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

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Abstract

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

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, 2 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 20mg/day 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 (Cheson 1999) 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 (Figure 1 and Supplementary Table 2A). Median PFS and OS were 4.1 months and 10.6 months, respectively (Figure 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[15] (i.e. absence of response to the last treatment or 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[16]. 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[15]. 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 (Figure 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 (Figure 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, 4 patients developed second primary malignancies (SPM) consisting in 1 acute myeloid leukemia (which occurred 8 months after the end of GALEN study treatment in a patient who had received 6 prior lines of chemotherapy), 1 basal cell carcinoma, 1 myelodysplastic syndrome (which occurred 6 months after GALEN discontinuation and 4 months after an autologous stem cell transplantation in a patient who had received 3 prior lines of chemotherapy) and 1 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: 4 due to lymphoma and 2 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 2 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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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; FB : nothing to disclose; SDG : nothing to disclose; GS : Honoraria : Novartis Pharmaceuticals Corporation, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Gilead, Kite, Merck, Servier, Morphosys, Roche, Grants : Roche; CF : nothing to disclose; 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; CMC : nothing to disclose; EVDN : nothing to disclose; PZ : nothing to disclose; MA : Advisory Board: Celgene, Grants: Celgene, Roche; CB : Advisory board : Roche and Janssen; CA: Advisory Board : Roche, Celgene, Takeda, Janssen, Amgen, Kite/Gilead; AVH : nothing to disclose; KVE : nothing to disclose; LM : nothing to disclose; ENV: Consultant : Janssen, Keocyt et Sanofi; PR : nothing to disclose; FM : Advisory Board : Roche, Celgene, Janssen, BMS, Gilead, Consultant : Epizyme, Gilead.

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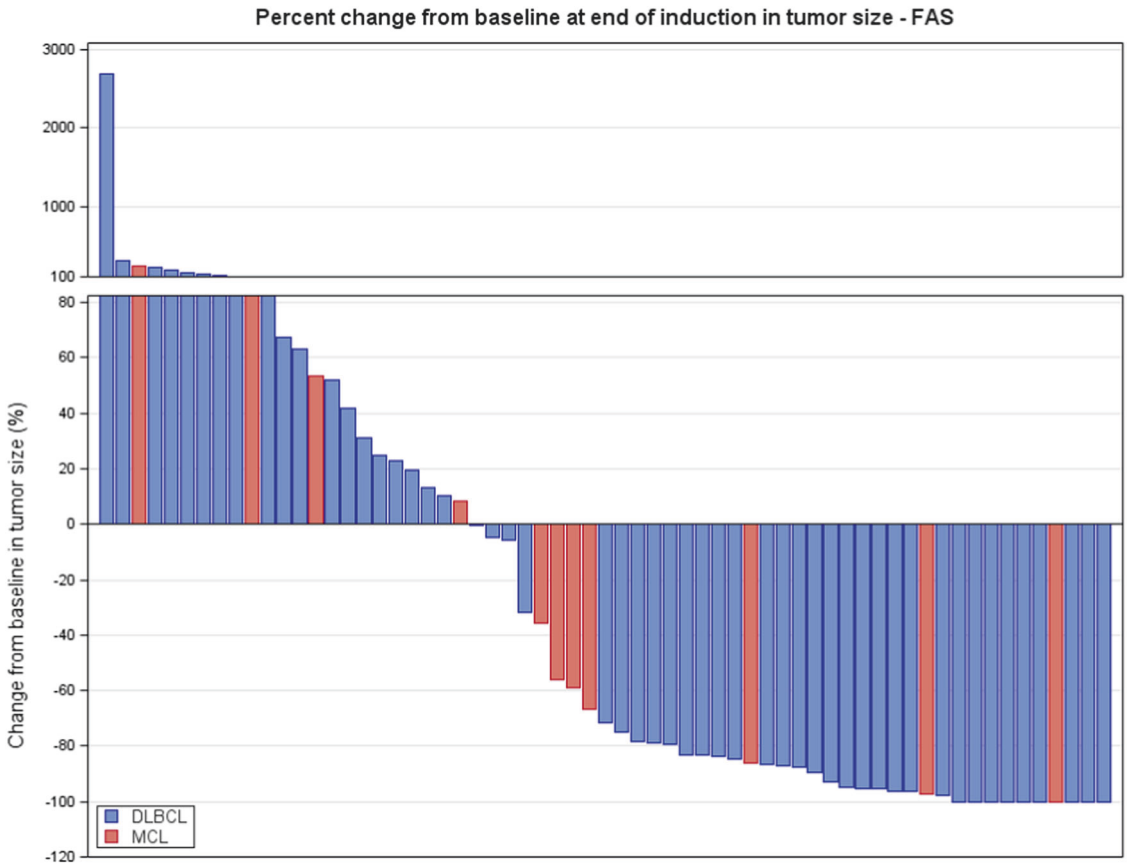

Fig. 1 Tumor regression at the end of induction

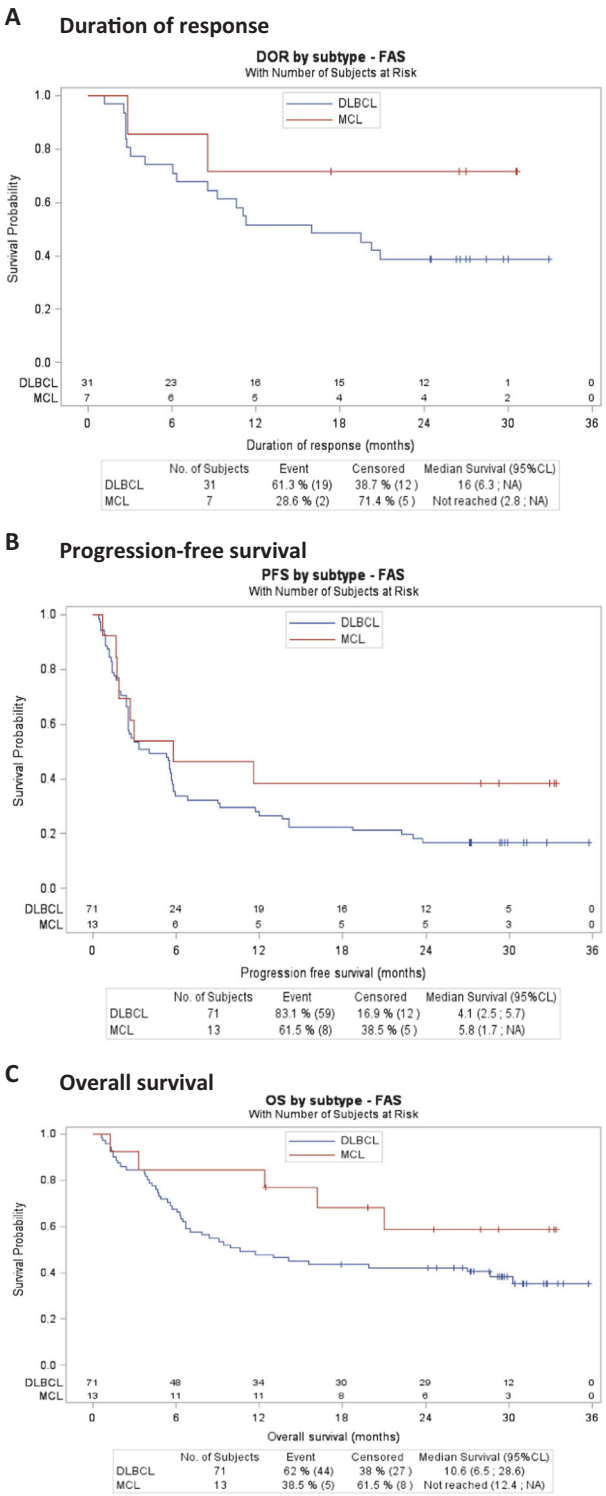

Fig. 2 Duration of response (**a**), progression-free survival (**b**), and overall survival (**c**) according to histology (DLBCL and MCL)

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 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 ≥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 ≥ 10mm, life expectancy ≥ 3 months, no central nervous system or meningeal involvement by lymphoma, no prior treatment with obinutuzumab or lenalidomide, an absolute neutrophil count (ANC) ≥1,500 cells/mm3, a platelet count ≥100,000/mm3 (100 x 10^9/L) unless due to lymphoma, serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN) unless disease involvement, serum total bilirubin ≤ 2.0 mg/dL (34 µmol/L), except if disease related or in case of Gilbert syndrome, a calculated creatinine clearance (Cockcroft-Gault formula or MDRD) of ≥ 30mL/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/mm3.

Dose modification and interruption criteria

Patients with moderate renal impairment ($30 \leq CrCl < 50$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[1]. 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[2]. 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[3], 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[4]) 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.

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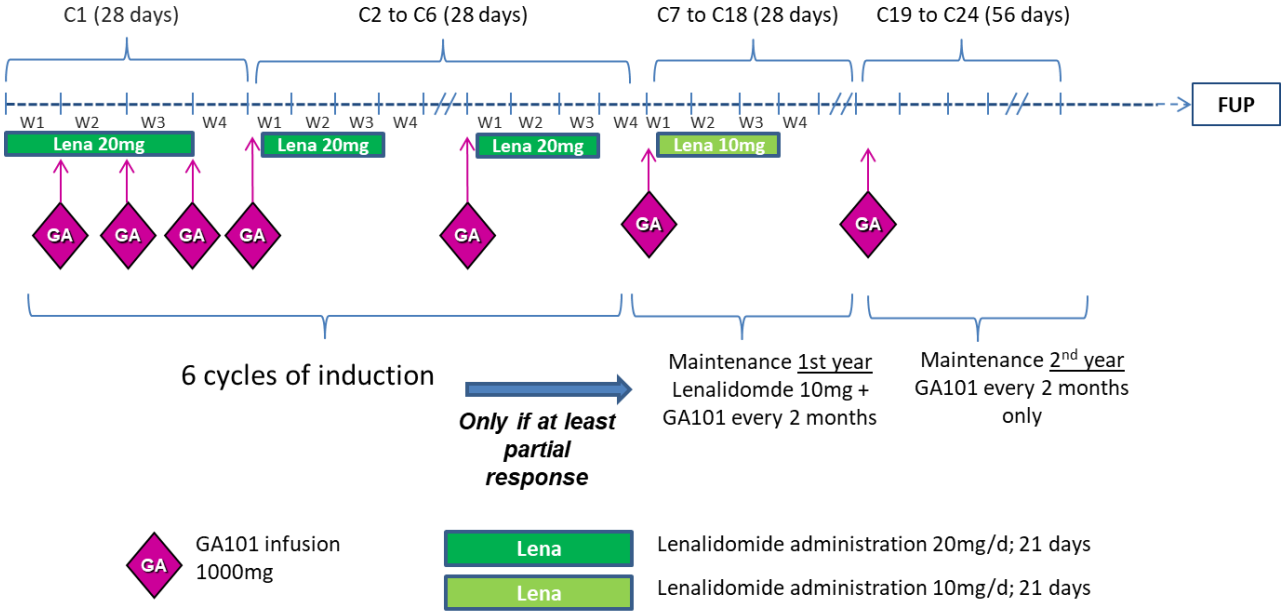
Supplementary Figures

Supplementary Figure 1. GALEN study design

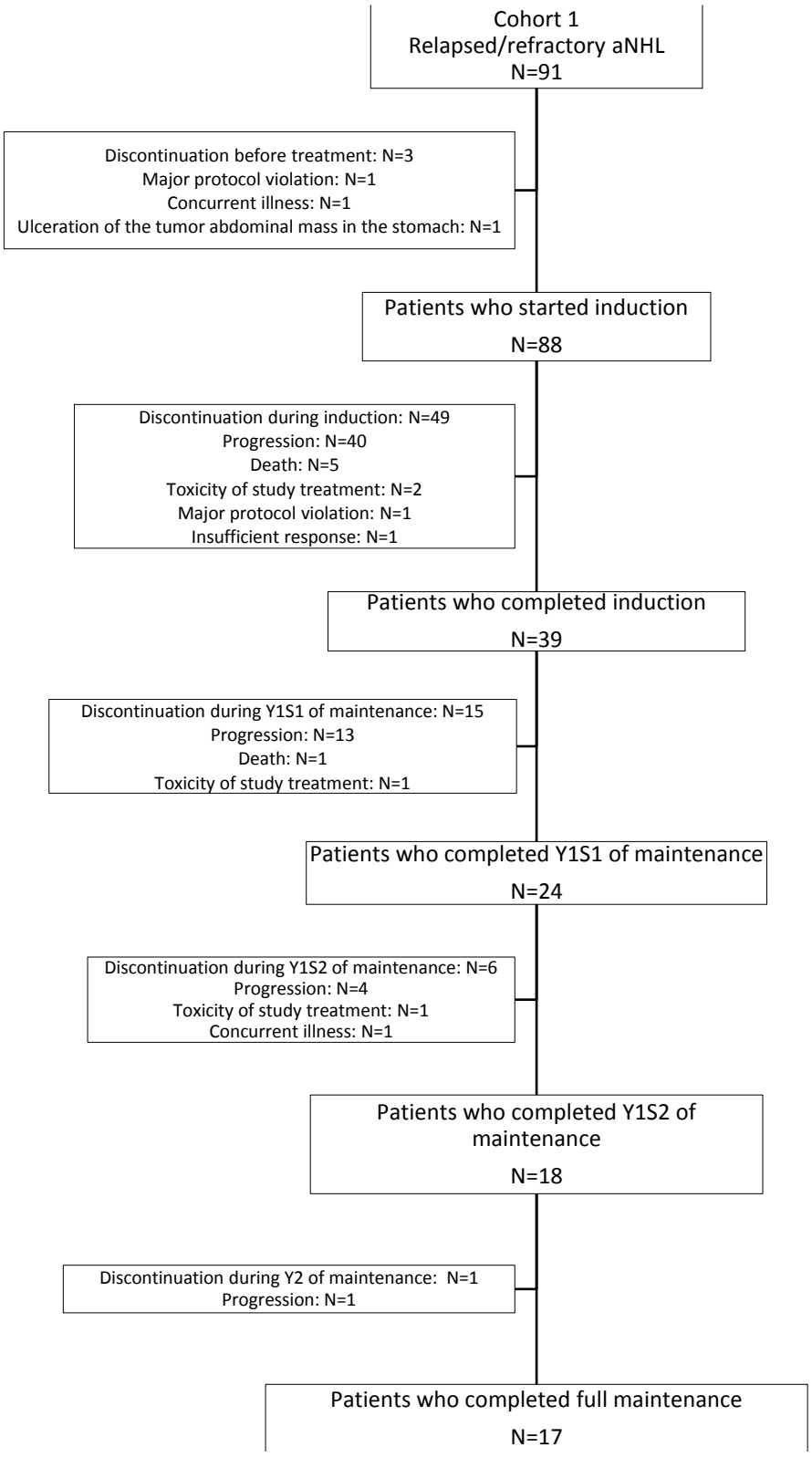
Patients received a combination of obinutuzumab and lenalidomide for a total of 6 cycles (induction). Subsequently, patients who achieved at least a partial response after 6 cycles received maintenance treatment. Induction consisted in 1) oral lenalidomide once daily at 20 mg on days 1-21 of a 28-day 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.



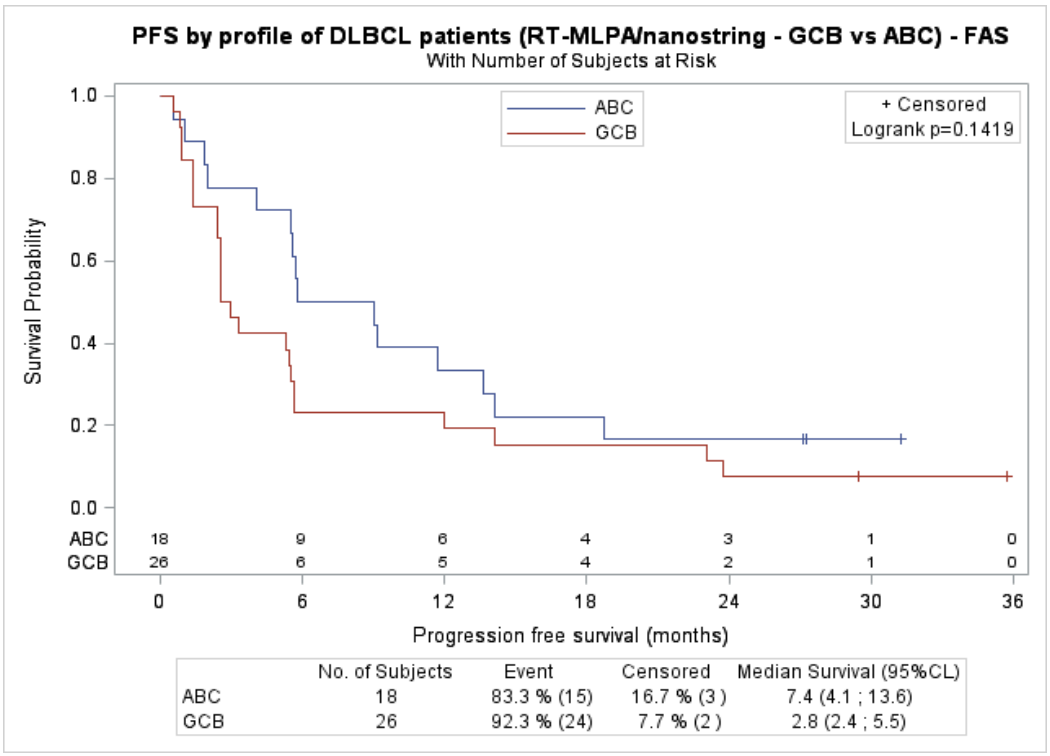
Supplementary Figure 2. GALEN study CONSORT diagram

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.

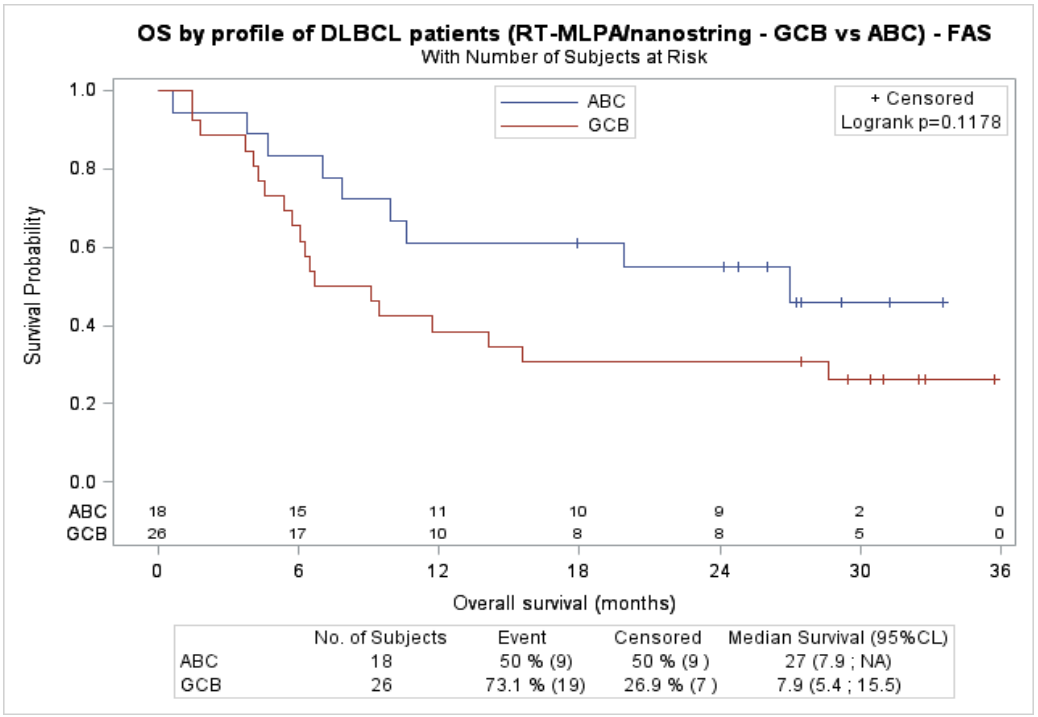


Supplementary Figure 3. Progression-free survival (A, C, E) and Overall survival (B, D, F) in DLBCL according to COO measured by Nanostring + RT-MLPA (A, B), nanostring (C, D), and IHC (E, F)

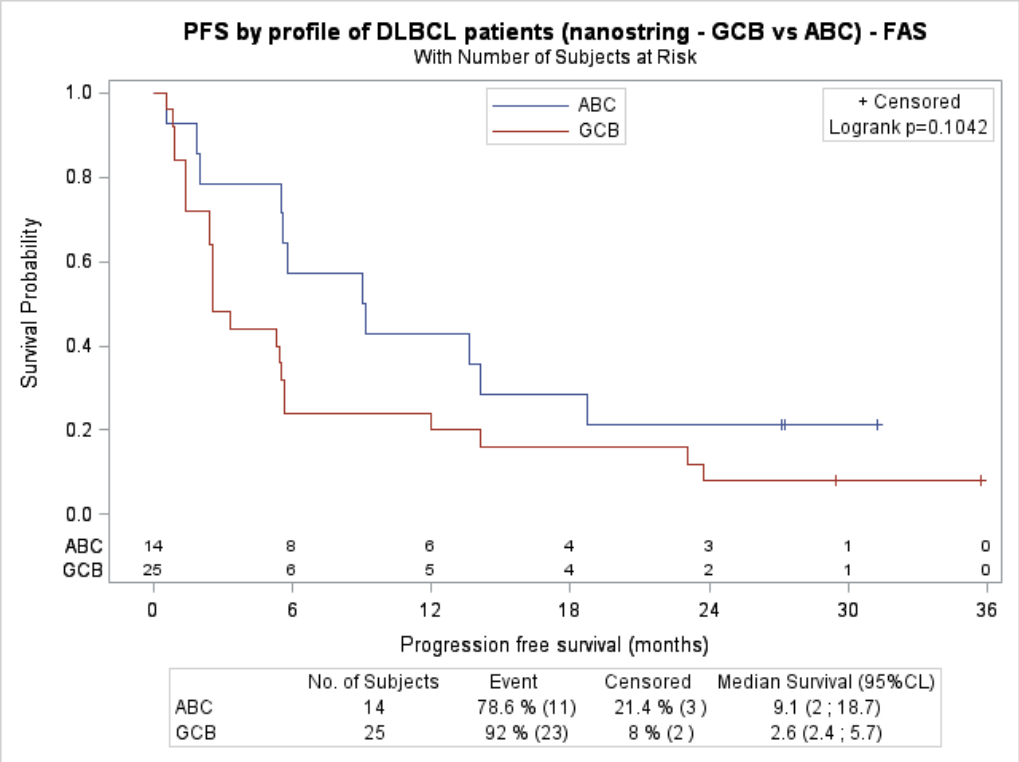
A. Progression-free survival



B. Overall survival

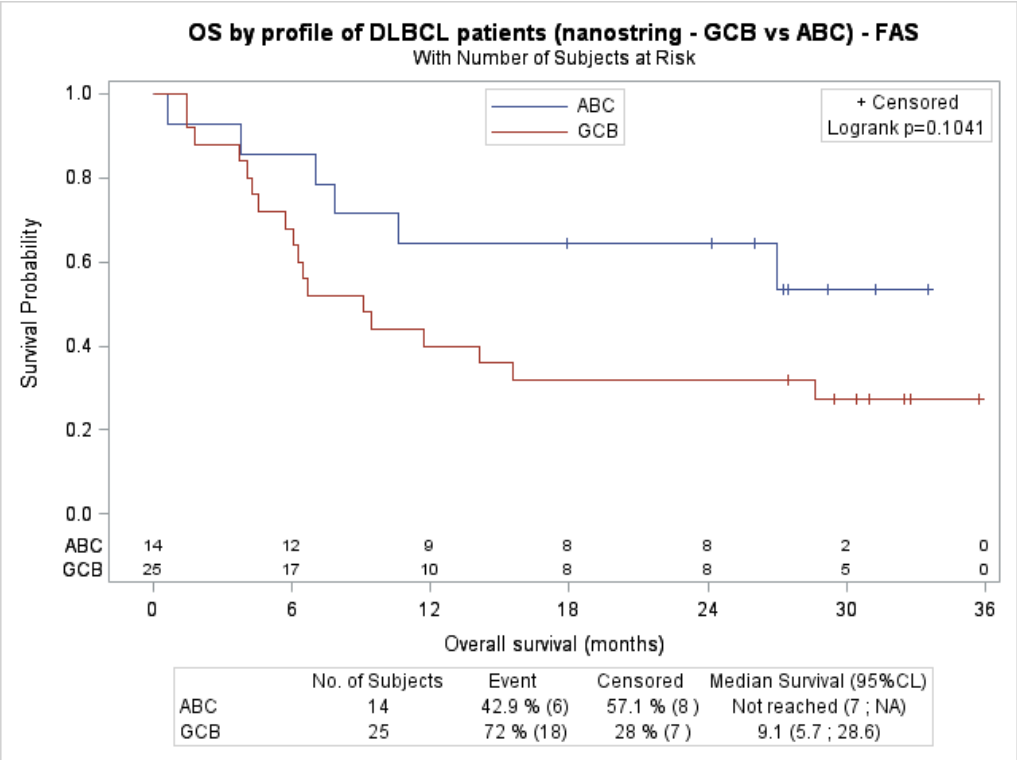


C. Progression-free survival



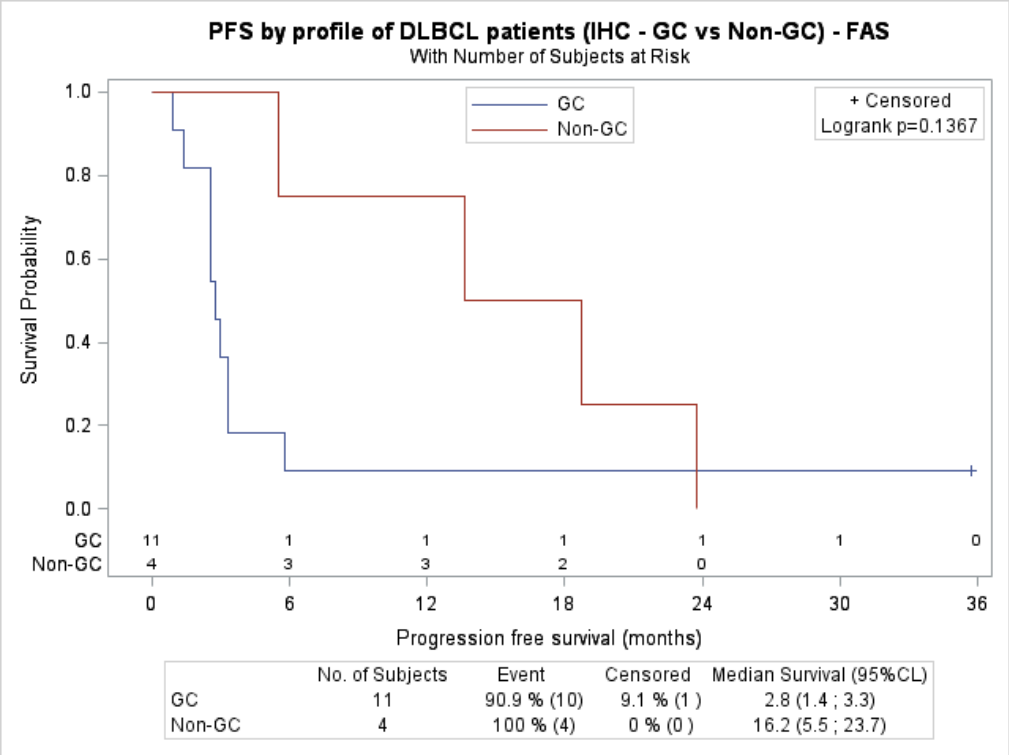
	No. of Subjects	Event	Censored	Median Survival (95%CL)
ABC	14	78.6 % (11)	21.4 % (3)	9.1 (2 ; 18.7)
GCB	25	92 % (23)	8 % (2)	2.6 (2.4 ; 5.7)

D. Overall survival



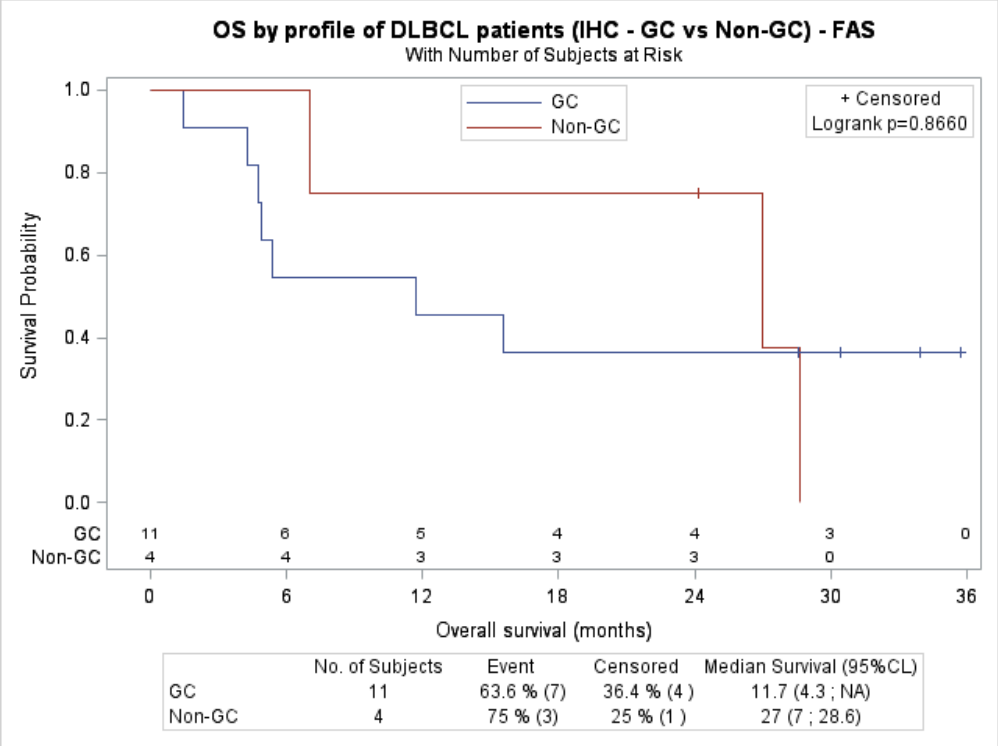
	No. of Subjects	Event	Censored	Median Survival (95%CL)
ABC	14	42.9 % (6)	57.1 % (8)	Not reached (7 ; NA)
GCB	25	72 % (18)	28 % (7)	9.1 (5.7 ; 28.6)

E. Progression-free survival



	No. of Subjects	Event	Censored	Median Survival (95%CL)
GC	11	90.9 % (10)	9.1 % (1)	2.8 (1.4 ; 3.3)
Non-GC	4	100 % (4)	0 % (0)	16.2 (5.5 ; 23.7)

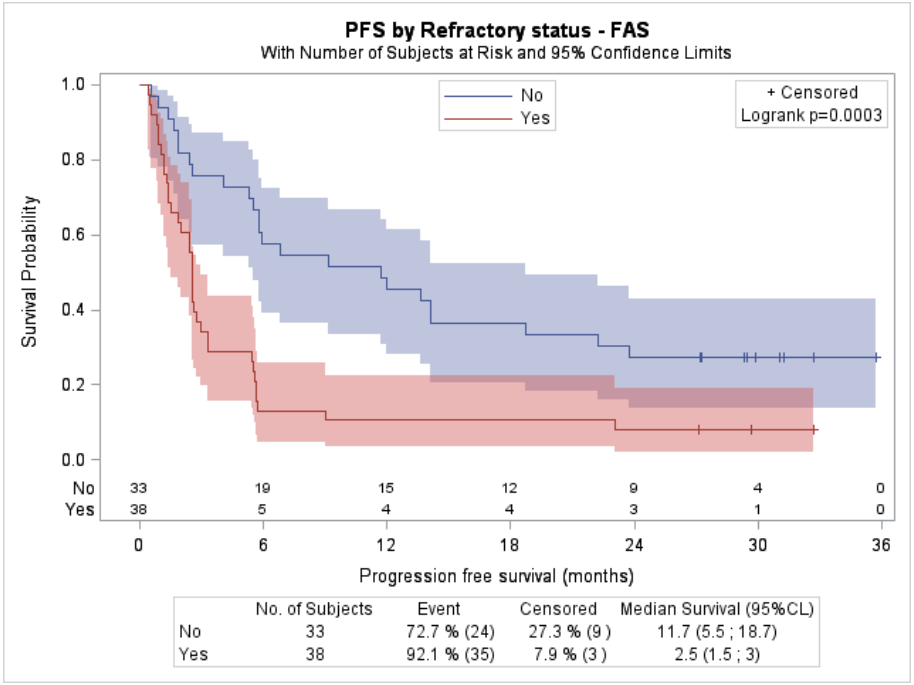
F. Overall survival



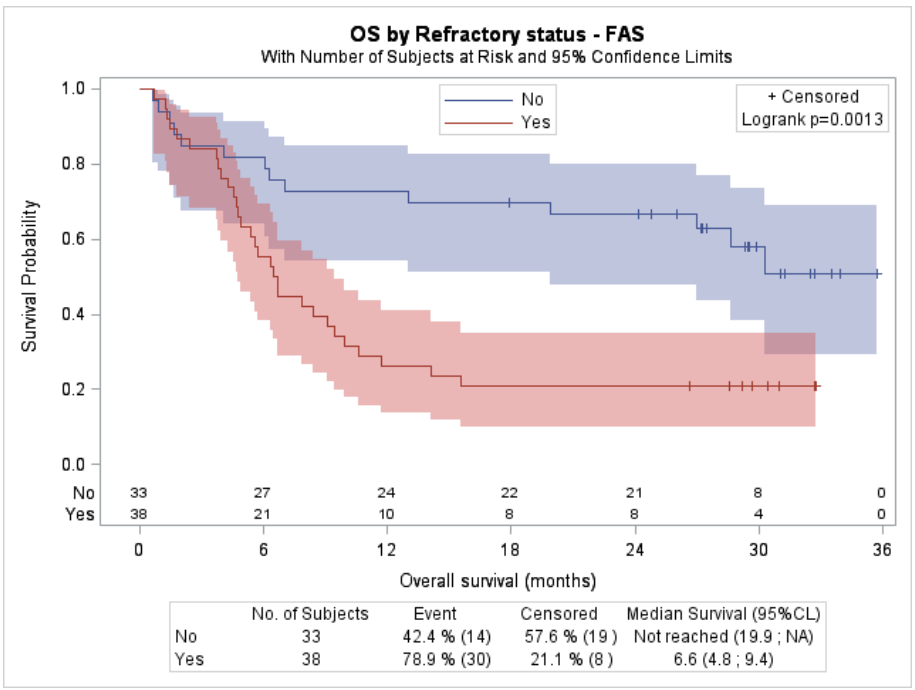
	No. of Subjects	Event	Censored	Median Survival (95%CL)
GC	11	63.6 % (7)	36.4 % (4)	11.7 (4.3 ; NA)
Non-GC	4	75 % (3)	25 % (1)	27 (7 ; 28.6)

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

	DLBCL (N=71*)	**MCL (N=13)**	**All pts (N=85**)**
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-naive*
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

			DLBCL (N=71)	MCL (N=13)	All pts (N=85)
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*

			DLBCL-ABC (N=18)	DLBCL-GCB (N=26)	p
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)

Adverse Event (%)	All Grades	Grade ≥ 3
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%)