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Obinutuzumab plus lenalidomide (GALEN) in advanced, previously untreated follicular lymphoma in need of systemic therapy

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- GALEN regimen is a potent regimen in first line FL in need of treatment with 94% ORR and 80% CMR and 82% 3-yr PFS according to Lugano 2014 post-hoc analysis
- Toxicity is concordant with previous studies in R/R setting and is mainly neutropenia (47% of grade ≥ 3)

ABSTRACT

Obinutuzumab and lenalidomide (GALEN) is an active immunomodulatory combination with a manageable safety profile in multiple types of lymphoma. We report efficacy and safety results for the phase 2 GALEN study in previously-untreated patients with advanced follicular lymphoma (FL).

Eligible patients aged ≥ 18 years had ECOG PS ≤ 2 , high-tumor burden, grade 1-3a FL. Induction treatment was obinutuzumab (1000 mg IV, days 8/15/22, cycle 1; day 1, cycles 2-6) plus lenalidomide (20 mg/day, days 1-21, cycle 1; days 2-22, cycles 2-6) for 6 cycles. Maintenance included obinutuzumab (1000 mg every 2 cycles) plus lenalidomide (10 mg, days 2-22) for ≤ 12 cycles (year 1) followed by obinutuzumab (1000 mg every 56 days) for 6 cycles (year 2). The primary endpoint was complete response rate (CRR) after induction per IWG 1999 criteria.

From October 2015 to February 2017, 100 patients were enrolled. CRR after induction was 47% and overall response rate (ORR) 92%. Post-hoc analyses per 2014 Lugano classification including patients with missing bone marrow assessments identified an additional 13 patients fulfilling CRR criteria, resulting in a complete metabolic response of 80% and ORR of 94%. At a median follow-up of 3.7 years, 3-year progression-free and overall survival were 82% and 94%, respectively. The most common adverse event was neutropenia (48% any-grade; 47% grade ≥ 3) but only 2% of patients presented febrile neutropenia; others were mainly grade ≤ 2 . No other specific grade ≥ 3 toxicity occurred at a frequency higher than 3%.

Overall, these results demonstrated promising clinical efficacy for the chemo-free backbone obinutuzumab and lenalidomide in previously untreated, high tumor burden FL patients. Except for neutropenia, the safety profile of the combination is remarkable. The study was registered with ClinicalTrials.gov, number NCT01582776

Keywords : follicular lymphoma, lenalidomide, obinutuzumab, maintenance therapy

INTRODUCTION

Follicular lymphoma (FL) is the most common indolent lymphoma, accounting approximately for 30% of cases.¹ During the 2 last decades, the addition of rituximab in combination with chemotherapy has significantly prolonged overall survival (OS), and maintenance therapy led to an almost doubled progression-free survival (PFS) following firstline induction.^{2,3}

Lenalidomide has demonstrated multiple immunomodulatory properties involving, among others, cytokine production alteration, amplified T-cell costimulation, and increased natural killer cell cytotoxicity.⁴⁻⁶ In vitro experiments demonstrated improved antibody-dependent, cell-mediated cytotoxicity and potent synergy between rituximab and lenalidomide. In FL patients, the association of lenalidomide and rituximab (thereafter referred to as R²) proved to be effective in the relapsed or refractory (R/R) setting and was recently approved given a significantly prolonged PFS over rituximab monotherapy.⁷⁻⁹ As firstline therapy, R² has shown efficacy results that appear comparable to immunochemotherapy with less toxicity.¹⁰⁻¹²

Obinutuzumab is an IgG1-type recombinant, humanized and glycoengineered type II anti-CD20 antibody.¹³ Compared to rituximab, obinutuzumab mediates greater antibody-dependent cellular cytotoxicity with reduced complement-dependent cytotoxicity.^{13,14} In FL, obinutuzumab in combination with chemotherapy demonstrated significantly prolonged PFS compared to firstline rituximab-based treatment and is now used worldwide.¹⁵

Given these observations, our cooperative group hypothesized that obinutuzumab and lenalidomide (thereafter referred to as the GALEN combination) would represent an attractive firstline treatment strategy for patients with FL to improve immune effector cell mechanisms. The recommended phase 2 dose of 20 mg for

lenalidomide, when associated with the 1000 mg fixed-dose obinutuzumab, was previously defined by our group in phase Ib.¹⁶ In R/R FL patients, this combination was safe and effective, with 68 of 86 evaluable patients (79%) responding at the end of the 6-month induction.¹⁷ At 2 years, PFS, duration of response (DOR) and OS were 65%, 70% and 87%, respectively. No unexpected safety signals emerged, and neutropenia was the most frequent grade ≥ 3 toxicity, with only 5% of patients experiencing febrile neutropenia.

Here, we report the phase 2 study results assessing the efficacy and safety of the GALEN combination in previously untreated FL patients.

PATIENTS AND METHODS

Patients

In this international multicenter phase 2 study, eligible patients were ≥ 18 years of age with biopsy-proven grade 1, 2 or 3a, CD20-positive FL, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2 , and no prior systemic treatment for lymphoma. Patients had to have a high tumor burden according to GELF criteria as defined by at least one of the following criteria: one lymphoma lesion greater than 7 cm, ≥ 3 separate nodes of ≥ 3 cm, symptomatic splenic enlargement or organ compression by lymphoma, the presence of B symptoms, pleural or peritoneal effusion, or lactate dehydrogenase or $\beta 2$ -microglobulin above the upper limit of the normal. Patients were required to comply with pregnancy prevention requirements, present with life expectancy of ≥ 3 months, and have measurable disease defined by ≥ 1 measurable lesion on computed tomography (CT) scan (transverse diameter > 1.5 cm and short axis ≥ 10 mm). Exclusion criteria were the presence of central nervous system involvement, known human

immunodeficiency virus or human T-cell leukemia virus type 1, or active hepatitis B or C viral infection. Patients with any serious active disease or co-morbid medical condition or pulmonary disease, or with prior history of malignancies other than lymphoma unless cancer-free for ≥ 5 years were ineligible. The use of corticosteroids ≥ 10 mg/day within the previous 28 days was prohibited. A prior watch and wait period or a treatment by radiotherapy were not considered as exclusion criteria. Histological diagnosis of FL was made by a local pathologist before inclusion. A centralized pathology review was performed by a pathology panel comprising ≥ 2 expert hematopathologists.

The study protocol was approved by local or national ethics committees according to the laws of each country, and undertaken in accordance with the Declaration of Helsinki and Good Clinical Practices. Patients were required to provide written informed consent before registration.

Treatment

All patients received an induction phase of six 28-day cycles with a combination of obinutuzumab (8 intravenous infusions of a 1000 mg flat dose on days 8, 15 and 22 of cycle 1 and on day 1 for cycles 2-6) and lenalidomide (20 mg/day on days 1-21 of cycle 1 and days 2-22 for cycles 2-6) as previously described.¹⁷ Subsequently, patients who achieved at least a partial response (PR) according to the International Working Group (IWG) 1999 criteria¹⁸ after 6 cycles received maintenance treatment. During the first year of maintenance (12 cycles of 28 days), patients received obinutuzumab (6 total infusions of 1000 mg, one per every 2 cycles of 28 days each) and lenalidomide (10 mg on days 2-22 of each 28-day for ≤ 12 cycles) until disease progression or treatment discontinuation. During the second year of maintenance (6 cycles of 56 days), patients received obinutuzumab (6 infusions of 1000 mg every

56 days) until disease progression or treatment discontinuation. The treatment schedule is summarized in Supplementary Fig S1.

All patients were required a daily aspirin (100 mg) for deep vein thrombosis (DVT) prophylaxis during through 28 days after the end of lenalidomide treatment. Patients unable to tolerate aspirin and those with a prior history of DVT or deemed high risk received low molecular weight heparin or warfarin (coumadin). G-CSF was permitted according to ASCO and ESMO guidelines and recommended if ANC was below 500/mm³ within any cycle. Treatment with G-CSF up to 3 days was allowed to reach ANC required to give the next cycle.

The percent of planned dose was calculated as follows: (total dose taken in mg)/(total dose expected in mg) x 100. It was computed for each drug and each treatment period (induction and maintenance).

Response Assessment

Computed tomography imaging of the chest, abdomen and pelvis with intravenous contrast was performed at baseline, after 3 cycles, at the end of induction, every 6 months during the 2 years of maintenance therapy, and thereafter every 6 months during follow-up, or until disease progression or relapse. Positron emission tomography (PET)/CT was optional, but performed for all patients at baseline and virtually all patients at the end of induction. Only PET for patients with Deauville score ≥ 3 ($N = 32$) or with missing Deauville score ($N = 4$) according to local evaluation at the end of induction were centrally reviewed. Patients with local Deauville score ≤ 2 ($N = 61$) were considered in complete metabolic response (CMR) without the need for central review. Patients with no PET at the end of induction ($N = 3$) were not evaluable.

Statistical Analysis

The primary endpoint was the complete response rate (CRR; complete response [CR] plus unconfirmed CR [CRu]) according to International Working Group (IWG) 1999 criteria¹⁸ at the end of 6 cycles of GALEN. Secondary endpoints for response according to IWG 1999 criteria¹⁸ were overall response rate (ORR) at the end of induction, ORR and CRR at the end of treatment (induction plus maintenance), and best response during treatment. PFS, time to next anti-lymphoma treatment (TNALT), DOR, OS and safety were also secondary endpoints. Response rates according to the Lugano 2014 classification¹⁹ at the end of induction were exploratory, post-hoc analyses not initially planned since the trial design was initiated in 2012. Progression of disease during the first 2 years following treatment start (ie, POD24) was also a post-hoc analysis.

The trial was designed to detect a CRR increase from 50% (null hypothesis) to 65% (alternative hypothesis) assuming a 90% power at an overall 5% (1-sided) significance level using a single-stage phase 2 design. Based on these hypotheses, null hypothesis (H_0 : CRR \leq 50%) would be rejected if the lower limit of the 90% CI was \geq 50%, meaning that at least 59 patients should be in CR at the end of induction. Considering a 7% dropout rate, 100 patients needed to be included according to sample size computation. Adverse events were evaluated in accordance with NCI-CTCAE criteria, version 4.03. Analyses were conducted using SAS version 9.3. The study was registered with ClinicalTrials.gov, number NCT01582776.

RESULTS

Patients

From October 2015 to February 2017, a total of 100 patients were enrolled in 21 centers from France and Belgium (Fig 1 CONSORT diagram). All patients were

evaluable for efficacy and safety. Ninety-six (96%) completed all 6 cycles of induction. Four patients discontinued treatment during induction due to progression ($N = 2$) or toxicity ($N = 2$). Seventy-three patients (73%) completed 2 years of maintenance. Sixteen patients discontinued during the first year of obinutuzumab and lenalidomide maintenance (8 for progression, 4 for toxicity, and 4 for other reasons), and 7 during the second year of obinutuzumab-only maintenance (2 for progression, 1 for toxicity and 4 for other reasons).

Patient characteristics are summarized in Table 1. Briefly, median age at enrollment was 60.5 years (range, 32-89), 45% male, and 75% ECOG PS 0. With regard to risk factors, 17%, 40%, and 43% of patients had respective low, intermediate, or high FL International Prognostic Index (FLIPI) score. Most patients had FL grade 1-2 (91%). Of note, nearly one-third of patients presented with bulky FL (ie, largest diameter > 7 cm).

Seventy-nine percent and 89% of patients received > 90% of the planned lenalidomide and obinutuzumab doses, respectively, during the six 28-day cycles of the induction phase. Including the maintenance phase, the percentage of planned doses for induction followed by maintenance was > 90% for 56% and 76% of patients receiving lenalidomide and obinutuzumab, respectively.

Efficacy

The CRR at the end of induction according to IWG 1999 criteria¹⁸ (primary endpoint), was 47% (90% CI [primary endpoint evaluation], 38% to 56% and 95% CI, 37% to 57%), with 20% CR and 27% CRu (Table 2). The PR rate was 45%, leading to an ORR of 92% (95% CI, 85% to 96%). Secondary endpoints of CRR and ORR at the end of treatment (induction plus maintenance) were 63% (95% CI, 52% to 72%) and 79% (95% CI, 70% to 87%), respectively (Table 2). Best CRR and ORR during the

entire treatment duration were 77% (95% CI, 68% to 85%) and 99% (95% CI, 95% to 100%), respectively (Table 2).

Thirty-two patients with no BM biopsy or with marrow involvement at baseline did not have a BM biopsy performed at the end of induction. Among them, 17 patients fulfilling CR or CRu criteria, based on reduction of tumor size by CT scan per IWG 1999 criteria,¹⁸ had to be reclassified as PR due to missing BM evaluation at the end of induction (Supplementary Table S1). According to Lugano 2014 classification,¹⁹ 13 of these 17 patients were in CMR at the end of induction. As a result, complete response according to Lugano 2014 classification¹⁹ at the end of induction was 80% (95% CI, 71% to 87%) and overall response was 94% (95% CI, 87% to 98%; Table 3). Of note, complete response at the end of treatment (i.e. after 30 months) or CR30 was 63% (95% CI, 52% to 62%) according to Cheson 99 criteria (Table 2).

After a median follow-up of 3.7 years (95% CI, 3.6 to 3.8), estimated 3-year PFS was 82% (95% CI, 73% to 88%), DOR was 83% (95% CI, 74% to 89%), TNALT was 85% (95% CI, 76% to 91%), and OS was 94% (95% CI, 87% to 97%; Fig 2A-D).

No significant response rate nor PFS duration differences were observed according to lenalidomide dose-intensity (<90 or ≥90%) received during induction (Supplementary Table S2 and Supplementary Fig S2). PFS was also consistent across all patient subgroups (Supplementary Fig S3).

Reaching a CMR according to Lugano 2014 criteria was associated with significantly prolonged PFS and TNALT ($P<.001$ for both, Supplementary Fig S4A and S4B). On the opposite, CR/CRu status was not predictive of a better outcome, most likely due to the high proportion of patients considered in PR according to Cheson 99 criteria (because of lack of BM reassessment) despite reaching CMR by PET-CT evaluation (Supplementary Fig S4C and S4D).

Of 98 patients evaluable for early progression (1 patient died of unrelated cancer without progression and 1 patient withdrew consent before 2 years), 14 patients (14%) experienced early POD24 after treatment initiation. Biopsy was performed at progression in 10 cases and histological transformation arose in 3 patients. Patients experiencing POD24 were confirmed to have a shorter subsequent OS ($P < 0.0001$; Supplementary Fig S5).

Safety

The most frequently reported adverse events (AEs) of any grade during treatment were asthenia (51%), neutropenia (48%), constipation (42%), cough (36%), and diarrhea (35%; Table 4). The vast majority of these AEs were of grade ≤ 2 , except for neutropenia. Forty-seven percent of patients experienced grade ≥ 3 neutropenia, but only 2 patients presented with febrile neutropenia. The second most frequent grade ≥ 3 was infusion-related reaction which occurred only in 3% of patients. Twenty-one patients experienced at least one serious AE (SAEs) during induction, 30 patients during maintenance and 14 patients after treatment. Treatment discontinuation occurred in 75 of patients. The most frequent reason for treatment discontinuation was neutropenia (37% of patients) and infection (20%), followed by infusion-related reaction (17%) and skin reaction (14%). Tumor flare was observed in only 4% of patients and only 1% was of grade 3. Seven patients permanently discontinued treatment due to toxicity (Fig 1). Thirty-two patients had lenalidomide dose modification and the main reason was neutropenia (26% of patients). Regarding AEs of infectious nature, 75% of patients experienced at least one infection throughout treatment, and most of them concerned the respiratory tract. No

specific period of occurrence (i.e., induction, first or second year of maintenance therapy) was observed. Only 8% of patients experienced grade ≥ 3 infectious AEs. Three fatal AEs were observed. A 78-year old female died from an intestinal adenocarcinoma during the first year of maintenance, a 68-year old man died from a lung adenocarcinoma following treatment completion, and a 70-year old man died from septic shock after cycle 4 of induction. All were considered unrelated to lenalidomide or obinutuzumab by the local investigators.

Eleven patients presented with a second primary malignancy (SPM) (Supplementary Table S3 and Supplementary Fig S6). One patient presented with 2 sequential second primary malignancies (lung adenocarcinoma followed by breast cancer). Altogether, 10 solid tumors and 2 hematological malignancies were noted. Two of these were considered unrelated to study treatment by local investigators. One patient had a lung adenocarcinoma diagnosed 6 months after inclusion but pulmonary nodules were present on baseline CT scan. One patient presented with a neuroendocrine pancreatic tumor diagnosed 7 months after inclusion, but the pancreatic tumor mass was already present at baseline. The 2 hematological SPMs were a Hodgkin lymphoma diagnosed 13 months after inclusion in a patient achieving a CRu after GALEN induction, and a peripheral T-cell lymphoma not otherwise specified, also diagnosed 13 months after inclusion in a patient achieving CR after induction. Finally, 2 SPMs were cutaneous basocellular and epidermoid carcinomas. Detailed list of other SPM is provided in Supplementary Table S3.

DISCUSSION

Results of the study show that obinutuzumab and lenalidomide in combination for 6 months, followed by a first year of maintenance with both drugs and a second year of

maintenance with obinutuzumab only, is active and safe in patients with previously untreated, high tumor burden FL. The primary endpoint of this phase 2 study (ie, CRR at the end of six 28-day cycles of GALEN) was not reached likely due to the missing BM assessments at the end of induction to confirm CR or CRu in 17 patients, even though the procedure was required per protocol, thus leading to their responses being classified as PR. In a post-hoc analysis according to PET/CT-based Lugano 2014 response assessments¹⁹ (criteria that were defined after study initiation), CMR was 80%, thus exceeding the primary response expectations, and ORR was 94%. Indeed, 13 of the aforementioned 17 patients who were classified as in PR per IWG 1999 criteria were classified as complete metabolic responses by PET/CT. Bone marrow involvement is a frequent observation in FL patients, and the definition for CR or CRu according to IWG 1999 criteria¹⁸ requires BM negativity at the end of treatment for all patients with an indeterminate, positive, or missing BM biopsy at baseline. However, several recent studies have demonstrated a low proportion of response reclassification based on BM assessment at the end of treatment (less than 5% of cases in the GALLIUM study and in other clinical trials).^{20,21} Altogether, these data largely support the evaluation of CMR according to post-hoc Lugano 2014 assessment¹⁹ in the present study.

The 80% CMR by Lugano 2014 response criteria in this study is in line with the high 92% CR reported by Nastoupil et al at first evaluation (day 1 of cycle 4) of a similar obinutuzumab and lenalidomide combination strategy in previously untreated patients with high tumor burden FL.²² In a subpopulation of the GALLIUM study, complete metabolic response by Lugano criteria was 73% (95% CI, 67% to 78%) in the rituximab-based chemotherapy group compared with 79% (95% CI, 74% to 83%) in the obinutuzumab-based chemotherapy group.²³ Complete response rate at 30-

month, or CR30, is a validated surrogate endpoint for PFS in FL. Here, CR30 according to Cheson 99 criteria was 63% compared to 48% as assessed by independent review committee (55% by investigator) in the R2 arm of treatment in the RELEVANCE trial.¹⁰ Although no formal comparison can be made, this strengthens the efficacy of the GALEN regimen.

After a median follow-up of 3.7 years, 3-year PFS was 82% per investigator assessment. The prolonged PFS observed in the study is consistent with the high CRR observed according to the Lugano 2014 criteria¹⁹ at the end of induction. In the rituximab plus chemotherapy followed by rituximab maintenance arms of the GALLIUM, PRIMA, and RELEVANCE randomized phase III trials, 3-year PFS rates (by investigator assessment) were 73% (95% CI, 69% to 77%), 75% (95% CI, 71% to 79%) and 78% (95% CI, 74% to 81%), respectively.^{10,15,24} In the rituximab plus lenalidomide arm of the RELEVANCE, Cancer and Leukemia Group B (CALGB) 50803, and M.D. Anderson Cancer Center studies, 3-year PFS rates were 77% (95% CI, 72% to 80%), 81% (95% CI, 69% to 89%) and 79% (95% CI, 67% to 92%), respectively.¹⁰⁻¹² Altogether and within all possible pitfalls of historical, cross-trial comparisons, obinutuzumab plus lenalidomide appears to represent a promising combination strategy. In the obinutuzumab plus chemotherapy arm of the GALLIUM study, 3-year PFS was 80% (95% CI, 76% to 84%), within the range of figures observed in the present study.¹⁵ Regarding early progression of disease, 14% of patients experienced POD24 in our study relative to 19% in the NLCS cohort after firstline R-CHOP,²⁵ 16% after rituximab plus chemotherapy and 10% after obinutuzumab plus chemotherapy in the GALLIUM study.²⁶ Therefore, the GALEN combination appears to limit early progression, at least as potently as anti-CD20 plus chemotherapy. Regarding treatment duration, shorter treatment with lenalidomide

and anti-CD20 have been used in R/R setting. Both AUGMENT and CALGB studies assessed the efficacy of a 12 months combination strategy.^{9,12} Extended duration in the MAGNIFY trial (NCT01996865) for 2 years and a half compared to rituximab alone will provide valuable information regarding the utility of prolonged combination strategy in R/R FL.⁷ Recently reported long-term follow-up of the RELEVANCE study shows that the association of rituximab and lenalidomide for the same duration as in the present study produces excellent long term outcome with a 6-year PFS of 60%, superimposable to the outcome yielded by rituximab plus chemotherapy.²⁷ Whether shorter duration of anti-CD20 and lenalidomide as in R/R FL could produce similar efficacy in first line remains hypothetical.

With respect to safety, obinutuzumab plus lenalidomide was well tolerated. The most frequent grade ≥ 3 AE was neutropenia, which occurred in 47% of patients, with only 2 patients experiencing febrile neutropenia. No other grade ≥ 3 AE occurred at a frequency $> 5\%$. Other frequent, but predominantly grade 1/2, any-grade AEs were asthenia (51%), digestive AEs (constipation 42%, diarrhea 35%), cough (36%), and infusion-related reaction during or after obinutuzumab infusion (28%). Although not directly comparable, the R² arm of the RELEVANCE trial reported 32% grade ≥ 3 neutropenia, and respective any-grade fatigue, constipation, diarrhea and infusion-related reaction in 23%, 35%, 37% and 13% of patients.¹⁰ As expected from the known safety profile of obinutuzumab, the GALEN regimen seems associated with a slightly increased risk of grade 3/4 neutropenia and of grade 1/2 infusion-related reaction, but comparable digestive grade 1/2 toxicity. Rash was similarly reported in 29% of patients in RELEVANCE with R² compared to 25% of patients receiving the GALEN combination. Twelve SPMs were observed here among 11 (11%) patients. Two were deemed unrelated to the GALEN regimen because of already-associated

abnormalities observed on patient's baseline CT. In a similar setting but after a shorter median follow-up of 38 months (compared to 46 months here), second primary cancers were reported in 38 patients (7%) in the R2 group including 25 patients who had invasive second tumors and 13 who had noninvasive second tumors. No new safety signals were therefore observed with the GALEN combination.

Results from our post-hoc evaluation of response by 2014 Lugano criteria reiterated the importance of integrating PET/CT-based assessments to provide a comprehensive evaluation of response, and better enable cross-trial comparison with current studies. Altogether and within the limitation of a non-controlled, phase 2 study, the combination of obinutuzumab and lenalidomide appears to offer a promising chemo-free backbone in previously untreated, high tumor burden FL to be further investigated and built on. Especially, other agents targeting the FL microenvironment or T-cell engager allowing concomitant use of anti-CD20 monoclonal antibodies would be attractive partners for future therapeutic association with the GALEN backbone.

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AUTHOR CONTRIBUTIONS

EB, RH and FM designed and performed the research and wrote the manuscript. All authors collected, analyzed and interpreted data.

DISCLOSURE

EB declares advisory boards for Roche, Takeda, BMS and Incyte, and honoraria for Novartis, Kite/Gilead and Roche; PF reports advisory boards and travel accommodation for Roche and Celgene/BMS; FB declares advisory boards for BMS; HT declares honoraria and advisory boards for Roche; FM reports consultancy Roche/genentech; advisory boards for Roche, BMS, Gilead, Novartis, Epizyme, Genmab, Abbvie, Kymera; the other authors declare no COI.

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FIGURE LEGENDS

FIG 1. CONSORT diagram

FIG 2. Progression-free survival (A), time to next anti-lymphoma treatment (B), response duration (C), and overall survival (D)

TABLE 1. Baseline Patient Characteristics

Characteristic	(N = 100)
Median age at inclusion, years (range)	60.5 (32-89)
Age group	
≤ 70 years	83 (83)
> 70 years	17 (17)
Sex	
Male	45 (45)
Female	55 (55)
ECOG PS	
0	75 (75)
1	24 (24)
2	1 (1)
Ann Arbor stage	
II	11 (11)
III	22 (22)
IV	67 (67)
Highest diameter > 7 cm	
No	69 (69)
Yes	31 (31)
Median time between biopsy of initial diagnosis and inclusion, months (IQR)	1.6 (1-3)
Initial histological diagnosis (per local assessment)	
CD20+ FL grade 2	72 (72)
CD20+ FL grade 1	13 (13)
CD20+ FL grade 3a	9 (9)
Other	6 (6)
CD20+ FL grade 1-2	5 (5)
Low grade FL	1 (1)
FLIPI group	
Low	17 (17)
Intermediate	40 (40)
High	43 (43)
LDH > ULN	
No	73 (73)
Yes	27 (27)
B-symptoms	
No	82 (82)
Yes	18 (18)
Bone marrow involvement*	
No	47 (52)
Yes	43 (48)
Missing	10
Beta-2 microglobulin > ULN*	
No	50 (52)

Characteristic**(N = 100)**

Yes	46 (48)
Missing	4

NOTE: Data are no. (%) unless otherwise specified.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, FL International Prognostic Index; IQR, interquartile range; LDH, lactate dehydrogenase; ULN, upper limit of normal.

*Calculated percentages excluded missing data.

TABLE 2. Response Rates According to IWG 1999 Criteria¹⁸ at the End of Induction (Primary Endpoint), End of Induction and Maintenance, and Best Response Rates

Response Status*	End of Induction (Primary Endpoint) (N = 100)	End of Induction and Maintenance [†] (N = 96)	Best Response Rates (N = 100)
ORR	92 (92) [85% to 96%]	76 (79) [70% to 87%]	99 (99) [95% to 100%]
CRR	47 (47) [37% to 57%]	60 (63) [52% to 72%]	77 (77) [68% to 85%]
CR	20 (20)	44 (46)	51 (51)
CRu	27 (27)	16 (17)	26 (26)
PR	45 (45)	16 (17)	22 (22)
SD	1 (1)	0 (0)	0 (0)
PD	2 (2)	9 (9)	1 (1)
Not evaluated	5 (5)	11 (11)	0 (0)

NOTE: Data are no. (%) [95% CI].

Abbreviations: CR, complete response; CRR, complete response rate (CR + CRu); CRu, CR unconfirmed; IWG, International Working Group; ORR, overall response rate (CR + CRu + PR); PD, progressive disease; PR, partial response; SD, stable disease.

*Patients without response assessment (due to whatever reason) were considered non-responders.

[†]Period of evaluation was after complete treatment for 74 patients (77%) and at premature withdrawal for 22 patients (23%).

TABLE 3. Response Rates at the End of Induction According to Lugano 2014 Response Classification (Exploratory Analysis)

Response Status*	(N = 100)
Overall metabolic response	94 (94) [87% to 98%]
Complete metabolic response	80 (80) [71% to 87%]
Partial metabolic response	14 (14)
No metabolic response (or stable disease)	2 (2)
Progressive metabolic disease	0 (0)
Not evaluable	4 (4)

NOTE: Data are no. (%) [95% CI].

*Response status was defined based on a 5-point scale according to PET/CT-guided assessments as outlined by Lugano 2014 revised criteria for response classifications.¹⁹

TABLE 4. Adverse Events (Safety Population [N = 100])

Adverse Events	Any Grade	Grade \geq 3
All adverse events	100 (100)	74 (74)
Asthenia	51 (51)	2 (2)
Neutropenia*	48 (48)	47 (47)
Constipation	42 (42)	0 (0)
Cough	36 (36)	2 (2)
Diarrhea	35 (35)	2 (2)
Infusion-related reaction	28 (28)	3 (3)
Bronchitis	27 (27)	0 (0)
Decreased weight	26 (26)	1 (1)
Arthralgia	25 (25)	0 (0)
Rash	25 (25)	2 (2)
Rhinitis	21 (21)	0 (0)
Nausea	18 (18)	1 (1)
Nasopharyngitis	17 (17)	0 (0)
Back pain	15 (15)	0 (0)
Pruritus	15 (15)	1 (1)
Urinary tract infection	15 (15)	0 (0)
Peripheral edema	13 (13)	1 (1)
Muscle spasms	12 (12)	1 (1)
Upper abdominal pain	11 (11)	0 (0)
Erythema	11 (11)	0 (0)
Peripheral neuropathy [†]	11 (11)	1 (1)
Sinusitis	11 (11)	0 (0)

NOTE: Data are no. (%).

*Included combined preferred terms: neutropenia, neutrophil count decreased, neutrophil percentage decreased, and band neutrophil count decreased.

[†]Included combined preferred terms: neuropathy peripheral, peripheral sensory neuropathy, and paresthesia.

FIG 1. CONSORT diagram

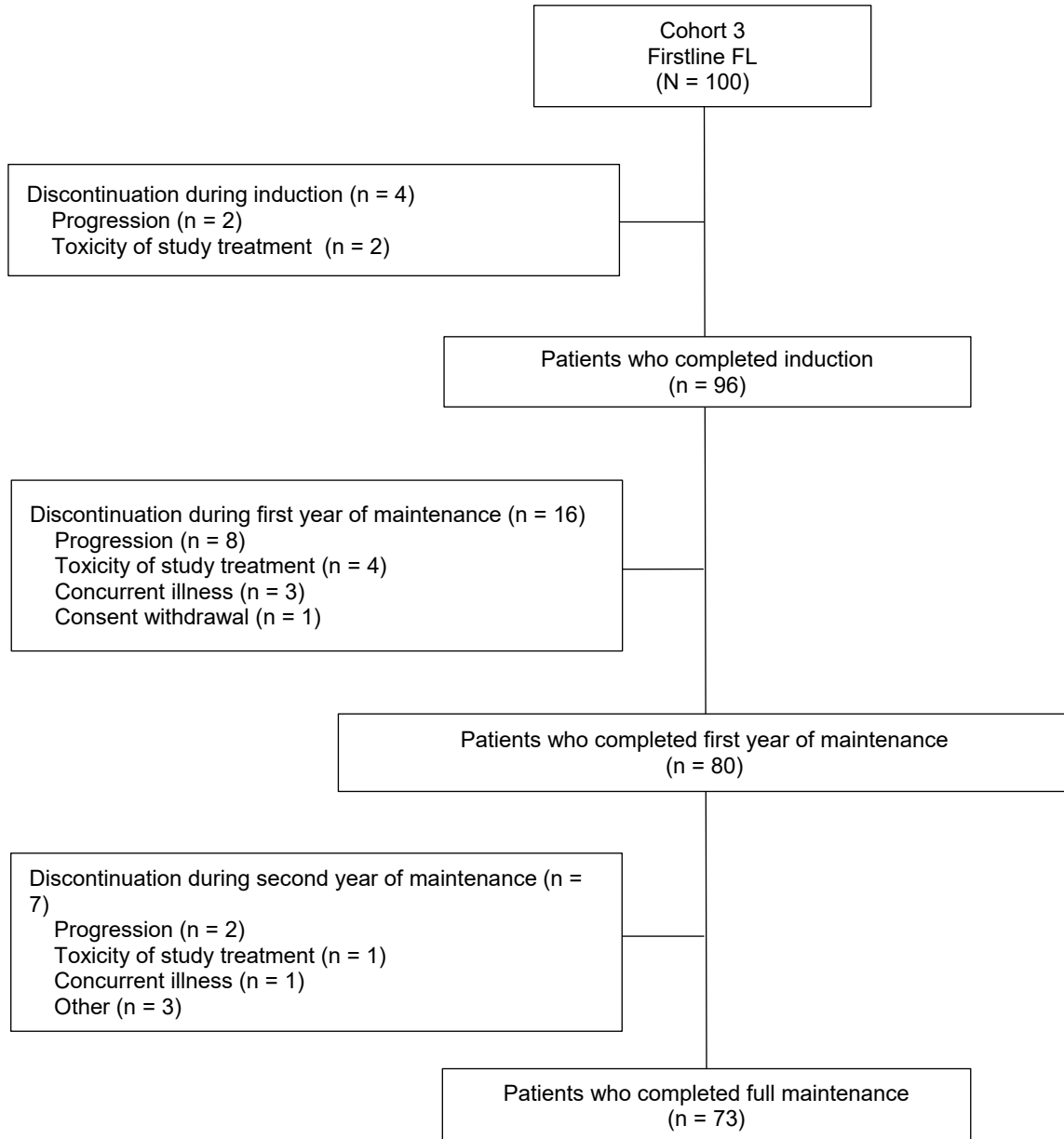


FIG 2. Progression-free survival (A), time to next anti-lymphoma treatment (B), duration of response (C), and overall survival (D)

