ORIGINAL ARTICLE

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

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ABSTRACT

BACKGROUND

Rituximab-based immunochemotherapy has improved outcomes in patients with follicular lymphoma. Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody. We compared rituximab-based chemotherapy with obinutuzumab-based chemotherapy in patients with previously untreated advanced-stage follicular lymphoma.

METHODS

We randomly assigned patients to undergo induction treatment with obinutuzumab-based chemotherapy or rituximab-based chemotherapy. Patients with a response received maintenance treatment for up to 2 years with the same antibody that they had received in induction. The primary end point was investigator-assessed progression-free survival.

RESULTS

A total of 1202 patients with follicular lymphoma underwent randomization (601 patients in each group). After a median follow-up of 34.5 months (range, 0 to 54.5), a planned interim analysis showed that obinutuzumab-based chemotherapy resulted in a significantly lower risk of progression, relapse, or death than rituximab-based chemotherapy (estimated 3-year rate of progression-free survival, 80.0% vs. 73.3%; hazard ratio for progression, relapse, or death, 0.66; 95% confidence interval [CI], 0.51 to 0.85; P=0.001). Similar results were seen with regard to independently reviewed progression-free survival and other time-to-event end points. Response rates were similar in the two groups (88.5% in the obinutuzumab group and 86.9% in the rituximab group). Adverse events of grade 3 to 5 were more frequent in the obinutuzumab group than in the rituximab group (74.6% vs. 67.8%), as were serious adverse events (46.1% vs. 39.9%). The rates of adverse events resulting in death were similar in the two groups (4.0% in the obinutuzumab group and 3.4% in the rituximab group). The most common adverse events were infusion-related events that were considered by the investigators to be largely due to obinutuzumab in 353 of 595 patients (59.3%; 95% CI, 55.3 to 63.2) and to rituximab in 292 of 597 patients (48.9%; 95% CI, 44.9 to 52.9; P<0.001). Nausea and neutropenia were common. A total of 35 patients (5.8%) in the obinutuzumab group and 46 (7.7%) in the rituximab group died.

CONCLUSIONS

Obinutuzumab-based immunochemotherapy and maintenance therapy resulted in longer progression-free survival than rituximab-based therapy. High-grade adverse events were more common with obinutuzumab-based chemotherapy. (Funded by F. Hoffmann–La Roche; GALLIUM ClinicalTrials.gov number, NCT01332968.)

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The combination of the anti-CD20 monoclonal antibody rituximab with chemotherapy has significantly improved outcomes in patients with newly diagnosed follicular lymphoma.[1-4] The use of rituximab maintenance therapy after induction is associated with a median progression-free survival of 6 to 8 years and an estimated overall survival rate of 87.4% at 6 years.[5] The majority of patients will eventually have a relapse, and early progression after first-line treatment is associated with shorter survival.[6]

Obinutuzumab (Gazyva [known as Gazyvaro in Europe], F. Hoffmann–La Roche) is a glycoengineered type II anti-CD20 monoclonal antibody that has lower complement-dependent cytotoxicity than rituximab but greater antibody-dependent cellular cytotoxicity and phagocytosis and greater direct B-cell killing effects.[7,8] The antitumor activity of obinutuzumab combined with chemotherapy has been observed in patients with chronic lymphocytic leukemia,[9] in patients with previously treated indolent and aggressive non-Hodgkin's lymphoma,[10,11] and in patients with rituximab-refractory indolent non-Hodgkin's lymphoma.[12]

In the GALLIUM trial, we compared the efficacy and safety of induction with obinutuzumab, as compared with rituximab, each combined with chemotherapy, followed by maintenance therapy with the same monoclonal antibody, in patients with previously untreated indolent non-Hodgkin's lymphoma (follicular lymphoma or marginal-zone lymphoma). The trial was powered to evaluate progression-free survival among patients with follicular lymphoma only, as reported in this article.

Methods

Patients

Eligible patients were 18 years of age or older with histologically documented, previously untreated, CD20-positive follicular lymphoma (grade 1 to 3a) who had advanced disease (stage III or IV, or stage II with bulk disease [tumor of ≥7 cm in the greatest dimension]), at least one lesion that could be assessed by bidimensional measurement, an Eastern Cooperative Oncology Group performance-status score of 0 to 2 (on a 5-point scale, with higher numbers indicating increasing disability), and adequate hematologic function. In all patients, treatment was indicated according to Groupe d'Étude des Lymphomes Folliculaires (GELF) criteria (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Full eligibility criteria are listed in the Supplementary Appendix.

Trial Design

Patients were enrolled between July 6, 2011, and February 4, 2014. Patients were randomly assigned in a 1:1 ratio to receive intravenous infusions of obinutuzumab at a dose of 1000 mg (on days 1, 8, and 15 of cycle 1 and on day 1 of subsequent cycles) or rituximab at a dose of 375 mg per square meter of body-surface area (on day 1 of each cycle) for six or eight cycles, depending on the chemotherapy regimen (see the Supplementary Appendix). The chemotherapy regimen — cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); or bendamustine — was stipulated at each site, with all the patients at each site receiving the same regimen. Standard chemotherapy doses were used (see the Supplementary Appendix). Patients who had a complete or partial response (according to the assessment method described below) at the end of induction therapy received maintenance treatment with the same antibody as they had received in induction, at a dose of 1000 mg of obinutuzumab or 375 mg of rituximab per square meter every 2 months for 2 years or until disease progression or withdrawal from the trial. No crossover was allowed. Patients who had stable disease at the end of induction therapy were followed on the same schedule but received no maintenance therapy. Details regarding premedications and permitted dose modifications are provided in the Supplementary Appendix.

Randomization was performed by means of an interactive voice-response or online response system with the use of a hierarchical dynamic randomization scheme and was stratified according to the chemotherapy regimen, the Follicular Lymphoma International Prognostic Index (FLIPI) risk group (low [≤1 risk factor], intermediate [2 risk factors], or high [>2 risk factors]; see the Supplementary Appendix),[13] and geographic region. The trial was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice. The protocol, available at NEJM.org, was approved by the ethics committee at each participating center. All the patients provided written informed consent.

The trial was designed by the academic au-

thors (from the German Low Grade Lymphoma Study Group, the U.K. National Cancer Research Institute, and the East German Study Group Hematology and Oncology) in collaboration with the sponsor. The authors confirm that they collected the data, with oversight by an independent data and safety monitoring committee during the conduct of the trial, and that the data were analyzed by the sponsor with input from the academic authors. The authors had access to the data and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by medical writers and was subsequently critically reviewed and revised by all the authors; medical writing assistance was provided under the direction of the first author and paid for by the sponsor. Agreements between F. Hoffmann–La Roche and the investigators and trial groups include data confidentiality.

TRIAL END POINTS

The primary end point was progression-free survival, as assessed by the investigator, among patients with follicular lymphoma. Progression-free survival was defined as the time from randomization to the earliest event of progression, relapse, or death from any cause. Progression-free survival was also assessed by an independent review committee. Secondary end points included the overall response rate at the end of induction therapy (as assessed with and without the use of ^{18}F-fluorodeoxyglucose–positron-emission tomography [FDG-PET]), event-free survival, disease-free survival, duration of response, overall survival, time to new antilymphoma treatment, and safety. Event-free survival was defined as the time from randomization to progression, relapse, death from any cause, or start of new antilymphoma treatment; and disease-free survival as the time from the date of first occurrence of a documented complete response to the date of disease progression, relapse, or death from any cause among patients who had had a complete response at any time before the start of new antilymphoma treatment. Additional exploratory end points, including pharmacokinetic and pharmacodynamic analyses, rate of transformation from follicular non-Hodgkin's lymphoma to diffuse large-cell lymphoma according to histologic assessment, and minimal residual disease status, were assessed but are not reported here.

Tumor response was assessed according to the revised response criteria for non-Hodgkin's lymphoma.[14] Assessments included computed tomography (CT), magnetic resonance imaging if CT was contraindicated, and bone marrow biopsy. An assessment of complete response that was based solely on imaging without confirmation by means of bone marrow testing was classified as a partial response. FDG-PET was not available at every site, and FDG-PET results are not reported here. Response was assessed after three treatment cycles (in patients who received bendamustine) or four cycles (in those who received CHOP or CVP) and on the completion of induction therapy, then every 2 months for 2 years (maintenance phase), and then every 3 to 6 months, with CT performed every 6 to 12 months, until progression or withdrawal from the trial.

All the adverse events were assessed and graded throughout the trial (see the Supplementary Appendix). Adverse events of grade 3, 4, and 5 indicate severe, life-threatening, and fatal adverse events, respectively. Serious adverse events include fatal or life-threatening events or events that cause (or prolong) in-patient hospitalization or substantial disability or incapacity. Regardless of grading (severity), some adverse events may also meet the criteria for a serious adverse event. An infusion-related event was considered to be an adverse event of special interest and was defined as any adverse event occurring either during infusion or within 24 hours after the infusion of any trial treatment that was judged by the investigator to be related to drug administration (either antibody or chemotherapy). Infusion-related events included various preferred terms in the *Medical Dictionary for Regulatory Activities*, version 18.1, such as infusion-related reaction, headache, hypotension, and others. Other prespecified categories and groupings of adverse events were also defined as being of special interest. The independent data and safety monitoring committee periodically reviewed safety data on the basis of analyses performed by an independent data coordinating center. Data review was performed by the sponsor and by medical staff employed by the trial investigators in Germany and the United Kingdom. Tissue samples were sent to central laboratories in Germany and the United Kingdom for retrospective confirmation of diagnosis.

STATISTICAL ANALYSIS

The sample size was calculated to give the trial 80% power to detect a difference in progression-

free survival between treatment groups that corresponded to a 26% lower risk of progression, relapse, or death with obinutuzumab-based chemotherapy than with rituximab-based chemotherapy (i.e., a hazard ratio of 0.74), at a two-sided alpha level of 0.05 (log-rank test). To achieve this, and allowing for one interim analysis of efficacy with the use of an O'Brien–Fleming boundary shape, 370 events of progression, relapse, or death were needed for the primary analysis of progression-free survival. We planned to enroll approximately 1200 patients with follicular lymphoma over a projected 49 months, and patients were to be followed for a further 29 months. The data reported in this article are from a prespecified efficacy interim analysis that was scheduled to take place after approximately 67% of the 370 events had occurred. The cutoff date for this analysis was January 31, 2016 (after 245 events had occurred), and the significance level at this analysis was 0.012. The sponsor endorsed the recommendation of the independent data and safety monitoring committee to analyze the trial data fully on May 25, 2016.

The efficacy analysis included all the patients who underwent randomization, and the safety analysis included all the patients who received any study treatment. Progression-free survival and other time-to-event end points were described with the use of Kaplan–Meier estimates, and treatment groups were compared with the use of log-rank tests, stratified according to chemotherapy regimen and FLIPI risk group. Estimates of the treatment effect were expressed as hazard ratios that were based on stratified Cox proportional-hazards models, including 95% confidence intervals. Response rates were compared with the use of Cochran–Mantel–Haenszel tests. A total of 19 subgroup analyses (not prespecified, according to the definition of Wang et al.[15]) were performed to assess the consistency of the treatment effect on progression-free survival within levels of baseline factors. Heterogeneity was assessed by providing effect estimates for each level of baseline factor and P values for interaction. No formal adjustment was made for multiple testing according to subgroup; approximately one P value for interaction of 0.05 or less would be expected by chance alone. All the presented P values are two-sided. Infusion-related events were compared between treatment groups with the use of a chi-square test, and confidence intervals for proportions were computed according to Wilson's method.

RESULTS

CHARACTERISTICS OF THE PATIENTS AND TREATMENT

A total of 1202 patients with follicular lymphoma that was diagnosed by investigators were enrolled (601 patients in the group that received obinutuzumab-based chemotherapy [obinutuzumab group] and 601 in the group that received rituximab-based chemotherapy [rituximab group]); these patients constituted the intention-to-treat population. Of these patients, 557 in the obinutuzumab group and 551 in the rituximab group completed induction therapy; 361 patients in the obinutuzumab group and 341 in the rituximab group completed maintenance therapy, with 60 and 54, respectively, still receiving maintenance therapy at the cutoff date. A total of 84 patients withdrew from the trial during induction therapy (37 patients in the obinutuzumab group and 47 in the rituximab group), mainly owing to adverse events (in 19 patients in each group) or disease progression (in 5 patients in the obinutuzumab group and 14 in the rituximab group). Withdrawals during maintenance therapy (in 118 patients in the obinutuzumab group and 132 in the rituximab group) were due mainly to disease progression (in 37 and 64 patients, respectively) or adverse events (in 51 and 38, respectively) (Fig. S1 in the Supplementary Appendix).

The median age of the patients in the intention-to-treat population was 59 years, and 53.2% of the patients were female. The demographic and disease characteristics, including prognostic factors, of the patients at baseline were well balanced between the two treatment groups (Table 1). The distribution of patients according to chemotherapy regimen was similar in the two treatment groups, with 57.1% of the patients receiving bendamustine, 33.1% CHOP, and 9.8% CVP.

Most patients were exposed to more than 90% of the planned dose intensity of antibody during the induction phase (593 of 595 patients [99.7%] in the obinutuzumab group and 594 of 597 [99.5%] in the rituximab group). The median duration of exposure to induction therapy was 25.1 weeks in each group, with median cumulative doses of 8000 mg in the obinutuzumab group and

Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Obinutuzumab Group (N=601)	Rituximab Group (N=601)
Age — yr		
Median	60	58
Range	26–88	23–85
Weight — kg		
Median	75.0	74.0
Range	35.3–155.0	32.4–158.0
Body-surface area — m^2		
Median	1.8	1.8
Range	1.2–2.6	1.1–2.8
Male sex — no. (%)	283 (47.1)	280 (46.6)
Ann Arbor stage at diagnosis — no. (%)		
I†	10 (1.7)	8 (1.3)
II	41 (6.8)	44 (7.3)
III	208 (34.6)	209 (34.8)
IV	339 (56.4)	336 (55.9)
Missing data	3 (0.5)	4 (0.7)
FLIPI risk status — no. (%)‡		
Low risk	128 (21.3)	125 (20.8)
Intermediate risk	224 (37.3)	223 (37.1)
High risk	249 (41.4)	253 (42.1)
B symptoms — no./total no. (%)§	201/601 (33.4)	206/600 (34.3)
Bone marrow involvement — no./total no. (%)	318/592 (53.7)	295/598 (49.3)
Extranodal involvement — no. (%)¶	392 (65.2)	396 (65.9)
Bulk disease — no./total no. (%)‖	255/600 (42.5)	271/600 (45.2)
Time from initial diagnosis to randomization — mo		
Median	1.5	1.4
Range	0.1–121.6	0.0–168.1
Chemotherapy regimen — no. (%)		
Bendamustine	345 (57.4)	341 (56.7)
CHOP	195 (32.4)	203 (33.8)
CVP	61 (10.1)	57 (9.5)

* The demographic and disease characteristics, including prognostic factors, of the patients at baseline were well balanced between the two treatment groups. Percentages may not total 100 because of rounding. CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone; and CVP cyclophosphamide, vincristine, and prednisone.

† A total of 18 patients who underwent randomization after being assessed by the investigators as having follicular lymphoma of Ann Arbor stage II, III, or IV, thus meeting trial eligibility criteria, had their classification revised to stage I disease after medical review; these patients were classified as having protocol violations.

‡ The risk groups according to the Follicular Lymphoma International Prognostic Index (FLIPI) are based on the number of risk factors: zero or one risk factor indicates low risk, two risk factors intermediate risk, and more than two risk factors high risk.

§ B symptoms are systemic symptoms such as weight loss, night sweats, and fever.

¶ Patients with bone marrow involvement were classified as having extranodal disease.

‖ Bulk disease was defined as a tumor that was 7 cm or larger in the greatest dimension.

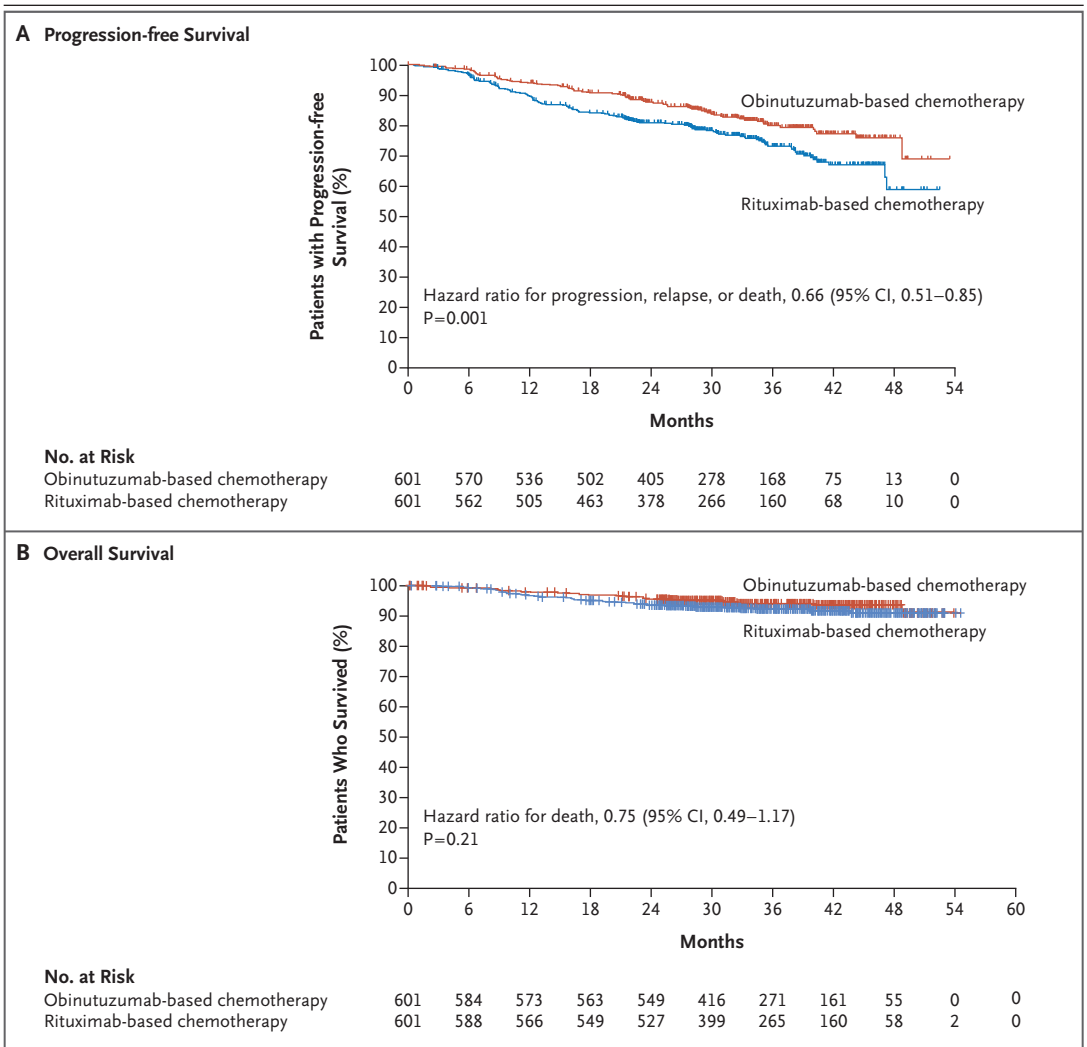

Figure 1. Kaplan–Meier Estimates of Investigator-Assessed Progression-free Survival and Overall Survival among Patients with Follicular Lymphoma.

Tick marks indicate censored data.

4526.5 mg in the rituximab group (Table S1 in the Supplementary Appendix). Of 1099 patients with follicular lymphoma who had a pathological sample analyzed centrally, the diagnosis was confirmed in 1061 (96.5%) (see the Patient Characteristics and Treatment section in the Supplementary Appendix).

EFFICACY

Primary Analysis

After a median follow-up of 34.5 months (range, 0 to 54.5), our hypothesis that obinutuzumab would be superior to rituximab with respect to the primary end point was confirmed at the planned interim analysis; the analysis in the intention-to-treat population of patients with follicular lymphoma showed significantly longer progression-free survival in the obinutuzumab group than in the rituximab group (estimated rate of progression-free survival at 3 years, 80.0% vs. 73.3%; hazard ratio for progression, relapse, or death, 0.66; 95% confidence interval [CI], 0.51 to 0.85; P=0.001). The number of investigator-assessed events of progression, relapse, or death in the analysis of progression-free survival was lower in the obinutuzumab group than in the

Table 2. Efficacy Results in the Intention-to-Treat Population.*

Variable	Obinutuzumab Group (N=601)	Rituximab Group (N=601)
Median observation time (range) — mo	34.8 (0 to 53.8)	34.4 (0 to 54.5)
Primary end point: investigator-assessed progression-free survival		
Patients with progression, relapse, or death — no. (%)	101 (16.8)	144 (24.0)
Rate of estimated 3-yr progression-free survival (95% CI) — %	80.0 (75.9 to 83.6)	73.3 (68.8 to 77.2)
Hazard ratio for progression, relapse, or death (95% CI)	0.66 (0.51 to 0.85)	
P value by log-rank test	0.001	
Independent review committee–assessed progression-free survival		
Patients with progression, relapse, or death — no. (%)	93 (15.5)	125 (20.8)
Rate of estimated 3-yr progression-free survival (95% CI) — %	81.9 (77.9 to 85.2)	77.9 (73.8 to 81.4)
Hazard ratio for progression, relapse, or death (95% CI)	0.71 (0.54 to 0.93)	
P value by log-rank test	0.01	
Treatment response at end of induction phase†		
Complete response or partial response	532 (88.5)	522 (86.9)
Difference (95% CI) — percentage points	1.6 (–2.1 to 5.5)	
P value by Cochran–Mantel–Haenszel test	0.33	
Complete response	117 (19.5)	143 (23.8)
Difference (95% CI) — percentage points	–4.3 (–9.1 to 0.4)	
P value by Cochran–Mantel–Haenszel test	0.07	
Duration of response in patients with complete or partial response†		
Patients with progression, relapse, or death — no./total no. (%)	88/571 (15.4)	124/567 (21.9)
Hazard ratio for progression, relapse, or death (95% CI)‡	0.66 (0.50 to 0.87)	
Disease-free survival among patients with complete response†		
Patients with progression, relapse, or death — no./total no. (%)	27/298 (9.1)	33/281 (11.7)
Hazard ratio for progression, relapse, or death (95% CI)‡	0.81 (0.48 to 1.35)	
Event-free survival as assessed by investigator		
Patients with progression, relapse, death, or start of new antilymphoma treatment — no. (%)	112 (18.6)	159 (26.5)
Hazard ratio for progression, relapse, death, or start of new antilymphoma treatment (95% CI)	0.65 (0.51 to 0.83)	
P value by log-rank test	<0.001	
Start of new antilymphoma treatment		
Patients who started new antilymphoma treatment — no. (%)	80 (13.3)	111 (18.5)
Estimated 3-yr rate of new antilymphoma treatment — % (95% CI)	87.1 (84.0 to 89.6)	81.2 (77.6 to 84.2)
Hazard ratio for new antilymphoma treatment (95% CI)	0.68 (0.51 to 0.91)	
P value by log-rank test	0.009	
Overall survival		
Patients who died — no. (%)	35 (5.8)	46 (7.7)
Estimated percentage of patients alive at 3 yr — % (95% CI)	94.0 (91.6 to 95.7)	92.1 (89.5 to 94.1)
Hazard ratio for death (95% CI)	0.75 (0.49 to 1.17)	
P value by log-rank test	0.21	

* All analyses were stratified according to FLIPI risk status and chemotherapy regimen. Percentage differences may not sum as expected because of rounding. Disease-free survival was defined as the time from the date of first occurrence of a documented complete response to the date of disease progression, relapse, or death from any cause among patients who had had a complete response at any time before the start of new antilymphoma treatment. Event-free survival was defined as the time from randomization to progression, relapse, death from any cause, or start of new antilymphoma treatment.

† The treatment response and duration of response were assessed by the investigator.

‡ No P value was be calculated for this analysis, as specified in the protocol.

Table 3. Adverse Events and Serious Adverse Events, According to Treatment Phase, and Selected Grade 3 to 5 Adverse Events during Treatment, According to Chemotherapy Agent and Treatment Phase in the Safety Population.*

Event	Overall Trial†		Induction Phase		Maintenance and Observation Phases		Follow-up	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=548)	Rituximab Group (N=535)	Obinutuzumab Group (N=427)	Rituximab Group (N=428)
No. of events	10,311	9343	7012	6533	3002	2578	295	230
Patients with ≥1 adverse event — no. (%)								
Any event	592 (99.5)	587 (98.3)	580 (97.5)	577 (96.6)	501 (91.4)	458 (85.6)	130 (30.4)	106 (24.8)
Event of grade 3 to 5	444 (74.6)	405 (67.8)	357 (60.0)	336 (56.3)	205 (37.4)	169 (31.6)	56 (13.1)	33 (7.7)
Event of grade 5‡	24 (4.0)	20 (3.4)§	4 (0.7)	3 (0.5)	10 (1.8)	10 (1.9)	10 (2.3)	7 (1.6)
Patients with ≥1 serious adverse event — no. (%)	274 (46.1)	238 (39.9)	166 (27.9)	144 (24.1)	134 (24.5)	110 (20.6)	47 (11.0)	34 (7.9)
Treatment-related adverse event — no. (%)								
Any event	564 (94.8)	547 (91.6)	—	—	—	—	—	—
Event leading to withdrawal of treatment	75 (12.6)	65 (10.9)	—	—	—	—	—	—
Event leading to any dose reduction	103 (17.3)	89 (14.9)	—	—	—	—	—	—
Serious adverse event leading to withdrawal of treatment — no. (%)	44 (7.4)	36 (6.0)	—	—	—	—	—	—
Serious adverse event leading to dose reduction — no. (%)	12 (2.0)	10 (1.7)	—	—	—	—	—	—
Grade 3 to 5 event, according to chemotherapy regimen — no./total no. (%)								
Neutropenia	—	—						
Bendamustine	—	—	73/338 (21.6)	87/338 (25.7)	49/312 (15.7)	29/305 (9.5)	6/270 (2.2)	1/263 (0.4)
CHOP	—	—	124/193 (64.2)	103/203 (50.7)	36/179 (20.1)	26/187 (13.9)	2/128 (1.6)	0
CVP	—	—	24/61 (39.3)	13/56 (23.2)	5/57 (8.8)	2/43 (4.7)	0	0
Infection¶	—	—						
Bendamustine	—	—	27/338 (8.0)	26/338 (7.7)	52/312 (16.7)	39/305 (12.8)	25/270 (9.3)	6/263 (2.3)
CHOP	—	—	14/193 (7.3)	13/203 (6.4)	7/179 (3.9)	11/187 (5.9)	2/128 (1.6)	2/143 (1.4)
CVP	—	—	3/61 (4.9)	4/56 (7.1)	5/57 (8.8)	1/43 (2.3)	1/44 (2.3)	2/45 (4.4)
Second neoplasm‖	—	—						
Bendamustine	—	—	0	0	21/312 (6.7)	18/305 (5.9)	14/270 (5.2)	2/263 (0.8)
CHOP	—	—	0	0	8/179 (4.5)	8/187 (4.3)	1/128 (0.8)	1/143 (0.7)
CVP	—	—	0	0	0	1/43 (2.3)	0	0

rituximab group (101 patients [16.8%] vs. 144 patients [24.0%]), which translated to a 34% lower risk of progression, relapse, or death (Fig. 1A).

Secondary Analyses

The results of the analysis of progression-free survival as assessed by an independent review committee (93 patients with disease progression, relapse, or death in the obinutuzumab group vs. 125 in the rituximab group; hazard ratio, 0.71; 95% CI, 0.54 to 0.93; P=0.01) were consistent with the results of the primary end-point analysis (Table 2, and Fig. S2A in the Supplementary Appendix). Among patients with a centrally confirmed diagnosis of follicular lymphoma (539 patients in the obinutuzumab group and 535 in the rituximab group), the findings regarding investigator-assessed progression-free survival were similar to those in the intention-to-treat population (86 vs. 128 events of progression, relapse, or death; hazard ratio, 0.64; 95% CI, 0.49 to 0.84; P=0.001). There were 35 deaths (5.8% of the patients) in the obinutuzumab group, as compared with 46 (7.7%) in the rituximab group, and the estimated percentages of patients who were alive at 3 years were 94.0% and 92.1%, respectively (hazard ratio for death, 0.75; 95% CI, 0.49 to 1.17; P=0.21) (Fig. 1B). Results of all the other time-to-event end points were consistent with those of the primary end point (Table 2, and Fig. S2B and S2C in the Supplementary Appendix). The overall response rate and the rate of complete response at the end of induction therapy were similar in the two groups (Table 2).

Post Hoc Analyses

Results of subgroup analyses of progression-free survival according to baseline characteristics (including bulk disease) and stratification factors at randomization were consistent with the result of the primary analysis and showed no evidence of heterogeneity of treatment effect (Fig. S3 in the Supplementary Appendix). The treatment benefit appeared to be stronger in women (hazard ratio for progression, relapse, or death in the obinutuzumab group vs. the rituximab group, 0.49; 95% CI, 0.33 to 0.74) than in men (hazard ratio, 0.82; 95% CI, 0.59 to 1.15); the P value for the interaction of treatment with sex was 0.06. The treatment did not interact with tumor volume (P=0.80), weight (P=0.27), body-surface area (P=0.12), or age (P≥0.30 for all age subgroups)

* Events included preferred terms defined with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 18.1. All the adverse events were assessed and graded throughout the trial (see the Supplementary Appendix). Adverse events of grade 3, 4, and 5 indicate severe, life-threatening, and fatal adverse events, respectively. Serious adverse events include fatal or life-threatening events or events that cause (or prolong) in-patient hospitalization or substantial disability or incapacity. Regardless of grading (severity), some adverse events may also meet the criteria for a serious adverse event.

† Data include adverse events occurring during the pretreatment, induction, maintenance and observation, and post-treatment follow-up phases; patients who had a given adverse event in more than one study phase are counted only once in the overall trial column. Data also include deaths in patients who had no other adverse events.

‡ Fatal adverse events (grade 5) during induction (which occurred in one patient each unless otherwise specified) were cardiogenic shock, pneumonia (in two), and dehydration in the obinutuzumab group and multiorgan failure, septic shock, and polyneuropathy in the rituximab group. Fatal adverse events that occurred after induction (in one patient each) were cardiogenic shock, gastric hemorrhage, death, pneumonia, staphylococcal bacteremia, acute lymphocytic leukemia, acute myeloid leukemia, hepatic neoplasm, acute lung injury, and respiratory failure in the obinutuzumab group and cardiac arrest, myocardial infarction, death, multiorgan failure, colon cancer, gastric cancer, lung adenocarcinoma, malignant melanoma, neuroendocrine carcinoma of the skin, and encephalopathy in the rituximab group. Fatal adverse events occurring in the follow-up phase were upper gastrointestinal hemorrhage, ill-defined disorder, pneumonia, lower respiratory tract infection, lung infection, respiratory tract infection, sepsis, non–small-cell lung cancer, and non–small-cell lung cancer of stage IV (in one patient each) and *Clostridium difficile* colitis, the myelodysplastic syndrome, and prostate cancer (all in one patient) in the obinutuzumab group; and general physical health deterioration, pneumonia, hypercalcemia, cerebral hematoma, cerebrovascular accident, ischemic stroke and chronic obstructive pulmonary disease (in one patient each) in the rituximab group.

§ Four additional deaths in the rituximab group are not included in this total. In line with the reporting rules in the protocol, they were considered to be temporally unrelated to the use of an investigational medicinal product and so were not reported as adverse events.

¶ Events were in the MedDRA system organ class "Infections and Infestations."

‖ Second neoplasm is the standardized MedDRA query for malignant or unspecified tumors that are diagnosed 6 months after the start of the study treatment.

(Figs. S3 through S6 in the Supplementary Appendix).

SAFETY

In the safety population of patients with follicular lymphoma, which included 595 patients in the obinutuzumab group and 597 in the rituximab group (see the Safety section in the Supplementary Appendix), more patients in the obinutuzumab group than in the rituximab group had adverse events of grade 3 to 5 and serious adverse events (Table 3). The most common adverse events of any grade in the whole trial were infusion-related reactions (in 59.0% of the patients in the obinutuzumab group and 48.9% of those in the rituximab group), nausea (in 46.9% and 46.6%, respectively), and neutropenia (in 48.6% and 43.6%) (Table S2 in the Supplementary Appendix). Adverse events that led to the discontinuation of at least one treatment occurred in 97 patients (16.3%) in the obinutuzumab group and in 85 (14.2%) in the rituximab group.

During the induction phase, the most common adverse events of grade 3 to 5 were neutropenia (in 37.1% of the patients in the obinutuzumab group and 34.0% of those in the rituximab group), leukopenia (in 7.7% and 8.0%, respectively), and infusion-related reactions (6.6% and 3.5%). The most common serious adverse events were infusion-related reactions (in 4.4% of the patients in the obinutuzumab group and 1.8% of those in the rituximab group), neutropenia (in 2.9% and 3.2%, respectively), febrile neutropenia (3.0% and 2.2%), and pyrexia (2.5% and 2.7%). Adverse events and serious adverse events were generally less common during maintenance therapy than during the induction phase, with neutropenia being the most common adverse event of grade 3 to 5 (in 16.4% of the patients in the obinutuzumab group and 10.7% of those in the rituximab group) and pneumonia being the most common serious adverse event (in 2.4% and 3.0%, respectively). Among the various chemotherapy regimens, treatment with bendamustine was associated with higher rates of grade 3 to 5 infection and second neoplasm during the maintenance and follow-up phases, whereas CHOP was associated with higher rates of grade 3 to 5 neutropenia during the induction phase (Table 3). Details are provided in Tables S3 and S4 in the Supplementary Appendix.

Analyses of adverse events of special interest (prespecified categories or groupings of adverse events) showed mostly higher rates of events in the obinutuzumab group than in the rituximab group, including infections, cardiac events (the frequency of which was not affected by exposure to an anthracycline), second neoplasms, infusion-related events, neutropenia, and thrombocytopenia (Table 4, and Table S5 in the Supplementary Appendix). Infusion-related events occurred in 406 patients in the obinutuzumab group and in 349 in the rituximab group. Events that were judged by the investigators to be wholly or partly due to antibody occurred in 353 of 595 patients (59.3%; 95% CI, 55.3 to 63.2) in the obinutuzumab group and in 292 of 597 (48.9%; 95% CI, 44.9 to 52.9) in the rituximab group ($P<0.001$). Of all the infusion-related events that were reported in each group, 1696 of 2023 (83.8%; 95% CI, 82.2 to 85.4) were considered by the investigators to be due to obinutuzumab and 1226 of 1540 (79.6%; 95% CI, 77.5 to 81.5) to be due to rituximab ($P=0.001$). Infusion-related events typically occurred during the first infusion, with a marked fall in frequency from cycle 2 onward.

Of the 81 deaths that occurred during the trial, 24 (in 4.0% of the patients) in the obinutuzumab group and 20 (in 3.4%) in the rituximab group were considered by the investigators to be due to adverse events. The fatal adverse events are listed in Table 3. Nonrelapse-related fatal adverse events were more common among patients who received bendamustine (5.6% of patients in the obinutuzumab group and 4.4% of those in the rituximab group) than among those treated with CHOP (1.6% and 2.0%, respectively) or CVP (1.6% and 1.8%). The nature and timing of these events are shown in Figure S7 in the Supplementary Appendix. The proportion of patients who had any degree of reduction in the immunoglobulin level was similar in the two treatment groups (Table S6 in the Supplementary Appendix).

DISCUSSION

The GALLIUM trial showed that progression-free survival was longer with obinutuzumab than with rituximab, but no significant difference was observed in the rate of response according to CT-based assessment. Overall survival was similar in the two groups. The trial was fully analyzed early after a planned interim analysis showed a 34% lower risk of progression, relapse, or death with obinutuzumab plus chemotherapy than with

Table 4. Adverse Events of Special Interest during Treatment, According to Prespecified Category, in the Safety Population.

Category	All Adverse Events		Adverse Events of Grade 3 to 5		Serious Adverse Events	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)
	number of patients (percent)					
Infection*	460 (77.3)	418 (70.0)	119 (20.0)	93 (15.6)	108 (18.2)	86 (14.4)
Neutropenia	301 (50.6)	269 (45.1)	273 (45.9)	236 (39.5)	50 (8.4)	44 (7.4)
Infusion-related event†						
Any event	406 (68.2)	349 (58.5)	74 (12.4)	40 (6.7)	33 (5.5)	14 (2.3)
Antibody-related event	353 (59.3)	292 (48.9)	63 (10.6)	30 (5.0)	28 (4.7)	12 (2.0)
Tumor lysis syndrome	6 (1.0)	3 (0.5)	6 (1.0)	3 (0.5)	3 (0.5)	1 (0.2)
Cardiac event‡	78 (13.1)	58 (9.7)	22 (3.7)	17 (2.8)	26 (4.4)	12 (2.0)
Thrombocytopenia	68 (11.4)	45 (7.5)	36 (6.1)	16 (2.7)	4 (0.7)	1 (0.2)
Second neoplasm§	43 (7.2)	30 (5.0)	28 (4.7)	16 (2.7)	31 (5.2)	17 (2.8)
Nonmelanoma skin cancer	18 (3.0)	14 (2.3)	7 (1.2)	3 (0.5)	9 (1.5)	3 (0.5)
Hematologic event¶	6 (1.0)	0	6 (1.0)	0	6 (1.0)	0
Other	22 (3.7)	18 (3.0)	17 (2.9)	15 (2.5)	18 (3.0)	16 (2.7)
Myelodysplastic syndrome	2 (0.3)	0	2 (0.3)	0	2 (0.3)	0
Gastrointestinal perforation	4 (0.7)	3 (0.5)	3 (0.5)	0	3 (0.5)	0
Hemorrhagic event	57 (9.6)	62 (10.4)	5 (0.8)	7 (1.2)	6 (1.0)	5 (0.8)

* Events were in the MedDRA system organ class "Infections and Infestations."
† Data included any adverse event that occurred during or within 24 hours after the infusion of obinutuzumab or rituximab and was considered by the investigator to be drug-related. Because this category included adverse events in any system organ class, some patients in this category are also counted in other categories (e.g., infection, neutropenia, tumor lysis syndrome, cardiac events, and thrombocytopenia).
‡ Events were in the MedDRA system organ class "Cardiac Disorders."
§ Details regarding second neoplasms are provided in Table S5 in the Supplementary Appendix.
¶ Hodgkin's disease developed in three patients as a second neoplasm, only one of whom had a baseline sample centrally analyzed (confirmed to be follicular lymphoma); samples for the other patients could not be evaluated or were not obtained. Other hematologic neoplasms were acute myeloid leukemia (in two patients) and acute lymphocytic leukemia (in one).

rituximab plus chemotherapy — a significant difference. Progression-free survival as assessed by an independent review committee and other time-to-event end points were consistent with this result.

The cumulative dose of monoclonal antibody in each group differed substantially (median dose, 8000 mg of obinutuzumab and 4526.5 mg of rituximab). However, the effect of this difference on relative efficacy is uncertain. The rituximab dose of 375 mg per square meter was selected because it is the approved dose and standard of care in patients with follicular lymphoma.[16] There are few data regarding the dose–response relationship for rituximab in patients with follicular lymphoma, but there is evidence that a dose of 375 mg per square meter administered every 8 weeks maintains adequate therapeutic levels during the maintenance phase.[5] The dose regimen that was used for obinutuzumab in our trial was based on data from phase 1 and phase 2 trials involving patients with indolent and aggressive non-Hodgkin's lymphoma that were designed to identify the dose associated with the highest efficacy and lowest rates of adverse events.[17] These studies did not compare obinutuzumab with rituximab. In univariate analyses in our trial, there seemed to be an influence of sex on the between-group difference in progression-free survival ($P=0.06$ for interaction of sex and treatment), but we found no influence of tumor volume, Ann Arbor stage, age, body-surface area, or weight.

The nature of the adverse events that were observed in patients with follicular lymphoma was consistent with the known safety profiles of the trial treatments. The rate of adverse events of grade 3 to 5 and the rate of serious adverse events were higher in the obinutuzumab group than in the rituximab group, but the frequency of fatal adverse events was similar in the two groups. Clinically relevant infusion-related reactions of grade 3 or higher occurred in 6.7% of patients who received obinutuzumab plus chemotherapy, which is similar to the rates reported in other studies involving patients with indolent lymphoma[12,18] and lower than the rates that have been reported in patients with chronic lymphoid leukemia and coexisting conditions.[9] The category of second neoplasms included tumors that were diagnosed at least 6 months after the start of treatment. Although there was no meaningful difference between the two antibodies in the overall incidence of invasive second cancers, six patients (1.0%) who received obinutuzumab plus chemotherapy had second hematologic neoplasms and two (0.3%) had the myelodysplastic syndrome; no patients in the group that received rituximab plus chemotherapy had second hematologic neoplasms or the myelodysplastic syndrome.

This trial was not designed to compare chemotherapy agents, and since the assignment of patients' chemotherapy was not randomized, there may be confounding differences between chemotherapy subgroups with regard to the characteristics of the patients at baseline. Bendamustine was associated with higher rates of severe infections than CHOP or CVP during the maintenance and follow-up phases. Although CHOP was associated with higher rates of early severe neutropenia than the other regimens, the low neutrophil counts did not translate into subsequent infection. During all phases of the trial, nonrelapse-related fatal adverse events were more common among patients who received bendamustine than among those who received CHOP or CVP, and although absolute numbers were small, the higher rate of fatal adverse events during the induction and maintenance phases among patients who received bendamustine is of concern in this population of patients. Recent data regarding the rates of molecular complete response in our trial suggest that less-intensive chemotherapy regimens given with obinutuzumab still have greater efficacy than when they are given with rituximab,[19] and they might be of value in frailer patients, for whom bendamustine or CHOP would be less suitable, while maintaining the overall beneficial effect of obinutuzumab.

In conclusion, the results of this large collaborative trial show that the replacement of rituximab with obinutuzumab in the context of immunochemotherapy and maintenance therapy in patients with previously untreated follicular lymphoma resulted in significantly longer progression-free survival. The frequency of high-grade adverse events was higher with obinutuzumab than with rituximab.

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APPENDIX

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REFERENCES

1. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725-32.
2. Herold M, Haas A, Srock S, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. J Clin Oncol 2007;25:1986-92.
3. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26:4579-86.
4. Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. Blood 2008;112:4824-31.
5. Salles G, Seymour JF, Feugier P, et al. Updated 6 year follow-up of the PRIMA study confirms the benefit of 2-year rituximab maintenance in follicular lymphoma patients responding to frontline immunochemotherapy. Blood 2013;122:Suppl:509. abstract.
6. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. J Clin Oncol 2015;33:2516-22.
7. Herter S, Herting F, Mundigl O, et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. Mol Cancer Ther 2013;12:2031-42.
8. Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 2010;115:4393-402.
9. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370:1101-10.
10. Radford J, Davies A, Cartron G, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). Blood 2013;122:1137-43.
11. Zelenetz AD, Mobasher M, Costa LJ, et al. Safety and efficacy of obinutuzumab (GA101) plus CHOP chemotherapy in first-line advanced diffuse large B-cell lymphoma: results from the Phase 2 GATHER study (GAO4915g). Blood 2013;122:Suppl:1820. abstract.
12. Sehn LH, Chua N, Mayer J, et al. A randomised controlled trial of obinutuzumab plus bendamustine versus bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma: primary results of the GADOLIN study. Lancet Oncol 2016;17:1081-93.
13. Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258-65.
14. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malig-

nant lymphoma. J Clin Oncol 2007;25:579-86.
15. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine — reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-94.
16. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011;377:42-51.
17. Cartron G, Hourcade-Potelleret F, Morschhauser F, et al. Rationale for optimal obinutuzumab/GA101 dosing regimen in B-cell non-Hodgkin lymphoma. Haematologica 2016;101:226-34.
18. Sehn LH, Goy A, Offner FC, et al. Randomized phase II trial comparing obinutuzumab (GA101) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: final analysis of the GAUSS study. J Clin Oncol 2015;33:3467-74.
19. Pott C, Hoster E, Kehden B, et al. Minimal residual disease in patients with follicular lymphoma treated with obinutuzumab or rituximab as first-line induction immunochemotherapy and maintenance in the phase 3 GALLIUM study. Blood 2016;128:Suppl:613. abstract.