Hematological Oncology
Hematol Oncol 2013; **31** (Suppl. 1): 96–150
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hon.2057

ORAL PRESENTATIONS

KEY NOTE LECTURES

001
HENRY KAPLAN MEMORIAL LECTURE
THE EVOLUTION OF LYMPHOMA UNDERSTANDING AND TREATMENT FROM 1-ICML (1981) TO 12-ICML (2013)

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The presentation of the Working Formulation for non-Hodgkin lymphomas by C. Berard was the highlight of 1-ICML, although at that time for Hodgkin lymphomas, the cell of origin was still unknown and even it could not yet be completely excluded, that Hodgkin lymphomas was not a neoplastic disease. Remembering that one realizes the huge evolution of our lymphoma understanding that has meanwhile taken place. ICML has hereby played a pivotal role not only as a platform for exchanging knowledge but also as an event catalyzing the initiation of collective efforts, which have led to some of the most significant achievements. So suffices here to mention the development of international prognostic index, the validation of the real classification, the definition of classification and staging of GI-non-Hodgkin lymphomas, the launch of international projects in the field of primary central nervous system lymphoma and peripheral T-cell lymphomas. This year was the third time that the closed workshop, which always proceeds the opening of ICML and which has been the starting point of the aforementioned projects, has been devoted to prognostic markers in diffuse large B-cell lymphoma under the heading 'Identification of diffuse large B-cell lymphoma subtypes: a way towards tailored treatment'. The formulation of the title of this year's workshop, the fact that the majority of the received abstracts for 12-ICML, are devoted to basic and translational research and the very structure of the current program, which is partly organized along pathways relevant both for the pathogenesis and the specific therapeutic targeting of lymphomas, underline the astonishing differences and the incredible progress realized between 1-ICML and 12-ICML.

002
HENRY RAPPAPORT MEMORIAL LECTURE
ILLUMINATING THE INCIPIENT EVENTS IN LYMPHOID NEOPLASMS

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There are no 'benign lymphomas', a fact due to the nature of lymphoid cells to circulate and home as part of their normal function. Thus, benign clonal expansions of lymphocytes are only rarely recognized when localized, possible exceptions being extranodal marginal zone lymphomas of MALT type, and the paediatric variant of follicular lymphoma (FL). Recent studies have identified a number of lymphoid proliferations that lie at the interface between benign and malignant. These include monoclonal B-lymphocytosis, follicular lymphoma *in situ*, and mantle cell lymphoma *in situ*. FL-like B-cells also can be identified in the peripheral blood in patients without clinical FL. These clonal proliferations carry many of the molecular hallmarks of their malignant counterparts, such as BCL2/IGH and CCND1/IGH translocations associated with follicular lymphoma *in situ* and mantle cell lymphoma *in situ*, respectively. If truly *in situ*, that is, confined to the germinal centre or mantle cuff, respectively, the risk of progression is low. Molecular characterization of these disorders and their malignant counterparts can serve to indentify the key alterations associated with clinical progression.
Historically, early or incipient forms of T/NK-cell neoplasia also have been identified, such as lymphomatoid papulosis and refractory celiac disease. More recently, an indolent form of T-cell lymphoproliferative disease affecting the gastrointestinal tract has been described. Usually, CD8+, the clonal cells are confined to the mucosa. The clinical course is chronic but non-progressive. NK-cell enteropathy is a clinically similar condition, composed of cytologically atypical NK-cells that may involve the stomach, small bowel or colon. Seroma-associated anaplastic large cell lymphoma associated with breast implants is a cytologically alarming lesion that is self-limited if confined to the seroma cavity. Atypical lymphoid proliferations that lie at the border of benign and malignant can serve as instructive models of lymphomagenesis. It is also critical that they be correctly diagnosed to avoid unnecessary and potentially harmful therapy.

003
JOHN ULTMANN MEMORIAL LECTURE
HODGKIN LYMPHOMA—THE GREAT TEACHER

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Background: Over the last 60 years, improved treatments for Hodgkin lymphoma have been introduced into clinical practice around the world with the result that at least 10,[6] patients have been cured of this previously lethal disease. We oncologists and hematologists have learned many lessons from this experience relevant not only to lymphoma treatment but also to the entire field of oncology. However, the learning is not finished. Re-examination of what we have learned correctly and, more importantly, what we think we have learned but which is wrong, continues to teach us valuable lessons.
Evidence and data: Specific areas in which valuable insights have emerged from clinical trials and institutional experiences concerning Hodgkin lymphoma include the following: (i) cure of the disease is not enough. The most exacting standard must be long-term well-being for our patients. (ii) Clinical trials are not enough. Trials remain the ultimate standard for comparison of differing treatments but must be complemented by population-based studies examining real world outcomes in all, not just selected, patients. (iii) A diagnosis of Hodgkin lymphoma is not enough. Subtypes, differing biology and different natural histories must be recognized. Nodular lymphocyte predominant Hodgkin lymphoma is and is not Hodgkin lymphoma. (iv) Chemo-sensitivity of relapsed Hodgkin lymphoma is not enough. Even doubly resistant disease can be cured. (v) Our current list of therapeutic agents and our methods of finding new agents are not effective enough. We need to move past empiric trial-and-error testing of new agents to biology-based targeting. (vi) We do not understand the reasons Hodgkin lymphoma develops well enough. The best approach by far for serious disease is prevention or, failing that, early detection, neither of which has been achieved for Hodgkin lymphoma, but both of which should yield to the new tools being provided to us in the fields of genomics and molecular biology.
Conclusions: Hodgkin lymphoma has an importance much exceeding its incidence-related impact. Through careful, re-iterative, self-critical re-examination of what we do not know, and more importantly, what we 'know' but which is not true about this disease, will continue to teach oncologists valuable lessons and guide us to better treatments for our patients.

CONTROVERSY I: IS R-CHOP THE STANDARD TREATMENT FOR HIGH RISK DLBCL?

004
PROS—R-CHOP IS THE CURRENT STANDARD THERAPY FOR PATIENTS WITH ADVANCED STAGE DLBCL

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Because the publication of the United States Intergroup High Priority Lymphoma Trial, which randomized patients between CHOP and three other higher intensity regimens, CHOP has been the standard chemotherapy backbone for treatment of advanced stage diffuse large B-cell lymphoma. Three large randomized trials subsequently demonstrated that the addition of rituximab to CHOP improves overall survival, and therefore, R-CHOP chemotherapy is now the worldwide standard treatment for this disease. Attempts at improving on R-CHOP have included increasing the dose intensity to every 14 days rather than every 21 days, or adding additional chemotherapy consolidation, including high-dose therapy and autologous

stem cell transplantation. Although phase 2 studies of these interventions have suggested promising leads, when randomized phase 3 studies have been conducted, there is no demonstrated overall survival benefit of these higher toxicity approaches when compared with R-CHOP alone. Indeed, the only proven survival advance in diffuse large B-cell lymphoma (DLBCL) over the past 30 years has been the routine incorporation of nontoxic rituximab into the CHOP chemotherapy program.Our understanding of the heterogeneous biology of DLBCL informs future trial opportunities. Gene expression profiling indicates that activated B-cell-type DLBCL has inferior prognosis compared with germinal centre B-cell-type DLBCL with conventional R-CHOP, and single agent activity of novel B-cell receptor signalling antagonists such as ibrutinib (Bruton's tyrosine kinase inhibitor) appears enhanced in activated B-cell -type DLBCL. Using immunohistochemistry to measure cmyc and bcl-2 expression, more than 20% of patients have 'double hit' histology, with exceedingly poor prognosis. Most of these patients are elderly, rendering dose intensification impossible. There is a rationale to consider aurora kinase inhibition or anti-apoptotic therapy in these patients. Finally, the microenvironment stromal signatures in DLBCL provide further opportunities for selective targeted therapeutic approaches for subsets of high risk patients. Therefore, new approaches for DLBCL should include early incorporation of rationally chosen targeted agents based upon the underlying biology of DLBCL, rather than increasing dose intensity with conventional chemotherapeutic approaches.

005

COS—R-CHOP IS NOT THE STANDARD FOR HIGH-RISK DLBCL

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Many strategies have been developed before the rituximab era to improve on CHOP21, including the design of dose-dense (CHOP 14), dose-intense (CHOEP, ACVBP) or pharmacokinetics-driven (DA-EPOCH) regimen and consolidation with high-dose therapy followed by autologous stem cell transplantation. Although the benefit conferred by the addition of rituximab to chemotherapy lead to reconsider the benefit of CHOP14 and the role of high-dose therapy as systematic first-line consolidation, both the ACVBP and DA-EPOCH regimen remain entirely valuable options. With R-CHOP-21, approximately half of the patients with diffuse large B-cell lymphoma (DLBCL) will progress or relapse. In a decision-making process based on age-adjusted international prognostic index (IPI), the use of the sole standard R-CHOP 21 regimen particularly seems questionable for patients <60 years with IPI score of ≥ 1. The clearest evidence in favour of R-ACVBP over R-CHOP was shown in the LNH 03-2B GELA multicentre, phase III, open-label, randomized trial in younger patients with an IPI of 1. Compared with R-CHOP-21, R-ACVBP produced superior 3-year event-free survival (81% vs 67%, $p = 0.0035$) and overall survival (OS) (92% vs 84%, $p = 0.0071$). Following the pioneering results of the National Cancer Institute, The Cancer and Leukemia Group B confirmed the value of DA-EPOCH-R in a multi-institutional phase II study showing 5-year OS rates of 84%, without significant grade 4 nonhematologic toxicities. An ongoing phase III trial (The Cancer and Leukemia Group B 50303) comparing R-CHOP versus DA-EPOCH-R in patients with newly diagnosed DLBCL. With increasing knowledge of the molecular pathogenesis of DLBCL, the true question appears not to be which is the best regimen for all patients but rather how to select the regimen best tailored to well molecularly characterized particular subgroups with poor prognosis. Poor-risk DLBCL can be defined in a number of ways, according to their cell of origin [germinal centre B-cell-like (GCB) versus non-germinal centre B-cell-like (non-GCB) phenotype], the presence of concurrent MYC and BCL2 breaks (i.e. MYC/BCL2 double-hit), or their MYC and/or BCL2 expression pattern using immunohistochesmitry. At present, the sole published comparison of different R-chemo regimen examining outcomes in these molecularly defined subtypes in the context of a randomized trial was the one performed within LNH 03-2B: interestingly, for patients with non-GCB tumours, progression-free survival and OS were significantly much longer with R-ACVBP compared with R-CHOP ($p = 0.007$, $p = 0.007$, respectively). Published correlations between molecular defined pattern and outcome with R-CHOP or other challenger regimen will be reviewed with a particular emphasis on recent comparative studies performed in the context of Lymphoma Study Association trials for patients <60 years with IPI score ≥ 1.

PLENARY SESSION

006

ITERATIVE GERMINAL CENTRE RE-ENTRIES OF MEMORY BCELLS WITH T(14;18) TRANSLOCATION AND EARLY STEPS OF FOLLICULAR LYMPHOMA PROGRESSION

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Introduction: The recent demonstration that memory B-cells can re-enter germinal centres (GC) and participate to new cycles of GC reactions has opened the possibility that multi-hit lymphomagenesis gradually occurs throughout successive passages of memory B-cells in GCs during a lifetime of immunological challenges. Here, we provide evidence for this scenario in follicular lymphoma (FL), a GC-derived malignancy initiated by the BCL2/IGH t(14;18) translocation.

Methods: We engineered an original sporadic BCL2 mouse model mimicking the rare occurrence of t(14;18) in humans (10^{-6}) through V(D)J recombination errors allowing to track the resultant BCL2-expressing clones during chronic antigenic challenge and underwent a molecular/imaging tracking of t(14;18) clones versus normal memory B-cells in paired lymphoid organs (spleen, lymph nodes and bone marrow) from healthy individuals.

Results: We first show that contrary to the current dogma, ectopic BCL2 expression is not sufficient to provoke the typical FL maturation arrest as GC B-cells, thereby suggesting that differentiated BCL2 memory B-cells must return to the GC to acquire additional oncogenic hits and 'fix' *in situ* growth. We next establish that iterative antigenic stimulation favours a massive enrichment of $BCL2,^+$ cells in GC/post-GC subsets, in line with a selective advantage in the dynamics of recall conferred to $BCL2,^+$ cells. Lastly, adoptive transfer experiments formally demonstrate that $BCL2,^+$ GC/post-GC cells are capable of re-entering GC and reinitiate GC reactions, eventually progressing into structures resembling *in situ* FL development. Strikingly, we find that in a fraction of 'healthy' individuals, such differentiation arrest already operated and that an expanded population of t(14;18) clones with FL-like features disseminate extensively in multiple lymphoid organs, including bone marrow, shaping the systemic presentation found in FL. Molecular backtracking of such clones in paired/remote lymphoid organs further confirm that t(14;18) clones systematically display an enhanced history of aberrant AID-mediated events compatible with iterative rounds of GC co-opting, yet not found in memory B-cells from the same donors.

Conclusions: We show that massive dissemination and progression to more advanced precursor stages occur asymptomatically over an extended period of time, by subverting the dynamic and plastic attributes of memory B-cells.

007

CHLORAMBUCIL PLUS RITUXIMAB PRODUCES BETTER EVENTFREE AND PROGRESSION-FREE SURVIVAL IN COMPARISON WITH CHLORAMBUCIL OR RITUXIMAB ALONE IN EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMA (MALT LYMPHOMA): FINAL RESULTS OF THE IELSG-19 STUDY

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Introduction: There is no consensus on the standard therapy of MALT lymphoma, apart from H Pylori eradication for localized gastric disease.

Aim: This study was launched by the International Extranodal Lymphoma Study Group to compare Chlorambucil (Chl) alone versus the combination of Chlorambucil and Rituximab (R-Chl). Rapid initial recruitment prompted the later addition of a third arm with Rituximab (R) alone.

DOI: 10.1002/hon

Methods: Patients (pts) with disseminated lymphoma or with localized disease not suitable for local therapy were randomized between 3 arms. In arm A, Chl was given at 6 mg/m,^{2} daily p.o. for 6 weeks. Responding patients and those with stable disease received Chl 6 mg/m,^{2} daily p.o. for 14 consecutive days every 28 days for 4 cycles. In arm B, R 375 mg/m,^{2} iv was added to Chl on days 1, 8, 15, 22, 56, 84, 112 and 140; R alone was given on the same schedule in arm C.
Results: We previously reported the outcomes for pts enrolled in the first two protocol arms (Zucca et al. JCO 2013); this is the first analysis of the whole study. Of 454 enrolled pts, 42 were excluded on the grounds of histology and 11 because of protocol violations; follow-up information on 8 pts is still pending. 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%, 81% had low or low-intermediate IPI (international prognostic index). Only 8% of the patients had a prior local therapy. Outcome analysis was performed on 130 pts randomized to Chl, 131 to R-Chl and 132 to R, with a median follow-up of 67 months. The 5-year event-free survival (EFS, primary endpoint) was significantly better for pts treated with R-Chl (70%; 95% CI, 61–77%) in comparison with those receiving Chl alone (52%; 95% CI, 42–60%; $p = 0.0005$) or R alone (51%; 95% CI, 40–61%, $p = 0.0015$). Progression-free survival (PFS) was also better in the combination arm in comparison with each single agent arms ($p = 0.0128$ and $p = 0.0058$ vs Chl and R, respectively). Overall survival (OS) was 90% at 5 years in the whole population (95% CI, 86–93%) and was not significantly different between treatment arms. No unexpected severe side effects were recorded. Hematologic toxicity was more pronounced in the R-Chl arm.
Conclusions: This is the largest randomized study ever conducted in MALT lymphoma and is the first trial to compare chemotherapy versus R and versus the combination of both. Longer EFS and PFS were attained in the R-Chl arm but this did not translate into improved OS.

008

SINGLE AGENT IBRUTINIB (PCI-32765) IS HIGHLY EFFECTIVE IN CHRONIC LYMPHOCYTIC LEUKAEMIA PATIENTS WITH 17P DELETION

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Background: Patients (pts) with chronic lymphocytic leukaemia (CLL) with deletion 17p (del 17p) have inferior outcomes with respect to progression-free survival and overall survival to standard chemoimmunotherapy. Ibrutinib (PCI-32765), an inhibitor of Bruton's tyrosine kinase, has demonstrated durable antitumour activity in high risk CLL. We conducted a phase II single agent ibrutinib study in pts selected for del 17p.
Methods: Both treatment naive (TN, $n = 15$, age 33–82) and relapsed/refractory (R/R, $n = 14$, age 56–79) pts were treated with 420 mg ibrutinib daily until disease progression. Response was evaluated at 6 months and every 6 months thereafter. 17p del was assessed by FISH cytogenetics. Spleen volumetry on CTs was quantified on a General Electric Advanced Workstation Server.
Results: We report on the first 29 pts with a median follow-up of 9 months. A total of 66% had Rai stage III/IV. At 6 months, 88% of pts (n=25 evaluable) had a nodal response (median reduction in lymph node size 70%), 48% had a partial response by IWCLL criteria and 40% had a partial response with lymphocytosis. There was one progressive disease (presumed transformation). A total of 93% of R/R pts and 82% of TN pts achieved a nodal response. Estimated event-free survival at 12 months is 90%. All pts also had reduction in splenomegaly, with a median reduction in spleen volume of 446 ml from pre-treatment (46%) ($n = 22$; 44–1716 ml). We repeated bone marrow biopsy and FISH at 6 months. Tumour burden in bone marrow biopsies ($n = 23$) decreased by a median 76% assessed by immunohistochemistry for CD79a. FISH was used to quantify the % of tumour cells with del 17p pre-treatment (12–97%) and at 6 months (0–92%; $n = 18$). In 15 pts, the % of tumour cells with 17p decreased (median reduction 55%) was unchanged in 1 and increased in 3 pts. Treatment was tolerated well with non-hematologic toxicities grade $\geq$3 (regardless of causality) in 14% of pts. Two deaths on study were not treatment-related.
Conclusions: Ibrutinib as a single agent is effective in both TN and R/R pts with del 17p CLL, achieving rapid control over disease in blood, nodes, spleen and marrow that is durable with an acceptable safety profile. Ibrutinib will be further investigated as a strategy for these high risk pts. This research was supported by the Intramural Research Program of the NIH, NHLBI.

SESSION 1—BIOLOGY OF DIFFUSE LARGE B-CELL LYMPHOMA

009

EPSTEIN-BARR VIRUS (EBV) POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA IS A NEOPLASM WITH PREFERENTIAL ACTIVATED GENE EXPRESSION SIGNATURE WHOSE OUTCOME RELIES ON CD30 EXPRESSION: A REPORT FROM THE INTERNATIONAL DLBCL RITUXIMAB-CHOP CONSORTIUM PROGRAM STUDY

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Introduction: EBV-positive diffuse large B-cell lymphoma (EBV+ DLBCL) of the elderly is a provisional entity within the WHO classification. Its frequency varies according to geographic regions, and its biological features are evolving.
Methods: A total of 451 de novo DLBCL patients were included in this study. All patients had available tissue microarrays from primary biopsy specimens, where HIV-negative were successfully studied by gene expression profiling (GEP) and were uniformly treated with rituximab-CHOP. Epstein-Barr virus encoded RNA (EBER) testing was performed by *in situ* hybridization. EBER reactivity in more than 10% of malignant cells was required for designation as EBV+. Patients with primary mediastinal DLBCL and post-transplantation lymphoproliferative disorders were excluded.
Results: EBER was positive in 27 (6%) patients, with an even distribution among age groups. The median age of EBV+ patients was 61 years (range, 37–86) and was similar to EBV− patients (64 years, range 18–90). Presenting clinical characteristics were similar between EBV+ and EBV− patients. However, an activated B-cell type signature was more frequent among EBV+ than EBV− patients, as shown either by GEP (70% vs 48%, $p = 0.04$) or immunohistochemistry using the Visco–Young algorithm (70% vs 49%, $p = 0.03$). CD30 was more frequently expressed in EBV+ DLBCL than EBV− DLBCL (48% vs 15%, $p < 0.0001$). Although no difference in expression of BCL2, MYC or both proteins was observed between the EBV+ and EBV− groups, EBV+ DLBCL patients were absent of detrimental TP53 mutation and rarely presented rearrangements involving BCL2, C-MYC or BCL6 gene (18%). Patients with EBV+ DLBCL compared with EBV− DLBCL appeared to have inferior 5-year overall survival (OS) (EBV+ 50% vs EBV− 62%, $p = 0.16$) and progression-free survival (PFS) ($p = 0.08$), although the differences were not statistically significant. This observation was confirmed after stratification for age. Conversely, CD30 expression conferred a dismal prognosis in EBV+ DLBCL cases (median OS of 37% and PFS of 35% in CD30+ EBV+ DLBCL vs OS 74% and PFS 56% in CD30− EBV+ DLBCL, $p = 0.02$ for OS and $p = 0.07$ for PFS). GEP revealed a unique expression signature in EBV+ DLBCL with NF-kB pathway activation.
Conclusions: EBV+ DLBCL patients represent a small proportion of DLBCL with similar clinical characteristics of their EBV− counterparts. These neoplasms have an activated B-cell type immunophenotype, unique GEP and genetic signatures. CD30 expression is common in EBV+ DLBCL and confers an adverse outcome.

010

THERAPEUTIC TARGETING OF CELL CYCLE DEREGULATION IN DIFFUSE LARGE B-CELL LYMPHOMA

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DOI: 10.1002/hon

Diffuse large B-cell lymphoma (DLBCL) is a clinically and biologically heterogeneous disease with a high proliferation rate. We recently identified a comprehensive set of copy number alterations (CNAs) that decreased p53 activity and perturbed cell cycle regulation in newly diagnosed primary DLBCLs ('complex DLBCLs') (cancer cell 2012; 22:359). Complex CNAs were associated with a significantly decreased 5-year overall survival in R-CHOP-treated DLBCL patients. The prognostic value of complex CNAs, deregulated cell cycle and increased activation of CDK4/6, CDK2 and CDK1 prompted our evaluation of the pan-CDK inhibitor, dinaciclib, in a panel of informative DLBCL cell lines. Proliferation was inhibited, and apoptosis was induced in all dinaciclib-treated DLBCL cell lines in a dose-dependent and time-dependent manner. Dinaciclib decreased the phosphorylation of RB1 at CDK4/6 and CDK2-specific sites (pS780 and pT821, respectively) and RNA polymerase II at the CDK9-specific pS2 site. Because pS2 phosphorylation is required for the pause release of RNA polymerase II after transcription initiation, transcripts with a short half-life (e.g. MCL-1 and MDM2) are predominately affected. Dinaciclib treatment markedly decreased the protein levels of the E3 ligase MDM2, and the anti-apoptotic BCL-2 family member, MCL-1. To gain additional insights into dinaciclib mechanism(s) of action, we performed transcriptional profiling of representative DLBCL cell lines treated with dinaciclib (or vehicle). Pathway and transcription factor binding site enrichment revealed significantly decreased E2F-target gene expression in dinaciclib-treated cells indicating that the pan-CDK inhibitor decreased cell-cycle progression and associated E2F activation. We also evaluated the *in vivo* efficacy of pan-CDK inhibition in dinaciclib-treated or vehicle-treated NSG mice xenotransplanted with the DLBCL cell lines. Dinaciclib treatment significantly reduced DLBCL growth and increased survival *in vivo*. These data suggest that genetically driven cell cycle deregulation in DLBCL may be amenable to pan-CDK inhibition and that further clinical investigation is warranted.

011

INTEGRATED ANALYSIS IDENTIFIED DELETION OF CDKN2A AS THE MOST FREQUENT AND UNIQUE GENOMIC ABNORMALITY IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) WITH STRONG PROGNOSTIC VALUE NOT OVERCOME BY A DOSE-INTENSIVE IMMUNOCHEMOTHERAPY. A LYSA STUDY

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Introduction: Gene copy number abnormalities (GCNA) play a crucial role in the development of DLBCL and are closely related to gene expression profiles (GEP), including the cell of origin (COO) molecular signatures. To identify new oncogenes or tumour suppressor genes (TSG) involved in DLBCL pathogenesis, an integrated analysis of high-resolution gene expression and copy number profiling was performed.

Methods: 202 patients with de novo CD20+ DLBCL enrolled in the prospective multicentric randomized LNH-03GELA trials were analysed. 116 patients were treated by rituximab (R)-CHOP/R-miniCHOP and 86 patients were treated by the high dose (R)-ACVBP regimen dedicated to patients younger than 60 years (y). Tumour samples were analysed by high resolution comparative genomic hybridization (CGH, 180 K) and gene expression arrays (U133+2). Minimal common regions (MCR), as defined by segments that affect the same chromosomal region in different cases, were delineated and merged with expression data to identify new potential driver genes.

Results: A total of 193 MCRs (penetrance $> 5\%$) are identified, delineating 504 genes. Among these genes, 53% display a significant association with gene expression. By this integrated approach, in addition to previously reported genes, several GCNA with a dosage effect and potential physiopathological impact are identified. The CDKN2A/2B tumour suppressor locus is deleted homozygously in 27% of cases, targeting 49% of ABC DLBCL cases. The deletion correlates to gene expression and adverse clinical factors, including age, IPI and performance status. The deletion is associated to a limited number of additional genomic abnormalities including trisomy 3, 18 and short losses/gains of chromosome 1, 2, 19 regions. With a median follow-up of 42.9 months, only CDKN2A/2B biallelic deletion correlates to a poor outcome in the entire cohort (4y – OS = 53% [39–72] vs 83% [76–90], $p < 0.0001$), in R-CHOP patients (4y – PFS = 43% [29–63] vs 66% [55–78], $p = 0.02$), and R-ACVBP patients (4y PFS = 49% [28–84] vs 83% [74–92], $p = 0.003$). CDKN2A deletion defines a GEP characterized by an enrichment of TP53-related genes and associated to an unfavourable prognostic impact independent of the IPI.

Conclusion: CDKN2A deletion constitutes the strongest and unique GCNA prognostic factor of resistance to R-CHOP, which is not overcome by a more intensified immunochemotherapy. Patients displaying this genomic abnormality warrant new and dedicated therapeutic approaches.

012

BIOLOGIC CHARACTERIZATION OF ADULT MYC-POSITIVE MATURE B-CELL LYMPHOMAS OTHER THAN MOLECULAR BURKITT LYMPHOMA WITHIN THE MMML COHORT

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Introduction: MYC translocations are the biologic hallmark of Burkitt lymphoma (BL) but also occur in other lymphomas. Accompanied by chromosomal breaks targeting the BCL2 and/or BCL6 oncogene, these MYC translocation-positive (MYC+) lymphomas are called 'double-hit' lymphomas (DHL), otherwise 'single-hit' lymphomas (SHL). However, the molecular make-up of DHL and SHL other than BL remains largely unknown. In addition, it is unclear whether differences exist according to MYC partner ('IG-MYC' or 'non-IG-MYC').

Methods: A total of 863 lymphomas were investigated as part of the Molecular Mechanisms in Malignant Lymphomas network project. These lymphomas have been extensively characterized by histomorphology, immunohistochemistry, molecular cytogenetics (FISH), array-CGH, mutational analysis (IGH, MYC, BCL6 and ID3), gene expression profiling (GEP) including MYC expression and overall survival. Of the 168 lymphomas with an MYC break, all cases with a molecular BL GEP and/or paediatric cases (age $\leq$18 years) were excluded to avoid inclusion of BL ($n = 88$). Results: A total of 80 MYC+ lymphomas were analysed: 31 SHL, 47 DHL (26 BCL2+/BCL6−/MYC+ , 1 BCL2+/MYC+ with unavailable BCL6 status, 14 BCL2−/BCL6+/MYC+ , 6 BCL2+/BCL6+/MYC+) and 2 incompletely analysed cases. Comparing SHL to DHL, there was no difference in MYC partner, genomic complexity, MYC expression, GEP or overall survival. DHL showed a more frequent germinal centre B-cell-like GEP and higher IGH and MYC mutation frequencies. Comparing BCL6+/MYC+ to BCL2+/MYC+ DHL, GEP revealed 130 differentially expressed genes. BCL2+/MYC+ DHL were associated with a germinal centre B-cell-like GEP. No significant differences were seen between BCL6+/MYC+ and BCL2+/MYC+ for type of MYC partner, genomic complexity and mutation frequency of IGH, BCL6 and MYC genes. Comparing IG-MYC+ to non-IG-MYC+ lymphomas revealed IG-MYC+ lymphomas to show significantly higher MYC levels than those with a non-IG-MYC translocation but no other substantial differences. Conclusions: Our data suggest that after excluding molecular BL, MYC+ lymphomas are biologically quite homogenous with SHL and DHL as well as IG-MYC+ and non-IG-MYC+ lymphomas sharing various molecular characteristics.

DOI: 10.1002/hon

013

INTEGRATED SEQUENCE ANALYSES OF BURKITT, FOLLICULAR AND DIFFUSE LARGE B-CELL LYMPHOMAS IN THE FRAMEWORK OF THE GERMAN ICGC MMML-SEQ

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Introduction: The International Cancer Genome Consortium (ICGC) aims at obtaining a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different tumour types. Within this international effort, the ICGC MMML-Seq network aims at sequencing 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: In accordance with the guidelines of the ICGC whole genomic sequencing of tumour cells (at least 60% purity) of GCB-lymphomas (to at least 30x) and paired normal controls is performed. Genomic sequencing is complemented by transcriptome, miRNAome and whole genome bisulfite sequencing. The present integrated interim analysis is based on sequence data from 29 cases. The ICGC MMML-Seq is funded by the German Federal Ministry of Education and Research (01KU1002A-J).

Results: On the basis of whole genome sequencing data the median number of potentially protein-changing mutations ranged from 35 in BL to 58 in DLBCL/IL. In contrast, the overall number of somatic mutations was at least 100fold higher in all analysed subtypes on the genome-wide level with a median of 4221 small variants in BL and of 10782 in DLBCL/IL. Regional clustering of single nucleotide variants (SNVs) and investigation of SNV mutation types in the context of the neighbouring bases provided evidence for different mutational mechanisms. Combined genomic and transcriptomic analyses identified various potential novel fusion genes. Transcriptional analyses not only confirmed different gene expression profiles between BL and DLBCL/FL but also provided evidence for differential exon usage and small RNA expression, which in part was associated with differential DNA methylation.

Conclusions: Our ongoing complete genomic and transcriptomic sequencing efforts and integrated analyses provide insights into the different mutational mechanisms and pathogenetic complexity of the various subtypes of GCB-lymphomas.

'FOCUS ON…' SESSION: PET-GUIDED TREATMENT DECISIONS

014

DOES QUANTITATIVE PET-CT PREDICT PROGNOSIS IN DIFFUSE LARGE BCELL LYMPHOMA (DLBCL)?

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Introduction: PET-CT using FDG demonstrates early response to chemotherapy in diffuse large B-cell lymphoma (DLBCL). Response assessment may be qualitative (5 point score, 5PS) or quantitative (percent change in maximum standardized uptake value, $dSUV_{max}$) but neither fully utilizes anatomic information from the PET-CT. This study examined whether baseline metabolic tumour volume (MTV), baseline total lesion glycolysis (TLG) and percent change in each after treatment (dMTV, dTLG) predicted clinical outcome.

Methods: A total of 85 patients with newly diagnosed DLBCL underwent routine PET-CT before and after two cycles of R-CHOP or R-CEpiOP chemotherapy. A nuclear physician blinded to outcomes assessed 5PS. MTV and TLG (calculated as MTV × meanSUV) were measured using PETRRA software. Non-categorical data were grouped into tertiles. Cox regression analysis was used to test the relationship between progression-free survival (PFS) and study variables.

Results: Median age was 57 years (range 25–86), most had advanced disease (stage 1–2 = 29%, 3–4 = 71%) and risk was evenly distributed (international prognostic index 0–1 = 32%, 2 = 20%, 3 = 20%, 4–5 = 28%). PFS was 81% at 1 year, 72% at 2 years and 68% at 3 years with median follow-up of 50 months. Univariate analyses showed statistically significant associations between PFS and international prognostic index (4–5 versus 0–1: hazard ratio (HR) = 3.74; 95% CI = 1.19–11.79; p-trend=0.04), 5PS (score 5 versus 1: HR = 5.53; 95% CI = 2.03–15.08; p-trend = 0.008), $dSUV_{max}$ (upper versus lower tertile: HR = 3.03; 95% CI = 1.27–7.24; p-trend = 0.009), MTV (upper versus lower tertile: HR = 3.34; 95% CI = 1.20–9.30; p-trend = 0.021) and TLG (upper versus lower tertile: HR = 3.81; 95% CI = 1.46–9.98; p-trend = 0.004). On multivariate analysis, $dSUV_{max}$ (HR = 5.29; 95% CI = 0.46–61.49; p-trend = 0.026) and especially TLG (HR = 5.64; 95% CI = 0.86–37.17; p-trend = 0.007) were independent predictors of PFS. dMTV and dTLG did not predict PFS.

Conclusions: This study confirms the predictive value of visual assessment by 5PS and quantitative assessment using $dSUV_{max}$ in DLBCL. Baseline MTV and TLG are additionally shown to be predictive of prognosis, but the change in these parameters after chemotherapy is not. Patients in the upper tertile of the TLG distribution had a fivefold increased likelihood of disease progression. The role of baseline TLG as a potential identifier of poor prognosis patients should be further explored.

015

FINAL RESULTS OF A PROSPECTIVE EVALUATION OF THE PREDICTIVE VALUE OF INTERIM PET IN PATIENTS WITH DLBCL UNDER R-CHOP-14 (SAKK 38/07)

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Introduction: Early assessment of response by a robust imaging tool is potentially useful in order to stratify diffuse large B-cell lymphoma (DLBCL) patients for risk-adapted tailored therapy strategies. Our main objective was to determine the prognostic impact of FDG-PET after 2 cycles of R-CHOP-14, prospectively and under standardized treatment and PET-evaluation criteria.

Methods: Patients with any stage of untreated DLBCL were treated with 6 cycles of R-CHOP-14, followed by 2 cycles of rituximab. PET exams were performed prior to therapy, after 2 cycles and 4 cycles (if PET after 2 cycles), and at the end of treatment. The primary endpoint was event-free survival at 2 years (2-year EFS). A positive PET was defined as a measurable and evaluable lesion(s) with a higher FDG uptake compared with mediastinal blood pool. PET exams were evaluated locally and by blinded central review. Binary outcomes and PET were associated by Fisher's exact test.

Results: Between November 2007 and May 2010, 156 patients with untreated DLBCL were prospectively enrolled into the trial of which 141 are evaluable. Median age was 59 years with a WHO performance status of 0 in 56%, PS1 in 36% and PS2 in 8% of cases. Ann Arbor stage I/II/III/IV was found in 17/48/32/44 (12/34/23/31%) patients. By local institution, 85 PET scans (60%) were defined as positive and 56 (40%) as negative after 2 cycles of R-CHOP-14. A 2-year EFS was significantly different for the PET and PET− patients (48% vs 70%; $p = 0.02$). Overall survival at 2 years was not significantly different: 87% for PET vs 91% for PET− patients ($p = 0.4$). All patients with a negative interim PET reached a complete response at the end of treatment, compared with 71% for PET patients ($p < 0.001$). By central review using the Deauville criteria/5-point scale defining a negative PET as a FDG uptake below liver background 2-year EFS was 40% for PET and 74% for PET− patients ($p < 0.001$).

DOI: 10.1002/hon

Conclusions: This is the largest completed prospective trial to investigate the value of interim PET under standardized treatment conditions and evaluation criteria in DLBCL. A 2-year EFS was superior in the PET negative group; this was found for local and central assessment of PET. The best separation of the two groups was found by using the Deauville criteria/5-point scale.

016

RESPONSE-ADAPTED THERAPY AND PREDICTIVE VALUE OF MID-TREATMENT PET SCANNING FOR DIFFUSE LARGE B-CELL LYMPHOMA. ECOG STUDY E3404

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Background: A positive mid-treatment PET predicted ≤20% 2-year progression-free survival (PFS) in patients (pts) with diffuse large B-cell lymphoma, with approximately 1/3 of pts remaining PET pos after 2–4 cycles.
Design: E3404 undertook to assess whether an early treatment change to four cycles of R-ICE might improve PFS in pts with a pos PET scan after three cycles of R-CHOP. Untreated pts with diffuse large B-cell lymphoma stage III, IV, bulky II, measurable and HIV neg were eligible. A repeat PET was performed after three cycles of R-CHOP. During the fourth cycle, the scan was scored as pos or neg by one reviewer (modified harmonization criteria). Persistently, PET pos pts received four cycles of R-ICE, whereas PET neg pts completed six cycles of R-CHOP. A ≥45% 2-year PFS for mid-treatment PET pos pts was seen as promising, with 88% power if 33 pts were accrued, requiring 99 pts total.
Results: Of 100 pts, 80 were eligible after pathology review. Males 58%; median age 62 (20–74); 14% international prognostic index (IPI) 0–1, 31% IPI 2, 36% IPI 3, 19% IPI 4–5. There are 76 out of 80 (95%) pts completed the first three cycles of R-CHOP. Of 74 pts continuing, 70 (95%) completed all treatments: 77% of mid-treatment PET pos and 98% of PET neg pts. Of 74 mid-treatment PET scans, 13 (18%) scored as pos and 61 (82%) as neg, much lower than expected. A 2-year PFS was 70% overall, 42% (90% CI, 19–63%) for mid-treatment PET pos pts and 76% (65–84%) for PET neg pts. The 80% CI included the 25% null hypothesis. A 3-year PFS was 68% (58–76%) for all pts, 33% (13–55%) for mid-treatment PET pos and 76% (65–84%) for PET neg pts. A 5-year overall survival was 87% (78–92%) and a 3-year overall survival was 69% (43–85%) for mid-treatment PET pos pts and 93% (86–97%) for PET neg pts. The predictive value of a neg mid-treatment PET scan for 2-year PFS after six cycles of R-CHOP did not differ among IPI groups: low 72.7% (44–92%), low int. 78.6% (53–94%), high int. 73.7% (52–89%) and high 76.9% (51–93%).
Conclusions: The 2-year PFS for mid-treatment PET pos pts after a change to R-ICE approached the promising level, but the CI was wide because of fewer pos scans than expected. In addition, variability in interpretation of mid-treatment PET as a binary variable in this study (reported separately, Blood 2010) implies that modifying treatment based on early PET scanning should remain investigational.

Support: PHS CA21115 CA23318 CA66636 CA16116 CA21076 CA13650, and NCI NIH DHHS

017

EVALUATION OF DUAL TRACER (FLT AND FDG) PET IMAGING AS PART OF RISK-ADAPTED THERAPY FOR PATIENTS (PTS) WITH ADVANCED STAGE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Introduction: R-CHOP-14 ×4 followed by ICE ×3, results in an 80% 5-year PFS (JCO 2010; 28 (23): 3754–3761); interim (int) FDG-PET-4 (FDG-4) did not predict outcome based upon biopsy (bx) results of a positive int FDG-4. In the current study, int evaluation included both an ^{18}F,-fluorothymidine (FLT)-PET as well as FDG-4. Proliferative index (PI) < or ≥80% risk adapted the consolidation therapy.
Methods: Eligible pts were <70 yrs with advanced stage DLBCL and subtypes. Pre-treatment (tx) evaluation included contrast-enhanced CT, FDG-PET and FLT-PET. Induction tx consisted of R-R-CHOP-14 x3 and CHOP-21 ×1. FDG-4 was performed 17–20 days after cycle 4 of therapy and a bx performed if pos. Consolidation was risk-adapted: FDG-4 neg or bx neg: ICE x3 for PI <80% and augmented RICE x2 for PI ≥ 80%. Pts with a pos bx were treated with augmented RICE x 2 followed by HDT/ASCR. Use of FLT-PET was exploratory. In cohort 1, it was repeated after cycle 1, and in cohort 2 after cycle 2. Int FDG-4 was interpreted using the Deauville criteria (value of 4 or 5 was pos). FLT-PET was interpreted visually (neg FLT = uptake decreased to < blood pool and background). ΔSUV >66% was scored as favourable for both tracers to provide standardization. Pre-treatment metabolic tumour volume (MTV) was also analysed.
Results: Sixty pts are evaluable; 50 underwent FLT-PET (10 pts could not be imaged due to lack of FLT availability or inability to schedule the test because of rapid tumour progression). At median follow-up of 40 months for surviving pts, the PFS and OS are 76.1% and 85.8%, respectively and no pre-tx prognostic factors impacted outcome including cell of origin or IPI. FDG-4 and int SUV max (>5) both predicted for PFS ($p = 0.03$ and 0.001, respectively). However, pts with FDG-4 pos, bx neg evaluation had the same outcome as those with neg FDG-4 ($p = 0.463$). The two FLT cohorts were combined because the results were not significantly different. Thirty-three, FLT-PET-1/2 scans were neg and 29 pts are progression-free (PF), including 8 pts with a pos FDG-4 (all had a neg bx and 7 are PF, hence 7 false pos FDG-4 scans). Among the 17 pts with pos FLT-PET-1/2, nine are PF. Nine FLT-PET-1/2 pos pts were FDG-4 neg and 7 are PF. Pts with both pos FLT and FDG-4 did poorly; only 2 of 8 patients are PF. MTV did not predict for PFS, full data to be presented at meeting. Conclusions: These results confirm the excellent PFS of our sequential R-CHOP-14/ICE program. Pts with a neg early FLT had an excellent outcome and likely no further int test is needed. In addition, pts with a neg FDG-4, and a pos FLT, also did well. A prospective multicentre study is needed to confirm these results However, patients with dual tracer positive disease did poorly and the addition of novel therapy which may include kinase inhibitors with or without transplant is warranted.

018

PET-CT FOR STAGING AND EARLY RESPONSE—RESULTS FROM THE RESPONSE ADAPTED THERAPY IN ADVANCED HODGKIN LYMPHOMA (RATHL) STUDY

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Introduction: PET-CT, with FDG is increasingly used to stage and assess early response to treatment in HL. Our aim was to determine 1) if PET-CT stages patients (pts) differently to CT and 2) the level of agreement amongst readers who measure early response.
Methods: Pre-treatment CT and PET-CT scans from pts in RATHL were given a stage using the Ann Arbor system. The local radiologist provided the CT stage and the PET-CT stage was done by a reader at the national core lab. Pts had 2 cycles of ABVD, then response was scored with a standard 5 point scale (Deauville criteria), according to the level of residual FDG uptake when compared with the pre-treatment scan. Readers at 'local' PET Centres were given the option to score scans, but the central score was used to guide treatment. Scores 1,2,3 were regarded as 'negative' (-ve), and pts were randomized to ABVD or AVD. Scores 4,5 were regarded as 'positive' (+ve) and pts had escalation to a BEACOPP regimen. A third PET-CT scan was done during BEACOPP treatment, pts were offered salvage therapy if +ve.
Results: 475 pts from the first 500 registered were analysed; 25 pts were excluded, mainly for failure to comply with imaging protocols. PET-CT and CT stage agreed perfectly in 373 (79%). In 6 pts, change in stage was likely due to differences in opinion between readers rather than the imaging techniques. PET-CT upstaged 65 pts (14%) and downstaged 37 pts (8%). Upstaging was due to additional nodal disease below the diaphragm in 16 pts and above the diaphragm in 3 pts. Upstaging was due to extranodal disease in bone marrow in 37 cases, and/or lung in 6 and/or liver in 2 and pleura in 1 case. 417/490 response scans were acquired at 'local' PET centres; 117/417 (28%) were scored locally and centrally reviewed. There was agreement that the scan was +ve or -ve in 106/

DOI: 10.1002/hon

117 (91%). In 7 pts the local report was +ve when the central report was -ve and in 4 pts the local report was -ve when the central report was +ve. The Kappa was 0.73 (95% CI 0.58–0.88) indicating good agreement.

Conclusions: Differences between PET-CT and CT alters staging in a considerable number of HL pts. There was good agreement between 'local' and central 'expert' readers when assessing early treatment response using the Deauville criteria. This should enable this method of reporting to be easily applied in clinical practice at the conclusion of the trial.

019

INTERIM RESULTS OF IIL-HD0801 STUDY ON EARLY SALVAGE WITH HIGH-DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANTATION IN ADVANCED STAGE HODGKIN'S LYMPHOMA PATIENTS WITH POSITIVE POSITRON EMISSION TOMOGRAPHY AFTER TWO COURSES OF CHEMOTHERAPY

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Introduction: A prospective multicentre study on early salvage with high-dose chemotherapy and autologous stem cell transplantation (ASCT) in advanced stage Hodgkin's lymphoma (HL) patients with positive positron emission tomography (PET-2 positive) after two courses of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) and on comparison of radiotherapy versus no radiotherapy in PET-2 negative patients in complete remission after 4 additional chemotherapy courses is ongoing.

Patients and Methods: At the time of interim analysis 417 patients were evaluable. In particular the focus was on PET-2 positive patients and on their outcome after salvage approach. PET-2 positive patients were scheduled for 4 courses of ifosfamide, gemcitabine, vinorelbine and prednisolone (IGEV) chemotherapy. After IGEV, a second PET evaluation was carried out: PET-IGEV negative patients received high-dose BEAM chemotherapy followed by ASCT, PET-IGEV positive patients received high-dose chemotherapy followed by two ASCT or one ASCT and one allogeneic stem cell transplant depending on donor availability.

Results: PET-2 positive ($n=81$) and PET-2 negative ($n=336$) patients did not differ for baseline characteristics. Baseline characteristics of PET-2 positive patients were as follows: 42 (52%) males, median age was 31 years, 73% ($n=59$) nodular sclerosis HL, 42 (52%) stage IV and 36% ($n=29$) bulky. A total of 55 PET-2 positive patients were evaluable after 4-IGEV courses: 32 (58.2%) obtained a negative PET and underwent ASCT. A total of 26 patients were restaged after ASCT, with 24 (92.3%) patients having a final negative PET, whereas only two having a positive PET. There were 23 (41.8%) patients who were PET positive after IGEV: six went out of therapy and the others are ongoing. At the time of analysis median time of follow up was 19 months. Updated results will be presented at the meeting.

Conclusions: These preliminary results showed that patients resistant to the initial treatment for residual PET-positive masses after the first two course of ABVD can be salvaged by early shift to high-dose chemotherapy supported by stem cell rescue.

'FOCUS ON. . .' SESSION: TRANSPLANT STRATEGIES

020

BENDAMUSTIN AS PART OF CONDITIONING REGIMEN FOR AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN PATIENTS WITH AGGRESSIVE LYMPHOMAS: A PHASE 2 STUDY FROM SPANISH GELTAMO GROUP

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Introduction: We have designed a prospective multicentre phase II study to evaluate the safety and efficacy of bendamustine as part of conditioning regimen in patients candidates to autologous stem cell transplantation with aggressive lymphomas.

Methods: Inclusion criteria were histologic diagnosis of (i) relapsed or refractory diffuse large B-cell lymphoma (DLBCL) or grade 3 B follicular lymphoma in partial response (PR) or complete remission (CR) after salvage therapy, or (ii) transformed DLBCL or peripheral T-cell lymphoma in first or subsequent PR or CR. Conditioning regimen consisted of bendamustine (200 mg/m^2 days 7 and 6), etoposide (200 mg/m^2 days 5 to 2), cytarabine (400 mg/m^2 days 5 to 2) and melphalan (140 mg/m^2 day 1) (BeEAM regimen). This trial was registered at EMEA (EUDRACT number 2010-020926-17). Here, we present the first interim analysis of the trial.

Results: Sixty patients (median age 54 years, range 27–70) from 21 Spanish GELTAMO hospitals were included. Histologies were 38 DLBCL, three grade 3 B follicular lymphoma, 12 transformed DLBCL and seven peripheral T-cell lymphoma. At transplant, 63.3% of the patients were in CR and 36.7% in PR. Median time to achieve $>0.5 \times 10,^9$/l neutrophils and $>20 \times 10,^9$/l platelets were 11 (range: 9 to 72) and 14 (range: 4 to 53) days, respectively. At the time of these report, three patients have not achieved $>20 \times 10,^9$/l platelets. A total of 23 serious adverse events have been reported, including seven infectious episodes, two of them resulting in respiratory failure and death of the patient without disease progression (3.3% of transplant-related mortality). Another major toxicity was acute renal failure, developed by five patients (8.3%) after bendamustine administration, reversible in all cases. Three of these patients had developed mild renal failure during the previous salvage therapy. Concerning response to transplant, 41 patients (80%) achieved CR, four (8%) PR and five patients (12%) did not respond. With a median follow up of 7 months (1–19), 1-year progression-free survival and overall survival were 70% and 92%, respectively. Ten out of 22 patients transplanted with active disease achieved CR after the transplant.

Conclusions: The BeEAM regimen is feasible and active in patients with aggressive lymphomas. Infectious complications and renal toxicity can occur and should be carefully monitored. Longer follow-up is needed to evaluate efficacy and safety of this regimen.

021

HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION FOR ELDERLY PATIENTS WITH RELAPSED/ REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: A RETROSPECTIVE ANALYSIS FROM THE ADULT LYMPHOMA WORKING GROUP OF THE JAPAN SOCIETY FOR HEMATOPOIETIC CELL TRANSPLANTATION

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Introduction: The standard treatment of patients with relapsed/ refractory DLBCL is high-dose chemotherapy and autologous stem cell transplantation (ASCT) with curative intent to the eligible patients. Commonly used exclusion criteria of this procedure include advanced age; however, the limit of the age eligible for ASCT remains controversial.

DOI: 10.1002/hon

Therefore, we evaluated the outcome of ASCT in elderly patients (≥60) with relapsed/refractory DLBCL.
Methods: Data from the Japan Society for Hematopoietic Cell Transplantation database were retrospectively analysed. Treatment related mortality (TRM), overall survival (OS) and progression-free survival (PFS) were evaluated. Age group was classified to three groups (60 to 64, 65 to 69 and over 70). Patient characteristics were analysed for their association with OS or PFS using Cox proportional hazard model.
Results: A total of 484 patients over age 60 who diagnosed with relapsed/refractory DLBCL received ASCT from 1993 to 2010. The median age of patients was 64 (range: 60–78) years, and the median follow-up duration of surviving patients after transplant was 26.5 months. Overall TRM was 4.1% at 100 days after transplant, 5.9% at 1 year and 10.7% at 3 years. Two-year PFS and OS after transplant was 48% (95%CI: 43–52%) and 58% (95%CI: 53–63%), respectively. No significant difference was observed in TRM among patients aged 60–64, 65–69, and 70 or older ($p = 0.60$). Multivariate analysis for OS identified three independent risk factors; age (65–69, HR: 1.49, 95%CI: 1.11–2.01; >70, HR: 1.90, 95%CI: 1.10–3.30), performance status at ASCT (PS2-4, HR: 1.63, 95%CI: 1.09–2.43), and response status at ASCT (not in remission, HR: 2.80, 95%CI: 1.94–4.04). Although the age of 65 years or older was a significant risk factor, the survival rate was acceptable even for patients aged 70 years or older resulting in two-year OS rate of 46% (95%CI: 29–61%).
Conclusion: Prognosis of elderly patients with DLBCL after ASCT was satisfactory, partly because of the patient selection. Further investigations are warranted to identify sufficient criteria for ASCT in elderly patients.

022

TREATMENT OUTCOMES FOR OLDER PATIENTS WITH RELAPSED/ REFRACTORY AGGRESSIVE LYMPHOMA RECEIVING SALVAGE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) ARE SIMILAR TO YOUNGER PATIENTS: A SUBGROUP ANALYSIS FROM THE PHASE III NCIC CTG LY12 TRIAL

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Background: Age > 60 years (y) is associated with a poor prognosis following treatment for aggressive lymphomas compared with younger patients (pts). Salvage chemotherapy followed by ASCT is the standard treatment for chemosensitive relapsed/refractory aggressive lymphoma. Although registry data suggest that pts aged >60 may benefit from ASCT, there are no prospective data comparing the efficacy of this aggressive approach in older patients, compared with pts aged <60. This subgroup analysis compares outcomes by intention with treat (ITT) between pts <60y to those >60y enrolled on NCIC CTG LY12.
Methods: From 8/2003 to 11/2011, 619 pts with relapsed/refractory aggressive NHL were stratified by centre, IPI risk factors at relapse, immunophenotype, prior treatment response and prior rituximab (R) treatment, and randomized to outpatient gemcitabine, dexamethasone, cisplatin (GDP) or standard dexamethasone, cytarabine, cisplatin (DHAP). Responding pts after 2–3 cycles proceeded to ASCT. The protocol was amended in 11/2005 to include R with GDP or DHAP for pts with CD20+ lymphoma. The main analysis of LY12 showed that the response rate (RR) to GDP was non-inferior to DHAP; we used the ITT analysis to compare RR, transplantation rate, event-free survival (EFS) and overall survival (OS) between pts age <60 or >60.
Results: 177 pts (28.6%) enrolled were older than 60y and 442 were younger. Pt characteristics were comparable between the two cohorts. Response to salvage therapy was 48.6% for pts >60 vs 43% for those <60 (95% CI: −3.1% to 14.3%, $p = 0.21$). Transplantation rates were also similar: 50.3% vs 49.8% (95% CI: −8.2% to 9.2%, $p = 0.87$) for older vs younger pts; stem cell mobilization failure occurred in 15.8% vs 14.2%. Rates of febrile neutropenia and adverse events requiring hospitalization were comparable (30.5% vs 22.9% and 37.9% vs 32.1%, for older and younger patients, respectively). With a median follow up of 53 months, 4 y OS was 36% and 40% for pts >60 and <60 ($p = 0.42$), and 4 y EFS was likewise not significantly different (20% vs 28%, $p = 0.43$). There was no difference in grade 3–4 toxicity or treatment-related mortality by age.
Conclusion: In this prospective randomized trial, pts aged >60 had a similar RR to salvage chemotherapy, transplantation rate and survival outcomes compared with younger pts, supporting the use of this intensive treatment approach in older individuals with relapsed/refractory NHL in the rituximab era.

023

CORD BLOOD TRANSPLANTATION FOR ADULT T-CELL LEUKAEMIA/ LYMPHOMA (ATL): A RETROSPECTIVE ANALYSIS FROM THE ATL WORKING GROUP OF THE JAPAN SOCIETY FOR HEMATOPOIETIC CELL TRANSPLANTATION

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Background: Allogeneic bone marrow and peripheral blood stem cell transplantation are the curative treatment for adult T-cell leukaemia/lymphoma (ATL). However, there is limited information about cord blood transplantation (CBT) for ATL.
Methods: Data from the Japan Society for Hematopoietic Cell Transplantation (JSHCT) database were retrospectively analysed.
Results: A total of 175 patients (pts) with ATL received CBT as the first transplant between January 2001 and December 2009. The median age was 55 years (range, 27–79). Sixty-three pts received full-intensity conditioning (47 pts received total body irradiation with a dose of 12 Gy), and 107 pts reduced-intensity conditioning (75 pts received fludarabine and melphalan). Median number of infused nucleated cells was 2.58 (0.36–5.34) × 107/kg. Among 175 pts, 46 (26%) were alive with a median follow-up period of 677 days (range, 0–2237). The 2-year and 5-year overall survival (OS) rate was 20.6% (95%CI; 13.8–27.4%) and 18.8% (95%CI; 11.8–25.8%), respectively. In the landmark analysis of patients who survived at least 60 days (landmark day), development of grade 1–2 acute GVHD was associated with higher 2-year OS of 42.7% (95%CI; 28.1–56.6%) as compared with the absence of acute GVHD with OS of 24.2% (95%CI; 11.2–39.8%), whereas occurrence of grade 3–4 acute GVHD was associated with lower OS ($p = 0.0006$). The cumulative incidence of relapse was 33.4% (95%CI; 26.0–41.0%). Two independent lower risk factors for relapse were identified by multivariate analysis: disease status at CBT (hazard ratio (HR) of CR vs NonCR, 0.22; 95% CI, 0.09–0.55; $p = 0.0011$) and time from diagnosis to CBT (HR of <200 days vs ≥200 days, 0.49; 95% CI, 0.26–0.90; $p = 0.023$). On the other hand, The cumulative incidence of treatment-related mortality (TRM) was high with 46.1% (95%CI; 38.2–53.7%).
Conclusion: CBT was identified to provide a cure for patients with ATL partly through graft-versus-ATL effect. Shortening the time from diagnosis to transplantation may improve the survival, which should be confirmed in prospective evaluation. High TRM of around 50% should be reduced by novel interventions.

024

OUTCOMES OF ALLOGENEIC STEM CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMA WITH CONCURRENT MYC AND BCL2 TRANSLOCATIONS: A SINGLE CENTRE RETROSPECTIVE ANALYSIS

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Background: B-cell non-Hodgkin lymphoma with concurrent MYC and BCL2 translocations ['double hit' (DH) lymphoma] is a recently identified entity associated with advanced stage at diagnosis and poor response rates to multi-agent chemotherapy +/− autologous stem cell transplantation. There are few reports of the use of allogeneic transplantation.
Methods: Samples referred to a single tertiary centre were analysed for MYC and BCL2

translocations if they had: diffuse large B-cell lymphoma with high proliferative index or atypia or B-cell lymphoma, unclassifiable. All samples were analysed by BCL2 and MYC dual colour breakapart probes. Karyotype was performed where possible. To test the utility of allogeneic transplantation for DH lymphoma, all patients treated with intensive chemotherapy from 2006–2013 were considered eligible for allogeneic transplantation if they had chemosensitive disease, were aged <70 years and had no co-morbidities excluding transplantation. A retrospective analysis of clinical and transplant outcomes was made via hospital clinical and electronic records.

Results: A total of 18 patients were treated for DH lymphoma from 2006–2013. Median follow up for the whole cohort, the transplant group and the non-transplant group was 287 days (20–2128), 656 days (210–2128) and 124 days (20–1479), respectively. Median age was 57 years (36–70). Presenting features at diagnosis were stage III/IV 83%, bone marrow/peripheral blood involvement 9/18 (50%). 9/18 (50%) patients proceeded to allogeneic transplantation. Donors were matched sibling 5/9 (55%), matched unrelated 4/9 (45%) and PBSC 9/9 (100%). Myeloablative versus reduced intensity conditioning was 22% versus 78%. A 3-year estimated overall survival for the transplant group and the non-transplant group was 78% and 19% ($p = 0.014$), respectively. A 3-year estimated progression-free survival for transplant and non-transplant was 76% and 22% ($p = 0.015$). In the transplant group 1, patient died of progressive lymphoma, and onw patient died from complications of acute graft-versus-host disease.

Conclusions: In this small single centre case series, allogeneic transplantation appears to be associated with durable remissions and prolonged survival in selected patients with DH lymphoma. Multi-centre collaboration is required to accrue patients with this rare sub-group for optimal assessment of therapeutic outcomes.

025

LONG TERM OUTCOMES AFTER FLUDA/CYCLOPHOSPHAMIDE REDUCED-INTENSITY CONDITIONING (RIC) ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR LYMPHOMAS: A BHS NATIONAL PROSPECTIVE TRIAL

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Background: Allogeneic HSCT offers a curative option for various hematological malignancies including lymphoproliferative diseases (LPD). The use of RIC allows to perform alloSCTin older patients or patients not eligible for myeloablative conditioning regimens. Long term follow up of RIC HSCT are lacking in the literature.

Aims: To report the 10 yrs follow-up of a prospective multicentre dose-finding study where the aim was to determine the optimal dose of ATG after RIC allo HSCT in malignant hemopathies. Lymphoproliferative disorders (LPD) were analysed separately.

Methods and patients: From 2000 to 2007, 83 patients with lymphoproliferative malignancies were evaluable for analyses: 22 (26%) chronic lymphocytic leukaemia (CLL), 52 (63%) non Hodgkin's lymphomas (NHL), 9 (11%) Hodgkin lymphomas (HL). All patients were treated with fludarabine 30 mg/m,^{2}/d × 4 days and cyclophosphamide 1000 mg/m,^{2} × 3 days. As GVHD prophylaxis, they received cyclosporine A and ATG 40 or 20 or 0 mg/kg. Allogeneic SCT was performed with peripheral stem cells from an HLA-sibling donor.

Results: A total of 83 pts were analysed. Median age was 51 (13–69) years old. Median follow up was 8 yrs (90 months). Only 15 pts (14%) were in true CR before transplant. 34 pts converted to CR after HSCT (total 59% CR). The overall survival (OS)/ 8 yrs was 47% (52% for CLL, 48% for NHL, 33 for HL)). OS was not affected by the doses of ATG. OS in NHL was lower in pts not in CR before transplant (60% vs 41%) although in CLL, status of the disease did not significantly affects OS (50% vs 52%). Transplant related mortality (TRM) was affected by age above 60, disease status before transplant and higher doses of ATG. Event-free survival (EFS) was 38%/ 8 yrs (36,4% for NHL, 48% for CLL, 11,1% for HL). Cumulative relapse rate was 35% but a plateau appears 50 Mos after SCT. EFS was not affected by age or disease status before transplant but was worse in HL (10%/8 yrs). Limited and extensive cGVHD was documented in 28 ans 17% respectively.

Conclusion: 1)Fluda/CPA/ATG-based RIC-HSCT enables transplant in older patients with LPD (45% OS, 29% EFS/8 yrs). 2)Low doses of ATG combined with CSA and MMF resulted in limited cGVHD and lower TRM. 3) This approach is curative in CLL and NHL pts even in pts with progressive or refractory disease before transplant.

'FOCUS ON. . .' SESSION: PRECLINICAL ASSAYS

026

BIOMIMETIC SYNTHETIC HIGH DENSITY LIPOPROTEIN NANOSTRUCTURES TARGET THE SR-B1 RECEPTOR, DIFFERENTIALLY MANIPULATE CELLULAR CHOLESTEROL FLUX IN LYMPHOMA CELLS, AND MODIFY CELL CYCLE, OXIDATION AND CHOLESTEROL SYNTHESIS GENES

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We report a nanoparticle-enabled therapy for B-cell lymphoma using synthetic, high-density lipoprotein nanoparticles (HDL-NPs). HDL-NPs target the high-affinity HDL receptor, scavenger receptor type B-1 (SR-B1) and differentially alter cholesterol flux in lymphoma cells. In contrast to natural HDLs, SR-B1 binding and relative cholesterol starvation induces apoptosis in B-cell lymphomas and inhibits lymphoma growth in a xenograft model. First, we measured the expression of SR-B1 in human lymphoma samples and from multiple cells and cell lines. We found overexpression in patients and in cell lines by comparison with normal B-cells. We then correlated HDL-NP uptake with cell expression of SR-B1. Further, we found that HDL-NPs compete with HDL and acetylated LDL, both of which target SR-B1, for lymphoma cell binding. Next, we used 3H-cholesterol cell labelling and scintillation counting to demonstrate that HDL-NPs reduce cholesterol uptake and enhance cholesterol efflux from tested B-cell lymphomas by comparison with natural HDL. Finally, we showed the HDL-NPs induced apoptosis in B-cell lymphoma lines and inhibited tumour growth in a xenograft model. To better understand the biology of HDL-NPs, we measured differential gene expression in Ramos cells after exposure to HDL and HDL-NPs. Relevent target genes were analysed for protein expression by immunoblot. Gene arrays demonstrated that cholesterol synthesis genes (e.g. insulin-induced gene 1, 7-dehydrocholesterol reductase and acetyl-CoA acetyltransferase 2) and cell cycle regulatory genes (cyclin-dependent kinase inhibitor 1A (p21, Cip1) were upregulated, and oxidant genes (e.g. glutathione peroxidase 1 and 4) were downregulated after HDL-NP treatment. Immunoblots confirmed upregulation of p21, p27 and p53. In conclusion, we report a template-directed and bio-functional therapeutic nanostructure that could shift the paradigm for treating lymphoma and other cancers. A combination of SR-B1 binding and manipulation of cholesterol flux is responsible for selective induction of apoptosis in B-cell lymphoma. Further, we have elucidated molecular signalling pathways that are altered by HDL-NP in Ramos and may explain the biologic consequences of impaired cholesterol flux in lymphoma cell lines.

027

CROSS-SPECIES DISSECTION OF FUNCTION, MECHANISM AND PREDICTIVE IMPACT OF THERAPY-RELATED PARACRINE SENESCENCE IN AGGRESSIVE B-CELL LYMPHOMA IN MICE AND MEN

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Introduction: DNA-damaging chemotherapy induces cellular senescence (therapy-induced senescence, TIS), a terminal cell-cycle arrest. TIS cells may crosstalk to non-senescent neighbours via cytokines and other senescence-associated factors. Utilizing a mouse lymphoma model and data from patients diagnosed with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP, we provide here evidence for an outcome-relevant paracrine-mediated secondary senescence program (SecS) *in vitro* and *in vivo*.

Methods: Lymphoma cells were treated (adriamycin, cyclophosphamide, or radiation) *in vitro* and *in vivo*. TIS and SecS were detected based on sen.-ass. beta-galactosidase activity, Ki67 staining and bromodeoxyuridine (BrdU) incorporation. The TIS secretome was analysed by transcriptomics and proteomics. Overall and progression-free survival in mice and patients was assessed by Kaplan-Meier analysis.

Results: Supernatant transfer from TIS lymphomas produced SecS in murine and human lymphoma cells. Secretome and functional analyses identified extracellular matrix proteins as SecS inducers in proliferating mouse lymphoma cells. Dissecting

DOI: 10.1002/hon

senescence-mediating pathways in secreting donor and in ligand-susceptible recipient lymphoma cells unveiled an essential role for a Smad3-driven donor and an LDL receptor-related protein 1 (LRP1)-governed recipient cell signalling network in SecS. Accordingly, mice harbouring TIS-capable but genetically SecS-defective lymphomas experienced inferior long-term outcome to therapy. Not only the recipient-sided LRP1 status but also an independent donor cell-derived secretor gene signature stratified outcome in mice. Strikingly, humanized versions of both classifiers were predictive in a cohort of 220 gene expression-profiled DLBCL patients, where they identified largely overlapping patient subgroups with superior prognosis, hereby suggesting SecS as the critical underlying treatment effector principle in humans as well.

Conclusions: Our study highlights the impact of secondary, paracrine-mediated senescence on treatment outcome in DLBCL, illustrates the power of mouse lymphoma models for cross-species investigations, and provides functional examples (which will be discussed at the meeting) for SecS-related non-genotoxic anticancer therapies.

028

THE NOVEL PROTEASOME INHIBITOR LU-102, BUT NOT BORTEZOMIB OR CARFILZOMIB, DECREASES P-IKB LEVELS IN MYELOMA CELLS, AND IS SYNERGISTIC WITH IBRUTINIB TO OVERCOME BORTEZOMIB/CARFILZOMIB RESISTANCE *IN VITRO*

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Acitve Bruton's tyrosine kinase (p-BTK) is expressed in the majority of primary myeloma cell samples. BTK activation leads to phosphorylation of IkB, subsequent proteasomal degradation of p-IkB and hence activation of NFkB, a key survival signal for B-cells and multiple myeloma (MM). Ibrutinib (IB), a specific BTK inhibitor, has preclinical activity against MM. Bortezomib (BT), the first in class proteasome inhibitor and standard therapeutic for MM, is predicted to interfere with proteasomal degradation of p-IkB and hence to limit the antimyeloma activity of IB. Novel proteasome inhibitors selectively target individual proteasome subunits, in contrast to BT: Carfilzomib (CF) is beta-5-selective, and LU-102 (LU) exclusively targets the BT/CF-insensitive beta-2 subunit. We hypothesized that selective proteasome inhibitors may have a higher potential for synergistic antimyeloma activity with IB than BT, because they are expected to have a weaker p-IkB stabilizing effect. We therefore compared the effects of BT, CF and LU on protein degradation, p-IkB levels and MM cell viability in combination with IB. IB treatment decreased p-BTK, p-IkB and viability in p-BTK-expressing myeloma cells. LU showed a tenfold higher synergistic myeloma cell killing in combination with IB (combination index, CI:0.075), compared with CF or BT (CI 0.63 and 0.83, respectively), and activated the intrinsic apoptotic pathway. LU did not interfere quantitatively with protein degradation and induced a concentration dependent decrease of p-IkB, both in contrast to CF and BT. When we challenged BT/CF resistant myeloma cells with the combination of LU and IB, >90% myeloma cell killing was achieved, whereas either drug alone had no effect. We conclude that the beta 2-selective proteasome inhibitor LU-102 provides superior synergistic antimyeloma activity in combination with IB than CF or BT. This may be due to the opposing effects of LU-102 and CF/BT on cellular p-IkB levels that depend on the general rate of protein degradation. Combining IB with Lu-102 is highly effective in particular against CF/BT-resistant myeloma cells *in vitro*.

029

DUAL TARGETING OF PROTEIN DEGRADATION PATHWAYS WITH THE SELECTIVE HDAC6 INHIBITOR, ACY-1215 (ACY), AND BORTEZOMIB (BOR), DEMONSTRATES SYNERGISTIC ANTITUMOUR ACTIVITY IN PRECLINICAL MODELS OF LYMPHOMA.

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Introduction: Isoform selective HDAC inhibitors are emerging as potentially more targeted agents, with theoretical advantages over pan-HDAC inhibitors. HDAC6 is a class IIb deacetylase that facilitates misfolded protein transport to the aggresome for proteolytic degredation. We investigated the therapeutic impact and mechanism of the selective HDAC6 inhibitor, ACY (Acetylon Pharmaceuticals, Inc) alone and in combination with Bor in preclinical models of lymphoma.

Methods: Cell viability was measured by Cell Titer-Glo. The IC_{50} values were calculated at 24–72 hrs of exposure. Cytotoxicity of ACY in combination with Bor was evaluated for schedule, concentration-effect relationship and synergy. Apoptosis was analysed with FACS analysis for Annexin V/PI and immunoblot for cleaved caspase-3 and PARP. Effects of ACY on apoptotic potential and unfolded protein response (UPR) were measured by immunoblot and immunoprecipitation.

Results: Single agent concentration-effect curves were generated for 17 cell lines (DLBCL, MCL, and TCL). Maximal cytotoxicity was observed at 48 hrs with IC_{50} values ranging from 240–3500 nM, with the most potent activity in DLBCL. In combination with Bor, the synergy (RRR) was seen in DLBCL (RRR = 0.39), MCL (RRR = 0.78), and TCL (RRR = 0.28). Cells most sensitive to ACY expressed higher baseline levels of pro-apoptotic proteins CHOP (C/EBP-homologous protein) and BIM, and lower levels of pro-survival proteins GRP78 and Bcl2. Treatment with ACY led to inhibition of the aggressome pathway evidenced by acetylation of a-tubulin and increased poly-ubiquitinated proteins. Upregulation of UPR was demonstrated by acetylation of GRP78 and subsequent dissociation of PERK, increased p-eIF2a, spliced XBP-1 and CHOP. The p65 NF-kB subunit was decreased with the combination. Cell death occurred via apoptosis. All pharmacodynamic effects were enhanced with the addition of Bor.

Conclusions: These are the first results to indicate that dual targeting of different protein degradation pathways may represent a novel and synergistic approach for the treatment of select lymphoma subtypes.

030

THE NOVEL 2ND GENERATION PROTEASOME INHIBITOR MLN9708 INDUCES REDOX- AND MAPK-RELATED CELL DEATH IN T-CELL LYMPHOMA (TCL) AND HODGKIN LYMPHOMA (HL) CELL LINES AND HUMAN LYMPHOMA XENOGRAFT MODELS

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Background: We investigated the therapeutic efficacy of the novel 2nd generation proteasome inhibitor, MLN9708, in TCL and HL cells through *in vitro* and *in vivo* tumour models and examined the biologic mechanisms of action.

Methods: TCL cell lines (Jurkat, Hut78 and HH) and HL cell lines (L428, L540, L1236) were treated with MLN9708 for 24–48 hours. We analysed apoptosis and oxidative stress by flow cytometry (FC), and expression of p21, MYC, and MAPK were analysed with Western blot. We interrogated signalling pathways with stably transfected shRNA knock outs (KO)/MLN9708. *In vivo* tumour growth inhibition and survival of tumour bearing SCID mice were determined using xenografts derived from Jurkat (TCL) and L540 (HL) cell lines.

Results: Treatment with 50 to 100 nanomolar (nM) of MLN9708 resulted in time-dependent and dose-dependent cytotoxicity in all cell lines. The IC50 values were 38nM, 52nM, and 41nM for Jurkat, Hut78, and HH, respectively, and 39nM, 60nM, and 117nM for L540, L1236, and L428, respectively. MLN9708 resulted in dose-dependent increase in apoptosis by Annexin-V/PI ($p < 0.001$), cleaved PARP, and activation of caspases 3, 8, and 9 in all cell lines. MLN9708 also resulted in increased oxidative stress and decreased intra-cellular glutathione (GSH) and it caused increased p21 expression and degradation of MYC protein. Moreover, these effects appeared to be redox-dependent as treatment with N-acetyl cysteine (NAC) abrogated apoptosis, oxidative stress, and MYC degradation. Additionally, MLN9708 treatment induced several changes in the MAPK signalling pathway. In TCL, it increased pERK and p-p38, whereas pJNK was decreased. Using shRNAs (with MLN9708), ERK and p38 KO had minimal effect in the TCL lines, however JNK KO resulted in increased cell death in Jurkat and Hut78 cells. In HL, ERK and JNK shRNA had minimal effect, whereas p38 KO increased the cytotoxic effect of MLN9708 in all HL cell lines. Finally, *in vivo* experiments with SCID tumour xenografts showed significant inhibition of tumour growth ($p < 0.001$) as well as significantly improved survival (p 0.001) in Jurkat and L540 models with MLN9708-treated mice versus controls.

Conclusions: Collectively, we found that MLN9708 induced potent cell death at nanomolar and clinically achievable concentrations in TCL and HL cell lines and *in vivo* xenograft models. In all cell lines, MLN9708 down-regulated MYC and cell death was redox-dependent. Further, in TCL, the cytotoxic effect of MLN9708 was mediated through JNK, whereas p38 was the dominant pathway in HL-related cell death.

031

PHARMACOLOGIC INHIBITION OF MALT1 BY DISTINCT PHENOTHIAZINES FOR A TARGET-DIRECTED THERAPY OF ABC-DLBCL

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DOI: 10.1002/hon

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Introduction: The cleavage activity of the MALT1 paracaspase is important for optimal lymphocyte activation and critical for the NF-kB driven survival of B-cell malignancies like MALT lymphoma or the activated B-cell subtype of diffuse-large B-cell lymphoma (ABC-DLBCL). Selective inhibition of MALT1 by small molecules therefore has a high clinical potential for a target-directed therapy of distinct MALT1-dependent B-cell neoplasms and immunological disorders.
Methods: We screened ~ 18.000 small molecules from the ChemBioNet library at the FMP (Berlin) for their MALT1 inhibitory potential, leading to the identification of distinct phenothiazine derivatives (PD) as potent MALT1 inhibitors. Subsequent cellular studies with the PD were performed to test their impact on T-cell activation (in murine CD4,$^{+}$T-cells, human PBMCs and Jurkat T-cells) and on MALT1-independent and dependent DLBCL cell-lines. Efficacy of the compounds was also determined in a preclinical xenogeneic tumour model *in vivo*.
Results: We identified three distinct phenothiazine derivatives (PD), mepazine, thioridazine and promazine, as potent, selective and non-competitive inhibitors of recombinant and cellular MALT1 protease. The PD impair T-cell activation and in addition reduce the anti-apoptotic NF-kB activity of ABC-DLBCL cell lines. As a consequence the PD elicit toxic effects selectively in ABC-DLBCL cells, leading to apoptosis and growth reduction of the cells *in vitro* and *in vivo*. Taken together the compounds reveal a high potency for an application in a target-directed treatment of MALT1-dependent lymphomas.
Conclusions: Our data provide a conceptual proof for a clinical application of distinct PD for the treatment of MALT1-dependent lymphoma. As phenothiazines are still used as antipsychotic and antihistaminic drugs, their well-defined toxicity, pharmacokinetics and pharmacodynamics may facilitate clinical trials for an off-label use of these compounds in ABC-DLBCL therapy. At present, we are comparing single and combinatorial administration of PD and the BTK inhibitor ibrutinib that is currently in clinical trials for relapsed/refractory ABC DLBCL.

'FOCUS ON...' SESSION: EARLY AND LATE TOXICITIES

032
IMMUNOCHEMOTHERAPY WITH BENDAMUSTINE-RITUXIMAB (BR) AS INDUCTION THERAPY FOR INDOLENT LYMPHOMAS RESULTS IN A SEVERE LYMPHOPENIA WITH LOW CD4+ AND CD8+ COUNTS WITHOUT AN INCREASE IN ATYPICAL INFECTIONS. FIRST RESULTS OF THE INFECTIOUS DISEASE (ID) PROJECT OF A PROSPECTIVE, RANDOMIZED, MULTICENTRE STUDY (STIL NHL 7-2008, MAINTAIN; NCT00877214)

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Introduction: Bendamustine-rituximab (B-R) is a National Comprehensive Cancer Network recommended first line treatment for indolent lymphomas, and the impact of this regimen on immunological and infectious disease (ID) parameters is not well described. Our trial of B-R induction followed by R maintenance includes a prospective investigation of ID parameters. Here, we present the first data for patients (pts) who completed B-R induction therapy (IT).
Methods: Pts received a maximum of six cycles of B-R as IT plus two additional courses of R. Immunological and ID parameters were investigated before IT, at the end of IT and during the R maintenance period.
Results: A total of 947 out of 1160 (81.6%) pts who completed IT were evaluable for white blood counts, 740 (63.8%) for Immunoglobuline level and 356 (30.7%) for antibody (AB) titers. The median white blood count dropped from 6600 to 3800/µl after IT. Neutrophils declined moderately from 3900 to 2400/µl, whereas lymphocytes decreased substantially from 1500 to 500/µl. Median pre-treatment counts of CD4+ and CD8+ cells were 555 and 316/µl, respectively. After IT, median counts were 118 and 198/µl, respectively. The CD4/CD8 ratio changed to an inverse ratio after IT (0.6). IgG levels dropped slightly from 8.65 to 7.51 g/l, IgM level from 0.76 to 0.42 g/l; AB titers (pneumococci and tetanus) remained stable. A total of 124 documented infections occurred, mostly pneumonia (44), therefrom three pneumocystis jiroveci (PcP) infections. A total of 17 pts (1.4%) died due to ID complications [nine sepsis, four PML (three proven, one probable), three pneumonias, one reactivated Hepatitis B).
Conclusion: Our results show substantial changes in CD4+ and CD8+ counts following B-R, with moderate decreases in neutrophils and changes in IgG level and AB titers. Close monitoring on ID complications and the use of supportive treatments, such as substitution of immunoglobulines, use of growth factors, PcP prophylaxis and prophylaxis of Hepatitis B reactivation is mandatory when required.

033
RISK OF DIABETES MELLITUS FOLLOWING TREATMENT OF HODGKIN LYMPHOMA

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Introduction: Recently, a relationship between radiotherapy to the pancreas and an increased risk of diabetes mellitus (DM) has been shown in childhood cancer survivors. Especially in the past, many Hodgkin lymphoma (HL) survivors received infradiaphragmatic radiation. These HL survivors may also experience an increased risk of DM. We evaluated the association between infradiaphragmatic radiation and DM risk in 5-year HL survivors. Methods: Our study cohort comprised 2325 5-year HL survivors, diagnosed before age 51 and treated between 1965 and 1995. Treatment and follow-up information was collected from medical records and questionnaires to general practitioners. DM cases were confirmed by general practitioners. Irradiation of the spleen and/or splenic hilum was used as proxy for radiation to the pancreatic tail. Cumulative incidence of DM was estimated, and risk factors for DM were evaluated using Cox regression.
Results: In our cohort of 2325 HL survivors, 159 cases of DM after HL were identified after a median follow-up of 21 years (range 10–47 years). Mean age at treatment was 28 years, mean age at diagnosis of DM was 52 years. Overall cumulative incidence of DM after 30 years of follow-up was 7.9% (95% confidence interval (CI): 6.5–9.3). After irradiation of the spleen/splenic hilum ($n = 657$), 30-year cumulative incidence of DM was 11.0% (95%CI: 8.2–14.4).
Radiation to the spleen/splenic hilum was associated with an increased risk of DM (hazard ratio: 1.7, 95%CI: 1.2–2.4), compared with patients who did not receive infradiaphragmatic radiotherapy (reference group). Infradiaphragmatic radiation to the para-aortic lymph nodes without radiation of the spleen/splenic hilum ($n = 343$) was not associated with an increased risk of DM (hazard ratio: 1.3, 95%CI: 0.8–2.0). Analyses were adjusted for age at HL diagnosis, gender, year of HL diagnosis and treatment with anthracycline-containing chemotherapy.
Conclusion: Radiation to the spleen/splenic hilum, leading to radiation exposure of the pancreatic tail, increased the risk of developing DM in 5-year HL survivors. Para-aortic radiation alone did not increase DM risk.

034
DOSES TO CAROTID ARTERIES AFTER MODERN RADIOTHERAPY FOR HODGKIN LYMPHOMA: IS STROKE STILL A LATE EFFECT OF TREATMENT?

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Introduction: The majority of Hodgkin lymphoma (HL) patients become long-term survivors. HL survivors are at an increased risk of stroke due to carotid artery (CA) irradiation. We evaluate 3D conformal radiotherapy (3DCRT), volumetric modulated arc therapy (VMAT) and proton therapy (PT) delivered as Involved Node RT (INRT) with the extensive Mantle Field (MF) by comparing doses to the carotid arteries and corresponding risk estimates.
Methods: We included a cohort of 46 supradiaphragmatic stage I–II classical HL patients. All patients were initially treated with chemotherapy and INRT delivered as 3DCRT (30 Gy). For each patient, we simulated a MF (36 Gy), VMAT and PT plan (30 Gy) and derived a linear dose-response curve for the 20 and 30 year absolute excess risk (AER) of stroke with each technique from published HL data,[1]. Statistical analyses were performed with repeated measures ANOVA.

DOI: 10.1002/hon

Abstract 034 Table 1. Mean dose (Gy) with 3D CRT, VMAT, PT and MF for the 46 HL patients.

	Mean dose, Gy (range)								
	3DCRT		VMAT		Proton		Mantle field		*p*-value
Right common carotid artery	20.3	(0–32.1)	23.2	(0.9–31.7)	21.1	(0–30.8)	37.6	(34.1–40.6)	<0.0001
Left common carotid artery	19.2	(0.1–31.6)	21.6	(2.4–33.0)	19.4	(0–30.8)	37.4	(32.8–40.4)	<0.0001
Right internal carotid artery	0.2	(0–24.7)	2.5	(0.1–27.4)	0	(0–28.1)	22.5	(7.1–34.5)	<0.0001
Left internal carotid artery	0.5	(0–25.3)	1.5	(0.1–25.7)	0	(0–25.8)	23.2	(8.1–33.7)	<0.0001
Right external carotid artery	0.8	(0–29.2)	2.5	(0–30.8)	0	(0–30.8)	27.2	(11.9–36.8)	<0.0001
Left external carotid artery	0.5	(0–29.4)	1.6	(0.1–28.6)	0	(0–29.5)	28.3	(12.5–37.4)	<0.0001

Results: The mean dose to the CAs are presented in table 1. For 3DCRT, VMAT, PT, and MF the 20 year AER (95% CI) of stroke is 0.76% (0.58–0.94%), 0.86% (0.65–1.06%), 0.78% (0.59–0.96%), and 1.52% (1.16–1.89%), $p < 0.0001$, and the 30 year AER is 1.40% (0.97–1.82%), 1.57% (1.09–2.05%), 1.43% (0.99–1.86%) and 2.80% (1.94–3.65%), $p < 0.0001$, respectively.
Conclusion: Modern RT significantly reduces the estimated risk of stroke for HL survivors. Even for the subset of patients where INRT will expose the carotid arteries to high doses the risk is minimal.,[1]De Bruin et al. JNCI 2009;101:928-937

035

RISK FACTORS FOR VALVULAR HEART DISEASE FOLLOWING HODGKIN LYMPHOMA

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Introduction: Mediastinal radiotherapy (MRT) for Hodgkin Lymphoma (HL) is known to increase cardiovascular (CV) morbidity in survivors of HL, including valvular heart disease (VHD). Little is known, however, about the dose-response for radiation-induced VHD or other risk factors for the disease.
Methods: We performed a nested case-control study of VHD in HL survivors. The cohort consisted of 1861 5-year survivors of HL, diagnosed between the ages of 14 and 41, treated between 1965 and 1995, and identified through hospital-based cancer registries in the Netherlands. Cases were those diagnosed with VHD (CTCAE v.4 grade ≥2) as a first CV diagnosis following treatment for HL. Controls, selected for each case, were free from a CV diagnosis at the cut-off date, matched for gender, era of diagnosis, age at diagnosis and follow-up interval. Detailed data were collected from patient records including HL staging, chemotherapy and radiotherapy (RT) treatment (both primary and salvage), other medical conditions and conventional CV risk factors. RT data included original RT prescriptions and x-ray imaging. RT doses to the heart and cardiac substructures were retrospectively estimated by reconstructing the RT treatment on surrogate computer tomography (CT) data sets using a CT-based RT treatment planning system.
Results: There were 89 cases identified and 200 controls selected. Of the cases, 45 presented with an aortic valve defect, 22 with a pulmonary valve defect, 12 with combined aortic and pulmonary valve defects and the remaining 10 with other combined valve defects. The median MRT dose in Gray and the median estimated mean heart dose (MHD) in an equivalent dose in 2 Gray fractions (EQD2) were both higher for cases than controls at 36.9 vs 31.9 ($p = 0.01$) and 30.6 vs 25.4 ($p = 0.002$) respectively. On multivariable analysis of treatment factors the MHD (Odds ratio (OR) = 1.82 per 10 EQD2, $p = 0.003$) and diagnostic splenectomy (OR = 2.34, $p = 0.01$) were associated with increased risk of VHD, but anthracycline treatment was not (OR = 1.21, $p = 0.78$).
Conclusions: The MHD received was higher for cases and associated with an increased risk of VHD in HL survivors. Further analysis will explore the dose-response for VHD-risk following MRT, benefitting future MRT planning and improving the counselling of patients regarding risks.

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INCREASED STOMACH CANCER RISK AFTER TREATMENT FOR HODGKIN LYMPHOMA

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Introduction: Subsequent malignancies are a leading cause of morbidity and mortality among Hodgkin lymphoma (HL) survivors. Although elevated risk of stomach cancer has been reported after HL, few studies have quantified stomach cancer risk in relation to radiation dose and specific chemotherapeutic agents.
Methods: We conducted an international case-control study of stomach cancer nested in a cohort of 19,882 HL survivors (diagnosed 1953–2005), including 89 cases and 190 matched controls. For each patient, we quantified cumulative doses of specific alkylating agents (AAs) and reconstructed radiation dose to the stomach tumour location, using detailed radiotherapy records. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression.
Results: For cases, the median interval from HL to stomach cancer was 15 years, and median age at stomach cancer diagnosis was 50 years. Stomach cancer risk increased with increasing radiation dose to the stomach (p trend<0.001) and with increasing number of AA-containing chemotherapy cycles (p trend = 0.02). Patients who received both ≥25 Gy radiation to the stomach and high-dose (≥5600 mg/m,^{2}) procarbazine had strikingly elevated stomach cancer risk (25 cases, 2 controls; OR = 77.5, 95% CI 14.7–1452, compared with <25 Gy radiation and <5600 mg/m,^{2} procarbazine; p interaction<0.001). Risk also was elevated (OR = 2.8, 95%CI 1.3–6.4) among patients who received ≥25 Gy radiation to the stomach but <5600 mg/m,^{2} procarbazine; however, no procarbazine-related risk was evident with <25 Gy radiation. Treatment with dacarbazine also increased stomach cancer risk (12 cases, 9 controls; OR = 8.8, 95%CI 2.1–46.6), after adjustment for radiation and procarbazine dose.
Conclusions: Stomach cancer risk was elevated in HL patients who received sub-diaphragmatic radiation, with striking risks for patients who also received high-dose procarbazine-containing chemotherapy. For current patients, risks and benefits of exposure to both procarbazine and sub-diaphragmatic radiotherapy should be weighed carefully. For patients treated previously, gastrointestinal symptoms should be evaluated promptly.

DOI: 10.1002/hon

037

SECOND PRIMARY MALIGNANCIES (SPM) IN CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)—A METAANALYSIS OF FOUR PROSPECTIVE TRIALS OF THE GERMAN CLL STUDY GROUP

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Introduction: CLL is associated with an increased risk of SPM. This analysis was performed to assess the frequency of SPM after first-line treatment.
Methods: Our database was searched for SPM in CLL patients (pts) treated within four prospective phase II/III trials. The trials evaluated fludarabine (F) versus F + cyclophosphamide (FC) [CLL4], chlorambucil (CLB) versus F [CLL5], FC without or with rituximab (FCR) [CLL8], and bendamustine + R (BR) [CLL2M].
Results: Follow-up data of 1458 pts were evaluated. Median observation times for CLL4, CLL5, CLL8 and CLL2M were 107, 70, 69 and 37 months for pts alive respectively. 270 SPM were observed in 239 pts (16.4%). Median times from start of treatment to onset of SPM were 50, 37, 22 and 19 months for CLL4, CLL5, CLL8 and CLL2M respectively. SPM were observed at rates of 21.3% for F, 17.7% for FC, 15.5% for CLB, 13.1% for FCR, and 11.1% for BR ($p = 0.03$). In therapy combinations with R versus without R, the occurrence of SPM was 12.7 versus 18.5% ($p = 0.004$). However, considering different observation times in Kaplan Meier estimation the difference was not confirmed with a SPM-free survival at 4.5 years of 89.2 versus 84.7 ($p = 0.1$). Age >65 years showed a significant influence on SPM ($p < 0.001$, HR 1.7). Most common malignancies were solid tumours ($N = 116$) including lung (28%), prostate (15%), kidney/bladder (10%), colorectum (9%), melanoma (8%) and breast (7%). Standardized incidence ratio showed a 1.23 fold increased risk of solid tumours in comparison with the age matched general population from the German cancer registry. 75 pts (5.1%) developed a Richter Syndrome. Most common hematologic neoplasia ($N = 38$) were AML/MDS (50%), indolent B-NHL (24%) and Burkitt/ALL (13%). Non-melanoma skin tumours ($N = 36$) and hematologic neoplasia did not correlate with type of first-line treatment.
Conclusion: CLL pts treated by chemotherapies or chemoimmunotherapies have a surprisingly high risk of developing SPM above 10%. Longer follow-up and additional analyses are needed to determine the factors that might contribute to development of SPM.

'FOCUS ON…' SESSION: NOVEL MONOCLONAL ANTIBODIES

038

NOVEL PI3K-d INHIBITORS DEMONSTRATEDMARKED CYTOTOXICITY IN T-CELL LYMPHOMA MODELS AND WERE SYNERGISTIC WITH A NOVEL ANTI-CD20 MAB, UBLITUXIMAB, IN LYMPHOMA MODELS

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Introduction: The delta (δ) isoform of PI3K is highly expressed in cells of hematopoietic origin and strongly upregulated in various hematologic malignancies. Recently, novel agents targeting PI3K-δ have been developed, with pharmacologic and pharmacodynamic features distinct from GS-1101 (CAL-101). We sought to determine the activity of two structurally related PI3K-δ inhibitors, TGR-1202 and TGR-5237, in B-cell and T-cell lymphoma models.
Methods: The activity of TGR-1202 on individual PI3K isoforms was determined in a cell-free system and in a cell-based assay. Cytotoxicity of TGR-1202 and TGR-5237 was studied in four mantle cell lymphoma cell lines, one T-ALL cell line (P12) and one cutaneous T-cell lymphoma cell line (H9). Growth inhibition and apoptosis were determined by flow cytometry. Potency of ublituximab (UTX) was determined in antigen recognition studies, and cell cycle progression was evaluated in four lymphoma cell lines, including Daudi, Raji, U266B1 and DB.
Results: In the enzyme-based assay, TGR-1202 demonstrated marked potency against PI3K-δ (IC_{50} 22 nM). TGR-1202 was 48–10 000-fold more selective for PI3K-δ relative to all other PI3K Class I isoforms. In the cell-based assay, the EC_{50} of TGR-1202 for PI3K-δ was 67 nM versus 92 nM with GS-1101. In the cytotoxicity assay of TGR-5237, the IC_{50} ranged from 10 uM to 50 uM for the four mantle cell lymphoma cells P12 line. Surprisingly, the cutaneous T-cell lymphoma cell line H9 was exquisitely sensitive to TGR-5237 (IC_{50} <0.1 uM). TGR-5237 induced concentration-dependent apoptosis in WSU-NHL, comparable with GS-1101. TGR-1202 caused a concentration-dependent accumulation of cells in the G2-M phase in Raji, Daudi, U266B1 and DB. Although TGR-1202 was not cytotoxic to CD20+ B-cells at 1 uM, combination with UTX increased CD20+ cell depletion by 20% at 0.1–10 ng/ml. Lastly, the combo of TGR-1202 and UTX markedly increased the % of cells in sub-G0 phase in Daudi and Raji cells, indicative of their synergy.
Conclusion: Two novel PI3K-δ inhibitors, TGR-1202 and TGR-5237, disrupted cell cycle progression, induced apoptosis and inhibited cell growth and proliferation in B-cell and T-cell lymphoma models. TGR-1202 enhanced the activity of ublituximab in CD20+ lymphoma cells. Both TGR-1202 and ublituximab are under clinical development for hematologic malignancies. Clinical studies evaluating the combination of these two agents are warranted.

039

PHASE I STUDY OF THE ANTI-CD22 ANTIBODY-DRUG CONJUGATE (ADC) DCDT2980S WITH OR WITHOUT RITUXIMAB (RTX) IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) B-CELL NON-HODGKIN'S LYMPHOMA (NHL)

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Background: DCDT2980S (DCDT) is an anti-CD22 monoclonal antibody (Ab) conjugated to MMAE, a potent anti-mitotic agent, with a maximum tolerated dose (MTD) of 2.4 mg/kg q21d and clinical activity in pts with R/R B-cell NHL at doses ≥ 1.8 mg/kg.
Methods: We evaluated safety, tolerability, pharmacokinetics (PK), and activity of DCDT q21d with or without RTX (375 mg/m,[2]), in pts with R/R B-cell NHL. At the single-agent MTD, expanded cohorts of pts with R/R DLBCL or indolent (i)NHL were evaluated.
Results: 45 pts enrolled in DCDT ≥ 1.8 mg/kg and 16 in the DCDT+RTX cohort. Median age was 66 yrs; 81% had an ECOG PS <2; median of 3 prior regimens (range 1–16); 93% prior RTX, 8% prior stem cell transplant. The MTD of DCDT+RTX was 2.4 mg/kg based on 1/11 pts with a DLT of Grade 4 neutropenia. The DCDT +RTX safety profile did not differ from DCDT alone. Among pts treated with DCDT ≥ 1.8 mg/kg and DCDT+RTX, treatment-emergent (TE) adverse events (AEs) in >15% of pts included fatigue (34%), diarrhoea (31%), nausea (28%), neutropenia (22%), anaemia (18%), constipation (16%), and decreased appetite (16%). TE Grade ≥ 3 AEs in >2 pts included neutropenia (18%), hyperglycemia (7%), and diarrhoea (5%); febrile neutropenia and infection occurred in 2% and 7% of pts. 33% pts experienced a serious AE. TE AEs related to peripheral neuropathy (PN) were reported in 17 (28%) pts (3 with Grade ≥ 3). Discontinuations for AEs were reported in 7 (17%) pts including 4 for PN. Two deaths judged unrelated to DCDT were reported. Exposure of Ab-conjugated (ac) MMAE, total Ab, and unconjugated MMAE increased with dose. Concentrations of unconjugated MMAE were >100-fold lower than those for acMMAE. RTX did not impact DCDT PK. Objective responses were observed in 9/30 (30%) DCDT and 5/15 (33%) DCDT+RTX pts. In R/R DLBCL, 6/17 responses (3 CR) were observed with DCDT and 3/8 (2 CR) with DCDT+RTX. In R/R iNHL, 3/11 responses (1 CR) and 1/5 response (CR) were observed with DCDT and DCDT+RTX respectively.
Conclusions: DCDT alone or combined with RTX was relatively well-tolerated with encouraging antitumour activity. Updates will be presented. A Phase II study of DCDT+RTX in R/R DLBCL and FL is ongoing.

040

PHASE I STUDY OF THE ANTI-CD79B ANTIBODY-DRUG CONJUGATE DCDS4501A IN RELAPSED OR REFRACTORY (R/R) B-CELL NONHODGKIN'S LYMPHOMA (NHL)

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DOI: 10.1002/hon

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DCDS4501A (DCDS), an anti-CD79b monoclonal antibody (Ab) conjugated to the anti-mitotic agent MMAE, had determined a recommended Phase II dose (RP2D) of 2.4 mg/kg every 21 days (q21d) with clinical activity in R/R B-cell NHL at doses ≥ 1.8 mg/kg. We continued to evaluated safety, tolerability, pharmacokinetics (PK) and activity of DCDS with or without RTX (375 mg/m,[2]) q21d in pts with R/R DLBCL and indolent (i)NHL.59 pts were treated with DCDS (6 at 1.8 mg/kg, 44 at 2.4 mg/kg) and DCDS +RTX (9, DCDS at 2.4 mg/kg). Median age 68 yrs (range 20–86); 90% ECOG PS <2; median 4 prior regimens (range 1–14); 97% had prior RTX; 29% had prior stem cell transplant.

The RP2D of DCDS+RTX was 2.4 mg/kg based on 1/9 pts with a DLT of Grade 4 neutropenia. The DCDS+RTX safety profile did not differ from DCDS alone. Treatment-emergent adverse events (AEs) included neutropenia (54%), diarrhoea (34%), pyrexia (34%), nausea (32%), AEs related to peripheral neuropathy (PN, 29%), thrombocytopenia (24%), and anaemia (20%). Grade ≥ 3 AEs, >2 pts included neutropenia (46%), thrombocytopenia (10%), anaemia (9%), hyperglycemia (7%), PN (5%), fatigue (5%) and diarrhoea (5%); febrile neutropenia and infection occurred in 5% and 10% of pts respectively. 36% pts reported a serious AE. Discontinuations for AEs were reported in 11 (19%) pts, 4 for PN. Four deaths unrelated to DCDS were reported. Ab-conjugated (ac) MMAE, total Ab, and unconjugated MMAE exposures increased with dose. Concentrations of unconjugated MMAE were >100-fold lower than those for acMMAE. RTX did not impact DCDS PK. Objective responses were observed in 22/40 (55%) DCDS and 7/9 (78%) DCDS+RTX pt. In R/R DLBCL, responses were observed in 8/22 (1 CR) treated with DCDS; none were treated with DCDS+RTX. In R/R iNHL, responses were observed in 7/12 (2 CR) treated with DCDS and 7/9 (1 CR) treated with DCDS +RTX. In R/R MCL, responses occurred in 4/4 pts and 1/3 pts treated with DCDS and DCDS+RTX respectively.

DCDS and DCDS+RTX were relatively well-tolerated, with neutropenia and PN being principal toxicities, and encouraging anti-tumour activity in heavily pretreated pts. Updates will be presented. A Phase II study of DCDS+RTX in R/R DLBCL and FL is ongoing.

041

THE EFFICACY AND SAFETY OF MOGAMULIZUMAB (KW-0761) IN MULTICENTRE PHASE II STUDY FOR PATIENTS WITH RELAPSED PERIPHERAL OR CUTANEOUS T-CELL LYMPHOMA

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Background: Mogamulizumab is a defucosylated humanized anti-CCR4 antibody with potent ADCC activity that has been approved for the treatment of relapsed/refractory CCR4-positive adult T-cell leukaemia-lymphoma in Japan. Based upon the results of a phase I study in Japan (J Clin Oncol 2010;28:1591) and a phase I/IIa study in the USA (ASH 2012), we evaluated the efficacy and safety of mogamulizumab in patients (pts) with peripheral T-cell lymphoma (PTCL) or cutaneous T-cell lymphoma (CTCL).

Methods: A multicentre phase II study in pts with relapsed CCR4-positive PTCL or CTCL who had received chemotherapy was conducted in Japan. The primary endpoint was objective response rate (ORR) and secondary endpoints included progression-free survival (PFS) and overall survival (OS). Pts received 1.0 mg/kg mogamulizumab intravenously once a week for 8 weeks. Responses were assessed after the 4th and 8th infusions of mogamulizumab by an independent efficacy assessment committee.

Results: A total of 38 pts were enrolled, and 37 pts {29 PTCL and 8 CTCL; 23 male (62%); median age 64 (range 33–80) years; median number of prior systemic chemotherapy regimens 2 (range 1–6)} received mogamulizumab. Of the 37 pts, 25 completed the scheduled 8 infusions. Nine pts discontinued because of progressive disease and 3 because of adverse events (AEs). ORR was 35% (13/37, 95% CI, 20 to 53), with complete response rate of 14% (5/37). In subgroup analysis, ORR in pts with PTCL and CTCL was 34% and 38%, respectively. Median PFS was 3.0 months (95% CI, 1.6 to 4.9), and median OS has not yet been reached. The most frequent grade 3/4 treatment-related AEs (TRAEs) were lymphopenia (73%), neutropenia (19%), leukopenia (14%) and skin disorders (11%). Fifteen severe TRAEs were observed in 8 pts, all of which improved. There was no treatment-related death or serious skin disorder.

Conclusions: Mogamulizumab showed promising antitumour activity with an acceptable toxicity profile in pts with relapsed PTCL or CTCL, warranting further investigation.

042

A PHASE I STUDY OF BISPECIFIC CD30/CD16A TANDAB ANTIBODY AFM13 IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

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AFM13 is a bispecific, tetravalent Tand Ab antibody construct designed for the treatment of Hodgkin Lymphoma (HL) and other CD30+ malignancies. AFM13 targets CD30 on HL tumour cells and recruits NK cells via CD16A. Preclinical data demonstrate specific and highly efficient anti-tumour activity by selectively recruited NK cells. This targeted immunotherapy addresses key deficiencies of antibodies: (i) reduced binding to the 158 F allotype of CD16A and (ii) non-selective binding to immune effector cells via both activating CD16A and non-signalling CD16B receptors. AFM13 was investigated in an open-label single-arm phase I dose escalation trial in heavily pre-treated patients with relapsed/refractory HL. The overall objective of this study was to evaluate the safety, tolerability, pharmacokinetics, antitumour activity and the maximum tolerated dose or optimal biological dose. Seven dose levels (0.01–7.0 mg/kg) were escalated in cohorts of three patients. Each patient received a cycle of four weekly doses and responders received a second cycle. All dose levels were well tolerated and safe, with grade 1–2 infusion reactions being the most frequent adverse event. AFM13 induced clinical benefit in 50% of patients and a reduction in tumour volume in a dose-response manner, demonstrating clinical activity of the drug. AFM13 mode of action was also analysed *ex vivo*. A significant dose-dependent increase in the activation of NK cells and a reduction in soluble CD30 levels demonstrated a correlation between antitumour activity and response biomarkers. A low level expression of CD30 on activated NK cells was observed in several patients. Because this has been reported elsewhere, we investigated whether it may affect NK cell cytotoxicity. The *ex vivo* evaluation of patient samples that received AFM13 and *in vitro* evaluation of activated NK cells demonstrated no inhibition of NK cell-mediated cytotoxicity. Furthermore, AFM13 exhibited a half-life of 1 day, which represented a substantial increase relative to that of alternative diabody-like formats currently being evaluated in the clinic for hematological malignancies. AFM13 has demonstrated encouraging biological activity and has a potential to become a new targeted therapy for heavily pre-treated patients with HL.

DOI: 10.1002/hon

'FOCUS ON...' SESSION: LYMPHOMA AND THE CNS

043

DEVELOPMENT OF NOVEL PATIENT-DERIVED XENOGRAFTS TO DISSECT THE PATHOGENESIS OF CNS LYMPHOMA

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Background. CNS manifestations of aggressive non-Hodgkin's Lymphoma are associated with serious morbidity and adverse prognosis. Primary CNS lymphomas (PCNSL) exhibit a dichomatous growth pattern, either dissemination within brain, typical at presentation, and/or leptomeningeal spread, common at relapse. Elucidation of the mechanistic basis of CNS lymphoma progression requires preclinical models that recapitulate their pathogenesis.
Methods: We developed a novel method to generate cell lines of CNS lymphoma that upon intracranial implantation recapitulate the disease. We are applying genomics, *in vitro* chemotaxis, preclinical testing of targeted therapies and neuroimaging to evaluate disease mechanisms of invasion and resistance.
Results: We developed 7 CNS lymphoma cell lines; 6 DLBCL (all ABC-type), 1 Burkitt; 5 from secondary CNS lymphoma (SCNSL), and 2 from PCNSL, of which 1 was treatment naïve. Intracranial implantation of lymphoma cells from these tumours within NSG mice provides a reproducible model to dissect the pathogenesis of CNS lymphomas. PCNSL specimens were 10X more efficient in CNS dissemination than SCNSL. High resolution array-CGH demonstrated that intracranial tumour growth was associated with retention of genomic aberrations of the original tumours (e.g. del 6q, gains on 12, etc). Infiltrative lymphomas expressed increased levels of MMP-7 transcripts. Therapeutic response to lenalidomide, minus and plus rituximab, was recapitulated in NSG mice, despite deficient T-cell and cytokine function. Metabolic imaging of model CNS lymphomas using magnetic resonance spectroscopy demonstrated significant intratumoural lactate production in the microenvironment, detectable before evidence of aberrant T2 signal and reduced diffusion. Lenalidomide reduced tumour expression of lactate dehydrogenase and lactate, consistent with an anti-proliferative effect.
Conclusions: To the best of our knowledge we have developed the first panel of patient-derived CNS lymphoma cell lines. We have used these to generate intracranial xenografts that provide a highly reproducible model system to dissect key elements of CNS lymphoma pathogenesis. We are using these models to identify genomic and metabolic aberrations predictive of early resistance to lenalidomide and other targeted therapies.

044

HIGH EFFICIENCY OF ICE (IFOSFAMIDE-CARBOPLATIN-ETOPOSIDE) IN RELAPSE/REFRACTORY PRIMARY CENTRAL NERVOUS SYSTEM AND INTRA-OCULAR NON-HODGKIN LYMPHOMA, AFTER FIRST LINE TREATMENT CONTAINING HIGH DOSES OF METHOTREXATE (MTX) AND CYTARABINE (ARAC). A MULTICENTRIC RETROSPECTIVE STUDY FROM 2010 TO 2012 ON 34 CASES. AN LOC NETWORK STUDY

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Background: Relapse and refractory primary central nervous system lymphoma (PCNSL) and primary intra-ocular lymphoma (PIOL) carry a very poor prognosis (i.e. 5 months, Jahnke J neurooncol, 2006). Because recent publications on first line treatment recommend high dose Mtx and AraC, salvage chemotherapy must use other drugs.
Methods: From June 2010 to November 2012, all relapse/refractory PCNSL and PIOL treated in first line by Mtx and AraC in two units of the Pitie-Salpetriere Hospital, Paris, France, and Rene Huguenin Center, St Cloud, France, were treated by ICE regimen: ifosfamide (5 g/m^2 at day 2), carboplatine (AUC 5 at day 2) and etoposide (100 mg/m^2/d days 1 to 3) every 3 to 4 weeks. Doses where adapted on patient general status and autologous stem cell transplantation (ASCT) proposed when possible.
Results: A total of 34 patients have been treated, 14 females and 20 males, median age 67 (28–84). Two received rituximab at day 1. Eight were refractory, 26 in relapse, with a mean progression-free survival of 300 days (38–1763), 11 had a second line and two a third before ICE. Localizations were 20 central nervous system (CNS), six CNS + spinal fluid, two CNS + PIOL, three PIOL and three spinal fluid. A total of 18 patients needed a dose reduction. During treatment, grade 3/4 WHO toxicities were 12 neutropenic fever (one death), 16 anaemia, 23 neutropenia, 23 thrombopenia and one CNS complication (coma and hypersalivation). ASCT have been made in 10 patients: seven in complete response (CR), two in partial response and one in CR after relapse post ICE. CR has been obtained in 19 patients (56%), partial in six, overall response 74%, with a mean follow-up of 502 days, 15/25 patients in response relapsed (only two after ASCT), median progression-free survival 90 days. A total of 21 patients died (19 by progression, one by pneumocystis in CR and one by sudden heart arrest in partial response). Median overall survival was 212 days for all patients but was not reached in case of ASCT [three deaths, only one by progression), mean follow up for surviving ASCT is 719 days (222–932)].
Conclusion: ICE regimen is very effective in relapse/refractory PCNSL and PIOL heavily treated by high dose Mtx and AraC, with a manageable toxicity. If ASCT is performed, overall survival is very high and relapses rare. ICE can represent a new standard in this setting.

045

RITUXIMAB, METHOTREXATE, PROCARBAZINE, VINCRISTINE AND INTENSIFIED CYTARABINE CONSOLIDATION FOR PRIMARY CNS LYMPHOMA (PCNSL) IN THE ELDERLY: AN LOC NATIONAL NETWORK STUDY (INCA)

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Introduction: Outcome of PCNSL remains poor, especially in older patients who develop a high rate of neurotoxicity with combined chemoradiotherapy and cannot be treated with intensive regimens. Methotrexate (MTX)-based chemotherapy needs therefore to be improved.
Methods: This retrospective, multicentre study analysed consecutive patients, aged over 60, suffering from newly diagnosed PCNSL, treated with the MPV-AAA regimen in five centres from December 2010 to December 2012. The MPV-AAA regimen corresponds to the established MPV-A regimen (Abrey et al, 2000) reinforced by 2 additional consolidation cytarabine cycles. The regimen consisted of three 28-day cycles of MTX (3.5 g/m^2 D1 and D15), procarbazine (100 mg/m^2 D1-7), vincristine (1.4 mg/m^2 D1 and D15), followed by three 28-day cycles of cytarabine consolidation (3 g/m^2 D1-2), associated with prophylactic G-CSF. Adding rituximab (375 mg/m^2 D1 and D15) was left at the discretion of each participating centre.
Results: 91 patients received the MPV-AAA regimen with rituximab (group A, $n = 40$ from 3 centres) or without (group B, $n = 51$ from 3 centres). Median age was 73 (range 61–87) in group A (vs 67 (range 60–83) in group B; $p = 0.02$) and median KPS was 60 in both groups (range 10–100). At time of analysis the median follow-up was 16.5 months. In group A, the objective response rate (CR+PR) was 79% [vs 54% in group B ($p = 0.04$)]; median PFS was 15.4 months in group A, 95% CI 5.9–25 m [vs 9.7 months, 95% CI 3.9–15.5 min group B; ($p = 0.8$)] and median OS was not reached in group A [vs 14.7 months, 95% CI 0–31.5 in group B ($p = 0.7$)]. Toxicity was mainly related to myelosuppression, with respectively 73%, 41% and 31% of grade III or grade IV lymphopenia, neutropenia and thrombopenia. Toxic deaths, all related to infectious complications, occurred in 7 patients in group A -[17%] - (vs 3 patients in group B -[6%]).
Conclusions: The MPV-AAA regimen seems comparable with the MPV-A regimen in term of efficacy (Omuro et al, abstract submitted, ASCO 2013). Rituximab might improve the objective response rate of MTX-based polychemotherapy at the price of a higher toxicity and warrants to be evaluated in prospective randomized trials.

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PHASE II TRIAL OF TEMSIROLIMUS FOR RELAPSED/REFRACTORY PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)

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DOI: 10.1002/hon

Introduction: Salvage treatment is poorly defined in PCNSL. This ongoing phase II study (NCT00942747) evaluates activity and toxicity of a temsirolimus (TEM) monotherapy in relapsed or refractory PCNSL and its penetration into cerebrospinal fluid (CSF).
Methods: Included are immunocompetent adults with PCNSL (histologically confirmed) after failure to high-dose methotrexate-based chemotherapy. The first cohort of six patients received 25 mg TEM, all following 75 mg TEM i.v. weekly. Primary endpoint is overall response rate (ORR), secondary endpoints are toxicity, progression-free survival (PFS) and CSF penetration of TEM and its metabolite sirolimus (SIR).
Results: Thus far, 28 of 37 patients planned with a median age 69 years (range, 43–81), median ECOG 2 (range, 0–3), and a median number of 2 previous treatment regimens (range, 1–5) have been enrolled. Median time from previous treatment to study treatment was 5 months (range, 0.7–14). Median number of TEM infusions is 8 (range, 1–28). Of 24 patients evaluable for efficacy 6 achieved a complete (CR) and 9 a partial response (PR) (ORR 63%); all but one responses were seen in the 75 mg dose group. Six patients had stable disease and 3 progressed. Median PFS is 2.2 months (95% CI, 1.3–3). Most frequent CTC≥IIIº events were: thrombocytopenia and hyperglycemia (each in 6 of 25 patients evaluable for toxicity), infection (pneumonia/pneumonitis) (5/25) as well as anaemia, neutropenia and rash/skin toxicity (3/25 each). One patient died after the first infusion due to cerebral haemorrhage while CTC IV thrombopenia. Fourteen blood/CSF pairs were collected in 9 patients (25 mg cohort: 10 pairs in 5 patients; 75 mg cohort: 4 pairs in 4 patients). Mean maximum blood concentration was 292 ng/ml for TEM and 37.2 ng/ml for SIR in the 25 mg cohort and 484 ng/ml (TEM) and 91.1 ng/ml (SIR) in the 75 mg cohort. No drug was detected in CSF (lower limit of detection 1 ng/ml) in either cohort.
Conclusions: Single agent TEM at a weekly dose of 75 mg shows surprisingly high activity in relapsed/refractory PCNSL, however, with notable toxicity. Neither TEM nor SIR was detected in the CSF.

047

A NEW PROGNOSTIC MODEL TO ASSESS THE RISK OF CNS DISEASE IN PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMA

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Introduction: Relapse or progression in the central nervous system (CNS) is a rare but mostly fatal event in patients (pts) with aggressive B-cell lymphoma. Identification of risk factors for CNS disease is necessary in order to decide which patients should undergo specific diagnostic, prophylactic, or therapeutic procedures.
Methods: We identified 2164 pts with aggressive B-cell lymphoma, 18–80 years of age, who had been treated with modern therapies including rituximab (R) and CHO(E)P. All pts were treated on prospective studies of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) and represent all age groups and IPI scores. A risk model was developed separating these pts into three risk categories for the development of CNS disease: rate of CNS disease at 2 years ≤1% (no necessity for diagnostic or prophylactic procedures), 2–10% (diagnostic procedures necessary), >10% (diagnostic and prophylactic procedures necessary). IPI factors, specific extranodal sites (Schmitz et al., Haematologica 2012; 97 (s1)), and other factors (B-symptoms) indicating a high risk of CNS disease in univariate analyses were entered into multivariable analyses in order to describe risk factor combinations the presence of which should trigger CNS-directed diagnostic and prophylactic measures.
Results: The final risk model for CNS disease we propose includes the following clinical factors: age > 60 years, LDH > N, stage 3 or 4, ECOG > 1, and involvement of the kidney. These five factors were used to separate three risk categories as defined in the methods section: 1104 pts (51%) with 0 or 1 factors had a 2-year rate of 0.6% (95% CI 0.2–1.0%), 945 pts (44%) with 2 or 3 factors had a 2-year rate of 4.1% (95% CI 2.7–5.5%) and 113 pts (5.2%) with 4 or 5 factors had a 2-year rate of 17.0% (95% CI 9.4–24.6%) for the development of CNS disease.
Conclusions: We propose a new prognostic model predicting the risk of secondary CNS disease in pts with aggressive B-cell lymphoma. This model identifies pts who do not need any diagnostic or prophylactic procedures (low risk group, rate of CNS disease ≤1%), pts who should have modern diagnostic workup including MR of the brain and FACS analysis of CSF (intermediate risk, rate of CNS disease 2–10%), and a small high risk group (rate of CNS disease at 17.0% at 2 years) members of which should have all available diagnostic work up and CNS-directed therapy possibly even without definitive proof of CNS disease.

048

EXTRALYMPHATIC CRANIOFACIAL DIFFUSE LARGE B-CELL LYMPHOMA: ROLE OF RADIOTHERAPY AND INTRATHECAL CNS PROPHYLAXIS

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Introduction: The role of radiotherapy and intrathecal prophylaxis in extralymphatic craniofacial involvement of aggressive B-cell lymphoma remains to be determined in the rituximab era.
Methods: In a retrospective subgroup analysis of nine consecutive prospective DSHNHL trials covering all diffuse large B-cell lymphoma risk groups from 18 to 60 years of age, patients with and without craniofacial involvement were compared with respect to clinical presentation, event-free and overall survival.
Results: A total of 336 sites of extralymphatic craniofacial involvement were observed in 284/3840 (7.4%) patients (orbita: 30, paranasal sinuses: 90; main nasal cavity: 38, tongue: 26, remaining oral cavity: 99, salivary glands: 53). In a multivariable analysis adjusting for international prognostic index risk factors, the addition of rituximab improved event-free survival and overall survival in both patients with and without craniofacial involvement. The 141 responding patients who received radiotherapy to sites of craniofacial involvement had a similar 3-year event-free (79% vs 79%; $p = 0.835$) and 3-year overall survival (88% vs 85%; $p = 0.311$) when compared with the 56 patients who did not receive radiotherapy. Without rituximab, the 2-year-rate of cumulative risk of central nervous system (CNS) disease was increased in 205 patients compared with 2586 patients without craniofacial involvement (4.2% vs 2.8%; $p = 0.038$), whereas this difference disappeared in patients who received CHOP(like) chemotherapy in combination with rituximab (1.7% in 77 patients compared with 2.9% in 946 patients without craniofacial involvement; $p = 0.868$). Of the 85 patients with craniofacial involvement who received intrathecal prophylaxis with methotrexate, the 2-year-rate of cumulative risk of CNS disease was 4.3% compared with 2.3% in 189 patients who did not ($p = 0.995$).
Conclusion: Rituximab eliminates the increased risk for CNS disease in patients with craniofacial involvement. As a practical consequence intrathecal prophylaxis and radiotherapy to sites of craniofacial involvement should not be given any more.

SESSION 2—CLL BIOLOGY

049

ASSOCIATION BETWEEN MOLECULAR LESIONS AND SPECIFIC B-CELL RECEPTOR SUBSETS IN CHRONIC LYMPHOCYTIC LEUKAEMIA

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Background: Genetic lesions and B-cell receptor (BCR) signalling are both oncogenic drivers in chronic lymphocytic leukaemia (CLL). However, little is known regarding the association between specific genetic aberrations and distinct stereotyped BCR subsets.
Methods: Mutations (TP53, NOTCH1, SF3B1, BIRC3, MYD88), chromosomal abnormalities (del13q, +12, del11q, del17p, BIRC3 deletion), and BCR

DOI: 10.1002/hon

stereotypy were investigated in 1419 newly diagnosed CLL. Associations between genetic lesions and BCR features were assessed by non-parametric binomial test and multiple hypothesis correction.
Results: Two BCR subsets, namely subset 2 (IGHV3-21) and 8 (IGHV4-39), showed distinctive patterns of genetic alterations. Subset 2 CLL were significantly enriched in SF3B1 mutations (52% of cases; $p < 0.001$). Conversely, SF3B1 mutations occurred at low prevalence in IGHV3-21 CLL with heterogeneous BCR (13%; $p = 0.002$). Subset 2 CLL lacked TP53 abnormalities, thus pointing to SF3B1 as the main driver of progressiveness in this subset. Consistently, subset 2 CLL harbouring SF3B1 mutations showed a higher probability of being treated at 5 years (67%) compared with subset 2 CLL with wild type SF3B1 (38%; $p = 0.064$) and to IGHV3-21 CLL with heterogeneous BCR (46%; $p = 0.076$). Subset 8 CLL were significantly enriched in +12 (87% of cases; $p < 0.001$) and NOTCH1 mutations (62% of cases). Conversely, +12 and NOTCH1 mutation prevalence was significantly lower in IGHV4-39 CLL with non-stereotyped BCR (27%; $p = 0.003$ and 8%; $p = 0.006$, respectively). The majority (62%) of subset 8 CLL had transformed to Richter syndrome (RS). All transformed cases carried both NOTCH1 mutations and +12, although this genetic association was never observed in non-transformed patients ($p = 0.017$).
Conclusions: These data suggest that: i) synergy of SF3B1 mutations and subset 2 BCR configuration promotes disease progression in IGHV3-21 CLL; and ii) cooperation between NOTCH1 mutations, +12, and subset 8 BCR configuration primes RS transformation in IGHV4-39 CLL. Taken together, our observations provide a proof of concept that specific BCR configurations may contribute to clonal selection of specific genetic lesions influencing CLL outcome.

050

MICRORNA MIR-150 CONTRIBUTES TO THE DISEASE AGGRESSIVENESS AND REGULATION OF B-CELL RECEPTOR SIGNALLING (BCR) IN CHRONIC LYMPHOCYTIC LEUKAEMIA

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Introduction: We and others have shown that expression of certain miRNAs associates with disease activity and pathogenesis of chronic lymphocytic leukaemia (CLL) (Calin et al. 2005; Mraz et al. 2012; Mraz et al. 2009). In this study, we screened TaqMan miRNA Cards (750 miRNAs) for abundantly expressed miRNAs in CLL cells hypothesizing that miRNAs with strong expression are more likely significantly involved in the regulation of key cell functions.
Results: We identified miR-150 as the most abundant miRNA in CLL cells and observed that its lower levels directly associated with stronger response to stimulation of B-cell receptor (BCR) on CLL cells with anti-IgM ($p < 0.05$, $n = 36$). To describe the genes regulated by miR-150, we performed microarray-based transcriptome analyses of 110 CLL samples. This identified differential expression of two genes with evolutionary conserved binding sides for miR-150 (GAB1 and FOXP1) between CLL cells expressing low versus high levels of miR-150. The immunoblot analysis of GAB1 and FOXP1 in CLL cells confirmed their higher protein levels in cases with low miR-150 expression ($p < 0.005$, fold change >10.0), and the transfection of CLL cells with artificial miR-150 led to GAB1/FOXP1 downregulation. GAB1 is an adaptor molecule that recruits PI3K to the cell membrane after BCR stimulation and is required for amplification of PI3K signalling and AKT activation (Ingham et al. 2001). FOXP1 is a transcription factor implicated in B-cell development and the progression of several B-cell lymphomas (Hu et al. 2006). Importantly, CLL cells with higher expression of GAB1 or FOXP1 were more responsive to BCR stimulation *in vitro* and higher expression of each associates with shorter overall survival (13.9 vs 22.7 years, 13.9 vs 21.1 years; $n = 168$; $p < 0.05$). Most notably, a reverse trend was observed for miR-150, where higher levels (>median) were associated with significantly longer overall survival (not-reached versus 13.9 years, $n = 168$, $p = 0.006$) in a multivariate analysis, which included other six routinely used prognostic markers. Additionally, we have noted differences in the methylation profile of miR-150 coding region after disease progression (serial CLL samples).
Conclusions: We conclude that miR-150 is a novel regulator of genes that control BCR-signalling, which is a factor that prominently affects the biology of malignant B-cells.
IGA MZCR NT11218-6/2010, FR-TI2/254.

051

IDENTIFICATION OF CIRCULATING CHRONIC LYMPHOCYTIC LEUKAEMIA INTRACLONAL SUBGROUPS WITH VARYING B-CELL RECEPTOR FUNCTION

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Introduction: Chronic lymphocytic leukaemia (CLL) is a tumour of circulating B-cells, variably stimulated and anergized following exposure to antigen in lymphoid tissues. Downmodulation of surface IgM (sIgM) occurs but expression and signal capacity can recover *in vitro*, and apparently *in vivo* during recirculation. Levels of sIgM may be critical to tumour cell behaviour and sensitivity to clinically relevant BCR-signalosome inhibitors.
Methods: A bead-bound anti-IgM assay was developed to discriminate and investigate phenotype and function of single CLL cells with different sIgM levels. Expression of Ig light chain, CD19, CD5, CD38, CD25 and CXCR4 and intracellular Ki67 were determined in flow cytometry. BCR signalling analysis of phosphorylated PLCgamma2 or ERK1/2 was determined by Phosflow in the presence or absence of clinical BTK inhibitor ibrutinib.
Results: individual circulating clones of CLL cases could be dissected into subgroups (SGs) according to sIgM expression level by differential binding to bead-bound anti-IgM. Four clear SGs 1 to 4 with increasing sIgM were identified in 37/37 cases. Engagement of sIgM induced phosphorylation of PLCgamma2 and ERK1/2 at levels ranging from very low in SG1 to high in SG4. Phosphorylation was suppressed by the BTK inhibitor ibrutinib. Expression of CXCR4 also increased from SG1 to SG4 but markers of activation and proliferation were dominant in SG1. Incubation of whole CLL populations *in vitro* led to striking increases in CXCR4 expression, as well as recovery of sIgM.
Conclusion: Clonal analysis reveals dynamic SGs following presumed antigen stimulation in tissues. SG4 represents a fully recovered, potentially dangerous population equipped to migrate to tissue and to receive a proliferative stimulus. SG1 likely represents a post-mitotic unresponsive 'resting' population. The suppressive effect of ibrutinib on the small SG4 population may be the critical factor in therapeutic success.

052

IMPACT OF INITIAL CLINICOBIOLOGICAL FEATURES, INCLUDING GENETIC MUTATIONS, IN THE DEVELOPMENT OF ACCELERATED CHRONIC LYMPHOCYTIC LEUKAEMIA OR TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA IN CLL

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Introduction: In CLL proliferation takes place mainly in the lymph node compartment. The presence of enlarged or highly active proliferation centres (PC), define accelerated CLL and correlates with poor survival. The aim is to analyse the impact of initial clinicobiological factors on the appearance of accelerated CLL or DLBCL transformation.
Methods: We studied 166 of 951 CLL patients (1990–2012) with available tissue biopsy. Histological review identified 104 standard CLL (63%), 37 accelerated CLL (22%) and 25 transformed cases (15%). The initial genetic features, including IGVH mutational status, NOTCH1, SFB3 and MYD88 mutations along with FISH data were assessed in peripheral blood.
Results: The initial clinical, histological and biological features according to the histological diagnosis are summarized in Table 1. Accelerated CLL were associated with an unmutated IGVH ($p = 0.035$), 17p deletion ($p = 0.017$), ZAP-70 ($p = 0.007$) and elevated LDH ($p = 0.016$) at diagnosis, whereas DLBCL transformation was associated to NOTCH1 mutation ($p = 0.025$) and a high beta-2-microglobulin ($p = 0.04$).

DOI: 10.1002/hon

Abstract 052 Table 1.

	Conventional CLL	Accelerated CLL	DLBCLt
Age	60	55	60
Binet (B/C)%	42	25	50
LDH (>450 UI/L)%	16	26	16
Beta2-microglob. (2.4 mg/L)%	47	54	63
Unmutated IGVH%	60	86	69
Mutated NOTCH1%	18	24	43
Mutated SF3B1%	18	7	10
Mutated MYD88%	0	0	0
Adverse cytogenetic (17p&11q del)%	41	33	40
ZAP-70 (≥20)%	50	83	75
CD38 (≥30)%	56	67	62
Time to biopsy (months)	32	34	53
Biopsy:	0	92	—
Expanded PC	0.6 (0–2.1)	2.4 (0.1–12)	—
Mitoses/PC (median, range)	10 (0–40)	40 (3–75)	—
Ki-67/PC (median, range)			
Survival from biopsy (median, CI95%, months)	87 (67–106)	33.7 (24–43)	5 (3.5–5.5)

IGVH in 95, MYD88 in 104, NOTCH1 in 97, SF3B1 in 70 and FISH in 76 cases. SFbx among groups was statistically different (p<0.001).

Conclusions: Different biological characteristics correlate with the development of accelerated CLL or DLBCL transformation, reinforcing the hypothesis that these are two distinct events in CLL with a negative impact on survival.

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CLINICAL IMPACT OF MUTATIONS IN GENES OF THE TOLL-LIKE RECEPTOR (TLR/MYD88) PATHWAY IN CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

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Introduction: Next generation sequencing has provided information on the spectrum of somatic mutations in CLL revealing the high heterogeneity of the disease. Mutations in TLR/MYD88pathway might affect the microenvironment by releasing prosurvival cytokines that can influence the clinical course of the disease. The aim of this study was to analyse the clinical and biological features of patients with CLL that have mutations in the TLR/MYD88 pathway.

Methods: mutations in MYD88,IRAK1, IRAK2, IRAK4, TLR2, TLR5, and TLR6 were investigated by whole-exome sequencing and Sanger analysis in 589 patients (354 M/235 F; median age 61 years). The clinical and biological features of these patients were analysed according to the mutational status of the genes.

Results: 23 of 589 (3.7%) patients had mutations in genes of this pathway: 17 patients in MYD88, 1 in both MYD88 and IRAK1, 1 patient in IRAK1, 1 in TLR2, 1 patient in TLR2 and TLR6, and 2 in TLR5. No mutations were found in IRAK2 or IRAK4. Patients with mutations in the TLR/MYD88 pathway were younger, had more frequently mutated IGHV, low expression of CD38 and ZAP-70, and normal values of B_2M. IgM monoclonal band was not observed in any mutated patient. TLR/MYD88 mutated patients have a significantly better OS (10-year: 94% vs 61%, $p = 0.006$), even when the analysis was restricted to patients younger than 50 years ($n = 147$, 10-year: 100% vs 68%, $p = 0.01$).

Conclusions: CLL patients with mutations in genes of the TLR/MYD88 pathway are diagnosed at younger age, showed favourable biological prognostic factors and had better outcome.

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OVER-EXPRESSION OF TP53 MRNA IN CHRONIC LYMPHOCYTIC LEUKAEMIA IS ASSOCIATED WITH LOW 13Q14 COPY NUMBER, REDUCED MIR-15A/16-1 LEVELS AND ADVERSE OUTCOME

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Abstract 053 Table 1.

Parameter	Category	Unmutated ($n = 566$)	Mutated ($n = 23$)	p
Age (years) median (range)		61 (24–94)	47 (32–72)	<0.0001
Binet stage	A/B/C	462/84/18	17/3/3	0.045
$Beta_2$microglobulin	High	196/478 (41%)	1/19 (5%)	0.001
IGHV	Unmutated	214/470 (45%)	3/21 (14%)	0.006
CD38	High	168/502 (33%)	2/23 (9%)	0.02
ZAP-70	High	167/473 (35%)	2/23 (9%)	0.02
10-year OS(95% CI)	All	61% (57–67)	94%(84–100)	0.006

DOI: 10.1002/hon

Introduction: TP53 mutation/deletion is strongly associated with adverse outcome in chronic lymphocytic leukaemia (CLL) and is accompanied by the under-expression of mRNA encoding TP53 and other genes on chromosome 17p (Lin et al, Br J Haemtol 2013;160:53). We speculated that TP53 mRNA levels might be reduced in other patients through alternative mechanisms, resulting in reduced p53 protein expression and adverse clinical outcome.
Methods: TP53 mRNA levels were measured by RT-qPCR in 104 CLL samples (including 15 with TP53 deletion and/or mutation) and related to p53 protein levels measured by flow cytometry, 13q14 copy number measured by FISH, overall survival (OS) and treatment-free survival (TFS). miR-15a and miR-16-1 levels were measured by qPCR in 12 CLL samples selected on the basis of high or low 13q14 copy number.
Results: TP53 mRNA levels varied widely among the 104 CLL samples analysed and were markedly increased in 18 samples (17%), all without TP53 deletion/mutation. The latter cases had a shorter OS ($p = 0.048$) and TFS ($p = 0.057$) compared with those with lower TP53 mRNA levels and no TP53 mutation/deletion. Furthermore, there was no correlation between TP53 mRNA levels and p53 protein expression. We speculated that the adverse outcome associated with high TP53 mRNA levels might reflect variation in the expression of miR-15a and miR-16-1 which are encoded at the minimum deleted region at 13q14 and include TP53 among their targets. In keeping with our hypothesis, 13q14 copy number correlated negatively with TP53 mRNA levels ($r = -0.43$, $p < 0.001$) and positively with miR-15a and miR-16-1 levels ($r = 0.64$, $p = 0.024$ and $r = 0.69$, $p = 0.013$, respectively), whereas the latter correlated negatively with TP53 mRNA levels ($r = -0.63$, $p = 0.027$ and $r = -0.51$, $p = 0.094$, respectively).
Conclusion: TP53 mRNA levels vary widely between individual CLL samples, high levels being associated with low 13q14 copy number, reduced levels of miR-15a/miR-16-1 and short survival. The adverse outcome associated with high TP53 mRNA levels most likely results from deletion of tumour suppressor genes at 13q14 and/or reduced miR-15a/miR-16-1 expression with consequent loss of oncogene repression.

SESSION 3—ADVANCES IN THE CLINICAL MANAGEMENT OF CLL

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DEVELOPMENT OF A COMPREHENSIVE PROGNOSTIC INDEX FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

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Introduction: Besides clinical staging, a number of biomarkers predicting overall survival (OS) in CLL have been identified. The multiplicity of markers, limited information on their independent value and a lack of understanding of how to interpret discordant markers are major barriers to use in routine clinical practice.
Methods: We performed a comprehensive analysis of 23 clinical and biological markers based on a dataset collected between 1997 and 2006 in 3 German CLL Study Group (GCLLSG) phase III trials to develop a novel prognostic index for previously untreated CLL patients (pts). An external validation was performed on a series of newly diagnosed CLL pts managed and prospectively observed at Mayo Clinic.Results: The GCLLSG dataset (1948 physically fit pts at early and advanced stage; median age 60 years (yr) (range 30–81); median observation time 63.4 months) was used as a training dataset. 7 parameters were identified as independent predictors for OS: sex, age, ECOG status, del 17p, del 11q, IGHV mutation status, thymidine kinase and β_2-microglobulin. By using a weighted grading of independent factors a prognostic score and index were derived separating 4 different pts risk groups: low risk (score 0–2), intermediate risk (score 3–5), high risk (score 6–10) and very high risk (score 11–14) with significant different OS rates and a C-statistic c = 0.75 [95.2%, 86.9%, 67.7% and 18.7% OS rates after 5 year for the low, intermediate, high and very high risk group respectively ($p < 0.001$)]. The validation cohort comprised of 676 newly diagnosed, previously untreated pts from the Mayo Clinic (median age 61.5 yr (range 32–89); median observation time 47.0 months). The 4 risk groups were reproduced with 98.3%, 95.4%, 75.4% and 10.8% OS rates after 5 yr. The prognostic index predicts OS independent of Rai/Binet stages and provides accurate estimations regarding time to first treatment (TTF).
Conclusions: By using a multi-step process including external validation, we developed a comprehensive prognostic index combining clinical, serum, and molecular information into a single risk score for pts with untreated CLL. The prognostic index provides more accurate prediction of both TTF and OS. To our knowledge this is the first prognostic model in CLL to reach the C-statistic threshold (c > 0.70) necessary to have utility at the level of the individual.

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OBINUTUZUMAB (GA101)+CHLORAMBUCIL (CLB) OR RITUXIMAB (R) + CLB VERSUS CLB ALONE IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) AND PRE-EXISTING MEDICAL CONDITIONS (COMORBIDITIES): FINAL STAGE 1 RESULTS OF THE CLL11 (BO21004) PHASE 3 TRIAL

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Introduction: Chemoimmunotherapy (CIT) is standard of care in young and physically fit patients (pts) with CLL. Development of CIT for older and less fit CLL pts is ongoing, but data from phase 3 trials are sparse. CLL11 is the largest trial to evaluate 3 treatments in previously untreated CLL pts with comorbidities: Clb alone, GA101 + Clb (GClb), R + Clb (RClb). The final analysis of CLL11 stage 1 efficacy and safety results is presented here.
Methods: Treatment-naïve CLL pts with a Cumulative Illness Rating Scale (CIRS) total score >6 and/or an estimated creatinine clearance (CrCl) <70 mL/min were eligible. Pts received Clb alone (0.5 mg/kg p.o. d1, d15 q28 days, 6 cycles), GClb (100 mg iv d1, 900 mg d2, 1000 mg d8, d15 of cycle 1, 1000 mg d1 cycles 2–6), or RClb (375 mg/m^2 iv d1 cycle 1, 500 mg/m^2 d1 cycles 2–6). Primary endpoint was investigator-assessed progression-free survival (PFS).
Results: Median age, CIRS score, and CrCl at baseline were 73 y, 8, and 61.1 mL/min for stage 1a (Clb vs GClb, 356 pts) and 73 y, 8, and 62.1 mL/min for stage 1b (Clb vs RClb, 351 pts, triggered by a different event rate). Key efficacy and safety results are below:
Conclusions: CIT with GClb or RClb significantly prolongs PFS vs Clb alone. The results demonstrate that GClb and RClb are very active in CLL and superior treament options in this population. GClb vs RClb will be compared in stage 2 analysis with more follow-up available.

DOI: 10.1002/hon

Abstract 056 Table 1.

	Stage 1a		Stage 1b	
	Clb	GClb	Clb	RClb
Total stage 1 *N* = 589	***N* = 118**	***N* = 238**	***N* = 118**	***N* = 233**
Median observation time, months	13.6	14.5	14.2	15.3
Overall response rate, %	30.2	75.5	30.0	65.9
Complete responses, %	0	22.2	0	8.3
Median PFS, months	10.9	23.0*	10.8	15.7
HR, CI, p	0.14, 0.09–0.21, <.0001		0.32, 0.24–0.44, <.0001	
Grade 3–5 adverse events during treatment, %	41	67	41	46
Infusion-related reaction	—	21	—	4
Neutropenia	15	34	15	25
Infections	11	6	11	8

* still immature, <20% at risk at time of median

Grade 3–4 infusion-related reactions with GClb occurred at first infusion only. Management required splitting the first dose over 2d.

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UPDATED RESULTS OF A PHASE I FIRST-IN-HUMAN STUDY OF THE BCL-2 INHIBITOR ABT-199 (GDC-0199) IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

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Background: Targeting BCL-2 is a promising strategy for treating chronic lymphocytic leukaemia (CLL), including disease refractory to fludarabine (F), or with del(17p). ABT-199 is a selective BCL-2 inhibitor with >500-fold higher affinity for BCL-2 (K_i <0.10 nM) than for BCL-X_L (K_i = 48 nM).

Methods: Objectives of this Ph 1 dose-escalation study include evaluations of safety, pharmacokinetics and preliminary efficacy of ABT-199 in patients (pts) with R/R CLL. A single oral dose was given followed by 6 days off drug, before continuous once daily dosing. After cohort 1, the initial dose was reduced and daily dosing modified to include a 2 or 3 step dose escalation to the target dose for each cohort.

Results: As of 11 January 2013, 56 pts have been enrolled (median age 67 year (range 36–86), 41 males and median 3.5 prior therapies (range 1–10)). There are 16 (29%) pts who had del(17p) and 18 (32%) F-refractory CLL. Median follow up is 6.3 months (range 0.03–16.5); 7 pts have been on study for more than 1 year. There are 13 pts discontinued, seven due to progressive disease and six for other reasons: tumour lysis syndrome (TLS; 2), other illness (2), thromboembolic event (1) and consent withdrawal (1). The most common non-hematological adverse events (AEs) (>15% pts) were nausea (36%), diarrhoea (30%), fatigue (25%), upper respiratory tract infection (23%) and cough (16%). Grade 3/4 AEs occurring in >5 pts were neutropenia 21 (38%), thrombocytopenia 6 (11%) and TLS 5 (9%). TLS occurred in 3/3 pts in cohort 1 and 2/53 pts with the modified stepped dosing schedule (dose-limiting toxicities). Additionally, one fatal AE occurred within 48 h of dose escalation to 1200 mg in a pt with laboratory evidence of TLS (dose-limiting toxicity). A total of 46 of 54 pts (85%) evaluable for efficacy achieved a response to ABT-199; 7 (13%) a CR or CR with incomplete count recovery and 39 (72%) a PR (30 confirmed by consecutive scans). 14/16 (88%) and12/16 (75%) of pts with del(17p) and F-refractory CLL, respectively, achieved at least a PR.

Conclusions: ABT-199 is highly active achieving an 85% overall response rate in R/R CLL, independent of high risk markers such as del(17p) and F-refractory disease. Additional dosing and scheduling modifications are currently being explored to minimize the risk of TLS (study status see clinicaltrials.gov NCT01328626).

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CORRELATION BETWEEN TP53 MUTATION OR DELETION AND EFFICACY WITH SINGLE-AGENT LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY (REL/REF) CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) (CC-5013-CLL-009 STUDY)

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Introduction: The immunomodulatory agent lenalidomide has shown single-agent activity in untreated or relapsed/refractory (rel/ref) CLL patients (pts), including pts with CLL lacking functional TP53, which is associated with poor outcomes in response to chemotherapy. Lenalidomide targets the microenvironment to restore functional immunity to drive the elimination of leukemic cells. Here, we report the efficacy of lenalidomide monotherapy in high risk rel/ref CLL pts.

Methods: This phase 2, multi-centre, double-blind, parallel-group adaptive design study evaluates the safety and efficacy of lenalidomide in pts with rel/ref CLL. Pts were randomized 1:1:1 to receive oral lenalidomide at a starting dose of 5, 10, or 15 mg daily on days 1–28 of their initial 28-day cycle, followed by intra-patient dose escalation in 5 mg increments every 28 days, up to 25 mg/day as tolerated. Samples to determine genetic status were collected at entry and analysed centrally.

Results: 103 pts were dosed and median age was 63.6 years (32–81). Currently, response data are available for 94 pts. Del(17p) and TP53 mutation were found in 21/87 (24.1%) and 36/92 (39.1%) pts, respectively. Del(17p) was seen in 3/56 (5.4%) pts without TP53 mutation, and 11/36 (30.6%) pts with TP53 mutation (5 TP53 mutation pts did not have results for del(17p) status). TP53 mutation showed an association with the following baseline clinical and laboratory characteristics, i.e. pts were more likely to have del(17p) (41.7% vs 5.5%), >65 years of age (69.4% vs 38.2%), high risk/Binet C (52.7% vs 34.6%), ALC>30 (58.3 vs 38.2),HgB <11 (44.4% vs 18.2%) and platelet count <150 (72.2% vs 36.4%). Del(17p) pts were more likely to have TP53 mutation (71% vs 55%), high risk/Binet C (66% vs 33%), Hgb <11 (52% vs 21%), and platelet count <150,000/mm^3 (76% vs 44%). The overall response rate (ORR) was 38.5% for all evaluable pts, 40.0% for pts without TP53 mutation, and 35.1% for pts with TP53 mutation. The ORR for pts with del(17p) was 22.7%. Conclusion: Single-agent lenalidomide treatment led to similar responses in rel/ref CLL pts with or without TP53 mutations, indicating that the activity of this agent in pts with CLL is not affected by loss of functional TP53.

DOI: 10.1002/hon

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EVIDENCE THAT ALLOGENEIC TRANSPLANTATION (ALLOHCT) CAN IMPROVE THE NATURAL COURSE OF POOR-RISK CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL): FINAL RESULTS FROM A RETROSPECTIVE DONOR VERSUS NO DONOR COMPARISON

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The aim of this study was to investigate if alloHCT can improve the dismal natural course of poor-risk CLL by performing for the first time a donor vs no-donor comparison.
Patient andStudy Design: In a single centre retrospective analysis, course and outcome of all patients with CLL referred between June 2005 and June 2012 for evaluation of alloHCT indication were assessed. Eligible were those patients who had a donor search indication according to the EBMT criteria or because of Richter's transformation. Patients for whom a 9/10 or 10/10 matched donor could be found within 3 months (D) were compared with patients without such a donor (ND). Primary endpoint was overall survival (OS) measured from the 3-month landmark after donor search initiation.
Results: Of 134 patients referred (median age 54 (37–70) years), an indication for donor search was seen in 113 (84%). In 8 of these a donor search was not performed because of refusal or comorbidity. Of the 105 patients who had a donor search initiated, 8 died or got lost before the 3-month landmark, leaving 97 patients evaluable (D 83; ND 14). D and ND patients were comparable for age, gender, time from diagnosis, number of previous regimens, and remission status at referral. Although only 63 of the 83 (76%) D patients were actually transplanted, survival prognosis was significantly better in the 83 D patients (hazard ratio 0.38, 95% CI 0.17–0.85; $p = 0.014$; estimated 2-year OS from the 3-month landmark 78% compared with 55%). The survival benefit of patients with a donor remained significant after Cox modelling stratified for EBMT indication and adjusting for possible prognostic covariates ($p = 0.026$). The only other variable significantly predicting poor OS from the 3-month landmark was a high number of pretreatment lines, whereas age and remission status at referral had no significant impact. Multivariate Andersen-Gill modelling to account for alloHCT as time-dependent intervention also confirmed the favourable effect of alloHCT on OS.
Conclusions: This study provides the first comparative evidence that alloHCT indeed may have the potential to improve the natural course of poor-risk CLL.

SESSION 4—FOLLICULAR LYMPHOMA

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THE STRUCTURE OF STEPWISE CLONAL EVOLUTION EVENTS SHAPING FOLLICULAR LYMPHOMA CODING GENOMES

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Background: Follicular lymphoma (FL) is currently incurable with conventional regimes and an attractive candidate for targeted therapies. We hypothesized that a hierarchy of mutations exists in FL and could impact opportunity for targeted therapies. In support of this, we recently reported subclonal dynamics in distinct FL tumour subpopulations (Green et al, Blood 2013). Here, we present definitive evidence for these evolution models in characterizing significantly more tumours at diagnosis and relapse of FL.
Methods: We examined clonal diversity in tumour subpopulations through a genetic analysis of their coding genomes and transcriptomes. We profiled whole-exomes of 82 flow sorted subpopulations from 24 FL patients, including tumours at diagnosis ($n = 24$), or at 1st ($n = 18$), 2nd ($n = 5$) or 3rd ($n = 1$) relapse/progression with or without intervening therapies.
Results: In a cohort of patients with serial biopsies ($n = 42$ tumours; 0.2–14 yrs between diagnosis/relapse, median 4.7 yrs) we identified new mutations, clonal dynamics, and relationships to natural history and intervening therapies. Using BCL2 translocations and phylogenies from ongoing immunoglobulin VH hypermutation at diagnosis and relapse as a framework for comparing mutational hierarchies, we resolved early versus late somatic events during tumour evolution. Surprisingly, subclonal representation was common in several genes thought to be drivers of pathogenesis including MLL2 and TNFRSF14, but not CREBBP which was invariably clonally dominant. We observed contrasting patterns of clonal evolution, reflecting either maintenance or loss mutations at relapse. In a discovery cohort ($n = 10$), we identified 877 somatic coding mutations in 569 unique genes, with an average of 103 mutations/case. Mutated genes were significantly enriched for those involved in chromosome and chromatin organization (FDR<0.001). We identified many novel genes not previously implicated in FL including TLR1, CD40, NOTCH1, IKZF2, CALR, NBPF14, ROS1 and ERBB2. Clonal dominance and recurrence frequency of these and other novel mutations within a validation cohort of 96 cases will be presented.
Conclusions: These observations establish a framework for a stereotyped hierarchy in genetic evolution during progression of FL and provide evidence for BCL2 translocations and CREBBP mutations as early events, with MLL2 and TNFRSF14 mutations as late events during disease evolution.

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THE STRUCTURE OF STEPWISE CLONAL EVOLUTION EVENTS SHAPING FOLLICULAR LYMPHOMA CODING GENOMES

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Background: Follicular lymphoma (FL) poses a clinical challenge with a progressive course typified by multiple relapses, eventual resistance to standard therapies and transformation (tFL) in a subset of patients to the more aggressive diffuse large B-cell lymphoma (DLBCL). Our current knowledge of the ontogeny, clonal dynamics of progression and recurring genetic events in FL are limited.
Methods: Paired-end whole genome sequencing (WGS) was performed on 6 paired FL-tFL cases with matched germline DNA (mean coverage 37x). The selection criterion was the availability of at least one preceding FL biopsy, a subsequent tFL and identical BCL2-IGH rearrangements confirming clonality. Prevalence screening was performed by targeted sequencing using Fluidigm-Miseq (mean 560x) on 16 genes in an additional 30 paired FL-tFL, and 100 independent diagnostic and/or relapse cases.
Results: Phylogenetic analyses identified two distinct evolution patterns. In 5 of the 6 cases, a high clonal semblance was observed between the paired FL-tFL biopsies (40–87%; mean 65%), compatible with successive relapse and transformation events arising from a dominant ancestral common progenitor cell (CPC) population, termed a 'rich' CPC. One solitary case harboured a unique pattern where only 4 non-synonymous mutations were shared, that we termed a 'sparse' CPC. In this case, distinct MLL2 and TNFRSF14 mutations occurred in both FL and tFL biopsies, appearing to emerge from independent clones supporting convergent evolution. Importantly, we observed mutations harboured within putative CPCs appeared to fall into 6 key functional pathways. Genes involved in chromatin regulation and immune modulation has previously been reported. In this analysis, we identify 4 new pathways commonly deregulated in both FL and tFL: B-cell development, JAK-STAT, BCR and NOTCH signalling. Targeted resequencing in genes that form two of these pathways, JAK-STAT signalling (STAT6, SOCS1, STAT3) and B-cell development pathways (EBF1, IKZF3, KLHL6) revealed mutations in 25% and 21% of the extension cases, respectively.
Conclusion: This study provides unequivocal evidence of a reservoir CPC population that is resistant to our current therapies and proposes that personalizing therapies to strategically target key genetic alterations within this ancestral clone represents an attractive therapeutic approach.

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MANAGING STAGE I–II FOLLICULAR LYMPHOMA WITH UPFRONT DEFINITIVE RADIATION THERAPY: THE FORTY-YEAR EXPERIENCE OF THE PRINCESS MARGARET CANCER CENTRE

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DOI: 10.1002/hon

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Introduction: Radiation therapy (RT) has traditionally been the therapeutic choice for patients (pts) with early-stage follicular lymphoma (FL). However, the expanding list of effective systemic therapy options has challenged this paradigm. This study describes the long-term outcomes of a consistent policy of definitive RT for stage I–II FL.
Methods: Through an institutional prospectively-maintained database, we identified pts diagnosed with stage I–II FL between 1967–2006 treated with RT for curative intent (dose ≥20 Gy). Outcome measures include: response to treatment, site of relapse, survival, and use and timing of chemotherapy as second-line therapy. Probabilities of death due to FL and relapse were estimated using competing risk approach.
Results: For the study period, 708 pts with stage I–II FL received definitive RT. Median follow-up for surviving pts was 12.5 years. 182 pts (26%) received combined modality therapy (CMT) upfront, 61.5% with CHOP-based chemotherapy. Pts receiving CMT were more likely to have stage II, grade 3, abnormal LDH or larger lymph node/extra-nodal disease at presentation. For the 526 pts treated with RT alone (median dose: 31 Gy, range: 20–47 Gy), complete response rate (CR/CRu) was 98.7%. Relapse rate at 10 years was 51.3% for the RT-alone group, and was significantly influenced by stage, tumour bulk and grade (univariate analysis). Crude rates of local and marginal relapse were 4.2% and 1.7%. For the 288 pts who relapsed or progressed after radiation alone, only 45.1% required chemotherapy at 10 years post-diagnosis (10-year post-relapse rate: 47.6%); the remaining pts were managed with further RT or observation. For all pts, 10-year overall survival was 65% (CMT: 66%; RT alone: 65%), and 10-year cause-specific survival was 80% (CMT: 79%; RT alone: 81%). 49 pts had biopsy-proven transformation to a more aggressive histology, for a crude transformation rate of 14.6% among relapsing pts (median time to transformation: 5.9 years).
Conclusions: RT alone is a good initial treatment for localized FL; although half of pts relapse within 10 years, a substantial proportion did not require systemic therapy and have prolonged survival.

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

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Background: On the basis of the activity of lenalidomide plus rituximab (LR) in patients with previously treated follicular lymphoma (FL), we conducted a multicentre phase 2 trial in untreated patients to better evaluate the efficacy and toxicity.
Methods: Patients with untreated FL, grade 1–3a, stage 3–4 or bulky stage 2, FLIPI 0–2, were eligible. Treatment consisted of lenalidomide 20 mg/day on days 1–21 of a 28-day cycle for 12 cycles plus rituximab administered weekly x 4 on cycle 1 and day 1 of cycle 4, 6, 8, and 10. Restaging occurred on weeks 10, 24, and 52, then q4 mo. for 2 years and q6 mo. until progression. Primary outcomes were RR and PFS.
Results: Sixty-six patients were enrolled. Three patients did not receive protocol treatment and were dropped from analyses. The median age was 53 y; 49.2% were male; 31% were FLIPI<2. Grade 3–4 toxicity that occurred in >5% of patients included neutropenia (20%), lymphopenia (8%), rash (8%), fatigue (6%), and leukopenia (5%). Grade 2+ toxicity in >5% of patients included fatigue (25%), infusion reaction (17%), upper respiratory reaction (13%), nausea (8%), constipation (7%), increased ALT (7%), hyperglycemia (7%), hypophosphatemia (7%), pain (6%), oral mucositis (5%), and myalgia (5%). Febrile neutropenia occurred in 1 patient (2%). Fifty-one patients (81.0%) completed 12 cycles of lenalidomide. Reasons for early termination included adverse events (6) and patient refusal (5). One patient stopped due to disease progression after initial response. Among the 54 patients with adequate data to evaluate response, the RR was 92.6%, including 39 (72.2%) complete responses (CR) and 11 (20.4%) partial responses; 2 (3.7%) were stable and 2 (3.7%) did not respond. The 2 non-responders stopped treatment early due to adverse events. CR was not associated with FLIPI, grade, or bulky disease. With a median follow-up of 1.3 y, 6 patients have progressed.
Conclusion: The combination of LR was well tolerated in patients with untreated FL, with the majority of patients completing planned therapy. The overall and CR rates were comparable with published chemotherapy-containing regimens and met predefined criteria for further study. Longer follow-up will be required to evaluate PFS.

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SALVAGE CHEMOTHERAPY (SC) AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR TRANSFORMED INDOLENT LYMPHOMA (TR): A SUBGROUP ANALYSIS OF NCIC CTG LY12

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Background: The treatment of indolent lymphoma which at relapse has transformed to an aggressive histology (TR) often includes SC and ASCT. Current data on outcomes are limited to retrospective and registry reports. NCIC CTG LY12 is a prospective, randomized phase III trial comparing gemcitabine, dexamethasone, cisplatin (GDP) to dexamethasone, cytarabine, cisplatin (DHAP) prior to ASCT. This analysis compares the results of SC and ASCT for TR with de novo diffuse large B-cell lymphoma (DL).
Methods: From 8/2003 to 11/2011, 619 patients (pts) with relapsed/refractory aggressive NHL were stratified by centre, IPI risk factors at relapse, immunophenotype, response duration and prior rituximab (R) treatment, and randomized to outpatient GDP or standard DHAP. Pts with documented TR who had received <3 regimens prior to transformation were eligible. Responding pts after 2–3 cycles proceeded to ASCT. The protocol was amended 11/2005 to include R SC for pts with CD20+ lymphoma.The main analysis of LY12 showed the response rate (RR) to GDP was non-inferior to DHAP; this dataset was used to compare RR, EFS and OS between pts with TR and DL.
Results: Of 619 enrolled pts, 89 (14%) had TR and 428 (71%) had DL. Baseline characteristics at entry are shown in Table 1. The RR to salvage chemotherapy was 54% in TR and 54% in DL ($p = 0.93$); there was no interaction between study arm and histology. Transplantation rates were similar: TR: 52%; DL: 52% ($p = 0.91$). Toxicities were also similar in TR and DL. With a median follow-up of 53 months, 4 y OS was 38% for TR and 41% for DL ($p = 0.61$); 4 y EFS was 26% for TR and 27% for DL ($p = 0.97$). For pts undergoing ASCT, 4 y EFS was 45% for TR and 46% for DL. Histology (TR or DL) was not a predictor of outcome in multivariate models of RR, PBSC mobilization, ASCT rate, OS or EFS.
Conclusions: Patients with relapsed or refractory TR lymphoma and DLBCL have similar outcomes with SC and ASCT.

Abstract 064 Table 1.

	TR	DL
n	89	428
Median age, y	56	55
Stage III–IV	79%	67%
LDH > N	58%	55%
>1 EN site	25%	26%
Prior rituximab	67%	76%
Refractory to primary Rx	26%	31%

DOI: 10.1002/hon

064 bis

INTERIM RESULTS FROM A PHASE 2 STUDY OF PI3Kd INHIBITOR IDELALISIB IN PATIENTS WITH RELAPSED INDOLENT NON-HODGKIN LYMPHOMA (INHL) REFRACTORY TO BOTH RITUXIMAB AND AN ALKYLATING AGENT

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Introduction: Patients with iNHL who are refractory to both rituximab and alkylating agents have few or no meaningful treatment options and are poorly studied to date. PI3K-delta signaling is critical for activation, proliferation and survival of B cells, and is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective, oral inhibitor of PI3Kδ with considerable activity in recurrent iNHL in a phase 1 trial (Kahl, ICML 2011). We have performed an interim analysis of an ongoing Phase 2 study that is evaluating idelalisib monotherapy in this highly refractory iNHL population.

Methods: Eligible pts included those with iNHL documented by imaging to be refractory to both rituximab and an alkylating agent and measurable disease. Idelalisib 150 mg PO BID is administered continuously until disease progression. Responses are evaluated by an independent central radiology and clinical review using standard criteria (Cheson, 2007). The datacut for this analysis is 16 weeks after the last patient enrolled in October 2012.

Results: Enrolled pts (n = 125) were 64% male, median age [range] of 64 [33-87] years. Indolent subtypes included 72 FL, 28 SLL, 10 LPL/WM, and 15 MZL. The median [range] number of prior therapies (most commonly BR and R-CHOP) was 4 [2-12], with 79% of pts refractory to ≥2 regimens and 74% refractory to their last regimen. Median time since completion of last regimen was 4.2 months. The overall response rate (ORR) is 50.4% (95% CI = 41.3, 59.5) with 5 CRs (4%), 58 PRs (46%), and 50 SD (40%). ORR for iNHL subtypes is: FL (49%), SLL (64%), LPL/WM (30%), and MZL (47%). ORR for pts with ≥4 therapies is 54% and for bendamustine refractory patients is 60%. Among responders, median duration of response is 11.9 months at this analysis. Median PFS for all pts is 11.4 months. The most common adverse events are (total%/≥G3%) diarrhea (37/10), fatigue (28/2), cough (26/0), nausea (22/2), pyrexia (22/1), and dyspnea (17/3). Based on central laboratory measurements, Grade ≥3 ALT/AST elevations have occurred in 13%. Grade ≥3 neutropenia occurred in 26%, thrombocytopenia in 6%, and anemia in 2%. Marrow function generally improved over time. 16% of pts have discontinued due to adverse events.

Conclusions: At this interim analysis, idelalisib has demonstrated remarkable efficacy with favorable safety in a well-defined, heavily pretreated, highly refractory population of patients with iNHL.

SESSION 5—TARGETING THE BCR-NFkB PATHWAYS

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THE IKB FAMILY MEMBER NFKBIZ REGULATES NF-KB SIGNALLING AND IS CRITICAL FOR SURVIVAL OF ABC DLBCL

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Introduction: The activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) is characterized by constitutive activation of the oncogenic NF-kB pathway. However, it still remains unclear how the expression of specific sets of NF-kB target genes is regulated in this lymphoma subtype.

Methods and Results: To obtain insights in NF-kB target gene regulation, we screened a gene expression cohort of 350 ABC and germinal centre B-cell-like (GCB) DLBCL patient samples to identify regulators of NF-kB signalling that are differentially expressed between these two subtypes. We identified NFKBIZ to be among the top genes to distinguish ABC and GCB DLBCL with NFKBIZ being highly expressed in ABC DLBCL ($p = 3.2 \times 10,^{-35}$) suggesting a role in the pathogenesis of this entity. NFKBIZ that encodes an IkB-like protein binds NF-kB subunits and enhances transactivation of some NF-kB target genes while repressing others. To functionally investigate the role of NFKBIZ, we knocked down its expression using specific shRNAs. Intriguingly, NFKBIZ downregulation was toxic to ABC but not to GCB DLBCL cell lines. To obtain further insights into the function of NFKBIZ, we profiled gene expression changes following NFKBIZ downregulation. Interestingly, NFKBIZ knockdown significantly downregulated a large number of known NF-kB target genes and previously described NF-kB gene signatures, implying that NFKBIZ is required for NF-kB signalling in ABC DLBCL. To understand how NFKBIZ interacts with NF-kB, we performed co-immunoprecipitations and detected an interaction of NFKBIZ with both p50 and p52 NF-kB subunits indicating that both the canonical and non-canonical NF-kB pathways are regulated by NFKBIZ. To determine which NFKBIZ target genes are regulated by the interaction with p50 and p52 respectively we separately knocked down p50 and p52 and performed gene expression profiling. By this approach, we identified a specific network of genes regulated by NFKBIZ/p50/p52 by which ABC DLBCL survival is mediated.

Conclusion: Collectively our data indicate that NFKBIZ regulates specific sets of NF-kB target genes in ABC DLBCL. We show that ABC DLBCLs depend on NFKBIZ signalling suggesting that it might serve as a potential molecular target for patients with ABC DLBCL.

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PRELIMINARY SAFETY AND EFFICACY OF IPI-145, A POTENT INHIBITOR OF PHOSPHOINOSITIDE-3-KINASE-δ,-g, IN PATIENTS WITH RELAPSED/REFRACTORY B-CELL LYMPHOMA

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Background: PI3-kinases are pivotal in cell signalling and regulate multiple cellular functions relevant to oncogenesis. IPI-145, a potent oral inhibitor of the PI3K-δ and PI3K-γ isoforms, is being developed in patients (pts) with hematologic malignancies. Early Phase 1 results in pts with B-cell lymphoma (BCL) are presented here.

Methods: This dose-escalation study evaluates the safety, maximum tolerated dose (MTD), clinical activity, and pharmacokinetics (PK)/pharmacodynamics (PD) of IPI-145. IPI-145 is given orally twice daily (BID) in 28-day cycles. Tumour response is based on standard disease-specific criteria. Expansion cohorts (EC) at ≤ the MTD are

DOI: 10.1002/hon

enrolling results overall, 65 pts have been dosed with IPI-145, including 31 pts with BCL (HL $n=3$, MCL $n=4$, aNHL $n=6$, iNHL $n=18$). The MTD was declared at 75 mg BID after 2 pts dosed at 100 mg BID experienced a dose-limiting toxicity in Cycle 1 (Grade [Gr] 3 rash, Grade 3 ALT elevation). PK predicts that IPI-145 at 25 mg BID inhibits PI3K-δ (>IC90) with increasing inhibition of PI3K-γ at steady state. BCL pts received doses between 15 mg to 100 mg BID; the median [range] number of cycles was 4 (1–13) and 48% remain on study. Treatment-related adverse events (TRAEs) occurred in 77% of pts with BCL.The most common ≥ Gr 3 TRAEs were neutropenia (23%) and elevated ALT (16%) with no association with increasing dose. TRAEs of interest include pneumonitis, pneumonia, colitis (each Gr 3), and pneumocystis pneumonia (Gr 5). Among the 29 evaluable pts with BCL (all dosed at ≤75 mg BID), the best ORR was 52% (4 CR, 11 PR) with 8 SD and 6 PD; in the subset of evaluable indolent BCL pts ($n=17$) the best ORR was 65% (2 CR, 9 PR) with 5 SD and 1 PD. Median time to response across all BCL pts was 1.8 months and all responses occurred within 3 months of first dose.

Conclusions: IPI-145 appears well tolerated and has shown clinical activity with rapid responses in pts with relapsed/refractory advanced BCL across the dose range examined. The MTD has been determined at 75 mg BIDand an EC at this dose is now enrolling BCL pts. Updated safety, efficacy, and PK/PD data from the 25 mg and 75 mg BID ECs will be presented.

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A PROSPECTIVE, MULTICENTRE, PHASE II STUDY OF THE BRUTON'S TYROSINE KINASE INHIBITOR IBRUTINIB IN PATIENTS WITH RELAPSED AND REFRACTORY WALDENSTROM'S MACROGLOBULINEMIA

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Introduction: MYD88 L265P is a mutation present in >90% of Waldenstrom's Macroglobulinemia (WM) patients that supports tumour growth via signalling involving Bruton's Tyrosine Kinase (BTK). Ibrutinib inhibits BTK, and *in vitro* induces apoptosis of WM cells bearing MYD88 L265P. In a Phase I study, 3 of 4 WM patients achieved durable partial responses (PR). We therefore initiated this trial to delineate the efficacy and tolerability of ibrutinib in relapsed or refractory WM.

Patients and Methods: Symptomatic WM patients who received at least 1 prior therapy were eligible. Intended therapy consists of 420 mg of oral ibrutinib daily for 2 years or progression or unacceptable toxicity.

Results: 35 patients including 12 with refractory disease were enrolled; 32 are currently evaluable for response and toxicity. Median baseline characteristics are the following: age 63, prior therapies 2 (range 1–6), hematocrit 30.8%, haemoglobin 10.6 g/dL, serum IgM 3190 mg/dL, serum M-protein 2.08 g/dL, B_2M 4.35 mg/L, bone marrow (BM) disease involvement 70%. At best response, median serum IgM levels and M-protein declined to 1,710 mg/dL and 0.89 g/dL, respectively ($p<0.00001$). Median hematocrit and haemoglobin rose to 38.1% and 13.1 g/dL, respectively ($p<0.00001$). 16 patients had a 6 month BM assessment showing tumour reduction from median of 80% to 50% ($p=0.006$). The best overall response rate using criteria adapted from the Third International WM Workshop is 81.3% (3 VGPR; 15 PR, 8 MR). Median time to response (MR or better) was 4 weeks. 5 patients have stable disease. Grade >2 treatment related toxicities include thrombocytopenia ($n=5$; 15.6%) and neutropenia ($n=3$; 9.3%). With a median follow-up of 18 weeks, 33 patients remain on study. Reasons for discontinuation included non-response ($n=1$) in a patient with wild type MYD88, and MDS/RAEB ($n=1$) in a heavily pre-treated patient who attained VGPR, but who had 5q deletions pre-dating protocol therapy.

Conclusions: Ibrutinib is a targeted, highly active and well-tolerated single agent therapy for patients with relapsed and refractory WM. Rapid reductions in serum IgM and improved red blood cell production occur in most patients.

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COMBINATIONS OF THE PI3Kd INHIBITOR IDELALISIB (GS-1101)WITH RITUXIMAB AND/OR BENDAMUSTINE ARE TOLERABLE AND HIGHLY ACTIVE IN PATIENTS WITH PREVIOUSLY TREATED, INDOLENT NON-HODGKIN LYMPHOMA (INHL): UPDATED RESULTS FROM A PHASE I STUDY

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Introduction: PI3K-delta signalling is critical for activation, proliferation and survival of B-cells, and is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective, oral inhibitor of PI3K-delta that has shown considerable monotherapy activity in recurrent iNHL (Kahl, ICML 2011) as well as combination therapy (Fowler, ASCO 2012).

Methods: This phase 1 study evaluated the activity of continuous (48 weeks) idelalisib (Id), 100 or 150 mg BID, in combination with rituximab (R) (375 mg/m,^{2} weekly ×8 doses) (Id+R), with bendamustine (B) (90 mg/m,^{2} ×2, for 6 cycles) (Id+B), or in combination with R (375 mg/m,^{2} on Day 1) and B (90 mg/m,^{2} ×2), for 6 cycles (Id+BR). Investigators assessed response according to standard criteria (Cheson 2007). Patients who continued to benefit were able to enrol on an extension study.

Results: Study enrolled 79 patients with relapsed/refractory iNHL, with 34 (43%) patients continuing on treatment in the extension protocol. The 3 cohorts included Id+R ($N=31$), Id+B ($N=34$) and Id+BR ($N=14$). Patients were 66% male, median age (range) of 63 (37-84) years, 41% with refractory disease, 89% stage III/IV, and 35% high FLIPI scores. The median (range) number of prior therapies was 3 (1-12). The median (range) duration of treatment was 10.2 (0.5–29.2) months. Overall response rate (ORR) was 64/79 (81%), with 21/79 (27%) CR. The ORR/CR for Id+R was 74%/19%, Id+B was 88%/27%, and Id+BR was 79%/43%. At 20 months, the PFS was 66%. For responders, 72% are progression free at 20 months. Most common adverse events included (total%/≥G3%) pyrexia (56/4), fatigue (43/4), nausea (42/0), rash (39/8), cough (35/0), diarrhoea (35/8), chills (18/0), URI (19/1), and pneumonia (17/15). Lab abnormalities included (total%/≥G3%) ALT/AST elevations (57/18).

Conclusions: Idelalisib-based combination therapy is highly active and well tolerated in patients with relapsed/refractory iNHL. These data support further clinical development. Phase 3 trials evaluating the efficacy of idelalisib in combination with R or BR in iNHL are ongoing (NCT01732913, NCT01732929).

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PHASE 1B STUDY COMBINING IBRUTINIB WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE (R-CHOP) IN PATIENTS WITH CD20-POSITIVE B-CELL NONHODGKIN LYMPHOMA (NHL)

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Background: Ibrutinib, a first-in-class oral Bruton's tyrosine kinase inhibitor, has demonstrated single-agent activity in a variety of relapsed or refractory B-cell malignancies with limited toxicity, making it an appropriate drug to combine with standard R-CHOP chemotherapy in patients with previously untreated NHL.

Methods: Patients received a daily oral dose of ibrutinib (280, 420, or 560 mg) in combination with standard doses of R-CHOP (rituximab,

DOI: 10.1002/hon

cyclophosphamide, doxorubicin, and vincristine on day 1, and prednisone on days 1 through 5 of each 21-day cycle for up to 6 cycles). The primary objective was to determine the recommended phase 2 dose (RP2D) of ibrutinib in combination with standard R-CHOP (IR-CHOP). Secondary objectives were to assess safety, overall response rate, pharmacokinetics, and pharmacodynamic biomarkers.
Results: Seventeen patients (7, 4, and 6 in increasing ibrutinib doses) were enrolled: 59% male, median age 65 (range 46–81) years, diffuse large B-cell lymphoma 47%, mantle cell lymphoma 29% and follicular lymphoma 24%. In the 280 mg cohort, 2 patients had dose-limiting toxicity (DLT): 1 with transient syncope and 1 with periorbital cellulitis; at 560 mg, 1 patient had gastritis (grade 2). The RP2D was established at 560 mg ibrutinib. The most common (≥ 20% of patients) adverse events (AEs) were neutropenia (77%), thrombocytopenia (65%), vomiting (59%), anaemia (53%), nausea (47%), fatigue (35%), headache (29%), constipation (24%), diarrhoea (24%), and dizziness (24%). To date, 6 patients completed 6 cycles of treatment, and 2 patients discontinued treatment (1 due to noncompliance with study drug and 1 due to non-DLT AE). At the time of this analysis, of the 10 patients with at least one post-baseline tumour assessment, the overall response rate was 100% (7 complete and 3 partial responses).
Conclusion: The combination of IR-CHOP has an acceptable safety profile. No new toxicities were noted with adding ibrutinib to R-CHOP. An expanded 560 mg ibrutinib cohort (RP2D) is being opened to further explore the safety and efficacy of IR-CHOP in patients with newly diagnosed diffuse large B-cell lymphomas.

SESSION 6—PATHOLOGY AND CLINICOPATHOLOGIC CORRELATIONS

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CLASSIFICATION OF NON-HODGKIN LYMPHOMA IN SIX GEOGRAPHIC REGIONS AROUND THE WORLD: REVIEW OF 4539 CASES FROM THE INTERNATIONAL NON-HODGKIN LYMPHOMA CLASSIFICATION PROJECT

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Introduction: The relative distribution of non-Hodgkin lymphoma (NHL) subtypes varies around the world, but a large comparative study has not been done. Therefore, we evaluated the relative frequencies of NHL subtypes in six regions of the world.
Methods: Five expert hematopathologists classified 4848 consecutive cases of NHL from 25 countries in six regions, including North America (NA), Central/South America (CSA), Europe (E), Southern Africa (SA), the Middle East/North Africa (ME), and the Far East (FE), using the WHO classification, and the results from the five latter regions were compared with NA. Results: Among the 4848 cases, 4539 (93.6%) were confirmed to be NHL, whereas the other 309 (6.4%) cases were diagnoses other than NHL and were excluded from further analysis. Compared with NA, all regions had significantly higher rates of misdiagnosed cases ($p < 0.05$). Higher M:F ratios were found in ME (1.8:1) and FE (1.7:1) compared with NA (1.1:1; $p < 0.05$). The median age at diagnosis was significantly lower in all regions (SA 45 yrs, ME 52 yrs, FE 53 yrs, CSA 58 yrs, and E 60 yrs) compared with NA (65 yrs; p 0.05). The proportions of B-NHL and T-NHL were similar to NA in all regions except FE, where increased T-NHL was observed. Four regions (CSA, SA, ME, and FE) had significantly more high-grade B-cell lymphomas compared with NA ($p < 0.05$). Diffuse large B-cell lymphoma was more common in CSA (40.5%), SA (40.8%), ME (49.4%), and FE (50.5%) than in NA (29.3%), whereas follicular lymphoma was lower in all five regions (9.4–20.7%) compared with NA (33.6%). Mantle cell lymphoma was less common in SA (2%) and ME (2.2%), and marginal zone lymphoma, MALT type, was lower in ME (2.7%). Burkitt-like lymphoma was particularly high in SA (10.1%) due to the AIDS epidemic, and CSA (3.0%) and FE (5.2%), had a high frequency of extranodal NK/T-cell NHL.
Conclusion: Our study is the first to systematically compare the relative frequencies of NHL subtypes around the world, and provides new evidence of significant geographic differences. Our findings suggest that differences in etiologic and/or host risk factors may be responsible, and epidemiologic studies are needed to better understand these differences.

071
SPLENIC DIFFUSE RED PULP LYMPHOMA HAS A DISTINCT PATTERN OF SOMATIC MUTATIONS AMONGST B-CELL MALIGNANCIES

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Background: Among splenic lymphomas with circulating cells presenting cytoplasmic projections, a homogeneous clinicopathological entity has been recently individualized as Splenic Diffuse Red Pulp Lymphoma (SDRPL) and introduced in the provisional «unclassifiable splenic lymphoma» category until more is known. Few studies described it and its relationship with other splenic lymphoma, especially with splenic marginal zone lymphoma, hairy cell leukaemia and hairy cell leukaemia-variant remains controversial. However, the distinction is important because the therapeutic approaches are distinct. Recent discovery of specific mutations in those entities or the recently described positive immunological marker CD180 in SDRPL may help to further assess the differential diagnosis.
Methods: To better understand this pathology, we investigated in a retrospective clinicopathological series of 42 SDRPL the immunoglobulin heavy variable gene sequence and for the first time the presence of BRAF V600E, Notch2 (exons 26, 27, 34), MyD88 L265P and TP53 (exons 2 to 11) gene mutations described as characteristics or recurrent in other splenic lymphomas. Genomic DNA was extracted from frozen peripheral blood or splenic samples and studied by direct sequencing or sensitive BRAF V600E high resolution melting analysis. Cases were selected on the presence of circulating lymphoid cells with a characteristic villous morphology and specific immunological profile including high CD180 expression assessed by flow cytometry. CD180 was also evaluated by immunohistochemistry on paraffin embedded spleen samples.
Results: Detailed clinicopathological review confirmed in a large cohort of patients previous description (Traverse-Glehen A et al, Blood 2008). Molecular analyses showed a particular IGHV mutational pattern with a low load of somatic mutation and overrepresentation of IGHV3-23 and IGHV4-34 without statistical significant clinicopathological correlation and without pronostic significance. Any cases were mutated for the other genes analysed. CD180 was strongly expressed in all cases as assessed by immunohistochemistry and also by flow cytometry.
Conclusion: These results: strengthen the concept that SDRPL does emerge as a new lymphoma entity with clinicopathological and molecular features distinct from the other splenic lymphomas.

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IN SITU FOLLICULAR LYMPHOMA: A GENETIC VIEWPOINT

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Introduction: Follicular lymphoma (FL) pathogenesis is a multi-hit process, starting with the hallmark t(14;18) translocation and escalating over many years throughout the accumulation of additional genetic alterations. However, oncogenic drivers associated with the malignant transformation of t(14;18) cells in 'healthy' individuals and symptomatic patients are to date unknown. Here, we sought to characterize such hits in rare histological entities representing distinct stages of early FL development and associated with variable rates of FL progression.
Methods: BCL2 germinal centres from a series of FL *in situ* (FLIS), partial involvement by FL (PFL), primary FL of the duodenum (DFL) cases, and overt FL controls were purified by laser capture micro-dissection when necessary, and

DOI: 10.1002/hon

genome-wide high-resolution 244 K comparative genomic hybridization microarrays was performed.
Results: Surprisingly, we found that numerous small and large (10kb–300Mb) alterations covering large sets of genes were present in all FL precursors (including FLIS), indicating that increased genomic instability is already at work and clonally tolerated in those cells. Among relevant genes and pathways, those related to the germinal centre reaction, oncogenes and tumour suppressors could be identified, including recurrent FL-related hits (e.g. BACH2, TNFRSF14). This suggests that (onco)genes that assumed to play major roles in (adverse) FL pathogenesis can be acquired very early in FL development and that selective pressure has already started to shape the genetic landscape of these early clonal proliferations. This was particularly apparent in PFL, in agreement with its postulated status as a manifestation of FL proper. However, notably, PFL had fewer genomic aberrations than FL but showed significant differences from FLIS and DFL, consistent with their known low progression rates.
Conclusions: Altogether, by further delineating distinctive and hierarchical molecular and genetic features of FLIS, DFL and PFL, our analysis adds to the importance of applying appropriate criteria for differential diagnosis. It also provides a first set of candidate gene alterations likely involved in the cascade of hits paving the various progression phases of early FL development, and which could be explored in prospective studies as innovative therapeutic targets adapted to early, asymptomatic FL.

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T(14;18) TRANSLOCATION: A PREDICTIVE BLOOD BIOMARKER FOR FOLLICULAR LYMPHOMA

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Introduction: The (14;18) translocation constitutes both a genetic hallmark and critical early event in the natural history of Follicular Lymphoma (FL). However, t(14;18) is detectable in the blood of otherwise healthy persons, and the relationship with progression to disease remains unclear. Here we sought to determine whether t (14;18) cells in healthy individuals represent tumour precursors, and if their detection could be used as an early predictor for FL.
Methods: Among 520,000 healthy participants enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, we identified 62 subjects who developed FL 2–315 months later. Prediagnostic blood from these and 143 controls were screened for t(14;18) by sensitive PCR-based assays, and clonal relationships between t(14;18) cells and FL were assessed by molecular backtracking of paired prediagnostic/tumour samples.
Results: Clonal analysis of t(14;18) junctions in prediagnostic blood versus paired tumour demonstrated that progression to FL occurred from t(14;18) precursors. Furthermore, data revealed that subjects who developed FL up to 10 years later showed a markedly higher t(14;18) prevalence and frequency than controls ($p < 10-3$). We estimate a 15-fold higher risk of subsequent FL in blood samples associated with high frequency (95% CI, 4.34 to 57.04; $p = 2.7 \times 10,^{-5}$). Remarkably, no significant frequency bias was observed close to diagnosis, and risk estimates remained significant irrespective of time to disease outcome (<6 years, OR, 18.2; 95%CI, 4.6 to 71.7; $p < 0.001$; >6y, OR,16.5; 95%CI, 3.2 to 85.6, $p = 0.001$).
Conclusions: High t(14;18) frequencies in blood from healthy individuals define the first predictive biomarker for lymphoma, effective years before diagnosis.

074
THE HOST GENETIC BACKGROUND MODULATES TREATMENT ACTIVITY AND TOXICITY IN FOLLICULAR LYMPHOMA: FIL-FOLL05 TRIAL

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Introduction: Though most follicular lymphoma (FL) biomarkers rely on tumour features, the host genetic background may also be relevant for outcome. Here we aimed at verifying the contribution of single nucleotide polymorphisms (SNPs) to prognostic stratification of FL treated with immunochemotherapy.
Methods: The study was based on 428/504 (85%) FL enrolled in the FOLL05 prospective trial comparing R-CVP vs R-CHOP vs R-FM as initial treatment. SNPs were selected because known to be relevant for: i) immunochemotherapy outcome or toxicity (MLH1 rs1799977, GSTA1 rs3957357, CYBA rs4673, NCF4 rs1883112, FCGR2A rs18011274, FCGR3A rs396991); ii) FL course (6p21.33 rs6457327). SNPs were genotyped on peripheral blood DNA samples. Primary endpoint was time to treatment failure (TTF).
Results: FCGR2A and FCGR3A, which have been suggested to influence rituximab single agent activity, did not affect TTF in the pooled analysis of the three FOLL05 treatment arms that combined rituximab with chemotherapy ($p = 0.742$ and $p = 0.252$, respectively). These results were consistent also after compensating for treatment received and FLIPI by multivariate analysis ($p = 0.793$ and $p = 0.490$, respectively). MLH1, which regulates the genotoxic effect of doxorubicin, affected TTF in the R-CHOP arm ($p = 0.011$), but not in arms lacking doxorubicin (R-CVP, $p = 0.298$; R-FM, $p = 0.601$). MLH1 impact on TTF was independent ($p = 0.004$) after adjusting for FLIPI by multivariate analysis. Concerning toxicity, both FCGR2A, which modulates rituximab binding to effector cells, and GSTA1, which is involved in cyclophosphamide detoxification, correlated with G3-4 neutropenia ($p = 0.026$ and $p = 0.018$, respectively).
Conclusions: These data indicate that: ii) MLH1 associates with outcome in FL treated with R-CHOP, thus providing a more general and prospective validation of the usefulness of this host-related biomarker in R-CHOP treated lymphomas; i) FCGR2A and FCGR3A have no impact when FL is treated with rituximab plus chemotherapy; iii) GSTA1 and FCGR2A may represent biomarkers for the identification of FL patients at risk of severe neutropenia.

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STUDY ON THE BIOLOGY AND TREATMENT OF MEDIASTINAL GREY ZONE LYMPHOMA

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Mediastinal grey zone lymphomas (MGZL) are tumours with morphologic and immunohistochemical features intermediate between those of classical Hodgkin lymphoma nodular sclerosis subtype (CHL-NS) and primary mediastinal B-cell lymphoma (PMBL). Due to their rarity, their clinicopathologic characteristics are poorly described and the optimal therapeutic approach is unknown. Historically, MGZLs were mostly categorized as anaplastic large cell lymphoma, Hodgkin like (ALCL-HL), and their outcome with HL treatments was poor. We prospectively evaluated 22 patients with a diagnosis of MGZL who received the DA-EPOCH-R regimen. We performed immunohistochemical analyses and gene expression profiling. Characteristics included median (range) age 33 (14–54) years; male sex 14 (62%); stage IV disease 3 (14%) and elevated LDH 10 (45%). CD20 was positive in 68%, CD30 in 100%, CD15 in 47%, BCL6 in 93% and DC-SIGN in 50%. At a median follow-up time of 49 months, the event-free (EFS) and overall survivals (OS) were 58% and 67%, respectively. Eight patients progressed or recurred and received mediastinal radiation and 3 remain in remission. Low absolute lymphocyte count (ALC) and DC-SIGN positive infiltrating cells portended a poor prognosis. GEP demonstrated that most MGZL cases were defined by a unique molecular signature, enriched in dendritic cell genes, similar to HL and B-cell genes, more similar to PMBL. Clinically, they appear to be more resistant to treatment than PMBL and may require mediastinal radiation. We hypothesize that MGZL is more closely related to CHL-NS with up-regulation of the B-cell program. Accrual continues.

DOI: 10.1002/hon

SESSION 7—PAEDIATRIC LYMPHOMA

076
ALK TYROSINE KINASE INHIBITORS FOR ALK+ ANAPLASTIC LARGE CELL LYMPHOMA (ALCL): PRELIMINARY CLINICAL EXPERIENCES AND PERSPECTIVES

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ALCL is the third most common paediatric NHL. Despite many different therapeutic approaches, the outcome for paediatric ALCL has remained the same for the last 20 years, i.e. about 75% EFS and 90% OS. Over 90% of paediatric ALCL express ALK via chromosomal translocation, with t(2;5) NPM-ALK fusion protein being the most common. The pharmacologic inhibitor of ALK and c-MET, crizotinib, was approved by the FDA in 8/2011 at a dose of 250 mg p.o. BID (about 150 mg/m,^{2}), after demonstrating efficacy in non-small cell lung cancer (NSCLC) with an ALK mutations, i.e. 60% overall response rate and 1–2% CR. Reports from phase I/II trials in NSCLC patients demonstrate the most common grade 3/4 toxicities to be hematologic (5–10%), primarily leukopenia. Other toxicities (<grade 3) include likely on-target effects of naturally expressed ALK or c-MET inhibition and include: visual disturbances (60%), rapid onset of low testosterone in males (>75%), transaminitis (5–10%), gastrointestinal toxicities (<5%), neurologic, e.g. dizziness/neuropathy (<5%). Children's Oncology Group (COG) conducted a phase I trial using crizotinib. Doses tested ranged from 100–365 mg/m,^{2}. Dose limiting toxicities (DLT) included: elevated liver function tests ($n=8$), neutropenia ($n=7$), diarrhoea ($n=2$), infections ($n=3$), dizziness ($n=1$), visual disturbance ($n=1$) and intracranial haemorrhage ($n=1$). The recommended phase II dose was determined to be 280 mg/m,^{2}. Though responses were seen in a few patients with neuroblastoma or myofibroblastic tumour, for the 10 ALCL patients the EFS was 90% and OS 100%, to date. ALCL patients received crizotinib at 165 mg/m,^{2} ($n=8$) and 280 mg/m,^{2} ($n=2$). On the basis of these results, a COG pilot study adding crizotinib at 165 mg/m,^{2} to the chemotherapy backbone of EICNHL ALCL99 has been approved to open in 2013. More details on the design and objectives of this study will be reviewed. In summary, preliminary data has demonstrated crizotinib to be very active with acceptable toxicity as a single agent in relapsed/refractory paediatric ALCL. Future studies are needed to determine the safety and efficacy of the addition of crizotinib to chemotherapy in newly diagnosed ALCL patients.

077
MECHANISMS OF RESISTANCE TO ALK TYROSINE KINASE INHIBITORS AND STRATEGIES TO OVERCOME THEM

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The Anaplastic Lymphoma Kinase (ALK) becomes a potent oncogene after chromosomal translocations and single point mutations in several human tumours, including anaplastic large cell lymphoma (ALCL), non-small cell lung cancer (NCSLC), inflammatory myofibroblastic tumour (IMT) and neuroblastoma. Cancer cells are 'addicted' to ALK constitutive activation and are highly sensitive to the targeted treatment with small-molecule inhibitors. Crizotinib, an oral ALK inhibitor, has provided dramatic clinical benefit in patients with NSCLC harbouring ALK rearrangements. Nonetheless, acquired drug resistance inevitably develops and leads to tumour progression and relapse. Different mechanisms of crizotinib acquired drug resistance have been recently reported both in cell lines and in patients. In general, three common mechanisms of resistance to ALK inhibition have been described: (i) amino acid mutations in the drug interaction domains, including the F1174L, L1196M, S1206Y, G1202R, 1151Tins and C1156Y mutations in NSCLC and L1196Q and I1171N mutations in ALCL; these mutations display differential sensitivity to next-generation ALK inhibitors such as CH5424802, Asp3026 and AP26113 (ii) gene amplification or overexpression of ALK, that require higher dosage of the ALK inhibitor; and (iii) activation of alternative compensatory signalling pathways that include other RTKs; in this context, we will show our recent findings of additional resistance mechanisms. Thus, the identification of the molecular mechanisms of crizotinib resistance in each patient will be strictly required in order to pursue the appropriate therapeutic options in ALK-driven tumours. Finally, additional therapies, such as ALK specific immunotherapy, will be discussed as a promising tool to be used in combination with targeted therapies to prevent the occurrence of resistant tumours.

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DETECTION OF ANTI-NPM-ALK CD8,$^+$ T-CELLS IN CHILDREN WITH NPM-ALK-POSITIVE ANAPLASTIC LARGE CELL LYMPHOMA (ALCL)

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Introduction: Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) constitutes an ideal model to study anti-tumour immune responses. The tumour cells express oncogenic ALK fusion proteins that act as tumour antigens. Patients with the NPM-ALK,$^+$ALCL can mount ALK-specific antibody and T-cell responses. ALK-specific antibody titers inversely correlate with outcome suggesting a role of the immune response in tumour control. T-cell responses against the ALK fusion protein were detected by reverse immunology approaches using ALK-derived peptides. But these analyses were limited to few HLA-alleles without covering the full immunogenicity of NPM-ALK and did not prove endogenous processing of the respective peptides. For a comprehensive analysis of NPM-ALK-specific T-cell responses, we used autologous dendritic cells [DCs], transfected with *in vitro*-transcribed (IVT) mRNA, as antigen-presenting and stimulator cells.
Methods: CD8,$^+$ T-cells of patients (are in remission) with NPM-ALK,$^+$ ALCL were stimulated with autologous DCs transfected with IVT-mRNA encoding full-length NPM-ALK. After one or two re-stimulations, T-cell responses were analysed with an IFN-γ ELISPOT assay. To assess both antigen reactivity and HLA restriction, responder T-cells were tested for the recognition of COS-7 cells co-transfected with the patients' individual HLA-class I alleles and NPM-ALKcDNA.
Results: In 4/8 patients with NPM-ALK,$^+$ ALCL, NPM-ALK-reactive T-cells could be detected and enriched after stimulation with mRNA-transfected DCs in peripheral blood samples collected one to ten years after treatment. In 3/4 NPM-ALK-reactive patients, recognition of NPM-ALK was restricted by HLA-C alleles, whereas in 1/4 reactive patient the response was restricted by HLA-B allele. No NPM-ALK-reactive T-cells could be detected in 10 healthy controls.
Conclusion: With this methodology NPM-ALK-specific CD8,$^+$ T-cells could be detected in the blood of 4/8 NPM-ALK,$^+$ALCL patients in remission as long as 10 years after diagnosis. Of note, in the majority of NPM-ALK-reactive cases, recognition of NPM-ALK was restricted by HLA-C alleles. Supported by 'von Behring-Röntgen Stiftung'.

079
CNS DISEASE IN PAEDIATRIC PATIENTS WITH B-CELL NON-HODGKIN LYMPHOMA AND BURKITT LEUKAEMIA—THERAPY AND OUTCOME IN THE B-NHL BFM 04 STUDY

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Introduction: In BFM studies 1986–2002 pEFS (5y) of patients (pts) with B-NHL and initial CNS disease (CNS+) was only 62±5%. In the B-NHL BFM 04 study fractionated intraventricular applied chemotherapy of previous studies was replaced by an intensified intrathecal (i.th.) triple therapy per lumbar puncture combined with high-dose (HD) methotrexate (MTX)/cytarabine as before.
Patients and Methods: From 03/2004 to 03/2011 728 protocol pts up to 18 years of age with B-NHL were enrolled. CNS+ was defined by detection of CSF-blasts and/or cranial nerve palsy (CNP) and/or intracerebral mass (ICM). CNS+ pts received a cytoreductive prephase and 6 courses based on dexamethasone, vincristine, ifosfamide, cyclophosphamide, doxorubicin, etoposide, MTX 5 g/m,^{2} i.v. (24h), intermediate/HD-cytarabine and a total of 14 i.th. MTX/prednisolone/

DOI: 10.1002/hon

cytarabine applications, 5 of them during the first 10 days of therapy. Part of pts participated in a phase II study receiving one dose of rituximab (375 or 700 mg/m,^{2}) prior to chemotherapy.

Results: Out of 728 B-NHL pts 82 (11%) were CNS+; 57 had CSF-blasts (+/− ICM, +/− CNP), 15 an ICM (+/− CNP, but no blasts), 10 CNP only. 68/82 CNS+ pts had Burkitt lymphoma/leukaemia, 11 diffuse large B-cell lymphoma, 3 other mature B-NHL. Central/peripheral neurotoxicities grade 3/4 were reported for 5 pts. Events were toxic death (3), relapse (13; 5 in CNS only, 4 CNS combined), second malignancy (1). 3y-pEFS of the 82 CNS+ pts was 78±5%; pEFS of 57 CNS+ pts with CSF-blasts (+/− ICM, +/− CNP) was 71±6% compared with 95±5% for 25 CNS+ pts without CSF-blasts ($p=0.015$); pEFS for 32 pts with CSF-blasts and ≥25% blasts in bone marrow (BM) was 53±9% (10 relapses; 7 CNS involved) vs 92±5% for 25 pts with CSF blasts and <25% blasts in BM ($p=0.0018$).

Conclusions: An intensified i.th triple drug therapy combined with BFM B-NHL-type therapy including MTX 5 g/m,^{2} i.v. over 24 h and HD-cytarabine proved feasible and highly efficacious for paediatric CNS+ B-NHL pts except those with CSF blasts and advanced BM involvement (Burkitt leukaemia) in whom CNS was the predominant site of failure. Further attempts to improve CNS control may focus on this small group of patients (4.4% of all B-NHL, 40% of CNS+ B-NHL).

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DIFFERENT PATTERN OF CHROMOSOMAL ALTERATIONS ACCORDING TO THE MORPHOLOGY AND THE AGE IN CHILDHOOD MATURE B-CELL LYMPHOMAS: REPORT OF THE FRENCH LMB2001/03 STUDY

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Background: We showed the prognostic impact of different chromosomal alterations in childhood mature B-cell lymphomas enrolled in the international FAB/LMB96 trial [Poirel HA et al, Leukemia, 2009].

Objectives: The aim of our study is to confirm these results on a new series of patients treated with the next French LMB2001/03 trial (2001–2011).

Results: Informative karyotype has been obtained in 180 (23%) of the 797 registered patients. 88% were locally assified as Burkitt lymphoma/leukaemia (BL), 8% as DLBCL, the morphological diagnosis was not specified or unavailable for the other 4%. MYC/8q24 locus is translocated in 146/150 (97%) BL while in 2/14 DLBCL. It is associated with 1 or more alteration in 64% cases in BL: 1q gain (32%), der(13q) (12%), del(6q) (7%), del(17p) and +7q (6%). The more frequent alterations detected in complex karyotype with 8q24 rearrangement are: der(13q) (26%), der(7q) and del(17p) (18%), del(6q) (16%). The karyotype is more frequently aneuploid and complex in DLBCL than in BL (aneuploidy: 57% vs 21% ; average number of chromosomal alterations: 4.4 vs 2.6). Among DLBCL, the 5 primary mediastinal B-cell lymphoma exhibit a distinct complex pattern of chromosomal aberrations. Chromosome alterations tends to vary according to the age. Lymphomas without MYC alteration occur in older patients (mean age: 11.1 vs 8.7 years old). Among BL, complexity of the karyotype increase with age (average number of chromosome alterations: 3.2 for children older than 10 years old vs 2.4 and 3.5 for children older than 15 years old).

Conclusion: This descriptive analysis confirms the different patterns of chromosomal alterations according to the morphology as previously reported and identifies variations with age which may explain the worse prognosis of adolescents. Multivariate analysis is ongoing to evaluate the prognostic significance of these different genetic biomarkers.

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PAEDIATRIC BURKITT LYMPHOMA OF THE NHL-BFM GROUP ANALYSED WITHIN THE ICGC-MMML-SEQ: WHOLE GENOME SEQUENCING DATA FROM 12 CASES

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Introduction: Burkitt lymphoma (BL) is the most common subtype of Non-Hodgkin lymphoma (NHL) in childhood. Newly diseased patients in Germany undergo diagnostics and treatment according to the NHL-BFM protocols. In the framework of International Cancer Genome Consortium (ICGC) the German ICGC MMML-Seq-Project funded by the German Federal Ministry of Education and Research (01KU1002A-J) performs whole genome sequencing of germinal centre derived B-cell lymphomas including paediatric BL from the NHL-BFM trial.

Patients and methods: Patients registered in the NHL-BFM data centre with Burkitt lymphoma diagnosed by a reference laboratory of the study group with sufficient and adequate lymphoma and paired control DNA and informed consent for the ICGC MMML-Seq were defined evaluable. All patients were treated according to the protocols NHL-BFM 95 or B-NHL BFM 04. Whole genome sequencing was performed on malignant cells from initial diagnosis (coverage >30×) and paired normal control. Datasets were analysed for somatic single-nucleotide variants (SNVs) and small indels.

Results: So far, analysis has been completed for samples from 12 patients, 11 boys and 1 girl, aged 4–18 years at time of diagnosis. Two patients suffered from relapse. Within the 12 patients a total of 33378 somatic SNVs were detected. The mean of somatic SNVs per case was 2413 (range 1635–4923). The median of potentially protein changing SNVs was 28 (range 18–46). Genes recurrently (> 3 cases) affected by protein-changing SNVs or small indels were MYC, TP53, SMARCA4, ID3, FBX011, CCND3, RHOA, P2RY8 and DDX3X. Nine out of 12 patients showed alterations in the recently described BL related pathway ID3-TCF3-CCND3 (Richter et al., Nat Genet, 2012; Schmitz et al., Nature, 2012; Love et al., Nat Genet, 2012). The two relapsed patients had 3832 and 4923 SNVs and 28 and 46 potentially protein changing mutations, respectively.

Conclusions: Whole genome sequencing of paediatric Burkitt lymphoma reveals a relatively homogeneous profile with ID3-TCF3-CCND3 pathway alterations in the majority of cases.

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TEN-YEAR FOLLOW UP OF PAEDIATRIC PATIENTS WITH NON-HODGKIN LYMPHOMA TREATED WITH ALLOGENEIC OR AUTOLOGOUS STEM CELL TRANSPLANTATION

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Introduction: Despite improvements in therapy for paediatric non-Hodgkin lymphoma (NHL), outcome for children with relapsed disease remains poor. Hematopoietic stem cell transplant (SCT) is often considered to improve survival but there is limited data on the use of SCT for the treatment of NHL in the paediatric setting. We report the outcome of 36 paediatric patients with NHL who underwent SCT at our institution with a median follow up of

9.75 years. To our knowledge this represents the largest cohort of paediatric patients with NHL treated with SCT at a single institution.
Methods: To evaluate the role of hematopoietic stem cell transplantation for children with NHL we reviewed 36 consecutive paediatric patients with NHL who underwent an allo-SCT ($n = 21$) or auto-SCT ($n = 15$) at our institution between 1982 and 2004. Pathologic classification included: lymphoblastic lymphoma ($n = 12$), Burkitt lymphoma ($n = 5$), diffuse large B-cell lymphoma ($n = 4$), anaplastic large cell lymphoma (ALCL) ($n = 13$), peripheral T-cell lymphoma ($n = 1$), and undifferentiated NHL ($n = 1$). Donor source for allo-SCT was an HLA-matched related donor ($n = 15$), a matched unrelated donor ($n = 4$), or a mismatched donor ($n = 2$). Twenty-eight patients (78%) had chemotherapy responsive disease at the time of transplant.
Results: OS and DFS were 55% and 53% with a median follow up of 9.75 years. Outcomes were similar in patients receiving auto-SCT and allo-SCT (DFS 53% in both groups). Patients with ALCL had a DFS of 76.9%. In contrast, of five patients transplanted for Burkitt lymphoma, none survived. DFS among patients with chemotherapy sensitive disease was superior compared with patients with relapsed/refractory disease (61% vs 25%, $p = 0.019$).
Conclusions: Allo-SCT and auto-SCT offer the prospect of durable, disease-free survival for a significant proportion of paediatric patients with relapsed/refractory NHL. Outcome is superior in patients with chemotherapy sensitive disease.

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CLINICAL PRESENTATION AND OUTCOME OF ADVANCED STAGE CLASSICAL HODGKIN'S LYMPHOMA IN CHILDREN: A RETROSPECTIVE STUDY

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Background: HL is one of the most curable malignancies of childhood. There is limited published data on outcome, local biology and prognostic factors. This retrospective study aims at understanding the clinicobiological differences from west, local prognostic factors, assessing the outcome and toxicity and optimizing the future treatment for this highly curable lymphoma while minimizing the acute and late toxicities.
Methods: 152 advanced stage Hodgkins lymphoma (Stage IIBX, III and IV) ≤ 15 years from January 2005 to December 2010 were analysed. All patients had received ABVD based chemotherapy followed by IFRT to the bulky/residual sites. Medical records and lymphoma clinic charts were reviewed for presenting symptoms, examination findings and treatment that includes chemotherapy regimen, number of chemotherapy cycles, second and subsequent lines of treatment, radiation therapy chart for field, volumes and doses. The response and toxicity to each line of treatment were recorded according to CTC version 3.0.
Results: The median age was 9.7 years and M:F ratio was 5.9:1.The major histologic subtype was mixed cellularity. Majority (73%) of patients had stage III disease with 80/152 (53%) of patients having 'B' symptoms and 69/152(45%) having bulky disease at presentation. Extranodal involvement was seen in 26% of patients. Involved field radiotherapy (IFRT) was given in 68 (44.7%) patients. A total of 83% patients had complete remission (CR) at the end of therapy, whereas 32(21%) patients progressed or relapsed. Median follow up was 37 months. At 3 years, OS and EFS rates were 83.6% and 78%, respectively. Survival rates were lesser as compared with the studies from west. CHIPS score was evaluated as a prognostic factor by evaluating four of the above mentioned factors (Stage IV, bulky mediastinal disease serum albumin and fever); event-free survival rate was 83% for patients with a CHIPS score of 0 or 1, 70% for those with a CHIPS score of 2, and 61% for those with a CHIPS score of 3 or 4.
Conclusion: This audit stresses the need to treat children with advanced stage Hodgkin lymphoma with risk stratified aggressive dose-intense combined modality treatment regimens to maximize the outcome with minimal morbidity and need for prospective validation of local prognostic factors in large scale multicentre clinical trials.

'FOCUS ON. . .' SESSION: OLD AND NEW RANDOMIZED TRIALS

084
THE BRIGHT STUDY OF FIRST-LINE BENDAMUSTINE-RITUXIMAB (BR) OR R-CHOP/R-CVP IN ADVANCED INDOLENT NONHODGKIN'S LYMPHOMA (NHL) OR MANTLE CELL LYMPHOMA (MCL)

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Introduction: This study compared the first-line bendamustine–rituximab (BR) with standard R-CHOP/R-CVP regimens for indolent non-Hodgkin's lymphoma (NHL)/mantle cell lymphoma (MCL).
Methods: Patients were assigned to R-CHOP or to R-CVP by site, and then randomized to 6–8 cycles of BR (bendamustine 90 mg/m,^{2} on days 1 and 2, rituximab 375 mg/m,^{2} on day 1, 28-day cycle) or the standard treatment (usual dosing, 21-day cycle). The primary measure was noninferiority of complete response (CR) rate in efficacy-evaluable patients.
Results: Starting in April 2009, 447 patients were randomized, 436 treated and 419 efficacy-evaluable (BR $n = 213$; R-CHOP/R-CVP $n = 206$). For randomized and evaluable patients, CR rates for BR were statistically noninferior. In randomized subgroups, CR rates for indolent NHL were similar between BR and R-CHOP/R-CVP; in MCL, BR ($n = 37$) was superior ($p = 0.018$) to standard therapy ($n = 37$, 62% of whom received R-CHOP). By committee/investigator assessment of available data at cut-off, 8%/8% of BR and 4%/11% of R-CHOP/R-CVP patients had progressed, relapsed or died. Most common adverse events (AEs) (%) of any grade for BR and R-CHOP/R-CVP were nausea (63, 48), fatigue (51, 50) and neutropenia (34, 40). Grade 3/4 AEs, primarily hematologic, occurred in 69% for R-CHOP vs 56% BR and 50% for R-CVP vs 56% BR. Most common laboratory grade 3/4 toxicities (%) for BR and R-CHOP/R-CVP were lymphopenia (62, 30), neutropenia (44, 70) and leukopenia (38, 54). Antiemetic use was similar between groups except aprepitant use was higher with R-CHOP (23%) than BR (9%) or R-CVP (3%). Colony-stimulating factors were given (per institutional standards) to 29% for BR and 43% for R-CHOP/R-CVP.

Abstract 084 Table 1.

CR rates

Population	BR%	R-CHOP/ R-CVP%	CR ratio (95% CI)	*p* value
Evaluable	31	25	1.26 (0.93–1.73)	0.0225[a]
Randomized	31	23	1.34 (0.98–1.83)	0.0084[a]
NHL				
Evaluable	28	25	1.11 (0.78, 1.59)	0.1903[a]
Randomized	27	23	1.16 (0.81–1.65)	0.1289[a]
MCL				
Evaluable	50	27	1.76 (0.91, 3.42)	0.0586[b]
Randomized	51	24	1.95 (1.01–3.77)	0.0180[b]

[a]Noninferior (margin of 0.88).
[b]Superior.

DOI: 10.1002/hon

Conclusions: In advanced indolent NHL and MCL, the CR rate of BR is noninferior to R-CHOP/R-CVP. In the small MCL group, the CR rate is twofold higher with BR. BR and R-CHOP/R-CVP have distinct AE profiles.

Support Teva BPP R&D, Inc.

085

GEMCITABINE, DEXAMETHASONE, CISPLATIN (GDP) COMPARED WITH DEXAMETHASONE, CYTARABINE, CISPLATIN (DHAP) SALVAGE CHEMOTHERAPY PRIOR TO AUTOLOGOUS STEM CELL TRANSPLANTATION FOR RELAPSED AND REFRACTORY AGGRESSIVE LYMPHOMAS: FINAL RESULT OF THE PHASE III NCIC CTG STUDY LY12

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Background: The optimum chemotherapy prior to autologous stem cell transplantation (ASCT) for patients (pts) with relapsed/refractory aggressive lymphomas has not been defined. We hypothesized that gemcitabine-based therapy is as effective as and less toxic that standard DHAP treatment.
Methods: From 8/2003 to 11/2011, 619 pts with relapsed/refractory aggressive NHL were stratified by centre, IPI risk factors at relapse, immunophenotype (B vs T/NK), prior treatment response and prior rituximab (R) treatment, and randomized to outpatient GDP or standard DHAP. Responding pts after 2–3 cycles proceeded to ASCT. The protocol was amended 11/2005 to include R with GDP or DHAP for pts with CD20 lymphoma. The study was designed to determine if the response rate (RR) to GDP was non-inferior to DHAP using a margin of 10%, and if the transplantation rate after GDP was superior.
Results: Patient characteristics: median pt age: 55 yrs (28.4% >60 years); histology: diffuse large B-cell lymphoma 71%, transformed 14%, T-cell/ALCL 10%; prior R treatment 67%. By intention to treat, the RR (CR/CRu/PR) for GDP was 45.2% and for DHAP 44.0%, meeting protocol criteria for non-inferiority of GDP ($p = 0.005$); per protocol analysis showed that this finding was robust. The transplantation rate was 52.1% for GDP vs 49.3% for DHAP ($p = 0.44$). At a median follow-up of 53 months, 4 yr EFS were 25.6% and 26.1% (HR 0.99, $p = 0.95$) and 4 yr OS 39.0% and 39.1% (HR 1.03, $p = 0.78$) for GDP and DHAP, respectively. GDP resulted in less grade 3–4 toxicity (47 vs 61%, $p = 0.0003$), febrile neutropenia (9 vs 23%, $p < 0.0001$), platelet transfusions (18% vs 32%, $p < 0.0001$) and AEs requiring hospitalization (18 vs 30%, $p = 0.0005$). Superior mean and greater-than-minimally-important QoL change scores vs baseline were seen after 2 treatment cycles for patients receiving GDP vs DHAP. Conclusion: The response rate to GDP is not inferior to the standard DHAP and resulted in similar rates of transplantation, EFS and OS with less toxicity, impairment of QoL and need for hospitalization. This study supports the use of GDP as a new standard in practice and in future studies of salvage therapy.

Supported by a grant from the Canadian Cancer Society Research Institute, Roche and Eli Lilly

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ALTERNATING COURSES OF 3X CHOP AND 3X DHAP PLUS RITUXIMAB FOLLOWED BY A HIGH DOSE ARA-C CONTAINING MYELOABLATIVE REGIMEN AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) INCREASES OVERALL SURVIVAL WHEN COMPARED WITH SIX COURSES OF CHOP PLUS RITUXIMAB FOLLOWED BY MYELOABLATIVE RADIOCHEMOTHERAPY AND ASCT IN MANTLE CELL LYMPHOMA: FINAL ANALYSIS OF THE MCL YOUNGER TRIAL OF THE EUROPEAN MANTLE CELL LYMPHOMA NETWORD (MCL NET)

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MCL outcome has improved during the last decades. High dose ARAC may improve prognosis.
Methods: To evaluate the potential superiority of a high dose ARA-C containing regimen, the MCL net initiated a randomized trial comparing six courses of CHOP plus Rituximab followed by myeloablative radiochemotherapy (12 Gray TBI, 2x60mg/kg Cyclophosphamide) and ASCT (control arm A) versus alternating courses of 3x CHOP and 3x DHAP plus Rituximab followed by a high dose ARA-C containing myeloablative regimen (10 Gray TBI, 4x1,5 g/m,[2] Ara-C, 140 mg/m,[2] melphalan) and ASCT (experimental arm B). Patient eligibility criteria included previously untreated MCL stage II–IV up to the age of 65 years. The primary end point time to treatment failure (TTF) was monitored continuously by a sequential procedure.
Results: From July 2004 to May 2010, 497 patients were randomized. The 455 patients evaluable for the primary analysis (19 no MCL, 13 not yet documented, 7 lost of follow up, 2 stage 1, and 1 R bendamustine chemotherapy) displayed the following characteristics (A vs B): median age 54 vs 56 year, male 79% vs 79%, stage IV 82% vs 81%, B symptoms 43% vs 31%, ECOG >2 4% vs 4%, elevated LDH 39% vs 35%, and MIPI low/int/high risk 60%/25%/15% vs 64%/23%/13%, respectively. After induction overall response was similar in both arms (90% vs 95%; $p = 0.19$) but CR and CR/CRu rates were significantly higher in arm B (25% vs 36%; $p = 0.012$ and 40% vs 54%; $p = 0.0003$). The number of patients transplanted was similar in both arms (72% vs 73%). After transplantation OR and CR rates were comparable in both arms (98% vs 97% and 63% vs 61%). After a median follow up of 51 months, TTF was longer in Arm B (46m vs 88m; $p = 0.0382$, HR 0.68) mainly due to a lower number of relapses after CR/CRu/PR ($n = 81$ vs 40). The rate of ASCT-related death in remission was similar in both arms (4% vs 4%). Although CR rate after ASCT was similar in both arms, remission duration (RD) after ASCT was superior in Arm B (49m vs 84m; $p = 0.0001$). At the time of final analysis, OS was superior in Arm B (NR vs 82m, $p = 0.045$). Safety after induction was comparable in both arms except for an increased grade 3/4 hematological toxicity, renal toxicity. Toxicities of both conditioning regimen were similar.
Conclusions: Induction regimen containing high dose ARA-C followed by ASCT should become the new standard of care of MCL patients <65 y.

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PRELIMINARY RESULTS OF PROSPECTIVE RANDOMIZED MULTICENTRE STUDY 'BEACOPP-14 VERSUS BEACOPPESCALATED IN PATIENTS WITH HODGKINS LYMPHOMA FROM POOR-PROGNOSIS GROUP'

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Introduction: The prospective randomized multicentre study of efficacy and toxicity of BEACOPP-14 vs BEACOPP-esc in high risk patients with Hodgkins lymphoma (HL) was initiated in six Ukrainian centres. The aim of study is to evaluate overall response rate (ORR), complete response rate (CRR), 2-year overall survival (OS), progression-free survival (PFS) and toxicity of both regimens.
Methods: Since September 2008 until February 2013, 198 patients with stage IIB with 1 unfavourable factor and stage III–IV, median age—29 years, 88 male and 110 female. Patients were randomized to BEACOPP-14 (91 patient, 6.12 ± 1.09 cycles per patients) or BEACOPP-esc (107 patient, 5.46 ± 0.92 cycles per patients) groups. The treatment efficacy in both groups was evaluated by Cheson criteria (1999, 2007). Toxicity rates were evaluated acording to NCI-CTC V.3.0. After completion of chemotherapy patients with initial sites >5 cm, residual lymph nodes >2 cm and PET-positive sites received radiotherapy (30–36 Gy). Additionally the similar group of patients, who received ABVD, was selected for the historical control from National Cancer Register.
Results: ORR in the BEACOPP-14 group was 95.32% and 94.29% in the BEACOPP-esc group, CRR was 75.2% and 61.4%, respectively (p>0.05). Maximal observation period was 54 months. 3-year OS in the BEACOPP-14 group was 100%, 93.45% in the BEACOPP-esc group and 91.8% in the ABVD group ($p > 0.05$). 3-year PFS was 93.45% and 95.60% respectively, ($p > 0.05$) and 84.6% in the ABVD group ($p < 0.05$). Incidence of anaemia was 63.18% vs 54.25% ($p < 0.05$)in the BEACOPP-esc group compared with the BEACOPP-14 group, neutropenia was 72.33% vs 62.09%, ($p < 0.05$) and

DOI: 10.1002/hon

thrombocytopenia was 27.65% vs 19.9%, respectively ($p > 0.05$).
Conclusions: ORR, CR and 2-year PFS were comparable in BEACOPP-esc and BEACOPP-14 groups and were significantly lower in the ABVD group. 2-year OS was comparable in all groups of patients. Hematological toxicity rate was significantly higher in the BEACOPP-esc group. Preliminary Results of this study warrant longer follow-up and further validation.

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FIRST-LINE R-CVP VERSUS R-CHOP INDUCTION THERAPY AND MAINTENANCE RITUXIMAB FOR INDOLENT LYMPHOMA. A MULTICENTRE PHASE III RANDOMIZED STUDY PLRG-4 BY THE POLISH LYMPHOMA RESEARCH GROUP

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Introduction: R-CHOP and R-CVP are established regimens for remission induction of indolent lymphoma. However, the evidence is limited if doxorubicin is beneficial enough to justify increased toxicity, given that maintenance rituximab improves progression-free survival in the first complete or partial remission of follicular lymphoma. Here we report on early results of a randomized study comparing R-CHOP and R-CVP.
Methods: Eligible were untreated patients in need of therapy with indolent lymphoma including follicular (FL), marginal zone including MALT (MZL), small lymphocytic (SLL), and lymphoplasmacytic (LPL). Patients stratified by histology and centre were randomized to R-CHOP or R-CVP × 8 or 6 cycles for early responders. Two months after induction patients started maintenance rituximab 375 mg/m,^{2} every 2 months × 12. Primary endpoint was event-free survival (EFS) from randomization to progression, relapse, end of protocol therapy due to intolerance, patient refusal or death from any cause. The study was designed to show 18-month difference in median EFS at 0.05 level of significance and a power of 80%. Current results are based on the planned interim analysis after 74 events. This study was supported by a research grant [ML19931] from Roche Polska Ltd.
Results: Between February 2007 and June 2011, 250 patients were enrolled and randomized to R-CHOP (127) or R-CVP (123). 7 patients did not start treatment, and 4 were withdrawn. Diagnosis was: FL in 99, MZL in 91, other in 49 pts. Median age was 56 (21–85), male: 44%, stage III–IV: 89%, IPI score 3–5: 50%. At the end of induction CR/PR rate was 36%/47% and 31%/51% in R-CHOP and R-CVP group (p NS). After a median of follow-up of 38 months, 3-year EFS was 69% and 65% ($p = 0.3$), 3-year OS was 93% and 96% ($p = 0.6$) in R-CHOP and R-CVP arm respectively. Grade III/IV adverse events occurred in 50 (R-CHOP) and 14 (R-CVP) patients: neutropenia 16 vs 3, infection 13 vs 2, second neoplasm 0 vs 2 ($p < 0.001$). 47 patients continue on maintenance rituximab.
Conclusions: After completion of the induction treatment by all patients and a median follow-up of 38 months, there was no significant difference in EFS or OS between R-CHOP and R-CVP arms. Toxicity during induction was higher with R-CHOP.

This study is registered with ClinicalTrials.gov at NCT00801281.

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BORTEZOMIB MAINTENANCE (BM) VERSUS CONSOLIDATION (BC) FOLLOWING AGGRESSIVE IMMUNOCHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) FOR UNTREATED MANTLE CELL LYMPHOMA (MCL): CALGB 50403

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Introduction: Aggressive immunochemotherapy and ASCT in CALGB 59909 achieved a median progression-free survival (PFS) in MCL of 5 years (Damon et al JCO,2009), but late recurrences occurred. Bortezomib has a 33% response rate in relapsed/refractory MCL. Using the CALGB 59909 treatment backbone, we evaluated tolerability and efficacy of adding post-transplant BC or BM in a randomized phase II trial.
Methods: The primary endpoint was PFS. Induction therapy was with 2–3 cycles of augmented R-CHOP (2000 mg/m,^{2}cyclophosphamide) and methotrexate (300 mg/m,^{2}) followed by high-dose cytarabine/etoposide/rituximab(R)/filgrastim (EAR) stem cell mobilization and cyclophosphamide/carmustine/etoposide (CBV) ASCT. After 2 doses of post-transplant R, patients were randomized to BC (1.3 mg/m,^{2} days 1, 4, 8, 11 of a 3 week cycle for 4 cycles) or BM (1.6 mg/m,^{2} weekly 4 of 8 weeks for 18 months) beginning at approximately day 90.
Results: 151 patients were enrolled at 14 sites and 147 received treatment. Median age was 59 (29–69); stage II (2.7%), III (12%), IV (86%); MIPI low (52.4%), int. (30.6%), high (17%); blastoid histology (14%); bone marrow involvement (81%). 118 (78%) underwent ASCT and 102 (68%) were randomized. Most withdrawals (45) were for progression (10) or adverse events (AEs) (19) including 4 treatment-related deaths. Following randomization, 34 (65%) completed BM and 33 (66%) completed BC. Withdrawal for AEs occurred in 14 (28%) of BC and 7 (13%) of BM patients ($p = 0.088$), most for cytopenias or peripheral neuropathy. With a median follow-up of 3.3 years from registration, 3-year PFS for all patients is 67% (58,74). The 2-year PFS from date of randomization in the BM and BC arms are 84% (70,92) and 89% (76,95), respectively. Progression occurred in 10 BM (5 post-treatment) and 9 BC patients (all post-treatment). 3 year PFS from time of transplant on CALGB studies 50403 ($n = 118$) and 59909 ($n = 66$), are 67% and 59% respectively ($p = 0.0086$).
Conclusions: Both BC and BM were feasible and tolerable, although BC was associated with more withdrawals for toxicity. In preliminary analysis PFS from time of transplant for 50403 was significantly longer than 59909. Further analyses will be presented.

'FOCUS ON. . .' SESSION: LYMPHOMA GENOMICS

090

HIGH RESOLUTION CHIP-SEQUENCING REVEALS NOVEL TARGETS AND PROGNOSTIC ROLE FOR SOX11 IN MANTLE CELL LYMPHOMA

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SOX11 (Sex determining region Y-box 11) expression is specific for MCL as compared with other Non-Hodgkin's lymphomas. However, the function and direct binding targets of SOX11 in MCL are largely unknown. We used high-resolution ChIP-Seq to identify the direct target genes of SOX11 in a genome-wide, unbiased manner and elucidate its functional significance. Pathway analysis identified WNT, PKA and TGF-beta signalling pathways as significantly enriched by SOX11 target genes. qCHIP confirmed that SOX11 directly binds to individual genes in these pathways in both MCL cell lines and patients. Interrogation of an 82 patient gene-expression dataset demonstrated that SOX11 mRNA expression was inversely proportional to Ki-67, a marker of cell proliferation. Functional studies using RNA interference demonstrate that SOX11 directly regulates WNT signalling and modulates chemotherapy sensitivity to cytarabine in MCL. We analysed SOX11 expression in independent well-annotated tissue microarrays from 131 patients treated at the University of Wisconsin (UW), Karolina Institute and British Columbia Cancer Agency (BCCA). Our findings suggest that high SOX11 expression is associated with improved survival in a subset of MCL patients, particularly those treated with intensive chemotherapy incorporating cytarabine. We have developed a transgenic mouse model to dissect the functional role of SOX11 in MCL pathogenesis. Transcriptional regulation of WNT and other biological pathways affects by SOX11 target genes may help explain the impact of SOX11 expression on patient outcomes.

DOI: 10.1002/hon

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DEREGULATION OF ETS1 AND FLI1 EXPRESSION IS RECURRENT IN DLBCL LEADING TO TUMOUR PROLIFERATION AND B-CELL MATURATION BLOCKAGE

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Introduction: DLBCL is the commonest lymphoma and a heterogeneous disease characterized by different genetic lesions. Genes involved in normal germinal centre (GC) differentiation (e.g. BCL6, BLIMP1/PRDM1) are often deregulated. It is likely that additional, still undescribed, genetic defects may contribute in the pathogenesis of the disease. Here, we functionally characterized two genes, mapped in a new region of recurrent gain at 11q24.3,in DLBCL samples.

Material and Methods: Clinical samples: DNA-profiling (Affymetrix 250K SNP, 166 cases), RNA-profiling (Affymetrix-GeneChip U133plus, 54 cases), immunohistochemistry and quantitative real-time-PCR. Cell lines: lentiviral infection of shRNAs targeting ETS1 and FLI1, electroporation, immunoblotting, real-time-PCR, proliferation assay, FACS, ChIP, RNA-profiling (Illumina-HumanHT-12v4 Expression-BeadChip).

Results: A recurrent gain at 11q24.3 was detected in 26% of DLBCL. It was associated with higher expression of the transcription factors ETS1 ($p = 0.013$) and FLI1 ($p = 0.008$). Silencing of both genes led to cell death and a block in proliferation in a DLBCL cell line bearing the same genomic lesion at 11q observed in clinical specimens. In five other DLBCL cell lines not bearing the 11q gain, only FLI1 silencing gave a similar phenotype, whereas ETS1 knockdown caused minimal effects. At a mechanistic level, we demonstrated that ETS1 negatively regulated BLIMP1 expression, the master regulator of plasma cell differentiation, by binding to its promoter region. Importantly, gene expression profiling analysis after ETS1 or FLI1 genetic silencing showed changes in the expression of several genes involved in cell cycle regulation, BCR signalling, plasma cell differentiation and chemotaxis.

Conclusions: In DLBCL, gain at 11q24.3 determines a high expression of ETS1 and FLI1 that might contribute to the neoplastic phenotype by sustaining cell growth and deregulating the normal GC transcriptional program. ETS1 would mainly act by blocking the late stages of B-cell differentiation toward plasma cell stage through direct suppression of PRDM1 expression, whereas FLI1 would mainly act as a pro-survival factor. MT, PB equally contributed.

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CONDITIONAL ACTIVATION OF THE HODGKIN LYMPHOMA ASSOCIATED HLH FACTORS ID2 AND ABF1 DISRUPTS B-CELL DIFFERENTIATION *IN VIVO*

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Among human lymphoid malignancies, classical Hodgkin lymphoma (cHL) constitutes one of the most prominent examples for lineage infidelity: in contrast to its origin from germinal centre (GC) or post-GC B-cells, the malignant Hodgkin/Reed-Sternberg (HRS) cells of cHL have lost a considerable part of the B-cell-specific gene expression program, accompanied by the upregulation of genes characteristic for other hematopoietic lineages. In previous work, we have demonstrated that the extinction of the B-cell gene expression program in HRS cells is linked to the functional inhibition of the B-cell-associated transcription factor E2A by overexpression of the antagonistic helix-loop-helix (HLH) factors ID2 and ABF1. To enable a detailed analysis of Id2- or Abf1-dependent effects on growth and differentiation of lymphoid cells *in vivo*, we have generated transgenic mice that allow for conditional activation of Id2 or Abf1 in a lineage- and stage-specific manner via Cre-mediated recombination from the Rosa26 gene locus. Breeding of Rosa26 Id2stopFL and Rosa26 Abf1stopFL mice to mb1-Cre mice that express Cre in early stages of B-cell differentiation revealed a pronounced block of B-cell development in the bone marrow. To activate Id2 or Abf1 specifically in GC B-cells, we used the Cγ1-Cre mouse strain in which Cre expression is induced by transcription of the immunoglobulin γ1 constant region gene segment, i.e. when B-cells enter the GC reaction. Analysis of Cγ1-Cre; Rosa26 Id2stopFL and Cγ1-Cre; Rosa26 Abf1stopFL mice demonstrated that both factors inhibit the response of mature B-cells to stimuli that induce class switch recombination or plasma cell differentiation *in vitro* as well as the GC response to immunization *in vivo*. Our experiments demonstrate that induction of Id2 or Abf1 results in disruption of the differentiation process of B-cells, which reflects a key aspect of cHL biology. These data support our hypothesis that the functional inhibition of E2A activity is a critical step in cHL pathogenesis.

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RECURRING ACTIVATION MUTATIONS AND SOMATIC DELETIONS REVEALED THROUGH WHOLE GENOME SEQUENCING IN WALDENSTRÖM'S MACROGLOBULINEMIA

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Background: Waldenstrom's Macroglobulinemia (WM) is an indolent non-Hodgkin's lymphoma whose genetic basis remains to be fully defined. We recently described the presence of a highly recurrent activating mutation in MYD88 L265P present in over 90% of patients with WM (Treon et al, NEJM 2012), and now present our expanded analysis of the genomic landscape revealed through whole genome sequencing (WGS).

Methods: WGS was performed using CD19+ selected bone marrow lymphoplasmacytic cells (LPC) from 55 WM patients along with sequencing of paired CD19+ depleted peripheral blood samples used as germline controls.

Results: On the basis of the patients analysed to date, after MYD88, the second most common somatic event was the presence of frame shift or nonsense mutations in the C-terminal domain of CXCR4 that were present in 8/30 (27%) patients. These mutations were either identical to or functionally similar to germ line variants associated with WHIM syndrome, which are known to confer constitutive CXCR4 signalling due to dysfunctional receptor endocytosis. Less common somatic variants were also identified in ARID1A (17%), MUC16 (13%), TRAF2 (10%), TRRAP (10%) and MYBBP1A (7%). Findings were confirmed by Sanger sequencing, and MYD88 and CXCR4 mutations were subjected to functional analysis which confirmed a role in the growth and survival of WM cells. Analysis of copy number alterations revealed the presence of 172 recurrent somatic deletions with a median length of 100Kb (range 100KB-1,100Kb). The top findings were confirmed by PCR based copy number assays on both somatic and germline tissue. Genes affected by validated deletions included BTG1 (90%), PRDM2 (80%), and LYN (70%). We further validated several novel translocations involved in the chromosome 6q deletions that are found in half of WM patients and documented one case of chromothripsis as the underlying aetiology of the deletion.

Conclusions: In addition to the activating mutation MYD88 L265P, there are a number of recurrent mutations identified by WGS that make up the genomic landscape of WM and are likely to play a role in disease pathogenesis.

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PLCG1 MUTATIONS IN CUTANEOUS T-CELL LYMPHOMAS

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DOI: 10.1002/hon

Introduction: Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of diseases characterized by clonal expansion of malignant T-cells in the skin. The molecular pathogenesis of CTCL is still basically unknown, although some data suggest that signalling from TCR is a driving force. However, the molecular mechanisms responsible for this activation have not been fully clarified.
Methods: We have studied the presence of somatic mutations in a selection of 524 genes belonging to TCR and related pathways (SureSelect target enrichment system (Agilent)). Tumoural and germinal DNA from 2 Tumoural-MF, 4 erythrodermic-MF and 6 SS patients were processed and sequenced with Genome Analyzer GA2 (Illumina) (PE-42bp). Sequencing data were first checked by FastQC and aligned to the human reference genome (GRCh37) using BWA and BFAST alignments. Somatic variants were identified using GATK. The GATK-QUAL field was employed for ranking selected somatic variants. Putative variants were manually reviewed and validated by capillary sequencing. FACS analysis was performed in CTCL cell lines to determine Th17/Treg phenotype. Immunohistochemical analysis for NFAT, p50 and p52 was also performed. qPCR-genotyping for specific variants was performed in a new cohort of 50 CTCL patients.
Results: Several mutations were found in genes belonging to pathways implicated in the Treg and Th17 regulatory pathways, NFkB and JAK/STAT. PLCG1 was found mutated in 3 samples, 2 of them sharing the same mutation. This mutation was further analysed by qPCR-genotyping in a new series of patients, being detected in 20% of samples.PLCG mutated cases showed a strong immunostaining for nuclear NFAT. Additionally, immunological studies performed by flow cytometry in CTCL cell lines show aberrant coexpression of TH17 and Treg phenotypes. Additional mutational analyses on the identified genes are currently being performed in a new set of SS and MF cases.
Conclusions: Activation of the TCR signalling pathway in CTCL might be partially dependent on the acquisition of somatic mutations in genes known to play essential roles in T-cell differentiation processes and acquisition of TH17 and Treg phenotypes. PLCG1 is frequently mutated in tumoural CTCL samples, which makes it a good choice as a diagnostic marker and also for selecting therapies. These mutated genes could facilitate the differential diagnosis of MF samples with other inflammatory conditions.

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NEXT-GENERATION SEQUENCING SUGGESTS THERAPEUTIC TARGETS IN PERIPHERAL T-CELL LYMPHOMA

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Introduction: Peripheral T-cell lymphoma (PTCL) comprises 18 diseases that are poorly understood and generally carry a worse prognosis than B-cell lymphomas. PTCL not otherwise specified (PTCL-NOS), a pathologic diagnosis of exclusion, is most common, making up 25–30% of cases. To shed light on PTCL biology and identify novel therapeutic targets, we undertook next generation DNA sequencing, fueled by a collection of fresh-frozen samples with matched normal DNA and a larger collection of paraffin-embedded cases.
Methods: We performed whole-exome sequencing of tumour and germline DNA derived from four patients with PTCL-NOS and one with the related disease angioimmunoblastic T-cell lymphoma (AITL). We used a PCR-amplicon sequencing approach to verify selected mutations. We extracted DNA from 61 paraffin-embedded cases and used PCR amplification to sequence the complete coding regions of 237 genes of interest, including those mutated in the whole-exome data and selected additional candidate genes.
Results: Whole-exome sequencing revealed an average of 99.4 non-synonymous coding mutations per case (range 44–188) and identified genes previously described as mutated in PTCL, including TET2, plus many additional candidates. Amplicon sequencing eliminated many artefacts from the whole-exome data and focused results on 15 highly promising candidates, including components of PI3K, MAPK, and NFkB signalling, DNA repair, and chromatin modification. Sequencing of paraffin cases is nearing completion and will better quantify the frequency of mutational deregulation of particular processes in PTCL.
Conclusions: Our data point to specific processes deregulated in PTCL, providing potential novel therapeutic targets. These include oncogenic signalling pathways and epigenetic regulatory mechanisms. Results from our collection of paraffin-embedded cases will help clarify the frequency of deregulation of particular processes and may aid sub-classification of the poorly defined PTCL-NOS entity. These results will inform the design of both pre-clinical studies and clinical trials of novel PTCL therapeutic strategies.

'FOCUS ON. . .' SESSION: EXTRANODAL LESIONS

096
PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEGTYPE (PCDLBCL-LT) HARBOURS THE GENETIC PROFILE OFNODAL ACTIVATED B-CELL DIFFUSE LARGE B-CELL LYMPHOMA (ABCDLBCL)

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PCDLBCL-LT is a separate entity sharing histological and phenotypical features of nodal ABC-DLBCL, especially IRF4 expression. The objective of this study was to screen PCDLBCL-LT for genetic alterations described in nodal ABC-DLBCL. Skin biopsies from 23 patients with PCDLBCL-LT were analysed retrospectively. FISH testing for BCL2, BCL6, MYC split, p16 and BLIMP1 deletion was performed on skin sections. Sequential FISH on the same slide with different probes was realized in order to relocalize tumour area on the slide and to better characterize samples with multiple FISH alterations. We searched for MYD88 mutations by Sanger sequencing. Among 23 patients, we detected cytogenetic or MYD88 alterations in all patients but one. Seven patients exhibited one anomaly, and 15 harboured multiples anomalies. We observed a BCL2/BCL6/MYC split in 1/23 (4.3%), 6/23 (26%) and 3/23 (13%) of cases, respectively. Cases with BCL2, BCL6 or MYC breakpoint were mutually exclusive. p16 deletion was observed in 5/23 (21.7%) and BLIMP1deletion on 11/18 (61%). FISH relocalization of abnormal nuclei showed that several FISH alterations were carried by the same nuclei.The L265P MYD88 mutation was found in 11/18 (61%) of cases. The study of somatic hypermutation and CDR3 IGH length also suggest the post-GC origin of cases tested. Contrary to most cutaneous lymphomas that rarely harbour the same genetic alteration of their nodal histological equivalent, PCDLBCL-LT seems to be a cutaneous counterpart of ABC-DLBCL with similar gene loci alterations and concomittant oncogenic L265P MYD88 mutation. In this small series, we did not find any prognosis impact of these alterations. The similarity with ABC-DLBCL is incentive to further explore common signalling pathways.

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THE ROLE OF RITUXIMAB AND PET IN THE TREATMENT OF PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

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Introduction: Third-generation MACOP-B (adriamycin, cyclophosphamide, vincristine, bleomycin, methotrexate and prednisone) regimen in combination with mediastinal radiotherapy (RT) seems to improve lymphoma-free survival of primary mediastinal large B-cell lymphoma (PMLBCL). In addition, the role of consolidative mediastinal RT remains unclear also with the improvement of PET use.
Patients and methods: Until 2002, MACOP-B plus RT was recommended at our institution in all PMLBCL patients. Between 2002 and 2011, 74 previously untreated PMLBCL patients were diagnosed and treated with MACOP-B plus rituximab and consolidative mediastinal RT (30–36 Gy). Fifty patients had stage II and 24 stage IIE–IV; bulky disease was documented in 93% of patients. Median age was 34 years (range, 17–62) and 59.5% were females. All patients were evaluated by CT and PET scan. After the final PET evaluation, PET-negative patients were observed, whereas PET-positive patients underwent mediastinal RT.Results: Finally, 61 (82.4%) patients achieved a complete response (CR); 51 (68.9%) presented final PET positive and were treated with local RT, whereas the other 23 (31.1%) had PET negative. Five patients relapsed within 12 months. At 10 years, overall survival was 82%, progression-free survival was 87.6% and disease-free survival (DFS) of the 61 patients who achieved CR was 90.5% (median follow-up 4 years). Regarding the DFS curve, no statistically significant differences were observed between the patient subset treated also with RT (PET positive) and patients only observed (PET negative): 90.7% (4/51 relapses) vs 90% (1/23 relapse)

DOI: 10.1002/hon

($p = 0.85$), respectively. Comparing these data with institutional historical records (before 2002), when the front-line for PMLBCL patients included MACOP-B plus RT without any decision related to PET results, the 10-year DFS was 82.8%.Conclusions: This study indicates that rituximab addition does not change the final results in terms of CRs and DFS utilizing third-generation regimens. In addition, the introduction of the PET-guided RT approach after MACOP-B plus rituximab leads to a patient tailored treatment that preserves the outcome and, at the same time, allows to reduce the use of RT.

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THE IMPACT OF RITUXIMAB AND RADIOTHERAPY ON OUTCOME OF PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMA AND SKELETAL INVOLVEMENT

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Introduction: To study clinical presentation and outcome of patients with aggressive B-cell lymphoma and skeletal involvement treated with and without rituximab.
Methods: Outcome of patients with skeletal involvement was analysed in a retrospective study of 9 consecutive prospective trials of the German High-Grade Non-Hodgkin Lymphoma Study Group.
Results: Of 3840 patients 292 (7.6%) had skeletal involvement. In a multivariable analysis of patients treated within the randomized MInT and RICOVER-60 trials, skeletal involvement was associated with a hazard ratio (HR) of 0.8 ($p = 0.181$) for event-free and 0.7 ($p = 0.083$) for overall survival for patients treated without, but with a HR of 1.5 ($p = 0.048$) for event-free and 1.1 ($p = 0.828$) for overall survival in patients treated with rituximab. This was due to the failure of rituximab to significantly improve the outcome of patients with skeletal involvement. In a Cox regression model of event-free survival adjusted for the IPI risk factors a relevant interaction term (HR 1.5; $p = 0.056$) between rituximab and skeletal involvement was observed. In contrast to rituximab, additive radiotherapy to sites of skeletal involvement was associated with a decreased risk [HR = 0.3 for event-free ($p = 0.001$) and HR = 0.5 ($p = 0.111$) for overall survival].
Conclusions: Rituximab failed to improve the outcome of DLBCL patients with skeletal involvement, although our data suggest a beneficial effect of radiotherapy to sites of skeletal involvement.

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A PROSPECTIVE PHASE II TRIAL OF AN L-ASPARAGINASE CONTAINING REGIMEN IN EXTRA NODAL NK/T-CELL LYMPHOMA

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Introduction: L-Asparaginase seems to have a particular efficacy in extra nodal NK/T-cell lymphoma, nasal type.
Methods: Twenty naive patients were included in a multicentric prospective phase II trial using the Aspametdex regimen (E coli-L-asparaginase 6000 UI/m,^{2} IM at day 2,4,6,8, methotrexate 3 gr/m,^{2} at day 1 and dexamethasone 40 mg at day 1 to 4 with 3 weeks cycles). After 3 cycles, patients with a localized disease received radiation (40 Gy) and patients with disseminated disease below 65 years of age received an intensive treatment with the BEAM regimen and stem cell support. Other patients received up to 6 cycles. The histology was centrally reviewed, EBV viremia and anti-asparaginase antibodies were regularly and centrally monitored. The response after 3 cycles was the primary end point.
Results: There were 13 men and 6 women (1 patient excluded after consent withdrawal), median age was 49 (33 to 78), 8 were in stage IV, 3 patients in stage IIE had node involvement. Median number of cycles was 3 (1 to 6). Four patients died rapidly and the response was assessed after 3 cycles in 15 patients, 11 patients were responders with 10 complete responses. Five of the 11 patients who had responded after 3 cycles relapsed including the one who received intensive treatment. Among the 8 patients treated by radiation one had no response prior to radiation and had a systemic relapse in the liver and bones; the 7 other patients responded to chemotherapy and only 1 relapsed at 3 months in cervical lymph nodes with no relapse within the radiation field. Of note 3 patients who had a good response but relapsed could reach a second complete remission using another asparaginase molecule. With a median follow up of 3 years for the 8 surviving patients the median survival time is 12 months. Performans status > 1 and fever were highly predictor of death ($p = 0.0002$ and O.0003). All the 14 patients who had serial antiasparaginase antibody assays became positive, 11 patients after the first cycle.
Conclusion: These data confirm the excellent activity of L-asparaginase containing regimens in extranodal NK/T-cell lymphoma but were disappointing compared with the results with the same protocol in relapsed/refractory patients (Blood 2011;117:1834-9). The inhibition of asparaginase by antibodies, present in all patients tested, could explain the high relapse rate. A systematic switch between asparaginase molecules could overcome this problem.

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BENDAMUSTINE PLUS RITUXIMAB IN FIRST LINE SYSTEMIC TREATMENT FOR EXTRANODAL MALT LYMPHOMA: FINAL RESULTS OF PHASE II TRIAL OF THE SPANISH LYMPHOMA STUDY GROUP (GELTAMO)

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Background: Management of MALT lymphoma requiring systemic treatment is currently controversial. We hypothesized that Bendamustine (B) plus Rituximab (R)+(BR) could be very active in first-line treatment for MALT lymphoma.
Patients and Methods: A nation-wide prospective phase II trial (EUDRACT 2008-007725-39) has been carried out in Spain by the GELTAMO group in untreated patients with CD20 MALT lymphoma requiring systemic therapy. Treatment: Bendamustine (90 mg/m,^{2} days 1–2) and Rituximab (375 mg/m,^{2} day 1), every 28 days. Pts received 4 or 6 cycles (if CR or PR after the 3,rd cycle, respectively). The aims were: feasibility and security of the combination and rate and quality of the responses, and event-free survival. From May 2009 to May 2010, 60 patients were enrolled. Clinical characteristics: median age 62 years (range 26–84); 34 (57%) female; Ann Arbor stage: III–IV in 34%; site of disease: stomach 33%, extra-gastric 57% and multifocal 10%.
Results: A total of 264 cycles of BR were delivered. Only 2 patients received less than 4 cycles. R dose was no modified at any cycle and only 4 patients required dose reduction of B (median dose intensity: 0.98). Only 2 patients have not completed treatment due to toxicity. Only 17 cycles (6%) were delayed. AEs G3-4 by cycle: neutropenia in 5.3%, lymphocytopenia in 9.85% and febrile neutropenia in 0.76% of cycles. A total of 25 G3-4 non-haematologic toxicities were documented in 12 pts. One patient did not have measurable disease, being excluded for efficacy evaluation. Overall response rate (ORR) after 3 cycles was 100%. CR/uCR rate after 3 cycles was 75% for all patients (90% in gastric, 64% in non-gastric and 83% in multifocal). At the end of treatment, ORR was 100% with CR/uCR of 98%. Only 14 pts (23%) required more than 4 cycles of BR. All our patients carrying t(11;18)(q21;q21) responded. With a median follow-up of 17 months (range, 6–42), two unrelated deaths have been recorded and one patient has relapsed.

DOI: 10.1002/hon

Conclusions: The combination of Bendamustine and Rituximab in first line for MALT lymphoma is safe and well accepted by patients. Clinical activity is very high, with a large majority of patients achieving CR after only 3 cycles. Our data demonstrate that immunochemotherapy with BR has an excellent efficacy with a low toxicity profile, making this response-adapted schedule a foremost therapeutic strategy for this type of lymphoma.

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CLINICAL OUTCOMES AND PATTERNS OF RELAPSE IN 320 PATIENTS WITH EARLY AND ADVANCED-STAGE MARGINAL ZONE LYMPHOMA: THE ROLE OF RADIOTHERAPY

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Introduction: We aim to report the characteristics and outcomes of marginal zone lymphomas (MZL) treated at a large cancer centre and to assess the role of radiation therapy (RT) in both early and advanced-stage disease.

Methods: We identified 320 patients with pathologically-confirmed MZL seen at our centre between 1992 and 2012. We collected information on disease and patient characteristics, initial and salvage treatments, relapses, and outcomes. Overall survival (OS) and relapse-free survival (RFS) were generated by the Kaplan-Meier method from the date of diagnosis to date of death/relapse.

Results: Of 320 total patients, 229 (72%) presented with stage I–II (early stage) disease, and 91 (28%) presented with stage III–IV (advanced stage). For early-stage patients, median age was 59 years (range 9–87). Median follow-up was 5 years (range 0–18.8). Primary tumour site was lung in 20%, stomach 19%, orbit 15%, skin 8%, parotid 6%, breast 5%, and various other sites. Initial treatment was RT in 46%, surgery 39%, observation 8%, immunotherapy 5%, and chemotherapy (CHT) 0.5%. Median RT dose was 30Gy (range 4–45). Of the 131 patients receiving RT, 5 (4%) relapsed in-field (3 stomach, 1 paraspinal mass, 1 breast), 5% relapsed regionally, and 17% had distant relapse. Overall 60/229 patients (26.5%) had relapse, at a median of 23 months after diagnosis; 11 were local, 18 regional, and 36 distant. Five-yr OS for early-stage was 88%; 10-yr OS was 71%. Median OS was not reached. Median RFS was 4.9 years (range 0–18.8). For advanced-stage patients, median age was 62 years (range 12–81). Median follow-up was 5.8 years (range 0.25–20.5). Initial site of advanced-stage MZL diagnosis was lymph node in 21%, skin 13%, lung 11%, bone marrow 10%, orbit 8%, breast 7%, and soft tissue 5.5%. Initial therapy was observation in 27.5%, CHT 19%, RT 15%, surgery 16.5%, rituximab 12%, and other 8%. Median RT dose was 30 Gy (range 4–50.4). Of the 68 cases receiving systemic therapy, CR/CRu rates were 54% after CHT and 32% after rituximab. Of the 30 patients receiving RT, only 2 (6.7%) relapsed in-field (orbit, cheek), one relapsed regionally, and 12 (40%) had distant relapse. Overall, 52/91 patients (57%) had relapse, 14 in a primary site and 36 distant, at a median of 27.5 months after diagnosis. In advanced-stage patients, 5-yr OS was 82% and 5-yr RFS was 35%. Median RFS was 3.2 years (range 0.2–17.3); this was significantly less than the early-stage group (log-rank, $p < 0.001$).

Conclusions: In one of the largest studies of MZL to date, we show that MZL is a heterogeneous disease with a long natural history, even in advanced-stage patients. In both early and advanced stages, RT provides excellent local control with rare in-field or regional failures.

'FOCUS ON. . .' SESSION: TREATING THE ELDERLY PATIENTS

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DISEASE CHARACTERISTICS, PATTERNS OF CARE, AND OUTCOMES OF FOLLICULAR LYMPHOMA (FL) IN THE OLDEST OLD: REPORT FROM THE US NATIONAL LYMPHOCARE STUDY (NLCS)

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Background: Data on disease characteristics, treatment patterns, and outcomes of patients (pts) >80 years (y) are rarely reported. The NLCS is a Genentech-sponsored prospective multicentre registry of FL pts without study-specific treatment. We used the NLCS database to better understand FL in pts>80 y.

Methods: Evaluable pts with FL in the NLCS were included. Using Pearson χ,[2] tests, associations of age groups with disease characteristics and response rate (RR) were examined. Median PFS and OS by treatment regimen were estimated for each age group. Cox regression adjusted for baseline disease factors and use of maintenance R (MR) were used to assess treatment differences in PFS and OS and the significance of age by treatment interactions.

Results: Of 2649 pts, 209 (8%) were >80 y. Significant differences between pts >80 and <60 y were observed (table).Pts >80 y were less likely to receive rituximab (R)+chemo than all other age groups [31% vs 52% (≤60), 50% (61–70), and 45% (71–80); p 0.001]. Use of anthracyclines was less frequent in pts >80 y vs others [29% vs 68% (<60), 65% (61–70), 50% (71–80); $p < 0.001$]. Use of MR was similar in all age groups (31%–36%) but was less in pts >80 who received R induction. When adjusting for MR and baseline factors, no treatment provided superior PFS in pts >80 y; in pts <60 y, R +chemo provided superiority.OS at 5 years was 59% and 92%for >80 and <60 y respectively. Cox modelling showed that lower haemoglobin (<12 g/dL) and male sex predicted worse OS ($p < 0.01$) but not PFS.

Conclusions: In the largest-ever published prospectively enrolled cohort of the oldest old FL pts, OS, PFS, RR, and treatment selection vary compared with younger pts.

Abstract 102 Table 1.

Baseline characteristics ($p < 0.05$), no. (%)	≤60 years (N = 1255)	>80 years (N = 209)
White race	1107 (88)	197 (94)
Stage IV	515 (41)	70 (34)
Gr 3 histology	212 (18)	51 (27)
≥5 nodal sites	476 (39)	35 (18)
Haemoglobin <12 g/dL	182 (16)	72 (38)
ECOG PS 0	672 (76)	59 (45)
Bone marrow involvement	419 (41)	36 (33)
RR ($p < 0.01$), %	75	66
Initial treatment ($p < 0.01$), no. (%)		
Watchful waiting	241 (19)	51 (24)
R	124 (10)	61 (29)
R+Chemo	649 (52)	65 (31)
Median F/U (year)	6.2	4.3
Median, year (95% CI)		
PFS	7.3 (6.5–7.8)	3.1 (2.3–4.4)
OS	Not reached	5.7 (5.0–6.6)

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INFERIOR OUTCOME OF ELDERLY DLBCL PATIENTS WITH 25- OH VITAMIN D DEFICIENCY TREATED WITH CHOP PLUS RITUXIMAB (R): RESULTS OF THE RICOVER-60 TRIAL OF THE GERMAN HIGH-GRADE NON-HODGKIN LYMPHOMA STUDY GROUP (DSHNHL)

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Introduction: Vitamin D deficiency was shown to be is associated with a worse outcome in patients with non-Hodgkin' s lymphoma (Drake et al., 2010). To study whether this observation could be confirmed in patients with aggressive B-cell lymphomas treated uniformly within a prospective trial, we analysed 25-OH vitamin D serum levels in patients treated within the RICOVER-60 trial of the DSHNHL.

Methods: 25-OH vitamin D serum levels were determined with a commercial chemoluminescence immunoassay in the serum from elderly patients of the RICOVER-60 trial, which compared six or eight cycles of CHOP, both with and without rituximab.

Results: 193 of 359 pts (53.8%) had vitamin D deficiency (<10 ng/ml) and 165/359 patients (46.0%) had vitamin D insufficiency (10–30 ng/ml) according to current definitions. When treated with R-CHOP, patients with vitamin D levels ≤8 ng/ml had a 3-year EFS of 59% compared with 79% of patients with vitamin D serum levels >8 ng/ml; the respective figures for 3-year overall survival were 70% and 82%, respectively. In R-CHOP pts these differences were significant in a multivariable analysis adjusting for IPI risk factors with a hazard

DOI: 10.1002/hon

ratio (HR) of 2.1 ($p = 0.008$) for EFS and a HR of 1.9 ($p = 0.040$) for OS. In pts treated without R effects of vitamin D deficiency were significant only for OS (HR 1.8; $p = 0.025$), but not with respect to EFS (HR 1.2; $p = 0.388$). These results were confirmed in an independent validation set of 63 patients treated within the prospective RICOVER-noRx study.
Conclusions: Vitamin D deficiency is with a significantly worse outcome of patients with DLBCL treated with R-CHOP. The stronger adverse effect of vitamin D deficiency in patients receiving rituximab suggests that vitamin D deficiency interferes with the mechanisms of action of this antibody. A prospective study evaluating the effects of vitamin D substitution on outcome of patients receiving R-CHOP is warranted.
Supported by Deutsche Krebshilfe.

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BRIEF RITUXIMAB, BENDAMUSTINE, MITOXANTRONE (R-BM) INDUCTION FOLLOWED BY RITUXIMAB CONSOLIDATION IN ELDERLY DE NOVO ADVANCED STAGE FOLLICULAR LYMPHOMA (FL) PATIENTS: A STUDY BY FONDAZIONE ITALIANA LINFOMI (FIL)

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Aim: to investigate safety and efficacy of a brief Bendamustine-containing regimen for treatment of elderly FL patients (pts).

Patients and methods: 76 elderly (age 65–80) pts were enrolled (Sept 2009–Nov 2011). Inclusion criteria were: untreated grade I, II and IIIa FL; advanced stage (III/IV) or stage II disease requiring treatment; FIT pts according to comprehensive geriatric assessment. Treatment plan was: 4 monthly courses of R-BM (375 mg/m,^{2} Rituximab day 1, 90 mg/Bendamustine days 1–2, 8 mg/m,^{2} Mitoxantrone day 1) followed by 4 weekly Rituximab as consolidation. PCR analysis for BCL2/IgH rearrangement was performed on bone marrow.
Results: Median age was 71 (65–79); 15% had stage II, 30% stage III and 55% stage IV; 59% pts had no comorbidity, 20% one and 21% ≥2 comorbidities; 60% pts were at high risk according to FLIPI. PCR analysis for Bcl2/IgH rearrangement was carried out in 57 pts at diagnosis: 39 (51%) were Bcl-2 positive. Seventy (92%) pts completed the planned treatment (60/70 in the planned time). Six pts did not complete treatment: 1 progressive disease (PD), 4 adverse events (2 prolonged neutropenia and 2 infections) and 1 worsening of performance status. Overall response to treatment was 92% with 58 (76%) complete remissions (CR) and 12 (16%) partial remissions (PR). Response to induction R-BM was: 41% CR, 52% PR and 7% SD/PD; 29 (72%) of the 40 pts in PR/SD after R-BM converted to CR following Rituximab consolidation. 23/39 pts Bcl-2 positive at diagnosis were evaluable after treatment: PCR negativity was achieved in 22/23 (96%) pts and 18/22 (82%) were also in CR. A total of 577 courses were given. The most frequent CTC grade 3–4 toxicity was neutropenia in 18% of the courses; 8 neutropenic fevers and 8 grade 3-infections were recorded. Two deaths were reported: one pneumonia with worsening of pre-existing pemfigo and one patient with hepatic metastasis of occult carcinoma diagnosed at final restaging.
Conclusions: A brief course of chemo-immunotherapy R-BM followed by Rituximab consolidation is safe and effective with a high CR rate in elderly pts with untreated advanced stage FL.

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MAJOR RESPONSES IN OVER 90% OF OLDER PATIENTS TREATED WITH F(C)R-BASED CHEMOTHERAPY—THE AUSTRALASIAN LEUKAEMIA AND LYMPHOMA GROUP (ALLG) CLL5/OFOCIR STUDY

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Introduction: Combination immunochemotherapy with fludarabine (F), cyclophosphamide (C) and rituximab (R) gave superior progression free and overall survival compared with FC in the CLL8 Study. The median age in CLL8 was 61 years compared with median age of CLL overall at 72 years.
Methods: Previously untreated fit patients with progressive CLL aged ≥65 were randomized to one of three treatment regimens FR5, FCR3 and FCR5 as follows: (i) F 24 mg/m,^{2} p.o. D1-5 + R (375 mg/m,^{2} C1, 500 mg/m,^{2} C2-6) iv D1 (FR5),(ii) F 24 mg/m,^{2} p.o. and C 150 mg/m,^{2} p.o. D1-3 + R iv D1 (FCR3) or (iii) F 24 mg/m,^{2} p.o. + C 150 mg/m,^{2} p.o. D1-5 + R iv D1 (FCR5), all given at 4 weekly intervals for an intended six cycles with no dose reduction. Therapy was delayed up to 2 weeks if there was grade 3 or 4 toxicity, and if unresolved, came off study.If toxicity resolved to grade 2 or less, therapy proceeded. Fitness was assessed as a Cumulative Illness Rating Scale (CIRS) score of ≤6.
Results: Recruitment of all 120 patients was completed in July 2012. This analysis was performed on 12 Feb 2013, seven months after last recruitment. Median age was 71 (range 65–83) years. Binet stage was progressive A 20 (16.7%), B 56 (46.7%) and C 44 (36.7%). Response data are shown for the overall total cohort with no analysis by treatment arm. There was grade 3/4 neutropenia in 39.8% and febrile neutropenia/infection in 15.9%.
Conclusions: Oral F(C)R therapy appears generally safe and well tolerated in CLL patients aged ≥65 years requiring first therapy based on incomplete data 7 months after recruitment. Using stringent stopping criteria, 35% stop early due to toxicity, intercurrent illness or patient choice, and 61.9% have a delay during therapy. Response rates are high with overall response rate of 92.4%, and complete remission in 40.5% at Final Staging 2 months after treatment.

Abstract 105 Table 1.

Response	Interim staging		Initial response		Final staging	
		(%)		(%)		(%)
Complete remission	37	36.3	54	60.7	32	40.5
Nodular partial remission	3	2.9	1	1.1	11	13.9
Partial remission	58	56.9	31	34.8	30	38.0
Stable disease	4	3.9	3	3.4	6	7.6
Progressive disease	0	0.0	0	0.0	0	0.0
Total	102	100.0	89	100.0	79	100.0

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SAFETY AND EFFICACY OF ABBREVIATED INDUCTION WITH ORAL FLUDARABINE (F) AND CYCLOPHOSPHAMIDE (C) COMBINED WITH DOSE-DENSE IV RITUXIMAB (R) IN PREVIOUSLY UNTREATED PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) AGED ≥65 YEARS: RESULTS OF A MULTICENTRE TRIAL (LLC 2007 SA) ON BEHALF OF THE FRENCH GOELAMS/FCGCLL/WM INTERGROUP

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Introduction: Elderly population is underrepresented in CLL trials and it is still unclear how FCR should be applied in this subgroup. We report results of

DOI: 10.1002/hon

induction with abbreviated FC and dose-dense R in the 200 first patients (pts) enrolled in the LLC 2007 SA trial.
Methods and patients: 194 stages B/C fit (CIRS < 6, CCR > 60 ml/min, PS < 1) pts (median age 71 y, 65% males, unmutated IgHV 57%, del11q 18%, t12 14%, del13q 57%) without del17p, were analyzable. FCR consisted of 4 monthly cycles of oral FC (F 40 mg/msq/d and C 250 mg/msq/d, x 3d) and iv R (375 mg/msq d1 cycle 1, 500 mg/msq d14 cycle 1, d1 and 14 of cycle 2, and d1 of cycles 3 and 4). MRD was analysed by 6-c FCM. After induction, pts were randomized between observation and maintenance rituximab.
Results: 88% received all 4 cycles. Less than 5% could not receive d14 R. Dose delay and dose reduction for cycles 2, 3, and 4 were 12% and 7%, 14% and 8%, 15% and 11%, respectively. Neutropenia g3/4 occurred after cycle 1, 2, 3 and 4, in 46%, 50%, 53%, and 46% of the pts. G-CSF was given in 32%, 46%, 48%, and 52% of them after cycles 1, 2, 3, and 4. G3/4 infections occurred in 6.7%, 4.8%, 7.1%, and 6.2% of the pts after each of the 4 cycles, and in 12.2% during the first year following randomization. In total, 6.3% of the 732 cycles were followed by febrile neutropenia or infection qualified as SAE. Six (3.1%) toxic deaths (all infections) occurred during induction. 158 pts (81%) could proceed to per protocol randomization. CR was observed in 19.7%, nPR in 2.7%, and PR in 73.9%, for an ORR of 96.3% (NCI 96). MRD eradication occurred in 59% (PB) and in 37% (BM) of the pts. Del11q and male gender predicted for lower probability of MRD eradication. OS at 36 months was 87%.
Conclusions: This approach could enable the safe administration of FCR to elderly fit CLL patients in first line. The response rate is high with MRD eradication rate in the range of reported results for younger patients after full iv FCR6. FC4R6 appears to be an adequate platform before post-induction intervention.

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FIRST LINE THERAPY OF ELDERLY PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)—LONG TERM FOLLOW-UP (FU) RESULTS OF A RANDOMIZED PHASE III STUDY OF THE GERMAN CLL STUDY GROUP (CLL5 STUDY OF THE GCLLSG)

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Introduction: Although chemoimmunotherapy regimens are standard first line therapy in physically fit CLL patients (pts), these regimens are too toxic in comorbid elderly pts. Hence chemomonotherapy still plays a role in this pt group. Results of long term FU of CLL pts aged 65 years or older receiving chlorambucil (Clb) or fludarabine (F) first line therapy within a multicentre phase III study are reported here.
Methods: From 07/1999 until 09/2004 193 pts were randomized to receive F (93) or Clb (100). Median observation time (MOT) for all pts alive was 68.1 months (mo) (89.9 mo for F versus (vs) 54.9 mo for Clb; $p = 0.098$). Pt characteristics were described previously (Eichhorst et al., Blood 2009). IGHV status was available in 42 and 46 pts, respectively (unmutated IGVH: 67% in F and 59% in Clb arm).
Results: Median progression-free survival (PFS) was 19.6 mo with F vs 15.6 mo with Clb ($p = 0.74$). In the Clb arm 33 pts received relapse treatment without documented progression in comparison with 16 in the F arm). Though event-free survival (EFS) was significantly longer in the F arm (18.7 mo vs 10.4 mo; $p = 0.012$), this advantage did not translate into a longer OS (49.8 mo vs 68.1 mo; $p = 0.7$). Standardized mortality ratio was calculated and showed a 5.14 (CI 4.29–6.11) increased risk of death in comparison with the age matched general population. In pts with unmutated IGHV F yielded longer PFS and EFS, but no longer OS (20.2 vs 16.2, $p = 0.03$; 18.7 vs 7.7, $p = 0.006$). No differences were observed in other subgroups. Second primary malignancies (SPM) occurred in 39 of 193 pts (20.2%). At time point of MOT 68.6% of patients in the F-arm were SPM-free versus 83.8% in the CLB-arm ($p = 0.09$). Six cases of hematological malignancies were reported (3.1%), 12 Richter transformations (RT) (6.2%) and 21 solid tumours (10.9%). RT occurred in tendency more frequent after F (8.6% vs 2.0%; $p = 0.05$). Standardized incidence ratio of solid tumours showed a 1.33 increased incidence (CI 0.81–2.05) only in elderly CLL patients.
Conclusion: Also after longer FU no survival benefit for F was observed though it yielded better EFS. SPM and especially RT were in tendency more frequent with F.

'FOCUS ON. . .' SESSION: MANTLE CELL LYMPHOMA

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DEEP B AND T-CELL REPERTOIRE SEQUENCING TO EVALUATE MINIMAL RESIDUAL DISEASE AND T-CELL RESPONSES IN A THERAPEUTIC VACCINE TRIAL FOR MANTLE CELL LYMPHOMA

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Background: A clinical trial is being conducted for mantle cell lymphoma (MCL) patients in first remission that interdigitates an autologous CpG-stimulated tumour cell vaccine with high dose therapy and autologous peripheral blood stem cell transplant (PSCT). In this trial, blood samples collected before and after vaccination and serially post-transplant are assayed for minimal residual disease (MRD) and T-cell repertoire using the LymphoSIGHT,™sequencing method.**Methods:** We identified clonal rearrangements of immunoglobulin heavy chain (IGH) in diagnostic samples and assessed MRD in follow-up samples. To quantify T-cell responses to tumour vaccinations, the same samples are used for amplification, sequencing and analysis of the TRB repertoire.
Results: MRD was detected in blood samples immediately post-transplant in 3 of 15 MCL patients, 2 of which ultimately relapsed. In these 2 cases, disease was detected by sequencing 14 and 4.5 months prior to detection by radiologic techniques. To identify T-cells specific to the cancer vaccination, we identified clonotypes that increased in frequency following the priming and boost vaccinations. Clonotypes that fit that profile are termed vaccination-responsive (VR). Patients could be stratified into two groups with high (> 40) or low (<40) numbers of VR clonotypes. Patients with high numbers of VR clonotypes are more likely to be MRD negative throughout the first year post-PSCT ($p = 0.018$, Table 1).
Conclusions: This high-throughput sequencing method for MRD quantification shows promise for predicting clinical relapse in MCL patients after PSCT. T-cell repertoire analysis identified clonotypes responding to the vaccination, and the presence of these vaccine-specific clonotypes correlates with MRD positivity at one year post-PSCT. Continued follow-up for molecular and clinical relapse is ongoing.

Abstract 108 Table 1.

	Patients with high number (>40) of vaccine responsive T-cells	Patients with low number (<40) of vaccine responsive T-cells
MRD	0	3
MRD-	8	1

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REPROGRAMMING MCL FOR CYTOTOXIC KILLING BY TARGETING CDK4/CDK6

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Introduction: Cell cycle dysregulation is a hallmark of mantle cell lymphoma (MCL) due to aberrant Cyclin D1 and CDK4 expression. By targeting CDK4, we have developed a novel strategy that both inhibits proliferation of MCL cells and reprograms them for cytotoxic killing. We have shown that: 1) inhibition of CDK4/6 with PD0332991, an oral selective and potent inhibitor, leads to early G1 arrest; 2) prolonged early G1 arrest (pG1) reprograms cancer cells to killing by diverse agents including bortezomib; 3) pG1 sensitization is amplified in synchronous S phase entry (pG1-S) upon PD0332991 withdrawal; and 4) PD0332991 inhibits CDK4 and induces pG1, resulting in durable clinical responses with an excellent toxicity profile in a phase I trial in MCL. To advance targeting CDK4/6 in MCL, we have now combined PD0332991 with bortezomib at reduced dose (1.0 mg/m,^{2}) in a phase I clinical trial (PDBtz) in previously treated MCL patients, and investigated the mechanism of clinical response from pG1 sensitization.

DOI: 10.1002/hon

Methods: PD0332991 was administered to MCL patients 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. We investigated genes that mediate pG1 sensitization by RNA-sequencing of primary MCL tumour cells isolated from serial lymph node biopsies at baseline, in pG1 (day 8) and in pG1-S (day 21) and by immunohistochemistry.
Results: PDBtz was well tolerated and appeared to have a PD0332991 dose-dependent clinical activity ($n = 16$). PD0332991 inhibited CDK4 and induced pG1 in all patients regardless of the clinical response, mutations in p53 or ATM, or 3'UTR deletion in Cyclin D1. No mutations were detected in CDK4. Importantly, induction of pG1 by PD 0332991 led to an imbalance in gene expression in MCL tumour cells because only genes programmed for early G1 were expressed in pG1. However, 21 of the 562 genes suppressed in pG1 (not programmed for early G1) (EdgeR, FDR 0.05) in clinically responding patients were conversely activated in the non-responding patients.
Conclusion: Targeting CDK4/6 with PD 0332991 induces pG1 in all MCL patients, which reprograms MCL for cytotoxic killing and is associated with clinical response to bortezomib through repression of selective cell cycle-coupled genes.

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A HIGH PIK3CA/PIK3CD MRNA RATIO IN MANTLE CELL LYMPHOMA CAN PREDICT RESISTANCE TO PI3Kδ INHIBITION AND IS MORE COMMON WITH MULTIPLE RELAPSE

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Introduction: Phosphoinositide-3 kinase (PI3K) signalling contributes to mantle cell lymphoma (MCL) pathogenesis. The PI3K p110δ isoform is enriched in leucocytes and is an attractive target but early phase studies of the P110δ inhibitor GS-1101 have reported inferior
Results: in MCL compared with CLL and indolent non-Hodgkin lymphoma. We investigated the role of class Ia PI3K isoforms and PTEN in relation to isoform selective PI3K inhibition in MCL.
Methods: Immunohistochemistry (IHC) for p110α, p110β, p110δ and PTEN was performed on MCL tissue microarrays (144 biopsies from 109 patients). Gene expression was determined by qRT-PCR. IgM F(ab') fragments were used for BCR stimulation. The isoform selective inhibitors A66 (p110α), TGX221 (p110β), GS-1101 (p110δ) and GDC0941 (predominantly p110α/δ) were used. Western blotting was used to assess downstream changes, whereas an ATP assay was used to determine cytotoxicity. 20 MCL primary samples and 2 cell lines (Granta519 and Jeko-1) were screened for mutations in PIK3CA and PIK3R1.
Results: IHC revealed that, although p110δ was highly expressed in MCL, p110α showed wide variation and p110β expression was the weakest. P110α expression increased significantly beyond first relapse ($p = 0.04$) and strikingly so in sequential biopsies ($p = 0.008$). Although GS-1101 was sufficient to abolish BCR mediated PI3K activation, additional p110α inhibition was required to abolish constitutive PI3K activation. GDC0941 was significantly more active in cell lines and primary MCL samples compared with GS-1101. Importantly, a high PIK3CA/PIK3CD mRNA ratio (>twice the ratio in healthy B-cell controls) identified primary samples that were resistant to GS-1101 and significantly more sensitive to GDC0941. This ratio also increased significantly with relapse. PTEN loss was seen in 16% of cases but was not associated with increased sensitivity to p110β inhibition. No activating mutations of PIK3CA or PIK3R1 were found.
Conclusion: Dual p110α/δ blockade appears to be necessary for effective PI3K inhibition in MCL, particularly with relapse. This will require testing in a clinical trial, but the PIK3CA/PIK3CD ratio may help identify tumours that are most likely to respond to these exciting agents.

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RADIOIMMUNOTHERAPY AS CONSOLIDATION IN MCL (MANTLE CELL LYMPHOMA)—8 YEARS FOLLOW-UP OF A PROSPECTIVE PHASE 2 POLISH LYMPHOMA RESEARCH GROUP STUDY

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Introduction: Considering elderly age and co-morbidities, less than 20% of MCL patients (pts) are candidates for high-dose chemotherapy with ASCT (autologous stem cell transplant) support, regarded as standard first-line approach. Radioimmunotherapy with 90Y ibritumomab tiuxetan (Y90) may be an alternative consolidation method, feasible for frail pts.
Methods: In 2005–2008, 46 MCL pts not eligible for ASCT were consolidated with Y90 after the initial response to the first ($n = 34$) or second line ($n = 12$) therapy in a prospective, multicentre 2 phase trial. At diagnosis: median age 60 (range 35–78), MIPI 5,8 (4–7), LDH IU/l 460 (165–850), stage IV (85%), B symptoms (70%); 26 pts received CHOP- or CHOP-like-, and 20 fludarabine based induction regimens. Eight years median follow-up and late adverse events are reported.
Results: Consolidation increased CR rate from 41% after induction to 87% after Y90. Median OS after Y90 was 6,5 years for pts consolidated after the first line therapy and 2.5 years for those in chemosensitive relapse. 26/46 pts died: 2 (4,3%) due to early complications (stroke and infection during post-treatment cytopenias), 5 (10,8%) after developing myelodysplastic syndrome (MDS) and 16 (38%) due to MCL relapse/progression. Median time to development of MDS and subsequent AML transformation were 26 (10–38) and 4,6 (1–7) months, respectively. All MDS cases were confirmed by histopathology, 4/5 in cytogenetic analysis: 1) 43–44,XY,del(3)(p21),−5,−7[4]/43,sl,−12,add(21)(q22)[10], 2) 47,XX,+11,add(17)(q25), 3) 42–45,XY,del(3)(p21),−5,r(7)(p22p12),del(12)(p11p13),−15, +mar1,+ mar2 [25cp], 4) 45,XX,−7,−16,−19,+mar1,+mar2 [6]; 4/5 MDS pts had previous fludarabine-based regimen, 1–previous ASCT.
Conclusion: Abbreviated chemotherapy followed by Y90 consolidation is an attractive therapy option for elderly-, frail pts with MCL. 40% of pts receiving Y90 as first-line consolidation are in continuous CR 8 years after diagnosis. MDS incidence in our series appears higher than reported in other studies, yet was confined to those with prior treatment with fludarabine or ASCT.

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OUTCOME AFTER RIC ALLO-STEM CELL TRANSPLANTATION FOR PATIENTS WITH MANTLE CELL LYMPHOMA WHO RELAPSED AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION: A RETROSPECTIVE STUDY OF THE SFGM-TC GROUP

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After autologous stem-cell transplantation (ASCT), MCL patients remain highly exposed to relapse. Then, reduced intensity conditioning allogeneic stem-cell transplantation (RIC-allo) is among therapeutic options. We performed a national survey conducted on behalf of the SFGM-TC group. Inclusion criteria were as followed: patients with MCL who relapsed after ASCT and for whom RIC-allo has been performed. Patients' characteristics ($n = 105$) were as followed: median age at diagnosis was 54 years (range, 30–65). Median PFS after ASCT was 4 years (range, 0.4–10). Median age at RIC-allo was 60 years (range, 39–68) and median time from ASCT to RIC-allo was 4 years (range, 0.4–10). Before RIC-allo, 85% of patients had received at least 2 lines of treatment. Sources of donor were: matched related donor in 35 cases, matched unrelated in 50 cases and mismatched donor in 20 cases (19%). Conditioning regimens were cyclophosphamide-based, fludarabine-based or busulfan-based in 20%, 33% and 47%, respectively. A low-dose TBI (Maximum dosing of 2Gy) was used in 27 patients. At time of RIC-allo, 63% ($n = 63$) of patients were in CR, 7% ($n = 7$) in PR and 20% ($n = 20$) with Progressive Disease (data missing in 10%).

Results: 20 patients (19%) experienced grade III/IV aGVHD and Extensive cGVHD was reported in 17 cases (16%). After RIC-allo, 81 (94%) patients reached at least PR. Median FU after RIC-allo was 52 months (range, 12.6–166). At time of the present analysis, median PFS was 21 months whereas median OS calculated from time of RIC-allo was 51 months. Median PFS and OS according to disease status at transplantation were 59m and 62m for patients in CR; 10m (PFS and OS) for patients in PR, 4.1m and 5m for patients in PD; respectively. Seventeen patients (17%) relapsed. Median time from RIC-allo to relapse was 6 months (range, 2–57) and 46 patients (44%) died. Causes of death were related to toxicity in 29 cases, lymphoma progression in 9 patients and other causes in six patients (data missing = 2).
Conclusion: Our ongoing analysis shows that incidence of relapse after RIC-allo remains high for MCL patients who have previously relapsed after ASCT. As expected, patients in CR at time of RIC-allo experience a longer PFS duration, underlying that new salvage therapies are highly warranted prior to RIC-allo.

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TARGETING THE IRF4/MYC AXIS IN BORTEZOMIB-RESISTANT MANTLE CELL LYMPHOMA WITH LENALIDOMIDE AND BET BROMODOMAIN INHIBITION

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Introduction: Despite the promising introduction of the proteasome inhibitor bortezomib (bz) in the treatment of mantle cell lymphoma (MCL), not all the patients respond and relapses frequently occur. Our aim was to unravel the intratumoural and environmental factors involved in bz resistance in preclinical models of MCL.
Methods: A set of MCL cell lines was engrafted onto immunodeficient mice, followed by gene expression profiling and immunohistochemical (IHC) analyses of representative tumours. The immunomoduladory drug lenalidomide was then applied to MCL cultures and MCL tumour bearing mice, either alone or in combination with bz or with the BET bromodomain inhibitor CPI-267203. Response to drugs and drug combinations was analysed by *in vivo* imaging, flow cytometry, western blot, antibody array, real-time PCR, immunofluorescence and IHC.
Results: We observed an increased tumourigenicity of bz-resistant MCL cell lines *in vivo*, that was associated with plasmacytic differentiation, including up-regulation of IRF4 and CD38 and secretion of CCL3. As lenalidomide has been shown to modulate IRF4 expression in various B-cell malignancies, we assessed its activity in *in vitro* and *in vivo* settings. *In vitro*, lenalidomide as single agent was found to exert antitumour activity in 4/11 MCL cell lines, corresponding to those cells with either primary or acquired resistance to bz. Lenalidomide-treated cells showed decreased MYC expression, increased cytosolic $p27^{KIP1}$ amounts and caspase-dependent apoptosis. Accordingly, mice bearing bz-resistant tumours and treated for 3 weeks with a lenalidomide regimen of 10–50 mg/kg/day, showed a 30 to 45% reduction in tumour burden when compared with vehicle-treated mice ($p < 0.05$), with several hallmarks of lenalidomide activity like IRF4 downregulation, CD80 and CD40L upregulation, decrease in mitotic index and MYC expression, $p27^{KIP1}$ cytosolic accumulation and caspase-3 processing. Importantly, the inhibition of tumour growth induced by the combination of lenalidomide with bz (0.15 mg/kg, twice a week) was 37% and 66% greater than that for lenalidomide alone and vehicle arms, respectively ($p = 0.02$). In addition, co-treatment of mice with lenalidomide plus CPI-267203, known to target MYC transcription, synergistically reduced MYC and IRF4 expression and tumour burden.
Conclusions: These results suggest that IRF4 and MYC are involved in bortezomib resistance in MCL, and that the combination of lenalidomide with a BET inhibitor may warrant clinical evaluation in MCL cases refractory to bortezomib.

SESSION 8: TARGETING THE LYMPHOMA EPIGENOME

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THE BRD-INHIBITOR OTX015 IS ACTIVE IN PRE-CLINICAL B-CELL LYMPHOMA MODELS AND AFFECTS RELEVANT PATHOGENETIC PATHWAYS

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Introduction: BET-bromodomain inhibitors are a promising new class of anti-cancer agents because BET family proteins BRD2/3/4 are chromatin adaptors, functionally linked to pathways important for cellular viability and cancer signalling. Here, we assess the *in vitro* activity and the mechanism of action of OTX015, a selective orally bioavailable BRD2/3/4 inhibitor, in a large panel of B-cell lymphoma cell lines.
Methods: MTT assays were performed after 72h of drug exposure. Cell cycle, apoptosis and senescence were evaluated before and after drug exposure. Gene expression profiling (GEP) was done with Illumina HumanHT-12 v4 Expression BeadChip.
Results: Anti-proliferative effect was seen in the vast majority of the cell lines. The median IC50s were 0.2 μM (0.01–13) in 13 diffuse large B-cell lymphomas (DLBCL), 0.2 μM (0.1–0.2) in 3 splenic marginal zone lymphomas, 2 μM (1 to >15) in four mantle cell lymphomas. OTX105 caused G1 cell cycle arrest and increased percentage of senescent cells. Apoptosis was observed only in 1 DLBCL cell line. OTX015 downregulated MYC in a dose-dependent and reversible way in all cells except 1 DLBCL cell line. NFKB target genes were affected, too. GEP was done in 3 DLBCL cell lines, exposed to 4–8 h DMSO or OTX015 (0.5 μM). Affected transcripts were significantly enriched of putative MYC/E2F1 targets, genes involved in cell cycle and chromatin structure, genes coding for members of the MYD88 pathway, and genes modulated by HDAC-inhibitors. Validation of the MYD88 pathways changes with also the demonstration of a decreased production of the cytokines IL10 and IL4 indicate that OTX015 might affect the MYD88/JAK/STAT pathway in DLBCL. Finally, the combination of OTX015 with the class I–II HDAC inhibitor Scriptaid was synergistic *in vitro*, in accordance with GEP data.
Conclusions: OTX015 showed cytostatic activity in a large series of B-cell lymphomas. Down-regulation of MYC appeared as the main effect, but other important pathways are modulated as well. The compound is worth of further investigation as a new promising therapeutic agent in lymphomas. *MB and PB equally contributed.*

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PRECLINICAL CHARACTERIZATION OF E7438: A POTENT, SELECTIVE INHIBITOR OF PROTEIN METHYLTRANSFERASE EZH2 WITH ROBUST ANTITUMOUR ACTIVITY AGAINST EZH2 MUTATED NONHODGKIN LYMPHOMA XENOGRAFTS IN MICE

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The coupled enzymatic activity of wild-type and mutant EZH2 results in hyper-trimethylation of histone H3 lysine 27 (H3K27), which drives lymphomagenesis in heterozygous patients bearing the EZH2 mutations. Through iterative medicinal chemistry we have developed a selective inhibitor of EZH2 with good pharmacological properties, E7438. E7438 binds to the enzyme in a manner competitive with S-adenosyl methionine (SAM) and a Ki for wild-type EZH2 of 2.5 nM. The compound potently inhibits all known mutants of EZH2 that have been identified in non-Hodgkin lymphoma (NHL) patient samples. E7438 displays about 35-fold less activity against the closely related enzyme EZH1, and is >4500-fold selective with respect to all other protein methyltransferases tested. Lymphoma cells treated with E7438 display concentration-dependent and time-dependent loss of H3K27 methylation with no effect on the methylation status of any other histone sites. The loss of H3K27 methylation results in selective killing of EZH2 mutant-bearing lymphoma cell lines. E7438 displays good oral bioavailability and pharmacokinetic properties. Various EZH2 mutant-bearing human lymphoma tumours were subcutaneously implanted in nude, SCID or NSG mice. Oral administration of E7438 to tumour bearing mice resulted in significant anti-tumour activity. The responses ranged from dose-dependent tumour growth inhibition to complete and sustained regressions. Mice and rats tolerated E7438 administration well at doses representing high multiples of doses that show antitumour activity in mice. Activity against the EZH2 target in both species was demonstrated by

DOI: 10.1002/hon

dose-dependent diminution of H3K27 trimethylation levels, assessed by ELISA and IHC, in samples of tumour, bone marrow, skin and peripheral blood mononuclear cells (PBMCs). The ability to measure dose-dependent changes in H3K27me3 levels in skin and PBMCs portends the use of signal from these surrogate tissues as a non-invasive pharmacodynamics biomarker in human clinical trials.

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SIRTUIN AND PAN-CLASS I/II DEACETYLASE (DACI) INHIBITION IS SYNERGISTIC IN PRECLINICAL MODELS AND CLINICAL STUDIES OF LYMPHOMAS

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Introduction: There is a critical inverse relationship between Bcl6 and p53, the functional status of which is linked to each transcription factor's degree of acetylation. Deacetylation of Bcl6 is required for its transcriptional repressor effects. Conversely, acetylation activates p53. One therapeutic strategy for lymphomas addicted to Bcl6 is the pharmacologic modification of Bcl6 and p53 using DACi and sirtuin inhibitors.
Methods: Cytotoxicity was measured by Cell titer-Glo and synergy calculated in 8 DLBCL cell lines (4 ABC, 4 GC) with 4 DACi (romidepsin, vorinostat, panobinostat belinostat) in combination with sirtuin inhibitor niacinamide (NIA). Modulation of Bcl6 and p53 pathways were analysed by immunoprecipitation and immunoblot. Apoptosis was measured by FACs for Yo-Pro-1/PI. *In vivo* effects were studied in a transgenic mouse model (λ-MYC crossed with CD19-mCherry luciferase) of spontaneous aggressive Bcl6+ B-cell lymphoma. A phase I clinical trial was conducted in patients with relapsed/refractory lymphoma. Vorinostat was given at 400 mg and NIA in escalating doses 20–100 mg/kg p.o. daily 14 of 21 day cycle. Results: Synergy was achieved predominantly in GC vs ABC cells. Romidepsin (R) plus NIA was the most potent doublet. Cells treated with DACi + NIA yielded increased acetyl-Bcl6, acetyl-p53, p21 and BLIMP-1. Mice treated with R + NIA achieved greatest reduction in tumour volume compared with single agents. Response correlated with pharmacodynamic endpoints. Twenty-five patients were enrolled. The median number of therapies was 4 (16 auto- and 4 allo-transplants). There were 12 grade 3–4 toxicities including neutropenia, infection, and transaminitis that occurred in 11 patients. MTD was defined as vorinostat 400 mg and NIA 80 mg/kg. The ORR = 24% (2 CRs, 3PRs), and an additional 57% patients achieved SD.
Conclusion: The data establish proof-of-principle that the Bcl6: p53 axis is a therapeutic target in DLBCL. Increasing evidence suggests that targeting the molecular subtypes of DLBCL will lead to new treatment paradigms for the disease.

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THE PAN-HISTONE DEACETYLASE INHIBITOR (HDACI) ABEXINOSTAT (PCI-24781): SIGNIFICANT CLINICAL ACTIVITY IN RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL) IN A MULTICENTRE PHASE II STUDY

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Background: Abexinostat (PCI-24781) is a novel oral pan-HDACi that has demonstrated potent preclinical activity in lymphoma cell lines and animal models (Evens et al, Clin Ca Res 2009). In a phase I single-agent study in patients (pts) with R/R hematologic malignancies, anti-tumour activity was noted in FL and mantle-cell lymphoma (MCL). On the basis of these encouraging single-agent abexinostat data, a phase II extension study was completed in R/R FL and MCL.
Methods: The primary objective of this multicentre phase II study (NCT00724984) was objective response rate (ORR, complete [CR] and partial remission [PR]). Abexinostat was given orally twice daily at 45 mg/m,^{2} on a 4-week cycle for 7 days/week every other week, which was established in the phase I study.
Results: 30 pts were enrolled ($n = 16$ FL, $n = 14$ MCL pts) of which 25 were response-evaluable. The median age was 67 years (36–81) and median prior therapies were 3 (1–5), and 33% had had prior stem cell transplant. The ORR was 48% in all pts. A reduction in tumour size was observed in 86% of FL pts, whereas the ORR in FL was 64% (intent-to-treat ORR 56%). Further, by 1999 IWC criteria, the complete remission rate in FL was 36%. The median duration of response (DOR) in FL was 18 months (7–24); there are 5 responding pts who remain on study without progression. Furthermore, 8/9 responding FL pts were on study >8 months and 5/9 pts were on >17 months. The median progression-free survival (PFS) for FL pts pts was 20.5 months (1–25). Among MCL pts, reduction in tumour size was noted in 27% and the ORR was also 27%. Median PFS in MCL pts was 4 months (1–12), whereas the DOR in the three responding patients were 6, 9 and 12 months. Therapy was overall well tolerated. The most common grade 3/4 related AEs (> 5% incidence) were thrombocytopenia (17%), neutropenia (13%), fatigue (13%) and anaemia (7%). There were no deaths reported on study. Pharmacodynamic analyses revealed that a majority of pts had increased tubulin acetylation in PBMCs, however this did not correlate with response or toxicity.
Conclusion: In this phase II study, the novel pan-HDACi abexinostat, was clinically active and overall well tolerated in R/R B-cell lymphoma. Moreover, there was significant clinical activity noted in FL with an ORR of 64%, which included a number of durable responses in this multiply relapsed pt population. Further examination of abexinostat in FL is warranted.

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A PHASE IB/II TRIAL OF ROMIDEPSIN IN ASSOCIATION WITH CHOP IN PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA (PTCL): THE RO-CHOP STUDY

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Background: Romidepsin is a histone deacetylase inhibitor approved by the FDA for patients with cutaneous T-cell lymphoma and PTCL who have received at least 1 therapy. In recurrent/refractory PTCL, it has been evaluated as a single agent in 2 phase II studies with overall response rates of 25–38% (Piekarz, Blood 2011 and Coiffier, J Clin Oncol 2012). Toxicity was mainly hematologic and digestive. The aim of the present study was to evaluate the safety, tolerability and efficacy of romidepsin in association with CHOP in patients with previously untreated PTCL.
Patients and Methods: Patients with PTCL were planned to receive eight cycles of CHOP (cyclophosphamide 750 mg/m,^{2} day 1, doxorubicin 50 mg/m,^{2} day 1, vincristine 1.4 mg/m,^{2} day 1, prednisone 40 mg/m,^{2} days 1–5) in association with varying doses of romidepsin. On the basis of pharmacokinetic data and results of previous phase II studies, the starting dose of 10 mg/m,^{2} days 1 and 8 was chosen. The dose-variation scheme followed a traditional '3+3' design. Dose-limiting toxicities (DLT) were considered during the first 2 cycles. DLT was initially defined as: Non-hematological toxicity grade 3–4 or hematological toxicity grade 3 lasting more than 7 days or grade 4 lasting more than 3 days. The protocol was subsequently amended to tolerate if lasting less than 10 (grade 3) or 7 days (grade 4).
Results: The phase Ib of the study has been completed with 18 patients analyzable for toxicity during the first 2 cycles: Significant, albeit tolerable hematological toxicity having been observed in the first two cohorts, the definition of DLT was modified during the course of the study. The dose of 12 mg/m,^{2} was chosen as the recommended dose for phase II. According to IHP 2007 criteria, 4 patients progressed during treatment; and 12 responded (partial response 2/18, complete response 12/18) for an overall response rate of 78% and a complete response rate of 66%. One PR patient converted to CR. The estimated progression-free survival is 57% at 12 months.
Conclusion: Romidepsin can be combined with CHOP at the price of foreseeable hematological toxicity. Some cardiovascular events have been observed but the relationship with romidepsin is questionable. The dose of 12 mg/m,^{2} on days 1 and 8 is currently evaluated in the phase 2 extension of the study, which has recently completed accrual. Response rates seem promising, but longer follow-up is needed. Results will be updated at the meeting, including results: for the phase II part.

SESSION 9—DLBCL, TREATMENT STRATEGIES

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RITUXIMAB MAINTENANCE TREATMENT VERSUS OBSERVATION IN PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMA: RESULTS OF THE AGMT NHL13 TRIAL

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Introduction: The clinical impact of maintenance treatment after intensive induction immunochemotherapy in diffuse large B-cell lymphoma (DLBCL) is still unclear. Rituximab (R) maintenance was not superior to observation in the ECOG 4494 study (Habermann TM et al. J Clin Oncol. 2006; 24:3121-7), which was unfortunately not fully powered for this analysis. The Austrian Study Group (AGMT) initiated a clinical trial (NHL13, Eudract Nr. 2005-005187-90, http://www.clinicaltrials.gov/ct2/show/NCT00400478?term=ML 18223&rank=1) to investigate the value of R maintenance in patients with DLBCL and follicular lymphoma grade 3B (FL G3B) in complete or unconfirmed complete remission (CR, CRu) after induction with R-CHOP-like chemotherapy.

Methods: In the NHL13 multicentre, prospective trial 683 previously untreated adult patients with DLBCL ($N = 662$) or FL G3B ($N = 21$) recruited in 27 countries (163 sites) between June 2004 and September 2008 were randomized. Inclusion criteria were DLBCL at all stages in CR or CRu after treatment with 4 to 8 cycles of R-CHOP like therapy. Patients were randomized between R maintenance (375 mg/m^2 every 2 months for 2 years) ($N = 338$) and observation only ($N = 345$). The last patient received R in September 2010. The study was closed after 148 events had been reached in March 2012. The primary endpoint of this study was event-free survival. Secondary endpoints included progression-free survival and overall survival. Data will be analysed using a Cox regression model.

Results: Both arms were well balanced regarding clinical presentation, sex or prognostic indices at study entry. No major safety signals were seen in 2 planned interim analyses. In the interim analysis in 2010 a significantly higher rate of infections (mainly NCI CTC V 2.0 grade 1 or 2) was noted in female patients in the R arm ($p = 0.004$). Final analysis will be performed in March 2013 and the data will be presented at the meeting.

Conclusions: The AGMT NHL13 trial should provide a definitive answer to the question whether Rituximab maintenance therapy is beneficial for patients with DLBCL and FL G3B in general or in particular subgroups.

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CHEMOIMMUNOTHERAPY WITH R-CHOP OR HIGH DOSE SEQUENTIAL THERAPY (R-HDS) WITH AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR HIGH RISK DLBCL PATIENTS: PRELIMINARY RESULTS OF THE RANDOMIZED RHDS0305 TRIAL BY GRUPPO ITALIANO TERAPIE INNOVATIVE NEI LINFOMI (GITIL)

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Background: Conflicting results have been reported by studies comparing conventional first-line therapy with high dose chemotherapy and ASCT in high-risk DLBCL patients. In 2005 we launched a multicentre phase III trial to compare R-CHOP-14 vs R-HDS (Clinical Trials.gov.number NCT00355199)

Patients and Methods: Patients without CNS involvement were enrolled according to an age between 18–60 years, stage > II B-bulk with ECOG-PS = 0–3 and age adjusted IPI (aaIPI) 2–3 or age 61–65 years with ECOG-PS = 0–2 and IPI >3. The control group received R-CHOP-14 (8 cycles). The R-HDS regimen has been previously described (Tarella, C et al.: Leukemia 2007). At the end, patients in both arms could receive involved field radiotherapy. The primary end-point was to test an increase of 2-year Event-Free Survival (EFS) from 50% in the R-CHOP arm to 70% in the intensified R-HDS arm.

Results: In this study 248 patients were enrolled (R-CHOP-14 = 127; R-HDS = 121) and 241 were evaluable: median age 51 (18–65); stage III/IV 93%; elevated LDH 87%; PS>1 61%; IPI = 2 51%; IPI >3 49%. The two arms were well balanced for all these features. Response rate in control and experimental arm were: CR 76% vs 76%, PR 4.7% vs 7.9%, NR/PD, 16.5% vs 9.6%, TRM 2.4% vs 4.4%. After a median follow-up of 37.2 months (0.3–89.2) the 2-year DFS for R-CHOP vs R-HDS was 77.7% vs 88.2% ($p = 0.054$), whereas the EFS was 64.6 vs 71.9% ($p = 0.245$). No difference was found in OS (72.4% vs 77.2%, $p = 0.424$). For patients with BM infiltration at diagnosis, the EFS was better if treated with R-HDS (80.8% vs 50.0% $p = 0.007$). A higher hematologic toxicity (CTC G>2) ($p < 0.001$) and more infectious complications ($p < 0.001$) were observed in the R-HDS arm.

Conclusion: The response rate, EFS and OS observed after R-CHOP and R-HDS were not different but a better DSF was observed for patients treated with R-HDS regimen. Moreover EFS of patients receiving high-doses therapy resulted significantly improved in patients with BM infiltration.

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ROLE OF RADIATION IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) IN THE RITUXIMAB ERA: A COMPREHENSIVE ANALYSIS FROM THE NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) LYMPHOMA OUTCOMES PROJECT

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Introduction: Standard therapy with RCHOP offers a favourable outcome in patients with DLBCL, however those who fail initial treatment will likely be incurable. Most of the data on the role of radiation therapy is from pre-rituximab era; to look at the potential role of consolidation RT in patients treated at the National Comprehensive Cancer Network institutions.

Methods: Newly diagnosed DLBCL patients between January 2001 and

DOI: 10.1002/hon

December 2008 were ($n = 841$). We only included patients who received RCHOP, and looked at the following: age at diagnosis, gender, stage, race, international prognostic index (IPI) score, presence of B symptoms, Bulky disease, type and number of cycles of chemotherapy, response to chemotherapy, use of radiation and site of failure in relation to radiation delivered. Univariate and multivariable survival analysis, as well as matched pair analysis, was performed to compare outcomes between receipt of RT group.

Results: 35% of the cohort received RT. Median age was 57 (range 17–90); median follow up was 4.5 years (range 0.5–10.7); 455 (54%) were male; 689 (82%) were Caucasian; 402 (48%) had stage I or II disease; 186 (22%) had IPI of 0; 446 (53%) had IPI of 1 or 2; 240 (29%) had B symptoms; and 192 (23%) had bulky disease. In terms of treatment, 710 (84%) had 6–8 cycles of RCHOP (74% of those with stage I or II and 94% of those with stage III/IV); 632 (75%) had a CR; the 5-year failure-free survival (FFS) was better in the RT group (83 and 76%, $p = 0.05$, Figure 1); as was the 5-year overall survival (OS) (91 and 83%, $p = 0.01$. Matched pair analysis was performed with 217 pairs matched by age, stage, IPI score, B symptoms, bulk of disease, and response to chemotherapy looking at the role of radiation, RT improved both OS and FFS in stage III/IV (HR = 0.53 and 0.77, respectively, $p = 0.07$ and 0.34) however, for stage I and II, because of low event occurrence, the HR for OS and FFS was 0.94 and 1.81, respectively ($p = 0.89$ and 0.15 respectively). The following factors affected FFS and OS on multivariate analysis: IPI score >3 (HR = 6.41 and 9.39; $p < 0.0001$ for both), CR response to therapy (HR = 0.57 and 0.5, $p = 0.001$ and 0.0009, respectively), presence of B symptoms (HR = 1.49 and 1.92, $p = 0.01$ and 0.001, respectively), bulky disease (HR = 1.37 and 1.67, $p = 0.07$ and 0.01, respectively), receiving radiation therapy (HR = 0.86 and 0.67, p(NS) = 0.4 and 0.08), and giving 6 or more cycles of RCHOP significantly affected only OS (HR = 0.56, $p = 0.01$). Failure occurred in 181/841 patients, 126 (70%) in the non-RT arm and 30% in the RT arm, details on site of failure were documented on 139/181 patients (Table 1). The recurrence rate in the original site of presentation was in 41 (33%) patients in the non-RT arm and 25% in the RT arm; outside of the radiation field was 31 (25%) in non-RT arm and 16 (29%) in the RT arm; and both same and outside of original field in 24(19%) in the non-RT arm and 13(24%) in the RT arm.

Conclusion: Patients with DLBCL who received RT had better OS and FFS and lower failure rate. In multivariate analysis model, IPI score and response to chemotherapy appeared to be the driving factors of outcome.

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THE ROLE OF RADIOTHERAPY TO BULKY DISEASE IN ELDERLY PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMA. RESULTS FROM TWO PROSPECTIVE TRIALS OF THE DSHNHL

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Introduction: Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is standard care for aggressive B-cell lymphoma. A prospective trial was performed to define the role of additive radiotherapy (RT) to primary bulky disease.

Methods: The best arm of the RICOVER-60 trial where patients received six cycles of CHOP-14 and eight applications of rituximab (6xR-CHOP-14+2R) plus involved-field RT (36 Gy) to sites of initial bulky (≥7.5 cm) disease and extralymphatic involvement was compared with a cohort who received the same immunochemotherapy, but without radiotherapy in an amendment to the RICOVER-60 trial (RICOVER-60-no-Rx) in a prospective fashion.

Results: After a median time of observation of 39 months, 164/166 RICOVER-60-no-Rx patients were evaluable. In a multivariable analysis of the intention-to-treat population adjusting for IPI risk factors and age (>70 years), 3-year event-free survival (EFS) of patients with bulky disease was inferior without additive radiotherapy (H [hazard ratio] 2.1 [95% CI 1.3–3.5], $p = 0.005$) with trends for inferior PFS (HR 1.8 [1.0–3.3], $p = 0.058$) and OS (HR 1.6 [0.9–3.1], $p = 0.127$). Excluding 11/47 patients in the RICOVER-noRx trial who violated the protocol by receiving RT, the multivariable analysis for the per-protocol population revealed a HR of 2.7 (1.3–5.9; $p = 0.011$) for EFS, 4.4 (1.8–10.6; $p = 0.001$) for PFS and 4.3 (1.7–11.1, $p = 0.02$) for OS.

Conclusions: Additive RT to primary bulky sites improves outcome of elderly patients with aggressive B-cell lymphomas. Whether RT can be spared in patients with (metabolic) CR after immunochemotherapy must be addressed in appropriately designed prospective trials.

Supported by Deutsche Krebshilfe.

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LONG-TERM EXPERIENCE WITH PET-GUIDED CONSOLIDATIVE RADIATION THERAPY (XRT) IN PATIENTS WITH ADVANCEDSTAGE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) TREATED WITH R-CHOP

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Background: Residual masses are often seen on post-therapy CT scans for DLBCL and the role of XRT remains unclear. Selective administration of XRT to PET-positive (PET-pos) sites is a rational approach that may enable eradication of residual disease while limiting toxicity to those most likely to benefit.

Method: Since 2005, pts with advanced (adv)-stage DLBCL in British Columbia (BC) have been treated with a systematic policy recommending a post-therapy PET for pts with residual masses > 2cm on CT, followed by XRT to all PET-pos sites if feasible. Pts with a negative PET (Pet-neg) are observed (regardless of initial or residual bulk), whereas pts who are PET-pos and not suitable for XRT are treated according to physician discretion. The BC Cancer Agency Lymphoid Cancer Database was used to identify all newly diagnosed pts with adv-stage DLBCL between Jan 2005 and Feb 2012 treated with curative intent R-CHOP who underwent a post-therapy PET scan. Exclusions: pts in CR on CT, primary progressive disease, HIV pos, PMBCL, transformed lymphoma.

Results: 262 pts were identified: median age 65 y (range 18–89 y); 60% male; 69% stage III/IV; 42% bulky site > 10cm; 48% IPI 3–5. Median follow-up for living pts is 45 m (range 4–93 m). 167/262 (64%) were PET-neg, 82/262 (31%) were PET-pos, and 13 (5%) had an indeterminate PET. Only 1/167 PET-neg pt received XRT. 60/82 (73%) PET-pos pts received XRT (30–45 Gy) to sites of PET positivity (56 single, 4 multiple fields). 22/82 (27%) PET-pos pts did not receive XRT: 13 not amenable; 7 physician choice; 2 biopsy neg. Only 10/60 PET-pos pts who received XRT have relapsed (6/10 in-field). The 4-y time to progression (TTP) and 4-y OS were similar for PET-pos pts who received XRT (TTP 81%; OS 85%) and PET-neg pts (TTP 74%; OS 83%) and was worse in PET-pos pts who did not receive XRT (TTP 33%; OS 30%).

Conclusion: Pts with adv-stage DLBCL with residual CT abnormalities after R-CHOP who receive consolidative XRT to sites of PET positivity have an unexpectedly favourable outcome, strongly supporting the rationale for the use of PET-guided XRT. Pts with PET-neg residual CT abnormalities also have a favourable outcome and should be spared unnecessary toxicity.

SESSION 10—FRONT-LINE TREATMENT OF HODGKIN'S LYMPHOMA

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A PHASE II TRIAL OF RESPONSE-ADAPTED THERAPY OF STAGES III–IV HODGKIN LYMPHOMA USING EARLY INTERIM FDG-PET IMAGING: US INTERGROUP S0816

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DOI: 10.1002/hon

Introduction: ABVD chemotherapy is standard treatment for advanced stage Hodgkin Lymphoma (HL) and cures ~70% of patients (pts). BEACOPPescalated cures more, but is more toxic and renders most recipients infertile. Early Fluoro-2-deoxy-D-glucose positron emission tomography (PET) may identify pts for whom standard ABVD will ultimately be ineffective, allowing an earlier switch to more intensive therapy. We examined a response-adapted approach in an attempt to increase efficacy while limiting treatment-related morbidity.
Methods: Four U.S. Cooperative Groups (SWOG, CALGB/Alliance, ECOG and the AIDS Malignancy Consortium) conducted a Phase II trial to test a 'response-adapted' approach based on an 'interim' PET/CT scan performed after 2 cycles of ABVD. Deauville criteria for PET were utilized (PET± score 4–5). Pts who were PET2-received an additional four cycles of ABVD (six total), whereas PET2+ pts were switched to BEACOPPescalated ×6 cycles.
Results: Between 7/1/2009 and 12/2/2012 371 pts with stage III–IV HL were enrolled, of whom 357 were eligible and evaluable. The median age was 32 (18–61), with 57% males, 80% white, 49% IPS 0–2, 51% IPS 3–7, and 4% HIV positive (13 pts). Of 357 pts with an interim PET2 scan evaluated by central review, 292 (82%) were PET− and 65 were PET+ (18%). 349 pts registered to continued therapy based on the interim PET result, 291 on continued ABVD and 58 on the BEACOPP arm. Seven of 65 PET+ pts (10%) did not receive BEACOPP due to pt or physician refusal. The Kaplan–Meier estimate for 1-year overall survival in HIV-negative pts is 98% (95% CI: 95%, 99%) and for 1-year progression-free survival (PFS) is 84% (95% CI: 79%, 89%). The landmark of 1-year PFS of PET2− pts planned to receive ABVD is 85% (95% CI: 79%, 90%) and for PET2+ pts planned to receive BEACOPP is 72% (95% CI: 55%, 84%), which appears promising compared with the 15–30% 2-year PFS expected in PET2+ pts. Three deaths occurred among 306 pts evaluable for toxicity, (1/259 [0.3%] on ABVD and 2/47 [4.2%] on BEACOPP).
Conclusions: Response-adapted therapy with centralized interim PET review is highly feasible in an intergroup setting. Early outcomes appear favourable with this strategy, though longer follow-up is essential.

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PET-CT ADAPTED THERAPY AFTER THREE CYCLES OF ABVD TO ALL STAGES OF HODGKIN LYMPHOMA: A REPORT FROM THE GATLA GROUP

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Objectives: Reduce therapy in patients (pts.) with stages I–IV of HL who achieve early CR with negative PET-CT. Intensify treatment, in pts. with positive PET-CT after 3 ABVD. Compare EFS and OS of this trial (LH-05) with our historical control (LH-96) when we used 3–6 ABVD adapted to stage plus involved field radio therapy (IFRT) in all pts.
Patients And Method: From October 2005, 238 newly diagnosed pts. with HL stages I–IV were enrolled in a prospective multicentre cooperative group (GATLA) trial. One hundred and forty seven (62%) had localized stage (I–IIA) and 91(38%) advanced stage (IIB–III–IV). All pts. were treated with 3 cycles of standard ABVD and evaluated with a PET-CT (PET-CT 3). Pts. with a negative PET-CT 3 were considered in CR and received no further therapy. Pts in partial response (PR) completed 6 ABVD and IFRT on PET-CT positive areas. Pts with less than PR received more aggressive chemotherapy.
Results: One hundred and sixty-eight (70%) achieved CR with negative PET-CT 3. Seventy (30%) were PET-CT 3 positive, 10/70 showed progressive disease. The other 60 pts were in PR with chemo-sensitive disease and completed a total of 6 ABVD and IFRT in PET-CT positive areas. Forty two achieved CR and 18 persisted with hypermetabolic lesions. With a median follow up of 44 months the EFS and OS for at 36 months is 78% and 96% respectively. Pts with negative PET-CT 3 had an EFS of 87% compared with 58% for pts. with positive PET-CT 3 ($p = 0.001$). In a multivariate analysis, the EFS was significantly associated with the result of PET-CT 3 (0.002), but not with stage at diagnosis ($p = 0.18$), extranodal areas ($p = 0.61$) or bulky disease ($p = 0.63$). When comparing the results of LH-05 with LH-96 there is no difference in EFS and OS at 36 months (83% vs 85% and 97 vs 96%, respectively) but in LH-05 only 30% received more than 3 cycles of ABVD and IFRT compared with 61% and 100% in LH-96.
Conclusion: With PET-CT adapted therapy after 3 ABVD, 168 pts. (70%) with stages I–IV received only 3 cycles of ABVD and no RT with an EFS and OS of 87% and 98% at 36 months. In the Cox regression model, PET-CT after 3 cycles of ABVD overshadows the prognostic value of stage at diagnosis, and emerges as a tool to stop treatment after 3 ABVD in pts with an early CR in stages I–IV.

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RESPONSES AND CHEMOTHERAPY DOSE ADJUSTMENT DETERMINED BY PET-CT IMAGING: FIRST RESULTS FROM THE INTERNATIONAL RESPONSE ADAPTED THERAPY IN ADVANCED HODGKIN LYMPHOMA (RATHL) STUDY

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Introduction: The aim of this prospective randomized study was to test whether interim FDG PET-CT scanning could be used to 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) fit for full course combination chemotherapy underwent paired baseline and 'interim' PET-CT scans after 2 cycles of ABVD (PET2). Quality control for PET-CT was supervised by a network of national core labs using common methods of scan acquisition and interpretation. Images were scored on a standard 5-point scale, as negative (score 1–3) or positive (score 4–5). Pts with negative scans were randomized to ABVD or AVD for 4 more cycles. Treatment for pts with positive scans was intensified to either BEACOPP-14 or escalated BEACOPP regimens for 8–9 weeks before a third PET-CT 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 was not advised for pts with negative scans, irrespective of baseline bulk or residual masses.
Results: 1214 pts were registered; 76 were withdrawn before PET2, mostly for failure to adhere to quality controls. Median age was 33, with 501 (41%) Ann Arbor stage II, 370 (30%) stage III and 341 (28%) stage IV. 740 pts (61%) had B symptoms and 388 (32%) bulky disease. PET2 results were available from 1130 patients and were negative in 944 (84%). There was no association of PET2 score with baseline stage, but bulky disease predicted for an excess of scores 3–5 and significantly more pts with bulk remained PET2 positive (p 0.001). 940 pts were randomized to continue ABVD or AVD. Among PET2 negative pts, 65% achieved CR or CRu, 27% PR, 2% SD and 2% PD by conventional re-staging at completion of therapy. Rates of CR/CRu were associated with PET2: score 1: 82%, score 2: 72%, score 3: 58% ($p < 0.01$). Those with positive PET2 who received intensified therapy with BEACOPP reached negative PET3 in 74% of cases.
Conclusions: This study confirms that standardized application of a 5 point reporting scale for PET-CT can be used to reliably measure early response to chemotherapy in advanced HL, and that escalation of therapy after a positive interim scan results in substantial PET response rates.

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ABVD (EIGHT CYCLES) VERSUS BEACOPP (4 ESCALATED CYCLES TO 4 BASELINE) IN STAGES III-IV LOW RISK HODGKIN LYMPHOMA (IPS 0–2): FINAL RESULTS OF LYSA H34 TRIAL

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DOI: 10.1002/hon

Introduction: Escalated BEACOPP achieved superior time to treatment to failure over ABVD in patients with disseminated Hodgkin lymphoma. However, later clinical trials have failed to confirm Overall Survival (OS) superiority over ABVD. Given the higher treatment related morbidity, whether or not BEACOPP should be given to low risk patients is still matter of debate.
Methods: Eligibility criteria: clinical stage III/IV HL, International prognostic score (IPS) ranging 0-2; age<60. Patients with IPS >2 were included in the EORTC Intergroup 20012 study (P. Carde, ASCO 2012). On Behalf of the Lymphoma Study Association (LYSA), we compared ABVD (8 cycles) versus BEACOPP (escalated 4 cycles to baseline 4), without irradiation. Randomization was stratified for institution. Primary endpoint was EFS, defined as treatment discontinuation, no complete response (CR) after 8 cycles, progression, relapse or death. Additional endpoints were CR, progression-free survival (PFS), OS and secondary malignancies.
Results: From February 2003 to august 2008, 150 pts were randomized (ABVD 80, BEACOPP 70): stage IV 48%, PS 0–1 96%, B-symptoms 58%, median age 28 y, males 50%. IPS was 0–1 for 64% of pts. Marrow involvement for 8%. There was no toxic death. Early discontinuation (prior to cycle 5) occurred in 10 and 9 pts, respectively (13%). Main reasons were treatment failure (3 and 2), patient refusal (3 and 2) and toxity (1 and 3). There were 1 crossover to BEACOPP and 3 to ABVD. CR was 85% for ABVD and 90% for BEACOPP. Relapses were more frequent in ABVD (14 vs 3 patients). Among them 9/14 and 3/3 received stem cell transplantation. Second cancer occurred in 5 ABVD and 1 BEACOPP pts (NHL 2 and 1, lung 1 and 0, other 2 and 0). Among the 5 ABVD pts, 3 received second line HL treatment. With a median follow-up of 5.5 yrs, 7 patients died: 6 in ABVD and 1 in BEACOPP (HL 3 and 0, 2nd cancer 2 and 1, other 1 and 0). EFS at 5 yrs was estimated at 62% vs 77%, respectively (HR = 0.6, $p = 0.07$). PFS at 5 years was 75% vs 93% (HR = 0.3, $p = 0.007$). OS at 5 years was 92 vs 99% (HR = 0.18, $p = 0.06$). Conclusion: EFS and OS were not different between treatment arms. However, more progressions/relapses were observed with ABVD. As in high risk group, additional considerations as late morbidity due to salvage treatment may help decisions making toward ABVD or BEACOPP for low risk patients.

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FOLLOW-UP OF THE 11-ICML WORKSHOP ON LYMPHOMA STAGING AND RESTAGING IN THE PET-CT ERA

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Background: The availability of new and effective therapies for lymphoma warrants staging and response criteria that are unambiguous and universally adopted for accurate patient assessment, ability to compare patients and results amongst studies. The first widely adopted response criteria were published in 1999 by the NCI-Working Group (Cheson, et al 1999) and the revision in 2007 by the International Working Group (Cheson, et al 2007) was the first to incorporate PET, flow cytometry, and immunohistochemistry.
Methods: Recognizing the progress made since their publication, a workshop was help at the 11th ICML in Lugano, Switzerland 2011 including leading hematologists, medical and radiation oncologists, pathologists, radiologists, and nuclear medicine physicians. The aims were to consider ways to improve, standardize and legitimize current and evolving staging procedures for nodal Non-Hodgkin and Hodgkin lymphoma, and to achieve a durable consensus that would be relevant for community physicians, investigator-led, cooperative group and registration trials.
Results: Since then, several meetings have been held, and a working group has proposed major changes in staging and response including PET-CT for all routinely avid histologies, but not as a basis to alter therapy based on interim imaging. Bone marrow biopsies are no longer required for Hodgkin and many diffuse large B-cell lymphomas. Routine surveillance using PET-CT is not warranted. A paper from the Imaging Subcommittee proposing methods to optimize interpretation of PET-CT and its incorporation into clinical trials has been submitted (Barrington, et al).
Conclusions: Following another workshop at the 12th ICML in 2013, final recommendations will be presented.

CONTROVERSY II: DOES RADIOTHERAPY REMAIN THE STANDARD COMPONENT OF TREATMENT IN EARLY STAGE HODGKIN LYMPHOMA?

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PROS—RADIOTHERAPY IN EARLY-STAGE HODGKIN LYMPHOMA

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The curative treatment of early Hodgkin lymphoma is one of the great success stories in oncology. A sequential and thorough approach in large randomized trials, exemplified by the German Hodgkin Study Group has led to substantial treatment reduction in treatment and established a standard of care based on minimal highly effective combined modality treatment (CMT) with 2 cycles of ABVD followed by 20Gy of involved field radiotherapy (RT) being highly effective, well tolerated standard of care for patients with stages IA/IIA, favourable, classical Hodgkin lymphoma. Whilst efforts to improve outcome further over 4 x ABVD and 30 Gy in the unfavourable group are ongoing, the focus in the favourable group has been on maintaining high cure rates but decreasing acute and late toxicity of treatment. The role RT plays in achieving this goal of cure has become highly controversial given the concerns of late toxicity affecting long term survival in a population of mostly young patients who can expect excellent outlook after treatment with prolonged survival of decades. The current scientific discussion is centred on finding the right balance between toxicity and cure of HL, with intensive efforts on response adapted treatment approaches potentially using FDG PET imaging to select patients who may have an excellent outcome with abbreviated chemotherapy alone. Whilst this approach appears highly promising, ongoing challenges remain regarding the routine interpretation of PET CT scans in clinical practice that suggest moving to risk adjusted approaches may be a little premature. Furthermore all of the emerging clinical trials using FDG PET continue to highlight the superiority of CMT over chemotherapy alone in progression-free survival along with the difficulties associated with interpretation of PET 'negative' even amongst expert panels. Currently there are simply too many well performed large randomized studies today demonstrating that abbreviated chemotherapy followed by small-field radiotherapy is the best available choice of treatment for patients and a lack of randomized trials comparing chemotherapy alone versus CMT to change practice. Therefore the evidence at the current time would suggest that outside of clinical trial the majority of patients with early stage Hodgkin Lymphoma are most safely treated with CMT.

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RADIOTHERAPY REMAINS THE STANDARD COMPONENT OF TREATMENT IN EARLY STAGE HODGKIN LYMPHOMA

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In the last 20 years, patients presenting with early stage Hodgkin Lymphoma could expect to be cured of their disease. Since mid-1980's we knew that the risks of dying from the late effects of treatment exceeded the risks of dying from Hodgkin lymphoma. Late effects were attributed to chemotherapy (MOPP induced acute leukemia) and radiotherapy (second cancers and heart disease). The universal use of the ABVD chemotherapy eliminated the concerns about treatment induced leukemia. In 1990's clinical trials tested lower amount of treatment with reduced dose and volume of radiation and shorter chemotherapy. Combined modality approaches became a standard of care. However, the studies of late effects clearly demonstrated that even low dose and reduced field radiotherapy increases second cancer risks. In early 1990's we embarked on a prospective randomized trial to test what was then our standard approach against treatment with ABVD alone. At 12 yrs the failure from disease progression rate for ABVD alone was 87% and the overall survival - 94%. The failure from progression was 92% with radiation based approach but the overall survival was lower at 87%. The main message from this trial is that ABVD alone cures Hodgkin lymphoma in approximately 90% of patients. The concerns about late effects of radiotherapy make this approach optimal for young patients and those in whom the geographic distribution of disease dictates radiation to organs particularly at risk for late effects – breasts in women, heart and lungs. However, such an approach mandates careful assessment of response to chemotherapy since the results of trials that use the combined modality approach report superior disease control rates and the reduced dose/volume radiotherapy component promises lower late effect risks. In addition the modern radiotherapy techniques including the use of CT planning, active breathing control and the pencil beam scanning proton beam therapy make radiotherapy vastly safer than 20 years

DOI: 10.1002/hon

ago. The current trials must focus on the overall long term complication free survival. It remains to be seen what proportion of patients with early stage HL should receive radiotherapy to secure the optimal long term outcomes.

PRESENTATION OF ONGOING TRIALS

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PHASE 3 TRIAL COMPARING GA101 (OBINUTUZUMAB) +CHOP (GCHOP) VERSUS RITUXIMAB +CHOP (R-CHOP) IN PREVIOUSLY UNTREATED DLBCL

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Introduction: Progress in the treatment of DLBCL was made with the effective addition of rituximab–a B-cell-depleting, anti-CD20 mAb–to standard CHOP chemotherapy. Yet, a significant number of patients (pts) remain uncured. There is an unmet need to further improve outcomes by offering more pts potentially curative therapy, particularly in the first-line setting. GA101, a glycoengineered, humanized, anti-CD20 mAb, induces increased direct cell death and ADCC vs rituximab. GA101's distinct mechanism of action may translate to improved efficacy. Phase 1/2 data suggest that GA101 monotherapy is well tolerated and effective in relapsed/refractory DLBCL, and data from indolent NHL confirm that GA101 can be added to CHOP without compromising dose intensity. It is hypothesized that adding GA101 to chemotherapy may confer additional benefit over rituximab + chemotherapy in previously untreated DLBCL.
Methods: GOYA (NCT012787441) is a phase 3, multicentre, open-label, randomized (1:1) study that will evaluate the efficacy and safety of G-CHOP vs R-CHOP in 1400 pts with previously untreated, CD20-positive DLBCL. GA101 1000 mg will be given on days 1, 8, and 15 of cycle 1 and day 1 of cycles 2–8 (21-day cycles). Rituximab 375 mg/m,^{2} will be infused on day 1 of cycles 1–8 (21-day cycles). Standard CHOP will be given for 6 or 8 cycles. Eligibility criteria include previously untreated CD20+ DLBCL; ECOG PS of 0–2; and high, high-intermediate, or low–intermediate risk IPI score or bulky disease with low risk IPI score. The primary endpoint is investigator-assessed PFS (ie, time to disease progression, relapse, or death). Secondary objectives include safety, OS, investigator—and independent review committee (IRC)—assessed overall response and CR rates at treatment end, IRC-assessed PFS, and time to next antilymphoma treatment.
Results: Enrollment began in July of 2011. GOYA will end ~78 months after first pt enrollment.
Conclusions: On the basis of the data from single-arm studies of GA101 in aggressive/indolent NHL, the randomized, phase 3 GOYA study will compare the efficacy and safety of G-CHOP vs R-CHOP induction therapy in DLBCL.

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GENE EXPRESSION PROFILING (GEP) TO IDENTIFY SUBTYPES OF DIFFUSE LARGE B-CELL LYMPHOMA (DLBL) FOR RANDOMISATION TO R-CHOP +/– BORTEZOMIB: A TRIAL IN PROGRESS IN THE UK NCRI AND SAKK LYMPHOMA GROUPS: REMODL-B, ISRCTN51837425

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Introduction: DLBL subtypes are identified by patterns of gene expression corresponding to germinal centre (GCB) or activated peripheral blood (ABC) B-cells. The outcomes of treatment with standard R-CHOP therapy are inferior for the ABC type in retrospective series, and this study investigates whether adding bortezomib can reverse this deficit. The trial uses GEP to stratify cases at entry, with adaptive statistical design to analyse the outcome by subtype at predefined timepoints.
Methods: Patients (pts) newly diagnosed with DLBL undergo staging and commence R-CHOP. During the first cycle, formalin-fixed paraffin-embedded (FFPE) tissue undergoes extraction of messenger RNA (Ambion RecoverAll™ Total Nucleic Acid Isolation Kit for FFPE) for GEP of 24 000 probe sets using Illumina cDNA-mediated Annealing, Selection, extension, and Ligation (DASL®) assay at the central laboratory. Cases are allocated to GCB, ABC or unclassified (U) type before the 2nd cycle, using an established algorithm based upon 20 genes. Pts with successful GEP are randomized to continue R-CHOP +/– bortezomib 1.3 mg/m,^{2} days 1+8 of cycles 2–6. The study will randomize a minimum 260 ABC type cases, to detect a difference in progression-free survival (PFS) of 10% with bortezomib, with two-sided significance 5% and 90% power. The design allows closure of randomisation for GCB cases if 6 month PFS is <80% after 55 receive R-CHOP-B. Futility analysis in GCB is planned after 73 treated with R-CHOP-B are followed for one year: if PFS is <85%, further exploration of bortezomib in this group is not warranted.
Results: During the first 14 months of recruitment, 242 samples have been analysed. 58 (24%) biopsies had inadequate material for GEP, but the remaining 184 were classified as 58 (32%) ABC, 104 (56%) GCB and 22 (12%) U. Successful classification was possible from both surgical and needle core biopsies. Median laboratory turnaround time was 11 working days and all results were available prior to the scheduled administration of cycle 2. Characteristics of the pts of different subtypes are shown in the table:
Conclusions: This study demonstrates the feasibility of GEP at diagnosis in a large trial, with some indication that baseline prognostic features may be adverse in ABC type DLBL. Recruitment to the study continues at a rate of approximately 25 per month in 100 centres.

Abstract 132 Table 1.

	ABC	GCB	U
Age: median	68	62	65
Age: range	23–86	27–82	32–81
% performance status 0–1	87	87	81
% at least one extranodal site	53	46	59
% bone marrow positive	11	25	47
% raised LDH	23	16	24
% IPI score >3	41	34	35

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A RANDOMIZED, MULTICENTRE, TWO-ARM PHASE III COMPARATIVE STUDY ASSESSING THE ROLE OF MEDIASTINAL RADIOTHERAPY AFTER RITUXIMAB-CONTAINING CHEMOTHERAPY REGIMENS TO PATIENTS WITH NEWLY DIAGNOSED PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL): THE IELSG-37 STUDY

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DOI: 10.1002/hon

Background: The most important open questions in the management of PMLBCL are (i) whether consolidation mediastinal radiotherapy (RT) is still required after a rituximab and anthracycline containing chemotherapy regimen (R-CHT) and (ii) if a negative PET/CT scan following R-CHT is a reliable indicator of cure making RT unnecessary.
Aim of the study: To assess the role of RT in PMLBCL patients with a PET-defined complete remission after R-CHT.
Study design: Patients with previously untreated PMLBCL will be enrolled. All patients will undergo a baseline PET/CT and then receive one of the standard R-CHT regimens currently in use for DLBCL (e.g. R-CHOP14/21, R-DA-EPOCH, R-ACVBP or R-M/VACOP-B). The PET/CT scans will be repeated at 5–6 weeks after the last R-CHT administration. After a mandatory central PET/CT review, all patients with a negative PET/CT scan (either with complete or partial radiological regression of the mediastinal mass), will be randomized to receive consolidation mediastinal RT or observation. Mediastinal RT (30 Gy) will commence within 8 weeks after the last administration of R-CHT. Complete response (CR) is defined as a negative PET scan or one having minimal residual uptake lower than mediastinal blood pool (MBP) activity (Deauville score 1–2). All randomized patients will continue participation in the treatment follow-up phase study for 60 months from randomisation and also at 10 years from randomization, long term safety information will be collected. The primary endpoint is the 2-year PFS after randomisation. Secondary endpoints are 5-years OS and long-term safety. The trial is powered to determine a non-inferior outcome in patients not receiving RT based on a sample size of 752 patients to be enrolled over 4 years of accrual.
Conclusion: The study should be able to demonstrate a non-inferior outcome in patients not receiving RT after R-CHT and may allow individualisation of treatment by adapting it to the PET response, thus limiting the indication for additional RT only to the patients who show an inadequate response to R-CHT.

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CLLM1: A RECRUITING PHASE 3 STUDY OF THE EFFICACY AND SAFETY OF LENALIDOMIDE AS MAINTENANCE THERAPY FOR HIGH-RISK PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA FOLLOWING FIRST-LINE THERAPY

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Introduction: The combined use of genetic markers and minimal residual disease (MRD) assessment allows to identify CLL patients (pts) with a poor outcome (median progression-free survival (PFS) of 22 months) after firstline treatment with fludarabine, cyclophosphamide and rituximab (FCR). High risk patients identified by this approach are potential candidates for maintenance strategies.
Methods: CLLM1 is a multicentre, randomized, double-blind, placebo-controlled, parallel-group phase 3 trial. The primary objective is to compare the efficacy of lenalidomide versus placebo maintenance therapy in high risk pts with the assumption of a 75% improvement of PFS. The secondary objectives are to evaluate overall survival and the safety of lenalidomide. To be considered eligible pts have to meet the criteria for high risk defined as MRD levels of $\geq 10,^{-2}$ or a combination of MRD levels of $\geq 10,^{-4}$ to $< 10,^{-2}$ with either an unmutated IGHV-status, del(17p) or TP53 mutation and must have achieved at least a partial response after at least 4 cycles with FCR, FR, Bendamustine-R or FC. Screening should be performed 56–140 days after completion of a first line therapy. The treatment schedule includes a dose escalation, starting with 5 mg study medication up to a target dose of 15 mg daily. Further escalation is guided by MRD assessment. If well tolerated, the study drug should be taken up to progression of disease.
Results: A total of 200 sites in five European countries will be activated. So far 27 pts were screened for participation in the trial. In compliance with the calculated MRD negativity rate after firstline, 64% (18) of them were not eligible for randomization. 7 pts were randomized and are under treatment, two pts are awaiting randomization. 193 subjects have to be randomized to achieve the recruitment goal of a total of 200 high risk pts. Serious adverse events have not been reported so far.
Conclusion: This phase 3 trial exploring the impact of maintenance with lenalidomide in high risk CLL patients while using a combination of biological risk factors for risk stratification is ongoing and open for recruitment.

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A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF IDELALISIB (GS-1101) IN COMBINATION WITH BENDAMUSTINE AND RITUXIMAB FOR PREVIOUSLY TREATED INDOLENT NON-HODGKIN LYMPHOMAS (INHL)

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Background: PI3K-delta is critical for activation, proliferation and survival of B-cells and plays a role in homing and retention in lymphoid tissues. PI3Kδ signalling is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective, oral inhibitor of PI3Kδ that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B-cells in lymphoid tissues (Lannutti et al, 2011). Phase 1 trials demonstrated that idelalisib is highly active in pts with heavily pretreated iNHL: pts experienced reductions in disease-associated chemokines, profound and rapid reductions in lymphadenopathy, and durable clinical benefit with an acceptable safety profile (de Vos et al, 2011).
Methods: 450 pts with previously treated iNHL, who have measurable lymphadenopathy, require therapy for iNHL, have received prior anti-CD20-antibody-containing therapy and chemotherapy, and who have iNHL that is not refractory to bendamustine (B) are randomized in a 2:1 ratio into Arm A or B. In Arm A, pts receive idelalisib at 150 mg BID continuously + rituximab (R) at 375 mg/m,^{2} every 28 days for six cycles + B at 90 mg/m,^{2} on days 1 and 2 of each 28-d cycle. In arm B, pts receive placebo BID instead of idelalisib. Stratification factors include tumour type (follicular lymphoma vs others), tumour burden (high vs low) and time since completion of last prior therapy for iNHL ($<$18 months vs $\geq$18 months). The primary endpoint is PFS, and key secondary endpoints include CR rate, ORR, lymph node response rate, and OS. This is an event-driven trial and primary endpoint evaluation will be based on independent central review. For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set using Kaplan–Meier methods and the stratified log-rank test. The study opened for enrollment in Dec 2012 (NCT01732926).

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THE 'RELEVANCE' TRIAL: A LYSA-SPONSORED PHASE 3 RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF RITUXIMAB PLUS LENALIDOMIDE VERSUS RITUXIMAB PLUS ANY CHEMOTHERAPY IN SUBJECTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA

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DOI: 10.1002/hon

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Background: Rituximab plus chemotherapy followed by rituximab maintenance is a standard of care for patients with previously untreated follicular lymphoma (FL) in need of treatment (Salles, Lancet 2011). Recently, the combination of lenalidomide and rituximab (R2) as initial treatment for follicular lymphoma was shown to be safe and produce high overall and complete response rates with 81% PFS at 3 years in a Phase 2 study of 46 patients with untreated, stage III/IV, indolent NHL including 48% of patients in need of treatment according to GELF criteria (Fowler et al, ASH 2012).
Methods: The primary objective of the study is to compare the efficacy of R2 to rituximab plus chemotherapy in patients with previously untreated FL (grade 1, 2, or 3a) and at least one GELF criterion (one lesion > 7 cm; three nodes ≥ 3 cm; symptomatic splenomegaly; organ compression, pleural, or peritoneal effusion; elevated LDH or β2-microglobulin; B symptoms). Patients are stratified by FLIPI score (0–1 vs 2 vs 3–5), age (>60 vs ≤60) and longest diameter of the largest node (>6 vs ≤6 cm), and randomized to receive either R2 (lenalidomide for a total of 18 cycles, 20 mg daily on days 2–22 every 28 days for 6 to 12 cycles, then 10 mg for responding patients; rituximab, 375 mg/m^2 on days 1, 8, 15 and 22 of cycle 1, day 1 of cycles 2 to 6; and every 8 weeks for 12 cycles) or Investigators Choice of 6 to 8 cycles of R-CHOP, R-CVP, or R-bendamustine, followed by rituximab maintenance in responding patients every 8 weeks for 12 cycles. Efficacy determination will be based upon the co-primary endpoints of complete response rate at 120 weeks and PFS using the IWG criteria (cheson 1999). The current design hypothesizes a superiority of the experimental arm. The total accrual goal is 1000 patients. The secondary objectives are to compare EFS, Time to Next Lymphoma Treatment, Overall Survival, minimal residual disease using PCR, and heath related quality of life.
Results: So far, 213 patients have been included in 50 centres in France, USA and Belgium. Additional centres from Australia (ALLG), Canada (NCCI-CTG), Germany (GLSG), Portugal, Spain (GELTAMO) and Italy will join the study in the second quarter of 2013.

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A PHASE 3 STUDY OF IBRUTINIB IN COMBINATION WITH BENDAMUSTINE AND RITUXIMAB (BR) IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED MANTLE CELL LYMPHOMA (MCL)

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Background: MCL is a distinct subtype of B-cell non-Hodgkin lymphoma (NHL) accounting for approximately 6% of NHL diagnoses. Current immunochemotherapy followed by rituximab maintenance.
Results: in a prolonged duration of remission, but a constant relapse pattern is still observed. Ibrutinib, an oral Bruton's tyrosine kinase (BTK) inhibitor, demonstrated promising single-agent activity in 115 patients with relapsed or refractory MCL who were enrolled in the phase 2 study PCYC-1104. The overall response rate (ORR) was 68%, with 46% of patients achieving partial response (PR) and 22% achieving complete remission (CR) (Wang ASH 2012). Blum et al (ASH 2012) demonstrated that ibrutinib can be safely combined with BR in a phase 1 combination study in relapsed or refractory NHL and that it enhanced BR's clinical activity with an ORR in 5 evaluable MCL patients of 100% (80% CR, 20% PR). These data suggest that combining ibrutinib with BR will improve the outcome of these patients.
Methods: The SHINE study, PCI-32765MCL3002, is a phase 3 double-blind, placebo controlled study of ibrutinib in combination with BR versus BR for the treatment of patients with newly diagnosed MCL. The study aims to enrol 520 patients (approximately 260 patients per arm). All patients will receive BR therapy for 6 cycles; those patients achieving a CR or PR will receive R maintenance for 2 years. In addition to BR and R, all patients will receive an oral daily dose of 560 mg ibrutinib or placebo concomitant with the chemotherapy and ongoing as a single agent until disease progression or unacceptable toxicity. The primary objective is to evaluate if the addition of ibrutinib to BR will result in prolongation of progression-free survival, with secondary objectives of evaluation of overall survival, ORR (CR PR), CR rate, duration of response, and safety. The study will enrol patients aged 65 years or older who are not suitable for high-dose chemotherapy. Key exclusion criteria include diagnosis or treatment for malignancy other than MCL, requirement for treatment with warfarin or equivalent vitamin K antagonists, and treatment with strong CYP3A4/5 inhibitors. Approximately 200 sites globally will enrol patients. Enrollment began in Q1 of 2013.

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ECHELON-2: PHASE 3 TRIAL OF BRENTUXIMAB VEDOTIN AND CHP VERSUS CHOP IN THE FRONTLINE TREATMENT OF PATIENTS (PTS) WITH CD30+ MATURE T-CELL LYMPHOMAS (MTCL)

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Introduction: MTCL including systemic anaplastic large cell lymphoma (sALCL) are aggressive neoplasms. Anthracycline-based multiagent chemotherapy regimens have demonstrated response rates ranging from 76 to 88%. Five-year overall survival rates range from 12 to 49% depending on the histologic subtype. Brentuximab vedotin (ADCETRIS®) is an antibody drug conjugate that has shown efficacy in a pivotal phase 2 study as a single agent in relapsed sALCL and evidence of clinical activity in combination with CHP in the frontline treatment of MTCL including sALCL in a phase 1 study.
Methods: This randomized, double-blind, placebo-controlled, multicentre, phase 3 study (NCT01777152) is evaluating the safety and efficacy of 1.8 mg/kg brentuximab vedotin with CHP (A+CHP) vs CHOP for frontline treatment of CD30+ MTCL. Pts must have FDG-avid disease by PET and measurable disease of at least 1.5 cm by CT. Approximately 300 pts will be randomized 1:1 to receive A+CHP or CHOP for 6–8 cycles (q3wk). Randomization will be stratified by ALK+ sALCL vs other histologic subtypes and IPI score (0–1, 2–3, or 4–5). The target proportion of pts with a diagnosis of sALCL will be 75%. The primary objective is to compare progression-free survival (PFS) between the 2 treatment arms as determined by an independent review facility (IRF). Secondary objectives include comparisons of PFS per IRF in sALCL patients, safety, overall survival, and complete remission rate between the 2 arms. After completion of treatment, pts will be followed for disease progression, medical resource utilization, quality of life, and survival. Post-treatment stem cell transplant is permitted. Efficacy assessments will use the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). CT and PET scans will be performed at baseline, after Cycle 4, and after the completion of treatment. CT scans will also be performed at regular intervals during follow-up until disease progression, death, or analysis of the primary endpoint. Safety assessments will occur throughout the study until 30 days after last dose of study treatment. Enrollment for this global trial began in early 2013.

'FOCUS ON...' SESSION: RELAPSING/REFRACTORY HODGKIN LYMPHOMA

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PILOT PHASE 2 STUDY OF IDELALISIB, A SELECTIVE INHIBITOR OF PI3Kδ, IN PATIENTS WITH HEAVILY PRETREATED HODGKIN LYMPHOMA (HL)

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DOI: 10.1002/hon

Background: PI3K-delta signalling is critical for activation, proliferation and survival of B-cells, plays a role in homing and retention in lymphoid tissues, and is hyperactive in many B-cell malignancies. Idelalisib (GS-1101) is a first-in-class, selective, oral inhibitor of PI3Kδ. Preclincal data demonstrated expression of PI3Kδ in HL cell lines and tumour sample RS cells, and idelalisib treatment decreased chemokine secretion and viability and increased apoptosis.
Methods: This phase 2 study evaluated continuous idelalisib monotherapy (150 mg BID) in pts with heavily pretreated HL. Response was evaluated based on investigator assessments using standard criteria (Cheson, 2007). Patients were followed until disease progression. Upon progression, patients were offered an increased dose of 300 mg BID.
Results: Study enrolled 25 pts with classical HL from October 2011 until November 2012, and is ongoing. Pts were male ($N = 11$) female ($N = 14$), median age of 42 years (range: 21-80). The median number of prior therapies was 5 (range: 3-9). Prior therapies included ABVD in 24/25 (96%), autologous SCT in 18/25 (72%), and brentuximab-vedotin in 22/25 (88%) of pts. At data cutoff (Jan 2013) the median duration of treatment was 3.7 months (range: 0.5–12.6). 13 pts have discontinued study, 10 due to progression, 2 due to investigator/pt request, and 1 due to AE. 3 pts have increased to the 300 BID dose. Preliminary data in evaluable pts: ORR was 3/20 (15%), with 2 PR (10%), and 1 CR (5%). 5 pts did not yet have response evaluation reported. PR durations were 2 months each. CR duration was 7 + months. 7/20 (35%) pts had SD, with durations from the start of treatment of 3+, 4, 4, 4, 6+, 8, and 11 months. Most common adverse events included (total%/≥G3%) fatigue (28/0), pyrexia (20/0), cough (20/0), vomiting (16/4), chills (16/0), rash (12/4), dyspnea (8/4), and diarrhoea (8/0). Lab abnormalities included (total%/≥G3%) ALT/AST elevations (56/20).
Conclusions: The oral PI3Kδ inhibitor idelalisib has demonstrated single-agent activity in intensively pretreated pts with HL, with an acceptable safety profile. Future studies will explore predictive biomarkers and mechanism-driven combination strategies.

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TWO-YEAR FOLLOW-UP OF PATIENTS WITH RELAPSED/REFRACTORY HODGKIN TREATED WITH BRENTUXIMAB VEDOTIN PRIOR TO REDUCED INTENSITY ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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Background: To examine the impact of brentuximab vedotin (b-vedotin) prior to reduced intensity allogeneic hematopoietic cell transplantation (RIC alloHCT), we performed a retrospective analysis of relapsed/refractory Hodgkin lymphoma (HL) patients who received b-vedotin at City of Hope (COH) and Seattle Cancer Care Alliance (SCCA) and then went on to receive RIC alloHCT. We previously reported a 1-year PFS of 92% and OS of 100% and now update after 2 years median followup. The historical 2 year PFS for HL patients who underwent RIC alloHCT without b-vedotin is around 23–32%.
Methods: Between October 2008 and December 2011, 54 patients with relapsed/refractory HL received b-vedotin at COH and SCCA via Seattle Genetics trials (SGN-35-03, 06, 07, and 08).18/54 (33.3%) patients subsequently underwent RIC alloHCT: 14 from COH and 4 from SCCA. 17/18 had prior autoHCT. The median number of prior regimen was 4. Conditioning regimens included: 13 fludarabine/melphalan, 3 fludarabine/cyclophosphamide (CY)/2Gy TBI, and 1 2Gy TBI. There were 7 matched related, 8 matched unrelated, and 3 haploidentical donors. 12 patients received tacrolimus (TAC)/sirolimus as graft-versus-host disease (GVHD) prophylaxis, 1 received mycophenolate mofetil (MMF)/cyclosporine, 2 received Cyclosporine/MMF, and 3 received CY/TAC/MMF. Patients were monitored for engraftment, aGVHD, cGVHD, chimerism, and infectious complications per institutional standards.
Results: The 2-year PFS was 57.5% and 2 year OS was 79.0% with a median followup of 24.9 months. At 2 years the relapse rate was 29.4% and non-relapse mortality was 13.8%. The rates of aGVHD and cGVHD were 67% and 50%, respectively. There was no grade III–IV aGVHD.There was no delayed engraftment or increased incidence of CMV/EBV infections. Causes of the 5 deaths were: 2 infections, 1 GVHD, 1 relapsed HL, 1 heart failure.
Conclusions: These data suggest that b-vedotin prior to RIC alloHCT in HL can yield prolonged disease control without a delay in engraftment, or increases in non-relapse mortality, GVHD, or post-transplant infectious complications. The 2 year PFS of 57.5% compares favourably with historical RIC alloHCT 2 year PFS of 23–32%. Such a strategy may allow more patients with relapsed/refractory HL to gain sufficient pre-transplant disease control to undergo this potentially curative procedure.

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PET-ADAPTED SEQUENTIAL THERAPY WITH BRENTUXIMAB VEDOTIN AND AUGMENTED-ICE INDUCES FDG-PET NORMALIZATION IN 92% OF PATIENTS WITH RELAPSED AND REFRACTORY HODGKIN LYMPHOMA

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Background: Pre-transplant FDG-PET (PET) normalization is a strong predictor of outcome following autologous stem cell transplant (ASCT) for relapsed or refractory (rel/ref) Hodgkin lymphoma (HL). Salvage therapy with ICE (ifosfamide, carboplatin, etoposide)-based induction results in PET normalization (PET-N) in 61% of patients (pts) and additional non-cross-resistant therapy with GND (gemcitabine, vinorelbine, doxil) results in PET-N in an added 18% (Moskowitz CH, et al. Blood 2012). The outcome for pts with normal pre-transplant PET is excellent, regardless of whether PET-N is achieved following ICE alone or ICE followed by GND; therefore the path to PET-N is less important than whether or not PET-N is achieved. Brentuximab vedotin (BV) is an anti-CD30 antibody drug conjugate approved for HL following failure of ASCT or 2 multi-agent therapies. We aimed to determine whether BV can replace ICE and/or increase the rate of PET-N through PET-adapted sequential administration with augmented ICE (augICE).
Methods: Pts with rel/ref HL who failed 1 prior regimen for HL are enrolling on this phase II trial. Pts receive BV, 1.2 mg/Kg IV weekly for 3 weeks on and 1 week off. Pts are re-evaluated by PET following 2 cycles of therapy. Pts who achieve PET-N (Deauville 1 or 2) proceed to ASCT. Pts with positive PET (Deauville >2) receive 2 cycles of augICE and are re-evaluated with PET. Those with PET-N proceed to ASCT; those with persistent PET abnormalities are treated as per the treating physician.
Results: 32 of planned 46 pts have enrolled and 24 have completed the induction program. The most common adverse events from BV are rash (77% all grades; 6% grade 3) and neuropathy (50% all grades, 13% grade 2). Of 24 evaluable pts, 8 (33%) achieved PET-N following BV alone, 22 of 24 (92%) achieved PET-N following the entire induction program. The 2 persistently PET positive pts after augICE received radiation therapy and achieved PET-N. All 24 pts proceeded to ASCT. 21 pts have completed ASCT and at 6 months median follow-up post ASCT, all but 1 (95%) remain in remission.
Conclusions: PET-adapted sequential salvage therapy with BV followed by augICE has allowed 33% of pts to avoid ICE-based therapy and results in PET normalization in >90% of pts. Updated results will be presented at the meeting.

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PROGNOSTIC FACTORS IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) HODGKIN'S LYMPHOMA (HL) TREATED WITH IGEV AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT): A ITALIANA LINFOMI (FIL)

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Introduction: Pts with R/R HL are treated with induction chemotherapy followed by ASCT. IGEV (ifosfamide, vinorelbine, gemcitabine) attainsboth highcomplete remission (CR) rate and mobilizing potential and itis the most widely used in this setting in Italy. We carried out a retrospective analysis in order to reassess the most common prognostic factors in a homogeneously treated pts population.
Methods: We collected data of pts treated with IGEV and ASCT in Italy from 1997 to 2007. Pts were at least 18 year old and were scheduled to receive 2 to 4 pre-

DOI: 10.1002/hon

Abstract 142 Table 1.

Characteristic	PFS 4 years	*p*-value	OS 4 years	*p*-value
All	52.3		73.3	
Age <40/≥40	53.3/50.9	0.793	78.0/63.3	0.015
Systemic symptoms A/B	57.3/33.6	<0.001	79.0/52.9	<0.001
Bulky no/yes	53.8/44.1	0.191	75.9/57.7	0.008
Stage I–II/III–IV	59.5/44.4	0.028	77.2/68.8	0.227
Rel>12/<12//Ref	62.7/62.1/42.6	<0.001	82.6/84.1/63.0	0.007

transplant IGEV courses. For each prognostic factor, the survival distribution was estimated through Kaplan–Meier method. Log-rank test was used to test differences between survival distributions in univariate analysis.

Results: 330 patents are evaluable. Main clinical characteristics: median age 32; M/F 57%/43%; previous regimens 1 64%, > 2 36%; refractory/relapsed 51%/49%; B symptoms 15%, bulky 21%, extranodal 13%. Post-IGEV CR was obtained in 39% of cases evaluated with CT scan, and in 52% of 204 cases evaluated with PET. Overall, 269 pts proceeded to transplant after IGEV or further chemo. With a median follow-up of 57.7 months for the whole population, median PFS was 50,6 months and median OS was not reached. The following table reports factors influencing4-year outcome in univariate analysis:

In multivariate analysis, relapsed versus refractory disease influenced both PFS and OS, whereas age, bulky disease and B symptoms influenced only OS.

Conclusions: factors influencing PFS and OS were identified, and will be used to build a prognostic score inIGEV homogenously treated patients with R/R HL.

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LONG-TERM OUTCOME OF ADULTS WITH FIRST RELAPSED OR REFRACTORY HODGKIN LYMPHOMA TREATED IN THE PROSPECTIVE LYSA/SFGM-TC H96 TRIALI

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Purpose: To assess prospectively the long-term efficacy and toxicity of autologous stem-cell transplantation (ASCT) for first relapsed or refractory Hodgkin lymphoma (HL) patients (pts) included in the H96 trial. The first analysis was published after a median follow-up of 51 months (Morschhauser F, J Clin Oncol 2008). Here we present an updated analysis after a median follow-up of 10.4 years.

Patients and Methods: H96 trial evaluated a risk-adapted salvage treatment with single or tandem ASCT for 245 HL pts. Poor-risk pts ($n = 150$) had primary refractory HL ($n = 77$) or unfavourable relapse (≥2 of the following risk factors at first relapse: time to relapse <12 months, stage III or IV at relapse, and relapse within previously irradiated sites, $n = 73$) and were eligible for tandem ASCT. Intermediate-risk pts ($n = 95$) had one risk factor at first relapse and were eligible for single ASCT.

Results: By intent-to-treat analysis, the 10-year freedom from second failure (FF2F) and overall survival (OS) rates were 64% and 70%, respectively, for the intermediate-risk group and 40% and 47%, respectively, for the poor-risk group. In the poor-risk group, outcomes were similar for primary refractory HL and unfavourable relapse (10-year OS 43% vs 51%, $p = 0.26$).

Disease status at time of transplantation (Cheson 1999) was a major prognostic factor driving outcome. In the poor-risk group, the 10-year OS was 68%, 58%, 16% and 22% for pts in complete remission (CR)/unconfirmed CR (CRu), partial remission (PR), stable disease (SD) and progressive disease (PD), respectively ($p < 0.0001$), without significant difference between CR/CRu and PR pts ($p = 0.12$). In the intermediate-risk group, 92/95 pts were in CR/CRu or PR at time of transplantation. The 10-year OS was 72% and 66% for pts in CR/CRu and PR, respectively, without significant difference ($p = 0.96$).

In the poor-risk group and the intermediate-risk group, the 10-year cumulative incidence of relapse was 51% and 27%, respectively. The main cause of death was HL ($n = 83$, 75% of causes of death), whereas other causes included secondary malignancy ($n = 10$), infection ($n = 5$), cardiac toxicity ($n = 2$) or other ($n = 10$).

Conclusion: With long-term follow-up, single ASCT remains appropriate for intermediate-risk pts. For poor-risk-patients, tandem ASCT remains a valuable option especially for patients in CR/CRu or PR at time of transplantation.

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SERUM TARC LEVEL MONITORING MAY PREDICT DISEASE RELAPSE DETECTED BY PET SCAN AFTER REDUCED-INTENSITY ALLOGENEIC STEM CELL TRANSPLANTATION IN HODGKIN'S LYMPHOMA PATIENTS

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Background. Relapsed and refractory Hodgkin's lymphoma (HL) patients may experience long-term survival after allogeneic transplant (alloSCT), but disease recurrence represents the main cause of treatment failure. PET (positron-emission tomography) scan is the most sensitive exam to monitor patients after alloSCT and PET-positive patients have a dismal outcome. Serum TARC (thymus and activation-regulated chemokine) is produced by Reed-Sternberg cells and may be a marker of disease. Objectives. Our study had the following aims: i) to assess whether serum TARC levels were correlated to disease status; ii) to correlate TARC levels with PET results after alloSCT; iii) to evaluate whether the combined results could increase the ability to assess or predict relapse. Patients and

Methods: Eighteen patients were evaluated (M/F = 11/7): median age was 31 years (range, 18–41); 16 had nodular sclerosis HL; disease status before alloSCT was CR $n = 6$, PR $n = 9$, SD/PD $n = 3$. Patients received reduced intensity conditioning regimen and peripheral stem cells from a sibling (matched $n = 6$, haploidentical $n = 1$) or unrelated ($n = 11$) donor.Median follow-up was 26 months (range, 11–40). PET scans were performed before transplant and every 3–6 months after alloSCT. Serum TARC levels were performed before and after alloSCT with a median time interval of 47 days (range, 10–700).

Results: Before alloSCT, the median serum TARC level was: 394 (range, 195–1332) in PET-negative patients, 2569 (range, 94–13 870) in PET-positive, 931 (range, 710–2690) in weakly positive (SUV ≤2.5 in previously involved sites) PET patients. After alloSCT, TARC was 558 (range, 31–7441) in always PET-negative patients compared with 13375 (range, 734–93541) in PET-positive ones ($p < 0.0001$). TARC was increasing in one patient who had a weakly positive PET at a previous disease site and returned <1000pg/mLwhen PET became negative after cyclosporine withdrawal. In 4 patients who relapsed after alloSCT TARC increased progressively (median fold increase: 5,2) before PET scan became positive. Considering TARC values done on the day of PET scans, the ROC curve showed that the cut off value of 1500 pg/mL had a sensitivity and specificity of 86% and 91%, respectively.

Conclusions: Serum TARC level correlated with HL tumour burden as detected by PET scan. Patients with disease after alloSCT had elevated TARC levels compared with those in CR. TARC monitoring may be able to predict PET positivity, thus potentially allowing immune manipulation before clinical relapse.

DOI: 10.1002/hon

'FOCUS ON. . .' SESSION: PHASE I–II TRIALS

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PRELIMINARY SAFETY AND EFFICACY OF IPI-145: A POTENT INHIBITOR OF PHOSPHOINOSITIDE-3-KINASE-δ,-γ, IN PATIENTS WITH RELAPSED/REFRACTORY CLL/SLL

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Background: PI3-kinases are pivotal in cell signalling and regulate multiple cellular functions relevant to oncogenesis. IPI-145, a potent oral inhibitor of the PI3K-δ and PI3K-γ isoforms, is being developed in patients (pts) with hematologic malignancies. Early Phase 1 results in pts with relapsed/refractory CLL/SLL (CLL) are presented here.
Methods: This dose-escalation (DE) study evaluates the safety, maximum tolerated dose (MTD), clinical activity, and pharmacokinetics (PK)/pharmacodynamics (PD) of IPI-145. IPI-145 is given orally twice daily (BID) in 28-day cycles. pAKT inhibition is measured from peripheral blood CLL cells. Tumour response is based on modified IWCLL guidelines criteria. Expansion cohorts (EC) with CLL pts ($n = 15$–20) at ≤ MTD are enrolling.
Results: Overall, 65 pts have been dosed with IPI-145, including 20 pts with CLL/SLL (5 pts in DE <25 mg BID and 15 pts in a 25 mg BID EC). The MTD was declared at 75 mg BID after 2 lymphoma pts dosed at 100 mg BID experienced a dose-limiting toxicity in Cycle 1 (Grade [Gr] 3 rash, Gr 3 ALT elevation). Among CLL pts, the median [range] number of cycles was 4.6 (1–15) and 75% remain on study. PD results show continuous 24 h inhibition of pAKT (Ser473) in primary CLL cells after a single dose of 25 mg. Treatment-related adverse events (TRAEs) occurred in 17 (85%) CLL pts, similar to the incidence in the total study population (77%). The most common > Gr 3 TRAEs in pts with CLL were neutropenia (20%), anaemia, stomatitis, and elevated ALT (10% each). Gr 4 TRAEs included Stevens Johnson-like syndrome and tumour lysis (1 pt), and pneumocystis infection (1 pt). TRAEs leading to discontinuation include pneumonitis ($n = 2$), oral mucositis ($n = 1$), and ALT/AST elevation ($n = 1$). Among 19 evaluable pts with CLL, 74% ($n = 14$) had a PR or nodal response after 2 cycles of IPI-145, with a best response to date of 10 PR, 8 SD (6 with nodal responses), and 1 PD.
Conclusions: IPI-145 appears well tolerated and has shown rapid clinical activity at the doses examined in pts with relapsed/refractory advanced CLL/SLL. The MTD has been determined at 75 mg BID. Updated safety, efficacy, and PK/PD data from CLL pts in DE and ECs at 25 mg BID and MTD will be presented.

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UPDATED RESULTS OF A PHASE I FIRST-IN-HUMAN STUDY OF THE BCL-2 INHIBITOR ABT-199 (GDC-0199) IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) NON-HODGKIN LYMPHOMA (NHL)

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Background: BCL-2 is highly expressed in NHL, including mantle cell lymphoma (MCL), and is a promising therapeutic target as it is critical to NHL pathogenesis and resistance to chemotherapy. ABT-199 is a selective inhibitor with >500-fold higher affinity for BCL-2 (K_i<0.10 nM) than BCL-X_L (K_i = 48 nM).
Methods: Objectives of this Ph 1 dose-escalation study include evaluations of safety, pharmacokinetics and preliminary efficacy in patients (pts) with R/R NHL. A single oral dose (50–400 mg) was administered followed by 6 days off drug prior to the initiation of continuous once daily dosing. Due to concerns of potential tumour lysis syndrome (TLS), a 2 to 3 wk lead-in period with step-wise escalation to the target cohort dose was implemented. Dose cohorts up to 900 mg have been evaluated to date.
Results: As of January 11, 2013, 31 pts have been enrolled (median age 68 y (range 35–85); 20 males; median 3 prior therapies (range 1–7)). 13 (42%) and 4 (13%) had bulky adenopathy (>5 and >10 cm, respectively). The most common AEs (≥15% of patients) were nausea (36%), diarrhoea (26%), dyspepsia, vomiting, fatigue, pyrexia and cough (16% each).Grade 3/4 AEs occurring in >1 patient were anaemia, neutropenia (4 pts each), febrile neutropenia (2 pts) and thrombocytopenia (3 pts). Gr 3/4 thrombocytopenia was not dose dependent. Two of 14 pts in cohort 5 experienced DLTs (Gr 3 febrile neutropenia and Gr 4 neutropenia) at the target dose of 600 mg. Gr 3 TLS was seen after the initial dose in 1 pt with bulky MCL (>10 cm). With a median follow-up of 5 months (range 0.5–15), 17 pts have discontinued: 13 due to PD, 2 due to AEs and 2 proceeded to BMT in ongoing response.For the 29 pts evaluable for efficacy, the overall response rate is 55%, with 1 CR (DLBCL) and 15 (52%) PR (8/8 MCL, 3/3 Waldenstrom macroglobulinemia, 2/7 follicular lymphoma and 2/7 DLBCL).
Conclusions: ABT-199 is highly active in R/R NHL, particularly in MCL. Additional dosing and scheduling modifications are currently being explored to optimize efficacy and safety. ABT-199 warrants further single-agent and combination trials in NHL. (study status see clinicaltrials.gov NCT01328626)

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CELL CYCLE INHIBITION WITH PD0332991 SENSITIZES MCL TO KILL BY BORTEZOMIB: A PHASE I TRIAL

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Introduction: Mantle cell lymphoma (MCL) is characterized by cell cycle dysregulation due to cyclin D1 and CDK4 overexpression. Targeting CDK4 is thus a novel therapeutic approach. We have shown that: 1) The selective, oral CDK4/CDK6 inhibitor PD0332991 induces prolonged early G1 arrest (pG1) in cancer cells; 2) pG1 sensitizes cancer cells to bortezomib killing; 3) pG1 sensitization is amplified upon PD0332991 withdrawal, when MCL cells enter S phase synchronously (pG1-S); and 4) PD0332991 inhibited CDK4 and induced pG1, resulting in durable clinical responses with an excellent toxicity profile in a phase I trial in MCL. On this basis, we performed a phase I trial of PD032991 plus bortezomib in previously treated MCL.
Methods: PD0332991 was administered orally at 75 mg, 100 mg, or 125 mg for 12 days. Bortezomib was given by IV or SC injection at 1 mg/m^2 on days 8 and 12 in pG1 and again on days 15 and 18 in pG1-S. Restaging was performed q2 cycles.
Results: Sixteen pts have been enrolled, 6 in dose level 1, 3 in dose level 2, 7 in dose level 3. The median age is 63.5 y (range 42–78). The median number of prior therapies is 3 (range 1–7). Two pts experienced DLT (level 1 and 3). Treatment-related grade 3–4 toxicity included: neutropenia (9), thrombocytopenia (6), and zoster (1). Treatment-related grade 1–2 toxicity occurring in >1 pt include: thrombocytopenia (6), anaemia (5), fatigue (4), nausea/vomiting (3), rash (3), constipation (2), cough (2), neuropathy (2), bleeding (2), diarrhoea (2), neutropenia (2). Reasons for stopping treatment included: progression (5), withdrawal of consent (4), DLT (2), neuropathy (1), non-compliance (1). No responding pts stopped treatment due to disease progression. Three pts remain on treatment at 6, 6, and 8 cycles. Inhibition of CDK4 and reduction in Ki67 was seen on day 8 in all pts at all dose levels. Four pts achieved a PR. Only 1/7 pts at dose level 3 experienced progression.
Conclusion: PD0332991 can be combined safely with bortezomib in pts with previously treated MCL. Hematologic toxicity is dose limiting. PD0332991 induces pG1 in all pts and appears to have promising clinical activity at dose level 3 with reduced-dose bortezomib. The genes that mediate PD0332991 sensitization are under investigation in serial biopsies.

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PHASE 1 STUDY OF R-CVP PLUS INOTUZUMAB OZOGAMICIN (INO) IN CD22+ B-CELL NON-HODGKIN LYMPHOMA (B-NHL)

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DOI: 10.1002/hon

Introduction: CD22 is expressed on most B-non-Hodgkin lymphomas (NHL); inotuzumab ozogamicin (INO) is an anti-CD22 antibody conjugated to calicheamicin. This study evaluated the safety and tolerability of INO plus R-CVP in patients (pts) with relapsed/refractory CD22+ B-NHL. Efficacy data were also collected.
Methods: Part 1 of this open-label study identified a maximum tolerated dose (MTD) of INO 0.8 mg/m,^{2} on day 2 plus R-CVP (rituximab 375 mg/m,^{2} cyclophosphamide 750 mg/m,^{2} and vincristine 1.4 mg/m,^{2} on day 1; prednisone 40 mg/m,^{2} on days 1–5) every 21 days. Subsequently, pts were enrolled in the MTD confirmation cohort (part 2, $n = 10$), which required a dose-limiting toxicity rate of $<33\%$ in cycle 1 and <4 pts discontinuing prior to cycle 3 due to an adverse event (AE) in the MTD expansion cohort (part 3, $n = 22$), which explored preliminary activity.
Results: Parts 2 and 3 enrolled 32 pts: 16 pts with diffuse large B-cell lymphoma, 15 with follicular lymphoma and one with mantle cell lymphoma. Median age was 64.5 years (range 44–81 years); 34% of pts had 1 prior regimen, 34% had 2, 28% had $\geq$3 and 3% had none (median 2; range 0–6). Median treatment duration was five cycles (range 1–6). Part 2 confirmed the MTD as standard dose R-CVP plus INO 0.8 mg/m,^{2}; 2/10 pts had a dose-limiting toxicity (grade 3 increased ALT/AST, grade 4 neutropenia requiring G-CSF). One pt discontinued because of an AE prior to cycle 3.
Common treatment-related AEs were thrombocytopenia (78%), neutropenia (66%), fatigue (50%), leukopenia (50%), nausea (41%) and lymphopenia (38%); common grade 3/4 AEs were neutropenia (63%), thrombocytopenia (53%), leukopenia (38%) and lymphopenia (31%). There was one case of treatment-related fatal pneumonia with grade 4 neutropenia. Ten pts discontinued treatment due to AEs; thrombocytopenia/delayed platelet recovery was the leading cause (grade 1/2, $n = 6$; grade 3/4, $n = 3$). Objective response rate (ORR) was 77% ($n = 24/31$ evaluable pts), including 26% ($n = 8/31$) with complete response (CR); three pts had stable disease. Of the pts with follicular lymphoma, ORR was 100% ($n = 15/15$), including seven pts with CR. Of the pts with diffuse large B-cell lymphoma, ORR was 60% ($n = 9/16$), including one pt with CR.
Conclusions: Results suggest that INO plus R-CVP has acceptable toxicity and promising activity in relapsed/refractory CD22+ B-NHL. The most common grade 3/4 AEs were hematologic. Follow-up for progression-free and overall survival is ongoing.

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TEMSIROLIMUS ADDED TO BENDAMUSTIN AND RITUXIMAB (BERT): PHASE I RESULTS OF A PHASE I/II-TRIAL IN PATIENTS WITH RELAPSED FOLLICULAR LYMPHOMA (FL) AND MANTLE CELL LYMPHOMA (MCL)

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Background: Current therapeutic options for relapsed lymphoma frequently achieve only short term remissions. mTOR inhibitors have been shown to be efficacious in different lymphoma entities. Temsirolimus (T) was superior to standard therapy in r/r MCL and a high response rate was observed in FL. Preclinical evaluation showed promising
Results: of combination of T with chemotherapy such as Bendamustine/Rituximab (BR). Therefore we initiated a phase I/II trial to establish a MTD of T added to BR (BeRT) and to evaluate the efficacy at the MTD. Here we report on the preliminary results of the phase I part.
Methods: Key inclusion criteria for this multicentre, prospective trial were: histologically proven FL or MCL (Cyclin D1 or t(11;14) positive), 1–3 prior treatments, no curative option, no refractoriness to B, measurable disease, ECOG < 3, sufficient bone marrow reserve and given informed consent. Treatment schedule consisted of: B 90 mg/m,^{2} day 1–2, R 375 mg/m,^{2} day 1 and T day 2, 8, 15 of a 28d cycle for a total of 4 cycles. The following dose cohorts for T were explored: A 25 mg, B 50 mg, C 75 mg.
Results: 15 patients have been included: histology was MCL in 11 and FL in 4 pts.; median age was 73 (51–75); 11 male, BM was involved in 33%; med prior lines: 2; prior HDT 27%. Grade 3/4 toxicities (n>1) were: lymphopenia in 13 (86%), leukopenia in 5 (33%), neutropenia in 4 (27%) and thrombopenia in 2(13%) patients. In 2 patients angioedema was noted days after the last dose of T, which might be due to concomitant ACE-inhibitor use. One pneumonitis occurred, which resolved with steroids and BeRT could be resumed w/o further problems. Frequent grade 1/2 findings were nausea in 6 (40%), fatigue in 8 (53%), mucositis in 6 and infections (e.g. stomatitis or skin infections) in 14 cases. Cohort A was expanded to 6 patients due to one case of hypertension 3 patients did not complete the treatment due to AE's. Although MTD was not reached, more cytopenias and dose delays were noted at the last dose level. Therefore the DSMB recommended a dose of 50 mg of T combined to BR for the phase II part. Altogether 14 /15 are evaluable for response: 1 CR, 11 PR, 2 SD (ORR 86%). PFS analysis is ongoing.
Conclusion: Temsirolimus can be safely combined to BR. ORR is encouraging and the phase II part of the trial has been initiated concordantly.

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PROSPECTIVE PHASE II CLINICAL TRIAL OF CARFILZOMIB, RITUXIMAB AND DEXAMETHASONE (CARD) IN WALDENSTROM'S MACROGLOBULINEMIA (WM).

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Bortezomib is active in Waldenstrom's macroglobulinemia (WM) but associated with considerable peripheral neuropathy (PN). The proteasome inhibitor carfilzomib (CFZ) was recently approved in the USA for relapsed/refractory myeloma. Herein, we examined the efficacy and safety of carfilzomib, rituximab and dexamethasone in 31 proteasome inhibitor-naïve and R-naïve symptomatic WM patients. Median baseline characteristics: age 61, prior therapies 0 (range 0–1), hematocrit 30.8%, haemoglobin 10.6 g/dL, serum IgM 3510 mg/dL, serum M-protein 2.09 g/dL, B2M 3.4 mg/L and bone marrow involvement 60%. Therapy consists of IV CFZ 20 mg/m,^{2}/36 mg/m,^{2} (cycle 1/cycles 2 and beyond) with IV dexamethasone (dex) 20 mg on days 1,2,8,9 and R 375 mg/m,^{2} on days 2,9 of each 21-day cycle. Treatment consists of six induction cycles, and then maintenance beginning 8 weeks after induction (given every 8 weeks for eight cycles; consists of CFZ 36 mg/m,^{2} and dex 20 mg on days 1,2 and R 375 mg/m,^{2} on day 2). Patients with IgM level >4000 mg/dL undergo plasmapheresis and/or have rituximab held until IgM $<$4000 mg/dL to prevent symptomatic IgM flare. Patients receive acyclovir (400 mg twice daily) and famotidine (20 mg twice daily) as concomitant medications. For all 31 patients, median serum IgM levels and M-protein declined to 1876 mg/dL and 0.99 g/dL, respectively ($p < 0.00001$). Median hematocrit and haemoglobin rose to 36.3% and 12.0 g/dL, respectively ($p \leq 0.0002$). A total of 23 patients concluded induction therapy with bone marrow tumour burden reduced from a median of 60% to 10% ($p = 0.008$). The best overall response for patients who concluded induction therapy was 74% (1 CR, 6 VGPR; 9 PR, 1 MR). With a median follow-up of 5.5 months, 24 patients remain on study, including eight currently on induction therapy. Median time to response (MR or better) was 2.1 months. Grade $\geq$2 treatment related toxicities include anaemia (6.5%), thrombocytopenia (3.2%, all grade 2), neutropenia (25.8%, 6.5% were grade 3/4), asymptomatic hyperbilirubin (6.5%), lipase (38.7%), reversible azotemia (3.2%), infusion site cellulitis (6.5%), febrile neutropenia (3.5%), dex-related hyperglycemia (64.5%), R-related infusion reactions (22.6%) and R-related IgM flare (22.6%). There were no grade $\geq$2 PN events, and no patient was removed for toxicity. Treatment discontinuation occurred for non-response ($n = 6$) and progressive disease ($n = 1$). Carfilzomib, rituximab and dexamethasone represents a novel, well tolerated and PN-sparing regimen for symptomatic WM.

SESSION 11—T-CELL NEOPLASIA

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CD30 IN PTCLS: CORRELATION BETWEEN RNA AND PROTEIN LEVELS IN A LARGE EUROPEAN SERIES FROM THE LYSA

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DOI: 10.1002/hon

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Introduction: Brentuximab vedotin, a conjugate of an anti-CD30 monoclonal antibody cAC10 with the cytotoxic agent monomethyl auristatin E, was recently FDA-approved for the treatment of relapsed or refractory Hodgkin's lymphoma and systemic anaplastic large cell lymphoma (ALCL), and its efficacy in other CD30 lymphomas, especially in peripheral T-cell lymphomas (PTCLs), is currently being investigated. However, the CD30 expression level in PTCLs is not thoroughly determined yet. The aim of the study was to assess CD30 expression, at the protein and mRNA levels, in a large series of non-cutaneous PTCLs from western Europe.
Methods: This study included 195 PTCLs cases diagnosed between 1999 and 2012, collected in the framework of a multicentric research consortium 'Tenomic'. It comprised PTCLs, not otherwise specified (PTCL NOS, $n=49$); angioimmunoblastic T-cell lymphomas (AITL, $n=48$); ALK-positive ($n=61$) and ALK-negative ($n=17$) systemic ALCL; extranodal NK/T-cell lymphomas (ENKTL, $n=10$); enteropathy-associated T-cell lymphomas (EATL, $n=7$), and adult T leukaemia/lymphoma HTLV1+ ($n=3$). CD30 was scored using a semiquantitative evaluation of the percentage of positive tumour cells and then grouped into five categories. Transcriptomic CD30 mRNA levels were evaluated in parallel ($n=110$) and compared with protein levels.
Results: CD30 expression was heterogeneous, except for ALCL. The overall percentage of cases with detectable CD30 expression (≥5%) was 69% in PTCL NOS, 66,6% in AITL, 30% in ENKTL, and 66,6% in adult T leukaemia/lymphomas with 28% of PTCL, NOS showing a strong expression. Furthermore, in each entities, we observed a significant correlation between protein and mRNA levels ($p=2.4$ 10–9)
Conclusion: In this large series of PTCLs 1) a broad heterogeneity of CD30 expression inside entities, especially in PTCL NOS. 2) a significant correlation of CD30 between the protein and the mRNA levels for all entities of PTCLs. Prospective clinical studies are needed to determine for each entity the appropriate cut-off value of CD30 expression correlating with antitumour activity of brentuximab.

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SAFETY AND EFFICACY OF BRENTUXIMAB VEDOTIN FOR TREATMENT OF RELAPSED OR REFRACTORY MATURE T-/NK-CELL LYMPHOMAS

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Introduction: Brentuximab vedotin (ADCETRIS®) is an anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E, a synthetic microtubule-disrupting agent.CD30 is a target antigen variably expressed on several non-Hodgkin lymphomas, including both B-cell and mature T-/NK-cell lymphomas. A phase 2, open-label, single-arm study was initiated to evaluate efficacy and safety of brentuximab vedotin in relapsed or refractory CD30+ non-Hodgkin lymphomas (NCT01421667).This subset analysis presents interim data for patients enrolled with CD30+ mature T-/NK-cell lymphomas.
Methods: Brentuximab vedotin 1.8 mg/kg is administered every 3 weeks until disease progression or unacceptable toxicity. Objective response rate is the primary endpoint (by Cheson 2007), and a secondary endpoint is correlation of CD30 expression with response.
Results: A total of 29 patients with mature T-/NK-cell lymphomas with variable CD30 expression as determined by immunohistochemical staining (range 0–90%) have been enrolled. Diagnoses included angioimmunoblastic T-cell lymphoma (AITL, $n=11$) and peripheral T-cell lymphoma not otherwise specified ($n=18$). Median age was 65 years (range 33–83), and 21 patients (72%) were male. Patients have received a median of two prior systemic therapies, 17 (59%) were refractory (including primary refractory or refractory to most recent prior therapy) and 12 (41%) were relapsed. Of the 22 patients with mature T-/NK-cell lymphomas who have had a response assessment, eight (36%) have achieved an objective response (6 CR, 2 PR), and median duration of response has not been reached. Of note, 5 of 10 patients (50%) with AITL have had an objective response (4 CR, 1 PR), and median duration of response has not been reached. Related adverse events (>10%) include fatigue (17%) and peripheral sensory neuropathy (14%). Neutropenia was the only adverse event ≥grade 3 occurring in more than two patients.Conclusions: In this interim analysis, antitumour activity has been demonstrated in AITL patients with a 50% objective response rate and median duration not reached. Analysis of correlation of CD30 expression with response is ongoing. Safety data are consistent with the profile of brentuximab vedotin.

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BELINOSTAT IN RELAPSED OR REFRACTORY PERIPHERAL T-CELL LYMPHOMA (R/R PTCL) SUBTYPE ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA (AITL): RESULTS FROM THE PIVOTAL BELIEF TRIAL

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Abstract 151 Table 1.

% of CD30 tumour cells	ALCL		PTCL $N=49$	AITL $N=48$	ENKTL $N=10$	EATL $N=7$	HTLV1 $N=3$
	ALK+ $N=61$	ALK− $N=17$					
0–<5%			15	16	7	7	1
5–24%			15	26	1		0
25–49%			5	2	1		1
50–75%			3	4	0		1
>75%	61	17	11	0	11		0
Positive cases (>5%)	100%	100%	69%	66.6%	30%	0	66.6%
Positive cases with strong expression (>50%)	100%	100%	28.5%	8.3%	10%	0	33.3%

DOI: 10.1002/hon

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Introduction: PTCL is a heterogeneous, aggressive disease with poor prognosis. AITL is a subtype representing 15–20% of PTCL. AITL treatment is similar to other forms of PTCL with 5-year OS rates of 10–32%.
Methods: BELIEF was a single-arm study of belinostat in patients with R/R PTCL after failure of ≥1 prior systemic therapies. Entry criteria were measurable disease, platelets≥ 50,000/μl, no prior histone deacetylase inhibitor (HDACi) therapy, and adequate organ function. PTCL was confirmed by central pathology review group (CPRG). Belinostat (1000 mg/m,^{2} IV × 5 days) was given as a 3 week cycle until progression or unacceptable toxicity. Tumour response was assessed by Cheson 2007 criteria. The primary endpoint was ORR. Subgroup analysis examined response by PTCL subtype.
Results: Of 129 patients enrolled with R/R PTCL, data presented here are from 22 patients with CRPG confirmed AITL, including 5 with baseline platelets <100,000/μl, a median age of 70 (range 48–78) years, 64% female, a median of 2 (range 1–5) prior therapies (21 CHOP/CHOP-like; 4 stem cell transplant), and 8 had bone marrow involvement. Belinostat was administered for a median of 4 cycles (1–29) with a median dose intensity of 94%. Dose reductions in 3 patients were due to grade 2 and 3 QTC prolongation in 1 patient, immune hemolytic anaemia, and hypokalemia/dyspnea/fever. Response rate for AITL was 45% (4 CR, 6 PR) with a median duration of response of 7.5 (1.6–29.4) months. Of the responders, 2 had baseline platelets of 78,000 and 79,000; with one patient achieving CR. Data is reported as of 31AUG2012, with 3 patients remaining on treatment at 55, 105, and 135 weeks and 19 discontinued. Discontinuations were due to PD in 14 patients, AEs in 2 and other reasons for 3. Sixteen patients have died, 5 were alive, and 1 was lost to follow-up. Median PFS and OS for patients with AITL were 5.8 and 9.2 mos, respectively.
Conclusions: Belinostat treatment resulted in a 45% response rate among patients with R/R AITL. The favourable safety profile observed warrants further investigation of belinostat-based regimens to optimize outcomes for AITL.

[Correction added on 9 July 2013, after print publication: In Results, the sentence, "Data is reported as of 31AUG2012, with 3 patients remaining on treatment at 55, 105, and 135 months and 19 discontinued" should read, "Data is reported as of 31AUG2012, with 3 patients remaining on treatment at 55, 105, and 135 weeks and 19 discontinued".]

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COMBINATION OF MOGAMULIZUMAB (KW-0761) WITH VCAP-AMPVECP (MLSG15) IS WELL TOLERATED AND EFFECTIVE AS AN INITIAL THERAPY FOR AGGRESSIVE ADULT T-CELL LEUKAEMIA-LYMPHOMA (ATL)

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Introduction: Mogamulizumab (Moga), a defucosylated humanized anti-CCR4 antibody, was approved for the treatment of relapsed/refractory adult T-cell leukaemia–lymphoma (ATL) in Japan in 2012. To examine the efficacy of the combination of Moga with standard chemotherapy, this multicentre, randomized, phase 2 trial was conducted for untreated aggressive ATL.
Methods: Previously untreated patients (pts) with CCR4-positive ATL were randomly assigned to receive mLSG15 plus Moga (arm A) or mLSG15 alone (arm B). The primary endpoint was complete response (CR) rate (%CR), and secondary endpoints included overall response rate (ORR), progression-free survival, overall survival and safety. Pts received four courses of mLSG15 regimen, with or without a total of eight doses of Moga (1.0 mg/kg) once every 2 weeks. The planned sample size, 22 pts per arm, provided a probability of 80% that %CR in arm A would have larger %CR when true %CR for arm A is 15% better than that for arm B.
Results: Of 54 pts randomized, 53 were treated (arm A: 29; arm B: 24). Male/female ratio was 53/47%, median age was 63 (37–81) and subtype was acute/lymphoma/unfavourable chronic, 70/25/6%. %CR and ORR in arms A and B were 52% (95%CI [CI]; 33, 71) versus 33% (CI; 16, 55) and 86% (CI; 63, 96) versus 75% (CI; 53, 90), respectively. The results in arm B were similar to the previously reported %CR of 40% and ORR of 72% (Tsukasaki et al, JCO 2007). ORR according to the disease subtype, in arms A and B, was 55% versus 29% for acute, 50% versus 43% for lymphoma and 33% versus 0% for unfavourable chronic. Median progression-free survival was 259 days (CI; 197, –) for arm A and 192 days (CI; 147, –) for arm B. Median overall survival was not reached in both arms. The most common treatment-related adverse events in each arm were neutropenia (100%, 96%), thrombocytopenia (100%, 96%), leukopenia (100%, 92%), lymphocytopenia (97%, 96%), anaemia (97%, 92%) and febrile neutropenia (90%, 88%). In arm A, skin disorders were more frequent but manageable, and no serious skin disorder such as Stevens-Johnson syndrome was observed. There was one treatment-related death, which was not related to Moga.
Conclusions: The combination of Moga with mLSG15 was well tolerated, and the study met its primary endpoint. These results suggest that the combination therapy is a rational treatment option for newly diagnosed aggressive ATL.

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INTENSIFIED CHEMO-IMMUNOTHERAPY FOR PATIENTS AFFECTED BY NODAL PERIPHERAL T-CELL LYMPHOMAS (PTCLS) AT DIAGNOSIS: FINAL RESULTS OF A PHASE II MULTICENTRE PROSPECTIVE TRIAL

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Introduction: Patients affected by PTCLs have poor survival with conventional therapy. On the basis of this finding, we conducted a prospective phase II study in young (A: ≥18 ≤60 years) and elderly (B: >60 and ≤75 years) patients (pts) at diagnosis. In young pts, the trial tested for the first time a consolidation with up-front allogeneic or autologous stem cell transplantation (autoSCT or alloSCT) based on a genetic stratification. In elderly pts, the trial tests only the role of chemo-immunotherapy.
Methods: Younger pts (A) received 2 courses of CHOP-21 with alemtuzumab (AL, 30 mg), 2 courses of Hyper-C-Hidam (methotrexate, cyclophosphamide, cytarabine). Responding pts received consolidation with up-front autoSCT or alloSCT. Elderly pts (B) received 6 cycles of CHOP-21 with AL (10 mg).
Results: 92 pts were enrolled, 86 fulfilled inclusion criteria (A: $n=61$; B: $n=25$). Clinical characteristics: PTCL-NOS 49%, AILT 24%, ALK-negative ALCL 22%, EATL 5%. International prognostic index ≥2, A: 69%; B:100%. For study A, at the end of induction phase, the ORR was 67% (CR, 56%; PR, 11%). Thirty-eight (62%) pts received consolidation: 14 autoSCT, 23 alloSCT and one maintained remission without any further treatment. Twenty-three did not receive consolidation for PD

DOI: 10.1002/hon

($n = 18$) or deaths for toxicity ($n = 5$). At a median follow-up of 40 months, 30 pts (49%) are alive in CR. The cumulative incidence of non-relapse mortality (NRM) was 13%. The estimated 4-years OS, PFS and DFS rates were 48.8% (95%CI, 37.6–63.2%), 44.0% (95%CI, 33.1–58.5%) and 79% (95%CI, 65.1–95.5%), respectively. At multivariable analysis, the CR maintained for at least 6 months had a dominant effect on PFS and OS. Transplanted pts had an advantage in OS (HR = 0.04, $p = 0.004$ for autoSCT; HR = 0.22, $p = 0.008$ for alloSCT). For study B, 13 pts (52%) maintained the response at least for 6 months and 8 pts (32%) are alive at last follow-up. The cumulative NRM was 12%. At median follow-up of48 months, the estimated 4-year OS, PFS and DFS were 31.5% (95% CI: 17.6–56.5%), 26.7% (95% CI: 13.6–52.3%) and 44.4% (95% CI: 24.6–80.5%), respectively.Conclusions: Considering the high-risk population, in younger pts the consolidation with up-front transplantation was associated to a prolonged DFS. In elderly, the chemo-immunotherapy program did not improve the outcome.

SESSION 12—LYMPHOMA MICROENVIRONMENT

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T-CELL AND MONOCYTE PROFILING SHOWS MARKED DIFFERENCES IN FRESH TISSUE GENE EXPRESSION BETWEEN POSITIVELY SELECTED TUMOUR INFILTRATING AND PERIPHERAL BLOOD CELLS IN FOLLICULAR NON-HODGKIN'S LYMPHOMA (FL): POSSIBLE ROLE OF HEAT SHOCK PROTEIN 70 (HSP70) AND B-CELL RECEPTOR ACTIVATING GENES IN DISEASE PROGRESSION AND TRANSFORMATION

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Introduction: T-cells and macrophages/monocytes (MM) have an important role in the biology of follicular lymphoma (FL). There is conflicting data on the number role of tumour-infiltrating T-cells (TIL) and MM in predicting outcome. A National Cancer Institute study showed prediction of survival in FL based on the gene expression profiling of TIL. Other studies have shown multiple TIL functional defects. However, these studies used non-trizol frozen material, and the selected cells were stimulated with CD3 and grown in culture that could have changed the signatures. In the National Cancer Institute study, T-cells were negatively selected and mixed with other non-B-cells, and the study did not look at peripheral blood (PB) T-cell or MM profiles. No studies have looked specifically at fresh MM signatures, although there are reports implicating their number in transformation to diffuse large B-cell lymphoma.
Aims and Methods: In the first stage reported here, we looked at positively selected TIL and MM gene expression profile signatures in fresh diagnostic samples of histologically confirmed grades 1–3a FL in 14 patients and compared the profiles with similarly selected cells from PB samples taken at the same time. The analysis was controlled with four histologically proven reactive hyperplasia lymph nodes. Tissue samples were digested with a cocktail of enzymes, Ficol separated and then positively selected for CD2, CD14 and CD19 in that order using microbead technology. CD2 selection and no expansion in culture were used to minimize T-cell receptor stimulation and change of expression. Some isolated T-cells were expanded in culture for purity assessment by flow cytometry. T-cells and MM were liquidized in Trizol prior to liquid nitrogen freezing. RNA was extracted at the same time and analysed using affymetrix microarray chips. Statistical analysis used three parameters to define significant change in expression: fold change of >1.5, p-value of $>1 \times 10,^{-3}$and FDR of <0.05. Samples were analysed as paired and pooled with a fold (over or under expressed) cut off threshold of 10. Results were validated with qPCR for 10 of the most under or overexpressed genes.
Results: T-cells: paired samples (10) showed 97 over-expressed (41) or under-expressed (56) genes in TIL compared with peripheral blood T-cell, whereas pooled samples (14) showed 778 over-expressed (380) or under-expressed (398) genes. The top over-expressed genes using both methods of analysis are CXCL13, a B-cell chemotactic gene, IGJ, which helps in Ig assembly, CTLA4, a regulatory molecule, and CD200, which delivers an inhibitory signal to macrophages. These define a T-helper phenotype. Several heat shock protein (HSP) genes are over expressed relating to HSP70 pathway. The top under-expressed genes include genes that regulate T-cell adhesion, migration and cytotoxicity such as a number of flow cytometry receptor genes needed for antibody dependant cell cytotoxicity, genes involved in adhesion and migration, and granzyme, granulosin, lysosyme and other genes involved in T-cell cytotoxocity. MMs: Only pooled analysis was performed as the cell numbers were too small to have paired analysis. Many more (3239) genes were over-expressed (1494) or under-expressed (1745) in lymph node compared with PB MM. The top over-expressed genes include genes that stimulate B-cell receptor, growth and transformation such as IGJ, BLNK, PAX5, PTTG1 and C4orf7, CXCL13, signal transduction inhibitors and again HSP70. The top under-expressed genes include those that regulate cell adhesion, proliferation, migration and survival, and flow cytometry receptors, IL-1 and complement genes necessary for cell cytotoxicity.
Conclusion: We believe this is the first study of this design with novel data suggesting that TIL and tissue MM support B-cell growth and transformation in FL whilst inheriting several defects in direct and indirect cell cytotoxicity. Over-expression of the HSP70 pathway supporting tumour growth and metastasis is a novel finding which could potentially lead to new treatment options. MMs appear to play a role in diffuse large B-cell lymphoma transformation of FL and their regulation may reduce the rate of progression and transformation.

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A DIFFUSE LARGE B-CELL LYMPHOMA ASSOCIATED MACROPHAGE TRANSCRIPTOME ANALYSIS REVEALS A UNIQUE M1-M2 POLARIZATION PROFILE THAT CHALLENGES CURRENT CONCEPTS ON THE LYMPHOMA MICROENVIRONMENT

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Transcriptomic studies in Diffuse Large B-cell Lymphoma revealed gene expression profiling (GEP) signatures enriched for macrophage genes, suggesting an immune response against lymphoma. We hypothesize that the malignant B-cells drive lymphoma-associated macrophage (LAM) dysfunction in DLBCL. To adress this we performed a comparative transcriptome analysis using DLBCL LAM and macrophages from reactive lymph nodes (rLN). CD36 macrophages were flow sorted from DLBCL and rLN. Amplified cDNA was hybridized to Affymetrix 1.0 ST arrays. Validation of specific transcripts was performed in an independent set. Protein expression was tested by IHC and immunofluorescence in tissue microarrays. Bioinformatics analysis of GEPs was used to define macrophage-enriched genes and specific M1/M2 signatures. *In vitro* co-culture systems were developed for functional validation. Unsupervised analysis allowed separation of LAMs from rLN controls. A 142 gene signature significantly distinguished DLBCL LAMs. This signature is highly enriched for transcripts involved in inflammatory and innate immune responses and wound healing, and has as top regulators both M1 and M2 cytokines, including IFNg and IL10/IL13. Comparative transcriptome analysis showed a significant overlap between our GEP signature and other macrophage studies, with both M1 and M2 being over-represented. Proteins such ALOX15, e-cadherin and IDO-1 are expressed in the stromal compartment in both DLBCL and rLNs. As expected, only a subset of CD68 macrophages in the microenvironment express these markers. We are now quantifying these macrophages and examining correlations with outcome in an independent set of 155 patients. Healthy donor macrophages were co-cultured with or without contact with normal tonsilar B-cells, GCB/ABC cell lines or tumour conditioned-media. Normal B-cells induced macrophage activation, similar to LPS, whereas malignant B-cells did not, suggesting dampening of innate immune responses. We are now exploring whether similar transcriptome changes as the ones found by GEP are being induced by malignant B-cells. DLBCL LAM have a unique M1/M2 polarization profile, potentially driven by their presence in the DLBCL microenvironment, challenging the concept of a pure dichotomy in macrophage phenotypes in the lymphoma microenvironment.

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CSF-1R INHIBITION DEPLETES TUMOUR-ASSOCIATED MACROPHAGES AND IS A RATIONAL NOVEL CLINICAL STRATEGY IN AGGRESSIVE B-LYMPHOMAS

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DOI: 10.1002/hon

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Introduction: Gene expression analysis of lymph nodes (LN) in B-cell non-Hodgkin lymphomas (B-NHL) suggests that macrophage activity is associated with a bad prognosis. Macrophages exhibit phenotypic plasticity; tumour-associated macrophages (TAM) display a pro-tumoural, alternatively activated phenotype in many non-lymphoid cancers. We tested the hypothesis that TAM influences the progression of B-NHL and might constitute effective therapeutic targets. Colony-stimulating factor-1 (CSF-1) is a macrophage-specific protein tyrosine kinase, controlling their formation, trafficking, differentiation and survival. We report the first ever use of a CSF-1R inhibitor in a model of B-NHL.
Methods: We interrogated 145 LN biopsies of diffuse large B-cell lymphoma for a relationship between TAM number, phenotype and lymphoma proliferation. We pursued proof-of-concept for a relationship between TAM and lymphoma using mouse models incorporating the Eu-myc/bcl-2 lymphoma. Adoptive transfer of bone marrow-derived macrophages of different phenotypes explored their impact on lymphoma progression. Macrophage depletion was studied with intravenous liposomal clodronate and with transgenic macrophage fas-induced apoptosis mice. We investigated the effects of AZD7507, a potent and specific CSF-1R inhibitor, on TAM numbers and lymphoma progression.
Results: (The following statements are statistically significant at $p < 0.05$) Most macrophages in diffuse large B-cell lymphoma express CD163, a marker of alternative activation, and their number correlates with lymphoma proliferation. Eu-myc/bcl-2 progresses with a rise in circulating CSF-1, IL-10, IL-6 and accumulation of TAM. Transfer of TAM-polarized bone marrow-derived macrophages to lymphoma-bearing mice augments disease progression. Depleting macrophages with liposomal clodronate or in the macrophage fas-induced apoptosis model retards lymphoma progression. AZD7507 depletes blood monocytes and LN macrophages and reduces lymphoma burden in the blood, liver and LN, with reduced tumour proliferation, decreased plasma IL-6 and increased IFN-g.
Conclusion: The reduction in TAM, monocytes, lymphoma burden and proliferation, justify further clinical investigation of CSF-1R inhibition in B-NHL.

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PHASE II SAFETY AND EFFICACY STUDY OF PIDILIZUMAB IN COMBINATION WITH RITUXIMAB IN PATIENTS WITH RELAPSED FOLLICULAR LYMPHOMA

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Introduction: The inhibitory programmed death (PD)-1 receptor is over-expressed on intratumoural T-cells in follicular lymphoma (FL) and impairs antitumour T-cell function. Pidilizumab (formerly CT-011), a humanized anti-PD-1 monoclonal antibody, enhances function of antitumour T and NK cells. Rituximab (R) activates NK cell-mediated antibody-dependent cellular cytotoxicity. Therefore, the combination of pidilizumab and R, which may activate both the innate (NK cells) and adaptive (T-cells) arms of the immune system and enhance clinical efficacy without increasing toxicity, was evaluated in a phase II clinical trial.
Methods: Pts with relapsed grade 1–2 FL were eligible. Treatment consisted of pidilizumab 3 mg/kg IV q 4 weeks (w) ×4 and R 375 mg/m,^{2} IV q w ×4. Pts with ≥ stable disease (SD) received 8 additional pidilizumab infusions q 4w. The primary objective was overall response rate (ORR) determination. Secondary objectives included toxicity, complete response (CR) rate, progression-free survival (PFS), and immune effects on T and NK cells.
Results: Of the 30 pts, 29 are evaluable. Median age was 61 (range 35–79), and FLIPI was low 41%, int 24%, high 35%. All had previous R, and 69% had prior chemo- or chemoimmunotherapy. Pidilizumab and R were well tolerated with no therapy-related grade 3/4 toxicities. 19 pts had an objective response (ORR of 66%), with 15 CRs (52%). 25 (86%) pts had tumour regression. After a median follow up of 21 mo, median PFS was 19.6 mo, and was not reached for the 15 CR pts. Clinical response was not associated with FLIPI, FLIPI2, prior chemotherapy or R doses, or prior duration of response ($p > 0.05$). However, PFS was associated with both FLIPI (median PFS low/int 24.1 vs high 12.65 mo; $p = 0.009$) and FLIPI2 (median PFS for low/int 24.1 vs high 13.47 mo; $p = 0.015$). Activation of T and NK cells was observed in both peripheral blood and tumour microenvironment after pidilizumab therapy.
Conclusions: The combination of pidilizumab and R was active and non-toxic in pts with relapsed FL. The ORR of 66% and CR rate of 52% compare favourably with previously reported R retreatment data (ORR of 40% and CR rate of 11%) in relapsed FL. These data support further evaluation of PD-1 targeted therapy in FL.

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CD163+ IDENTIFIES A HIGHLY IMMUNOSUPPRESSIVE SUBSET OF MONOCYTIC-MYELOID DERIVED SUPPRESSOR CELLS (MOMDSC) IN POOR-RISK DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): AN ALLG LABORATORY SUB-STUDY OF NHL21.

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Introduction: Recent data suggests that circulating lymphocytes and monocytes are functionally interlinked in diffuse large B-cell lymphoma (DLBCL). Additionally, the tumour immune microenvironment has prognostic relevance. The association between tumour immune microenvironment and circulating cells remains to be defined. CD163 marks tumour associated macrophages, which are enriched within DLBCL nodes. Previously, we identified circulating CD163+monocytes as implicated in the lymphopenia of Hodgkin lymphoma.
Methods: Paired blood samples were taken pre-therapy and d21 post-cycle 4 of R-CHOP (at time of interim-PET/CT), in 73 patients with poor-risk DLBCL (77% stages III–IV), enrolled in an ongoing prospective Australasian Leukaemia and Lymphoma Group trial (ACTRN12609001077257) and compared with 23 age/gender matched healthy participants.
Results: Pre-therapy, transcriptome profiling showed strong CD163 enrichment within monocytes compared with post-cycle 4 and healthy participants. Circulating CD163 correlated with CD14+HLA-DRlo moMDSC ($r = 0.7$, p 0.0001) and CD163+moMDSC were fourfold higher in interim-PET/CT positive patients compared with those becoming negative ($p < 0.0001$). Plasma CD163 (pCD163) was markedly elevated pre-therapy ($p < 0.001$) and correlated with intra-tumoural CD163 expression. Lymphocyte/monocyte ratios were not associated with interim-PET/CT status. However, pCD163 associated with low lymphocyte count ($p = 0.01$) and lymphocytes/CD163 +moMDSC ratios were strikingly higher in interim-PET/CT negative versus interim-PET/CT positive patients (each $p \leq 0.0003$). Consistent with an immunosuppressive phenotype, CD163+moMDSC were low in co-stimulatory and migratory molecules. CD163 expression on monocytes negatively correlated with T-cell proliferation and monocyte depletion enhanced rituximab-mediated NK-cell ADCC, CD4+ and CD8+ T-cell proliferation.
Conclusion: This is the first study to show that CD163+ identifies a highly immunosuppressive subset of moMDSC in DLBCL. Circulating effector lymphocytes and CD163+moMDSC are inter-related biomarkers of interim-PET/CT status, implicating monocytes as a potential therapeutic target.
The NHL21 clinical study was supported by Roche Products Pty Ltd, Australia.

DOI: 10.1002/hon