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Lymphoma

Obinutuzumab plus Lenalidomide (GALEN) for the treatment of relapse/refractory aggressive lymphoma: a phase II LYSA study

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Lenalidomide is a potent immunomodulatory agent that has demonstrated clinical activity in the treatment of both diffuse large B cell lymphomas (DLBCL) and mantle cell lymphomas (MCL). In relapsed/refractory (R/R) DLBCL, two large prospective studies evaluating lenalidomide monotherapy demonstrated an overall response rate (ORR) of 28% ($N = 108$) and 27.5% ($N = 51$), respectively [1, 2]. In patients with R/R MCL patients, lenalidomide induced an ORR of 40% ($N = 170$) [3, 4]. In 2013, the FDA approved lenalidomide for the treatment of R/R MCL.

Obinutuzumab is a unique type II glycoengineered monoclonal anti-CD20 antibody (Ab) with increased ADCC and increased direct cell death induction compared to rituximab. In monotherapy, obinutuzumab demonstrated efficacy in patients with MCL and DLBCL [5]. The ORR after treatment with obinutuzumab monotherapy was 28% and 27% in R/R DLBCL and MCL, respectively [5].

Furthermore, the combination of lenalidomide and rituximab (R^2 regimen) demonstrated promising efficacy in patients with follicular lymphoma (FL) [6, 7], MCL [8, 9], and DLBCL [10–13]. We hypothesized that the combination of obinutuzumab (GA) with lenalidomide (LEN) might be even more efficient while retaining a good safety profile. In a phase I_B study, we previously identified 20 mg/day

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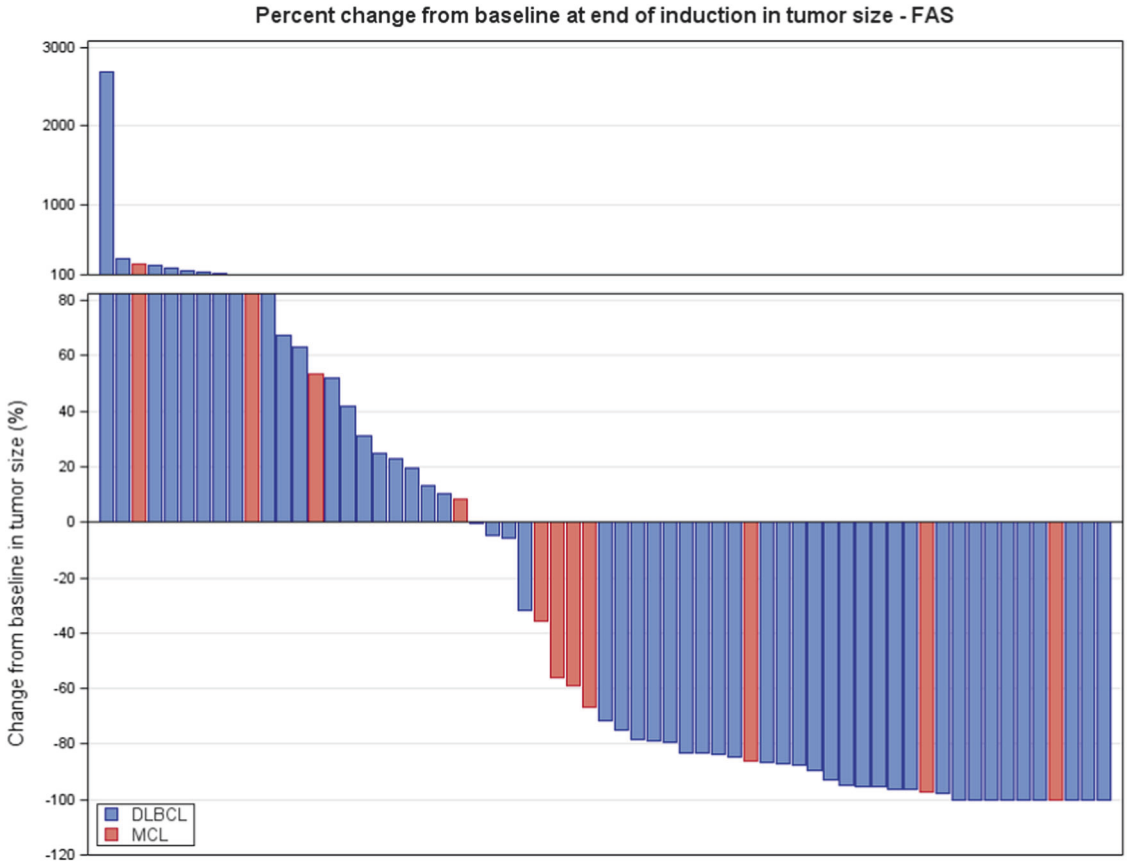

Fig. 1 Tumor regression at the end of induction

as the recommended dose (RD) of lenalidomide in combination with obinutuzumab for the induction phase [14]. In this phase II study, we assessed the efficacy and safety of the combination of obinutuzumab with lenalidomide (GALEN) for patients with R/R aggressive lymphoma (i.e., DLBCL and MCL). Patient eligibility, study design, and statistical analysis are summarized in Supplementary Information and Supplementary Figure 1.

From June 2014 to March 2015, 91 patients were enrolled and 85 patients were assessable for the GALEN combination. Median age for the entire cohort was 70 years (range 48–84). The median number of prior therapies was 2 (1–9). Sixty-eight percent of the patients were refractory to rituximab and/or to the last line of therapy. The patient population was composed of 71 DLBCL and 13 MCL. One patient had an aggressive lymphoma which was unclassified. Baseline characteristics of the patients at enrollment are listed in Supplementary Table 1. Overall, 39 patients (45.9%) completed induction (32 DLBCL and 7 MCL) and 17 pts (20.0%) completed maintenance (13 DLBCL, 4 MCL) (Supplementary Figure 2). After a median follow-up of 2.5 years, 50 pts (58.8%) died, mainly due to lymphoma (88%).

For the entire cohort ($N = 85$), the ORR at the end of induction treatment by IWG criteria [15] was 36.5% (95% CI, 26.3–47.6) (Supplementary Table 2A). Thus, the primary endpoint of the study was not met (cf Statistical Analysis in Supplementary Information).

In DLBCL patients ($N = 71$), the ORR and CR/CRu at the end of induction treatment by IWG criteria (Cheson 1999) was 35.2% (95% CI, 24.2–47.5) and 18.3% (95% CI, 10.1–29.3), respectively (Fig. 1 and Supplementary Table 2A). Median PFS and OS were 4.1 months and 10.6 months, respectively (Fig. 2 and Supplementary Table 2A). Outcome of DLBCL patients was also analyzed according the cell of origin (COO) as determined by immunohistochemistry (IHC) using the Hans algorithm and by gene expression profile (GEP) using the nanostring and the RT-MLPA technologies. The two GEP methods were concordant and complementary for determining the COO (Supplementary Table 4). Overall response, PFS and OS tended to be better in the ABC *versus* the GCB-subtype, although the differences were not statistically significant (Supplementary Table 2B and Supplementary Figure 3). There was no difference in efficacy between de novo versus transformed DLBCL nor according to cereblon expression or the number of prior treatments (data not shown). Finally, refractory patients ($N = 38$) as defined by the SCHOLAR-I study [16] (i.e., absence of response to the last treatment or

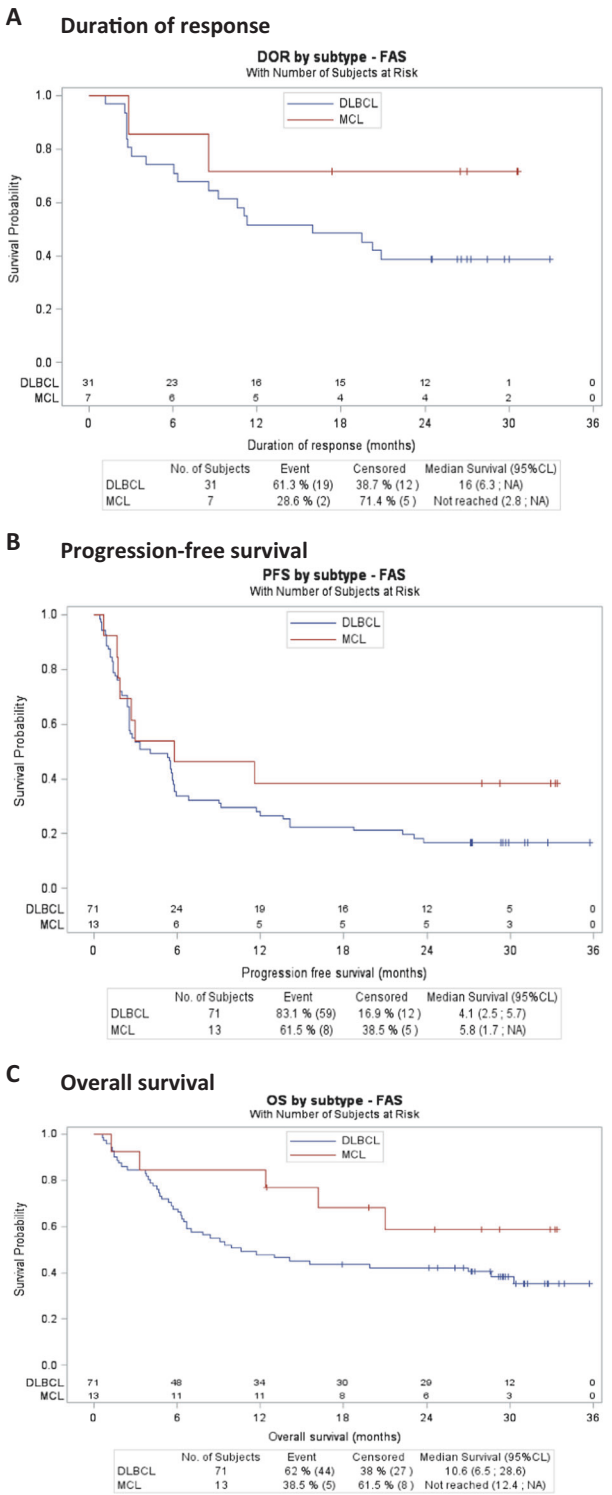

Fig. 2 Duration of response (**a**), progression-free survival (**b**), and overall survival (**c**) according to histology (DLBCL and MCL)

relapse within 12 months from autologous stem cell transplantation) had a significantly worse outcome compared to non-refractory patients ($N = 33$) with an ORR of 13.2% and a median OS of 6.6 months (Supplementary Table 2C and Supplementary Figure 4). Conversely, among non-refractory DLBCL, the ORR was 60.6% including 33.3% CR, the median PFS was 11.7 months, and the median OS was not reached. The largest study evaluating the R^2 regimen (N = 45) in R/R DLBCL reported an ORR of 33%, including 22% CR, a median PFS of 3.7 months and a median OS of 10.7 months [12]. While these results appear similar to ours, both studies cannot be compared directly. Notably, the proportion of refractory patients (not described in the study of Wang et al.) was particularly high in our study (up to 70% of the patients) which negatively affected the results of efficacy. The GOYA study did not demonstrate superiority of obinutuzumab over rituximab in combination with first-line chemotherapy [17]. However, one should be careful not to extrapolate these results to chemo-free regimen since the mechanism of action (including the synergy with lenalidomide) may be different. Czuczman et al. previously demonstrated that lenalidomide monotherapy was more efficient in the ABC-subtype compared to the GCB-subtype of DLBCL [1]. With the GALEN regimen, the same trend was observed and this combination seemed to overcome the negative prognostic impact of non-germinal center DLBCL. When applying the GALEN regimen in refractory DLBCL, the outcome remained poor with a median OS of 6.6 months. These results are similar to those described with standard chemotherapy in the SCHOLAR-I study in which the median OS was 6.3 months [16]. Nevertheless, although the OR rate with the GALEN regimen was low in this population (13.2%), some patients experienced prolonged remissions with a median duration of response of 20.2 months (Supplementary Table 2C and Supplementary Figure 4).

In MCL patients ($N = 13$), the ORR and CR/CRu at the end of induction treatment by IWG criteria (Cheson 1999) was 46.2% (95% CI, 19.2–74.9) and 15.4% (95% CI, 1.9–45.5), respectively (Fig. 1 and Supplementary Table 2A). With a median follow-up of 2.5 years, median PFS and OS were 5.8 months and not reached, respectively (Fig. 2 and Supplementary Table 2A). Trněný et al. demonstrated that lenalidomide monotherapy induced an ORR of 40% ($N = 170$) including 5% of CR/CRu in R/R MCL (MCL-002/SPRINT trial) [3]. With a median follow-up of 15.9 months, the median PFS was 8.7 months. Another study, conducted by Wang et al., evaluated the combination of lenalidomide and rituximab in R/R MCL patients ($N = 44$ at the recommended dose) [8]. The ORR was 57% including 36% of CR. With a median follow-up of 23.1 months, the median PFS was 11.1 months. In our study, the results appear inferior (OR = 46.2%, CR/CRu = 15.4%, median PFS = 5.8 months). However, the number of MCL patients in our study is limited ($N = 13$). Furthermore, most of our patients were refractory or had relapsed after intensive therapy, suggesting that their disease might have been more severe or resistant. Indeed,

53.8% of our patients had received prior ASCT versus 13% in the study by Wang et al.

The safety population included 88 patients who received at least one drug. The most common and severe (≥grade 3) adverse events occurring during induction are reported in Supplementary Table 3. The most frequent toxicities consisted in neutropenia (54.5%), fatigue (36.4%), constipation (31.8%), and diarrhea (26.1%). Other AEs of interest included rash (9.1%), febrile neutropenia (4.5%), infusion-related reactions (4.5%), tumor flare reactions (4.5%), and tumor lysis syndrome (1.1%). Three patients (3.4%) experienced venous thrombosis despite systematic prophylaxis. The most severe toxicities (≥grade 3) consisted in neutropenia (50.0%), thrombocytopenia (13.6%), and anemia (10.2%). Finally, four patients developed second primary malignancies (SPM) consisting in one acute myeloid leukemia (which occurred 8 months after the end of GALEN study treatment in a patient who had received six prior lines of chemotherapy), one basal cell carcinoma, one myelodysplastic syndrome (which occurred 6 months after GALEN discontinuation and 4 months after an autologous stem cell transplantation in a patient who had received three prior lines of chemotherapy) and one stomach adenocarcinoma. Overall, 26 (29.5%) patients had a dose reduction of lenalidomide because of toxicity and 4 (4.5%) patients prematurely and permanently discontinued the treatment because of toxicity. Six patients died during GALEN treatment: four due to lymphoma and two from concurrent illness (influenza respiratory infection and hemorrhage, respectively). There was no unexpected toxicity based on the known side effects of obinutuzumab and lenalidomide. In the largest study evaluating the R^2 regimen in R/R DLBCL ($N = 45$) [12], the most common grade 3-4 adverse events were neutropenia (53%), thrombocytopenia (33%), anemia (18%). There were few grade 3–4 non-hematological events. These side effects are comparable to the ones observed with the GALEN regimen.

Overall, the chemo-free GALEN regimen is effective and well tolerated in R/R patients with aggressive lymphoma. Thus, the GALEN regimen may represent an option in DLBCL patients with R/R disease after two lines of conventional chemotherapy, especially in ABC-DLBCL. Whether this regimen may be superior to the R^2 regimen (rituximab-lenalidomide) remains to be determined.

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Compliance with ethical standards

Conflict of interest RH: Honoraria: Bristol-Myers Squibb, Novartis, Janssen, Celgene, Consultant: Bristol-Myers Squibb; GC: Honoraria: Sanofi, Gilead, Janssen, Roche, Celgene, Consultant: Roche and Celgene; GS: Honoraria: Novartis Pharmaceuticals Corporation, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Gilead, Kite, Merck, Servier, Morphosys, Roche, Grants: Roche; KB: Honoraria: Takeda, Roche, Gilead, Advisory Board: Takeda, Roche; MM: Travel grants: Gilead, Roche, Abbvie, Advisory board: Abbvie, Takeda; PF: Honoraria: Gilead, Roche, Abbvie, Janssen, Consultant: Janssen, Gilead; SLG: Honoraria: Roche, Janssen, Celgene, Servier, Gilead, Advisory board: Roche, Janssen, Celgene, Research funding: Roche, Janssen, Celgene; HT: Honoraria: Celgene, Roche, Karyopharm, Astra-Zeneca, Bristol-Myers Squibb, Grants: Celgene; ROC: Honoraria: Celgene, Abbvie, Janssen, Consultant: Roche, Takeda, Merck, BMS, Research funding: Roche, Gilead; MA: Advisory Board: Celgene, Grants: Celgene, Roche; CB: Advisory board: Roche and Janssen; CA: Advisory Board: Roche, Celgene, Takeda, Janssen, Amgen, Kite/Gilead; ENV: Consultant: Janssen, Keocyt et Sanofi; FM: Advisory Board: Roche, Celgene, Janssen, BMS, Gilead, Consultant: Epizyme, Gilead. All the remaining authors declare that they have no conflict of interest.

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Chronic myeloproliferative neoplasms

Determinants of long-term outcome in type 1 calreticulin-mutated myelofibrosis

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Somatic driver mutations in exon 9 of the calreticulin (*CALR*) gene were first identified in 2013 [1], with a reported mutational frequency of 15–25% in essential thrombocythemia (ET) [2] and 25–35% in primary myelofibrosis (PMF) [3]. Over 80% of these mutations constitute variants defined as either type 1, a 52 bp deletion (p.L367fs*46), or type 2, a 5 bp TTGTC insertion (p.K385fs*47) [1]. Subsequent reports have exposed these mutants' differential distribution according to disease subtype [4] in addition to their phenotypic and prognostic disparities in both ET and PMF [5, 6]. Importantly, type 1 *CALR* variants, which comprise ~70% of all *CALR* mutations in PMF [1], have emerged as a phenotypically and prognostically distinct mutational subset, clustering with lower dynamic international prognostic scoring system (DIPSS)-plus scores and significantly favorable survival rates compared with both *CALR* type 2 and *JAK2* mutated cohorts [5, 7, 8]. Moreover, molecular interactions between *CALR* type 1 and additional genetic lesions such as *ASXL1* are of proven prognostic relevance [9]. Despite these advances however, little is known about the natural history of *CALR* type 1-mutated PMF. Firstly, independent clinical, cytogenetic, and molecular predictors of survival have not yet been appraised in a strictly *CALR* type 1-mutated PMF population. Furthermore, it is not clear whether long-term survival in this strictly molecularly defined subgroup can be reliably assessed using contemporary prognostic models. The current study comprehensively documents the molecular correlates and determinants of long-term outcome, as measured by overall (OS), leukemia-free (LFS), and

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