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Immunochemotherapy and Maintenance With Obinutuzumab or Rituximab in Patients With Previously Untreated Marginal Zone Lymphoma in the Randomized GALLIUM Trial

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ABSTRACT

The aim of this study was to explore the efficacy and safety of obinutuzumab (G)- versus rituximab (R)-chemotherapy in a subgroup of patients with previously untreated marginal zone lymphoma (MZL) in the phase III GALLIUM trial (NCT01332968). Patients had stage III/IV (or stage II with bulky disease), splenic, nodal, or extranodal MZL requiring treatment. Patients were randomized 1:1 to receive G- or R-chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone; cyclophosphamide, vincristine, and prednisone; or bendamustine, allocated at patient level). Patients with complete/partial response at the end of induction (EOI) received G/R maintenance. Investigator-assessed progression-free survival (PFS), other time-to-event endpoints, response, and safety were assessed. Overall, 195 patients with MZL were included in this analysis: G-chemotherapy (n = 99), R-chemotherapy (n = 96). Median observation time: 59.3 months. No meaningful difference was observed between arms for PFS (4-y PFS rates: G-chemotherapy, 72.6%; R-chemotherapy, 64.1%), other time-to-event endpoints, or EOI response rates (by computed tomography [CT; G-chemotherapy, 81.8%; R-chemotherapy, 81.3%] and positron emission tomography CT [G-chemotherapy, 79.2%; R-chemotherapy, 87.5%]). All patients experienced ≥ 1 adverse event (AE). G-chemotherapy was associated with a higher incidence of grade 3–5 (86.1% versus 77.4%), grade 5 (14.9% versus 9.7%), and serious (66.3% versus 51.6%) AEs versus R-chemotherapy. Both arms had a higher incidence of grade 3–5 and serious AEs than patients with follicular lymphoma (GALLIUM), with G-chemotherapy being less tolerable than R-chemotherapy. Based on the observed tolerability of G-chemotherapy versus R-chemotherapy, and the comparable efficacy of G-chemotherapy and R-chemotherapy in this analysis, G-chemotherapy cannot be recommended as first-line treatment for MZL.

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INTRODUCTION

Marginal zone lymphoma (MZL) comprises a diverse group of B-cell malignancies that account for approximately 8% of all non-Hodgkin lymphomas (NHLs).^{1,2} MZL is classified into 3 subtypes based on molecular characteristics and sites involved: extranodal MZL (also known as mucosa-associated lymphatic tissue [MALT] lymphoma), splenic MZL, and nodal MZL.³ First-line treatment for symptomatic MZL varies according to subtype and underlying etiology but typically involves the anti-CD20 antibody, rituximab (R), as monotherapy or combined with chemotherapy (R-chemo).^{1,4–6}

In a previous study of 454 patients with MALT lymphoma, R plus chlorambucil was shown to have greater efficacy than either R or chlorambucil alone as a first-line treatment.^{7,8} A favorable outcome with R-chemo as a first-line treatment was also demonstrated in another study of 60 patients with MALT lymphoma.⁴ However, patients with MZL are often underrepresented in studies of other more common indolent NHLs, and there is a lack of large clinical trials evaluating immunochemotherapy in this population.⁹

Obinutuzumab (GA101; G) is a glycoengineered, type II anti-CD20 monoclonal antibody that increases direct cell death induction and antibody-dependent cell-mediated cytotoxicity/

antibody-dependent cellular phagocytosis compared with R.^{10–12} The Phase III GALLIUM (NCT01332968) trial evaluated the efficacy and safety of G plus chemotherapy (G-chemo) followed by G maintenance compared with R-chemo followed by R maintenance in patients with previously untreated advanced indolent NHL.¹³ Overall, 1401 patients were included in the GALLIUM trial: 1202 patients with previously untreated follicular lymphoma (FL) and 199 patients with previously untreated MZL.

This exploratory analysis evaluated the efficacy and safety of G-chemo followed by G maintenance compared with R-chemo followed by R maintenance in patients with previously untreated MZL in the GALLIUM trial.

MATERIALS AND METHODS

Study design and participants

The design of the phase III, randomized GALLIUM trial has been described elsewhere.¹³ Briefly, 1202 patients with previously untreated FL, and an additional cohort of up to 200 patients with MZL were enrolled (Suppl. Figure S1, online only). The number of patients with MZL enrolled in GALLIUM was based on a feasibility assessment completed prior to the trial; therefore, results from patients with MZL are exploratory only and not powered to detect relevant efficacy differences.

Patients had to be ≥ 18 years of age; have histologically documented, previously untreated, CD20-positive, indolent B-cell NHL consisting of FL, splenic, nodal, or extranodal MZL; stage III/IV or stage II bulky disease (≥ 7 cm) requiring treatment; at least 1 bidimensionally measurable lesion (> 2 cm in its largest dimension by computed tomography [CT] scan or magnetic resonance imaging); adequate hematologic function; and an Eastern Cooperative Oncology Group performance status of 0–2. For patients with splenic MZL, an enlarged spleen on a CT scan or extending ≥ 2 cm below the costal margin by physical examination constituted measurable disease. For an enlarged liver to constitute the only measurable disease parameter, a liver biopsy showing proof of NHL in the liver, was required. For patients with symptomatic splenic, nodal, or nongastric extranodal MZL, disease had to be previously untreated or had relapsed following local therapy only (ie, surgery or radiotherapy) and in need of therapy, as assessed by the investigator. For patients with symptomatic gastric extranodal MZL, it was a condition of entry that *Helicobacter pylori*-negative disease was *de novo* or had relapsed following local therapy and required treatment, as assessed by the investigator, or that *Helicobacter pylori*-positive disease had remained stable, progressed, or relapsed following antibiotic therapy and required treatment, as assessed by the investigator. Full inclusion/exclusion criteria have been published previously.¹³

Patients with MZL were randomized 1:1 separately from patients with FL, stratified by chemotherapy, International Prognostic Index (IPI), and geographic region, to induction treatment comprising either G (1000 mg on day [D] 1, 8, and 15 of cycle 1 and D1 of subsequent cycles), or R (375 mg/m² on D1 of each cycle) in combination with chemotherapy, for 6 or 8 cycles depending on chemotherapy regimen. The chemotherapy regimen was selected for each patient, individually, by the investigator and comprised either cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP; every 3 wk for 6 cycles), cyclophosphamide, vincristine, and prednisone (CVP; every 3 wk for 8 cycles), or bendamustine (benda; every 4 wk for 6 cycles). Patients who achieved a complete response (CR) or partial response at end of induction (EOI) continued to receive G or R as maintenance every 2 months for 2 years or until disease progression (PD).

The GALLIUM trial was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice, and the protocol was approved by the

ethics committees of all participating centers. All patients provided written informed consent.

Study endpoints

The primary endpoint in the FL population of the GALLIUM trial was investigator-assessed progression-free survival (PFS). In the MZL population, the following endpoints were exploratively evaluated: investigator-assessed PFS; overall survival (OS); time to next anti-lymphoma treatment (TTNT); overall response rate and CR rate at EOI by CT alone and CT incorporating positron emission tomography (PET); and safety. Investigator-assessed PFS by MZL subtype and chemotherapy arm was also explored.

PFS was defined as the time from randomization to the earliest event of progression, relapse, or death from any cause. PFS for patients without documented PD or death was censored at the time of the last tumor assessment. Tumor response was assessed using the modified response criteria for NHL, applied to the MZL population accordingly.¹⁴ Response assessments were performed after 3 cycles (in patients who received benda) or 4 cycles (in patients who received CHOP/CVP), on the completion of induction therapy, then every 2 months for 2 years (maintenance phase), and then every 3–6 months, with CT performed every 6–12 months, until progression or withdrawal from the trial.

Statistical analyses

Exploratory efficacy endpoints were assessed in all randomized patients with confirmed MZL (modified intent-to-treat [mITT] population). Safety was assessed in all patients who received any study treatment (safety-evaluable population). Kaplan-Meier estimates were used to describe PFS and other time-to-event endpoints; treatment arms were compared using log-rank tests, stratified by chemotherapy regimen, and IPI risk group. Hazard ratios (HRs) based on stratified Cox proportional-hazards models, including 95% confidence intervals (CIs), were used to estimate treatment effect. Cochran-Mantel-Haenszel tests were used to compare response rates.

Data access

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 here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase of patient reidentification.

RESULTS

Patient population and baseline demographics

Overall, 199 patients with MZL were randomized in the trial; however, 4 patients had another diagnosis and were excluded from this analysis. Therefore, 195 patients with MZL were included in the mITT population; of these, 99 patients were randomized to G-chemo and 96 patients were randomized to R-chemo (Suppl. Figure S2, online only).

Induction therapy was completed by 88 patients and maintenance therapy was completed by 57 patients in both the G-chemo and R-chemo arms. In total, 18 patients were withdrawn from study treatment during induction (G-chemo: $n = 11$ and R-chemo: $n = 7$) and 53 patients were withdrawn from study treatment during maintenance (G-chemo: $n = 27$ and R-chemo: $n = 26$); the most common reason for treatment withdrawal was adverse events (AEs).

Baseline characteristics were mostly well balanced between study arms and chemotherapeutic regimens (Table 1). The median age of patients in the mITT population was 63.0 years (range, 29–88; splenic, 63.0 y [range, 46–85 y]; nodal, 62.0 y [range, 30–80 y]; extranodal, 63.0 y [range, 29–88 y]), and 50.3% of the patients were male. Patient distribution by chemotherapy regimen was similar between treatment arms, with 73.7% versus 68.8% of patients in the benda group, 14.1% versus 18.8% of patients in the CHOP group and 12.1% versus 12.5% of patients in the CVP group, in the G-chemo and R-chemo arms (mITT population), respectively.

Efficacy

As of the clinical cutoff date, February 12, 2018, the median observation time for this analysis was 59.3 months (range, 0.2–76.3 mo). No significant difference was observed for the G-chemo arm compared with the R-chemo arm for PFS (4-y PFS rates: 72.6% and 64.1%, respectively; HR, 0.79; 95% CI, 0.47–1.31; $P = 0.35$; Table 2; Figure 1).

For investigator-assessed PFS by MZL subtype, no difference between subtypes was observed (Suppl. Figure S3, online only). For patients treated with G-chemo, 4-year PFS rates were: 67.0% (splenic), 75.6% (nodal), and 76.1% (extranodal); for patients treated with R-chemo, 4-year PFS rates were: 70.7% (splenic), 67.5% (nodal), and 55.4% (extranodal; Suppl. Figure S4). Similarly, no difference between subgroups was observed for investigator-assessed PFS by chemotherapy arm (4-y PFS rate [pooled treatment arms]: benda, 70.1%; CHOP, 63.0%; CVP, 62.4%; Suppl. Figure S3, online only).

Four-year OS rates were similar between treatment arms (G-chemo: 81.8% and R-chemo: 78.1%). Overall, 19 patients (19.2%) who received G-chemo and 22 patients (22.9%) who received R-chemo died during the trial (HR, 0.82; 95% CI, 0.44–1.51; $P = 0.52$; Table 2; Figure 2).

Four-year TTNT rates were slightly higher with G-chemo versus R-chemo (74.8% and 68.6%, respectively). In total, 26

patients (26.3%) in the G-chemo arm and 32 patients (33.3%) in the R-chemo arm received a subsequent anti-lymphoma therapy (HR, 0.75; 95% CI, 0.45–1.27; $P = 0.29$; Table 2; Figure 2).

At EOI, 81.8% of patients in the G-chemo arm and 81.3% of patients in the R-chemo arm achieved an overall response (OR) by CT alone ($P = 0.92$); similar OR rates were observed for CT incorporating PET (G-chemo: 79.2% and R-chemo: 87.5%; $P = 0.82$; Table 2). CR was also similar between arms by both CT alone (G-chemo: 17.2% and R-chemo: 17.7%) and CT incorporating PET (G-chemo: 45.8% and R-chemo: 59.4%).

Safety

The safety population included 101 patients in the G-chemo arm and 93 patients in the R-chemo arm (Table 3). A statistical analysis of the difference in AEs, specifically grade 5 AEs, between treatment arms was not possible due to the low number of events, and as the study was not powered for safety. Overall, all patients in both treatment arms experienced at least 1 AE (Table 3).

A higher incidence of grade 3–5 AEs occurred in the G-chemo arm (86.1%) compared with the R-chemo arm (77.4%) (Table 3). The most common grade 3–5 AEs were neutropenia (49.5%), thrombocytopenia (11.9%), and pneumonia (10.9%) in the G-chemo arm, and neutropenia (38.7%), infusion-related reactions (11.8%), and febrile neutropenia (9.7%) in the R-chemo arm (Suppl. Table S1, online only).

Grade 5 (fatal) AEs were more frequent in the G-chemo arm (14.9%; cardiac failure, general physical health deterioration, neutropenic sepsis, pneumonia, infective exacerbation of chronic obstructive airways disease, lower respiratory tract infection, lung infection, pneumonia fungal, sepsis, gastric cancer, lung adenocarcinoma, esophageal cancer, acute respiratory distress syndrome, chronic obstructive pulmonary disease, dyspnea [all $n = 1$]) compared with the R-chemo arm (9.7%; autoimmune hemolytic anemia, neutropenic sepsis, pneumonia, cholangiocarcinoma, ductal adenocarcinoma of pancreas, lung

Table 1.
Baseline Demographic and Disease Characteristics (Modified Intent-to-Treat Population).

Baseline Characteristic	G-Benda (n = 73)	G-CHOP (n = 14)	G-CVP (n = 12)	G-Chemo (Total) ^a (N = 99)	R-Benda (n = 66)	R-CHOP (n = 18)	R-CVP (n = 12)	R-Chemo (Total) ^b (N = 96)
Median age, y (range)	65.0 (36–85)	62.5 (40–76)	62.0 (48–75)	63.0 (36–85)	62.5 (29–88)	57.5 (40–71)	70.0 (50–78)	62.0 (29–88)
Male, n (%)	42 (57.5)	8 (57.1)	4 (33.3)	54 (54.5)	29 (43.9)	11 (61.1)	4 (33.3)	44 (45.8)
MZL subtype, n (%)								
Nodal	29 (39.7)	6 (42.9)	1 (8.3)	36 (36.4)	19 (28.8)	5 (27.8)	6 (50.0)	30 (31.3)
Extranodal	14 (19.2)	4 (28.6)	6 (50.0)	24 (24.2)	24 (36.4)	11 (61.1)	2 (16.7)	37 (38.5)
Splenic	30 (41.1)	4 (28.6)	5 (41.7)	39 (39.4)	23 (34.8)	2 (11.1)	4 (33.3)	29 (30.2)
Ann Arbor stage at diagnosis, n (%)								
I	6 (8.2)	0	0	6 (6.1)	0	0	0	0
II	1 (1.4)	0	0	1 (1.0)	1 (1.5)	1 (5.6)	1 (8.3)	3 (3.1)
III	8 (11.0)	1 (7.1)	1 (8.3)	10 (10.1)	10 (15.2)	1 (5.6)	3 (25.0)	14 (14.6)
IV	58 (79.5)	13 (92.9)	11 (91.7)	82 (82.8)	55 (83.3)	16 (88.9)	8 (66.7)	79 (82.3)
IPI score, n (%)								
Low (0–2)	39 (53.4)	6 (42.9)	5 (41.7)	50 (50.5)	35 (53.0)	11 (61.1)	4 (33.3)	50 (52.1)
High (3–4)	34 (46.6)	8 (57.1)	7 (58.3)	49 (49.5)	31 (47.0)	7 (38.9)	8 (66.7)	46 (47.9)
Any extranodal involvement, n (%)	67 (91.8)	14 (100.0)	11 (91.7)	92 (92.9)	60 (90.9)	16 (88.9)	9 (75.0)	85 (88.5)
Bone marrow involvement, n (%)	54 (74.0)	10 (71.4)	5 (45.5) ^c	69 (70.4) ^d	39 (62.9) ^e	10 (55.6)	8 (72.7) ^f	57 (62.6) ^g
Bulky disease (≥ 7 cm), n (%)	41 (56.2)	6 (42.9)	7 (58.3)	54 (54.5)	28 (42.4)	6 (33.3)	8 (66.7)	42 (43.8)

^a73.7%, 14.1% and 12.1% of patients in the benda, CHOP and CVP group, respectively.

^b68.8%, 18.8%, and 12.5% of patients in the benda, CHOP, and CVP group, respectively.

^c $n = 11$.

^d $n = 98$.

^e $n = 62$.

^f $n = 11$.

^g $n = 91$.

Benda = bendamustine; chemo = chemotherapy; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP = cyclophosphamide, vincristine, and prednisone; G = obinutuzumab; IPI = International Prognostic Index; MZL = marginal zone lymphoma; R = rituximab.

Table 2.
Overview of Efficacy (Modified Intent-to-Treat Population).

Variable	G-Chemo (N = 99)	R-Chemo (N = 96)
Median observation time ^a (range), mo	58.6 (0.6–76.0)	61.1 (0.2–76.3)
INV-assessed PFS		
Patients with event, n (%)	27 (27.3)	34 (35.4)
4-y PFS, % (95% CI)	72.6 (61.8–80.8)	64.1 (52.9–73.2)
Hazard ratio (95% CI) ^b	0.79 (0.47–1.31)	
P^c	0.35	
OS		
Patients with event, n (%)	19 (19.2)	22 (22.9)
4-y OS, % (95% CI)	81.8 (72.3–88.3)	78.1 (68.0–85.3)
Hazard ratio (95% CI) ^b	0.82 (0.44–1.51)	
P^c	0.52	
TTNT		
Patients with event, n (%)	26 (26.3)	32 (33.3)
4-y TTNT, % (95% CI)	74.8 (64.8–82.3)	68.6 (58.0–77.0)
Hazard ratio (95% CI) ^b	0.75 (0.45–1.27)	
P^c	0.29	
INV-assessed response at EOI by CT alone, n (%)		
ORR	81 (81.8)	78 (81.3)
P^d	0.92	
CR	17 (17.2)	17 (17.7)
P^d	0.83	
PR	64 (64.6)	61 (63.5)
P^d	0.80	
SD	4 (4.0)	1 (1.0)
P^d	0.17	
PD	3 (3.0)	3 (3.1)
P^d	0.92	
Unable to evaluate	6 (6.1)	7 (7.3)
Missing (NA)	5 (5.1)	7 (7.3)
INV-assessed response at EOI by CT incorporating PET, n (%)	N = 24	N = 32
ORR	19 (79.2)	28 (87.5)
P^d	0.82	
CR	11 (45.8)	19 (59.4)
P^d	0.80	
PR	8 (33.3)	9 (28.1)
P^d	0.92	
Unable to evaluate	5 (20.8)	1 (3.1)
Missing (NA)	0	3 (9.4)

^aObservation time is defined as the time from the minimum of randomization date/first study treatment administration date until the last date that the patient was known to be alive.

^bStratified analysis; stratification factors: IPI and chemotherapy regimen.

^cLog-rank test.

^dCochran-Mantel-Haenszel.

Chemo = chemotherapy; CI = confidence interval; CR = complete response; CT = computed tomography; EOI = end of induction; G = obinutuzumab; INV = investigator; IPI = International Prognostic Index; NA = not available; ORR = overall response rate; OS = overall survival; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; R = rituximab; SD = stable disease; TTNT = time to next anti-lymphoma treatment.

neoplasm malignant, non-small cell lung cancer, cerebrovascular accident, emphysema [all n = 1]) (Table 3); however, in total, the number of deaths due to any cause was lower in the G-chemo arm versus the R-chemo arm (19.2% versus 22.9%). Infections (n = 7); respiratory, thoracic, and mediastinal disorders (n = 3); and second malignancies (n = 3) were the most common fatal AEs in the G-chemo arm. The most common fatal AEs in the R-chemo arm were second malignancies (n = 4) and infections (n = 2). Some of the fatal infectious events in both arms occurred long after treatment discontinuation (G-chemo: neutropenic sepsis, D1333 [~3.6 y] and R-chemo: pneumonia, D1155 [~3.2 y]; Suppl. Table S2, online only). In the G-chemo arm, 40.0% of patients with a fatal AE had a Charlson comorbidity index score of 1–2, versus 22.2% in the R-chemo arm.

A higher serious adverse event (SAE) rate occurred in the G-chemo arm (66.3%) compared with the R-chemo arm (51.6%) (Table 3). The most common SAEs were pyrexia and pneumonia in the G-chemo arm (18.8% and 12.9%, respectively) and pyrexia and infusion-related reactions (both 7.5%) in the R-chemo arm. Patients treated with G-chemo experienced more grade 3–5 AEs and SAEs compared with patients treated with R-chemo, regardless of chemotherapy regimen.

AEs of special interest were also more frequent in the G-chemo arm compared with the R-chemo arm for infections (85.1% versus 74.2%, respectively) and balanced between arms for second neoplasms (12.9% versus 11.8%, respectively) (Table 3).

A similar number of patients discontinued treatment due to AEs in the G-chemo arm and the R-chemo arm (25.7% versus 20.4%, respectively; Table 3). Overall, the most common AE leading to treatment discontinuation was neutropenia in both the G-chemo and R-chemo arms (6.9% and 3.2%, respectively).

Neutropenia was the most common grade 3–5 AE in all chemotherapy arms, with a greater incidence occurring in patients treated with G versus R (G-benda, 45.9%; R-benda, 34.9%; G-CHOP, 64.3%; R-CHOP, 55.6%; G-CVP, 58.3%; R-CVP, 36.4%; Suppl. Table S1, online only). Fatal AEs were more frequent in the G-benda arm (13 patients [17.6%]) and R-benda arm (6 patients [9.5%]) compared with other chemotherapies (Table 3).

During the maintenance phase, 96.5% of patients in the G-chemo arm and 95.1% of patients in the R-chemo arm had an any grade AE. Grade 3–5 AEs were experienced by 40.7% of patients in the G-chemo arm and 45.7% of patients in the R-chemo arm, the most common of these was neutropenia in both arms (G-chemo, 14.0%; R-chemo, 18.5%). Four patients in each arm (G-chemo, 4.7%; R-chemo, 4.9%) had a fatal AE (Suppl. Table S3, online only).

Overall, 50.5% of patients in the G-chemo arm and 46.9% of patients in the R-chemo arm received prophylactic granulocyte-colony stimulating factor treatment.

DISCUSSION

Overall, the median observation time of this analysis of patients with MZL was 59.3 months. No notable difference in investigator-assessed PFS was observed between the 2 study arms. Consistent with this finding, no clinically relevant differences between G-chemo and R-chemo were observed for the other time-to-event endpoints (OS and TTNT). The efficacy results observed in this MZL population differ to the results observed in the FL population, in which, G-chemo resulted in significantly longer PFS than R-chemo.¹³

The 4-year PFS rate observed here for R-chemo (64.1%) was lower than the 5-year PFS rate in a prior study evaluating R-chemo in previously untreated patients with MALT lymphoma (R plus chlorambucil: 72%).^{7,8} This difference in efficacy could be due to the R-chemo-treated MALT population having a better baseline disease profile compared with the patients in this trial treated with G-chemo or R-chemo (Ann Arbor stage >2: 44.7% versus 92.9% and 96.9%; bone marrow involvement: 22.7% versus 70.4% and 62.6%, respectively); another factor that could have contributed to this efficacy difference is that GALLIUM also included patients with nodal and splenic MZL. The 4-year PFS rate reported here for R-chemo was also lower compared with the 5-year PFS rate with R monotherapy in another study in patients with MZL (64.1% versus 71%, respectively); however, only patients with splenic MZL were included in this study.¹⁵ Moreover, an open-label, single-arm, phase II study, also in patients with splenic MZL, observed a 3-year PFS rate of 90% with R-benda.¹⁶ Additionally, a phase II clinical trial that evaluated the efficacy and safety of R-benda in patients with MALT lymphoma demonstrated a 7-year PFS rate of 92.8%; however, this difference in efficacy could be due to a

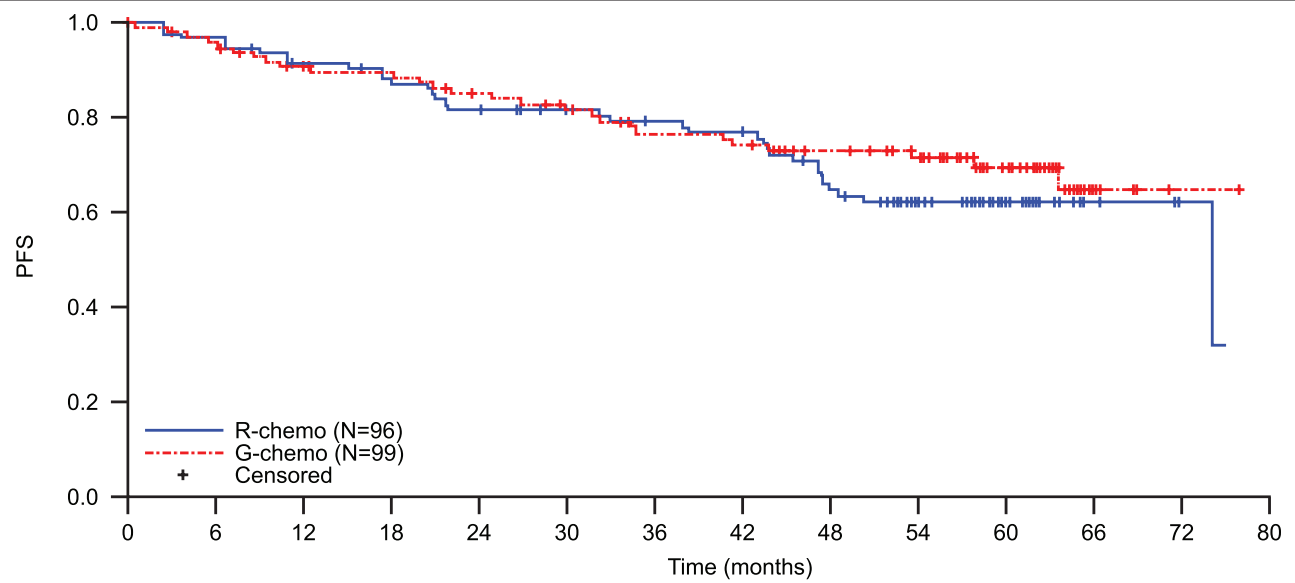


Figure 1. Kaplan-Meier plot of investigator-assessed progression-free survival in patients with MZL. Chemo = chemotherapy; G = obinutuzumab; MZL = marginal zone lymphoma; PFS = progression-free survival; R = rituximab.

greater number of patients with Ann Arbor stage III/IV disease included in the GALLIUM study compared with the aforementioned phase II trial (97% versus 34%, respectively).¹⁷

The safety results reported here showed an increased frequency and severity of AEs compared with the aforementioned trial evaluating immunochemotherapy with R-chemo in MALT lymphoma,^{7,8} and a trial evaluating targeted therapy with ibrutinib in patients with previously untreated MZL.⁹ Overall, there was a high incidence of grade 3–5 AEs, fatal AEs, and SAEs in both treatment arms of the MZL population of GALLIUM, with higher rates observed in patients who received G-chemo compared with R-chemo (grade 3–5 AEs, 86.1% versus 77.4%; fatal AEs, 14.9% versus 9.7%; SAEs, 66.3% versus 51.6%). Although the incidence of fatal AEs in this analysis was high, there was an extensive follow-up and some fatal AEs occurred long after the last study drug administration, with 1 case occurring on D2254 (~6.2 y).

The nature of the AEs was consistent with the profile observed in the FL population in the GALLIUM trial; however, compared with patients in the FL population, those with MZL had a higher incidence of grade 3–5 AEs in both treatment arms (G-chemo, 86.1% versus 79.2%; R-chemo, 77.4% versus 71.2%) and SAEs (G-chemo, 66.3% versus 48.7%; R-chemo, 51.6% versus 42.2%).¹⁸ In an attempt to alleviate the high incidence of AEs associated with chemotherapy, a number of phase II, chemotherapy-free clinical trials with novel agents are currently underway that may challenge the future use of immunochemotherapy and provide an alternative for patients with MZL.^{19,20} A greater proportion of patients in the MZL population compared with the FL population had extranodal involvement at baseline, which is expected due to the inclusion of patients with extranodal MZL (G-chemo, 92.9% versus 65.2%; R-chemo, 88.5% versus 65.9%), and bone marrow involvement at baseline (G-chemo, 70.4% versus 53.7%; R-chemo, 62.6% versus 49.3%), which could explain the worse safety profile observed in the MZL population.

The most common fatal AEs were infections; respiratory, thoracic, and mediastinal disorders; and second malignancies in the G-chemo arm, and second malignancies and infections in the R-chemo arm. Fatal infections occurred more frequently

in the G-chemo arm compared with the R-chemo arm. A higher proportion of patients who had a fatal AE in the G-chemo arm compared with the R-chemo arm had a Charlson comorbidity index score of 1–2 (40.0% versus 22.2%, respectively); this may be associated with the higher incidence of fatal AEs observed in the G-chemo arm compared with the R-chemo arm.

The evaluation of safety by chemotherapy arm is limited by the small number of patients in the CHOP and CVP arms, but no notable differences were observed between any of the chemotherapeutic arms.

Limitations of the current analysis include: the GALLIUM trial was not powered to detect significant differences in outcome in the MZL population; and the MZL subgroup was evaluated in a post hoc, rather than a prospectively defined analysis. Additionally, MZL subtypes (nodal, extranodal, and splenic) were not equally distributed among treatment groups, possibly due to the limited number of patients with MZL in the study.

To our knowledge, this is the largest trial comparing 2 anti-CD20 monoclonal antibodies in the immunochemotherapy of patients with previously untreated MZL; however, treatment guidelines still lack sufficient evidence, and future trials to investigate efficacious agents in MZL are required.¹

In conclusion, the current analysis of this large, randomized clinical trial in patients with previously untreated (or locally treated symptomatic) MZL did not indicate a difference in PFS between treatment arms. Both the G-chemo and R-chemo arms had a higher incidence of grade 3–5 AEs compared with previous trials evaluating immunochemotherapy in patients with MZL, with G-chemo being less tolerable than R-chemo. Based on these results, G-chemo cannot be recommended for the first-line treatment of patients with MZL; first-line therapy with R monotherapy should be considered as a less aggressive treatment option for this patient population. There remains a need for further studies to develop evidence-based treatment guidelines for previously untreated patients with MZL. At present, R-chemo remains the standard in first-line treatment for symptomatic MZL; bende as a chemotherapy backbone should be used with caution, especially in the elderly or frail and particularly during

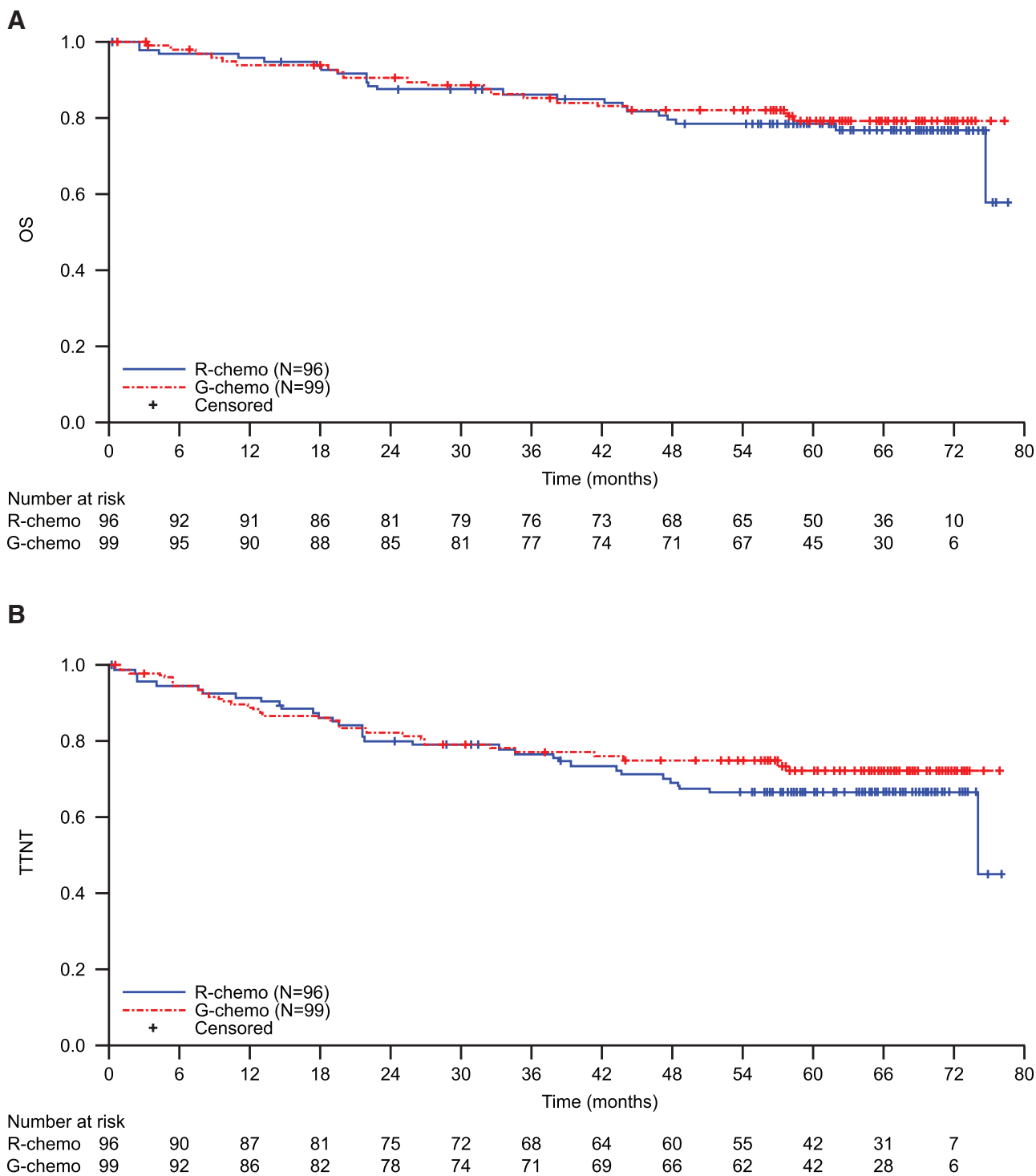


Figure 2. Kaplan–Meier plots of (A) overall survival and (B) time to next anti-lymphoma treatment. Chemo = chemotherapy; G = obinutuzumab; OS = overall survival; R = rituximab; TTNT = time to next anti-lymphoma treatment.

the coronavirus disease 2019 pandemic, and in this case, anti-bacterial and antiviral prophylaxis is recommended.

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AUTHOR CONTRIBUTIONS

MH, EH, WH, and RM were involved in study design. MH, WH, and RM conducted the study. MH, AT, MT, WH, and RM were involved in recruitment and follow-up of patients. MT involved in data collection. MH, EH, MT, TN, AK, and WH were involved in data analysis. MH, EH, MT, TN, AK, WH, and RM were involved in data interpretation.

Table 3.**Adverse Events^a by Chemotherapy Arm.**

n (%) of Patients Reporting ≥1 Event	G-Benda (n = 74)	G-CHOP (n = 14)	G-CVP (n = 12)	G-Chemo (Total) (N = 101) ^b	R-Benda (n = 63)	R-CHOP (n = 18)	R-CVP (n = 11)	R-Chemo (Total) (N = 93) ^b
Any AE	74 (100.00)	14 (100.0)	12 (100.0)	101 (100.0)	63 (100.0)	18 (100.0)	11 (100.0)	93 (100.0)
Grade 3–5 AE	64 (86.5)	13 (92.9)	10 (83.3)	87 (86.1)	48 (76.2)	15 (83.3)	8 (72.7)	72 (77.4)
Grade 5 AE	13 (17.6)	2 (14.3)	0	15 (14.9)	6 (9.5)	2 (11.1)	1 (9.1)	9 (9.7)
Infections	6 (8.1)	1 (7.1)	0	7 (6.9)	2 (3.2)	0	0	2 (2.2)
SAE	52 (70.3)	8 (57.1)	7 (58.3)	67 (66.3)	35 (55.6)	6 (33.3)	6 (54.5)	48 (51.6)
Any AESI								
Infections ^c	62 (83.8)	12 (85.7)	12 (100.0)	86 (85.1)	47 (74.6)	13 (72.2)	9 (81.8)	69 (74.2)
Second neoplasms ^d	12 (16.2)	0	1 (8.3)	13 (12.9)	7 (11.1)	3 (16.7)	1 (9.1)	11 (11.8)
AE leading to treatment discontinuation	21 (28.4)	1 (7.1)	3 (25.0)	26 (25.7)	15 (23.8)	2 (11.1)	1 (9.1)	19 (20.4)

^aSafety population (all randomized patients who received at least 1 dose of study drug; note: 3 patients randomized to R-chemo received G [n = 2] or no antibody [n = 1]).

^bIncludes 1 patient in each arm who did not receive chemotherapy.

^cAll events in MedDRA System Organ Class "Infections and Infestations."

^dStandardized MedDRA query for malignant or unspecified tumors occurring >6 mo after treatment.

AE = adverse event; AESI = adverse event of special interest; benda = bendamustine; chemo = chemotherapy; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP = cyclophosphamide, vincristine, and prednisone; G = obinutuzumab; MedDRA = Medical Dictionary for Regulatory Activities; R = rituximab; SAE = serious adverse event.

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MH received consultancy/advisory fees from Celgene, Gilead, and F. Hoffmann-La Roche Ltd; he received research funding from F. Hoffmann-La Roche Ltd. EH received travel support from F. Hoffmann-La Roche Ltd. AJ received honoraria and consultancy fees from Janssen, AbbVie, AstraZeneca, Beigene, Bristol-Meyers Squibb, MSD, Gilead, Novartis, Amgen, F. Hoffmann-La Roche Ltd, and Sanofi-Genzyme. HM received honoraria from Janssen and an advisory board role with AstraZeneca. AT served on an advisory board with BeiGene, AstraZeneca, Janssen, and AbbVie. MT received honoraria and consultancy fees from Janssen, Gilead Sciences, Bristol-Meyers Squibb, Amgen, AbbVie, Takeda, F. Hoffmann-La Roche Ltd, and MorphoSys, and honoraria from Incyte. TN and AK are employed by and have equity ownership interests in F. Hoffmann-La Roche Ltd. WH received honoraria from F. Hoffmann-La Roche Ltd, Janssen, Gilead Sciences, and Celgene; consulting/advisory fees from F. Hoffmann-La Roche Ltd, Janssen, and Gilead Sciences; speakers' bureau for F. Hoffmann-La Roche, 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. RM received honoraria from F. Hoffmann-La Roche Ltd and Janssen. All the other authors have no conflicts of interest to disclose.

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