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### ► To cite this version:

Roch Houot, Guillaume Cartron, Fontanet Bijou, Sophie de Guibert, Gilles A Salles, et al.. Obinutuzumab plus Lenalidomide (GALEN) for the treatment of relapse/refractory aggressive lymphoma a phase II LYSA study. *Leukemia*, 2019, 33 (3), pp.776-780. 10.1038/s41375-018-0282-y . hal-01903056

**HAL Id: hal-01903056**

**<https://univ-rennes.hal.science/hal-01903056>**

Submitted on 13 Nov 2018

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# 1 Obinutuzumab plus Lenalidomide (GALEN) for the treatment of 2 relapse/refractory aggressive lymphoma: a phase II LYSA study

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43  
44 **Running title:** Obinutuzumab plus Lenalidomide in aggressive lymphoma

45 **Abstract word count:** 186 words

46 **Text word count:** 1,424/1,500 words

47 **Figures:** 2

48 **Tables:** 0

49 **Supplementary Information:** 1

50 **Supplementary Figures:** 4

51 **Supplementary Tables:** 4

52 **References:** 16

53 **Key words:** Obinutuzumab, Lenalidomide, Diffuse large B cell lymphoma, Mantle cell lymphoma

54

1 **Abstract**

2

3 The combination of rituximab and lenalidomide previously demonstrated promising efficacy in  
4 patients with aggressive non-Hodgkin lymphomas (aNHL), including diffuse large B cell lymphoma  
5 (DLBCL) and mantle cell lymphoma (MCL). Here, we evaluated the combination of Obinutuzumab, a  
6 type-II anti-CD20 antibody, with lenalidomide (GALEN regimen) in patients with relapsed/refractory  
7 (R/R) aNHL. A total of 85 patients (71 DLBCL and 13 MCL) received both study drugs. The overall  
8 response (OR) at the end of induction was 35.2% for DLBCL and 46.2% for MCL patients. With a  
9 median follow-up of 2.5 years, the median PFS and OS were 4.1 months and 10.6 months for DLBCL,  
10 and 5.8 months and not reached for MCL, respectively. Subgroup analysis based on cell of origin  
11 showed that efficacy of the GALEN regimen tended to be better in ABC-DLBCL compared to GC-  
12 DLBCL with an OR of 44.4% vs 23.1%, and a median OS of 27 months vs 7.9 months. Most common  
13 grade 3 and 4 adverse events were neutropenia (50.0%) and thrombocytopenia (13.6%). Overall, the  
14 chemo-free GALEN regimen may represent an option in some subsets of patients with R/R aggressive  
15 lymphoma.

16

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

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

11 Furthermore, the combination of lenalidomide and rituximab (R<sup>2</sup> regimen) demonstrated promising  
12 efficacy in patients with follicular lymphoma (FL)<sup>6,7</sup>, MCL<sup>8,9</sup>, and DLBCL<sup>10-13</sup>. We hypothesized that the  
13 combination of obinutuzumab (GA) with lenalidomide (LEN) might be even more efficient while  
14 retaining a good safety profile. In a phase I<sub>b</sub> study, we previously identified 20mg/day as the  
15 recommended dose (RD) of lenalidomide in combination with obinutuzumab for the induction  
16 phase<sup>14</sup>. In this phase II study, we assessed the efficacy and safety of the combination of  
17 obinutuzumab with lenalidomide (GALEN) for patients with R/R aggressive lymphoma (i.e. DLBCL and  
18 MCL). Patient eligibility, study design, and statistical analysis are summarized in Supplementary  
19 Information and Supplementary Figure 1.

20 From June 2014 to March 2015, 91 patients were enrolled and 85 patients were assessable for the  
21 GALEN combination. Median age for the entire cohort was 70 years (range 48-84). The median  
22 number of prior therapies was 2 (1-9). Sixty-eight percent of the patients were refractory to  
23 rituximab and/or to the last line of therapy. The patient population was composed of 71 DLBCL and  
24 13 MCL. One patient had an aggressive lymphoma which was unclassified. Baseline characteristics of  
25 the patients at enrollment are listed in Supplementary Table 1. Overall, 39 patients (45.9%)  
26 completed induction (32 DLBCL and 7 MCL) and 17 pts (20.0%) completed maintenance (13 DLBCL, 4  
27 MCL) (Supplementary Figure 2). After a median follow-up of 2.5 years, 50 pts (58.8%) died, mainly  
28 due to lymphoma (88%).

29 For the entire cohort (N=85), the ORR at the end of induction treatment by IWG criteria (Cheson  
30 1999) was 36.5% (95% CI, 26.3-47.6) (Supplementary Table 2A). Thus, the primary endpoint of the  
31 study was not met (cf Statistical Analysis in Supplementary Information).

32 In DLBCL patients (N=71), the ORR and CR/CRu at the end of induction treatment by IWG criteria  
33 (Cheson 1999) was 35.2% (95% CI, 24.2-47.5) and 18.3% (95% CI, 10.1-29.3), respectively (Figure 1  
34 and Supplementary Table 2A). Median PFS and OS were 4.1 months and 10.6 months, respectively  
35 (Figure 2 and Supplementary Table 2A). Outcome of DLBCL patients was also analyzed according the

1 cell of origin (COO) as determined by immunohistochemistry (IHC) using the Hans algorithm and by  
2 gene expression profile (GEP) using the nanostring and the RT-MLPA technologies. The two GEP  
3 methods were concordant and complementary for determining the COO (Supplementary Table 4).  
4 Overall response, PFS and OS tended to be better in the ABC *versus* the GCB-subtype, although the  
5 differences were not statistically significant (Supplementary Table 2B and Supplementary Figure 3).  
6 There was no difference in efficacy between *de novo versus* transformed DLBCL nor according to  
7 cereblon expression or the number of prior treatments (data not shown). Finally, refractory patients  
8 (N=38) as defined by the SCHOLAR-I study<sup>15</sup> (i.e. absence of response to the last treatment or relapse  
9 within 12 months from autologous stem cell transplantation) had a significantly worse outcome  
10 compared to non-refractory patients (N=33) with an ORR of 13.2% and a median OS of 6.6 months  
11 (Supplementary Table 2C and Supplementary Figure 4). Conversely, among non-refractory DLBCL, the  
12 ORR was 60.6% including 33.3% CR, the median PFS was 11.7 months, and the median OS was not  
13 reached. The largest study evaluating the R<sup>2</sup> regimen (N=45) in R/R DLBCL reported an ORR of 33%,  
14 including 22% CR, a median PFS of 3.7 months and a median OS of 10.7 months<sup>12</sup>. While these results  
15 appear similar to ours, both studies cannot be compared directly. Notably, the proportion of  
16 refractory patients (not described in the study of Wang *et al*) was particularly high in our study (up to  
17 70% of the patients) which negatively affected the results of efficacy. The GOYA study did not  
18 demonstrate superiority of obinutuzumab over rituximab in combination with first-line  
19 chemotherapy<sup>16</sup>. However, one should be careful not to extrapolate these results to chemo-free  
20 regimen since the mechanism of action (including the synergy with lenalidomide) may be different.  
21 Czuczman *et al* previously demonstrated that lenalidomide monotherapy was more efficient in the  
22 ABC-subtype compared to the GCB-subtype of DLBCL<sup>1</sup>. With the GALEN regimen, the same trend was  
23 observed and this combination seemed to overcome the negative prognostic impact of non-germinal  
24 center DLBCL. When applying the GALEN regimen in refractory DLBCL, the outcome remained poor  
25 with a median OS of 6.6 months. These results are similar to those described with standard  
26 chemotherapy in the SCHOLAR-I study in which the median OS was 6.3 months<sup>15</sup>. Nevertheless,  
27 although the OR rate with the GALEN regimen was low in this population (13.2%), some patients  
28 experienced prolonged remissions with a median duration of response of 20.2 months  
29 (Supplementary Table 2C and Supplementary Figure 4).

30 In MCL patients (N=13), the ORR and CR/CRu at the end of induction treatment by IWG criteria  
31 (Cheson 1999) was 46.2% (95% CI, 19.2-74.9) and 15.4% (95% CI, 1.9-45.5), respectively (Figure 1 and  
32 Supplementary Table 2A). With a median follow-up of 2.5 years, median PFS and OS were 5.8 months  
33 and not reached, respectively (Figure 2 and Supplementary Table 2A). Trněný *et al* demonstrated  
34 that lenalidomide monotherapy induced an ORR of 40% (N=170) including 5% of CR/CRu in R/R MCL  
35 (MCL-002/SPRINT trial)<sup>3</sup>. With a median follow-up of 15.9 months, the median PFS was 8.7 months.

1 Another study, conducted by Wang *et al*, evaluated the combination of lenalidomide and rituximab  
2 in R/R MCL patients (N=44 at the recommended dose)<sup>8</sup>. The ORR was 57% including 36% of CR. With  
3 a median follow-up of 23.1 months, the median PFS was 11.1 months. In our study, the results  
4 appear inferior (OR=46.2%, CR/CRu=15.4%, median PFS=5.8 months). However, the number of MCL  
5 patients in our study is limited (N=13). Furthermore, most of our patients were refractory or had  
6 relapsed after intensive therapy, suggesting that their disease might have been more severe or  
7 resistant. Indeed, 53.8% of our patients had received prior ASCT *versus* 13% in the study by Wang *et*  
8 *al*.

9 The safety population included 88 patients who received at least one drug. The most common and  
10 severe ( $\geq$  grade 3) adverse events occurring during induction are reported in Supplementary Table 3.  
11 The most frequent toxicities consisted in neutropenia (54.5%), fatigue (36.4%), constipation (31.8%),  
12 and diarrhea (26.1%). Other AEs of interest included rash (9.1%), febrile neutropenia (4.5%), infusion-  
13 related reactions (4.5%), tumor flare reactions (4.5%) and tumor lysis syndrome (1.1%). Three  
14 patients (3.4%) experienced venous thrombosis despite systematic prophylaxis. The most severe  
15 toxicities ( $\geq$  grade 3) consisted in neutropenia (50.0%), thrombocytopenia (13.6%) and anemia  
16 (10.2%). Finally, 4 patients developed second primary malignancies (SPM) consisting in 1 acute  
17 myeloid leukemia (which occurred 8 months after the end of GALEN study treatment in a patient  
18 who had received 6 prior lines of chemotherapy), 1 basal cell carcinoma, 1 myelodysplastic syndrome  
19 (which occurred 6 months after GALEN discontinuation and 4 months after an autologous stem cell  
20 transplantation in a patient who had received 3 prior lines of chemotherapy) and 1 stomach  
21 adenocarcinoma. Overall, 26 (29.5%) patients had a dose reduction of lenalidomide because of  
22 toxicity and 4 (4.5%) patients prematurely and permanently discontinued the treatment because of  
23 toxicity. Six patients died during GALEN treatment: 4 due to lymphoma and 2 from concurrent illness  
24 (influenza respiratory infection and hemorrhage, respectively). There was no unexpected toxicity  
25 based on the known side effects of obinutuzumab and lenalidomide. In the largest study evaluating  
26 the R<sup>2</sup> regimen in R/R DLBCL (N=45)<sup>12</sup>, the most common grade 3-4 adverse events were neutropenia  
27 (53%), thrombocytopenia (33%), anemia (18%). There were few grade 3-4 non-hematological events.  
28 These side effects are comparable to the ones observed with the GALEN regimen.

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

33

34

35 **Acknowledgments**

1 We thank the patients and their families; the Lymphoma Academic Research Organization team for  
2 the management of the study, in particular Elise Gaire and Clémentine Joubert; the reviewers at the  
3 Lymphoma Study Association (LYSA) notably Luc Xerri, Peggy Dartigues, Bettina Fabiani, Danielle  
4 Canioni, Catherine Chassagne-Clement, Camille Laurent, Véronique Meignin; the Independent Data  
5 Monitoring Committee (André Bosly, Catherine Sebban and Natacha Heutte); and all the  
6 investigators. Funding support and drug supply were provided by F. Hoffmann La Roche Ltd and  
7 Celgene Corporation.

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9  
10 **Conflict of interest**

11 RH : Honoraria : Bristol-Myers Squibb, Novartis, Janssen, Celgene, Consultant : Bristol-Myers Squibb;  
12 GC : Honoraria : Sanofi, Gilead, Janssen, Roche, Celgene, Consultant : Roche and Celgene; FB :  
13 nothing to disclose; SDG : nothing to disclose; GS : Honoraria : Novartis Pharmaceuticals Corporation,  
14 Amgen, Bristol-Myers Squibb, Celgene, Janssen, Gilead, Kite, Merck, Servier, Morphosys, Roche,  
15 Grants : Roche; CF : nothing to disclose; KB : Honoraria : Takeda, Roche, Gilead, Advisory Board :  
16 Takeda, Roche; MM: Travel grants : Gilead, Roche, Abbvie, Advisory board : Abbvie , Takeda; PF:  
17 Honoraria : Gilead, Roche, Abbvie, Janssen, Consultant : Janssen, Gilead; SLG: Honoraria : Roche,  
18 Janssen, Celgene, Servier, Gilead, Advisory board : Roche, Janssen, Celgene, Research funding :  
19 Roche, Janssen, Celgene; HT : Honoraria : Celgene, Roche, Karyopharm, Astra-Zeneca, Bristol-Myers  
20 Squibb, Grants: Celgene; ROC : Honoraria : Celgene, Abbvie, Janssen, Consultant : Roche, Takeda,  
21 Merck, BMS, Research funding : Roche, Gilead; CMC : nothing to disclose; EVDN : nothing to disclose;  
22 PZ : nothing to disclose; MA : Advisory Board: Celgene, Grants: Celgene, Roche; CB : Advisory board :  
23 Roche and Janssen; CA: Advisory Board : Roche, Celgene, Takeda, Janssen, Amgen, Kite/Gilead; AVH :  
24 nothing to disclose; KVE : nothing to disclose; LM : nothing to disclose; ENV: Consultant : Janssen,  
25 Keocyt et Sanofi; PR : nothing to disclose; FM : Advisory Board : Roche, Celgene, Janssen, BMS,  
26 Gilead, Consultant : Epizyme, Gilead.

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3

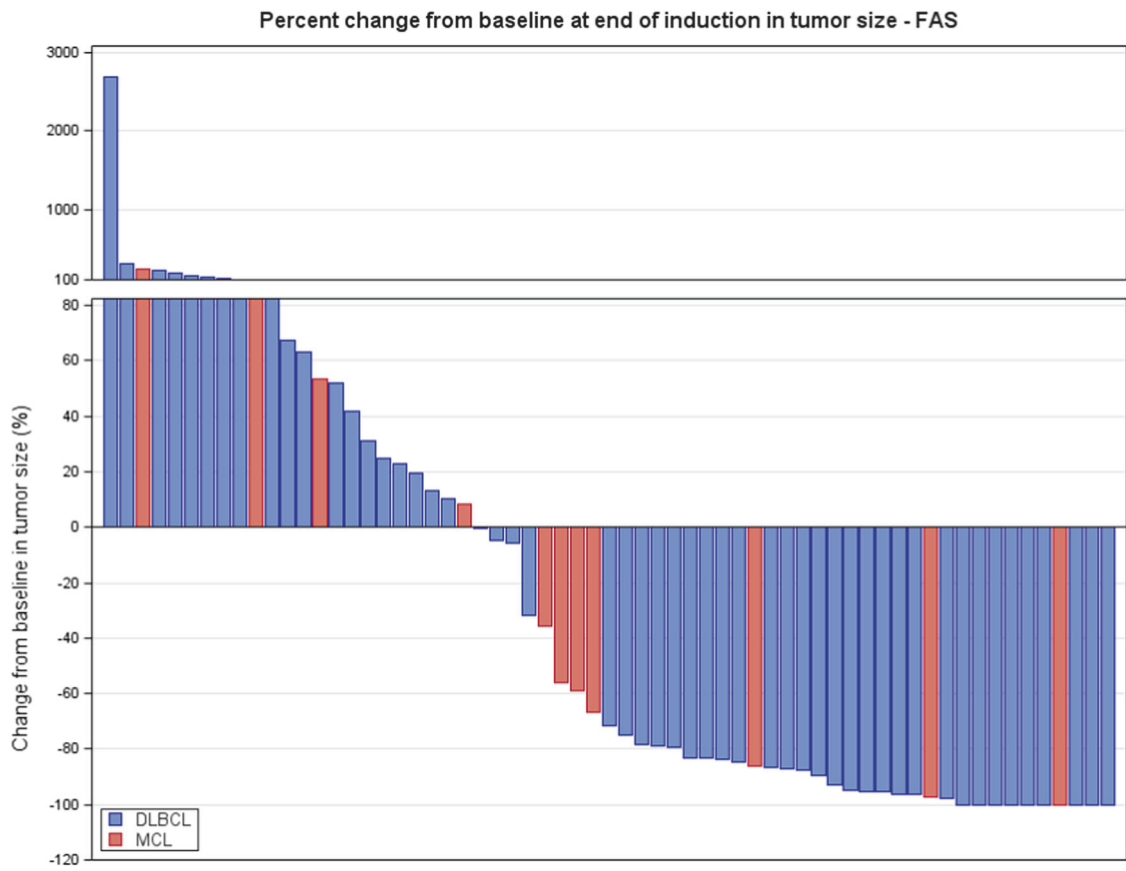
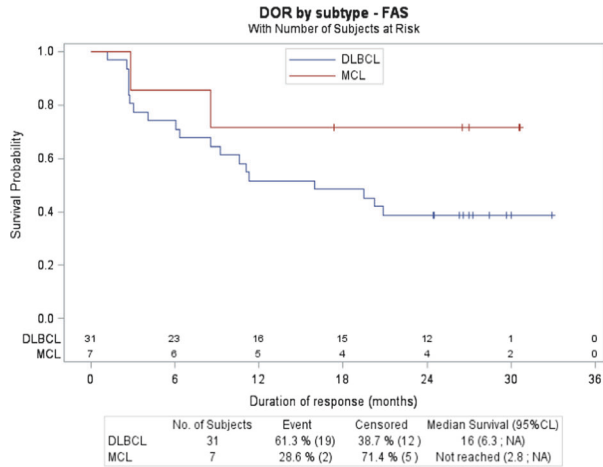
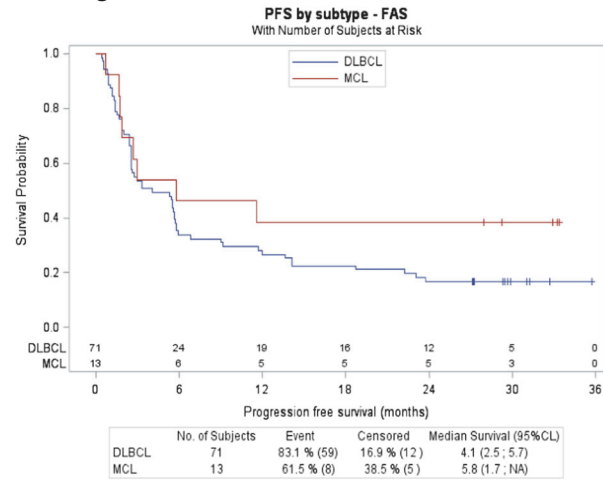


Fig. 1 Tumor regression at the end of induction

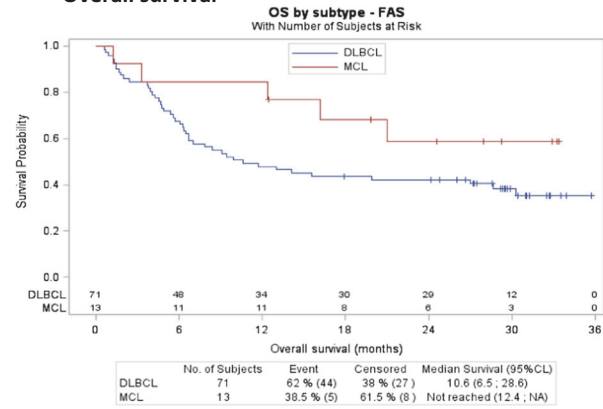
**A Duration of response**



**B Progression-free survival**



**C Overall survival**



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

## Supplementary Information

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

#### Patients and Methods

##### *Study design*

The GALEN study is a multicenter, phase Ib/II trial that was sponsored by the Lymphoma Academic Research Organization (LYSARC). The study was conducted in accordance with the International Conference on Harmonization for Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by local- and country-specific ethics review committees. Each patient provided written informed consent in compliance with national requirements before study enrollment and/or evaluation of patient eligibility for the study. The trial is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as NCT01582776.

##### *Patients eligibility*

Patients were eligible if they had relapsed or refractory DLBCL (including transformations of low-grade lymphoma into DLBCL) or MCL. Additional inclusion criteria included the following: relapsed or refractory after  $\geq 1$  prior rituximab-containing regimen with no curative option, age 18 years or more, Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2, at least one bi-dimensionally measurable nodal or tumour lesion defined as greatest transverse diameter  $> 1.5$  cm and a short axis  $\geq 10$ mm, life expectancy  $\geq 3$  months, no central nervous system or meningeal involvement by lymphoma, no prior treatment with obinutuzumab or lenalidomide, an absolute neutrophil count (ANC)  $\geq 1,500$  cells/mm<sup>3</sup>, a platelet count  $\geq 100,000$ /mm<sup>3</sup> ( $100 \times 10^9$ /L) unless due to lymphoma, serum SGOT/AST or SGPT/ALT  $\leq 3.0$  x upper limit of normal (ULN) unless disease involvement, serum total bilirubin  $\leq 2.0$  mg/dL ( $34 \mu\text{mol/L}$ ), except if disease related or in case of Gilbert syndrome, a calculated creatinine clearance (Cockcroft-Gault formula or MDRD) of  $\geq 30$ mL/min. Patients with calculated creatinine clearance between 30 and 50ml/min could be included but lenalidomide dose was adjusted (see “Treatment” paragraph below).

## **Treatment**

All patients received a combination of obinutuzumab and lenalidomide for a total of 6 cycles (induction). Subsequently, patients who achieved at least a partial response received maintenance treatment (Figure 1).

### *Induction*

Patients received 1) oral lenalidomide once daily at 20 mg on days 1-21 of a 28-day cycle for the first cycle and on days 2-22 of a 28-day cycle for cycles 2 to 6, and 2) obinutuzumab at a flat dose of 1000mg on D8, D15, and D22 of the first cycle and at D1 of cycles 2 to 6 (total of 8 infusions).

### *Maintenance*

Patients who achieved at least a partial response after 6 cycles received maintenance treatment for 2 years. During the first year of maintenance (12 cycles of 28 days), patients received obinutuzumab (6 infusions of 1000mg every 2 cycles of 28 days) and lenalidomide (10mg on days 2-22 of a 28-day cycle during a maximum of 12 cycles). During the second year of maintenance (6 cycles of 56 days), patients received obinutuzumab every 2 months (6 infusions of 1000mg), without lenalidomide.

### *Prophylactic measures*

All subjects were required to take a daily aspirin (100 mg) for deep vein thrombosis (DVT) prophylaxis during lenalidomide treatment and until 28 days after lenalidomide end of treatment. Subjects who were unable to tolerate aspirin and subjects with prior history of DVT or at high risk received low molecular weight heparin therapy or warfarin (coumadin) treatment. Growth factors (G-CSF) were administered for 3 days whenever neutrophils count drops below 500/mm<sup>3</sup>.

### *Dose modification and interruption criteria*

Patients with moderate renal impairment ( $30 \leq \text{CrCl} < 50\text{ml/min}$ ) could be included but lenalidomide was started at a lower dose of 10mg once daily. It was possible to increase lenalidomide dose at 15mg at cycle 3 if patient did not encounter toxicity. Lenalidomide dose could be adjusted in case of significant toxicity (see "Protocol" in Supplementary Annex). There was no dose adjustment for obinutuzumab.

## **Evaluation of response**

Patients were evaluated by computed tomography scans (CT) and positron emission tomography-computerized tomography scan (PET) at baseline, after 3 and 6 cycles during induction, and every 3 months during maintenance (for a maximum of 2 years) and at the end of treatment. Bone marrow examination was performed at baseline and repeated at the end of induction if positive at baseline.

### ***Evaluation of toxicity***

All adverse events (AEs) reported by the patient or observed by the investigator were collected from the case report form in predefined categories. An AE was defined as any adverse change from the patient's baseline condition, whether it was considered related to treatment or not. Each AE was graded according to the National Cancer Institute Common Terminology Criteria grading system version 4. The following AEs were recorded in additional detail: grade 3 to 5 toxicities, grade 2 to 5 infections and neurologic toxicities, and any toxicity (regardless of grade) resulting in dose modification.

### ***Cell of Origin characterization and cereblon expression***

Histologic diagnoses were centrally reviewed by expert pathologists (L. Xerri, P. Dartigues, B. Fabiani, D. Canioni, C. Chassagne-Clement, C. Laurent and V. Meignin). For DLBCL, expression of CD10, BCL6, and MUM1 was examined by immunohistochemistry to classify all cases as GCB or non-GCB using the Hans algorithm<sup>1</sup>. Cell of origin was also determined in DLBCL patients by molecular testing from formalin-fixed paraffin-embedded tissue using NanoString gene expression profiling technology and RT-MLPA<sup>2</sup>. Cereblon expression was determined using RT-MLPA.

### ***Statistical Analysis***

The primary endpoint of the study was to assess the efficacy of the GALEN regimen as measured by the overall response rate (ORR) at the end of 6 cycles according to the Cheson 1999 criteria. Sample size was calculated based on the primary endpoint. Using a single-stage phase II design<sup>3</sup>, we designed the trial to have 95% power to detect an increase in the ORR from 28% (corresponding to the efficacy of obinutuzumab monotherapy in the GAUGUIN study<sup>4</sup>) to 48% according to Cheson 1999 criteria at the end of induction at the overall 2.5% (1-sided) significance level. 95% confidence limits of response rates were calculated according to Exact Pearson-Clopper method.

The secondary endpoints were safety, complete response (CR) rate after 3 and 6 cycles, ORR and CR rate at the end of maintenance treatment, best overall response rate (BOR), event Free Survival (EFS), progression free survival (PFS), duration of response (DOR), and overall survival (OS). Survival functions were estimated using Kaplan-Meier method with appropriate 95% CIs. Baseline prognostic factors were compared using chi-square test and Cox proportional-hazards regression model to estimate hazard ratios and 95% CIs. All analyses were performed with SAS 9.3 software. Efficacy analysis was conducted on the full analysis set defined as all patients who signed the informed consent and treated with GA101 and Lenalidomide. Safety was reviewed every 6 months by an independent data monitoring committee.

## References

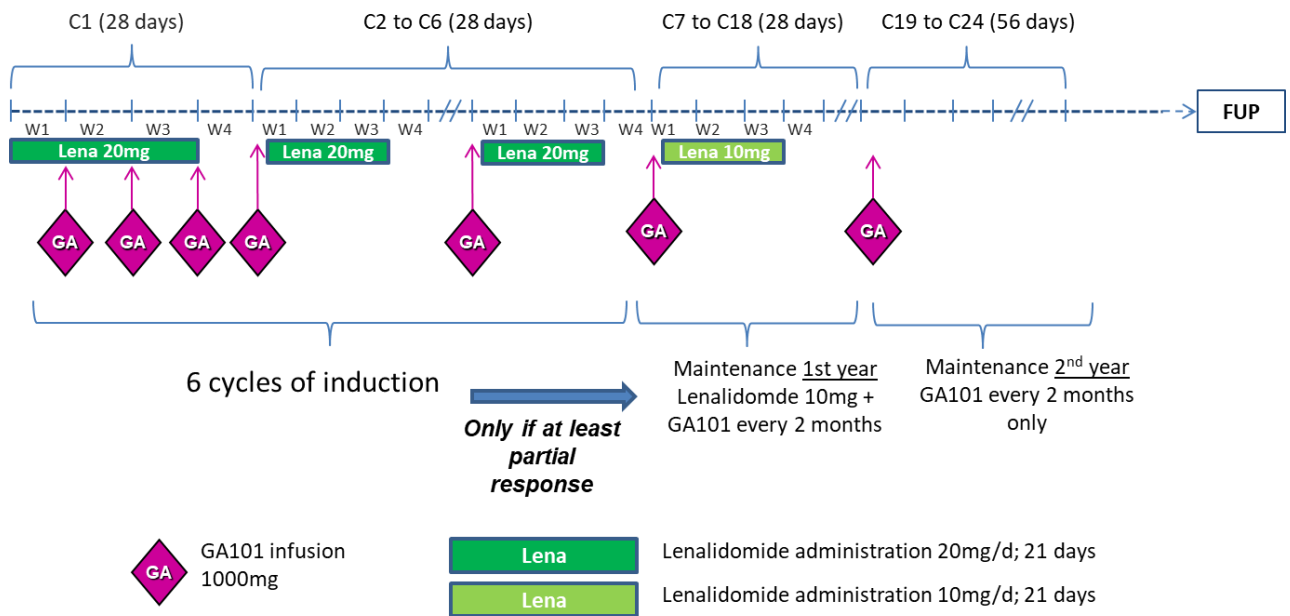
- 1 Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G *et al.* Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* 2004; **103**: 275–82.
- 2 Bobée V, Ruminy P, Marchand V, Viailly P-J, Abdel Sater A, Veresezan L *et al.* Determination of Molecular Subtypes of Diffuse Large B-Cell Lymphoma Using a Reverse Transcriptase Multiplex Ligation-Dependent Probe Amplification Classifier. *J Mol Diagnostics* 2017; **19**: 892–904.
- 3 A'Hern RP. Sample size tables for exact single-stage phase II designs. *Stat Med* 2001; **20**: 859–866.
- 4 Morschhauser FA, Cartron G, Thieblemont C, Solal-Céligny P, Haioun C, Bouabdallah R *et al.* Obinutuzumab (GA101) monotherapy in relapsed/refractory diffuse large b-cell lymphoma or mantle-cell lymphoma: Results from the phase II GAUGUIN study. *J Clin Oncol* 2013; **31**: 2912–2919.

# Supplementary Figures

## Supplementary Figure 1. GALEN study design

Patients received a combination of obinutuzumab and lenalidomide for a total of 6 cycles (induction). Subsequently, patients who achieved at least a partial response after 6 cycles received maintenance treatment. Induction consisted in 1) oral lenalidomide once daily at 20 mg on days 1-21 of a 28-day cycle for the first cycle and on days 2-22 of a 28-day cycle for cycles 2 to 6, and 2) obinutuzumab at a flat dose of 1000mg on D8, D15, and D22 of the first cycle and at D1 of cycles 2 to 6 (total of 8 infusions).

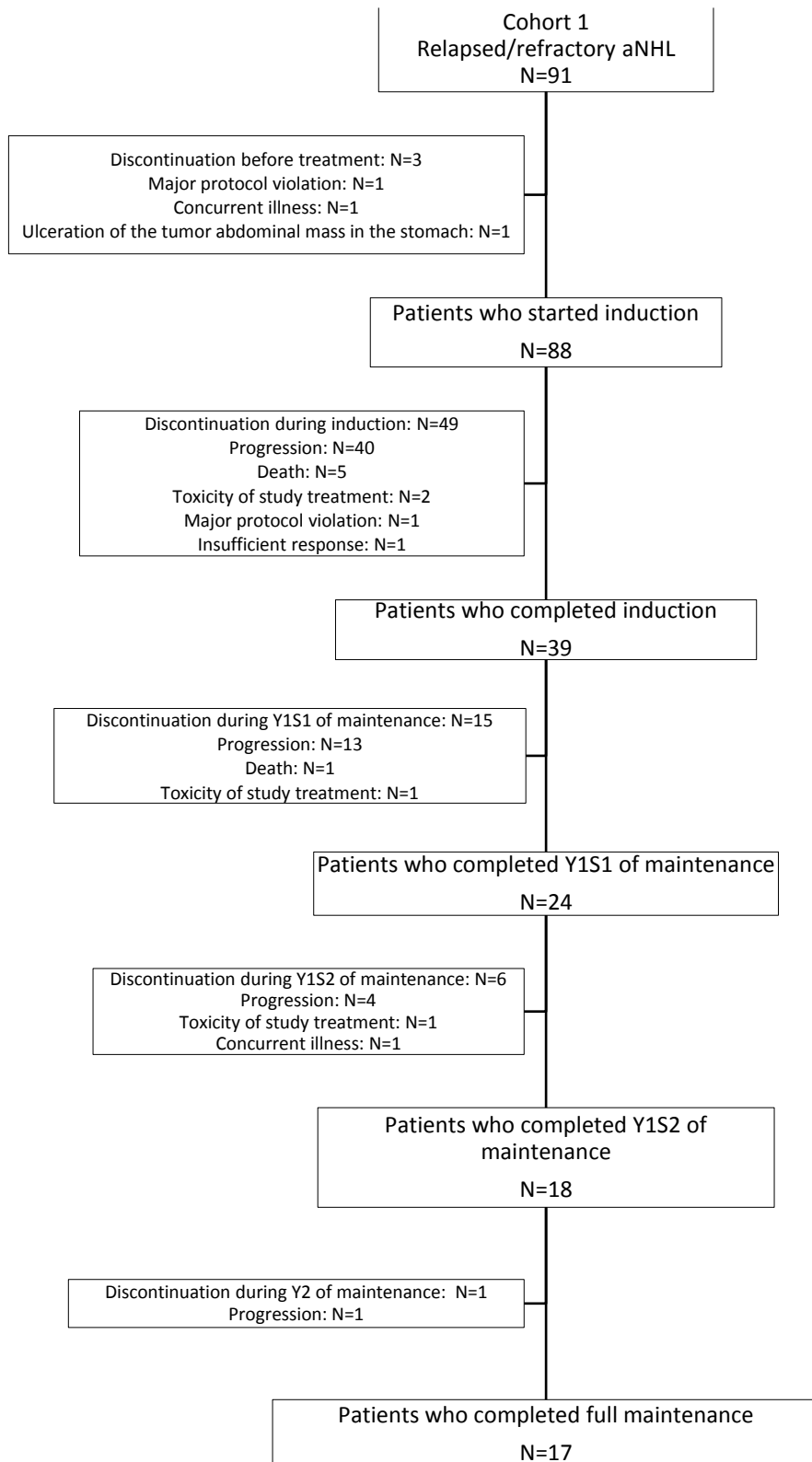
Patients who achieved at least a partial response after 6 cycles received maintenance treatment for 2 years. During the first year of maintenance (12 cycles of 28 days), patient received obinutuzumab (6 infusions of 1000mg every 2 cycles of 28 days) and lenalidomide (10mg on days 2-22 of a 28-day cycle during a maximum of 12 cycles). During the second year of maintenance (6 cycles of 56 days), patients received obinutuzumab every 2 months (6 infusions of 1000mg), without lenalidomide.





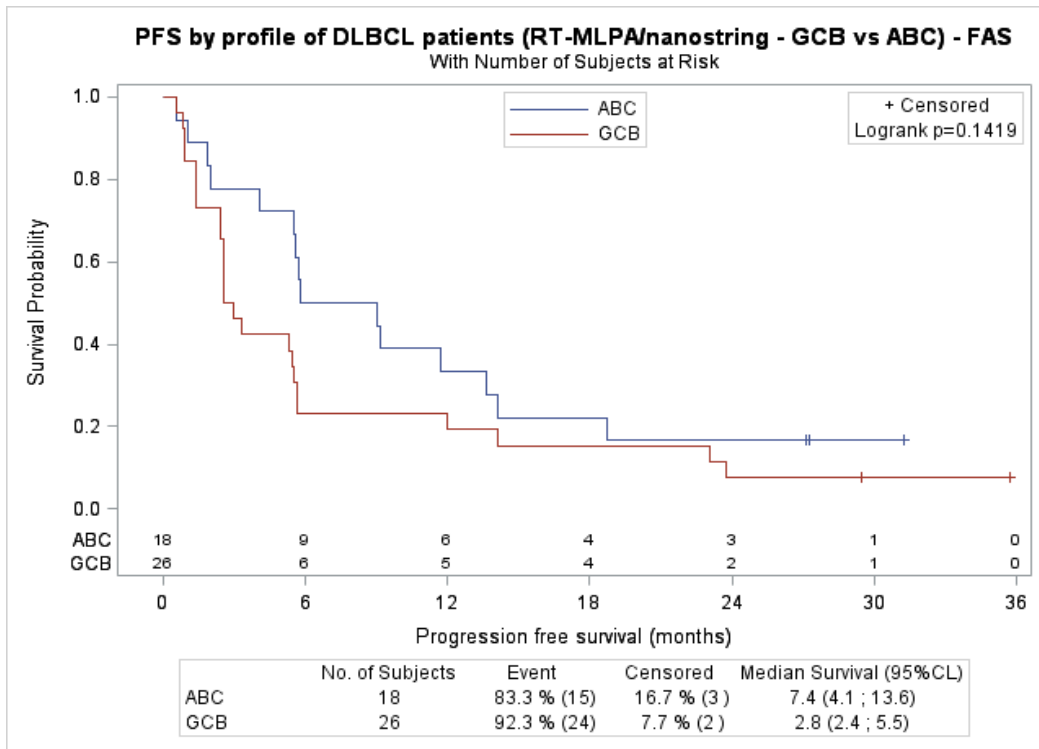
**Supplementary Figure 2. GALEN study CONSORT diagram**

Three patients were withdrawn before receiving any treatment due to major protocol violation, concurrent illness or ulceration of the tumor in the stomach and 3 patients received one of both study drugs. Four patients discontinued the treatment prematurely because of toxicity.

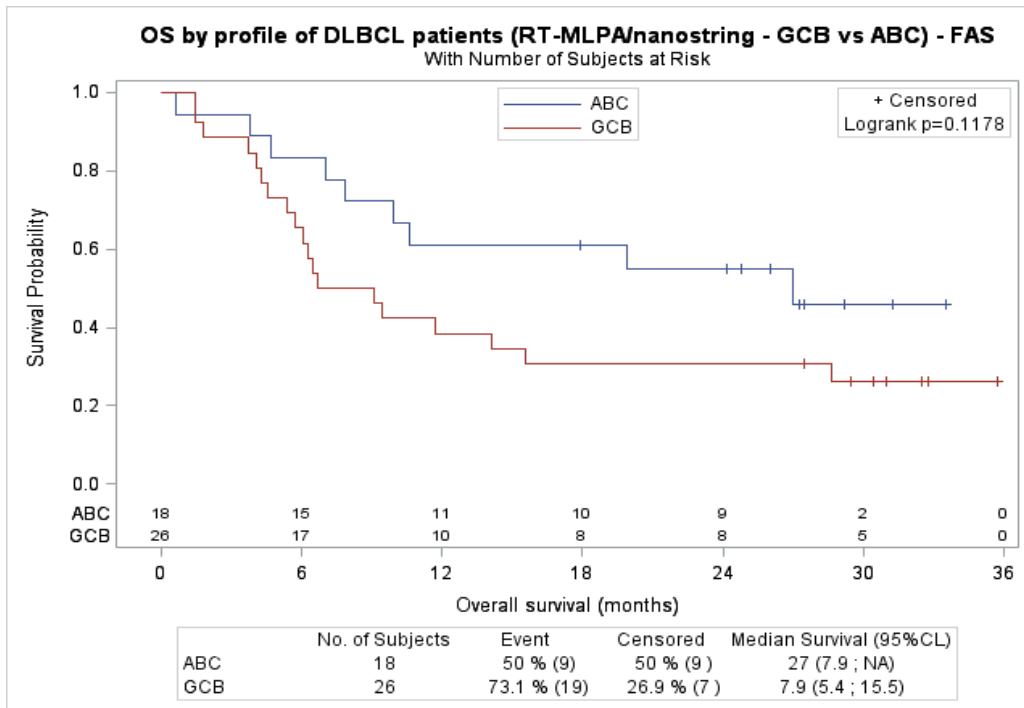


**Supplementary Figure 3. Progression-free survival (A, C, E) and Overall survival (B, D, F) in DLBCL according to COO measured by Nanostring + RT-MLPA (A, B), nanostring (C, D), and IHC (E, F)**

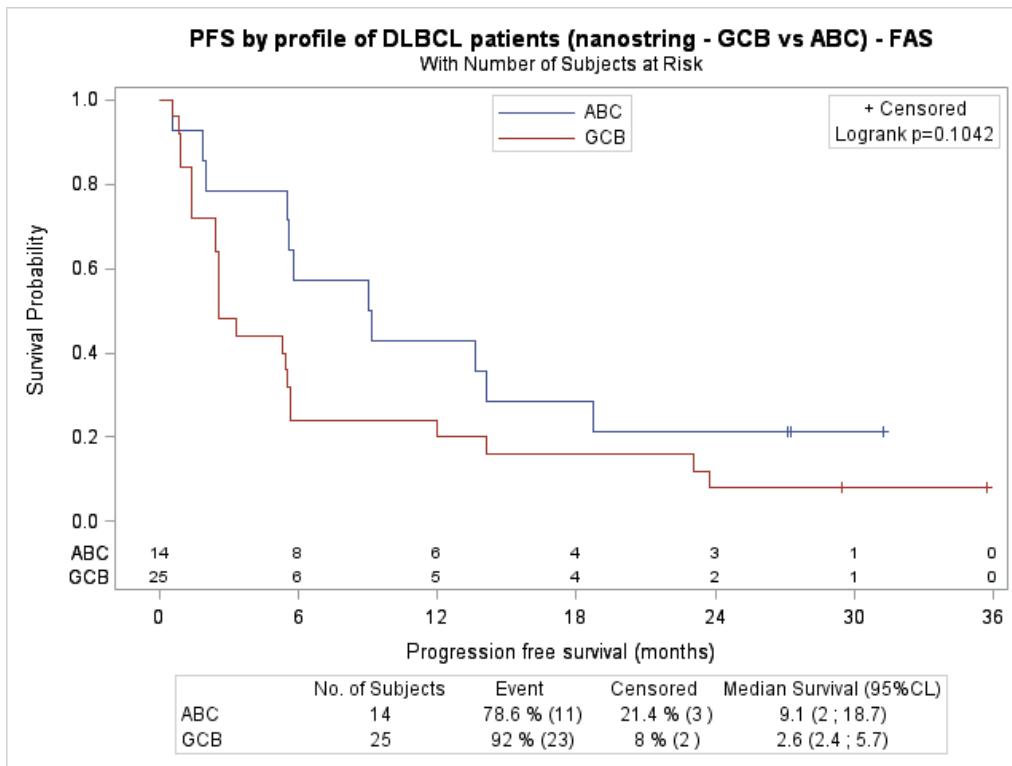
**A. Progression-free survival**



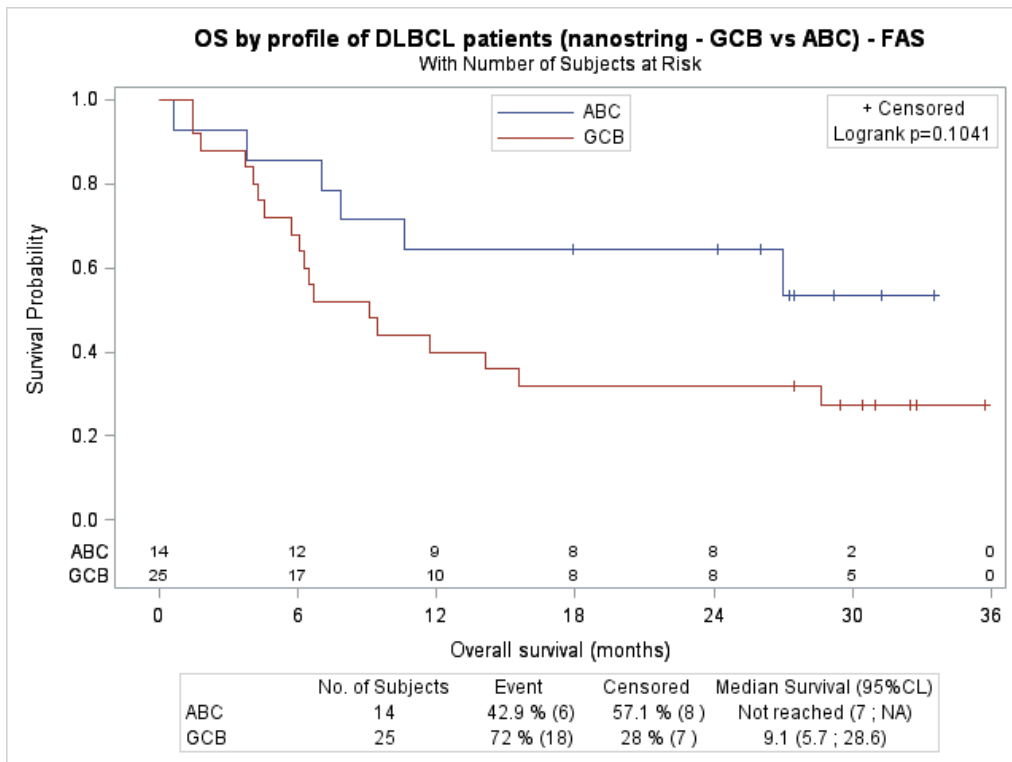
**B. Overall survival**



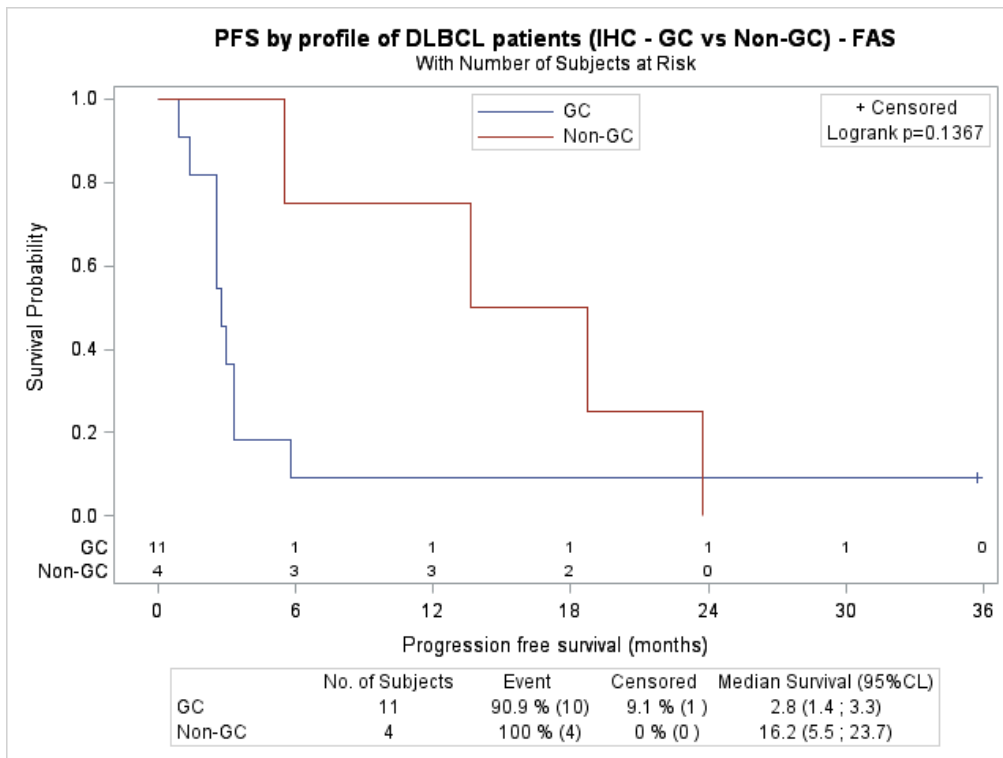
### C. Progression-free survival



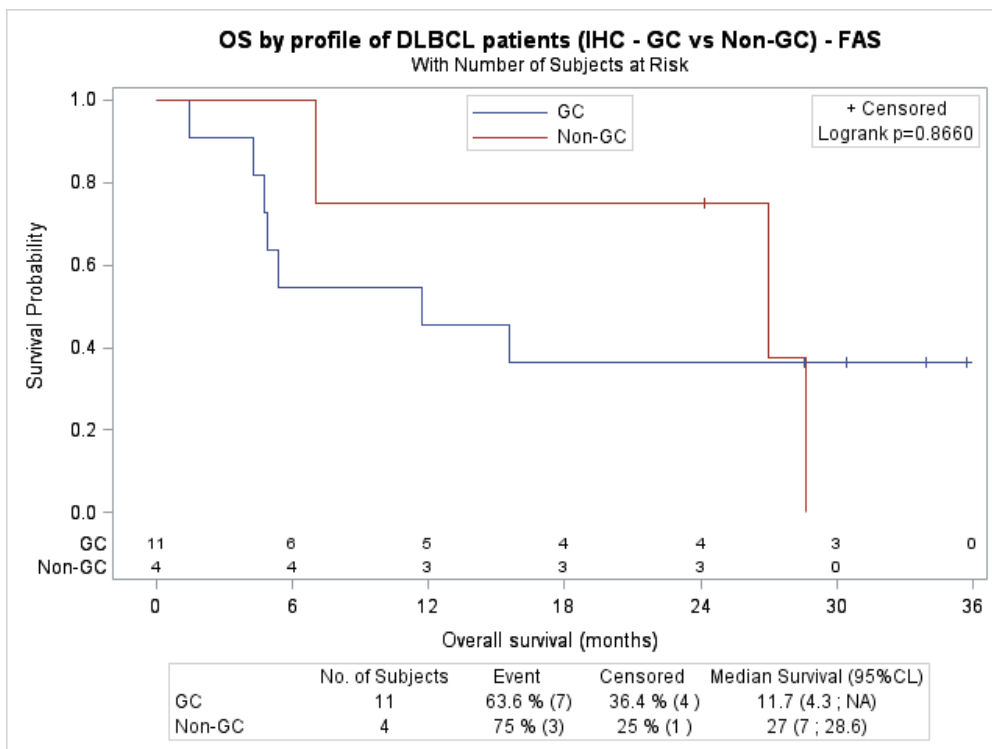
### D. Overall survival



### E. Progression-free survival

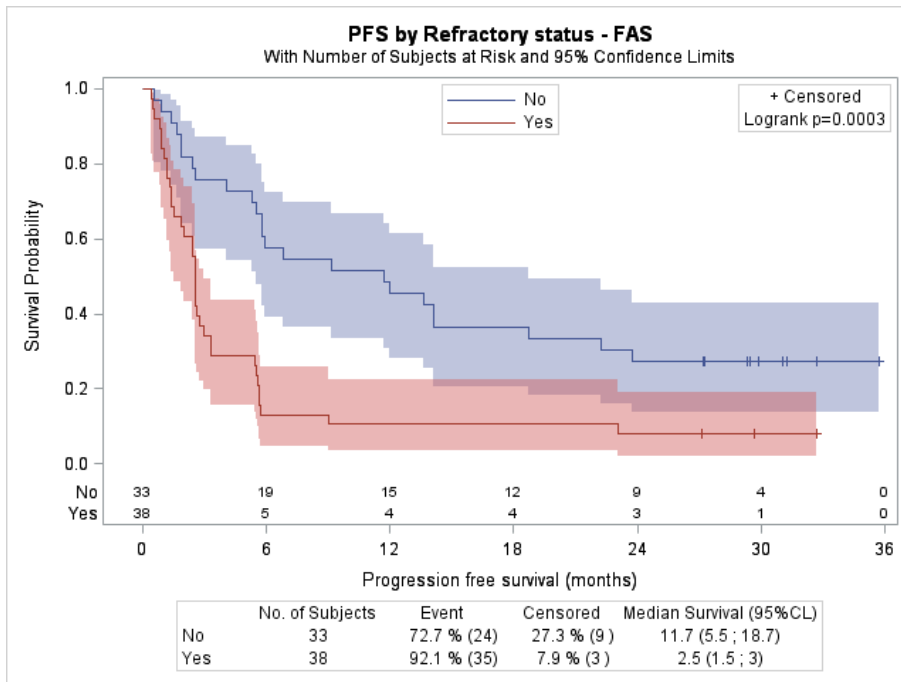


### F. Overall survival

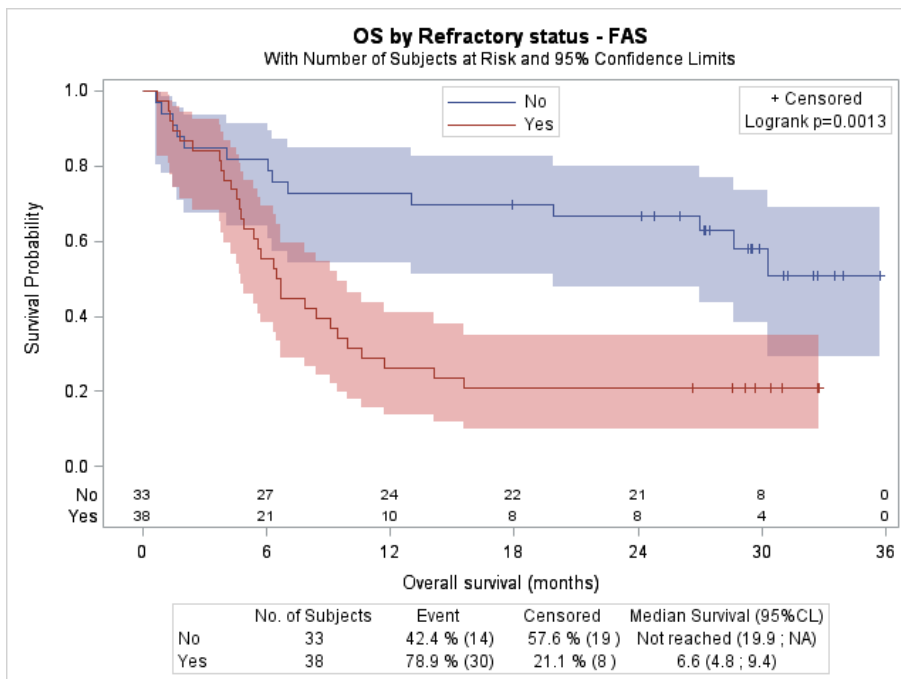


**Supplementary Figure 4. Progression-free survival (A) and Overall survival (B) in refractory vs non-refractory DLBCL**

**A. Progression-free survival**



**B. Overall survival**



## Supplementary Table

**Supplementary Table 1. Patients' characteristics**

	<b>DLBCL (N=71*)</b>	<b>MCL (N=13)</b>	<b>All pts (N=85**)</b>
Median age (min-max)	70 (48-84)	67 (56-77)	70 (48-84)
Sex (M/F)	44/27	10/3	55/30
Performance status 0-1/2	56/15	12/1	69/16
Ann Arbor stage I-II/III-IV	13/58	1/12	14/71
B-symptoms (no/yes)	63/8	12/1	75/10
Median number of prior therapies (min-max)	2 (1-9)***	2 (1-5)****	2 (1-9)
IPI (0-2/3-5)	23/47	N/A	N/A
MIPI (low/int/high)	N/A	7/3/3	N/A
Prior ASCT	10 (14.1%)	7 (53.8%)	17 (20.0%)
Refractory to Rituximab	44 (62.0%)	7 (53.8%)	52 (61.2%)
Refractory to last treatment	38 (53.5%)	6 (46.2%)	45 (52.9%)
Refractory to Rituximab and/or last treatment	50 (70.4%)	7 (53.8%)	58 (68.2%)
Refractory to last treatment or relapse within 12 months after ASCT	38 (53.5%)	6 (46.2%)	45 (52.9%)

*\*Including 53 (74.6%) de novo and 18 (25.4%) transformed DLBCL*

*\*\*One patient had an aggressive lymphoma unclassified*

*\*\*\*All but 6 patients (92%) had received prior anthracycline treatment*

*\*\*\*\* All but 1 patient (92%) were ibrutinib-naïve*

*ASCT, Autologous Stem Cell Transplantation*

**Supplementary Table 2. Efficacy of GALEN in aggressive NHL patients (A) and in DLBCL subsets according to the COO (B) and according to the refractory status (C)**

**A. Efficacy of GALEN in aggressive NHL patients**

			<b>DLBCL (N=71)</b>	<b>MCL (N=13)</b>	<b>All pts (N=85)</b>
Response at the end of induction	IWG 1999	ORR, % (95% CI)	35.2 (24.2-47.5)	46.2 (19.2-74.9)	36.5 (26.3-47.6)
		CR/CRu, % (95% CI)	18.3 (10.1-29.3)	15.4 (1.9-45.5)	17.6 (10.2-27.4)
	IWG 2007	ORR, % (95% CI)	29.6 (19.3-41.6)	38.5 (13.9-68.4)	30.6 (21.1-41.5)
		CR, % (95% CI)	16.9 (9.0-27.7)	23.1 (5.0-53.8)	17.6 (10.2-27.4)
Median DOR in months (95% CI)			16.0 (6.3-NR)	NR (2.8-NR)	19.4 (8.6-NR)
Median PFS in months (95% CI)			4.1 (2.5-5.7)	5.8 (1.7-NR)	4.1 (2.5-5.8)
Median OS in months (95% CI)			10.6 (6.5-28.6)	NR (12.4-NR)	14.1 (7.0-30.3)

**B. Efficacy of GALEN in ABC vs GC-DLBCL\***

			<b>DLBCL-ABC (N=18)</b>	<b>DLBCL-GCB (N=26)</b>	<b>p</b>
Response at the end of induction	IWG 1999	ORR, % (95% CI)	44.4 (21.5-69.2)	23.1 (9.0-43.7)	0.191
		CR/CRu, % (95% CI)	11.1 (1.4-34.7)	15.4 (4.4-34.9)	1.000
	IWG 2007	ORR, % (95% CI)	38.9 (17.3-64.3)	19.2 (6.6-39.4)	0.183
		CR, % (95% CI)	11.1 (1.4-34.7)	11.5 (2.5-30.2)	1.000
Median DOR in months (95% CI)			10.6 (2.7-NR)	11.1 (2.5-NR)	0.9784
Median PFS in months (95% CI)			7.4 (4.1-13.6)	2.8 (2.4-5.5)	0.1419
Median OS in months (95% CI)			27.0 (7.9-NR)	7.9 (5.4-15.5)	0.1178

*\*COO was determined by GEP using Nanostring and RT-MLPA. Two patients remained unclassified and were not included in this analysis*

### C. Efficacy of GALEN in refractory vs non-refractory DLBCL

			Refractory* (N=38)	Non Refractory (N=33)	p
Response at the end of induction	IWG 1999	ORR, % (95% CI)	13.2 (4.4-28.1)	60.6 (42.1-77.1)	<0.001
		CR/CRu, % (95% CI)	5.3 (0.6-17.8)	33.3 (18-51.8)	0.002
	IWG 2007	ORR, % (95% CI)	10.5 (2.9-24.8)	51.5 (33.5-69.2)	<0.001
		CR, % (95% CI)	10.5 (2.9-24.8)	24.2 (11.1-42.3)	0.124
Median DOR in months (95% CI)			20.2 (2.7-NR)	13.6 (6-NR)	0.8841
Median PFS in months (95% CI)			2.5 (1.5-3.0)	11.7 (5.5-18.7)	p=0.0003 HR=2.61 (1.53-4.48)
Median OS in months (95% CI)			6.6 (4.8-9.4)	NR (19.9-NR)	p=0.0013 HR=2.77 (1.45-5.27)

*\*A patient was defined as refractory according to the criteria used in the SCHOLAR-I study (i.e. patients who did not respond to the last treatment or patients who relapsed within 12 months from autologous stem cell transplantation).*



**Supplementary Table 3. Adverse events during GALEN treatment (N=88)**

<b>Adverse Event (%)</b>	<b>All Grades</b>	<b>Grade <math>\geq</math> 3</b>
Neutropenia	54.5	50.0
Fatigue/asthenia	36.4	3.4
Constipation	31.8	0
Diarrhea	26.1	4.5
Cough	25.0	1.1
Thrombocytopenia	18.2	13.6
Bronchitis	18.2	3.4
Nausea	17.0	0
Anemia	15.9	10.2
Dyspnea	15.9	4.5
Weight decrease	15.9	1.1
Leukopenia	14.8	11.4
Muscle spasms	13.6	0
Peripheral neuropathy	13.6	0
Peripheral edema	12.5	1.1
Pruritus	11.4	0
Vomiting	11.4	2.3
Decreased appetite	10.2	1.1
Rash	9.1	1.1
Abdominal pain	6.8	0
Febrile neutropenia	4.5	4.5
Infusion-related reaction	4.5	1.1
Tumor flare reaction	4.5	1.1
Venous thrombosis	3.4	0
Pulmonary embolism	3.4	3.4
Tumor lysis syndrome	1.1	0

**Supplementary Table 4. COO measured by Nanostring and RT-MLPA among DLBCL patients**

		Nanostring				TOTAL (N=71)
		GCB (N=25)	ABC (N=14)	Failure (N=7)	Not analyzed (N=25)	
RT-MLPA	GCB	11 (44.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	12 (16.9%)
	ABC	0 (0.0%)	13 (92.9%)	4 (57.1%)	0 (0.0%)	17 (23.9%)
	Failure	6 (24.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	7 (9.9%)
	Unclassified	8 (32.0%)	1 (7.1%)	1 (14.3%)	0 (0.0%)	10 (14.1%)
	Not analyzed	0 (0.0%)	0 (0.0%)	0 (0.0%)	25 (100%)	25 (35.2%)