Post ICML Significant Highlights

Post ICML Lugano Lymphoma Highlights 2017

PROGRAMME & ABSTRACT BOOK

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Post ICML Significant Highlights

Post ICML Lugano Lymphoma Highlights 2017

Thursday 6th July 2017

Brunei Gallery, SOAS, Thornhaugh St, London, WC1H 0XG

Chairs: Dr Robert Marcus *(King's College Hospital, London)*
Professor David Linch *(University College London)*

09:30	Advances in molecular diagnostics	Dr Cathy Burton *HMDS Leeds*
10:00	Transplantation update in lymphoma	Dr Stephen Robinson *University Hospital Bristol*
10:30	Chronic lymphocytic leukaemia	Dr George Follows *Addenbrooke's Hospital Cambridge*
11:00	*Coffee break & exhibition*	
11:30	Hodgkin's lymphoma	Dr Graham Collins *Oxford University Hospitals*
12:00	MALT & marginal zone lymphoma	Dr Christopher McNamara *University College London Hopital*
12:30	*Lunch & exhibition*	
13:30	CNS lymphoma	Dr Kate Cwynarski *University College London Hopital*
14:00	Follicular lymphoma	Dr Wendy Osborne *Freeman Hospital, Newcastle*
14:30	Mantle cell lymphoma	Professor Simon Rule *Derriford Hospital, Plymouth*
15:00	*Coffee break & exhibition*	

15:30	T-cell lymphoma	Dr Christopher Fox *Nottingham University Hospitals*
16:00	Diffuse large B cell lymphoma	Dr Andrew McMillan *Nottingham University Hospitals*
16:30	CAR - T cell therapy update & other immunotherapies	Professor Karl Peggs *University College London Hospital*
17:00	Take home messages ...	
17:30	*Close of main meeting and refreshments*	

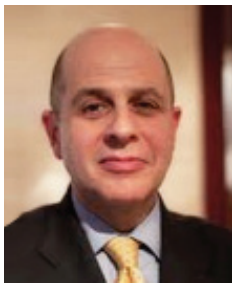
Takeda Oncology sponsored satellite session

How best to integrate targeted treatment in relapsed/refractory Hodgkin's lymphoma

17:45	Chair introduction	Dr Graham Collins *Oxford University Hospitals*
17:50	Targeted treatment in the pre-transplant setting	Dr Graham Collins *Oxford University Hospitals*
18:00	Targeted treatment in the post-transplant setting	Professor Karl Peggs *University College London Hospital*
18:10	What is the optimal sequencing of targeted treatments?	Dr Cathy Burton *HMDS Leeds*
18:20	Panel discussion with audience participation	
19:00	Meeting summary and close	Dr Graham Collins *Oxford University Hospitals*
19:00	*Supper*	

This satellite meeting is organised and funded by Takeda UK and is intended for healthcare professionals only and will include information on Takeda medicines

Chairmen



Dr Robert Marcus
King's College Hospital

Dr Robert Marcus, MA, FRCP, FRCPath is Consultant Haematologist at King's College Hospital, London. He qualified in Medicine from University College Hospital Medical School in London in 1977 and specialised in haematology at the Royal Postgraduate Medical School and the Royal Free Hospital. Prior to joining King's in 2008, Dr Marcus was Consultant Haematologist in Addenbrooke's Hospital in Cambridge for 20 years where he established the bone marrow transplant unit and developed a particular interest in lymphoma and related disorders.

Dr Marcus' research interests include the development of novel therapies for lymphoma, and has been a Chief Investigator in a large number of practice changing studies. Recently he has developed further expertise in the management of cerebral lymphoma and lymphoproliferative disorders in patients with HIV and after organ transplantation. Dr Marcus was until recently the chairman of the NCRI low-grade lymphoma working party designing new studies in this field and has been examiner for the Royal College of Pathologists.

He is medical advisor to the Lymphoma Association, and Vice President of Leukaemia Care. Dr Marcus has authored more than 150 peer-reviewed manuscripts and reviews, including national guidelines on follicular, cerebral and post transplant lymphoma. He has co-edited 4 books, including new text books on multiple myeloma and lymphoma, published in 2013 by Cambridge University Press. Special interests: haemato-oncology, with a special interest in lymphoma, Hodgkins disease and other lymphoproliferative disorders of blood and bone marrow.

Professor David Linch
University College London

David Linch, FRCP, FRCPath, FMedSci is Professor of Haematology and Head of the Department of Haematology at University College London (UCL). He qualified in Medicine from Cambridge University and the Middlesex Hospital Medical School in 1975, and then undertook SHO and Registrar positions in General Medicine before entering Haematology.

He commenced his research career at UCL as a Wellcome Trust Clinical Research Fellow and then an MRC Travelling Research Fellow to the Dana Faber Cancer Institute in Boston. In 1984 he was appointed to a Senior Lecturership at the Middlesex Hospital and following the first of several London Medical School mergers he was appointed to a Chair of Haematology at UCL in 1988. He took up the Headship of the Department of Haematology in 1992 and from 2004 to 2007 was the Chairman of the Division of Cancer Medicine at UCL.

He is currently the Director of the UCL/UCLH Biomedical Research Centre Cancer Programme. His laboratory research has been in the field of myelopoiesis and myeloid leukaemias and his clinical research has been focussed on the treatment of leukaemia and lymphoma with a particular focus on the development of high dose therapy strategies. He was the Goulstonian Lecturer of the Royal College of Physicians in 1988 and the recipient of the British Society of Haematology Gold Medal in 2006. Professor Linch was the Director of the British National Lymphoma Investigation, Chairman of the UK Lymphoma Group and then the first Chairman of the NCRI Lymphoma Clinical Studies Group. He has published numerous papers and has an H-factor of 76. He is the President of the Lymphoma Association, a national patient advisory and support organisation.

Speakers

Dr Cathy Burton
HMDS Leeds

Dr Cathy Burton studied medicine at University of Cambridge. After Haematology training in London, she moved to Leeds, completing a MD in Hodgkin lymphoma and then became an Academic Clinical Lecturer. In 2009, Dr Burton was appointed as a Consultant Haematologist at St James's University Hospital, Leeds, specialising in Lymphoma and Diagnostics. In 2014 she became Clinical Lead of the Haematological Malignancy Diagnostic Service in Leeds. She is a member of the NCRI Lymphoma Clinical Studies Group and Hodgkin lymphoma subgroup as well as a member of the Lunenberg Lymphoma Biomarker Consortium, an international collaboration studying the application of biomarker analyses to clinical practice in lymphoma.

Dr Stephen Robinson
University Hospital Bristol

Dr Robinson trained in medicine at the Royal Free Hospital, London graduating in 1992. He trained in Haematology between 1995 and 2002 at University College London. He was awarded a PhD for research into developmental aspects of human dendritic cells in 1998. Since 2002 he has worked as a Consultant Haematologist in the Bone Marrow Transplant Unit at University Hospital Bristol with a specialist interest in malignant lymphoma and stem cell transplantation. Since 2014 he has been the Clinical Director of the Bristol Cancer Institute. Dr Robinson is currently conducting research into reduced intensity allogeneic stem cell transplantation in lymphoma and is the Scientific Secretary of the EBMT Lymphoma Working Party.

Dr George Follows
Addenbrooke's Hospital

Dr Follows received his Medical degree from Oxford University Medical School before completing his medical training in Newcastle, Edinburgh and PhD at Leeds University. After a period in post-doctoral research at Cambridge University, he was appointed Clinical Lead for lymphoproliferative disorders and haematology clinical trials in Cambridge in 2007. He chaired the UK CLL Forum from 2012 to 2016 and has authored / co-authored peer reviewed papers published in many of the world's leading medical journals covering various areas of haematological biology and malignancy.

Dr Graham Collins
Oxford University Hospitals

Dr Collins trained in medicine at Cambridge and St Bartholomew's and the Royal London Hospitals. His specialist haematology training was in Oxford. Dr Collins chairs the Hodgkin lymphoma national study group and T cell lymphoma working group. He was also a member of the lymphoma guidelines development group of NICE and co-authored the national guidelines for relapsed Hodgkin Lymphoma.

Dr Christopher McNamara
University College London Hospital

Dr Christopher McNamara is a Consultant Haematologist at University College London Hospital. He was previously consultant haematologist at the The Royal Free London. His interests include clinical trials and lymphoma diagnostics.

Dr Kate Cwynarski
University College London Hospital

Dr Kate Cwynarski is a Haem-Oncologist specialising in Lymphoma and CLL at University College London Hospital, London, UK. She trained at King's College, Hammersmith Hospital and Royal Free Hospital, London UK and received her MRC-funded PhD in immunology at Imperial College, London, UK.

Her sub-specialist interests include Primary Central Nervous System (CNS) Lymphoma, HIV-related lymphoma and T-cell Lymphomas. She is Co-lead of the UK Primary CNS Lymphoma (PCNSL) Group and is a member of the National Cancer Research Institute (NCRI) Lymphoma Clinical Studies Group.

Dr. Cwynarski is involved in many clinical trials, has co-authored BCSH guidelines and she has authored or co-authored over 50 journal articles in Lancet Haematology, *Journal of Clinical Oncology, Blood, AIDS, British Journal of Haematology and Bone Marrow Transplant*.

Dr Wendy Osborne
Freeman Hospital, Newcastle

Dr Wendy Osborne is a Consultant Haematologist at the Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust. She graduated with First Class Honours from Newcastle University in 1998 and completed her General Medical Training at Queens Medical Centre, Nottingham. Dr Osborne worked in haematology departments in Glasgow before returning to Newcastle to undertake Higher Specialist Training.

Dr Osborne is a member of the NCRI High Grade lymphoma sub-group and BSH lymphoma special interest group and is a principal investigator and co-investigator for numerous clinical trials. Dr Osborne is the teaching lead for the haematology undergraduate programme at Newcastle University and was appointed Associate Lecturer status in 2016.

Professor Simon Rule
Derriford Hospital, Plymouth

Professor Rule is Consultant Haematologist in Derriford Hospital Plymouth and Professor of Clinical Haematology at Plymouth University Medical School. He is Associate Medical Director for R & D director at Derriford and chair of the NCRN low grade lymphoma trials committee. He sits on the clinical trials committee for Leukaemia and Lymphoma Research and on the editorial board of Haematologica. His specific area of interest is in mantle cell lymphoma and is currently the chief investigator for multiple studies being conducted at local, national and international level. He is an author on over 140 publications.

Dr Christopher Fox
Nottingham University Hospitals

Christopher Fox is a Consultant Haematologist at Nottingham University Hospitals NHS Trust. He was awarded a PhD from the University of Birmingham for research into Epstein-Barr virus and the pathogenesis of T and NK lymphoproliferative disease and remains involved in this field of research.

He is a member of the NCRI Lymphoma Clinical Studies Group, a core member of the high-grade sub-group, the T cell working group, and co-chairs the CNS lymphoma working group. He is Principal Investigator for multiple phase I-III studies in lymphoma and CLL. He has published papers in peer-reviewed journals including Lancet Haematology, Blood, Leukemia, Clinical Infectious Diseases, Haematologica, British Journal of Haematology and Bone Marrow Transplantation.

Dr Andrew McMillan
Nottingham University Hospitals

Dr Andrew McMillan is a Consultant Haematologist at Nottingham University Hospitals NHS Trust and has a specialist interest in the treatment of lymphoma. He has previously Chaired the National Cancer Research Institute High Grade Lymphoma Subgroup. He has been Chief Investigator or UK lead on a number of NCRI and International clinical research protocols. He is also a member of the NCRI acute lymphoblastic leukaemia subgroup and the National Chemotherapy Clinical Reference group.

He trained at University College Hospital and the Royal Free Hospital and has published papers and on Lymphoma, Acute Lymphoblastic Leukaemia and Autologous Stem cell Transplantation.

Professor Karl Peggs
University College London Hospital

Karl Peggs is a Senior Lecturer in Stem Cell Transplantation and Immunotherapy at UCL and Honorary Consultant in Haematology/Transplantation at UCL Hospitals. He received his preclinical training and MA at Cambridge University, completing his clinical training at Oxford University Medical School. Following qualification he completed general medical training at Addenbrookes Hospital Cambridge, and specialist haematology training at the John Radcliffe Hospital, Oxford and subsequently UCLH, London. During this time he spent three years in the research group of Professor Stephen Mackinnon, establishing adoptive cellular therapies for cytomegalovirus. After taking the position of Senior Lecturer at UCL in 2003, he spent 2 years at Memorial Sloan Kettering Cancer Institute, New York, in the laboratory of Professor James Allison, studying murine models of regulatory checkpoint blockade.

His research interests include immune reconstitution, pathogen-specific adoptive cellular therapies, and regulatory checkpoint-directed immunotherapeutics. He is member of the Leukaemia and Lymphoma Research Clinical Trials Committee, a Trustee of the Teens Unite charity, and has contributed to several international working parties on infectious complications and relapse following stem cell transplantation. He is Chief Investigator for 4 UKCRN national studies investigating transplantation in Hodgkin Lymphoma and cellular therapies for cytomegalovirus.

Advances in Molecular Diagnostics

Abstracts Selected by Dr Cathy Burton

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

C Burton[1], **S Barrans**[1], S Ahmed[1], MA Bentley[2], A Clipson[3], M Wang[3], J Taylor[1], R Detute[1], DR Westhead[2], MA Care[2], MQ Du[3], A Davies[4], PW Johnson[4]

[1]*HMDS, Leeds Cancer Centre, Leeds, UK*
[2]*School of Molecular and Cellular Biology, University of Leeds, UK*
[3]*Division of Molecular Histopathology, University of Cambridge, UK*
[4]*University of Southampton, Cancer Research UK Centre, Southampton, UK*

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

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

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

Table 1.

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

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

PROGNOSTIC SIGNIFICANCE AND CORRELATION TO GENE EXPRESSION PROFILE OF *EZH2* MUTATIONS IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBL) IN 2 LARGE PROSPECTIVE STUDIES

TE Cummin[1], S Araf[2], M Du[3], S Barrans[4], MA Bentley[5], A Clipson[3], M Wang[3], S Ahmed[4], T Rahim[2], C Shah[6], D Hamid[7], J Dhondt[7], T Maishman[7], N Vaughan-Spickers[7], C Pocock[8], A Forbes[9], A O'Callaghan[10], D Westhead[5], GO Griffiths[7], J Fitzgibbon[2], RM Tooze[11], MA Care[11], CH Burton[4], AJ Davies[12], PW Johnson[12]

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[8]*Haematology Department, East Kent Hospitals University NHS FoundationTrust, Canterbury, UK*
[9]*Haematology Department, Royal Cornwall Hospital, Truro, UK*
[10]*Haematology Department, Queen Alexandra Hospital, Portsmouth, UK*
[11]*Faculty of Medicine and Health, Leeds Institute of Cancer & Pathology, University of Leeds, UK*
[12]*Cancer Research UK Centre, University of Southampton, UK*

Introduction: *EZH2*, a histone methyl transferase subunit of Polycomb repressor complex 2, is frequently mutated in DLBL. Inhibitors of EZH2 have demonstrated promising responses in early clinical trials. We examined the frequency of EZH2 mutation in 2 large prospective series of DLBL and correlated this to clinical outcomes in relation to other biological features.

Methods: Patients (pts) received standard immunochemotherapy regimens as first-line treatment for DLBL. Sanger sequencing (SS) focusing on "hotspot" mutation sites in exons 16 and 18 was successful in 1052 of 1097 DLBL samples enrolled in the UK NCRI Molecular Profiling for Lymphoma (MaPLe) study. Next generation sequencing (NGS) using Fluidigm Access Array PCR and Illumina MiSeq was used to profile a separate cohort of 365 pts enrolled in the UK NCRI/ SAKK REMoDL-B trial (NCT01324596) (CRUKE/10/024). In these cases, cell of origin (COO) was determined by gene expression profiling (GEP) using Illumina WG-DASL.

Results: *EZH2* mutations were detected in 9% of DLBL pts (98/1052) by SS and 15% (54/365) by NGS. Ninety-five percent of mutations were at Y646 position in exon 16. *EZH2* mutations were strongly associated with GCB subtype, occurring in 27% of cases (50/185) versus 0/106 in ABC subtype and (4/71) in unclassified subtype ($P < .0001$). Overall, *EZH2* mutations were not significantly associated with age, sex, performance status, stage, or IPI, compared to unmutated GCB DLBL. PFS was similar between EZH2 mutated and unmutated GCB DLBL subtype: 78.5% vs 80.7% at 30 months, HR 1.06 (95% CI, 0.62-1.81) ($P = .844$). A subset of GCB cases showed Burkitt-like GEP, associated with inferior progression free survival (PFS) HR 2.21 (95% CI, 1.28-7.73) ($P = .012$), among which 11/24, where mutation status was available, had *EZH2* mutations. There was heterogeneity in progression free survival identified by presence or absence of *EZH2* mutations and Burkitt-like gene expression signature.

Conclusions: *EZH2* mutations are significantly associated with the DLBL GCB-subtype and more common in cases identified as Burkitt-like by GEP. Overall outcomes are similar in mutant and wild-type cases when adjusted for COO and IPI, but Burkitt-like cases that carry *EZH2* mutations may be a preferential subset in which to test targeted therapies.

MUTATIONAL SIGNATURES IN GERMINAL CENTER DERIVED B-CELL LYMPHOMAS FROM ADULT PATIENTS ANALYZED IN THE ICGC MMML-SEQ CONSORTIUM

D Huebschmann[1], K Kleinheinz[1], R Wagener[2], H Kretzmer[3], UH Toprak[1], SH Bernhart[3], C Lopez Gonzales[2], M Kreuz[4], R Eils[1], M Hansmann[5], S Hoffmann[3], M Hummel[6], W Klapper[7], C Lawerenz[1], M Loeffler[4], P Möller[8], J Richter[7], P Rosenstiel[9], A Rosenwald[10], S Stilgenbauer[11], M Weniger[12], L Trümper[13], R Küppers[12], M Schlesner[1], R Siebert[2]

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[11]*University Medical Center Ulm, Department for Internal Medicine III, Hematology, Oncology and Rheumatology and Infectious Diseases, Germany*

[12]*University of Duisburg-Essen, Medical School, Institute of Cell Biology (Cancer Research), Essen, Germany*
[13]*Georg August University of Göttingen, Department of Hematology and Oncology, Göttingen, Germany*

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

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

Results: Clusters of mutations at different levels of mutation density were extracted: Kataegis (rainfalls, high mutation density at single sample level) and Psichales (intermediate mutation density at single sample level). Genomic regions affected by the respective processes recurrently across the cohort were called regions of interest (ROIs). 253 Psichales-ROIs were identified and were enriched in late replicating regions of the genome. 166 Kataegis-ROIs were identified, 42/64/17/4 of which were known targets of aberrant somatic hypermutation (SHM) / were located within the immunoglobulin (IG) loci / overlapped with lymphoma-associated genes / overlapped with cancer genes known from other entities, respectively. Kataegis-ROIs were enriched in early replicating regions of the genome. In an analysis of mutational signatures, 11 known signatures including clocklike signatures (e.g. spontaneous deamination), DNA repair defect signatures, an APOBEC signature and the B-cell specific signature AC9 (attributed to AID and polymerase η) were found. Furthermore, we discovered three new signatures (L1 – L3). L1 was enriched at the IG loci. L2 was specifically enriched in the constant domains of the IGH locus.

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

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

A Mottok[1], GW Wright[2], A Rosenwald[3], G Ott[4], C Ramsower[5], E Campo[6], RM Braziel[7], J Delabie[8], DD Weisenburger[9], JY Song[9], JW Chan[9], JR Cook[10], K Fu[11], T Greiner[11], E Smeland[12], H Holte[13], B Glinsmann-Gibson[5], RD Gascoyne[1], LM Staudt[14], ES Jaffe[15], JM Connors[1], D Scott[1], C Steidl[1], LM Rimsza[5]

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[5]*Department of Laboratory Medicine and Pathology, Mayo Clinic, Scottsdale, USA*
[6]*Hematopathology Unit, Hospital Clinic Barcelona, Spain*
[7]*Department of Pathology, Oregon Health & Science University Portland, USA*
[8]*Department of Pathology, University Health Network, Toronto, Canada*
[9]*Department of Pathology, Hematopathology Section and Lymph Node Registry, City of Hope Medical Center, Duarte, USA*
[10]*Department of Laboratory Medicine and Pathology, Cleveland Clinic, Cleveland, USA*
[11]*Department of Pathology, University of Nebraska Medical Center, Omaha, USA*
[12]*Department of Immunology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo, Norway*
[13]*Department of Oncology, Division of Cancer Medicine, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway*
[14]*Center for Cancer Research, Lymphoid Malignancies Branch, National Cancer Institute, Bethesda, USA*
[15]*Hematopathology Section, National Cancer Institute, Bethesda, USA*

Introduction: Primary mediastinal large B cell lymphoma (PMBCL) is recognized as a distinct lymphoma entity in the current World Health Organization classification. However, the diagnosis relies on integration of clinical characteristics and presentation since a reliable distinction from diffuse large B cell lymphoma (DLBCL) solely based on morphological or immunophenotypic features can be difficult. Gene expression profiling studies provided evidence that PMBCL can be distinguished from DLBCL on a molecular level and supported a strong relationship between PMBCL and classical Hodgkin

lymphoma. Because these studies were performed using snap-frozen tissue, the molecular classification of PMBCL has not penetrated into clinical practice. We sought to develop a robust and accurate molecular assay for the distinction of PMBCL from DLBCL based on gene expression measurements in routinely available formalin-fixed, paraffin-embedded (FFPE) biopsies.

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

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

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

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

CH Burton[1], D Scott[2], AA Kirkwood[3], M Gandhi[4], J Radford[5], S Barrington[6], M Federico[7], S Luminari[8], J Trotman[9], L Berkhan[10], FA D'Amore[11], P Kamp[11], G Enblad[12], D Molin[13], R Chalkley[1], P Smith[3], L Stevens[3], T Roberts[3], P Patrick[3], F Chan[2], Y Harvey[2], A Mottok[2], R Gascoyne[2], P Johnson[14]

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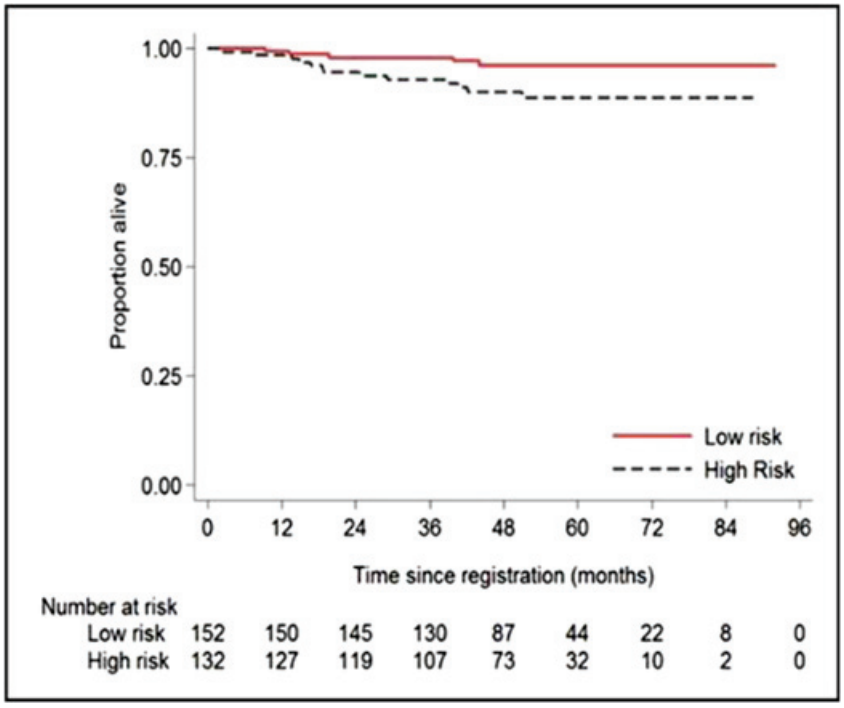
Introduction: The challenge in classical Hodgkin lymphoma (CHL) is stratifying therapy to maximise success while minimising side effects. Response-adapted therapy using FDG-PET scans after 2 cycles of ABVD (PET2) is an effective strategy, but this approach results in 2 months of suboptimal treatment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

Methods: RNA was extracted from 315 diagnostic FFPET biopsies from the RATHL trial, a subset representative of the total group of trial pts enrolled. The "26 gene" assay (23 genes of interest, 3 reference genes) was performed on the NanoString platform (NanoString Technologies, Seattle, WA) as a "locked" biomarker as previously described (Scott et al., J Clin Oncol 2013; 31:692-700). The threshold previously described was trained on overall survival (OS) after ABVD. The performance of the assay at predicting PET2 and OS in RATHL was tested using this threshold, then receiver operating characteristic (ROC) analysis was used to assess if a better threshold could be found for our cohort.

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

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

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



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

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Introduction: Recently, we described a 23-gene gene expression-based biomarker that was prognostic for overall survival (OS) in patients (pts) with locally extensive and advanced stage classical Hodgkin lymphoma treated with ABVD chemotherapy (Scott et al. *J Clin Oncol*2013). The observation that the results of PET scan after 2 cycles (PET2) of ABVD

is highly prognostic of progression free survival (PFS) has led to the design of response-adapted trials, where pts with a positive PET2 receive more intensive regimens aiming to improve outcomes. The purpose of this study was to test whether the 23-gene assay could predict PET2 results, allowing rational selective escalation of treatment from the time of diagnosis. The US Intergroup S0816 trial was a response-adapted trial in advanced stage (III and IV) classical Hodgkin lymphoma, with escalation to escBEACOPP where the PET2 was Deauville 4 or 5 (Press et al. *J Clin Oncol* 2016).

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

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

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

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

GENOTYPING OF CLASSICAL HODGKIN LYMPHOMA ON THE LIQUID BIOPSY

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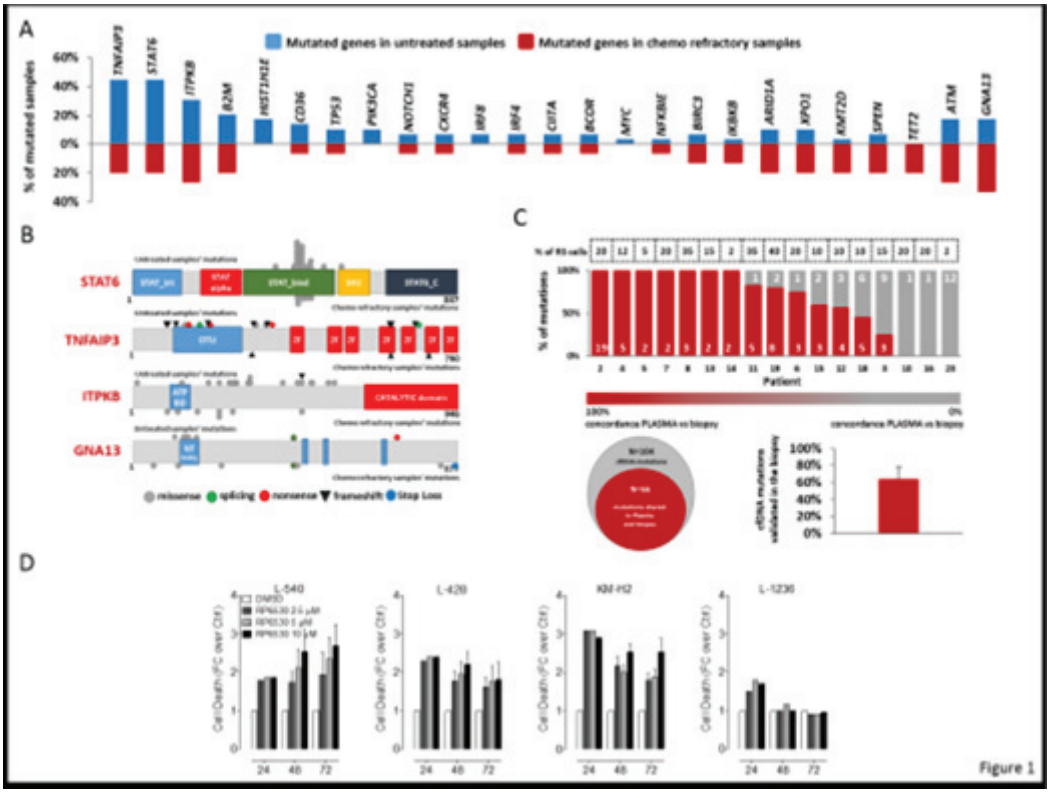
Introduction: The mutational profile of cHL is poorly characterized, and the genetics of refractory disease is unknown. This study aims at: i) providing the evidence that the mutational profile of cHL can be tracked by using plasma cfDNA; and ii) characterizing the genetics of newly diagnosed cHL and,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

Methods: The study includes 29 newly diagnosed and 15 chemorefractory cHL provided with plasma cfDNA and germline gDNA. Paired gDNA from tumor tissue biopsies was available for 17 patients, including 3 cases for which Reed-Sternberg (RS) enriched areas were macrodissected. Plasma cfDNA, normal gDNA and tumor gDNA were subjected to targeted ultra-deep next generation sequencing by using the CAPP-seq strategy and Illumina platforms (sensitivity of $3x10^{-3}$).

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

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

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



Transplantation Update in Lymphoma

Abstracts Selected by Dr Stephen Robinson

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

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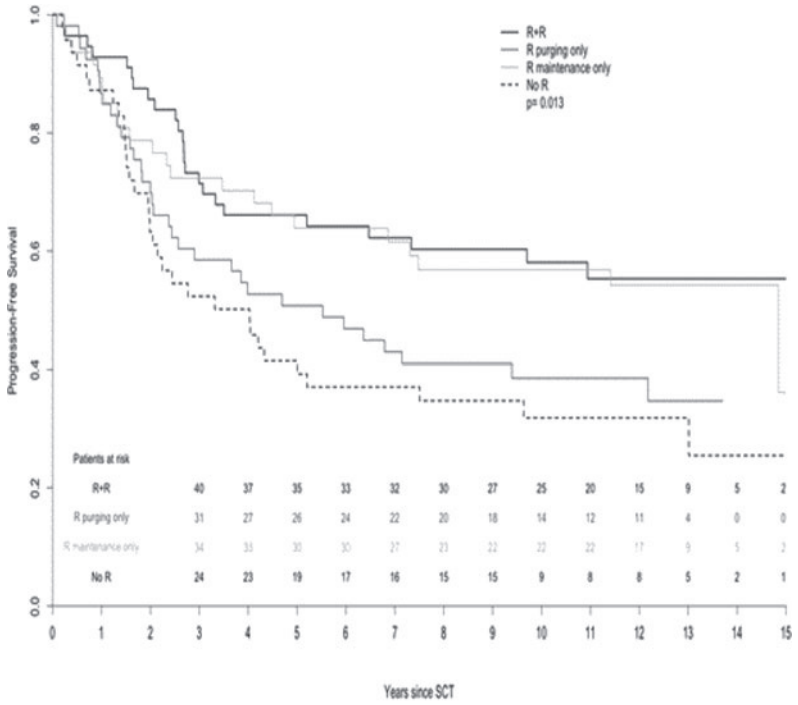
Purpose: To evaluate the long- term effects of in vivo purging with rituximab 375 mg/m^2 weekly x 4(RP) and maintenance rituximab 375 mg/m^2 every 2 months for 4 doses (RM) on progression free survival (PFS) in patients with relapsed FL receiving a BEAM autograft (ASCT).

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

Results: Baseline pt characteristics are reported in Table 1. In the IRGDP arm 11/14 pts received an ibrutinib dose intensity of >90%. The ORR to IR-GDP was 28.6% (CR 0, PR 28.6%, SD 28.6%, PD 14.3%, inevaluable 28.6%). 8 SAEs including 2 grade 5 events (1 sepsis, 1 pneumonia) and 3 grade 3 infectious events were reported in the IRGDP arm. Median neutrophil and lymphocyte counts were 1.75 (0.920.7) and 0.23 (0.15-0.3) at time of onset of infection. The ORR to R-GDP was 50.1% (CR 6.3%, PR 43.8%, SD 12.5%, PD 37.5%, inevaluable 0). Among patients assigned to R-GDP there were no infections grade 3 or higher; there were 4 SAEs and no grade 5 events. At the time of database lock (median f/u 3.5 months, range 0.7-9.2), all patients were off protocol treatment (IR-GDP:R-GDP; death 2:0;, AE 1:0, PD prior to completion of protocol therapy 1:4; patient choice 0:1 and treatment complete 10:11) with 19 pts having a progression event (IR-GDP:R-GDP; on treatment 3:3; during follow-up 5:5; death without PD 2:1) and 11 alive without PD (IR-GDP 4, R-GDP 7).

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

TABLE 1

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

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

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

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

Results: Out of the 300 enrolled patients, 176 were evaluable for mutations. Median follow-up of the cohort was 36 months, and 3 years PFS and OS were 66% and 86%, respectively. Patients not included in the study, due to unavailable tumor DNA (n = 124) showed superimposable clinical features and outcome. Mutations of *TP53* (9% of cases) and *KMT2D* (11% of cases) associated with an increase in the hazard of progression both in univariate analysis as well as after adjusting for MIPI, Ki67 and blastoid variant: HR 3.87 (95% CI 1.64 to 9.13), $p < 0.002$ and HR 3.66 (95% CI 1.77 to 7.56), $p < 0.001$,

respectively. These results translated into an increase of the hazard of death in both *TP53* and *KMT2D* mutated patients both in univariate analysis as well as adjusting for MIPI, Ki67 and blastoid variant HR 4.26 (95% CI 1.34 to 13.57), $p = 0.014$ and HR 3.09 (95% CI 1.07 to 8.86), $p = 0.036$, respectively. On these bases, a survival model was proposed based on the *TP53* and *KMT2D* mutation status: 3-years PFS and OS were 25% and 64% for patients carrying either *TP53* or *KMT2D* mutations or both vs 75% and 92% for patients without any of these mutations (Figure 1).

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

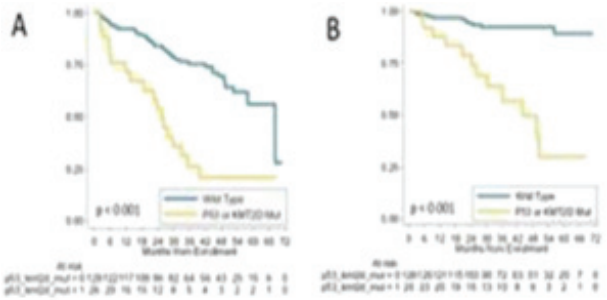

Figure 1: PFS (A) and OS (B) by TP53 and/or KMT2D mutational status

NIVOLUMAB FOR RELAPSED/ REFRACTORY CLASSICAL HODGKIN LYMPHOMA AFTER AUTOLOGOUS TRANSPLANT: FULL RESULTS AFTER EXTENDED FOLLOW-UP OF THE PHASE 2 CHECKMATE 205 TRIAL

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Introduction: Nivolumab (nivo), a programmed death-1 immune checkpoint inhibitor, is indicated for pts with relapsed/ refractory classical Hodgkin lymphoma (RR cHL) following autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV). Initial results from the phase 2 CheckMate 205 trial of nivo for RR cHL after ASCT (NCT02181738) demonstrated high objective response rates (ORR), encouraging duration of response (DOR), and an acceptable safety profile (Younes A et al., *Lancet Oncol* 2016). Given limited treatment options post-ASCT, it is key for pts that the therapy offered has high potential for durable remissions. Here we report extended follow-up for all pts with RR cHL after failure of ASCT in CheckMate 205.

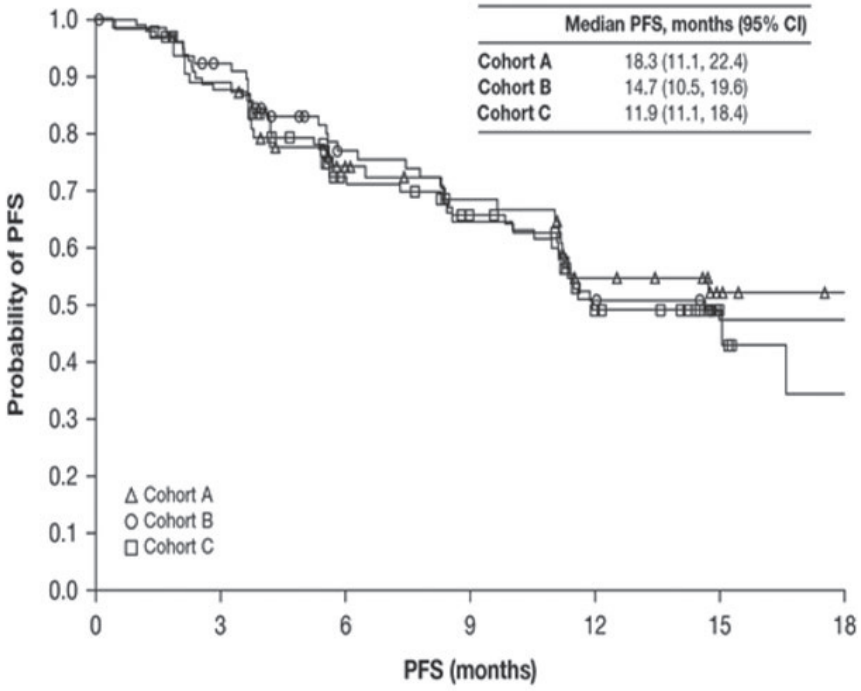
Methods: CheckMate 205 enrolled adult pts with RR cHL after ASCT into 1 of 3 cohorts (A: naïve to BV; B: BV only after ASCT; C: BV before and/or after ASCT). All pts received nivo 3 mg/kg q2w until progression or unacceptable toxicity. In Cohort C, pts with complete response (CR) for 1 y were to discontinue nivo and could resume at relapse. Primary endpoint was ORR per IRC. DOR was a secondary endpoint; progression-free survival (PFS), overall survival (OS) and safety were exploratory endpoints.

Results: Of 243 pts treated, 63 were BV-naïve (Cohort A), 80 had BV after ASCT (Cohort B), and 100 had BV before (*n* = 33), after (*n* = 58) or before and after (*n* = 9) ASCT (Cohort C). Median (range) age was 34 (18–72) y; 77% of pts had stage III+ disease at study entry. Fewer BV-naïve pts had ≥4 prior lines of therapy (16% vs 69% with prior BV). As of Dec 2016 database lock, median follow-up was 19, 23, and 16 mo for Cohorts A, B, and C, respectively, and 40% of pts remained on treatment. ORR was 65% in BV-naïve pts (Cohort A), 68% in pts with BV after ASCT (Cohort B), and 73% in pts with BV before and/or after ASCT (Cohort C), with CR in 29%, 13%, and 12% of pts, respectively. In BV-naïve pts, median DOR was 20 mo; in BV treated pts, median DOR was 16 and 15 mo in Cohorts B and C, respectively. For pts with CR, DOR was 20 mo in BV-naïve pts (Cohort A) and ≥15 mo in BV-treated pts (Cohorts B and C); for pts with partial response (PR), DOR was 17 and ≥11 mo, respectively. PFS by cohort is shown (Figure), with extended median PFS observed in all 3 cohorts for pts with CR (≥17 mo), PR (≥15 mo), and stable disease (≥9 mo). Median OS was not reached. The most common drug-related AEs were fatigue (23%), diarrhea (15%), and infusion reactions (IRs; 14%); the most common drug-related serious AEs were IRs (2%) and pneumonitis (1%). To facilitate translation to practice, efficacy results recategorized by sequencing of prior BV will be presented.

Conclusions: Regardless of BV treatment history, high levels of response to nivo were seen across cohorts of pts with RR cHL after ASCT. Notably, with extended follow-up both CRs and PRs remain durable.

Study support: BMS; medical writing support: M Thomas (Caudex).

Figure. PFS according to treatment cohort



Patients at risk							
Cohort A	63	56	41	36	26	18	14
Cohort B	80	70	50	42	33	27	27
Cohort C	100	85	56	44	25	8	4

Chronic Lymphocytic Leukaemia

Abstracts Selected by Dr George Follows

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

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Introduction: The prospective, open-label, multicenter phase-II CLL2BAG trial is based on the theoretical "sequential triple-T" concept [Hallek M., Blood 2013; 122(23): 3723-34] of a tailored and targeted treatment aiming for total eradication of minimal residual disease (MRD). It investigates a sequential treatment with a bendamustine (B) debulking, followed by obinutuzumab (G) and venetoclax (A) as induction and maintenance therapy in an all-comer population of physically fit and unfit, treatment-naïve (TN) and relapsed/refractory (R/R) CLL pts.

Methods: Pts with an absolute lymphocyte count ≥25.000/µl and/or lymph nodes ≥5 cm received 2 cycles of B as debulking (70 mg/m2 d1&2 q28 days), unless contraindicated. In the induction G (1000 mg) was administered 3 times in cycle 1 (days 1/2, 8 & 15) and every 4 weeks in cycles 2-6. A was added in cycle 2 with a dose ramp-up (to 400 mg daily) over 5 weeks and several safety precautions. In the maintenance therapy, daily intake of A was continued and G administered every 3 months until achievement of a MRD-negative complete response or for up to 24 months. The primary endpoint is the overall response rate (ORR) at the end of induction therapy; secondary endpoints include MRD evaluations, safety and survival parameters. This primary endpoint analysis is based on uncleaned data, the final analysis will be presented at the meeting.

Results: Between May 2015 and January 2016, 66 pts were enrolled; 3 pts with <2 induction cycles were excluded from the analysis as predefined by protocol (2 R/R pts died of a sepsis and 1 TN pt discontinued due to toxicity).34 pts were TN and 29 had R/R CLL (median number of prior therapies: 2, range: 1-8). Median age was 59 (28-77) years, the median CIRS score was 2 (0-14). 11 of 59 pts (19%) had a del(17p) and 14 (24%) had a del(11q); 45 of 61 (74%) had an unmutated IGHV status. 45 pts (71%) received B debulking, 18 (29%) pts immediately started with the induction. 60 pts completed 6 induction cycles with G and A. With an ORR of 97% at the end of induction, the primary endpoint was met: all TN (100%) and all but two of the R/R pts (93%) responded. According to investigator assessment, 6 pts had a CR/CRi, 19 pts an unconfirmed clinical CR/CRi and 36 pts a PR. MRD negativity (<10-4 by flow cytometry) in peripheral blood (pB) was achieved in 56 pts (89%); MRD assessment from bone marrow was available in 8 pts and were all negative.As of January, 9th 2017, 83 serious adverse events (SAEs) were reported in 37 pts, including 69 SAEs (83%) related to study treatment. 66 SAEs (80%) were CTC°3-4 and 1 had a fatal outcome (sepsis in 4th induction cycle). Most SAEs occurred in the R/R cohort and during the induction phase (see table). 5 laboratory TLS occured in 5 patients (1 during bendamustine debulking, 1 in induction cycle 1 with obinutuzumab, 2 in cycle 3 and 1 in cycle 4 with obinutuzumab and venetoclax).

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

	all patients (n= 62)	treatment-naive (n=34)	relapsed/refractory (n= 28)
Total number of SAEs	83	22	61
- SAEs related to study treatment	69	19	50
Time point of occurence [1 missing]			
- Debulking	12	9	3
- Induction	63	10	53
- Maintenance	4	2	2
- Follow-up	3	-	3
Severity			
- CTC grade I/II	16	7	9
- CTC grade III/IV	66	15	51
- CTC grade V	1	-	1
Outcome [1 missing]			
- resolved	74	20	54
- resolved with sequelae	2	1	1
- persisting	5	1	4
- fatal	1	-	1
Infections			
- Pneumonia	9	-	9
- other respiratory tract infections [incl. bronchitis, sinusitis]	6	1	5
- Skin infections [incl. 1 herpes zoster]	2	1	1
- Urinary tract	1	-	1
- other [incl. 2 CMV oesophagitis & 1 viral hepatitis]	9	2	7
Febrile Neutropenia	6	2	4
Pyrexia	4	2	2
Neutropenia	7	1	6
Thrombocytopenia	4	-	4
Hemolysis	1	-	1
Infusion related reactions	6	2	4
Cytokine release syndrome	1	1	-
Tumor lysis syndromes	5	2	3
Cardiovascular events			
- myocardial infarction, acute coronary syndrome	5	3	2
- hypertensive crisis	1	-	1
Secondary primary malignancies			
- skin cancer [incl. 1 melanoma, 3 squamous cell and 1 basal cell carcinoma]	5	-	5
- bladder and prostate cancer (1 each)	2	2	-
- pleural effusion related to CLL	1	1	-

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

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

Methods: This is an ongoing phase I/Ib investigator-initiated trial with primary endpoints of recommended phase 2 dose (RP2D) and safety/ tolerability. Secondary endpoints include ORR and CR rates, PFS, and OS. Pts receive daily ibrutinib (560 mg MCL, 420 mg CLL) and TGR1202. TGR-1202 doses from 400 mg to 800 mg were evaluated in a standard 3 + 3

design. Pts continue both drugs until progression or unacceptable toxicity. Eligibility criteria: ≥1 prior therapy, ECOG PS ≤2, and adequate hematologic and organ function. Prior PI3K/BTK inhibitors were allowed. Lugano Classification (MCL) and IW-CLL criteria were used to evaluate efficacy.

Results: Thirty-three pts have enrolled on study,including 15 MCL and 18 CLL pts. The median age at enrollment was 67 yrs. (range 48-83). The median number of prior therapies was 3 for MCL (range 2-5, including 4 with prior autoSCT) and 2 for CLL (range 1-6). In CLL pts, del(17p) was present in 4/17 (24%), del (11q) in 7/17 (41%), and unmutated IGHV in 11/17 (65%). In phase I, no DLTs occurred in either arm, and the RP2D of TGR1202 for both MCL and CLL was 800 mg. In a combined safety analysis of both arms (n = 33), hematologic toxicity included neutropenia (36%, 12% gr3/4), thrombocytopenia (21%, 3% gr3), and anemia (21%, 3% gr3). All grade non-hematologic toxicities in >10% of pts included: nausea (36%, all gr1/2), fatigue (33%, all gr1/2), diarrhea (33%, all gr1/2), and dizziness (24%, all gr1). Transaminitis (all gr1) was observed in 7/33 (21%) pts. SAEs included 2 pts each with: gr3/4 lipase elevation, gr3 hypophosphatemia, CNS aspergillus infection, and atrial fibrillation, and 1 pt each with: adrenal insufficiency (gr3), influenza A infection (gr4), *C. difficile* infection (gr4), and sudden death of uncertain cause. Two pts had dose reduction of TGR-1202 (dizziness, nausea), and 3 pts had dose-reduction of ibrutinib (atrial fibrillation, palpitations, vitreous hemorrhage). In MCL, with a median time on study of 10.9 mo. (range 1.1-19.8 mo.), the ORR is 85% (11/13), including 1 CR. In CLL, with a median time on study of 11 mo. (range 0.1-23.5 mo.), the ORR is 89% (16/ 18), with 1 pt achieving iwCLL CR, and 1 pt with radiographic CR. The 1 year PFS and OS for MCL are 37% and 52%, and for CLL both are 94%.

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

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

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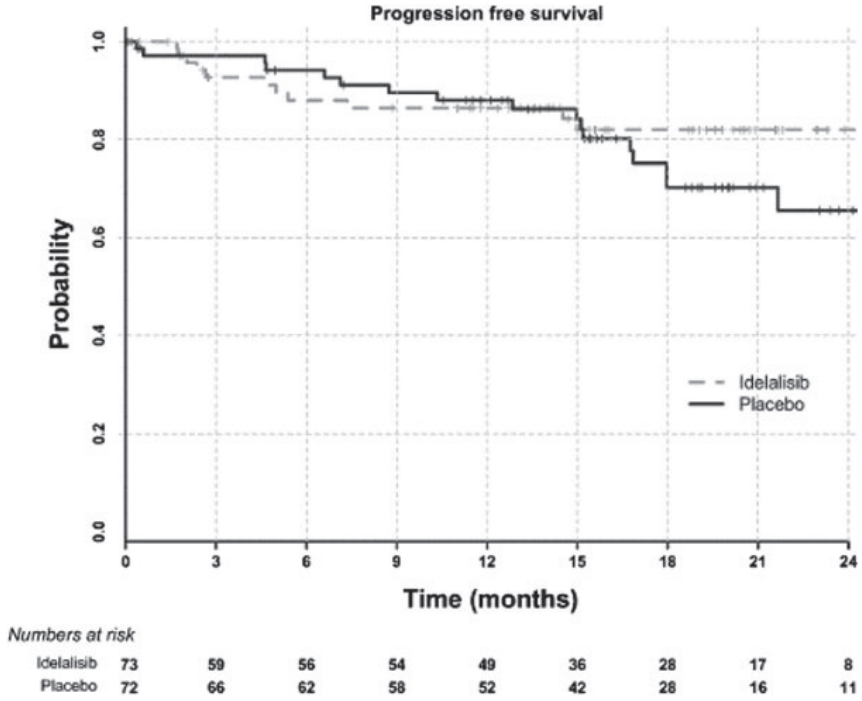
Introduction: The Phase 3 RIAltO trial opened in December 2011 to compare ofatumumab plus chlorambucil (O + C) with ofatumumab plus bendamustine (O + B) in patients with previously untreated chronic lymphocytic leukaemia (CLL) considered unfit for FCR (fludarabine, cyclophosphamide, rituximab). A protocol amendment was introduced in September 2014 to investigate the addition of idelalisib (first-inclass inhibitor of the p110δ isoform of phosphoinositol-3 kinase) or placebo. Review of safety data in January 2016 revealed excessive toxicity due to idelalisib, and recruitment was suspended. All idelalisib/placebo treatment was withdrawn from the trial in March 2016 following safety analysis of idelalisib registration studies and recommendations from Gilead Sciences Ltd and regulatory authorities. Here, we present a preliminary analysis of the cohort of patients in RIAltO who received idelalisib or placebo.

Methods: Patients were eligible for inclusion if they had previously untreated CLL requiring treatment by NCI/IWCLL criteria, were considered unfit for FCR and did not have any contraindications to the study drugs. Consenting patients underwent an unblinded 1:1 randomisation to ofatumumab (300 mg iv day 1 and 1000 mg iv day 8 of cycle 1; 1000 mg iv day 1 of cycle 2 onwards) plus either chlorambucil (10 mg/m^2 day 1-7, repeated every 28 days for 312 cycles) or bendamustine (70

mg/m2 iv day 1-2 for 3-6 cycles) and a double-blinded 1:1 randomisation to concurrently administered placebo or idelalisib (150 mg bd for up to 3 years). Co-trimoxazole prophylaxis was recommended. Study drugs were continued until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). The post-treatment reporting period for serious adverse events (SAEs) was 6 months for grade 3-4 infections and 28 days for other events.

Results: 145 patients received idelalisib (73) or placebo (72), with a median idelalisib exposure time of 2.5 months. As of March 2017, SAEs were reported in 77% of idelalisib-treated patients (81 grade 34 and 8 grade 5) compared to 39% in the placebo group (35 grade 34 and 2 grade 5). The frequency of SAEs in the idelalisib-treated group was similar in both chemotherapy arms. Grade 5 events in this group included sepsis (1), lung infection (3), febrile neutropenia (2), myocardial infarction (1) and sudden death NOS (1). After a median followup of 15 months, 17 PFS events have been observed in the placebo group compared with 11 in the idelalisib group.

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



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

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

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

Results: Among 3552 reviewed GCLLSG trial participants, 152 were aged ≥80 years at initiation of frontline treatment. Pts were identified from CLL11 (*n* = 132), CLL1 (*n* = 3), CLL5 (*n* = 1), CLL7 (*n* = 3), CLL8 (*n* = 2), CLL9 (*n* = 9), and CLL10 (*n* = 2). Median age was 82 years (range 80-90). Concomitant diseases were present in 99% of the pts and median cumulative illness rating scale (CIRS) score was 8 (0-18). Median creatinine clearance was 46 mL/min (range 17-99 mL/min). Distribution of CLL-IPI risk groups was as follows: 6% low, 19% intermediate, 61% high, and 14% very high. Most pts had Binet stage B (36%) or C (43%). Chemoimmunotherapy with chlorambucil plus obinutuzumab (CLB-OB) or chlorambucil plus rituximab (CLB-R) was administered to 61 (40%) and 56 (37%) pts, respectively. Remaining pts received chlorambucil alone (CLB, n = 19), fludarabine (F, n = 10), F/cyclophosphamide (FC, n = 1), FC/rituximab (FCR, n = 2), or bendamustine/rituximab (BR, n = 3). Rates of grade 3 or 4 neutropenia and infections were 35% and 13%, respectively. Premature treatment discontinuations occurred in 15% of cases and were mostly due to adverse events. The total overall response rate was 92% with 13% complete remissions. Median observation time for all pts was 40.7 months. Median progression-free survival (PFS) and treatment-free survival (TFS) were 17.2 and 32.3 months. A total of 47 pts (31%) received at least one further line of treatment. Median overall survival (OS) was 48.3 months, with adverse events(22%) and progressive CLL (15.8%) being the most frequent causes of death. Standardized mortality ratio was calculated and showed a 1.99 (CI 1.54-2.53) increased risk of death as compared to an age- and sex-matched general population. Independent prognostic factors for OS were 17p deletion and elevated serum thymidine kinase.

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

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

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

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

Results: 126 pts were randomized at sites in the US and Israel, with 117 pts treated (59 on UTX + IB, 58 on IB alone). Median age 67, median of 3 prior therapies (range 1-8), > 70% of were male. High-risk cytogenetics were relatively balanced between the arms with ~50% having del17p. UTX + IB was well tolerated, with infusion reactions the most prevalent

AE (44%, GR3/4 5%). Neutropenia was comparable with the combination (17%, Gr3/4 7% vs. 10%, Gr3/4 9%), and other AE's were similar or lower with UTX + IB vs. IB alone (all grades), including fatigue (17% vs. 31%), dizziness (12% vs. 21%), contusion (12% vs. 26%), anemia (10% vs. 16%), and myalgia (9% vs. 14%). At median follow-up of 12 months, best ORR per independent radiology and hematology review for UTX + IB was 80% vs. 47% for IB alone ($p < 0.001$). While not powered for secondary endpoints, observed advantages were seen in PFS and radiographic CR rate in the UTX + IB arm. CR and MRD confirmation is ongoing. MedianTTR for the combo was 1.97 mos vs. 3.8 mos for IB alone. Both arms have responses pending confirmatory assessments.

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

HIGH OVERALL RESPONSE RATE WITH THE BTK INHIBITOR BGB-3111 IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA: AN UPDATE ON SAFETY AND ACTIVITY

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Introduction: BGB-3111 is a potent, highly specific, and irreversible Bruton tyrosine kinase (BTK) inhibitor, with greater selectivity for BTK vs other TEC- and EGFR-family kinases and favorable pharmacokinetic and pharmacodynamic properties. BGB-3111 was shown to achieve complete, continuous BTK occupancy in peripheral blood mononuclear cells and lymph nodes and was associated with durable clinical responses in patients (pts) with CLL/SLL and Waldenström macroglobulinemia. Here, updated preliminary safety and activity data in relapsed/refractory (R/R) and treatment-naïve (TN) pts with CLL/ SLL are reported.

Methods: This is an open-label, multicenter, phase 1b study of BGB3111 in pts with B-cell malignancies. Pts with R/R CLL/SLL were included in dose escalation, and both TN and R/R CLL/SLL pts were included in expansion cohorts at the recommended phase 2 dose (320 mg/d, given once daily [QD] or split as a twice-daily [BID] dose). Adverse events (AEs) are reported per Common Terminology Criteria for AEs version 4.03, and response per the modified iwCLL criteria (Hallek 2008, Cheson 2012 clarification for novel therapies).

Results: As of 15 Dec 2016, 68 pts with CLL/SLL (50 R/R and 18 TN) were enrolled: 4 pts in dose escalation and 64 in cohort expansion at doses of 160 mg QD ($n = 3$), 160 mg BID ($n = 25$), and 320 mg QD ($n = 40$). Patient characteristics are shown in Table 1.

Safety: Median follow-up was 7.2 (range, 0-23.3) months. The most frequent AEs of any cause were bruising (35%) and petechiae (11%), upper respiratory tract infection (28%), fatigue (25%), cough (22%), and diarrhea (21%). Four serious AEs related to BGB-3111 were seen in 3 pts: grade (Gr) 2 cardiac failure, Gr 2 pleural effusion, Gr 3 purpura, and Gr 3 pneumonia. The case of Gr 3 purpura (subcutaneous hemorrhage) was the only major bleeding event reported. Atrial fibrillation (Gr 3) occurred in 1 pt. One pt discontinued BGB-3111 for an AE (pleural effusion).

Activity: Of the 54 pts evaluable for response (>12 weeks follow-up or discontinuation before 12 weeks), the objective response rate was 96% (52/54), with partial response in 67% (36/54), partial response with lymphocytosis in 30% (16/54), stable disease in 1 R/R pt, and no assessment for 1 R/R pt because of AE. No instances of disease progression or Richter transformation were reported.

Conclusions: BGB-3111 is well tolerated and highly active in R/R and TN CLL/SLL. With only 7.2 months of median follow-up, only 1 toxicity-related discontinuation, and no progressive disease seen thus far on study.

TABLE: Baseline characteristics and summary of TLS risk reduction* in moderate- and high-risk patients.

Parameter	TN† (n=162)	R/R† (n=262)
ALC ≥25K at baseline, n (%)	116 (72)	125 (48)
Bulky disease (LDi ≥5 cm) at baseline, n (%) LDi ≥10 cm LDi ≥5 cm to <10 cm	58 (36) 8 (5) 50 (31)	159 (61) 13 (5) 146 (56)
Bulky disease (LDi ≥5 cm) at first assessment, n (%)	8/148 (5)	45/247 (18)
Patients with high risk for TLS at baseline, n (%) Reduced to moderate risk* Reduced to low risk*	46 (28) 3/46 (7) 40/46 (87)	86 (33) 39/86 (45) 39/86 (45)
Patients with moderate risk for TLS at baseline, n (%) Reduced to low risk*	86 (53) 71/86 (83)	118 (45) 81/118 (69)
Patients with low risk for TLS at baseline, n (%)	30 (19)	58 (22)

*Over the duration of ibrutinib treatment. TLS risk categories as defined by the venetoclax USPI: low-risk (ALC <25K and LDi <5 cm), moderate-risk (ALC ≥25K or LDi ≥5 cm but <10 cm), and high-risk (ALC ≥25K and LDi ≥5 cm; or any ALC with LDi ≥10 cm).

† 1% of TN and 33% of R/R patients had del17p chromosomal abnormality.

OUTCOMES OF PATIENTS POST IBRUTINIB TREATMENT FOR RELAPSED / REFRACTORY CLL: A UK AND IRELAND ANALYSIS

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Introduction: Following discontinuation of ibrutinib, the outcome for many patients remains poor. This analysis was undertaken to gain a better understanding of how these challenging patients have been managed in the UK / Ireland.

Methods: Data were collected on ibrutinib patients registered with the UK CLL Forum who had discontinued ibrutinib for any reason.

Results: Of the original 315 study patients, 140 have now stopped taking ibrutinib and 103 have died (median overall survival (mOS) 72 days from stopping (range: 0–919)). Patients stopped ibrutinib due to one of 6 broad reasons:

1. Adverse event (AE) – infection (*n* = 21; 15%)
2. AE – other (*n* = 41; 29%)
3. Second primary malignancy (*n* = 13; 9%)
4. Progressive Disease–CLL (PD CLL) (*n* = 25; 18%)
5. Progressive Disease–Richter's transformation (PDRT) (*n* = 28; 20%)
6. Other (predominantly no data given) (*n* = 12; 9%)

Patients who stopped ibrutinib due to a non-infectious AE had the best survivals with 17/41 (41%) still alive. (mOS: 245 days (0– 919)). The poorest survivals were seen for patients with PDRT where only 3 patients from 28 are still alive (Figure 1A). The rate of discontinuation of ibrutinib has reduced over time with 26.3% stopping in the first year, 16.8% (12.5–22.4)) in the second year and 11% beyond the second year (although follow-up is less complete). Of the patients who stopped in the first year, 54% were due to AEs, 23.4% PDRT and 13% PDCLL. After year 1, the proportion stopping due to AEs and PDRT fell to 40% and 19.6%, whereas the proportion stopping due to PDCLL increased to 29.4%.Within the first year, there was no access to venetoclax in the UK and Ireland and all 10 patients who stopped ibrutinib due to PDCLL died with a median survival of 33 days (0-360). Beyond the first year, 15 patients stopped ibrutinib due to PDCLL. Of these, 5 have died (managed with palliative care (n = 3), idelalisib/rituximab (n = 1), no data (n = 1)) and 10 are still alive. Of these 10, 1 has

been treated with R-idelalisib (34 days post ibrutinib cessation), and 9 have been treated with venetoclax with a median follow-up of 107 days (9–498) post ibrutinib. Four other patients who stopped ibrutinib for non-PDCLL reasons have also been treated with venetoclax, with 2 still alive on therapy. Figure 1B compares the OS of patients who stopped ibrutinib for PDCLL within the first year and beyond 1 year. There is a marked survival advantage for patients relapsing beyond 1 year with over 60% reduction in the risk of death (HR: 0.33 (0.11–0.98); p = 0.0333). In contrast, patients stopping ibrutinib for all other reasons show no survival difference whether they stop within the first year or beyond.

Conclusions: While the relative rate of ibrutinib discontinuation reduces with time on therapy, the proportion stopping for PDCLL increases. OS appears best for patients who stop for non-infectious AEs and for PDCLL patients, survival appears better if progression occurs later. This may partly reflect biologically less aggressive disease, although access to venetoclax for patients relapsing beyond one year is also likely to have been significant.

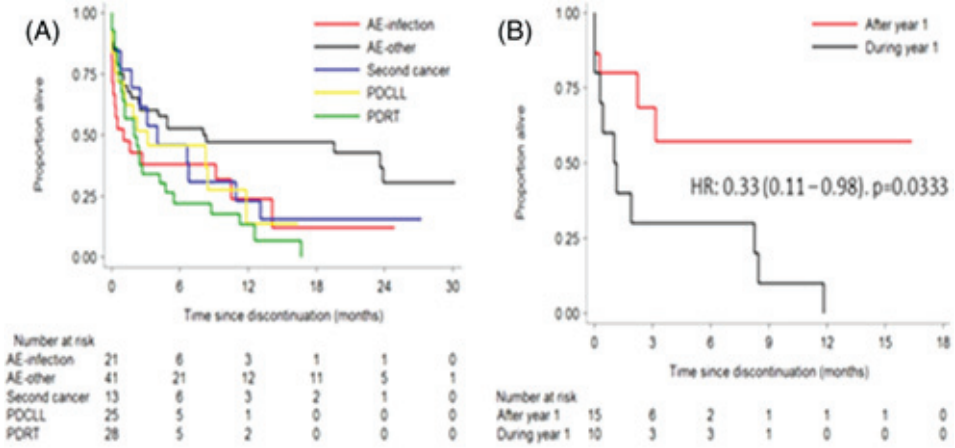

Figure 1. A: Survival of patients post cessation of ibrutinib separated by reason for ibrutinib cessation.
B: Survival of patients who stopped ibrutinib for PD-CLL within the 1st year and beyond the 1st year

Hodgkin's Lymphoma

Abstracts Selected by Dr Graham Collins

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

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

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

Results: MTV/TLG using SUV ≥ 2.5 and TLG compared to liver were associated with PFS and progression or death from HL (HL event) in the first 100 pts but the 41% method was not. MTV/TLG were then measured using SUV ≥ 2.5 in all UK pts, split into training and validation sets of 571 and 277. Pts with PET2+ scans had significantly higher total and bulk MTV and TLG than pts with PET2- scans; all $p < 0.0002$.

Cox and logistic regression were used to assess association of MTV/TLG and other baseline factors with PFS and HL events by 3 yr. In univariable analysis (UV) age, stage, B-symptoms and TLG (total and bulk) were associated with PFS, but MTV and PET extranodal sites were not. Age, B-symptoms and total TLG were significant in multivariable (MV) analysis.

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

A threshold of 3318 g (optimal by Youden's index) was used to divide pts into high and low total TLG groups. HL event rate at 3y was 12.8% for all pts with low TLG vs. 23.9% for all pts with high TLG; HR 2.2 (95%CI: 1.5-3.4), $p < 0.001$. After a negative PET2, the rate of progression or death from HL was 21.5% vs 10.9% for high and low TLG respectively at 3y. The groups diverged further at 5y with rate of HL events of 31.0% and 13.1% for high and low TLG. Similar results were obtained in the validation set, suggesting that the threshold derived from the training set was reliable.

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

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

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

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

Results: As of Feb 9, 2017, 31 pts were randomised and had a median age of 38 years (range 22–81). Five and 8 pts had disease progression following auto-SCT and allo-SCT, respectively; the remaining pts were SCT-ineligible. Pts received a median of 6 cycles (range 1–23) of avelumab to date. In 30 pts analyzed for safety, the most common treatment-related adverse events (TRAEs) of any grade were infusion-related reaction (IRR; 26.7%), nausea (20.0%), rash (20.0%), and fatigue (13. 3%).Two pts (6.7%) discontinued treatment due to IRR. Grade ≥ 3 TRAEs occurred in 11 pts (36.7%); there were no treatment-related deaths. Two pts who had received prior allo-SCT developed grade 3 liver graft vs host disease (GVHD), which completely resolved after immunosuppressive therapy and discontinuation of avelumab. ORR across all 31 pts was 54.8% (95% CI 36.0–72.7) with 2 complete responses (CRs; 6.5%) and 15 partial responses (PRs; 48.4%). Responses were observed in all dosing groups (ORR range 14.3%–83.3%). ORR in the 5 post-auto SCT pts was 20.0% (95% CI 0.5–71.6) with 1 PR. ORR in the 8 post-allo SCT pts was 75.0% (95% CI 34.9–96.8) with 1 CR (12.5%) and 5 PRs (62.5%).

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

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

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

Methods: In this phase 2 multicenter study, patients with previously untreated limited stage HL received ABVD induction followed by BV consolidatoin (NCT01578967). The primary objective was to estimate the proportion of patients who achieve PET-negative disease after ABVD followed by BV. The goal was to achieve negative PET and avoid radiation in

>85% of patients. Patients received 2 to 6 cycles of ABVD based on their baseline risk factors and the interim PET scan result. Approximately 6 weeks after induction, 1.8 mg/kg of BV was given every 3 weeks for 6 cycles.

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

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

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

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

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

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

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

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

Results: Patient characteristics are outlined in the Table. From the start of BV, the median progression-free survival (PFS) for all pts was 5.6 months (95% confidence interval (CI) 4.4 - 12.2 months) and median overall survival (OS) was 37.2 months (95% CI 18.3 months - not reached (NR)) (Figure A & B). The overall response by CT or PET-CT to BV was 56% (complete metabolic response/complete response/complete response unconfirmed (CMR/CR/CRu) 29%; partial metabolic response/ partial response (PMR/PR) 27%). 34% had a SCT after BV with no further treatment. 27% required further treatment post-BV pre-SCT. Pts consolidated with either an auto or alloSCT had a superior PFS (Figure C) and OS (Figure D) to those not receiving consolidative SCT ($p < 0.001$ for auto and alloSCT vs. non-SCT for median PFS (auto: NR (95% CI 17.0 months – NR) vs allo: NR (95% CI 5.6 months – NR) vs non-SCT: 3.0 months (95% CI 2.5 - 4.4 months)). The median duration of response for pts entering CR was superior to PR, consistent with prior reports (Figure E). Using multivariate Cox regression, pts with improved performance status and haemoglobin at first relapse had improved PFS from the start of BV.

Conclusion: We demonstrate that BV has effective activity (ORR 56%) allowing bridge to SCT in a cohort of high risk SCT-naive, predominantly refractory cHL. 34% are consolidated by SCT post-BV (median of 4 cycles) and a further 27% are salvaged to SCT following inadequate BV response. 39% do not reach SCT and have poor outcomes, with PFS of 3.0 months, demonstrating the unmet need to improve outcomes in those unsuitable for SCT.

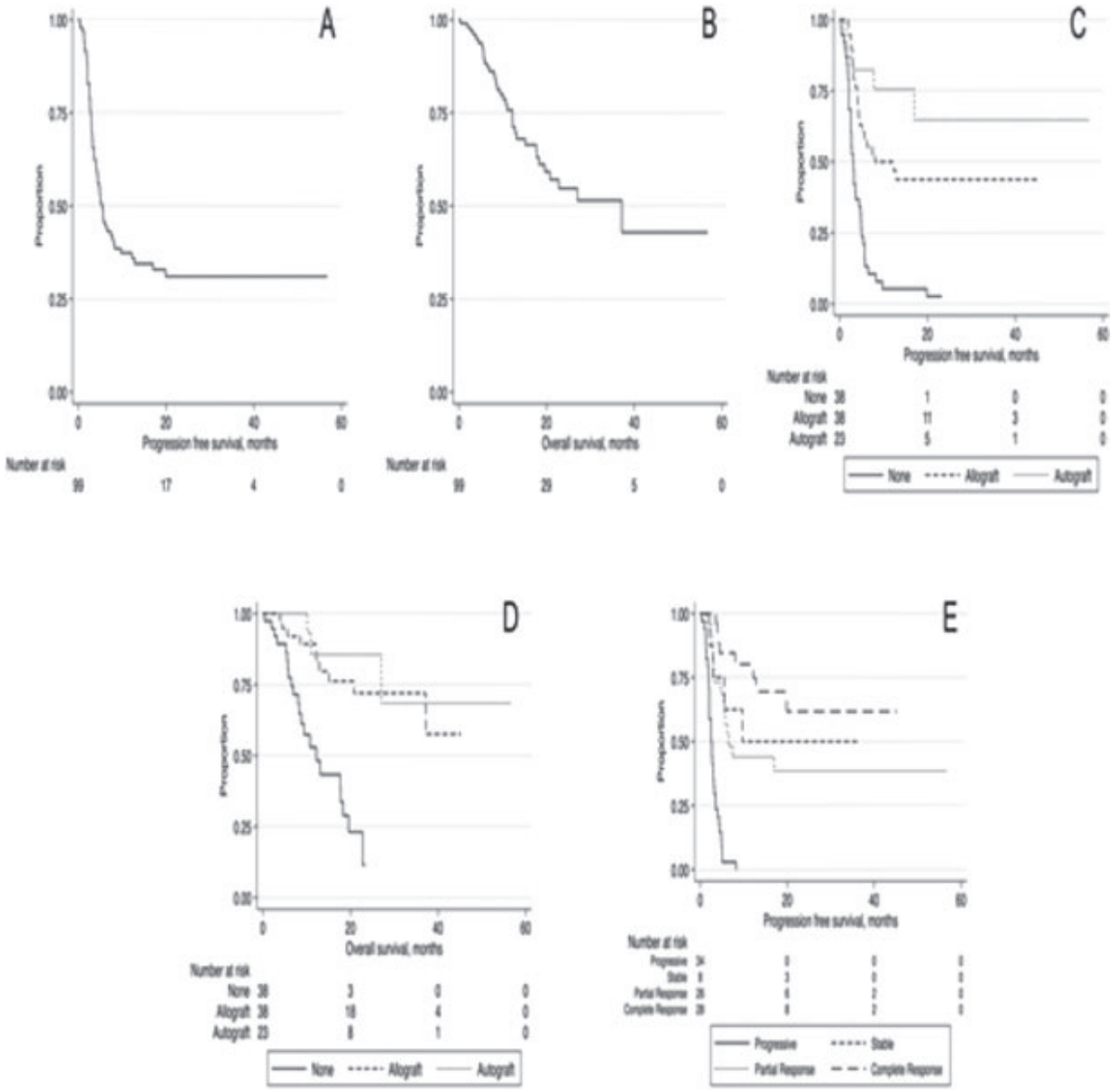

TABLE 1

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

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

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

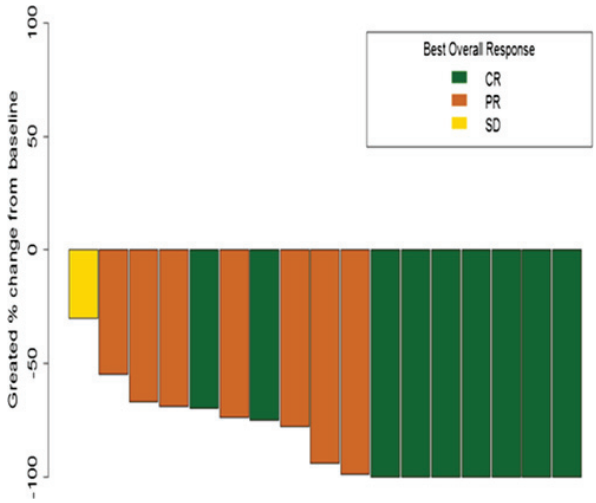
Methods: Patients with confirmed R/R HL were treated with Nivo 3 mg/kg and BV 1.2 mg/kg (Arm D) or 1.8 mg/kg (Arm E) with a 3 + 3 design, and an expansion cohort (Arm F) of 9 patients. BV and Nivo are given every 21 days for 16 cycles; Nivo may be continued for an additional year. Dose limiting toxicity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

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

Safety: Nineteen of 19 patients are evaluable for safety. There were 2 significant treatment related adverse events (AEs): 1 patient in Arm E experienced a DLT (pneumonitis grade 3 with grade 3 dyspnea and hypoxia, and typhilits), and made a full recovery; 1 elderly patient in Arm F had grade 5 pneumonitis occurring in cycle 2. There were no other Grade 4 or 5 AEs; grade 3 AEs were one each: rash, puritis, and neutropenia. The most common grade 1-2 AEs were: transaminitis (9), peripheral sensory neuropathy (8), and rash (6); other grade 1-2 AEs included: diarrhea (4), blurry vision (3), and myalgias (2). One grade 1-2 infusion reaction was noted, this patient was able to receive subsequent therapy with pre-medication.

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

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



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

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

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

Results: Of the 62 enrolled pts (52% female, median 36 years), 45% had primary refractory HL. 61 pts received combination treatment (tx): 53 pts completed 4 cycles, 5 pts remain on tx and 4 pts discontinued due to pt decision (2), adverse event (AE,1) and investigator decision (1). Infusion-related reactions (IRRs) occurred in 41%, most frequently during the Cycle 2 BV infusion, and required dose interruptions in 25%. The rate of Gr 3 IRRs was <5%. 60 pts (98%) had tx-emergent AEs prior to ASCT (66% ≤ Gr 2, 28% Gr 3, and 5% Gr 4); Gr 1 nausea (49%) and fatigue (33%) were most frequent. Excluding IRRs, potential immune-related AEs (IrAE) occurred in 72% of pts (66% ≤ Gr 2, 5% Gr 3, 2% Gr 4) with Gr 1 diarrhea (25%) as the most common. Systemic steroids were required in 4 pts (<10%); 1 pt each experienced Gr 4 pneumonitis and colitis, Gr 2 pneumonitis, Gr 3 diarrhea and Gr 2 colitis, and Gr 3 AST elevation. The CR rate was 64%, (55 efficacy evaluable pts; 53% Deauville ≤2, 11% Deauville 3) with an objective response rate of 85%. 4 pts (7%) had stable disease and 3 pts (5%) progressed on tx. To date, 29 pts have initiated ASCT with a median $4.7x10^6$ CD34+ cells/kg collected, and median time to neutrophil and platelet engraftment of 11.5 and 16 days. No unusual post-ASCT toxicities were observed. Observed effects on the immune system, evaluated in peripheral blood, include a decrease in CD30+ T-regulatory cells after Cycle 1 BV while cytotoxic CD8+ T lymphocytes remained stable. With BV + nivo, CD4+ T cells increased, and T-cell receptor sequencing revealed clonal expansion. Serum TARC levels decreased with BV alone, while inflammatory mediators including IFNγ and CXCL10 increased.

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

MALT & Marginal Zone Lymphoma

Abstracts Selected by Dr Christopher McNamara

WHOLE-EXOME-SEQUENCING OF NODAL MARGINAL ZONE LYMPHOMAS IDENTIFIES RECURRENT MOLECULAR LESIONS IN GENES INVOLVED IN CHROMATIN REMODELLING AND NOTCH SIGNALLING

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V. Pillonel and D. Juskevicius contributed equally to this study.

Introduction: Nodal marginal zone lymphoma (NMZL) is a rare form of small B-cell lymphoma. NMZL has no disease-defining phenotype, and the diagnostic borders to other small B-cell lymphomas are blurred. NMZL is poorly studied and orphan for molecular diagnostic markers. To better understand the pathogenetic mechanisms involved in NMZL, we aimed to comprehensively characterize the genetic background of NMZL at the single nucleotide variation level.

Methods: Genomic DNA was extracted from frozen biopsies and formalin-fixed paraffin-embedded tumor samples (>70% tumor cell fraction). Sanger sequencing was performed to exclude cases with MYD88 L265P mutation typical for lympho-plasmacytic lymphoma (LPL). Whole-exome-sequencing (WES) of 6 NMZL and 6 paired nontumor samples was performed to identify novel somatic mutations. Mutated genes discovered by WES were investigated by targeted high throughput sequencing (HTS) on larger collectives of NMZL and B-cell lymphomas.

Results: By means of WES, a total of 655 nonsilent somatic mutations were identified, including 608 point mutations and 47 small insertion/ deletion events. On average, samples contained 110 mutations (ranging from 68 to 216 lesions per case). In total, 46 candidate genes affected in at least 2 of the 6 NMZL were identified. Among the recurrently altered genes, we found *CAMK2D, EBF1, HIST1H1C, IGLL5, KMT2D, KMT2C, TET2,* and *TNFRSF14*. Based on genes found to be recurrently mutated in the discovery genomes as well as genes recently reported to be recurrently affected in NMZL (Spina et al., Blood 2016), we complemented an existing lymphoma-customized targeted sequencing panel and used it to identify mutations in an extended screening cohort of 25 NMZL and 40 other small B-cell lymphomas, including LPL, extranodal MZL, and unclassifiable "grey zone" cases with features of both LPL and NMZL. Preliminary results show that among the most frequently affected genes in NMZL were genes encoding for chromatin remodelling and transcriptional regulation pathways, including *KMT2D, KMT2C, KLF2, HIST1H1C, CAMK2D, EBF1,* and *TET2*. We also noted frequent mutations in the NOTCH signalling pathway, including *NOTCH2, SPEN, DTX1,* and *CREBBP*.

Conclusions: Collectively, our findings extend the current knowledge on the pathogenetic mechanisms involved in NMZL. We identified somatic mutations potentially helpful for NMZL diagnostics. Together with another recent study on NMZL (Spina et al., Blood 2016), our data provide a comprehensive mutation profile for NMZL, which can help discriminating this entity from other morphologically and/or clinically related entities such as LPL and splenic MZL. We further suggest in silico pathways that play an important role in NMZL and, therefore, may represent potentially targetable signaling cascades, which could be targeted in novel treatment strategies.

SAFETY AND EFFICACY OF SINGLE-AGENT IBRUTINIB IN PATIENTS WITH RELAPSED/ REFRACTORY (R/R) MARGINAL ZONE LYMPHOMA (MZL): A MULTICENTER, OPEN-LABEL, PHASE 2 STUDY

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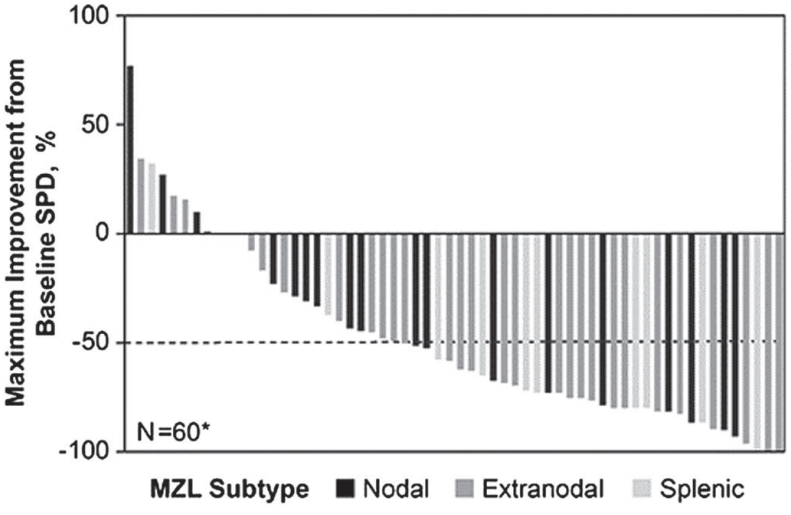
Introduction: MZL is often linked to chronic infection, which can induce B-cell receptor signaling, resulting in aberrant B-cell growth. By blocking BTK, a critical component of B-cell receptor signaling, ibrutinib (ibr) may be an attractive therapy for MZL. We evaluated the efficacy and safety of single-agent ibr in patients (pts) with R/R MZL. No approved agents for MZL existed at study initiation.

Methods: Pts had histologically confirmed MZL, ECOG PS of ≤2, and received ≥1 prior therapy including at least 1 anti-CD20 monoclonal antibody (mAb)-containing regimen or monotherapy rituximab (RTX). All pts received ibr 560 mg orally once daily until progression or unacceptable toxicity. The primary study end point was overall response rate (ORR) as assessed by an independent review committee (IRC) per 2007 IWG criteria. Secondary end points were duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Results: 63 pts (extranodal [*n* = 32], nodal [*n* = 17], and splenic [*n* = 14]) were enrolled. Median age was 66 y (range, 30-92); 92% had ECOG PS of 0-1. Median number of prior systemic therapies was 2 (range, 1-9) with 35% receiving ≥3 prior therapies and 22% refractory to most recent therapy. 17 pts (27%) had received only monotherapy RTX, and 40 (63%) had received at least one anti-CD20 mAb-containing chemoimmunotherapy regimen. At a median follow-up of 19.4 mo, the ORR per IRC was 48% (2 CRs and 27 PRs). Time to best response was 5.2 mo. Thirty-five percent had stable disease (SD), and the clinical benefit rate (CR + PR + SD) was 83% per IRC, with 78% showing some tumor reduction (Figure). Median DOR was not reached (NR) (95% CI: 16.7, NR), and the median PFS was 14.2 mo (95% CI: 8.3, NR). Median PFS by subtype was 19.4 mo for splenic, 13.8 mo for extranodal, and 8.3 mo for nodal MZL. The overall median OS was NR (95% CI: NR, NR). The most common adverse events (AEs ≥20%) of any grade included fatigue (44%), diarrhea (43%), anemia (33%), nausea (25%), thrombocytopenia, arthralgia, and peripheral edema (24% each), cough (22%), and dyspnea and URTI (21% each). Bleeding occurred in 59% of pts, with 1 grade 5 cerebral hemorrhage. Atrial fibrillation occurred in 4 (6%) pts, all grade1-2 events. Three treatment-emergent AEs resulted in death due to disease progression, cerebral hemorrhage, and parainfluenza infection leading to multiple organ failure. Overall, 39 pts (62%) discontinued treatment (PD: 32%; AEs: 17.5%, withdrawal of consent: 6%; physician decision: 6%).

Conclusions: Single-agent ibr achieved a high ORR and durable responses across all MZL subtypes, and produced clinically meaningful tumor shrinkage; the treatment was well tolerated (all grade 1-2 AEs). The promising results of this trial led to the US FDA approval of ibr for pts with MZL requiring systemic therapy with ≥1 prior anti-CD20 based therapy, allowing treatment without chemotherapy.

Figure. Maximum Percentage Decrease From Baseline SPD by Investigator Assessment



*3 patients had PD and were non-evaluable after first dose of ibrutinib.

PHASE IIIB STUDY OF LENALIDOMIDE PLUS RITUXIMAB FOLLOWED BY MAINTENANCE IN RELAPSED OR REFRACTORY NHL: ANALYSIS OF MARGINAL ZONE LYMPHOMA

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Introduction: Lenalidomide combined with rituximab (R^2) has shown synergistic effects in preclinical settings. R^2 is also clinically active and tolerable non-chemotherapy regimen in untreated and relapsed or refractory (R/R) patients with indolent non-Hodgkin lymphoma (NHL), including marginal zone lymphoma (MZL). The clinical potential of R^2 supports further study in MZL and its subtypes.

Methods: MAGNIFY (NCT01996865) is a phase IIIb, multicenter, open-label study of R/R NHL patients with grades 1-3b follicular lymphoma (FL; including transformed FL), MZL, and mantle cell lymphoma (MCL). Patients receive 12 cycles of R^2 (oral lenalidomide 20 mg/d, d1-21 of a 28-d cycle; intravenous rituximab 375 mg/m2, d1, 8, 15, 22 of cycle 1 and d1 of subsequent odd cycles). Following R2 induction, those with stable disease or better are randomized 1:1 to maintenance R^2 (oral lenalidomide 10 mg/d, d1-21 of a 28-d cycle; rituximab 375 mg/m^2, d1 of every other cycle) or rituximab alone (375 mg/m^2, d1 of every other cycle). The primary endpoint is progression-free survival (PFS); secondary endpoints include safety, overall survival, and response rates. This analysis focuses on MZL and includes the 3 subtypes: MALT, splenic MZL, and nodal MZL.

Results: As of April 14, 2016, the R/R NHL population (N = 155) was composed of 27 (17%) patients with MZL, including 13 nodal MZL, 8 splenic MZL, and 6 MALT (4 without gastric involvement). The median age of MZL patients was 65 y (range, 46-85), most (81%) with stage III/ IV disease at study entry and all with ECOG PS 0-1. Patients with MZL had a median of 1 prior treatment regimen (range, 1-4), with 8 (30%) patients having ≥2. The most common prior therapies were rituximab alone (44%), bendamustine/rituximab (BR; 26%), or R-CHOP–like regimens (26%); 37% were refractory to rituximab, defined as best response of SD/PD to rituximab/R-containing regimen or CR/PR <6 mo after last rituximab dose. The overall response rate (ORR) during induction in 22 evaluable MZL patients was 55% (45% CR/CRu); response assessment was too early with no reported efficacy in nonevaluable patients. Responses by subtype are shown in Table 1. The most common grade 3/4 treatment-emergent adverse events in MZL patients during induction were hematologic, 9 (33%) neutropenia and 3 (11%) thrombocytopenia.

Conclusions: R^2 induction showed favorable activity and tolerable safety profiles in R/R patients with MZL. Enrollment in MAGNIFY is ongoing.

TABLE 1 Best response in evaluable patients with R/R MZL during R2 induction.

Response status, n (%)	MALT (n=6)	Splenic MZL (n=5)	Nodal MZL (n=11)	Evaluable MZL (N=22)
ORR95% CI	3 (50) 12%-88%	3 (60) 15%-95%	6 (55) 23%-83%	12 (55) 32%-76%
CR/CRu	3 (50)	1 (20)	6 (55)	10 (45)
PR	0	2 (40)	0	2 (9)
SD	3 (50)	2 (40)	4 (36)	9 (41)
PD*	0	0	1 (9)	1 (5)

*Includes PD and/or death prior to response evaluation completion.

LONG-TERM RESULTS OF THE MULTICENTER PHASE II TRIAL WITH BENDAMUSTINE AND RITUXIMAB AS FIRST LINE TREATMENT FOR PATIENTS WITH MALT LYMPHOMA (MALT-2008-01)

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Background: Optimal treatment of patients with MALT lymphoma with systemic therapy is not established. To date, combinations of Rituximab with Chlorambucil (RChl) or Bendamustine (RB) have demonstrated promising results. We report the long term results of the MALT 2008-01 phase II trial that used the combination of Rituximab and Bendamustine in a response-adapted protocol.

Patients and methods: A prospective multicenter phase II trial (EUDRACT 2008-007725-39) has been carried out in Spain by the GELTAMO group in untreated patients with CD20+ MALT lymphoma requiring systemic therapy. Treatment: Bendamustine (90 mg/m^2 d12) and Rituximab (375 mg/m^2 d1), every 28 d. Pts received 4 or 6 cycles (if CR or PR after the 3rd cycle, respectively). The aims were: feasibility and security of the combination and outcome. Clinical characteristics: median age 62 years (range, 26-84); 34 (57%) female; Ann Arbor stage: III-IV in 34%; site of disease: stomach 33%, extra-gastric 58% and multifocal 8%.

Results: Sixty pts were enrolled but 3 were subsequently identified ineligible and were not included in the analysis of response and survival. A total of 264 cycles of RB were delivered in the whole population. Number of cycles administered per pt: <4 in 2 (3%), 4 in 44 (73%) and 6 in 14 (23%). Grade 3-4 adverse events in 56 (21%) cycles. At early response assessment after 3 cycles, 43 (75%) achieved CR or uCR and 14 (25%) PR%. At the end of treatment, overall response rate was 100% (CR/uCR: 98%). Presence of t (11;18)(q21;q21) was identified in nine (16%) pts and did not influence response. After a median follow-up of 82 months, 8 events were recorded and EFS at 7 years was 88%. No differences according to the primary site of disease, stage, or number of cycles administered were found. PFS at 7 years was 93% (94% for gastric and 92% for non-gastric). One gastric pt relapsed in the stomach with DLBCL transformation and 4 from non-gastric sites had also relapse (2 with DLBCL transformation and 3 at different site from origin). Three pts have died (2 due to unrelated causes and 1 with transformation to DLBCL and multiple relapses). OS at 7 years was 96%. No myelodisplastic syndrome or acute leukemia occurred, but other neoplasias were observed in 3 pts (1 tongue epidermoid carcinoma, 1 GIST and 1 granular lymphoproliferative disorder of NK-cells). Prophylaxis with cotrimoxazole was done in 39% of cases. During follow-up, 3 pts had opportunistic infections (1 herpes zoster, 1 CMV and 1 lung infection by Nocardia).

Conclusions: The RB combination with a response-adapted schedule in the first line treatment of MALT lymphoma is safe and achieved rapid and sustained long-term responses with 88% EFS and 94% of PFS at 7 years. These long term results with a very brief (4 cycles in 75% of patients) and tolerable treatment are the best obtained to date with rituximab plus chemotherapy.

CNS Lymphoma

Abstracts Selected by Dr Kate Cwynarski

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

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

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

Results: Of 1418 pts, 19.7% were categorised by CNS IPI score as low risk (0–1) for CNS relapse, 63.0% as intermediate risk (2–3) and 17.3% as high risk (4–6). After 29.0 mo (range 0.1–56.6) median observation, 40 (2.8%) pts developed CNS relapse (21 G-CHOP; 19 R-CHOP). Median time to CNS relapse was 8.5 mo (range 0.9–43.5); 2-yr CNS relapse rates were 3.0% overall and 0.8%, 2.1% and 9.3%, for the low, intermediate and high risk CNS IPI subgroups, respectively. COO was available in 933 pts (65.8%). In these pts, 2-yr relapse rates were 1.4%, 2.2% and 10.3% for the low, intermediate and high risk CNS IPI subgroups, respectively (Figure A). Pts with activated B-cell-like (ABC) and unclassified subtypes had significantly higher CNS relapse risk vs the germinal-center B-cell-like subtype (2-yr rates: 6.9%, 4.8% vs 1.5%, respectively). The impact of dual BCL2 and MYC protein expression on CNS relapse risk is being evaluated and will be presented. On MV analysis, CNS IPI score (hazard ratio [HR] 2.06; 95% CI 1.50– 2.82, p < 0.001) and ABC (HR 4.37; 95% CI 1.84–10.37, *p* < 0.001) or unclassified COO subtypes (HR 3.94; 95% CI 1.45–10.68, p = 0.007) were associated with CNS relapse risk.Three risk subgroups were identified according to presence of high CNS IPI score and/or ABC/unclassified COO (*n* = 933): low risk (L-R, no risk factors; *n* = 450, 48.2%); intermediate risk (I-R, 1 risk factor [high CNS IPI or ABC/unclassified COO]; *n* = 408, 43.7%); and high risk (H-R, both risk factors [high CNS IPI and ABC/unclassified COO]; *n* = 75, 8.0%). Two-yr CNS relapse risk was 0.5% (L-R), 4.7% (I-R) and 15.2% (H-R) (Figure B).

Conclusions: CNS IPI score and ABC/unclassified COO subtypes were independent risk factors for CNS relapse in DLBCL in the GOYA study. Combining these factors improved prediction of CNS relapse vs CNS IPI alone and stratified pts into 3 risk groups, including a small but notable subgroup (8.0%) of pts with a very high risk of CNS relapse (2-yr risk: 15.2%).

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

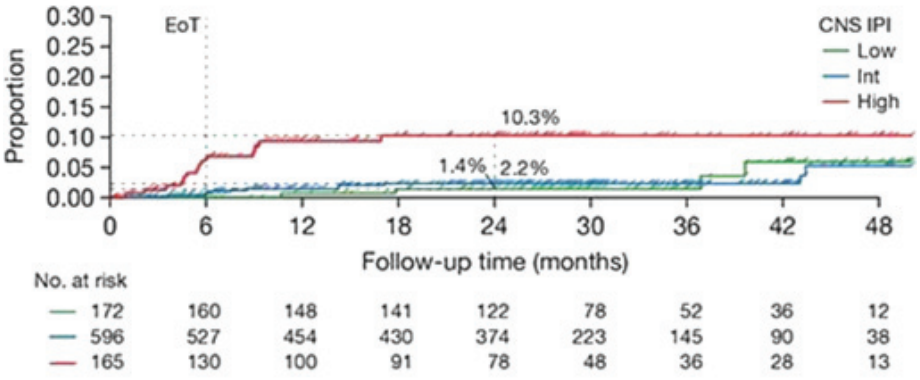
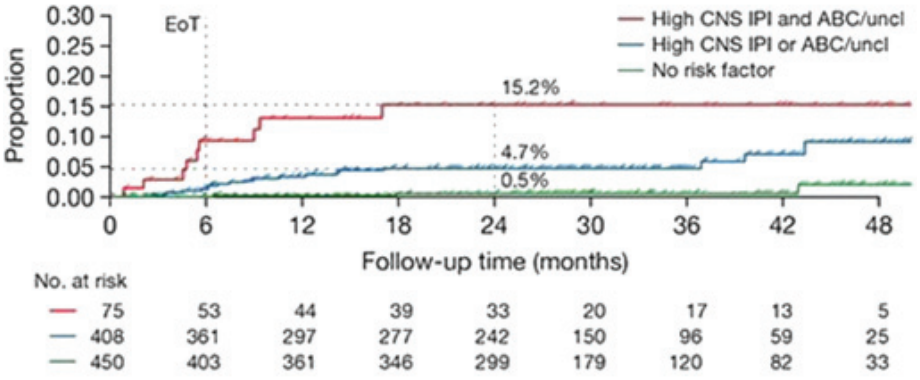


Figure B. Risk of CNS relapse by high CNS IPI and/or ABC/unclassified COO, COO population (n=933)



EoT, end of treatment.

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

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

This prospective, multicenter, open-label phase II, was designed for immuno-competent patients over 18 with a refractory or relapse of PCNSL or primary vitreo-retinal lymphoma (PVRL) of DLBCL type. The treatment consisted in ibrutinib monotherapy given orally at 560 mg daily until disease progression or unacceptable toxicity. Additional corticosteroids treatment was allowed during the first 4 weeks of treatment in case of a threatening or symptomatic edema. The primary objective of the study was the disease control (DC) rate (CR + CRu + PR + SD) after two months of treatment. Patients were evaluable for response if they received ≥90% of the expected dose during the first month of treatment. A total of 35 evaluable patients were required for the final analysis (P0 < 10%; P1 hypotheses >30%). Results of the interim analysis were encouraging with a DC achieved in 15/18 patients (83%, IC 95%, [59-96%]) after two months of treatment. NCT02542514.

Between September 2015 and June 2016, 52 patients were recruited in 10 French centers of the French LOC network for PCNSL. Forty-three patients (24 females; 19 males) are evaluable for response (median age: 70 y, range 52-81). Initial diagnoses were PCNSL (n = 30) and PVRL (n = 13). Patients were included in the study for a relapse (n = 31) or a progressive disease (n = 12). At time of inclusion in the study, disease status was PCNSL (n = 29) and PVRL or isolated intraocular relapse of a PCNSL (n = 14). Four patients had a concomitant meningeal involvement. ECOG performance status was 0, 1 and 2 in 11, 22 and 10 patients respectively. All the patients had previously received high-dose methotrexate-based chemotherapy. Six patients had previously received high-dose chemotherapy followed by autologous stem cell transplantation. Patients had received ≥2 prior treatments in 25 cases. Twenty-seven patients prematurely interrupted ibrutinib treatment between cycle 2 and cycle 15 (median time: 3 months, range, 0.9-13 months), because of a progressive disease (*n* = 22), toxicity (*n* = 1, grade 3 hyphema), other (*n* = 4). Among the 52 patients included in the study, two patients experienced a pulmonary aspergillosis with a favorable (*n* = 1) and a fatal outcome (*n* = 1). Ibrutinib was detectable in the CSF (> 0.15 ng/ml) in all the samples tested (*n* = 26). Thirteen patients are currently on treatment ≥ 6 months, including 8 patients ≥ 12 months. The analysis of the primary end-point of the 43 evaluable patients is ongoing and results will be presented.

CHECKMATE 647: A PHASE 2, OPEN-LABEL STUDY OF NIVOLUMAB IN RELAPSED/ REFRACTORY PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA OR RELAPSED/REFRACTORY PRIMARY TESTICULAR LYMPHOMA

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Introduction: Primary central nervous system lymphoma (PCNSL) and primary testicular lymphoma (PTL) are rare and clinically aggressive forms of large B-cell lymphoma with similar genetic signatures. Prognosis is poor and treatment options are limited for patients (pts) with relapsed/refractory PCNSL or PTL, highlighting a high unmet medical need. Both tumors exhibit frequent 9p24.1 copy number alterations (CNAs) and associated expression of the programmed death-1 (PD-1) ligands, PD-L1 and PD-L2 (Chapuy B, Roemer MG, et al. *Blood* 2016;127:869–81). Activation of PD-1 signaling via PDL1/PD-L2 limits T-cell responses, potentially inhibiting antitumor immune surveillance.

Nivolumab (nivo) is an immune checkpoint inhibitor that targets PD-1 to restore T-cell activation and antitumor immune responses. Nivo has demonstrated efficacy in relapsed/refractory classical Hodgkin lymphoma, which is characterized by 9p24.1 CNAs and PD-L1 and PD-L2 upregulation (Roemer MG, et al. *J Clin Oncol* 2016;34:2690–7; Younes A, et al. *Lancet Oncol* 2016;17:1283–94), suggesting that the same mechanism of action may be effective in PCNSL or PTL. In a retrospective study of 5 pts with relapsed/refractory PCNSL or PTL who were treated with nivo, all pts obtained clinical and radiographic responses (4 complete radiographic responses and 1 partial radiographic response in a pt with PCNSL),

and 3 pts remain progression free at 13 + –17+ mo (Nayak L, et al. *Blood* 2017, in press). The current study evaluates the efficacy, safety, and tolerability of nivo in relapsed/refractory PCNSL or PTL.

Methods: CheckMate 647 (NCT02857426) is a phase 2, open-label, single-arm, 2-cohort trial assessing single-agent nivo treatment in pts with relapsed/refractory PCNSL or PTL. Adult pts with pathologically confirmed PCNSL or PTL who relapsed or did not respond to ≥ 1 line of systemic therapy, with Karnofsky Performance Status score ≥ 70, are eligible. Pts with PCNSL must have ≥ 1 measurable brain lesion; pts with PTL require ≥ 1 measurable extranodal lesion. Pts should have tumor tissue available for PD-L1 expression testing. Pts with intra-ocular lymphoma without evidence of brain disease, pts with PCNSL who cannot undergo MRI, and those with PCNSL with systemic disease are not eligible. Both cohorts will receive nivo monotherapy. The primary endpoint is objective response rate (ORR), assessed by a blinded independent central review committee. Secondary endpoints include progression-free survival, investigator-assessed ORR and duration of response, and overall survival. All analyses will be performed separately in each cohort. Treatment of 65 pts is planned. Accrual is ongoing.

Study support: Bristol-Myers Squibb (BMS). Writing assistance by M Arancillo of Caudex, funded by BMS.

Follicular Lymphoma

Abstracts Selected by Dr Wendy Osborne

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

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

Methods: We conducted a multicentre retrospective study of pts who received RT for stage I-II FL, staged by PET-CT. Eligible pts were ≥18 years with grade 1-3A FL. Disease site, maximal bulk, and FL Prognostic Index (FLIPI) were recorded. Additional inclusion criteria were RT dose ≥24Gy, follow up ≥3 months, and no prior Rx. Primary outcomes were local control, freedom from progression (FFP) and overall survival (OS). Secondary outcomes were response rate by PET-CT and toxicity. OS and FFP were estimated with Kaplan-Meier, and uni- and multivariate analyses of prognostic factors performed with Cox Regression.

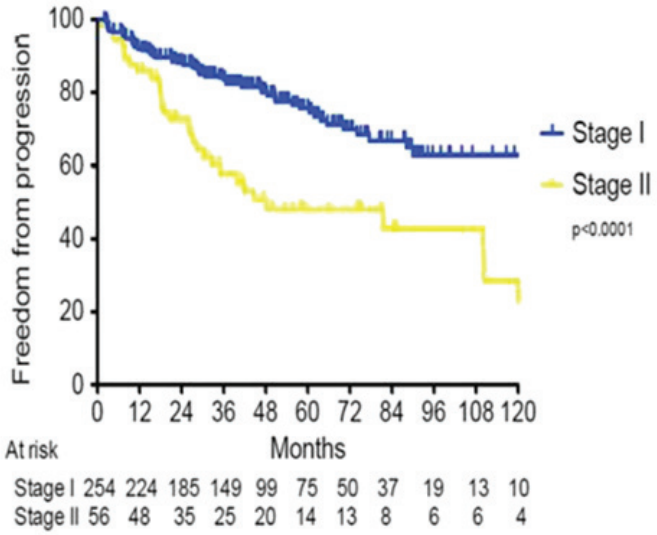
Results: 310 pts treated from 2000-2016 at 11 centres were eligible for analysis. Pre-treatment characteristics included age (median 58 years, range 20-84), female sex (*n* = 160, 51.6%), stage I disease (*n* = 254, 81.9%), FLIPI score (median 1, range 0-3), B-symptoms (*n* = 2, 0.6%), bulk of disease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

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

On multivariate analysis of prognostic factors including age, stage, grade, bulk, FLIPI, RT dose, nodal versus extra nodal site, and CMR status; stage II disease (HR = 2.51, 95% CI: 1.53-3.77, $P = 0.0001$) and failure to achieve CMR (HR = 3.11, 95% CI = 1.35-7.16, $P = 0.008$) were significantly associated with worse FFP. Toxicity data were available on 284 pts. 67 pts (23.5%) had grade 1-2 toxicities, with only 1 case of grade 3 toxicity (dysphagia).

Conclusion: Outcome after RT in PET-CT staged pts appears to be better than in earlier series, particularly in stage I disease, suggesting that the curative potential of RT for truly localised FL may have been underestimated.

Figure. Freedom from progression by stage



CVP OR R-CVP GIVEN AFTER INVOLVED-FIELD RADIOTHERAPY IMPROVES PROGRESSION FREE SURVIVAL IN STAGE I-II FOLLICULAR LYMPHOMA: RESULTS OF AN INTERNATIONAL RANDOMIZED TRIAL

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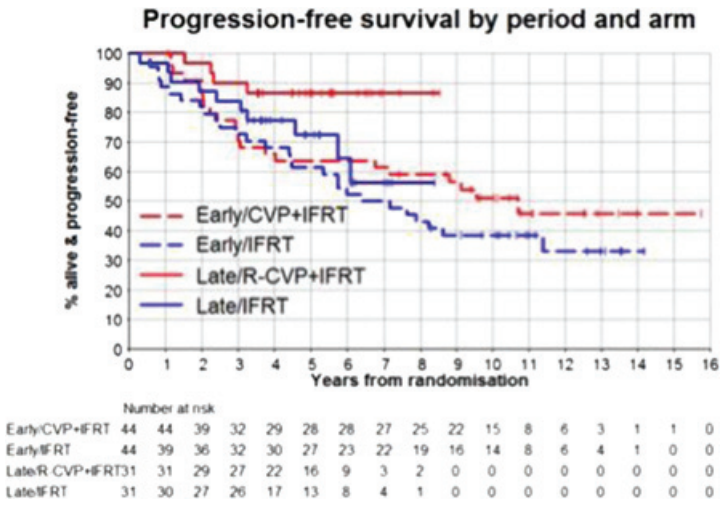
Aim: Curative-intent involved field radiation therapy (IFRT) is a standard treatment for stage I-II follicular lymphoma (FL). It achieves durable local disease control and can produce life-long remissions. However ≥50% of patients relapse, generally outside irradiated volumes. We conducted a randomized controlled trial (RCT) to determine if systemic therapy could improve progression free survival (PFS).

Patients and Methods: Patients from Australia, New Zealand and Canada with stage I-II FL of grade 1, 2 or 3a were enrolled after mandatory CT scans and marrow biopsies. PET staging was permitted. Patients were randomized to either; Arm A: 30Gy IFRT alone or Arm B: IFRT followed by 6 cycles of cyclophosphamide 1000 mg/m^2 IV D1, vincristine 1.4 mg/m^2 D1 and prednisolone 50 mg/m^2 D1-5 (CVP), stratified by center, stage, age and PET. A protocol amendment in 2006 added Rituximab 375 mg/m^2 D1 to arm B (R-CVP).

Results: Between February 2000 and July 2012, 150 patients were recruited: 75 per arm: 44 arm B patients were allocated CVP and 31 R-CVP. Median age was 57 (range 30-79) years, 52% were male, 75% had stage 1 and 48% were PET-staged. Only 8% had an extranodal site (ENS). Median potential follow-up was 9.6 years (range, 3.1-15.8). PFS was significantly superior for arm B (IFRT + systemic therapy) compared to arm A [HR 0.57 (0.34-0.95); p = 0.033]. At 10 years PFS was 58% (95% CI 46-74%) for arm B and 41% (95% CI 30-57%) for arm A. Patients randomized to R-CVP had a substantially superior PFS to those contemporaneously randomized to IFRT alone, [HR 0.26 (0.07-0.97); p = 0.045]. In univariate analysis, patients who had ENS (p = 0.02), fewer involved regions (p = 0.047) and PET staging (p = 0.056) also had improved PFS. Transformation to high-grade lymphoma occurred in 4 patients in arm B compared to 10 in arm A (p = 0.1). Overall survival (OS) is not currently significantly different between arms (HR 0.62, p = 0.4); 10 year rates 95 vs 87% for arms B and A respectively. Only 2 patients had isolated in-field relapses, therefore systemic therapy primarily prevented progression outside RT fields. Only 3 cases with grade 3-4 acute and 1 case with grade 3 late radiation toxicities were observed. Systemic therapy was associated with 29 cases of grade 3 toxicity and one of grade 4 (neuropathy). One treatment-associated death occurred per arm.

Conclusion: Treatment with 6 cycles of CVP or R-CVP after IFRT significantly improved PFS compared to IFRT alone. Further follow up is required to detect any potential effect of systemic therapy on OS.



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

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

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

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

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

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

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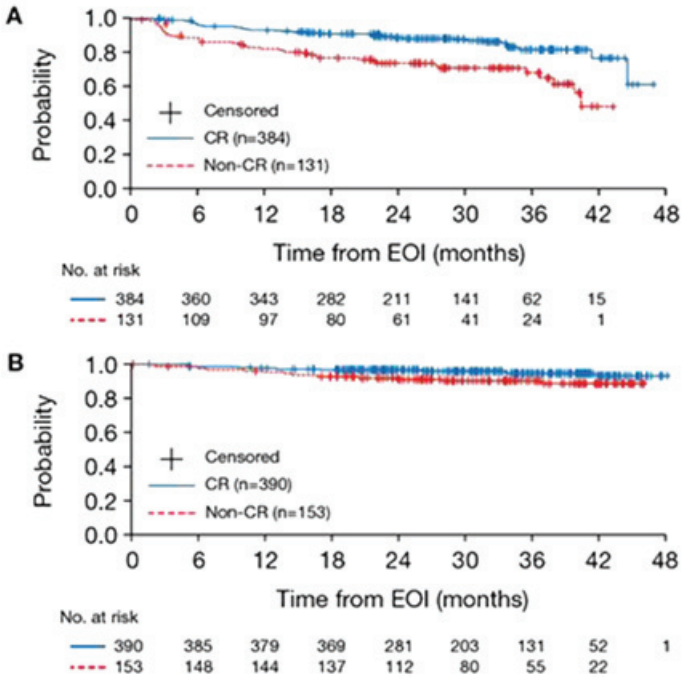
Introduction: The prognostic value of ^{18}F-FDG PET-CT (PET) response assessment after first-line (1 L) immunochemotherapy for advanced-stage symptomatic follicular lymphoma (FL) has been reported in several smaller trials. We evaluated the prognostic value of PET complete remission (PET-CR) status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

Methods: 1202 pts with previously untreated FL (ITT population) were randomised 1:1 to receive induction therapy comprising chemotherapy plus 1000 mg obinutuzumab (G; D1, 8, 15 C1 then D1 subsequent cycles) or 375 mg/m^2 rituximab (R; D1 each cycle), for 8 x 21-day cycles (CHOP, CVP) or 6 x 28-day cycles (bendamustine). PET scans, introduced after an early protocol amendment (July 2011), were taken at baseline and end of induction (EOI) visits and assessed by the investigator (INV) and an independent review committee (IRC) comprising two radiologists, with a third adjudicator; final response was determined by a clinician. Response was assessed by CT and PET plus bone marrow biopsy, applying the revised International Working Group (IWG) criteria (Cheson 2007, Juweid 2007). EOI PET-CR status was compared with pt characteristics, CT-based response, PFS and OS.

Results: Of 609 pts with a baseline PET scan, 595 had detectable lesions, and 535 also had an evaluable PET at EOI. Baseline disease and demographic characteristics were similar in the PET-evaluable and non-PET populations. Pts with non-available (n = 52) and non-evaluable (n = 8) scans were considered as non-responders; these pts and those who progressed prior to EOI were excluded from landmark PFS analyses. At EOI 390/595 (65.5%) pts had achieved a PET-CR according to IRC, comprising 212/297 (71.4%) G-chemo pts and 178/298 (59.7%) R-chemo pts. After a median follow-up of 34.5 months, EOI PET-CR status was highly prognostic of both PFS (PET-CR vs PET-non CR: HR 0.39; 95% CI 0.25–0.60; $p < 0.0001$) and OS (HR 0.41; 95% CI 0.19–0.86; $p = 0.018$; see Figure). 2.5-year PFS from EOI was 87.6% (95% CI 83.5–90.8) for PET-CR pts compared with 70.9% (95% CI 61.3–78.6) for PET-non CR pts; corresponding OS was 96.6% (95% CI 94.1–98.1) vs 90.9% (95% CI 84.7–94.6). IRC PET status was prognostic in both G- and R-treated populations. Concordance between INV and IRC evaluation was 68.6%.

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

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



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

THE RISK OF TRANSFORMATION OF FOLLICULAR LYMPHOMA "TRANSFORMED" BY RITUXIMAB: THE ARISTOTLE STUDY PROMOTED BY THE EUROPEAN LYMPHOMA INSTITUTE

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

Methods: Patients included in the Aristotle (**A**ssessing the **Ris**k of **T**rans**f**orma**t**ion and Outcome of Follicular **L**ymphoma in the Immunochemotherapy **E**ra) study come from clinical trials or lymphoma registries collected by ten different European Lymphoma Groups. The present study is restricted to cases diagnosed between 1997 and 2013 with biopsy proven HT,

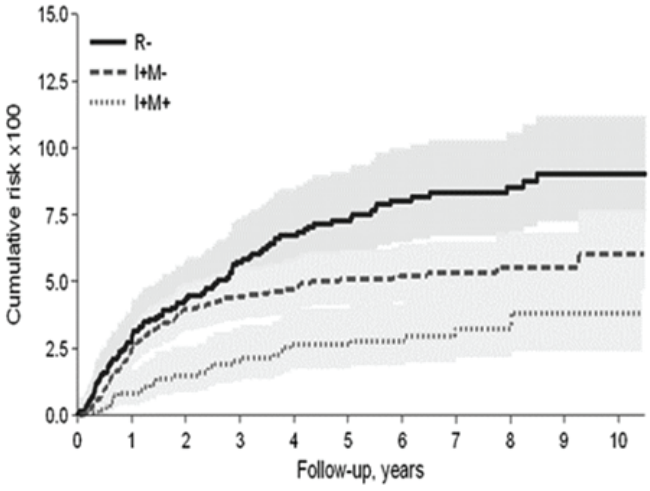
as reported by the participating Institutions, and in which transformation was diagnosed as the first event after initial therapy (regardless of whether patients had been managed expectantly at diagnosis or not). Primary endpoints were the cumulative risk of HT and survival after transformation (SAT).

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

The risk of transformation at 10 years was 6.2 (5.4-7.3) for R+, and 9.0 (7.2-11.1) for R-, respectively. Moreover, at 10 years the risk of transformation was 6.0 (95%CI 4.7-7.6) for patients who received R only in Induction (I + M-) and 3.8 (95%CI 2.4-5.9) for patients treated with R in induction and maintenance (I + M+) (Figure 1). After a median follow-up of 55 months (range 1-167) since HT, 248 deaths were recorded, with a SAT of 41% (95% CI 36-46) and 31% (95% CI 25-38) at 5 and 10 years, respectively.

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

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



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

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

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

Results: 1202 FL pts were randomised. Baseline characteristics were generally similar across chemo groups, although B and CVP pts had relatively more comorbidities, e.g. gastrointestinal and vascular disorders, than CHOP pts. After 41.1 months' median follow-up, investigator (INV)-assessed PFS remained superior for G-chemo relative to R-chemo (HR, 0.68; 95% CI 0.54–0.87; p = 0.0016) with consistent HRs across chemo groups (Figure). HRs for secondary time-to-event endpoints were supportive of the primary analysis. Difference in frequency of grade 3–5 AEs between arms was highest with CHOP and CVP (Table). Rates of second neoplasms and grade 3–5 infections were similar in G and R arms for CHOP and CVP but not for B. In all chemo groups, SAEs were more frequent with G than R, and AEs causing treatment discontinuation and fatal AEs were similar. Reductions in T-cell counts were more pronounced and prolonged in the B group than CHOP or CVP groups.

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

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

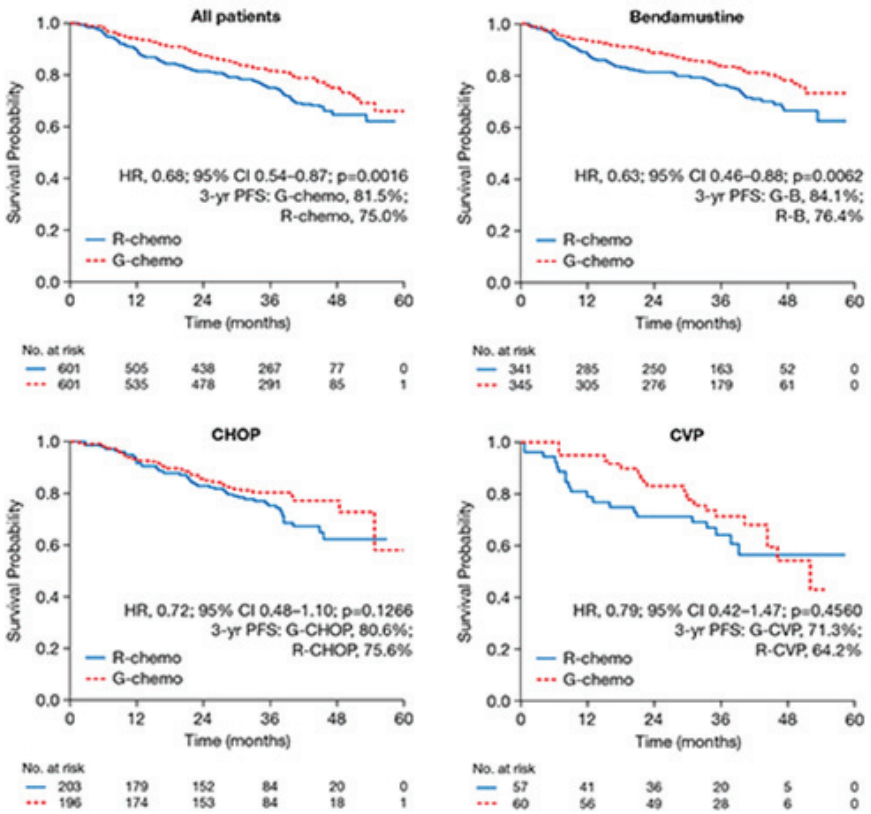

TABLE 1 Safety summary (number [%] of FL pts* with ≥1 AE).

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

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

Mantle Cell Lymphoma

Abstracts Selected by Professor Simon Rule

P53 BUT NOT SOX11 IHC HAS PROGNOSTIC VALUE INDEPENDENT OF MIPI AND KI-67 IN PROSPECTIVE TRIALS OF THE EUROPEAN-MCL NETWORK

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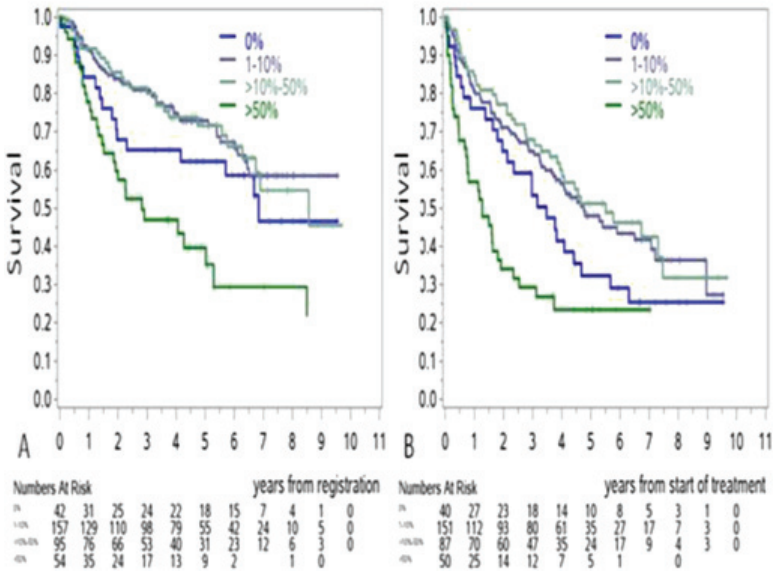
Introduction: Mantle cell lymphoma (MCL) is an aggressive B-cell lymphoma with poor outcome. Currently, prediction of time to treatment failure and overall survival is based on the clinical factors included in the mantle cell lymphoma international prognostic index (MIPI) and proliferation assessed by Ki67 (*Hoster, JCO 2016*). P53 and SOX11 immunohistochemistry might improve risk stratification.

Methods: All patients were treated in the MCL Younger (*Hermine, Lancet 2016*) and MCL Elderly trials (*Kluin-Nelemans, NEJM 2012*) of the *European MCL Network*. Formalin fixed paraffin embedded (FFPE) diagnostic patients' material was analyzed by SOX11 and P53 immunohistochemistry (IHC) on either tissue microarrays or whole tissue sections. SOX11 was scored as negative (0% positivity), 1 - 10% (low expression) or >10%. P53 was classified as negative (0% positivity), 1 - ≤ 10% (low), >10-50% (intermediate) or >50% (high expression).

Results: For 365 MCL patients FFPE material was available for IHC. No survival difference was observed for patients with and without IHC data available. SOX11 negativity (0%) was detected in 3% (n = 9) and low SOX11 expression (1-10%) in 5% (n = 16) of patients. In univariate analysis both negative and low SOX11 expression were associated with shorter overall survival. However, in multivariate analyses including MIPI and Ki67 only low SOX11 expression retained significance. SOX11 expression was not significantly associated with time to treatment failure. High, intermediate, low and lack of P53 expression were detected in 16% (n = 54), 27% (n = 95), 45% (n = 157) and 12% (n = 42) of samples, respectively. High P53 expression was a strong predictor of inferior OS (Figure 1A) and TTF (Figure 1B) compared to low P53 expression in univariate (OS hazard ratio, HR, 3.0, $p < 0.0001$, TTF HR 2.5, $p < 0.0001$) and multivariate analyses adjusting for MIPI and Ki-67 (OS HR 2.0, $p = 0.010$, TTF HR 1.9, $p = 0.0083$). In contrast, intermediate P53 expression displayed a similar outcome as low P53 expression, whereas lack of P53 expression showed a tendency towards inferior outcome (adjusted OS HR 1.5, $p = 0.18$, adjusted TTF HR 1.4, $p = 0.22$).

Conclusions: In 365 patients treated in prospective trials of the European MCL Network, patients with high P53 expression >50% had a shorter time to treatment failure and poor overall survival independent of both MIPI and Ki-67. Thus we recommend to incorporate P53 IHC in routine diagnostic practice. Future studies should investigate novel therapeutic strategies in these high risk patients.

Figure 1: Prognostic value of p53 IHC score for overall survival (A) and time to treatment failure (B)



FIRST-LINE TREATMENT OF INHL OR MCL PATIENTS WITH BR OR R-CHOP/R-CVP: RESULTS OF THE BRIGHT 5-YEAR FOLLOW-UP STUDY

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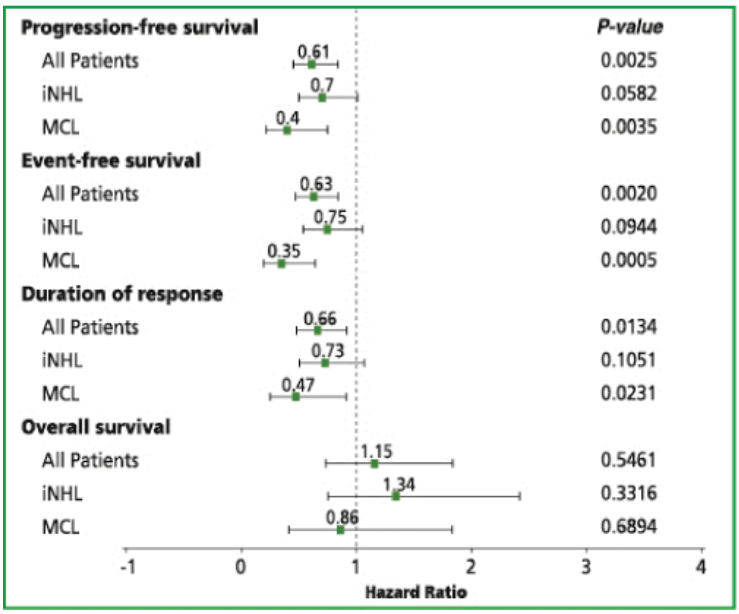
Introduction: BRIGHT, a phase 3, open-label, noninferiority study comparing efficacy and safety of bendamustine plus rituximab (BR) vs rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP) in treatment-naive patients with indolent non-Hodgkin lymphoma (iNHL) or mantle cell lymphoma (MCL), showed that the complete response rate for first-line BR was statistically noninferior to R-CHOP/R-CVP (Blood 2014;123:2944-52). Patients were monitored for ≥5 years to assess the overall effect of BR or R-CHOP/R-CVP in a controlled clinical setting. This analysis reports the time-to-event variables of the 5-year follow-up study.

Methods: Patients with iNHL or MCL randomized to 6-8 cycles of BR or R-CHOP/R-CVP underwent complete assessments at end of treatment, then were monitored regularly. Progression-free survival (PFS), event-free survival (EFS), duration of response (DOR), and overall survival (OS) were compared using a stratified log-rank test.

Results: Of 447 randomized patients, 224 received BR, 104 R-CHOP, and 119 R-CVP; 419 entered the follow-up study. The median follow-up time was 65.0 and 64.1 months for BR and R-CHOP/R-CVP, respectively. The 5-year PFS rate was 65.5% (95% confidence interval [CI]: 58.5-71.6) and 55.8% (48.4-62.5), and OS was 81.7% (75.7-86.3) and 85% (79.3-89.3) for BR and R-CHOP/R-CVP, respectively. The hazard ratio (95% CI) for PFS was 0.61 (0.45-0.85; *P* = .0025), EFS 0.63 (0.46-0.84; *P* = .0020), DOR 0.66 (0.47-0.92; *P* = .0134), and OS 1.15 (0.72-1.84; *P* = .5461) comparing BR vs R-CHOP/R-CVP. Similar results were found in iNHL [PFS 0.70 (0.49-1.01; *P* = .0582)] and MCL [PFS 0.40 (0.21-0.75; *P* = .0035)], with the strongest treatment effect in MCL (Figure). Use of rituximab maintenance was similar, 43% in BR and 45% in R-CHOP/R-CVP. Bendamustine was included as second-line in 27 (36%) of the 75 patients requiring therapy who originally received R-CHOP/R-CVP. Comparable safety profiles with expected adverse events were observed in the follow-up study in BR vs R-CHOP/R-CVP.

Conclusions: The long-term follow-up of the BRIGHT study has confirmed that PFS, EFS, and DOR were significantly better for BR, and OS was not statistically different between BR and R-CHOP/R-CVP. The safety profile was as previously reported.

Figure. Hazard ratios of time-to-event variables and their 95% confidence intervals – investigator assessment of randomized patients.



FIRST LINE TREATMENT BY THE RIBVD REGIMEN ELICITS HIGH CLINICAL AND MOLECULAR RESPONSE RATES AND PROLONGED SURVIVAL IN ELDERLY MCL PATIENTS; FINAL RESULTS OF A LYSA GROUP TRIAL

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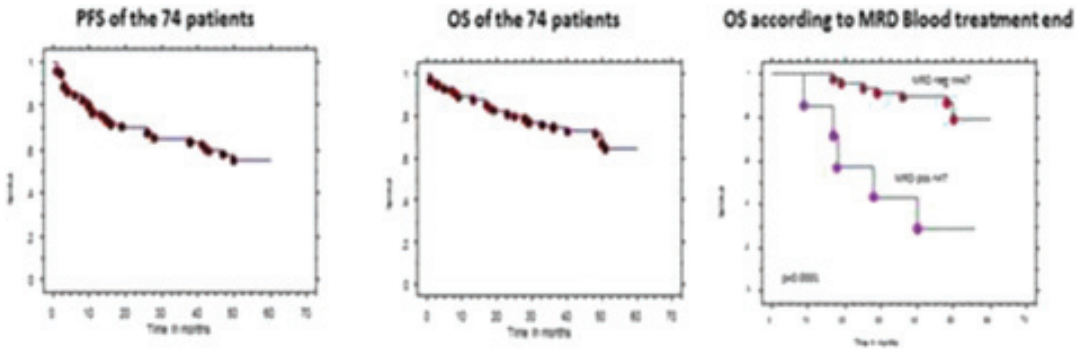
Introduction: Eight R-CHOP21 cycles followed by rituximab maintenance is considered as the standard first-line treatment for elderly mantle cell lymphoma (MCL) patients. Complete response (CR) and undetectable minimal residual disease (uMRD) rates remain sub-optimal with tR-CHOP regimen (CR rate 30-35%, MR after 8 cycles 67%) and this translates to shorter response duration. Recently VR-CAP, integrating bortezomib to RCHOP has proved superiority to both R-CHOP and the R-BAC regimen (rituximab bendamustine cytarabine) has given also promising results. In this setting, we have explored the association rituximab-bendamustine-bortezomib and dexamethasone in the RiBVD regimen.

Methods: In this prospective phase II study, all patients >65 years old with newly-diagnosed MCL were treated by the RiBVD regimen (inclusion criteria: AA stage II-IV, PS < 3, no active HIV, HBV or HCV infections, no renal or cardiac dysfunction, no diabetes). RiBVD was administered every 4 weeks: rituximab, 375 mg/m^2 IV on day(D)1; bendamustine at 90 mg/m^2 IV on D1 and D2; dexamethasone 40 mg IV on D2 and bortezomib1.3 mg/m^2 subcutaneously on D1, 4, 8 and 11. Patients received a total of 6 cycles, if they responded (IWG criteria) after 4 cycles. No maintenance was delivered. MRD was centrally evaluated by RQ-PCR using patient specific IGH VDJ targets, and the FDG-PET response was evaluated visually according to Deauville criteria. The primary objective was to prolong PFS by 6 months (m) compared to the 18 m PFS reported for R-CHOP21. In order to define superiority of the RiBVD, PFS > 65% (H1) was required at 18 m. Treatment failure was considered if PFS at 18 m was 50%. With alpha and beta risks of 5% and 20%, respectively, 69 patients needed to be enrolled. Secondary objectives were to evaluate toxicity, known prognostic indices, response FDG-PET imaging and MRD.

Results: Seventy four patients were enrolled; 80% (*n* = 58) had high MIPI score. ORR and CR were 84% (*n* = 62/74) and 75% (*n* = 56/74), respectively. After 6 cycles, 78% (*n* = 46/59) were FDG-PET negative; 87% (47/54) and 76% (35/46) had uMRD in blood (PB) and bone marrow (BM), respectively. With a median follow-up of 52 m the primary objective was reached (24 m PFS = 70%). Four years OS was 86.6% for uMRD patients at the end of treatment, compared to 28.6%, detectable MRD patients; $p < 0.0001$). Neither the MIPI score nor FDG-PET responses were predictive of OS. Toxicities were mainly hematologic with grade 3/4 neutropenia in 51% and thrombopenia in 36%. The principal grade 3/4 extra-hematologic toxicities were fatigue (19%), neuropathy (14%), cardiac (7%) or febrile neutropenia (5%).

Conclusion: The RiBVD regimen is active and well tolerated in MCL patients who are unable or unwilling to receive dose intensive therapy including high risk patients.



IBRUTINIB-RITUXIMAB FOLLOWED BY REDUCED CHEMO-IMMUNOTHERAPY CONSOLIDATION IN YOUNG, NEWLY DIAGNOSED MANTLE CELL LYMPHOMA PATIENTS: A WINDOW OF OPPORTUNITY TO REDUCE CHEMO

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Introduction: The ibrutinib–rituximab combination produced durable responses in 88% of relapsed/refractory mantle cell lymphoma (MCL) patients, providing a "Window" of opportunity to use chemotherapy-free induction with ibrutinib-rituximab followed by fewer cycles of chemo-immunotherapy in young, fit patients with newly diagnosed MCL.

Methods: Enrollment began in June 2015 for a Phase II single-center clinical trial consisting of a chemotherapy-free phase of ibrutinib-rituximab treatment (Part 1) until best response, followed by a shortened intense chemo-immunotherapy course (Part 2) among newly diagnosed MCL patients of ≤65 years. We previously presented the initial results of this trial with ibrutinib-rituximab and consolidation (Wang et al., ASH 2016). Here, we report updated data with a longer follow-up duration. The primary objective was to evaluate the response rate. Ibrutinib is dosed at 560 mg orally, daily, continuously. Rituximab is dosed at 375 mg/m^2 IV weekly x 4 during cycle 1 (28 days cycle), then day 1 of cycles 3-12. Intense

chemo-immunotherapy consists of rituximab plus cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD); alternating every 28 days with rituximab plus high-dose methotrexate-Ara C. If in complete remission (CR) after ibrutinib-rituximab treatment, only 4 cycles of intense chemo-immunotherapy are given. If the patient is in partial response or progression, and if responding to intensive chemo-immunotherapy, a total of 2 cycles of chemo-immunotherapy therapy are administered beyond achievement of CR.

Results: As of March 3, 2017, 50 patients were evaluable for response. Of the evaluable patients, overall response rate (ORR) to chemotherapy-free therapy alone was **100**% (50), with CR in 80% (40) and PR in 20% (10). Thirty-three (33) patients have completed both Parts 1 and 2 and all have achieved CR (i.e., ORR =100%). In Part 1, the most common grade 1-2 non-haematological (non-heme) adverse effects (AEs) were fatigue (50), diarrhea (28), rash (29), myalgia (41), oral mucositis (52), peripheral neuropathy (19), nausea (25), blurred vision (19), edema (23), constipation (18), dry eyes (18), and dizziness (22). Grade 3 non-heme AEs included fatigue (4), nausea (2), infection (3) and dyspnea (2). No grade 4-5 non-heme toxicities were observed in Part 1. Grade 3-4 heme AEs included lymphocytosis (22), thrombocytopenia (13) and leukopenia (15).

Conclusions: These updated data indicate that ibrutinib-rituximab induction in newly diagnosed, young MCL patients was efficacious and well-tolerated, providing a window of opportunity for less chemo-immunotherapy needed for consolidation.

Table 1. Response rates from the Window Study: a phase II clinical trial.

Response	Chemo-free induction (Part 1), N=50	Chemo-immune consolidation (Part 2), N=33
CR	40 (80%)	33 (100%)
PR	10 (20%)	0 (0%)
ORR	**50 (100%)**	**33 (100%)**

IBRUTINIB VS TEMSIROLIMUS: THREE-YEAR FOLLOW-UP OF PATIENTS WITH PREVIOUSLY TREATED MANTLE CELL LYMPHOMA FROM THE PHASE 3, INTERNATIONAL, RANDOMIZED, OPEN-LABEL RAY STUDY

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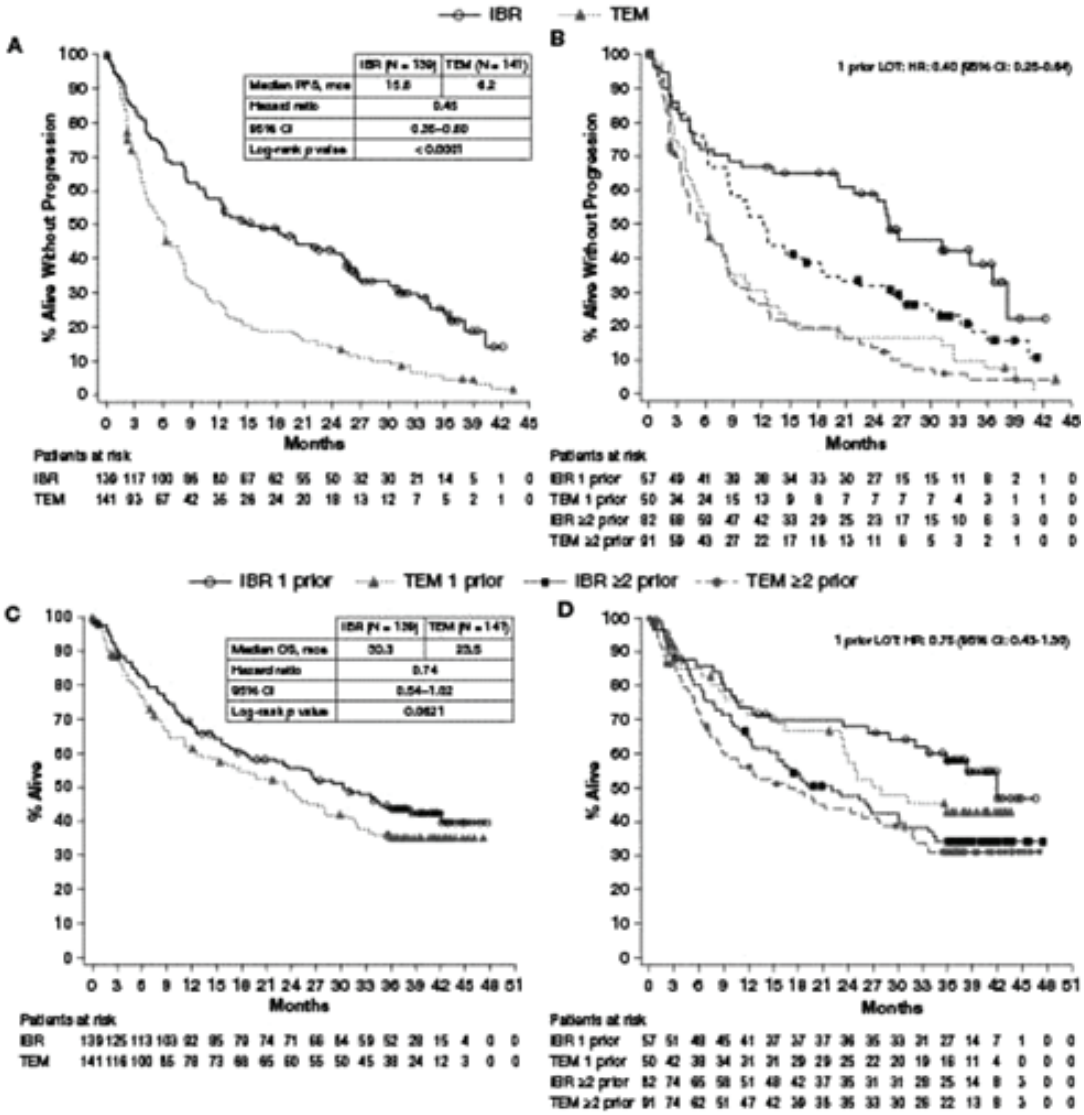
Introduction: Ibrutinib (IBR), a first-in-class, once-daily, oral, covalent inhibitor of Bruton's tyrosine kinase, is highly active in relapsed/refractory (R/R) MCL. The phase 3, randomized, open-label RAY study compared IBR with temsirolimus (TEM) in patients (pts) with R/R MCL and ≥1 prior rituximab-containing therapy. At median 20.0 month follow-up, IBR was superior to TEM for independent review committee-assessed progression-free survival (PFS) (HR: 0·43; 95% CI: 0·32-0·58; $p < 0.0001$) (Dreyling et al. Lancet 2016). Here, we present 3-year follow-up results (end of study).

Methods: 280 pts were randomized 1:1 to oral IBR (560 mg once-daily; $n = 139$) or IV TEM (175 mg: days 1, 8, 15 of C1; 75 mg: days 1, 8, 15 of subsequent cycles; $n = 141$) until disease progression/unacceptable toxicity. Long-term efficacy was investigator-assessed.

Results: At a median follow-up of 39 months (mos) for IBR and TEM, respectively, median PFS was 15.6 mos vs 6.2 mos (HR [95% CI], 0.45 [0.35-0.60]; $p < 0.0001$) (Figure 1A); median PFS for pts with only 1 prior line of therapy (LOT) was 25.4 mos (IBR) vs 6.2 mos (TEM) (HR: 0.40; 95% CI: 0.25-0.64) (Figure 1B). Overall response rate (ORR) was 77.0% (IBR) vs 46.8% (TEM); CR rate was 23.0% vs 2.8% ($p < 0.0001$). ORR for pts with 1 prior LOT was 75.4% (IBR) vs 52.0% (TEM); CR rate was 33.3% vs 4.0%. Median duration of response was 23.1 mos (IBR) vs 6.3 mos (TEM). Median time to next treatment was 31.8 mos (IBR) vs 11.6 mos (TEM) (HR [95% CI], 0.33 [0.24-0.46]; $p < 0.0001$). PFS2 was 26.2 mos (IBR) vs 15.4 mos (TEM) (HR [95% CI], 0.67 [0.50-0.90]; $p < 0.0079$). With 39% of pts randomized to TEM crossing over to IBR, median overall survival (OS) was 30.3 mos (IBR) vs 23.5 mos (TEM) (HR: 0.74; 95% CI: 0.54-1.02; $p = 0.0621$) (Figure 1C); median OS for pts with 1 prior LOT was 42.0 mos (IBR) vs 27.0 mos (TEM) (HR: 0.75; 95% CI: 0.43-1.30) (Figure 1D). Median treatment duration was 14.4 mos (IBR) vs 3.0 mos (TEM), with 24% of IBR pts and 0 TEM pts on treatment at study end. Despite differences in exposure, overall frequency of adverse events (AEs) was lower with IBR vs TEM. AEs leading to treatment discontinuation: 17.3% (IBR) vs 31.7% (TEM). Most common treatment-emergent AEs: diarrhea, fatigue, cough (IBR) and thrombocytopenia, anemia, diarrhea (TEM). Grade ≥ 3 AEs: 74.8% (IBR) and 87.1% (TEM). Serious AEs: 56.8% (IBR) and 59.7% (TEM).

Conclusions: RAY study 3-year follow-up results are consistent with primary analysis, showing clinically meaningful, statistically significant improvement of PFS for IBR vs TEM, with a strong trend in OS favoring IBR, despite nearly 40% crossover. Pts who had received IBR after only 1 prior LOT had the most durable and best PFS and OS outcomes, supporting earlier use of IBR in R/R MCL. Significantly longer PFS2 for IBR suggests treatment benefit is maintained after next LOT. No new safety signals were observed. Despite longer exposure, IBR pts experienced fewer grade 3/4 AEs and treatment discontinuations due to AEs.

Figure 1. PFS (A) and PFS by line of therapy (B) and OS (C) and OS by line of therapy (D).



COMBINATION IBRUTINIB (IBR) AND VENETOCLAX (VEN) FOR THE TREATMENT OF MANTLE CELL LYMPHOMA (MCL): PRIMARY ENDPOINT ASSESSMENT OF THE PHASE 2 AIM STUDY

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Background: Both ibr and ven have activity in relapsed/refractory (R/R) MCL, but complete remissions (CR) are attained in <25% with either. We sought to determine the activity of the combination in an investigator-initiated, phase 2 study.

Methods: Enrolment of 24 patients (pts) with R/R (*n* = 23) or frontline (*n* = 1) MCL completed in 09/16. Pts received 4 weeks of ibr (560 mg/d), followed by introduction of ven (weekly ramp-up to target 400 mg/d). The primary endpoint was CR rate at week 16, as assessed by PET/CT, BMAT, flow & molecular MRD, and endoscopy (if baseline gut involvement). Response was calculated separately with and without knowledge of the PET result by IWG criteria (Cheson JCO 2007), in order to compare with published studies (ibr, 9% CR at wk16; ven, best CR rate 21%).

Results: Median age of pts was 68 (range, 47-81) years. For the R/R pts (*n* = 23), median lines of prior therapy was 2 (1-6), 48% were refractory to last treatment, and 30% had failed previous autologous SCT. As of data cutoff on Jan 11 2017, 18 pts remain on therapy, and 6 stopped treatment due to progressive disease (4), adverse event (1) or unrelated death (1). At week 16, ORR was 71% (63% CR) and 80% of complete responders were flow-cytometry negative in the marrow (sensitivity 10^{-3} to 10^{-4}). Using CT without PET, the comparison responses were CR 42%, CRu 17%, PR 17% (ORR 78%). After a median follow-up of 8.3 (range 1.4-17.7) months, the 8-month estimates of PFS and OS months are 74% and 81%. Adverse events ≥20%, irrespective of attribution, were fatigue (71%), diarrhea (67%), nausea (50%), URTI (38%), gastro-esophageal reflux (33%), neutropenia (33%), cough (25%) and bruising (21%); with the exception of neutropenia (25% grade 3-4), these were predominantly grade 1-2 in severity. Tumour lysis syndrome occurred in 2 pts with high tumour burden, leading to revision of the protocol ven starting dose from 50 mg, to 20 mg/d.

Conclusion: The combination of ibr and ven was tolerable and achieved CR rate of 63% at week 16 in pts with MCL. The efficacy results compare favorably with historical results, and warrant further phase III investigation.

T-Cell Lymphoma

Abstracts Selected by Dr Christopher Fox

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

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More than 20 Peripheral T-cell lymphoma (PTCL) entities are recognized in the WHO classification. Their prognosis is usually very poor and their diagnosis is often challenging for pathologists. Up to 30% of cases thus remain not classifiable (PTCL Not Otherwise Specified, NOS) and there is an important need for alternative diagnostic strategies. Here, we developed a parsimonious GEP assay applicable to a routine diagnostic workflow to differentiate the main PTCL entities and characterize the heterogeneity of PTCL-NOS.

A Reverse Transcriptase-Multiplex Ligation dependant Probe Amplification (RT-MLPA) assay was designed to evaluate the expression of 20 markers. It simultaneously addresses the expression of 18 genes routinely tested by immunohistochemistry (IHC) or selected from GEP studies. It also assesses the EBV infection status (*EBER1*) and the presence of *RHOA*G17 V and *IDH2*R172K/T mutations.

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

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

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

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

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

Results: From March 2012 to November 2016, 87 patients were accrued from 47 sites (U.K. n = 46, Australia n = 1). The trial profile is shown in Figure 1. On 22.11.2016 the independent data monitoring committee recommended the trial should close early as the primary endpoint would not be met. Baseline characteristics are shown in Table 1. EOT response is currently evaluable for n = 72, CR/CRu Arm A = 57.1% and Arm B = 43.2% (p = 0.24). Overall rates of grade ≥ 3 toxicity were similar between arms, 67.0% vs 73.0% (p = 0.64); however more ≥3 grade neutropenia (p = 0.036) and febrile neutropenia (p = 0.03) were seen in Arm A; while Arm B had more ≥3 grade thrombocytopenia (p = 0.03). At a median follow-up of 18.1 months, there was no difference in 2-yr overall survival (Arm A = 53.1%, Arm B = 64.7%, p = 0.56) or progression-free survival (Arm A = 36.0%, Arm B = 39.0%, p = 0.81).

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

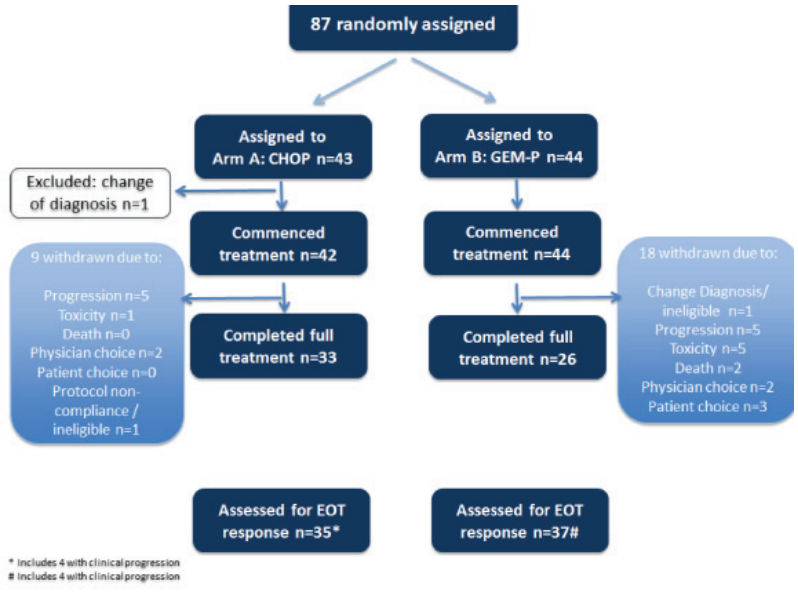

Figure 1: Trial profile

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

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

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

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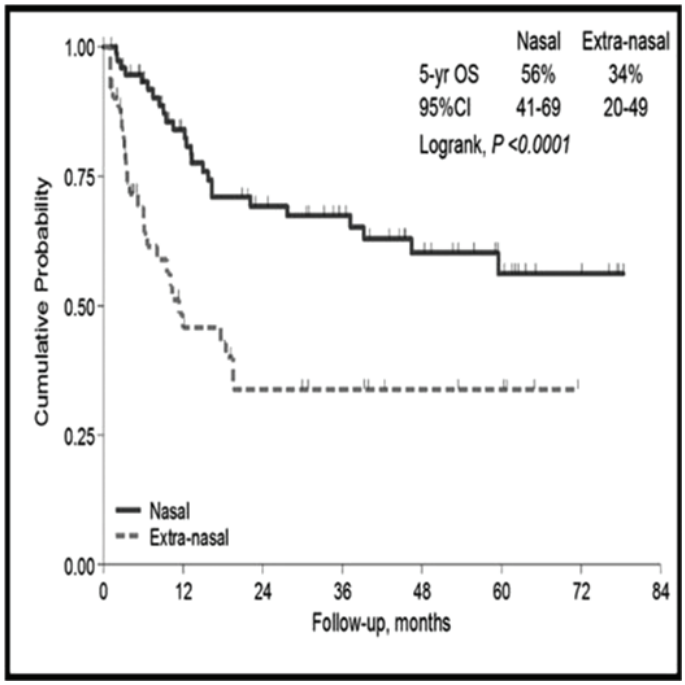
Introduction: Extra-nodal NK/T cell lymphoma (NKTCL) is a distinct clinicopathological entity characterised by a cytotoxic T or NK cell phenotype and invariable Epstein Barr virus (EBV) infection of the malignant clone. An invasive nasal and upper aero-digestive mass is the dominant clinical presentation,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

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

Result: From a total of 1,369 evaluable PTCL cases, 140 (10.2%) were confirmed as NKTCL following international histopathologic panel review. As anticipated, NKTCL cases, as a proportion of all PTCL cases, varied across geographical regions (Asia 28%, South America 9.3%, U.S.A 7.6%, Europe 6.4%). The median age at diagnosis was 52.5 years with a male predominance (66%). Stage III/IV disease was seen in 39% patients, whilst bulky disease >5 cm (7.4%) and BM involvement (9.8%) were uncommon. Data on therapy was available in 111 (79%) patients, of whom 103 (93%) received chemotherapy (CHT) as part of first-line treatment. Sixty-four patients (58%) additionally received concurrent or sequential radiotherapy (RT), whilst 13 patients (11.7%) underwent high-dose therapy as consolidation. Five patients (4.5%) underwent RT only, whilst 3 (2.7%) received palliative care only. Of 103 patients treated with chemotherapy, 41 (40%) received anthracycline-containing regimens whilst 36 (35%) received L-asparaginase-based schedules. With a median follow-up of 39 months, the median PFS for (*n* = 139) NKTCL patients was 33 months (95%CI 7-58) with marked delineation for nasal and extra-nasal cases; 72 months (95%CI 27-118) and 10 months (95%CI 1-20) respectively. For the whole cohort (*n* = 140) the median OS was 46 months, translating to a 5-yr OS of 56% and 34% for nasal and extra-nasal cases respectively (*p < 0.0001*, *Figure*). Cause of death was most commonly attributable to lymphoma (61%) and infection (15%).

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



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

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

Methods: Patients who were newly diagnosed as ENKTL in stageI-IV from 18 to 80 years with ECOG PS of 0 ~ 3 were eligible for enrollment. GAD-M regimen (gemcitabine 1000 mg/m^2; ivdrip, d1, d8, PEG-aspargase 2500 U/m^2; im. d1, dexamethasone 20 mg, ivdrip. d1-3, Methotrexate 3000 mg/ m^2; civ 12-hour, d1) was planned as the protocol treatment. The regimen was repeated every three weeks. For stage I/II patients, 2-4 cycles of GAD-M regimen followed by EIFRT and additional 4-2 cycles. For stage III/IV, GAD-M regimens were repeated for six cycles. The primary endpoint was overall response rate (ORR) after six cycles of GAD-M. Secondary endpoints were 3-year progression-free survival(PFS), 3-year overall survival(OS), and toxicity. Response was assessed using the revised International Workshop Criteria. Toxicity was graded according to the Common Terminology Criteria for Adverse Events v4.0.

Results: 41 patients were enrolled from Oct 2013 to Aug 2015. 36 patients were evaluable for response. The baseline clinical characteristics were as follows: the median age, 45 years (range: 18-75 years); >60 years, 13.5%; female, 30.6%; ECOG PS >1, 13.9%; stageI/II, 86.1%; elevated LDH, 27.8%. After 2 cycles of GAD-M, ORR in all and stageI/II were 94.4% (34/36) and 100% (31/31), respectively. CR rate were 50% (18/36) and 54.8% (17/31), respectively. After 6 cycles ORR in all and stageI/II were still 94.4% (34/36) and 100%(31/36), respectively. CR rate increased to 83.3% (30/36) and 90.32% (28/31), respectively. At median follow-up of 23.3 months, 3-year PFS was 72.1% (Figure 1A), 3-year OS was 76.3% (Figure 1B). According to the stage, 3-year PFS for stage I/II and III/IV were 77.3% and 40.0%, respectively. 3-year OS were 79.3% and 60.0%, respectively. The most common hematologic adverse event of grade 3/4 was anemia (52.8%). The major non hematologic side effects were hypoalbuminemia (100%), increased transaminases (88.9%) and hyperbilirubinaemia (52.8%). Although grade 1/2 nonhematologic toxicities were frequent during GAD-M treatment. Grade 3/4 toxicities were few. One patients died of treatment related toxicity, who was 61-year-old man died of electrolyte disorders caused by severe vomiting. Other patients didn't suffer from this adverse event.

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

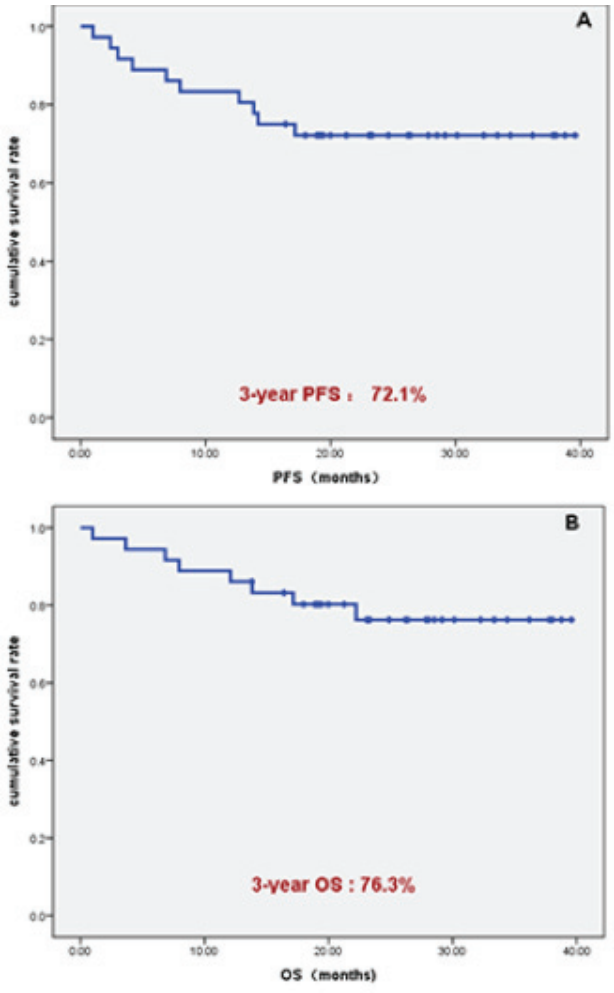

Figure 1: The survival curves of PFS and OS.

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

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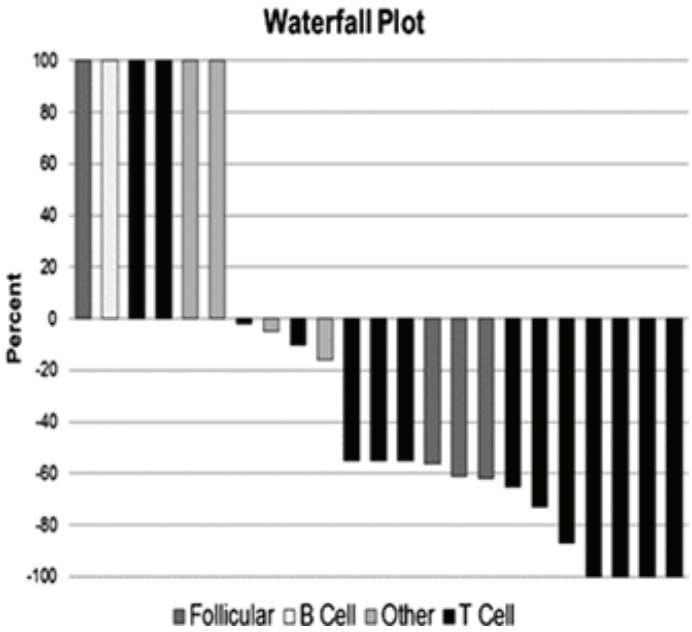
Introduction: PTCL is a heterogeneous group of lymphomas in which only 25% of patients experience long-term survival. As a single agent in the relapsed setting romidepsin (R) and pralatrexate (P) have response rates of 25-38% and 29-54% respectively across phase I/II studies. Preclinical studies of P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

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

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

Conclusions: Results from the phase I study established that the combination of P + R given on the D1, 15 Q28D schedule is safe and well tolerated. These data support the lineage specific activity of the P + R combination with a 71% ORR in PTCL. A multicenter Phase II study of P + R is now enrolling patients with PTCL.



Diffuse Large B Cell Lymphoma

Abstracts Selected by Dr Andrew McMillan

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

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

Methods: Tazemetostat 800 mg is administered po BID. Tumour tissue is analysed prospectively to guide cohort assignment based on EZH2 hot spot activating mutations (Y646X, A682G, A692V) using a **cobas**® EZH2 Mutation Test (Roche Molecular Systems, in development). A 62-gene panel is used to assess tissue DNA and circulating tumour DNA (ctDNA) for biomarkers of tazemetostat sensitivity. Key inclusion criteria include: ≥18 yrs old; ≥2 prior treatment regimens; measurable disease; and adequate organ function. The primary endpoint is overall response rate (ORR). Secondary endpoints include progression-free survival and safety/tolerability. Enrolment for monotherapy has been completed in 3 cohorts with wt EZH2 and is ongoing in 2 cohorts of mutant EZH2. Enrolment for a tazemetostat combination with prednisolone in wt EZH2 DLBCL was recently initiated.

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

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

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

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

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

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

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

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

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

Conclusions: Pola at 1.8 mg/kg in combination with R-CHP in 1 L DLBCL has an acceptable safety profile and produced promising response rates at the end of treatment. The majority of the patients in this trial represented a poor prognosis group by age and IPI. In this context, treatment response to this regimen may warrant further exploration.

R-CHOP +/-RADIOTHERAPY IN NON-BULKY LIMITED-STAGE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): FINAL RESULTS OF THE PROSPECTIVE RANDOMIZED PHASE III 02-03 TRIAL FROM THE LYSA/GOELAMS

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Introduction: The benefit of radiotherapy (RT) following chemotherapy in limited-stage diffuse large B-cell lymphoma (DLBCL) remains controversial. Before the Rituximab (R) era, randomized trials have reported conflicting results. We conducted a randomized trial in patients with non-bulky (tumor size <7 cm) limited-stage DLBCL to evaluate the benefit of RT following R-CHOP.

Methods: Patients were stratified according to the Miller modified IPI (mIPI) including LDH (normal/elevated), ECOG performance status (0-1/2-3), age (<60/>60 yrs) and disease stage (I/II). The patients received 4 or 6 consecutive cycles of R-CHOP delivered every two weeks, followed or not by RT at 40 Gy delivered 4 weeks after the last R-CHOP cycle. All patients were evaluated by FDG-PETs performed at baseline, after 4 R-CHOP cycles and at the end of treatment. The primary objective of the trial was event-free survival (EFS) from randomization.

Results: The trial randomized 165 patients in the R-CHOP arm and 169 in the R-CHOP + RT arm. Response assessment was performed after the fourth cycle of R-CHOP based on clinical examination, CT-scan and PET. CR was observed in 281 patients (88%) and PR in 38 (12%), without any difference between the two arms. R-CHOP cycles 5 and 6 were delivered to 123 and 118 patients respectively (61/57 in the R-CHOP arm and 62/61 in the R-CHOP + RT arm). According to initial randomization, among the 281 patients in CR following R-CHOP, 144 received RT and 137 did not receive any further treatment. Eight patients declined RT for personal reasons. 27 out of the 38 partial responders received 2 additional cycles of R-CHOP and RT, 5 received 2 additional R-CHOP cycles without RT, and 3 were delivered high dose chemotherapy: complete response was finally documented in 28 cases and the 10 remaining patients were still considered in PR. In an intent to treat analysis, with a median follow-up of 64 months, five-year EFS was not statistically different between the two arms, with 89% ± 2.9 in the R-CHOP arm vs 92% ± 2.4 in the R-CHOP + RT arm (HR 0.61, 95%CI 0.3 to 1.2, $p = 0.18$). Five-year overall survival was also not different at 92% (95% CI: 89.5-94.5) for patients assigned to R-CHOP alone, and 96% (95% CI: 94.3-97.7) for those assigned to R-CHOP + RT, (p = ns).

Conclusion: R-CHOP alone is not inferior to R-CHOP14 followed by RT in patients with non-bulky limited-stage DLBCL. We recommend that these selected patients who reach complete remission based on PET evaluation after 4 or 6 R-CHOP cycles should be spared additional RT, thus avoiding long-term radiation-related toxicity. (ClinicalTrials.gov number, NCT00841945).

RADIOTHERAPY TO BULKY DISEASE PET-NEGATIVE AFTER IMMUNOCHEMOTHERAPY CAN BE SPARED IN ELDERLY DLBCL PATIENTS: RESULTS OF A PLANNED INTERIM ANALYSIS OF THE FIRST 187 PATIENTS WITH BULKY DISEASE TREATED IN THE OPTIMAL > 60 STUDY OF THE DSHNHL

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Background: Radiotherapy (RT) to bulky sites improves outcome of elderly DLBCL patients [Pfreundschuh et al., Lancet Oncol 2008; 9: 105-116; Held et al., J Clin Oncol 2014; 32:112-1118]. Whether RT can be spared in patients with a PET-negative bulk after R-CHOP was prospectively addressed in OPTIMAL >60. To assure that patients with bulky disease were not put at risk by this PET-based omission of radiotherapy, a planned interim analysis was performed.

Patients and Methods: 61 to 80 y-old pts. with untreated DLBCL were randomized to 6xCHOP-14 or 6xCHLIP-14 (liposomal instead of conventional vincristine, 2 mg/m^2 [uncapped]) plus 8 x rituximab 375 mg/m^2 (R) q 2 wks. or 12xR (days -4, -1,1,4,14,28,42,56,91,126,175, 238). Pts. with bulk (> = 7.5 cm) that remained PET-positive after chemotherapy were assigned to RT (39.6 Gy), while PET-negative bulks were observed.

Results: 187/505 (37%) had bulky disease and were compared to 117/306 (38%) RICOVER-60 pts. (38%) who had received 6xCHOP-14 + 8R. OPTIMAL > 60 pts. were older (70 vs. 68 years) and had more IPI = 3 (33% vs. 29%) and IPI = 4,5 (34% vs. 23%) compared to RICOVER-60. PET was performed in 166/187 OPTIMAL > 60 bulk pts. (reasons for no PET: early death: 5; excessive toxicity: 3; protocol violation: 1, non-compliance: 4, change of diagnosis: 6, others: 2). 80/166 (48%) bulks remained PET-positive and 62/80 (78%) were irradiated (reasons for no RT: progression: 8; medical reasons: 9; negative biopsy: 1), reducing RT from 67/117 (57%) in RICOVER-60 by 42% to 62/187 (33%) in OPTIMAL > 60. Despite the unfavorable demographics, outcome of the 187 bulk pts. in OPTIMAL > 60 was non-inferior to RICOVER-60 in an intention-to-treat analysis, not even in the least intensive of the 4 OPTIMAL > 60 treatment arms consisting of 47 pts. who received 6xCHOP-14 + 8R. 2-year PFS and OS in OPTIMAL > 60 was 79% and 88%, respectively, compared to 75% and 78% of the 117 RICOVER-60 pts. In a multivariable analysis adjusting for the IPI risk factors, the hazard ratio of the OPTIMAL > 60 compared to the RICOVER-60 bulk pts. was 0.7 (95% CI: 0.3; 1.5; p = 0.345) for PFS and 0.5 (95% CI: 0.2; 1.3; p = 0.154;p = 0.154) for OS.

Conclusion: Radiotherapy can be spared in PET-negative bulks, resulting in a 42% reduction of patients who receive radiotherapy without compromising the outcome of these patients. *Supported by Amgen, Roche, Spectrum.*

DIFFERENTIAL EFFICACY OF BORTEZOMIB IN SUBTYPES OF DIFFUSE LARGE B-CELL LYMPHOMA (DLBL): A PROSPECTIVE RANDOMISED STUDY STRATIFIED BY TRANSCRIPTOME PROFILING: REMODL-B

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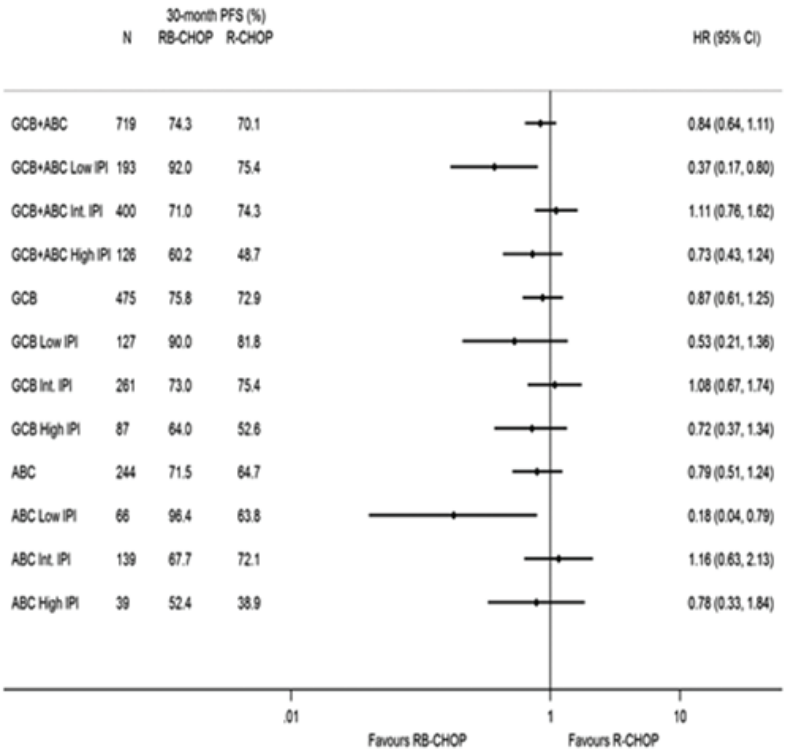
Background: DLBL subtypes identified by patterns of gene expression correspond to germinal center (GCB) or activated (ABC) B-cells like. The latter demonstrate dysregulation of the NF-KB pathway. Outcomes of treatment with R-CHOP are inferior for ABC DLBL in retrospective series. This study investigated whether adding bortezomib (B), a putative NF-KB inhibitor, can reverse this phenotype.

Methods: The REMoDL-B study was a collaboration between the UK NCRI group and the SAKK. Patients (pts) newly diagnosed with DLBL commenced conventional R-CHOP. During the first cycle, whole transcriptome expression profiling (GEP) was performed on formalin-fixed paraffin-embedded tissue by Illumina DASL array. Pts with successful GEP were randomised (1:1) to continue R-CHOP +/- bortezomib (1.3 mg/m2 IV or 1.6 mg/m2 SC) days 1 + 8 for cycles 2-6. The primary endpoint was progression-free survival for the GCB + ABC population; the study was powered for a 10% benefit in PFS from bortezomib.

Results: Between 6/2011 and 5/2015, 1076 eligible pts were registered. Median age was 64 yrs (20-86); Stage I 2.9%; II 27.5%; III 30.8% and IV 38.8%. The distribution of IPI scores: Low, 25.7%; low int 25.9%; high int. 30.6%, high 17.8%. There was no difference in baseline demographics between arms. Cell of origin results were: GCB *n* = 475 (44.1%); ABC *n* = 244 (22.7%); unclassified (U) *n* = 199 (18.5%); no profile *n* = 158 (14.6%). Mutational frequency of *MYD88, PRDM1, CD79B* was higher in ABC, whilst mutations in *CREBBP, EZH2, DDX3X, FAS* and *KMT2D* were more frequent in GCB. ABC pts were older (median age ABC 67 yrs; GCB 63 yrs; U 63 yrs; $P < 0.005$). Bulk was more common in the GCB (GCB 33.8%; ABC 20.7%; U 27.8%; $P < 0.001$). RB-CHOP was not associated with increased haematological toxicity; Grade ≥ 2 neuropathy occurred in 20.7% RB-CHOP *vs* 12.5% R-CHOP pts.

There was no difference in PFS in the combined GCB + ABC population between RB-CHOP and R-CHOP; HR = 0.84; $P = 0.225$. PFS at 30 months (PFS30) was 74.3% and 70.1% respectively. Bortezomib did not significantly affect PFS in either the GCB pts HR = 0.87;$P = 0.458$ (PFS30 75.8% vs 72.9%) or ABC pts HR = 0.79; $P = 0.309$ (PFS30 71.5% vs 64.7%). However, pts with low IPI had a significantly better PFS when bortezomib was added to R-CHOP, HR = 0.37; $P = 0.012$. This benefit was seen only in the ABC group. There was no difference in overall survival between arms HR = 0.85 (0.59-1.23); $P = 0.397$. Retrospective application of a Burkitt-like (BL) molecular classifier identified a group of GCB pts (17%) with particularly poor prognosis. BL pts had a higher mutational burden than other GCB with an excess of c-*MYC* rearrangements or extra copies (44/61 available). There was a trend towards improved PFS in BL pts treated with bortezomib (HR = 0.56; $P = 0.069$).

Conclusion: The addition of bortezomib to R-CHOP chemotherapy in DLBL may result in PFS benefit in sub-groups of patients defined by molecular phenotyping. Cancer Research UK E/10/024.



PROGNOSTIC IMPACT OF BCL2 AND MYC EXPRESSION AND TRANSLOCATION IN UNTREATED DLBCL: RESULTS FROM THE PHASE III GOYA STUDY

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Introduction: DLBCL pts with tumours co-expressing BCL2 and MYC (dual-expressor, DE) or with dual gene translocations (double-hit, DH) have poor outcomes but prognostic relationships between cell-of-origin (COO) subtype (ABC vs GCB) and BCL2/MYC are unclear. We report predefined exploratory analyses of the prognostic effects of BCL2 positivity (+), MYC+, DE and DH, in relation to COO, in the Phase III GOYA study (NCT01287741).

Methods: Pts with previously untreated DLBCL were randomised 1:1 to receive obinutuzumab or rituximab plus 6 or 8 cycles of CHOP. Using a Ventana investigational-use IHC assay (BCL2 antibody clone, 124; c-MYC, Y69), pretreatment tumour samples were analysed at a central laboratory. Samples stained within the limit of BCL2 (≤4 months, 30°C) and MYC (≤12 months, 30°C) antigen stability were included in primary analyses; sensitivity analyses included all samples. Scoring algorithm incorporated % of tumour cells stained and intensity: BCL2 IHC+, moderate/strong in ≥50% of tumour cells; MYC IHC+, ≥40% of tumour cells. Vysis LSI Dual Color Break Apart FISH Probes identified BCL2 and MYC translocations: FISH+, ≥50%. COO classification of RNA extracts used a NanoString Lymphoma Subtyping gene expression assay. Univariate Cox regression analysis of investigator-assessed PFS was performed. Covariates for multivariate analysis were treatment arm (Tx), IPI score, no. of CHOP cycles and COO.

Results: Baseline characteristics, including IPI score, were similar for biomarker evaluable and ITT populations. Prevalence of BCL2 IHC+, MYC IHC+, DE and DH was 49%, 83%, 42% and 3.6%, respectively. Prevalence by COO: BCL2 IHC+, 75% in ABC and 38% in GCB; MYC IHC+, 95% in ABC and 76% in GCB; DE, 72% in ABC and 29% in GCB; DH, 7% in GCB and 0% in ABC (19/20 DH pts were GCB; 1 unclassified). In univariate analysis, BCL2 IHC+, DE and DH were associated with poorer prognosis (Table). Multivariate analysis confirm the poor prognosis of BCL2 IHC+ pts, independent of Tx, IPI score, no. of CHOP cycles and COO. Context-dependent effects of MYC IHC+ suggest an association with poorer prognosis in BCL2 IHC- pts while BCL2 IHC+ pts drive a suggested prognostic effect in DE pts (Figure). Poor prognosis of DH pts was independent of Tx, IPI score and no. of CHOP cycles, but no. of pts was low.

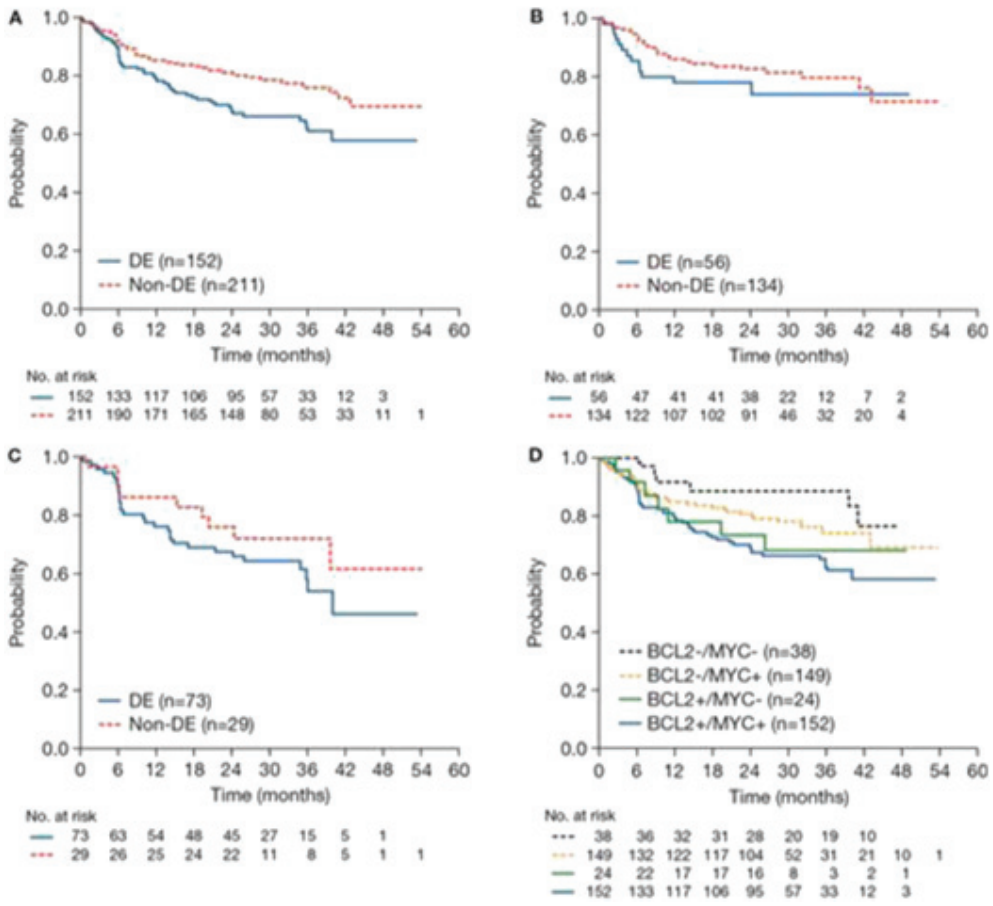
Conclusions: Robust identification and analysis of biomarker subgroups confirm the prognostic importance of DH and BCL2 IHC+, and demonstrate that the prognostic effect of BCL2 IHC+ is independent of COO in DLBCL pts in the GOYA study.

Table 1. Prognostic effect of key biomarkers in pts with previously untreated de novo DLBCL*

Biomarker	Status (no. of pts, events)	3-year PFS, % (95% CI)	Univariate analysis HR (95% CI)	Multivariate analysis† HR (95% CI)
BCL2 IHC (N=366)	Positive (178; 61) Negative (188; 40)	63 (55–71) 78 (70–84)	1.77(1.19–2.64)	1.72(1.05–2.82)
MYC IHC (N=373)	Positive (309; 90) Negative (64; 13)	68 (62–74) 81 (69–89)	1.60(0.89–2.86)	1.24(0.65–2.36)
BCL2/MYC IHC (N=363)	DE (152; 53) Non-DE (211; 47)	63 (54–71) 76 (69–82)	1.69(1.14–2.51)	1.44(0.88–2.35)
BCL2/MYC FISH (N=560)	DH (20; 8) Non-DH (540; 135)	55 (29–75) 73 (68–77)	2.16(1.06–4.42)	2.11(1.03–4.32)

*Samples from pts in the 2 treatment arms were pooled for these analyses. HR compares positive vs negative for BCL2 IHC and MYC IHC, DE vs non-DE for BCL2/MYC IHC and DH vs non-DH for *BCL2/MYC* FISH.†Multivariate model with treatment arm, IPI score, planned number of CHOP cycles and COO subtype (ABC or GCB) as covariates for each biomarker, except for *BCL2/MYC* FISH where COO was not included as a covariate (note that no DH patients had ABC subtype). Patients who did not have COO information available or had unclassified COO subtype were excluded from multivariate analyses. Multivariate analysis populations were: BCL2 IHC (N=293: positive, 148; negative, 145; ABC, 102; GCB, 191), MYC IHC (N=298: positive, 245; negative, 53; ABC, 102; GCB, 196), BCL2/MYC IHC (N=292: DE, 129; non-DE, 163; ABC, 102; GCB, 190).

Figure. Kaplan-Meier curves of investigator-assessed PFS according to biomarker status in the following subgroups: comparison of DE vs non-DE pts in the A) total (N=363), B) GCB (N=190) and C) ABC (N=102) populations, and comparison of BCL2 IHC+/- vs MYC IHC+/- pts in the D) total (N=363) population



CAR - T Cell Therapy Update & Other Immunotherapies

Abstracts Selected by Professor Karl Peggs

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

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

Methods: Results of a planned interim analysis of a single-arm, open-label, multicenter, global phase 2 trial of CTL019 in pts ≥ 18 y with R/R DLBCL (JULIET;NCT02445248) are reported. Industry-manufactured CAR T cells were provided to pts at 27 centers on 4 continents using a global supply chain. Pts had received ≥2 lines of chemotherapy and had disease progression after or were ineligible for autologous stem cell transplant (autoSCT). Autologous T cells were transduced with a lentiviral vector encoding an anti-CD19 CAR, expanded, cryopreserved, shipped, and infused at study sites. The primary endpoint (centrally reviewed by an independent review committee) was best overall response rate (ORR: CR + partial response [PR]).

Results: 141 pts were enrolled. Following restaging, bridging therapy, and lymphodepleting chemotherapy (fludarabine 25 mg/m^2/cyclophosphamide 250 mg/m^2/day × 3 days or bendamustine 90 mg/m^2/day × 2 days), 85 pts received a single dose of CTL019 transduced cells (median, 3.1 × 10^8 [range, 0.1-6.0 × 10^8] cells). Median time from infusion to data cutoff (December 2016) was 3.7 mo. Median age was 56 y (range, 24-75) and median prior lines of antineoplastic therapy was 3 (range, 2-7). 51% of pts had prior autoSCT. Among 51 pts with ≥3 mo follow-up or earlier discontinuation, best ORR was 59% (95% CI, 44%-72%) with 43% CR and 16% PR; the primary endpoint was met. CR and PR rates at 3 mo were 37% and 8%, respectively. All pts in CR at 3 mo remained in CR at data cutoff. Efficacy was observed across prognostic subgroups. Median duration of response was not reached. CTL019 was detectable in peripheral blood by quantitative PCR for up to 355 days in responders. Cytokine release syndrome (CRS) was graded using the UPenn scale and managed by a protocol-specific algorithm. CRS occurred in 57% of infused pts (17% grade 3; 9% grade 4); no CRS-associated deaths occurred. 16% of pts received tocilizumab for CRS management. 13% of pts had grade 3/4 neurologic adverse events (AEs), managed with supportive care; no cerebral edema was reported. Grade 3/4 cytopenias lasting >28 days and grade 3/4 febrile neutropenia occurred in 21% and 14% of pts, respectively. 3 pts died from disease progression within 30 days of infusion. No deaths were attributed to CTL019.

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

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

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

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

Results: As of January 27, 2017, 111 pts from 22 institutions were enrolled; 101 pts (91%) received axi-cel. Median age was 58 y (range, 23-76), 67% male, 85% stage III-IV, 47% IPI 3-4, 77% refractory to ≥2nd line of therapy, and 21% relapsed ≤12 m of ASCT. Axi-cel was successfully manufactured in 110/111 (99%) pts with an average turnaround time from apheresis to the clinical site of 17 d.

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

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

*****Drs Neelapu and Locke contributed equally to this study.

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

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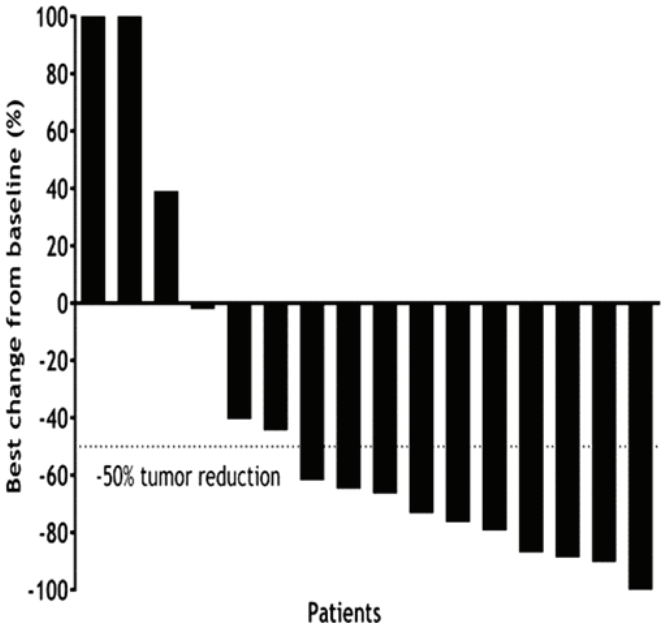
Introduction: PMBCL frequently harbors genetic abnormalities at the 9p24 locus, resulting in overexpression of the PD-1 ligands PD-L1 and PD-L2. This may serve as an immune evasion mechanism for this tumor type that could be targeted with PD-1 blockade. In a phase 1 clinical trial, the anti–PD-1 antibody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

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

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

Conclusions: In this ongoing global trial, pembrolizumab showed promising antitumor activity and a manageable safety profile in patients with rrPMBCL (including heavily pretreated patients), similar to results of the Phase 1b KEYNOTE-013 trial. Enrollment is ongoing.



HIGH CR RATES IN RELAPSED/REFRACTORY (R/R) AGGRESSIVE B-NHL TREATED WITH THE CD19-DIRECTED CAR T CELL PRODUCT JCAR017 (TRANSCEND NHL 001)

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Background: JCAR017 is a second-generation, CD19-directed, 4-1BB CAR T cell product comprising CD8 and CD4 CAR T cells in a 1:1 ratio. A multicenter phase 1 trial of JCAR017 in R/R B-cell NHL (NCT02631044) is underway.

Methods: Patients with R/R DLBCL, PMBCL, FL grade 3B, or MCL and adequate organ function are eligible. There was no minimum ALC requirement for apheresis; no test expansion was required. Treatment includes lymphodepletion with fludarabine and cyclophosphamide, followed by JCAR017. Multiple dose levels (DLs)/administration schedules of JCAR017 are being evaluated. Study objectives include safety, PK, and antitumor response.

Results: As of November 23, 2016, 28 patients have been treated and are evaluable for safety and efficacy. Nineteen were male, 9 female; 25 DLBCL, 2 MCL, and 1 FL grade 3B. Median age was 63 years (range 37-79), median number of prior therapies was 4 (range 1-8), 23 (82%) were refractory to their last chemotherapy, and 16 (57%) had prior transplant. No severe cytokine release syndrome (sCRS) was observed; 10 patients had grade 1-2 CRS (1 received tocilizumab). Five patients developed neurotoxicity, including 4 grade 3-4; all events resolved in the 4 patients who had adequate follow up. Median onset of CRS and neurotoxicity were 5 and 11 days, respectively. Four deaths after disease progression occurred, none related to JCAR017. In 20 patients treated at DL1 (5×10^7 cells), the RR was 80% with 60% achieving CR. One patient with secondary CNS involvement achieved CR without neurotoxicity. JCAR017 was detected at 3 and 6 months in responding patients, including some who relapsed; higher mean peak levels were detected in patients with durable response at 3 months. Data on patients treated at DL2 (1×10^8 cells), alternative dose schedules, tumor biopsy, and additional biomarkers will be presented.

Conclusions: Treatment with JCAR017 results in high CR rate in patients with heavily pretreated R/R DLBCL. Relapses can occur despite persistence of JCAR017, suggesting tumor immune evasion mechanisms may contribute to relapse. Observed toxicities are manageable and occurred at rates lower than those reported for other CD19-directed CAR T cell products.

A PHASE I TRIAL OF 19-28Z CAR-T CELLS POST-HIGH DOSE THERAPY AND AUTOLOGOUS TRANSPLANTATION (HDT-ASCT) FOR RELAPSED AND REFRACTORY (R/R) B-CELL NON-HODGKIN LYMPHOMA (B-NHL)

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Introduction: HDT-ASCT is the standard of care for patients with rel/ref diffuse large B-cell lymphoma (DLBCL). Herein, we report safety and efficacy data on 15 patients of our phase I clinical trial of 19-28z CAR-T post HDT-ASCT for poor-risk r/r aggressive B-NHL (NCT01840566).

Methods: Eligibility for this study includes poor-risk r/r aggressive histology B-NHL chemosensitive to salvage therapy with either: 1) FDG-PET (+) following 2 cycles of salvage therapy or 2) bone marrow involvement of B-NHL at time of r/r disease. T cells were retroviral transduced with anti-CD19 scFV linked to CD28 and CD3ζ signaling domains. Patients underwent BEAM conditioned HDT-ASCT and 19-28z CAR-T were administered on days +2 and +3.

Results: Fifteen patients with a median age of 61 years (range: 34-75 years) were treated on study, $n = 14$ at dose level (DL) #1 (5 $x10^6$ 19-28z CAR-T/kg) and $n = 1$ at DL #2 (1 $x10^7$ CAR-T/kg). See table for full characteristics and status following study treatment. One dose limiting toxicity was observed at both DL #1 and DL #2. Ten of 15 patients experienced toxicity with either grade 2-4 neurotoxicity and/or cytokine-release syndrome (CRS). All study related toxicities were fully reversible with tocilizumab +/- corticosteroids. One death on study was secondary to pulmonary mucormycosis and not attributable to 19-28z CAR-T. Toxicity events were associated with longer persistence of 19-28z CAR-T at a median of 11 days compared to a median 4 days in patients without toxicity ($p = 0.05$). Peak 19-28z CAR-T expansion did not correlate to toxicity. Comprehensive serial serum cytokine analysis revealed upregulation of IFN-gamma ($p < 0.001$) and a trend toward upregulation of IL-10 ($p = 0.07$) were associated with toxicity following 19-28z CAR-T infusion. At a median follow-up for survivors of 31 months, the 2 year progression-free survival (PFS) is 30% (95% CI: 20-70%, Figure 1). There was no observable associated between 19-28z CAR-T peak expansion, persistence in days or cytokine changes and PFS. Two of the 10 patients with progression of disease (POD) were CD19 (-) on re-biopsy.

Conclusions: This study established safety of 19-28z CAR-T at 5 $x10^6$ 19-28z CAR-T/kg following consolidative HDT-ASCT for poor-risk rel/ref aggressive B-NHL. Persistence of 19-28z CAR-T was associated with toxicity, though not efficacy as measured in PFS. Strategies to enhance durability of response to CAR-T in this setting are in development.

Table 1: Patient Characteristics

Patient	Age	Disease	No. lines of prior therapy	Disease at HDT-ASCT	Dose Level	Toxicity	Status Post-HDT-ASCT months (mo, * ongoing CR)
1	34	transformed FL (tFL)	3	PET(+) PR	1	Yes	POD/41 mo
2	68	DLBCL	4	PET(+) PR	1	Yes	CR*/41 mo
3	56	transformed MZL	2	PET(+) PR, BM involved	1	No	POD/12 mo
4	59	tFL/double-hit (DHL)	2	PET(+) PR	2	Yes	CR*/35 mo
5	66	DLBCL	3	PET(+) PR	1	No	CR*/31 mo
6	64	CD5+ DLBCL	2	PET(+) PR	1	No	POD/6 mo
7	65	Burkitt lymphoma	2	PET(+) PR BM involved	1	Yes	POD/2 mo
8	56	DLBCL/DHL	2	PET (+) PR	1	Yes	NRM/1 mo
9	51	DLBCL	2	PET (+) PR	1	No	POD/3 mo
10	61	Blastoid MCL	4	PET CR, BM involved	1	Yes	POD/2 mo
11	75	Richter's	2	PET (+) PR	1	Yes	CR*/21 mo
12	45	tFL	8	PET (+) PR	1	Yes	POD/2 mo
13	61	DLBCL	2	PET (+) PR	1	Yes	POD/3 mo
14	35	DLBCL	3	PET (+) PR	1	No	POD/3 mo
15	68	DLBCL	3	PET (+) PR	1	Yes	POD/14 mo

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