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ORIGINAL REPORT

Immunochemotherapy With Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety

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ABSTRACT

Purpose
The GALLIUM study (ClinicalTrials.gov identifier: NCT01332968) showed that obinutuzumab (GA101; G) significantly prolonged progression-free survival (PFS) in previously untreated patients with follicular lymphoma relative to rituximab (R) when combined with cyclophosphamide (C), doxorubicin, vincristine (V), and prednisone (P; CHOP); CVP; or bendamustine. This report focuses on the impact of chemotherapy backbone on efficacy and safety.

Patients and Methods
A total of 1,202 patients with previously untreated follicular lymphoma (grades 1 to 3a), advanced disease (stage III or IV, or stage II with tumor diameter ≥ 7 cm), Eastern Cooperative Oncology Group performance status 0 to 2, and requiring treatment were randomly assigned 1:1 to G 1,000 mg on days 1, 8, and 15 of cycle 1 and day 1 of subsequent cycles or R 375 mg/m^2 on day 1 of each cycle, for six to eight cycles, depending on chemotherapy (allocated nonrandomly by center). Responding patients received G or R for 2 years or until disease progression.

Results
Baseline Follicular Lymphoma International Prognostic Index risk, bulky disease, and comorbidities differed by chemotherapy. After 41.1 months median follow-up, PFS (primary end point) was superior for G plus chemotherapy (overall hazard ratio [HR], 0.68; 95% CI, 0.54 to 0.87; *P* = .0016), with consistent results across chemotherapy backbones (bendamustine: HR, 0.63; 95% CI, 0.46 to 0.88; CHOP: HR, 0.72; 95% CI, 0.48 to 1.10; CVP: HR, 0.79; 95% CI, 0.42 to 1.47). Grade 3 to 5 adverse events, notably cytopenias, were most frequent with CHOP. Grade 3 to 5 infections and second neoplasms were most frequent with bendamustine, which was associated with marked and prolonged reductions in T-cell counts. Fatal events were more frequent in patients treated with bendamustine, possibly reflecting differences in patient risk profiles.

Conclusion
Improved PFS was observed for G plus chemotherapy for all three chemotherapy backbones. Safety profiles differed, although comparisons are confounded by nonrandom chemotherapy allocation.

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ASSOCIATED CONTENT

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Data Supplements
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INTRODUCTION

Follicular lymphoma (FL) is the most common type of indolent B-cell non-Hodgkin lymphoma (NHL). In patients requiring therapy, the combination of rituximab (R) with chemotherapy followed by R maintenance is standard treatment.[1] The choice of chemotherapy backbone is usually determined by local policies or algorithms, the most commonly used being cyclophosphamide (C), doxorubicin, vincristine (V), and prednisone (P; CHOP), CVP, and bendamustine.[2-5] Recent results from two randomized phase III studies in patients with indolent NHL showed that progression-free survival (PFS) and/or event-free survival was longer with R plus bendamustine than with R plus CHOP or CVP as induction

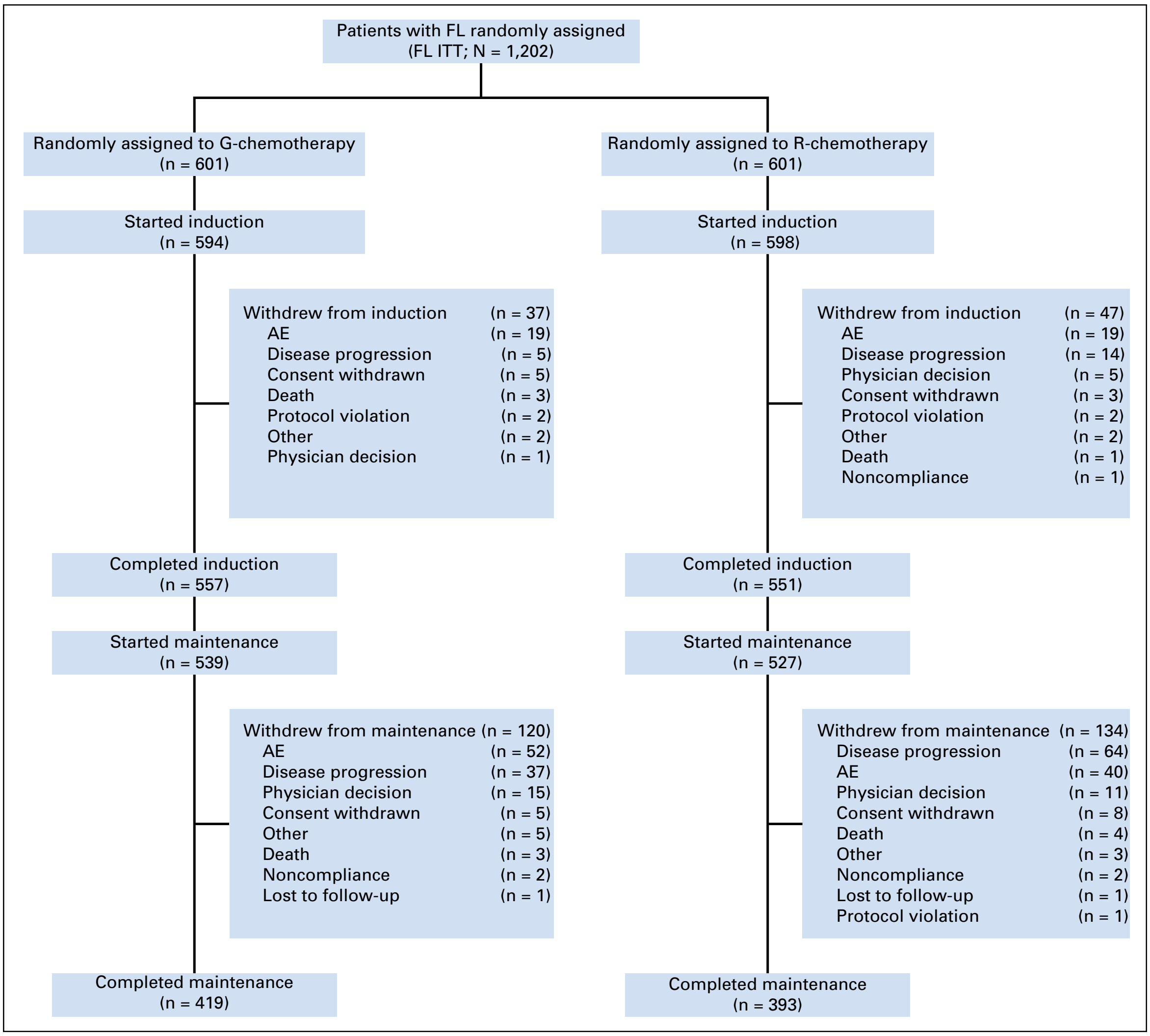

Fig 1. CONSORT diagram. Patient disposition in all patients with follicular lymphoma. AE, adverse event; FL, follicular lymphoma; G-chemotherapy, obinutuzumab plus chemotherapy; ITT, intention-to-treat; R-chemotherapy, rituximab plus chemotherapy.

treatment.[6,7] In the randomized FOLL-05 study, 8-year PFS rates were higher for R-CHOP than for R-CVP.[8]

The GALLIUM study compared obinutuzumab (GA101; G) plus chemotherapy with R plus chemotherapy followed by G or R maintenance, respectively, and found that investigator-assessed PFS in 1,202 previously untreated patients with FL was superior with G plus chemotherapy (hazard ratio [HR], 0.66; 95% CI, 0.51 to 0.85; $P = .0012$), with a 3-year PFS proportion of 80% (control, 73%).[9] The present analysis of GALLIUM describes the impact of the three different chemotherapy backbones on the efficacy and safety of the two treatment arms in patients with FL, using an updated data set (data cutoff: September 10, 2016).

PATIENTS AND METHODS

Study Design and Participants

GALLIUM is an open-label, randomized parallel-group study, described in full previously.[9] Eligible patients were age ≥ 18 years with histologically documented, previously untreated grade 1 to 3a FL who had stage III or IV disease (or stage II with bulky disease, ie, largest tumor diameter ≥ 7 cm), Eastern Cooperative Oncology Group performance status 0 to 2, adequate hematologic parameters, and with an indication for treatment according to GELF (Groupe d'Étude des Lymphomes Folliculaires) criteria.

GALLIUM was conducted in line with the International Conference on Harmonization guidelines for Good Clinical Practice, and the protocol was approved by the Ethics Committees of participating centers and registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01332968). All patients provided written informed consent.

Procedures

Patients were randomly assigned 1:1 to induction therapy with intravenous infusions of G 1,000 mg (days 1, 8, and 15 of cycle 1 and day 1 of subsequent cycles) or R 375 mg/m^2 (day 1 of each cycle) for six or eight cycles, depending on chemotherapy. Treatment allocation was stratified by: chemotherapy regimen, Follicular Lymphoma International Prognostic Index (FLIPI) risk group, and geographic region. The chemotherapy regimen—CHOP, CVP, or bendamustine—was selected by each center before the study started, with all patients at a given center receiving the same regimen; standard doses were used.[9] Patients with complete or partial response at the end of induction (EOI) received maintenance with the same

Table 1. Baseline Patient Demographics and Disease Characteristics by Treatment Arm and by Chemotherapy Regimen (follicular lymphoma intention-to-treat population)

Characteristic	Obinutuzumab Plus Chemotherapy (n = 601)	Rituximab Plus Chemotherapy (n = 601)	Bendamustine (n = 686)	CHOP (n = 399)	CVP (n = 117)
Age, years	60 (26-88)	58 (23-85)	60 (23-88)	57 (31-85)	59 (32-85)
Age ≥ 70	97 (16)	106 (18)	122 (18)	56 (14)	25 (21)
Age ≥ 80	11 (2)	19 (3)	23 (3)	3 (1)	4 (3)
Male	283 (47)	280 (47)	332 (48)	177 (44)	54 (46)
Ann Arbor stage at diagnosis, patients with data*					
I and II†	51 of 598 (9)	52 of 597 (9)	57 of 680 (8)	31 of 399 (8)	15 of 116 (13)
III and IV	547 of 598 (91)	545 of 597 (91)	623 of 680 (92)	368 of 399 (92)	101 of 116 (87)
FLIPI					
Low (0-1)	127 (21)	125 (21)	149 (22)	75 (19)	28 (24)
Intermediate (2)	225 (37)	223 (37)	263 (38)	137 (34)	48 (41)
High (≥ 3)	249 (41)	253 (42)	274 (40)	187 (47)	41 (35)
Bone marrow involvement, patients with data	318 of 592 (54)	295 of 598 (49)	354 of 676 (52)	197 of 397 (50)	62 of 117 (53)
Extranodal involvement‡	392 (65)	396 (66)	460 (67)	251 (63)	77 (66)
Bulky disease (≥ 7 cm), patients with data	255 of 600 (43)	271 of 600 (45)	274 of 686 (40)	206 of 398 (52)	46 of 116 (40)
Time from initial diagnosis to random assignment, months	1.5 (0.1-121.6)	1.4 (0.0-168.1)	1.5 (0.1-103.5)	1.4 (0-168.1)	1.2 (0.2-86.4)
Charlson Comorbidity Index score ≥ 1§	114 (19)	140 (23)	163 (24)	69 (17)	22 (19)

NOTE. Data are No. (%) or median (range).

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; FLIPI, Follicular Lymphoma International Prognostic Index.

*Revisions of Ann Arbor stage (two patients) and FLIPI group (one patient) were made since the primary analysis (updates to database).

†Eighteen patients in this group (obinutuzumab arm, 10; rituximab arm, eight) were randomly assigned to study treatment after being assessed as stage II or above by the investigators (so meeting study eligibility criteria) but were reassessed as stage I after medical review, and so classified as protocol violations.

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

§Scored retrospectively on the basis of conditions reported on medical history page of case report form.

antibody as received during induction (ie, G 1,000 mg or R 375 mg/m^2) every 2 months for 2 years or until disease progression if earlier. Primary prophylaxis with colony-stimulating factors was recommended for patients age ≥ 60 years and those with comorbidities and strongly recommended during cycle 1 of G plus CHOP. Antibiotic and antiviral prophylaxis was used according to guidelines of participating centers.

Tumor response was assessed using the 2007 revised response criteria for NHL and Lugano 2014 criteria.[10,11] T-cell counts in peripheral blood were determined by flow cytometry at a central laboratory, and immunoglobulin levels were assayed locally. Charlson Comorbidity Index (CCI) for each patient was scored retrospectively on the basis of conditions reported on the medical history page of the case report form.

Outcomes

The primary study end point was investigator-assessed PFS (time from random assignment to the earliest of disease progression, relapse, or death as a result of any cause) in patients with FL. PFS for patients without disease progression, relapse, or death was censored at the time of the last assessment. PFS was also assessed by an Independent Review Committee (IRC). Response rates at EOI, with and without ^{18}F-fluorodeoxyglucose positron emission tomography (PET) scan assessed by 2007 revised criteria,[10] were secondary end points. Other secondary end points included overall survival (OS), time to next antilymphoma treatment (TTNALT), and adverse events (AEs). Exploratory end points included EOI response rate with ^{18}F-fluorodeoxyglucose PET scan assessed by IRC according to Lugano 2014 criteria,[11] counts of CD3$^+$, CD4$^+$, and CD8$^+$ T cells in peripheral blood, and immunoglobulin levels.

Statistical Analysis

The results reported in the primary paper[9] were from a preplanned efficacy interim analysis (cutoff date: January 31, 2016). The data reported herein are from an updated analysis with a data cutoff of September 10, 2016, providing an additional 6.6 months of median follow-up.

Efficacy analysis was performed on all randomly assigned patients with FL; safety analysis included all those who received any study treatment. PFS and other time-to-event end points are described using Kaplan-Meier estimates, and antibody treatment arms were compared using log-rank tests, stratified by chemotherapy and FLIPI. Estimates of the treatment effect were expressed as HRs on the basis of stratified Cox proportional hazards models, including 95% CIs. Response rates were compared using Cochran-Mantel-Haenszel tests. Subgroup analyses were performed to assess treatment effect on PFS for selected baseline parameters; heterogeneity of treatment effect across chemotherapy regimens was assessed by interaction test, which is the recommended statistical method,[12] while acknowledging that this has limited power.

The study was not designed to assess differences in outcomes between the nonrandomized chemotherapy groups or between G and R in any of the individual chemotherapy groups, and so lacked statistical power to detect whether any observed differences were significant. Statistical analyses were performed with SAS v9.2 (SAS Institute, Cary, NC) and R v3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics and Treatment

The intention-to-treat FL population comprised 1,202 patients (601 per treatment arm); by chemotherapy group, patient numbers were: bendamustine, 345; CHOP, 196; and CVP, 60 in the G arm and 341, 203, and 57, respectively, in the R arm. Patient disposition is shown in Figure 1, and the distribution of enrolled patients by country and by chemotherapy regimen is found in the Data Supplement.

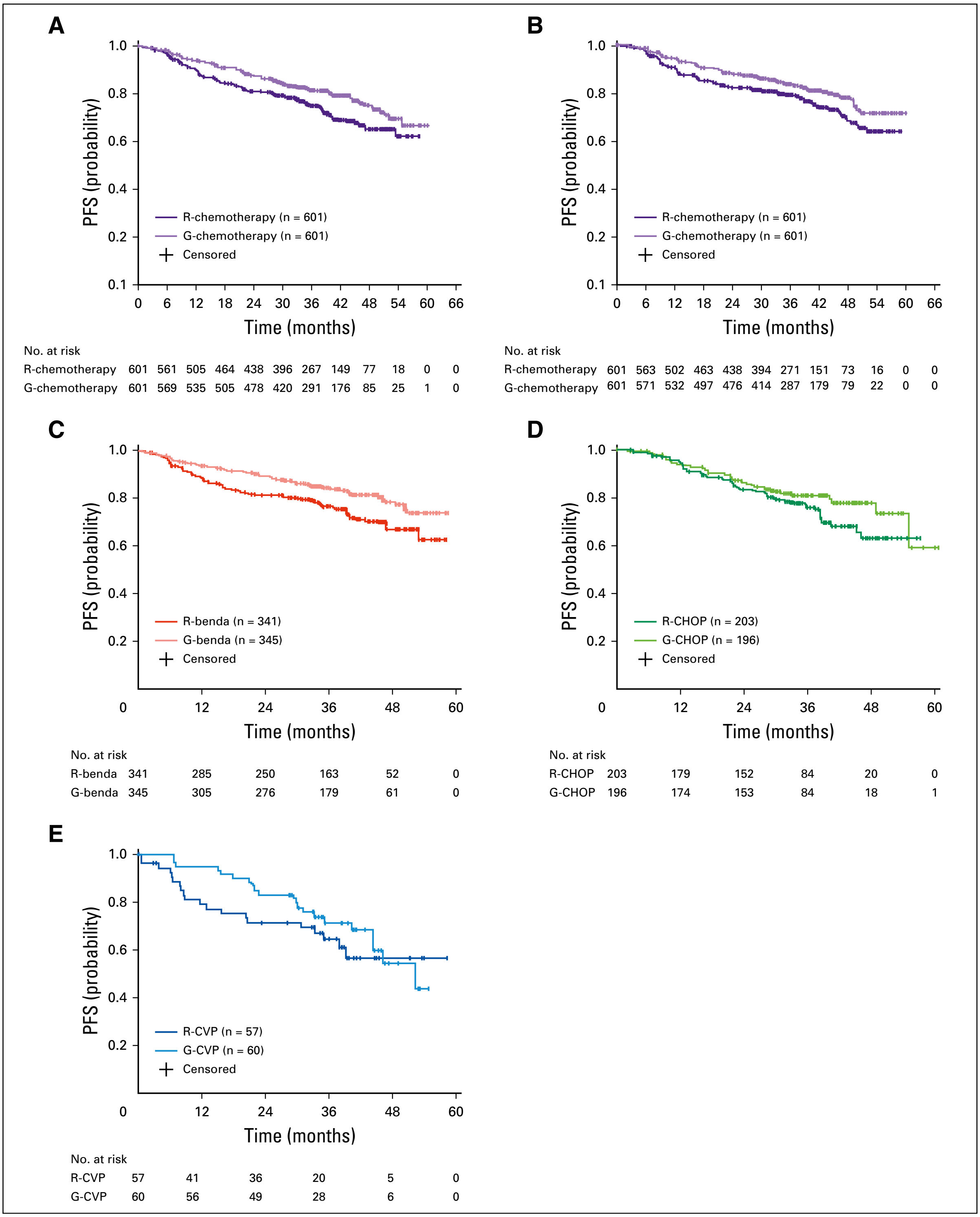

Fig 2. Kaplan-Meier plots of progression-free survival (PFS) in all patients with follicular lymphoma assessed by (A) investigator, and (B) independent review committee. (C-E) Investigator-assessed PFS by chemotherapy group: (C) bendamustine; (D) cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); (E) cyclophosphamide, vincristine, and prednisone (CVP). G-benda, obinutuzumab plus bendamustine; G-chemotherapy, obinutuzumab plus chemotherapy; R-benda, rituximab plus bendamustine; R-chemotherapy, rituximab plus chemotherapy.

Baseline patient and disease characteristics by treatment arm were reported in the primary paper[9]; updated data are shown in Table 1 and the Data Supplement. Comparing baseline data by allocated chemotherapy showed some notable differences between groups. Compared with patients assigned to receive bendamustine and CVP, relatively more patients assigned to receive CHOP (47%) were in the FLIPI high-risk group (bendamustine, 40%; CVP, 35%), and relatively more had bulky disease (52% *v* 40% and 40%, respectively); comorbidities were more common in the bendamustine group (24% with CCI score ≥ 1 *v* 17% [CHOP] and 19% [CVP]), and relatively fewer patients in the CHOP group (1%) were age ≥ 80 years than in the other groups (3%, bendamustine; 3%, CVP; Table 1).

Efficacy

After a median follow-up of 41.1 months, investigator-assessed PFS in all patients with FL was significantly longer in the G plus chemotherapy arm (HR, 0.68; 95% CI, 0.54 to 0.87; *P* = .0016), as was IRC-assessed PFS (HR, 0.72; 95% CI, 0.56 to 0.93; *P* = .012; Fig 2 and Table 2). The benefit of G over R was seen with all three chemotherapy backbones (interaction test *P* = .75) with HRs for investigator-assessed PFS of 0.63 (95% CI, 0.46 to 0.88) for bendamustine, 0.72 (0.48 to 1.10) for CHOP, and 0.79 (0.42 to 1.47) for CVP. In addition, 3-year PFS rates were higher for G plus chemotherapy than R plus chemotherapy (Fig 2 and Table 2). For all three chemotherapy backbones, TTNALT was longer with G plus chemotherapy, with no evidence of interaction (*P* = .48), although the observed benefit was lower for the CHOP backbone than for the other backbones (Table 3; Data Supplement). Response rates at EOI as assessed by computed tomography scan plus PET scan showed no significant differences between G and R for any of the chemotherapy backbones (Table 3).

OS data remain immature: 43 (7%, G plus chemotherapy) and 52 (9%, R plus chemotherapy) patients died, resulting in an HR for OS of 0.82 (95% CI, 0.54 to 1.22; *P* = .32; Table 2). The frequency of deaths was higher in patients treated with bendamustine (10%; 66 of 686) than in patients treated with CHOP (5%; 20 of 399) or CVP (8%; nine of 117).

Safety

Overall safety results were in line with the results of the primary analysis, with more patients receiving G plus chemotherapy

Table 2. Summary of Efficacy Results (follicular lymphoma intention-to-treat population)

End Point	Obinutuzumab Plus Chemotherapy (n = 601)		Rituximab Plus Chemotherapy (n = 601)
Observation time, months, median (range)	41.1 (0-61.1)*		41.0 (0.1-61.8)
Investigator-assessed PFS			
Events	120 (20)		161 (27)
Estimated 3-year PFS, % (95% CL)	82 (78, 85)		75 (71, 78)
HR (95% CL)		0.68 (0.54, 0.87)	
Stratified log-rank *P* value†		.0016	
IRC-assessed PFS			
Events	108 (18)		141 (23)
Estimated 3-year PFS, % (95% CL)	83 (80, 86)		79 (75, 82)
HR (95% CL)		0.72 (0.56, 0.93)	
Stratified log-rank *P* value†		.012	
Treatment response (CT plus PET scan) at end of induction, investigator assessed according to 2007 revised response criteria[10]			
CR or PR	254 of 297 (86)		242 of 298 (81)
Percentage difference (95% CL), stratified		4.3 (−1.8, 10.5)	
Stratified *P* value, Cochran-Mantel-Haenszel test†		.17	
CR	184 of 297 (62)		169 of 298 (57)
Percentage difference (95% CL), stratified		5.2 (−2.8, 13.3)	
Stratified *P* value, Cochran-Mantel-Haenszel test†		.32	
Treatment response (CT plus PET scan) at end of induction, assessed by IRC according to Lugano 2014 criteria[11]			
CMR or PMR	248 of 297 (84)		234 of 298 (79)
Percentage difference (95% CL)		5.0 (−1.5, 11.5)	
Stratified *P* value, Cochran-Mantel-Haenszel test†		.30	
CMR	232 of 297 (78)		217 of 298 (73)
Percentage difference (95% CL)		5.3 (−1.8, 12.4)	
Stratified *P* value, Cochran-Mantel-Haenszel test†		.18	
Time to start of new antilymphoma treatment			
Events	86 (14)		120 (20)
Estimated 3-year TTNT, % (95% CL)	87 (84, 90)		81 (78, 84)
HR (95% CL)		0.68 (0.52, 0.90)	
Stratified log-rank *P* value†		.007	
Overall survival			
Events	43 (7)		52 (9)
Estimated proportion alive at 3 years, % (95% CL)	94 (92, 96)		92 (90, 94)
HR (95% CL)		0.82 (0.54, 1.22)	
Stratified log-rank *P* value†		.32	

NOTE. Data are No. (%) unless otherwise shown.
Abbreviations: CL, confidence limits; CMR, complete metabolic response; CR, complete response; CT, computed tomography; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; IRC, independent review committee; PET, positron emission tomography; PFS, progression-free survival; PMR, partial metabolic response; PR, partial response; TTNT, time to next treatment.
*Observation time of 0 months corresponds to patients who were lost to follow up immediately after enrolment, with no additional follow up obtained in the updated analysis.
†Stratified for FLIPI and chemotherapy regimen.

Table 3. Summary of Efficacy Results by Chemotherapy Regimen (follicular lymphoma intention-to-treat population)

End Point	Bendamustine Obinutuzumab (n = 345)	Bendamustine Rituximab (n = 341)	CHOP Obinutuzumab (n = 196)	CHOP Rituximab (n = 203)	CVP Obinutuzumab (n = 60)	CVP Rituximab (n = 57)
Investigator-assessed PFS						
Events	60 (17)	88 (26)	39 (20)	53 (26)	21 (35)	20 (35)
Estimated 3-year PFS, % (95% CL)	84 (79, 88)	76 (71, 81)	81 (74, 86)	76 (68, 81)	71 (57, 81)	64 (49, 76)
HR (95% CL)	0.63 (0.46, 0.88)		0.72 (0.48, 1.10)		0.79 (0.42, 1.47)	
Stratified log-rank *P* value*	.0062		.13		.46	
IRC-assessed PFS						
Events	58 (17)	79 (23)	37 (19)	47 (23)	13 (22)	15 (26)
Estimated 3-year PFS, % (95% CL)	85 (81, 89)	81 (76, 85)	82 (75, 87)	77 (70, 82)	77 (63, 86)	77 (63, 86)
HR (95% CL)	0.67 (0.48, 0.94)		0.83 (0.54, 1.28)		0.70 (0.33, 1.49)	
Stratified log-rank *P* value*	.02		.40		.35	
Time to new antilymphoma treatment						
Events	47 (14)	72 (21)	28 (14)	33 (16)	11 (18)	15 (26)
Estimated proportion not started new treatment at 3 years, % (95% CL)	87 (83, 91)	80 (75, 84)	87 (82, 91)	85 (80, 90)	87 (75, 93)	74 (61, 84)
HR (95% CL)	0.62 (0.43, 0.89)		0.89 (0.54, 1.47)		0.60 (0.27, 1.30)	
Stratified log-rank *P* value*	.009		.65		.19	
Treatment response (CT plus PET scan) at end of induction, investigator assessed according to 2007 revised response criteria[10]						
CR or PR	148 of 173 (86)	131 of 165 (79)	91 of 103 (88)	91 of 103 (88)	15 of 21 (71)	20 of 30 (67)
Percentage difference (95% CL)	6.2 (−2.3, 14.6)		0.0 (−9.3, 9.3)		4.8 (−23.8, 33.3)	
Stratified *P* value, Cochran-Mantel-Haenszel test*	.11		.98		.72	
CR	109 of 173 (63)	100 of 165 (61)	68 of 103 (66)	63 of 103 (61)	7 of 21 (33)	6 of 30 (20)
Percentage difference (95% CL)	2.4 (−8.3, 13.1)		4.9 (−8.8, 18.5)		13.3 (−14.3, 41.0)	
Stratified *P* value, Cochran-Mantel-Haenszel test*	.63		.52		.36	
Treatment response (CT plus PET scan) at end of induction, assessed by IRC according to Lugano 2014 criteria[11]						
CMR or PMR	149 of 173 (86)	137 of 165 (83)	85 of 103 (83)	80 of 103 (78)	16 of 21 (76)	19 of 30 (63)
Percentage difference (95% CL)	3.1 (−4.9, 11.1)		4.9 (−6.6, 16.3)		12.9 (−15.1, 40.9)	
Stratified *P* value, Cochran-Mantel-Haenszel test*	.38		.35		.40	
CMR	144 of 173 (83)	127 of 165 (77)	76 of 103 (74)	71 of 103 (69)	14 of 21 (67)	18 of 30 (60)
Percentage difference (95% CL)	6.3 (−2.6, 15.1)		4.9 (8.0, 17.7)		6.7 (−23.0, 36.3)	
Stratified *P* value, Cochran-Mantel-Haenszel test*	.13		.44		.80	

NOTE. Data are No. (%) unless otherwise shown.
Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CL, confidence limits; CMR, complete metabolic response; CR, complete response; CT, computed tomography; CVP, cyclophosphamide, vincristine, and prednisone; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; IRC, independent review committee; PET, positron emission tomography; PFS, progression-free survival; PMR, partial metabolic response; PR, partial response.
*Stratified for FLIPI and chemotherapy regimen.

(449 of 595; 75%) than R plus chemotherapy (409 of 597; 69%) having grade 3 to 5 AEs. The most common grade 3 to 5 AEs in both treatment arms were cytopenias (particularly neutropenia), infusion-related reactions, and pneumonia (Table 4; Data Supplement). Substantial differences were observed, however, between the chemotherapy backbones, with more pronounced differences between treatment arms in the frequency of grade 3 to 5 AEs and serious AEs in patients treated with CHOP and CVP than in patients treated with bendamustine. In addition, the proportion of fatal AEs occurring in patients who had not previously started new anticancer treatment was higher with bendamustine treatment (4%) than with CHOP (2%) or CVP (2%; Table 4).

In an additional six patients treated with bendamustines (G plus chemotherapy arm, n = 4; R plus chemotherapy arm, n = 2), fatal AEs occurred after patients had started new systemic anticancer treatment either for disease progression (n = 4) or new malignancies (n = 2); in five of the six patients, the fatal event was an infection. Fifteen of 39 patients with fatal AEs that occurred before new anticancer treatment (bendamustine, 14; CHOP, one) either had a CCI score ≥ 1, or were ≥ 80 years of age, or had Eastern Cooperative Oncology Group performance status of 2; an additional five patients (bendamustine, n = 4; CVP, n = 1) had more than one of these risk factors (Data Supplement). In patients age ≥ 70 years at enrollment, fatal events that occurred before new anticancer treatment were more common with bendamustine (16 of 119, 13%) than CHOP (one of 55, 2%) and CVP (one of 25, 4%), whereas in patients younger than 70 years of age, the incidence was similar (14 of 557, 3%; six of 341, 2%; and one of 92, 1%, respectively).

The frequency of all grade 3 to 5 AEs was higher in patients treated with CHOP than in patients treated with bendamustine and CVP, driven by the higher frequency of cytopenias in the CHOP group. Grade 3 to 5 infections, however, occurred more frequently in the patients treated with bendamustine (Table 4), a difference that was driven by higher rates of events during the maintenance phase (Data Supplement).

Table 4. Summary of Adverse Events in the FL Safety Population by Treatment Arm and Chemotherapy Regimen

Patients Reporting ≥ 1 AE	G Plus Bendamustine (n = 338)	R Plus Bendamustine (n = 338)	G Plus CHOP (n = 193)	R Plus CHOP (n = 203)	G Plus CVP (n = 61)	R Plus CVP (n = 56)	G Plus Chemotherapy (n = 595)	R Plus Chemotherapy (n = 597)
AEs (any grade)	338 (100)	331 (98)	191 (99)	201 (99)	61 (100)	56 (100)	593 (100)	585 (98)
Grade 3-5 AEs	233 (69)	228 (67)	171 (89)	151 (74)	42 (69)	30 (54)	449 (75)	409 (69)
Neutropenia	100 (30)	102 (30)	137 (71)	111 (55)	28 (46)	13 (23)	265 (45)	226 (38)
Leucopenia	11 (3)	15 (4)	39 (20)	34 (17)	1 (2)	1 (2)	51 (9)	50 (8)
Febrile neutropenia	18 (5)	13 (4)	22 (11)	14 (7)	2 (3)	2 (4)	42 (7)	29 (5)
Infusion-related reactions	18 (5)	10 (3)	17 (9)	9 (4)	2 (3)	3 (5)	40 (7)	22 (4)
Pneumonia	23 (7)	17 (5)	5 (3)	8 (4)	0	4 (7)	28 (5)	29 (5)
Thrombocytopenia	20 (6)	11 (3)	15 (8)	5 (2)	1 (2)	0	36 (6)	16 (3)
Anemia	8 (2)	5 (1)	15 (8)	8 (4)	1 (2)	0	24 (4)	13 (2)
Dyspnea	6 (2)	3 (1)	8 (4)	3 (1)	2 (3)	3 (5)	17 (3)	9 (2)
Serious AEs	176 (52)	160 (47)	76 (39)	67 (33)	26 (43)	19 (34)	281 (47)	246 (41)
Deaths*	28 (8)	37 (11)	11 (6)	9 (4)	3 (5)	6 (11)	42 (7)	52 (9)
Fatal AEs	20 (6)	16 (5)	3 (2)	4 (2)	1 (2)	1 (2)	24 (4)	21 (4)
Fatal AEs occurring before start of NACT	16 (5)	14 (4)	3 (2)	4 (2)	1 (2)	1 (2)	20 (3)	19 (3)
AEs causing treatment discontinuation	52 (15)	48 (14)	32 (17)	31 (15)	11 (18)	9 (16)	98 (16)	88 (15)
Selected AE categories of special interest (grade 3-5)								
Neutropenia†	107 (32)	107 (32)	142 (74)	115 (57)	29 (48)	14 (25)	278 (47)	236 (40)
Infections‡	89 (26)	66 (20)	23 (12)	25 (12)	8 (13)	7 (13)	121 (20)	98 (16)
Opportunistic infections, including herpes zoster§	10 (3)	6 (2)	5 (3)	2 (1)	0	0	15 (3)	8 (1)
Second neoplasms‖	21 (6)	12 (4)	7 (4)	7 (3)	1 (2)	2 (4)	29 (5)	21 (4)
Nonmelanoma skin cancer	7 (2)	3 (1)	0	0	1 (2)	0	8 (1)	3 (1)
Hematologic tumors¶	3 (1)	0	3 (2)	0	0	0	6 (1)	0
Other solid tumors	11 (3)	9 (3)	4 (2)	7 (3)	0	2 (4)	15 (3)	18 (3)
Cardiac events#	13 (4)	12 (4)	6 (3)	5 (2)	4 (7)	0	23 (4)	17 (3)

NOTE. Data presented as No. (%). Grade ≥ 3 adverse event preferred terms are those with frequency of ≥ 5% for any antibody plus chemotherapy combination shown.
Abbreviations: AE, adverse event; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; FL, follicular lymphoma; G, obinutuzumab; NACT, new anticancer therapy; R, rituximab.
*One additional patient died (randomly assigned to G plus bendamustine) but was excluded from the FL safety population because they did not receive any study drug; this patient was included in the FL intention-to-treat population.
†Neutropenia and associated complications reported as AEs (not based on laboratory values).
‡Any adverse event in system organ class Infections and Infestations.
§Fungal infections, cytomegalovirus, herpes zoster, and *Pneumocystis jirovecii* pneumonia.
‖Malignant or unspecified tumors occurring > 6 months after first study drug intake (standardized Medical Dictionary for Regulated Activities query).
¶Hodgkin disease (n = 3), acute myeloid leukemia (n = 2), and acute lymphocytic leukemia (n = 1).
#Any adverse event in system organ class Cardiac Disorders.

Grade 3 and 4 neutropenia (for both treatment arms) was most common in patients treated with CHOP, particularly during induction (Data Supplement), and occurred more frequently with G than R in patients treated with CHOP and CVP, but not in patients treated with bendamustine. Prophylactic use of colony-stimulating factors at any time was more frequent in patients treated with CHOP (56%) than patients treated with bendamustine (15%) or CVP (20%). Anti-infective prophylaxis was also used more frequently in patients treated with CHOP (Data Supplement). The frequency of grade 3 to 5 second neoplasms was slightly higher in patients treated with bendamustine than other patients, the difference being driven mainly by nonmelanoma skin cancers (Table 4; Data Supplement).

In patients treated with bendamustine, marked reductions in $CD3^+$ and $CD3^+CD4^+$ T cells were seen during induction in both antibody arms, with prolonged recovery during and after maintenance; changes in T-cell counts in patients treated with CHOP and CVP were negligible (Figs 3A-3C). Over the whole study period, reductions from baseline in IgA, IgG, and IgM levels were similar in both antibody arms, with little difference among the three chemotherapy regimens (Data Supplement).

DISCUSSION

On the basis of this updated analysis of previously untreated patients with advanced-stage FL in the GALLIUM study, which confirmed the superiority of G over R when combined with either bendamustine, CHOP, or CVP chemotherapy for induction followed by 2 years of antibody-only maintenance, there were notable differences among the three chemotherapy backbones. Patient allocation to chemotherapy was not random, resulting in differences in baseline characteristics among chemotherapy groups, with more patients with bulky disease and high-risk FLIPI in the CHOP-assigned group, and older age and higher comorbidity index in the bendamustine-assigned group. Nonetheless, several interesting results emerged. The use of G prolonged PFS in all three chemotherapy groups. Although the benefit of G over R, as shown by Kaplan-Meier curves for TTNALT, seemed less pronounced in the CHOP group, this might have been due to inadequate statistical power to detect treatment differences for any of the chemotherapy regimens, and an interaction test provided no statistical evidence that the treatment effect on TTNALT was affected by chemotherapy.

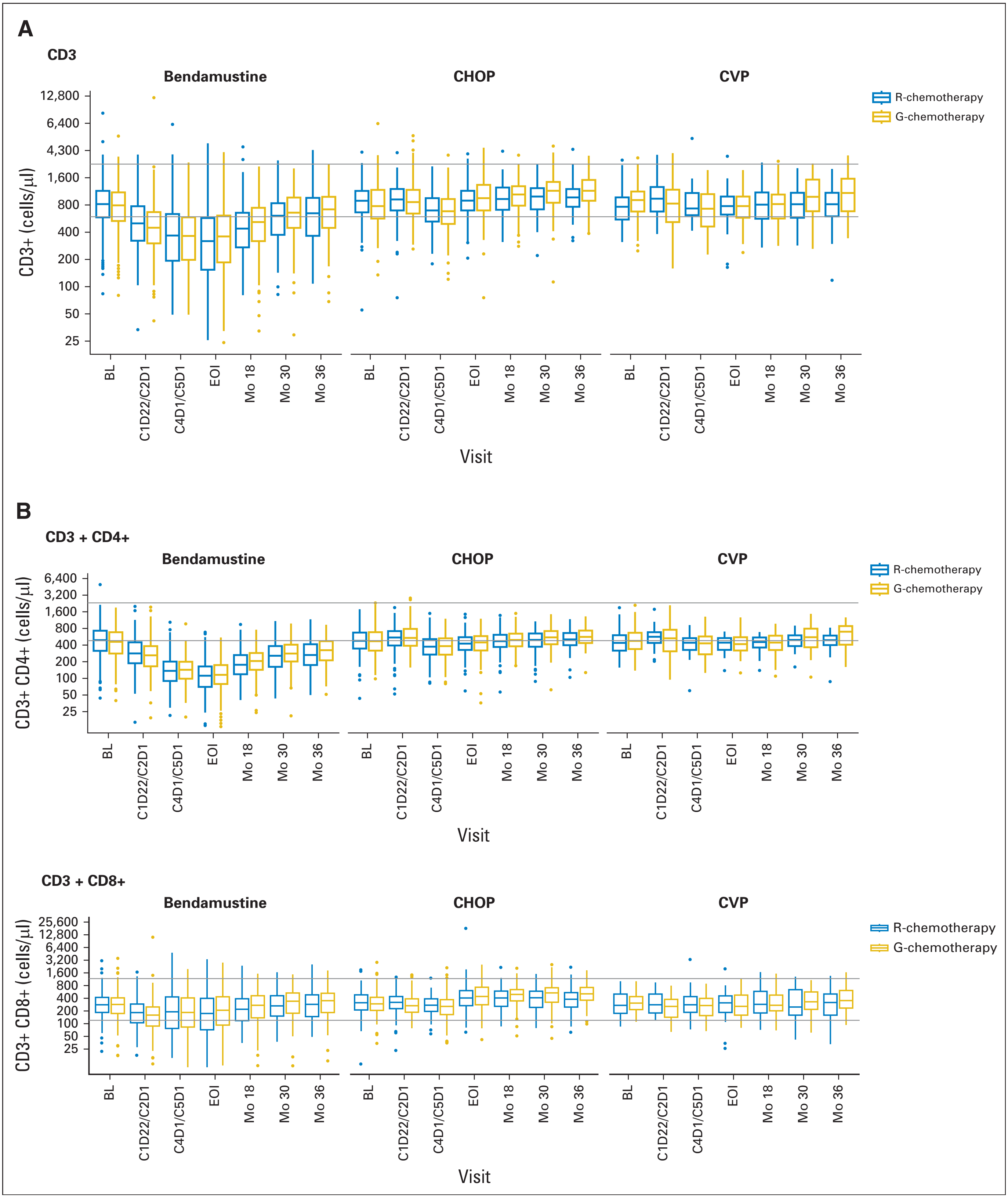

Fig 3. T-cell counts over time by treatment arm and chemotherapy regimen: (A) $CD3^+$ cells; (B) $CD3^+CD4^+$ and $CD3^+CD8^+$ cells. Horizontal gray lines are upper and lower limits of normal range. BL, baseline; C, cycle; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; D, day; EOI, end of induction; G-chemotherapy, obinutuzumab plus chemotherapy; Mo, month; R-chemotherapy, rituximab plus chemotherapy.

Three-year PFS rates were highest in the bendamustine group and lowest in the CVP group, suggesting that CVP was the least efficacious partner. This finding is consistent with the latest results of the randomized FOLL-05 study of R plus chemotherapy in patients with FL, whose authors reported 8-year PFS rates of 46% for CVP and 57% for CHOP.[8] Two other studies showed bendamustine to be a more efficacious partner for R: first, the phase III trial by Study Group Indolent Lymphomas (StiL), which compared R plus bendamustine with R plus CHOP in a subgroup of patients with FL, with surprisingly poor PFS results for R-CHOP; and second, the BRIGHT study, which found that PFS was longer with R plus bendamustine than with R plus CHOP or CVP.[6,7] Both trials included patients with nonfollicular histology, and neither included a maintenance phase.

The most interesting and clinically relevant data from the current analysis, however, relate to AEs. As previously reported, grade 3 to 5 AEs were more common with G plus chemotherapy than with R plus chemotherapy, with higher rates of neutropenia, infections, infusion-related reactions, and thrombocytopenia.[9] Analysis by chemotherapy backbone revealed a higher frequency of grade 3 to 5 AEs with G plus chemotherapy in patients receiving CHOP or CVP but not in patients receiving bendamustine. Overall, grade 3 to 5 events were more frequent in patients treated with CHOP than patients treated with bendamustine or CVP, primarily because of a higher rate of cytopenias. For grade 3 to 5 infections, however, the frequency was higher with bendamustine than with CHOP or CVP in both the G and R treatment arms; this difference was particularly evident during the maintenance and follow-up phases. A possible explanation for this finding may be the substantial and long-lasting suppression of $CD3^+$ and $CD3^+CD4^+$ T cells in the bendamustine group. Similar findings were reported in heavily pretreated patients with indolent lymphomas who received R plus bendamustine.[13] A sustained decrease in $CD4^+$ and $CD8^+$ T-cell counts after first-line treatment of indolent lymphomas with R plus bendamustine was also described by Burchardt et al,[14] although infectious complications did not increase. Severe lymphocyte count reductions were more common with bendamustine than CHOP when used with R in the BRIGHT study, although severe neutropenia was more frequent with CHOP.[4] In line with the BRIGHT results and the current GALLIUM analysis, the StiL trial also found that serious cytopenias were more common with R plus CHOP than with R plus bendamustine for patients with previously untreated indolent NHL, but infections were also found to be more frequent in the CHOP group.[5] This contrasts with our results, although it should be noted that prophylaxis with colony-stimulating factors in GALLIUM was used more frequently in patients treated with CHOP than in patients treated with bendamustine.

Fatal AEs were more common with bendamustine than with CHOP or CVP. This difference in safety profile was not reported in previous studies and may be attributable to the nonrandomized allocation to chemotherapy in GALLIUM, so relatively more patients in the bendamustine group were ≥ 80 years of age, had poor performance status, and/or had comorbidities. In addition, AE monitoring and follow-up was probably more rigorous in GALLIUM. The higher incidence of second neoplasms in patients treated with bendamustine was primarily driven by a higher incidence of nonmelanoma skin cancers.

Although GALLIUM was not designed to detect significant differences between antibody arms at the chemotherapy backbone level, and such a comparison is confounded by imbalances in baseline characteristics due to the nonrandomized selection of chemotherapy, our results demonstrate that the efficacy benefits of G persisted with all three chemotherapy backbones. Safety profiles differed, however, with cytopenias being more common with CHOP and severe infections more common with bendamustine. Fatal AEs were also more common with bendamustine, although this finding was probably confounded by age, comorbidities, and initiation of new anticancer therapy. The nature of AEs in patients with FL in GALLIUM in this analysis was consistent with the known safety profiles of the study treatments. Hence, although G can be considered as the new standard anti-CD20 antibody for first-line therapy of FL, the most appropriate chemotherapy partner should be selected with care, taking individual patient characteristics and risk profiles into consideration.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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