Indolent lymphoma

295 ANALYSIS OF PROGNOSTIC FACTORS IN 424 MALT LYMPHOMA PATIENTS TREATED IN THE IELSG-19 MULTICENTER RANDOMISED STUDY

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The IELSG-19 randomized study comparing chlorambucil (C) alone versus the combination of C and rituximab (R) versus the sole R is the largest prospective randomized trial ever conducted in MALT lymphoma. Main contributors were the Italian Lymphoma Foundation, the GELA group, Cancer Research UK, the Catalan Hematology Group and the Oncology Institute of Southern Switzerland. All MALT lymphoma pts with localized disease at any extranodal site who did not respond or were not suitable to local therapy (including *H.pylori*-negative gastric lymphomas) or those who failed antibiotic therapy were eligible, as well as those with disseminated or multifocal MALT lymphoma. The present analysis refers to 424 evaluable pts. One hundred thirty seven pts were randomized to C, 140 to C plus R and 147 pts to R alone. Stomach was the primary lymphoma site in 179 pts (42.2%), while 245 pts (57.8%) had a non-gastric presentation. In 120 pts (30.5%) lymphoma involved more than 1 extranodal site. Lymph node involvement was present in 154 pts (36.3%); 168 pts (42.6%) had advanced stage (Ann Arbor III-IV). ECOG performance status was reported in 393 pts and was 0 in 297 them (70%). According to the international prognostic index (IPI), 66 pts (17%) had intermediate-high risk and only 9 a high risk score (2%). B-symptoms were present in 43 of 294 pts (10.9%) and LDH levels were higher than normal in 42 (10.7%) of 393 pts. Median age was 61 years (range, 26-81). After a median follow-up of 3.2 years, EFS was 66%, PFS 74% and OS 94%. At multivariate analysis, nodal involvement, B-symptoms, lower levels of serum protein concentration and unfavourable IPI scores were independently associated with shorter EFS and PFS, after adjustment by treatment arm. Analysis of prognostic variables is ongoing to identify the main predictive factors and to develop a MALT-lymphoma specific prognostic system.

296 PREVALENCE OF *CHLAMYDOPHILA PSITTACI* AND *BORRELIA BURGDORFERI* INFECTIONS IN A SERIES OF 108 PRIMARY CUTANEOUS LYMPHOMAS

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Introduction: Several lymphoma subtypes, especially of MALT-type (MZL), have been related to infectious agents. *Borrelia burgdorferi s.l.* (Bb) has been associated with different forms of primary cutaneous lymphomas (PCL). *Chlamydophila psittaci* (Cp) has been mainly associated, with some geographical variability, with ocular adnexal MALT lymphomas. Preliminary data on a retrospective series suggested that Cp could be associated with diffuse large B-cell lymphomas (DLBCL) of the skin. In this study, we investigated the prevalence of Bb and Cp infections in cutaneous biopsies from 108 patients with PCL.

Materials and Methods: PCL included 18 DLBCL, 24 follicular lymphomas (FL), 31 MZL, and 35 mycosis fungoides. Negative controls consisted of 19 normal skin samples. *Cp, C. pneumoniae and C. trachomatis* infections were evaluated with three different PCR targeting 16S-23S region, outer membrane protein A and heat shock protein 60. Bb infection was investigated with two PCR targeting *hbb* and *flagellin* genes, respectively. Specificity of the amplified fragments was confirmed by direct sequencing of sense and anti-sense strands of purified PCR products. Sequence specificity was assessed by BLAST search and heterogeneity of PCR sequences across the different samples was investigated by the MultAlin software. Differences in infections prevalence among different lymphoma categories and controls were analyzed by using the X^2 or Fisher exact tests for categorical variables.

Results: Cp DNA was detected in one (5%) control, in one (6%; p= 1.00) DLBCL, in five (21%, p= 0.21; C. psittaci in four and C. pneumoniae in one) FL, in one (3%; p= 1.00) MZL, and in none (0%; p= 0.35) mycosis fungoides. Bb DNA was not detected in controls, FL, MZL, and mycosis fungoides; a single case of the 14 assessable DLBCL resulted positive (7%; p= 0.66) for Bb DNA.

Conclusions: Prevalence of Cp infection in PCL is similar to those reported in controls; only FLs show a non-significant trend to a higher prevalence. Bb is not associated with PCL in Northern Italy, confirming the geographical variability in this association. This study does not support a pathogenic role of Bb and Cp in PCL and the consequent rationale for the adoption of antibiotic therapy.

297 A PHASE II STUDY TO INVESTIGATE THE PREVALENCE OF INFECTIOUS AGENTS IN OCULAR ADNEXAE MARGINAL ZONE LYMPHOMA (OAMZL) AND THE EFFICACY OF ANTIBIOTIC THERAPY (IELSG#27 TRIAL)

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Background: OAMZL is associated with *Chlamydophila psittaci (Cp)* infection. *Cp* eradication with doxycycline (DOX) is followed by lymphoma regression in ~50% of patients (pts). Related studies were retrospective, with a single prospective trial mostly including pts with relapsed disease. This is the first prospective phase II trial addressing *Cp* prevalence and DOX activity in pts with newly diagnosed limited-stage OAMZL (NCT01010295).

Aims: To define the prevalence of chlamydiae infections, to evaluate bacterial eradication and anti-lymphoma activity of DOX in OAMZL.

Methods: The IELSG #27 trial had two parts: A) therapeutic part and B) molecular part. Pts with stage-IEA OAMZL and measurable disease were enrolled in part A, and received DOX 100 mg bid for 21 days. Pts with other lymphomas, benign lesions or MZL not eligible for part A entered the part B andwere treated following local practice. Chlamydiae infections were evaluated on diagnostic biopsies by three PCR (TETR, OmpA, hsp60). The same PCRs were used on conjunctival swabs and peripheral blood mononuclear cells (PBMC) collected before and after (at 3 & 12 months) DOX to monitor bacterial eradication.

Results: From 2006 to 2010, 54 pts were enrolled. Prevalence data are available for 44 cases: *Cp* was detected in biopsies of 32 (86%) of 37 assessed OAMZL and in 4 of 7 non-MZL. All cases were negative for the other Chlamydiae.

Twenty-eight of the 34 OAMZL pts enrolled in part A were assessable for *Cp* eradication (positive PCR on pre-DOX swabs in 8, PBMC in one or both in 19). All pts completed DOX treatment. Thirteen pts (46%) achieved *Cp* eradication (negative PCR in post-DOX samples); *Cp* was detected again at one year of f-up in two of them.

Lymphoma response was complete in 6 pts and partial in 15 (ORR= 62%, 95%CI: 46-78%), 12 had SD and one PD. At a median f-up of 24 months (range 3-51), 15 responders are relapse-free, while 6 responders and 6 no-responders experienced PD, with 2-year PFS of 54±10%. A trend to a higher response rate (82% vs. 53%; p=0.12) and PFS (2-yr: 74% vs. 52%; p=0.18) in eradicated pts was observed.

Conclusions: *Cp* infection is common in OAMZL at diagnosis. First-line DOX was associated with lymphoma regression in 62% of pts. However, DOX failed to eradicate *Cp* infection in half of pts, with a negative impact on outcome. Studies aimed to improve antibiotic efficacy are warranted.

298 A PHASE II STUDY OF LENALIDOMIDE IN PATIENTS WITH MALT-LYMPHOMA

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Background: MALT lymphoma is among the more common lymphoma entities and shares certain features with multiple myeloma. In view of this and the activity of lenalidomide in various B-cell lymphomas we have initiated a phase II study to evaluate the efficacy of lenalidomide in patients with MALT-lymphoma.

Patients and Methods: Patients with histologically verified advanced MALT-lymphoma (in case of gastric MALT-lymphoma with demonstrated refractoriness to HP-eradication) were included in the study. Treatment consisted of lenalidomide 25 mg p.o. days 1 - 12 with a 7 day-break after each cycle for a maximum of 6 courses. Restaging was scheduled after 3 and 6 cycles.

Results: A total of 18 patients were included in the trial (10 female/8 male); 5 had gastric and 13 extragastric lymphoma (6 orbital, 4 pulmonary, 1 parotid, 1 intestinal and 1 subcutaneous). Currently, 12 patients are available (9 after 3 and 3 after 6 cycles): 2 patients have achieved a CR (one after 3 and one after 6 courses) and 9 a PR (8 with ongoing therapy, one after 6 courses) and one SD. Two patients withdrew consent after the first course (due to itching/skin toxicity and fatigue). One patient showed transformation to DLBCL after initial PR of gastric MALT-lymphoma. Side effects consisted of neutropenia (grade 3 in 2 patients) and thrombocytopenia (grade 3 in one patient), two episodes of pneumonia as well as pruritus and exanthema in 5 cases (necessitating hospitalization in one patient), fatigue (2 patients), mild nausea (2 patients) and mild conjunctivitis, cramps and paresthesia in one patient each.

Conclusion: These preliminary data suggest activity of lenalidomide in MALT lymphoma with manageable toxicity. The final results of the study are awaited.

299 BENDAMUSTINE AND RITUXIMAB AS FIRST LINE TREATMENT FOR PATIENTS WITH MALT LYMPHOMA. AN INTERIM REPORT OF A PHASE 2 TRIAL IN SPAIN (GELTAMO MALT-2008-01)

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Background: There is not an established treatment for MALT lymphoma. For local advanced, refractory or disseminated disease diverse chemotherapy treatments have been used. However, the results are not conclusive.

Patients and Methods: Phase II trial (EUDRACT 2008-007725-39) carried out in Spain by the GELTAMO group in untreated patients with disseminated or multifocal MALT lymphoma or with localized gastric MALT refractory to *HP* eradication. Treatment: Bendamustine (90 mg/m^2 d1-2) and Rituximab (375 mg/m^2 d1), every 28 d. Pts were evaluated after 3 cycles: if complete remission (CR), pts received a further cycle (total 4) and if partial response (PR), pts received 3 more cycles (total 6). The aims were: feasibility and security and rate and quality of the responses, and event free survival. Here we report the interim results of the trial at 18 months.

Results: Characteristics of 44 pts enrolled: median age 66 y; 61% female; Ann Arbor: 43% stage I, 21% II and 36% III-IV; B-symptoms 11%. 48% had gastric lymphoma and the remaining in other MALT sites. Forty pts have received at least 3 cycles and 34 have completed treatment. Overall response rate (ORR) after 3 cycles was 100% with CR of 85% (34/40). Gastric lymphoma had slightly better CR (90% vs 81%, p:0.381). In the 34 who have completed treatment plan (4 or 6 cycles), ORR is 100% with CR of 97% (CR 31, uCR 2, PR 1). Only 5 pts (15%) have needed a total of 6 cycles. With a median follow-up of 9 months (3-17), no patient has relapsed. A total of 171 cycles of R-B were delivered in the whole population. Only 13 grade 3-4 CTC or severe adverse events have been reported (in 12 pts). Only 2 patients have not completed treatment due to toxicity. Grade 3-4 haematologic toxicity was infrequent: neutropenia in 3% of the courses.

Conclusions: Combination of Bendamustine and Rituximab in first line treatment of MALT lymphoma achieved a CR of 97%. Interestingly, a large majority of pts required only 4 cycles. This regimen was safe and well accepted, making this response-adapted schedule a foremost therapeutic strategy for this type of lymphoma.

300 RESULTS OF FDG PET-CT IMAGING BEFORE AND AFTER THE INDUCTION TREATMENT ARE RELATED TO DIFFERENT CLINICO-BIOLOGICAL FEATURES AND CAN PREDICT THE OUTCOME OF PATIENTS WITH FOLLICULAR LYMPHOMA (FL)

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Introduction: The role of FDG PET-CT either at staging or to assess response after treatment is not yet established in FL. The aim of this study was to analyze the relationship between the results of PET-CT and main clinico-biological features, and its usefulness to predict the outcome in a series of patients with FL.

Patients and Methods: One hundred and sixteen patients (62M/54F; median age, 59 years) diagnosed with FL (grade 1, 31; grade 2, 26; grade 3a, 34; grade 3b, 9; not determined, 16) in a 6-year period in two institutions were the subjects of the study. Whole-body [^{18}F] FDG-PET-CT was performed in all patients at baseline and in 90 after treatment. PET-CT images were analyzed visually and semi-quantitatively by calculating the standardized uptake value (SUV). Proliferative index was measured by Ki-67 expression. The distribution according to the FLIPI score was: low risk 36%, intermediate risk 29% and high risk 42%. Ninety six patients received rituximab-containing combinations. Complete response (CR) rate was 66%. After a median follow-up of 2.9 years, 3-year progression-free survival (PFS) and overall survival (OS) were 78% and 93%, respectively.

Results: Initial PET-CT showed [^{18}F] FDG uptake in 105 of 107 assessable patients (98%), with a median SUV of 6.9 (range, 2-24). Nine cases with localized stage and negative PET were excluded. PET detected more lesions than CT scan in 27 cases. There was a correlation between initial PET-TC and histological grade (p=0.01), as well as high serum LDH (p=0.002) and Ki-67 (p=0.06). After induction, PET-CT was negative in 66 patients and positive in 24 (median SUV 3.5, range 2-23). There was also a correlation between post-treatment PET-TC and FLIPI score (p=0.02). Six (20%) of CR patients still showed [^{18}F] FDG uptake. PET-CT negative patients had longer PFS and OS than those PET-CT positive (p=0.003 and p=0.01, respectively). When patients with grade 3b FL were excluded, the difference in terms of PFS maintained (3-year PFS: 89 vs. 58% for PET-CT negative vs. positive, respectively; p=0.003).

Conclusion: PET-CT before treatment is related to histological grade and proliferation. PET-CT after treatment could predict the outcome of the patients in terms of PFS.

301 ELEVATED PRETREATMENT SERUM CYTOKINES PREDICT DISEASE RELAPSE AND A POOR PROGNOSIS IN FOLLICULAR B-CELL NON-HODGKIN LYMPHOMA (FL) PATIENTS

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Background: While clinical prognostic factors such as those included in the Follicular Lymphoma International Prognostic Index (FLIPI) predict outcome in FL patients, predicting the outcome of patients might be further refined using biological factors. We tested whether pretreatment serum cytokines could provide additional prognostic information in FL patients.

Methods: Newly diagnosed FL patients prospectively had 30 serum cytokines measured pre-treatment using a multiplex ELISA. 400 non-lymphoma controls were used to establish normal cytokine ranges. Principal components analysis (PCA) was performed on the combined FL and control dataset to identify cytokine profiles. Cox proportional hazards models were used to evaluate the association between cytokines and event-free survival.

Results: 211 FL patients were included. The median age was 60 years (range 24-94) and 54% were male. 73 (34%) patients were initially observed while 29 (14%) received rituximab alone and 109 (52%) received combination therapy. At a median follow-up of 49 months (range 13-86), 103 patients (48%) had relapsed and 19 patients had died (9%). Three cytokine profiles were determined based on PCA analyses. 115 FL patients (53%) had a normal cytokine profile similar to the general population of controls; 81 (37%) had a lymphoma specific cytokine profile associated with elevation of IL-2R, IL-12, CXCL9, and CXCL10; 15 (7%) had a profile associated with a non-specific cytokine elevation. Patients with an abnormal cytokine profile (either lymphoma or non-specific) had a significantly worse event-free (HR=1.92, 95%CI:1.29-2.84, p=0.001) than those with a normal cytokine profile; the association strengthened after adjustment for the FLIPI and treatment in the Cox model (EFS HR=2.11, 95%CI:1.40-3.19, p=0.0004). An elevated cytokine profile was associated with early relapse or progression in both the subset of patients who were initially observed (p=0.01) as well as the subset who received immunochemotherapy (p=0.04).

Conclusion: An abnormal serum cytokine profile is associated with shorter time to relapse in patients with FL.

302 RISK FACTORS FOR HISTOLOGICAL TRANSFORMATION (HT) FROM FOLLICULAR (FL) TO DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): A POPULATION-BASED ANALYSIS FROM THE DANISH LYMPHOMA REGISTRY, LYFO

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Introduction: FL is characterised by an indolent clinical behaviour. However, in a fraction of patients it transforms to a more aggressive histology, often with a rapid clinical course and shortened survival. Hence, prediction of the transformation risk is important for a risk adapted treatment strategy. The aim of the study was to identify clinicopathological parameters at diagnosis influencing occurrence of HT in patients with FL.

Materials and methods: 2554 FL cases diagnosed 1983-2009 were identified from LYFO. We defined HT as the conversion of FL grade I-II to grade III or of any FL to DLBCL. Of these, 108 (4%) had both biopsy-proven HT and an evaluable set of clinicopathological parameters required for inclusion in the study. Uni- and multivariate Cox-regression analysis was performed.

Results: The cohort (N=2554) had a median age of 60yrs (15-97yrs) with a M/F ratio of 0.85.For HT cases median age at diagnosis was 59yrs (28-85 yrs) and the M/F ratio 1.08. Of all FL cases analysed at diagnosis 20.6% had elevated s-LDH, 65.7% disseminated disease (stage III-IV) and 32.4% presented with extranodal manifestations. Poor performance score (WHO 2-4) was found in 8% of cases and 24.7% experienced B-symptoms. At univariate level risk of HT was significantly increased by a high FLIPI score, extranodal localization and in particular by an elevated pretherapeutic s-LDH. Interestingly hypogammaglobulinemia also significantly predicted the risk of HT. In fact in multivariate analysis the three parameters that, despite being statistically interrelated, retained the strongest predictive value for subsequent HT were hypogammaglobulinemia (p=0.005 HR=2.05 (1.24-3.41)), elevated s-LDH (p=0.001 HR=2.09 (1.33-3.26)) and extranodal disease (p<0.001 HR=2.17(1.44-3.26)). The simultaneous presence of two or more of these factors had additive predictive value for the HT endpoint.

Conclusion: Pretherapeutic presences of elevated s-LDH, extranodal disease and/or hypogammaglobulinemia in FL patients significantly impact the risk of subsequent HT.

303 EARLY STAGE FOLLICULAR LYMPHOMA: ROLE OF MOLECULAR MONITORING IN PATIENTS TREATED WITH LOCAL RADIOTHERAPY ± RITUXIMAB

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Background: Conventional treatment of stage I-II follicular lymphoma (FL) is local radiotherapy (RT), which allows eradication of the disease in about 50% of patients. Very few data are available on the role of anti-CD20 MoAb and of minimal residual disease (MRD) evaluation in this setting.

Methods: 41 consecutive patients with a confirmed diagnosis of stage I/II FL were investigated by PCR in order to identify the presence of Bcl-2 rearranged cells in the bone marrow (BM) and/or peripheral blood (PB). All patients were treated with involved field RT (36 Gy). Subsequently, MRD was evaluated every 6 months.

Results: PCR analysis revealed Bcl-2 rearranged cells in 24/41 patients (58.5%) at presentation. After irradiation of the sole site of the disease, Bcl-2 rearranged cells disappeared in 15 of the 24 (62.5%) patients positive at baseline; in 8 (19.5%) MRD was positive, while 1 patient refused the test. After a median follow up of 50 months, 5 patients (12.2%) had a clinical relapse. MRD evaluation demonstrated that:

· 17/41 Bcl-2 negative patients at the basal evaluation were not subsequently retested; only 1/17 patients had a clinical relapse (the new biopsy documented a mantle cell lymphoma).

· Of the 15 patients positive at baseline and who became negative after RT, 3 have had a molecular relapse during the follow-up, leading in one case to an overt clinical relapse.

· Of the 8 patients persistently Bcl-2 positive after radiotherapy, 3 had a clinical relapse. Rituximab (375 mg/m^2 x 4) was administered to 5 patients with a persistently positive Bcl-2 after RT: 3 of them became Bcl-2 negative.

Discussion: Viable Bcl-2+ cells can be demonstrated in the BM and/or PB of the majority of stage I-II FL patients (despite a negative BM biopsy). Irradiation of the sole nodal/extranodal disease sites allows disappearance of Bcl-2+ cells in the majority of previously positive patients (62.5%). Pre-treatment Bcl-2 BM and/or PB evaluation has a prognostic role: no clinical relapses were observed in Bcl-2 negative cases at baseline except for one patient, relapsed as mantle cell. MRD evaluation has a prognostic role: among 32 Bcl-2 negative patients after treatment, 2 relapses (6.2%) were observed (1 relapsed as mantle cell), while among 8 Bcl-2 positive patients after treatment 3 relapses (37.5%) were observed.

Prognosis of early stage FL treated with local RT ± rituximab is excellent: only 5 patients have so far relapsed at a median follow up of 50 months.

304 FINAL RESULTS OF RITUXIMAB PLUS CHLORAMBUCIL COMBINATION IN NAIVE FOLLICULAR LYMPHOMA PATIENTS

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Introduction: Although Follicular lymphoma (FL) still remains an incurable disease, the combination of Rituximab with standard chemotherapy has significantly improved the outcome of FL with prolonged progression-free survival, overall response and median time to treatment failure (TTF) of FL patients.

Material and Methods: From 2001 to 2010 75 patients with histological confirmed FL received Rituximab plus Chlorambucil (R-Chl) as first-line treatment. All the patients underwent to an induction phase with four weekly infusions of Rituximab at 375 mg/sqm and 6 consecutive weeks of Chl at 6mg/sqm/daily. After restaging, all patients with stable or responsive disease (complete or partial remission respectively) proceeded to a consolidation phase with 4 monthly Rituximab infusions and 14 days of Chl each month.

Results: Clinical response and toxicity were evaluable in sixty-five (86.6%) of treated patients. The median age was 56 years (range 29-79). The majority of them (75%) presented stage III-IV; 78% grade 1-2; 28% at least one extranodal site and 29% bulky disease. In 59 evaluable patients FLIPI was as follows: 52% 0-1; 25% 2; 14% >2. After the induction phase, ORR was 98%, with 14 patients (21%) showing a complete response (CR) and 50 a partial response (PR). At the end of treatment, 49 patients (75%) achieved a CR and 15 PR. The mean daily dose of Chl received during the induction phase was 10 mg, while in the prolonged treatment was 8 mg. No significant haematological toxicity has been reported with discontinuation of Chl in only one patient for a persistent G3 neutropenia after the first consolidation cycle. One HBsAg positive patient did not completed the schedule because of AST/ALT elevation. After a median follow up of 34 months (range 9-188), 62 patients are alive and 42 patients (65%) are still in CR. Thirteen patients (20%) relapsed/progressed with a median time to further treatment of 29 months (range 11-98) with only one dying for disease.

Conclusions: Our data suggest that the combination of Rituximab and chlorambucil is safe and feasible in previously untreated FL patients. The efficacy of this regimen is similar to other more aggressive therapy, but with a significantly lower and manageable toxicity profile. For the above reasons, the combination of Rituximab and Chlorambucil may be considered as a valid first-line treatment option, especially in those not suitable for aggressive regimens.

305 BENDAMUSTINE FOR PATIENTS WITH INDOLENT LYMPHOMA – A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS (RCT)

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Background: Survival of patients with indolent lymphoma has improved in the recent decade. While it is clear that the addition of rituximab to induction chemotherapy improves survival of these patients, it is unclear which is the best chemotherapy to combine with rituximab. None of the chemotherapy regimens that had been compared in randomized controlled trials, were superior in terms of overall survival (OS).

A number of RCTs have examined the effect of bendamustine in patients with indolent lymphoma. Progression free survival (PFS) was similar or prolonged with bendamustine compared to other chemotherapy and an OS benefit has not been shown. In order to evaluate the effect of bendamustine on the OS of patients with indolent lymphoma we performed a systematic review and meta-analysis.

Methods: We included RCTs that compared bendamustine to other chemotherapy regimens for patients with indolent lymphoma. In December 2010 we searched *The Cochrane Library*, MEDLINE, LILACS, conference proceedings, and databases of ongoing trials. The primary outcome was all cause mortality. Relative risk (RR) for dichotomous data and hazard ratio (HR) for time to event data were estimated and pooled.

Results: We identified 4 trials, conducted between the years 1994 and 2010 randomizing 1251 patients. Studies characteristics are presented in Table.

Patients treated with bendamustine had an improved OS compared to controls, RR for death 0.80; 95% CI 0.67 - 0.97, $I^2 = 0$. After excluding the trial with only CLL patients the RR is 0.82; 95% CI 0.67 - 1.01.

PFS was improved with bendamustine, HR 0.47; 95% CI 0.39 - 0.57. The rate of complete remission improved with bendamustine compared to controls, RR 2.31; 95% CI 1.07 - 4.96, random effects model, $I^2 = 88\%$. The rate of grade 3/4 adverse events was unaffected RR 1.21; 95% CI 0.99 - 1.48.

Discussion: This meta-analysis shows for the first time that bendamustine improves OS and PFS of patients with indolent lymphoma and CLL compared to other chemotherapy. These results should be interpreted cautiously due to the wide clinical heterogeneity of patients and treatments. Further trials of a more homogenous group should be performed to explore the role of bendamustine in various lymphoproliferative neoplasms.

Study	# patients	Bendamustine (B) regimen	Comparator
Rummel 2009	549	rituximab (R)B	RCHOP
Rummel 2010	219	RB	R fludarabine
Knauf	319	B	Chlorambucil
Herold	164	B vincristine prednisone	COP

306 LENALIDOMIDE PLUS RITUXIMAB LEADS TO A HIGH RATE OF DURABLE RESPONSES IN PATIENTS WITH RELAPSED/ REFRACTORY INDOLENT NON-HODGKIN'S LYMPHOMA

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Background: Although indolent non-Hodgkin's lymphomas (iNHLs) are responsive to initial therapy, patients continue to experience a relapsing and progressive disease course and most remain incurable with current treatments. Lenalidomide is an immunomodulatory agent which enhances rituximab-mediated antibody-dependent cellular cytotoxicity. In preclinical models, combining lenalidomide and rituximab (R2) improved antitumor activity relative to either agent alone. Here we provide an update of the results from a phase 2 trial investigating clinical activity and safety of R2 in relapsed/refractory (rel/ref) patients with iNHL.

Material and Methods: Patients had rel/ref iNHL with measurable disease, ≥1 prior therapy, and ECOG Performance Status ≤2. Lenalidomide 25 mg/day was initially administered on days 1–21 of each 28-day cycle until disease progression, while rituximab 375 mg/m^2 IV was administered on day 15 of cycle 1, and repeated weekly for a total of 4 doses. A second 4-weekly course of rituximab was permitted after cycle 2 for patients achieving less than complete response (CR). After 2 of the first 4 patients developed grade 3 tumor lysis syndrome, the protocol was amended to reduce the lenalidomide dose to 20 mg, with allopurinol prophylaxis. The primary end point was overall response rate (ORR). Secondary end points were response duration, overall survival, progression-free survival (PFS), and safety.

Results: Of the 21 enrolled patients, 16 had follicular lymphoma (FL). The median age was 60 years (range 50–91), median number of prior therapies was 3 (range 1–11), and 7/21 (33%) patients were rituximab-refractory. The median number of cycles received was 8 (range 2–33). The most common grade 3–4 adverse events were lymphopenia (25%), neutropenia (19%), fatigue (13%), and hyponatremia (19%). For the 18 evaluable patients, the ORR (at least partial response) was 78%, including 6 patients (33%) with CR. At a median follow-up of 9 months, median PFS was 13 months. Notably, the ORR in patients with FL was 86%, including 50% CR. FcgRIIIa genotype data was available for 11 patients with FL: 1 patient had V/V, 6 patients were heterozygous (F/V), and 4 patients had F/F. The ORR was 100% in the V/V type, 100% in the V/F type, and 50% in the F/F type. Median PFS was 14.85 months in the V/F type and 8.31 months in the F/F type.

Conclusion: Our data suggest that the R2 combination has significant clinical activity without appreciable toxicity in patients with rel/ref iNHL, and may overcome the previously reported lower activity of single-agent rituximab in patients with the low-affinity type FcgRIIIa receptor.

307 EFFICACY AND SAFETY OF BORTEZOMIB-RITUXIMAB (VCR) VS RITUXIMAB (R) IN PATIENTS (PTS) WITH RELAPSED, R-NAÏVE/-SENSITIVE FOLLICULAR LYMPHOMA (FL): OUTCOME ACCORDING TO PRIOR THERAPY

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Introduction: FL pts typically receive multiple lines of therapy with decreasing efficacy over the course of their illness. Identification of agents with improved activity in pre-treated pts is an important goal. The phase 3 LYM3001 trial showed improvements in overall response and CR rates and PFS with VcR vs R in 676 pts with relapsed FL. Here we report activity and safety by line of therapy and prior R.

Material and Methods: Pts with relapsed grade 1/2 FL were randomized to five 5-week cycles of VcR (Vc 1.6 mg/m^2, d 1, 8, 15, 22; R 375 mg/m^2, d 1, 8, 15, 22, cycle 1, and d 1, cycles 2-5) or R alone on the same schedule.

Results: Of 336/340 pts in the VcR/R arms, 143/137, 85/90, and 108/113 had received 1, 2, or ≥3 prior lines of therapy, respectively; 191/190, 105/107, 29/30, and 11/13 pts had received 0, 1, 2, or ≥3 prior R-containing lines. Median PFS in VcR vs R pts was 16.6 vs 12.5 mo (HR 0.794, p=0.137), 13.0 vs 9.0 mo (HR 0.748, p=0.117), and 10.0 vs 9.2 mo (HR 0.944, p=0.718) in pts with 1, 2, and ≥3 prior lines of therapy; in pts with 0, 1, or 2 prior R treatments, PFS was 14.0 vs 11.4 mo (HR 0.749, p=0.023), 11.7 vs 9.2 mo (HR 0.902, p=0.556), and 9.0 vs 6.9 mo (HR 0.773, p=0.404), respectively. Response rate was higher with VcR vs R in pts with 1 (71% vs 53%, p=0.003) and 2 (65% vs 43%, p=0.004) but not ≥3 (52% vs 50%) prior lines. In pts with 1/>1 prior line, rates of adverse events (AEs), grade ≥3 AEs, and serious AEs were similar within the VcR arm (94%/95%, 46%/46%, 16%/19%) but higher in pts with >1 prior line within the R arm (74%/81%, 13%/26%, 8%/13%).

Conclusions: Vc enhances the activity of R in previously treated FL pts who are R-naive and in those who have received multiple lines of chemotherapy. This confirms that Vc may confer benefit in relapsed FL and suggests a potential role in enhancing activity of current regimens used as initial therapy.

308 BORTEZOMIB PLUS RITUXIMAB (VCR) VS RITUXIMAB ALONE (R) IN PATIENTS (PTS) WITH HIGH-RISK, RELAPSED FOLLICULAR LYMPHOMA (FL)

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Introduction: The phase 3 LYM3001 trial in pts with relapsed FL demonstrated higher overall response (ORR: 63% vs 49%) and CR (25% vs 18%) rates, and prolonged PFS (median 12.8 vs 11.0 mo) with addition of Vc to R. We report findings in pts with high-risk FL (FLIPI score ≥3 and high tumor burden by modified GELF criteria), who typically have a poor prognosis and need better treatment options, and may particularly benefit from novel, active regimens.

Material and Methods: Pts with grade 1/2 FL were randomized to five 5-week cycles of VcR (Vc 1.6 mg/m^2, d 1, 8, 15, 22; R 375 mg/m^2, d 1, 8, 15, 22, cycle 1, and d 1, cycles 2-5; N=336) or R alone (N=340).

Results: 103/98 VcR/R pts had high-risk FL; median age was 61/60 yrs, 51%/43% were male, 76%/66% were Caucasian and 19%/30% Asian, 34%/33% had ≥3 prior lines, and 39%/41% had prior R. ORR was 59%/37% (p=0.002), CR/CRu rate was 13%/6% (p=0.145), and durable (≥6 mo) response rate was 45%/26% (p=0.008) with VcR/R. Median PFS was 9.5/6.7 mo (HR 0.667, p=0.012), median time to next treatment was 14.8/9.1 mo (HR 0.762, p=0.103), and median OS was 37.8/41.5 mo (1-yr OS 83.1%/76.6%, HR 0.907, p=0.657) with VcR/R. 64%/53% of VcR/R pts completed 5 cycles, with grade ≥3 AEs in 51%/32% and serious AEs in 22%/16% of pts. Common grade ≥3 AEs were neutropenia (18%/6%), anemia (4%/5%), diarrhea (8%/0), and thrombocytopenia (5%/2%).

Conclusion: Pts with high-risk FL treated with VcR had significantly higher response rates and longer PFS than pts receiving R alone, with greater clinical benefit than in the overall population; additional toxicity was acceptable and did not affect treatment feasibility.

309 BENDAMUSTIN (B) AND RITUXIMAB (R) IN THE TREATMENT OF RELAPSED INDOLENT CD20+ NON-HODGKIN-LYMPHOMA - A PHASE II STUDY OF THE EAST GERMAN STUDY GROUP OF HAEMATOLOGY AND ONCOLOGY (OSHO #072)

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Background: Promising results have been reported in several studies evaluating the combination of B plus R in patients with relapsed/refractory indolent lymphomas. Overall response rates (ORR) of 93%, including a 64% rate of complete remissions (CR) could be observed.

Material and Methods: This prospective, non-randomized multicenter phase II trial was initiated in June 2004. The recruitment was finished in June 2009. Patients with relapsed/refractory CD20+ B-cell-Lymphoma or mantle cell lymphomas got an induction therapy with Rituximab 375 mg/m^2 (day 1) plus Bendamustine 90 mg/m^2 (day 1+2) for up to 6 cycles. After 6 cycles patients with CR or PR were recruited for a consolidation treatment with Rituximab (375 mg/m^2, bimonthly for maximal 4 infusions). The consolidation started 8 weeks after the last cycle of the induction therapy. The primary endpoint was event-free survival (EFS). Secondary endpoints were the rate of remissions (CR+PR), toxicity, and overall survival (OS).

Results: In this interim analysis 62 of 63 enrolled patients were evaluable. All 62 patients finished the induction protocol. The median follow up was 31 months. The histological findings of the patients were: follicular lymphoma (33), mantle cell lymphoma – MCL (15), LPIC (8), marginal zone (5) and not classified indolent (2)

lymphoma. Median age was 67 years (45-85). Patient's history showed one (44), two (14) or three (5) prior treatment regimes. The overall response rate (ORR) was 83% after induction chemotherapy (44% CR, 39% PR). 13% of the patients reached a CR during the consolidation treatment after only a PR at the end of the induction therapy. CR rate was 57% after consolidation. Both median EFS and PFS were similar 41 months. The two-year-EFS was 58%. The two-year-OS was 77%. The observed hematologic toxicity was a reversible myelosuppression (WHO° III/IV leucocytopenia (10%), thrombocytopenia (6%), and anemia (2%). Only a low number of non-hematological side effects was seen (WHO° III/IV infections 1.2%).

Conclusion: BR is a highly effective protocol in the treatment of relapsed NHL regarding the remission rates and PFS for about 2 years. Furthermore, our data indicate that the toxicity of the investigated combination therapy is safely to manage. The treatment was well tolerated even in elderly patients. The treatment can be recommended for outpatients with relapsed low-grade lymphoma.

310 TIME TO NEXT ANTI-LYMPHOMA THERAPY (TTNT) AND TREATMENT-FREE INTERVAL (TFI) WITH BORTEZOMIB-RITUXIMAB (VCR) VS RITUXIMAB (R) IN PATIENTS (PTS) WITH RELAPSED FOLLICULAR LYMPHOMA (FL)

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Introduction: TTNT is an increasingly important endpoint in FL, and a good measure of clinical benefit of treatment. The phase 3 LYM3001 trial showed higher response rates and longer PFS with VcR vs R in pts with relapsed FL. We report analyses of TTNT and TFI, which were pre-defined endpoints in the trial.

Material and Methods: Pts with grade 1/2 FL were randomized to five 5-wk cycles of VcR (Vc 1.6 mg/m^2, d 1, 8, 15, 22 with R 375 mg/m^2, d 1, 8, 15, 22, cycle 1, and d 1, cycles 2-5) or R alone.

Results: After a median follow-up of 33.9 mo, 181/336 (54%) VcR and 204/340 (60%) R pts had received subsequent therapy. Median TTNT (23.0 vs 17.6 mo, HR 0.799, p=0.024) and TFI (17.7 vs 13.0 mo) were longer with VcR vs R. Sensitivity analyses, excluding pts who discontinued due to adverse events, had peripheral neuropathy (PN) at any time, or had PN at progression, confirmed the TTNT benefit of VcR, which was not affected by Vc-related PN. Type/intensity of subsequent therapy were similar in each arm. Median TTNT/TFI were longer with VcR vs pts' last prior therapy (23.0/17.7 vs 20.9/15.5 mo) but similar for R (17.6/13.0 vs 17.8/13.4 mo). Prior therapies were similar between arms; 43% VcR and 44% R pts had prior R. Subgroup analyses indicated longer TTNT with VcR vs R in pts with high tumor burden (16.9 vs 13.5 mo, HR 0.751, p=0.024) and pts aged ≤65 yrs (22.9 vs 16.1 mo, HR 0.747, p=0.01). A tendency for longer TTNT with VcR was also seen in pts with FLIPI ≥3 (17.1 vs 14.4 mo, HR 0.760, p=0.067) and pts who had no prior R (27.7 vs 21.2 mo, HR 0.778, p=0.064). Median TTNT with VcR vs R was 19.6 vs 14.6 mo (HR 0.822, p=0.182) in pts with prior R.

Conclusions: VcR demonstrated prolonged TTNT and TFI vs R, and resulted in longer TTNT and TFI vs last prior therapy. TTNT benefit was seen across subgroups, including pts with high tumor burden.

311 RITUXIMAB PLUS SARGRAMOSTIM FOR THE TREATMENT OF NEWLY DIAGNOSED FOLLICULAR LYMPHOMA: FINAL RESULTS OF A PHASE II STUDY

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Background: Rituximab (R) works in part through antibody dependant cellular cytotoxicity (ADCC). Several cytokines can enhance ADCC.Sargramostim (granulocyte macrophage-colony stimulating factor - GM-CSF) is an FDA-approved cytokine that stimulates the proliferation and differentiation of hematopoietic progenitor cells. In addition to stimulating multi-lineage hematopoietic recovery GM-CSF may augment dendritic cell numbers and promote antigen presentation. We and others (Cartron G, JCO 2008) have explored the combination of R + GM-CSF for patients (pts) with follicular lymphoma (FL). Following encouraging pilot experience (Liu N. ASH 2003) in 2006 we organized a multi-center trial of R + GM-CSF for pts with untreated FL.

Methods: Pts with untreated FL were eligible for study. R was administered at 375mg/m2 once weekly x 4 weeks plus GM-CSF, 250 μg sc three times weekly x 8 weeks. The planned sample size was 52 with a primary endpoint of complete response (CR) rate at 3 mo. Secondary endpoints included progression free survival (PFS) and safety of the combination. Response was assessed using the 1999 International Working Group Criteria.

Results: From 12/2006-5/2009, 52 pts enrolled and all were eligible for assessment. The median age was 56 (31-78) and 62% were male.56% of patients had intermediate or high risk FLIPI.Fifteen (29%) pts had bulky disease (>5cm) and 29 (56%) pts had elevated B2M.Tolerance was good and effects attributable to GM-CSF were minor. Absolute granulocyte count above 15K occurred in only 2 pts; conversely, ≥ grade 3 neutropenia occurred in 8 pts. No significant infections occurred. At 3 months, the overall response rate was 69%, including 23% of pts with a CR. With continued follow up response rates improved (ORR 74%, CR 42%). Twenty four (46%) pts remain in remission without further treatment. At a median follow up of 14 mo, the median PFS of all pts was 28 mo including pts with bulky disease (median PFS, 16 mo). No difference in PFS was observed when comparing FLIPI score (0-1) vs (2-3) or B2M.

Conclusion: Rituximab plus GM-CSF is well tolerated and active in untreated pts with FL.There did not appear to be a significant difference in outcomes when comparing FLIPI scores, although PFS was inferior in patients with bulky disease. Randomized studies are required to determine whether this combination is superior to rituximab as a single agent.

312 IMPACT OF RITUXIMAB MAINTENANCE TYPE AND FCGRIIA AND FCGRIIIA GENOMIC PROFILE IN PATIENTS WITH PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA

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Background: The PRIMA study has shown that maintenance with Rituximab (R) during 2 years improve progression free survival in pts with previously untreated follicular lymphoma (FL) responding to immunochemo. Polymorphisms in the IgG Fc receptor FcgRIIIa and FcgRIIa genes have been associated with response in several lymphoma types. The aim was to retrospectively analyse our experience with R maintenance (RM) in pts with previously untreated FL responding to rituximab or immunochemotherapy and, also to analyse the impact of polymorphisms regarding progression free survival, incidence of hypogammaglobulinemia and Ig levels.

Patients and Methods: pts with FL in CR or PR after first-line R o R-Chemo received RM: type 1) R 375 mg/m^2/week x 4 consecutive weeks every 6 months during 2 years or type 2) R 375 mg/m^2 every 3 or 2 months during 2 years. FcgRIIa and FcgRIIIa genotypes were determined by allelo-specific PCR.

Results: 39 consecutive pts included. Characteristics: median age 66 y; 44% male; Ann Arbor III-IV: 85%; B-symptoms: 11%; FLIPI 3 or more: 48%. Induction treatment: 15% chemo, 8% R and 77% R-chemo. 56 pts received antracyclin-containing chemo. Status at starting RM: CR in 80% and PR in 20%. Type of RM: RM1 in 41% and RM2 59%. FcgRIIa HH 22%, HR 5% and RR 56%, and FcgRIIIa VV 28%, VF 54% and FF 8%. At a median follow-up since first RM of 40 months (3-106), 9 pts have relapsed and 4 died. Overall and progression free survival at 4 years were 95% and 79%, respectively. Antracyclin-containing chemotherapy was significantly associated with a different probability of progression (HR 5.2; 95% CI 1.1-25.1, p=0.022), but not the following variables: status prior to maintenance, type of maintenance and FcgRIIa or FcgRIIIa genotype. Hipogammaglobulinemia was present in 41% and 49 % of pts before and after R maintenance, respectively. Levels of IgM diminished at the end of maintenance in pts with FcgRIIa HR-RR (p=0.019) and in those with FcgRIIIa VF-FF (p=0.017). IgG and IgA levels did not significantly change during maintenance.

Conclusions: R maintenance for 2 years in pts with previously untreated follicular lymphoma (FL) responding to immunochemotherapy is a very active therapeutic strategy, especially in those pts receiving induction antracyclin-containing chemo. The two schedules of R maintenance were effective and all pts benefited independently of FcgRIIa and FcgRIIIa genomic profile. Levels of IgM were significantly influenced according to FcgRIIa and FcgRIIIa genotypes.

313 FCGR3A POLYMORPHISM DOES NOT SIGNIFICANTLY AFFECT RESPONSE AND OUTCOME OF FOLLICULAR LYMPHOMA PATIENTS TREATED IN THE PRIMA STUDY WITH RITUXIMAB AND CHEMOTHERAPY FOLLOWED BY RITUXIMAB MAINTENANCE OR OBSERVATION

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Background: Previous studies demonstrated that a polymorphism (SNP) of the *FCGR3A* gene modifying the 158 amino-acid position was correlated with response rate and progression free survival (PFS) in patients with follicular lymphoma (FL) treated with rituximab (R) monotherapy. The prognostic role of *FCGR3A* SNP in FL patients treated with R-chemotherapy (CT) remained controversial and was not evaluated in the context of R maintenance.

Patients/Methods: We analysed *FCGR3A* polymorphisms in patients treated in the PRIMA study (Salles, Lancet 2011) to investigate whether the presence of phenylalanine (F)/ valine (V) alleles could influence i) response rates at the end of R-CT induction and R maintenance treatment ii) PFS from the initiation of treatment or from the date of randomisation. Genomic DNA was extracted from blood samples of 460 patients having signed a specific informed consent form and analysed using a Taqman based assay.

Results: Initial characteristics were comparable between this group and the PRIMA cohort and R maintenance effect was confirmed in this studied population. The distribution of the VV, VF and FF alleles of *FCGR3A* was 15%, 47% and 38%, respectively. *FCGR3A* SNP was not associated with any initial characteristics of patients. After R-CT, complete response (CR) and unconfirmed CR rates were 34%/31%, 35%/32% and 34%/32% in VV, VF in FF alleles, respectively ($P = .86$). Similar results were obtained when considering only patients (81%) having received R-CHOP in induction therapy. At the end of R maintenance, response rate was also not significantly different between the different *FCGR3A* alleles ($P = .18$). With a median follow-up of 42 months from registration, PFS was not significantly different between *FCGR3A* VV, VF and FF carriers either from the start of induction therapy (69.9%, 65.2%, 63.6% $P = .68$) or from time of randomisation in patients randomized in R maintenance (71.9%, 65%, 74% $P = .67$) or observation (60.5%, 48.8%, 51.5% $P = .48$).

Conclusions: *FCGR3A* SNP does not appear to influence the response rate after R-chemotherapy alone or followed by maintenance in this prospective study. Other SNPs possibly influencing R activity are currently being evaluated.

314 RADIOIMMUNOTHERAPY (RIT) WITH ^{177}LUTETIUM-DOTA-RITUXIMAB (^{177}LU-D-R): FINAL RESULTS OF A PHASE I/II - STUDY IN 31 PATIENTS WITH RELAPSING FOLLICULAR, MANTLE CELL AND OTHER INDOLENT B-CELL LYMPHOMAS

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Introduction: ^{177}Lutetium linked to the chimaeric anti-CD20 antibody rituximab (R) with DOTA as chelator emits beta-rays (0.497MeV) and a gamma-component suitable for imaging. Handling is less hazardous than for ^{131}I and the beta-component may provide a more favourable tumour/non-tumour ratio than ^{90}Y. Our aim was to determine the maximum tolerated dose (MTD) and to explore clinical response.

Material and Methods: From 02/02 to 05/09 31 pts were treated in 7 cohorts (m:17, f: 14, median # of pretreatments (Tx): 3 [2-7], 22/31 had received R pre RIT). Tx consisted of R (250mg/m^2) on d1 and d8 and ^{177}LU-D-R on d8. Pts were hospitalized for 5 days for imaging and, at higher doses, to fulfilradiation safety requirements. Dose escalation was done in steps of 5 mCi/m^2. Reassessment was on week 10.

Results: Toxicity: Gr II fatigue and Gr I nausea were reported on the days following Tx. Anemia Gr II occurred at levels 4, 5 and 7 each and one level 7 pt requiredtransfusions. Neutrophils: Gr III was observed at levels 3-6, Gr IV in one pt at level 7. This pt succumbed to sepsis inneutropenia. Tc: One Gr III at levels 4-6 (nadir: wk 7) was observed. One brief Gr IV episode was seen in 1 of 5 pts at level 3 and in one pt at level 7. After a maximum observation time of 103 mo no MDS or AML have occurred.

Responses were seen at all dose levels. *Mantle cell lymphoma (n=14):* All pts progressed after a median of 6 mo (1-27) and died after a median of 17 mo (13-95). One pt responded twice (25 and 27 mo). Median time to next treatment (TTNT) was 9 mo (1-26) in 13 of 14 pts. *Follicular lymphoma (n=13):* Five of 11 pts reached CR and 8/13 pts are alive after a median of 84 mo (32-103). Four pts remain in remission without further Tx 32+, 34+, 99+, 99+ mo post RIT.Median TTNT in 7 pts requiring Tx was6 mo (2-44). *Other lymphomas (n=4):* One pt with indolent NOS lymphoma progressed on ^{177}Lu-D-R and died 46 mo later. One pt with a transformed FL progressed and is in CR after an auto-transplant (50 mo+). One pt with marginal zone lymphoma (MZL) is in a CR (29 mo+) and one progressed and is in CR (23 mo+) after an allo-transplant.

Conclusions: The MTD of ^{177}LU-D-R was reached at 50 mCi/m^2. Non hematologic toxicity was negligible. Responses were seen in all lymphoma entities and at all dose levels tested. Further testing is warranted in follicular and MZL.

315 AUTOLOGOUS STEM CELL TRANSPLANTATION WITH IMMUNOTHERAPY INDUCES PROLONGED CLINICAL AND MOLECULAR REMISSIONS AND MAY CURE PATIENTS WITH RECURRENT FOLLICULAR LYMPHOMA

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Introduction: We hypothesized that the addition of immunotherapy to HDT/ASCT may augment "in vivo" graft purging and achieve more effective eradication of minimal residual disease (MRD) post ASCT. This may lead to improved PFS and OS.

Methods: We conducted 3 sequential IRB approved prospective phase 2 trials of HDT/ASCT combined with immunotherapy in patients with relapsed FL from 1997-2010. Patients received either a-interferon (a-IFN), Rituximab (R) or and R+ a-IFN post ASCT. An in vivo purge of lymphoma cells from the stem collection was performed in trials 2 and 3 with one or three doses of R respectively during the stem cell mobilization.

Results: 72 patients from the 3 trials are included. Median age was 47 (30-71) and patients were a median of 31 mo (9-197) from diagnosis. 53% were male. Median FLIPI score was 2. Median # of prior chemotherapies was 1. Median number of cycles of salvage chemotherapy was 4 (2 - 10). 66 patients proceeded to ASCT. 6 patients were not transplanted either do to disease progression (2), failed stem cell mobilization (3) or cardiomyopathy (1). Median time to last follow was 84.5 mo (7-166). 32 patients (47%) relapsed and 20 (29%) have died. 5 Year PFS was 39% (14-66%), 63% (43-83%), and 59% (40-78%) for Protocols 1,2 and 3 respectively. 5 Year OS (with 95% confidence intervals) was 85%(77-99%), 78% (61-95%) and 80% (65-99%). MRD assessment by PCR was collected on 48 patients. Compared with study 1, the increased use of R pre SC collection improved in vivo purging by 2 logs. In Protocol 3, 56% had MRD negative apheresis products. 91% of 46 evaluable patients achieved molecular remission post stem cell transplant. Twenty-nine patients (40%) remain in molecular and clinical remissions at their last follow-up date. Significant toxicities include prolonged hypogammaglobulinemia, interstitial pneumonitis and second malignancies and will be presented.

Conclusions: HDT + ASCT combined with R +/- a-IFN produces durable PFS and molecular remissions. Some patients may be cured or develope effective immune control of their lymphoma.

316 OUTCOME OF PATIENTS WITH TRANSFORMED INDOLENT NON-HODGKIN LYMPHOMA REFERRED FOR AUTOLOGOUS STEM CELL TRANSPLANTATION

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Background: The optimum treatment of patients with transformed indolent non-Hodgkin lymphoma (TRIL) is unclear. A number of factors influence the choice of treatment for a given patient. Limited published data support the efficacy of autologous stem cell transplantation (ASCT) for this condition; however, these data are restricted by small sample sizes, analyses of database registries or phase II designs, and variable follow-up. There are no studies describing the management of these patients in the rituximab era.

Materials And Methods: This is a retrospective, single center study of 110 transplant-eligible patients with biopsy-proven TRIL who were consecutively referred to the ASCT Program at our institution between 1996-2009. Patients received anthracycline or platinum-based salvage therapy to assess chemotherapy sensitivity; responders proceeded to peripheral blood stem cell mobilization and ASCT. The high dose therapy regimen consisted of etoposide 60 mg/kg day –4 and melphalan 180 mg/m^2 day –3 (+/- 1200 cGy TBI in 6 fractions) with stem cell infusion day 0.

Results: The median age at transformation was 64 (range 30-65) years, and the median time to transformation was 3.4 years (range 0-22). 29 (26%) had prior rituximab exposure. Patients received a median of 2 salvage regimens for TRIL (range 0-4); 66% received an anthracycline, 78% received platinum, and 43% received rituximab.52 (47%) proceeded with ASCT, and 58 (53%) did not because of progressive disease (n=40), inability to collect/mobilize stem cells (n=8), death due to toxicity of salvage chemotherapy (n=1) and other reasons including comorbidity (n=9). 5 yr OS and PFS post ASCT were 45% and 40%, respectively. PFS was not influenced by the timing of ASCT for TRIL (part of first or second-line therapy, p=0.450) or the addition of rituximab to salvage (p=0.503). Those transplanted after 2004 had improved 3 yr OS (72% vs 39%, p=0.004) but differences in 3 yr PFS (54 vs 27%, p=0.064) were not statistically significant. Transplant-related mortality was 4%. Among non-transplanted patients, those with progressive disease had 5 yr OS of 5%, while those not transplanted

for other reasons (n= 18) had 5 yr OS of 68%, which was similar to that of patients undergoing ASCT (p=0.253).

Conclusions: Ability to proceed to ASCT and outcomes after ASCT are consistent with results for other aggressive NHL. Outcomes following ASCT appear to have improved over the last 5 years, although the role of rituximab as part of salvage chemotherapy in this patient population requires further evaluation.

317 PRIMARY INTESTINAL FOLLICULAR LYMPHOMA: A SINGLE INSTITUTION STUDY OF 40 CASES IN THE RITUXIMAB ERA

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Background: Follicular lymphoma (FL) is the second common subtype of non-Hodgkin's lymphomas in western countries and Japan. Primary intestinal follicular lymphoma (PIFL) is a relatively rare lymphoma. Recently, PIFL have been gradually well known among hematologists, gastrointestinal endoscopists, and pathologists, and have established new variant of FLs in the World Health Organization (WHO) classification 4th edition. We report the clinicopathological findings and outcome of PIFL in the rituximab era.

Patients and Methods: From September 2001 to June 2010, 40 patients (pts.) were diagnosed PIFL, and treated at the Cancer Institute Hospital.All the histopathology samples were reviewed according to the WHO classification by expert hematopathologists.

Results: Baseline pt. characteristics included a median age of 61 years (range, 46-78 years), 16 men and 24 women, 19 pts. (47.5%) with stage I (according to the International Workshop staging classification in Lugano 1993), four (10%) with stage II2, four (10%) with stage IIE, and 13 (32.5%) with stage IV. Twenty-five pts. (62.5%) have low risk of original FLIPI, five (12.5%) have intermediate risk, and eight (20%) have high risk (two were not evaluated). Fourteen pts. (35%) have low risk of FLIPI2, nineteen (47.5%) have intermediate risk, and four (10%) have high risk (three were not evaluated). The most frequent site was the second portion of duodenum (67.5%) presenting as multiple small white granular polyps. Grade 1 and 2 of follicular lymphoma were 27 pts (67.5%) and seven (17.5%). Twenty-three pts. (57.5%) have received rituximab or rituximab containing chemotherapy included of 18 treated with rituximab maintenance therapy, and 12 (30%) have received localized radiation therapy. At a median follow-up of 43 months (range 7.5-113), the 4-year progression-free survival and overall survival rates were 78.9% and 92.9%, respectively. Seven pts were confirmed progression disease, and one died from progression of lymphoma, and another from acute myeloid leukemia.

Conclusions: We reconfirmed to characterize the clinicopathlogical features of the PIFL in the rituximab era. To date, endoscopic devices, such as double balloon enteroscopy and video capsule endoscopy are in progress for diagnosis of small intestinal involvement of lymphoma. Using of new endoscopic devices, the diagnosis of PIFL will increase in early stages. PIFL demonstrated excellent prognosis in the rituximab era.

318 PATTERN OF INFECTIONS OBSERVED DURING THE MAINTENANCE PHASE IN THE PRIMA STUDY

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Introduction: Efficacy of rituximab maintenance (RM) after immuno-chemotherapy induction in first line treatment of follicular lymphoma demonstrated a significant benefit on progression free survival in the PRIMA study (Salles et al., Lancet 2011). One of the critical aspects of this maintenance procedure is its harmlessness regarding the most frequent adverse event, i.e. infectious complications. We then examined in more details the characteristics of infections occurring in the PRIMA study.

Methods: Out of 1019 patients randomized in PRIMA study, 1009 patients were assessed for safety (508 in observation (OBS), 501 in RM); all reported AE/SAEs were examined.

Results: The most common AE were grade 2–4 infections in 197(39%) patients in the RM arm and 123 (24%) patients of the OBS arm, respectively (risk ratio 1·62, 1·35–1·96; p<0·0001). The five most common infections reported in the RM and OBS arms were bronchitis, upper respiratory tract infections, sinusitis, nasopharyngitis (in aggregate 114 and 61 cases, respectively) and urinary tract infections (14 and 9, respectively). The cumulative numbers of Herpes viruses-related infections were 19 and 12, respectively. Infectious AEs that occurred with a higher incidence (≥ 2% difference) in the RM arm were bronchitis (11% vs. 6%), upper respiratory tract infection (6% vs. 2%) and sinusitis (4% vs. 2%); only 1 and 2 febrile neutropenia episodes did occur. There were 26 (5%) AE considered as being serious related to infection in the RM arm vs. 6 (1%) in the OBS arm. The number of infections recorded at each rituximab cycle did not increase over time. There were no more infectious AE in patients below 65 years, between 65 to 74 years, over 75 years. The pathogens documented were usually common. Four patients in the RM arm discontinued treatment as a result of infections (2 hepatitis, 1 endocarditis, 1 mycobacterial infection). There were 2 fatal infections in the RM arm (1 hepatitis, 1 JC virus) and 2 in the OBS arm (1 sepsis, 1 JC virus) (both JC virus infections occurred after investigational drugs treatment for progression).

Conclusion: These data indicate that although infections are more common during rituximab maintenance, only a few are severe, and the majority of them can be managed in daily practice.

319 BENDAMUSTINE ALONE AND IN COMBINATION WITH CD20-DIRECTED MONOCLONAL ANTIBODY THERAPY IS ACTIVE IN PATIENTS WITH RELAPSED OR REFRACTORY WALDENSTROM'S MACROGLOBULINEMIA

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Bendamustine is a recently approved agent for the treatment of relapsed/refractory indolent non-Hodgkin's lymphoma (NHL) with structural similarities to both alkylating agents and purine analogs. Its efficacy however in the relapsed/refractory setting of Waldenstrom's Macroglobulinemia (WM) remains to be determined. We therefore examined the treatment outcome for 30 relapsed/refractory WM patients following bendamustine containing therapy. The median number of prior treatments for these patients was 2 (range 1-9), and 16 (53%) patients were refractory to their previous therapy. Treatment consisted of bendamustine (90 mg/m2 IV on days 1, 2) and rituximab (375 mg/m^2 IV on either day 1 or 2) for 24 patients. Six rituximab-intolerant patients received bendamustine alone (n=4) or with ofatumumab (1000 mg IV on day 1; n=2). Each cycle was 4 weeks, and median treatment cycles was 5. At best response, median serum IgM declined from 3,980 to 698 mg/dL (p<0.0001), and hematocrit rose from 31.9% to 36.6% (p=0.0002). Overall response rate was 83.3%, with 5 VGPR, 20 PR. The overall and major response rate for patients who received bendamustine with rituximab was 79%, including all 5 VGPR patients. All 4 patients who received bendamustine alone, as well as the 2 patients who received bendamustine with ofatumumab achieved a PR.Among all patients, those with a baseline IgM ≥6,000 mg/dL, 3/6 (50%) responded, versus 22/24 (92%) patients with a baseline IgM ≤6,000 mg/dL (p=0.04). Responses were observed among relapsing (13/14; 93%); refractory (12/16; 75%); previous nucleoside analogue treated (13/14; 93%); previous bortezomib treated (12/13; 92%) and previous cyclophosphamide treated (10/11; 91%) patients. Resolution (n=4) or improvement (n=3) of adenopathy/and or spenomegaly occurred in the seven patients with pre-therapy extramedullary disease. The median estimated progression free survival for all patients was 13.2 months. Overall therapy was well tolerated. Prolonged myelosuppression was more common in patients who received prior nucleoside analogues. Bendamustine alone and in combination with CD20-directed monoclonal antibody therapy is active in patients with relapsed or refractory Waldenstrom's Macroglobulinemia.