free-OS was defined as OS without moderate or severe cGVHD according to NIH cGVHD staging. In other words, we wanted to examine the proportion of patients in complete remission and not receiving any immune suppressive treatment.

Patients' median age was 33 years (range, 18-60 y). At alloSCT, 44% of patients were in CR, 31% in PR, 25% were in SD or PD; only 11% did not receive autologous transplant before alloSCT. Donors were HLA identical (42%), MUD (29%), or haploidentical (29%). Most patients received mobilized peripheral blood stem cells. Median follow-up was 5.4 years (range, 1.5-11.8 y). Five-year OS, PFS, and relapse were 59% (CI95% 47-74), 46% (CI95% 34-60), and 38% (CI95% 23-49). Non-relapse mortality (NRM) peaked at 17% (CI95% 6-26) at 1 year. Twenty patients had acute GVHD (32%, grade III 2%), 26 patients (42%) had cGVHD, 20 (32%) had moderate or severe cGVHD. Patients with cGVHD at last follow-up were 13 (21%), and those with moderate or severe cGVHD were 9 (14%). One-year GFRS was 34% (CI95% 24-49), GFRS at 5 years was 26% (CI95% 17-41). cGVHD-free OS was 58% (95% 47-72) at 1 year, and 51% (CI95% 40-65) at 5 years.

In multivariate analysis, GFRS was reduced in patients with SD or PD at transplant (HR = 2.29, CI95% 1.03-5.10, P=.040) because of a higher relapse rate. cGVHD-free OS was reduced in patients with SD or PD at alloSCT (HR = 4.91, CI95% 1.83-13.13, P = .001). T-depleted haploidentical graft reduced OS and NRM (HR = 3.81, CI95% 1.36-10.66, P = .010; HR = 7.63, CI95% 1.07-54.31, P = .042). Patients with

SD or PD had reduced OS, PFS, and relapse (HR = 4.01, CI95% 1.34-11.97, $P = .012$; HR = 5.54, CI95% 2.13-14.37, $P < .001$; HR = 6.75, CI95% 2.07-21.96, $P = .001$).

Long term OS in R/R HL is 59%; GFRS in these patients is 34% at 1 year and 26% at 5 years. Most patients allografted for R/R HL eventually survive without moderate to severe cGVHD and cGVHD-free OS is 51%. Therefore, this survival outcome should be the benchmark to compare results of novel drugs such as checkpoint inhibitors in R/R HL patients.

Keywords: allogeneic stem cell transplant (alloSCT); Hodgkin lymphoma (HL)

168 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 difficult therapeutic challenge as standard ABVD outcome in this patient subset proved unsatisfactory compared to adults. Bendamustine (Be) and brentuximab vedotin (BV) are well-tolerated and effective drugs in relapsing HL, but scarce and preliminary data exist on first-line treatment of elderly HL with this drug combination.

Patients and Methods: A prospective multicenter open-label phase I/II study was launched in 2015 aimed at assessing the safety and efficacy of Be-BV combination in elderly HL patients (HALO study). BV: 1.2 mg/kg D1 and Be 90 mg/m²/day were administered in days 1 and 2, every 3 weeks for 6 cycles, in advanced-stage (IIB-IVB) patients aged 60 to 80 years (NCT identifier, 02467946). A nondecisional FDG-PET after the second cycle: (PET-2) was planned and images centrally reviewed using the Lugano criteria and Deauville 5 point scale (DS). Patients with progressive disease at any time or not in CR after 4 cycles were addressed to salvage therapy. The study was split in 2 phases: a phase 1 (12 patients) aimed to assess the feasibility and phase 2 (48 patients) to assess the efficacy (CR rate) of Be-BV combination. Secondary endpoints were the efficacy of Be-BV combination (3-Y PFS and OS) and the prediction of treatment outcome by PET-2.

Results: So far, 22 patients have been enrolled. The mean age was 69,6 (62-79) and M/F ratio 14/8. Histology breakdown was HL, classic NOS, 6; classic, nodular sclerosis 9, classic mixed cellularity 7, and lymphocyte rich 0. Mean hemoglobin value was 12.82 gr/dl, WBC 9.09 × 10³/μl, Albumin 2.4 gr/l, LDH 452 U/l. The Ann-Arbor stage was IIB in 4, III in 9, and IV in 9 patients. B-symptoms were present in 14/22. IPS was 0 to 1 in none, 2 to 3 in 15, >3 in 7. The median Medical Outcome Study (MOS) physical function score was 52.5% (20-90) and 70% had a time to "up and go" score of >13.5 seconds. Twenty-one severe (grade 3-4) WHO toxicities were recorded neutropenia (9), thrombocytopenia (3), CMV reactivation (1) rash maculo-papular (1), drug hypersensitivity (1), liver toxicity (2), pulmonary embolism (1), stomatitis (2), pyrexia (1). No treatment-related deaths have been recorded, and the nonrelapse mortality is 0. Fifteen patients concluded the entire course of treatment: 13 (87%) achieved CR while 2 showed disease progression after 2 and 6 cycles. All 15 underwent PET-2: 12 were in complete metabolic response (DS score, 1-3); 1 patients had score 4 and achieved CR at the end of treatment. Two had score 5: both showed disease progression after 2 and 6 cycles. After a mean follow-up of 271 (135-445) days 10/15 (67%) are still in continuous CR: 2 showed disease progression during or immediately after treatment and 3/15 showed disease relapse, +303 days, +378 days, +488 days after registration.

Conclusion: Although preliminary, these data suggest that (1) the Be-BV combination is feasible and safe with a manageable hematological toxicity; (2) the drug combination is highly effective in elderly HL patients.

Keywords: bendamustine; brentuximab vedotin; Hodgkin lymphoma (HL)

169 REAL LIFE EXPERIENCE WITH BRENTUXIMAB VEDOTIN: THE ITALIAN STUDY ON 234 RELAPSED/REFRACTORY HODGKIN'S LYMPHOMA

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Introduction: Data from phase III studies may not be sufficient to determine the whole description of a drug in routine use: the assessment of drugs during daily clinical practice may reveal evidence of additional side effects or change in efficacy, triggering sometimes withdrawal or changing indication. Observational studies can be an objective way of mapping risks in the real life. Despite the known potential bias of all the retrospective observational studies, reports on the real life experience in lymphoma patients make an important contribution to medical knowledge prior to market authorization and widespread utilization.

Methods: A large Italian multicenter observational retrospective study was conducted on the use of brentuximab vedotin (BV) for patients with relapsed Hodgkin's lymphoma (HL) in the everyday clinical practice according to an Italian national law (Law 648/96: "medicinal products that are provided free of charge on the national health service" active for BV from November 2012 to July 2014") to check if clinical trial results are confirmed even in a real life context. Primary endpoint was the best response; secondary endpoints were the overall response rate at the end of the treatment, duration of response, survival, and the safety profile.

Results: Two hundred thirty-four CD30+ HL patients were treated. Best response was observed after a median of 4 cycles in 140 patients (59.8%): 74 (31.6%) patients obtained a complete response (CR) and 66 (28.2%) achieved a partial response (PR); overall response rate at the end of the treatment was 48.3% (62 CR and 51 PR). The best response rate was higher in the elderly subset (>60 y): 14 (50%) CR and 5 (17.8%) PR. Disease free survival was 26.3% at 3 years and progression free survival 31.9% at 4.5 years. We identified 30 long-term responders (patients with a response \geq 12 months) of whom 18 are still in CR, 7 with a consolidative SCT, and 11 without any consolidative procedure. Duration of response did not differ who achieved at least PR and then either did or did not undergo consolidative SCT. Overall, the treatment was well tolerated in everyday clinical practice, and the toxicity profile was closely similar to the previously published data; no death has been linked to BV-induced toxicity.

Conclusions: The results of this large retrospective study of 234 relapse/refractory HL in the daily practice support the BV efficacy with manageable toxicity superimposable to the one reported in clinical trials results; in particular, there is the confirmation of the similar activity in different settings, eg, in elderly patients, and of the response duration independently by the transplant consolidation. The relevance of

the CR status after 4 cycles and the role of BV as a bridge to ASCT for the chemorefractory patients were also pointed up.

Keywords: brentuximab vedotin; Hodgkin lymphoma (HL)

170 A PILOT STUDY OF BRENTUXIMAB VEDOTIN AND AVD CHEMOTHERAPY FOLLOWED BY 20 Gy INVOLVED-SITE RADIOTHERAPY IN EARLY STAGE, UNFAVORABLE RISK HODGKIN LYMPHOMA

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Introduction: The combination of brentuximab vedotin (BV) with AVD chemotherapy followed by 30 Gy involved-site radiotherapy (ISRT) for the treatment of early stage, unfavorable risk Hodgkin lymphoma (HL) has demonstrated promising efficacy and an acceptable safety profile in the first cohort of this pilot study (Kumar et al., Blood, 2016). In cohort 2, we evaluated whether the reduced dose of ISRT to 20 Gy decreased RT-related toxicity while maintaining efficacy.

Methods: Patients received 4 cycles of BV 1.2 mg/kg with AVD chemotherapy every 2 weeks followed by 30 Gy ISRT in cohort 1 and 20 Gy ISRT in cohort 2. Eligible patients had untreated stage I/II classical HL with any of the following unfavorable risk factors: bulky disease (maximal transverse or coronal diameter > 7 cm on CT), elevated ESR, extranodal involvement, >2 lymph node sites, or infradiaphragmatic disease. Patients with stage IIB disease with disease bulk or extranodal involvement were eligible. PET/CT after 2 and 4 cycles and ISRT were interpreted with the Deauville 5-point scale (negative = 1-3). The primary endpoint of cohort 2 was to evaluate preliminary efficacy by complete response (CR) rate.

Results: In cohort 2, 29 patients were enrolled from May 2015 to October 2016 with median age of 33 (range, 19-55), 100% stage II, 69% with disease bulk (>7 cm), 38% elevated ESR, 38% B-symptoms, 21% extranodal involvement, 69% >2 involved lymph node sites, and 3% infradiaphragmatic disease. Twenty patients (69%) had bulky anterior mediastinal masses, ranging from 7 to 17.3 cm. Nine patients (31%) had advanced stage disease by the GHSG criteria: IIBX (n = 7) and IIBXE (n = 2).

In cohort 2, 90% and 93% of patients achieved a negative PET scan after 2 and 4 cycles of therapy, respectively. Of the 2 patients with

positive PET-4 scans, one underwent a biopsy that was negative for HL, and the other had residual FDG-uptake in a location not amenable to biopsy. Both patients received ISRT. The 25 patients who completed combined modality therapy (CMT) have achieved CRs. To date, the duration of remission ranges from 2 to 13 months, and no relapses have occurred. The efficacy is similar across cohorts 1 and 2 with interim PET negative rates of $\geq 90\%$, and all patients who completed CMT have achieved a CR (Figure 1). In cohort 1, 2 patients had biopsy-proven primary refractory HL after 4 cycles of chemotherapy, and in cohort 2, there have been no treatment failures.

Conclusion: BV + AVD x 4 cycles followed by 20 Gy ISRT has promising preliminary efficacy for the treatment of early stage, unfavorable risk HL, including a high proportion of patients with bulky disease. As with 4 cycles of escalated BEACOPP tested in the GHSG HD11 clinical trial, 20 Gy ISRT may be adequate consolidation after BV + AVD x 4 cycles. We recommend that BV + AVD x 4 + 20 Gy ISRT is studied in a larger, randomized prospective study for early stage, bulky HL. Updated response data for all patients will be presented at the meeting.

Keywords: brentuximab vedotin; Hodgkin lymphoma (HL)

171 OUTCOMES OF TREATMENT FOR OBESE PATIENTS WITH ADVANCED HODGKIN LYMPHOMA IN THE RATHL TRIAL (CRUK/07/033)

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Introduction: With obesity levels increasing, optimal chemotherapy (CT) dosing for overweight patients is a significant issue. Although guidelines recommend obese patients should be dosed on full body weight, clinicians continue to cap doses through fear of excess toxicity. It is not clear whether this affects treatment outcomes, particularly in diseases treated in anticipation of cure, such as Hodgkin lymphoma (HL), where the role of body mass index (BMI) on survival is unknown. **Methods:** Adult patients (pts) with newly diagnosed HL (Ann Arbor stages IIB–IV, or IIA with bulk or ≥ 3 involved sites) underwent paired baseline and interim PET-CT scans after 2 cycles of ABVD (PET2).

Treatment was intended to be given at full dose and on schedule, irrespective of blood counts, provided pts were well. Pts with negative PET2 were randomized to ABVD or AVD for 4 more cycles. Pts with positive PET2 proceeded to intensification with BEACOPP-14 or escalated BEACOPP. BMI was recorded at trial entry, individual drug doses administered, and toxicity scores were recorded for each cycle.

Results: BMI data was analysed for 1199 eligible pts. A total of 25.4% were overweight (BMI 25–30), 14.9% obese (BMI 30–40), and 1.3% very obese (BMI 40+). CT doses of $< 90\%$ were given significantly more often to pts with BMI ≥ 30 in almost all cycles. For example in cycle 1: at least one drug was given at $< 90\%$ in 20% pts with BMI ≥ 30 , versus 12.4% of pts with BMI < 30 ($P = .008$). Grade III/IV neutropenia was not significantly different according to BMI however, nor was the use of G-CSF. Among 190 obese/very obese pts, dose reductions to $< 90\%$ did not significantly affect the risk of grade III/IV haematologic toxicity, but the PET2 results showed a trend towards more positive scans (19.4% vs 9.9%, $P = .1$). PFS and OS were not affected by dose reduction among the obese group, either across all pts or selecting only those with negative PET2. No significant difference in PFS or OS was detected when analysing the whole study population according to BMI.

Conclusion: Elective dose reductions were more common in pts with BMI ≥ 30 , but this did not reduce their risk of grade III/IV neutropenia. Conversely, administering full body surface area-based dosing for weight did not result in a higher incidence of grade III/IV haematology toxicity. Among obese pts, modest dose reductions do not appear to lessen the risk of myelosuppression or to adversely affect treatment outcomes, and in this study which mandated close adherence to dose intensity, there was no evidence of worse outcomes among obese pts.

Keywords: ABVD; Hodgkin lymphoma (HL); positron emission tomography (PET)

172 MORTALITY RATES REMAIN INCREASED IN YOUNG PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA EVEN AFTER YEARS IN REMISSION: RESULTS FROM A NORDIC LYMPHOMA Group STUDY

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Introduction: Classical Hodgkin lymphoma (cHL) is one of the success stories of modern oncology, and today, more than 90% of the patients are alive 5 years postdiagnosis. Late-onset toxicities have however been a major concern for long-term outcomes in younger cHL

survivors. As reports of such late effects are typically based on patients treated with outdated therapy, we therefore, in this study, compared mortality rates in young cHL patients with contemporary treatment to a sex, age, and calendar year matched group from the general population.

Methods: This study was based on the nationwide Danish and Swedish lymphoma registries. cHL patients diagnosed in the period 1995 to 2013 at the age of 18 to 49 years were included. These patients were treated with chemotherapy alone or received combination therapies that included involved node or involved field radiotherapy (RT). Standardized mortality ratios (SMRs) were determined at baseline and for patients who were event free (free from relapse and death) 60 months (EFS60) postdiagnosis.

Results: In total, 1012 Danish and 1412 Swedish patients were included. Patients were followed up to 20 years. Median ages were 31 and 29 years, and the male to female ratios were 1.26 and 1.04 for Danish and Swedish patients, respectively. The baseline SMR was 5.67 (95% CI, 4.61-6.91) for Danish patients versus 6.84 (5.55-8.43) for Swedish patients. The SMRs attenuated with longer time in remission in both countries. For patients reaching EFS60, the SMRs were 2.62 (1.72-3.81) and 2.54 (1.60-4.04) in the Danish and Swedish cohort, respectively (Table 1). Elevated SMRs were observed in virtually all clinical subgroups and were similar by country (Table 1). Pooled analyses and estimation of loss in expectation of life due to cHL will follow.

Conclusions: We observed a general trend over time of the mortality among the cHL patients approaching that of the general population conditional on longer time in remission. However, even in the modern treatment era, we could confirm the presence of long-term excess mortality even among patients that remained in remission up to 5 years.

Keywords: classical Hodgkin lymphoma (cHL)

173 PREDICTED CARDIAC AND SECOND CANCER RISKS IN HODGKIN LYMPHOMA PATIENTS TREATED WITH ADVANCED PROTON BEAM THERAPY COMPARED TO PHOTON RADIOTHERAPY

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Introduction: To estimate cardiovascular and second cancer risks for Hodgkin lymphoma (HL) patients treated with deep inspiration breath hold (DIBH) proton pencil beam scanning (PBS). To compare those risks with optimised DIBH photon radiotherapy (RT) delivered using both partial arc volumetric photon RT (PartArc) and field in field 3-dimensional conformal RT (3D-CRT).

Methods: Sixteen HL patients were treated with DIBH-PBS involved site RT at 30 Cobalt-Gray equivalent (CGE) in 15 fractions. The average age was 30.8 years (range, 18-48), and the average PTV volume was 1385 cc (range, 766-2134). For every patient clinically deliverable, PartArc and 3D-CRT plans were produced by a different institution. PTV coverage was evaluated and dosimetric parameters such as body integral dose (BDI), Dmean, Dmax, D2%, and V(5,10,20,30) Gy were compared for organs at risk including 12 cardiac substructures. Cardiovascular and second cancer risks were estimated using published dose-response relationships. Wilcoxon signed-rank test was used to assess statistical significance of the differences.

Results: There were no significant differences in PTV coverage between the 3 techniques, except from an increased V107% for 3D-CRT (419 cc) compared to PartArc (7 cc) and PBS (4 cc). The BDI for PBS (2.1 Gy) was 57.0% and 65.0% lower compared to PartArc (4.9 Gy) and 3D-CRT (5.9 Gy), respectively ($P = .007$). PBS reduced the mean dose to the heart, lungs, breast, oesophagus, and larynx compared to 3D-CRT and PartArc by between 1.0 and 5 Gy ($P < .05$). PBS increased the V30 Gy and D2% to the lungs, heart, and oesophagus compared to PartArc by 5.0%, 6.0%, 20.0% and 1.1 Gy, 2.0 Gy and 1.0 Gy, respectively ($P < .05$). There were no significant differences to the thyroid. The highest differences were observed in the spinal cord where PBS reduced the D2% and Dmax by almost 85.0% (25.0 Gy) compared to both photon techniques ($P < .05$). Cardiac and second cancer risks were estimated for the 3 techniques (see Table 1).

TABLE 1 Standardized mortality ratios (SMR) from diagnosis and conditioned on being event free at 2 and 5 years postdiagnosis

	SMR (95% CI) from diagnosis		SMR (95% CI) conditioned on 5-year EFS	
	Denmark	Sweden	Denmark	Sweden
All patients	5.67 (4.61 - 6.91) n = 1012	6.84 (5.55 - 8.43) n = 1412	2.62 (1.72 - 3.81) n = 716	2.54 (1.60 - 4.04) n = 943
Limited stage	3.51 (2.32 - 5.11) n = 426	3.41 (2.27 - 5.13) n = 651	2.34 (1.17 - 4.18) n = 323	1.50 (0.67 - 3.34) n = 460
Advanced stage	7.37 (5.77 - 9.28) n = 586	10.36 (8.09 - 13.26) n = 748	2.85 (1.63 - 4.63) n = 393	3.91 (2.22 - 6.88) n = 479
Male	4.87 (3.7 - 6.29) n = 560	6.68 (5.17 - 8.64) n = 721	2.46 (1.43 - 3.94) n = 390	2.11 (1.14 - 3.92) n = 472
Female	7.40 (5.31 - 10.04) n = 452	7.17 (5.02 - 10.26) n = 691	2.93 (1.40 - 5.39) n = 326	3.42 (1.71 - 6.84) n = 471
2-4 cycles of chemotherapy and RT	2.88 (1.49 - 5.03) n = 309	2.98 (1.76 - 5.03) n = 416	3.00 (1.20 - 6.18) n = 227	1.05 (0.34 - 3.25) n = 322
6-8 cycles of chemotherapy and no RT	5.87 (4.3 - 7.83) n = 498	7.61 (5.26 - 11.03) n = 515	1.86 (0.80 - 3.66) n = 340	3.56 (1.60 - 7.92) n = 333
Age 18-34	9.79 (7.29 - 12.87) n = 599	8.45 (6.35 - 11.25) n = 975	3.34 (1.60 - 6.13) n = 416	3.77 (2.09 - 6.82) n = 679
Age 35-39	3.92 (2.89 - 5.20) n = 413	5.62 (4.14 - 7.63) n = 437	2.32 (1.35 - 3.72) n = 300	1.68 (0.80 - 3.53) n = 264

Abbreviations: CI, confidence interval, RT, radiotherapy.

TABLE 1 Cardiac and second cancer risks predicted for HL patients

Cardiac Risk	3D-CRT	95% CI	PartArc	95% CI	PBS	95% CI
AER 30-year Cardiac Mortality (%)	2.00	0.88-3.11	1.59	0.67-2.51	1.26	0.67-1.86
RR CHF (based on MHD)	1.09	0.97-1.22	1.04	1.00-1.09	1.02	1.01-1.03
RR CHF (Based on LVD)	1.21	0.99-1.42	1.12	1.00-1.24	1.04	1.01-1.08
RR VHD	1.76	1.41-2.11	1.47	1.21-1.72	1.27	1.08-1.47
RR CHD	1.84	1.56-2.12	1.67	1.43-1.91	1.57	1.40-1.75
Second Cancer Risk						
RR Breast	1.41	1.21-1.62	1.40	1.21-1.59	1.23	1.13-1.34
RR Lung	2.55	2.32-2.78	2.32	2.13-2.51	1.79	1.68-1.91
RR Oesophagus	8.25	7.51-8.99	7.62	7.02-8.21	6.61	6.07-7.15

Conclusions: PBS reduced predicted cardiac and second cancer risks for HL patients compared to 3D-CRT and PartArc RT

Keywords: Hodgkin lymphoma (HL)

174 CARDIAC DISEASE PREDICTION FOLLOWING HODGKIN LYMPHOMA: AN EORTC LYMPHOMA GROUP AND GELA FOLLOW-UP STUDY

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Introduction: Hodgkin lymphoma (HL) survivors are known to suffer from an excess risk of cardiac disease (CD) due to radiation and anthracyclines. However, CD is also associated with other risk factors. The purpose of the study was to evaluate the impact of treatment and patient characteristics on the risk of subsequent CD in the EORTC (European Organisation for Research and Treatment of Cancer)-GELA (Groupe d'Étude des Lymphomes de l'Adulte, now LYSA) cohort of HL patients treated in 9 randomized trials from 1964 to 2004 (n = 6658). **Methods:** Incidence of CD was reported during follow-up and through a patient-reported questionnaire (LSQ), mailed in 2009 to 2010 (56.7% of all patients alive with known address). Comorbidities were registered

at LSQ completion. A multivariate Cox proportional hazards regression model on first CD, stratified by trial, was fitted on treatment variables (mean radiation dose to the heart and cumulative doses of anthracyclines and vinca-alkaloids) as well as patient characteristics at treatment start (age, gender, country, gender*age, smoking, family history of CD, BMI). Model reduction was performed with the backward selection procedure at a 5% threshold level. Estimated hazard ratios (HRs) were presented with their 95% confidence intervals (CI) and tested at the 5% two-sided significance level. Data from H1 to H8 trials were used to build the model; the model validation was performed based on H9 trial data using measures of discrimination (C-index).

Results: A total of 1919 patients responded to the LSQ, 49% were males and the median age at treatment start was 29 years (range, 10-69). A total of 85.9% had early-stage disease, and 1293 patients received both radiotherapy and anthracyclines. The median duration of follow-up was 14 years (range, 5-44). A total of 416 patients (21.7%) reported CD events. The model built included mean radiation dose to the heart (HR = 1.02 per Gy increase; 95% CI, 1.00-1.03; P = .019), cumulative dose of anthracyclines (HR = 1.17 per 100 mg/m² increase; 95% CI, 1.00-1.37; P = 0.05), age (HR = 1.04 per year increase; 95% CI, 1.03-1.05; P < .001), and BMI (HR = 1.05; 95% CI, 1.02-1.09; P < .001). The resulting linear predictor was LP = [0.017 × heart dose] + [0.002 × dose anthracyclines] + [0.037 × age] + [0.053 × BMI]. The C-index was moderate at 0.57 (95% CI, 0.39-0.74). There was a strong association between CD and post-treatment smoking and comorbidities such as high blood pressure, high cholesterol levels, diabetes, and elevated BMI.

Conclusions: Following treatment for HL, the subsequent risk of CD is influenced by radiation dose to the heart, the cumulative dose of anthracycline but not vinca-alkaloids, and age and BMI at treatment start. However in this cohort of HL patients, the overall cardiac risk is only partly explained by treatment exposure. The poor model performance (low C-index) may be explained by important posttreatment events such as later occurrence of established cardiac risk factors.

Keywords: Hodgkin lymphoma (HL)

175 USEFULNESS OF N-TERMINAL BRAIN NATRIURETIC PEPTIDE LEVELS AND FRESCO SCALE FOR THE PREDICTION OF ANTHRACYCLINE-INDUCED

CARDIOMYOTOXICITY IN PATIENTS WITH HODGKIN LYMPHOMA

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Introduction: Cardiomyotoxicity is a characteristic adverse effect of anthracyclines that may occur both acute/subacute and long term. Early detection of asymptomatic cardiac dysfunction may be important to prevent irreversible heart damage. Recently, our group has demonstrated that baseline NT-proBNP levels and FRESKO scale are accurate predictors of anthracycline-induced cardiomyotoxicity (AIC) in diffuse large B-cell lymphoma patients treated with R-CHOP, and can identify groups of patients with different risk. Our aim was to validate the usefulness of NT-proBNP and FRESKO scale for the prediction of AIC in adult patients with Hodgkin lymphoma (HL) treated with anthracycline containing-chemotherapy.

Methods: Ninety five pts with HL from 05/2004 to 05/2014. Excluded: HIV infection (8), other causes (13). Left ventricular ejection fraction (LVEF) determined by high resolution echocardiography and NT-proBNP were performed prior initiation of treatment, at the end and every 6 to 12 months thereafter. AIC was defined as LVEF <55%, decrease >15% if prior LVEF <55% and/or clinical manifestations of heart failure (CHF). FRESKO scale for predicting 10-year cardiovascular risk was used. C statistic was determined for the different values of NT-proBNP and FRESKO scale, and competitive risk analysis was performed in the evaluation of AIC.

Results: Median age 37 years (IQR, 17-78), 54% male, median NT-proBNP 71.1 pg/mL (IQR, 4-5252), median LVEF 65% (IQR, 54-76%), and medium scale FRESKO 4.5 (IQR, 0.2-10.7). NT-proBNP was correlated with FRESKO scale ($P = .04$), but not with LVEF ($P = .99$). ABVD was administered in 88% of pts. Mediastinum radiotherapy in 25 pts (33.8%). With a median follow-up of 86.5 months (95% CI, 78-95.5), 11 cardiac events were observed (1 clinical CHF + normal LVEF, 3 clinical CHF + LVEF low, 7 low LVEF without CHF). Cumulative incidence of AIC was 7.1% at 12 months (95% CI, 2.9-16.9), 14.8% at 24 months (95% CI, 8.0-27.5), and 14.8% at 5 years (95% CI, 8.0-27.5), and both NT-proBNP and FRESKO predicted an increased cumulative incidence

of AIC (Hazard ratio, 1.49 [95% CI, 1.12-1.99; $P < .006$] and 1.33 [95% CI, 1.14-1.57; $P < .0001$], respectively). Competing risks analysis (AIC and death) showed a significantly increased risk of AIC in patients with NT-proBNP >600 pg/mL (HR, 4.87 [95% CI, 1.42-16.66; $P < .012$]). In addition, scores of FRESKO >4.5% or >7% also predicted an increased risk of AIC (HR, 3.90 [95% CI, 1.22-12.50; $P = .022$] or 9.45 [95% CI, 3.39-26.34; $P < .0001$, respectively]).

Conclusions: Long-term cardiac events in survivors of HL are well-recognized toxicities of chemotherapy and radiotherapy, but according to our results, anthracycline-induced cardiomyotoxicity might appear early, during the first 2 years in up to 15% of patients. NT-proBNP levels and cardiovascular risk factors measured through the FRESKO scale might be of help for identifying those cases at the highest risk.

Keywords: anthracycline; Hodgkin lymphoma (HL)

176 DOSE AND/OR VOLUME REDUCTION USING CONSOLIDATION VOLUME RADIATION THERAPY (CVRT) LOWERS DOSE TO HEART AND LUNGS IN EARLY-STAGE HODGKIN LYMPHOMA PATIENTS WITH BULKY DISEASE

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Introduction: Patients with early stage, unfavorable Hodgkin lymphoma (HL) received 4 cycles of brentuximab vedotin (Bv) and doxorubicin, vinblastine, and dacarbazine (AVD) followed by consolidative radiation (RT) on a multicenter pilot trial testing stepwise reductions in RT dose and field. In cohort 1, patients who completed all planned therapy including involved-site RT (ISRT) to 30.6 Gy have had no relapses with 2.4-year median follow-up. Given these excellent results, patients in cohort 2 received reduced-dose ISRT to 20 Gy, and patients in cohort 3 currently receive consolidation volume radiation therapy (CVRT) to 30.6 Gy. CVRT is an experimental radiation volume targeting only residual CT abnormalities measuring ≥ 1.5 cm in any dimension in PET-negative patients.

Methods: The RT plans of 17 patients from cohort 1 and 20 from cohort 2 with untreated, stage II HL with bulky disease >7 cm were included for analysis. Theoretical CVRT plans to 30.6 Gy and 20 Gy were created for the cohort 2 patients. RT doses to the heart and lungs were compared between the theoretical plans (CVRT 30.6 Gy and CVRT 20 Gy) and the delivered ISRT plans (ISRT 30.6 Gy and ISRT 20 Gy).

Results: Seventy-one percent of patients in cohort 1 and 85% of cohort 2 were treated using deep inspiration breath hold (DIBH) to maximally spare heart and lung. Planning target volumes (PTV) for all 4 plans as well as medians and ranges for their relevant dosimetric parameters are listed in Table 1. Reducing the prescribed ISRT dose from 30.6 Gy to 20 Gy resulted in a 24% reduction in mean heart dose (MHD) and a 32% reduction in mean lung dose (MLD).

The median theoretical CVRT PTV for cohort 2 patients was 58% smaller than the delivered ISRT PTV. Reducing the irradiated volume alone to minimal CVRT fields without reducing the dose decreased the MHD by 30% and the total lung V20 by 57%. However, compared to the ISRT 20 Gy plan, the CVRT 30.6 Gy plan only reduced the MHD and MLD by 8% and 11%, respectively. Reducing both the volume irradiated and the prescribed dose (CVRT 20 Gy) achieved the lowest possible heart and lung doses.

Conclusions: Significant reductions in RT exposure to heart and lungs can be achieved using reduced-dose ISRT to 20 Gy in early stage, HL patients with bulky disease who are PET-negative after 4 cycles of Bv and AVD. Additional reductions in volume using CVRT along with reduced dose to 20 Gy may be able to further minimize RT dose to heart and lung. The disease control with this approach requires longer follow-up in larger groups of patients.

Keywords: brentuximab vedotin; classical Hodgkin lymphoma (cHL)

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OVERALL AND DISEASE-SPECIFIC SURVIVAL OF PATIENTS WHO SURVIVED HODGKIN LYMPHOMA AND DEVELOPED GASTROINTESTINAL CANCER

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Purpose: The risk of gastrointestinal cancer is increased in Hodgkin lymphoma (HL) survivors treated with abdominal radiation treatment (RT) and/or alkylating chemotherapy (CT). This study aims to evaluate whether survival of patients who survived HL and developed

Table 1		Cohort 1 ISRT 30.6Gy (Delivered)	Cohort 2 ISRT 20Gy (Delivered)	Cohort 3A CVRT 30.6Gy (Theoretical)	Cohort 3B CVRT 20Gy (Theoretical)
Planning Target Volume (PTV)		969cc (259-2871cc)	1072cc (450-2635cc)	449cc (99-908cc)	
Organ	Dosimetric Parameter				
Heart	V30 (%)	7.1 (0.0-29.6)	0.0	4.2 (0.0-10.9)	0.0
	Maximum Dose (Gy)	32.7 (0.7-33.9)	21.6 (9.6-23.0)	32.2 (6.8-35.0)	21.4 (0.8-23.6)
	Mean Dose (Gy)	10.5 (3.5-21.9)	8.0 (1.5-18.5)	7.4 (0.4-9.7)	4.6 (0.4-15.3)
Right Lung	V20 (%)	16.7 (2.5-38.0)	2.6 (0.0-21.2)	7.6 (2.7-12.4)	1.9 (0-5.9)
	V10 (%)	28.6 (9.0-58.3)	18.8 (7.3-42.6)	16.7 (5.2-25.5)	13.6 (0.0-24.3)
	Mean Dose (Gy)	9.0 (3.8-15.5)	6.2 (2.8-9.9)	5.7 (1.9-7.2)	4.1 (1.2-7.8)
Left Lung	V20 (%)	21.5 (8.9-38.4)	3.6 (0.0-14.3)	8.9 (1.1-42.7)	0.9 (0.0-4.5)
	V10 (%)	38.5 (12.7-68.4)	20.4 (8.0-55.9)	16.8 (1.8-52.5)	10.6 (1.4-55.9)
	Mean Dose (Gy)	9.6 (4.9-15.7)	5.9 (3.1-11.5)	5.7 (1.2-14.9)	3.7 (0.9-11.5)
Total Lung	V20 (%)	18.5 (10.2-36.3)	3.2 (0.1-14.2)	7.9 (2.1-15.7)	1.6 (0.1-4.2)
	V10 (%)	31.9 (21.1-55.0)	21.7 (7.6-46.9)	16.8 (6.4-27.8)	11.4 (5.3-29.1)
	Mean Dose (Gy)	9.2 (6.6-14.9)	6.3 (2.9-10.4)	5.6 (2.6-7.1)	4.0 (1.8-7.6)

gastrointestinal cancer differs from survival of first primary gastrointestinal cancer patients.

Patients and Methods: Overall and cause-specific survival rates of gastrointestinal (GI) cancer patients in a Dutch HL survivor cohort (n = 104, including esophageal, gastric, small intestinal, and colorectal cancer) were compared with survival of patients with a first primary GI cancer (n = 1025), generated through the Netherlands Cancer Registry by case matching on tumour site, gender, age, and year of diagnosis. Cox proportional hazards regression was used for survival analyses. Multivariable analyses were adjusted for GI cancer stage, grade of differentiation, surgery, RT, and CT.

Results: Patients with GI cancers after HL were diagnosed at a median age of 54 years (interquartile range, 45-60). No differences in tumor stage or frequency of surgery were found between patients with GI cancer after HL and patients with first primary GI cancer. Patients with GI cancer after HL less often received RT (8% vs 23% in first primary GI cancer patients, $P < .001$) and CT (28% vs 41%, $P = .01$) for their GI tumor. Compared with patients with first primary GI cancer, overall and disease-specific survival rates of patients with gastrointestinal cancer after HL were worse (univariable hazard ratios [HRs] 1.30 [95% confidence interval (CI), 1.03-1.65], $P = .03$, and HR, 1.29 [95% CI, 1.00-1.67], $P = .049$, respectively). Adjustment for stage, grade, and treatment did not materially affect these risk estimates (HR, 1.33 [95% CI, 1.05-1.68], $P = .02$, and HR, 1.33 [95% CI 1.03-1.72], $P = .03$, respectively), indicating that the difference in survival between the 2 groups could not be explained by differences in stage, grade, or treatment. Mortality from other causes was slightly but not significantly higher in patients with GI cancer after HL

compared with patients with first primary GI cancer (HR, 1.44 [95% CI, 0.81-2.56]; $P = .22$).

Conclusion: Long-term overall and disease-specific survival of GI cancer in HL survivors are worse compared with first primary GI cancer patients. This survival difference, albeit not large, might result from a worse response of the tumour to treatment due to different pathogenesis of treatment-induced GI cancers.

Keywords: Chemotherapy; Hodgkin lymphoma (HL)

AGGRESSIVE LYMPHOMAS

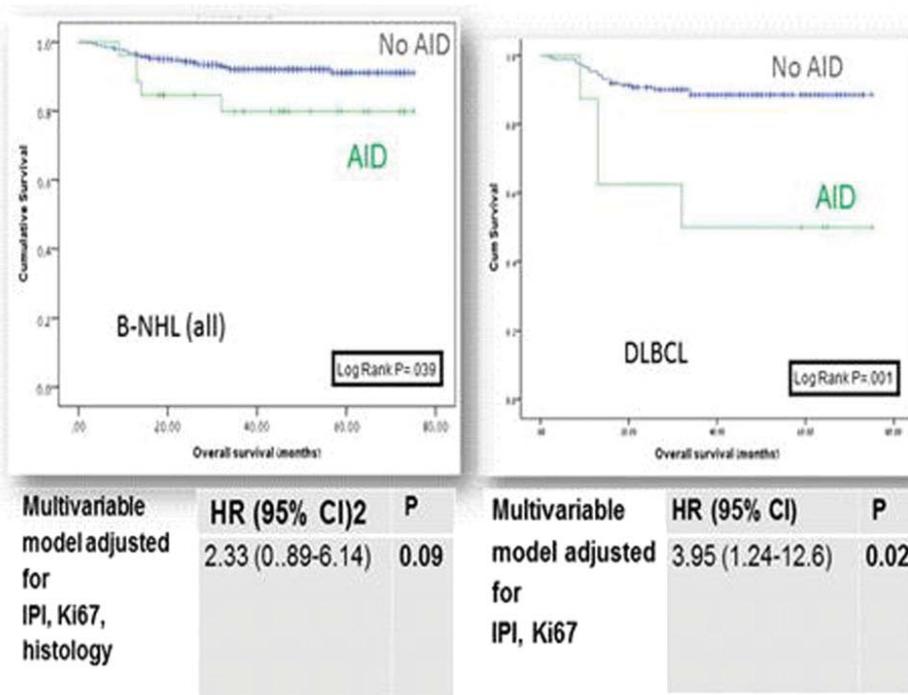
178 AUTOIMMUNE DISEASE (AID) IS BOTH A RISK FACTOR AND A PROGNOSTIC FACTOR AFFECTING SURVIVAL IN PATIENTS WITH B-CELL NON-HODGKIN LYMPHOMA (NHL)

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Background: Although the association between autoimmune diseases (AIDs) and the risk of NHL has been repeatedly shown, the association

Overall survival by B-cell activated auto-immune disease



of AID with survival after the onset of lymphoma has rarely been investigated. We hypothesized that rituximab-based therapy would improve survival in B-cell-mediated AID-associated lymphoma, given its beneficial clinical effect in AID. We aimed to examine the association between pre-existing AIDs and B-NHL and the possible influence of AIDs on NHL outcome.

Methods: In this hospital-based case-control study in Hadassah-Hebrew University Medical Center, we recruited 435 newly-diagnosed adult (>18 years) CD20+ B-NHL patients diagnosed 2009 to 2014 and 414 controls frequency-matched by age and sex to cases. The study is based on questionnaires in Hebrew, English, and Russian that included sociodemographic variables, medical information including a history of AIDs and medications; pathology confirmation; and chart review. We examined the association between NHL and AIDs in general, B- and T-cell-mediated AIDs and autoimmune thyroid diseases, using logistic regression, reporting odds ratios (OR), and 95% confidence intervals (CI). In the second part of the study, we compared overall (OS) and relapse-free survival (RFS) in B-NHL patients with and without AID. We constructed Kaplan-Meier curves for univariate analysis, and multivariable Cox regression models adjusting for important patient and disease characteristics such as Ki67% staining, international prognostic index score (IPI), and histological subgroup.

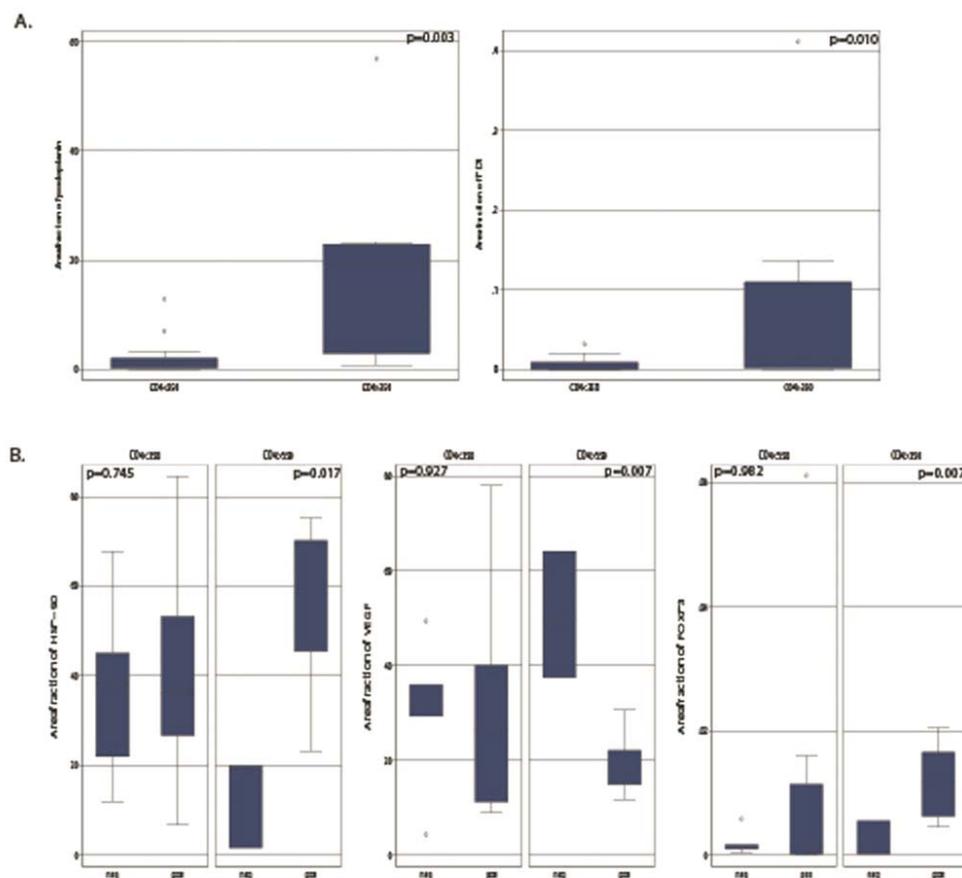
Results: B-NHL risk was associated with the presence of AIDs (OR = 1.98; 95% CI, 1.01-3.9) especially those mediated by B-cell activation (OR = 5.97; 95% CI, 2.3-15.6). The strongest association was observed for marginal zone lymphoma (OR = 13.2, 95% CI, 4.02-43.6).

Time to relapse for all B-NHL patients with AIDs was significantly shorter (mean of 49.21 months [± 3.22]) than for patients without AID (mean of 59.74 months [± 1.62]), hazard ratio (HR) = 1.7 (95% CI, 1.03-2.79), after adjusting for IPI, Ki67% staining, and histological subgroup. Specifically in DLBCL, in which >99% received rituximab-based therapy, both RFS and OS were adversely affected by the presence of B-cell mediated AIDs with HR = 7.84 (95% CI, 2.86-21.5) and 3.99 (95% CI, 1.24-12.6), respectively (see figure).

Conclusions: Beyond the well-known association between AIDs and B-NHL (particularly AIDs mediated by B-cell activation), we found in addition that AID is an adverse prognostic factor in B-cell lymphoma. AID-associated B-NHL patients have poorer outcomes. Specifically, B-cell mediated AID results in inferior RFS and OS in DLBCL, suggesting that rituximab-based therapy does not provide adequate coverage for the subgroup of patients. Further exploration of molecular subtypes and mechanisms of resistance of B-NHL associated with AID is warranted.

Keywords: B-cell lymphoma; immune system; prognostic indices

Figure 1.



Markers of tumor microenvironment differ with level of immune reconstitution, and viral status. *Neg* denotes EBV negative lymphoma, *pos* denotes EBV positive lymphoma. Both programmed death 1 (PD1) and podoplanin (marker of follicular dendritic cells) are differentially expressed according to peripheral CD4 count (A), and heat shock protein 90 (HSP-90), vascular endothelial growth factor (VEGF) and FOXP3 also differed with viral status (B).

179 MICROENVIRONMENTAL FEATURES REFLECTING IMMUNOCOMPETENCE ARE STRONG OUTCOME DETERMINANTS IN HIV-ASSOCIATED LYMPHOMA

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Introduction: An increased risk of lymphoma in HIV-infected patients is well recognized, despite the introduction of combination antiretroviral therapy (cART). Initiation of cART may not always lead to successful immune reconstitution and viral suppression, and we hypothesized that features within the tumor microenvironment might differ inherent to peripheral CD4 count and HIV RNA load.

Methods: We included a population-based cohort of 69 patients with HIV-associated lymphoma. Adequate diagnostic tissue samples were included in a tissue micro array. Patients were grouped according to CD4 cell count (</≥ 350 × 10⁶/L) and HIV RNA level (undetectable vs other) at lymphoma diagnosis. Biomarkers were examined using immunohistochemistry. Outcome was assessed by Kaplan-Meier.

Results: The inhibitory molecule programmed death 1 had significantly higher expression in patients with CD4 > 350 ($P = .010$), and also the marker of follicular dendritic cells podoplanin was differentially expressed ($P = .003$), indicating a possible continuum from HIV-related benign lymphadenopathy. Plasma HIV RNA level at lymphoma diagnosis likewise correlated with podoplanin ($P = .025$), and loss of follicular dendritic cells showed a trend towards inferior outcome. As expected, the number of tumoral granzyme B positive cells correlated with that of CD8+ T-cells ($P = .0006$), but did not differ in relation to peripheral CD4 count. Despite the role of macrophages as viral reservoir for HIV, there was no correlation between either viral load or CD4 count and macrophage markers (CD68 and CD163). However, in the DLBCL subgroup, the CD68^{high} subset had a significantly superior OS (log rank $P = 0.021$). This remained significant in multivariate analysis. Lymphomas were EBV positive in 55% of cases, but EBV status did not differ with CD4 count and had no influence on outcome in this cohort. The small chaperone protein heat shock protein 90 (HSP90) has been implicated in both EBV-driven lymphomagenesis and HIV-1 reactivation from latency. We found that the expression of HSP90 was significantly higher in EBV-positive lymphomas ($P = .016$; Figure 1), and that a high expression correlated with better OS in the whole cohort as well as in the DLBCL subgroup (log rank $P = .005$ and $.029$, respectively). This was further accentuated in EBV-positive tumors (log rank_{EBV+} $P = .007$; log rank_{EBV-} $P = .964$). After adjusting for CD4 level in a bivariate Cox model, HSP90 retained independent prognostic influence (HR, 0.20 [95% CI, 0.06-0.66]; $P = .008$). Also tumor-infiltrating FOXP3-

positive cells and blood-vessel density differed according to viral status and immune reconstitution (Figure 1).

Conclusion: In HIV-associated lymphoma, immune status reflects on the microenvironment. Varying microenvironmental features may offer some of the explanation why developing lymphoma while on cART is a negative prognostic feature, despite the generally improved treatment results.

Keywords: B-cell lymphoma; Epstein-Barr virus (EBV); human immunodeficiency virus (HIV)

180 OUTCOME PREDICTION IN DIFFUSE LARGE B-CELL LYMPHOMA CAN BE GREATLY IMPROVED BY ALTERNATIVE USE OF CLINICAL INFORMATION: A N

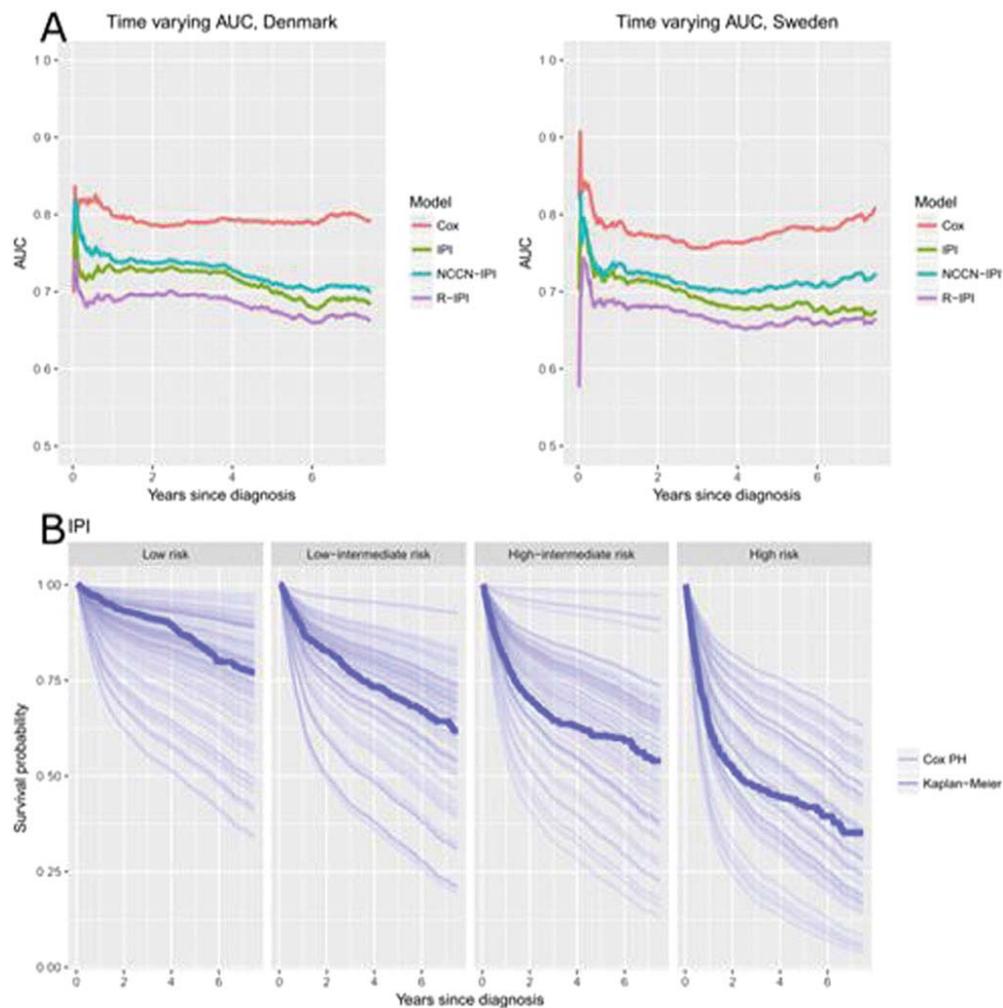
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Introduction: Outcome prediction in diffuse large B-cell lymphoma (DLBCL) mainly relies on clinical prognostic indices. The International Prognostic Index (IPI) and derived models assign patients to a limited number of risk groups based on dichotomized clinical variables. In this study, we investigated whether predictive accuracy was improved by using the same clinical variables in continuous or categorical form.

Methods: This study was based on the Danish Lymphoma Register and the Swedish Lymphoma Register. The inclusion criteria were (a) newly diagnosed DLBCL without CNS (and/or intravitreal) involvement at baseline in the period 2006-2014, (b) R-CHOP, R-CEOP, or R-CHOEP therapy, (c) age ≥18 years, and (d) information on age, Ann-Arbor stage, ECOG performance status, and number of extranodal sites. Furthermore, information on normalized lactate dehydrogenase (LDH) values (measured LDH/upper normal reference limit) at time of diagnosis was required for Danish patients. For Swedish patients, normalized LDH was imputed. Kaplan-Meier estimates were used to estimate survival within risk groups of the IPI, R-IPI, and NCCN-IPI. Cox proportional hazards (CPH) models were used to model the linear effects of continuous variables and to provide model-based estimates of survival.

Results: 2,696 Danish and 2,657 Swedish DLBCL patients were included. Figure 1A summarizes the model performance as measured by the time-varying AUC. In both cohorts, the following ranking of the models, from best to worst performing model, was seen: (1) the CPH model, (2) the NCCN-IPI, (3) the IPI, and (4) the R-IPI. Figure 1B



shows the survival curves within IPI risk groups of 250 randomly selected Danish patients as modeled by the CPH model and estimated using the Kaplan-Meier method. The spread of the CPH curves within each of the IPI groups and overlap between IPI groups illustrates the limitation of the group-based prognostic models for individual outcome assessment.

Conclusions: Prognostic assessment of newly diagnosed DLBCL can be substantially improved by predicting survival probabilities from a model, based on continuous variables instead of allocating patients to predefined groups. This study also shows that, when appropriately used, simple clinical information will (likely in combination with molecular genetics) be an important resource for better individual outcome prediction in lymphoma.

Figure 1A. The time-varying AUC corresponding with the risk groups of the IPI-like indices and a Cox proportional hazards model with the IPI variables in continuous form.

Figure 1B. Survival estimates of 250 randomly selected patients in the Danish cohort predicted from the Cox proportional hazards model and estimated using the Kaplan-Meier method for each IPI class. There is a notable spread of the modeled-based survival estimates within each risk group and a certain overlap of estimated survival curves between risk groups.

Keywords: diffuse large B-cell lymphoma (DLBCL)

181 SIMULTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) AND FOLLICULAR LYMPHOMA (FL) AT THE DIAGNOSIS HAS SIMILAR OUTCOME AS DLBCL

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Background: DLBCL is considered as curable lymphoma subtype with decreasing relapse risk compared to incurable FL with sustained relapse risk. Histological transformation of FL into DLBCL represents

a risk of 3% per year. There is a proportion of patients (pts) with simultaneous occurrence of DLBCL and FL (DLBCL/FL) in the same lymph node (LN). These pts are treated as DLBCL. The outcome of these pts was not described yet, and these pts are usually excluded from DLBCL and FL trials.

Methods: Data of newly diagnosed pts have been prospectively collected in the Lymphoma Project NiHiL since 1999. Altogether, 201 DLBCL/FL pts diagnosed in 2002 to Jan 2016 were confirmed by histopathological review. The percentage of DLBCL and FL components was established. The clinical characteristics, treatment and outcome were analysed. Two comparator groups were selected, the DLBCL patients of GC subtype (Hans algorithm) (n 304, dg 2005 to Jan 2016) and FL pts (n 1420, dg 2005 to Jan 2016), both groups treated by Rituximab (R) chemo. Outcome of these subgroups was compared by logrank test.

Results: Out of 201 DLBCL/FL pts, grade of FL part was evaluated as G1-G3A in 87 (43.3%), G3B in 89 (44.3%) and G3 without specification in 25 (12.4%). The proportion of DLBCL component was $\geq 50\%$ in 105 pts (55.9%). The median age was 61 years (29 to 97) and male/female ratio 1.12/1. The IPI score was low and lowintermed (LI) vs highintermed (HI) and high in 58.7% vs 41.3% resp. The FLIPI score was good, intermed and high in 33.0%, 21.0% and 46.0% resp. R was used in 181 pts (87.9%), CHOP in 166 (82.6%) and other chemo in 35 (17.4%) pts. The OS and PFS probability at 5 years was 77.2% and 66.4% resp. with median follow-up 5.6 year. The DLBCL GC comparator group had median age 64.5 years (19 to 88), HI and high risk IPI was found in 47.8% pts. The FL comparator group had median age 59 years (27 to 90); FLIPI good, intermed and high risk score were in 22.2%, 29.3% and 48.5% resp. The cohorts were not different from the DLBCL/FL group in terms of patients characteristic. The 5-year OS probability for DLBCL/FL1-3A, DLBCL/FL3B, DLBCL GC and FL

cohorts were 76.1%, 81.8%, 79.9% and 86.5% resp. ($p = 0.001$; Figure 1). The 5-year PFS probability for DLBCL/FL1-3A, DLBCL/FL3B, DLBCL GC and FL cohorts were 63.3%, 71.8%, 71.6% and 62.8% resp. ($p = 0.14$). FL had statistically better outcome for OS. RM was used in 20 pts, in both subgroups DLBCL/FL1-3A (n 10) as well as DLBCL/FL3B (n 8) and DLBCL/FL 3 (n 2). When compared to pts without RM, there was identified a trend for better PFS in RM cohort with 5-year PFS 89.5% vs cohort w/o RM with 5-year PFS 74.4% ($p = 0.15$; Figure 2).

Forty-six relapses in DLBCL/FL pts were observed, 19 pts with histological verification of relapse. Out of these, 7 pts (36.8%) relapsed as DLBCL, 6 (32.0%) as FL, 5 pts (10.8%) as DLBCL/FL and 1 pts into B NHL.

Conclusions: Our analysis shows that DLBCL/FL behaves as GC DLBCL with the same OS probability. RM for patients with DLBCL/FL G1-G3A might improve the outcome, but more data are needed.

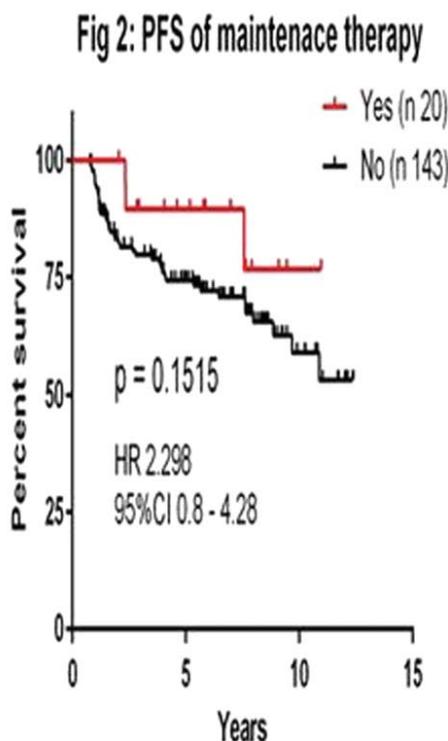
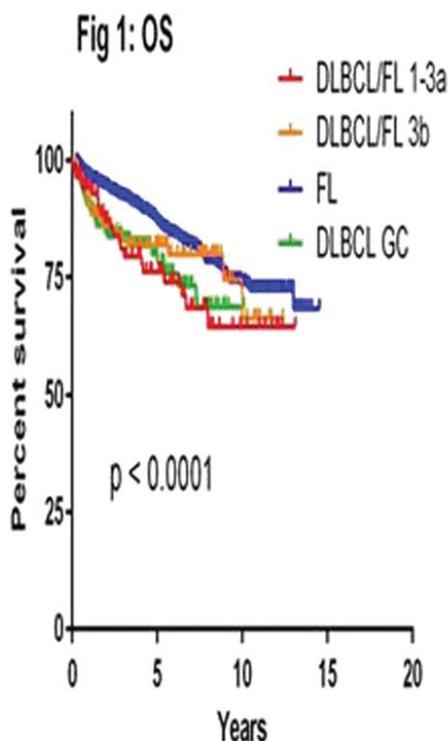
Supported by grant of Ministry of Health of the Czech Republic MZ VES 16-31092A.

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

182 HIGH-RISK PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA ARE NOT ENROLLED ON CLINICAL TRIALS

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Background: Contemporary precision medicine trials in DLBCL often require real-time central pathology review for enrollment. Central review may lead to treatment delays and prevent high-risk patients (pts) with aggressive presentations from enrolling onto clinical trials. We explored reasons pts with DLBCL were not enrolled on trials and the implication of non-enrollment on trial design and interpretation.

Methods: We retrospectively analyzed all pts with histologic diagnosis of DLBCL or HGBL from 4/14 to 6/16 at the University of Rochester. Therapeutic trials open during this time included 3 sponsored and 2 NCTN studies. The Kaplan-Meier method was used to estimate the distribution of progression-free survival (PFS; time from start of treatment until progression/death or until the last date the patient was known to be progression free) and overall survival (OS).

Results: 140 pts were identified; 22% ($N = 30$) enrolled on a trial. Reasons for non-enrollment included (1) protocol ineligibility ($n = 58$); (2) physician choice ($n = 24$); and (3) patient choice ($n = 20$). Reasons were unclear in 8 pts. Of the 24 pts who were not enrolled due to physician choice, 21 required urgent treatment secondary to symptoms or rapid progression. Compared to pts treated on trial, pts with rapid progression had higher risk clinical features (Table). There was a trend towards a lower 1-year PFS rate in pts who required urgent treatment compared to those on trial (72.1% vs 56.1%; $p = 0.08$). There was no statistical difference in OS.

Conclusions: At our institution, for patients with DLBCL meeting trial eligibility criteria, 42% required urgent chemotherapy and failed to enroll. Exclusion of these high-risk patients in precision medicine trials has important implications in the interpretation and generalizability of clinical trials in DLBCL. In this curable malignancy, excluding high-risk patients from trials limits the event rate and associated power to demonstrate impact of novel therapies.

Keywords: diffuse large B-cell lymphoma (DLBCL)

TABLE 1

	Total, N=47	On trial N=30	Off trial N=17
Median Age (yrs)	66	66	66
ECOG \geq 2 (%)	21	13	35
Stage (%)*			
Limited	32	40	18
Advanced	68	60	82
Elevated LDH (%)*	57	47	77
IPI (%)*			
0-1	21	27	12
2	15	17	12
3	34	43	18
4-5	30	13	59
GCB (%)	51	47	59
Non-GCB (%)	49	53	41
MYC Rearrangement (%)	13	7	24

183 LONG-TERM FOLLOW-UP AFTER LOCALIZED RADIOTHERAPY IN PATIENTS WITH TRANSFORMED B-CELL LYMPHOMA TREATED WITH RITUXIMAB-CONTAINING CHEMOTHERAPY

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Introduction: Histologic transformation (HT) refers to a biologic event leading to the development of aggressive histology in patients (pts) with indolent B-cell lymphoma (iB-NHL). HT is still a critical event because of its poorer prognosis even in the rituximab era. The optimal therapeutic strategy for pts with HT has not been well established. Although localized HT is often experienced in clinical practice, the role of localized radiotherapy (LRT) remains unclear. LRT to HT lesions in selected patients is considered to be a rational treatment approach that may enable eradication of the HT component with limited toxicity. The objective of this study was to investigate the role of LRT to HT lesions.

Methods: We retrospectively analyzed pts who were diagnosed with diffuse large B-cell lymphoma (DLBCL) transformed from iB-NHL, such as follicular lymphoma and marginal zone lymphoma, undergoing rituximab-containing chemotherapy at our institution between 2003 and 2015. Pts were divided into 2 groups: DLBCL with pre-existing or co-existing iB-NHL. The former was presumed to be DLBCL developed from previously diagnosed iB-NHL, and the latter was DLBCL with co-existing iB-NHL. Progression-free survival (PFS) was calculated from the date of DLBCL diagnosis to disease progression or death from any cause. Overall survival (OS) was calculated from the date of DLBCL diagnosis to death from any cause.

Results: We identified 100 DLBCL pts, of which 42 with pre-existing and 58 with co-existing iB-NHL were used as subjects in this analysis. The median age was 58.5 years (range: 26-83). In the 42 pts of the pre-existing group, 8 pts presented with clinical stage (CS) I disease, 4 with CS II, 6 with CS III, and 24 with CS IV at the time of diagnosis of transformation. Among them, 11 pts (26%), 8 with localized and 3 with advanced disease, received LRT, and all but one exhibited no disease progression with a median follow-up duration of 33 months (range: 1-140). The estimated 5-year PFS rates of LRT and no LRT were 91% and 15%, respectively ($p < 0.01$) (Figure 1A). On the other hand, among the 58 pts of the co-existing group, 23 pts (40%), 22 with localized and 1 with advanced disease, received LRT. Nineteen pts remained progression-free with a median follow-up duration of 97 months (range: 15-169). The 10-year PFS rates of LRT and no LRT cohorts were 75% and 48%, respectively ($p = 0.04$) (Figure 1B). Of the total 34 pts who received LRT in both groups, 32 pts (94%) experienced no disease progression within radiation fields. However, OS rates between LRT and no LRT were not significantly different.

Figure: PFS with or without Localized RT

Figure 1A: DLBCL with pre-existing indolent B-NHL

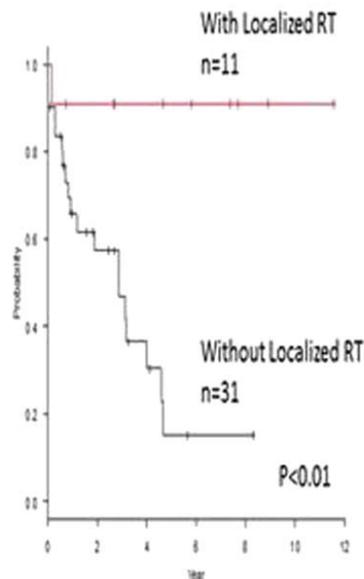
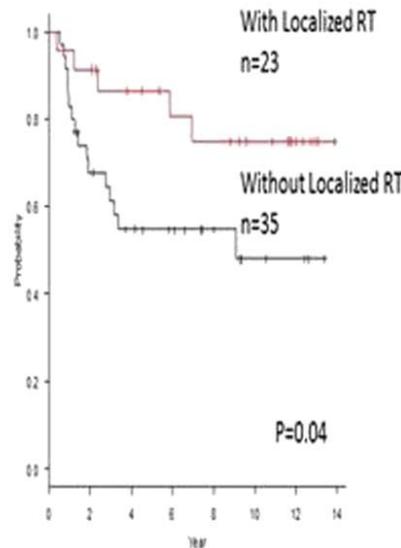


Figure 1B: DLBCL with co-existing indolent B-NHL



Conclusion: Pts with DLBCL transformed from iB-NHL who received LRT achieved excellent infield disease control and significantly better PFS, supporting the rationale for the administration of LRT to HT lesions. Further investigations are needed in order to confirm our retrospective observations.

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

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OBINUTUZUMAB-MINICHOP FOR THE TREATMENT OF ELDERLY UNFIT PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA. A STUDY OF THE FONDAZIONE ITALIANA LINFOMI

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Introduction: We conducted a prospective, multicentre, single-arm, phase 2 study to evaluate activity and safety of Obinutuzumab (GA101)-miniCHOP combination in elderly unfit patients with diffuse large B-cell lymphoma (DLBCL).

Methods: Eligible patients were elderly subjects (≥ 65 years) with a newly diagnosed DLBCL. All patients were required to be unfit at Comprehensive Geriatric Assessment. Patients received miniCHOP (400 mg/m² cyclophosphamide, 25 mg/m² doxorubicin, 1 mg vincristine on day 1 of each cycle, and 40 mg/m² prednisone on days 1-5) every 21 days, combined with GA101 1000 mg on day 1, 8, 15 of cycle 1 and on day 1 of subsequent cycles. Treatment plan consisted of 6 cycles of GA101-miniCHOP followed by 2 additional doses of GA101. The use of G-CSF was mandatory. The primary end point was complete response rate (CRR) according to Cheson 1999 criteria. Safety of GA101-miniCHOP was a secondary end point. The sample size was estimated according to an optimal Simon 2-stages design.

The study was designed to assess whether GA101-miniCHOP could increase the CRR compared to historical data. The null hypothesis (p_0) has been set equal 0.60 on the basis of what reported by Peyrade et al (*Lancet Oncol*, 2011), and the alternative hypothesis (p_1) was set at 0.75, with a type I and II error of 10% and 90%. A total of 71 patients were required with at least 48 CR to conclude for the efficacy of treatment. An interim analysis was planned after 34 patients, and at least 22 CR were required to proceed with enrollment. Analysis was by intention to treat. We here report the results of the stage 1.

Results: Thirty-four patients were enrolled from August 2015 to June 2016 by 15 Italian centers. One patient was subsequently excluded due to violation of inclusion criteria. Median age was 82 years (68–89), 18 were males, and IPI was 3–5 in 21 cases. Overall, 228 cycles were delivered, and 27 patients completed all 6 planned courses. Treatment was interrupted in 4 patients due to adverse events (AE) and in 2 due to lack of response. Final response was reported as CR in 14 patients (42%) and partial in 8 (24%); 10 patients had stable or progressive disease (30%), and 1 patient (3%) was not assessed. AEs were reported in 28 cases: hematological grade 3–4 AEs included neutropenia (13 cases, 39%) and thrombocytopenia (1 case, 3%); grade 3–4 non-hematological AEs occurring in more than one case included skeletal muscle (2 cases, 6%) and metabolic disorders (3 cases, 9%). With the observed CR rate, the study has failed the planned interim analysis, and enrollment has been interrupted.

Conclusions: GA101-miniCHOP is active and well tolerated for the treatment of elderly unfit patients affected by DLBCL. Based on initial study assumptions and on the observed CRR, at the interim analysis, we will not be able to demonstrate the initial study hypothesis that GA101-miniCHOP could improve results of historical data obtained with R-miniCHOP in this setting of patients.

Keywords: diffuse large B-cell lymphoma (DLBCL); elderly; obinutuzumab

185 END OF TREATMENT PET-CT PREDICTS PROGRESSION-FREE SURVIVAL IN DLBCL AFTER FIRST-LINE TREATMENT: RESULTS FROM THE PHASE III GOYA STUDY

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Introduction: Establishing a new clinical trial end point, such as end of treatment (EOT) complete response assessed by ¹⁸F-FDG-PET (PET-CR), would allow early assessment of therapeutic efficacy. The prognostic value of EOT PET-CR for PFS and OS in DLBCL patients (pts) has been reported in several small studies, but requires confirmation in a large data set. We investigated the prognostic value of EOT PET for PFS in a large pt cohort treated with obinutuzumab (G) or rituximab (R) plus CHOP in the phase III GOYA study (NCT01287741; Vitolo 2016).

TABLE Comparison of m5PS and IWG₂₀₀₇ response assessment by IRC at EOT

m5PS*, n	IWG ₂₀₀₇ , n						Total, n (%)
	CR	PR	SD	PD	NE	NA [†]	
CR	814	77	3	9	15	1	919 (68.9)
PR/PRM	40	84	3	13	2	1	143 (10.7)
SD/NMR	0	5	2	15		0	22 (1.6)
PD	15	17	2	31	3	0	68 (5.1)
NE	3	0	0	0	1	0	4 (0.3)
NA [†]	8	25	3	13	15	114	178 (13.3)
Total, n (%)	880 (66.0)	208 (15.6)	13 (1.0)	81 (6.1)	36 (2.7)	116 (8.7)	1334 (100)

*m5PS response was derived from integration of clinical review of bone marrow and other biopsy results, responses were therefore modified in some patients by missing/positive bone marrow or other biopsy findings. [†]Responses preceded by anti-lymphoma treatment are recorded as NA. CR, complete response; IWG₂₀₀₇, International Working Group 2007; m5PS, modified Lugano criteria; NA, not available; NE, not evaluable; NMR, non-metabolic responder; PD, progressive disease; PR, partial response; PRM, modified partial metabolic response (complete response not confirmed in bone marrow).

Methods: Pts aged ≥ 18 years, with an ECOG performance status ≤ 2 and IPI score of ≥ 2 , were enrolled, as well as low-risk pts with IPI scores of 1 (not due to age alone) or 0 (with bulky disease). Pts were randomised 1:1 to receive 8 \times 21-day cycles of G (1000 mg IV on days [D] 1, 8, and 15, cycle [C] 1 and D1, C2-8) or R (375 mg/m² IV on D1, C1-8) plus 6 or 8 cycles of CHOP (number of cycles preplanned for all pts at each site). Pts had an EOT PET-CT assessment 6-8 weeks after completion of treatment. PET-CT data were analysed according to Lugano criteria (based on Deauville 5-point scale; JCO 2014) modified in some patients by biopsy findings (m5PS; Table footnote), and revised International Working Group criteria (IWG₂₀₀₇; JCO 2007), at an independent central review facility by 3 radiologists plus a clinical reviewer. PET-CR status, according to each criteria, was compared with PFS.

Results: Of 1418 enrolled pts, 1346 had a baseline PET scan, and 1334 had detectable lesions. Baseline clinical characteristics, eg, age, stage and IPI, were similar between treatment arms. There was no statistical difference in PFS between the treatment arms; thus, the entire cohort was analysed as a whole. Results at EOT by m5PS and IWG₂₀₀₇ criteria are presented (Table). After a median follow-up of 29 months, EOT PET-CR was highly predictive of PFS using m5PS or IWG₂₀₀₇; m5PS-based PET-CR yielded a lower hazard ratio (HR 0.27; 95% CI 0.20-0.38; $p < 0.001$) than IWG₂₀₀₇ (HR 0.34; 95% CI 0.25-0.46; $p < 0.001$; Figure). 2.5-yr PFS from EOT for m5PS response was

86.1% (95% CI 83.3-88.5) in pts achieving PET-CR vs 58.8% (95% CI 49.3-67.1) in pts who did not.

Conclusions: This large prospective study confirms PET-CR as a strong predictor of PFS in DLBCL after 1 L immunochemotherapy, applying m5PS or IWG₂₀₀₇ criteria; m5PS provided a slight advantage. Meta analyses of these data with other prospective studies would be needed to further evaluate the potential surrogacy of PET-CR for PFS as a novel end point for future clinical trials.

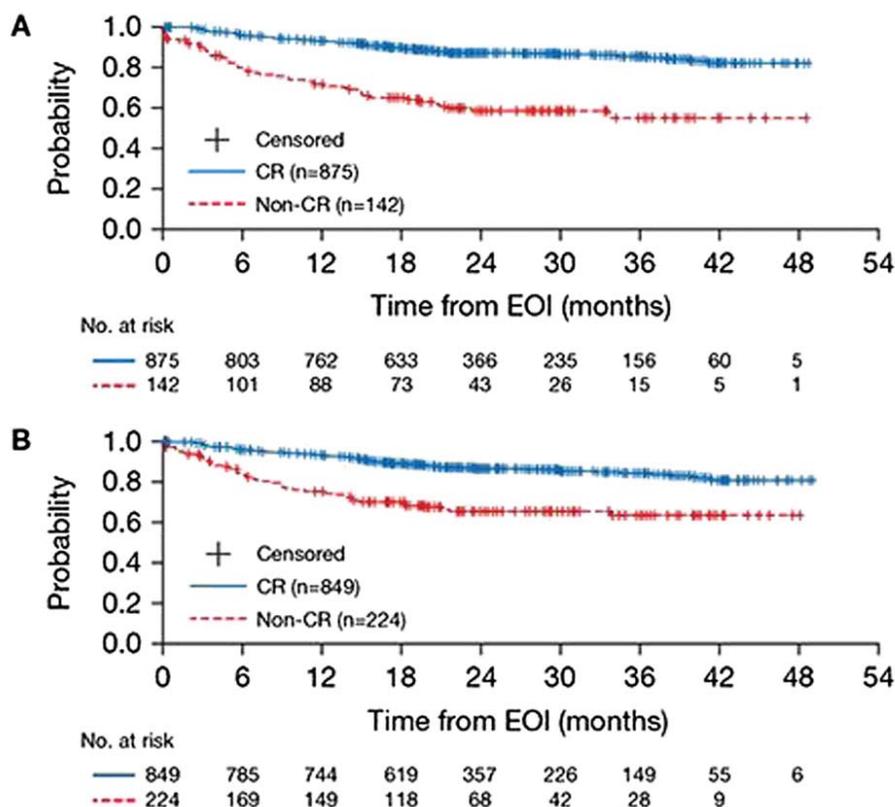
Keywords: diffuse large B-cell lymphoma (DLBCL); positron emission tomography (PET); prognostic indices

186 RITUXIMAB SC And IV PLUS CHOP SHOW SIMILAR EFFICACY AND SAFETY IN THE RANDOMISED MABEASE STUDY IN FIRST-LINE DLBCL

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Figure. Analysis of PFS from EOT (landmark) according to CR vs non-CR* status assessed by A) m5PS (N=1017) and B) IWG₂₀₀₇ (N=1073) criteria, both by IRC (ITT population)



*For m5PS criteria, 'non-CR' includes PR/PRM, and SD/NMR; for IWG₂₀₀₇ criteria, 'non-CR' includes PR and SD. Patients in the PET-ITT population who progressed (had a CT-based PD assessment) before or at EOT were excluded.

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Introduction: Intravenous (IV) rituximab plus chemotherapy is standard treatment for diffuse large B-cell lymphoma (DLBCL). A subcutaneous (SC) formulation of rituximab may simplify treatment and reduce burden. MabEase (NCT01649856) studied efficacy, safety and patient (pt) satisfaction with rituximab SC or IV plus cyclophosphamide, vincristine, doxorubicin and prednisolone (CHOP) as first-line DLBCL treatment.

Methods: Pts were randomised 2:1 to rituximab SC (IV 375 mg/m² cycle 1; SC 1400 mg cycles 2-8) or IV (375 mg/m² cycles 1-8) plus CHOP every 14 or 21 days. The primary end point was investigator-assessed complete response (CR)/unconfirmed CR (CRu) at the end of induction (EOI). Secondary end points included safety, survival, treatment satisfaction (Cancer Treatment Satisfaction Questionnaire [CTSQ], Rituximab Administration Satisfaction Questionnaire [RASQ]) and time savings. Follow-up continued until at least 24 months after EOI in the last patient recruited.

Results: Of 576 pts (381 SC; 195 IV), 572 (378 SC; 194 IV) received treatment. EOI CR/CRu rates were 50.6% (95% CI 45.3-55.9) and 42.4 (95% CI 35.1-49.7) in the SC and IV groups, respectively (Table). After 35 months' median follow-up, median progression-free survival (PFS), event-free survival (EFS) and overall survival (OS) were not reached in either arm, and no statistically significant differences were observed between treatment arms. PFS, EFS and OS rates were also similar at 24 months' follow-up (non-significant differences; Table). Grade ≥ 3 adverse events (58.3% SC; 54.3% IV) and administration-related reactions (21% in both groups) were similar between arms. Of SC recipients, 5.7% had injection site reactions vs none in the IV group ($p < 0.001$). Febrile neutropenia occurred more often in the SC arm (12.5% vs 6.9% in IV, $p = 0.06$). RASQ scores for 'impact on activities of daily living', 'convenience' and 'satisfaction' were improved with SC vs IV; CTSQ scores were similar between arms (Figure). When pts in the SC group were asked, if given the option, which treatment they would prefer, 90.8% stated a preference for SC over IV. Median administration time (6 minutes SC vs 2.6-3.0 hours IV) and chair/bed and overall hospital times were shorter with SC than with IV treatment.

Conclusions: Rituximab SC had similar efficacy and safety to the IV form, with improvements in pt satisfaction ratings, and administration/hospital time savings. Our findings support the use of rituximab SC in this setting.

TABLE Efficacy endpoints in the intent-to-treat population

Efficacy endpoint	Rituximab SC plus CHOP		Rituximab IV plus CHOP	
	N	% (95% CI)	N	% (95% CI)
End of induction treatment				
CR/CRu	342	50.6 (45.3-55.9)	177	42.4 (35.1-49.7)
PR	342	31.6 (26.7-36.8)	177	35.6 (28.6-43.1)
PD	342	3.8 (2.0-6.4)	177	6.2 (3.1-10.8)
ORR	342	82.2 (77.7-86.1)	177	78.0 (71.1-83.8)
24 months' follow-up				
PFS*	342	75.0 (69.9-79.4)	177	81.5 (74.7-86.6)
EFS**	342	68.6 (63.3-73.4)	177	74.6 (67.3-80.5)
OS [†]	342	87.4 (83.2-90.5)	177	88.0 (82.0-92.1)

* $p=0.175$.

** $p=0.314$.

[†] $p=0.302$.

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

187 R-COMP vs R-CHOP AS FIRST-LINE THERAPY FOR DIFFUSE LARGE B-CELL LYMPHOMA IN PATIENTS OLDER THAN 60 YEARS: RESULTS FROM A RANDOMIZED PHASE 2 STUDY FROM THE SPANISH GELTAMO GROUP

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Introduction: The use of non-pegylated liposomal doxorubicin (Myocet[®]) in DLBCL has been investigated mostly in retrospective and single-arm prospective studies. The main objective of this study was to evaluate the benefit, in terms of cardiac toxicity, of the substitution of conventional doxorubicin as part of R-CHOP therapy by the

non-pegylated liposomal doxorubicin (Myocet[®], R-COMP arm) in patients ≥ 60 years with de novo DLBCL or grade 3b FL.

Methods: Prospective randomized phase 2 trial (ClinicalTrials.gov Identifier: NCT02012088) of newly diagnosed patients with DLBCL or grade 3b FL ≥ 60 years old with baseline left ventricular ejection fraction (LVEF) $> 55\%$. Patients were randomized to R-COMP or R-CHOP (every 21 days for 6 cycles, with a dose of conventional doxorubicin or Myocet[®] of 50 mg/m²/cycle). Primary end point was to evaluate the differences in subclinical cardiotoxicity, defined by a decrease in LVEF to $\leq 55\%$ at the end of treatment (measured by echocardiography at 1 and 4 months after therapy). Secondary objectives were efficacy, safety and differences in the variations of cardiac biomarkers (troponin and N-terminal pro B-type natriuretic peptide [NT-proBNP]).

Results: 91 patients from 15 Spanish hospitals were included, 46 received R-COMP and 45 R-CHOP, without significant differences between arms regarding baseline characteristics and efficacy (Table).

Subclinical cardio-toxicity: No differences between arms were observed in the number of patients with LVEF $\leq 55\%$ determined at the end of treatment or at 4 months and in the troponin and NT-proBNP levels through treatment period and follow-up (Table).

Serious adverse events (SAEs): A total of 62 SAEs were reported in 38 patients (40 in 21 patients from R-COMP group and 22 in 17 patients from R-CHOP group), including 16 infections (10 in R-COMP and 6 in R-CHOP) and 16 episodes of febrile neutropenia (10 in R-COMP and 6 in R-CHOP). Four patients showed cardiovascular events: atrial fibrillation ($n = 1$, R-COMP group), supraventricular tachycardia ($n = 2$, R-CHOP group) and myocardial infarction ($n = 1$, R-CHOP group).

Conclusions: R-COMP is a feasible immunochemotherapy schedule for patients with de novo DLBCL ≥ 60 years, with identical efficacy to R-CHOP. However, in our series, the use of non-pegylated doxorubicin instead of conventional doxorubicin was not associated with less early cardiotoxicity. Longer follow-up is needed to determine whether this drug could have a benefit in late-onset cardiac toxicity.

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

188 ANTHRACYCLINE DOSE INTENSIFICATION IN DIFFUSE LARGE B-CELL LYMPHOMA

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	R-CHOP (n=45)	R-COMP (n=46)	P value
Male, n (%)	17 (38)	24 (52)	0.168
Median age (range), years	74 (60-84)	74 (60-86)	0.542
ECOG <2 , n (%)	37/45 (82)	39/46 (85)	0.742
Ann-Arbor III-IV, n (%)	35/44 (79)	33/46 (72)	0.389
IPI ≥ 3 , n %	20/43 (46)	18/45 (40)	0.538
Baseline LVEF, median (range), %	63 (55-81.4)	65 (55-87.1)	0.242
LVEF $<55\%$ at end of therapy, n (%)	3/37 (8)	3/42 (7)	1
LVEF $<55\%$ at 4 months of therapy, n (%)	3/31 (10)	4/34 (12)	1
Increased troponin levels at Cycle 3, n (%)	26/29 (90)	32/34 (94)	0.654
Increased troponin levels at Cycle 6, n (%)	28/29 (97)	23/28 (82)	0.102
Increased troponin levels at month 4, n (%)	13/24 (54)	11/26 (42)	0.402
Increased NT-proBNP levels at Cycle 3, n (%)	13/24 (54)	11/26 (42)	0.402
Increased NT-proBNP levels at Cycle 6, n (%)	28/29(97)	23/28 (82)	0.102
Increased NT-proBNP levels at month 4, n (%)	13/24 (54)	11/26 (42)	0.572
OR, n (%)	36/36 (100)	41/42 (98)	1
CR, n (%)	27/36 (75)	29/42 (69)	0.560
2 year PFS (95% CI)	60% (45%, 75%)	61% (45%, 77%)	0.6
2 year OS (95% CI)	77% (64%, 90%)	73% (58%, 88%)	0.913
Patients with SAEs, n (%)	17/45 (38)	21/46 (46)	0.446
Neutropenia grade ≥ 3 , n (%)	22/45 (49)	19/46 (41)	0.467
Anemia grade ≥ 3 , n (%)	2/45 (4)	4/46 (9)	0.677
Thrombocytopenia grade ≥ 3 , n (%)	3/45 (7)	4/46 (9)	1

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous subtype of non-Hodgkin lymphoma varied with clinical, immunophenotypic and genetic features. Anthracycline is considered as the key cytotoxic agent of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). However, whether anthracycline dose intensification can improve the prognosis needs to be addressed.

Methods: In this phase III randomized trial, we assigned 400 patients with untreated DLBCL between the age of 16 and 60 years to receive six courses of regimen on a 21-day basis, at either the standard dose (doxorubicin 50 mg/m², R-CHOP50 or epirubicin 70 mg/m², R-CEOP70) or a high dose (epirubicin 90 mg/m², R-CEOP90), followed by additional two cycles of rituximab consolidation. The primary end point was progression-free survival. Moreover, whole genomic sequencing (WGS) and whole exome sequencing (WES) were performed on tumor samples of 28 and 63 patients, respectively.

Results: In the intention-to-treat analysis, R-CEOP90 resulted in higher 2-year progression-free survival rate than R-CHOP50/R-CEOP70 (90.3% vs 82.2%, $P = 0.016$). The rates of serious adverse events were similar among the three groups. Median follow-up was 24.2 months. In subgroup analysis, good R-IPi and germinal center B-cell origin benefited from intensified anthracycline dose. As revealed by WGS/WES, frequent mutated genes (>5%) were enriched in pathways as previously reported by Western population (ASH abstract, Blood 2016 128:152): NOTCH (CTBP2, MAML2, DTX1, NOTCH2, SGK1, NCOR2), TP53 (TP53, FAS, TP73), JAK-STAT (PIM1, SOCS1, STAT3), epigenetic (KMT2D, ARID1A, TET2, CREBBP/EP300, TAF1), BCR (CD79B/CD79A, NFKBIE, CARD11, LYN), toll-like/TNF receptor (MYD88, TNFAIP3, TRAF2), PI3K (KLF2, MTOR, RAG1, FOXO1, BCL2L11, GNA13), MAPK (FGFR3, DUSP2, ETS1), B-cell differentiation (PRDM1 and IRF4), immune surveillance (B2M, HLA-B, CIITA, CD58) and cell cycle (ATM, MYC, CCND3). Two novel pathways were identified:

TCR/NK-mediated cytotoxicity (NFATC1 and KIR2DL1) and EBV/ HBV infection (DDX3X and HSPG2). Pathway-specific genes less frequently observed than Western population (<5%) were NOTCH (NOTCH1, NOTCH3, FBXW7), JAK-STAT (STAT6), epigenetic (EZH2 and MEF2B), BCR (BCL10, PRKCB, MALT1), PI3K (ID3, TCF3, PTEN, PIK3CD, PIK3R1, PIK3CA), MAPK (BRAF, MAP4K1, KRAS, MAP3K7), B-cell differentiation (BCL6 and IRF8) and cell cycle (CDKN2A, CDK6, RB1). Clinical relevance study on gene mutations was ongoing.

Conclusions: This is the first prospective study on anthracycline dose intensification in Chinese DLBCL cohort. High-dose epirubicin improved progression-free survival in young adults with DLBCL. Significant difference in gene mutation pattern was observed between Chinese and Western population. (ClinicalTrials.gov number: NCT00049517).

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

189 PHASE 2 RANDOMIZED TRIAL COMPARING STANDARD RCHOP VERSUS BRCA AS FIRST LINE TREATMENT IN YOUNG PATIENTS WITH HIGH-RISK DLBCL. A STUDY FROM SPANISH GROUP GELTAMO

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Introduction: Survival of DLBCL patients with high IPI treated with RCHOP is poor. Combination of RCHOP with new drugs is an attractive approach, along with performing an evaluation with PET/CT after 2-4 cycles to change therapy if an early CR is not achieved.

Methods: Clinical trial comparing 6 cycles of RCHOP vs BRCAP, a modified RCHOP changing vincristine by bortezomib 1.3 mg/m² sc days 1, 8, and 15 of a 21-day cycle (ClinicalTrials.gov Identifier: NCT01848132). Inclusion criteria: ≤70 years, DLBCL, aalPI 2-3 or 1 with increased beta2microglobulin. Primary end point: proportion of patients who survives free of event at 2 years. Centralized pathology review was performed in all cases; samples were classified as germinal center B-cell-like (GCB) vs non-GCB by immunohistochemistry (Hans algorithm). PET/CTs were performed at baseline, after 2, 4, and 6 cycles, and were reviewed at real time by at least 3 experts of a central panel. Response at the end of therapy was analyzed following the visual method (Deauville scale), and PET2/PET4 were evaluated using the semiquantitative method. Persistent disease at PET4 was considered failure of therapy, and patients were withdrawn from trial treatment.

Results: 121 patients were included; evaluable population per-protocol consisted of 115 (diagnosis not confirmed in 6). Fifty-six patients were treated in the experimental arm (BRCAP) and 59 in the control arm (RCHOP). Median age: 57.1 years (limits 23-70), 57 (49.6%) males. Characteristics at diagnosis: non-GCB subtype 38/103 (36.9%), immunohistochemical co-expression of MYC/BCL2 49/91 (53.8%), stage III-IV 107 (93.0%), ≥2 extranodal locations 58 (50.4%), ECOG 2-3: 36 (31.3%), increased LDH 90 (78.3%), increased beta2microglobulin 75 (65.2%), aalPI 3: 31 (27.0%). No differences were found between arms. Thirty-one (27.0%) patients required of pre-phase treatment. The mean relative dose intensity for bortezomib was 88.9%. Thirty (27.8%) out of 108 patients who have completed 4 cycles had a PET4 positive and were withdrawn of the study therapy. Intention-to-treat CR at the end of therapy (PET4-/PET6-): 28 (50.0%) in BRCAP vs 26 (44.0%) in RCHOP ($p = 0.5$). CR among patients with non-GCB subtype: 15/20 (75.0%) in BRCAP vs 7/16 (43.8%) in RCHOP ($p = 0.087$). The proportion of patients who survives free of event at 2 years was 33 (58.9%) in BRCAP vs 35 (59.3%) in RCHOP ($p = 0.97$). The proportion of patients with non-GCB subtype who survives free of event at 2 years was 14/21 (66.7%) in BRCAP vs 9/16 (56.3%) in RCHOP ($p = 0.73$). After a median follow-up of 14.8 months, estimated 2-year EFS was 52.3% in BRCAP vs 46.3% in RCHOP [HR 0.84 (95% CI 0.49-1.45)], and 2-year OS was 72% in BRCAP vs 71.0% in RCHOP [HR 0.80 (95% CI 0.34-1.83)].

Conclusions: No significant differences were found between RCHOP and BRCAP in terms of CR and proportion of patients free of event at 2 years in this very high-risk population of young DLBCL patients.

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

190 PHASE 1B STUDY OF PEMBROLIZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (RRPMBCL): UPDATED RESULTS FROM THE KEYNOTE-013 TRIAL

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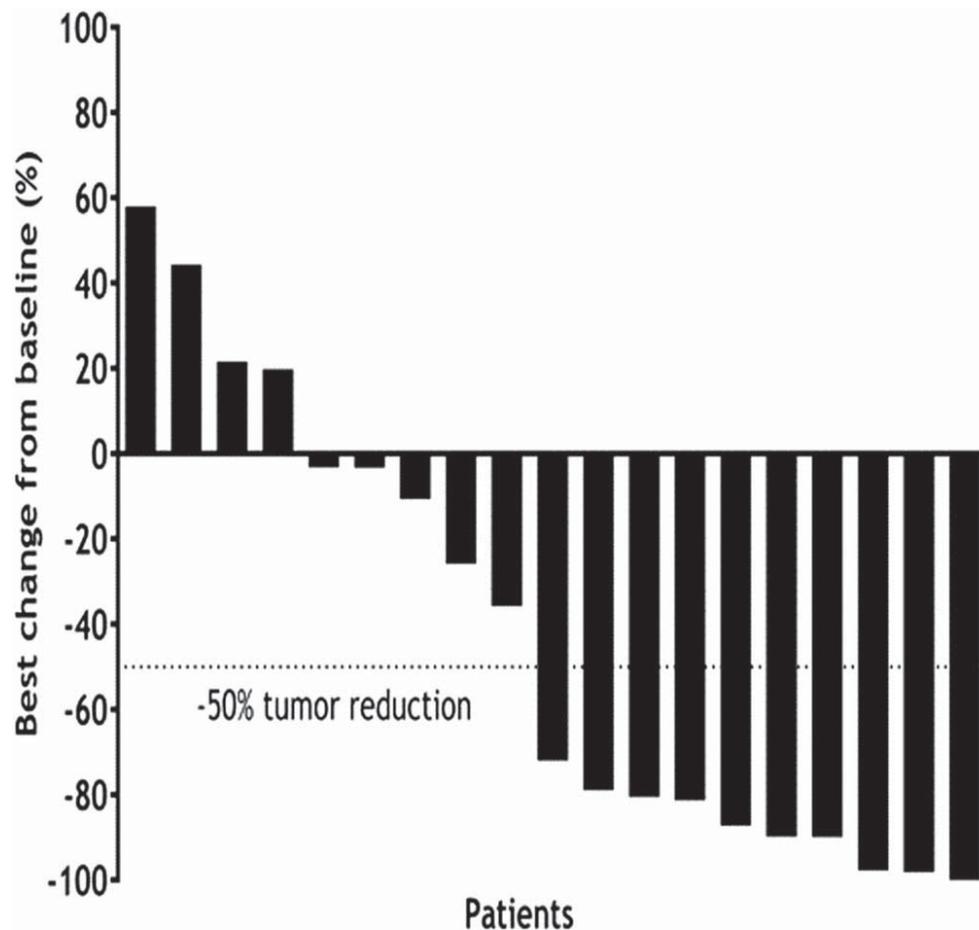
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Introduction: Current treatments for rrPMBCL often yield poor outcomes, but PMBCL's genetics may make it susceptible to PD-1 blockade. The multicenter, multicohort KEYNOTE-013 (NCT01953692) phase 1b trial evaluates safety, tolerability, and antitumor activity of the anti-PD-1 monoclonal antibody pembrolizumab in patients (pts) with hematologic malignancies.

Methods: An independent cohort of KEYNOTE-013 is enrolling PMBCL pts who relapsed after or are ineligible for autologous stem-cell transplant (SCT). Pts initially received pembrolizumab IV 10 mg/kg every 2 weeks (Q2W), later changed to an equivalent regimen of 200 mg every 3 weeks (Q3W). Treatment continues for 2 years or until unacceptable toxicity or confirmed disease progression. Treatment response is radiographically evaluated using 2007 response criteria at week 6, 12, and every 9 weeks thereafter. Primary end points were safety and objective response rate (ORR). Safety population: all pts with ≥1 dose of study drug. Efficacy population: all pts who progress prior to or reach the first efficacy evaluation.

Results: By the analysis cutoff date (January 3, 2017), 22 pts had been enrolled in the PMBCL cohort, 21 were treated, and 19 were radiographically evaluable. Overall, 67% of pts had ≥3 prior lines of therapy, and 67% were ineligible for autologous SCT due to chemorefractory disease. Median follow-up duration was 14.3 months (range, 0.6 to 34.7 months). In the safety population, 14 pts (67%) experienced treatment-related adverse events (TRAEs): 4 pts with grade 3 TRAEs (neutropenia $n = 2$, fatigue $n = 1$, increased alanine aminotransferase $n = 1$) and 1 with a grade 4 TRAE (neutropenia). An additional patient had grade 4 venoocclusive liver disease after allogeneic SCT during the follow-up period after pembrolizumab discontinuation. Seven pts had serious AEs. There were no treatment-related deaths. In the efficacy population (19 evaluable pts and 1 with clinical progression before the first efficacy evaluation), ORR was 50%: 5 pts (25%) each achieved partial or complete response (CR). Five others (25%) had stable disease as best response. Of evaluable pts, 15 (79%) had target lesion reductions (Figure). Median duration of response (DOR) was not reached (range, 1.4 to 28.9 months); DOR in pts with CR ranged from 1.4 to 27.1 months. There were 8 ongoing responses, including 5 in pts who discontinued treatment. Seventeen pts discontinued treatment due to progressive disease on imaging ($n = 7$), clinical progression ($n = 5$), physician decision ($n = 2$), patient decision, CR, or AE ($n = 1$ each); 2 pts were discontinued after completing the maximum 2 years of treatment and remain in remission.

Conclusions: In these heavily pretreated rrPMBCL pts, pembrolizumab had a manageable safety profile and promising antitumor activity. A global multi-center phase 2 trial (KEYNOTE-170) is currently further evaluating single agent pembrolizumab in rrPMBCL.



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

191 RITUXIMAB, LENALIDOMIDE, AND IBRUTINIB ALONE AND COMBINED WITH CHEMOTHERAPY FOR PATIENTS WITH NEWLY DIAGNOSED DIFFUSE LARGE B- CELL LYMPHOMA

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Background: Diffuse large B-cell lymphoma (DLBCL) is categorized by the cell of origin (COO) classification system into germinal center (GCB) and non-GCB subtypes. Both the immunomodulatory agent lenalidomide (L) and BTK inhibitor ibrutinib (I) have shown promising activity in the non-GCB DLBCL subtype as a single agent and in combination with chemotherapy. Preclinical studies demonstrate L + I results in synthetic lethality in non-GCB DLBCL via interferon signaling (Yang et al; Cancer Cell, 2012), but no trials have evaluated the efficacy in newly diagnosed patients. We present the first “window of

opportunity” trial to use targeted therapy (rituximab, R + L + I) prior to chemotherapy in newly diagnosed DLBCL patients.

Methods: In this investigator-initiated phase II trial, patients receive standard R q 21 days (d), L 25 mg po d1-10, I 560 mg po d1-21, and after two 21d RLI cycles or with progression start standard chemotherapy (initially dose adjusted EPOCH q 21d for 6 cycles, but the randomized 50303 study results prompted an amendment to allow either EPOCH or CHOP). L + I dosing may be reduced if significant toxicity criteria are met. Key eligibility criteria include histologically confirmed, treatment-naïve non-GCB DLBCL, age \geq 18 years, and measurable disease. COO will be determined via immunohistochemistry (IHC) for eligibility and NanoString for confirmation. Patients are restaged with PET/CT (Lugano criteria, Cheson et al, JCO 2014). The primary objectives are to determine the overall response rate (ORR) after 2 cycles of RLI and complete response (CR) rate after 6 cycles of RLI + chemotherapy. Secondary objectives include safety and survival outcomes. Exploratory objectives include evaluation of baseline and therapy induced changes in gene and protein expression, mutations, and immune cell subsets in comparison with clinical outcomes. The trial will accrue 60 patients with Bayesian futility and toxicity monitoring rules.

Results: At data cutoff of 3/15/17, 13 patients have enrolled, 1 withdrew consent after 1 cycle, all are available for toxicity and 11 for efficacy. The median age is 65 years, 75% are female, and the median IPI is 2 with 42% having an IPI of 3-5. All patients are non-GCB via IHC testing. Toxicities are noted for no significant rash in any patients and one

case of invasive aspergillosis of the brain on a patient treated with high-dose steroids. All patients have efficacy reassessment after RLI window with an ORR of 82% and CR rate of 42%. The 6 patients who have completed all therapy have all achieved a CR.

Conclusions: The combination of RLI has shown impressive efficacy both alone and with chemotherapy in this ongoing study in newly diagnosed non-GCB DLBCL. One patient had an invasive fungal infection, prompting a protocol amendment to prohibit steroid use during the window portion, and no further events have occurred. Additional results will be presented at the meeting.

Keywords: diffuse large B-cell lymphoma (DLBCL); ibrutinib; lenalidomide

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SAFETY AND CLINICAL ACTIVITY OF TEMSIROLIMUS IN COMBINATION WITH RITUXIMAB AND DHAP IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA—REPORT OF THE PROSPECTIVE, MULTICENTER PHASE II STORM TRIAL

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Purpose: To evaluate the safety, tolerability and efficacy of the combination of the mTOR inhibitor Temezirolimus and a standard salvage regimen (R-DHAP) in patients with relapsed or refractory diffuse large cell B-cell lymphoma (DLBCL).

Methods: This is a prospective, multicenter, phase II, open-label study. Patients with relapsed or refractory DLBCL with a maximum of two prior treatment lines were eligible. The STORM regimen consisted of Rituximab 375 mg/m² (day 2) and DHAP (Dexamethasone 40 mg days 3-6, Cisplatin 100 mg/m² day 3, Cytarabine 2 × 2 g/m² day 4) with Temezirolimus added on day 1 and 8 of a 21-day cycle, with 2-4 cycles planned. In part I, dose levels of 25, 50, 75 and 100 mg for Temezirolimus were predefined. Based on the observed toxicity profile, the independent data safety committee recommended a Temezirolimus dose of 25 mg given on day 1 and 8 for the part II extension cohort of the trial.

Results: We here report on 55 patients (pts), 15 from part I and 40 from part II. Five pts were not evaluable for response. Of the evaluable 50 patients, median age was 63 years, and median number of prior regimen was 1. Temezirolimus dose was 50 mg on day 1 and 8 in 7 pts from the part I of the trial and 25 mg in the remaining 48 pts. The overall response rate was 78% (39/50pts) with 28 partial and 11 complete responses. In addition, two patients with SD had a negative PET-CT; however, because no baseline PET-CT was available, these patients were not assessed as responses. After a median follow-up of 10 months for the total study population, median PFS and OS have not been reached. Early safety analysis includes preliminary data of 22 pts. The most frequent non-hematologic side effects were nausea (14 pts, 64%), epistaxis (11 pts, 50%), fatigue (12 pts, 55%), fever (11 pts, 50%) and diarrhea (11 pts, 50%). Frequent grade 3/4 events ($n > 2$) included leukopenia (21 pts, 95%), thrombocytopenia (20 pts, 91%), lymphopenia (11pts, 50%), anemia (8 pts, 36%), neutropenia (10 pts, 45%), renal failure (3 pts, 20%) and infections (7 pts, 32%, bladder infection, esophagus infection, central venous access infection, soft tissue infection, mucositis). Two therapy-related deaths occurred (one patient died from sepsis during neutropenia, another from cerebral bleeding, both events occurring after cycle 3).

Conclusion: Temezirolimus can be safely added to DHAP and Rituximab with promising activity.

Keywords: diffuse large B-cell lymphoma (DLBCL); mTor inhibitors; salvage treatment

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

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Introduction: Patients (pts) with persistent DLBCL after two lines of therapy have limited effective treatment options. The nuclear export protein exportin 1 (XPO1) is upregulated in hematologic malignancies, including DLBCL. Selinexor (SEL), an oral XPO1 inhibitor, causes sequestration of tumor suppressor proteins including p53, p21, and I κ Ba, the latter of which serves to suppress NF- κ B-driven transcription, along with reductions in c-Myc and Bcl family proteins. In a phase I clinical study pts with relapsed/refractory (R/R) DLBCL treated with SEL, an overall response rate (ORR) of 32% including 4 CRs was shown. **Methods:** Pts with R/R DLBCL were randomized to 60 or 100 mg of SEL twice weekly (8 doses) per 28-day cycle. Pts were also stratified by DLBCL subtype (GCB or non-GCB). The primary objectives are to determine the ORR, and safety of 60 v 100 mg doses. Disease response was assessed by an Independent Central Radiological Review (ICRR), using the Lugano Classification (Cheson, 2014). Pt tissue samples were also collected to evaluate cytogenetics.

Results: 72 pts were enrolled: 37 pts on 60 mg and 35 pts on 100 mg. Both groups had a median of 3 prior treatment regimens. The most common related Grade 1/2 adverse effects (AEs) were fatigue (47%), nausea (46%), anorexia (42%), and vomiting (33%). Common Grade 3/4 AEs were thrombocytopenia (39%), fatigue (18%), neutropenia (18%), and anemia (13%). They were managed with dose interruption/reduction, platelet stimulators, and/or standard supportive care. Grade 3/4 fatigue (26% v 11%) and thrombocytopenia (46% v 32%) were higher in 100 mg arm as compared to the 60 mg arm. Among the 63 evaluable pts, the ICRR determined ORR was 28.5% (Table). Nine responders, including 6 CR, remain on treatment. Responders on the 60 mg arm have a median time on treatment of 8.9 months as compared to 3.8 months on the 100 mg arm. Evaluation of molecular predictors of response is currently ongoing including investigation of translocations in c-Myc and Bcl proteins as well as targeted sequencing for alterations in genes commonly mutated in B-cell malignancies.

Conclusion: SEL monotherapy shows activity in pts with R/R DLBCL including in pts with GCB subtype. 60 mg SEL twice weekly was more tolerable than 100 mg twice weekly, with fewer dosing interruptions due to toxicity. Objective responses to SEL were durable at 60 mg BIW, suggesting these responses were associated with clinical benefit. Molecular predictors of response are being evaluated.

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

194 BENDAMUSTINE AS PART OF CONDITIONING REGIMEN FOR AUTOLOGOUS STEM-CELL

TABLE 1 ICRR–best response

Category	N	ORR (%)	CR (%)	PR (%)	SD (%)	DCR (%)
All Doses	63	18 (28.5%)	7 (11.1%)	11 (17.4%)	9 (14.2%)	27 (42.8%)
60 mg	32	9 (28.1%)	4 (12.5%)	5 (15.6%)	3 (9.3%)	12 (37.5%)
100 mg	31	9 (29%)	3 (9.6%)	6 (19.3%)	6 (19.3%)	15 (48.3%)
GCB-Subtype	32	8 (25%)	3 (9.3%)	5 (15.6%)	6 (18.7%)	14 (43.7%)
Non-GCB Subtype	31	10 (32.2%)	4 (12.9%)	6 (19.3%)	3 (9.6%)	13 (41.9%)

TRANSPLANTATION IN PATIENTS WITH AGGRESSIVE LYMPHOMAS: FINAL ANALYSIS OF A PHASE 2 STUDY FROM GELTAMO

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Introduction: We conducted a phase 2 trial (ClinicalTrials.gov Identifier: NCT01296256) to evaluate the safety and efficacy of bendamustine as part of conditioning regimen for autologous stem-cell transplantation (ASCT) in patients with aggressive lymphomas.

Methods: Inclusion criteria were histologic diagnosis of (i) relapsed or refractory diffuse large B-cell lymphoma (DLBCL) or grade 3B follicular lymphoma (FL) in partial response (PR) or complete remission (CR) after salvage therapy or (ii) transformed DLBCL or peripheral T-cell lymphoma (PTCL) in first or subsequent PR or CR. Conditioning regimen consisted of bendamustine (200 mg/m², days -7 and -6), etoposide (200 mg/m², days -5 to -2), cytarabine (400 mg/m², days -5 to -2), and melphalan (140 mg/m², day -1) (BendaEAM regimen). Primary

end point was progression-free survival (PFS) at 3 years. Secondary end points were toxicity, response to transplant, and overall survival (OS).

Results: Sixty patients (median age 55 [28-71] years, 50% male) from 22 Spanish hospitals were included from May 2011 to November 2012. Histologies were as follows: 40 DLBCL, 3 grade 3B FL, 13 transformed DLBCL, and 7 PTCL. 82% of patients had received two or more lines of treatment prior to ASCT. Thirty-seven patients (62%) were in metabolic CR (assessed by PET/CT) at the time of transplant and 23 (38%) in PR.

All patients (except one who died early) engrafted after a median of 11 (9-72) and 14 (4-53) days, respectively, to achieve $>0.5 \times 10^9/l$ neutrophils and $>20 \times 10^9/l$ platelets. A total of 39 serious adverse events were reported before day +100, including 14 infectious episodes, 2 of them resulting in respiratory failure and death of the patient (3.3% of transplant-related mortality), and 5 episodes of renal failure after bendamustine administration, reversible in all cases. Non-relapse mortality after day +100 was 3.3% (1 patient from Wernicke's encephalopathy and 1 from infectious complications).

Regarding response to transplant, 45 patients (75%) achieved CR and 6 (10%) PR. With a median follow-up of 49 months (34-63), 23 patients had relapsed disease, 3 had secondary neoplasms (2 myelodysplastic syndrome and 1 cholangiocarcinoma), and 18 patients died. Estimated 3-year PFS and OS were 58% and 75%, respectively. Patients with PET+ disease at study entry had significantly worse PFS (23% vs 70% at 4 years, $p < 0.01$) and OS (56 vs 80% at 4 years, $p = 0.041$) than patients who underwent the ASCT in metabolic CR, and this was the only prognostic factor affecting both PFS (RR 0.27 [0.12-0.56]) and OS (RR 0.39 [0.15-0.99]) in the multivariate analysis.

Conclusions: BendaEAM conditioning is a safe, feasible, and active regimen in patients with aggressive lymphomas. Infectious and renal toxicities should be carefully monitored. Our long-term results indicate that efficacy is similar to that previously reported with other regimens most commonly used like BEAM, although patients who are not in metabolic CR before transplant have poor outcomes.

Keywords: autologous stem-cell transplantation (ASCT); bendamustine; diffuse large B-cell lymphoma (DLBCL)

195 REDUCED INTENSITY (FB2) Vs REDUCED TOXICITY MYELOABLATIVE (FB3-4) FLUDARABINE/BUSULFAN-BASED CONDITIONING REGIMENS FOR NON-HODGKIN LYMPHOMA (NHL) ALLOGRAFTED PATIENTS

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Introduction: Fludarabine/busulfan-based conditioning regimens are widely used in Europe for this purpose. Busulfan dose intensity discriminates between reduced intensity (FB2, 2 days of busulfan at 4 mg/Kg/d per os or 3.2 mg/kg/d iv) and reduced-toxicity myeloablative (FB3/FB4, 3 or 4 days of busulfan at 4 mg/kg/d per os or 3.2 mg/kg/d iv) conditioning regimens. While some data have been recently published showing some advantages of higher busulfan dose intensity for myeloid malignancies, there is no such data available in the lymphoid setting.

Methods: This was a large retrospective, registry study conducted on behalf of the Francophone de Greffe de Moelle et de Thérapie Cellulaire, including all adults allografted in France between January 2004 and December 2014 for NHL ($n = 378$). We aim to compare various outcomes between those who received FB2 ($n = 277$) or FB3/FB4 ($n = 101$) as conditioning regimens.

Results: Both groups were comparable for the following variables: median follow-up (FB2: 24.9 vs FB3/4: 23 months), gender (male 61% vs 53%), disease type (low-grade lymphoma 25% vs 21%, mantle-cell lymphoma 17% vs 13%, high-grade lymphoma 25% vs 21%, T-cell lymphoma 32% vs 45%), disease status at transplant (complete remission/very good partial response 64% vs 62%, partial response 28% vs 31%, active disease 8% vs 7%), donor type (sibling 43% vs 49.5%, matched unrelated 56% vs 47%). FB2 patients were significantly older (median 57.3 vs 53.1 years, $p = 0.07$), have been transplanted more recently (median year of transplant: 2011 vs 2010, $p = 0.001$) and have been more previously autografted (69% vs 50.5%, $p = 0.001$). FB3/4 patients have been allotransplanted earlier during the evolution of their disease (median time between diagnosis and allograft 18.2 vs 33.8 months, $p < 0.0001$).

In univariate analysis, 2-year OS (FB2 66.5% vs 60.3%, $p = 0.33$), lymphoma-free survival (FB2 57.9% vs 49.8%, $p = 0.26$), relapse incidence (FB2 23% vs 29.1%, $p = 0.32$) and NRM (FB2 19% vs 21.1%, $p = 0.91$) were similar between both groups. Cumulative incidence of grade 3-4

acute (FB2: 11.2% vs 18%, $p = 0.08$) and extensive chronic (FB2: 17.3% vs 10.7%, $p = 0.18$) GVHD were also comparable as well as 2-year GVHD free/relapse-free survival (FB2: 44.4% vs 42.8%, $p = 0.38$). In multivariate analysis, there was a trend for worse outcome using FB3/FB4 regimens (OS: HR 1.46, 95%CI: 0.96-2.23, $p = 0.07$; LFS: HR 1.43, 95%CI: 0.99-2.06, $p = 0.05$; RI: HR 1.54, 95%CI: 0.95-2.48, $p = 0.07$). These results were also confirmed using a propensity score-matching strategy including 184 FB2 and 98 FB3/4 patients.

Conclusion: This large retrospective study showed that reduced toxicity myeloablative fludarabine/busulfan regimens did not improve outcomes of adults allografted for NHL. FB2 conditioning regimen still should be considered as the standard of care conditioning regimen in this setting.

Keywords: allogeneic stem-cell transplant (alloSCT); busulfan; non-Hodgkin lymphoma (NHL)

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DOUBLE-EXPRESSOR LYMPHOMAS DO NOT HAVE INFERIOR OUTCOME AFTER AUTOLOGOUS STEM-CELL TRANSPLANT IN THE FIRST LINE TREATMENT

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Introduction: Small subgroup of double-hit (DH) or larger one of double-expression (DE) diffuse large B-cell lymphomas (DLBCL) were shown to have worse outcome compared to non-DH and non-DE lymphomas. It has been demonstrated that intensive treatment and high-dose therapy (HDT) with ASCT could improve the results compared to standard treatment. Relapsed/refractory DE DLBCL have however still inferior PFS after ASCT (Herrera, JCO 2016). We have performed the analysis of DE DLBCL patients (pts.) who were transplanted as part of the first-line treatment and compared them to the transplanted non-DE DLBCL pts.

Methods: Eligible for the analysis were consecutive pts. with DLBCL not otherwise specified, diagnosed in single center between 2002 and 2015, treated with rituximab and anthracycline-based chemotherapy who underwent HDT and ASCT as part of the first-line therapy either planned (R-MegaCHOP/ESHAP/BEAM or PET-RIMCEB study GovTrial No: NCT00558220) or pts. who underwent ASCT because of partial remission (PR) only at the end of the induction. Only pts with tissue blocks available for histopathological review (VC, RJ, JS, LB) were eligible for analysis. Cell of origin (COO) was examined by immunohistochemistry (Hans 2004); for MYC and BCL2, all patient were scored semiquantitatively in 10% increments with cutoff values of 40% for MYC and 70% for BCL2. Pearson chi-square, Mann-Whitney, Kaplan-Meier and log rank tests were used.

Results: The cohort consists out of 67 pts. with median age 49 years (21-69), 61% men, high LDH in 90%, intermediate-high and high a-IPI risk resp. in 54% and 37% pts. resp. (there were only 7% low/low-intermediate risk pts). There were 52% of non-GCB and 48% of GCB patients, and 24% of DE and 76% of nonDE. ASCT was planned in 73% of patients (66% with MegaCHOP/+ESHAP regimen) and response driven (PR only) after R-CHOP induction in 27% pts. PET before ASCT was performed in all pts. and was negative in 69%, positive in 25% and inconclusive in 6% pts. With median follow-up 6.5 years, the 7-year probability of PFS and OS was 76% and 81%. There was no PFS difference between DE and non-DE (HR 1.3; 0.44-4.01; p ns; 63.8% vs 78.2%, at 7 y) nor OS difference (HR 0.51; 95% CI 0.17-1.93; p ns; 86.5% vs 77.9%, at 7 y) (Figure 1). There was also no PFS difference between GCB and non-GCB (HR 1.02; 95% CI 0.39-2.66; p ns; 75% vs 74.8% at 7 y) nor OS difference (HR 1.6; 95% CI 0.56-4.61; p ns; 74.9% vs 85% at 7 y). In this cohort, preASCT PET positivity was not predictive for significantly worse PFS (HR 1.59; 95% CI 0.52-5.55; p ns; 70.6% vs 78.9% at 7 y) or OS (HR 1.45; 95% CI 0.42-5.75; p ns; 76.5% vs 84.1% at 7 y).

Conclusions: Double-expressor DLBCL had no worse outcome vs non-DE in the cohort of consecutively treated high-risk pts, when HDT and autologous stem-cell transplant were used as part of the first-line treatment. This observation suggests that in clinically high-risk young patients, the impact of double BCL2 and MYC expression is reduced, and/or intensive immunotherapy with ASCT could overcome it.

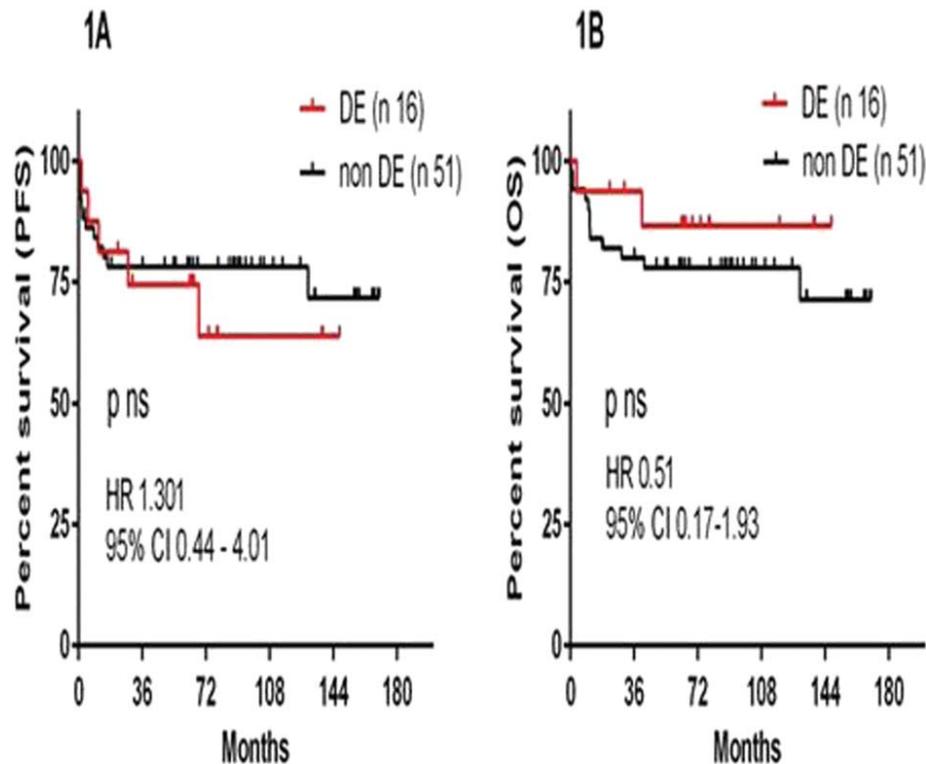
Keywords: "double-hit" lymphomas; autologous stem-cell transplantation (ASCT); diffuse large B-cell lymphoma (DLBCL)

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DIRECT-ACTING ANTIVIRALS DURING OR AFTER IMMUNO-CHEMOTHERAPY IN HEPATITIS C VIRUS-ASSOCIATED DIFFUSE LARGE B-CELL LYMPHOMAS

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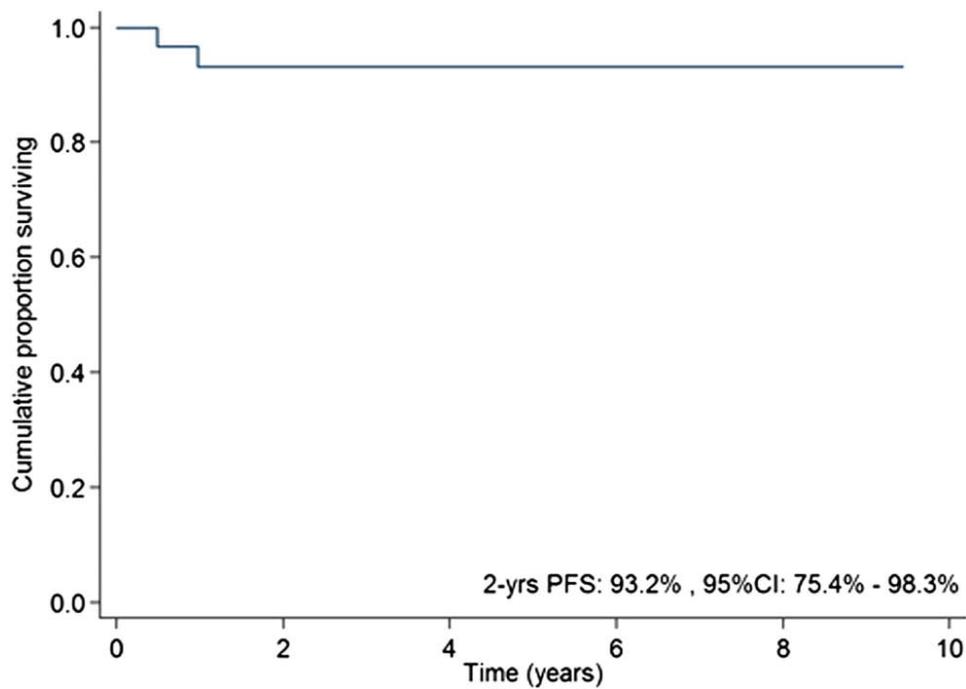
Introduction: Direct-acting antivirals (DAAs) demonstrated >90% sustained virological responses (SVR) across all genotypes in hepatitis C virus (HCV)-infected patients (pts), without significant side effects. Updated international guidelines suggest HCV eradication by DAAs in pts with HCV+ diffuse large B-cell lymphoma (DLBCL) achieving complete response (CR) after 1st line immunochemotherapy (I-CT), although limited experiences substantiate this recommendation. Moreover, no data concerning concurrent administration of DAAs with I-CT have been reported.

Methods: We retrospectively analyzed virological and hematological outcome and survival of 32 consecutive pts with HCV+ DLBCL treated at 16 centers with DAAs regimens either concurrently (Concurrent Cohort, ConC: $n = 7$) or subsequently (Sequential Cohort, SeqC: $n = 25$) to 1st line I-CT.

Results: Thirty-one pts had *de novo* DLBCL (5 with low-grade component) and 1 transformed marginal-zone lymphoma. Germinal-center

(GC)/non-GC cases according to Hans were 37/63%. Median age was 62 years (33-80), stage was III/IV in 28 pts (87.5%), IPI high/high-intermediate in 15 pts (47%). Extranodal sites were involved in 18 pts (56%) (liver in 8 and kidney in 4), spleen in 16 (50%) and bone marrow in 10 (31%). Genotype was 1 in 20 (63%), 2 in 10 (31%), 3 and 4 in 1 pt (3%). Cirrhosis was evidenced in 7 pts (22%) by liver biopsy and/or FibroScan. Seven pts (22%) previously failed interferon-based antiviral therapy (AT). I-CT was R-CHOP(-like) in 30 pts and R-ACVBP in 2. Anthracyclines dose was reduced in 10 pts (median 45%). I-CT was completed in all but 3 pts due to toxicity. Overall, 30/31 evaluable pts obtained CR (97%), while 1 progressed. All pts received appropriate DAAs according to genotype: 30 pts sofosbuvir (SOF)-based regimens (SOF-ledipasvir in 11, SOF + ribavirin [RBV] in 10, SOF + daclatasvir in 7, SOF + simeprevir in 2) and 2 pts ombitasvir-paritaprevir-ritonavir + dasabuvir. Median AT duration was 12 weeks (12-24). Overall, among 27 assessable pts at the time of present analysis 25 achieved SVR (93%), 4/5 (80%) in ConC and 21/22 (95%) in SeqC. The 2 non-responders achieved SVR after a 2nd DAA regimen. DAAs were well tolerated, with only 7 pts (22%) experiencing 13 grade (g) 1-2 adverse events (AEs) in SeqC (g 1 fatigue in 4, g 2 RBV-related anemia in 2 pts), while no AE was recorded in ConC. One pt treated concurrently (14%) experienced hepatic toxicity (g 4), compared to 14 pts (56%; g 1-2 in 9, g 3-4 in 5) treated sequentially ($p = 0.08$). At a median follow-up of 2.3 years (0.3-9.4), no pt died (OS 100%), 2 pts progressed (2 y PFS 93.2%, 95% CI: 75.4-98.3%) (Figure 1) and 1 developed hepatocellular carcinoma (2 y EFS 88.5%, 95% CI: 68.0-96.2%). IPI ≥ 2 extranodal sites and albumin < 3.5 g/dl retained prognostic value on PFS ($p < 0.01$).

Conclusions: Excellent outcome of this selected retrospective series suggests benefit of HCV eradication by DAAs either after or during I-



CT in HCV+ DLBCL. Moreover, concurrent DAAs and R-CHOP administration resulted feasible and effective and may prevent hepatic toxicity of I-CT.

Keywords: diffuse large B-cell lymphoma (DLBCL); hepatitis C

198 CURRENT THERAPY OF SECONDARY CNS INVOLVEMENT IN MALIGNANT LYMPHOMA: DATA FROM A MULTICENTER PROSPECTIVE INTERNATIONAL REGISTRY

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Introduction: CNS involvement is a rare complication of systemic lymphoma. With conventional therapy, the prognosis of secondary CNS lymphoma is poor with median overall survival (OS) in most series of approx. 6 months. The optimal therapeutic management has not been established thus far.

Methods: Since 2011, 181 patients have been included in an ongoing prospective international registry. Here, data of the first 173 patients included until November 2016 is presented.

Results: 30 patients had CNS involvement at diagnosis (cohort I) and 143 at progression/relapse (cohort II). The median age was 63 years (26-86). Of 155 patients with complete data available, 122 (79%) had aggressive B-cell lymphoma, 25 (16%) indolent lymphoma, 5 (3%) mantle cell lymphoma and 3 (2%) T-cell lymphoma. Simultaneous systemic involvement was found in 42% of patients in cohort II. Therapy for CNS involvement and outcome was analyzed in 99 patients thus far (16 in cohort I and 83 in cohort II). Systemic therapy alone was given to 48 (49%), systemic + intrathecal therapy to 43 (43%), intrathecal therapy alone to 5 (5%), radiotherapy alone to 2 (2%); one patient did not receive any treatment. Systemic chemotherapy was high-dose methotrexate (HDMTX)-based in 81 (89%) and high-dose cytarabine (HDArC)-based in 53 (58%); 61 (61% of all) patients received rituximab systemically. Liposomal cytarabine was the most frequent intrathecal therapy given in 30 out of 48 patients (63%). High-dose chemotherapy followed by autologous stem-cell transplantation (HD-ASCT) was performed in 25 (25%) patients. The median progression-free survival (PFS) was 5.9 months (95% CI 3.1-8.7), the median OS 18.6 months (95% CI 10.3-26.9). On univariate analysis, CNS lymphoma at diagnosis, no meningeal involvement, better ECOG performance status, treatment with rituximab, HD-ASCT and response to therapy were associated with better outcome. On multivariate analysis, a prognostic role for CNS involvement at first diagnosis and HD-ASCT (for OS) and no meningeal involvement (for both PFS and OS) was found with response to CNS therapy being the dominating prognostic factor (for both OS and PFS).

Conclusions: This is the largest prospective series on CNSL in the era of modern lymphoma therapies. Our results suggest that with intensive HDMTX- and HDArC-based chemotherapy, the outcome of

secondary CNS lymphoma patients can be improved, particularly if HD-ASCT can be applied.

Keywords: autologous stem-cell transplantation (ASCT); extranodal lymphomas; methotrexate (MTX)

199 VALIDATION OF THE CNS INTERNATIONAL PROGNOSTIC INDEX IN A LARGE ASIAN COHORT-DATA FROM THE SINGAPORE LYMPHOMA STUDY GROUP

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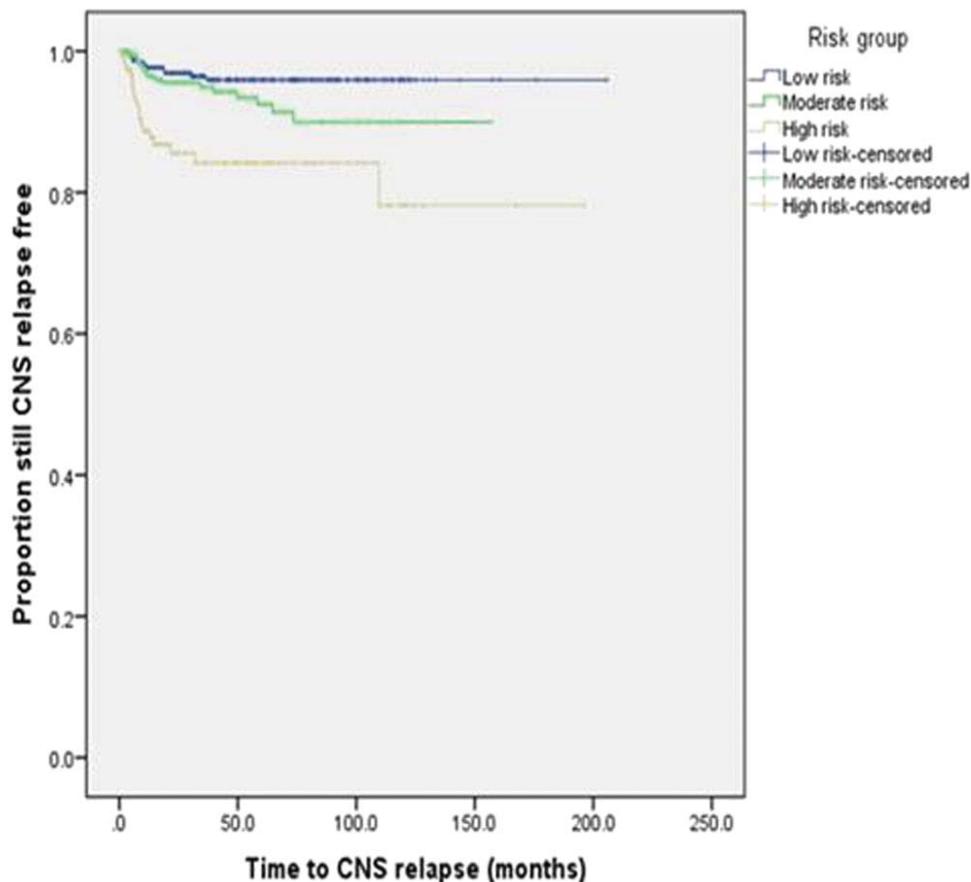
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Introduction: Central nervous system (CNS) relapse in diffuse large B-cell lymphoma patients is associated with poor outcomes. In attempts to identify which patients are at the highest risk and that may benefit from prophylactic measures, various models including the CNS-International Prognostic Index (CNS-IPI) have been derived. We retrospectively analyzed the incidence and characteristics of our own patients suffering CNS relapse and attempted to validate the CNS-IPI in this large Asian cohort.

Method: From the databases of 2 large lymphoma centers in Singapore, we included 812 DLBCL patients sequentially diagnosed and treated with R-CHOP (or R-EPOCH) between 2001 and 2015. All transformed lymphoma, retroviral positive cases, patients treated without curative intent, and CNS involvement at first diagnosis were excluded. The effect of CNS-IPI variables of age, extranodal (EN) sites, lactate dehydrogenase (LDH), performance status, stage, and kidney/adrenal involvement on CNS relapse was examined in univariate and multivariate models. Validation of the CNS-IPI involved assessing discrimination and calibration. Discrimination was assessed via the concordance and area under curve (AUC) and calibration by graphical

TABLE 1

N = 812	Results of Multivariable Analysis for all variables in CNS-IPI		
	HR	95% CI	P value
Stage 3 - 4	2.512	1.103-4.197	0.025
Age > 60	1.463	0.826-2.590	0.192
ECOG >1	2.346	1.180-4.665	0.015
EN sites > 1	1.016	0.503-2.050	0.965
LDH > normal	1.376	0.672-2.815	0.383
Kidney/ adrenal involved	3.324	1.666-6.633	0.001



display of Kaplan-Meier curve for the risk stratification groups defined by CNS-IPI.

Results: The median age was 59 years, and median follow-up in surviving patient was of 4 years. CNS relapse occurred in 49 patients (6%). According to the CNS-IPI, 319, 336, and 157 patients were low, intermediate, and high risk with CNS relapse seen in 3.4%, 5.4%, and 12.7%, respectively. The CNS-IPI model had fair performance in our cohort with AUC value 0.69. Univariate analysis found all CNS-IPI variables to be significantly associated with CNS relapse except for age > 60 years. Multivariate analysis showed only disease stage, adrenal/kidney involvement and ECOG >1 to be significant (Table). Using these 3 variables, we derived a risk model which defined 358, 332, and 122 patients into low, intermediate, and high-risk groups with relapses in 3%, 6.3%, and 13.9%, respectively (Figure 1). The median OS in patients suffering CNS relapse was 1.5 years with only 22% still alive.

Conclusion: We found that a model based just on ECOG, stage, and kidney/adrenal involvement performed equally well as the 6-factor CNS-IPI model. Using this 3-factor model, fewer patients would be identified as high risk, and therefore, fewer subjected to prophylactic measures against CNS relapse.

Keywords: CNS prophylaxis; diffuse large B-cell lymphoma (DLBCL); R-CHOP

200 PROPHYLAXIS WITH HIGH-DOSE METHOTREXATE SIGNIFICANTLY REDUCES CNS DISSEMINATION IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) AND HIGH-RISK CNS-IPI SCORE

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Introduction: CNS relapse is an uncommon but lethal event in DLBCL pts. Early detection and effective CNS prophylaxis reduce related mortality. Evidence supporting the use of intravenous high-dose-methotrexate (HD-MTX)-based prophylaxis is growing; however, prophylaxis cannot be indicated in every DLBCL pt, and risk predictors with high diagnostic sensitivity remain to be defined. Recently, a reproducible model to estimate the risk of CNS relapse in DLBCL pts was reported (Schmitz N, *et al.* JCO 2016). With this "CNS-IPI," based on IPI parameters and involvement of adrenal gland and kidney, the CNS relapse rate was >10% in high-risk pts; however, the role of CNS prophylaxis in these pts remains to be defined. On this background, we analysed the value of CNS-IPI and the role of HD-MTX-based prophylaxis in high-CNS-IPI pts in a mono-institutional series of 242 pts with DLBCL treated in the rituximab era.

Methods: Consecutive HIV-neg adults with DLBCL treated with R-CHOP or similar were considered. CNS, mediastinal and leg-type DLBCL, transformed lymphomas and pts registered in prospective trials were excluded. Following institutional guidelines, pts with high-CNS risk diagnosed after 2007 received CNS prophylaxis, consisting

of 3-4 cycles of MTX 3 g/m² ± intrathecal chemo (IT). CNS-IPI was estimated as reported. For this analysis, pts with testicular involvement were considered at high risk independently of IPI values.

Results: 242 pts were analyzed (median age 66, range 18-89). CNS-IPI was 0-1 (low risk) in 77 (32%), 2-3 (intermediate) in 90 (37%) and ≥4 (high) in 75 (31%). Prophylaxis with HD-MTX ± IT was indicated in 36 pts: 5 with low risk, 7 with intermediate risk and 24 with high risk. CNS prophylaxis was well tolerated; unexpected toxicity and interruptions due to toxicity were not recorded. At a median follow-up of 65 months (12-171), 11 (4.5%) pts experienced CNS relapse: 6 in the brain, the others in the meninges. CNS relapse rate was 1% (1/77) in low-risk pts, 0% (0/90) in intermediate-risk pts and 13% (10/75) in high-risk pts (low-intermediate vs high; $p = 0.00001$), with a 5-year actuarial risk of 2% (95%CI = 0-5), 0% and 19% (95%CI = 10-28), respectively ($p = 0.00001$). Eight of these pts died of CNS progressive lymphoma.

In the 75 pts with high CNS-IPI, CNS relapse occurred in 20% (10/51) of pts who did not receive CNS prophylaxis and in 0% (0/24) of pts who received HD-MTX ($p = 0.02$), with a 5-year actuarial risk of 32% (95%CI = 18-46) and 0% ($p = 0.008$). Overall, 33 high-risk pts experienced relapse, and CNS and lymph nodes were the most commonly involved sites.

Conclusions: With the limitations of a retrospective series, this study shows that HD-MTX prophylaxis is highly effective in pts with DLBCL and high risk of CNS relapse defined by the CNS-IPI and testicular involvement. CNS prophylaxis may contribute to appreciably improve survival of high-risk pts as the incidence and high mortality of CNS relapse.

Keywords: CNS prophylaxis; diffuse large B-cell lymphoma (DLBCL)

201 THE 5-YEAR FOLLOW-UP RESULTS OF THE C5R PROTOCOL WITH RITUXIMAB AND INTRATHECAL LIPOSOMAL CYTARABINE FOR PRIMARY CNS LYMPHOMA: A PROSPECTIVE PHASE 2 STUDY OF THE LYSA

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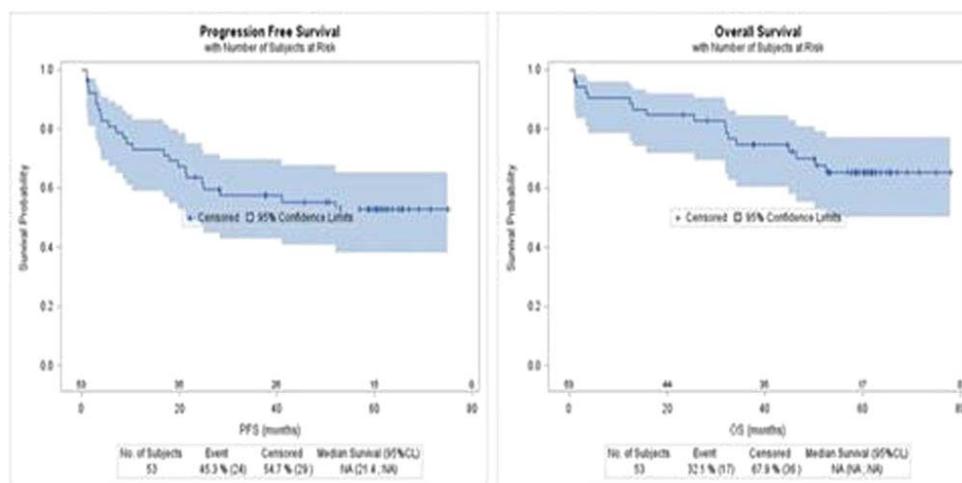
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Introduction: We developed in the LNHCP93 trial an intensive high-dose methotrexate and cytarabine containing chemotherapy (CT) derived from CT regimens used for Burkitt lymphomas (C5R protocol)



followed by brain radiotherapy (RT) showing favorable long-term survival in PCNSL patients younger than 60 years. We prospectively evaluated the addition of intravenous rituximab and intrathecal (IT) liposomal cytarabine to the C5R protocol before RT for 18 to 60 years old immunocompetent patients with a confirmed CD20 positive diffuse large B-cell lymphoma PCNSL. We present the updated results of this multicentric prospective phase 2 study from the LYSA with a median follow-up 59 months (min: 1.1-max: 77.8).

Methods: Fifty-three patients included between August 2007 and September 2011 received two courses of methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone (COPADEM) followed by two courses of methotrexate, cytarabine (CYM) administered at 21-day intervals from day 1 to day 21. At each day 1, intravenous rituximab 375 mg/m² and at each day 3 IT liposomal cytarabine 50 mg were infused. After immuno-CT, a brain RT was planned for all patients. The primary objective of this study was the complete and unconfirmed complete response rate (CR/CRu) after immuno-CT, according to IPCG response criteria. Neurotoxicity was evaluated by a Mini-Mental State Examination (MMSE) test.

Results: The median age of the 53 PCNSL patients was 55 years (range, 36-60), 57% were male, 42% had a performance status (PS) > 1, 55% had an involvement of deep structures of brain, 45% a high CSF protein level and 36% a high LDH level. Forty-five patients (85%) completed the fourth cycles of immune-CT, and three patients (5.7%) died of acute toxicity. Forty-two patients (79%) underwent RT. We showed an improvement of the CR/CRu after immuno-CT from 33% in the LNHCP93 to 66% in the R-C5R protocol ($P < 0.001$). We showed no additional severe toxicities with the addition of intravenous rituximab and IT liposomal cytarabine. The 5-year progression-free survival (PFS) rate of whole cohort was 53% (95%CI, 38% to 66%) (Figure). For patients with 0-1 and 2-4 adverse IELSG prognostic scores, the 5-year PFS rates were 69% and 46%, respectively ($P = 0.13$). The 5-year overall survival (OS) rate for whole cohort was 65% (95%CI, 50% to 77%) (Figure). For patients with 0-1 and 2-4 adverse IELSG prognostic scores, the 5-year OS rates were 91% and 54%, respectively ($P = 0.02$). From baseline to 6-12 months, the median MMSE improved from 26 (3-30) ($N = 42$) to 29 (23-30)

($N = 13$) and was at 30 (29-30) ($N = 3$) at the last follow-up (54-60 months).

Conclusions: R-C5R protocol provided high CR/CRu rates (66%) and favorable long-term outcomes with a 5-year PFS and OS of 53% and 65%, respectively. These results compared favorably with historical controls of LNHCP93 trial who presented a 5-year PFS and OS of 31% and 42%, respectively.

Keywords: primary CNS lymphoma (PCNSL); rituximab

202 DOSE-DENSE CHEMOIMMUNOTHERAPY AND CNS PROPHYLAXIS IN PATIENTS WITH HIGH-RISK DLBCL: A COMPARISON OF Nordic CRY-04 and CHIC STUDIES

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Background: 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 investigated the efficacy of dose-dense chemoimmunotherapy and systemic CNS prophylaxis in two completed Nordic trials including patients less than 65 years with high-risk DLBCL. We combined individual patient data from these studies to compare clinical outcome and prognostic factors in patients treated with CNS prophylaxis given in the beginning (CHIC) vs at the end (CRY-04) of therapy.

Patients and Methods: Inclusion criteria were age 18-65 years, primary DLBCL or grade 3 follicular lymphoma without signs of CNS involvement, WHO performance score 0-3, age-adjusted International Prognostic Index (aIPI 2-3) and/or involvement of anatomical sites associated with an increased risk for CNS recurrence (e.g. testis, facial sinuses, orbita). In CRY-04, six courses of R-CHOEP14 were followed by HD-Mtx and HD-Ara-C. In CHIC, treatment consisted of two courses of HD-Mtx in combination with R-CHOP14, followed by four courses of R-CHOEP14 and one course of R-HD-AraC. In addition, liposomal AraC was administered intrathecally at courses 1, 3 and 5. Primary end points were failure free survival (FFS; disease progression, discontinuation of protocolled therapy due to toxicity, death from any cause) at 3 years and CNS progression rate at 1.5 years. Secondary end points included progression-free survival (PFS; disease progression or death from any cause) and overall survival (OS) at 3 years.

Results: Among 303 patients enrolled in the trials (CRY-04, $n = 160$ and CHIC, $n = 143$), 295 (CRY-04, $n = 154$ and CHIC, $n = 139$) met inclusion criteria and were evaluable for baseline characteristics and primary end points. Median age (54 and 56 years, $p = 0.222$), male/female ratio, stage and aIPI scores were comparable in the two cohorts. Three-year FFS was 63% in CRY-04 and 77% in CHIC ($p = 0.018$) after a median follow-up of 5 and 3 years, respectively. Cumulative incidence rates of CNS progression were 5.0% and 2.4% ($p = 0.22$), and 3-year OS 80% and 86% ($p = 0.508$), respectively. Treatment in the CHIC reduced the risk of systemic progression (aIPI adjusted RR = 0.484, 95%CI 0.300-0.782, $p = 0.003$). PFS benefit with CHIC vs CRY-04 was observed across pre-specified subgroups, and particularly in patients <60 years old ($p = 0.007$), with low proliferation index (Ki67 expression <75%, $p = 0.029$), and BCL2 positivity ($p = 0.006$). In the subsets of patients with available PET data, Deauville score 5 at the end of treatment was associated with increased rate of progression and death in both trials ($p = 0.012$). Only one out of 17 biopsies from PET positive lesions (DS 3-5) contained vital lymphoma tissue.

Conclusions: Our results derived from trial data with homogenous treatment support the use of HD-Mtx in the beginning rather than at the end of therapy. Superior outcome seems to be primarily due to better systemic control of the disease. In addition, number of CNS recurrences is reduced.

Keywords: CNS prophylaxis; diffuse large B-cell lymphoma (DLBCL); immunochemotherapy

INFECTIONS AND THERAPY-ASSOCIATED DEATHS IN ELDERLY PATIENTS WITH DLBCL UNDERGOING R-CHOP IMMUNOCHEMOTHERAPY

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Background: To study if anti-infective prophylaxis with aciclovir and cotrimoxazole is effective in preventing infections in pts. receiving R-CHOP, we compared infections and treatment-related deaths in two prospective DSHNHL trials with different anti-infective strategies.

Methods: 61- to 80-year-old pts. in RICOVER-60 study [Pfreundschuh et al; Lancet Oncol 2008; 9:105-116] received 6 or 8 cycles of CHOP-14 with or without 8 applications of rituximab. Anti-infective prophylaxis consisted of ciprofloxazine (500 mg/d) during days of severe leukocytopenia (<1000/mm³). In OPTIMAL > 60, pts. were randomized to 6xCHOP-14 or 6xCHLIP-14 (conventional substituted by liposomal vincristine [2 m/m², uncapped]) in combination with rituximab, 8 applications q 2 weeks or 12 applications between days -4 and 238 in a 2 × 2 factorial design. In OPTIMAL > 60, anti-infective prophylaxis consisted of cotrimoxazole (2 double-strength doses twice every week p.o.) and aciclovir (4 × 400 mg/d p.o.) in addition to ciprofloxazine.

Results: In RICOVER-60, grade 3&4 infections in 232 patients (IPI = 1 and bulky disease or IPI > 1) receiving 6xCHOP-14 + 8R were 6% (76/1200) per cycle and 28% (60/218) per patient. OPTIMAL > 60 pts. were older (70 vs 68 years) and had more IPI = 3 (33% vs 29%) and IPI = 4.5 (34% vs 23%) compared to RICOVER-60. With intensified anti-infective prophylaxis in OPTIMAL > 60, there were no differences with respect to infections between the 4 treatment arms. Despite the considerably less favourable demographics of the OPTIMAL > 60 study, grade 3&4 infections were 4% (83/1987) per cycle and 18% (64/365 pts. with toxicity documentation) per patient, significantly less than in RICOVER-60 (per cycle: $p = 0.007$; per patient: $p = 0.004$). Even more importantly, treatment-related deaths (defined as all non-lymphoma associated deaths during and within 2 months after the end of chemotherapy) went down from 15/232 (7%) in RICOVER-60 to 7/385 (2%) in OPTIMAL > 60 ($p = 0.003$).

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ANTI-INFECTIVE PROPHYLAXIS WITH ACICLOVIR AND COTRIMOXAZOLE SIGNIFICANTLY REDUCES THE RATE OF

Conclusion: Anti-infective prophylaxis with cotrimoxazole and aciclovir in addition to ciprofloxazine significantly reduced the rates of severe infections and treatment-related deaths in elderly patients receiving R-CHOP supporting the use of this anti-infective strategy in all DLBCL patients receiving R-CHOP.

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

204 FREQUENCY OF PERFORATION & IMPACT OF BOWEL REST IN AGGRESSIVE NON-HODGKIN LYMPHOMA WITH GASTROINTESTINAL INVOLVEMENT: AN INTERNATIONAL, MULTI-CENTER RETROSPECTIVE STUDY

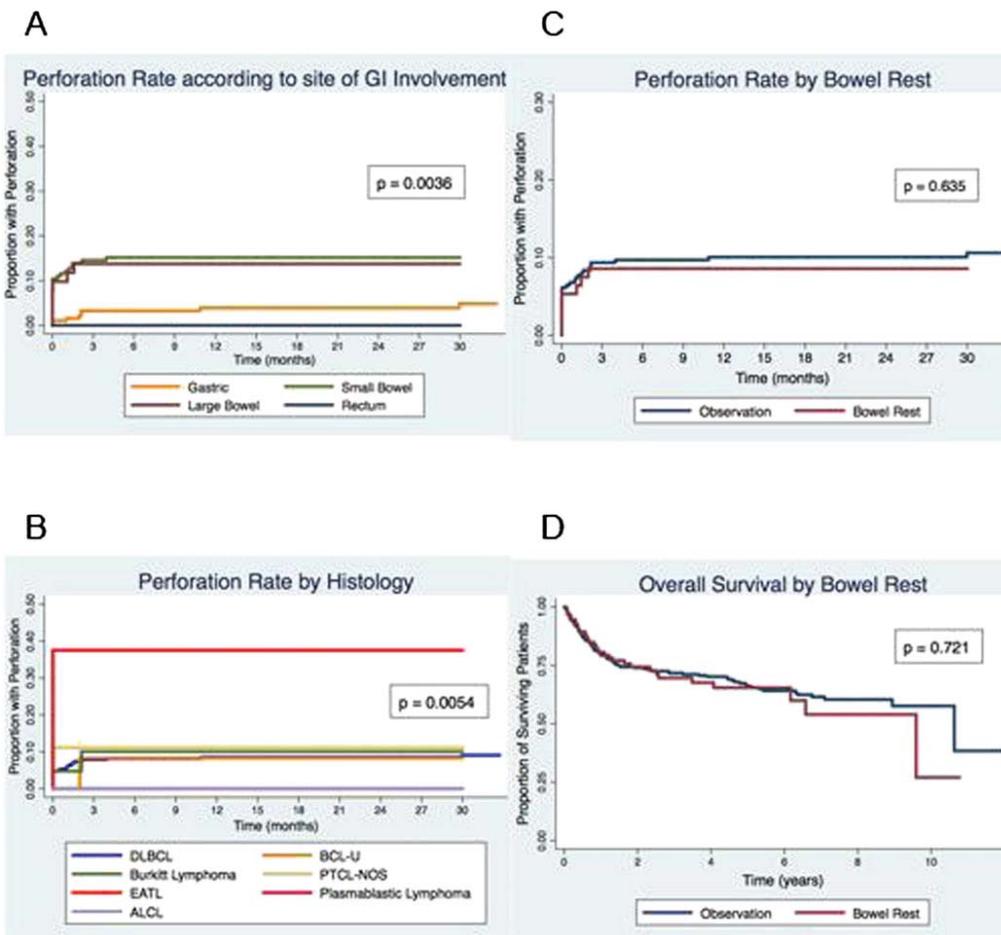
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Introduction: The gastrointestinal (GI) tract is involved in 10-15% of patients with newly diagnosed non-Hodgkin lymphoma (NHL) and can lead to perforation, peritonitis and death. Some physicians advocate admission for the first cycle of chemotherapy to facilitate early recognition and rapid surgical intervention. Others also employ bowel rest and prescribe total parenteral nutrition (TPN) to reduce peritoneal contamination in the event of perforation. However, it is unclear if these measures are effective.

Methods: We performed a multi-centre, retrospective analysis of patients with newly diagnosed aggressive NHL with GI involvement defined by either tissue biopsy or imaging between 1st January 2006 and 1st January 2016. Two centers employed bowel rest as a routine measure, while two did not. The Kaplan-Meier method was used to measure time from diagnosis to perforation and death or last follow-up. Univariate and multivariate analysis of factors associated with perforation and survival was performed using Cox regression.

Results: We identified 419 patients, 204 (49%) treated as outpatients and 215 (51%) as inpatients. Of inpatients, 106 (49%) received bowel rest; 109 (51%) did not. After a median follow-up of 3.6 years (range 0.1-11.9), 41 (9.8%) perforated; 28 (68%) at presentation or prior to chemotherapy. Excluding these, the median time to perforation was 28 days (2-877). Diffuse large B-cell lymphoma accounted for 85% of patients (357), high-grade B-cell lymphoma 3% (13), Burkitt lymphoma 5% (21), peripheral T-cell lymphoma 2% (9) and enteropathy associated T-cell lymphoma (EATL) 4% (16). There were one case each of plasmablastic lymphoma and anaplastic large cell lymphoma (0.4%).



The perforation rate varied according to site (Figure 1A) and histology (Figure 1B). By multivariate analysis, small bowel involvement (HR 3.3; 95% CI 1.4-7.5, $P = 0.005$), large bowel involvement (HR 3.25; 95% CI 1.2-9.2, $P = 0.026$), EATL (HR 3.2; 95% CI 1.3-8.0, $P = 0.012$) and ECOG > 1 (HR 2.0; 95% CI 1.1-3.9; $P = 0.035$) were associated with increased perforation risk. Bowel rest was not associated with differences in rates of perforation (8.5% v 10.2%, $p = 0.635$; Figure 1C), peritonitis (75% v 58%, $p = 0.448$), surgery (75% v 97%, $P = 0.092$) or overall survival (HR = 1.1, 95% CI 0.7-1.6, $P = 0.721$; Figure 1D).

Conclusions: Perforation occurs in 9.8% of patients with aggressive NHL and GI involvement, mostly at initial presentation, prior to chemotherapy. Small and large bowel involvement, EATL and poor ECOG are associated with increased risk of perforation. These data do not support a benefit for bowel rest and TPN in the management of unselected patients with aggressive NHL and GI involvement.

Keywords: chemotherapy; extranodal lymphomas; non-Hodgkin lymphoma (NHL)

MANTLE CELL LYMPHOMA

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LONG-TERM FOLLOW-UP UPDATE FOR PATIENTS ENROLLED IN ECOG 1405

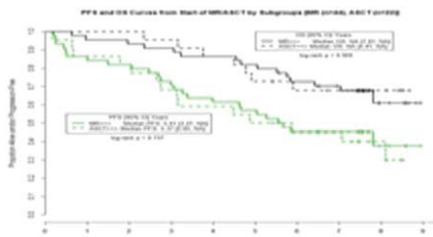
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Introduction: The phase II study, E1405 was conducted by the Eastern Cooperative Group to evaluate the efficacy of bortezomib when combined with modified R-hyperCVAD (VcR-CVAD) followed by maintenance rituximab (MR) in the first line treatment of mantle cell lymphoma (MCL). After VcR-CVAD induction, patients (pts) were offered to come off study to receive an autologous stem-cell transplantation (ASCT) consolidation or maintenance rituximab therapy. The primary end point was complete remission (CR/CRu), median follow-up of 4.5 years as assessed by the trial investigators, and has been reported previously [Chang et al. Blood 2014. 123:1665-1673]. Herein, we report updated PFS for pts treated with maintenance rituximab versus consolidation with ASCT, and compared the genome-wide methylation and transcriptomic patterns for those pts achieving CR versus PR.



Methods: Pts with untreated mantle cell lymphoma, with measurable disease were treated with 6 cycles of the induction regimen VcR-CVAD, consisting of rituximab, bortezomib, cyclophosphamide, doxorubicin, vincristine, and dexamethasone. Pts with at least partial response (PR) were eligible to proceed with MR, 375 mg/m² weekly \times 4 every 6 months for 16 doses or ASCT if deemed eligible. Pts who underwent ASCT were followed for PFS and OS outcomes. Seventy-five pts were treated; 67 pts completed all 6 induction cycles; 22 continued to ASCT; 44 went to MR. CTs performed at baseline, after VcR-CVAD cycles 2, 4, and 6, every 6 months for 5 years, then yearly. Pts were followed until progression and for survival to 10 years from study entry. PETs performed after VcR-CVAD induction for pts with residual masses >1.5 cm and PET imaging was required after MR in pts with residual masses >1.5 cm, who were not previously found to be in CR. We carried out high-resolution genome-wide methylation analysis using enhanced RRBS (ERRBS) from paraffin-embedded tissue as per Akalin et al. (PLOS Genetics, 2012). Similarly, RNA-Seq libraries were constructed from total RNA and paired-end 100 base pairs sequencing was performed on an Illumina HiSeq2500.

Results: With 8 years of follow-up data, there was no difference in PFS and OS among pts who received ASCT vs MR following VcR-CVAD induction therapy in this study (Figure 1). Differential analysis of gene expression and methylation data identified loci associated with increasing depth of response (CR vs PR). Integration of gene expression and methylation identified signatures that are currently being validated in independent cohorts of MCL patients. Results from these analyses will be updated at the time of the meeting.

Conclusions: Updated results from this study indicate that MR following induction is a feasible option over ASCT after VcR-CVAD induction. Despite on average, being an older cohort with higher MIPIs, the MR arm achieved statistically equivalent outcomes, as those undergoing ASCT. Integrative analysis of gene expression and methylation data identified loci associated with long term CR.

Keywords: gene expression profile (GEP); mantle cell lymphoma (MCL); rituximab

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MANTLE CELL LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE: A RETROSPECTIVE MULTICENTER OBSERVATIONAL STUDY OF THE EUROPEAN MANTLE CELL LYMPHOMA NETWORK

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Introduction: A clinical variant of MCL with an indolent course and a median survival of more than 7 yrs is well described in literature. At diagnosis, this variant usually presents with splenomegaly and leukocytosis without nodal involvement. The involvement of extranodal sites (ES) is frequent in classical nodal MCL but the isolated extranodal disease (ED) is very rare and there are no studies evaluating the outcome of these forms.

Methods: A retrospective observational study was conducted on behalf of European MCL Network to describe clinical characteristics and outcome of MCL presenting with isolated ED. We included patients with MCL confirmed by cyclin D1 and/or t(11,14) detection, diagnosed since 1998 to 2014, with isolated ED. Cases with Waldeyer's ring involvement have been included whereas pts with splenomegaly and leukemic disease were not.

Results: We collected data on 127 pts: 77 pts (61%) were male with a median age of 65 yrs (34-94) and Ann Arbor stage I-II in 75 pts (59%). Bone marrow (BM) involvement at diagnosis was detected in 27/120 evaluable pts (22%). ES included Waldeyer's ring (38 pts, 30%), gastroenteric tract (32 pts), ocular adnexa (16), oral cavity and salivary glands (17) and others (14); 10 pts showed multiple ES. The blastoid or pleomorphic variant was documented in 10 and 4 pts (11%) respectively; cyclin D1 was negative in 3 pts and CD5 negative in 14 (all t 11;14-positive by FISH). Ki67 was <30% in 47/72 (65%) evaluable pts. sMIPI was low in 58 (46%) and intermediate/high in 69 pts (54%).

Various treatments were used, including radiotherapy (27/124; 22%), rituximab single agent (4/124), anthracyclines-based regimens (41/124) or cytarabine-based regimens (15/124). Twenty-eight pts received HD-cytarabine followed by ASCT and 3 pts were not treated. ORR was 97% (75% CR) with a median DOR of 37 months (1.5-176). With a median follow-up of 74 months (6-181), 5-year PFS was 52% (CI 95%: 42%-61%) (median 70 mos) and 5-year OS was 71% (CI 95%: 61%-78%) (median not reached); 32 pts relapses and 10 progress (in 91% of cases in the same or different ES). The cumulative incidence of second malignancies was 8% at 5-yrs.

In univariate analysis, lower sMIPI ($p < 0.001$), Ki67 < 30% ($p:0.062$, $p:0.004$) as well as age < 65 yrs ($p < 0.001$) and ECOG 0 ($p < 0.001$) associated to longer PFS and OS, respectively. No differences were found on PFS and OS in terms of anatomic location of ES ($p:0.945$,

$p:0.503$), therapy regimen and ASCT ($p: 0.059$, $p: 0.153$), stage ($p:0.111$, $p:0.677$) as well as cytology ($p:0.856$, $p:0.294$).

In multivariable analysis only age (HR: 2.9, $p:0.001$; HR: 6.1, $p < 0.001$) and ECOG (HR: 3.1, $p < 0.001$; HR: 3.1, $p:0.001$) confirmed their statistically significant impact on PFS and OS respectively.

Conclusion: Pts with isolated ED at diagnosis showed a good prognosis and an indolent course with relapses in ES similarly to MALToma. This clinical variant of MCL, which we can define as MALT-oma like MCL, should be acknowledged to avoid over treatment.

Keywords: mantle cell lymphoma (MCL); Waldeyer ring

207 VENETOCLAX (VEN) IN PATIENTS WITH RELAPSED/REFRACTORY NON-HODGKIN LYMPHOMA (NHL)

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Background: VEN is a selective orally bioavailable BCL-2 inhibitor. The dose-escalation Phase 1 study of VEN in 106 patients (pts) with relapsed/refractory NHL reported an ORR of 44%. Most pts had diffuse large B-cell/follicular lymphoma; we report on updated results in pts with less common NHL subtypes.

Methods: VEN was administered and continued until progressive disease (PD)/unacceptable toxicity, in dose cohorts ranging from 300 to 1200 mg. Adverse events (AEs) were assessed by NCI-CTCAE v4.0 and response by 2007 Cheson IWG response criteria, utilizing CT scans beginning at wk 6.

Results: 35 of 106 pts had mantle cell lymphoma (MCL, $n = 28$), marginal zone lymphoma (MZL, $n = 3$) or Waldenström macroglobulinemia (WM, $n = 4$). Pts were enrolled from Sept 2011 to Aug 2014. The current analysis reports pt status as of Jan 03, 2017. Eight of 35 pts (23%) continue on treatment and the median time on drug for these pts is 34 months (range 30-54). Most common all grade treatment emergent AEs were nausea (51%), diarrhea (49%) and fatigue (34%); grade 3/4 AEs in >10% of pts were neutropenia and anemia (17% each). Laboratory TLS was reported in a single pt who had bulky MCL. The overall rate of infections was 51% and grade 3/4 infections was 23%. MCL pts (median age: 72 years) had received a median of 3 (1-7) prior treatments (tx). Median time from start of prior tx to start of VEN was 13 mo (2-148) and median time from end of prior tx to start of VEN was 8 mo (0.7-147). The median time on VEN was 11 mo (0.2-42).

ORR was 75% ($n = 21$ responders), 6 pts (21%) achieved CR at a median of 4.4 mo (range 1.2-16.1) on VEN. Four pts with CR and two pts with PR remain on study (DORs: 25-40 mo). One pt with a PR proceeded to elective allogeneic stem-cell transplant and remained disease free at last protocol defined follow-up (24 mo after coming off study). Median PFS was 11 mo and DOR was 15 mo for the MCL cohort.

MZL pts (median age: 63 years) had received a median of 4 (2-6) prior tx. Time from start of prior tx to start of VEN was 8, 14, 73 mo and time from end of prior tx to start of VEN was 6, 8, 53 mo. Time on VEN was 5, 1, 35 mo. One pt (6 prior tx) received VEN for <1 mo due to progressive cytopenias; 1 pt (4 prior tx) achieved a PR with VEN at wk 6 but had PD at wk 16; 1 pt (2 prior tx) achieved PR at wk 6, with DOR 32+ mo and remains in PR and on study at 35+ mo. WM pts (median age: 67 years) had a median of 4 (3-5) prior tx. Time from start of prior tx to start of VEN was 5, 18, 33, 67 mo and time from end of prior tx to start of VEN was 4, 10, 29, 66 mo and time on VEN was 42, 17, 54, 20 mo. All pts achieved PR (at wks 6 [$n = 2$], 16 and 36), with DORs of 11, 12, 38 and 50+ mo (latter is ongoing and remains on study at 54+ mo).

Conclusions: VEN monotherapy has a tolerable safety profile with a low rate of serious infections in MCL, MZL and WM pts. ORR was high and many responses durable; median PFS and DOR suggest significant activity in MCL pts. Further investigation of VEN in each disease is indicated.

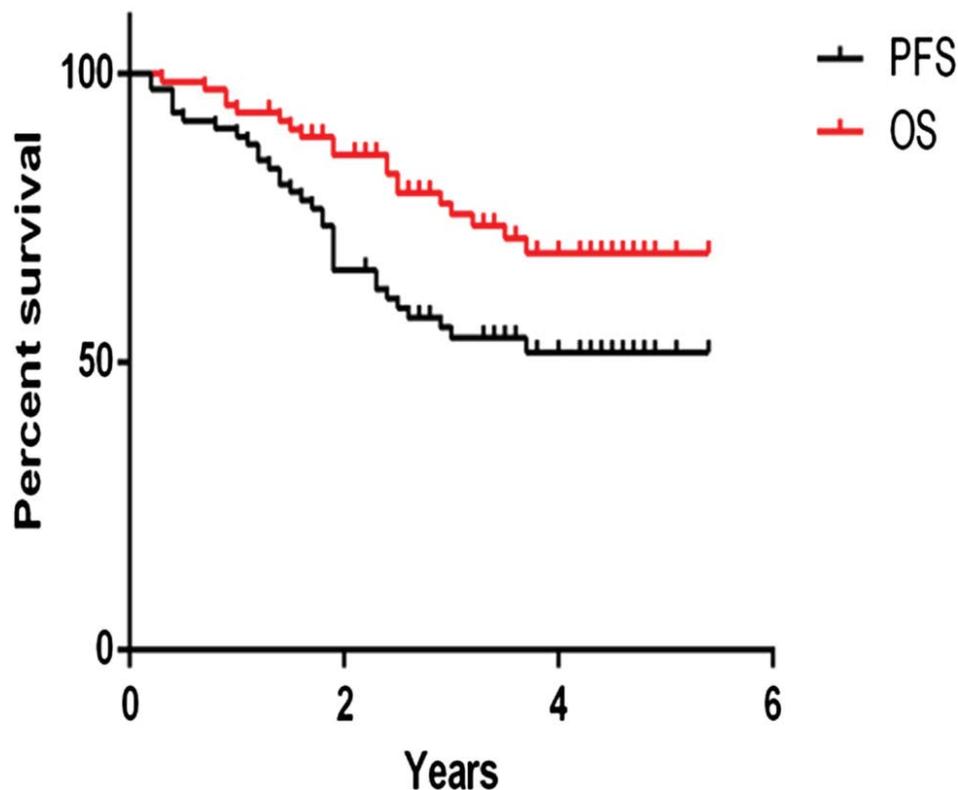
Keywords: ABT-199; non-Hodgkin lymphoma (NHL)

208 R-CHOP/R-HDAC AND RITUXIMAB MAINTENANCE RESULTS IN HIGH COMPLETE REMISSION RATE, MINIMAL RESIDUAL DISEASE NEGATIVITY, AND EXCELLENT SURVIVAL IN ELDERLY MCL PATIENTS

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PFS and OS (73 pts)



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Introduction: Mantle cell lymphoma (MCL) is an incurable subtype of B-cell non-Hodgkin lymphoma. Implementation of high-dose cytarabine (HDAC) into induction therapy followed by stem-cell transplantation and rituximab maintenance (RM) became standard of care for the younger patients with newly dg. MCL. Treatment of the transplant-ineligible patients is still largely based on CHOP or alkylating agents and RM.

Methods: We conducted a multicenter observational study designed by the Czech lymphoma study group (CLSG-MCL-01, GovTrial #NCT03054883), which prospectively analyzed safety and efficacy of alternating 3 + 3 cycles of R-CHOP and R-HDAC (1 or 2 g / m², 2 doses over 24 hours) for newly diagnosed transplant-ineligible MCL patients. Pathological review of all samples was performed. MRD assessment was implemented in Euro-MRD member CLIP laboratory Prague. Primary objectives included response after induction by PET-CT, and progression-free survival (PFS). Secondary objectives included safety, overall survival (OS), and prognostic significance of PET imaging and minimal residual disease (MRD) after induction.

Results: 73 patients were enrolled with median age 70 years. Most patients had intermediate (39.7%) and high-risk (50.7%) disease according to MCL International Prognostic Index (MIPI). Out of the 56 analyzed biopsies 55.4% revealed high proliferation index by Ki-67 ($\geq 30\%$). The overall response rate in the 68 evaluable patients was 95.6% by PET-CT, including 80.9% complete remissions. MRD was evaluated after induction in 54 patients using paired samples of bone marrow (BM) and peripheral blood (PB). Grade 3-4 hematologic and non-hematologic toxicity was documented in 48% and 20.5% patients, respectively. RM was initiated in 59 patients. At the median follow-up of 43.8 months, median PFS and OS were not reached and were 53.9% and 71.3% at 4 years, respectively. For pts on RM 4-year PFS and OS was 61% and 77.2%, respectively. By univariate analysis MIPI, Ki-67 ($\geq 30\%$), bulky disease (≥ 5 cm), involvement of the spleen, and MRD in PB after induction correlated with PFS. Interestingly, MRD in BM after induction did not correlate with PFS or OS. Multivariate analysis revealed that MIPI, bulky disease ≥ 5 cm, achievement of PET-negativity, and MRD in PB after induction independently correlated with PFS.

Conclusion: Alternating R-CHOP and R-HDAC represents feasible and very effective regimen for elderly/comorbid MCL patients. The observed loss of predictive value of MRD in BM after induction appears to be impacted by rituximab maintenance.

Financial Support: AZV 17-28980A, P27/2012, NPU I nr.LO1604.

Keywords: Ara-C; mantle cell lymphoma (MCL); minimal residual disease (MRD)

209 MAINTENANCE RITUXIMAB IMPROVES SURVIVAL IN NEWLY DIAGNOSED MANTLE CELL LYMPHOMA PATIENTS: ANALYSIS OF THE CZECH LYMPHOMA STUDY GROUP

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Introduction: Mantle cell lymphoma (MCL) is a rare, aggressive and incurable lymphoma subtype. Implementation of rituximab, intensive protocols with high-dose cytarabine (HDAC) and autologous stem-cell transplant (ASCT) consolidation have improved a survival in all patient subgroups. Routine application of maintenance rituximab (MR) in first remission is still controversial.

Methods: Analysis of 701 MCL patients with centrally reviewed diagnosis who have been treated with rituximab-based induction regimen from 11/1999 to 6/2015 was performed. The median age at diagnosis was 66 (28-87) years. Advanced disease (Ann Arbor stages III and IV) was present in 92% of cases. MIPI score was low in 19.7%, intermediate in 30.9% and high in 49.4% patients, respectively. Induction regimens used were as follows: R-CHOP/R-CHOP like in 65.0%, intensive HDAC-containing in 25.3% and non-anthracycline regimen in 9.7% of the patients. Consolidation with ASCT was done in 25.1%. Treatment response was assessable in 658 (93.9%) of the cases: of them 381 (57.9%) achieved first complete (CR1) or partial (153, 23.3%) (PR1) remission. We compared an outcome of 283 (53.0%) CR1/PR1 patients who received MR (MR+) with 251 (47.0%) CR1/PR1 pts without maintenance (MR-). Survival was calculated from the date of diagnosis (OS, PFS) and from the date of the response assessment (OSr, PFSr).

Results: When compared MR+ with MR- controls, we did not find differences in terms of clinical stage, MIPI or ECOG distribution, nor in the HDAC or ASCT application. MR+ cohort tends to be older than MR- group (mean 65.2 vs 63.5 y, $P = 0.04$). With median follow-up of 4.4 years, 237 (44.4%) patients progressed or relapsed, and 206 (38.6%) have died. Five-year overall survival in all CR1/PR1 patients (5-y OS) was 63.7% (95% CI 0.59-0.68) and five-year progression-free survival (5-y PFS) 44.4% (95% CI 0.40-0.49). 5-y OSr in MR- group was 50.0% compared to 71.7% in MR+ ($P < 0.001$, HR = 0.35). 5-y PFSr was 39.6% in MR- and 56.4% in MR+ group, respectively ($P < 0.001$).

Conclusions: Maintenance therapy rituximab in MCL patients after first line therapy has significantly improved both OS and PFS compared to the patients with observation only. Maintenance of the first remission remains crucial for a long-term disease control in MCL and results in a significant survival benefit.

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Keywords: mantle cell lymphoma (MCL); rituximab

210 RITUXIMAB MAINTENANCE AFTER NORDIC PROTOCOL (R-MAXICHOP/HD- ARAC/ASCT) SIGNIFICANTLY PROLONGS SURVIVAL IN YOUNG MANTLE CELL LYMPHOMA PATIENTS

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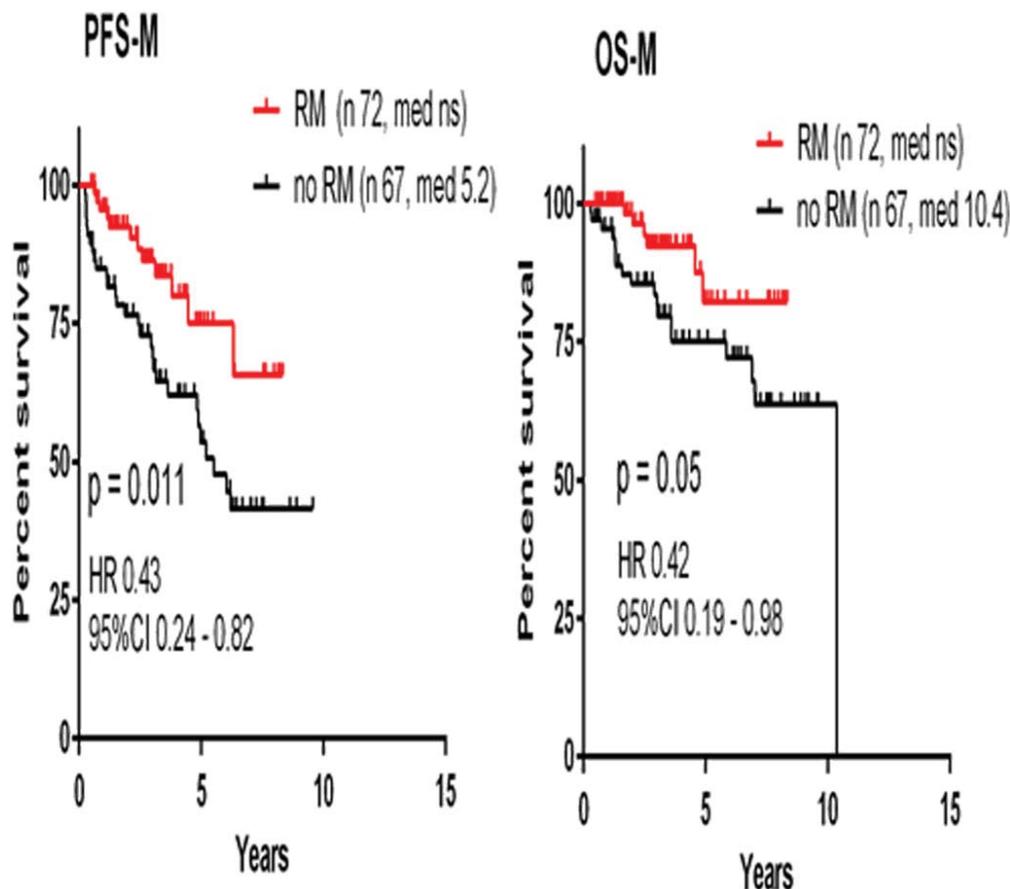
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Introduction: Mantle cell lymphoma (MCL) is an incurable subtype of B-NHL. Implementation of high-dose cytarabine (HDAC) into induction followed by high-dose therapy and stem-cell transplantation (HDT-SCT) and rituximab maintenance (RM) became standard of care for the younger patients with newly dg. MCL.

Methods: We retrospectively analyzed data of 148 pts with newly dg. MCL from the Czech Lymphoma Study Group Registry. The pts were treated with the Nordic protocol (Geisler et al. Blood, 2008) in 3 hematology centers in the Czech Republic since 1.1.2006 until 31.1.2015. Consolidation with HDT-SCT was carried out in most pts, who achieved response after induction. Administration of RM every 2-3 months, usually for the total of 8-12 doses, depended on the practice of the particular center.

Results: Median age was 57 years (men : women = 2:1). MIPI low, intermediate, and high risk was observed in 59 (40.4%), 56 (38.4%), and 31 (21.2%) pts, resp. Bone marrow involvement was found in 78.4% pts, splenomegaly in 53.8% pts, extranodal (EN) involvement in 52.8%, bulky disease ≥ 10 cm in 16.3%. Out of 91 analyzed biopsies 44% revealed high proliferation index by Ki-67 ($\geq 30\%$). Two pts died during induction from septic shock. Therapy was changed in 3 pts because of insufficient response after 3 cycles, and 143 pts (96.6%)



completed the induction. ASCT with BEAM was performed in 125 pts (87.4%). Two pts died from septic shock during HDT-SCT. In the subgroup of 139 pts, who were evaluated by CT after induction (and before HDT-SCT) the ORR was 100% (74.8% CR, 25.2% PR). By March 1, 2017, the median follow-up of the living pts was 4 years. At that time, 41 out of 148 (27.8%) analyzed pts experienced disease relapse, and 32 pts (21.6%) had died (8 in remission). Median PFS and OS of the total cohort reached 6.7 and 10.9 years, respectively. Out of the 141 pts, who completed induction (with or without ASCT), 2 pts progressed before the first scheduled dose of RM could be given (≤ 3 months after end of the induction/ASCT), 72 pts received RM, and 67 pts were observed only. RM vs observation (no RM) led to improvement of PFS-M (PFS since the last treatment) at 4 years 80.1% versus 61.2% (HR 0.43; CI 95% 0.24-0.82, p 0.011) and OS-M at 4 years 92.3% versus 75.2% (HR 0.42; CI 95% 0.19-0.98; p 0.05) (see Figure). Rituximab maintenance led to 57% risk reduction of progression and 58% risk reduction of death.

Conclusion: Nordic protocol represents safe and very effective regimen for younger MCL patients. The analysis confirmed significant impact of rituximab maintenance on prolonged survival with 58% risk reduction of death.

Financial Support: AZV 17-28980A, PRVOUK-27/LF1/1.

Keywords: Ara-C; mantle cell lymphoma (MCL); rituximab

211 SAKK 36/13-IBRUTINIB AND BORTEZOMIB FOLLOWED BY IBRUTINIB MAINTENANCE IN PATIENTS WITH RELAPSED AND REFRACTORY MANTLE CELL LYMPHOMA: PHASE I REPORT OF A PHASE I/II TRIAL

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Introduction: Mantle-cell lymphoma (MCL) remains incurable with frequent relapses, limited treatment options and progressively shorter disease-free survival with every relapse. The Bruton's tyrosine kinase inhibitor ibrutinib (IBRU) and the proteasome inhibitor bortezomib (BOR) have both single agent activity and regulatory approval in MCL. IBRU and BOR both result in a downregulation of NF- κ B activity via different molecular targets. IBRU resistance involves mutations in genes of the NF- κ B pathway. The combination of both drugs provides synergistic cytotoxicity in BOR-sensitive and refractory MCL *in vitro*.

Methods: We included patients (pts.) with confirmed MCL, refractory or relapsed after ≤ 2 lines of a non-BOR-containing chemotherapy (incl. high-dose chemotherapy), and excluded pts. with prior BOR/IBRU therapy, with CNS disease, in need of anticoagulation (warfarin, vitamin K antagonists), and with active Hepatitis B, C or HIV infection. Pts. received 6 21-days cycles of IBRU + BOR, followed by IBRU maintenance until disease progression or unacceptable toxicity. To establish the recommended phase II dose, a 3 + 3 dose escalation design was used. BOR was given s.c. at the labelled dose (1.3 mg/m², days 1, 4, 8, 11 q3w), and IBRU continuously at 420 mg/day (level 1), and 560 mg/day (level 2). Dose-limiting toxicities (DLTs) were assessed in cycle 1 and were defined as study drug-related adverse events (AE, CTCAE, v4.0) including ≥ 7 missed days of IBRU, ≥ 2 missed doses of BOR, delay of >2 weeks of cycle 2, hematological DLTs (ANC < 0.5 for ≥ 7 consecutive days, febrile neutropenia, and G4 thrombocytopenia), and non-hematological DLTs \geq G3. The antitumor activity of the combination was a secondary objective.

Results: No patient experienced a DLT during the first cycle, the minimum of 9 pts. was needed. The most frequent AEs of the combination treatment included thrombocytopenia (8 pts), peripheral polyneuropathy (PNP) and fatigue (6 pts. each), anemia and diarrhea (5 pts. each). The majority of the AEs were G1 & 2. Six pts. experienced G3 AEs with thrombocytopenia (3 pts.), PNP, lung infections, lymphocyte count decreased (2 pts.), and one pt had a G4 thrombocytopenia. Although considered G1, an unexpected AE in 5 pts. was an injection site reaction. In a protocol amendment, 8 mg dexamethasone will now be allowed as co-medication prior to injecting BOR. At data cut-off (January 31, 2017), 2 pts. had stopped therapy because of progressive disease (one at end of cycle 3, one during maintenance). 3 pts. are in follow-up incl. 1 pt who went on to successful stem-cell transplantation.

Conclusions: IBRU with twice-weekly BOR at 1.3 mg/m² s.c. can safely be administered. We define IBRU 560 mg/day as the recommended phase II dose for the combination with standard dose BOR. The safety and clinical efficacy of dose is currently being tested in the ongoing phase II part of this trial. (ClinicalTrials.gov Identifier: NCT02356458).

Keywords: bortezomib; ibrutinib; mantle cell lymphoma (MCL)

212 PHASE I/II CLINICAL TRIAL OF AN ACTIVATED WHOLE TUMOR CELL VACCINE FOLLOWED BY TRANSFER OF IMMUNE T CELLS IN PATIENTS WITH MANTLE CELL LYMPHOMA

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Introduction: We report interim results of a CpG-activated whole tumor cell vaccine for patients with newly diagnosed Mantle Cell Lymphoma (MCL). This phase I/II trial (NCT00490529) had the primary end points of safety and freedom from minimal residual disease (MRD) at 1 year post autologous stem-cell transplant (ASCT). Secondary end points include time to treatment failure (TTF) from initial chemotherapy, overall survival (OS), and T cell immune response.

Methods: Prior to treatment, patient-specific vaccines were made by activating freshly collected tumor cells with PF-3512676 (CpG) followed by radiation (200 Gy). Patients with a partial or complete response after standard immunochemotherapy received three subcutaneous injections with the vaccine product together with additional CpG (18 mg). T-cells were collected by leukapheresis after the last vaccine and cryopreserved. The day after an ASCT, the T-cell product was infused and a 4th vaccination was given. A 5th booster vaccination was given ~3 months post ASCT. Blood samples were collected at various time points for measurement of anti-tumor immune responses and for detection of MRD by VDJ high throughput sequencing of blood mononuclear cells (ClonoSeq™).

Results: Between April 2008 and August 2016, 65 patients were enrolled and 43 patients have completed ASCT and are included in the safety analysis. The CpG MCL vaccine was well tolerated. The most common toxicity was grade I/II erythematous rash at the injection site (98%), and no unexpected toxicities were seen before or after ASCT. 34 patients are at least 1 year post ASCT and included in the primary analysis. 31 (91%) patients were MRD negative at the previously validated threshold (1 MCL clone per 10,000 input genome equivalents of DNA). MRD negativity at 1-year post ASCT predicted longer subsequent remission duration ($p < 0.0001$) and survival ($p = 0.0021$). Lower levels of MRD down to 1 per million were occasionally detected but were not associated with relapse or survival. Median TTF and OS have not been reached (NR) with an average follow-up of 4.91 years. By comparison a contemporaneous cohort of similar patients with MCL who received the same ASCT at our institution, but with no vaccine, have a median TTF of 4.03 years ($p = 0.164$). Analysis of the vaccine characteristics revealed that patients whose tumor cells demonstrated CpG-induced elevation of PD-L1 had significantly worse TTF (2.4 years vs NR, $p = 0.0037$) and OS (3.2 years vs NR, $p = 0.0042$). We also detected tumor-specific CD4+ and CD8+ T cell immune responses following vaccination.

Conclusion: The addition of a CpG-activated, autologous tumor cell vaccination and adoptive immune T-cell product to standard therapy for MCL is feasible and safe. At this interim analysis, vaccinated patients had freedom from MRD at 1 year post transplant that surpasses previously reported rates.

Keywords: B-cell lymphoma; mantle cell lymphoma (MCL); minimal residual disease (MRD)

213 OBINUTUZUMAB PLUS IBRUTINIB IN RELAPSE/REFRACTORY MANTLE CELL LYMPHOMA PATIENTS: FIRST RESULTS OF THE OASIS PHASE I TRIAL

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Rational: Mantle Cell Lymphoma (MCL) cell survival and drug resistance are dependent on B-cell-receptor signaling, Bcl-2 protein and microenvironment. Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor that is approved in the US and EU for previously-treated MCL. It inhibits both tumor cell proliferation and binding to the microenvironment. Mechanisms of resistance to ibrutinib are not fully understood but BTK or BCR signaling cascade mutations have been described. (Chiron et al. Cancer Discovery). Venetoclax is a Bcl-2 inhibitor. Expression of BCL-2 family proteins Mcl-1 and Bcl-xL are hypothesized to confer resistance to venetoclax. These proteins are upregulated by the tumor microenvironment but downregulated by ibrutinib (Touzeau CCR 2011, Chiron Oncotarget 2015). Our preclinical investigations show that microenvironment-dependent long-term expansion and drug resistance to venetoclax are counteracted by obinutuzumab (type II glycoengineered humanized anti-CD20 antibody) (Chiron et al. Blood 2015).

Study Design: The Oasis trial (NCT02558816) has been designed to assess the safety and tolerability of the obinutuzumab/ibrutinib (step A) and obinutuzumab/ibrutinib/venetoclax (step B) combinations in patients with relapsed/refractory MCL. Oasis is a multicenter, non-randomised, phase I study for relapsed/refractory MCL. **Step A** evaluates the safety of obinutuzumab (1000 mg IV C1D1, 8,15, then C2-6 D1 and every 2 months until C24) plus ibrutinib (560 mg/d until progression) ($n = 9$). **Step B** follows if no unacceptable toxicity is observed and its primary objective is to determine the maximal tolerated dose of obinutuzumab/venetoclax/ibrutinib. Venetoclax is administered from C1bis (C1bisW1 20 mg/d, C1bisW2 50 mg/d, C1bisW3 100 mg/d and C1bisW4: 200 and from C2: 400 or 600 or 800 mg/d) ($n = 24$).

Results: We present the step A results. Enrolment in step A started in October 2015 has been completed in June 2016 ($n = 9$). Median age at inclusion is 64 y (range 58-82) and median lines of treatment prior inclusion is 1 (1-4). No DLT or unacceptable toxicity have been reported during the first 2 cycles. 37 grade 3-4 AEs in 8 patients have been reported during the first 6 cycles (including 20 that occurred during the first 2 cycles). According to Lugano 2014 criteria, 7 patients reached CR at C6 and one reached PR. One patient had progressive disease after end of C1 and died 2 months later. The median follow-up is 8 months for CR patients. All CR and PR patients remain

under treatment (including 4 patients who received more than 10 cycles).

Conclusion: Obinutuzumab/ibrutinib combination has manageable safety profile and provides promising early clinical activity with high response rates in R/R MCL. Enrolment in step B (Obinutuzumab/ibrutinib/Venetoclax) started in October 2016. Three patients has been included in the first cohort (Venetoclax = 400 mg). Data regarding step B will be updated in the final presentation.

Keywords: mantle cell lymphoma (MCL)

214 RITUXIMAB MAINTENANCE AFTER AUTOLOGOUS STEM-CELL TRANSPLANTATION IN PATIENTS WITH MANTLE CELL LYMPHOMA, FINAL RESULT OF THE LyMA TRIAL CONDUCTED ON BEHALF THE LYSA GROUP

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Mantle cell lymphoma (MCL) accounts for approximately 6% of non-Hodgkin lymphoma (NHL) in adults. MCL commonly responds to initial therapy but inevitably patients relapse and response duration decreases from one salvage therapy to the next. Indeed, there is an urgent need to control and/or eradicate residual MCL cells that are responsible for early and late relapses. Maintenance with Rituximab (RM) after R-CHOP has been shown to prolong OS in elderly MCL patients treated with R-CHOP (Kluin-Nelemans et al. NEJM). Induction with high-dose cytarabine followed by autologous stem-cell transplant (ASCT) consolidation is standard of care for young patients but RM after ASCT has never been investigated so far. The LyMa trial

(ClinicalTrials.gov: NCT00921414) is a prospective international randomized phase III trial that investigated RM after ASCT in young previously untreated MCL patients. Patients were included at diagnosis (<66y; stage >I, untreated, diagnosis of MCL according to WHO 2008 classification). Induction immuno-chemotherapy consisted of 4 courses of R-DHAP every 21 days (Rituximab, Dexamethasone, High-dose cytarabine, salt Platinum) followed by ASCT consolidation. Patients who were not in response (CR/CRu or PR) after R-DHAP received 4 additional courses of R-CHOP-14 before ASCT. The conditioning regimen for ASCT was R-BEAM. Patients in response after ASCT were randomized (1:1) between RM or no RM. RM consisted of one infusion of Rituximab (375 mg/m²) every 2 months for 3 years. The primary end point was event-free survival (EFS) calculated from time of randomization; events were defined as disease progression, relapse, death, severe infection or allergy to Rituximab. Progression-free survival (PFS) and overall survival (OS) from time of diagnosis and time of randomization were secondary end points. The interim analysis showed a trend for a longer EFS and PFS in favor of RM arm. (Le Gouill et al., ASH 2014, abs 146). Herein, we present the results of the final analysis.

Results: Two hundred and ninety-nine patients were enrolled from September 2008 to August 2012. Demographic and clinical characteristics of the patients were as followed: median age of 57y (27-65), 79% of male, MIPI-low in 53.2%, MIPI-I in 27.4% and MIPI-H in 19.4%. After inclusion, 277 patients completed the 4 courses of R-DHAP. The CR/CRu rate after R-DHAP was 77.3% and ORR was 89.3%. Twenty patients received R-CHOP. In all, 257 patients (including 12 patients who received R-DHAP/R-CHOP) underwent ASCT. After ASCT, 240 patients were randomized (RM, n = 120; no RM, n = 120). Median follow-up (mFU) from inclusion and from randomization were 54.4 m (52.7-59.2) and 50.2 m (46.5-54.2), respectively. The mPFS and mOS from inclusion in an intention to treat analysis were not reached; the 4y-PFS and OS were 67.8% (95%CI, 62.1 to 72.8) and 78% (95%CI; 72.8 to 82.3), respectively. According to EFS definition, 47 (39.2%) patients had an event in the no RM versus 25 (20.8%) in the RM arm. The mEFS from randomization was not reached in both arms. The 4y-EFS was 61.4% (95%CI; 51.3 to 69.9) in the no RM arm vs 78.9% (95%CI; 69.6 to 85.6) in the RM arm (p = 0.0012). The EFS duration was significantly superior in the RM arm with a 54.3% reduction in the risk of event (Hazard ratio (HR) = 0.457; 95%CI, 0.28 to 0.74; p = 0.0016). The median PFS and OS from randomization were not reached in both arms. The 4y-PFS and OS from randomization were superior in the RM arm: 82.2% (95%CI; 73.2 to 88.4) vs 64.6% (95%CI; 54.6 to 73) (p = 0.0005) and 88.7% (95%CI; 80.7 to 93.5) vs 81.4% (95%CI; 72.3 to 87.7) (p = 0.0413). Patients in the RM arm had a 60% reduction of risk of progression (HR = 0.4; 95%CI, 0.23 to 0.68; p = 0.0007) and a 50% reduction of risk of death (HR = 0.5; 95%CI, 0.25 to 0.98; p = 0.0454). The per protocol analysis yielded similar results.

In conclusion, the LyMa trial demonstrates for the first time that RM after ASCT prolongs EFS, PFS and OS. Thus, 4 courses of R-DHAP plus ASCT (without TBI) followed by RM maintenance (one infusion every 2 month for 3 years) is a new standard of care for young MCL patients.

Keywords: autologous stem-cell transplantation (ASCT); mantle cell lymphoma (MCL)

INDOLENT LYMPHOMAS

215 BIOMARKER ANALYSIS OF PATIENTS WITH FOLLICULAR LYMPHOMA TREATED WITH IBRUTINIB IN THE PHASE 2 DAWN STUDY

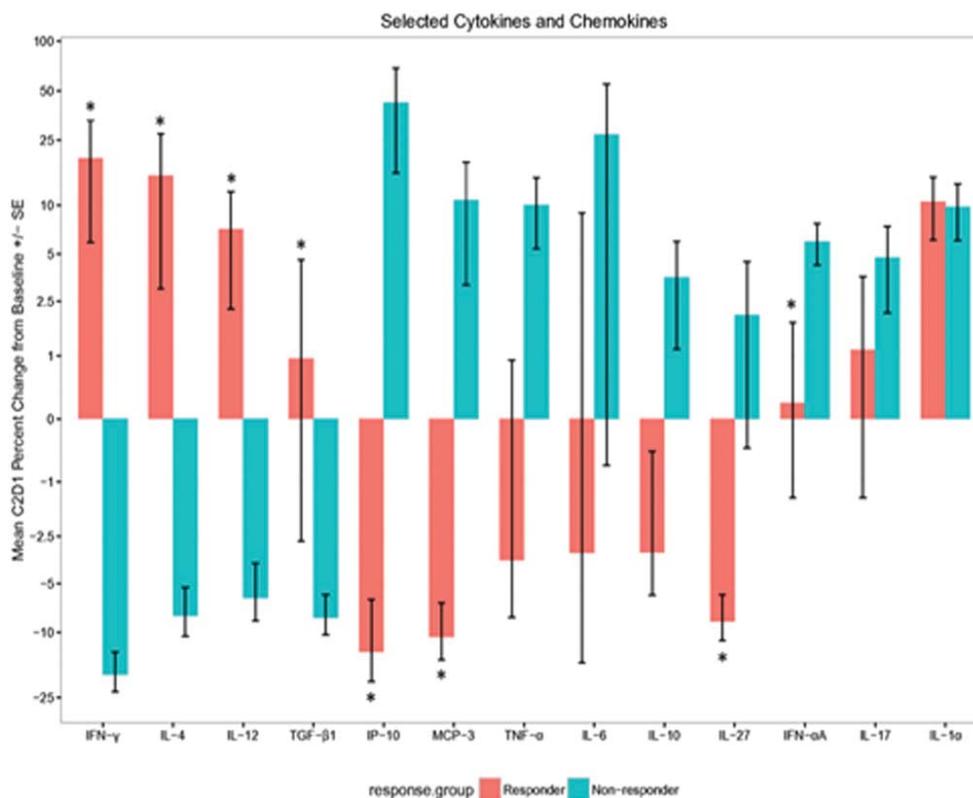
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Background: Ibrutinib (ibr), a first-in-class, oral, covalent Bruton's tyrosine kinase inhibitor, is approved for and has demonstrated robust activity in various B-cell non-Hodgkin lymphomas. The DAWN study (FLR2002, NCT01779791) investigated the efficacy and safety of single-agent ibr in chemoimmunotherapy (CIT)-refractory follicular lymphoma (FL) patients (pts). Ibr may modulate T-cell activity via

Figure. Changes in selected cytokines for ibrutinib-treated FL patients from baseline to cycle 2, day 1.



C2D1, cycle 2 day 1; IL, interleukin; IP-10, IFN- γ -induced protein 10; MCP-3, monocyte chemotactic protein-3; TNF, tumor necrosis factor.

*indicates significant difference ($p < 0.05$) in change from baseline versus non-responders.

inhibition of interleukin-2-inducible T-cell kinase by activating T-helper 1 (Th1) cells (Dubovsky, et al. Blood 2013). We describe the effect of ibr treatment on T-cells and cytokines in pts in the DAWN study.

Methods: This was a multicenter, single-arm, phase 2 study of ibr in FL pts with ≥2 prior lines of therapy and progressive disease (PD) ≤ 12 months after CIT regimen. Pts received ibr (560 mg QD) on a 21-day cycle until PD or toxicity. A protocol amendment allowed continued ibr treatment in clinically stable/improving pts with radiological evidence of PD (new lesion/increase ≥50%) to account for “pseudo-PD”. The primary end point was the overall response rate (ORR) (complete response [CR] + partial response). Flow cytometry assessed T-cell subsets in peripheral blood at baseline (C1D1) and at cycle 3 (C3D1) for 57 pts (14 responders, 43 nonresponders); cytokine and chemokine analyses were performed at C1D1 and at cycle 2 (C2D1) for 50 pts (21 responders, 29 nonresponders).

Results: The DAWN study results have been presented (Gopal A, et al. ASH 2016); ibr achieved an ORR of 20.9% (CR rate, 10.9%). Flow cytometry analysis revealed CD4 + CD25 + CD127⁻ T_{regs} were downregulated at C3D1 in responders (CR + PR, mean decrease 17 to 12.9% CD4, *p* = 0.02) but not in nonresponders (11.5 to 10.4% CD4, *p* = 0.17). There were no differences between responders and nonresponders in a large panel of inflammation-related cytokines and chemokines at C1D1, confirmed by gene expression profiling in the tumor. After 21 days, Th1 cytokines interferon (IFN)-γ and interleukin (IL)-12 were increased in responders but decreased in nonresponders (*p* = 0.0025 and *p* = 0.035, respectively; Figure). The chemokines IFN-γ-induced protein 10 and monocyte-chemotactic protein 3 were decreased in responders but increased in nonresponders (*p* = 0.022 and 0.016, respectively). Available data in pseudo-PD pts showed a similar trend of decreased T_{regs} at C3D1

as responders, but the cytokines showed a similar trend as nonresponders.

Conclusions: In ibr-responding pts at early time points, T_{regs} were downregulated and Th1-associated cytokines IFN-γ and IL-12 were increased. This shift in T-cell population may be linked to the antitumor response; in nonresponders, these cytokines were decreased but T_{regs} were not. Chemokine changes suggest variation in chemoattraction. These data suggest that immunomodulatory effects of ibr could play a role in its antitumor activity in FL; combinations with other therapies may prove beneficial.

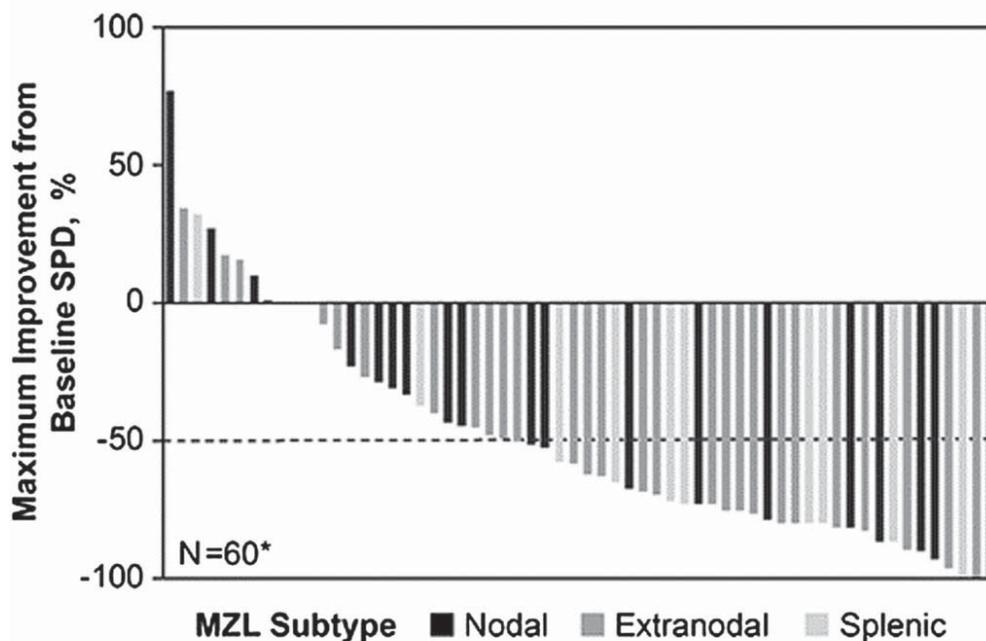
Keywords: follicular lymphoma (FL); ibrutinib; immunomodulators (IMiDs)

216 SAFETY AND EFFICACY OF SINGLE-AGENT IBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) MARGINAL ZONE LYMPHOMA (MZL): A MULTICENTER, OPEN-LABEL, PHASE 2 STUDY

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Figure. Maximum Percentage Decrease From Baseline SPD by Investigator Assessment



*3 patients had PD and were non-evaluable after first dose of ibrutinib.

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Introduction: MZL is often linked to chronic infection, which can induce B-cell receptor signaling, resulting in aberrant B-cell growth. By blocking BTK, a critical component of B-cell receptor signaling, ibrutinib (ibr) may be an attractive therapy for MZL. We evaluated the efficacy and safety of single-agent ibr in patients (pts) with R/R MZL. No approved agents for MZL existed at study initiation.

Methods: Pts had histologically confirmed MZL, ECOG PS of ≤ 2 , and received ≥ 1 prior therapy including at least 1 anti-CD20 monoclonal antibody (mAb)-containing regimen or monotherapy rituximab (RTX). All pts received ibr 560 mg orally once daily until progression or unacceptable toxicity. The primary study end point was overall response rate (ORR) as assessed by an independent review committee (IRC) per 2007 IWG criteria. Secondary end points were duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Results: 63 pts (extranodal [$n = 32$], nodal [$n = 17$], and splenic [$n = 14$]) were enrolled. Median age was 66 y (range, 30-92); 92% had ECOG PS of 0-1. Median number of prior systemic therapies was 2 (range, 1-9) with 35% receiving ≥ 3 prior therapies and 22% refractory to most recent therapy. 17 pts (27%) had received only monotherapy RTX, and 40 (63%) had received at least one anti-CD20 mAb-containing chemoimmunotherapy regimen. At a median follow-up of 19.4 mo, the ORR per IRC was 48% (2 CRs and 27 PRs). Time to best response was 5.2 mo. Thirty-five percent had stable disease (SD), and the clinical benefit rate (CR + PR + SD) was 83% per IRC, with 78% showing some tumor reduction (Figure). Median DOR was not reached (NR) (95% CI: 16.7, NR), and the median PFS was 14.2 mo (95% CI: 8.3, NR). Median PFS by subtype was 19.4 mo for splenic, 13.8 mo for extranodal, and 8.3 mo for nodal MZL. The overall median OS was NR (95% CI: NR, NR). The most common adverse events (AEs $\geq 20\%$) of any grade included fatigue (44%), diarrhea (43%), anemia (33%), nausea (25%), thrombocytopenia, arthralgia, and peripheral edema (24% each), cough (22%), and dyspnea and URTI (21% each). Bleeding occurred in 59% of pts, with 1 grade 5 cerebral hemorrhage. Atrial fibrillation occurred in 4 (6%) pts, all grade 1-2 events. Three treatment-emergent AEs resulted

in death due to disease progression, cerebral hemorrhage, and parainfluenza infection leading to multiple organ failure. Overall, 39 pts (62%) discontinued treatment (PD: 32%; AEs: 17.5%, withdrawal of consent: 6%; physician decision: 6%).

Conclusions: Single-agent ibr achieved a high ORR and durable responses across all MZL subtypes, and produced clinically meaningful tumor shrinkage; the treatment was well tolerated (all grade 1-2 AEs). The promising results of this trial led to the US FDA approval of ibr for pts with MZL requiring systemic therapy with ≥ 1 prior anti-CD20-based therapy, allowing treatment without chemotherapy.

Keywords: BTK; ibrutinib; marginal zone lymphoma (MZL)

217 PROGRESSION-FREE SURVIVAL FOLLOWING LENALIDOMIDE-BASED TREATMENT IS SIGNIFICANTLY LONGER IN EXTRAGASTRIC THAN IN GASTRIC MARGINAL ZONE B-CELL LYMPHOMA OF THE MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA (MALT LYMPHOMA)

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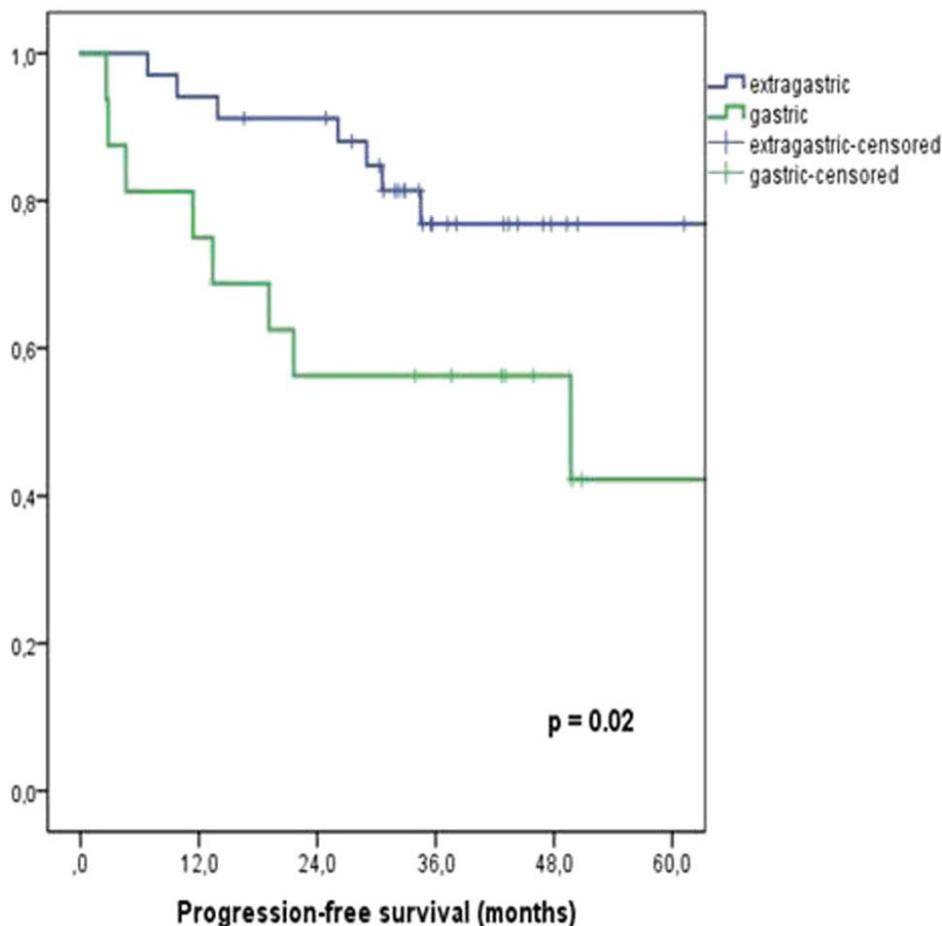
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Background: Based on recent data, lenalidomide (LEN) +/- rituximab (R) is active and safe for the treatment of Helicobacter pylori (HP)-eradication refractory and extragastric lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma). However, only little is known about differences in behavior of gastric and extragastric disease treated with LEN.

Methods: We have systematically investigated a potential correlation of primary tumor site and outcome to LEN-based treatment in a series of 50 patients with MALT lymphoma treated at the Medical University Vienna 2009-2014. Patients received LEN monotherapy (25 mg d1-21, 1-6 courses) or R-LEN (LEN 20 mg d1-21, R 375 mg/m² d1, 1-8 courses) in a 4-week cycle. All subjects were treated within registered phase II trials (www.clinicaltrials.gov; NCT01611259, NCT00923663).

Results: Median age at LEN-treatment start was 67 years (range, 33-85) with 62% (31/50) being female. Primary localization of lymphoma was the stomach in 32% (16/50) while the majority of patients had extragastric disease (68%, 34/50). The most common extragastric manifestation were the ocular adnexa accounting for 34% (17/50); further tumor sites included the lung, parotid glands, breast, liver, colon, skin and kidney; 34% (17/50) had disseminated disease (Ann Arbor stage III or IV). Distribution of age, gender and dissemination status did not differ between gastric and extragastric patients (p-values non-significant); however, patients with gastric disease had received significantly more often prior immuno-/chemotherapy (50% vs. 18%,



$p = 0.02$). Overall response rate (ORR) in the entire collective was 74%, with 50% achieving a complete remission (CR). ORR (75% vs. 74%, $p = 0.912$) and CRs (50% vs. 50%, $p = 1.0$) did not differ significantly between patients with gastric and extragastric disease, but looking at long-term outcome, estimated progression-free survival (PFS) was significantly longer in patients with extragastric versus gastric disease (not reached vs. 50 months; $p = 0.02$). The absolute relapse rate was 32% for all patients, and 56% for gastric versus 21% for extragastric disease ($p = 0.01$). Multivariate analysis by Cox regression including dissemination status, prior treatment and initial localization confirmed primary gastric disease as independent risk factor for worse PFS in patients treated with (R-)LEN ($p = 0.04$). After a median follow-up time of 42.8 months, two patients have died due to progression of lymphoma, both being of gastric origin.

Conclusion: Our data suggest that patients with extragastric disease have a superior long-term outcome following LEN-based treatment if compared to primary gastric disease. This finding could potentially influence patient selection for this novel treatment approach. Because HP eradication is standard of care for gastric MALT lymphoma, we cannot rule out a certain bias by prior interventions. This warrants further investigation.

Figure 1. PFS in extragastric versus gastric MALT lymphoma patients treated with (R-)LEN.

Keywords: indolent lymphoma; lenalidomide; non-MALT marginal zone lymphomas.

218 BEYOND MAXIMUM GRADE: A NOVEL, LONGITUDINAL TOXICITY OVER TIME (TOXT) ADVERSE EVENT ANALYSIS OF LENALIDOMIDE IN FOLLICULAR LYMPHOMA IN CALGB 50401 (ALLIANCE)

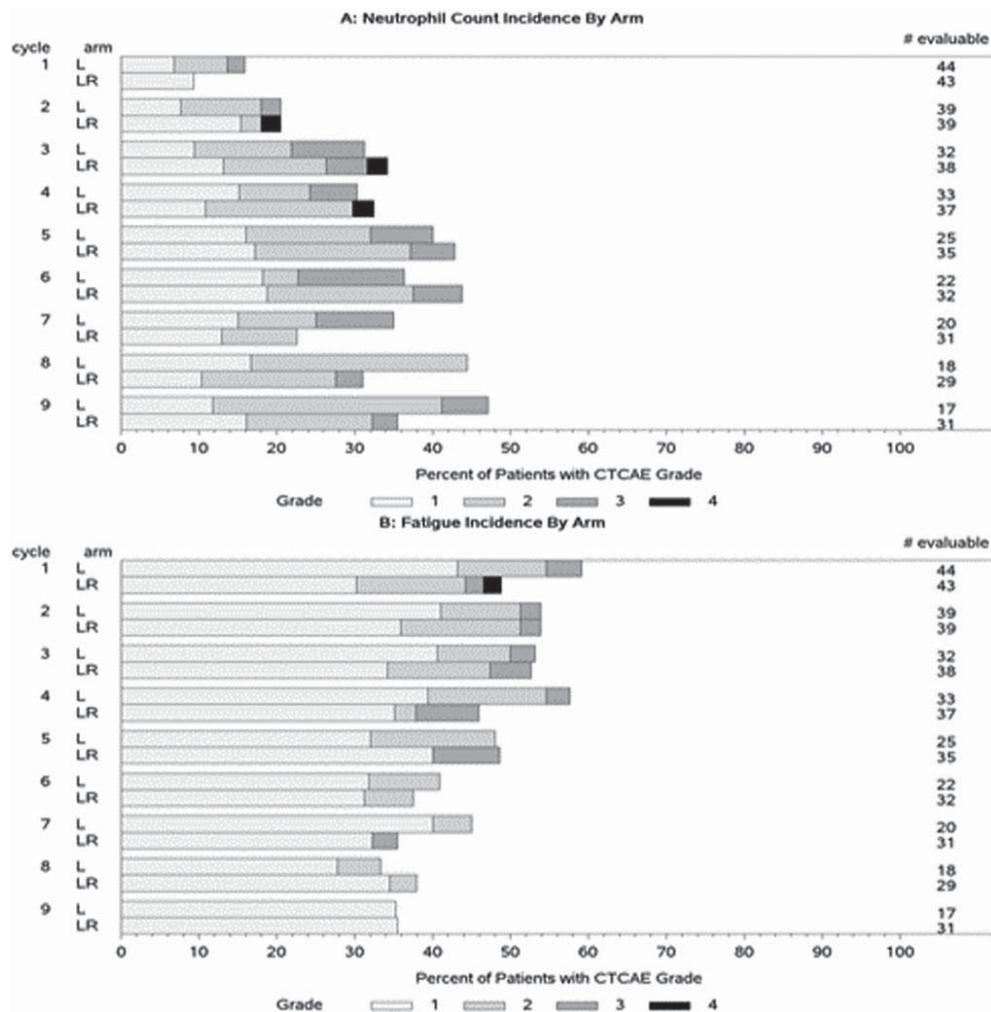
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Introduction: Chronically administered agents are increasingly used to treat indolent lymphomas. Tables of high grade (gr) adverse events (AEs) do not provide a time profile of AEs by severity and duration or



describe longer lasting, low gr AEs pertinent to patients (pts) receiving continuous therapies for months to years. We developed a novel approach for AE analysis, the Toxicity over Time (ToxT, Thanarajasingam et al., *Lancet Oncol* 2016), a standardized package of graphical and analytical assessments that depicts AEs longitudinally. In Alliance A151617, we applied ToxT analyses to a phase II randomized multicenter trial to characterize time course and severity of AEs associated with lenalidomide (L) alone or with rituximab (LR) in pts with relapsed follicular lymphoma (FL).

Methods: CALGB 50401 accrued 94 pts (L = 48, LR = 46). L was given in both study arms on days 1–21 of a 28-day cycle. ToxT plots depicting summary statistics or individual pt data over discrete time points were combined with longitudinal techniques (repeated measures modeling, time-to-event and area-under-curve [AUC] analyses) including assessment of chronic low gr events.

Results: Standard CTCAE analysis identified neutropenia and fatigue as the most common gr 3+ adverse events on L and LR (16% v 20%, respectively, for neutropenia, and 9% v 13% for fatigue). With ToxT analyses, bar charts of incidence and gr per cycle (c) define the AE trajectory, showing a steady rise in neutropenia incidence and gr in both arms as treatment continued. Among pts on LR

(Panel A), 4/43[9.3%] experienced gr1 neutropenia at c1 and 11/31[35.4%] experienced gr \leq 3 at c9. In contrast, fatigue decreased in incidence and gr for pts in both arms over time (Panel B, 20/43[46.5%] gr1 \leq 3 fatigue at c1 versus 11/31[35.5%] gr1 at c9 on LR). Stream plots depict decreasing mean gr of fatigue over time for both arms (mean across all gr including gr0 was 0.8 and 0.7 on L and LR, respectively, at c1 and drop to 0.4 and 0.4 by c9). Time-to-event bar charts indicate that for pts on LR, onset and worst gr fatigue (median: 8 and 8 days) occur early. In contrast, onset and worst gr of neutropenia occur late (median: 57 and 86 days). AUC analyses showed a similar burden of chronic low gr fatigue in both arms over time (AUC of 3.2 and 4.0 [$p = 0.39$] on L and LR, respectively).

Conclusions: ToxT analyses provide precise descriptions of cytopenia and fatigue trajectory and continuous low gr toxicity from lenalidomide that are not identified by standard CTCAE analysis. Characterizing the timeframe of toxicity is relevant in low-grade lymphomas treated with continuous therapies, as it can provide reassurance and education to pts and prescribers as well as optimize AE monitoring or symptom control interventions. It may also guide rational dosing and future trial design. Longitudinal AE analysis offers a more comprehensive, patient-centered

toxicity assessment of chronically administered therapy for indolent lymphomas.

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

219 TREATMENT WITH COMBINATION OF LENALIDOMIDE AND RITUXIMAB ACHIEVES DURABLE RESPONSES IN A LONG TERM FOLLOW UP OF PATIENTS WITH INDOLENT NON-HODGKIN'S LYMPHOMA

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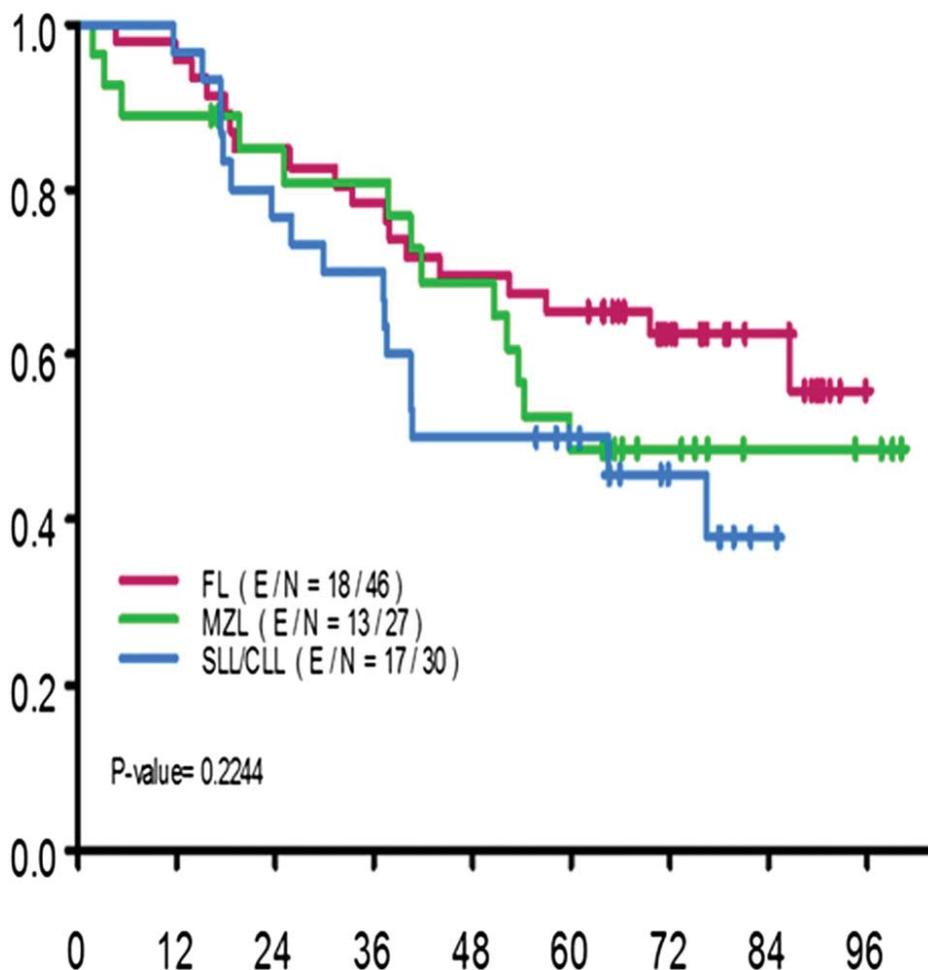
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Introduction: Standard front line treatment for indolent non-hodgkin's lymphoma (iNHL) is effective but is associated with short- and long-term toxicity, and many patients relapse within 5 years. Novel approaches targeting the immune microenvironment may provide alternative therapeutic strategies with improved outcomes. The immunomodulatory combination, lenalidomide with

rituximab (R2), has been associated with high response rates and acceptable safety in iNHL (Fowler 2014), however, long-term outcomes regarding this approach are lacking. We report the mature follow up of patients treated with lenalidomide-rituximab on a phase II clinical trial.

Methods: We conducted a phase II study of R2 in untreated iNHL. Lenalidomide was given orally at 20 mg/day on days 1-21 of all 28-day cycles for follicular lymphoma (FL) and marginal zone lymphoma (MZL). In small lymphocytic lymphoma (SLL), dose began at 10 mg/day to avoid tumor flare. Rituximab was given at 375 mg/m² on day 1 of each cycle. Patients responding after 6 cycles could continue therapy for up to 12 cycles. Tumor assessment (CT and physical exam) was performed at study entry, every 3 months for 2 years, every 6 months in year 3, and then annually. Patients were monitored for long-term toxicity and secondary cancers.

Results: All 110 patients were enrolled between 6/2008 and 8/2011, and 103 were evaluable for response assessment. At data cut, median follow up was 7.2 years. The 5-year progression free survival in FL, MZL and SLL is 65% (95% CI, 0.53-0.81), 48% (95% CI, 0.32-0.73) and 50% (95% CI, 0.35-0.72), respectively. Median progression free survival has not been reached in the FL subset. No unexpected late toxicities were observed. Ten secondary malignancies were reported (two localized skin cancers), and only one case of aggressive transformation has occurred. Seven deaths were reported during follow up.



Conclusions: Lenalidomide plus rituximab is highly effective and well tolerated as initial treatment for iNHL and produces durable responses with few late effects, particularly in FL. An international phase 3 study (NCT01476787) is ongoing comparing this regimen to chemotherapy in untreated follicular lymphoma.

Best Response and progression free survival with extended follow up

	FL (n=46)	MZL (n=27)	SLL (n=30)	All evaluable (n=103)
ORR, n (%)	45 (98)	25 (93)	24 (80)	94 (91)
CR, n (%)	42 (91)	19 (70)	9 (30)	70 (68)
Median PFS (months)	not reached	59.79	52.63	86.56
5yr PFS	65%	48%	50%	56%
95% CI	(0.53-0.81)	(0.32-0.73)	0.35-0.72)	(0.48-0.67)

Keywords: immunomodulators (IMiDs); indolent lymphoma; lenalidomide.

220 MINIMAL RESIDUAL DISEASE AND OUTCOMES IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA (FL) IN THE PHASE III GADOLIN TRIAL OF OBINUTUZUMAB AND BENDAMUSTINE VS BENDAMUSTINE

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Introduction: Minimal residual disease (MRD) response after first-line treatment of FL may predict outcome; however, data are limited in the relapsed/refractory (r/r) setting. We previously described MRD assessment in r/r FL in the randomised GADOLIN study (NCT01059630; Pott C, et al. ASH 2015). Here, we report updated

results for MRD status for the full population. MRD kinetics post-induction with respect to treatment efficacy and prognosis are reported for the first time.

Methods: Patients (pts) received obinutuzumab (G) + bendamustine (B) (90 mg/m²) followed by G maintenance, vs B (120 mg/m²) alone. MRD was analysed by t(14;18) real-time quantitative PCR (RQ-PCR) and/or allele-specific immune gene (IGH or IGK) RQ-PCR in pts with a clonal marker at diagnosis: at mid-induction (MI), end of induction (EOI) and 6-monthly intervals to 24 months post EOI/discontinuation. MRD status was negative (i.e. MRD response achieved) if RQ-PCR and subsequent nested PCR were negative.

Results: Of 335 randomised pts with FL, a clonal marker was detected in 228/319 (71%) pts with baseline samples (baseline-evaluable population, BEP). Compared with the BEP, the population with a detectable marker was enriched for higher stage, worse FLIPI and bone marrow (BM) involvement. MI and EOI samples were analysed for 88 and 118 pts, respectively. MRD negativity in peripheral blood (PB) occurred early during induction and was more frequent with G + B: 41/52 (79%) pts were MRD negative at MI vs 17/36 (47%) in the B arm ($p = 0.0029$). At EOI, MRD responses further increased: 54/63 (86%) pts receiving G + B achieved MRD negativity in PB and/or BM vs 30/55 (55%) in the B arm ($p = 0.0002$) (Table). Pts with complete/partial response who were MRD negative at EOI had improved PFS and OS vs MRD-positive pts; hazard ratios (adjusted for treatment): PFS, 0.33 (95% CI 0.19–0.56, $p < 0.0001$), OS, 0.39 (95% CI 0.19–0.78, $p = 0.008$). Clinical outcome and MRD kinetics were highly impacted by post-induction treatment; MRD negativity was generally sustained with G maintenance, whereas MRD-negative pts in the B arm (no maintenance) converted back to MRD positivity and relapsed early (Figure).

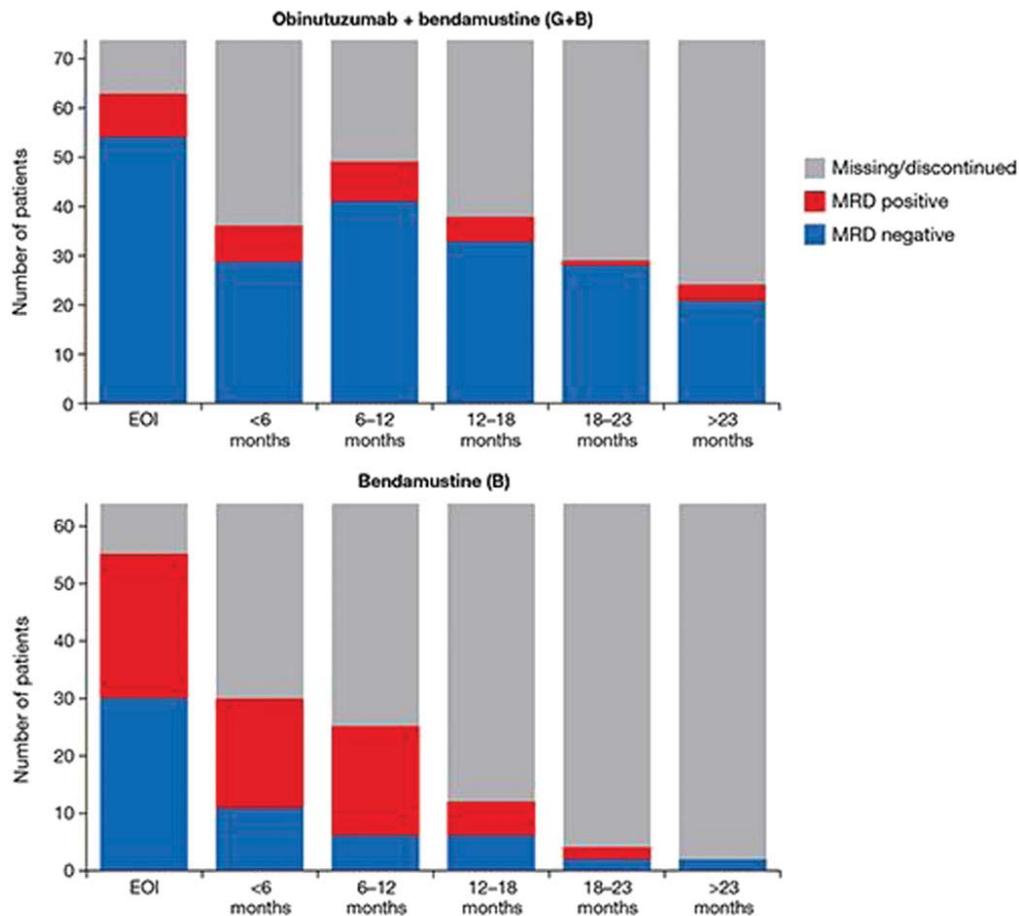
Conclusions: MRD status at EOI was a sensitive marker of treatment efficacy, demonstrating that adding G to B-based treatment significantly contributes to the speed and depth of response. MRD-negative pts after G + B appeared to benefit from G maintenance, which potentially preserved MRD negativity and helped to control lymphoma regrowth.

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

Table. MRD Status by Treatment Arm at MI and EOI

Arm	MRD-positive, n (%)	MRD-negative, n (%)	Total, n
MI* (PB)			
G+B	11 (21.2)	41 (78.8)	52
B	19 (52.8)	17 (47.2)	36
EOI† (PB and/or BM)			
G+B	9 (14.3)	54 (85.7)	63
B	25 (45.5)	30 (54.5)	55

* $p=0.0029$. † $p=0.0002$, G+B vs B.MI, mid-induction; MRD, minimal residual disease; EOI, end of induction.

Figure. MRD status during induction and maintenance (G+B) or follow-up (B)

MRD status presented for 74 patients in the G+B arm and 64 patients in the B arm who provided ≥ 1 MRD sample at EOI (PB/BM) and/or any of the post-induction timepoints (PE).

221 R-CP CHEMOIMMUNOTHERAPY IN PATIENTS WITH IGM PARAPROTEINAEMIC NEUROPATHY PRODUCES IMPROVEMENTS IN FUNCTIONAL, ELECTROPHYSIOLOGICAL AND SEROLOGICAL OUTCOMES

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Introduction: Peripheral neuropathy is a well-recognized complication of IgM paraproteinaemia associated with both underlying NHL (usually LPL) and IgM MGUS. In 60% of cases, the M protein shows reactivity to myelin-associated glycoprotein (MAG). Anti-MAG antibodies have been shown to be neuropathic, and the natural history of the neuropathy is of persistent functional decline with poor response to immunomodulatory agents. We postulated that the neuropathic component may respond better to

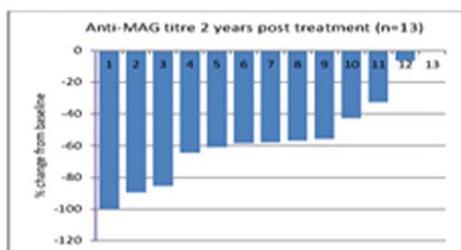
combination therapy than to chemo or immunotherapy alone as seen in LPL.

Methods: A total of 25 patients (16 IgM MGUS, 8 LPL, 1 CLL) were treated with 6 cycles every 21 days of rituximab 375 mg/m² and cyclophosphamide 750 mg/m² i/v on day 1 and 5 days of oral prednisolone 50 mg/m². Assessments carried out at baseline and then at 3 months, 1 and 2 years post-treatment were serum paraprotein and Anti-MAG titres, standardised neurological functional scores—Overall Neuropathy Limitation Score (ONLS), MRC Sum Score for muscle power, Sensory Sum Score and standard nerve conduction studies (NCS) as well as patient reported outcome measures (PROMS). BM biopsy and CT scans were performed at baseline and at 3 months post treatment to assess remission status.

Results: The treatment was well tolerated. Post treatment, the ONLS was significantly improved at 1 year, $p = 0.006$ and MRC motor score at 2 years, $p = 0.031$. In NCS, mean sensory action potential sum score improved and mean distal motor latency sum score reduced. In PROMS at 1 year, 44% reported improvement in symptoms, 28% reported a stabilisation of symptoms previously deteriorating before treatment and only 24% reported continuing slow deterioration.

		Baseline	1 yr post treatment	2 yrs post treatment
ONLS	No. of patients	25	25	18
	Median (IQR)	3 (2; 3.5)	2 (1; 2.5)	1 (0.25; 3)
	P value (post treatment compared to baseline)	n/a	p=0.006*	p=0.053
MRC sum score	No. of patients with baseline weakness	18	18	13
	Median (IQR)	76 (69.5; 77)	76 (72; 80)	79 (74; 80)
	P value (post treatment compared to baseline)	n/a	p=0.131	p=0.031*

p values: Wilcoxon signed ranks test.



All patients with underlying NHL achieved at least a partial remission at 3 months post-treatment. IgM paraprotein levels fell in all 25 patients from a baseline median level of 4.7 g/l to 2.25 g/l at 3 months, $p = 0.000$ and to 1.95 g/l at 2 years, $p = 0.000$. In patients with Anti-MAG antibody, levels fell from a baseline median of 38,956 to 14,783 units by 2-year post-treatment, $p = 0.002$.

Conclusion: In patients with IgM paraproteinaemic neuropathy, a disease with poor outcomes and response to treatment, R-CP chemoimmunotherapy is well tolerated and capable of inducing sustained significant improvement for at least 2 years in NCS, ONLS, motor scores and PROMS which correlate with significant reductions in both IgM paraprotein and Anti-MAG antibody. We plan to pursue these results with an RCT.

Keywords: immunochemotherapy; lymphoplasmacytic lymphoma/Waldenstroem (LPL/WM); monoclonal gammopathy of undetermined significance (MGUS).

222 BENDAMUSTINE-RITUXIMAB (BR) VERSUS R-CHOP AS UPFRONT THERAPY FOR INDOLENT B-CELL LYMPHOMAS: A COMPARATIVE, POPULATION-BASED ANALYSIS

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Introduction: Bendamustine with rituximab (BR) showed an advantage over RCHOP as upfront therapy for indolent B-cell lymphomas in

phase 3 trials, but results may differ when applied in older, unselected patients in the community. Our objective was to compare treatment outcomes with BR and RCHOP as applied in the United States (US), using causal inference methods in population-based data.

Methods: Using Medicare insurance claims linked to the Surveillance, Epidemiology, and End Results cancer registry, which encompasses ~28% of the US population, we identified patients, age 65 years or older, diagnosed with follicular (FL, excluding grade 3), mantle cell, marginal zone (MZL), or lymphoplasmacytic lymphoma (LPL), who initiated first-line BR or RCHOP-like chemotherapy in 2009–2013. We balanced the treatment arms with respect to multiple clinical confounders using a propensity score with inverse probability of treatment weighting. We then compared toxicities (defined by hospital and outpatient diagnoses, in log-binomial models), costs to Medicare accrued during 6 months from the start of therapy (in a log-gamma model, inflation adjusted to 2013 dollars), and overall survival (OS, Cox model), reporting estimates with bootstrapped 95% confidence intervals (CI).

Results: Treatment selection between BR ($N = 711$, median 5 cycles) and RCHOP ($N = 530$, median 6 cycles) was highly physician dependent (intraclass correlation, 50%) and shifted over years: BR was prescribed to 10% of patients in 2009, and 76% in 2013. Compared with RCHOP, patients receiving BR had no significant difference in B symptoms, sex, race, or poverty status, but were significantly older (median 76 vs. 73 y) and had more often poor performance status, kidney or heart disease, MZL/LPL, and less often stage I lymphoma. Adjusting for all those differences, the risk of hospitalizations and several other toxicities was significantly lower after BR (Table). Adjusted 3-year OS was 60% for RCHOP and 57% for BR, not significantly different. Adjusted mean Medicare payments during therapy were \$57,753 for RCHOP and \$70,919 for BR ($P < .0001$). Gross cost of chemotherapy drugs was \$36,127 and \$54,405, respectively.

Conclusions: BR largely replaced RCHOP as upfront treatment for older patients with indolent lymphomas in the US community. Outcomes with BR are reassuringly similar to clinical trials, with no OS difference, and lower risk of severe toxicities. Despite this, BR results in higher short-term costs of care, driven by the cost of bendamustine.

Outcome	Risk ratio (BR vs. RCHOP)	95%CI	P
Hospitalization	0.70	0.60-0.82	<.001
Infection	0.58	0.47-0.71	<.001
Cardiovascular event	0.73	0.60-0.87	.001
Transfusion	0.44	0.32-0.61	<.001
Rash	2.20	1.27-3.81	<.001
Overall survival	1.06	0.74-1.53	.68

Keywords: bendamustine; follicular lymphoma (FL); indolent lymphoma.

223 A DOUBLE-BLIND, RANDOMIZED PHASE 3 STUDY TO COMPARE EFFICACY AND SAFETY OF CT-P10 TO RITUXIMAB IN COMBINATION WITH CVP IN PATIENTS

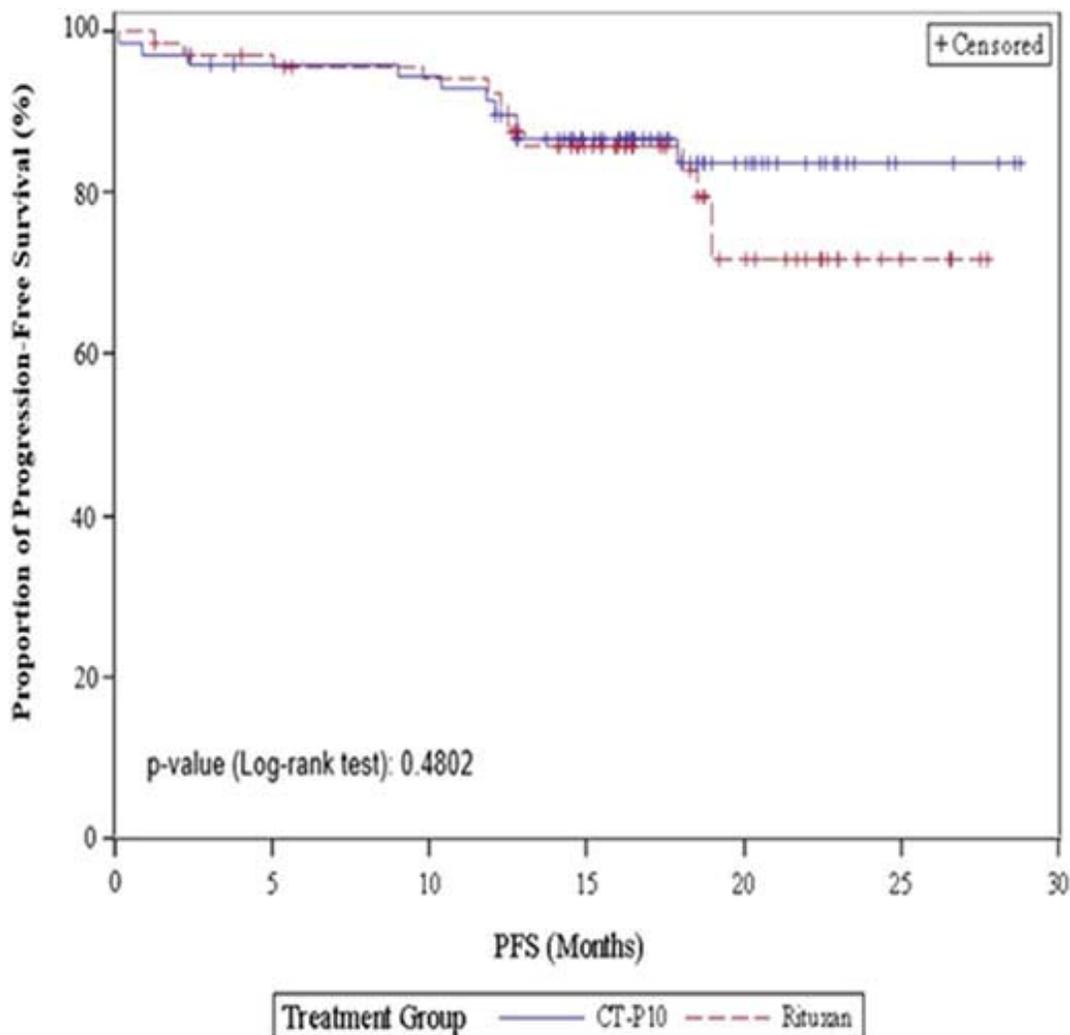
WITH ADVANCED-STAGE FOLLICULAR LYMPHOMA

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Summary of efficacy and safety over 24 weeks treatment

N (%)	CT-P10 (N=66)	RTX (N=68)
ORR (CR+CRu+PR)	64 (97.0)	63 (92.6)
Complete response (CR)	20 (30.3)	15 (22.1)
Unconfirmed CR (CRu)	6 (9.1)	8 (11.8)
Partial response (PR)	38 (57.6)	40 (58.8)
	(N=70)	(N=70)
TEAE related to the study drug		
Treatment-emergent adverse event (TEAE)*	37 (52.9)	34 (48.6)
Serious TEAE*	6 (8.6)	4 (5.7)
Infusion-related reaction*	15 (21.4)	17 (24.3)
Infection*	6 (8.6)	9 (12.9)

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Introduction: CT-P10 is the first biosimilar of innovator rituximab (RTX), approved for all indications by the EMA. CT-P10 has demonstrated pharmacokinetics (PK) and efficacy equivalence in patients with rheumatoid arthritis (Yoo, ACR 2016) and PK equivalence in patients with advanced follicular lymphoma (AFL) (Coiffier, ASH 2016). This study aimed to demonstrate non-inferiority (NI) of efficacy and PK equivalence between CT-P10 and RTX in patients with newly diagnosed AFL (NCT02162771).

Methods: A total of 140 patients were randomized in a 1:1 ratio to receive CT-P10 or RTX (375 mg/m² i.v.) plus CVP (cyclophosphamide, vincristine and prednisone) every 3 weeks over 8 cycles. Overall response rate (ORR) according to the 1999 IWG criteria based on best overall response over 24 weeks was assessed by the independent review committee.

Results: An ORR of 97.0% and 92.6% and a CR/CRu of 39.4% and 33.8% for CT-P10 and RTX, respectively, was observed after 8 cycles of therapy (Table 1). Based on this, the therapeutic NI of CT-P10 to RTX with regard to ORR over 8 cycles was demonstrated as the difference in ORR between the two groups was 4.3%, and the lower bound of the two-sided 95% CI was -4.25%. The lower bound (-4.25%) was greater than the pre-defined NI margin (-7%), by this fulfilling the criteria for NI of CT-P10 to RTX.

At a median follow-up of 17 months, 10 patients in the CT-P10 group and 13 patients in the RTX group experienced disease progression or death. There was no statistically significant difference between the two groups for PFS (P-value: 0.4802, Log-rank test) although the median PFS survival has not been reached in either arm as a longer follow-up is required (Figure 1).

Median number of B-cells decreased to the lower limit of quantification (LLOQ) after the 1st infusion and remained at the LLOQ over 8 cycles in both groups. Overall safety profile of CT-P10 was consistent with that of RTX (Table). and the proportion of patients with positive anti-drug antibody was similar between the two groups (4.3% and 2.9%) over 24 weeks. No progressive multifocal leukoencephalopathy or Hepatitis B virus reactivation was reported in both groups.

Conclusions: This study demonstrates therapeutic NI of CT-P10 to RTX plus CVP in previously untreated AFL. CT-P10 was well tolerated, and the safety profile including immunogenicity of CT-P10 was comparable to that of RTX over 8 cycles.

Keywords: follicular lymphoma (FL); rituximab.

224 CHARACTERISTICS AND OUTCOMES OF RELAPSED FOLLICULAR LYMPHOMA AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION IN THE RITUXIMAB ERA

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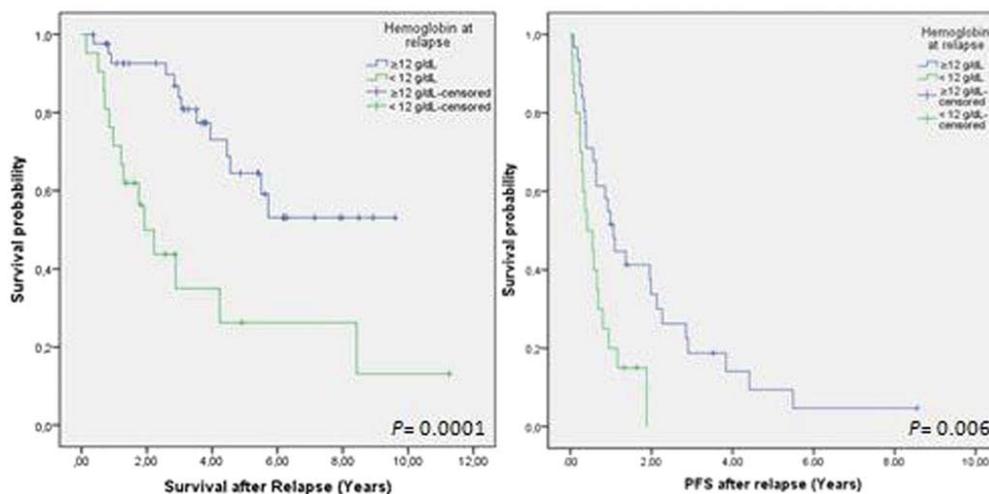
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Introduction: Despite substantial improvements in overall survival of patients (pts) with follicular lymphoma (FL), number of them experience disease progression after 1st line therapy. Autologous Stem Cell Transplantation (ASCT) is one of the therapeutic options in 2nd line, but a significant proportion of pts still progress after ASCT. Characteristics and outcomes of disease recurrence after ASCT is not well defined in the rituximab era; therefore, management of relapsed FL (R-FL) after ASCT still remains heterogeneous, debated and may represent a difficult challenge.

Methods: In this multicentric retrospective study, we evaluated clinical, biological, and histological parameters of R-FL patients after ASCT. Patients who 1) were rituximab naive at transplant, 2) had a previous history of histological transformation before ASCT or 3) had already been treated with a 1st ASCT were all excluded. Survival times were

Figure 1. Survival after relapse and Progression Free Survival. Kaplan-Meier representation of Survival after Relapse and Progression Free Survival after Relapse according to Hemoglobin level.



constructed with the Kaplan–Meier method and compared by the log-rank test. Prognostic factors for relapse and outcome were analyzed by Cox proportional hazards regression model.

Results: From 2000 to 2014, 95 FL patients (median age = 57 years) presenting disease progression after ASCT were identified. Patients had received a median of two lines (range 2–6) of prior therapy before ASCT. Rituximab maintenance was administered in 13%. Histological transformation at relapse was observed in 16% of the pts. Median follow-up after ASCT was 5.1 years. The median survival after relapse (SAR) and median progression free survival (PFS) after relapse were 4.4 and 0.8 years, respectively. Multiple treatment options were adopted, including immunochemotherapy ($n = 39$, 43%), new agents ($n = 13$, 14.5%), rituximab single agent ($n = 13$, 14.5%), allogeneic transplant ($n = 12$, 13%) or radiation ($n = 5$, 6%). In univariate analysis, delay (<2 years) between ASCT and progression, age (55 years) at relapse, lack of CR after ASCT, number of lines (≥ 3) prior to ASCT, histologic transformation at relapse, high serum $\beta 2$ -microglobulin (>ULN) or anemia (Hb < 12 g/dL) at relapse as well as high FLIPI risk category at relapse were all significantly associated with a worse SAR ($p = .036$, $p = .005$, $p = .05$, $p = .029$, $p = .039$, $p = .032$, $p = .001$ and $p = .024$ respectively). In multivariate analysis, anemia (<12 g/dL) remained the most relevant adverse factor for PFS (HR = 2.32; 95%CI [1.19–4.53]) and OS [HR = 3.12; 95%CI [1.03–9.44]) for pts who progressed after ASCT (Figure 1).

Conclusions: This report reveals that the prognosis of pts with R-FL after ASCT is quite heterogeneous. Some patients can experience a prolong survival while others have a very poor prognosis. Categorizing pts into distinct risk groups at relapse after ASCT will help to select the optimal therapeutic strategy for individual pts and also interpret the value of allogeneic-SCT or innovative approaches (such as CAR-T cells) in this situation.

Keywords: autologous stem cell transplantation (ASCT); follicular lymphoma (FL); salvage treatment.

225 AUTOLOGOUS STEM CELL TRANSPLANTATION MAY POTENTIALLY ABROGATE THE NEGATIVE PROGNOSTIC EFFECT OF EARLY RELAPSE AFTER CHEMO OR IMMUNOCHEMOTHERAPY IN FOLLICULAR LYMPHOMA

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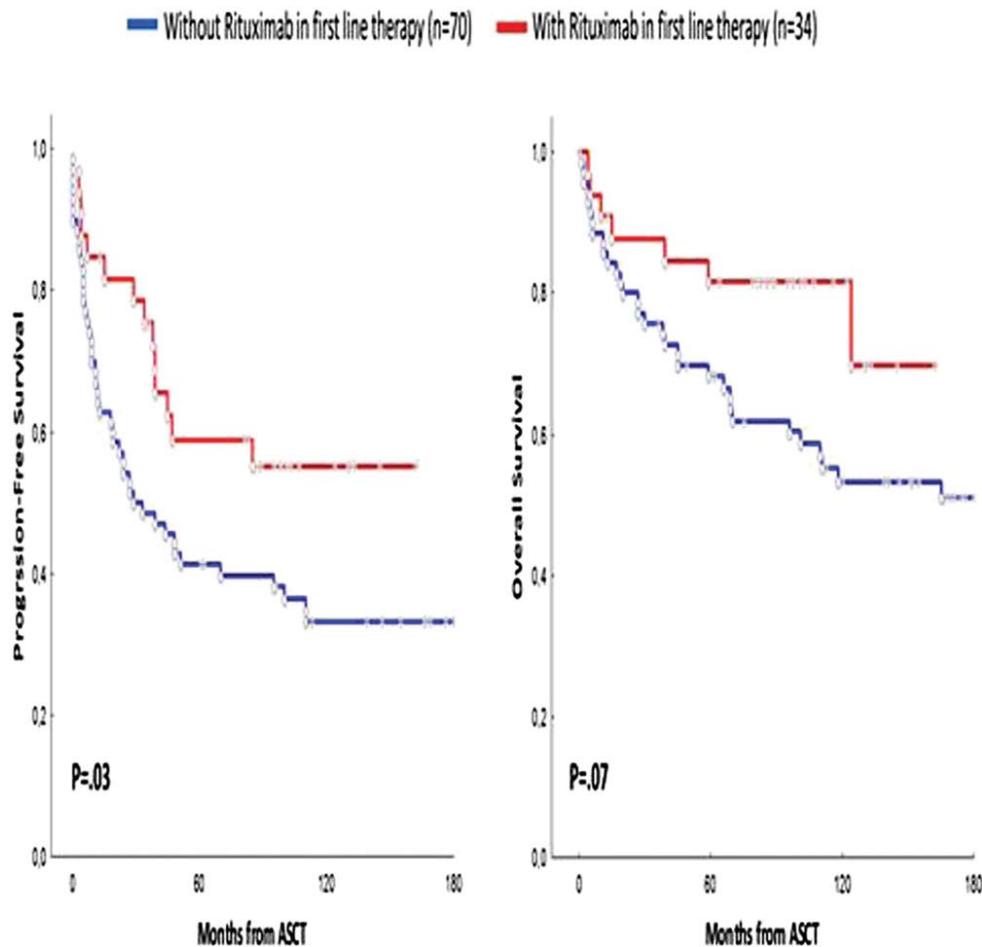
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Introduction: Rituximab plus chemotherapy is the standard induction therapy in Follicular Lymphoma (FL); however, those patients who present progression of the disease within the 2 years after diagnosis are associated with poor outcomes (Casulo et al JCO 2015). Autologous Stem Cell Transplantation (ASCT) have shown an Overall Survival (OS) benefit in relapsed FL after a rituximab-free induction regimen; nevertheless, its effect in early relapse FL is uncertain, above all in patients who received a rituximab-based first line therapy.

Patients and Methods: A total of 249 FL patients who were included in the GELTAMO registry received a first ASCT between 1989 and 2007 in either second complete response (CR2) or second partial response (PR2). In 165 patients (133 transplanted in CR2 and 32 in PR2), the duration of response after induction treatment was known, and they were the purpose of this analysis. From them, 105 patients (64%) progressed during the first 24 months from diagnosis (early progression).

Results: Median follow-up from ASCT for the 165 patients is 12.3 years. Median time to progression after induction therapy was 10 months (0.1 to 23 m) and 60 months (24 to 185 m) for patients with or without early progression, respectively. Patients in the early progression group were older (51 vs 47 years; $P = .02$), but there were no significance differences in terms of sex (male sex in 49.5% vs 53%) or number of patients with high-risk FL International Prognostic Index (FLIPI) score (28% vs 12%; $P = .1$) or FLIPI 2 score (12.5% vs 12%). There were no differences in the use of either anthracycline (70% vs 75%) or rituximab (25% vs 35%; $P = .2$) as a part of first line therapy, in the source of progenitor cell (peripheral blood in 85% vs 82%) or in the conditioning regimen administered (body irradiation-based regimen in 8% vs 9%). There were no differences in PFS ($P = .1$) nor in OS ($P = .1$) between patients who progressed or not within the first 24 months after diagnosis. Ten-year PFS and OS from the time of ASCT for patients relapsing within the first 2 years after FL diagnosis ($n = 105$) was 40% and 61%, respectively. In this subgroup of 105 patients, those who received rituximab in the first line therapy ($n = 34$) had a 10-year PFS and OS of 58% and 78%; while rituximab naïve patients ($n = 70$) showed a 10-year PFS and OS of 33% and



53%; respectively (Figure 1). Additionally, patients who obtained a CR ($n = 84$) after the rescue treatment had a better OS ($P = .01$) but not PFS ($P = .09$) than those who were transplanted in PR ($n = 21$).

Conclusion: ASCT may potentially abrogate the negative prognostic effect of early relapse after chemo or R-chemotherapy in patients who are sensible to rescue treatments. Very long-term FL disease free survival is nearly 60% in patients who relapse after a rituximab-containing regimen and who are sensitive to a new regimen of R-chemotherapy; however, the value of ASCT in refractory patients must be elucidated.

Keywords: autologous stem cell transplantation (ASCT); follicular lymphoma (FL).

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AUTOLOGOUS TRANSPLANTATION IMPROVES SURVIVAL IN PATIENTS WITH FOLLICULAR LYMPHOMA EXPERIENCING EARLY THERAPY FAILURE AFTER FRONTLINE CHEMOIMMUNOTHERAPY: AN NLCS AND CIBMTR ANALYSIS

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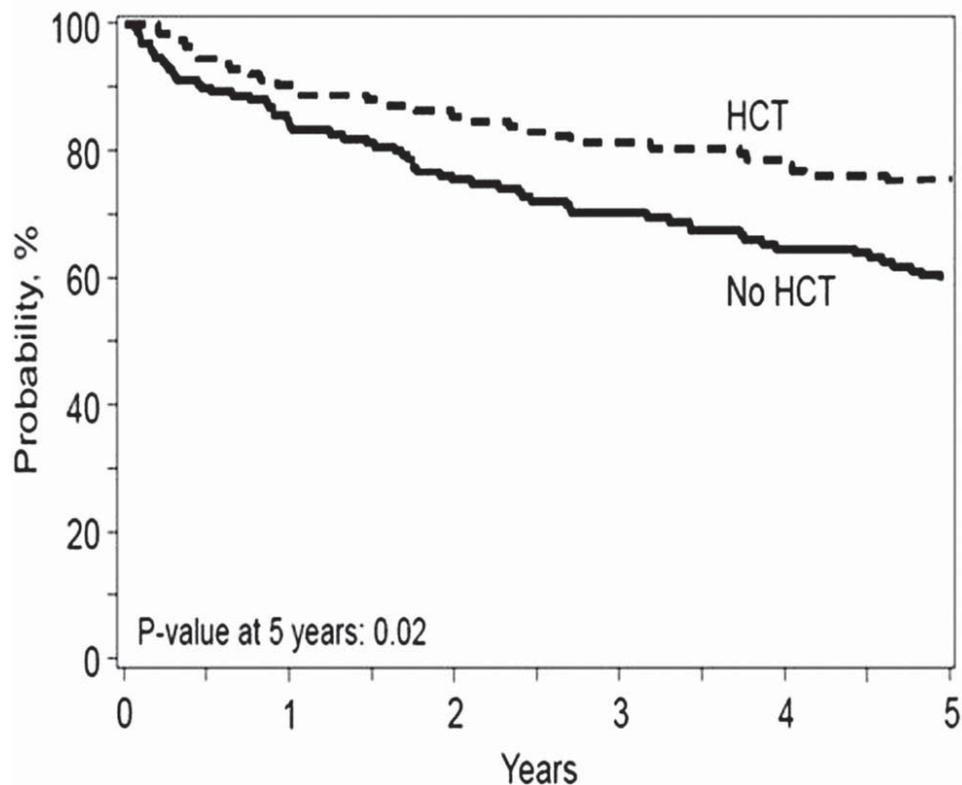
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Introduction: Patients with follicular lymphoma (FL) experiencing early therapy failure (ETF) within 2 years of starting frontline chemoimmunotherapy have poor overall survival (OS). We analyzed data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and National LymphoCare Study (NLCS) to determine whether autologous hematopoietic cell transplant (autoHCT) can improve outcomes in this high-risk subgroup of FL.

Methods: In this study, ETF was defined as failure to achieve at least a partial response after first-line chemoimmunotherapy or lymphoma relapse/progression within 2 years of starting first-line chemoimmunotherapy. NLCS FL patients fulfilling these criteria and not undergoing autoHCT represent the non-autoHCT cohort of this analysis. The autoHCT cohort comprised CIBMTR patients with ETF undergoing autoHCT. All patients received rituximab-based chemotherapy as frontline treatment.

Results: A total of 174 non-autoHCT patients and 175 autoHCT patients were identified and analyzed. The two groups were well balanced, except for a higher proportion of Caucasian patients, grade 3

Overall Survival Between Patients Receiving HCT Within 1-year of Therapy Failure



histology and more frequent use of anthracycline-based frontline therapies in the autoHCT cohort. There was no difference in 5 year OS between the two groups (60% vs 67%, respectively; $p = 0.16$). A planned subgroup analysis showed that patients with ETF receiving autoHCT soon after treatment failure (≤ 1 year of ETF; $n = 123$) had higher 5 year OS than those without autoHCT (73% vs 60%, $p = 0.02$). On multivariate analysis, early use of autoHCT was associated with a significantly reduced risk of mortality (HR = 0.63, 95%CI: 0.42–0.94, $p = 0.02$).

Conclusion: FL patients with ETF after front-line chemoimmunotherapy lack optimal therapy. We demonstrate improved OS when receiving autoHCT within 1 year of treatment failure. Results from this unique collaboration between the NLCS and CIBMTR support consideration of early consolidation with autoHCT in FL patients experiencing ETF.

Keywords: follicular lymphoma (FL).

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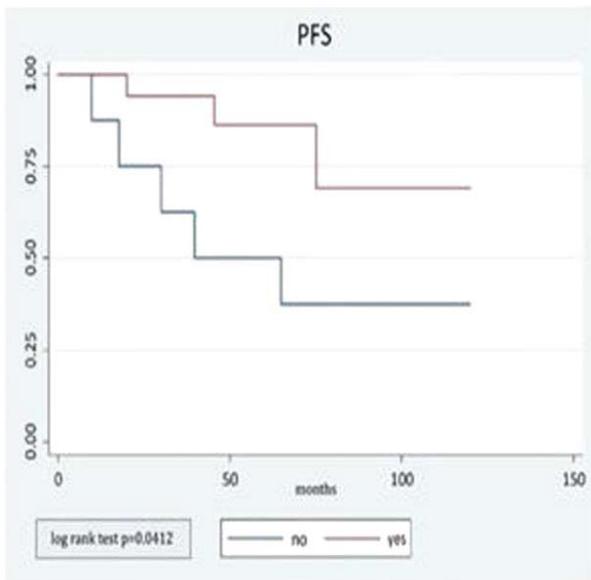
Introduction: In stage I–II follicular lymphoma (FL), *BCL2/IGH*+ cells can be detected in the peripheral blood (PB) and/or bone marrow (BM) in a high proportion of cases. We analyzed the prognostic impact of MRD in localized FL and explored the possibility of a MRD-guided rituximab therapeutic approach after standard involved field-radiotherapy (IF-RT).

Methods: Between 2000 and 2016, 67 consecutive patients with stage I/II FL were investigated for the *BCL2/IGH* rearrangement by qualitative PCR in the PB and BM, and (when available) in lymph nodes (LN). MRD was monitored every 6 months in patients positive at baseline. RQ-PCR and droplet digital PCR (ddPCR) were retrospectively performed in 30 MBR+ cases. All patients were treated with IF-RT (24–30 Gy); from 2005, patients who were MRD+ after IF-RT received rituximab (R) (375 mg/m² × 4). The median follow-up is 67 months (17–183).

Results: At baseline, 72% of patients were *BCL2/IGH*+: 54% MBR+, 9% mcr+, 9% minor *BCL2* rearrangement+. Of the 13 evaluable

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MINIMAL RESIDUAL DISEASE (MRD) IN EARLY STAGE FOLLICULAR LYMPHOMA CAN PREDICT PROGNOSIS AND DRIVE RITUXIMAB TREATMENT AFTER RADIOTHERAPY



LNs, 11 showed the same molecular marker identified in the PB/BM; 2 cases, negative in the PB/BM, showed a rearrangement in the LN. IF-RT induced an MRD negativity in 50% of baseline positive cases. R was administered to 19 MRD+ patients after IF-RT and an MRD-status was achieved in 16 (84%); 9/16 patients (56.3%) remain persistently MRD-, and none has so far relapsed ($p = 0.02$). Eight MRD+ patients did not receive R (pre-2005) and 6 (75%) have relapsed ($p = 0.025$). Progression-free survival (PFS) was significantly longer for MRD+ patients treated with R compared to untreated MRD+ patients ($p = 0.0412$) (Figure 1).

Overall, of the 39 patients with molecular follow-up, 18 were persistently MRD+ and 21 MRD-. Ten of the 18 (55.5%) MRD+

patients relapsed, while this occurred only in 3/21 (14.3%) of the MRD- patients ($p = 0.015$). PFS was significantly better for MRD- patients ($p = 0.0163$).

RQ-PCR-defined tumor burden at diagnosis predicted the MRD clearance after IF-RT ($p = 0.0027$), whilst it predicted PFS only when assessed by ddPCR ($p = 0.026$). The 10-year PFS and OS are 66% (95% CI: 51%–77%) and 96% (95% CI: 76%–99%), respectively.

Conclusions: Early stage FL has a heterogeneous disease extension profile: 2 of our cases were truly localized, with a molecular marker only in the LN. On the contrary, when *BCL2/IGH+* circulating cells are detectable at diagnosis, ddPCR is a powerful tool to quantify tumor circulating levels and to predict prognosis. IF-RT in localized FL is the undisputed first-line treatment, but alone it often does not clear circulating FL cells. R administration in MRD+ patients decreased significantly the risk of a subsequent relapse and improved PFS. We strongly suggest treating patients suffering from early stage FL through an MRD-guided treatment with R after IF-RT.

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

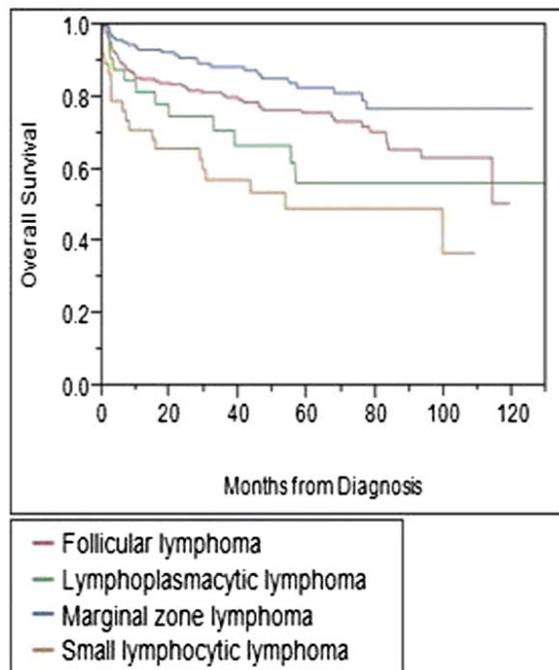
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LOW GRADE B-CELL NON-HODGKIN LYMPHOMAS INVOLVING THE CENTRAL NERVOUS SYSTEM: AN ANALYSIS FROM THE NATIONAL CANCER DATABASE

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Overall survival of CNS low grade B-cell NHLs by Histologic Subtype



Introduction: Central nervous system (CNS) involvement from low grade B-cell non-Hodgkin lymphomas (NHL) is rare and has only been reported as case series. The distribution, demographics and outcomes of patients with low grade CNS NHLs have not been well characterized.

Methods: The National Cancer Database (NCDB) represents ~70% of cancer cases in the United States. Using the 2004–2013 NCDB extranodal NHL database, we identified all CNS B-cell NHLs based on ICD-O-3 site and histology codes. Primary or secondary CNS involvement could not be determined.

Results: Out of 9435 CNS NHL cases, 475 [5.03%] had low grade histologies. In this group, the median age at diagnosis was 58 years [range 19–89]. Majority of the cases were female [56%], White, non-Hispanic [72%], privately insured [53%], with no comorbidities [74%] and treated in academic/research programs [38%]. Site of CNS disease was not specified in 22%. HIV status was known in 318 cases (6.3% positive). The brain [44%] was the most common site of involvement followed by spinal cord [19%] and meninges [15%]. Follicular lymphoma (FL) [48%] was the most common histology overall followed by marginal zone (MZL) [37%], small lymphocytic (SLL) [8%] and lymphoplasmacytic lymphomas (LPL) [7%]. MZL was the most common histology in the brain [44%] and meninges [61%] while FL was most common in the spinal cord [77%] and nervous system, NOS, [69%]. Cranial nerves and eye (retina/optic nerve) involvement was very rare [2 and 1 case each—both MZL]. The overall survival (OS) of CNS B-cell NHL was significantly better if histology was low grade vs other [5-year OS 74% vs 32%, $P < 0.0001$]. Among CNS low grade B-cell NHLs, 5-year OS was significantly affected by histology [MZL 83%, FL 75%, LPL 56% and SLL 50%, $P = 0.0003$] and site of disease [spinal cord 89%, meninges 78% and brain 63%, $P = 0.03$] in addition to age at diagnosis and co-morbidities on both uni- and multivariate analysis. Survival was not influenced by sex, race, insurance, year of diagnosis, facility type or location.

Conclusions: CNS involvement with low grade B-cell NHL is rare but has a relatively good outcome with most patients surviving beyond 5 years. FL and MZL are the more common low grade histologies. Both histology and disease site are important factors affecting survival.

Keywords: B-cell lymphoma; extranodal lymphomas; primary CNS lymphoma (PCNSL).

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CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES FOR YOUNG PATIENTS WITH FIRST-LINE FOLLICULAR LYMPHOMA: A POOLED ANALYSIS OF 4249 PATIENTS FROM THE FLASH DATABASE.

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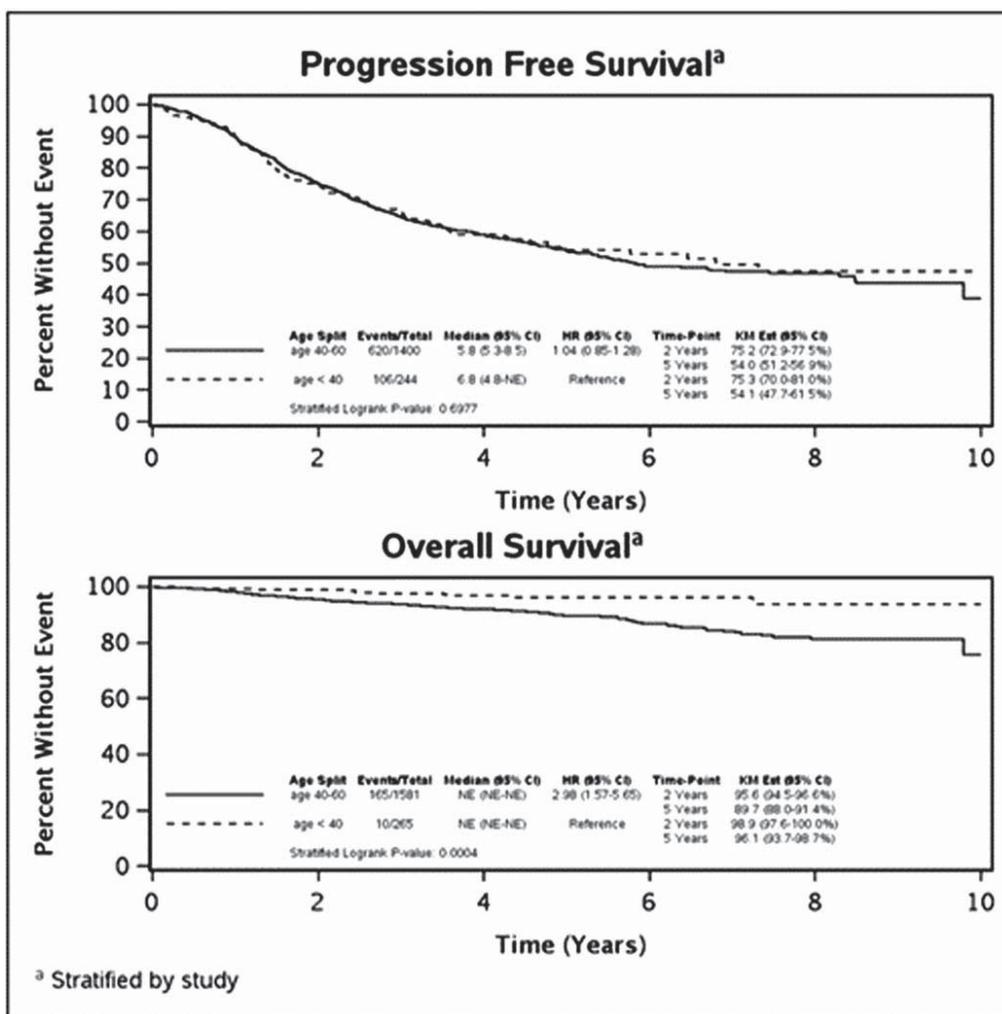
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Introduction: Although advanced age is a well-known adverse prognosis factor in first-line FL, with age >60 being one of the five adverse prognosis factor retained in the FLIPI score, little is known about characteristics and treatment outcomes for young patients. The Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) group conducted a pooled analysis to compare characteristics and treatment outcomes of young patients aged <40 to patients aged 40–60.

Method: Individual patient data from 18 randomized first-line trials included in the FLASH database were obtained for 4249 patients aged <60. Early disease outcomes were evaluated by complete response rate at 24 and 30 months after enrollment (i.e., initiation of induction treatment; CR24 and CR30). Time to progression (TTP), progression-free survival (PFS) and overall survival (OS) were defined in the primary FLASH study (Shi Q et al., JCO 2016). Multivariable stratified Cox models and logistic regression with generalized estimating equation were used to assess the associations between age <40 and outcomes. Variables adjusted were FLIPI risk group, rituximab use and performance status (PS).

Results: Among 4249 patients included in 18 trials, 673 (16%) were <40 and 3576 (84%) 40–60. The two groups were similar in Ann Arbor stage, FLIPI risk group, use of rituximab, ECOG PS group (0–1 or ≥2), LDH value, Hb and B2-microglobulin at baseline. Young patients differed significantly only in the number of involved nodal areas (≥5 in



73% of young patients vs 66%, $p = 0.0021$). The two groups had similar CR24 (32% vs 29%, $p = 0.32$), CR30 (31% vs 30%, $p = 0.57$), 5-year estimates for PFS of 44% (95% CI = 41–49 for young patients and 43–46 for patients 40–60) ($p = 0.30$) and TTP (median TTP 3.9 y vs 4.0 y, HR = 0.96, 95% CI = 0.86–1.08, $p = 0.52$). OS was significantly higher for young patients with 5-year estimates of 88% (95% CI = 85–90) versus 84% (95% CI = 83–86) ($p = 0.003$). After adjusting with FLIPI risk group, rituximab use and PS, age <40 was a significant predictor of OS, but not of PFS, TTP or achievement of CR30. Of note, for patients having received rituximab in their first line treatment ($n = 1846$), patients <40 ($n = 265$) and patients aged 40–60 ($n = 1581$) had respective 5-year estimates for PFS of 54% (95% CI = 48–62) and 54% (95% CI = 51–57) ($p = 0.70$) and for OS of 96% (95% CI = 94–99) versus 90% (95% CI = 88–91) ($p = 0.0004$) (Figure). No significant difference in OS was observed between the 2 groups for patients not having received rituximab in first line. These data suggest that among patients treated with rituximab, despite an identical PFS, survival outcomes were statistically higher in the <40 group compared to 40–60.

Conclusions: This study reports the clinical characteristics and outcomes in the most important cohort of young patients aged <40 with first-line FL. Age <40 y did not appear to influence the treatment outcome, but was associated with a significantly longer OS.

Keywords: follicular lymphoma (FL); prognostic indices.

230 PATIENTS WITH FOLLICULAR LYMPHOMA (FL) IN MAINTAINED COMPLETE RESPONSE (CR) AT 30 MONTHS SHOW A SURVIVAL SIMILAR TO A SEX- AND AGE-MATCHED SPANISH GENERAL POPULATION

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Introduction: FL is an indolent lymphoma characterized by the responsiveness to therapy followed by repeated relapses. The use of immunochemotherapy has allowed high CR rates with substantial advances in PFS and OS. However, patients who experience early progression still have poor outcome, whereas on the contrary, life expectancy of those with durable responses seems reasonably good. CR at 30 months has recently been suggested as potential surrogate for PFS in these patients. The aim of the present study was to analyze the group of patients in maintained CR at 30 months and to compare their OS with that of the general population.

Methods: The training cohort consisted of 263 patients (median age, 59 years; F/M, 142/121) consecutively diagnosed with FL grades 1, 2 or 3a in two centers between 2004 and 2014, with the only criterion being the need of treatment that consisted of rituximab combinations (61% R-CHOP). Response was evaluated by CT scan. A “land-mark” at 30 months from diagnosis was established to assess survival. Relative survival (RS) was analyzed with respect to the sex- and age-matched Spanish population. An independent series of 693 patients (median age, 58 years; F/M, 380/313) diagnosed with FL in 19 Spanish hospitals from the GELTAMO group were used as validation cohort.

Results: In the training cohort, 79% of patients achieved CR/CRu, 17% PR and 4% showed failure to treatment. After a median follow-up of 7.1 years, 10-year PFS and OS were 49% and 78%, respectively. During the follow-up prior to 30 months, 66 patients (43 in CR/CRu and 23 in PR) eventually progressed, whereas 21 PR patients reached CR status. As shown in the table, after excluding 14 patients who died before the land-mark, 188 were in maintained CR and 61 had eventually progressed. In table and figure, OS and RS of these groups are detailed. No decrease in the life expectancy was observed for patients in CR at 30 months. Interestingly, in this group, the quality of response (CR vs. PR) nor PET/CT-assessed response (negative vs. positive) did not influence significantly RS. Initial high β_2 microglobulin and high-risk FLIPI were associated with poorer OS. The impact of CR at 30 months on RS was validated in the independent GELTAMO series as shown in the table.

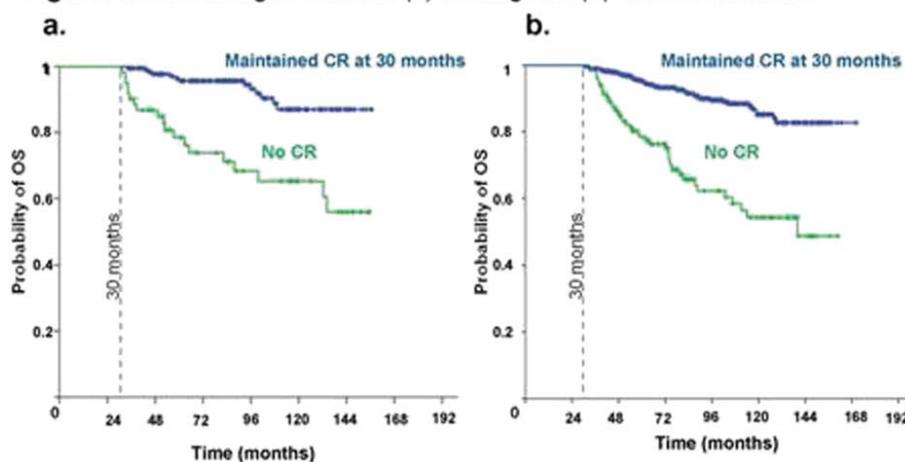
Conclusion: Patients with FL treated with immunochemotherapy who maintain CR at 30 months from diagnosis show similar survival than a sex- and age-matched general population. This information should be taken into account when these patients are considered candidate for potentially toxic treatments.

Status at 30 months	N	Training			Validation		
		Response after induction, n	10-year OS	10-year Relative survival*	N	10-year OS	10-year Relative survival*
Maintained CR	188	CR/CRu, 167 PR, 21	87%	100%	499	85%	100%
No CR	63	CR/CRu, 41 PR, 20 Failure, 2	53%	65%	194	40%	59%

*With respect to a sex- and age-matched general Spanish population; Patients died before the land-mark (30 months) are not included in this table.

Keywords: follicular lymphoma (FL).

Figure. OS according to status in (a) training and (b) validation cohorts



231 POD24 AND CR30 ARE PROMISING SURROGATE ENDPOINTS FOR ASSESSING THE OUTCOME OF PATIENTS WITH ADVANCED STAGE FOLLICULAR LYMPHOMA ENROLLED IN THE FOLLO5 TRIAL BY FIL.

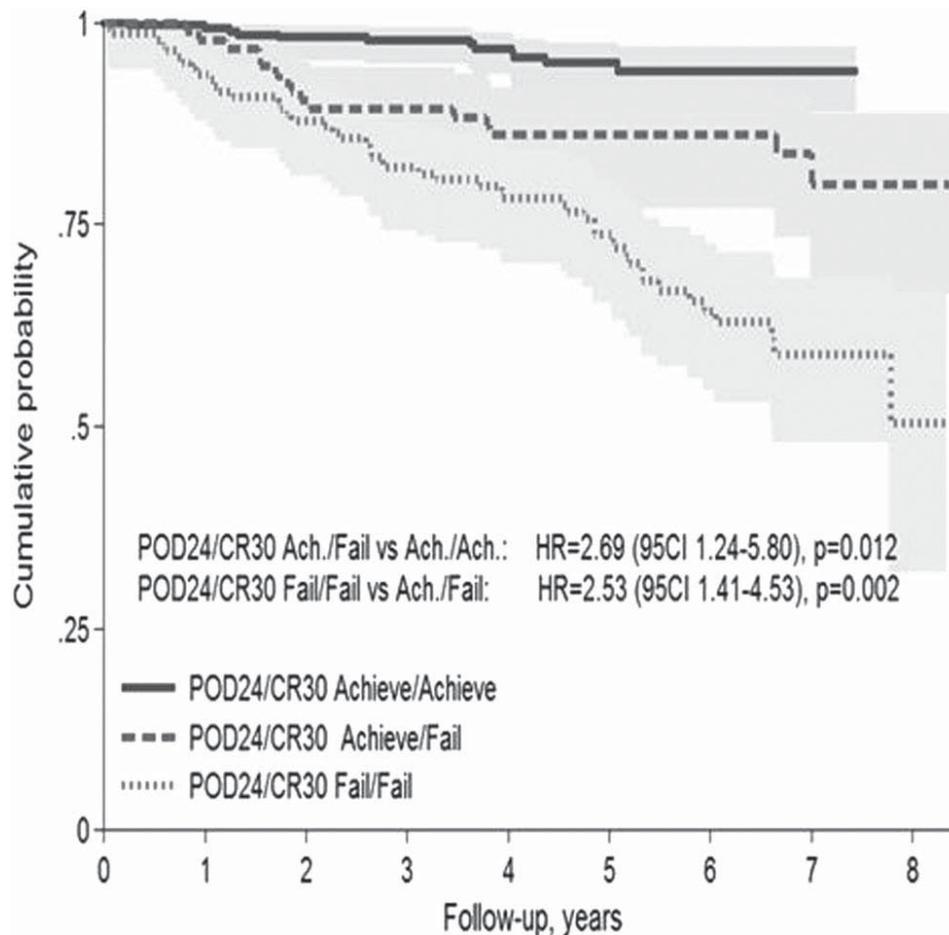
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Introduction: In an indolent disease like Follicular lymphoma (FL), the availability of validated and accurate early surrogates of survival would allow a faster assessment of treatment efficacy. Recently, the progression of disease within 24 months after diagnosis (POD24) and the lack of complete remission within 30 months after diagnosis (CR30) were suggested as promising early endpoints as they were both highly predictive of survival. We investigated the role of POD24 and of CR30 in our series of patients with advanced stage FL prospectively enrolled in the FOLLO5 trial (NCT00774826). The aim of this analysis was to validate the main study results with POD24 and CR30 and to further assess their impact on patients' outcome.

Methods: From March 2006 to September 2010, 534 patients were enrolled into the FOLLO5 trial, by 58 Italian Institutions. Patients were randomized among R-CVP, R-CHOP or R-FM. POD24 and CR30 were



correlated with Progression free survival (PFS) and Overall Survival (OS). CR30 was calculated according to original method (Qian Shi et al. JCO, 2017). To align the endpoints, POD24 and CR30 are labeled as fail (F) for progression within 24 months, no CR30 and achieve (A) for no POD24 and achieve CR30, respectively.

Results: Median follow-up was 84 months (range 1–119). One hundred and forty-one patients (28%) failed POD24, and 235 (47%) failed the CR30 endpoint. Five-year OS was 79% and 95% for patients failing and achieving POD24 ($p < 0.001$) and was 82% and 98% for patients failing to achieve and achieving CR30 ($p < 0.001$). Prognostic role of POD24 and CR30 was observed for all three study arms ($p < 0.001$). Both indexes retained their prognostic role for OS after adjustment by FLIPI ($p < 0.001$) and FLIPI2 ($p < 0.001$). In POD24 analysis, the OR adjusted by FLIPI2 between R-CHOP vs. R-CVP was 0.70 (95%CI 0.43–1.13, $p = 0.148$) and 0.58 (95%CI 0.36–0.94, $p = 0.027$) between R-FM vs. R-CVP. In CR30, the OR adjusted by FLIPI2 between R-CHOP vs. R-CVP was 0.63 (95%CI 0.40–0.98, $p = 0.043$) and 0.57 (95%CI 0.36–0.89, $p = 0.013$) between R-FM vs. R-CVP. Five-year OS was 95% for patients achieving both POD24 and CR30 (267; 53%), 86% for those failing CR30 (94; 19%) and 74% for patients failing both POD24 and CR30 (141; 28%) (Figure 1. OS stratified by groups obtained combining POD24 with CR30).

Conclusions: In patients with advanced stage FL who received standard immunochemotherapy in the FOLL05 trial, both POD24 and CR30 were significant prognostic factors for OS although. CR30 was better than POD24 to identify low risk patients, while POD24 was more accurate for the identification of high-risk subjects. POD24 and CR30 showed a comparable behavior and a satisfying correlation with PFS and can be used for the early assessment of patient outcome.

Keywords: follicular lymphoma (FL).

232 DEFINING PROGRESSION FREE SURVIVAL AFTER MULTIPLE LINES OF THERAPY AND IMPACT OF DYNAMIC CHANGES IN FLIPI FOR MULTIPLY RELAPSED FOLLICULAR LYMPHOMA IN THE RITUXIMAB ERA

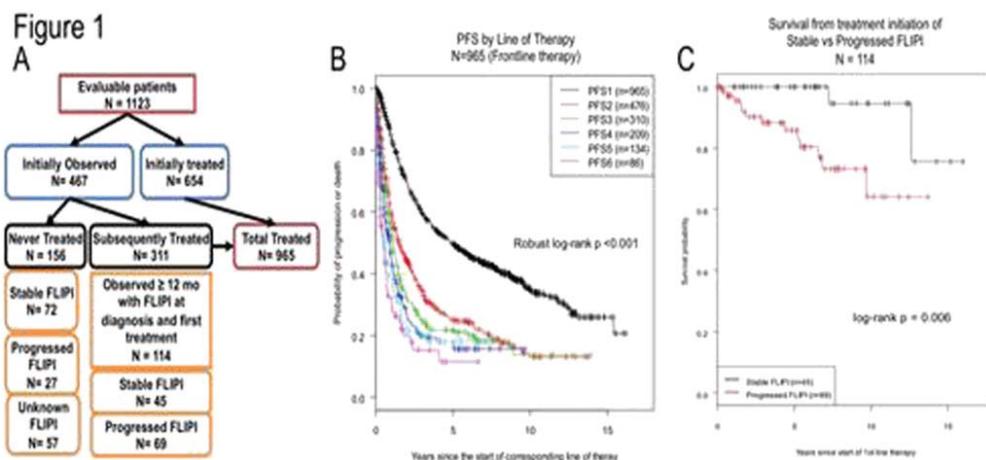
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Introduction: Management of follicular lymphoma (FL) requires multiple lines of therapy despite improved outcomes. We sought to 1) define treatment outcomes after multiple lines of therapy and 2) examine impact of FLIPI score changes on the outcome of initially observed patients.

Methods: We identified 1446 adult patients (pts) with newly diagnosed FL from 1998–2009 and 1123 pts met eligibility for analysis (323 pts excluded for divergent lymphoma histology at diagnosis, inadequate follow up, or concurrent second malignancies). Intent to observe was assessed by physician intent at first evaluation. FLIPI risk category was calculated serially with stable FLIPI defined as low/intermediate that did not change from diagnosis to start of therapy (low-low, int-int) and progressed FLIPI defined as increased category from diagnosis to start of therapy (low-int, low-high, int-high).

Results: The median follow up 8.2 yrs (range 0.2–16.8), median age at diagnosis was 57.1 yrs (range 19.6–93.7), and 761 pts (67.8%) had stage III/IV disease; 467 pts (42%) were initially observed (28.5% stage I/II, 69.8% stage III/IV, 1.7% stage unknown) of which 156 pts never required therapy based on last follow-up or death and 311 pts subsequently required therapy. Median observation for pts initially monitored was 3.78 yr (95% CI 3.3–4.3, range 0.24–16.6). Median observation for pts never requiring therapy was 7.2 yrs (range 0.2–16.7). In total, 967 pts required therapy (Fig. 1A). Five-year OS for low, int, and high FLIPI are 96.7%, 92.8%, and 81.8%. Median OS for the entire group and stage III/IV pts was not reached. PFS decreased with more lines of therapy: PFS1 4.9 yrs, PFS2 1.5 yrs, PFS3 1.1 yrs, PFS ≥ 4 was less than 1 yr (Figure 1B). Next, we evaluated the clinical significance of sequential FLIPI assessments in pts who were initially observed. We identified 114 pts initially observed ≥ 12 months with



multiple FLIPI assessments, including diagnosis and start of therapy. FLIPI risk category progressed in 60.5% ($N = 69$), which was associated with inferior outcome compared with pts with stable FLIPI (39.5%, $N = 45$), $p = 0.006$ (Figure 1C). In contrast, annual FLIPI risk categories over 5 yrs in 156 observed pts who never required therapy were stable in 72 (46%), progressed in 27 (17%), were not assessed in 57 (37%). Pts with progressed versus stable FLIPI had higher risk of transformation (25.2% vs 11.3%, $p < 0.001$) and were treated more often initially with R-monotherapy (38.8% vs. 19.1%, $p < 0.001$).

Conclusions: Despite improvement in OS over the last two decades, PFS after 4th line of therapy remains less than 1 year. The data benchmarks PFS by lines of therapy, which will facilitate drug development in pts with multiply relapsed FL. The inferior outcome for pts who progress and alter their FLIPI may represent pts with adverse biology at diagnosis. We hope to identify biomarkers in this high-risk group that would permit identification for early treatment intervention.

Keywords: follicular lymphoma (FL).

233 TIME FROM DIAGNOSIS TO 2ND TREATMENT IS A PROMISING SURROGATE FOR OVERALL SURVIVAL IN PATIENTS WITH ADVANCED STAGE FOLLICULAR LYMPHOMA

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Introduction: It is difficult to demonstrate an overall survival (OS) benefit in trials of early therapy vs observation in asymptomatic patients (pts) with follicular lymphoma (FL) who do not meet established criteria for treatment. Time to New Treatment (TTNT) is difficult to interpret. Time from diagnosis to 2nd treatment (TD2T) is potentially a preferable endpoint that balances exposure to therapy. We hypothesize that TD2T might be a surrogate for OS.

Methods: We identified 584 consecutive pts at our institution, diagnosed 1998–2007 with advanced stage FL grade 1–3A for whom intention was observation ($n = 248$) or therapy ($n = 338$). Median time to 1st treatment (TT1T), TD2T, TTNT, and OS were estimated using the subdistribution function, and modified Kendall's tau (mK) was used to assess correlation between survival endpoints. We performed landmark analyses and compared OS to the age/sex-matched US population using a standardized mortality ratio (SMR) method.

Results: At a median follow-up of 10.4 years (yrs), pts who were initially observed have a median TT1T of 3.6 yrs and TD2T of 13.1 yrs, and 10-yr treatment-free survival of 25%. The 10-yr OS is 84%. The

observed mortality exceeds the general population (SMR 1.56, $p = 0.002$). TD2T is strongly correlated with OS with initial observation (mK 0.46, $p = 0.004$) or therapy (mK 0.53, $p < 0.0001$), but TT1T is not. Among observed pts, TD2T <5 yrs is associated with inferior survival ($p = 0.03$) and increased mortality relative to the general population (SMR 3.91, $p < 0.001$). Pts who require immediate therapy have an inferior OS (HR 0.7, $p = 0.047$) and corresponding inferior TD2T (HR 0.6, $p < 0.0001$) compared with those who are observed (expected in this retrospective analysis due to confounding by indication), but a comparison of TTNT is misleading and suggests better outcomes (HR 1.5, $p < 0.0001$).

Conclusion: The outstanding expected survival in pts with advanced stage FL grade 1–3A who are initially observed supports an active surveillance approach in appropriately selected pts, and future trials might restrict eligibility to high-risk pts expected to have inferior survival. Use of TTNT or PFS in trials of early therapy vs observation can be misleading, while TD2T is potentially a preferable endpoint that balances exposure to therapy. TD2T is strongly correlated with OS, while the duration of initial observation is not. TD2T is therefore a potential surrogate for OS, although more is needed to rigorously establish surrogacy.

Keywords: follicular lymphoma (FL).

234 STATIN USE AND PROGNOSIS IN 12,865 NON-HODGKIN LYMPHOMA PATIENTS TREATED IN THE RITUXIMAB-ERA

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Introduction: Statin use has been associated with improved cancer-specific outcomes among patients with several cancer forms, including in a few studies of lymphoma. At the same time, *in vitro* data suggests that statins may inhibit rituximab binding and thus impair the efficacy of rituximab. Most clinical studies have had limited power to address this concern as well as to investigate major subtypes separately. We aimed to assess if statin use at non-Hodgkin lymphoma (NHL) diagnosis is associated with lymphoma-specific survival in NHL overall and subtypes.

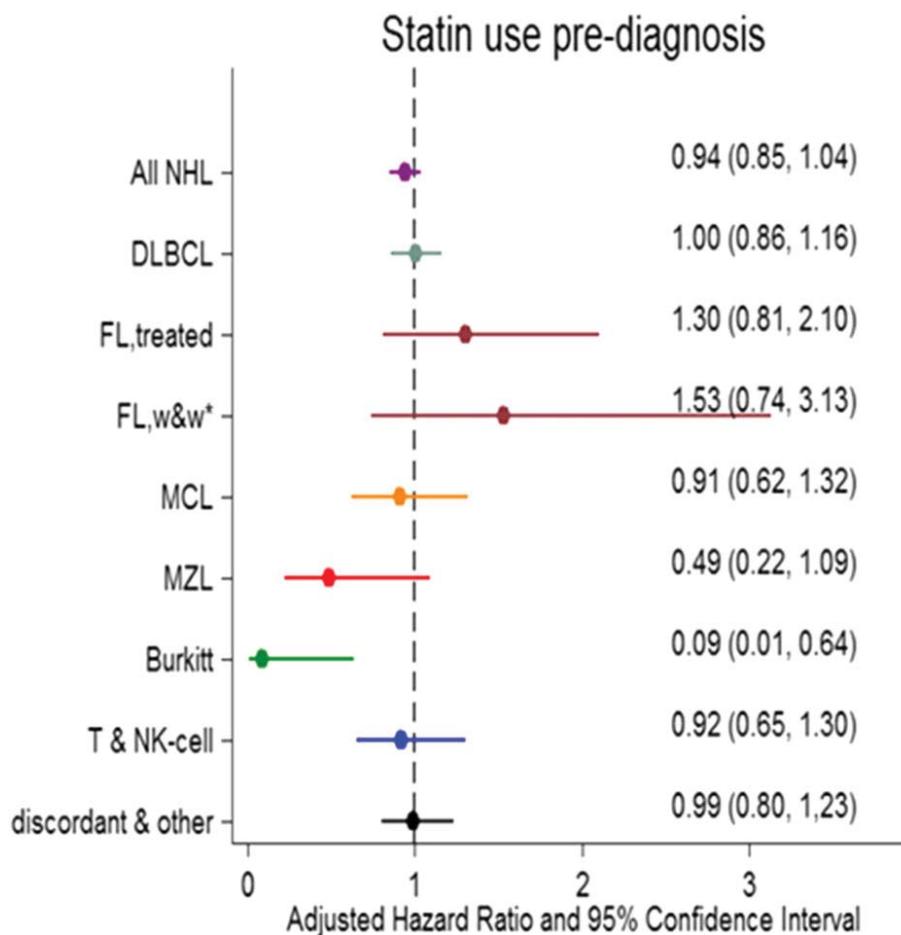
Methods: Using the National Swedish Lymphoma register linked with the population-based Prescribed Drug and Cause-of-Death registers, we identified all persons diagnosed with NHL from January 1, 2007, until Dec 31, 2013. Persons with any dispensing of statins during a 6-month period before diagnosis were considered statin users. We used Cox proportional hazards models to compute risk of lymphoma-specific death among statin users compared to non-users for NHL overall and subtypes, with subgroup analyses of treated and non-treated follicular lymphoma (FL). Models were adjusted for age, sex, year of diagnosis, education level, aa-IPi score and concomitant medication with anticoagulants, diuretics, beta-blockers, ACE inhibitors, calcium blockers and anti-diabetics to capture comorbidity.

TABLE 1 Patient characteristics (N=12,865)

		No statin before diagnosis (n=10,470, 81%)	Lymphoma-specific death (n=2,135, 20%)	Statin before diagnosis (n=2,395, 19%)	Lymphoma-specific death (n=596, 25%)
Length of Follow-up, years		2.2 [0.0-7.0]		1.7 [0.0-7.0]	
Major subtype	FL	1,430 (14)	132 (9)	335(14)	49 (15)
	DLBCL	3,294 (31)	927 (28)	872 (36)	288 (33)
	Mantle Cell Lymphoma	595 (6)	174 (29)	177 (7)	51 (29)
	Marginal Zone Lymphoma	651 (6)	63 (10)	121 (5)	8 (7)
	Burkitt Lymphoma	111 (1)	51 (29)	20 (1)	5 (25)
	T- and NK-cell	778 (7)	295 (40)	144 (6)	53 (37)
	Discordant and other	3,611(34)	518 (14)	726 (30)	142 (20)
Demographics					
Sex	Female	4,730 (45)	968 (20)	927 (39)	227 (24)
	Male	5,740 (55)	1,167 (20)	1,167 (20)	369 (25)
Age, years	Age at diagnosis	67 (18-105)		73 (34-95)	
Disease characteristics					
Stadium	I-II	2,537 (24)	295 (12)	520 (22)	79 (15)
	III-IV	5,984 (57)	1,413 (24)	1,377 (57)	395 (29)
	Primary extra nodal	1,238 (12)	226 (18)	320 (13)	68(21)
	Missing	711 (7)	201(28)	178 (7)	52(31)
WHO performance status	Asymptomatic	5,790 (55)	466 (8)	1,082 (45)	104 (10)
	Symptoms-ambulatory	2,883 (28)	759 (26)	788 (33)	220 (28)
	<50% in bed daytime	720 (7)	318 (44)	212 (9)	91 (43)
	>50% in bed daytime	557 (5)	315 (57)	162 (7)	99 (61)
Bulky disease	Bedbound	280 (3)	193 (69)	96 (4)	68 (71)
	Missing	240 (2)	84 (35)	55 (2)	14 (25)
	Yes	1,360 (13)	394 (29)	291 (12)	96 (33)
	No	8,554 (82)	1,575 (18)	1,971 (82)	452 (23)
Age adjusted IPI score	Missing	556 (5)	166(30)	133 (6)	48(36)
	0-1	3,558 (34)	520 (15)	747 (31)	134 (18)
	≥2	1,901 (18)	724 (38)	484 (20)	214 (44)
B-symptoms at diagnosis	Missing	5,011 (48)	891 (18)	1,164 (49)	248 (21)
	Yes	3,346 (32)	1,046 (31)	730 (30)	283 (39)
	No	6,668 (64)	892 (13)	1,541 (64)	259 (17)
LDH at diagnosis	Missing	456(4)	197 (43)	124 (5)	54 (44)
	Elevated	4,249 (41)	1,238 (29)	1,009 (42)	364 (36)
	Normal	5,584 (53)	699 (13)	1,244 (52)	182 (15)
Other medications before diagnosis	Missing	637 (6)	198 (31)	142 (6)	50 (35)
	Betablockers	1,801 (17)	513 (28)	1,271 (53)	328 (26)
	Diuretics	1,650 (16)	528 (32)	836 (35)	224 (27)
	ACE inhibitors	1,831 (17)	476 (26)	1,305 (54)	316 (24)
	Calcium blockers	1,105 (11)	300 (27)	689 (29)	182 (26)
	Anticoagulants	1,931 (18)	605 (31)	1,664 (69)	451 (27)
	Diabetes medications	497 (5)	132 (27)	553 (23)	140 (25)

Results: Among 12,865 NHL patients (4,166 diffuse large B-cell, DLBCL, 1,765 FL, 772 mantle cell, MCL, 772 marginal zone, MZL, 131 Burkitt, 922 T- and NK-cell and 4,337 discordant or other lymphomas), 19% used statins at diagnosis. At end of follow-up (Sept 2013), 2,731 (21%) had died from lymphoma. We found no association

between statin use and lymphoma-specific mortality for NHL overall, adjusted HR 0.94 (0.85, 1.04) or its subtypes (DLBCL 1.00 (0.86, 1.16), treated FL1.30 (0.81, 2.10), FL “watch and wait” 1.53 (0.74, 3.13), MCL 0.91 (0.62, 1.32), MZL 0.49 (0.22, 1.09), T- and NK-cell 0.92 (0.65, 1.30), discordant or other lymphomas 0.99 (0.80, 1.23)).



However, for Burkitt lymphoma, we found a statistically significant decreased lymphoma-specific mortality, adjusted HR 0.09 (0.01, 0.64). Further dose-response analyses are planned.

Conclusions: In this very large population-based unselected lymphoma population, statins were not associated with worse outcomes and thus appear safe to use during lymphoma treatment. Interestingly, Burkitt patients using statins had a statistically significant decreased lymphoma-specific mortality.

Keywords: non-Hodgkin lymphoma (NHL); statins.

CLL

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IBRUTINIB INCREASES THE SYSTEMIC EXPOSURE OF RITUXIMAB: PHARMACOKINETIC RESULTS FROM THE HELIOS TRIAL

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Introduction: In the phase 3 HELIOS trial, coadministration of ibrutinib with bendamustine + rituximab (I + BR) improved patient outcomes compared with placebo + BR (Pbo + BR) in patients with

previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma. We used a modeling approach to explore the pharmacokinetic (PK) interactions between ibrutinib, B, and R from the HELIOS trial.

Methods: In total, 578 patients were randomized to 420 mg ibrutinib ($n = 289$) or pbo ($n = 289$) in combination with 6 cycles of BR until disease progression or unacceptable toxicity. B was dosed at 70 mg/m² on days 2–3 of cycle 1 and days 1–2 of cycles 2–6; R was dosed at 375 mg/m² on day 1 of cycle 1 and 500 mg/m² in cycles 2–6.

Ibrutinib PK samples were obtained from all patients at predose, 1, 2, and 4 hr on day 1 of cycles 1 and 2. In a subset of patients, B PK samples were obtained on day 2 of cycles 1 and 2 at predose, end of infusion, and at 1, 2, and 4 hr; R samples were obtained on days 1 and 15 of cycle 1, predose on day 1 of cycles 2–6, and day 1 of cycles 7–9, in the washout phase.

Dose-normalized B and R concentration-time data were stratified by treatment. R PK was assessed using a nonlinear mixed-effects compartmental approach (NONMEM v7.1.0). R v3.2.4 (www.R-project.org) was used for model diagnostics and plots.

Results: Ibrutinib PK data were assessed in 280 patients. BR PK data were assessed in 178 patients (84 [Pbo + BR] and 94 [I + BR]). Dose-normalized plasma concentration-time data of B from both arms were comparable, indicating that ibrutinib did not alter B PK. Systemic exposure of R was higher with I + BR than with Pbo + BR; mean predose serum concentrations were 2- to 3-fold higher in the first three cycles

and 1.2- to 1.7-fold higher in subsequent cycles (Figure). Systemic exposure of ibrutinib (mean AUC_{ss} ± SD = 447.5 ± 298.2 ng·h/mL) was comparable to those observed with single agent ibrutinib in other trials, indicating that BR did not impact ibrutinib PK.

A previously reported population PK model, which includes a clearance term decreasing exponentially with time, was used to model R exposure ($n = 147$). Inclusion of both treatment arm as a categorical covariate and tumor burden as a continuous time-varying covariate on overall R clearance significantly improved the fitting of the data.

No relevant differences in safety profile were observed between the I + BR and Pbo + BR arms with the increase in R exposure. All-grade infusion-related reactions were reported in 22% of the Pbo + BR arm and 16.7% of the I + BR arm; the incidence of chills was comparable (~11%). Dose interruptions, dose reductions, and discontinuations due to infusion-related reaction were more frequent with Pbo + BR (34.8% vs. 27.9%).

Conclusions: I + BR led to greater dose-normalized systemic exposure of R compared with Pbo + BR. The modeling data suggest that R disposition is, at least in part, target mediated. Further studies are needed for a fully mechanistic representation of R disposition, which may provide insight into the clinical significance of these findings.

Keywords: chronic lymphocytic leukemia (CLL); ibrutinib; rituximab.

236 EFFECT OF SINGLE-AGENT IBRUTINIB ON TUMOR DEBULKING AND REDUCTIONS IN TUMOR LYSIS SYNDROME (TLS) RISK IN PATIENTS (PTS) WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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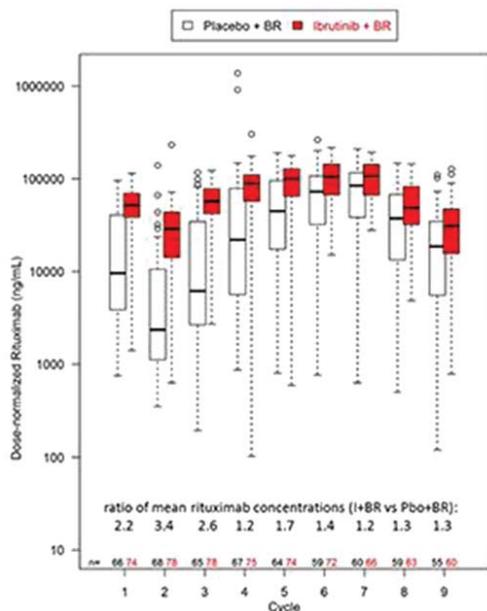


Figure: Dose-normalized mean rituximab plasma concentration-time profile from patients treated with placebo (Pbo; white) or ibrutinib (I; red) in combination with a bendamustine and rituximab (BR) regimen. Ratios of mean rituximab concentration (ibrutinib over placebo) at each cycle are presented. The extremes of the box identify the 25th and 75th percentiles; the whiskers represent 1.5-fold the interquartile range; observations outside the whiskers are represented as open circles (considered outliers); and n at the bottom of the plot refers to the number of samples analyzed at each cycle.

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Introduction: Ibrutinib (ibr), a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase, is approved in the EU for the treatment of CLL. Ibr results in rapid reduction in lymphadenopathy, often accompanied by early, transient lymphocytosis. Venetoclax (ven) received FDA accelerated approval for relapsed del17p CLL and EMEA conditional approval for relapsed CLL and has notable risk of TLS that is associated with increased disease bulk defined by absolute lymphocyte count (ALC) and lymph node (LN) diameter. Translational studies suggest synergistic anti-tumor activity of ibr plus ven. We assessed how ibr lead-in may reduce TLS risk for ven in considering this combination.

Methods: Data from 3 single-agent ibr (420 mg once daily until PD/intolerance) studies in CLL/SLL were analyzed ($N = 424$): PCYC-1102 in relapsed/refractory (R/R) pts ($n = 67$) and treatment-naïve (TN) pts ≥ 65 y ($n = 27$); RESONATE (PCYC-1112) in R/R pts ($n = 195$); and RESONATE-2 (PCYC-1115) in TN pts ≥ 65 y excluding del17p ($n = 135$). TLS risk categories were defined per ven USPI (Table). First CT response assessment occurred on day 56 (PCYC-1102), 78 (RESONATE), and 113 (RESONATE-2).

Results: Approximately, 80% of pts were moderate or high risk for TLS at baseline (Table). Baseline largest diameter of LN (LDi) ≥ 5 cm was more common in R/R vs TN pts. In both groups, the proportion of pts with LDi ≥ 5 cm decreased at first CT assessment (Table). Bulky disease resolved to LDi < 5 cm in 90% of TN and 85% of R/R pts with baseline LDi ≥ 5 cm. Median baseline ALC was higher in TN pts vs R/R pts (49 vs $21 \times 10^9/L$). ALC initially increased in many pts, but decreased with continued ibr. During ibr therapy, 87% of TN and 45% of R/R pts with high-risk TLS at baseline were reduced to low risk, and the majority of moderate-risk TLS pts were reduced to low risk (Table). At first

TABLE: Baseline characteristics and summary of TLS risk reduction* in moderate- and high-risk patients.

Parameter	TN [†] (n=162)	R/R [†] (n=262)
ALC $\geq 25K$ at baseline, n (%)	116 (72)	125 (48)
Bulky disease (LDi ≥ 5 cm) at baseline, n (%)	58 (36)	159 (61)
LDi ≥ 10 cm	8 (5)	13 (5)
LDi ≥ 5 cm to < 10 cm	50 (31)	146 (56)
Bulky disease (LDi ≥ 5 cm) at first assessment, n (%)	8/148 (5)	45/247 (18)
Patients with high risk for TLS at baseline, n (%)	46 (28)	86 (33)
Reduced to moderate risk*	3/46 (7)	39/86 (45)
Reduced to low risk*	40/46 (87)	39/86 (45)
Patients with moderate risk for TLS at baseline, n (%)	86 (53)	118 (45)
Reduced to low risk*	71/86 (83)	81/118 (69)
Patients with low risk for TLS at baseline, n (%)	30 (19)	58 (22)

*Over the duration of ibrutinib treatment. TLS risk categories as defined by the venetoclax USPI: low-risk (ALC $< 25K$ and LDi < 5 cm), moderate-risk (ALC $\geq 25K$ or LDi ≥ 5 cm but < 10 cm), and high-risk (ALC $\geq 25K$ and LDi ≥ 5 cm; or any ALC with LDi ≥ 10 cm).

[†] 1% of TN and 33% of R/R patients had del17p chromosomal abnormality.

assessment, 54% of TN and 45% of R/R pts were moderate risk, and 7% and 14% were high risk, respectively; a minority of pts had increased risk due to transient ALC increase. In RESONATE-2, 82% of TN pts were moderate to high risk for TLS at baseline (32% high-risk); 88% of high-risk TLS was reduced to low risk. At first assessment in RESONATE-2, 50% were moderate risk, and high-risk TLS was reduced to 8%. **Conclusions:** Our analyses demonstrate that most pts with baseline high-risk TLS were reduced to moderate or low risk at first assessment. This suggests that tumor debulking with ibr lead-in may effectively reduce TLS risk for ven and the intensity of TLS monitoring for ibr + ven in pts with CLL.

Keywords: chronic lymphocytic leukemia (CLL); ibrutinib; tumor lysis syndrome.

237 HIGH OVERALL RESPONSE RATE WITH THE BTK INHIBITOR BGB-3111 IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA: AN UPDATE ON SAFETY AND ACTIVITY

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Introduction: BGB-3111 is a potent, highly specific, and irreversible Bruton tyrosine kinase (BTK) inhibitor, with greater selectivity for BTK vs other TEC- and EGFR-family kinases and favorable pharmacokinetic and pharmacodynamic properties. BGB-3111 was shown to achieve complete, continuous BTK occupancy in peripheral blood mononuclear cells and lymph nodes and was associated with durable clinical responses in patients (pts) with CLL/SLL and Waldenström macroglobulinemia. Here, updated preliminary safety and activity data in relapsed/refractory (R/R) and treatment-naïve (TN) pts with CLL/SLL are reported.

Methods: This is an open-label, multicenter, phase 1b study of BGB-3111 in pts with B-cell malignancies. Pts with R/R CLL/SLL were

included in dose escalation, and both TN and R/R CLL/SLL pts were included in expansion cohorts at the recommended phase 2 dose (320 mg/d, given once daily [QD] or split as a twice-daily [BID] dose). Adverse events (AEs) are reported per Common Terminology Criteria for AEs version 4.03, and response per the modified iwCLL criteria (Hallek 2008, Cheson 2012 clarification for novel therapies).

Results: As of 15 Dec 2016, 68 pts with CLL/SLL (50 R/R and 18 TN) were enrolled: 4 pts in dose escalation and 64 in cohort expansion at doses of 160 mg QD ($n = 3$), 160 mg BID ($n = 25$), and 320 mg QD ($n = 40$). Patient characteristics are shown in Table 1.

Safety: Median follow-up was 7.2 (range, 0-23.3) months. The most frequent AEs of any cause were bruising (35%) and petechiae (11%), upper respiratory tract infection (28%), fatigue (25%), cough (22%), and diarrhea (21%). Four serious AEs related to BGB-3111 were seen in 3 pts: grade (Gr) 2 cardiac failure, Gr 2 pleural effusion, Gr 3 purpura, and Gr 3 pneumonia. The case of Gr 3 purpura (subcutaneous hemorrhage) was the only major bleeding event reported. Atrial fibrillation (Gr 3) occurred in 1 pt. One pt discontinued BGB-3111 for an AE (pleural effusion).

Activity: Of the 54 pts evaluable for response (>12 weeks follow-up or discontinuation before 12 weeks), the objective response rate was 96% (52/54), with partial response in 67% (36/54), partial response with lymphocytosis in 30% (16/54), stable disease in 1 R/R pt, and no assessment for 1 R/R pt because of AE. No instances of disease progression or Richter transformation were reported.

Conclusions: BGB-3111 is well tolerated and highly active in R/R and TN CLL/SLL. With only 7.2 months of median follow-up, only 1 toxicity-related discontinuation, and no progressive disease seen thus far on study.

	TN CLL/SLL (n=18)	R/R CLL/SLL (n=50)	Overall (N=68)
Demographics			
Median (range) age, y	71.6 (62-87)	65.5 (24-82)	68 (24-87)
Median no. of prior therapies	0	2 (1-7)	1 (0-7)
Median (range) follow-up, mo	5.1 (0.2-9)	10.5 (0-23.3)	7.2 (0-23.3)
Safety, n (%)			
Any AE	13 (72)	48 (96)	61 (90)
Grade ≥ 3 AE	3 (14)	18 (38)	21 (31)
Serious AE related	0	3 (6)	3 (4)
AEs leading to Rx discontinuation	0	1 (2)	1 (2)
Fatal AE	0	0	0
Efficacy (best response), n (%)			
ORR	N=13 13 (100)	N=41 39 (95)	N=54 52 (96)
CR	0	0	0
PR	7 (54)	29 (71)	36 (67)
PR-L	6 (46)	10 (24)	16 (30)
SD	0	1 (2)	1 (2)
PD	0	0	0
Discontinued before assessment	0	1 (2)	1 (2)

AE, adverse event; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; R/R, relapsed/refractory; Rx, treatment; SD, stable disease; TN, treatment-naïve.

Keywords: BTK; chronic lymphocytic leukemia (CLL); small lymphocytic lymphoma (SLL).

238 LONG-TERM EFFICACY AND SAFETY IN THE RESONATE STUDY: IBRUTINIB IN PATIENTS WITH PREVIOUSLY TREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITH UP TO FOUR YEARS FOLLOW-UP

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Introduction: Ibrutinib, a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase, is indicated by the US FDA and EMEA for patients with CLL and allows for treatment without chemotherapy. RESONATE™ is a phase 3 trial of ibrutinib vs ofatumumab in relapsed CLL/SLL. This report includes updated safety and efficacy results with up to 4-year follow-up.

Methods: Eligible patients had ≥ 1 prior therapy. Patients received 420-mg ibrutinib PO until disease progression or ofatumumab up to 24 weeks. At interim analysis (median 9 months follow-up), superiority of ibrutinib vs ofatumumab for PFS and OS was declared by the data

monitoring committee, and ibrutinib access was recommended for all ofatumumab patients. For this long-term follow-up analysis, efficacy was investigator assessed. OS was censored at crossover for patients who received ibrutinib after ofatumumab.

Results: Of 391 patients enrolled, 195 were randomized to the ibrutinib arm and 196 to the ofatumumab arm. The median age was 67 years (age ≥ 70 years in 40%) and 57% had advanced disease (Rai stage III/IV). Median follow-up for the ibrutinib arm was 44 months (53 months max). Ibrutinib significantly prolonged PFS vs ofatumumab (median NR vs 8 months, [HR 0.133; $P < 0.0001$]; 3-year PFS 59% vs 3%). Significant PFS benefits were observed across patient subgroups. PFS on ibrutinib for the del11q subgroup trended to have the most favorable outcome, although PFS was not statistically different between ibrutinib patients with del17p vs del11q vs those without these FISH abnormalities. At analysis, with the majority of ofatumumab patients (68%) crossing over to ibrutinib, OS was longer for ibrutinib vs ofatumumab (median OS not reached for either arm). The 3-year OS for ibrutinib was 74%. ORR with ibrutinib was 91% with CR/CRi rates that increased over time (9% at current follow-up). With extended ibrutinib therapy, improvements in baseline cytopenias were observed for hemoglobin (85%), platelet (95%), and absolute neutrophil counts (95%). The AE profile of ibrutinib was consistent with previous reports. Major hemorrhage occurred in 6%, grade ≥ 3 atrial fibrillation in 6%, and grade ≥ 3 hypertension in 8% of patients over a 4-year follow-up period. Rates of most grade ≥ 3 AEs decreased from year 1 to years 2–3 including neutropenia (18% vs 8%), pneumonia (11% vs 4%), and atrial fibrillation (4% vs 2%). Most frequent reasons for ibrutinib discontinuations were disease progression (27%) and AE (12%). At analysis, 90 patients randomized to ibrutinib (46%) continue ibrutinib therapy.

Conclusions: Long-term results of the international phase 3 RESONATE trial support the tolerability of extended ibrutinib treatment and continue to demonstrate sustained PFS and OS including in patients with high-risk cytogenetics. The results in patients with relapsed CLL with del17p or del11q abnormalities compare favorably to prior reports from phase 2 trials.

Funding source: Pharmacys LLC, an AbbVie Company.

Keywords: BTK; chronic lymphocytic leukemia (CLL); ibrutinib.

239 OUTCOMES WITH BRUTON TYROSINE KINASE INHIBITION IN RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA AFTER PROGRESSION ON VENETOCLAX

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Introduction: The BCL2 inhibitor venetoclax entered clinical practice in the USA and Europe after the BTK inhibitor (BTKi) ibrutinib had become standard of care for relapsed CLL. Recent data indicate that venetoclax is efficacious after progression on ibrutinib (Jones *et al.*, ASH, 2016), but efficacy of BTKi after progressive disease (PD) on venetoclax has not been explored. We report outcomes of CLL/SLL receiving BTKi treatment after PD on venetoclax.

Methods: Of 67 consecutive patients with BTKi naive relapsed/refractory CLL/SLL treated on early phase venetoclax trials at two Australian centers (June 2011–March 2016), 10 received subsequent BTKi, either ibrutinib 420 mg daily or a novel BTKi on trial. Responses to BTKi were assessed according to iwCLL criteria with the 2012 Cheson addendum for novel therapies and analysed as of 1st October 2016.

Results: Of the 67 patients on venetoclax, eight developed progressive CLL/SLL. Six of these received ibrutinib as their next therapy, all commencing within 2 months of ceasing venetoclax (Table). The two patients who did not receive ibrutinib progressed before this agent was available in Australia. Five of the six patients receiving ibrutinib achieved a PR at a median 6 (4–9) months. One patient had SD at 2 months. After a median follow up of 10 months (6–16), three remain alive with ongoing clinical response to BTKi at 6, 13 and 16 months. The other 3 died of PD. An additional four patients

TABLE 1 CLL patients with PD on venetoclax, receiving BTKi

Variable	All patients	Progressive CLL	CLL post RT salvage
Number (N)	10	6	4
Age, median (range)	69.5 (47 – 78)	72 (65 – 78)	63.5 (47 – 73)
Prior Therapies, median (range)	3.5 (1 – 6)	4.5 (1 – 6)	3 (2 – 6)
Fludarabine Refractory, n (n/N%)	8/10 (80%)	5/6 (83%)	3/4 (75%)
Bulky Disease, n (n/N%)	5/10 (50%)	3/6 (50%)	2/4 (50%)
Venetoclax <400mg/day, n (n/N%)	4/10 (40%)	2/6 (33%)	2/4 (50%)
Concurrent Rituximab, n (n/N%)	2/10 (20%)	1/6 (17%)	1/4 (25%)
Del11q, n (n/N%)	3/10 (30%)	1/6 (17%)	2/4 (50%)
Del17p, n (n/N%)	5/10 (50%)	2/6 (33%)	3/4 (75%)
Del17p &/or TP53Mutation, n/n (%)	5/9 (56%)	2/6 (33%)	3/3 (100%)
Complex Karyotype, n/n(%)	4/7 (57%)	3/5 (60%)	1/2 (50%)
IGHV Unmutated, n/n(%)	5/6 (83%)	3/4 (75%)	2/2 (100%)

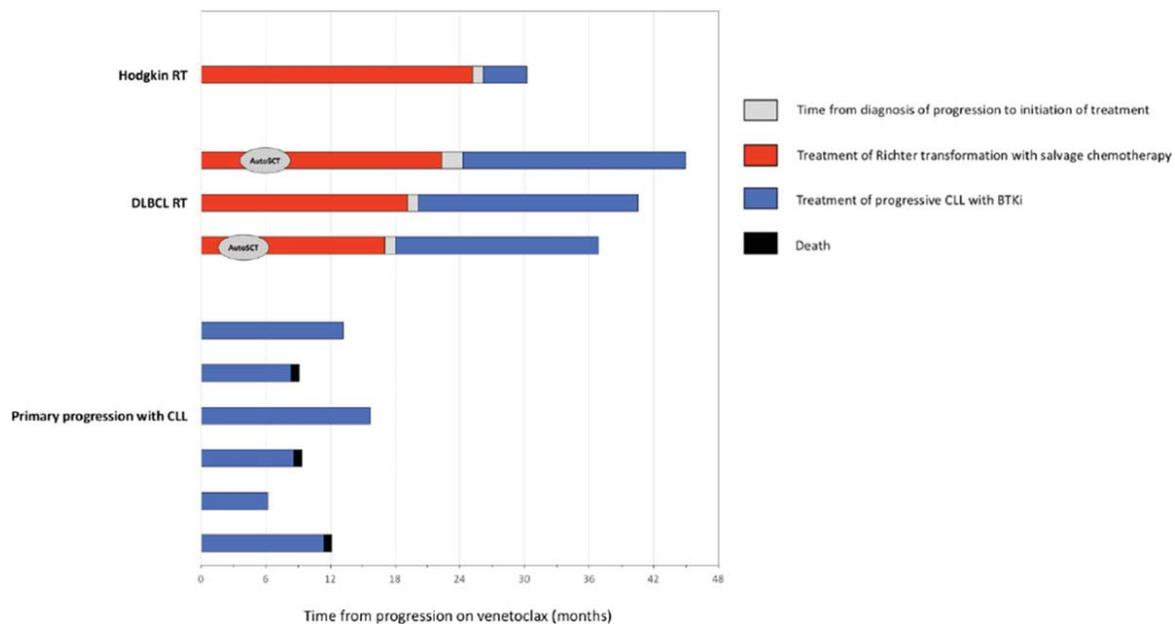


Figure 1 Progressive CLL after venetoclax, treated with BTKi.

received BTKi for progressive CLL after initially requiring salvage therapy for Richter transformation on venetoclax. All 4 had achieved a clinical response of their large cell lymphoma (3 CR, 1PR) with salvage chemotherapy, prior to BTKi (ibrutinib $n = 3$; novel BTKi $n = 1$) after subsequent CLL progression. All attained a PR and remain in ongoing response at 3, 19, 21, 20 months on BTKi (Figure 1). No unusual toxicities of BTKi were seen.

Conclusions: Amongst this population with multiply relapsed CLL, confirmed responses were seen with BTKi therapy in 9/10 patients post PD on venetoclax. Together with the data for venetoclax after ibrutinib failure, these findings suggest that cross-resistance between BCL2 and BTK inhibitors is not manifest in most patients and justify the use of BTKi therapy after failure of venetoclax in BTKi-naïve patients.

Keywords: B-cell receptor (BCR); BCL2; chronic lymphocytic leukemia (CLL).

240 OUTCOMES OF PATIENTS POST IBRUTINIB TREATMENT FOR RELAPSED/REFRACTORY CLL: A UK AND IRELAND ANALYSIS

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Introduction: Following discontinuation of ibrutinib, the outcome for many patients remains poor. This analysis was undertaken to gain a better understanding of how these challenging patients have been managed in the UK / Ireland.

Methods: Data were collected on ibrutinib patients registered with the UK CLL Forum who had discontinued ibrutinib for any reason.

Results: Of the original 315 study patients, 140 have now stopped taking ibrutinib and 103 have died (median overall survival (mOS) 72 days

from stopping (range: 0–919)). Patients stopped ibrutinib due to one of 6 broad reasons:

1. Adverse event (AE) – infection ($n = 21$; 15%)
2. AE – other ($n = 41$; 29%)
3. Second primary malignancy ($n = 13$; 9%)
4. Progressive Disease–CLL (PD CLL) ($n = 25$; 18%)
5. Progressive Disease–Richter's transformation (PDRT) ($n = 28$; 20%)
6. Other (predominantly no data given) ($n = 12$; 9%)

Patients who stopped ibrutinib due to a non-infectious AE had the best survivals with 17/41 (41%) still alive. (mOS: 245 days (0–919)). The poorest survivals were seen for patients with PDRT where only 3 patients from 28 are still alive (Figure 1A). The rate of discontinuation of ibrutinib has reduced over time with 26.3% stopping in the first year, 16.8% (12.5–22.4) in the second year and 11% beyond the second year (although follow-up is less complete). Of the patients who stopped in the first year, 54% were due to AEs, 23.4% PDRT and 13% PDCLL. After year 1, the proportion stopping due to AEs and PDRT fell to 40% and 19.6%, whereas the proportion stopping due to PDCLL increased to 29.4%. Within the first year, there was no access to venetoclax in the UK and Ireland and all 10 patients who stopped ibrutinib due to PDCLL died with a median survival of 33 days (0–360). Beyond the first year, 15 patients stopped ibrutinib due to PDCLL. Of these, 5 have died (managed with palliative care ($n = 3$), idelalisib/rituximab ($n = 1$), no data ($n = 1$)) and 10 are still alive. Of these 10, 1 has been treated with R-idelalisib (34 days post ibrutinib cessation), and 9 have been treated with venetoclax with a median follow-up of 107 days (9–498) post ibrutinib. Four other patients who stopped ibrutinib for non-PDCLL reasons have also been treated with venetoclax, with

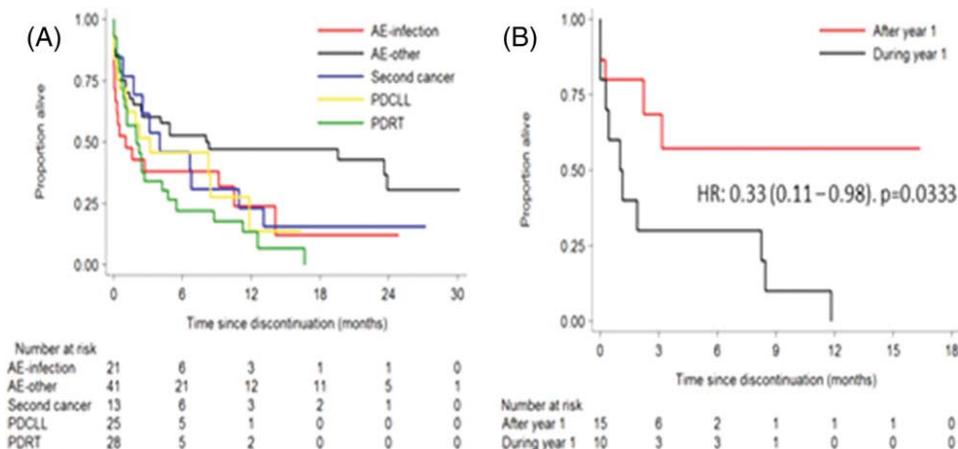


Figure 1. A: Survival of patients post cessation of ibrutinib separated by reason for ibrutinib cessation. B: Survival of patients who stopped ibrutinib for PD-CLL within the 1st year and beyond the 1st year

2 still alive on therapy. Figure 1B compares the OS of patients who stopped ibrutinib for PDCLL within the first year and beyond 1 year. There is a marked survival advantage for patients relapsing beyond 1 year with over 60% reduction in the risk of death (HR: 0.33 (0.11–0.98); $p = 0.0333$). In contrast, patients stopping ibrutinib for all other reasons show no survival difference whether they stop within the first year or beyond.

Conclusions: While the relative rate of ibrutinib discontinuation reduces with time on therapy, the proportion stopping for PDCLL increases. OS appears best for patients who stop for non-infectious AEs and for PDCLL patients, survival appears better if progression occurs later. This may partly reflect biologically less aggressive disease, although access to venetoclax for patients relapsing beyond one year is also likely to have been significant.

Keywords: ABT-199; chronic lymphocytic leukemia (CLL); ibrutinib.

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IBRUTINIB FOR RELAPSED / REFRACTORY CLL: AN UPDATE OF THE UK AND IRELAND ANALYSIS OF OUTCOMES IN 315 PATIENTS

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Introduction: The UK CLL Forum recently published the largest real-world data set of patients treated with ibrutinib for relapsed/refractory CLL (*Haematologica*, 2016). We have now updated our database with an additional 14 months median follow-up.

Methods: Data were collected retrospectively from 62 centres, and discontinuation free survival (DFS) and overall survival (OS) were analysed and stratified by baseline and treatment-related characteristics.

Results: Of the original 315 patients, 103 have now died, 37 are alive but have stopped ibrutinib, and 175 continue to take the drug. With a median 30 months follow-up, 54.4% (95% CI: 48.5–60.0) of

patients are still taking ibrutinib and 66.1% (60.4–71.3) are still alive. Despite the additional follow-up, with univariable analysis, we could still not show any deleterious effect of 17p deletion or number of prior lines of therapy on discontinuation-free survival or overall survival (OS) (OS for 17p deleted vs 17p wildtype: 68.6% vs 67.8%; OS for number of prior lines 1 vs 2 vs 3+: 66.0% vs 64.9% vs 66.6%). However, increased age and poorer pre-treatment performance status remain associated with ibrutinib discontinuation and earlier death. With our original publication, we were unable to demonstrate any survival detriment for dose-reduced patients, although patients who had treatment breaks >14 days, had inferior outcomes. Of the 48 patients who had dose-reduced ibrutinib without treatment breaks in the first year, 17 have now stopped the drug, 10 have died, 25 continue on dose-reduced ibrutinib and 6 are back to standard dose. To analyse on-going potential effects of first year dose reductions and treatment breaks, we classified all patients who were alive at 1 year into one of 4 different groups depending on first year treatment, namely, A: standard dosing with no breaks >14 days; B: dose reductions but no breaks >14 days; C1: temporary treatment breaks >14 days (but re-taking ibrutinib by 1 year); C2: permanent discontinuation of ibrutinib within the first year. Figure 1 plots DFS and OS with 18 months median follow-up for these patients beyond one year. There is no statistical difference in DFS and OS between groups A and B (DFS; 76.7% (68.3–83.1) vs 71.1% (53.3–83.1), $p = 0.23$; OS; 88.1% (81.6–92.5) vs 83.7% (66.8–92.5), $p = 0.75$). However, patients who had temporary breaks >14 days (C1) or permanently stopped ibrutinib (C2) within the first year have impaired survival over the next 18 months compared with groups A and B (OS C1: 63% (41.4–78.5); OS C2: 40.6% (22.7–57.8)). This represents a 3.1-fold and 7.7-fold respective increase risk of death for groups C1 and C2 compared with standard dosed patients.

Conclusions: Over half of patients are still taking ibrutinib and two thirds of patients are alive with 30 months median follow-up. Although temporary or permanent cessation of therapy within the first year strongly associates with earlier death, a direct causal

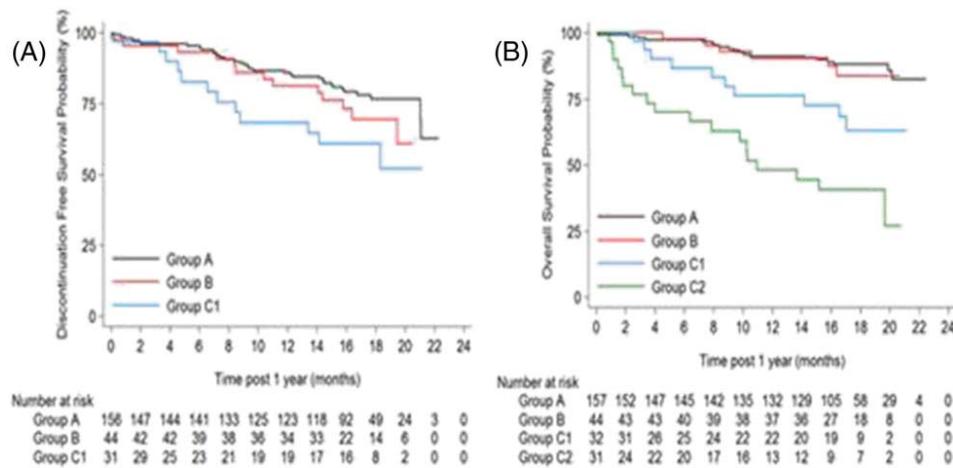


Figure 1. A: Discontinuation Free Survival of patients beyond 1 year for patients grouped by first year ibrutinib dose modifications (A: standard dosing, B: dose reductions but no breaks, C1: temporary breaks). **B:** Overall Survival of patients beyond 1 year for patients grouped by first year dose reductions (C2: permanent break).

relationship between these factors is not proven by this association, as there are multiple additional confounding medical factors which can influence OS.

Keywords: chronic lymphocytic leukemia (CLL); ibrutinib.

NK AND T-CELL LYMPHOMAS

242 REDEFINING THE ROLE OF ETOPOSIDE IN PERIPHERAL T-CELL LYMPHOMA TREATMENT

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Introduction: Peripheral T-cell lymphomas (PTCL) represent a heterogeneous group of neoplasms with an aggressive biological course and a poor clinical outcomes. Unfortunately, despite its less than satisfactory results, cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) remains de facto standard, as there lacks evidence of other regimens being superior. Contradicting results have been reported on the role of etoposide in treatment of T-cell lymphomas. In this study, we aimed to thoroughly analyze the impact of incorporating etoposide to first-line treatment in a large population-based cohort of systemic PTCL patients.

Methods: Using the merged data from the Korean National Health Insurance Service (NHIS) and National Cancer Registry, all patients diagnosed with non-cutaneous, non-leukemic adult PTCL patients (>20 years old) between January 1, 2002, and December 31, 2010,

TABLE. Treatment outcomes and toxicity.

	Group1 N=748	Group2 N=678	Group3 N=507	P
Outcomes				
PFS (median [range])	144.5 (44 - 1219)	128 (48 - 280)	23 (12.5 - 54.5)	<.0001
OS (median [range])	775 (139 - 1758.5)	537 (246 - 1383)	368 (88 - 612)	<.0001
5-year survival (%)	184 (24.63)	121 (17.87)	21 (4.12)	<.0001
Death				
Early mortality	72 (9.63)	44 (6.5)	59 (11.59)	0.0001
Total mortality	202 (27.04)	187 (27.62)	130 (25.54)	0.675
Toxicity				
Hospitalization days (median [range])	40 (19 - 77)	70(38 - 123)	43.5 (19 - 84)	<.0001
Anemia requiring tf (%)	328 (43.9)	533 (78.6)	265 (52.3)	<.0001
Thrombocytopenia requiring tf (%)	460 (61.5)	606 (89.4)	338 (66.7)	<.0001

PFS, progression free survival; OS, overall survival; tf, transfusion.

were identified. After excluding 311 patients for not receiving any treatment or insufficient data, a total of 1933 patients were evaluated for clinical characteristics and treatment outcomes.

Results: There were 1075 mature T-cell lymphomas (55.6%), 445 angioimmunoblastic T-cell lymphomas (23.0%), 326 anaplastic large cell lymphomas (16.9%) and 40 intestinal T-cell lymphomas (2.1%). The median age at PTCL diagnosis was 58 (range 46–68 years). Approximately, 38.7% (748) of the 1933 patients received CHOP or CHOP-like regimens (CVP, hyperCVAD/MA), 35.1% (678) received CHOP-like regimen plus etoposide, 5.9% (113) underwent other backbone chemotherapy plus etoposide, and 20.3% (394) underwent other treatments. The patients were divided into 3 groups according to their first-line treatment for outcome analyses: group 1, CHOP or CHOP-like regimens; group 2, CHOP or CHOP-like regimens plus etoposide; and group 3, all others. Group 1 was associated with longest PFS ($P < 0.001$) and OS ($P < 0.001$). Even when adjusted for lymphoma stage, age and underlying condition, addition of etoposide remained an unfavorable prognostic marker for both PFS (HR 2.432, $P = 0.0076$) and OS (HR 1.303, $P = 0.0374$). Adding etoposide led to longer hospitalization day and cytopenias requiring transfusion (Table).

Conclusions: This is one of the largest population-based PTCL cohort and provides important information on outcomes of PTCL outside of clinical trials setting. Addition of etoposide to CHOP-like regimens does not warrant better PFS nor OS for PTCL patients, regardless of age at diagnosis.

Acknowledgement: This study was supported by the National Cancer Center, Korea (NCC-1632080).

Keywords: etoposide; peripheral T-cell lymphomas (PTCL); T-cell lymphoma (TCL).

243 PROGNOSTIC FACTORS AND IMPACT OF ETOPOSIDE IN ADULTS WITH SYSTEMIC ALK-POSITIVE ANAPLASTIC LARGE-CELL LYMPHOMA: A POOLED ANALYSIS OF SIX STUDIES

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Introduction: Systemic ALK-positive anaplastic large-cell lymphoma (ALCL) comprises 1% of adult lymphomas. Because of disease rarity, prognostic factors were evaluated in most retrospective studies by pooling ALK-positive and ALK-negative ALCL, two distinct entities. Moreover, the role of etoposide is still a matter of debate. The purpose of our study was to assess prognostic factors and impact of etoposide in a large cohort of adults with systemic ALK-positive ALCL.

Methods: Eligibility criteria for the pooled analysis were as follows: published study, diagnosis of systemic ALK-positive ALCL after initial centralized pathologic review, age ≥ 18 years, HIV-negative serology, first-line treatment including at least one cycle of systemic chemotherapy. A minimum dataset was required (IPI factors, bone marrow involvement, and first-line chemotherapy regimen). Individual patient data were collected and pooled from six studies and subsequently grouped in 4 cohorts (France [2 studies]), Germany, Japan and IPTCL-Mayo Clinic). The associations between patient characteristics or treatment type and progression-free survival (PFS) or overall survival (OS) were analyzed by Cox survival models stratified by cohort and assessed by Log-Likelihood Ratio (LLR) tests with predictive C-index measurement.

Results: Individual data were obtained from 265 patients. Median age was 34 years (18–76), with 31 patients >60 years (12%). IPI score was 0–1 (56%), 2 (23%), 3 (14%) and 4–5 (7%), respectively; 261 (99%) patients received an anthracycline-based regimen, and 108 (41%) received an etoposide-based induction therapy. Complete response rate was 85%. With a median follow-up time of 4.9 years, 5-year PFS and OS rates were 70% (95% CI, 64% to 76%) and 81% (95% CI, 76% to 86%), respectively. For patients >60 years, 5-year PFS and OS rates were 55% (95% CI, 38% to 77%) and 64% (95% CI, 48% to 86%), respectively. IPI score had the best predictive value for OS (LLR $p < 5.10 \times 10^{-6}$, C-index 0.71), without significant heterogeneity between cohorts (LLR $p = 0.37$). Patients who received an etoposide-based induction therapy had significantly improved outcomes, with respective 5-year PFS and OS of 82% vs 61%, and 92% vs 73%. For patients ≤ 60 years, in stratified Cox models including etoposide-based induction therapy and IPI, both factors remained independently prognostic for PFS ($p < 0.01$ for both factors) and OS ($p < 0.02$ for both factors). In the whole cohort, in a stratified model adjusting for the age, etoposide-based induction therapy and IPI remained independently prognostic for PFS ($p < 0.01$ for both factors) and OS ($p < 0.01$ for both factors).

Conclusions: IPI is a strong independent predictor of outcome in adults with systemic ALK-positive ALCL. Etoposide-based induction therapy is associated with better PFS and OS independent of IPI and age. These results should be confirmed by prospective studies.

Keywords: ALK; anaplastic large cell lymphoma (ALCL); etoposide.

244 OUTCOME OF PATIENTS WITH RELAPSED AND REFRACTORY PERIPHERAL T CELL LYMPHOMA INTENDED FOR STEM CELL TRANSPLANT

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Introduction: Most patients with peripheral T-cell lymphoma (PTCL) relapse after initial therapy. Transplant eligible patients receive second-line chemotherapy and planned stem cell transplant (SCT). Retrospective series suggest some patients are cured with this approach. However, there is little data on outcomes from the time of relapse/progression.

Methods: We identified patients >14 years with 'nodal' PTCLs (diagnosed 1981–2015) who had relapsed/refractory disease after first-line curative intent chemotherapy. Patients planned for curative SCT were included. Outcomes were assessed from time of relapse/progression and from time of SCT.

Results: A total of 84 patients were included: 59 (70%) relapsed and 25 (30%) refractory. The latter were more likely to have IPI >1 at the time of recurrence ($n = 17, 68\%$ vs $n = 27, 46\%$; $p = 0.034$). Most received multi-agent chemotherapy as second-line therapy ($n = 64, 76\%$) with GDP the favoured regimen ($n = 41, 49\%$). Eleven patients went directly to high-dose cyclophosphamide and SCT in the early treatment era and two patients with isolated bone marrow disease had no second-line therapy pre-SCT. In patients receiving systemic therapy prior to SCT ($n = 71$), ORR was 72% (CR 32%) and 27% had PD. In total, 57 patients (68%) received an SCT (34 autologous [auto], 23 allogeneic [allo]). Those receiving alloSCT were younger (median age 47 years), more likely to have an elevated LDH (62% vs 24%; $p = 0.010$) and a greater proportion had refractory disease (35% vs 15%, $p = 0.079$). Overall, 27 (32%) patients did not undergo SCT: PD ($n = 18$); toxicity/comorbidities ($n = 4$); patient refusal ($n = 4$); no matched donor ($n = 1$).

Median follow up was 5.9 years. From the time of relapse, the 2-y PFS was 31.4% and 2-y OS was 52.6%. Two-year estimates from the time of transplant were 47.6% and 59.0%, respectively. The 2-y postSCT outcomes for autoSCT and alloSCT were similar (PFS 40.1% vs 61.4%, $p = 0.238$; OS 56.8% vs 63.3%, $p = 0.984$).

Post relapse/progression 2-y PFS and OS were similar in relapsed and refractory patients (PFS 34.1% vs 25.2%, $p = 0.214$; OS 58% vs 40%, $p = .289$). Likewise, no significant difference was seen in 2-y post SCT PFS (46.2% vs 53.3%, $p = 0.301$) or OS (60.9% vs 52.7%, $p = 0.903$). Outcomes were similar across PTCL subtypes, although sample sizes were small (Table 1).

Conclusions: In transplant-eligible relapsed/refractory PTCL, ~30% were cured with estimates approaching 50% in those able to receive

TABLE 1 Patient characteristics at time of relapse and outcomes by histologic subtype

		52 (15-59)			
Median age, y (range)		54 (64)			
Male sex, n (%)		44 (52)			
Subtype, n (%)	PTCL NOS	44 (52)			
	ALCL	10 (12)			
	ALK+	16 (19)			
	ALK-	14 (17)			
	Angioimmunoblastic				
Stage, n (%)	I/II	17 (20)			
	III/IV	68 (80)			
ECOG PS, n (%)	0-1	61 (73)			
	≥2	18 (21)			
	Not available	5 (6)			
Elevated LDH, n (%)	No	40 (48)			
	Yes	33 (39)			
	Not available	11 (13)			
IPI, n (%)	0-1	28 (33)			
	2-3	42 (50)			
	4-5	2 (3)			
	Not available	12 (14)			
Subtype	Transplant Rate, n(%)	Post Relapse/Progression		Post SCT	
		2 y PFS (p=0.60)	2 y OS (p=0.86)	2 y PFS (p=0.31)	2 y OS (p=0.61)
PTCL	26 (59)	34.0%	55.4%	51.3%	58.9%
ALCL					
ALK+	9 (90)	40.0%	46.7%	55.6%	55.6%
ALK-	12 (75)	12.5%	43.8%	27.3%	53.8%
AITL	10 (71)	39.3%	57.1%	55.6%	70.0%

a SCT. Progressive disease following second-line therapy was the main reason for not proceeding to SCT, highlighting the need for novel agents in this setting. Use of alloSCT is promising in patients with refractory disease.

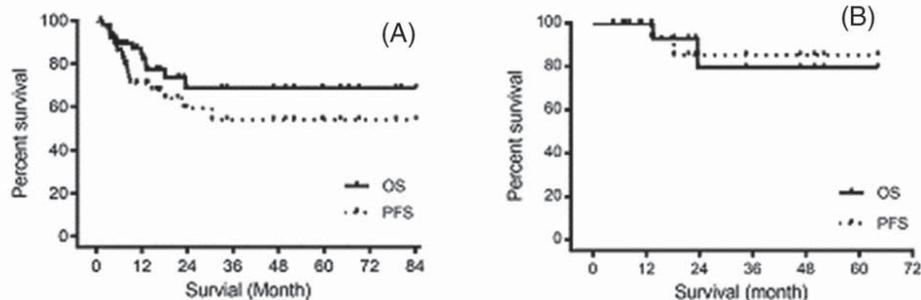
Keywords: high-dose therapy (HDT); peripheral T-cell lymphomas (PTCL); salvage treatment.

245 A MULTI-CENTER STUDY OF GLIDE CHEMOTHERAPY CONSOLIDATED WITH AUTOLOGOUS STEM CELL TRANSPLANTATION FOR NEWLY DIAGNOSED STAGE IV AND RELAPSED EXTRANODAL NATURAL KILLER/T-CELL LYMPHOMA PATIENTS

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Figure-1: OS and PFS of whole cohort (A) and ASCT patients (B)



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Introduction: Long-term survival of advanced-stage and relapsed extranodal NK/T cell lymphoma (ENKTL) is 33%–45%. Our previous study of GLIDE (gemcitabine, L-asparaginase, ifosfamide, dexamethasone and etoposide) chemotherapy reported complete response (CR) rate, and 3-year overall survival (OS) of these patients were 57.1% and 56%, respectively. The role of ASCT as consolidation in these patients is unclear. To address this issue, we analyzed the efficacy and safety of our treatment strategy, GLIDE induction followed by ASCT, in newly diagnosed stage IV and relapsed ENKTL.

Patients and methods: We treated 60 patients with newly diagnosed stage IV ($n = 49$) and relapsed ($n = 11$) ENKTL from 2010 to 2016. The median age at recruitment was 38 years and the median follow-up period was 13.4 months. Patients were treated with GLIDE every 4 weeks, and responses were evaluated with PET/CT every 2 cycles. Patients achieving CR underwent ASCT or continued with GLIDE up to 6 cycles. Others finished 6 cycles of GLIDE. Overall response rate (ORR), CR, OS and progression free survival (PFS) were calculated using standard methods. Statistical analysis was done using Fishers exact test or Chi-square test/Kruskal-Wallis test. Kaplan-Meier method was used for time-to-event analysis including overall survival and progression free survival. The Log-rank test was used to evaluate the difference in time-to-event endpoints between patient groups.

Results: Fifty-seven patients had finished planned treatment with 1 withdraw of informed consent after cycle 1, and 2 death of sepsis during cycle 1 and cycle 2 respectively. Twenty-one patients underwent ASCT. The ORR was 81.4%, and the CR was 69.5% with early CR (CR after 2 cycles) of 57.6%. Estimated 5-year OS and PFS rates of the whole cohort and patients underwent ASCT were 68.7%, 54.0%, 79.6% and 85.2%, respectively. Univariate analysis revealed that ECOG ≤ 1 , IPI ≤ 2 , early CR and ASCT were associated with less relapse and death. Multivariate analysis showed ECOG ≥ 2 was an independent risk factor for disease progression (HR = 4.321, 95% CI 1.127 ~ 16.572, $P = 0.033$) and death (HR = 46.254, 2.150 ~ 993.190, $P = 0.014$), and ASCT is associated with better PFS (HR = 0.058, 95% CI 0.007 ~ 0.495, $P = 0.009$) and OS (HR = 0.019, 95% CI 0.001 ~ 0.596, $P = 0.024$). Figure 1 highlights the OS and PFS of whole cohort (A) and ASCT patients (B).

Myelosuppression was the most common adverse reaction (AE). The incidences of level 4 neutropenia, thrombocytopenia and anemia were 46.6%, 28.6% and 5.3%, respectively. The most common non-hematologic AE was fever with neutropenia (36.5% of total cycles), while others were mild and manageable.

Conclusions: GLIDE is an effective regimen for newly diagnosed stage IV and relapsed ENKTL. Up-front ASCT after achieving CR can reduce relapse and prolong survival. Treatment related adverse reactions and support care need concerns.

Keywords: autologous stem cell transplantation (ASCT); Chemotherapy; T-cell lymphoma (TCL).

246 ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (ALLO-HSCT) FOR PATIENTS WITH RELAPSED/REFRACTORY SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA (R/R SALCL). A RETROSPECTIVE ANALYSIS OF THE LYMPHOMA WORKING PARTY-EBMT.

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Rationale: Allo-HSCT is a potentially curative therapy for patients with sALCL who relapse or fail to respond to 1st-line therapy. Brentuximab vedotin (BV) is an anti-CD30 antibody-drug conjugate approved for treatment of R/R sALCL, but its potential effect as a bridge to

allo-HSCT is largely unknown. The objective of this study was to analyze the results of allo-HSCT in R/R sALCL with special emphasis on the role of BV before allo-HSCT.

Patients and Methods: Forty-four patients [24 women, median age at HSCT 39 (19–67) years] with sALCL were reported to the EBMT Lymphoma Database between January 2010 and December 2014; 23 patients were ALK positive, and 20 were negative. Time interval between diagnosis and allo-HSCT was 17 (5.5–106) mo, 25 patients (57%) had received ≥ 3 lines of therapy before transplant, and 50% of the patients had failed a prior auto-HSCT; 20 patients were allografted using HLA identical sibling donors, in 21 (48%) conditioning regimen was of reduced intensity and 34 patients (79%) had chemosensitive disease at the time of transplant.

Results: A total of 23 patients (52%) received BV before allo-HSCT (median time from BV start date to SCT is 3.8 months (IQR 1.8–5.7)); there were no significant differences between them and the non-BV group with the exception of number of treatment lines before allo-HSCT (38% received 3 or more lines in the non-BV group vs 74% in the BV group, $p = 0.04$). Median number of BV doses received was 4 (1–16); 73% ($n = 17$) of the patients received BV either as second line [7 patients (30%)] or third line [10 patients (43%)] of therapy. Overall response rate was 87% [52% complete remission (CR)], and median number of doses to achieve the best response was 3 (2–7); 3-year non-relapse mortality (NRM) and incidence of relapse (IR) after allo-HSCT were 6.9 (95% 1.7–17.1) and 40% (95% 25–54.6) for the whole series, respectively, with no significant differences between the BV and non-BV groups; 1-year cumulative incidence of acute graft versus host disease (aGVHD) and chronic GVHD were 30% (95%CI 15–47) and 48% (95%CI 32–62), respectively. With a median follow up of 39 (12–69) mo for alive patients, 3-year progression-free survival (PFS) and overall survival (OS) were 53% (95% 40–71) and 74% (95% 61–89), respectively, with no significant differences between both groups of patients. Univariate analysis showed that number of treatment lines (more than 3) and disease status at allo-HSCT (remission) were the only adverse prognostic factor for both IR and PFS ($p = 0.04$ and 0.01 for IR and $p = 0.03$ and 0.001 for PFS, respectively). OS was lower and incidence of chronic GVHD higher in the ALK negative group ($p = 0.04$ and $p = 0.02$, respectively).

Conclusions: Allo-HSCT is a valid treatment strategy for patients with R/R sALCL with more than 50% of the patients alive and disease-free 3 years after the procedure. In this analysis, the use of BV before allo-HSCT does not seem to hamper the long-term outcomes of this strategy.

Keywords: allogeneic stem cell transplant (alloSCT); anaplastic large cell lymphoma (ALCL); brentuximab vedotin.

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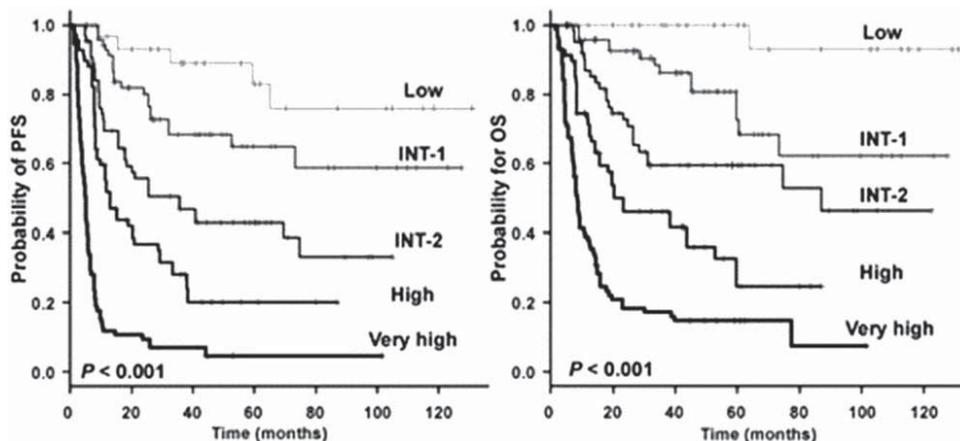
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Background: Nodal peripheral T-cell lymphomas (PTCLs) consist of PTCL not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large-cell lymphoma-anaplastic lymphoma kinase positive (ALCL-ALK+), and ALCL-ALK-. Clinical assessments before and after treatment are essential to predict survival in nodal PTCL. However, limited data are available regarding the prognostic significance of National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) as a pre-treatment clinical tool and post-treatment PET-CT scan indicating tumor viability in patients with nodal PTCL. The primary aim was to establish a risk model for nodal PTCL based on NCCN-IPI and post-treatment PET-CT scan.

Method: In this retrospective, multicenter, cohort study, patients were eligible if they were diagnosed with nodal PTCL from Jan 2005 to June 2016, received systemic chemotherapy, and had the results of PET-CT scan at the time of diagnosis and at the end of treatment, which was assessed using 5-point Deauville score. The study excluded ALCL-ALK+.

Results: A total of 396 patients were screened. Seventy patients were excluded from the analysis: unavailable pre- or post-treatment PET scans, no systemic treatment, uncertain histology, and ALCL-ALK+. Thus, 326 patients were analyzed. The median age was 61 years (range, 18–86) and 209 (64%) were male. PTCL-NOS ($N = 172$, 53%) was the most common subtype, and AITL ($N = 111$, 34%) and ALCL-ALK- ($N = 43$, 13%) followed. Patients were categorized into low ($N = 42$, 13%), low-intermediate (LI, $N = 108$, 33%), high-intermediate (HI, $N = 136$, 42%), and high ($N = 40$, 12%) risk groups according to the NCCN-IPI. Based on the Deauville criteria, post-treatment PET-CT scan was scored as 1 ($N = 130$, 40%), 2 ($N = 47$, 14%), 3 ($N = 60$, 18%), 4 ($N = 27$, 8%), and 5 ($N = 62$, 19%). Because the number of

247 RISK STRATIFICATION BASED ON NCCN-IPI AT THE TIME OF DIAGNOSIS IN COMBINATION WITH POST-TREATMENT PET-CT SCAN FOR THE TREATMENT OF NODAL PERIPHERAL T-CELL LYMPHOMA



progression in Deauville score 3 (40/60, 67%) was significantly different from score 2 (21/47, 45%; $P = 0.023$) and 4 (24/27, 89%; $P = 0.030$), we categorized patients into 3 groups: Deauville score 1–2, 3, and 4–5.

With a median follow-up of 54.7 months (IQR, 30.2–84.5), 5-year PFS rate was 35.7% (95% CI, 30.0–41.4), and OS rate was 47.1% (95% CI, 40.8–53.4). NCCN-IPI risk and post-treatment PET-CT scan were independently associated with PFS in multivariate analysis (for LI NCCN-IPI, hazard ratio [HR] 1.615, 95% CI 0.838–3.113; HI NCCN-IPI, HR 3.063, 95% CI 1.626–5.769; high NCCN-IPI 4.475, 95% CI 2.231–8.977; $P < 0.001$: for post-treatment Deauville score 3, HR 1.895, 95% CI 1.281–2.801; score 4–5, HR 6.916, 95% CI 4.948–9.667; $P < 0.001$). We stratified patients into 5 groups based on risk of progression: low (low NCCN-IPI and Deauville score 1–2), INT-1 (low NCCN-IPI and score 3, or LI NCCN-IPI and score 1–2), INT-2 (HI NCCN-IPI and score 1–2), high (high NCCN-IPI and score 1–2, or LI to high NCCN-IPI and score 3), and very high (score 4–5). The risk model showed a strong association with PFS and OS (Figure 1).

Conclusion: This study proposes a new risk stratification model incorporating baseline NCCN-IPI in combination with post-treatment Deauville score on PET-CT scan in patients with newly diagnosed nodal PTCL.

Keywords: peripheral T-cell lymphomas (PTCL); positron emission tomography (PET); prognostic indices.

248 THE ROLE OF ^{18}F FDG-PET/CT IN PERIPHERAL T-CELL LYMPHOMA (PTCL): INITIAL RESULTS OF THE UK NCRI MULTICENTRE PHASE II RANDOMISED CHEMO-T TRIAL PET/CT SUBSTUDY

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Introduction: The evidence base for positron emission tomography/computed tomography (PET/CT) (PET) in PTCL comes from retrospective studies. Herein, we report the initial results of a PET substudy within a prospective trial for patients with previously untreated PTCL.

Methods: The UK NCRI phase II randomised multicenter CHEMO-T trial compared the regimens of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) with gemcitabine, cisplatin and methylprednisolone (GEM-P) in previously untreated patients aged ≥ 18 years with stage I (bulky)–IV disease of the following subtypes: PTCL not otherwise specified (PTCL NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL) ALK negative, enteropathy-associated T-cell lymphoma (EATL) and hepatosplenic gamma delta T-cell lymphoma. In November 2016, the study closed early to recruitment due to an inferior complete response (CR/CRu) rate at end of treatment (EOT) by CT in the GEM-P arm compared to the CHOP arm.

TABLE 1

EOT CT		
EOT PET	CR/CRu	PR/SD/PD
CR	20	5
PR/SD/PD	4	17

Proportion of agreement: 37/46 (80.4%).

All patients had baseline (BL) and EOT PETs performed in accordance with the study protocol. The primary study endpoint was to compare the CR/CRu rate by contrast-enhanced CT at EOT between arms according to the IWG 1999 criteria. Secondary endpoints included a comparison of EOT response by CT versus PET.

All PET scans were centrally reviewed while blinded to the patient's clinical status. The following parameters were assessed at BL and EOT: Deauville score (DS), mean, max and peak standardized uptake values (SUVs) and metabolic tumour volume (MTV). At EOT, a DS of 1–2 by PET was negative, a DS of 3–5 was positive. For patients with biopsy-proven bone marrow (BM) involvement at randomisation, PET at BL was reviewed to assess for BM FDG avidity. In an exploratory analysis, PET scores at BL (DS, max/mean/peak SUVs and MTV) were associated with overall response (ORR) by PET.

Results: BL central PET review has been completed for 58 (PTCL NOS $n = 23$, AITL = 25, ALCL ALK negative $n = 10$) of the 87 patients accrued at time of study closure. All patients had FDG-avid disease at BL (DS = 3 5.2%, DS = 4 28.6%, DS = 5 67.2%). For patients with BM involvement at BL and an evaluable PET ($n = 19$), 7 (36.8%) had BM uptake on PET. EOT PET response has been completed for 41/87 patients, with DS as follows: 1–2 = 78.1%, 3 = 7.3% and 4–5 = 14.6%. ORR by PET was 80.4% (CR = 56.9%, PR = 23.5%). The proportion of agreement in determination of CR versus PR/SD/PD between PET and CT is shown in Table 1. MTV at BL was the best predictor of response on EOT PET.

Conclusion: All PTCL subtypes evaluated to date were FDG avid at BL. In PTCL, PET does not appear to be a sensitive tool for determination of BM infiltration. In the determination of CR the proportion of agreement between EOT CT and PET was 80.4%. In an exploratory analysis, MTV at BL was the score most associated with ORR by PET. The updated complete analysis ($N = 87$) including correlation of PET scores at BL and PET response with survival will be presented at the meeting.

Keywords: peripheral T-cell lymphomas (PTCL); positron emission tomography (PET).

249 RESPONSE BY STAGE IN CD30-POSITIVE (CD30+) CUTANEOUS T CELL LYMPHOMA (CTCL) PATIENTS RECEIVING BRENTUXIMAB VEDOTIN (BV) VS PHYSICIAN'S CHOICE (PC) IN THE PHASE 3 ALCANZA STUDY

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Introduction: The phase 3 ALCANZA study showed significant improvements in rate of objective response lasting ≥ 4 months (ORR4) with BV vs PC of methotrexate (MTX) or bexarotene (Bex) for the treatment of CD30+ CTCL. Here, we examine response according to disease stage and across disease compartments in patients (pts) treated on the ALCANZA study.

Methods: Adults with previously treated CD30+ mycosis fungoides (MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL) were randomized to BV 1.8 mg/kg IV, Q3W, for up to 16 three-week cycles, or PC of MTX 5–50 mg PO, QW, or Bex 300 mg/m² (target dose) PO, QD, for up to 48 weeks. Pts were classified according to baseline Tumor-Node-Metastasis-Blood (TNMB) stage per investigator (INV) as part of global assessment; presence of baseline blood disease was also determined by independent review (IRF). Pts with B2 disease were ineligible. ORR4 was determined by IRF of global response in all

compartments using consensus criteria (modified severity weighted assessment tool for skin evaluation by INV, radiographic assessment by IRF, and MF Sézary cell count by IRF). We compared ORR4, ORR, and complete response (CR) rate by disease stage, TNMB stage, and baseline blood disease in the intent-to-treat (ITT) population.

Results: The ITT population included 128 pts (97 MF, 31 pcALCL). After a median follow-up of 22.9 months, ORR4 with BV was greater than PC in both MF (50% vs 10%) and pcALCL (75% vs 20%). This was consistent across all MF disease stages; stage IA–IIA, 40% vs 22% (95% CI for rate difference: –16.6%, 49.4%); stage IIB, 63% vs

TABLE 1 Response by baseline clinical characteristics and TNMB stage per INV as part of global assessment in the ITT population

	BV (N=64)				PC (N=64)			
	Total N (%)	ORR4 n (%)	ORR n (%)	CR n (%)	Total N (%)	ORR4 n (%)	ORR n (%)	CR n (%)
MF patients	48 (75)	24 (50)	31 (65)	5 (10)	49 (77)	5 (10)	8 (16)	0
Stage ^a								
IA–IIA	15 (31)	6 (40)	8 (53)	1 (7)	18 (37)	4 (22)	5 (28)	0
IIB	19 (40)	12 (63)	13 (68)	3 (16)	19 (39)	1 (5)	3 (16)	0
IIIA–IIIB	4 (8)	2 (50)	3 (75)	0	2 (4)	0	0	0
IVA	2 (4)	2 (100)	2 (100)	1 (50)	9 (18)	0	0	0
IVB	7 (15)	2 (29)	4 (57)	0	0	NA	NA	NA
Skin								
T1	5 (10)	1 (20)	1 (20)	0	1 (2)	0	1 (100)	0
T2	13 (27)	7 (54)	10 (77)	1 (8)	20 (41)	4 (20)	4 (20)	0
T3	25 (52)	13 (52)	16 (64)	4 (16)	24 (49)	1 (4)	3 (13)	0
T4	5 (10)	3 (60)	4 (80)	0	4 (8)	0	0	0
Node								
N0	25 (52)	14 (56)	18 (72)	4 (16)	23 (47)	2 (9)	5 (22)	0
N1–NX	23 (48)	10 (43)	13 (57)	1 (4)	26 (53)	3 (12)	3 (12)	0
Visceral ^b								
M0	41 (85)	22 (54)	27 (66)	5 (12)	48 (98)	5 (10)	8 (17)	0
M1	7 (15)	2 (29)	4 (57)	0	0	NA	NA	NA
Blood ^c								
B0	43 (90)	23 (53)	28 (65)	4 (9)	41 (84)	4 (10)	6 (15)	0
B1	4 (8)	1 (25)	2 (50)	1 (25)	7 (14)	1 (14)	2 (29)	0
B2 ^d	0	NA	NA	NA	1 (2)	0	0	0
pcALCL patients	16 (25)	12 (75)	12 (75)	5 (31)	15 (23)	3 (20)	5 (33)	1 (7)
Disease involvement								
Skin-only	9 (56)	8 (89)	8 (89)	4 (44)	11 (73)	3 (27)	5 (45)	1 (9)
Extracutaneous disease	7 (44)	4 (57)	4 (57)	1 (14)	4 (27)	0	0	0
Skin								
T1	1 (6)	1 (100)	1 (100)	1 (100)	4 (27)	1 (25)	2 (50)	0
T2	3 (19)	3 (100)	3 (100)	1 (33)	5 (33)	0	1 (20)	0
T3	12 (75)	8 (67)	8 (67)	3 (25)	6 (40)	2 (33)	2 (33)	1 (17)
Node								
N0	10 (63)	8 (80)	8 (80)	4 (40)	11 (73)	3 (27)	5 (45)	1 (9)
N1–N3	6 (38)	4 (67)	4 (67)	1 (17)	4 (27)	0	0	0
Visceral								
M0	12 (75)	9 (75)	9 (75)	5 (42)	14 (93)	3 (21)	5 (36)	1 (7)
M1	4 (25)	3 (75)	3 (75)	0	1 (7)	0	0	0

B, blood; BV, brentuximab vedotin, CR, complete response; ITT, intent-to-treat, M, metastases; MF, mycosis fungoides; NA, not applicable; N, node; ORR, overall response rate; ORR4, response lasting at least 4 months; PC, physician's choice; pcALCL, primary cutaneous anaplastic large cell lymphoma; T, tumor.

^aOne patient in each arm had incomplete staging data and are not included in the table: one patient in the BV arm had partial response, one patient in the PC arm had no response.

^bOne patient in the PC arm had no biopsy performed to confirm visceral staging, and had no response.

^cOne patient in the BV arm had incomplete blood staging data, and had a partial response.

^dOne patient in the PC arm had confirmed blood stage B1 at screening, and B2 at baseline.

5% (25.4%, 80.9%); stage IIIA–IIIB, 50% vs 0% (–45.2%, 98.7%); stage IVA, 100% vs 0% (14.9%, 100.0%); and stage IVB, 29% vs not applicable. Table shows response according to baseline clinical and TNMB stage per INV. For MF, ORR4 was 25% (1/4) with BV vs 13% (1/8) with PC for pts with blood involvement (\geq B1), and 43% (10/23) with BV vs 12% (3/26) with PC for pts with nodal involvement (\geq N1). Out of 35 MF pts with blood disease per IRF (non-B0 blood stage), ORR in the blood compartment was 94% with BV vs 41% with PC; CR rate in the blood compartment was 89% vs 41%. In pcALCL pts, the ORR4 was 89% (8/9) with BV vs 27% (3/11) with PC in pts with skin-only disease (95% CI for rate difference: 17.9%, 88.3%), and 57% (4/7) with BV vs 0% (0/4) with PC in pts with extracutaneous disease (–9.0%, 93.2%).

Conclusions: Significant and durable clinical activity was observed across disease stages and compartments with BV in CTCL pts requiring systemic therapy.

Keywords: brentuximab vedotin; CD30; cutaneous T-cell lymphoma (CTCL).

250 PATIENT-REPORTED OUTCOMES AND QUALITY OF LIFE IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA: RESULTS FROM THE PHASE 3 ALCANZA STUDY

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Introduction: As cutaneous T-cell lymphoma (CTCL) is a chronic, incurable disease, maintaining quality of life (QoL) is a key issue; yet CTCL is associated with significant symptom burden, including pruritus and skin lesions that are highly detrimental to patients' (pts) well-being. The Phase 3 ALCANZA study showed significantly improved rate of objective response lasting \geq 4 months (ORR4) with decreased symptom burden in CD30-positive (CD30+) CTCL treated with brentuximab vedotin (BV) vs physician's choice (PC) of methotrexate (MTX) or bexarotene (Bex). Here, we further examine QoL in pts enrolled to the ALCANZA study.

Methods: Adults with previously treated CD30+ mycosis fungoides (MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL) were randomized 1:1 to BV 1.8 mg/kg IV, Q3W, or PC for up to 16 three-week cycles. Patient-reported outcomes included Skindex-29 (symptom domain, key secondary endpoint; emotion and functioning domains, secondary endpoints), FACT-G (secondary endpoint), and EQ-5D (exploratory endpoint) questionnaires, administered on day 1 of cycles 1, 2, 4, 6, 8, 10, 12, 14, and 16, at end of treatment (EOT), and during post-treatment follow-up in the intent-to-treat (ITT) population. Minimally important differences (MID) for Skindex-29 symptom domain were estimated to be 9.0–12.3 using distribution-based methods. Scores were also summarized with descriptive statistics. Associations between QoL scores and clinical response or peripheral neuropathy (PN, a known BV toxicity) were also assessed.

Results: In total, 128 pts were included in the ITT population (97 MF, 31 pcALCL). Skindex-29 showed significantly greater symptom reduction in the BV arm compared with the PC arm, with a mean maximum reduction of –27.96 versus –8.62, respectively; a difference of –18.9 (95% CI: –26.6, –11.2; adjusted $p < 0.001$), which exceeds the MID. In the BV arm, mean change from baseline symptom burden score decreased \geq MID by cycle 4 lasting until EOT. Such a decrease was not observed in the PC arm. The majority of pts in the BV arm had reductions in symptom burden, regardless of CR/PR status. Among BV pts, mean maximum reduction in Skindex-29 symptom domain in pts with PN was –35.54 vs –11.11 in pts with no PN; mean maximum reductions in symptom burden were similar in pts with Grade 2/3 PN (–36.72) vs Grade 1 PN (–33.33). Mean change from baseline of FACT-G total scores were similar between BV (0.15) and PC (–2.29) arms. No substantial differences in QoL were observed on EQ-5D US time trade-off (TTO), UK TTO, or visual analog scores, and the mean changes from baseline to EOT visit in the BV arm were 0.02, 0.03, 0.8 compared to –0.02, –0.04, –2.0 in the PC arm.

Conclusions: BV did not adversely affect QoL in CTCL pts compared with MTX or Bex, and QoL was unaffected by the presence of PN in pts receiving BV. Superior reductions in symptom burden

were observed in the BV arm. Skin-symptom reductions were rapid and durable.

Keywords: brentuximab vedotin; CD30; cutaneous T-cell lymphoma (CTCL).

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A PHASE 1/2 STUDY OF BRENTUXIMAB VEDOTIN IN PEDIATRIC PATIENTS WITH RELAPSED/REFRACTORY (R/R) SYSTEMIC ANAPLASTIC LARGE-CELL LYMPHOMA (SALCL) OR R/R HODGKIN LYMPHOMA (HL)

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Objective response determined by Independent Review Facility (IRF) using the Revised Response Criteria for Malignant Lymphoma (Cheson et al. <i>J Clin Oncol</i> 2007)							
Endpoint, n (%) [95% CI]	Patient group						
	1.4 mg/kg phase 1 only (N=3)	1.8 mg/kg phase 1 only (N=8)	1.8 mg/kg phase 1/2 HL only (N=15)	1.8 mg/kg phase 1/2 sALCL only (N=17)	1.8 mg/kg phase 1/2 sALCL in first relapse only (N=10)	1.8 mg/kg all patients (N=32)	All patients* (N=35)
CR	0 [0, 71]	4 (50) [16, 84]	5 (33) [12, 62]	7 (41) [18, 67]	4 (40) [12, 74]	12 (38) [21, 56]	12 (34) [19, 52]
PR	0 [0, 71]	1 (13) [0, 53]	2 (13) [2, 40]	2 (12) [1, 36]	2 (20) [3, 56]	4 (13) [4, 29]	4 (11) [3, 27]
ORR (CR + PR)	0 [0, 71]	5 (63) [24, 91]	7 (47) [21, 73]	9 (53) [28, 77]	6 (60) [26, 88]	16 (50) [32, 68]	16 (46) [29, 63]
SD	2 (67) [9, 99]	2 (25) [3, 65]	2 (13) [2, 40]	5 (29) [10, 56]	3 (30) [7, 65]	7 (22) [9, 40]	9 (26) [12, 43]
PD	1 (33) [1, 91]	1 (13) [0, 53]	6 (40) [16, 68]	3 (18) [4, 43]	1 (10) [0, 45]	9 (28) [14, 47]	10 (29) [15, 46]

CR, complete response; PR, partial response; ORR, overall response rate; SD, stable disease; PD, progressive disease

*1 patient died in C2D4 without a post baseline efficacy assessment

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Introduction: Despite high overall 5-year survival rates for childhood HL and sALCL, improved options are needed for patients (pts) who do not respond to, or relapse following, initial therapy. This phase 1/2 open-label, dose-escalation trial (NCT01492088) evaluated the safety, PK, and antitumor activity of the antibody-drug conjugate, brentuximab vedotin (BV), in pediatric pts with R/R HL or sALCL for whom treatment alternatives do not exist.

Methods: BV was administered by intravenous infusion once every 21 days for up to 16 cycles, starting at 1.4 mg/kg up to 1.8 mg/kg to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). BV treatment beyond 16 cycles was permitted for pts with continued benefit. Overall response rate (ORR) was evaluated after 2 cycles and overall survival (OS) was assessed up to 2 years after last pt enrolment. Other secondary endpoints included time to progression/response (TTP/TTR), event/progression-free survival (EFS/PFS), safety, and PK parameters.

Results: Thirty-six pts age range 7 to <18 years were enrolled and received BV. MTD was not reached. RP2D was determined to be 1.8 mg/kg. Sixteen R/R HL and 17 R/R sALCL pts were treated at the RP2D; 3 R/R HL pts were treated at 1.4 mg/kg. Pts received a median 7 (range 1–20) cycles of BV. Median follow-up at data-cut was 19.7 months. ORR (CR + PR) per IRF was 46% with an overall median TTR of 2.7 months. Overall (per IRF) median TTP was 4.8 months; EFS and PFS were 3.0 and 4.8 months, respectively. Median OS was not reached. In pts treated at the RP2D, greater clinical activity was seen in sALCL vs HL: ORR 53 vs 47%, median TTR 1.5 vs 2.7 months, TTP 6.2 vs 4.8 months, PFS 6.2 vs 3.8 months, and EFS 4.8 vs 2.1 months. After BV, 17 pts (47%) proceeded to transplant (including 9 sALCL pts, 6 of whom were first relapse pts). The highest ORR of 60% was seen in first relapse sALCL pts treated at the RP2D. Common treatment-related adverse events (AEs) included pyrexia (44%), nausea (36%), and paresthesia (19%). The most common grade \geq 3 AEs (16/36 pts) were neutropenia (11%), increased GGT (6%), and pyrexia (6%). Twelve pts (33%) experienced peripheral neuropathy (PN) of grade 1/2/3 (25%/6%/3%), with 83% resolving/improving by end of treatment; no pt discontinued due to PN. There were 4 treatment-related serious AEs in 3 pts (all grade 3: hepatotoxicity, febrile neutropenia, pneumonia, and anaphylaxis). One on-study death was reported but was considered unrelated to study drug per investigator.

Conclusions: Response rates were clinically meaningful in this R/R HL and sALCL population with 47% of pts proceeding to transplant. This study shows BV is a feasible treatment option in pediatric HL and sALCL that can facilitate relapsed pts proceeding to transplant. A future study is ongoing to address the efficacy/safety of BV with chemotherapy in pediatric pts with newly diagnosed HL.

Keywords: anaplastic large cell lymphoma (ALCL); brentuximab vedotin; Hodgkin lymphoma (HL).

252 PROGNOSTIC FACTORS IN PATIENTS WITH RELAPSED OR REFRACTORY SYSTEMIC ANAPLASTIC LARGE T-CELL LYMPHOMA (ALCL) RECEIVING BRENTUXIMAB VEDOTIN AND OUTCOME AFTER TREATMENT FAILURE.

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Background: Brentuximab vedotin (BV) has shown significant clinical activity in anaplastic large T-cell lymphoma (ALCL). However, the management of those who relapse or have disease progression on BV is challenging. We sought to evaluate the features that may be associated with the response to BV and to assess the outcome after the disease progression.

Method: This is a multicenter retrospective study analyzing the outcome of patients who received BV for relapsed or refractory systemic ALCL. A total of 55 patients that had been treated with BV for relapsed or refractory disease were identified. Characteristics at the start of BV were analyzed for their association with failure free survival (FFS) and overall survival (OS). Failure of BV was defined by disease progression, relapse or change of therapy. Patients who received a stem cell transplant (SCT) were censored at the time of transplant for the FFS analysis.

Results: The median age of patients at the time of the first cycle of BV was 55 years (range 13–88); most patients were male (82%), and the majority had refractory disease (53%). ALK positive in 14 cases (25%). BV therapy was started within 1 year of the initial diagnosis in 52% of patients. A total of 11 patients (20%) had undergone SCT prior to BV.

Overall response rate was 71%, including CR in 45%. With a median follow-up of 30 months, the median FFS was 15 months, and the median OS was not reached. The 2-year FFS and OS was 31% and 59%, respectively. In patients who received BV following failure of primary CHOP (like) therapy, the ORR and CR were 69% and 54%, respectively. Outcomes were similar in patients who had received a prior SCT (2-y FFS 30%, 2-y OS 57%) or had received BV either pre-SCT or were transplant ineligible (2-y FFS 30%, 2-y OS 64%). Twenty-one patients went on to SCT (auto $n = 13$; allo $n = 8$) following response to BV.

By univariate analyses, PS (0–1 vs >2), sIPI (0–1 vs 2–3 vs 4–5), and interval from diagnosis (\leq 1 year vs >1) were associated with a shorter FFS. Multivariate analysis showed only sIPI to be independently associated with FFS (Hazard ratio [HR] 2.6, $p = 0.004$). Univariate analysis for association with OS determined PS, extranodal involvement (\leq 1 vs >1), high LDH, sIPI, refractory disease (vs relapse) to be associated with shorter OS. Multivariate analysis identified sIPI (HR 3.7, $p = 0.001$) and refractory disease (HR 2.6, $p = 0.036$) to be

independently associated with OS. Twenty-two patients had PD on BV, and two had treatment tolerance requiring a change in therapy. In this group ($n = 24$), the median OS after BV failure was only 3 months, and 2-year OS was 30%. Of 6 long-term (>1 year) survivors, five underwent subsequent SCT (allo $n = 3$, auto $n = 2$). One had good response to investigational clinical trial treatment, and one had localized indolent disease.

Conclusions: Refractory disease to last therapy and higher sIPI at start of BV were associated with inferior outcomes in ALCL following BV. Further, patients with disease progression after use of BV have a dismal outcome.

Keywords: anaplastic large cell lymphoma (ALCL); brentuximab vedotin; prognostic indices.

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CASE MATCH CONTROL ANALYSIS OF PROPEL REVEALS A SURVIVAL ADVANTAGE FOR PATIENTS WITH RELAPSED PTCL RECEIVING PRALATREXATE: A NOVEL APPROACH TO BENCHMARK DRUGS IN RARE DISEASES

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Introduction: Overall survival (OS) remains the gold standard proof of clinical benefit, best assessed in randomized Phase 3 clinical studies. The conduct of randomized studies in PTCL would take protracted periods of time to conduct, are expensive with minimal commercial return, and could become irrelevant as other new agents emerge. Virtually all drugs in this setting are approved on surrogate endpoints like progression free survival (PFS) or complete response (CR) rates in single arm Phase 2 studies. A middle-ground approach involves using case-matched control analyses (CMCA), which are statistically more robust and can provide insights into the likelihood of success in the randomized setting. CMCA require access to large well-annotated datasets. We established an integrated international database of patients with R/R PTCL in order to clarify the survival advantage of pralatrexate in patients with R/R PTCL, using the original raw data from the PROPEL study. The control population is derived from a collection of 4 historical databases. These databases were all annotated with the criteria used to define the PROPEL study population. The analysis was conducted by an independent statistician in collaboration with investigators from Columbia University.

Methods: The propensity score was used to match cases and controls. The match process was based on histology, number of previous treatments, age at diagnosis, and sex. With 1:1 match, the process identified 83 cases and 83 controls. The CMCA population includes 68.7% female from cases and 66.3% from controls. For cases and controls, the age distributions are similar. About 60% of patients received less than three previous treatments in both cases and controls (58% vs

59%). More than half of the patients in both cases and controls had PTCL-unspecified. Other histology above 10% are AILT and ALCL.

Results: A total of 83 patients out of 109 treated on the PROPEL study were successfully matched. OS was plotted for each of the two study populations. The survival curves for the control population were found to be identical to that reported for this population from other published datasets. The OS was 4.04 months (95% CI 2.83, 5.78). The median number of prior therapies was 3, with 19% of patient receiving more than 5 lines of prior therapy. The median OS in for the pralatrexate treated cohort in this analysis was 16.6 months (95% CI: 11.99–25.56). There was a highly significant difference in the OS between these two populations, with a hazard ratio of 0.426 (95% CI: 0.296–0/61).

Conclusion: This CMCA demonstrates a highly significant difference in OS in favor of patients treated with pralatrexate. This approach can be used to better understand how new drugs in orphan diseases perform in heterogeneous patient populations. Additional statistical and sensitivity analyses will be reported.

Keywords: peripheral T-cell lymphomas (PTCL); pralatrexate.

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A POST-MARKETING SURVEILLANCE STUDY OF 703 PATIENTS TREATED WITH CHIDAMIDE FOR PERIPHERAL T-CELL LYMPHOMA (PTCL) IN CHINA. HDAC STUDY GROUP OF UNION FOR CHINA LYMPHOMA INVESTIGATORS (UCLI)

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Introduction: The efficacy and safety of chidamide, a novel subtype-selective histone deacetylase (HDAC) inhibitor, have been demonstrated in a pivotal phase 2 clinical trial (CHIPEL study) and were recently approved by China Food and Drug Administration (CFDA) for the treatment of patients with relapsed or refractory peripheral T cell lymphoma (PTCL). The purpose of this post-marketing surveillance study was to further elucidate the real-world utilization of chidamide in relapsed or refractory PTCL.

Methods: Patients with confirmed PTCL who experienced progression after one prior therapy received chidamide as monotherapy or combined with chemotherapy regimens. Assessment of response was made according to International Working Group criteria. The primary end point was overall response rate (ORR).

Results: A total of 703 patients were enrolled from April 2015 to August 2016 in mainland China. For patients received chidamide monotherapy ($n = 462$), ORR and disease control rate (DCR) were 47.0% and 72.7%, respectively. The ORR and DCR were 60.2% and 78.0%, respectively, in patients received chidamide-based combination therapy ($n = 241$). Significantly higher ORRs were achieved from chidamide-based combination therapy compared to monotherapy in patients with IPI 2-3 (62.3% vs. 47.1%, $P < 0.01$) and IPI 4-5 (54.9% vs. 35.9%, $P < 0.05$), suggesting combination therapy could improve efficacy for patients with medium-high risk. Most adverse events (AEs) were grade 1 to 2. AEs of grade 3-4 that occurred in $\geq 5\%$ patients received chidamide monotherapy were thrombocytopenia (11.0%), neutropenia (9.7%), and anemia (6.1%), respectively. For

patients received chidamide-based combination therapy, grade 3-4 AEs occurred in $\geq 5\%$ patients were mainly thrombocytopenia (27.4%), neutropenia (25.3%), anemia (13.3%), and fatigue (10.8%).

Conclusions: These results demonstrate that chidamide has a favorable efficacy and an acceptable safety profile in refractory and relapsed PTCL. Chidamide-based combination therapy is well tolerated and could be a promising new regimen in PTCL patients, especially in those with medium-high risk, although further investigation will be needed.

Keywords: Chemotherapy; peripheral T-cell lymphomas (PTCL).

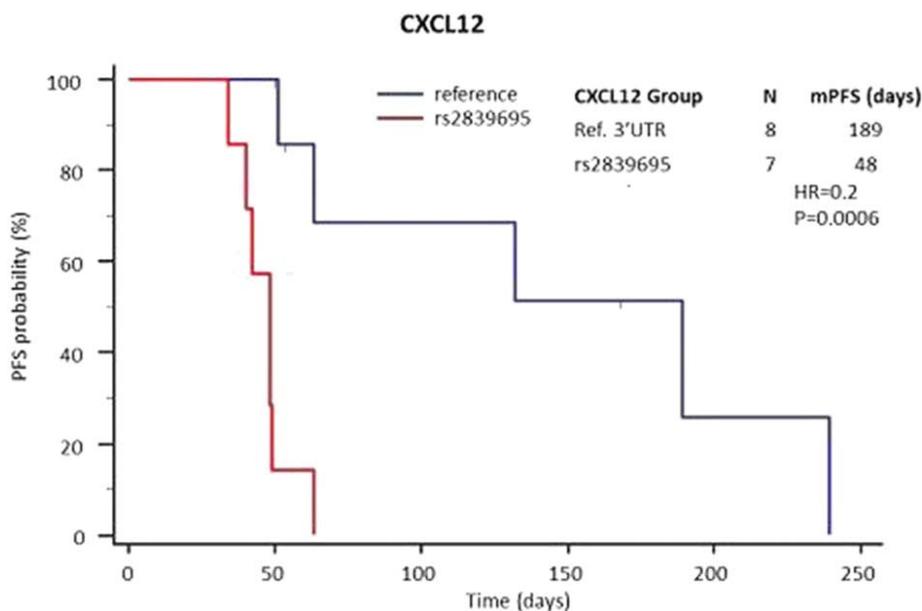
255 PRELIMINARY RESULTS FROM AN OPEN-LABEL, PHASE II STUDY OF TIPIFARNIB IN RELAPSED OR REFRACTORY PERIPHERAL T-CELL LYMPHOMA

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Introduction: Tipifarnib is a potent and selective inhibitor of farnesyltransferase (FT). FT catalyzes post-translational attachment of farnesyl groups required for localization of signaling molecules to the inner cell membrane. CXCL12 is a chemokine that is essential for hematopoietic stem cell (HSC) homing to the bone marrow and lymphoid organs and for maintenance of HSCs and immune cell progenitors. CXCL12 is known to signal in part through HRAS, a signaling protein



that is uniquely farnesylated. Tipifarnib has been shown to be well tolerated and to have a 41% response rate (7 responses out of 17 patients) in patients (pts) with T-cell non-Hodgkin Lymphoma, including 4 objective responses in 8 pts with peripheral T-cell lymphoma (PTCL) (Witzig et al., 2011). Building on this prior experience, we report herein the preliminary efficacy, safety, and biomarker data from our ongoing Phase 2 study in PTCL.

Methods: This Phase 2 study is a multi-institutional, single-arm, open-label, two-stage (11 + 7) study designed to determine the efficacy and safety of tipifarnib in pts with relapsed/refractory (R/R) PTCL. Pts with R/R PTCL after prior cytotoxic systemic therapy, aged ≥ 18 years old, and with a performance status of 0–2 were eligible. The primary endpoint of the study is overall response rate. Based on activity observed in the first 18 pts in the study, the protocol has been amended and enrollment is ongoing to an expansion cohort in AITL ($N = 12$). Enrolled pts are treated with tipifarnib 600 mg administered orally twice daily on days 1–7 and 15–21 of 28-day treatment cycles until progression of disease or unacceptable toxicity. Clinical trial information: NCT02464228.

Results: At data cut-off (2/15/2017), 18 pts (2 AITL, 1 ALK- ALCL, 15 PTCL-NOS) were treated with tipifarnib. Most common treatment-related AEs (grade ≥ 3) were myelosuppression, including neutropenia (61%), anemia (39%), and thrombocytopenia (39%). A total of 3 pts achieved a partial response (2 AITL; 1 PTCL-NOS), and 3 additional pts experienced stable disease >6 months. Tumor DNA from 16 pts was sequenced using DNA next-generation sequencing (NGS). A high rate of CXCL12 3'UTR single nucleotide variation (SNV) was observed. Seven of 16 pts carried the rs2839695 variant while an additional patient carried a novel variant. The presence of 3'UTR SNVs was associated with low levels of CXCL12 gene expression and disease progression (Figure) while all pts deriving clinical benefit from tipifarnib carried reference (wild type) 3'UTR CXCL12 and had tumors that expressed high levels of mRNA for this chemokine. Testing of circulating CXCL12 levels is ongoing.

Conclusions: Although this study is ongoing, these preliminary data indicate that tipifarnib is generally well tolerated and has antitumor activity, particularly in pts with AITL histology, absence of 3'UTR CXCL12 SNV, and high levels of CXCL12 gene expression.

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

256 SAFETY AND EFFICACY OF MOGAMULIZUMAB IN PATIENTS WITH ADULT T-CELL LEUKEMIA-LYMPHOMA IN JAPAN: INTERIM RESULTS OF POSTMARKETING ALL-CASE SURVEILLANCE

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Introduction: Mogamulizumab (Moga), approved in Japan in 2012, is a defucosylated humanized monoclonal antibody targeting C-C chemokine receptor 4 (CCR4), which is expressed on adult T-cell leukemia-lymphoma (ATL) cells. We report the interim results of the postmarketing all-case surveillance to evaluate the safety and efficacy of Moga in patients with CCR4-positive relapsed or refractory ATL.

Methods: This surveillance was initiated on May 29, 2012, in Japan (UMIN00025368). Data were to be collected for all patients who started the treatment before May 1, 2013. All patients were scheduled to receive Moga 1.0 mg/kg intravenously once weekly for 8 weeks, alone or in combination with other modalities.

Results: Data were obtained from 489 of 596 patients. After excluding unevaluable patients, 484 patients were included in the safety analysis, and 442 were included in the efficacy analysis. In 30.6% (148/484) of patients, Moga was used in combination with other modalities which were mainly cytotoxic agents. Adverse drug reactions (ADRs) were reported in 74.0% (358/484) of patients, of which 35.7% (173/484) were serious and 6.2% (30/484) were fatal. Common non-hematological ADRs included infusion reaction, rash, erythema, pyrexia, cytomegalovirus infection or viremia, pneumonia, and tumor lysis syndrome; hematological ADRs included leukopenia, febrile neutropenia, neutropenia, and thrombocytopenia. The priority survey items of infusion reaction, skin disorder, infection, immune disorder, and tumor lysis syndrome were reported in 29.3% (142/484), 34.3% (166/484), 22.1% (107/484), 3.5% (17/484), and 2.5% (12/484) of patients, respectively. Common skin disorders included rash, erythema, and pruritus. Stevens-Johnson syndrome and toxic epidermal necrosis were reported in 0.8% (4/484) and 0.6% (3/484) of patients, respectively. Forty-two patients received Moga before allogeneic hematopoietic stem cell transplantation (HSCT). Among them, graft-versus-host disease (GVHD) developed in 59.5% (25/42) of patients; grade III or IV GVHD occurred in 28.6% (12/42). In twenty-nine patients who were treated by Moga after allogeneic or isogeneic HSCT, 17.2% (5/29) experienced GVHD after starting Moga.

The best overall response rate was 57.7% (255/442), 58.2% (78/134) in patients with combination therapy, and 57.5% (177/308) in patients with Moga alone. Patients with skin disorder showed higher response rates than patients without (78.0% [124/159] vs. 47.3% [131/277], respectively) ($P < 0.001$).

Conclusions: The ADRs observed in this surveillance showed similar trends to those in clinical trials, while administration of Moga before allogeneic HSCT may unfavorably influence the occurrence of severe GVHD. Moga is considered to be an acceptable option for this patient cohort; however, caution is needed against potentially serious or fatal ADRs.

Keywords: human T-lymphotropic virus (HTLV); monoclonal antibodies (MoAb); T-cell lymphoma (TCL).

257 TARGETING THE T-CELL RECEPTOR B- CONSTANT DOMAIN FOR

IMMUNOTHERAPY OF T-CELL MALIGNANCIES

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Introduction: Mature T-cell lymphomas are typically aggressive, treatment-resistant and associated with poor prognosis. Immunotherapy has been limited by a lack of target antigens discriminating malignant from healthy T-cells. While B-cell cancer immunotherapy targets pan B-cell antigens, causing normal B-cell depletion, pan T-cell depletion would be prohibitively toxic. We propose a strategy for targeting a pan T-cell antigen without causing T-cell aplasia.

The α/β T-cell receptor (TCR) is expressed on >90% of T-cell lymphomas and all normal T-cells. The β -constant region comprises 2 functionally identical genes: TRBC1 and TRBC2. Each T-cell expresses only one. Hence, normal T-cells are a mixture of individual cells expressing either TRBC1 or 2, while a clonal T-cell cancer expresses TRBC1 or 2 in its entirety. We hypothesised immunotherapy against either TRBC1 or 2 could target a whole cancer but preserve many normal T-cells.

Methods: Standard techniques including flow cytometry, enzyme-linked immunosorbent assays, Cr⁵¹-release cytotoxicity assays, viral peptide T-cell stimulation, immunohistochemistry, and *in vivo* bioluminescence imaging.

Results: Despite almost identical sequences, we identified an antibody with unique TRBC1 specificity. Flow cytometry in normal donors ($n = 27$) and T-cell cancer patients ($n = 18$) revealed median T-cell TRBC1 proportion of 35% (range 25–47%). Viral-specific T-cells for Epstein Barr virus, cytomegalovirus, or adenovirus contained similar TRBC1 proportion, suggesting depletion of either subset would not remove immunity. Conversely, TCR+ cell lines ($n = 8$) and primary T-cell cancers ($n = 55$) across many histological subtypes were restricted to one compartment (34% TRBC1).

As proof of concept for TRBC-selective therapy, we developed anti-TRBC1 chimeric antigen receptor (CAR) T-cells. After retroviral transduction of healthy donor T-cells, comprising mixed TRBC1/2 populations, 90% expressed CAR. No detectable TRBC1 T-cells remained. Anti-TRBC1 CAR killed multiple TRBC1 cell lines ($p < 0.001$), autologous normal TRBC1 cells ($p < 0.001$), and primary cells from patients with TRBC1 tumours; and did not kill TRBC2 cell lines or autologous normal TRBC2 cells. We developed murine models of disseminated TRBC1 cancer by engrafting Jurkat or H9 cells in NSG mice. While control CAR recipients progressed, mice receiving anti-TRBC1 CAR had disease clearance ($p < 0.0001$) and prolonged overall survival ($p < 0.05$). Finally, mice were engrafted with equal proportions of TRBC1- and TRBC2-Jurkat cells. We observed specific eradication of TRBC1 and not TRBC2 cells by anti-TRBC1 CAR ($p < 0.001$).

Conclusions: We describe a novel approach to treatment of T-cell malignancies distinguishing between 2 possible TCR β -chain constant regions. Using CART-cells targeting TRBC1 we have demonstrated proof of concept. Unlike strategies targeting the entire T-cell population, TRBC targeting could eradicate a T-cell tumour while preserving sufficient normal T-cells to maintain cellular immunity.

Keywords: peripheral T-cell lymphomas (PTCL); T-cell receptor (TCR); T-cells.

NEW DRUG DEVELOPMENT

258 DEVELOPMENT OF NOVEL, NON-TOXIC RIFAMYCINS THAT REVERSE DRUG RESISTANCE IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Introduction: Refractory/relapsed disease remains a primary cause of morbidity and mortality in DLBCL patients. We have discovered novel non-toxic rifamycins that potently reverse drug-resistance in DLBCL cells.

Methods: CHOP-resistant DLBCL cells were generated from the CRL2631 cell line by “on-off” cycles of CHOP treatment, analogous to clinical therapy. The CHOP-resistant cells were used in high-throughput screening of a collection of 50,000 drug-like molecules to identify compounds that reverse CHOP-resistance. The FDA-approved drug, rifabutin, was identified as a non-cytotoxic compound that potently reversed resistance to CHOP. Structure-Activity-Relationship (SAR) studies on rifabutin were conducted, which led to the generation of a new more potent CHOP-chemosensitizing agent, designated RTI-79.

Results: RTI-79 was highly synergistic with CHOP in a variety of DLBCL cells. Combination therapy of doxorubicin + RTI-79 in mouse xenograft models of DLBCL was more effective at repressing tumor growth than doxorubicin alone. Two companion dogs afflicted with CHOP-relapsed DLBCL treated with combination CHOP + rifabutin showed regression of DLBCL. RTI-79 lowered the doxorubicin IC₉₀ and IC₉₉ in a dose-dependent manner in CD20-positive B cells in bone marrow aspirates from both CHOP-naïve and CHOP-relapsed human patients, and in a metastatic DLBCL-diseased lymph node. RTI-79

potentiated the activity of many chemotherapeutics, including daunorubicin, epirubicin, vinblastine, etoposide, paclitaxel, and topotecan. RTI-79's PK characteristics are similar to rifabutin and exhibited no overt toxicity in mice at high doses. RTI-79 did not exacerbate the known cardiotoxicity associated with doxorubicin as evaluated by body weight, CBCs, and heart function via echocardiograms. RTI-79 rapidly induced intracellular ROS and increased both mitochondrial membrane potential and fission. The anti-oxidant quercetin antagonized both RTI-79-induced ROS and potentiation of doxorubicin cytotoxicity. RTI-79 reduced expression of the anti-oxidant regulator protein, Nrf-2, potentially through upregulation of SYVN1, an E3 ubiquitin ligase that interacts directly with Nrf-2. Moreover, RTI-79 caused upregulation of proteins involved in the unfolded protein response (UPR).

Conclusions: RTI-79 has a broad spectrum of action in both double- and triple-hit DLBCL and synergizes with many different chemotherapeutics to restore drug sensitivity. RTI-79 works by increasing intracellular ROS, primarily superoxide, through redox cycling. RTI-79 triggers the UPR that results in increased ubiquitination and loss of Nrf-2. Thus, RTI-79 induces oxidative stress by increasing ROS and reducing Nrf-2's ability to respond to ROS. This unique pleiotropic chemosensitizing mechanism provides a novel approach for treating drug resistant cancers.

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

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DEVELOPMENT OF NOVEL PRECLINICAL MODELS OF SECONDARY RESISTANCE TO THE PI3K δ INHIBITOR IDELALISIB IN SPLENIC MARGINAL ZONE LYMPHOMA (SMZL)

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Background: Targeting the BCR signaling is one of the main novel therapeutic approaches for lymphoma patients. Different drugs with distinct or overlapping targets are now in the clinical setting including PI3K δ inhibitor (i) idelalisib. A better understanding of mechanisms of action and resistance to the drug could lead to rationally designed therapies and potential strategies to prevent resistance. Hence, we generated resistant *in vitro* clones to idelalisib in SMZL models.

Materials and Methods: VL51 and Karpas1718 cells were exposed to IC90 concentration of idelalisib for several weeks until they acquired specific drug resistance (resistant). Cell lines were cultured upon the same conditions with no drug exposure (parental). Proliferation of acquired stable resistance was tested by MTT assay (72 hrs) in resistant and parental after 2 weeks of drug-free culture. IC50 values were estimated. Multi-drug resistance phenotype (MDR1 expression, real-time PCR) was discarded. Gene expression profiling (GEP) was

obtained with the Illumina-HumanHT-12 Expression-BeadChips and analyzed with moderated t-test and GSEA.

Results: VL51 cells resistant to idelalisib exhibited over tenfold increase in their IC50 versus their parental cells (12.5 vs 1.2 μ M). Karpas1718 reached a sixfold increase (10 vs 1.5 μ M). To assess whether the acquired resistance to idelalisib was specific for PI3K δ inhibition, we performed MTT assay for idelalisib, dual PI3k-mTOR i PQR309, PI3K δ / γ i duvelisib and mTOR i everolimus. Resistant clones showed similar sensitivity than parental when exposed to PQR309 or everolimus. Duvelisib antitumor activity was decreased but not abolished in resistant cells. Expression profiles of resistant and parental cells were compared. Signatures related to FGFR mutations, DNA recombination and Isotype switching processes and to silencing of *PIK3CA*, *SYK*, *GSK3A/B* and *AKT1* were enriched in the resistant clones of both cell lines. BCR and NF κ B signaling gene sets were enriched in VL51 resistant clones but decreased in Karpas1718 resistant clones suggesting different mechanisms of resistance. The latter cells showed an increase in cell cycle genes and MYC targets. Consistent with the BCR genes changes, enrichment of AICDA off-targets was evident in VL51 resistant and for Karpas1718 parental clones. *CD79A*, *CD19*, *CXCR4* (upregulated), *CDKN2C*, *CDKN2A* (downregulated) were among the affected genes in resistant VL51, while *BIRC3*, *CARD11*, *CXCR5*, *CD37* (downregulated) in resistant Karpas1718.

Conclusions: We presented two novel models, derived from SMZL, of secondary resistance to the PI3K δ i idelalisib. These models, apparently driven by different biologic processes, will help in clarifying mechanisms of resistance to the drug and to evaluate alternative therapeutic approaches.

Keywords: Idelalisib (CAL-101, GS-1101); PI3K/AKT/mTOR; splenic marginal zone lymphoma (SMZL).

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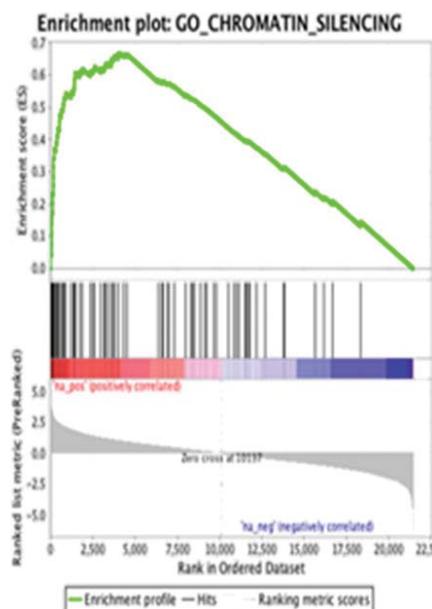
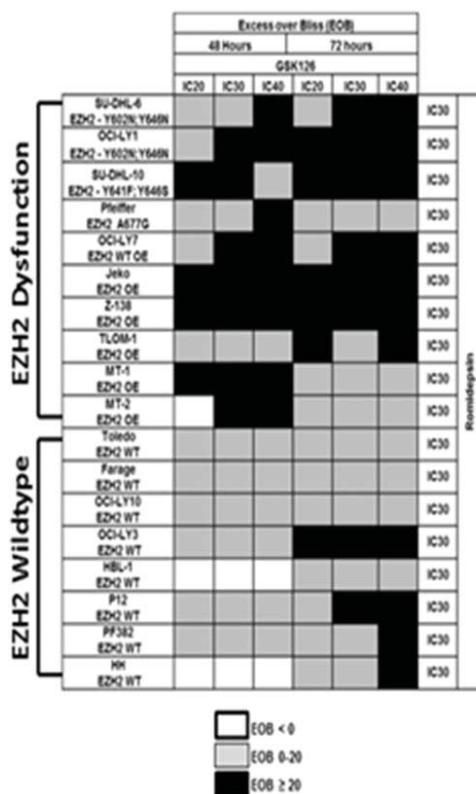
DUAL INHIBITION OF EZH2 AND HDAC IS SYNERGISTIC IN EZH2 DYSREGULATED LYMPHOMAS

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Introduction: EZH2 is the catalytic subunit of the PRC2 complex and induces tri-methylation of H3K27. Activating mutations in EZH2 are found in 7–12% of FL and 22% of GC-DLBCL. Mutations in the histone acetyltransferases (HATs) CBP and p300 have been implicated in B- and T-cell lymphomas. Given the presence of EZH2 and HAT dysregulation in B-cell lymphomas, we hypothesized that EZH2 and HDAC inhibitors would be synergistic.

Methods: Lymphoma cell lines ($n = 21$) were treated with the EZH2 and HDAC inhibitors GSK126 (G) and romidepsin (R). Cells were co-exposed to G and R over 72 hrs. Cell viability was assessed via Cell titer-Glo assay, and IC₅₀ values were computed. Synergy was assessed by Excess over Bliss (EOB), where EOB > 10 represents synergy. Four



GC-DLBCL cell lines were treated with the combination of G and R for evaluation of H3 methylation, acetylation, and effects on the PCR2 complex by co-immunoprecipitation and western blot. Pre-treatment RNA-seq libraries were developed for the purpose of GSEA and mutational analysis.

Results: Cell lines with known EZH2 dysregulation were more sensitive to G as exhibited by lower IC₅₀ after 6-day exposure. There was no association between HAT mutation and R sensitivity. Simultaneous exposure to G and R in GC-DLBCL cell lines demonstrated potent synergy as represented by EOB > 30. Synergy was also present in ATLL cell lines (EOB 28), which are known to have EZH2 dysregulation, as well as non-GC DLBCL cell lines (EOB 47). Drug schedule did not impact synergy. The combination led to a decrease in H3K27 methylation an increase in acetylation as well as dissociation of the PRC2 complex, HDAC2 and DNMT3L as compared to single agent exposure. Decreased protein expression of PRC2 complex members and increased p21, caspase 3 and PARP cleavage were more notable in the combination as compared to single agents. Based on the finding that HDAC2 dissociated from PRC2 complex after combination treatment, a selective HDAC1/2 inhibitor, ACY957, was combined with G which demonstrated potent synergy in 4 GC-DLBCL cell lines. Mouse xenograft models are underway.

GSEA identified synergistic cells lines (EOB >20) to be enriched in pathways involved with chromatin silencing, gene silencing, epigenetic regulation of gene expression, and protein acetylation. Differential gene expression revealed that synergistic cell lines are characterized by a GC genotype as noted by a relative decrease in JAK1, DUSP2 and increase in MBD3.

Conclusions: Inhibition of EZH2 and HDAC is highly synergistic and leads to the dissociation of PRC2 complex. Reversing transcriptional inhibition using dual inhibition of EZH2 and HDAC may serve as a precision medicine approach for lymphomas that are enriched in a chromatin silenced state as identified by GSEA.

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

261 STRO-001, A NOVEL ANTI-CD74 ANTIBODY DRUG CONJUGATE (ADC) FOR TREATMENT OF B-CELL NON-HODGKIN'S LYMPHOMAS (NHL)

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Introduction: STRO-001 is a novel CD74-targeting ADC comprised of an anti-CD74 human IgG1 antibody (Ab) conjugated to a non-cleavable maytansinoid linker-warhead. Precise site-specific conjugation enabled by our cell-free antibody synthesis technology produced a well-defined homogeneous ADC with a drug-antibody ratio (DAR) of 2. Conjugation sites were selected based on highest stability both in vitro and in vivo. The aim of this study was to investigate the

Table with SP7219 binding capacity (copy/cell) and STRO-001 cell killing EC₅₀

	Cell Line	ABC (Antibody Binding Capacity)	STRO-001 Cell Killing	
			EC ₅₀ (nM)	Span (%)
Activated B-cell-like Diffuse Large B-Cell Lymphoma	OCI-Ly3	77,435	0.46	96
	U2932	10,649	1.3	80
	RIVA (RI-1)	BD	3.3	77
	SU-DHL-2	BD	>100	
Germinal Center B-cell-like Diffuse Large B-Cell Lymphoma	WSU-DLCL2	51,090	0.17	97
	WSU-NHL	49,925	0.69	96
	SU-DHL-4	49,603	0.24	97
	Pfeiffer	47,123	0.54	88
	SU-DHL-6	23,235	0.56	96
	OCI-Ly1	21,529	0.69	96
	HT	20,788	0.34	68
	NUDUL-1	13,040	0.3	98
Mantle Cell Lymphoma	OCI-Ly19	BD	1.3	38
	Mino	28,117	0.68	97
	JVM-2	23,672	1.7	55
	JeKo-1	14,754	0.41	97
	Rec-1	8,247	13	45

BD=Below detection (detection threshold = 4131)

therapeutic potential of STRO-001 in NHL cell lines and xenografts. A toxicology study was conducted in cynomolgus monkeys (cynos).

Methods: Biotinylated unconjugated Ab was used for immunohistochemistry (IHC). Flow cytometry was used for measuring CD74 expression. STRO-001 was used to determine the EC₅₀ and percent span of killing in NHL cell lines. The anti-tumor activity of STRO-001 in NHL xenografts was examined. STRO-001 was administered to cynos at doses of 1, 3, 10 and 30 mg/kg on days 1 and 15.

Results: CD74 expression was evaluated by IHC on duplicate core (matched pair) biopsies. Medium to high CD74 expression in >70% of cells was observed in 86/100 DLBCL, 22/28 follicular lymphoma and 49/78 MCL samples. In vitro cytotoxicity assays show potent activity of STRO-001 in a diverse panel of B-cell tumor lines with EC₅₀ values ranging from 0.17–13 nM. CD74 cell surface expression is required for STRO-001 cytotoxicity, but expression level does not correlate with in vitro potency ($R^2 = 0.4154$). STRO-001 exhibits dose-dependent tumor growth inhibition in rituximab-resistant SU-DHL-6 xenografts starting at 2.5 mg/kg weekly × 3 doses. STRO-001 + bendamustine/rituximab (BR) further improves tumor suppression in SU-DHL-6 xenografts compared to vehicle ($p = 0.002$) or BR alone ($p = 0.02$). Studies with an MCL model, Jeko-1, demonstrate robust STRO-001 anti-tumor activity compared to vehicle ($p < 0.0001$) starting at a single 3 mg/kg dose, with a single 10 mg/kg dose resulting in tumor regression for up to 64 days posttreatment. STRO-001 treatment 14 days post tumor inoculation was used to evaluate disease progression in the disseminated Mino MCL model. Vehicle-treated animals developed advanced progressive disease, with median survival of 81 days. In contrast, all Mino xenografts treated with STRO-001 at 3 or 10 mg/kg were alive and disease free at the time of sacrifice 135 days post inoculation. STRO-001 demonstrated B-cell depletion in cynos, confirming the intended PD effect. Myelosuppression was observed at the highest dose, with no off-target toxicity.

Conclusions: STRO-001 demonstrates potent in vitro cytotoxicity in NHL cell lines and anti-tumor activity in NHL xenograft models, including prolonged survival in the disseminated Mino MCL model. STRO-001 depletes B cells in a dose-dependent manner. Clinical studies of this novel ADC for treatment of B-cell malignancies are under development.

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

262 COMBINATORIAL SCREENING OF THE PI3K INHIBITOR COPANLISIB IN T CELL LYMPHOMAS

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Introduction: T-cell lymphomas represent a group of disorders for which therapeutic improvements are still widely needed. Here, we performed a screening of copanlisib, a pan class I phosphatidylinositol-3-kinase (PI3K) inhibitor (i) with predominant inhibitory activity against both PI3K- δ and PI3K- α isoforms, as single agent and in combination with several other anti-cancer agents on a panel of cell lines derived from anaplastic large cell lymphoma (ALCL), peripheral T cell lymphoma (PTCL) and Sèzary syndrome (SS).

Methods: Cell lines derived from ALCL (SU-DHL-1, L82, MAC1, KARPAS299, KI-JK), PTCL (FEPD, HH) and SS (H9, HUT78) were exposed to increasing doses of copanlisib alone and in combination with increasing doses of other compounds using the fixed ratio set-up. Tested compounds were anti CD30 antibody-drug conjugate brentuximab, ALK-i crizotinib, CDK-i ro niciclib, DNA damage agent bendamustine, HDAC-i panobinostat and romidepsin, immunomodulatory lenalidomide, JAK1/2-i ruxolitinib, BTK-i ibrutinib, MALT-i MI2, proteasome-i bortezomib, BCL2-i venetoclax, CDK4/6-i palbociclib, the BET-i BAY 1238097, and the PTEFb/CDK9-i BAY 1143572. Synergy was assessed with Chou-Talalay combination index (CI): synergism (<0.9), additive (0.9–1.1), antagonism/no benefit (>1.1). Gene expression profiling was done using the Illumina-HumanHT-12 Expression-BeadChips and GSEA (FDR < 0.25).

Results: Copanlisib had a median IC50 of 285 nM (50–1660 nM). Among the other compounds, the most active were bortezomib (IC50 3.1 nM; 1.6–6 nM), romidepsin (IC50 2.4 nM; 1.8–7.7 nM), panobinostat (IC50 10.2 nM, 3.8–14 nM), ro niciclib (IC50 21.1 nM, 13.4–50.1 nM). Different copanlisib-containing combinations, tested in the 9 cell lines, were synergistic: copanlisib with palbociclib (7/9 cell lines), panobinostat (7/9), BAY 1238097 (6/9), venetoclax (5/9), romidepsin (5/9), ruxolitinib (4/9), lenalidomide or BAY 1143572 or brentuximab or crizotinib (3/9). The most promising combinations were copanlisib/venetoclax and copanlisib/palbociclib, with a median CI < 0.7 in 3 cell lines. High expression of genes involved in interferon signaling and TP53 pathway were associated with synergism to copanlisib/venetoclax, while MYC target genes and cell cycle signaling were associated with resistance to the combination. Largely, the opposite was observed for copanlisib/palbociclib, with synergism in cells with high expression of E2F targets and genes involved in cell cycle and resistant in cells with expression of transcripts involved in interferon and TP53 signaling.

Conclusion: Copanlisib was active in T-cell lines derived from ALCL, PTCL and SS. The combinations with the BCL2-inhibitor venetoclax and with the CDK4/CDK6-inhibitor were the most synergistic and the specific GEP features might predict lymphomas that could benefit from these regimens.

Keywords: ABT-199; peripheral T-cell lymphomas (PTCL); PI3K/AKT/mTOR.

263 COPANLISIB IN COMBINATION WITH ANTI-PD-1 INDUCES REGRESSION IN ANIMAL TUMOR MODELS INSENSITIVE OR RESISTANT TO THE MONOTHERAPIES OF PI3K AND CHECKPOINT INHIBITORS

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Introduction: The PI3K pathway is activated in many cancers, yet the ability of PI3K inhibitors to induce tumor cell death is limited. On top of directly targeting tumor cells, the efficacy of PI3K inhibition can also

derive from modulating the tumor microenvironment. It has been shown that inhibition of PI3K δ or PI3K γ led to anti-tumor activity via targeting regulatory T cells (T_{reg}) and immuno-suppressive myeloid cells, respectively. However, the overall outcomes of inhibiting PI3K (isoforms) signaling in different subtypes of immune cells during development and activation are still to be elucidated. Furthermore, it has been shown that cancer cell-intrinsic activation of PI3K is associated with resistance to immune checkpoint blockers (ICB). Therefore, combination strategies of ICB and PI3K inhibitors with different isoform profiles should be investigated.

Methods: Copanlisib, a predominant PI3K α /d inhibitor, was administered on an intermittent intravenous dosing schedule. Flow cytometric analysis was performed using fluorochrome-labeled monoclonal antibodies (mAbs; anti-CD19, anti-CD45, anti-CD3, anti-CD4, anti-CD8, anti-FOXP3, anti-CD206, anti-F4-80, GR-1, anti-CD49B, anti-PD-L1, anti-CD11b, anti-PD-1, and anti-INF γ) and IA-IE dye from Biolegend, BD, eBioscience and Invitrogen. IHC analysis was performed to investigate the interaction of immune cells and tumor/tumor stromal cells. The levels of inflammatory cytokines were analyzed using MSD Multiplex assays. The anti-tumor efficacy was investigated in mouse syngeneic xenograft tumor models.

Results: In the A20 DLBCL syngeneic mouse model with tumor intrinsic regulation of the immunosuppressive environment, treatment of copanlisib resulted in effective down regulation of tumor-infiltrating T_{reg}s and an increase of INF γ ⁺ CD44⁺ cells in tumors. Consequently, partial responses (PRs) were observed in 75% of mice treated with copanlisib in combination with a surrogate anti-mouse PD-1 (aPD-1, BioXCell) compared to 0% PR in the monotherapy groups. In an aPD-1-insensitive non-MSI^{high} CT26 CRC model, combination treatment of copanlisib and aPD-1 led to complete tumor regression and thereafter no tumor growth in a re-challenge study conducted 3 months after stopping treatment. This result indicates that copanlisib and an aPD-1 combination can generate tumor specific memory T cells and prevent tumor recurrence. The detailed molecular and cellular mechanisms by which PI3K inhibitor copanlisib modulates immune cells and inhibits tumor survival will be presented.

Conclusions: In contrast to monotherapies, copanlisib in combination with ICB has the potential to overcome resistance and induce responses by directly targeting tumors and by stimulating anti-tumor immune responses.

Keywords: diffuse large B-cell lymphoma (DLBCL); PI3K/AKT/mTOR.

264 PD-1 IMMUNE CHECKPOINT BLOCKADE IMPROVES ANTI-CD20 BASED IMMUNOTHERAPY IN FOLLICULAR LYMPHOMA

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Follicular lymphoma (FL) represents the second most common subset of NHLB. Among the mechanisms of action of MABs, antibody dependent cellular cytotoxicity (ADCC) plays an important role and can be mediated by TCRV γ 9V δ 2 lymphocytes (LT γ δ) and particularly in FL with antiCD20 MABs. Moreover, LT γ δ express immunological checkpoint markers targetable by promising specific inhibitors. Thus, PD1 axis targeting appears to be relevant to optimize the effect of immunochemotherapy used so far. Here, we hypothesized that PD1 blockade could potentiate antiCD20 MABs-induced ADCC in FL models.

We used a 3D model (MALC) of FL, mimicking the pathology. Anti-CD20 MABs were provided by Roche Glycart and antiPD1 MAB by pharmacy department IUCT. ADCC were determined by flow cytometry. The LT γ δ were obtained from healthy donors or from FL biopsies provided by EFS and department of pathology IUCT (Toulouse), respectively.

Several results were obtained: i) Transcriptomic, immuno-histochemical and flow cytometry analyses in FL biopsies revealed that LT γ δ subset was the most abundant population of cytotoxic immune cells, ii) localized in peri-follicular area, and iii) the population expressing the most PD1. To study the impact of PD1 targeting, we modeled LT γ δ -tumor cells by using MALC co-cultured with normal LT γ δ and showed that i) LT γ δ expressed PD-1 and were able to mediate ADCC in presence of anti-CD20 MABs and ii) PDL1-PDL2 were overexpressed on MALC. By treating with antiPD1 MAB, we showed i) a direct effect in term of target cell death and MALC volume reduction and ii) an improvement of ADCC induced by anti-CD20 MABs, with a more pronounced effect with GA101 compared to RTX.

These results bring evidences for considering PD1-PDL1/2 axis targeting in combination with anti-CD20 MABs as a promising therapeutic strategy in FL. Ongoing in vivo experiments will be presented in Lugano.

Keywords: follicular lymphoma (FL); immune system; obinutuzumab.

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NOVEL TARGETED STRATEGIES TO OVERCOME MICROENVIRONMENT-DEPENDENT RESISTANCE IN MANTLE CELL LYMPHOMA

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Introduction: Mantle cell lymphoma (MCL) accumulates in lymph nodes (LN) and disseminates early on in extranodal tissues, but little attention has been paid to the importance of microenvironments in this pathology. Further investigations integrating the key role of

surrounding cells are now needed to overcome drug resistance in this incurable malignancy.

Methods: Despite a significant level of the proliferation index Ki67 in LN, we did not detect any proliferating peripheral blood (PB) MCL cells, suggesting a major role of the tumor ecosystem. To determine interactions that could support survival and proliferation, primary MCL cells were cocultured in several conditions ex vivo. In all the 21 samples tested, CD40L induced cell-cycle progression, which was amplified by a MCL-specific cytokine cocktail (Ck) (Chiron et al., Blood 2016). Now, to characterize the microenvironment-dependent molecular modulations, we performed RNA-seq in MCL cells from PB or cocultured ($n = 8$) and compared with genes expressed in MCL cells from LN and PB (Geo, PB $n = 77$, LN $n = 107$).

Results: More than 65% of genes induced in the "CD40L + Ck" coculture model are also upregulated in the LN compared to PB. Our model recapitulates molecular signatures that are characteristic of MCL such as cell cycle, BCR, NF κ B/NIK and survival, confirming the relevance of the coculture. We further studied the coculture-induced regulation of genes belonging to the survival signature and especially the druggable Bcl2 family. We first observed that microenvironment signalings result in an unbalanced regulation of anti- and pro-apoptotic proteins in MCL, but not in normal B cells (CD19 + CD5+). The major regulation was an increase in expression of Bcl-xL associated with a downregulation of Bim and Noxa. Using the functional BH3-profiling assay, we demonstrated that, whereas PB MCL cells are dependent on Bcl2 for survival, Bcl-xL upregulation was responsible for loss of mitochondrial priming and resistance. Consequently, whereas Bcl2 BH3-mimetic efficiently triggered apoptosis in PB MCL, cells protected by the microenvironment were resistant.

We then hypothesized that targeting BclxL could increase treatment efficacy. Using our coculture model, we developed efficient targeted strategies (i.e., BTK inhibitor, Type II anti-CD20), which counteract BclxL overexpression and overcome drug resistance in primary cells ex vivo. This strategy should target cells protected into their niches and our ongoing Trial (NTC#02558816) will rapidly determine in vivo efficacy in MCL.

Conclusions: In summary, we reported here the development of a model that provides new insights into the microenvironment-dependent molecular regulation. Our increased understanding of intrinsic abnormalities and the integration of extrinsic signaling offer new opportunities to design mechanism-based strategies to overcome drug resistance in MCL and other B-cell malignancies.

Keywords: ABT-199; ibrutinib; mantle cell lymphoma (MCL).

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EFFECTIVE THERAPY BY ANTI-CD81 AGAINST B CELL LYMPHOMAS ENGAGES BOTH DIRECT AND INDIRECT IMMUNE MECHANISMS

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Introduction: The tetraspanin CD81, originally named Target of an Anti-Proliferative Antibody-1 (TAPA-1), was discovered by screening monoclonal antibodies able to inhibit B-cell lymphoma proliferation. In B cells, CD81 associates with CD19 forming the CD19/CD21/CD81 complex that lowers the threshold of BCR-initiated B-cell activation.

Methods: Antibodies: spontaneous class-switched mouse anti-human CD81 5A6 IgG2a hybridomas were selected and subcloned. 5A6 V_H and V_L regions were inserted upstream of human IgG1 and IgG4 vectors.

In vitro: antibody dependent cell cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC): Fluorescently-labeled lymphoma cells were incubated overnight with purified human NK cells, or with human serum for 1.5 hrs, respectively. Cell death was determined by 7AAD/Annexin-V positive cells.

In vivo: SCID mice were injected i.v. with Raji-luciferase cells; tumor uptake on day 5 was ensured by bioluminescence imaging, followed by treatment with the indicated antibodies (Figure, top).

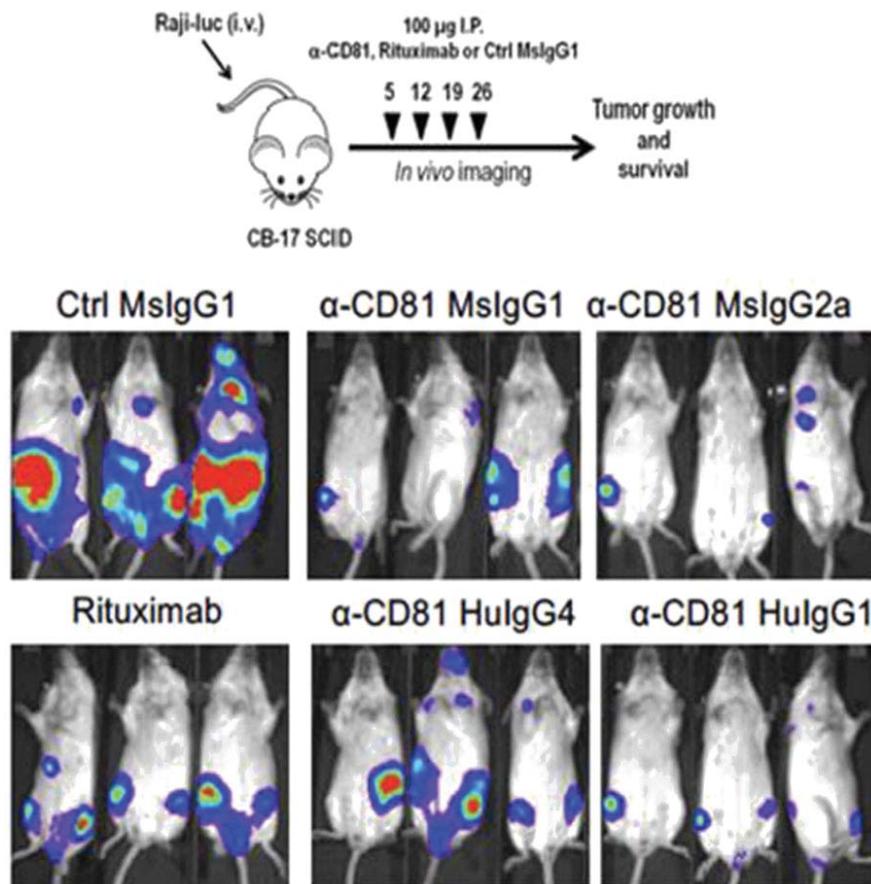
Results: The original mouse anti-human CD81 mAb, 5A6, is unique in its direct cytotoxic effect against B-cell lymphomas, other anti-CD81 mAbs do not share this ability. We compared the ability of 5A6 (ADCC^{LOW}) to Rituximab (ADCC^{HIGH}) to control growth of a lethal dose of Raji B-cell lymphoma in SCID mice. We found that 4 weekly injections of either antibody equally affected tumor

growth and increased survival by comparison to a control antibody. We then generated ADCC^{HIGH} versions of 5A6, mouse IgG2a and chimeric human IgG1 and compared their efficacy to Rituximab in vitro. Interestingly, while chimeric IgG1 5A6 and Rituximab mediated similar ADCC levels, both mouse IgG2a and chimeric IgG1 induced very high CDC levels, whereas mouse IgG1, chimeric IgG4 and Rituximab support low CDC levels. Next, we challenged SCID mice with Raji cells, followed by antibody injection on day 5 post-tumor challenge. Remarkably, chimeric IgG1 and mouse IgG2a controlled tumor growth better than Rituximab (Figure, bottom); moreover, survival was best extended to mice treated with the mouse IgG2a.

Rituximab depletes normal B cells in vivo; CD81 is also expressed on normal cells. To determine the relative CDC sensitivity of lymphoma cells to PBMCs, we mixed Raji B-cell lymphoma with PBMC at increasing ratios. We found that Raji cells were almost 90% sensitive to CDC-mediating anti-CD81 mAbs even when present at a 1000:1 ratio, whereas only 5–10% of normal PBMC were sensitive to anti-CD81 mAb.

Conclusions:- Endowing the anti-CD81 5A6 antibody with ADCC and CDC capabilities increases its in vivo efficacy in a xenograft model.- B-cell lymphoma cell lines are selectively sensitive to anti-CD81 therapy.- Safety and efficacy of targeting CD81 in immunocompetent human CD81 transgenic mice are in progress.

Keywords: B-cell lymphoma.



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A PHASE I STUDY OF UTOMILUMAB (PF-05082566), A 4-1BB/CD137 AGONIST, IN COMBINATION WITH RITUXIMAB IN PATIENTS WITH CD20⁺ NON-HODGKIN'S LYMPHOMA

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Introduction: 4-1BB (CD137, TNFRSF9) receptor agonists enhance cytotoxic T-cell and NK cell responses, including antibody (Ab)-dependent cellular cytotoxicity, and have shown antitumor activity in preclinical models. Utomilumab (Uto), a fully human IgG2 monoclonal Ab, binds to human 4-1BB with high affinity and specificity and activates 4-1BB while blocking binding to endogenous 4-1BB ligand. Initial findings from the dose-finding cohorts of this study were presented previously. We report here updated results and data from the expansion cohort in patients (pts) with rituximab (R)-refractory follicular lymphoma (FL).

Methods: The dose-finding component of this phase I study evaluated Uto at doses ranging from 0.03 to 10 mg/kg in combination with R at the standard 375 mg/m² dose in pts with relapsed or refractory CD20⁺ non-Hodgkin's lymphoma (NHL), using a time-to-event continuous-reassessment-method design. In the expansion cohort, pts with R-refractory FL received Uto at the 1.2 mg/kg dose level. Pts received Uto on day 1, every 4 weeks up to 24 months and R from day 7, weekly for 4 weeks. The primary endpoint was dose-limiting toxicity (DLT) in the first 2 cycles, with safety, pharmacokinetics, and antitumor activity as secondary endpoints, and pharmacodynamics as an exploratory endpoint.

Results: As of Nov 2016, 48 pts with CD20⁺ NHL including FL (*n* = 33), mantle cell (*n* = 6), diffuse large B cell (*n* = 3), marginal zone (*n* = 2), small lymphocytic (*n* = 2), and other (*n* = 2) lymphoma were treated with Uto combined with R. Approximately 50% of pts had received ≥3 prior anticancer therapies; 24/33 pts with FL had R-refractory disease. No DLTs were observed, and no pt discontinued treatment due to treatment-related adverse events (AEs). Of the 48 treated pts, 27% had grade ≥ 3 treatment-emergent AEs. The most common treatment-related AEs were fatigue (25%), infusion-related reaction (23%), and diarrhea (10%). Uto exposure appeared to increase with increasing

doses. One (2%) of 43 anti-drug Ab (ADA) evaluable pts had treatment-induced ADA/neutralizing Ab against Uto. The objective response rate (ORR) across all Uto dose levels tested was 23% (11/48). In all FL pts, the ORR was 27% (9/33) and 33% (8/24) in FL pts with R-refractory disease with 4 complete and 4 partial responses. In the expansion cohort of pts with R-refractory FL, the ORR was 44% (4/9). Pharmacodynamic effects of Uto, including increases in circulating CD8⁺ T cells and soluble 4-1BB, were observed at dose levels between 0.06 and 10 mg/kg. Enrollment into the expansion is ongoing.

Conclusions: The combination of Uto with R showed a highly favorable tolerability profile with no DLTs observed and no substantial hematologic, hepatic, or immune-related toxicity reported. The preliminary evidence of clinical activity observed in R-refractory FL pts supports further evaluation of Uto plus R, especially in pts requiring treatment regimens with reduced toxicity.

Keywords: B-cell lymphoma; non-Hodgkin lymphoma (NHL); rituximab.

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EXPRESSION OF LAG-3 DEFINES EXHAUSTION OF INTRATUMORAL PD-1⁺ T CELLS AND CORRELATES WITH POOR OUTCOME IN FOLLICULAR LYMPHOMA

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Exhausted T cells typically express PD-1, but expression of PD-1 is not limited to exhausted cells, and many PD-1 expressing cells are simply activated and exhibit appropriate immune function. In this study, we therefore sought to determine which PD-1⁺ T cells were truly exhausted. Although expected to be functionally suppressed, we found that the population of intratumoral PD-1⁺ T cells were predominantly responsible for production of cytokines and granules. This surprising finding prompted us to explore the involvement of other exhaustion markers including LAG-3 to specifically identify functionally exhausted T cells. We found that LAG-3 was expressed on a subset of intratumoral T cells from FL and LAG-3⁺ T cells almost exclusively came from the population of PD-1⁺ cells. CyTOF analysis revealed that intratumoral LAG-3⁺ T cells were phenotypically heterogeneous as LAG-3 was expressed on a variety of types of T-cell subsets. In contrast to PD-1⁺LAG-3⁻ cells, intratumoral PD-1⁺LAG-3⁺ T cells exhibited reduced capacity to produce cytokines (IL-2 and IFN-γ) and granules (perforin and granzyme B). LAG-3 expression could be substantially upregulated on CD4⁺ or CD8⁺ T cells by IL-12, a cytokine that has been shown to induce T-cell exhaustion and be increased in the serum of lymphoma patients. Furthermore, we found that blockade of both PD-1 and LAG-3 signaling enhanced the function of intratumoral CD8⁺ T cells resulting in increased IFN-γ and IL-2 production. Clinically, LAG-3 expression on intratumoral T cells correlated with a poor outcome in FL patients. Taken together, we find that LAG-3 expression is necessary to identify the population of

intratumoral PD-1⁺ T cells that are functionally exhausted and, in contrast, find that PD-1⁺LAG-3⁻ T cells are simply activated cells that are immunologically functional. These findings may have important implications for immune checkpoint therapy in FL.

Keywords: follicular lymphoma (FL); immunosuppression; T-cells.

269 A DUAL TARGETING CAR-T CELL APPROACH FOR THE TREATMENT OF B CELL MALIGNANCIES

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Introduction: Chimeric Antigen Receptors (CARs) are artificial T-cell receptors which graft an antibody-like specificity onto a T cell. CAR T-cell therapies directed against CD19 have shown activity against several B-cell malignancies including chemo-refractory disease, and, for a proportion of patients, clinical responses are sustained. More recently, CAR T cells directed against CD22 have also shown activity against B-cell ALL (B-ALL). An emerging limitation of current CAR T-cell therapy for B-cell cancers is relapse due to target antigen down-regulation or loss. We describe a CAR T strategy which simultaneously targets both CD19 and CD22 and thereby may reduce relapse caused by antigen escape.

Methods: We constructed a bicistronic retroviral vector encoding both an anti-CD19 CAR and an anti-CD22 CAR. Co-expression was achieved by a self-cleaving viral 2A peptide sequence. The antigen binding domains of both CARs were humanized to minimize immune rejection. Each CAR was optimized for maximal activity and included an OX40 co-stimulatory domain or a 41BB co-stimulatory domain in addition to a CD3 zeta activating domain. We enhanced the performance of the CD22 CAR by incorporating a novel pentameric spacer domain derived from the collagen oligomeric matrix protein. Standard in vitro and in vivo functional assays were performed.

Results: Binding kinetics of humanized binding domains were within 0.76 nM for CD19 and 6 nM for CD22 of parental mAb. Independent expression of both CARs was demonstrated on the surface of T cells by staining with recombinant soluble CD19 and CD22. T cells expressing this dual CAR displayed cytotoxicity towards Raji cells expressing both CD19 and CD22 and the CD19-knockout variant with comparable efficacy. In addition, this dual CAR could stimulate cytokine release (interferon- γ and IL2) and T cell proliferation in response to CD19 and CD22 or to CD22 alone. CAR T cells were tested against Raji cell xenograft in an NSG mouse model.

Conclusion: We have designed, tested and optimised a humanised dual anti-CD19/anti-CD22 CAR cassette which directs T cell responses against target cells expressing either or both CD19 and CD22. This construct will soon be tested in a phase I clinical trials for the treatment of relapsed/refractory adult and paediatric ALL and DLBCL.

Keywords: immune system.

270 LOW LEVELS OF IMMUNO-SUPPRESSOR CELLS PROMOTE RESPONSES TO A HAPLOIDENTICAL NATURAL KILLER CELL THERAPY AND INDUCE REMISSIONS IN NON-HODGKIN LYMPHOMA

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Introduction: Patients with chemotherapy refractory non-Hodgkin lymphoma (NHL) have poor prognosis. Recent advances in cellular therapies and immunotherapies suggest that targeting tumor with an activated immune system overcomes chemo-resistance, and early clinical experience with these approaches has yielded remarkable therapeutic success.

Methods: We report a novel phase 2 clinical trial in patients with poor prognosis refractory non-Hodgkin lymphoma testing the efficacy of haploidentical donor NK cell therapy (NK dose $1.5-8 \times 10^7$ NK cells/kg) with rituximab and IL-2. The primary objective was overall response rate at 2 months by PET imaging. Secondary objectives were safety and tolerability, in vivo expansion of allogeneic NK cells and predictors of response.

Results: The cellular product was infused with a median total nuclear cell (TNC) dose of 4.3×10^7 /kg (range 1.9–7.7) and contained 40.2% NK cells (median; range 12–88%). Therapy was tolerated without cytokine release syndrome, neurotoxicity graft-versus-host-disease. Of 14 (of 16 treated) evaluable patients, 4 had objective responses (28%) at 2 months: 2 had complete response lasting 3 and 9 months. Circulating donor NK cells persisted for at least 7 days after infusion with 0.5–90% of donor-specific NK cells. Responding patients (R) had markedly lower levels of circulating host derived Tregs (17 ± 4 vs. 307 ± 152 cells/ μ L; $p = 0.008$; Figure) and myeloid derived suppressor cells (MDSC) at baseline ($6.6\% \pm 1.4\%$ vs. $13\% \pm 2.7\%$; $p = 0.06$; Figure) than non-responding patients (NR). Lower circulating Tregs correlated with low serum levels of IL-10 (R 2 0.64; $p = 0.003$; $n = 11$), suggestive of an attenuated immuno-suppressive milieu. Higher levels of PD-1 and TIGIT on host T cells before and after therapy were associated with lack of response. Endogenous IL-15 levels were higher in responders than non-responding patients at the day of NK cell infusion (30 ± 8 4 vs. 19 ± 4 pg/ml; $p = 0.0201$) and at day 14 (10 ± 6 vs. 45 ± 2 pg/ml; $p = 0.01$) and correlated with NK cytotoxicity as measured by expression of CD107a (R 2 = 0.74; $p = 0.0006$; $n = 5$).

Conclusion: In summary, our observations support development of donor NK cellular therapies for advanced NHL as a strategy to overcome chemoresistance. Therapeutic efficacy may be further improved through disruption of the immunosuppressive environment and infusion of exogenous IL-15. (clinicaltrials.gov NCT01181258).

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

271 A PHASE I STUDY OF CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELLS DIRECTED AGAINST CD19 IN PATIENTS WITH RELAPSED OR REFRACTORY CD19(+) B CELL LYMPHOMAS: INTERIM ANALYSIS

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Introduction: Patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) have poor outcomes with currently available strategies. Based on the promising results seen in patients treated with anti-CD19 CAR T-cell therapy in R/R B-NHL, we initiated the phase I study evaluating the safety and efficacy in patients with R/R B-NHL (NCT02842138). Autologous T cells were genetically modified to express a chimeric antigen receptor consisting of an anti-CD19-scFv domain with CD3 ζ and 4-1BB signaling domains.

Methods: Patients received CAR T-cell infusion after a conditioning regimen of cyclophosphamide (250 mg/m²) and fludarabine (25 mg/m²) daily for 3 days. Three CAR T cell doses were tested: 5 \times 10⁴, 1 \times 10⁵, and 1 \times 10⁶ CAR T cells/kg, respectively. Primary endpoints include safety and pharmacokinetics (PK) of CAR T cells. Secondary endpoints include complete and overall response (CR, OR) rates and duration of response (DOR) per International Working Group Criteria (Cheson, J Clin Oncol 2007).

Results: As of March 2017, 14 patients were enrolled, 10 patients underwent response evaluation. Median age of the 10 evaluable patients was 37 years (range 24–68), 4 females and 6 males, 3 follicular lymphoma (FL) and 7 diffuse large B-cell lymphoma (DLBCL). Median number of prior therapies was 2.5 (range 2–7). The first group of three patients (2 FL and 1 DLBCL) received 5 \times 10⁴ CAR T cells/kg. Two FL patients achieved partial remission (PR) on day 28, and one of the patients achieved complete remission (CR) 3 months later. The second group of three patients (1 FL and 2 DLBCL) received 1 \times 10⁵ CAR T cells/kg. The FL patient achieved PR on day 28. The last group of four patients (all were diagnosed with DLBCL) received 1 \times 10⁶ CAR T cells/kg. Three patients achieved PR on day 28 (75%). One patient attained PD on day 28 and died 10 days later due to disease progression. A significant CAR T-cell expansion was detected in this case. On day 26, 26.8% of her PBMC were CAR T cells. Interestingly, PD1 expression was significant in her expanded CAR T cells. Approximately 78.3% of CD8+ CAR T cells and 71.4% of CD4+ CAR T cells expressed

PD1 on day 26, as compared to 22% and 42% on day 13, respectively. Increased PD1-expressing CAR T cells were also found in other patients' peripheral blood. No serious adverse event (sAE) was observed in all patients. Two patients experienced mild fever (grade 1–2). In vivo expansion of CAR T cells was detected in all patients between day 14 and 28. All responding patients are still in remission at the last follow-up (Range: 2.5–9 months).

Conclusions: This study demonstrated early promising activity of anti-CD19 CAR T cells in patients with R/R B-NHL. The toxicities of CRS were mild and manageable. Our study also provided the first clinical evidence that expanded CAR T cells could express PD1. Blocking PD1 pathway may enhance the effector function of CAR T cells and improve the clinical outcomes of CAR T-cell therapy.

Keywords: B-cell lymphoma; CD19; immune system.

272 PRODUCT CHARACTERISTICS ASSOCIATED WITH IN VIVO EXPANSION OF ANTI-CD19 CAR T CELLS IN PATIENTS TREATED WITH AXICABTAGENE CILOLEUCEL (AXI-CEL)

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Introduction: Axi-cel (formerly KTE-C19) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy. ZUMA-1 is a multicenter, registrational trial of axi-cel in patients with refractory aggressive non-Hodgkin lymphoma. In a prespecified interim analysis, ZUMA-1 met its primary endpoint, with a 76% objective response rate and a 47% complete response rate (Blood 2016;128:LBA-6). Post-treatment CAR T-cell blood levels were associated with objective response. Here, we describe novel associations between product characteristics and CAR T-cell levels in patients.

Methods: CAR T-cell characteristics in axi-cel produced from 62 patients were analyzed by flow cytometry and modeled against CAR T cell levels. *In vivo* CAR T-cell levels were measured by qPCR. T-cell expansion during production (fold expansion/total days in culture) was compared with CAR T cell blood levels, using a partition analysis with expansion rates of ≥ 1 vs < 1 . Wilcoxon 2-sample test and linear regression were used.

Results: Axi-cel contained CCR7+ T cells (median, 42%; range, 15–73%), with naïve (CD45RA+/CCR7+; median, 12%; range, 1–57%), central memory (CD45RA-/CCR7+; median, 29%; range, 12–49%) phenotypes, and more differentiated CCR7- effector memory and effector T cells. On infusion, CAR T cells expanded rapidly, reaching peak levels within 2 weeks (median, 43 cells/ μ L; range, 1–1513), and were also measurable in all patients at 1 month (median, 2 cells/ μ L; range, 0.03–89). The CCR7+/CCR7- T cell ratio in axi-cel associated positively with peak ($P = 0.001$) and cumulative ($P = 0.003$) CAR T-cell levels through 1 month. More rapid expansion of axi-cel lots during production (≥ 1.0 -fold/d; $n = 18/62$) was associated with higher cumulative levels of CAR T cells ($P = 0.03$). Other product characteristics, eg, CD4/CD8 ratio or number of infused T cells, were not significantly associated with CAR T cell blood levels.

Conclusions: An association was observed between CAR T-cell expansion *in vivo* and both the T-cell growth rate during production and product cell phenotype pretreatment. A key attribute of axi-cel product was the presence of CCR7+ naïve/central memory T cells, without upfront T-cell subset selection.

*Drs. Neelapu and Locke contributed equally to this work.

Keywords: CD19; non-Hodgkin lymphoma (NHL); T-cells.

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SAFETY AND CLINICAL ACTIVITY OF RP6530, A DUAL PI3K δ / γ INHIBITOR, IN PATIENTS WITH ADVANCED HEMATOLOGIC MALIGNANCIES: FINAL ANALYSIS OF A PHASE 1 MULTI-CENTER STUDY

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Background: RP6530 is a novel, next generation, highly specific dual PI3K δ / γ inhibitor with nano-molar inhibitory potency. Preliminary results demonstrated acceptable safety profile and anti-tumour activity in patients (pts) with advanced hematologic malignancies (ASH 2015). Herein, we present the final analysis from a Phase 1 study of RP6530 (NCT02017613).

Methods: A standard 3 + 3 dose escalation design was implemented. Pts with relapsed or refractory hematologic malignancies having ECOG performance status (PS) ≤ 2 , measurable/evaluable disease, and life expectancy of at least 12 weeks were eligible. Primary endpoints included assessment of DLTs, determination of MTD. RP6530 was given orally twice/three times a day in 28-day cycles. Fine immunomonitoring of lymphocyte populations and subsets was performed on thawed peripheral blood cells.

Results: From Dec 2013 to May 2016, 35 pts (63% males) with median age of 54 years (range 20–83 years) were enrolled across various dose levels (25–1200 mg BID and 600–800 mg TID). Pts were heavily pretreated and the median number of prior therapy was 6 (range 1–13)] with 26 (74.2%) pts being refractory to the last treatment regimen. The ECOG PS was ≤ 1 in 32 cases. The median number of treatment cycles was 2.5 (range, 0.26–19 cycles). There was no DLT. Majority of AEs were mild and resolved either spontaneously or with concomitant medications. Except three Grade 3 events [hypertriglyceridemia ($n = 1$), neutropenia ($n = 2$)], no other grade 3–5 AEs or SAEs were deemed related to RP6530. There was no withdrawal or dose reduction due to related events. Activity of study drug was noticed at ≥ 200 mg BID. The ORR was 19% (95% CI: 7–36%); 2 CR (6%) and 4 PR (13%). Responding pts included HL ($n = 4$), PTCL ($n = 1$) and DLBCL ($n = 1$). Interestingly, HL pts ($n = 15$) showed an ORR of 29% with median DoR of 8 months (range 2–14). Clinical responses (CR/PR) were associated with a progressive reduction in pAKT expression in circulating lymphocytes as early as 2 hours after the first dose. PK indicated a dose-proportional increase in plasma concentrations. We identified dose-independent leukocyte dynamics in the peripheral blood of pts that were associated with response to treatment. Pts with CR or PR displayed a decrease in circulating CD4+ conventional and regulatory T cells as well as B cells, but not CD8+ T or NK cells at 2 months after treatment.

Conclusions: RP6530 demonstrated an acceptable safety with no DLT and a promising clinical activity in pts with advanced, heavily pretreated relapsed/refractory hematologic malignancies. Clinical activity was manifested by a significant reduction in peripheral blood cell pAKT expression levels. Decrease in conventional and regulatory CD4+ T cells and B cells was associated with response. RP6530 is an attractive therapeutic option in combination with targeted agents. Phase II study in NHL pts is ongoing at an optimal dose.

Keywords: classical Hodgkin lymphoma (cHL); non-Hodgkin lymphoma (NHL); PI3K/AKT/mTOR.

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A PHASE 1 STUDY OF BET INHIBITION USING RG6146 IN RELAPSED/REFRACTORY (R/R) MYC-EXPRESSING DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)

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Introduction: Bromodomain and extraterminal (BET) proteins are transcription cofactors that participate in several oncogenic processes in DLBCL, including MYC regulation. BET inhibitors (BETi) have demonstrated activity in DLBCL preclinically, in part by disrupting BET binding to super-enhancer sites of several cell-essential genes, including MYC. BET inhibition may therefore be a therapeutic strategy in DLBCL, including MYC-expressing disease. RG6146 is a novel, noncovalent subcutaneous (sc) BETi in early clinical development. We report safety, pharmacokinetics (PK), pharmacodynamics (PD),

Summary of key RG6146 PK and PD parameters following 0.45mg/kg QD dosing

Endpoints Day Parameter	PK					PD (CD11b) 15		
	1		15			Predose % Change from baseline	2 h	4 h
	C _{max} ng/mL	AUC _{24h} ngh/mL	C _{trough} ng/mL	C _{max} ng/mL	AUC _{24h} ngh/mL			
N	15	15	10	10	10	12	12	12
Mean	986	4246	145	1333	8862	(44)	(43)	(43)
SD	328	1099	35	516	1368	22	23	26
CV (%)	33	26	24	39	15	49	54	61

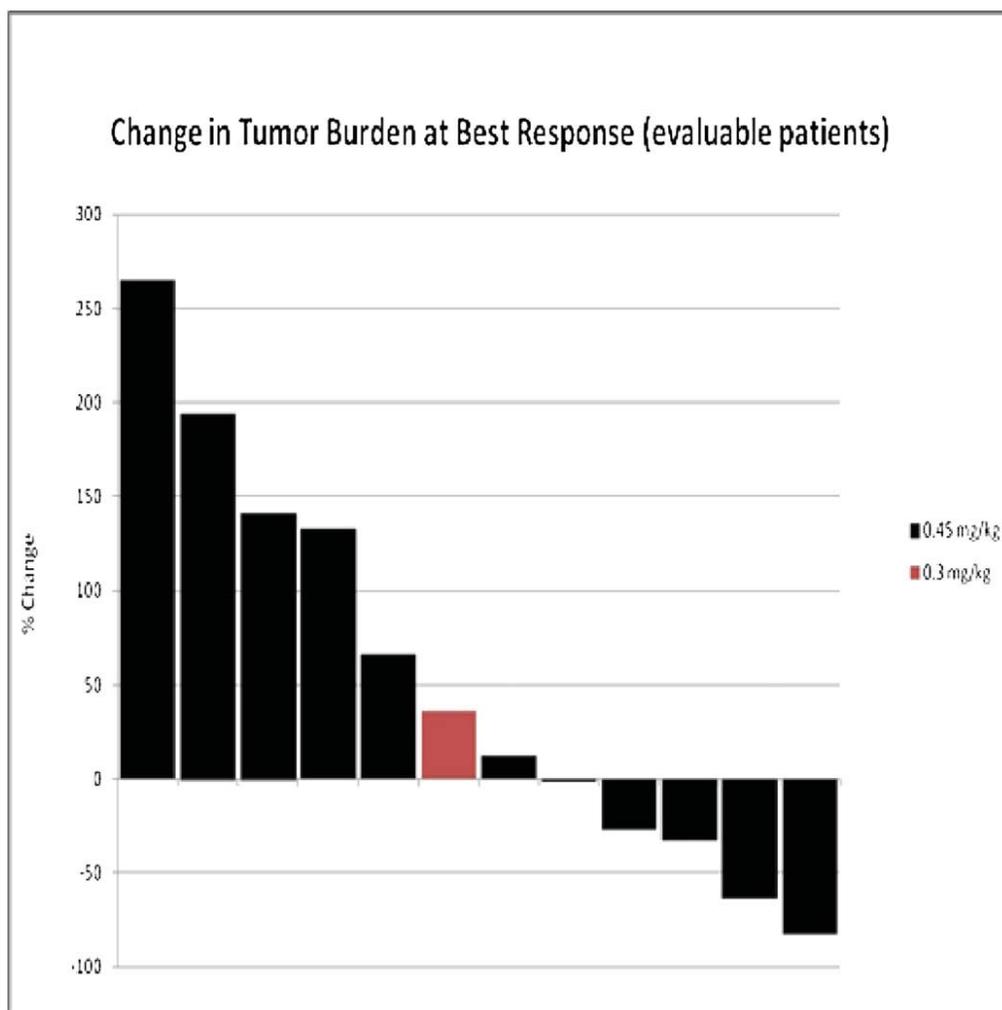


Figure 1 Summary of Response Data

and preliminary clinical response data for a cohort of DLBCL patients enrolled within a larger phase I study (NCT01967362).

Methods: DLBCL patients with R/R disease after ≥ 2 lines of therapy and abnormal MYC expression (IHC or FISH) were eligible. RG6146 was given as 0.3 or 0.45 mg/kg daily sc on either 3 of 4 or 2 of 3 week schedules. Disease assessment followed the Lugano criteria. CD11b expression on monocytes was assessed as a PD biomarker by flow cytometry.

Results: A total of 19 patients received RG6146 sc 0.30 mg/kg \times 21d q4wks ($n = 2$), 0.45 mg/kg \times 21d q4wks ($n = 2$), or 0.45 mg/kg \times 14d q3wks ($n = 15$). Median age was 67 years (range 49–82); median number of prior treatments was 3 (range 2–6). Grade (G) 3/4 treatment-related toxicities included thrombocytopenia ($n = 2$, both G4), neutropenia ($n = 1$, G4), fatigue ($n = 1$, G3), hyperglycemia ($n = 1$, G4), hyperbilirubinemia ($n = 1$, G3), and hyperuricemia ($n = 1$, G3). At 0.45 mg/kg \times 14d q3wks, 2 patients had objective PR. Seven patients came off study for disease progression within the first cycle. The intent to treat ORR was 11%, and 17% in the evaluable population (Figure 1). PK measurements showed that RG6146 half-life was approximately 10 hr with low-to-moderate variability for C_{max} and AUC (Table). CD11b expression showed $\sim 50\%$ reduction by day 15; SD or PR patients displayed significant reductions, with greatest decrease $\sim 70\%$.

Conclusions: RG6146 has an acceptable safety profile in patients with R/R MYC-expressing DLBCL. Its ability to down-regulate CD11b on monocytes supports the putative mechanism of action that RG6146 prevents BET co-activator loading at super-enhancers, and may provide a PD marker to guide dose and schedule optimization. RG6146 can induce objective responses and tumor shrinkage in chemorefractory patients, suggesting disruption of super-enhancer loading of BETs with RG6146 may be a viable therapeutic strategy in DLBCL. Combination studies are planned.

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

single-agent activity in r/r DLBCL, predominately of the non-germinal center (non-GCB) phenotype. This phase I study is the first to evaluate the combination of ibrutinib with rituximab, ifosfamide, carboplatin and etoposide (R-ICE) in ASCT-eligible r/r DLBCL patients.

Methods: Patients with r/r DLBCL are eligible for study. The phase I study design is a standard 3×3 dose escalation of ibrutinib at 420 mg (dose level [DL] #1), 560 mg (DL #2) and 840 mg (DL #3) on days 1–21 with standard dosing of R-ICE for 3 cycles, every 21 days. The primary objective is to determine the safety of ibrutinib + R-ICE. Secondary objectives include response according to Deauville (D) criteria.

Results: Twenty patients have enrolled: 19 patients are evaluable for toxicity, and 18 are evaluable for response. The median age is 62 years (range 19–75 years). Histologies include: GCB DLBCL $n = 3$, non-GCB DLBCL $n = 7$, primary mediastinal large B-cell lymphoma $n = 4$ and transformed small lymphocytic lymphoma (tCLL/SLL) $n = 5$. Seventeen patients had primary refractory or relapsed DLBCL < 12 months from initial diagnosis. There were no dose-limiting toxicities (DLTs) seen at DL #1 ($n = 3$), 2 ($n = 3$), or 3 ($n = 13$). The majority of patients (18/19) experienced transient grade 3 or 4 hematologic toxicities with hematopoietic recovery prior to each cycle. One patient had grade 3 atrial fibrillation and was removed from study. Fourteen of the 18 patients evaluable for response underwent R-ICE-primed CD34+ hematopoietic progenitor cells (HPCs) apheresis procedures on study; 13 successfully collected HPCs with a median of 5.5×10^6 CD34+/kg (range 1.7–8.6). One HIV+ patient failed to collect HPCs in the setting of febrile illness. Four patients were intended to proceed to allogeneic transplant. Of the 18 patients evaluable for response, $n = 9$ achieved complete metabolic remission (CMR, D1-3), $n = 7$ achieved partial remission (PR, D4), and $n = 2$ had stable disease (SD) for an overall response rate of 89%. Excluding the patient removed from study for toxicity, 6/6 patients (100%) with non-GCB phenotype disease achieved a CMR. At a median follow-up for survivors of

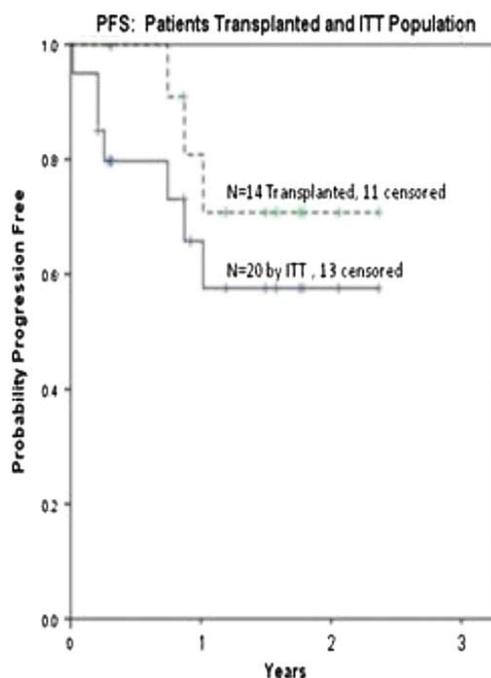
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A PHASE I STUDY OF IBRUTINIB COMBINED WITH RITUXIMAB, IFOSFAMIDE, CARBOPLATIN, AND ETOPOSIDE IN PATIENTS WITH RELAPSED OR PRIMARY REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Background: In the post-rituximab era, half the patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) are ineligible for autologous stem cell transplantation (ASCT) secondary to unresponsive disease. The Bruton's tyrosine kinase inhibitor ibrutinib has



16 months, the 1-year PFS in transplanted patients and by intent-to-treat (ITT) is 71% and 57%, respectively (Figure 1).

Conclusion: Ibrutinib dosed at 840 mg daily in combination with R-ICE is well tolerated and enables HPC collection. Encouragingly, 89% of patients achieved a response; including 100% CMR in patients with non-GCB phenotype disease. These results compare favorably to historic cohorts. Later phase studies for this treatment program are warranted, particularly for r/r non-GCB patients.

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

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PRELIMINARY RESULTS OF A PHASE 1B STUDY OF TIRABRUTINIB (GS-4059/ONO-4059) IN COMBINATION WITH ENTOSPLETINIB IN PATIENTS WITH B-CELL MALIGNANCIES

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Introduction: Tirabrutinib (GS-4059/ONO-4059) selectively and irreversibly inhibits Bruton's tyrosine kinase (BTK) and entospletinib selectively inhibits spleen tyrosine kinase (SYK).

Methods: This ongoing phase 1b study is evaluating the safety and tolerability of tirabrutinib combined with entospletinib in patients with previously treated CLL, FL, SLL, MCL, MZL, WM, or non-GCB DLBCL. The study design uses 3 + 3 dose escalation (Table) with expansion cohorts at potential phase 2 doses.

Results: With a median duration of treatment of 22 weeks (range 3–56), 26/32 enrolled patients continue on treatment. The median age was 70 (43–85) years and 59% were men. Patients had the following

diseases: CLL (n = 9), non-GCB DLBCL (7), FL (6), WM (5), MCL (2), SLL (2), and MZL (1). The median number of prior therapies was 2 (1–5). Five patients discontinued all study treatment, 4 due to disease progression (DLBCL × 2, MCL, MZL) and one due to withdrawal of consent. There has been 1 death on study (due to progressive disease). The maximum tolerated dose was not reached. Approximately 90% of patients treated reported a treatment-emergent AE (TEAE) of which 48% were grade ≥ 3. Grade ≥ 3 TEAEs that were present in more than 1 patient were neutropenia (4), anemia, thrombocytopenia, pneumonia and AST/ALT elevation (2 each). The TEAEs present in >10% of patients were fatigue (7), petechiae (5), asthenia, constipation, contusion, dyspepsia, neutropenia and rash (4 each). No patients discontinued treatment due to AEs and all 5 patients with interruption of treatment for an AE successfully re-initiated therapy. A total of 17 patients were evaluable for best overall response with the results as follows: 11 with partial responses (2 each with CLL, DLBCL, FL, SLL, WM, 1 with MCL); 4 with stable disease; 2 with progressive disease.

Conclusions: Tirabrutinib (GS-4059/ONO-4059) at up to 160 mg in combination with entospletinib up to 400 mg daily was safe and well tolerated, supporting the continued clinical evaluation of the combination for the treatment of B-cell malignancies. Clinical trial information: NCT02457598.

Keywords: B-cell lymphoma; BTK; SYK.

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COMBINATION OF TGR-1202, UBLITUXIMAB, AND BENDAMUSTINE IS SAFE AND HIGHLY ACTIVE IN PATIENTS WITH ADVANCED DLBCL AND FOLLICULAR LYMPHOMA.

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Introduction: TGR-1202 is a next generation, once daily, PI3Kδ inhibitor, active in patients (pts) with rel/ref hematologic malignancies that has demonstrated a notably differentiated safety profile, including in long-term follow-up (Burris, 2016). Ublituximab (UTX)

TABLE Dose Escalation Cohorts

Dose Level	tirabrutinib		n	entospletinib		n
	A			B		
1	40 QD	200 QD	3	-	-	
2	80 QD	200 QD	6	40 QD	400 QD	3
3	150 QD	200 QD	3	80 QD	400 QD	15
4				160 QD	400 QD	2

is a novel glycoengineered mAb targeting a unique epitope on the CD20 antigen. Bendamustine (Benda) is an active chemotherapy agent in pts with lymphoma. The combination of UTX + TGR-1202 is tolerable and active in pts with rel/ref hematologic malignancies and is under Phase 3 testing for pts with CLL and under Phase 2b testing for pts with DLBCL. This Phase 1 trial evaluates the safety and efficacy of UTX + TGR-1202 + Benda in pts with advanced diffuse large B-cell lymphoma (DLBCL) and Follicular Lymphoma (FL).

Methods: Eligible pts had rel/ref DLBCL or FL with an ECOG PS \leq 2 w/o limit to number of prior therapies. ANC of \geq 750 and Platelets \geq 50,000 was permitted. Pts refractory to prior PI3K δ , Benda, or anti-CD20 therapy were eligible. UTX was dosed on Days 1, 8, 15 of Cycle 1, Day 1 of Cycle 2–6, followed by Cycle 9 and 12. TGR-1202 was started at 800 mg QD with a –1 dose reduction cohort at 600 mg if not tolerated in \geq 2/6 pts. Benda was dosed at 90 mg/m² on Days 1 and 2 of Cycles 1–6 only. Primary endpoints included safety and efficacy (Cheson 2007).

Results: Twenty-three pts were evaluable for safety: 15 diffuse large B-cell (DLBCL) and 8 follicular (FL). Med age 68 yo (range 31–81); 12 M/11 F; median prior treatment regimens = 2 (range 1–6); 12 pts (52%) were refractory to their immediate prior treatment and to prior CD20 therapy, and 7 pts had progressed post-transplant. ECOG PS 0/1/2 (3/18/2). Initially, 2/4 pts at 800 mg TGR-1202 experienced AE's in Cycle 1 that led to treatment interruption (rash, neutropenia); thus, the 600 mg dose of TGR-1202 was explored. No additional Cycle 1 treatment delays were reported at the 600-mg dose level, which was later expanded, and the 800-mg TGR-1202 dose is now being evaluated with stricter eligibility criteria to require an ANC of \geq 1.0, and the use of growth factor support in cycle 1 is now encouraged. The most common AE's included diarrhea (39%; G3/4 4%), decreased appetite (35%; G3/4 4%), nausea (30%; G3/4 4%), asthenia (26%; G3/4 4%) and neutropenia (22%). The only Grade 3/4 AE reported in >10% of pts was neutropenia (22%). Two pts had a TGR-1202 dose reduction. Nineteen pts (11 DLBCL/8 FL) were evaluable for efficacy: ORR amongst all pts was 79% (15/19) with 42% (8/19) achieving a complete response (CR), of which 5 were DLBCL and 3 FL. ORR in the respective groups is as follows:

Group	N	ORR (%)	CR N (%)	PR N (%)	SD N (%)
DLBCL	11	73%	5 (45%)	3 (27%)	1 (9%)
FL	8	88%	3 (38%)	4 (50%)	-

Median follow-up time on study is 6 mos for all pts (range 1–14+ mos).

Conclusions: The combination of UTX, TGR-1202, and bendamustine has exhibited manageable toxicity with significant activity in advanced DLBCL and FL pts including an encouraging 42% CR rate (45% in DLBCL and 38% in FL). Enrollment continues at the 800-mg TGR-1202 dose level with the use of growth factor prophylaxis. Safety and efficacy data for all pts will be updated at the meeting. Based upon the early activity of the triplet, future registration directed studies are being planned.

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

278 LENALIDOMIDE AND OBINUTUZUMAB WITH CHOP FOR NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA: PHASE I/II RESULTS

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Introduction: Standard initial therapy for diffuse large B-cell Lymphoma (DLBCL) is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) which cures ~65% of patients. Obinutuzumab (O) is a CD20 monoclonal antibody with increased antibody dependent cell-mediated cytotoxicity in comparison with rituximab. Lenalidomide (L) is toxic to DLBCL via interferon signaling and immunomodulation. The GOYA study found RCHOP was as effective as OCHOP in patients with unselected newly diagnosed DLBCL. We hypothesize the combination of OLCHOP will be well tolerated and have a complete response (CR) rate \geq to OCHOP (57% in GOYA trial, Vitolo et al., ASH 2016). We performed a phase Ib/II study of OLCHOP in patients with newly diagnosed DLBCL to assess the safety and efficacy of this combination.

Methods: Patients with newly diagnosed, CD20+ DLBCL were eligible if they have measurable disease, age \geq 18 years, and adequate organ function. In the Phase Ib trial, Obinutuzumab was dosed at 1000 mg IV days 1, 8, and 15 during cycle 1, and day 1 on cycles 2–6. CHOP was dosed in a standard fashion. The initial cohort in Phase Ib (PhIb) tested the safety of lenalidomide dose at 15 mg daily days 1–14 cycles 1–6, with lower dose cohorts only if dose limiting toxicities (DLT) occurred in the first cycle. An additional 44 patients were enrolled in Phase II (PhII) at the maximum tolerated dose (MTD). The primary objectives of this phase Ib/II trial were to determine the MTD and efficacy of LOCHOP. Correlative studies, including minimal residual disease, cell of origin determination, and immune profiling are planned on blood and tumor samples.

Results: In the six patients treated in PhIb, no DLT were identified at lenalidomide dose 15 mg. An additional 44 patients were enrolled in PhII, and as of 3/15/17 all are evaluable for safety and 33 for efficacy with an end of therapy assessment. The median age was 62.5 years (26–83), with 44% males and a median IPI of 2 and NCCN IPI of 2.5. Five patients had double hit DLBCL, 5 patients had Double Expressor DLBCL, and 24 patients had non-GCB DLBCL. Common toxicities encountered in PhIb include neutropenia (Grade 3: 50%, Grade 4: 33%), thrombocytopenia (grade 3: 17%), and rash (grade 2: 17%), with similar findings in PhII. All six patients in PhIb achieved a CR. In the PhII trial, of 27 patients with response data available at submission, 25 have a CR, 1 has a partial response, and 1 has progression. In the combined evaluable patients, the overall response rate is 97%, with CR rate of 94%.

Conclusions: The combination of OLCHOP is well tolerated, with no DLT encountered in the PhIb trial, and impressive efficacy in this single center single arm Phase Ib/II trial. Adverse events do not appear to be

different than expected with standard RCHOP. Results from additional patients will be presented at the ICML meeting.

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

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ONGOING PHASE 1/2 STUDY OF INCB050465, A SELECTIVE PI3Kδ INHIBITOR, FOR THE TREATMENT OF PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) B-CELL MALIGNANCIES (CITADEL-101)

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Introduction: INCB050465 is a potent, selective PI3Kδ inhibitor (≥19,000-fold selectivity for PI3Kδ vs other isoforms), which has demonstrated linear pharmacokinetics (PK) and achieved exposure levels several-fold greater than the IC₉₀ for PI3Kδ inhibition at the recommended phase 2 dose (ASH 2016; Abstract 4195). Here, we report emerging safety and efficacy results from pts receiving INCB050465 monotherapy for r/r B-cell malignancies in an ongoing phase 1/2 study (NCT02018861).

Methods: Eligible pts (≥18 y) had ECOG PS ≤2 (≤1 during dose escalation), normal liver and kidney function, and no autologous HSCT within 3 months or allogeneic HSCT within 6 months of screening. The protocol was initiated with a single-pt cohort, treated with oral INCB050465 5 mg QD. Subsequent cohorts used a 3 + 3 design and evaluated doses of 10–45 mg QD. Based on PK/PD, the 20 and 30 mg QD cohorts were expanded. Responses were assessed Q9W using Lugano Classification or International Working Group on Chronic Lymphocytic Lymphoma (CLL) criteria.

Results: As of the data cut-off (Nov 1, 2016), 52 pts were treated (median age, 65 y [range, 30–88]; disease subtypes: diffuse large B-cell lymphoma [DLBCL; n = 14], follicular lymphoma [FL; n = 10], Hodgkin lymphoma [HL; n = 9], marginal zone lymphoma [MZL; n = 8], CLL [n = 6], mantle cell lymphoma [MCL; n = 5]). Approximately 62% of

pts had ≥3 prior systemic regimens; 31% had prior HSCT. Median duration of therapy was 3.3 months (range, 0.6–13.4); no DLTs were identified. Approximately 67% of pts discontinued therapy, most commonly for disease progression (31%) and AEs (25%). Approximately 33% of pts had dose interruption; 4% had reduction. Most common nonhematologic AEs (all grade [Gr]; Gr ≥3) were nausea (38%; 0%), diarrhea (31%; 6%), and vomiting (25%; 0%). Gr ≥3 hematologic AEs included neutropenia (21%), lymphopenia (17%), thrombocytopenia (10%), and anemia (4%). Approximately 40% of pts had serious AEs, most frequently colitis, diarrhea, and hypotension (all n = 3). A total of 1 pt had Gr 3 pneumonitis; none had *Pneumocystis jirovecii* pneumonia (PJP) or Gr ≥2 elevated transaminase. Objective responses (OR) occurred at all doses (Table), except 5 mg QD; 90% of the ORs were observed at the 9-week disease assessment.

Conclusion: INCB050465 demonstrated manageable toxicities with no clinically meaningful transaminitis or PJP. OR rates were generally high and most responses (90%) were observed at the 9-week disease assessment. Different dosing regimens/schedules, long-term safety, and disease-specific cohorts are being evaluated.

	N ^a	Objective Response, n (%)	Complete Response, ^b n	Partial Response, ^b n
NHL	31	19 (61)	10	9
DLBCL	14	5 (36)	3	2
FL	9	7 (78)	2	5
MZL	4	4 (100)	2	2
MCL	4 ^c	3 (75)	3	0
CLL	6 ^c	2 (33)	0	2
HL	8	1 (13)	0	1

^a7 pts were not evaluable for response because they had not reached a postbaseline assessment as of the data cutoff date.

^bRadiologic/metabolic.

^c1 patient with MCL and 3 with CLL had previously received ibrutinib; among these 4 pts, 1 objective response (partial response in CLL) was observed in this study.

Keywords: B-cell lymphoma; non-Hodgkin lymphoma (NHL); PI3K/AKT/mTOR.

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THE IMMUNOLOGIC DOUBLET OF LENALIDOMIDE PLUS OBINUTUZUMAB IS HIGHLY ACTIVE IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA, RESULTS OF A PHASE I/II STUDY

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Introduction: Relapsed follicular lymphoma (FL) remains a challenge and salvage regimens are associated with toxicity and limited control. Clinical outcomes are linked to dynamic changes in the immune micro-environment and novel immune-based approaches such as

lenalidomide and rituximab are highly active in both frontline and relapsed disease. Obinutuzumab has increased antibody dependent cellular cytotoxicity (ADCC) compared to rituximab in preclinical models and is approved for FL. We hypothesized that the immunologic properties of obinutuzumab and lenalidomide would be synergistic in relapsed FL. The study's objectives were to determine the MTD of lenalidomide with obinutuzumab and describe the efficacy of the combination.

Methods: This open label phase I/II study enrolled relapsed/refractory Gr 1–3a FL. Exclusions included transformation, prior malignancy, and infection. Lenalidomide was given on D 2–22 with 1000 mg obinutuzumab on D1, 8, 15, and 22 of cycle 1 and monthly on D 1 for up to 12 cycles. Extended dosing with obinutuzumab was given every 2 months thereafter for up to 30 months total in patients (pts) who responded following doublet therapy. During phase I, three escalating dose levels were planned with 10, 15, and 20 mg of lenalidomide. Phase II planned to enroll 30 pts at MTD with efficacy and safety as primary endpoints.

Results: All 36 pts with FL enrolled (6 in dose escalation and 30 at MTD), and all are eligible for efficacy and safety analysis. The median age was 65 with a median of 2 prior therapies. No DLTs were observed in phase I, and 20 mg of lenalidomide was used for the phase II dose. To date, the most common all grade non-hematologic toxicities included fatigue (83%), diarrhea (67%), and rash (53%). Grade 3+ toxicities included neutropenia (23%), infection (11%), and fatigue (8%). The overall response rate was 100% with 78% (95% CI: 60.85–89.88%), of pts attaining complete remission (CR/Cru). At a median follow up of 14 months, 10 pts progressed. The estimated 24 month PFS is 61% (95% CI: 43–87%).

Conclusions: Lenalidomide and obinutuzumab is highly active with durable remissions in relapsed FL, with all pts responding and 78% achieving CR. The majority of pts remain on therapy and the combination appeared safe. Correlatives are ongoing to identify biomarkers of response and frontline studies of the combination are currently enrolling.

Keywords: follicular lymphoma (FL); immunomodulators (IMiDs); monoclonal antibodies (MoAb).

281 INTEGRATED SAFETY DATA WITH COPANLISIB MONOTHERAPY FROM PHASE I AND II TRIALS IN PATIENTS WITH RELAPSED INDOLENT NON-HODGKIN'S LYMPHOMA

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Introduction: Phosphatidylinositol 3-kinase (PI3K) is a therapeutic target for patients (pts) with indolent non-Hodgkin's lymphoma (iNHL). Copanlisib is a pan-Class I PI3K inhibitor with predominant activity against PI3K- α and PI3K- δ isoforms. In contrast to oral PI3K inhibitors that are dosed continuously, intermittent IV administration of copanlisib has demonstrated a different safety profile. We report results here from a pooled safety analysis.

Methods: Safety data from 4 studies (NCT00962611, NCT01660451 parts A and B, and NCT02155582) including iNHL pts were pooled for analysis. All pts had received IV copanlisib on days 1, 8, and 15 of a 28-day cycle at either 0.8 mg/kg or an equivalent fixed dose of 60 mg. Treatment emergent adverse events (TEAE) were reported using MedDRA terms and worst NCI CTCAE grading.

Results: A total of 168 pts with iNHL were available for safety analysis, including follicular (75%) and marginal zone lymphoma (15%) pts. Median prior lines of therapy was 3 (range 1–10); including rituximab ($n = 168$) and alkylating agents ($n = 167$). The mean duration of treatment was 30.2 weeks (± 30.4) and mean number of cycles 7.5 (± 7.6). The most common TEAEs (occurring in $\geq 20\%$ of the pts) were transient hyperglycemia (51%), diarrhea (36%), transient hypertension (35%), fatigue (29%), nausea (26%), neutropenia (25%), and pyrexia (24%). The most common grade 3 TEAEs ($\geq 5\%$) were hyperglycemia (32%), hypertension (27%), neutropenia (8%), and pneumonia (8%); hyperglycemia and hypertension were transient and largely asymptomatic. Grade 4 TEAEs ($\geq 5\%$) were neutropenia (12%) and hyperglycemia (6%). Serious TEAEs ($\geq 2\%$) were pneumonia (10%), pyrexia, hyperglycemia and pneumonitis (5% each), neutropenia, diarrhea and lung infection (2% each). There were six grade 5 TEAEs, with 3 reported as drug-related: lung infection, respiratory failure, and embolism. Infections ($\geq 5\%$) included upper respiratory (14%), pneumonia (11%), bronchitis (9%), urinary (7%), oral herpes (6%), and rhinitis (5.4%). Opportunistic fungal infections occurred in 3 pts; two *Pneumocystis jiroveci* pneumonia and one bronchopulmonary aspergillosis. GI toxicity included grade 3 diarrhea (5%) and one case of colitis (grade 4) was reported. Suspected non-infectious pneumonitis was reported in 9% (3% grade 3 and no grade 4/5). Treatment discontinuations due to TEAEs (24%) included pneumonitis (2%), neutropenia, thrombocytopenia, fatigue, pneumonia, platelet count decreased, and hyperglycemia (1.8% each).

Conclusions: Integrated safety analysis demonstrates that copanlisib had a tolerable and manageable safety profile with a low rate of severe gastrointestinal toxicities, hepatotoxicities, pneumonitis, and opportunistic infections. The most common grade 3 AEs were transient hyperglycemia and transient hypertension, both of which were predictable and manageable and did not lead to significant discontinuation.

Keywords: non-Hodgkin lymphoma (NHL); PI3K/AKT/mTOR.

282 LYMRIT 37-01: UPDATED RESULTS OF A PHASE I/II STUDY OF ¹⁷⁷LU-LILOTOMAB SATETRAXETAN, A NOVEL CD37-

TARGETED ANTIBODY- RADIONUCLIDE-CONJUGATE IN RELAPSED NHL PATIENTS

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Introduction: Lutetium (¹⁷⁷Lu) lilotomab satetraxetan (Betalutin®) is a novel beta-emitting anti-CD37 ARC in a ready-to-use formulation. CD37 is highly expressed (>90%) in B-cell NHL, providing an alternative target to CD20. LYMRIT 37-01 is a phase I/II, open-label, dose-escalation study to evaluate the safety and preliminary efficacy of Betalutin® monotherapy in patients (pts) with relapsed non-Hodgkin's lymphoma (NHL). We present updated safety and efficacy data for all pts as of February 13, 2017.

Methods: Pts with histologically confirmed NHL (follicular (FL) grade I–IIIA, mantle cell (MCL) and marginal zone (MZL)) relapsing after ≥1 prior therapy with <25% bone marrow involvement, platelets (plt) >150 × 10⁹/L, no prior SCT/RIT, and a life expectancy of ≥3 months were enrolled into 1 of 4 dose-escalation arms (part 1) to determine the optimal lilotomab pre-dose and Betalutin® regimen for further evaluation in an expanded cohort (part 2). All pts received pre-treatment with rituximab. Responses were assessed using Cheson IWG response criteria (including CT and PET-CT scans) beginning at week 12.

Results: A total of 56 patients have been enrolled; 43 are evaluable for safety and 38 for efficacy. Patients who had reached their platelet/neutrophil nadir were included in the safety assessment. NHL subtypes were FL (n = 31), MCL (n = 4), and MZL (n = 8). The number of prior therapies ranged from 1 to 8. A total of 38 pts received lilotomab 40 mg pre-dose (Arm 1). A total of 10 pts received lilotomab 100 mg/m² pre-dose (Arm 4). Arms 2 and 3 without lilotomab pre-dosing were discontinued. Treatment-emergent grade 3/4 AEs in ≥2 pts were neutropenia (42/19%), thrombocytopenia

(28/23%), leukopenia (44/7%) and lymphocytopenia (35/2%); all were reversible. Treatment emergent SAEs in ≥2 pts were thrombocytopenia (n = 2) and atrial fibrillation (n = 2). For patients receiving 15 MBq/kg Betalutin®, mean platelet and neutrophil nadirs were 62 and 1.0 × 10⁹/L with 40 mg lilotomab pre-dose (n = 25) compared to 124 and 2.1 × 10⁹/L with 100 mg/m² (n = 3) lilotomab pre-dose, respectively.

The ORR for all pts was 63% (CR 29%) and 65% (CR 27%) for FL pts. Tumor reductions were seen in 84%. The ORR for 22 pts receiving lilotomab 40 mg/15 MBq/kg Betalutin® (Arm 1 MTD) was 64% (CR 36%).

Best Response	All (N=38)	FL (N=26)
Overall response rate (CR+PR)	24 (63%)	17 (65%)
CR	11 (29%)	7 (27%)
PR	13 (34%)	10 (38%)
SD	6 (16%)	3 (12%)
PD	8 (21%)	6 (23%)
Not evaluable	1	1

Conclusions: Betalutin® has promising single agent activity in relapsed NHL and was generally well tolerated. A higher lilotomab pre-dose may allow administration of a higher and potentially more efficacious dose of Betalutin®—evaluation is ongoing and updated safety/efficacy results will be reported at the meeting.

Keywords: indolent lymphoma; non-Hodgkin lymphoma (NHL); radioimmunotherapy (RIT).

283 INTERIM DATA FROM THE FIRST CLINICAL STUDY OF ADCT-301, A NOVEL PYRROLOBENZODIAZAPINE-BASED ANTIBODY DRUG CONJUGATE, IN RELAPSED/REFRACTORY HODGKIN/NON-HODGKIN LYMPHOMA

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Introduction: Expression of CD25 occurs in many lymphomas, including Hodgkin (HL), peripheral T cell, cutaneous T cell, and diffuse large B cell. ADCT-301 is an antibody drug conjugate comprising a human monoclonal antibody against CD25 conjugated to a potent pyrrolobenzodiazepine dimer toxin. ADCT-301 has demonstrated potent anti-tumor activity in pre-clinical studies against CD25-expressing hematological malignancies. This first in human clinical trial

of ADCT-301 is currently enrolling patients (pts) with relapsed HL and NHL. Interim data are reported here.

Methods: Relapsed/refractory HL or NHL pts who have no available established therapies known to provide clinical benefit at their current disease state are being recruited to a dose escalation (part 1) and dose expansion (part 2) phase I study. The primary objectives of part 1 are to assess the safety and tolerability and define a maximum tolerated dose (MTD) of ADCT-301 to recommend for part 2. The primary objective of part 2 will be to evaluate the safety and tolerability of ADCT-301 at this recommended dose. Efficacy (overall response rate, duration of response, progression-free survival, subtype-specific responses, and overall survival), pharmacokinetics, pharmacodynamics, and anti-drug antibody activity are also being assessed. Patients receive IV infusions of ADCT-301 every 3 weeks (1 cycle) from a starting dose cohort at 3 µg/kg with subsequent cohorts enrolled at escalating doses according to a continual reassessment method. No intra-patient dose escalation is allowed.

Results: As of 8 Feb 2017, 18 pts (11 male, 7 female; median age: 44 yrs [range 23–79]); median number of previous therapies: 4 [range 1–10]) with HL (n = 10) or NHL (n = 8) have been treated with ADCT-301 doses ranging from 3 to 45 µg/kg (median number of cycles: 2 [range 1–12]; median duration of treatment: 43 days [range 21–251]). A total of 4 pts have reported DLTs: 1 with maculopapular rash at 8 µg/kg; 1 with oral mucositis and small bowel enteritis at 20 µg/kg; 1 with elevated creatine phosphokinase at 30 µg/kg; and 1 with maculopapular rash and pruritus at 30 µg/kg. Treatment-emergent adverse events have been reported in 16 (88.9%) pts, including anemia (4 [22.2%] pts), pruritus (4 [22.2%] pts), and maculopapular rash (4 [22.2%] pts). The first disease responses were seen at 30 µg/kg: 1 HL pt achieved a complete response, and 1 HL pt achieved a partial response. A total of 6 pts achieved stable disease as their best response including 1 HL pt at 13 µg/kg who has remained progression-free for >30 weeks (>10 cycles).

Conclusions: This dose escalation and expansion study will identify the MTD of ADCT-301 and provide a preliminary assessment of its single-agent anti-tumor activity and toxicity profile in R/R HL and NHL. Dose

escalation (part 1) is continuing. Further initial safety, tolerability, and efficacy results are expected later this year. <http://clinicaltrials.gov/show/NCT02432235>

Keywords: Hodgkin lymphoma (HL); monoclonal antibodies (MoAb); non-Hodgkin lymphoma (NHL).

284 POLATUZUMAB VEDOTIN PLUS BENDAMUSTINE AND RITUXIMAB OR OBINUTUZUMAB IN RELAPSED/ REFRACTORY FL OR DLBCL: UPDATED RESULTS OF A PHASE 1B/2 STUDY

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Table 1. Best Overall Response by PET/CT*

Response	P1b				P2	
	FL		DLBCL		FL	DLBCL
N (%)	Pola+BR (N=6)	Pola+BG (N=6)	Pola+BR (N=6)	Pola+BG (N=6)	Pola+BG (N=20)	Pola+BG (N=21)**
ORR	6 (100)	6 (100)	3 (50)	5 (83)	16 (80)	12 (57)
CR	4 (67)	5 (83)	2 (33)	4 (67)	12 (60)	7 (33)
PR	2 (33)	1 (17)	1 (17)	1 (17)	4 (20)	5 (24)
SD	0	0	0	0	1 (5)	3 (14)
PD	0	0	2 (33)	1 (17)	1 (5)	3 (14)
Unevaluable	0	0	1 (17)	0	2 (10)	3 (14)

*Using Modified Lugano 2014 criteria **1 pt not dosed

Introduction: Transplant ineligible patients (pts) with relapsed/refractory (R/R) FL or DLBCL have poor outcomes. Polatuzumab vedotin (pola), an antibody drug conjugate that targets delivery of the microtubule inhibitor MMAE to cells expressing CD79b, + rituximab (R) has showed promising responses in R/R FL and DLBCL. Adding bendamustine (B) to pola-R and substituting obinutuzumab (G) for R could improve outcomes. We report updated results from the Phase (P) 1b/2 study evaluating pola + BR or BG and the P2 expansion cohorts evaluating pola + BG in patients (pts) with R/R FL and DLBCL (ClinicalTrials.gov NCT02257567).

Methods: All pts provided informed consent to participate in the study and were treated with pola (1.8 mg/kg) + B (90 mg/m²) and R (375 mg/m²) or G (1000 mg) every 28 days (FL) or 21 days (DLBCL) for 6 cycles. Responses were assessed by modified Lugano 2014 criteria after 3 cycles, end of treatment (tx), and every 6 months (mo) for 2 years during follow-up (fu).

Results: As of 14 Nov 2016, 65 pts were enrolled: 24 pts (12 FL, 12 DLBCL) in P1b and 41 pts (20 FL and 21 DLBCL) in P2. In safety evaluable pts, FL pts (N = 32) were median age 63 yr (37–86), 82% ECOG 0–1, 6% ECOG 2, 44% FLIPI1 3–5, 78% Stage III/IV, 2 (1–7) median lines of prior tx, 38% refractory to last tx, 13% prior transplant (BMT). DLBCL pts (N = 32) were median age 66 (30–86), 88% ECOG 0–1, 13% ECOG 2, 59% IPI 3–5, 75% Stage III/IV, 2 (1–7) median lines of prior tx, 82% refractory to last tx, 3% prior BMT.

Among 64 pts who received ≥1 dose, adverse events (AEs) that occurred in >20% of pts were fatigue (67%), nausea (54%), diarrhea (54%), vomiting (42%), pyrexia (39%), and constipation (39%). As expected, grade (Gr) 3/4 cytopenias were common: neutropenia (34% FL, 28% DLBCL), thrombocytopenia (16% FL, 13% DLBCL), and anemia (6% FL, 9% DLBCL). Tx emergent neuropathy occurred in 19/64 (30%) of pts, with 1 Gr 3 event, and led to pola discontinuation in 1 pt, dose reduction in 2 pts, and interruption in 1 pt.

In FL (n = 32), 75% (24/32) had Gr 3/4 AEs and 41% (13/32) had serious AEs (SAEs). The only SAE occurring in ≥10% was infection (22%). The most common Gr 3/4 non-heme AEs were infection (16%) and hypokalemia (9%). AEs led to study tx discontinuation in 6 pts. B was stopped in 2 pts due to Gr 3 thrombocytopenia. Of 4 deaths, 2 were PD and 2 were Gr 5 AEs (1 tx related: PML). In DLBCL (n = 32), 88% (28/32) had Gr 3/4 AEs and 63% (20/32) had SAEs. SAEs occurring in ≥10% of pts were infection (33%) and pyrexia (22%). The most common Gr 3/4 non-heme AEs were febrile neutropenia (13%), fatigue (13%), and diarrhea (13%). AEs led to study tx interruption in 19 pts and discontinuation in 8 pts. There were 13 deaths: 9 PD, 4 AE (all unrelated to tx). Responses are shown in Table 1.

Median duration of response (DoR) for FL P1b pts was 16 mo (median fu 14.5 mo) but not reached for FL P2 (median fu 6.5 mo) and DLBCL P1b/2 (median fu 13.7 mo P1b, 6.4 mo P2).

Conclusions: Updated evaluation of pola + BR and pola + BG shows promising durable responses and an acceptable safety profile in heavily pre-treated R/R FL and DLBCL pts. Safety and efficacy data will be updated at the time of presentation.

Keywords: antibody-dependent cytotoxicity (ADC); non-Hodgkin lymphoma (NHL); obinutuzumab.

285 YourTreatmentChoices: FAST ACCESS TO TRIALS PROGRAMME

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Introduction: YourTreatmentChoices aims to develop an innovative approach to patient access to cancer clinical trials, including blood malignancies. The YourTreatmentChoices website is integrated with a bespoke clinical trial database of more than 86,000 recruiting trials. The Fast Access to trials Programme was conducted as part of YourTreatmentChoices and is comprised of 25 blood cancer clinical trials (SADAL, Epizyme/Eisai, Polatuzumab, SGN35-023, TAK659, PIX-R, ACERTA, INCA, TIER, ROMICAR, DI-B4, UKALL 11, UKALL 14, MMY3007, TOURMALINE, AML 18, VITAL, AML19, MUK 7, FLAIR, Fusion NHL001, PRONTO, Chemo T, ReThink, RIALTO), including lymphomas, from 20 sponsors. The studies were conducted at 4 trial sites: 1) The Christie Hospital, The University of Manchester and the Christie NHS Foundation Trust, Manchester, UK; 2) Cancer Research UK Centre, Southampton General Hospital, University of Southampton, Southampton, UK; 3) Centre for Clinical Haematology, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; and 4) Barts Cancer Institute, Centre for Haemato-Oncology, Queen Mary University of London, London, UK.

Methods: Six and 2-month social media campaigns were conducted by Bloodwise and Tomorrow's Medicines Ltd, respectively. Bloodwise utilised Twitter, Facebook, blogs, and newsletters as part of their campaign while Tomorrow's Medicines Ltd used only Facebook. The database architecture was developed to accommodate for the differences in language used by patients, oncologists, and clinical trial sponsors simultaneously translating lay terminology, medical terminology (WHO-ICD 0-3) and clinical trial terminology. The programme utilised 3 eligibility algorithms, which were developed by Tomorrow's Medicines Ltd, to facilitate patient interaction with research nurses at clinical trial sites. The algorithms developed, which connect eligible patients and trial sites, iteratively execute a bespoke combination of functions including translation, screening, matching, and messaging with increasing specificity.

Results: Between June 2016 and December 2016, Bloodwise sent 102 tweets and 6 Facebook posts. Tomorrow's Medicines Ltd sent 135 Facebook posts during October and November 2016. The website received 23,000 visits from 9,704 patients with blood cancer worldwide. The engagement rate (patients who answered screening questions) was 6.7% and the match rate was 53 patients per month. The average time for a patient to establish eligibility and connect with a trial site and a research nurse was 13.9 hours. The average number of messages between the patient and the trial nurse was 8.6. The number of matches generated to at least one trial was 446 while 204 profiles were not matched to any of the 25 trials in the programme. Eligibility rate of matched patients compared with the single trial industry standard was 75% compared with 4.7% for the Echelon1 trial (an international phase 3 frontline trial of therapy in advanced classical Hodgkin Lymphoma) used as comparison.

Conclusions: Our data demonstrate that the YourTreatmentChoices website effectively connects eligible patients with clinical trials and research sites enabling patients to participate in their own treatment choices by providing improved access to clinical trials. It also gives the clinical research community improved access to patients who may be eligible for enrolment in certain clinical trials where eligibility criteria may be difficult to fulfil. These results suggest that use of social media linked to an online matching tool can be a powerful adjunct to clinical trial recruitment and potentially accelerate the development

of new medicines.

Keywords: Hodgkin lymphoma (HL); multiple myeloma (MM); non-Hodgkin lymphoma (NHL).

286 INCREASING CROSS-REFERRAL AND RECRUITMENT TO CLINICAL TRIALS: A NEW APPROACH

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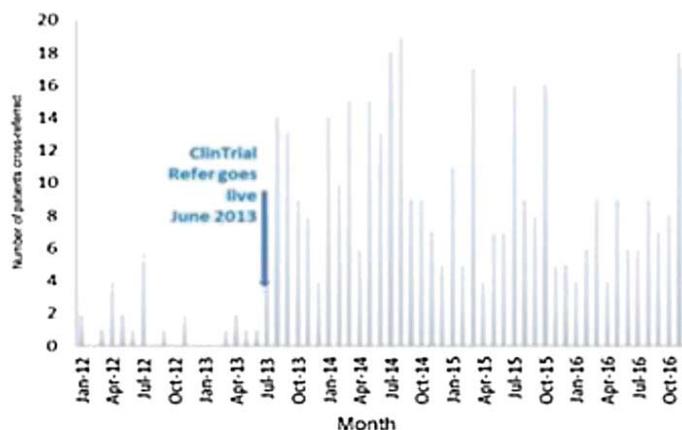


Figure 1a

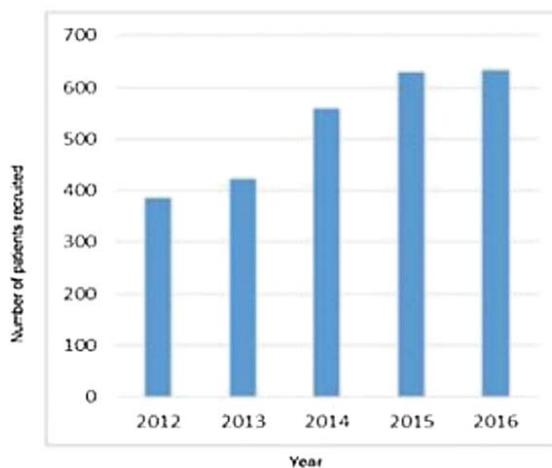


Figure 1b.

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Background/Aims: The Haematology Clinical Research Network of New South Wales and the Australian Capital Territory (HCRN NSW/ACT) comprises public hospital clinical trial unit managers committed to collaboration in clinical research. In June 2013, the HCRN and NSW haematologists launched the ClinTrial Refer Application (App) on iTunes and Google play. This smartphone and iPad/Tablet tool provided clinicians, research staff, and patients with instant knowledge of our currently recruiting trials and was associated with an immediate increase in inter-hospital cross-referrals of patients for trials. We aimed to measure this increased referral and trials recruitment and create a not-for-profit template App transferrable to other trial portfolios.

Methods: Cross-referral, recruitment, and staffing data were obtained from each of the 19 contributing hospitals from Jan 2012 to Dec 2016. Modified versions of the App were created with other cancer networks, establishing search functions unique to each network's geography and/or tumour stream. Newly derived Apps had to conform to the specifications of ClinTrial Refer, including being publically available, free to download, and hosting only publically listed data of current recruiting trials.

Results: There was an immediate and sustained increase in cross-referrals for haematology clinical trials: median 1 (range 0–6) to 8/month (4–19), Figure 1a, across NSW/ACT, a state-wide 63% increase in recruitment from 386 patients in 2012 to 612 in 2016, Figure 1b, and a 60% increase in unit staffing from 36.8 staff in 2012 to 59.0 staff in 2016.

Fourteen other Australian haematology/other cancer Apps, a New Zealand haematology and French lymphoma App, have since been derived from the original. Re-design for the needs of each network ranged from a simple re-configuration of the logo, splash screen and recruiting locations to providing mutational status or age criteria. The back-end database of listed trials, selection criteria, and recruiting sites can be instantly updated ensuring currency of trial information. The early adopters within other cancer research networks have reported a similar increase in trials recruitment. Recognising ClinTrial Refer as an effective tool for patients to identify recruiting trials close to home, cancer consumer groups have posted the Apps on their websites.

Conclusions: An instantly accessible, simple smartphone Application in the clinician and study coordinators' pockets has provided better knowledge management of local trials across the spectrum of haematology malignancies. A tool to facilitate collaboration in clinical research, it has significantly enhanced cross-referral and recruitment, increasing patient access to emerging therapies and supporting the viability of haematology trial units across Australia and beyond. ClinTrial Refer has been rapidly adapted to suit the trials portfolios of other clinical trial networks.

Keywords: chronic lymphocytic leukemia (CLL).

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ORAL AZACYTIDINE (AZA) AND ROMIDEPSIN (R) REVEALS PROMISING ACTIVITY IN PATIENTS WITH RELAPSED OR REFRACTORY (R/R) PERIPHERAL T-CELL LYMPHOMA (PTCL)

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Introduction: The PTCL may be the prototypical 'epigenetic disease'. It is the one disease for which HDAC inhibitors (HDACi) have been shown to have universal activity, and multiple lines of evidence have established that the PTCL carry recurrent mutations in important genes governing genome wide methylation, including TET2, IDH1/2, and DNMT3. While commonly invoked as a reason to explain sensitivity to HDAC inhibitors, the fact is that only hypomethylating agents (HoMe) and not HDAC inhibitors would be expected to affect this underlying biology. Previous work from our group has established that there are major class effects between HoMe and HDACi in preclinical models of TCL, and in combination effect unique patterns of gene expression and methylation different from the single agents.

Methods: A 3 + 3 dose-escalation design started with AZA = 100 mg and R = 10 mg/m² with increasing days of exposure over increasing dose cohorts (7 cohorts). The primary objective was to determine maximum tolerated dose (MTD) and dose limiting toxicity (DLT) as a function of dose and schedule; secondary objectives included ORR (CR + PR), progression free survival (PFS), and duration of response (DOR). Patients in Phase 1 were required to have relapsed lymphoma of any subtype, ECOG PS <2, and adequate organ and marrow function. There was no upper limit to the number of prior therapies or transplantation. The Phase 2 exclusively enrolls patients with PTCL.

Results: A total of 27 patients were enrolled and evaluable for toxicity. Median age was 51 years old (23–79) and 58% were male. The population was heavily treated with a median number of prior therapies of 6 (1–18). A total of 15 patients had prior autologous stem cell transplant, 1 prior allogeneic transplant. Histologies included HL/other (46%), B cell (31%), and T cell (23%). There were 5 DLTs across all cohorts, 3 at the highest dose level of AZA = 300 mg days 1–21 and R = 14 mg/m² days 8, 15, and 22, which included neutropenia (N = 2) and thrombocytopenia. The MTD was AZA = 300 mg days 1–14 and R = 14 mg/m² days 8, 15, and 22. Other Grade 3 or 4 toxicities included febrile neutropenia, and thrombocytopenia, of which only 2 were Grade 4. Of 24 evaluable patients, the ORR was 25% (6/24) with 13% CR. Among patients with non-T-cell and T-cell lymphoma, the ORR was 11% (2 of 19) and 80% (4 of 5), respectively, with only 1 patient achieving a CR in the former group, and 2 of 4 achieving CR among the TCL. First dose PK revealed the AUC for R 10 and 14 mg/m² were 2021.5 ± 1461.3 h*ng/mL, and 1765.9 ± 1002.0 h*ng/mL,

respectively. The median $t_{1/2}$ was 4.8 and 2.4 h, respectively. These data are comparable to historical single agent values.

Conclusions: While a small population of TCL patients, these clinical findings are the first clue that novel backbones could be active in TCL. Gene expression profiling on peripheral blood mononuclear cells from all patients is underway, a multicenter Phase II study of AZA + R is now enrolling patients with PTCL.

Keywords: epigenetics; histone deacetylase inhibitors; T-cell lymphoma (TCL).

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CD70 EXPRESSION IN CUTANEOUS T CELL LYMPHOMA (CTCL) PATIENTS AND MECHANISMS OF ACTION OF ARGX-110 IN SKIN: HISTOPATHOLOGICAL AND CLINICAL DATA

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Introduction: With only limited expression in normal tissues and strong expression on tumor cells, CD70 is a very attractive target for antibody-based therapy. Glyco-engineered ARGX-110 blocks CD70-CD27 signaling, which is thought to inhibit evasion of tumor immune surveillance as well as inhibiting tumor cell proliferation and survival, whereas its effector functions being complement dependent cytotoxicity (CDC), antibody dependent cellular phagocytosis (ADCP), and enhanced ADCC efficiently kill CD70-expressing tumor cells. An ongoing phase I/II study, including at the moment 84 CD70 positive patients with solid tumors and hematological malignancies treated with ARGX-110 monotherapy every 3 weeks, is showing disease control and response in 9/16 Relapse refractory CTCL patients, prompting us to further explore the expression patterns of CD70 as well as a possible mechanism of action in this patient population.

Methods: As part of the above study, the results from 16 RR CTCL patients are described. Immunohistochemistry was used for staining formalin-fixed paraffin-embedded (FFPE) CTCL skin biopsies to investigate CD70 expression in treated as well as untreated patients. Additional markers were included to elucidate the possible mechanisms of action of ARGX-110 in the skin of CTCL patients.

Results: Immunohistochemistry showed overexpression of CD70 (>10%) in 28/36 CTCL patient samples, including the 16 patients treated with ARGX110 in the study. In samples collected pre- and during treatment with ARGX-110, the expression appear to be predominantly localized in the neoplastic cells of the skin.

Among such patients, 56% presented a degree of disease response of which 3 reached Partial Response (PR): Best Response in the skin of Mycosis fungoides and Sézary Syndrome patients was measured by mSWAT: PR in 2 patients, with another 6 patient showing stable disease. Such clinical results correlated with decreased levels of CD70 expressing CD4+ tumor cells. A patient with Subcutaneous panniculitis-like T-cell lymphoma, with CD8+ T cells expressing high levels of CD70 before treatment, showed decreased numbers of CD8+ neoplastic cells after treatment with ARGX-110 and reached Partial Response in skin by PET/CT scan. No relevant treatment-related toxicity was observed in these patients. Interestingly, histopathological, cellular, and clinical data are indicating regression from plaques to patch of the cutaneous lesions in combination with CD8+ reactive T cells infiltration of the tumor microenvironment, strongly suggesting restoration of the immune surveillance as ARGX-110 mode of action in the skin.

Conclusions: CD70 is expressed at high levels on neoplastic cells of CTCL and clinical anti-tumor activity in patients with various types of CTCL is observed after treatment with ARGX-110, indicating ARGX-110 as a safe and promising treatment option for R/R CTCL.

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

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PH 1 TRIAL EVALUATING MRG-106, A MICRORNA-155 INHIBITOR, ADMINISTERED BY INTRATUMORAL, SUBCUTANEOUS, OR INTRAVENOUS DELIVERY IN CUTANEOUS T-CELL LYMPHOMA (CTCL) PATIENTS

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miR-155-5p is a well-described oncomiR associated with poor prognosis in multiple malignancies, particularly lymphoma and leukemia. Skin biopsies from mycosis fungoides (MF) patients have increased miR-155-5p, with the highest levels seen in tumor-type lesions. MRG-106

is an oligonucleotide inhibitor of miR-155-5p selected based on its anti-proliferative activity in MF cell lines. MRG106-11-101 is a first-in-human study of MRG-106 designed to evaluate its safety, tolerability, pharmacokinetics (PK), and preliminary efficacy in MF patients.

This Phase 1 trial employs a dose-escalation design to evaluate intratumoral (IT), subcutaneous (SC), or intravenous (IV) administration of MRG-106. Patients were required to have biopsy-proven stage I–III MF and plaque- or tumor-type lesions. Subjects received MRG-106 for 1–2 weeks via IT injection, or for 4 weeks via SC or IV administration. Subjects enrolled with SC or IV delivery had the option to extend treatment beyond the initial 4-week cycle.

Eighteen patients (14 M/4F, median age 60 years) have been dosed via IT (6 subjects, 75 mg/dose), SC (3 subjects each in 300, 600, or 900 mg/dose cohorts), or IV (3 subjects, 300 mg/dose) administration. Three subjects in the SC cohorts continued dosing beyond the first 4 weeks. Seventeen of 18 patients tolerated the dosing well with only mild or moderate injection site reactions in 8 patients. Sixteen of 18 patients completed dosing as scheduled. MRG-106 related adverse events were generally mild or moderate in severity. One event of grade 3 pruritus associated with a possible skin flare as judged by the investigator resulted in treatment discontinuation. The MTD has not been reached.

In the IT cohort, a reduction of $\geq 50\%$ in the baseline index lesions CAILS score was observed in the MRG-106 treated lesions in all 4 evaluable patients who completed dosing; the responses were maintained to the End of Study visit on Day 28 or 35. Pre- and post-treatment skin biopsies of MRG-106-injected lesions showed a reduction in infiltrating malignant lymphocytes, with one patient's lesion demonstrating complete loss of the neoplastic infiltrate. Expression analysis (mRNA) of the pre- and post-treatment biopsies showed reduced expression of genes associated with the PI3K/AKT, JAK/STAT, and NF κ B survival pathways and increased expression of cell death-associated genes consistent with the expected MRG-106 mechanism of action.

In the SC cohorts, 5 of the 8 patients that completed dosing had reductions from their baseline total skin disease mSWAT score of $>25\%$ and of these; 2 patients from the 300 mg cohort showed reductions from their baseline mSWAT of 50% or greater. An additional patient in the 600-mg cohort achieved $>50\%$ reduction in their mSWAT after 2.5 cycles of treatment during the extension phase. The efficacy measures for subjects dosed with 300 mg IV are being collected and will be presented as available. Enrollment is ongoing.

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

PUBLICATIONS

BIOLOGY

290 QUANTITATIVE ANALYSIS OF MYD88 L265P MUTATIONS BY DIGITAL PCR IS AN INDEPENDENT PROGNOSTIC FACTOR FOR CNS RELAPSE AS WELL AS SYSTEMIC RELAPSE AND POOR OUTCOME

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous disease. While 30% to 55% patients achieve a durable cure, the remaining patients eventually die of the DLBCL, especially central nervous system (CNS) relapse is potentially lethal with no standard salvage treatments. We previously reported that absolute peripheral monocyte count (AMC) at diagnosis predicts CNS relapse. Recently gain-of-function mutations in MYD88 L265P have been detected in part of DLBCL, however, an influence of the mutation on survival is unclear. Digital PCR method was introduced to analyze molecular mutations quantitatively, however, analysis of MYD88 by digital PCR has not been reported yet. The purpose of this study was to clarify the value of quantitative analysis of MYD88 L265P mutations by using digital PCR on biological features and clinical outcomes.

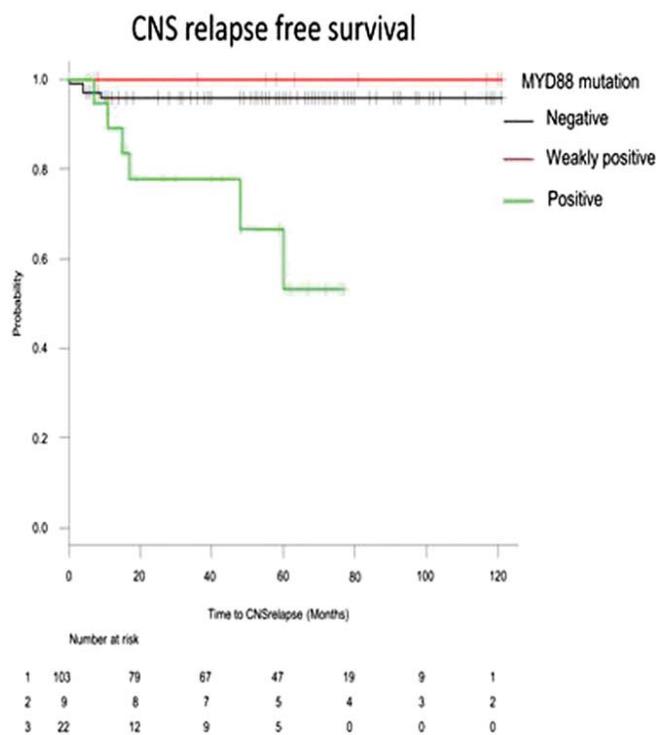
Methods: We retrospectively analyzed the data from a total of 134 patients (74 men/60 women; median age, 67 y), consecutively diagnosed with DLBCL according to the WHO classification who were treated at our single institution between 2005 August and 2014 April. We exclude the data if IgH rearrangement by Southern blot analysis was absent expecting at least 5% of lymphoma cells in the sample. MYD88 L265P mutation was examined by using digital PCR assay and also investigated the associated clinicopathologic factors.

Results: MYD88 L265P mutations at least 5% (range from 7.5% to 89%) were found in 22 (16.4%) patients. MYD88 L265P mutations were seen more frequently in patients with a non-GC subtype, CD5 positive, high AMC ($>0.5 \times 10^9/L$), extra-nodal involvement, B symptom, significantly

($P < .05$). All 21 patients with inconclusive positive digital PCR (range from 0.01% to 1.01%) underwent allele-specific nested PCR; only 9 (42.8%) of 21 patients had a positivity. The remaining 103 patients were negative. We, in turn, analyzed survival data per three groups: positive ($>5\%$), weakly positive, and negative. With a median follow-up periods of 64 months for the survival patients, only positive ($>5\%$) patients showed inferior CNS relapse-free survival at 5 years (53% versus 100%, 96%; $P = .0001$), progression-free survival at 5 years (39.4% versus 88.9%, 83.1%, $P = .0002$), and overall survival at 5 years (52.3% versus 88.9%, $P = .001$). MYD88 L265P positive ($>5\%$) was an independent variable predicting CNS relapse in the multivariate analysis (hazard ratio 5.1; 95% confidence interval, 1.2-22.9, $P = .02$).

Conclusions: This is the first report that MYD88 L265P mutation detected by digital PCR is an independent prognostic factor for CNS relapse. This suggests that MYD88 L265P mutation can be a second hit mutation of DLBCL and play a crucial role in disease progression, however, R-CHOP may overcome as far as mutated cells are within a small amount. Allele-specific PCR results can be over-diagnosis for the marker. The additional drug such as Bruton's tyrosine kinase inhibitor might be helpful.

Keywords: diffuse large B-cell lymphoma (DLBCL); MYD88



291 HIGH PREVALENCE AND CLINICAL SIGNIFICANCE OF ONCOGENIC CD79B AND MYD88 MUTATIONS IN PRIMARY TESTICULAR DIFFUSE LARGE B-Cell Lymphoma: A RETROSPECTIVE STUDY IN CHINA

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Activating mutations in *CD79B* and myeloid differentiation primary response gene 88 (*MYD88*) have recently been found in a subset of activated B-cell-like subtype of diffuse large B-cell lymphoma (ABC-DLBCL). Primary testicular DLBCLs (PT-DLBCLs) have uniform activated B-cell-like subtype characteristics. However, the studies on the *CD79B* and *MYD88* mutation in PT-DLBCL have been limited, and the clinical significance remains unclear. Therefore, in this study, we investigate the prevalence of *CD79B* and *MYD88* mutations and their relation to clinical significance in a cohort of Chinese testicular DLBCL patients. We examined the mutational status of *CD79B* and *MYD88* and both the gene amplification and protein expression of *MYD88* in 18 cases of PT-DLBCL tissue samples. Sanger sequencing was performed to detect oncogenic *CD79B* and *MYD88* mutations. *MYD88* gene amplification and protein expression were analyzed by quantitative PCR and by immunohistochemistry, respectively. Immunophenotypically, *MYD88* protein stain was positive in 88.89% (16/18) cases. Fourteen of 18 (77.78%) cases tested positive for p65 in the nucleus, indicating activation of the NF κ B signaling pathway. Genetically, *CD79B* mutation was found in 8/18 (44.44%) cases, and the *MYD88* L265P mutation was found in 11/18 (61.11%) cases. The *MYD88* L265P mutation coexisted with a *CD79B* mutation in 6 cases, which constituted 75% of *CD79B* mutants and 54.5% of *MYD88* L265P cases. Furthermore, *MYD88* is significantly amplified in PT-DLBCL. However, the amplification status showed no correlation with its mutational status or protein expression. Both *MYD88* and *CD79B* mutational status and expression of *MYD88* showed no significant correlation with the patient's age, non-GCB/GCB subtype, Ann Arbor stage, p65 protein expression, and double expression of BCL-2 and c-MYC ($P > .05$). Survival analyses showed that patients with *MYD88* L265P mutation and p65 expression had a significantly poorer OS ($P < .05$).

We demonstrated a high prevalence of *CD79B* and *MYD88* L265P mutation in PT-DLBCL, and *MYD88* L265P and p65 protein expression was a significant prognostic indicator. Our results suggest that *MYD88* and *CD79B* mutations are important drivers of immune-privileged site-associated DLBCL (IP-DLBCL) and potential therapeutic targets for personalized treatment.

Keywords: diffuse large B-cell lymphoma (DLBCL); *MYD88*; NF- κ B

292 MOLECULAR ANALYSIS OF PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE

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Introduction: Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) is thought to most closely resemble diffuse large B-cell lymphoma of activated B-cell type (ABC-DLBCL) at the molecular level. However, studies on the gene expression and mutational profile of PCDLBCL-LT have, to date, been limited.

Methods: Twenty-one cases of PCDLBCL-LT, identified according to WHO classification criteria, were studied. Gene expression profiling was performed using the Illumina whole genome DASL assay on RNA extracted from FFPE sections, $n = 9$; by targeted expression using the HTG EdgeSeq Diffuse Large B-Cell Lymphoma Cell of Origin Assay (DLBCL COO) directly from FFPE section, $n = 6$; or both $n = 2$. Cell of Origin (COO) was assigned using the DAC classifier (Care et al, PLOS ONE 2013) or the HTG DLBCL COO classifier, respectively. Targeted Sanger sequencing was performed on DNA extracted from FFPE sections to look for mutations/indels in reported hot spot regions in *CARD11* (ex-6-10 transcript NM_001324281.1 chr7:2,976,679-2,984,188), *CD79B* (ex5-6 transcript NM_001039933.2 chr17:62,006,527-62,006,867), and *MYD88* (ex5 transcript NM_002468.4 chr3:38,182,504-38,182,688) using 2009 GRCh37/hg19 assembly. Fluorescence in situ hybridisation (FISH) was performed on FFPE sections using Dako breakapart probes for *MYC*. Cases with an identified *MYC* gene rearrangement (*MYC-R*) were also analysed using probes to *BCL2* and *BCL6*.

Results: A COO was successfully assigned in 17 cases; 12/17 activated B-cell type (ABC), 4/17 type III or unclassifiable, and one germinal centre B-cell type (GCB). Sanger sequencing was informative in 19 cases. An *MYD88* mutation was present in 13/19 (10 ABC profile, 2 unclassified/type III, and 1 not known), *CD79b* mutations in 5/19 (4 ABC profile and 1 not known), and *CARD11* mutations in 3/19 (2 ABC profile and 1 type III). All cases with *CD79b* and *CARD11* mutations also had *MYD88* mutations. *MYC-R* was identified in only 2/20 cases, both displaying an ABC profile. One also harboured a *BCL6* rearrangement together with an *MYD88* mutation, and the other had mutations of *MYD88* and *CARD11*.

Conclusions: Our results confirm previous studies, classifying the majority of PCDLBCL-LT as ABC-DLBCL. The frequency of *MYD88* mutations is high (68%), suggesting a close relationship to ABC-DLBCL arising at immune privileged sites such as the central nervous system and testis. Network analysis of gene expression data is underway to test this hypothesis, and the results will be presented at the meeting. In contrast to some previous studies, *MYC-R* are present in only rare cases. *MYC-R* is not mutually exclusive to an ABC profile and may be accompanied by a second genetic "hit," such as a *MYD88* mutation or a *BCL6* translocation. These results have implications when considering novel therapies for PCDLBCL-LT, particularly those targeting B-cell and toll-like receptor signalling pathways.

Keywords: activated B-cell-like (ABC); cutaneous B-cell lymphoma (CBCL); MYD88

293 GENETIC LANDSCAPE OF HEPATITIS B VIRUS-ASSOCIATED DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: HBV infection is a leading risk factor for hepatocellular carcinoma and is especially prevalent in South and East Asia. Epidemiological studies have also suggested an association of HBV infection with non-Hodgkin's lymphoma (NHL), especially in diffuse large B-cell lymphomas (DLBCL). However, how HBV infection contributes to lymphomagenesis remains elusive.

Methods: We performed whole exome/genome sequencing and transcriptome analysis on altogether 96 DLBCL samples, including 21 HBsAg-positive and 75 HBsAg-negative tumor biopsies. The mutation prevalence of selected genes was investigated in altogether 203 DLBCL samples, out of which 44 were HBsAg-positive.

Results: Patients in the HBsAg-positive group were characterized by a younger age, higher International Prognostic Index (IPI), and a more advanced disease stage at diagnosis. Furthermore, they showed a significantly worse overall survival as compared to HBsAg-negative patients. Somatic mutation analysis suggested that HBsAg-positive tumors carried a significantly higher number of nonsilent mutations in the coding genome as compared to the HBsAg-negative tumors. Furthermore, a distinct mutational profile was identified in HBsAg-positive tumors, with a number of potential cancer drivers being mutated at a significantly higher frequency in HBsAg-positive tumors, including *TMSB4X*, *FAS*, *BCL6*, *KLF2*, *EBF1*, *CXCR4*, and *TP73*. Moreover, the HBsAg-positive tumors were also associated with unique gene expression profiles.

Conclusions: Genetic study may help us to further understand the pathogenesis of HBV-associated lymphomas. HBsAg-positive DLBCLs show distinct clinical and molecular features and should probably be considered as a new subtype of DLBCL.

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

294 MOLECULAR LANDSCAPE OF RELAPSE/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Patients with relapsed or refractory diffuse large B-cell lymphoma (r/rDLBCL) after standard immuno-chemotherapy often do poorly with conventional treatments. At this stage of disease, early-phase clinical trials can provide access to new drugs with alternative mechanisms of action. Next-generation sequencing (NGS) panels can rapidly identify recurrent molecular abnormalities, thus helping to develop a precision medicine approach in which patients could be oriented in different clinical trials.

Objectives and Method: Objectives were (1) to provide an insight into the molecular landscape of r/rDLBCL and (2) to tailor the choice of innovative treatments for individual patients within a panel of early-phase clinical trials. The studied population was patients with r/rDLBCL. The molecular profile was determined at relapse, on tumor fresh biopsy by a molecular portrait containing a panel of genes known to be the target of recurrent molecular abnormalities. Next-generation sequencing in the hot spot region of 39 genes was performed, with two full-length genes sequencing (*EZH2* and *KDM6A*). All patients gave their written informed consent.

Results: A relapse lymphoma molecular portrait was performed in 52 patients. The histological subtypes per Hans algorithm was GC (n = 27/52; 52%), ABC (n = 20/52; 39%), and not classified (n = 5; 9%). Fourteen out of the 52 (27%) patients had a transformation from indolent non-Hodgkin lymphoma. The median age was 67 (45-82) years. All patients had previously received rituximab plus anthracycline-based chemotherapy. The patients had previously received a median of 2 (1-8) chemotherapy lines. Auto-stem cell

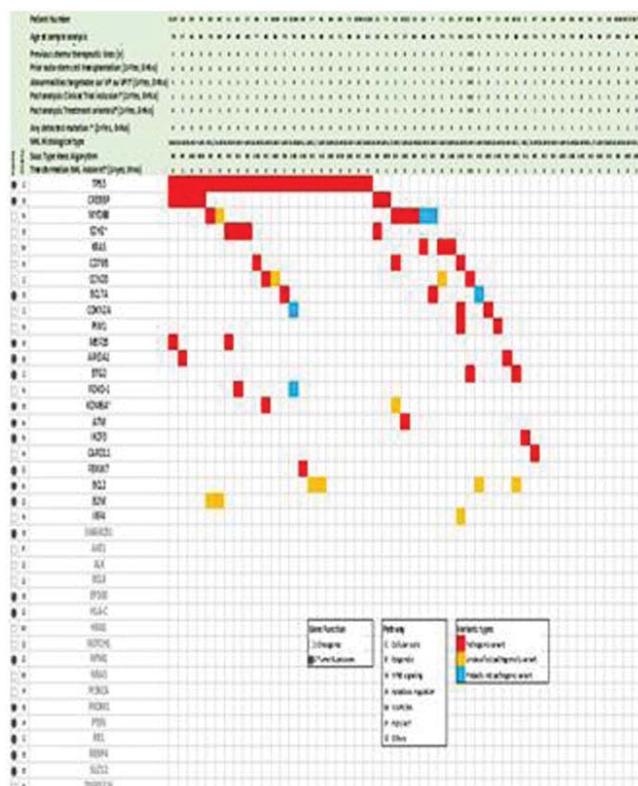


Figure 1

transplantation were performed in 11 (21%) patients. The most common molecular abnormalities were *TP53* mutations in 22 pts (42%), *CREBBP* in 6 pts (12%), *MYD88* in 4 pts (8%), and *EZH2* in 4 pts (8%) (Figure 1). Twelve pts (23%) had no mutation detected with our panel of genes. Molecular abnormalities involved the cell cycle regulation (27pts; 52%), epigenetics (16 pts; 31%), NF κ B pathway (15 pts; 29%), and apoptosis (5 pts; 9%). Through the NGS, a mutation orientating to a molecular targeted therapy was found in 28 pts (54%). The molecular portrait guided the choice for an innovative treatment as part of an early-phase clinical trial in 11 (21%) patients.

Conclusion: The first gene recurrently mutated in r/rDLBCL is *TP53*. The implementation of a molecular portrait can help to guide the choice of an innovative treatment in up to 54% of patients. These data support molecular precision medicine programs in patients with r/rDLBCL.

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

295 GENETIC HETEROGENEITY IN B-CELL LYMPHOMA DETECTED BY NEXT-GENERATION SEQUENCING (NGS) TECHNOLOGY IN A COHORT OF 150 CHINESE PATIENTS

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Introduction: Lymphoma is one of the most common malignancies originating from cells of the immune system. In this study, we performed state-of-art next-generation sequencing (NGS) to uncover genetic alternations in a cohort of Chinese patients with B-cell lymphomas, which account for approximately 95% of lymphomas. Our results reveal a genetic profile that is descriptive in the Chinese population and provide insights to facilitate lymphoma diagnosis and therapy.

Methods: A cohort of 150 B-cell lymphoma patients were enrolled for whole exome sequencing (WES) using a HiSeq X instrument (Illumina, San Diego, CA). Genomic DNAs were prepared using the TruSeq Exome Library Prep Kit per vender's instructions (Illumina, San Diego, CA). Mutation sequences were determined by WES Base calling analysis using Illumina bcl2fastq software, version 2.15.

Results: We detected a total of 743 mutations in 57 genes and the average mutation rate per patient was 4.95. The most frequently mutated genes included *ITPKB* (28.00%), *KMT2D* (23.33%), *ID3* (21.33%), *PIM1* (18.67%), *CCND3* (18.00%), *SPEN* (17.33%), *TP53* (14.00%), *KMT2C* (12.67%), *TNFAIP3* (12.00%), *CD79B* (11.33%), *CIITA* (11.33%), *DTX1* (11.33%), *ARID1A* (10.67%), and *B2M* (10.67%). *ITPKB* regulates the levels of a large number of inositol

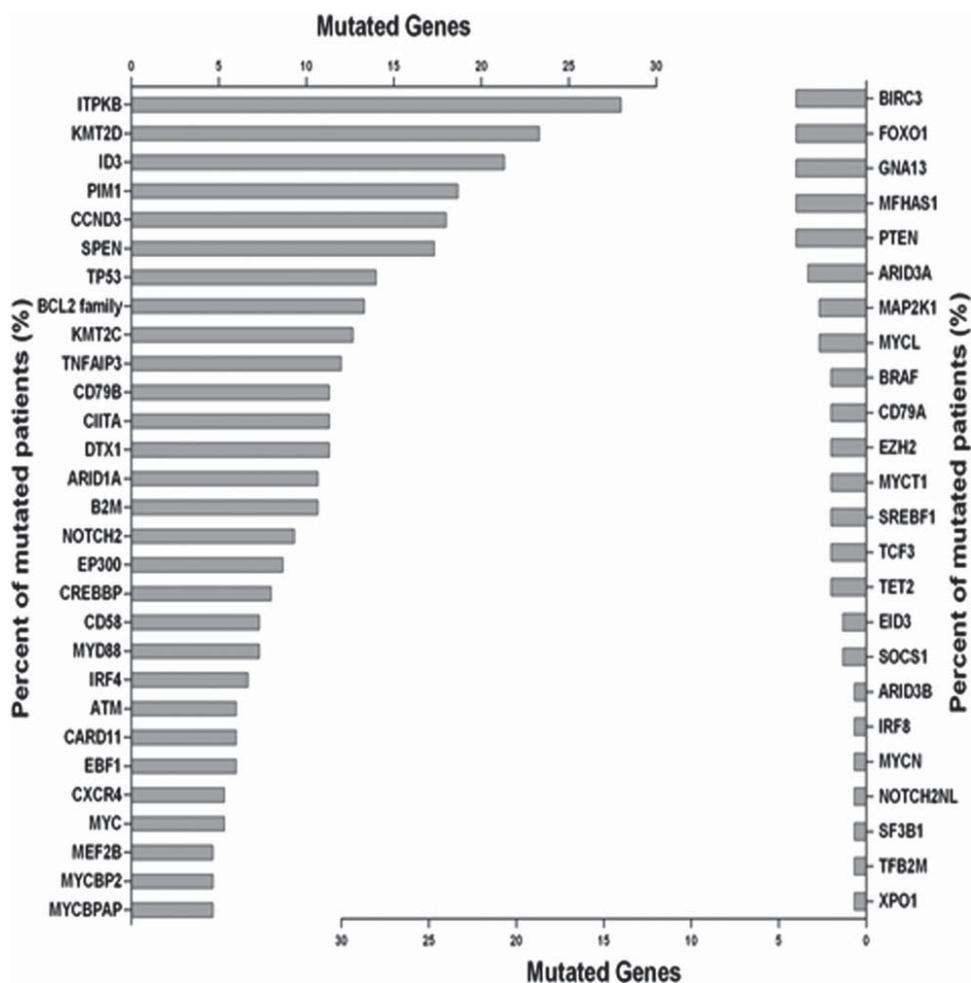


Figure 1: Mutation frequencies determined by WES in 150 Chinese patients with B-cell lymphoma

polyphosphates important in cellular signaling required for T-cell and B-cell development. Somatic mutations of KMT2D are predominantly found in follicular lymphoma (FL), resulting in the inability of KMT2D to activate gene transcription through H3K4 methylation. ID3 is a negative regulator of TCF3, which activates the prosurvival phosphatidylinositol-3-OH kinase pathway by enhancing B-cell receptor signaling in B-cell lymphomas. Specific pathways important in lymphomagenesis that likely were altered in this cohort of patients include apoptosis/cell cycle (CCND3, TP53, BCL2 family genes at 13.33%, FOXO1 4%, GNA13 4%, MFHAS1 4%, MYC 5.33%, XPO1 0.67%); immunity (B2M, CD58 7.33%, CIITA); NOTCH (NOTCH2 9.33%, DTX1, SPEN); NFκB (PIM1, TNFAIP3, CARD11 6%, IRF4 6.67%, MYD88 7.33%); epigenetic regulation (CREBBP 8%, EP300 8.67%, EZH2 2%, KMT2C, KMT2D, MEF2B 4.67%); MAP kinase (BRAF at 2%, MAP2K1 2.67%); and BCR (CD79A 2%, CD79B, ID3, ITPKB, TCF3 2%). PTEN (4%), TET2 (2%), and transcription factors ARID1A and ARID3A/B (4%), which are members of the SWI/SNF family, were also detected in this cohort of patients.

Conclusions: Our study demonstrates that B-cell lymphoma is characterized by remarkable genetic heterogeneity. The frequently mutated genes involved in different pathways identified by NGS may be further exploited for improving diagnosis and personalized therapies for patients with B-cell lymphomas.

Keywords: B-cell lymphoma; immune system; molecular genetics

296 IDENTIFYING SOMATIC MUTATIONS IN CELL-FREE DNA OF AGGRESSIVE LYMPHOMA PATIENTS: FIRST CELL-FREE DNA RESULTS FROM THE MOLECULAR PROFILING FOR LYMPHOMA (MAPLE) STUDY

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Introduction: Capturing the genomic landscape of a cancer located in multiple anatomical sites from a single biopsy is complicated by intertumour and intratumour heterogeneity. Recent work in solid tumours suggests that analysis of cell-free (cf) circulating tumour (ct) DNA might enable global characterisation of mutational profiles. However, cfDNA is primarily composed of DNA released by blood cells undergoing apoptosis; hence, ctDNA abundance and variant allele frequencies are very low, and comparable to the sequencing error rate, making development of reliable assays technically challenging, requiring optimisation of wet methods and bioinformatics. As part of the

Molecular profiling for Lymphoma (MaPLe) study, we developed a ctDNA test to establish the relationship between variants found in lymphoma biopsy samples and those observed in the cell free DNA (cfDNA).

Methods: A targeted panel of 50 genes was used to investigate cfDNA of patients from the MaPLe study with a confirmed diagnosis of diffuse large B-cell lymphoma (DLBCL). Lymphoma tissue and cfDNA from plasma were collected from 15 patients. Sequencing libraries were created using a combination of unique molecular tags (Thruplex Tag-seq) and a hybridisation and capture approach (IDT lockdown probes) and sequenced on the HiSeq2500 (Illumina). A number of different bioinformatic methods were compared: Briefly, alignment was carried out using BWA (v. 0.7.12) or Bowtie2 (v.2.2.4), deduplication was performed using Connor (v.0.5) or Curio, and variant calling was achieved using intersects of a number of different variant callers and Bayesian statistics.

Results: Total cfDNA extracted from 5 to 13.5 mL plasma varied from 36 to 2259 ng, with median value of 160 ng. Despite low inputs, libraries were successfully performed from all 15 cfDNA samples. Coverage of at least 1000× was calculated to be 99% across the targeted regions. Combining dilution experiments and molecular barcoding, we have been able to accurately detect known variants at allele frequencies of 0.2%, approaching the theoretical limit of detection. Preliminary results indicate that cfDNA variants may be called at frequencies as low as 0.05% if ultradeep (100 000×) targeted sequencing is performed. Comparison of the mutational spectra identified in cfDNA and in paired biopsies will be presented, as well as a comparison of results obtained with tagged and untagged libraries and different bioinformatic approaches.

Conclusion: We describe a novel highly sensitive approach for driver mutation specific detection of ctDNA in plasma from DLBCL patients. Our work in progress suggests ctDNA could be used to identify and track targetable mutations and to monitor presence of minimal residual disease.

Keywords: diffuse large B-cell lymphoma (DLBCL)

297 COMPREHENSIVE CHARACTERIZATION OF MUTATIONS, GENE EXPRESSION, AND IMMUNE REPERTOIRES IN MALIGNANT LYMPHOMA BY ANCHORED MULTIPLEX PCR AND NEXT-GENERATION SEQUENCING

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Background: Malignant lymphoma can be driven by a diversity of mutation types and can be classified into subtypes based on characteristic mutations or gene expression profiles. Furthermore, the spectrum of antigen receptors, or the immune repertoire, provides a means to identify malignant clones, enabling disease monitoring in response to

various interventions. However, comprehensive characterization of mutations, gene expression, and immune repertoires is challenging, as specific assays are required for each. We developed targeted NGS assays based on Anchored Multiplex PCR (AMP) that enable comprehensive mutation detection, gene expression analysis, and characterization of the expressed immune repertoire.

Methods: AMP uses molecular barcodes (MBCs) ligated to cDNA ends and gene-specific primers for amplification, enabling open-ended sequencing of target regions to identify both known and unknown mutations, including novel gene fusions. MBC adapters ligated to RNA fragments prior to amplification enable relative gene expression analysis. Furthermore, open-ended amplification enables immune chain mRNA interrogation from a single side, eliminating the need for opposing primers that bind within the highly variable V-segment and thus preventing clone dropout due to somatic hypermutation. This also facilitates CDR3 sequence capture from highly fragmented RNA inputs.

Results: We developed primer sets to detect known and unknown mutations and analyze relative gene expression levels in lymphoma. Here, we show the ability of this assay to detect characteristic IGH fusions as well as detect partner-gene expression levels in diffuse large B-cell lymphoma (DLBCL). Furthermore, this assay enabled NGS-based expression profiling for identification of DLBCL subtypes in a small cohort of samples. We also developed the Archer Immunoverse assay for sequencing of the expressed B-cell and T-cell repertoire. We validated the quantitative reproducibility and sensitivity of the AMP-based IGH assay using mRNA isolated from peripheral blood leukocytes of healthy and B-cell chronic lymphocytic leukemia (B-CLL) donors. Our data showed high reproducibility between replicates and quantitative clone tracking down to 0.01%, with the ability to determine IGHV mutational status. Furthermore, we identify a high-frequency B-cell clones in FFPE DLBCL samples as well as hypermutation status.

Conclusions: AMP-based NGS enables detection of mutations, gene expression, and the expressed immune repertoire for comprehensive characterization and monitoring of malignant lymphoma.

Keywords: gene expression profile (GEP); gene rearrangement; immunophenotype

298 KLOTHO SUPPRESSES TUMOR GROWTH OF T-CELL LYMPHOMA VIA INHIBITING IGF-1R SIGNALING

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Introduction: Klotho is a transmembrane protein and acts as an upstream modulator of insulin-like growth factor-1 receptor (IGF-1R) signaling, which was indicated to be involved in the pathogenesis of solid cancer and hematological malignancies, including T-cell lymphoma. Although Klotho was recently identified as a tumor suppressor in several types of human malignancies, the potential role of Klotho in T-cell lymphoma has never been investigated. In the present study, we

aimed to investigate the expression level and the molecular events of Klotho in T-cell lymphoma.

Methods: Lymph node samples from 35 newly diagnosed T-cell lymphoma and 20 reactive hyperplasia cases were collected with informed consents. Immunohistochemistry (IHC) assays were assessed for Klotho expression. Normal peripheral blood mononuclear cells were isolated with informed consents from healthy donors. Expression levels of Klotho mRNA and protein in T-cell lymphoma cells were determined by quantitative RT-PCR and western blotting. Lentivirus vectors either encoding Klotho (LV-KL) or empty lentiviral vector (LV-Con) were stably transfected into T-cell lymphoma cells. Cell viability and apoptosis were analyzed by cell counting kit-8 and Annexin V-PE/7AAD staining.

Results: We observed markedly decreased level of Klotho protein in the lymph nodes of T-cell lymphoma. Klotho positive rate was 14% (5 of 35) in T-cell lymphoma tissues whereas 75% (15 of 20) in normal lymph nodes. Reduction of Klotho was also confirmed in T-cell lymphoma cell lines (Jurkat, Molt-3, Karpas 299, and MyLa 3676) at mRNA and protein levels.

To explore the function relevance of Klotho in the progression of T-cell lymphoma, T-cell lymphoma cell lines (Jurkat, Molt-3, Karpas 299, and MyLa 3676) were stably transfected with either Klotho-overexpression lentivirus vectors or empty vector control. Significant decreased of cell viabilities was noted in T-cell lymphoma cells transfected with LV-KL, compared with those transfected with LV-Con.

Cells transfected with LV-KL exhibited enforced apoptosis rates in T-cell lymphoma cell lines. In addition, apoptotic promotion effect of Klotho was confirmed by Western blotting analysis. Remarkable reduction of anti-apoptotic protein Mcl-1 and total Caspase-3 protein were observed in Jurkat and Karpas 299 cell lines.

Jurkat and Karpas 299 cells transfected with LV-KL revealed significantly decreased phosphorylation level of IGF-1R. Moreover, the downstream targets of IGF-1R signaling, including AKT and ERK1/2, were also inhibited by Klotho overexpression.

Conclusions: Our observations identified for the first time that loss of Klotho expression contributed to the development of T-cell lymphoma via activating IGF-1R. Klotho may serve as a potential target for the therapeutic intervention of T-cell lymphoma.

Keywords: T-cell lymphoma (TCL)

299 METADHERIN PROMOTES THE INVASIVENESS OF DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is one of the most common non-Hodgkin's lymphoma (NHL) in the world. In recent years, using of monoclonal anti-CD20 antibody rituximab has significantly improved the outcomes of DLBCL patients. Yet there are still more than 30% DLBCL patients that have bad

outcomes. It will be necessary to find effective chemotherapy regimens to manage DLBCL. Although the risk factors for DLBCL are well known, the molecular and cellular mechanisms contributing to the invasiveness are poorly understood. In our previous studies, we have shown that MTDH functioned as an oncogene in the development and progression of DLBCL by activating Wnt/ β -catenin signaling. Recently, abundant experimental findings had shown that MTDH could regulate epithelial to mesenchymal transition (EMT) in several malignant diseases. At present study, we aimed to investigate the function of MTDH in the roles of invasion and migration in DLBCL.

Methods: The function of MTDH about invasion and migration in DLBCL was investigated by several following experimental techniques. The DLBCL cell lines LY8 were used in this study. Expression analyses in cell lines was performed by real-time PCR (RT-PCR) and Western blotting, compared with peripheral blood mononuclear cells (PBMCs) from the whole blood of healthy donors. MTDH expression in a group of 30 DLBCL patients was assessed by immunohistochemistry (IHC). Fifteen reactive hyperplasia patients were used as controls. Lentivirus transfection was used to knockdown the expression of MTDH. The abilities of migration and invasion of LY8 cell line were assessed by transwell assay. Changes of EMT markers were performed by western blotting.

Results: We found that MTDH protein was overexpressed in LY8 cell lines compared with peripheral blood mononuclear cells' (PBMCs) from healthy samples ($P < .05$). IHC assay showed that the expression MTDH protein had significant correlations with the clinical characteristics and the presence of B symptoms of DLBCL ($P < .05$). While it had no association with patient age and gender ($P > .05$). MTDH knockdown reduced the abilities of migration and invasion of LY8 cells. Downregulation the expression of MTDH resulted in a lower migration ratio ($21.67\% \pm 4.410\%$) compared with the control cells ($51.08\% \pm 8.816\%$). Also, the number of invasive cells was less than the control's (39.33 ± 7.446 vs 153.0 ± 9.452 , $P < .001$). Moreover, we found that there was a positive correlation between MTDH and two EMT markers, ZEB1 and vimentin.

Conclusions: Our data further confirm that MTDH is connected with the development of DLBCL. MTDH can promote the invasiveness of DLBCL. Moreover, there might be an EMT-like process regulated by MTDH in DLBCL. However, specific mechanism about these biologic behaviors needs further investigation and studies.

Keywords: diffuse large B-cell lymphoma (DLBCL)

300 WHOLE-EXOME ANALYSIS OF ABNORMALITIES LEADING TO WALDENSTRÖM'S MACROGLOBULINEMIA TRANSFORMATION INTO AGGRESSIVE LYMPHOMA

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R. García-Sanz¹

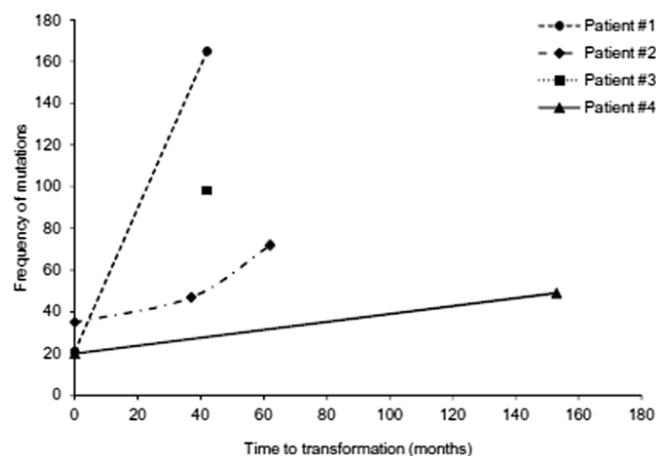
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Introduction: Waldenström's macroglobulinemia (WM) is characterized by bone marrow infiltration with lymphoplasmacytic lymphoma and the presence of an IgM monoclonal component. Although it has an indolent clinical course, transformation of WM to diffuse large B-cell lymphoma (DLBCL) occurs in up to 10% of patients and is associated with an adverse outcome. Despite of the progress about WM mutational profile, the mechanisms involved in the transformation to aggressive lymphoma have not been yet described. Here, we performed the first whole-exome sequencing study of WM patients who evolved to DLBCL and report the genetic alterations that may drive this process.

Patients and Methods: Matched tumour DNA at diagnosis and transformation and germline DNA from four patients diagnosed with transformed WM were included in the study. In one case, the diagnosis sample was not available. One extra sample corresponding to WM progression prior to transformation was also included. Cases were diagnosed according to the 2016 revision of the WHO classification. Sample tumour infiltration by flow cytometry was available in all cases. V(D)J rearrangements confirmed the same clone of matched tumour samples. Enrichment and generation of libraries were performed with the Agilent SureSelectXT2 Human All Exon V5 kit. Paired-end sequencing was carried out in the Illumina HiSeq 2000 platform with a depth of coverage ranging from 150 \times to 200 \times . Algorithms and non-commercial pipelines were used to call variants.

Results: After filtering out polymorphisms, a total of 421 nonsynonymous variants (NSV) in 355 genes were identified in the four patients. Of them, 39 (11%) were identified only in WM, 49 (14%) at both events, and 267 (75%) only at transformation. We observed a much higher frequency of mutated genes at transformation than at diagnosis (median 85 vs 21, $P < .001$), with a median gain of 70 variants (range 39-144) per case from WM to DLBCL. The number of gains was not correlated with the time to transformation (Figure 1). Recurrent NSV among different patients were identified. Thus, MYD88 L265P was present in all tumour samples, CD79B Y96C/H in 2/3 at diagnosis and 3/4 at transformation and CELSR2, FAM135B, IGFN1, and ZFH4 in at least two cases. At transformation, the most frequently acquired mutations affected FRYL, HNF1B, PER3, PIM1, and PTPRD. A fifth patient has also been tested at diagnosis and



transformation for *CD79B* mutations, and he presented a mutated *CD79B* gene at both moments.

Conclusions: Our results suggest that transformation depends on the frequency and specificity of acquired variants, rather than on the duration of its evolution. Recurrent mutations gained in some genes at transformation could represent cooperating events in the selection of the clones responsible for disease progression. Finally, the frequent mutation observed in the *CD79B* gene in this specific subset of patients, when it would be expected in ~10% of WM cases, implies that it could be a potential biomarker predicting transformation in WM. Results on four additional transformed WM cases will be presented at the meeting.

Keywords: diffuse large B-cell lymphoma (DLBCL); molecular genetics; Waldenström's macroglobulinemia (WM)

301 IDENTIFICATION AND GENE EXPRESSION ANALYSIS OF THE SIDE POPULATION SUBCLONE IN MANTLE CELL LYMPHOMA

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Introduction: It has been increasingly understood that seemingly effective treatments merely remove the bulk of tumor cells, while more rare cancer stem cells reside. The treatment resistant cells soon repopulate and form new tumor mass. These are often selected by the exposure to therapy and thus increasingly resistant. One way of identifying such cells is through analysis of the side population (SP) in tumor masses. In this study, we investigated the presence of SP in twenty-five lymphoma cell lines, representing five different types of B-cell lymphomas.

Methods: Cells were labelled with fluorescent DNA-binding dye Hoechst 33342, and SP cells were identified as a subpopulation of cells that have an elevated rate of Hoechst efflux. All samples were analyzed on a FACS Aria II (BD Bioscience, San Jose, CA, USA). Using cell sorting, both SP and non-SP cells could be isolated. The presence of SP was assessed in MCL patient samples and cell lines derived from MCL, FL, DLBCL, Burkitt's lymphoma (BL), and CLL. Subsequent gene expression analysis was performed using Affymetrix Human Transcriptome Array 2.0 (HTA 2.0; Affymetrix Inc, Santa Clara, CA, USA).

Results: The presence of SP was limited to one mantle cell lymphoma (MCL) derived primary sample (P3) and cell line (REC-1). Downstream analysis involving in vitro cultivation of sorted SP shows that SP cells are able to grow and differentiate into daughter cells and non-SP cells. Of interest, the frequency of SP cells was enriched when wild type REC-1 cells were exposed and became resistant to chemotherapy. Moreover, a differential gene expression profile between SP cells and non-SP cells was revealed by comprehensive gene expression analysis showing deregulation of group of genes involved in cell proliferation, cell cycle regulation, cell migration, BCR signaling, cancer progression,

and tumorigenesis. Of major importance, validation of gene expression results reveal that SP, compared to non-SP, exhibits significantly higher expression levels of CD44 and CD69, known to be involved in cancer stem cells and lymphocyte proliferation, respectively.

Conclusion: We show that SP is found among MCL patients and that genes involved in several cell signaling pathways are deregulated in SP derived from both REC-1 and patient material. This indicates that REC-1 can serve as a tool for future screening efforts. Importantly, we show evidence that CD69 and CD44 are commonly upregulated in SP cells from MCL patient material and could have important functional roles in relapse and treatment resistance.

Keywords: flow cytometry; mantle cell lymphoma (MCL)

302 NPM1-ALK OVEREXPRESSION-DRIVEN TOXICITY IN ALCL IS PARTNER DEPENDENT AND DRIVEN BY PHOSPHORYLATION OF NOVEL SUBSTRATES LEADING TO OVERSTIMULATION OF BIOSYNTHETIC PATHWAYS

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Introduction: Activation of the tyrosine-kinase domain of anaplastic lymphoma kinase (ALK) drives malignant growth in subsets of several cancers as part of oncogenic fusions resulting from chromosomal rearrangements. ALK stimulates several oncogenic pathways, including JAK/STAT3, MEK/ERK, and PI3K/AKT. Clinically, 70% of anaplastic large-cell lymphoma (ALCL) and ~5% of nonsmall-cell lung cancer (NSCLC) are ALK+. ALK tyrosine-kinase inhibitors (TKIs) are approved for treatment of NSCLC and are under investigation in ALCL. Clinical resistance in lung cancer typically develops within 10 to 12 months is due to, most commonly, activation of alternate pathways or second-site kinase-domain mutations. We and others previously reported that, unlike NSCLC, ALCL tumor cells have great difficulty finding alternate pathways to replace ALK and instead upregulate expression of the NPM1-ALK fusion to maintain survival during inhibitor exposure. Strikingly, we found a toxic overdose of ALK signaling when inhibitors are withdrawn from overexpressing cells, triggering death. Here, we explore the mechanisms by which ALK overactivation drives cellular toxicity.

Materials and Methods: We have generated multiple models of ALK+ ALCL with resistance to all generations ALK inhibitors. We employed RNAseq and phosphoproteomics to reveal candidate drivers of death upon ALK overexpression. We have generated multiple variant alleles of NPM1-ALK that enable us to interrogate the role of ALK's fusion partner in mediating these effects.

Results: All generations of ALK inhibitors drive NPM1-ALK overexpression as the most frequent resistance mechanism in ALCL, but

increased ALK activity upon inhibitor withdrawal is universally toxic. Extensive interrogations with targeted inhibitors and genetic approaches revealed that none of ALK's well-characterized downstream pathways is a key driver of overdose toxicity. Interestingly, while overexpression of NPM1-ALK confers selective disadvantage, elevated levels of activated ALK kinase domain alone do not. RNAseq analysis reveals hyperstimulation of protein biogenesis and RNA processing as cells die due to NPM1-ALK overdose. Phosphoproteomics results align with RNAseq data showing increased phosphorylation of proteins driving the same pathways. Taken together our results show the NPM1 translocation partner plays a key role driving NPM1-ALK overdose in ALCL by promoting phosphorylation of novel substrates.

Conclusions: In contrast to ALK+ NSCLC, ALCL cannot easily bypass a need for ALK by activating alternate pathways. NPM1-ALK overexpression-driven toxicity is partner dependent, driving death associated with hyperactivation of protein and RNA processing pathways. Drugs that drive ALK toward phosphorylation of noncanonical substrates therefore represent a novel therapeutic strategy worth pursuing in ALCL and other ALK-driven malignancies.

Keywords: ALK; anaplastic large cell lymphoma (ALCL)

303 MIR146-B EXPRESSION LEVELS CORRELATE WITH BIOLOGICAL AND CLINICAL FEATURES IN T-LGL LEUKEMIA

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Introduction: T-large granular lymphocytes leukemia (T-LGLL) is a rare disease characterized by the clonal expansion of T-large granular lymphocytes (T-LGLs), with CD8+/CD4- or less frequently CD4+/CD8^{dim/-} phenotype. LGL proliferation is maintained through defective apoptosis due to the activation of many survival signals, JAK/STAT signalling representing one of the most important deregulated pathways in T-LGLL. Moreover, somatic *STAT3* mutations conferring constitutive activation have been described in 30% to 40% of patients. Although *STAT3* is a known oncogene inducer, its relationship with microRNAs (miRNAs) has not yet been extensively evaluated in T-LGLL patients. Besides, many miRNAs act both as tumor suppressors and oncogenes in hematological malignancies where they contribute to oncogenesis dysregulating cell survival and proliferation. Based on these premises, we investigated whether *STAT3* could carry out its pathogenetic role in T-LGLL through an altered expression of miRNAs.

Methods: Six patients and 3 healthy controls were enrolled in a pilot study. *STAT3* mRNA expression and protein activation levels were analyzed by real time PCR and Western blot, respectively. The expression level of 756 mature miRNAs was assessed by using a TaqMan-based low density array on purified LGLs. Experimental data

were analyzed by ViiA7 RUO software, and the relative miRNA expression values were calculated using U6 as endogenous control. Results of this pilot study were validated on additional 12 T-LGLL patients and 3 healthy control subjects.

Results: Two clusters were identified by hierarchical cluster analysis (HCL): Cluster A included healthy controls and CD4+/CD8^{dim/-} LGL patients characterized by comparably low levels of *STAT3* activation (*S3_{low}*) and absence of *STAT3* mutations. Cluster B included 4 patients with CD8+/CD4- phenotype (3 with *STAT3* mutation) characterized by high levels of *STAT3* activation (*S3_{high}*). Comparative analysis of the miRNAs expressed identified 33 miRNAs upregulated and 8 miRNAs downregulated in *S3_{high}* as compared to *S3_{low}*, with 31/41 of these miRNAs level of expression being correlated with the level of *STAT3* expression/activation in LGL. Finally, 4 miRNAs expression levels were correlated with clinical characteristics, that is, the absolute neutrophil count (ANC), haemoglobin, and platelet count. In detail, miR-146b expression levels were significantly lower in CD8+/CD4- LGLs and were inversely correlated to *STAT3* phosphorylation levels and ANC.

Conclusions: These data firstly describe the miRNA pattern in T-LGLL, providing evidence that a series of miRNAs are correlated with biological features like LGL phenotype and *STAT3* activation/expression and mutations and clinical features, mainly neutropenia. These data will be further validated to identify the molecular connection between miR-146b and development of neutropenia.

Keywords: JAK/STAT; microRNA; non-Hodgkin lymphoma (NHL)

PATHOLOGY

304 FOLLICULAR LARGE CLEAVED CELL (CENTROCYTIC) LYMPHOMA: A DISTINCTIVE BUT UNRECOGNIZED VARIANT OF FOLLICULAR LYMPHOMA

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Introduction: The WHO classification recommends the subdivision of follicular lymphoma (FL) into three grades based on the average number of centroblasts per high-power field in the neoplastic follicles. However, we have encountered cases of FL in which the follicles are comprised predominately of large cells with cleaved nuclei (large

centrocytes), but without enough centroblasts to meet the WHO criteria for grade 3 FL (FL3), and have classified such cases as follicular large cleaved cell lymphoma (FLC). The objective of this study was to describe the pathologic and clinical features of a large series of patients with FLC.

Methods: The pathologic features of 72 cases of FLC were evaluated, including morphometry, immunostaining, and cytogenetic studies. Clinical features were tabulated and compared to a series of patients with the other subtypes of FL (332 FL1/2, 181 FL3), and survivals were compared for those treated with anthracycline-based chemotherapy plus rituximab.

Results: FLC has a follicular growth pattern with pale follicles at low magnification and frequent follicular and/or interfollicular fibrosis. Cytologically, the cells are predominantly large cleaved cells (centrocytes) with moderately coarse to fine chromatin, absent or inconspicuous nucleoli, and small to moderate amounts of pale cytoplasm. The mean nuclear diameter of the large cleaved cells was 10.1 μ , similar to centroblasts and approximately twice that of small lymphocytes. The t(14;18) was present in 83% of the cases, and a high proportion expressed BCL2 (84%), BCL6 (100%), and CD10 (88%) and had high ($\geq 30\%$) Ki67 proliferation (81%). However, almost one-half of the cases of FLC were misdiagnosed as low-grade FL. The clinical features of patients with FLC were similar to those with the other types of FL, and survival was excellent with anthracycline-based chemotherapy plus rituximab. The 5-year overall survival (OS) of these patients was 95% and the 5-year event-free survival (EFS) was 90%. No significant differences in OS were found between FLC, FL1/2, FL3A, or FL3B. However, FLC and FL3A had significantly better EFS than either FL1/2 ($P = .05$) or FL3B ($P = .028$).

Conclusions: FLC is a distinctive variant of follicular lymphoma, which should be recognized in future lymphoma classifications. The correct diagnosis of FLC is critical for the selection of appropriate therapy.

Keywords: B-cell lymphoma; follicular lymphoma (FL); R-CHOP

305 UNFAVORABLE PROGNOSTIC IMPACT OF MYC INCREASED COPY NUMBER (ICN) IN PATIENTS WITH DIFFUSE LARGE B-CELL (DLBCL) AND HIGH-GRADE LYMPHOMA TREATED WITH IMMUNOCHEMOTHERAPY

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Introduction: MYC rearrangements occur approximately in 5% to 15% of DLBCL and are known to unfavorably impact on patient (pt) survival. Also, numerical aberrations of MYC seem to influence the outcome of these pts, but there is no consensus on their correct identification and prognostic significance. We report a single center experience on the clinical outcome of pts with MYC ICN in the setting of aggressive B-cell lymphoma.

Methods: A total of 408 consecutive pts with de novo (354) or transformed (TL) (34) DLBCL or B-cell lymphoma unclassifiable (BCLU) (20) were studied by FISH using splitsignal DNA probes (Dako) specific for MYC, BCL2, and BCL6 from 2011 to 2016. Sixty evaluable nuclei with complete signals were scored. MYC ICN was defined when ≥ 3 copies were identified. Amplification was defined as countless copies of MYC resulting in a "cloud-like" FISH pattern. Cutoff for positive MYC expression by immunohistochemistry (IHC) was $>40\%$.

Results: Of 93 pts with MYC abnormalities (22.8%), 33 (35.5%) had translocations (MYC-T), 56 (60.2%) had ICN (MYC-ICN) (3-10 copies per cell in 47, not evaluable in 9 cases), and 4 (4.2%) had amplification (MYC-AMP). MYC-T included 9 single-hit (SH), 18 double-hit (DH), and 6 triple-hit (TH) DLBCL. Their overall survival (OS) was similar ($P = .9$). Overall, increasing copies correlated with worsening OS, with MYC-ICN > 7 and MYC-AMP having the worst prognosis ($P = .01$) (Figure A). Among MYC-ICN, presence of ≤ 4 copies subdivided pts in two subgroups with significantly different OS ($P = .04$). The clinical features and OS of the 4 groups MYC-T, MYC-ICN ≤ 4 , MYC-ICN > 4 , and MYC-AMP are summarized in Table I and Figure B. BCLU clustered in the MYC-T group ($P = .03$), whereas $>80\%$ of MYC-ICN pts had DLBCL ($P = 0.06$). MYC IHC was strongly positive in $>90\%$ of cases with MYC-T and MYC-ICN > 4 and was low in the only MYC-AMP pt with a favorable outcome. Intensified therapy (R-DA-EPOCH, Burkitt's-like or ASCT consolidation) was given to 54% of pts, without significant advantage.

Conclusions: Our study demonstrates that numerical aberrations of MYC are common in aggressive B-cell lymphomas and significantly impact on prognosis. MYC ICN > 4 and particularly "amplification" are associated with an inferior outcome; their biological significance and the possible benefit of specific or intensified therapeutic strategies need further investigation.

Keywords: diffuse large B-cell lymphoma (DLBCL); fluorescence in situ hybridization (FISH); MYC

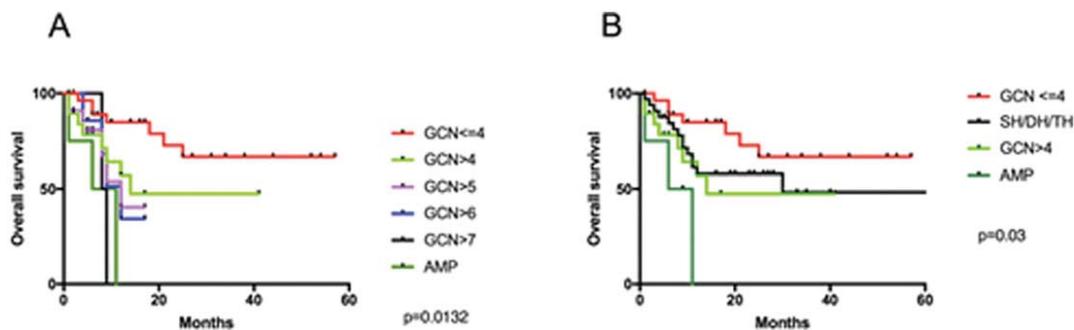


TABLE 1

	MYC-T	MYC-ICN ≤ 4	MYC-ICN > 4	MYC-AMP	P value
N	33	28	19	4	-
Median age (range)	67 (29-88)	65.5 (22-85)	71 (30-80)	67 (58-74)	0.8
Male, n (%)	23 (70)	19 (68)	9 (47)	4 (100)	0.15
Stage III-IV, n (%)	24/30 (80)	21/27 (78)	13/16 (81)	4 (100)	0.7
IPI 3-4, n (%)	19/27 (70)	15/25 (60)	12/15 (80)	4 (100)	0.3
IHC MYC POS	22/23 (96)	10/13 (77)	13/14 (93)	2/3 (66)	0.2
DLBCL	20 (60)	24 (86)	16 (84)	2 (50)	0.06
TL	8 (24)	4 (14)	3 (16)	1 (25)	0.3
BCLU	5 (15)	0	0	1 (25)	0.03
CHOP-like, n (%)	9 (27)	14 (50)	12 (63)	2 (50)	0.07
Intensified, n (%)	21 (63)	10 (36)	6 (31)	2 (50)	0.07
Palliative	43 (10)	44 (14)	1 (6)	0	0.66

306 PROGNOSTIC IMPACT OF “MYC/BCL-2 DOUBLE EXPRESSORS” IN DIFFUSE LARGE B-CELL LYMPHOMA

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Background: The presence of MYC and BCL2 and/or BCL6 rearrangements (double-/triple-hit lymphoma) in DLBCL seems to be associated with a dismal bad prognosis. On the other hand, immunohistochemical (IHC) analysis has revealed that concurrent protein expression of MYC and BCL2 in DLBCL (“so-called double expressors”) could have a prognostic impact associated with a nongermlinal center phenotype.

Objectives: The aim of this study was to clarify the clinical prognostic value of immunostaining and chromosomal translocation of MYC, BCL2, and BCL6 in a series of 102 adults consecutively diagnosed of DLBCL in our institution from 2001 to 2015.

Patients and Methods: One hundred and two patients were included. MYC, BCL2, and BCL6 rearrangements were detected by FISH, and expressions of MYC, BCL2, and BCL6 proteins were investigated by IHC. Some of them were analyzed retrospectively in tissue microarray (TMA). Dual positivity for MYC (cutoff >40%) and BCL2 (cutoff >50%) proteins identified a double protein expressor (DE) phenotype. Cell of origin (COO) classification was achieved using the Hans algorithm. Overall survival (OS) and time to progression (TTP) were estimated by the Kaplan-Meier method.

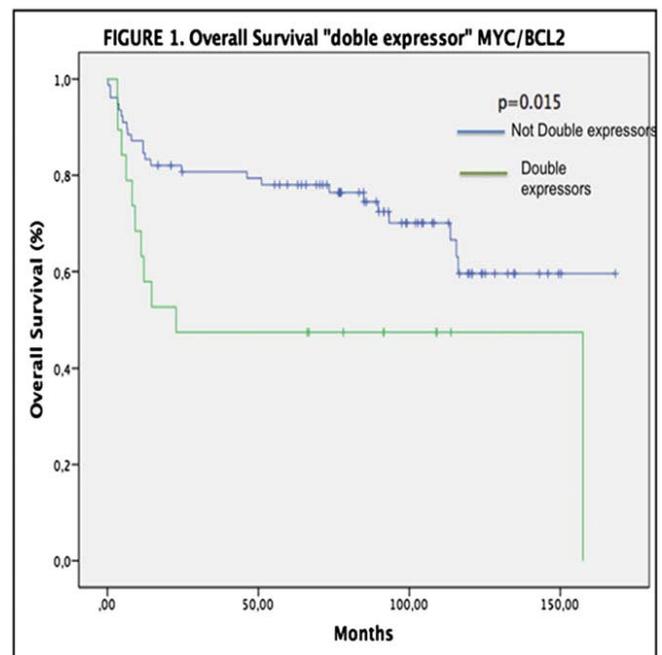
Results: Median age of the series was 67 years (range 26-89) with a slight male predominance 53 (52%). Median follow-up period was 78 months (range, 0-168). All patients were treated with immunochemotherapy schedules, mostly R-CHOP and some cases methotrexate/cytarabine based. COO determination revealed 43 (42,6%) cases to be GCB subtype and 57 (57,4%) cases ABC. The main clinical characteristics are detailed in Table 1. Only 10 of

cases (10,2%) had MYC and BCL2 rearrangements (DHIT). No differences in terms of OS and TTP between DHIT patients ($P = .57$ and $P = .61$).

MYC protein overexpression occurred in 32 (31,4%) patients and 20 (19,6%) of them overexpressed both MYC and BCL2. As had been reported before, DE cases appear more common in the ABC subtype (75%). DE patients had significantly worse 5-year OS and TTP at 5 years than non-DE (47% versus 66%, $P = .015$ and 64% vs 84%, $P = .055$, log-rank test), as shown in Figure 1. Eleven DE patients needed a minimum of two lines of treatment, and three of them (15%) received an autologous transplant consolidation.

A total of 75% of DE patients belonged to the nongermlinal center group. Stratifying all patients into GCB and non-GCB subtypes, only ABC had significantly worse both OS and PFS.

Conclusions: In our experience, double expression of myc/bcl-2 proteins had an adverse prognostic impact with conventional R-CHOP and identified a poor-risk subset of patients where new treatment options are needed. In our hands, double-hit patients had similar prognosis than the rest of patients, probably due to the small



	N (%)	OS / P	PFS / P
Age			
≤60	40 (39,2%)	0,027	0,04
>60	62 (60,8%)		
Stage			
I-II	42 (41,2%)	0,241	0,149
III-IV	60 (58,8%)		
IPI risk group*			
0-2	45 (51,1%)	0,823	0,571
3-5	43 (48,9%)		
Treatment response*			
CR	80 (79,2%)	0,000	0,000
Others	21 (22,8%)		
COO classification*			
GCB	43 (42,2%)	0,056	0,028
ABC	58 (56,9%)		
Double expressor			
No	78 (69,2%)	0,015	0,055
Yes	19 (42,1%)		
Double HIT			
No	88 (89,8%)	0,57	0,61
Yes	10 (10,2%)		
Cell of origin			
GCB subtype	43 (42,6%)	0,017	0,003
ABC subtype	58 (57,4%)		

Table 1: Clinicopathological characteristics.

sample size and the use of methotrexate/cytarabine regimens. Moreover, cell of origin classification with a Hans scheme is a good prognostic tool to discriminate an aggressive clinical course in our series.

Keywords: “double-hit” lymphomas; activated B-cell-like (ABC)

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BCL2 MRNA OR PROTEIN ABUNDANCE IS SUPERIOR TO GENE REARRANGEMENT STATUS IN PREDICTING CLINICAL OUTCOMES IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: *BCL2* is important in lymphomagenesis and represents a candidate biomarker in DLBCL. However, the optimal approach for ascertaining *BCL2* status in biopsy specimens is uncertain. Here, we determined *BCL2* rearrangement status by fluorescence in situ hybridization (FISH), mRNA abundance by NanoString, and protein

abundance by immunohistochemistry (IHC) or quantitative immunofluorescence (IF) in pretreatment FFPE biopsy specimens to ascertain the most clinically meaningful measures.

Methods: We identified 56 cases of *de novo* DLBCL treated with R-CHOP from which pretreatment FFPE biopsy samples were available. To quantify *BCL2* expression by IF, digital images were created by scanning histology sections coimmunostained for *BCL2* and CD20, then *BCL2* fluorescence signals were quantified objectively in CD20-positive cells.

Results: *BCL2* rearrangement or, interestingly, increased copy number of *BCL2* was associated with greater mRNA and protein abundance according to either IHC or IF ($P < .005$ for all comparisons). *BCL2* mRNA abundance was associated with elevated protein abundance by IHC ($P < .0001$) and IF ($r_s = 0.65$; $P < .0001$) (Figure 1). In contrast, *MYC* gene rearrangement, but not increased copy number, was associated with more *MYC* mRNA and more protein based on IHC ($P < .005$ for all comparisons). Elevated *BCL2* expression was associated with a reduced complete response rate to R-CHOP (mRNA, $P = .002$; IHC, $P = .03$; IF, $P = .03$) and reduced overall survival (OS; mRNA, $P = .045$; Figure 1), whereas neither *BCL2* rearrangement ($P = .48$), *MYC* rearrangement ($P = .83$), *MYC* mRNA ($P = .08$) or protein expression ($P = .56$), *MYC/BCL2* “double-hit” ($P = .75$), nor “dual expression” status ($P = .41$) was associated with reduced OS.

Conclusions: Genetic alterations exert oncogenic effects by altering protein function or abundance. We used objective, quantitative data from FFPE samples to confirm the association between

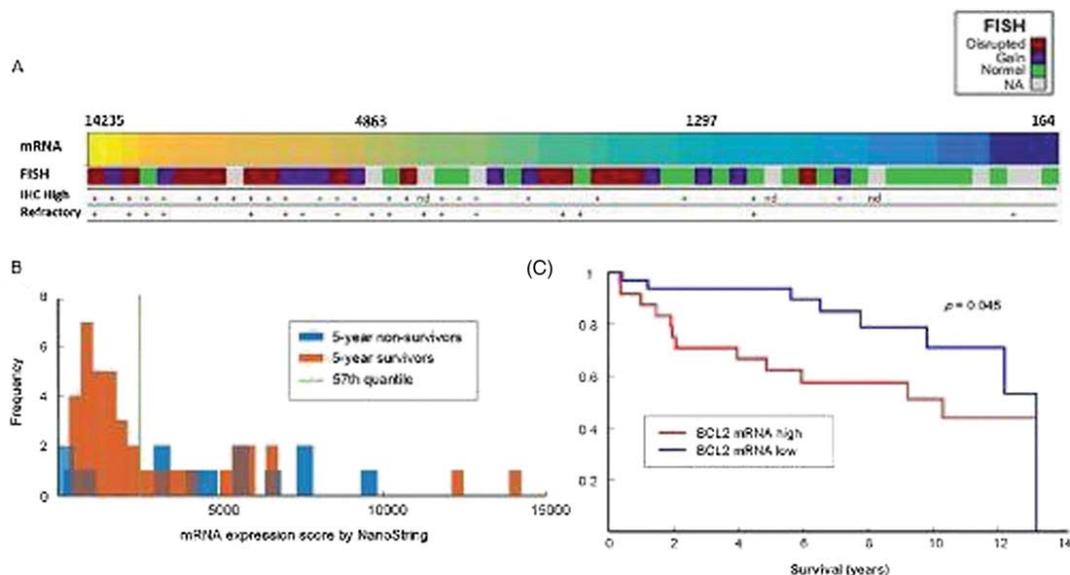


Figure 1. Associations between *BCL2* mRNA abundance, gene rearrangement, protein expression, response to treatment and overall survival.

(A) *BCL2* mRNA abundance was associated with *BCL2* gene rearrangement (FISH, red), copy number gain (FISH purple), elevated protein abundance (IHC High), as well as resistance to R-CHOP therapy (Refractory). (B) Based on visual inspection of the histogram, a cut-point was determined (57th quantile) (green line) to separate cases into *BCL2* mRNA-high and -low categories. (C) *BCL2* mRNA-high cases (red) had inferior 5-year overall survival compared to *BCL2*-low cases (blue; $p=0.045$).

rearrangement of the *BCL2* or *MYC* gene with mRNA- and protein-based measures of expression and suggest that elevated *BCL2* expression is superior to gene arrangement status in predicting clinical outcomes in DLBCL. Interestingly, prognostic power is not increased when measures of *MYC* status are considered. Objective, quantitative measures of *BCL2* expression applicable to FFPE samples have a potential role in identifying DLBCL cases that are likely to be resistant to R-CHOP therapy.

Keywords: “double-hit” lymphomas; *BCL2*; diffuse large B-cell lymphoma (DLBCL)

308 THE CLINICAL SIGNIFICANCE OF C-MYC EXPRESSION, REARRANGEMENT, AND COPY NUMBER GAIN IN EXTRANODAL NK/T-CELL LYMPHOMA: A RETROSPECTIVE STUDY IN CHINA

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Extranodal NK/T-cell lymphoma (ENKTL), nasal type, is an aggressive lymphoma characterized by rapid clinical progression, unfavourable prognosis, and short survival time. The aim of this study is to investigate the correlation between c-MYC protein expression, gene rearrangement, gene copy number, and the prognosis of ENKTL. Immunohistochemistry for CD20, CD3, CD56, TIA-1, Ki-67, and c-MYC was performed on tissue sections from 68 patients diagnosed with ENKTL. In situ hybridization was performed to detect EBV-

encoded small RNA (EBER). C-MYC genetic alterations (located on chromosome 8q24) were detected by using fluorescence in situ hybridization (FISH). Sixty cases of nasopharyngeal mucosal lymphoid tissue hyperplasia were selected as a normal control group of c-MYC gene and protein. Immunophenotypically, CD3 and TIA-1 were positive in all cases, CD56 was positive in 54 cases (79.41%), and CD20 was all negative. Ki-67 proliferation index of more than 50% accounted for 94.12% (64/68). In situ hybridization for EBER was positive in all cases. The positive expression rate of c-MYC (>40% of tumor cells with nuclear staining regarded as positive) in ENKTL was 50% (34/68), which was much higher than those in nasopharyngeal mucosal lymphoid tissue hyperplasia (0%, 0/60) ($P < .05$). C-MYC protein overexpression was associated with treatment efficacy. Patients with high expression of c-MYC have poor treatment efficacy ($P < .05$). Fluorescence in situ hybridization results showed that c-MYC gene rearrangements were not detected in any cases, but 26.47% (18/68) had increased c-MYC gene copy number. The gain of c-MYC copy number was positively correlated with c-MYC protein expression ($P < .05$). Kaplan-Meier analysis showed that the OS of the patients in c-MYC positive expression group was significantly shorter than that of the patients with negative expression group ($P < .05$). The gain of c-MYC copy number was not associated with prognosis ($P > .05$). Multivariable Cox regression analysis further confirmed that clinical stage and c-MYC positive expression could be as independent prognostic factors in patients with ENKTL. The abnormal expression of c-MYC protein may play an important role in the development and progression of extranodal NK/T-cell lymphoma and influence the prognosis of patients.

Keywords: MYC; non-Hodgkin lymphoma (NHL); T-cell lymphoma (TCL)

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CD30 EXPRESSION IN DIFFUSE LARGE B-CELL LYMPHOMA CORRELATES WITH NON-GCB SUBTYPE BUT DOES NOT HAVE PROGNOSTIC IMPACT IN PATIENTS TREATED WITH FIRST LINE R-CHOP/R-CHOP-like

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Background: DLBCL is a heterogeneous disease with 30% of patients presenting as refractory/relapsing disease following R-CHOP treatment. New prognostic factors to identify the poor-risk population and alternative therapies for them are needed. CD30 is a member of the tumour necrosis factor receptor super family and is expressed by several types non-Hodgkin lymphomas. Brentuximab vedtin, an anti-CD30 antibody, is used in clinical practice for Hodgkin lymphoma and systemic anaplastic large-cell lymphoma. The significance of CD30 expression in DLBCL remains unknown. We aimed to study the expression of CD30 in a large cohort of the novo DLBCL patients homogeneously treated with R-CHOP/R-CHOP-like to evaluate its correlation with characteristics at diagnosis and its impact in clinical outcome.

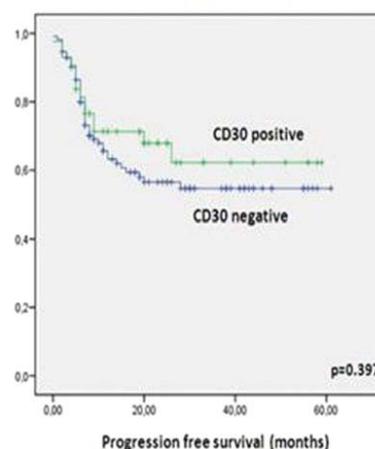
Methods: We prospectively registered all patients diagnosed of DLBCL between January 2012 to August 2016. Pathology review was performed in all cases. Patients with primary central nervous system DLBCL, transformed lymphoma, or post-transplant DLBCL were excluded. Immunohistochemistry was performed on 4 microns' paraffin sections using routine protocols, CD30 expression was analysed using the antibody CD30 clone BerH2, dilution 1:30; Dako; staining in more than 10% of the malignant cells was considered positive. Samples were classified as germinal center B-cell-like (GCB) vs non-GCB per Hans algorithm.

Results: Among the 174 cases analyzed, CD30 was expressed in 47 (27.0%). Characteristics at disease presentation are shown in Table 1. The expression of CD30 was significantly higher in the non-GCB subtype cases ($P = .0001$) and in younger patients <60 ($P = .015$). One hundred fifty-five patients were homogeneously treated, 139 with R-CHOP and 16 with R-CHOP-like, and were included in the outcome analyses. Overall response rate was similar in both groups, 77/111 (68.8%) in

TABLE 1

	CD30- n = 111	CD30+ n = 44	P value
Age ≥ 60	80 (63%)	20 (42.6%)	.01
Male	66 (52%)	20 (42.6%)	.27
ECOG ≥ 2	37 (29.1%)	10 (21.3%)	.30
Ann Arbor III-IV	88 (69.3%)	31 (66%)	.67
Bulky mass (>5 cm)	48 (37.8%)	21 (44.7%)	.41
Extranodal involvement	94 (74%)	34 (72.3%)	.82
B symptoms	37 (29.1%)	14 (29.8%)	.93
Elevated LDH	72 (56.7%)	27 (57.4%)	.92
Non-GCB	54 (42.5%)	37 (78.7%)	.00
IPI 3-5	76 (59.8%)	22 (48.9%)	.12

Image 1. Progression free survival for patients homogeneously treated by R-CHOP / R-CHOP like:



CD30- vs 35/44 (79.9%) in CD30+. With a median follow-up of 15 months, no differences were found neither in PFS or OS (Figure 1). In the multivariate analyses including the following independent variables, gender, B symptoms, Bulky mass (>5 cm), cell of origin (GCB vs non-GCB), IPI, and CD30 expression, IPI 3-5 was the only factor significantly related with poor PFS (HR 2.36, 95% CI, 1.303-4.302, $P = .005$). **Conclusion:** CD30 is expressed in one-third of DLBCL patients, in whom an anti-CD30 therapy could be used. CD30 expression is significantly higher in patients with non-GCB DLBCL, however, its expression does not influence either response to R-CHOP/R-CHOP-like therapy or survival.

Keywords: CD30; diffuse large B-cell lymphoma (DLBCL)

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ANALYSIS OF PRECLINICAL AND CLINICAL SAMPLES AFTER TREATMENT WITH A CD37 TARGETING ANTIBODY DRUG CONJUGATE (AGS67E) SUPPORT A HIGH LEVEL OF CD37 EXPRESSION IN NHL

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Introduction: AGS67E is an antibody drug conjugate against CD37 bound to monomethyl auristatin E (MMAE) via a protease-cleavable linker currently being investigated in subjects with relapsed/refractory NHL in a phase I dose-escalation study. CD37 is expressed in normal white blood cells (WBCs: B and T lymphocytes, NK cells, monocytes, and neutrophils). CD37 is also highly expressed in CLL, AML, and NHL, including 80% expression in DLBCL, as detected in tumor microarrays (TMA) of formalin-fixed paraffin-embedded (FFPE) tumor samples using the proprietary vCD37-9a73.1 antibody (Pereira et al., 2015). In contrast, the percentage of CD37 expression in DLBCL was recently determined to be 40% using a commercial antibody (2B8) on FFPE samples (Xu-Monette et al., 2016). Clinical and preclinical results, including a comparison of vCD37-9a73.1 with commercially available anti-CD37 reagents, are presented here in order to clarify the CD37 expression in DLBCL and in NHL in general.

Methods: CD37 expression was investigated on WBCs by flow cytometry and on archived FFPE tumor samples by immunohistochemistry (IHC) from subjects in the phase I trial using the proprietary anti-CD37 antibody (vCD37-9a73.1). This antibody was selected for flow cytometry since it could detect CD37 on the surface of cells in the presence of AGS67E and showed similar CD37 levels to other anti-CD37 proprietary antibodies tested. The vCD37-9a73.1 and 2B8 antibodies were evaluated by IHC in FFPE cells and xenografts with different levels of CD37 mRNA levels, as well as in TMA of NHL.

Results: CD37 expression in patient's WBCs was downregulated after AGS67E dosing, presumably due to AGS67E-mediated, dose-dependent decreases in WBCs. Furthermore, samples were CD37 positive as detected by both AGS67E and vCD37-9a73.1. These data support vCD37-9a73.1 as a suitable reagent for CD37 detection. IHC data from FFPE tumor samples from subjects enrolled in the ongoing phase I clinical trial with a variety of NHL pathologies demonstrated that CD37 was expressed in 100% of the samples examined (23 subjects) with an average H-score of 270 (maximum is 300), including 7 subjects with DLBCL (average H-score 277). Overall, the level and degree of expression were slightly higher than previously seen in TMA samples of NHL (~80%) with the same antibody and significantly higher than those reported with the 2B8 antibody. Evaluation of CD37 expression using vCD37-9a73.1 side-by-side with 2B8 in FFPE cells, xenografts, and TMA of NHL indicated that vCD37-9a73.1 has better sensitivity and specificity compared to 2B8 under the conditions tested.

Conclusions: The data presented here demonstrated a high level of expression and CD37 detection of ≥80% in NHL, including DLBCL.

Keywords: CD37; diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL)

311 ROLE OF GENETIC POLYMORPHISMS ON R-CHOP EFFICACY IN DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS: AN INTERIM ANALYSIS OF A MULTICENTER PROSPECTIVE PHARMACOGENETIC STUDY

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Introduction: Standard chemotherapy represented by the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen is successful in about 60% of patients (pts) with diffuse large B-cell lymphoma (DLBCL). Pts who do not benefit from this treatment, due to the development of tumor drug resistance, have a very poor prognosis.

Currently, knowledge on reasons of treatment-related failures in DLBCL are scanty and predictive biomarker of response are largely unknown. We hypothesized that polymorphisms of gene involved in the pharmacokinetics and pharmacodynamics of drugs included in R-CHOP regimen may play a role in predicting the outcome in DLBCL pts. Thus, we designed a multicentre prospective pharmacogenetic trial aimed at identifying gene polymorphisms potentially predictive of drug efficacy/resistance in DLBCL pts treated with R-CHOP. We are reporting update data of an interim analysis on the first 80 enrolled pts.

Methods: The study includes chemonaive DLBCL pts (Ann Arbor I-IV stages) candidate to an R-CHOP standard treatment. The ethical committee of each participating centre approved the pharmacogenetic protocol, and all pts signed a written informed consent.

In this interim analysis, the impact of single nucleotide polymorphisms (SNPs) on R-CHOP efficacy was evaluated by objective response (OR) rate, progression-free survival (PFS), and overall survival (OS).

The efficacy of R-CHOP was evaluated according to Cheson criteria by performing standard hematochemical and instrumental (TC and FDFG-PET) tests and defining complete remission (CR), partial remission (PR), and non response or progressive disease (PD).

Genomic DNA was extracted from peripheral blood of 80 pts. SNPs analysis was performed by an Affimetrix array. To date, 21 SNPs from 19 candidate genes (ABCB1, ABCC1, ABCC2, ABCG2, CYBA, CYP2C9, FCGR2A, GSTP1, IL2, MARCKS, MLH1, NCF4, NQO1, NQO2, RAC2,

1. Pereira et al. *Mol Cancer Ther.* 2015;14(7):1650-60
2. Xu-Monette et al. *Blood.* 2016;128(26):3083-3100

TNF, TOP2A, TP53, and TUBB) involved in pharmacokinetics and pharmacodynamics of R-CHOP (www.pharmgkb.org) selected and analysed in relation to R-CHOP efficacy. Univariate and multivariate logistic regression analyses were performed to evaluate associations between SNPs and clinical/pathological characteristics or survival parameters (PFS and OS).

Results: Median age was 63 years. There were 37 men and 43 women. A total of 47.5% of pts were in stage I-II and 52.5% of pts in stage III-IV. 27.5% of pts had bulky disease; 43.8% of pts had involvement of extranodal site. 47.5% of pts had pathological LDH value. According to the revised IPI, 15% of pts were in the low-risk group, 58.7% in the intermediate, and 26.3% in the high-risk group. Overall, 468 courses of R-CHOP had been administered (mean: 5.85 courses, range: 4-6). A total of 88.7% of pts had CR to R-CHOP whereas the remaining showed PR or SD (7.5%) or PD (3.8%). Multivariate analysis identified *FCGR2A* rs1801274 as a predictor of PFS ($P = .045$). Pts with HR or RR genotypes showed shorter PFS than pts with HH genotype (HR: 2.437, 95% CI, 1.020-5.823). No statistically significant correlation was found between SNPs and OS.

Conclusions: Our preliminary data obtained in a limited number of pts show an association between a SNP of the low affinity *FCGR2A* gene involved in the activity of rituximab and PFS. Further insights will derive from the completion of pts accrual to reach the planned number of cases at the end of our study.

Acknowledgements: This work was supported by a grant from the Associazione Giacomo Onlus, Castiglioncello (LI), Italy to E.M. and Cassa di Risparmio di Firenze, Firenze, Italy to S.N.

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

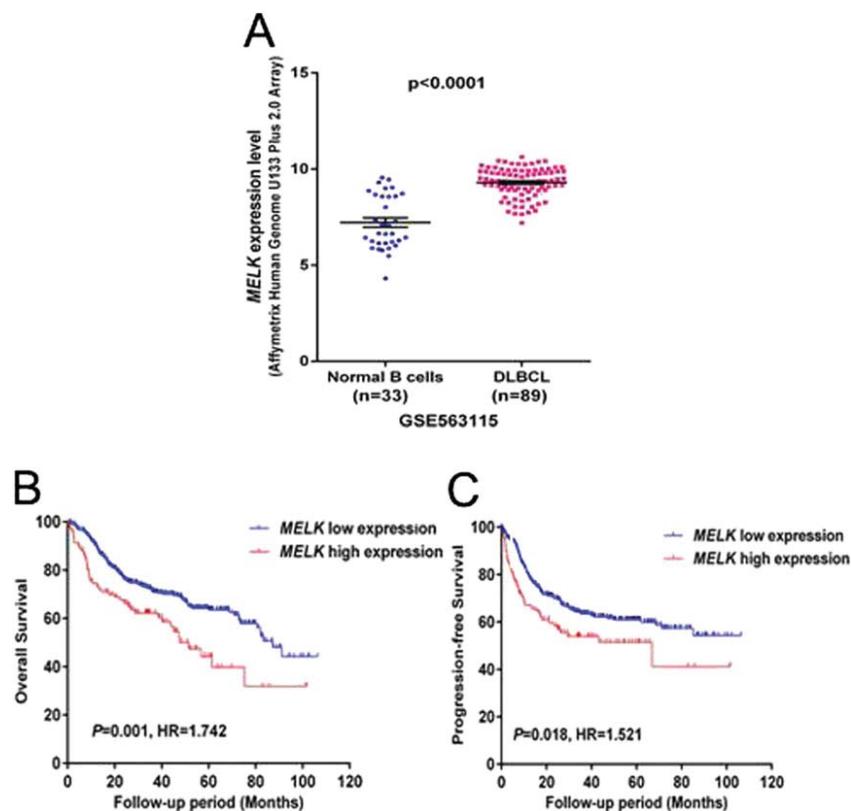
312 MELK SERVES AS A POTENT INDEPENDENT BIOMARKER TO PREDICT SURVIVAL OF DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS TREATED WITH RITUXIMAB-CHOP REGIMEN

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Introduction: Maternal embryonic leucine zipper kinase (MELK) is a novel oncogene, which plays pivotal roles in maintenance of cancer stem cells and cancer cell survival. However, the clinical significance of MELK in the progression of diffuse large B-cell lymphoma (DLBCL) remains poorly understood. Currently, 30% to 40% DLBCL patients remain incurable with standard therapy (cyclophosphamide, doxorubicin, vincristine, prednisone combined with rituximab, and R-CHOP), resulting in multiple studies on identifying effective prognostic biomarker. Herein, we aimed to assess prognostic significance of MELK in DLBCL patients with R-CHOP regimen.

Methods: MELK expression pattern in DLBCL and normal lymph node tissues was characterized in microarray from Gene Expression Ominous (GEO) GSE56315. Prognostic value of MELK expression was evaluated in 471 de novo DLBCL patients treated with R-CHOP, collected as part of the International DLBCL R-CHOP Consortium Program Study, on tissue microarray from GSE31312 using Affymetrix GeneChip Human Genome HG-U133 Plus 2.0 chips. Optimal cutoff value of MELK expression was determined by calculating Youden's



index from receiver operating characteristic (ROC) curve. Kaplan-Meier survival curve analyses with log-rank test, univariate and multivariate Cox regression model analyses of overall survival (OS), and progression-free survival (PFS) were performed. Gene ontology (GO) and kyoto encyclopedia of genes and genomes (KEGG) analysis in whole-genome profiling were conducted to predict potential functions of MELK in DLBCL.

Results: Markedly increased expression of MELK in DLBCL tissues (9.299 ± 0.081 , $n = 89$) compared with B cells from normal tonsil tissues (7.218 ± 0.243 , $n = 33$) were observed (Figure A). Furthermore, in the cohort of 471 DLBCL patients with R-CHOP treatment, stratified high MELK expression is closely associated with advanced Ann Arbor stage ($P = .026$), high IPI score ($P = .036$), activated B-cell-like (ABC) DLBCL subtype ($P = .013$), and patients' non-CR rates ($P = .001$). Kaplan-Meier survival curve analyses indicated MELK overexpression was of significant correlation with inferior OS ($P = .001$) and PFS ($P = .018$) (Figure B, C). Multivariate Cox regression analysis adjusting for validated significant parameters in univariate analysis confirmed independent prognostic value of MELK in OS of DLBCL patients (HR: 1.600; 95% CI, 1.096-2.335, $P = .015$). Functional enrichment assays indicate that MELK is tightly associated with biological processes including cell division, apoptosis process and cell cycle. Besides, MELK might contribute to cancer progression of DLBCL via regulating PI3K/Akt, Ras, and p53 signaling pathways.

Conclusions: We identify that MELK is an independent prognostic marker in DLBCL patients with R-CHOP regimen. Further prospective validation are warranted to stratify patients groups with DLBCL, thus formulating individual therapeutic strategies and improving patients' survival.

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

313 BMI-1 PROTEIN EXPRESSION AS A NEGATIVE INDEPENDENT PROGNOSTIC FACTOR IN DLBCL

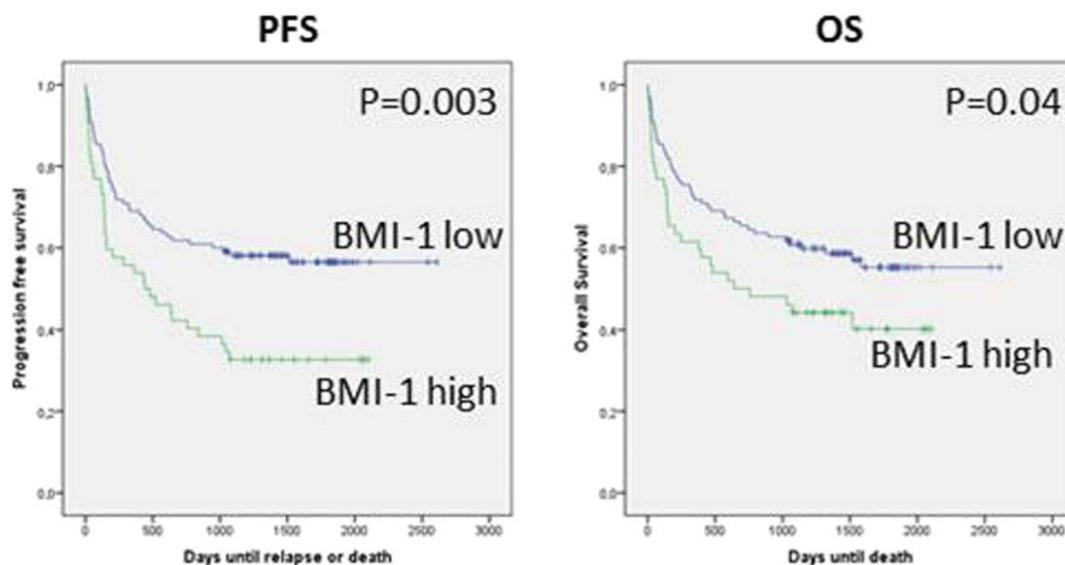
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Introduction: The BMI-1 gene belongs to the polycomb group family and was originally identified as a proto-oncogene during lymphoma development. In diffuse large B-cell lymphoma (DLBCL), high BMI-1 gene expression can be used in distinguishing cell of origin (COO). Expression of BMI-1 protein in DLBCL is however poorly investigated. We aimed to investigate if BMI-1 protein expression was a prognostic factor in a consecutive cohort of patients with DLBCL.

Methods: All patients with DLBCL diagnosed and treated 2009-2011 at Copenhagen University Hospital Herlev were collected consecutively and classified according to morphology and COO by immunohistochemistry (IHC, Hans algorithm). BMI-1 protein expression was investigated retrospectively by IHC. A total of 212 patients (163 primary + 49 transformed DLBCL) were included—176 of the patients had received intensive chemotherapy (R-CHOP/R-CHOEP in 174 patients).

Results: Tissue was available for BMI-1 analysis in 162 patients. Median BMI-1 expression was 40% with IQR 10-80%. High BMI-1 expression $\geq 80\%$ was seen in 32% (52/162) of patients and in 30% (42/139) of the patients whom had been intensively treated. Treatment regimens were comparable between patients with high and low BMI-1 expression. A tendency towards an association between high BMI-1 expression and nonGCB profile ($P = .07$) and transformed lymphoma ($P = .07$) was observed (chi-square). High BMI-1 expression was not associated with bone marrow involvement ($P = .5$), extra nodal involvement ($P = .2$), performance status ($P = .3$), IPI score ($P = .9$), Ann Arbor stage ($P = .14$), or proliferation rate ($P = .7$) (chi-square). High BMI-1 expression had negative prognostic impact on both PFS and OS in univariate survival analysis (log rank); PFS (HR 1.9, $P = .003$), OS (HR 1.6, $P = .04$) (figure). In multivariable analysis (Cox proportional hazards models) including IPI, COO, and BMI-1 ≥ 80 , both high BMI



expression (PFS [HR 2.3, $P = .001$] and OS [HR 1.9, $P = .009$]) and IPI (PFS [HR 1.7, $P = .001$] and OS [HR 1.8, $P = .001$]) were independent prognostic factors. This was also seen in the subgroup of intensively treated patients. In univariate analysis, similar trends were seen when only patients with primary DLBCL were included.

Conclusions: In this prospective cohort of DLBCL, high BMI-1 expression was a negative independent prognostic factor of both PFS and OS in univariate and multivariate analysis adjusting for IPI and COO. The prognostic effect was seen in all patients, including subgroups of intensively treated patients as well as patients with primary DLBCL (trends). High BMI-1 expression was related to non-GCB phenotype and transformed lymphoma (trends). Thus, BMI-1 expression is a possible novel negative prognostic biomarker in DLBCL and should be further investigated.

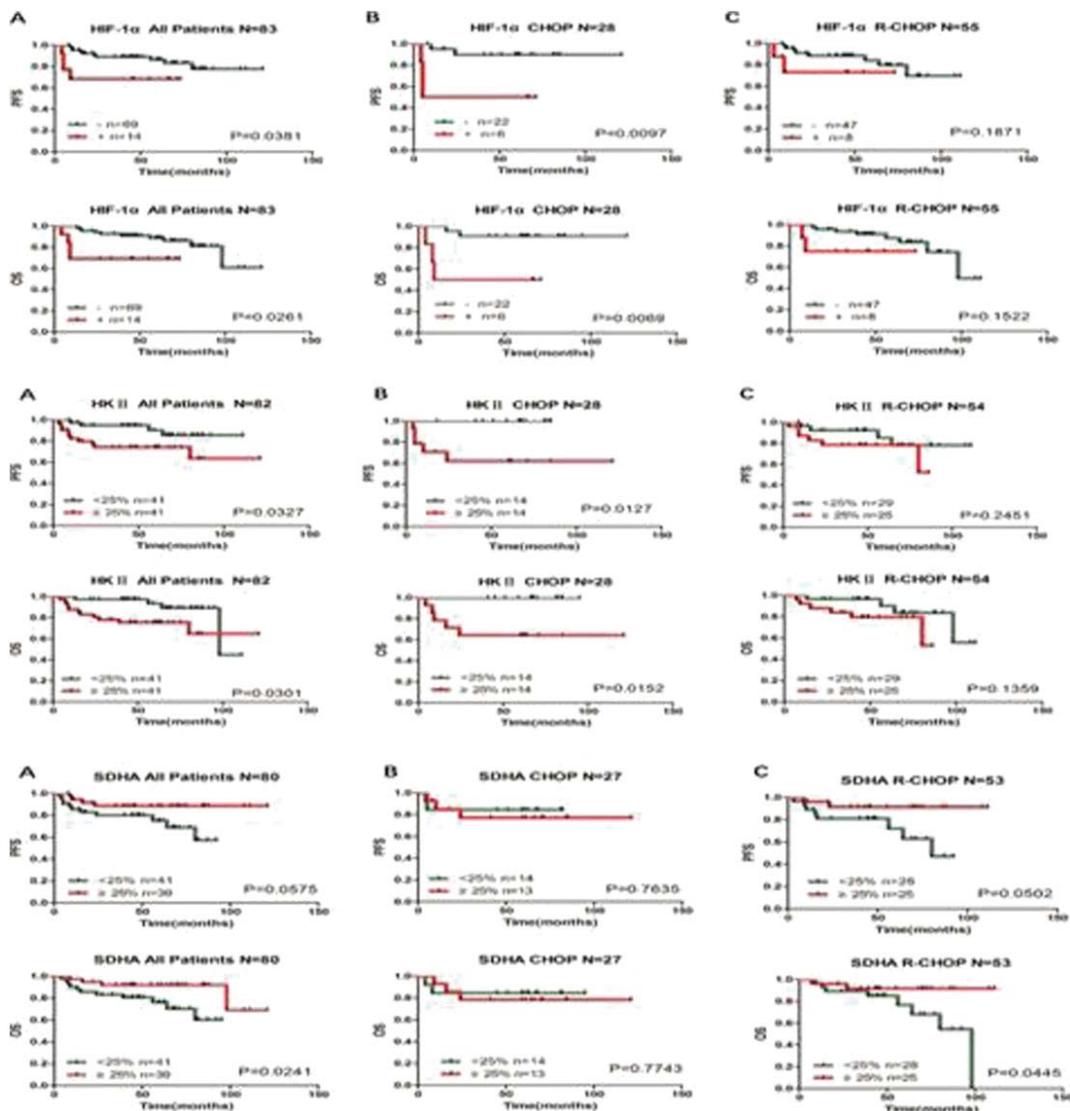
Keywords: diffuse large B-cell lymphoma (DLBCL); prognostic indices

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Introduction: Diffuse large B-cell lymphoma is a highly heterogeneous entity with varied clinical manifestation and prognosis. Although the immunochemotherapy improves treatment responses, approximately 40% of the patients still eventually endure refractory/relapsed diseases. So how can we identify patients who are unlikely to be cured with conventional therapy and thus to optimize the strategy have become extremely meaningful. The metabolic reprogramming is a remarkably distinct character of tumor cells and is linked to proliferation, drug resistance, survival advantages, and tumor progression. Malignant tumor cells prefer glycolysis rather than aerobic oxidation even under aerobic surroundings. Furthermore, this altered metabolism is an active adjustment regulated by hypoxia inducible factor 1 α (HIF-1 α) in a reversible manner. The aim of this study is to clarify the role of the balance between glycolysis and aerobic oxidation in DLBCL and to explore the potential of targeting abnormal metabolic phenotype for NHL.

314 ROLE OF THE ABNORMAL HIF-1 α - GLYCOLYSIS-AEROBIC OXIDATION PATHWAY IN NON-HODGKIN LYMPHOMA AND THE INTERVENTION STUDY



Methods: Expressions of HIF-1 α , key enzymes of glycolysis pathway hexokinase II (HKII), and aerobic oxidation pathway succinate dehydrogenase (SDHA) in lymphoma samples from DLBCL patients were detected by immunohistochemistry, and the association between expression levels and clinical outcomes were analyzed. SU-DHL-4 cells and Raji cells were stably transfected with lentiviral vectors carried with short hairpin RNA targeting either *HIF-1 α* gene or *HKII* gene and control vectors encoding a nonmammalian shRNA.

Results: Retrospective analysis of the 83 newly diagnosed DLBCL patients showed that HIF-1 α ⁺, HKII^{high} and SDHA^{low} were significantly correlated with inferior PFS and OS. A small subset of patients was identified that the H-H-S group (HIF-1 α ⁺HKII^{high}SDHA^{low}), representing that critical regulator and enzymes of glycolysis-aerobic oxidation pathway are all abnormally expressed, had significantly inferior PFS (3-year PFS, 14.3% vs 78.3%, $P = .001$) and OS (3-year OS, 14.3% vs 89.9%, $P < .001$) compared to the non-H-H-S group. Prognostic factors such as LDH, Ki67, SUVmax, IPI, and non-GCB subtype significantly differed between H-H-S group and non-H-H-S group. Furthermore, H-H-S group was demonstrated as an independent prognostic factor. *HKII* gene silencing significantly suppressed proliferation and abnormal glycolytic metabolism of lymphoma cells as well as enhanced cell apoptosis and sensitivity to chemotherapeutic drugs. Same phenomena were found while *HIF-1 α* was interfered by specific shRNA.

Conclusions: The abnormal HIF-1 α -glycolysis-aerobic oxidation pathway might act as a prognostic indicator in DLBCL. Knocking down either *HIF-1 α* gene or *HKII* gene could rescue malignant biological phenotypes of lymphoma cells, suggesting that targeting malignant metabolic phenotype may be a promising approach for refractory/relapsed lymphoma.

Keywords: diffuse large B-cell lymphoma (DLBCL); prognostic indices; R-CHOP

315 CYTOPLASMATIC LOCATION OF NR4A1 IN AGGRESSIVE LYMPHOMAS IS ASSOCIATED WITH A FAVOURABLE CANCER SPECIFIC SURVIVAL

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The nuclear orphan receptor NR4A1 is downregulated in 70% of aggressive lymphomas and exerts an essential tumor suppressor function. In the current study, we examined the clinic-pathological relevance of expression patterns of NR4A1 in primary aggressive lymphomas (diffuse large B-cell lymphoma and follicular lymphoma III). Therefore, we performed a histology-based comprehensive study on NR4A1 expression in our cohort of aggressive lymphomas ($n = 60$) and nonneoplastic lymph nodes ($n = 5$) and evaluated cytoplasmatic

NR4A1 expression. Within the lymphomas, a varying percentage of aggressive lymphoma cells exhibited a cytoplasmatic NR4A1 expression with distinct intensities, whereas none of the nonneoplastic germinal center B cells expressed cytoplasmatic NR4A1. By dividing the patients' cohort into two groups using the median of lymphoma cells (median = 40%) exhibiting a cytoplasmatic NR4A1 expression (as opposed to a nuclear or no NR4A1 expression), a significant association between high cytoplasmatic NR4A1 expression and favourable cancer-specific survival was observed. After a median observation time of 99.3 months, the difference in overall survival between the two groups was 74 months ($P = .022$, log-rank test). Further, high cytoplasmatic NR4A1 expression occurred more frequent in GCB-DLBCL compared to the NGCB-subtype (66.7% vs 36.8%, $P = .019$). Several reports described the role of cytoplasmatic NR4A1 expression in the induction of mitochondrial cell death due to an interaction of the nuclear receptor with Bcl-2 present in the mitochondrial membrane. Therefore, we performed immunohistochemical analysis of cleaved caspase 3 in our lymphoma cohort and detected that the percentage of cytoplasmatic NR4A1 expressing cells was significantly associated with the number of lymphoma cells exhibiting a cleaved caspase 3 (Spearman $\rho = 0.741$, $P < .001$). Remarkably, a significantly higher number of lymphoma exhibited cleaved caspase 3 in GCB-DLBCLs compared to the NGCB-subtype (65.2 positive cells per mm² vs 21.2 positive cells per mm², $P = .005$). However, the mRNA expression levels of XPO1 responsible for the nuclear export of NR4A1 revealed no significant difference between high and low/no cytoplasmatic NR4A1 expressing lymphomas.

Our data suggest that in patients with aggressive lymphoma, high NR4A1 expression in the cytoplasm is associated with a favourable lymphoma-specific survival, presumably by causing mitochondrial cell death via its interaction with BCL2.

Keywords: diffuse large B-cell lymphoma (DLBCL); molecular genetics; prognostic indices

316 TUMOR NECROSIS AS A PROGNOSTIC FACTOR OF DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH R-CHOP THERAPY

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Tumor necrosis (TN) can lower responsiveness to chemotherapy and confer basic resistance to anticancer therapy. We investigated the association of TN with poor clinical features and outcome in diffuse large B-cell lymphoma (DLBCL). We examined the presence or absence of TN in 476 DLBCL patients of who received R-CHOP (rituximab,

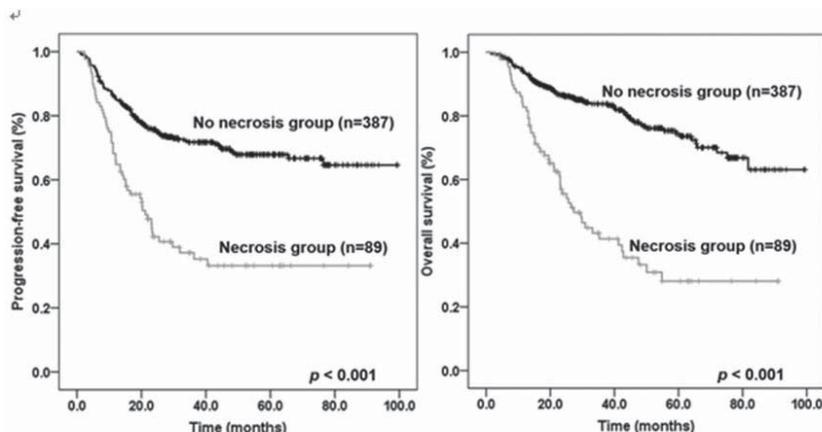


Figure 1. Progression-free survival (PFSs) and overall survival (OS) of patient with and without tumor necrosis. PFS and OS of the tumor necrosis group were significantly lower than the nonnecrosis group (PFS, $p < 0.001$; OS, $p < 0.001$).

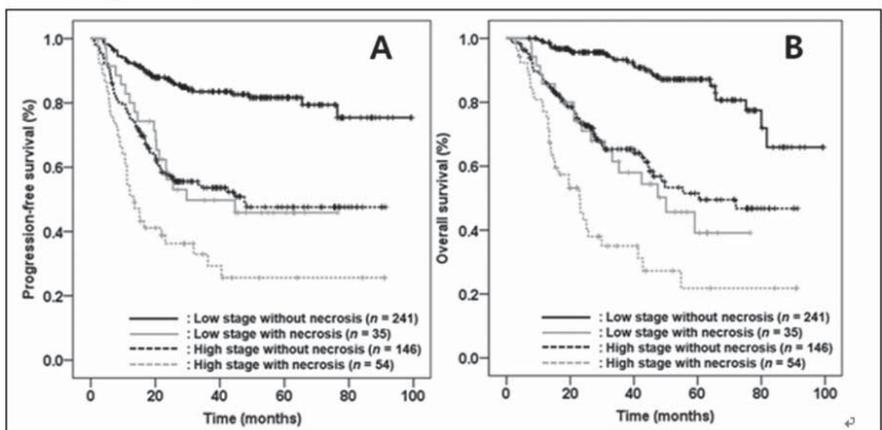


Figure 2. Progression-free survival (PFSs) and overall survival (OSs) based on combined clinical impacts of two prognostic factors: Ann-Arbor stage (low versus high stage) and tumor necrosis (versus without necrosis). PFS and OS of the group having low stage without necrosis were significantly higher than other patient groups (PFS, $p = 0.001$; OS, $p = 0.004$). Survival of high stage patients with necrosis were significantly lower than other groups (PFS, $p = 0.005$; OS, $p = 0.009$). However, low stage patients with necrosis had similar survival to as high stage patients without necrosis (PFS, $p = 0.687$; OS, $p = 0.225$).

cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy. Eighty-nine (18.7%) patients had TN at diagnosis. Patients with TN had a progression-free survival (PFS) and overall survival (OS) of 39.3% and 46.7%, whereas patients without TN had a PFS and OS of 73.4% and 82.6%. Adverse clinical factors of poor Eastern Cooperative Oncology Group performance status \geq grade 2 ($P = .005$), elevated lactate dehydrogenase ratio >1 ($P < 0.001$), advanced Ann Arbor stage ($P = .002$), and bulky disease ($P = .026$) were more prevalent in the TN group than the non-TN group. Cox regression model analysis revealed TN as an independent prognostic factor for PFS and OS in DLBCL (PFS, hazard ratio [HR] = 1.967, 95% confidence interval [CI], 1.399-2.765, $P < .001$; OS, HR = 2.445, 95% CI, 1.689-3.640, $P < .001$). The results indicate that TN could reflect adverse clinical features and worse prognosis in DLBCL patients receiving R-CHOP therapy.

Keywords: diffuse large B-cell lymphoma (DLBCL); prognostic indices; R-CHOP

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Diffuse large B-cell lymphoma (DLBCL), the most common type of non-Hodgkin lymphoma, is recognized as a heterogeneous disease with distinct molecular subtypes derived from different stages of B-cell differentiation. The contribution of the tumor microenvironment to the pathogenesis and tumor survival of DLBCL is poorly understood. However, several recent studies have yielded intriguing findings and shed some light on the possible roles of the microenvironment.

In this retrospective study, data from 29 patients diagnosed with DLBCL between 2009 and 2013 were reviewed. All patients had pathologically confirmed DLBCL and had been treated with the R-CHOP regimen. In these patients, we correlated the expression of CD3 staining for T cells, tryptase staining for mast cells, CD68 for tumor-associated macrophages (TAMs), and CD31 staining for blood vessels.

CD68 and tryptase expression, as well as MVD, were increased in chemo-resistant patients compared to chemosensitive patients. Tryptase expression showed a positive correlation with MVD, supporting a role for mast cells in DLBCL tumor angiogenesis, while the CD68 correlation with MVD was not significant, indicating a different role for TAMs rather than angiogenesis in DLBCL. A statistically significant difference was observed in the expression of CD3 in patients with bulky disease. Specifically, a higher expression of CD3 was observed in nonbulky disease patients (mean expression 52.91%, $n = 20$) compared to bulky disease patients (mean expression 34.9%, $n = 9$), P value $< .05$. The reduction in T cells in bulky disease patients contributes to loosen the immune control over the tumor, resulting in an increased cell proliferation, leading to large tumor cell masses, which are predictive of poor prognostic and clinical outcomes. CD3 showed a positive correlation with tryptase and MVD, while multiple regression analysis efficaciously predicted MVD depending on CD3 and tryptase as predictors, supporting a complex interplay between these cells in sustaining tumor angiogenesis in DLBCL patients.

The improved understanding of tumor biology and of the role of the tumor microenvironment has led to advances in the diagnosis, classification, prognostics, as well as novel treatments of patients with hematologic malignancies. In particular, translational research, leading to drugs that target the interaction between the tumor microenviron-

ment and malignant cells, has provided many promising new approaches to cancer therapy. Ongoing dynamic and correlation studies of tumor biology and the contribution of the tumor microenvironment should be promoted in the context of novel drug development in order to identify optimal therapies for various lymphomas and improve the curability of these diseases.

Keywords: diffuse large B-cell lymphoma (DLBCL)

318 EBV INFECTION PROMOTES TUMOR INFILTRATING LEUCOCYTE AND IMMUNE ESCAPE IN PLASMABLASTIC LYMPHOMA ACCORDING TO GENE EXPRESSION PROFILING

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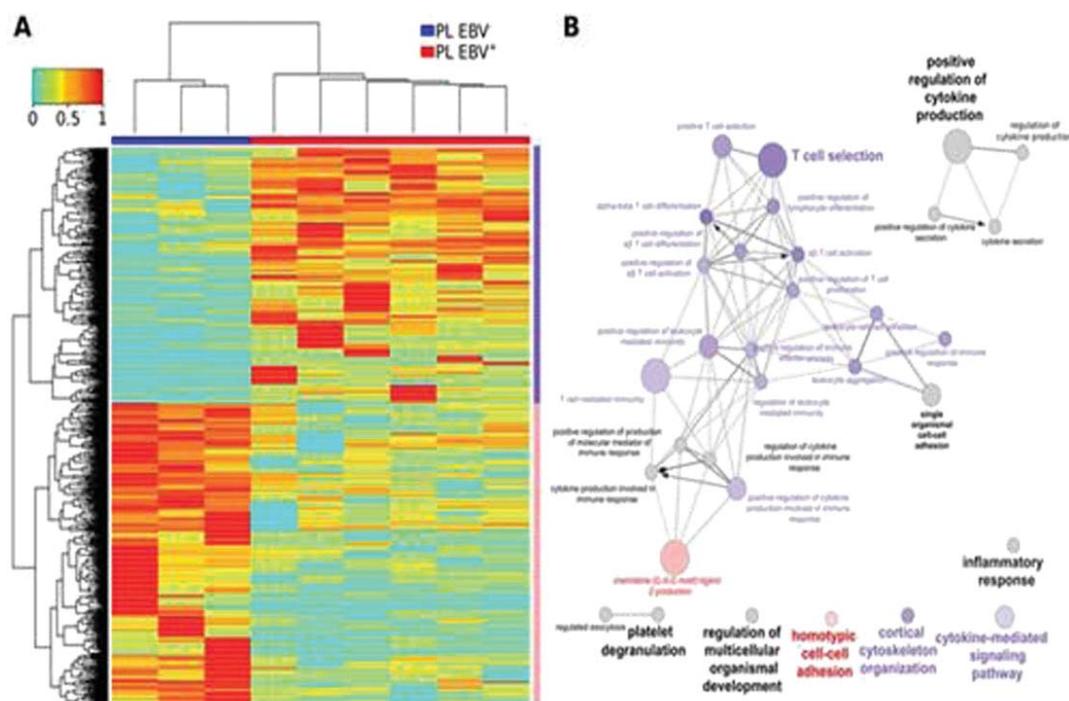


Figure 1: Molecular profiling and pathways analysis in EBV⁺ and EBV⁻ plasmablastic lymphomas.

A: Unsupervised hierarchical clustering of 1213 genes detected as differentially expressed in EBV⁻ ($n=3$, blue bar) and EBV⁺ ($n=6$, red bar) PL. The color bar denotes z-score adjusted expression values, cyan used for lower expression and red for higher expression levels. Data are represented in a grid format in which each column represents a single patient, and each row a single gene. The dendrogram shows the degree to which the expression pattern of each gene is correlated with that of the other genes. **B:** Functional network of the differentially expressed genes in EBV⁻ and EBV⁺ PL, using the GO biological process terms. The node circle size represents the number of genes in the pathway and the node circle colors (pink and purple) correspond to the genes clustering (genes up-regulated in EBV⁻ or EBV⁺ PL respectively).

Plasmablastic lymphoma is a subtype of diffuse large B-cell lymphoma occurring frequently in HIV-positive individuals and most often associated with Epstein Barr virus (EBV) infection. Despite recent therapeutic progress, plasmablastic lymphoma still is an aggressive lymphoma with adverse prognosis. The aim of this study was to investigate whether the emerging strategies of immune checkpoint blockade could be efficient for plasmablastic lymphoma patients. Here, we produced and analyzed the transcriptomic profiles of such tumors to address this question. Unsupervised hierarchical analysis of plasmablastic lymphoma samples showed that plasmablastic lymphoma segregated according to their EBV status. Moreover, we report that EBV⁺ plasmablastic lymphoma shows a significant association with abundant leucocyte infiltrate and selective T-cell activation signatures together with high level of inhibitory receptors and immune checkpoint markers (see Figure 1). We propose that EBV infection induced an antiviral cytotoxic immunity, which progressively exhausted and promoted the tolerogenic tumor microenvironment of plasmablastic lymphoma. Hence, most EBV⁺ plasmablastic lymphoma patients presenting an early stage of cancer immune-editing process appear eligible for ICB immunotherapies.

Keywords: Epstein-Barr virus (EBV); expression arrays; immune system

319 ARE DIFFERENCES BETWEEN PEDIATRIC EBV-ASSOCIATED LYMPHOMAS AND CARRIERS REGARDING LATENCY PROFILE AND MICROENVIRONMENT COMPOSITION INVOLVED IN LYMPHOMAGENESIS?

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Introduction: In Argentina, 90% of patients are seropositive for Epstein-Barr virus (EBV) by 3 years old, whereas EBV presence is statistically associated with Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL) in patients younger than 10 years, suggesting a relationship between low age of infection and B-cell lymphoma development.

Aim: To compare viral latent proteins and microenvironment composition in EBV-associated lymphomas derived from the germinal center (GC) and post-GC with the same areas in tonsils from EBV carriers, to investigate whether an alteration of this scenario could be related to pediatric lymphomagenesis.

Methods: Formalin-fixed paraffin-embedded (FFPE) biopsy samples from 26 DLBCL, 55 HL, and 41 tonsils from EBV carriers were analyzed. Immunohistochemistry for LMP1, EBNA2, CD4, CD8, Foxp3

and GrB, and EBERs in situ hybridization were performed. Positive cells were counted within EBV⁺ milieu.

Results: Latency II pattern (LMP1+ EBNA2⁻) was predominant in HL (100%), DLBCL (55%), as well as in pediatric carriers (90%). CD4⁺ cell count displayed no differences between EBV⁺ and EBV⁻ HL or DLBCL ($P > .05$, Mann Whitney [MW] test), whereas statistically higher CD4⁺ cells were counted at the EBV⁺ GC in pediatric carriers ($P = .014$, MW test). CD8⁺ cells did not exhibit statistical differences neither in EBV-associated lymphomas nor in benign conditions at the CG, and the same was observed for Foxp3 regulatory cells ($P > .05$, MW test). In contrast, CD8⁺ cell count were statistically higher exclusively at EBV⁺ + subepithelial region in tonsils, compared to EBV⁻ ($P = .0039$, MW test). Finally, higher cytotoxic activity evaluated by GrB expression displayed a trend in EBV⁺ DLBCL ($P = .057$, MW test) but no in HL. In pediatric carriers, GrB did not shown differences in cytotoxic activity according to EBV presence at the CG ($P > .05$, MW test). In fact, GrB cytotoxic activity was prevalent only at the EBV⁺ subepithelial region ($P = .042$, MW test).

Conclusions: Latency II pattern prevails in both EBV-associated lymphomas and in EBV⁺ GC from carriers, indicating that LMP1 expression may collaborate in the lymphomagenesis process at the GC in pediatric patients from our country. Cytotoxic activity against EBV infection may be only relevant in DLBCL, and in EBV⁺ subepithelial regions in pediatric carriers, whereas in EBV⁺ HL is not increased, in contrast to previously described. CD4⁺ T helper cell response plays a key role at the GC region in EBV carriers, by helping to the overall immune response in the control of viral infection and restricting latency expression to type II pattern, and ultimately, by limiting cell outgrowth. Failure in this process may trigger malignant transformation in pediatric EBV-associated lymphomas.

Keywords: B-cell lymphoma; Epstein-Barr virus (EBV); germinal center (GC)

320 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.

Materials and Methods: We studied 1511 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 2016 with a panel of different antibodies for hematolymphoid processes employing the technique of immunohistochemistry in paraffin blocks. The manual and automated immunohistochemical 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 (1095 cases) (72,46%). The B-cell lymphomas CD20 positive were 1018 cases (67,37%). The most frequent histopathological type was the diffuse large B-cell lymphomas (550 cases) (36,39%). The peripheral T-cell lymphomas (67 cases) and anaplastic large-cell lymphomas (51 cases) were the most principal types diagnosed in the group of non-Hodgkin's T-cell lymphomas (118 cases in total) (7,80%). The extranodal location were 740 cases (48,97%), and the head and neck location was the most common site diagnosed in this group (148 cases) (20%).

Conclusion: The study demonstrated the different histologic types, location, and frequencies of the lymphomas in our daily work of a period of time of 10 years in the Immunohistochemistry Laboratory at the Pathology Department.

Keywords: B-cell lymphoma; non-Hodgkin lymphoma (NHL); T-cell lymphoma (TCL)

321 PAN-LYMPHOMA CLASSIFICATION

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Introduction: Cell of origin classification of diffuse large B-cell lymphoma (DL-BCL) using gene expression signatures identifies patients with distinct molecular features and survival outcomes. Whilst the identification of activated B-cell (ABC) and germinal center B-cell (GCB) subtypes of DL-BCL is now routinely used in diagnostics, however, a significant proportion of patients display gene expression signatures that are intermediate between classes. Whilst some of these intermediate cases display genuine hallmarks of both ABC or GCB subtypes, leading to an intermediate DL-BCL COO-UNC type, others appear to display distinct molecular signatures. It is possible that that these signatures represent inherent noise in the expression profiling process, or biological noise resulting from, for example, high levels of T-cell infiltration in samples. A more intriguing possibility is that these cases represent intermediate types between DL-BCL and other types

of lymphoma. The existence of intermediate molecular signatures raises important questions about which type of treatment is most applicable for these cases. Yet the identification of intermediate molecular signatures is challenging, because existing classification algorithms have tended to focus on a small subset of lymphoma types rather than across the pan-lymphoma spectrum. Moreover, it is not clear what features would be needed to identify the relationship between patients to diverse lymphoma classes.

Methods: To address this issue, we have developed a pan-lymphoma classifier using a support vector machine (SVM) with an embedded recursive feature selection (RFS) algorithm. Our training and test dataset consisted of 431 samples, spanning eight different types of lymphoma: ABC (49), GCB (133), COO-UNC (40), Burkitt's (60), Hodgkin's (43), PMBL (35), PBL (39), and Plasmacytoma (32). Gene expression profiles for each sample were obtained using the Illumina DASL platform. We trained the SVM using 10-fold cross-validation with a 70:30 train/test split. On each iteration of the RFS, we removed the single least informative probe. We repeated this until a significant drop in average accuracy of the SVM was reached.

Results: Initially training the SVM on 1125 probes, we obtained a pan-lymphoma average classification accuracy of 91%. We then used the SVM-RFS to obtain a list of just 23 probes that gave rise to an average classification accuracy of 86%. This allowed us to develop a between-class distance metric as a score of the relative association of any given sample to a lymphoma class. Retrospective classification of COO-UNC samples showed some share molecular features associated with non-DL-BCL classes.

Conclusions: SVM-RFS appears to be a robust approach for identifying classes of lymphoma from underlying molecular phenotypes. A small number of most informative genes provide a separation of cases into subtypes that is in excellent agreement with laboratory diagnoses.

Keywords: activated B-cell-like (ABC); GCB lymphoma subtype; gene expression profile (GEP)

322 MINIMAL RESIDUAL DISEASE BY NEXT-GENERATION SEQUENCING IN MANTLE CELL LYMPHOMA: THE BIOINFORMATICS TOOL HASHCLONE

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Introduction: Minimal residual disease (MRD) assessment by PCR (ASO qPCR) is useful for response evaluation in lymphoma. Nevertheless, labor intensiveness, failure of marker identification and false-negative results routinely affect PCR success. Next-generation sequencing (NGS) has been applied to MRD studies, showing good performances

and overcoming some of PCR limitations. However, every NGS experiment is strictly dependent on computational analysis that manages the huge volume of deep sequencing data. Here, we present HashClone, a new easy-to-use bioinformatics tool that provides marker assessment at diagnosis and MRD monitoring over time. HashClone was tested in mantle cell lymphoma (MCL), with the aims to detect the major clone and monitor it over time during clinical follow-up.

Methods: Five MCL patients, enrolled in a Fondazione Italiana Linfomi (FIL) prospective clinical trial, were studied for immunoglobulin heavy chain rearrangements (IGH) detection and MRD monitoring using both ASO-qPCR and a BIOMED II amplicon-based NGS approach. Overall, for each patient peripheral blood and bone marrow samples from diagnosis, 3 artificial follow-ups and samples collected during the clinical follow-up were analysed. HashClone analysis was focused, firstly, on the identification of a set of putative clones, independently from any biological knowledge. Then, IGH rearrangements identification was carried out thanks to the link to IMG2 database. Finally, NGS MRD results were compared to data previously obtained by ASO qPCR.

Results: Overall, the HashClone performances were tested on 39 MCL samples. For the 5 diagnostic samples, HashClone identified an average value of 1008 putative clones (range 540-1379). Of these, only 25 displayed a frequency higher than 5% and thus were considered representative of the disease. However, only 21 out of 25 clonotypes were recognized as B-cell clones after IMG2 filtering. Finally, each of all the 5 diagnostic samples displayed only one predominant clone, with a median frequency of 98% (range 92%-99%). Compared to Sanger sequencing, all the major clones showed the same IGH rearrangement with a 100% of nucleotide homology in 4/5 cases. In one patient, 3 mismatches, not affecting the patient-specific insertions ("N regions"), decreased the homology to 98%. Overall, the correlation analysis showed a high concordance between ASO qPCR and NGS ($r^2 = 0.85$). Moreover, considering single patients, superimposable performances were observed (Figure 1).

Conclusion: HashClone is a new bioinformatics tool for the identification of IGH clonality in NGS experiments, able to detect and monitor the major B-cell clone in MCL. It is not affected by biologic biases and is able to follow the temporal evolution of the IGH repertoire at several time points ("MRD monitoring"). Since this is the first HashClone application, the tool needs to be fine-tuned and validated on large samples series, before being used in prospective MRD-based clinical trials.

Keywords: B-cell lymphoma; immunoglobulins (Ig); minimal residual disease (MRD)

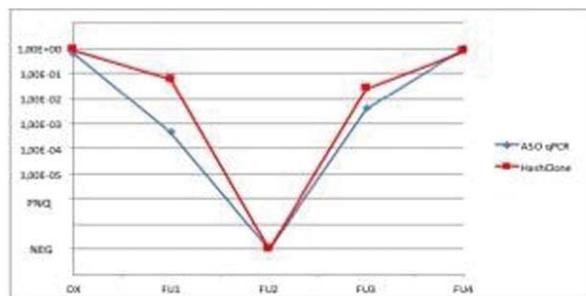


Fig 1: MRD trend obtained from ASO q-PCR (blue line) and HashClone (red line) of Patient E

PET IMAGING

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PET-CT-ADAPTED THERAPY FOR ADVANCED HODGKIN LYMPHOMA: A SYSTEMATIC REVIEW OF THE LITERATURE

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Introduction: Interim PET/CT performed after 2 chemotherapy cycles (PET-2) is an accepted prognostic tool in Hodgkin lymphoma (HL). Tailoring treatment based on PET-2 results may improve outcomes of standard therapy. The purpose of this study is to evaluate the effect of PET adapted strategy on overall survival and progression-free survival (PFS) of patients with advanced-stage HL.

Methods: We performed a systematic review and included studies in which interim PET/CT results served as a decision-making tool for escalation or de-escalation of treatment in patients with early unfavorable and advanced HL. In February 2017, we searched electronic databases, conference proceedings, and databases of ongoing trials. Two reviewers appraised the quality of trials and extracted data. The primary outcome was PFS.

Results: We identified 13 studies (3 randomized controlled trials, 8 noncomparative phase II trials, and 2 retrospective studies), conducted between the years 1999 and 2013 (3 ongoing), including 9071 patients. Three performed either escalation or de-escalation of therapy if PET-2 was positive or negative, respectively; 6 trials performed escalation and 4 de-escalation only (Table). In 9 trials, PET-2 was interpreted by Deauville's criteria. Median follow-up was 2 to 10 years. Escalation studies: In 7 escalation trials, baseline therapy was ABVD and in two escalated (esc) BEACOPP. Escalation protocols included IGEV followed by stem cell transplantation in one trial and escBEACOPP in 8 trials, 2 of them randomized patients to rituximab. PET-2 was positive in 12% to 40%. PFS in the PET-2 positive arms ranged between 50% and 93%. PFS in the PET-2 negative arms ranged between 81% to 87%. De-escalation studies: In 5 de-escalation trials, baseline therapy was escBEACOPP, in two studies 2 to 3 cycles of ABVD. De-escalation scheme consisted of 4 ABVD cycles in 3 trials, no further treatment in one trial and randomization to either 4 ABVD or 4 AVD in one trial. PET-2 was positive in 12% to 31%. PFS in the PET-2 positive arms ranged between 47% and 87%. PFS in the PET-2 negative arms ranged between 80% and 94%.

Conclusions: Our results suggest that an interim PET-adapted approach of escalating or de-escalating therapy is feasible. PFS results in PET-2 positive patients are highly variable and therefore should be interpreted cautiously while negative PET-2 results predict favorable outcome.

Keywords: Hodgkin lymphoma (HL); positron emission tomography (PET)

Therapy escalation if PET-2 positive						
Study	study design	Baseline therapy	Escalation strategy	% Positive interim PET	PET2 POS	PFS/FFS/FFS
Borchmann, 2017	Phase II 1100 patients	2 cycles rituximab + ABVD	6 cycles rituximab + ABVD vs. 4 cycles rituximab + ABVD + rituximab	40%	3y PFS: 84.0% 5y PFS: 71.4%	3y PFS: 85.7% 5y PFS: 73.6%
Johnson, 2014	Phase II 1214 patients	2 cycles ABVD	4 cycles ABVD vs. 4 cycles ABVD + 4 cycles AVD	14.3%	3y PFS: 67.5%	3y PFS: 65.7%
Zinzani, 2014	Phase II 520 patients	2 cycles ABVD	4 cycles ABVD vs. 4 cycles ABVD + 4 cycles AVD	20%	2y PFS: 76%	2y PFS: 61%
Fress, 2014	Phase II 358 patients	2 cycles ABVD	4 cycles ABVD vs. 4 cycles ABVD + 4 cycles AVD	18%	2y PFS: 64%	2y PFS: 62%
Dann, 2014	Phase II 111 patients with IPS<3	2 cycles ABVD	4 cycles ABVD vs. 4 cycles ABVD + 4 cycles AVD	12%	5y PFS: 60%*	5y PFS: 62%*
Gottalini, 2015 interim analysis	Phase II 773 patients	2 cycles ABVD	4 cycles ABVD vs. 4 cycles ABVD + 4 cycles AVD	19.8%	4y PFS: 62%	4y PFS: 65%
Ganesan, 2015	Phase II 50 patients	2 cycles ABVD	4 cycles ABVD vs. 4 cycles ABVD + 4 cycles AVD	14%	2y PFS: 50%	2y PFS: 62%
Gottalini, 2011	Phase II 165 patients	2 cycles ABVD	4 cycles ABVD vs. 4 cycles ABVD + 4 cycles AVD	17%	2y PFS: 65%	2y PFS: 92%
Dann, 2011	Phase II 77 patients with IPS<3	2 cycles ABVD	4 cycles ABVD vs. 4 cycles ABVD + 4 cycles AVD	16% positive PET scan 15% positive PET-CT	10 y PFS: 63%*	10 y PFS: 67%*
Therapy de-escalation if PET-2 negative						
Study	study design	Baseline therapy	De-escalation strategy	% Positive interim PET	PET2 POS	PFS/FFS/FFS
Johnson, 2014	Phase II 1214 patients	2 cycles ABVD	4 cycles ABVD vs. 4 cycles AVD	14.3%		3y PFS: 65.7% AVD group: 6.5%
Ferrel, 2014 interim analysis	Phase I 401 patients, 144 patients advanced HL	3 cycles ABVD	no further treatment	31% PET3 pos (entire cohort, all advanced disease cohort)	3y PFS: 57.1% PET3 pos: 57.1%	3y PFS: 90% advanced disease cohort
Kedmi, 2016 Avigdor, 2010	Phase II / retrospective 48 patients / 24 patients	2 cycles rituximab + ABVD	4 cycles ABVD vs. 4 cycles AVD	25%	5y PFS: 60%*	5y PFS: 60%
Dann, 2014	Phase II 74 patients with IPS<3	2 cycles ABVD	4 cycles ABVD	19%	5y PFS: 60%	5y PFS: 62%
Ganesan, 2015 interim analysis	Phase II 523 patients	2 cycles ABVD	Standard arm: 4 cycles ABVD vs. 4 cycles AVD Experimental arm: 4 cycles AVD	12% 13%	2y PFS: 72.9% standard arm: 75.1% experimental arm: 70.8%	2y PFS: 92.8% standard arm: 94% experimental arm: 91.6%
Deauville, 2015	retrospective 44 patients	2 cycles ABVD	4 cycles ABVD	14%	2y PFS: 47%	2y PFS: 67%
Dann, 2011 Dann, 2007	Phase II 47 patients with IPS<3	2 cycles ABVD	4 cycles ABVD	20% positive PET scan 22% positive PET-CT	10 y PFS: 63%* positive interim scintigraphy: 63%*	10 y PFS: 67%* negative interim scintigraphy: 67%*

* includes all patients with the mentioned interim scintigraphy result, regardless of IPS (IPS<3 and IPS<3)

324 PRELIMINARY RESULTS OF A PHASE II STUDY USING RESPONSE-ADAPTED THERAPY FOR LIMITED-STAGE DIFFUSE LARGE B-CELL LYMPHOMA BASED ON INTERIM PET/CT

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Introduction: Limited-stage diffuse large B-cell lymphoma (DLBCL) is a high curable disease with R-CHOP immunochemotherapy. For patients achieving complete response by interim [18F]fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT), previous study showed therapy could be safely de-escalated by omitting the subsequent chemotherapy or radiotherapy. We conducted a phase II study to adapt the therapy based on the response assessed by the interim PET/CT.

Methods: Patients with low risk (IPI 0-2), limited-stage DLBCL were initially treated with 4 cycles of R-CHOP. PET/CT scans were performed at baseline and after 4 cycles. Patients with negative PET (Deauville scores 1-2) received 2 cycles of rituximab monotherapy, unless they had any risk factors (primary mediastinal large B-cell lymphoma, extra-nodal primary, or bulky disease).

Patients with abovementioned risk factors received another 2 cycles of R-CHOP as routine practice. Patients with positive PET, but achieving partial response (PR) received another 4 cycles of R-CHOP and repeated PET/CT scan at the end of treatment.

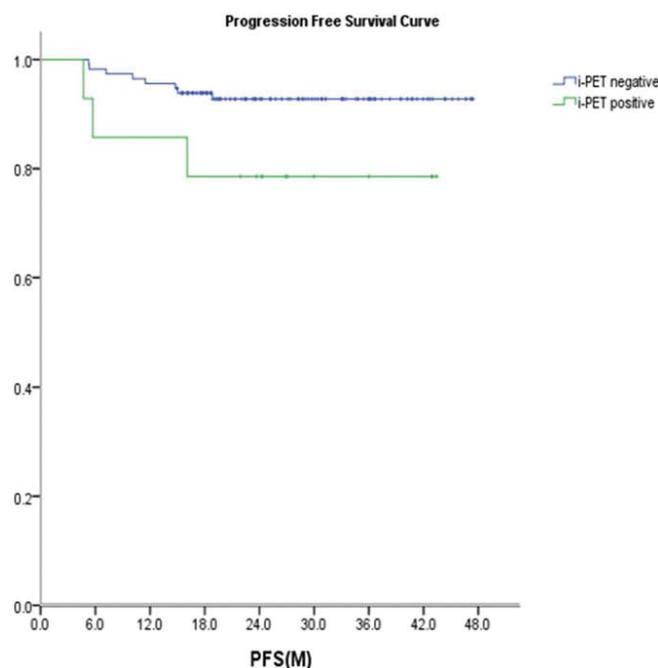


Figure 1: Progression-free survival curve between i-PET/CT negative and positive patients

TABLE 1 Patients characteristics

Characteristics	Nr. (%)
Nr. of patients	129
Age, y	
Median (range)	50 (18-77)
≤60 y	103 (79.8)
>60 y	26 (20.2)
Gender	
Male	70 (54.3)
Female	59 (45.7)
Primary sites	
Nodal	71 (55.0)
Extra-nodal	58 (45.0)
Stage	
I	54 (41.9)
II	75 (58.1)
ECOG	
0	72 (55.8)
1	57 (44.2)
B symptoms	
No	119 (92.2)
Yes	10 (7.8)
LDH	
Normal	122 (94.6)
Elevated	7 (5.4)
IPI	
0	99 (70.7)
1	27 (20.9)
2	3 (2.4)

Abbreviations: PS, performance status; LDH, lactate dehydrogenase; IPI, International Prognostic Index.

Patients with stable and progressive disease were managed by salvage chemotherapy. The primary end point was progression-free survival (PFS) at 3 years.

Results: From December 2012 to September 2015, a total of 143 patients were enrolled and finally 129 with baseline and interim PET/CT scans were analyzed for efficacy. Based on Deauville criteria, 114 PET/CT scans (88.4%) were reported as negative (Deauville scores 1-2). Among 15 patients with positive PET, 14 had PR and 1 had stable disease. With a median follow-up time of 28.2 months, the estimated 3-year PFS rate was 91.3%. Patients with negative interim PET had a higher 3-year PFS rate (92.8%) than patients with positive results (78.6%) with a boardline *P* value of 0.062. The estimated 3-year PFS had no statistically significance between patients with nodal and extra-nodal primary (91.5% vs 91.0%, *P* = .978).

Conclusion: For patients with limited-stage DLBCL, the results of interim PET/CT may predict PFS and adapt the subsequent treatment. For CR patients without risk factors, the extra 2 cycles of CHOP might be omitted without compromising the efficacy, which needs to be confirmed in a randomized study.

Keywords: diffuse large B-cell lymphoma (DLBCL); positron emission tomography (PET); reduced-intensity conditioning regimen (RIC)

325 PROGNOSTIC SIGNIFICANCE OF INTERIM ¹¹C-METHIONINE PET FOR THE TREATMENT OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)

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Background: Lymphoma arising in the central nervous system (CNS) has a dismal prognosis. Chemotherapy options are limited considering very few drugs are adequately permeable through the blood brain barrier. Antimetabolites such as methotrexate (MTX) and cytarabine (Ara-C) constitute the backbone of most anti-PCNSL regimens with overall response rates (ORR) of 40% to 90%. Nevertheless, long-term survival rates are not satisfactory.

Aim: The study prospectively investigated that ¹¹C-methionine PET-CT (¹¹C-MET PET) may provide additional prognostic information of mid-response assessment prior to completion of chemotherapy in PCNSL.

Patients and Methods: Thirty newly diagnosed patients with PCNSL were enrolled between November 2013 and August 2016. Both brain MRI and ¹¹C-MET PET analysis were performed at the time of diagnosis and after four infusions of high-dose MTX in induction chemotherapy. The clinical prognostic factor was assessed according to International Extranodal Lymphoma Study Group (IELSG) guideline. Tumor to normal tissue ratio (T/N ratio) on ¹¹C-MET PET was estimated as the ratio of maximal ¹¹C-MET uptake of the lesion to that of the contralateral normal gray matter. The optimal cutoff values of T/N ratio for recurrence were identified by receiver operating characteristic (ROC) curve, plotting Kaplan-Meier survival curves and comparing them using the log rank test.

Results: All patients had diffuse large B-cell lymphoma with median age of 66.5 years (range: 44-80). Four patients could not be evaluated the interim ¹¹C-MET PET due to disease progression or treatment-related mortality. Four patients proceed to frontline autologous stem cell transplantation as a consolidation. Patients were categorized into low (*N* = 5, 16.1%), intermediate (*N* = 14, 45.2%), and high (*N* = 12, 38.7%), risk groups according to IELSG prognostic score. Fourteen patients developed a recurrence with median follow-up of 11.8 months. Ten out of 12 patients with a high T/N ratio (>1.67) experienced a relapse. Cox regression analysis showed a high T/N ratio (>1.67) was significantly associated with a worse progression-free survival (odds ratio, 10.87; 95% confidence interval [CI], 1.43-82.93; *P* = .021).

Conclusion: Interim ¹¹C-MET PET based on T/N ratio assessment was independent predictive factor in patients with PCNSL.

Keywords: non-Hodgkin lymphoma (NHL); positron emission tomography (PET); primary CNS lymphoma (PCNSL)

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HISTOLOGICAL VALIDATION BY IMAGING-GUIDED CORE NEEDLE-CUTTING BIOPSY OF 4- TO 5-POINT SCALE DEAUVILLE CRITERIA (DC): RETROSPECTIVE ANALYSIS IN HODGKIN LYMPHOMA AT RESTAGING

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Background: The ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography combined with computed tomography (PET-CT) is fundamental in staging and posttreatment restaging of Hodgkin lymphoma (HL). It is necessary to distinguish the responders from the nonresponders at the end of induction chemotherapy (2-6 ABVD cycles). The DC recommend a 5-point scale rather than taking a binary decision (PET positive/negative). An accurate judgement of residual lesions scored as 4-5 is crucial to define salvage chemotherapy with autologous stem cell transplantation (SCT). We retrospectively evaluated postinduction chemotherapy restaging with FDG PET-CT scans in a group of HL patients. The positive predictive value and specificity of DC were assessed by using histological examination; in particular, in our Institution, all residual lesions scored as DC 4 or 5 systematically underwent imaging-guided core needle-cutting biopsy (CNCB).

Methods: We retrospectively included all FDG PET-CT examinations at restaging performed on 194 patients treated for HL between January 2008 and December 2016 at the Hematology Department of Federico II University of Naples. We considered only patients with positive PET findings (4-5 DC score) that needed an histological clarification, if possible, to define further therapy.

Results: Of all patients, 23/194 (12%) were scored with DC 4 and 13/194 (7%) DC 5. The persistently high uptake was investigated by histological examination in 34/36 patients. On the basis of histological findings, 10/34 patients were categorized as true positives, in 22/34 cases, false-positive lesions were depicted, while in 2/34 cases, the core needle samples were inadequate and thus these patients were excluded. Hence, for the final analysis, 32 patients were assessed. The specificity of FDG PET-CT classified with the DC for restaging HL patients was 0.87 (95% CI, 0.8227-0.9227) with a positive predictive value of 0.31 (95% CI, 0.1612-0.5001). DC 4-5 scored patients resulting positive for malignancy from CNCB were treated with a salvage scheme (chemotherapy and SCT), while a previously planned radiotherapy or "watch and wait approach" was performed for those who had negative histological results. After 24 months median

TABLE 1

Deauville score at restaging after frontline therapy with ABVD	Number of patients	Number of patients excluded from analysis	Number of true-positive cases	Number of false-positive cases	Specificity 95% CI	Positive predictive value 95% CI
4 (moderately > LIVER)	23	2	3 (14.3%)	18 (85.7%)	0.8953 0.8397-0.9368	0.1429 0.0304-0.3634
5 (markedly > LIVER and/or new lesion)	13	2	7 (63.6%)	4 (36.4%)	0.9747 0.9364-0.9931	0.6364 0.3079-0.8907

follow-up, further PET examinations showed no pathological uptake in the 22 patients with false-positive lesions.

Conclusions: Prospective multicenter studies are required to obtain histological validation of DC score, especially in the real life. Radiotherapy can be considered a therapeutic option for residual lesions in patients with score 4-5 without the histological confirmation of disease recurrence.

Keywords: Deauville's criteria; Hodgkin lymphoma (HL); positron emission tomography (PET)

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VISUAL VERSUS METABOLIC TUMOUR VOLUME ASSESSMENTS AS PREDICTORS FOR OUTCOME IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: A SINGLE SITE RETROSPECTIVE STUDY IN 118 PATIENTS

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Background: Automated quantitative measurement of metabolic tumour volume (MTV) has gained interest lately in diffuse large B-cell lymphoma (DLBCL). However, simple measurements of tumor volume may not reflect disease severity in DLBCL adequately. Other characteristics such as infiltrative growth and metabolic heterogeneity⁶ play an equally important role. Additionally, MTV measurements depend on cumbersome delineation of lesions by automated software, which is time consuming. Hence, our aim was therefore to devise a simple visual alternative to MTV measurements.

Materials and Methods: Pretherapy ¹⁸F-FDG PET/CT scans in 118 patients with newly diagnosed DLBCL were analyzed both quantitatively and visually. Quantitative parameters included MTV2.5 (SUVmax 2.5 cutoff), MTV41 (41% SUVmax isocontour cutoff), and tumour lesion glycolysis (TLG) and were obtained using Hermes TumourFinder®. Visual evaluations included a subjective binary

prediction based on a qualitative integrated assessment of tumor morphology, burden and organ involvement (good/poor prognosis). Also, assessment of the tumor burden on a visual analog scale (VAS), tumor burden estimated volume (eMTV), and tumor burden high or low (binaryMTV) was performed. Three experienced nuclear medicine physicians who were blinded to clinical outcome performed visual evaluations. Association between MTV ratings and overall survival was evaluated by Kaplan-Meier curves and log-rank test. Interobserver variability was evaluated by Fleiss' kappa for multiple observers.

Results: In the quantitative analysis, MTV2.5 performed borderline significantly better (log rank $P = .08$) than corresponding MTV41 (log rank $P = .83$) in predicting prognosis. Neither TLG2.5 (log rank $P = .18$) nor TLG41 (log rank $P = .33$) was significantly associated to survival. By visual analysis, all three reviewers were able to significantly stratify patients into good/poor prognosis (reviewer A log rank $P = .002$, reviewer B log rank $P = .016$, and reviewer C log rank $P = .012$) with fair interobserver agreement (Fleiss' kappa 0.47). Tumour burden VAS, eMTV, and binaryMTV did not significantly stratify patients into a good or poor prognosis.

Conclusion: The ability to recognize complex disease patterns and predict outcome was surprisingly good when left to the judgement of nuclear medicine specialists experienced in lymphomas. We do not recommend replacement of standardized measures such as MTV2.5, which ensures reproducibility. This study reiterates the value and importance of good clinical judgements and emphasizes that simple automatized MTV measures may not fully inform about prognosis in complex diseases.

Keywords: diffuse large B-cell lymphoma (DLBCL); F-18-fluorodeoxyglucose (FDG); positron emission tomography (PET)

328 UTILITY OF BASELINE ASSESSMENT WITH FDG-PET-CT COMPARED WITH CT SCANNING IN PEOPLE WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Introduction: We sought to establish whether a baseline FDG-PET-CT offers increased sensitivity compared to a baseline CT scan in people with diffuse large B-cell lymphoma (DLBCL) with Lugano stage II disease or above and to assess whether this might affect subsequent clinical decision making.

Methods: We retrospectively reviewed all patients with newly diagnosed DLBCL over a 4-year period who had both an FDG-PET-CT and conventional CT scanning prior to any treatment. Discordance between the two studies was noted and the potential impact of this on clinical decision making was assessed, according to current British or international guidelines, specifically relating to the selection of primary treatment and the decision to offer therapy to prevent relapse in the central nervous system.

Results: Between 2012 and 2016, there were 101 patients, M:F 59:42, aged 20 to 89 (median 54), who had a confirmed diagnosis of DLBCL (de novo DLBCL NOS 91; primary mediastinal B-cell lymphoma 4; previous low grade lymphoma with histological transformation to DLBCL 6) and had undergone both FDG-PET CT and a CT scan, which were available. In 39 cases (38%), there was discordance between the two imaging modalities. Anatomical sites detected by FDG-PET-CT but not by CT included: bone (13), spleen (5), adrenal gland (3), lymph nodes that were normal by size criteria but strongly tracer-avid (3), liver (2), and mediastinal soft tissue (2). Assessed by CT alone, 14 patients would have met formal criteria for the application of methotrexate via the parenteral or intrathecal route. With the information gleaned from FDG-PET-CT, a further 4 patients would have met criteria for this intervention. In addition, 3 patients who were assessed as having limited stage disease by CT had evidence of advanced-stage disease by FDG-PET CT scanning (splenic uptake, lymph nodes that were normal by size-criteria on CT that were clearly abnormal on FDG-PET-CT). This migration of their stage meant they would have received standard chemotherapy rather than being considered for combined modality therapy. FDG-PET-CT identified areas not related to lymphoma determined either on biopsy or clinical follow-up, thyroid disease (3), and nonspecific intestinal uptake for which no cause was found (2).

Conclusions: In many patients, FDG-PET-CT identifies abnormalities not detected on CT scanning, even when the latter is reported by an expert lymphoma radiologist. Only a small number of these discordant findings result in a change in patient management, but these may have significant impact on individual patient outcomes. Therefore, we agree with the Lugano classification recommendation, published by Cheson et al, that FDG-PET CT should be applied at diagnosis in all patients with DLBCL. A biopsy or close clinical follow-up of atypical findings discovered on FDG-PET-CT is important, as findings other than lymphoma may produce a false-positive scan.

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

329 WHOLE-BODY DIFFUSION-WEIGHTED MR IMAGING IN LYMPHOMA SURVEILLANCE

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Introduction: Diffusion-weighted MRI (DW-MRI) allows for whole-body imaging without the use of intravenous contrast, radiation, or fludeoxyglucose (¹⁸F-FDG). We present imaging findings of whole-body MR with DWI in lymphoma to illustrate the emerging role of MR in lymphoma imaging and discuss salient clinical aspects.

Methods: A total of 414 whole-body MRI exams with DWI were performed at our institution between September 1, 2015, and February 17, 2017. Approximately 60% of patients had treated or untreated indolent lymphoma including follicular lymphoma or marginal zone lymphoma. Approximately 25% of patients had a history of treated

Hodgkin lymphoma (cHL) or treated diffuse large B-cell lymphoma (DLBCL). Imaging was performed on a 3-Tesla MR scanner (GE Healthcare, Milwaukee, WI, USA) using GEM surface coils, with acquisition of axial and coronal T2-weighted images. Diffusion-weighted sequences were acquired using a body coil and b values of 400 s/mm². Postprocessing autobind of diffusion-weighted sequences and T2-weighted sequences allowed for a contiguous series of images from the level of the maxillary sinus through the groin, with images similar to fused FDG-PET and CT images. No intravenous contrast was administered to patients. We correlated imaging findings with relevant clinical and histological data from patient electronic medical records.

Results: As a high cellularity tumor, lymphoma showed restricted diffusion on DWI images and allowed for easy depiction of tumor in noncontrast MR images (figure). Most importantly, we found that whole-body MR with diffusion was a useful application for the follow-up of indolent lymphoma, as many of these patients are not actively treated but monitored over years. As image interpretation is based on the size of lesions, DWI added additional value by allowing easy identification of areas of interest. Posttreatment changes, small lymph nodes (<1.6 cm, long axis), and superficial nodes like inguinal nodes or neck nodes may show restricted diffusion, and comparison with prior studies was often necessary to exclude a clinically significant process. A major shortcoming of our whole-body MR protocol was the limited depiction of small (size <1 cm) pulmonary nodules, although subcentimeter nodules are generally monitored when first found on CT.

Conclusions: Whole-body MR with DWI represents a novel surveillance modality for survivors of potentially curable lymphoma (DLBCL and cHL) and patients with indolent lymphoma who are being monitored expectantly. Given its advantages, including avoidance of radiation exposure and intravenous contrast, whole-body MR may be preferable to CT surveillance for lymphoma patients with nonspecific findings requiring serial assessment and for those who require expectant monitoring of their lymphoma.

Keywords: indolent lymphoma; magnetic resonance imaging (MRI)

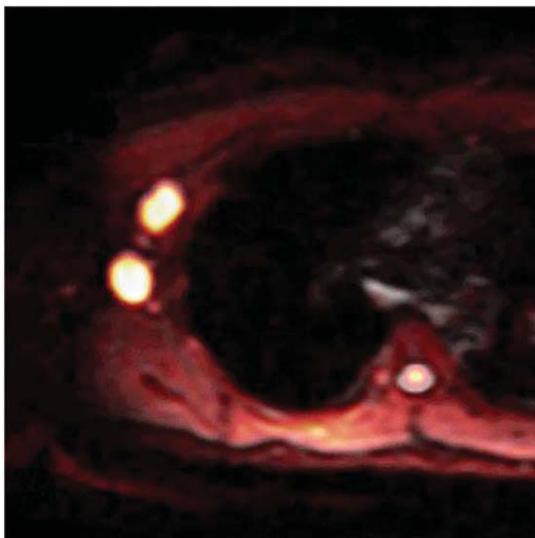


Figure: MR image of the chest with right axillary adenopathy (fused T2/diffusion image). No intravenous contrast

HODGKIN LYMPHOMA

330 NONINVASIVE PRENATAL TESTING AND INCIDENTAL DETECTION OF MATERNAL HODGKIN'S LYMPHOMA

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Introduction: Noninvasive prenatal testing (NIPT) to detect fetal aneuploidy by massive parallel sequencing of cell-free DNA (cfDNA) from maternal serum is getting widely accepted genetic test due to its high specificity and sensitivity for the detection of trisomies 21, 18, and 13. NIPT is a recently established advanced aneuploidy screening, but not a diagnostic test. Positive results consistent with aneuploidy require confirmation by a diagnostic procedure to determine fetal karyotype. The cfDNA in the plasma of pregnant women is a mixture of the placental and the maternal cfDNA. Some cfDNA results are discordant with the direct fetal karyotype. Among other explanations, discordant NIPT results may suggest an undiagnosed maternal cancer.

Case report: We report 26-year-old pregnant women, with a pregnancy after hormonal stimulation. She had NIPT (Prendia START®) performed because of the risk of trisomy 13 and 18 of 1:573. The NIPT result showed normal fetal karyotype and substantial imbalances affecting several chromosomes as amplification of 4q23-q24, 9q24, amplification 1q and 8q, terminal deletion 4q, and proximal deletion 5q and 10q. The strength of signal implied maternal origin. Maternal Hodgkin's lymphoma was suspected. We saw an asymptomatic patient at 18 weeks of gestation, with enlarged left supraclavicular lymph node (3 cm), mild anemia (Hb 10,7 g/dL), ESR (45 mm/h), and CRP (41 mg/L). A lymph node biopsy revealed a NS Hodgkin's lymphoma (HL). A chest MRI showed a confluent anterior mediastinal mass and several pathologically enlarged lymph nodes in the left hilar and paraaortic regions. Based on recommendations and the patient wish, a close observation until delivery was conducted. The patient was clinically stable during that period, with slightly progressive supraclavicular lymph nodes. We performed PET/CT following spontaneous delivery of a healthy girl at 38 weeks of gestation. Results revealed also infradiaphragmatic lymphatic involvement corresponding to stage IIIA with bulky mediastinal mass. According interim PET/CT, the patient achieved metabolic complete remission after 2 cycles of ABVD. After 6 cycles of ABVD irradiation of the mediastinal mass was discussed, the patient decided for no irradiation.

Conclusion: In our patient, genomic aberrations known to occur in HL were detected in cfDNA incidentally when routine NIPT was performed. The presence of DNA derived from Reed-Stenberg cells within circulating cfDNA indicates a relevance of the concept of liquid biopsy for HL patients. It opens new opportunities for the exploring the

diversity of HL, for the detection of somatic mutations and the development of biomarkers for HL.

Keywords: ABVD; Hodgkin lymphoma (HL)

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ALCOHOL-INDUCED PAIN AND PRURITUS IN HODGKIN LYMPHOMA

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Alcohol-induced pain and pruritus are two well-known but rare symptoms in Hodgkin lymphoma (HL). There are no studies addressing these symptoms in modern materials. We studied frequency and characteristics of alcohol-induced pain and pruritus and whether these symptoms correlate with known prognostic factors or survival.

This was a retrospective case-control study performed at the Department of Oncology, Uppsala University Hospital. Data were collected from medical records. A total of 201 patients were >18 years and had information about initial symptoms. Seventy-one patients were included in the analysis: 48 patients with pruritus, 7 with alcohol-induced pain and 20 controls (actively denying both symptoms).

The frequency of pruritus was 24% (48/201) and of alcohol-induced pain 3.5% (7/201). Erythrocyte sedimentation rate (ESR) was significantly higher in the groups with pruritus and alcohol-induced pain ($P = .0016$, $P = .0082$, respectively), and there was a tendency of lower B hemoglobin in those with pruritus ($P = .07$). Patients with pruritus and early-stage disease had more risk factors than controls with early-stage disease ($P = .04$). No differences were seen in age, stage, frequencies of B symptoms, histological subtype, bulky disease, or extranodal disease. For both symptoms, there was a tendency of a higher proportion of women than in the control group (57% for alcohol induced pain, 63% for pruritus, and 40% for controls). A tendency of a poorer time to progression was seen in the group with pruritus compared to controls ($P = .06$), while no difference was seen for patients with B symptoms compared to those with no B symptoms ($P = .4$).

The frequencies of these symptoms correspond with earlier studies. Patients with pruritus and alcohol-induced pain have a higher degree of systemic inflammation than patients that actively denied these symptoms and the patients with pruritus showed a tendency to a poorer time to progression. Further studies will be performed on the tumor material and correlated to the control group.

Keywords: Hodgkin lymphoma (HL)

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20-YEAR FOLLOW-UP OF HODGKIN LYMPHOMA: PREDICTORS OF SURVIVAL AND SECONDARY MALIGNANCIES

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Introduction: The prognosis of Hodgkin lymphoma (HL) has improved significantly with the implementation of a risk-adapted treatment that combines chemo and radiotherapy. Nevertheless, the benefit in terms of overall survival (OS) has been jeopardized by long-term toxicity. The identification of risk factors is crucial to assign each patient to a well-defined risk group and prevent undertreatment or overtreatment, minimizing the risk of relapse and long-term toxicity.

Aim: Analyze the risk factors associated with survival and assess the frequency of secondary malignancies with an ABVD-based regimen that restricted radiotherapy only to bulky disease.

Materials and Methods: We retrospectively analyzed HL patients diagnosed in 4 centers in Tarragona area (Catalonia, Spain), between 1995 and 2015, treated uniformly according to a local protocol. Patients were assigned into 4 groups: G1: favorable early stage: ABVD × 6 cycles, G2: Bulky early stage without other risk factors: ABVD × 6 + IFRDT. G3: unfavorable early stage (B symptoms) and advanced stage without bulky disease: ABVD × 8, G4: Bulky advanced stage: AVBD × 8 + IFRDT. Kaplan-Meier method and log rank test were used for survival analysis. Cox proportional hazard model was used for univariate analysis to identify predictive factors for OS. Factors with significance ($P < .05$) were considered for multivariate Cox regression.

Results: A total of 183 patients were analyzed with a median follow up of 82 months (range 1-244). Male/female ratio was 1.29. Median age was 36 years (range 16-82). Complete response was achieved in 160 patients (87.4%). The estimated OS at 20 years for the whole group was 62.7%.

In univariate analysis, worse OS was found in patients with increased LDH, non-NS subtype, albumin <3.5 g/dL, B symptoms, HIV+, advance stage and ESR >50 mm (log rank $P = .012$; $P = .049$; $P = .024$; $P = .002$; $P = .005$; $P = .004$, and $P = .001$, respectively). The multivariate Cox regression analysis identified B symptoms and ESR >50 mm as independent prognostic factors for OS ($P = .002$; $P = .006$, respectively).

Furthermore, B symptoms was also found as an independent prognostic factor for OS in patients with localized stage disease ($n = 94$; $P = .018$), while ESR >50 mm and increased LDH were independently associated with worse OS in patients with advanced disease stage ($n = 89$; $P = .014$ and $P = .038$). Secondary malignancies were observed in 18 patients (9.8%). The most frequent were hematological in 6 patients (3 myelodysplastic syndrome and 3 non-Hodgkin lymphoma), gynecological in 4 patients (2 breast cancer and 2 adnexal carcinoma), and colorectal in 2 patients. Two patients developed 2 malignancies.

Conclusion: Our risk adapted protocol showed a good rate of response and overall survival with low rate of secondary malignancies. B symptoms and elevated ESR were independently associated with OS in

the whole group. B symptoms was also associated with OS in patients with localized disease while ESR >50 mm and increased LDH were associated with OS in patients with advanced disease.

Keywords: Hodgkin lymphoma (HL)

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THE IMPORTANCE OF PHYSICAL ACTIVITY IN ADULT LYMPHOMA SURVIVORS—SINGLE CENTER'S EXPERIENCE WITH THE SUPERVISED AEROBIC AND RESISTANCE TRAINING PROGRAM

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Introduction: Thanks to novel agents, intensive immuno/chemotherapy and improved supportive care, the number of lymphoid malignancies survivors is increasing rapidly. However, the intensive common treatment combinations (including corticosteroids and drugs with myotoxic and neurotoxic potential) often lead to global loss of physical fitness. Based on the results of breast cancer and colorectal studies, decrease of physical strength and endurance has negative effects not only on the quality of life but also on overall and progression free survival. Yet, few similar trials have been performed in lymphoma patients. We evaluated feasibility, safety, and measurable effectiveness of regular supervised combined aerobic and resistance training on the physical fitness of lymphoma in first remission.

Patients and Methods: Between the years 2013 to 2016, we assigned 33 patients with newly diagnosed Hodgkin (HL = 6) and B-non-Hodgkin lymphomas (B-NHL = 27), all Caucasians, age median 57 (19;73), undergoing conventional intensive immune-chemotherapy (B-NHL - 6 cycles RCHOP: rituximab, cyclophosphamide, doxorubicine, vincristine, prednisone, HL - 6 cycles of escalated BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) and achieved complete remission. To evaluate all main aspects of physical fitness, spiroergometry (aerobic capacity), heart rate variability (vegetative balance), and hand grip test (muscle strength) were performed prior to training initiation and again when completed. Training intervention consisted from individualized supervised 12-week exercise program. The training lesson was 3 times a week and consisted of an aerobic activity 30 minutes, 15 minutes of muscle strength exercise, and 10 minutes of stretching.

Results: From the 33 patients of this prospective trial, 27 completed the program. Paired assessment was available in 23 patients (spiroergometry, hand grip). Due to technical difficulties, heart rate

variability has been evaluated in 13 patients only. In spite of relatively small number of cases, significant improvement of the sympathico-vagal balance and aerobic capacity was observed ($P = .041$). Aerobic capacity measured in all 23 patients increased significantly ($P = .037$). On the other hand, there was no improvement in the muscle strength of all evaluated muscle group was observed ($N = 23$ pts, $P = .92$). There were no adverse events associated with the training.

Conclusions: Based on the results, we conclude that combined intensive training program is feasible and despite its short duration (12 weeks), brings measurable positive results in lymphoma patients treated with intensive regimes. Whereas endurance and vegetative balance was improved, the muscle strength remained decreased.

More prospective trials to find the optimal balance of frequency, duration, and the training composition will be necessary.

Keywords: B-cell lymphoma; Hodgkin lymphoma (HL)

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PROGNOSTIC SIGNIFICANCE OF TRYPTOPHAN CATABOLISM IN NEWLY DIAGNOSED HODGKIN LYMPHOMA

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Introduction: Indoleamine 2,3-dioxygenase 1 (IDO1, IDO) is a tumor microenvironment factor that suppresses antitumor immune responses. IDO is, therefore, an attractive target for cancer immunotherapy, with several IDO inhibitors currently being investigated. This study determined the prognostic significance of tryptophan (Trp) catabolism in patients with newly diagnosed Hodgkin lymphoma (HL). **Patients and Methods:** Serum Trp and kynurenine (Kyn) levels in 52 HL patients were measured using an ultraperformance liquid chromatography–tandem mass spectrometry system and associations with various clinical parameters analyzed. IDO expression was evaluated within affected lymph nodes of HL patients.

Results: Enrolled HL patients comprised 30 males and 22 females (age range, 15–81; median, 45 y), with overall survival (OS) at 5 years of 88.6%. Patients were divided into 2 groups according to their serum Kyn/Trp ratio (Kyn [$\mu\text{mol/L}$]/Trp [$\mu\text{mol/L}$] $\times 10^3$) since high IDO activity results in increased Kyn and decreased Trp concentrations, meaning a high serum Kyn/Trp ratio. Of 7 factors determining the prognostic score for advanced HL, a high serum Kyn/Trp ratio (≥ 42.57) was significantly associated with low Hb (< 10.5 g/dL, $P = .007$) and lymphocytopenia ($< 600/\text{mm}^3$, $< 8\%$

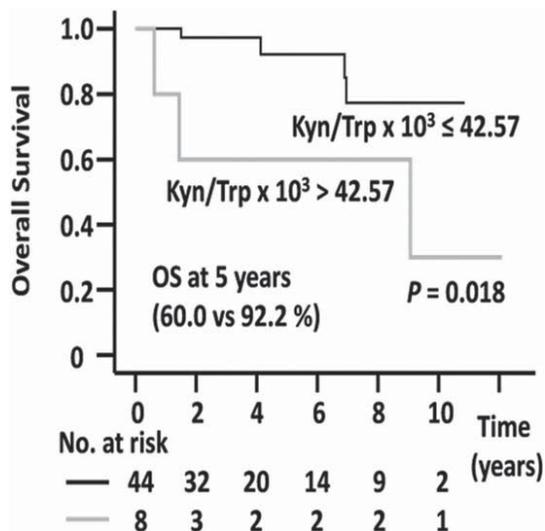


Figure 1 Overall survival of HL patients according to the serum Kyn/Trp ratio

of white blood cell [WBC], or both, $P = .004$), but was not associated with age (\geq or <45 years), serum Alb ($<$ or ≥ 4.0 g/dL), Ann Arbor stage (IV or I-III), sex, or WBC (\geq or $<15\ 000$ /mm³). OS was significantly shorter in patients with a high serum Kyn/Trp ratio compared to those with a low ratio (OS rate at 5 years, 60.0 vs 92.2%, $P = .018$; **Figure**). OS was also shorter in patients with stage IV compared to those with stage I-III lymphoma (OS rate at 5 y, 78.8% vs 91.9%, $P = .015$), and in those with lymphocytopenia compared to those without (OS rate at 5 y, 71.4% vs 92.0%, $P = .010$). There were no significant differences in OS according to age, sex, Hb or Alb level, or leukocytosis. Accordingly, multivariate analysis for OS in the 52 HL patients was performed using the following 3 variables: Ann Arbor stage (I-III or IV), lymphocytopenia (presence or absence), and serum Kyn/Trp ratio (\leq or >42.57). Of these, only the serum Kyn/Trp ratio significantly affected OS (Hazard ratio 7.577; 95% confidence interval, 1.362-42.160). In immunostaining analyses, HL tumor cells (Hodgkin or Reed-Sternberg cells) were negative, but macrophages and dendritic cells in the microenvironment were positive for IDO. A significant positive correlation existed between the serum Kyn/Trp ratio and the degree of histologically IDO positive cells in the tumor microenvironment.

Conclusions: Quantification of serum Kyn and Trp is useful for predicting the prognosis of an individual HL patient. Furthermore, HL, especially in those patients with a high serum Kyn/Trp ratio, is an appropriate disease for testing novel cancer immunotherapies targeting IDO.

Keywords: Hodgkin lymphoma (HL); immune system

335 TREATMENT OUTCOMES FOR HODGKIN'S LYMPHOMA PATIENTS AGED 60 AND OLDER: A REPORT FROM THE BRAZILIAN PROSPECTIVE HODGKIN'S LYMPHOMA REGISTRY

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Introduction: Despite substantial progress in the treatment of Hodgkin's lymphoma (HL), older patients remain an unmet treatment need.

Methods: We have analyzed the clinical features and outcomes of patients registered in the Brazilian Prospective HL Registry with age ≥ 60 and compared them to younger patients.

Results: Among 624 patients diagnosed with classical HL from 2009 to 2014 and treated with ABVD, 63 (10%) patients were 60 years or older. Females comprised 35 patients (56%), and 45 patients (72%) had advanced disease by GHSG criteria. In comparison to patients younger than 60, older patients were more likely to present anemia (46% vs 27%, $P = .003$), to have a high-risk IPS score (59% vs 33%, $P < .0001$), and histopathology other than nodular sclerosis (51% vs 20%, $P < .0001$).

Median follow-up was 35.6 months (0.53-94) for all patients. The 3-year PFS in younger and older patients were 75% and 60% ($P < .0001$), respectively. The 3-year OS in younger and older patients were 92% and 69% ($P < .0001$), respectively.

Older patients were also more likely to have a lower socioeconomic status (SES, 48% vs 28%, $P = .003$) and a lower educational level (25% vs 3%, $P < .0001$). A higher mortality rate during ABVD treatment was observed in older patients who had a lower SES, compared to those with a higher SES (33% vs 10%, $P = .057$). Moreover, the effect of SES on outcomes was particularly pronounced in older patients. The 3-year PFS in younger patients with higher and lower SES were 78%

TABLE 1 Association of level of education, age, time to diagnosis and lower SES

Level of education	Age (years, median)	Time to diagnosis (in months, median)	SES	
			Lower	Higher
Illiterate to incomplete elementary school (≤ 4 years of schooling)	58	7.5	70%	30%
Complete elementary school (5 years of schooling)	40	6	64%	36%
Complete middle school (9 years of schooling)	30	6	40%	60%
High school	26	6	21%	79%
Complete higher education	30	4	4%	96%

Abbreviation: SES: socioeconomic status.

and 68% ($P = .008$) respectively, while in older patients, it was 80% and 43% ($P = .004$) respectively.

Table 1 highlights the strong association of both the level of education and SES with age in Brazilian patients. The educational level might influence directly the patient's capacity to recognize the potential graveness of lymphoma symptoms, as suggested by the longer time to diagnosis in illiterate individuals. Similarly, the level of education might impair the patient's ability to promptly react to complications of treatment. Moreover, the prevalence of comorbidities could differ according to the SES.

Conclusions: Older Brazilian patients have advanced disease and non-nodular sclerosis subtype more often than younger patients. Treatment outcomes are inferior in older patients. These findings appear to be strongly associated with the lower educational level and lower SES observed in older patients.

Keywords: ABVD; Hodgkin lymphoma (HL)

336 ATTENDANCE TO HODGKIN LYMPHOMA SURVIVORSHIP CARE CLINICS IN THE NETHERLANDS

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Background: Survivors of Hodgkin lymphoma (HL) are at risk for late adverse effects of treatment. The Dutch BETER consortium, consisting of health care providers, researchers, and patient representatives, has set up survivorship care clinics (=BETER clinics), where HL survivors are screened for late effects. Patients eligible for the BETER clinics are: ≥ 5 -year HL survivors, treated for HL after

1965, aged 15-60 years at first HL treatment and current age ≤ 75 years.

Methods: In order to assess patient characteristics and clinical attendance rates, descriptive statistics were calculated for data on HL survivors who were invited to attend BETER clinics in the University Medical Center Utrecht (Utrecht), Erasmus MC Cancer Institute (Rotterdam), Radboud University Medical Center (Nijmegen), VU University Medical Center (Amsterdam), and Antoni van Leeuwenhoek hospital (Amsterdam).

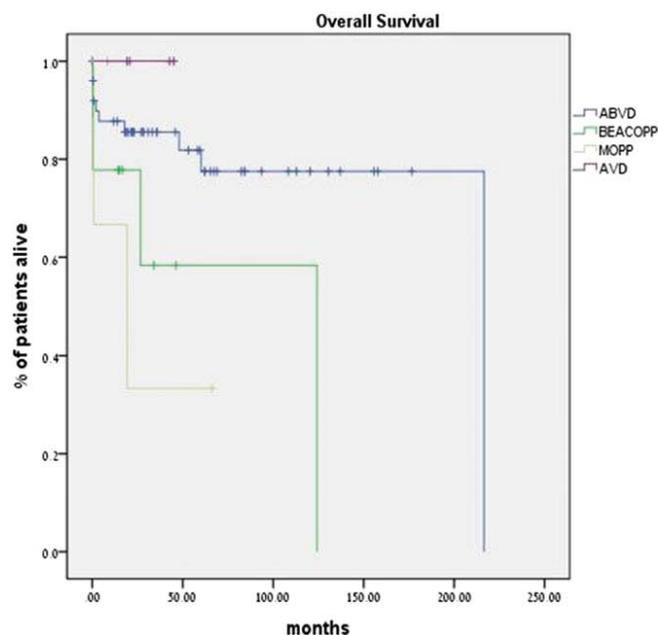
Results: Overall, 584 survivors were invited to attend one of the 5 BETER clinics. Of those who were invited 80% responded and 57% attended the clinic. Median age at invitation was 49 years (interquartile range [IQR]: 41-57 y), median age at HL diagnosis 27 years (IQR: 22-34 y), and median time since diagnosis 19 years (IQR: 12-26 y). Forty-six percent of HL survivors were still under surveillance at the outpatient clinics of the corresponding center. These patients were transferred to the new BETER clinic where follow-up care is adapted to the new screening guidelines. Most common reasons not to attend were undergoing surveillance or treatment for late effects elsewhere (73%) and unwillingness to attend (19%; eg, due to financial or emotional burden). Survivors who were no longer under surveillance were less likely to attend the BETER clinic. Ninety-four percent of survivors who were still under surveillance attended the BETER clinic, opposed to 30% of survivors who were no longer under surveillance. Survivors initially invited by letter were more likely to attend (43%) than those who were first contacted by phone (37%). Age at invitation and age at HL diagnosis were similar in those who did and did not attend.

Conclusions: These preliminary data show that 57% of HL survivors who were invited, attended a BETER clinic. Unfortunately, survivors who were no longer under medical surveillance were less likely to attend, especially when first contacted by phone. Future, more detailed evaluation of (non-)attendance in the BETER clinics may reveal the need for additional measures to improve the BETER survivorship care program.

Keywords: Hodgkin lymphoma (HL)

337 OUTCOME PREDICTORS IN ELDERLY HODGKIN'S LYMPHOMA PATIENTS PLACEHOLDER

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Background: Despite a profound improvement in the clinical outcome of young HL patients, in the elderly, 5-year survival is estimated at only 40% to 55%. This difference is attributed to the increased rate of comorbidity, treatment toxicity, dose reductions, and lack of standard treatment recommendations in this age group. Under representation of this age group in clinical studies and perhaps different disease biology in the elderly might also contribute to this difference.

Methods: All consecutive patients (age ≥ 60), diagnosed with HL between 1998 to 2016 were retrospectively reviewed. Clinical data were recorded and statistical analysis, looking at survival predictors, was performed.

Results: Ninety-five patients were identified. Median age at diagnosis was 71 (range, 60-89) years. Sixty-three (69%) patients had advanced disease, mean international prognostic score (IPS) was 3.5 ± 1.4 . Forty-four (46%) patients had significant lung or heart disease at diagnosis. Fifty-nine (63%) patients received first line treatment with ABVD and 17 (18%) received BEACOPP-like therapy. Sixty-seven (82%) patients achieved complete remission, 6 (7%) achieved a partial response, 7 (9%) were primary refractory, and 9 (10%) died during induction. Fifteen (21%) patients experienced relapse. At 5 years progression free survival (PFS) and overall survival (OS) were 53.5% and 78% respectively.

A significant heart/lung disease was associated with shorter PFS (median PFS 18.9 mo vs not reached at a median follow-up of 5 y, $P = .04$). Age, disease status at presentation (early vs advanced, favorable vs unfavorable, and IPS), and treatment regimen had no a statistically significant impact on PFS (5-y PFS = 55% with ABVD vs 50% with

BEACOPP-like, 50% with AVD and 33% with MOPP). Nevertheless, 5 year OS in patients receiving ABVD was significantly higher than reported with other therapies (82% with ABVD vs 58% with BEACOPP, $P = .04$). [Figure].

Restricted analysis, assessing factors that predict the outcome of ABVD treated patients only, found. A higher risk for relapse in patients with a reduced lymphocyte recovery at 12 months post therapy (average lymphocyte count 1250 vs 2057/ml, $P < .01$).

Conclusions: Treatment outcome in our study was comparable or even superior to previously published cohorts. Traditional outcome measures for HL were not predictive according to our results. Nevertheless, cardio-respiratory disease was associated with shorter PFS, and the employment of a non-ABVD regimen was associated with shorter survival. A delayed lymphocyte recovery predicted a higher risk for relapse in ABVD treated patients.

Larger studies, investigating prognostic factors and new therapies in elderly HL patients are warranted.

Keywords: Hodgkin lymphoma (HL)

338 25(OH) VITAMIN D SERUM LEVELS ASSOCIATE WITH PATIENT CHARACTERISTICS AND OUTCOME IN HODGKIN LYMPHOMA

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Introduction: Low serum 25(OH)D levels have been shown to be associated with inferior outcome in non-Hodgkin lymphomas [Drake et al., *J Clin Oncol* 2010; 28:4191] as diffuse large B cell lymphoma [Bittenbring et al., *J Clin Oncol* 2014; 32:3243], and follicular lymphoma [Kelly et al., *J Clin Oncol* 2015; 33:1482]. The aim of our study was to evaluate vitamin 25(OH)D levels in patients with Hodgkin lymphoma (HL) and analyze for associations with clinical characteristics and clinical outcome.

Methods: We studied 76 patients with cHL (40 females, 36 males, median age 33 years), diagnosed at our Institution between 2014 and 2016. Treatment consisted in ABVD (66 patients), BEACOPP d.e. (7 patients), and COPP (2 patients). One patient received only radiotherapy. Serum samples for vitamin D quantification were collected before the first day of chemotherapy. 25(OH)D was measured in patients' sera using a standardized clinical assay, the DiaSorin LIAISON 25-OH vitamin D TOTAL. 25(OH)D levels were defined according to 3 conditions: deficient (<10 ng/ml), insufficient (10-30 ng/ml), and sufficient (>30 ng/ml).

Results: The median 25(OH)D level at diagnosis was 20.6 ng/ml (range, 5.5 to 42.3 ng/ml). 25(OH)D levels were considered normal in 8 (10.5%) patients, insufficient in 59 (77.5%) patients, and deficient in 9 (12%) patients. Looking at patient characteristics, 25(OH)D levels were

lower in patients with age over 60 years ($P = .002$), reduced performance status (ECOG > 1) ($P = .01$), stage IV disease ($P = .01$), and IPS (Hasenclever) score > 2 ($P = .002$). Furthermore, levels were lower in patients with hemoglobin below 10.5 g/dl ($P = .06$). No association was found with gender, albumin level, B symptoms. In addition, there was a significant seasonal variation, with 25(OH)D levels to be lowest in the first quarter and highest in the third quarter ($P = .03$). FDG-PET evaluation after 2 cycles of chemotherapy according to the 5-point Deauville scale was available in 66 patients. Vitamin D levels were not associated with interim PET response. With a median of 12 months follow-up of patients is still short. Patients with deficient levels ($n = 9$) had a significantly worse PFS than patients with higher levels ($n = 67$) ($P = .002$). The probability of progression-free survival at 12 months was 87% (95% CI, 75%-94%) in patients with 25(OH)D levels > 10 ng/ml, while patients with levels < 10 ng/ml had a 12 months PFS of 47% (95% CI, 12%-76%). We included 25(OH)D levels, IPS (that includes age, stage and hemoglobin level), ECOG, and season in a multivariate Cox analysis. Deficient 25(OH)D level had a borderline significance (HR, 5.65; 95% CI, 0.98-32.55; $P = .05$).

Conclusions: 25(OH)Vitamin D serum levels are frequently low in patients with Hodgkin lymphoma and are associated with patient-related and disease-related characteristics. Our preliminary analysis suggests that low 25(OH)D levels might be associated with worse prognosis.

Keywords: Hodgkin lymphoma (HL); prognostic indices

339 IMPACT ON SURVIVAL OF EARLY DETECTION OF RECURRENCE IN THE FOLLOW-UP OF HIGH RISK HODGKIN LYMPHOMA IN FIRST COMPLETE REMISSION

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Introduction: Despite the high complete response (CR) rate to anthracycline-including first-line therapy, approximately one third of patients with advanced-stage Hodgkin lymphoma (HL) relapses. Many relapses (30%-50%) are clinically asymptomatic, without any physical and/or laboratory signs. For patients at high-risk of relapse, a close monitoring, based on imaging procedures, is justified if an early detection of recurrence would allow a timely administration of salvage therapy and a survival improvement.

Aims: The purpose of this study was to evaluate the response rate to salvage therapy of relapsed HL by comparing patients who received surveillance with conventional clinical assessments versus patients who received surveillance with imaging procedures.

The primary end-point was to assess the rate of CR (confirmed by FDG PET/TC performed before ASCT) to salvage therapy at relapse.

Secondary endpoints were the overall rate of recurrence after first CR, the stage and extranodal involvement at relapse, and the disease-free survival (DFS) from the end of salvage treatment.

Methods: Between June 2001 and December 2009, we analyzed 306 patients with high-risk HL in CR after anthracycline-including induction treatment. In this case-control study, the first cases ($n = 156$) consisted of patients who received a conventional follow-up program including symptom assessment, blood tests, and physical examination; in these patients, imaging procedures were performed only in case of suspected relapse (historical cohort). Subsequent patients ($n = 150$) received routine imaging procedures comprising ultrasonography (US) for the evaluation of superficial, antero-superior mediastinal, abdominal, and pelvic lymph nodes (SMAP-US), and chest radiography (CXR), as integrated part of the follow-up strategy (imaging group). Follow-up procedures were performed at 4, 8, 12, 16, 20, 24, 30, 36, 48, 60, 84, and 108 months after treatment discontinuation in both groups. Relapses were documented by histologic examination in both groups. When relapse was documented, all patients received salvage therapy with high-dose chemotherapy (DHAP), for at least 2 courses, followed, in case of CR, by ASCT.

Results: After a median 62-months observation (range, 4-108), 83 patients, evenly distributed in the 2 groups, had disease relapse. Of these, 29 of 43 patients (67.4%) of the historical cohort vs 17 of 40 patients (42.5%) of the imaging group showed a larger spread of disease at restaging, ie, stage superior to IIB, and a more frequent extranodal involvement [10/43 (23.3%) patients in the historical cohort vs 3/40 (7.5%) patients in the imaging group; $P = .01$]. Furthermore, asymptomatic relapses were 60.4% (26/40) in the imaging group and 39.5% (17/43) in the historical group, $P = .02$. CR rate with second line therapy was higher in the imaging group (27/40, 67.5%) compared with the historical cohort (19/43, 44.2%; $P = .032$). The 3-year DFS was 75% in the imaging group and 36% in the historical cohort ($P = .02$).

Discussion: This is the first prospective case-control study using SMAP-US plus CXR to monitor patients with advanced stage HL. We show that SMAP-US plus CXR is a valuable tool to improve follow-up in patients with high-risk of recurrence. Our data indicate that the early detection of HL recurrence allows to begin rescue therapy in patients with a more limited nodal and extranodal disease and, consequently, increases its effectiveness in terms of probability to response and DFS.

Keywords: Hodgkin lymphoma (HL); salvage treatment

340 LONG-TERM QUALITY OF LIFE IN PATIENTS WITH ADVANCED HODGKIN LYMPHOMA: A SYSTEMATIC REVIEW

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Introduction: The incidence of Hodgkin lymphoma (HL) shows a clear bimodal distribution with the first peak in young adults and the second peak in the elderly. Treatment—usually with combination chemotherapy (CT) and/or radiotherapy (RT)—has resulted in high survival rates compared to other cancers, even in patients with advanced disease. However, many patients experience long-term health problems due to therapy-related side effects, which may impact on their quality of life (QoL).

Methods: A literature search was conducted in MEDLINE, EMBASE, and the Cochrane Library (accessed July 29th). The scope of the systematic review (SR) included the identification of studies reporting on clinical outcomes, resource use, and QoL (patients and caregivers). Publications reporting on QoL in patients with advanced disease are the focus of the current publication.

Results: Ten publications reporting on QoL were identified. The majority of studies were cross-sectional, cohort studies, and included HL survivors (mean age, 35–47 years) who had been treated with combination CT with or without RT and were no longer receiving treatment for their disease. Five publications were from one group in the US (N = 273 patients), who found that, using a range of measures evaluating current psychosocial adaptation, HL survivors (mean, 6.3-y posttreatment) were at an increased risk of psychological distress, sexual problems, infertility, and additional treatment- and disease-related medical problems. The other studies, which included three from the Netherlands (N = 43–180 across studies) and one each from Germany (N = 126) and Austria (N = 98), used the cancer-specific EORTC-QLQ-C30 questionnaire, among others. EORTC-QLQ-C30 scores were significantly worse in HL survivors (mean > 4.5 y posttreatment across studies) compared to historical control populations across a number of functioning domains (role, emotional, cognitive, and social), together with elevated levels of fatigue, dyspnoea, and diarrhoea. Dyspnoea was also significantly worse in HL survivors who had been treated with high dose carmustine-containing regimens vs conventional CT (various regimens). Dyspnoea and diarrhoea may be due to the long-term effects of CT-induced pulmonary toxicity (eg, from bleomycin or high dose carmustine) and gastrointestinal toxicity (eg, anthracyclines, bleomycin, or the vinca-alkaloids). In addition, there were significantly higher rates of dyspnoea, pain, and fatigue and worse physical functioning in patients treated with both CT/RT compared with those treated with either RT or CT alone, which may be due to cumulative toxicities of CT and RT.

Conclusions: Many HL survivors experience a substantial adverse impact on their QoL, even many years after curative treatment. New treatment regimens that have fewer side-effects are needed to improve the long-term health and QoL of patients with advanced HL.

Keywords: Hodgkin lymphoma (HL)

341 ASSESSMENT AND FOLLOW UP OF BONE MINERAL DENSITY USING CT ATTENUATION MEASUREMENTS IN HODGKIN LYMPHOMA PATIENTS

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Introduction: Bone density loss and increased risk for osteoporosis are a cause for concern in Hodgkin lymphoma (HL) patients, but there are no recommendations regarding identification and follow-up of patients at high risk. Evidence support the using of CT images obtained for other reasons to identify patients with osteoporosis without additional radiation exposure or cost. We hypothesized that routinely performed PET-CT scans in HL patients could be informative in assessing bone density changes during and after treatment.

Methods: In this retrospective single-center study, 97 patients aged 18 to 74 years old with HL that were treated with standard first-line chemotherapy regimens (ABVD and/or Esc. BEACOPP) were reviewed. Patients with bone marrow involvement by lymphoma or who lacked the appropriate scans were excluded (17 patients). PET-CT scans performed at diagnosis, at treatment end, and approximately 1 year after completion of therapy were used for bone density assessment by measuring attenuation of lumbar vertebrae given in Hounsfield units (HU). Based on previous studies, CT-attenuation value of 160 HU was used for defining osteopenia.

Results: Comparing scans from diagnosis with treatment end demonstrated significant density reduction of 14.2% [$P < .001$], with slight improvement on follow-up scans (10.6% reduction at follow-up vs baseline, [$P < .001$]). Nine patients (11%) has already been osteopenic at diagnosis, while 12 additional patients (15%) became osteopenic only after treatment. In univariate analysis, younger age, higher attenuation values at diagnosis and higher total doses of corticosteroids were correlated with greater density reduction. However, older age and lower CT-attenuation at diagnosis were associated with osteopenic density values after treatment. Multivariate model found attenuation values at diagnosis as the only significant predictor for both attenuation reduction and osteopenia after treatment. No association with gender or B symptoms was found. Patients with greater decrease in bone density during treatment had greater improvements at follow-up [$P < .001$]. ROC analysis identified that a cutoff value of 216 HU at diagnosis was 92% sensitive and 76% specific for predicting osteopenia after treatment.

Conclusion: Attenuation measurements in routinely performed PET-CT scans of HL patients demonstrated a significant decline in bone density over treatment, with modest recovery on follow-up. Younger patients with higher attenuation values at diagnosis had a greater decline in bone density over treatment. However, older age and lower attenuation at diagnosis predicted the development of osteopenia after treatment, with its potential clinical consequences. This method, which do not entail additional radiation exposure, if validated, has the potential to detect high risk patients and to aid clinicians in decision-making regarding monitoring and therapeutic intervention in these patients.

Keywords: Hodgkin lymphoma (HL)

342 SECOND MALIGNANCIES AND CARDIOVASCULAR DISEASES IN LONG- TERM HODGKIN LYMPHOMA SURVIVORS: THE ISTITUTO NAZIONALE TUMORI OF MILAN (INT) EXPERIENCE

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Background: Survivors of Hodgkin lymphoma (HL) are at risk of late effects from chemotherapy (CT) and radiation therapy (RT), including second malignancies (SMs) and cardiovascular diseases (CVDs). Nevertheless, after ≥ 5 years from end of front-line treatment (EOT), HL patients are referred to general practitioners, and structured survivorship care is still limited. Most data on iatrogenic late effects derive from registries or self-reported interviews, while data of clinical outcome of adult HL survivors followed in survivorship clinics (SC) are scant.

Aims: Adult HL survivors in complete remission for ≥ 5 years from EOT were identified and offered tailored follow-up in a dedicated SC, in order to evaluate the incidence of late complications and to define appropriate follow-up guidelines.

Methods: Medical records of adult HL survivors, treated for HL after 1970, with current age ≤ 75 years, who underwent a visit at the SC of INT, were analyzed to evaluate the incidence of SMs and CVDs. Results were correlated to the treatment modalities, and descriptive statistics were calculated.

Results: From May 2014 to January 2017, 333 HL survivors (145 males, 188 females), with a median age at HL diagnosis of 32 years (range, 18-65 y), underwent a routine visit at SC. Forty-two percent had been treated for stage I-II A and 58% for stage IIB, III, or IV HL. The majority of patients (76%) had received combined modality treatment, 16% CT only and 8% RT only.

Fifty patients (15%) developed second malignancies at a median age of 51 years (range, 23-75) with 8 patients diagnosed with more than one cancer. We observed cancers of the breast in 24 patients (7%), bladder/kidney/prostate in 10 (3%), thyroid in 6 (2%), colon in 3 (1%), lung in 2 (0.6%), melanoma in 2 (0.6%), soft tissue sarcoma in 2 (0.6%), non HL in 5 (1.5%), and acute promyelocytic leukemia in 1 patient. Among patients developing breast cancer, 96% had previously received ≥ 30 Gy mantle (14) or mediastinum field (9) RT. Previous neck RT was delivered to 5/6 patients with thyroid cancer. Overall, median time from EOT to second malignancy was 227 months (range, 6-489). Furthermore, 29 patients (9%) developed basal cell carcinoma (multiple in 15 patients).

Cardiovascular disease occurred in 104 patients (31%) at a median of 13.5 years from EOT and comprised 24 coronary artery disease (14

myocardial infarction), 13 heart failure, 46 moderate or severe valvular disease, and 6 cerebrovascular disease. Valvular disease was strongly associated with RT, as 85% of affected patients had previously received mediastinal RT.

Conclusions: Results of this observational study confirm that a substantial proportion of patients face one or more serious late complications of HL treatment and specific health resources for tailored follow-up programs as well as harmonization and evaluation of appropriateness and cost-effectiveness of current screening guidelines are warranted to improve health in adult HL survivors.

Keywords: Hodgkin lymphoma (HL)

343 PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA (CHL) AND TREATMENT FAILURE DESPITE A NEGATIVE iPET HAVE POOR OUTCOMES AS PATIENTS WITH POSITIVE IPET AND TREATMENT ESCALATION

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Purpose: Despite high NPV of iPET(–) in patients with cHL about 10% progress after ABVD and their prognosis is not well described. This study investigated clinical characteristics including New Model of Risk

Factors (NMRF)* and the long-term outcomes of patients with iPET(-) and treatment failure [iPET(-)&TF] compared to iPET(+) patients and treatment escalation [iPET(+)&TE].

Patients and Methods: Data of 38 international patients with iPET(-) and subsequent treatment failure [iPET(-)&TF] and 31 with iPET(+)&TE were included (Table 1). Patients with iPET(-)&TF had second line treatment with different types of chemotherapy and ASCT whereas 28 patients with iPET(+)&TE were intensified with escalated BEACOPP and 3 with other second line chemotherapy and ASCT. iPETs were interpreted according to the Deauville scale as: (-)-(score 1-3) and (+)-(score 4,5). The primary endpoints were overall survival (OS) and failure free survival (FFS) [death or second progression for iPET1(-)&TF or first progression for iPET(+)&TE patients after TE] since the last ABVD cycle.

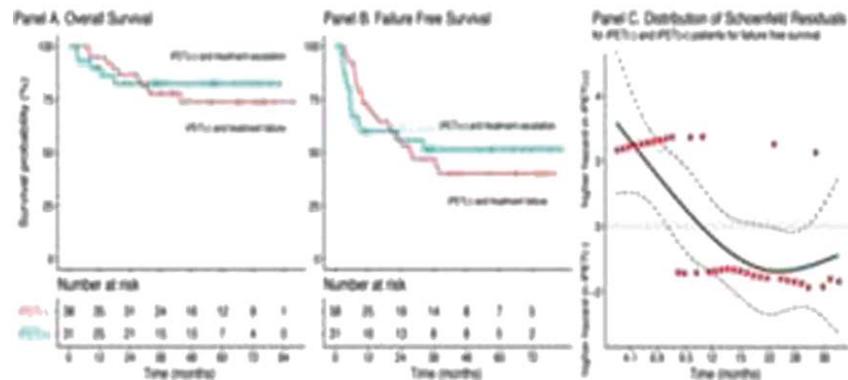
Results: The median follow-up for surviving patients was 57.5 (4-91) months. The 2 cohorts were not different with regard to sex, age,

stage, and presence of B symptoms, bulky mass and extranodal disease. In iPET(-)&TF group, there was more early stage and with mixed cellularity subtype patients. The distribution of IPS (>2 vs 0-2) in advanced stage patients was not different between 2 groups. In parallel, the % of patients with NMRF-2 (presence of both risk factors: albumin < 35 g/l and either ALC < 1400 or <12%) was not significantly different (42% vs 29%). Nine (24%) iPET(-)&TF and 5(16%) iPET(+)&TE died. In the iPET(-)&TF group, most (78%) of patients died after 12 months whereas in iPET(+)&TE most (80%) of deaths occurred before 12 months since last ABVD cycle (Figure 1A). The probability of 4-year OS was 0.74 (95% CI, 0.59-0.89) and 0.83 (95% CI, 0.69-0.96), respectively ($P^{**} = .7$). Failure events happened in 21 (55%) of iPET(-)&TF and 14 (45%) of iPET(+)&TE patients. Similarly, the hazard of failure was higher in first 12 month for iPET(+)&TE whereas after 12 months higher for iPET(-)&TF group.(Figure 1C). The probability

TABLE 1 Demographics and treatment outcome of patients

		Interim PET(-) and Treatment Failure	Interim PET(+) and Treatment Escalation	P
No.		38	31	
Age	Years	37.5(18-82)	32.2(18-65)	.1
Sex	Female/male	18/20	11/20	.31
Histological type	NS	27	22	
	MC	5	1	
	LR	3	4	.05
	LD Unknown	0 3	4 0	
Clinical stage	I-IIA	10	4	
	IIB-IV	28	27	.17
IPS advanced patients	IPS:>2(%)	17(61%)	17 (63%)	.9
B-symptoms	Yes (%)	26 (68%)	25 (81%)	.25
Bulky disease	Yes (%)	19 (50%)	17 (55%)	.69
Extranodal disease	Yes (%)	21 (55%)	15 (48%)	.57
Lymphocyte count < 1400	Yes (%)	23 (61%)	11 (35%)	.04
Lymphocyte <12%	Yes (%)	15 (39%)	15 (48%)	.46
Albumin <35 g/l	Yes (%)	18 (47%)	14 (45%)	.85
NMRF = 2*	Yes (%)	16 (42%)	8 (29%)	.26
Follow-up of alive patients (months)	Median	61	56	
	Min-Max	16-91	4-84	
Type of relapse after completion of first line treatment: iPET2(-): 4-6 x ABVD; iPET2(+)-2 x ABVD + treatment intensification	Primary refractory	23 (61%)	9 (75%)	
	Early 3-12 months	10 (26%)	1 (8%)	0.42
	Late > 12 months	5 (13%)	2 (17%)	
Brentuximab after 1st Failure	Yes (%)	5 (13%)	4 (13%)	.98
Auto-SCT any time during Treatment	Yes (%)	25 (66%)	5 (16%)	.0003
Allo-SCT	Yes (%)	3 (8%)	3 (9%)	.9
1st Failure	Yes(%)	21(55%)	14(45%)	
	4-y FFS 95% CI	0.40 0.24-0.57	0.52 0.33-0.70	.1**
Survival	Dead	9(24%)	5(16%)	
	4-y OS 95%CI	0.74 0.59-0.89	0.83 0.69-0.96	.7**
Alive at last follow-up		29	26	
Alive in CR (%)		24 (83%)	24 (92%)	

Figure 1.
The probability of overall survival (Panel A), failure free survival (Panel B) and distribution of Schoenfeld residuals for FFS (Panel C) in patients with iPET(-) and treatment failure and iPET(+) and interim treatment escalation



of 4-year FFS was 0.40 (95% CI, 0.24-0.57) for iPET(-)&TF and 0.52 (95%CI, 0.33-0.70) for iPET(+)&TE group ($P^{**} = 0.1$).

Conclusion: The long-term outcome of patients who progress despite negative iPET is poor and might be worse than iPET(+) patients and treatment escalation. NMR2 is present in $\approx 30\%$ of ABVD not responding patients.

*New Model of Risk Factors- Dann et al. (Blood 128:3001, 2016)

**Weighted log-rank test with Renyi supremum statistic and Peto-Peto weights.

Keywords: classical Hodgkin lymphoma (cHL); Deauville's criteria; positron emission tomography (PET)

344 CHEMOTHERAPY OR COMBINED MODALITY THERAPY FOR EARLY-STAGE HODGKIN LYMPHOMA

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Background: Hodgkin lymphoma (HL) most commonly develops in young adults and is successfully treated in the overwhelming majority of patients with current treatment programs. This has driven efforts to maintain high cure rates while minimizing long-term toxicity of therapy. The optimal strategy to accomplish these 2, potentially conflicting, objectives is controversial. We reviewed our institutional experience with chemotherapy alone (ChT) or combined modality therapy (CMT), with a special focus on long-term risks of treatment.

Materials and Methods: This IRB-approved retrospective study identified all patients treated at Duke University Medical Center for stage I-II classical HL from 1992 to 2012. Only patients in a complete response (CR) by functional imaging (gallium or PET-CT) after chemotherapy were included. Kaplan-Meier estimates of progression-free survival (PFS) and overall survival (OS) were calculated. A multivariate analysis evaluated factors associated with improved outcomes.

Results: One hundred thirty six patients with a CR to ChT (gallium, $n = 48$; PET-CT, $n = 88$) were identified. ChT consisted of ABVD or ABVD hybrids in $\approx 90\%$ of patients. Consolidation radiation therapy

(RT) was administered to 117 while 19 were observed. There were no differences in baseline prognostic factors between cohorts. In the CMT group, the median RT dose was 24 Gy (range, 18-36 Gy). For CMT and ChT alone patients, 5-year progression-free survival was 97% (95% CI, 91%-99%) and 84% (95% CI, 57%-94%). Corresponding 10-year values were 93% (95% CI, 82%-97%) and 84% (57%-94%). On multivariate analysis, use of CMT was the only predictor of improved progression-free survival (HR, 0.21; 95% CI, 0.05-0.91).

OS at 10 years for CMT was 96% (95% CI, 90%-99%) and for ChT alone was 94% (95% CI, 65%-99%). The only statistically significant factor associated with improved OS on multivariate analysis was younger age (HR, 0.05; $P = .04$). Secondary malignancy risk was nearly equivalent at 10 years, with 3% (95% CI, 1%-8%) and 6% (95% CI, 1%-35%) in the CMT and chemotherapy alone groups, respectively. Only one secondary malignancy, a papillary thyroid cancer, developed in the ChT alone group. There were 7 secondary neoplasms in the CMT group. These included acute myelogenous leukemia, follicular lymphoma, diffuse large B-cell lymphoma, small cell lung cancer, colon cancer, and 2 basal cell carcinomas. The small cell lung cancer was the only malignancy clearly arising within the RT field, occurring in an active smoker 13 years after treatment. There were no cardiac events in the follow-up period.

Conclusions: Following a complete metabolic response to ChT, the addition of consolidative RT results in superior progression-free survival in early-stage Hodgkin lymphoma. The risk of secondary malignancies and cardiac disease was quite low after conformal RT using modest doses. CMT remains the most effective approach to cure Hodgkin lymphoma. However, methods to identify patients with residual disease after ChT, beyond PET-CT, are needed to improve the therapeutic ratio.

Keywords: ABVD; Hodgkin lymphoma (HL)

345 CHEMOTHERAPY AND RADIATION IMPROVE SURVIVAL IN EARLY STAGE CLASSICAL HODGKIN LYMPHOMA: A STATEWIDE CANCER REGISTRY ANALYSIS

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Introduction: Early stage classical Hodgkin lymphoma (cHL) has been shown to have an excellent outcome. Recent studies have therefore focused on decreasing the toxicity that results from the addition of radiation therapy to chemotherapy. However, it remains unclear whether omitting radiation as part of the initial therapy of cHL is associated with a similar survival. The aim of this study is to investigate the outcomes observed in a statewide cancer registry for cHL patients treated with chemotherapy alone versus patients treated with chemotherapy and radiation.

Methods: All adult patients (older than 18) diagnosed with cHL in Kentucky Cancer Registry (KCR) from 2005 to 2014 were retrospectively reviewed. Baseline characteristics (age at diagnosis, gender, histology, stage, B symptoms, extranodal involvement, and the site involved) were collected. First line treatment and overall survival outcomes were reviewed. Stage I and II patients without B symptoms were considered favorable, while those with B symptoms were considered unfavorable. Patients with stage III and IV disease were given an advanced stage designation. To adjust for selection bias, patient deaths during the first 6 months of diagnosis were censored for overall survival analysis.

Results: A total of 961 patients were identified. Median age was 41 (range, 18-91), 60.9% (n = 585) were younger than 50, and 55.5% were males. Only 1.7% (n = 16) had extranodal involvement at presentation. Of those with known histology (78.6%), the most common was nodular sclerosis (71.2%), followed by mixed cellularity (22.8%), lymphocyte rich (3.8%), and lymphocyte depleted (1.9%). Median follow-up time was 45 months (range, 0-136). The 10-year overall survival for the favorable group (n = 329) was 77% (95% CI, 71.1-88.8) versus 68% for the unfavorable group (n = 144) and 42% for the advanced group (n = 372) (P < .001). There was no statistical difference in survival between stage I (n = 170), and stage II (n = 385) disease (P = .99). In the favorable risk group, those who received chemotherapy alone (n = 145) were compared to those who received combined chemotherapy and radiation (n = 148). The 10-year overall survival for the cohort receiving chemotherapy and radiation was 87% compared to 75% for those receiving only chemotherapy (P < .001) (Figure 1). When adjusted by multivariate analysis for risk factors affecting 10 year survival of the favorable cohort, only age < 50 and the treatment modality were independently associated with a statistically significant difference in overall survival [HR of 0.11 (P < .001) and 3.94 (P = .001), respectively].

Conclusion: Our large data cohort shows the presence of B symptoms was more prognostic than the number of nodal regions involved for early stage disease. Although the use of radiation as part of initial therapy for early stage disease might have increase long-term toxicity, it continued to provide superior survival at 10 years.

Keywords: Chemotherapy; Hodgkin lymphoma (HL)

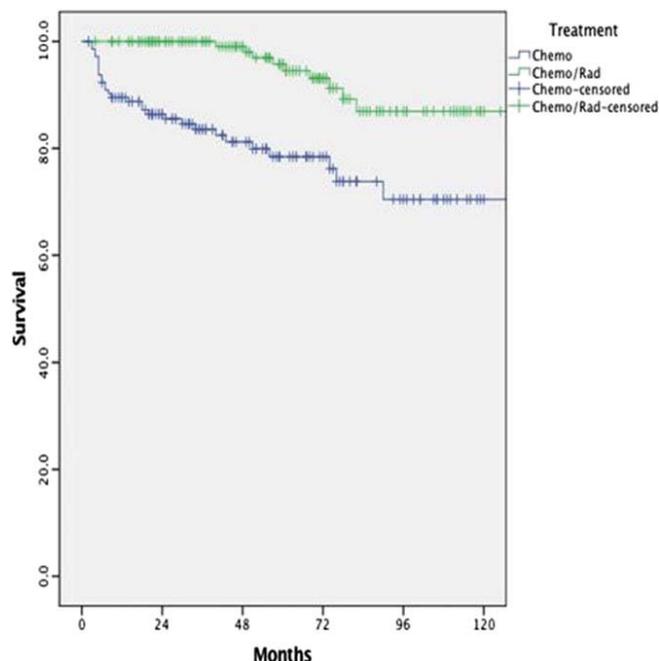


Figure 1: Kaplan-Meier estimated overall survival rates at 10 years

346 EXCELLENT OUTCOME IN HODGKIN LYMPHOMA WITH ABVD AND CMT: A SINGLE-CENTRE RETROSPECTIVE ANALYSIS

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Background: ABVD alone or in combination with radiotherapy(CMT) is the mainstay of therapy for Hodgkin lymphoma (HL). We retrospectively evaluated outcome of HL patients followed up at Haemato Oncology Care Centre, Vadodara, India, between 2007 to 2016.

Methods: Sixty-three patients were analysed for this study, males 65% (n = 41), females 35% (n = 22). The median age was 28 years (range, 8 y to 75 y). Classical Hodgkin lymphoma 93% (n = 59) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) 7% (n = 04). Stage I 1.6% (n = 1), Stage II 25.4%(n = 16), Stage III 58.6%(n = 37), Stage IV 14.3%(n = 09). B symptoms present in 58.6% (n = 37), Bulky disease in 12% (n = 8). ABVD 6 cycles given to Stage IIB, III, IV, and 4 cycles given to (II A). All patients with Bulky disease 9.6% (n = 6) received radiation therapy post completion of ABVD.Two patients with bulky disease (3%) refused to take radiation therapy. Interim PET post 2 cycles of ABVD done in all patients. Bone marrow examination at the end of treatment done only in patients with Stage IV disease. One patient of NLPHL Stage I did not receive any treatment, follow up every 3 months done. One patient had bilateral pulmonary thrombo embolism at diagnosis, received enoxaparin

1 mg/kg SC, BID till completion of chemotherapy. Kaplan–Meier survival estimates were used to evaluate progression-free survival (PFS) and overall survival (OS).

Results: The median follow-up was 49 months (range, 2–107 months). PET CR1 achieved after II cycles of ABVD in 96% (n = 60) and progression of disease in 3.2% (n = 2). Four patients (6%) relapsed within 18 months, of 4 relapsed, 50% (n = 2) patients received salvage chemotherapy (DHAP n = 1, GCD n = 1), both achieved PET CR2. Only 1 patient of CR 2 undergone BEAM auto PBSCT. Five-year PFS and OS were 71.4% and 90.4%, respectively. For early stage (IIA), PFS and OS were 73.1% and 94.1%, respectively, whereas for advance stage (IIB, III, IV), PFS and OS were 69.7% and 86.8%, respectively. Adversed events observed during therapy were pulmonary fibrosis in 6.5% (n = 4), constipation in 3% (n = 2), convulsion in 3% (n = 2), neutropenia grade III, IV % 6.5% (n = 4), peripheral neuropathy 6.5% (n = 4), mucositis with esophagitis 1.6% (n = 1), invasive aspergillosis pneumonia 1.6% (n = 1), fungal nail infection 1.6% (n = 1), herpes zoster 1.6% (n = 1). Posttreatment sequelae observed in total 4.8% patients (n = 3), coronary artery disease n = 1 (3 y post CMT), bilateral idiopathic lower limb edema n = 1 (1 y post ABVD), hepatic epithelial hemangioendothelioma n = 1 (1 y post auto PBSCT), one patient died of disease progression (post CR2). Lost to follow-up total were 17% (n = 11), with complete remission status 3% (n = 2), with relapse status 4% (n = 3), with progression of disease 3% (n = 2), with disease status not known 6% (n = 4).

Conclusions: Patients with HL on ABVD or CMT who achieved PET CR, irrespective of stage and unfavourable risk factor, have an excellent prognosis. Low cost and limited manageable regimen-related toxicity make it feasible to achieve higher cure rate in even economically challenged patients of Hodgkin lymphoma at our centre.

Keywords: ABVD; Hodgkin lymphoma (HL)

347 COMBINATION OF IDARUBICIN, VINBLASTINE, DACARBAZINE, AND GEMCITABINE (IVDG) AS THERAPY FOR ELDERLY PATIENTS WITH HODGKIN LYMPHOMA WITH CARDIAC AND PULMONARY COMORBIDITY

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Introduction: Elderly people comprise from 15% to 35% of all newly detected patients with Hodgkin's lymphoma (HL). The choice of treatment for patients over 60 years demands much more personalized approach than in younger ones. The ABVD regimen, though performing acceptable hematologic toxicity and efficiency, is

associated with 24% risk of pulmonary toxicity induced by bleomycin and 18% mortality associated with treatment rate in patients ≥ 60 years of age. More intensive programs are associated with even higher mortality rate in this age group. This trial was aimed to compare efficacy and toxicity of the combination of idarubicin, vinblastine, dacarbazine, and gemcitabine (IVDG) and the ABVD regimen.

Methods: Single-center, prospective, controlled, randomized noninferiority study was started in 2009. All patients over 60 years with newly diagnosed HL were included, regardless of the number and severity of comorbidities. The median age was 67 in the ABVD group and 70 in the IVDG group. Both groups were balanced by stage, IPS, other prognostic factors of HL, the number of cases with chronic heart failure (NYHA 2–3), and chronic obstructive pulmonary disease. Number of cases with coronary heart disease was higher in the IVDG group—16 compared to 8 in the ABVD group ($P = .04$). Seventeen patients received ABVD therapy, 20 patients—IVDG regimen: idarubicin 5 mg/m² IV days 1, 15, vinblastine 5 mg/m² IV days 1, 15, dacarbazine 375 mg/m² IV days 1, 15, gemcitabine 800 mg/m² IV days 1, 15. Cycles were repeated every 14 days. In cases of severe (grade ≥ 3) hematologic toxicity doses gemcitabine and dacarbazine were reduced by 30% and 20%, respectively. Radiotherapy 30 Gy was performed on residual tumor masses only in patients with partial remission: n = 5 (25%) in IVDG group and n = 8 (47%) in ABVD group ($P = .26$).

Results: Frequency of complete (CR) and partial (PR) responses did not significantly differ between IVDG and ABVD groups: CR was diagnosed in 14 and 10 patients, respectively ($P = .5$); PR—in 3 and 4 patients, respectively ($P = .7$). Five-year overall survival rate was -49% in the IVDG group vs -22% in the ABVD group ($P = .41$). In both groups, no infectious or hemorrhagic complications were diagnosed. Grade 3 hematologic toxicity was observed in 4 (25%) patients in the IVDG group, and 3 patients received reduced doses of gemcitabine and dacarbazine. Frequency of pulmonary fibrosis, detected by CT scans after the completion of therapy, was significantly lower in the IVDG group—0 cases vs 4 (24%) in ABVD group ($P = .004$).

Conclusions: IVDG regimen can be offered as a first-line therapy in elderly patients with HL, especially in those with concomitant cardiac or pulmonary diseases. The efficacy of the IVDG regimen appears comparable to ABVD, with more acceptable profile of pulmonary and cardiac toxicity.

Keywords: ABVD; elderly; Hodgkin lymphoma (HL)

348 HIGH-DOSE BENDAMUSTINE PLUS BRENTUXIMAB COMBINATION IS EFFECTIVE AND HAS A FAVOURABLE TOXICITY PROFILE IN THE TREATMENT OF REFRACTORY AND RELAPSED HODGKIN LYMPHOMA

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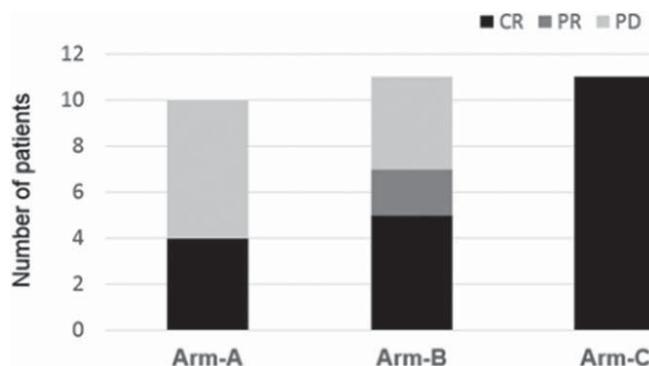
Introduction: The management of patients with refractory or relapsed Hodgkin lymphoma (HL), especially after autologous stem cell transplantation (ASCT), remains controversial. Bendamustine has demonstrated efficacy in several lymphoproliferative disorders, but limited data are available regarding the schedule in patients with HL, in particular its dosage and the possible combinations for a synergistic effect. Brentuximab vedotin is a CD30-directed antibody-drug conjugate, currently approved for the treatment of relapsed or refractory HL. The objective of this retrospective observational trial was to evaluate efficacy and safety of salvage cytotoxic regimens in patients with refractory and/or relapsed HL. Three different regimens were evaluated.

Methods: From May 2011 to December 2016, 32 consecutive patients (19 M/13 F) with a median age of 31.7 years (range, 16–73) received a salvage regimen after failure of ASCT. Patients were by chance assigned to one of these 3 arms: standard dose bendamustine (90 mg/sqm) days 1 and 2 plus standard DHAP schedule (every 4 weeks) × 3 cycles (Arm A, n = 10 cases), brentuximab single agent 1.8 mg/kg (every 3 weeks) × 4 to 8 cycles (Arm B, n = 11 cases), high dose bendamustine (120 mg/sqm) days 1 and 2 plus brentuximab 1.8 mg/kg (day 3) × 4 to 6 cycles (Arm C, n = 11 cases). Each cycle in arm C was repeated every 28 days, and growth factor support was systematically administered, in association with antimicrobial prophylaxis. The treatment efficacy in each arm was evaluated according to Revised Response Criteria for Malignant Lymphoma by Cheson et al. Any adverse event occurred was recorded and classified for type and grade using NCI-CTCAE criteria (v 4.0).

Results: In arm A, the overall response rate (ORR) was 40% (4/10 patients), with 4 (40%) complete remission (CR) and 6 (60%) progressive disease (PD). Hematological toxicity was grade 3 thrombocytopenia in 4 patients (40%) and bone marrow aplasia in 1 patient (10%); extrahematological toxicity was gastrointestinal toxicity of grade 2 in 6 patients (60%) and grade 1 in 3 patients (30%). In arm B, ORR was 63.6% (7/11 patients), with 5 (45%) CR, 2 (18%) partial response (PR), and 4 (36%) PD. Hematological toxicity was grade 2 neutropenia in 4 patients (36%), extrahematological toxicity was grade 3 neuropathy in 2 patients (18%). In arm C, ORR was 100% (11/11 patients), with 11 CR followed by SCT (second autologous transplant, 6 cases; and haploidentical transplant, 5 cases) with persistence of complete remission in all patients at a median follow-up of 33.4 months (range, 12–60). Hematological toxicity was grade 3 thrombocytopenia in 4 patients (36.3%); extrahematological toxicities were increase of transaminase (grade 2) in 3 patients (27%) and cytomegalovirus (CMV) reactivation in 2 patients (18%), treated successfully with valganciclovir. Three patients had fever during infusion at first cycle, together with a skin rash, managed with corticosteroid injections, and a successful antihistamine plus corticosteroid prophylaxis in the next cycles of treatment.

Conclusions: High-dose bendamustine plus brentuximab has shown relevant efficacy and a relatively good safety profile in a setting of heavily pretreated patients with HL. Adequate monitoring of CMV reactivation is recommended. This combination could be considered as a bridge to second autologous or allogeneic SCT. However, these results should be validated by controlled and prospective studies involving larger number of patients.

Keywords: bendamustine; brentuximab vedotin; Hodgkin lymphoma (HL)



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ADVANCED HODGKIN LYMPHOMA IN THE EAST OF ENGLAND CANCER NETWORK: A 10-YEAR COMPARATIVE ANALYSIS OF OUTCOMES FOR ABVD AND ESCALATED-BEACOPP TREATED PATIENTS AGED 16 TO 59

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Introduction: In the UK, most young patients with advanced-stage Hodgkin lymphoma (HL) are managed with ABVD. However, following the 10-year update of the GHSG HD9 study in 2009, escalated-BEACOPP (escB) was introduced by some centres to improve disease control in poor-risk patients. We present a 10-year retrospective multicentre analysis for advanced-stage HL patients, aged 16 to 59, diagnosed between 2004 and 2014 in the East of England Cancer Network and treated predominantly outside of clinical trials.

Methods: We collected data retrospectively from 8 centres using electronic medical records and cancer registry data. Only patients with ≥18 months follow-up were included. The 5-year PFS and OS were estimated using the Kaplan-Meier method, and subgroups compared using the standard log-rank test.

Results: We identified 250 patients (stage 2A bulk–4B) treated in the East of England Cancer Network over a 10-year period from a referral population of 2.64 million (incidence: 0.95 per 100 000). Six of the 8 centres introduced escB for poor-risk patients; 44 patients were treated with escB, 202 with ABVD, 3 with alternative regimens, and

1 died pretreatment. The median age at diagnosis was 35 years (16-59), and the median follow-up was 72 months (19-139). The 5-year PFS for all patients was 82%, and 5-year OS was 92%. There was a physician-patient preference to treat poor-risk patients with escB, as a greater proportion of escB patients had a high international prognostic score (IPS 3+) compared with ABVD patients (escB 75% vs ABVD 38%, $P < .0001$). For the whole cohort, PFS was better for escB patients (5-year PFS 95% vs 80%; HR 4.3 [95% CI, 1.97-9.70], $P = .026$), with no difference in OS (5-year OS 97% vs 92%; HR 2.6 [95% CI, 0.69-10.40], $P = .312$). However, patients with IPS 3+ had both a PFS and OS advantage when treated with escB compared with ABVD (5-year PFS 96% vs 74%; HR 9.24 [95% CI, 3.43-24.89], $P = .012$; 5-year OS 100% vs 84%; $P = .033$). Twenty-nine ABVD patients and 3 escB patients had ≥ 1 subsequent stem cell transplant (including 6 allografts post-ABVD and 3 allografts post-escB). There was equal use of consolidative radiotherapy in both treatment groups (11%). Treatment-related infertility is an important consideration for escB patients. Of the 20 premenopausal women treated with escB, 11 of the 14 (78.6%) aged <30 years at diagnosis regained menstrual periods during follow-up, 5 (45.5%) of whom subsequently conceived (6 live births, 1 miscarriage, 1 termination). Only 1 of the 6 (16.7%) premenopausal women aged >30 years at diagnosis regained menstrual periods, which were not sustained beyond 3 years.

Conclusions: Our data reflect clinical trials results that indicate a first-remission PFS but not OS advantage for unselected young advanced-stage HL patients treated with escB compared with ABVD. However, our data strongly suggest that patients with a poor IPS score derive a PFS and OS benefit from treatment with escB compared with ABVD.

Keywords: ABVD; BEACOPP; Hodgkin lymphoma (HL)

350 BRENTUXIMAB VEDOTIN AND BENDAMUSTINE AS SALVAGE THERAPY FOR PRIMARY REFRACTORY OR RELAPSED HODGKIN LYMPHOMA: A MULTICENTRE EXPERIENCE OF THE POLISH LYMPHOMA RESEARCH GROUP

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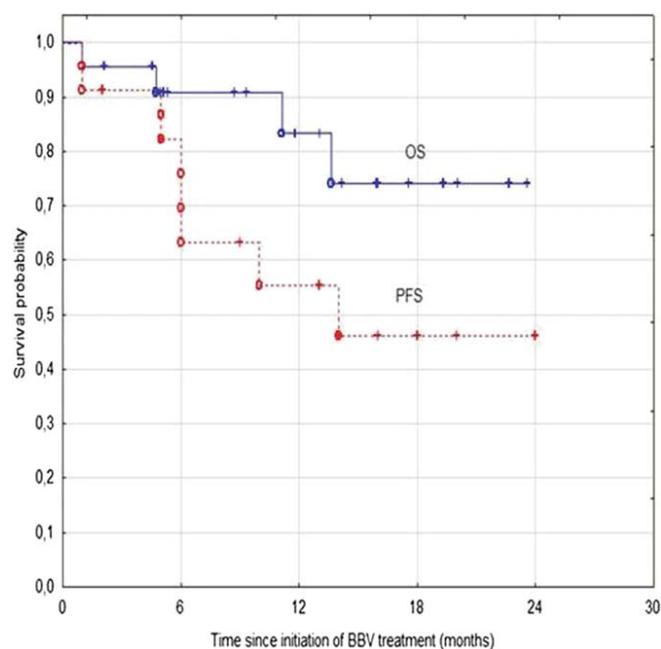
Introduction: An optimal therapy for patients with primary refractory or relapsed (R/R) Hodgkin lymphoma (HL) who did not respond to standard salvage chemotherapy has not been established. Brentuximab vedotin (BV) and bendamustine (B) used in monotherapy both have shown to be active in R/R HL and both are included in

therapy options in these clinical settings. However, the combination of BV with B (BVB) has been investigated in only few clinical trials. Here, we report our experience of BVB given to patients with R/R HL.

Methods: Since March 2015, the patients with R/R HL treated at one of the centers involved in the present retrospective analysis were considered to receive BVB (BV 1.8 mg/kg on day 1 and B 90 mg/m² on days 1 and 2 of a treatment cycle repeated every 21 days). The choice of BBV as salvage therapy was based on the decision of the responsible physician.

Results: Between March 2015 and February 2017, BVB regimen was administered to 24 patients (median age, 33 years; range, 18-60) with primary refractory ($n = 8$) or relapsed HL ($n = 16$), who were treated with a median of 3.5 (range, 2-12) prior chemotherapy lines. Ten of 24 patients were given BVB for relapse after autologous stem cell transplant (SCT), and 4 for relapse after allogeneic SCT preceded by autologous SCT. The patients received a median of 2 (range, 1-6) BVB courses. The toxicities of a total 66 BVB cycles were analyzed. The grade 3-4 toxicities were myelosuppression and infections. Grade 3-4 neutropenia occurred in 2 (8%) and thrombocytopenia <75 G/L in 3 patients (12%). Two of 66 cycles (3%) in 2 patients (8%) were complicated by pneumonia. There were 2 early deaths, 1 due to progression of HL, and 1 due to pneumonia in a patient treated after allogeneic SCT. The overall response rate was 82%, with 10 (41%) complete and 10 (41%) partial metabolic response assessed by positron emission tomography. After a median follow-up of 12 months (range, 2-24), 20 patients remain alive. Fifteen of them are in complete remission. Four patients have proceeded to autologous SCT and other 4 to allogeneic SCT. The probability of overall survival for the whole group at 18 months is 74% (95% CI, 47-90). The estimated median progression-free survival time is 14 months (95% CI, 10-19) (Figure).

Conclusions: Our experience suggests that BVB is a feasible regimen with acceptable toxicity profile and significant response rate in heavily pretreated patients with R/R HL. Moreover, these results indicate that BVB may be successfully used as a bridge to SCT and warrant further



studies to compare prospectively the efficacy of BvB with BV in monotherapy in R/R HL.

Keywords: bendamustine; brentuximab vedotin; Hodgkin lymphoma (HL)

351 HIGH RESPONSE RATES AND SAFE TOXIC PROFILE OF BRENTUXIMAB VEDOTIN/ BENDAMUSTINE COMBINATION IN HEAVILY PRETREATED PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA (HL)

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Introduction: HL complete remission rate after first line treatment reaches to 80% to 90%. However, about 10% of these patients (pts) are refractory and 10% to 30% relapse after achieving a complete remission (CR). High dose chemotherapy followed by autologous stem cell transplant (ASCT) has been standard of care for suitable pts with relapsed/refractory (R/R) HL. Patients who relapse after ASCT have a dismal prognosis. Recently, new treatment options have emerged, such as the antiCD30 antibody-drug conjugate brentuximab vedotin (Bv) that is associated with an overall response rate (ORR) of 75% and CR rate of 34%. In the present study, we evaluated toxicity, efficacy, and duration of response (DOR) of Bv and bendamustine (BvB) combination. **Methods:** We retrospectively analyzed 27 histologically confirmed R/R classical HL pts from 3 cancer centers treated between 2007 and 2016 with at least 3 cycles of BvB. At the time of this analysis, 24 pts were evaluable. The median age was 24 (15-75). Median number of prior treatment lines was 3 (2-5), including ASCT (13 pts, 54%) and allogeneic transplantation (alloSCT, 4 pts, 16.6%). The scheme was administered by i.v. infusion of 1.8 mg/kg brentuximab on day 1 and 90 mg/m² bendamustine on days 1 and 2 every 3 weeks as an outpatient regimen. Pts received a median of 6 (3-16) cycles. Kaplan-Meier estimates of progression free survival (PFS) and overall survival (OS) were performed. Toxicity was recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Response was assessed by PET-CT in 18 pts (75%) and CT-scan in 6 pts (25%).

Results: The ORR was 87%; 54% (13/24) achieved CR, and 33%(8/24) partial remission. Toxicity was observed in 10/24 (41%) pts; grade 2 infusion-related reactions in 3/24 (13%) pts, grade 3 hematologic toxicity in 3/24 (13%) pts, neurologic toxicity grade 3 in 3/24 (13%) pts, and grade 4 in 1/24 (4%) pts with no drug discontinuation. One patient (pt) died due to encephalopathy of unknown origin. The median follow-up was 12 (3-29) months since the beginning of BvB. The median OS was not reach. Median DOR in the CR group was 14 months. A PFS of 80% was observed at 12 months. One pt died due to disease progression. Six patients received consolidation treatment, including 4

ASCT with successful stem cell collection (SCC) and 2 alloSCT. Five pts showed disease progression, all of whom received nivolumab as salvage regimen.

Conclusions: Our data showed a high response rate (87% ORR and 54% CR) with the BvB combination with a PFS of 80% at 12 months. The median DOR of the CR remission group was 14 months, highlighting durable responses. BvB has shown an acceptable toxic profile with only 1 grade 4 adverse event and was able to be delivered as an outpatient regimen. The combination allowed a successful SCC. BvB is a promising salvage treatment for heavily pretreated R/R HL pts. Large investigational trials are necessary to warrant these results.

Keywords: bendamustine; brentuximab vedotin; Hodgkin lymphoma (HL)

352 BRENTUXIMAB VEDOTIN: A RETROSPECTIVE MULTICENTER ANALYSIS OF ITS INDICATION, SAFETY AND EFFICACY IN ARGENTINA

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Purpose: We performed a retrospective multicenter study in Argentina to collect information on patients (pts) with relapsed refractory classical Hodgkin Lymphoma (cHL) treated with brentuximab vedotin (BV). Our purpose was to learn from our own experience, not only on the efficacy and toxicity of this new treatment option but also on the details of its indication. All patients that had treatment with BV were included with no exclusion criteria. The primary endpoint was best

response. Response duration, survival data, and toxicity profile were secondary endpoints.

Patients and Methods: Between 8/2011 and 2/2017, 102 pts that received BV were reported. Median age was 32 (range, 16-73), 56 (55%) were primary refractory. Sixty-six (65%) received BV after ASCT failure, and 39 of these relapsed in the first year. The median number of previous treatment was 3 (range, 2-7). At the time of initiation of BV, 79 (77%) were resistant to the last line of therapy. BV was indicated at 1.8 mg/kg as IV infusion. Seventy-eight (77%) received BV as monotherapy, and 24 (23%) received BV combined with chemotherapy of which 19/24 was with bendamustine (BvB). For the pts that received BV as monotherapy, the median number of cycles was 6.5 (1-16), only 6 pts received all 16 cycles. The median time of first assessment of response was after 4 cycles. Four patients had dose reduction due to toxicity.

Results: Seventy-one patients treated with Bv as monotherapy were evaluated for response. The most common adverse events (AE) for were nausea, vomiting and diarrhea (24%), infections (26%), peripheral sensory neuropathy (21%), and neutropenia (16%), 21 Grade 3-4 AE were reported, including 1 seizure, 1 aseptic meningitis, and 1 cerebral syndrome in 3 pts treated with BvB. The overall response (CR + PR) was 60% with 22 (31%) pts achieving a CR, 21 (29.6%) pts a PR, and 8 pts showed progressive disease. With a median follow-up of 13 months, the PFS and OS at 24 months was 30% and 78% for all pts. For pts in CR, the PFS at 24 months was 82%. In a multivariate analysis for obtaining CR after BV considering: Bulky disease, dose density of treatment, 2 vs more than 2 lines of prior treatment and primary or early relapse vs late relapse, the only significant prognostic factors were being primary refractory or having a first relapse within the first year ($P = .019$). Of the 19 patients that received BvB, 15 were evaluable at the time of this analysis, and they were analyzed separately. The ORR for this group was 80% with 5pts (33%) achieving a CR and 7 (47%) PR.

Conclusions: This is the first and only retrospective multicenter trial showing the Argentine experience with brentuximab. Our findings add to the growing body of evidence supporting the efficacy of Bv as monotherapy and the high ORR and CR of the combination of BvB and warrant a confirmatory randomized trial to re-examine the benefit of this drug combination over BV as monotherapy.

Keywords: brentuximab vedotin; Hodgkin lymphoma (HL)

353 NIVOLUMAB FOR RELAPSED OR REFRACTORY HODGKIN LYMPHOMA: EXPERIENCE IN TURKEY

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TABLE 1 Patient demographics and disease and response characteristics (n = 63)

Median age, y	29 (18-75)
Male/female (n)	38/25
ECOG status ≤ 1	36 (89%)
B symptoms present	32 (51%)
Stage 3-4 disease ^a	43 (80%)
Median nr. of lines of previous therapy	5 (2-11)
5 or more lines	37 (59%)
Previous stem cell transplantation	44 (70%)
Autologous	42 (67%) ^b
Allogeneic	12 (19%) ^c
Previous brentuximab vedotin (BV) treatment	48 (76%)
Refractory to BV ^d	30 (65%)
Median follow-up under nivolumab (months)	6 (1-18)
Median cycles of nivolumab	11 (1-32)
Early response (≤12 weeks of treatment)	
CR	15 (26%)
PR	25 (42%)
SD	7 (12%)
PD	12 (20%)
Late response (≥16 weeks of treatment)	
CR	9 (24%)
PR	16 (43%)
SD	2 (6%)
PD	10 (27%)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

^aStage at the time of nivolumab initiation was available for 54 patients.

^bOne patient received autologous stem cell transplantation 2 times.

^cTen patients received autologous stem cell transplantation before allogeneic stem cell transplantation.

^dBrentuximab vedotin response data were not available in one patient and one patient underwent autologous stem cell transplantation after brentuximab vedotin treatment but before the response evaluation.

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Background: PD-1 inhibitors have been approved by FDA for patients who relapse following autologous stem cell transplantation (SCT) and brentuximab vedotin (BV) therapy. This retrospective multicenter study aimed to provide information about the efficacy and safety of nivolumab in the “real-life” setting in Turkey.

Methods: Twenty-three centers participated in this study. Eligible patients (pts) were required those treated with at least 1 cycle of nivolumab and with available response evaluation. Pts received nivolumab via a named-patient program, and it was administered at a dose of 3 mg/kg iv over 60 min q2wk. The study was approved by the local ethical committee. Radiological response evaluation was performed in the early (at or before 12th week of treatment) and late (at

or after 16th week of treatment) settings, according to the Lugano Classification and its update regarding immunomodulatory therapy.

Results: Between 06/2015 and 11/2016, 87 pts were enrolled in the study. Two, 19, and 3 pts who had not yet received nivolumab, had not reach the time for early radiological evaluation, and who died before any radiological evaluation were excluded from the analysis. Thus, 63 pts were retrospectively analyzed (Table 1). The overall response rate (ORR) was 68% (95% CI, 0.020-0.28) among 59 pts evaluated in 12 weeks of treatment, and its ORR was 67% after 16 weeks of treatment (95% CI, 0.004-0.26). Estimated OS was 95% (95% CI, 0.80-0.98) and estimated PFS was 71% (95% CI, 0.55-0.82) at 12 months. Median OS was not reached, while, according to the late response rates, the median PFS was 14 months. However, it was only 3 months in pts with PD at the late radiological evaluation.

Regarding responses to last treatment prior to nivolumab, we detected that 28 (67%) of 42 PD cases had objective early responses and 70% of 23 PD cases with late response evaluation had ORR (4 CR,12 PR). Eight pts had SCT following nivolumab. Among 5 pts who had been treated by allo-SCT, 4 had CR at the time of SCT, and they are alive with ongoing response. Safety profile was acceptable, and only 2 pts required cessation of nivolumab due to serious adverse events (autoimmune encephalitis and aggravation of graft versus host disease). At the time of analysis, 40 pts were still on nivolumab (64%). Among the 40 pts with early objective responses to nivolumab, 35 (88%) showed ongoing responses. All 24 pts with objective responses in the late evaluation had ongoing responses at the time of analysis.

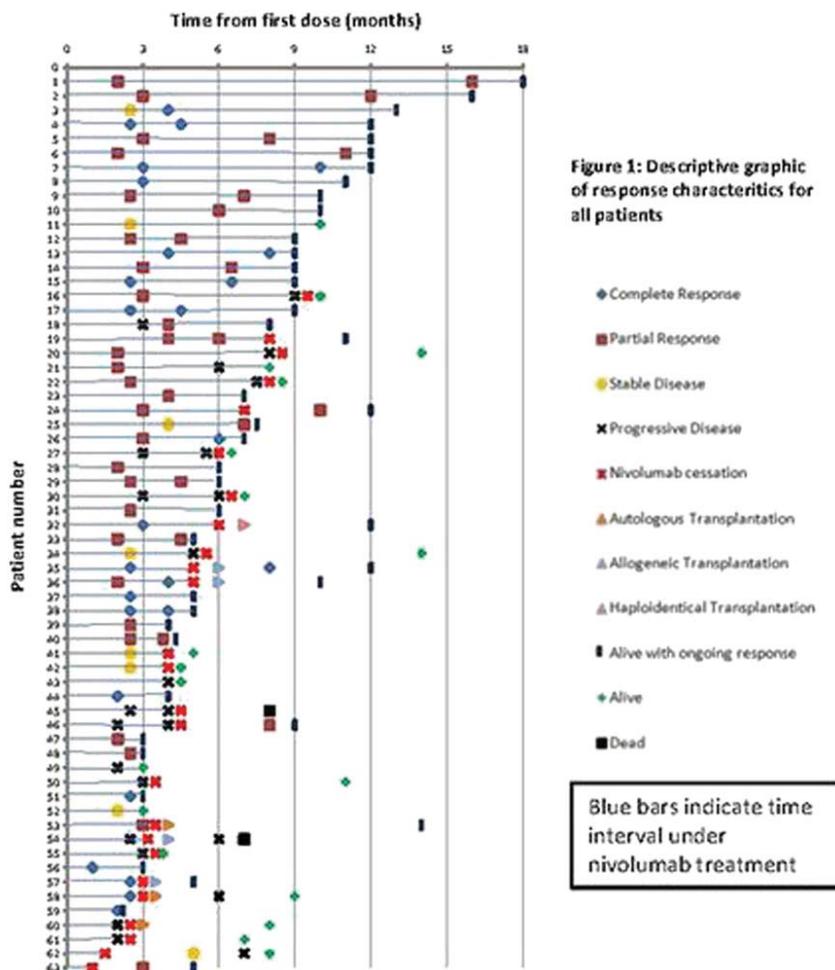


Figure 1: Descriptive graphic of response characteristics for all patients

Conclusion: PD-1 blockers are new options to meet the unmet need in patients with cHL refractory to BV treatment, and possibly a bridge for these patients before SCT.

Keywords: Hodgkin lymphoma (HL); immunomodulators (IMiDs)

354 OUTCOMES OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (ALLO-SCT) for HODGKIN'S LYMPHOMA: A SINGLE INSTITUTION EXPERIENCE

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Introduction: Hodgkin lymphoma relapsing after autologous SCT (auto-SCT) has a dismal outcome with conventional salvage chemotherapy. Allo-SCT is a potentially curative option for these patients.

Methods: We analyzed retrospectively the outcomes of 23 patients of our institution undergoing related, unrelated, or haploidentical donor reduced intensity conditioning regimen (RIC) allo-SCT for relapsed and refractory Hodgkin lymphoma between May 2002 and February 2017.

Results: The median age at allo-SCT was 30 (range, 14-56). The median number of treatments before allo-SCT was 4 (range, 2-5). An auto-SCT had been performed prior to allo-SCT in 96% (n = 22) of the patients. Disease status at allo-SCT was complete remission in 22% (n = 5), partial response in 74% (n = 17), stable disease in 4% (n = 1). All patients received RIC regimens based on fludarabine. The 52% of the patients received matched sibling donor grafts, 22% matched-unrelated donor grafts, and 26% received haploidentical donor grafts. The median time from auto-SCT to allo-SCT was 32 months (range, 15-43 months). Acute GVHD (grade I-III) developed in 9 patients (39%). Chronic GVHD developed in 11 (48%) of the patients. Six patients (23%) died from early transplant-related mortality (before day +100 after allo-SCT). With a median follow-up of 16 months (r: 1-158 months), 10 patients (43%) experienced relapsed. The progression free survival and overall survival were 37% and 56% at 1 year and 18% and 32% at 3 years.

Conclusion: Allo-SCT represents an attractive option for young patients with chemosensitive disease. The use of RIC regimens has been able to decrease the nonrelapse mortality. However, the high-relapse rate remains a significant issue in this setting.

Keywords: allogeneic stem cell transplant (alloSCT); Hodgkin lymphoma (HL)

355 ACHIEVEMENT OF COMPLETE REMISSION AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION IS STRONGLY CORELATED WITH IMPROVED SURVIVAL OF PATIENTS WITH HODGKIN LYMPHOMA

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Introduction: Several parameters at diagnosis and during autologous stem cell transplant (ASCT) have been reported to influence survival of patients with Hodgkin lymphoma (HL) who underwent ASCT.

Methods: This retrospective study included a total of 78 patients (42 males/36 females) who underwent ASCT between 2005 and 2012. All patients were initially treated with ABVD protocol, in relapse/refractory HL with salvage regimens DHAP/ICE, and with BEAM as conditioning regimen before ASCT. Evaluation of disease status was performed according to Cheson criteria.

Results: Median age at ASCT was 32 years. Low International Prognostic Score (IPS 0-2) had 21 patients (26.9%), and high (IPS ≥3) had 57 (73.1%). I and II clinical stage according to Ann Arbor had 30 patients (38.5%), while III and IV had 48 (61.5%). Presence of B symptoms had 67 patients (85.9%) and bulky disease 40 (51.3%). Bone marrow infiltration had 3 patients (3.8%). The average of transplanted CD34+ cells in HL patients was 7.45×10^6 /kg. After initial chemotherapy complete, partial remission, stable, and progressive disease had 31 patients (39.7%), 9 (11.5%), 24 (30.8%), 14 (17.9%), and after ASCT, 39 (50.0%), 27 (34.6%), 3 (3.8%), and 9 (11.5%), respectively. Of 47 patients, who did not initially achieve complete remission (CR), 22 (46.8%) had CR after ASCT. Median duration of initial event-free survival was 8 months (range, 1-120 months), event-free survival after ASCT was 23.5 months (1-119 months), and overall survival was 72.5 months (12-192 months). Among analyzed parameters, IPS influenced initial event-free (Log Rank = 6.950, $P = .008$) and event-free survival after ASCT (Log Rank = 3.899, $P = .049$) as well as overall survival (Log Rank = 3.944, $P = .047$). Achieving CR after initial chemotherapy influenced duration of initial event-free survival (Log Rank = 17.439, $P < .0001$), but did not have influence either on event free survival after ASCT or on overall survival ($P > .05$). However, achievement of CR after ASCT strongly influenced both event-free survival after ASCT (Log Rank = 35.529, $P < .0001$), and overall survival (Log Rank = 29.182, $P < .0001$).

Conclusions: Our data suggest that achievement of CR after ASCT is one of the major parameters that influence survival of patients who underwent ASCT.

Keywords: autologous stem cell transplantation (ASCT); Hodgkin lymphoma (HL)

356 SERUM BIOMARKERS TARC AND IL-6 PREDICT RELAPSE RISK IN HODGKIN LYMPHOMA PATIENTS UNDERGOING AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

Biomarker Group (Pre-AHCT and D28 post AHCT)	N	2-Year Relapse (95% CI)	P-value
IL-6			0.01
Low / Low	5	0%	
High / High	24	58% (40-78%)	
Low / High	6	0%	
High / Low	6	33% (10-81%)	
TARC			<0.01
Low / Low	16	0%	
High / High	13	69% (45-91%)	
Low / High	3	67% (23-99%)	
High / Low	9	56% (28-86%)	

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Introduction: Serum biomarkers in classical Hodgkin Lymphoma (cHL) reflect both tumor biology and immune microenvironment. We sought to determine the prognostic value of cHL serum biomarkers in predicting relapse following autologous hematopoietic cell transplantation (AHCT).

Methods: Nine serum biomarkers (IL-6, IL-10, IL-13, sCD30, sIL-2R, TARC, Galectin-1, CD68, and CD163), collected pre- and day 28 post AHCT were evaluated in 61 patients. We calculated optimal cutpoints for each biomarker with primary endpoint 2-year relapse.

Results: Patients had either relapsed cHL (66%) or primary refractory (34%) and 88% had chemosensitive disease. Almost half were in complete remission (47% CR, 41% PR) and 28% of patients received ≥ 2 salvage chemotherapy regimens prior to AHCT. Patients received CBV (64%), BEAM (33%) conditioning and 2 patients received total lymphoid irradiation. After adjusting for disease status, B-symptoms, and stage in multivariate Cox analysis, 2 biomarkers TARC and IL-6 significantly impacted risk of relapse. Higher pre-AHCT serum levels of TARC (≥ 343.6 $\mu\text{g}/\text{dl}$) and IL-6 (> 2.15 $\mu\text{g}/\text{dl}$) conferred an increased risk of relapse at 2 years with hazard ratios (HR) 4.26 (1.35-13.48); $P = .01$ and HR 8.56 (1.91-38.30), $P = .01$. In cohort to 29 patients in metabolic remission (CR) pre-AHCT, cumulative incidence of relapse with high TARC level was 51% (95% CI, 26%-81%) compared to 19% (95% CI, 6%-48%; $P = .06$) with low TARC levels. Cumulative rate of relapse at 2 years by composite of high/low biomarker serum levels prior to AHCT and day 28 posttransplant are shown in Figure.

Conclusion: Elevated serum biomarkers may identify cHL patients at increased risk for relapse and offer opportunities for intervention, such as intensified peri-transplant and post-AHCT maintenance therapy.

Keywords: autologous stem cell transplantation (ASCT); classical Hodgkin lymphoma (cHL); prognostic indices

AGGRESSIVE LYMPHOMAS

357 THE CLINICAL OUTCOME AND PROGNOSIS OF PEDIATRIC MATURE B CELL LYMPHOMA

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Background: To improve the clinical outcome and prognosis of mature B cell lymphoma, we use modified LMB89 protocol (high dose, short course) combined with correctly diagnosis and precisely individually treatment.

Purpose: Summarize the clinical pathology characteristics of pediatric B cell lymphoma, compare the outcome of 2 protocols, BCH-2003 vs BCH-2009 (both were modified from LMB 89).

Methods: From March 2003 to June 2015, 246 cases of B cell lymphoma were enrolled. According to the treatment time, 246 patients were divided into 2 groups, BCH-2003(71 cases) and BCH-2009 (175 cases). In group 03, on the basis of different stage and risk factor, there were 3 subgroup: A, B, and C. However, in group 09, according to the stage, risk factor, biomarkers, MDD test, and CNS status, there were A, B1, B2, C1, C2, and C3 subgroups, the treatment course range from 4 months to 6 months separately. Four evaluations were on day 7, after the third and the fifth course, and off treatment separately, and we could tailor the treatment to the evaluation results.

Results: Among the 246 cases, 195 were BL (79.2%), 7 were BLL (2.8%), 40 were DLBCL(16.2%), and 3cases were FL (1.2%). The most common symptoms were acute abdomen, facial, and cervical mass. One hundred six cases had BM involvement, which contains 79 leukemia stage, 51 cases had CNS involvement. For the stage, 28 cases were stage I-II (11.4%), stage III-IV were 218 (88.6%). The median follow-up time was 88.7 months (1-146 months), and all cases were off treatment.

In group 03, 5y-OS was 85.2%, 5y-EFS was 83.1%. In group 09, 5y-OS was 87.4%, and 5y-EFS was 83.8%. There were 35 events (2003, n = 10; 2009, n = 25), PD cases were 11, relapse cases were 13, 12/13 cases were relapsed within 6 months off treatment, only the rest 2 cases were alive. Eleven cases were chemo-related death, and 4 cases were quit the treatment. Univariate analysis showed stage IV, CNS involvement, unable to get CR after 3 months treatment, bulky disease, leukemia stage were prognostic factor.

Conclusion: The clinical outcome of B cell lymphoma was substantial improved under the BCH-B-NHL protocol, which was modified from LMB89 (high dose, short term). The prognosis of group 09 was better than group 03, although there was no statistics significance between 2 groups. Prognosis factor were stage IV, CNS involvement, unable to get CR after 3 months treatment, bulky disease, and leukemia stage.

Keywords: B-cell lymphoma; chemotherapy

358 THE PROGNOSTIC IMPLICATION OF THE PRETREATMENT NUTRITIONAL STATUS IN DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS TREATED WITH RITUXIMAB-BASED CHEMOTHERAPY

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Background: Pretreatment nutritional status has been noted to be an important prognostic factor in various types of malignancies, but its prognostic significance is not still investigated in diffuse large B-cell lymphoma (DLBCL) patients in the rituximab era.

Method: A retrospective cohort of 297 patients with newly diagnosed DLBCL treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) were analyzed to reveal the prognostic significance of the controlling nutritional status (CONUT) score. The CONUS was calculated by the serum albumin concentration, the total peripheral lymphocyte count, and the total cholesterol concentration, which has been developed to screen nutritional status in the early stage of the diseases.

Result: The mean follow-up duration was 39.9 months (95% confidence interval [CI], 36.7-43.3 months). At a CONUS cutoff of <2 vs ≥ 2, a trend towards longer 5-year progression-free survival (PFS, CONUS 0 vs 1/2, 76.5% vs 63.6%, respectively; $P = .088$) was observed in all of the treated patients. In germinal center (GC) type subgroup, the lower CONUS group showed a significantly longer 5-year PFS (CONUS 0 vs 1/2, 80.1% vs 69%, respectively; $P = .048$). Five-year PFS and overall survival (OS) were significantly better in patients with the lower Glasgow prognostic score (GPS), the lower Ann Arbor stage, the better Eastern Cooperative Group (ECOG) performance status, and the lower international prognostic indices (IPI). In multivariate analysis, the lower international prognostic indices was the only significant poor prognostic factor for PFS (hazard ratio [HR], 2.56; 95% confidence interval [CI], 1.33-4.91; $P = .005$), but for OS, the GPS (HR, 2.1; 95% CI, 1.07-4.51; $P = .019$) and the ECOG

performance status (HR, 2.2; 95% CI, 1.07-4.51; $P = .33$) were significant prognostic factors.

Conclusion: Pretreatment nutritional status calculated by the CONUS has the possibility of predictive value of progression-free survival in DLBCL patients treated with rituximab-based regimen, especially in GB type patients.

Keywords: diffuse large B-cell lymphoma (DLBCL); prognostic indices; rituximab

359 PROGNOSTIC ROLE OF THE NEUTROPHIL-TO-LYMPHOCYTE RATIO IN PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Introduction: Neutrophil-to-lymphocyte ratio (NLR) is one of parameters complete blood cell count (CBC) tests provide and has been reported to be an easily-accessible prognostic marker in aggressive cancer including non-Hodgkin lymphoma (NHL). Primary CNS lymphoma (PCNSL) is an extranodal NHL with highly aggressive features. However, the importance of NLR has never been assessed in PCNSL.

Methods: This retrospective study enrolled 62 biopsy-proven patients whose baseline NLR was available and reviewed their medical records

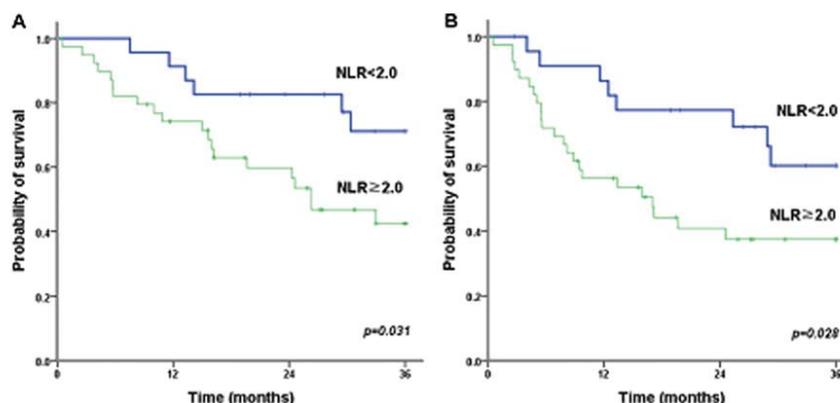


Figure 1. Kaplan-Meier curves of overall survival (A) and progression-free survival (B) according to neutrophil-to-lymphocyte ratio (NLR) at diagnosis in patients with PCNSL performed methotrexate-based induction therapy.

TABLE 1 Univariable analyses for overall survival and progression-free survival

		OS			PFS		
		HR	(95% CI)	<i>p</i>	HR	(95% CI)	<i>p</i>
NLR	<2	1			1		
	≥2.0	2.64	(1.06, 6.58)	0.038	2.41	(1.07, 5.42)	0.034
Age	≤60	1			1		
	>60 years old	2.36	(0.99, 5.64)	0.053	2.01	(0.92, 4.36)	0.079
ECOG Ps	≤1	1			1		
	>1	2.43	(1.11, 5.32)	0.026	1.62	(0.78, 3.34)	0.196
IELSG score	≤2	1			1		
	>2	3.25	(1.24, 8.52)	0.016	2.22	(0.97, 5.01)	0.060
Location	Non-deep	1			1		
	Deep lesion	0.69	(0.31, 1.51)	0.349	0.57	(0.27, 1.20)	0.138
CSF protein	Normal	1			1		
	Elevated	1.62	(0.20, 12.8)	0.649	2.22	(0.29, 17.1)	0.444
LDH	Normal	1			1		
	Elevated	2.59	(1.15, 5.84)	0.022	2.71	(1.28, 5.75)	0.009
Induction regimen	R-mop	1			1		
	MOP	5.90	(0.80, 43.8)	0.083	4.04	(0.96, 17.0)	0.056
CRP	Normal	1			1		
	Elevated	0.71	(0.23, 2.17)	0.547	0.95	(0.37, 2.46)	0.921
PLR	<97	1			1		
	≥97	2.82	(0.97, 8.18)	0.057	3.62	(1.26, 10.4)	0.017
RDW	<14.2	1			1		
	≥14.2	3.41	(1.27, 9.17)	0.015	2.71	(1.04, 7.12)	0.042

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IELSG, International Extranodal Lymphoma Study Group; WBRT, Whole Brain Radiation Therapy; PLR, Platelet-to-lymphocyte ratio.

to compare high (≥2.0) and low NLR group in terms of clinical characteristics and outcomes.

Results: The low NLR group showed significantly better response rates to induction chemotherapy vs the other one ($P = .041$). With a median follow-up of 41.5 months, the high NLR group revealed significantly worse 3-year overall survival (OS) (42.5 vs 71.2%; $P = .031$), and 3-year progression-free survival (PFS) (37.3 vs 60.1%; $P = .028$). In univariable Cox analysis, high NLR at diagnosis was a poor prognostic factor for both 3-year OS (HR, 2.64; 95% CI, 1.06-6.58; $P = .038$) and 3-year PFS (HR, 2.41; 95% CI, 1.07-5.42; $P = .034$). However, multivariable analyses adjusting for IELSG score and induction chemotherapy regimen showed no statistical significance albeit high NLR's tendency towards worse 3-year OS (HR, 2.36; 95% CI, 0.84-6.62; $P = .102$) and worse 3-year PFS (HR, 2.28; 95% CI, 0.93-5.63; $P = .073$).

Conclusions: In conclusion, given the fact that it is simple and easy to obtain, NLR might play a potential role in prognostication of PCNSL from the very beginning of patient journey.

Keywords: non-Hodgkin lymphoma (NHL); primary CNS lymphoma (PCNSL); prognostic indices

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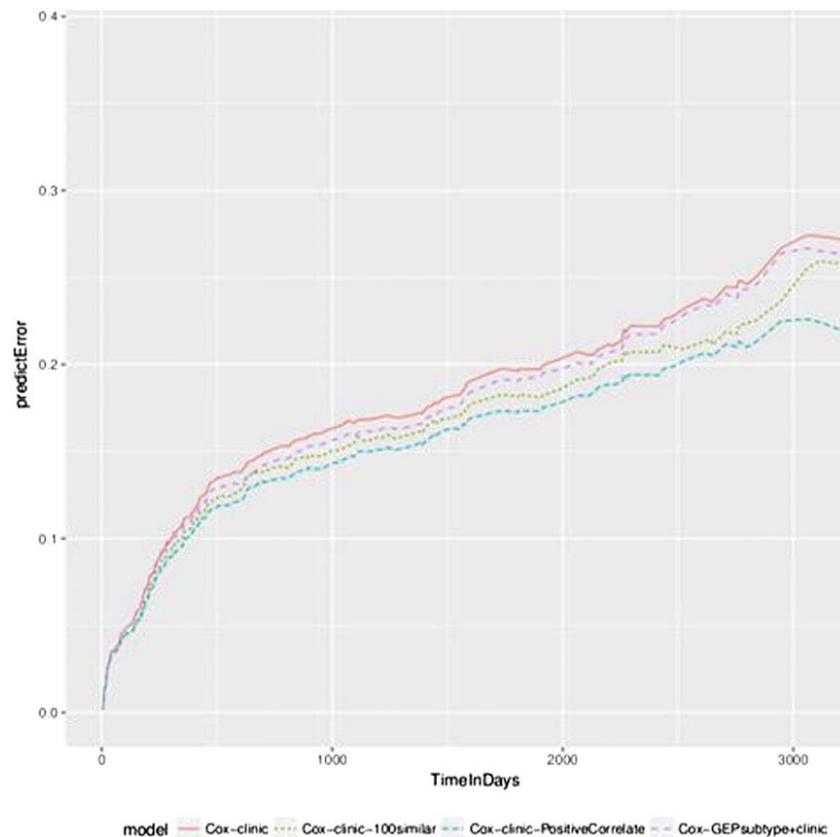
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Introduction: Aggressive non-Hodgkin B cell lymphomas are a heterogeneous group that is usually divided into established categories, such as Burkitt lymphoma and subtypes of diffuse large B cell lymphoma. Advances in genomic profiling have confirmed that these categories have characteristic oncogenic mechanisms, but also reveal significant number of cases that are intermediate between established categories; leading to difficulties in diagnosis, prognosis, and prediction of treatment outcome. Another recent development is the availability of large databases containing genomic molecular data with linked clinical variables and outcome information. Here, we investigate whether using these databases to search for sets of patients with molecularly similar profiling represents a viable alternative to category-based methods, and preliminary findings are presented.

Methods: Using several publicly available and study-specific datasets, we determined genes consistently associated with prognosis. Molecular similarity between patients was defined using the correlation coefficient of prognostic gene expression, and this was further

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A CATEGORY-FREE APPROACH TO PROGNOSTIC MODELLING IN AGGRESSIVE NON-HODGKIN B CELL LYMPHOMAS BASED ON LARGE PATIENT DATABASES



improved by machine learning methods. Prognostic modelling employed multivariate Cox proportional hazard models on selected clinical variables. Training was performed on defined sets of cases identified molecularly similar for each individual case, and on all cases in the database; Cox proportional hazard models including clinical variables and molecular categories was also learned, as an additional comparison. Various models were assessed by the average time dependent Brier score.

Results: Gene set enrichment analysis showed that activated B-cell like signatures and cell cycle signatures are highly enriched amongst prognostically unfavourable genes, while germinal centre B-cell like signatures and signatures associated with immune response are highly enriched amongst favourable genes. Figure 1 shows that personalised survival models learned from various subsets of molecularly similar patients provide superior prognostic predictions.

Conclusion: These preliminary results support the use of patients with molecularly similar disease from large databases in personalized prognostic and predictive modelling, an approach that should increase in power as patient databases grow in size and molecular content.

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

361 GRADE 1-2 NEUTROPENIA AFTER FIRST TREATMENT FOR DIFFUSE LARGE B-CELL LYMPHOMA IS ASSOCIATED WITH A

BETTER OUTCOME COMPARED TO GRADE 3-4—A DANISH POPULATION-BASED COHORT STUDY

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Introduction: Neutropenia may be required to ensure efficiency of a chemotherapeutic treatment and is one argument for dose adjusted regimens. We investigated the prognostic implications of the grade of neutropenia, after first chemotherapy, for patients with diffuse large B-cell lymphoma (DLBCL).

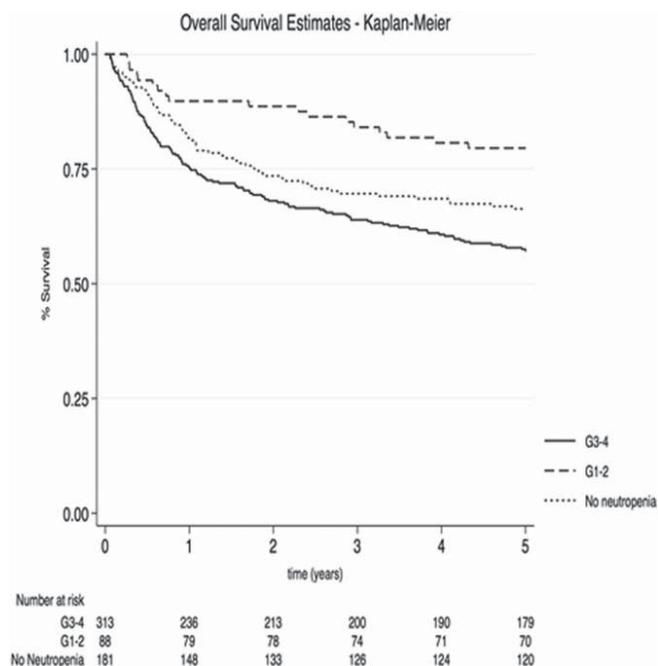
Methods: Data from patients, diagnosed with DLBCL between 2000 and 2012, were retrieved from Danish registries and from laboratories connected with the treating facilities. Inclusion criteria; a first time verified diagnosis of DLBCL without signs of transformation, treated with combination chemotherapy containing doxorubicin, and not having primary CNS-lymphoma. G-CSF was applied according to local guidelines. We graded nadir values of neutrophils ($10^9/L$) 8 to 10 days after first treatment: **G3-4:** <0.5 , **G1-2:** $0.5- < 2.0$, and **No Neutropenia (NN):** ≥ 2.0 . The NCCN-IPI indices were calculated. Survival analysis were restricted to patients without bone marrow infiltration of DLBCL. The 5-year overall survival (5yOS) proportion was estimated with the Kaplan-Meier method according

TABLE 1 ^aNot all categories sum to 863 due to missing data on bone marrow and LDH.

	All ^a (%)	Grade 3-4 <1.0 ^a	Grade 1-2 1.0-2.0	No Neutropenia > 2.0
	n = 863	465 (54)	142 (17)	256 (30)
Median age, y (range)	66 (16-95)	67 (18-92)	63.5 (16-89)	64 (16-95)
NCCN risk groups, %				
Low risk	68 (8)	22(5)	17 (12)	29 (11)
Low-intermediate risk	288 (33)	135 (29)	64 (45)	89 (35)
High-intermediate risk	352 (41)	199 (43)	45 (32)	108 (42)
High risk	335 (13)	109 (24)	16 (11)	30 (18)
Gender				
Male	472 (55)	233 (50)	91 (64)	148 (58)
Female	391 (45)	232 (50)	51 (35)	108 (42)
Ann Arbor stage				
I-II	311 (36)	177 (30)	67 (47)	100 (39)
III-IV	552 (64)	312 (70)	75 (53)	156 (61)
Bone marrow involved				
Yes	157 (19)	102 (22)	23 (17)	32 (13)
No	691 (81)	355 (78)	115 (83)	221 (87)
Lactate dehydrogenase				
≤1*ref	368 (43)	173 (37)	79 (56)	116 (46)
>ref - 3*ref	366 (43)	206 (44)	47 (33)	113 (45)
>3*ref	127 (15)	86 (19)	16 (11)	25 (10)
Age category (years)				
<41	58 (7)	26 (6)	12 (9)	20 (7)
41-60	235 (27)	119 (26)	37 (26)	79 (31)
61-75	372 (43)	207 (44)	66 (47)	99 (39)
>75	198 (23)	113 (24)	27 (19)	58 (23)
Cox model estimates				
+ rituximab				
Crude	n = 712	1 (ref)	0.51 (0.34-0.75)	0.89 (0.48-0.84)
Adjusted for NCCN-IPI		1 (ref)	0.63 (0.43-0.93)	0.79 (0.60-1.04)
- rituximab				
Crude	n = 151	1 (ref)	0.52 (0.28-0.97)	0.56 (0.33-0.97)
Adjusted for NCCN-IPI		1 (ref)	0.68 (0.36-1.29)	0.62 (0.36-1.07)

to the defined groups. Using Cox regression model, we estimated the corresponding crude NCCN-IPI adjusted hazard ratios using **G3-4** as reference, both stratified on rituximab treatment. The proportional hazards assumption was assessed with log-log plots and regarded fulfilled.

Results: Of 3531 patients who fulfilled the criteria, 863 (24%) had available nadir values on days 8, 9, or 10 after therapy. Grade 3-4 neutropenia was present in 465 (54%) patients. Prevalence of **G3-4** was correlated with higher NCCN-IPI group, specifically elevated lactate dehydrogenase concentration, higher disease stage, and extranodal disease in the bone marrow had a higher prevalence of **G3-4** (Table 1). No association was seen between gender or comorbidity (data not shown) and neutropenia. Rituximab-treated



patients with **G3-4** had a 5y OS of 53% (95% confidence interval [95% CI], 48-58), **G1-2**: 72% (95% CI, 62-80), and **NN** 66% (95% CI, 0.60-0.72), respectively (Figure 1). Corresponding hazard ratios (HR) are shown in Table 1. In the multivariable model with **G3-4** as reference, patients with **G1-2** nadir had a HR of 63% (95% CI, 43-93) for death and **NN** had a HR of 79% (95% CI, 60-1.04).

Conclusions: We found that patients with grade 1-2 neutropenia had an increased 5-year survival compared to patients with grade 3-4 and compared to patients without neutropenia, both crude and adjusted for NCCN-IPI

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

362 CARDIAC LYMPHOMAS: INCIDENCE AND OUTCOME IN NEWLY DIAGNOSED NON- HODGKIN'S LYMPHOMAS. ANALYSIS FROM THE CZECH LYMPHOMA STUDY GROUP (CLSG) DATABASE

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Introduction: Cardiac involvement by non-Hodgkin's lymphoma (NHL) is uncommon. Secondary cardiac involvement was discovered in 10% to 25% of patients with advanced disease mainly at autopsy. Primary cardiac lymphoma is extremely rare (less than 2% of all resected cardiac tumors and 0.5% of extranodal lymphomas). Real incidence of heart involvement among newly diagnosed NHL patients is unknown as well as treatment results and prognosis.

Methods: Between 1999 and 2016, through the prospectively maintained multicentric CLSG database, 14 275 consecutive patients with newly diagnosed NHL were identified. Initial staging included at least a thoracic and abdominal CT scan, unilateral bone marrow biopsy, blood count, and LDH level. Treatment and outcomes including response, time to progression, and survival were collected annually.

Results: At the time of the retrospective analysis, there were 13 362 of NHLs with completed staging data. Some extranodal disease was identified in 9764 patients including 99 patients with infiltration of pericardium (0.7%) and 16 pts (0.16%) with direct infiltration of the heart. None of these 16 pts with cardiac lymphoma had isolated disease, but 4/16 cases had very limited additional lymphoma extent (the only one lymph node). Three of these 16 patients also had infiltrated pericardium. Elevated serum LDH was seen in 15/16 pts, and 9/16 pts developed systemic symptoms, whereas 8/16 patients had performance status ≥ 2 . The median age was 55 years (range, 21-74 years), with a preponderant proportion of men (10/16; 62.5%). Diffuse large B-cell lymphoma (DLBCL) was the most frequent histology subtype (10/16; 62.5%) including of 1 PMBL and 1 DLBCL/Burkitt lymphoma, 2/16 were ALCLs, 2 lymphoblastic lymphomas, 1 Burkitt lymphoma and 1 case of B-NHL.

The median follow-up of this cohort is nearly 4 years. Eight patients were treated with CHOP-like regimens, 6 patients received more aggressive conventional therapy (CHOP/HyperCVAD/HD-MTX, CODOX-M/IVAC), and 3 patients were consolidated with high-dose chemotherapy with autologous stem cell transplantation. A response to first-line therapy was evaluable in 12/16 patients, 3 (19%) patients died during induction (one of them due to lymphoma progression). 11/12 (92%) pts reached remission including 8/12 complete responses. Totally, there were 6/16 progressions and 5/16 deaths

during the follow-up; progressions are tightly associated with death. Five-year overall and progression-free survivals were 71% and 60%, respectively.

Conclusion: Cardiac involvement is very rare in NHL patients at initial diagnosis. Despite heart infiltration, aggressive lymphoma subtype, and initial poor performance status, the long-term outcome and prognosis are good.

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Keywords: extranodal lymphomas

363 LOW ABSOLUTE PERIPHERAL BLOOD CD4+ T-CELL COUNT PREDICTS POOR PROGNOSIS IN R-CHOP-TREATED PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Background: The absolute peripheral blood lymphocyte count at diagnosis is known to be a strong prognostic factor in patients with diffuse large B-cell lymphoma (DLBCL) treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), but it remains unclear as to which peripheral blood lymphocyte population is reflective of DLBCL prognosis.

Methods: In this cohort, 355 patients with DLBCL treated with R-CHOP from 2006 to 2013 were analyzed. At diagnosis, lymphocyte subset counts in the peripheral blood were calculated from the percentages obtained by flow cytometry.

Results: Box plot analysis illustrated that patients survived till the last follow-up after R-CHOP treatment had a higher absolute lymphocyte count (ALC), absolute CD4+ T-cell count (ACD4C), absolute CD8+ T-cell count (ACD8C), absolute monocyte count (AMC) than those died during the study period. To determine the cutoff value for evaluating individual lymphocyte subsets at diagnosis, we performed area under the ROC curve (AUC) analysis and then, the optimal ALC, ACD4C, ACD8C, and AMC cutoff values were determined as 1380×10^6 , $343 \times 10^6/L$, 191×10^6 , and $549 \times 10^6/L$ as negative survival markers, respectively. ALC had strong correlations not only with ACD4C ($R = 0.76$) but also with ACD8C ($R = 0.68$) using Pearson's correlation coefficients. Low ACD4C at diagnosis negatively correlated with the overall response rate and the complete response rate significantly ($P < .00001$). An ACD4C $< 343 \times 10^6/L$ had a significant negative impact on the 5-year progression-free survival and the overall survival as compared to an ACD4C- $343 \times 10^6/L$ [73.7% (95% confidence interval (CI), 66.7-79.5) versus 50.3% (95% CI, 39.0-60.6), $P < .00001$ and 83.3% (95% CI, 77.1-88.0) versus 59.0% (95% CI, 47.9-68.5), $P < .00000001$,

respectively]. Multivariate analysis revealed that the ACD4C was an independent prognostic marker [hazard ratio = 2.2 (95% CI, 1.3-3.7), $P < .01$]. Low ACD8C and high AMC were not associated with poor OS in multivariate analysis. The OS was synergistically lower in the low ACD4C group among patients with high IPI, non-GC DLBCL, or high AMC, respectively (the 5-year OS was 37.2%, 48.9%, and 48.3%, respectively). The 5-year OS rates were 81.0% and 58.7% in the high the ACD4C to AMC ratio (CD4MR) and low CD4MR groups ($P < .00001$).

Conclusion: A low ACD4C at diagnosis served as an independent poor prognostic marker in patients with DLBCL. The OS was synergistically lower in the low ACD4C group among patients with high IPI, non-GC DLBCL, or high AMC, respectively.

Keywords: CD4; diffuse large B-cell lymphoma (DLBCL); R-CHOP

364 EPSTEIN-BARR VIRUS LOAD IN PLASMA IS AN EARLY BIOMARKER OF HIV-RELATED LYMPHOMAS

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Introduction: Epstein-Barr virus (EBV) has been detected in the tumor cells of some non-Hodgkin lymphomas (NHL) and Hodgkin lymphomas (HL), and EBV DNA has been found in the plasma of immunocompetent patients with HL. In HIV-related lymphomas, the importance of EBV DNA load as potential lymphoma biomarker has been scarcely studied.

Methods: One hundred and fifteen patients with NHL (HIV-infected = 57 and HIV-uninfected = 34) and HL (HIV-infected = 16 and HIV-uninfected = 8) were studied. EBV loads were determined in plasma by means of real-time PCR (EBV PCR kit, Qiagen GmbH, Hilden, Germany) at lymphoma diagnosis and in a group of HIV-infected patients, also at 1 year before diagnosis (N = 11) and at complete response (CR) (N = 34). EBER expression was studied by in situ hybridization in tumor biopsies. The following clinical and biological parameters were collected: age, gender, ECOG score, extranodal and bulky disease, B symptoms, Ann-Arbor stage, serum lactate dehydrogenase and beta2-microglobulin, HCV and HBV serology, history of opportunistic infection and of AIDS-defining illness, onset of combination antiretroviral therapy, CD4-counts, HIV loads, date of lymphoma diagnosis, type and date of response, relapse date, last follow up or death date. McNemar's and Wilcoxon tests were used to compare quantitative and qualitative variables, respectively. Survival analyses were performed using the Kaplan-Meier method.

Results: At diagnosis, EBV loads were detectable in more HIV-infected patients than HIV-uninfected (48% vs 14%, $P = .002$) and in more HL cases than NHL (70% vs 26.3%, $P = .006$). In HIV-infected patients, detectable EBV load was associated with EBER expression, 66.6% of the patients with detectable EBV loads had EBER-positive tumors, and 92% of the patients with undetectable EBV loads had EBER-negative tumors ($P = .003$). The remaining clinical-biological features were not associated with detectable EBV loads. In HIV-uninfected patients, associations between EBV load and EBER expression ($P = .006$) and EBV load and HBV infection ($P = 0.017$) were observed. From 16 of 34 (47%) HIV-infected patients with detectable EBV loads at lymphoma diagnosis, 15 had undetectable EBV loads at CR ($P < .001$) (Figure 1). The exception was one patient with HL whose EBV load substantially decreased at CR but was still detectable. Moreover, 4 of 7 HIV-infected patients with detectable EBV loads at diagnosis had detectable loads 1 year before diagnosis, and no patient with negative EBV loads at diagnosis had detectable loads before it, pointing EBV load could be used as an early biomarker of lymphoma. EBV load at diagnosis had neither impact on overall survival nor progression-free survival.

Conclusions: EBV load in plasma can be used as early biomarker of lymphoma in HIV-infected patients since EBV loads can be detected up to 1 year before lymphoma diagnosis and are virtually undetectable at lymphoma CR.

Keywords: Epstein-Barr virus (EBV); human immunodeficiency virus (HIV); immunodeficiency-associated lymphomas

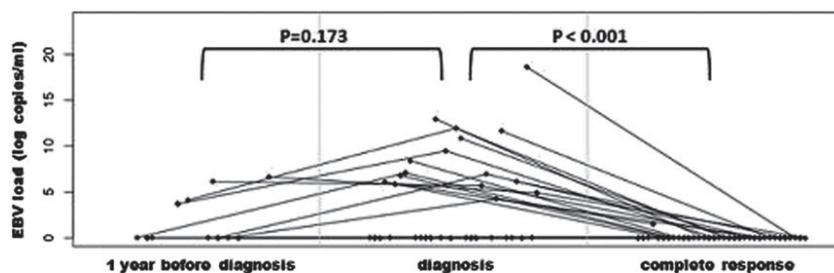


Figure 1. EBV loads of HIV-infected patients with lymphoma at three clinical points. Lines connect EBV determinations of the same patient.

365 THE NEGATIVE PROGNOSTIC SIGNIFICANCE OF SERUM IMMUNOGLOBULIN PARAPROTEIN IN PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, which is characterized by rapidly proliferating cells expressing B cell-associated antigens CD19, CD20, CD22, and CD79a. Immunoglobulins (Ig) are produced by terminally differentiated B cells, with the capacity to produce antibodies with high affinity for the immunizing antigen that are composed by 2 heavy and 2 light chains. Serum immunoglobulin paraprotein can be

detected in a subset of DLBCL patients during our daily clinical practice. However, little data were reported about either the prevalence or spectrum of Ig paraprotein in DLBCL. To better describe this issue, we conducted the study.

Methods: In total, 599 patients were diagnosed with DLBCL, and 245 patients in the admission panel with serum monoclonal immunoglobulin test were enrolled. Data collected of clinical characteristics at diagnosis included: age, gender, Ann arbor stage, Eastern Cooperative Oncology Group performance status (ECOG-PS), serum lactate dehydrogenase (LDH), the number of extranodal sites involved (ESI), International Prognosis Index (IPI), MUM1 expressed in tumor tissue, β 2-microglobulin (β 2-MG), serum albumen (ALB). Hans classification of germinal center B-cell (GCB) or non-GCB type was used for DLBCL classification. Univariate analysis was used to assess associations between survival and potential risk factors, including Ig paraprotein. All the factors further entered into multivariate analysis to figure out whether they had prognostic independence.

Results: The median age at diagnosis was 57 years (range, 14-88 y). The median follow-up time from initial diagnosis was 28 months

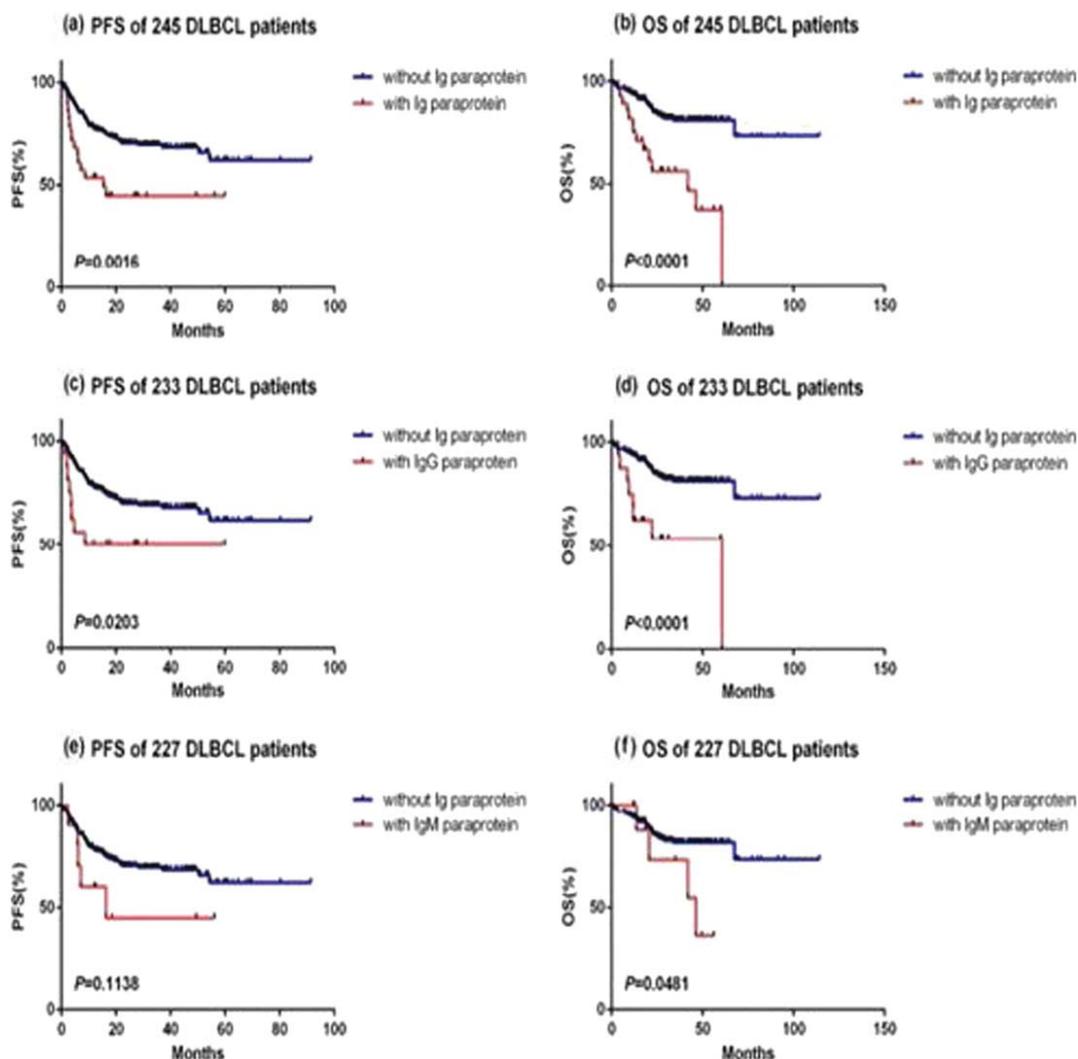


Figure legend: Fig. a. Survival curve of DLBCL patients with and without Ig paraprotein for PFS; b. Survival curve of DLBCL patients with and without Ig paraprotein for OS; c. Survival curve of DLBCL patients with IgG paraprotein and without Ig paraprotein for PFS; d. Survival curve of DLBCL patients with IgG paraprotein and without Ig paraprotein for OS; e. Survival curve of DLBCL patients with IgM paraprotein and without Ig paraprotein for PFS; f. Survival curve of DLBCL patients with IgM paraprotein and without Ig paraprotein for OS.

(range, 2-114 months). Strong correlations of serum Ig paraproteinemia with MUM1, β 2-MG were observed. Other risk factors had no significant relationship with the occurrence of Ig paraproteinemia. Ig paraprotein, Ann Arbor stage, ECOG-PS, LDH, ESI, β 2-MG, ALB, and Hans classification were the adverse factors in determining progression-free survival (PFS) (Fig. a). After multivariate analysis, Ig paraprotein, Ann Arbor stage, LDH were the independent prognostic factors and strongly associated with PFS. Ig paraprotein, Ann Arbor stage, LDH, β 2-MG, ALB, and Hans classification were the adverse factors in determining overall survival (OS) (Fig. b). After multivariate analysis, Ig paraprotein, LDH and β 2-MG were the independent prognostic factors and strongly associated with OS. We also analyzed the association between survival and different type of Ig paraprotein, respectively. There was significant difference between DLBCL patients with IgG paraprotein and without Ig paraprotein in both PFS ($P = .005$) and OS ($P < .001$) (Fig. c and d). Same results were not observed for IgM paraprotein either PFS ($P = .087$) or OS ($P = .060$), but a statistical trend can be seen (Fig. e and f). Ig paraprotein was an independently prognostic predictor for both PFS and OS, thus we included IPI and Ig paraprotein to generate a new prognostic index called MPI and compared its predictive abilities with IPI alone and Ig paraprotein alone for PFS and OS. MPI was generated by the sum of IPI and 2.6 additional point for Ig paraproteinemia according to its HR ($MPI = IPI + 2.6 * Ig$), if exists.

Conclusions: DLBCL patients with serum Ig paraproteinemia represent a subgroup with inferior clinical outcome. Serum Ig paraprotein might be applied for the assessment of prognosis in patients with DLBCL. The explicit relationship between DLBCL survival and different types of Ig paraprotein still remains unclear and needs further study.

Keywords: diffuse large B-cell lymphoma (DLBCL); prognostic indices

366 CONSOLIDATION RADIOTHERAPY DOES NOT IMPROVE THE OUTCOME AS COMPARED WITH CHEMOTHERAPY ALONE IN PATIENTS WITH LIMITED STAGE DIFFUSE LARGE B-CELL LYMPHOMA OF WALDEYER'S RING

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Introduction: Consolidation radiotherapy after chemotherapy is commonly used in limited stage diffuse large B-cell lymphoma (DLBCL) of Waldeyer's ring. However, its role remains controversial, especially for patients achieving complete response (CR) after immunochemotherapy.

Methods: We retrospectively and unselectively analyzed 72 patients with stage I/II DLBCL of Waldeyer's ring in our center. Eligible patients needed to receive at least 3 cycles of R-CHOP regimen and achieved CR either assessed by CT, MRI, or PET scan.

TABLE 1 Patient characteristics

	CT + RT		CT		p value
	No.	%	No.	%	
Nr. of patients	30		42		
Age, years					
Median(range)	57(29-79)		57(22-72)		
≤ 60	21	70.0	32	76.2	0.557
> 60	9	30.0	10	23.8	
Gender					
Male	18	60.0	22	52.4	0.521
Female	12	40.0	20	47.6	
Primary site					
Oropharynx	21	70.0	36	85.7	0.106
Nasopharynx	9	30.0	6	14.3	
B symptoms					
Yes	3	10.0	3	7.1	1.000
No	27	90.0	39	92.9	
Ann Arbor stage					
I	9	30.0	15	35.7	0.612
II	21	70.0	27	64.3	
ECOG PS					
0	17	56.7	24	57.1	0.968
1	13	43.3	18	42.9	
LDH level					
Normal	29	96.7	40	95.2	1.000
Elevated	1	3.3	2	4.8	
IPI					
0	21	70.0	31	73.8	0.767
1	9	30.0	10	23.8	
2	0	0.0	1	2.4	

CT: chemotherapy, RT: radiotherapy, PS: performance status, LDH: lactate dehydrogenase, IPI: International Prognostic Index.

Results: Among 72 patients, 30 patients were treated with chemotherapy followed by radiotherapy (CT + RT group), and the median dose of RT was 36 Gy; 42 patients were treated with chemotherapy alone (CT group). Both groups were balanced for major characteristics as shown in Table 1, and the median cycles of chemotherapy were 6 in both groups. With a median follow-up time of 53 months, 5 patients had recurrent disease, and 3 died. Among 5 relapsed patients, only 1 had oropharyngeal primary, and other 4 had nasopharyngeal primary. Regarding initial treatment, 2 patients received combined treatment, and 3 received chemotherapy alone. The 5-year progression-free survival (PFS) rates were 93.3% in CT + RT group and 92.5% in CT group with a P value of .896. The 5-year overall survival (OS) rates were 96.7% and 94.4%, respectively ($P = .649$). Since 4 of 15 patients with nasopharyngeal primary relapsed, we did a subgroup analysis, which showed both 5-year PFS and OS rates in oropharynx group was higher as compared with those in nasopharynx group (PFS: 98.2% vs 73.3%, $P = .001$; OS: 100% vs 79.0%, $P = .001$). Moreover, primary site was confirmed to be the only independent prognostic factor for PFS in multivariate analysis ($P = .012$, HR 16.858 [95% CI, 1.883-150.933]).

Conclusions: In patients with limited stage DLBCL of Waldeyer's ring achieving CR after immunochemotherapy, consolidation radiotherapy

does not improve the treatment outcome. Nasopharyngeal primary could be an unfavorable factor, which should be confirmed in large population or prospective studies.

Keywords: diffuse large B-cell lymphoma (DLBCL); immunochemotherapy; Waldeyer ring

367 TREATMENT OUTCOMES USING INVOLVED FIELD AND INVOLVED SITE RADIOTHERAPY FOR NHL AND HL: RETROSPECTIVE ANALYSIS FROM A LARGE UK RADIOTHERAPY CENTRE

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Introduction: Radiation remains the most active modality in the treatment for most types of lymphomas such as combined modality of treatment (CMT) for limited stage high grade (HG NHL) and classical Hodgkin's lymphoma (HL) and radiation alone for low grade limited stage lymphomas (LG NHL). Radiation is also used as consolidation at the end of chemotherapy for advanced stage HG NHL and HL at the site of bulky disease. Radiotherapy has evolved over last few decades. A large phase III randomised clinical trial with more than 1000 patients with a median follow up of 5.6 years has shown no loss of efficacy for dose of 24 Gy in 12 fractions for LG NHL and 30 Gy in 15 fractions for HG NHL as compared to 40 to 45 Gy. Involved site radiotherapy (ISRT) is now standard of care based on recommendations published in 2013. *Clinical target volume (CTV)* in ISRT is based on macroscopic disease present at the time of diagnosis. We present here the retrospective analysis of the radiotherapy outcomes with IFRT prior to recommendations and ISRT after the recommendations.

Methods: This retrospective study included 145 lymphoma patients from 2010 to 2015 with median follow up of 30.5 months (1-83). Patients were identified from the radiotherapy database, and further

TABLE 1

	DLBL	FL	HL
Male/female (%)	32(54%)/ 26(44%)	13 (36%)/ 23 (64%)	28 (56%)/ 22 (44%)
Age: Median/ range	65 (16-87)	66 (32-93)	37 (16-80)
Limited / advanced stage	53/6	31/2	41/9
IFRT/ ISRT	16/43	15/21	22/28
Relapse rate	12%	25%	16%
Relapse rate (Pearson chi-square 2-sided test; p value)	0.318	0.007 In favour of ISRT	0.7
TTF related to IFRT/ISRT (log rank test; P value)	0.472	0.011 In favour of ISRT	0.65

data were collected from electronic patient records. Statistical analysis was carried out on IBM SPSS Statistics version 24 for windows. Time for treatment failure (TTF) was calculated from date of radiotherapy to progression. Overall survival (OS) was calculated from the date of radiotherapy to last follow-up or death. Clinical notes were reviewed to identify the site of failure with respect to within radiation field or close to the radiation field or distant failure.

Results:

Conclusion: Our large retrospective real life data confirm ISRT is non-inferior to IFRT. The differences seen in FL cohort may be due to better staging in recent years with increased use of staging PET scans.

Keywords: follicular lymphoma (FL); Hodgkin lymphoma (HL); non-Hodgkin lymphoma (NHL)

368 R-CHOP IS NOT EFFECTIVE REGIMEN IN CD5(+)/DLBCL DIAGNOSED BY FLOW-CYTOMETRY/IMMUNOHISTOCHEMISTRY, KARYOTYPE AND BCL2/BCL6 STATUS AND EXPRESSION

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Background: CD5(+)/DLBCL was included in the WHO 2008 classification as a separate immunohistochemical subgroup along with germinal centre B-cell-like (GCB) and non-GCB. BCL2 overexpression (compared to normal T and B lymphocytes) is observed in GCB/non-GCB and CD5(+)/DLBCL. CD5(+)/DLBCL patients (pts) usually progress rapidly, are resistant to R-CHOP immunochemotherapy, and have worse prognosis than other DLBCL. We have described a diagnostic algorithm for identifying CD5(+)/DLBCL with and without CD10 expression based on flow-cytometry immunophenotyping (FCM) that often correlates with extra copy and rearrangement of BCL2/BCL6 assessed in fine needle aspiration biopsy (FNAB) samples. Here, we show pathological/clinical features of 26 CD5(+)/CD10(+) and 34 CD5(+)/CD10(-) DLBCL pts compared to control 154 CD5(-)/CD10(+) GCB and 127 CD5(-)/CD10(-) non-GCB patients treated with R-CHOP.

Methods: Sixty pts [CD5(+)/CD10(+): male/female 12/14, median age/range 68/24-86/ and CD5(+)/CD10(-): male/female 23/11, median age/range 52/19-82/] with a diagnosis of CD5(+)/DLBCL based on WHO 2008 classification were treated with R-CHOP as first-line therapy. NCCN-IPI score 3 or 4 were found in 54% and 61%, respectively. All cases were evaluated by FCM examination, by karyotyping and FISH(BCL2/BCL6/MYC probes).

Fig 1A. Progression free survival

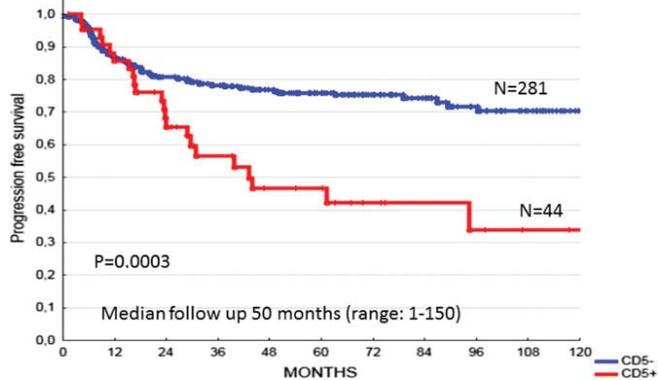
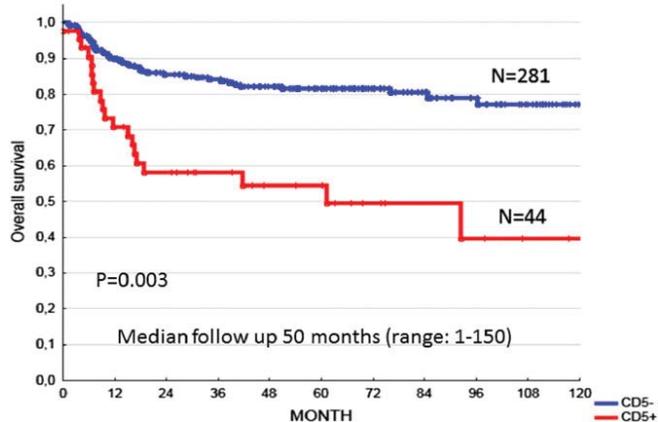


Fig 1B. Overall survival



Results: Considering the cell-of-origin, there were 26 CD5(+)/CD10(+) GCB and 34 CD5(+)/CD10(-) non-GCB DLBCL. Karyotype was successfully assessed in 43%, *BCL2*, *BCL6*, *MYC* abnormalities were found in 65%, 30%, and 26% in CD5(+)/CD10(+), and in 66%, 70%, and 23% in CD5(+)/CD10(-), respectively, of cases. *BCL2* overexpression by FCM was found in 58% of both DLBCL subgroups. Complete response was achieved in 65% of CD5(+)/CD10(+), and 66% of CD5(+)/CD10(-) pts. Five-year PFS was 46% [95%CI.(30%,62%)] and 75% [95%CI.(70%,80%)] for CD5(+) and CD5(-)DLBCL, respectively ($P = .0003$) (Figure 1A). 5-year OS was 54% [95%CI.(39%,70%)] and 81% [95%CI.(76%,86%)] for CD5(+) and CD5(-) DLBCL, respectively ($P = .003$) (Figure 1B).

Conclusions: Detection of CD5/CD10/*BCL2* expression by means of FNAB/FCM procedure completed within 1.5 hour appears as reliable/easy and cost-effective method for diagnosing CD5(+) DLBCL with *BCL2* overexpression compared with routine but less sensitive immunohistochemistry method. Both CD5(+)/DLBCL subgroups have worse prognosis compared to CD5(-)/DLBCL. Future studies should investigate novel therapeutic strategies in these high risk pts.

Keywords: CD5; diffuse large B-cell lymphoma (DLBCL); R-CHOP

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RESPONSE OF DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH R-CHOP AND PROGNOSTIC FACTORS ASSOCIATED: A SINGLE INSTITUTION ANALYSIS IN LIMA, PERU

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL. Add of rituximab to CHOP (R-CHOP) for treatment of DLBCL has demonstrated a benefit in response rate (RR), disease-free survival (DFS), and overall survival (OS). The main objective of this study was to describe the response rates, survival, and prognostic factors.

Methods: In a retrospective study, we analyzed response rate, survival, and prognostic factors in patients with DLBCL treated with R-CHOP at Instituto Nacional de Enfermedades Neoplásicas (INEN) between 2011 and 2014, Lima, Peru. The response was evaluated using RECIST 1.1 criteria and survival probability according to Kaplan-Meier method and the comparison of the survival curves were performed using Log-rank or Breslow test.

Results: During the study period, 162 patients were treated with RCHOP. The median age was 58 years (range: 18-89 years), 40% were >60 years, 55.6% male sex, 37% had an ECOG performance status 3-4, 39% had extranodal primary, 59% had B symptoms and 62.3% stage III-IV. Forty-three percent were of poor prognostic according to R-IPI (Revised international prognostic index). Eighty-eight percent of patients were treated with ≥ 4 cycles of R-CHOP. According to RECIST 1.1 criteria, 51.3% and 36.4% patients achieved complete response (CR) and partial response (PR), respectively; 15.2% of patients with CR and 67.9% with PR had recurrence and progression disease, respectively. The median follow-up was 3 years, and 42.6% of patients died. The median OS was not achieved, the 3 years OS was 57.4% and DFS rate for patients who achieved CR was 83.7%, respectively. In the univariate analysis, the survival curves had statistical difference in age (<60 vs >60), sex (F vs M), ECOG (0-1 vs 2-4), Stage (I-II vs III-IV), WBC (10 vs $>10 \times 10^3/\mu\text{L}$); however, in multivariate analysis, the prognostic factors for OS were sex (M), ECOG (2-4), stage (III-IV), and WBC (>10) ($P < .05$).

Conclusions: In this cohort, the response rates and survival were lower than reported in other studies probably due to most patients had disseminated disease. Prognostic factors were similar than other reports.

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

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TREATMENT OF HIGH RISK AGGRESSIVE B CELL LYMPHOMAS WITH DA EPOCH R—A RETROSPECTIVE ANALYSIS

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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 diffuse large B cell lymphoma (HR DLBCL) in phase II trials. In our centres, HR DLBCL - defined as double-hit Lymphoma(DHL)/double expressor Lymphoma (DEL) 2, grey zone lymphomas (GZL) or high/ high-intermediate risk NCCN IPI, - BL and PMBCL are treated with DA EPOCH R. **Methods:** Retrospective analysis of toxicity and efficacy in DA EPOCH R treated patients.

Results: So far, 51 previously untreated patients with a median age of 54a (28a-79a) have been treated with a total of 282 cycles of DA EPOCH R: 29 HR DLBCL, 14 PMBCL, 8 BL. Two patients are still on treatment. Dose escalation according to hematological toxicity was possible in 40 (78%) patients—but only in 5 (33%) of 15 patients >65a. Twenty-two (61%) of 36 patients aged <65a received at least dose level 3 (144%). Due to peripheral sensory neuropathy, Vincristine had to be dose reduced in 39% of all cycles. Other CTCAE grade III/IV non-hematopoietic toxicities were infrequent and manageable. After a median follow-up of 14 months, overall survival (OS) rate is 82% and PFS 76% for all 51 patients. OS rate and PFS is 86% and 88% in BL, 91% and 92% in PMBCL after a median observation of 15 months (BL) and 12 months (PMBCL). In 29 high risk DLBCL patients (11 DEL, GZL, 13 high/high intermediate NCCN IPI), OS is 77%, and PFS is 69% after a median follow up of 17 month (Table 1). OS and PFS for DEL is 88% and 68% after a median observation time of 13 months. As prescribed in literature prognosis of relapsed or refractory patients is poor: 8 of 11 (6 HR DLBCL, 1 BL, 1 PMBCL) relapsed/refractory died.

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 is not an alternative treatment for standard risk DLBCL but might be an option for high

risk DLBCL and is challenging more toxic regimens like R ACVBP or R Hyper CVAD.

Table 1: Progression free survival HR DLBCL, n = 29

Keywords: B-cell lymphoma; DA-R-EPOCH; diffuse large B-cell lymphoma (DLBCL)

371 R- DAEPOCH AS A FIRST LINE TREATMENT FOR HIGH GRADE B CELL LYMPHOMA AND DIFFUSE LARGE B CELL LYMPHOMA WITH UNFAVORABLE FEATURES

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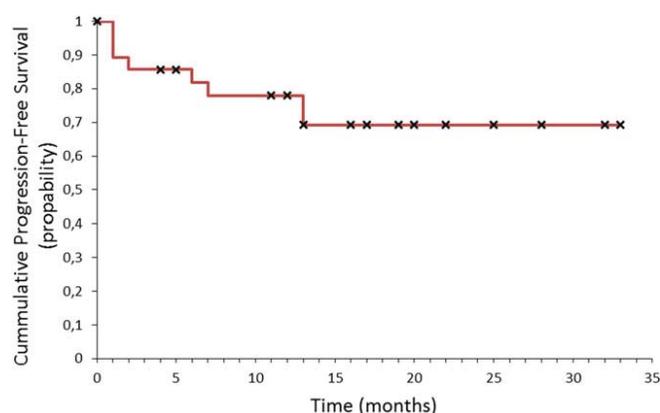
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Diagnosis of high grade B lymphoma (HGBL) with MYC and BCL2 and/or BCL6 rearrangement, HGBL, NOS according to 2016 update of WHO classification or diagnosis of CD5+ diffuse large B cell lymphoma (DLBCL) results in poor prognosis with an increased risk of death and risk of progression compared to other DLBCL subtypes after RCHOP treatment. Here, we evaluated R-DAEPOCH regimen (rituximab with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) as a first-line treatment for patients with aggressive B-cell lymphoma and autologous stem cell transplantation (ASCT) as a part of the first-line treatment for selected patients with additional aggressive features.

Methods: R-DAEPOCH was administered to 34 patients (pts) with previously untreated large B cell lymphoma: DLBCL, NOS (13 pts), HGBL-R (11 pts), HGBL, NOS (4 pts), primary mediastinal B-cell lymphoma - PMBL (5 pts) and DLBCL, leg type (1 pt). In addition, 8 patients had double/triple hit lymphoma, 12 - one-hit lymphoma and 10 - non-hit lymphoma, mostly with BCL2 overexpression. Median age (range) was 52 (35-76). Clinical stage III or IV, IPI 3 or more, and elevated LDH were found in 31pts (90%), 24pts (73%) and 18pts (53%), respectively. Of 13 pts planned to ASCT, 11 pts (33%) underwent consolidation procedure with ASCT.

Results: Of 34 pts, 28 pts (82%) completed 6 cycles of R-DAEPOCH. Thirteen pts (38%) received central nervous system (CNS) prophylaxis with methotrexate. The doses of doxorubicin and etoposide were escalated in 17 pts (50%), and toxicity was tolerable in all patients. In 28 evaluable pts, overall and complete response rate after 6 cycles was 86% and 54%, respectively. With median follow-up of 11 months (range, 1-23), the probability of 1 year overall survival (OS) was 80% [95% C.I.(66%,94%)]. Progression free survival (PFS) at 1 year was



50%[95%C.I. (30%,70%)]. Diagnosis of HGBL, age, IPI score 3 or more had no influence on OS and PFS ($P = \text{NS}$). We observed significantly prolonged OS ($P = .04$) but not PFS ($P = .06$) in patients who underwent ASCT comparing to other patients. The main toxicity was neutropenia grade 3 or more in 26 pts (76%). Four patients (12%) died due to toxicity of treatment: septic shock in 3 pts and pulmonary embolism in 1 patient.

Conclusion: R-DAEPOCH regimen is the promising therapeutic option in first-line treatment for aggressive B cell lymphoma with increased risk of death and risk of progression. Consolidative ASCT after R-DAEPOCH may benefit in prolonged OS. Toxicity of R-DAEPOCH is substantial but tolerable in high grade B lymphoma patients with poor risk.

Keywords: “double-hit” lymphomas; DA-R-EPOCH

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R-DA-EPOCH IMPROVES THE OUTCOME OVER THAT OF THE R-CHOP REGIMEN FOR DLBCL PATIENTS BELOW 60 YEARS, GCB PHENOTYPE, AND THOSE WITH HIGH IPI, BUT NOT FOR DOUBLE EXPRESSOR LYMPHOMA

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Purpose: About one third of patients with diffuse large B-cell lymphoma (DLBCL) were resistant to standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy, associated with rapid clinical progression and short survival time. Many attempts have been made to improve the treatment for DLBCL. This study was to compare the R-DA-EPOCH (dose adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and R-CHOP regimens as first-line therapy in DLBCL patients.

Methods: A total of 393 patients with de novo DLBCL were enrolled in our cohort, among which 241 cases in this study were treated with R-CHOP and 152 cases received R-DA-EPOCH as the first-line immunochemotherapy, while 289/393 cases were evaluable for response.

Results: Overall, 157 patients (65.1%) and 110 patients (72.3%) achieved complete remission, 36 (14.9%) and 16 patients (10.5%)

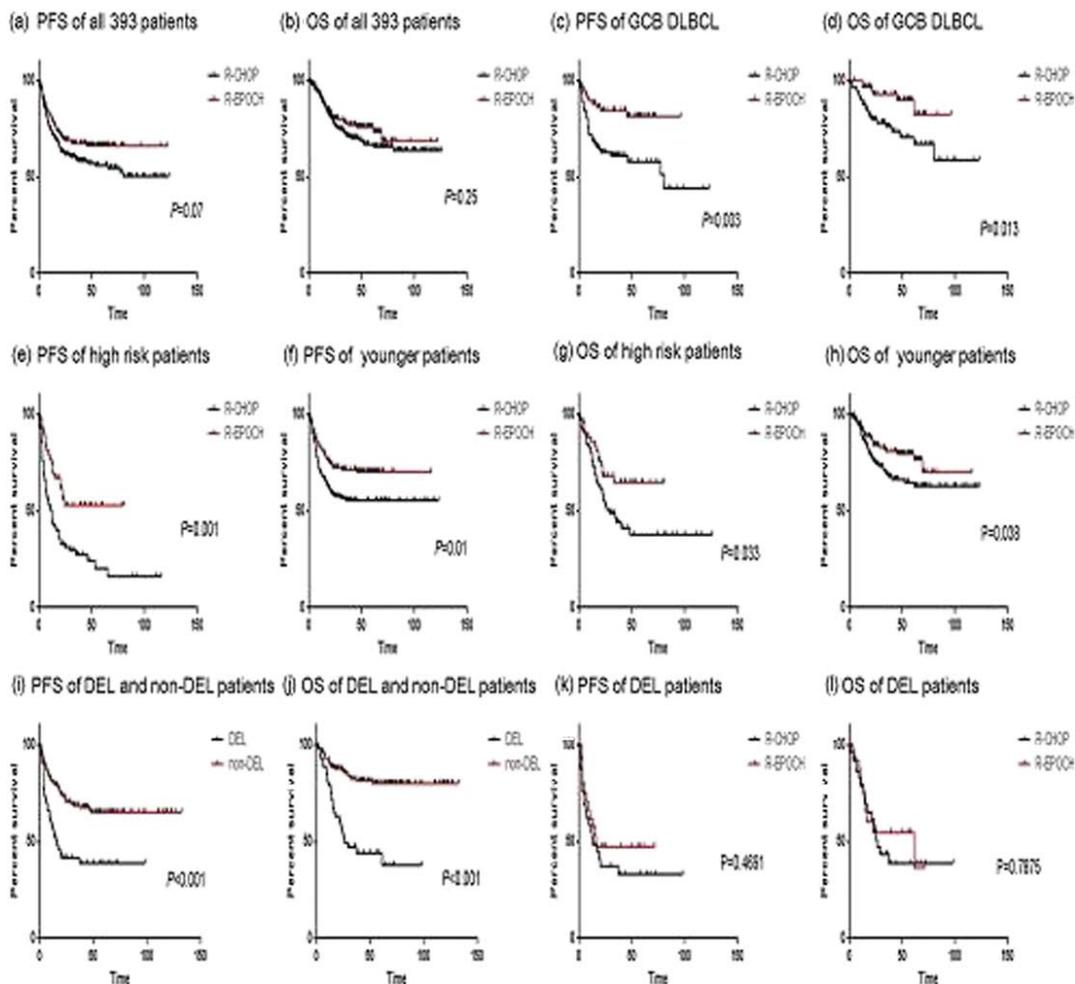


Figure legend: Fig. Survival outcomes of 2 regimens. (a) PFS of 2 regimens in all patients. (b) OS of 2 regimens in all patients. (c) PFS of 2 regimens in patients with GCB phenotype. (d) OS of 2 regimens in patients with GCB. (e) PFS of 2 regimens in patients with high risk. (f) PFS of 2 regimens in patients below 60 years old. (g) OS of 2 regimens in patients with high risk. (h) OS of 2 regimens in patients below 60 years old. (i) PFS in patients with DEL and non-DEL. (j) OS in patients with DEL and non-DEL. (k) PFS of 2 regimens in patients with DEL. (l) OS of 2 regimens in patients with DEL.

achieved partial remission, 3 (1.24%) and 5 patients got stable disease, and 42 (17.4%) and 20 patients (13.2%) exhibited progressive disease for R-CHOP and R-DA-EPOCH regimens, respectively. After a median follow-up of 46 months (range 14 to 126 months), no statistical difference was found in patients treated with R-DA-EPOCH compared to R-CHOP in all patients ($P = 0.07$ for PFS, $P = 0.25$ for OS, Fig. a and b). However, subgroup analysis according to cell of origin showed R-DA-EPOCH regimen resulted in significant better PFS and OS than R-CHOP regimen ($P = 0.003$ for PFS, $P = 0.013$ for OS, Fig. c and d) in patients with germinal center B-cell (GCB) phenotype. Furthermore, when categorizing patients according to International Prognostic Index (IPI) into low-risk (IPI 0-2) and high-risk group (IPI 3-5) as well as aged younger or older than 60 years, significant better PFS and OS were found in high-risk group and younger group ($P = 0.001$, 0.01 for PFS, respectively, Fig. e and f; $P = 0.033$, 0.038 for OS, respectively, Fig. g and h). But survival superiority of R-DA-EPOCH therapy did not remain in patients with non-GCB phenotype, low IPI, and patients older than 60 years ($P = 0.96$, 0.93 , and 0.42 for PFS, respectively; 0.67 , 0.64 , and 0.17 for OS, respectively). We also compared 2 regimens in patients with double expressor lymphoma (DEL). In 189 patients with immunohistochemical data of Myc and Bcl-2, we found 53 DEL patients (cutoff: 40% for Myc and 50% for Bcl-2). The prognosis of DEL patients was significant worse than non-DEL patients ($P < 0.001$ for PFS, $P < 0.001$ for OS, Fig. i and j), but R-DA-EPOCH regimen may not overcome the poor prognosis ($P = 0.47$ for PFS, $P = 0.79$ for OS, Fig. k and l).

Conclusion: Compared with R-CHOP, continuous-infusion R-DA-EPOCH regimen may not improve the treatment outcomes in all patients; however, patients younger than 60 years, with GCB phenotype, and those with high IPI will benefit from R-DA-EPOCH therapy. No survival benefit was observed in patients with DEL treated with R-DA-EPOCH compared to R-CHOP regimen.

Keywords: DA-R-EPOCH; diffuse large B-cell lymphoma (DLBCL)

373 NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA BENEFIT FROM THE ADDITION OF THYMOSIN ALPHA 1 TO R-CHOP: A PROPENSITY MATCHED STUDY FROM SINGLE INSTITUTION

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Introduction: The addition of rituximab to CHOP regimen (R-CHOP) has been confirmed to improve the outcome of DLBCL patients. However, unsatisfied therapeutic outcome still occurs in a small percentage of DLBCL. To explore the role of immune modulators combined with immunochemotherapy, we conducted a population-based propensity score match (PSM) study to assess the impact of thymosin $\alpha 1$ in adult

DLBCL patients treated by R-CHOP at Sun Yat-Sen University Cancer Centre (SYSUCC), China.

Methods: All patients with newly diagnosed DLBCL in SYSUCC from 01/2004 to 12/2011 were analyzed retrospectively. DLBCL patients treated by R-CHOP plus thymosin $\alpha 1$ were selected, and a 1:1 well-balanced thymosin-free cohort was generated by PSM. We compared the clinical characteristics, objective responses, long-term survival and the rates of HBV reactivation of these patients between R-CHOP plus thymosin group and R-CHOP group. Standard R-CHOP was administered to all DLBCL every 3 weeks for 6 cycles. Thymosin 1.6 mg was given every 2 days subcutaneously.

Results: A total 882 consecutive patients were evaluated, and 546 received R-CHOP were screened. 102 patients treated by thymosin $\alpha 1$ during and after R-CHOP for median 5.5 (3.0 to 30.0) months were collected, and a match cohort of 102 patients was generated by PSM. Major clinical characteristics of the 2 groups were listed in Table 1. After median follow-up of 64.4 (24.1-136.7) months, the median overall survival (OS) time and progression-free survival (PFS) time of the 2 groups were both not reached. 5-year PFS were

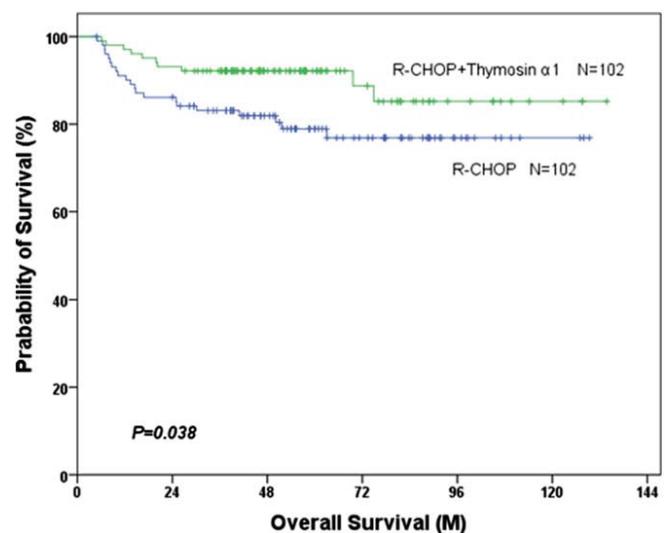


Figure 1: Kaplan-Meier overall survival (OS) curves for R-CHOP plus thymosin $\alpha 1$ group and R-CHOP group.

TABLE 1 Clinical characteristics at baseline and therapeutic outcome of R-CHOP plus thymosin $\alpha 1$ group and matched group.

Characteristics		R-CHOP + Thymosin $\alpha 1$ N = 102	R-CHOP N = 102	P value
Gender	Male	60(58.8)	64(62.7)	0.566
	Female	42(41.2)	38(37.3)	
AGE N (%)	≤ 60 Y	78(76.5)	79(77.5)	0.868
	> 60 Y	24(23.5)	23(22.5)	
IPI N (%)	0-1	70(68.6)	70(68.6)	0.812
	2	17(16.7)	18(17.6)	
	3	13(12.7)	10(9.8)	
	4-5	2(2.0)	4(3.9)	
Response N (%)	CR	84(82.4)	82(80.4)	0.719
	ORR	101(99.1)	98(96.1)	
5-year PFS %		79.0	73.8	0.183
5-year OS %		89.2	76.6	0.038

79.0% vs 73.8% ($P = 0.183$), respectively. 5-year OS was significantly improved in the R-CHOP plus thymosin $\alpha 1$ group in comparison to the R-CHOP group (89.2% vs 76.6%, $P = 0.038$) (Figure 1). Meanwhile, HBV infection rates of the 2 groups were 29.4% (30/102) and 30.4% (31/102) respectively at baseline. Only 1 patient experienced hepatitis B virus reactivation in the R-CHOP group. No difference was observed on the incidences of severe infection event between the 2 groups.

Conclusions: Our preliminary results showed R-CHOP plus thymosin $\alpha 1$ may improve the survival of newly diagnosed DLBCL patients. Further clinical trials are urgently needed to determine the clinical role of thymosin $\alpha 1$ in the immunochemotherapy of DLBCL patients.

Keywords: diffuse large B-cell lymphoma (DLBCL)

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OUTCOME OF DIFFUSE LARGE B-CELL LYMPHOMA IN PATIENTS OVER THE AGE OF 70 YEARS: REAL-WORLD EXPERIENCE IN A LARGE U.K. DISTRICT GENERAL HOSPITAL

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Introduction: The incidence of diffuse large B-cell lymphoma (DLBCL) is increasing, and 40% of all new diagnoses are in patients over 70 years. In this age group, treatment toxicities and comorbidities can limit therapeutic options. We report our experience of treating elderly patients with DLBCL with curative intent.

Methods: Between 08/2004 and 08/2015, 48 patients over 70 years (range 70–88), who were diagnosed with DLBCL, were treated with 6 cycles R-CHOP21 and 2 Rituximab(R). Vincristine was capped at 1 mg. CNS prophylaxis was given as required. Prophylactic aciclovir, co-trimoxazole and G-CSF were given. 37 patients were 70–79 years, and 11 patients were over 80 years. All patients had adequate cardiac function. Patients aged 70–79 years with a good PS/no significant comorbidities were treated with 100% dose doxorubicin for all cycles while those with a poor PS/multiple comorbidities were commenced on 50% doxorubicin in cycle 1 and escalated (25% increments) in subsequent cycles as tolerated. All patients >80 years were treated with an escalating approach.

Results: The median age was 75.5 years. 21 patients between 70 and 79 years received full-dose chemotherapy; 16 patients in this age group received an escalating regimen. All patients >80 years (11) were treated with the escalating dose approach. 6/48 patients died during treatment; 3 died of disease, 2 of sepsis and 1 unknown. 42/48 patients completed 6 \times RCHOP + 2 R. Of these, 3 had primary refractory disease and 1 died of sepsis 2 months post-treatment. Of the remaining 38 who completed treatment, 14 patients received a cumulative dose of 100% doxorubicin, 12 patients received a cumulative dose between 80% and 99% and a further 12 patients received a cumulative dose of less than 80%. The mean IPI score of those patients receiving full-dose doxorubicin was significantly lower than those

receiving attenuated doses (2.6 vs 3.3; $p = 0.023$). Chemotherapy-related toxicities occurred in 17/21 (80%) patients treated with full-dose doxorubicin (12—grade 1/2 and 5—grade 3/4) and in 16/27 (53%) patients treated with the escalating dose approach (7—grade 1/2 and 9—grade 3/4)— $p = 0.052$. The median progression-free survival PFS has not been reached in either group. There was no significant difference in overall survival (OS) at 36 months in the patients treated with full-dose doxorubicin compared to those treated with attenuated doxorubicin (37.4% vs 69%; $p = 0.982$).

Conclusions: We found that escalating doses of doxorubicin as part of RCHOP for the treatment of DLBCL in elderly, frail patients (with a mean IPI score higher than those treated with full-dose doxorubicin), did not compromise survival outcome. A trend towards lesser toxicities was observed in the escalating dose group, but this was not statistically significant due to small numbers. In summary, this approach is an effective means of administering anthracycline-based chemotherapy in older patients.

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

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THE ROLE OF MAINTENANCE THERAPY IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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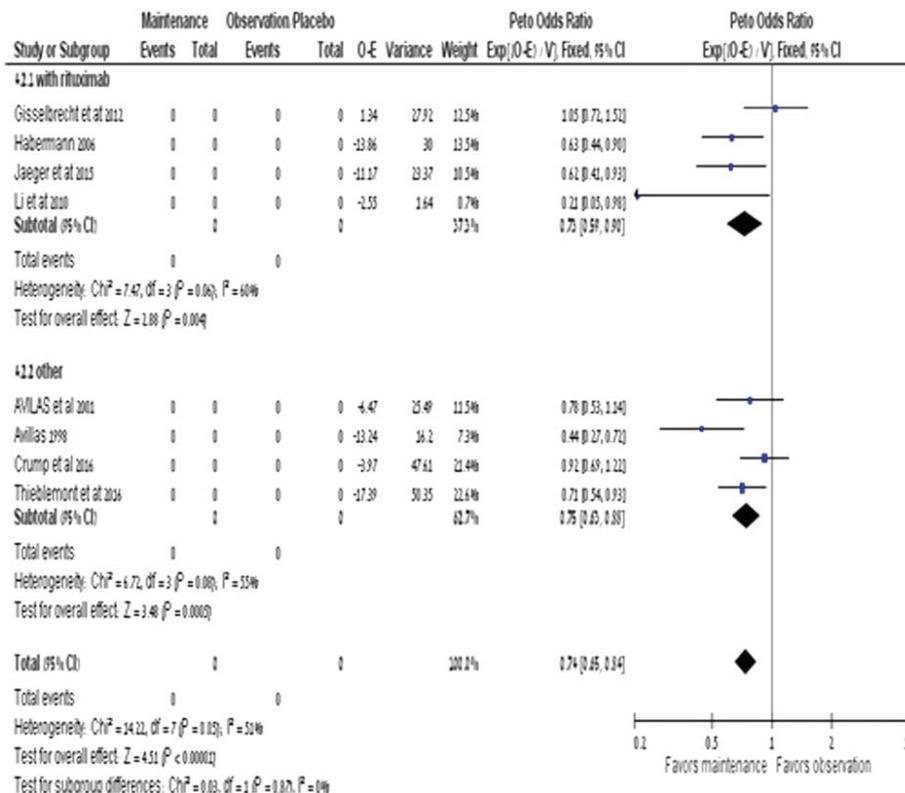
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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. Although R-CHOP is nowadays considered the standard of care for DLBCL, there are still approximately 40% of patients with refractory disease or relapse, especially in the first 2 years. For these patients, aggressive strategies as stem-cell transplantation is an option. Yet this approach is not feasible for all patients.

Our study's aim was to examine the efficacy and safety of maintenance therapy compared to observation in patients with DLBCL after achieving complete (CR) or partial response (PR) following induction therapy.

Methods: Systematic review and meta-analysis of randomized controlled trials including patients with DLBCL who achieved CR or PR after first-line treatment with chemotherapy +/- rituximab and comparing maintenance therapy with observation or placebo. The Cochrane Library, MEDLINE, conference proceedings and references were searched until January 2017. Two reviewers appraised the quality of trials and extracted data. Primary outcome was overall survival (OS). Secondary outcomes included all-cause mortality at 1 year, relapse rate and safety.

Results: Our search yielded 14 trials conducted between the years 1981 and 2016, including 3677 patients. In 6 and in 2 trials, rituximab was added to all and to half of the patients receiving induction therapy, respectively. Median age of patients in the trials was 49 to 70 years. Nine trials included patients at any International Prognostic Index



(IPI) while 4 of them included patients with intermediate-high and high risk age-adjusted IPI.

Regarding maintenance therapy, 7 trials included rituximab as the maintenance therapy, 3 included Interferon alfa as maintenance, 2 included immunomodulatory drugs (thalidomide and lenalidomide), one trial included cyclophosphamide and prednisone and one included the serine threonine kinase inhibitor enzastaurin.

Data from 9 trials were available for analysis of OS. Maintenance treatment did not improve OS compared to observation, HR 0.98, 95% confidence interval (CI), 0.85-1.13, $I^2 = 0$. Results were the same in a subgroup analysis by the type of maintenance (rituximab vs other). Maintenance therapy did not decrease all-cause mortality at 1 year. However, it decreased relapse rate and improved disease control (HR 0.78, 95% CI, 0.65-0.93, $I^2 = 52$, random effects model and HR 0.74, 95% CI, 0.65-0.84, $I^2 = 51$, respectively). Disease control was significantly improved in the subgroup of studies evaluating rituximab as maintenance. Regarding safety, neutropenia and infections grade 3-4 were statistically significantly more common on the maintenance arm as compared to the observation arm.

Conclusions: Maintenance therapy in patients with DLBCL achieving CR or PR after induction therapy did not affect OS, yet it decreased relapse rate and improved disease control at the cost of a higher infection rate.

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

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Introduction: Double hit lymphoma is a highly aggressive B-cell lymphoma subtype characterised by rearrangements of the MYC and BCL2 genes. Prognosis is poor, and there is no accepted standard of care.

Methods: All patients with rearrangements in MYC and BCL2 by fluorescence in situ hybridisation were identified by the Northern Genetics Service. Retrospective data were collected on all available patients including demographic and disease-specific variables, and treatment delivered. Response to primary treatment, relapse free and overall survival were then estimated.

Results: Between January 2006 and October 2016, 66 patients with a lymphoid malignancy had chromosomal rearrangements identified in both MYC and BCL2. Retrospective data were available for 50 patients. Patient and disease characteristics are summarised in Table 1. Details of treatment were available in 49 patients. 86% ($n = 42$) received chemotherapy. Of these, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) was given in 62% ($n = 26$). R-CODOX-M/IVAC (rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate, ifosfamide and cytarabine) was the primary therapy in 17% ($n = 7$). Nine patients had other regimes including R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin) ($n = 2$), R-GCVP (rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone) ($n = 2$), DA-EPOCH-R (rituximab,

376 DOUBLE HIT LYMPHOMA IN THE NORTHERN REGION OF ENGLAND—A RETROSPECTIVE ANALYSIS OF PATIENT AND DISEASE CHARACTERISTICS, TREATMENT DELIVERED AND SURVIVAL

cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone) ($n = 1$), rituximab-bendamustine ($n = 1$), R-CEOP (rituximab, cyclophosphamide, etoposide, vincristine and prednisolone) ($n = 1$), R-GDP (rituximab, gemcitabine, cisplatin and dexamethasone) ($n = 1$) and a local ALL protocol ($n = 1$).

Consolidation with allogeneic stem cell transplantation was performed in 14% ($n = 7$) of patients and autologous transplantation in 10% ($n = 5$). One patient underwent tandem autologous and allogeneic transplantation.

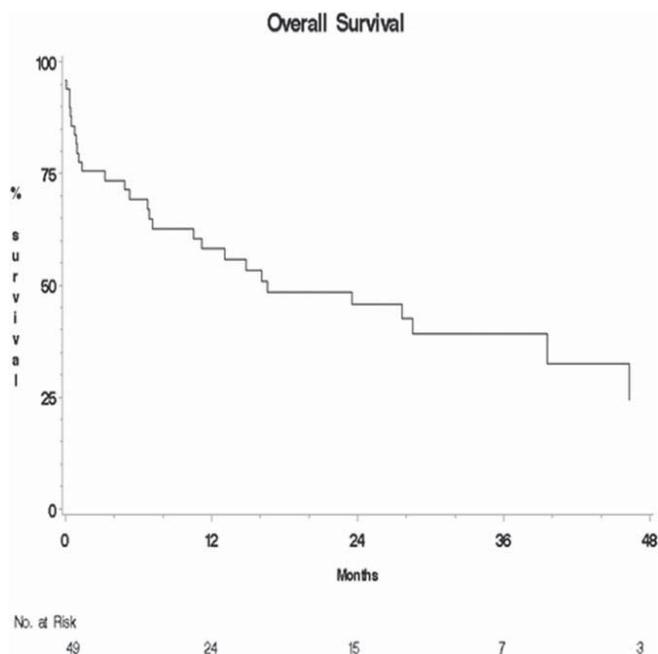
Median follow-up was 27 months (interquartile range: 11, 32). 33 (66%) patients relapsed or died. Median relapse free survival was 12.5 months (95% CI, 4.6, 22.3), and median overall survival was 16.6 months (95% CI, 6.9, 39.5). Of 49 patients, 16 are still alive in first remission.

Conclusions: This real-world retrospective study validates previous data regarding the poor prognosis of this disease. A range of treatment protocols were used with no clearly superior regime.

The role of consolidation with transplant in first remission remains unclear, and our data highlight the need for further research into this patient group and confirm this is an area of unmet need.

TABLE 1

Factor	Total cohort (N = 50) N (%)
Sex	
Male	28 (56%)
Female	22 (44%)
Median age, years (range)	65 (37-89)
Stage	
I	2 (4%)
II	4 (8%)
III	9 (18%)
IV	35 (70%)
Extranodal sites	
0-1	30 (60%)
>1	20 (40%)
LDH	
Elevated	43 (86%)
Normal	7 (14%)
ECOG performance status	
0	12 (24%)
1	16 (32%)
2	14 (28%)
3	5 (10%)
4	3 (6%)
International Prognostic Index (IPI)	
0	1 (2%)
1	3 (6%)
2	10 (20%)
3	15 (30%)
4	15 (30%)
5	6 (12%)
Bulk disease (>7.5 cm)	
Present	26 (52%)
Absent	24 (48%)



Keywords: "double-hit" lymphomas; chromosomal translocations; induction treatment

377 NEGATIVE IMPACT OF ZOLEDRONIC ACID IN R-CHOP TREATED DLBCL WITH BONE METASTASIS

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H. Yamauchi¹ | K. Ueda¹ | Y. Mishima¹ | M. Yokoyama¹ |
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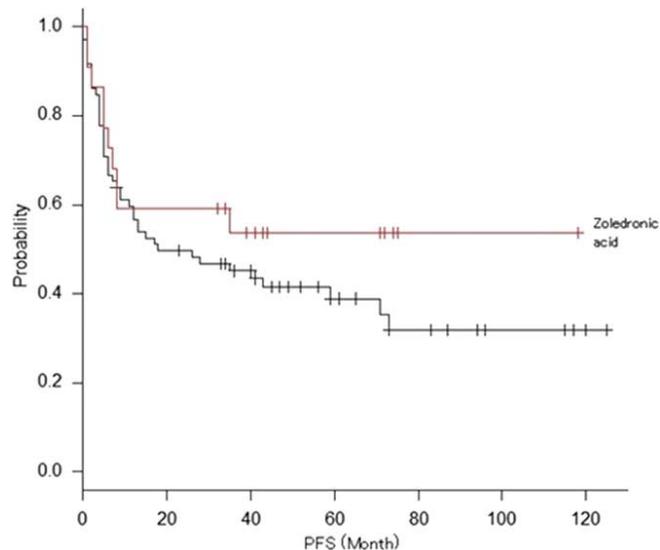
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Introduction: Zoledronic acid was the first bisphosphonate to reduce skeletal complications in patients with bone metastases from solid tumors. Furthermore, some studies suggested improved survival with zoledronic acid in patients with multiple myeloma, although the efficacy of zoledronic acid for diffuse large B-cell lymphoma (DLBCL) with bone lesions remains unclear. The aim of our study was to evaluate clinical efficacy of zoledronic acid in DLBCL patients with bone lesions.

Methods: We retrospectively analyzed 96 de novo DLBCL patients with bone lesions who have been treated with R-CHOP regimen in our hospital from February 2004 to March 2017. We diagnosed the bone lesions by PET-CT or gallium scintigraphy. The median cycles of R-CHOP were 6 (range 1-8). Twenty-two of 94 patients (23%) were administered zoledronic acid (4 mg/month) treatment during R-CHOP chemotherapy. We compared complete remission (CR) rate, progression-free survival (PFS), and overall survival (OS) between patients with or without the use of zoledronic acid.

Results: Their median age was 67 (range 29-85) years old. Fifty-three patients (55%) were with good risk; forty-three patients (45%) were with poor risk of revised IPI score. Fifty-nine patients (61%) achieved



CR after R-CHOP treatment. And median time to CR was 4 months. Fourteen of 59 patients (24%) with CR received zoledronic acid. CR rate did not relate to zoledronic acid treatment significantly ($p = 1.0$). Median follow-up was 40.5 months. Three-year OS was 65.5% vs 69.3%, and 3-year PFS was 45.2% vs 53.7%, respectively. There was no significant difference both in OS ($p = 0.774$) and PFS ($p = 0.269$) according to the use of zoledronic acid treatment.

Conclusions: Our retrospective study suggested that zoledronic acid did not have influence on CR rate, OS, and PFS in DLBCL patients with bone lesions.

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

378 DIFFUSE LARGE B-CELL NON-HODGKINS LYMPHOMA: R-MINI-CHOP OR PHYSICIAN'S CHOICE DOSE-ADJUSTED CHEMOTHERAPY IN PATIENTS OVER 80 YEARS OLD

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is an increasingly common cancer in elderly patients. Current recommendations favour the use of R-mini-CHOP ⁽¹⁾ (50% R-CHOP; rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone) as a compromise between efficacy and safety. We aim to present our experience treating DLBCL in this population.

Method: We performed a retrospective analysis of medical records for all patients aged over 80 years diagnosed with DLBCL at our institution over a 3-year period between 2010 and 2013. Data were extracted on age, performance status (PS), stage, age-adjusted International Prognostic Index (IPI) score, chemotherapy regime, and survival. Chemotherapy results were compared with R-mini-CHOP published data.

Results: 38 DLBCL cases were diagnosed with a median age of 85 (range 80-94). All cases were fully assessed clinically and discussed at our multidisciplinary team (MDT) meeting. 12 patients received best supportive care, 9 had palliative radiotherapy, and 17 received chemotherapy. 11 patients received physician's choice dose-adjusted chemotherapy (80% R-CHOP ($n = 6$); R-CHOP with 75% doxorubicin ($n = 1$); cyclophosphamide and etoposide ($n = 2$); R-PmitCEBO($n = 2$)) with a mean age adjusted IPI of 1.5 in this group. 6 received R-mini-CHOP with a mean age-adjusted IPI of 2.5.

Median survival was 41 months with physician's choice chemotherapy with 64% 2-year survival. Median survival was 5 months with R-mini-CHOP with 0% 2-year survival.

12 deaths occurred: 3 due to unrelated medical issues; 6 due to disease progression; and 3 were treatment related. Two were due to neutropenia in the physician choice group (18.2%), with one death in the R-mini-CHOP group (16.7%).

Conclusion: Chemotherapy decisions should be based on patient fitness and risk. Improved outcomes were seen in fitter patients treated with more aggressive chemotherapy compared to published results with R-mini-CHOP without increased mortality.

References: Peyrade et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2011; 12: 460-68.

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

Patients over 80 years old			
	Peyrade et al.	R-Mini-CHOP	non-R-Mini-CHOP
Median Age	83 years	83.5 years	82 years
Performance Status			
0	18%	0% (n=0)	0% (n=0)
1	48%	33% (n=2)	64% (n=7)
2+	34%	67% (n=4)	36% (n=4)
IPI			
0	10%	0% (n=0)	9% (n=1)
1	24%	17% (n=1)	45% (n=5)
2	44%	17% (n=1)	36% (n=4)
3	21%	67% (n=4)	9% (n=1)
Median survival	29 months	5 months	41 months
2 year overall survival	59%	0% (n=0)	64% (n=7)

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TREATMENT AND SURVIVAL OF PRIMARY EFFUSION LYMPHOMA (PEL): A POPULATION-BASED STUDY AMONG 25 PATIENTS DIAGNOSED IN THE NETHERLANDS BETWEEN 2002 AND 2015

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Introduction: PEL is an extremely rare, albeit devastating subtype of non-Hodgkin lymphoma (NHL). Treatment information on PEL exclusively comes from the few available single-center or multicenter studies with small, selected patient series. Therefore, information from a non-selected group of patients at the population level is needed to complement those studies. Here, we report the outcomes of a nationwide population-based study on treatment and survival among newly diagnosed patients with PEL in the Netherlands.

Methods: We selected all patients diagnosed with PEL in the Netherlands between 2002 and 2015 from the nationwide Netherlands Cancer Registry ($N = 25$; median age, 53 years; range, 30–81 years). Data on patient characteristics at diagnosis and treatment were available for individual patients. Overall survival (OS) and progression-free survival (PFS) were calculated to assess patient outcome.

Results: The majority of patients were male (88%) and HIV positive (76%). Prior Kaposi sarcoma was present in 28% of patients. None of the patients had prior Castleman disease. HIV-negative PEL patients were older than HIV-positive PEL patients (median age, 70 vs 49 years; $P = 0.011$). At the time of PEL diagnosis, 14 (74%) of 19 HIV-positive patients were on highly active antiretroviral therapy (HAART). All patients had a lymphomatous effusion in ≥ 1 serous cavity, with pleural effusions being the most frequent (84%), followed by peritoneal (56%) and pericardial effusions (8%). Ten (40%) patients also had extracavitary localizations. Eight (28%) patients received no therapy. Of those who received first-line therapy, CHOP or CHOP-like regimens were most commonly applied (15/17; 82%), followed by one

patient who received prednisone alone and one patient who initiated HAART alone. Three patients received CHOP with high-dose methotrexate. Nine of 15 patients (60%) who received chemotherapy attained a complete or partial remission, of which 3 eventually relapsed. Four patients had progressive disease, and in 2, the response was unknown. Six patients received second-line therapy, consisting of a variety of regimens. All 12 HIV-positive patients who received first-line chemotherapy were on HAART.

The median OS for the entire cohort was 7.6 months (Figure 1A). Nine (36%) patients are still alive. The median follow-up for patients still alive is 26.2 (range, 8.9–130.3) months. For 15 patients who received first-line chemotherapy, the median PFS was 14.7 months (Figure 1B).

Conclusion: This nationwide population-based study shows that, in an era with contemporary HAART and well-established NHL therapy, PEL is still associated with a poor prognosis. Nevertheless, it seems that prolonged survival can be achieved in selected patients who can attain and maintain a remission after chemotherapy. Information from population-based studies can support clinical decision making in PEL.

Keywords: chemotherapy; human immunodeficiency virus (HIV); non-Hodgkin lymphoma (NHL)

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BURKITT LYMPHOMA–MULTICENTER RETROSPECTIVE DATA ANALYSIS FROM THE CZECH LYMPHOMA STUDY GROUP–NIHIL PROJECT

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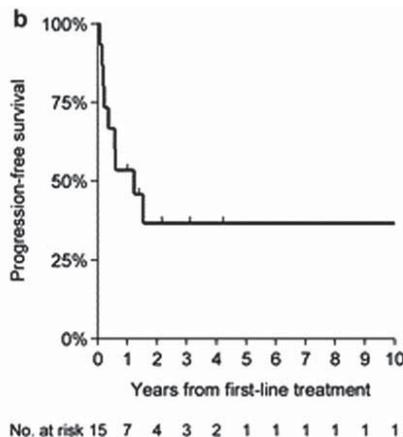
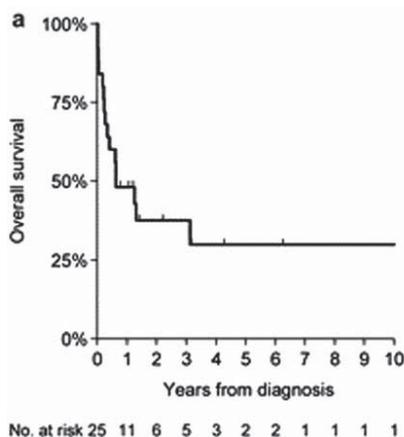


Table 1

Factor	All patients (n = 101)	Patients ≤ 60 year-old (n = 79)	Patients > 60 year-old (n = 22)	p-value
Median age, years	45 (18-84)	38 (18-60)	71 (61-84)	
Gender: men	75/101 (74%)	58/79 (73%)	17/22 (77%)	0.95
CS IV	65/99 (66%)	51/79 (64%)	14/20 (70%)	0.86
B-symptoms	54/101 (53%)	43/79 (54%)	11/22 (50%)	0.90
LDH > normal value	69/99 (70%)	54/79 (68%)	15/20 (75%)	0.78
PS ECOG >1	41/101 (41%)	28/79 (35%)	13/22 (59%)	0.081
"Bulky disease" ≥5 cm	57/90 (63%)	44/72 (61%)	13/18 (72%)	0.56
IPI 3-5	52/97 (54%)	38/79 (48%)	14/19 (73%)	0.077
EN involvement	85/101 (84%)	64/79 (81%)	21/22 (96%)	0.18
CNS involvement	16/100 (16%)	11/79 (14%)	5/20 (25%)	0.38
BMI involvement	34/96 (35%)	28/76 (37%)	6/20 (30%)	0.77
Intensive CT	82/98 (84%)	72/79 (91%)	10/19 (53%)	0.0006
Rituximab administration	81/101 (80%)	64/79 (81%)	17/22 (77%)	0.90
Overall response	79/100 (79%)	65/79 (82%)	14/21 (66%)	0.21
CR achievement	74/100 (74%)	62/79 (78%)	12/21 (57%)	0.09

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Introduction: Burkitt lymphoma (BL) is a rare subtype of non-Hodgkin lymphoma (NHL) with an aggressive behaviour. The purpose of this retrospective study was to analyze the treatment and outcome of sporadic BL pts prospectively recorded in the Czech Lymphoma Study Group (CLSG) Registry.

Methods: The NiHiL Registry prospectively collects newly diagnosed pts with NHL from the majority of lymphoma referral centers. Out of 14 047 pts registered between 1999 and 2016, 118 (0.84%) pts were diagnosed with BL. We analyzed 101 pts with sporadic BL. The clinical characteristics of pts are summarized in Table 1. Low-risk BL was present in 10% pts. Chemotherapy (CT) alone was used in 18% pts. Rituximab + CT were used in 82% pts—64 (81%) younger pts and 16 (73%) older pts. Intensive CT regimen was used in 82 (84%) pts—in younger pts (91%) and older pts (53%): CODOX-M (17pts), CODOX-M/IVAC (51pts) and others (14pts). Curative surgery was performed in 9% pts. Radiotherapy was used in 11% pts.

Results: The median follow-up was 4.2 years. There were statistically significant differences in intensity of administered CT between younger ≤60 years and older pts >60 years ($p = 0.0006$). Overall response rate (ORR) after the first-line treatment was 79% (CR 74%, PR 5%, SD 1% and PD 13%). Median PFS and OS was not reached in pts ≤ 60 years; in pts > 60 years, median PFS was 0.62 year ($p = 0.003$) and median OS 1.17 years ($p = 0.001$). Five-year OS was 77% (pts ≤ 60 y) and 40% (pts > 60 y), respectively. Thirty-three pts died (disease progression 19 pts, treatment toxicity 9 pts, second tumor 1 patient (p), other cause 1 p and unknown cause in 3 pts). Univariate analysis identifies age > 60 years ($p = 0.0001$), PS ECOG > 1 ($p < 0.0001$), Ann Arbor stage IV ($p = 0.003$), LDH > normal value ($p = 0.026$), EN involvement ($p = 0.02$), CNS involvement ($p = 0.0002$), bone marrow involvement ($p = 0.0008$), IPI score 3-5

($p = 0.0004$), failure of CR achievement of CR ($p < 0.0003$) and non-intensive CT ($p = 0.012$) as risk factors for OS. All mentioned factors and "bulky disease" ≥5 cm ($p = 0.03$) predicted a significantly shorter PFS. CNS involvement and failure of CR achievement were independent factors for shorter OS while failure of CR achievement, EN involvement and Ann Arbor stage IV were independent risk factors for shorter PFS in multivariate analysis (Table 2).

Conclusions: Burkitt lymphoma belongs to the curable lymphomas in younger patients, but the prognosis is poor in elderly pts, as only minority of them tolerate intensive CT. Prospective clinical studies are still needed to determine an optimal effective therapy for relapse/refractory and elderly pts with BL.

Keywords: Burkitt lymphoma (BL)

381 PRELIMINARY ANALYSIS OF LENALIDOMIDE MAINTENANCE AFTER METHOTREXATE-TEMOZOLOMIDE- RITUXIMAB INDUCTION IN OLDER PATIENTS WITH PCNSL

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Introduction: Management of PCNSL in patients age > 70 represents a significant problem. While there is evidence that high-dose chemotherapeutic consolidation improves outcomes, dose-intensive chemotherapy is not an option for most older PCNSL patients.

Methods: Given the promising results of our phase I dose-escalation trial of lenalidomide (len) minus and plus rituximab in relapsed PCNSL/SCNSL and with maintenance len at relapse (ICML 2015, ASCO 2016), we are testing the hypothesis that low dose len is well

tolerated as maintenance after first PR or CR in older patients (age > 70) with PCNSL, in lieu of WBRT or high-dose chemotherapeutic consolidation.

Results: Thus far, 9 patients have been treated with len maintenance (5-10 mg/d) after methotrexate, temozolomide rituximab (MT-R induction); median age 76 years (range 70-87). With an overall median follow-up of 18 months, the median month on len maintenance is 9 (range 1-51). Two patients received len plus maintenance rituximab, every 6 months. Thus far, only 2 patients have exhibited progressive disease with len maintenance, at 5 and 40 months, respectively. The later patient, who had achieved only a PR after renal failure with first-line induction MT-R, was re-induced with M + R and then resumed len at a higher dose of 10 mg/d, with remission now exceeding 18 months. Len maintenance has generally been well tolerated, with no deaths related to therapy or disease progression. Only 2 toxicities potentially related to therapy have mandated cessation of len maintenance: one recrudescence of arthralgias (grade 2) in a patient with a history of polymyalgia rheumatica and one subdural hematoma, likely related to aspirin. One patient treated with len plus rituximab maintenance experienced a grade 4 infection that was easily managed and resumed len maintenance without sequelae.

Conclusions: These preliminary data suggest that low-dose len maintenance at 5-10 mg/d on a 21-d schedule is tolerated as maintenance therapy after MT-R induction in older patients with PCNSL. Further studies are needed to validate these data and to evaluate efficacy in terms of time to progression.

Keywords: immune system; lenalidomide; primary CNS lymphoma (PCNSL)

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EFFECTIVE TREATMENTS ARE REQUIRED FOR PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) WITH PRIMARY REFRACTORY DISEASE

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Introduction: Around 30% of DLBCL patients present a refractory/relapsing disease following R-CHOP. Rituximab-containing salvage chemotherapy followed by autologous stem cell transplant (ASCT) in chemosensitive patients remains the standard of care. We aimed to study the clinical features and outcome of patients diagnosed of DLBCL, homogeneously treated in first line with R-CHOP/R-CHOP-like who have primary refractory disease (PRD).

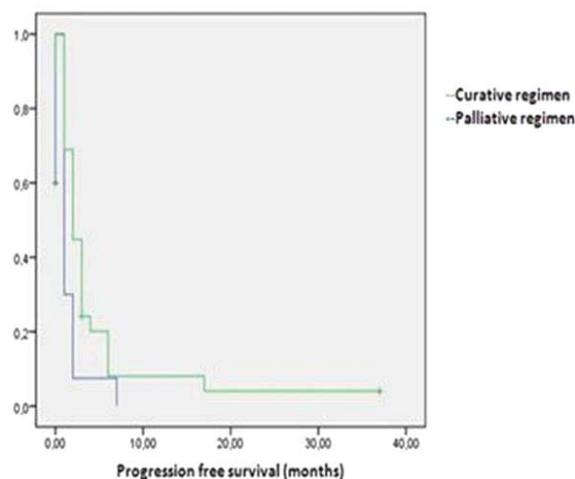
Methods: Three hundred and sixty-seven patients were diagnosed of DLBCL between January 2004 and August 2016; 317/367 (86.3%) were treated with R-CHOP/R-CHOP-like. Forty-four (13.9%) patients had PRD. Risk factors at diagnosis for PRD were assessed including gender, age, ECOG, Ann Arbor, B-symptoms, bulky disease, extranodal involvement and elevated LDH.

Results: Among the 44 PRD patients, 15 (median age of 76 years) were considered unfit, 11 received supportive care and 4 were treated with palliative chemotherapy (cyclophosphamide/prednisone). Twenty-nine (66%) were eligible for salvage therapy. Characteristics at the time of salvage therapy: median age 50 years (range 21-71), males 19 (65.5%), ECOG 2-4: 16 (55.2%), Ann Arbor stage III-IV: 23 (79.3%), B-symptoms 9 (31%), bulky disease (20.7%), extranodal involvement 20 (69%), high LDH 19 (65.5%), IPI 3-5: 21 (72.4%). Salvage therapies used were R-ESHAP 23 (79.4%), R-ICE 1 (3.5%), MTX-ARAC 4 (13.8%) and intensive Burkitt-like therapy 1 (3.4%). Twelve (41.4%) did not complete the treatment: 2 (6.8%) for toxicity (1 cardiac event, 1 septic shock) and 10 (34.4%) for progression. The intention-to-treat response rate was CR 1 (3.5%), PR 4 (13.8%), refractory disease/progression 22 (75.8%), not evaluable 2 (6.9%). Five patients underwent ASCT (conditioning regimen: BEAM). One died due to septic shock and 4 progressed. One patient was rescued with a third line, R-ICE, and allogeneic transplant, and he is currently in CR at 7 months. Median PFS was 2 months (95% CI, 1.2-2.7), and median OS was 5 months (95% CI, 3.4-6.6). Median PFS was 1 month (95% CI, 0.19-1.80) and median OS 1 month (95% CI, 0.19-2.42) for the 15 PRD patients treated with palliation (Figure 1). In the multivariate analysis, risk factors at diagnosis among the 317 patients treated with R-CHOP significantly related to PRD to R-CHOP were B-symptoms (HR 1.94, 95% CI, 1.05-3.61, $p = 0.034$) and elevated LDH (HR 3.92, 95% CI, 1.61-9.51, $p = 0.003$).

Conclusion: DLBCL patients refractory to first-line R-CHOP are not rescued with current salvage therapies. In this setting, DLBCL must be considered an incurable disease with a very short survival, similar to that of patients treated with palliative care. Patients with B symptoms and elevated LDH at diagnosis have a significant higher risk to be refractory to R-CHOP. It is imperative to identify early these patients and to design new therapies for them.

Keywords: diffuse large B-cell lymphoma (DLBCL)

Figure 1. Progression free survival in patients who present primary refractory disease



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LENALIDOMIDE IN COMBINATION WITH R-ESHAP IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: A PHASE 2 STUDY FROM THE SPANISH GROUP GELTAMO

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Introduction: Diffuse large B-cell lymphoma (DLBCL) patients with relapsed or refractory disease after rituximab-containing therapy have poor outcomes with current salvage regimens. We conducted a phase 1b/2 trial to analyze the safety and efficacy of adding lenalidomide to R-ESHAP regimen (LR-ESHAP). The phase 1b part of the trial has been completed, and lenalidomide 10 mg/day was identified as the maximum tolerated dose (Br J Haematol 2016; 173: 245-52). Here we present the preliminary results of the phase 2 part (ClinicalTrials.gov Identifier: NCT02340936).

Methods: Eligible patients must have relapsed or refractory DLBCL after first-line treatment with rituximab combined with an anthracycline-containing regimen. Subjects received 3 cycles of lenalidomide 10 mg given on days 1 to 14 of every 21-day cycle, in combination with R-ESHAP at standard doses. Responding patients received BEAM conditioning followed by autologous stem-cell transplantation (ASCT). The primary end point was overall response rate (ORR) after 3 cycles of therapy. Secondary end points were complete remission (CR) rate, stem-cell mobilization activity, progression-free survival (PFS), overall survival (OS), and toxicity.

Results: A total of 46 patients (median age 58 [23-69] years, 56.5% male) were included (January 2012-November 2015). Evaluable population per-protocol consisted of 44 patients. Forty-two serious adverse events were reported during 128 cycles of LR-ESHAP, including 14 episodes of febrile neutropenia (11%), 12 infections (9%), 2 renal disorders, 3 cardiac disorders, 3 thrombosis, and 8 other toxicities, all of them recovered except 1 case of colon adenocarcinoma. There were no treatment-related deaths. Forty out of 44 patients (91%) received the planned 3 cycles of treatment (2 without lenalidomide in the third cycle). ORR to LR-ESHAP was 68% (41% CR). Patients with relapsed

disease had significantly better ORR and CR rates (87% and 67%, respectively) than patients in PR after first-line (77% and 31%) or with primary refractory disease (<PR) (37% and 25%) ($p = 0.004$ and 0.02 , respectively). Evaluation of response according to cell of origin (COO) is ongoing. So far, 30 and 21 patients, respectively, have been analyzed according to Hans' algorithm (ORR of 62% and 44% in germinal-center B-cell-like [GCB] [$n = 21$] and non-GCB [$n = 9$] groups, respectively, $p > 0.1$) and gene expression profiling (ORR of 71%, and 75% in GCB [$n = 14$], and activated B-cell-like [ABC] [$n = 4$] groups, respectively, $p > 0.1$). Thirty-nine out of 42 patients (93%) were successfully mobilized after one ($n = 32$) or 2 ($n = 7$) mobilization procedures, and 28 (64% of evaluable patients) underwent ASCT according to protocol, one of them after bone-marrow harvest. With a median follow-up of 15 months (11-53), the estimated 2-year PFS and OS were 54% and 52%, respectively.

Conclusions: LR-ESHAP is safe, feasible, and associated with high-response rates in rituximab-pretreated relapsed or refractory DLBCL patients. Efficacy analysis according to COO and other biological factors is ongoing.

Keywords: diffuse large B-cell lymphoma (DLBCL); lenalidomide; salvage treatment

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RITUXIMAB, BENDAMUSTINE AND CYTARABINE (R-BAC) IN PATIENTS WITH RELAPSED-REFRACTORY AGGRESSIVE B- AND T-CELL LYMPHOMA

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Introduction: Relapsed or refractory (R/R) aggressive lymphomas (i.e. diffuse large B-cell lymphoma [DLBCL]) have poor outcome, especially if not candidate to consolidative autologous stem cell transplant (ASCT). No standard therapy exists for elderly or frail patients in the R/R setting. The combination of rituximab and bendamustine is associated to overall response (OR) of 40 to 50%, and median progression-free survival (PFS) of 3 to 8 months.

Pre-clinical data showed that bendamustine and cytarabine are highly synergistic on aggressive T- and B-cell lymphoma cell lines, similarly to mantle cell lymphoma, overcoming resistance to the single agents. For this reason, we performed a pilot multicenter study aimed at evaluating the safety and efficacy of the combination of rituximab, bendamustine and cytarabine (R-BAC), as salvage treatment in R/R aggressive B- and T-cell lymphomas not eligible to consolidative ASCT.

Methods: Twenty-three patients with R/R aggressive lymphoma (12 DLBCL, 9 transformed [t-DLBCL and 2 peripheral T-cell lymphoma), aged 37-84 years (median 68), were included and treated in 3

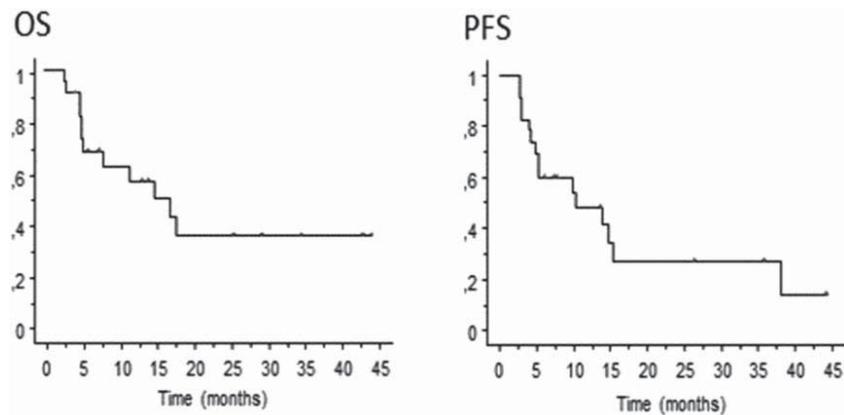


Figure 1

Hematology Institutions. R-BAC consisted of rituximab (R, 375 mg/m² intravenously [IV], day 1), bendamustine (B, 70 mg/m² IV, days 2 and 3), and cytarabine (500 mg/m², IV on days 2 to 4) every 21 days, up to 6 cycles. T-cell lymphomas did not receive R.

All patients had received anthracycline containing induction therapy (CHOP or CHOP-like), 5 (22%) had previous ASCT, and median number of previous treatment was 2 (range 1-4). Median time from initial lymphoma diagnosis was 29 months (4-120). Overall, 57% had relapsed disease, and 43% had refractory disease, with 17% of patients being refractory both to CHOP and DHAP/GDP. Response was assessed according to IWG 2007 criteria.

Results: Patients received a median of 4 cycles of R-BAC (2-6). Overall, OR was 74%, and CR was 52%. Among different histologies, OR was 75% in DLBCL (CR 58%), 78% in t-DLBCL (CR 56%), and 50% in T-cell lymphoma (one partial remission, one stable disease). Refractory patients had an OR of 60% (CR 30%). The median overall survival and PFS were 15.4 (9-19) and 10.2 (7-14) months, respectively (Figure 1). Median duration of response was 14.7 months (4-24). Treatment was well tolerated, with main toxicity being hematological, as expected. Treatment discontinuations before cycle 4 were due to toxicity/adverse events in 17%, progressive disease in 17%, and other reasons in 13%. Nine patients (39%) received cytarabine dose reduction (2 days instead of 3), due to advanced age or toxicity. Neither number of previous lines nor relapsed vs refractory disease were associated with significantly different PFS.

Conclusions: R-BAC had promising activity with an acceptable toxicity profile in this small explorative cohort of heavily pretreated R/R aggressive lymphomas. Our results suggest that R-BAC should be further investigated in this setting.

Keywords: diffuse large B-cell lymphoma (DLBCL); salvage treatment

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PATIENTS' DECISION-MAKING, EXPERIENCES AND PREFERENCES REGARDING PIXANTRONE TREATMENT IN RELAPSED AGGRESSIVE B-CELL LYMPHOMA: RESEARCH PROTOCOL FOR A LONGITUDINAL QUALITATIVE STUDY

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Background: There is a lot of speculation about why and how patients decide to use invasive treatment in an advanced stage of cancer, but the body of research is limited. The present longitudinal qualitative study reflects real-life practice of Pixantrone use and aims to collect data on the patients' considerations, expectations of and experiences and trajectories in their quality of life values in a Dutch clinical setting. Hence, why do patients choose for this treatment, while the treatment success rate is low and curative cannot be achieved, and once chosen, what conditions would patients like to satisfy and how do they experience the treatment?

Methods and Design: This is a non-interventional longitudinal and multicenter study. Patients are eligible if they are >18 years, have an ECOG performance score ≤2, and have a relapsing or refractory aggressive B-cell lymphoma, treated with at least 2 prior regimens. If patients refuse study participation after being informed by the investigator, reasons for refusal (if given) will be recorded. Those who participate will receive several interviews accompanied by 2 QOL questionnaires. Based on the required sample size, we aim to include 20 patients over a period of 2 years.

Discussion: Patient-oriented outcomes play an increasingly important role from both a clinical and pharmaco-economical perspective within the Dutch Health Care System. In the Netherlands, so far a very small number of patients has been treated with Pixantrone. We will investigate patients' considerations, expectations and experiences regarding Pixantrone treatment. Secondly, we want to know if such treatment affects the quality of life. Gaining a better understanding of treatment-related decision-making and experiences and once chosen treatment experiences, could facilitate decision-making for patients and doctors in future.

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

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RESULTS OF A PROSPECTIVE PHASE II TRIAL WITH OFATUMUMAB AS PART OF

REDUCED INTENSITY CONDITIONING REGIMEN IN HIGH-RISK NON-HODGKIN B LYMPHOMA PATIENTS: A GELTAMO TRIAL

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Allogeneic transplantation (AlloSCT) is the only curative option for high-risk non-Hodgkin lymphoma (NHL) patients. Reduced intensity conditioning (RIC) is commonly used in these patients, but best regimen is still not fully established. Treatment with anti-CD20 monoclonal antibodies improved outcome of NHL, but they have not been widely used in AlloSCT. Rituximab has been added to the conditioning regimen in the setting of AlloSCT, but there are no data about new anti-CD20 monoclonal antibodies as Ofatumumab and its effect on disease control, graft versus host disease (GVHD) incidence and long-term response.

We designed a phase II clinical trial (NCT01613300) with Ofatumumab as a part of a RIC regimen in high-risk non-Hodgkin lymphoma patients. Primary end point was grade 3-4 acute GVHD rate, and secondary end point was complete response (CR) rate.

Patients and Methods: Inclusion criteria were: less than a partial response (PR) after 2 lines of chemotherapy, relapse after an autologous SCT (ASCT), evidence of disease 3 months after ASCT, failure in mobilization for ASCT, or PR after a previous relapse after 2 lines of treatment with risk factors such like CR <12 months after ASCT. Conditioning regimen: Ofatumumab 300 mg day -20, 2000 mg days -13 and -6 and 1000 mg days +1 and +8, plus fludarabine 150 mg/msq days -7 to -3 and melphalan 70 mg/msq days -2 and -1. In relapses <12 months after ASCT: melphalan 70 mg/ msq + Thiotepa 5 mg/msq day -8. GVHD prophylaxis: sirolimus + tacrolimus.

Results: We included 33 patients from 6 centers. Two patients abandoned the protocol, so 31 patients were evaluable.

Median age was 51 years (30-65). Donor was HLA identical in 23 (74%). Diagnosis were diffuse large B-cell lymphoma (DLBCL) in 21 patients (64%), mantle cell lymphoma (MCL) in 6 (28%), grade 3 follicular lymphoma (FL) in 3 (9%) and transformed NHL in 3 (9%). Eighteen (55%) had received a prior ASCT, 70% had stage IV disease, 73% had received 3 or more lines of therapy and 42% were not in CR before AlloSCT.

Infusions were well tolerate, with 5 cases of grade I-II cutaneous rash, 1 case of grade I headache and 1 grade II allergic reaction, all of them resolved.

At day +100, 24 patients (77%) were in CR, 1 (2%) was in PR and 4 (6%) experienced disease progression; 2 patients were not evaluable because of early mortality.

Acute GVHD was diagnosed in 25 (76%) with 5 cases (14%) of grade 3-4 aGVHD. In 73% of patients, GVHD achieved CR after treatment. Chronic GVHD appeared in 13/29 (48%) patients alive at day +100, at it was mild or moderate in 97%.

At last follow-up, 5 patients relapsed after a median of 3 months (1-6) and overall mortality rate was 42% ($n = 13$); cause of death was progression disease in 3 and transplant related mortality in 10. Estimated progression-free survival (PFS) at 24 months was 50%, with a median estimated PFS of 23 months (6-39).

Conclusion: Ofatumumab is feasible as a part of RIC regimen in high-risk B NHL patients. Although aGVHD rate was 76%, there were no grade 4 cases and 73% of patients responded to treatment achieving CR. Based on these data, future prospective studies are warranted.

Keywords: allogeneic stem cell transplant (alloSCT); non-Hodgkin lymphoma (NHL); ofatumumab

387 IMPACT OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER SUBTYPE ON SURVIVAL

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Introduction: Post-transplant lymphoproliferative disease (PTLD) arises in the setting of immunosuppression following solid organ transplantation (SOT) or hematopoietic stem cell transplantation. PTLD incidence ranges from 1% to 20% in SOT; mortality estimates of >30% make this entity a significant life-threatening complication of transplantation. PTLD is broadly categorized into 4 groups: early; polymorphic; monomorphic, including T/natural killer cell neoplasms and most B-cell neoplasms; and classical Hodgkin lymphoma. The heterogeneity of PTLD histology, compounded by relative disease rarity and absence of a standard treatment approach, has made evaluating clinical outcomes in specific patient populations difficult. We analyzed data from a systematic review of the literature to investigate the impact of PTLD histologic subtype on survival in a large dataset.

Methods: Case series were identified on PubMed using the search terms "post-transplant lymphoproliferative disorder/disease," "PTLD," and "solid organ transplantation," with additional publications identified through reference lists of these papers. Inclusion criteria were: 1) articles published in English between January 1, 1974 and July 1, 2016 with pathology diagnosis and survival details; 2) adult cases following SOT. Patient characteristics, immunosuppressive regimen, treatment, survival, and follow-up time of 306 cases were extracted from 94 articles and combined with 11 cases from our institution. Patients with recorded subtype information were included in survival analysis ($n = 243$). Kaplan-Meier analysis compared overall survival (OS) for 4 major subtypes (polymorphic, monomorphic B-cell, monomorphic T-cell, and Hodgkin-type neoplasms), and for 4 subgroups of

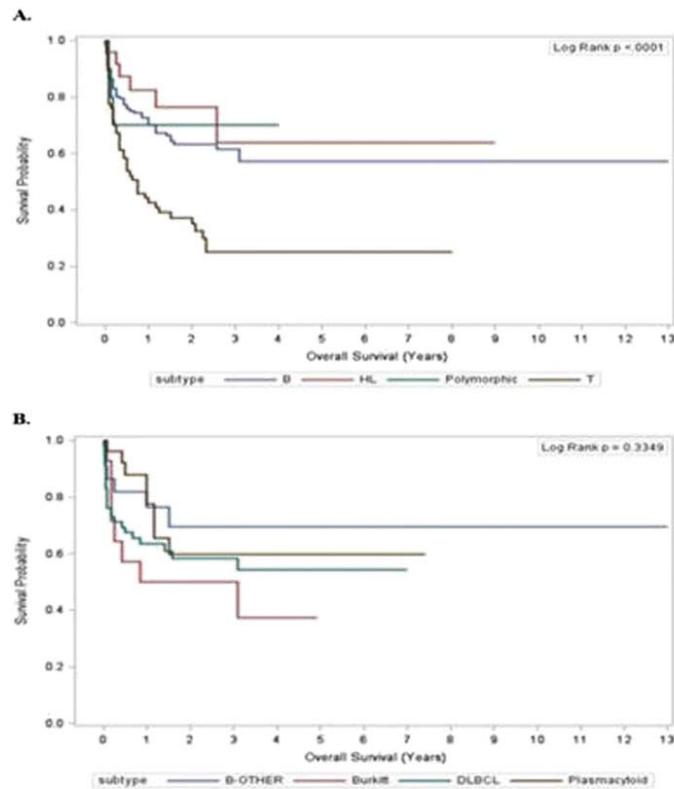


Figure 1. Overall survival in patients with PTLD by histologic subtype (A) and in patients with B cell PTLD by B cell subgroup (B). Abbreviations: B, monomorphic B cell; HL, Hodgkin lymphoma; T, monomorphic T cell; DLBCL, diffuse large B cell lymphoma.

B-cell neoplasms. Univariate and multivariable Cox proportional hazard regression analyses were performed to identify predictors of OS for each subtype and B-cell subgroup.

Results: OS was significantly different among polymorphic (median 18 months), Hodgkin-type (15 months), monomorphic B-cell (14 months) and monomorphic T-cell neoplasms (7 months, $p < 0.001$, **Figure 1a**). Significant differences in OS among B-subgroups were not detected, but there was a trend towards decreased survival in Burkitt-type PTLD (**Figure 1b**). Kidney transplant and treatment with reduction of immunosuppression were associated with increased OS in multivariable analysis in B-cell neoplasms. Younger age and immunosuppression with azacitidine were associated with decreased OS in T-cell neoplasms.

Conclusions: Histologic subtype represents an important factor in PTLD prognosis, with T-cell monomorphic subtype exhibiting a particularly poor OS. The possibility of lower survival in certain subsets of B-cell PTLD should be explored in future studies and suggests the need for subtype-specific treatment strategies to improve outcomes.

Keywords: immunosuppression; post-transplant lymphoproliferative disorders (PTLDs)

388 PTLD: SURVIVAL AND ANALYSIS OF PROGNOSTIC FACTORS IN A COHORT OF 138 PATIENTS FROM A SINGLE INSTITUTION

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Introduction: The outcome and prognostic factors of post-transplant lymphoproliferative disorder (PTLD) varies in currently reported literature. We present one of the largest single institution retrospective analysis from University of Florida.

Methods: Patient population was identified from EMR and charts were reviewed to collect data. Primary outcome was overall survival (OS) and secondary outcome was identification of prognostic factors.

Results: We identified 138 patients with PTLD from Sept 1994 to Feb 2016 (liver 34%, kidney 23%, heart 21%, lungs 12%, kidney-pancreas 2% and BMT 6%). After survival analysis, 131 patients were further followed for secondary outcomes. 36% ($n = 47$) were less than 18 years of age, 60% ($n = 83$) were males. The median age of PTLD diagnosis was 44 years and the median duration from transplant to PTLD was 4.4 years. Pathology was early lesion 6% ($n = 8$), polymorphic 17% ($n = 23$), monomorphic 71% ($n = 93$), Hodgkin/like 4.5% ($n = 6$). Extra-nodal site involvement was 61% ($n = 80$), most common being GI tract. Ann Arbor stage distribution was stage I/II 50% ($n = 65$), stage III/IV 46% ($n = 60$). Initial treatment was immunosuppression (IS) reduction alone in 24% ($n = 31$), Rituximab (R) 24% ($n = 31$), chemotherapy (+/- R) 46% ($n = 60$). Most common chemotherapy regimen was CHOP (+/- R) 27% ($n = 36$). After first line, 48% patients had complete remission (CR), 18% partial remission (PR) and 15% progressive disease (PD). Second line treatment was required in 33% ($n = 44$) and 10% ($n = 13$) patients required 3rdline

treatment. Final analysis showed 61% ($n = 80$) achieved CR, 17% ($n = 22$) had PD, 56% ($n = 74$) patients were alive and 49% ($n = 64$) are alive without PTLD. Median OS was 14.99 years. Multivariate analysis identified transplant age, type of organ transplant, PTLD diagnosis age, performance status, IPI score, episodes of acute graft rejection, previous history of malignancy and recipient EBV status as prognostic factors ($p < .05$).

Conclusions: This study from a leading regional transplant center shows notable OS which is likely from improved immunosuppressive regimens, treatment modalities and large pediatric population. We identified various prognostic factors affecting survival and propose validation to generate prognostic score.

Keywords: post-transplant lymphoproliferative disorders (PTLDs)

389 ALLOGRAFT REJECTION ASSOCIATED WITH IMMUNOSUPPRESSION REDUCTION FOR POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER: A 20-YEAR SINGLE-INSTITUTIONAL EXPERIENCE

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Introduction: Post-transplant lymphoproliferative disorder (PTLD) is a rare, but potentially fatal complication of transplantation and therapeutic immunosuppression (IS). The cornerstone of PTLT management is reduction of IS, which carries the risk of allograft rejection.

Methods: Retrospective analysis of patients diagnosed with PTLT after solid organ (SOT) or allogeneic stem cell transplant (HSCT) at the University of Florida were identified through a review of individual EMR charts. This analysis focused on rates of allograft rejection and graft failure with RI (immunosuppression reduction).

Results: Of 138 patients diagnosed with PTLT between 1994 and 2016, 66 patients were treated RI, 15.9% ($n = 22$) experienced allograft rejection during PTLT treatment. The primary organ of transplant and rejection included liver (35%), lung (25%), heart (10%), HSCT (15%) and kidney (15%). Median age at PTLT diagnosis was 14.5 years (range 2-59), males (50%) and median time from transplant to PTLT diagnosis was 25 months (range 0-173). RI was documented as a component of initial PTLT treatment in 21/22 (95%) patients, with 2/22 (9%) undergoing complete withdrawal of immunosuppression, 14/22 (63.6%) partial RI (withdraw of one or more drugs) and 4/22 (18%) dose reductions of their established IS regimen. One lung recipient (5%) was transitioned to an alternative agent, and one patient had no documented records of IS adjustment. Treatment for acute rejection included observation 2/22 (9%), pulse steroids 11/22 (50%) or IS increase 14/22 (64%). 7/22 (31.8%) received combination steroids and increased IS. Allograft failure developed in 7/22 (31.8%) (2 kidney, 2 lung, 1 heart, 1 liver, 1 BMT). Allograft failure was not shown to

correlate with IPI score at diagnosis, organ transplanted, induction therapy at transplant or 3-year OS. Of note 5/7 (71%) of patients with allograft failure received Rituximab as part of initial treatment, versus 5/15 (33.3%) patients whose grafts survived.

Conclusions: RI is the primary modality of treatment for PTLT, acute graft rejection was seen in 16% patients, allograft failure was only seen in 10% of the patients who were treated with RI.

Keywords: immunosuppression; non-Hodgkin lymphoma (NHL); post-transplant lymphoproliferative disorders (PTLDs)

390 POST-TRANSPLANT MONOMORPHIC BURKITT'S LYMPHOMA: CLINICAL CHARACTERISTICS AND OUTCOME OF A MULTICENTER SERIES

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Introduction: Post-transplant lymphoproliferative disorders (PTLD) are lymphoid neoplasms that develop after hematopoietic stem-cell (HSCT) or solid organ transplantation (SOT) and are associated with immunosuppressive therapy (IS) and Epstein-Barr virus (EBV). Burkitt's monomorphic PTLT (BL-PTLT) is an uncommon subtype of PTLT. To gain insight into this rare lymphoma, the clinical features of a series of adult BL-PTLT included in GELTAMO registry were retrospectively reviewed.

Methods: Patients diagnosed with BL-PTLT from 1996 to 2015 were retrospectively identified in the registry from 8 transplant centers. Patients with PTLT negative for MYC breaks were excluded.

Results: Twenty-three patients with the diagnosis of BL-PTLT were included. Thirteen patients were female and the median age at diagnosis was 45 years (23-71 yrs). Twenty-one patients underwent SOT (13 kidney, 4 liver, 2 lung and 2 heart) and 2 HSCT. Median time from transplant to BL-PTLT was 5.7 years (2 months to 21.7 yrs) and 18 patients had stage IV. All patients were receiving IS at the time of diagnosis. Serum LDH was increased in 19/21 patients. Immunohistochemistry analyses ($n = 19$) revealed that all cases were CD20, CD10, and BCL6 positive and negative for BCL2. Ki67 expression was >90% in all cases. BCL2 and BCL6 translocations analyzed by FISH

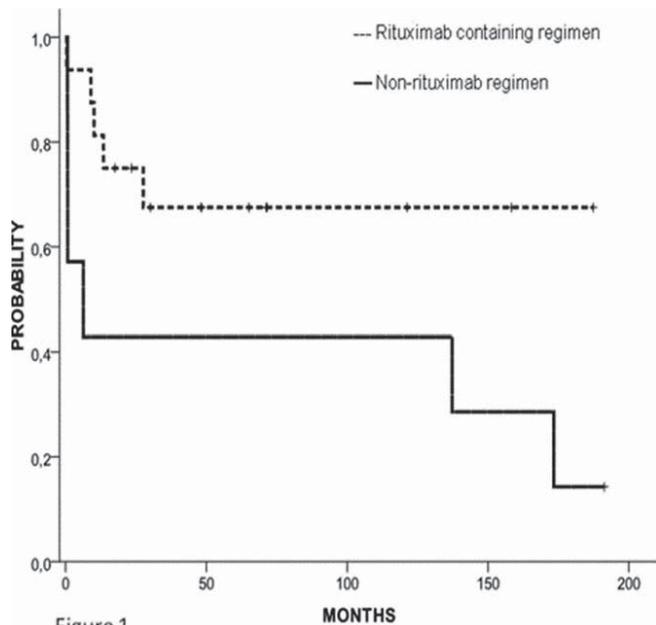


Figure 1

were not present in any case (12/12). In situ hybridization for EBV was positive in 9 of 13 cases. Thirteen patients were treated with immunochemotherapy, including R-CHOP ($n = 9$), BURKIMAB ($n = 3$) (Ribera et al., Cancer 2013) containing high-dose MTX plus Ara-C along with rituximab and R-EPOCH ($n = 1$). Three patients only received 4 courses of rituximab. Finally, 7 patients diagnosed in the pre-rituximab era were treated with CHOP ($n = 2$), CODOX-M/IVAC ($n = 1$) and other dose-intensive chemotherapy combinations ($n = 4$). Seventeen patients received CNS prophylaxis. Nineteen patients finished the initial treatment and 16 obtained a complete remission (CR). Four patients died during treatment, 1 due to progression and 3 due to sepsis. Eight patients relapsed at a median time of 6 months (3 months-10 yrs), 2 of them only in CNS. All patients treated with rituximab alone required further chemotherapy to achieve CR. Four of 7 patients obtained CR with salvage therapy. After a median follow-up of 68 months (17-191 months), 11 patients remained in CR. The 2-year overall survival was 65% for the whole series, 75% for the 16 patients receiving rituximab-containing therapies and 43% for the 7 patients without rituximab (figure 1).

Conclusion: In this retrospective series BL-PTLD appears as an aggressive variety of PTLT usually diagnosed late in the evolution after transplant. BL-PTLD seems to achieve a good response to the immunochemotherapy combinations, including R-CHOP or to more intensive regimens like Burkitt-based therapy and a poor response to rituximab alone. For patients not candidate to intensive regimens, R-CHOP could be an appropriate alternative.

Keywords: Burkitt lymphoma (BL); post-transplant lymphoproliferative disorders (PTLDs)

391 PRESENTATIONS, TREATMENT COMPLICATIONS AND OUTCOMES IN

HCV-INFECTED B-CELL LYMPHOMA PATIENTS TREATED WITH IMMUNOCHEMOTHERAPY: A SINGLE INSTITUTE RETROSPECTIVE STUDY

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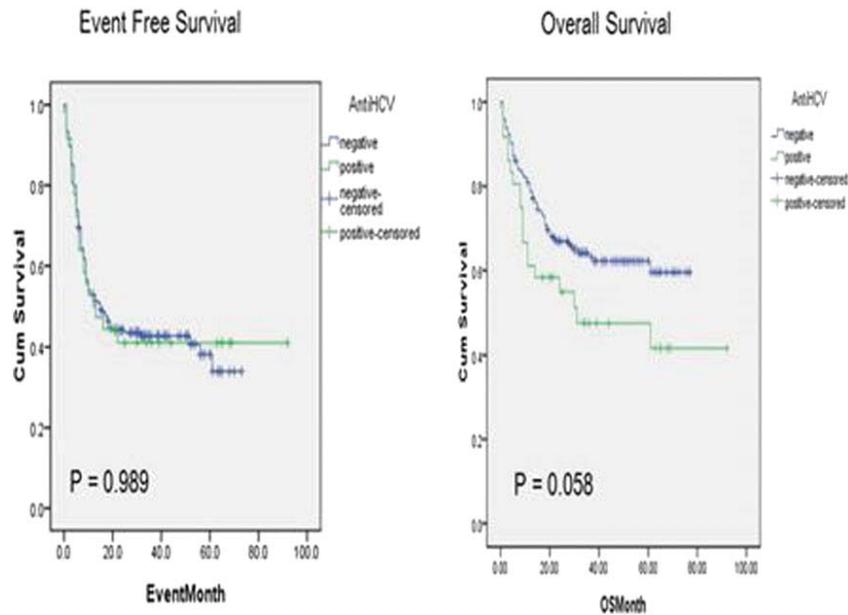
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Numerous epidemiologic studies show an association between hepatitis C virus (HCV) and B-cell lymphomas. However, limited studies focused on hepatic consequences after immunochemotherapy, and the prognostic role of HCV is still a matter of debate. We retrospectively analyzed the clinical presentations, hepatic complications, and outcome of B-cell lymphoma patients who were HCV-infected and not HCV-infected.

During 2008 to 2013, there were 230 newly diagnosed lymphoma patients who were negative for HBsAg received rituximab-containing chemotherapy as their first-line therapy in our institute. Thirty-six patients (15.7%) were positive for anti-HCV and 194 patients were negative. Most common lymphoma subtypes were DLBCL (73.5%) and follicular lymphoma (19.1%). DLBCL patients had a higher anti-HCV positive rate than FL (18.3% vs 5.6%, $P = 0.015$). Anti-HCV-positive patients had higher baseline AST and ALT levels (AST, 57.7 ± 46.5 U/L vs 31.1 ± 25.9 U/L, $P < 0.001$; ALT, 51.6 ± 51.0 U/L vs 25.6 ± 30.6 U/L, $P < 0.001$), and more liver cirrhosis before treatment (19.4% vs 2.2%, $P < 0.001$). However, spleen involvement (30.6% vs 21.2%, $P = 0.227$), extranodal involvements more than one site (27.8% vs 29.4%, $P = 0.706$), and other parameters are similar in both groups.

The most common treatment regimens were R-CHOP like (65.7%) and R-COP (24.8%). After chemotherapy, the patients who were positive for anti-HCV developed more hepatitis (defined as ALT >40 U/L) (80.6% vs 59.8%, $P = 0.018$) and severe hepatitis (defined as ALT >200 U/L) (30.6% vs 7.7%, $P < 0.001$). One HCV-positive patient died of hepatic failure after salvage therapy (ESHAP), which was administered at 3 months after last cycle of R-CHOP. The reduction rate of chemotherapy dose ($<90\%$ of standard dose) due to hepatotoxicity occurred more often in HCV-infected patients (19.4% vs 2.4%, $P = 0.001$). Chemotherapy early stop is defined as patients received less cycles of chemotherapy than initial planning or guideline. Chemotherapy early stop rate for all causes was similar in both groups (38.9% vs 26.7%, $P = 0.143$), but early stop specifically due to hepatotoxicity was slightly higher in patients with HCV infection (3/36 (8.3%) vs 3/165 (1.8%), $P = 0.072$).

The median follow-up time was 21.6 months (range, 1.3-92.8 months) for patients who were HCV-positive and 30.7 months (range, 0.7-78.1 months) for those who were HCV-negative. Complete remission rates were 58.3% and 55.2% in HCV-positive and HCV-negative patients, respectively. Partial response rates were 25.0% and 23.7% in HCV-positive and HCV-negative, respectively. No significant difference was observed in event free survival according to HCV infection (3-year EFS, 41.0% vs 42.8%, $P = 0.989$). The overall survival tended to be worse in patients who were positive



for anti-HCV than those negative for anti-HCV (3-year OS, 47.6% vs 63.2%, $P = 0.058$).

Our results showed that HCV-lymphoma patients have more hepatic complications, more chemotherapy reduction/early stop due to hepatotoxicity, and may have an inferior overall survival.

Keywords: B-cell lymphoma; hepatitis C; rituximab

392 TREATMENT PATTERNS AND OUTCOMES IN THE DLBCL COHORT OF A STUDY (MONITOR-GCSF) ASSESSING BIOSIMILAR FILGRASTIM FOR PROPHYLAXIS OF CHEMOTHERAPY-INDUCED/FEBRILE NEUTROPENIA

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Introduction: Biosimilars present opportunities for sustainability of cancer treatment.¹ Indeed, biosimilars of filgrastim are widely used in the prophylaxis of chemotherapy-induced (CIN) and febrile neutropenia (FN). However, there are limited observational data on the use of granulocyte-colony stimulating factor (G-CSF) in non-Hodgkin's lymphoma and its aggressive subtypes including diffuse large B-cell lymphoma (DLBCL). MONITOR-GCSF is a pan-European, multicenter, prospective, observational study aiming to describe treatment patterns and clinical outcomes in patients receiving biosimilar filgrastim (Zarzio®/Zarxio®/EP2006, Hexal AG) in the prophylaxis of CIN/FN. This analysis aimed to describe patient characteristics, biosimilar filgrastim treatment patterns, and outcomes in the DLBCL cohort of the MONITOR-GCSF study.

Methods: The study cohort included a total of 245 evaluable patients with stage 3 or 4 DLBCL receiving up to 6 chemotherapy cycles. Patients were treated as per their physician's best judgement.

Results: Mean (\pm SD) age was 62.7 (\pm 14.7) years; mean body weight was 73.4 (\pm 16.45) kg; 58.8% of patients were male; and 42% of patients had stage 3 disease. CIN (any grade) occurred in 16.7% ($n = 41$) of patients in Cycle 1 and in 35.5% ($n = 87$) of patients in all cycles. FN occurred in 2.4% ($n = 6$) of patients in Cycle 1 and in 9.8% ($n = 24$) of patients in all cycles. Grade 3-4 FN occurred in 2% of patients ($n = 5$) in Cycle 1 and in 9.4% of patients ($n = 23$) in all cycles. The most frequent adverse event was bone pain, reported in 2.9% of patients ($n = 7$), followed by arthralgia (0.8%; $n = 2$) and back pain (0.8%; $n = 2$) (Table 1).

Conclusions: This analysis reports that the efficacy and safety of biosimilar filgrastim in real-life practice in patients with DLBCL are similar to the known efficacy and safety profile of reference filgrastim. This supports the use of biosimilar filgrastim in real-world use and extends the efficacy and safety from its clinical development program.

Reference: 1. Taberero J, et al. ESMO Open 2016;1:e000142.

Keywords: diffuse large B-cell lymphoma (DLBCL); filgrastim; G-CSF

TABLE 1 Adverse events reported in patients with DLBCL.

Adverse events	N	%
Bone pain	7	2.9
Arthralgia	2	0.8
Back pain	2	0.8
Blood alkaline phosphatase increased	1	0.4
Constipation	1	0.4
Hepatitis (acute)	1	0.4
Hypotension	1	0.4
Injection site pain	1	0.4
Musculoskeletal pain	1	0.4
Musculoskeletal stiffness	1	0.4
Myalgia	1	0.4
Pyrexia	1	0.4

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OUTCOMES IN PEDIATRIC PATIENTS WITH POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD): ANALYSIS OF A 20-YEAR SINGLE-INSTITUTIONAL EXPERIENCE

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Introduction: Post-transplant lymphoproliferative disorder (PTLD) is the most frequent malignant complication of organ transplantation in children. PTLD often arises in the setting of prior Epstein-Barr virus (EBV) infection and therapeutic immunosuppression (IS) for prevention of allograft rejection. Treatment strategies with IS reduction, anti-CD20 antibody (rituximab) and chemotherapy (CTX) have continued to improve survival outcomes. We present a large, single-institutional experience of pediatric patients from the University of Florida.

Methods: A retrospective analysis of pediatric patients (<18 years) diagnosed with PTLD after solid organ or allogeneic stem cell transplant (HSCT) was performed through a review of individual electronic medical records.

Results: Of 138 PTLD cases diagnosed between 1994 and 2017, 49 pediatric patients (47% liver, 22% heart, 22% kidney, 6% lung, and 2% HSCT) were identified and analyzed for secondary outcomes. Median age at transplant and PTLD diagnosis were 19 months and 7 years, respectively. Fifty-three percent ($n = 26$) were males. The median interval from transplant to PTLD was 35 months. Pathology included early lesions (12%, $n = 6$), polymorphic (27%, $n = 13$), monomorphic (53%, $n = 26$), Hodgkin-like (4%, $n = 2$), EBV+ by EBER PCR (67%, $n = 33$) and CD-20+ (67%, $n = 33$). Extra-nodal site involvement was identified in 53% ($n = 26$), the most common site being the GI tract. Ann Arbor stage III/IV was present in 47% ($n = 23$). Initial PTLD management was IS reduction alone in 37% ($n = 18$), rituximab (R) in 18% ($n = 9$) and CTX with or without (R) in 39% ($n = 19$). The most common CTX regimen was R + cyclophosphamide 27% ($N = 13$). After first-line therapy, 55% patients had complete remission (CR), 25% partial remission (PR) or stable disease (SD) and 6% progressive disease (PD). A 2nd line treatment was required in 39% ($n = 19$) and 8% ($n = 4$) required 3rd line treatment. During PTLD treatment 25% ($n = 12$) experienced acute organ rejection, with 4% ($n = 2$) developing allograft failure. Final analysis showed 84% ($n = 41$) achieved CR, 8% ($n = 4$) had PD, 78% ($n = 38$) patients were alive and 76% ($n = 37$) are alive without PTLD.

Conclusions: Despite nearly 50% of patients having stage III/IV disease and extranodal involvement, our transplant center reports encouraging outcomes in survival and allograft function. We identified multiple prognostic indices (performance status, IPI score, graft rejection, malignancy history and recipient EBV status), which in the future could help

generate a prognostic scoring system for this population. While these outcomes are promising, 25% of patients did not achieve long-term PTLD remission with modern treatment modalities. This illustrates the need for novel therapies for pediatric patients with PTLD to achieve cure rates above 90%, which are attainable in other childhood lymphomas.

Keywords: Epstein-Barr virus (EBV); non-Hodgkin lymphoma (NHL); post-transplant lymphoproliferative disorders (PTLDs)

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TREATMENT OF NEWLY DIAGNOSED CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA PATIENTS BASED ON CO-MORBIDITIES & PERFORMANCE STATUS: A SINGLE-CENTRE EXPERIENCE

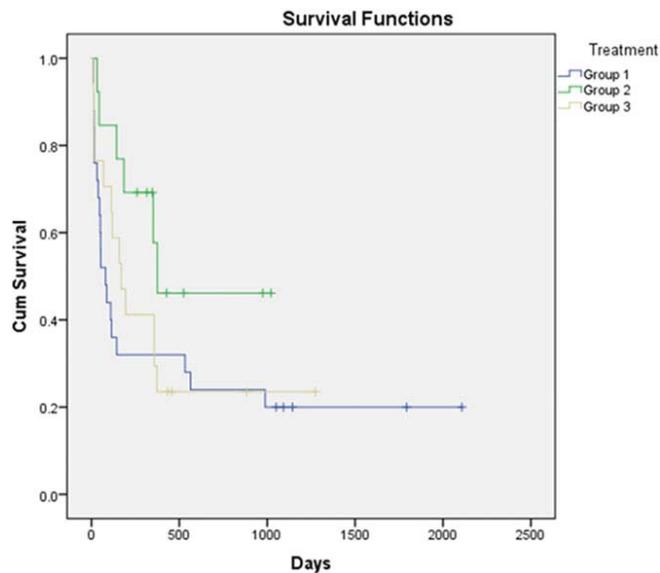
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Introduction: Combination chemotherapy incorporating high dose methotrexate (HD-Mtx) and high dose cytarabine (Ara-C) is the standard chemotherapeutic approach for newly diagnosed primary CNS lymphoma (PCNSL)¹. However, patients >60 years old account for 50% of cases and combining HD-Mtx with Ara-C can be associated with high toxicity and early mortality². The management of secondary CNS lymphoma (SCNSL) is less clear, but is often based upon a similar approach. We present a tertiary centre experience in management of primary (PCNSL) and secondary CNS lymphoma (SCNSL), with therapy based on co-morbidities and performance status.

Method: We performed a retrospective analysis of patients with a diagnosis of CNS lymphoma seen at our centre between 2011 and 2016. These were categorized into 3 groups, Group 1: treatment of newly diagnosed PCNSL prior to September 2014 where majority of patients received HD-Mtx & Ara-C combination chemotherapy, Group 2: treatment of PCNSL after September 2014 where patients were selected based on co-morbidities, Group 3: treatment of newly diagnosed SCNSL. The median survival for each group was estimated using the Kaplan-Meier method and log-ranked test. 30 day and 90 day survival between groups 1 and 2 were compared using unpaired t test.

Results: 60 pts with a median age of 65 years old were recruited. 40 pts were diagnosed to have PCNSL at presentation, while 20 patients had SCNSL. 5 pts were excluded from this study as they did not receive any treatment. In group 1, 21 pts (84%) received combination chemotherapy incorporating HD-Mtx and Ara-C, 3 pts (12%) received HD-Mtx monotherapy and 1 pt (4%) received radiotherapy only. In group 2, 7 pts (53.8%) received HD-Mtx and Ara-C as part of MATRIX protocol or with single agent rituximab, 3 pts (23%) received HD-Mtx as part of RMP protocol or with single agent rituximab, 1 pt (7.7%) received a single alkylating agent and 1 pt (7.7%) received radiotherapy only. In group 3 15 pts (88.3%) received chemotherapy incorporating HD-MTX and Ara-C, 2 pt (11.8%) received HD-MTX without Ara-C. 30 day mortality was 7 (28%) in group 1 and 0 in group 2 (0%) ($p = 0.03$). 90 day mortality was 7 (28%) in group 1 and 2 in group 2



(15.4%) ($p = 0.39$). A Kaplan Meier curve of all 3 groups is illustrated below.

Conclusion: This single centre study demonstrated that patient selection, based upon comorbidities and performance status, for high dose combination chemotherapy in the treatment of PCNSL improves 30 day mortality, often associated with death from myelosuppression due to chemotherapy. This also applies to patients with SCNSL in subgroup analysis. Longer follow-up of patients will be needed to further demonstrate an overall survival benefit.

Keywords: chemotherapy; primary CNS lymphoma (PCNSL)

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395 CHARACTERISTICS AND NATURAL HISTORY OF PRIMARY VITREORETINAL LYMPHOMA (PVL) COMPARED TO THE PRIMARY LYMPHOMA OF THE CNS (PCNSL)

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Aim: Primary vitreoretinal lymphoma (PVL) is considered to be a subtype of primary CNS lymphoma and they often receive systemic

treatment (Tx) based on PCNSL protocols instead of local Tx (intraocular methotrexate or local irradiation). In this work, we aimed to compare characteristics and natural history of these 2 lymphoma subtypes.

Methods: Patients diagnosed and treated in General University Hospital, Prague, for PVL or PCNSL were compared according to their basal characteristics, prognostic factors, overall and progression-free survival (OS). Statistics were performed with chi-square, Mann-Whitney and log-rank tests. Results are given as medians.

Results: Ten patients with PVL and 59 patients with PCNSL were diagnosed and treated in Charles University General Hospital, Prague from 2002 to 2016. PVL patients were diagnosed by cytology and FACS, while all PCNSL patients had brain biopsy. All PCNSL patients had ophthalmological examination. PVL and PCNSL patients were of similar age (57 v. 65 years, $p = \text{NS}$) and sex distribution. Five patients with PCNSL had intravitreal involvement (8%), 3 of them presented initially with visual impairment. PVL patients had better performance status (Karnofsky, 100 v. 60%, $p = 0.00006$), otherwise the pretreatment characteristics were similar. Six patients with PVL received systemic Tx in comparison to all PCNSL patients ($p = 0.002$). Six and 22 patients, respectively, received rituximab in first-line treatment ($p = \text{NS}$). Median follow-up for living patients was 57 (PVL) and 69 months (PCNSL, $p = \text{NS}$).

Patients with PVL had better PFS (39.9 v. 18.6 months, $p = 0.04$) and OS (not reached v. 32.8 months, $p = 0.006$). The only negative prognostic factor identified for PFS and OS in PCNSL patient was age over 50 years, while no prognostic factor was found in PVL patients. However, patients with PVL over 50 years still had better PFS and OS than corresponding PCNSL patients (39.9 v. 12.7 months, $p = 0.04$, and NR v. 23.9 months, $p = 0.002$). Patients with PVL who received only local Tx had similar prognosis than patient treated systemically. Rituximab did not improve outcome in either group of patients.

Conclusion: Although PVL and PCNSL are closely related diseases, in our institution, patients with PVL had better prognosis than PCNSL patients. This difference was not explained by pretreatment factors. Although in a small number of pts, it seems that first-line local Tx for PVL could give the same results as systemic Tx.

Keywords: extranodal lymphomas; primary CNS lymphoma (PCNSL)

396 CNS RELAPSE IN PATIENTS WITH DLBCL ACCORDING TO CNS-IPI SCORE AND THE INITIAL THERAPY

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Aim: Secondary central nervous system (CNS) relapse is an uncommon but fatal complication of diffuse large B-cell lymphomas (DLBCL). We analyzed the data of patients with DLBCL and studied the incidence of CNS relapse among them according to their CNS-IPI score and the initially therapy they had received.

Methods: We analyzed 411 patients with DLBCL (209 M/202F) with a median age of 66 years (range: 24-88) and median follow-up of 72 months (range: 4-385). With CHOP regimen were treated 110 patients and with R-CHOP 301 patients.

Results: Low CNS-IPI score had 159 patients (Group A), 170 had intermediate (Group B) and 82 had high risk for CNS relapse (Group C) according to their CNS-IPI score. CNS relapse was observed in 2 patients from group B and 2 patients from group C. Among patients who relapsed both patients from group B had extranodal involvement of testis while one patient from group C had adrenal extranodal involvement and the second one had stomach and bone marrow infiltration at the time of the initial diagnosis. One patient with testicular involvement and the patient with adrenal involvement had received intrathecal methotrexate prophylaxis combined with R-CHOP regimen. The rest of the patients who relapsed had received CHOP regimen without intrathecal prophylaxis. The rates of relapse among low, intermediate and high CNS-IPI groups were 0%, 1.17% and 2.44% accordingly. The rate of relapse among patients treated with CHOP (1.8%) was higher than the rate of relapse among patients treated with R-CHOP (0.64%). One patient denied any further therapy after relapse and 3 patients were treated with high dose Methotrexate and brain radiation. All patients died within 4 months after the diagnosis of the relapse.

Conclusion: Although CNS-IPI score is a useful tool in predicting the risk of CNS relapse patients with testicular involvement and intermediate CNS-IPI score may be in higher risk than calculated.

Keywords: CNS prophylaxis; diffuse large B-cell lymphoma (DLBCL)

397 INITIAL MANAGEMENT OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA IN SPAIN IN THE LAST DECADE. THE EXPERIENCE OF THE GELTAMO AND SPANISH NEURO-ONCOLOGY GROUPS

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Introduction: Primary central nervous system lymphoma (PCNSL) is a challenging tumour frequently misdiagnosed and associated with a considerable diagnostic delay. Outcome of PCNSL patients not included in clinical trial may be substantially different. We describe the clinical outcome of a non-selected, representative series of PCNSL diagnosed in the last decade in Spain.

Methods: We present a retrospective series of 314 immunocompetent adults diagnosed of PCNSL between 2005 and 2014 from 22 institutions from Spain.

Results: 314 patients (M/F, 164/150) with a median age of 65 years [range 18-82] were included in the study. Seventy-one percent of patients had an Eastern Cooperative Oncology Group (ECOG) ≥ 2 at diagnosis. Ninety-six percent were diffuse large B-cell lymphoma. Most frequent symptoms at presentation were focal deficit (45.5%) and cognitive impairment /or psychiatric (39%). Visual deficit was presented in 29 (9.2%). Magnetic resonance imaging (MRI) was performed at a median of 22 [1-708] days after the first symptom. Atypical contrast enhancement (ring or non-homogeneous) on MRI was present in 33.8% of patients. Steroids were administered before surgery in 52.5% of patients and withheld before surgery in 32% of them. Diagnosis was done by biopsy or resection in 79.6% and 20%, respectively. Median time from clinical onset to pathological diagnosis was 45 [4-817] days, being it longer in those patients with ECOG ≥ 2 comparing with ECOG < 2 (53 vs 31 days, $p = 0.003$). Median time from clinical onset to start initial treatment was 63 [7-846] days. Time from MRI was performed to pathological diagnosis was longer in those who had received steroids than other not (40 vs 18 days, $p = 0.003$). Nineteen percent of patients never received any treatment, most of them due to old age and/or ECOG ≥ 2 at diagnosis. In the case of patients receiving treatment, first line included chemotherapy alone based in high dose methotrexate in 189 patients (74.7%) or associated with radiotherapy, 41 patients (16.2%) and radiotherapy alone, 23 (9.1%). Moreover, 61 patients (24.1%) received autologous stem cell transplantation as consolidation. Median overall survival for patients treated with radiotherapy alone was 12.5 months (IC 95%, 5.9-19), if received chemotherapy alone was 13.9 months (IC 95%, 9.9-19.9), for those treated with chemotherapy plus radiotherapy was 30.2 months (IC 95%, 14.8-45.6) and those who received an autologous transplant was 72.9 months (IC 95%, 66.7-79.1). For the whole series, univariate analysis showed the absence of cognitive impairment /or psychiatric symptoms ($p = 0.001$), absence of visual deficit ($p = 0.026$),

age ≤ 60 years ($p < 0.0001$), male sex ($p = 0.012$) and ECOG < 2 ($p < 0.0001$) as the most important variables predicting better survival at diagnosis. However, in the multivariate analysis, only age ≤ 60 years ($p < 0.005$), male sex ($p = 0.04$) and ECOG < 2 ($p < 0.0001$) were prognostic factors for better outcome.

Conclusions: Steroid administration was associated with a diagnostic delay. Younger patients, ECOG < 2 and male gender were independent prognostic factors of better survival. Prospective studies are necessary to validate these findings.

Keywords: diffuse large B-cell lymphoma (DLBCL); methotrexate (MTX); primary CNS lymphoma (PCNSL)

398 CRANIOTOMY VERSUS BIOPSY FOR PRIMARY CNS LYMPHOMA: AN INSTITUTIONAL SERIES AND NATIONWIDE NCDB-PUF AND SEER DATABASE STUDY

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Introduction: Historically, resection for Primary Central Nervous System Lymphoma (PCNSL) was considered high-risk and not beneficial. We investigated survival following craniotomy in 3 modern and complementary datasets.

Methods: The National Cancer Database-Participant User File (NCDB-PUF) ($n = 9,435$), the Surveillance, Epidemiology, and End Results Program (SEER) ($n = 5,615$), and an institutional series (IS) ($n = 132$) were used. We identified prognostic scales and investigated their effects on survival.

Results: In NCDB, craniotomy was associated with increased survival over biopsy (23.16 vs 11.6 months, HR 1.26, $p < 0.001$), with a similar trend in IS (HR 1.48, $p = 0.15$). In SEER, gross total resection (GTR) was associated with increased survival over biopsy (29 vs 10 months, HR 1.22, $p < 0.001$). (GTR vs STR vs biopsy was associated with a 22% interval increase in risk of mortality (HR 1.22, $p < 0.001$). We explored factors that might influence the relationship between craniotomy and survival, and found that within Recursive Partitioning Analysis class 1 (RPA1), craniotomy was associated with increased survival over biopsy in NCDB (106.78 v. 32.85 months, HR 1.56, $p < 0.001$). The survival benefit associated with craniotomy was smaller for RPA > 1 (17.71 vs 10.28 months, HR 1.23, $P < 0.001$). We created a surgical risk category (RC) considering lesion access, which was predictive of survival (HR 2.27, $p = 0.003$). Craniotomy was only associated with increased survival over biopsy for patients with low-RC (133.37 vs 37.21 months, HR 2.16, $p = 0.040$).

Conclusion: Craniotomy is associated with increased survival over biopsy for PCNSL. Cytoreductive surgery might play a therapeutic role for these tumors, but to attribute causality and address biases, prospective studies are necessary. The design of such studies should stratify patients by prognostic factors.

Keywords: primary CNS lymphoma (PCNSL)

399 FERTILITY AND SOCIAL REINTEGRATION AFTER MODIFIED CODOX-M/IVAC WITH OR WITHOUT RITUXIMAB: A QUESTIONNAIRE SURVEY OF NON- HODGKIN LYMPHOMA

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Introduction: Although malignant lymphoma is one of the most common malignancies among adolescents and young adults (AYAs), there has been limited information regarding their long-term outcome after completion of anti-lymphoma therapies, especially for non-Hodgkin lymphoma. Modified (m) CODOX-M/IVAC \pm rituximab (R) therapy is one of the most frequently applied intensive regimens, mainly for patients (pts) with Burkitt lymphoma (BL) and primary mediastinal large B-cell lymphoma (PMBL) at our institution [Int J Hematol. 2010 and Hematol Oncol. 2013]. We aimed to investigate the long-term outcome after mCODOX-M/IVAC \pm R therapy focusing on fertility and social reintegration.

Methods: We conducted a questionnaire survey of pts with BL or PMBL who underwent mCODOX-M/IVAC \pm R as an initial therapy between 2003 and 2015 at our institution. Quality of life (QOL) was assessed using the 36-Item Short Form Health Survey (SF-36) version 2.

Results: A total of 65 pts were eligible; however, 5 pts were lost to follow-up. Finally, 60 pts (16 BL and 44 PMBL) were identified as subjects of this study. At the time of abstract preparation, 75% (45 pts: 29 females and 16 males) of questionnaires were retrieved. Median age at diagnosis was 34 years (range, 16-55) and median follow-up duration was 6 years (range, 1-16). Of 26 premenopausal females at initial diagnosis, fertility preservation was performed in 8 pts (30%) as follows: gonadotropin-releasing hormone analog (7), embryo cryopreservation (2) and oocyte cryopreservation (1). Menstrual recovery was observed in 21 out of the 26 premenopausal pts (80%) after completion of therapy with a median of 2.3 months, whereas 5 (19%) became amenorrheic. Of 16 males, sperm cryopreservation had been performed in 6 (38%). After the end of therapy, 5 pregnancies and 3 deliveries were observed. Regarding marital status, 3 were divorced and 5 got married. Furthermore, all 4 students returned to school within 7 months after the therapy. Of 36 working adults, 25 pts (69%) came back to their full-time work with a median of 4 months after completion of the therapy. The SF-36 showed that the physical component summary score of all pts was higher than Japanese national norms and the other summary scores were also comparable with the norms.

Conclusions: To the best of our knowledge, this is the first report evaluating QOL after mCODOX-M/IVAC \pm R therapy. Our findings

TABLE 1

	Total (N = 45) N (%)	PMBL (n = 36) n (%)	BL (n = 9) n (%)
Sex			
Female	29 (64)	26 (72)	3 (33)
Male	16 (35)	10 (27)	6 (66)
Age			
Median, years (range)	34 (16-55)	34 (19-52)	34 (16-55)
Follow-up from diagnosis			
Median, years (range)	6 (1-16)	5 (1-11)	8 (1-16)
Fertility preservation (premenopausal female, n = 26)			
Yes	8	7	1
Gonadotropin-releasing hormone analog	7	6	1
Embryo cryopreservation	2	2	0
Oocyte cryopreservation	1	1	0
No	18	17	1
Fertility preservation (male, n = 16)			
Yes (sperm cryopreservation)	6	4	2
No	10	6	1
Pregnancy after therapy			
Yes	5 (11)	4 (11)	1 (11)
Female	4 (8)	3 (8)	1 (11)
Male	1 (2)	1 (2)	0
No	40 (88)	32 (88)	8 (88)
Delivery after therapy			
Yes	3 (6)	3 (8)	0
Female	2 (4)	2 (5)	0
Male	1 (2)	1 (2)	0
No	42 (93)	33 (91)	9 (100)
SF-36v2 summary score, median (range)			
Physical component summary	56.1 (40.5-68.4)	56.4 (40.5-68.4)	55.3 (46.4-62.6)
Mental component summary	49.5 (13.5-71.2)	49.5 (13.5-71.2)	51.0 (42.0-65.7)
Social-role component summary	51.6 (19.8-71.2)	51.5 (19.8-71.2)	53.1 (47.0-58.4)

demonstrate that this intensive regimen retains the potential for reproduction and social reintegration in pts with BL and PMBL, including AYAs.

Keywords: Burkitt lymphoma (BL); primary mediastinal large B-cell lymphoma (PMLBCL)

400 PRELIMINARY RESULTS FOR A MULTIMODALITY IMAGING APPROACH FOR EARLY DETECTION AND PREDICTION OF CARDIOTOXICITY IN DOXORUBICIN- TREATED PATIENTS WITH MALIGNANT LYMPHOMA

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Introduction: Doxorubicin is a cornerstone of curative lymphoma treatment. However, doxorubicin therapy is often limited by cardiac side effects including high-mortality heart failure (HF). Signs of

cardiotoxicity often appear too late to avoid irreversible myocardial damage. Several different imaging modalities for early detection of chemotherapy-induced cardiomyopathy are being investigated including rubidium 82 positron emission tomography (82Rb PET) for perfusion imaging, iodine 123 metaiodobenzylguanidine (123I MIBG) for imaging of cardiac autonomic innervation, and cardiac magnetic resonance (MR) for imaging of left and right ventricular function, atrial and ventricular volumes, myocardial mass and interstitial fibrosis.

Methods: The study is a prospective, clinical, single-centre study. The study population will consist of 70 consecutive chemotherapy-naïve lymphoma patients scheduled for intended curative doxorubicin-containing chemotherapy without planned mediastinal radiation therapy. Patients undergo supplementary imaging procedures as outlined below:

1. Baseline 82Rb PET, 123I-MIBG and MR (prior to treatment)
2. Acute 82Rb PET and MR (within 1 week of the first treatment)
3. Subacute 123I-MIBG (after 2-3 months of therapy)
4. Late MR (1 year after the start of treatment)

Here, we present the results from the baseline and acute PET and MR scans for the first 50 included patients.

Results: Of the 50 patients, one died before the acute imaging procedures while 3 were excluded before baseline imaging due to compliance problems. One patient was excluded due to disease downstaging resulting in omission of doxorubicin from the treatment

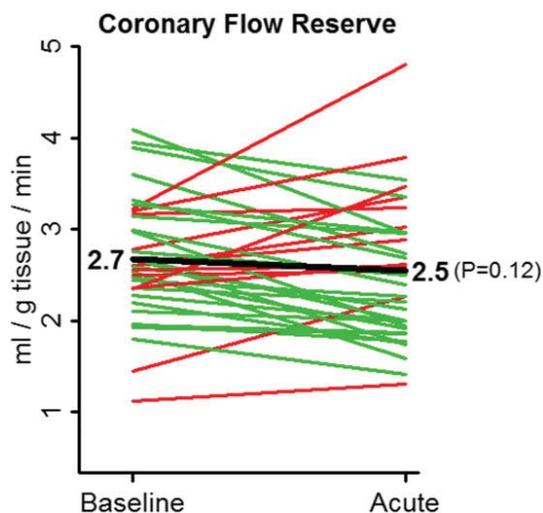


Figure 1: Changes in coronary flow reserve (CFR) from baseline to acute 82Rb PET. Increases and decreases in CFR are represented with red and green lines, respectively.

plan. In 2 cases acute imaging was not performed due to severe treatment-related side effects.

There were no significant differences between baseline and acute 82Rb PET scans although we did register a non-significant decline in coronary flow reserve (CFR) including 15 patients with a decrease >10% (Figure 1). Cardiac MR revealed a near-significant increase in left ventricular ejection fraction ($p = 0.05$) accompanied by a non-significant increase in left ventricular end-diastolic volume ($p = 0.11$) and a significant increase in stroke volume ($p = 0.02$).

Conclusions: Our results indicate that cardiac imaging may provide acute signs of doxorubicin cardiotoxicity. Here, we demonstrate changes in left ventricular function with cardiac MR. Although 82Rb PET imaging did not show any immediate effect on perfusion parameters after doxorubicin exposure, a subgroup of patients did demonstrate a marked decrease in CFR. In our future studies, we will investigate whether these acute changes translate into an increased risk of myocardial fibrosis and HF at 12 month follow-up.

Keywords: doxorubicin; magnetic resonance imaging (MRI); positron emission tomography (PET)

MANTLE CELL LYMPHOMA

401 PROGNOSTIC VALUE OF KI-67, MIPI SCORE AND SUV MAX OF THE PET SCAN: RESULT OF A SINGLE CENTER EXPERIENCE WITH MANTLE-CELL LYMPHOMAS

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Introduction: Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin lymphoma with highly variable behaviors in terms of survival data. Recently, the European Mantle Cell Lymphoma Network reported that the Ki-67 index combined with MIPI allows refining the risk stratification. Beside these 2 complementary prognostic factors, the role of 18-fluorodeoxyglucose (FDG)-positron emission tomography (PET) and primarily the level of maximum standardized uptake value (SUVmax) (hyper metabolic activity) is poorly investigated in the literature.

Population and Methods: We thus retrospectively reviewed 65 MCL patients admitted in our Institute for treatment. Pathological, phenotypical and cytogenetic data were independently reviewed. MIPI scores (according to E. Hoster, BLOOD 2008) and Ki-67 index (according to published guidelines) were calculated. When available, 18-FDG PET/CT scan at diagnosis was reviewed to determine maximal SUV. Patients were then stratified according to the MIPI scores and High, Low and intermediate risk groups were correlated with the maximum SUV. Overall survival was evaluated by Cox regression model.

Results: Fifty-three patients (pts) were evaluable for MIPI score and outcome, Ki-67 index value was available in 30 pts and 24 pts had a PET/CT scan at diagnosis. Median age at diagnosis was 62 (40-85) years old. In the low risk group (MIPI 0-3), median age was 61 (42-77) years old, median overall survival (OS) was 148 Months (Mo), median SUV max was 2.86 (2.0-8.4) and 4% had Ki-67 > 30%. In the intermediate risk group (MIPI, 4-5) median age was 65 (54-79) y.o., median OS was 63 Mo, median SUV max was 6.31 (4.7-10.4) and Ki-67 was >30% in 36% of the pts. In the high-risk group (MIPI 6*) median age was 71 (47-85) y.o, median OS was 36 Mo, median SUV max was 8.25 (2.0-15.6) and Ki67 > 30% in 57%. In the "blastoid" MCL group, median age was 58 (40-77) years old median OS was 57 Mo, median SUV max was 13.9 (2.6-23.1) and 40% had Ki67 > 30%. Interestingly before the era of Ibrutinib treatment, Ki-67 index had an independent prognostic value that disappears after treatment with anti-BTK.

Conclusion: Our small series of MCL confirms the prognostic value of MIPI scores (med OS of 148, 63 and 36 months in High, intermediate and Low risks pts respectively) and poor outcome of blastoid histology (med OS 57 mo). The median SUV max value of the initial 18-FDG PET/CT was higher in the high risk and blastoid MCLs and a high SUV seems to correlate with a poor outcome. However, in the era of very effective treatment such as Ibrutinib, these prognostic markers deserves confirmation in wider series.

Keywords: mantle cell lymphoma (MCL); positron emission tomography (PET); prognostic indices

402 AUTOLOGOUS STEM CELL TRANSPLANTATION IS INFREQUENTLY UTILIZED BUT ASSOCIATED WITH IMPROVED OVERALL SURVIVAL IN ELDERLY PATIENTS WITH MANTLE CELL LYMPHOMA

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Introduction: Use of autologous stem cell transplant (ASCT) in mantle cell lymphoma (MCL) is associated with prolonged survival. However, there are concerns about the safety/efficacy of ASCT in individuals over 65 years leading to its under-utilization in this population. We describe the use of ASCT and outcomes in MCL patients 65 years and older using the using the National Cancer Database (NCDB).

Methods: The NCDB aggregates about 70% of newly diagnosed cancer cases in the United States annually and was queried for diagnoses of MCL in patients ≥ 65 years. Patients were excluded if they had previous cancer diagnoses, only received single-agent chemotherapy, or died or were lost follow-up within 60 days of initiation of chemotherapy. The oldest patient to receive ASCT was 75 years, therefore we excluded non-transplant patients over that age to better match the groups. Overall survival (OS) was defined as months from diagnosis to death or last follow-up. Factors associated with increased use of

ASCT and OS were carried out by logistic regression and Cox proportional hazards models respectively. Kaplan-Meier curves were generated stratified by transplant status.

Results: 2264 patients with MCL who were 65-75 years at diagnosis were identified. 270 (11.9%) received ASCT at any time during their course. Median age was 70 years. Median follow-up for all patients was 65 months. In multivariable (MV) analysis, predictors of ASCT were found to be treatment at academic program (OR 3.69; $p < 0.01$), facility location (West > Midwest > South > NE; $p < 0.01$), resided in the area with higher education ($p = 0.01$), lower Charlson-Deyo score ($p = 0.03$), higher stage ($p = 0.01$), use of prednisone ($p < 0.01$), closer location to treatment center (OR 1.05; $p = 0.02$), and younger age at diagnosis (OR 0.77 with increasing age; $p < 0.01$). Patients who underwent ASCT had a median OS of 99 vs 56 months for patients who did not have ASCT ($p < 0.01$; Figure 1). Predictors of OS by MV analysis are listed in the Table.

Conclusions: Elderly patients who undergo ASCT for MCL have longer OS than those patients who do not. While the retrospective nature of database review and bias does influence interpretation, there is a 4.5-year increase in OS in patients who received ASCT. Predictors of use of ASCT include academic program, private insurance, higher socioeconomic status, and location close to a transplant center. Future

TABLE 1 Multivariable analysis of factors associated with OS

		HR	HR p-value	Type 3 p-value
Receipt of transplant		0.54	<0.01	<0.01
Location	NE	1.28	0.01	0.05
	South	1.1	0.22	
	Midwest	1.12	0.23	
	West	-	-	
Male sex		1.24	<0.01	<0.01
HS degree*	>20%	1.41	<0.01	<0.01
	13-20%	1.51	<0.01	
	7-12.9%	1.33	<0.01	
	<7%	-	-	
Charlson-Deyo score	2+	1.63	<0.01	<0.01
	1	1.42	<0.01	
	0	-	-	
Yr of dx	2004-2007	1.43	<0.01	<0.01
	2008-2009	1.18	0.16	
	20010-2011	1.13	0.32	
	2011-2013	-	-	
Stage	IV	1.46	0.01	0.01
	III	1.46	0.03	
	III	0.97	0.88	
	I	-	-	
Obs time*	0-15	2.1	<0.01	<0.01
	16-27	1.39	<0.01	
	28-42	1.2	0.047	
	43-771			
Age at dx		1.04	<0.01	<0.01

*HS degree = % of individuals in patients zip code without a high-school degree

*Obs time = Number of days between diagnosis and initiation of chemotherapy

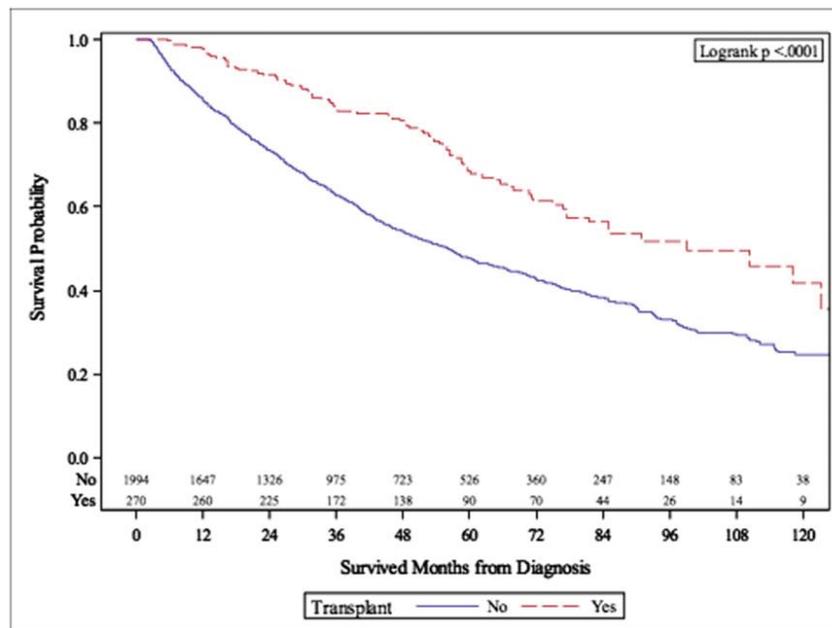


Figure 1 Association between ASCT and OS in elderly MCL patients.

efforts should aim to improve access to care for all patients with MCL so that they can be evaluated for all available effective therapies.

Keywords: autologous stem cell transplantation (ASCT); elderly; mantle cell lymphoma (MCL)

403 SHORT COURSE OF R-HYPERCVAD/MTX/ ARA-C FOLLOWED BY ASCT AS FIRST-LINE THERAPY IN MANTLE CELL LYMPHOMA PATIENTS PROLONGS PROGRESSION-FREE SURVIVAL TO MORE THAN 9 YEARS

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Introduction: Mantle cell lymphoma (MCL) is considered an incurable disease with an historical median OS around 3-4 years with short PFS periods. Regimens that include high-dose cytarabine and consolidation with autologous stem-cell transplant (ASCT) have become standard therapy for fit patients. The median PFS reported after 4-6 cycles HyperCVAD followed by ASCT consolidation is 4.5 years (Ahmadi et al., BMT 2012). Nevertheless, toxicity is high and many patients cannot obtain stem cells for transplant. In this setting, some groups use 6-8 cycles R-HyperCVAD without ASCT consolidation, achieving the same median PFS of 4.6 years (Romaguera et al., Br J Hematol 2010).

We present our experience treating fit patients with MCL in first line with a short course of 2 cycles of R-HyperCVAD followed by consolidation with ASCT.

Methods: From January 2002 to August 2016, all patients diagnosed with MCL treated in first line with a short course of 2 cycles of R-HyperCVAD and ASCT were included in this retrospective analysis. International working group response assessment criteria were used.

Results: 85 MCL patients were registered: 7(8.2%) did not receive immediate therapy, 44(52.4%) were not eligible for intensive therapy and 33 (39.3%) were treated with R-HyperCVAD. Characteristics at diagnosis of these 33 patients: M/F ratio: 26/7 (78.8%/21.2%), median age: 63(40-73) y.o, ECOG 0-1: 26(86.7%), Ann Arbor stage III-IV 28/31 (90.3%), MIPI score: low: 5(16.7%), intermediate: 17(56.7%) and high risk: 8(26.7%). Thirty (90.9%) patients completed 2 cycles of R-HyperCVAD. Discontinuation causes were: 2 deaths for sepsis and 1 CNS progression. Intention to treat response rate was: CR 26 (78.8%), PR 2, (6.0%), progressive disease 3 (9.0%) and not evaluable 2 (6.0%). Among the 28 patients in CR/PR considered eligible for ASCT consolidation, 8 patients were not transplanted: 4(14.3%) had harvest failure (no plerixafor availability), 2 persistent toxicity, 1 rejected, 1 unknown cause. Conditioning regimen was BEAM/LACE in 18 (90%) patients and cyclophosphamide-TBI in 2(10%). One patient died 10 days after infusion because of a septic episode. With a median follow-up of 35 (1-131) months, the median PFS was 73.0 (95% CI, 38.2-107.8) months (6.08 years) for the whole group, 114 (47.3-180.7) months (9.4 years) for the transplanted patients vs 21 (3.1-38.9) months (1.8 years) for the non-transplanted group. The median OS was 123 (31.9-214.1) months. Median OS was not reached for the transplanted group vs 31.0 (7.5-54.6) months for non-transplanted group.

Conclusion: A short course of R-HyperCVAD achieves a very high remission rate in fit MCL patients. Two thirds of the patients completed the planned therapy with ASCT consolidation. Those patients have an excellent outcome with a PFS of more than 9 years.

Keywords: autologous stem cell transplantation (ASCT); hyper-CVAD; mantle cell lymphoma (MCL)

404 IMPROVED OUTCOME FOR PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA (MCL) WHO STOP IBRUTINIB +/- RITUXIMAB FOR REASONS OTHER THAN PROGRESSION OF DISEASE

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Background: Ibrutinib produces a high rate of response in patients with previously treated mantle cell lymphoma (MCL). However, patients who discontinue therapy due to disease progression have a poor overall survival rate (OS; median 8.4 months). The outcome of patients who discontinue ibrutinib due to reasons other than progression has not been well described.

Methods: Retrospective review of single institutional patients who received ibrutinib with or without rituximab both on and off protocol for relapsed/refractory MCL.

Results: Between 2011 and 2017, 24 patients who received ibrutinib ± rituximab had their treatment discontinued for reasons other than progression after a median of 14 months of therapy (range 2-57 months), the most common reason being due to infection (see table), and have since been observed without therapy. After a median follow-up of 13 months from discontinuation of ibrutinib therapy, the median OS is 13 months and likely to improve, since 14 patients are still in CR/PR, with all of them alive except for one. Ten patients have relapsed/progressed and of these, 6 have died (4 from disease). The patients who have not progressed had a mean duration of ibrutinib ± rituximab treatment of 22 months compared to 13 months

for those who progressed. Among the 10 patients with progressive disease, the median time to progression was 11 months. Patients who received ibrutinib alone had more frequency of relapse (8/15) than patients who received ibrutinib with rituximab (2/9).

Conclusion: Patients who discontinue ibrutinib while responding have better outcomes than patients who discontinue ibrutinib due to disease progression. A longer duration of ibrutinib therapy appears to prolong response duration. Further exploration of outcomes and correlation with pre-treatment variables will be explored and presented at the symposium.

Reasons for Discontinuation of Therapy

Keywords: ibrutinib; mantle cell lymphoma (MCL); rituximab

INDOLENT LYMPHOMA

405 PROGRESSION-FREE SURVIVAL SHORTENS AFTER EACH RELAPSE IN PATIENTS WITH FOLLICULAR LYMPHOMA TREATED IN THE RITUXIMAB ERA

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Introduction: Follicular lymphoma (FL) is an indolent lymphoma characterized by long survival but with frequent relapses. Before the use

TABLE 1

Ibrutinib	Ibrutinib and rituximab
Bruising/thrombocytopenia	Atrial fibrillation
Diarrhea	Atrial fibrillation
Yeast infection	Bleeding
Pneumonia	Bleeding
Pneumonia	Diarrhea
Pneumonia	Infection (liver lesions)
Sinusitis	Colitis
Septic arthritis	Pneumonia
Mouth sores	Secondary cancer (esophageal)
Pneumonia	
Pneumonia	
Secondary cancer (lung)	
Secondary cancer (lung)	
Travel issues	
Travel issues	

TABLE 1

Phase of disease	N	5-year PFS	10-year OS	10-year relative OS*
First line	349	59.0%	72.7%	83.2%
Second line	124	36.0%	46.6%	55.1%
Third line	51	25.8%	16.3%	21.1%

of rituximab, the clinical course of these patients showed an increasingly shorter duration of response after each relapse. Few studies have analyzed the pattern of relapses in patients treated with rituximab. In this study, we have analyzed if this pattern of shortened responses is observed in patients receiving rituximab.

Methods: From 570 patients consecutive diagnosed with FL in 2 institutions between 2001 and 2014, we selected 349 patients (median age, 58 years; F/M 188/161; grade 1 74/297, grade 2 155/297, grade 3a 68/297) who had criteria for treatment and received chemoimmunotherapy. Patients with a diffuse large B-cell lymphoma component, histological grade 3b and primary cutaneous or duodenal FL were not included. The pattern of relapses and the duration of response after each treatment were analyzed.

Results: 219 patients received R-CHOP, 87 R-CVP, 32 R-FCM and 11 other treatments. The overall response rate was 97%, with 252 patients achieving CR and 85 PR. After a median follow-up of 6.5 years (range, 0.22-14.5), 124 patients (36%) eventually relapsed/progressed with a 5-year PFS of 63% (95% CI, 58-69%). Among these cases, 73 patients had no further relapse, 36 a second relapse and 15 a third or further relapse. The median PFS was 10.1 years (95% CI, 7.3-12.8) after initial treatment, 2.4 years (95% CI, 1.2-3.7) after second-line treatment and 1.8 years (95% CI, 1.2-2.4) after third-line (Figure). Median PFS after first-line treatment was significantly longer in patients who achieved CR compared to those in PR (not reached vs 3 years; $p < 0.001$) and in those who received rituximab maintenance (not reached vs 7.1 years for maintenance vs observation, respectively; $p = 0.001$). PFS after second line treatment was not significantly impacted by the duration of first relapse (≤ 2 vs > 2 years), the use of maintenance in first-line treatment, or intensification with ASCT. The 10-year OS of the series was 72.7% (95% CI, 66.3-79.2%). Median

OS in first, second and third line of treatment was not reached, 7.6 and 2.6 years, respectively. As detailed in the table, relative OS with respect to the Spanish general population showed a decrease in life expectancy of 17%, 45% and 79% at first, second and third phase of the disease.

Conclusions: Duration of response still shortens after each relapse in patients with FL treated in first line with rituximab combinations.

Keywords: follicular lymphoma (FL); rituximab

406 RADIOIMMUNOTHERAPY FOR FOLLICULAR LYMPHOMA ACHIEVES EXCELLENT LYMPHOMA CONTROL IN FIRST LINE AND RELAPSE: 8-YEAR FOLLOW-UP DATA OF 281 PATIENTS FROM THE INTERNATIONAL RIT-REGISTRY

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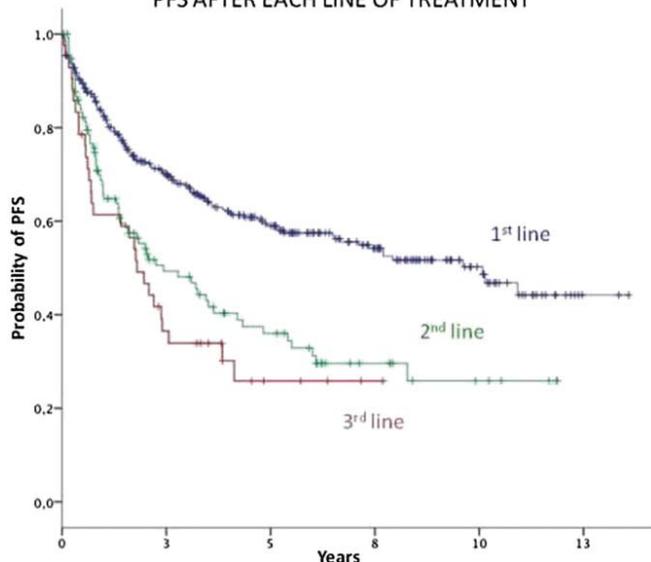
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Introduction: Radioimmunotherapy (RIT) in follicular lymphoma (FL) has successfully been evaluated in several clinical trials for first-line treatment, consolidation after salvage therapy and as part of high dose conditioning regimens in autologous stem cell transplantation. To assess the efficacy of RIT in daily clinical practice, data on 1105 lymphoma patients, treated with RIT between December 2006 and November 2009, were collected in an international, web-based RIT network (RIT-NT). Here we present long-term follow-up results of FL patients treated with RIT and documented in the RIT-NT.

Methods: All centres participating in the international RIT-NT with registered follicular lymphoma pts. contributed to the long-term follow-up.

Results: 479 out of the 1105 lymphoma patients registered in the RIT-NT suffered from FL. Data from 281 pts. (59%) with FL are available for follow-up with a median follow-up time of 8.2 years after RIT. Median age was 58 years. 52.3% of the patients were female and

PFS AFTER EACH LINE OF TREATMENT



47.7% were male. 58.4% had stage IV, 25.4% stage III, 10.3% stage II and 4.9% stage I disease. RIT was given as first-line therapy (primary treatment and consolidation) in 18.5% of pts., and for relapse (recurrence, chemo-refractory, conditioning) in 81.5% of pts. In the first-line group, 76.9% achieved a CR, 9.2% a PR, 1.9% a SD and 1.9% had progressive disease. For patients treated in relapse, CR rate was 48.5%, PR 16.6%, SD 2.6%, and 10.5% had PD. Median PFS for all pts. was 2.54 years, median OS was not reached. Median PFS (not reached) and OS (not reached) was significantly better for pts. treated with RIT in first line, compared to pts. who received RIT in relapse (median PFS 2.11 years and OS 10.8 years; $p = 0.0037$ and $p = 0.0021$ respectively). 8 year PFS was 33.9% for all pts., 53.6% for first line and 29.6% for relapsed pts. 8-yr-OS for all pts. was 58.8%, 78.1% for first and 54.5% for relapsed pts. Of the 281 pts, 35 (12.5%) pts. developed a secondary malignancy and 16 (5.7%) experienced transformation of FL to aggressive lymphoma. Secondary malignancies were: MDS 3 pts., AML 5 pts., NHL 4 pts. The remaining 23 pts. developed solid tumors incl. 4 with basal cell cancer.

Conclusion: Radioimmunotherapy is a safe and effective therapy option for treatment naïve and relapsed follicular lymphoma with an 8 year PFS of 53.6% and 29.6%, respectively. Incidence of MDS and AML (2.8% after a median follow-up of 8 years) was not increased as compared FL patients treated without RIT. RIT remains a very safe and effective chemo-free treatment for FL.

Keywords: follicular lymphoma (FL); radioimmunotherapy (RIT)

407 BEYOND RITUXIMAB MAINTENANCE. RELAPSING FOLLICULAR LYMPHOMA DURING OR AFTER END OF RITUXIMAB MAINTENANCE: ANALYSIS OF CZECH LYMPHOMA STUDY GROUP (CLSG) DATABASE

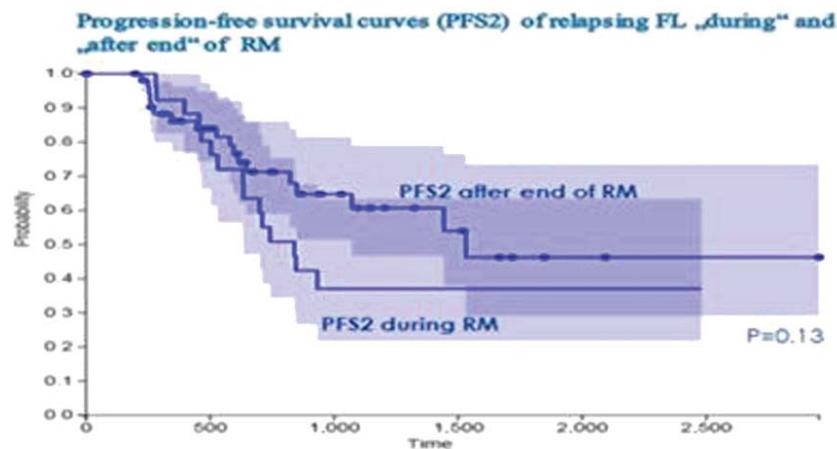
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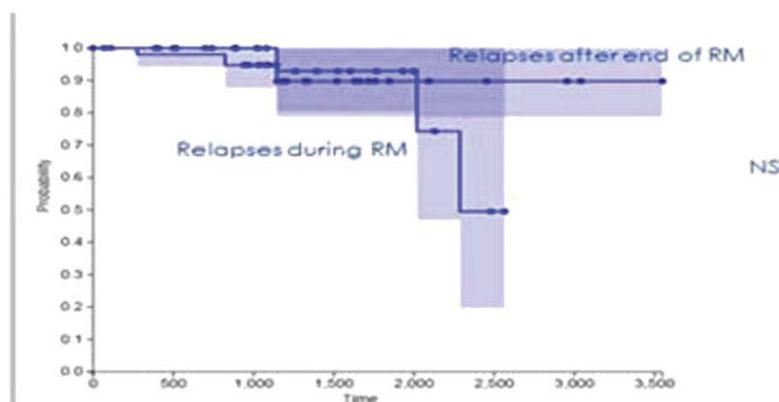
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Overall survival curves of relapsing FL „during“ and „after end“ of RM



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Introduction: Rituximab maintenance (RM) improves progression-free survival (PFS) in advanced indolent follicular lymphoma (FL). Despite this fact, some proportion of patients relapse during or after RM. This cohort is not well described and its outcome and prognosis are unknown.

Methods: Between 01/2002 and 12/2012, 1456 patients with initially diagnosed FL grade 1-3A were registered in the prospectively maintained multicentric CLSG database. For the analysis, relapsed FLs during (at least one dose given) or after end of RM and initially treated with R-CHOP induction were selected.

Results: There were 519 patients treated with RM in first line, 117 pts relapsed during maintenance or after the last dose, and 88 cases of them received RCHOP induction. Global 5-year PFS was in RCHOP/RM arm about 74%. For 88 relapsed pts, median of administered RM doses was 8 (1-29), and median duration of maintenance was 1.67 (0-2.1) yr. At the time of relapse, median of age was 62 ys, and 9/88 (10%) pts transformed into FL3B or DLBCL. Generally, at relapse there were observed less advanced lymphomas compared to initial FL diagnoses. Clinical stage I or II had 32/88 vs 3/88 ($p < .001$) pts, B-symptoms developed 14 vs 28 ($p < .02$) of them, bone marrow involvement was present in 13 vs 61 ($p < .001$) cases, elevated LDH was in 14 vs 42 ($p = .013$), and bulky disease >7.5 cm was in 13 vs 35 patients ($p < .01$). Twenty-nine (33%) relapses occurred during RM with median 4 (1-9) doses given; 6 pts relapsed within 6 months since the end of RCHOP (double refractory patients).

Totally, 13/88 (15%) relapsed pts remain without any therapy, whereas 75 (85%) received systemic treatment including 24 (27%) cases consolidated with autologous (ASCT) and 1 case with allogeneic stem cell transplantations. Rituximab alone or in combination was given to 59/88 (67%) patients. There were differences in subsequent therapy between cohort progressed "during RM" and arm relapsing "after end of RM." Patients relapsed "during RM" were more often treated with platinum-based regimens (59% vs 25%; $p = .005$), and consolidated more with ASCT (48% vs 17%; $p = .014$).

From the relapse, OS in 5 yrs was about 90% and 5-yr PFS was 43%. There were no significant differences between cohort relapsing "during RM" or "after RM" in overall survival. However, PFS showed some trend to be better in "after RM" arm ($p = .13$).

Conclusion: At the time of first relapse during or after RM, patients showed significantly less advanced FL compared to initial diagnosis, and some proportion does not require any therapy. Long-term survivals (OS, PFS) were generally well. Significantly more intensive therapy was used in patients progressed "during RM," which could positively impact survival parameters.

Keywords: follicular lymphoma (FL); R-CHOP; rituximab

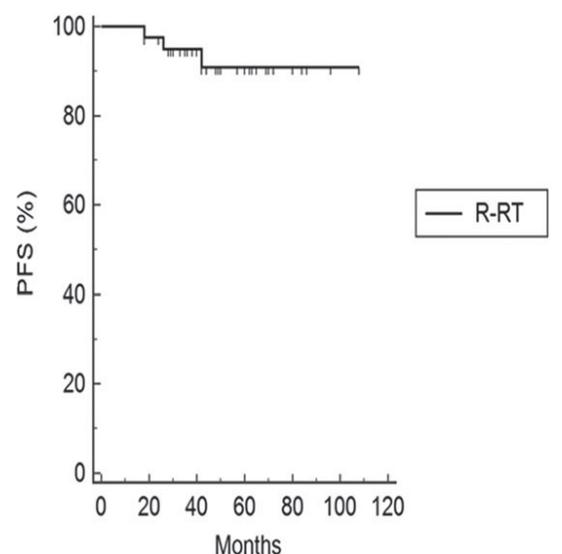
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Introduction: Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin lymphoma; early stage disease can be cured in a significant proportion of cases with involved-field radiotherapy (IF-RT) alone; however, nearly 50% of the patients will ultimately relapse, the majority with lymphoma recurring in non-irradiated areas, with a 5-year local PFS of 80%. A combined association of RT with chemotherapy could increase treatment efficacy, but early and late toxic effects could be unacceptable. In vitro synergistic effect between R and RT has been observed, but clinical data that correlate potential benefit of this association in FL patients are limited.

Methods: In this multicenter study, we retrospectively analyzed a cohort of 41 consecutive, early stage, newly diagnosed FL patients referring to Hematology Divisions of Siena and Florence University Hospitals from 2007 to 2014 receiving rituximab (R) and IF-RT as first-line treatment. Diagnosis was made according to WHO classification; R 375 mg/m² was administered weekly for a total of 4 courses, before or after IF-RT. Primary outcome was PFS; secondary end points were CR rate, OS, and safety.

Results: Median age was 63 years (range 23-88), male/female distribution was 19:22. Among them, 35/41 patients (80.5%) were diagnosed with stage IA and 6/41 (19.5%) with stage IIA FL; none had B symptoms, and only 1 patient presented with bulky disease. Beta2 microglobulin was above upper limit in 11/41 patients (26.8%); ECOG performance status was 0-1 in all cases. According to FLIPI2 index, 18/41 patients (44%) presented low risk, 22/41 patients (54%) presented intermediate risk, while the remaining patient was high risk.



408 RADIOTHERAPY PLUS RITUXIMAB AS FIRST-LINE REGIMEN FOR LOCALIZED FOLLICULAR LYMPHOMA

IF-RT was administered with a median dose of 24 Gy (range 20-44 Gy). Bone marrow PCR-BCL2 was positive in 3/41 patients (7%). All patients achieved CR; after a median follow-up of 46 months (range 18-108), all patients remain alive, with only 3 patients relapsing after 18, 26, and 42 months, respectively. Estimated 5-year PFS is 90% with a median PFS not reached (Figure 1). Interestingly, 2 patients experienced contralateral relapse in the irradiated area. No hematological toxicity was reported after R administration, and infusional reaction was mild and manageable. After RT, only transient grade 1-2 mucositis and skin rash were observed.

Conclusions: In this study, we suggest R in association with IF-RT could represent a suitable first-line treatment option for early stage FL patients, with higher efficacy and no additional toxicity compared to available published data about RT alone. These promising results need to be confirmed in prospective studies, but could pay the way towards an increasing chance of disease eradication.

Keywords: follicular lymphoma (FL); rituximab

409 RETROSPECTIVE ANALYSIS ON R-DHAP/ OX AND ASCT AS SALVAGE TREATMENT FOR RELAPSED/REFRACTORY HIGH-RISK FOLLICULAR LYMPHOMA

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Introduction: Follicular lymphoma (FL) relapsing within the first 2 years from frontline chemo-immunotherapy is associated with a median overall survival of 5 years from the time of progression, and optimal subsequent treatment remains uncertain. Rituximab, dexamethasone,

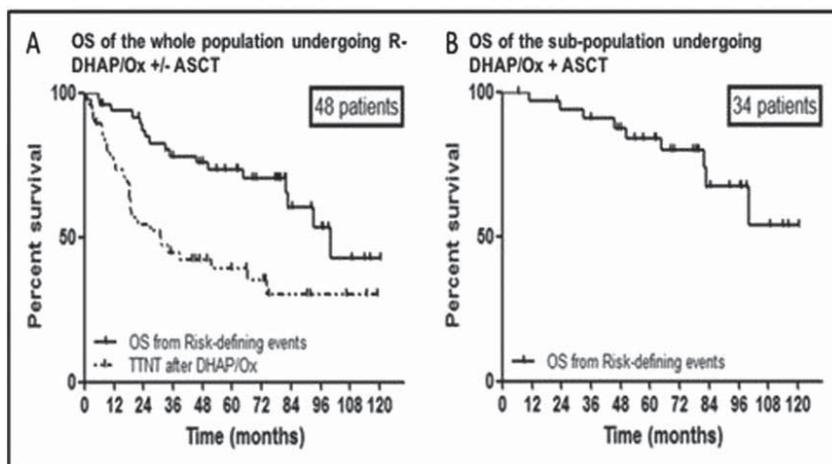
high-dose cytarabine, and cisplatin/oxaliplatin (R-DHAP/Ox), followed by autologous stem cell transplant (ASCT), could be a reasonable option because it has shown efficacy in diffuse large B-cell lymphoma with germinal center subtype.

Methods: We retrospectively analyzed patients with FL relapsing within 2 years after first-line chemo-immunotherapy who received subsequent R-DHAP/Ox. Exclusion criteria were histologic grade 3B and transformation to DLBCL before R-DHAP/Ox. Overall survival (OS) was calculated from risk-defining events as described in the LymphoCare study (Casulo et al. JCO 2015). Time to next therapy (TTNT) was calculated from the end of one line of therapy to start of the subsequent therapy. Survival end points were estimated with the Kaplan-Meier method.

Results: Data from 67 patients were collected, from 3 Italian institutions; 48 patients were eligible. Characteristics of the population are summarized in the table. First-line therapy was R-CHOP in 37 (77%), R-fludarabine-mitoxantrone in 4 (8.3%), R-CVP in 2 (4.1%), R-bendamustine in 2 (4.1%), R-FND, R-chlorambucil, and R-HDS (HD sequential of etoposide, cyclophosphamide, mitoxantrone,

TABLE 1

Characteristic	LymphoCare patients Early POD (n = 110)		Italian patients Early POD (n = 48)	
	No.	%	No.	%
Age, y				
Median		58		52
Range		31-88		29-72
Sex				
Female	38	35	16	34
Male	72	65	32	66
Histologic grade				
1 or 2	63	66	39	81
3a	33	34	9	19
Missing		14		0
FLIPI score				
Low, 0 to 1	10	12	8	16
Intermediate, 2	29	34	15	32
High, 3 to 5	47	54	24	52
Missing		24		1



melphalan + ASCT) in 1 (2.1%). Thirty-four 34 (70.8%) patients underwent 1 line of therapy prior to R-DHAP/Ox, 11 (22.9%) underwent 2 lines of therapy, and 3 (6.3%) had 3 or more lines before R-DHAP/Ox. The median TTNT from first-line was 14.3 months (range 10.6-19.4).

With a median follow-up of 66 months, the 5-year OS was 73.1% (95% CI, 61-85%). Among the 34 patients that underwent ASCT, the 5-year OS was 84% (95% CI, 72-98%). Time to next treatment (TTNT) after DHAP/Ox was 30.9 months (95% CI, 18-47%). Stem cell collection failure was reported in 6 cases (12.5%). Four cases (8.3%) of transformation to DLBCL and 3 (6.2%) secondary malignancies (2 myeloid disorders, 1 bladder carcinoma) were reported.

Conclusions: In this population of high-risk, early relapsing FL, R-DHAP/Ox +/- ASCT was found to be active, with a TTNT significantly longer than that experienced following first-line therapy. This population had very similar FLIPI risk scores compared to the LymphoCare study population but appears to have experienced better survival outcomes. Late events continue to occur, and cure appears unlikely. Prospective studies of R-DHAP/Ox +/- ASCT are warranted in this high-risk FL population.

Keywords: autologous stem cell transplantation (ASCT); DHAP; follicular lymphoma (FL)

410 PROLONGED MOLECULAR AND CLINICAL REMISSIONS IN FOLLICULAR LYMPHOMA PATIENTS TREATED WITH HDT/ASCT AND COMBINATION IMMUNOTHERAPY WITH RITUXIMAB AND INTERFERON α

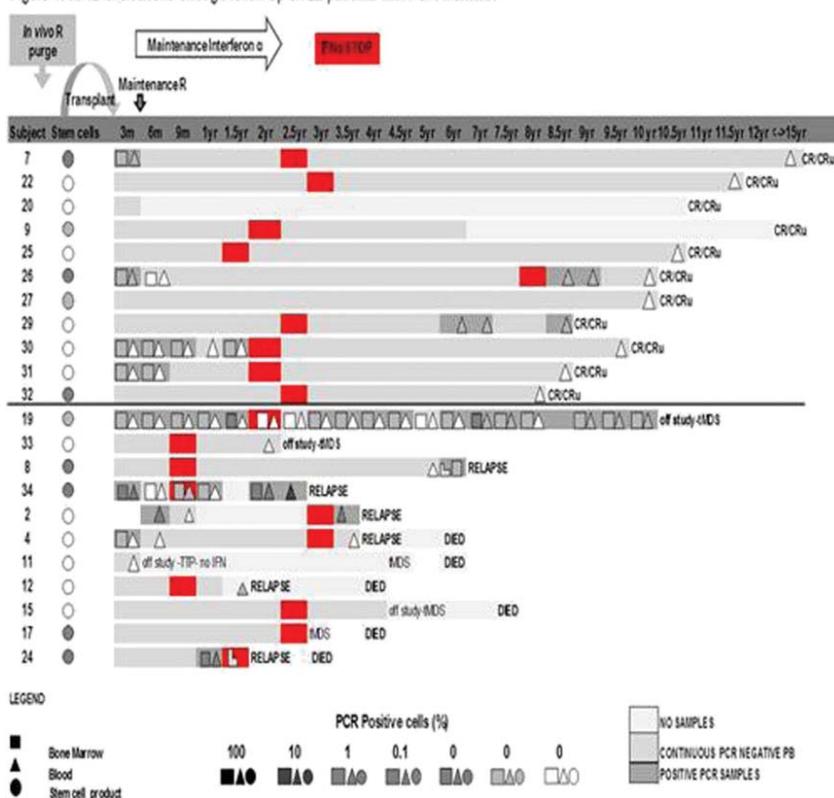
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Introduction: Follicular lymphoma is an indolent disease with a relapsing remitting course and shorter remission periods with each successive treatment. The median PFS and OS for patients who relapse within 12 m of prior therapy are 13 m and 60 m, respectively. Strategies to improve outcome including combining autologous stem cell transplant (ASCT) with effective immunotherapies such as rituximab (R) and/or interferon α (IFN α) could be considered. Detailed long-term data, including impact of minimal residual disease (MRD) status on PFS, are lacking for combination approaches such as this. We present long-term follow-up of a median 10 y of PFS and MRD on a cohort of 30 patients who received ASCT followed by maintenance R-IFN α .

Methods: Patients in 1st or 2nd relapse were enrolled in this prospective study. Salvage included CHOP or DHAP with 3 weekly infusions of R prior to stem cell harvest as an "in vivo purge". Patients then received high-dose therapy with cyclophosphamide, BCNU and etoposide followed by ASCT. IFN α began at 3-m post ASCT for 2 y with 6 weekly infusions of R from week 14. Response assessment included clinical, radiographic, and MRD assessments of bone marrow (BM) and peripheral blood (PB). Real-time quantitative PCR was used to evaluate MRD on the apheresis product and on BM and PB Q3m

Figure 1. MRD evaluations through follow-up on 22 patients with PCR markers.



post ASCT for 1 y and Q6m from then on. An extended follow-up study included MRD assessment on patients who remained in CR.

Results: From July 2000 to September 2009, 36 patients were enrolled with a mean age of 47 y (30–66 y). Sixty-seven percent of patients had stage IV disease, 50% had a FLIPI score of 3 or 4, and the median time from previous chemotherapy to enrolment was 12.8 m. Six patients were not transplanted.

The median follow-up was 124 m (range 23–194 m), the 10-y OS and EFS was 69% and 40%, respectively, in the ITT population, and 50% and 56% in the SCT group. There was evidence of plateau at 100-m post ASCT. Seven transplanted patients died: 4 from progressive disease and 3 from secondary malignancies.

Of the 30 transplanted, there were PCR markers for 22 (73%). Although 10/22 (45%) stem cell collections were MRD+, PFS was not significantly different from patients transplanted with MRD– grafts. Clinical and molecular remission in PB was achieved after R-IFN in 5 of 7 patients who were MRD positive in the BM at 3-m post ASCT. Both of these results suggest that R-IFN may be effective in eradicating MRD post ASCT. There appears to be good correlation between MRD assessment on PB and clinical response/relapse (Figure 1).

Fifteen patients reached 100-m EFS, and of these, 9 PCR evaluable patients were also in molecular remission. Uni- and multi-variate analyses were performed.

Conclusion: This prospective study demonstrates promising clinical and molecular outcomes in patients with FL treated with R-purging followed by R-IFN post ASCT. Correlation is demonstrated between prolonged clinical remission and MRD negativity in PB.

Keywords: autologous stem cell transplantation (ASCT); follicular lymphoma (FL); minimal residual disease (MRD).

411 AN INTERNATIONAL COMPARISON OF THE EFFICACY, COST AND MYELOTOXICITY OF FIRST-LINE THERAPY FOR ADVANCED FOLLICULAR NON-HODGKIN LYMPHOMA

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Introduction: All 6 principal published clinical trials of rituximab-related induction chemo-immunotherapy of advanced follicular lymphoma have been reviewed. This study details the efficacy, cost, duration and toxicity of each regimen and compares these parameters with our own long-term experience of iodine-131-rituximab radioimmunotherapy (¹³¹I-RIT). Given the long natural history of the disease and durable response, progression free survival (PFS) and time-to-next-treatment (TTNT) were taken to be the major indices of efficacy.

Methods: Trials were selected based upon their analysis of rituximab-related induction regimens. Studies included were Hiddemann et al. 2005 publication of the GLSG experience, Rummel et al. 2013 publication of the *Stil* experience, Federico et al. 2013 FOLLO5 experience, Flinn et al. 2014 *BRIGHT* study, Fowler et al. 2014 *MD Anderson* experience and Marcus et al. 2016 update on the *phase III GALLIUM* study. Comparison was made with the updated McQuillan et al. 2014 *phase II INITIAL* study of first-line ¹³¹I-RIT. Patient demographics, duration of follow-up, cost of induction (for a BSA of 1.75m², based on the combined drug cost as per the Australian Pharmaceutical Benefit Scheme), duration of induction, outcomes (ORR, PFS, TTNT), myelotoxicity and incidence of secondary malignancies are reported. Where PFS/TTNT were not specified by histologic subtype, estimates reported are based upon analysis of the relevant published survival curves where available. In the event of similar outcomes, superior efficacy was assigned to the trial with a longer duration of follow-up.

Results: Similar patients demographics were noted across all trials. With respect to efficacy, ¹³¹I-RIT demonstrated superior ORR with a high CR rate. Taking into account the lengthy follow up duration (>10-years), time-dependent efficacy outcomes of PFS and TTNT were also superior for ¹³¹I-RIT. Median 5-yr TTNT was reached at 42 months with R-CHOP and is yet to be reached with other combinations. ¹³¹I-RIT was considerably more affordable than the other regimens as a result of only requiring 4 standard therapy doses of rituximab total.

	McQuillan et al.	Marcus et al.		Hiddemann et al.	Federico et al.	Rummel et al.		Flinn et al.		Fowler et al.
	Australia	International		Germany	Italy	Germany		International		USA
Induction	Iodine-131 + R	O + Chemo	R + Chemo	R-CHOP x6-8	R x6-CHOP x6	BR x6	R-CHOP x6	BR x6-8	R-CHOP/R-CHOP (x6-8)	RI x12
Min. cost of induction	€ 8,892.07	€ 22,702.50	€ 13,612.92	€ 13,612.92	€ 13,612.92	€ 26,024.70	€ 13,612.92	€ 26,024.70	€ 13,612.92	€ 75,271.44
ORR	98.5%	88.5%	85.9%	96%	93%	93%	91%	>99%	94%	98%
CR	88%	19.5%	23.8%	20%	72%	40%	30%	30%	25%	87%
PR	20%	69.2%	63.2%	77%	20%	53%	62%	69%	69%	12%
PFS	76.4% (10-yr)	80% (3-yr)	73.3% (3-yr)	78% (3-yr)	68% (3-yr)	60% (5-yr)	40% (5-yr)	Not reported	Not reported	78.5% (3-yr)
Median PFS (months)	Not reached	Not reached	Not reached	Not reached	Not reached	Not reached	41	Not reported	Not reported	Not reached
Next treatment	13% (10-yr)	13% (3-yr)	13% (3-yr)	Not reported	Not reported	27% (5-yr)	42% (5-yr)	Not reported	Not reported	Not reported
Median TTNT (months)	Not reached	Not reached	Not reached	Not reported	Not reported	Not reached	42.3	Not reported	Not reported	Not reported
Neutropenia (3/4)	21%	43.9%	37.9%	63%*	50%	20%*	69%*	44%*	70%*	35% [†]
Thrombocytopenia (3/4)	8.8%	6.0%	2.7%	Not reported	3%	5%*	6%*	7.2%*	6.5%*	4% [†]
Secondary Malignancy	4%	4.7%	2.7%	Not reported	3%	8%*	9%*	Not reported	Not reported	4.5% [†]
MDS/AI (n=)	0	Not reported	Not reported	Not reported	0	1	1	Not reported	Not reported	0

R: rituximab; O: obinutuzumab; B: bendamustine; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP: cyclophosphamide, vincristine and prednisolone; L: lenalidomide

Results are presented in order of efficacy from left to right

Table 1: Comparison of induction therapies for FL.

With respect to myelotoxicity, ^{131}I -RIT had the lowest incidence of grade 3/4 neutropenia and, conversely, the highest incidence of grade 3/4 thrombocytopenia. The lowest incidence of thrombocytopenia was observed with RCHOP and was consistent across trials. MDS/AL was reported at 5-yr follow up in a single study; 1 MDS in a patient-receiving BR and 1 AL in a patient-receiving RCHOP. This study also reported the highest incidence of second malignancy 8% and 9% with respect to BR and RCHOP.

Conclusion: Based upon 10-year follow-up, iodine-131-rituximab radioimmunotherapy is apparently on this analysis the most efficacious, most affordable and most practical of all published induction therapies for advanced follicular lymphoma.

Keywords: 131-iodine; follicular lymphoma (FL); induction treatment.

412 CLINICAL CHARACTERISTICS AND PROGNOSIS OF ELDERLY (>70 YEARS) FOLLICULAR LYMPHOMA IN THE RITUXIMAB ERA: MULTICENTRE RETROSPECTIVE ANALYSIS OF THE GELTAMO SPANISH GROUP

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Introduction: Follicular lymphoma (FL) is the most common indolent lymphoma, with a median age at diagnosis of 60 years. Although more than 25% of cases are patients over 70 years, there are no standardized strategies for this group of patients with greater fragility and comorbidity, and very little information regarding the disease characteristics and its prognosis is available. The aim of the present study is to analyse the clinical characteristics, treatment and outcomes in FL patients >70 years in a large retrospective series.

Patients and Methods: A total of 1822 patients (grade 1, 2, and 3A) diagnosed of FL between 2000 and 2012 from 19 Spanish centres from GELTAMO group were included in the study. From them, 453 (25%) had >70 years at diagnosis.

Results: Median follow-up was 6 years. There were higher frequency of female patients (60% vs. 52%, $p < 0.001$), 3A histology (23% vs. 16%, $p = 0.003$), elevated $\beta 2$ microglobulin (51% vs. 28%, $p < 0.001$), and high-risk FLIPI (49% vs. 26%, $p < 0.001$) in FL >70 years. According to treatment, patients >70 years were more commonly in watch and wait strategy (13% vs. 7%) or received palliative treatment (9% vs. 1%, $p < 0.001$) as compared to <70 years group. In those receiving curative treatment, a higher use of Adriamycin (41% vs. 64%,

TABLE 1 Basal characteristics according to age at diagnosis.

Variable	<70 years n = 1369 (75%)	≥70 years n = 453 (25%)	P value
Sex female	708 (52%)	274 (60%)	<0.001
Histological grade			0.003
1-2	1029 (84%)	292 (77%)	
3A	198 (16%)	85 (23%)	
Ann Arbor			NS
I-II	306 (23%)	112 (25%)	
III	253 (19%)	77 (17%)	
IV	792 (59%)	254 (57%)	
FLIPI			<0.001
0-1 (low risk)	479 (40%)	79 (19%)	
2 (intermediate risk)	412 (34%)	131 (32%)	
3-5 (high risk)	318 (26%)	199 (49%)	
B2-microglobulin elevated	322 (28%)	193 (51%)	<0.001
First-line strategy			<0.001
Watch & Wait	96 (7%)	57 (13%)	
Palliative	8 (1%)	39 (9%)	
Curative intention	1259 (92%)	357 (79%)	
With rituximab	1016 (80%)	297 (74%)	NS
With Adriamycin	822 (64%)	162 (41%)	<0.001
With Fludarabine	252 (20%)	19 (5%)	<0.001
Response to first line			<0.001
CR	995 (79%)	250 (64%)	
PR	221 (17%)	89 (23%)	
No response / PGR	48 (4%)	51 (13%)	
Transformation	89 (7%)	26 (6%)	NS

$p < 0.001$) and fludarabine (5% vs. 20%, $p < 0.001$) was observed in <70 years. However, when R-CHOP efficacy was analysed, the response rate was similar in both groups (77% vs. 78%, $p = \text{NS}$). Furthermore, although the 5-year (70% vs. 90%, $p < 0.001$) and 10-year (49% vs. 81%, $p < 0.001$) overall survival was significantly shorter in >70 years, the mortality due to lymphoma was similar in both groups (73% vs. 61%, $p = \text{NS}$).

Conclusions/Comments: FL patients >70 years old show unfavourable clinical characteristics at diagnosis and receive a different treatment than FL <70 years, probably due to a higher fragility. However, since the efficacy of standard treatment seems similar independently of age, the inclusion at diagnosis of comorbidity indexes (i.e. CIRS-G) is required to allow the identification of those cases subsidiary to receive standard treatment.

Keywords: elderly; follicular lymphoma (FL).

413 ASSESSMENT INDEX OF CLINICAL TRANSFORMATION FROM FOLLICULAR LYMPHOMA (FL) TO DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) IN THE RITUXIMAB ERA

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TABLE 1

Risk factors	Regression Coefficients	Odds ratio (95% CI)	P-value	Scores
Rapid nodal growth	2.3419	10.4 (2.24-48.3)	0.003	1
Bulky ≥ 6 cm	2.4996	12.2 (1.45-102)	0.021	1
Hgb < 12 g/dL	2.1521	8.6 (1.69-43.9)	0.010	1
LDH > normal upper limit	2.3567	10.6 (2.4-46.4)	0.002	1
Assessment index	All pts (n = 76)	FL (n = 42)	HT (n = 34)	Percentages of HT (%)
0	23	22	1	4
1	24	17	7	29
2	14	3	11	79
3	12	0	12	100
4	3	0	3	100

Introduction: Histological transformation (HT) remains a critical event because the prognosis of FL with HT is poorer than that of FL without HT even in the rituximab era. The diagnosis of HT by biopsy is the gold standard diagnostic approach. However, it is not always possible to obtain a biopsy such as when disease progression is in an inaccessible area. Indeed, more than half of the diagnoses of HT are based on clinical criteria without histological confirmation according to doctor's discretion in several previous reports. Hence, estimates of the true incidence of HT have wavered partly because the reliable definition of clinical transformation has never been established. To propose a new assessment index of clinical transformation that is easy to use in both daily practice and clinical trials in the rituximab era, we conducted this retrospective analysis.

Methods: We retrospectively analyzed patients (pts) who were initially diagnosed with FL and underwent biopsy at the time of disease progression at our institution between 2000 and 2016 and constructed an assessment index based on clinical covariates obtained by a multivariate logistic regression model.

Results: In total, 459 pts were diagnosed as having FL (grade 1–3a) with a median follow-up duration of 9 (range, 0.7–16) years. Disease progression was observed in 184 pts, and 80 pts (43%) had histological documentation (FL in 42, HT with DLBCL in 34, HT other than DLBCL in 4). Finally, we identified 76 pts with biopsy-proven FL or HT with DLBCL as subjects of this analysis. HT occurred at a median of 5.5 (range, 0.2–16) years from initial FL diagnosis, and the 5-year overall survival rate from HT was 62%. In the multivariate analysis, rapid nodal growth, bulky disease ≥ 6 cm, elevated serum lactate dehydrogenase (LDH) level and serum hemoglobin (Hgb) level <12 g/dL were identified as the risk factors of HT. The weights of variables were decided based on the regression coefficients, and we derived the final assessment index consisting of the above four factors (score of 1 each). The percentages of HT were as follows: score 0, 4%; score 1, 29%; score 2, 79%; score 3, 100%; and score 4, 100%, respectively (Table 1).

Conclusions: Although further investigation, especially a validation study with a large number of pts, is needed to confirm our results, this new assessment index of clinical transformation is likely to be a simple and valuable tool for the diagnosis of HT, especially for patients on whom it is difficult to perform a biopsy.

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

414 RISK OF SECONDARY HEMATOLOGICAL MALIGNANCY IN PATIENTS WITH FOLLICULAR LYMPHOMA

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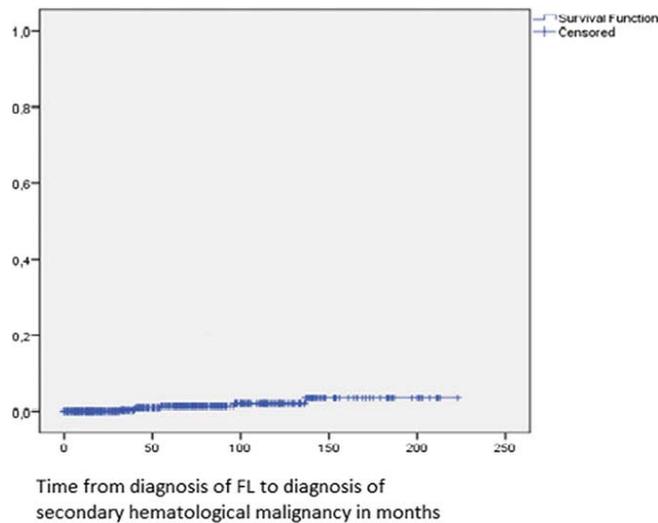
Introduction: Follicular lymphoma (FL) is the most common indolent lymphoma. Most of the patients with FL respond to first-line treatment. Relapses are common, and many patients need to be re-treated. There has been major improvement in treatment of indolent non-Hodgkin lymphomas in last 10 years. This is the result of the use of therapeutic antibodies such as rituximab. With improved survival patients have potentially more time to develop secondary malignancies.

Secondary malignancies are important causes of morbidity and mortality in patients with indolent lymphomas. Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are important subsets of secondary malignancies. Incidence of secondary hematological malignancies among different lymphomas is largely unknown.

We collected data of patients with FL to find out the incidence of secondary hematological malignancies. We also wanted to know if the incidence is related to certain types of treatment or chemotherapy regimens.

Methods: This is a retrospective registry study. Clinical data were collected from three hospitals in Finland and from one hospital in Spain. We analyzed clinical data from hospital records of all patients with FL diagnosed between 1997 and 2016. A total of 492 patients were included in this study. Information such as age, stage, details of treatment, possible relapses, current status and details about secondary hematological malignancy was investigated.

Results: Median follow-up time was 6.2 years. Mean age at the time of diagnosis was 59 (17–88) and half (50.2%) were women. Altogether



86% of patients received treatment for lymphoma; 1-year PFS was 89.2% and 5-year PFS 58.3%; 5-year DSS was 90.5% and 5-year OS 81.9%.

Six patients (1.2%) developed secondary hematological malignancy. There were 3 cases of MDS, 2 cases of AML and 1 case of acute lymphoblastic leukemia; 5-year risk for secondary hematological malignancy was 1.3%.

In patients treated with stem-cell transplantation (SCT), the risk of secondary hematological malignancy was 6.5% compared to only 0.8% ($P = ns$) in patients treated without SCT. In patients treated with fludarabine, the risk of secondary hematological malignancy was 5.6%, and correspondingly, the risk was 0.8% ($P = ns$) in patients treated without fludarabine. In patients treated with anthracyclines the risk of secondary hematological malignancy was 1.8% and in patients treated without anthracyclines the risk was 0% ($P = ns$).

Conclusions: With current treatment, the prognosis of follicular lymphoma is relatively good. Risk of secondary hematological malignancy is low if anthracyclines, fludarabine or SCT isn't used in the treatment. Especially, SCT is associated with higher risk for secondary malignancies. When prognosis is getting better, it's important to pay attention to which patients are treated with SCT.

Keywords: follicular lymphoma (FL).

415 THE PROGNOSTIC VALUE OF FLIPI IN THE ERA OF RITUXIMAB

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Introduction: Follicular Lymphoma International Prognostic Index (FLIPI) was developed in the pre-rituximab era to predict the outcome of follicular lymphoma (FL) patients. With the introduction of rituximab (R) into treatment, the predictive value of FLIPI needed reassessment. We performed a retrospective study to evaluate the prognostic value of FLIPI in the era of rituximab.

Methods: One hundred and eleven FL patients (pts) with evaluable FLIPI, needing therapy, were included in the study. They induction

TABLE 1 Hazard ratios for OS and PFS by FLIPI prognostic groups in R-chemo pts ($N = 111$).

FLIPI	OS HR (95% CI), p	PFS HR (95% CI), p
Intermediate vs. low	0.61 (0.17–1.16) $p = 0.442$	0.75 (0.29–1.90) $p = 0.546$
High vs. low	2.93 (1.14–7.53) $p = 0.025$	1.58 (0.71–3.54) $p = 0.261$

regimen was R-CHOP in 106 pts (95.5%) and R-CVP in 6 pts. With Cox model, we evaluated hazard ratios (HR) for overall survival (OS) and progression free survival (PFS) for intermediate risk versus low-risk FLIPI group and high-risk versus low-risk group.

Results: Among 111 pts, 43% were over 60 years old, and 85% had stage III–IV disease. According to FLIPI score, 34 pts (30.6%) were categorized as low-risk, 35 pts (31.5%) as intermediate-risk and 42 pts (37.9%) as high-risk pts. At a median follow-up of 4.5 years, the 5-year PFS and OS for all 111 pts were 54% and 82%, respectively. The 5-year PFS for low-, intermediate- and high-risk FLIPI pts was 53%, 64% and 49% ($p = 0.148$) and the 5-year OS 87%, 91% and 67%, respectively. The difference in OS was significant ($p = 0.002$). HR for OS was 2.93 for the high-risk FLIPI group compared to the low risk group (95% CI 1.14–7.53, $p = 0.025$) and HR for PFS was 1.58 for the high-risk FLIPI group compared to the low-risk group (CI 0.71–3.54, $p = 0.261$). There were no differences in any outcome between the low and the intermediate-risk groups (Table1).

Conclusions: FLIPI retained its prognostic value in terms of OS in the era of rituximab. High-risk FLIPI patients receiving induction R-chemo had a significantly worse survival compared to the low-risk patients. However, we did not confirm the adverse impact of high FLIPI in terms of PFS in this group of pts. It seems that rituximab in induction therapy eliminated the unfavorable influence of high FLIPI and thus diminished its prognostic significance for disease progression.

Keywords: follicular lymphoma (FL); prognostic indices; rituximab.

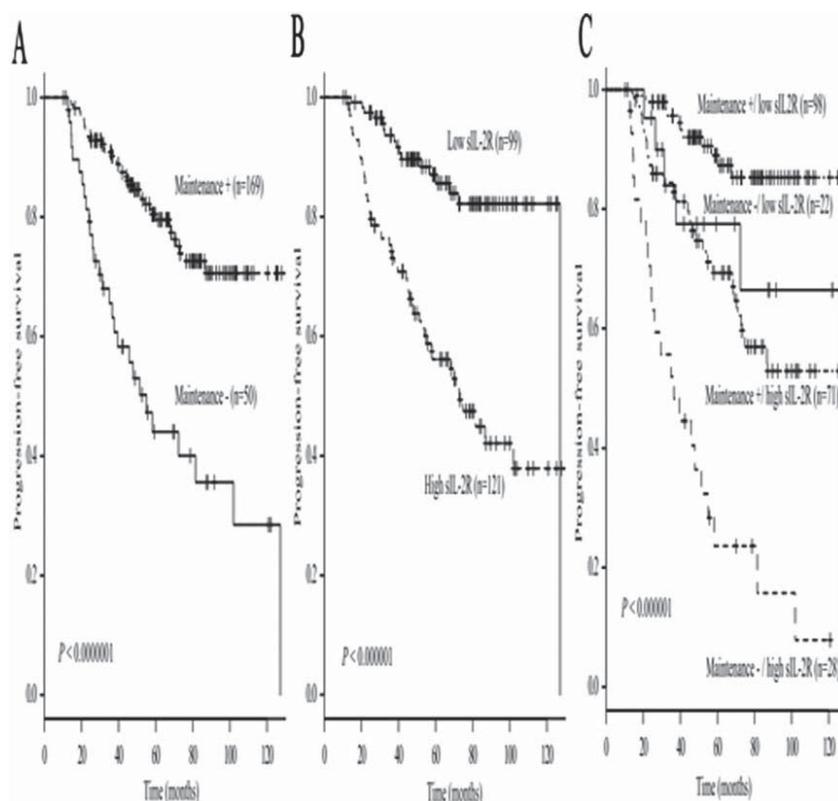
416 PRETREATMENT SOLUBLE INTERLEUKIN-2 RECEPTOR LEVEL WAS A ROBUST PROGNOSTIC FACTOR IN FOLLICULAR LYMPHOMA IN RITUXIMAB ERA

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Background: Robust prognostic markers as well as rituximab maintenance has been unknown in follicular lymphoma (FL). Soluble interleukin-2 receptor (sIL-2R) reflects activity, tumor burden, and prognosis of lymphoma.

Methods: To aim to investigate whether sIL-2R was prognostic marker equivalent to rituximab maintenance, we retrospectively analyzed 219 patients with FL grade 1–3a, who achieved objective



response by R-CHOP or R-CVP. Rituximab maintenance (single infusion for four weeks every six months for maximum of two years) was given to 169 patients (77%) with median duration of 1.6 years.

Results: Baseline characteristics are following: aged >60 was 105 (47%), men was 92 (42%), stage III/IV was 174 (79%), nodal lesions > four sites was 118 (54%), grade 3a was 33 (15), bone marrow involvement was 84 (40%), elevated LDH was 36 (16%), hemoglobin <12 g/dl was 27 (12%), bulky disease (tumor diameter > 6 cm) was 43 (20%), β 2MG > 2 mg/dl was 83 (37%), and $SUV_{max} > 10$ was 48 (22%). FLIPI classified patients into 99 (45%) as low FLIPI, 55 (25%) as intermediate FLIPI, and 66 (30%) as high FLIPI, respectively. FLIPI2 classified patients into 40 (18%) as low FLIPI2, 130 (59%) as intermediate FLIPI2, and 50 (23%) as high FLIPI2, respectively. Pretreatment sIL-2R (median 871 IU/ml, range 115–13700) was significant higher in patients, who experienced a relapse. ROC curve illustrates 1070 IU/ml as adequate cut-off value to predict relapse of FL in this cohort (AUC = 0.7, 95%CI = 0.62–0.78). Elevated LDH, stage III/IV, involved nodal sites >4, bone marrow involvement, bulky disease, elevated β 2MG, $SUV_{max} > 10$ in PET scan, high FLIPI, and high FLIPI2 were statistically associated with high sIL-2R, respectively. At the median follow-up time of 74.2 months, the six-year PFS was 75.1% (95% CI = 66.5–81.8) in the maintenance + group versus 44.1% (95%CI = 28.5–58.6) in the maintenance group ($P < 0.0000001$) and 84.0% (95%CI = 74.4–90.2) in the low sIL-2R group versus 51.1% (95%CI = 39.8–61.3) in the high sIL-2R groups, respectively ($P < 0.000001$). The six-year PFS was 84.8%, 78.4%, 58.5%, and 48.1% in the maintenance+/low sIL-2R, maintenance-/low sIL-2R, maintenance+/high sIL-2R, and maintenance-/high sIL-2R groups, respectively ($P < 0.000001$). Multivariate analysis showed that high

sIL-2R (hazard ratio 2.7, 95% confidential interval = 1.3–5.6, $P < 0.01$) was an independent factor of poor PFS as well as elevated β 2MG and no rituximab maintenance.

Conclusions: Pretreatment high sIL-2R level was an independent poor-prognostic factor and also a surrogate marker of the presence of aggressive component in FL in this cohort.

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

417 LONG-TERM FOLLOW-UP AND PREDICTORS OF POOR OUTCOME IN PATIENTS WITH FOLLICULAR LYMPHOMA UNDERGOING FRONT-LINE TREATMENT WITH CHEMOIMMUNOTHERAPY: A SINGLE CENTER EXPERIENCE.

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Introduction: The combination of anti-CD20 with different chemotherapy regimens (chemoimmunotherapy) is currently the standard of care for most patients with newly diagnosed follicular lymphoma (FL). However, data regarding long-term results of these regimes are scarce.

Methods: We performed a retrospective study in 65 consecutive patients with newly diagnosed FL (grade I, II or IIIa) diagnosed at our

institution between 2004 and 2016 and receiving treatment with chemoimmunotherapy. Progression-free survival (PFS) and global survival (OS) rates were estimated using the method of Kaplan–Meier. Univariate and multiple Cox regression models were used to assess the effect of covariates on PFS and OS.

Results: Median (range) age at diagnosis was 62 years (32–83). Forty-eight percent of patients had high-risk FLIPI and 36.7% were high-risk FLIPI-2. Patient characteristics are shown in the Table 1. The most commonly front-line therapies administered were R-CHOP (56.9%) and R-CVP (40%). Rituximab maintenance was administered to 48 patients (73.8%). Overall, 67.2% of patients achieved complete remission (CR) and 12.5% partial remission (PR) with no significant differences between both regimens. After a median follow-up of 60 months (range, 0–185), 67.7% of patients are still in CR, 15.4% have relapsed, and 23.1% have died. Neither the median PFS nor the median OS were reached. The estimated 5-year PFS and OS among all patients were 67.4% and 83.4%, respectively. Variables influencing PFS and OS in the univariate analysis were age > 60 years ($p = 0.02$), Hb <12 g/dL ($p = 0.036$), raised serum LDH ($p = 0.001$), albumin <3 mg/dL ($p = 0.029$), high-risk FLIPI ($p = 0.01$), high-risk FLIPI-2 ($p = 0.001$), not receive Rituximab maintenance ($p = 0.04$), disease progression <2 years after diagnosis ($p < 0.0001$), and disease refractoriness ($p < 0.0001$). Multivariate analysis confirmed raised serum LDH ($p = 0.034$) and refractoriness to front-line

therapy ($p = 0.021$) as the two variables affecting OS while disease progression <2 years after diagnosis was the only variable affecting PFS ($p = 0.007$).

Conclusions: Our results show that refractoriness to chemoimmunotherapy and early progression after treatment were the most relevant variables affecting outcome of patients. Both factors should be used to stratify the risk of patients with FL. Likewise, we did not find any OS and PFS advantage among patients receiving maintenance.

UNL, upper normal limit.

Keywords: follicular lymphoma (FL).

418 GENE POLYMORPHISMS AS PREDICTORS OF TREATMENT EFFICACY AND TOXICITY IN PATIENTS WITH INDOLENT NON- HODGKIN LYMPHOMAS RECEIVING BENDAMUSTINE AND RITUXIMAB

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TABLE 1 Patient demographic and baseline clinical features.

Variable	N° (%)
Age, yr	
≤60	31 (47.7)
>60	34 (52.3%)
Sex	
Male	29 (44.6)
Female	36 (55.4)
Ann Arbor stage	
I-II	13 (20)
III-IV	52 (80)
Hemoglobin, g/dL	
≥12	39 (69.6)
<12	17 (30.3)
Serum lactate dehydrogenase (LDH)	
≤UNL	43 (70.5)
>UNL	18 (29.5)
β₂-Microglobulin	
≤UNL	32 (68.1)
>UNL	15 (31.9)
N°. of nodal, sites	
< 5	40 (63.5)
≥ 5	23 (36.5)
Longest diameter of lymph node, cm	
≤ 6	35 (67.3)
> 6	17 (32.7)
Bone marrow involvement	
(-)	43 (66.1)
(+)	22 (33.8)

Introduction: Indolent non-Hodgkin lymphomas (iNHL) and mantle-cell lymphoma (MCL) have a heterogeneous behavior, impacted by biological and clinical parameters. Bendamustine is widely used in association with rituximab to treat iNHL and MCL. The variability in treatment efficacy and toxicity could be related to genetic factors of the host, such as germline single nucleotide polymorphisms (SNPs) in genes that affect drug disposition, pharmacodynamics and the components of reactive microenvironment. Deregulation of some components of the immune system and angiogenesis could play a role for tumor growth and survival. Genetic variants in immune and inflammatory response genes (such as the ones coding for IL-10 and IL-6) and in angiogenic factors (such as VEGF) could affect clinical outcome and side effects.

Methods: In this study, we would like to demonstrate a correlation between SNPs and treatment outcome in iNHL and MCL patients receiving standard doses of bendamustine and rituximab. This study includes the collection of clinical and biological data with DNA extraction and genetic analyses. We will investigate some SNPs that have already been associated with treatment efficacy and toxicity in NHL patients. All samples were genotyped for the IL-2 (rs2069762), IL-10 (rs1800890, rs10494879), VEGFA (rs3025039), IL-8 (rs4073), CFH (rs1065489) and MTHFR (rs1801131) SNPs by allelic discrimination assays using TaqMan SNP Genotyping Assays containing primers forward and reverse and allele-specific MGB (Minor Groove Binder) probes. SNPs assays were executed on a Rotor Gene 3000 platform system and the analysis of genotyping were performed using the Rotor Gene Software.

Results: We have enrolled 54 consecutive iNHL and MCL patients, and herein, we report a pivotal analysis of the first 30 patients that received rituximab 375 mg/m² and bendamustine 90 mg/m² every

28 days for up to 6 cycles both as first-line treatment (24/30) and as ≥ 2 nd line regimen (6/30). Overall response rate was 100% (CR rate 80%). Treatment toxicity included grade 3–4 neutropenia (12/30 patients), infections (9/30 patients; 1/9 grade ≥ 3), skin rash (13/30 patients; 1/13 grade ≥ 3). SNPs in IL-2, IL-8, MTHFR were observed in 12, 12 and 15 patients, respectively; while the other investigated genes were wild type for all patients. We did not report any correlation between SNP and CR rate. However, we observed an association between SNP in IL-2 (rs2069762) and skin rash ($p = 0.03$).

Conclusion: We confirm treatment efficacy and manageable toxicity of rituximab and bendamustine for iNHL and MCL patients; median follow-up is too short to report survival analyses. Preliminary results of our study suggest a possible role for cytokine SNPs in bendamustine-related toxicity that needs to be confirmed in a larger cohort.

Keywords: B-cell lymphoma; bendamustine; SNP.

419 PROGNOSTIC VALUE OF LYMPHOCYTE/ MONOCYTE RATIO AND NEUTROPHIL/ LYMPHOCYTE RATIO AT DIAGNOSIS OF FOLLICULAR LYMPHOMA.

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Introduction: The clinical course and prognosis of follicular lymphoma (FL) are diverse and associated with a patient's immune response. Previous studies reported that peripheral blood cell count ratios are associated with prognosis in a number of cancer types. Thus, we investigated the lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR) at diagnosis as prognostic factors for patients with FL, including those receiving radiotherapy.

Methods: We reviewed patients with FL in Tuen Mun Hospital, Hong Kong, from 1994 to 2012 ($n = 61$). We determined the best LMR and NLR cut-off values using receiver-operating characteristic curves. The extent to which progression-free survival (PFS) and overall survival (OS) differed by NLR and LMR cut-off values was assessed using Kaplan–Meier analysis and log-rank tests. A Cox proportional hazards model was utilized to adjust for covariates.

Results: The best cut-off values for NLR and LMR were 2.18 and 5.33, respectively. The median PFS was 5.4 years. After multivariate adjustment, high NLR (≥ 2.18) at diagnosis was associated with poorer PFS, with a hazard ratio (HR) of 2.32 (95% confidence interval [CI] 1.06, 5.07), whereas high LMR (≥ 5.33) at diagnosis was associated with better PFS with an HR of 0.37 (95% CI 0.14, 0.95). NLR and LMR were shown to be independent prognostic factors of PFS in FL, even after multivariate adjustment for follicular lymphoma international prognostic index (FLIPI), age, and other factors.

Conclusions: NLR and LMR are low cost and widely available biomarkers for clinicians who may use these in combination with FLIPI to better predict prognosis.

Keywords: B-cell lymphoma; follicular lymphoma (FL); prognostic indices.

TABLE 1 Univariate and multivariate analyses for progression-free survival in NLR and LMR, $n = 61$.

Characteristics for NLR	Univariate HR (95% CI)	Model 1: Adjusted HR (95% CI)	Model 2: Adjusted HR (95% CI)	Model 3: Adjusted HR (95% CI)
NLR, ≥ 2.18 vs. < 2.18	2.17 (1.10–4.31)	2.22 (1.10–4.50)	2.29 (1.05–4.98)	2.32 (1.06–5.07)
FLIPI1 scores, 3–5 vs. 0–2	3.04 (1.49–6.18)	2.64 (1.16–6.03)	2.56 (0.76–8.59)	2.26 (0.60–8.52)
Sex, male vs. female	1.15 (0.60–2.23)	1.10 (0.51–2.39)	0.94 (0.36–2.42)	0.90 (0.34–2.39)
Age per one year increase	1.03 (1.01–1.05)	1.02 (0.99–1.04)	1.02 (0.99–1.06)	1.02 (0.99–1.06)
B symptoms	1.31 (0.46–3.70)		1.43 (0.37–5.57)	1.46 (0.38–5.66)
Per mm increase in ESR	1.00 (0.98–1.01)		0.99 (0.98–1.01)	0.99 (0.98–1.01)
Bone marrow involvement	1.83 (0.95–3.54)		0.85 (0.32–2.23)	0.91 (0.33–2.55)
Disease bulk > 6 cm	1.62 (0.81–3.24)			1.23 (0.50–3.00)
Characteristics for LMR				
LMR, ≥ 5.33 vs. < 5.33	0.47 (0.22–1.01)	0.43 (0.20–0.93)	0.43 (0.18–1.05)	0.37 (0.14–0.95)
FLIPI1 scores, 3–5 vs. 0–2	3.04 (1.49–6.18)	2.64 (1.14–6.12)	1.95 (0.55–6.90)	1.43 (0.36–5.72)
Sex, male vs. female	1.15 (0.60–2.23)	1.25 (0.60–2.60)	1.05 (0.44–2.51)	0.92 (0.37–2.30)
Age per one year increase	1.03 (1.01–1.05)	1.02 (0.99–1.04)	1.02 (0.99–1.06)	1.03 (0.99–1.07)
B symptoms	1.31 (0.46–3.70)		1.52 (0.39–5.92)	1.47 (0.38–5.68)
Per mm increase in ESR	1.00 (0.98–1.01)		0.99 (0.98–1.01)	0.99 (0.98–1.01)
Bone marrow involvement	1.83 (0.95–3.54)		1.08 (0.39–2.98)	1.36 (0.45–4.13)
Disease bulk > 6 cm	1.62 (0.81–3.24)			1.69 (0.65–4.37)

Model 1: Adjusted for age, sex, and FLIPI1 score.

Model 2: Model 1 plus B symptoms, ESR, and bone marrow involvement.

Model 3: Model 2 plus disease bulk > 6 cm.

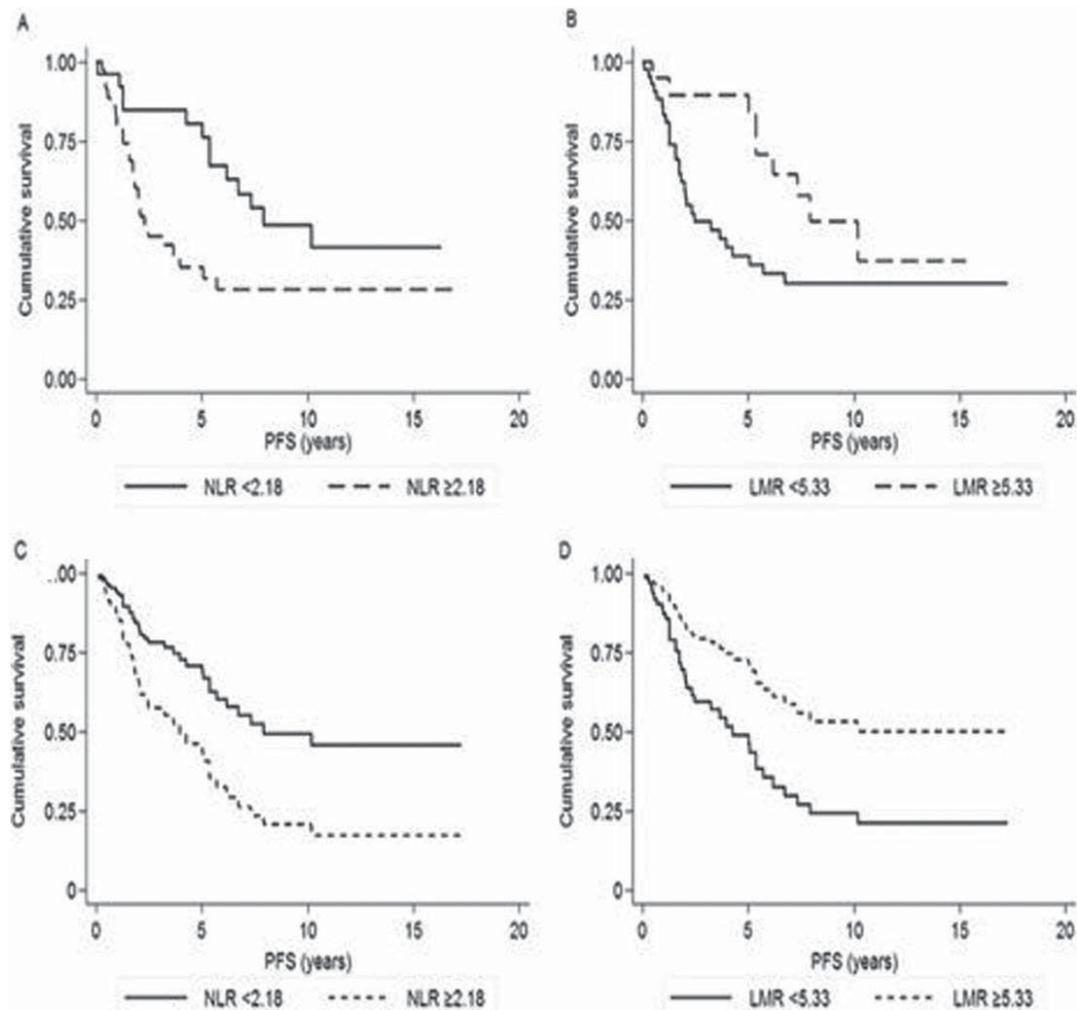


Figure 1. Univariate and multivariate Kaplan–Meier curves. Univariate Kaplan–Meier curves for (A) NLR at diagnosis and (B) LMR at diagnosis; and multivariate Kaplan–Meier curves for (C) NLR at diagnosis and (D) LMR at diagnosis ($n = 61$).

420 THE VALUE OF PROGNOSTIC NUTRITIONAL INDEX AT DIAGNOSIS IN PATIENTS WITH FOLLICULAR LYMPHOMA: A RETROSPECTIVE COHORT STUDY

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Introduction: The clinical course and prognosis of follicular lymphoma (FL) is diverse. Studies about prognostic nutritional index (PNI), a marker of host inflammatory and nutritional status, indicated that it is associated with prognosis in a number of cancer types but, its value in FL is unknown. Thus, we studied the prognostic significance of PNI at diagnosis for patients with FL, including those receiving radiotherapy.

Methods: We reviewed FL patients in Tuen Mun Hospital, Hong Kong, from 1994 to 2012 ($n = 61$). PNI was calculated by serum albumin (g/L) + $5 \times$ absolute lymphocyte count ($10^9/L$). We determined the best PNI cut-off value using receiver operating characteristic curves. The

extent to which progression-free survival (PFS) and overall survival differed by PNI cut-off was assessed using Kaplan–Meier and Log rank test. Cox proportional hazards model was utilized to adjust for covariates.

Results: The best cut-off for PNI was 48. Median PFS was 5.4 years. Patients who died within 3 years had a lower median PNI at baseline (Ranksum test $P = 0.014$). After multivariate adjustment, high PNI (≥ 48) at diagnosis is associated with superior PFS with a hazard ratio of 0.34 (95% confidence interval 0.16–0.72).

Conclusions: PNI was shown to be an independent prognostic factor of PFS in FL, even after multivariate adjustment. PNI is low cost and widely available biomarker for clinicians who may use these in combination with FLIPI to better predict prognosis.

Keywords: follicular lymphoma (FL); non-Hodgkin lymphoma (NHL); prognostic indices.

421 A RETROSPECTIVE STUDY OF THE DIAGNOSIS AND THE TREATMENT- ASSOCIATED MORTALITY OF PATIENTS WITH PRIMARY OCULAR ADNEXAL

TABLE 1 Univariate and multivariate analysis for Progression-Free Survival in PNI ($n = 61$).

Characteristics for PNI	Univariate HR (95%CI)	Model 1: Adjusted HR (95%CI)	Model 2: Adjusted HR (95%CI)	Model 3: Adjusted HR (95%CI)
PNI ≥ 48 vs. <48	0.44 (0.23–0.85)	0.44 (0.23–0.86)	0.34 (0.16–0.72)	0.34 (0.16–0.72)
FLIPI1 score 3–5 vs. 0–2	3.04 (1.49–6.18)	2.76 (1.23–6.20)	3.35 (1.04–10.7)	2.97 (0.82–10.80)
Sex male vs. female	1.15 (0.60–2.23)	1.17 (0.54–2.53)	1.21 (0.49–3.00)	1.17 (0.46–2.96)
Age: per 1 year increase	1.03 (1.01–1.05)	1.01 (0.99–1.04)	1.01 (0.97–1.04)	1.01 (0.97–1.05)
B symptoms	1.31 (0.46–3.70)		1.22 (0.32–4.62)	1.24 (0.33–4.68)
Per mm increase in ESR	1.00 (0.98–1.01)		0.99 (0.97–1.00)	0.99 (0.97–1.00)
Bone marrow involvement yes vs. no	1.83 (0.95–3.54)		0.80 (0.30–2.10)	0.87 (0.31–2.44)
Disease bulk >6 cm	1.62 (0.81–3.24)			1.21 (0.49–3.01)

Abbreviations: PNI, prognostic nutritional index; FLIPI1, follicular lymphoma international prognostic index 1; ESR, erythrocyte sedimentation rate; HR, hazard ratio.

Model 1: Adjusted for age, sex and FLIPI1 score.

Model 2: Model 1 plus B symptoms, ESR and bone marrow involvement.

Model 3: Model 2 plus disease bulk >6 cm.

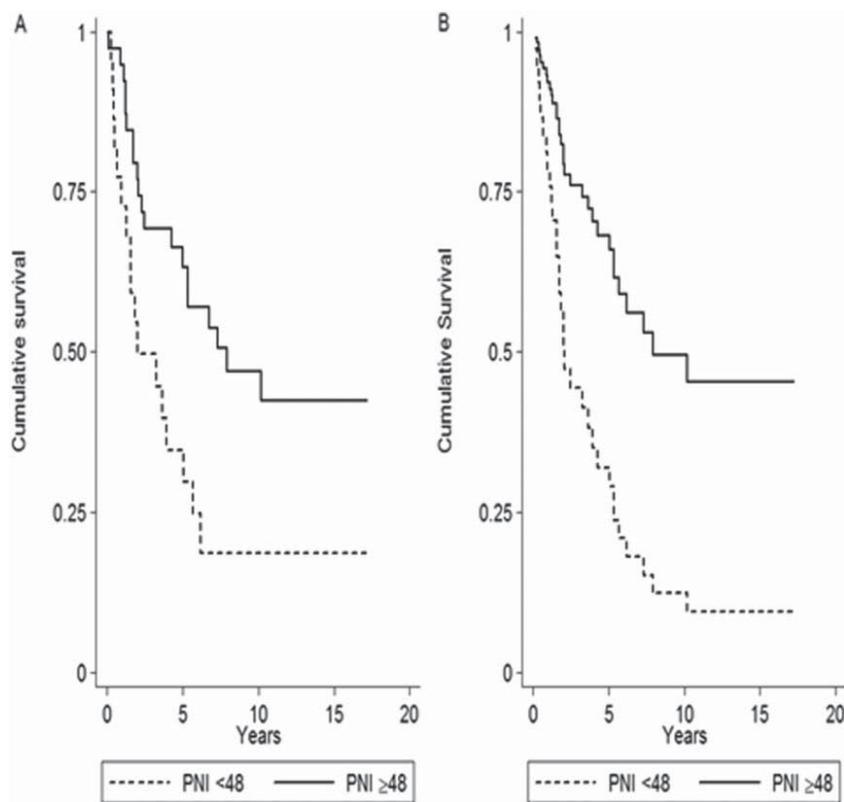


Figure 1. Univariate and multivariate Kaplan–Meier curves of PFS. (A) Univariate Kaplan–Meier curve for PNI at diagnosis ($n = 61$) and (B) Multivariate Kaplan–Meier curve for PNI at diagnosis ($n = 61$).

MUCOSA-ASSOCIATED LYMPHOID TISSUE (POA-MALT) LYMPHOMA IN JAPAN.

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Introduction: POA-MALT lymphoma is a relatively rare disease and detailed diagnoses and treatment-associated prognoses have not been reported on sufficiently. Here, we have analyzed a series of POA-MALT lymphoma cases in the southern area of Japan and examined the diagnosis, the treatment, and the prognosis for this disease.

Method: From 1991 through 2016 in the southern area of Japan, cases of POA-MALT lymphoma were retrospectively analyzed based on their

pathological and molecular diagnoses. In addition, their treatment-associated prognoses were evaluated.

Results: A total of 82 cases of POA-MALT lymphoma (female/male; 37/45) with a median age of 53.0 years (range, 21–85; mean, 63.6) were analyzed over a median observation period of 9.9 years (mean, 6.9); 44 patients (54%) were diagnosed with IgH rearrangement using southern blot and/or PCR analysis and pathological decision, and 10 patients (12%) were diagnosed with flow cytometer analysis (CD5–, CD10–, CD20+, CD79a+, and κ or λ chain access) and pathological decision. The rest of the 28 patients (34%) were diagnosed employing pathological decision only. All patients (except watchful waiting patients, $n = 78$) achieved complete remission after the initial treatment. One patient died after a recurrence, and another patient died from another malignancy. A total of 68 patients (87.2%) presented a disease-free status after initial treatment during their observation periods. As treatment, radiotherapy-based strategies (over 30Gy) were administered with 17 patients (21%, group A). Immunotherapy, including rituximab, was administered to 21 patients (26%, group B). Surgical extraction only was selected for 40 patients (48%, group C). Watchful waiting was selected with 4 patients (5%, group D). Recurrence after the initial treatment was found in one patient (5.9%) out of group A, in 2 patients (9.5%) out of group B, and in 7 patients (25%) including 2 patients' experiencing mortality out of group C, respectively. Kaplan–Meier estimates for the PFS at 5 years were 82% in group A, 66% in group B, and 47% in group C, respectively.

Conclusions: In our current study, the patients with POA-MALT lymphoma showed a 32% recurrence rate at 5 years after the initial treatment. However, radiotherapy-based strategy shows a low rate of recurrence (18%) at 5 years. POA-MALT lymphoma is an indolent disease shows slow progression and has a relatively better prognosis. Clear diagnosis and radiotherapy-based initial treatment should improve the prognosis for POA-MALT lymphoma.

Keywords: Mucosa-Associated Lymphoid Tissue (MALT).

422 CLINICAL FEATURES AND SURVIVAL OUTCOMES ON LYMPHOPLASMACYTIC LYMPHOMA PATIENTS WITH NON-IGM PARAPROTEINEMIA COMPARED WITH IGM PARAPROTEINEMIA IN KOREA

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Introduction: The incidence of lymphoplasmacytic lymphoma (LPL), a relatively rare subset of non-Hodgkin lymphoma, has been suggested lower in Asian population than in Western countries. Non-IgM LPL is rare and accounts for less than 5% of the total LPL cases. There have been few studies comparing the clinical features and survival outcomes between patients with non-IgM LPL and LPL/Waldenström macroglobulinemia (WM) in East Asia. In this study, we evaluated clinical features and survival outcomes of LPL with non-IgM compared with LPL/WM in Korea.

Method: A retrospective analysis was performed for patients diagnosed with non-IgM LPL and LPL/WM at Asan Medical Center between January 2001 and March 2016. Clinical features and survival outcomes were compared between the two groups.

Result: A total of 19 patients were categorized into non-IgM ($n = 8$, 42.1%) and LPL/WM ($n = 11$, 57.8%) groups. The median age at diagnosis was 65.5 (62 to 69) and 57 (range 47 to 66) years, respectively; 7 (87.5%) patients in non-IgM LPL and all patients in LPL/WM were men. There were no statistically significant differences in baseline characteristics between non-IgM LPL and LPL/WM groups, except the proportion of high/high-intermediate subset according to International prognostic index (IPI) (75% vs 18.2%, $p = 0.024$). The patients in LPL with non-IgM group more frequently showed extranodal involvement of ≥ 2 (62.5% vs. 27.3%) and demonstrated higher level of beta-2-microglobulin level than those in LPL/WM group [median, 12.8, (range, 2.3–41.0) vs. 3.7, (2.2–30.0)] without statistical significance. Patients were treated with heterogeneous regimens including CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CVP (cyclophosphamide, vincristine, prednisone), and fludarabine. The median overall survival of the LPL with non-IgM group was shorter than that of LPL/WM (10 months [95% CI, 0–36.3] vs median 81 months [95% CI, 0–168]; $p = 0.124$).

Conclusion: Despite a small number of patients and heterogeneous treatment, more unfavorable prognostic factors with regard to IPI in non-IgM LPL group might be consistent with worse survival outcomes compared to LPL/WM group. These findings suggest IPI might be useful for predicting prognosis in non-IgM LPL and LPL/WM. Further studies are needed to clarify the clinical features and survival outcomes between two groups.

Keywords: lymphoplasmacytic lymphoma (LPL); lymphoplasmacytic lymphoma/Waldenström (LPL/WM).

EXTRANODAL LYMPHOMAS

423 PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA—THE ROLE OF MEDIASTINAL RADIATION

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Introduction: Primary mediastinal large B-cell lymphoma (PMLBCL) is a rare subtype of diffuse large B-cell lymphoma. The most standard approaches include a combination of immunotherapy and mediastinal radiotherapy (RT). Because mediastinal RT is associated with significant long-term toxicities, it was necessary the development of effective therapeutic strategies (rituximab with increased dose intensity regimens) that changed the need for routine RT.

Patients and Methods: Fifteen patients with diagnosis of PMLBCL between 2005 and 2015 were treated according to protocol DA-R-

EPOCH (infusional dose-adjusted etoposide, doxorubicin and cyclophosphamide with vincristine, prednisone and rituximab).

Patients were classified into 3 risk groups (according to presence of pleural/pericardial effusion and IPI high/intermediate-risk or high-risk). Residual disease (RD) was evaluated by FDG-PET and defined as score 2 according to Deauville Criteria and partial response (PR) defined as score 4–5 with a reduction >50% in size of mass.

Results: Median age at diagnosis was 29 (21–43) years, age <40 years in 86.7% ($n = 13$).

Eleven patients (78.6%, $n = 14$) had a bulky disease (tumor mass >10 cm), and 6 (42.9%, $n = 14$) had superior vena cava syndrome at presentation. Presence of pleural/pericardial effusion in 7 patients (53.8%, $n = 13$) and pulmonary involvement in 5 (38.5%, $n = 13$).

According to the prognostic score, two patients (15.4%) were classified as high risk (2 adverse factors), five (38.5%) in intermediate risk (1 factor) and six (42.2%) in low risk (0 factors).

All patients were treated with 6 cycles of immunochemotherapy. Seven patients (46.7%) achieved complete response (CR), confirmed by FDG-PET in five. Another 3 (20%) had RD. All patients who achieved CR/RD did not perform RT with an event-free survival (EFS) of 100%. PR was attained in 3 patients (20%), two had high-risk disease. All patients in PR were submitted to RT, reaching CR (confirmed by FDG-PET) without relapse during the follow-up time.

Progressive/stable disease was observed in 2 patients (13.3%). They were submitted to autologous stem cell transplant reaching CR.

With a median follow-up of 52 (14–116) months, it was obtained an overall survival/EFS of 100% without evidence of disease. No cardiac events or second tumors were observed, so far.

Conclusion: The use of therapeutic approaches with rituximab and increased dose intensity regimens (like DA-R-EPOCH) has shown excellent efficacy and challenge the need for mediastinal radiation (5-year OS and EFS >90%, according to data from several studies).

In conclusion, our results indicate that patients who had CR/RD evaluated by FDG-PET after treatment with DA-R-EPOCH, EFS was 100% with a median follow up of 52 months. In these patients, the use of DA-R-EPOCH obviated the need for routine mediastinal RT. In patients with persistent disease after treatment, RT is a necessary approach though.

Keywords: DA-R-EPOCH; primary mediastinal large B-cell lymphoma (PMLBCL).

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PRIMARY EXTRANODAL NON-HODGKIN'S LYMPHOMA OF THE LIVER (PLL)

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PLL is very rare disease. Frequency of PLL ranged from 0.019 to 0.04% according to the literature. Diagnosis of PLL is difficult and often confusing. Due to the rarity of the disease program for the treatment of PLL is not sufficiently developed.

Aim: Determine clinical and laboratory characteristics of patients with PLL. To evaluate effectiveness of therapy depending on the histological variants (HV) of PLL.

Our study included 553 patients (pts) with diffuse large B-cell lymphoma DBCL and 298 pts with indolent lymphomas (IL). Patients were observed at Cancer Research Center from 1999 to 2016.

Among pts with IL, there were 166 pts without hepatitis B(HBV) and hepatitis C (HCV) infection, 101 pts with HCV and 31 pts with HBV. PLL was diagnosed in 8 pts. All pts were infected by HCV. Man : female ratio was 7:1. The median age was 41 years; 2 pts had infiltrative form of lymphoma, 6 nodular. Morphological types were follicular lymphoma in 5 pts, lymphoma marginal zone in 3 pts.

Symptoms of intoxication was at 1 pts. LDH was elevated in all 8 pts (median 980 IU/l). ALT and AST were also elevated in all pts. The median was 280 IU/l and 212 IU/l, respectively. The median GGT was 153 U/l, median alkaline phosphatase(AP) was 670 IU/L. All pts had high-level of HCV RNA. Median – 5.5×10^5 copies/ml.

Among pts with DBCL, there were 26 pts with HBV, 102 pts with HCV and 425 pts didn't have infection. PLL was identified in 13 pts. 11 pts have HCV, 1 pt – HBV and 1 pt – haven't hepatitis markers. Two pts with HCV had simultaneous HIV infection, it were 11 men and 2 women. Median age was 43 years. HV were GCB (6 pts only with HCV) and non-GCB (other 7 pts). All pts had nodular form of liver damage. Intoxication was in 3 pts. LDH was elevated in all pts (median – 1290 IU/l), ALT and AST were also elevated in all pts, median was 390 IU/l and 194 IU/l, respectively. Median of GGT – 253 IU/l, median AP was 590 IU/L. Level of HCV RNA was high, median – 1.6×10^6 copies/ml.

At whole group, the AFP levels were normal in all pts. Median time from detection infection was 144 mth.

CT features was hypodensitive of lymphoma lesions as in nodes well as in infiltrative form. Liver cirrhosis was only in 2 pts.

Six pts with IL as first-line antiviral therapy (AVT) had interferon + ribavirin. CR – 4 pts, 1 pt – PR, 1-PD. Polychemotherapy(PCT) R-CHOP was in 3 pts.CR-2 PD-1. Disease free survival (DFS) after AVT was 61 mth.

All pts with DBCL with HCV treated by CHOP/R-CHOP and AVT. Pts with HIV infection was conducted antiretroviral therapy. CR was achieved in 8 pts, PR – 3 pts and 2 pts – PD. All pts after PCT with HCV received supportive therapy AVT for 2 years. DFS in pts with GCB lymphoma was 38 mth. DFS in pts with non-GCB lymphoma was 9 mth.

Conclusions: PLL is a rare disease associated HCV infection. PLL more often young men with long-term HCV fection. AVT interferon + ribaverin is very important part in program of therapy of PLL.

Keywords: hepatitis C; non-Hodgkin lymphoma (NHL).

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OUTCOME OF PRIMARY DIFFUSE LARGE B-CELL LYMPHOMA OF THE STOMACH – A SINGLE INSTITUTE EXPERIENCE

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Background: To evaluate the prognostic factors and treatment outcome of patients with primary diffuse large B-Cell lymphoma (DLBCL) of the stomach treated at a single institution.

Methods: Between January 2005 to December 2012, 125 patients with DLBCL of the stomach were treated. Median age was 49 years, and majority of the patients (69%) were men; 23% had a WHO performance status (PS) of 2 or more; 36% presented with stage I, 43% had stage II, and 21% had stage III–IV disease. On initial endoscopy, 46% had single lesions. As per the international prognostic index (IPI), 59.5% were low risk, 23% were low intermediate, 13 were intermediate, and 4.5% were high risk. Treatment comprised of chemotherapy (CTh) alone for 39%, Surgery (Sx) and CTh for 22.5%, CTh and radiotherapy (RT) for 33%, and all three modalities were used in 5.5%. Amongst those receiving RT, 37% were treated using 3D-CRT technique, and 64.5% received an RT dose of >40Gy.

Results: After a median follow-up of 54 months, the 5-year PFS & OS were 57% and 68%, respectively. On multivariate analysis; age \geq 50 yrs (HR = 2.17, p = 0.013), WHO PS \geq 2 (HR = 1.91, p = 0.045) and presence of multiple or diffuse lesions on endoscopy (HR = 2.17, p = 0.020) were found to have a significant negative influence on the OS. The IPI was also found to be a significant prognostic indicator for 5 year OS: low = 78.5% vs. low-intermediate = 61.4% vs. intermediate = 42.4% vs. high = 28.6%, p < 0.001. Combined modality treatment resulted in a significantly better outcome than CTh alone (5 year OS: CT + RT = 79.3% vs. Sx + CT = 73.2% vs. Sx + CT + RT = 76.2% vs. CT Alone = 55.5%, p = 0.005). On multivariate analysis, the hazard ratio for death in patients receiving CT alone was 2.31 (p = 0.010). The PFS (p < 0.001) and OS (p = 0.001) rates were significantly better for patients receiving an RT dose of >40Gy.

Conclusions: Age at diagnosis, WHO PS, Hb level, IPI, and the number of lesions in the stomach significantly influenced outcome in patients with primary gastric DLBCL. Combined modality treatment, comprising of CTh & RT (with an RT dose of 45Gy), results in satisfactory outcome in patients with this uncommon neoplasm.

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

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LONG-TERM FOLLOW-UP OF PATIENTS WITH NON-HODGKIN PRIMARY DIFFUSE LARGE B-CELL LYMPHOMA OF THE STOMACH: BETTER OUTCOME AFTER IMMUNOCHEMOTHERAPY

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Introduction: Primary gastric lymphomas include a histologically and biologically heterogeneous group of neoplasms. The majority has diffuse large B-cell (DLBCL) histology and comprises the most common site of extranodal non-Hodgkin lymphomas (NHLs). While gastric DLBCLs are frequent, sufficient data to guide the optimal care are still limited.

Methods: We retrospectively evaluated the trends in clinical presentation, management and outcome among 165 consecutive patients with a biopsy-proven primary gastric DLBCL who were seen in the years 1980–2014. Information on patients' characteristics and outcome was obtained from a prospectively maintained database. The study cohort was divided into two subgroups based upon the era of treatment (before and after rituximab – CHOP versus R-CHOP) in order to assess the impact of immunochemotherapy in patients' outcome. Overall survival (OS) analysis was conducted for the entire period (1980–2014) and additionally performed on the first 100 months of every study cohort since the therapeutic approaches were applied at different time intervals. Statistical analysis was performed on SPSS software (version 23.0).

Results: The study included 165 patients (55% male and 45% female) with a median age of 61 years (range 17–83). Disease stage III and IV was found in 15%, an ECOG performance status \geq 2 was recorded in 24%, while 24% of the patients had increased LDH. The majority of the patients (84%) was treated with chemotherapy: 84 (60%) patients received CHOP-based regimen, while 55 (40%) were treated with the addition of Rituximab (R) to CHOP (R-CHOP). Twenty-five patients (15%) were treated with gastrectomy \pm radiotherapy (13 and 9 patients, respectively). A combination of surgery and chemotherapy was used in 58 (35%) patients, while in 4 both chemotherapy and radiotherapy was applied. Lastly, 9 patients were treated with a multi-disciplinary approach including surgery, chemotherapy and radiotherapy. No difference regarding sex, disease stage, ECOG performance status, or LDH levels was noted among the study subgroups. The median OS for the entire population was 16.58 years. The median OS in the first 100 months of the patients treated with R-CHOP-based regimens has not been reached yet, while for those treated with CHOP was 94 months (log-rank = 0.005). In contrast, the median OS for those who did not receive chemotherapy was only 21 months (log-rank = 0.005).

Conclusions: A better outcome was observed in the patients treated with immunochemotherapy and not subjected to surgery.

Keywords: diffuse large B-cell lymphoma (DLBCL); extranodal lymphomas; rituximab.

427 TREATMENT STRATEGIES AND PROGNOSTIC FACTORS OF PRIMARY GASTRIC DIFFUSE LARGE B CELL LYMPHOMA: A RETROSPECTIVE STUDY OF 303 CASES FROM CHINA LYMPHOMA PATIENT REGISTRY

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Introduction: Primary gastric diffuse large B cell lymphoma (PGDLBCL) is the common primary extranodal DLBCL, with higher incidence in Asian than in Western countries. However, the optimal treatment for PGDLBCL remains controversial. We thus conducted a retrospective analysis of 303 cases to evaluate present treatment strategies and prognostic factors of PGDLBCL.

Methods: From three centers of the China Lymphoma Patient Registry (CLAP), 303 PGDLBCL cases from January 1994 to December 2015 were retrospectively analyzed. Patients were classified into four groups: chemotherapy (C, 192 cases), surgery (S, 21 cases), chemotherapy + surgery (C + S, 78 cases), and watch and wait (12 cases).

Results: The 3-year progression-free survival (PFS) and 3-year overall survival (OS) of the entire cohort were 75.3% and 80.3% (median follow-up time: 42 months). PFS ($p = 0.122$) and OS ($p = 0.451$) were similar among the four treatment groups. In the chemotherapy-treated cohort, group C + S had higher PFS than group C (83.7% vs. 71.8%, $p = 0.013$). Its OS was also relative higher, even without statistical significance (86.6% vs. 78.5%, $p = 0.097$). The inclusion of radiotherapy during initial treatment (23 cases) in this cohort did not improve PFS (57.9% vs. 76.2%, $p = 0.017$) or OS (73.7% vs. 81.1%, $p = 0.220$). Rituximab did not show significant clinical benefit in our study (PFS: 78.1% vs. 71.1%, $p = 0.205$; OS: 83.9% vs. 75.7%, $p = 0.052$). Treatment-related complications included gastrointestinal bleeding (22 cases), perforation (4 cases), and obstruction (4 cases), which correlated with poorer outcomes (PFS: 50.7% vs. 78.1%, $p = 0.005$; OS: 59.2% vs. 83.3%, $p < 0.001$). Glucocorticoid in chemotherapy increased incidence of complications ($p = 0.035$). The univariate analysis revealed prognostic factors as age, Lugano stage, ECOG, B symptom, International Prognosis Index, LDH, HGB, ESR, β 2-MG, lesion in cardia, prior gastrointestinal bleeding, and complications. The multivariate analysis showed that B symptom (Relative rate (RR) = 2.82, $p = 0.016$), lesion in cardia (RR = 2.86, $p = 0.039$), LDH (RR = 4.65, $p < 0.001$) and gastrointestinal bleeding before treatment (RR = 3.08, $p = 0.005$) were highly predictive for poor PFS, and the latter two factors also predicted poor OS (RR = 4.08, $p = 0.004$; RR = 3.18, $p = 0.001$).

Conclusions: Our results indicated that chemotherapy + surgery is a considerable choice to improve the survival of PGDLBCL. The inclusion of radiotherapy during initial treatment did not improve survival

in our study. Due to elevated risk of complication, glucocorticoid could be removed from chemotherapy. B symptom, lesion location, LDH, and gastrointestinal bleeding before treatment are independent predictors of poor outcomes. This retrospective, multicenter analysis provides the largest sample size study for PGDLBCL, but the future prospective trial is warranted.

Keywords: extranodal lymphomas.

428 CLINICAL FEATURES AND PROGNOSIS OF PRIMARY GASTRIC DIFFUSE LARGE B CELL LYMPHOMA: A RETROSPECTIVE ANALYSIS OF 139 CHINESE CASES WITH IMMUNOPHENOTYPING FROM CLAP

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Introduction: Diffuse large B cell lymphoma (DLBCL) can be classified into germinal center B-cell-like (GCB) and non-GCB subtypes with immunophenotyping. Non-GCB subtype showed poorer survival than GCB subtype in most studies. Primary gastric DLBCL (PGDLBCL) is relative common in China with good outcome. We carried out a retrospective analysis of 139 cases to characterize the clinical features and prognostic factors of PGDLBCL with different immunophenotypes.

Methods: From two centers of the China Lymphoma Patient Registry (CLAP), 139 PGDLBCL cases (from January 1994 to December 2015) were retrospectively analyzed. They were categorized into GCB (51 cases) and non-GCB (88 cases) subtypes according to the expression of CD10, Bcl6 and MUM1.

Results: Pathological specimens were acquired by gastroscopy biopsy (114 cases) and surgery (25 cases). The following properties were similar in GCB and non-GCB PGDLBCL ($p > 0.05$): Lugano stage, B symptom, ECOG, International Prognosis Index, lesion location, and gastrointestinal bleeding before treatment. The 3-year progression-free survival (PFS) and 3-year overall survival (OS) of the entire cohort were 78.1% and 81.6% (the median follow-up time was 38.5 months). Patients with GCB did not show any statistically significant difference in survival from those with non-GCB (PFS: 80.5% vs. 76.8%, $p = 0.161$; OS: 80.5% vs. 82.5%, $p = 0.901$). Positive expression of Bcl6 (75.1% vs. 93.5%, $p = 0.004$) and Bcl2 (69.7% vs. 87.7%, $p = 0.039$) both correlated with poor OS, compared to specimens lacking these two biomarkers. Most patients (94.2%) received chemotherapy \pm surgery as initial treatment, while others only received surgery or watch and wait. In the chemotherapy-treated cohort, patients received rituximab-combined chemotherapy appeared to have better outcome, but without statistically significance (PFS: 80.7% vs. 68.0%, $p = 0.457$; OS: 86.2% vs. 67.8%, $p = 0.124$). Rituximab did not show clinical benefit in either GCB or non-GCB subtype ($p > 0.05$). Treatment-related complications

included gastrointestinal bleeding (8 cases), perforation (3 cases), and obstruction (2 cases), which showed no correlation with immunophenotypes.

Conclusions: This retrospective study revealed that PGDLBCL with different immunophenotypes had similar clinical features, treatment-related complications, and outcome. The positive expression of Bcl2 or Bcl6 predicts poor OS in PGDLBCL.

Keywords: extranodal lymphomas; germinal center B cell-like (GCB).

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CNS TARGETING CHEMOTHERAPY IS ASSOCIATED WITH SUPERIOR SURVIVAL IN PATIENTS WITH TESTICULAR LYMPHOMA – RESULTS FROM FINNISH-DANISH RETROSPECTIVE STUDY

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Introduction: Testicular lymphoma, mainly diffuse large B-cell lymphoma (DLBCL), is a rare malignancy affecting mostly elderly men, and is associated with increased risk of central nervous system (CNS) progression. Eligible patients commonly receive CNS targeted methotrexate or cytarabine as prophylaxis, administered either as high dose systemic (HD) or intrathecal (IT) treatment. However, the data supporting the benefit of CNS prophylaxis are limited. We retrospectively analyzed the results of different CNS prophylaxis modalities in our institutions.

Methods: We searched the pathology databases at three Southern Finland University Hospitals as well as the Danish Lymphoma Registry for testicular DLBCLs. Clinical characteristics at diagnosis, treatment information, and survival data were collected.

Results: Altogether 231 cases were identified. Median age at diagnosis was 67 years (range 36–93). Disease was limited to the testis in 94 patients. For the entire cohort, 5-year progression-free (PFS), and overall survival (OS) rates were 46% and 52%, respectively. High International Prognostic Index (IPI ≥ 3) was recorded in 30% of the patients, correlating with poor survival (5-y PFS 25% vs 60%, $p < 0.001$ and OS 32% vs. 70% $p < 0.001$). Seventeen patients (7%) experienced CNS progression during the course of disease. Eleven of the CNS recurrences occurred after first line therapy.

One-hundred and ninety-four patients were treated with curative intent. CNS targeting chemotherapy was given to 125 (64%) patients; HD either with or without IT treatment to 77 (40%), and IT only to 48 (25%). These patients were younger (<70 yrs. of age 24,8% vs 14,5%, $p < 0.001$) than the patients treated without CNS targeting agents. Thus, survival analyses of the treatment effect were stratified

according to age. Both CNS targeting therapies improved survival over conventional treatment (OS: 5-y 68% vs 39%, $p < 0,001$, HR 0,50 95% CI 0,341–0,737; PFS: 5-y 61% vs 32%, $p = 0.001$, HR 0,541, 0,374–0,783). In addition, a trend towards better outcome was observed in the patients treated with HD therapy in comparison to IT only treatment (OS: 75% vs 58%, $p = 0.118$, HR 0,643, 95% CI 0,368–1,123 and 5-y PFS 66% vs 51%, $p = 0.097$, HR 0,656, 95% CI 0,399–1,080). High IPI (≥ 3) was associated with the increased risk of CNS recurrence (HR 10,222, 95% CI 2,702–38,671) and death (HR 3,066, CI 2,058–4,568). Treatment modalities had no significant impact on CNS recurrence.

Conclusions: We present a large cohort of testicular DLBCL patients. The results support the use of CNS targeting chemotherapy, although the survival benefit of these regimens might be partially due to better systemic control of the disease rather than prevention of CNS progression. Our aim is to further characterize the biomarkers associated with outcome in this cohort.

Keywords: CNS prophylaxis; diffuse large B-cell lymphoma (DLBCL); testicular lymphoma.

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3D CONFORMAL RADIOTHERAPY (3D-CRT) AT PRIMARY ORBITAL LYMPHOMA (OL) WITH DIFFERENT FRACTIONATION

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Introduction: improve the efficiency of the treatment of OL using 3D-CRT and different fractionation.

Methods: A total of 48 patients treated with radiotherapy or chemoradiotherapy in 2003–2016 years – 3D-CRT and 2D-RT. There were 30 patients with orbital, 14 with conjunctival, 2 with the chorioid, 2 – eyelid involvement. When the retrobulbar structures involved, we used photon beam 6 MeV, CTV included the entire orbit; PTV – 5–7 mm. If tumor was superficial, we used electron beam 4–6 MeV, CTV included conjunctival fornices and eyelid with tumor. Pre-radiation preparation was performed on a CT simulator Toshiba Aquilion, contouring station – FocalPro and MonacoSim 5.0. Radiological monitoring plan carried out on 3D-planning Precise PLAN and Xio systems. RT was on line electron accelerators Elekta Precise, Elekta Axesse, Philips 75-5. We used the conventional fractionation, CF (27 patients) and multifractionation, MF (21 patients – 1.2 Gy twice a day). The total dose average was 36.2 ± 0.9 Gy and had no differences with the 2D-RT and 3D-CRT.

Results: All 48 patients had the effect, and it was similar ($p > 0.1$) in a group of 3D-CRT (complete remission – 20 of 24 patients, 83.3%, a partial – 4–16.7%), and 2D-RT – 22 of 24 (91.7%) and 2 of 24 (8.3%) patients. Early side effects (SE) were in 89.6% of patients: 3D-CRT 20 patients – 83, 3%, 2D-RT 23 (95.8%) ($p > 0.1$) They were conjunctivitis and epidermitis 1–2 grades. After a course of radiotherapy, ophthalmologic parameters did not change. SE had no difference in various

modes of fractionation (92.6% – CF, 85.7% – MF ($p > 0.1$), and dose delivery methods (2D – 95.8%; 3D – 83.3%, $p = 0.06$), a strong tendency to reduce radiation reactions using 3D-CRT. Analyzing SE of different fractionation modes and different ways of planning, we found that the MF and 3D-CRT SE were in 2 of 21 (9.5%) patients, while CF and 3D-CRT – 18 of 27 (66.7%) patients ($p < 0.01$); at MF and 2D-RT – 16 of 21 (76.2%) patients, while CF and 2D-RT – 7 out of 27 (25.9%) ($p < 0.05$). Thus, the smallest number of SE observed in the group of MF 3D-CRT; at CF and 2D-RT SE were significantly increased than with 3D-CRT and MF ($p < 0.05$); the number of SE at CF (3D) and MF (2D) did not differ. Total dose is evaluated on intact eyes in 28 patients with involvement of the orbit. With 3D-CRT (14 patients) the average of total dose on the intact eye was 2.0 ± 0.2 Gy; at 2D-RT (14 patients) – 5.7 ± 1.2 Gy, $p < 0.05$.

Conclusion: The modern approaches in radiation therapy of patients with OL (MF, 3D-CRT) at preservation of high antitumor effect promote decrease of quantity of early reactions, and 3D-CRT also to the considerable (by 2 and 5 times) to decrease in total dose on an intact eye.

Keywords: extranodal lymphomas; extranodal marginal zone lymphoma of MALT type; non-Hodgkin lymphoma (NHL).

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ABSOLUTE PERIPHERAL MONOCYTE COUNT PREDICTS PROGRESSION-FREE SURVIVAL IN EXTRANODAL MARGINAL ZONE LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE

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Introduction: To describe the clinical characteristics and outcomes of 112 mucosa-associated lymphoid tissue (MALT) lymphoma, analyze the prognostic factors and investigate the prognostic value of peripheral monocytes at diagnosis in patients with MALT lymphoma.

Methods: One hundred and twelve patients with MALT lymphoma were studied including 41 patients with gastrointestinal (GI) involvement and 71 patients with non-GI involvement: 35 ocular adnexa; 9 lung; 8 parotid; 5 thyroid; 3 subcutaneous tissue; 2 thachea; 2 tonsil; 2 submandibular gland; 2 thymus; 1 bladder; 1 oral cavity and 1 breast. The 22.3% patients had advanced Ann Arbor stage. Comparisons

between GI and non-GI patients showed a larger percentage of B symptoms and lymph nodes involvement in GI MALT lymphoma patients.

Results: A total of 101 patients (90.2%) made response to the first-line treatment, and there was no significant difference between the two groups. With a median follow-up duration of 31 months, estimated of progression-free survival (PFS) and overall survival (OS) at 5 years was 85.5% and 92.9%, respectively. Neither PFS nor OS showed significant difference between the two groups. Multivariate analysis showed that lymph nodes involvement, International Prognostic Index (IPI) and absolute monocyte counts (AMC) were independent significant prognostic factors for PFS (Fig. 1).

Conclusion: MALT lymphoma is an indolent lymphoma with a long-term survival. The presence of lymph nodes involvement, IPI ≥ 3 and high AMC at diagnosis were significantly associated with inferior PFS.

Keywords: extranodal marginal zone lymphoma of MALT type; prognostic indices.

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TREATMENT RESULTS ACCORDING TO CELLULAR SUBTYPES OF GASTRIC MALT LYMPHOMA

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Introduction: Although gastric MALT lymphoma is rare disorder, much work have been done. However, relationship between its treatment methods by histological subtypes has not well studied. In particular, role of etiologic factors may be different in various cellular subtypes of gastric MALT lymphoma, and this may change the treatment strategy of disease.

Methods: We analyzed the treatment results of 106 patients with MALTS, average age of 54.7 ± 0.4 years. Men was 37 (34.9%), 69 women (65.1%). Histological verification of small-cell type of tumor found in 49 (46.2%) patients, intermediate type in 35 (33.0%) and in 22 (20.8%) mixed type lymphoma of the stomach. By classification of Lugano (1993) 1st stage in 69 (65.1%) patients, IIE in 14 (13.2%), II1 in 16 (15.1%), II2 in 7 (6.6%). Contamination degree by H.Pylori was defined as mild, moderate and high. Each histological subtype analyzed according to contamination degree by H.Pylori. Patients with high contamination degree underwent eradication therapy, moderate degree – eradication + chemotherapy (CHOP) and mild degree – chemotherapy. Rituximab was used in CD20 positive samples.

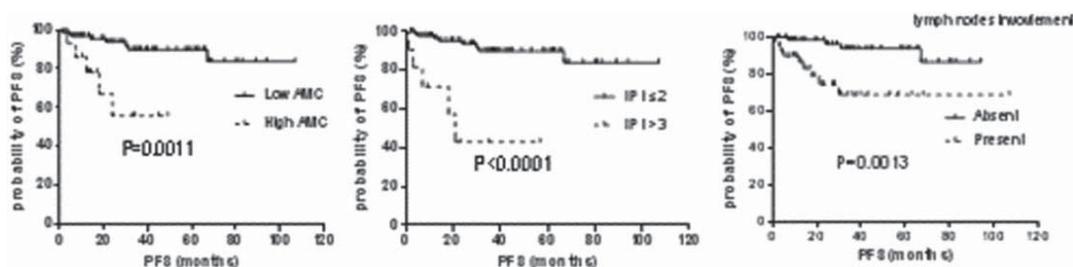


Figure 1. PFS according to the absolute monocyte counts (AMC) (A), IPI (B) and lymph nodes involvement (C) at diagnosis.

Results: A total of 36 patients of small cellular subtype patients were high degree contamination, and we recommended eradication therapy. Complete response rate was 69.4% during one-year observation period. In recurrent cases, we used chemotherapy and achieved complete response, but 3 of them had complication of bleeding and carried out gastric resection. Other patients were moderate and mild degree contamination and checked for CD20 and 12 out of them were positive. We recommended rituximab with chemotherapy. Complete response was 100% in 36 months observation.

Patients with intermediate cellular type were (20 patients) 57.1% H. Pylori high contamination degree and underwent eradication therapy. However, complete response was 45%. CD20 was positive in all recurrent cases and in patients with other degrees of contamination. Using rituximab gave 90% complete response and 2 patients developed complications with bleeding.

A total of 18 patients of mixed cellular subtype were mild and moderate degree contamination, and CD20 was positive in all patients. We recommended chemotherapy with rituximab, and complete response was 81.8% (15 out of 18); 4 patients were high degree contamination, but we could not achieve complete response and recommended chemotherapy with rituximab. Complete response was 100% in 38-month observation period.

Conclusion: Eradication therapy has beneficial effects in small cellular subtype with high contamination degree. However, its effectiveness is low in other cellular subtypes. Treatment with rituximab and chemotherapy was effective in CD20 cases with mild and moderate degree of contamination and in recurrent cases.

Keywords: CD20; Mucosa-Associated Lymphoid Tissue (MALT); rituximab.

433 INCIDENCE AND OUTCOME OF PRIMARY EXTRANODAL FOLLICULAR LYMPHOMAS. ANALYSIS FROM THE CZECH LYMPHOMA STUDY GROUP (CLSG) REGISTRY

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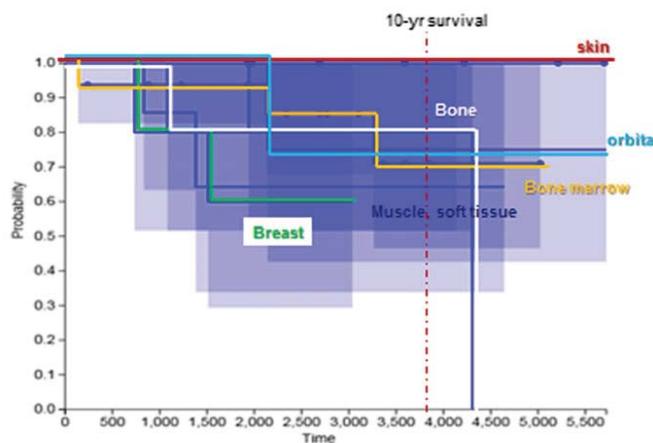
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Introduction: Primary extranodal follicular lymphoma (FL) is very rare and heterogenous subgroup, which is not well described up to now. We decided to better analyze the incidence, clinical parameters and outcome of primary extranodal FLs.

Methods: Between 1994 and 2016, 2453 patients with newly diagnosed follicular lymphoma (grade 1–3A) were registered in the prospectively maintained multicentric Czech Lymphoma Study Group (CLSG) database. Initial rigorous staging included at least a thoracic and abdominal CT scan, and unilateral bone marrow biopsy. Treatment and outcomes including response, time to progression, and survival were collected annually. Enrolled patients are followed until death, withdrawal of consent, or loss of follow-up. For the analysis, the patients with no nodal involvement were selected.

Results: Totally, we identified 97/2453 (4%) patients with indolent FL and exclusively extranodal involvement among all FLs. There were

OS CURVES ACCORDING TO LOCALITY OF PRIMARY EXTRANODAL FL



37/97 (38%) men, median of age was 62 (21–90) years, and 60/97 (62%) patients had FL grade I or II (28/97 grade unknown). One localization only was involved in 73/97 (75%) cases, B-symptoms were present in 5/87 (6%), and lactatede hydrogenase was elevated in 26/97 (30%) patients. The most frequent involved localities were skin 21/97 (22%), bone marrow 16/97 (16%), GIT 14/97 (14%), orbital adnexa 10/97 (10%), bones 9/97 (9%), and mamma 8/97 (8%). Some treatment was administered in 84/97 (87%) patients, whereas 13/97 (13%) cases are observed without any therapy. Conventional chemotherapy was administered in 46/97 (47%) patients, and 39 (40%) of them received CHOP-like regimens. Rituximab was given in 39/97 (40%) cases. Radiotherapy alone was given in 15/97 (15%) patients. Response to therapy was evaluated in 79/84 treated patients, where 65/79 (82%) patients obtained complete remission, 32 (33%) patients relapsed and 17/97 (17.5%) of them died. Progression-free survivals in 5 and 10 years were 68% and 54%; overall survivals were 88% and 72%, respectively. All 13 patients who were on “watch and wait”(GIT = 3, orbita = 3, skin = 3, other =4) were with no progression with median follow up 2.2 (1.1–6.6) years. There were no differences in OS between “watch and wait” subgroup and treated patients. Survival differences among various locality were identified in skin vs. all other non-skin extranodal FL ($p=0.01$; Figure).

Conclusion: Primary extranodal FL is rare variant of this disease, with heterogenous manifestation and generally good response and prognosis. With an exception of skin FL, there was no difference in survival according to localization of FL.

Keywords: extranodal lymphomas; follicular lymphoma (FL).

CLL

434 MYD88 MUTATIONS PREDICT UNFAVORABLE PROGNOSIS IN CHRONIC

LYMPHOCYTIC LEUKEMIA PATIENTS WITH MUTATED *IGHV* GENE

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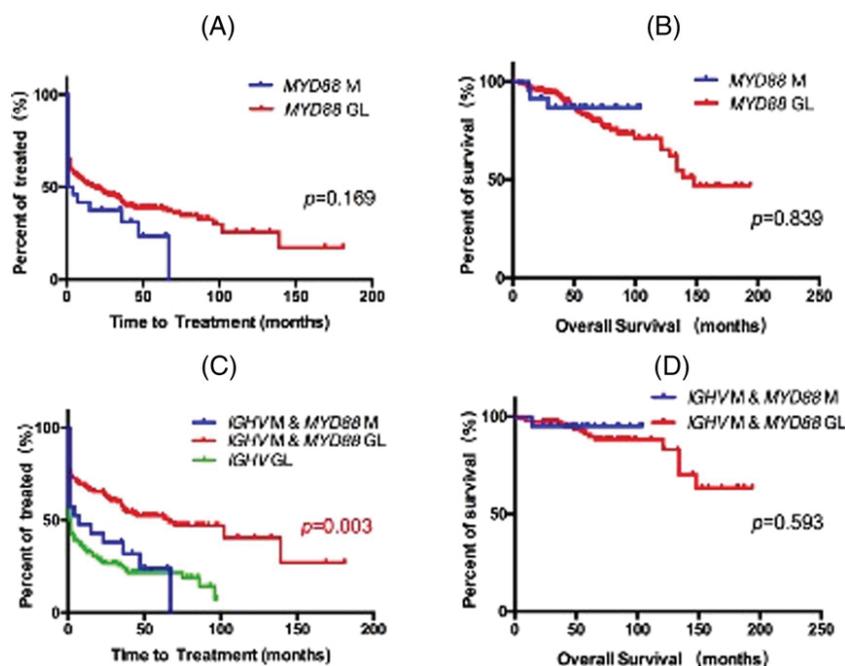
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Introduction: Myeloid differentiation primary response gene 88 (*MYD88*) L265P mutations have been identified as a diagnostic biomarker in Waldenstrom's Macroglobulinemia (WM). However, little is known about the incidence and prognostic value of *MYD88* mutations in Chinese chronic lymphocytic leukemia (CLL) patients.

Methods: Using Sanger sequencing along with allele-specific polymerase chain reaction (AS-PCR), we studied the incidence, clinical associations and prognostic impact of *MYD88* mutations in 284 Chinese CLL patients.

Results: *MYD88* mutations were detected in 25/284 (8.8%) previously untreated CLL patients in our center, including all mutations in exon 3-5. The hotspot L265P substitution was detected in 18/284 (6.3%) cases by AS-PCR. CLL patients carrying *MYD88* mutations had a lower CD38 positive rate ($p = 0.011$) and CD200 MFI ($p < 0.001$) than those with wild-type *MYD88* did. In addition, *MYD88* mutations were more common in patients with mutated immunoglobulin heavy chain variable region (*IGHV*, 22/25 vs.143/254, $p = 0.001$). No correlation was observed between *MYD88* mutations with other clinical characteristics including age, sex, Binet stage, CD23 and molecular abnormalities. Multivariate analysis confirmed *MYD88* mutations to be an independent prognostic factor for shorter time-to-treatment in the *IGHV*-mutated subgroup.

Conclusions: Our study reported the higher incidence of *MYD88* mutation in Chinese CLL patients than in Caucasia CLL cases, implying potential differences in genotype among ethnic groups might affect



the onset and progression of CLL. *MYD88* mutations independently associate with shorter TTT in M-CLL subgroup, identifying cases with rapid progression.

Keywords: chronic lymphocytic leukemia (CLL); *MYD88*; prognostic indices.

435 DEFINITION OF DISEASE-PROGRESSION RISK STRATIFICATION IN UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA USING COMBINED CLINICAL, MOLECULAR AND VIROLOGICAL VARIABLES

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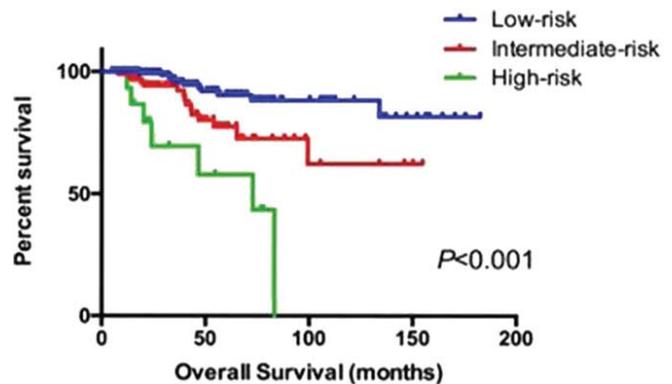
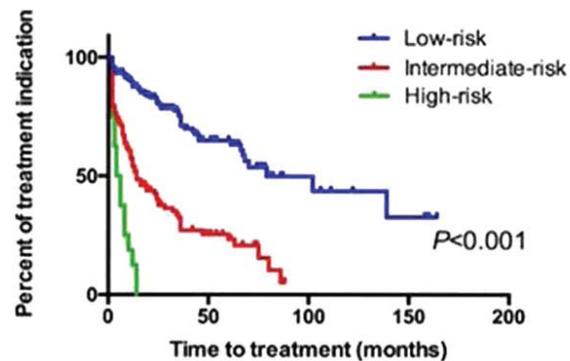
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Introduction: Chronic lymphocytic leukemia (CLL) is a chronic lymphoproliferative disease characterized by highly biological heterogeneity and variable clinical course. Previous researches showed that 30%–40% of patients with CLL could survive for decades of years without initial need for treatment, while some patients rapidly succumb to the progression of disease. In recent years, data on prognostic value of molecular mutations and viral infections on CLL continue accumulating. Our study was determined to define variables correlated with time-to-treatment (TTT) in Chinese with chronic lymphocytic leukemia (CLL) and use these variables to develop a prognostic score. We determined correlation of the prognostic score with survival and compared this score with those developed for persons of predominately European descent with CLL in this study.

Methods: We collected clinical, molecular, serologic and virological parameters of 334 newly diagnosed and untreated CLL patients. Utilizing Chi-square test, survival analysis, log-rank test and Cox hazard regression analysis, we checked the correlations between variables and prognosis of our patients.

Results: By analyzing 334 newly diagnosed and untreated CLL patients without treatment indication, we demonstrated that Binet stage B/C, lymphocyte level, *TP53* abnormality, *IGHV* non-mutation and evidence of HBV and EBV infection were independently associated with TTT in multivariate analyses. We used these data to construct a prognostic scoring system that divided subjects into three cohorts of low, intermediate and high risks with median TTTs of 102 months (95% confidence interval 50–154 months), 15 months (5–25 months) and 6 months (3–9 months; *p*-value for trend <0.001). Corresponding median OS from diagnosis were not reached, not reached and 73 months (55–91 months; *p*-value for trend <0.001).

Conclusions: We improved current risk stratification for patients with untreated CLL using combined clinical, molecular and virological variables and defined three different risk groups with this novel stratification system. Some variables associated with TTT in Chinese with CLL are similar to those of persons of predominately European descent whereas others such as virus infections differ or have not been carefully studied in large cohorts. Our prognostic score may help identify Chinese with CLL with brief TTTs and survivals and prompt early interventions.



Keywords: chronic lymphocytic leukemia (CLL); Epstein-Barr virus (EBV); hepatitis B.

436 PORTUGUESE REAL-LIFE EXPERIENCE WITH IBRUTINIB OUTSIDE CLINICAL TRIALS – A MULTICENTER ANALYSIS

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Factors	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Age > 60 y	1.098	0.781–1.546	0.590	–	–	–
Sex (male)	1.083	0.762–1.540	0.657	–	–	–
Binet B/C	3.174	2.267–4.445	<0.001	2.474	1.725–3.546	<0.001
ALC > 50 × 10 ⁹ /L	1.749	1.263–2.422	0.001	1.604	1.118–2.302	0.010
ALB < 40 g/L	1.180	0.787–1.770	0.423	–	–	–
TK-1 > ULN	0.825	0.448–1.519	0.537	–	–	–
β2-MG > ULN	1.291	0.853–1.955	0.227	–	–	–
HBsAg+	3.669	2.360–5.703	<0.001	1.985	1.208–3.263	0.007
TP53 disruption	2.682	1.841–3.907	<0.001	1.737	1.150–2.623	0.009
EBV positive	3.418	2.022–5.778	<0.001	2.739	1.585–4.733	<0.001
11q deletion	1.831	0.944–3.210	0.052	–	–	–
NOTCH1 mutation	1.604	0.504–5.106	0.424	–	–	–
+12	1.252	0.713–2.199	0.434	–	–	–
13q14 deletion	0.907	0.536–1.533	0.715	–	–	–
6q23 deletion	0.872	0.390–1.945	0.737	–	–	–
IGHV unmutated	2.034	1.466–2.821	<0.001	1.679	1.198–2.353	0.003
MYD88 mutation	1.062	0.600–2.333	0.882	–	–	–
SF3B1 mutation	1.933	0.373–3.880	0.882	–	–	–
CD38(≥30%)	1.368	0.881–2.126	0.163	–	–	–
ZAP70(≥20%)	1.154	0.778–1.713	0.476	–	–	–

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Introduction: Bruton's tyrosine kinase inhibitor, ibrutinib, was recently approved for treatment-naïve, relapsed/refractory and del(17p)/TP53 mutated chronic lymphocytic leukemia (CLL). Discrepancies between clinical trials and routine healthcare are commonly observed in hematology–oncology. We aimed to evaluate the real-world clinical characteristics and drug-related toxicities of patients with CLL treated with ibrutinib in Portugal.

Methods: We conducted a multicenter (13 institutions) retrospective observational study of 70 patients diagnosed with CLL that began treatment with ibrutinib between May 2014 and January 2017. We evaluated patient characteristics, biological features of the disease, previous therapy, toxicities, and overall survival (OS). All patients received ibrutinib as a single agent, all but 5 at an initial dose of 420 mg daily. Clinical data were analyzed using IBM® SPSS® Statistics version 22.0.

Results: Median age of the cohort was 68 years (IQR: 63–74); 41 patients (58.6%) were male. Median CIRS score was 4 (2–6); ECOG performance status score was 0–1 in 90.5% and 2–4 in 9.5% of evaluable patients; 65.7% were staged as Rai III/IV and 61.4% as Binet C; 54.4% had del(17p) and 11.9% del(11q); 15.7% were treatment naïve; median number of previous lines of therapy for CLL was 2 (1–3); 50% were previously treated with fludarabine and 74.3% with rituximab-containing regimens.

Median duration of ibrutinib treatment was 7.7 months (3–15.5); median follow-up was 8.7 months (4–18.3). Adverse events (AEs) were identified in 87.1% of patients; 51.4% had severe AEs (SAEs – CTCAE grade ≥ 3). The most frequent AE was infection, in 41.4% of patients (69% SAEs), followed by thrombocytopenia (40%–21.4% of which

SAEs), neutropenia (35.7%–48% of which SAEs), anemia (28.6%), diarrhea (25.7%), bleeding (21.4%–40% of which SAEs), and arthralgia (20%). AEs led to ibrutinib dose reduction in 18.6% and temporary suspension in 31.4% of patients. Discontinuation-free survival at median follow-up was 82.9%. Ibrutinib was discontinued in 16 patients (22.9%): 5 due to progression, 2 prior to allogeneic hematopoietic stem cell transplantation, 1 due to loss of follow-up, and the remaining 8 because of AEs (50% infectious). OS at median follow-up was 82.9%. 14 patients died, 6 due to disease progression, 5 due to infection, 2 due to hemorrhage, and 1 of sudden death. ECOG 2–4 was significantly associated with an increased risk of death (log-rank p-value 0.013; HR 4.06, 95% CI: 1.22–13.5). OS wasn't significantly different in patients with and without del(17p).

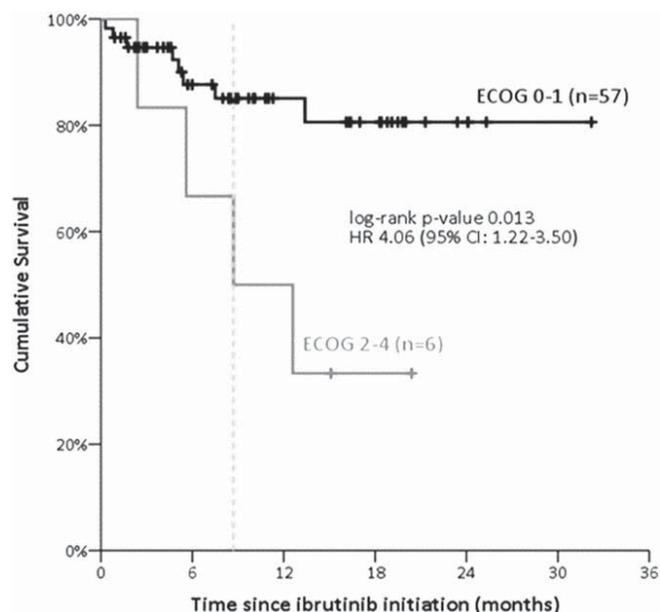
Conclusions: The incidence of SAEs was similar to the one reported in the RESONATE trial, proving the safety of ibrutinib as a single agent in CLL. As suggested in the literature, ibrutinib seems to overcome the negative prognostic impact of del(17p). ECOG performance status remains an important predictor of mortality in this population.

Keywords: chronic lymphocytic leukemia (CLL); ibrutinib.

437 EFFECTS ON THE HUMAN IMMUNE SYSTEM AFTER OBINUTUZUMAB MONOTHERAPY TREATMENT

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Obinutuzumab is an engineered monoclonal antibody designed to attack and destroy targeted B-cells, both directly and together with the human immune system. Natural Killer (NK) cells represent the innate immune system that fights against tumors and Obinutuzumab induces NK cell antibody-dependent cell-mediated cytotoxicity (ADCC). In our study, we confirm that Obinutuzumab monotherapy produces NK cell depletion in the peripheral blood of patients with Chronic Lymphocytic Leukemia (CLL). This depletion may be reversible in patients that achieve the complete elimination of the neoplastic CLL B-cells. Combination of Obinutuzumab with NK or lymphokine-activated killer (LAK) cells may help to optimize the potential of this novel anti-CD20 monoclonal antibody.

Objective: Investigate the effects on the human immune system after Obinutuzumab monotherapy treatment in patients with CLL.

Method: Eight patients (4 previously untreated and 4 refractory/relapsed) diagnosed with CLL and small lymphocytic lymphoma (SLL) were studied. To evaluate these effects, we analyzed the distribution of CD4⁺ and CD8⁺ T-cells, B-cells and NK cells in the peripheral blood of CLL patients who were treated with Obinutuzumab in monotherapy. The distribution of peripheral blood lymphocyte was examined prior to each dose of Obinutuzumab, and 24–72 hours post-infusion. Analyses were performed by flow cytometry with monoclonal antibodies against CD3, CD4, CD8, CD19 and CD56+.

Results: After 24–72 hours of Obinutuzumab infusion, CD4⁺ T-cells and CD8⁺ T cells were significantly decreased in peripheral blood compared to prior to therapy. This reduction in the CD4⁺ T-cells persisted after 6 cycles of Obinutuzumab (1235 cells/ml basal vs 662 cells/ml after 6 cycles, $p \leq 0.05$), but not in CD8⁺ T cells (1235 cells/ml basal vs 836 cells/ml after 6 cycles).

Interestingly, we also noted significant differences in the NK cell compartment after 24–72 hours (490 cells/ml basal vs 50 cells/ml 24–72 h

post-infusion, $p \leq 0.05$), and at cycle 6 (490 cells/ml basal vs 149 cells/ml after 6 cycles, $p \leq 0.05$).

Discussion: Obinutuzumab induces depletion of NK cells in patients with Chronic Lymphocytic Leukemia. We hypothesize that NK cell restoration could be in relationship with the destruction of the great leukemic burden induced by the initial NK-ADCC effect.

Conclusion: Obinutuzumab monotherapy produced greater or similar NK cell depletion compared with patients treated with immuno-chemotherapy such as Rituximab-Bendamustine or R-CHOP. Further studies are necessary to determine if pre-treatment levels of NK cells may be a new prognostic and predictor factor to response to obinutuzumab.

Keywords: antibody-dependent cytotoxicity (ADC); chronic lymphocytic leukemia (CLL); obinutuzumab.

438 COMPARISON OF INNATE IMMUNITY CHANGES FOLLOWING IBRUTINIB AND VENETOCLAX TREATMENT OF RELAPSED CHRONIC LYMPHOCYTIC LEUKAEMIA

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Introduction: Chronic Lymphocytic Leukaemia (CLL) is associated with profound immunodeficiency and immune dysregulation. Dysfunction of cells of the innate immune system including NK cells, monocytes, and DCs may play important roles in CLL progression, limiting anti-tumour immune response and contributing to the CLL supportive microenvironment. CLL has been shown to be sensitive to immunological control either via monoclonal antibody therapy, immunomodulatory drug therapy or allogeneic transplant. Targeted small molecule inhibitors, including the BTK inhibitor Ibrutinib and the Bcl-2 inhibitor Venetoclax have revolutionised CLL treatment, yet detailed understanding of their immunological impact is still unfolding.

Methods: Peripheral blood mononuclear cells were isolated from patients enrolled on ethically approved biomarker studies appended to either approved clinical trials or standard of care. Patients were treated with either Ibrutinib ($n = 12$) or Venetoclax ($n = 6$) for CLL progressing after initial standard chemotherapy. Samples were obtained immediately prior to treatment initiation (baseline) and after 12 months of therapy and from healthy age-matched donor controls ($n = 10$). Analysis was performed by flow cytometry using a BD LSRFortessa™ to profile the immune cell subsets using standard antibody panels to identify CD4⁺ and CD8⁺ T cells, NK cells, monocytes, myeloid-derived suppressor cells (MDSC), dendritic cells (mDC) and $\gamma\delta$ T cells. The relative frequencies and absolute count of immune

subsets were calculated. Wilcoxon test or Kruskal-Wallis ANOVA using $p < 0.05$ determined statistical significance.

Results: Compared to pre-treatment baseline samples, both Ibrutinib and Venetoclax treatment resulted in a significant increase in the frequency and absolute number of both MDSC (HLADR⁺CD11b⁺CD33⁺) and normal monocytes (HLADR⁺CD11b⁺CD33⁺) to the same level (Ibrutinib) or in excess (Venetoclax) to those seen in healthy controls (Fig. 1). The frequency of mDC (HLADR⁺CD11c⁺) was significantly increased following Ibrutinib (but not Venetoclax) treatment.

Following both Ibrutinib and Venetoclax treatment, a significant increase in the frequency of NK cells (CD3⁺CD56⁺) was seen, although only Venetoclax treatment resulted in a normalisation of NK cells comparable to healthy controls. Both Ibrutinib and Venetoclax treatment resulted in a significant increase in the frequency of $\gamma\delta$ T cells.

Conclusion: BTK and Bcl-2 inhibitors have different effects on innate immune subsets. Whilst the immunological profile of patients improves with both, immunological recovery is greatest in those treated with Venetoclax. This provides an opportunity for the potential introduction of immunotherapies following small molecule therapy to promote anti-CLL immunity and improve durability of responses.

Keywords: chronic lymphocytic leukemia (CLL); immune system.

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CHRONIC LYMPHOCYTIC LEUKEMIA INVOLVEMENT OF CENTRAL NERVOUS SYSTEM: A SINGLE CENTRE EXPERIENCE

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Introduction: Chronic lymphocytic leukemia (CLL) involvement of central nervous system (CNS) is reported to be rare, mainly due to only occasional appear of predominantly non-specific neurological symptoms. Neurologic complications arising from direct leukemic involvement of CNS is stated in only 1% of patients (pts) with CLL. There is no treatment consensus with similar results of intrathecal

chemotherapy or whole-brain irradiation, but some more recent studies reported more encouraging data with application of immunochemotherapy or tyrosine kinase inhibitor, ibrutinib. CLL with CNS involvement is related with poorer outcome, especially for pts with unfavorable cytogenetic (17p deletion).

Methods: We presented a small series of four pts that were diagnosed and treated in our Institution. All pts met the International Workshop on CLL diagnostic criteria (2008). Diagnosis of CNS involvement was established via neuroimaging methods such as MRI, as well as cerebrospinal fluid (CSF) cytology, and CSF multiparameter flow cytometry immunophenotyping method (CSF FCM).

Results: All pts were men with average age of 55.25 years (yrs). On CNS onset, all had disseminated disease and 17p deletion was registered in one case. Average latency period from CLL to CNS onset was 2.91 yrs. We registered heterogeneous neurological symptoms on CNS onset, including bradypsychia, headaches, nausea, vomiting, dysphasia, repeated unconsciousness, urinary incontinence, dyslexia, lack of fine motor control, diplopia and bilateral eyelid swelling. Diagnostics included positive CSF cytology in three cases, CSF FCM was performed in all of our cases. MRI scan was performed in all cases and was conclusive in three (75%) cases. On CLL onset, two pts were treated with systemic chemotherapy, FC (fludarabine, cyclophosphamide) in one case and CHOP (cyclophosphamide, doxorubicine, vincristine, prednisolone) in other, third was initially treated with corticosteroid therapy due to immunological thrombocytopenia and fourth was on "watch and wait" policy, due to comorbidities. Two of our pts were treatment naïve on CNS onset. When CLL in CNS was diagnosed, systemic chemotherapy was applied in all cases. First patient received high-dose methotrexate with intrathecal therapies, second R(rituximab)-FC, and two received DHAP regimen (dexametasona, high-dose cytarabine, cisplatin) in two cases. Average and median OS from CNS onset was 4 and 3.5 months, respectively, with lethal outcome in 75% of cases in our follow-up.

Conclusions: CLL in CNS is still rarely diagnosed, primarily due to the presence of heterogeneous, non-specific neurological symptoms, or their absence. The most effective diagnostics includes MRI, CSF-FCM, and if it is possible PCR detection of CLL cells in CSF. Our results confirm the poor therapeutic outcome and short survival in our group of pts.

Keywords: chronic lymphocytic leukemia (CLL); flow cytometry; immunochemotherapy.

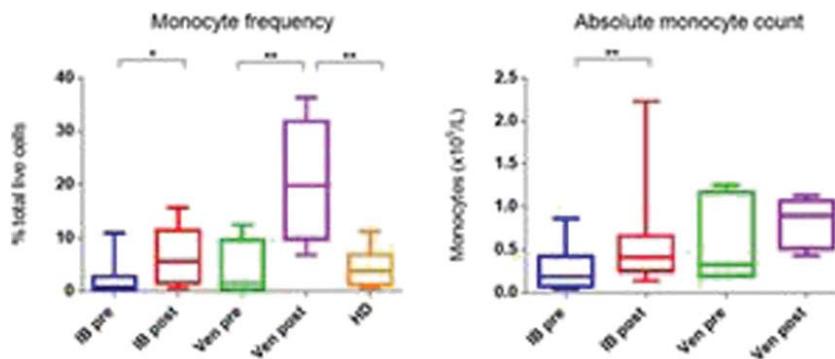


Figure 1. The frequency and absolute count of monocytes in patients treated with Ibrutinib (IB) or Venetoclax (VEN)

PLASMA CELL DISORDERS

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MINIMAL RESIDUAL DISEASE ASSESSMENT IN MULTIPLE MYELOMA: UTILITY AND FEASIBILITY IN RESOURCE CONSTRAINT SETTINGS OF INDIA

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Introduction: Financial means of a patient is major factor influencing management of multiple myeloma (MM) in India. Outside of clinical trials, physicians have to settle for varying drug combinations with/without autologous stem cell transplant (ASCT). The cost of treating MM with ASCT at our institute is around USD 3000. The financial burden mostly falls on the patient, as public/private medical insurances are available only to minority. Most state-funded tertiary care hospitals can provide serum protein electrophoresis (SPE), immunofixation electrophoresis (IFX), and morphological assessment of bone marrow (BM) plasma cell (PC) percentages. We introduced minimal residual disease (MRD) assessment by multicolour flow cytometry (MFC) at subsidized cost and analyzed its utility and feasibility.

Methods: A total of 52 newly diagnosed MM patients were included in the study. Upfront therapy included lenalidomide or thalidomide or cyclophosphamide in combination with Bortezomib and dexamethasone. Financial constraints in majority made ASCT possible only in 16 patients. MRD assessment on BM aspirate was done at end-induction or day +100 post-transplant. Six-colour flow cytometry was used for MRD assessment with pre-titrated cocktails of CD38, CD138, CD19, CD45, cytoplasmic kappa and lambda light chains, CD56, CD81, CD27, CD28, and CD200 in combinations of 3 tubes. At least 1 million events were acquired in each tube, and MRD positivity was reported at a sensitivity of 0.01%. This test was offered at a cost of USD 37 (INR 2500).

Results: There were 32 men and 20 women with mean age of 53.4 years. MFC identified 22 (42%) individuals with residual clonal PCs (range = 0.01 to 6.44%), including 3 in ASCT group. Positive IFX was noted in 12 and M-band in 8 out of 22 MRD-positive patients. BM morphology revealed >5% PCs in 4 out of 22 MRD-positive patients. PC percentage on morphology was significantly higher in MRD-positive group ($p = 0.05$), whereas the leukocyte counts were lower ($p = 0.005$). However, no significant difference was noted between the MRD status and age and sex distribution, mean values of hemoglobin, platelet count, serum creatinine, serum calcium and serum albumin. Mean follow up of around 13 months did not reveal a statistical difference in overall and progression-free survival between MRD-positive and negative groups.

Conclusions: MRD by MFC is sensitive technique and should be feasible at a relatively low cost (<50 USD) in most state-funded hospitals in

India. In our hands, it had a better sensitivity than SPE and IFX in assessing residual disease, and we propose its routine incorporation in monitoring of MM. Although, we could not demonstrate difference in overall and progression-free survival based on MRD status, it is understandable that a longer follow up and upgradation to 8 to 10 colour flow with increased sensitivity of MRD detection would be able to show more realistic outcomes.

Keywords: flow cytometry; minimal residual disease (MRD); multiple myeloma (MM).

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HIGH EFFICACY AND SAFETY OF VTD AS AN INDUCTION PROTOCOL IN NEWLY DIAGNOSED MM PATIENTS ELIGIBLE FOR HDT/AUTOSCT – A REPORT OF POLISH MULTIPLE MYELOMA STUDY GROUP

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Introduction: Three drug bortezomib-based regimens are nowadays generally recommended standard induction therapy for transplant-eligible patients with newly diagnosed multiple myeloma (MM). The choice between different regimens depends on drug availability in particular countries, their toxicity profile and local preferences. **Aims:** The aim of this retrospective analysis was to evaluate the efficacy and safety of VTD regimen in newly diagnosed MM patients eligible for HDT/autoSCT in routine clinical practice.

Methods: We collected the clinical data of 169 patients qualified to HDT/autoSCT treated with VTD as an induction regimen in 14 Polish

hematology centers. VTD protocol recommended by Polish Multiple Myeloma Study Group was as follows: bortezomib: 1.3 mg/m² (days 1, 4, 8, 11), thalidomide: 100–200 mg a day (days 1–21), dexamethasone 20 mg a day (days: 1, 2, 4, 5, 8, 9, 11, 12) or 40 mg a day (days 1–4), every 21 days. Adverse events (AEs) were graded according to CTCAE v4.0. The analysis involved also the impact of VTD regimen on efficiency of stem cells mobilization as well as high-dose therapy/autologous stem cell transplantation (HDT/autoSCT) procedure.

Results: In the cohort of 169 patients, median age was 59 years (range 36–70). ISS stage 1 was found in 30.8% of patients, ISS 2 and 3 in 20.7% and 45.5%, respectively. Median number of VTD cycles was 5. In 81.6% of patients, bortezomib was administered subcutaneously. Thalidomide dose was 100 mg a day in 85.1% of patients. Bortezomib dose was reduced in 43 patients (25.4%) with peripheral polyneuropathy as the most common reason (75%). The most common grade 3/4 adverse event was polyneuropathy, observed in 20 patients (11.8%) and neutropenia, noted only in 5 patients (3%). Response rate-PR was achieved in 95% of patients, including 5.6% of sCR, 27.1% of CR and 35.1% of VGPR. So far, stem cell mobilization was performed in 110 patients, most commonly used protocols were cyclophosphamide (42.9%) and cytosine arabinoside (36.2%). In 69.3% of patients, one apheresis allowed to obtain the number of stem cells sufficient for transplantation. Median yield of CD34+ cells was 11×10^6 /kg (max 55.7×10^6 /kg). HDT/autoSCT was performed so far in 89 patients with MEL 200 protocol as conditioning regimen in 77.6% of patients. Median number of transplanted CD34+ cells was 4.4×10^6 /kg. Median time to reach ANC count >0.5 G/L and PLT count >20 G/L was 11 days and 12 days, respectively. In the evaluation of response 100 days after HDT/autoSCT performed in 81 patients, sCR rate increased from 5.6% to 12.7% and CR from 27.1% to 36.7%.

Conclusions: VTD regimen allowed to achieve ≥PR in 95% of patients including ≥VGPR in 64.8% of patients as compared to 73.5% ≥ PR including 36% of ≥nCR achieved in patients treated with CTD in our previous study (Dmoszynska et al. Leuk Res 2010). In 96% of patients subsequently undergoing stem cell mobilization, sufficient number of CD34+ cells was obtained during first procedure. HDT/autoSCT further increased response rate after VTD induction (≥CR up to 43.5%, ≥VGPR up to 83.5%).

Keywords: autologous stem cell transplantation (ASCT); bortezomib; multiple myeloma (MM).

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DARATUMUMAB, BORTEZOMIB AND DEXAMETHASONE (DVD) VS BORTEZOMIB AND DEXAMETHASONE (VD) IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM): EFFICACY AND SAFETY UPDATE (CASTOR)

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Introduction: Daratumumab (D), a human, CD38-targeting mAb, is well tolerated and induces deep and durable responses in patients (pts) with RRMM. We provide an update of CASTOR (NCT02136134), a multicentre, phase 3, randomised study of DVD vs Vd in RRMM.

Methods: All pts received ≥1 prior line of therapy (LOT) and were administered 8 cycles (Q3W) of Vd (1.3 mg/m² SC bortezomib on days 1, 4, 8, and 11; 20 mg PO/IV dexamethasone on days 1–2, 4–5, 8–9, and 11–12) ± D (16 mg/kg IV once weekly in Cycles 1–3, every 3 weeks for Cycles 4–8, then every 4 weeks until progression). Bortezomib-refractory pts were ineligible. Minimal residual disease (MRD) was assessed upon suspected CR and at 6 and 12 months following the first dose at sensitivities of 10⁻⁴, 10⁻⁵, and 10⁻⁶ using the ClonoSEQ™ assay (Adaptive Biotechnologies, Seattle, WA).

Results: Pts received a median (range) of 2 (1–10) prior LOTs; 66% were previously treated with bortezomib, and 21% were refractory to lenalidomide in their last prior LOT. After a median follow-up of 13.0 months, PFS was significantly prolonged with DVD vs Vd (median, not reached vs 7.1 months; HR, 0.33; 95% CI, 0.26–0.43; *P* < 0.0001). This PFS benefit was seen regardless of number of prior LOTs received, with greatest benefit observed in 1 prior line pts (median, not reached vs 7.9 months; HR, 0.22; 95% CI, 0.14–0.34; *P* < 0.0001). ORR was also significantly higher for DVD vs Vd (84% vs 63%), along with ≥VGPR (62% vs 29%) and ≥CR (26% vs 10%; *P* < 0.0001 for all). MRD-negative rates were ≥4-fold higher at all three sensitivity thresholds with DVD vs Vd (10% vs 2% at 10⁻⁵ threshold). Pts who achieved MRD negativity demonstrated prolonged PFS compared with MRD-positive pts; 37 (15%) and 58 (24%) deaths were observed in DVD vs Vd, respectively, and follow up is ongoing. The most common grade 3/4 TEAE was thrombocytopenia (45% vs 33%). Updated efficacy and safety data will be presented.

Conclusions: DVd provided significant benefits with respect to PFS, ORR, depth of response, and MRD-negative rate vs Vd. no new safety signals were reported. These data continue to support the use of DVd in RRMM pts and indicate that pts with 1 prior LOT will derive the most benefit.

Keywords: CD38; monoclonal antibodies (MoAb); multiple myeloma (MM).

443 DARATUMUMAB, LENALIDOMIDE, AND DEXAMETHASONE (DRD) VS LENALIDOMIDE AND DEXAMETHASONE (RD) IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM): EFFICACY AND SAFETY UPDATE (POLLUX)

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Introduction: Daratumumab (D) is a human CD38-targeting mAb that significantly prolongs progression-free survival (PFS) when added to standard-of-care regimens in patients (pts) with RRMM. We examined updated efficacy and safety data from POLLUX (NCT02076009), a randomised phase 3 study of DRd vs Rd in RRMM.

Methods: Pts with ≥ 1 prior line of therapy (LOT) received Rd (25 mg PO lenalidomide on days 1–21 of each q4w cycle; 40 mg dexamethasone weekly) \pm D (16 mg/kg IV qw for cycles 1 and 2, q2w for cycles 3–6, then q4w until disease progression). Pts refractory to

lenalidomide were ineligible. Minimal residual disease (MRD) was assessed on bone marrow samples at time of suspected complete response (CR) and at 3 and 6 months post-suspected CR at sensitivities of 10^{-4} , 10^{-5} , and 10^{-6} via next-generation sequencing (Adaptive Biotechnologies, Seattle, WA).

Results: Pts received a median (range) of 1 (1–11) prior LOT. 55% received prior IMiDs (18% lenalidomide). Based on previous median follow-up of 17.3 months, DRd significantly prolonged PFS (median, not reached vs 17.5 months; HR, 0.37; 95% CI, 0.28–0.50; $P < 0.0001$) and significantly improved overall response rate (ORR; 93% vs 76%, $P < 0.0001$) vs Rd. DRd induced higher rates of deep responses vs Rd (\geq very good partial response [VGPR]: 78% vs 45%; \geq CR: 46% vs 20%; all $P < 0.0001$) and included MRD negativity, which was >3 -fold higher across all 3 sensitivity thresholds for DRd vs Rd (25% vs 6% at the 10^{-5} threshold). MRD-negative pts demonstrated longer PFS vs MRD-positive pts. Follow up for overall survival (OS) is ongoing (OS events: 40 [14%] in DRd and 56 [20%] in Rd). No new safety signals were identified with longer follow up. Updated efficacy and safety data based on approximately 25-month follow up will be presented at the meeting.

Conclusions: DRd provided significant benefits vs Rd in terms of PFS, ORR, and MRD negativity, and the favourable safety profile of DRd was maintained with longer follow up. These data further validate the use of DRd in RRMM pts who received ≥ 1 prior therapy.

Keywords: CD38; monoclonal antibodies (MoAb); multiple myeloma (MM).

NK AND T-CELL LYMPHOMAS

444 EPIDEMIOLOGICAL AND HUMANISTIC BURDEN OF CUTANEOUS T-CELL LYMPHOMAS: RESULTS OF a SYSTEMATIC REVIEW

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Introduction: Cutaneous T-cell Lymphomas (CTCL) are characterised by the expansion of malignant T cells within the skin. Many patients with aggressive subtypes relapse following first-line systemic chemotherapy. Various novel systemic therapies are therefore under investigation for treatment of relapsed disease.

Methods: A systematic review was performed in December 2016 to identify published evidence for the epidemiology of CTCL and impact on quality of life (QoL).

Results: Thirteen studies reported the incidence of CTCL (US, $n = 8$; Europe, $n = 3$; Iran, $n = 2$). The age-adjusted incidence was found to

range between 0.16 and 0.87 per 10^5 person-year ($n = 7$) and the annual incidence ranged from 0.39 to 0.9 per 10^5 ($n = 6$), with higher values being reported for the US compared with Europe or Asia. Evidence from seven studies (US, $n = 4$; Europe, $n = 3$) indicate that the incidence of CTCL has increased over time. An analysis of Surveillance, Epidemiology and End Results (SEER) data from 1973 to 2002 reported an increase in incidence of 2.9×10^{-6} per decade to 0.96 per 10^5 persons for 1998–2002. Various CTCL subtypes are recognised: mycosis fungoides (MF) is the most common subtype (45%), peripheral T-cell lymphomas accounts for 25% of cases and Sezary syndrome (SS), a particularly aggressive subtype for 1.3%. Twelve studies reported the impact of CTCL on QoL, with more advanced disease stage associated with poorer QoL. Various aspects of QoL (emotion, symptom, and function) were affected in patients with CTCL, with symptoms including fatigue, pain, insomnia, and pruritus reported. Pruritus is a frequently reported outcome in CTCL and was associated with all stages of disease and with poorer QoL. There is no standard therapy, but recommended options include skin-directed agents for early disease and systemic cytotoxic and targeted therapies for advanced disease. However, approximately, 65% of patients relapse following first-line therapy. For example, one study ($n = 168$) reported a response rate of 39% (complete response rate, 6.5%) to first-line therapy (including skin-directed therapies or systemic therapies) and an overall response rate of 15% (complete response rate, 1.7%) to second-line therapies. Five-year overall survival (OS) for patients with MF/SS diagnosed with advanced disease is generally less than 50%. For example, a study of 1502 patients with MF/SS from a single centre in the UK reported 5-year OS to range from 47% for patients with stage IIIA disease to 18% for patients with stage IVB disease.

Conclusions: CTCLs are rare malignancies, but the incidence appears to be increasing. Many patients with more aggressive disease relapse following first-line systemic therapy. Pruritus, a common and often severe symptom at all stages of disease, adversely affects QoL. There is a need for better treatments which address this burden, especially for patients with aggressive relapsed disease.

Keywords: cutaneous T-cell lymphoma (CTCL); mycosis fungoides (MF); Sezary syndrome.

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ALK EXPRESSION PLAYS DIFFERENT ROLES IN ANAPLASTIC LARGE-CELL LYMPHOMAS AND OUTCOME OF CRIZOTINIB USE IN RELAPSED/REFRACTORY ALK+ PATIENTS IN A CHINESE POPULATION

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Introduction: The prognostic value of anaplastic lymphoma kinase (ALK) expression in patients with anaplastic large-cell lymphoma (ALCL) remains controversial. The survival of relapsed/refractory ALK+ patients is still poor regardless of subsequent chemotherapy. Data on the clinical features of ALCL in a Chinese population are limited.

Methods: We retrospectively reviewed 1293 patients with pathologically diagnosed lymphoma at Guangdong General Hospital from June 2007 through August 2016, 50 of whom had systemic ALCL. We evaluated the incidence of ALCL, clinical characteristics, survival status, and outcome of crizotinib use in four relapsed/refractory ALK+ patients.

Results: Of the 1293 patients, 1193 (92.3%) had non-Hodgkin's lymphoma and 53 (4.4%) had ALCL. A total of 50 systemic ALCL patients, with a median age of 34 years, were evaluated. Among them, 33 (66.0%) were ALK+ and 17 (34.0%) were ALK-. The median follow-up time was 52.7 months. Most patients were men (70.0%) with advanced stage disease (III/IV, 76.0%), and 52.0% of patients presented with B symptoms. Patients with ALK+ were significantly younger than those with ALK- (28 vs. 56 years, $P < 0.001$). ALK+ patients had better progression-free survival (PFS) and overall survival (OS) than ALK- patients (PFS: 60.1 vs. 9.4 months, $P = 0.017$; OS: not reached vs. 32.7 months, $P = 0.021$). Multivariate analyses identified ALK+ expression, early stage disease (I/II), and absence of bone marrow involvement as independent prognostic factors for PFS and OS. In total, 15 ALK+ patients relapsed; 4 were treated with crizotinib and 2 died. All four patients showed CR after 1 month of crizotinib use; one patient received autologous stem cell transplantation, two underwent allogeneic hematopoietic stem cell transplantation, and the other patient became resistant to crizotinib after 3 months and died of quickly progressive disease.

Conclusions: Our results suggest that ALK expression has different prognostic significance in patients with ALCL. Relapsed ALK+ patients can increasingly be treated with targeted therapies, such as crizotinib, although they will inevitably develop acquired resistance. Mechanisms underlying early relapse after chemotherapy and resistance to crizotinib need further investigation.

Keywords: ALK; anaplastic large cell lymphoma (ALCL).

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CIRCULATING LOW ABSOLUTE CD4⁺ T CELL COUNTS MAY PREDICT POOR PROGNOSIS IN PATIENTS WITH EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

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Introduction: Extranodal natural killer/T cell lymphoma, nasal type (ENKTL) is a rare subtype of non-Hodgkin lymphomas. Host immunity

plays a role in lymphoma progression, analysis of which may provide useful information for assessing prognosis. Meanwhile, data of the role of specific circulating lymphocyte subsets as host immune factor in the progression of ENKTL is limited. This study aims to investigate the clinical correlation and distribution of circulating absolute CD4⁺ T cell counts (ACD4C) in ENKTL.

Methods: We retrospectively searched the medical records of 88 patients with untreated ENKTL diagnosed at the Department of Hematology at the First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital) from August 1, 2009 to May 31, 2016. The distribution and prognostic value of ACD4C at diagnosis was analyzed.

Results: The result showed that low ACD4C at diagnosis was significantly associated with stage III/IV ($P = 0.001$), B symptoms ($P = 0.020$), elevated serum lactate dehydrogenase (LDH) ($P < 0.001$), regional lymphadenopathy ($P = 0.015$), high-intermediate and high-risk International Prognosis Index (IPI) ($P < 0.001$) and Korean Prognostic Index (KPI) ($P < 0.001$). As well, we also found that low ACD4C have significant link to decreasing monocytes ($P = 0.001$), anemia ($P = 0.049$) and thrombocytopenia ($P = 0.014$). There were significant differences in both overall survival (OS) ($P < 0.001$) and progression-free survival (PFS) ($P < 0.001$) between ACD4C $< 0.3 \times 10^9/L$ cohort and ACD4C $\geq 0.3 \times 10^9/L$ cohort (Fig. A and B). With the median follow-up time of 33 months, patients who had ACD4C $< 0.30 \times 10^9/L$ had worse survival with the 3-year OS of 36.9% versus 81.2% in patients with high ACD4C, and the 3-year PFS of 32.1% versus 67.0%. The 5-year OS and PFS were 36.9% vs. 62.8% and 24.1% vs. 67.0% between ACD4C $< 0.3 \times 10^9/L$ cohort and ACD4C $\geq 0.3 \times 10^9/L$ cohort, respectively. The median OS time was 14 months, and the median PFS was 5.5 months in low ACD4C cohort, while the median OS and PFS were not reached in ACD4C $\geq 0.3 \times 10^9/L$ cohort. In univariate analysis, the results also demonstrated that B symptoms, poor PS, stage III/IV, primary extranasal presentation, regional lymphadenopathy, anemia, high and intermediate-high risk IPI and KPI were related with worse OS and PFS. Moreover, the multivariate Cox analysis identified the ACD4C as an independent predictor for OS ($P = 0.029$; relative risk, 2.632; 95% CI 1.104–6.276) and PFS ($P = 0.010$; relative risk, 2.719; 95% CI 1.264–5.849).

Conclusions: This retrospective study demonstrated that low ACD4C as important immune factor was associated with poorer survival and could act as a negative predictor for patients with ENKTL. It was supposed that ACD4C play an important role in the pathogenesis and progression of ENKTL.

Keywords: peripheral T-cell lymphomas (PTCL); prognostic indices.

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DUSP22 AND TP63 REARRANGEMENTS PREDICT OUTCOME OF ALK-NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA: A DANISH COHORT STUDY

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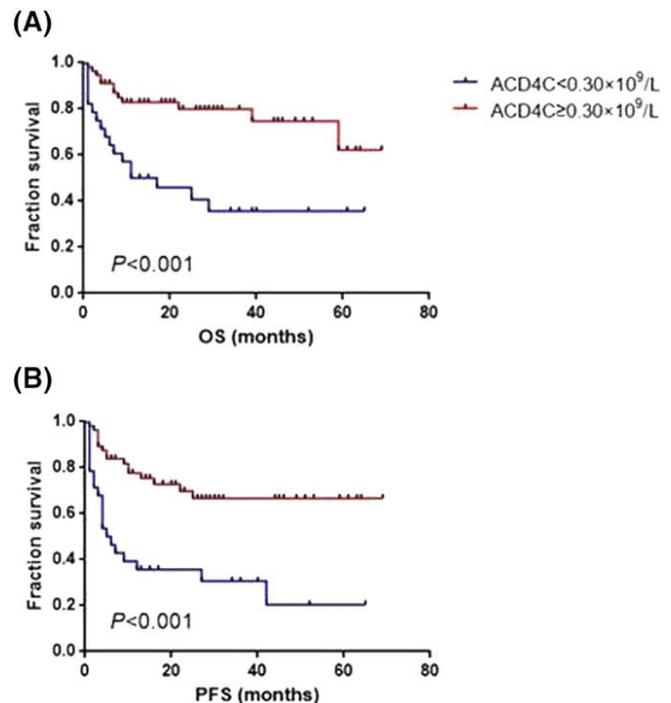


Figure legend: Fig. According to ACD4C at time of diagnosis, OS (A) and PFS (B) of 88 patients with ENKTL estimated by the method of Kaplan-Meier.

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Anaplastic large cell lymphomas (ALCLs) are among the most common systemic peripheral T-cell lymphomas (PTCLs) and are classified into anaplastic lymphoma kinase (ALK) positive and negative subtypes. Overall, patients with ALK-positive ALCLs have outcomes superior to those with ALK-negative ALCLs. However, a single retrospective study identified marked heterogeneity of clinical outcomes among ALK-negative ALCLs based on stratification by rearrangements of *DUSP22* or *TP63*.

Here, we sought to validate this observation in an independent, population-based cohort of 138 Danish PTCLs. *DUSP22* rearrangements were seen in 5/27 ALK-negative ALCLs (19%) and *TP63* rearrangements were seen in 2/27 (7%). Patients with *DUSP22*-rearranged ALCL had a 5-year overall survival (OS) rate of 80%, similar to that of ALK-positive ALCL (85%). Both patients with *TP63*-rearranged ALCL died with refractory disease within 2 years of diagnosis. Patients with triple-negative ALCL lacking rearrangements of *ALK*, *DUSP22*, and *TP63* had an intermediate 5-year OS rate of 33%. Differences in outcomes among genetic subgroups of ALCL were significant ($P < 0.02$).

These findings provide independent evidence that *DUSP22* and *TP63* rearrangements are strong outcome predictors in ALK-negative ALCL, support routine testing for these alterations in patients with this disease, and open opportunities for risk-adapted therapy based on genetic stratification. Accordingly, the predictive significance of *DUSP22* and *TP63* rearrangements is currently being evaluated further in the setting of a large Nordic PTCL trial of up-front ASCT (NLG-T-01).

Keywords: anaplastic large cell lymphoma (ALCL); gene rearrangement.

448 SERUM 2-HYDROXYGLUTARATE, A PREDICTIVE BIOMARKER OF THE PRESENCE OF *IDH2* MUTATIONS IN AITL PATIENTS

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Introduction: Mutations in isocitrate dehydrogenase 2 gene (*IDH2*) contribute to malignant progression of angioimmunoblastic T-cell lymphoma (AITL) and produce the oncometabolite 2-hydroxyglutarate (2-HG). 2-HG is considered as a predictor of the presence of *IDH2* mutations in acute myeloid leukemia. In this study, we investigated whether, in AITL, serum 2-HG would predict the presence of *IDH2* mutations at diagnosis.

Methods: Serum samples from 65 AITL patients were analyzed for 2-HG using a liquid chromatography tandem mass spectrometry (LC-MS/MS) method allowing simultaneous quantification of both L and D enantiomers of 2-HG. *IDH2* mutational status was determined in corresponding AITL tissue samples (from the TENOMIC cohort of the LYSA) using a next-generation sequencing method and/or allele-specific PCR (R172G, R172K, R172S, and R172T).

Results: Among the 65 patients, 21 presented an *IDH2* mutation (8 R172K; 7 R172G; 3 R172S; 2 R172T; 1 R172M). In patients with *IDH2*, mutation 2-HG serum levels were significantly higher than in patients with *IDH2* wild-type ($p < 0.0001$). Area under the receiver operating characteristic curves (ROC) for 2-HG and D/L ratio were 80% and 87%, respectively. The optimum diagnostic cut-off of 2-HG between *IDH2* mutated and wild-type was 2.5 μ M (sensitivity, 82%; specificity, 85%). Quantification of the D/L ratio

with a cutoff at 3 increased sensitivity and specificity (94%; 90% respectively).

Conclusions: Our results suggest that serum 2-HG and D/L ratio could be used as a predictive biomarker of the presence of *IDH2* mutations in AITL patients. Impact of the variant allele frequency (VAF) on 2-HG is currently under evaluation.

Keywords: angioimmunoblastic T-cell lymphoma (AITL).

449 THE VALUE OF PET/CT IN DETECTING BONE MARROW INVOLVEMENT IN PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA

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Introduction and Aims: Positron emission tomography using 18F fluorodeoxyglucose with computed tomography (PET/CT) is increasingly used for staging and treatment evaluation of lymphomas. In peripheral T cell lymphoma (PTCL), FDG avidity is variable. The purpose of this study is to evaluate FDG avidity in PTCL and to appraise the role of PET/CT in identifying bone marrow (BM) involvement.

Methods: A retrospective cohort study of patients with newly diagnosed or relapsed PTCL, treated with any chemotherapy regimen between 2008 and 2015 in a single tertiary center. Patients who did not have pre-treatment PET/CT (P-PET/CT) were excluded. Demographic, clinical and laboratory data were recorded from patients' files until the latest follow-up available and for at least 6 months after completion of chemotherapy administration. P-PET/CT studies were centrally reviewed and reported using 3 methods of evaluation: visual assessment, maximal SUV reported and Deauville 5-point score (DS) evaluation. DS of 3 and above was considered positive. PET/CT was interpreted as positive if any of the three evaluation methods was positive. Outcomes included the avidity of P-PET/CT in PTCL and the concordance between bone marrow involvement and PET/CT.

Results: Data of 60 patients with PTCL were collected; 20 patients were excluded due to absence of P-PET/CT. Thus, 40 patients (38 with newly diagnosed disease) were included in this analysis. The most frequent histological diagnoses were PTCL-NOS and anaplastic large cell lymphoma-ALK negative (ALCL-ALK negative). Median age was 54 years. The median follow-up was 31 months (23–40). The median overall survival and the PFS for the whole cohort were 39 months (27–51) and 16 months (7–24), respectively. Eighty-five percent of the patients received induction treatment of CHOP-like or CHOP-ICE, the rest of the patients received various regimens; 70% of patients achieved complete remission; however, only 37% patients proceeded to high-dose chemotherapy with stem cell rescue; 36/40 (90%) patients had positive P-PET/CT. Bone marrow biopsy (BMB) was not

done in 5/40 patients on diagnosis. Bone marrow infiltration was detected by PET/CT in 7/35 (20%) and by BMB in 5/35 (14%) cases. There was concordance between PET/CT and BMB in 27 patients (77%), 25 with negative PET/CT and BMB results and 2 with positive PET/CT and BMB results. Discordant results were observed in 8 patients. The sensitivity, specificity, positive predictive value and negative predictive value (NPV) of PET/CT for bone marrow involvement were 40%, 83%, 28.5% and 89%, respectively.

Conclusions: Our study shows that 90% of PTCL are FDG avid at baseline, as one would expect with aggressive lymphoma. As the NPV of PET/CT for BM involvement is high, a negative PET/CT rules out bone marrow involvement.

Keywords: peripheral T-cell lymphomas (PTCL); positron emission tomography (PET).

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EFFICACY AND SAFETY OF PEGASPARGASE, GEMCITABINE, DEXAMETHASONE, AND CISPLATIN COMBINED CHEMOTHERAPY IN NEWLY DIAGNOSED EXTRANODAL NK/T CELL LYMPHOMA

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Introduction: Up to now, although L-asparaginase-based regimens such as SMILE, AspaMetDex, are recommended for chemotherapy of extranodal NK/T-cell lymphoma (NKTCL), there is no optimal protocol for the disease. Combined pegaspargase, gemcitabine, dexamethasone, and cisplatin (P-GDP) have been reported to be effective. We slightly modified the P-GDP protocol and retrospectively investigated the efficacy and safety of the modified P-GDP in the treatment of newly diagnosed NKTCL patients.

Methods: Patients with a newly diagnosed stage I to IV NKTCL and received modified P-GDP were retrieved. The protocol of modified P-GDP was as follows: pegaspargase, 2500 IU/m² (cap 3750 IU) intramuscular on day 4; gemcitabine, 850 mg/m² intravenous on days 1 and 8; cisplatin, 20 mg/m², intravenous on days 1 to 3; and dexamethasone, 40 mg/d intravenous on days 1 to 4.

Results: Between September 2013 and November 2015, a total of 37 patients were retrospectively analyzed. Patients' median age was 42 years, and 27 (73%) had localized disease. Patients were subjected to 1 to 9 cycles of P-GDP chemotherapy, and the median number of cycles was 3. The overall response rate (ORR) was 83.8% (31/37), with 30 patients (81.1%) achieved complete response (CR) and one patient (2.7%) achieved partial response (PR). The median follow-up time was 23 months (range 2 to 40 months). The 18-month overall survival (OS) and progression-free survival (PFS) were 83.7% and 83.6%, respectively. For those stage I/II and stage III/IV patients, 18-month PFS were 92.1% and 60%, respectively. Grade 3/4 neutropenia occurred in 19 patients (51.3%), and grade 3/4 thrombocytopenia occurred in 18 patients (48.6%). Grade 3/4 hypofibrinogenemia

occurred in 11 patients (29.7%). No grade 3/4 allergy, thrombosis, or pancreatitis occurred. No treatment-related death occurred.

Conclusions: Modified P-GDP chemotherapy is effective and tolerable in newly diagnosed NKTCL. Prospective trials with more samples are needed to confirm the results.

Keywords: Chemotherapy; peripheral T-cell lymphomas (PTCL).

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A PHASE II TRIAL OF BENDAMUSTINE, CARBOPLATIN AND DEXAMETHASONE (BCD) FOR REFRACTORY OR RELAPSED PERIPHERAL T-CELL LYMPHOMA (BENCART): A CONSORTIUM FOR IMPROVING SURVIVAL OF LYMPHOMA (CISL) TRIAL

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Background: There is no standard salvage chemotherapy for relapsed or refractory peripheral T-cell lymphomas (PTCLs). In BETLY trial, which is sole prospective trial for bendamustine in refractory or relapsed T-cell lymphoma, bendamustine showed an encouraging high response rate across the two major PTCL subtypes, independent of age and prior treatment, with acceptable toxicity in refractory or relapsed PTCLs. We planned this trial to investigate the efficacy and toxicity of bendamustine, carboplatin and dexamethasone (BCD) for relapsed or refractory PTCLs, which would be expected to show more promising clinical outcomes than that of bendamustine single therapy.

Patients and Methods: Patients with relapsed or refractory PTCLs with more than one previous regimen regardless stem cell transplantation are eligible, and totally, 30 patients are needed. BCD treatment, which consist of bendamustine 80 mg/m² intravenously (i.v.) on Days 1 and 2, carboplatin AUC 5.0 i.v. on Day 1, and dexamethasone 40 mg orally on Days 1–4, was planned up to six treatment cycles without progressive disease and Peg-GCSF was supported at every cycle. Autologous stem cell transplantation (ASCT) after 3 cycles of BCD could be proceeded for eligible patients.

Results: Twenty-eight eligible patients were evaluated for toxicity and response. The diagnoses of participants included 15 cases of

PTCL-NOS (54%), five cases of angioimmunoblastic T-cell lymphoma (18%) and four cases of ALK-negative anaplastic large cell lymphoma (14%) among others. The median age of the patients was 59 years (range, 23–75 years). After treatments with BCD, which delivered a median of three BCD cycles, there were 8 patients with complete responses (CR; 30%) and seven with partial responses (PR; 25%). The overall response rate (RR) was 55%. Five patients preceded to ASCT, and three patients finally achieved CR. The median progression free survival was 4.8 months with a median follow-up duration of 4.5 months. In a total of 85 cycles of BCD, grade 3 or 4 neutropenia, thrombocytopenia and anemia occurred in 17.6%, 38.8% and 16.5% of cycles, respectively. Only one patient experienced febrile neutropenia.

Conclusions: BCD is an effective salvage regimen for relapsed or refractory PTCLs and can be administered with acceptable toxicity.

Keywords: bendamustine; peripheral T-cell lymphomas (PTCL); salvage treatment.

452 PEGYLATED LIPOSOMAL DOXORUBICIN COMBINED WITH CYCLOPHOSPHAMIDE, VINCRIStINE/VINDESINE, AND PREDNISONE IN PATIENTS WITH AGGRESSIVE T-CELL LYMPHOMA: PRELIMINARY RESULTS OF APHASE II STUDY

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Introduction: Anthracycline-based chemotherapy is commonly used as the first line treatment for aggressive T-cell lymphoma. The aim of this study was to evaluate the efficacy and toxicity of pegylated liposomal doxorubicin (PLD) combined with cyclophosphamide, vincristine/vindesine, and prednisone in patients with aggressive T-cell lymphoma.

Methods: Patients with newly diagnosed aggressive T-cell lymphoma except for NK/T-cell lymphoma were eligible and treated with 6 cycles of PLD (40 mg/m² day 1), cyclophosphamide (750 mg/m² day 1), vincristine (1.4 mg/m² day 1) or vindesine (2 mg/m² day 1) and prednisone (100 mg days 1–5). The primary endpoint was the overall response rate (ORR).

Results: A total of 40 patients were enrolled, and 39 were evaluable for response assessment. The patient characteristics were shown in Table 1. The ORR was 84.6%, and 18 patients (46.2%) achieved the complete response (CR). The ORRs of patients with 3 major histology (PTCL nos, ALCL and AITL) were 72.2%, 90.9% and 100%, respectively. The common grade 3/4 toxicities included neutropenia (87.5%), anemia (17.5%), pneumonia (15%) and mucositis (7.5%). Although 7 patients (17.5%) developed hand-foot syndrome and only 1 was grade 3, no treatment-related mortality was observed.

Conclusions: This PLD-containing regimen is effective and tolerable in patients with aggressive T-cell lymphoma. Longer follow-up time is needed for analyzing the survival results.

Table 1: Patient Characteristics

	No	%
Total number	40	100
Age, year		
Median (range)	55 (25–70)	
≤60	28	70
>60	12	30
Gender		
Male	25	62.5
Female	15	37.5
ECOG PS		
0	11	27.5
1	29	72.5
B symptoms		
Yes	10	25
No	30	75
LDH		
Elevated	12	30
Normal	28	70
Ann Arbor stage		
I	3	7.5
II	9	22.5
III	10	25
IV	18	45
IPI		
0–1	20	50
2	17	42.5
3	3	7.5
Histology		
PTCL nos	19	47.5
ALCL	11	27.5
ALK+	6	15
ALK-	5	12.5
AITL	9	22.5
SPTCL	1	2.5

PS: performance status; LDH: lactate dehydrogenase; IPI: International Prognostic Index; PTCL nos: peripheral T-cell lymphoma, not otherwise specified; ALCL: anaplastic large cell lymphoma; AITL: angioimmunoblastic T-cell Lymphoma; SPTCL: subcutaneous panniculitis-like T-cell lymphoma

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

453 THE EFFECT OF LONG-TERM MAINTENANCE CHEMOTHERAPY FOR AGGRESSIVE ADULT T CELL LEUKEMIA/ LYMPHOMA

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Introduction: In aggressive adult T-cell leukemia/lymphoma (ATL), the prognosis is extremely poor. The reasons are the invasion of multiple organs, drug resistance, immune deficiency and an attack at old age.

Recently, mLSG15 regimen is thought to be the standard therapy and improves the prognosis, but the median survival time (MST) is 13 months (ms). Intensive chemotherapy is repeated in mLSG15 regimen, it is difficult to refrain for frail or elderly patients. Moreover, intensive chemotherapy makes their quality of life (QOL) to be poor. Anti-CCR4 antibody therapy is useful too. Though, the prognosis of ATL is still remained worse than the other lymphoma. In our hospital, some patients received long-term maintenance chemotherapy (MC). Among these patients, 8 of 16 were achieved long-term survival, longer than 30 ms. Therefore, to confirm the effect of MC, the retrospective study was performed under the permission of the Institutional Review Board. **Methods:** Except smoldering and chronic type, in aggressive ATL treated in our hospital from April 2003 to September 2014, eligible 30 cases were analyzed. Their median age was 68 years old. Acute type was 11 cases, and lymphoma type was 19 cases. They received some induction therapy, respectively. Thirty cases were classified into three groups. Group 0 contained 14 cases not received MC and includes 9 high risk (HIGH) cases. Either in remission or not, 16 of 30 cases received MC continuously as long as possible. Group 1 contained 11 cases and received oral administration of MC with sobuzoxane (SBZ): 400 mg and etoposide (ETO): 25 mg, twice a week to once 3 weeks, include 7 cases of intermediate risk (INT) and 2 cases of low risk (LOW). Group 2 contained 5 without HIGH cases received MC intravenous administration of respective way with cyclophosphamide, ifosfamide, ETO, MTX or VCR, etc. Risk classification adopted Katsuya's study.

Results: MST of groups 0, 1, and 2 were 2.5, 31, and 12.5 ms. For about group 1 + 2, it was the cohort that received MC; MST was apparently longer than group 0 (25 vs 2.5 ms). The cases received MC were longer MST than that of already known in Japan, HIGH (6.3 vs 3.6 ms), INT (31 vs 7 ms), LOW (32.5 vs 16.2 ms) and acute type (12.8 vs 8.3 ms), lymphoma type (32.3 vs 10.6 ms). Adverse event did not arise. MC contributed to economic benefits, too.

Conclusions: With MC, MST was far superior to another, for example, in our data (25 vs 2.5 ms) or Japanese already known data. Between group 1 and 2, MST (31 ms) of group 1 was excellent. Group 0 contained many HIGH cases that meant poor prognosis and needed more intensive therapy than MC. In opposition, group 1 + 2 contained many frail and/or with complications cases, so that they could not receive enough standard therapy but received inevitably mild MC. Thus long-term MC is highly recommended for QOL and longer term survival of ATL, especially in INT, LOW and lymphoma type of ATL with unacceptable to the transplantation.

Keywords: Chemotherapy; T-cell lymphoma (TCL).

454 RICHTER TRANSFORMATION OF T-CELL LARGE GRANULAR CELL LEUKEMIA

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Although Richter transformation is known as transformation of B-chronic lymphocytic leukemia to diffuse large B-cell lymphoma, transformation of T-cell neoplasm is extremely rare and only several cases with transformation of T-cell large granular cell leukemia (T-LGL) have appeared so far. We report 4 cases of CD30-positive Peripheral T-cell lymphoma, nos (PTCL-nos) that subsequently occurred in patients with T-LGL.

The median age when the diagnosis of T-LGL made was 62 years old with a range from 59 to 80 years. The female/male ratio was 1:3. Interval between T-LGL and PTCL-nos ranged from 10 months to 6 years. The lesions of PTCL-nos were of generalized lymphadenopathy in 2 cases, multiple liver tumors in 1 case and right axillar lymph node swelling in 1 case. Three cases died after 1 to 6 months after transformation. Flow cytometry showed CD2 (4/4), sCD3 (4/4), CD4 (4/4), CD5 (3/4), CD8 (0/4), CD10 (0/4), CD16 (0/3), CD19 (0/4), CD30 (0/3), CD57 (1/3), TCRαβ (2/2) in T-LGL and CD2 (2/2), sCD3 (0/2), CD4 (2/2), CD5 (0/2), CD8 (0/2), CD10 (0/2), CD16 (0/2), CD19 (0/4), CD30(2/2) in PTCL-nos. In PTCL-nos, a diffuse proliferation of pleomorphic large cells with immunohistochemical expression of cCD3 (3/4), CD4 (3/4), CD5 (0/4), CD8 (0/4), CD10 (0/4), CD20 (0/4), CD30(4/4), TIA-1(3/4), Granzyme B(3/4), ALK(0/4) was observed. EBER in situ hybridization showed no positive signals in all cases of PTCL-nos. Southern blotting demonstrated same rearrangement bands of TCR-Cβ1 in both T-LGL and PTCL-nos samples (examined 2 cases). Oncoscan analysis was examined in 5 cases (2 cases of T-LGL and 3 cases of PTCL-nos) and showed that gain of 7, 12 and 17q and loss of 10 and 17p were found in PTCL-nos, but not in T-LGL.

We will discuss mechanism of transformation. It may be stated that T-cell Richter transformation was CD30(+) PTCL-nos transformed from CD4(+) T-LGL.

Keywords: peripheral T-cell lymphomas (PTCL); Richter's syndrome (RS).

455 CLINICO-PATHOLOGICAL PROFILE AND CMYC IMMUNOREACTIVITY OF ALK POSITIVE LARGE B CELL LYMPHOMA: REPORT OF NINE CASES.

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Background: ALK+ large B-cell lymphoma (LBCL) is an aggressive non-Hodgkin lymphoma listed as a distinct entity in the WHO Classification. It has poor response to conventional therapies. It occurs in both nodal and extranodal location. Although it appears to be very rare, the probable cause of under diagnosis is due to its morphologic and immunophenotypic overlap with other hematologic disorders.

Methods: All cases of Alk + LBCL diagnosed on histopathology were retrieved from the departmental archives. Detailed morphological and immunohistochemical evaluation was done. Clinical data was collected, and clinicopathological correlation was done.

Results: Nine cases of ALK + LBCL, which were diagnosed over a period of 6 years (2012–2017), were studied. Out of 9 patients, 7 were male and 2 were female with median age of 51 yr (age range: 14 to 63 yrs). Most common presentation was lymphadenopathy ($n = 3$). The extra-nodal sites includes skin ($n = 2$), nasal mass ($n = 2$), gastrointestinal tract and mediastinal mass one each. Most of the case has stage IV ($n = 6$) with high IPI score. The most consistent marker positive is CD138, EMA and ALK (cytoplasmic) while negative markers are CD3, CD20, and CD30 and PAX5. One case showed nuclear, cytoplasmic and membranous ALK positivity. The abnormal phenotype includes CD20 focal in one case, CD30 (one case). One case was mis-diagnosed as plasmacytoma initially. Three cases are positive for CMYC while only one case showed positivity for BCL2. The pediatric cases are treated with BFM 90 protocol and shows partial remission after two cycles of therapy. Adult cases mostly treated with CHOP regimen and one case DA-EPCOH. The two cases show complete remission while four cases show progressive disease.

Conclusion: ALK + LBCL has varied clinical presentations and morphologically mimics high-grade lymphomas. CMYC over expression is seen in 30% of cases. ALK immunohistochemistry can show all patterns of positivity. No definite chemotherapy is available. An extensive immunohistochemical panel is mandatory for a definitive diagnosis. More studies require establishing the role of CMYC in prognostication of this entity.

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

456 GEMCITABINE PLUS LIPOSOMAL DOXORUBICIN FOR RELAPSED REFRACTORY T-CELL LYMPHOMAS

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Introduction: Gemcitabine (G) has single agent activity in T-cell lymphomas (TCL) with response rates >50% in the relapsed refractory (RR) setting. Liposomal doxorubicin (LD) has activity in TCL both as a single agent and in combination, with response rates ranging from 40% to 84%. Given the safety profile and activity of these agents in TCL and lack of alternative therapies, G plus LD (GLD) was administered to patients with RR-TCL who were ineligible for clinical trial and had no other treatment options.

Methods: Patients with RR-TCL treated with GLD were identified retrospectively for study inclusion using electronic medical records (EMR)

under an IRB-approved protocol. Data collection included patient demographics, diagnosis, current, previous, and subsequent treatment regimens, best response, time to progression/death, and toxicities. Best response was assessed using published criteria for peripheral-TCL (PTCL) and cutaneous-TCL (CTCL) and as documented by the treating physician. Toxicities were assessed per Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Treatment regimens included G 1000 mg/m² and LD 15 mg/m² on days 1 and 8 every 21 days, or days 1 and 15 every 28 days.

Results: Eighteen patients met inclusion criteria and baseline characteristics/regimen details are shown in Table 1. All patients were included in the progression free survival (PFS), overall survival (OS), and safety/toxicity assessments. Fifteen patients received at least 1 full cycle of therapy and were assessed for disease response. The overall response rate (ORR) was 40%. Stable disease (SD) was seen in 27% of patients. For all patients, the median PFS was 3.9 months and median OS was 9.7 months. Of the patients with complete/partial responses or SD, 73% had a skin response to therapy. Subsequent therapy included hematopoietic stem cell transplant (HCST) in 6 of 18 (33%) patients. Eleven patients required dose delays during therapy, while two patients needed a dose reduction. Grade 3/4 hematologic toxicities included neutropenia (33%), thrombocytopenia (17%), and anemia (39%). One patient died of pneumonitis, which was assessed as treatment related.

Conclusions: Treatment with GLD shows an acceptable toxicity profile in heavily pre-treated patients with RR-TCL. RR-CTCL patients with advanced skin stage (T3, T4) achieved very good disease control with treatment. Six patients (5 CTCL and 1 PTCL) proceeded to HCST following treatment with GLD.

TABLE 1

Baseline Characteristics, $n = 18$ (%)	
Age (median)	60 years
Male	12 (67%)
Caucasian	14 (78%)
ECOG performance status	
0–1	14 (78%)
2–3	4 (22%)
Diagnosis	
PTCL	5 (28%)
CTCL	13 (72%)
Sézary syndrome (SS)	1 (0.1%)
Mycosis Fungoides (MF)	12 (92%)
Number of previous therapies*	
0–3	9 (50%)
4–6	4 (22%)
>6	5 (28%)
Prior anthracycline therapy	10 (56%)
Regimen details	
Treatment days 1 and 8 every 21 days	9 (50%)
Treatment days 1 and 15 every 28 days	8 (44%)
Other [^]	1 (0.1%)
*Topical therapies, phototherapy, systemic retinoids, interferon-alfa, denileukin difitox, vorinostat, romidepsin, brentuximab, pralatrexate, and multi-agent chemotherapy regimens [^] G 800 mg/m ² days 1 and 8 + LD 20 mg/m ² day 1 every 21 days	

Keywords: T-cell lymphoma (TCL).

457 THE EFFICACY AND TOLERANCE OF CHIDAMIDE, PREDNISONE, CYCLOPHOSPHAMIDE AND THALIDOMIDE (C-PCT) IN RELAPSED OR REFRACTORY PERIPHERAL T-CELL LYMPHOMA: A PILOT STUDY

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Introduction: The aim of this study was to evaluate the clinical efficacy and safety of chidamide, prednisone, cyclophosphamide and thalidomide (C-PCT) in relapsed or refractory (R/R) Peripheral T-cell lymphoma (PTCL). The primary endpoint was overall response rate (ORR).

Methods: Between June 2015 and September 2016, 12 Chinese patients with R/R PTCL were enrolled in this study. The median age was 52 years (range 28–69). Four patients were males, and 8 were females. Four (33.3%) patients were diagnosed as subtypes of PTCL not otherwise specified (PTCL, NOS), 4 (33.3%) were angioimmunoblastic T-cell lymphoma (AITL), 2 (16.7%) were type II enteropathy-associated T-cell lymphoma (EATL-II), 1 (8.3%) was ALK negative anaplastic large-cell lymphoma (ALK- ALCL) and 1 (8.3%) was cutaneous T-cell lymphoma (CTCL). Majority (11/12, 91.7%) of patients had an Ann Arbor stage III or IV, the only patient with CTCL had a TNMB stage IIB; 75% (9/12) patients had poor performance status, with ECOG 2 or more. The median IPI score was 2 (range 1–5) and 50% of patients had IPI between 3 and 5. The median number of prior systemic chemotherapies was 2 (range 1–4), 10 (83.3%) patients presented with PD to last line of prior systemic chemotherapy at enrollment, 1 was in SD, only 1 achieved PR but failed to autologous stem cell mobilization. C-PCT regimen was administered orally until disease progression or unacceptable toxicity.

Results: The median time on treatment was 12 months (range 3–18 months). The ORR was 83.3% (10/12), 5 (41.7%) and 4 (33.3%) patients achieved CR and PR, respectively, 1(8.3%) patients obtained SD and 2 (16.7%) patients presented with PD. The median time to response was 3 months (range 3–6 months). All (100%, 4/4) the AITL patients responded to C-PCT regimen, including 2 CR and 2 PR; Notably, the patient relapsed after autologous stem transplantation (ASCT) achieved PR at 3 months and experienced further CR at 9 months. Approximately 75% (3/4) of PTCL-NOS patients achieved CR and 2 patients of EATL-II achieved PR and SD, respectively. The patient with CTCL progressed to the previous systemic chemotherapies and achieved PR at 3 months. With a median follow-up of 13 (3–18) months, 2 patients relapsed and 3 patients died of PD. The median overall survival (OS) and progression-free survival (PFS) have not been reached. The most common grade 3/4 adverse events were neutropenia (22%), thrombocytopenia

(16%) and anemia (20%). Moreover, one patient experienced epstein-barr virus reactivation.

Conclusions: C-PCT as salvage therapy was effective with manageable toxicity for patients with R/R PTCL. Further prospective trials are warranted to validate the efficacy of C-PCT in a large cohort of patients.

Keywords: Chemotherapy; peripheral T-cell lymphomas (PTCL).

DRUGS PRECLINICAL

458 ESTABLISHED CELL LINES AND PATIENT- DERIVED XENOGRAPTS REPRESENT EQUALLY RELEVANT MODELS OF AGGRESSIVE LYMPHOMAS

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Patient-derived xenografts (PDXs) became standard tools of preclinical research bridging the gap between established cell lines and primary tumor samples. While PDXs are now generally regarded as true representatives of the particular malignancies in human, biological relevance of the cell lines has been repeatedly questioned.

In this study, we robustly characterized 7 newly derived PDXs and 5 cell lines established from patients with relapsed/refractory non-Hodgkin lymphomas. In 3 cases, a PDX and a cell line were derived from one patient, which enabled their direct comparison by whole-exome sequencing (WES), locus-specific and multi-color FISH, flow cytometry, and gene expression profiling.

Both the PDXs and the cell lines captured majority of somatic mutations and karyotype aberrations harbored by the original lymphoma cells with no fundamental difference between the two types of preclinical models. The FISH and WES data strongly suggest that both the cell lines and PDXs represent only subclonal populations contained within the primary lymphoma specimen.

The results indicate that lymphoma cell lines represent relevant models of a small fraction of relapsed, usually treatment-refractory,

microenvironment-independent, aggressive lymphomas with complex karyotype changes enriched in aberrations of *TP53*, *MYC* and *CDKN2A* genes. The key difference between PDXs and cell lines appears to dwell in the capability of PDXs to be derived from less-aggressive lymphomas including microenvironment-dependent and treatment-naïve cases.

Keywords: gene expression profile (GEP); mouse models; non-Hodgkin lymphoma (NHL).

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CONSTITUTIVE EXPRESSION OF γ H2AX PREDICTS BETTER RESPONSE TO HISTONE DEACETYLASE INHIBITOR IN DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: γ H2AX is a robust marker for cell DNA damage response. Usually, it can disappear if damaged DNA is repaired. Constitutive γ H2AX physiologically maintains telomere and cell senescence. Mouse model study suggested that H2AX suppresses myc-induced lymphogenesis. However, the significance of constitutive γ H2AX in malignant tumor remains elusive. Histone deacetylase inhibitors (HDACIs) show better efficacy in relapsed and refractory T-cell lymphoma than diffuse large B-cell lymphoma (DLBCL). Triggering DNA damage signaling is a key mechanism of HDACIs actions. The study explored the relevance of constitutive γ H2AX to HDACIs response in DLBCL. It will contribute to get prognostic marker of HDACIs and to discover new approach of increasing HDACIs activity in DLBCL.

Methods: Tissue microarray in combination with immunohistochemistry was applied to examine the expression of γ H2AX in one hundred and six patients with newly diagnosed DLBCL. Six cell lines were used to determine the association of constitutive γ H2AX with chidamide-induced apoptosis, including double-hit cell lines Dohh2, Ros50 and Val. H2AX, and its shRNAs were transduced with lentivirus vector. Xenograft mice were used to evaluate the action of chidamide on tumor growth in vivo.

Results: Forty-four percent (47/106) of patients presented constitutive expression of γ H2AX, which was identical with H2AX expression. The proportion of germinal-center B-cell (GCB) subtype was higher in patients with constitutive expression of γ H2AX (30%, 14/47 vs. 17%, 10/59; $p < 0.05$) using Han's algorithm. Two cell lines had constitutive high expression of γ H2AX and H2AX including double-hit cell line Ros50, while other four cell lines showed weak expression including double-hit cell lines Dohh2 and Val. Chidamide induced obvious apoptosis in constitutive high-expression cell lines, whereas modest apoptosis in weak expression cell lines. A chidamide-induced continuous rise of acetylated histone 3 was found in cell lines with constitutive high expression, not in those with weak expression. The transduction of H2AX led to high expression of γ H2AX and increased chidamide-induced apoptosis in OCI-Ly8 cell line. Knockdown H2AX with its shRNAs decreased

expression of γ H2AX and weakened chidamide-induced apoptosis in OCI-Ly7 cell line. Chidamide significantly inhibited tumor growth in xenograft mice with constitutive high expression of γ H2AX, compared to those with weak expression.

Conclusions: Constitutive expression of γ H2AX may be a prognostic marker for HDACIs response in DLBCL. The modality of increasing γ H2AX expression can be used to raise the efficacy of HDACIs.

Keywords: diffuse large B-cell lymphoma (DLBCL); histone deacetylase inhibitors.

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EXPRESSION OF PIM KINASES IN REED-STERNBERG CELLS FOSTERS IMMUNE PRIVILEGE AND TUMOR CELL SURVIVAL IN HODGKIN LYMPHOMA

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Introduction: Reed-Sternberg (RS) cells of classical Hodgkin lymphoma (cHL) express multiple immunoregulatory proteins that shape the cHL microenvironment and allow tumor cells to evade immune surveillance. Expression of certain immunoregulatory proteins is modulated by pro-survival transcription factors, such as NF κ B and STATs. Since these factors also induce expression of the oncogenic PIM1/2/3 serine/threonine kinases and since PIMs modulate transcriptional activity of NF κ B and STATs, we hypothesized that these kinases support RS cell survival and foster their immune privilege. Herein, we investigated PIM1/2/3 expression in cHL and assessed their role in developing RS cell immune privilege and survival.

Methods: Expression analyses in cell lines were performed by immunoblotting and qRT-PCR. PIM1/2/3 expression in a group of 67 cHL patients was assessed by immunohistochemistry. Impact of NF κ B inhibition on PIM expression was assessed by qRT-PCR in RS cells expressing I κ B-superrepressor or with siRNA-silenced NF κ B subunits. JAK2 inhibition was achieved with momelotinib or fedratinib. PIM1/2/3 expression knockdown was achieved by siRNAs. MTS assay and FACS-AnnexinV were used to investigate cellular proliferation and apoptosis. NF κ Bp65 activity was measured using DNA binding assays. PD-L1/2, CD25 and CD69 surface expression was assessed by flow cytometry. For *in vivo* studies, RS cells were xenografted subcutaneously into NSG mice. Animals with established disease were

randomized and given orally 50 mg/kg sel24 or vehicle (H₂O) for 21 days. Tumor growth was measured using callipers.

Results: PIM1/2/3 were ubiquitously expressed in primary and cultured RS cells but not in healthy donor-derived peripheral B cells. PIM1/2/3 expression was driven by JAK-STAT and NFκB activity. Genetic or chemical PIM inhibition with a newly developed pan-PIM inhibitor, sel24, induced RS cell apoptosis. PIM inhibition decreased cap-dependent protein translation, blocked JAK-STAT signaling, and markedly attenuated NFκB-dependent gene expression. In a cHL xenograft model, sel24 delayed tumor growth by 95.8% ($p = 0.0002$). Furthermore, sel24 decreased the expression of multiple molecules engaged in developing the immunosuppressive microenvironment, including galectin-1 and PD-L1/2. In co-culture experiments, Jurkat T-cells incubated with sel24-treated RS cells exhibited higher expression of CD25 and CD69 activation markers than T-cells co-incubated with control RS cells.

Conclusions: Taken together, our data indicate that PIM kinases in cHL exhibit pleiotropic effects, orchestrating tumor immune escape and supporting RS cell survival. Inhibition of PIM kinases decreases RS cell viability and disrupts signaling circuits that link these cells with their niches. Thus, PIM kinases are promising therapeutic targets in cHL.

Keywords: Hodgkin lymphoma (HL); immune system; JAK/STAT.

461 TARGETING HEAT SHOCK PROTEIN 90 AND ITS DOWNSTREAM SIGNALING HUBS FOR THE TREATMENT OF MANTLE CELL LYMPHOMA

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Introduction: Characterized by aberrant expression of cyclin D1, mantle cell lymphoma (MCL) is a distinct, especially aggressive, and highly heterogeneous mature B-cell lymphoma. Heat shock protein 90 (HSP90) has become an attractive therapeutic target in treating many cancers including blood cancers.

Methods: In the current study, using cultured cell, xenograft mouse models and patients' peripheral blood, we sought to evaluate the effects of HSP90 inhibition and its downstream signaling hubs on mantle cell lymphoma.

Results: In our study, we show that ganetespib, a clinically promising and actively investigated second-generation HSP90 inhibitor, dramatically reduced growth of mantle cell lymphoma cell lines in a dose-dependent manner. It induced G2/M cell-cycle arrest and apoptosis in Jeko-1 and Granta-519, and it significantly inhibited growth of xenograft tumors *in vivo*. Furthermore, a panel of signaling network proteins with a hub of HSP90 was screened for the effects of ganetespib and these pathways were studied mechanistically. Its downstream signaling hubs, common transcription factors (TFs), were identified and proved. We found inhibiting these TFs can reach similar

inhibition effects as HSP90 and even decrease side effects of HSP90. Results of H&E staining, TUNEL assays, and immunohistochemistry staining of proliferation, apoptosis and other pathway relevant biomarkers in xenograft tumors revealed significant differences in tumors treated by ganetespib or by inhibiting these TFs. In addition, lymphoma cells from patients' samples from peripheral blood were tested by ganetespib or by inhibiting these TFs.

Conclusions: In summary, our data suggest that targeting downstream TFs of HSP90 and HSP90 itself can be potentially used for the molecularly targeted therapy of MCL patients.

Keywords: mantle cell lymphoma (MCL).

462 L-TYPE CAV 1.2 CALCIUM CHANNEL PARTICIPATES IN RITUXIMAB-INDUCED APOPTOSIS IN DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Calcium signaling plays critical roles in rituximab-induced apoptosis, which is precisely manipulated by calcium channel and pump. This study aimed to explore the effect and influential factors of L-type calcium channel on rituximab-induced apoptosis in diffuse large B-cell lymphoma (DLBCL).

Methods: The expression of all components of L-type calcium channels was compared between rituximab-resistant and -sensitive patients with gene expression profiling data. The differential gene was confirmed using quantitative real-time PCR, and its protein expression was detected using the immunohistochemistry and Western blotting assay in samples of patients and cell lines. The calcium influx and cell apoptosis were examined with flow cytometry in *in vitro* cell lines. Small hairpin RNAs (shRNAs) and miRNA were transduced into cell lines with lentivirus vector. Xenograft mouse model was used to validate the action of L-type calcium channel to rituximab-induced apoptosis *in vivo*.

Results: The expression of calcium channel alpha 1C (CACNA1C, encoding CaV 1.2 subunit) displayed an inverse relationship to rituximab resistance in DLBCL patients. In *in vitro* cell lines, the downregulation of CACNA1C expression by its shRNAs, reduced the level of rituximab-induced apoptosis; rituximab-induced calcium influx and apoptosis were altered by modulators of L-type calcium channel. In xenograft models, modulators of L-type calcium channel and CACNA1C shRNA also changed rituximab-induced tumor shrinkage. Higher level of miRNA-363 was found to link with poor response to rituximab combined with CHOP in DLBCL patients. We further validated that miRNA-363 epigenetically regulated the expression of CACNA1C in this study.

Conclusions: L-type CaV 1.2 calcium channel modulates rituximab-induced apoptosis and manipulating this calcium channel may increase the action of rituximab in DLBCL.

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

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MALT1 INHIBITION USING THE SMALL MOLECULE INHIBITOR MI-2 EFFICIENTLY INDUCES APOPTOSIS IN CLL CELLS

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The NFκB pathway plays a crucial role in cancer cell survival, proliferation and acquisition of resistance to therapy. Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) is an intermediary protein paracaspase important in the classical activation of NFκB. Previous studies have postulated an important role for NFκB in facilitating BCR signaling in CLL cells. Mi-2 is a novel irreversible small molecule inhibitor of MALT1. Herein, we studied the effect of MALT-1 inhibition, using Mi-2, on the survival of CLL cells. Mi-2 rapidly reduced CLL cell viability in a dose-dependent manner. This effect was associated with the intrinsic apoptotic pathway activation, a robust increase in cleaved PARP and accompanied by a prominent decrease in Mcl-1 and BCL2 levels. The pro-apoptotic effect of Mi-2 was observed in CLL cells of both low and high-risk prognostic features. Accordingly pre-treatment with Mi-2 resulted in inhibition of IκB phosphorylation after BCR activation or even reduction below its basal level. Taken together, our results provide proof of the concept that MALT1 inhibition by the small molecule Mi-2 can efficiently induce apoptosis in CLL cells. In light of the importance of the BCR and NFκB pathways in the pathogenesis of CLL, MALT1 is a potential therapeutic target in this disease. This is particularly important in the era of novel agents used to treat CLL, when resistance to these drugs emerges over time.

Keywords: B-cell receptor (BCR); chronic lymphocytic leukemia (CLL); MALT1.

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BORTEZOMIB PREVENTS DEVELOPMENT OF CYTARABINE RESISTANCE IN A MANTLE CELL LYMPHOMA *IN VITRO* MODEL

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Introduction: Addition of high-dose cytarabine to mantle cell lymphoma (MCL) treatment regimens has significantly prolonged survival of patient subgroups, but relapses are common and are usually associated with treatment resistance. Thus, understanding the molecular mechanism(s) responsible for resistance and to identify predictive markers for resistance and/or sensitizing agents would be of great

clinical value. Using a molecularly reproducible cytarabine resistance model established from the Z138 MCL cell line, we aim to identify molecular markers for prediction of treatment responses. We are also investigating strategies to prevent development of resistance or to re-sensitize cytarabine resistant cells.

Methods: We have established a cell model where resistance is reproducibly developed in 21 days of cytarabine treatment (0.3 μM) from pre-treated cells. Resistant cells will be referred to as Z138-CytR and pre-treated cells as Z138-CytES0. Molecular changes in relation to the transformation steps were investigated by protein and gene expression analysis, and based on these results, candidate substances were chosen and their effects on resistance development were evaluated primarily based on proliferation.

Results: Gene expression profiling revealed that major transcriptional changes occur during the initial phase of adaptation to cellular growth in cytarabine containing media, and only few genes were deregulated upon development of resistance. Instead, resistance to cytarabine was confirmed to be mediated by down-regulation of the dCK protein, responsible for activation of nucleoside analogue prodrugs. Consequently, Z138-CytR cells showed cross-resistance to other nucleoside analogues including gemcitabine, cladribine and fludarabine. We have identified substances with growth reducing effect on both Z138-CytES0 and Z138-CytR cells, among them the protease inhibitor bortezomib (Figure 1A–C). We also found that bortezomib prevents, but cannot overcome, resistance development (Figure 1D–E). Based on altered expression levels of key proteins, possible involvement of the NF-κB-pathway in cytarabine resistance is currently investigated.

Conclusions: We have created a cell model, where cytarabine resistance can be obtained from pre-treated cells in a precise and timely predictable manner. DCK has been confirmed as a key player in cytarabine resistance in MCL, but cannot be used to predict survival or time to relapse in diagnostic samples. Development of cytarabine resistance can be prevented but not overcome by co-treatment with bortezomib *in vitro*.

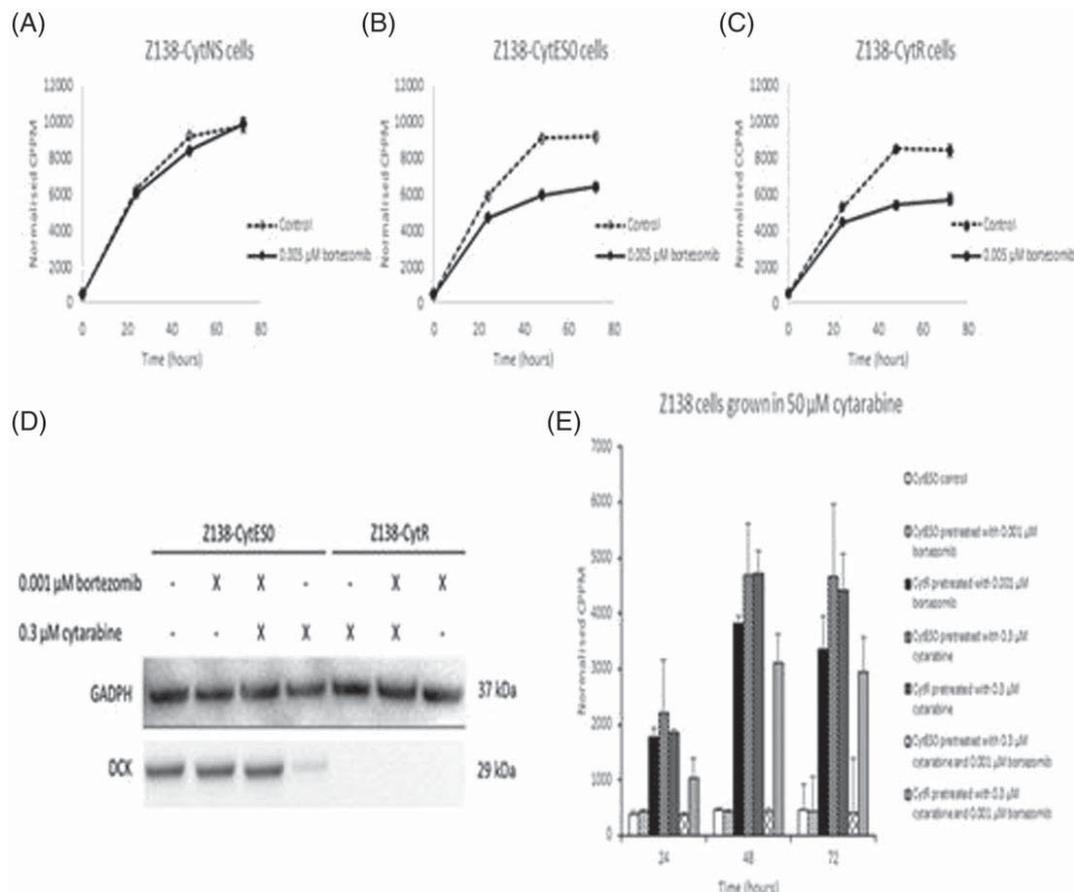
Keywords: Ara-C; bortezomib; mantle cell lymphoma (MCL).

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GSK-3β INHIBITOR, 9-ING-41 REDUCES CELL VIABILITY AND HALTS PROLIFERATION OF B-CELL LYMPHOMA

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Introduction: Glycogen synthase kinase-3 beta (GSK-3β) is an important signaling molecule involved in cell proliferation and survival. The



complexities of GSK-3β interactions with the PI3K/AKT/mTOR signaling, cyclin-dependent kinases (CDK) and anti-apoptotic protein bcl-2 have been described but are poorly understood in the context of lymphomagenesis and cancer therapeutics. We explore the anti-tumor effects of GSK-3β inhibitor, 9-ING-41, in lymphoma cell lines as a single agent and in combination with novel agents comprising Bcl-2 inhibitor (ABT-199), CDK-9 inhibitor (BAY-1143572) and p110δ-PI3K inhibitor (CAL-101).

Methods: Burkitt (Daudi), GC DLBCL (SUDHL-4, Karpas 422) double-hit DLBCL (KPUM-UH1), and ABC DLBCL (TMD8) cell lines were treated with 1 μM 9-ING-41. Cell viability on day 3 and proliferation over 7 days were measured using MTS assays. Apoptotic pathways recruited by 9-ING-41 treated cells were evaluated using Luminex assays and analyzed with unpaired t-test. For analyzing additive effects with other novel agents, cell lines were treated with dose-response series of 9-ING-41 (5 nM–5 μM) with either ABT-199 (0.5 nM–5 μM), BAY-1143572 (0.01–100 μM) or CAL-101(0.01–100 μM) and day 3 viability was measured using MTS assay.

Results: Cell viability was reduced by 40–70% ($p < 0.05$; Fig. 1) and all cell lines underwent growth arrest (proliferation <30% relative to control; $p < 0.05$) upon 1 μM 9-ING-41 treatment. Luminex analysis of apoptotic pathways revealed a significant increase in active caspase 3 in all cell lines ($p < 0.001$) except TMD8. Co-treating SUDHL-4 and KPUM-UH1 cells with 0.5 μM 9-ING-41 showed eightfold and twofold reduction in IC₅₀ values of ABT-199, respectively (Table 1). The remaining cell lines were insensitive to ABT-199. The combination of BAY-1143572 with 0.5 μM 9-ING-41 also showed eightfold reduction

in IC₅₀ value of the former in SUDHL-4 cells, but no significant benefit in other cell lines. For the combination of 9-ING-41 and CAL-101, no significant changes in IC₅₀ values of CAL-101 were measured across cell lines.

Conclusions: GSK-3β inhibitor, 9-ING-41, reduced viability and proliferation in aggressive B-cell lymphoma cells, in an apoptosis-dependent manner. 9-ING-41 demonstrates promising in vitro activity, irrespective of cell of origin and adds to the effects of ABT-199 and BAY-1143572. Efforts to better characterize anti-tumor mechanisms of GSK-3β inhibitors as single agents and in combination with novel agents are warranted.

Keywords: ABT-199; diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL).

466 METABOLIC CHANGES ASSOCIATED WITH METFORMIN POTENTIATES ANTI-BCL-2 INHIBITOR, ABT-199, AND CDK9 INHIBITOR, BAY-1143572 AND REDUCES VIABILITY OF LYMPHOMA CELLS

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Table: IC-50 concentrations for novel agents ± 0.5 mM 9-ING-41

	Daudi	SUDHL-4	KPUM-UH1	Karpas 422	TMD8
ABT-199	NR	~400 nM	~50 nM	NR	NR
ABT-199 + 9-ING-41	NR	~50 nM	~25 nM	NR	NR
BAY-1143572	~9 μ M	~8 μ M	NR	NR	~9 μ M
BAY-1143572 + 9-ING-41	~8 μ M	~1 μ M	NR	NR	ND
CAL-101	NR	~10 μ M	NR	NR	~1 μ M
CAL-101 + 9-ING-41	NR	~10 μ M	NR	NR	ND

NR = not-reached; ND = not-determined (9-ING-41 single agent more effective)

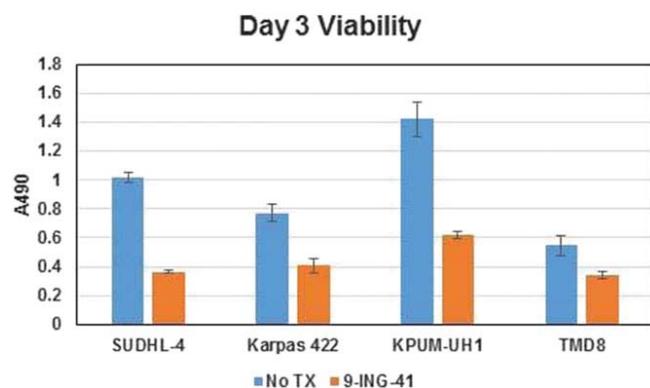


Fig. 1

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Introduction: Metformin exerts anti-tumor effects in part by activating AMP-activated protein kinase (AMPK) with resultant reduction in pro-survival mTOR signaling. Here, we test the hypothesis that metformin induces cell death by altering mitochondrial metabolism in lymphoma cell lines. As Bcl-2 proteins, cyclin-dependent kinases (CDK) and Phosphoinositol-3-kinase (PI3K) also influence mitochondrial physiology and metabolism, we also explored the additive effects of metformin with novel agents including the Bcl-2 inhibitor (ABT-199), the CDK9 inhibitor (BAY-1143572) and the p110 δ -selective PI3K inhibitor (CAL-101).

Methods: Daudi (Burkitt), SUDHL-4 (GC DLBCL), Jeko-1 (MCL) and KPUM-UH1 (double hit DLBCL) cells were plated in 96-well plates and treated with varying doses of metformin (0–5000 μ M). Hoechst 33342 DNA-binding dye or MTS assays were used to measure proliferation and cell viability, respectively. Perturbations in oxidative and glycolytic metabolism were monitored via Seahorse XF Energy

Phenotype kits. Lastly, efficacy of combination therapy was evaluated in cells co-treated with metformin and ABT-199 or BAY-1143572 or CAL-101.

Results: Daudi and SUDHL-4 cells showed 80% and 50% reduction in viability, respectively, with metformin at levels greater than 1 mM at day 7, while KPUM-UH1 and Jeko-1 cells were unaffected. The Seahorse analyses showed reduction in oxidative phosphorylation, in cells treated with 1mM metformin with a corresponding increase in glycolysis. Co-treating KPUM-UH1 and SUDHL-4 cells with 10 mM metformin resulted in 1.4-fold and 8.8-fold decreases, respectively, in IC₅₀ values of ABT-199 at day 3 (Table 1). Jeko-1 and Daudi cells were resistant to ABT-199. By contrast, 3-fold and 10 fold reduction in IC₅₀ values of BAY-1143572 in Daudi and Jeko-1, respectively, was seen in the presence of 10 mM Metformin, and SUDHL-4 or KPUM-UH1 cells were unaffected. No change in IC₅₀ value for CAL-101 was observed.

Conclusions: Metformin induces significant changes in cellular metabolism leading to decreased proliferation and viability in lymphoma cell lines. The combination of metformin and the anti-Bcl-2 agent ABT-199 achieves an additive effect in DLBCL (including double hit) cell lines, whereas the combination with CDK9 inhibitor BAY-1143572 provides more selective additive anti-tumor effect in Burkitt and MCL cell lines. These data support the idea of targeting cancer metabolism with metformin in novel combinatorial therapeutic strategies.

Keywords: “double-hit” lymphomas; ABT-199; B-cell lymphoma.

467 THE BRUTON'S TYROSINE KINASE INHIBITOR IBRUTINIB EXERTS IMMUNOMODULATORY ACTIVITY TOWARDS TUMOR-INFILTRATING MACROPHAGES

Table: IC-50 concentrations for novel agents ± 10 mM metformin

	Daudi	SUDHL-4	KPUM-UH1	Jeko-1
ABT-199 alone IC-50	NR	~800 nM	~10 nM	NR
ABT-199 + Metformin IC-50	NR	~90 nM	~7 nM	NR
BAY-1143572 alone IC-50	~9 μ M	~1 μ M	~10 μ M	~10 μ M
BAY-1143572 + Metformin IC-50	~3 μ M	~1 μ M	~10 μ M	~1 μ M
CAL-101 alone IC-50	NR	~10 μ M	~100 μ M	~100 μ M
CAL-101 + Metformin IC-50	NR	~10 μ M	~100 μ M	~100 μ M

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The Bruton's tyrosine kinase (Btk) inhibitor ibrutinib has demonstrated promising efficacy in a variety of hematologic malignancies. However, the precise mechanism of action of the drug remains to be fully elucidated. Tumor-infiltrating macrophages presented in the tumor microenvironment have been shown to promote development and progression of B-cell lymphomas through cross talk mediated by secreted cytokines and chemokines. Because Btk has been implicated in Toll-like receptor (TLR) signaling pathways that regulate macrophage activation and production of proinflammatory cytokines, we investigate the immunomodulatory effects of Btk inhibitor on macrophages. Our results demonstrate that Btk inhibition efficiently suppresses production of CXCL12, CXCL13, CCL19, and VEGF by macrophages. Furthermore, attenuated secretion of homeostatic chemokines from Btk inhibitor-treated macrophages significantly compromise adhesion, invasion, and migration of lymphoid malignant cells and even those not driven by Btk expression. The supernatants from Btk inhibitor-treated macrophages also impair the ability of endothelial cells to undergo angiogenic tube formation. Mechanistic analysis revealed that Btk inhibitors treatment downregulates secretion of homeostatic chemokines and cytokines through inactivation of Btk signaling and the downstream transcription factors, NF- κ B, STAT3, and AP-1. Taken together, these results suggest that the encouraging therapeutic efficacy of Btk inhibitor may be due to both direct cytotoxic effects on malignant B cells and immunomodulatory effects on macrophages present in the tumor microenvironment. This novel mechanism of action suggests that, in addition to B-cell lymphomas, Btk inhibitor may also have therapeutic value in lymphatic malignancies and solid tumors lacking Btk expression.

Keywords: BTK; ibrutinib; macrophages.

468 THE EFFECT OF AN IMMUNOMODULATORY DRUG ON THE VIABILITY AND SURFACE MOLECULE EXPRESSION OF CHRONIC LYMPHOCYTIC LEUKEMIA CELLS

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Introduction: Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of mature CD5⁺ CD23⁺ B cells in the peripheral

blood, bone marrow and secondary lymphatic tissues. It is well known that the progression of CLL is highly dependent on the tumor microenvironment. Lenalidomide (Celgene) is an immunomodulatory drug with significant therapeutic activity in CLL. In this study, we investigated how lenalidomide influence the viability and surface molecule expression, especially of markers involved in costimulation, migration and activation of CLL cells and how change the cytokine production of bone marrow stromal cells (BMSCs).

Methods: Peripheral blood mononuclear cells (PBMCs) from 15 CLL patients were cultured in the presence of 10 μ M lenalidomide for 7 days. CLL cells were cultured alone or together with BMSCs, as modelling the bone marrow microenvironment. The expression of various cell surface molecules (CD5, CD19, CD80, CD86, CD49d, ROR1, CD44) and the apoptosis rate of CLL cells was assessed by flow cytometry.

Results: BMSC co-culture reduced the spontaneous apoptosis rate of CLL cells, but lenalidomide totally abrogated the protective effect of BMSCs. In most of the CLL cases, (13/15) cultured without BMSCs showed no or just slight difference in viability after lenalidomide treatment, but 2 cases had significantly higher cell death rate. Elevated level of CD5, CD19, CD49d, CD38 and CD44 was detected on CLL cells co-cultured with BMSCs compared to CLL cells cultured alone, but this effect was inhibited by adding lenalidomide. Lenalidomide induced elevated co-stimulatory molecule expression, namely, CD80 and CD86.

Conclusions: Our results suggest that lenalidomide did not affect directly the viability of CLL cells but effectively inhibit the survival signals coming from the protective microenvironment. To this indirect effect can contribute the decreased level of surface markers, which are known to form microenvironmental interactions. Furthermore, the increased co-stimulatory molecule expression on CLL cells can lead to effective anti-tumor response.

Keywords: chronic lymphocytic leukemia (CLL); lenalidomide.

469 MOLECULAR MECHANISMS AND COMBINATION STRATEGIES WITH PI3K AND BTK INHIBITORS TO OVERCOME INTRINSIC AND ACQUIRED RESISTANCE IN PRECLINICAL MODELS OF ABC-DLBCL

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Introduction: Inhibition of BTK with ibrutinib has demonstrated clinical efficacy in ABC-DLBCL. However, ABC-DLBCL patients with CD79B^{WT} and MyD88^{mut} or CARD11^{mut} did not respond to ibrutinib.

Recent approval of idelalisib for the treatment of indolent NHL (iNHL) as monotherapy highlighted selective inhibition of PI3Kd as an effective therapeutic strategy. However, idelalisib did not show activity in DLBCL in a Phase I study. Here, we investigated the molecular mechanism underlying the intrinsic and acquired resistance to idelalisib and ibrutinib and further propose a combination strategy to achieve sustained tumor regression in ABC-DLBCL.

Methods: Nuclear NF- κ B activation was determined using luciferase reporter, IHC, RT-PCR and protein ELISA assays. *In vitro* and *in vivo* mechanisms of action were addressed by assessing the activities of the key survival signaling pathways. *In vitro* and *in vivo* anti-tumor activities were investigated using cell lines and patient derived xenograft (PDX) ABC-DLBCL models. RNAseq and NGS are used to determine the genetic alterations in the tumors that are refractory or developed acquired resistance to copanlisib and/or ibrutinib.

Results: We found that high PI3K α expression and PI3Kd in ABC-DLBCL modulates not only p-AKT but also nuclear NF- κ B activity via p-IkBa and cIAPs. PI3K δ selective inhibition by idelalisib, but not dual inhibition of PI3K α /d by copanlisib, showed incomplete inhibition of p-AKT and more importantly, caused rebound activation of NF- κ B in both BCR-dependent and BCR-independent ABC-DLBCL cells. In addition, dual PI3K α /d inhibition by copanlisib enhanced anti-tumor profile *in vitro* and *in vivo*, including ibrutinib-resistant CD79^{wt}/MyD88^{mut} and/or CARD11^{mut} tumor models compared to the selective inhibitors of PI3K δ , PI3K α or BTK. Furthermore, rebound activation of BTK and AKT was identified as a resistance mechanism limiting ABC-DLBCL to show robust responses to PI3K and BTK inhibitor monotherapies, respectively. Interestingly, the outcome of copanlisib and ibrutinib combination was different in ABC-DLBCL. Thus, *in vitro* synergistic effect was observed in ibrutinib-responsive tumor cell lines, while antagonistic effect was found in ibrutinib-resistant tumor model. *In vivo*, in tumors with CD79^{mut}/MyD88^{mut}, combination of copanlisib and ibrutinib led to faster onset and higher complete response rate, as well as significantly prolonged time to tumor recurrence. Furthermore, genetic alterations in tumors refractory to or relapsed from copanlisib and ibrutinib combination treatment will also be discussed.

Conclusions: Our findings provide additional insights into intrinsic and acquired resistance mechanisms in response to selective PI3K δ and BTK inhibitors and provide a rationale for clinical testing of PI3K α /d and BTK inhibitors in combination for the treatment of ABC-DLBCL.

Keywords: BTK; diffuse large B-cell lymphoma (DLBCL); PI3K/AKT/mTOR.

470 AZACYTIDINE AND DECITABINE EXHIBIT DIFFERENTIAL EFFECTS ON CYTOTOXICITY AND METHYLATION AND EXHIBIT CLASS SYNERGY WITH HDACI IN MODELS OF PTCL

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Introduction: The PTCL represent a challenging group of lymphoid malignancies with a poor outcome. The PTCL appear to be the prototypical 'epigenetic disease', based on the following observations: (1) it is the one disease for which HDAC inhibitors have been shown to have universal activity; (2) multiple lines of evidence have begun to establish that the PTCL are characterized by recurrent mutations in important genes governing genome wide methylation, including TET2, IDH1/2, and DNMT3. While commonly invoked as a reason to explain sensitivity to HDAC inhibitors, the fact is only hypomethylating agents and not HDAC inhibitors, would be expected to affect this underlying biology.

Methods: We have compared Azacitidine (AZA) and Decitabine (DEC) activities in a panel of cell lymphoma (TCL) cell lines with regard to their dose response effects on cell viability, apoptosis, DNMT protein expression, DNA methylation and gene expression (GEP). We have also evaluated the preclinical merits of combining the hypomethylating (HoMe) agents and HDAC inhibitors using cytotoxicity assay (CellTiter Glo), gene expression profiling, methylation array and mouse models. We have performed RNASeq analysis on TCL cell lines to identify unique gene sets perturbed by the AZA-Romi combination.

Results: AZA and DEC demonstrated different effects on cell viability, apoptosis, DNMT levels and DNA methylation. Significant heterogeneity in DEC sensitivity was seen among the lines studies, which was not noted with AZA exposure. AZA was consistently more potent than DEC at high drug concentration (>1 μ M) but DEC was active at lower drug concentration (<0.1 μ M). The difference in activity was mirrored by the dose-dependent effects of AZA and DEC on markers of apoptosis. A strong correlation between DNMT depletion and DNA methylation was noted for both drugs, though the concentration: effect relationships were different. DEC demonstrated DNMT1 and DNMT3A depletion and DNA hypomethylation at lower concentrations (10–100 nM) than AZA (100 nM–1 μ M). However, while the DNMT1 and DNMT3A expression was restored at 48 and 72 hours post exposure to DEC, their depletion persisted after 48 or 72 hours following AZA exposure. Class synergy was noted for both HoMe agents across all HDACi studied (vorinostat, belinostat, panobinostat and romidepsin). The synergy was mainly dependent on HDACi and not HoMe agent concentrations, and confirmed in PTCL xenografts. Genome wide methylation and GEP revealed unique patterns associated with the combinations not seen in the singles agent exposures.

Conclusions: These data suggest that HoMe based combinations are active and synergistic in models of TCL. Concentrations that induce DNMT loss may be a valuable biomarker in identifying optimal doses for clinical development. Methylation array from patients treated on a Phase 1 of Aza-Romi will be correlated with clinical findings and reported.

Keywords: Chemotherapy; histone deacetylase inhibitors; peripheral T-cell lymphomas (PTCL).

471 TARGETING BCL-2 IN ALK+ ALCL: AT THE CROSSROADS BETWEEN AUTOPHAGY AND APOPTOTIC CELL DEATH

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Introduction: Our research team has long been working on anaplastic large cell lymphoma (ALCL), a peripheral T-cell non-Hodgkin lymphoma representing up to 20% of childhood lymphomas. In more than 70% of the cases, the oncogenic tyrosine-kinase NPM-ALK is responsible for the tumorigenic process. Although chemotherapeutic treatments have proven to be efficient against the disease, relapses occur in approximately 30% of cases, thus revealing the need for new therapeutic weapons such as targeted therapies. Crizotinib is a specific inhibitor of the ALK activity, currently used in phase II clinical studies; however, resistance to this drug has already been reported. Our team has previously shown that Crizotinib treatment of ALK+ ALCL was responsible for promoting a cytoprotective type autophagy, which in turn may lead to the selection of Crizotinib-resistant cells. Interestingly, we recently observed that Crizotinib inhibition of ALK activity also induces expression of Bcl-2, which is often downregulated in ALK+ ALCL. Bcl-2 is a well-known oncogene and has been firmly established as both an anti-apoptotic factor and a key autophagy regulator.

Methods: We carried out several in vivo and in vitro experiments to knock down the expression of BCL2 by miR-34a overexpression.

Results: We show that blocking the Crizotinib-induced expression of Bcl-2 through overexpression of miR-34a (also used in clinical trials) enhances the anti-tumorigenic effect of Crizotinib. We demonstrate that Bcl-2 blockade not only increases Crizotinib induced apoptotic cell death but also results in an intensified autophagic flux, that switches from cytoprotective type to deleterious type, thus enhancing the anti-tumorigenic effect of Crizotinib.

Conclusion: Taken together, our data suggest that through Bcl-2 targeting, the Crizotinib/miR-34a combination represents a promising therapeutic alternative to current treatments and provide new insights into cross-regulations between apoptosis and autophagy in lymphomas upon targeted-therapy.

Keywords: ALK; anaplastic large cell lymphoma (ALCL); BCL2.

PHASE I-II

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A PRELIMINARY EFFICACY STUDY OF CHIDAMIDE IN COMBINATION WITH DICE REGIMEN ON RELAPSED OR REFRACTORY B CELL LYMPHOMAS

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Introduction: As an epigenetic modulation drug, chidamide, a novel subtype-selective histone deacetylase inhibitor, has been approved for the treatment of patients with relapsed or refractory peripheral T cell lymphoma (PTCL) in China. This study was to explore the potential efficacy and adverse events of chidamide combined with DICE (dexamethasone, ifosfamide, cisplatin, and etoposide) regimen on relapsed or refractory B-cell lymphomas.

Methods: Patients confirmed with relapsed or refractory B-cell lymphomas were treated with oralchidamide (20 mg, twice per week) in combination with DICE regimen for up to 6 cycles. DICE regimen: dexamethasone 10 mg/d, ifosfamide 1,000 mg/m²/d, cisplatin 25 mg/m²/d, and etoposide 60 mg/m²/d, intravenously, d1–d4, 21 d as a cycle. Patients achieving complete remission (CR) or partial remission (PR) after 2 cycles could receive 2 or 4 consolidation cycles followed by autologous stem cell transplantation (ASCT) or choose to continue chidamide monotherapy for maintenance. The efficacy and adverse events were evaluated. The overall response rate (ORR) including CR, unconfirmed CR (CRu), and PR was evaluated as the primary endpoint.

Results: A total of 45 patients enrolled from multi-centers were treated, including 31 (68.9%) DLBCL, 3 (6.7%) FL, 5 (11.1%) MCL, and 6 (13.3%) B-NHL. Median age was 54 years (range 29 to 70) with 62.2% males ($n = 28$). The median number of previous treatment was 2 (range 1 to 6). The diseases were assessed and classified in stage I (9%), II (13%), III (22%), IV (47%), and not defined (9%). To date, 9 patients have not reached the time for evaluation, and 4 patients were not evaluable (1 discontinued due to AE, 2 withdrew or released, and 1 withdrew due to no benefit observed). Of 32 patients evaluable for efficacy, the ORR was 65.6% (21/32) with CR/CRu rate of 18.8% (6/32). In general, the higher beneficial rate was observed in patients with disease stage I/II. The ORR in B-cell lymphoma subtypes were comparable, but higher rate of CR was observed in DLBCL patients. Furthermore, patients with GCB potentially had a higher beneficial rate compared with other DLBCL subtypes. Grade 3/4 AEs (>10%) included lymphopenia (48.9%), neutropenia (42.2%), thrombocytopenia (17.8%), and anaemia (17.8%). A total of 6 patients had no grade > 3 AEs. No treatment-related death occurred.

Conclusions: The combination of chidamide with DICE regimen appears to have effective clinical activity in relapsed or refractory B-cell lymphoma. Future prospective trial is warranted.

Keywords: B-cell lymphoma; epigenetics; histone deacetylase inhibitors.

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ABSENCE OF PHARMACOKINETIC INTERACTION OF OFATUMUMAB AND BENDAMUSTINE IN PATIENTS WITH INDOLENT B-CELL NON-HODGKIN'S LYMPHOMA (INHL)

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Introduction: Bendamustine (BEN) is approved for the treatment of refractory iNHL, and the combination therapy BEN with rituximab (R) exhibited clinical efficacy in the treatment of relapsed iNHL. The patients with iNHL relapse inevitably; hence, there is an unmet need for well-tolerated efficacious therapies. Ofatumumab (OFA) is an anti-CD20 human monoclonal antibody currently in use for the treatment of chronic lymphocytic leukemia (CLL) and is investigational therapy for the treatment of iNHL. The combination of BEN with OFA may provide additional clinical benefit in patients with iNHL. This study evaluated the pharmacokinetics (PK) drug-drug interaction of OFA and BEN in combination therapy and the safety in patients with previously untreated or relapsed iNHL.

Methods: In Phase I open-label study, patients (aged ≥ 18 years) with previously untreated or relapsed iNHL were randomized 1:1 to Arm A (OFA + BEN) or Arm B (OFA alone) to receive 4–8 cycles (28 days) of treatment. Patients in Arm A received single-sequence treatment of BEN, then OFA + BEN, BEN (90 mg/m²) on days 1 and 2 every 28 days for up to 8 cycles, and OFA (1000 mg) on day 1 of weeks 2,

3, and 4 of cycle 1 and on day 1 of cycles 2–8. Patients in Arm B received OFA alone with same dosing; all patients gave informed consent. Blood samples including all end-of-infusion (EOI) PK samples were collected for plasma concentration over time. The primary PK parameters C_{max} , AUC_{last} , AUC_{inf} were derived using non-compartmental analysis. All adverse events (AEs) and severe AEs (SAEs) were recorded.

Results: Thirty-two patients were randomized (15 Arm A; 17 Arm B), 3 patients in Arm A discontinued treatment due to consent withdrawal (2 patients) and infusion related AE (1 patient). All 32 patients were included for safety and PK concentration evaluation, 30 patients (15 in each arm) were evaluated for PK parameters. Patient and disease characteristics were similar between treatment arms. PK concentration profiles and PK parameters of OFA were similar when administered alone or in combination with BEN; as compared to OFA alone, there was a decrease of 14% in C_{max} and 15% in AUC_{last} when OFA was co-administered with BEN, which was not considered relevant (Figure 1). BEN PK concentration profiles and PK parameters were similar with or without OFA co-administration (Figure 1). All patients reported AEs. The most frequent treatment-related AEs were infusion related reaction in 53% and 47%, nausea in 33% and 35%, fatigue in 33% and 18% patients in Arm A and Arm B, respectively. Cytopenias were present in 40% (Arm A) and 6% (Arm B) patients. Percentages of patients with grade 3/4 AEs were higher in Arm A (53%) compared to Arm B (24%). In Arm A, 4 SAEs were related to study treatment while none in Arm B.

Conclusions: No relevant PK drug-drug interaction was observed with OFA and BEN combination. OFA alone or in combination therapy exhibited manageable safety profile in patients with iNHL.

Keywords: bendamustine; non-Hodgkin lymphoma (NHL); ofatumumab.

Table 1. Primary PK parameters and Statistical Analysis of the primary PK parameters for OFA and BEN

OFA – PK parameter population	Geometric mean (95% CI)		%CV _b		Median (Min-Max)		Geometric Least Square Mean		Ratio (90% CI)
	OFA + BEN	OFA alone	OFA + BEN	OFA alone	OFA + BEN	OFA alone	OFA + BEN	OFA alone	
* AUC_{inf} (hr* μ g/mL)	56100 (i)	65400 (8490-504000)	-	23.0	56100 (56100-56100)	66300 (55700-76800)	56100	65400	0.857 (0.148-4.97)
AUC_{last} (hr* μ g/mL)	91700 (77400-109000)	108000 (84500-138000)	28.7	46.4	94500 (47500-131000)	126000 (50300-204000)	91700	108000	0.850 (0.666-1.08)
C_{max} (μ g/mL)	383 (341-429)	443 (380-515)	19.2	28.0	363 (276-517)	481 (275-606)	383	443	0.864 (0.741-1.01)
BEN – PK parameter population	OFA + BEN	BEN alone	OFA + BEN	BEN alone	OFA + BEN	BEN alone	OFA + BEN	BEN alone	Ratio
AUC_{inf} (hr* μ g/L)	6740 (5540-8210)	6880 (5390-8770)	35.2	44.0	6610 (3580-13900)	6320 (4120-14100)	6720	6780	0.991 (0.842-1.17)
AUC_{last} (hr* μ g/L)	6740 (5540-8210)	6880 (5390-8770)	35.2	44.0	6610 (3580-13900)	6320 (4120-14100)	6720	6780	0.991 (0.842-1.17)
C_{max} (μ g/L)	5880 (4640-7440)	6060 (4910-7500)	42.6	38.0	5440 (3250-11600)	58600 (3430-11700)	5880	6020	0.977 (0.797-1.20)

*No conclusion could be drawn with respect to AUC_{inf} due to very limited sample size (n=2 in OFA alone arm and n=1 in OFA + BEN arm); %CV_b, Between-subject coefficient of variation CV_b (%)

474 ME-401, A NOVEL, ORAL, POTENT AND SELECTIVE INHIBITOR OF PHOSPHATIDYLINOSITOL 3-KINASE P110 δ (PI3K δ) IN EARLY CLINICAL DEVELOPMENT FOR B-CELL LYMPHOID MALIGNANCIES

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Introduction: ME-401 is a novel inhibitor of PI3K δ , a key intracellular kinase in the BCR signaling pathway. First generation PI3K δ inhibitors are active in chronic lymphocytic leukemia (CLL) and follicular lymphomas (FL) but have some limitations. ME-401 has been advanced into clinical development because it is highly selective to the δ isoform, exhibits high potency for its target, results in high volume of biodistribution, and is expected to have better exposure and wider safety margins than earlier PI3K δ inhibitors. A study in healthy volunteers provided the basis for the starting dose in a Phase 1b study in patients with FL and CLL.

Methods: The safety, pharmacokinetic (PK), and pharmacodynamic (PD) of ME-401 was evaluated in 21 healthy subjects administered single-ascending oral doses from 10 to 150 mg. The PD of ME-401 was assessed by the basophil activation test (BAT) on whole blood via CD63 expression following ex-vivo stimulation with an anti-FC ϵ R1 monoclonal antibody. A Phase 1b study was initiated in relapsed/refractory (R/R) FL and CLL using a dose escalation adaptive design with the continuous reassessment method, with 6 planned patients per dose level, and up to 12 patients allowed per cohort, and dose-limiting toxicities (DLT) assessed on Day 56. The objectives of the study are to evaluate ME-401 safety, DLT, maximum tolerated dose, minimum biologically effective dose, and recommended phase 2 dose.

Results: In healthy volunteers, ME-401 had linear PK over the doses studied and a half-life of ~28 hours, supporting once daily dosing. Significant BAT inhibition was observed at all dose levels. Plasma concentrations required for 50% and 90% inhibition (EC₅₀ and EC₉₀) were 0.6 ng/mL (1.0 nM) and 5 ng/mL (8.7 nM), and doses \geq 60 mg resulted in >90% BAT inhibition. At 60 mg, the mean C_{max} of 9 ng/mL and AUC (0-inf) of 234 ng*h/mL are substantially lower than the no-adverse effect level C_{max}(570 and 180 ng/mL, rat and dog, respectively) and AUC(0-inf) (9,250 and 1,740 ng*hr/mL, rat and dog, respectively) in toxicology studies. In the CLL/FL study, dose level 1 was selected as 60 mg, 2-fold lower than would be allowed from toxicology studies, because it results in >90% inhibition in the BAT assay. Of 6 patients enrolled to date to dose level 1, 2 are evaluable for DLT, 1 withdrew at Day 28 for personal reasons, and 5 continue on treatment. ME-401 has been well tolerated; there have been no DLT, and objective responses have been observed.

Conclusions: ME-401 is distinguished by its distribution profile, indicating it readily distributes out of the central compartment and into cells, a desired pharmacological behavior of a small molecule targeting an intracellular kinase. ME-401's potency in preclinical studies and its large exposure margins demonstrated by toxicology studies, suggest a favorable therapeutic window. The ongoing Phase 1b study is evaluating whether these findings would be validated in CLL and FL where PI3K δ inhibition has known clinical activity.

Keywords: B-cell receptor (BCR); follicular lymphoma (FL); PI3K/AKT/mTOR.

475 ONO-4059 (GS-4059), A NEXT GENERATION BTK INHIBITOR, MONOTHERAPY IN PATIENTS WITH B-CELL MALIGNANCIES IN THE JAPANESE PHASE 1, DOSE-ESCALATION STUDY

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Introduction: Bruton's tyrosine kinase (BTK) plays an important role in B-cell signaling, cell proliferation and survival. The highly selective BTK inhibitor, ONO-4059 (GS-4059) showed manageable safety and tolerability as a single agent in B-cell non-Hodgkin lymphoma (B-NHL) and chronic lymphocytic leukemia (CLL) in an European phase 1 study (Walter et al. Blood 2016). This phase 1 study was designed to evaluate the maximum tolerated dose, safety, efficacy and pharmacokinetics (PK) of ONO-4059 as monotherapy in Japanese patients (pts) with relapsed or refractory B-NHL and CLL. This was a company sponsored trial (Ono Pharmaceutical Co., Ltd.).

Methods: Pts with previously treated B-NHL/CLL were eligible. Four dose cohorts consisted of 160 mg QD, 320 mg QD, 480 mg QD and 300 mg BID were defined as cohort 1 to 4, respectively. Pts were enrolled using a 3 + 3 dose escalation design, and were observed for a 28-day period to identify dose-limiting toxicity (DLT). All pts provided written informed consent.

Results: Seventeen pts were enrolled ($n = 3, 3, 4,$ and 7 in cohort 1–4, respectively) and 9 pts remained on study as of March 7, 2016. The disease subtypes enrolled were FL $n = 5$, MCL $n = 4$, non-GCB DLBCL $n = 4$, DLBCL $n = 1$, WM $n = 2$, and CLL $n = 1$. Median age was 70 yrs [range, 37–80], and median number of prior therapy was 3 [range 1–11]. Maximum tolerated dose (MTD) was not reached though one DLT of grade 3 pneumonitis was observed in cohort 4. The most common AEs were rash (35%) and vomiting (29%), but no grade ≥ 3 was

reported. The most common grade ≥ 3 AEs were neutropenia (18%) and anemia (12%).

The overall response rate (ORR) was 71% (12/17 pts) and median progression-free survival (PFS) was not estimable across all cohorts; ORR in each subtype was 80% (4/5 pts) in DLBCL with 1 CR, 20% (1/5) in FL, and 100% in MCL with 2 CR, WM, and CLL. Interestingly, 4 pts with DLBCL who achieved objective responses had no CD79A/B, MYD88 and CARD11 mutations. Of note, CARD11 mutation was identified in one DLBCL pt who had disease progression. Furthermore, one CLL pt who had TP53 mutation, del 13q, and del 17p achieved PR and remained on therapy. The tendency of CXCL-10 increase was observed in pts who achieved objective responses. Increases in C_{max} and AUC were approximately dose-proportional from 160 to 480 mg QD. The mean half-life ($t_{1/2}$) of ONO-4059 was comparable across dose levels.

Conclusions: MTD was not reached, and the safety profiles in Japanese pts with B-NHL/CLL were similar to previous findings in the European Phase 1 study. ORR was observed in 71% of pts including 4 DLBCL with no mutations of CD79A/B, MYD88 and 1 CLL with TP53 mutation, del 13q and del 17p, that is promising data for future development. ONO-4059 exhibited approximately dose-proportional exposure, and there was little accumulation of exposure following multiple doses. Further investigation is warranted.

Keywords: B-cell lymphoma; B-cell receptor (BCR); BTK.

476 PHARMACOKINETIC ANALYSIS AND CLINICAL RESULTS OF THE PHASE 1 DOSE ESCALATION AND EXPANSION CXD101 TRIAL IN RELAPSED, REFRACTORY LYMPHOMA

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Introduction: CXD101 is a novel class I-selective HDAC inhibitor (HDACi). It is specific to class I HDAC1 isoforms and has no activity against class II HDAC. CXD101 induces specific HDAC inhibition and enhanced histone acetylation in a time and dose-dependent fashion *in vitro*, in treated canine and murine leucocytes *in vivo*, and in human leucocytes treated *ex vivo*. CXD101 has an improved pharmacokinetic (PK) profile compared to other HDACi in pre-clinical studies.

Methods: We determined the maximal tolerated dose (MTD) of CXD101 in a dose escalation study in advanced cancer. The dose

was escalated from 1 mg bd for 5 days (d) in a 21D cycle (C), following a 3 + 3 design. A preliminary efficacy analysis was performed. A total of 39 pts were enrolled; 36 were exposed to CXD101.

Results: The MTD and recommended phase II dose (RP2D) was 20 mg bd. In 17 lymphoma pts dosed at ³16mg bd, 3 had partial responses (2 Hodgkin lymphoma post allograft, 1 refractory angioimmunoblastic T-cell lymphoma) and 1 complete response (relapsed follicular lymphoma) (overall response 23.5%) alongside 7 pts gaining benefit with stable disease. Responses were durable (203d, 161d, 141d (ongoing), and 176d (ongoing), respectively). Tumour volume reduction was seen in 56%. The frequent adverse effects (AEs) were fatigue, nausea and cytopenias. CXD101 was well tolerated and all AEs were manageable. CXD101 showed considerable variation in uptake, but peak concentrations were reached at 1–4 hours (h) post dosing (mean time to peak on d5: 2.3 ± 1.1 h). The mean PK data for C1 and 2 are shown (Table 1). Even at 25 mg b.d., there was no detectable drug at the next d1. $T_{1/2}$ was 5–12 h, with a longer $t_{1/2}$ on d5, C1 (d1 6.8 ± 3.8 h, d5 10.2 ± 4.3 h). CXD101 did not accumulate; the ratio between the area under the curve (AUC) on d1 and d5 was 2–3, with a mean of 2.86 ± 0.94 . There was a linear relationship between dose and AUC, C_{max} and C_{min} (8 h post-dose) for both cycles and days (shown C1 d5: Fig 1A–C), although there was some inter-individual PK parameter variation (R^2 coefficient 0.86–0.91). The mean accumulation ratio was consistent with a terminal $t_{1/2}$ of 19.5 h. The average C_{max} to C_{min} at RP2D ranged 300–200 nM, well within the biologically active range *in vitro*.

Conclusion: The peak concentration was at 1–4 h, $t_{1/2}$ was 5–12 h, with little accumulation with multiple cycles. There was a linear relationship between CXD101 dose and AUC, C_{max} and C_{min} . CXD101 has encouraging, durable activity in Hodgkin lymphoma, T-cell lymphoma, and follicular lymphoma in the early stages of its development.

Keywords: histone deacetylase inhibitors.

477 SAFETY RUN-IN OF COPANLISIB IN COMBINATION WITH RITUXIMAB PLUS BENDAMUSTINE IN PATIENTS WITH RELAPSED INDOLENT NON-HODGKIN'S LYMPHOMA

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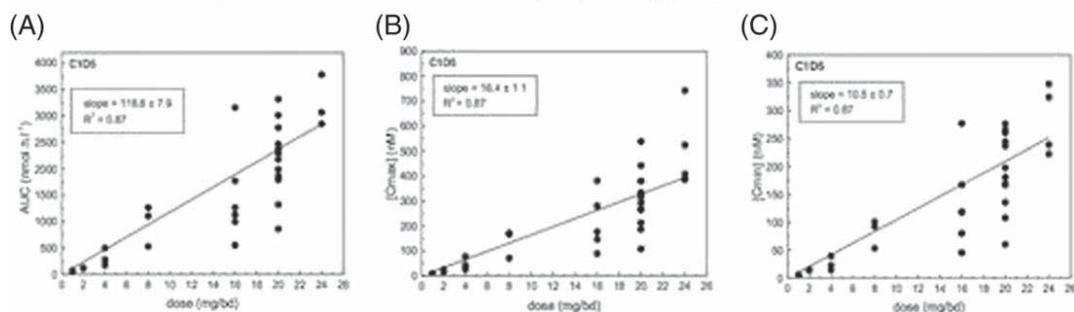
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Table 1: Mean PK data for Cycle 1 and 2 (n = 3 unless otherwise stated)

	Dose mg/day	Cycle	AUC _{0-8h} nmol.h.L ⁻¹	AUC _{SS} nmol.h.L ⁻¹	AUC _{0-8h} /AUC _{SS}	C _{max,SS} nM	C _{min,SS} nM	T _{max,SS} h	Half-life (Day 1) h	Half-life (Day 5) h
Mean	2	1	26.9	56.9	2.1	8.4	5.2	2.0	9.3 [‡]	8.6
SD			4.8	16.2	0.2	1.5	1.1	0.0	0.8	1.1
Mean	2	2	29.1	57.7	2.0	8.6	5.6	2.4	4.7	9.4
SD			12.8	23.2	0.1	3.7	2.4	0.6	0.8	0.6
Mean	4	1	49.2	123 [‡]	2.8	20.1 [‡]	14.3 [‡]	4.0 [‡]	6.0	5.5
SD			9.4	3.5	0.6	6.5	0.8	0.0		
Mean	4	2	49.9 [‡]	117 [‡]	2.2	15.8 [‡]	10.1 [‡]	2.6 [‡]	6.6	9.7
SD			19.6	74.2	0.6	10.6	6.0	0.8		
Mean	8	1	105	320	3.0	49.2	25.8	1.4	8.4	7.6
SD			54.9	166	0.1	25.7	12.7	0.5	4.0	1.0
Mean	8	2	82.9	310 [‡]	4.1	41.2 [‡]	26.8 [‡]	2.0 [‡]	5.7	9.5 [‡]
SD			23.8	256	2.7	28.8	21.3	0.0	1.1	2.2
Mean	16	1	376	971	3.0	137	82.6	1.9	5.1	8.4 [‡]
SD			237	388	1.0	56.7	25.4	2.0	1.7	1.8
Mean	16	2	500 [‡]	1010	2.6	170	108	2.0	6.1 [‡]	12.0
SD			149						2.1	
Mean	32	1	590 [*]	1483 [^]	2.8	204 [^]	135 [^]	1.7 [^]	6.8 [*]	11.4 [^]
SD			272	912	0.9	108	81	0.5	4.1	5.7
Mean	32	2	592 [#]	1307	2.4	199	134	3.3	10.1 [#]	10.2 [‡]
SD			229	518	0.5	84.3	52.6	2.5	9.0	5.4
Mean	40	1	773 ⁼	2190 ⁼	2.9 ⁼	306 ⁼	192 ⁼	2.7 ⁼	6.9 ⁼	10.1 ⁼
SD			247	689	0.7	115	67.7	0.8	3.4	6.1
Mean	40	2	777 [∞]	2110 [§]	2.8	283 [§]	211 [§]	2.6 [§]	5.6 [§]	11.9 [*]
SD			291	899	0.8	123	94.9	1.1	2.3	5.0
Mean	48	1	944 [#]	3733 [§]	4.1	491 [#]	316 [#]	1.5 [#]	7.9 [#]	10.9 [#]
SD			477	1077	1.4	151	89.5	0.7	4.6	3.4
Mean	48	2	911 [§]	2478	2.8	420	266	2.0	5.3	11.0
SD			50						0.7	

‡ n = 2; # n = 5; § n = 4; ^ n = 6; * n = 7; = n = 8; § n = 10; ∞ n = 11; = n = 12; where no SD is given n = 1.

Figure 1A-C: Effect of dose on AUC, C_{max} and C_{min} at cycle 1 day 5



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Introduction: Copanlisib (BAY 80-6946) is a pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant activity against α and δ isoforms and has been shown to provide clinical benefit in patients (pts) with relapsed/refractory indolent B-cell non-Hodgkin's lymphoma (iNHL). Recent closure of studies combining the PI3K inhibitor idelalisib in combination with rituximab and bendamustine (R-B) due to safety concerns has raised doubts about the viability of such combinations. We therefore conducted a safety run-in of copanlisib

in combination with R-B in relapsed iNHL pts to ascertain the safety and tolerability of the combination prior to initiation of enrollment in a randomized double-blinded placebo-controlled phase III study (NCT02626455; CHRONOS-4).

Methods: Patients with relapsed iNHL (4 subtypes: follicular [FL], marginal zone [MZL], small lymphocytic and lymphoplasmacytoid/Waldenström macroglobulinemia [LPL-WM]), who had received ≥ 1 prior line of treatment including rituximab were eligible. Copanlisib plus R-B was tested in a 3 + 3 design at two dose levels (45 and 60 mg) administered on days 1, 8 and 15 of a 28-day cycle. R was administered IV q4w at 375 mg/m² on day 1 and B administered IV at 90 mg/m² on days 1 and 2 for a total of 6 cycles. The primary objective was to determine the recommended phase III dose (RP3D) of the combination and the occurrence of dose-limiting toxicities (DLTs) in cycle 1.

Results: Ten pts were treated; 7 FL, 1 MZL, and 2 LPL-WM; 3 in the 45 mg copanlisib cohort and 7 in the 60 mg cohort. There were no DLTs. As of December 15, 2016, the median number of cycles received was 3, with 0/3 pts in the 45 mg dose cohort and 6/7 pts in the 60 mg cohort on active treatment. Four pts discontinued due to drug related AE: 3 related to copanlisib + R-B and 1 related to R-B. The most common TEAEs were neutrophil count decreased (80%), nausea (70%), platelet count decreased and hyperglycemia (60%), mucositis and fatigue (50%). No grade 5 TEAEs were reported. The most common grade ≥ 3 TEAEs included: neutrophil count decreased (50%), hyperglycemia (50%), lymphocyte count decreased (30%), white blood cell count decreased (20%) and hypertension (20%). Three pts had infections and infestations: one patient in the 45 mg cohort with lung infection grade 4, and 2 pts with infections-other in the 60 mg cohort (grade 2). No cases of non-infectious pneumonitis were reported. Two pts had serious TEAE (both in the 45 mg cohort): lung infection grade 4 and hypereosinophilia grade 3; both patients recovered. Tumor assessment was performed at 12 weeks and responses were seen in all 7 evaluable pts (2 CR and 5 PR).

Conclusions: Copanlisib was safe and tolerable for both cohorts (45 and 60 mg) in combination with R-B and initial efficacy was promising. No DLTs were observed and the Data Monitoring Committee recommended proceeding with the phase III at 60 mg copanlisib plus R-B. Enrollment is expected to begin May 2017.

Keywords: non-Hodgkin lymphoma (NHL); PI3K/AKT/mTOR.

478 IBRUTINIB IN ASSOCIATION WITH R-DHAP/OX FOR PATIENTS WITH RELAPSED/REFRACTORY B-CELL LYMPHOMA: PRELIMINARY RESULTS OF THE BIBLOS PHASE IB LYSA STUDY

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Introduction: Ibrutinib (Ibru), an inhibitor of Bruton's tyrosine kinase, is efficient, in monotherapy, for treatment of relapsed or refractory (R/R) mantle cells lymphoma and R/R chronic lymphocytic leukemia (Wang, 2013). The safety and activity of Ibru in combination with R-CHOP or R-Benda has also been evaluated (Younes, 2014; Maddocks 2015). We conducted a phase Ib study to assess of the safety of Ibru associated with R-DHAP or R-DHAOx for patients (pts), with R/R B-cell lymphoma candidates for autologous stem cell transplantation (ASCT).

Methods: Pts were planned to receive 3 cycles, every 21 days, of rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP) or oxaliplatin (R-DHAOx) in association with escalating doses of Ibru given on D1 to D21. Dose level (DL) 1 was 420 mg/day. The dose-variation scheme followed a "3 + 3" design (DL-1: 280 mg/day; DL2: 560 mg/day). Dose-limiting toxicities (DLT defined as: non-hematological toxicity grade (Gr) 3-4 excluding alopecia, diarrhea and/or nausea/vomiting and/or fatigue/asthenia for <7 days, any Gr ≥ 2 hemorrhagic events, any Gr ≥ 1 intracranial hemorrhage and any Gr ≥ 4 hematological toxicity >7 days) were considered during the first cycle. DLT.

Results: Between 05/14 and 07/15, 25 pts were treated (R-DHAP: 13, 1 non evaluable; R-DHAOx: 12). In the DL1 cohort, DLTs related to Ibru were observed in 3/6 pts receiving R-DHAOx (Gr3 cutaneous eruption, Gr3 febrile neutropenia and infection, Gr4 thrombocytopenia) and in 3/6 pts receiving R-DHAP (Gr4 cutaneous eruption, Gr4 thrombocytopenia and Gr4 sepsis). A total of 13 pts were treated at DL-1 with 1 pt experiencing DLT in each cohort (R-DHAP group: Gr4 thrombocytopenia and Gr4 gastric hemorrhage, Gr3 atrial fibrillation; R-DHAOx group: Gr3 epigastric pain). 6 (50%) pts treated with Ibru at the dose of 420 mg and 10 (77%) of those treated at the dose of 280 mg received more than 80% of the planned dose. All pts experienced ≥ 1 adverse events (AE) and Gr3-4 hematological AEs (neutropenia: 17 pts; thrombocytopenia: 25 pts). Overall, 3 pts presented serious hemorrhagic AE, 4 developed cutaneous eruptions. 1 died (cardiac toxicity assessed as unrelated to Ibru). Ibru was discontinued in 9 pts (7 for toxicities or DLTs, and 2 due to pt's decision). Response to treatment was evaluable in 16 pts (64%) and 14 responded to the treatment (8 (50%) CR and 6 (37%) PR. Stem cells were harvested in 16 pts and all of them underwent ASCT (CD34+ cells $>3.0 \times 10^6$ /kg in 94% of the collected pts after 1 sole apheresis).

Conclusions: Preliminary results show that the R-DHAP/Ox plus Ibru. (given from D1 to D21) regimen led to several DLTs. Since underdosing (280 mg) might not optimal to achieve an optimal response, a new dose escalation phase with Ibru given only from D5 to D18 with pharmacokinetics analyses was performed. The results of this will be presented. Expansion phase will open for inclusion in a few weeks.

Keywords: autologous stem cell transplantation (ASCT); B-cell lymphoma; Ibrutinib.

479 ENGAGING ADMINISTRATIVE DATA TO DETERMINE TIME TO DIAGNOSIS AND TREATMENT OF LYMPHOMA: A POPULATION BASED STUDY

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Introduction: The province of Manitoba (MB) has a goal of reducing time from suspicion of cancer to treatment to a target of 60 days. Most patients with suspicious symptoms present to primary care and referral is after diagnosis is confirmed. Time from suspicion to diagnosis, (diagnostic delay [DD]), is hypothesized to be inadequately captured in cancer centre records and we aimed to refine a method to identify milestones starting from initial health care contact to obtain baseline measures of delay.

Methods: This study examined DD, treatment delay (TD) and system delay (SD) in patients (>17) diagnosed with B-cell lymphomas from 2005 to 2010 using administrative data (MB Cancer Registry, MB Health billing and Hospital Abstract data) and chart review of a random subset of patients. A triangulated data approach, using an iterative consultative process, identified events likely related to subsequent lymphoma diagnosis and milestones. By linking to referring provider, date of high suspicion (HS) was identified and intervals were calculated for DD, TD and SD. SD from the chart review and the algorithm was compared with quintile regression. Cumulative incidence curves of SD were generated assessing patient factors (age, gender, lymphoma subtype, stage, socioeconomic status) and system factors (route of HS, treatment type, continuity of care, region of residence). The difference between variables was tested using the log rank test with significance defined as p value ≤ 0.05 .

Results: The cohort included 1295 patients (51.7% male), median age 65 (17–100) with aggressive NHL (43.6%), indolent NHL (34%), HL (12%) and other B lymphomas (10.4%). Chart review was only able to identify HS in 22/112 patients and underestimated SD by a median of 22 days. A total of 297/1295 (22.9%) of patients have never been treated, with 6.1% (79/1295) and 10.5% (136/1295) due to death within 1 and 3 months of diagnosis, and remaining 12.4% (161/1295) alive without treatment to date. Overall, only 14.8% of patients met the target for SD with median SD 128 days (90%ile 324 days), DD 85 days (90%ile 278 days) and TD 41 days (90%ile 83 days). Lymphoma subtype (see Figure 1), age (older patients longer delays, $p = 0.009$), stage (stage IV shorter SD, $p < 0.0001$), route of HS (ER first presentation, $p < 0.0001$), first treatment type (chemotherapy shorter than radiation, $p = 0.02$) influenced SD whereas gender, socioeconomic status, place of residence, and continuity of primary care did not.

Conclusions: SD was long with some patients vastly exceeding acceptable time frames. DD accounted for two thirds of SD. This interval is underestimated by chart review, our methodology more reliably identifies HS and allows study on a population basis. To reduce

SD a clinical pathway with goal timelines and emphasis on aggressive subtypes/presentations has been developed and disseminated. This serves to direct process improvement and as a reference for clinicians and further research design.

Figure 1 Cumulative Time from High Suspicion (HS) to Treatment by Lymphoma Category

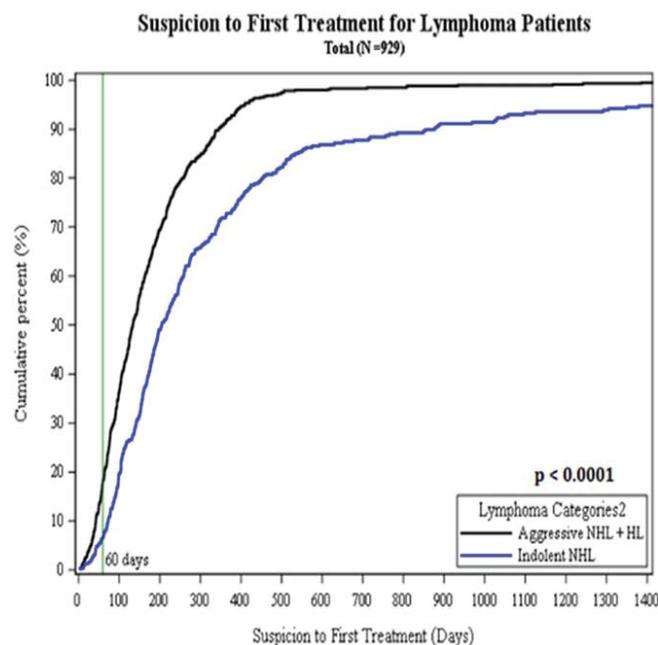
Keywords: B-cell lymphoma.

480 PHASE I/II STUDY OF CHOEP PLUS LENALIDOMIDE AS INITIAL THERAPY FOR PATIENTS WITH STAGE II-IV PERIPHERAL T-CELL NON-HODGKIN LYMPHOMA: PHASE I RESULTS FROM THE T-CELL CONSORTIUM

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Introduction: Lenalidomide (len) is an immunomodulatory agent with single agent activity in relapsed and refractory peripheral T-cell lymphoma (PTCL). CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) is a common initial regimen. We report



the completed phase I portion of our trial establishing the maximum tolerated dose (MTD) of len with standard dose CHOEP.

Methods: Eligible patients had newly diagnosed PTCL, ANC ≥ 1000 cells/mm³, platelets ≥ 100 K/mm³, and adequate organ function. A 3 + 3 design was used. CHOEP dosing was standard with len given on days 1–10 of 21-day cycle at dose levels of 10, 15 and 20 mg. Patients could receive up to 6 cycles of len-CHOEP with the option of len maintenance (10 mg) for 1-year or consolidative autologous stem cell transplant (ASCT). Growth factor support was mandatory. Patients were eligible for determination of MTD if they received 100% of planned dosing in cycle 1 or experienced a treatment-related dose limiting toxicity (DLT). All investigators monitored for cumulative toxicities.

Results: Twelve patients with PTCL-NOS ($N = 5$) and AITL ($N = 7$) enrolled into the phase I portion. Median age was 62 years (range 38–77) and 8 of 12 were male. Four patients were treated at 10 mg without DLTs; 1 ineligible for MTD determination due to <100% doses received in cycle 1. Four patients were treated at 15 mg; 1 ineligible for MTD determination due to <100% doses received in cycle 1. A DLT of grade 3 diarrhea was seen at the 15-mg dose level in 1 patient. Based on significant cumulative hematologic toxicities in later cycles, an additional 4 patients were enrolled at the 10 mg dose level with 1 DLT in the additional patients; incomplete ANC recovery at day 28. In total, 8 patients were dosed at the 10-mg level and collectively a len dose of 10 mg days 1–10 was considered to represent the MTD. To date 5 patients have completed all 6 cycles. Dose reduction/discontinuation of len occurred in 4 patients. Reasons for discontinuing len-CHOEP prior to 6 cycles were diarrhea ($N = 1$), investigator decision ($N = 1$; proceed to ASCT after 5 cycles), and progression ($N = 1$). Overall, in the 12 patients evaluable for safety, grade 3–4 hematologic toxicities included neutropenia ($N = 8$), anemia ($N = 6$), and thrombocytopenia ($N = 6$) with neutropenic fever seen despite growth factor support in 4 patients. Non-hematologic grade 3–4 toxicities were diarrhea ($N = 1$), hypotension ($N = 1$), and mucositis ($N = 1$). To date, 3 patients have proceeded to len maintenance and 3 patients have proceeded to ASCT.

Conclusions: Higher than expected cumulative hematologic toxicities were seen in later cycles of len-CHOEP. As a result, len at a dose of 10 mg days 1–10 was determined to be the MTD when combined with CHOEP. The phase II cohort is currently accruing with evaluation of the complete response rate as a primary study endpoint.

Keywords: lenalidomide; peripheral T-cell lymphomas (PTCL).

481 DUAL PI3K δ/γ INHIBITOR RP6530 IN PATIENTS WITH RELAPSED/REFRACTORY T-CELL LYMPHOMA: DOSE ESCALATION FINDINGS.

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Introduction: The δ and γ isoforms of PI3K play a distinct role in the growth and survival of T-cell lymphoma (TCL). RP6530 is a novel, highly specific dual PI3K δ/γ inhibitor with nano-molar inhibitory potency for both isoforms. Herein, we present results from an ongoing Phase 1/1b, dose escalation study in TCL (NCT02567656).

Methods: The study consists of a standard 3 + 3 dose escalation cohort to determine the maximum tolerated dose (MTD), followed by two expansion cohorts: Peripheral TCL (PTCL) ($n = 20$) and Cutaneous TCL (CTCL) ($n = 20$). Patients (Pts) with a diagnosis of TCL who have received at least one prior systemic therapy were eligible. The study also evaluated pharmacokinetics, pharmacodynamics, and anti-tumor activity of RP6530 administered orally twice daily (BID) in 28-day cycles. Dose limiting toxicity (DLT) was defined by a toxicity of \geq grade 3 using the CTCAE V4.03 that is considered related to treatment during the first cycle.

Results: To date, nineteen pts (9 PTCL and 10 CTCL; 12 males and 9 females) have been enrolled at four dose levels: 200 mg BID ($n = 4$), 400 mg BID ($n = 4$), 800 mg BID (fasting) ($n = 5$) and 800 mg BID (fed) ($n = 6$). The median age was 63 years (range 40–76). Pts received a median of 3 (range: 1–7) prior treatment regimens; 12 pts had relapsed disease after last treatments whereas 7 pts had refractory disease. RP6530 was well tolerated up to 800 mg (fasting) dose. No DLT was not observed at dose levels 200 mg BID, 400 mg BID and 800 mg BID (fasting). At 800 mg BID (fed), which theoretically provides higher drug exposure than fasting dose, three DLTs were observed (transaminitis grade 3, rash grade 3 and neutropenia grade 3) in 6 patients. Therefore, 800 mg BID (fasting) was considered a MTD. The most common related adverse events were transaminitis (32%), fatigue (26%) and rash (26%). There were no related SAEs. In all related grade 3 events, withholding study drug and monitoring at least once weekly until the event resolves to grade 1 was recommended. In two cases of transaminitis, steroid was started as it was deemed immune mediated. No pt discontinued treatment due to safety reason. Dose-proportional increases in plasma concentrations were observed in PK. Five pts experienced rapid disease progression during first cycle and discontinued treatment prematurely. Response assessment in fourteen pts at Cycle 3, Day 1 demonstrated an overall response rate of 36% with one complete response in PTCL (7%) and four partial responses (2 PTCL and 2 CTCL) (29%). Six pts had stable disease (43%).

Conclusion: Dose escalation study demonstrated an acceptable safety and tolerability up to RP6530 800 mg BID (Fasting) with promising clinical activity in pts with TCL. A dose of 800 mg BID (fasting) was considered a MTD. The results support further evaluation of RP6530 in pts with mature T-cell lymphomas. Dose expansion at 800 mg BID (fasting) is currently ongoing.

Keywords: PI3K/AKT/mTOR; T-cell lymphoma (TCL).

MISCELLANEOUS

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PICC-RELATED THROMBOSIS IN PATIENTS WITH AGGRESSIVE LYMPHOMA TREATED WITH DA-EPOCH—HOW TO PREVENT IT?

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Introduction: Peripherally inserted central catheters (PICCs) are long-term catheters appropriate for administration of continuous infusions such as DA-EPOCH protocol. The main complications associated with PICC-lines are infections and PICC-related thrombosis. Data on the incidence and prevention of PICC-related thrombosis in patients with lymphoma are limited. In this study, we investigated the role of anti-thrombotic prophylaxis in patients with aggressive non-Hodgkin lymphoma (NHL) treated with DA-EPOCH \pm rituximab (DA-EPOCH \pm R).

Methods: From September 2009 to March 2017, 95 patients with newly diagnosed aggressive NHL were treated with DA-EPOCH \pm R regimen at our institution. A single lumen 5Fr PICC was used in all patients. Antithrombotic prophylaxis was given per treating physician discretion, starting from the day of PICC insertion. Dalteparin 2500 to 5000 IU or enoxaparin sodium 4000 IU qD were used as low molecular weight heparin (LMWH) prophylaxis. Two-tailed Fisher's test was used for comparison and the P value of less than 0.05 was considered significant.

Results: There were 55 males and 40 females with a median age of 62 years (range 21–82 y). Eight patients had T-cell lymphoma, and 88 had B-cell NHL. Nine patients had PICC-related thrombosis (9.5% of all patients). Six patients developed PICC-related thrombosis during the first cycle, one during the second cycle, and two during the third cycle of DA-EPOCH \pm R. All events occurred in the group of 68 patients who did not receive antithrombotic prophylaxis/treatment (incidence 13.2%). Antithrombotic prophylaxis was given in 17 (18%) patients: ten patients received low-dose LMWH for prophylaxis for one or two cycles of DA-EPOCH \pm R, and seven patients received Aspirin 100 mg for prophylaxis. In additional ten patients, full-dose LMWH was given for deep vein thrombosis at presentation and continued in prophylactic dose. None of the patients that received prophylaxis/treatment developed PICC-related thrombosis (0/27). However, this result did not reach the level of statistical significance ($P = 0.056$). There was no hemorrhage related to antithrombotic treatment/prophylaxis.

Conclusions: The incidence of PICC-related thrombosis in patients without antithrombotic prophylaxis was 13.2%, and two-thirds occurred during the first cycle. In contrast, the patients who received any type of antithrombotic prophylaxis or treatment had no PICC-related thrombosis. Although the level of statistical significance has not been reached ($P = 0.056$), our results suggest that patients with

aggressive lymphoma may benefit from the prophylaxis with low-dose LMWH during the first two cycles of DA-EPOCH \pm R.

Keywords: DA-R-EPOCH; EPOCH; non-Hodgkin lymphoma (NHL).

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HIGH RATE OF MORBID CENTRAL LINE ASSOCIATED COMPLICATIONS DURING TREATMENT WITH DOSE-ADJUSTED R-EPOCH THERAPY FOR NON-HODGKIN LYMPHOMA

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Introduction: Certain aggressive non-Hodgkin lymphoma (NHL) subtypes are often treated with infusional dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-R-EPOCH). Unlike other regimens such as rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), DA-R-EPOCH requires a central line. In practice, we have observed clinically meaningful line-associated complications (LAC) in patients (pts) treated with DA-R-EPOCH. With the ongoing use of this regimen, we sought to identify the rates and correlates of LAC in this population, and compare them to the rates of LAC in pts with NHL treated with R-CHOP.

Methods: We retrospectively identified all pts treated with DA-R-EPOCH at the Wilmot Cancer Institute between 3/2011 and 10/2015. We also identified a concurrent cohort of pts treated with R-CHOP, matching for stage. Our primary endpoint was the rate of LAC, including venous thromboembolism (VTE), chemotherapy extravasation, and line-associated infection (LAI) diagnosed during treatment. Our secondary endpoint was the rate of VTE during therapy. Rates and 95% confidence intervals (95% CI) were calculated for all endpoints, and compared using Fisher's exact test. Univariate logistic regression was used to calculate odds ratios to evaluate potential predictors.

Results: A total of 43 pts received DA-R-EPOCH during the study period. A total of 17 pts (39.5%, 95% CI 0.25–0.56) experienced at least 1 LAC: 15 pts (35%, 95% CI 0.21–0.51) had VTE; 3 pts had LAI; and 2 pts with extravasations. A total of 44 pts received R-CHOP during the study period. A total of 8 pts (18.2%, 95% CI 0.08–0.32) experienced at least 1 LAC. Compared to the R-CHOP cohort, pts treated with DA-R-EPOCH experienced a significantly higher rate of LAC ($p = 0.03$). In the DA-R-EPOCH cohort, grade 3 toxicity was seen in 41% (7/17): 4 pts with VTE, and 3 pts with LAI. Both extravasation events were grade 2, and both occurred with mediports. In univariate analysis, BMI ≥ 35 kg/m² and using a peripherally inserted central catheter (PICC) line were significantly associated with an increased risk of VTE ($p = 0.04$ and $p = 0.02$, respectively).

Conclusions: Approximately 40% of pts receiving DA-R-EPOCH therapy for treatment of NHL developed LAC, almost half of whom experienced grade 3 toxicities. The rate of LAC was significantly greater in

pts undergoing therapy with DA-R-EPOCH, compared to R-CHOP. Clinicians need to balance these risks when selecting therapy, particularly with the lack of randomized data to support the DA-R-EPOCH approach in many circumstances. Given observed extravasations, when administering DA-R-EPOCH, we avoid mediports in favor of PICC lines; however, this approach carries a significant risk of VTE. Future studies are needed to evaluate the role of prophylactic anticoagulation in this population.

Keywords: DA-R-EPOCH; non-Hodgkin lymphoma (NHL); R-CHOP.

484 SUBCUTANEOUS RITUXIMAB IN B-CELL NON-HODGKIN LYMPHOMA: A SINGLE- CENTER EXPERIENCE

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Introduction: A subcutaneous (SC) formulation of Rituximab has been recently developed for follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). The safety profile is similar to intravenous (IV) formulation, except for increased skin reactions in the area of Rituximab SC injection. These administration-related reactions (ARRs) consisted mainly of erythema, pruritus, induration and pain at the injection site, generally being grade 1–2 and without needing specific treatment. Our aim was to evaluate the safety profile of Rituximab SC after EMA approval in the daily clinical practice in our Institution.

Patients and Methods: B-cell non-Hodgkin Lymphoma (B-NHL) patients (pts) over 18 years of age consecutively treated with Rituximab SC from January 2016 to January 2017 were included. All pts received injections of 1,400 mg Rituximab SC either with chemotherapy or alone as maintenance. ARR were registered at 15 min (early ARRs) and at 24 hours (late ARRs) after Rituximab SC administration. Severity, time of onset, need for treatment and clinical follow-up were assessed for all ARRs.

Results: A total of 184 Rituximab SC injections were administered in 49 B-NHL pts (26 FL, 18 DLBCL, 5 others B-NHL). Complete records regarding ARRs were available for 160 injections (87%). Median number of Rituximab SC injections per patient was 3 (range 1–7). Approximately 49% of the Rituximab SC injections were administered in combination with chemotherapy, and 51% were administered alone as maintenance. Six pts were on anticoagulation. *Safety profile:* related ARRs were reported in 20% of all Rituximab SC injections. Early ARRs were observed in 14% ($n = 23$), 52% of them remaining at 24 hours. All early ARRs were grade 1–2: 14 painless erythema at the injection site, 1 painful erythema, 6 local pain without erythema, 1 hematoma and 1 dizziness. Only one early ARRs required specific treatment with a favorable outcome. Late ARRs were observed in 6% ($n = 10$) of the Rituximab SC injections, being all grade 1–2 and circumscribed to the injection site: 4 painless erythema, 4 local pain without erythema, 1 cellulitis and 1 pruritus in the injection area. Of note, most first ARRs occurred in the fist rituximab SC injection. There was no statistically

significant association between the occurrence of ARRs and time interval from premedication to Rituximab SC injection, use of anticoagulants or schedule of treatment used.

Conclusions: Our study supports the safety of Rituximab SC formulation in daily clinical practice, likely reducing chair time in the Day Unit and improving patient satisfaction and quality of life.

Keywords: non-Hodgkin lymphoma (NHL); rituximab.

485 PHARMOVIGILANCE OF RITUXIMAB BIOSIMILAR IN THE TREATMENT OF LYMPHOMAS IN ARGENTINA

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Introduction: Novex® is a biosimilar of the reference product MabThera®/Rituxan® commercialized in Argentina by Laboratorio Elea. As part of its Risk Management Plan (RMP), and as defined in Argentinean regulation, Laboratorio Elea implemented an active pharmacovigilance program and periodically reports its status and results to ANMAT.

Methods: A prospective treatment Registry for NOVEX® was implemented since its launching. Physicians prescribing NOVEX® were requested to fill a form indicating age, gender, treatment start date, treated pathology, dosing and dose frequency for each patient. After a preset time, they were asked about treatment outcome and Adverse Event occurrences. Each adverse event occurrence was reported as an Individual Case Safety Report (ICSR). MedDRA (version 19.1) was used for codification.

Results: From November 26th, 2014, to February 28th, 2017, a total of 583 non-Hodgkin Lymphoma (NHL) patients who had been prescribed NOVEX® were registered. A total of 378 of these patients had at least 1 follow-up point and were included for analysis, see table 1 for distribution per indication. Approximately 53% male. Mean age 64.7 years. Treatment duration interquartil range (IQR): 155–306 days, mean 233 days and median 214 days. Mean of cycles administrated 5.7 (range 1–12) Total number of received Individual Case Safety Reports (ICSR) was 15, indicating a relative frequency of 4% ICSR. Occurrence rates were 1.0 report per 100 administered cycles, and 0.018 per 100 treatment days. A total of 10 out of the 15 reports being serious. Out of the 15 received ICSRs, 8 Acute infusion related reactions (AIRR) were reported, 4 of them being serious. A total of 7 of the 8 AIRR occurred during 1st Rituximab infusion. Other manifestations different to AIRR were: Pneumonia (2), Arrhythmia (1), Ischemic Stroke (1), Restless Leg Syndrome (1), Progressive Multifocal Leukoencephalopathy (1),

Cytopenia (1) and Bullous Dermatitis (1). One report included more than 1 manifestation.

Additionally, we detected the occurrence of off-label use(*) in 6.6% treatments.

Conclusion: The activities developed under this active pharmacovigilance program are showing great value allowing us to continuously monitor the safety profile of this biosimilar product. In this report the biosimilar product NOVEX® showed a safety profile similar to what has been described with the reference product. Therefore, in terms of tolerability, the biosimilar product has a comparable profile with the reference product.

Keywords: monoclonal antibodies (MoAb); non-Hodgkin lymphoma (NHL); rituximab.

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REAL-LIFE USE OF BENDAMUSTINE FOR B-CELL NON-HODGKIN LYMPHOMA IN A COMMUNITY HOSPITAL IN JAPAN—RE-TREATMENT WITH BENDAMUSTINE IS SAFE AND FEASIBLE

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Introduction: Bendamustine is an alkylating agent with antimetabolite properties that has little cross resistance to other alkylating agents and purine analogues. It has shown to be effective in treatment of relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphomas (NHL). Combination of bendamustine with rituximab is currently actively incorporated not only in R/R settings but also in first line treatment of these diseases. Once patients relapse after bendamustine (B)-containing therapy, data is limited on whether retreatment with bendamustine is feasible. In this study, we assessed the utility of B-containing regimen in a community hospital in Japan, especially focusing on the feasibility of retreatment with bendamustine.

Methods: Patients with B-NHL treated with B-containing therapy were identified from our pharmacy database. Relevant clinical information was retrospectively collected from the patients' medical record.

Results: We identified 39 patients with B-NHL treated with B-containing therapy. The median age of the patients was 70 years old (range 39–88). The male to female ratio of the patients was 25:14. Twenty-nine patients were initially diagnosed as indolent B-NHL (follicular lymphoma (FL): 23, mantle cell lymphoma (MCL): 4, small lymphocytic lymphoma (SLL): 1, splenic marginal zone lymphoma (SMZL): 1), and the remaining 10 had diffuse large B-cell lymphoma

Table 1: Distribution per indication of patients included in the analysis

Indication	#	%
Follicular non-Hodgkin lymphoma	195	51.6%
Diffuse large B-cell non-Hodgkin's lymphoma	114	30.2%
Chronic lymphocytic leukemia	44	11.6%
Other non-Hodgkin lymphomas*	25	6.6%

(DLBCL). The median number of treatment prior to bendamustine use was 1 (range 1–17). Patients were treated with a median of 3 (range 1–66) cycles of B-containing regimen, and the overall response rate (ORR) was 59.0% (CR: 10, PR: 13, SD: 6, PD: 10). The median overall survival and progression-free survival was 60 (0.5–68.8+) months and 10 (0.3–68.6+) months, respectively. Among these patients, 10 were retreated with B-containing therapy at subsequent relapses. The median time from initial treatment was 14.8 (range 9.1–38.0) months. Seven patients had FL, 2 had DLBCL and 1 had MCL. The ORR of second bendamustine treatment was 100% (CR: 3, PR: 7). Among the 8 patients who subsequently relapsed or had progression of disease, 4 patients were further treated with B-containing regimen, and the median number of bendamustine treatment beyond first progression among all 10 patients was 5 (range 1–13) cycles. There was no apparent increase of infection after retreatment with bendamustine.

Conclusions: Treatment of R/R B-NHL with B-containing therapy in a single institute yielded similar results to previous reports. Retreatment with B-containing regimen showed high response rate with few complications, making multiple retreatment possible in some patients. Bendamustine retreatment should be considered a treatment option in patients relapsed beyond first treatment with bendamustine.

Keywords: B-cell lymphoma; bendamustine.

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THALIDOMIDE IN RELAPSED LYMPHOMA: 5 YEARS OF EXPERIENCE FROM SOUTHEND UNIVERSITY HOSPITAL NHS FOUNDATION TRUST

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Introduction: Thalidomide is an immunomodulatory and anti-inflammatory drug with well-documented efficacy in the treatment of multiple myeloma, both as initial therapy and in relapsed disease. Known side effects include venous thrombosis, fatigue, peripheral neuropathy and constipation. However as an oral drug with minimal myelosuppression, thalidomide is suitable for patients unable to tolerate more conventional chemotherapy or for whom regular hospital attendances are too demanding. Data from clinical trials and case series in a range of both B- and T-lymphoproliferative disorders show broad efficacy of thalidomide. The unusual and multiple modes of action of thalidomide suggest potential in treating disease resistant or refractory to conventional chemotherapy. This is further supported by exceptional case studies such as a refractory AITL patient achieving CR with thalidomide/dexamethasone and a post-allograft DLBCL patient achieving CR on thalidomide/rituximab. We have been using Thalidomide in relapsed and frail lymphoma patients at Southend for a number of years with anecdotally good outcomes. We decided to conduct a retrospective study of lymphoma patients treated with thalidomide

to assess the rates of response and overall survival, as well as examining the side effect profile.

Methods: Data from 2012 to 2016 were collected retrospectively from pharmacy records for all lymphoma patients treated with thalidomide. The majority of these patients were multiply relapsed. Patients were all started on 50 mg daily, with dose escalation to 200 mg daily as tolerated, in addition to pulsed dexamethasone.

Results: 27 patients were treated: - 11 DLBCL (2 transformed low-grade) - 3 Follicular lymphoma - 2 B-NHL unspecified - 3 Hodgkin's disease - 2 Waldenström's macroglobulinaemia - 1 mantle cell - 5 angioimmunoblastic T cell - Age range of patients 52–58 (median age 75) - Line of treatment was 1–5 (median 2) - 17/27 patients were treated for >4 weeks (others stopped due to SEs or early relapse/death) - 7 of those 17 achieved disease control for >6 months.

Conclusion: The patients examined in this study were all multiply relapsed and/or too frail for conventional chemotherapy. Prognosis in such a cohort is very poor and, unsurprisingly, many of the cases we looked at died shortly after starting treatment. However, a subset of these patients achieved long disease control—one patient is still alive 5 years after starting thalidomide. Thalidomide has a variety of mechanisms including immunomodulatory and anti-angiogenic properties so it is a logical choice of treatment in chemotherapy-resistant cases. Given the generally well-tolerated side effect profile and low cost of thalidomide not to mention the ease of administration, a trial of thalidomide is worth considering when no other options remain, where it may buy precious months, or even years, of life.

Keywords: B-cell lymphoma; immunomodulators (IMiDs); T-cell lymphoma (TCL).

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COMPARATIVE ANALYSIS OF PREDICTIVE MODELS FOR THROMBOEMBOLIC EVENTS IN LYMPHOMA PATIENTS

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Introduction: Actual guidelines recommend Padua and Khorana score for thromboembolic (TE) risk estimation for cancer patients in general. These existing models are quite limited for designation of lymphoma patients for TE events, as their development is not based on features specific for hematological patients. The aim of this study was to compare diagnostic performance of these suggested predictive models, as well as Thrombosis lymphoma (Throly) score, developed by our group, which is more specific for lymphoma patients.

Methods: The study population included all consecutive patients with a histological confirmed diagnosis of non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and chronic lymphocytic leukemia (CLL)/

small lymphocytic lymphoma (SLL), who were treated in the Lymphoma Departments of Clinical Center Serbia and Clinical Center Kragujevac. From January 2006 to December 2014, data were prospectively collected and entered into the institutional Lymphoma database. The study population was divided based on a split-sample random method into the model developing and validation cohorts. The ThroLy model was developed using data solely from a derivation cohort, which included 1236 patients. Variables were evaluated by univariate logistic regression analysis, while the model was developed using a stepwise multivariate logistic regression analysis. Once a final model was defined, patients were divided into *low risk* and *at risk* groups. The final model was assessed in the validation cohort (584 patients). The studied population was also divided, based on Khorana and Padua score, into *low risk* and *at risk* groups.

Results: The incidence of thromboembolism was 81 (5.3%) in the newly diagnosed patients and 18 (6.2%) in relapsed patients. Overall, 35.4% (35/99) of the patients with thromboembolism experienced the event before the start of chemotherapy. The majority of patients (64.6%) had TE events during chemotherapy or within 3 months after chemotherapy. Cohorts were balanced regarding the incidence of events (5.3% and 5.5% in derivation and validation cohort, respectively). For patients classified *at risk* according to ThroLy score in derivation cohort, the model produced negative predictive value (NPV) of 98.5%, positive predictive value (PPV) of 25.1%, sensitivity of 75.4%, and specificity of 87.5%. In validation cohort PPV for Throly score was 28.9%. Padua and Khorana score had PPV of 15.5% and 14.8% in derivation, and 11.5% and 14.8% in validation cohort, respectively.

Conclusion: Lymphoma patients are at increased risk of thromboembolic events but thromboprophylaxis in these patients is largely underused. ThroLy score is more specific for lymphoma patients than suggested Padua and Khorana score, but external validation in large prospective cohort studies is required.

Keywords: Hodgkin lymphoma (HL); non-Hodgkin lymphoma (NHL).

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INCIDENCE AND SURVIVAL OF NON-HODGKIN LYMPHOMA AT ONCOSALUD—AUNA: A DYNAMIC COHORT STUDY

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Background: Non-Hodgkin lymphoma (NHL) is the most common malignancy in many countries and regions; it represents the twelfth cause of death in the world and the eleventh cause of death in the Peruvian population. The incidence of lung cancer in a population affiliated with a prepaid system is important for the implementation of prevention programs. The aim of study was to determine the incidence rate of NHL in a population of affiliates and the survival rate of patients treated in a private institution (ONCOSALUD—AUNA).

Methods: In a study of dynamic cohort, the incidence of LNH was evaluated in a population of affiliates to ONCOSALUD—AUNA

between 2008 and 2013 ($n = 1,096,140$). Overall survival (OS) was evaluated in patients treated in ONCOSALUD—AUNA between 2000 and 2005 ($n = 114$). The incidence rate was calculated based on new cases/persons-year of observation. The OS was calculated according to Kaplan-Meier method.

Results: The median age was 33 years, and 55.7% were women. A total of 2,611,438.3 persons-year of observation was produced, and 284 affiliates were diagnosed with NHL. The median age at diagnosis was 65 years. The standardized incidence rate by age was 6.4 per 100,000 persons-year (5.6 and 7.8 in women and men per 100,000 persons-year, respectively), and 74 years cumulative risk was 0.7% (0.6 and 0.9% in women and men, respectively). For survival assessment, the median age was 63 years, 52.6% were women and 48.0% had advanced disease (CS III: 14.0% and CS IV: 34.0%). With a 11.3-year follow-up, the median survival was not achieved. The OS rate at 5 and 10 years were 56.8% and 52.1%, not showing significant difference in relation to sex ($p = 0.107$, although female patients had a better survival), and shows significant difference according age (<60 vs. >60 years: $p < 0.001$) and clinical stage (CS I-II vs. III-IV: $p = 0.008$).

Conclusions: The incidence rate of NHL in our population is similar than reported by the IARC for the Peruvian population. The survival rate at 5 and 10 years is similar to reported for other series.

Keywords: non-Hodgkin lymphoma (NHL).

490 LANGERHANS CELL HISTIOCYTOSIS IN ADULTS IS ASSOCIATED WITH INCREASED HEMATOLOGIC AND SOLID MALIGNANCIES

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Introduction: Langerhans cell histiocytosis (LCH) is a rare disorder of histiocyte proliferation occurring predominantly in children. Previous retrospective and small case studies have suggested higher rates of both hematologic and solid malignancies among LCH patients, possibly due to treatment with tumorigenic agents such as etoposide. Here, we report on our 25-year institutional experience of adult LCH patients with additional malignancies, in an era prior to the widespread use of etoposide.

Methods: We identified 170 consecutive patients over 18 years of age who presented with histologically confirmed LCH (S100+, CD1a+) at our center between 1990 and 2015. Demographics and detailed oncologic history was recorded to identify patients with additional malignancies, excluding non-melanoma skin cancers. The Kaplan-Meier method was used to estimate overall survival.

Results: Of 170 consecutive adult LCH patients, 62 (36.5%) patients had an additional malignancy. There were a total of 81 malignancies among the 62 patients, with 47 (58%) occurring before LCH diagnosis, 18 concurrent (≤ 3 months; 22%) with LCH diagnosis, and 16 (20%)

after. Fifteen patients presented with 2 malignancies in addition to their LCH diagnosis, and 2 patients presented with ≥ 3 malignancies. Median age was 65 years (range 28–90) with a median follow-up of 3.5 years (0–22). Median overall survival (OS) was 11.2 years, with 45 (72.5%) alive at last follow-up. The following distribution among lymphomas, other hematologic malignancies, and solid tumors were observed: 10 (12%), 7 (9%), and 64 (79%). The most commonly observed lymphomas included follicular lymphoma (30%), classical Hodgkin's lymphoma (20%), and B-cell lymphoma (20%). Most common hematologic malignancies included acute myeloid leukemia and multiple myeloma (29% each). The most common solid tumor histologies were lung (24%), breast (15%), and colorectal cancer (11%).

Conclusions: Our cohort of adult LCH patients demonstrates an exceptionally high number of malignancies. Although our retrospective study is open to referral bias, our findings are consistent with numerous published small retrospective studies and case reports. Other large retrospective studies were performed when etoposide was widely used, and etoposide was suggested as a possible cause for an observed increase in hematologic malignancies after LCH treatment. Yet our study shows an increased prevalence of other malignancies before or concurrent with LCH diagnosis and thus suggests a cause of malignancy independent of LCH treatment. Further exploration of the biology of this rare disease may elucidate the mechanism of increased second malignancies.

Keywords: etoposide; histiocytes.

491 A PROSPECTIVE STUDY TO EVALUATE THE UTILITY OF GERIATRIC ASSESSMENT AND INTERVENTION IN PATIENTS WITH LYMPHOPROLIFERATIVE DISORDERS IN A TERTIARY HOSPITAL

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Introduction: Haematological malignancies are frequent in elderly and its management represent a challenge to be solved. The geriatric assessment (GA) is useful in elderly patients with cancer. However, there is little information regarding its usefulness in lymphoma patients. Our aim in this study is to evaluate the utility of GA in older patients with lymphoproliferative disorders.

Patients and Methods: Since 05/2015, patients older than 70 y/o diagnosed with lymphoma in our centre were invited to participate in this study. Patients considered not eligible for treatment were excluded. All patients included were subjected to G8 screening and integral GA before the beginning of treatment. Five follicular lymphoma patients on "watch and wait" strategy were excluded for

N of patients		36
Age (median, percentiles)		77 (75-81)
Gender	n (%)	
	male	15
	female	19
Diagnosis	n (%)	
	DLCL	21
	FL	6
	ML	6
	HL	2
	HCL	1
Stage	n (%)	
	I-III	11 (30,5)
	III-IV	25 (69,5)
Treatment	n (%)	
	R-CHOP	20
	R-BEND	6
	R-MONO	3
	others	7
N of cycles (median, percentiles)		6 (4-6)
T. adjustment	n (%)	16 (44,5)
Infections	n (%)	12 (33)
Hematis tx	n (%)	12 (33)
Pletelets tx.	n (%)	3 (2)
Hospital admission	n (%)	19 (52)
Days of admision (mean, range)		46 (1-183)

Table 1. Characteristics of patients, disease and treatment. Data for the global population and divided by G8 screening tool. *n*: number, DLCL diffuse large cell lymphoma, FL follicular lymphoma, ML marginal lymphoma, HL Hodgkin lymphoma, HCL hairy cell leukaemia, R-MONO: Rituximab monotherapy, tx: transfusion. Others include: 1 RCVF, 2 MTX, 1 2CDA, 2 ABVD, 1 CRD

TEST	n (%)
G8	
≥ 14 (fit)	10 (28)
< 14 (no fit)	26 (72)
Dukes	
≥ 32 (normal social support)	34 (95)
< 32 (low social support)	2 (5)
Barthel	
> 90 (normal)	34 (95)
61-90 (moderate dependence)	2 (5)
21-60 (severe dependence)	0 (0)
≤ 20 (total dependence)	0 (0)
Charlson	
0-2 (low comorbidity)	29 (82)
≤ 7	36 (100)
MNA-SF	
12-14 (normal)	16 (44)
8-11 (malnutrition)	15 (41)
≤ 7 (desnutrition)	5 (14)
SPPB	
normal	10 (28)
(n: 32) mild	2 (5)
moderate	10 (28)
severe	10 (28)
Fried	
no fragile	17 (55)
(n:31) fragile	14 (45)

Table 2. Results of geriatric assessment tests

analysis. G8 screening tool with a cut off of 14 divided the patients into two groups: those considered fit (+14 pts) who wouldn't receive geriatric follow up, and patients considered unfit (-14 pts) who would receive geriatric follow-up and intervention if required. The trial was approved by local ethic committee. Geriatrics syndromes evaluated (at months 0, 4, 8, 12, and 18-24) were fragility, malnutrition, syncope, dizziness, urinary incontinence, gait abnormalities, falls, osteoporosis, dementia, behavioural disturbance, delirium, depression, sleep disturbance, pressure ulcers and chronic ache. Tests performed: Dukes scale (social support), Barthel and Lawton scales (activities of daily living), Charlson scale (comorbidities), MNA-SF (nutritional assesment), SPPB (funcionality), and FRIED sacale (fragility).

Results: For this interim analysis, 36 patients were considered valid (treated patients). We identified 10 patients fit and 26 patients unfit. Patient's characteristics are included in table 1. Basal geriatric assessment is included in table 2. The median follow-up was 12 months. One year event free survival (EFS) was 73%, overall survival (OS) was

85%, and cumulative incidence of non-relapse mortality (NRM) was 15.5%. Geriatric intervention was required in 66.7% of patients. Two patients (8.7%) considered initially as fit, changed during follow-up to the unfit group. In 87% of cases, a new previously unknown disturbance was detected by geriatric intervention. Polypharmacy (three or more drugs) was identified in 65% of patients. In 82% of unfit cases, a new geriatric syndrome was detected (gait abnormalities, chronic ache, and urinary incontinence). Adjustment of treatment by geriatric intervention occurred in 75% of patients. Participation of the geriatricians in the decisions regarding chemotherapy treatment affected 8.3% of the cases.

Conclusions: Geriatric intervention in patients with lymphoma changes the management of these patients and may influence their outcome. The future results of this study will help us to establish the benefits of adequate basal geriatric assessment and intervention.

Keywords: elderly; immunochemotherapy; performance status.

ABSTRACTS

ONGOING TRIALS

ORAL PRESENTATIONS

OT01

ROBUST: PHASE III RANDOMIZED STUDY OF LENALIDOMIDE/R-CHOP VS PLACEBO/R-CHOP IN UNTREATED ABC-TYPE DIFFUSE LARGE B-CELL LYMPHOMA AND FEASIBILITY OF CELL OF ORIGIN SUBTYPING

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Introduction: The activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) is associated with inferior survival following chemoimmunotherapy. Lenalidomide, an immunomodulatory agent, has significant single-agent activity in relapsed/refractory DLBCL, predominantly ABC type, alone and in first line DLBCL plus R-CHOP (i.e., R²-CHOP). Until recently, real-time identification of cell of origin (COO) subtype as a biomarker to inform treatment decisions was not feasible due to technological limitations. The DLC-002 (ROBUST) randomized, phase III study (NCT02285062) is currently evaluating first line R²-CHOP vs placebo-R-CHOP in ABC-DLBCL, as determined by gene expression profiling (GEP).

Methods: Patients are randomized 1:1 to oral lenalidomide (15 mg, d1-14/21) + standard R-CHOP or placebo-R-CHOP for 6 cycles with 2 optional, additional rituximab doses. Adult patients must have untreated, ABC-type CD20+ DLBCL, IPI score ≥ 2 , and stage II-IV disease. The primary endpoint is progression-free survival (PFS). A central pathology lab determines COO type on FFPE biopsy samples within approximately 3 days using real-time GEP with the NanoString nCounter Dx analysis system. Subtype turnaround time is defined as number of days between central pathology sample receipt and when results are provided to the study site.

Results: As of 24 Feb 2017, DLBCL subtyping was attempted in 1,530 patients, of whom 1,402 had samples successfully tested. COO results were 43% ABC and 57% non-ABC (GCB + unclassified). Samples from 128 patients, or about 8% of those screened for COO, were unacceptable due to various technical reasons such as incorrect or insufficient material, and low tissue RNA concentration or purity. Samples were analyzed in four central pathology labs located in the UK (X2), USA, and China, which together achieved a mean turnaround time of 2.56 days. As of 24 Feb 2017, 439 patients were randomized to treatment in ROBUST.

Conclusions: Enrollment began in Jan 2015, with the goal of randomizing 560 patients by Aug 2017. Real-time COO assessment is feasible in this study with a short turnaround time. The percentage of ABC patients is similar to that reported in the literature. The ROBUST study is the first phase III trial of ABC-type DLBCL to use real-time GEP for patient eligibility, thus providing a significant advance in precision therapy in DLBCL.

Keywords: activated B-cell-like (ABC); diffuse large B-cell lymphoma (DLBCL); lenalidomide.

OT02

PHASE II STUDY OF DURVALUMAB (ANTI-PD-L1) COMBINED WITH EITHER R-CHOP OR LENALIDOMIDE AND R-CHOP IN PREVIOUSLY UNTREATED, HIGH-RISK DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: The PD-1/PD-L1 pathway is used by tumor cells as an essential immune checkpoint and may serve as a promising target to improve anticancer immune response. High expression of PD-L1 in diffuse large B-cell lymphoma (DLBCL) has been shown to be a negative prognostic factor for overall survival. Durvalumab (MEDI4736) is a high-affinity human IgG1 monoclonal antibody that selectively blocks PD-L1 from binding to PD-1 and CD80. Early preclinical and clinical

activity of durvalumab supports further study in high-risk DLBCL subtypes. The primary study objective is to evaluate the clinical activity of durvalumab with R-CHOP in non-activated B-cell-like (non-ABC; Arm A) and durvalumab with lenalidomide + R-CHOP (R²-CHOP) in ABC (Arm B) previously untreated DLBCL.

Methods: This represents a phase II, open-label, two-arm, global, multicenter study of durvalumab in combination with R-CHOP or R²-CHOP in patients with previously untreated, high-risk DLBCL (MEDI4736-DLBCL-001; EUDRACT 2015-005173-20; NCT03003520). High-risk DLBCL is defined as Ann Arbor stage III/IV or II with bulky disease (≥ 7.0 cm), in addition to intermediate-high/high IPI ≥ 3 or NCCN-IPI ≥ 4 . For study inclusion, patients must also have CD20+ DLBCL, ECOG performance status 0–2, and no prior antilymphoma treatment. During induction cycle 1, all patients receive durvalumab + R-CHOP21 concurrent with gene expression profiling using NanoString technology to determine cell-of-origin. From cycle 2 onwards, non-ABC patients (Arm A) receive intravenous (IV) durvalumab 1125 mg on day 1 plus R-CHOP21 for a total of 6 or 8 cycles; ABC patients (Arm B) receive oral lenalidomide 15 mg/day on days 1–14 in addition to durvalumab + R-CHOP21. Responding patients in both arms will have consolidation with durvalumab 1500 mg IV day 1 of every 28-day cycle for up to 12 months from induction cycle 1, day 1. The primary endpoint is 2-year progression-free survival (PFS); secondary endpoints include safety (per NCI CTCAE v4.03) and clinical response to treatment in biomarker-defined subpopulations (tumor and peripheral blood); exploratory endpoints are PFS at 12 months, PK/PD, and complete response rate.

Conclusions: The target enrollment is 120 patients, with recruitment ongoing. This study examines the clinical potential for combined durvalumab \pm lenalidomide with standard R-CHOP in high-risk DLBCL.

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

OT03 CHECKMATE 647: A PHASE 2, OPEN-LABEL STUDY OF NIVOLUMAB IN RELAPSED/REFRACTORY PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA OR RELAPSED/REFRACTORY PRIMARY TESTICULAR LYMPHOMA

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Introduction: Primary central nervous system lymphoma (PCNSL) and primary testicular lymphoma (PTL) are rare and clinically aggressive forms of large B-cell lymphoma with similar genetic signatures. Prognosis is poor and treatment options are limited for patients (pts) with relapsed/refractory PCNSL or PTL, highlighting a high unmet medical need. Both tumors exhibit frequent 9p24.1 copy number alterations (CNAs) and associated expression of the programmed death-1 (PD-1) ligands, PD-L1 and PD-L2 (Chapuy B, Roemer MG, et al. *Blood* 2016;127:869–81). Activation of PD-1 signaling via PD-L1/PD-L2 limits T-cell responses, potentially inhibiting antitumor immune surveillance.

Nivolumab (nivo) is an immune checkpoint inhibitor that targets PD-1 to restore T-cell activation and antitumor immune responses. Nivo has demonstrated efficacy in relapsed/refractory classical Hodgkin lymphoma, which is characterized by 9p24.1 CNAs and PD-L1 and PD-L2 upregulation (Roemer MG, et al. *J Clin Oncol* 2016;34:2690–7; Younes A, et al. *Lancet Oncol* 2016;17:1283–94), suggesting that the same mechanism of action may be effective in PCNSL or PTL. In a retrospective study of 5 pts with relapsed/refractory PCNSL or PTL who were treated with nivo, all pts obtained clinical and radiographic responses (4 complete radiographic responses and 1 partial radiographic response in a pt with PCNSL), and 3 pts remain progression free at 13 + –17+ mo (Nayak L, et al. *Blood* 2017, in press). The current study evaluates the efficacy, safety, and tolerability of nivo in relapsed/refractory PCNSL or PTL.

Methods: CheckMate 647 (NCT02857426) is a phase 2, open-label, single-arm, 2-cohort trial assessing single-agent nivo treatment in pts with relapsed/refractory PCNSL or PTL. Adult pts with pathologically confirmed PCNSL or PTL who relapsed or did not respond to ≥ 1 line of systemic therapy, with Karnofsky Performance Status score ≥ 70 , are eligible. Pts with PCNSL must have ≥ 1 measurable brain lesion; pts with PTL require ≥ 1 measurable extranodal lesion. Pts should have tumor tissue available for PD-L1 expression testing. Pts with intra-ocular lymphoma without evidence of brain disease, pts with PCNSL who cannot undergo MRI, and those with PCNSL with systemic disease are not eligible. Both cohorts will receive nivo monotherapy. The primary endpoint is objective response rate (ORR), assessed by a blinded independent central review committee. Secondary endpoints include

progression-free survival, investigator-assessed ORR and duration of response, and overall survival. All analyses will be performed separately in each cohort. Treatment of 65 pts is planned. Accrual is ongoing.

Study support: Bristol-Myers Squibb (BMS). Writing assistance by M Arancillo of Caudex, funded by BMS.

Keywords: monoclonal antibodies (MoAb); primary CNS lymphoma (PCNSL); testicular lymphoma.

OT04

MCL-R2 ELDERLY: A PHASE III STUDY OF THE EUROPEAN MCL NETWORK ASSESSING EFFICACY OF ALTERNATING IMMUNOCHEMOTHERAPY (R-CHOP / R-HAD) AND A RITUXIMAB-LENALIDOMIDE MAINTENANCE

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Background: In prior studies, we have established a cytarabine-containing induction regimen as the standard approach in younger MCL patients (*Hermine, Lancet* 2016) whereas rituximab maintenance has improved survival rates both in older patients (*Kluin-Nelemans, NEJM* 2012) and younger patients after autologous stem cell transplantation

(*Le Gouill, ASH* 2016). In addition, a recent phase II study suggested high efficacy with a rituximab-lenalidomide (R2) combination (*Ruan, NEJM* 2015).

Methods: The MCL-R2 Elderly trial is a phase III study of the European MCL network comparing 8 cycles of R-CHOP versus an alternating induction (3 cycles of R-CHOP / 3 cycles of R-HAD) in older MCL patients followed by combined maintenance (R2) vs. rituximab alone in patients responding to induction. The primary endpoint of the trial is to evaluate whether the addition of lenalidomide to standard rituximab-maintenance improves outcome compared to standard rituximab maintenance after response to induction chemotherapy. Secondary endpoints include overall survival, response rate according to IWG criteria and other efficacy parameters, safety, and MRD (minimal residual disease). For induction, randomization is stratified according to country and MIPI and for maintenance additionally according to type of, and response to, induction. Key inclusion criteria are patient ≥ 60 years of age with untreated MCL ineligible for autologous transplant, but fit enough to tolerate the R-HAD therapy, Ann-Arbor stage II-IV and ECOG PS 0-2. Key exclusion criteria are poor renal, hepatic, or bone marrow functions unless related to lymphoma, HIV, HCV positivity, active HBV infection, poor cardiac function, CNS involvement by lymphoma, contraindication for medical DVT prophylaxis, and prior other malignancies if not disease-free for ≥ 5 years.

Evaluation including detection of MRD is performed after cycle 4 of induction, at the end of induction treatment, every 6 months during maintenance and follow-up. A maximum number of 633 subjects will be randomized for induction and 443 for maintenance.

Results: Since November 2013, 285 patients have been included, with France, Belgium, Germany, Netherlands, Portugal, and Spain currently recruiting and Poland being initiated within the next weeks. So far, 178 patients have been randomized for the maintenance part which is in line with the expected number of patients. At least one MRD sample has been collected from 212 of 263 cases (81%).

An IDMC will regularly review safety issue and especially secondary primary malignancies. So far, the IDMC has analyzed the clinical course of the first 60 patients randomized for maintenance with 25 patients receiving lenalidomide maintenance for more than 6 months and recommended continuation of the study without any safety concerns.

Conclusion: The study is ongoing and open for inclusions with an accrual rate that correspond to our hypothesis.

Keywords: Ara-C; lenalidomide; mantle cell lymphoma (MCL).

OT05

PHASE 3 STUDY OF IBRUTINIB IN COMBINATION WITH VENETOCLAX IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA (MCL)

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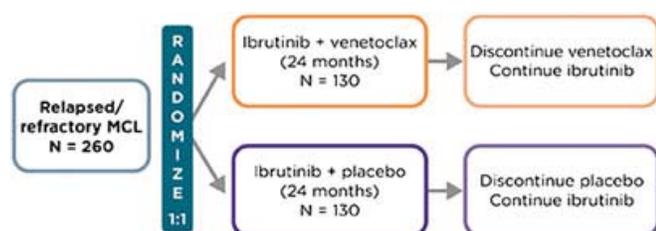
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Introduction: Treatment of patients (pts) with relapsed/refractory (R/R) MCL remains a challenge due to limited single-agent efficacy and no standard of care (Campo *Blood* 2015). Ibrutinib (ibr), a first-in-class, once-daily, oral inhibitor of Bruton's tyrosine kinase (BTK), is approved in the EU for the treatment of R/R MCL. Venetoclax (ven) is approved in the EU for the treatment of chronic lymphocytic leukemia (CLL) pts with del17p or TP53 mutation who are unsuitable for or have failed a B-cell receptor pathway inhibitor as well as for patients without del17p or TP53 mutation who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor. Combination ibr + ven induces synergistic apoptosis in MCL cell lines (Portell *Blood* 2014). In the ongoing trial of ibr and ven in R/R MCL, 7 pts achieved a complete response, including minimal residual disease clearance, among 10 pts who completed response assessments (Tam HAA 2016). Both agents have individually achieved response rates of 67–75% in R/R MCL (Wang *Blood* 2015; Davids *JCO* 2017). PCYC-1143, a phase 3 multinational, randomized, double-blind study, will compare efficacy and safety of ibr + ven to ibr + placebo (plb) in R/R MCL pts.

Methods: PCYC-1143 will start with an open-label safety run-in period to evaluate the occurrence of tumor lysis syndrome and dose-limiting toxicities with ibr + ven during a minimum of 5 weeks. Key eligibility criteria include pathologically confirmed MCL in tumor tissue (documented overexpression of cyclin D1 or relevant markers by cytogenetics, FISH, or PCR), with measurable disease (≥ 2 cm in the longest diameter and measurable in 2 perpendicular dimensions per computed tomography); 1–5 prior treatment regimens for MCL; and failure to achieve at least partial response with, or documented disease progression after, the most recent treatment regimen. Pts with a history of central nervous system lymphoma or prior treatment with ibr, ven, or any other BTK or BCL-2 inhibitors, are excluded. Pts will receive ibr 560 mg once daily and ven starting at 20 mg on day 1 with gradual ramp-up to a target dose of 400 mg once daily.

Upon completion of the run-in period, the study will transition to a randomized, double-blind design. Eligible pts will be randomized 1:1 to ibr + ven or ibr + plb (Figure) administered using a ramp-up schedule. Pts will be treated for 24 months with a combination, followed by single-agent ibr until disease progression, unacceptable toxicity, or withdrawal of consent. Ven and plb will be discontinued after 24 months of treatment. The primary objective is progression-free survival.



Keywords: B-cell receptor (BCR); ibrutinib; mantle cell lymphoma (MCL).

OT06 A HEAD-TO-HEAD PHASE 3 STUDY COMPARING BGB-3111 AND IBRUTINIB IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA

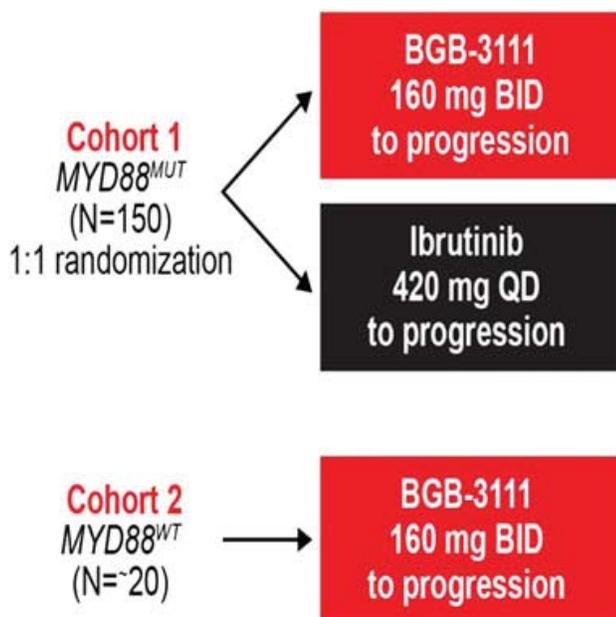
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Introduction: Bruton's tyrosine kinase (BTK) is a critical component of the B-cell receptor signaling cascade. Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies including Waldenström macroglobulinemia (WM), particularly WM harboring the MYD88 mutation (*MYD88^{MUT}*). BGB-3111 is a novel second-generation, potent, specific, and irreversible BTK inhibitor. Preclinical data in cell lines and primary patient samples show specific and profound BTK inhibition, with minimal inhibition of off-target kinases such as EGFR, ITK, JAK3, HER2, and TEC. Preliminary clinical data indicate that BGB-3111 treatment in patients with relapsed/refractory (R/R) WM induces deep and sustained responses, with a high (39%) very good partial response (VGPR) rate. Based on these encouraging results with a higher VGPR rate than previously reported for ibrutinib in R/R WM patients, we hypothesized that BGB-3111 achieves a more complete inhibition of BTK in lymph nodes with deeper tissue penetration than ibrutinib, resulting in improved efficacy and, based on its higher selectivity, a better safety profile for BGB-3111 than ibrutinib.

Methods: To test these hypotheses, we have designed a head-to-head, randomized, open-label, global phase 3 study to compare the efficacy and safety of BGB-3111 with those of ibrutinib in patients with R/R or treatment-naïve WM, the latter being unsuitable for treatment with standard chemoimmunotherapy. Approximately 150 *MYD88^{MUT}* WM patients in need of treatment will be enrolled into cohort 1 and randomized to 1 of 2 treatment arms (cohort 1; BGB-3111 160 mg orally twice daily [arm A] or ibrutinib 420 mg/d orally [arm B]) in a 1:1 ratio. Patients with wild-type *MYD88* (*MYD88^{WT}*), which is estimated to be present in approximately 10% of enrolled patients, will be enrolled into cohort 2 and will receive BGB-3111 160 mg orally twice daily on a third, nonrandomized study arm (arm C). The study schema is depicted in Figure 1. Patients will be treated until disease progression. Key eligibility criteria include age ≥ 18 years, histologically confirmed WM requiring treatment per the seventh International Workshop on WM, Eastern Cooperative Oncology Group performance status of 0–2, and adequate hematologic function. The primary objective is to demonstrate superiority of BGB-3111 to ibrutinib in terms of the

proportion of patients achieving complete response or VGPR, as determined by an independent review committee by modified Owens criteria (*Br J Haematol.* 2013;160:171 and National Comprehensive Cancer Network Guidelines). Key secondary end points include major response rate, duration of response, progression free survival, and safety. Study recruitment is ongoing, with the first patient enrolled in January 2017 and participating sites in Europe, Asia-Pacific, and North America (NCT03053440).



Keywords: BTK; ibrutinib; Waldenström's macroglobulinemia (WM).

PUBLICATIONS

OT07 PHASE I/II STUDY OF BRENTUXIMAB VEDOTIN IN REFRACTORY/RELAPSED HODGKIN LYMPHOMA PATIENTS TREATED BY CHEMOTHERAPY (ICE) IN SECOND LINE BEFORE AUTOLOGOUS TRANSPLANTATION.

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Introduction: About 10–15% of patients with localized and 25–30% with disseminated classical HL failed to respond or relapse after primary conventional treatment. Autologous stem cell transplantation (ASCT) is

a standard of care after salvage chemotherapy leading to an increased disease free survival (DFS). With this strategy approximately 60% to 80% of patients proved to be chemo sensitive become eligible for ASCT. As the disease status before ASCT appears to be the most important factor predicting outcome, second line chemotherapy has to be more efficient. Brentuximab-Vedotin (BV), a CD30-directed antibody conjugated to the highly potent anti-microtubule agent monomethyl auristatin E (MMAE), has shown significant activity in a phase II single arm, open label, multicenter pivotal study (SG035-0003) in patients with relapsed or refractory HL, of whom 71% had primarily refractory disease. Given the above, it seems to be logical and feasible to use BV in patients treated with ICE before auto SCT to induce a significantly higher (metabolic) CR rate, as judged by FDG-PET negativity. Otherwise, Moskowitz et al. have reported that negativity of FDG-PET improves EFS (>80% compared with 28.9% for those patients with improvement of CT but with persistent PET positivity).

Methods: In order to increase the complete response (CR) rate judged by FDG-PET in patients with primary refractory or first relapse cHL, we added Brentuximab Vedotin to ICE (Ifosfamide, carboplatine, and etoposide) chemotherapy (ICE-BV).

In the first dose-finding part of the study (phase I), the optimal dose of BV with ICE (3 cycles) will be established. In the second part the efficacy of BV with ICE will be assessed at the fixed optimal dose level of both BV and ICE.

Results: Phase I study was activated in 5 centers of the LYSA group and 10 patients have already been enrolled. Patients received 3 cycles of ICE-BV and one cycle of BV before ASCT. Three patients were enrolled in the first cohort, BV: 1.2 mg/kg and 7 patients in cohort two (BV: 1.8 mg/kg). Clinical characteristics at inclusion were median age: 29.5 years (range: 22–55), sex ratio (M/F): 6/4, and status of the disease: refractory: 3 patients and relapse: 7 patients. Efficacy and toxicity are currently analyzed.

Conclusion: The first part of ICE-BV before ASCT in R/R HL patients has been completed. Phase II will start after the validation of BV dose by the Independent Data Monitoring Committee (IDMC).

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

OT08 A PHASE 1/2 STUDY OF PIXANTRONE, ETOPOSIDE, BENDAMUSTINE AND, IN CD20+ TUMORS, RITUXIMAB IN PATIENTS WITH RELAPSED AGGRESSIVE B- OR T-CELL LYMPHOMAS—THE P[R]EBEN STUDY

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Introduction: Aggressive non-Hodgkin lymphoma (aNHL) relapsing after high-dose therapy or, in not transplant-eligible patients (pts), after 1st-line chemotherapy, represents an unmet clinical need. Therefore, we aimed at evaluating a salvage combination regimen (PREBEN/PEBEN) based on pixantrone, an aza-anthracenedione recently approved in Europe for pts with multiply relapsed or refractory aNHL, etoposide, bendamustine and, in CD20+ tumors, rituximab. A preliminary pre-trial experience on heavily pre-treated pts with relapsed aNHL of B- or T-cell phenotype showed good feasibility and efficacy and was previously reported. On this background, the Nordic Lymphoma Group launched an open label phase 1 (dose finding)/2 study (EudraCT no.2015-000758-39) testing the feasibility and efficacy of the PREBEN regimen in relapsed aNHL of B- or T-cell phenotype. Here, we present the preliminary data of the first 12 enrolled pts.

Methods: The trial design subdivides pts in 'fit' and 'frail' according to predefined criteria. 'Fit' patients enter phase 1 with a phase 2 expansion at maximum tolerated dose (MTD) level. 'Frail' patients enter directly phase 2 at baseline dose level. This consists of Pixantrone 50 mg/m² i.v. day 1 + 8, Etoposide 100 mg i.v. day 1, Bendamustine 90 mg i.v. day 1 with or without the addition of Rituximab 375 mg/m² i.v. day 1. A maximum of 4–6 three-weekly cycles is given. PET/CT is performed after cycle 2 and at the end of therapy. Dose escalation is done according to a Bayesian design. Primary end-points are MTD (phase 1) and overall response rate (ORR) (phase 2).

Results: Of the 12 pts enrolled, 8 are males and 4 females. The age range is 39–80 yrs. The histological diagnosis at relapse was diffuse large B-cell lymphoma (DLBCL) in 8 pts and peripheral T-cell lymphoma in 4 pts. Two pts entered the phase 1 ('fit') trial at baseline level and 10 entered the phase 2 'frail' part of the trial. All pts had IPI > 2 prior to salvage start. The mean N of previous regimens was 3 (range 1–5). Three pts had previously undergone autologous stem cell transplant. Ten pts have initiated/undergone therapy; two patients have not initiated their 1st cycle yet. Of the 10 treated pts, all had a partial (N = 6, 60%) or complete (N = 4, 40%) metabolic response (ORR 100%) after 2 cycles. One of the complete responses was seen in a previously transplanted pt with stage IV relapse including bone lesions. Response durations range between 4 and 7+ months. The treatment schedule was feasible and most patients received it on an outpatient basis. The most common grade 3–4 toxicity was of hematological type (mainly neutropenia and thrombocytopenia). At the now completed first dose level of phase 1, one MTD was recorded due to grade 4 neutropenia. Grade 3–4 infections were seen in 2 pts and were manageable.

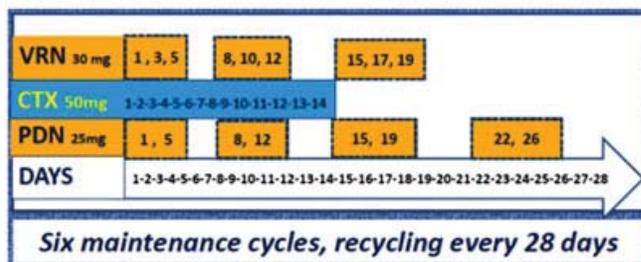
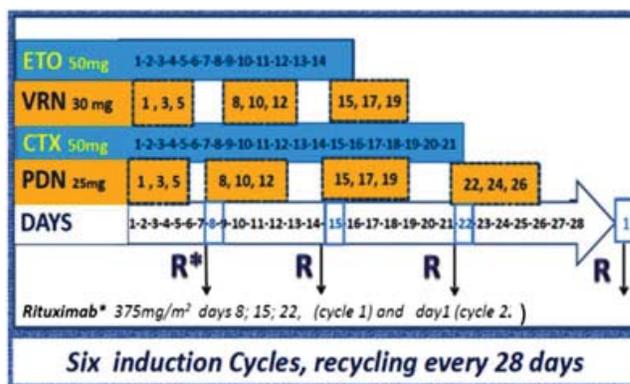
Conclusions: In this high-risk population of relapsed aNHL, the PREBEN/PEBEN salvage schedule is feasible (outpatient regimen) and the preliminary efficacy data are promising.

Keywords: diffuse large B-cell lymphoma (DLBCL); peripheral T-cell lymphomas (PTCL); salvage treatment.

OT09 DEVEC: A PHASE II STUDY OF METRONOMIC CHEMOTHERAPY IN ELDERLY NON-FIT PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMAS (PROMOTED BY FIL)

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Background: There is an unmet need for active treatments in elderly, non-FIT patients, with aggressive lymphomas, allowing to preserve patient's Quality of life (QoL). Moving forward to setting up a suitable schedule, we devised a metronomic chemotherapy (MTN-CHT) protocol, termed DEVEC, consisting of prednisolone (PDN), cyclophosphamide (CTX), etoposide (ETO), oral vinorelbine (VRN) ± rituximab(RTX). Since February 2011, this MTN-CHT schedule, was adopted in six clinical centres affiliated with the FIL. Candidate for this palliative schedule were aggressive B and T cell lymphoma patients, considered unfit for standard chemotherapies. Forty-two patients (31 DLBCL and 11 PTCL), with a median age of 79 years, were evaluated for outcome analysis. The schedule was well tolerated even in frail pts; hematologic toxicity was moderate and manageable with GF. The rate of extra-hematologic toxicity of grade ≥ 3 was 19%, mostly due to

infections. Only 3/42 (7%) pts discontinued treatment because of toxicity or death. The overall response rate (ORR) was 64.3% including 23.8% CR, 4.7% unconfirmed CR (uCR) and 38% PR. The median overall survival (OS) and progression free survival (PFS) were 15 (95% CI = 8.645–21.355) and 10 (CI 95% = 5.520–14.480) months, respectively. On the basis of these results and giving the lack of MTN-CHT trials in lymphoma patients, the elderly commission of the FIL released in November 2016 the DEVEC trial (EUDRACT 2016-003703-62).

Methods/Design: This is an open label, non-randomized, multicentre, phase II study, to evaluate the efficacy and safety of DEVEC oral schedule (fig1) in large B-cell (LBCL) and Burkitt lymphoma (BL) diagnosed in elderly unfit and frail patients who are R/R after previous treatment, and in super-frail patients at disease onset. Patients will be enrolled according to Bryant & Day two-stage optimal design. Co-Primary Objectives:

- 1) To explore the activity of the DEVEC induction + maintenance schedule;
- 2) To explore the safety of the DEVEC induction + maintenance schedule.

Secondary Objectives: To evaluate the ORR (CR, Cru, PR) and the Clinical Benefit evaluated at the end of induction (EOI) cycles. OS, PFS, EFS, DFS, to assess QoL.

Treatment Schedule:

A) Induction phase: six courses (q 28 days) of PDN + ETO + VRN + CTX, ±RTX. Patients in PR and SD after 2 cycles will continue with additional 4 courses. At the end of the induction phase patients in ≥PR will continue treatment with

B) Maintenance phase: six courses of PDN + VRN + CTX. (q28 days).

Primary Endpoints: The primary efficacy endpoint is defined in terms of CRR (CR + Cru rate). The primary safety endpoint is defined as incidence, nature, and severity of adverse events.

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

OT10 PET/CT-GUIDED BIOPSY FOR THE DIAGNOSIS OF LYMPHOMA

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Introduction: Biopsy of affected tissue is required for lymphoma diagnosis at onset and relapse and to plan adequate treatment. Open incisional biopsy is traditionally the method of choice, with an accuracy of approximately 100%. Nevertheless, it requires hospitalization, availability of an

operating room and sometimes general anesthesia and is associated with several drawbacks (morbidity, surgical complications, tumor contamination of surrounding tissues). The development of ultrasound and computed tomography (CT)-guided biopsies has almost overcome these disadvantages. However, a variable proportion of non-diagnostic procedures is reported, leading to an accuracy that ranges between 50% and 80%. Functional imaging, such as fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT, is a procedure which can potentially be used to drive biopsy to the most metabolically active area within a lymph node (figure) or extranodal masses which sometimes show no morphologically detectable changes on CT scan.

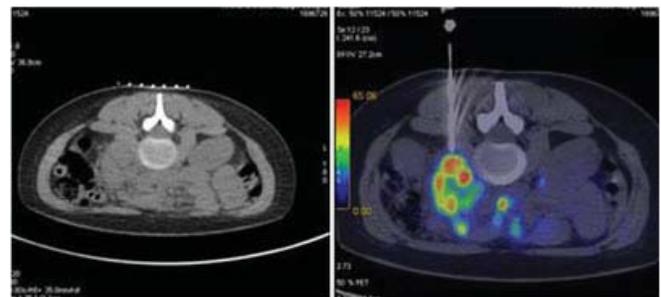
Methods: One hundred patients with suspect lymphoma at onset or relapse are expected to be enrolled in 3 years, provided they show FDG-avid findings. Patients are excluded if pregnant, breastfeeding or in case fine-needle PET/CT-guided biopsy is contraindicated. Diagnostic accuracy will be compared to published data concerning conventional imaging. Specimen adequacy will also be evaluated. The trial is supported by the Italian Association for Cancer Research (Progetto AIRC IG 2015 Id 17781).

Results: Data are available for the first 32 patients. Thirty-four procedures have been performed: 3 (8.8%) were interrupted because of pain but could be successfully repeated in 2 cases. Biopsy target was lymph node in 19 cases and extranodal site in 13 (bone in 8 cases, soft tissue in 3, liver and kidney in 1 each). Median SUVmax of target lesions was 11.5 (4.9–37.7). Insufficient samples were obtained in 9.7% of cases (3 out of 31 successful procedures), whereas in all other instances the tissue was considered adequate to formulate a diagnosis (table).

Diffuse large B-cell lymphoma	10
Follicular lymphoma	7
Metastases of carcinoma	3
Hodgkin lymphoma	2
Normal tissue/Inflammation	2
Anaplastic large T-cell lymphoma	1
Acute lymphoblastic leukemia	1
Marginal zone lymphoma	1
Mantle cell lymphoma	1

Mean sample length was 10 mm (standard deviation ±6 mm). The mean amount of affected tissue in collected samples was 56% (±33%) and the mean proportion of fibrosis/bone was 37% (±32%). No severe adverse events were reported during or after each procedure.

Conclusions: Patients can benefit from a minimally invasive procedure which allows a timely and accurate diagnosis of lymphoma at onset or relapse. Cost and time savings will be evaluated once enrolment is fully completed.



Keywords: positron emission tomography (PET).

OT11 FIL-PTCL13: PHASE IB/II 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. New therapeutic options are needed. Consolidation with autologous stem cell transplantation (autoSCT) can be considered a standard strategy in young patients with chemo-sensitive disease; however, 25–30% of patients do not become transplant eligible due to primary refractory or early progressive disease. To increase the response rate pre-autoSCT, we designed the PTCL13 study (NCT02223208), with CHOEP in combination with romidepsin (Ro-CHOEP), a non-cross resistant agent that showed antitumor activity in T-cell lymphomas and a manageable toxicity profile in combination with chemotherapy, followed by high-dose chemotherapy plus SCT.

Methods: PTCL13 is a phase Ib/II study. Inclusion criteria are stage II–IV patients aged 18–65, with newly diagnosis of peripheral T-cell lymphomas including PTCL not otherwise specified, angioimmunoblastic, ALK negative anaplastic; no other subtypes are included. The primary endpoint of the phase Ib part of the study is to define the maximum tolerated dose (MTD) of romidepsin in combination to CHOEP chemotherapy; the primary endpoint of the phase II is progression free survival at 18 months. Here, we describe the phase Ib: PTCL13 has 6 CHOEP courses every 21 days combined with romidepsin at the dose of 10 or 12 or 14 mg/ms at days 1 and 8 of each cycle. Responsive patients after will continue the program with one cycle of DHAP (cisplatin, citarabine, desamethasone) followed by

stem cell harvest. Patients in complete remission after the 6 Ro-CHOEP will proceed to autologous stem cell transplant; patients in partial remission and with an available donor will be considered for alloSCT upfront.

Results: The first patient was enrolled in September 2014. As of March 11th 2017, 17 patients were enrolled into the phase Ib part. The first 3 patients were treated with romidepsin at 12 mg/ms; no dose limiting toxicities (DLT) were observed. According to the continual reassessment method, the following 3 patients were treated with romidepsin at 14 mg/ms and one DLT was reported. The following triplets of patients were all treated with romidepsin at 14 mg/ms. All diagnoses were centrally reviewed and tissue samples and blood cells were collected in order to perform additional biological analysis.

Conclusions: Enrollment began in September 2014, with the goal of enroll 21–24 patients in the phase Ib part and 110 patients in the phase II part of the trial. The MTD of romidepsin in addition to CHOEP followed by high dose chemotherapy and SCT is not yet defined. We expect to open the enrollment into the phase II part of the study in the next few months.

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

OT12 A MRD-GUIDED APPROACH FOR THE COMBINATION OF IBRUTINIB TO VENETOCLAX IN RELAPSED/REFRACTORY PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (IMPROVE STUDY)

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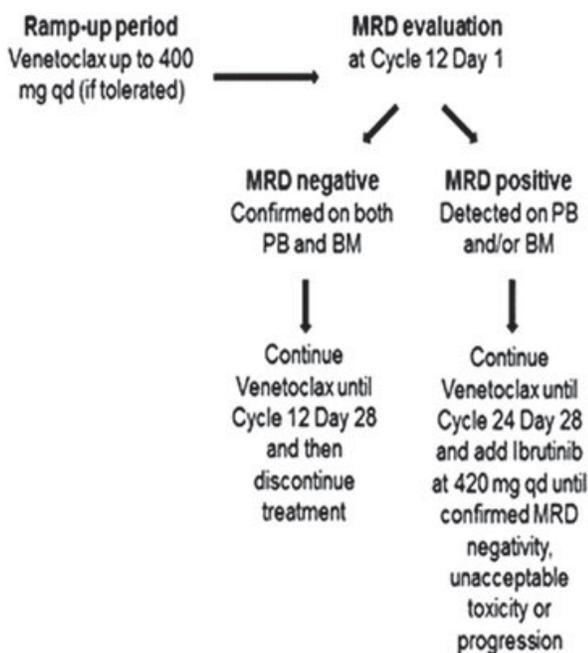
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Novara, Italy;¹⁷ Hematology & Transfusion Medicine, L. Sacco University Hospital & School of Medicine, Milan, Italy

Introduction: The therapeutic armamentarium for chronic lymphocytic leukemia (CLL) has recently gained novel effective agents, based on B-cell receptor signaling inhibition. These agents rarely achieve deep responses in relapsed/refractory (R/R) CLL, and patients with unfavorable characteristics tend to relapse over time. Venetoclax, a highly selective BCL2 inhibitor, demonstrated 80% response rate (5% minimal residual disease -MRD- negative responses) in R/R CLL, including high risk patients and has recently granted approval by FDA and EMA. Venetoclax combined with anti-CD20 antibodies improved MRD-negativity rate, a valuable treatment goal, as it correlates with prolonged progression-free and overall survival. The optimal combination for venetoclax is still to be defined but in vitro results support the association of venetoclax and ibrutinib to achieve better disease control in CLL and mantle-cell lymphoma (MCL). Initial results for ibrutinib and venetoclax in R/R MCL documented that both drugs can be used at the standard dose without any relevant unmanageable or unexpected adverse events.

Methods: We designed a Phase 2a, multicenter, open-label uncontrolled study aimed at determining therapeutic benefits of the addition of ibrutinib to venetoclax in patients with R/R CLL based on a MRD-guided approach. According to optimal Simon Two-Stage design (type I standard error 0.05, power 95%), with a null hypothesis of 5% MRD-negative CR at 12 months, the alternative hypothesis is based on a MRD-negative CR of 30% with venetoclax and ibrutinib. A total of 31 patients should be enrolled to reach the target of 29 MRD positive patients. An interim analysis is planned after the enrolment of the first 9 MRD positive patients: study will complete the accrual if at least 1/9 patients will obtain a MRD negative CR 12 months after starting ibrutinib.

Results: Venetoclax will be administered as single agent up to 400 mg QD [Ramp-up period] and continued thereafter. At Cycle 12 Day 1, MRD in the peripheral blood (PB) will be evaluated in patients with CR or PR by flow cytometry (Figure 1).



All MRD negative subjects (MRD level in the PB <10⁻⁴ in the PB and in the BM) will discontinue venetoclax at the end of Cycle 12. All MRD positive subjects (MRD level in the PB >10⁻⁴) and patients with stable disease without any contraindications to ibrutinib will continue venetoclax and start treatment with ibrutinib at the standard dose for CLL of 420 mg QD. Venetoclax and ibrutinib will be administered until confirmed MRD negativity, unacceptable toxicity or disease progression. In MRD positive responders after 2 years, venetoclax will be interrupted while ibrutinib will be continued as per standard of care.

Conclusions: A total of 17 Italian sites will be participating to this trial. The study has been approved by San Raffaele Hospital Ethics Committee on March 9th, 2017. AIFA approval is expected by May 12th, 2017. Recruitment will be open by the first week of June 2017.

Keywords: ABT-199; chronic lymphocytic leukemia (CLL); ibrutinib.

OT13 PHASE 3 STUDY OF IBRUTINIB IN COMBINATION WITH RITUXIMAB VERSUS PLACEBO IN COMBINATION WITH RITUXIMAB IN PATIENTS WITH TREATMENT-NAÏVE FOLLICULAR LYMPHOMA (PERSPECTIVE)

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Introduction: Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin lymphoma and has a limited number of chemotherapy-free options for treatment-naïve (TN) patients who are older or who have comorbidities. Ibrutinib, a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase, is approved in the EU for the treatment of various B-cell malignancies. In a phase 2 study, frontline treatment with ibrutinib in combination with rituximab (4 weekly doses without maintenance) demonstrated an overall response rate of 85% (35% complete response) with a median follow-up of 22 months and an 18-month PFS rate of 87% (Fowler, *Blood* 2016). PERSPECTIVE (PCYC-1141, NCT02947347), a randomized, double-blind, placebo-controlled phase 3 trial that builds on the phase 2 study, will be conducted in two parts and will evaluate (1) whether frontline treatment with ibrutinib in combination with rituximab results in prolongation of PFS compared with rituximab alone and (2) whether continuous treatment with ibrutinib affects PFS outcomes compared to finite treatment.

Methods: Approximately 440 patients with TN FL will be randomized to receive either ibrutinib or oral placebo once daily; all patients will

be administered 4 weekly doses of rituximab followed by maintenance. After at least 2 years of treatment during Part 1, patients randomized to ibrutinib who remain on ibrutinib will be re-randomized in Part 2 to either continue ibrutinib or switch to placebo. Patients must meet at least one Groupe d'Etude des Lymphomes Folliculaires (GELF) criterion and be at least ≥ 70 years of age or between ages 60 to 69 with one or more comorbidities (creatinine clearance 30–59 mL/min or ECOG performance status of 2). Key exclusion criteria include any prior treatment for FL, evidence of central nervous system involvement, or transformation. Analyses will be conducted in two distinct parts, both with a primary endpoint of PFS. The study is currently in progress with sites planned in the US, EU, and Asia Pacific.

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

OT14 AN ONGOING PHASE 2 STUDY OF IBRUTINIB COMBINED WITH VENETOCLAX IN PATIENTS WITH TREATMENT-NAÏVE CLL/SLL

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Introduction: Younger, fit patients (pts) with CLL generally receive first-line treatment with chemoimmunotherapy (CIT) regimens such as fludarabine, cyclophosphamide and rituximab (FCR), which can eliminate minimal residual disease (MRD) (Bottcher, JCO 2012; Strati, Blood 2014). MRD has emerged as an important endpoint that correlates with survival. MRD-negative remission with FCR is less

frequent, however, in pts with unmutated IGHV genes and del(17p) (Thompson, Blood 2016). Ibrutinib (ibr), a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase, is approved in numerous countries globally for the treatment of CLL and allows for treatment without chemotherapy. The phase 3 RESONATE-2 study (PCYC-1115) of single-agent ibr demonstrated superior progression-free survival and overall survival versus chlorambucil in older treatment-naïve (TN) pts with CLL regardless of IGHV gene status (Burger, NEJM 2015). Venetoclax (ven), an oral inhibitor of BCL2, received US FDA accelerated approval for relapsed del(17p) CLL, and EMEA conditional approval for relapsed CLL. In a phase 2 study of relapsed del(17p) CLL, ven showed 79% overall response rate with peripheral blood MRD negativity achieved in 17% of pts (40% of pts with available samples) (Stilgenbauer, Lancet Oncol 2016). A non-CIT regimen of ibr + ven may potentially lead to deep and durable remissions that may allow for consideration of a treatment-free interval. PCYC-1142 (NCT02910583) will determine the MRD-negative clinical response rate with ibr + ven in TN CLL/SLL pts and evaluate whether discontinuing ibr in MRD-negative pts allows for a treatment holiday based on disease-free survival (DFS).

Methods: PCYC-1142 is a multicenter, double blind, placebo-controlled, randomized, phase 2 study comparing ibr to placebo after attaining MRD-negative response with combination ibr + ven administered during pre-randomization. Key eligibility criteria include age 18–69 years; adequate hepatic, renal, and hematologic function; and no known allergy to xanthine oxidase inhibitors and/or rasburicase for pts at risk for tumor lysis syndrome. In pre-randomization, pts will receive single-agent ibr lead-in for three 4-week cycles followed by ibr + ven for at least twelve 4-week cycles. The primary endpoint during pre-randomization is MRD-negative clinical response rate. In the randomization phase, pts will be randomized based on MRD status. Pts with confirmed MRD-negative response after at least 12 cycles of ibr + ven will be randomized to blinded treatment with ibr (ven discontinued) versus placebo (both ibr and ven discontinued). Pts without confirmed MRD-negative response will be randomized to open-label treatment with continued ibr + ven versus ibr alone (ven discontinued). The primary endpoint in the randomized phase is MRD-negative DFS. The study commenced in October 2016 with recruitment targeting 150 pts.

Keywords: chronic lymphocytic leukemia (CLL); ibrutinib.

Supporting information

Table with conflicts of interest provided by authors during abstract submission is available and can be requested contacting 14-ICML Secretariat (abstract@lymphcon.ch).

14-ICML SATELLITE SYMPOSIA PROGRAMS AND ABSTRACTS (updated on May 21 2017)

Tuesday, June 13, 2017

Room BI 12:00 – 14:00	CELLTRION HEALTHCARE THE 1ST BIOSIMILAR RITUXIMAB BASED ON CLINICAL EVIDENCE Chair: C. Buske, Ulm (Germany)
12:00 – 12:20	WELCOME AND INTRODUCTION: PERCEPTUAL EVOLUTION ON BIOSIMILAR C. Buske, Ulm (Germany)
12:20 – 12:40	REDUCING BUDGETS, INCREASING ACCESS L. Gulácsi, Budapest (Hungary)
12:40 – 13:10	THE RATIONALE OF BIOSIMILARITY J. Gonçalves, Lisboa (Portugal)
13:10 – 13:40	CLINICAL EVIDENCE OF BIOSIMILAR RITUXIMAB W.S. Kim, Seoul (South Korea)
13:40 – 14:00	BIOSIMILAR IN ONCOLOGY: YESTERDAY, TODAY AND A LOOK AHEAD Panel Discussion

C. Buske¹, L. Gulácsi², J. Gonçalves³, W. S. Kim⁴.

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In February 2017, the rituximab biosimilar CT-P10 (Truxima®) was approved by the European Medicines Agency (EMA) for all indications held by the rituximab reference product, including non-Hodgkin's Lymphoma (NHL) and chronic lymphocytic leukaemia (CLL). This decision marks the beginning of an exciting new era for biosimilar anticancer drugs, providing an opportunity to address the rising costs of cancer treatment and increase patient access to biologic therapies.

As a growing number of biologic drug patents expire, a significant increase in the use of biosimilars in oncology and other diseases is predicted. In 2016 alone, the EMA approved two monoclonal antibody biosimilars (of infliximab and etanercept), while the US Food and Drug Administration (FDA) approved three such biosimilars (of infliximab, etanercept and adalimumab).

A favourable shift in the perception of biosimilars by healthcare providers has also occurred over recent years. In a survey of European Crohn's and Colitis Organisation (ECCO) members, confidence in biosimilars increased from 39% in 2013 to >80% in 2015 [1]. In the US, 82% of physicians surveyed by the Biosimilars Forum believed biosimilars would expand treatment options and provide savings to patients and the healthcare system [2].

The potential budgetary impact of biosimilars was recognised recently by the European Society for Medical Oncology (ESMO) who noted in a position paper that "If properly developed clinically, manufactured to the correct standards and used appropriately [biosimilars] can positively impact the financial sustainability of healthcare systems, globally" [3]. The budgetary impact of the introduction of CT-P10 within 28 European countries for the treatment of NHL and CLL has been predicted using a budget impact analysis model.

While budgetary savings are predicted with the use of biosimilars, the development of these agents is still associated with substantial costs. Approval of biosimilars by the EMA or the FDA is governed by well-defined regulatory requirements, involving detailed comparisons with the reference product in nonclinical and clinical studies [4,5]. The decision to approve a biosimilar candidate is only made when the 'totality of evidence' shows that there are no clinically meaningful differences in terms of safety and efficacy versus the reference product. CT-P10 and reference rituximab have identical primary structures and highly similar higher-order structures. CD20-binding affinities and *in vitro* functional activities related to putative mechanisms of action of rituximab have also been shown to be highly similar between the two products.

CT-P10 and reference rituximab have been extensively compared in randomised, controlled clinical trials. The pharmacokinetics of CT-P10 and reference rituximab were shown to be equivalent in phase 1 and phase 3 trials in patients with rheumatoid arthritis [6,7], and in a phase 3 trial in patients with advanced follicular lymphoma [8]. Highly similar efficacy was also demonstrated in the phase 3 trials in rheumatoid arthritis and

follicular lymphoma. In all clinical studies, the safety and immunogenicity profiles of CT-P10 and reference rituximab were comparable. Phase 3 trials of CT-P10 in NHL are ongoing.

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Keywords: chronic lymphocytic leukemia (CLL); non-Hodgkin lymphoma (NHL); rituximab

Tuesday, June 13, 2017

Room BII 12:00 – 14:00	NOVARTIS PHARMACEUTICALS CORPORATION CHALLENGES AND OPPORTUNITIES IN THE MANAGEMENT OF AGGRESSIVE B CELL LYMPHOMAS Chair: S.J. Schuster, Philadelphia, PA (USA)
12:00 – 12:05	OPENING REMARKS BY THE CHAIR
12:05 – 12:35	NOVEL APPROACHES IN THE ALGORITHM FOR MANAGEMENT OF AGGRESSIVE B CELL LYMPHOMAS P. Borchmann, Cologne (Germany)
12:35 – 13:05	AGGRESSIVE B CELL LYMPHOMAS: THE ROLE OF STEM CELL TRANSPLANT IN THE ERA OF TARGETED THERAPIES A. Sureda, Barcelona (Spain)
13:05 – 13:35	EXPERIENCES FROM THE USE OF INVESTIGATIONAL CAR T CELL THERAPIES IN B CELL LYMPHOMAS S.J. Schuster, Philadelphia, PA (USA)
13:35 – 14:00	PANEL DISCUSSION

Tuesday, June 13, 2017

Room A 15:30 – 17:30	GILEAD SCIENCES ADVANCING PROGNOSTICATION AND TARGETED STRATEGIES IN CLL AND FL Co-chairs: M. Ghielmini, Bellinzona (Switzerland) and M. Hallek, Cologne (Germany)
15:30 – 15:35	WELCOME AND INTRODUCTION M. Ghielmini, Bellinzona (Switzerland)
15:35 – 15:50	DECIPHERING THE MOLECULAR LANDSCAPE IN CLL: NEW TREATMENT CHALLENGES D. Rossi, Bellinzona (Switzerland)
15:50 – 16:05	UNTANGLING THE COMPLEXITIES OF FL: CURRENT TREATMENT CHALLENGES A. Davies, Southampton (UK)
16:05 – 16:20	HIGH RISK VERSUS LOW RISK IN FL: PROGNOSTICATION FOR A PRECISION APPROACH B. Kahl, Saint Louis (USA)
16:20 – 16:30	CROSS-TALK: SIMILARITIES AND DIFFERENCES IN APPROACHES TO RISK STRATIFICATION AND TREATMENT IN CLL AND FL Led by M. Ghielmini, Bellinzona (Switzerland)
16:30 – 16:50	HITTING THE RIGHT TARGETS IN CLL AND FL: FROM PATHWAY TO PRACTICE M. Hallek, Cologne (Germany) and M. Ghielmini, Bellinzona (Switzerland)
16:50 – 17:05	TARGETED TREATMENTS IN CLL AND FL: SEQUENCING OR COMBINATIONS? A. Zelenetz, New York, NY (USA)
17:05 – 17:25	CROSS-TALK: MAKING INFORMED TREATMENT CHOICES IN CLL AND FL Led by M. Hallek, Cologne (Germany)
17:25 – 17:30	SUMMARY AND CLOSE M. Hallek, Cologne (Germany)

Dramatic progress has been made in our understanding of the clinical, biological and molecular heterogeneity of chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL); however treatment challenges remain, particularly in patients with high-risk disease. This symposium brings together world-leading experts to help address the question of how we can integrate the latest knowledge into clinical practice to help guide treatment choices for patients with high-risk CLL and FL.

Notable advances in our understanding of the molecular complexities and clonal/subclonal architecture of CLL have led to improved prognostic risk stratification.¹⁻⁴ Given their value as predictive biomarkers of resistance to chemo(immuno)therapy, current guidelines recommend testing for del(17p)/TP53 variants in patients requiring therapy.^{5,6} Testing for complex karyotype has not been routinely performed in clinical practice. However, it has recently re-emerged as a potential predictor of response to newer targeted agents.⁷⁻⁹ This, together with a growing understanding of the clinical significance of novel mutations in CLL, has added a layer of complexity to our understanding of how best to tailor treatment for high-risk patients.

In FL, while our understanding of the biological explanations for differences in patient risk has improved, the treatment of high-risk FL continues to pose a challenge. Novel prognostic indices that incorporate both clinical and genetic determinants of poor risk are being developed to help identify high-risk subgroups at diagnosis,¹⁰ however, to date these are not validated in clinical practice. Treatment decisions continue to be defined by clinical and biological characteristics e.g. duration of response to first-line treatment, but there is a growing awareness of the role of genetic/epigenetic features and the impact of the microenvironment in FL outcomes.^{11,12} A session dedicated to prognostication in FL, will explore the need for a precise approach to risk stratification and provide expert insights into the future of prognostic tools in FL.

This symposium will review FL and CLL side-by-side, to enable contrasts and similarities to be discussed. Following discussion of ongoing clinical challenges in CLL and FL, the second half of the symposium will focus on the molecular characterization of CLL and FL. Here the experts will discuss how our understanding of molecular pathways (BTK, PI3K and BCL2) can be applied in clinical practice to help select the best target. They will also discuss the clinical implications of targeting these pathways in CLL and FL with a focus on the potential differences in efficacy and safety. The final presentation will cover optimal combination and sequencing of targeted agents in CLL and FL, and provide an expert perspective on how best to integrate novel agents into clinical practice.

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

Tuesday, June 13, 2017

Room B I 15:30 - 17:30	BRISTOL-MYERS SQUIBB IMMUNO-ONCOLOGY RESEARCH IN LYMPHOMA: PRESENT AND FUTURE Chair: G. Collins, Oxford (UK)
15:30 - 15:35	WELCOMING REMARKS G. Collins, Oxford (UK)
15:35 - 15:55	LYMPHOMA N REVIEW: CHALLENGES IN TODAY'S CLINICAL PRACTICE G. Collins, Oxford (UK)
15:55 - 16:15	ONGOING EXPLORATIONS OF IMMUNO-ONCOLOGY IN CLASSICAL HODGKIN LYMPHOMA P. Brice, Paris (France)
16:15 - 16:35	PURSUIING EXISTING NEEDS THROUGH INVESTIGATIONS IN NON-HODGKIN LYMPHOMA: IMMUNO-ONCOLOGY AND MORE T.M. Illidge, Manchester (UK)
16:35 - 16:55	LIGHTING THE WAY: INFORMING LYMPHOMA PATHOLOGY WITH BIOMARKER RESEARCH D. de Jong, Amsterdam (The Netherlands)
16:55 - 17:25	OPEN DISCUSSION WITH THE EXPERTS All
17:25 - 17:30	CLOSING REMARKS G. Collins, Oxford (UK)

G. Collins¹¹ *Haematology: Clinical Haematology, Oxford Cancer and Haematology Centre, Oxford, United Kingdom.*

Immuno-oncology (I-O) research and development has helped to evolve our understanding of lymphoma and potential options for treating it. Recent clinical trials in I-O have made significant progress in increasing our understanding of investigational therapies, including the response to treatment in patients who relapse after failing prior standard treatment options. This promising momentum is continuing, with ongoing clinical trials investigating new uses for current and novel I-O therapies, as well as innovative treatment combinations for lymphoma. The findings from these current and future trials, as well as from ongoing basic research, will help expand our understanding of potential treatment options for patients and contribute valuable insights towards our understanding of the pathology of lymphoma.

Immuno-Oncology Research in Lymphoma: Present and Future, is an educational satellite symposium moderated by Dr. Graham Collins (UK) that aims to describe existing unmet medical needs in the clinical management of lymphoma and ongoing and future research with I-O therapies. The study of the potential for I-O as a treatment option in lymphoma will be discussed and will include review of current research across various patient populations, as well as the challenges and specific considerations that are of clinical importance in the context of I-O therapies. Ongoing research with novel I-O agents in lymphoma will also be reviewed. Dr Collins will provide an overview of lymphoma management and treatment-related challenges within lymphoma, highlighting current I-O therapy options and clinically relevant considerations. Dr Pauline Brice (FR) will discuss current data and ongoing I-O research to address unmet needs in patients with classical Hodgkin lymphoma, while Dr Pier Luigi Zinzani (IT) will discuss current research efforts, including I-O studies, to help address unmet clinical needs and contribute to a better understanding of non-Hodgkin lymphoma disease pathology. Finally, Dr Daphne De Jong (NL) will discuss how outcomes from biomarker research are shaping the evolution of lymphoma research with I-O therapies and informing new approaches to clinical trials.

Tuesday, June 13, 2017

Room B II 15:30 – 17:30	SERVIER ONCOLOGY MANAGEMENT OF MULTIPLY RELAPSED AGGRESSIVE NHL: NEW PERSPECTIVES Co-chairs: R. Pettengell, London (UK) and E. Van Den Neste, Brussels (Belgium)
15:30 - 15:35	INTRODUCTION E. Van Den Neste, Brussels (Belgium)
15:35 – 15:55	TREATMENT LANDSCAPE OF B-CELL-NHL PATIENTS, LOOKING INTO THE FUTURE OF NEW STRATEGIES P.L. Zinzani, Bologna (Italy)
15:55 – 16:10	PATIENTS WITH RELAPSED DLBCL WHO FAIL SECOND-LINE SALVAGE THERAPY: MONOTHERAPY VERSUS COMBINATION THERAPY E. Van Den Neste, Brussels (Belgium)
16:10 – 16:25	PIXANTRONE FOR THIRD- AND FOURTH-LINE TREATMENT OF RELAPSED/REFRACTORY NON-HODGKIN B-CELL LYMPHOMA R. Pettengell, London (UK)
16:25 – 16:55	PATIENT CASE 1 – A. Hayat, Galway (Ireland) PATIENT CASE 2 – K. Hübel, Cologne (Germany)
16:55 – 17:15	PANEL DISCUSSION All Faculty
17:15 – 17:20	CONCLUSION R. Pettengell, London (UK)

E. Van Den Neste¹, P. Zinzani², R. Pettengell³, A. Hayat⁴, K. Hübel⁵.

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About 85% of non-Hodgkin lymphomas (NHLs) are of B-cell origin, with diffuse large B-cell lymphoma (DLBCL) as the most frequent (37%). International management guidelines for aggressive NHL recommend R-CHOP or R-CHOP-like therapy in the 1st line.¹ In general, 60% of patients achieve complete remission, 10% have primary refractory disease, and 30% relapse (mostly within 2 years). The population with refractory/relapsed (RR) NHL is very heterogeneous and has poor life expectancy. Transplant-eligible patients receive salvage chemotherapy, followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT). The CORAL study² found that R-DHAP and R-ICE salvage regimens have similar efficacy, but differing toxicity profiles. Patients with early relapse appeared to have better survival if they had not received prior rituximab, implying that relapsed patients who received rituximab 1st line represent a high unmet need. Patients who fail ASCT or are transplant-ineligible generally receive palliative treatment or enter clinical trials; there is no standard of care and again a high unmet need. A retrospective analysis of CORAL

patients who could not proceed to ASCT and failed 2nd line showed 39% overall response rate (ORR) to 3rd line chemotherapy with 27% complete response (CR)/unconfirmed CR (CRu) and 4.4 mo median overall survival (OS).³ A recent multicohort study, SCHOLAR-1, in patients with refractory DLBCL reported ORR of 20% to 30% and median OS around 6 mo.⁴ Pixantrone is the first and only therapy in RR aggressive B-cell NHL 3rd or 4th line to be approved by the European Medicines Agency. A multicentre, randomised, active-controlled study evaluated the efficacy and safety of monotherapy with pixantrone in patients with RR aggressive NHL who had received ≥ 2 prior therapies; patients also had to have had a ≥ 6 -month response to anthracycline to be eligible.⁵ Patients were randomly assigned to pixantrone dimaleate or physician's choice of comparator. The results showed a significant improvement in rates of CR/CRu (20.0% vs 5.7%, $p = 0.021$) and ORR (37.1% vs 14.3%, $p = 0.003$). Pixantrone was effective in patients who had received a significant lifetime dose of anthracyclines, and the efficacy of pixantrone was shown to be independent of prior rituximab. Pixantrone had a manageable safety profile; the main toxicity was neutropenia and there was no significant cardiotoxicity. The benefit of pixantrone has not been formally established in the 5th line or beyond. It is currently indicated for adult patients with multiply RR aggressive B-cell NHL, thereby filling a large unmet clinical need in this field.

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Tuesday, June 13, 2017

Room A 19:30 – 21:00	ROCHE IMPROVING TREATMENT STRATEGIES FOR PATIENTS WITH FOLLICULAR LYMPHOMA: HOW TO TRANSLATE NOVEL STUDY DATA INTO CLINICAL PRACTICE Chair: B.D. Cheson, Washington D.C. (USA)
19:00 – 19:10	WELCOME AND INTRODUCTION B.D. Cheson, Washington D.C. (USA)
19:10 – 19:35	THE PATIENTS' PERSPECTIVE AND QUALITY OF LIFE IN FOLLICULAR LYMPHOMA R. Pfau, Aesch (Switzerland)
19:35 – 20:00	HOW CAN WE IMPROVE FIRST-LINE TREATMENT FOR FOLLICULAR LYMPHOMA AND HOW TO MEASURE IMPROVEMENT? M. Rummel, Giessen (Germany)
20:00 – 20:25	RECENT ADVANCES IN TREATMENT FOR PATIENTS WITH FOLLICULAR LYMPHOMA A. Davies, Southampton (UK)
20:25 – 20:50	MANAGEMENT OF PATIENTS WITH FOLLICULAR LYMPHOMA IN THE FUTURE G. Salles, Lyon (France)
20:50 – 21:00	CLOSING REMARKS B.D. Cheson, Washington D.C. (USA)

Tuesday, June 13, 2017

Room B I 19:00 – 21:00	BAYER SHIFTING PARADIGMS IN THE MANAGEMENT AND TREATMENT OF INDOLENT NHL* Co-chairs: M. Ghielmini, Bellinzona (Switzerland) and M. Dreyling, Munich (Germany)
	WELCOME M. Ghielmini, Bellinzona (Switzerland) and M. Dreyling, Munich (Germany)
	DIFFERENTIAL BIOLOGY OF PI3K INHIBITORS IN NHL G. Lenz, Muenster (Germany)
	EMERGING CHEMO-FREE TREATMENT STRATEGIES IN INDOLENT NHL J.P. Leonard, New York, NY (USA)
	CLINICAL EXPERIENCE WITH COPANLISIB IN RELAPSED/REFRACTORY INDOLENT LYMPHOMA G. Follows, Cambridge (UK)
	PANEL DISCUSSION/Q&A M. Ghielmini, Bellinzona (Switzerland) and M. Dreyling, Munich (Germany)

*Copanlisib is an investigational agent currently in clinical trials and is not approved by Swissmedic, the FDA, EMA, or other health authorities. The efficacy and safety of copanlisib have not been established. / Bayer (Schweiz) AG, Grubenstrasse 6, 8045 Zurich, Switzerland

Tuesday, June 13, 2017

Room B II 19:00 – 21:00	TAKEDA ONCOLOGY TARGETING CD30 IN LYMPHOMA: A MARKER FOR CHANGE? Co-chairs: A. Engert, Cologne (Germany) and K.J. Savage, Vancouver (Canada)
19:00 – 19:05	WELCOME AND INTRODUCTIONS A. Engert, Cologne (Germany) and K.J. Savage, Vancouver (Canada)
19:05 – 19:25	CD30: FROM DIAGNOSTIC MARKER TO THERAPEUTIC TARGET A. Engert, Cologne (Germany) and K.J. Savage, Vancouver (Canada) PANEL DISCUSSION: ROLE OF CD30 All
19:25 – 19:45	DIRECTING TREATMENT TO CD30-DEFINED MALIGNANCIES: A FOCUS ON RELAPSED/REFRACTORY HODGKIN LYMPHOMA A. Sureda, Barcelona (Spain)
19:45 – 20:05	BEYOND THE RELAPSED/REFRACTORY HODGKIN LYMPHOMA PATIENT: WHAT ARE OUR OPTIONS IN THE FRONTLINE SETTING? A. Engert, Cologne (Germany)
20:05 – 20:25	CD30-POSITIVE PERIPHERAL T-CELL LYMPHOMA K.J. Savage, Vancouver (Canada)
20:25 – 20:45	CD30-POSITIVE CUTANEOUS T-CELL LYMPHOMA S. Horwitz, New York (USA)
20:45 – 20:55	PANEL DISCUSSION / Q&A SESSION: HOW I TREAT CD30-POSITIVE LYMPHOMA All
20:55 – 21:00	CONCLUSIONS AND MEETING CLOSE A. Engert, Cologne (Germany) and K.J. Savage, Vancouver (Canada)

A. Engert¹, A. Sureda², S. Horwitz³, K.J. Savage⁴.

¹ University Hospital of Cologne, Cologne (Germany), ² Institut Catala D'Oncologia, L'Hospitalet de Llobregat, Barcelona (Spain), ³ Memorial Sloan Kettering Cancer Center, New York, NY (USA), ⁴ Centre for Lymphoid Cancer, British Columbia Cancer Agency, Vancouver (Canada).

CD30 is a transmembrane glycoprotein, and a member of the tumor necrosis factor receptor family.¹ It is ubiquitously expressed on the malignant Reed-Sternberg cells of classical Hodgkin lymphoma (HL), as well as in anaplastic large cell lymphoma (ALCL), and it is variably expressed in many other subtypes of non-Hodgkin lymphoma.² Due to its limited expression in healthy tissue and on resting leukocytes,² CD30 is an ideal target for therapeutic intervention. Brentuximab vedotin is the first CD30-directed antibody-drug conjugate that has received regulatory approval for the treatment of relapsed/refractory HL and systemic ALCL based on the results of two pivotal phase 2 studies.^{3–6} Furthermore, based on the results of the phase 3 AETHERA trial, brentuximab vedotin was approved for consolidation of HL patients at increased risk of relapse or progression post-autologous stem cell transplant.^{5,7} The most common adverse events of any grade in these studies include: peripheral neuropathy, nausea, diarrhoea, fatigue, vomiting, alopecia, pruritus, pyrexia, decreased appetite and hypertriglyceridemia.^{3–7} The recently disclosed data from the phase 3 ALCANZA trial of brentuximab vedotin versus physician's choice in previously treated CD30-positive cutaneous T-cell lymphoma patients will be discussed.⁸ Brentuximab vedotin is currently being investigated as first-line therapy in advanced-stage HL patients in combination with AVD in the phase 3 ECHELON-1 trial,⁹ and in combination with CHP in the phase 3 ECHELON-2 trial in CD30-positive mature T-cell lymphoma patients.¹⁰ During this symposium, our panel of experts will discuss the evolving role of CD30, from diagnostic marker to therapeutic target, in the management of CD30-positive lymphomas. Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited provided financial support for this symposium.

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Keywords: brentuximab vedotin; CD30

Wednesday, June 14, 2017

Room A 19:00 – 21:00	JANSSEN PHARMACEUTICAL COMPANIES OF JOHNSON & JOHNSON CURRENT CONTROVERSIES IN B-CELL LYMPHOMAS: HOW TO MANAGE PATIENTS WITH HIGH UNMET NEEDS Chair: M. Ghielmini, Bellinzona (Switzerland)
19:00 – 19:10	WELCOME AND INTRODUCTION M. Ghielmini, Bellinzona (Switzerland)
19:10 – 19:35	CURRENT DILEMMAS IN DIFFUSE LARGE B-CELL LYMPHOMA G. Lenz, Berlin (Germany)
19:35 – 19:55	CLINICAL COMPLEXITIES IN MANTLE CELL LYMPHOMA S. Rule, Plymouth (UK)
19:55 – 20:15	CHALLENGING CASES IN FOLLICULAR LYMPHOMA C. Buske, Ulm (Germany)
20:15 – 20:30	NEW OPTIONS IN THE MANAGEMENT OF MARGINAL ZONE LYMPHOMA C. Thieblemont, Paris (France)
20:30 – 20:45	WALDENSTRÖM'S MACROGLOBULINEMIA – WHERE NEXT? S. Treon, Boston MA (USA)
20:45 – 21:00	PANEL DISCUSSION AND CLOSING REMARKS M. Ghielmini, Bellinzona (Switzerland) and all faculty

Wednesday, June 14, 2017

Room B 19:00 – 21:00	ABBVIE, INC. NOVEL TREATMENTS IN RELAPSED/REFRACTORY CLL: PRESENT AND FUTURE Chair: U. Jäger, Vienna (Austria)
19:00 – 19:05	CHAIR'S WELCOME AND INTRODUCTION U. Jäger, Vienna (Austria)
19:05 – 19:15	SETTING THE SCENE: THE BURDEN OF RELAPSED/REFRACTORY CLL U. Jäger, Vienna (Austria)
19:15 – 19:35	HISTORICAL PERSPECTIVES ON RELAPSED/REFRACTORY CLL THERAPY D. Rossi, Bellinzona (Switzerland)
19:35 – 20:00	CURRENT TARGETED TREATMENT OPTIONS IN RELAPSED/REFRACTORY CLL B. Eichhorst, Cologne (Germany)
20:00 – 20:20	NEW AGENTS IN DEVELOPMENT: INNOVATIONS IN RELAPSED/REFRACTORY CLL V. Leblond, Paris (France)
20:20 – 20:45	ROUNDTABLE DISCUSSIONS All
20:45 – 20:55	AUDIENCE Q&A All
	CHAIR'S SUMMARY AND CLOSE U. Jäger, Vienna (Austria)

Thursday, June 15, 2017

Room A 19:00 – 21:00	CELGENE MANAGEMENT OF B-CELL NON-HODGKIN LYMPHOMA: WHERE ARE WE NOW AND WHERE ARE WE GOING? Chair: G. Salles, Lyon (France)
19:00 – 19:10	WELCOME AND INTRODUCTION G. Salles, Lyon (France)
19:10 – 19:30	HURDLES AND UNMET NEEDS IN THE MANAGEMENT OF INDOLENT NHL G. Salles, Lyon (France)
19:30 – 19:50	PROGRESS AND PROMISE: CURRENT AND FUTURE PERSPECTIVES ON THERAPY OF INDOLENT NHL N.H. Fowler, Houston, TX (USA)
19:50 – 20:00	Q&A All Faculty
20:00 – 20:20	IMPROVING FRONTLINE TREATMENT OUTCOMES IN DLBCL U. Vitolo, Turin (Italy)
20:20 – 20:40	NEXT GENERATION THERAPIES IN B-CELL NHL: THE ROLE OF PROTEIN HOMEOSTASIS A. Gandhi, Summit, NJ (USA)
20:40 – 20:50	Q&A All Faculty
20:50 – 21:00	CONCLUDING REMARKS G. Salles, Lyon (France)

N. Fowler¹, A. Gandhi², G. Salles³, U. Vitolo⁴.

¹ MD Anderson Cancer Center, University of Texas, Houston, TX, United States, ² Celgene, Summit, NJ, United States, ³ Department of Hematology, Lyon Sud University Hospital, Pierre-Bénite, France, ⁴ Department of Oncology and Hematology, University Hospital Città della Salute e della Scienza, Turin, Italy.

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of cancers with variable clinical characteristics, severity, and sensitivity to therapeutic interventions. The vast majority (85–90%) of NHLs arise from B-lymphocytes, encompassing aggressive subtypes such as diffuse large B-cell lymphoma (DLBCL) and indolent forms such as follicular lymphoma (FL).

The clinical landscape of B-cell NHL continues to evolve. Although rituximab-based immuno-chemotherapy provides a foundation for treatment currently in the frontline setting, it shows variable efficacy for a number of clinical subtypes and the majority of patients will eventually experience relapse requiring subsequent treatment. To progress the management of B-cell NHL, personalization and optimization of frontline therapy, as well as the development of more effective salvage strategies, are needed. Personalizing front-line treatment, through the tailored use of therapeutic regimens dependent on the NHL cellular subtype, has already shown beneficial outcomes. This is particularly apparent in DLBCL where subtypes, identified based on cell-of-origin determination, respond differently to current regimens in preliminary trials. Strategies such as the addition of novel drugs to conventional immuno-chemotherapy may also contribute to improved overall outcomes in newly diagnosed patients. However, there remains an unmet need to optimize the methods to identify high-risk patients who are unlikely to respond to standard immuno-chemotherapy and therefore have a poor prognosis.

Innovations in the biological understanding of B-cell NHL have provided insights in the development of novel non-chemotoxic treatments, particularly suited for patients with indolent lymphomas and those with a limited response to immuno-chemotherapy. These include combinations of immunomodulatory agents with B cell-specific antibodies, drugs targeting signal transduction pathways, protein homeostasis, the immune checkpoint pathway, and bispecific T-cell engagers. With promising pre-clinical and clinical results for some of these, the challenge moving forward is therefore how to maximize clinical efficacy and ensure safety of these novel agents. The growing number of novel approaches currently being examined may provide additional effective treatment options for patients with B-cell NHL, moving the management of this disease to a more individualized setting in the future.

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

Thursday, June 15, 2017

Room B 19:00 – 21:00	MUNDIPHARMA MEDICAL COMPANY - TEVA ONCOLOGY CHEMOTHERAPY IN INDOLENT LYMPHOMA - DYING OR WELL ALIVE? Chair: M. Ghielmini, Bellinzona (Switzerland)
19:00 – 19:05	WELCOME AND INTRODUCTION M. Ghielmini, Bellinzona (Switzerland)
19:05 – 19:25	THE ROLE OF INDUCTION CHEMOTHERAPY FOR THE EFFICACY OF MAINTENANCE IN FOLLICULAR LYMPHOMA M. Dreyling, Munich (Germany)
19:25 – 19:45	CAN WE FORESEE A CHEMO-FREE TREATMENT FOR FOLLICULAR LYMPHOMA? M. Ghielmini, Bellinzona (Switzerland)
19:45 – 20:00	ROUNDTABLE DISCUSSION All Faculty
20:00 – 20:20	CAN WE FORESEE A CHEMO-FREE TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKEMIA? D.M. Brander, Durham, NC (USA)
20:20 – 20:40	NEW CHEMOTHERAPEUTIC AGENTS FOR LYMPHOMA O. O'Connor, New York, NY (USA)
20:40 – 20:55	ROUNDTABLE DISCUSSION All Faculty
20:55 – 21:00	CONCLUSION AND CLOSURE M. Ghielmini, Bellinzona (Switzerland)

Friday, June 16, 2017

Room A 18:30 – 19:30	ONCOLOGY INSTITUTE OF SOUTHERN SWITZERLAND - IOSI "THE BIG DEBATE: POINT COUNTER POINT" HAVE NEW DRUGS MADE STEM CELL TRANSPLANTATION OBSOLETE? Chair: M. Ghielmini, Bellinzona (Switzerland) Supported by Gilead Sciences Europe Ltd who provided funding. - CLL: yes: J.G. Gribben, London (UK) vs no: D.G. Maloney, Seattle, WA (USA) - HL: yes: P. Borchmann, Cologne (Germany) vs no: A. Sureda, Barcelona (Spain) - FL: yes: J.P. Leonard, New York, NY (USA) vs no: S. Montoto, London (UK)
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Friday, June 16, 2017

Room B 18:45 – 20:45	KITE PHARMA ENGINEERED T-CELL THERAPY: CAR-T'S ESTABLISHING A NEW PARADIGM OF TREATMENT IN RELAPSED AND REFRACTORY NHL? Chair: G. Salles, Lyon (France) Co-chair: P. Dreger, Heidelberg (Germany)
18:45 – 19:00	INTRODUCTION AND A REVIEW OF THE CURRENT RELAPSED AND REFRACTORY NHL LANDSCAPE G. Salles, Lyon (France)
19:00 – 19:30	THE IMMUNE SYSTEM, T-CELL BIOLOGY AND THE RATIONALE FOR CAR-T THERAPY J.G. Gribben, London (UK)
19:30 – 19:55	THE DEVELOPMENT OF KTE-C19, THE FIRST CAR-T DEVELOPED FOR R/R NHL - A REVIEW OF FULL DEVELOPMENT THROUGH TO THE ZUMA-1 FINAL ANALYSIS S. Neelapu, Houston, TX (USA)
19:55 – 20:20	PREPARING THE CENTERS TO MANAGE CAR-T PATIENTS M.J. Kersten, Amsterdam (The Netherlands)
20:20 – 20:40	ROUNDTABLE Q&A SESSION
20:40 – 20:45	CLOSING REMARKS P. Dreger, Heidelberg (Germany)

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