Hematological Oncology
Hematol Oncol 2015; **33**: 100–180
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hon.2227

ORAL PRESENTATIONS

KEY NOTE LECTURES

001

HENRY KAPLAN MEMORIAL LECTURE

THERAPY OF LYMPHOMA INSPIRED BY FUNCTIONAL AND STRUCTURAL GENOMICS

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Diffuse large B cell lymphoma (DLBCL) is a heterogeneous diagnostic category that is composed of two prominent molecular subtypes, termed activated B cell-like (ABC) and germinal centre B cell-like (GCB). These DLBCL subtypes are now viewed as molecularly distinct diseases since they arise from distinct stages of normal B cell development, require distinct recurrent genetic abnormalities to become malignant, have distinct cure rates with current chemotherapy regimens, and respond differentially to targeting agents. We defined a 'chronic active' form of B cell receptor (BCR) signalling that activates NF-κB and sustains ABC DLBCL viability. Over one fifth of ABC DLBCLs have mutations affecting the CD79B or CD79A subunits of the BCR that augment BCR signalling. To attack chronic active BCR signalling therapeutically, we initiated clinical trials in relapsed/refractory DLBCL of ibrutinib, an irreversible and highly selective inhibitor of BTK. Ibrutinib monotherapy induced a high rate of complete and partial responses in ABC DLBCL, while GCB DLBCL tumours rarely responded. Genetic analysis of responding tumours demonstrated enrichment for those with CD79B mutations, but most responses were observed in tumours with wild type BCR subunits. This observation allowed us to define a non-genetic mechanism of BCR activation that depends on reactivity of the lymphoma BCR to self antigens. We have also defined other oncogenic signalling pathways in ABC DLBCL that cooperate with BCR signalling to sustain cell survival, including the MyD88 pathway, which is activated by oncogenic *MYD88* mutations in ~40% of cases. To extend the efficacy of ibrutinib in ABC DLBCL, we have identified additional therapeutic targets in the oncogenic signalling pathways including (1) ubiquitin ligases, such as LUBAC, (2) the MYD88-associated kinase IRAK4, (3) the PI(3) kinase pathway, and (4) BCL2. Several synergistic, mechanism-based drug combinations that exploit these redundant survival pathways will be discussed.

002

HENRY RAPPAPORT MEMORIAL LECTURE

MANTLE CELL LYMPHOMA, AN UNFOLDING STORY FROM THE MICROSCOPE TO THE GENOME

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Mantle cell lymphoma (MCL) is a paradigm on how the iterative crosstalk between microscopic and molecular perspectives led from initial discoveries to subsequent refinement and definition of a lymphoma entity that in turn settled the framework for improved management strategies. The early linkage between not well-defined small B-cell lymphomas and the t(11;14) started the road for the recognition of a specific disease that postulated that the normal counterpart was the naïve B-cell of the follicular mantle zone. The identification of CCND1 as the elusive target oncogene of this translocation provided a powerful diagnostic tool to recognize the broader spectrum of morphological patterns, cytological variants and clinical evolution that configured the entity. In turn, a more precise identification of the tumours facilitated a better understanding of their molecular pathogenesis that integrates progressive deregulation of cell cycle mechanisms, DNA damage response alterations and activation of cell survival pathways, altogether associated with an aggressive clinical course. The identification of MCL cases negative for CCND1 or with an unexpected indolent behaviour challenged basic concepts and led to a better understanding of its heterogeneity. Two major subtypes of the disease have been recognized. The conventional MCL originates in a B-cell with no or slight exposure to the germinal centre microenvironment, develops increasing chromosomal instability and clinically has a tendency to nodal dissemination and an aggressive evolution. On the contrary, a subset of MCL seems to derive from a cell which has experienced the germinal centre, carries stable karyotypes and clinically tends to present with a leukaemic non-nodal disease and a prolonged indolent course. New players in the pathogenesis of the disease have been identified such as the transcription factor SOX11, highly expressed in conventional MCL but not or at very low levels in non-nodal subtypes, may interfere with the normal B-cell differentiation programme and may contribute to the aggressive behaviour of the tumours. Recent genomic sequencing studies are uncovering novel mutated genes that target different pathways such as NOTCH, chromatin modification or NFkB. These discoveries expand our understanding of the pathogenesis of the tumour and offer new perspectives for therapeutic intervention and monitoring of the disease. MCL represents a paradigm of lymphoma pathology as an integrative discipline bringing together basic and clinical perspectives with fruitful pathways of discovery and improvement of clinical practice.

003

JOHN ULTMANN MEMORIAL LECTURE

THIRTY YEARS OF PROGRESS IN CUTANEOUS LYMPHOMA RESEARCH

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Cutaneous lymphomas are rare and their diagnosis and management often challenging. Before the 1980s, mycosis fungoides (MF) and Sezary syndrome (SS)—collectively termed cutaneous T-cell lymphoma (CTCL)—were the only known types of cutaneous lymphoma. Research focused particularly on new techniques facilitating differentiation early stages of MF and SS from benign inflammatory dermatoses. Cutaneous lymphomas other than MF/SS were not yet recognized in classification systems for non-Hodgkin lymphomas and simply considered and treated as systemic lymphomas with skin localizations. In the 1980s, several European groups of dermatologists and pathologist started to classify cutaneous lymphomas according to the criteria of the Kiel classification, using newly developed immunohistochemical methods. These clinicopathologic studies demonstrated that malignant lymphomas other than MF/SS can present in the skin without any evidence of extracutaneous disease and that these primary cutaneous lymphomas have a different clinical behaviour than histologically similar nodal lymphomas involving the skin secondarily. These studies resulted in the

delineation of several new types of CTCL and CBCL, which now have been included as separate entities in recent classifications for non-Hodgkin lymphomas (WHO-EORTC classification; WHO 2008 classification). Recognition of these primary cutaneous lymphoma in recent classification systems should guarantee better diagnosis and treatment. In the last decade, genetic and epigenetic studies in different types of primary cutaneous lymphomas have further enhanced our understanding of the molecular pathways involved in the pathogenesis of these lymphomas and provided important new diagnostic and prognostic markers. The clinical importance of these recent developments in cutaneous lymphoma research will be illustrated for two groups of patients, who have probably benefited most from it: patients with the histology of a diffuse large B-cell lymphoma and patients with a primary cutaneous CD30-positive proliferation.
Collaboration between dermatologists, pathologists and oncologists has been essential for defining new entities and classifications. Such an international multidisciplinary approach, which should include clinicians, basic scientists and biostatisticians, is also indispensable for optimal translation of results from basic science into clinical practice and is the best guarantee for further advances in the diagnosis and treatment of patients with a cutaneous lymphoma.

AACR-ICML JOINT SESSION: SPECIAL LECTURES

004
UPDATE ON THE REVISION OF THE WHO LYMPHOMA CLASSIFICATION

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The ongoing evolution of lymphoma classifications is a well-recognized fact of life. With the first of the modern WHO classifications of malignant lymphomas published in 2001, its revision published in 2008, and major advances in the lymphoma field over the last 7 years, another revision of the classification and its accompanying monograph is clearly needed. A process similar to that in the past was therefore begun in 2012 with a series of meetings among the current editors, representing the European Association for Haematopathology and the Society for Hematopathology. As was the case before each of the prior WHO classifications, a meeting of a Clinical Advisory Committee was held 31 March–1 April 2014 that included both haematopathologists and, most importantly, clinical haematologists/oncologists. Although originally only a web-based update was planned, as of May 2014, the International Agency for Research on Cancer (IARC) agreed to also publish hard copy and eBook versions of the revised monograph which will be an updated fourth edition (not a 5th edition due to other volumes in the 4th edition of the WHO Classification of Tumours series not yet completed). As of March 2015, the major changes required in the classification and monograph have been agreed upon, and hopefully, work will begin on the monograph shortly. Changes are anticipated among the more indolent and more aggressive B- and T-cell neoplasms. Although some provisional entities will be 'promoted' to distinct entities (e.g. ALK negative anaplastic large cell lymphoma) and some new provisional entities will be added (e.g. indolent T-cell lymphoproliferative disorder of the gastrointestinal tract), no new definite entities can be included because the revision is not a truly new edition. While there are some changes in the actual classification and some changes in nomenclature (e.g. a new approach to dealing with 'double hit' aggressive B-cell lymphomas), many of the changes reflect updates concerning currently recognized entities. There should not be any major surprises for those who keep up on this field given that the WHO classification and criteria for each entity often simply serve to codify up-to-date existing diagnostic and clinical practices and represent an international consensus about potentially controversial topics. Finally, it should be recognized that what will be presented is subject to change until the new monograph is its final form, which is expected in 2016.

005
WHAT'S NEW IN MULTIPLE MYELOMA?

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For decades, the diagnosis of MM required the presence of end organ damage, specifically hypercalcaemia, renal failure, anaemia, and bone lesions (referred to as CRAB features), felt to be attributable to the clonal plasma cell proliferative disorder. The requirement for end organ damage was meant to prevent patients with monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM) from being treated with chemotherapy. However, such a requirement also prevented early diagnosis and treatment of MM when the disease was in its most susceptible state. Furthermore, waiting for serious end organ damage to occur before starting therapy is not appealing when one considers the dramatic advances in MM therapy over the last decade. To solve this dilemma, the International Myeloma Working Group (IMWG) encouraged studies to identify biomarkers that reliably distinguished patients with MM from those with premalignant SMM before the development of end organ damage. In 2014, based on validated biomarkers, the IMWG published revised diagnostic criteria for MM that represents a paradigm shift in the approach to the disease. According to the updated criteria, MM is now defined by the presence of 10% or more clonal plasma cells in the bone marrow (or a biopsy proven plasmacytoma) plus one or more of the following myeloma defining events (MDEs): CRAB features (hypercalcaemia, light chain cast nephropathy, anaemia, or osteolytic bone lesions) felt secondary to the underlying plasma cell disorder, clonal bone marrow plasma cells ≥60%, serum free light chain ratio ≥100 (provided involved serum FLC level is ≥100 mg/L), or >1 focal lesion on magnetic resonance imaging (MRI) of whole body or spine and pelvis. In addition, bone disease can now be diagnosed using computed tomograph (CT) or positron emission tomography-computed tomography (PET-CT). Other salient changes include updated definition and classification of solitary plasmacytoma, SMM, and MGUS. It is expected that these criteria will enable initiation of therapy to high risk patients before serious end organ damage and eventually lead to better outcomes.
Major advances have also occurred in the treatment of MM. Lenalidomide and low dose dexamethasone (Rd) were found to prolong survival compared with a previous standard of melphalan, prednisone, and thalidomide (MPT). In a large randomized trial, the combination of carfilzomib plus Rd was superior to Rd in relapsed MM in terms of response, progression free, and overall survival. Pomalidomide, a new immunomodulatory agent, has shown significant clinical benefit in relapsed refractory MM. Panobinostat, a pan deacetylase inhibitor, appears to prolong progression free survival in relapsed MM but has toxicity issues that need to be worked out. Additional new drugs with promising activity include ixazomib, elotuzumab, daratumumab, filanesib, and dinaciclib.

CONTROVERSY
EARLY-STAGE HL: SHOULD INTERIM PET-BASED THERAPY BE CONSIDERED ROUTINE CLINICAL PRACTICE?

006
NO POSITION

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A large number of observational studies have shown excellent prognostic value of early interim PET in both early and advanced stage Hodgkin lymphoma (HL). In this disease, which is characterized by high cure rates and serious concerns about late treatment-related morbidity and mortality, there is a demand for a more individualized, risk-adapted approach. Many patients are currently subject to over-treatment, but on the other hand, a substantial number of patients, mainly with advanced disease, still experience treatment failure and ultimately die from the disease. In the absence of strong pre-treatment predictive markers, early interim PET has been regarded as an important tool for a more patient-tailored therapy, and a number of ongoing or recently completed trials have investigated early PET-response adapted therapy. In some trials, early interim PET has been used to select good responders for less therapy (omission of radiotherapy and abbreviated chemotherapy), while in other trials, PET is used to select patients who respond poorly to standard therapy and thus might benefit from a shift to a more aggressive approach.

While some single-arm studies have shown results in favour of early PET-response adapted therapy, preliminary results from the only randomized trial published so far were regarded as negative. Furthermore, both the observational studies and the clinical trials have been hampered by a lack of standardization of PET methodology and interpretation, and this makes comparison of results and implementation into routine clinical practice very problematic. Recent attempts to ensure a more standardized patient preparation, image acquisition, image interpretation and reporting will hopefully reduce the variability, but PET-negative versus PET-positive patients are still not sufficiently well defined.

With a number of PET-response adapted HL trials yet unreported, it is too early to rule out that therapy-based early interim PET will eventually find its place in the management of HL. But based on the available evidence, it cannot be advocated in routine clinical practice yet.

007

YES POSITION

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Background: Because almost all otherwise healthy adult patients who present with limited stage Hodgkin lymphoma can be cured, the treating specialist must design a treatment strategy that maximizes the likelihood of cure while, **at the same time**, minimizing cost, inconvenience, toxicity and long-term ill effects. Interim FDG-PET provides the tool necessary to make that careful choice.

Evidence: At least 90% of patients with limited stage Hodgkin lymphoma are cured with combined modality treatment employing brief chemotherapy followed by planned involved field radiation (IFRT). One must ask, however, if a one-size-fits-all or a more personalized approach is more desirable. The HD6 NCIC CTG/ECOG study showed that chemotherapy with ABVD alone led to a **12-year** overall survival of 94%, the best outcome ever reported for limited-stage Hodgkin lymphoma, and demonstrated that approximately 80% of patients with limited stage Hodgkin lymphoma can be cured with ABVD alone. The PET-response adapted RAPID trial conducted in the UK and the EORTC/GELA/FIL HD10 trial, with an aggregate 850 patients, showed that approximately 80% achieve a PET-negative response after 2 to 3 cycles of ABVD with a negative predictive value above 90%, permitting a useful thought experiment. Consider 100 patients given 2 cycles of ABVD followed by IFRT: 95 are cured and 4 of the 5 who relapse are cured with secondary autologous haematopoietic stem cell transplant (ASCT). For comparison, consider 100 patients treated with 2 cycles of ABVD and then assessed with PET scan: 80 have a negative PET scan and complete treatment with 2 more cycles of ABVD; 20 with a positive PET scan and complete treatment with IFRT; and 8 relapse and are treated with ASCT. Compare the total treatment burden visited on the 2 patient populations. The former 100 patients receive 200 cycles of ABVD, 100 IFRTs and 5 ASCTs; the latter, 400 cycles of ABVD, 20 IFRTs and 8 ASCTs. In both groups, 99% of patients are cured so the choice between them must be based on relative toxicity, cost and impact on quality of life. The former strategy results in 5 ASCTs and the latter 8. However, with the first strategy, 80 of the 100 patients were exposed to radiation entirely unnecessarily because it exposes *every* patient to radiation. With the same number of patients cured, the overall balance of cost, toxicity, inconvenience and risk of major late side effects must favour avoidance of all of that unnecessary radiation.

Conclusion: Interim PET-guided management of limited stage Hodgkin lymphoma is here to stay, for sound therapeutic, economic and clinical reasons.

PLENARY SESSION

008

RESPONSE-ADAPTED THERAPY BASED ON INTERIM FDG-PET SCANS IN ADVANCED HODGKIN LYMPHOMA: FIRST ANALYSIS OF THE SAFETY OF DE-ESCALATION AND EFFICACY OF ESCALATION IN THE INTERNATIONAL RATHL STUDY (CRUK/07/033)

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Introduction: This prospective randomized study was designed to test whether interim FDG PET-CT scanning could assess early chemotherapy response and 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). Quality control for PET-CT was supervised by national core labs using standard methodologies. Images were centrally reviewed using the 5-point scale as negative (1–3) or positive (4–5). Pts with negative scans were randomized to ABVD or AVD for 4 more cycles. Pts with positive scans proceeded to intensification with either 4 BEACOPP-14 or 3 escalated BEACOPP before a third scan (PET3). Pts with negative PET3 completed a further 2 BEACOPP-14 or 1 eBEACOPP; pts with positive PET3 received off-study salvage regimens. Radiotherapy (RT) was not advised for pts with interim negative scans, irrespective of baseline bulk or residual masses.

DOI: 10.1002/hon

Results: 1214 pts were registered; 77 were withdrawn before PET2, mostly for breaching PET quality control standards. Median age was 33 years, with 500 (41%) stage II, 372 (31%) stage III and 342 (28%) stage IV. 445 (37%) pts had international prognostic score (IPS) ≥3. PET2 results from 1137 pts were negative in 954 (84%). 952 pts were randomized to continue ABVD or AVD, of whom 17 were ineligible and excluded from analyses. 33 (4%) pts received consolidation RT. With median follow-up of 32 months, PFS at 3 years was the same for ABVD: 85.45% (95% CI: 83.42–89.70) and for AVD: 84.48% (82.47–88.97). There was similarly no difference in 3-year OS: for ABVD, 97.0% (94.5–98.4), and for AVD, 97.5% (95.1–98.7). Prognostic factors for treatment failure after negative PET2 were initial stage ($p = 0.01$) and IPS ($p = 0.05$), but not bulk, B symptoms or PET2 score (1 vs 2 vs 3). ABVD showed more pulmonary toxicity than AVD, with significant differences between the arms in changes of transfer factor at end of therapy ($p < 0.001$), 1 year ($p < 0.001$) and 2 years ($p = 0.049$). 174 pts with positive PET2 had intensified therapy and achieved negative PET3 in 74%. In this group, 3-year PFS was 68% and OS 86%, with no difference in the non-randomized comparison between eBEACOPP and BEACOPP-14. There have been 53 deaths in the whole study (only 19 due to HL) for overall 3-year PFS of 83% (80–85) and OS of 95% (94–97).

Conclusions: This study suggests that interim PET-CT can be used to guide subsequent treatment, despite more treatment failures among PET-negative pts than previously reported in retrospective series. Omission of bleomycin following negative interim PET reduces pulmonary toxicity without loss of efficacy. These encouraging overall results support response-adapted therapy, with selective use of intensive chemotherapy and consolidation RT.

009

ADDITION OF THIOTEPA AND RITUXIMAB TO ANTIMETABOLITES SIGNIFICANTLY IMPROVES OUTCOME IN PRIMARY CNS LYMPHOMA: FIRST RANDOMIZATION OF THE IELSG32 TRIAL

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Abstract 009 Table 1.

	A ($n = 75$)	B ($n = 69$)	C ($n = 75$)	p
Median age (range)	58 (18–70)	57 (24–70)	57 (29–70)	NS
Male	46 (61%)	44 (64%)	46 (61%)	NS
ECOG PS >1	27 (36%)	23 (33%)	24 (32%)	NS
Low IELSG risk	14 (19%)	12 (17%)	13 (17%)	NS
Intermediate IELSG risk	47 (63%)	44 (64%)	47 (63%)	NS
High IELSG risk	14 (19%)	13 (19%)	15 (20%)	NS
Intraocular disease	5 (7%)	1 (1%)	1 (1%)	NS
Meningeal involvement	2 (3%)	2 (3%)	3 (4%)	NS
Feasibility and toxicity				
Actually delivered courses[a]	223 (74%)	236 (86%)	274 (91%)	
Relative dose intensity MTX	92%	84%	85%	NS
Relative dose intensity ARAC	87%	81%	80%	NS
Relative dose intensity R	–	82%	83%	NS
Relative dose intensity TT	–	–	76%	–
G4 neutropenia[a]	99 (44%)	119 (50%)	153 (56%)	0.01
G4 thrombocytopenia[a]	116 (52%)	140 (59%)	200 (73%)	0.0001
G4 anaemia[a]	9 (4%)	6 (3%)	14 (5%)	NS
G ≥ 3 febrile neutrop./infections[a]	43 (19%)	31 (13%)	45 (16%)	NS
G4 hepatotoxicity[a]	6 (3%)	3 (1%)	1 (1%)	NS
G4 nephrotoxicity[a]	0 (0%)	0 (0%)	1 (1%)	NS
Toxic deaths[b]	7 (9%)	3 (4%)	3 (4%)	NS
Autologous stem cell collection	48/51 (94%)	44/46 (96%)	60/64 (94%)	NS
Median of collected stem cells (× 10^6 CD34+ cells/kg bw)	12.3	15	8.2	NS
Activity and efficacy				
Complete remission rate (95% CI)	23% (14–31)	31% (21–42)	49% (38–60)	A vs B: 0.29 A vs C: 0.0007 B vs C: 0.02
Overall response rate (95% CI)	53% (42–64)	74% (64–84)	87% (80–94)	A vs B: 0.01 A vs C: 0.00001 B vs C: 0.05
2-year failure-free survival	34 ± 6%	52 ± 6%	64 ± 6%	A vs B: 0.01
5-year failure-free survival	34 ± 10%	43 ± 8%	54 ± 11%	A vs C: 0.0001 B vs C: 0.17
2-year overall survival	40 ± 6%	58 ± 6%	66 ± 6%	A vs B: 0.05
5-year overall survival	27 ± 7%	50 ± 7%	66 ± 6%	A vs C: 0.003 B vs C: 0.30

[a] Percentage on the number of delivered courses.

[b] Percentage on the number of enroled patients.

DOI: 10.1002/hon

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Introduction: IELSG #32 is an international randomized phase II trial addressing the tolerability and efficacy of adding rituximab (R) ± thiotepa (TT) to methotrexate (MTX)-cytarabine (ARAC) combination, followed by a 2nd randomization comparing consolidation with whole-brain irradiation (WBRT) or autologous stem cell transplantation (ASCT) in patients (pts) with primary CNS lymphoma (PCNSL) (NCT01011920). Herein, we report results of the first randomization.

Methods: HIV-neg pts 18–70 year old and ECOG PS ≤3 (PS ≤2 if age 66–70 years) with new histology-proven PCNSL and measurable disease were randomly assigned to receive four courses of MTX 3.5 g/m^2 d1 + ARAC 2 g/m^2 × 2/d d2–3 (arm A), or MTX-ARAC + R 375 mg/m^2 d-5 and 0 (arm B), or MTX-ARAC-R + TT 30 mg/m^2 d4 (arm C). ASC were collected after the second course. Response was assessed after the 2nd and 4th courses; pts with responsive disease were further randomized between WBRT and BCNU-TT conditioned/ASCT. Histology and neuroimaging were centrally reviewed. Primary endpoints were CRR (1st random) and 2-year FFS (2nd random). Sample size was estimated on the basis of 2nd random: with P0 65% and P1 85% (one-sided test; α 5%; β 95%), 52 patients/arm required.

Results: 227 pts (median age 58 years; 18–70) were enroled in 52 centres of 5 countries; 8 pts were excluded due to misdiagnosis, systemic disease or concomitant cancer. No differences in clinical presentation among 3 arms (A 75; B 69; C 75) were observed (Table). 733/876 (84%) planned courses were delivered. G4 haematological toxicity was more common in arm C, but infective complications were similar in the 3 arms. G4 non-haematological toxicities were rare. Chemotherapy was interrupted due to toxicity in 21 (9%) pts; 13 (6%) pts died of toxicity. ASC were collected in 152/161 (94%) pts.

Arm C was significantly more active, with a CRR of 49% and an ORR of 87%; 118 pts (A 35; B 35; C 48) were referred to 2nd random (59 pts/arm). At a median follow-up of 20 months (7–60), 111 pts remain failure-free (A 25; B 37; C 49), with 2-year FFS of 34 ± 6%, 52 ± 6% and 64 ± 6% ($p = 0.0006$), respectively. 124 pts are alive (A 31; B 41; C 52), with 2-year OS of 40 ± 6%, 58 ± 6% and 66 ± 6% ($p = 0.01$), respectively.

Conclusions: The addition of TT and R to MTX-ARAC (MATRIX regimen) is associated with significantly improved response, FFS and OS rates in PCNSL pts. With the exception of greater haematological toxicity, MATRIX was not associated with higher rates of severe complications, allowed preservation of antimetabolites dose intensity and permitted high rates of successful ASC collection.

010

NIVOLUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY LYMPHOID MALIGNANCIES AND CLASSICAL HODGKIN LYMPHOMA: UPDATED RESULTS OF A PHASE 1 STUDY (CA209-039)

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Introduction: The PD-1 pathway functions as a checkpoint which limits T-cell mediated tumour immune responses. Nivolumab (NIVO), a fully human IgG4 monoclonal PD-1 blocking antibody, potentiates T-cell activity. Prior results from this study (median follow-up 40 weeks) showed that NIVO was tolerated and achieved an overall response rate of 87% in classical Hodgkin lymphoma (cHL), 40% in follicular B-cell lymphoma (FBL), 36% in diffuse large B-cell lymphoma (DLBCL) and 17% in T-cell non-Hodgkin lymphoma (T-NHL). The stable disease rate in multiple myeloma (MM) was 67%. Herein, we report the updated follow-up and safety profile of this study.

Methods: Patients (pts) were treated using a dose-escalation design (1 and 3 mg/kg) of NIVO administered every 2 weeks (wks) for 2 years. Responses were assessed using standard criteria. Primary endpoint was safety. The secondary endpoint was efficacy.

Results: 105 pts were enroled (23 cHL, 31 B-NHL, 23 T-NHL, 27 MM and 1 chronic myelogenous leukaemia). Pts were heavily pretreated with 88%, 78%, 68% and 66% of pts with cHL, T-NHL, B-NHL and MM, respectively, having received ≥3 prior regimens. Previous ASCT was reported for 75% of pts with cHL, 56% of MM, 13% of B-NHL and 9% of T-NHL. As of 1/8/2015, median duration of follow-up was 62 wks (range: 2 to 106+ wks).

DOI: 10.1002/hon

Abstract 010 Table 1.

Tumour	Objective response, *n* (%)	Complete response, *n* (%)	Partial response, *n* (%)	Stable disease, *n* (%)	Median weeks of response duration (range)	Ongoing responders, *n* (%)
cHL (*n* = 23)	**20 (87)**	**4 (17)**	**16 (70)**	**3 (13)**	**NR (2 to 76+)**	**10 (50)**
B-NHL (*n* = 31)	**8 (26)**	**3 (10)**	**5 (16)**	**16 (52)**	**NR (6+ to 81+)**	**4 (50)**
Diffuse large B-cell lymphoma (*n* = 11)	4 (36)	2 (18)	2 (18)	3 (27)	22.1 (6 to 73+)	1 (25)
Follicular B-cell lymphoma (*n* = 10)	4 (40)	1 (10)	3 (30)	6 (60)	NR (23+ to 81+)	3 (75)
Other B-cell lymphoma (*n* = 10)	0	0	0	7 (70)	–	–
T-NHL (*n* = 23)	**4 (17)**	**0**	**4 (17)**	**10 (43)**	**NR (11 to 63+)**	**3 (75)**
Cutaneous T-cell lymphoma mycosis fungoides (*n* = 13)	2 (15)	0	2 (15)	9 (69)	NR (24+ to 36+)	2 (100)
Peripheral T-cell lymphoma (*n* = 5)	2 (40)	0	2 (40)	0	NR (11 to 63+)	1 (50)
Other cutaneous T-cell lymphoma (*n* = 3)	0	0	0	0	–	–
Other non-cutaneous T-cell lymphoma (*n* = 2)	0	0	0	1 (50)	–	–

Drug-related adverse events (DrAEs) occurred in 71 (67%) pts. The most common DrAEs occurring in >5% were fatigue (15%), rash (11%), diarrhoea, pneumonitis, pruritus (each 9%), pyrexia (8%), thrombocytopenia, decreased appetite (each 7%), hypocalcaemia, lipase increased, leukopenia, lymphopenia (each 6%) and nausea (5%). Serious DrAE in ≥5% of pts included pneumonitis (5%).

Efficacy results shown below.

The rate of stable disease in MM (*n* = 27) was 63%. Among the 20 responding cHL pts, 10 discontinued NIVO, 6 (1 CR and 5 PR) to undergo SCT, 3 for disease progression and 1 for toxicity (MDS, thrombocytopenia), and 10 (7 PR and 3 CR) continue to respond. Among responding B- and T-NHL pts, 1/4 DLBCL, 3/4 FL and 3/4 T-NHL pts remain in response. In this updated analysis, median duration of response has not been reached in cHL, B-NHL and T-NHL.

Conclusions: Encouraging, durable objective responses were observed in cHL, DLBCL and FL, including CR and PR. NIVO treatment remains safe and tolerable with a safety profile similar to that in solid tumours, and further analysis is warranted in cHL and selected B-NHLs and T-NHLs.

'FOCUS ON…' SESSION: IMIDs IN LYMPHOMA

011

INDEPENDENT REVIEW OF CT RESPONSES IN THE TRIAL SAKK35/10 COMPARING RITUXIMAB WITH OR WITHOUT LENALIDOMIDE IN UNTREATED FL PATIENTS IN NEED OF THERAPY

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Introduction: The randomized phase-2 trial SAKK 35/10 was conducted by the Swiss Group for Clinical Cancer Research (SAKK) and the Nordic Lymphoma Group (NLG) to compare the activity of single-agent rituximab (R) versus rituximab plus lenalidomide (RL) in the first-line treatment of symptomatic/progressive follicular lymphoma (FL). Primary endpoint [complete remission (CR/CRu) at week 23] assessment by the trial investigators has been reported previously [Kimby et al. Blood 2014.124(21):799]. Here, we report the results of an independent response review (IRR) of CT scans.

Methods: Patients (pts) with untreated FL, grades 1 to 3a and in need of systemic therapy, were randomized either to R (rituximab 375 mg/m^2 at weeks 1, 2, 3, 4, 12, 13, 14 and 15) or to RL (same R schedule plus lenalidomide 15 mg daily, from 14 days before the first until 14 days after the last rituximab administration). The sample size was calculated to allow the detection of a 20% increase of the CR/CRu rate, with 90% power and type I error 0.10; a one-sided *Z*-test for proportions was used to compare the 2 arms. Treatment was discontinued in pts who did not achieve at least a 25% reduction in the sum of product of tumour diameters at week 10. CT scans were taken at the time of inclusion, at week 10 and at week 23, but only the first and the last were independently reviewed by 2 expert radiologists.

Results: 154 pts (82 women and 72 men, median age 62 years, 47% of them with FLIPI high-risk score) were randomized; 77 were allocated to R and 77 to RL. Response assessment from IRR showed a significantly higher CR/CRu rate in the RL arm, both in the intention-to-treat [61% (95% CI: 49–72%) vs 36% (95% CI: 26–48%), $p = 0.0008$] and the per-protocol population [67% (95% CI: 53–78%) vs 42% (95% CI: 29–54%), $p = 0.002$]. Response assessment by the investigators (local evaluation reviewed by the trial chairs) and by the IRR are summarized in the table below.

DOI: 10.1002/hon

Abstract 011 Table 1. Response at week 23 in the intention-to-treat population according to either the IRR or the investigator

	IRR		Investigator assessment	
	Arm R (*N* = 77) *n* (%)	Arm RL (*N* = 77) *n* (%)	Arm R (*N* = 77) *n* (%)	Arm RL (*N* = 77) *n* (%)
CR/CRu	28 (36)	47 (61)	19 (25)	28 (36)
PR	16 (21)	13 (17)	28 (36)	35 (45)
SD	7 (9)	2 (3)	6 (8)	4 (5)
PD	3 (4)	1 (1)	2 (3)	3 (4)
NE[a]	23 (30)	14 (18)	22 (29)	7 (9)

[a]Patients not evaluable at week 23 including those with early PD or not achieving a minimal response at week 10.

Conclusions: Addition of lenalidomide significantly improved the CR/CRu rate. This benefit appeared higher in the IRR than in the investigator assessment. This may depend on the fact that the IRR considered only the target lesions measurable on CT scans, while the investigator assessment required the ascertained normalization of all lymphoma-related parameters (bone marrow, LDH and other laboratory or clinical abnormalities) to define the response. Time will tell if this response improvement will translate into longer progression-free and overall survival.

Response at week 23 in the intention-to-treat population according to either the IRR or the investigator assessment

012

RITUXIMAB + LENALIDOMIDE IN MALT LYMPHOMA: FINAL RESULTS

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Background: As both lenalidomide (LEN) and the anti-CD20 antibody rituximab (R) have shown activity in extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma), we have performed a phase II study of R + LEN in patients with MALT lymphoma.

Methods: Patients (pts) with histologically verified gastric or extragastric MALT lymphoma received RIT 375 mg/m^2 i.v. on day 1 and oral LEN at a dose of 20 mg daily given on days 1–21. Therapy was repeated every 28 days with restaging after 3 and 6 cycles. Patients with at least stable disease after 3 cycles received another 3 cycles. In patients not in CR after after 6 cycles another 2 cycles were applied (maximum of 8 cycles). Patients with progressive disease at any time were taken off study. All pts received prophylactic ASA (100 mg daily) for the duration of treatment, and allopurinol (300 mg daily) for the first 4 weeks of therapy. The primary endpoint of the study was objective response rate, with the secondary endpoint being safety and tolerability.

Results: A total of 50 patients had to be enroled to achieve the planned 46 evaluable patients (4 dropouts), and all 46 (28f/18m) have undergone at least 1 restaging investigation. The most common primary localizations were the ocular adnexa (15 pts), stomach (13 pts), and lung (7 pts); the remaining pts had MALT lymphoma of the parotid, colon, small intestine, liver, and subcutaneous tissue, respectively. Nine pts were pretreated, 2 pts having relapsed after CR from LEN monotherapy and 6 with R-containing regimens [AM1]. The overall response rate was 37/48 (80%), with 25 complete (54%, including the 2 patients pretreated with LEN and 4/6 with R) and 12 partial remissions (26%). In total, 12 pts converted from PR to CR with longer treatment duration. Eight pts were stable (17%), while only 1 pt progressed. Toxicities were mostly non-haematologic with exanthema in 17 patients being the most common event (grade I/II in 15). Two pts had diarrhoea, nausea, and joint-pain III; one pt had vertigo III; and 2 pts had infections necessitating hospitalization. Haematologic side effects included leucopenia (10 pts; 3 pt grade III), thrombocytopenia (5 pts; I/II), and anaemia (6 pts; 2 grade III). Dose reductions were performed in 10 pts (8 to 15 mg and 2 to 10 mg), while 4 pts discontinued treatment early due to toxicities.

Summary/Conclusions: The final results of the first study on efficacy of R + LEN plus RIT in MALT lymphoma suggest high activity of the combination with an increase by combination over single agent therapies within the excpected range. R + LEN was also active in patients pretreated with single agents, and toxicities were manageable and mostly non-haematological.

013

LENALIDOMIDE ADDED TO BENDAMUSTINE-RITUXIMAB FOR UNTREATED CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL): A PHASE 1 STUDY

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Introduction: Lenalidomide is an immunomodulator with activity in newly diagnosed and relapsed CLL. Bendamustine-rituximab (BR) is a widely used upfront regimen. We conducted a phase I trial combining lenalidomide (len) with BR.

Methods: Patients had untreated CLL with an indication for therapy, ANC ≥1000, platelets ≥50000, and adequate organ function. A 3 + 3 design was used with 10 additional patients treated at the MTD. Escalating doses of len were added to standard dose BR, with bendamustine dosed at 90 mg/m^2 on days 1–2 of each 28-day cycle. Len was given on days 8–22 in cycle 1 to minimize the risk of tumour lysis syndrome, and days 1–21 in subsequent cycles. The starting dose level for len was 2.5 mg. Level 2 was 2.5 mg for cycle 1 and escalated to 5 mg with cycle 2. Level 3 was 5 mg for cycle 1, then 10 mg with cycle 2. Patients could receive up to six cycles. All patients received allopurinol, aspirin, and pegfilgrastim support. DLT was assessed during cycle 1 of dose level 1, and cycles 1–2 of subsequent dose levels. Response assessment was by the 2008 IW-CLL criteria.

Results: Twenty-three patients were accrued. Median age was 64 years (range 43–85). Thirty-five per cent of patients had Rai stage 3/4, 52% had unmutated *IGHV*, and 26% had 11q deletion. No subjects had 17p deletion. Dose level 2 had one DLT of pulmonary embolism (PE). Dose level 3 was declared the MTD. Eleven subjects completed six cycles; median number of cycles was 5 (<1–6). Reasons for discontinuation were neutropenia (3), PE (2), rash (2), zoster (1), thrombocytopenia (1), Hodgkin lymphoma Richter's transformation (1), withdrawal of consent (1), and physician decision (1). Most common toxicities of any grade were rash ($n = 14$), fatigue (13), nausea (11), fever (10), anaemia (9), thrombocytopenia (6), cough (5), and diarrhoea (5). Five patients were suspected of tumour flare, 4 of whom were treated with steroids and the other spontaneously remitted. No tumour lysis syndrome was seen. Grade 3–4 toxicities occurring in >1 patient were rash ($n = 6$), neutropenia (4), febrile neutropenia (3),

DOI: 10.1002/hon

anaemia (2), and pneumonitis (2). One subject developed CMV reactivation. Dose reductions were required in 9/13 subjects at the MTD due to neutropenia (6), rash (3), and anaemia (1). The ORR and CRR in all patients were 87% and 39%, respectively. Among patients treated at the MTD, the ORR and CRR were 92% and 31%. With a median follow-up of 18 months, only one patient has developed disease progression, at 21 months. All patients remain alive at last follow-up.

Conclusions: Len-BR results in high efficacy in previously untreated CLL, but with increased toxicity compared with what would be expected from BR alone. Notable toxicities were rash, neutropenia despite pegfilgrastim support, and pulmonary embolism despite aspirin. Given the rate of toxicities and dose reductions after the DLT assessment period, the 10 mg len dose may be too high for most patients.

014

RITUXIMAB, LENALIDOMIDE, BENDAMUSTINE SECOND LINE THERAPY IN MANTLE CELL LYMPHOMA: A PHASE II STUDY OF THE FONDAZIONE ITALIANA LINFOMI (FIL)

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Introduction: Rituximab (R), lenalidomide (L), and bendamustine (B) showed significant activity and good safety profile in relapsed or refractory (R/R) mantle cell lymphoma (MCL). We performed a prospective, multicentre, phase II single arm study, to evaluate safety and efficacy of the combination of R, L, and B (R2B regimen) as second line therapy in MCL.

Methods: During the induction phase (cycles 1 to 4, every 28 days), patients received R 375 mg/m^2 on day 1, L 10 mg/day on days 1 to 14, and B 70 mg/m^2 on days 2 and 3. Patients who achieved complete or partial response (CR, PR) continued to the consolidation phase, which consisted of treatment with R 375 mg/m^2 on day 1 and L 15 mg/day on days 1 to 21 for two cycles every 28 days. Patients in CR and PR continued to the maintenance phase with L monotherapy 15 mg/day on days 1 to 21 every 28 days for additional 18 cycles. The primary objective of the study was to evaluate CR after induction and consolidation phases. Minimal residual disease (MRD) was analysed by IGH or Bcl-1 based nested (n) and quantitative (q) PCR in peripheral blood (PB) and bone marrow (BM) after the end of the induction and consolidation phase and during L maintenance. Cereblon expression was evaluated by immunohistochemistry on the baseline biopsies, and the results were correlated with the outcome.

Results: Forty-two patients (1 blastoid variant), median age 70 years (range 45–86), were enroled. Overall response (OR) and CR after the induction plus consolidation phases were 79% (33/42) and 55% (23/42), respectively. An MRD marker was identified in 86% (36/42); molecular response by n-PCR on PB and BM were 62% (18/29) and 52% (15/29) after induction, and 67% (18/27) and 43% (12/28) after consolidation. Median molecular burdens (PB/BM) were 1.3E10 – 2 and 2.6E10 – 2 at baseline and shrank to 0 after induction (18 patients evaluated in q-PCR). After a median follow-up of 20 months (range 10–27), the 12- and 24-month PFS and OS were 66% and 51%, and 83% and 66%, respectively. At present, no clinical or laboratory parameters, Cereblon expression included, related with the response rate or PFS; at a preliminary analysis, there is a trend for better PFS in patients achieving MRD negativity. Grade 3–4 neutropenia and thrombocytopenia were documented during the induction and consolidation phases in 69% and 14% of patients, respectively; 65% of patients experienced grade 3–4 neutropenia also during the maintenance. Non-haematologic toxicity was low. Three patients developed grade 3 (1) and 4 (2) infectious complications during the induction and maintenance phases, respectively.

Conclusions: The results from this study indicate that R2B therapy has a high therapeutic activity in R/R MCL even in terms of molecular response and is feasible also in elderly pre-treated patients.

015

RITUXIMAB, BENDAMUSTINE AND LENALIDOMIDE IN PATIENTS WITH RELAPSED/REFRACTORY AGGRESSIVE B-CELL LYMPHOMA NOT ELIGIBLE FOR SALVAGE CHEMOTHERAPY. PHASE II TRIAL—SAKK 38/08

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Introduction: Although the majority of patients (pts) are cured with R-CHOP, pts with relapsed/refractory diffuse large B-cell lymphoma (DLBC) have a dismal outcome. A substantial proportion of these pts is not eligible for salvage regimens. In addition, frail pts often do not qualify for first-line anthracycline-based treatment. No standard therapy is available for these pts.

Methods: Pts with refractory/relapsed DLBCL not suitable for salvage regimens or anthracycline-based first-line chemotherapy were eligible. The phase II used lenalidomide (L) at the recommended dose level of 10 mg on days 1–21 based on the phase I results with bendamustine (B) 70 mg/m^2 on days 1 and 2 and rituximab (R) 375 mg/m^2 on day 1 for 6 courses every 4 weeks. The primary outcome was overall response (OR) defined as complete response/complete response unconfirmed or partial response (CR/CRu + PR). Secondary endpoints were CR/CRu rate,

DOI: 10.1002/hon

Abstract 015 Table 1.

	Total 41 patients (%)
Gender	24 (59%) males
	17 (41%) females
Age, years	75 (40–94)
Median (min–max)	
Clinical active co-morbidities	36 (88%)
Performance status	
0	15 (37%)
1	20 (49%)
>2	6 (14%)
B-symptoms	11 (27%)
Bone marrow involved	5 (12%)
Extranodal involvement	
0	12 (29%)
1	15 (37%)
2	9 (22%)
>3	5 (12%)
Ann Arbor stage	
I/II	15 (37%)
III/IV	26 (63%)

event-free survival (EFS), progression-free survival (PFS), response duration, time to progression (TTP), overall survival (OS) and safety. Forty-one pts were needed for a power of 80% and a significance level of 5% to reject the null hypothesis of an OR rate ≤ 35% versus OR rate ≥ 55%. ClinicalTrials.gov number NCT00987493.

Results: 41 pts were included, into this prospective, multicentre phase II trial. 13 (32%) pts were not eligible for anthracycline-based first-line chemotherapy, 22 (54%) pts had relapsed, and 6 (15%) pts were refractory to previous treatment and not eligible for salvage therapy. 28 (68%) pts had at least 1 prior anti-lymphoma therapy. 25 (61%) pts achieved CR/CRu + PR (95% CI; 44.5%–75.8%), allowing to reject the null hypothesis. Best response was as follows: CR/CRu in 15 (37%) pts, PR in 10 (24%) pts; SD in 2 (5%) pts; PD in 10 (24%) pts; 4 pts were not evaluable. AE grade > 3: haematologic (54%), fatigue (15%), skin toxicity (15%), infection (15%) and 2/5 deaths (CNS haemorrhage and pneumonitis) judged as possibly associated with trial medication. The median response duration was 6.8 months (95% CI 3.4–12.3), median TTP was 6.4 months (95% CI 2.4–8.6), median EFS was 3.7 months (95% CI 1.8–5.2) and median PFS was 4.8 months (95% CI 2.4–6.7), respectively. Median OS was 14.4 months (95% CI 4.9–25.8). After a median follow-up of 19.3 months (range 0.2–37.9), 16 (39.0%) pts are still alive.

Conclusion: RBL has promising activity in relapsed/refractory as well as in previously untreated DLBCL patients not suitable for standard anthracycline-based chemoimmunotherapy.

016

A PHASE I/II TRIAL OF THE COMBINATION OF ROMIDEPSIN AND LENALIDOMIDE IN PATIENTS WITH RELAPSED/REFRACTORY LYMPHOMA AND MYELOMA

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Background: Epigenetic manipulation and immunomodulation are therapeutic strategies in haematologic malignancies. Romidepsin, a histone deacetylase inhibitor, and lenalidomide, an immunomodulatory agent, both have efficacy and lack cumulative toxicity in relapsed/refractory lymphoma and myeloma.

Methods: The phase I portion of this study was reported at ASCO 2014. The MTD defined in cycle 1 was romidepsin 14 mg/m^2 IV on days 1, 8, and 15 and lenalidomide 25 mg oral on days 1–21 of a 28-day cycle. Patients (pts) with relapsed/refractory lymphoma including Hodgkin lymphoma (HL) were treated to progression or intolerance. Disease-specific cohorts in T-cell lymphoma (TCL), B-cell lymphoma (BCL), and multiple myeloma were enroled at the MTD with an assessment of an optimal maintenance dose (tolerable dose for long-term treatment) assessed over 4 cycles. We report the results of the lymphoma subjects.

Results: 47 pts with relapsed/refractory lymphoma (21 TCL, 20 BCL, 6 HL) were enroled, and 30 were treated at the MTD (15 BCL, 15 TCL). Four pts did not receive drug due to inadequate blood counts before day 1. 43 pts were evaluable for toxicity. Median age was 64 years with 53% male ($n = 23$). Of the 30 pts treated at the MTD, 21 required subsequent dose reductions. The most common reasons for dose reduction were neutropenia, thrombocytopenia, and/or fatigue. Of the 25 pts on therapy for ≥4 cycles, the median dose was romidepsin 8 mg/m^2 and lenalidomide 15 mg. Of 43 pts, 12 (28%) patients remain on therapy (3 CR, 6 PR, 3 SD) at a median of 33 weeks (range: 9–107 weeks). 20 patients discontinued for progression, 8 for toxicity and 3 for transplant. The median number of treatment cycles was 4 (range: 1–27). The ORR by intent to treat was 44% (19/43). 4 pts were not evaluable for response (3 stopped for toxicity in cycle 1 without progression and one on steroids for ITP with PET normalization prior to dose 1 remained in CR). Of 39 pts evaluable for efficacy, the ORR was 49% (19/39). ORR by subtypes in TCL, BCL, and HL, respectively, were 53% (10/19; CR 2, PR 8), 44% (7/16, CR 3, PR 4), and 50% (2/4, CR 1, PR 1). The median time to response was 8 weeks (range: 3–39 weeks). The median OS was not reached. Median event-free survival and progression-free survival were 17 and 19 weeks (median EFS for TCL 16 weeks, BCL 18 weeks, HL 31 weeks). 33% of pts (13/39) were progression free at 6 months.

56% of pts had AEs ≥ Grade 3, with the most common (≥10%) being neutropenia (51%), thrombocytopenia (51%), anaemia (49%), and electrolyte abnormalities (K, Phos, glucose, and Mg) (28%).

Conclusions: The combination of romidepsin and lenalidomide appears to have significant clinical activity in relapsed/refractory lymphoma (ORR 49%) with acceptable safety profile supporting continued assessment in this population. While the MTD was reached at romidepsin 14 mg/m^2 and lenalidomide 25 mg, dose reductions were required frequently for patients on continued therapy.

'FOCUS ON…' SESSION: GENOMIC ALTERATIONS

017

SEQUENCE-BASED PANOMICS ANALYSES BY THE ICGC MMML-SEQ DECIPHERS MULTI-LAYER PATHWAY DEREGULATION IN GERMINAL CENTRE DERIVED B-CELL LYMPHOMAS

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DOI: 10.1002/hon

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Introduction: The International Cancer Genome Consortium (ICGC) aims at cataloging genomic, transcriptomic and epigenomic changes in a wide range of tumour types (www.icgc.org). Within the ICGC, the ICGC MMML-Seq network aims at sequencing up to 250 germinal-centre B-cell derived lymphomas (GCB-lymphomas) including follicular (FL), diffuse large B-cell (DLBCL) and Burkitt lymphomas (BL), as well as intermediate DLBCL/BL (IL).

Methods: The ICGC MMML-Seq funded by the German Federal Ministry of Education and Research (01KU1002A-J) performs sequencing of whole genomes (WGS) of tumour cells of GCB-lymphomas (to at least 30×) and paired normal controls, of transcriptomes (RNAseq) and of miRNAomes. DNA methylation is determined by whole genome bisulfite sequencing (WGBS) and/or Illumina 450K arrays. Basic workup comprises histopathologic panel review, FISH analysis for recurrent translocations, Affymetrix 6.0 SNP-array analysis and in part karyotyping. Sorted lymphocyte populations from non-tumourous tonsils are being sequenced as controls. Findings are extended to the MMML cohort containing more than 800 molecularly characterized B-cell lymphomas. Sequence findings are intersected with lymphoma reference epigenomes from the IHEC project BLUEPRINT.

Results: WGS analysis has been finished for 138 lymphoma/germline pairs, RNAseq for 165 and miRNAseq for 103 lymphomas, respectively. DNA methylation has been determined in 178 lymphomas by 450 K arrays and by WGBS in a subset of 29 GCB-lymphomas and four controls. WGS analysis detected the genes *MYC, TP53, ID3, CCND3, FBXO11* and *SMARCA4* as most frequently mutated in BL and *BCL2*, *CREBBP*, *MLL2* and *TNFRSF14* in FL. In DLBCL, the landscape of mutated genes is highly heterogeneous. In all subtypes, more than 98% of mutations occurred outside coding regions. On the genome level, subtypes markedly differ with regard to number, clustering and signature of mutations. Combined analysis of WGBS and RNAseq identified 8207 differentially methylated regions between FL and BL where methylation state and expression of associated genes correlated (cDMRs). These cDMRs are enriched in signalling pathways differentially activated in BL and FL and affected regulatory mechanisms altered by recurrent mutation in a large fraction of BL including cell cycle control, the ID3/TCF3 complex and the SWI/SNF remodelling complex.

Conclusion: Integration of genomic, transcriptomic and epigenomic analysis deciphered multi-layer deregulation of pathways and complexes in GCB-lymphomas. Moreover, our global analyses of the epigenomic architecture of GCB-lymphomas connect specific epigenetic modifications and lymphoma entities and suggest that deregulation of the SWI/SNF complex by *SMARCA4* mutation is of pathogenetic importance in a major subset of BLs.

018

STRUCTURAL VARIANTS IN GERMINAL CENTRE-DERIVED B-CELL LYMPHOMAS: ANALYSES IN THE FRAMEWORK OF THE ICGC MMML-SEQ PROJECT

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Introduction: Somatic structural variants (SVs) comprise unbalanced forms of variation, like deletions, duplications, and insertions, and balanced forms, such as inversions and balanced translocations. These changes in cancer genomes can have important effects such as oncogene amplification, tumour suppressor gene disruption, or fusion gene formation. In the framework of the German BMBF-funded ICGC MMML-Seq-Project, we aimed at identifying such structural changes. To this end, we combined data from whole genome and transcriptome sequencing in germinal centre-derived B-cell (GCB) lymphomas.

Methods: A total of 103 GCB lymphomas (22 BL, 35 FL, 13 FL/DLBCL, 2 Intermediate and 31 DLBCL) were included in the present analysis. These were analysed by fluorescence *in-situ* hybridization (FISH) using the probes for LSI BCL6, LSI MYC (DC, BA), LSI IGH/MYC, CEP8 Tri-colour, LSI IGH, and LSI BCL2 (all from Abbott Molecular), as well as by whole genome (WGS) and transcriptome sequencing according to the standards of the ICGC (www.icgc.org).

Results: From the WGS data, approximately 4000 somatic SVs were detected by DELLY (Rausch et al., 2012) in the 103 GCB lymphomas including 1621 deletions, 1249 duplications, 684 inversions, and 443 translocations. While WGS was less efficient than FISH in detecting translocations of the *BCL2*, *MYC*, *BCL6*, or *IGH* locus due to their association with repetitive regions, it facilitated the discovery of genes recurrently involved in SV like *ARID5B*, *ANKS1A*, *CD58*, *PTPRD*, *GPC5*, and *GNA13*. Selected SVs were verified by PCR and Sanger sequencing. In addition, to further validate the incidence of these SVs, FISH analysis was performed in an independent cohort of GCB cell lymphomas.

DOI: 10.1002/hon

Conclusion: Whole genome sequencing reveals a complex landscape of SVs in GCB lymphomas. The combination of genomic and transcriptomic analysis allows the discovery of potential new fusion transcripts. However, whole genome sequencing might miss some somatic changes detectable by molecular cytogenetics, in particular those lying in complex repetitive areas of the genome.

The ICGC MMML-Seq project is funded by the Federal Ministry of Education and Research in Germany (BMBF) within the Program for Medical Genome Research (01KU1002A to 01KU1002J).

019

COMPREHENSIVE GENOMIC PROFILING OF DIFFUSE LARGE B-CELL LYMPHOMA IN THE CLINICAL SETTING

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Introductions: Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin B-cell lymphoma, exhibits known molecular heterogeneity, and in some patients remains resistant to standard and salvage chemotherapeutic regimens. Comprehensive genomic profiling (CGP) of DLBCL may guide more effective targeted combination therapies in these patients, as it simultaneously detects all classes of clinically and biologically relevant mutations with high sensitivity and specificity and is suitable for formalin-fixed paraffin-embedded needle core and aspiration specimens. We interrogated 125 DLBCLs with a novel NGS-based CGP assay (FoundationOne® Heme) in order to delineate the genomic landscape and identify potential clinically relevant therapeutic targets.

Methods: Genomic profiles of 125 DLBCL specimens received in a CLIA-certified, CAP-accredited, NYS-approved laboratory were successfully characterized by FoundationOne® Heme. Sequencing libraries targeting 405 cancer-related genes by DNA-seq and 265 frequently rearranged genes by RNA-seq were sequenced to high depth (Illumina HiSeq), averaging 498× for DNA and ~7M on-target unique pairs for RNA, to enable the sensitive and specific detection of substitutions, indels, copy number alterations, and gene rearrangements.

Results: Somatic driver alterations were identified in all 125 cases with clinically relevant mutations observed in 97 (78%) patients. A high mean mutation burden was seen with, on average, 6.5 alterations per patient. Genomic alterations previously described in DLBCL were confirmed in this study, including *MLLT3* (39.2%), *TP53* (31.2%), *CDKN2A* (30.4%), *BCL2* (28.8%), *BCL6* (20%), *CREBBP* (20%), and *MYC* (12%). Importantly, several clinically relevant alterations with known associated therapies were detected, including *EZH2* (11.2%), *TET2* (8.8%), *CD79* (7.2%), and *PTEN* (4.8%). Therapeutically targetable kinase mutations, more commonly associated with solid tumours (eg. *RET*, *ALK*, *BRAF*, *HRAS*, *NRAS*, *FGFR2*, and *ERBB2 amp*) were also identified though at lower frequency (<3%). Amplification was confirmed in 18 genes including *REL*, *MYC*, and *CD274*/*PDCD1LG2* (*PD-L1*/*PD-L2*), while commonly described *IGH-BCL2*/*BCL6*/*MYC* gene rearrangements and *ALK* fusions, intragenic rearrangement in *CARD11* and *CREBBP*, and truncating rearrangements in tumour suppressors like *ATM* and *RB1* were also seen.

Conclusions: Comprehensive genomic profiling visualizes a complex genomic landscape in DLBCL that may impact diagnosis and prognosis, may deepen our understanding of underlying biologic pathways, and may guide targeted combination therapy in relapsed patients with limited treatment options.

020

TARGETED GENOMIC SEQUENCING PROSPECTIVELY IDENTIFIES CLINICALLY RELEVANT GENETIC ALTERATIONS ACROSS LYMPHOMA SUBTYPES

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Introduction: Prior sequencing studies of primary lymphoma cells used a variety of sequencing methods, depth of coverage, and specimen source leading to inconsistent characterization of genetic alterations (GAs) across different studies. As more therapeutic trials select patients based on the presence of actionable GA in their tumour cells, it is important to precisely describe the incidence of specific GA using the same clinical assay across different lymphoma histologic subtypes. In this study, we benchmark the distribution of GAs across all lymphoma subtypes by prospectively analyzing 103 cases of lymphoma and performing comprehensive DNA/RNA targeted sequencing of genes commonly found in haematologic malignancies using the Foundation One Heme (F1H) clinical assay.

Methods: Patients seen in the MSKCC lymphoma service were prospectively offered targeted genomic sequencing of their lymphoma specimens through F1H. Archived specimens (FFPE $N = 75$, peripheral blood $N = 20$, and BM aspirate $N = 8$) were sequenced to high, uniform coverage averaging >600× for DNA and >20 million pairs for RNA. GAs were determined, including base substitutions, small insertions and deletions, rearrangements, and copy number alterations. Significant non-synonymous variants were identified as mutations from the COSMIC database, amplifications of established oncogenes, or homozygous deletions and/or clear loss-of-function mutations of known tumour suppressors. Fisher's exact test with Monte Carlo estimation corrected by false discovery rate was used for associations.

Results: We profiled 103 lymphoma specimens from 101 patients. Samples were banked for a median of 31 days prior to genomic analysis, range 1 day to 6.5 years. Sequencing data resulted a median of 17 days from sample date receipt by Foundation Medicine. GAs were identified in 97% of samples, median of 4 GAs/sample. The most common GAs were TP53 (28%), BCL2 (23.3%), MLL2 (22%), BCL6 (16%), and TNFAIP3 (15%). 85% of samples had clinically relevant GAs with potential prognostic and therapeutic implications. The most common clinically relevant GAs were TP53, BCL2, CDKN2A/B, and CREBBP. While samples are not paired biopsies, gene and biological signatures appear stable before and after initial therapy.

Conclusions: Application of a comprehensive next generation targeted genomic sequencing assay provides an opportunity to describe the spectrum and incidence of

DOI: 10.1002/hon

Abstract 020 Table 1.

	Sample source of genomic analysis		Total	
Subtype	Previously untreated N	Previously treated N	N	%
DLBCL	21	16	37	*35.9*
T-cell	7	9	16	*15.5*
FL	4	11	15	*14.6*
CLL	5	7	12	*11.7*
MCL	5	4	9	*8.7*
MZL	1	5	6	*5.8*
Other	1	2	3	*2.9*
BL	0	2	2	*1.9*
HL	1	1	2	*1.9*
Grey zone	1	0	1	*1.0*
Total	46	57	103	*100*

GAs across different lymphoma subtypes. This approach will facilitate the design of basket trials selecting patients based on shared GAs rather than histologic subtype.

021

POSTTRANSPLANT DIFFUSE LARGE B-CELL LYMPHOMA AND BURKITT LYMPHOMA: NEW GENETIC FINDINGS

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Introduction: Posttransplant lymphoproliferative disorders (PTLDs) are heterogeneous and potentially fatal disorders that arise in up to 20% of organ transplant recipients. Molecular pathogenesis of PTLD is poorly understood.

Methods: The study was performed using conventional cytogenetics, FISH, array CGH (aCGH), gene expression profiling, immunohistochemistry and bioinformatics.

Results: We investigated 28 posttransplant (PT) DLBCL of non-GCB origin and 7 PT-BL selected from a cohort of 174 monomorphic PTLD collected in our institution between 1989 and 2012. As control, 19 non-GCB DLBCL and 4 typical BL from immunocompetent hosts (IC) were included.

PT-DLBCLs comprised 22 EBV^+ and 6 EBV^- cases. Array CGH identified genomic imbalances in 10/22 EBV^+ and in 5/6 EBV^- cases. Comparison of genomic profiles of PT-DLBCL with profiles of 11 IC-DLBCL showed that EBV^- PT-DLBCL share several common imbalances with IC-DLBCL and that both groups significantly differentiate from EBV^+ PT-DLBCL. Further integrative genomic and transcriptomic analysis identified 29 dysregulated genes mapped in the differentially represented regions in EBV^+ PT-DLBCL, including the underrepresented chromosome 3 and downregulated *FOXP1*/3p13 (confirmed by IHC) and overrepresented 9p and upregulated *CCKN2A*/9p21. Ingenuity pathway analysis showed that most of the dysregulated genes form an interaction network.

PT-BLs comprised 2 EBV^+ and 5 EBV^- cases. All cases showed a gene expression profile of molecular BL. Four of them were t(8q24/*MYC*)-positive, while all 3 cases lacking *MYC* translocation (EBV^-) displayed the 11q-gain/loss pattern recently described by Salaverria et al. (2014). The minimal gained region defined by aCGH spans an ~4 Mb area at 11q23.3 and associates with upregulation of *USP2*, *CBL2* and *PAFAH1B2*. The minimal lost region spans ~13.5 Mb at 11q24.1q25 and includes a few candidate downregulated genes, including *TBRG1*, *EI24* and *ETS1*. Further studies showed that the majority of dysregulated 11q23q24 genes are involved in the TP53 and MYC networks, suggesting that the 11q-gain/loss aberration is a molecular variant of t(8q24/MYC).

Conclusions: (i) Genomic features of posttransplant non-GCB DLBCL support our previous observation of a biological similarity between EBV^- PT-DLBCL and IC-DLBCL, and the concept that EBV^- PT-DLBCL represent coincidental lymphomas in immunosuppressed patients. (ii) The most distinctive features of EBV^+ PT-DLBCL when compared with EBV^- PT-DLBCL/IC-DLBCL are underrepresentation of chromosome 3/downregulation of *FOXP1*/3p13 and overrepresentation of 9p/upregulated *CCKN2A*/9p21, pointing to a different molecular pathogenesis of both subgroups. (iii) PT-BL are frequently MYC-negative and characterized by a 11q-gain/loss pattern. This novel aberration is significantly more frequent in PT-BL (43%) than in IC-BL (3%).

022

MICRORNA-150 INFLUENCES MICROENVIRONMENTAL INTERACTIONS AND PROGNOSIS OF FOLLICULAR LYMPHOMA

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Introduction: We and others have shown that deregulation of microRNAs (miRNAs) is associated with the biology of B cell malignancies (Musilova and Mraz, Leukemia, 2015). MicroRNA miR-150 is of particular interest as its expression level has been shown to determine BCR propensity in chronic lymphocytic leukaemia (CLL) B cells (Mraz et al., Blood, 2014).

Methods: We analysed the role of miR-150 in microenvironmental interactions and the prognosis of follicular lymphoma and other B-cell malignancies by techniques of RT-PCR, stromal cell co-culture, miRNA transfection, and anti-IgM stimulation.

Results: First, we analysed miR-150 expression in 90 follicular lymphoma (FL) samples [fresh frozen and formalin-fixed paraffin-embedded tissues (FFPE)]. miR-150 expression was significantly lower in patients with high Ki67 positivity (>20%; $P = 0.003$) and a high FLIPI score (3–5; $P = 0.03$). We also observed significantly reduced miR-150 levels in FLs which transformed to DLBCL compared to the samples before transformation ($P = 0.01$), and miR-150 was significantly less expressed in DLBCL than FL (fold-change 4.1, $P < 0.001$). FL patients with low miR-150 levels (<median) had significantly shorter survival [6.2 years vs not reached; $P = 0.007$; HR 3.0 (CI: 1.3–6.8)]. To determine the potential reason for variable miR-150 levels in B cells, we tested the effect of microenvironmental interactions. In this experiment, a short-term (48 h) co-culture of B cell lymphoma cells with stromal cells (HS-5) led to down-regulation of miR-150 levels ($P < 0.05$). Next, we investigated the role of miR-150 in cell migration by silencing a miR-150 target that we have identified, namely GAB1, in lymphoma cell lines. The transfection of siGAB1 resulted in a significant reduction of B cell migration towards stromal cells compared with the control (Transwell assay, Corning; $P < 0.05$) and significantly reduced BCR signalling after anti-IgM treatment (10 µg/mL, assessed by calcium flux).

Conclusion: Low miR-150 levels associate with a shorter overall survival in FL. This could be used as a reasonable prognostic marker since high miRNA stability allows analyses of miR-150 levels from FFPE samples. Interactions with stromal cells and/or the soluble factors that they are producing down-modulates miR-150 levels in B cells, which further supports their migratory potential and BCR-signalling propensity.

This study was supported by the following: SoMoPro II-no. 4SGA8684; NGS-PTL(306242); EHA Fellowship award; IGA MZ CR NT11218-6/2010; MUNI/A/1180/2014; and CZ.1.05/1.1.00/02.0068. G. P. is a city of Ostrava scholarship holder; M. J. is a Brno PhD Talent Scholarship holder.

'FOCUS ON…' SESSION: CLINICOPATHOLOGICAL CORRELATIONS

023

FREQUENCIES OF LYMPHOMA ENTITIES AND IMPACT OF DIAGNOSTIC REVIEW: A FRENCH EXPERIENCE ON 35.753 LYMPHOMAS OVER 2010–2013

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Introduction: The diagnosis of haematologic malignancies remains challenging in a proportion of cases. In 2010, the French National Cancer Agency (INCa) established the 'Lymphopath network' consisting of 33 reference centres to provide, prior to treatment, a pathological review by expert haematopathologists of every newly diagnosed lymphoma or suspected lymphoma for optimal clinical management. We report here the results of this second pathology review, including rates of diagnosis changes and their putative impact as well as the relative frequencies of lymphoma entities in France.

Methods: Expert diagnoses according to the criteria of the 2008 WHO classification, after slide review and additional ancillary techniques performed in the reference centres, were entered in a central national database. From 2010 to 2013, a total of 42146 samples were reviewed. Discordant diagnoses among extra-cutaneous lymphomas were carefully examined by a haematologist and recorded as major or minor depending on the expected therapeutic impact.

Results: Of the 42146 samples reviewed, 35 753 were newly diagnosed as lymphomas whereas the remaining cases ($n = 6393$) included reactive lymphoid conditions ($n = 4610$) or non-lymphoid malignancies (including especially myeloma and leukaemic disorders) ($n = 1783$). Lymphomas comprised 31 401 non-cutaneous lymphomas [77% B-cell non-Hodgkin lymphoma (NHL), 7% T-cell NHL and 15% Hodgkin lymphomas] and 4352 cutaneous lymphomas (66% T-cell NHL and 34% B-cell NHL). Among non-cutaneous lymphomas, diffuse large B-cell lymphoma (DLBCL) is the most prevalent B-cell lymphomas (42% of B-cell lymphoma) followed by follicular lymphoma (22%), whereas among peripheral T-cell lymphoma (PTCL), angio-immunoblastic T-cell lymphoma (36%) was more frequent than PTCL not otherwise specified. The discordance rate between the referral and final diagnosis was 17.2%. In 15% of cases, diagnostic changes were estimated to result in a change in patient management. Main discrepancies were observed in misclassified small B-cell lymphomas and PTCL subtyping. 6.4% of discordances were due to an unspecified lymphoma diagnostic. Changes between benign versus malignant lymphoid conditions and between Hodgkin lymphoma versus NHL represented less than 2% of discrepancies. Minor discordances (2.2%) mostly interested FL misgrading and DLBCL subtypes discrepancies. In more than 25% of all discordances, reclassification resulted from the application of additional immunostainings (all cases) and molecular studies (PCR and FISH) in 11% and in 15%, respectively.

Conclusion: Our study highlights the importance of specialized centralized review of lymphoma diagnosis not only in the setting of clinical trials but also in routine clinical practice for optimal patient management.

024

RITUXIMAB TREATMENT IN FOLLICULAR LYMPHOMA CIRCUMVENTS THE PROGNOSTIC VALUE OF INTRA-TUMOURAL T-CELLS: AUTOMATED IMAGE ANALYSIS OF THE LYSA PRIMA TRIAL

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Background: It appears from previous immunohistochemical studies that the prognostic value of intratumoural T-cell subsets in FL remains controversial. Potential biases that could explain discrepancies include the relatively small size of the series, the lack of uniform treatment and randomized trails and the bad reproducibility of manual counting among pathologists.

Methods: In order to address these issues, we have used computer-assisted image analysis in a large series of FL samples from patients enroled in the randomized PRIMA trial, in which Rituximab was used in the standard treatment arm and in an experimental maintenance arm as well. Immunohistochemistry was performed on TMA paraffin biopsy samples collected at the time of diagnosis. We used antibodies recognizing various T-cell subsets including CD3, CD4, CD8, PD1, FOXP3 and ICOS. From the initial population of 1135 patients from the PRIMA study, pathological material after quality control was available and could be successfully analysed in 417, 418, 287, 406, 379 and 369 patients for CD3, CD8, CD4, PD1, ICOS and FOXP3, respectively.

Results: There was no significant difference in the clinico-pathological characteristics of patients corresponding to the analysed samples when compared with the total

DOI: 10.1002/hon

population of PRIMA patients. When the median value of positivity in the whole cohort of patients was used as a cut-off, there was no significant correlation with either PFS or OS and the positivity of any T-cell marker. Similarly, when each T-cell marker was used as a continuous variable, no significant correlation could be observed. We have then used the X-tile method in order to determine a significant cut-off for each marker. Again, no significant correlation could be found for any marker, although there was a trend for patients with high CD3 values to be associated with a better outcome.

Conclusion: These results obtained from the largest series of FL biopsy samples ever reported suggest that intra-tumoural T-cell subsets including PD1+ TFH and FOXP3+ Treg cells do not bear any prognostic significance in FL patients treated at the Rituximab era.

025

CELL OF ORIGIN (COO) ASSIGNMENT IN TRANSFORMED FOLLICULAR LYMPHOMA

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Introduction: In follicular lymphoma (FL), the median overall survival time for newly diagnosed patients is currently well beyond 10 years. Nonetheless, in 20–30% of patients, within 10 years, the disease transforms into an aggressive lymphoma subtype, an event associated with increased morbidity, need for treatment and risk of lymphoma-related death. Despite an increasingly refined understanding of the mutational landscape of transformed follicular lymphoma (TFL), the biological correlates underpinning poor outcome for TFL patients are imperfectly understood. In a prior study assessing the gene expression profile of TFL, all classifiable cases ($n = 18$) were of germinal centre B-cell (GCB) phenotype and none were of the activated B-cell (ABC) phenotype, although 3 cases out of an independent cohort of 35 (9%) were assigned to the non-GCB phenotype using immunohistochemistry (Davies et al, BJH, 2007). As subtype-specific efficacy of novel agents is actively pursued in *de novo* diffuse large B-cell lymphoma (DLBCL), it is relevant to ask whether TFL can be similarly divided into distinct transcriptional phenotypes.

Methods: Out of a cohort of 148 formalin-fixed and paraffin-embedded TFL samples, 112 (76%) had a morphology akin to DLBCL, as opposed to unclassifiable B-cell lymphoma (BCLU) or composite histologies. We applied the Lymph2Cx assay, a digital gene expression (NanoString)-based test, to RNA extracted from these 112 samples, as previously described (Scott et al, Blood, 2014). A tissue microarray was constructed, and chromosomal rearrangements of *BCL2*, *BCL6* and *MYC* were assessed by fluorescence *in situ* hybridization (FISH) breakapart assays.

Results: The Lymph2Cx assay provided sufficient digital gene expression counts to allow for class assignment in 109 out of the 112 cases (97%). Of these 109 samples, 87 (80%) were assigned to the GCB subtype, 17 (16%) to the ABC subtype and 5 (4%) were unclassified. *BCL2* translocations were found in 65 out of 72 cases (90%) that were interpretable by FISH and that had a GCB phenotype, but only in 5 out of 14 cases (36%) with an ABC phenotype. This difference was statistically significant ($p < 0.001$). The prevalence of *BCL6* and *MYC* translocations did not significantly differ between the subtypes.

Conclusions: Our data show that a majority of TFL cases with DLBCL morphology (80%) are of the GCB subtype when assessed using the Lymph2Cx assay. However, a significant minority (16%) are of the ABC subtype and characterized by a low prevalence of *BCL2* translocations. Future studies are needed to assess whether these subtypes differ in outcome and molecular ontogeny, which would potentially make them amenable to distinct therapeutic targeting.

026

NOTCH1/2 MUTATIONS ARE RECURRENTLY FOUND IN CYCLIN D1-NEGATIVE SOX11-POSITIVE MANTLE CELL LYMPHOMA

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Introduction: Recurrent chromosomal alterations in Cyclin $D1^-/SOX11^+$ mantle cell lymphoma (MCL) were recently described, but other molecular alterations contributing to the pathogenesis of these MCL variant are not well known. *CCND2* translocations are found in around half of these patients, but primary alterations in the remaining cases have not been identified. Mutations of *NOTCH1*, *NOTCH2*, *MEF2B, BIRC3, WHSC1, ATM* and *TP53* are recurrent in Cyclin $D1^+$ MCL, but their incidence in Cyclin $D1^-$ MCL is still unknown.

Methods: Fifty-four Cyclin $D1^-/SOX11^+$ MCL were investigated by FISH, array CGH, gene expression profiling and quantitative PCR. We also performed Sanger sequencing of *TP53, MEF2B, WHSC1, BIRC3, NOTCH1* and *NOTCH2* mutational hot spots.

Results: FISH screening detected *CCND2* translocations in 26 Cyclin $D1^-/SOX11+$ MCL cases (48%). Of note, two cases carried a break in one allele and high level amplification of the remaining allele. Analysis of *IG* genes revealed that *CCND2*-negative Cyclin $D1^-$ MCL do not carry aberrations affecting *IGH*, *IGK* and *IGL* genes with the exception of two cases that had *IGH* breaks and moderate levels of Cyclin D2 expression. The global genomic profile and the complexity of the 45 cyclin $D1^-$ $SOX11^+$ MCL patients analysed by copy number arrays were similar to the conventional Cyclin $D1^+$ MCL. Of note, cases without *CCND2* translocation carried significantly more frequent losses of 1p21.3-p12, whereas 3q24-qter gains and losses of 3p14.2-p12.2 were more frequently found in the *CCND2*-translocation positive cases ($p = 0.04$). Gene expression profiles of Cyclin $D1^-$ $SOX11^+$ MCL were similar to conventional Cyclin $D1^+$ MCL.

Mutational analysis showed *NOTCH1* or *NOTCH2* mutations in 6 of 49 (12%) cases analysed. These mutations were equally found in both groups of cases with and

DOI: 10.1002/hon

without *CCND2* translocations. Two of 52 cases (3.8%) carried *MEF2B* mutations, whereas *WHSC1* mutations were found in only one case of 54 cases studied (1.8%). *BIRC3* mutations were absent in the 53 cases studied. Four out of five cases with 17p deletion carried *TP53* mutations.

Deletions of 17p were associated with a worse prognosis [3-year overall survival (OS) 0% vs 71%, $p < 0.001$], whereas patients carrying *NOTCH1/2* mutations showed a tendency towards worse prognosis although did not reach statistical significance (3-year OS 40% vs 62%, $p = 0.1$).

Conclusions: Our data indicate that primary genetic translocations involving *IG* genes are generally absent in *CCND2*-translocation negative MCL. On the other hand, the genetic profile of Cyclin $D1^-$ MCL seems to be similar to conventional Cyclin $D1^+$ MCL in terms of gene expression, copy number and mutations. Further studies are needed to show whether Cyclin $D1^-$ MCL carry specific mutations in addition to those reported in Cyclin $D1^+$ MCL.

027

CLINICOPATHOLOGICAL STUDY OF HHV8-NEGATIVE BODY CAVITY-BASED LYMPHOMA (BCBL)

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Background: HHV8-negative body cavity-based lymphoma (BCBL) or 'primary effusion lymphoma (PEL)-like lymphoma' is very rare and is not defined in the current lymphoma classification.

Methods: We collected data of possible BCBL cases diagnosed between 1990 and 2014 from 52 institutions in Japan and analysed clinicopathological features. BCBL was defined as lymphoma that developed in body cavity effusion (pleural effusion, pericardial effusion, and ascites) without mass formation or extra-cavitary lesions at diagnosis and was classified into PEL (HHV8-positive) and HHV8-negative BCBL based on HHV8 status of lymphoma cells. The HHV8 status was assessed by anti-LANA-1 antibody and/or polymerase chain reaction for HHV8 of body-cavity effusion sample.

Results: Case report form of 95 patients was collected. With central review, we excluded 26 patients and 69 patients with BCBL were identified. Out of them, 64 and 5 were compatible with the diagnosis of HHV8-negative BCBL and PEL, respectively. In the 64 patients with HHV8-negative BCBL, male to female ratio was 1.7:1, and median age at diagnosis was 77 years (57–98); HIV was negative in all of the 58 patients who were tested. Involved sites were pleural effusion (77%), pericardial effusion (59%), and ascites (11%), respecively. Multiple sites were involved in 26 cases, and another 22 cases showed bilateral pleural effusion. Tumour cells expressed CD20 in 61 cases (95%). Immunoglobulin light chain restriction was detected in 36/55 (66%). EBER *in situ* hybridization was positive in 5/42 (12%). Median MIB-1 index was 74% (3–93). According to the Hans criteria, 24 of 31 cases (77%) showed non-GCB phenotype. The MYC gene rearrangement was found in 6/20 (30%) by FISH. In 56 cases, systemic therapy was initiated within 3 months after diagnosis. The most common first-line systemic therapy was CHOP or CHOP-like ($n = 48$). Of the 56 cases, the overall response rate was 96% with 75% achieving a complete remission. Out of 8 patients without systemic treatment at diagnosis, systemic treatment was initiated in only 1 patient at 30 months due to re-emergence of effusion and 4 patients had had no systemic treatment for a median of 24 (5–147) months. With a median follow-up of 25 (0–145) months, 2-year OS, PFS, and TTP of HHV8-negative BCBL were 83.3%, 72.9%, and 83.8%, respectively. Nineteen patients relapsed after achieving response: the same body-cavity effusion alone ($n = 8$), different body-cavity effusion ($n = 2$), and intra- or extra-cavitary tumour mass formation ($n = 9$). Fifteen patients died, and the causes of death were lymphoma ($n = 11$) and others ($n = 4$).

Conclusions: This retrospective study on HHV8-negative BCBL showed that it mainly affects HIV-negative elderly and lymphoma cell express B cell markers. Almost all of the patients responded to systemic treatment, and its prognosis was favourable.

028

GREY ZONE LYMPHOMA BETWEEN CLASSICAL HODGKIN LYMPHOMA AND DIFFUSE LARGE B CELL LYMPHOMA: A LYSA RETROSPECTIVE ANALYSIS

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Introduction: Grey zone lymphomas (GZL), described as lymphomas with intermediate features between classical Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL), especially primary mediastinal large B-cell lymphoma (PMBCL), were defined as an entity in the 2008 WHO classification. However, the diagnosis remains a challenge for the pathologist, and precise criteria are warranted. Furthermore, very scarce data exist on the best therapeutic options for these patients (pts).

Method: We performed a multicentre retrospective analysis of GZL diagnosed in LYSA clinical centres since 1997. Biopsies were centrally reviewed. Among the 152 proposed cases, 138 had confirmed histology of GZL. Clinical and treatment data have been collected for 124 patients.

Results: GZL cases were classified as cHL-like, PMBCL-like, intermediate morphology, sequential (presence of cHL and PMBCL at different times) or composite (cHL and PMBCL at the same time) with the following repartition: 49%, 17%, 20%, 10% and 6%, respectively. All cHL-like cases showed diffuse and intense CD20 expression. Among PMBCL-like cases, 15/21 expressed CD20 and all expressed CD30 and/or CD15 with intense and diffuse pattern.

DOI: 10.1002/hon

Only 10% of pts were EBV+ without characteristic of EBV associated B-cell lymphoma. The majority of pts had a mediastinal involvment (81%). Thirteen pts had a sequential form with a median of 7 months (m) between diagnosis and relapse (1.4–45 m). Among them, 10 cHL relapsed in PMBCL and 3 PMBCL in cHL. Among the 111 pts without sequential form, 90 had a follow-up (FU) longer than 1 year. The sex ratio was 1.25, median age 38 years. After a median FU of 31 m, the median event-free survival (EFS) was 73 m with 2-year and 5-year EFS of 65% and 58%, respectively. The 2-year and 5-year overall survival (OS) were 84% and 66%, respectively. Treatment regimen consisted in HL-like (ABVD or escBEACOPP) for 37% of the pts, or DLBCL-like (R-chemo, namely R-CHOP or R-ACBVP) for 62% without significant differences in CR rate, EFS and OS between the 2 strategies. However, escBEACOPP seems to offer more CR than ABVD and R-chemo (90% vs 53%, 75%, $p = 0.02$ and 0.05, respectively). Pts treated with escBEACOPP also tended to have a longer OS and EFS than the others. Thirty-one pts relapsed, most of them (81%) in the first year. The median OS after relapse was 18 m. Pts with a mediastinal involvement at diagnosis were younger (median 33 years vs 52 years) and had more ECOG-PS > 1 (19% vs 0%, $p = 0.04$). These pts had higher rate of primary refractory disease and worse EFS and OS ($p = 0.09$, 0.06 and 0.03, respectively) than those without mediastinal mass. In multivariate analysis, ECOG-PS > 1 and LDH level were prognostic for EFS, and ECOG-PS > 1, aaIPI score, LDH level and serum albumin for OS. The different GZL subtypes had similar outcome. Among the 31 relapses, 13 pts are alive, 11 of them being rescued with ASCT.

Conclusion: GZL is a heterogeneous entity with a poor outcome compared to cHL or PMBCL, due to a substantial proportion of pts with early failure. Pts seem to benefit from intensive treatment such as escBEACOPP in first line and ASCT as salvage if needed.

'FOCUS ON…' SESSION: TRANSPLANTATION

029

BEAM PLUS RITUXIMAB OR RADIOIMMUNOTHERAPY VERSUS BEAM FOR AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN RELAPSED FOLLICULAR LYMPHOMA: A RETROSPECTIVE STUDY OF THE LWP-EBMT

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Background and aims: Relapse remains the most common cause of failure of ASCT for recurrent follicular lymphoma (FL). We hypothesized that the incorporation of rituximab (R) or radioimmunotherapy (Ibritumomab tiuxetan: Zevalin®; Z) in the high-dose regimen (HDR) might reduce the relapse rate and improve the outcome of ASCT in this setting.

Patients and methods: Between 2004 and 2012, 2359 patients (57% male, median age at ASCT: 56, range: 19–77) who had an ASCT for relapsed FL with BEAM with or without R (R-BEAM) or Z (Z-BEAM) were reported to the EBMT and included in this study. Patients who had received other drugs in addition to BEAM were not eligible. We conducted a comparison of BEAM ($n = 1973$), Z-BEAM ($n = 207$) versus R-BEAM ($n = 179$). Overall survival (OS) and event-free survival (EFS) were estimated using the Kaplan–Meier product-limit estimate and were compared by the log-rank test in univariate analyses. Estimates of non-relapse mortality (NRM) and cumulative incidence of relapse (RI) were calculated using cumulative incidence rates to accommodate competing risks and were compared by Gray's test. Multivariate analyses of OS and EFS were performed using Cox regression modelling stratified for variables not respecting the proportional hazard assumption. Multivariate analyses of RI and NRM were performed using Fine and Gray regression models.

Results: The BEAM, Z-BEAM and R-BEAM groups were balanced for age, time from diagnosis to ASCT and disease status at ASCT (which was sensitive disease in 98%, 95% and 88%). However, in comparison to BEAM, Z-BEAM patients were transplanted more recently, had a male predominance and were less likely to be in a good performance status (PS). After a median follow-up of alive patients of 17 months (interquartile range 3.9–40.3), 29% of patients in the BEAM group relapsed in comparison with 31% in the Z-BEAM and 29% R-BEAM cohort. 1946 (17%), 31 (15%) and 23 (15%) patients died in the BEAM, Z-BEAM and R-BEAM cohorts, respectively. Compared to BEAM, there were no significant differences in Z-BEAM or R-BEAM patients for NRM [HR: 0.88 (95% CI: 0.4–1.94); $p = 0.74$ and HR: 1.24 (95% CI: 0.57–2.72); $p = 0.59$], nor on RI [HR = 1.02 (0.78–1.33); $p = 0.89$ and HR = 0.92 (0.68–1.23); $p = 0.58$]. Similarly, no significant differences between BEAM and Z-BEAM or R-BEAM cohorts were found for OS [HR = 0.93 (95% CI: 0.64–1.35); $p = 0.71$ and HR = 0.78 (95% CI: 0.51–1.2); $p = 0.26$] or EFS [HR = 0.93 (0.71–1.23); $p = 0.63$ and HR = 1.1 (CI95%: 0.84–1.41); $p = 0.51$]. Multivariate analysis considering HDR, age, gender, disease status, PS and time from diagnosis to ASCT identified sensitive disease status (HR 0.38; $p < 0.0001$), time from diagnosis to ASCT >2y (HR 0.67; $p = 0.006$) and female gender (HR 0.84; $p = 0.033$) but not HDR as significant predictor for RI.

Conclusions: Based on the matching factors used, this study failed to show a benefit of adding Z or R to BEAM in ASCT for relapsed FL. However, the limitations of registry analyses have to be taken into account, and prospective trials are needed for definite information.

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OUTCOME OF REDUCED INTENSITY ALLOGENEIC STEM CELL TRANSPLANTATION FOR FOLLICULAR LYMPHOMA RELAPSING AFTER A PREVIOUS AUTOLOGOUS STEM CELL TRANSPLANT

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The prognosis for patients with follicular lymphoma (FL) who relapse after an autologous stem cell transplant is poor. A variety of different treatment strategies may be

DOI: 10.1002/hon

employed including alternative immunochemotherapy, novel agents or a reduced intensity allogeneic SCT (RICalloSCT). There is limited published data describing the outcome of RICalloSCT in this setting. The Lymphoma Working Party of the EBMT therefore conducted an analysis of a large cohort of patients undergoing RICalloSCT for FL relapsing after an autoSCT.

Methods: We conducted a retrospective analysis from the EBMT database. Eligible patients had a diagnosis of FL, were aged 18–70 years and had relapsed after a prior autoSCT. Tandem transplants and cord blood transplants were excluded. Data analyses was performed using Kaplan Meier estimates and cumulative incidence analyses.

Results: 183 patients with a median age at diagnoses of 45 years (range 21–69 years) were identified. 119 were male and 64 female; the stage at diagnosis was stage I 7, stage II 12, stage III 32 and stage IV 120; and 30% of patients had B symptoms at diagnosis. The median time from diagnosis to RICalloSCT was 62 months (range 11–253 months). All patients had undergone a prior autoSCT at a median of 30 months (range 1–248 months) prior to the RICalloSCT. The patients had received a median of 4 lines (range 3–10) of therapy prior to the RICalloSCT. At the time of transplant, 77.5% of patients had chemosensitive disease and 16% had chemoresistant disease, 2% were in untested relapse. All patients received a reduced intensity conditioned allogeneic SCT from either a sibling 41%, unrelated donor 53% or mismatched sibling donor 6%. 95% of patients engrafted and 4% of patients died prior to engraftment. The cumulative incidence of acute GVHD was 45% and chronic GVHD 51.2%. With a median follow-up of 59 months for surviving patients, the non-relapse mortality (NRM) was 27% at 2 years. The relapse/progression rate was 11% at 2 years and 16% at 5 years and was significantly lower in patients with chemosensitive disease at transplantation (HR 0.46, CI 0.24–0.75, $p = 0.02$). The 2 and 5 year progression free survival (PFS) was 62% and 50%, respectively, and was significantly better in patients with chemosensitive disease at transplant (HR 0.42, CI 0.24–0.75, $p = 0.003$). Older patients (>45) had a significantly worse PFS (HR 1.80, CI 1.1–2.9, $p = 0.016$). The 2 and 5 year overall survival was 63% and 55%, respectively, and was significantly worse in patients over the age of 45 years (HR 1.66, CI 1.0–2.7, $p = 0.04$). Patients with chemosensitive disease had a superior OS (HR 0.38, CI 0.2–0.7, $p = 0.001$).

Conclusion: This is the largest cohort of patients with follicular lymphoma undergoing a RICalloSCT following failure of a prior autologous SCT. These data suggest that a RICalloSCT is an effective salvage strategy in this setting particularly in younger patients with chemosensitive disease at transplant.

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A UK LYMPHOMA CLINICAL STUDY GROUP PHASE II EVALUATION OF HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN INTESTINAL AND OTHER AGGRESSIVE T-CELL LYMPHOMAS

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Background: Prognosis for peripheral T-cell lymphomas (PTCL) remains poor with 35–40% 5-year survival using CHOP-like chemotherapy. Following promising regional results using intensive chemotherapy and autologous transplant (ASCT) in first CR for enteropathy-type lymphomas, we prospectively evaluated the regimen in a multicentre setting. A major amendment to include other histological subtypes was added later. Target recruitment of 60 patients was not reached. Several centres cited resource issues as a reason for not opening the study but treated patients according to the protocol.

Methods: Patients were recruited to this phase II, open-labelled study from 10 UK centres between September 2009 and July 2014. Patients received 1 cycle of CHOP followed by 3 cycles of alternating IVE/Methotrexate and consolidative BEAM ASCT in those achieving CR. The main objective was to assess the efficacy and toxicity of the regimen, with a primary end-point of survival at 1 year. Secondary endpoints were toxicity and feasibility of a coordinated approach to treatment.

Results: 22 patients were enroled, 12 ITCL/ETL, 8 PTCL and 2 ALK negative Anaplastic T-cell lymphoma, median age was 56 years (29–71) with 15 males and 7 females. At study entry, 21/22 patients were ECOG 0–1. Disease was staged using Lugano (intestinal patients) or Ann Arbor (nodal patients) staging systems. Staging was unknown for 1 intestinal patient. 10 patients (45%) had advanced disease either Ann Arbor Stage III/IV or Lugano stage IV.

Toxicity was mainly haematological with neutropenia in all patients and thrombocytopenia in 18 (82%) patients. There were 17 infective episodes and 9 episodes of febrile neutropenia (1 grade 5). Dose omissions/reductions were required in 5 patients during IVE/Methotrexate due to toxicity. Other grade III/IV adverse events occurring in more than 10% of patients were diarrhoea (23%) and hypokalaemia (14%). ORR was 73%, (CR 50%, PR 23%) with PD in 2 patients and NR in one. Responses were unassessable in 2 patients (due to death) and unknown in 1 (trial withdrawal). 14 (63%) patients proceeded to ASCT. Of the remaining 8; 4 withdrew from the study, 2 died and 2 failed to harvest sufficient stem cells. Median OS was not reached, and median PFS was 13 months (median follow up 22 months). 12-month OS and PFS were 64% (95% CI 40–80) and 59% (95% CI 36–76), respectively. 10 patients developed PD, 4 at the original site and 6 in new areas. In total there were 8 deaths, 6 disease related, 1 due to toxicity and 1 due to other causes.

Conclusions: High dose chemotherapy followed by ASCT consolidation showed good outcomes at 1 year, when delivered in a multicentre setting, with acceptable toxicity in patients with aggressive T-cell NHL. Clinical trials in this group of patients are badly needed, but our experience demonstrates that changes to UK trial setup regulations may be needed to encourage more centres to participate in studies in rare cancers.

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ALLOGENEIC TRANSPLANTATION FOR T-CELL LYMPHOMAS: NO DIFFERENCE IN OUTCOME BETWEEN PATIENTS ALLOGRAFTED UP-FRONT AND IN FIRST CHEMOSENSITIVE RELAPSE

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Introduction: Despite novel therapies are under investigation in peripheral T-cell lymphomas (PTCL), the majority of the patients (pts) have a dismal outcome. Allogeneic stem cell transplantation (AlloSCT) seems an effective approach in the salvage setting, but small series of pts have been transplanted at diagnosis.

Methods: We report the long-term outcome (median follow-up of 60 months) of 72 pts affected by PTCL who underwent AlloSCT at diagnosis (Allo1) ($n = 23$) or for

DOI: 10.1002/hon

chemosensitive relapse (Allo2) ($n = 49$) that have been enroled in two transplantation protocols. Pathological classification included: 20 PTCL-not otherwise specified (unspecified), 2 anaplastic large cell lymphoma (ALCL) and 1 rare subtype in Allo1 group; 18 unspecified, 11 ALCL, 8 AILD and 12 rare subtypes in Allo2 group, respectively. Donor source was an HLA-matched related donor [$n = 39$; $n = 13$ Allo1, $n = 26$ Allo2 ($p = 0.80$)], a matched or mismatched unrelated donor [$n = 25$; $n = 10$ Allo1, $n = 15$ Allo2 ($p = 0.30$)] and an haploidentical donor [$n = 8$, only in the Allo2 group]. All the pts underwent transplant with chemosensitive disease: 45 (63%) in CR [$n = 20$ in Allo1, $n = 25$ Allo2 ($p = 0.003$), respectively]; 27 in PR (37%) [$n = 3$ in Allo1, $n = 24$ Allo2 ($p = 0.003$), respectively]. In the Allo2 group, 37 pts (75%) were allografted in first and 12 in second relapse.

Results: In the Allo1 group, at a median follow-up of 59 months, 15 of 23 (65%) pts are alive in CR, 4 (17%) died for progressive disease (PD), 3 for non-relapse mortality (NRM) and 1 for myocardial infarction. In the Allo2 group, at a median follow-up of 64 months, 31 of 49 (63%) pts are alive (29 in CR),11 (22%) died for PD, 6 for NRM and 1 for a second cancer. Five years crude cumulative incidence of relapse was 18% and 38% in Allo1 and Allo2 group ($p = 0.11$), respectively. Five-year relapse-free survival (RFS), PFS and OS were as follows: 80%, 60% and 62% in Allo1 group; 61%, 47% and 59% in Allo2 group without any statistical difference. However, we observed a significant difference in PFS between pts allografted at diagnosis and those in second relapse (5-year PFS 61% vs 16%, $p = 0.0044$) but not between diagnosis and first relapse (5-year PFS 61% vs 57%, $p = 0.92$). When only pts affected by unspecified PTCL were analysed, we confirmed a trend for better PFS if pts received allograft at diagnosis or in first relapse as compared with second relapse (5-year PFS: 65% vs 55% vs 25%, $p = 0.2$). Pts who went to allotransplant in first CR did not have a significant advantage [5-year PFS and OS: 59% versus 43% ($p = 0.44$); 60% vs 58% ($p = 0.82$) in the Allo1 and Allo2 groups, respectively].

Conclusions: Despite the limitations due to the sample size and the variety of subtypes included, AlloSCT should be not indicated as a consolidation of first complete remission outside a clinical trial.

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ALLOGENEIC OR AUTOLOGOUS TRANSPLANTATION AS FIRST-LINE THERAPY FOR YOUNGER PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA—RESULTS OF THE INTERIM ANALYSIS OF THE AATT TRIAL

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Background: Outcome of most patients (pts) with peripheral T-cell lymphoma (PTCL) is poor after conventional chemotherapy. As autologous (autoSCT) and allogeneic transplantation (alloSCT) gave encouraging results in pts with relapsed/refractory PTCL we did the AATT (=**A**utologous or **A**llogeneic **T**ransplantation in **T**-Cell Lymphoma) study in pts with newly diagnosed PTCL and present the results of a pre-planned interim analysis leading to early termination of the trial.

Methods: This was a randomized phase III study comparing alloSCT with autoSCT in younger pts (18–60 years) with PTCL. Primary endpoint was event-free survival (EFS). Treatment started with four courses of CHOEP-14 (cyclophosphamide, adriamycin, vincristine, etoposide and prednisone). Pts achieving CR/PR/SD proceeded to one course of DHAP (high-dose ara-C, *cis*-platinum and dexamethasone) and stem cell collection in pts randomized to autoSCT or without suitable donor. BEAM/autoSCT or fludarabine, busulfan, and cyclophospamide (Glass et al., Lancet Oncology 2014; 15 757–15 766)/alloSCT was to follow within 4–6 weeks.

Results: From 03/2011 to 08/2014, 104 pts were enroled. Fifty-eight pts randomized before 30 June 2013 were eligible for this interim analysis. Median age was 50 (24–60) years, 64% of pts were male, and 38 pts had an aaIPI of 2 or 3. Only 62% of pts completed treatment as per protocol. 11 pts randomized to autoSCT did not proceed to transplantation because of progressive disease or no response ($n = 8$), infection ($n = 1$) or change of histology ($n = 2$). Only 13 pts (46%) randomized to alloSCT actually received it. Fifteen pts were not allografted due to progressive disease ($n = 10$) or lack of a fully matched donor ($n = 5$). Four of these latter pts received autoSCT; one patient experienced mobilization failure. Twenty-one pts have died 68–705 days after randomization. Twelve pts died of lymphoma (7 in the auto and 5 in the allo arm), 2 pts died from salvage therapy (1 in each arm) and 1 pt from EBV-pos PTLD (in the allo arm). Two allografted pts died from early (d +21, +65) and two from late infections (d +549, +577), the latter with cGvHD. Two pts died from acute GvHD (d +24, d +85). One-year EFS was 41% (95% CI 27%–54%), and OS was 69% (95% CI 57%–82%) on the intent-to-treat-population.

Conclusions: This analysis showed no significant differences in survival for pts randomized to autoSCT or alloSCT. Most importantly, >30% of pts randomized to ASCT or alloSCT did not make it to transplantation mostly because of early lymphoma progression. A conditional power calculation showed a low probability (<10%) that the primary endpoint could still be met. Therefore, the data safety monitoring board in agreement with DSHNHL and LYSA representatives decided to prematurely stop patient accrual.

034

POST TRANSPLANT CYCLOPHOSPHAMIDE REDUCES NONRELAPSE MORTALITY OF HAPLO-IDENTICAL TRANSPLANTS YIELDING SIMILAR OUTCOMES AS WITH MATCHED SIBLING DONORS

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Background: Allogeneic stem cell transplantation (SCT) can provide long-term disease control for non-Hodgkin lymphoma (NHL), but its use depends on the

DOI: 10.1002/hon

availability of a matched donor. The recent introduction of post-transplant cyclophosphamide (post-SCT cy) has largely facilitated haplo-SCT. Here, we compare the outcome post-SCT cy-based haplo-SCT with that of traditional haplo-SCT with antibody-mediated T-cell depletion, and with other graft sources in patients with advanced NHL.

Methods: Information of patients with mantle cell lymphoma (MCL), DLBCL, T-cell lymphoma (TCL) and follicular lymphoma (FL) who received an SCT from a sibling donor (SIB), 10/10 matched unrelated donor (MUD), haplo-identical donor (HAPLO) or cord blood (CORD) between 2007 and 2012 was downloaded from the EBMT database. Centres were contacted to provide details of donor and recipient HLA reports and immunosuppression for haplo-transplants.

Results: 2798 patients met the inclusion criteria. 2065 received a transplant from a SIB, 447 from a MUD, 167 from CORD (18 MCL, 36 DLBCL, 43 FL and 70 TCL) and 119 from a HAPLO donor (16 MCL, 30 DLBCL, 22 FL and 51 TCL). For 99 HAPLO patients, additional information on immunosuppression details after haplo-transplant was available. 60 HAPLO patients were treated with post-SCT cy, and 39 patients received other protocols. Patient characteristics were balanced except for higher median age in the post-SCT cy group. Overall survival (OS) was significantly better for post-SCT cy treated HAPLO patients than for alternative haplo protocols ($p = 0.0052$, HR 0.43). More NRM deaths after alternative haplo protocols accounted for the difference in OS ($p = 0.032$, HR 1.8), whereas relapse rates were similar. Observed trends for better OS of post-SCT cy-treated patients held true separately for B- and T-cell lymphomas.

Comparison of post-SCT cy haplo-transplants with alternative donor types demonstrated similar OS of SIB-, MUD- and post-SCT cy haplo-transplants, although the patients undergoing haplo-transplants were in more advanced disease stages, poorer performance status and were older. OS of CORD and alternative haplo transplants were significantly worse compared to SIB, MUD and post-SCT cy haplo-transplants ($p < 0.001$), which was attributable to lower NRM ($p < 0.001$). Acute severe GvHD (grade 3–4) incidences were not different between donor groups, but post-SCT cy haplo-transplants had a trend towards lower chronic GVHD incidences.

Conclusions: Haplo-donors and immunosuppression with post-SCT cy is a valuable alternative to SIB or MUD transplants in NHL patients, whereas alternative HAPLO and CORD transplants are associated with increased post-transplant mortality.

'FOCUS ON…' SESSION: NOVEL AGENTS

035

LIPID ADDICTION OF DLBCL: INVOLVEMENT OF PI3K SIGNALLING AND POTENTIAL THERAPEUTIC STRATEGIES VIA FATTY ACID SYNTHASE SMALL MOLECULE INHIBITORS

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Introduction: Fatty acid (FA) metabolism is altered in several cancers through increased *de novo* synthesis of lipids via up-regulation of FASN and increased utilization of lipids via β-oxidation. The dependence of diffuse large B-cell lymphoma (DLBCL) on FA metabolism and associated signalling pathways are largely unknown.

Methods: Cerulenin [FASN inhibitor (i)], orlistat (FASN/lipoprotein lipase-i), and BKM120 (PI3K-i), small molecules, were studied in OCI-LY3, OCI-LY19, SUDHL4, SUDHL6, and SUDHL10 DLBCL cell lines for impact on FA inhibition and induction of cell death. Global transcriptome analysis of FASN inhibition was performed with Affymetrix Human 2.0 ST Genechip.

Results: Analysis of differentially expressed gene sets comparing germinal centre (GC) and non-germinal centre (non-GC) B-cell tumours with normal cells showed significant overexpression of genes related to PI3K and lipid metabolism in GC B-cell tumours. Further, OCI-LY3, SUDHL4, and SUDHL6 grown in the presence of lipoprotein-depleted serum showed exquisite sensitivity to lipid deprivation resulting in near complete cytotoxicity, as determined by MTT, and apoptosis by cleaved caspase 3 and PARP and AnnexinV/PI. Moreover, these effects were completely rescued by very low density lipoprotein supplementation to growth medium. Treatment with pharmacological inhibitors of FASN (cerulenin or orlistat) resulted in a dose- and time-dependent reduction in cell viability in all DLBCL cell lines. Furthermore, global transcriptome analyses after cerulenin exposure revealed prominent down-regulation of interferon (IFN) factors and PI3K signalling for all DLBCL cell types. Phosphorylation of PI3K substrates was down-regulated following cerulenin treatment in DLBCL cells, as predicted. In addition, treatment with BKM120 in OCI-LY3 (non-GC), SUDHL6, and SUDHL10 (GC) DLBCL cell lines was shown to strongly down-regulate FASN expression, and it resulted in dose-dependent cytotoxicity and apoptosis across all cell lines. Finally, treatment with BKM120 in combination with cerulenin potentiated cell death in OCI-LY3 and SUDHL10 cells.

Conclusions: Multiple FA pathways are constitutively activated in DLBCL, which were independent of cell of origin, and the survival of DLBCL appears strongly dependent on lipid metabolism. In addition, inhibition of FASN was regulated through PI3K-dependent pathways. Collectively, this work indicates that targeting FA metabolism may be used as a potential novel therapeutic strategy for DLBCL. Further investigation is required to delineate the mechanisms through which PI3K regulates FASN expression and to determine the clinical implications of FASN inhibition.

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EZH2 AND MYD88 MUTATIONS APPEAR ASSOCIATED WITH ANTITUMOUR ACTIVITY OF THREE NEW BET BROMODOMAIN INHIBITORS (BAY-5627, BAY-7575 AND BAY-8097) IN PRECLINICAL LYMPHOMA MODELS

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Introduction: Novel active compounds are needed to improve the outcome of lymphoma patients. The relevance of the epigenome as a therapeutic target is underlined by the proteins involved in transcription regulation and recurrently deregulated in patients. BET bromodomain inhibitors have shown anti-tumour activity in several pre-clinical lymphoma models, and objective responses have been observed in phase I studies. Here, we characterized three new BET bromodomain inhibitors (BAY-5627, BAY-7575 and BAY-8097) in a large panel of lymphoma models, correlating the sensitivity to genetic and biologic features.

Methods: Cells were exposed to increasing concentrations of each compound, and MTT assay was performed at 72 h. The panel comprised 27 diffuse large B-cell lymphomas (DLBCL), 10 mantle cell lymphomas (MCL), 3 splenic marginal zone

DOI: 10.1002/hon

lymphomas (SMZL), 9 anaplastic large T-cell lymphomas, 1 pro-lymphocytic leukaemia and 1 primary mediastinal large cell lymphoma. Sensitivity was correlated with baseline gene expression profiles (GEP) and genetic features.

Results: BAY-5627, BAY-7575 and BAY-8097 showed anti-tumour activity with median IC50 (50%-inhibitory concentration) values of 70 nM (95% CI, 54–90 nM), 100 nM (75–120) and 208 nM (157–260), respectively, with a very similar pattern of activity (*R* values, 0.78–0.9). The compounds had higher activity in B-cell than in T-cell models ($P < 0.001$), while no differences were observed among B-cell tumour types (DLBCL, MCL and SMZL) or DLBCL subtypes (ABC and GCB). The anti-tumour activity was mainly cytostatic, as demonstrated by LC50 (50%-lethal concentration) values higher than 1 μM in all the groups. However, depending on the compound, 10–16% (5–8/50) of the cell lines (DLBCL and MCL) presented LC50 values more similar to their IC50, indicating the occurrence of cell death. Indeed, 5/6 DLBCL cell lines exposed to the compounds for 72 or 96 h underwent apoptosis (Annexin-V/7-AAD staining). The anti-proliferative activity was not associated with *MYC*/*BCL2*/*BCL6* single/double translocations, *MLL2*, *FOXO1* mutations or *TP53* status. *EZH2* and *MYD88* mutations were associated with higher sensitivity among all the cell lines ($P = 0.018$ and 0.008, for BAY-5627) and within ABC- (MYD88, $P = 0.05$) or GCB-DLBCL (EZH2, $P = 0.04$). Transcripts with higher expression in the most sensitive DLBCL cells (BAY-5627 IC50 < 100 nM) were enriched of genes involved in JAK/STAT, IFN and BCR signalling, not of MYC targets, while the less sensitive DLBCL (IC50 > 100 nM) had higher expression of genes involved in cell cycle, chromatin structure and E2F1 targets.

Conclusions: BAY-5627, BAY-7575 and BAY-8097 showed promising activity in preclinical models of mature lymphomas, which strengthen the rationale for their clinical development. The identified mutations and features associated with response will need validation, but they also suggest possible combinatorial schemes.

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VENETOCLAX (ABT-199/GDC-0199) MONOTHERAPY FOR RELAPSED/REFRACTORY (R/R) MULTIPLE MYELOMA (MM): PHASE 1 RESULTS

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Background: The anti-apoptotic protein BCL-2 has been implicated in mediating the survival of MM cells. Venetoclax (VEN) is a potent, selective, orally bioavailable small-molecule BCL-2 inhibitor. VEN induces cell death in MM cell lines and primary samples *in vitro*. Certain genetic subtypes of MM cells are particularly sensitive to VEN, including t(11;14)-positive (pos) cells, which express a high ratio of *BCL2* to *MCL1* (VEN resistance factor). The current Ph 1 study evaluates safety, efficacy, and PK in pts with R/R MM, including those with cytogenetic abnormalities.

Methods: Primary objectives are to evaluate safety, PK, and RPTD; other objectives include preliminary efficacy and impact of chromosomal abnormalities. In dose-escalation cohorts, venetoclax was given PO daily at 300, 600, 900, or 1200 mg after a 2-week dose ramp-up. Pts were monitored for tumour lysis syndrome (TLS).

Results: As of 12/19/2014, there were 28 pts with median age 65 (12/16F/M); 9 ISS stage I, 11 stage II, and 6 stage III. Median (range) prior therapies: 6 (1–13). 23 had prior bortezomib (15 refractory), 26 lenalidomide (12 refractory), and 13 auto-HSCT. 10 pts had t(11;14), 2 had t(4;14), 4 had del 17p, and 13 had del 13q. AEs in ≥20% pts: diarrhoea (32%), nausea (32%), neutropenia (21%), and fatigue (21%). Grade 3/4 AEs (≥10%): thrombocytopenia (18%), anaemia (14%), and neutropenia (14%). 7 pts had SAEs, with 1 (epigastric pain) possibly related to venetoclax. 17 pts have discontinued (D/C): 14 due to PD, 2 for AEs (worsening shortness of breath or hypokalemia), and 1 withdrew consent; 11 still receiving therapy. 2 deaths occurred (both PD). 2 DLTs were seen at 600 mg (cohort was expanded): epigastric pain and nausea with abdominal pain. No pt had TLS. Preliminary PK ($n = 11$; 300 and 600 mg): mean C_{max} and AUC_{24} were ~dose-proportional with high intra-dose variability. 21 of 28 pts were evaluable for preliminary efficacy.

Abstract 037 Table 1. Best response by t(11;14) status

n (%)	t(11;14)-pos (*n* = 7)	t(11;14)-neg[a] (*n* = 14)	All evaluable pts (*n* = 21)
Complete response (CR)	1 (14%)	0	1 (5%)
Partial response (PR)	1 (14%)	0	1 (5%)
Minimal response	1 (14%)	0	1 (5%)
Stable disease	2 (29%)	9 (64%)	11 (52%)
Disease progression	1 (14%)	2 (14%)	3 (14%)
Discontinued	1 (14%)	3 (21%)	4 (19%)
Overall response rate (CR + PR)	2 (29%)	0	2 (10%)
Median (range) time on study (ToS), months[b]	5.1 (1.2–8.6)	1.9 (0.4–6.8)	2.5 (0.4–8.6)

[a]Status negative or undetermined.
[b]Defined as time from first dose to data cut-off (active patients) or last dose (discontinued patients).

M-protein response (mean best % change) was favourable in t(11;14) pts (−64.1% vs +21.9%, $p = 0.0196$) and del 13q-neg pts (−51.3% vs +1.4%, $p = 0.0220$).

Conclusions: Venetoclax monotherapy was well tolerated in heavily pretreated R/R MM. Responses (including CR), longer ToS, and reduced M-protein were observed in t(11;14) pts. These early results suggest that venetoclax has single agent activity, most prominently in t(11;14) pts. RPTD was achieved; the study is now enroling in the safety expansion cohort at 1200 mg (with 2-week ramp-up), and additional biomarker assessments are in progress.

038

TGR-1202, A NOVEL ONCE DAILY PI3Kδ INHIBITOR, DEMONSTRATES CLINICAL ACTIVITY WITH A FAVOURABLE SAFETY PROFILE, LACKING HEPATOTOXICITY IN PATIENTS WITH CLL AND B-CELL LYMPHOMA

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DOI: 10.1002/hon

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Background: TGR-1202 is a novel, next generation PI3Kδ inhibitor which lacks the hepatotoxicity associated with other PI3Kδ inhibitors and is active in patients (pts) with advanced heme malignancies (ASH 2014). Herein, we present updated safety and efficacy results from a Ph I study of TGR-1202 in pts with rel/ref CLL and B-cell lymphoma.

Methods: TGR-1202 administered orally once daily following a 3 + 3 dose escalation design. Eligible pts have rel/ref B-cell non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia (CLL), or other B-cell malignancy and an ECOG PS ≤ 2. Endpoints: safety, PK/PD, and efficacy.

Results: As of Feb 2015, 58 pts were evaluable for safety including CLL, FL, Hodgkin's (HL), DLBCL, MCL, and MZL. Median age 63 yo (range: 22–85), 72% male, ECOG 0/1/2: 19/38/1, median prior Tx: 3 (range: 1–14), 48% refractory to prior Tx. Safety: The only Gr ≥ 3 AE in ≥10% of pts was neutropenia (10%). AEs (all grades, all causality) in >20% of pts were limited to diarrhoea (34%), fatigue (31%), nausea (29%), and cough (26%). All diarrhoea events Gr1/2, except one Gr3 event occurring in a pt in Cyc 1, persisted for 2 days and resolved without dose interruption. Notably, in contrast to similar agents, no drug-related hepatotoxicity or colitis has been observed to date (ave time on study 7 Cyc). 2 episodes of Gr3 fatigue at 1800 mg of a new micronized formulation met the criteria for DLT. Expansion cohorts are open at 800 (CLL) and 1200 mg (NHL). Efficacy: A strong exposure–response relationship has been observed. Of 14 evaluable CLL pts, 13 (93%) achieved a nodal PR (median nodal ↓ of 76%), of which 7 (50%) achieved a PR per Hallek 2008 criteria. Responses have been limited in pts with DLBCL and HL. Of the 12 evaluable FL pts, 8 (67%) remain on study progression-free (range 7–99+ weeks), with 3 achieving a PR, notably being the 3 pts exhibiting the highest TGR-1202 plasma concentrations.

Conclusions: TGR-1202 is well tolerated in pts with rel/ref heme malignancies with no reported hepatotoxicity or colitis (41% of pts on study 6+ Cyc) and promising activity in CLL and NHL. Enrolment continues in expansion cohorts.

039

ONGOING, FIRST-IN-HUMAN, PHASE 1 DOSE-ESCALATION STUDY OF INVESTIGATIONAL SYK INHIBITOR TAK-659 IN PATIENTS WITH ADVANCED SOLID TUMOURS OR LYMPHOMA

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Introduction: Spleen tyrosine kinase (SYK) is a nonreceptor cytoplasmic kinase that binds to phosphorylated immunoreceptor tyrosine-based activating motifs. SYK plays a key role in B-cell receptor signalling-driven tumourigenesis, representing a potentially valid therapeutic target in various B-cell malignancies. TAK-659, a reversible SYK inhibitor, inhibited SYK activity in cell lines and showed antitumour activity in lymphoma xenograft models (Huck et al, ASCO 2014, Abstract 8580). Primary objectives of this study (NCT02000934) were to evaluate the safety and MTD of TAK-659; secondary objectives included preliminary antitumour activity and pharmacokinetics (PK) of TAK-659.

Methods: Pts aged ≥18 years with advanced solid tumours/lymphoma, for which standard treatment is not available or no longer effective, received oral TAK-659 daily (QD, 60–120 mg) in 28-d cycles. To determine the MTD, dose escalation proceeded via modified titration design based on DLT or any drug-related grade ≥2 adverse event (AE) during cycle 1 (C1). Blood samples for plasma PK assessments were collected pre-dose and post-dose between d1 and d15 of C1. Response assessments per RECIST for solid tumours and per IWG criteria for lymphoma were performed between d22 and d29 (pre-dose) of C2, C4, and C6, and every 3 cycles thereafter.

Results: At data cut-off (17 Dec 2014), 15 pts were enroled [11 pts at 60 mg, 7 solid tumour, 4 diffuse large B-cell lymphoma (DLBCL) and 4 pts at 120 mg, all solid tumour]; pts received a median of 2 cycles at 60 mg and all pts at 120 mg had 1 cycle. C1 DLTs occurred in 1 pt at 60 mg (grade 3 asymptomatic aspartate aminotransferase elevation) and 2 pts at 120 mg (grade 3 and 4 asymptomatic lipase elevation). Dose escalation is ongoing. Grade ≥3 drug-related AEs occurred in 2 (18%) pts at 60 mg and 3 (75%) at 120 mg; only anaemia (1 at 60 mg, 2 at 120 mg) and increased lipase (2 at 120 mg) were seen in >1 pt overall. Three pts discontinued due to AEs (1 at 60 mg, 2 at 120 mg), and 4 pts died on study (3 at 60 mg, 1 at 120 mg; deaths were not related to TAK-659). Plasma PK data was evaluated in 11 pts across both doses. PK of TAK-659 is characterized by rapid absorption (median T_{max} 2 h), moderate variability in steady-state exposures (47% coefficient of variation for d15 AUC_{tau}), mean peak-to-trough ratio of 2.7 at steady state, and mean accumulation of 2.7-fold after repeated QD dosing for 15 d. In 5 response-evaluable pts (4 DLBCL) by data cut-off, 2 DLBCL pts at 60 mg showed signs of response after 2 cycles, 1 PR, and 1 with 25% tumour reduction. Post data cut-off, 1 of 2 DLBCL pts at 80 mg achieved PR after 1 cycle. Updated results will be presented at the meeting.

Conclusions: TAK-659 60 mg QD appears to have acceptable safety ($n = 15$) and PK ($n = 11$) profiles to date. PK data support oral and continuous once-daily TAK-659 dosing. Preliminary response data show early signs of antitumour activity. Two expansion arms are planned for pts with DLBCL and chronic lymphocytic leukaemia.

040

ARGX-110, A NOVEL MONOCLONAL ANTIBODY TARGETING CD70, IS ASSOCIATED WITH BIOLOGICAL ACTIVITY IN PATIENTS WITH RELAPSED/REFRACTORY T-CELL LYMPHOMAS

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Introduction: CD70 is a cell surface marker of lymphocyte activation providing growth and survival signals via its receptor, CD27, as well as stimulating the

DOI: 10.1002/hon

immunosuppressive activity of regulatory T cells (T_{reg}). Overexpression of CD70 has been documented in a variety of solid and haematological malignancies. ARGX-110 is a novel anti-CD70 defucosylated monoclonal antibody active against both CD70-bearing tumour cells (via enhanced ADCC and CD70 blockade) and CD70-dependent T_{reg} stimulation (immune checkpoint inhibition).

Aim of the Study: We conducted a phase I trial to investigate the tolerability and maximum tolerated dose (MTD) of ARGX-110 in metastatic solid tumours and haematological malignancies. Results of the lymphoid malignancy cohort are reported in this abstract.

Population and Methods: Patients with advanced malignancies expressing CD70 by immunohistochemistry (>10% tumour cells, 2+/3+ intensity) have received ARGX-110 at doses ranging from 0.1 to 10 mg/kg administered intravenously once every 3 weeks until disease progression or withdrawal for toxicity.

Results: Fifteen patients with lymphomas have been included in the study: diffuse large b cell lymphoma (DLBCL, $n = 3$), peripheral T-cell lymphoma (PTCL-NOS, $n = 2$, angio-immunoblastic T-cell lymphoma (AITL), $n = 2$), Waldenström's macroglobulinemia (WM, $n = 3$), Hodgkin disease (HD, $n = 2$), mantle cell lymphoma (MCL, $n = 1$) and Sézary syndrome (SS, $n = 2$). Median age was 62.5 (range: 41–81) years, and median number of prior regimens was 4 (range: 1–7). All patients were refractory or had relapsed after prior treatment. Drug-related adverse events (AEs) were documented in 10 patients. Most were grade 1 or 2 in severity. The most frequent AEs were infusion-related reaction ($n = 4$, all grade 2) and fatigue ($n = 2$, all grade 2). Drug-related grade 3 anaemia and thrombocytopenia were documented in 1 patient with WM. No auto-immune AEs were observed. The MTD was not reached. We observed a biologic response in three patients: >90% reduction in the circulating malignant ($T\text{-plasmin}^+$) clone in 2 patients with SS (treated at 0.1 and 10 mg/kg, respectively) and resolution of auto-immune hemolytic anaemia associated with a minor response according to Cheson 2007 criteria in 1 patient with AITL (5 mg/kg dose). Clinical benefit/stable disease > 6 months was observed in 1 patient with SS (0.1 mg/kg).

Conclusion: ARGX-110 was well tolerated by this heterogeneous Phase 1 population of heavily pretreated patients, and further clinical investigation in T-cell lymphomas is warranted.

'FOCUS ON…' SESSION: SHORT- AND LONG-TERM TOXICITY OF LYMPHOMA THERAPIES

041

PULMONARY FUNCTION AND GRADE 3/4 CLINICAL EVENTS IN PET NEGATIVE PATIENTS TAKING PART IN THE INTERNATIONAL RATHL TRIAL (CRUK/07/033): A COMPARISON OF 12 VS 4 DOSES OF BLEOMYCIN

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Introduction: Bleomycin is associated with acute/chronic pulmonary toxicity that may be fatal. In the RATHL trial, patients (pts) who were PET negative after ABVD × 2 were randomized to continue with either ABVD × 4 or AVD × 4, and this provided an opportunity to compare the effects of 12 versus 4 doses of bleomycin on pulmonary function in a newly diagnosed, advanced Hodgkin lymphoma population.

Methods: 1214 pts, median age 33 years, were recruited to RATHL. 935 PET 2 negative pts were randomized to ABVD (Arm A) or AVD (Arm B), and 928 started their randomized allocation. Extra baseline demographics, smoking status, ethnicity and respiratory co-morbidities (CoMo) were collected in 735 pts. Linear regression was used to identify associations between baseline characteristics and changes in % diffusing capacity of the lung for carbon monoxide (DLCO) from baseline to end of treatment (EOT) or 1 year. This was adjusted for baseline DLCO to allow for regression to the mean. For pts whose DLCO was reduced >10% by EOT, Cox regression assessed time to return to within 10% of baseline values.

Results:19 grade 3/4 clinical pulmonary events occurred with more in Arm A (13/468, 3%) than Arm B (6/440, 1%).

Changes in DLCO from baseline to EOT and 1 year were available for 642 and 454 pts, respectively. Pts in Arm A had a mean 8.7% (95% CI: 6.10–11.36) greater fall in DLCO at EOT than those in Arm B, and although the mean for both groups improved by 1 year, the mean remained 6.06% (2.67–9.43) lower for pts in Arm A. 183/325 (63.1%) pts in Arm A and 117/317 (43.7%) pts in Arm B had a >10% drop in DLCO by EOT ($p < 0.001$); of these, 99 (54.1%) and 76 (65.0%), respectively, had returned to within 10% of baseline after a median of 18.7 months ($p < 0.001$). Further analyses of baseline characteristics were split by arm. In both arms, age and sex were significantly associated with DLCO at EOT with a larger fall seen with increasing age (≥2% fall in mean DLCO for each decade) and in females. There was also a suggestion of a relationship with ethnicity, with DLCO in Asian pts falling further than in Caucasians; these effects remained in the multivariable analysis. Age and CoMo were significantly associated with a fall in DLCO at 1 year for pts in Arm A, but this effect was not seen in Arm B.

In both groups, there was no clear association between smoking and DLCO at baseline or 1 year, or between smoking and time to recovery. There was no evidence to suggest that patients with a low baseline DLCO (<75% predicted) had a greater fall in DLCO by EOT.

Conclusions: 12 doses of bleomycin in ABVD × 6 were associated with more grade 3/4 clinical pulmonary events, significantly greater falls in DLCO and slower recovery towards baseline values than 4 doses of bleomycin in ABVD × 2. Whilst numbers are small in some groups, there is a suggestion that pts who were female, older or of Asian ethnicity were at greatest risk of a decline in pulmonary function. A low baseline DLCO did not appear to predict for a worse outcome.

042

SYK AND PI3Kδ PATHWAY INHIBITION RESULTED IN INCREASED RATES OF PNEUMONITIS: IMPLICATIONS FOR DEVELOPING FUTURE SMALL MOLECULE COMBINATIONS

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DOI: 10.1002/hon

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Introduction: B-cell receptor signalling including activation of SYK and PI3Kδ has been implicated in the pathogenesis of CLL, DLBCL, FL, and MCL. Single-agent kinase inhibitors that target BCR-mediated kinases have demonstrated clinical benefit; however, complete responses are infrequent, and relapse remains the norm. Simultaneous inhibition of distinct but tightly integrated kinases has the potential for synergistic antitumour activity, overcoming resistance and eradicating residual disease. Entospletinib (ENTO, GS-9973) and Idelalisib (IDELA) are both oral, selective inhibitors (SYK and PI3Kδ, respectively). *In vitro*,combination of these agents demonstrated synergistic anti-tumour activity in CLL and NHL cells.

Methods and Subjects: This Phase 2 trial planned to enrol patients (pts) with CLL or NHL (4 cohorts) of 40 pts each. All pts underwent intra-pt dose escalation starting with 400 mg of ENTO up to a maximum 800 and 100 mg of IDELA up to 150 mg; escalations occurred at 2, 2, and 4 weeks; both agents were given on a BID schedule. Tumour imaging was conducted at weeks 8, 16, and 24. Response was evaluated according to standard criteria.

Results: The study initiated in July 2013, and at time of study termination, 66 pts with CLL (35) or NHL (31) were enroled (14 FL, 6 DLBCL, 3 MCL, 3 MZL, 2 LPL/WM, and 3 SLL). Median age was 68 (range 28–92), 53% were male. The median number of prior treatment regimens was 3 (range 1–9), with 47% having progressed within 6 months (mos) of prior treatment. The study was terminated early due to the development of pneumonitis in 12 pts (18%), including grade 3 or 4 in 9 pts (14%) with 2 fatal events. Median time to onset of pneumonitis was 2.8 mos ranging from 1.7 to 4.9 mos. Pts presented with fever, progressive hypoxia, and ground glass pulmonary infiltrates by CT. Additional grade 3 or 4 adverse events/lab abnormalities occurring in >10% of pts included neutropenia (21%), rash (18%), pneumonia/lung infection (14%), and ALT/AST elevation (17%). The median treatment exposure was 2 mos (range, 0–6 mos); 21 (60%) and 7 (20%) of CLL pts achieved a partial response (PR) and stable disease, while 9 (29%) and 15 (48%) of NHL pts achieved a PR and stable disease, respectively. Correlative analyses demonstrate increased plasma cytokines including IL-6, IL-7, IL-8, and IFNγ, in pts developing pneumonitis.

Conclusions: Despite promising single agent activity in CLL and NHL, dual selective inhibition of SYK and PI3Kδ resulted in an unexpectedly high rate of pneumonitis and required early closure of the study. The current paradigm for developing combinations with novel agents and dose-limiting toxicity windows designed for myelosuppressive chemotherapy are not adequate. Future investigations combining agents that target BCR signalling require novel study designs and prolonged monitoring to ensure safety.

043

CARDIOVASCULAR DISEASE AFTER THERAPY FOR HODGKIN LYMPHOMA: A DETAILED ANALYSIS OF 9 COLLABORATIVE EORTC-LYSA TRIALS

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Introduction: Cardiovascular disease (CVD) following treatment is an important concern for cancer survivors, especially in young patients with a favourable prognosis. However, our current knowledge is limited by the retrospective nature of the available data: yes versus no to chemotherapy, and only prescribed radiotherapy dose or field type. The purpose of our study was to quantify the effect of individual exposure on the risk of CVD in a cohort of Hodgkin lymphoma patients treated in nine randomized trials from 1964 to 2004 ($n = 6658$).

Methods: The cumulative dose of anthracyclines and vinca-alkaloids, and the mean radiation dose to the heart, cardiac substructures, and carotid arteries were reconstructed individually from the clinical report forms. Incidence of CVD was reported during follow-up and through a patient-reported questionnaire, mailed in 2009 to 2010. A Cox proportional hazards regression analysis was performed to quantify the effect of initial chemotherapy and radiation on first cardiovascular event.

Results: Information on primary treatment was complete for 6039 patients; 41% were treated after 1995. A total of 703 first CVDs occurred; the most frequent events were myocardial infarction/angina, congestive heart failure, arrhythmia, and valvular disease. Based on initial treatment, only mean heart radiation dose and the cumulative dose of anthracyclines were significant predictors of CVD, with an increase in hazard ratio of 1.5% (95% CI: 0.6–2.4%) per 1 Gy mean heart dose and 7.7% (95% CI: 2.1–13.7%) per 50 mg/m^2 of anthracyclines. The effect of relapse treatment is currently being investigated.

Conclusions: The excess relative risk of cardiovascular disease from heart irradiation and anthracyclines is quantified at specific dose levels. The results of our study highlight the importance of the continued effort to limit unnecessary treatment exposure.

044

A RADIATION DOSE–RESPONSE RELATIONSHIP FOR RISK OF CORONARY HEART DISEASE IN SURVIVORS OF HODGKIN LYMPHOMA: A CASE–CONTROL STUDY

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DOI: 10.1002/hon

Introduction: The prognosis of Hodgkin lymphoma (HL) patients has improved tremendously over time, but treatment causes excess cardiovascular morbidity and mortality in long-term survivors. We aimed to identify risk factors for coronary heart disease (CHD), in particular to assess the cardiac radiation dose–response relationship and to quantify the separate and combined effects of radiation dose, chemotherapy and established cardiovascular risk factors.

Methods: A nested case–control study was conducted in a cohort of 5-year HL survivors, treated in the Netherlands between ages 5–50 years in the period 1965–1995 ($n = 2617$). Cases with CHD as first cardiovascular event were matched to controls on sex, age and date of HL diagnosis. Mean heart dose (MHD) was estimated using a recently developed method based on percentage cardiac contour within the field from simulation X-rays, equivalent dose in 2 Gy fractions (EQD2) of the dose prescribed to the mediastinum and a correction factor.

Results: The study included 337 cases and 986 matched controls. Median age at HL diagnosis was 32.5 years for both cases and controls. The median time to CHD was 17.7 years (range 5.1–41.8 years). 90% of the cases and 79% of the controls received mediastinal radiotherapy. The median dose prescribed to the mediastinum was 37 Gy (range 20–43 Gy). Preliminary analyses show that patients treated with mediastinal radiotherapy had a 3.0-fold increased risk of developing CHD (95% CI: 1.7–5.3). Patients treated with mediastinal RT before age 26 had a 6.8-fold increased risk of developing CHD (95% CI: 1.6–29.9). Preliminary radiation dosimetry analyses were based on 163 cases and 511 controls. The median MHD was 22.0 Gy (range 4.1–38.4 Gy). Compared to patients without radiation exposure of the heart, CHD risks increased for patients with MHDs of <20, 20–25, 25–30 and ≥30 Gy by factors of 1.2, 1.6, 2.5 and 1.8, respectively (p_{trend}: 0.02). Findings regarding the precise shape of the dose–response curve will be available in June. Smoking at time of HL diagnosis was associated with an increased risk of CHD (odds ratio (OR): 1.3, 95% CI: 1.01–1.8). Smoking did not modify the risk of CHD after mediastinal RT. Diabetes mellitus (OR: 1.7, 95% CI: 1.2–2.4) and hypercholesterolemia (OR: 3.2, 95% CI: 2.4–4.4) at end of follow-up were also independently associated with increased CHD risk but did not modify the effect of MHD.

Conclusions: Risk of CHD increases with increasing MHD. The shape of the dose–response curve is currently being studied. The effect of MHD was not modified by smoking at HL diagnosis or by diabetes mellitus or hypercholesterolemia at the end of follow-up.

045

ANTICOAGULANT/ANTIPLATELET THERAPY CONCOMITANT WITH IDELALISIB IN CHRONIC LYMPHOCYTIC LEUKAEMIA AND INDOLENT NHL: USE AND OUTCOMES

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Introduction: Chronic lymphocytic leukaemia (CLL) and indolent NHL (iNHL) both tend to occur in the elderly, who may have comorbidities that increase the risk of thrombosis. Use of anticoagulant (AC)/antiplatelet (AP) therapy is associated with both advanced age and the presence of CLL or NHL. Idelalisib (IDELA) is a selective oral PI3Kδ inhibitor approved for use in relapsed CLL [in combination with rituximab (R)] and indolent non-Hodgkin's lymphoma (as monotherapy). The use and outcomes of AC/AP therapy in IDELA registrational clinical trials were characterized in this post hoc analysis.

Methods: Frail patients with relapsed CLL (including those with any degree of thrombocytopenia) were randomized to receive a combination of continuous IDELA 150 mg BID or placebo (PBO) with 8 R doses in the phase 3 Study 312-116 (NCT01539512). In the phase 2 Study 101-09 (NCT01282424), patients with refractory iNHL received IDELA 150 mg BID until disease progression or unacceptable toxicity. Grade 1, 2, and ≥3 bleeding events using MedDRA preferred terms and CTCAE were analysed.

Results: A total of 343 patients participated in the 2 trials. In the phase 3 CLL study, grade ≥3 thrombocytopenia was reported at baseline in 18 patients (16%) on IDELA + R and 31 (29%) on PBO + R. In each study, 45% of patients used concomitant AC/AP; the most common were aspirin, enoxaparin, and warfarin. AC/AP use was more frequent in patients treated with IDELA + R versus PBO + R. The proportion of patients with bleeding events was similar with IDELA, IDELA + R, and PBO + R. Of the 28 patients receiving warfarin, 9 had bleeding events [3 IDELA + R (all grade 1); 2 PBO + R (all grade 1); 4 IDELA pts (grade 1, $n = 3$; grade 2, $n = 1$)]. Grade ≥3 bleeding events occurred in 1 IDELA + R, 1 PBO + R, and 3 IDELA patients.

Conclusions: AC/AP use involved almost half of the IDELA registrational trial population. Overall, rates of bleeding events were moderate and similar with IDELA + R versus IDELA + PBO; grade ≥3 events were uncommon. There was no specific trend observed with AC/AP and bleeding events in the 2 arms of the CLL study.

Abstract 045 Table 1.

	CLL		iNHL
n (%)	IDELA + R *n* = 110	PBO + R *n* = 108	IDELA monotherapy *n* = 125
Patients receiving AC/AP	60 (55)	38 (35)	56 (45)
Aspirin	42 (38)	21 (19)	30 (24)
Enoxaparin	11 (10)	6 (6)	19 (15)
Warfarin	8 (7)	9 (8)	11 (9)
Patients with ≥1 bleeding event (any grade)			
Overall	15 (14)	20 (19)	17 (14)
Grade 1/2	14 (13)	19 (18)	14 (11)
Patients on AC/AP	*n* = 60	*n* = 38	*n* = 56
Received AC	9	4	13
Received AP	5	3	6
Event at any time	10 (17)	6 (16)	14 (25)
Event on AC/AP	7 (12)	5 (13)	8 (14)
Patients not on AC/AP	*n* = 50	*n* = 70	*n* = 69
Event at any time	5 (10)	14 (20)	3 (4)

Funded by Gilead Sciences.

DOI: 10.1002/hon

046

PATTERNS OF COGNITIVE DIFFICULTIES AFTER TREATMENT FOR LYMPHOMA

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Introduction: Research into managing the late effects of cancer treatment has predominantly focused on physical and emotional components, rather than cognitive side effects. Patients describe the 'chemo-brain' phenomenon, but little research has been done to understand and manage the cognitive difficulties experienced by lymphoma patients following treatment. The aim of our study was to establish the type and extent of impaired cognition in working age patients following lymphoma treatment, and to explore how these relate to well-being.

Methods: We studied 32 lymphoma patients (Hodgkin $n = 19$, diffuse large B-cell $n = 10$, and Burkitt $n = 3$), between 16 and 50 years old (median 36.5 years) and between 6 months and 6 years following treatment with chemotherapy +/− radiotherapy (median 3.05 years). None had received radiotherapy to the brain. Patients were compared to age, education, and sex-matched controls on 12 tests of cognitive function (measuring memory, attention, and executive functions) and 6 self-assessment questionnaires (measuring subjective cognitive failures, mood, fatigue, and quality of life).

Results: Compared to matched controls, patients performed poorly on verbal fluency ($F_{1,61} = 4.22$, $p < 0.05$), task switching ($F_{1,61} = 4.61$, $p < 0.05$), visuospatial abilities ($F_{1,61} = 36.7$, $p < 0.001$), delayed visual memory ($F_{1,61} = 7.34$, $p < 0.01$), recognizing previously studied words ($F_{1,61} = 9.44$, $p < 0.001$), and made more errors when processing information quickly ($F_{1,61} = 7.17$, $p < 0.01$). They reported higher levels of cognitive failures ($F_{1,58} = 12.1$, $p < 0.001$), fatigue ($F_{1,58} = 13.4$, $p < 0.001$), depression ($F_{1,58} = 99.8$, $p < 0.01$), anxiety ($F_{1,58} = 22.2$, $p < 0.001$), and a low quality of life ($F_{1,58} = 25.8$, $p < 0.001$). In patients, better verbal memory was associated with a higher quality of life ($r = 0.46$, $p < 0.01$) and lower depression levels ($r = -.37$, $p < 0.05$). Difficulties in processing information rapidly were associated with a lower mood ($r = -.39$, $p < 0.05$). Time since treatment was related to performance decreases in task switching ($r = -.47$, $p < 0.01$) and increases in delayed memory ($r = 0.43$, $p < 0.05$).

Conclusions: Following treatment for lymphoma, patients exhibited difficulties in tests of memory, executive functions, processing speed, and visuospatial ability, suggestive of frontal-subcortical pathology. Associations between cognition, aspects of well-being, and time since treatment were observed, but better powered trials are needed to establish potential causal relationships between these factors. Research designed to understand which of these difficulties are temporary or long lasting, and to establish their neural base, is warranted in order to target potential biological mechanisms. Once these knowledge gaps have been filled, we will be able to devise and test appropriate interventions to address the cognitive impairments associated with treatment for lymphoma.

SESSION 1: LYMPHOMA BIOLOGY AND GENOMICS I

047

GERMINAL CENTRES AND LYMPHOMAGENESIS

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Germinal centres (GCs) are involved in the selection of B cells secreting high-affinity antibodies and are also the origin of most human B cell lymphomas. Recent progress has been made in identifying the functionally relevant stages of the GC and the complex trafficking mechanisms of B cells within the GC. These studies have identified transcription factors and signalling pathways that regulate distinct phases of GC development. Notably, these factors and pathways are hijacked during tumourigenesis, as revealed by the analysis of the genetic lesions associated with various types of B cell lymphomas, including follicular lymphoma (FL) and diffuse large B cell lymphoma (DLBCL). These analyses have identified the recurrent alteration of important mechanisms, including those involved in chromatin remodelling, transcriptional control of apoptosis and differentiation, NF-kB activation and immune escape. The differential involvement of these pathways in the various subtypes of DLBCL (*de novo* GCB and ABC subtypes, and those deriving from the transformation of FL and chronic lymphocytic leukaemia) suggests alternative therapeutic strategies in the management of these malignancies.

048

WHOLE EXOME SEQUENCING OF REFRACTORY AGGRESSIVE B-CELL LYMPHOMAS IDENTIFIED RECURRENT MUTATIONS OF THE *EXPORTIN 1* GENE (*XPO1*) IN PRIMARY MEDIASTINAL B-CELL LYMPHOMA SUBTYPE. A LYSA STUDY

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Introduction: Although diffuse large B-cell lymphoma (DLBCL) has largely benefited from immunochemotherapy combinations in the past decade, 30% to 40% of patients still do not respond to treatment or relapse rapidly, underlying the need for understanding the mechanisms involved and identifying predictive biomarkers. To address this issue, we performed whole exome sequencing (WES) in a cohort of refractory/relapsed (RR) DLBCLs included in the LYSA clinical trial program.

Methods: Fourteen normal/tumoural pairs of exomes from patients who progressed or relapsed within 12 months were sequenced on a HiSeq2000 platform. These cases had been classified as GCB ($n = 4$), ABC ($n = 4$), primary mediastinal B-cell lymphoma (PMBL) ($n = 4$) subtypes or unclassified ($n = 2$), using Affymetrix U133 + 2 arrays. To refine the results obtained with WES, we performed high-throughput targeted resequencing in 216 patients enroled in the LNH03 LYSA (LYmphoma Study Association) clinical trial programme and sequenced additional cohorts by Sanger method to assess the frequency and specificity of the candidate mutations.

Results: WES identified several recurrent somatic mutations that are under investigation. Among candidate mutations, we identified a recurrent point mutation (p. E571K) targeting the Exportin 1 gene (*XPO1*) in 2/4 RR PMBL. *XPO1* encodes a cargo protein mediating the nuclear export of multiple tumour suppressor proteins, including p53. Targeted resequencing was performed in four cohorts including

DOI: 10.1002/hon

GEP-defined PMBLs ($n = 36$, cohort 1), PMBLs defined by histological criteria ($n = 81$, cohort 2), Hodgkin lymphoma (HL) cases and gray-zone lymphomas (GZL) (22 HLs and 19 Reed–Sternberg micro-dissected HLs, 20 GZLs, cohort 3) and DLBCL-NOS ($n = 194$, 81 ABC, 81 GCB, 32 unclassified, cohort 4). *XPO1* mutations were observed in 16/36 (44%) cases of PMBL cohort 1 and 10/81cases (12%) of cohort 2. By contrast, no mutation was observed in cohort 3, and only 3 cases (1.5%) were mutated in cohort 4. Copy number gains of *XPO1* were observed in 8/22 PMBL cases (3 to 7 copies). In cohort 1, *XPO1* mutation was significantly associated with a decreased PFS and OS [3y OS = 74% CI95% (55–100) as compared to 3y OS = 95% (86–100), log-rank test $p = 0.04$]. The highly recurrent E571K variant (27/29 mutations) is located in the NES binding groove related to the cargo function. The effects of KPT-185, a small inhibitor of nuclear export (SINE) that blocks *XPO1*-dependent nuclear export, were assessed in 3 PMBL cell lines (MedB-1, Karpas1106 and U2940) using cell proliferation and apoptosis assays. The *XPO1* E571K mutated MedB-1 cells showed a decreased response to the compound compared to the 2 other cell lines which are *XPO1* wild type.

Conclusions: *XPO1* mutations represent a new distinctive genetic feature of the PMBL subtype and could be a biomarker with prognostic impact. The effect of the recurrent E571K variant on the cargo function of XPO1 is currently investigated.

049

RECURRENT SOMATIC MUTATIONS IN DIFFUSE LARGE B CELL LYMPHOMA ASSESSED BY HIGH-THROUGHPUT TARGETED SEQUENCING HIGHLIGHT MOLECULAR SUBTYPES' GENETIC DIVERGENCE: A LYSA STUDY

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Introduction: Gene expression profiling (GEP) has identified three main subtypes of diffuse large B cell lymphoma (DLBCL): germinal centre B-cell like (GCB), activated B-cell like (ABC) and primary mediastinal B-cell lymphoma (PMBL). Although next generation sequencing (NGS) has enabled a more detailed genomic characterization of DLBCL, the mutation patterns observed in different studies have been heterogeneous, highlighting the need for a consensus gene panel. Furthermore, the prognostic value of these mutations has yet to be evaluated in prospective clinical trials.

Methods: A Lymphopanel designed to identify mutations in 34 genes important for lymphomagenesis was used to sequence tumour DNA of 216 patients with *de novo* DLBCL in prospective, multicentric and randomized LNH-03B clinical trials led by the Groupe d'Etude du Lymphome Adulte (GELA), using the Ion PGM™ system. GEP identified 81 GCB, 81 ABC, 32 unclassified and 22 PMBL samples.

Results: The Lymphopanel was informative for 96% of patients: 13975 variants were identified with a median sequencing depth of 225x, and 1075 (7.7%) were validated after filtering for variant quality, SNPs and functional relevance. The mean mutation rate per megabase was 56.7, and PMBL subtype was significantly more mutated than the other subtypes ($p = 7.4 \times 10e{-}5$).

We confirmed that the ABC subtype is dominated by NFkB pathway mutations (46% of variants), the GCB subtype is dominated by epigenetic pathway mutations (34% of variants) and the PMBL subtype is frequently mutated in JAK-STAT and immunity pathways (respectively 27% and 22% of variants). The Lymphopanel confirmed subtype-enriched mutations such as *MYD88*, *PIM1*, *CD79B* and *IRF4* variants among ABC, *BCL2*, *CREBBP*, *EZH2*, *MEF2B* and *TNFRSF14* variants among GCB and *SOCS1*, *STAT6* and *TNFAIP3* variants among PMBL.

The immunity pathway seems to play a crucial role in PMBL, with respectively 59%, 36% and 45% of patients presenting mutations in *B2M*, *CD58* and *CIITA*. These mutations mostly lead to truncated proteins, suggesting a predilection for immune system escape in PMBL. *ITPKB*, *MFHAS1* and *XPO1* mutations, whose roles in lymphomagenesis are unclear, were heavily weighted toward PMBL and presented mutations in respectively 40.9%, 27.3% and 31.8% of PMBL patients. *XPO1* mutations especially were almost exclusively PMBL specific.

Furthermore, clinical correlations were found for certain gene mutations among the total cohort, notably with age (*B2M*, *CD79B*, *CIITA*, *KMT2D*, *MYD88*, *SOCS1*, *STAT6*, *ITPKB* and *XPO1*), Ann Arbor stage (*B2M*) and IPI (*B2M* and *STAT6*). *TNFAIP3* mutations in ABC patients were associated with a less favourable OS (FDR $<$ 10e $-$ 3) and PFS (FDR = 0.014).

Conclusion: This large, prospective study demonstrates the contribution of NGS with a consensus gene panel to the goal of precision therapy in DLBCL, enabling the identification of recurrent mutations with clinical, therapeutic and prognostic impact.

050

A MODIFIED AUTOANTIGEN IS THE FIRST MOLECULARLY DEFINED RISK FACTOR AND A DOMINANT ANTIGENIC TARGET/STIMULUS OF THE B-CELL RECEPTOR FROM ABC-TYPE DLBCL

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Introduction: Chronic antigenic stimulation may play an important role in the pathogenesis of malignant lymphomas. We have previously shown that hyperglycosylated neurabin/SAMD14 is the antigenic target of the B-cell receptor (BCR) of 2/3 of all primary CNS lymphomas, but BCR for peripheral DLBCL has not been defined to date.

Methods: BCRs were expressed as recombinant Fabs based on corresponding pairs of functional variable region heavy and light chain genes, which had been amplified from isolated genomic DNA of snap-frozen lymphoma specimens and DLBCL-derived cell lines. The purified BCR-Fabs were checked for binding to proteins expressed on macroarrays of human cDNA expression libraries.

Results: The BCR from 10 DLBCL cell lines (5 of the germinal centre type and 5 of the activated B-cell type) were tested on the protein macroarray. None of the GC-type BCR reacted with any of the proteins expressed on the protein macroarray, but the BCR from 3/5 (60%) of the ABC-derived cell lines reacted with ARS2 (arsenite resistance protein 2), a conserved mammalian protein which is important for microRNA biogenesis. Isoelectric focusing and phosphatase treatment of ARS2 derived from ABC cell lines with a BCR specific for ARS2 revealed that ARS2 was hypophosphorylated (hypo-ARS2) in the respective cell lines. Analysis of peripheral blood lymphocytes from patients with DLBCL of unknown cell of origin and healthy controls revealed that 5/100 (5%) of patients, but only 1/200 (0.5%) of controls were carriers of hypo-ARS2, resulting in a 10×

DOI: 10.1002/hon

increased risk for healthy carriers of hypo-ARS2 to develop DLBCL. All patients with BCRs targeting ARS2 had polyclonal antibodies against ARS2 in their serum.

Conclusions: Hypo-ARS2 is the first molecular defined risk factor for DLBCL identified to date. The increased risk for healthy carriers of this posttranslational modification to develop DLBCL supports the hypothesis of chronic antigenic stimulation as an important factor in the pathogenesis of DLBCL and indicates that posttranslationally modified autoantigens are a frequent target and stimulus for DLBCL-BCR. That antibodies against ARS2 are found in the respective patients suggests that the DLBCL evolves from a polyclonal B-cell response against this autoantigen. Investigations into the mechanism underlying the hypophosphorylation of ARS2 are underway, and therapeutic options will be discussed.

Supported by Wilhelm-Sander-Stiftung.

051

THE ROLE OF TONIC BCR SIGNALLING IN A MOUSE MODEL OF MYC-DRIVEN LYMPHOMA

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Introduction: Burkitt lymphoma (BL) is an aggressive, germinal centre-derived, B cell lymphoma resulting from chromosomal translocations juxtaposing the MYC proto-oncogene to immunoglobulin (Ig) gene regulatory sequences. BL tumour cells feature tonic, antigen-independent, B cell antigen receptor (BCR) signalling. Whereas several indirect evidences suggest that BCR influences BL growth, a formal genetic proof for this is yet missing. This work overcomes this limitation establishing a mouse model of BL where ablation of the BCR is genetically induced in established tumour B cells.

Methods: We analysed lambda λ-MYC transgenic mice carrying a loxP-flanked pre-rearranged Ig V_H gene (B1-8f) to conditionally ablate BCR expression in established MYC-driven mature B cell lymphomas, by means of Cre/loxP technology.

Results: Primary B cell lymphomas isolated from lambda λ-MYC; B1-8f mice resembled phenotypically and histologically human BL. Tumours expressed consistently surface IgM and displayed tonic BCR signalling. Upon induction of Cre-mediated recombination, *ex vivo* isolated primary lymphomas showed efficient ablation of surface BCR expression. BCR-less tumour B cells grew both *in vitro* and *in vivo* in the absence of their BCR^+ counterparts. Instead, strikingly, competition assays based on *in vitro* co-cultures and co-injection of BCR^+/BCR^- lymphomas in immunoproficient synegenic mice revealed a consistent counter selection of tumour cells lacking the antigen receptor. Data to be presented will reveal key signalling pathways through which the BCR sustains optimal fitness of MYC-transformed B cells. Moreover, we report the isolation of tumour clone variants that have escaped BCR dependence in competition assays. Whole exome sequencing on the latter clones revealed the existence of a conserved set of genes conferring resistance of MYC lymphomas to BCR inactivation.

Conclusions: We applied genetics to study the role of tonic BCR signalling in a mouse model of MYC-driven lymphoma. We show that whereas inactivation of the antigen receptor does not prevent growth of lymphoma B cells, BCR is essential for optimal fitness of MYC-transformed B cells. These findings are relevant for BL biology as they explain why BL cells retain consistently BCR expression in spite of undergoing continuous Ig somatic hypermutation. Our results are also relevant for the clinical setting as they predict that anti-BCR therapies may unleash BCR-less clones that are otherwise outcompeted by their BCR^+ counterparts.

052

RECURRENT MTORC1-ACTIVATING *RRAGC* MUTATIONS ARE A FEATURE OF FOLLICULAR LYMPHOMA

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Background: Follicular lymphoma (FL) is an incurable B-cell malignancy characterized by the t(14;18) and mutations in one or more components of the epigenome. Whilst frequent gene mutations in signalling pathways, including JAK-STAT, NOTCH and NF-κB, have also been defined, the spectrum of these mutations typically overlaps with closely related diffuse large B-cell lymphoma (DLBCL). Through a combination of discovery exome and extended targeted sequencing, we reveal recurrent somatic mutations in components of the mTOR pathway uniquely enriched in FL patients.

Methods: Whole exome sequencing (WES) was conducted on 24 FL matched tumour/normal samples from 5 patients that had multiple episodes of FL but had not undergone transformation. Prevalence screening and clonality were assessed by targeted deep sequencing of candidate genes in an extension cohort of 176 FL cases and further Sanger sequencing in 329 related mature B-cell NHLs. Wild-type (WT) and mutant *RRAGC* were expressed in HEK-293T for downstream functional experiments.

Results: Novel somatic mutations in *RRAGC* encoding a Rag GTPase protein (RagC) were identified in 4 of the 5 untransformed FL WES cases. Clonal density plots demonstrated the *RRAGC* mutations resided within the dominant clone, with temporal analyses of biopsies from the same individual showing mutation stability with disease progression. *RRAGC* mutations were identified in 16% of our FL extension cohort but were rare or absent in other B-NHL entities. Mutations were mainly missense (93%), heterozygous and clustered within the nucleotide-binding domain of RagC. The somatic origin of 10 of these mutations was confirmed by sequencing of matched constitutional DNA. A search for additional mutations in regulatory components upstream and downstream of the pathway uncovered co-occurring mutations in 2 subunits of the v-ATPase complex, in more than half of *RRAGC* mutated cases.

DOI: 10.1002/hon

Together, Rag GTPases form a super-complex with the v-ATPase, Ragulator and SLC38A9 on the lysosomal surface and promote amino acid-mediated activation of the mechanistic target of rapamycin complex 1 (mTORC1). By transiently expressing RagC mutants ($RagC^{muts}$) in HEK-293T cells, we showed increased co-immunoprecipitation with a key regulatory component of mTORC1, raptor, compared to wild-type. Furthermore, stable overexpression of the $RagC^{muts}$ not only activated mTORC1 but rendered it resistant to leucine or arginine deprivation, as indicated by phosphorylation of a canonical mTORC1 substrate. Finally, whilst all $RagC^{muts}$ were activating, mutations at amino acid residue Serine-75 led to mTOR activation by specifically disrupting nucleotide binding.

Conclusion: Overall, the emergence of frequent, gain-of-function *RRAGC* mutations that are clonally represented and maintained during progression provides an excellent candidate for therapeutic targeting.

SESSION 2: ADVANCES IN CLL

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IN-VIVO STUDIES OF KINETICS IN CHRONIC LYMPHOCYTIC LEUKAEMIA PROVIDE DEFINITIVE EVIDENCE OF LYMPH-NODE RE-ENTRY AND SUGGEST THAT THERE IS A NON-PROLIFERATIVE SUB-CLONE

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Introduction: It is now accepted that chronic lymphocytic leukaemia (CLL) is a two-compartment disease. Proliferation takes place in the lymph node compartment as a result of interaction with antigen and co-stimulation from the microenvironment. Proliferated cells are subsequently released into the peripheral blood compartment. It is assumed that some cells re-circulate to the lymph node to undergo a further round of proliferation, but this has not been formally studied *in vivo*. Characterization of trafficking is essential to fully understand the biology of disease and to provide insight into the mechanism of action of novel agents that impact on this process.

Methods: We have performed *in-vivo* studies in 10 patients using deuterated (D2) glucose to label a cohort of proliferating cells that could be tracked by serial sampling of blood and lymph nodes. Deurterium enrichment was analysed in flow-sorted CLL cells using gas chromatography mass spectrometry.

Results: Analysis of release and disappearance of recently proliferated cells into the peripheral blood demonstrated significant heterogeneity. Median time to maximum release into the circulation was 7 days (range = 2–28 days), and a median of 75% labelled cells remained detectable after 56 days (range = 3.7–88.5%).

Fine needle aspirate sampling of the lymph node revealed increased labelling in the lymph node between days 7 and 28, confirming re-entry of recently proliferated cells from the peripheral blood.

Previous studies have shown that recently proliferated cells have low CXCR4/high CD5 and that CXCR4 is re-expressed, enabling lymph-node re-entry. We measured D2 enrichment in sub-clones defined by CXCR4/CD5 and found that CXCR4 was re-expressed by labelled cells after 14 days. Interestingly, a separate sub-clone with constant high CXCR4/low CD5 was identified that appeared to be non-proliferative, that is, remained a discrete unlabelled population throughout the study period.

Having identified a non-proliferative sub-population, we investigated whether this population had an anergic phenotype (low sIgM expression). We sub-sorted labelled CLL cells according to sIgM and found that D2 enrichment was minimal in cells with lowest sIgM expression.

Conclusions: Here, we have provided insights into the rate of release and disappearance of recently proliferated CLL cells and have provided the first *in-vivo* evidence of re-homing of CLL cells to the lymph-node compartment. Secondly, these studies have identified a quiescent sub-population that may be unresponsive to agents that target the B cell receptor. Lastly, we have provided evidence that deuterium labelling could be used as a tool for studying the mechanism of drug action in CLL.

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THE INTERNATIONAL PROGNOSTIC INDEX FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL-IPI)—AN INTERNATIONAL META-ANALYSIS

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Background: In the era of more effective treatments for CLL, the established clinical staging systems (Rai/Binet) do not accurately discriminate between prognostic groups. Despite the introduction of several new prognostic markers, there is no system integrating the major clinical, biological and genetic variables into one widely accepted prognostic system. We therefore performed a comprehensive analysis of 26 prognostic factors to develop an internationally applicable prognostic index for patients (pts) with CLL (CLL-IPI).

Methods: The data from 8 phase III trials from France, Germany, UK, USA and Poland comprised our full analysis set (FAS) including 3472 previously untreated pts at early and advanced stage of disease with a median age of 61 years (yr) (range 27–86) and a median observation time (OT) of 80 months (ms). The FAS was randomly divided into training and internal validation datasets [TD, 2308 (67%); IVD, 1164 (33%)]. Methods of multivariable statistics were applied, and the main end point was overall survival (OS). Handling of missing data was performed with complete case analysis using a 4 step-down procedure accounting for the degree of completeness of data. The model was externally validated in a third dataset composed of 845 newly diagnosed CLL pts from Mayo Clinic [median age 62 yr (range 25–89); median OT 63 ms].

Results: Based on 1192 (52%) pts from the TD, 5 independent predictors for OS were identified: age (cut-off, 65 yr), clinical stage (Binet A/Rai 0 vs Binet B-C/Rai I–IV), del(17p) and/or *TP53* mutation, *IGHV* mutation status (MS) and serum β_2-microglobulin (B2M) [cut-off, 3.5 mg/L]. Applying weighted grading of the independent factors based on regression parameters, a prognostic index was derived separating 4 different risk groups [low (score 0–1), intermediate (score 2–3), high (score 4–6) and very high risk (score 7–10)] with significantly different OS [93%, 79%, 64% and 23% OS at 5 yr, respectively, $p < 0.001$; *C*-statistic $c = 0.724$ (95%

DOI: 10.1002/hon

CI, 0.69–0.76)]. This multivariable model was confirmed on the IVD [575 (49%) pts; 91%, 80%, 52% and 19% 5-yr OS, $p < 0.001$, $c = 0.777$ (95% CI, 0.73–0.82)]. In the external Mayo set, the 5-yr OS of the CLL-IPI risk groups was 97%, 91%, 68% and 21% [$p < 0.001$, $c = 0.790$ (95% CI, 0.74–0.85)]. Further, the CLL-IPI provides accurate estimation regarding time to first treatment within this cohort (81%, 47%, 30% and 19% patients free from treatment at 5 yr, $p < 0.001$).

Conclusion: We report the development and validation of a weighted, integrated prognostic score and index derived from a broad number of established prognostic markers. The resulting CLL-IPI combines the most important genetic risk factors (*IGHV* MS, del(17p)/*TP53* mutation) with traditional clinical stage, age and B2M into an easily applicable prognostic index for CLL pts. Moreover, it both discriminates between prognostic groups and may help to inform regarding current treatment recommendations.

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EFFICACY OF IBRUTINIB VERSUS OFATUMUMAB BY CYTOGENETIC AND CLINICAL SUBGROUPS IN A PHASE 3 TRIAL IN PATIENTS WITH PREVIOUSLY TREATED CLL/SLL

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Background: Implications of various prognostic factors and genetic markers in CLL/SLL are not fully understood. Ibrutinib (Imbruvica®) is a first-in-class, once-daily, oral, covalent BTK inhibitor approved by EMA for adult CLL pts with ≥1 prior therapy and first-line CLL pts with del17p or *TP53* mutation who are unsuitable for chemotherapy. Here, we report updated efficacy results analysed by cytogenetics or prior therapies and safety from the phase 3 RESONATE™ study of ibrutinib (ibr) versus ofatumumab (ofa) in relapsed/refractory CLL/SLL.

Methods: Pts ($N = 391$) received oral ibr 420 mg daily until disease progression/unacceptable toxicity or IV ofa up to 24 weeks. Primary endpoint was IRC-assessed PFS; secondary endpoints were OS and IRC ORR (Byrd et al, NEJM 2014). Pts on ofa were allowed to crossover to ibr at interim analysis. Investigator-assessed efficacy and safety are presented.

Results: Pts were randomized to ibr ($n = 195$) or ofa ($n = 196$). Median age was 67 years. Pts had a median 3 (ibr) or 2 (ofa) prior therapies. At baseline, 32% had del17p, 32% del11q, 24% complex karyotype (≥3 abnormalities), and 68% unmutated *IGHV*; 30% had mutations ($N = 266$) in *NOTCH1*, 30% *SF3B1*, 48% *TP53*, and 2% *MYD88*. Median PFS was significantly longer for ibr versus ofa [NR vs 8.1 months (HR 0.106, 95% CI 0.073–0.153, $P < 0.001$)]; 12-month PFS was 84% versus 18% ($P < 0.001$). ORR was 90% for ibr versus 25% for ofa ($P < 0.0001$); 8% of ibr pts achieved PR with lymphocytosis, and 6% had CR/CRi. Objective response rate and 12-month PFS by subgroup are presented in the Table. Compared with ofa, improvement of ORR and PFS with ibr was independent of baseline genetics, complex karyotype, or number of prior therapies ($P < 0.001$ for all). PFS was significantly improved in ibr pts with 1 versus >1 prior therapy (median PFS = NR for each; HR = 3.108; 95% CI 0.959–10.07; $P = 0.046$). In ofa pts, *NOTCH1*, complex karyotype, unmutated *IGHV*, del17p, and del11q were associated with inferior PFS.

Median treatment duration was 16 months for ibr versus 5 months for ofa. Most AEs were grade 1. Most common grade 3/4 AEs for ibr were neutropenia (18%), pneumonia (9%), thrombocytopenia (6%), anaemia (6%), and hypertension (6%). Atrial fibrillation was reported in 7% of ibr pts. 76% of ibr pts continue treatment on study.

Conclusions: Consistent with phase 2 results (Byrd et al. NEJM 2013), ibr significantly improved PFS, OS, and ORR versus ofa in CLL/SLL pts with ≥1 prior therapy,

Abstract 055 Table 1. Investigator-assessed efficacy outcomes

	12-month PFS[a]		ORR[a]	
Subgroup, %	**Ibrutinib (*n* = 195)**	**Ofatumumab (*n* = 196)**	**Ibrutinib (*n* = 195)**	**Ofatumumab (*n* = 196)**
All patients	84%	18%	90%	25%
Median prior therapies				
1	94%[b]	22%	100%[b]	24%
2	84%[b]	30%	79%[b]	33%
≥3	80%[b]	10%	78%[b]	16%
Del11q	89%	8%[b]	79%	10%[b]
Del17p	79%	17%[b]	86%	19%
Complex karyotype	72%	3%[b]	74%	3%[b]
IGHV				
Unmutated	86%	13%[b]	86%	23%
Mutated	86%	29%[b]	75%	24%
Novel gene mutations[a]	**Ibrutinib (*n* = 121)**	**Ofatumumab (*n* = 145)**	**Ibrutinib (*n* = 121)**	**Ofatumumab (*n* = 145)**
NOTCH1	85%	11%[b]	83%	23%
SF3B1	87%	16%	84%	23%
TP53	88%	16%	80%	16%

[a] $P < 0.001$ for 12-month PFS (Z test) and $P < 0.0001$ for ORR (Fisher's exact test) except for 2 prior therapy, where $P = 0.0005$.

[b] $P < 0.05$ within an arm for overall PFS (unstratified log-rank test) and ORR (Fisher's exact test).

DOI: 10.1002/hon

independent of high-risk baseline genetics or number of prior therapies. Pts receiving ibrutinib in the 2nd-line had better outcomes than those with ≥2 prior therapies.

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BFR (BENDAMUSTINE, FLUDARABINE, RITUXIMAB) ALLOGENEIC CONDITIONING IMPROVES SURVIVAL IN CLL

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Background: Bendamustine is a novel active agent in CLL patients (pts) with favourable safety profile. We have recently reported the preliminary results of allogeneic stem cell transplantation (alloSCT) in lymphoma/CLL pts after BFR conditioning (Khouri et al. *Blood* 2014; 124:2306). Herein, we report more mature outcomes in CLL. Results and safety were compared with a previous regimen using FCR (fludarabine, cyclophosphamide, and rituximab).

Patients and Methods: We studied 89 CLL pts treated on 3 trials (one includes consecutive FCR-BFR) at our centre. Twenty-six (29%) pts received BFR, and 63 (71%) received FCR. The BFR regimen consisted of bendamustine 130 mg/m^2 IV daily on days −5 to −3 prior to transplantation, thus substituting the cyclophosphamide in the FCR regimen. The dose and schedule of fludarabine (30 mg/m^2 IV daily × 3) and rituximab (375 mg/m^2 IV on day –13 and 1000 mg/m^2 on days −6, +1, and +8) were similar in both regimens. Tacrolimus and mini-methotrexate were used for GVHD prophylaxis. In addition, thymoglobulin 1 mg/kg IV was given on days −2 and −1 in patients receiving a matched unrelated donor (MUD).

Results: Patient characteristics were similar in both groups and included median age (58 years in both), median number of prior therapies (3 in both), and % pts with β2-microglobulin >3 mg/L at study entry, refractory disease (38% in BFR vs 48% in FCR, $P = 0.4$), presence of 17p deletion [27% in BFR vs 24% (8/33) in FCR], unmutated status [19/21 (90%) of BFR vs 22/24 (92%) in FCR], and peripheral blood stem cell source (92% in BFR vs 87% in FCR). However, more pts received their transplants from unrelated donors in the BFR group than the FCR group (54% vs 32%, $P = 0.05$). Ten (38%) BFR pts versus 2 (3%) FCR pts did not experience severe neutropenia ($P < 0.001$), and 21 (81%) versus 39 (63%), respectively, did not require platelet transfusions ($P = 0.08$). Median follow-up time for pts in the BFR and FCR groups were 29 (range 19–60) and 104 (range, 34–195) months. The 3-year overall survival (OS) estimates in the BFR and FCR groups were 82% versus 51% ($P = 0.03$), and the 3-year progression-free survival estimates were 63% versus 27% ($P = 0.001$). The 3-year OS improvements were seen across the prognostic factors studied for BFR and FCR, respectively: MUDs (93% vs 30%), presence of 17p deletion (86% vs 50%), age >50 (79% vs 50%), β2-microglobulin >3 mg/L (73% vs 45%), >3 prior lines of therapy (70% vs 43%), and recent years of transplant (82% vs 47%). Treatment-related mortality was 11% and 27% ($P = 0.05$) at 2 years. The incidence of acute grade 3 GVHD was 4% and 10% in the BFR and FCR groups, respectively, despite the higher % of MUD transplants in BFR. Grade 4 acute GVHD was not observed in either group. The 3-year incidence of extensive chronic GVHD in the BFR versus FCR groups was 45% versus 58% ($P = 0.01$).

Conclusions: This is the first study to show that conditioning in alloSCT for CLL pts matters with an improved survival after BFR when compared to the FCR regimen.

SESSION 3: MANTLE CELL LYMPHOMA

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PI3K INACTIVATION AND REDOX STRESS MEDIATES THERAPEUTIC TARGETING OF CDK4 IN MCL

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Introduction: Cell cycle dysregulation is a hallmark of MCL due to aberrant cyclin D1 and CDK4 expression. By inhibiting CDK4/CDK6, we have developed a novel strategy that both inhibits proliferation of MCL cells and reprograms them for cytotoxic killing. We showed that (1) inhibition of CDK4/6 with an oral selective inhibitor palbociclib (PD 0332991, Ibrance) leads to early G1 arrest; (2) prolonged early G1 arrest (***pG1***) reprograms cancer cells to cytotoxic killing; (3) pG1 sensitization is amplified in synchronous S phase entry (***pG1-S***) upon palbociclib withdrawal; and (4) in a phase I trial in recurrent MCL, palbociclib inhibits CDK4 and induces pG1 in MCL cells, resulting in a durable clinical response. We have now investigated the mechanism for targeting CDK4/6 in a phase I clinical trial combining palbociclib with bortezomib at a reduced dose (1.0 mg/m^2) (PalBtz) in recurrent MCL.

Methods: Palbociclib was administered on days 1–12 of a 21-day cycle to induce pG1; bortezomib was given on days 8 and 11 in pG1 and on days 15 and 18 in pG1-S. To discover genes that mediate pG1 sensitization, we performed longitudinal whole exome- and transcriptome sequencing and Western blotting of MCL tumour cells isolated from lymph node biopsies at baseline, in pG1 (day 8) and in pG1-S (day 21), and functional analysis by gene targeting in MCL cell lines.

Results: PalBtz was well tolerated and exhibited a durable palbociclib dose-dependent clinical activity ($n = 16$), achieving one CR (>880 days) with only one progression at the optimal dose combination ($n = 6$). Palbociclib inhibited CDK4 and induced pG1 in all patients despite PI3K amplification, deletion and mutation in ATM or p53 or UTR in cyclin D1. pG1 led to PI3K inactivation and an imbalance in gene expression in primary MCL cells as only genes programmed for early G1 were expressed. However, <1% of the 1400 genes suppressed (not programmed) in pG1 in clinically responding patients were activated in non-responding patients. These genes were critical for redox homeostasis, suggesting that redox stress mediates pG1 sensitization.

Conclusion: This study represents the first investigation of genes that discriminate sensitivity from resistance in selective targeting of CDK4/CDK6 in human cancer. It is also the first integrative longitudinal analysis of whole exome- and whole transcriptome sequencing in concert with protein expression analysis and functional studies in primary lymphoma cells. Through longitudinal functional genomics, we demonstrate that palbociclib inhibition of CDK4 induces pG1 in all MCL patients, which sensitizes MCL for clinical response to bortezomib through PI3K inactivation and suppression of genes for redox homeostasis.

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PROGNOSTIC VALUE OF PROLIFERATION, CYTOLOGY, AND GROWTH PATTERN IN MANTLE CELL LYMPHOMA: RESULTS FROM RANDOMIZED TRIALS OF THE *EUROPEAN MCL NETWORK*

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DOI: 10.1002/hon

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Introduction: Mantle cell lymphoma (MCL) is an aggressive B-cell malignancy with considerable variability of clinical outcome that can be partly explained by clinical characteristics (MIPI: age, performance status, LDH and WBC) but also by histopathological features like cytology, growth pattern and tumour cell proliferation (Ki-67 index). Based on the data from two recently completed large randomized trials of the *European MCL Network*, MCL Younger and MCL Elderly, we aimed to comparatively evaluate these prognostic factors.

Methods: Patients with previously untreated MCL of stages II–IV were treated with of immuno-chemotherapy induction, followed by autologous stem cell transplantation in MCL Younger and by maintenance with rituximab or interferon-α in MCL Elderly. Experienced hemato-pathologists of the *European MCL Pathology Panel* retrospectively evaluated MCL cytology (blastoid: blastic or pleomorphic, non-blastoid: classical or small-cell), growth pattern (diffuse vs non-diffuse) and the Ki-67 index according to published guidelines (*Klapper et al., J Hematopathol 2009*). We performed multivariable Cox regression analyses on progression-free (PFS) and overall survival (OS) adjusting for MIPI to identify independent prognostic factors.

Results: Diagnostic tumour samples from 709 of 832 randomized MCL patients were collected at participating reference pathology labs in Germany, France, Belgium or Italy. The Ki-67 index was assessed in 508 patients (94 insufficient staining and 74 non-adequate material, e.g. bone marrow trephines). Median age was 62 years (range, 30–83), and according to MIPI, 41% had low, 35% intermediate and 24% high risk; 10% had blastoid MCL, and median Ki-67 index was 20% (2%–97%). In univariable analyses, blastoid cytology, diffuse growth and higher Ki-67 index were associated with shorter PFS and OS. However, only the Ki-67 index provided additional prognostic information to MIPI. By a simple combination of MIPI and the Ki-67 index, using the previously established 30% cut-off (*Determann et al., Blood 2008*), patients could be stratified into four groups with largely diverging PFS (5-year rates, 67%, 46%, 29% and 16%, $p < 0.0001$) and OS (5-year rates, 85%, 72%, 43% and 17%, $p < 0.0001$), independent of patient age and treatment strategy.

Conclusions: Our results from a large cohort of MCL patients treated according to current standard of care provide evidence that the Ki-67 overcomes cytology and growth pattern as prognostic factors in MCL. The new combination of Ki-67 index and MIPI may allow a refined risk classification.

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RITUXIMAB, BENDAMUSTINE AND CYTARABINE (RBAC500) AS INDUCTION THERAPY IN ELDERLY PATIENTS WITH MANTLE CELL LYMPHOMA: A PHASE 2 STUDY FROM THE FONDAZIONE ITALIANA LINFOMI

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Introduction: The combination of rituximab (R, 375 mg/m^2 intravenously [IV], day 1), bendamustine (B, 70 mg/m^2 IV, days 2 and 3) and cytarabine (800 mg/m^2 IV on days 2 to 4) was highly active in patients with mantle-cell lymphoma (MCL) in a phase 2 study (R-BAC; Visco et al, JCO 2013). Overall, this regimen was well tolerated, but haematologic toxicity was quite relevant, especially in terms of transient grades 3 to 4 thrombocytopenia (76% of cycles). Aiming at reducing the haematologic toxicity, the Fondazione Italiana Linfomi (FIL) designed a phase 2 trial adopting the R-BAC schedule but lowering cytarabine dose to 500 mg/m^2 (RBAC500).

Methods: Patients with newly diagnosed MCL, aged 61 to 80 years, not eligible for autologous transplant and fit according to the comprehensive geriatric assessment were enroled. The primary endpoints were complete remission rate (CR) measured by FDG-PET according to Cheson criteria 2007, and safety. Secondary endpoints included rate of molecular response (MR), progression-free (PFS) and overall survival (OS). The Bryant and Day two-stage design was adopted to calculate the sample size. FDG-PET results were evaluated with the five-point scale visual method of Deauville, while MR was assessed by nested-PCR using patient specific *IGH* or *BCL1* based targets.

Results: Starting from May 2012 to February 2014, 57 patients from 29 centres were recruited and treated. Central pathology revision was performed in 87% of cases. Median age was 71 years (range 61–79), 75% were males and 91% had Ann Arbor

DOI: 10.1002/hon

stage III/IV disease. Mantle Cell International Prognostic Index (MIPI) was low in 15%, intermediate in 40%, high in 45% and 9% had the blastoid variant. Overall, 53 patients (91%) received at least 4 cycles, while 36 (63%) had 6 cycles (median 5.3 cycles per patient). Fifteen patients (26%) discontinued treatment because of toxicity/adverse events that mainly consisted of prolonged hemo-toxicity between cycles (11). Only one patient discontinued due to progressive disease. Grade 3 or 4 neutropenia and thrombocytopenia were observed in 49% and 52% of administered cycles, respectively. Febrile neutropenia occurred in 6%. Extra-haematologic toxicity was mainly cardiac (5%). Overall response rate was 96%, and CR was 93%. The MR rate at the end of treatment was 76% on peripheral blood and 55% on bone marrow (BM) samples. With a median follow-up of 18 months (11–34), the projected 2-year PFS (± confidence interval) was 83% ± 5% and the OS 91% ± 4%. The MIPI score (high vs low/int), blastoid variant vs classical and the failure of achieving MR on BM samples were the only statistically significant adverse prognostic factors for PFS.

Conclusions: The R-BAC500 regimen can be safely administered as first line therapy to elderly patients with MCL. Hematologic toxicity is substantially reduced compared to our previous experience. With 93% of FDG-PET negative CR, 55% MR on BM and a projected 2-year PFS of 83% without maintenance therapy, the R-BAC500 regimen is a highly effective treatment for patients with MCL.

060

LENALIDOMIDE-RITUXIMAB-BENDAMUSTINE IN FIRST LINE FOR PATIENTS > 65 WITH MANTLE CELL LYMPHOMA: FINAL RESULTS OF THE NORDIC LYMPHOMA GROUP MCL4 (LENA-BERIT) PHASE I/II TRIAL

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Introduction: Mantle cell lymphoma (MCL) is mainly a disease of the elderly and associated with poor prognosis. Younger patients may be cured with high-dose chemotherapy, but for the older patient population, a standard therapy has to be defined. In this multi-centre open-label phase I/II trial, we evaluate the addition of lenalidomide (L) to rituximab-bendamustine (R-B) followed by 7 months of single agent lenalidomide in untreated patients > 65 years with MCL.

Methods: Eligibility criteria were patients >65 years, or ≤65 years, unable to tolerate high-dose therapy, with previously non-treated MCL, stages II–IV. Primary endpoints were maximally tolerable dose (MTD) of L, and PFS. Patients received six cycles q4w of L-B-R (L D1–14, B 90 mg/m^2 iv D1–2 and R 375 mg/m^2 iv D1) followed by single L, D1–21, q4w, 10 mg in cycles 7–8 and 15 mg in cycles 9–13.

Results: 51 patients were enroled between 2009 and 2013. Median age was 72 years. In phase I, MTD of L was defined as 10 mg when given cycles 2–5. Overall response rate (ORR) after six cycles was 91%, and complete remission rate (CRR) was 78%. 1.5 months after completed therapy, ORR was 80% and CRR was 78%. At the same time points, 56% and 64%, respectively, were MRD negative. At a median follow-up time of 31 months, median PFS was 42 months (95% CI 29.5–54.5) and median overall survival was 53 months. To date, 12 deaths have occurred, 6 due to progressive disease, 3 due to toxicity, 2 due to secondary primary malignancy and 1 of other cause. Infection was the most common non-haematological grade 3–5 event and occurred in 21 patients. Opportunistic infections occurred in 3 patients, 2 PCP and 1 CMV retinitis.

Conclusions: By omitting L from the first cycle, L-B-R may be a feasible regimen in patients with MCL with high response rates, also according to MRD. We observed a high degree of serious infections which limits its use to elderly patients.

This study was registered at http://clinicaltrials.gov as NCT00963534.

061

RITUXIMAB MAINTENANCE VERSUS WW AFTER R-DHAP PLUS ASCT IN UNTREATED PATIENTS WITH MCL: INTERIM ANALYSIS OF THE LYMA TRIAL, A LYSA STUDY

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The LyMa (ClinicalTrials.gov, NCT00921414) is a prospective randomized phase III trial conducted by the LYSA group. The study assessed the potential benefit of Rituximab maintenance after autologous stem cell transplantation (ASCT) in young previously untreated mantle cell lymphoma (MCL) patients (<66 years).

Patients were enroled at times of diagnosis. All patients received 4 courses of R-DHAP followed by ASCT (4 additional courses of R-CHOP were given to patients who did not reach at least a PR after R-DHAP). The conditioning regimen of ASCT was Rituximab (500 mg/m^2) plus BEAM. Patients achieving a complete or partial response after ASCT were randomly assigned between 3 years of Rituximab maintenance therapy (375 mg/m^2, one injection every 2 months) versus wait and watch (WW) (1:1).

The primary endpoint was EFS at 4 years after randomization, EFS being defined as death of any cause, disease progression, severe allergic reaction or severe infection to Rituximab. PFS and OS were secondary objectives. Herein, we present the first planned interim analysis. Analysis was performed by intention to treat.

From September 2008 to August 2012, 299 patients were included (one patient withdrawn his consent, data of one patient with incomplete data at time of the present analysis). Median age at registration was 57 years (27–65), and 236 (78.9%) patients were male. MIPI score was low in 53.2% ($n = 159$), intermediate in 27.4% ($n = 82$) and high in 19.4% ($n = 58$). In all, 257 (86%) patients proceeded to ASCT. The CR/CRu rates before and after ASCT were 81,4% and 92.7%, respectively. Last update was performed in November 2014. Median follow-up calculated from time of inclusion is 40.6 months. For all patients, median PFS and OS are not reached. The estimates 3-year PFS and OS are 75% (95% CI, 69.5–79.6) and 83.4% (95% CI, 78.5–87.3), respectively. Last randomization was done in February 2013. Two hundred and thirty-eight patients were randomized: 119 patients were assigned to rituximab maintenance and 120 to WW. The mFU ($n = 238$) calculated from date of randomization is 34.3 months. The 3-year EFS is 88.1% (95% CI, 79.5–93.2) in the Rituximab maintenance arm versus 73.4% (95% CI, 62.6–81.6) in the WW arm ($p = 0.0057$). The 3-year OS does not differ between the two groups (85.5 in the WW arm vs 93.1% in the maintenance arm; $p = 0.7175$). This planned interim analysis of the LyMa trial shows that 3 years of rituximab maintenance after

DOI: 10.1002/hon

R-DHAP plus ASCT as first-line treatment for young patients with MCL significantly improves EFS and PFS.

062

RESULTS OF A RANDOMIZED PHASE II TRIAL OF R-HCVAD VERSUS R-BENDAMUSTINE FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTS FOR PATIENTS WITH MANTLE CELL LYMPHOMA: US INTERGROUP S1106

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Introduction: Aggressive chemoimmunotherapy followed by autologous stem cell transplantation (ASCT) leads to durable remissions in young patients with mantle cell lymphoma (MCL). While R-HyperCVAD/MTX/ARA-C (RH) is highly effective, R-Bendamustine (RB) is an active regimen with outpatient administration. S1106 (SWOG) was conducted to choose the best induction regimen: (a) RH versus (b) RB followed by ASCT as a new intensive platform for future trials.

Methods: This randomized intergroup (SWOG/ECOG/CALGB) phase II trial had a primary objective to estimate 2-year PFS, with secondary assessment of response rates (ORR, CR and PR), overall survival, toxicities and MRD (minimal residual disease). Inclusion criteria were untreated stage III or IV or bulky stage II MCL, Cyclin D1 +, age > 18 but < 65, and adequate organ function. Randomization was stratified by MIPI score. Patients received either 4 cycles of RH or 6 cycles of R-B followed by ASCT.

Results: This study was closed after 53 patients were accrued: 18 in RH and 35 in RB. The groups were well balanced (Table 1) except for more women in the RH group. The ORR was 93.8% in RH as compared to 85.7% in RB among evaluable patients. The CR were 31.2% and 42.8%, and PR were 62.5% and 42.8% for RH and RB, respectively. 1 patient in RH and 5 patients in RB were inevaluable due to treatment discontinuation. RH had significantly more marrow toxicity with increased grade 3 and 4 thrombocytopenia (69% vs 17%), anaemia (56% vs 8.6%), neutropenia (63% vs 34%) and febrile neutropenia (31% vs 14%).

The study was closed prematurely due to inadequate mobilization in RH. Only 4 out of 16 patients on RH and 21 out of 35 patients in RB underwent ASCT (25 total); the rest could not complete treatment for reasons summarized in Table 1. The median follow-up among surviving patients is 23.7 m (range, 1–34.3 m). The estimated 1-year PFS were 94% and 87%, and 2-year PFS were 87% and 87% for RH and RB, respectively. MRD detection using Sequenta technology is being assessed.

Conclusions: Both RH and RB are active regimens with similar response rates, 1-year PFS rates and 2-year PFS rates. However, RH had more haematologic toxicity and stem cell mobilization rates were lower than expected in this multicentre trial. RB seems less myelosuppressive, but due to the premature closure, the study did not reach statistical significance for 2-year PFS to declare RB as an effective induction regimen. Identifying the optimal induction regimen in MCL remains an important area of investigation.

SESSION 4: PAEDIATRIC LYMPHOMA

063

NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA IN CHILDREN AND ADOLESCENTS: THERAPEUTIC APPROACHES AND GREY ZONE TO MATURE B-NHL

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Since the World Health Organization (WHO) recognized nodular lymphocyte-predominant Hodgkin lymphoma (nLPHL) as a distinct entity, new interest arose on applying different treatment approaches for classical Hodgkin lymphoma (cHL) and nLPHL. Children with nLPHL have an OS of approximately 100%, and nLPHL is frequently found as a localized, early stage disease. A meta-analysis of the French, UK, and German trial series showed that surgery alone was a feasible option for localized disease and yielded a long-term relapse-free survival of 67%. The North American Childrens' Oncology Group (COG) prospectively evaluated 52 paediatric patients with stage I single-node disease treated with surgery alone. Twelve patients who had stage IA relapse went on to receive chemotherapy and had a 3-year OS of 100%; none of the patients required radiation. For nLPHL patients with incomplete resection, anthracycline-free chemotherapy combinations may be more efficacious than RT-only approaches, such as those used in adult patients. A retrospective case series reported on a 3-year freedom from treatment failure of 74% and OS of 100% for patients receiving cyclophosphamide, vinblastine, and prednisone (CVP) chemotherapy. Only patients who did not have at least an unconfirmed complete remission (CRu) were treated with more intensive chemotherapy. In a prospective COG trial, 137 low-risk patients receiving 3 cycles of doxorubicin, vincristine, prednisone, and cyclophosphamide (AV-PC) had a 4-year EFS of 88% and a 4-year OS of 100%. Only 11 patients did not achieve CR with this treatment and required IFRT. In a large retrospective report on 394 adult patients with nLPHL treated on cHL studies with a combination of chemotherapy and RT, the relapse rate was not different between nLPHL and cHL patients.

In contrast, the entity grey zone lymphoma (GZL), as defined by the WHO, is a rare disease with very intriguing features but lacking standard treatment approaches. The features of GZL are intermediate between cHL and diffuse large B-cell lymphoma or primary mediastinal B cell lymphoma (PMBL) or between nLPHL and T-cell-rich B cell lymphoma or other variants. In a retrospective analysis, distinct histological patterns of nLPHL in adults have been correlated to prognostic factors. GZL has been successfully treated either according to protocols for cHL or mature B-cell non-Hodgkin lymphoma, depending on whether the diagnosis was made at initial presentation or at the time of relapse/progression. A preliminary analysis of the German HL and NHL registries revealed that paediatric patients with GZL were either treated with standard HL regimens, like OEPA-COPDAC ± RT, or according to intensive PMBL regimens, such as dose-adjusted rituximab, etoposide, prednisone, cyclophosphamide, and doxorubicin (DA-R-EPOCH). For successfully treating such rare entities, establishing a proper histopathological diagnosis, including confirmation by expert pathology review, is of utmost importance. Combined efforts for harmonization of diagnostic criteria across paediatric lymphoma study groups are required to facilitate global trials on these rare entities.

064

NEW TARGETS FOR THE TREATMENT OF MATURE B-CELL NON-HODGKIN LYMPHOMAS

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DOI: 10.1002/hon

Abstract 062 Table 1.

	R-HCVAD (*n* = 16)	R-Bendamustine (*n* = 35)
Age	58 (44–66)	57 (33–64)
Male	9 (56%)	32 (91%)
Female	7 (44%)	3 (9%)
Performance status		
0	10 (63%)	26 (74%)
1	6 (38%)	9 (26%)
Disease stage		
III	1 (6.2%)	3 (8.5%)
IV	15 (93.7%)	32 (91.4%)
Bulky disease		
No	15 (94%)	32 (91%)
Yes	1 (6%)	3 (9%)
B sx		
Yes	5 (31%)	10 (29%)
No	11 (69%)	25 (71%)
BM involvement		
Positive	13 (81%)	31 (89%)
Negative	3 (19%)	4 (11%)
Extranodal involvement		
Yes	14 (88%)	32 (91%)
No	2 (13%)	3 (9%)
Eleavated LDH		
Yes	5 (31%)	9 (26%)
No	11 (69%)	26 (74%)
MIPI score		
Intermediate/high	5 (31%)	13 (37%)
Low risk	11 (69%)	22 (63%)
All evaluable patients		
ORR	93.8% (95% CI: 69.8%, 99.8%)	85.7% (95% CI: 69.7%, 95.2%)
CR	5 (31%)	15 (43%)
PR	10 (63%)	15 (43%)
Inadequte	1 (6%)	5 (14%)
All evaluable patients		
1-year PFS	94% (95% CI: 63.2%, 99.1%)	87% (95% CI: 69.8%, 95.1%)
1-year OS	93% (95% CI: 61.3%, 99%)	91% (95% CI: 73.5%, 96.8%)
2-year PFS	87% (95% CI: 55.8%, 96.5%)	87% (95% CI: 69.8%, 95.1%)
2-year OS	86% (95% CI: 55.0%, 96.4%)	91% (95% CI: 73.4%, 96.8%)
Reasons for early off treatment or not going to ASCT	Failure to collect stem cells 5 Thrombocytopenia 4 Pancytopenia 1 Others 2	Failure to collect stem cells 1 Patient choice 4 Progressive disease 2 Neutropenia 1 Allergy 1 Seizure 1 Insurance denial 1 Others 3
Grade 3/4 haematological toxicities (induction only)	Anaemia 56% Neutropenia 63% Febrile neutropenia 31% Thrombocytopenia 69%	Anaemia 8.6% Neutropenia 34.3% Febrile neutropenia 14% Thrombocytopenia 17%
Grade 3/4 non-haematological toxicities (induction only)	ALT increased (6.3%) AST increased (6.3%) Catheter related infection (6.3%) Dehydration (6.3%) DLCO decreased (6.3%) Diarrhea (6.3%) Hyperglycaemia (12.5%) Hypokalemia (25%) Hypophosphatemia (25%) Nausea (6.3%) Rash (6.3%)	Hypokalemia (5.7%) Arthralgia (2.9%) Catheter related infection (2.9%) Enterocolitis infection (2.9%) Fatigue (2.95) Hypoalbuminia (2.9%) Hypophosphatemia (2.9%) Infusion related reactions (2.9%) Infection (2.9%) Myalgia (2.9%) Pain in extremity (2.9%)

(Continues)

DOI: 10.1002/hon

Abstract 062 Table 1. (Continued)

	R-HCVAD ($n = 16$)	R-Bendamustine ($n = 35$)
		Pruritis (2.9%) Rash (2.9%) Sore throat (2.9%) Tumour pain (2.9%) UTI (2.9%) Vascular access complication (2.9%)

Whole exome sequencing (WES) by next generation sequencing (NGS) has completely redefined the genetic landscape of mature B-cell non-Hodgkin lymphomas (NHL) by identifying recurrent single nucleotide variants and providing new therapeutic opportunities. Some of these somatic mutation target genes that play a crucial role in B-cell function (BCR signalling, NFκ-B pathway, Toll-like receptor signalling, and the PI3K pathway), immunity, cell cycle/apoptosis, or chromatin modification. Some driver mutations represent the Achilles Heel of the tumours and may be translated into therapeutic interventions. BCR signalling is targeted by inhibitors of the early components of the pathway, such as BTK, SYK, PKCβ, or PIK3δ, whereas the NF-KB pathway is targeted by upstream and downstream inhibitors (proteasome/ubiquitin complex) or more pleiotropic agents (lenalidomide). In this review, following an overview of the somatic mutations reported in mature B-cell malignancies, especially in diffuse large B-cell lymphomas and Burkitt lymphomas in both adults and children, we focus on activating and clustered driver mutations targeting genes including *MYD88, CD79A/B, EZH2*, and *CARD11* and discuss their clinical and therapeutic relevance in the precision medicine era.

065

RESULTS OF THE RANDOMIZED TRIAL EURO-LB02 ON LYMPHOBLASTIC LYMPHOMA IN CHILDREN AND ADOLESCENTS—A REPORT OF THE EUROPEAN INTERGROUP FOR CHILDHOOD NON-HODGKIN LYMPHOMA

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Introduction: To conduct an intergroup trial based on non-Hodgkin's lymphoma-Berlin-Frankfurt-Münster (NHL-BFM)90 protocol and to test in patients with T-lymphoblastic lymphoma (T-LBL) whether replacing prednisone by dexamethasone in induction increases event-free survival (EFS) and whether maintenance therapy can be reduced.

Methods: The reference arm was NHL-BFM90 (prophylactic cranial radiotherapy omitted). T-LBL patients were randomized to dexamethasone (10 mg/m^2/d) or prednisone (60 mg/m^2/d) in induction (Randomization 1) and maintenance therapy (Randomization 2) resulting in a therapy duration of 18 or 24 months (factorial design).

Results: 319 eligible patients (66 precursor-B-cell lymphoblastic lymphoma [pB-LBL], 233T-LBL, 20 ambiguous) were accrued when the stopping rule for toxic death (TD) monitoring was met and the trial had to be closed prematurely.

Median follow-up was 6.8 (3.0–10.3) years. For all patients, 5-year EFS was 82 $\pm$ 2% (12 TD, 5 secondary malignancy [SM], 43 non-response/relapse [CNS $n = 9$, all received prednisone in induction]).

186 of 239 patients eligible for Randomization 1 were randomized. 5-year EFS was 85 $\pm$ 4% for those assigned to dexamethasone ($n = 98$; 4 TD, 10 non-response/relapse, 1 SM) and 84 $\pm$ 4% for those assigned to prednisone ($n = 88$; 2 TD, 13 non-response/relapse, 1 SM). With dexamethasone, toxicity and treatment delay were significantly increased. For Randomization 2, 5-year EFS after month 18 was 96 $\pm$ 3% versus 94 $\pm$ 3% for patients receiving 18 ($n = 45$) and 24 months ($n = 67$) therapy, respectively.

Conclusions: The study questions could not be answered. Our data suggest dexamethasone to more efficaciously prevent CNS relapses in T-LBL patients but to be burdened with higher toxicity.

066

RELAPSES IN CHILDREN/ADOLESCENTS WITH MATURE B-CELL LYMPHOMA/LEUKAEMIA TREATED IN THE RITUXIMAB ERA—A STUDY OF THE SOCIÉTÉ FRANÇAISE DES CANCERS DE L'ENFANT

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Introduction: To describe relapsed B-cell lymphoma or leukaemia in children/adolescents initially treated with LMB regimen and their outcome in the

DOI: 10.1002/hon

rituximab era and to analyze response to second line chemo-immunotherapies, relapses in the French LMB2001 study were reviewed.

Methods: Between February 2001 and December 2011, 37 patients of 803 (4.6%) relapsed: 29 had Burkitt and 8 large-cell histology. There were 25 males and median age at diagnosis was 10.3 years (R, 1.9–17.9). One patient was initially treated in risk Group A, 24 in Group B and 12 in Group C. Twenty-seven patients had LDH level > 2 N.

Results: Mean time to relapse after diagnosis was 4.7 months (2.4; 10.8) in Burkitt lymphoma (BL) and 10.9 months (3.9; 31) in all large-cell histology. Twenty-one patients had a relapse in one site (5 in the central nervous system) and 16 at multiple sites. Relapses occurred in the primary site in 16 pts (43%), in the bone marrow in 14 pts (38%) and in the central nervous system in 11 pts (30%). Data on second line treatment are currently available for 29 patients. Among them, 24 received rituximab (R) as salvage therapy mainly in addition to ICE ($n = 15$ pts) and/or CYVE ($n = 13$ pts) and/or high-dose MTX ($n = 4$ pts) regimen. Salvage response (complete + partial remission) rates were 46% (6/13 patients) with R + CYVE after group B therapy and 50% (7/14 evaluable patients) with R + ICE after group B or C therapy. Eighteen patients also received high-dose chemotherapy followed by autologous ($n = 12$) or allogeneic ($n = 6$) transplant. With a median follow-up of 5.3 years, the 1- and 3-year survival rates of the 37 patients were 40.5% and 37.6%, respectively.

Conclusion: In the rituximab era, survival remains poor after relapse in children and adolescents with mature B-cell lymphoma/leukaemia. Response rates to second line chemo-immunotherapies including rituximab are insufficient, and new drugs are urgently need to improve disease control before consolidation.

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TREATMENT AND CHARACTERIZATION OF PATIENTS WITH BURKITT LYMPHOMA (BL): RESULTS FROM A SINGLE INSTITUTION IN NORTHERN UGANDA

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Introduction: BL is the most common paediatric cancer in equatorial Africa and is curable with chemotherapy alone. In 2004, the International Network for Cancer Treatment and Research, with investigators from African countries, initiated a uniform treatment protocol for newly diagnosed patients with BL. Here, we show results from St Mary's Hospital Lacor (LH), which joined the study in 2010.

Methods: Previously untreated patients with morphologically confirmed BL between 2 and 60 years with a signed informed consent were eligible for the study. Physical examination, abdominal/pelvic US, CXR, bone marrow (BM) exam and CSF cytology were performed at presentation. Treatment consisted of a First Line (FL) regimen that included CTX, VCR and low-dose MTX plus intrathecal therapy (IT) on days 1, 4 and 8. Patients who failed to achieve CR to FL or who relapsed early were eligible for a Second Line (SL) regimen consisting of ifosfamide, etoposide and cytarabine with IT therapy. Treatment was free of charge, but food and transportation were not. Most patients requested discharge between treatment cycles for socio-economic reasons. To allow this, we gave IT therapy on days 1, 2 and 3 in cycles subsequent to the first.

Results: 118 eligible patients were enroled at LH from March 2010 to December 2012 (follow-up 2–4 years). The M:F ratio was 1.9:1. Median age was 8 (range 2–46 years). The abdomen was the most common site of disease (79%) followed by jaw (42%) and CNS (25%), but not all patients had a CSF or BM examination at presentation. 98 of the 118 patients achieved CR, 12 partial response (PR), 2 NR and 6 were not evaluable for response (5, early deaths; 1, abandoned treatment). 28 patients (28.6%) relapsed. In all, 32 patients received SL therapy. EFS and OS for the entire series were 56% and 71%, respectively, at 3 years from presentation. In patients who received SL, OS was 48% at 2 years. Patients who received SL for relapse had improved survival compared to those who received SL for PR ($p = 0.012$). Compared to other participating institutions, LH patients had more CNS disease at presentation ($p = 0.0017$) and relapse ($p < 0.0001$). OS, however, was not significantly different.

Conclusions: Both FL and SL were feasible and OS excellent in African patients treated in a rural hospital where intensive monitoring and advanced supportive care are unavailable. Most patients achieved CR to FL, but patients with PR, or who relapsed, could be salvaged by SL. CNS disease at presentation was associated with a higher rate of CNS relapse and a worse outcome. Based on extensive previous data, we anticipate prolonged remission in patients who remain in CR for at least a year from the start of therapy or relapse. Results from LH are consistent with those from the other centres (>600 patients). It is likely that alternate cycles of FL and SL would further improve outcome.

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RISK-ADAPTED APPROACH FOR PATIENTS WITH RELAPSED OR REFRACTORY ALCL—FINAL REPORT OF THE PROSPECTIVE ALCL-RELAPSE TRIAL OF THE EICNHL

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Introduction: In retrospective analyses, survival of children and adolescents with relapsed anaplastic large cell lymphoma (ALCL) reaches more than 50% with consolidation strategies as different as Vinblastine monotherapy or autologous or allogeneic blood stem cell transplantation (SCT). We tested the efficacy of a risk-adapted approach stratified according to time of relapse and immunophenotype.

Patients and Methods: Between 10/2004 and 02/2014, 118 patients (pts) were registered to the prospective ALCL-Relapse trial. Re-induction therapy was ICM/ICE for patients with progression during first-line therapy (risk arm 1). Patients with CD3-positive relapse after initial therapy (risk arm 2) or those with relapse of a CD3-negative ALCL within 12 months after initial diagnosis (risk arm 3) were reinduced with high dose aracytidine and etoposide. Patients in risk arm 1 or risk arm 2 were eligible for allogeneic SCT after TBI-based conditioning (therapy group A, goal: increase of 3y-EFS to 50%). Patients in risk arm 3 were consolidated by autologous SCT after BEAM conditioning (therapy group B, goal: to maintain 3y-EFS of 53%). Patients with relapse of CD3-negative ALCL >12 months after initial diagnosis (risk arm 4) received weekly

DOI: 10.1002/hon

Vinblastine over a period of 24 months (therapy group C, goal: to maintain 3y-EFS of 75%). The autologous treatment group was closed 06/2012 after an interim analysis. Outcome analysis in treatment groups could be performed on 97 protocol pts (missing data, 2 pts; CNS-positive, 5 pts; exclusion criteria, 7 pts; group B after 06/2012, 7 pts).

Results: With a median follow-up of 5.0 years (0.5–9.7), the 3y-EFS and -OS of the 97 protocol pts were 59 ± 5% and 78 ± 4%, respectively. Survival was comparable for all 118 registered pts. The 3y-EFS and -OS of the 97 protocol pts according to treatment group were as follows: A (45 pts), 64 ± 7% and 73 ± 7%; B (31 pts), 35 ± 9% and 77 ± 8%; C (21 pts), 85 ± 8% and 90 ± 7%. Among group A pts, 19 in risk arm 1 had an EFS and survival of 41 ± 11% and 57 ± 11%, while EFS and OS of the 26 pts in risk arm 2 were 81 ± 8% and 84 ± 7%.

Conclusions: Autologous SCT with BEAM was not effective for patients with relapse of a CD3-negative ALCL. Allogeneic SCT offers a chance of cure for patients with progression during therapy. Survival of patients with relapse of a CD3-positive ALCL is high after allogeneic SCT, though this includes TBI-based myeloablative conditioning. Vinblastine monotherapy achieves a high rate of long-term remission in patients with a late relapse of CD3-negative ALCL. Vinblastine warrants further evaluation as front-line monotherapy in ALCL particularly in those patients identified to have good or intermediate risk disease.

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LYMPHOMA ASSOCIATED WITH A CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY SYNDROME: CLINICAL DESCRIPTION IN A FRENCH COHORT

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Introduction: The recessive constitutional mismatch repair deficiency (CMMRD) syndrome is a rare childhood cancer predisposition syndrome (OMIM #276300) due to biallelic deleterious germline mutations in MMR genes, leading to a broad spectrum of childhood malignancies including haematologic, brainandcolorectal cancers and a cutaneous phenotype commonly described as an association of café-au-lait macules (CALMs) and other features reminiscent of neurofibromatosis type 1 (NF1). Cells carrying MMR mutations are known to be resistant to several chemotherapy agents including methylating or thiopurine agents.

Methods: A retrospective analysis of all the 31 cases of CMMRD diagnosed in French constitutional genetics laboratories led to the identification of 11 patients who developed a lymphoma. We here describe their clinical characteristics, treatment and outcome.

Results: Overall, 12 patients developed 14 lymphomas: T lymphoblastic lymphomas in 11 cases, Burkitt lymphoma i1 and diffuse large B cell in 2. There were 9 males and 3 females. Median age at diagnosis of the first cancer was 5 years (1.2–20). Initial localizations were abdominal in two patients with B cell lymphomas and mediastinal in all other patients with B and T cell lymphomas combined with a pleural effusion in 2, a testicular localization in 1, liver involvement in 1 and bone marrow involvement in 1. All patients were classified as stage III according to the St Jude's staging system. The lymphoma was the first tumour in 8 patients and occurred as the second or third malignancy in 4 patients. All patients but one had associated cutaneous manifestations including café-au-lait spots.

Patients were treated according to the protocol adapted to the histologic subtype with no dose modifications: LMB89 for Burkitt lymphoma, RCHOP for the adult patient with large B cell lymphoma and LMT or EuroLB02 protocols for patients with T-NHL. One died before starting treatment, and one patient died of disease progression during induction. A complete remission was obtained in the other 10 patients. Two of them suffered from an early relapse at 8 and 10 months from diagnosis. Two patients had late (>4 years) relapses of a T-NHL which could be clearly identified as a second lymphoma in one case. Overall, 10 patients died (median survival from diagnosis of the first tumour: 4.3 years), 5 from lymphoma progression and 5 from a second malignancy.

Conclusion: Outcome of patients with CMMRD associated lymphoma is dismal. Specific treatment may be required to reduce the risk of failures in this rare syndrome.

SESSION 5: T-CELL LYMPHOMA

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T-CELL PROJECT: AN INTERNATIONAL, PROSPECTIVE, OBSERVATIONAL STUDY OF PATIENTS WITH AGGRESSIVE PERIPHERAL NK/T-CELL LYMPHOMA. LESSON FROM THE FIRST 1308 PATIENTS

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DOI: 10.1002/hon

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Introduction: Due to their uncommonness, a satisfactory understanding of prognosis and biology of peripheral NK/T-cell lymphomas (PTCLs) is still awaited. The T-Cell Project, promoted by the International T-Cell Lymphoma Project, builds on the retrospective study carried on by the network, and its aim is to prospectively collect accurate data to improve knowledge on these diseases.

Patients and Methods: Eligible patients (pts) with first diagnosis of aggressive, mature PTCLs were prospectively registered at a dedicated website via secure HTTP protocols, and baseline clinical, laboratory and disease extent data, therapy details, and outcome data were collected. Central review of diagnostic biopsy was planned.

Results: From Sept 2006 to Jan 2015, 1308 pts were registered by 73 sites from 14 countries worldwide, and 1248 have been validated so far (22 pts were excluded for various reasons and 38 considered as misdiagnosed after review). Main patients' characteristics, including distribution of histologic subtypes, are shown in the Table. PTCL-NOS is the most frequent subtype, accounting for 451 cases (36%). Distribution of subtypes among different geographic areas superimposes literature data, AITL being more frequent in Europe and USA (21% each), ALCL, ALK− in South America (25%) and NK cell in Asia (29%). Most patients were at low/low-intermediate risk according both to IPI and PIT (61% and 60%). Therapy data were available for 959 pts. Chemotherapy alone or in combination with radiotherapy was the preferred choice in 90% of pts. Antracycline- and etoposide-containing regimens were adopted in 84% and 22% of pts, respectively (both in 12%). Stem cell transplant was adopted to consolidate initial response in 7% of pts, with different geographic distribution (USA 14%, EU 8%, Asia 6% and South America 2%). With induction therapy, 451 (54%) pts achieved a CR and 159 (18%) a PR. After a median follow-up of 35 mos, 518 deaths have been recorded (41%). Five-year overall (OS) and progression-free survivals (PFS) were 44% (95% CI 40–47) and 33% (95% CI 30–37), respectively. The ALCL, ALK+ showed the best 5-year OS (73%, 95% CI 61–82).

Conclusions: T-Cell Project confirms that an international collaboration is feasible and productive. The generally poor outcomes observed in the vast majority of PTCL subtypes highlight the urgent need for more efficient treatment strategies. In this respect, the bio-repository of the study could serve as a valuable source for the development of new and possibly more effective targeted therapies.

Abstract 070 Table 1.

Patients' characteristics (1248)	N	%
Age, years; mean (range)	56 (18–89)	
Male gender	757	61
Histology:		
PTCL, NOS	451	36
AITL	223	18
ALCL, ALK−	179	14
ALCL, ALK+	107	9
NKTCL	138	11
Extranodal PTCLs, other	107	9
Unclassifiable PTCLs	43	3
ECOG-PS > 1 (1118)	285	25
B-symptoms (1118)	550	49
Stages III–IV (903)	621	69
Therapy given with curative intent (959)	887	92

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THE GENETIC LANDSCAPE OF HEPATOSPLENIC T-CELL LYMPHOMA REVEALS NOVEL STRATEGIES FOR TREATMENT AND RISK-STRATIFICATION

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Hepatosplenic T cell lymphoma (HSTL) is an aggressive form of non-Hodgkin lymphoma that is characterized by a young age of onset and an unusually dismal prognosis. Little is known about the role of genetic mutations in the disease. Here, we describe the application of whole exome sequencing of 30 HSTLs to define the genetic landscape of the disease. The histone methyltransferase *SETD2* was found to be the most frequently mutated gene in HSTL. SETD2 mutations were predominantly silencing frameshift and nonsense mutations indicating *SETD2* as a novel tumour suppressor in HSTL. An integrated analysis of genetic features with clinical outcomes identified associations between isochromosome 7q and SETD2 mutations and overall survival in HSTL patients.

In addition, HSTLs were characterized by frequent mutations in *STAT5B*, *SMARCA2*, *ARHGEF28*, *PIK3CD* and *TET1*. Further functional studies of *STAT5B* and *PIK3CD* mutations in HSTL showed cooperative roles in regulating IL2 signalling and cellular proliferation/survival. Interestingly, none of the HSTL mutated genes found are frequently mutated in other T cell lymphomas. Conversely, we did not observe mutations in HSTL in genes previously associated with other T cell lymphomas including *RHOA*, *TET2* and *IDH2*. We also sequenced the only known mouse model of HSTL and found significant overlap in mutations and pathways related to chromatin modification, signal transduction, DNA repair and cell cycle progression in both human and mouse tumours.

Our work thus defines the genetic landscape of HSTL and implicates novel gene mutations linked to HSTL pathogenesis, therapeutic targets and clinical outcomes.

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A PTCL, NOS SUBSET WITH MOLECULAR AND CLINICAL FEATURES SIMILAR TO AITL

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DOI: 10.1002/hon

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Introduction: Peripheral T-cell lymphomas (PTCL) are rare and heterogenous disorders. The most common types in Europe are angioimmunoblastic T-cell lymphoma (AITL), thought to derive from follicular helper lymphocytes (T_{FH}), and PTCL, not otherwise specified (PTCL-NOS), an exclusion category. Up to 30% of PTCL-NOS, however, express T_{FH}-associated markers. Here, we compare the clinical and molecular features of T_{FH}-like PTCL-NOS with AITL and other PTCL, NOS.

Methods: 83 AITL and 63 PTCL-NOS cases (TENOMIC, LYSA) with available gene expression profiles (GEP) were included. PTCL-NOS were segregated according to T_{FH}-like features. AITL, T_{FH}-like and non-T_{FH}-like PTCL-NOS were compared in terms of pathological, clinical and molecular features (GEP; array comparative genomic hybridization; and mutational status of *TET2*, *DNMT3*, *IDH2* and *RHOA*).

Results: 27 of 63 PTCL, NOS, lacking AITL morphological features, were considered T_{FH}-like based on the expression of three T_{FH} markers in tumour cells (CXCL13, BCL6, CD10, ICOS, and PD1 and/or 2) the presence of some immunohistochemical features reminiscent of AITL (B-blasts, EBER+ cells, and FDC expansion).

Frequencies of occurrence of selected AITL-linked clinical features show that T_{FH}-like PTCL-NOS are statistically indistinguishable or similar to AITL but significantly different from non-T_{FH}-like PTCL-NOS (Table 1).

T_{FH}-like PTCL-NOS and AITL exhibited a similar frequency of *RHOA*, *TET2* and *DNMT3* mutations, which were either absent or rare in non-T_{FH}-like PTCL-NOS. *IDH2* were mutated almost exclusively in AITL (Table 1). CNVs of T_{FH}-like PTCL-NOS were intermediate between non-T_{FH}-like PTCL-NOS and AITL.

Using principal component analysis, GEP of T_{FH}-like PTCL-NOS cluster with AITLs without forming a T_{FH}-like only group. T_{FH}- and AITL-associated signatures were significantly enriched in T_{FH}-like more than in non-T_{FH}-like PTCL-NOS. Enrichment analysis also revealed differences in the expression of apoptosis-, proliferation-, hypoxia- and angiogenesis-linked signatures in T_{FH}-like versus non-T_{FH}-like PTCL-NOS.

Conclusion: T_{FH}-like PTCL-NOS exhibit clinical and molecular features either indistinguishable from AITL, or intermediate between non-T_{FH}-like PTCL, NOS and AITL, suggesting that they may represent high tumour-content AITL with partial microenvironment background loss.

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RADIATION THERAPY FOR PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA (PCALCL): AN INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP (ILROG) MULTI-INSTITUTIONAL EXPERIENCE

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Abstract 072 Table 1. Clinical features, mutations and CNVs in T_{FH}-like PTCL, NOS compared with non-T_{FH}-like PTCL, NOS and AITL

Clinical variables	AITL ($n = 87$)	TFH-like ($n = 27$)	Non-TFH-like ($n = 35$)	p-value[a]
Sex (M/F)	48/39	14/13	25/10	0.19
Stage (0–1/2–4)	1/79	1/24	4/29	0.03
ECOG (0–1/2–4)	36/38	16/6	21/11	0.07
IPI (0–2/3–5)	5/6	2/4	3/1	0.54
Coombs (+/−)	29/24	3/5	0/6	0.03
Hypergammaglobulinemia (<16/≥16 g/dL)	20/25	4/11	3/15	0.1
Mutations	**AITL ($n = 61$)**	**TFH-like ($n = 20$)**	**Non-TFH-like ($n = 24$)**	**p-value[a]**
TET2 (mut, %mut)	30 (49.2%)	13 (65.0%)	4 (16.7%)	$<1.0 \times 10^{-2}$
DNMT3 (mut, %mut)	19 (30.6%)	3 (15.8%)	1 (4.2%)	0.02
IDH2 (mut, %mut)	20 (33.3%)	1 (5.3%)	0 (0.0%)	$<1.0 \times 10^{-3}$
RHOA (mut, %mut)	32 (64.0%)	7 (35.0%)	0 (0.0%)	$<1.0 \times 10^{-7}$
Copy number variations	**AITL ($n = 74$)**	**TFH-like ($n = 22$)**	**Non-TFH-like ($n = 31$)**	**p-value[b]**
Average gains per sample	9	15	23	AITL vs TFH-like: 0.25; AITL vs non-TFH-like: 0.01; TFH-like vs non-TFH-like: 0.02
Average losses per sample	15	22	33	

[a]Fisher's exact test. [b]*T*-test.

DOI: 10.1002/hon

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Introduction: Primary cutaneous anaplastic large cell lymphoma (pcALCL) is a rare cutaneous T cell lymphoma where radiation therapy (RT) is often the primary modality of treatment. The purpose of this study is pool data from ILROG (institutions which specialize in the treatment of rare lymphomas) to determine if there is a dose response rate associated with tumour stage or outcome.

Methods: The study included a retrospective analysis of patients with pcALCL who received RT following initial diagnosis or for local failure after surgical excision. Data collected for each patient included the following: initial stage of disease, RT modality (electron/photon), total dose, fractionation, response to treatment and local recurrence. RT was delivered at the following participating institutions: Stanford University, Dana-Farber Cancer Institute, Yale University, Peter MacCallum Cancer Centre and University of Toronto.

Results: 49 patients (pts) were identified that met the eligibility criteria. 30 pts (61.2%) had stage T1a or T1b disease, 14 pts (28.6%) had stage T2a or T2b disease and 5 pts (10.2%) had stage T3a or T3b disease. 3 patients (6.1%) had extensive limb disease (ELD) at initial presentation or progressed to ELD.

58 distinct radiation fields were irradiated with a mean dose of 34.0 Gy (range 6–50.4 Gy). Complete response (CR) was achieved in 54 out of 58 irradiated fields (93.1%), and a partial response (PR) was achieved in 4 out of 58 fields (6.9%).

In the fields where a complete response was achieved, there was only 1 local recurrence (1.7%) after 36 Gy and this patient eventually died of disease. No other patients in the cohort died of disease. The median follow-up time for all pts was 57 months after completion of RT (range 0–187 months).

Conclusion: RT with doses $\geq$20 Gy is effective at achieving >92% CR for pcALCL regardless of tumour stage. Most members of ILROG used doses in the range of 30–40 Gy however lower doses, similar to those used for primary cutaneous follicle centre cell, and marginal zone lymphomas appear to be just as effective. These valuable contributions from members of ILROG allowed us to perform radiation dose analyses on this rare lymphoma.

Abstract 073 Table 1. Dose per Radiation Treatment Field and Response

Dose (Gy)	CR	PR	Total
6	1	0	1
20	4	0	4
25	2	0	2
26.6	1	0	1
30	10	0	10
30.6	4	0	4
34	0	1	1
35	3	1	4
35.1	2	0	2
36	12	0	12
37.5	1	0	1
40	10	0	10
43.2	1	0	1
44	1	1	2
45	2	0	2
50.4	0	1	1

074

TEN YEARS MEDIAN FOLLOW-UP OF THE NORDIC NLG-T-01 TRIAL ON CHOEP AND UPFRONT AUTOLOGOUS TRANSPLANTATION IN PERIPHERAL T-CELL LYMPHOMAS

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Introduction: From 2001 to 2007, we conducted a large phase II study (NLG-T-01) in systemic peripheral T-cell lymphoma (PTCL) to evaluate the upfront efficacy of CHOEP + autologous transplant. The full analysis of the trial, with 5 years median follow-up (FU), was previously reported (d'Amore et al, JCO 2012). Here, we present a long-term FU of the same study cohort.

Methods: 160 PTCL patients were originally enroled. ALK+ anaplastic large-cell lymphoma (ALCL) was excluded. FU began on the date of chemotherapy start and, for the present analysis, ended on Q3, 2014. Since the median age of the study population was rather high (median: 57 years) for a transplantation cohort, the selected outcome parameters included overall (OS), progression-free (PFS) and disease-specific survival (DSS). Time-to-event end points were calcuated by means of Kaplan–Meier estimates with 95% Greenwood confidence bands. Log-rank tests and Cox regression models were used to analyze prognostic factors at uni- and multivariate level.

Results: At a median FU of 10 years (range: 7–13 years), 71 of 160 intention-to-treat population (ITTP) patients were still alive and in remission. The causes of death for the 89 deceased patients were distributed as follows:

The 10-year OS, PFS and DSS for the whole ITTP were 41%, 38% and 51%, respectively (all CI95% within +/− 10% range). With regard to the 4 main histological subtypes, survival values for PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic (AILT) and enteropathy-associated T-cell lymphoma (EATL) did not differ substantially from the 5-year median FU analysis. Despite of 5 late deaths, 2 of which lymphoma-related due to late relapses, ALK-negative ALCL still had the best long-term outcome (10-year OS, PFS and DSS 48%, 48% and 67%, respectively). Two notable features from the multivariate analysis of long-term outcome determinants were (i) the significant impact of the IPI on both OS and DSS for PTCL-NOS and AILT, but not ALCL and (ii) a highly significant gender-specific outcome difference in favour of female PTCL patients (10-year DSS of 68% vs 47%).

Conclusions: This is by far the longest follow-up of PTCL patients prospectively treated with intensive chemotherapy and upfront autologous transplant. Although late lymphoma-related events were seen, the overall outcome is still encouraging. ALCL (only ALK-negative included) retained an outcome advantage compared to other major PTCL subtypes, which was not influenced by the IPI. Female patients had a markedly superior outcome overall and subtype specific. Efforts are ongoing to biologically characterize long-term remitters and primary refractory patients.

Abstract 074 Table 1.

Causes of death	Time from diagnosis <24 months	<60 months	≥60 months	Total
Lymphoma	56 (86.2%)	8 (50.0%)	4 (50.0%)	68 (76.4%)
Toxicity	6 (9.2%)	1 (6.3%)	0 (0.0%)	7 (7.9%)
Toxicity—off protocol	2 (3.1%)	0 (0.0%)	0 (0.0%)	2 (2.3%)
Second malignancy	0 (0.0%)	4 (25.0%)	1 (12.5%)	5 (5.6%)
Other causes	1 (1.5%)	3 (18.8%)	2 (25.0%)	6 (6.7%)
Unknown	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (1.1%)
N of deaths	65	16	8	89

075

5-YEAR FOLLOW-UP OF THE SMILE PHASE II STUDY FOR NEWLY-DIAGNOSED STAGE IV, RELAPSED OR REFRACTORY EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

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Introduction: Extranodal NK/T-cell lymphoma, nasal type (ENKL) is one of the uncommon subtypes of lymphoma, and its prognosis used to be poor. We previously conducted the SMILE phase II study for ENKL patients with newly diagnosed stage IV, relapsed or refractory disease, and have shown that the treatment response is significantly improved.

Methods: In the SMILE phase II study, patients were treated with 2 courses of SMILE, accompanied by the physician's choice of additional SMILE, and/or autologous/allogeneic transplant. The study protocol included a long-term follow-up of up to 5 years. Patient condition and survival data were updated as of November 2014.

Results: Data of all 20 survived patients were updated. No patients were lost during follow-up. The median period of survival was 74 months (range: 59 to 85 months). No patients received additional therapy other than SMILE or stem cell transplantation until relapse, as defined in the protocol. The overall survival (OS) and progression-free survival (PFS) at 5 years were 47% (95% CI: 31%–62%) and 39% (95% CI: 24%–54%), respectively. Three patients experienced relapse after the first analysis, but two patients died, one with disease and the other with chronic graft-versus-host disease. The other two patients were alive with disease, both of whom experienced recurrence of disease after autologous transplant.

Abstract 075 Table 1. The 5-year OS and PFS

Post SMILE therapy	*N*	5y-OS	(95% CI)	5y-PFS	(95% CI)
Allo SCT	17	53%	(28%–73%)	53%	(28%–73%)
Auto SCT	4	75%	(13%–96%)	25%	(1%–67%)
SMILE chemotherapy only (total 3–6 cycles)	17	35%	(14%–57%)	29%	(11%–51%)

Conclusions: These findings suggest that durable long-term survival can be obtained for ENKL patients by SMILE chemotherapy. The significance of autologous transplant should be determined by further studies with a large number of patients.

SESSION 6: INTERFERING WITH BCR-NFKB PATHWAYS

076

INTRODUCTION: BCR SIGNALLING AND SURVIVAL PATHWAYS IN LYMPHOMA

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Several lines of evidence support the role of B-cell receptor (BCR)-mediated survival signals in certain B-cell malignancies. The BCR complex includes membrane-bound immunoglobulin and the disulfide-linked heterodimer, Igα and Igβ (also termed CD79α and β). BCR signalling induces receptor oligomerization and phosphorylation of Igα and β immunoreceptor tyrosine-based activation motifs (ITAMS) by SRC family kinases. Following ITAM phosphorylation, the spleen tyrosine kinase (SYK) is recruited and activated, engaging additional adaptor proteins and initiating downstream signalling through phosphatidylinositol-3-kinase (PI3K), NFκB and extracellular signal-related kinase (ERK)-mitogen-activated protein kinase (MAPK) pathways. After ligand binding, BCRs cluster and rapidly associate with cholesterol-enriched membrane microdomains termed lipid rafts. SYK is recruited to BCR clusters associated with lipid rafts, and protein tyrosine phosphorylation is enhanced in these regions.

In addition to ligand-induced receptor aggregation and activation, normal mature B cells rely upon 'tonic' BCR-dependent survival signals. Tonic BCR signalling was initially defined in murine models in which BCR ablation or Igα mutation triggered the apoptosis of normal mature B cells. In follow-up studies, BCR ablation was combined with activation of specific BCR-dependent signalling cascades to delineate the nature of tonic BCR survival signals. PI3K/AKT signalling, but not NFκB or MAPK kinase activation, rescued the survival of BCR-deficient B cells. These studies defined important differences between PI3K/AKT-dependent tonic BCR survival signals and those resulting from activation of additional downstream pathways following BCR engagement.

DLBCLs are clinically and genetically heterogeneous disorders in which subsets of tumours share certain molecular features. In the cell-of-origin (COO) classification, groups of DLBCLs share components of their transcriptional profiles with normal B-cell subtypes, including germinal centre B cells (GC) and activated B cells (ABC). In comparison to GC DLBCLs, ABC tumours more frequently exhibit constitutive activation of NFκB and genetic alterations of several NFκB pathway components.

Using an alternative approach to define DLBCLs with shared molecular features, we previously applied consensus clustering methods to the transcriptional profiles of primary DLBCLs and identified 3 highly reproducible tumour groups—BCR, OxPhos (oxidative phosphorylation) and HR (host response). 'BCR' DLBCLs have

DOI: 10.1002/hon

increased expression of multiple components of the BCR signalling pathway and reliance upon BCR-mediated survival signals. BCR-dependent and BCR-independent/OxPhos DLBCLs have distinctive metabolic features that are linked to the functional state of upstream BCR signalling components (Caro et al, *Cancer Cell* 2012; 22:547–560).

In recent studies, we characterized distinct SYK/PI3K/AKT-dependent BCR viability pathways in DLBCL cell lines and primary tumours with high and low baseline NFκB activity (BCR-dependent ABC-type and GC-type DLBCLs) and defined the importance of SYK/PI3K/AKT-dependent signalling in both groups (Chen et al, *Cancer Cell* 2013; 23: 826–838). In addition, we identified SYK/PI3K/AKT-dependent cholesterol biosynthesis as a feed-forward mechanism of preserving the integrity of BCRs in lipid rafts in BCR-dependent DLBCLs with low- or high- baseline NFκB. These functional and genetic studies, which will be discussed, provide a framework for analysing targeted inhibition of specific components of the proximal BCR signalling pathway in well-defined DLBCL subtypes and set the stage for further clinical analysis of selected BCR pathway inhibitors.

077

IBRUTINIB IS HIGHLY ACTIVE AND PRODUCES DURABLE RESPONSES IN PREVIOUSLY TREATED WALDENSTRÖM'S MACROGLOBULINEMIA

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Background: $MYD88^{L265P}$ and $CXCR4^{WHIM}$ are highly prevalent somatic mutations in Waldenström's macroglobulinemia (WM). $MYD88^{L265P}$ triggers WM growth via BTK, a target of ibrutinib. $CXCR4^{WHIM}$ mutations confer *in vitro* resistance to ibrutinib. We report on the first prospective study of ibrutinib in WM, and impact of MYD88 and CXCR4 mutations on treatment outcome.

Methods: Symptomatic WM patients with >1 prior therapies were eligible. Ibrutinib (420 mg) was administered daily until progression, or unacceptable toxicity.

Results: 63 patients with a median of 2 prior therapies (40% with refractory disease) were enroled. Post-therapy, median serum IgM levels declined from 3520 to 880 mg/dL; haemoglobin rose from 10.5 to 13.8 g/dL, and bone marrow involvement declined from 60% to 25% ($p < 0.01$ for all comparisons). Overall and major response rates were 90.5% and 73.0%, and the median times to at least minor and major responses were 4 and 8 weeks, respectively. Fifty-six (88.9%) patients expressed $MYD88^{L265P}$, and 21 (33.9%) had $CXCR4^{WHIM}$ mutations. Overall and major response rates were highest in patients with $MYD88^{L265P}CXCR4^{wild\text{-}type\ (WT)}$ (100% and 91.2%), followed by $MYD88^{L265P}CXCR4^{WHIM}$ (85.7% and 61.9%), and $MYD88^{WT}CXCR4^{WT}$ (71.4% and 28.6%) mutation status. Overall and major response rates improved with prolonged therapy (>6 cycles) in patients with $MYD88^{L265P}CXCR4^{WT}$ and $MYD88^{L265P}CXCR4^{WHIM}$, with more pronounced improvements occurring for the latter. Best serum IgM and haemoglobin responses were also impacted by tumour genotype, with improvements most evident in patients with $MYD88^{L265P}CXCR4^{WT}$ and least in those with $MYD88^{WT}CXCR4^{WT}$. The 2-year PFS and overall survival rates were 69.1% and 95.2%, respectively. Subset analysis showed that $MYD88^{WT}CXCR4^{WT}$ mutation status associated with inferior progression-free survival. Grade > 2 treatment-related toxicities included neutropenia (22.2%) and thrombocytopenia (14.3%) that were more common in heavily pre-treated patients, atrial fibrillation in patients with a prior arrhythmia history (3.2%), procedure-related bleeding (3.2%), and epistaxis related to marine oil supplements (3.2%). Serum IgA and IgG levels were unchanged, and treatment-related infections were infrequent.

Conclusions: Ibrutinib is highly active, produces durable responses, and is well tolerated in previously treated WM patients. MYD88 and CXCR4 mutation status impact response and progression-free survival to ibrutinib in this patient population.

078

THE NOVEL DUAL PI3K/MTOR INHIBITOR PQR309 SHOWS PRECLINICAL ACTIVITY AS SINGLE AGENT OR IN COMBINATION AND TARGETS CENTRAL SIGNALLING PATHWAYS IN B-CELL LYMPHOMAS

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Introduction: PQR309 is a novel oral PI3K/mTOR inhibitor, being now evaluated as single agent in a phase I study in solid tumours (NCT01940133). Here, we present pre-clinical data on its activity and mechanism of action in lymphomas.

Methods: 40 B-cell lymphoma cell lines, including 27 diffuse large B cell lymphoma (DLBCL), 10 mantle cell lymphoma (MCL), and 3 splenic marginal zone lymphoma (SMZL). IC_{50} were calculated with the MTT assay on cells treated (72 h) with increasing doses of PQR309, a second dual PI3K/mTOR inhibitor (GDC0980) and the PI3Kdelta inhibitor idelalisib. Synergism was assessed with the Chou–Talalay combination index (CI) after exposing (72 h) cells to increasing doses of PQR309 alone or in combination with increasing doses of other agents. Gene expression profiling (GEP) was performed with Illumina HumanHT12 Expression BeadChips.

Results: PQR309 had potent anti-proliferative activity: DLBCL, median IC_{50} 166 nM (95% CI 128–343 nM); MCL, 235 (155–381); and SMZL, 214 (188–304). Activated B-cell like (ABC) and germinal centre B-cell like (GCB) DLBCL were equally sensitive. The effect appeared mainly cytostatic (apoptosis in 1/7 cell lines with 500 nM PQR309, 72 h). PQR309 and GDC0980 presented a highly correlated pattern of anti-proliferative activity ($R = 0.9$). Idelalisib was less active, and the pattern of sensitivity was less correlated with PQR309 or GDC0980 ($R = 0.6$). PQR309 (1 μM) was able to inhibit IgM stimulation-induced pAKT(Ser 473) in 3/3 DLBCL and 3/3 MCL.

At GEP, 19 untreated DLBCL sensitive cells (PQR309 IC50 < 200 nM) had higher expression of transcripts involved in BCR pathway/signalling, kinase regulation, and immune system. Conversely, the 6 less sensitive cells ($IC_{50} > 200$ nM) had higher baseline expression of members of proteasome pathway, oxidative phosphorylation, and translation initiation.

DOI: 10.1002/hon

GEP in treated cells (4 GCB, 4 ABC DLBCL; DMSO or 1 μM PQR309; 4, 8 and 12 h) showed that PQR309 affected, in a time-dependent manner, relevant biologic pathways. Down-regulated transcripts were enriched of MYC targets, genes involved in NFKB/MYD88/BCR/IFN signalling, apoptosis, DNA damage, and proteasome. Transcripts up-regulated were enriched of genes involved in cell cycle and senescence, up-regulated after MYD88 silencing, down-regulated by PI3K, involved in packaging of telomere and in autophagosome, and up-regulated by inhibitors of HDAC, BET Bromodomain, and JAK2. CXCR4, PIM1, YPEL5, TP63, HRK (up), LYAR, CCDC86, HSPA8, and PAK1IP1 (down) were among the most affected genes.

PQR309 was synergistic with ABT199 (TMD8 CI 0.5; U2932 CI 0.07), ibrutinib (TMD8 CI 0.6; U2932 CI 0.6), lenalidomide (TMD8 CI 0.5; U2932 CI 0.5), and additive with bortezomib (TMD8 CI 0.9; U2932 CI 0.9).

Conclusions: PQR309 showed strong anti-proliferative activity in lymphomas, affecting central signalling pathways. These data provide the rationale for the lymphoma-dedicated phase I trial (NCT02249429).

079

PHASE 1 STUDY OF PI3KΔ INHIBITOR INCB040093 ALONE OR IN COMBINATION WITH SELECTIVE JAK1 INHIBITOR INCB039110 IN PATIENTS WITH RELAPSED/REFRACTORY B-CELL MALIGNANCIES

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Introduction: Inhibiting the PI3K or JAK-STAT pathways may be therapeutic in B-cell malignancies due to their contribution to tumour growth and survival and effects on the tumour microenvironment. Furthermore, inhibition of both pathways may be synergistic due to JAK-STAT augmentation of B-cell receptor activation of the NFκB pathway.

Methods: This ongoing dose escalation study with expansion cohorts enroled adult patients with relapsed/refractory B-cell malignancies. Patients received INCB040093 monotherapy (100 mg once daily, 100 mg twice daily, 150 mg twice daily, or 300 mg once daily) or INCB040093 in combination with INCB039110 (INCB040093: 150 mg daily, 100 mg twice daily, or 150 mg twice daily; INCB039110: 400 mg or 600 mg once daily). Safety, efficacy, and pharmacodynamics were evaluated.

Results: Enrolled patients ($N = 83$) had follicular lymphoma ($n = 19$), classical Hodgkin lymphoma (cHL; $n = 17$), diffuse large B-cell lymphoma (DLBCL; $n = 15$), chronic lymphocytic leukaemia/small lymphocytic lymphoma ($n = 13$), or other subtypes ($n = 19$). At baseline, the median age was 61 years and 70% were men. The median number of prior treatment regimens was 4, and 24% of patients had undergone prior haematopoietic stem cell transplantation. The median exposure during the study was 185 days [range: 5–491+ (ongoing)] for INCB040093 alone and 99 days [range: 6–337+ (ongoing)] for INCB040093 + INCB039110. The most common adverse events were fatigue (28%), headache (19%), and pyrexia (19%). The most common grade ≥ 3 adverse event was pneumonia (6%). The most common laboratory abnormalities were liver enzyme elevations and cytopenias. One patient had a dose-limiting toxicity on INCB040093 100 mg twice daily (gastrointestinal bleed secondary to gastric DLBCL regression). Dosing regimens of INCB040093 100 mg twice daily and INCB040093 100 mg twice daily + INCB039110 400 mg once daily were selected for expansion cohorts based on the incidence of liver enzyme elevations with INCB040093 and cytopenias with INCB040093 + INCB039110 at higher doses. At the selected doses, pAKT was decreased by ≈90% at trough on INCB040093, and IL-6-induced pSTAT3 was decreased an average of 65% on INCB039110. Of 75 patients evaluated for a response thus far, 28 responses have been reported. Notably, for evaluable patients with cHL ($n = 15$), the objective response rate was 60% (3 complete responses). Complete responses were observed in both of the patients enroled with the non-germinal centre B-cell-like subtype of DLBCL.

Conclusions: Treatment with INCB040093 ± INCB039110 was tolerable and produced responses, including complete responses, in patients with heavily pretreated relapsed/refractory B-cell malignancies. Given this activity, the study was expanded to enrol additional cohorts of patients with relapsed/refractory B-cell malignancies such as cHL and DLBCL, and a phase 2 study was initiated in patients with relapsed/refractory cHL.

080

A FIRST-IN-HUMAN TRIAL OF CUDC-907, AN ORAL, FIRST-IN-CLASS, DUAL INHIBITOR OF PI3K AND HDAC, IN PATIENTS WITH REFRACTORY/RELAPSED LYMPHOMA AND MULTIPLE MYELOMA

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Introduction: CUDC-907 is an oral inhibitor of class I and II HDAC as well as class I PI3K enzymes. Anti-tumour effects of CUDC-907 have been demonstrated in B-cell lymphoma and multiple myeloma xenografts via inhibition of PI3K/AKT, JAK/STAT and MAPK pathways.

Methods: In a standard First-in-Human Phase I 3 + 3 dose escalation and expansion trial, CUDC-907 was administered on 3 dosing schedules: once daily (QD), intermittent (i.e. twice [BIW] or thrice [TIW] weekly), and five days on/two days off (5/2) in 21-day cycles. Re-staging was performed every 2 cycles.

Results: 51 subjects received CUDC-907 at doses starting at 30 or 60 mg and up to 150 mg depending on the schedule tested. Dose limiting toxicities occurred in 3 subjects: 1 at 60 mg QD (hyperglycaemia and diarrhoea); 1 at 150 mg BIW (hyperglycaemia); and 1 at 150 mg TIW (diarrhoea). The most common treatment-related adverse events (AEs) were diarrhoea (45%), fatigue (31%), nausea (20%) and thrombocytopenia (14%). The most common treatment-related AEs of Grade ≥ 3 intensity included thrombocytopenia (14%), neutropenia (4%) and diarrhoea (4%). Among 41 subjects evaluable for disease response, 4 objective responses were observed: 1 subject with diffuse large B-cell lymphoma (DLBCL) achieved complete response (CR) and 3 subjects with DLBCL or transformed follicular lymphoma (t-FL/DLBCL) achieved partial response (PR). Stable disease (SD)

DOI: 10.1002/hon

Abstract 080 Table 1.

Dose cohorts							
Schedule	Dose (mg)	Enrolled subjects (*n*)	Cycles: median (min–max)	Dose limited toxicities (DLTs)	CR (*n*)	PR (*n*)	*N* (%) of subjects with tumour regression (CR + PR + reduction < 50%)
QD	30–60	10	4.5 (1–34)	Diarrhea, hyperglycaemia[a]	–	2	3 (38)
BIW	60–150	12	5 (2–11)	Hyperglycaemia[b]	–	1	7 (58)
TIW	60–150	15	4 (1–19)	Diarrhea[c]	–	–	5 (38)
5/2	60	14	2 (1–7)	None	1	–	4 (50)

[a] 60 mg QD. [b] 150 mg BIW. [c] 150 mg TIW.

lasting a median of 101 days (40–717) has been observed in 22 (54%) subjects including Hodgkin's lymphoma (HL) ($n = 8$), DLBCL and t-FL/DLBCL ($n = 3$), and MM ($n = 3$). Accumulation of active metabolite was only observed on the QD dosing schedule, and a trend of dose-dependent increase in CUDC-907 plasma exposure was observed in the BIW and TIW dosing schedules.

Conclusion: The safety profile of CUDC-907 for gastrointestinal, haematologic and hyperglycaemic AEs was predictable based on experience with other HDAC and PI3K inhibitors. AEs have been reversible and managed with standard interventions or dose interruption, and fatigue and thrombocytopenia have not been dose limiting. CUDC-907 has achieved objective responses and long-term stable disease across multiple tumour types and dosing schedules, with objective response achieved in a heavily pretreated DLBCL patient population. Maximum tolerated dose was not reached in the intermittent or 5/2 schedules, and expansion is being studied at the 60 mg 5/2 dose level based upon efficacy and toxicity profiles demonstrated in this FIH trial.

'FOCUS ON…' SESSION: IMAGING

081

USE OF THE LUGANO CLASSIFICATION CRITERIA FOR PET/CT ASSESSMENT OF PRIMARY MEDIASTINAL B-CELL LYMPHOMA AFTER IMMUNOCHEMOTHERAPY AND IRRADIATION IN THE IELSG-26 STUDY

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Introduction: Primary mediastinal large B-cell lymphoma (PMBCL) commonly affects young adults, and treatment with multiagent chemotherapy regimens and rituximab, often with consolidation radiotherapy, gives 5-year survival rates over 90%. However, salvage treatment for the few patients who failed by initial therapy has poor results. This study assessed the accuracy of [18F] FDG positron emission tomography/computed tomography (PET/CT) after immunochemotherapy (R-CT) and mediastinal irradiation (RT), using the recently published criteria of the Lugano classification to predict the outcome of patients with PMBCL.

Methods: Among 125 patients prospectively enroled, in the IELSG26 study, 88 were eligible for central review of PET/CT scans at 8 weeks after the completion of RT. Responses were evaluated using the 5-point Deauville scale (DS) at the end of induction R-CT and after consolidation RT. According to the Lugano classification, a complete metabolic response (CMR) was defined by a DS ≤ 3.

Results: The CMR (DS: 1,2,3) rate increased from 74% (65 patients) after R-CT to 89% (78 patients) after RT (see Table below). The residual uptake after RT was slightly higher than the liver uptake in 6 (DS 4; 7%), and markedly higher in 4 (DS 5; 4%), of 10 patients (11%). These patients had a significantly poorer 5-year PFS and OS. At a median follow-up of 60 months, no patients with a CMR after RT have relapsed. Among the 10 patients who did not reach a CMR, 3 had progression of disease after RT and died: a positive predictive value of 30%. These 3 cases were all classified as DS 5, while all patients with DS 4 had good outcomes without recurrence.

Conclusions: A CMR defined by a DS ≤ 3 identifies almost all the patients projected to be alive and progression-free at 5 years, confirming the excellent negative predictive value of the Lugano classification criteria in PMLBCL patients. Notably, the few patients with DS 4 also had an excellent outcome, suggesting that they do not necessarily require additional therapy, since the residual FDG uptake may be due to an inflammatory reaction.

Abstract 081 Table 1.

	After R-chemo		After RT	
Deauville scale	*N*	%	*N*	%
1	7	8	34	39
2	34	39	34	39
3	24	27	10	11
4	18	20	6	7
5	5	6	4	4

DOI: 10.1002/hon

082

PET SCORE FOLLOWING 3 CYCLES ABVD HAS GREATER PROGNOSTIC VALUE THAN PRE-TREATMENT RISK STRATIFICATION IN THE RAPID TRIAL IN EARLY STAGE HODGKIN LYMPHOMA (HL)

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Introduction: Accurate stratification of patients (pts) to facilitate individualized treatment approaches is an important goal in HL where cure rates are high, but late treatment toxicity can undermine long-term survival. In this study, the prognostic performance of pre-treatment factors and PET response after 3 cycles ABVD were compared in pts with early stage HL taking part in the RAPID trial.

Methods: 602 pts, median age 34 years, with stages IA/IIA HL and no mediastinal bulk, were registered into RAPID 2003–2010. Following 3 cycles ABVD, 571 pts had a PET scan reported as 'negative' (score 1 or 2 on a 5-point scale) in 426 (74.6%) pts or 'positive' (score 3, 4 or 5) in 145 (25.4%) pts. 420 of 426 PET negative pts were randomized between involved field radiotherapy (IFRT, $n = 209$) and no further treatment (NFT, $n = 211$); 145 PET positive pts received a 4th cycle ABVD and IFRT. Risk stratification data were available in 495 (87.6%) and 482 (85.3%) pts using EORTC/GHSG criteria, respectively, and although not used as selection factors for trial entry, 62.6% and 67.8% pts were in the favourable category. Cox regression was used to investigate the association between PET score and risk stratifications with HL-specific event-free survival (HL-EFS); study grouping was also included in each model.

Results: After a median follow-up of 5 years from registration, 522 (92.4%) pts have had no HL event and 43 (7.6%) pts have had an event (38 alive with progression, 5 HL-deaths). There was no evidence of an association between EORTC ($p = 0.60$) or GHSG ($p = 0.60$) risk stratifications at baseline and HL-EFS; however, PET score after 3 cycles ABVD was highly significant ($p = 0.001$). High PET score was associated with an increased risk of progression or HL-death, both with and without adjustment ($ps = 0.001$) for the baseline risk stratifications which remained statistically non-significant (EORTC: $p = 0.48$; GHSG: $p = 0.62$). Pts with a PET score of 5 had a higher risk than all other PET scores (HR = 5.1 va PET score 1, 95% CI: 2.1 to 11.9; HR = 3.2 vs PET score 2, 95% CI: 1.2 to 8.5; HR = 9.3 va PET score 3, 95% CI: 2.8 to 31.3; HR = 6.7 vs PET score 4, 95% CI: 1.4 to 31.3). Including non-HL deaths (i.e. progression-free survival and the primary endpoint in RAPID) gave similar results.

Conclusion: For pts in the RAPID trial, PET score after 3 cycles ABVD has greater prognostic value than pre-treatment risk stratification. This finding that supports the role of PET in early stage HL will be further investigated in future trials.

Abstract 082 Table 1. HL-specific event-free survival events, by PET score following 3 cycles ABVD and baseline risk stratifications

	Alive without progression	Alive with progression	HL-deaths	Total
PET score = 1	280 (93.6%)	19 (6.4%)	0 (0.0%)	299
PET score = 2	111 (91.7%)	9 (7.4%)	1 (0.8%)	121
PET score = 3	86 (95.6%)	3 (3.3%)	1 (1.1%)	90
PET score = 4	30 (93.8%)	2 (6.3%)	0 (0.0%)	32
PET score = 5	15 (65.2%)	5 (21.7%)	3 (13.0%)	23
EORTC = favourable	284 (91.6%)	25 (8.1%)	1 (0.3%)	310
EORTC = unfavourable	172 (93.0%)	9 (4.9%)	4 (2.2%)	185
GHSG = favourable	299 (91.4%)	24 (7.3%)	4 (1.2%)	327
GHSG = unfavourable	144 (92.9%)	10 (6.5%)	1 (0.6%)	155

083

BASELINE TOTAL METABOLIC VOLUME (TMTV0) PREDICTS THE OUTCOME OF PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) ENROLLED IN THE LNH07-3B LYSA TRIAL

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Introduction: The total metabolic volume assessed on the baseline FDG-PET is a novel approach of tumour burden measurement quantifying the most active part of the tumour. It has been reported to influence DLBCL outcome in a retrospective series (Eur J Nucl Med Mol Imaging 2014, 41: 2017). We designed a study evaluating the TMTV0 prognosis value in patients prospectively enroled in a phase II randomized trial testing 2 R-chemo regimens and a PET-driven consolidation strategy (NCT00498043), and its adding value compared to the prognosis impact of early PET response.

Methods: Eligible pts for the present study had to be enroled in the LNH07-3B trial and to have a baseline PET available for central review and TMTV0 calculation. All pts were 18–59y, with a previously untreated aaIPI 2–3 DLBCL and were randomly assigned to 4 cycles of either R-ACVBP14 or R-CHOP14 induction. Consolidation treatment was driven by centrally reviewed PET assessment after 2 (PET2) and 4 (PET4) induction cycles as previously published (Blood 2011, 118: 37). TMTV0 was computed on pretreatment PET by summing the metabolic volumes of the individual lesions using the 41% SUVmax thresholding method already described in lymphoma (Eur J Nucl Med Mol Imaging 2014,41: 1113). Pts with a reduction of SUVmax >70% between baseline PET and PET4 (DSUV0–4) were considered good responders.

Results: 164 pts with a median age of 45y were included: 97% had stage III/IV, 27% a bulky mass >10 cm, 95% elevated LDH and 24% ECOG ≥ 2. Median TMTV0 was 373 mL (17–4339). Using the 75th percentile of the TMTV0 distribution as cut-off (660 mL), 39 pts (24%) had a high TMTV0. A high TMTV0 was not related to tumour bulk, Ann Arbor stage, elevated LDH or treatment arm but was more frequent in pts with ECOG ≥ 2 (38%) than those with ECOG < 2 (20%) ($p < 0.04$). With a median 45 months follow-up, 34 (21%) pts progressed or

DOI: 10.1002/hon

relapsed and 22 (13%) died. Pts with a high TMTV0 had a significantly lower PFS and OS than those with a TMTV0 < 660 mL (4y-PFS: 64% vs 81%, $p = 0.015$ and 4y-OS: 73% vs 90%, $p < 0.04$, respectively). Inversely a tumour bulk >10 cm did not influence patients' outcome. The 141 pts (84%) who achieved a DSUV0-4 > 70% had a significantly better outcome than those with a DSUV under the cut-off (4y-PFS: 83% vs 30%, $p < 0.0001$; and 4y-OS: 90% vs 60%, $p < 0.0001$). Then, 3 groups could be identified: pts with either TMTV0 < 660 mL and DSUV0-4 > 70% ($n = 109$; 69%), or TMTV0 > 660 mL or DSUV0-4 < 70% ($n = 41$; 26%), or TMTV0 > 660 mL and DSUV0-4 < 70% ($n = 7$; 4%) had a 85%, 71% and 14% 4y-PFS ($p < 0.0001$) and a 92%, 74% and 50% 4y-OS ($p < 0.0001$). The patients of these 3 groups had a similar outcome when treated with R-ACVBP or R-CHOP14 regimen induction.

Conclusions: The TMTV0 predicts the outcome of young high risk DLBCL pts independently of the early metabolic response to treatment. The combination of TMTV0 and DSUVmax allows identifying 3 subsets of DLBCL pts with significantly different outcome that may help clinician to better tailor therapy.

084

PROGNOSTIC VALUE OF BASELINE TOTAL METABOLIC TUMOUR VOLUME (TMTV0) MEASURED ON FDG-PET/CT IN PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA (PTCL)

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Introduction: The prognostic value of the metabolic tumour volume measured on a baseline FDG-PET/CT (TMTV0) has never been assessed in peripheral T-cell lymphoma (PTCL). Our study investigated in patients with FDG-avid PTCL categories (J.Clin.Oncol, 2014:32;3048) the prognostic impact of TMTV0 on PFS and OS and its adding value to other prognostic characteristics.

Methods: From April 2006 to September 2014, 108 patients from 5 LYSA centres with newly diagnosed nodal presentation T-cell lymphoma were retrospectively included: 43 angioimmunoblastic T-cell lymphoma; 38 anaplastic large cell lymphoma (ALCL), including 14 ALK positive and 24 ALK negative cases; and 27 peripheral T-cell lymphoma not otherwise specified (NOS). All had a baseline FDG-PET/CT. TMTV0 was computed by summing the metabolic volumes of all nodal and extranodal lesions using the 41% thresholding of lesion's SUVmax method with a high interobserver reproducibility already described in lymphoma (Eur J Nucl Med Mol Imaging 2014,41: 1113). Optimal TMTV0 cut-off to predict PFS and OS was determined by ROC curves, and Kaplan Meier curves were obtained. A multivariate analysis was performed using a Cox model.

Results: 108 patients with a median age of 58 years were enroled: 91% had stage III/IV, 98% elevated LDH, and 45% Prognostic Index for PTCL (PIT) score >1. 80% of them were treated by CHOP-like chemotherapy, the others by ACVBP. Patient SUVmax, median of 14 (range: 3.4 to 39) was not related with outcome. Median pre-therapy TMTV0 was 224 cm^3 (range: 5–3824 cm^3), with no significant difference between the 4 histologies. With a median follow-up of 23 months, the 2y-PFS was 49% and the 2y-OS 67% in the whole population. Using a cut-off of 230 cm^3, a high TMTV0 ($n = 53$) was predictive of a shorter PFS (2y-PFS: 26% vs 71% $p < 0.0001$ HR = 4) and OS (2y-OS: 50% vs 80% $p = 0.0005$ HR = 3,1). In univariate analysis, PIT score > 1 was associated with a significant worse outcome (2 y-PFS: 32% vs 64%, $p = 0.004$ HR = 2.3 and 2y-OS: 53% vs 80%, $p = 0.001$ HR = 3.1). In multivariate analysis, TMTV0 was an independent predictor of PFS and OS from PIT ($p = 0.0002$, $p = 0.03$). TMTV0 combined with PIT score identified 3 groups with very different outcome: patients with MTV ≤ 230 cm^3 and PIT ≤ 1 ($n = 40$, 38%), or patients with MTV > 230 cm^3 or PIT > 1 ($n = 31$, 30%), or patients with MTV > 230 cm^3 and PIT > 1 ($n = 33$, 32%) had a 73%, 50%, and 19% 2y-PFS ($p < 0.0001$) and a 81%, 68%, and 43% 2y-OS ($p = 0.0002$).

Conclusion: Baseline metabolic tumour volume is an independent predictor of outcome in patients with peripheral T-cell lymphoma. Combining PIT and TMV0 individualized 3 risk categories of patients with significant different outcome which may be used to stratify patients in prospective trials.

085

LITTLE VALUE OF ROUTINE SURVEILLANCE IMAGING FOR PRIMARY CNS LYMPHOMAS IN FIRST REMISSION: RESULTS FROM A DANISH MULTICENTRE STUDY

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Introduction: Many patients with primary CNS lymphomas (PCNSL) respond to treatment, but relapse is common. Routine magnetic resonance imaging (MRI) studies are often performed to detect recurrent PCNSL at an early, asymptomatic stage. The present study examined the relapse detection patterns and the use of surveillance MRI in cohort of Danish PCNSL patients.

Method: Candidates for the present study were identified by searching the Danish Lymphoma Registry (LYFO). The following criteria were used to select patients: (1) histology confirmed PCNSL diagnosed 2002–2012, (2) CR/CRu or partial response (PR) after first-line therapy, and (3) entering into a post-therapy follow-up scheme. Medical records were retrieved and reviewed for details regarding relapse, relapse detection methods, and results of MRI studies.

Results: A total of 94 patients with PCNSL were included in the study. The vast majority of the patients had DLBCL (95%). Eighty-six patients (92%) achieved a CR/CRu, and eight patients (8%) achieved a PR after first-line therapy. After a median follow-up of 58 months (reverse Kaplan–Meier method), relapse was diagnosed in 37/94 patients (39%). Relapse investigations were initiated outside preplanned FU visits in 35/37 patients (95%, 95% CI 82–99). Self-reported symptoms suspicious of recurrent PCNSL lead to the detection of relapse in 36/37 patients (97%, 95% CI 86–100). Some of the common symptoms were cognitive impairment (36%),

DOI: 10.1002/hon

paralysis (25%), symptoms of raised intracranial pressure (17%), cerebellar symptoms (8%), and sensory disturbances (6%). A total of 156 routine MRI studies were performed in the first 2 years of follow-up (median 1 MRI study, range 0–6) and led to the detection of one asymptomatic relapse. The positive and negative predictive values (PPV and NPV) of routine MRI studies were 10% (95% CI 3–45) and 98% (95% CI 94–100), respectively. A total of 89 MRI studies were performed in response to clinical symptoms. Four symptomatic patients relapsed within 6 weeks of a negative MRI study. The PPV and NPV of MRI studies performed in response to clinical symptoms were 90% (95% CI 74–98) and 93% (95% CI 83–98), respectively.

Conclusion: Relapsed PCNSL was almost exclusively diagnosed as a result of patient-reported symptoms presented outside preplanned visits. Interestingly, a normal MRI examination in symptomatic patients does not fully exclude a pending relapse. The negligible contribution of routine MRI to the detection of relapsed PCNSL may be explained by the aggressive nature of the disease leading to a very short symptomatic disease phase. Routine MRI imaging has no clear role in the follow-up of PCNSL patients in first remission.

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ROUTINE IMAGING FOR DIFFUSE LARGE B-CELL LYMPHOMA IN FIRST REMISSION IS NOT ASSOCIATED WITH BETTER SURVIVAL: A DANISH-SWEDISH POPULATION-BASED STUDY

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Background: Routine surveillance imaging plays a limited role in detecting recurrent diffuse large B-cell lymphoma (DLBCL), and the value of routine imaging is controversial. The present population-based study compares the post-remission survival of Danish and Swedish DLBCL patients—two neighbouring countries with comparable treatment guidelines but with completely different traditions for routine surveillance imaging.

Methods: Patients enroled in the Danish (LYFO) and Swedish population-based lymphoma registries were included by following criteria: (a) newly diagnosed DLBCL in the period 2007–2012, (b) age 18–65 years, and (c) CR after 1st line treatment with R-CHOP/CHOEP. We selected the age category 18–65 years, since 1st and 2nd line therapies are highly standardized for these patients (2nd line: high-dose therapy if feasible). The Danish and Swedish haematology/oncology services are fully publicly funded. Follow-up (FU) for Swedish patients included symptom assessment, clinical examinations, and blood tests with 3-month intervals for 2 years and with longer intervals later in follow-up. Imaging was only performed in response to suspected relapse. FU for Danish patients was equivalent but included additional routine surveillance imaging (usually half-yearly CT for 2 years as a minimum). Clinico-pathological features were retrieved from the national lymphoma registries, and vital status was updated using the civil registries. OS was defined as the time from end of treatment until death/censoring. Relapse data are continuously updated in the LYFO, and cumulative incidence rates for progression (relapse and death) were calculated for the Danish patients.

Results: A total of 525 Danish and 696 Swedish patients were included. Danish and Swedish patients had similar male:female ratio, median age, and proportion of IPI high risk disease (IPI > 2). After a median FU of 51 months, the 3-yr OS for the entire patient cohort was 92% (95% CI 90–93). There was no survival difference between Danish and Swedish patients ($P = 0.5$, log-rank). Age >60 years (HR 2.3, $P < 0.01$), elevated LDH (HR 2.3, $P < 0.01$), B-symptoms (HR 1.6, $P = 0.02$), and ECOG performance ≥2 (HR 1.8, $P = 0.04$) at diagnosis were associated with inferior post-remission OS in multivariate Cox analysis, whereas an imaging-based FU strategy (country of FU) was not prognostic. An imaging-based FU strategy also had no impact on the post-remission OS for patients grouped according to the IPI scores ($P = 0.2$ for IPI ≤ 2 and $P = 0.8$ for IPI > 2). The cumulative 2-year progression rate was 6% (95% CI 4–9) for patients with IPI ≤ 2 versus 21% (95% CI 13–28) for patients with IPI > 2.

Conclusions: The vast majority of young DLBCL patients in CR stay in remission, and only a small minority will benefit from a relapse-oriented FU program. More importantly, the post-remission survival rates were completely identical for Danish and Swedish patients despite the widespread use of routine imaging in Denmark, favouring a non-imaging-based FU strategy for DLBCL in 1st CR.

'FOCUS ON…' SESSION: TARGETING CD30

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BRENTUXIMAB VEDOTIN PLUS AVD FOR NON-BULKY LIMITED STAGE CLASSICAL HODGKIN LYMPHOMA: A PHASE 2 TRIAL

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Introduction: ABVD plus radiation produces a high cure rate in limited stage Hodgkin lymphoma (HL) but carries risks of bleomycin-lung injury and late radiation toxicity. Brentuximab vedotin is highly active in relapsed HL and has been combined with AVD. We evaluated brentuximab vedotin (Adcetris®) plus AVD (A-AVD) without radiation as initial therapy for non-bulky stage I–II HL.

Methods: This is a multicentre phase 2 study. Patients received a lead in cycle of brentuximab monotherapy 1.2 mg/kg on days 1 and 15, followed by an exploratory PET scan. Patients then received 4–6 cycles of A-AVD, based on interim PETCT response after cycle 2 of combination therapy. The primary endpoint is complete response rate (CRR). A sample size of 34 was required to detect a CRR of 93% with 91% power and alpha error of 0.10.

Results: Thirty-four patients were enroled. The median age is 36 (20–75) years. Risk is early favourable in 62% while early unfavourable in 38%. The best CRR was 100%. After the monotherapy lead in cycle, 18/34 subjects (53%) were in CR. After 2 cycles of A-AVD, 33 were in CR (97%), and 1 was removed for toxicity. At end of treatment (EOT), 31 (91%) were in CR, 1 had progressive disease (PD), and 2 were removed for toxicity. No subjects required >4 cycles of treatment. At EOT, 8 subjects had PET scans interpreted as positive on central review, 7 of which were felt to be inflammatory by investigators. Six of these were in confirmed CR on brief follow-up scan with no intervening therapy, while 1 with new FDG avidity at EOT after interim CR was given 2 additional cycles of AVD and was in confirmed CR. The case of PD was treated with salvage therapy and ASCT, achieving CR. At a median follow-up of 14 months, the PFS and OS are 94% and 97%, respectively. The most common adverse events were

DOI: 10.1002/hon

peripheral sensory neuropathy (PSN) (74%), fatigue (71%), nausea (24%), neutropenia (68%), anaemia (56%), constipation (56%), diarrhoea (35%), abdominal pain (32%), ALT elevation (29%), and febrile neutropenia (29%). Grade 3–4 toxicity occurred in 26 of 34 (76%) patients, most commonly neutropenia (56%), febrile neutropenia (29%), and PSN (24%). One elderly patient died of neutropenic sepsis in the first A-AVD cycle. One patient was removed for grade 2 hypersensitivity despite premedication. Given the high rate of neutropenic fever, the protocol was amended to include routine GCSF support, with a reduction in events. Brentuximab dose reductions were required in 38% of subjects, most for PSN. Among 25 subjects with PSN, the worst grade was 3 in 8 subjects, and grade 1–2 in 17. At a limited follow-up of 7 months, 72% of affected subjects have persisting PSN, including 2 with grade 3 toxicity. The median time to resolution is 9 months.

Conclusions: A-AVD ×4 produced a high CRR but with more toxicity than expected from AVD alone, particularly PSN and neutropenic fever. Given the overlapping mechanism of action and toxicity profile between brentuximab and vinblastine, our next study will combine brentuximab with AD. False positive PET scans were common on EOT imaging and warrants further attention.

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PRELIMINARY EFFICACY AND SAFETY OF BRENTUXIMAB VEDOTIN AND AVD CHEMOTHERAPY FOLLOWED BY INVOLVED-SITE RADIOTHERAPY IN EARLY STAGE, UNFAVOURABLE RISK HODGKIN LYMPHOMA

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Background: The concurrent administration of brentuximab vedotin (BV) with AVD chemotherapy followed by radiotherapy has not been studied for frontline treatment of early stage Hodgkin lymphoma (HL). This pilot study assesses the safety and efficacy of BV + AVD chemotherapy followed by 30 Gy involved-site radiotherapy (ISRT) to treat early stage, unfavourable risk HL.

Methods: Eligible patients were untreated stage I/II, classical HL with any of these unfavourable risk factors: bulky mediastinal mass (≥1/3 max transverse thoracic diameter on PA-CXR or ≥10 cm by CT imaging in transaxial plane), ESR ≥ 50 mm/h or ESR ≥ 30 mm/h in patients with 'B' symptoms, extranodal involvement, >2 lymph node sites, or infradiaphragmatic disease. Stage IIB disease with disease bulk or extranodal involvement were included. Treatment included BV 1.2 mg/kg with AVD q2weeks × 4 cycles followed by 30 Gy ISRT. The primary endpoint is to evaluate the regimen safety, including pulmonary toxicity. PET/CT after 2 and 4 cycles were interpreted using the Deauville 5-point scale (negative scan = Deauville 1–3).

Results: Interim data for the first 25 of a planned 30 patients are presented. Median age was 32 (range, 18–59) years, 44% female, 100% stage II, 48% with disease bulk, 48% elevated ESR (≥50), 52% B-symptoms, 28% extranodal involvement, 40% >2 involved lymph node sites, and 4% with infradiaphragmatic disease. Patients with disease bulk had anterior mediastinal masses measuring >10 cm by CT in transverse plane (range, 10–16.9 cm). Nine patients had advanced stage disease by the GHSG criteria: 4 with IIBX, 3 with IIBE, and 2 with IIBXE disease. Eighty-eight perc ent of patients (21/24) achieved a negative PET scan after 2 cycles, and 82% of patients with disease bulk were PET-2 negative (9/11). Ninety per cent of patients (19/21) achieved a negative PET scan after 4 cycles of therapy. The 2 patients with a positive PET-4 scan had a positive biopsy consistent with refractory HL and were treated off study. The treatment was well tolerated. No pulmonary toxicity has been observed. Serious adverse events were reported in 7 patients, including febrile neutropenia, fever, peripheral neuropathy, and hypertension. One patient discontinued treatment due to grade 3 peripheral neuropathy after one treatment with BV + AVD. Median follow-up is 7 months. The 15 patients who have completed combined modality therapy and end-of-treatment imaging have achieved complete responses, and no relapses have occurred to date. The duration of remission for these patients ranges from 1 to 14 months.

Conclusion: BV + AVD followed by 30 Gy ISRT is well tolerated with no evidence of significant pulmonary toxicity. Most evaluable patients (≥88%) achieved negative interim PET scans after 2 and 4 cycles of BV + AVD, suggesting this is a highly active treatment even in patients with substantial disease bulk. Updated safety and response data will be presented at the meeting.

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SEQUENTIAL BRENTUXIMAB VEDOTIN AND AVD FOR OLDER HODGKIN LYMPHOMA PATIENTS: INITIAL RESULTS FROM A PHASE 2 MULTICENTRE STUDY

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Background: Standard chemotherapeutic regimens elicit inferior survival and are associated with increased toxicity in older Hodgkin lymphoma (HL) patients (pts). We initiated a multicentre study examining brentuximab vedotin (BV) given sequentially before and after chemotherapy for this pt population (NCT01476410).

Methods: Older pts (i.e. ages ≥60 years) with stage II–IV, untreated HL were eligible. All pts received 2 lead-in cycles of single-agent BV 1.8 mg/kg (q 3 weeks), followed by 6 cycles of standard doxorubicin, vinblastine, and dacarbazine (AVD) chemotherapy. Responding pts then proceeded to consolidation therapy (Tx) with 4 cycles of BV. Study design is a Simon's two-stage with plan of 48 total pts. The primary endpoint is complete remission (CR) rate after AVD (i.e. prior to BV consolidation) using revised Cheson criteria utilizing FDG-PET/CT. If ≥12 CRs were observed among 20 evaluable pts, accrual continued to the second stage.

Results: 26 pts enroled to the first stage of the study, of which 20 were evaluable for response. Characteristics for all pts include median age 69 years (60–88), median ECOG performance status 1 (0–2), 92% with stage III/IV disease, IPS 3–7 in 54%, and median CIRS co-morbidity score of 5 (0–19). Six pts were non-evaluable for response [$n = 4$ due to toxicity with BV lead-in ($n = 1$ treatment-related mortality due to pancreatitis), $n = 1$ withdrew consent and refused Tx]. Among 20 evaluable

DOI: 10.1002/hon

Abstract 089 Table 1. Older HL pts with at least one related toxicity, by grade (n = 26)

Grade	Number of pts with at least 1 event	% of pts with at least 1 event
1	22/26	85%
2	20/26	77%
3	12/26	46%
4	8/26	31%
5	1/26	3.8%

pts, the overall response rate (ORR) to BV lead-in was 85% with 30% CR. After 3 cycles of AVD, the ORR and CR rates were 95% and 70%, respectively. Among 17 pts who have completed chemotherapy thus far, ORR and CR rates are both 94%. Frequencies of adverse events (AEs) are noted in Table 1. Grade 3/4 AEs occurring in >1 pt were as follows: infection (15%), pancreatitis (4%), and peripheral neuropathy (PN) (4%); 31% of pts experienced grade 2 PN. Reasons for discontinuation of Tx included the following: 7/26 (27%) completed Tx; 7/26 (27%) on active Tx; 4/26 (15%) due to non-PN toxicity (grade 2: infusion reaction, hepatic, and pneumonitis; and grade 3: wound infection); 3/26 (12%) discontinued for PN (all grade 2 status-post cycles 6, 8, and 10); 3/26 (12%) refused additional Tx; 1/26 (4%) due to lack of response; and 1 (4%) death. At a median follow-up of 12 months, 92% of all pts are alive, and notably, 95% of all evaluable pts are free of disease.
Conclusions: Sequential Tx integrating BV before and after AVD chemotherapy for newly diagnosed older HL pts is feasible and promising. The pre-planned interim analysis confirmed the requisite CR rate needed for continuation to the second stage of this multicentre phase II study.

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A PHASE 1 STUDY OF BRENTUXIMAB VEDOTIN (BV) AND BENDAMUSTINE (B) IN RELAPSED OR REFRACTORY HODGKIN LYMPHOMA (HL) AND ANAPLASTIC LARGE T-CELL LYMPHOMA (ALCL)

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Introduction: Patients with relapsed or refractory HL or ALCL remain incurable with standard therapies. Bv is an antibody drug conjugate that has become the preferred treatment option for patients who have relapsed after or are ineligible for autologous stem cell transplant (ASCT). Bendamustine has also demonstrated substantial activity and tolerability in several lymphoma subtypes including HL. We planned this phase I–II trial to evaluate the tolerability and activity of this potentially promising combination; the phase I results are reported here.
Methods: In the Phase 1 portion, we evaluated 5 dose levels of brentuximab and bendamustine: (1) Bv = 1.2 mg/kg; B = 70 mg/m^2; (2) Bv = 1.2 mg/kg; B = 80 mg/m^2; (3) Bv = 1.8 mg/kg; B = 80 mg/m^2; (4) Bv = 1.8 mg/kg; B = 90; and (5) Bv = 1.8 mg/kg and B = 100 mg/m^2. Accrual followed a classic Fibonacci dose escalation, with 3 patients being treated at each dose level. Dose limiting toxicity, defined as any CTC version 4 Grade 3 or 4 toxicity (except for modifications for haematologic and GI toxicity along with alopecia and fatigue), led to expansion of the dose cohort.
Results: 28 patients were enroled in the Phase 1 portion of which 18 were male, 27 had HL and 1 ALCL, the median number of prior systemic therapies was 5 (range 1–14), and with 17 patients having had prior ASCT and 11 prior radiation. The maximum tolerated dose was Bv 1.8 mg/m^2 and bendamustine 90 mg/m^2. DLT was not reached at dose level 4; it was decided not to further explore level 5 where the doses exceeded the standard single agent dose of both drugs. To date, 27/28 patients are evaluable for response. Four patients (15%) obtained complete response, and 13 (48%) had a partial response for an overall response rate of 63%. Four patients had stable disease. Among the 9 patients who had prior Bv, 4 responded (44%) (PR = 4, SD = 2, PD = 3), and of the 4 patients who had prior B, 2 responded (50%) (PR = 2, SD = 1, PD = 1). The Phase 2 portion of the study is now enroling, where an additional 37 patients will be accrued. In addition, plasma and serum biomarkers are being prospectively collected for correlation with toxicity and response.
Conclusions: In this heavily treated population of HL and ALCL, the combination of Bv and B represents a very effective and tolerable regimen.

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BRENTUXIMAB VEDOTIN DEMONSTRATES ANTITUMOUR ACTIVITY IN CD30+ DLBCL

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Introduction: While many patients (pts) with diffuse large B-cell lymphoma (DLBCL) have long-term remissions with frontline rituximab (R)-chemotherapy, no standard therapy exists for relapsed DLBCL pts who are not candidates for, or relapse after, stem cell transplant. This phase 2, open-label study assessed brentuximab vedotin (BV) (ADCETRIS®), an anti-CD30 antibody-drug conjugate, in relapsed/refractory CD30+ DLBCL and in DLBCL with undetectable CD30 (CD30u). This planned subset analysis presents interim data for BV monotherapy and for BV + R (NCT01421667).
Methods: Eligible pts had ECOG ≤2, relapsed/refractory DLBCL, and either detectable CD30 or CD30u per local lab by visual assessment of immunohistochemistry staining (IHC) using the anti-CD30 BerH2 antibody. Subsequent central review of CD30 expression was done by visual assessment and computer-assisted methods for pts treated with BV alone. BV 1.8 mg/kg IV was given every 3 weeks alone or was given with R 375 mg/m^2 for up to 8 cycles, then BV alone. The primary endpoint was objective response rate (ORR) (Cheson 2007) for BV alone and safety for BV + R.
Results: 118 pts were enroled: 65 CD30+ (49 BV and 16 BV + R) and 53 CD30u (BV). Most pts were heavily pretreated with refractory DLBCL. All pts had elevated

DOI: 10.1002/hon

Abstract 091 Table 1.

	CD30+		CD30u
	BV + R (*N* = 16)	**BV (*N* = 49)**	**BV (*N* = 53)**
Male, *n* (%)	12 (75)	28 (57)	26 (49)
Median age, years (min, max)	62 (22, 78)	62 (17, 85)	65 (21, 91)
Median prior therapies, (min, max)	2 (1, 3)	2 (1, 6)	2 (1, 4)
Refractory to most recent therapy, *n* (%)	10 (63)	40 (82)	37 (70)
Refractory to frontline, *n* (%)	10 (63)	37 (76)	35 (66)
Median baseline sCD30, ng/mL (min, max)	306 (63, 1070)	206 (36, 9429)	153 (53, 1696)
Median % CD30 expression (min, max)[a]	ND	37 (0.2, 99.8)	2 (0, 54)
ORR, *n* (%)[b]	6 (46)	20 (42)	13 (27)
CR	2 (15)	9 (19)	5 (10)
PR	4 (31)	11 (23)	8 (16)
SD	4 (31)	12 (25)	8 (16)
PD	3 (23)	16 (33)	26 (53)
ORR in refractory pts, *n* (%)[c]	4 (50)	16 (41)	7 (21)
Duration of response, months (min, max)[b]	2.1 (1.4, 10.7+)	5.6 (0+, 22.7+)	2.0 (0.5, 8.1+)
Median PFS, months (min, max)[b]	2.8 (1.2, 12+)	4.0 (0.6+, 24+)	1.4 (0.4, 12.2+)
Median PFS for CR, months (min, max)[b]	NR (9.7, 12+)	17.7 (4, 24+)	NR (2.7+, 12.2+)
Median follow-up, months (min, max)	10.4 (0.7, 15.0+)	8.1 (1.1, 36.9+)	3.8 (0.7, 12.9+)

NR, not reached; ND, not done.

[a] By computer-assisted IHC.

[b] Efficacy-evaluable pts: CD30+ BV + R (*N* = 13), CD30+ BV (*N* = 48), and CD30u BV (*N* = 49).

[c] Efficacy-evaluable pts: CD30+ BV + R (*N* = 8), CD30+ BV (*N* = 39), and CD30u BV (*N* = 34).

soluble CD30 at baseline. The majority of CD30+ pts on BV had a higher % CD30 by computer-assisted IHC than by visual assessment, and some CD30u pts had quantitative CD30 expression by computer-assisted IHC. For CD30u pts with available results, analysis of CD30 mRNA showed levels comparable to the CD30+ pts. The median number of treatment cycles was 4 for both the CD30+ pts on BV (range, 1–19) and on BV + R (range, 1–15). CD30u pts received a median of 2 cycles (range, 1–12); 8 remain on treatment. The ORR for CD30+ pts was 43% (42% BV, 46% BV + R) and 27% for CD30u pts.

Adverse events (AEs) occurring in >15% of pts in any arm included fatigue, nausea, neutropenia, diarrhoea, peripheral sensory neuropathy, pyrexia, and vomiting. Neutropenia was the most frequent treatment-related ≥ Grade 3 AE. Ten deaths occurred ≤30 days after treatment and were all disease related, except 1 due to treatment-related toxic epidermal necrolysis (CD30+ BV + R) and 1 due to unrelated cardiac arrest (CD30u).

Conclusions: BV alone and BV + R showed greater activity in CD30+ DLBCL pts compared to CD30u pts. Toxicity was similar across arms and aligns with the current BV safety profile. Biomarker analyses are ongoing. Response rates and alternative methods of assessing CD30 appear to support the targeted mechanism of action for BV.

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UPDATED RESULTS OF A PHASE 2 TRIAL OF BRENTUXIMAB VEDOTIN COMBINED WITH RCHOP IN FRONTLINE TREATMENT OF PTS WITH HIGH-INTERMEDIATE/HIGH-RISK DLBCL

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Introduction and Methods: Pts with high-intermediate/high-risk DLBCL have relatively poor outcomes with RCHOP. Single-agent brentuximab vedotin (ADCETRIS®) has shown activity in pts with relapsed or refractory DLBCL (CD30+ pts, 17% CR; CD30− pts, 10% CR). In this study, pts were randomized to 6 cycles of BV + RCHOP: 1.2 or 1.8 mg/kg BV q3 wks IV with standard RCHOP. Key inclusion criteria were standard IPI scores of 3–5 or age-adjusted IPI (aaIPI) scores of 2–3 (high-intermediate/high risk). Disease response was per Cheson 2007 with PET/CT.

Results: At the planned interim analysis, 53 pts were enroled and 51 were treated. At baseline, 62% were high-intermediate risk (IPI 3, aaIPI 2) and 38% were high

DOI: 10.1002/hon

risk (IPI 4–5, aaIPI 3). 70% had Stage IV disease, and 28% had an ECOG score of 2. Due to an increased rate of G3 neuropathy seen early in the 1.8 mg/kg BV + RCHOP arm (30% vs 8%), an SMC recommended treatment continues at 1.2 mg/kg BV + RCHOP.

At EOT, the ORR was 97% with 80% PET-negative CR (1.2 mg/kg BV + RCHOP, 86% CR; 1.8 mg/kg BV + RCHOP, 75% CR) for 30/51 pts with an assessment. CD30+ pts ($n = 13$) had a higher CR rate than CD30− pts ($n = 16$) (92% vs 69%); 4 CD30− and no CD30+ pts have progressed after a median follow-up of 5 months. CR rates were similar between ABC and GCB subtypes.

Treatment-emergent AEs occurred in 96% of treated pts; the most frequent (≥30%) were nausea, fatigue, peripheral sensory neuropathy, diarrhoea, anaemia, decreased appetite, febrile neutropenia, and vomiting. ≥G3 events occurring in >20% of pts were febrile neutropenia (27%), neutropenia (25%), and anaemia (24%). AEs of neuropathy (mostly G1/2) occurred in 55% (38%, 1.2 mg/kg BV + RCHOP; 77%, 1.8 mg/kg BV + RCHOP). AEs caused discontinuations in 10% of pts; 2 pts died due to AEs (sepsis or hypovolemic shock), and 3 pts died following progression.

Conclusion: BV + RCHOP has encouraging activity in frontline high-intermediate/high-risk DLBCL; data suggest that the CR rate in CD30+ pts was higher than in CD30− pts. When combined with RCHOP, BV is better tolerated at 1.2 mg/kg than 1.8 mg/kg due to reduced neuropathy. The protocol has been amended to assess the safety and activity of 1.8 mg/kg BV + RCHP in CD30+ high-intermediate/high-risk DLBCL pts.

'FOCUS ON…' SESSION: EPIDEMIOLOGY AND INFECTIONS

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INTERNATIONAL DLBCL STUDY FINDS BIOLOGICAL HETEROGENEITY BETWEEN ETHNICALLY DIVERSE COUNTRIES BUT SIMILAR IPI-ADJUSTED OUTCOMES

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Introduction: Cancer centres in non-Western countries may wish to compare their results against published studies predominantly based on high-income Caucasian populations. Achievement of similar results may be confounded if disease biology is different in low or middle income countries. Biological variation may arise from ethnic diversity which may influence disease or host response, or environment which may influence causation. The International Atomic Energy Agency sponsored a prospective cohort study of diffuse large B-cell lymphoma (DLBCL) in countries from 5 UN-defined geographical regions to test this hypothesis.

Methods: To seek between-country biological variation, we used a prognostic six gene expression model, validated for outcome prediction independent of the IPI [1] and matched biological variation against survival at 2 years. Consented patients with DLBCL in Chile, Hungary, S Korea (high income $n = 121$), Brazil, Thailand, Turkey (upper-middle income $n = 120$), India, and the Philippines (lower middle income $n = 52$) were treated with R-CHOP between 2008 and 2013. RNA from fixed diagnostic tissue was shipped to a central laboratory. Expression of LMO2, BCL6, FN1 and BCL2, SCYA3, CCND2 was assayed by Taqman QPCR and relative quantification assigned based on expression ratio to normalized copy number. The combined 6-gene score was calculated as published [1]. Variation in gene expression by country was investigated using analysis of variance, while variation in event-free (EFS) and overall survival (OS) was investigated using Cox proportional-hazards models.

Results: Survival at 2y for all patients recruited into the international study cohort was EFS 79% (95%CI 74 83%), OS 86% (81-89%) [2]. Of these, 156 patients from 7 countries (excl. Brazil) had complete gene expression data. There was significant inter-country variation for all 6 genes individually ($p < 0.0001$) and when combined in the 6-gene model ($p < 0.0001$). Unadjusted 2y EFS and OS for the whole cohort showed little inter-country heterogeneity; after adjustment for IPI, there was no inter-country difference for EFS ($p = 0.58$) or OS ($p = 0.63$). Further analysis, of 120 cases with matched clinical and gene-expression data, likewise found no between-country difference in survivals that could be related to variation in individual gene expression or the combined 6-gene score.

Conclusions: Identified biological variation within DLBCL between countries did not translate into differences in outcomes at 2y. Our study provides important evidence that oncologists in ethnically diverse, middle income countries can benchmark their IPI-adjusted survivals for DLBCL to published results from high income, predominantly Caucasian populations.

Reference:

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INVOLVEMENT OF MORAXELLA CATARRHALIS IN THE PATHOGENESIS OF HODGKIN LYMPHOMA (NODULAR LYMPHOCYTE PREDOMINANT TYPE, IGD-POSITIVE)

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Introduction: Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a rare type of Hodgkin lymphoma. In contrast to Hodgkin–Reed–Sternberg cells in classical Hodgkin lymphoma, lymphocyte predominant (LP) cells, the tumour cells in NLPHL, show functional variable region genes of immunoglobulins with ongoing somatic hypermutation. Chronic B cell receptor (BCR) stimulation has been

DOI: 10.1002/hon

proposed to play a central role in the pathogenesis of NLPHL. However, the mechanisms underlying this stimulation are poorly understood. Aim of the study was to identify potential target antigens of BCRs of LP cells, with emphasis on autoantigens and bacterial structures.

Methods: Recombinant Fab-fragments were constructed of corresponding immunoglobulin heavy and light chain variable regions from LP cells isolated by laser capture microdissection from cryopreserved NLPHL specimens.

Results: Fab-fragments of 9 NLPHL cases were constructed. The autoantigenic structures ribosomal protein S27a and pyruvate carboxylase were identified as target antigens of the LP cell-BCR of two NLPHL patients. When tested on the lysates from 10 bacterial strains, the recombinant Fabs of 2 further patients with NLPHL (IgD+) reacted with the lysate from Moraxella catarrhalis (MC). MC is a common bacterium colonizing the upper respiratory tract, which expresses a 200 kDa IgD-binding protein (MID/hag) enabling MC to bind to the Fc part of IgD and thus activating IgD carrying B-cells. IgD+ NLPHL are a peculiar clinical subgroup of NLPHL, with a strong male predominance and particularly occurring in the paediatric age group. Analysis of additional IgD+ NLPHL cases revealed that the LP cell-BCR of altogether 4/5 IgD+ NLPHL cases reacted specifically with the DNA-directed RNA polymerase subunit beta of MC (rpoC), a protein of 155 kDa. One of these patients with available serum was shown to contain polyclonal rpoC-antibodies in the serum.

Conclusions: This is the first study to show an association between MC and IgD+ NLPHL, suggesting a causal role of MC in the pathogenesis of IgD+ NLPHL. MC is presumably capable of binding the BCR of IgD+ LP-cells via its IgD-binding protein and can mediate chronic antigenic stimulation of B-cells with specificity of MC-rpoC. The presence of polyclonal serum antibodies against MC-rpoC in patients with IgD+ NLPHL suggests that NLPHL is the result of a clonal evolution from a polyclonal B-cell response against MC-rpoC. Our findings are fundamental for the understanding of the pathogenesis of this peculiar clinical subtype of NLPHL and might have relevance for the prophylaxis and treatment of this disease.

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EPSTEIN–BARR VIRUS DNA LOAD IN CHRONIC LYMPHOCYTIC LEUKAEMIA IS AN INDEPENDENT PREDICTOR OF CLINICAL COURSE AND SURVIVAL

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Introduction: The relation between Epstein–Barr virus (EBV) DNA load and clinical course of patients with chronic lymphocytic leukaemia (CLL) is unknown.

Methods: We assessed EBV DNA load by quantitative PCR at CLL presentation in mononuclear cells (MNC) of 220 consecutive patients that were enroled between June 2007 and December 2013 and followed up in two major Institutions as part of the prospective CLL-Veneto registry. These patients constituted a learning set for prognostic considerations. A subsequent retrospective cohort of 112 patients with CLL was used for independent confirmation (validation set). In all patients, biological material was collected at diagnosis, before receiving any cytotoxic treatment. In 20 patients, EBV DNA load was also assessed on plasma samples, and in five cases, DNA was extracted both from MNC and sorted CD19+ CD5+ B-cells for comparison of EBV DNA load. Forty-one age-matched healthy subjects were tested for EBV DNA load on MNC with the same methods.

Results: EBV DNA load was detectable in 59% and high (≥2000 copies/μg DNA) in 19% of patients. EBV DNA load was significantly higher in CLL patients than in healthy subjects ($P < 0.0001$). Patients tested on sorted B-lymphocytes had similar EBV DNA load compared to MNC, while EBV DNA was consistently undetectable in the plasma of tested patients, irrespectively of EBV DNA load in MNC. No relation was found between high EBV DNA load and clinical stage or biological variables, except for 11q deletion ($P = 0.004$), CD38 expression ($P = 0.003$), and *NOTCH1* mutations ($P = 0.03$). High EBV DNA load led to a 3.14-fold increase in the hazard ratio of death and to a shorter overall survival (OS; $P = 0.001$), and increasing levels EBV DNA load were directly associated to worse outcome. Poor OS was attributable, at least in part, to shorter time-to-first-treatment (TTFT, $P = 0.0008$), with no higher risk of Richter's transformation or second cancer. Multivariate analysis selected high levels of EBV DNA load as an independent predictor of OS after controlling for confounding clinical and biological variables. Either detectable EBV DNA load (55% of patients, ≥2000 copies/μg DNA in 22%) or the predictive value of EBV DNA load was confirmed in the validation set, both in terms of OS and TTFT.

Conclusions: EBV DNA load in MNC at presentation is an independent predictor of OS in patients with CLL. Further studies are needed to clarify whether EBV has an active role in enhancing CLL progression or is merely a manifestation of the underlying immunosuppressed state associated with the disease.

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EXPOSURE TO HEPATITIS B VIRUS (HBV), FAMILY HISTORY, AND B-CELL NON-HODGKIN LYMPHOMA (B-NHL): A CASE–CONTROL STUDY AMONG JEWS AND ARABS IN ISRAEL AND THE WEST BANK

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Introduction: Although Hepatitis C is an established risk factor for B-NHL, the aetiologic role of HBV is less clear. This analysis focuses on associations between exposure, development of a chronic carrier state, and antibody response to HBV and B-NHL.

Methods: A unique collaborative case–control study among Israeli Jews (IJ) and Palestinian Arabs (PA) based on questionnaires, histopathology review and serology by ELISA in 822 incident (307 PA/515 IJ) B-NHL cases and 713 healthy controls. We report pooled odds ratios (OR) and 95% confidence intervals (CI), adjusting for sex, age and ethnicity.

DOI: 10.1002/hon

Results: (1) Exposure: Hepatitis B core antibody seropositivity (Anti-HBc+) differed between the two populations: 14.8%/14.2% among IJ cases/controls compared to 33.6%/35.4% in PA cases/controls ($P < 0.01$), with no case–control differences (OR 0.93, CI:0.71–1.22).

(2) Chronic carrier state: HBsAg was detected in 2% IJ cases versus 0.5% controls, and in 5.4% PA cases versus 3.4% controls (OR 1.87, CI: 0.91–3.86). This association was statistically significant in the DLBCL subtype ($N = 425$) (OR 2.5, CI:1.18–5.45). The prevalence of HBsAg + among those exposed to HBV (AntiHBc+) was higher in cases (15%) than in controls (7.8%) ($P = 0.03$). Of interest, a significant association between a positive family history of haematopoietic cancer in 1st degree relatives and HBsAg + (OR 2.69, CI: 1.02–7.1) was observed.

(3) Antibody response to HBV: We found a significant negative association between Hepatitis B surface antibody (Anti-HBs+) and B-NHL in the pooled analysis (OR 0.73, CI: 0.58–0.93). This protective association was observed whether it derived from natural exposure (OR 0.72, CI: 0.53–0.98) or vaccine exposure (OR = 0.74, CI: 0.53–1.04), and was noted for DLBCL specifically (OR 0.71, CI: 0.53–0.95). No significant associations were observed for follicular NHL ($N = 183$) or other subtypes.

Conclusions: Serologic evidence of exposure to HBV, as reflected by anti-HBc alone, does not appear to be a risk factor for B-NHL in our study populations. However, chronic HBsAg carriers are at increased risk for B-NHL, specifically DLBCL. Among exposed individuals, a chronic carrier state was more prevalent in cases than controls. Our results raise the possibility of a link between inability to clear the virus and B-NHL; the association with positive family history of haematologic malignancies in chronic carriers further supports the notion of an inherited joint susceptibility to both B-NHL and a chronic carrier state. The negative association between an antibody response to both naturally occurring and vaccine-induced exposure to HBV and B-NHL implies that immune competence is protective against B-NHL or alternatively may reflect diminished immune response to HBV in B-NHL cases due to the lymphoma itself or its treatment. Prospective studies may clarify the role of HBV vaccination in the prevention of B-NHL in endemic populations.

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EBV POSITIVE DLBCL OF THE ELDERLY IS A HETEROGENEOUS DISORDER WITH OUTCOME PREDICTED BY ITS IMMUNE MICROENVIRONMENT

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Introduction: The prognosis of EBV+ DLBCL of the elderly remains controversial, being associated with adverse outcome in some series. There remains little known regarding the influence of the tumour microenvironment (TME) on its outcome. Digital multiplex gene expression (DMGE) based on nanoString© technology is an innovative method of measuring gene expression from FFPE-based specimens. Use of DMGE in EBV+ DLBCL has not been reported.

Methods: We analysed 255 FFPE biopsies from patients with DLBCL treated with R-CHOP chemo-immunotherapy. EBV-related genes and key TME genes were assayed.

Results: EBER-ISH (the 'gold-standard') was performed in 48 cases. EBER expression on the nanoString platform correctly identified EBV-tissue status in 46 (96%). In one EBER-ISH-ve tissue, DMGE identified high levels of EBER and other EBV-related genes such as LMP1 and LMP2, consistent with EBV-tissue positivity that failed detection by EBER-ISH. All patient samples positive by EBER-ISH were detected by DMGE. Overall, by nanoString, EBER expression was markedly elevated in 21 (8%) of 255 patients.

Survival data were available in 158 DLBCL patients (median follow-up 4 years). In these, EBER-positivity by DMGE was associated with inferior 5-year overall survival (OS) of 48% compared to 75% in EBV-tissue negative patients ($p = 0.015$). The individual IPI factors and the IPI score did not differ between EBV+ and EBV− patients. EBV+ DLBCL tissues had elevated CD8 and IFNγ compared to EBV-negative tissues, consistent with a localized effector T-cell response to EBV-expressing malignant B-cells ($p = 0.02$ and $p = 0.03$). However, this was countered by higher levels of the immune checkpoint/suppression markers LAG3 ($p = 0.006$), IL1R2 ($p = 0.0015$) and TIM3 ($p = 0.05$). PD-1, PD-L1 and PD-L2 gene counts were equivalent. The levels of CD163, a marker of tumour associated macrophages (TAMs), was markedly higher in EBV+ DLBCL ($p = 0.009$). Notably, using the CD163:CD68 gene expression ratio as a measure of M2 tumour promoting TAMs, EBV+ DLBCL clustered into two distinct groups, with disparate 5-year OS of 100% in 'low' M2 score patients and 14% in 'high' M2 score ($p = 0.0006$). The poor prognosis group had a 6-fold increase in M2 compared to the good outcome group.

Conclusions: DMGE is highly sensitive for detecting EBV+ DLBCL and enables simultaneous quantification of other factors that may have prognostic importance such as the TME. Using the nanoString platform, the inferior outcome of EBV+ DLBCL compared to EBV-negative DLBCL was confirmed. EBV+ DLBCL had a distinct TME, with elevated immune effectors and checkpoints. The M2 score was able to segregate EBV+ DLBCL into groups with highly contrasting survival outcomes to R-CHOP, indicating that the TME and not EBV-tissue positivity per se is the principal determinant of survival. M2 targeted therapies may have utility in this disease and should be further explored.

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THE ROLE OF HBV-INFECTION IN CHRONIC LYMPHOCYTIC LEUKAEMIA

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Introduction: The prevalence of hepatitis B virus (HBV) infection in China is high compared with European and North American countries, whereas incidence of chronic lymphocytic leukaemia (CLL) is low. The objective of our study is to determine the frequency and impact of HBV infection in persons with CLL.

Methods: 411 newly diagnosed consecutive subjects with CLL were studied. HBV infection, defined as HBsAg-positive or HBcAb-positive. Detailed clinical and biological features of the subjects were interrogated for associations with HBV infection. Associations between HBV infection and interval from diagnosis to time-to-treatment (TTT) and overall survival (OS) were also studied.

Results: 88 subjects (22%) were HBV-positive at diagnosis. HBV-positive subjects were younger, and had lower haemoglobin concentrations and platelet and albumin levels, higher thymidine kinase-1 levels, *ATM* deletion, un-mutated *IGHV* and *TP53* disruption compared with subjects who were HBV-negative at diagnosis. Per cent

DOI: 10.1002/hon

CD19, CD23, CD22, CD20 and CD38 expression and mean fluorescence intensity (MFI) were also increased in subjects HBV-positive at diagnosis, and there was a significant association with use of *IGHV*4-39 and BCR subset 8 genes. In multivariate analyses, HBV-positivity was associated with an increased risk of transformation to Richter syndrome [HR, 4.43 (95% CI, 1.04–18.8); $P = 0.044$], briefer TTT [median 3 months (range, 0–96 months) vs 15 months (0–164 months); $P = 0.302$] and worse OS [HR 2.36 (1.07–9.99); $P = 0.040$].

Conclusion: Clinical and biological features of CLL differ in persons who are HBV-positive or -negative at diagnosis. Subjects who were HBV-positive had a greater risk of transformation to Richter syndrome, briefer TTT interval and worse survival. Whether HBV-infection predisposes to developing CLL and alters the course of CLL or both is unknown.

'FOCUS ON…' SESSION: MANAGEMENT OF T-CELL LYMPHOMA

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CHOEP VERSUS CHOP GIVES BETTER RESULTS IN FIRST-LINE THERAPY OF T-CELL LYMPHOMA. A RETROSPECTIVE ANALYSIS FROM CZECH LYMPHOMA STUDY GROUP (CLSG) DATABASE

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Introduction: T-cell lymphoma (TCL) is a heterogenous group of rare lymphomas with global poor prognosis. CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen shows insufficient efficacy, and the promising addition of etoposide to CHOP (CHOEP) and/or upfront consolidation with autologous stem cell transplantation (auto-SCT) have never been tested in randomized trials.

Patients and Methods: In analysis of potential prognostic factors, we included 677 patients with newly diagnosed TCL registered into CLSG database between 1999 and 2014. Data about 1st line therapy were available for 652 patients; 352 patients (54%) were treated by CHOP or CHOEP. For 1st line chemotherapy analysis, only patients younger than 60 years were included, which results in 133 patients treated with CHOP and 52 patients with CHOEP. To analyse the effect of consolidation with auto-SCT, we selected patients younger 60 years, who were treated with CHOP or CHOEP in 1st line and with no progression/relapse or death during first 12 months after diagnosis. All patients meeting mentioned criteria were separated in two subgroups depending on whether auto-SCT was made or not. In total, we analysed 21 patients with auto-SCT and 72 patients without auto-SCT.

Results: Out of 677 patients with any type of TCL were identified: 248 (37%) PTCL, 39 (6%) AITL, 211 (31%) ALCL, 62 (9%) of T-NHL and the remaining 17% cases showed less frequent histological subtypes (NK/T, EATL, MF…). Median age was 59 years (range; 18–89 years), the majority of patients were males 414 (61.2%) and median follow-up for surviving patients was 3.3 years (range; 0. 1–15 years). In the entire cohort, the multivariable analysis showed the association of male gender, age ≤ 60 years, stage III/IV, performance status ≤ 2, bulky tumour and elevated lactate dehydrogenase, with shorter overall survival (OS) and progression-free survival (PFS), p 0.05.

Evaluable patients treated with CHOEP versus CHOP had better 5-year PFS 56.7% (41.4–72.0; CI 95%) versus 36.8% (27.1–46.4; CI95%) (p.02), which was projected into trend to better OS 64.7% (49.3–80.0; CI 95%) versus 54.3% (44.0–64.6; CI 95%) (p.09). Clinical and demographical parameters were similar in both subgroups. Auto-SCT as consolidation in the 1st line seemed to have no influence on outcome in patients with TCL. The 3-year PFS and OS for younger patients pre-treated with CHOP/CHOEP regardless subtype was 89.1% and 82.7%, respectively, and were similar to 3-year PFS and OS in nontransplanted patients 88.7% and 79.0%.

Conclusion: This population-based analysis describes the relative frequency of TCL in Czech Republic and also identifies some factors with prognostic impact, which support previously published results. Interestingly, the addition of etoposide to CHOP had a beneficial influence, but the consolidation with auto-SCT cannot probably augment the effect.

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LONG-TERM OUTCOME OF ADULTS WITH ALCL AFTER THE FIRST RELAPSE/PROGRESSION: A LYSA STUDY

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Introduction: Long-term outcomes of adults with systemic anaplastic large-cell lymphoma (ALCL) after the first relapse/progression are not definitively established and should be evaluated.

Methods: We previously reported the long-term outcomes of adult patients treated at first diagnosis of systemic ALCL in three LYSA prospective clinical trials (Sibon D et al, J Clin Oncol 2012). All patients had confirmed systemic ALCL after immunohistopathologic review and defined ALK expression status. Here, we report the long-term outcomes of these patients after the first relapse/progression.

Results: Among the 138 (64 ALK+ and 74 ALK−) adult patients treated at first diagnosis in clinical trials, 40 (14 ALK+ and 26 ALK−) relapsed/progressed after the frontline chemotherapy and their long-term outcomes were analysed. Median follow-up of relapsed patients was 12.5 years (ALK+ 13.6 years; ALK− 12.1 years). The median age at first relapse/progression was 35 (19–76) years for ALK+ patients and 61 (34–82) years for ALK− patients. All patients relapsed/progressed after polychemotherapy with an anthracycline-based regimen. Five (4 ALK+ and 1 ALK−) patients relapsed/progressed after planned high-dose therapy/autologous stem-cell

DOI: 10.1002/hon

transplantation as first-line treatment consolidation. Median time from initial inclusion in clinical trials to relapse/progression after primary therapy was 6 months (46 days–2.8 years) for ALK+ patients and 11 months (32 days–5.6 years) for ALK− patients. Median progression-free survival (PFS) after the first relapse/progression (second PFS) was 5 months for ALK+ patients and 4 months for ALK− patients. Median overall survival (OS) after the first relapse/progression was 11.9 months for ALK+ patients and 7.7 months for ALK− patients, and 10-year OS rates were 14% for ALK+ patients and 15% for ALK− patients, without significant difference ($p = 0.99$). ALCL was the main cause of death. Impact of treatments will be presented.

Conclusions: Most patients with first-relapsed/progressive ALCL have poor outcomes with short survival, without significant difference between ALK+ and ALK− patients. These results could be used as reference in the evaluation of new drugs for relapsed/progressive ALCL.

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PROSPECTIVE PHASE II TRIAL OF LENALIDOMIDE IN ASSOCIATION WITH CHOP IN ELDERLY PATIENTS WITH ANGIOIMMUNOBLASTIC T CELL LYMPHOMA (AITL): INTERIM ANALYSIS OF A LYSA STUDY

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Introduction: Angioimmunoblastic T-cell lymphoma (AITL) is one of the most frequent subtypes of T-cell lymphoma in Western countries. Its treatment remains ill-defined with only 30% of patients (pts) experiencing long-term disease-free survival when treated with anthracycline-based regimens. AITL derives from follicular helper T cells and associates with a unique cell microenvironment. Owing to this microenvironment and given the promising activity of lenalinomide in a relapsed setting, we postulated that AITL patients might benefit from a treatment with lenalinomide combined with a classical CHOP regimen.

This multicentre, open label, phase 2 trial (NCT01553786) investigates the combination of lenalidomide with CHOP in previously untreated elderly pts.

Patients and Methods: Patients older than 59 years were treated with 8 cycles of lenalidomide + CHOP 21 (lenalidomide 25 mg/day (d), d1 to 14—cyclophosphamide 750 mg/m^2, d1—doxorubicin 50 mg/m^2, d1—vincristine 1.4 mg/m^2, d1—prednisone 40 mg/m^2 d1 to 5, with pegfilgrastim at day 6) and received intrathecal methotrexate as central nervous system prophylaxis. A thrombosis prophylaxis was mandatory. A dose adjustment of lenalidomide was planned according to toxicities. A PET was performed at diagnosis and at the end of treatment. Tumour samples and PET were centrally reviewed.

The primary objective was to evaluate the complete response (CR) rate based on a visual interpretation (Deauville five-point scale) of PET according to the Lugano 2014 Classification.

Secondary endpoints were safety, progression-free survival and overall survival. Based on a Simon two-stage design comparing a CR rate of 60% with treatment to an unacceptable CR rate of 45% (CHOP alone), 17 or more CR out of 37 evaluable pts were required to declare the treatment worthy of further testing.

Results: Between 11/2011 and 07/2014, 38 pts were enroled, 37 being evaluable. Median age at diagnosis was 68 (59–79) years, 47% were male, 68% had a performance status of 0 to 1, 97% an Ann Arbor stage > III, 84% IPI > 3 and 82% a PIT score > 2. The mean number of cycles delivered was 5.9.

A total of 21 pts received the 8 planned cycles. A metabolic CR was obtained in 17 pts [46% (IC95%:29.5–63.1)], 3 pts achieved a partial response, 12 progressed and 5 could not be evaluated (one death of a septic shock after cycle 1, one retrieval of consent, 2 pts with a major protocol violation retrieved after one cycle and one pt who refused to continue lenalidomide after one cycle).

Toxicity was in the range of CHOP regimen with 70% and 30% grade 4 neutropenia and thrombocytopenia, respectively. Four episodes of thrombosis occurred during treatment. No second cancer was reported.

Conclusion: This pre-planned interim analysis shows that a combination of 25 mg of lenalidomide for 14 days with CHOP cycles gives acceptable activity and toxicity in AITL elderly pts. The study will continue as planned for a total of 70 evaluable pts.

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CLINICAL OUTCOMES AND PROGNOSTIC FACTORS OF UP-FRONT AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH EXTRANODAL NK/T-CELL LYMPHOMA

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Introduction: Limited data exist on up-front autologous stem cell transplantation (ASCT) in extranodal NK/T-cell lymphoma (ENKTL). The aim of this study was to investigate clinical outcomes and prognostic factors in patients (pts) with ENKTL treated by up-front ASCT.

Methods: We consecutively enroled pts with ENKTL who achieved CR or PR after primary therapy and underwent up-front ASCT from 9 institutions from Jan 2004 to Dec 2013. Pts who underwent salvage ASCT were excluded. Pts were classified as limited or advanced diseases according to Ann Arbor stage, and NK/T-cell lymphoma prognostic index (NKPI) was determined for prognosis.

DOI: 10.1002/hon

Results: A total of 62 pts (43 male, 19 female) with median age of 45.5 years (range, 18–64) was included. Thirty-one pts (50%) were advanced disease, and 22 (36%) had B symptoms at diagnosis. ECOG performance status was ≥ 2 in 7 (11%), and serum LDH level was elevated in 28 (45%). Thus, 42 pts (68%) were classified as high risk (≥2 factors) by NKPI. Pts with advanced disease were associated with a higher risk of NKPI and more frequent extra-upper aerodigestive (EUA) origin. Fifty-one pts (82%) received non-anthracycline-based chemotherapy. The median time from diagnosis to ASCT was 6.7 months (range, 3.2–10.3).

Pre-transplant disease status consisted of CR in 38 pts (61%) and PR in 24 pts (39%), and final post-transplant response included CR in 47 pts (78.3%). Early progression within 3 months following ASCT occurred in 8 pts (12.9%). At a median follow-up of 43.3 months (3.7–114.6), 3-year PFS and OS were 52.4% (95% CI, 39.9–64.9) and 60.0% (95% CI, 47.5–72.5), respectively. Pts with limited disease had significantly better 3-year PFS (64.5% vs 40.1%, $P = 0.017$) and OS (67.6% vs 52.3%, $P = 0.048$) than those with advanced disease.

Multivariate analyses were performed separately in 2 steps. In the first step, analysis included all pts ($N = 62$) and demonstrated that high risk NKPI (HR, 2.85; 95% CI, 1.09–7.49), poor ECOG performance status (HR, 4.31; 1.48–12.60), and PR at ASCT (HR, 4.12; 1.90–8.91) were independent predictors for worse PFS. In the second step, pts were stratified by stage. In the advanced stage group ($N = 31$), PR at ASCT (HR, 3.09; 1.06–9.05) and anthracycline-based chemotherapy (HR, 10.44; 2.02–53.96) were associated with higher risk of progression. In the limited stage group ($N = 31$), high risk NKPI (HR, 3.92; 1.05–14.67) and EUA origin (HR, 11.60; 2.29–58.83) were independent predictors for increased risk of progression, while radiotherapy (HR, 0.24; 0.06–0.92) was associated with lower risk of progression.

Conclusion: This study is the first to investigate clinical outcomes of up-front ASCT with a large patient cohort, considering rarity of ENKTL. Our study represents that up-front ASCT is an active treatment for ENKTL patients responding to primary therapy. NKPI and pre-transplant response were important factors for predicting clinical outcomes, particularly NKPI in limited disease and pretransplant response in advanced disease.

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P-GEMOX REGIMEN FOLLOWED BY EXTENSIVE INVOLVED-FIELD RADIOTHERAPY FOR NEWLY DIAGNOSED STAGE I/II ENKTL

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Background: Extranodal natural killer/T-cell lymphoma, nasal type (ENKTL) is an aggressive form of non-Hodgkin lymphoma. Optimal therapeutic strategies for ENKTL have not been fully defined yet. Although radiotherapy is regarded a curative approach, approximately 25–50% patients experience local relapse or systemic failure who receive RT alone. The addition of chemotherapy to radiotherapy may reduce the risk of recurrence. Therefore, we evaluated the efficacy and safety of induction P-Gemox regimen in patients with newly diagnosed stage I/II ENKTL.

Methods: We conducted this pilot study to evaluate the efficacy and safety of pegaspargase combined with gemcitabine and oxaliplatin (P-Gemox) followed by extensive involved-field radiotherapy (EIFRT) in patients with stage I/II ENKTL. We enroled 56 newly diagnosed stage I/II patients. All patients received P-Gemox chemotherapy. The P-Gemox dosage was as follows: gemcitabine 1000 mg/m^2 was administered intravenously for 30 minutes on days 1 and 8; oxaliplatin 100 mg/m^2 was given on day 1, and pegaspargase was administered in deep intramuscular injection of 2000 U/m^2 at two different sites on day 1. The regimen was repeated every 3 weeks. Patients underwent 4 cycles of induction chemotherapy, followed by EIFRT. After achieving complete response (CR), partial response (PR), or stable disease (SD). EIFRT was given at the dosage of 56 Gy in 28 fractions over 4 weeks. Primary EIFRT was delivered using 6-MeV linear accelerator using 3-dimensional conformal treatment planning. Clinical target volume (CTV) included gross tumour volume with a margin of at least 20 mm and the bilateral nasal cavity, bilateral parasinusess. Planning target volume (PTV) included CTV with a 5 mm margin. For stage IIE disease, CTV and PTV also included the involved the cervical lymph node area.

Results: The median follow-up was 35.2 months (range: 10.6–51.4 months). The objective response rates (ORR) of P-Gemox regimen was 89.3% (50/56), 35 (62.5%) patients achieved CR, and 15 (26.8%) patients achieved PR, respectively. After EIFRT, ORR increased to 94.6% (53/56) and CR rate increased to 89.3% (50/56). The 4-year overall survival (OS) and progression-free survival (PFS) rates were 90.7 ± 4.0% and 89.1 ± 4.2% for the whole cohort(Figure 1A,B). The OS and PFS of stage I patients were superior to patients with stage II (Figure 2A,B). No treatment-related death was observed. No allergic reactions occurred. Common toxicities (>50%) were neutropenia (80.3%), thrombocytopenia (55.3%), and hypoproteinemia (75.0%). Hypofibrinogenemia was 44.6%. The most common grade III/IV toxicities (>10%) were granulocytosis (23.2%), thrombocytopenia (19.6%), and hypoproteinemia (10.7%).

Conclusion: The P-Gemox regimen followed by radical radiotherapy yielded very promising long-term survival for patients with stage I/II ENKTL with good tolerance. Further investigation of P-Gemox in a larger series of patients is required

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HDAC INHIBITOR COMBINATIONS EXHIBIT SYNERGY IN PRECLINICAL AND CLINICAL EXPERIENCES IN DRUG RESISTANT T-CELL LYMPHOMA

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Introduction: The T-cell lymphomas typically respond poorly to conventional chemotherapy. Epigenetic lesions including mutations in TET2, IDH1/2 and DNMT3 seem to be clustered in TCL. In addition, HDAC inhibitors have only exhibited activity in patients with TCL, where 3 have FDA indications. Given these observations, HDAC inhibitor combinations provide a rational platform for developing novel treatment regimens in TCL.

Methods: The HDAC inhibitors romidepsin (R) or belinostat (B) were evaluated in combination with pralatrexate (P) and/or hypomethylating agents [5-azacytidine (5AZ) or decitabine (D)] in models of TCL, using standardized cell lines and NOG mice. Detailed PK and PD studies were performed. Early studies of R + P and R + 5-AZ are conducted in patients with R/R lymphoma.

Results: R + P exhibited marked synergy in a panel of TCL lines and a bioluminescent mouse model of TCL producing a significant survival advantage. 3-D US imaging revealed even larger tumours in xenografted NOG mice treated with R + P achieved remissions associated with a survival advantage. PK and PD studies confirmed accumulation of R and P in tumour tissue, which correlated with PD studies demonstrating potent induction of apoptosis. R + D produced synergy with low

DOI: 10.1002/hon

synergy coefficients. The synergy was dependent on the concentration of the HDAC inhibitor. Gene expression array and methylation profiling revealed differentially expressed genes and modulated pathways for each of the single treatment conditions and combination. 944 unique genes were modulated by the combination supporting the idea of molecular synergism. These data demonstrate that combinations of DNMTI and HDACIs are potently synergistic in models of T-cell lymphoma and capable of reversing the malignant signature. Mouse experiments supported the merit of B + D compared to single agents. Based on these results, 2 trials were opened with R + P and R + 5AZ in patients with B- and T-cell lymphoma. R up to 12 mg/m^2 and P up to 20 mg/m^2 were safe, with no mucositis or Grade 3 or 4 thrombocytopenia. Among 18 patients treated with R + P, 9 patients had T-cell lymphoma. Among 7 evaluable patients, all 7 achieved a response, including 3 CR. Several patients were bridged to a definitive stem cell transplant. Among 18 patients on the R + 5AZ study, 5 had R/R PTCL, of which 3 were evaluable. All 3 achieved a response, with 2 of them in CR. One patients with a CD8(+)-cytotoxic CTCL experienced clinical resolution of her disease, which progressed following cessation of treatment. The response rate for both studies for evaluable patients with PTCL was 100% on the dose escalation portion of these clinical studies. These important translational experiences suggest that rational combinations of drugs active in PTCL have efficacy in heavily treated patients.

Conclusions: HDAC inhibitor based combinations exhibit marked potent activity in both the preclinical and clinical settings.

'FOCUS ON…' SESSION: NEW DRUG COMBINATIONS

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UBLITUXIMAB (TG-1101), A NOVEL GLYCOENGINEERED ANTI-CD20 MAB, IN COMBINATION WITH IBRUTINIB ACHIEVES 95% ORR IN PATIENTS WITH HIGH-RISK RELAPSED/REFRACTORY CLL

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Introduction: Ublituximab (UTX) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC). Two Phase I trials of single agent UTX in rel/ref CLL reported significant response rates with rapid and sustained lymphocyte depletion. Herein, we report safety and efficacy data on the combination of ublituximab with the novel BTK inhibitor ibrutinib in patients with previously treated CLL.

Methods: Eligible patients had rel/ref CLL/SLL, with an ECOG PS < 3. Study design consists of a 6-patient safety run-in followed by open enrolment. UTX (cohorts of 600 and 900 mg) was administered on Days 1, 8, and 15 in Cycle 1 followed by Day 1 of Cycles 2–6. Ibrutinib was started on Day 1 daily at 420 mg. Response by CT scan was assessed prior to Cycles 3 and 6. Primary endpoint for safety run-in: safety and dose limiting toxicities (DLTs). Phase II endpoints: ORR, CR rate, MRD (−/+), and safety. Responses assessed per iwCLL (Hallek, 2008) criteria.

Abstract 105 Table 1.

Type	Pts (*n*)	CR (*n*)	PR* (*n*)	PR (*n*)	nPR (*n*)	SD (*n*)	ORR (%)
High risk (17p/11q/p53 mut)	21	1 (5%)	2 (10%)	17 (81%)	–	–	95
Total CLL	40	1 (3%)	3 (8%)	31 (78%)	1 (3%)	1 (3%)	88

PR*, CR pending bone marrow confirmation; nPR, nodal PR.

Results: 44 CLL pts were enroled: 22M/22F, median age 71 years (range 39–86), median ECOG of 1, median prior Tx = 2 (range 1–7), 36% with >3 prior regimens, prior purine analog = 50%, and prior alkylating agent = 64%. No DLTs were observed during the safety run-in. Gr 3/4 AEs occurring in > 5% of pts were limited to anaemia and neutropenia. There have been no 10% or > reported Grade 3/4 AEs. Ibrutinib was dose reduced in 2 patients (1 diarrhoea, 1 rash) with 1 patient discontinuing treatment due to an ibrutinib related AE (rash). No patients had their ublituximab dose reduced (infusion interruptions only due to IRRs). As of February 2015, 40/44 pts are evaluable for response. Best response to treatment is as follows: UTX appears to control ibrutinib-related lymphocytosis with median 75% decrease in ALC from baseline by end of Cycle 3.

Conclusions: The combination of ublituximab and ibrutinib was both well tolerated and highly active in patients with relapsed or refractory CLL. Notably, a 95% ORR was observed in patients with high-risk CLL, with responses attained rapidly (median TTR: 8 weeks). The addition of ublituximab appeared to mitigate ibrutinib-related lymphocytosis producing earlier clinical responses than historically seen with ibrutinib monotherapy. A randomized Phase 3 study evaluating the combination of ublituximab and ibrutinib compared to ibrutinib alone in patients with high-risk CLL is underway.

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THE CHEMOTHERAPY-FREE TRIPLET OF UBLITUXIMAB, TGR-1202, AND IBRUTINIB IS SAFE AND HIGHLY ACTIVE IN RELAPSED B-CELL MALIGNANCIES

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DOI: 10.1002/hon

Introduction: Multiple active novel targeted agents are emerging for B-cell malignancies, but few studies have successfully and 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, PI3Kδ inhibitor, active in patients with rel/ref haematologic malignancies (Burris, 2014). This Phase 1 trial evaluates the safety of the first triplet combination of a novel anti-CD20 + - PI3Kδ + BTK inhibitor in patients with various B-cell malignancies.

Methods: Eligible patients had rel/ref CLL (including Richter's transformation) or B-cell NHL with an ECOG PS ≤ 2 w/o limit to number of prior therapies. Patients refractory to prior PI3Kδ or BTK inhibitors were eligible. CLL and NHL cohorts were evaluated independently in a 3 + 3 dose escalation design to evaluate safety and dose limiting toxicities (DLTs). UTX was dosed at 900 mg on D 1, 8 and 15 of Cyc 1 and 2 and D 1 on Cyc 4, 6, 9 and 12. TGR-1202 was dose escalated (400, 600, 800 and 1200 mg). Ibrutinib was dosed at 420 (CLL) or 560 mg (NHL). Patients were instructed to take their TGR-1202 in the morning with food and the ibrutinib in the evening. Preliminary efficacy was examined (CLL per Hallek 2008/NHL per Cheson 2007).

Results: As of Feb 2015, 13 patients were evaluable for safety: 4 follicular (FL), 3 CLL/SLL, 2 diffuse large B-cell (DLBCL), 2 mantle cell (MCL), 1 marginal zone (MZL) and 1 Richter's DLBCL. Med age 62 yo (range 51–85); 11M/2F; median prior therapy regimens = 4 (range 1–5). No DLTs have occurred up to the current dose (CLL cohort at 600 mg TGR-1202 and NHL cohort at 800 mg TGR-1202). Diarrhoea was the highest reported adverse event (AE) at 38% (no G 3/4). To date, Grade 3/4 events thought to be at least possibly related to one or more of the 3 drugs have been minimal with 1 case of pneumonia (G 3) reported. No dose reductions have occurred to date. Seven patients were evaluable for efficacy. Overall response rate was 86% (6/7 patients) as follows: FL (2), CLL/SLL (2), MZL (1) and MCL (1). All responses were observed by week 8 (1 CR/5 PRs) with an average 83% reduction in tumour burden at first scan. 1 FL stage IV patient who was previously refractory to ibrutinib and to rituximab achieved a partial response at week 8. Patients remain on study from 1 to 6+ months.

Conclusions: To date, this is the first combination of an anti-CD20, a PI3Kδ and a BTK inhibitor. The combination of UTX, TGR-1202 and ibrutinib was well tolerated with significant early activity across heavily pre-treated and high-risk B-cell malignancies. Dose escalation continues with TGR-1202 now at 800 mg. Based upon the early activity of the triplet, Phase II studies are planned.

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A PHASE 1 STUDY OF PI3Kδ INHIBITOR INCB040093 ALONE OR IN COMBINATION WITH SELECTIVE JAK1 INHIBITOR INCB039110 IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA

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Introduction: Treatment options for patients with relapsed or refractory classical Hodgkin lymphoma (cHL) have limited efficacy. Preclinical and early clinical evidence suggests that inhibition of the JAK-STAT or PI3K pathways may be efficacious in cHL, both directly and through modulation of the tumour microenvironment. Furthermore, inhibition of both pathways may be synergistic.

Methods: This ongoing, open-label, dose escalation study enroled adult patients with relapsed/refractory B-cell malignancies, including cHL. Patients received INCB040093 monotherapy (100 mg once daily, 100 mg twice daily, 150 mg twice daily, or 300 mg once daily) or INCB040093 in combination with INCB039110 (INCB040093: 150 mg daily, 100 mg twice daily, or 150 mg twice daily; INCB039110: 400 mg or 600 mg once daily). Safety, efficacy, and pharmacodynamics were evaluated. Data from the patients with relapsed or refractory cHL are reported herein.

Results: At the time of the current analysis, 17 patients with relapsed or refractory cHL had been enroled. At baseline, the median age was 34 years and 59% were men. Prior to study entry, patients had received a median of 5 treatment regimens, 82% had undergone haematopoietic stem cell transplantation, and all had received brentuximab vedotin therapy. The median exposure to treatment in this study was 209 days [range: 22+ (ongoing)–388]. The most common nonhaematologic adverse events (all grades) in this cHL cohort were fatigue (41%), headache (35%), and decreased appetite (35%). One nonhaematologic grade ≥ 3 adverse event occurred in >1 patient: pneumonia (12%). Rates of all-grade neutropenia, thrombocytopenia, and anaemia were 47%, 47%, and 41%, respectively. Grade ≥ 3 thrombocytopenia occurred in 18% of patients. No patients with cHL experienced a dose-limiting toxicity. Of 6 evaluable patients receiving INCB040093, the objective response rate (ORR) was 50%, including 1 complete response (CR). Of 9 evaluable patients receiving INCB040093 + INCB039110, ORR was 67%, including 2 CRs. A dose response in efficacy was not evident in this limited dataset of proximate dose cohorts. Based on pharmacodynamics and the safety profile of higher dose levels in the overall study population, INCB040093 100 mg twice daily and INCB040093 100 mg twice daily + INCB039110 400 mg once daily were selected for expansion. At these doses, ORR in the cHL cohort was 50% for INCB040093 and 75% (1 CR) for INCB040093 + INCB039110.

Conclusions: INCB040093 alone or in combination with INCB039110 was generally well tolerated in this heavily pretreated population of patients with relapsed or refractory cHL. The efficacy seen in this limited number of evaluable patients compares well to approved therapies and investigational agents for cHL. These results warranted further investigation of INCB040093 ± INCB039110 in patients with relapsed or refractory cHL, leading to the initiation of a phase 2 study.

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ABT-199 TRIGGERS APOPTOSIS AND AUGMENTS IBRUTINIB CYTOTOXICITY IN CXCR4 WILD-TYPE AND WITH MUTATED WALDENSTRÖM MACROGLOBULINEMIA CELLS

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Introduction: Ibrutinib, and oral Bruton tyrosine kinase (BTK) inhibitor, was recently approved by the United States Food and Drug Administration for treatment of Waldenström Macroglobulinemia (WM), wherein it produces partial but not complete responses regardless of CXCR4 mutational status (Treon et al, New Engl J Med 2015). MYD88 L265P, a mutation seen in over 90% of patients with WM, triggers BTK, the target of ibrutinib, though the mechanism responsible for persistent WM cell survival in patients on active ibrutinib therapy remains to be clarified. BCL-2 is potent anti-apoptotic factor, which is

DOI: 10.1002/hon

overexpressed in WM cells. The BCL-2 inhibitor ABT-199 has shown activity in a small subset of WM patients (Davids et al, ASH 2013). The role of BCL-2 as a putative mediator of ibrutinib resistance and the potential synergistic interactions of ABT-199 and ibrutinib were examined in these studies.

Methods: Transcriptome analysis for 63 WM patients genotyped for MYD88 and CXCR4 mutation status was performed. WM cell lines were engineered to express CXCR4 wild-type and WHIM-mutated receptors, and BCL-2 protein expression was assessed in the presence or absence of SDF-1a. Cell lines, as well as primary WM cells from untreated patients, and patients on ≥6 months of active ibrutinib therapy were treated *ex vivo* with ibrutinib alone, ABT-199 alone, and ibrutinib and ABT-199 in combination, and apoptotic signalling assessed.

Results: Transcriptome analysis showed high rates of transcription for BCL-2 in CXCR4 wild-type and WHIM mutated WM patient cells. BCL-2 was similarly expressed in CXCR4 wild-type and WHIM engineered WM cells, and treatment with SDF-1a had no impact on BCL-2 expression. Ibrutinib triggered caspase-3 and PARP activation in both CXCR4 wild-type and WHIM engineered WM cells, though full apoptotic progression assessed by Annexin V staining 18–72 h out was limited. Treatment of CXCR4 wild-type and WHIM engineered WM cells with ibrutinib and ABT-199 resulted in robust apoptotic progression, which was also observed in primary WM cells from untreated, as well as on active ibrutinib treatment patients.

Conclusions: The results suggest that BCL-2 restrains ibrutinib-triggered apoptosis in WM cells and support investigation of ABT-199 alone, and in combination with ibrutinib in patients with WM. A Phase II study of ABT-199 in WM has been initiated, and a trial examining the combination of ibrutinib with ABT-199 is contemplated.

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VENETOCLAX (ABT-199/GDC-0199) IN COMBINATION WITH BORTEZOMIB AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: PHASE 1B RESULTS

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Background: The anti-apoptotic proteins BCL-2 and MCL-1 promote multiple myeloma (MM) cell survival. Bortezomib (BTZ) can inhibit MCL-1 activity by increasing the MCL-1 antagonist, NOXA. Venetoclax (VEN) is a selective, orally bioavailable, small-molecule BCL-2 inhibitor, which enhances BTZ efficacy in MM xenograft models. Chromosomal abnormalities can also influence sensitivity of MM cells to treatment. This Ph 1 study evaluates VEN with BTZ and dexamethasone (Dex) in patients (pts) with relapsed/refractory MM, including subsets of patients with chromosomal abnormalities.

Methods: Objectives include safety, pharmacokinetics, preliminary efficacy, maximum therapeutic dose, and cytogenetic results of VEN with BTZ and Dex. Pts received VEN (50–500 mg PO daily) in cycles (C) 1–11 per designated dose escalation cohorts (continual reassessment); BTZ (1.3 mg/m^2 SC, days [D] 1, 4, 8, and 11) and Dex (20 mg PO, D1, 4, 5, 8, 9, 11, and 12) in C1–8 (21D); BTZ + Dex D1, 8, 15, and 22 in C9–11 (35D); and VEN alone ≥ C12.

Results: 32 pts were enroled as of 12/18/2014: median age 65; 12/20F/M. 12 were ISS stage I, 7 stage II, and 10 stage III. Median (range) prior therapies: 5 (1–15). 26 pts received prior BTZ (10 refractory), 26 had prior lenalidomide, and 20 auto-HSCT. 3 pts had t(11;14), 4 had t(4;14), 7 had del 17p, and 18 had del 13q. AEs in ≥20% pts: constipation (41%), diarrhoea (38%), peripheral edema (28%), thrombocytopenia (31%), peripheral neuropathy (28%), insomnia (28%), dyspnea (25%), and anaemia (22%). Grade 3/4 AEs (≥10%): thrombocytopenia (25%) and anaemia (13%). 14 pts had SAE: none VEN-related. Reason for discontinuation (n = 17): PD (n = 14), AEs (n = 2: adenocarcinoma, cardiac, and respiratory decompensation), and consent withdrawal (n = 1). 3 deaths occurred (due to PD); 1 DLT at 300 mg (cardiac decompensation attributed to Dex). No TLS occurred. Dose-normalized exposure when given with BTZ + Dex (n = 30) was similar to VEN alone.

Abstract 109 Table 1. Preliminary efficacy (best response) by BTZ and cytogenetic status

n (%)	Refractory (*n* = 10)	Sensitive (*n* = 16)	Naïve (*n* = 6)	del 17p-pos (*n* = 7)	del 17p-neg (*n* = 24)	t(4;14)-pos (*n* = 4)	t(4;14)-neg (*n* = 27)	All patients (*n* = 32)
Stringent complete response (sCR)	0	1 (6%)	0	0	1 (4%)	0	1 (4%)	1 (3%)
Complete response (CR)	0	0	2 (33%)	0	2 (8%)	0	2 (7%)	2 (6%)
Very good partial response (VGPR)	0	2 (13%)	1 (17%)	0	3 (13%)	1 (25%)	2 (7%)	3 (9%)
Partial response (PR)	0	7 (44%)	2 (33%)	2 (29%)	7 (29%)	1 (25%)	8 (30%)	9 (28%)
Minimal response (MR)	1 (10%)	0	0	0	1 (4%)	0	1 (4%)	1 (3%)
Stable disease (SD)	3 (30%)	4 (25%)	0	2 (29%)	4 (17%)	2 (50%)	4 (15%)	7 (22%)
Progressive disease (PD)	4 (40%)	1 (6%)	1 (17%)	3 (43%)	3 (13%)	0	6 (22%)	6 (19%)
Discontinued	2 (20%)	1 (6%)	0	0	3 (13%)	0	3 (11%)	3 (9%)
Overall response rate (sCR + CR + VGPR + PR)	0	10 (63%)	5 (83%)	2 (29%)	13 (54%)	2 (50%)	13 (48%)	15 (47%)
Median (range) time on study (Tos), months[a]	1.3 (0.3–4.8)	5.0 (0.7–9.5)	5.0 (1.4–9.4)	2.5 (0.3–7.2)	4.3 (0.7–9.5)	5.8 (1.1–9.5)	4.0 (0.3–9.4)	4.0 (0.3–9.5)

[a]Defined as time from first dose to data cut-off (active patients) or last dose (discontinued patients).

DOI: 10.1002/hon

M-protein reduction (mean best % change) was favourable in BTZ sensitive pts (−50.5% vs −10.7% in BTZ naïve and −4.9% in BTZ refractory pts); M-protein reductions were also observed in del 17p-negative pts (−46.2%) and t(4;14) pts (−52.7%).

Conclusions: Venetoclax with BTZ and Dex has an acceptable safety profile in heavily pretreated MM. These early data suggest that this combination which targets both BCL-2 and MCL-1 resulted in anti-tumour activity, particularly in pts naïve or sensitive to prior BTZ. Dose escalation continues at 600 mg, and biomarker analyses are ongoing.

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CANCER ENERGY METABOLISM AS A THERAPEUTIC TARGET IN REFRACTORY MYC+ DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Most cancers depend for their energy to a more primitive metabolism than normal tissue. To increase their metabolism, cancer cells derive their energy from aerobic glycolysis with a shift from ATP generation through oxidative phosphorylation to ATP generation through glycolysis, requiring glutamine and exhibiting a 'glutamine addiction'. This metabolism pathway is regulated especially by the mTOR/phosphatidylinositol 3-kinase (mTOR/PI3K) pathway. c-MYC acts as an integrator and accelerator of cellular metabolism and proliferation, playing a major role in glutamine metabolism and glutamine transporter to finally realize a biological loop between glutamine, mTOR and c-MYC. MYC + DLBCL is associated with a very poor prognosis because of refractoriness to chemotherapy. We designed an innovative therapeutic strategy to stop this metabolic reprogramming by using L-aspariginase as an inhibitor of glutamine uptake and temsirolimus as an mTOR inhibitor.

Methods: Patients with relapsed/refractory MYC-rearranged DLBCL, adequate performance status and organ functions were eligible. Treatment combined L-asparaginase (Kidrolase®, Jazz Pharmaceutical, 6000 UI/m2) on days 1, 3, 5, 7, 9, 11 and 13 of a 4-weeks cycle, mTOR inhibitors (temsirolimus 75 mg D1, 7 and 14) and rituximab (375 mg/m2 D1 and 7). Patients received a maximum of 4 cycles, until limiting toxicity or disease progression. The primary endpoint was the overall response rate.

Results: Nine pts were enroled. Median age was 60 years (range: 30–71). They were 3 female and 6 male. All patients present MYC+ DLBCL either single hit (4) or double hit (2) or triple hit (3); 7 GC and 2 non-GC, with a high expression of ki67 (med 90%; range 60%–90%). All pts present with a refractory disease after a median of 2 prior lines (range: 2–4), Ann Arbor stage IV and high LDH level. Three pts completed 4 cycles, and 1 patient 2 cycles in complete response (CR). Five patients completed 1 or less than 1 cycle. The overall response rate was 44% (4/9), and 3 pts achieved a CR. Of the 9 pts, 3 progressed on therapy, one relapsed 4 months after the end of treatment. The most common reason for discontinuing treatment was progressive disease. Median duration of response was 6 months (range, 4–6 months). Thrombosis was a frequent toxicity grade 3/4 occurring in 2 patients. Grade 3 hepatic toxicity occurred in one patient during the first cycle.

Conclusion: First results of this innovative association targeting cancer energy metabolism appear very exciting in relapsed/refractory MYC + DLBCL. Preliminary evidence suggests thrombosis and hepatic complications as potential limiting toxicities. Phase 1/2 study with an association of Erwinia asparaginase and new m-TORC1/C2 inhibitor is in discussion.

Acknowledgement: CT is supported by the Nella and Amadeus Barletta Foundation.

'FOCUS ON…' SESSION: ONGOING TRIALS

Please see last section of this publication 'ONGOING TRIALS'

SESSION 7: LYMPHOMA BIOLOGY AND GENOMICS II

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ISOCITRATE DEHYDROGENASE (IDH) MUTATIONS IN ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA (AITL)

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Angioimmunoblastic T-cell lymphoma (AITL) is one of the three most common peripheral T-cell lymphoma (PTCL) subtypes, along with anaplastic large cell lymphoma and PTCL not otherwise specified (PTCL-NOS). AITL normally presents as a systemic disease, with polyadenopathy and a variety of immunologic abnormalities, and carries a poor prognosis. Based on molecular marker expression and microarray expression profiling, AITL is thought to arise from the follicular T-helper (TFH) cells that are present in germinal centres and cooperate with B-cells in mounting an effective immune response. Mutations in genes known to affect epigenetic regulation are common in AITL and include loss-of-function mutations in TET2 and DNMT3A, and gain-of-function mutations in IDH2. Point mutations in the motility and adhesion gene RhoA are also a common event in this disease. Despite the increased understanding of AITL in recent years, the molecular pathogenesis and other underlying genetic events driving AITL are largely unknown. IDH2 R172 mutations cause a gain of enzymatic function resulting in the production of the oncometabolite 2-hydroxyglutarate, and are present in approximately 20–45% of AITL cases, but not in other types of PTCL. There are no clinical or pathological differences among AITL patients based on IDH2 status, and their prognoses are the same. IDH1 mutations have not been detected in AITL patients, supporting the concept that IDH1 and IDH2 mutations can have different effects depending on cellular context. Unlike in other haematological malignancies, most notably acute myeloid leukaemia (AML), IDH2 mutations co-occur with TET2 mutations in AITL, further indicating that the role of IDH mutations in tumourigenesis may differ in these diseases. As in AML, the identification of IDH2 mutations in AITL presents an opportunity to develop a mechanistic model of the disease, develop clinically useful biomarkers, and evaluate novel therapeutic strategies. Inhibitors of mutant IDH2 are currently producing promising results in phase I clinical trials in haematological malignancies, and it remains to be seen whether these agents will prove useful in the management of AITL. Characterization of appropriate mouse models should soon yield fresh insights into the role of IDH2 mutations in AITL.

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RECURRENT MUTATIONS IN TCR (PATHWAY)-RELATED GENES IN T_{FH}-DERIVED PERIPHERAL T-CELL LYMPHOMAS

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Introduction: AITL and a subset of PTCL, NOS are known to derive from CD4 follicular helper T (T_{FH}) cells. Recently, we and others described by targeted classical or next generation sequencing (NGS) recurrent mutations in the epigenetic modifiers *TET2, IDH2* and *DNMT3A* as well as in TCR signalling genes *RHOA* and rarely *FYN*. Except for *TET2*, none of these variants correlated with patient survival. Here, we used NGS, with specific focus on TCR signalling, to expand on the characterization of the mutational landscape of T_{FH}-derived PTCLs and investigate its potential clinical impact.

Methods: Mutation pattern and copy number variations (CNV) derived from whole genome/exome sequencing (WG/ES) analysis of 9 paired normal and tumour cell-rich AITL samples combined with gene expression profiles (GEP) of 5 AITL and 5 normal sorted T_{FH} cell samples were used for gene prioritization. A set of 60 genes (43 related to TCR signalling) was selected for deep sequencing (MiSeq, validated on PGM) in an extended cohort of clinically annotated samples (72 AITL and 13 T_{FH}-like PTCL, NOS from the Tenomic consortium of the LYSA) with available GEP. Clinical and biological relevance of the detected variants was assessed by an integrated analysis of the mutational status, GEP and clinical information.

Results: Targeted deep sequencing identified 57 variants in 23 genes (Table 1) confirming a high mutation rate in *RHOA* but also, at lower frequency, mutations in other genes, such as *CD28, PLCG1, CTNNB1, GTF2I, PDPK1, VAV1* and *PIK3R1*. Remarkably, in addition to frequent mutations in *TET2*, *DNMT3a* and *IDH2*, 76.4% of the patients carried mutations in at least one gene of TCR signalling, of which 30.6%, 21.2%, and 62.4% of the patients harboured variants in PIK3, PLCG and Rho-GTPases pathways. Cases with mutations in PIK3 and/or PLCG pathway showed enrichment in gene signatures reflecting higher proliferative activity and TCR activation. Indeed, *PLCG1* variants were found to be activating, leading to increased NF-AT activity. PIK3 and/or PLCG pathway mutated patients had significantly shorter event free survival (CHOP-treated patients; HR = 2.44, $p = 0.005$) and a trend for lower overall survival (all cohort; HR = 1.52, $p = 0.12$) than wild-type individuals.

Conclusion: A large proportion of T_{FH}-derived PTCL, NOS (76.4%) harbour frequent mutations of genes in TCR signalling. Mutations in PIK3 and PLCG pathway components were associated with worse EFS. Further studies to explore their biological, clinical and therapeutic relevance are warranted.

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HBZ, BCL-XL, AKT, AND LOSS OF *INK4A/ARF* SYNERGISTICALLY TRANSFORM PRIMARY MURINE T CELLS AND ELICIT ATL-LIKE DISEASE IN MICE

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Introduction: Adult T-cell leukaemia/lymphoma (ATL) is a human T-cell leukaemia virus type-1 (HTLV-1)-induced neoplasm with poor prognosis. ATL occurs in only 5% of HTLV-1 carriers. ATL development takes about 60 years after HTLV-1 infection. Such a long latency period suggests the requirement of accumulation of many genetic abnormalities for the disease to develop. However, genetic abnormalities that are critical for the development of ATL remain unidentified. We previously established an *in vitro* culture system that allows gene transduction in primary murine T cells. Our examination of ATL samples revealed elevated expression of *AKT* and *BCL-xL* and genetic loss of *Ink4a/Arf*. We examined the possible synergism between HTLV-1-encoded *HBZ* and the abovementioned 3 genes in our mouse model.

Methods: Fetal liver cells isolated from *Ink4a/Arf*-null mouse were induced to differentiate into T cells *in vitro* (iT-cells$^{(p16-/-)}$). iT-cells$^{(p16-/-)}$ were retrovirally transduced with *HBZ*, containing 35 bp of the 5′-non-coding region, *BCL-xL*, and myristoylated *Akt*. Cells were then monitored for cell growth *in vitro*, or they were transplanted intravenously into NSG mice.

Results: We compared the cell growth of iT-cells$^{(p16-/-)}$ expressing the 3 genes or any possible combination of 2 genes in the absence of cytokines and found that only cells expressing the 3 genes proliferated. All NSG mice ($n = 7$) transplanted with iT-cells$^{(p16-/-)}$ expressing the 3 genes rapidly died (<105 days) or developed leukaemic bone marrow, thymic hyperplasia, and splenomegaly with massive infiltration of CD4 single-positive or CD4/8 double-positive T cells. Peripheral blood smears from the mice showed many cells with lobulated nuclei, resembling 'flower cells' that are the hallmark of the acute type of ATL in humans. All secondary B6 mice ($n = 9$) that received a transplant of the spleen or thymus cells from the primary mice also rapidly died (<2 months) or developed the disease, demonstrating the tumour-propagating ability of the cells. In contrast, 4 of 5 NSG mice transplanted with iT-cells$^{(p16-/-)}$ expressing BCL-xL and Akt, but not HBZ, survived for >160 days.

Conclusion: In this study, we demonstrated that the HBZ plays a critical role in transforming primary murine T cells and in the development of ATL-like disease in mice. To the best of our knowledge, this is the first report of synergy between HBZ, BCL-xL, Akt, and loss of *Ink4a/Arf* in the development of ATL-like disease.

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WHOLE GENOME SEQUENCING IN THE FRAMEWORK OF ICGC MMML-SEQ IDENTIFIES *PCBP1* AS RECURRENTLY MUTATED IN BURKITT LYMPHOMA

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DOI: 10.1002/hon

Abstract 112 Table 1. AITL and T_{FH}-like PTCL, NOS mutational landscape. A, AITL; T, T_{FH}-like; 12 cases bearing no mutation are not shown; I, mutated; ., non-mutated; m, missing.

Genes	pts A	recurrence (%) A	AITL	Tfh	All
RHOA	6	5	62,5	46,2	60,0
TET2	5	5	50,0	66,7	52,3
DNMT3a	6	5	32,1	11,1	29,2
IDH2	5	6	31,7	0,0	26,8
CD28	5	4	11,1	0,0	9,4
PLCG1	4	4	8,3	15,4	9,4
CTNNB1	4	4	5,6	7,7	5,9
GTF2I	4	4	5,6	7,7	5,9
PDPK1	4	3	5,6	0,0	4,7
VAV1	3	3	4,2	7,7	4,7
PIK3R1	3	3	2,8	15,4	4,7
FYN	3	3	2,8	7,7	3,5
KRAS	3	3	1,4	15,4	3,5
NLRP4	3	3	1,4	15,4	3,5
MDN1	3	3	1,4	7,7	2,4
CDK1 1B	3	3	1,4	0,0	1,2
LCK	3	3	1,4	0,0	1,2
CEP170	3	3	1,4	0,0	1,2
WDFY3	3	3	1,4	0,0	1,2
VAV2	3	3	1,4	0,0	1,2
TRAF6	3	3	1,4	0,0	1,2
LRP6	3	3	1,4	0,0	1,2
AKT1	3	3	1,4	0,0	1,2
MAPK3	3	3	1,4	0,0	1,2
PIK3R5	3	3	1,4	0,0	1,2
PIK3CA	3	3	0,0	7,7	1,2
# variants	6	5 5 5 6 5 4 4 4 4 4 3 3 3 3 3 3 3 3 4 6 3 2 2 2 4 3 3 3 2 2 2 3 3 2 1 1 1 1 1 1 2 2 3 2 2 1 1 1 1 1 2 2 2 2 2 2 2 3 1 5 2 1 2 1 0 2 1 1 1 1 1 1	2,2	2,1	2,2

DOI: 10.1002/hon

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Introduction: The biologic hallmark of Burkitt lymphoma is the *IG-MYC* translocation. However, the sole presence of this translocation is insufficient to drive lymphomagenesis, and additional genetic changes are required for malignant transformation. Recent studies, using next generation sequencing approaches, have identified genes like *ID3*, *TCF3* or *CCND3* to be recurrently mutated in Burkitt lymphoma. However, other genes may also contribute to Burkitt lymphomagenesis.

Methods: Pre-treatment tumour tissue and germline material of 17 patients with Burkitt lymphoma were analysed in the framework of the BMBF-funded International Cancer Genome Consortium - Molecular Mechanisms in Malignant Lymphoma by Sequencing (ICGC MMML-Seq, grants 01KU1002A to 01KU1002J) project by whole-genome and transcriptome sequencing. For validation, the complete *PCBP1* gene was analysed by Sanger sequencing in an independent cohort of 28 *IG-MYC* positive molecularly defined Burkitt lymphomas and 16 Burkitt lymphoma cell lines. The effects of missense mutations on PCBP1 interactions were predicted using Mechismo.

Results: Somatic mutations in the *PCBP1* gene were identified by whole genome sequencing in 3/17 (18%) Burkitt lymphomas and by Sanger sequencing in 3/28 (11%) in an independent validation cohort of *IG-MYC* positive molecularly defined Burkitt lymphomas. In addition, 6/14 (43%) investigated Burkitt lymphoma cell lines carried mutations in *PCBP1*. Mutations consisted of 3 nonsense, 7 missense and 2 frameshift mutations and predominantly (10/12, 83%) affected the part of the gene encoding the KHIII domain due to complete loss of the domain or amino acid exchange, hereby potentially interfering with various functions of PCBP1 including nuclear trafficking, pre-mRNA splicing and RNA/DNA interactions of the protein. Furthermore, 7 out of 12 mutations (58%) affected one or both nuclear localization signal(s). Analysis of available transcriptome data ($n = 3$) showed a balanced expression of the wild-type and the mutated allele in two cases and in one case (harbouring a frameshift mutation leading to truncation after KH I domain) a fivefold lower relative expression of the mutated allele likely due to nonsense-mediated decay. Remarkably, all six *PCBP1* mutated cases (6/6, 100%) expressed MUM1/IRF4 by immunohistochemistry, while this was seen in only 12/31 (39%) of unmutated cases.

Conclusions: *PCBP1* was identified as a recurrently mutated gene in 13% of primary Burkitt lymphomas and 43% of Burkitt lymphoma cell lines. The mutations predominantly affected the KHIII domain of the protein and might represent an additional genetic mechanism involved in Burkitt lymphomagenesis.

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GENE, MIRNA AND PATHWAY SPECIFIC PROTEIN EXPRESSION ANALYSIS IN NEWLY DIAGNOSED MYC/BCL2 DOUBLE EXPRESSING DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is a clinically, immunophenotypically, and genetically heterogeneous disease. Patients with *MYC* and *BCL2* (or *BCL6*) translocation have a poor prognosis. Further, concurrent protein expression of MYC and BCL2 regardless of gene translocation status has been suggested to represent a poor prognostic marker for DLBCL. We evaluated gene expression using NanoString® technology and immunohistochemistry (IHC) of key targetable pathways to a panel of DLBCL patients.

Methods: Patients newly diagnosed with DLBCL at MSKCC between 1990 and 2014 with adequate biospecimens were evaluated. 152 patients were included in the survival analysis. An IHC cut-off value of 40% for MYC and 70% for BCL2 was applied for determination of MYC/BCL2 expression in the tumour cells. IHC of MYC, BCL2, p-STAT3, p-AKT, p-ERK, p-RPS6KB1, BRD4, FOXP1, p53, MDM2, p16, β-catenin, BAFFR, CD40, and CD71 were performed for 110 samples. Gene expression analysis was performed using total RNA extracted from FFPE tissue samples of MYC/BCL2 double positive (DP) and double negative (DN) cases ($N = 16$), and analysed on NanoString nCounter® system for 122 genes and 800 miRNAs. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Optimal cut-offs for IHC markers were obtained using maximally selected statistics methodology. The Wilcoxon Rank Sum test was used to examine the differential expression of genes and miRNAs, and adjusted for multiple testing using false discovery rate approach.

Results: For advanced stage DLBCL patients treated with R-CHOP based therapy ($N = 152$), the 2-yr overall (OS) and progression-free survival (PFS) was 80.6% and 67.5% in DP, and 97.4% and 88.9% in DN patients ($p = 0.0342$ and 0.0385, respectively, median follow-up of 1.83 years (range 0.06–12.8)). Distribution of cell of origin, IPI, and stage between DP and DN patients were similar.

Gene expression was analysed for a subset of DP ($N = 7$) and DN ($N = 9$) patients. Eleven genes (ALDH18A1, ANTXR1, ITGAL, LDHA, SULF1, TCF4, ADAM12, CD40, NDUFA12, SPARC, and THBS2) were found to be differentially expressed between DP and DN cases; however, no differentially expressed miRNA was identified. Among the IHC markers evaluated, FOXP1 > 25%, BRD4 > 50%, p-STAT3 > 0%, p-RPS6KB1 > 50%, and CD40 > 75% were significantly associated with MYC/BCL2 protein expression status (adjusted $p = 0.0001$, 0.0017, 0.0029, 0.011, 0.042).

Conclusions: We confirmed that concurrent expression of MYC and BCL2 using cut-off values of 40% and 70% is associated with inferior OS and PFS in patients with advanced stage newly diagnosed DLBCL. In a small set of DP and DN cases, 11 genes including CD40 were differentially expressed. MYC/BCL2 expression was associated with higher expression of FOXP1, BRD4, p-STAT3, p-RPS6KB1, and CD40 at the protein level. Our results suggest a potential role for JAK/STAT, BET, or mTOR inhibitors as novel therapeutic approaches for MYC/BCL2 double expressing DLBCL.

DOI: 10.1002/hon

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MECHANISMS OF MALIGNANT TRANSFORMATION IN TP53 WILD-TYPE BURKITT LYMPHOMA IDENTIFIED BY INTEGRATION OF MOLECULAR AND FUNCTIONAL GENOMICS DATA

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Introduction: Burkitt lymphoma (BL) is an aggressive mature B-cell lymphoma characterized by oncogenic *MYC* activation. Recent studies identified recurrent mutations of *TCF3* and *ID3* in a large proportion of BL. Oncogenic activation of MYC and mitogenic signalling promote cell growth, but also apoptosis and senescence by activation of stress responses including the p53 pathway. About 40–50% of BL patients carry mutations in the tumour suppressor gene *TP53*, leading to an impaired response to these stress signals. In BL with functional p53, the mechanisms that promote survival were not systematically investigated. Our aim was to identify driver lesions specific to BL without *TP53* mutation promoting tumour survival and growth.

Methods: We analysed differential copy number changes (CNA) and gene expression in 67 BL patients and 205 diffuse large B-cell lymphoma patients from the Molecular Mechanisms of Malignant Lymphoma (MMML) consortium according to their *TP53* mutation status. For an unbiased functional analysis, we performed an RNAi drop-out screen on a panel of representative BL cell lines ($n = 8$) with defined genetic background.

Results: In order to identify *TP53*-dependent viability genes, we chose 4 BL cell lines that carry mutations in *TP53* and show impaired p53 pathway response and 4 cell lines with wild-type *TP53* and an intact p53 pathway. These cells were infected with a pooled shRNA library targeting ~5000 genes with 5–6 shRNAs per gene. Toxic shRNAs were identified by comparison of shRNA counts on day 2 and day 14 post-infection as determined by high-throughput sequencing. As expected, shRNAs targeting common viability genes as ribosomal and proteasomal proteins showed the strongest depletion in all cell lines. We identified 81 genes that showed increased toxicity in cell lines with wild-type *TP53* and 88 genes that were significantly enriched for toxicity in mutant *TP53* cell lines. These genes are involved in the *TP53* pathway and in cell cycle control. Integration of RNAi viability data with CNA and gene expression analysis from BL patients showed that the gene with the highest p53-dependent toxicity is located within a minimally gained region that is associated with *TP53* wild-type patients. Validation studies confirmed the p53-dependent toxicity in single gene knock-downs, and we demonstrated that toxicity was caused by strong cell cycle arrest.

Conclusions: BL is known to be driven by the oncogene MYC and mitogenic signalling. Cooperating lesions as mutation of *TP53* are needed to escape oncogene-driven apoptosis and senescence. In the presence of functional *TP53*, we identified an alternative disease driver in BL with *TP53* wild-type controlling cell cycle progression, which may be exploited therapeutically.

SESSION 8: HODGKIN'S LYMPHOMA

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BIOLOGY OF HODGKIN'S LYMPHOMA

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The Hodgkin and Reed/Sternberg (HRS) tumour cells in classical Hodgkin lymphoma are still enigmatic lymphoma cells. Nevertheless, progress has been made in the last years in our understanding of the pathogenesis and pathophysiology of this malignancy. It is now clear that several master transcription factors contribute to the lost B cell phenotype of the mature B cell-derived HRS cells and their acquisition of a phenotype and gene expression programme that does not resemble any normal cell in the immune system. Further insights into the deregulation of gene expression in HRS cells is currently being obtained from a refined comparison of the global gene expression of HRS cells and normal B cell subsets, revealing a particular relationship of HRS cells to normal CD30-positive B cells. Cell tracking studies showed that the mononuclear Hodgkin cells give rise to the bi- or multinucleated Reed/Sternberg cells through a process of incomplete cytokinesis and subsequent refusion of daughter cells. The list of recurrent genetic lesions in the HRS cells is increasing, and pathogenetic mechanisms beyond deregulation of the NF-κB and JAK/STAT pathways are emerging. It is also becoming clearer how HRS cells orchestrate their microenvironment. This includes attraction and modification of cells that provide survival and proliferation signals for the HRS cells, as well as numerous strategies of the HRS cells to evade from an attack by cytotoxic cells. This knowledge is currently being used to develop novel immunotherapeutic treatment strategies. The molecular analysis of composite Hodgkin and non-Hodgkin lymphomas provided novel insights into the relationship between these types of lymphomas.

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INTERIM PET-ADAPTED CHEMOTHERAPY IN ADVANCED HODGKIN LYMPHOMA (HL). RESULTS OF THE SECOND INTERIM ANALYSIS OF THE ITALIAN GITIL/FIL DH0607 TRIAL

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DOI: 10.1002/hon

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Introduction: Interim FDG-PET performed after 2 chemotherapy cycles (PET-2) is the most powerful predictor of treatment (Tx) outcome in ABVD-treated, advanced-stage classical HL (cHL); however, there is no proof that adapting treatment on PET-2 result could increase the efficacy of standard ABVD.

Methods: In the HD 0607 clinical trial (ClinicalTRial.gov identifier 00795613), advanced-stage (IIB–IVB) cHL patients (pts) are treated with 2 ABVD courses, followed by a PET-2. The latter is centrally reviewed by an expert panel, using the Deauville rules. PET-2+ pts are randomized to either BEACOPP escalated (Be) plus BEACOPP baseline (Bb) (4 + 4 courses) or Be + Bb (4 + 4) and Rituximab (R). PET-2 negative pts are treated with 4 additional ABVD and, upon CR enter, randomized to either consolidation radiotherapy (Rxt) on the sites of initial bulky disease or no RxT.

Results: 773 cHL pts were consecutively enroled and scanned with PET-2; 151 (19.5%) resulted positive (97 score 4, 51 score 5) and 622 (80.5%) negative. Overall Tx response could be assessed in a cohort of 500 fully restaged after lymphoma Tx, with a minimum follow-up of 2 years after *x* end: 98 (19.7%) had a positive and 400 (80.3%) a negative PET-2. The relative median dose intensity for initial ABVD, Be, Bb and ABVD ± RxT was 100.5 (96.0–102.4), 85.5 (74.6–95.1), 87.1 (74.0–96.8) and 97.6 (92.8–100.9), respectively. Among 89 PET-2+ pts evaluated at the Tx end, CR was achieved in 66 (74.2%), PR in 4 (4.5%) Progression or Relapse (Pro/Rel) in 16 (18%), SD in 2 (2.2%) and not evaluable (NE) in 1 (1.1%). Among 393 PET-2− pts evaluated at Tx end, CR was achieved in 375 (95.4%), PR in 3 (.76%), Pro/Rel in 10 (2.5%), SD in 4 (1%) and NE in 1 (.24%). The median follow-up from enrolment into the trial was 1044 days (IQR 765–1290). At the last follow-up, among 89 PET-2 pts, 55 (61.8%) are in CCR (continuous CR), 5 in CR (5.6%), 12 in SD/PD (13.5%), 7 in Relapse (8%), 2 not evaluable (2.2%) and 8 pts died (8.9%). Ten PET-2+ pts (10.2%) died: 6 for Pro/Rel and 4 for TRM (toxicity 2, Pneumonia 1, Septic Shock 1). At the last follow-up, among 393 PET-2 negative pts, 343 (87.3%) are in CCR (continuous CR), 5 in CR (1.3%), 9 in SD/PD (2.3%), 25 in Relapse (6.4%), 3 not evaluable (.76%) and 8 pts (2%) died. Ten (2.5%) PET-2− pts died: 4 for Rel/Pro, 5 for TRM, (toxicity 2, Lung Infection 1, Fungal Infection 1, Pulmonary Fibrosis 1) and 1 for Suicide. The 4-y FFS and OS were 62% and 86%, 85% and 95%, and 81% and 93% for PET-2+, PET-2− pts and for the entire population, respectively. Overall, Tx was well tolerated: 144 serious adverse events (SAE) were reported: WHO grade 0 + 1: 105, grade 2: 19, grade 3: 15 and grade 4 + 5: 5.

Conclusions: These preliminary findings suggest that (1) an early switch from ABVD to escalated BEACOPP can be safely done in PET-2 positive pts. (2) Overall, the long-term Tx outcome for the entire patient cohort, in term of FFS, seems slightly superior to standard ABVD, but a longer follow-up is needed.

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INTERIM PET RESPONSE-ADAPTED THERAPY IN ADVANCED STAGE HODGKIN'S LYMPHOMA: FINAL RESULTS OF THE PHASE II PART OF THE FONDAZIONE ITALIANA LINFOMI (FIL) HD0801 STUDY

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Introduction: The clinical impact of positron emission tomography (PET) evaluation performed early during first-line therapy in advanced Hodgkin's lymphoma patients, in terms of providing a rationale to shifting poorly responding patients onto a more intensive regimen (PET response-adapted therapy), remains to be confirmed.

Methods: The phase II part of this multicentric study involved 519 advanced-stage 'de novo' Hodgkin's lymphoma patients, who received an initial doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) treatment and who were offered an early ifosfamide-containing (IGEV) salvage treatment followed by stem cell transplantation (a single autologous transplantation if PET-negative after IGEV, or a tandem autologous + allogeneic versus a double autologous transplantation if PET-positive after IGEV and with or without an HLA-matched donor, respectively) in case they showed a positive PET evaluation after 2 ABVD cycles (PET2). The primary endpoint was the 2-year progression-free survival, calculated for both PET2-negative patients (who completed a full 6-cycle ABVD treatment) and PET2-positive ones. Overall survival was a secondary endpoint. The trial was registered under EudraCT (2008-002684-14) and ClinicalTrials.gov (NCT 00784537).

Results: PET2 was positive in 103 of the 512 evaluable patients. Among them, 81 received the scheduled salvage regimen with at least one autologous transplantation, 15 remained on ABVD (physician's decision mostly because of minimally positive PET2), 5 received an alternative treatment, and 2 were excluded because of diagnostic mistake. On an intention-to-treat analysis, the 2-year progression-free survival was 76% for PET2-positive patients (regardless the salvage treatment they received) and 81% for PET2-negative ones. When calculated for the only 81 PET2-positive patients who received the IGEV salvage treatment and the subsequent stem cell transplantation, the 2-year PFS was 74%.

Conclusions: Advanced Hodgkin's lymphoma patients at high risk of failure can benefit from early treatment intensification with autologous transplantation, as confirmed by the possibility of salvaging more than 70% of PET2-positive patients through obtaining the same 2-year progression-free survival of the PET2-negative subgroup.

DOI: 10.1002/hon

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ANALYSIS OF PRIMARY-REFRACTORY HODGKIN LYMPHOMA PTS IN A RANDOMIZED, PLACEBO-CONTROLLED STUDY OF BRENTUXIMAB VEDOTIN CONSOLIDATION AFTER AUTOLOGOUS STEM CELL TRANSPLANT

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Introduction: The AETHERA trial demonstrated that consolidative treatment (tx) with brentuximab vedotin (BV) post-ASCT significantly improved PFS per independent review in pts with HL (HR = 0.57). Overall, adverse events (AEs) were consistent with the known safety profile of BV. The two most common AEs in the BV arm [vs placebo (PBO)] were peripheral sensory neuropathy (56% vs 16%) and neutropenia (35% vs 12%). 2 pts died ≤40 days of the last dose of BV, both due to acute respiratory distress syndrome. 60% of pts were refractory to frontline (FL) tx, an important risk factor for relapse post-ASCT. Historical 2-yr PFS and 3-yr OS rates in primary-refractory pts post-ASCT are <40% and <50%, respectively (Sweetenham, 1999). We performed a post-hoc analysis of PFS by investigator review in pts on the AETHERA trial who failed to achieve complete remission after FL tx in order to assess the efficacy of BV in these pts at high risk of progression post-ASCT.

Methods: This phase 3, double-blind, placebo-controlled study randomized pts to receive BV 1.8 mg/kg q3wk or placebo for 16 cycles after ASCT. Pts were required to have 1 of 3 entry criteria: refractory to FL tx, relapse <12 mos after FL tx, or extranodal involvement at time of pre-ASCT relapse. Pts must have achieved a response of at least stable disease to salvage tx pre-ASCT. Data were analysed per investigator, which included clinical lymphoma assessments.

Results: 329 pts were randomized at 78 sites in the US and Europe. Primary-refractory pts comprised 60% of the intent-to-treat (ITT) population (99 BV, 97 PBO). The median age of these pts was 32 yrs, and 51% were male. Reasons for tx discontinuation included completion of all 16 cycles of tx (51% BV, 49% PBO), progressive disease (20% BV, 43% PBO), and AEs (26% BV, 6% PBO).

On the BV and PBO arms, 2-yr PFS rates per investigator were 65% and 45% in the ITT population and 60% and 42% in primary-refractory pts, respectively. Subgroup analyses of primary-refractory pts by disease characteristics as well as number of risk factors showed that PFS was improved broadly across subgroups (HR <1, BV vs PBO; Table). There was greater PFS benefit with BV versus PBO in pts with multiple risk factors for progression. 3-yr OS rates were not different between arms (81% BV, 79% PBO; HR = 1.19).

Conclusions: BV consolidation post-ASCT improved PFS in primary-refractory pts, as well as across several subgroups of this population at high risk of progression post-ASCT. 2-yr PFS and 3-yr OS rates compared favourably with historical controls.

Abstract 120 Table 1.

Subgroup	*N*	PFS hazard ratio (95% CI)
Treatments pre-ASCT		
2	97	0.79 (0.44–1.40)
>2	99	0.39 (0.22–0.71)
B symptoms after failure of frontline therapy		
Yes	56	0.36 (0.19–0.72)
No	139	0.63 (0.38–1.04)
Extranodal disease at time of pre-ASCT relapse		
Yes	53	0.37 (0.18–0.78)
No	143	0.61 (0.37–0.98)
Risk factors[a]		
≥1	196	0.55 (0.37–0.83)
≥2	175	0.47 (0.31–0.72)
≥3	110	0.40 (0.24–0.66)

[a] Risk factors = best response of PR or SD to salvage therapy pre-ASCT, refractory to FL therapy, relapsed <12 mos after FL therapy, >2 treatments pre-ASCT, B symptoms after failure of FL therapy, and extranodal disease at pre-ASCT relapse.

SESSION 9: INDOLENT LYMPHOMA

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RISK OF TRANSFORMATION OF FOLLICULAR LYMPHOMA AND OUTCOME IN THE IMMUNOCHEMOTHERAPY ERA: ANCILLARY STUDY FROM THE PRIMA TRIAL

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Introduction: Follicular lymphoma (FL) is the most frequent low-grade NHL. Outcome of histological transformation (HT), considered as very poor, has been scarcely studied in the immunochemotherapy era. The aim of this study was to evaluate the incidence of HT in a prospective cohort of patients treated with immunochemotherapy, to assess risk factors and outcome of this event.

DOI: 10.1002/hon

Method: PRIMA was a multicentre phase 3 trial evaluating the impact of rituximab (R)-maintenance on high tumour burden FL patients treated with R-chemotherapy (R-CHOP, R-CVP or R-FCM). Patients responding to R-chemotherapy were randomized between R-maintenance and observation. Among the 1017 responding and randomized patients, a first recurrence was observed in 463 patients; among them, 194 had a histological documentation, 40 showing an HT and 154 a FL histology.

Results: The estimated annual transformation rate was 1.5%. The median time from randomization to transformation was shorter than FL relapse (9.6 months vs 22.8, respectively, $p = 0.018$). Patients who had a HD and those who did not had comparable initial characteristics except for anaemia (29.9% vs 19.7% for patients with and without histological documentation, respectively, $p = 0.011$). We compared initial characteristics of the 40 patients with HT and 708 without (154 relapsing patients with FL histology and 554 nonrelapsing patients). Patients with HT had more frequently altered ECOG-PS ($p < 0.001$), anaemia ($p < 0.001$), high LDH level ($P = 0.029$), B symptoms ($p = 0.042$) and high FLIPI score ($p = 0.007$) at diagnosis. The histological grade at diagnosis was also a risk factor for HT ($p = 0.02$). Age, gender, number of involved sites, bulky disease, albumin, β2microglubulin level or Ann Arbor stage at diagnosis did no impact HT incidence. Initial induction regimen, quality of response and R-maintenance did not impact the HT incidence either. Among 194 relapsing patients who had a histological documentation, ECOG-PS and FL grade were the only identified risk factors for HT ($p = 0.029$ and 0.03, respectively). A majority of patients with HT received R-DHAP or R-ICE as salvage; 17 (42%) received an autologous stem cell transplantation (ASCT). Patients with HT presented less CR/CRu (45.8% vs 65.2%, $p = 0.03$), more progressive disease (31.4% vs 11.6%, $p = 0.005$) than FL-histology patients at treatment evaluation. OS of patients with HT was shorter [median OS 3.8 years vs 6.4, HR 3.9 (2.2–6.9), $p < 0.001$] than FL-histology patients. Patients with HT reaching ASCT had an improved OS [median NR vs 3.4 years with and without ASCT, respectively, HR 0.14 (0.04–0.47), $p = 0.0002$].

Conclusion: In this large series of high tumour burden FL patients treated with immunochemotherapy, HT is a quite rare event occurring early during FL evolution. ECOG-PS, anaemia, LDH level, B symptoms, FLIPI score and histological grade at diagnosis are risk factors for HT at first recurrence. HT patients have a poor response to salvage treatment and a poor OS. Nevertheless, when achievable, ASCT improve outcome of HT patients.

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COMPLETE RESPONSE RATE AT 30 MONTHS (CR30) AS A SURROGATE ENDPOINT IN FIRST-LINE FOLLICULAR LYMPHOMA: A PROSPECTIVELY SPECIFIED ANALYSIS USING INDIVIDUAL PATIENT DATA

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Introduction: Progression-free survival (PFS) has been the primary endpoint for the approval of first-line interventions in follicular lymphoma (FL), but the extended follow-up needed (projected median ≥7 y) to accrue mature PFS data is a hindrance to therapeutic development. The Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) group conducted a prospectively specified meta-analysis to

Abstract 122 Table 1.

		Trial-level surrogacy		Patient-level surrogacy
	***N* of trials (*N* of pts)**	**R^2_{WLS} (95% CI)**	**R^2_{Copula} (95% CI)**	**HR[a] (95% CI)**
Overall	13 (3837)	0.88 (0.77–0.96)	0.86 (0.72–1.00)	0.703 (0.598–0.827)
With/without rituximab				
Rituximab trial	9 (2851)	0.85 (0.62–0.97)	0.80 (0.56–1.00)	0.701 (0.576–0.853)
Non-rituximab trial	4 (986)	0.91 (0.05–1.00)	0.96 (0.90–1.00)	0.709 (0.531–0.945)
Treatment setting				
Induction trial	8 (2207)	0.89 (0.75–0.98)	0.89 (0.74–1.00)	0.829 (0.678–1.013)
Maintenance trial	5 (1630)	0.93 (0.84–1.00)	0.89 (0.71–1.00)	0.526 (0.403–0.686)
Stage				
Stage I–III	12 (1207)	0.59 (0.25–0.87)	0.59 (0.24–0.95)	0.718 (0.527–0.979)
Stage IV	12 (2585)	0.92 (0.85–0.97)	0.94 (0.87–1.00)	0.739 (0.607–0.900)
FLIPI				
Low to intermediate	10 (1882)	0.45 (0.02–0.93)	0.57 (0.17–0.97)	0.720 (0.569–0.910)
High	9 (1415)	0.87 (0.68–0.98)	0.73 (0.42–1.00)	0.701 (0.528–0.931)

Note: Some studies were excluded because of small sample size or unavailable data.

Abbreviation: CI, confidence interval; CR30, complete response rate at 30 months; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; PFS, progression-free survival; pts, patients.

[a] Hazard ratio measures the association between CR30 and PFS at the individual patient level in a 30-month stratified landmark analysis.

DOI: 10.1002/hon

evaluate whether treatment effect on CR30, an earlier endpoint, could accurately predict treatment effect on PFS.

Methods: Randomized studies of first-line treatments in FL with an active comparator, reported on/after 1990, ≥100/50 overall/FL patients, and with available individual patient data (IPD) were eligible. Association between CR30 and PFS was assessed at the trial and patient level. Trial-level correlation of CR30 with PFS was evaluated using both linear regression (R^2_{WLS}) and copula bivariate (R^2_{Copula}) models. Prespecified criteria for CR30 surrogacy required either R^2_{WLS} or R^2_{Copula} ≥0.80, with the lower bound of the 95% confidence interval (CI) >0.60 and neither R^2 value <0.70. Patient-level association between CR30 and PFS was assessed using a stratified Cox model. The minimum treatment effect on CR needed to predict a significant PFS difference was calculated.

Results: From 348 references identified, 13 trials were eligible; 8 explored induction and 5 explored maintenance regimens; IPD for 3837 patients were accessible. At the trial level, the prespecified threshold for surrogacy was met: R^2_{WLS} of 0.88 (95% CI, 0.77–0.96) and R^2_{Copula} of 0.86 (95% CI, 0.72–1.00), demonstrating that treatment effects on CR30 predict effects on PFS in previously untreated FL. Sensitivity analyses by treatment type (± rituximab) or setting (maintenance vs induction) supported the robustness of the primary analysis. Patient-level surrogacy measures were also consistently strong (Table). Correlation of treatment effects on CR30 and on PFS was more marked in patients with more aggressive disease (stage IV or high FLIPI score). A minimum 10% improvement in CR30 over a control rate of 50% predicted significant improvement in PFS.

Conclusions: Correlation between treatment effect on CR30 and on PFS in first-line chemo/immunotherapy FL trials was highly consistent across trial- and IPD-based surrogacy estimation methods and across sensitivity analyses. These data validate CR30 as a surrogate endpoint in first-line FL and support its use to accelerate drug development in this setting.

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PRIMARY RESULTS FROM THE PHASE III GADOLIN STUDY OF OBINUTUZUMAB PLUS BENDAMUSTINE VERSUS BENDAMUSTINE ALONE IN RITUXIMAB-REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA

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Introduction: Treatment options are limited and outcomes poor for rituximab-refractory (Rit-Ref) indolent non-Hodgkin lymphoma (iNHL). Bendamustine (B) has shown a median progression-free survival (PFS) outcome of 9 months and a response duration of 10 months in Phase II trials in Rit-Ref iNHL. Obinutuzumab [GA101/Gazyva (G)] is a glycoengineered type II anti-CD20 antibody with activity and acceptable safety in Rit-Ref NHL. Here, we present primary results from a Phase III trial investigating the combination of obinutuzumab plus bendamustine versus bendamustine alone in Rit-Ref iNHL.

Methods: GADOLIN (NCT01059630) is a Phase III open-label study in patients with CD20-positive Rit-Ref iNHL. In the B arm, patients received B 120 mg/m^2 (days 1 and 2, cycles 1–6) alone; in the GB arm, patients received B 90 mg/m^2 (days 1 and 2, cycles 1–6) in combination with G 1000 mg (GB; days 1, 8 and 15 of cycle 1 and day 1 of cycles 2–6) for up to six 28-day cycles. Non-progressing patients in the GB arm received further G monotherapy every 2 months for up to 2 years. The primary endpoint was PFS assessed by an independent radiology facility (IRF), with 80% power to detect a 43% improvement in median PFS.

Results: In the protocol-specified interim analysis, 396 patients were randomized to receive B [n = 202 (198 were treated)] or GB (n = 194). The IDMC recommended to unblind the study as the primary endpoint had been reached (4 February 2015). Baseline characteristics were balanced between the treatment arms. Median age was 63 years, and patients had received a median of two prior therapies. The median observation time was 20 months for B and 22 months for GB. IRF-assessed median PFS was 14.9 months for B and not reached (NR) for GB [hazard ratio (HR) 0.55, 95% confidence interval (CI): 0.4–0.74; p = 0.00011]. The median investigator-assessed PFS was 14 months for B and 29 months for GB (HR 0.52, 95% CI: 0.39–0.70; $p < 0.0001$). There were no significant differences in IRF-assessed overall response rate (63.0% B vs 69.1% GB) or complete response (12.2% B vs 11.2% GB) at the end of induction, in IRF-assessed best overall response up to 12 months from the start of treatment (76.6% B vs 78.6% GB) or in preliminary overall survival (OS; median OS NR in either arm). In the treatment period, there were fewer Grade ≥3 adverse events with B than with GB (62.1% B vs 68% GB), notably neutropenia (26.3% B vs 33.0% GB) and infusion-related reactions (3.5% B vs 8.8% GB), but more Grade ≥3 thrombocytopenia (16.2% B vs 10.8% GB), anaemia (10.1% B vs 7.7% GB) and pneumonia (5.6% B vs 2.6% GB).

Conclusions: G in combination with B (90 mg/m^2) followed by G maintenance significantly improved PFS versus B alone (120 mg/m^2) in Rit-Ref iNHL. This clinically meaningful PFS improvement with GB represents the first randomized evidence of benefit for a novel anti-CD20 antibody in patients with rituximab-refractory iNHL.

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A SIMPLE AND EFFECTIVE MALT LYMPHOMA-SPECIFIC PROGNOSTIC INDEX GENERATED FROM THE DATASET OF THE IELSG-19 CONTROLLED CLINICAL TRIAL

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DOI: 10.1002/hon

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Introduction: Differently from the other main B-cell lymphoma subtypes, there are no prognostic indices specific for MALT lymphomas. The IELSG-19 randomized trial was launched by the International Extranodal Lymphoma Study Group to compare either Chlorambucil alone (Chl) or Rituximab alone (R) versus the combination of both drugs (R-Chl) in MALT lymphoma patients (pts) in need of front-line systemic therapy.

This study may offer the opportunity to study the prognostic factors in a uniform group of prospectively collected pts managed in the Rituximab era.

Aim: This study explored the possibility to generate an efficient and simple MALT-lymphoma specific prognostic index using the clinicopathological information from the IELSG-19

Methods: We analysed the IELSG19 study dataset (393 pts with complete records at a median follow up of 67 months) used for our previous report on outcome (Zucca et al. 12-ICML). The correlation between clinical features at study entry and event-free (EFS), progression-free (PFS) or overall (OS) survival has been explored at both univariate (log rank test) and multivariate (Cox regression) analysis.

Results: This preliminary analysis includes 393 pts with complete data. The primary lymphoma site was the stomach in 43%, lymph node involvement was present in 34%, LDH was elevated in 10% and 44% had stage >2. A backward selection, using a significance level of 0.05 for dropping variables, was employed to build a Cox proportional hazards model, starting from the model with all the prognostic variables identified by univariate analysis of EFS and PFS (age >70 years, impaired performance status, elevated LDH, Ann Arbor stage >2, non-gastric localization, nodal involvement and presence of >1 extranodal site). Beta-2 microglobulin was not included in the model due to the high rate of missing observations. The resulting final model comprised the age >70 years, elevated LDH and stage >2, and a prognostic score based on the presence of 0, 1 or >1 of these adverse factors was able to discriminate 3 risk groups with different 5-year EFS (72%, 58% and 26%; $p < 0.001$) and 5-year PFS (78%, 63% and 29%; $p < 0.001$). The model was also efficaciously predicting the risk of death (5-year OS, 99%, 92% and 74%; $p < 0.001$).

Conclusions: This model, based on age >70, LDH and stage, was generated within the largest randomized study ever conducted in MALT lymphoma and may be a simple and powerful tool to identify patients at increased risk of progression or death. It will be further tested using the final dataset of the study with longer (approx. 24 additional months) follow-up. The new index will be validated in an independent patient set. Final analysis will be presented at the meeting.

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BING-NEEL SYNDROME: A MULTI-INSTITUTIONAL RETROSPECTIVE STUDY

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Introduction: Waldenström Macroglobulinemia (WM) is an IgM-secreting lymphoplasmacytic lymphoma (LPL). Bing–Neel syndrome (BNS) is a rare complication seen in patients with WM, in which the LPL cells gain access to the central nervous system (CNS). The objective of this study is to describe the characteristics of patients with BNS, as well as the diagnostic and therapeutic approaches and outcomes.

Methods: Patients >18 years of age with a pathological diagnosis of WM and radiological and/or pathological evidence of WM involvement in the CNS were included. Characteristics as well as diagnostic procedures and therapies are presented descriptively. We estimated the time from WM diagnosis to BNS diagnosis and the time from BNS diagnosis to last follow-up or death (overall survival) using the Kaplan–Meier method.

Results: A total of 34 patients with BNS from eight centres were included in our study form a cohort of approximately 3000 WM patients for a crude incidence of 1%. Twenty patients (59%) were from the USA and 14 (41%) from Europe. The median age at WM diagnosis was 56 years (range 38–74 years), and the median age at BNS diagnosis was 62 years (range 39–76 years) for a median time from WM to BNS of 36 months (range 0–192 months). Nine patients (30%) were diagnosed with BNS at the time of WM diagnosis. There was a slight male predominance (56%). The median number of treatments for WM prior to BNS diagnosis was 1 (range 0–5); 100% of the patients received rituximab, 79% alkylating agents, 25% nucleoside analogs and 25% proteasome inhibitors. Seven patients (29%) were receiving active therapy for WM, while BNS was diagnosed, and from these, 6 patients (86%) were responding. The most common symptoms were limb motor deficits (38%), altered mental status (32%) and visual abnormalities (18%). Brain MRI showed leptomeningeal enhancement in 59%, and spinal MRI in 63% patients tested. Cytology showed evidence of BNS in 82%, flow cytometry in 84%, IgH PCR in 94% and MYD88 L265P PCR in 100%patients tested. The median haemoglobin level at BNS diagnosis was 12 g/dL (range 9–16 g/dL), and the median IgM level was 1310 mg/dL (range 28–5942 mg/dL). The most common frontline agents used to treat BNS were intrathecal chemotherapy (66%), high-dose methrotexate (41%) and rituximab (41%); 28% achieved a complete response, 38% partial response and 34% no response to therapy. The median number of lines of therapy for BNS was 1 (range 1–5). Three patients (9%) underwent autologous transplant for BNS. After a median follow-up of 30 months, the estimated 3-year OS was 59% (95% CI 39–75%). The most common cause of death was BNS progression in 77%.

Conclusion: BNS is a rare complication observed in approximately 1% of patients with WM. BNS can occur at any time during the course of the disease and even when patients are responding to systemic therapy. The diagnosis should be made using a combination of radiological and pathological tests. The treatment of BNS is heterogeneous and has not been standardized. Most of the deaths due to BNS progression are seen within 2 years of BNS diagnosis.

DOI: 10.1002/hon

SESSION 10: AGGRESSIVE LYMPHOMA

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GRAY ZONE LYMPHOMA (GZL): CHARACTERISTICS, OUTCOMES AND PROGNOSTICATION AMONG A LARGE MULTICENTRE COHORT

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Introduction: GZL with features intermediate between classical Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL) is a challenging disease entity that typically presents with mediastinal involvement. There are no standard treatment guidelines, and there remains a lack of data regarding prognostication.

Methods: We examined detailed clinical features and outcomes among a large cohort of GZL patients (pts) treated across 19 North American centres (2001–2012).

Results: We identified 112 GZL pts; 43% presented with primary mediastinal disease (MGZL), while 57% had no mediastinal involvement (NMGZL). NMGZL pts were older (50 vs 37 years, $P = 0.0001$) and presented more often with >1 extranodal site (27% vs 8%, $P = 0.014$) and advanced stage (81% vs 13%, respectively, $P = 0.0001$), but less bulk (8% vs 44%, respectively, $P = 0.0001$). Accordingly, NMGZL pts had worse prognostic scores versus MGZL (IPI 3–5: 30% vs 6%, $P = 0.001$; IPS 3–7: 23% vs 4%, $P = 0.0001$). For pathology, 93% of all pts had + CD20 staining by IHC. The most common frontline treatments (Tx) were CHOP +/− rituximab (CHOP+/−R) 46%, ABVD+/−R 30%, and dose-adjusted (DA) EPOCH-R 10%. At 31-month median follow-up, 2-year progression-free survival (PFS) and overall survival (OS) were 40% and 88%, respectively. Despite presenting with lower risk disease, outcomes for MGZL appeared similar to NMGZL pts. Factors predicting PFS on univariable analyses are shown in Table 1. On multivariable analyses, poor performance status predicted PFS (HR 2.94, 95% CI 1.19–7.22, $P = 0.02$) and stage 3/4 predicted OS (HR 4.89, 95% CI, 1.00–24.18, $P = 0.05$). For Tx, pts treated with ABVD+/−R had inferior 2-year PFS compared with DLBCL-directed Tx (CHOP+/−R and DA-EPOCH-R) (23% vs 52%, $P = 0.03$); this finding persisted on Cox regression (HR 1.88, 95% CI 1.03–3.83, $P = 0.04$). In addition, pts who received rituximab with frontline Tx versus not had improved 2-year PFS (51% vs 22%, respectively, $P = 0.01$). Interestingly, the significance of CD20 persisted on Cox regression controlling for rituximab (CD20 0.35, 95% CI 0.16–0.75, $P = 0.007$; rituximab HR 0.55, 95% CI 0.33–0.93, $P = 0.025$). Further, the favourable effect of rituximab remained significant after controlling for IPI (HR 0.35, 95% CI 0.18–0.69, $P = 0.002$). And among relapsed/refractory GZL pts, 2-year OS was improved for pts who had stem cell transplant (88% vs 67%, $P = 0.01$); this finding persisted on Cox regression controlling for IPI (HR 0.14, 95% CI 0.02–0.95, $P = 0.04$).

Conclusions: We describe a unique clinical subtype (i.e. NMGZL) with distinct characteristics, yet similar outcomes as MGZL. We also identified several clinical factors that predicted pt outcome. Additionally, data here suggest GZL outcomes are superior when treated with a DLBCL-specific regimen.

Abstract 126 Table 1. Univariable prognostic factor analyses

Baseline clinical factors	PFS			OS		
	HR	95% CI	P	HR	95% CI	P
Age (continuous)	0.99	0.97–1.00	0.16	1.01	0.97–1.04	0.69
Gender (male vs female)	0.84	0.51–1.40	0.50	1.51	0.40–5.70	0.54
B symptoms (yes vs no)	1.56	0.92–2.65	0.09	10.31	1.31–81.46	0.03
ECOG performance status (2–4 vs 0–1)	3.37	1.69–6.70	0.0005	2.34	0.50–11.02	0.28
Haemoglobin <10.5 g/dL (no vs yes)	0.47	0.12–1.76	0.26	0.51	0.29–0.91	0.02
LDH (normal vs increased)	0.54	0.31– 0.93	0.03	0.64	0.20–2.10	0.46
ESR (normal vs increased)	0.36	0.10–1.25	0.10	[a]	[a]	[a]
Albumin < 4.0 g/dL (no vs yes)	0.57	0.32–1.02	0.06	0.29	0.08–1.09	0.07
Bone marrow involved (yes vs no)	1.10	0.50–2.41	0.81	1.08	0.13–8.77	0.94
>1 extranodal site (yes vs no)	1.62	0.89–2.94	0.12	2.69	0.79–9.20	0.12
Bulky disease (yes vs no)	0.85	0.46–1.56	0.59	2.03	0.59–6.96	0.26
Stage at diagnosis (3–4 vs 1–2)	1.96	1.18–3.28	0.009	10.98	1.40–85.85	0.02
Prognostic score IPI (continuous)	1.48	1.19–1.82	0.0003	1.94	1.19–3.16	0.008
Prognostic score IPS (continuous)	1.26	1.03–1.54	0.02	2.06	1.24–3.42	0.005

[a] Too few events to provide an accurate estimate for Cox overall survival models.
Abbreviations: PFS, progression-free survival; OS, overall survival; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; IPS, International Prognostic Score; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; IPI, International Prognostic Index.

DOI: 10.1002/hon

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RATIOS OF T-CELLS TO TUMOUR-ASSOCIATED MACROPHAGES AND PD-1 AXIS MOLECULES, ADD TO THE PREDICTIVE POWER OF CONVENTIONAL PROGNOSTICATORS IN DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: Risk stratification of diffuse large B cell lymphoma (DLBCL) requires identification of patients with disease that is not cured despite initial R-CHOP. Although the prognostic importance of the tumour microenvironment is established, the optimal strategy to quantify it is unknown..

Methods: The relationship between immune effector and inhibitory (checkpoint) genes was assessed by nanoString™ in 252 paraffin-embedded DLBCL tissues. A model to quantify net anti-tumoural immunity as an outcome predictor was tested in 158 R-CHOP-treated patients and validated in tissue/blood from two independent R-CHOP-treated cohorts of 233 and 140 patients, respectively.

Results: T and NK-cell immune effector molecule expression correlated with tumour-associated macrophage and PD-1/PD-L1 axis markers consistent with malignant B-cells, triggering a dynamic checkpoint response to adapt to and evade immune surveillance. A tree-based survival model was performed to test if immune effector to checkpoint ratios were prognostic. The CD4*CD8*:(CD163/CD68)*PD-L1 ratio was better able to stratify overall survival than any single or combination of immune markers, distinguishing groups with disparate 4-year survivals (92% versus 47%). The immune ratio was independent of and added to the revised international prognostic index (R-IPI) and cell-of-origin (COO). Tissue findings were validated in 233 DLBCL R-CHOP-treated patients. Furthermore, within the blood of 140 R-CHOP-treated patients immune effector: checkpoint ratios were confirmed as highly informative predictors of outcome.

Conclusions: Ratios of immune effectors to checkpoints augment COO and R-IPI in DLBCL, are applicable to paraffin-embedded biopsies, and have potential utility to assist patient selection to clinical immunotherapeutic trials.

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CONTINUED RISK OF RELAPSE INDEPENDENT OF TREATMENT MODALITY IN LIMITED STAGE DIFFUSE LARGE B-CELL LYMPHOMA: FINAL AND LONG-TERM ANALYSIS OF SWOG STUDY S8736

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Introduction: For patients (pts) with stage I/II diffuse large B-cell lymphoma (DLBCL), the phase III SWOG S8736 study demonstrated that 3 cycles of CHOP + radiotherapy (CHOP3 + RT) improved 5-year (yr) progression-free (PFS) and overall survival (OS) when compared to 8 cycles of CHOP (CHOP8); however, longer follow-up suggested inferior outcomes in the combined modality arm (Miller, ASH 2001). Here, we describe long-term and final analysis of SWOG S8736.

Methods: From 1988 to 1995, 395 pts with limited stage DLBCL were randomized to CHOP8 ($n = 197$) or CHOP3 + RT ($n = 198$; 4000–5500 cGy, started 3 weeks following last cycle of CHOP). PFS/OS were primary endpoints. PFS was calculated from date of randomization until progression/relapse/death. OS was calculated from date of randomization until death.

Results: As previously published, clinical characteristics were balanced between the treatment arms (Miller, NEJM 1998). 77% and 95% of patients completed all planned therapy for CHOP8 and CHOP3 + RT, respectively, with 15% and 2% of patients discontinuing therapy for adverse events, respectively. Among evaluable patients ($n = 277$), the overall response rate was 86% [76% complete response (CR)] and 92% (76% CR) in the CHOP8 and CHOP3 + RT groups, respectively. Median follow-up of all pts is now 17.7 yrs. As reported, the 5-yr PFS estimate favoured the CHOP3 + RT group (74%) versus the CHOP8 group (67%). However, 10- and 15-yr PFS estimates in the CHOP3 + RT group (54% and 40%) were no different from the CHOP8 group (55% and 41%; $p = 0.91$), with continued relapses observed beyond 5 yrs in both arms. Median PFS was 12.1 and 11.1 yrs for the CHOP8 and CHOP3 + RT groups, respectively. Similarly, while 5-yr OS estimates were higher for the CHOP3 + RT group (82%) compared to the CHOP8 group (74%), the 10- and 15-yr OS estimates in the CHOP3 + RT group (63% and 46%) were similar to the CHOP8 group (61% and 46%; $p = 0.66$). Median OS of the CHOP + RT and CHOP groups were the same at 13.6 and 13.3 yrs, respectively. As a relative comparison, S0014 (Persky, JCO 2008), a phase II trial of rituximab plus CHOP3 + RT in high risk limited stage DLBCL now has a median follow-up of 12 yrs. Notably, there is a similar pattern of continued relapse with estimated 10-yr PFS of 60.8% (95% CI: 47.1%, 72.0%) and 10-yr OS of 69.3% (95% CI: 55.8%, 79.5%).

Conclusions: Although 5-yr PFS/OS were improved in limited-stage DLBCL pts receiving CHOP3 + RT versus CHOP8, extended survival data with over 17 years of follow-up show similar PFS/OS with continuous treatment failure without a plateau in both arms. While not entirely identical populations, even the addition of rituximab as per S0014 to combined modality therapy does not appear to mitigate the continued relapse risk, underscoring the value of prolonged observation and possible unique biology of limited stage DLBCL.

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TREATMENT SELECTION AND SURVIVAL OUTCOMES IN EARLY-STAGE DIFFUSE LARGE B-CELL LYMPHOMA: DOES MODERN CHEMOTHERAPY REPLACE THE NEED FOR RADIOTHERAPY?

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Introduction: The choice between chemotherapy alone and chemotherapy plus consolidation radiotherapy for diffuse large B-cell lymphoma (DLBCL) remains controversial. We aimed to define factors affecting treatment selection and resulting survival outcomes in the era of modern chemotherapy.

Methods: We identified 59 255 stage I–II DLBCL patients treated with multi-agent chemotherapy alone or multi-agent chemotherapy plus consolidation radiotherapy

DOI: 10.1002/hon

between 1998 and 2012 from the National Cancer Database, which captures an estimated 70% of cancers diagnosed in the USA. Univariate and multivariate analyses were performed to identify socio-demographic, treatment, and tumour characteristics predictive of overall survival and treatment utilization. Propensity-adjusted Cox proportional hazards ratios for survival were used.

Results: Of the included 59 255 DLBCL patients, 46% had stage II disease, 42% had extra-nodal disease, and 58% were older than 60 years. Chemotherapy was initiated at a median of 24 days (interquartile range: 13–39) after diagnosis, and radiotherapy was initiated at a median of 133 days after diagnosis (interquartile range: 104–168). The median radiotherapy dose was 36.0 Gy (interquartile range: 30.6–40.0 Gy), with the proportion of patients receiving > 36.0 Gy significantly decreasing from 62% in 1998 to 23% in 2012 ($p < 0.0001$). Intensity modulated radiotherapy was utilized in 9% of the combined modality group and significantly increased from 0% in 1998 to 24% in 2012 ($p < 0.0001$). Only 39% received chemotherapy plus radiotherapy, and this proportion significantly declined from a peak of 47% in 2000 to nadir of 32% in 2012 ($p < 0.0001$). Treatment selection was significantly influenced by race, comorbidity, insurance type, education quartile, facility type, facility location, age, stage, B-symptoms, distance from treatment facility, and year of diagnosis. Median follow-up was 60 months (interquartile range: 33–93). Estimated 5-year and 10-year overall survival was 79% and 59% for all patients, 75% and 55% for patients receiving multi-agent chemotherapy alone, and 82% and 64% for patients receiving combined modality therapy ($p < 0.0001$). Even after adjusting for immortal-time and indication bias, combined modality multi-agent chemotherapy plus radiotherapy was associated with better overall survival (HR 0.66, 95% CI 0.61–0.71, $p < 0.0001$) than multi-agent chemotherapy alone.

Conclusions: Utilization of consolidation radiotherapy after multi-agent chemotherapy in DLBCL is decreasing in the era of modern chemotherapy despite increased adoption of lower radiotherapy doses and modern radiation techniques. Selection of treatment strategy is affected by both classical prognostic features and socioeconomic factors. Abandonment of combined modality chemotherapy plus radiotherapy in favour of multi-agent chemotherapy alone negatively affects survival and should be cautioned.

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FRONT LINE THERAPY WITH R-CODOX-M AND R-IVAC IN POOR RISK DIFFUSE LARGE B CELL LYMPHOMA (IPI 3–5) YIELDS A GOOD OUTCOME WITHOUT TRANSPLANTATION: A PHASE 2 UK NCRI/LLR TRIAL

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Introduction: R-CHOP is the standard of care for patients with diffuse large B cell lymphoma (DLBCL); however, poor risk patients (IPI 3–5) still have an inadequate outcome. High dose chemotherapy and peripheral blood stem cell transplantation (HDC + PBSCT) in first remission and selection of cases for intensification based on interim PET scanning have not demonstrated a proven benefit. This is the first report of a prospective, multi-centre phase 2 trial of the use of the Burkitt lymphoma regimen, CODOX-M, and IVAC with the addition of Rituximab (8×375 mg/m^2), in unselected patients with high intermediate or high risk IPI.

Methods: 113 patients with DLBCL from 32 UK sites were treated between May 2008 and April 2013, 4 were ineligible and were excluded from all analyses. Median age was 50 years (19–65). IPI scores were 3, $n = 70$ (64%); 4, $n = 38$ (35%); and 5, $n = 1$ (1%). The performance status (PS) was 0, $n = 20$ (18.2%); 1, $n = 29$ (26.4%); 2, $n = 42$ (38.5%); and 3, $n = 18$ (16.5%). 11 patients had proven CNS disease. All patients were treated with the modified CODOX-M and IVAC regimen including CNS-directed therapy [Mead et al Ann Oncol. 2002 Aug; 13(8):1264–74] with the addition of 8 doses of rituximab. The primary endpoint of the study was progression-free survival (PFS); we aimed to show an increase from 45% to 60% at 2 years. Secondary endpoints included toxicity, CR rate, and overall survival (OS).

Results: 83 (76.2%) received 4 cycles of treatment. Although all patients experienced grade 3–4 toxicities, there were only 5 (4.6%) treatment-related deaths (all PS 3). The response observed was CR/CRu, $n = 50$ (45.9%); PR, $n = 32$ (29.4%); SD, $n = 3$ (2.8%); PD/relapse, $n = 6$ (5.5%); and not assessable or missing in 18 (16.5%). 36 patients have progressed or died. At 2 years, the PFS estimate is 67.9% (95% CI: 58.1–75.9), and at the median follow-up of 36.5 months, it is 64.9% (54.5–73.4). Currently, no PFS events have been seen past this point, but further follow-up is needed as 11 patients are progression free, on trial but yet to reach 2 years (min: 17 months). The OS estimate at 36.5 months is 74.1% (63.9–81.7). If analysed as per age-adjusted IPI, there was 1 aaIPI 1 patient (0.9%), 52 patients were aaIPI 2 (47.7%), and 56 were aaIPI 3 (51.4%). The PFS at 2 years is 75% (60.9–84.6) for aaIPI 2 and 60.5% (46.1–72.3) for aaIIPI 3.

Conclusion: The R-CODOX-M and R-IVAC regimen can be delivered to patients with poor risk DLBCL in a multicentre setting. The proportion of patients with a poor PS reflects the initial severity of the disease, and these patients are rarely included in clinical trials. High rates of haematological toxicity and consequent infection are inevitable with treatment of this intensity but appear acceptable when compared with other treatments such as HDC + PBSCT. The PFS for these patients appears promising, may be superior to R-CHOP, and similar to the first remission PBSCT results which have been reported in aaIPI 2 and 3 patients; however, further follow-up is needed.

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VALIDATION OF THE GERMAN HIGH-GRADE NON-HODGKIN LYMPHOMA STUDY GROUP (DSHNHL) PROGNOSTIC MODEL FOR CNS RELAPSE IN A LARGE COHORT OF PET/CT STAGED PATIENTS

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DOI: 10.1002/hon

Introduction: Central nervous system (CNS) relapse in patients with diffuse large B-cell lymphoma (DLBCL) is an infrequent but usually fatal complication. Our goal was to investigate the external validity of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) prognostic model based on the 5 IPI factors (age >60 years, elevated LDH, stage III/IV, >1 extranodal site, and ECOG performance status >1) in addition to kidney/adrenal involvement (Savage 394a, ASH 2014) in an independent large cohort of R-CHOP treated DLBCL patients staged with PET/CT

Methods: This is a retrospective study of patients with newly diagnosed DLBCL presenting to hospitals in Denmark and the Peter MacCallum Cancer Centre (Australia). All patients underwent staging with PET/CT and were treated with R-CHOP or similar first-line chemotherapy, with or without CNS prophylaxis and/or radiotherapy. Patients with CNS involvement at diagnosis were excluded. Consecutive patients were identified through searches in national/local lymphoma registries and screened for eligibility. Medical records were reviewed for clinical information and outcome. The Kaplan–Meier method was used to estimate time to CNS relapse and cumulative incidences.

Results: A total of 1290 PET/CT-staged DLBCL patients with data for all DSHNHL risk factors available were included, with the following characteristics: 65% age >60y, 49% elevated LDH, 63% stages III–IV, 23% >1 extranodal site, 13% performance status >1, and 4% kidney/adrenal involvement. Patients with 0–1 (34%), 2–3 (48%), or >3 (18%) risk factors were categorized as low-risk, intermediate risk, and high-risk for CNS relapse, respectively. With a median follow-up of 43 months ($P = 0.19$ for difference between the 3 risk groups), 51 (4%) developed CNS relapse. The median time to CNS relapse was 9 months (range 4–78 months). The cumulative incidences of CNS relapse at 2 years were 0.5% (95% CI 0.1–1.9%) for low risk, 2.5% (95% CI 1.5–4.2%) for intermediate risk, and 12.3% (95% CI 8.3–18.0%) for high risk. Within the high-risk group, 85/235 patients received CNS prophylaxis (IT alone 22%, systemic 31%, both 47%). The number of CNS events was similar for high-risk patients treated with and without CNS prophylaxis (12% for both, $P = 1.0$).

Conclusions: The prognostic model for CNS relapse proposed by the DSHNHL predicts CNS relapse in PET/CT-staged DLBCL patients treated with immunochemotherapy despite frequent use of CNS prophylaxis. The use of CNS prophylaxis did not reduce the risk of CNS events in high-risk patients, but prospective studies are warranted to define optimal strategies to effectively reduce this complication.

SESSION 11: PRIMARY CNS LYMPHOMA

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HIGH FREQUENCY OF *MYD88* MUTATIONS IN VITREORETINAL B-CELL LYMPHOMA: A VALUABLE TOOL TO IMPROVE DIAGNOSTIC YIELD OF VITREOUS BODY ASPIRATES

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Introduction: Vitreoretinal diffuse large B-cell lymphoma (VRL) is a rare ocular malignancy. Most cases represent either primary VRL or involvement by primary central nervous system lymphoma (PCNSL). VRL is usually diagnosed by cytological, immunocytochemical and molecular examination of vitreous body aspirates. Separation from uveitis can be difficult due to inconclusive cytological features. A feature of B-NHL in immune-privileged sites is a high frequency of *MYD88* mutations. The aim of our study was to assess the frequency of *MYD88* mutations in VRL and to investigate their diagnostic potential in a large series of vitrectomy specimens.

Methods: DNAs of 69 patients with suspicion of VRL were retrospectively investigated for $MYD88^{L265P}$ mutation by allele-specific PCR. *MYD88* exon 3 and 4 hotspot regions were sequenced in VRL samples wild type for $MYD88^{L265P}$. Samples had previously been analysed by cytology, immunocytochemistry and for immunoglobulin heavy chain (IGH) rearrangements. Clinical presentation, disease course, cytology and original diagnoses were correlated with the presence of *MYD88* mutations. As validation cohort, 21 archival vitrectomy DNA samples previously diagnosed in Liverpool were analysed in comparison.

Results: A primary diagnosis of VRL was rendered in 14 (20%) patients, whereas 55 (80%) patients remained negative or inconclusive for VRL. A clonal IGH rearrangement was identified in 12/14 VRL. *MYD88* mutation was detected in 8/14 (57%) initially diagnosed VRL, whereas 6/14 patients (43%) showed $MYD88^{WT}$. In the cases previously diagnosed as negative or inconclusive for VRL, a $MYD88^{L265P}$ mutation was identified in 6 patients (13%), whereas the remaining 49 patients (87%) were $MYD88^{WT}$. Clinical data and follow-up confirmed a diagnosis of VRL in 21/69 (35%) patients including 13/14 patients with an initial diagnosis of VRL, and all 6 $MYD88^{L265P}$ patients originally considered negative or inconclusive for VRL. In the Liverpool comparison, collective $MYD88^{L265P}$ was detected in 75% of VRL.

Conclusions: (1) Detection of *MYD88* mutations is a very useful tool for diagnosis of VRL in cases with insufficient cytological evidence of malignancy or lack of clonal IG rearrangements. (2) The high frequency (67%) of $MYD88^{L265P}$ detected in our series further supports that primary VRL and PCNSL correspond to a single entity.

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GENETIC BASIS OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Introduction: Primary central nervous system lymphoma (PCNSL) is a rare subtype of lymphoma, of which approximately 95% are diffuse large B-cell lymphomas (DLBCLs). Despite the substantial development of intensive chemotherapy during the past two decades, clinical outcome of PCNSL has been poorly improved

DOI: 10.1002/hon

especially in elderly and so has been our knowledge about the molecular pathogenesis of PCNSL, in terms of driver alterations that are relevant to lymphomagenesis.
Method: To delineate the genetic basis of PCNSL pathogenesis, we performed a comprehensive genetic study, in which paired tumour/normal DNAs from 32 PCNSL cases were analysed by whole-exome sequencing (WES). Significantly mutated genes identified by WES and previously known mutational targets in systemic DLBCL were further screened for mutations using SureSelect-based targeted deep sequencing (Agilent) in an extended cohort of PCNSL cases ($N = 85$). Copy number variations have been also investigated using SNP array-karyotyping.
Results: The mean number of nonsynonymous mutations identified by WES was 240 per sample, which outnumbered the figure in systemic DLBCL and characterized by high number of somatic hypermutations (SHM) involving non-Ig genes. Higher representation of mutations within RGYW/WRCY (15.5%) or DGYW/WRCH (20.9%) hotspot motifs targeted by SHM supported the prevalence of SHM in PCNSL. Significantly mutated genes were evaluated using MutSigCV to identify 12 significantly mutated genes ($q < 0.1$), including MYD88, PIM1, TMEM30A, PRDM1, HIST1H1C, B2M and several previously unreported mutational targets in systemic DLBCL or PCNSL. The pattern of frequently mutated genes in PNCSL was more uniform compared with that in systemic DLBCL and similar to that found in the activated B cell subtype of DLBCL (ABC-DLBCL), which was in accordance with the previous report of immunophenotypic analysis of PCNSL. Subsequent targeted sequencing identified 54 mutations per sample on average, substantial fractions of which were explained by SHM. Mutations implicated in constitutive NF-KB/BCR activity were most frequently observed, including those in MYD88 (79%), CD79B/A (63%), CARD11 (17%) and TNFAIP3 (11%). CNVs of chromosome 6p including HLA loci (90%) and mutations of B2M (14%) and CD58 (12%) were also commonly detected, suggesting the importance of escape from immunosurveillance in the pathogenesis of PCNSL. SHM were observed in most cases (93%), which affected not only known targets of activation-induced cytidine deaminase (AID) including PIM1, IGLL5 and BTG2 but also novel target genes involved in cell proliferation, apoptosis or B-cell development.
Conclusion: WES and follow-up sequencing of a large cohort of PCNSL cases revealed the genetic landscape of PCNSL, which were though to be involved in the activation of constitutive NF-KB/BCR signalling, escapes from immunosurveillance as well as highly frequent SHM.

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RITUXIMAB, METHOTREXATE, PROCARBAZINE AND LOMUSTINE FOR ELDERLY PRIMARY CNS LYMPHOMA PATIENTS—THE PRIMAIN STUDY BY THE GERMAN COOPERATIVE PCNSL GROUP

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Introduction: Primary central nervous system lymphoma (PCNSL) is an aggressive non-Hodgkin lymphoma mostly of B-cell origin, which exclusively invades the CNS compartment at diagnosis. Elderly patients account for 50% of all PCNSL cases, and there is no standard treatment for this vulnerable population.
Methods: We conducted a multicentre prospective single-arm study for elderly immunocompetent patients ≥ 65 years with newly diagnosed PCNSL. Treatment included 3 cycles repeated every 14 days; each consisted of the following: Rituximab 375 mg/m^2 [days −6 (only cycle 1), 1, 15, and 29], Methotrexate 3000 mg/m^2 (days 2, 16, and 30), Procarbazine 60 mg/m^2 (days 2–11), and Lomustine 110 mg/m^2 (day 2). This was followed by 6 cycles of monthly procarbazine 100 mg (5 days) maintenance, which could also be started if not all 3 cycles were completed. After an amendment, lomustine was dropped from R-MPL due to increased toxicity. Afterwards, patients were treated according to the R-MP protocol. Primary endpoint was rate of complete remissions on magnet resonance imaging 4 weeks after completion of 3 R-MP(L) cycles. Quality of life was evaluated using the EORTC QLQ-30 questionnaire. The trial was registered at clinicaltrials.gov (NCT 00989352).
Results: Between 2009 and 2013, 112 patients have been registered at 20 German centres (56 for R-MPL and R-MP, respectively), 4 excluded because not eligible. Median age and Karnofsky performance scale were 73 (range 66–85) years and 70% (30%–100%), respectively. In the preliminary analysis, best-documented overall response rate was 74% (46 complete and 34 partial remissions). 42 (39%) patients achieved the primary endpoint after 3 cycles of R-MP(L). 54 (50.0%) patients commenced maintenance therapy with procarbazine. In the entire group, median progression-free (PFS) and overall survival (OS) was 11.5 (24-month probability for PFS 38%, 95% CI 28%–48%) and 22.7 (24-month probability for OS 48%, 95% CI 38%–58%) months, respectively. Of 54 deaths, 6 were treatment related. Further analyses including stratification by R-MPL and R-MP will be presented at the meeting.
Conclusion: The PRIMAIN study is the largest prospective study particularly designed for elderly patients (≥65 years) with newly diagnosed PCNSL. R-MP seems to be a feasible and effective treatment for this vulnerable patient population and warrants further investigation. Final effectiveness and safety results will be presented at the meeting.

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MANAGEMENT AND OUTCOME OF PRIMARY CNS LYMPHOMA AT FIRST RELAPSE/PROGRESSION: ANALYSIS OF 256 PATIENTS FROM THE FRENCH LOC NETWORK

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DOI: 10.1002/hon

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Introduction: A significant proportion of primary CNS lymphoma (PCNSL) patients is refractory or relapses after first-line therapy. Clinical presentation and therapeutic management of patients with relapsed/refractory (R/R) PCNSL are heterogeneous. The aim of this study was to analyze the characteristics, management, and outcome of R/R PCNSL patients after first-line therapy.

Methods: We analysed patients with R/R PCNSL who had been prospectively registered in the database of the French LOC network between 2011 and 2014.

Results: Among 563 PCNSL patients registered in the LOC database, we identified 256 patients with relapse ($N = 93$, 16.5%) or refractory ($N = 163$, 29.0%) disease after a median follow-up of 9 (0.3–43.0) months. Median age was 68 (26–93) years. Most patients (92.6%) had received a methotrexate-based chemotherapy as first-line treatment. First relapse/progression occurred after a median progression-free survival from diagnosis (PFS1) of 5.1 (0.3–35.8) months. Relapse/progression was asymptomatic in 25.5% of the cases, mostly diagnosed on systematic neuroimaging. Overall survival after relapse/progression (OS2) was 3.5 (0–29.6) months for the entire cohort. At first relapse/progression, 28.2% of the patients received palliative care. All of them died within 5 months with a median OS2 of 0.6 months. The remaining patients (71.8%) received salvage chemotherapy (methotrexate, cytarabine or ifosfamide-based regimens) without (79.5%) or with (20.5%) consolidation therapy consisting in radiotherapy (14.7%) or intensive chemotherapy followed by autologous stem-cell transplantation (ICT + ASCT) (85.3%). Survival was significantly longer in patients receiving consolidation therapy with a median PFS2 (PFS from first relapse/progression) of 13.5 versus 2.6 months and a median OS2 not reached versus 6.7 months ($p < 0.01$). In patients receiving ICT + ASCT, 44.8% (13/29) experienced a PFS2 longer than their PFS1. Survival was significantly worse in refractory patients and in relapsed patients with a PFS1 < 1 year (median OS2 = 2.1 and 3.7 months, respectively) compared to relapsed patients with a PFS1 > 1 year (median OS2 not reached, $p < 0.01$). Other prognostic factors were age (< vs > 60 years), Karnofsky index (KI, > vs < 70%), administration of a salvage therapy, and administration of Rituximab. In multivariate analysis, three prognostic factors remained statistically independent: performance status (KI), duration of first remission (PFS1), and administration of a salvage therapy.

Conclusions: One fourth of R/R PCNSL are asymptomatic, underlining the need for systematic neuroimaging in surveillance. Duration of first remission (PFS1) is a strong prognostic factor. Salvage chemotherapy followed by consolidation with ICT + ASCT is associated with prolonged remission in a subset of patients.

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PHASE I/II STUDY OF TEDDI-R WITH IBRUTINIB IN UNTREATED AND RELAPSED/REFRACTORY PRIMARY CNS LYMPHOMA

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Introduction: Primary central nervous system lymphoma (PCNSL) is a rare diffuse large B-cell lymphoma (DLBCL). It is derived from an activated B-cell and harbours mutations affecting the B-cell receptor (BCR) and MyD88. We previously demonstrated that ibrutinib, an inhibitor of BTK, targets BCR signalling and is effective in patients with relapsed and refractory systemic ABC DLBCL.

Methods: TEDDI-R (temozolomide, etoposide, doxil, dexamethasone, ibrutinib and rituximab) (with intraventricular cytarabine) was designed around therapeutic principles for systemic DLBCL and CNS penetration. Methotrexate was excluded due to antagonism with ibrutinib *in vitro*. Untreated or relapsed/refractory PCNSL patients were eligible and received ibrutinib (560 mg/day PO) for 14 days in a 'window' prior to cycle 1 followed by brain MRI/FDG-PET and then 6 cycles of DA-TEDDI-R every 21 days. Plasma and CSF PKs of ibrutinib and its metabolite PCI-45227 were analysed. CSF penetration (AUC_{CSF}:AUC_{PLASMA}) was corrected for human plasma binding: parent: 97.3%; metabolite: 91%. DA-TEDDI-R safety was evaluated on cycle 1 in the

Abstract 136 Table 1.

	Plasma ibrutinib PK				CSF ibrutinib PK				
Patient #	**C_{max} (nM)**	**T_{max} (h)**	**AUC_{0-10} (nM h)**	**$T_{½}$ (h)**	**C_{max} (nM)**	**T_{max} (h)**	**AUC_{0-last} (nM h)**	**AUC_{CSF}:AUC_{Plasma} uncorrected (%)**	**AUC_{CSF}:AUC_{Plasma} corrected (%)**
1	502	1	1232	10.2	1.99	2	7.7 (10 h)	0.6	23.7
2	145	2	471	4.6	0.69	2	2.4 (6 h)	0.5	21.4
3	77	2	347	3.1	1.28	2	4.4 (6 h)	1.3	55.8
4	72	1	202	2.6	1.54	4	5.5 (10 h)	2.7	100

		Ibrutinib outcome			C2 TEDDI-R outcome		
Patient #	**Prior Rx**	MRI	PET	Response	MRI	PET	Response
1	Refractory	PR	Neg	PR	CR	Neg	CR
2	Untreated	NE	↓	NE	CR	Neg	CR
3	Refractory	PR	Neg	PR	CR	Neg	CR
4	Untreated	PR	↓	PR	PR	PR	PR
5	Refractory	PR	↓	PR	TE	TE	TE
6	Relapsed	PR	↓	PR	TE	TE	TE

DOI: 10.1002/hon

first 6 patients. CSF PKs of TEDDI drugs and molecular analysis of FFPE biopsies are ongoing.

Results: Six patients have enroled; 6 have completed the ibrutinib window, and 4 patients completed at least 2 cycles of DA-TEDDI-R. Patients 1, 3, 5 and 6 had relapsed/refractory PCNSL (1–5 prior treatments), and patients 2 and 4 were untreated. PK in patients 1–4 showed CSF penetration of ibrutinib and its metabolite (Table 1). When corrected for protein binding, CSF penetration was 21.4–100% for ibrutinib and 48–120% for its metabolite. CSF concentrations $> IC_{50}$ were maintained for up to 6 h. Following ibrutinib alone, of 5 evaluable patients, all 5 demonstrated tumour improvement. DA-TEDDI-R was tolerated without DLT. Patients 1, 2 and 3 achieved CR after cycle 2 of DA-TEDDI-R and patient 4 achieved PR.

Conclusions: Ibrutinib is active in PCNSL and achieves meaningful CSF concentrations. DA-TEDDI-R is a novel treatment for PCNSL and leverages molecular and therapeutic principles developed for the curative treatment of systemic ABC DLBCL. Accrual continues.

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LENALIDOMIDE IS HIGHLY ACTIVE IN RECURRENT CNS LYMPHOMAS: PHASE I INVESTIGATION OF LENALIDOMIDE PLUS RITUXIMAB AND OUTCOMES OF LENALIDOMIDE AS MAINTENANCE MONOTHERAPY

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Introduction: There is an unmet need for effective therapies for relapsed CNS lymphomas. Lenalidomide (CC-5013) is active as a single agent in aggressive NHL, particularly in ABC-type DLBCL. We recently demonstrated the activity of lenalidomide in treatment of refractory intraocular and CNS NHL (JCO, 2011). These observations are the basis for this first trial of IMiD® therapy in CNS NHL, as monotherapy, and in patients with inadequate responses to lenalidomide, in combination with intravenous plus intraventricular rituximab. (NCT01542918). In an independent set of patients, we test the hypothesis that lenalidomide maintenance is feasible and effective after front-line salvage in relapsed CNS lymphomas.

Methods: The primary objective of the phase I study is to determine safety and efficacy of lenalidomide at 3 dose levels (10, 20, and 30 mg) in refractory CD20+ CNS NHL. Secondary endpoints include the following: (1) determination of CSF penetration by lenalidomide; (2) feasibility of combined intraventricular and intravenous rituximab; and (3) evaluation of effects of lenalidomide on tumour microenvironment. In parallel, we determine feasibility and PFS of maintenance lenalidomide after salvage therapy in an independent cohort of relapsed/refractory CNS lymphoma patients.

Results: Nine subjects with refractory CNS DLBCL (7 PCNSL, 2 SCNSL; median age 63 years, range 46–77) were treated on the phase I protocol. Of 8 evaluable subjects, 6 achieved PR or better at 1 month with lenalidomide monotherapy: 2 CRs, 1 PR in brain NHL; 1 CR of CSF NHL; and 1 CR, 2 PRs of intraocular NHL. Three patients maintain responses to lenalidomide monotherapy > 6 months and 2 beyond 1.1 years. An independent cohort of 10 patients with recurrent, refractory CNS DLBCL (8 PCNSL, 2 SCNSL; median age 70 years, range 59–81) received lenalidomide monotherapy (5–10 mg) as maintenance after first-line salvage. Salvage interventions included resection, gamma knife and/or methotrexate-rituximab. With median follow-up of 18 months, PFS for this cohort is impressive: 5 patients have maintained durable responses ≥ 2 years. Using HPLC-MS/MS, we demonstrated lenalidomide penetration in ventricular CSF (0.6–7.9 ng/mL) in each of 4 patients, 12–15 h after dosing at 20 mg. Metabolomic profiling revealed that CSF lactate correlated with clinical response. Finally, we demonstrated that lenalidomide is associated with a rapid and reversible effect on macrophage polarization to an M1, iNOS+ phenotype.

Conclusions: Lenalidomide penetrates ventricular CSF, exhibits novel effects on tumour microenvironment, and is active in relapsed CNS DLBCL. In addition, we provide the first evidence that maintenance lenalidomide may potentiate PFS after salvage therapy in relapsed, refractory CNS DLBCL.

SESSION 12: IMMUNOTHERAPY

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IMMUNOTHERAPY OF LYMPHOMA 2015

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Therapies that employ the immune system should apply especially to lymphoma, the cancer of the immune system. We are currently witnessing an explosion of immunotherapies for cancer.

These include therapies that:

Target the tumour

- engineered antibodies
- antibody-drug conjugates
- bispecific antibodies
- T-bodies (CAR T cells)

Target the host

- enhancing ADCC
- removing checkpoints on the immune system

Target both the tumour and the host.

Examples of each of these forms of immunotherapy will be presented and discussed. Intensive preclinical and clinical work is now searching for the best combinations of immunotherapies and 'targeted therapies'. Parallel advances in these two fields provide a great opportunity and at the same time a challenge for the design of clinical trials. Some combinations will prove synergistic and some antagonistic. Some of these answers can be determined in preclinical models, and some will only be apparent in clinical trials.

In addition, combining agents developed by different commercial entities will require new models of collaboration, financial support and eventual marketing.

The goal for immunotherapies, as for all new therapies, is to improve efficacy, reduce toxicity and be practical and cost effective in our care delivery systems.

With the new forms of immunotherapy, this may be possible.

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PHASE II TRIAL OF CHIMERIC ANTIGEN RECEPTOR MODIFIED T CELLS DIRECTED AGAINST CD19 IN RELAPSED/REFRACTORY DIFFUSE LARGE B CELL, FOLLICULAR, AND MANTLE CELL LYMPHOMAS

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Background: Autologous T cells expressing a chimeric antigen receptor with an external anti-CD19 single chain antibody domain and CD3ζ and 4-1BB signalling domains (CTL019 cells) mediate anti-tumour effects in patients (pts) with relapsed/refractory CD19+ leukaemias. We are conducting a phase II clinical trial of CTL019 cells in relapsed/refractory CD19+ non-Hodgkin lymphomas.

Methods: Eligible pts have CD19+ diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), or mantle cell lymphoma (MCL), with anticipated survival less than 2 years. After collection of peripheral blood leukocytes, pts receive lymphodepleting chemotherapy based on histology and past therapies. One to 4 days after chemotherapy, pts receive 5×10^8 CTL019 cells intravenously. Blood and marrow samples are collected for correlative studies. Initial response assessment is 3 months after infusion. Enrollment began in February 2014; data are reported through February 2015.

Results: 29 pts (19 DLBCL; 8 FL; 2 MCL) have enroled. Median age is 56 years (range: 25–77), male:female ratio is 17:12, median number of prior therapies is 4 (range: 1–8), and number of pts with prior ASCT is 9 (31%). At enrolment, stages were as follows: IV 16 pts (55%); III 5 pts (17%); II 6 pts (21%); IE 2 pts (7%); and LDH was increased in 20 pts (69%). None of the FL pts had responded to the therapeutic regimen preceding CTL019 protocol therapy. Eight pts are not evaluable for response (DLBCL 7; FL 1): 3 pts were removed from study before T-cell infusion due to progressive disease; 1 pt withdrew consent; 3 pts had inadequate *in vitro* T-cell expansion; and 1 pt received less than the protocol-specified cell dose. 20 pts received CTL019 per protocol-specified cell dose (12 DLBCL; 7 FL; 1 MCL). Pre-infusion chemotherapy regimens were EPOCH (2 pts), cyclophosphamide (9 pts), radiation + cyclophosphamide (2 pts), bendamustine (6 pts), and cyclophosphamide-fludarabine (1 pts). Cytokine release syndrome occurred in 15 pts (grade 2 in 13 pts; grade 3 in 2 pts). Neurologic toxicity occurred in 3 pts: transient delirium (grade 2 in 1 pt; grade 3 in 1 pt), and 1 pt had possibly related, grade 5 encephalopathy. For 19 pts evaluable for response at 3 months (12 DLBCL; 7 FL), overall response rate is 68% (DLBCL 50%; FL 100%). Best responses using CT-based international workshop criteria (Cheson et al, 1999) are as follows: DLBCL CR/CRu 42% (5/12 pts), PR 8% (1/12 pts), FL CR/CRu 57% (4/7 pts), and PR 43% (3/7 pts). Progression-free survival for evaluable pts at median follow-up 6 months is 59% (DLBCL 37%; FL 100%).

Conclusions: CTL019 cells induce durable responses in pts with relapsed/refractory DLBCL and FL with acceptable toxicity.

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A PHASE IIA STUDY OF SINGLE-AGENT MOR208, AN FC-OPTIMIZED ANTI-CD19 ANTIBODY, IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA

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Introduction: There remains a high unmet medical need for new therapies for patients (pts) with relapsed or refractory (R-R) B-cell non-Hodgkin's lymphoma (NHL). MOR208 is an Fc-engineered humanized monoclonal antibody that targets the B-cell-specific antigen, CD19.

Method: This is a non-randomized, open-label, multicentre, two-stage, phase IIa study of MOR208 in pts with R-R NHL previously treated with rituximab who were not candidates for high-dose chemotherapy with stem cell support. Adult pts with diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), or other indolent NHL (iNHL) were treated with single-agent MOR208, at an intravenous dose of 12 mg/kg, weekly, over two 28-day cycles. Pts with at least stable disease according to the 2007 International Response Criteria were to continue treatment with MOR208 for another cycle. Pts achieving a complete or partial response (CR or PR) could then receive maintenance MOR208 every 2 or 4 weeks, depending on the investigator's decision, until progression. Overall response rate (ORR = CR + PR) was the primary endpoint.

Results: By 17 November 2014, all pts ($N = 89$) had been enroled (DLBCL, $n = 35$; FL, $n = 31$; MCL, $n = 12$; iNHL, $n = 11$); median age was 67 (range 35–90) years. Of these pts, 88% had stage III–IV disease and the median number of prior therapies was 2 (range 1–4). The mean number of cycles completed was 2.2 (0–3). The investigator-assessed responses across all NHL subtypes are shown in Table 1; the highest ORR was recorded in the DLBCL cohort (26%). Preliminary median duration of response was 7.7 months in the DLBCL cohort and 2.6 months in the FL cohort. Grade ≥3 non-haematologic treatment-emergent adverse events (TEAEs) were recorded in 30 pts (34%); disease progression, reported in 10 pts (11%), was most common. Grade ≥3 haematologic TEAEs were recorded in 8 pts (9%); neutropenia, reported in 5 pts (6%), was most common. Infusion-related reactions, reported in 8 pts (9%), were all grades 1–2 except for one case of dyspnea, which was grade 4. There were no treatment-related deaths.

Conclusions: MOR208 demonstrated encouraging single-agent efficacy with CRs observed in pts with R-R DLBCL, FL, and iNHL. MOR208 is well tolerated without significant infusional toxicity. Protocols are being developed to investigate MOR208 in combination with other agents.

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PHASE I, FIRST-IN-HUMAN TRIAL OF BI 836826 (AN ANTI-CD37 ANTIBODY) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

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DOI: 10.1002/hon

Abstract 141 Table 1. Investigator-assessed responses in NHL subtypes (safety population)

Response, *n*	NHL cohort				
	DLBCL (*N* = 35)	**FL (*N* = 31)**	**MCL (*N* = 12)**	**iNHL (*N* = 11)**	**Overall (*N* = 89)**
CR	2	1	0	1	4
PR	7	6	0	3	16
SD	5	14	6	3	28
PD	11	4	5	3	23
NE	10	6	1	1	18
ORR, *n* (%)	**9 (26)**	**7 (23)**	**0 (0)**	**4 (36)**	**20 (22)**

CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; NE, not evaluable; iNHL, indolent non-Hodgkin's lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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Background: BI 836826 is a novel Fc-engineered IgG1 type II antibody targeting CD37, a tetraspanin predominantly expressed on normal and malignant B-cells, with a dual cytotoxic mode of action by directly inducing apoptosis and increasing antibody-dependent cellular cytotoxicity. *Ex vivo*, BI 836826 results in a greater depletion of CLL cells than rituximab, irrespective of genetic risk. This ongoing Phase I study investigates the maximum tolerated dose (MTD), safety, pharmacokinetics (PKs) and efficacy of BI 836826 in pts with R/R CLL (NCT01296932; 1270.1).

Methods: Eligible pts had ≥2 prior therapy lines, adequate organ function, neutrophils ≥1000/μL and platelets ≥25 000/μL, and were treated with increasing doses of BI 836826 as a rate-controlled intravenous infusion (modified 3 + 3 design). In Course 1, 10% of the total BI 836826 dose (not exceeding 10 mg) was administered on day 1 with the remaining dose administered on day 2 of a 14-day course. In subsequent courses, BI 836826 was administered on day 1. MTD will be determined based on dose-limiting toxicity [DLT, defined as any drug-related non-haematologic adverse event (AE) ≥ grade (G) 3, except infusion-related reactions (IRRs)] during the first treatment course.

Results: To date, 33 pts [mean age 66.2 years; 70% male; 36.4% Binet stage C or Rai III/IV; median 4 (range 2–10) prior therapy lines] have been treated [1 mg ($n = 3$), 3 mg ($n = 3$), 9 mg ($n = 6$), 25 mg ($n = 6$), 50 mg ($n = 3$), 100 mg ($n = 3$), 200 mg ($n = 6$) and 400 mg ($n = 3$)]. Baseline molecular genetics were del(17p) and/or TP53 mutation (63.6%) and del(11q) (29.0%); 72.7% had unmutated IGHV. Four treatment courses were planned; 18 pts (54.5%) completed 8 courses. Five pts (15.2%) received >8 courses due to sustained clinical benefit. One pt (200 mg) had a DLT of G3 hypophosphatemia. MTD has not been determined. Most frequent AEs were IRRs (66.7%), chills (60.6%), pyrexia (51.5%), anaemia (42.4%), thrombocytopenia (42.4%), neutropenia (39.4%), diarrhoea (36.4%) and nausea (33.3%). Drug-related AEs included IRRs (66.7%), chills (57.6%), pyrexia (48.5%), neutropenia (36.4%) and thrombocytopenia (27.3%). Serious AEs included pyrexia (9.1%), neutropenia, leukopenia, cardiac failure and IRRs (all 6.1%). PK exposure increased with increasing doses, and short half-lives were observed. Of 26 evaluable pts (i.e. received full intended dose) at ≥9 mg, overall response rate was 42.3% (all partial remission; investigator assessment); 14 pts (53.8%) had stable disease. Of 23 pts at ≥9 mg with elevated baseline counts, 78.3% had a ≥50% lymphocyte reduction and 52.2% had a reduction to <4000/μL, including pts with high-risk genetic features.

Conclusions: Promising responses have been observed with BI 836826, even at low doses, with an acceptable safety profile. AEs were predominantly IRRs and cytopenias which were manageable with routine supportive care. These data support further clinical evaluation of BI 836826.

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TWO DOSES OF POLATUZUMAB VEDOTIN IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL): DURABLE RESPONSES AT LOWER DOSE

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Introduction: Based on early evidence of cumulative toxicity of polatuzumab vedotin (PoV; anti-CD79b antibody-drug conjugate) at a dose of 2.4 mg/kg (Morschhauser ASH 2014; NCT01691898), a dose of 1.8 mg/kg was explored. We report updated results of the dose comparison. Safety and efficacy of PoV after 8 treatment cycles were also analysed.

Methods: Patients (pts) with R/R FL received PoV at 2.4 or 1.8 mg/kg with rituximab (R) 375 mg/m^2, q21d until progression or unacceptable toxicity. Five pts with R/R FL from the Phase 1 study (Palanca-Wessels ASH 2013) treated with PoV 2.4 mg/kg were included in the analysis. Data at completion of PoV treatment were compared with data after 8 cycles.

Results: Forty-five pts received PoV + R (25, 2.4 mg/kg; 20, 1.8 mg/kg). Median follow-up was 14 mo. in the 2.4 mg/kg group versus 8 mo. in the 1.8 mg/kg group. When limited to the first 8 treatment cycles, median follow-up was similar at 6 mo. for both groups. Baseline characteristics were balanced between the two cohorts, except for age (median 68 y 2.4 mg/kg; 62 y 1.8 mg/kg) and tumour volume (SPD 1824 mm^2 at 2.4 mg/kg, 2655 mm^2 at 1.8 mg/kg). Forty per cent (10/25, 2.4 mg/kg) and 50% (10/20, 1.8 mg/kg) pts were refractory to their last treatment. At data cut-off for this analysis, pts received a median of 10 and 9.5 treatment cycles in the 2.4 and 1.8 mg/kg groups, respectively, with median dose intensities through cycle 8 of 88% and 99%, respectively. Safety is shown in the Table. Peripheral neuropathy (PN) was more frequent with PoV 2.4 mg/kg, and discontinuation (d/c) rates due to all causes were 56% versus 30% with the 1.8 mg/kg dose. After 8 treatment

DOI: 10.1002/hon

Abstract 142 Table 1.

Adverse events, *n* (%) (MeDRA SOC)	PoV 1.8 mg/kg All cycles (*N* = 20)	PoV 2.4 mg/kg All cycles (*N* = 25)	PoV 1.8 mg/kg 8 cycles (*N* = 20)	PoV 2.4 mg/kg 8 cycles (*N* = 25)
Any AE Grade 3–4	10 (50)	13 (52)	10 (50)	13 (52)
Neutropenia	7 (35)	4 (16)	7 (35)	4 (16)
Febrile neutropenia	2 (10)	1 (4)	2 (10)	1 (4)
Serious AE	6 (30)	8 (32)	6 (30)	6 (24)
Deaths	–	1 (4)	–	–
AE leading to study discontinuation	6 (30)	14 (56)	5 (25)	7 (28)
Grade 2–4 periph. neuropathy[a]	8 (40)	18 (72)	5 (25)	10 (40)
Grade 3+ infection	1 (5)	3 (12)	1 (5)	2 (8)

AE per CTCAE V4.03. AEs G3/4 ≥ 10% reported.
[a]MedDRA SMQ peripheral neuropathy (wide).

cycles, d/c rates were similar for both doses (28% vs 25%). An 84-year old pt in the 2.4 mg/kg cohort died 2 mo. after cycle 12 due to pulmonary congestion.

Safety profiles of PoV + R for all treatment cycles and truncated after cycle 8

ORR was similar for both levels: 19/25 (76%) at 2.4 mg/kg and 15/20 (75%) at 1.8 mg/kg. CRs were achieved in 11/25 (44%) patients at 2.4 mg/kg and 2/20 (10%) patients at 1.8 mg/kg. Duration of response was 12 mo. for 2.4 mg/kg and not estimable for 1.8 mg/kg group. After 8 cycles, ORR remained similar (64% for 2.4 mg/kg and 60% for 1.8 mg/kg). Median PFS was 15 mo. at 2.4 mg/kg and not reached in the 1.8 mg/kg group.

Conclusions: PoV + R in R/R FL showed high ORR at both doses, with higher CR at 2.4 mg/kg. D/c rates, mostly due to cumulative PN, were high. AEs and d/c rates were reduced at both doses if only the first 8 cycles are considered versus those through study completion. The safety of PoV can be improved by shorter treatment and/or lower dose. Updated PFS will be presented.

SESSION 13: TARGETING INTRACELLULAR PATHWAYS

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GENETIC AND EPIGENETIC HETEROGENEITY OF MALIGNANT LYMPHOMA: CHALLENGING FEATURES

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The recent advances in technology, such as next generation sequencing (NGS), have resulted in the identification of hundreds of genetic and epigenetic aberrations in various types of lymphoma. Most lymphomas are characterized by genetic alterations that are specific to the type of lymphoma. However, these genetic alterations are not completely associated with a single disease entity, suggesting that they are not individual determinants of disease entity. The same was true for chromosome translocations. For example, characteristic chromosomal translocations have been also observed in double- and triple-hit lymphomas or a different disease entity. These indicate that a single genetic alteration is not sufficient for the development of malignancy. NGS has revealed a number of genetic alteration landscapes for each lymphoma, with shared genetic alterations being observed among various types of lymphoma. These features pose challenging questions regarding the mechanism of lymphoma development, diagnosis, and therapeutic approaches. Increasing evidence has suggested that alterations frequently occur in multiple genes encoding the same intracellular signal transduction pathways, resulting in the same outcome, as observed in the T-cell- and B-cell-receptor signalling pathways and NF-κB signalling pathways. Therefore, there is an urgent clinical need for molecular therapies targeting the mutated genes that affect these signalling pathways. The uncovered genetic alterations have therefore provided a rationale for molecular targeted therapy; in fact, these alterations have resulted in significant improvements in the field of targeted therapy. However, the combination of molecular therapy and conventional chemotherapy and/or antibody therapy remains to be explored. It is also of interest to evaluate the effect of an inhibitor that is specific to a certain molecule when a downstream gene of the same signal transduction pathway is altered. This would raise further questions regarding the diagnostic and therapeutic stratification of lymphomas. I believe that the 13-ICML meeting would provide us with interesting clues and ideas for future lymphoma studies.

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EPIGENETIC CONTROL OF CELLULAR SENESCENCE IN TUMOUR DEVELOPMENT AND LYMPHOMA TREATMENT

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Introduction: Epigenetic deregulation, for example, via the histone H3 lysine 4 (H3K4) histone methyltransferase (HMT) MLL2 or the H3K27 HMT EZH2, is an emerging feature of B-cell malignancies. Previously, we reported an essential, tumour-suppressive role for the H3K9 HMT Suv39h1 in oncogene-induced senescence (OIS) as a barrier to lymphoma development *in vivo* (Braig-M et al., Nature, 2005). Senescence, a terminal cell-cycle arrest condition characterized by S-phase entry-controlling trimethylation of H3K9, is not only an oncogene-evoked failsafe mechanism but occurs in response to DNA-damaging agents as therapy-induced senescence (TIS). In the current study, we focus, in addition to Suv39h1, on the H3K9-active demethylases LSD1 and JMJD2C in both OIS and therapy-induced senescence (TIS) in aggressive B-cell lymphoma.

Methods: LSD1- or JMJD2C- or empty vector-infected fibroblasts were stably transfected with *H-Ras*^{G12V} to induce OIS. Subsequently, cell growth, senescence, colony formation in soft agar and tumour formation in nude mice were assessed. Likewise, primary Eμ-*myc* transgenic mouse lymphomas with and without H3K9-targeting activities (i.e. Suv39h1 deficiency or LSD1/JMJD2C overexpression) were generated and exposed to senescence-inducing chemotherapeutic agents as well as pharmacological LSD1/JMJD2C inhibitors *in vitro* or *in vivo*. Senescence was analysed by staining for senescence-associated b-galactosidase (SA-b-gal) activity, H3K9me3, Ki67 and BrdU incorporation, and chromatin immunoprecipitation. Lymphoma formation and treatment responses *in vivo* were monitored by luciferase and GFP imaging, SA-b-gal/Ki67 staining *in situ*, and overall survival of the mice was assessed by Kaplan Meier analysis.

Results: H3K9-active demethylases—like overexpression of a dysfunctional H3R9 mutant—blocked and even reversed OIS, and permitted direct transformation under oncogenic Ras. In Myc-driven lymphomas, either loss of Suv39h1 or overexpression of LSD1 or JMJD2C cancelled TIS *in vitro* and *in vivo*. Notably, H3K9me3-impaired lymphomas resembled control lymphomas in their proliferation rate and

DOI: 10.1002/hon

sensitivity to drug-induced apoptosis, but displayed significantly shorter progression-free and overall survival after chemotherapy. Extended data sets on LSD1 and JMJD2C expression in human diffuse large B-cell lymphoma samples and their correlation to treatment outcome will be presented at the meeting.

Conclusions: The data underscore the essential and dynamic role of the H3K9me3 mark in OIS and TIS, and unveil the oncogenic potential of H3K9 demethylases, thereby providing a mechanistic basis for JMJD2C- or LSD1-targeting strategies in lymphoma therapy.

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PHASE 1 STUDY OF E7438 (EPZ-6438), AN ENHANCER OF ZESTE-HOMOLOG 2 (EZH2) INHIBITOR: DOSE DETERMINATION AND PRELIMINARY ACTIVITY IN NON-HODGKIN LYMPHOMA

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Background: E7438 (EPZ-6438) is a selective, small molecule inhibitor of EZH2, the catalytic subunit of the polycomb repressive complex 2 that methylates H3K27. Hypertrimethylation of H3K27 (H3K27Me3) appears tumourigenic in various malignancies, including B-cell non-Hodgkin lymphomas (NHL), and inhibition of H3K27Me3 with EZH2 inhibitors shows activity in models of both EZH2 mutant and wild-type (WT) NHL. Phase 1 dose escalation has been performed with the aim of determining the maximum tolerated dose (MTD) in patients (pts) with B-cell lymphoma or advanced solid tumours. The goal of this investigation was to determine an optimal E7438 dose for further evaluation in NHL pts based on modelling of pharmacokinetic (PK), pharmacodynamic (PD), safety and efficacy data.

Methods: E7438 was administered PO BID continuously to cohorts of 3 to 6 pts up to a maximum dose of 1600 mg BID. Blood samples for PK and paired skin biopsies for PD analysis were collected. PD samples were stained with H3K27Me3-specific antibody. The per cent change of H3K27Me3 positive cells from baseline to Cycle 1 day 28 was determined, and a PK/PD relationship was analysed. Tumour response assessments were performed every 8 weeks. Archival tumour tissue was analysed for EZH2 mutations (hotspot codons Y646, A682, and A692).

Results: As of 7 Nov 2014, 24 pts have been enroled and treated at 5 dose levels of 100, 200, 400, 800, and 1600 mg BID. Of these, 12 were NHL pts, including follicular lymphoma (FL, $n = 5$), diffuse large B-cell lymphoma [DLBCL, $n = 6$, including 1 pt with primary mediastinal B-cell lymphoma (PMBCL)], and marginal zone lymphoma ($n = 1$). Median age was 62 years (range 24–84). 1 DLT of thrombocytopenia has been reported at 1600 mg BID; MTD was not reached. E7438 PK exhibited rapid absorption ($T_{max} = 1$–2 h), dose-related increase in exposure, and rapid elimination (half-life ~4 h). There was an exposure-related decrease in H3K27Me3 positive cells in skin that was described by an inhibitory E_{max} model. The model predicted E7438 exposure associated with 90% of maximal inhibition in the skin ($IC_{90} = 4421$ ng h/mL) which correlated with steady state E7438 exposure following 800 mg dose administration (mean Day 15 AUC = 4553 ng h/mL). 10 NHL pts had tumour assessments by the time of cut-off. Objective responses were demonstrated in 3 of 5 evaluable DLBCL pts [1 transformed DLBCL, 100 mg BID; 1 PMBCL, 200 mg BID; and 1 DLBCL (non-germinal centre subtype), 800 mg BID] and in 1/4 FL at 800 mg BID, with the longest treatment duration of 44 weeks at the time of the data cut-off. 11 pts were analysed for EZH2 mutation, all were wild-type. Updated data including duration of response will be presented.

Conclusions: Preliminary responses in NHL were demonstrated across dose levels. Based on safety, preliminary efficacy, and PK/PD analysis, 800 mg BID is the recommended adult Phase 2 dose of E7438. Further cohort expansion is ongoing.

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SELINEXOR SHOWS ACTIVITY IN DOUBLE-HIT DIFFUSE LARGE B-CELL LYMPHOMA IN PRE-CLINICAL MODELS AND IN PATIENTS WITH RELAPSED/REFRACTORY DOUBLE-HIT DLBCL

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Introduction: Double hit diffuse large B-cell lymphoma (DH-DLBCL) involves translocations of *MYC* and either *BCL2* or *BCL6.* This form of DLBCL has a poor prognosis and lacks standard-of-care therapy. Selinexor, an oral selective inhibitor of nuclear export (SINE), inhibits XPO1 to force the nuclear retention and activation of >10 tumour suppressor proteins. Selinexor also reduces protein levels of c-myc and BCL2/6 through nuclear retention of eIF4E and therefore provides a rational therapy for DH-DLBCL.

Methods: *In-vitro and in-vivo* effects of selinexor were evaluated in DBLCL lines. In a phase 1 clinical study (NCT01607892), pts with heavily pretreated DLBCL were given 8 or 10 doses oral selinexor in 28-day cycles. Selinexor doses ranged from 3 to 80 mg/m^2. A minority of the pts had DH-DLBCL as determined by FISH.

Results: Selinexor showed potency against the DH-DLBCL line DoHH2 ($IC_{50} = 110$ nM) comparable to cell lines with either *MYC* or *BCL2* mutations (Mdn $IC_{50} = 82$ nM, $n = 10$), but is less potent in lines without mutations in either gene (Mdn $IC_{50} = 520$ nM, $n = 4$). Selinexor (10 nM) was found to reduce cytoplasmic c-Myc, Bcl2 and Bcl6 in OCI-Ly7 (mt *MYC*) cells. Selinexor had equivalent *in-vivo* efficacy at MTD (15 mg/kg, 3× weekly QoD) in DoHH2 and Toledo (wt MYC and BCL2) xenografts (65% and 60% tumour growth inhibition, respectively). Six pts [5M/1F, median age 62, median 2.5 prior treatment regimens (range 2–6)] were DH-DLBCL in an ongoing phase 1 study (see table). Toxicities were similar to the other pts in the study, and no clinically significant organ dysfunction or cumulative toxicities were observed. In the DH-DLBCL pts, there were 3 responses as of 20 Feb 2015: One PET-confirmed complete response (CR, >10 mo) with pt continuing on

DOI: 10.1002/hon

Abstract 146 Table 1. Prior therapies of DH-DLBCL pts

Pt	Prior therapies (duration in mo)	Months on Selinexor	Response on Selinexor
1	CHOP-R-Met (3), RICE (1)	17.1+	CR
2	CHOP-R (4.1), RICE (<1), Ifo-Etop-Ofat-G-CSF(<1), BEAM-R-ASCT (<1)	2.1+	PR
3	R (Unk), CHOP-R (5), R-Benda (3), RICE (2), R-DHAP (2.5), BEAM (<1)	7	PR
4	CHOP-R (3.5), Gem-Cis-Dex (2.2), Ibrut-Len (1.8)	3.4	SD
5	CHOP-R-Met (3.5), RICE (3)	1.8	PD
6	CHOP-R-Met (2), R-Cyclo-Etop (<1)	<1	NE

+, pt is still on treatment.

study for > 17 mo; two pts with partial response (PR) with one pt on study 7 mo before progression, and one continuing on study > 2 mo; one pt with stable disease (SD; 45% reduction) on study 3.4 mo before progression; one pt with progressive disease; and one pt not evaluable for response.

Conclusions: Selinexor is potently active against a DH-DLBCL cell line *in vitro* and in a xenograft model. Single agent oral selinexor has shown early clinical activity with promising disease control in a small cohort of pts with DH-DLBCL. Results from this study have led to a Phase 2b study in pts with relapsed/refractory DLBCL of any subtype including DH-DLBCL (NCT02227251).

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PHASE 1 PRELIMINARY SAFETY, EFFICACY AND BIOMARKER DATA FROM VENETOCLAX (ABT-199/GDC-0199) + BENDAMUSTINE AND RITUXIMAB IN R/R NON-HODGKIN'S LYMPHOMA

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Abstract 147 Table 1.

Cohort	1	2	3	4	5	6	7[a]	8[a]
Pts, *n*	4	4	4	3	3	4	5	6
VEN, mg	50	100	100	100	200	200	400	400
Schedule, d/C	3	3	7	28	28	7	7	28
DLT: thrombocytopenia, *n*					1			
DLT: febrile neutropenia, *n*					1			
DLT: Stevens–Johnson syndrome, *n*[b]								1

[a]Post-amendment to G-CSF prophylaxis and DLT criteria. [b]Likely due to allopurinol, pt discontinued.

Background: Venetoclax (VEN) is a selective, potent, orally bioavailable BCL-2 inhibitor with single agent activity in relapsed/refractory (R/R) non-Hodgkin's lymphoma (NHL). VEN enhances bendamustine (B) and rituximab (R) efficacy in NHL xenograft models. This study evaluates VEN + BR in patients (pts) with R/R NHL.

Methods: Primary objectives were safety, PK, determination of the MTD, and recommended Phase 2 dose of VEN + BR; preliminary efficacy was a secondary objective; biomarker analysis was an exploratory objective. Dose escalation (DE) used a 3 + 3 design on a 28-day (d) cycle (C) with 3 VEN schedules: 3, 7 and 28 d/C. The BR regimen was 6 C: B (2 d/C, 90 mg/m^2) and R (1 d/C, 375 mg/m^2). DLTs for DE were assessed during C1. First response assessment was on C3 d1. Baseline lymph node (LN) biopsies were analysed for MYC and BCL-2 family member expression. Pts who completed VEN + BR with continued tolerability and without disease progression could continue VEN monotherapy up to 2 years.

Results: As of 1/9/15, 33 pts were treated: 20 (61%) FL, 10 (30%) DLBCL, and 3 (9%) MZL. Median age was 62 (29–90) years. All had prior R or R-combination, of which 32 (97%) had R-based chemotherapy. 8 (24%) had prior B or BR. 16 (48%) are active; 17 discontinued (12 PD, 2 AEs, 1 withdrew consent, 1 non-compliance, and 1 completed induction regimen). Median time on study was 90 d (1–876); 15 (45%) completed 6 C of VEN + BR. The most common AEs (>25%) were nausea (58%), anaemia, neutropenia (each 42%), thrombocytopenia, diarrhoea (each 39%), hyperglycaemia (36%), and vomiting, hypokalemia, and fatigue (each 27%). The most common gr 3/4 AEs (>10%) were neutropenia (30%), leukopenia, thrombocytopenia, lymphopenia (each 21%), and anaemia (18%). The most frequent SAE was febrile neutropenia (9%). No drug-related AEs led to death.

Co-administration of BR did not significantly impact VEN PK. 29 pts were evaluable for objective response, including 2 that discontinued before 1st assessment. The objective response rate (ORR) was 66% in all pts: 6 (21%) CR and 13 (45%) PR. In pts with FL, the ORR was 74%. Biomarker analysis of 11 LN biopsies (6 FL, 3 MZL, and 2 DLBCL) showed moderate to high BCL-2 expression with mixed expression of VEN resistance factors BCL-XL and MCL-1. Objective responses were observed in 2 (1 CR and 1 PR) of 3 MYC/BCL-2 double positive tumours.

Conclusions: VEN + BR has a tolerable safety profile in pts with R/R NHL. Early responses are seen across cohorts. Analysis of putative biomarkers is ongoing. The MTD has not been reached; cohort 9 is enroling at 600 mg 28 d/C.

DOI: 10.1002/hon