Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study

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Obinutuzumab Combined with Lenalidomide (GALEN) for Relapsed or Refractory Follicular B-Cell Lymphoma: A Phase 2 Study by the Lymphoma Study Association

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Research in Context

Evidence before this study

Before undertaking this study, we considered the fact that there is no clear standard of care, but there are new immunomodulatory treatment options, for patients with relapsed/refractory follicular lymphoma. Efficient conventional treatment options include autologous stem cell transplantation in early relapsed follicular lymphoma (progression of disease <2 years after diagnosis; POD24) and immunochemotherapy regimens such as obinutuzumab-bendamustine (G-benda) in patients with refractory disease. Recently, patients with relapsed/refractory follicular lymphoma have been successfully treated an immunomodulatory regimen combining lenalidomide with rituximab.

Added value of this study

Our data suggest that lenalidomide plus obinutuzumab—a glycoengineered type II anti-CD20 monoclonal antibody that has shown greater antibody-dependent cellular cytotoxicity, phagocytosis, and direct B-cell killing effects compared with rituximab—may be better than lenalidomide plus rituximab for treating patients with POD24, and similarly efficient to autologous stem cell transplantation and approved PI3K inhibitors in this setting and G-benda in patients with refractory disease.

Implications of all the available evidence

Results of this study evaluating the efficacy and safety of combining lenalidomide with obinutuzumab for induction therapy and using lenalidomide for maintenance provide evidence to expand immunomodulatory treatment options for patients with relapsed/refractory follicular lymphoma, including those with POD24 and refractory disease. GALEN may also constitute a

potential backbone for new regimens as investigated in the combination triplet with atezolizumab.

Keywords: follicular lymphoma, lenalidomide, obinutuzumab, refractory, relapsed

ABSTRACT

Background: Lenalidomide plus rituximab can treat patients with relapsed/refractory follicular lymphoma. Obinutuzumab enhances antibody-dependent cellular cytotoxicity, phagocytosis, and direct B-cell killing better than rituximab. Our aim was to determine efficacy and safety of lenalidomide plus obinutuzumab for treating relapsed/refractory follicular lymphoma.

Methods: This is an ongoing, phase 2, open-label, multicenter study of patients with CD20-positive, relapsed/refractory follicular lymphoma (≥1 previous rituximab-containing regimen). Patients received oral lenalidomide 20 mg plus IV-infused obinutuzumab 1000 mg (six 28-day cycles; induction), 1-year maintenance with lenalidomide 10 mg ([12] 28-day cycles; days 2–22) plus obinutuzumab 1000 mg (alternate cycles), and 1-year maintenance with obinutuzumab 1000 mg (six 56-day cycles; day 1). Primary endpoint was overall response rate (ORR) at induction end per 1999 International Working Group criteria. Adverse events (AEs) were monitored.

Findings: Eighty-six patients were evaluable for efficacy (88 for safety). ORR at induction end was 79·1% (95% CI, 68·9–87·1), meeting the pre-specified primary endpoint. Median follow-up for survival was 2·6 years (interquartile range, 2·2–2·8). At 2 years, event-free survival was 62.3% (95% CI, 51·1–71·7), progression-free survival 64·7% (95% CI, 53·5–73·8), duration of response 69·6% (95% CI, 57·2–79·0), and overall survival 86·9% (95% CI, 77·6–92·5). Most common AEs were asthenia (n=54, 61·4%), neutropenia (n=38, 43·2%), bronchitis (n=36, 40·9%), diarrhea (n=35, 39·8%), and muscle spasms (n=34, 38·6%). Neutropenia was the most common grade ≥3 toxicity; 4 (4·5%) patients had febrile neutropenia. Fifty-seven serious AEs were in 30/88 patients (34·1%); 18/88 (20·5%) deaths occurred (progressive lymphoma [n=10], infection [n=4], related cancer [n=1], and unknown cause [n=3]). No AEs were unanticipated.

Interpretations: Lenalidomide plus obinutuzumab is effective for patients with relapsed/refractory follicular lymphoma, including those with early relapse, with no increased toxicity compared with previous reports for lenalidomide plus rituximab.

Funding: The Lymphoma Academic Research Organisation (LYSARC) sponsored the study, and Celgene and Roche provided investigator-initiated study grants.

INTRODUCTION

Follicular lymphoma is characterized by a defective immune microenvironment that suppresses normal T- and natural killer (NK)-cell activity, and by a long natural history of disease with repeated relapses in many. More recent treatments include immunomodulatory agents[1-5] and phosphoinositide 3′-kinase (PI3K) inhibitors.[6,7] Lenalidomide is an immunomodulatory drug that has direct antiproliferative activity on lymphoma cells, enhances T-cell and NK-cell function, and improves antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis.[8] When combined with rituximab, a CD20 type I antibody, lenalidomide has synergistic effects in preclinical lymphoma models.[9-11] This immunomodulatory, lenalidomide-rituximab combination showed promising activity in patients with relapsed or refractory follicular lymphoma.[1-4]

Obinutuzumab (Gazyva [known as Gazyvaro in Europe], F. Hoffmann–La Roche) is a glycoengineered, type II anti-CD20 monoclonal antibody, which, versus rituximab, has lower complement-dependent cytotoxicity but greater ADCC and phagocytosis as well as direct B-cell killing effects.[12,13] Obinutuzumab with lenalidomide also had an additive effect in triggering NK-cell activation in vivo.[14] Clinically, obinutuzumab-based immunochemotherapy and maintenance therapy were effective in patients with rituximab-refractory, indolent non-Hodgkin's lymphoma.[5,15,16]

We hypothesized that obinutuzumab plus lenalidomide may be more effective than lenalidomide plus rituximab, and in 2012, a phase 1b/2 study was initiated to assess the safety and antitumor efficacy of obinutuzumab and lenalidomide (GALEN) to treat patients with relapsed/refractory follicular lymphoma. The phase 1b study demonstrated satisfactory safety of the combination given during 6 months and established the recommended phase 2 dose of

lenalidomide as 20 mg, for use in combination with a fixed dose of obinutuzumab 1000 mg.[17] Here, we report results of the phase 2 part of the study assessing efficacy and safety of the GALEN regimen with an additional 2 years of maintenance in patients with relapsed/refractory follicular lymphoma.

METHODS

Study design and participants

This was a phase 2, open-label, multicenter study sponsored by the Lymphoma Academic Research Organisation (LYSARC) to assess the efficacy and safety of obinutuzumab plus lenalidomide in patients with relapsed/refractory follicular lymphoma. Patients were enrolled from 24 LYSARC centers in France. The protocol was approved by the central Independent Ethics Committee and the Agence Nationale de Sécurité du Médicament et des Produits de Santé; the study was conducted according to the principles of the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. All patients gave written informed consent before participating. The study (GALEN trial; NCT01582776) was registered with ClinicalTrials.gov.

Eligible patients were ≥18 years of age with histologically confirmed (local pathology report) CD20-positive relapsed/refractory follicular lymphoma of World Health Organization grade 1, 2, or 3a. Patients had received ≥1 systemic rituximab-containing regimen, had no further curative option, and had life expectancy of ≥3 months. Additional inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, at least 1 measurable lesion on computed tomography (CT) scan (transverse diameter >1·5 cm and short axis ≥10 mm), and willingness to comply with lenalidomide pregnancy prevention requirements.

Patients were excluded if they had CNS or meningeal involvement by lymphoma, HIV or positive hepatitis B/C serology, serious comorbidities (eg, cardiac disease), other previous malignancies within 5 years, psychiatric illness, or significant laboratory abnormalities if they were not due to lymphoma (eg, absolute neutrophil count <1·5 x 10^9/L, platelet count <100 x 10^9/L, aspartate aminotransferase or alanine aminotransferase ≥3·0 times upper limit of normal, serum total bilirubin >34 µmol/L, or calculated creatinine clearance <30 mL/min). Patients with neuropathy higher than grade 2 or with a history of progressive multifocal leukoencephalopathy were excluded. Previous treatment with lenalidomide or obinutuzumab, recent anticancer drug therapy (within 28 days), or use of corticosteroids >10 mg/day (within 28 days) were additional exclusion criteria.

Procedures

Patients with creatinine clearance ≥50 mL/min received lenalidomide 20 mg as established in the phase 1b study plus obinutuzumab 1000 mg (GALEN regimen) as induction therapy for 6 cycles (cycle = 28 days). Patients with creatinine clearance of 30–50 mL/min received lenalidomide at 10 mg/day. Lenalidomide was given as 20 mg orally once daily on days 1–21 of cycle 1 and days 2–22 of cycles 2–6, in combination with IV infusions of obinutuzumab (1000 mg) given on days 8, 15, and 22 of cycle 1 and on day 1 only of cycles 2–6 (total of 8 infusions) (figure 1). Patients who achieved at least a partial response (PR) after 6 months of induction therapy were eligible to enter the maintenance phase. During year 1 of maintenance therapy (12 cycles; cycles 7–18), patients received lenalidomide 10 mg on days 2–22 of each cycle for a maximum of 12 cycles, combined with obinutuzumab 1000 mg on day 1 every 2 cycles (cycles 7, 9, 11, 13, 15, and 17; total of 6 infusions), as tolerated, until disease

progression. During year 2 of maintenance (6 cycles; cycles 19–24), patients took obinutuzumab 1000 mg alone on day 1 of every 56-day cycle (total of 6 infusions). Patients who were not eligible for maintenance therapy had safety follow-up at 28 days after the last treatment and for 3 years thereafter.

Lenalidomide dose was adjusted or interrupted in cases of toxicity during treatment defined by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4·03). Doses were successively reduced from 20 mg to 15, 10, and 5 mg, with no more than 1 dose reduction per cycle and no dose re-escalation permitted. Patients not tolerating the lowest applicable dose were discontinued from treatment. Obinutuzumab dose was not adjusted, but postponed in cases of toxicity until resolution of adverse events (AEs).

Steroid premedication was administered before the first obinutuzumab infusion. All patients took daily aspirin (100 mg) for deep vein thrombosis (DVT) prophylaxis; those with aspirin intolerance, DVT history, or high DVT risk received low-molecular-weight heparin or warfarin instead.

Outcomes

The primary efficacy outcome was the overall response rate (ORR) following lenalidomide 20 mg plus obinutuzumab 1000 mg at the end of the induction phase according to the response criteria for non-Hodgkin's lymphomas initially developed by an International Working Group (IWG) reported in Cheson et al (1999).[18] The ORR encompasses complete response (CR), complete response unconfirmed (CRu), and PR. Secondary efficacy endpoints were complete response rate (CR/CRu) after 3 and 6 cycles (induction); CR and ORR at end of maintenance; best ORR during the induction phase according to Cheson et al 1999 and 2007[18,19]; as well as

event-free survival (EFS), progression-free survival (PFS), duration of response (DOR), and overall survival (OS). Safety was a secondary endpoint, including AEs during induction and maintenance and the incidence of second primary malignancy (SPM) for up to 3 years during maintenance.

Post hoc analyses included outcomes within patient subgroups with early relapse (progression of disease within 24 months of initial chemoimmunotherapy;[20] POD24) versus late relapse (>24 months), refractory disease (i.e., no response or progressive disease within 6 months of last rituximab-containing regimen and/or last treatment received) versus non-refractory disease, number of previous regimens, and tumor bulk.

CT scan imaging with IV contrast (chest, abdomen, and pelvis) and positron emission tomography (PET) scan were performed at baseline, intermediate assessment (after 3 cycles), and the end of the induction phase; CT was repeated (PET optional) every 6 months for 2 years or until disease progression or relapse. At baseline, a central pathology review was also performed on new biopsies prior to enrollment or prior biopsies from initial diagnosis. To confirm CR/CRu, patients with positive bone marrow at screening were required to have a post-screening bone marrow biopsy within 28 days of first achieving radiological and clinical CR/CRu.

Safety evaluations throughout the phase 2 trial included AEs according to system organ class preferred term, vital signs, hematologic and biochemical laboratory tests, clinical and neurologic exams, B-symptoms, and ECOG performance status. AEs and serious AEs (SAEs) were reported continuously during the induction and maintenance phases until 28 days after the last treatment administration or up to the end of classical follow-up (2 years). Follow-up for SPM was continued every 6 months until 3 years after the end of lenalidomide.

AEs and SAEs were evaluated according to NCI-CTCAE criteria and graded 1–5 for intensity, and were categorized by treatment relatedness. SAEs were those causing significant disability, hospitalization, life-threatening status, or death; SPM was an SAE. AEs of special interest included infusion-related reaction (IRR), rash, tumor lysis syndrome, and tumor flare reaction.

Statistical analysis

We hypothesized that the primary endpoint (ORR according to IWG 1999 criteria) would increase from 50% (efficacy of obinutuzumab monotherapy in the GAUGUIN study[21]) to 70% following 6 treatment cycles. Sample size calculations indicated that 79 patients would be needed in the relapsed/refractory follicular lymphoma cohort to detect this increase, assuming 95% power at an overall 2·5% (1-sided) significance level using a single-stage, phase 2 design.[22] Target enrollment was 90 patients to account for a 15% dropout rate.

The efficacy population (full analysis set) included all patients who received ≥1 dose of both obinutuzumab and lenalidomide, and the safety population (safety set) included all those who received ≥1 dose of either investigational drug. Safety analyses were summarized descriptively. Response rates were reported as percentages with 95% confidence intervals (CIs) of patients. Time-to-event data were presented as Kaplan-Meier plots for time to first event and as summary tables for fixed time points. Median time to event and response rates were calculated with 95% CIs. Chi-square test analysed the effect of prognostic factors on response rates (post hoc analyses), and Cox proportional-hazards regression model was used to estimate hazard ratios and 95% CIs. All analyses were performed with SAS 9·3 software. Safety was reviewed every 6 months by an independent data safety monitoring committee.

Role of the funding source

LYSARC, the primary sponsor of the trial, was involved in the management of the study, statistical analyses, and data review. Celgene and Roche provided additional investigator-initiated research funding. Celgene and Roche provided a courtesy review of manuscript prior to submission, but the authors had final decisions for content reporting in the manuscript. Celgene and Roche had no role in study design, data collection, data analysis, or data interpretation. LYSARC, FM (corresponding author) and RH had access to the raw data. The corresponding author had the final responsibility to submit for publication.

RESULTS

Figure 1 presents the flow of patients through the study. A total of 89 patients with relapsed/refractory follicular lymphoma were recruited from June 11, 2014 to December 18, 2015. A total of 88 patients were in the safety set and 86 patients were in the full analysis set for efficacy. A total of 75/88 patients (85·2%) completed 6 cycles of therapy (induction) and started the first year of maintenance treatment; 56/88 patients (63·6%) completed all 18 cycles with lenalidomide and entered one year of maintenance with obinutuzumab, of which 43/88 (48·9%) completed maintenance and 2 remained on maintenance (figure 1).

Demographic and clinical patient characteristics are described in table 1. Median age was 64 years and 62·8% (54/86) of patients were men. At baseline, most patients had ECOG performance status of 0 (72·1% [62/86]) and Ann Arbor stage of 3–4 (83·7% [72/86]). Patients had received between 1 and 7 previous therapies (median of 2). At baseline, 24 of 86 patients (27·9%) had POD24, and 23 of 86 (26·7%) had refractory disease. Of note, upon central

pathology review, 3 patients proved to have diffuse large B-cell lymphoma (DLBCL) and 1 additional patient had a DLBCL component at inclusion, but all were kept in the efficacy analysis.

Most patients in the safety set (n=88) received a starting dose of lenalidomide of 20 mg (n=81; 92·0%) in the induction phase, while the remainder (n=7; 8·0%) received 10 mg because of creatinine clearance ≥30 to <50 mL/min at baseline. Twenty-eight patients had to reduce dose of lenalidomide. Nine patients had a missed or reduced dose of obinutuzumab, all during cycle 1. A percentage of planned doses taken (PPD; total dose taken [mg]*100/total dose expected [mg]) of ≥90% was observed in 54/88 patients (61·4%) for lenalidomide and in 74/88 patients (84·1%) for obinutuzumab during the induction phase (appendix pg 1). A PPD of ≥90% was also seen in 69·5% (41/59) of patients for lenalidomide and 94·8% (56/59) of patients for obinutuzumab at the end of the first year of maintenance, and in 76·8% (43/56) of patients for obinutuzumab in the second year of maintenance (appendix pg 1).

The primary endpoint of ORR (CR/CRu/PR) at the end of induction in the full analysis set (n=86) was 79·1% (95% CI, 68·9–87·1; CR/CRu = 38·4%, 95% CI, 28·1–49·5) according to IWG 1999 criteria (table 2), which corresponded to 75·6% (95% CI, 65·1–84·2; CR = 46·5%, 95% CI, 35·7–57·6) according to IWG 2007 criteria (appendix pg 2). The ORR therefore met its prespecified efficacy threshold (ie, lower bound of 95% CI excluding 50%). The best ORR during the study was 83·7% (95% CI, 74·2–90·8) according to IWG 1999 criteria.

Median follow-up for survival analyses was 2·6 years (interquartile range, 2·2–2·8). Figure 2 presents the results for PFS, DOR, and OS to a maximum follow up of 3·3 years (minimum 0 years). At 2 years, EFS was 62.3% (95% CI, 51·1–71·7), PFS was 64·7% (95% CI, 53·5–73·8), DOR was 69·6% (95% CI, 57·2–79·0), and OS was 86·9% (95% CI, 77·6–92·5).

In the post hoc analyses, numerically similar values were found in ORR for patients with POD24 (n=24) versus later relapse at >2 years (n=62) by both IWG 1999 and 2007 criteria. In addition, 2-year outcomes showed similar PFS and OS for POD24 versus later relapse groups (appendix pg 3-6). Worse ORR using IWG 1999 was observed for patients with refractory disease (n=23) versus those with non-refractory disease (n=63) at the end of induction therapy, but no significantly different results were found between these subgroups using IWG 2007 for ORR, PFS, and OS (appendix pg 3-6).

Responses were also assessed according to the number of previous treatments defined as 1 (n=42), 2 (n=19), or ≥3 (n=25) previous treatment lines. Increasing numbers of treatments were associated with progressively lower ORR when analyzed by IWG 2007 criteria, but not by IWG 1999 (appendix pg 3-6). A similar pattern for number of previous treatments was found for 2-year PFS and OS rates (appendix pg 3-6). In contrast, tumor bulk (measured as either <5 cm versus ≥5 cm, or <7 cm versus ≥7 cm) did not appear to influence ORR, PFS, or OS.

Nearly all patients (86/88; 97·7%) had ≥1 AE during the induction period, and 54 of 56 evaluable patients (96·4%) had ≥1 AE through the second maintenance year. The most common AEs (≥10% of patients) and all grade ≥3 AEs are listed in table 3. The most common AEs (all grades) were asthenia (54/88, 61·4%), neutropenia (38/88, 43·2%), bronchitis (36/88; 40·9%), diarrhea (35/88; 39·8%), and muscle spasms (34/88, 38·6%); 19·3% (17/88) of patients had a rash and 14·8% (13/88) pruritus (table 3). Neutropenia was the most common toxicity of grade ≥3, followed by thrombocytopenia (table 3); 4 (4·5%) patients had febrile neutropenia. AEs of special interest (all grades) included IRR in 14/88 patients (15·9%), serious infections in 13/88 (14·8%), SPM in 8/88 (9·1%), tumor flare in 2/88 (2·3%), and tumor lysis syndrome in 2/88 (2·3%). Patients with SPMs included 5/88 (5·7%) basal cell carcinoma, 2/88 (2·3%) squamous

cell carcinoma, and 1 case each of myelodysplastic syndrome, melanoma, and transitional cell carcinoma.

Of 145 AEs leading to discontinuation, 15 (10·3%) in 14 patients led to permanent study discontinuations due to AEs of grade 2 or higher. Eight patients discontinued the study due to drug toxicity with lenalidomide only, 1 with obinutuzumab only, and 5 with lenalidomide and obinutuzumab. The most common AEs leading to any discontinuation were neutropenia (n=25; 28·4%), IRR (n=12; 13·6%), bronchitis (n=8; 9·1%), thrombocytopenia (n=5; 5·7%), and diarrhea (n=5; 5·7%).

A total of 57 SAEs were reported during the study by 30/88 patients (34·1%), which included 28 SAEs during the induction phase. Eighteen (20·5%) deaths occurred; these were due to progressive lymphoma (n=10), infection (n=4), related cancer (n=1), and unknown cause (n=3). The 4 lethal infections included an 83-year-old woman who died of treatment-related febrile neutropenia after 1 treatment cycle, a 74-year-old man with multiple underlying comorbidities and lung involvement who died of pneumonia while in stable disease after 4 treatment cycles, a 67-year-old man who died of H1N1 influenza pneumonia after 9 treatment cycles, and a 70-year-old woman who died of sepsis following subsequent treatment 18 months after stopping GALEN due to progressive disease.

DISCUSSION

The results of this phase 2 study show that induction therapy with obinutuzumab and lenalidomide followed by maintenance therapy with obinutuzumab is effective for many patients with relapsed/refractory follicular lymphoma. The primary endpoint was met with an ORR of 79·1% (CR/CRu of 38·4%) based on IWG 1999 criteria at the end of induction, confirming on a

larger scale (higher number of patients) the preliminary efficacy signal observed in the phase 1b study.[17] Remarkably, comparable efficacy results were observed in this study between patient subgroups of POD24, or early relapse, versus later relapse (≥2 years), with ORRs of 70·8% versus 82·3%, respectively (IWG 1999 criteria), CR/CRu of 33·3% versus 40·3%, PFS of 62·5% versus 65·5%, and OS of 82·8% versus 88·5%. Obinutuzumab plus lenalidomide therefore was effective as shown by 2-year outcomes (PFS and OS) in the overall patient group, as well as in poor-risk subgroups with POD24[20] or refractory disease. In fact, there were no significant differences in 2-year PFS and OS between subgroups, particularly for POD24.

This data set has several limitations. First, we did not conduct an independent radiology review. Second, the number of patients in our study with POD24 (28%) was low. Lastly, our study does not have a control arm; thus, only historical cross-comparisons and subgroup analysis comparisons with other treatments studied independently could be made.

In this context, the most appropriate trial for comparison of our results with lenalidomide plus rituximab is MAGNIFY, a phase 3b trial of relapsed/refractory follicular lymphoma patients (N=117) who could be refractory to rituximab, in which the percentage of POD24 was slightly higher (33% vs 27·9% reported here). MAGNIFY showed that lenalidomide with rituximab achieved a best ORR of 66% versus the 83·7% reported here (POD24: 47% vs 75·0%) and 1-year PFS of 49% vs 75·0% for POD24 patients,[3] suggesting that lenalidomide plus obinutuzumab may be possibly better in patients with POD24 post rituximab-chemotherapy.

Our results are also consistent with disease control observed for autologous hematopoietic stem cell transplantation (ASCT) in patients with POD24 of follicular lymphoma after systemic treatment from two retrospective studies.[23,24] Patients with early treatment failure having ASCT for relapsed/refractory follicular lymphoma (n=175) had 2-year OS of 82%, close

to that observed in GALEN (POD24, 82·8%).[23] In another study, ASCT afforded 2-year PFS of 63·5% for POD24 versus 62·5% in GALEN.[24]

Interestingly, two others recent studies evaluating PI3K inhibitors, copanlisib[25] and idelalisib,[26] found similar efficacy in POD<24 versus the POD>24 groups, questioning the prognostic significance of POD24 when using new potent regimens as salvage therapy, especially those containing immunomodulatory drugs such as lenalidomide and PI3K.[27]

Comparisons of our results with previous studies of patients with refractory disease are hampered by the slightly different definitions of refractoriness, but 2-year PFS was similar to that with bendamustine plus obinutuzumab in the GADOLIN study (approximately 50%).[28,29] Of note, as for GADOLIN, the 2-year obinutuzumab maintenance may also partly explain our favorable results. Even with between-study methodologic differences, lenalidomide plus obinutuzumab appears to be roughly comparable to other combination therapies for refractory disease.

The safety profile of obinutuzumab used with lenalidomide was acceptable, with no unexpected toxicity. The most common AEs, including grade ≥3, with lenalidomide plus obinutuzumab were comparable to those of lenalidomide plus rituximab reported in the ALLIANCE,[1] MAGNIFY,[3] and AUGMENT[4] trials, although reporting differences make cross-study comparisons difficult. Overall, the safety profile with lenalidomide plus obinutuzumab was not better or worse than that reported with lenalidomide plus rituximab.[1,3,4]

Additional long-term follow-up is needed to determine the full impact of lenalidomide maintenance therapy given for 12 months at the lower dose of 10 mg as in this phase 2 trial, and also given its acceptable safety and efficacy profile in the 6-month, phase 1b study.[17]

In conclusion, obinutuzumab plus lenalidomide appears to be a safe and effective immunomodulatory second-line treatment option for relapsed/refractory follicular lymphoma, with efficacy even in poor-risk patients with early relapse or refractory disease. Based on previously published studies, effectiveness with obinutuzumab plus lenalidomide appears potentially similarly efficient to the most active conventional regimens used in relapsed/refractory follicular lymphoma, including ASCT, G-bendamustine, and PI3K inhibitors, and appears to be at least comparable and maybe better than lenalidomide with rituximab with no additional safety concerns, making this regimen a valuable second-line treatment option consideration. The GALEN regimen has been further shown as effective without unexpected toxicity in patients with advanced, untreated follicular lymphoma in need of systemic therapy.[30] In patients with relapsed/refractory follicular lymphoma, GALEN is also being evaluated combined with atezolizumab,[7] and versus umbralisib plus obinutuzumab or chemotherapy plus obinutuzumab in another study (NCT03269669) by the National Cancer Institute.

Contributors

FM and RH designed the study, developed the protocol and reviewed the statistical analyses; FM had the most contribution in manuscript development. All authors recruited patients, and reviewed, revised and approved the paper.

Declarations of interest: FM received a research grant or has served as a consultant, advisor and/or speaker to AbbVie, Celgene, Epizyme, Gilead, Janssen, Novartis, and Roche. SLG received research support from Roche Genentech; and serves on the advisory board for Celgene and Roche Genentech. PF consults for AbbVie, Celgene, Gilead, Janssen, and Roche. GAS

serves on the advisory board for Abbvie, Acerta, Amgen, BMS, Epizyme, Gilead, Janssen, Merck, Morphosys, Novartis, Pfizer, and Servier; and has received research support from Celgene and Roche. HT consults for Astra-Zeneca, BMS, Karyopharm, and Roche. CB serves on the advisory board for Roche. CH serves on the advisory board for Celgene and Roche; and consults for Amgen, Gilead, Janssen, and Takeda. GC consults for Celgene and Roche; and reports honoraria from Celgene, Gilead, Janssen, Roche, and Sanofi. RH reports honoraria from BMS, Celgene, Janssen, and Novartis. All other authors declare no competing interests.

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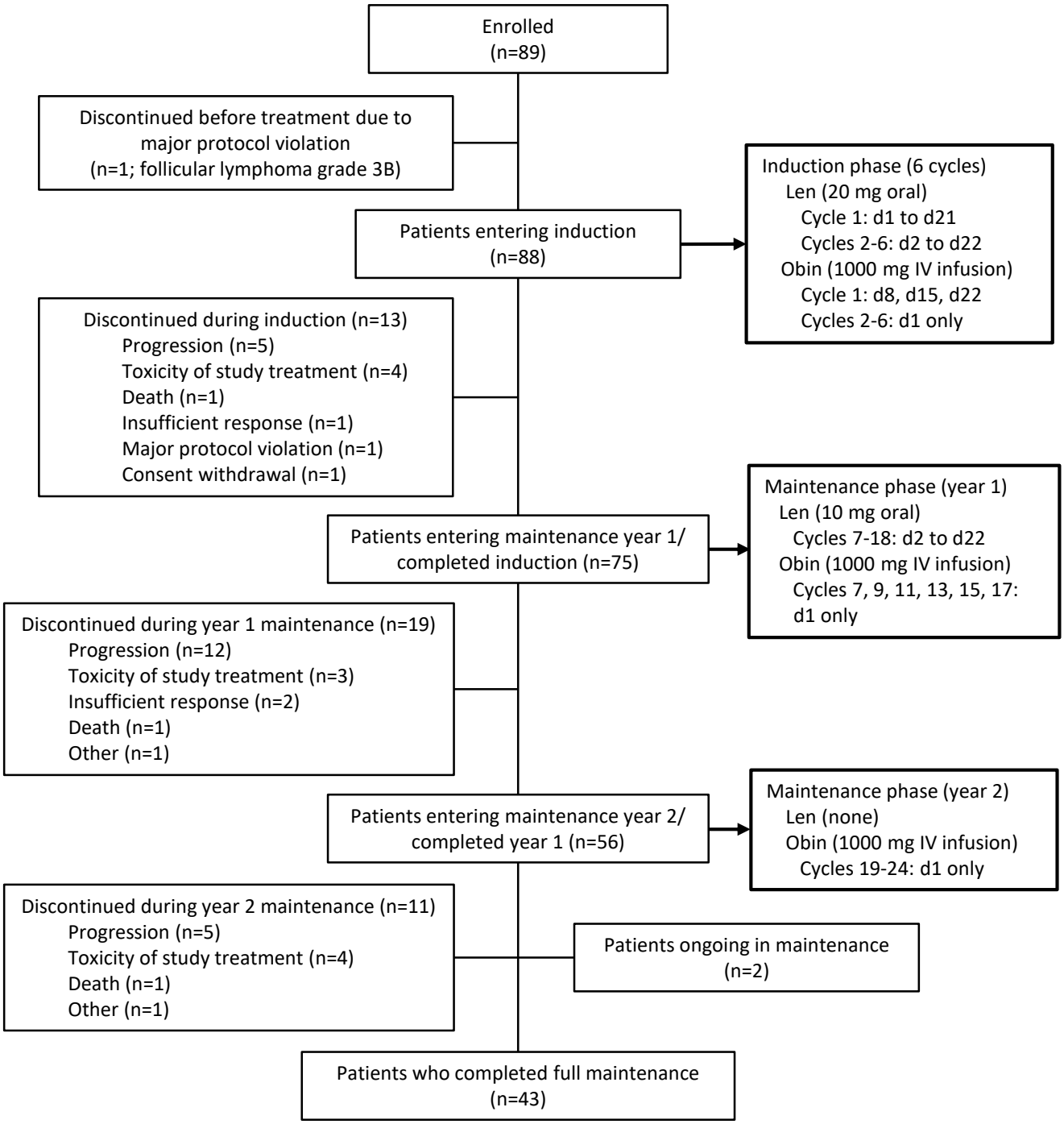
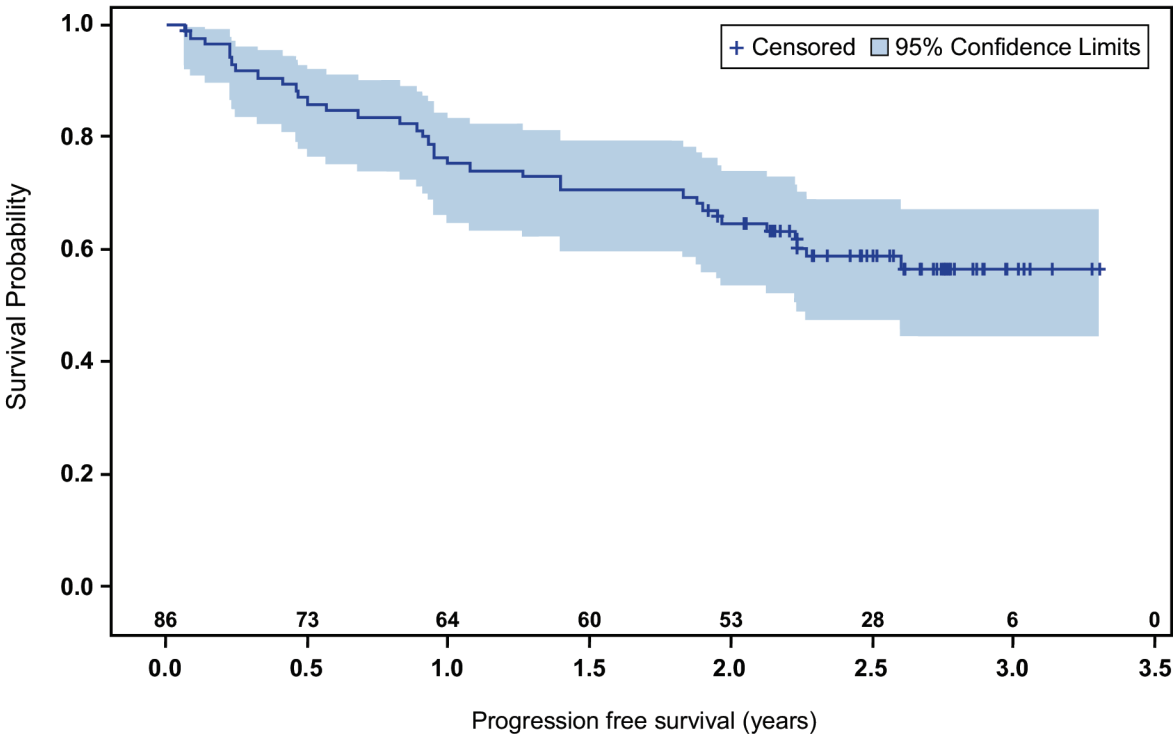
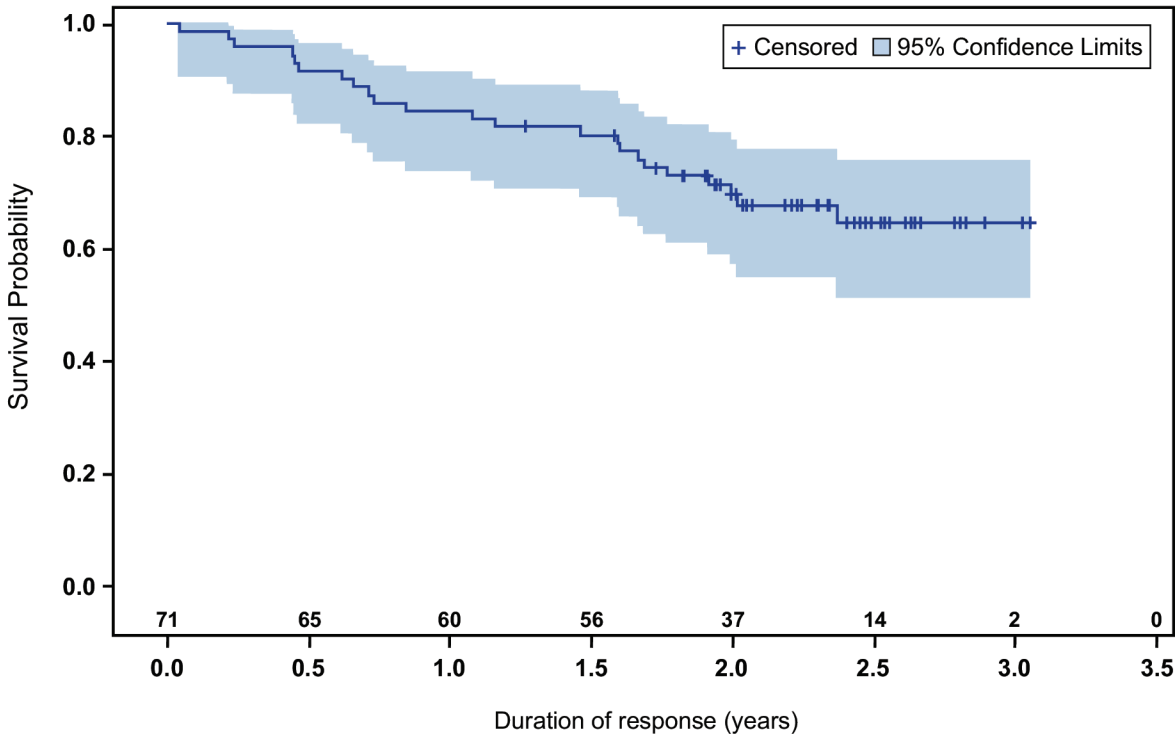

Enrolled
(n=89)
Discontinued before treatment due to major protocol violation
(n=1; follicular lymphoma grade 3B)
Patients entering induction
(n=88)
Induction phase (6 cycles)
Len (20 mg oral)
Cycle 1: d1 to d21
Cycles 2-6: d2 to d22
Obin (1000 mg IV infusion)
Cycle 1: d8, d15, d22
Cycles 2-6: d1 only
Discontinued during induction (n=13)
Progression (n=5)
Toxicity of study treatment (n=4)
Death (n=1)
Insufficient response (n=1)
Major protocol violation (n=1)
Consent withdrawal (n=1)
Patients entering maintenance year 1/ completed induction (n=75)
Maintenance phase (year 1)
Len (10 mg oral)
Cycles 7-18: d2 to d22
Obin (1000 mg IV infusion)
Cycles 7, 9, 11, 13, 15, 17: d1 only
Discontinued during year 1 maintenance (n=19)
Progression (n=12)
Toxicity of study treatment (n=3)
Insufficient response (n=2)
Death (n=1)
Other (n=1)
Patients entering maintenance year 2/ completed year 1 (n=56)
Maintenance phase (year 2)
Len (none)
Obin (1000 mg IV infusion)
Cycles 19-24: d1 only
Discontinued during year 2 maintenance (n=11)
Progression (n=5)
Toxicity of study treatment (n=4)
Death (n=1)
Other (n=1)
Patients ongoing in maintenance
(n=2)
Patients who completed full maintenance
(n=43)

A) Progression-free survival



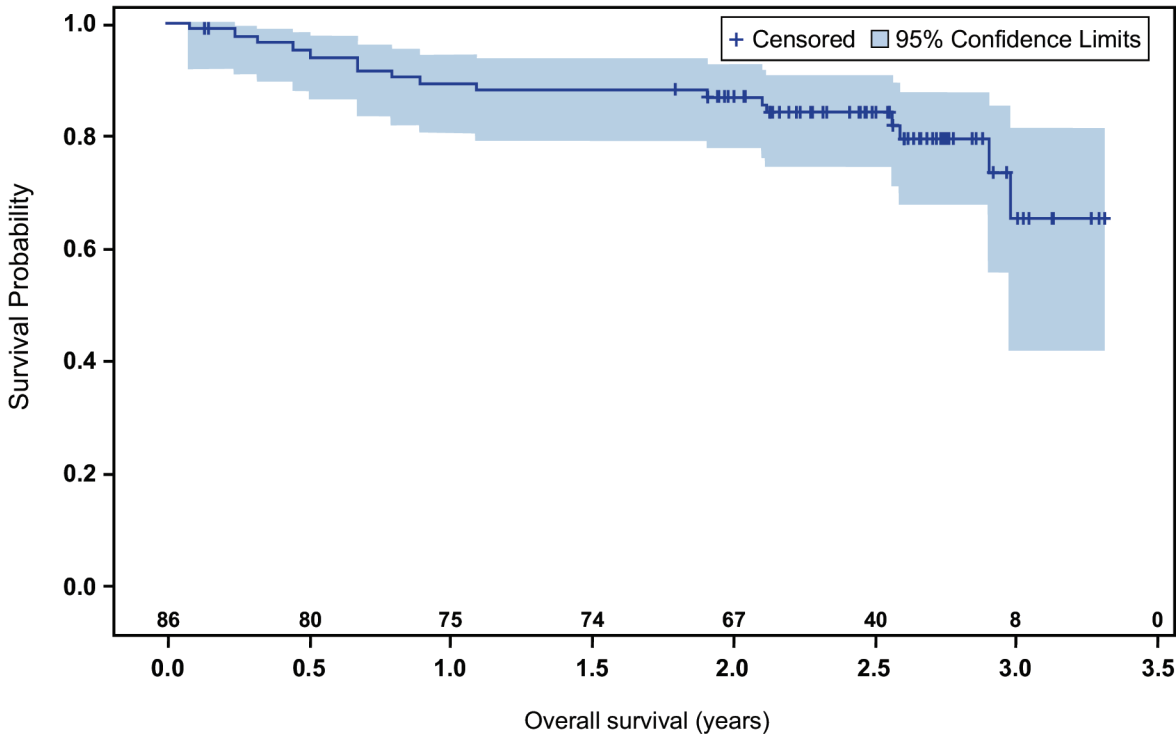
No. of Subjects	Event	Censored	Median Survival (95% CL)
86	40.7% (35)	59.3% (51)	Not reached (2.2; NA)

B) Duration of response



No. of Subjects	Event	Censored	Median Survival (95% CL)
71	32.4% (23)	67.6% (48)	Not reached

C) Overall survival



No. of Subjects	Event	Censored	Median Survival (95% CL)
86	19.8% (17)	80.2% (69)	Not reached (3; NA)

Table 1: **Demographic and clinical characteristics of patients with relapsed/refractory follicular lymphoma at baseline**

Characteristic	Full analysis set (n=86)*
Age, yr	
Mean±SD	63·3±10·7
Range	39–87
Sex	
Male	54 (62·8)
Female	32 (37·2)
Histology (local)[†]	
CD20+ FL grade 1	28 (32·6)
CD20+ FL grade 2	28 (32·6)
CD20+ FL grade 3a	11 (12·8)
CD20+ DLBCL lymphoma	2 (2·3)
Other[‡]	17 (19·8)
Number of prior therapies	
Mean±SD	2·1±1·5
Median	2·0
Range	1–7
Time from biopsy (initial diagnosis) to inclusion, mo	
Mean±SD	85·9±56·6
Median	73·7
Range	12–254
Type of relapse	
Early (POD24)	24 (27·9)
Late	62 (72·1)
Refractory to a rituximab-containing regimen	
No	66 (76·7)
Yes	20 (23·3)
Refractory to prior lymphoma therapy	
No	71 (82·6)

Characteristic	Full analysis set (n=86)*
Yes	15 (17·4)
Ann Arbor stage	
1 and 2	14 (16·3)
3 and 4	72 (83·7)
Performance status (ECOG)	
0	62 (72·1)
1	21 (24·4)
2	3 (3·5)
Bone marrow involvement (n=79)	
No	57 (72·2)
Yes	22 (27·8)
LDH (IU/L) (n=84)	
Normal	58 (69·0)
> Upper limit of normal	26 (31·0)
B-symptoms	
No	72 (83·7)
Yes	14 (16·3)
Calculated FLIPI score (n=84)	
0–1	20 (23·8)
2	30 (35·7)
3–5	34 (40·5)
Tumor bulk	
≥5 cm	30 (34·9)
≥7 cm	11 (12·8)

ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; LDH, lactate dehydrogenase; POD24, progression of disease within 24 months of initial chemotherapy; WHO, World Health Organization.

*Study group number is 86 unless otherwise reported, indicating missing values. Data are reported as n (%) unless otherwise indicated.

[†]71 (82·6%) patients had a new biopsy prior to enrollment; for the remaining 15 patients, enrollment was granted on a prior biopsy showing follicular NHL grade 1–3a, mainly at initial diagnosis.

[‡]Other includes 3 reports unavailable; 2 FL; 2 FL low grade; 2 FL grade 3B; 2 CD20+ FL grade unspecified or unknown; and one each of CD20 + FL

lower grade; CD20+ DLBCL lymphoma (on 08/12/08) and then CD20+ FL grade 2 (03/12/08); centrocytic FL; FL grade 1; marginal zone lymphoma; and mixed FL (phenotype b), low malignancy, stage AA 4 (medullary).

Table 2: **Response rates (n [%]) after induction, overall response rate at end of induction, and best overall response rate according to International Working Group 1999 Criteria**

	Full analysis set (n=86)*
CR	23 (26·7)
CRu	10 (11·6)
PR	35 (40·7)
SD	5 (5·8)
PD	7 (8·1)
Not evaluated	6 (7·0)
ORR at end of induction	79·1 (95% CI, 69·0–87·1)
Best ORR during induction	81.4 (95% CI, 71·6–89·0)
Best ORR during treatment	83·7 (95% CI, 74·2–90·8)

CR, complete response; CRu, complete response unconfirmed; PD, progressive disease; PR, partial response; SD, stable disease.

*Data are presented as n (%).

Evaluation was considered performed if a clinical examination or a PET or CT scan was done. Patients with missing assessments were considered nonresponders.