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ORIGINAL REPORT

Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study

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ABSTRACT

Purpose
To perform an updated analysis of the randomized phase III GADOLIN trial in patients with rituximab-refractory indolent non-Hodgkin lymphoma treated with obinutuzumab (GA101; G) and bendamustine (B).

Patients and Methods
Patients with histologically documented, rituximab-refractory CD20$^+$ indolent non-Hodgkin lymphoma received G 1,000 mg (days 1, 8, and 15, cycle 1; day 1, cycles 2 to 6) plus B 90 mg/m^2/d (days 1 and 2, all cycles) or B 120 mg/m^2/d monotherapy. Patients who did not experience disease progression with G-B received G maintenance (1,000 mg every 2 months) for up to 2 years. The primary end point was progression-free survival (PFS).

Results
Of 413 randomly assigned patients (intention-to-treat [ITT]: G-B, n = 204; B monotherapy, n = 209), 335 had follicular lymphoma (FL; G-B, n = 164; B monotherapy, n = 171). After a median follow-up of 31.8 months, median PFS in ITT patients was 25.8 months (G-B) and 14.1 months (B monotherapy; hazard ratio [HR], 0.57; 95% CI, 0.44 to 0.73; $P < .001$). Overall survival (OS) also was prolonged (HR, 0.67; 95% CI, 0.47 to 0.96; $P = .027$). PFS and OS benefits were similar in patients with FL. Grade 3 to 5 adverse events (AEs) were reported by 148 (72.5%) and 133 (65.5%) patients in the G-B and B monotherapy arms, respectively, most commonly neutropenia (G-B, 34.8%; B monotherapy, 27.1%), thrombocytopenia (10.8% and 15.8%), anemia (7.4% and 10.8%), and infusion-related reactions (9.3% and 3.4%). Serious AEs occurred in 89 G-B patients (43.6%) and 75 B monotherapy patients (36.9%); fatal AEs occurred in 16 (7.8%) and 13 (6.4%), respectively.

Conclusion
This updated analysis confirms the PFS benefit for G-B shown in the primary analysis. A substantial OS benefit also was demonstrated in the ITT population and in patients with FL. Toxicity was similar for both treatments.

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INTRODUCTION

Despite improvements in the efficacy of initial treatments for patients with indolent non-Hodgkin lymphoma (iNHL),[1-3] including follicular lymphoma (FL), a significant proportion of patients becomes resistant to treatment or experience a relapse and require subsequent therapies.[4,5] Approved options in this setting are limited, and outcomes in these patients, especially those refractory to rituximab, remain unsatisfactory. The GADOLIN study compared the efficacy and safety of obinutuzumab (G) plus bendamustine (B) induction followed by G maintenance (G-B arm), with B induction alone (B monotherapy arm) in patients with rituximab-refractory iNHL. Median progression-free survival (PFS) assessed by an independent review committee (IRC) was not reached in the G-B arm (n = 194) and was 14.9 months in the B arm

ASSOCIATED CONTENT

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Data Supplement

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Table 1. Baseline Patient Demographics and Disease Characteristics

Characteristic	ITT Population, No. (%)		Patients With FL, No. (%)	
	G-B	B Monotherapy	G-B	B Monotherapy
No. of patients	204	209	164	171
Median age, years (range)	63 (34-87)	63 (21-87)	63 (34-87)	64 (35-87)
Male sex	116 (56.9)	122 (58.4)	91 (55.5)	98 (57.3)
iNHL subtype				
FL	164 (80.4)	171 (81.8)	164 (100)	171 (100)
Marginal zone lymphoma	28 (13.7)	19 (9.1)	NA	NA
Small lymphocytic lymphoma	12 (5.9)	18 (8.6)	NA	NA
Waldenström macroglobulinemia	0	1 (0)	NA	NA
FL grade at initial diagnosis*				
1 or 2	NA	NA	130 of 164 (79.3)	124 of 171 (72.5)
3a	NA	NA	26 of 164 (15.9)	35 of 171 (20.5)
Other†	NA	NA	8 of 164 (4.9)	12 of 171 (7.0)
FLIPI*‡				
Low (0-1)	NA	NA	42 of 164 (25.6)	35 of 170 (20.6)
Intermediate (2)	NA	NA	51 of 164 (31.1)	60 of 170 (35.3)
High (≥ 3)	NA	NA	64 of 164 (39.0)	69 of 170 (40.6)
Bone marrow involvement*	64 of 197 (32.5)	70 of 195 (35.9)	44 of 159 (27.7)	51 of 160 (31.9)
Extranodal involvement*	113 of 204 (55.4)	103 of 208 (49.5)	87 of 164 (53.0)	80 of 170 (47.1)
Bulky disease (> 6 cm)*	70 of 204 (34.3)	74 of 206 (35.9)	53 of 164 (32.3)	60 of 169 (35.5)
Mean time from initial diagnosis to randomization, years (range)	4.2 (0.3-32.1)	4.2 (0.3-29.9)	4.3 (0.3-32.1)	4.3 (0.3-29.9)
Number of prior regimens§				
1	101 (49.5)	86 (41.1)	84 (51.2)	73 (42.7)
2	63 (30.9)	76 (36.4)	50 (30.5)	60 (35.1)
3	28 (13.7)	30 (14.4)	22 (13.4)	24 (14.0)
4	8 (3.9)	14 (6.7)	4 (2.4)	12 (7.0)
≥ 5	4 (2.0)	3 (1.4)	4 (2.4)	2 (1.2)
Median time since completion of last regimen§, months (range)	3.9 (0.1-128.4)	3.9 (0.5-64.0)	3.9 (0.7-128.4)	3.7 (0.5-64.0)
Refractory to last regimen§	188 (92.2)	193 (92.3)	154 (93.9)	158 (92.4)
Refractory to rituximab and alkylator agent in any treatment line‖	158 (77.5)	170 (81.3)	129 (78.7)	137 (80.1)
No. of rituximab regimens to which patients were refractory				
1	165 (80.9)	162 (77.5)	132 (80.5)	133 (77.8)
2	33 (16.2)	37 (17.7)	27 (16.5)	33 (19.3)
3	2 (1.0)	9 (4.3)	1 (0.6)	4 (2.3)
4	1 (0.5)	1 (0.5)	1 (0.6)	1 (0.6)
Rituximab-refractory type				
Rituximab plus chemotherapy	166 (81.4)	161 (77.0)	139 (84.8)	129 (75.4)
No response or PD during or in the 6 months after rituximab induction (with or without chemotherapy)	77 of 166 (46.4)	89 of 161 (55.3)	57 of 139 (41.0)	65 of 129 (50.4)
PD during or in the 6 months after rituximab maintenance	85 of 166 (51.2)	71 of 161 (44.1)	79 of 139 (56.8)	63 of 129 (48.8)
Other¶	4 of 166 (2.4)	1 of 161 (0.6)	3 of 139 (2.2)	1 of 129 (0.8)
Rituximab monotherapy	38 (18.6)	48 (23.0)	25 (15.2)	42 (24.6)

NOTE. Data were collected at baseline unless otherwise indicated.
Abbreviations: B, bendamustine; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; G, obinutuzumab; iNHL, indolent non-Hodgkin lymphoma; ITT, intention to treat; NA, not applicable; PD, progressive disease.
*Patients with data.
†Grade 3 (patients not designated in the case report form as having grade 3a or 3b), variants or unclassified.
‡Status at initial diagnosis for patients with FL only.
§Any treatment.
‖Patients who were refractory to rituximab and alkylator agent in the same or separate regimens.
¶Patients who progressed > 6 months after last rituximab dose but within 6 months after best response and patients whose refractory status could not be classified because of insufficient detail in the case report form.

(n = 202) after median observation times of 21.9 and 20.3 months, respectively; risk of progression or death was reduced by 45% (hazard ratio [HR], 0.55; 95% CI, 0.40 to 0.74; $P < .001$).[6] At the time of the primary analysis (cutoff date, September 1, 2014), overall survival (OS) data were immature but suggested an advantage for the G-B arm. Seventeen additional patients were enrolled after the cutoff date. We present a planned updated analysis of time-to-event and safety results in all GADOLIN patients and report results in the FL subpopulation separately.

PATIENTS AND METHODS

GADOLIN study methods are described in full elsewhere.[6] The main details are described in this article.

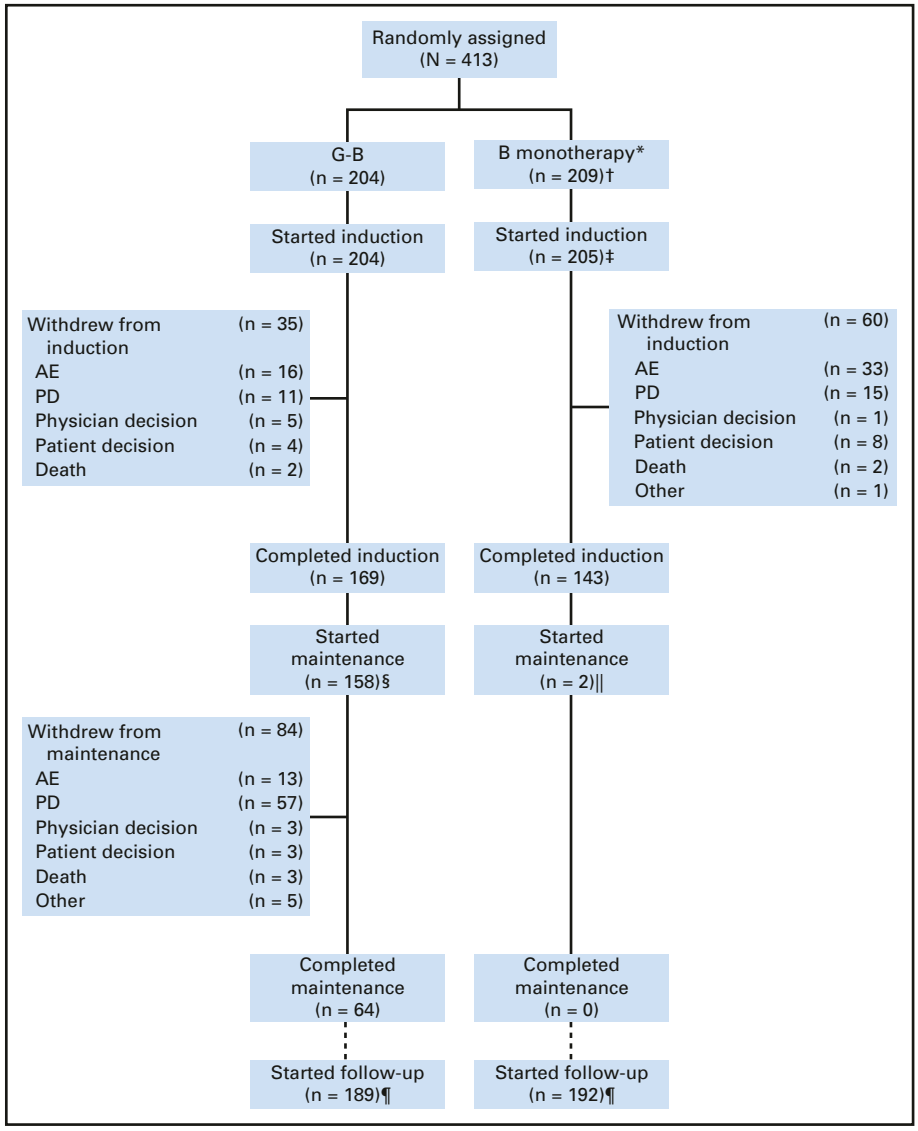

Fig 1. CONSORT diagram. Patient disposition, intention-to-treat (ITT) population. *After completing the full induction treatment schedule, two patients crossed over from the bendamustine (B) monotherapy arm and started obinutuzumab (G) maintenance. They were censored from progression-free survival (PFS) analysis at the time of crossover, and for all other analyses, they were included in B monotherapy arm. †Four patients did not start B induction treatment because of withdrawal of consent before the first dose (n = 3) or physician decision (n = 1). ‡Induction was ongoing for two patients. (Note: Although the patients received the last dose of induction before the clinical cutoff date of April 1, 2016, they are shown here as induction ongoing because the treatment completion page of the electronic case report form was not completed until after the clinical cutoff date.) §Maintenance ongoing for 10 patients. ||Maintenance ongoing for the two patients who crossed over. ¶One hundred twenty-three patients (G-B) and 110 patients (B monotherapy) still in follow-up. AE, adverse event; PD, progressive disease.

Study Design

GADOLIN is an open-label, randomized, phase III study conducted at 83 hospital and community sites in 14 countries in Europe, Asia, and North and Central America. Patients were randomly assigned 1:1 to receive G-B (G 1,000 mg intravenously [IV] on days 1, 8, and 15 of cycle 1 and day 1 of cycles 2 to 6 plus B 90 mg/m^2/d IV on days 1 and 2 of cycles 1 to 6) or B alone (120 mg/m^2/d IV on days 1 and 2 of each cycle for up to six cycles); each cycle was 28 days. Patients in the G-B arm without evidence of progression after induction received G maintenance administered 1,000 mg IV every 2 months for 2 years or until disease progression.

Randomization was stratified according to iNHL subtype (follicular, nonfollicular), refractory type (rituximab monotherapy, rituximab plus chemotherapy, including induction followed by rituximab maintenance), number of prior therapies (two or fewer, more than two), and geographic region. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization guidelines for Good Clinical Practice; patients gave written informed consent. The protocol was approved by ethics committees at participating centers and registered at ClinicalTrials.gov.

Patients

Eligible patients were age ≥ 18 years with histologically documented, CD20$^+$ iNHL refractory to rituximab, at least one bidimensionally measurable lesion (largest dimension, > 1.5 cm by computed tomography scan), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and previous treatment for lymphoma (including up to four chemotherapy-containing regimens). Rituximab refractory was defined as nonresponse to or progression during any prior rituximab-containing regimen (monotherapy or combined with chemotherapy) or progression within 6 months of the last rituximab dose in the induction or maintenance settings. Key exclusion criteria were treatment with B in the previous 2 years, prior treatment with G, significant cardiovascular or pulmonary disease, active infections, and CNS lymphoma.

Study End Points

The primary end point was PFS (time from randomization to the earliest of progression, relapse, or death as a result of any cause) as assessed by IRC.[6] Secondary end points assessed were PFS by investigator, OS (time from randomization to date of death), time to new antilymphoma treatment (TTNT), and safety (adverse events [AEs]).

Assessments

Tumor response was assessed according to revised response criteria for NHL.[7] Computed tomography but not positron emission

tomography (PET) was used because at the time the study was designed, PET was not considered standard for trials that assessed PFS in patients with iNHL, and data on its prognostic value in this population were not available.

AEs and serious AEs (SAEs) were monitored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). AEs were collected for different periods for the two treatment arms (Data Supplement). Study drug–related SAEs were collected indefinitely. An infusion-related reaction (IRR) was defined as any AE attributable to the administration of G and/or B that occurred during or within 24 hours of infusion.

Statistical Analysis

The primary analysis of GADOLIN was based on a protocol-specified interim efficacy analysis conducted after 175 (67%) of the targeted 260 IRC-assessed PFS events were observed, which confirmed that the primary end point had been met.[6] The clinical cutoff date for that analysis was September 1, 2014. This article reports the results of an updated analysis, with a clinical cutoff date of April 1, 2016, which provides a median of 11 months of additional follow-up. The planned sample size was 410 patients enrolled over 54 months and followed for an additional 23 months after the last enrollment.[6] Enrollment was completed on January 7, 2015.

Efficacy assessment was performed on the intention-to-treat (ITT) population, defined as all randomly assigned patients. PFS and other time-to-event end points were assessed using the Kaplan-Meier method and compared using stratified log-rank tests unless otherwise specified; 95% CIs were calculated using Greenwood's formula. Exploratory subgroup analyses of investigator-assessed PFS were performed for baseline patient characteristics that were either prospectively defined in the statistical plan (ie, sex, FL or other histologies, baseline ECOG performance status [0 to 1 or 2]) or post hoc but before study unblinding by the sponsor. All P values presented are two-sided, and $P < .05$ is considered significant. Safety analysis included all patients who received any amount of G or B.

RESULTS

Patients

A total of 413 patients were randomly assigned (ITT population: G-B, n = 204; B monotherapy, n = 209) of whom 335 (81%) had an FL diagnosis (G-B, n = 164; B monotherapy, n = 171); nonfollicular subtypes are listed in Table 1. Patient disposition is shown in Figure 1 for ITT patients and in the Data Supplement for patients with FL. At the time of the analysis, two patients in the B group were still receiving induction therapy, and 10 were still receiving G maintenance. Of 158 G-B patients who started maintenance, 84 withdrew, mostly as a result of disease progression (n = 57 [36%]). Of the patients who started post-treatment follow-up, 123 (60.3%) of 189 administered G-B and 110 (52.6%) of 192 administered B monotherapy remained in follow-up at the time of analysis. Median observation times are listed in Table 2.

At baseline, demographic and clinical characteristics and treatment history in the ITT population were well balanced between treatment arms (Table 1). Most patients (79%) were refractory to one rituximab-containing regimen and 17% to two (Table 1). For patients with FL, baseline characteristics also were well balanced, and refractory status and treatment history were similar to that of the overall ITT population (Table 1).

Ninety percent of patients in the ITT population received ≥ 90% of the total planned G dose in the induction phase; 79% in the G-B arm and 77% in the B monotherapy arm received ≥ 90% of the total planned B dose (Data Supplement). Median cumulative dose of B was 1,920 mg in the G-B arm and 2,368 mg in the B arm. The number of patients with at least one reduction in

Table 2. Summary of Efficacy

End Point	ITT Population, No. (%)		Patients With FL, No. (%)	
	G-B	B Monotherapy	G-B	B Monotherapy
No. of patients	204	209	164	171
Median observation time*, months (range)	34.0 (0.4-65.9)	30.0 (0.0-65.1)	32.6 (0.4-65.9)	29.3 (0.0-65.1)
PFS assessed by investigator				
Events	115 (56.4)	146 (69.9)	93 (56.7)	125 (73.1)
Median (95% CL), months	25.8 (19.5, 41.1)	14.1 (12.6, 16.0)	25.3 (17.4, 36.0)	14.0 (11.3, 15.3)
HR (95% CL, stratified† log-rank P value)	0.57 (0.44, 0.73); $P < .001$		0.52 (0.39, 0.69); $P < .001$	
OS				
Events	52 (25.5)	73 (34.9)	39 (23.8)	64 (37.4)
Median (95% CL), months	NE	NE (48.2, NE)	NE	53.9 (40.9, NE)
HR (95% CL, stratified† log-rank P value)	0.67 (0.47, 0.96); $P = .0269$		0.58 (0.39, 0.86); $P = .0061$	
Time to start of new antilymphoma treatment				
Events	100 (49.0)	139 (66.5)	82 (50.0)	121 (70.8)
Median (95% CL), months	40.8 (28.3, NE)	19.4 (16.2, 24.3)	33.6 (25.3, NE)	18.0 (15.4, 21.3)
HR (95% CL, stratified analysis)‡	0.59 (0.45, 0.77)		0.57 (0.43, 0.75)	
End of induction response (IRC)§				
Overall response rate (complete or partial response)	136 of 204 (66.7)	134 of 208 (64.4)	111 of 164 (67.7)	111 of 170 (65.3)
Percentage difference (95% CL, stratified P value by Cochran-Mantel-Haenszel test†)	2.24 (−7.20, 11.69); $P = .83$		2.39 (−8.07, 12.85); $P = .70$	

Abbreviations: B, bendamustine; CL, confidence limit; FL, follicular lymphoma; G, obinutuzumab; HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; NE, not estimated; OS, overall survival; PFS, progression-free survival.

*Time from random assignment date until last date known to be alive.

†Stratification factors were indolent non-Hodgkin lymphoma subtype (follicular *v* other; ITT population only), refractory type (rituximab monotherapy *v* rituximab plus chemotherapy), and prior therapies (two or fewer *v* more than two).

‡Exploratory analyses only; no P values calculated.

§Patients who had an end-of-induction response assessment or withdrew prematurely.

B dose during induction was 34 (16.7%) of 204 for G-B and 49 (23.9%) of 205 for B monotherapy. Median duration of maintenance therapy was 521 days (range, 15 to 729 days; Data Supplement).

Efficacy

At a median follow-up of 31.8 months, PFS events (assessed by investigator) had occurred in 115 patients in the G-B arm (56.4%) and 146 in the B monotherapy arm (69.9%) among the ITT population. Median PFS was significantly longer in the G-B arm (25.8 months; 95% CI, 19.5 to 41.1 months) than in the B arm (14.1 months; 95% CI, 12.6 to 16.0 months), with an HR for progression or death of 0.57 (95% CI, 0.44 to 0.73; $P < .001$; Table 2; Fig 2). A treatment benefit with G-B also was seen for OS; 52 patients in the G-B arm (25.5%) and 73 in the B arm (34.9%) died (HR, 0.67; 95% CI, 0.47 to 0.96; $P = .0269$; Table 2; Fig 3). TTNT in the G-B arm was more than twice as long as in the B arm (41 *v* 19 months, respectively; Table 2; Fig 4). Efficacy outcomes in patients with FL were consistent with the results in the ITT population, with significant benefits in favor of the G-B arm for PFS, OS, and TTNT (Table 2; Figs 2-4).

PFS was longer with G-B than with B monotherapy in the majority of patient subgroups analyzed (ITT and FL populations; Data Supplement). Subgroups with no evidence of G-B benefit had small patient numbers or were highly heterogeneous (eg, patients without FL in the ITT analysis). These analyses were not powered to detect a difference between treatment arms.

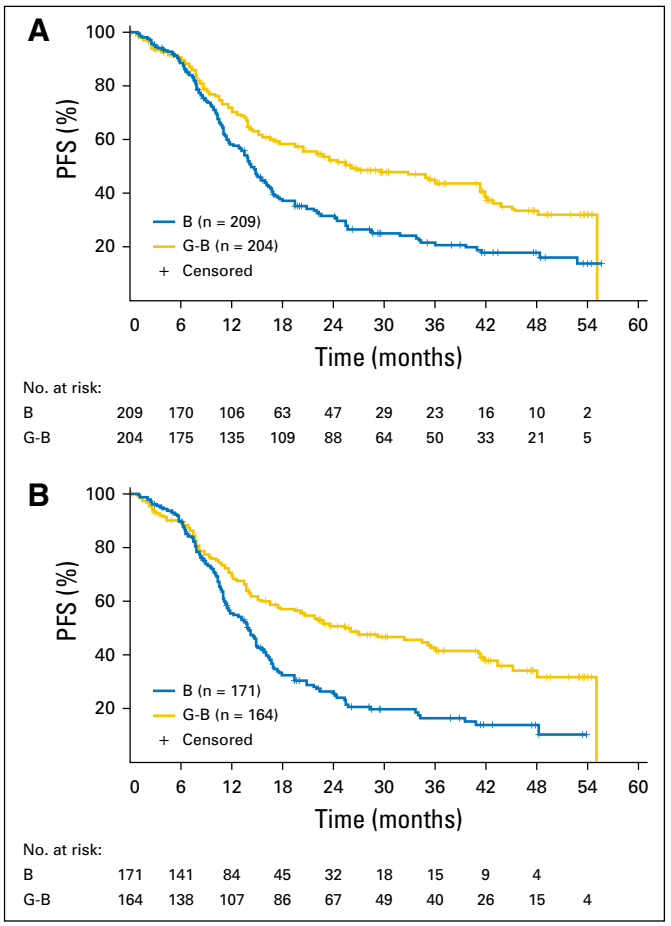

Fig 2. Kaplan-Meier plots of investigator-assessed progression-free survival (PFS) in (A) the intention-to-treat population and in (B) patients with follicular lymphoma. B, bendamustine; G, obinutuzumab.

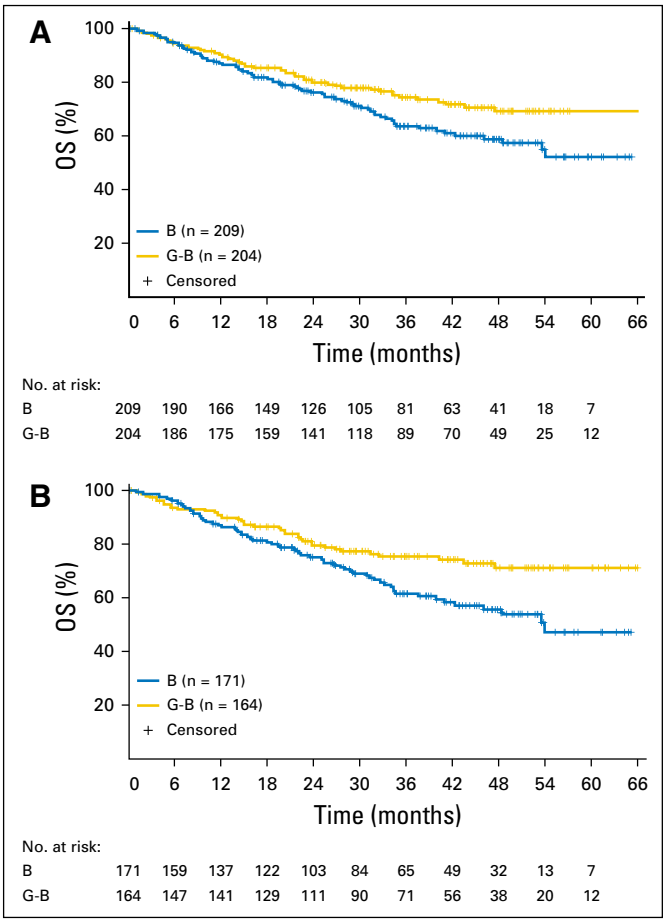

Fig 3. Kaplan-Meier plots of overall survival (OS) in (A) the intention-to-treat population and in (B) patients with follicular lymphoma. B, bendamustine; G, obinutuzumab.

Safety

Six patients randomly assigned to B monotherapy received no treatment, so 407 patients (G-B, n = 204; B monotherapy, n = 203) were eligible for the safety analysis. Most patients (n = 402 [98.8%]) reported at least one AE during the study. The most common AEs of any grade throughout the study in both arms were IRRs, nausea and fatigue (mostly grade 1 or 2), and neutropenia (mostly grade 3 or 4; Data Supplement). Grade 3 to 5 AEs were reported by 148 (72.5%) and 133 (65.5%) patients in the G-B and B monotherapy arms, respectively (Table 3; Data Supplement). AEs that caused discontinuation of any treatment were reported by 41 (20.1%) and 35 (17.2%) patients in the G-B and B arms, respectively.

In the induction phase, AE profiles for the two treatments were similar (Table 3). Twenty-nine patients in the G-B arm (14.2%) and 35 in the B monotherapy arm (17.1%) reported AEs that caused withdrawal from at least one treatment. The most common grade 3 to 5 AE during induction in both arms was

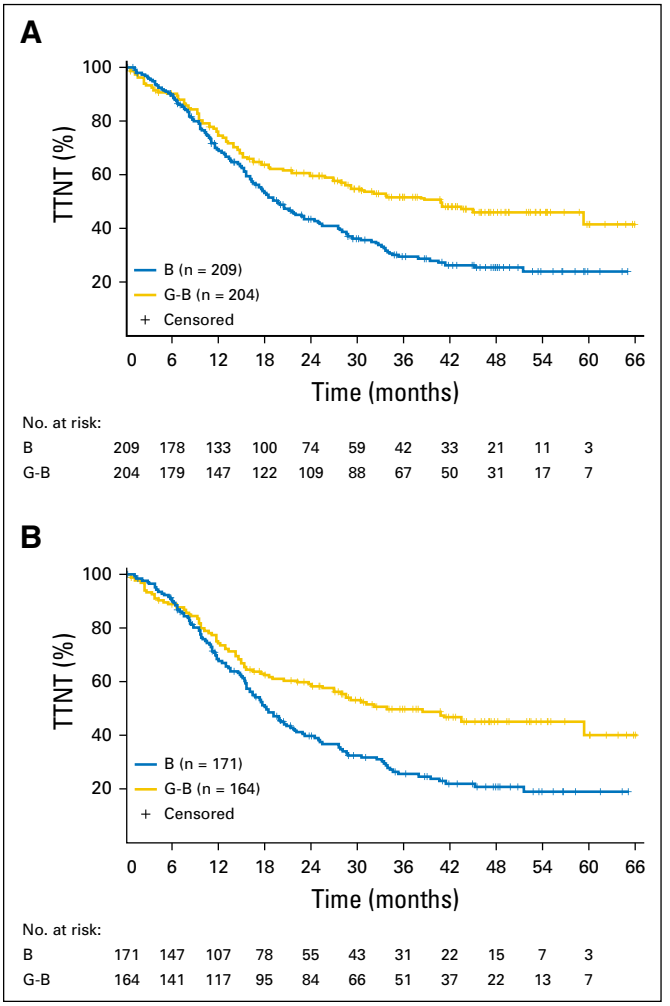

Fig 4. Kaplan-Meier plots of time to new antilymphoma treatment (TTNT) in (A) the intention-to-treat population and in (B) patients with follicular lymphoma. B, bendamustine; G, obinutuzumab.

neutropenia (G-B, n = 56 [27.5%]; B monotherapy, n = 55 [26.8%]). Grade 3 or 4 IRRs occurred in 18 patients in the G-B arm (8.8%) and seven patients in the B arm (3.4%) during induction; five (2.5%) and two (1.0%) patients, respectively, discontinued study treatment during induction because of IRRs, but none withdrew for this reason during maintenance.

During G maintenance, the most common AEs of any grade were infections in 81 (51.3%) of 158 patients, although only 16 patients had infections of grade ≥ 3. Neutropenia occurred in 21 patients (13.3%; grade 3 to 5 in 17 [10.8%]), and IRRs occurred in 13 patients (8.2%; grade 3 in only one). Five patients (3.2%) withdrew from G during maintenance because of AEs. The most common AEs reported during the post-treatment phase were infections (Data Supplement).

Over the entire study, SAEs were reported by 89 (43.6%) and 75 (36.9%) patients in the G-B and B arms, respectively, with febrile neutropenia (n = 11 [5.4%]), IRRs (n = 7 [3.4%]), and pneumonia (n = 7 [3.4%]) the most common in the G-B arm and pneumonia (n = 12 [5.9%]) and sepsis (n = 7 [3.4%]) the most common in the B arm (Data Supplement). Fifty-two G-B arm patients (25.5%) and 73 B arm patients (36.0%) died, most commonly as a result of disease progression (n = 36 [17.6%] and n = 60 [29.6%], respectively). The proportion of patients with grade 5 (fatal) AEs was similar in each arm (n = 16 [7.8%] and n = 13 [6.4%], respectively; Table 3). Deaths were considered treatment related in five and four patients in the G-B and B arms, respectively.

Malignant or unspecified tumors of any grade that started at least 6 months after commencing treatment affected 14 patients in the G-B arm (6.9%) and 11 in the B arm (5.4%); eight patients in each arm had grade 3 to 5 AEs (Data Supplement). Cardiac disorders were more common in the G-B arm, with the most common grade 3 to 5 AEs being atrial fibrillation (G-B, n = 2; B monotherapy, n = 1) and cardiac failure (G-B, n = 2; Data Supplement). Results in the FL safety population were similar to those in the overall safety population (Data Supplement).

DISCUSSION

The current study confirms that after an overall median follow-up of 31.8 months (11 months longer than that reported in the initial publication), the combination of G-B followed by G maintenance significantly prolongs investigator-assessed PFS relative to B monotherapy in patients with rituximab-refractory iNHL, with the median PFS > 2 years in the G-B arm. The median PFS of 14 months in the B arm was better than expected on the basis of previous studies,[8,9] which could reflect differences in selection criteria (eg, patients with transformation were excluded from GADOLIN) or general improvements in patient management. All GADOLIN patients were refractory to rituximab, with > 90% refractory to the last treatment and 79% refractory to both rituximab and alkylators; therefore, these patients represent a population with poor prognostic features.

Other time-to-event end points strongly support the superiority of the G-B regimen. TTNT was prolonged in the iNHL population (HR, 0.59) and in patients with FL (HR, 0.57). Most importantly, OS was prolonged, with HRs of 0.67 in the iNHL population and 0.58 in patients with FL. A greater number of patients treated with B monotherapy withdrew from the study for disease progression or toxicity than with G-B. Of other approved regimens for relapsed and refractory iNHL, idelalisib was approved in the United States on the basis of efficacy results that are modest compared with the G-B results in the current study (response rate, 57% [6% complete response]; median PFS, 11 months; median OS, 30 months).[10] ^{90}Y-ibritumomab tiuxetan is an additional option in this setting but is used infrequently partly because of eligibility restrictions, logistical considerations, and concerns about secondary acute myeloid leukemia and myelodysplastic syndrome.[11] Of the approved therapies, only G-B has demonstrated a survival benefit compared with a standard regimen in a randomized trial.

Time to a clinically meaningful worsening of quality of life in GADOLIN was longer in the G-B arm than in the B monotherapy arm, and relatively more patients who received G-B had meaningful improvements in quality-of-life scores.[12] The proportions of patients in the two arms who reported grade 3 to 5 AEs throughout the study was slightly higher in the G-B arm (72.5%) than in the B

Table 3. AEs by Treatment Phase (Safety Population)

AE	Overall Study*, No. (%)		Induction, No. (%)		Maintenance, No. (%)	Post-Treatment Follow-Up†, No. (%)		
							After Induction	
	G-B	B Mono	G-B	B Mono	G	After Maintenance	After G-B	After B Mono
No. of patients	204	203	204	205	158	146	42	191
No. of events	3,187	2,565	2,219	2,242	777	177	14	334
Patients with at least one								
AE	202 (99.0)	200 (98.5)	199 (97.5)	201 (98.0)	126 (79.7)	63 (43.2)	5 (11.9)	104 (54.5)
Grade 3-5 AE	148 (72.5)	133 (65.5)	113 (55.4)	108 (52.7)	53 (33.5)	38 (26.0)	5 (11.9)	50 (26.2)
Grade 5 AE (fatal)	16 (7.8)‡	13 (6.4)‡	3 (1.5)‡	5 (2.4)‡	1 (0.6)‡	9 (6.2)	3 (7.1)	8 (4.2)
SAE	89 (43.6)	75 (36.9)	58 (28.4)	45 (22.0)	26 (16.5)	25 (17.1)	5 (11.9)	36 (18.8)
AE that led to withdrawal of any treatment	41 (20.1)	35 (17.2)	29 (14.2)	35 (17.1)	13 (8.2)	0	0	0
AE that led to any study drug modification	102 (50.0)	86 (42.4)	86 (42.2)	87 (42.4)	32 (20.3)	0	0	0

Abbreviations: B, bendamustine; AE, adverse event; G, obinutuzumab; mono, monotherapy; SAE, serious adverse event.
*Includes AEs that occurred during the induction, maintenance, and post-treatment follow-up phases; patients who had a given AE in more than one study phase are only counted once in the overall study column.
†Patients who entered follow-up after completing the maintenance or induction phases or withdrawing early from either phase. Safety data post-treatment were collected in a similar way for the B monotherapy and G-B arms after a protocol amendment (Data supplement; Patients and Methods); before this, collection of most safety data for the B monotherapy arm finished at end of induction.
‡Fatal AEs during induction were agranulocytosis, colorectal cancer, and vascular pseudoaneurysm (G-B arm) and adenocarcinoma, *Pneumocystis jirovecii* pneumonia, sepsis (two patients), and tumor lysis syndrome (B monotherapy arm). Fatal AEs after induction were acute myeloid leukemia, chronic renal failure, coxsackie myocarditis, *Escherichia* sepsis, fungal sepsis, gastroenteritis, graft-versus-host disease, intestinal adenocarcinoma, myelodysplastic syndrome, myocardial infarction, pseudomonal sepsis, sepsis, and T-cell lymphoma (G-B arm) and acute myeloid leukemia, ischemic stroke (two patients), leukemia, neutropenic sepsis, pneumonia, *P jirovecii* pneumonia, and sepsis (B monotherapy arm).

arm (65.5%) partly because of a higher rate of grade 3 and 4 IRRs (9.3% and 3.4%, respectively). However, the frequency of grade 5 AEs in each arm was similar (7.8% and 6.4%, respectively). During induction, fewer grade 3 to 5 thrombocytopenias and infections were reported with the G-B arm than with the B arm, whereas grade 3 to 5 IRRs and cardiac events were slightly more frequent with G-B. Neutropenia and infections were the most common grade 3 to 5 AEs during G maintenance (10.8% and 10.1%, respectively). Grade 5 neoplasms were reported in five patients in the G-B arm and three in the B arm. Although the updated analysis confirmed the relative safety of both strategies, the current findings contrast somewhat with results from the GALLIUM study, which compared rituximab and G for induction (with chemotherapy) followed by antibody alone for maintenance in previously untreated patients with FL.[13] In GALLIUM, toxicity seemed greater (including fatal AEs) in B-treated patients, possibly augmented by the use of G; however, because patients were not randomly assigned according to chemotherapy, differences between chemotherapy groups in baseline patient characteristics, including comorbidities, might have biased the results.[14] The overall frequency of fatal AEs in GADOLIN was similar for the two arms despite a longer treatment period in the G-B arm. In the current analysis, cardiac events were more common in the G-B arm than in the B arm, including those of grades 3 to 5; however, events were varied, with no clear explanation or cause.

We observed similar rates of complete response and overall response in the two arms at the end of induction on the basis of standard response criteria for NHL without PET.[7] However, despite receipt of a lower dose of B than those in the B monotherapy arm, patients in the G-B arm experienced significantly more-frequent eradication of residual disease both during and after induction treatment,[15] which supports a role for G as both induction and maintenance treatment.

Despite all enrolled patients being refractory to at least one previous rituximab regimen, some possibly could have responded to repeat therapy, which the inclusion of a rituximab-based control arm might have helped to assess. However, allocation of patients to a treatment to which they were refractory would have been difficult to justify. The decision to use G in induction as well as in maintenance was based on experience with rituximab, which was more beneficial when used in this way than as maintenance only in the EORTC-20981 study (median PFS, 4.4 and 3.1 years, respectively).[16] The 120 mg/m^2 dose of B (the approved dosage for monotherapy) was less well tolerated than the 90 mg/m^2 dose used in patients who received G-B; more patients in the B arm than in the G-B arm had to withdraw from the induction phase or to have the B dose reduced as a result of AEs. However, the proportion of patients in the B arm who received at least 90% of the planned dose of B (77%) was similar to that in the G-B arm (79%).

In conclusion, the efficacy of G-B demonstrated in the initial analysis[6] was confirmed by this updated analysis, which included more patients and 11 months of additional follow-up. The initial analysis resulted in approval of this regimen for patients with relapsed and refractory FL, and this updated analysis confirms a role for G-B in rituximab-refractory iNHL. Of note, a substantial survival benefit of the G-B regimen was seen, with a relative reduction in the risk of death of 33% in patients with iNHL and 42% in patients with FL. Despite the addition of the antibody, few additional toxicities were noted. Because G-B prolonged OS, PFS, and TTNT compared with B monotherapy in rituximab-refractory FL, this supports the conclusion that G-B is the preferred option in the treatment of these patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study

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