Hematological Oncology
Hematol Oncol 2015; **33**: 322–332
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hon.2230

ONGOING TRIALS

ORAL PRESENTATIONS:

OT01
THE IELSG-37 STUDY: A RANDOMIZED TRIAL ASSESSING THE ROLE OF MEDIASTINAL RADIOTHERAPY AFTER FRONT-LINE RITUXIMAB AND ANTHRACYCLINE CONTAINING REGIMENS IN PATIENTS WITH PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL)

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Background: W hether consolidation radiotherapy (RT) is required in PMLBCL after rituximab-containing and anthracycline-containing immunochemotherapy (R-Chemo) remains controversial.

Aim of the study: To assess the role of RT in PMLBCL patients with a PET-defined complete remission after R-CHT. Study design: Patients with previously untreated PMLBCL will be enrolled. All patients will undergo a baseline PET/CT and then receive one of the standard R-CHT regimens currently in use for DLBCL (e.g. R-CHOP14/21, R-DA-EPOCH, R-ACVBP or R-M/VACOP-B). The PET/CT scans will be repeated at 5–6 weeks after the last R-Chemo administration. After a mandatory central PET/CT review by an expert panel of nuclear physicians, all patients with a negative PET/CT scan (i.e., Deauville score 1–3) will be randomized to receive consolidation mediastinal RT (30 Gy) or observation. The primary endpoint is the 2-year PFS after randomization. Secondary endpoints are 5-year OS and long-term safety. The trial is powered to determine a non-inferior out come in patients not receiving RT; 540 patients will have to be enrolled.

Preliminary results: At the end of February 2015, 152 patients have been enrolled from different countries (Italy: 115, Ukraine: 19, Norway: 6, Switzerland: 6, UK: 3, Sweden: 2, Canada: 1); 116 completed the R-Chemo and had their restaging PET/CT scans centrally reviewed. When the study began, the concordance within the expert panel in reporting PET results was only moderate, despite the use of standardized criteria; however, the agreement significantly improved after a training process which involved revision and discussion of practical rules for scan interpretation and reporting. Twenty-five patients have been randomized to RT and 24 to observation.

Conclusion: The definition of metabolic complete remission has recently changed with the inclusion of patients with Deauville score 3 who represent a setting where information on the need of RT is particularly missing. The results of this ongoing study will hopefully provide this information and may allow individualization of treatment by adapting it to the PET response, thus limiting the indication for additional RT only to the patients who show an inadequate response to R-Chemo.

OT02
ROCHOP STUDY: A PHASE III RANDOMIZED STUDY OF CHOP COMPARED TO ROMIDEPSIN-CHOP IN UNTREATED PERIPHERAL T-CELL LYMPHOMA

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Treatment of de novo peripheral T-cell lymphomas (PTCL) is characterized by high rate of primary failure with classical CHOP or CHOP-like regimen and a high rate of subsequent relapse. As a consequence, no more than 30–40% of patients can be cured by this combination. Nevertheless, CHOP regimen is considered as a standard because others regimens failed to demonstrate survival advantage. Romidepsin is a histone deacetylaseinhibitor FDA-approved in relapse/refractory PTCL. Recently, the final results of a LYSA phase Ib-2 study combining romidepsin and CHOP have been accepted for publication (*The Lancet Haematology*, in press). The recommended dose of romidepsin was 12 mg/m^2 at D1 and D8 of each cycle of CHOP. Toxicity was mildly increased, particularly thrombocytopenia and nausea-vomiting. Efficacy seemed promising with a complete response rate of 51% (according to 2007 IWG criteria) and a partial response rate of 17%. With a median follow-up of 17.5 months, estimated progression-free survival (PFS) and overall survival (OS) at 18 months were 57% and 76,5%.

Ro-CHOP study is an international phase III study comparing 6 cycles of CHOP21with 6 cycles of romidepsin-CHOP21 (NCT01796002), romidepsin being given at 12 mg/m^2 D1 and D8 of each CHOP21 cycle. Patients are randomized 1:1 and stratified according to IPI score, age and histology. Key inclusion criteria are patients 18–80 years with de novo untreated PTCL, whatever Ann-Arbor stage and a ECOG PS 0–2. Key exclusion criteria are other subtypes of lymphoma, HTLV1 positivity, any cardiac abnormality, poor renal, hepatic and marrow functions unless related to lymphoma, and patients planned for autologous or allogeneic stem cell transplantation. Evaluation is performed after C3, at the end of treatment and at each follow-up visit. All suspicion of clinical or radiological relapse are reviewed in real time by independant radiologist and hematologist to confirm progression or relapse. Primary objective is PFS assessed independently according to 1999 IWG criteria. Secondary objectives include overall survival and other efficacy parameters, analysis of response rate according to 2007 IWG criteria and Lugano criteria, safety, quality of life and biological ancillary studies. A total of 420 subjects will be enrolled in the study. An independant IDMC will review safety issues every 50 patients included and who have completed treatement. One interim

analysis for futility will be performed after 30% (84 events) of the total number of planned events (278 events). At the end of February 2015, 108 patients have already been included. New countries (Singapore) and new centers in opened countries will be opened during Q1–Q2 2015 and others participating countries are under discussion. An update on enrolment will be presented during the meeting. Finally, conclusion of the first IDMC meeting, held on January 2015, will be presented.

OT03
CLL2-BIG, -BAG, -BCG AND -BIO: FOUR PHASE-II TRIALS EVALUATING A SEQUENTIAL TAILORED AND TARGETED REGIMEN AIMING FOR TOTAL ERADICATION OF MRD IN AN ALL-COMER CLL POPULATION

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Introduction: The therapeutic landscape in chronic lymphocytic leukemia (CLL) currently undergoes considerable changes with different CD20-antibodies and novel targeted drugs with exciting efficacy and tolerability becoming available. Yet, it is uncertain if these drugs should be added to chemoimmunotherapy to increase the efficacy or if the chemotherapeutic agents should be reduced or replaced to decrease toxicity. Also, it is unknown, if these agents should be administered until progression or if termination of treatment is possible in case of a deep remission. The German CLL Study Group therefore proposed a theoretical "sequential triple-T" concept of a tailored and targeted treatment aiming for a total eradication of minimal residual disease (MRD) with an optional debulking treatment with mild chemotherapy followed by an induction and a MRD-tailored maintenance treatment with an antibody and a kinase inhibitor or bcl-2-antagonist [Hallek M., ASH 2013].

Methods: Four phase-II trials were designed based on this triple-T concept for first-line and relapse treatment of an all-comer population of physically fit and unfit CLL patients. After a debulking with 2 cycles bendamustine (which may be omitted in case of a low tumor burden or contraindications), 6 cycles of induction treatment and up to 24 months of maintenance therapy will be administered until achievement of a MRD negative complete remission. Each trial evaluates a different combination of an oral targeted drug (continuous daily administration) and CD20-antibody for induction and maintenance treatment: ibrutinib and GA101 (obinutuzumab) in the CLL2-BIG-trial, ABT-199 (venetoclax) and GA101 in CLL2-BAG-, CAL-101 (idelalisib) and GA101 in CLL2-BCG- and ibrutinib and ofatumumab in the CLL2-BIO-trial. Primary endpoint of all trials is overall response rate (ORR) at the end of induction therapy; secondary endpoints include ORR after maintenance, progression-free and overall survival. However, these trials are not designed for comparisons of the different combinations. 62 patients will be recruited into each of the four multicenter, open-label trials.

Results: Thus far, the CLL2-BIG-trial has started recruitment, CLL2-BAG and -BCG are currently under review by the competent authorities and CLL2-BIO is prepared for submission. As of 27th February 2015, 16 pts were included into the CLL2-BIG-trial, among them 7 for first-line and 9 for relapse treatment. In 13 of these pts, a debulking with bendamustine before initiation of treatment with GA101 and ibrutinib was recommended. Serious adverse events have not been reported so far.

Conclusion: These 4 trials with different combinations of CD20-antibodies and oral targeted drugs will investigate (almost) chemotherapy free, targeted regimen, which are tailored to the pt's individual disease burden and time point of achievement of total disease eradication (MRD negativity).

OT04
PHASE 2 STUDY OF VENETOCLAX (GDC-0199/ABT-199) PLUS BENDAMUSTINE AND RITUXIMAB (BR) VS. BR OR VENETOCLAX PLUS RITUXIMAB IN RELAPSED/REFRACTORY FL

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Introduction: Follicular lymphoma (FL) typically responds well to initial therapy, followed by subsequent relapse. With each relapse, subsequent therapy becomes less effective and patients experience shorter durations of response. Despite improvements in response rates, progression-free survival and overall survival with the addition of rituximab to chemotherapy, new treatment options are needed to further improve outcomes. FL is usually characterized by presence of the chromosomal translocation t(14:18), which results in overexpression of the anti-apoptotic molecule Bcl-2. Through its role in inhibition of apoptosis, Bcl-2 is thought to contribute to resistance to chemoimmunotherapy such as BR. Venetoclax, a selective, potent, orally bioavailable Bcl-2 inhibitor, is currently in development for the treatment of B-cell malignancies. Preclinical and preliminary clinical data suggest that combination of venetoclax plus rituximab or BR is feasible and might improve lymphoma response over rituximab or chemotherapy alone. This study will evaluate the efficacy and toxicity of the combination of venetoclax plus rituximab and venetoclax plus BR in patients with relapsed/refractory FL, the latter compared with patients who receive BR alone.

Methods: This open-label study aims to enroll approximately 156 patients in North America, Europe and Asia Pacific. Patients will be assigned to chemotherapy-free or chemotherapy-containing cohorts at the discretion of the Investigator. Patients in the chemotherapy-free cohort (Arm A) will receive venetoclax 800 mg daily for 1 year plus rituximab (375 mg/m^2 on Days 1, 8, 15 and 22 of Cycle 1, and on Day 1 of Cycles 4, 6, 8, 10 and 12 [28-day cycles]). The first 6 patients assigned to the chemotherapy-containing cohort will comprise the safety run-in group. These patients will receive venetoclax 600 mg daily plus BR for up to 6 cycles, and safety will be assessed after the observation window of 28 days. Based on observed safety in this group, the designated dose for Arm B will be chosen. Remaining patients assigned to the chemotherapy-containing cohort will be randomized 1:1 to Arm B or C. Patients in Arm B will receive venetoclax for 1 year at the designated daily dose, plus 6 cycles of BR (rituximab 375 mg/m^2 on Day 1 and bendamustine 90 mg/m^2 on Days 1 and 2 of each 28-day cycle). In Arm C, patients will receive the BR regimen alone. Key eligibility criteria include an age ≥18 years, histologically confirmed Grade 1, 2 or 3a FL, ECOG PS of 0, 1, or 2, and adequate hematologic function. The primary endpoint is complete response (CR) rate defined by positron emission tomography (PET). Secondary endpoints include CR rate determined by computed tomography, objective response rate, duration of response, survival outcomes and incidence of adverse events. The study opened in December 2014, and the estimated primary completion date is March 2018 (NCT02187861).

OT05
DLC-002 (ROBUST): PHASE III RANDOMIZED, EFFICACY AND SAFETY STUDY OF LENALIDOMIDE PLUS R-CHOP VS R-CHOP IN PATIENTS WITH UNTREATED ABC-TYPE DIFFUSE LARGE B-CELL LYMPHOMA

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DOI: 10.1002/hon

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Introduction: In diffuse large B-cell lymphoma (DLBCL), the activated B cell-like subtype (ABC) is associated with inferior PFS and OS compared with germinal center B cell-like (GCB) DLBCL following R-CHOP-based chemotherapy. Lenalidomide, an immunomodulator with antineoplastic and antiproliferative activity, has shown significant single-agent activity in relapsed/refractory DLBCL, predominantly the ABC type. In 2 independent, single-arm, phase II studies from the Mayo Clinic and Fondazione Italiana Linfomi groups, first-line lenalidomide combined with R-CHOP (R2-CHOP) showed improved efficacy over historical R-CHOP controls. Improved outcomes with R2-CHOP primarily appear in the non-GCB-type DLBCL assessed by immunohistochemistry. The objective of the DLC-002 (ROBUST) multicenter, international study is to evaluate the efficacy and safety of R2-CHOP vs placebo–R-CHOP in patients with previously untreated ABC-type DLBCL, determined by gene expression profiling (GEP).

Methods: In this phase III, placebo-controlled, double-blinded trial (NCT02285062), patients with ABC-type DLBCL are randomized 1:1 to oral lenalidomide (15 mg, days 1–14/21-day cycle) plus standard-dose R-CHOP or placebo–R-CHOP, every 21 days for 6 cycles with 2 optional, additional doses of rituximab until PD, intolerability, inadequate response, or withdrawal of consent. Key eligibility criteria include previously untreated, histologically confirmed ABC-type CD20+ DLBCL (WHO classification), age 18–80 years, IPI score ≥2, Ann Arbor stage II–IV, and adequate organ function. A central pathology lab will determine ABC type on FFPE biopsy samples within 3 days using real-time GEP with the NanoString nCounter Analysis System (Scott et al. *Blood.* 2014;123:1214–1217). The primary study endpoint is PFS; secondary endpoints include EFS, OS, ORR, CR, duration of CR, time to next lymphoma therapy, and health-related QOL. Responses will be measured per 2007 IWG criteria with PET. Additional biological analyses for MRD detection are planned.

Conclusions: Enrollment began in January 2015, with the goal of randomizing 560 patients over an estimated 34-month accrual period. Expected accrual completion is planned by October 2017. The DLC-002 study is the first phase III trial in ABC-type DLBCL to use real-time GEP to assess patient eligibility, thus allowing precision therapy in patients with DLBCL.

OT06
RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE 3 STUDY OF IBRUTINIB/OBINUTUZUMAB VS. CHLORAMBUCIL/OBINUTUZUMAB FOR TREATMENT-NAÏVE CLL/SLL (PCYC-1130; ILLUMINATE)

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Introduction: Patients with CLL may not be candidates for fludarabine-based chemoimmunotherapy regimens if they are older, have comorbidities, or if their cancers are positive for del(17p). There are few safe and effective treatment options for this population. Chlorambucil in combination with obinutuzumab (Gazyva®), which produced a progression-free survival (PFS) of 26.7 months (Goede, 2014), has recently been approved as a first-line treatment option for these hard-to-treat patients. In a recent trial in treatment-naïve (TN) patients with CLL (median age 71 y), single-agent ibrutinib (IMBRUVICA®) resulted in an overall response rate (ORR) of 71% (complete response [CR], 13%), partial response with lymphocytosis of 13%, and an estimated 22-month PFS and overall survival (OS) of 96% each (O'Brien, 2014). The response to ibrutinib in this population contrasts favorably to single-agent chlorambucil, which rarely produces CRs. In addition, the clinical activity of ibrutinib appeared independent of poor prognostic factors, including del(17p). It is reasonable to ask if the combination of ibrutinib with obinutuzumab will have greater clinical activity than chlorambucil/obinutuzumab in the first-line setting.

Methods: iLLUMINATE is an ongoing trial of TN patients with CLL and small lymphocytic lymphoma (SLL) who have active disease requiring therapy. Patients with CLL/SLL who are TN will be enrolled in the trial if they meet 1 of the following criteria: CIRS >6, estimated CrCL ≥30 but <70 mL/min, del17p or TP53 mutation, or are ≥65 years of age. Key exclusion criteria include any prior treatment for CLL, evidence of CNS involvement, or Richter's transformation. Approximately 212 patients will be randomized in a 1:1 ratio to daily ibrutinib (420 mg per day until progressive disease [PD] or unacceptable toxicity) or oral chlorambucil (0.5 mg/kg D1 and D15 of each 28-day cycle for 6 cycles). Intravenous obinutuzumab will be given to all patients for 6 cycles according to the product label. The primary endpoint is PFS assessed by Independent Review Committee (IRC). Secondary endpoints include ORR, minimal residual disease-negative response rate, OS, hematologic improvement, patient-reported outcomes, safety, and tolerability. Patients on the chlorambucil/obinutuzumab arm may cross over to ibrutinib after IRC-confirmed PD if they meet treatment criteria. Enrollment is planned in approximately 16 countries including the US, EU, Australia, and New Zealand.

Results: Enrollment for this trial is ongoing.

Conclusion: This randomized, multicenter, open-label, phase 3 trial compares the chemotherapy-free combination of ibrutinib and obinutuzumab to chlorambucil/obinutuzumab in TN patients with CLL who are not candidates for fludarabine-based chemoimmunotherapy due to comorbidity, age, or presence of del(17p).

POSTER PRESENTATIONS:

OT07
CHRONOS-1: PHASE II TRIAL OF INTRAVENOUS PHOSPHATIDYLINOSITOL-3 KINASE ALPHA/DELTA INHIBITOR COPANLISIB IN PATIENTS WITH RELAPSED/REFRACTORY INDOLENT NHL

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Background: Copanlisib is a novel pan-Class I phosphatidylinositol-3-kinase (PI3K) inhibitor with potent preclinical inhibitory activity against both PI3K-δ and PI3K-α isoforms. A phase II study of copanlisib in 67 patients with relapsed/refractory indolent or aggressive lymphoma reported a promising overall response rate of 47% in heavily pretreated indolent NHL patients (Dreyling et al., ASH 2014). An expansion cohort of 120 patients with indolent NHL is currently enrolling. The objective of the study is to evaluate the efficacy and safety of copanlisib in patients with indolent B-cell NHL relapsed after or refractory to standard therapy (NCT01660451).

DOI: 10.1002/hon

Methods: This is a multi-institutional international phase II study. Patients with histologically confirmed indolent B-cell NHL are eligible; histologies to include: follicular lymphoma (FL) grade 1–2–3a, marginal zone lymphoma (MZL; splenic, nodal, or extra-nodal), small lymphocytic lymphoma (SLL) with absolute lymphocyte count $< 5 \times 10^9$/L at the time of diagnosis/study entry, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM). Patients must have relapsed or are refractory after ≥ 2 prior lines of therapy (refractory defined as not responding to a standard regimen or progressing within 6 months of the last course of a standard regimen; patients must have received Rituximab and alkylating agents). Patients will receive 60 mg of copanlisib administered intravenously on days 1, 8 and 15 of a 28-day cycle. Patients are treated until disease progression or intolerable toxicity. Radiologic tumor assessments are performed every 2 cycles during the 1st year. Adverse events are collected and graded using NCI-CTCAE v4. The primary endpoint is overall objective response rate (ORR), defined as a complete response (CR) or partial response (PR). Secondary objectives include duration of response (DOR), progression-free survival (PFS), overall survival (OS), and Quality of Life questionnaire (FACT-Lym symptoms subscale and total score) at week 16. Assuming a one-sided alpha of 0.025, 90% power and a true ORR of 75%, a total of 120 patients will be required.

Results: The trial is currently enrolling patients.

Conclusions: The primary endpoint is overall objective response rate.

OT08
DESIGN OF A PHASE 1/2, OPEN-LABEL, DOSE-ESCALATION TRIAL OF THE TOLL-LIKE RECEPTOR ANTAGONIST IMO-8400 IN PATIENTS WITH MYD88 L265P-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Diffuse large B-cell lymphoma (DLBCL) is an aggressive and potentially lethal disease comprising multiple subtypes exhibiting genetic and biological heterogeneity. About 10% of all DLBCL patients, including about 30% of patients with the activated B-cell-like (ABC) subtype, harbor the MYD88 L265P oncogenic mutation. The MYD88 L265P mutation is also present in Waldenström's macroglobulinemia (~90%), chronic lymphocytic lymphoma (~5–10%) and other cancers. MYD88 is an adapter protein in the signaling pathway of Toll-like receptors (TLRs), which play a central role in the innate immune system. The MYD88 L265P oncoprotein binds constitutively to TLRs 7 and 9 and amplifies receptor signaling and cytokine induction, thereby promoting tumor cell survival and proliferation. Observational data have shown significantly inferior overall survival and progression free survival in patients with DLBCL harboring the MYD88 L265P mutation compared to wild type, including in patients treated with first-line R-CHOP. IMO-8400 is an investigational, synthetic, oligonucleotide-based antagonist of TLRs 7, 8 and 9. IMO-8400 inhibited tumor growth, cytokine secretion, and key cell signaling pathways including IRAK1/IRAK4, NF-κB, STAT3, p38 and BTK compared to untreated mice in xenograft models using the MYD88 L265P-positive human lymphoma cell lines OCI-Ly10 and TMD8. In previously completed Phase 1 and 2 trials in healthy volunteers and subjects with moderate to severe plaque psoriasis, IMO-8400 was generally well tolerated and demonstrated evidence of clinical activity. Based on these data, we designed a Phase 1/2, multicenter, open-label, dose-escalation trial of IMO-8400, the first study of a drug candidate specifically targeting the MYD88 L265P mutation in DLBCL.

Methods: The primary study objective is to evaluate the safety and tolerability of escalating IMO-8400 doses. Secondary objectives include preliminary evaluation of clinical response based on international guidelines, identification of an optimal dose for further clinical evaluation and characterization of IMO-8400 pharmacokinetics. Key study entry criteria include adults ≥18 years with relapsed or refractory DLBCL harboring the MYD88 L265P mutation. Patient screening involves gene sequencing by a designated accredited laboratory. The study will enroll 3 escalating dose cohorts (n = 3–6 each) and treat subjects with subcutaneous injections of 0.6, 1.2 and 2.4 mg/kg/week of IMO-8400, respectively, for 24 weeks with provisions for extending the treatment period. Additionally, 2 expansion cohorts will enroll up to 9 subjects each at 0.6 mg/kg and the maximum tolerated dose defined by dose escalation procedures for 24 weeks. The trial is currently open for enrollment and is actively screening patients at multiple clinical sites in the United States (NCT Identifier: NCT02252146).

OT09
IBRUTINIB IN COMBINATION WITH RITUXIMAB FOR RELAPSED MANTLE CELL LYMPHOMA: AN UPDATE FROM A PHASE II CLINICAL TRIAL

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Introduction: Single-agent ibrutinib is effective for relapsed mantle cell lymphoma (MCL). During the initial tumor reduction phase, ibrutinib often induces lymphocytosis (Wang, et al, NEJM), which is due to MCL cell migration from the home environment into the peripheral blood. Intravenous rituximab can contact the tumor cells in peripheral blood once infused; therefore, ibrutinib and rituximab may be an efficacious combination.

Methods: We presented the preliminary results of a single-center phase II clinical trial with ibrutinib in combination with rituximab for relapsed MCL (Wang et al, ASH 2014). Here, we report updated data with twice the follow-up duration. Among 50 patients with MCL, 100% received prior rituximab, 77% received prior Hyper-CVAD, 75% received prior bortezomib, and 20% received prior lenalidomide treatments. Rituximab was dosed at 375 mg/m^2 IV weekly × 4 during cycle 1 (cycle = 28 days), then on day 1 of every cycle from 3 to 8, and thereafter once every other cycle up to 2 years. Ibrutinib was dosed at 560 mg orally, daily, continuously. With a median follow up time of 11.37 months (3.58–15.93), 50 patients are evaluable for toxicity and efficacy as of Jan 31, 2015.

Results: Thirty-seven (37) patients have Ki-67 levels < 50%. Twenty-three (23) patients came off the study due to the following: secondary malignancies (2), social issues (1), atrial fibrillation (3), bleeding (1), withdrew consent (1), death-unrelated (1), and stem cell transplantation (5). Nine (9) patients, 7 with Ki-67 values ≥ 50%, and 2 with Ki-67 values < 50%, came off the study due to progressive MCL (5 never responded, 4 responded then progressed). No deaths were caused by therapy. Grade 3 hematologic toxicity events included neutropenia (1) and thrombocytopenia (1).

DOI: 10.1002/hon

The most common grade 1–2 non-hematological events were fatigue (24), diarrhea (21), myalgia (18), dyspnea (18), blurred vision (15), nausea (12), and dry eye (15). The efficacy data are shown in Table 1. To date, the ORR is 88%, with CR at 40% and PR at 48%. In this study, the CR rate is high in the context of historical data (21% by single-agent ibrutinib). Median response duration and PFS have not been reached. Of the relapsed/refractory 37 MCL patients with Ki-67 < 50%, the ORR is 100% (51.4% for CR and 48.6% for PR).

Conclusions: While this trial is ongoing, these updated data indicate that the ibrutinib–rituximab combination is well-tolerated and efficacious, especially in patients with Ki-67 levels < 50%.

Abstract OT09 - Table 1 The best response related to Ki-67

	All *n* (%)	Ki-67 < 50%	Ki-67 ≥ 50%
Evaluable Patients	50	37	12
ORR	44 (88%)	37 (100%)	6 (50%)
CR	20 (40%)	19 (51.4%)	1 (8.3%)
PR	24 (48%)	18 (48.6%)	5 (41.7%)
SD	3 (6%)	0 (0%)	3 (25%)
PD	3 (6%)	0 (0%)	3 (25%)
Duration of Response	NR	NR	NR
PFS	NR	NR	NR

OT10
EFFICACY AND SAFETY OF LENALIDOMIDE AND RITUXIMAB VS PLACEBO AND RITUXIMAB IN A PHASE 3 TRIAL IN RELAPSED/REFRACTORYNON-HODGKIN LYMPHOMA

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Introduction: Lenalidomide (Revlimid®) is an immunomodulatory agent with immunostimulatory, anti-inflammatory, and antiangiogenic properties. Preclinical studies demonstrated that the immunological function of tumor-infiltrating lymphocytes is suppressed in follicular lymphoma (FL) cells, but can be restored after treatment with lenalidomide (Ramsay, *Blood*, 2009). In phase 2 trials with lenalidomide + rituximab (R^2), patients with newly diagnosed indolent non-Hodgkin lymphoma (iNHL) and FL achieved overall response rates (ORR) of 90% (Fowler, *Lancet Oncol*, 2014) and 93% (Martin, ICML, 2013), respectively. In relapsed/refractory (R/R) iNHL, treatment with R^2 resulted in 73% ORR (36% complete response [CR]) in R/R FL (Leonard, ASCO 2012 oral presentation), and 80% ORR (55% CR) in marginal zone lymphoma (MZL; Raderer, EHA 2014 oral presentation) patients. These preclinical and phase 2 results support further investigation of R^2 therapy in R/R iNHL.

Methods: AUGMENT is a multicenter, double-blind, randomized, phase 3 trial investigating the efficacy and safety of R^2 (experimental arm) versus placebo + -rituximab (P + R; control arm) in patients with R/R iNHL. Eligibility criteria include: grade 1, 2, or 3a FL or MZL; previous treatment with systemic chemotherapy and/or immunotherapy; relapsed or refractory to last treatment; rituximab-sensitivity; ≥1 measurable lesion; and adequate hematologic, liver, and renal function. Approximately 350 patients will be randomized 1:1 to either R^2 or P + R. In the R^2 group, patients will receive lenalidomide (20 mg/day; days 1 to 21 of each 28-day cycle for up to 12 cycles) + rituximab (375 mg/m^2; days 1, 8, 15, 22 of cycle 1 and day 1 of cycles 2 to 5). Patients in the P + R group will receive treatment following the same schedule. The primary endpoint is progression-free survival, and key secondary endpoints will include rate of durable CR, overall survival, ORR, safety, and time to next anti-lymphoma treatment. Study sample size was determined using a stratified log-rank test and will be adequate to detect a progression-free survival hazard ratio of 0.625 with one-sided $\alpha = 0.025$ with 90% power. The AUGMENT trial is currently enrolling patients (NCT01938001).

OT11
FIL-VERAL12: PHASE II RANDOMIZED STUDY WITH RITUXIMAB-DHAP +/- BORTEZOMIB AS INDUCTION IN YOUNG RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA ELIGIBLE TO TRANSPLANT

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Introduction: The addition of rituximab to CHOP improved prognosis in diffuse large B-cell lymphoma (DLBCL) patients. Furthermore, patients that experienced relapsed or refractory disease had a dismal prognosis. The best salvage regimen is not yet established, but a cisplatin-containing regimen (DHAP, cisplatin, high-dose citarabine, dexamethasone) is worldwide accepted as a good option. Bortezomib had proven activity in aggressive lymphoma (especially mantle cell lymphoma) subtypes; when combined to chemotherapy DAEPOCH, showed promising activity in non-germinal center derived DLBCL. On these bases, the Fondazione Italiana Linfomi designed the VERAL12 trial, with the aim to evaluate whether the addition of Bortezomib to Rituximab-DHAP (BR-DHAP) is more active in term of PET-defined complete response (CR) than standard R-DHAP, as induction therapy before high dose chemotherapy with stem cell transplantation (SCT).

Methods: VERAL12 was a prospective, multicenter, two-arm randomized phase II screening trial (NCT01805557). The primary study endpoint is CR assessed by PET-scan after 4 cycles of chemotherapy R-DHAP or BR-DHAP. Secondary endpoints were: overall response rate, progression free survival, overall survival, toxicity, mobilizing potential (amount of CD34 + stem cell collected /Kg) and feasibility (defined as the proportion of randomized patients successfully completing transplantation). According to a one-sided test with an alpha-error of 0.10 and a beta-error of 0.20, and assuming a 30% CR for the standard arm R-DHAP and an expected CR rate in experimental arm of 50%, a sample size of 108 patients (54 for each arm) is required. Inclusion criteria are: young patients (18–65 years) affected by relapsed/refractory DLBCL after first line R-CHOP or GA101-CHOP, eligible to high-dose therapy. All relapsed patients will be re-biopsied for centrally histological review and classification according to cell of origin profile. Patients are stratified by relapsed or refractory and randomized 1:1 to receive: (i) the standard salvage therapy R-DHAP every 28 days for 4 cycles and (ii) subcutaneous 1.5 mg/sqm Bortezomib on days 1 and 4 of each 4-week cycle in addition to the same regimen (BR-DHAP). Restaging, mobilization and harvesting of peripheral stem cell are performed after the second course. Conclusions. Enrolment began in January 2013, with the goal of randomizing 108 patients; at February 2015, 38 patients have been enrolled.

DOI: 10.1002/hon

OT12
A PHASE I TRIAL TO EVALUATE THE SAFETY AND ACTIVITY OF A-DENDRITIC CELL-BASED IMMUNOTHERAPY IN INDOLENT NON-HODGKIN LYMPHOMAS (IFN-DC-2 STUDY)

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Background: Immuno-chemotherapy has led to a dramatic improvement in progression free survival and overall survival of Indolent B-cell Lymphoma patients (I-NHL). However I-NHL remain incurable and there is a need for novel therapies, with less toxicity and more specific targeting of tumor cells. Recently two studies have shown the potential efficacy of active immunotherapy by repeated administration of autologous dendritic-cells in both relapsed/refractory and de novo I-NHL. The Experimental Immunotherapy Unit at ISS has developed a particularly effective modality of ex vivo differentiation of DC from human monocytes in the presence of GM-CSF and type IFN-α. The DC generated by this method, designated IFN-DC, exhibit a phenotype of highly active partially mature DC, endowed with a high migratory and immuno-stimulatory ability and with a peculiar efficiency in inducing a TH1 type immune response and CD8+ T cells against a variety of antigens.

Methods: The IFN-DC-2 study is a phase I to evaluate safety and tolerability as well as immune and clinical responses of a IFN-DC based therapy in combination with rituximab for the treatment of patients with advanced I-NHL. The Primary endpoints are (I) *evaluation of safety and tolerability of treatment* and (II) *evaluation of tumor-specific immune responses* by determining the following: (i) tumor-specific immune response in peripheral blood; (ii) intratumoral infiltration of immune cells; and (iii) DTH test. The secondary endpoint is clinical response.

Study population: 18–75 years patients with relapsed or refractory I-NHL (Follicular, Marginal or Lymphoplasmocytic subtypes) after one or more lines of treatment, not needing immediate retreatment basing on the GELF Criteria.

Treatment: Patients are divided into two groups (ten for each group) both receive intranodal injection of rituximab (5–10 mg, depending on the size of the lymph node) in combination with low (group 1) or high doses (group 2) of IFN-DC (20×10^6 or 60×10^6cells respectively). IFN-DC will be administered one day after treatment with rituximab. Treatment regimen foresees eight injection cycles. Rituximab and IFN-DC are administered by intranodal direct injection (IDI).

Results: The study started in October 2014 and up to now four patients have been enrolled. No serious adverse events have been reported so far, while immunological and clinical evaluations are ongoing.

Conclusions: Although DC-based immunotherapy represents a promising approach for treating lymphoma, there is a strong need for consensus on the optimal protocol and type of DC to be used. The IFN-DC-2 trial evaluates the safety, feasibility and potential activity of two different doses of highly active IFN-DC combined with rituximab in Relapsed/Refractory I-NHL patients. Furthermore, specifically designed biological assessments will help to identifiyng predictive markers of clinical activity.

OT13
THE "ELDERLY PROJECT" BY THE FONDAZIONE ITALIANA LINFOMI (FIL): A PROSPECTIVE MULTIDIMENSIONAL ASSESSMENT OF ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: The initial approach to elderly patients with Diffuse Large B-Cell Lymphoma (DLBCL) is mostly based on a subjective judgment of the physician. Comprehensive Geriatric Assessment (CGA) is based on the use of the ADL (Activity of Daily Living), IADL (Instrumental ADL) and CIRS-G (Comorbidity Index Rating Scale for Geriatrics) scales and represents a tool to standardize initial patients fitness status and for planning systemic therapy.

Objectives: FIL designed a prospective study with the aim of providing clinicians with a standardized tool to assess CGA in elderly patients with DLBCL before treatment start and to validate CGA results on a large series of patients.

Methods: This study was conducted using a web based tool to perform CGA evaluation of all patients ≥ 65 years with DLBCL at time of diagnosis. Patients younger than 80 years, without impairment of ADL and IADL and without severe comorbidities were considered FIT; those with intermediate fragility or those older than 80 years with FIT profile were classified as UNFIT (UN); those with severe impairment of ADL, IADL and CIRS and those older than 80 years with an UN profile were classified as FRAIL (FR). The planned sample size was 600 patients.

Results: The study started in December 2013. At time of current analysis 260 patients have been registered by 25 centres: 45%, 20%, and 35% were classified as FIT, UN and FR, respectively. Median age was 75 years (65–94), 27% ≥ 80 years and 66% in stages III and IV.

By univariate analysis, the three categories differed in terms of median age (72, 78 and 79; $p < 0.001$), B-symptoms (23%; 19% and 38%; $p = 0.016$) and ECOG PS > 1 (10%, 14% and 40%; $p < 0.001$) for FIT, UN and FR respectively.

Regarding CGA items, 77% and 55% of the patients did not have impairment of ADL (score 6) and IADL (score 8). Sixty-four (25%) did not have any comorbidity at CIRS scale and 17% had at least one of grade 3; the most frequent grade 3 events were those referred to heart (4%), vascular system (3%) and eyes, ears, nose, throat and larynx (3%). Data on planned treatment were available in 217 patients (82%, 87% and 89% FIT, UN and FR respectively). For all FIT and UN patients was scheduled chemotherapy with rituximab; R-CHOP-like regimen was planned in 90% and 82% of FIT and UN patients. FR patients were treated with R-CHOP like regimen (60%), R-CVP (10%) and R-Benda (7%). Only 9% of these patients were

DOI: 10.1002/hon

referred to a palliative treatment. Dose reduction was scheduled in 12% and 19% for UN and FR respectively.

Conclusion: The initial data show that currently many italian centres treat elderly DLBCL with CHOP-like regimens independently from fitness status. CGA represents an objective assessment of elderly subjects with DLBCL that can be used to assist physicians in the initial approach to the patient. This project has the aim of extending and simplifying the use of CGA, to further validate it and to identify possible new criteria to improve our ability to select patients.

OT14
CLLR3 A RANDOMIZED PHASE II TRIAL EVALUATING THE CHEMOTHERAPIES FC/ B COMBINED WITH GA101 FOLLOWED BY GA101 MAINTENANCE IN RELAPSED/ REFRACTORY CLL

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Introduction: GA101 (Obinutuzumab) has demonstrated high efficacy in relapsed/ refractory chronic lymphocytic leukemia (CLL) patients (pts) and has also shown superiority to rituximab in combination with chlorambucil. Furthermore, FCR (fludarabine + cyclophosphamide + rituximab) and BR (bendamustine + rituximab) are active in patients with relapsed/ refractory CLL. In the first line setting, there is no strict rationale for FC versus B in combination with a CD20 antibody as both therapies have their advantages and therefore both regimens are being used broadly in clinical routine. Hence, a combination immunochemotherapy with FC + GA101 (FCG) or B + GA101 (BG) might further improve the therapeutic outcome in relapsed/ refractory CLL. Furthermore, there has been no systematic approach yet to evaluate if GA101 is superior to rituximab in all therapy settings underlining the need for further evaluation of GA101 containing regimens in regard to future combination therapies including new substances.

Methods: The CLLR3 trial is a prospective, multicenter, randomized phase-II trial for pts with relapsed and/or refractory CLL. Hundred physically fit patients (assessed by CIRS score < 6) will be randomized to receive up to 6 cycles of FCG or BG as induction therapy. After assessment of response to induction therapy, pts in response will receive a maintenance therapy with GA101 every 3 months for a maximum period of 2 years or until progression. As primary objective, the efficacy of the two regimens will be evaluated using the best overall response rate (ORR) as primary endpoint. Besides safety, the secondary endpoints include other efficacy parameters like progression-free and overall survival as well as minimal residual disease levels.

Results: The study is actively recruiting. As of Feb 27th 2015, 16 of 31 centers have been initiated so far. A total of 35 centers is planned. 6 pts have already been included, 3 receive FCG, 3 are under treatment with BG. As for serious adverse events (SAEs), 1 pt experienced a grade 3 infusion-related reaction to the first dose of GA101. 1 other major event has been reported (grade 4 pancytopenia).

Conclusions: In this randomized phase-II trial, two standard chemotherapies for fit pts with relapsed CLL are combined with the type II CD20-antibody GA101. GA101 has shown to be superior to rituximab in combination with chlorambucil in unfit patients with co-existing comorbidities but has not yet been evaluated in combination with chemotherapy for physically fit pts. With this promising combination, we expect to improve responses and prolong remissions with an adequate safety profile in the refractory/ relapsed CLL setting. Additionally, these data will be of great interest for future therapy concepts comparing immunochemotherapy with chemotherapy-free regimen.

OT15
PHASE IB STUDY EXPLORING IL-6 RECEPTOR BLOCKADE TO PREVENT INFUSION-RELATED REACTIONS IN PATIENTS WITH PREVIOUSLY UNTREATED CLL RECEIVING OBINUTUZUMAB PLUS CHLORAMBUCIL

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Introduction: Infusion-related reactions (IRRs) are frequently observed with the first infusion of anti-CD20 monoclonal antibodies (mAb), yet current premedication strategies have proved ineffective at completely eliminating them. In early phase clinical studies of obinutuzumab in patients with chronic lymphocytic leukemia (CLL), the development of IRRs was associated with a marked increase in circulating pro-inflammatory cytokines, particularly IL6 and IL8, and this phenomenon was limited to the first infusion. Obinutuzumab is a humanised, glycoengineered, type 2 anti-CD20 mAb that has demonstrated superior efficacy when combined with chlorambucil compared to rituximab plus chlorambucil in previously untreated patients with CLL and comorbidities. The safety profile of obinutuzumab is generally similar to rituximab with the exception of IRRs, which occur at greater overall incidence and severity but are also restricted to the first infusion. The commonest symptoms include nausea, chills, hypo/hypertension, pyrexia, flushing, tachycardia, dyspnoea, headache, diarrhoea and vomiting. Other more severe symptoms such as bronchospasm, laryngeal edema and atrial fibrillation have been reported. Tocilizumab is a humanised mAb that blocks the IL6 receptor and has shown promise in the treatment of patients with cytokine-release syndromes. The addition of tocilizumab to standard premedication prior to obinutuzumab may protect patients from severe IRRs.

Methods: This is a multicentre, double-blind, randomised, placebo-controlled study to evaluate the safety of tocilizumab versus placebo in combination with standard premedication prior to obinutuzumab plus chlorambucil. Patients with treatment naïve $CD20^+$ CLL; life expectancy >6 months; a total cumulative illness rating scale score >6 and/or creatinine clearance <70 mL/min and adequate haematological function (except for abnormalities caused by CLL) are eligible for enrolment. Approximately 60 patients will receive 6 cycles of obinutuzumab (1000 mg IV administered as 100 mg on cycle 1 day 1 (C1D1) and 900 mg on C1D2, 1000 mg on C1D8 and C1D15; 1000 mg on D1 only for subsequent cycles) plus chlorambucil (0.5 mg/kg on D1 and D15 of each 28-day cycle) over a 6-month period. A single infusion of tocilizumab IV (starting at 8 mg/kg) or placebo will be administered with standard premedication (paracetamol, antihistamine, and a corticosteroid) on C1D1 prior to the first infusion of obinutuzumab. Primary outcome measures include the incidence and severity of IRRs, and the incidence and severity of adverse events (AEs).

DOI: 10.1002/hon

Secondary measures include incidence of AEs of special interest, overall response, and minimal residual disease negativity rate. This trial is anticipated to open in April 2015; participating countries currently include the United Kingdom, Spain, Italy and Israel. Details can be found at ClinicalTrials.gov (NCT02336048).

PUBLICATIONS:

OT16
POST-AUTHORISATION OBSERVATIONAL SAFETY STUDY OF BRENTUXIMAB VEDOTIN IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA AND SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA: ARROVEN STUDY

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Introduction: Brentuximab vedotin has conditional approval in Europe for adult patients with relapsed/refractory (R/R) CD30+ Hodgkin lymphoma (HL) or systemic anaplastic large cell lymphoma (sALCL). ARROVEN is an ongoing, multi-centre, post-authorisation safety study required by the European Medicines Agency to further evaluate brentuximab vedotin's safety profile in a real-world patient population. Currently available data will be presented.

Methods: The objectives of ARROVEN are to evaluate the occurrence of serious adverse events (SAEs) and AEs of special interest considered related to brentuximab vedotin (peripheral neuropathy, neutropenia, infections, hyperglycaemia, and hypersensitivity reactions) and to identify peripheral neuropathy risk factors. R/R CD30+ HL and sALCL patients aged ≥18 years are eligible if planned to start or recently commenced brentuximab vedotin as part of routine practice. No study specific visits are mandated; safety data are collected from information recorded in medical records, typically every ~3 months until death, withdrawal, or loss of follow-up.

Results: Between June 2013 and January 2015, 62 patients (mean age 47.6 years [range 19–82]) were enrolled at 21 sites; 39 had HL and 18 sALCL (5 unknown). Patients received a median of 4 treatment cycles (range 1–12). AEs were reported in 45 patients, the most common ($n \geq 4$) included peripheral neuropathy ($n = 18$), infections ($n = 14$), neutropenia ($n = 13$), hypersensitivity reactions, and lethargy (each $n = 4$). No hyperglycaemia events were reported. In the 18 patients with peripheral neuropathy, all 21 events were 'sensory, motor, or other'; peripheral neuropathy risk factors are not yet evaluable. Grade ≥3 AEs were reported in 24 patients; grade ≥3 AEs in >1 patient included infections ($n = 8$), neutropenia ($n = 6$), and peripheral neuropathy ($n = 2$). Grade 4 toxicity occurred in seven patients and included infection ($n = 4$), progression with sepsis ($n = 2$), neutropenia ($n = 2$), thrombocytopenia ($n = 1$), and tumour lysis syndrome ($n = 1$ sALCL patient). Twenty-one patients had SAEs, including 11 with drug-related SAEs; the most common ($n \geq 2$) were infection ($n = 9$) and peripheral neuropathy ($n = 4$). No cases of progressive multifocal leukoencephalopathy, Stevens–Johnson syndrome, toxic epidermal necrolysis or acute pancreatitis were reported. Two patients discontinued brentuximab vedotin, 1 due to grade 5 multi-organ failure during cycle 1 and 1 due to grade 3 pleural effusion plus grade 5 bronchopneumonia during cycle 4. In total, four patients died on study, 3 due to pneumonia and 1 due to disease progression.

Conclusions: These data indicate brentuximab vedotin is associated with a manageable safety profile in the conditionally approved indications. The severity and frequency of toxicities observed are consistent with the known safety profile and pivotal phase 2 studies of brentuximab vedotin. ARROVEN is ongoing.

OT17
PHASE 4, OPEN-LABEL, SINGLE-ARM STUDY OF BRENTUXIMAB VEDOTIN IN PATIENTS WITH RELAPSED OR REFRACTORY SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA

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Introduction: Approximately 50% of patients with systemic anaplastic large cell lymphoma (sALCL) relapse after first-line multiagent chemotherapy, with no established standard of care for subsequent treatment. Based on the results of a pivotal phase 2 study (NCT00866047), brentuximab vedotin, an anti-CD30 antibody–drug conjugate, received conditional EU approval for the treatment of adult patients with relapsed or refractory (R/R) sALCL and accelerated approval in the US for the treatment of relapsed patients after failure of ≥1 prior multiagent chemotherapy regimen. In the phase 2 study, patients with R/R sALCL ($N = 58$) receiving brentuximab vedotin 1.8 mg/kg IV every 3 weeks achieved an objective response rate (ORR) of 86%, with 57% of patients achieving complete remission (CR), and a median progression-free survival (PFS) of 13.3 months. This confirmatory, phase 4, open-label, single-arm, multicenter study (NCT01909934) will further evaluate the efficacy and safety of single-agent brentuximab vedotin in patients with R/R sALCL who have failed ≥1 multiagent chemotherapy regimen, as required for full approval in the EU.

Methods: At least 45 sALCL patients will be enrolled from approximately 20 study centers (mainly in Europe). Eligible patients are those aged ≥18 years, with histologically confirmed R/R sALCL, who have previously received ≥1 multiagent chemotherapy regimen (CHOP or equivalent regimens with curative intent). Patients must have measurable disease (≥1.5 cm) by computed tomography, and evidence of R/R disease by biopsy and/or fluorodeoxyglucose-avid disease by positron emission

DOI: 10.1002/hon

tomography. Patients with prior allogeneic transplant are excluded from the study. Patients will receive brentuximab vedotin 1.8 mg/kg as a single IV infusion on Day 1 of 3-week cycles, for up to 16 cycles or until disease progression or unacceptable toxicity. The primary endpoint is ORR according to independent review; secondary endpoints include duration of response, CR rate, PFS, overall survival (OS), proportion of patients receiving hematopoietic stem cell transplant following study treatment, adverse events, pharmacokinetics and immunogenicity of brentuximab vedotin. Additional exploratory endpoints include time to progression, time to response, B-symptom resolution, biomarkers of response, quality of life data, and healthcare utilization. Disease status (for ORR and PFS) will be assessed every 3 months from the end of treatment (EOT) until disease progression, death, or study closure. OS will be assessed every 3 months from EOT for 18 months, and then every 6 months thereafter until death or study closure. The study will be closed when 50% of patients have had an OS event or 5 years after enrollment of the last patient. No formal statistical hypothesis testing will be performed; statistical analyses will be descriptive in nature. Enrollment is ongoing.

OT18
BRENTUXIMAB VEDOTIN (BV) PLUS RITUXIMAB (R) AS FRONTLINE THERAPY FOR PATIENTS (PTS) WITH CD30+ AND/OR EBV+ LYMPHOMA: AN ONGOING PHASE I–II STUDY

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Introduction: Chemoimmunotherapy (CIT) is associated with excess toxicity and mortality among patients with PTLD (Choquet, 2007). A risk-stratified sequential therapy (RSST) approach, in which CIT is reserved for those with inadequate response to R, may improve outcomes (Trappe, 2012). However, <30% treated as such are spared CIT. BV is an antibody–drug conjugate that yields high overall response rate (ORR) in pts with relapsed/refractory CD30+ lymphoma. We hypothesized that a combination of BV and R would give higher ORR than R alone and would limit exposure to CIT.

Methods: We initiated a Phase I/II trial investigating the safety and efficacy of the combination of BV and R in pts with untreated CD30+ and/or EBV+ lymphoma. Induction consisted of R 375 mg/m^2 and BV 1.2 mg/kg, days 1, 8, and 15, with an additional dose of R on day 22, followed by restaging. Pts with PR or CR could receive a second identical induction at discretion of treating investigator, followed by maintenance therapy (MT), or move directly to MT. MT consisted of BV 1.8 mg/kg every 3 weeks and R 375 mg/m^2 every 6 weeks for up to one year. Adverse events (AE) were graded per CTCAE 4.0. Response criteria were based on the Revised Response Criteria for Malignant Lymphoma. The primary objectives were to evaluate safety of BV plus R (phase I) and to determine the ORR (phase II). Secondary objectives were to assess progression-free survival (PFS) and overall survival (OS).

Results: Nine patients have enrolled; toxicity and efficacy data are available for eight, who are included in this analysis (Table 1). Median age was 61, and half were male. Six had PTLD. The most frequent Grade 3/4 AE were lymphopenia and neutropenia. The most frequent AE of any grade were anemia, transaminitis, and lymphopenia. A dose reduction was not required after treatment of six patients on phase I, which is now complete. Among eight evaluable pts, five achieved a CR (63%), and three SD, as best response. At median follow up of 13 months, PFS and OS were 83% and 100%, respectively. After failure of BV + R, two pts received R-CHOP and achieved CR, while one patient refused further therapy and has not had documented progression since. Updated results will be presented at the meeting.

Conclusions: BV + R has acceptable toxicity, excellent efficacy, and appears capable of sparing the majority of pts with CD30+ and/or EBV+ lymphoma exposure to CIT. Phase II accrual is ongoing.

Abstract OT18 - Table 1

Patient	Age	Sex	Transplant/Condition	Histology	Stage	IPI Score	EBV Status	CD30 Status	Best Response
1	72	Female	Heart	P	4	2	+	+	CR
2	40	Female	IBD	M	1	0	–	+	CR
3	69	Male	Kidney	M	3	3	–	+	CR
4	57	Male	Kidney	HL	3	1	–	+	CR
5	66	Female	MS	TCL	1	2	+	–	SD
6	48	Male	Kidney	M	4	1	–	+	SD
7	71	Female	Kidney	M	3	3	–	+	CR
8	56	Male	Kidney	M	1	2	–	+	SD
9	35	Male	Heart	P	4	2	+	+	N/A

IBD, Inflammatory Bowel Disease; IPI, International Prognostic Index; P, Polymorphic B-cell histology; M, Monomorphic B-cell histology (DLBCL); HL, Hodgkin-like; TCL: T cell lymphoma; MS, multiple sclerosis; N/A, not available at time of submission.

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OT19
REGISTRY OF THE GERMAN CLL STUDY GROUP: LONG-TERM FOLLOW-UP OF PATIENTS WITH CLL, B-PLL, T-PLL, SLL, T/NK-LGL, HCL AND RICHTER'S TRANSFORMATION

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DOI: 10.1002/hon

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Introduction: The most frequent primary endpoint in phase III trials in CLL is progression-free survival (PFS). However, the most important endpoint is overall survival (OS) which is usually a secondary endpoint in such trials. Recently published phase III trials in CLL showed median observation times ranging from 22 to 41 months, which is sometimes not sufficient for statistical analyses on OS. Furthermore, the outcome after progression with responses to subsequent therapies and the occurrence of late toxicities, such as MDS/AML, and second malignancies are of utmost importance for evaluation of a long-term treatment benefit. Furthermore, patients (pts) participating in clinical trials do not necessarily represent the average patient treated outside of clinical studies and little is known about the implementation of research-supported treatment improvement into routine care. Therefore, the German CLL Study Group (GCLLSG) established a registry for pts with CLL and other related rare lymphoproliferative malignancies.

Material and Methods: After approval of the local ethic committee in 2012, the registry was initiated in August 2013. All pts with confirmed diagnosis of CLL, B-PLL, T-PLL, SLL, T/NK-LGL, HCL or Richter's transformation are eligible for participation in the registry. Enrolment is possible at any time during disease progression. At timepoint of enrolment and prior to each new treatment basic information on the disease (stage, molecular genetics, cytogenetics) are collected. Pts are followed on an annual basis. Besides information on treatment, response to treatment, occurrence of secondary or concomitant diseases and secondary malignancies, a special interest is focused on the patient's quality of life and medication adherence based on EORTC QLQ-C30, QOL-CLL16, EORTC QLQ-FA13 and MARS-D questionnaires.

Results: 1483 pts have been enrolled to the registry since August 2013. Most of them ($N = 1420$; 95.8%) were diagnosed with CLL, 1.8% ($N = 26$) with SLL, 0.9% ($N = 14$) with T-PLL, 0.5% ($N = 7$) with T/NK-LGL and 0.7% ($N = 10$) with HCL. Median age is 70.6 years (range 30–93). 2.8% ($N = 41$) of the pts are younger than 50 years, 25% ($N = 373$) of the patients are between 50 and 65 years, 57.9% ($N = 859$) are between 65 and 80 years, and 14.1% ($N = 210$) of the pts are 80 years or older. 61.1% ($N = 905$) of the pts are male. A majority of 1260 pts (85.0%) has not participated in any clinical trial. 43% ($N = 612$) of the CLL patients and 39.0% ($N = 25$) of pts with the other entities have received at least one treatment so far. Death was reported for 1.2% ($N = 17$) of the pts within the first year of the registry.

Conclusion: To our knowledge, this is the largest registry for pts with CLL and the first one for other, rare lymphoproliferative malignancies. Results of further analysis regarding treatment, treatment outcome, secondary malignancies and quality of life in pts treated in and outside of clinical trials are eagerly awaited.

OT20
A PHASE II TRIAL OF OFATUMUMAB FOR MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA (MALT LYMPHOMA)

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Introduction: The monoclonal antibody rituximab has been tested for MALT lymphoma and has shown symptomatic activity, but however, a relatively low rate of complete remissions (CRs). As to date no standard treatment for Helicobacter pylori (HP)-eradication refractory or extragastric disease has been defined, new approaches are warranted. Based on the data generated in other B-cell malignancies ofatumumab (OFA) appears to be an attractive agent for the treatment of MALT lymphoma patients.

Methods: This is a single center phase II study to evaluate the capacity and safety of OFA to induce objective responses in patients with advanced MALT lymphoma (in case of gastric MALT lymphoma with demonstrated refractoriness to HP-eradication). OFA monotherapy was given at four weekly doses (1000 mg i.v., weeks 1,2,3,4) followed by four doses at 2-month intervals, starting at week 8. Restaging is performed at weeks 12, 24 and at the end of treatment. The planned number of patients is 16.

Results: To date a total of 10 patients have been included in the trial (6 female/ 4 male) with three having localized gastric MALT lymphoma, four localized orbital MALT lymphoma, one bladder lymphoma and two patients with disseminated disease. Three patients were treatment naïve, while seven had received at least one prior treatment including HP-eradication therapy. The median age at treatment start was 70 years (range 58–77). All patients had an ECOG performance status below two, but however, a total of seven patients had more than four significant comorbidities. At the time of this interim analysis seven patients were evaluable for response i.e. had at least one restaging. Two patients had a CR, two a partial remission (PR), and three stable disease (SD) with no patient progressing under OFA-treatment. Thus the overall response rate was 57% (4/7) and the disease control rate 100%. Four patients have already finished treatment (SD $n = 2$, PR = 1, CR $n = 1$) while the remaining are still under therapy. Tolerability of treatment (evaluable $n = 10$) was excellent with no related adverse events greater CTCAE grade I except infusion reaction grade II in seven patients during the first OFA-application which could be easily handled with steroids. No hematologic adverse events beside lymphopenia grade II ($n = 2$) have occurred. However, one patient was taken off-study due to unrelated prolonged hospitalization for erysipelas. Median follow-up time was 5.4 months (range 1–16).

Conclusion: This is the first study on OFA for patients with MALT lymphoma and preliminary data suggest activity and the ability for disease stabilization with no patient progressing during treatment. Toxicities were negligible even in elderly patients with significant comorbidities. More mature results will be presented at the meeting as recruitment is currently ongoing.

OT21
AUTOLOGOUS EBV-SPECIFIC T CELLS (CMD-003): PROCESS DEVELOPMENT AND LOGISTICS IN A MULTICENTRE, MULTINATIONAL PHASE 2 TRIAL FOR TREATMENT OF EBV-ASSOCIATED NKT CELL LYMPHOMA

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Introduction: NKT lymphoma is characterized by EBV expression and an aggressive course in advanced stages. Patients with advanced NKT cell

DOI: 10.1002/hon

lymphoma may achieve transient benefit with asparaginase-based chemotherapy, but durations of response are relatively short and associated with significant toxicities; hence there is a need for safer and more effective therapy.

Methods: The Center for Cell and Gene Therapy (CAGT) at Baylor College of Medicine (BCM), Texas Children's Hospital and The Methodist Hospital in Houston, Texas, in collaboration with Cell Medica, developed the current manufacturing process for autologous EBV-specific T cells (CMD-003). The process uses 100 mL of patient-derived whole blood as starting material, collected at the clinical site and shipped to the central manufacturing facility. T cells are initially expanded by stimulating peripheral blood mononuclear cells (PBMCs) with autologous dendritic cells pulsed with peptide libraries representing the EBV antigens LMP1, LMP2, BARF1 and EBNA1 in the presence of cytokines. A second expansion is performed using irradiated, autologous T cell antigen presenting cells, pulsed with the same peptide libraries, together with an irradiated HLA negative cell line, engineered to express costimulatory molecules. The resultant cell product is comprised of CD4+ and CD8+ T cells that respond to one or more EBV-specific antigens. The drug product is prepared by formulating with cryopreservation medium. The product bags are transferred to a validated vapour phase liquid nitrogen shipper for transport to the clinical site. The complete process requires approximately 40 days from blood collection to patient dosing. This product is currently being tested in the CITADEL study (NCT01948180), a global phase 2 single armed study in patients with advanced NKT lymphoma who have relapsed after asparaginase based treatments.

Results: We have qualified the manufacturing process, including starting material and final product shipping to allow US-based manufacturing for clinical sites in France, Germany, South Korea, UK and US. We have received regulatory authorization to begin clinical testing in Germany and the UK (through the European Voluntary Harmonization Process) and in the US. Various logistical issues have been resolved to ensure quality of the starting material, successful patient blood collection and effective international transportation to and from the central manufacturing facility. The first patient was treated on 11 Feb 2015.

Conclusions: A fully GMP compliant process to support a global clinical trial of an autologous cell therapy from a single manufacturing facility has been validated; this includes the complete transfer from an academic setting to an industry platform. The clinical trial is ongoing and accruing patients.

OT22
STATE-WIDE COLLABORATION IN DEVELOPING A SMART-PHONE APP INCREASING KNOWLEDGE OF AND PATIENT CROSS-REFERRAL TO CLINICAL TRIALS

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Introduction: Poor recruitment to lymphoma trials is partly attributed to the broad spectrum of trials across numerous uncommon lymphoid histologies. It is difficult to maintain knowledge of current recruiting trials in the context of rapid therapeutic developments. The 18 public hospitals of the Haematology Clinical Research Network, New South Wales (NSW), Australia aimed to develop a smart-phone Application, (App) to facilitate rapid access to accurate information on local trials and increase patient referrals.

Methods: Key objectives were to develop an iOS & Android App (named ClinTrial Refer) that was free to download, simple to use and effective. Only publically listed data was to be uploaded. Endpoints were rates of App usage, and trial referrals. With end-user feedback (clinicians, trial managers & patients), App specifications were refined with successive iterations. Designed with key search filters of Disease, Location & Sponsor, the App has an easy to navigate listing of currently recruiting haematology trials. Useful features include: listing of inclusion/exclusion criteria; direct links to ClinTrials.gov; and alert notifications. Easy real-time data entry into a streamlined back-end database ensures currency of trial information, managed at a local level.

Results: Since launching on iTunes and Google Play in June 2013, usage metrics reveal ClinTrial Refer has had 2266 users, over 19820 sessions lasting an average 53 s. Of these, 89% are repeat users for an average 15 sessions with 170 users per month. There has been cross-site referral of 200 patients (average 10.5 per month, range 4–18) for clinical trials: a major and sustained increase over previous referral estimates of 1.8 per month. There has been a 33% increase in trials recruitment from 306 patients in 2012 to 460 in 2014 and a 30% increase in trials unit staffing across NSW. Currently recruiting to 33 lymphoma, 16 myeloma and 10 CLL App listed studies, NSW sites have been leading international recruiters to several studies. The referral of patients from rural NSW and private haematologists has been a notable achievement of this collaboration. A template for any clinical trials collaborative the App has since been replicated for eight other Australasian cancer trial networks.

Conclusion: ClinTrial Refer is an instantly accessible and simple mobile App in the pockets of clinician researchers, trials staff & patients. It has increased haematologists' knowledge of the local trial portfolio and has facilitated considerable cross-site collaboration and viability of trials units across the State with a marked increase in patient access to numerous emerging therapies across all lymphoproliferative diseases.

Supporting information

Table with conflicts of interest provided by authors during abstract submission is available as online-only supplementary material at the publisher's web site.

DOI: 10.1002/hon