20 mg. Preliminary efficacy data suggest high activity, with an independent review committee-assessed Modified Lugano response rate of 89% and a CR rate of 67% (Table). Median progression-free survival was 19 months (median follow-up duration 8.95 mo in the efficacy-evaluable population).

Summary/Conclusion: The safety profile of Pola-G-Len is consistent with known profiles of the individual drugs. Response rates at EoI with Pola-G-Len are promising, with high CR compared with available R/R FL treatments.

S103 OBINUTUZUMAB PLUS DHAP FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION PLUS OBINUTUZUMAB MAINTENANCE PROVIDES A HIGH MRD RESPONSE RATE IN UNTREATED MCL PATIENTS, LYMA-101 - A LYSA TRIAL

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Background: Achievement of prolonged minimal residual disease (MRD) negativity after both induction and ASCT is a strong independent prognostic marker in mantle cell lymphoma (MCL). A high-dose aracytine (HA) and salt platinum-containing (P) chemotherapy regimen with Rituximab followed by autologous stem cell transplantation (ASCT) has been considered as a standard of care for untreated younger patients with MCL (Le Gouill et al NEJM 2017). Obinutuzumab is a glycoengineered, type II, anti-CD20 monoclonal antibody designed to improve the antibody-dependent cellular cytotoxicity compared to Rituximab. In vitro experiments suggest that Obinutuzumab may provide better anti-MCL activity than Rituximab but no in vivo data are available regarding Obinutuzumab in naïve MCL patients.

Aims: The LYMA-101 study is a prospective and open phase II trial testing the effect of Obinutuzumab in untreated MCL patients under 66 years of age and eligible for intensive therapy. Induction consisted of 4 cycles of Obinutuzumab-DHAP (O-DHAP) before consolidation with ASCT (BEAM conditioning plus Obinutuzumab) followed by Obinutuzumab maintenance for 3 years then Obinutuzumab on-demand for MRD positive patients.

Methods: The LYMA-101 primary objective was the MRD negativity rate after 4 cycles of O-DHAP. MRD in the BM was assessed by IGH clonosepoc or KI-JJ PCR, and quantification with a sensitivity of at least 10-4 was reach by dd-PCR following Euro-MRD lymphoma group guidelines. We hypothesized that O-DHAP would be considered as an effective induction chemotherapy regimen if MRD negativity was ≥70%. We calculated that a minimum of 83 patients should be included (a risk of 0.05 and b of 0.20 one-sided test).

Results: We enrolled 86 patients between Nov 2016 and May 2018. One patient withdrew consent before starting treatment. Sixty-three patients (73.3%) were male and median age was 55.5 years (32–65). MIPIb risk scores were low in 47 (54.7%) and 9 (10.5%) cases, respectively. MIPI and patient withdrew consent before starting treatment. Sixty-three patients underwent ASCT and 68 started Obinutuzumab maintenance. Twelve patients stopped treatment before ASCT (including disease progression in 5/12 with a median of 6 months [3-12]); 3, before maintenance (2 because of AE in 5/24 [7 cases]); and 9 during maintenance (including disease progression in one case, death in another, and AE in 4 cases or other maladies in 2 cases). In the whole population (n = 85), 3 patients progressed, three died. At one year, PFS is 93.4% (IC95%, 84.7–97.2) and OS is 96% (IC95%, 88.1–98.7). No serious AE were observed, with grade 1-2 toxicity, without myelosuppression, and overlapped that of either drug when used alone.

Summary/Conclusion: The LYMA-101 trial successfully achieved its primary endpoint (84.9% of MRD BM negativity after induction) and demonstrates the high efficacy of O-DHAP as induction chemotherapy regimen with an unprecedented high level of MRD negativity. Longer FU is needed to evaluate patients with MRD-negative CR/PR after O-DHAP/Obinutuzumab on-demand maintenance. However, both PFS and OS are highly encouraging at one year.

S104 THE BRAF INHIBITOR VEMURAFENIB COMBINED WITH RITUXIMAB PRODUCES A HIGH RATE OF DEEP AND DURABLE RESPONSES IN RELAPSED OR REFRACTORY HAIRY CELL LEUKEMIA: UPDATED RESULTS OF A PHASE-2 TRIAL

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Background: Up to 50% of hairy cell leukemia (HCL) patients relapse after purine analogs. We identified the BRAF-V600E kinase mutation as the genetic cause of HCL (Tiacci et al., NEJM 2011). We then documented, in 26 relapsed/refractory patients treated with the oral BRAF inhibitor vemurafenib for a median of 16 weeks, 96% of overall responses (including 35% complete remissions - CR), obtained after a median of 8 weeks (Tiacci et al., NEJM 2015). However, residual bone marrow (BM) HCL cells persisted even in CR patients (5–10%) and the median relapse-free survival among all responding patients was 9 months.

Aims: Since HCL strongly expresses CD20, rituximab could improve the efficacy of BRAF inhibition by targeting leukemic cells resistant to vemurafenib.

Methods: In this academic, phase-2, single-arm, single-center trial (Eu-draCT 2014-003046-27), relapsed/refractory HCL patients received vemurafenib (960 mg b.i.d.) for a median of 16 weeks, 96% of overall responses, including 35% complete remissions - CR), obtained after a median of 8 weeks (Tiacci et al., NEJM 2015). However, residual bone marrow (BM) HCL cells persisted even in CR patients (5–10%) and the median relapse-free survival among all responding patients was 9 months.

Results: We enrolled 31 patients (median age: 59 years) with a median of 3 previous therapies, including 8 primary refractory cases (26%). Toxicity was mostly of grade 1-2, with myelosuppression, and overlapped that of either drug when used alone. Strikingly, a CR was achieved by 26/27 (96%) patients evaluable for efficacy, including 23 patients with complete platelet recovery at the end of treatment who however normalized the platelet count soon after; and 2 patients with complete resolution of splenomegaly who nonetheless remain in otherwise continuous CR at 22.5 and 25 months from the end of treatment. Among the 26 CR cases, all previously treated with purine analogs, there were also some patients previously refractory to rituximab (n = 3) and/or who had relapsed after a prior BRAF inhibitor (n = 7; 5 obtained a short-lived PR and 2 a CR after treatment with the BRAF inhibitor). Notably, a CR was obtained after just 4 weeks of vemurafenib and two concomitant doses of rituximab in 15/24 evaluable patients (63%). Minimal residual disease (MRD) by allele-specific PCR (sensitivity: 0.03% BRAF-V600E alleles) was absent in the BM of 17/26 (65%) patients; in 8/17 patients (47%), MRD clearing was obtained before rituximab consolidation.

Progression-free survival (PFS) in the 29 evaluable patients was 83% at a median follow-up of 29.5 months (range: 2–45) (Fig. 1A). Progressions (n = 5) always occurred in cases who were MRD-positive, including 3/5 patients whose immediate prior treatment was a BRAF inhibitor (leading to PR in all 3 cases). Indeed, PFS was significantly longer in MRD-negative CR cases (100% in 17 patients at 30.5 months of median follow-up) than in MRD-positive CR cases (44% in 9 patients at a median follow-up of 24.5 months) (p = 0.001; Fig. 1B). In subsequent