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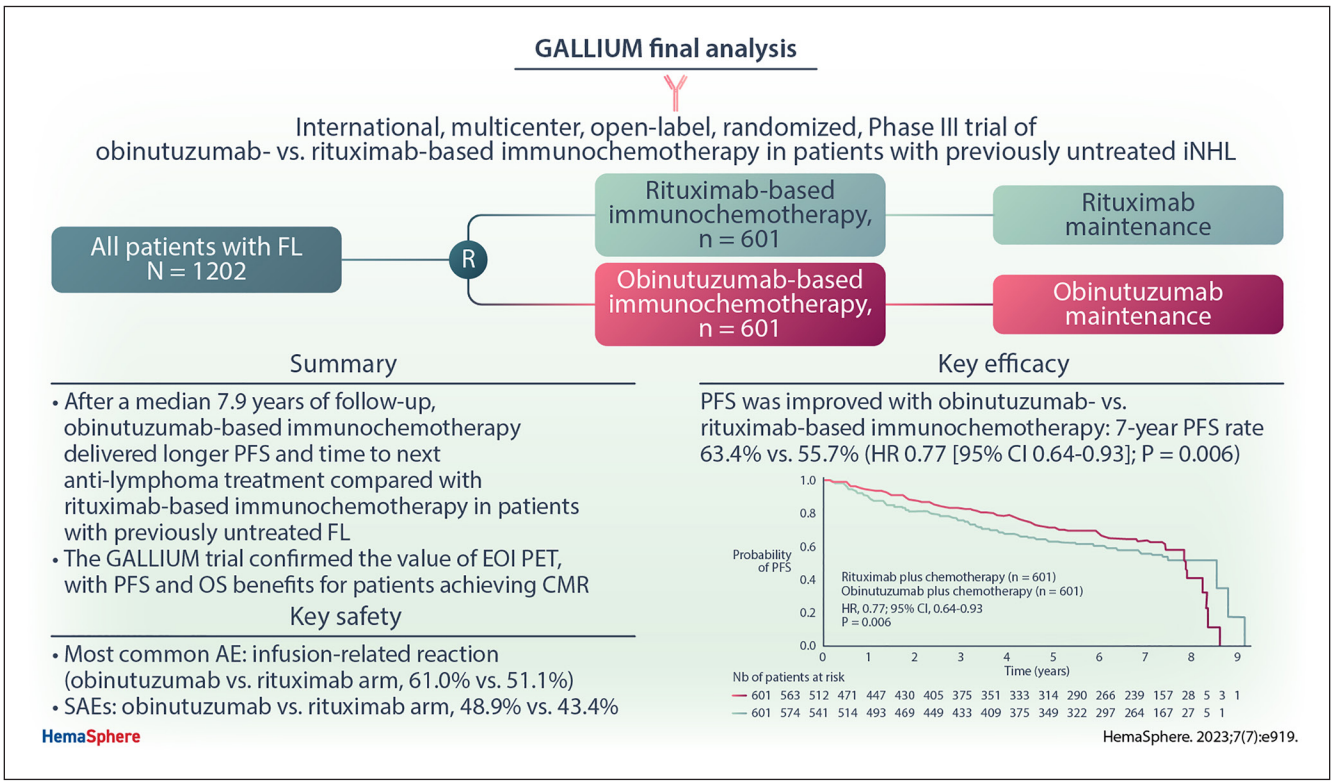
GRAPHICAL ABSTRACT



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Obinutuzumab Versus Rituximab Immunochemotherapy in Previously Untreated iNHL: Final Results From the GALLIUM Study

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ABSTRACT

The phase III GALLIUM trial assessed the safety and efficacy of obinutuzumab-based versus rituximab-based immunochemotherapy in patients with previously untreated follicular lymphoma (FL) or marginal zone lymphoma (MZL). At the primary analysis, the trial met its primary end point, demonstrating improvement in investigator-assessed progression-free survival (PFS) with obinutuzumab-based versus rituximab-based immunochemotherapy in patients with FL. We report the results of the final analysis in the FL population, with an additional exploratory analysis in the MZL subgroup. Overall, 1202 patients with FL were randomized 1:1 to obinutuzumab- or rituximab-based immunochemotherapy followed by maintenance with the same antibody for up to 2 years. After a median 7.9 (range, 0.0–9.8) years of follow-up, PFS remained improved with obinutuzumab- versus rituximab-based immunochemotherapy, with 7-year PFS rates of 63.4% versus 55.7% (P = 0.006). Time-to-next antilymphoma treatment was also improved (74.1% versus 65.4% of patients had not started their next antilymphoma treatment at 7 y; P = 0.001). Overall survival was similar between the arms (88.5% versus 87.2%; P = 0.36). Irrespective of the treatment received, PFS and OS were higher in patients with a complete molecular response (CMR) versus those with no CMR (P < 0.001). Serious adverse events were reported in 48.9% and 43.4% of patients in the obinutuzumab and rituximab arms, respectively; there was no difference in the rate of fatal adverse events (4.4% and 4.5%, respectively). No new safety signals were reported. These data demonstrate the long-term benefit of obinutuzumab-based immunochemotherapy and confirm its role as a standard-of-care for the first-line treatment of advanced-stage FL, taking into account patient characteristics and safety considerations.

INTRODUCTION

Follicular lymphoma (FL) is the most common type of indolent non-Hodgkin lymphoma (iNHL), representing 35% of all cases of NHL and 70% of iNHL cases diagnosed in the United States and Western Europe.[1] Marginal zone lymphoma (MZL) accounts for ≈8% of all NHL cases.[2]

Although rituximab-based immunochemotherapy has significantly improved outcomes for patients with previously untreated FL, most patients experience relapse and shorter durations of remission with subsequent lines of treatment.[3–7] Approximately 20% of those who experience progression of disease do so within 2 years of initiating first-line treatment (POD24), with early progression associated with inferior

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overall survival (OS).[8,9] Lymphoma, particularly histologic transformation, remains the leading cause of death for patients with FL.[1] Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody, with lower complement-dependent cytotoxicity but greater antibody-dependent cellular cytotoxicity, phagocytosis, and direct B-cell killing effects than rituximab.[10,11]

GALLIUM (NCT01332968) was a phase III, randomized trial of obinutuzumab- versus rituximab-based immunochemotherapy in patients with previously untreated, advanced-stage iNHL.[12] As initially reported after a median follow-up of 34.5 months, the trial met its primary end point, demonstrating an improvement in progression-free survival (PFS) with obinutuzumab versus rituximab in the FL population with a hazard ratio (HR) of 0.66; this PFS benefit was maintained in a subsequent analysis after 5 years of follow-up (HR, 0.76).[12,13]

In a secondary analysis of this study in patients with FL, end-of-induction (EOI) complete metabolic response (CMR) rate by positron emission tomography-computed tomography (PET-CT) was found to be higher with obinutuzumab-based immunochemotherapy, and achieving a CMR was associated with improved PFS and OS.[14] In a separate analysis, an association was also observed between minimal residual disease (MRD) status at EOI and PFS, with MRD negativity being associated with improved PFS.[15] In a combined multivariate analysis, EOI, PET, and MRD status were independently predictive of PFS.[16] A previous analysis of this study identified a lower rate of POD24 events with obinutuzumab- versus rituximab-based immunochemotherapy (57/601 versus 98/601), and confirmed the findings from previous studies that POD24 was associated with poorer OS in comparison with no-POD24 (2-y OS post-24-mo landmark: 82.4% versus 98.2%; age-adjusted HR, 12.2). The average HR-based reduction in the risk of a POD24 event in the obinutuzumab arm relative to the rituximab arm was 46.0% (95% confidence interval [CI], 25.0-61.1%; $P = 0.0003$).[17]

The GALLIUM trial also included 195 patients with MZL. An exploratory analysis of this subgroup with a median follow-up of 59.3 months demonstrated that there was no meaningful difference in PFS with obinutuzumab- versus rituximab-based immunochemotherapy. Increased toxicity was observed with obinutuzumab-based immunochemotherapy in patients with MZL in comparison to those with FL.[18]

Due to the long natural history of iNHL, long-term outcomes are important for patients and their clinicians when choosing front-line treatment regimens. This analysis with a longer follow-up aimed to determine the long-term efficacy and safety of obinutuzumab- versus rituximab-based immunochemotherapy. We also sought to explore whether the association between PET remission status at EOI and survival outcomes was maintained with extended follow-up. We report the final analysis of the GALLIUM study after 8 years of follow-up, focusing on the FL cohort.

METHODS

Study design and patient population

GALLIUM (NCT01332968) was an international, multicenter, open-label, randomized, phase III trial of obinutuzumab- versus rituximab-based immunochemotherapy in patients with previously untreated, advanced-stage iNHL. The full study details have been reported.[12,18] Briefly, patients were ≥18 years old with histologically documented, previously untreated, CD20+ iNHL (FL grade 1–3a or MZL [splenic, nodal, or extranodal]), with advanced-stage disease (stage III or IV, or stage II with bulk ≥7 cm), in need of treatment per Groupe d'Etude des Lymphomes Folliculaires criteria, and had an Eastern Cooperative Oncology Group performance status of 0–2.

Patients were randomized 1:1 to receive obinutuzumab (1000 mg; intravenously [IV] on days 1, 8, and 15 of cycle 1 and on day 1 of subsequent cycles) or rituximab (375 mg/m^2; IV on day 1 of each cycle) plus chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone [CHOP]; cyclophosphamide, vincristine, and prednisolone [CVP]; or bendamustine) for 6 or 8 cycles depending on the chemotherapy backbone. Patients with a CT-based complete or partial response (CR or PR) received maintenance treatment with the same antibody for 2 years or until disease progression or withdrawal. Patients with stable disease (SD) at EOI did not receive maintenance and underwent observation until disease progression or withdrawal. Patients with MZL were randomized separately to those with FL. The chemotherapy backbone was not randomized and was selected at each institution. The study was not designed to assess differences according to the chemotherapy backbone.

GALLIUM was performed in accordance with the principles of the Declaration of Helsinki, International Council on Harmonization Good Clinical Practice guidelines, and other applicable regulations and laws. Before initiation of the study, the protocol was approved by the required independent ethics committees, institutional review boards, and regulatory authorities. These bodies also approved all protocol amendments ahead of any changes being implemented. All patients provided signed informed consent before study entry.

Study end points and assessments

The primary end point was PFS, as assessed by the investigator, in patients with FL. Secondary end points included OS, time-to-next antilymphoma treatment (TTNLT), event-free survival (EFS), and safety. EFS was defined as the time from the date of randomization to the date of disease progression, death from any cause, or start of a next antilymphoma treatment. PFS in patients with MZL was assessed as an exploratory end point.

Detailed methods of response assessments have previously been reported.[12,14,18] The first 170 patients enrolled with FL underwent a fluorodeoxyglucose (FDG)-PET scan. FDG-PET assessment was optional for subsequent patients. PET assessment was retrospectively reported by the Independent Review Committee using the Lugano 2014 criteria.[12,14,19,20] Patients with SD at the end of the 2-year observation period, and those with a CR or PR at the end of maintenance, underwent disease assessments every 3 months for 3 years, and then every 6 months, until the end of the study or disease progression.

All adverse events ([AEs]; related and unrelated) were recorded up to 28 days after the last dose of study drug, and grade ≥3 AEs were recorded up to 6 months after the last dose of study drug. Grade 3 or 4 infections (related and unrelated) were recorded up to 24 months after the last dose of study drug, and unrelated serious AEs (SAEs) were recorded up to 12 months after the last dose. Study drug-related SAEs and second malignancies were recorded indefinitely, including after the study had closed.

Statistical analyses

Detailed statistical methods were previously reported.[12,18] The study planned to enroll ≈1200 patients with FL and an additional 200 patients with MZL.

This final analysis was performed based on all data collected up to the last-patient last-visit at the cutoff date of July 30, 2021.

RESULTS

Patient disposition and treatment

Overall, 1401 patients were enrolled and randomized, 1202 of whom had FL (obinutuzumab arm, n = 601; rituximab arm, n = 601; Figure 1), and 199 of whom had MZL. Four patients in the MZL cohort were retrospectively found to have another diagnosis and were excluded; 195 patients were included in the intent-to-treat population (obinutuzumab arm, n = 99;

rituximab arm, n = 96).[18] Baseline patient characteristics have previously been reported,[12,18] and were well-balanced between treatment arms (Suppl. Table S1) but differed according to the allocated chemotherapy backbone.[12,18,21]

In the FL population, 603 patients completed follow-up (Figure 1; obinutuzumab arm, n = 318; rituximab arm, n = 285). In total, 158 patients in the obinutuzumab arm and 181 patients in the rituximab arm withdrew from study treatment, of these, 121 and 134, respectively, withdrew during the maintenance phase. The main reasons for withdrawal during the maintenance phase were AEs (n = 52 in the obinutuzumab arm and n = 41 in the rituximab arm), progressive disease (n = 37 and n = 64, respectively), and physician decision (n = 15 and n = 11, respectively).

At the time of data cutoff, median observation time was 7.9 (range, 0.0–9.8) years in the FL population; 7.8 (range, 0.0–9.7) years in the obinutuzumab arm and 7.9 (range, 0.0–9.8) years in the rituximab arm. The median duration of maintenance treatment was 93.1 weeks with both obinutuzumab and rituximab. In the MZL population, median observation time was 7.9 (range, 0.0–9.9) years; 7.8 (range, 0.1–9.9) years in the obinutuzumab arm, and 8.0 (range, 0.0–9.7) years in the rituximab arm.

Efficacy

Overall FL population

After 8 years of follow-up, investigator-assessed PFS was improved in the obinutuzumab versus rituximab arm in patients with FL (7-y PFS rate, 63.4% versus 55.7%, respectively; HR, 0.77 [95% CI, 0.64-0.93]; P = 0.006) (Table 1; Figure 2A). Since the primary analysis, an additional 105 events had occurred in the obinutuzumab arm, and 100 in the rituximab arm. At the cutoff, 168 and 220 patients in the obinutuzumab and rituximab arms, respectively, had documented disease

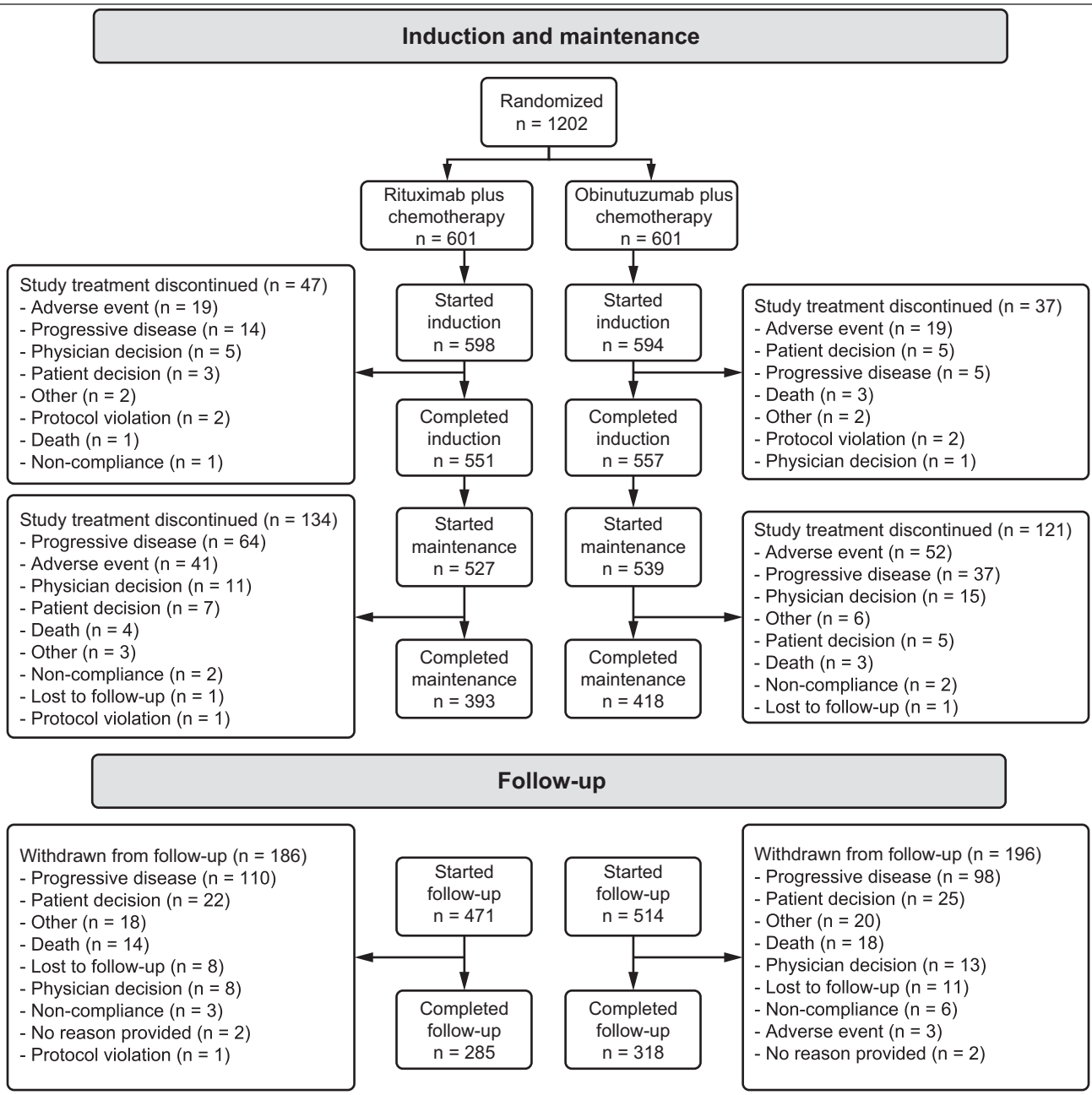

Figure 1. Patient disposition (FL population) at the completion of study (July 30, 2021). FL = follicular lymphoma.

progression. Biopsies were not mandatory at relapse, and data on biopsy at progression are only available for 69 patients, representing 18% of all patients with progressive disease. Biopsy-confirmed transformation to diffuse large B-cell lymphoma (DLBCL) was reported in 25 of 601 (4.2%) and 30 of 601 (5.0%) patients in the obinutuzumab and rituximab arms, respectively, representing 25 of 168 (14.9%) and 30 of 220 (13.6%) progression events. Investigator-assessed 7-year EFS rate was also improved in the obinutuzumab versus rituximab arm (62.2% versus 53.9%; HR, 0.74 [95% CI, 0.62-0.89]; *P* = 0.002; Table 1; Figure 2B). At 7 years, 74.1% of patients in the obinutuzumab arm and 65.4% in the rituximab arm were alive and had not yet started their next antilymphoma treatment (HR, 0.71 [95% CI, 0.58-0.87]; *P* = 0.001). At the data cutoff, 369 patients had started their next antilymphoma treatment (160 in the obinutuzumab arm and 209 in the rituximab arm; Table 1; Figure 2C).

Overall, 162 patients had died; 76 in the obinutuzumab arm and 86 in the rituximab arm. Since the primary analysis, 81 patients had died, 41 and 40 in the obinutuzumab and rituximab arms, respectively. The 7-year OS rate was 88.5% in the obinutuzumab arm versus 87.2% in the rituximab arm (HR, 0.86 [95% CI, 0.63-1.18]; *P* = 0.36) (Table 1; Figure 2D). Progressive disease was considered to be the primary cause of death for 4.2% and 6.0% of patients in the obinutuzumab and rituximab arms, respectively. Death attributable to AEs occurred in 4.4% of patients in the obinutuzumab arm and 4.5% of patients in the rituximab arm. The incidence of death due to progressive disease since the primary analysis at 3 years was low, occurring in 13 (2.2%) and 14 (2.3%) patients in the obinutuzumab and rituximab arms, respectively. In an exploratory analysis of OS by reason for death, the small difference in OS between treatment arms appeared to be driven by more deaths due to progressive disease in the rituxmab versus obinutuzumab arm (Suppl. Figure S1).

Table 1

Efficacy Results in the FL Population

	Obinutuzumab (N = 601)	Rituximab (N = 601)
Median observation time (range), y	7.8 (0.0-9.7)	7.9 (0.0-9.8)
Investigator-assessed PFS		
Patients with event, n (%)	206 (34.3)	244 (40.6)
Estimated 7-y PFS rate, % (95% CI)	63.4 (59.0-67.4)	55.7 (51.3-78.9)
Hazard ratio (95% CI)	0.77 (0.64-0.93)	
P-value	0.006	
Investigator-assessed EFS		
Patients with event, n (%)	215 (35.8)	258 (42.9)
Estimated 7-y EFS rate, % (95% CI)	62.2 (57.9-66.3)	53.9 (49.5-58.1)
Hazard ratio (95% CI)	0.74 (0.62-0.89)	
P-value	0.002	
Investigator-assessed TTNLT		
Patients with event, n (%)	160 (26.6)	209 (34.8)
Patients free from NLT at 7 y,[a] % (95% CI)	74.1 (70.3-77.5)	65.4 (61.4-69.2)
Hazard ratio (95% CI)	0.71 (0.58-0.87)	
P-value	0.001	
OS		
Patients with event, n (%)	76 (12.6)	86 (14.3)
Estimated 7-y OS rate, % (95% CI)	88.5 (85.6-90.9)	87.2 (84.1-89.7)
Hazard ratio (95% CI)	0.86 (0.63-1.18)	
P-value	0.36	

[a]Patients who were alive and had not started next lymphoma treatment at 7 y.

CI = confidence interval; EFS = event-free survival; FL = follicular lymphoma; NLT = next lymphoma treatment; OS = overall survival; PFS = progression-free survival; TTNLT = time-to-next lymphoma treatment.

Subgroup analysis of PFS

In a preplanned subgroup analysis of PFS according to the baseline characteristics and stratification factors, no strong evidence of heterogeneity of treatment effect was observed for the majority of factors (Figure 3). However, Follicular Lymphoma International Prognostic Index (FLIPI) score appeared to have an effect on the PFS benefit (Suppl. Figure S2). A PFS benefit was observed in the obinutuzumab versus rituximab arm in patients with an intermediate-to-high (2–5) FLIPI score (n = 951), with a 7-year PFS rate of 62.9% versus 51.8%, respectively (HR, 0.70 [95% CI, 0.57-0.86]; *P* < 0.001). However, there was no benefit in those with a low (0–1) FLIPI score (n = 251; 7-year PFS was 65.4% versus 70.1%, respectively; HR, 1.20 [95% CI, 0.75-1.90]; *P* = 0.45).

Survival by CMR status

In the FL cohort, 595 patients had a PET scan at EOI before maintenance, of whom 519 were included in the landmark OS population and 508 patients were included in the landmark analysis of PFS. As previously reported, 78.8% versus 72.5% of patients achieved a CMR by PET scan in the obinutuzumab versus rituximab arms, respectively.[14] Irrespective of treatment received, investigator-assessed PFS was higher in patients with a CMR (n = 449) versus those with no CMR (n = 56) (HR, 0.31 [95% CI, 0.22-0.46]; *P* < 0.001) (Figure 4A). The 7-year PFS rate from EOI was 57.2% in those with a CMR versus 26.5% in those without a CMR. OS was also greater in patients with a CMR (n = 450) versus those with no CMR (n = 69) (HR, 0.30 [95% CI, 0.18-0.52;] *P* < 0.001) (Figure 4B); the 7-year OS rate was 90.2% versus 73.2%, respectively.

Of note, in patients achieving a CMR (n = 449), PFS was greater in the obinutuzumab versus rituximab arm (HR, 0.72 [95% CI, 0.52-0.99]; *P* = 0.04) (Figure 5A); the 7-year PFS rate was 62.5% versus 51.4%, respectively. In patients without a CMR (n = 56 [rituxumab arm, n = 31; obinutuzumab arm, n = 25]), the 7-year PFS rate was 37.8% in the obinutuzumab arm, and was not estimable in the rituximab arm (HR, 0.53 [95% CI, 0.25-1.10]; *P* = 0.09). At the time of cutoff, 64.0% of patients in the obinutuzumab arm and 77.4% of patients in the rituximab arm had experienced a progression event (Figure 5A). The 7-year OS rate was similar between treatment arms in patients with a CMR (90.6% in the obinutuzumab arm versus 89.8% in the rituximab arm; HR, 1.09 [95% CI, 0.61-1.93]; *P* = 0.77) (Figure 5B). In those without a CMR, the 7-year OS rate was 82.8% in the obinutuzumab arm versus 66.7% in the rituximab arm (HR, 0.84 [95% CI, 0.32-2.24]; *P* = 0.73).

MZL population

The 7-year PFS rate in the MZL population was 59.8% in the obinutuzumab arm versus 52.2% in the rituximab arm (HR, 0.77 [95% CI, 0.49-1.21]; *P* = 0.26). Further efficacy data for the MZL population are presented in the Supplemental Digital Content (Suppl. Table S2 and Suppl. Figure S3).

Safety

The FL safety population included 595 patients treated with obinutuzumab-based immunochemotherapy and 597 patients treated with rituximab-based immunochemotherapy; the primary safety data have previously been published.[12] Overall, after 7.9 years of follow-up, the most common AEs were infusion-related reaction (obinutuzumab versus rituximab arm, 61.0% versus 51.1%), neutropenia (46.% versus 51.3%), and nausea (50.4% versus 49.9%; Suppl. Table S3). The most common grade 3–5 AEs were neutropenia (obinutuzumab versus rituximab arm, 46.7% versus 40.4%), leukopenia (8.9% versus 9.7%), and febrile neutropenia (7.6% versus 4.7%; Suppl. Table S4). In total, 48.9% of patients in the obinutuzumab arm and 43.4% of patients in the rituximab arm experienced an SAE. In the obinutuzumab arm, 17.2% of patients experienced an SAE

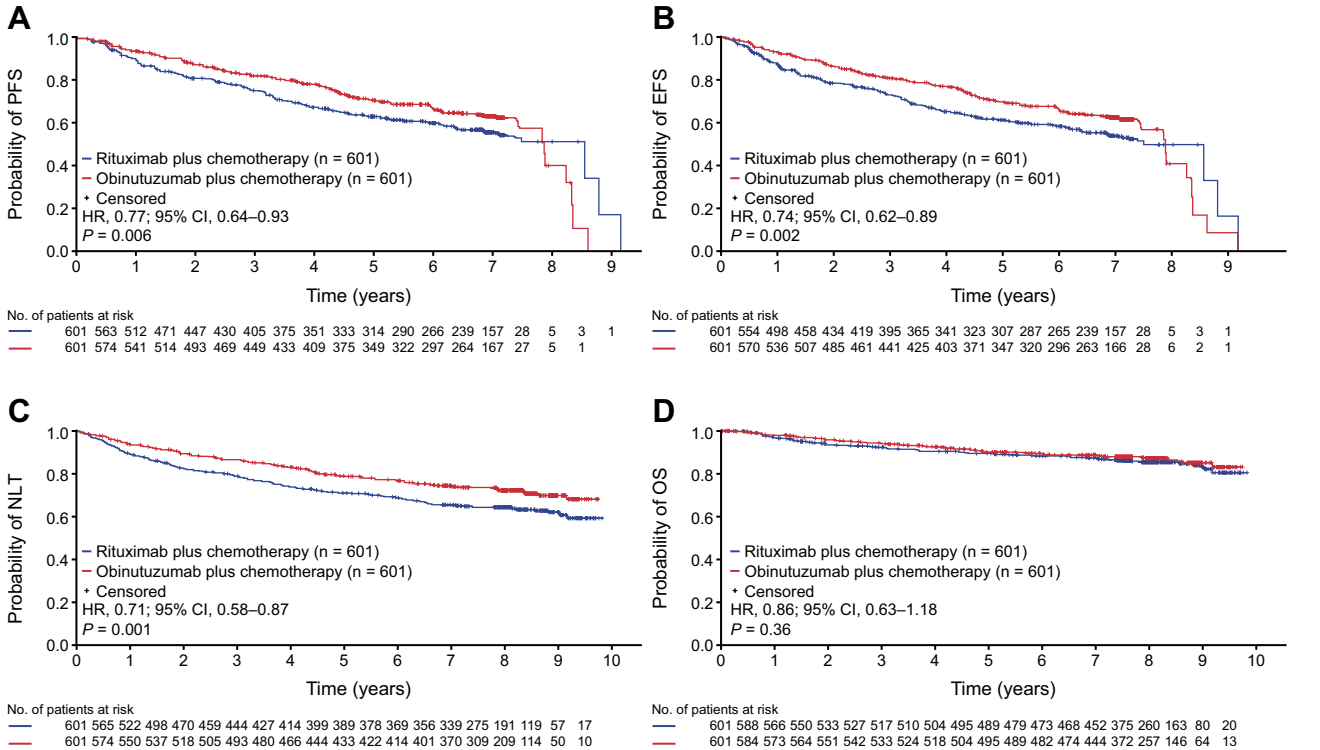

Figure 2. Kaplan–Meier estimates of PFS, EFS, TTNLT, and OS by treatment arm in the FL population. (A) PFS. (B) EFS. (C) TTNLT. (D) OS. Event-free probabilities became unreliable toward the end of the study when only around 10%–20% of patients remained at risk.[22] CI = confidence interval; EFS = event-free survival; HR = hazard ratio; NLT = next lymphoma treatment; OS = overall survival; PFS = progression-free survival; TTNLT = time-to-next lymphoma treatment.

during the observation/follow-up phase, compared with 14.5% of patients in the rituximab arm (Table 2). The most common SAEs reported during the follow-up phase were in the System Order Class of infections and infestations, which were reported in 6.6% and 6.3% of patients in the obinutuzumab and rituximab arms, respectively. In particular, pneumonia was reported in 1.9% and 2.1% of patients, respectively, during the observation/follow-up phase (Suppl. Table S5).

Since the primary analysis, 2 fatal AEs had occurred in the obinutuzumab arm (both received induction obinutuzumab plus CHOP) and 7 had occurred in the rituximab arm (1 received induction rituximab plus CHOP and 6 received rituximab plus bendamustine). Most fatal AEs occurred in patients receiving bendamustine with no difference between treatment arms; fatal AEs were reported in 20 (5.9%) patients who received obinutuzumab plus bendamustine and in 21 (6.2%) patients who received rituximab plus bendamustine.

The rate of second malignancies (including malignant and unspecified tumors), reported at least 6 months after the first study drug administration, was 13.1% in the obinutuzumab arm and 9.9% in the rituximab arm (grade ≥3, 8.4% and 6.5%, respectively). The difference between arms was primarily driven by the incidence of nonmelanoma skin cancers (obinutuzumab arm, 3.9%; rituximab arm, 2.8%) and hematological malignancies (obinutuzumab arm, 1.2%; rituximab arm, 0.3%) (Suppl. Table S6).

Safety data for the MZL population are included in the Supplemental Digital Content (Suppl. Tables S7 and S8).

DISCUSSION

The key finding of this final report of the GALLIUM trial, with median a follow-up of 8 years, was that a long-term PFS benefit was sustained with obinutuzumab-based compared with rituximab-based immunochemotherapy in patients with previously untreated FL. The HR of 0.77 was consistent with the HRs of 0.66 and 0.76 reported after 3 and 5 years of follow-up, respectively.[12,13] A similar number of PFS events had been reported in each arm since the primary analysis (105 and 100 in the obinutuzumab and rituximab arms, respectively), suggesting that the improvement observed with obinutuzumab was predominantly driven by a lower rate of early progression events and highlighting the importance of achieving a deep first remission. Kaplan–Meier curves for PFS started to separate after 4 months in favor of obinutuzumab, and then remained separated until they crossed at 8 years. However, due to the low number of patients remaining at risk beyond 7.5 years, Kaplan–Meier estimates became unreliable beyond this point.[22] The improvement in PFS in the obinutuzumab arm translated into a longer TTNLT, with fewer patients having started their next antilymphoma treatment at the 7-year timepoint in comparison with the rituximab arm. In the obinutuzumab arm, 74.1% of patients had not required further therapy at 7 years compared with 65.4% in the rituximab arm, representing a 29% reduction in risk. These findings suggest that the front-line treatment with obinutuzumab-based immunochemotherapy ultimately reduced the treatment burden for these patients.

In the subgroup analysis of PFS according to the baseline characteristics and stratification factors, no strong evidence of meaningful heterogeneity of treatment effect was observed for the majority of factors, except for FLIPI score. A PFS benefit was observed with obinutuzumab in patients with an intermediate-to-high risk score (n = 951; 79% of the study population). These findings were consistent with the primary analysis.[12]

The true rate of disease transformation to DLBCL at progression was difficult to assess, as biopsies were not mandatory at relapse and were only reported for 18% of all patients with progressive disease. With the caveat that patients with more aggressive disease may have been preferentially biopsied, 80% of the 69 biopsies showed disease transformation to DLBCL,

Characteristics at baseline	Total n	Rituximab plus chemotherapy (N = 601) n	Rituximab plus chemotherapy (N = 601) Events	Obinutuzumab plus chemotherapy (N = 601) n	Obinutuzumab plus chemotherapy (N = 601) Events	Hazard ratio	95% CI
All patients	1202	601	244	601	206	0.78	(0.65–0.94)
Sex							
Male	563	280	124	283	118	0.87	(0.67–1.12)
Female	639	321	120	318	88	0.68	(0.51–0.89)
Race							
Asian	198	98	43	100	33	0.65	(0.41–1.02)
White	968	481	191	487	170	0.82	(0.67–1.01)
Other	36	22	10	14	3	0.41	(0.11–1.50)
Bulky disease (≥7 cm)							
Yes	525	270	118	255	94	0.75	(0.57–0.98)
No	675	330	125	345	111	0.80	(0.62–1.03)
B symptoms (≥1)							
Yes	407	206	82	201	75	0.91	(0.66–1.24)
No	794	394	162	400	131	0.71	(0.57–0.90)
Ann Arbor stage							
I	18	8	2	10	4	1.51	(0.28–8.29)
II	85	44	14	41	13	0.77	(0.35–1.66)
III	417	208	82	209	70	0.82	(0.59–1.12)
IV	675	337	145	338	117	0.73	(0.58–0.94)
Missing	7	4	1	3	2	3.71	(0.32–42.39)
ECOG PS							
0–1	1161	576	231	585	198	0.78	(0.65–0.95)
2	38	23	12	15	7	0.79	(0.29–2.10)
ADL							
0–2	10	7	2	3	0	<0.01	(0.00–NE)
3–4	9	5	3	4	2	0.35	(0.04–3.39)
5–6	922	463	186	459	154	0.74	(0.60–0.92)
Outside valid range	98	46	14	52	18	1.20	(0.60–2.42)
IADL							
0	2	1	0	1	0	NE	(NE–NE)
1–4	23	14	7	9	3	0.65	(0.17–2.51)
5–8	1005	501	194	504	172	0.81	(0.66–1.00)
Outside valid range	27	11	6	16	4	0.22	(0.05–0.87)
FLIPI							
Low	251	125	34	126	42	1.22	(0.77–1.92)
Intermediate	448	222	92	226	69	0.61	(0.45–0.84)
High	503	254	118	249	95	0.77	(0.59–1.01)
Chemotherapy regimen							
CHOP	399	203	93	196	76	0.81	(0.60–1.10)
CVP	117	57	30	60	26	0.62	(0.37–1.05)
Bendamustine	686	341	121	345	104	0.79	(0.61–1.03)
Geographic region							
Asia	185	93	42	92	31	0.63	(0.39–1.00)
Eastern Europe	157	79	39	78	26	0.73	(0.44–1.20)
North America	152	77	29	75	27	0.92	(0.54–1.57)
Other	127	65	20	62	17	0.74	(0.38–1.44)
Western Europe	581	287	114	294	105	0.78	(0.60–1.02)

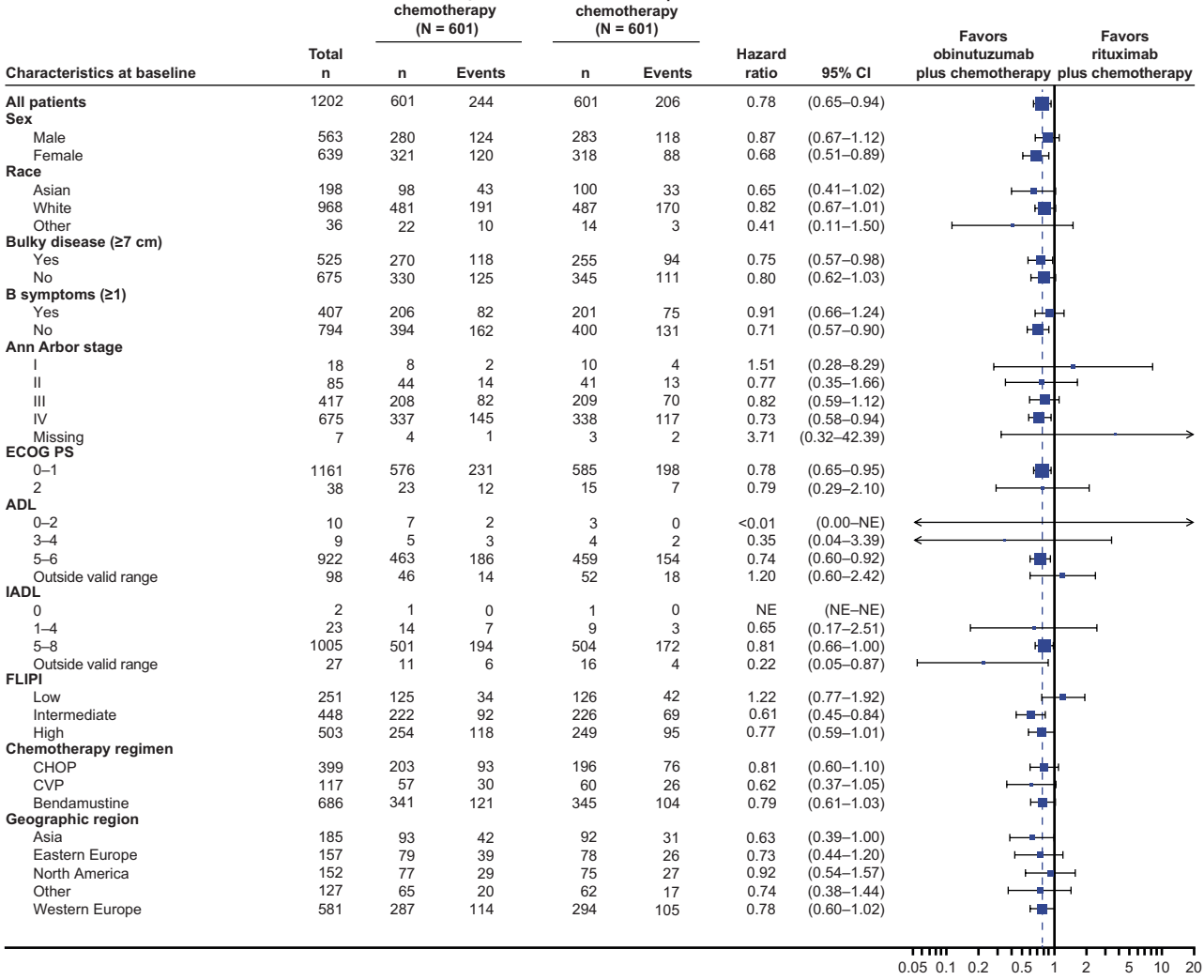

Figure 3. Forest plot for PFS in the FL population according to the baseline characteristics and stratification factors (unstratified analysis). ADL = activities of daily living; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; CI = confidence interval; CVP = cyclophosphamide, vincristine, and prednisolone; ECOG PS = Eastern Cooperative Oncology Group performance status; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; IADL = instrumental activities of daily living; NE = not evaluable; PFS = progression-free survival.

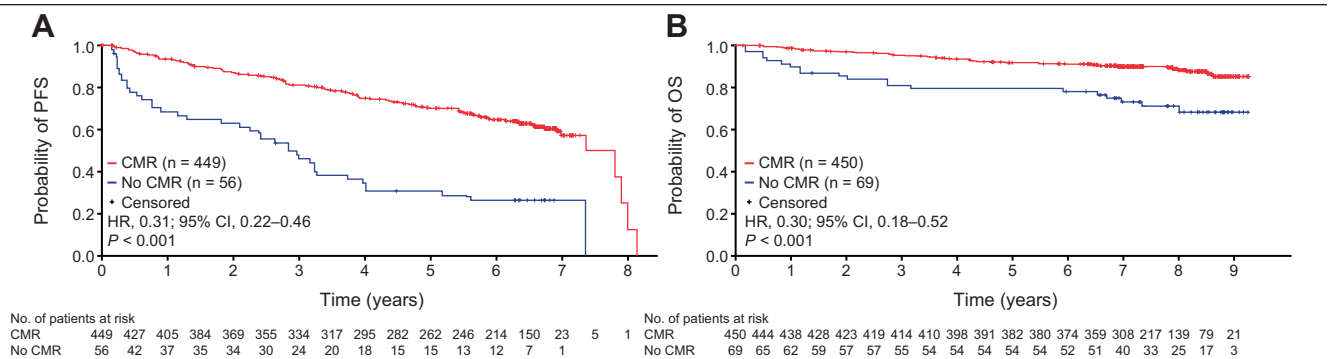

Figure 4. Kaplan–Meier estimates of PFS and OS by EOI PET response status in the FL population. (A) PFS. (B) OS. Event-free probabilities became unreliable toward the end of the study when only around 10%–20% of patients remained at risk.[22] CI = confidence interval; CMR = complete metabolic response; EOI = end of induction; FL = follicular lymphoma; HR = hazard ratio; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival.

with no obvious difference in rate between the 2 arms. The rate of documented histological transformation was comparable to that observed in the Phase III PRIMA study.[23] Furthermore, in a separate analysis of the GALLIUM study, the majority of transformation events (77.5%) occurred within 2 years of randomization,[24] consistent with findings from the PRIMA study, in

which over 50% of transformation events occurred within the first year of follow-up.[23]

While PFS was improved with obinutuzumab-based immunochemotherapy, OS was similar between treatment arms; a HR of 0.84 was observed for obinutuzumab versus rituximab with wide CIs. It should be noted that this trial was not powered to detect differences in OS and few deaths had occurred in either arm. An exploratory analysis revealed a reduction in deaths due to progressive disease in the obinutuzumab arm. The lack of OS benefit observed with obinutuzumab-based immunochemotherapy is consistent with a number of previous studies comparing different rituximab-based immunochemotherapy regimens in previously untreated FL, where improvements in PFS did not translate into an OS benefit.[25–27] Relatively few deaths had occurred in either arm at the time of this analysis (obinutuzumab arm, 13%; rituximab arm, 14%). This challenge of identifying an OS difference in front-line trials reflects the potent antilymphoma effect of the primary treatment, the indolent nature of FL, and the effectiveness of salvage therapies in this treatment setting.

We previously reported that a lower rate of POD24 events was observed in patients treated with obinutuzumab- versus rituximab-based immunochemotherapy,[17] but this difference has not translated into an OS benefit with obinutuzumab. Therefore, despite having been validated in large datasets from pooled trials,[9] this raises the question of whether POD24 can be reliably used as a surrogate marker for OS in trials of patients with previously untreated FL receiving obinutuzumab-based treatments.

This trial is the largest to assess the value of EOI PET imaging in patients with previously untreated FL,[14] now with the benefit of long-term follow-up. We confirmed the long-term value of EOI PET assessment, with a substantial PFS and OS benefit sustained for patients achieving a CMR versus those with no CMR (including a partial metabolic response, no metabolic response, or progressive metabolic disease[14]). The 7-year PFS and OS rates of 57% and 90%, respectively, in those achieving a CMR provides confidence in their favorable long-term outcomes, for both patients and physicians. Of interest, the impact of obinutuzumab in improving PFS was suggested across both EOI PET populations: those achieving and those not achieving CMR. In the future, EOI PET assessment may enable response-adapted maintenance therapy in FL, and this is currently being assessed in a number of ongoing, international clinical trials.[28,29]

Importantly, no new safety signals were observed in either treatment arm since the primary analysis, with the longer observation time of 8 years. Overall, obinutuzumab was associated with a manageable safety profile. Although concerns have previously been raised regarding the rate of fatal AEs observed in patients treated with anti-CD20 antibodies plus bendamustine compared with CHOP or CVP, data from this final analysis confirm that the rate of fatal AEs was similar between the obinutuzumab and rituximab arms. However, the rate of

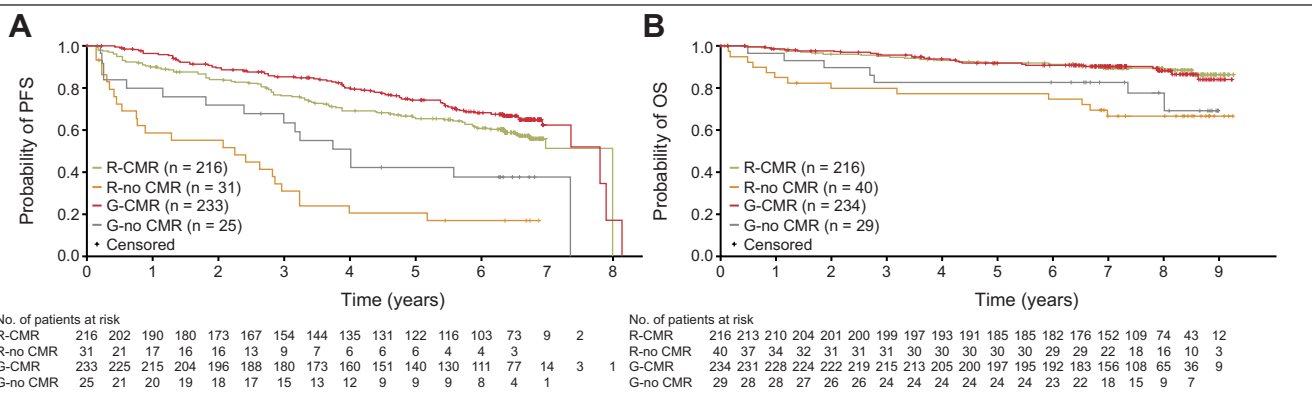

Figure 5. Kaplan–Meier estimates of PFS and OS by treatment arm and EOI PET response status in the FL population. (A) PFS. In patients achieving a CMR (obinutuzumab arm vs rituximab arm): HR, 0.72; 95% CI, 0.52-0.99; *P* = 0.04. In patients with no CMR: HR, 0.53; 95% CI, 0.25-1.10; *P* = 0.09. (B) OS. In patients achieving a CMR (obinutuzumab arm vs rituximab arm): HR, 1.09; 95% CI, 0.61-1.93; *P* = 0.77. In patients not achieving a CMR: HR, 0.84; 95% CI, 0.32-2.24; *P* = 0.73. Event-free probabilities became unreliable toward the end of the study when only around 10%–20% of patients remained at risk.[22] CI = confidence interval; CMR = complete metabolic response; EOI = end of induction; FL = follicular lymphoma; G = obinutuzumab; HR = hazard ratio; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; R = rituximab.

Table 2

Summary of Safety in the FL Population

	Induction Phase		Maintenance Phase		Observation/Follow-up Phase	
	Obinutuzumab (N = 595)	Rituximab (N = 597)	Obinutuzumab (N = 540)	Rituximab (N = 526)	Obinutuzumab (N = 577)	Rituximab (N = 572)
Any grade AEs, n (%)	589 (99.0)	585 (98.0)	517 (95.7)	479 (91.1)	254 (44.0)	208 (36.4)
Grade ≥3 AEs, n (%)	368 (61.8)	350 (58.6)	216 (40.0)	174 (33.1)	123 (21.3)	90 (15.7)
SAEs, n (%)	168 (28.2)	147 (24.6)	132 (24.4)	114 (21.7)	99 (17.2)	83 (14.5)
Most common AEs of particular interest, n (%)						
Neutropenia	270 (45.4)	257 (43.0)	114 (21.1)	79 (15.0)	21 (3.6)	12 (2.1)
Grade ≥3	241 (40.5)	223 (37.4)	100 (18.5)	63 (12.0)	20 (3.5)	10 (1.7)
Infections	309 (51.9)	294 (49.2)	382 (70.7)	317 (60.3)	113 (22.7)	105 (18.4)
Grade ≥3	45 (7.6)	45 (7.5)	65 (12.0)	54 (10.3)	50 (8.7)	33 (5.8)
IRRs	410 (68.9)	354 (59.3)	45 (8.3)	45 (8.6)	1 (0.2)	1 (0.2)
Grade ≥3	72 (12.1)	43 (7.2)	4 (0.7)	2 (0.4)	0	0

AE = adverse event; FL = follicular lymphoma; IRR = infusion-related reaction; SAE = serious adverse event.

grade ≥3 AEs observed with obinutuzumab in the induction and maintenance phase should be taken into account when selecting which antibody and chemotherapy backbone to use for individual patients, especially during the evolving COVID-19 pandemic.

The GALLIUM study also included 195 patients with previously untreated MZL. Consistent with the primary analysis, no PFS benefit was observed with obinutuzumab- versus rituximab-based immunochemotherapy. Due to this, along with the observed toxicity profile of obinutuzumab-based immunochemotherapy in this population, this treatment regimen cannot be recommended for the first-line treatment of patients with MZL.[18]

The main strengths of this study were that it was a large, randomized, phase III study with a head-to-head comparison of 2 anti-CD20 monoclonal antibodies combined with a choice of 3 established chemotherapy regimens, and an extended duration of follow-up as presented in this analysis. A weakness of the study was that chemotherapy allocation was not randomized, and as such there were imbalances in baseline characteristics between chemotherapy regimens.[21] Comparisons of efficacy and safety between the different chemotherapy backbones are therefore confounded.[21] Another drawback was that PET, now considered to be the standard method of response assessment, was not universally required at EOI. However, this study still represents the largest cohort of patients with an EOI PET assessment in a prospective trial of previously untreated FL. Finally, it has previously been suggested that the increased efficacy of obinutuzumab relative to rituximab is a dose effect, therefore confounding direct comparisons of efficacy.[30] Modeling has suggested that this is not the case, with increased doses of rituximab unable to match the activity of that observed with the fixed dosing regimen of obinutuzumab.[12,31] However, this question cannot be definitively answered based on the available data.

In conclusion, after a median observation time of 8 years, a meaningful improvement in PFS was maintained with obinutuzumab- versus rituximab-based immunochemotherapy in patients with previously untreated FL. Of note, in a disease characterized by recurrent relapses, 7-year PFS rates were high in both the arms (63.4% in the obinutuzumab arm; 55.7% in the rituximab arm), with a relatively low rate of PFS events since the primary analysis. This raises the question as to the potential for a "function cure" for many achieving a CMR with these regimens in this setting. The safety data reported here are consistent with the primary and updated analyses,[12,13] with no new safety signals observed.

These findings confirm the superiority of obinutuzumab-based immunochemotherapy over rituximab-based immunochemotherapy in delivering longer PFS and time-to-next antilymphoma treatment in patients with previously untreated FL. No significant difference in OS was observed, which was not unexpected given that the trial was not powered to detect differences in OS in this indolent lymphoma with long survival, and in which highly effective regimens are available at relapse. Obinutuzumab-based treatment should therefore be considered as a standard-of-care in suitable patients, taking into account the patient characteristics and drug safety profiles, which is of particular importance during the ongoing COVID-19 pandemic.

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AUTHOR CONTRIBUTIONS

JFS, JT, MD, MH, RM, WH, and WT contributed to the design of the study. CB, DC, EP, GC, JFS, JT, MJSD, MH, RM, T-YL, WH, WT, and X-NH were involved in the conduct of the study. AG, CB, DC, EP, GC, JFS, JGG, JT, MD, MJSD, MH, RM, T-YL, WH, and X-NH were involved in the recruitment and follow-up of patients. CB, DC, EP, GC, JGG, MJSD, T-YL, WH, WT, and X-NH were involved in the collection of data. AK, DC, DK, GC, JGG, MD, TN, WH, and WT performed the data analysis. AK, CB, DC, DK, EP, GC, JFS, JGG, JT, MJSD, MH, MD, RM, TN, WH, and WT contributed to the data interpretation. All authors were responsible for the review and approval of the article.

DATA AVAILABILITY

For eligible studies, qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing this request, platform is Vivli: https://vivli.org/ourmember/roche/. For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://go.roche.com/data_sharing. Anonymized records for individual patients across >1 data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

DISCLOSURES

WT reports honoraria from F. Hoffmann-La Roche Ltd, Gilead Sciences, and Bristol-Myers Squibb, consultancy fees from F. Hoffmann-La Roche Ltd, Bristol-Myers Squibb, Incyte, and Takeda, and travel and conference registration fees from F. Hoffmann-La Roche Ltd, Gilead Sciences, and Takeda. WH reports honoraria from F. Hoffmann-La Roche Ltd, Janssen, Gilead Sciences and Celgene; a consulting/advisory role for F. Hoffmann-La Roche Ltd, Janssen and Gilead Sciences; speakers' bureau for F. Hoffmann-La Roche Ltd, Janssen and Gilead Sciences; research funding from F. Hoffmann-La Roche Ltd, Janssen and Bayer; and travel expenses/accommodation from F. Hoffmann-La Roche Ltd, Janssen and Gilead Sciences. CB reports honoraria and speakers' bureau fees from, and a consulting/advisory role for F. Hoffmann-La Roche Ltd, Pfizer, Janssen, Hexal, Celltrion Healthcare, AbbVie, Novartis, Bayer, MorphoSys, Regeneron Pharmaceuticals, and BeiGene; and research funding from F. Hoffmann-La Roche Ltd, Janssen, Celltrion Healthcare, AbbVie, Bayer, Amgen, and MSD. GC reports a consultancy role for F. Hoffmann-La Roche Ltd and Celgene; and honoraria from Bristol-Myers Squibb, Sanofi, Janssen, Gilead Sciences, AbbVie, Takeda, F. Hoffmann-La Roche Ltd, and Celgene. DC acknowledges support and funding from the Royal Marsden NIHR Biomedical Research Center. MJSD reports research funding from F. Hoffmann-La Roche Ltd. JGG reports grants and personal fees from Celgene, AstraZeneca and Janssen; and personal fees from AbbVie, Gilead, Karyopharm, MorphoSys, Novartis, and T.G. Therapeutics.EP reports speakers' fees from Gilead Sciences, advisory board fees from BeiGene, virtual conference attendance fees from Celgene, and travel and conference registration fees from Takeda. MD reports research funding from AbbVie, Bayer, Bristol-Myers Squibb/Celgene, Gilead Sciences/Kite, Janssen, and F. Hoffmann-La Roche Ltd; honoraria from Amgen, AstraZeneca, Gilead Sciences/Kite, Janssen, Lilly, Novartis, and F. Hoffmann-La Roche Ltd; and membership on an entity's Board of Directors or advisory committees for AstraZeneca, BeiGene, Bristol-Myers Squibb/Celgene, Gilead Sciences/Kite, Janssen, Lilly/Loxo Oncology, Novartis, and F. Hoffmann-La Roche Ltd. JFS reports speakers' bureau fees, advisory board fees, and research funding from AbbVie, advisory board fees from AstraZeneca, advisory board fees from BeiGene, advisory board fees and research funding from Bristol-Myers Squibb, scientific advisory board membership from Genor Biopharma, advisory board fees from Gilead, advisory board fees and research funding from Janssen, advisory board fees, speakers' bureau fees, research funding and expert testimony fees from F. Hoffmann-La Roche Ltd, and advisory and expert testimony fees from TG Therapeutics. JT reports research funding from F. Hoffmann-La Roche Ltd, Celgene, Janssen, PCYC, and BeiGene. DK, TGN, and AK is employed by and has equity ownership interests in F. Hoffmann-La Roche Ltd. MH reports a consultancy/advisory role with Celgene, Gilead, and F. Hoffmann-La Roche Ltd and research funding from F. Hoffmann-La Roche Ltd. RM reports honoraria from F. Hoffmann-La Roche Ltd and Janssen. All the other authors have no conflicts of interest to disclose.

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