Efficacy and safety of obinutuzumab for the first-line treatment of follicular lymphoma: a subgroup analysis of Chinese patients enrolled in the phase III GALLIUM study

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Abstract

Backgrounds: GALLIUM is a global phase III study that demonstrated significant improvements in progression-free survival (PFS) for obinutuzumab plus chemotherapy (G-chemo) *vs*. rituximab plus chemotherapy (R-chemo) in previously untreated patients with follicular lymphoma (FL). This study aimed to report the results of a subgroup of patients in China.

Methods: Patients were randomized to G-chemo or R-chemo. Responders received maintenance therapy for 2 years or until disease progression. The primary endpoint was investigator (INV)-assessed PFS. Secondary endpoints included the overall response rate (ORR) and complete response rate (CRR) at the end of induction chemotherapy, overall survival (OS), and safety.

Results: Overall, 58 patients with FL were randomized to the G-chemo ($n = 25$) and R-chemo arms ($n = 33$). The INV-assessed PFS rate at 3 years was 81.8% in the G-chemo arm, *vs*. 70.2% in the R-chemo arm (hazard ratio 0.35; 95% confidence interval: 0.09–1.34; $P = 0.1120$). The INV-assessed CRRs (without positron emission tomography [PET]) in these arms were 24.0% and 21.2%, respectively, whereas the ORRs were 80.0% and 90.9%, respectively. INV-assessed CRR-PET was 52.6% in the G-chemo, *vs*. 60.9% in the R-chemo. Median OS was not reached in either arm. Grade 3 to 5 adverse events were more frequent in the R-chemo arm (97.0% *vs*. 88.0%).

Conclusions: The results of this subgroup analysis were consistent with those of the global population, and they suggest that G-chemo has a positive benefit–risk profile in patients from China with FL.

Trial registration: ClinicalTrials.gov, No. NCT01332968.

Keywords: Chinese; Follicular lymphoma; GALLIUM; Obinutuzumab; Rituximab

Introduction

Follicular lymphoma (FL) is the most common type of indolent B-cell non-Hodgkin lymphoma (NHL). Overall, FL is less common in China than in the United States and Western Europe, accounting for <10% of NHL cases.[1-3] However, a recent study found that the mortality rates of lymphoma and myeloma in China increased annually between 2004 and 2016. The incidence, mortality, and prevalence of FL within China vary by geographic region and ethnic group.[4]

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Over the last two decades, immunochemotherapy with the anti-CD20 monoclonal antibody rituximab has significantly improved outcomes in patients with FL.[5-8] Chinese guidelines for the first-line treatment of FL currently recommend rituximab in combination with chemotherapy. These combinations include rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); rituximab plus cyclophosphamide, vincristine, and prednisone (CVP); and rituximab plus bendamustine.[3,9,10]

Obinutuzumab (GA101) is a glycoengineered type II anti-CD20 monoclonal antibody, compared to rituximab, has improved pharmacodynamic properties including greater antibody-dependent cytotoxicity and enhanced direct B-cell death, and these effects translate into improved clinical outcomes.[11,12] Recently updated US National Comprehensive Cancer Network guidelines recommend the use of obinutuzumab in combination with chemotherapy (G-chemo) for patients with previously untreated FL.[13] Furthermore, G-chemo is approved in the United States and Europe for treating patients with previously untreated FL.[14,15]

GALLIUM is an ongoing global phase III study comparing the efficacy and safety of G-chemo with rituximab plus chemotherapy (R-chemo), followed by maintenance with obinutuzumab or rituximab alone in previously untreated patients with indolent NHL.[16] The GALLIUM study demonstrated that G-chemo was associated with significantly better progression-free survival (PFS; primary endpoint) than R-chemo in previously untreated patients with FL,[16] and clinically meaningful improvements were observed after a median follow-up of >6 years.[17]

To date, trials of obinutuzumab in Chinese patients have not demonstrated any ethnic differences. For example, in the GERSHWIN trial of patients with relapsed/refractory NHL, the safety and efficacy of obinutuzumab monotherapy in Chinese patients with B-cell lymphoma were similar to those of previous studies of non-Chinese patients.[18] A subgroup analysis (Chinese subgroup) was conducted in patients with FL enrolled in the GALLIUM study across 13 study sites in China. This analysis aimed to evaluate the efficacy and safety of G-chemo in patients from China with previously untreated FL and determine whether the benefit–risk balance of G-chemo in these patients is consistent with that observed in the global study population.

Methods

Ethics approval

The study was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice, and the study protocol was approved by all relevant local Ethics Committees (No. A2013-005-07). All patients provided written informed consent.

Patient population

The eligibility criteria were as follows: ≥18 years old; histologically documented, previously untreated, CD20-positive FL (grade 1–3a); advanced disease (stage III/IV, or stage II with largest tumor diameter ≥ 7 cm); at least one bidimensionally measurable lesion; Eastern Cooperative Oncology Group performance status 0 to 2; adequate hematologic function; and a requirement for treatment according to the Groupe d'Étude des Lymphomes Folliculaires criteria.[19]

Study design and treatments

This was an exploratory subgroup analysis of patients enrolled into the phase III, open-label, multicenter, randomized GALLIUM study at sites in China (hereafter referred to as Chinese patients). Patients were enrolled between April 24, 2013 and December 28, 2013 and randomized (1:1) to receive intravenous infusions of obinutuzumab at a dose of 1000 mg (on days 1, 8, and 15 of cycle one and on day 1 of subsequent cycles) or rituximab at a dose of 375 mg/m^2 of body surface area (on day 1 of each cycle) for six or eight cycles depending on the chemotherapy regimen. The choice of chemotherapy was decided by each study center, and the regimen consisted of either six cycles of CHOP or eight cycles of CVP. Although bendamustine was approved in many countries at the time of enrollment, it was not approved for treatment in China; therefore, no patients in the Chinese subpopulation received bendamustine. Patients who were allocated to the CHOP regimen received antibody monotherapy for an additional two cycles (ie, eight cycles of obinutuzumab or rituximab in total). Patients with a complete response (CR) or partial response at the end of induction (EOI) therapy received maintenance therapy with obinutuzumab 1000 mg or rituximab 375 mg/m^2 every 2 months for 2 years or until disease progression. Patients with stable disease did not receive maintenance therapy [Supplementary Figure 1, http://links.lww.com/CM9/A746].

Study endpoints

The primary endpoint of GALLIUM was investigator (INV)-assessed PFS (defined as the time from randomization to progression, relapse, or death from any cause). Secondary endpoints included PFS assessed by an independent review committee (IRC), the overall response rate (ORR) and CR rate at EOI, overall survival (OS), event-free survival (EFS), disease-free survival (DFS), the duration of response (DOR), and the time to new anti-lymphoma treatment (TTNALT). Safety was monitored throughout the study.

Assessments

Tumor response was assessed according to the Revised Response Criteria for Malignant Lymphoma[20] with and without ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET). Assessments included computed tomography (CT), magnetic resonance imaging if CT was contraindicated, and bone marrow biopsy. Response was assessed after four CHOP or CVP treatment cycles, at EOI, and then every 2 months for 2 years (maintenance phase). Further assessments were performed every 3 to 6 months thereafter, with CT performed every 6 to 12 months, until progression or study withdrawal. Adverse events (AEs),

serious AEs (fatal, life threatening, prolongs inpatient hospitalization, persistent or significant disability/incapacity, induce later fertility abnormalities etc; SAEs), and AEs of special interest (AESIs) were assessed throughout the study.

Statistical analyses

The clinical cut-off date was September 10, 2016 for both the global and Chinese subgroup efficacy analyses (snapshot: November 25, 2016) and safety analysis (snapshot: May 5, 2017). For the global GALLIUM population, the sample size was calculated to give the trial 80% power to detect a difference in PFS between the treatment groups that corresponded to a 26% lower risk of progression, relapse, or death for the G-chemo group compared to the R-chemo group. The study was not powered to detect differences in an exploratory single-country subgroup analysis.

Efficacy analyses included all randomized patients with FL (intent-to-treat [ITT] population). All patients with FL who received any study treatment were included in the safety analysis. Time-to-event endpoints (including PFS) were described using Kaplan-Meier estimates, and treatment arms were compared using log-rank tests stratified by the type of chemotherapy and Follicular Lymphoma International Prognostic Index (FLIPI). Treatment effect estimates were expressed as hazard ratios (HRs) based on stratified Cox proportional-hazards models and presented with 95% confidence intervals (CIs). Response rates were compared using stratified Cochran-Mantel-Haenszel tests. Two-sided *P* values were reported. Statistical analyses were conducted using SAS v9.4 (SAS Institute, Inc., Cary, NC, USA).

Full details of the study methodology have been previously published.[16]

Results

Patients characteristics

The characteristics of the Chinese subgroup are presented in Figure 1. In total, 58 patients with FL were enrolled from 13 study sites in China and included in the efficacy analysis (Chinese ITT subpopulation: G-chemo, $n = 25$; R-chemo, $n = 33$). All randomized patients with FL in the Chinese subpopulation received study treatment, and they were included in the safety analysis. Overall, 20 (80.0%) patients in the G-chemo group and 29 patients (87.9%) in the R-chemo group completed induction therapy, and maintenance therapy was completed by 18 (72.0%) patients in the G-chemo arm and 21 (63.6%) patients in the R-chemo arm. At the clinical cut-off date, 19 patients had withdrawn from the study (G-chemo, $n = 7$; R-chemo, $n = 12$) as presented in Figure 1.

Baseline demographic characteristics were generally well balanced across the two treatment arms. The prevalence of advance disease was higher in the G-chemo arm than in the R-chemo arm [Table 1]. The majority of patients were allocated to receive CHOP chemotherapy (R-chemo, 93.9%; G-chemo, 88.0%), and the remaining patients received CVP. The median time on study was 37.1 months (range: 0.9–40.6).

Efficacy

The results for INV-assessed PFS in the Chinese ITT subpopulation are presented in Figure 2A. Treatment with G-chemo resulted in a clinically meaningful (65%) reduction in the risk of progression or death compared to R-chemo. The number of PFS events was four (16.0%) in the G-chemo arm, *vs*. nine (27.3%) in the R-chemo arm (HR = 0.35; 95% CI = 0.09–1.34; $P = 0.112$, stratified log-rank test). The estimated proportion of patients who were progression-free at 3 years was 81.8% (95% CI = 58.5–

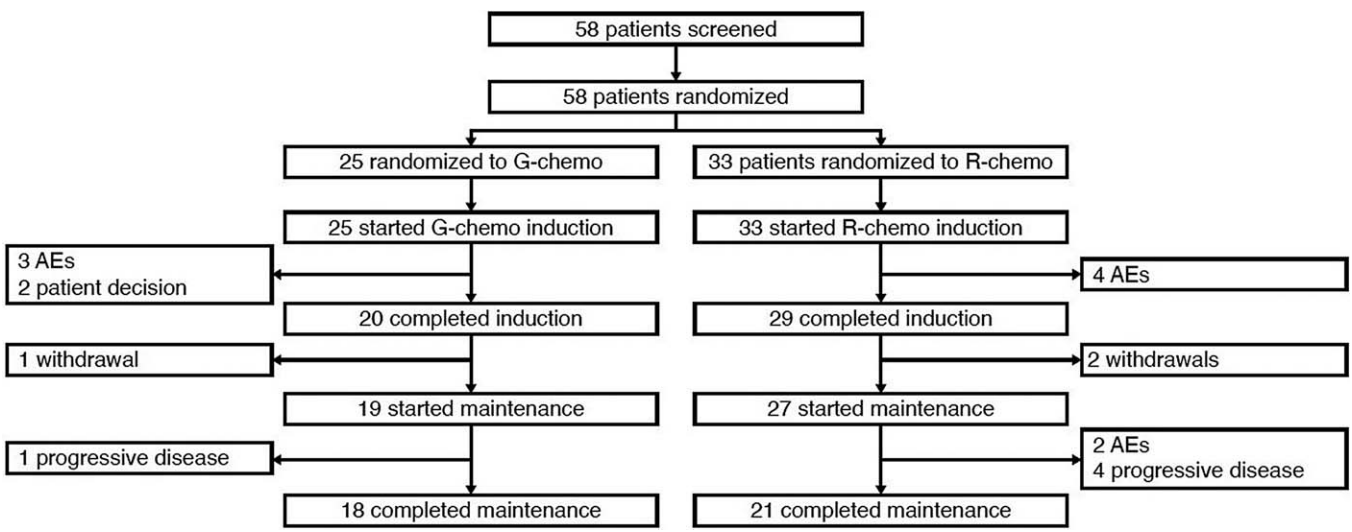

Figure 1: Flowchart of patient treatment. AE: Adverse event; G-chemo: Obinutuzumab-chemotherapy; R-chemo: Rituximab-chemotherapy.

Table 1: Baseline patient demographics and disease characteristics (Chinese ITT subpopulation).

Characteristic	G-chemo (n = 25)	R-chemo (n = 33)
Median age, years (range)	52 (31–67)	48 (31–79)
Male, n (%)	12 (48.0)	16 (48.5)
ECOG PS 0–1, n (%)	25 (100.0)	33 (100.0)
Ann Arbor stage at diagnosis, n (%)		
I	1 (4.2)	0
II	0	1 (3.0)
III	11 (45.8)	25 (75.8)
IV	12 (50.0)	7 (21.2)
Missing	1	0
FLIPI, n (%)		
Low (0, 1)	7 (28.0)	8 (24.2)
Intermediate (2)	7 (28.0)	16 (48.5)
High (≥3)	11 (44.0)	9 (27.3)
FLIPI 2, n (%)		
Low (0)	5 (20.0)	8 (24.2)
Intermediate (1–2)	12 (48.0)	19 (57.6)
High (≥3)	8 (32.0)	6 (18.2)
Bone marrow involvement, n (%)	9 (36.0)	7 (21.2)
Extranodal involvement, n (%)	12 (48.0)	13 (39.4)
Bulky disease (≥ 7 cm), n (%)	10 (40.0)	12 (36.4)
B-symptoms*	10 (40.0)	16 (48.5)
Median time from initial diagnosis to randomization, months (range)	1.23 (0.3–31.5)†	1.38 (0.2–33.5)
Chemotherapy regimen, n (%)		
CHOP	22 (88.0)	31 (93.9)
CVP	3 (12.0)	2 (6.1)

*Fever, night sweats, and/or weight loss. †Data missing for one patient. CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: Cyclophosphamide, vincristine, and prednisone; ECOG PS: Eastern Cooperative Oncology Group performance status; FLIPI: Follicular Lymphoma International Prognostic Index; G-chemo: Obinutuzumab chemotherapy; ITT: Intent-to-treat; R-chemo: Rituximab chemotherapy.

92.8) in the G-chemo arm, *vs.* 70.2% (95% CI = 50.5–83.2) in the R-chemo arm [Figure 2A].

The results of PFS based on IRC assessments were consistent with the analysis of INV-assessed PFS. In total, there were 14 IRC-assessed PFS events in the Chinese subpopulation, including 4 (16.0%) events in the G-chemo arm and 10 (30.3%) events in the R-chemo arm (stratified HR = 0.29; 95% CI = 0.08–1.11; P = 0.058; Figure 2B). At the clinical cut-off date, the 3-year OS rate was 95.5% (95% CI = 71.9–99.4) in the G-chemo arm, compared to 90.2% (95% CI = 72.5–96.7) in the R-chemo arm (P = 0.45). Median OS was not reached in either treatment arm [Figure 2C].

Based on the INV assessment (CT and clinical data without FDG-PET), the CR rate in the G-chemo arm was 24.0% (95% CI = 9.4–45.1), and the ORR was 80.0% (95% CI = 59.3–93.2). In the R-chemo arm, the CR rate was 21.2% (95% CI = 9.0–38.9), and the ORR was 90.9% (95% CI = 75.7–98.1). The INV-assessed CR rates with PET for G-chemo and R-chemo were 52.6% and 60.9%, respectively [Table 2].

Comparisons of the two treatment arms with respect to INV-assessed secondary efficacy endpoints (DOR, DFS, EFS, and TTNALT) are summarized in Supplementary Table 1, http://links.lww.com/CM9/A746.

The results of subgroup analyses of PFS (by INV and IRC assessment) according to baseline demographics, prognostic factors, and stratification factors are presented in Supplementary Figure 2, http://links.lww.com/CM9/A746.

Safety

All Chinese patients in both treatment arms experienced at least one AE (any grade) [Table 3]. The most common AEs (≥30% in either treatment arm, G-chemo *vs.* R-chemo) were leukopenia (72.0% *vs.* 78.8%), neutropenia (64.0% *vs.* 72.7%), infusion-related reaction (IRR; 56.0% *vs.* 45.5%), pyrexia (48.0% *vs.* 36.4%), thrombocytopenia (40.0% *vs.* 21.2%), increased alanine aminotransferase levels (36.0% *vs.* 21.2%), bone marrow failure (32.0% *vs.* 15.2%), and alopecia (16.0% *vs.* 36.4%). All AEs affecting ≥10% of patients in either treatment arm are presented in Supplementary Table 2, http://links.lww.com/CM9/A746. A higher proportion of patients in the G-chemo arm experienced SAEs (44.0% *vs.* 33.3%) [Table 3]. The most common SAEs (G-chemo *vs.* R-chemo) were febrile neutropenia (4.0% *vs.* 6.1%), sinus bradycardia (8.0% *vs.* 0.0%), lung infection (4.0% *vs.* 9.1%), IRR (8.0% *vs.* 0.0%), interstitial lung disease (8.0% *vs.* 9.1%), and hypotension (8.0% *vs.* 0.0%), whereas all other SAEs were isolated cases.

The incidence of grade 3 to 5 AEs, AESIs, and AEs leading to discontinuation or dose modification of any study drug is summarized in Table 3. Overall, the incidence of grade 3 to 5 AEs in the Chinese subpopulation was numerically higher in the R-chemo arm (97.0%) than in the G-chemo

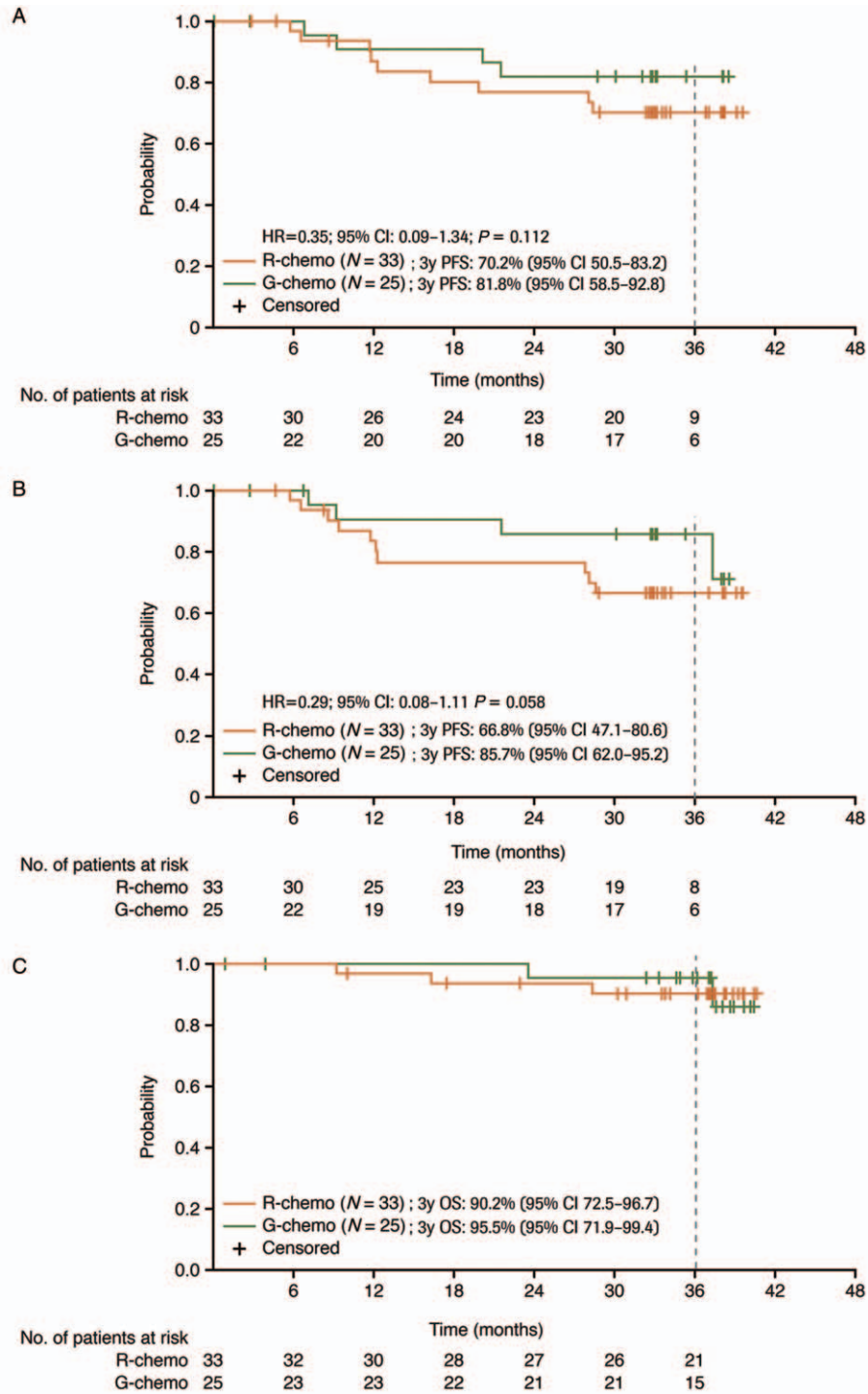

Figure 2: Kaplan-Meier curves of (A) INV-assessed PFS, (B) IRC-assessed PFS, and (C) OS (Chinese ITT subpopulation). G-chemo: Obinutuzumab chemotherapy; INV: Investigator; IRC: Independent review committee; ITT: Intent-to-treat; OS: Overall survival; PFS: Progression-free survival; R-chemo: Rituximab chemotherapy.

arm (88.0%). The incidence of grade 3 to 5 IRR was 12.1% in the R-chemo arm, *vs.* 20.0% in the G-chemo arm. No patients withdrew from treatment because of an IRR. AEs leading to dose modifications were more frequent in the G-chemo arm (80.0%) than in the R-chemo arm (63.6%).

Two patients (6.1%) in the R-chemo arm experienced a fatal AE. One patient experienced grade 5 lung adenocarcinoma, which was considered by the INV to be related to study treatment, and the other patient had a cerebrovascular accident considered unrelated to treatment. There were no deaths attributable to AEs in the G-chemo arm.

Discussion

This subgroup analysis of the GALLIUM study demonstrated the efficacy and safety of G-chemo in 58 Chinese

Table 2: Comparison of INV- and IRC-assessed EOI response rates without and with PET (Chinese ITT subpopulation).

Variables	INV-assessed		IRC-assessed	
	G-chemo ($n = 25$)	R-chemo ($n = 33$)	G-chemo ($n = 25$)	R-chemo ($n = 33$)
Without PET				
CR or PR, *n/N* (%)	20/25 (80.0)	30/33 (90.9)	21/25 (84.0)	29/33 (87.9)
CR, *n/N* (%)	6/25 (24.0)	7/33 (21.2)	10/25 (40.0)	11/33 (33.3)
With PET				
CR or PR, *n/N* (%)	16/19 (84.2)	19/23 (82.6)	16/19 (84.2)	18/23 (78.3)
CR, *n/N* (%)	10/19 (52.6)	14/23 (60.9)	14/19 (73.7)	12/23 (52.2)

CR: Complete response; EOI: End of induction; G-chemo: Obinutuzumab chemotherapy; INV: Investigator; IRC: Independent review committee; ITT: Intent-to-treat; PET: Positron emission tomography; PR: Partial response; R-chemo: Rituximab chemotherapy.

Table 3: Summary of AEs after treatment of G-chemo or R-chemo (*n* [%]).

Variable	G-chemo ($n = 25$)	R-chemo ($n = 33$)
Any AE	25 (100.0)	33 (100.0)
Grade 1 to 2	3 (12.0)	1 (3.0)
Grade 3 to 4	22 (88.0)	30 (90.9)
Grade 5	0	2 (6.1)[§]
Serious AE	11 (44.0)	11 (33.3)[‖]
AE leading to discontinuation of any study drug[*]	3 (12.0)	7 (21.2)
AE leading to dose modification of any treatment	20 (80.0)	21 (63.6)
AESI (any grade)[†]		
Neutropenia	18 (72.0)	25 (75.8)
Infection	9 (36.0)	15 (45.5)
IRR	16 (64.0)	15 (45.5)
Thrombocytopenia	10 (40.0)	7 (21.2)
Acute thrombocytopenia	2 (8.0)	0
Hemorrhagic event	1 (4.0)	1 (3.0)
Cardiac AE	8 (32.0)	3 (9.1)
Tumor lysis syndrome	0	0
GI perforation	0	0
Second malignancy	0	2 (6.1)[¶]
Hepatitis B reactivation[‡]	1 (4.0)	1 (3.0)

[*] Chemotherapy, G or R. [†]Grade 3 to 5 AESI (G-chemo *vs*. R-chemo): neutropenia, 60.0% *vs*. 72.7%; infections, 12.0% *vs*. 24.2%; IRR, 20.0% *vs*. 12.1%; thrombocytopenia, 20.0% *vs*. 6.1%, acute thrombocytopenia 4.0% *vs*. 0; hemorrhagic events, 0 *vs*. 3.0%; cardiac AEs, excluding IRR, 4.0% *vs*. 0. [‡]One grade 1AE during maintenance (G-chemo) and one grade 3 AE during induction (R-chemo). [§]Lung adenocarcinoma ($n = 1$) and cerebrovascular accident ($n = 1$). [‖]Includes two grade 5 AE. [¶]One grade 1 AE and one grade 5 AE. AEs: Adverse event; AESI: AE of special interest; G-chemo: Obinutuzumab chemotherapy; GI: Gastrointestinal; IRR: Infusion-related reaction; R-chemo: Rituximab chemotherapy.

patients with previously untreated FL. G-chemo produced a clinically meaningful improvement in INV-assessed PFS *vs*. R-chemo, and AEs were manageable. Overall, the data were comparable with the results from the global GALLIUM FL population. At the time of the current analysis, the OS results were relatively immature.

EOI response rates according to CT were similar between the R-chemo and G-chemo arms and comparable to those reported in the global GALLIUM FL population.[16] In this study, response was assessed both with and without PET imaging at EOI. The response assessment with PET, which more accurately identifies residual lymphoma than CT alone, may be prognostic for outcome.[21] In the global GALLIUM FL population, the CR rates were comparable between the arms; however, because of the limited sample size of the Chinese subpopulation, no firm conclusions can be drawn in the present analysis.

Overall, the nature and severity of AEs reported in Chinese patients in the G-chemo arm were consistent with the safety profile observed in the global FL population in the GALLIUM study,[16] as well as the already known safety profile of G-chemo. There were no unexpected safety findings for obinutuzumab, and AEs were clinically manageable. The incidence of thrombocytopenia (G-chemo, 40.0%; R-chemo, 21.2%), neutropenia (G-chemo, 72.0%; R-chemo, 75.8% R-chemo), and grade 3 to 5 IRRs (G-chemo, 20.0%; R-chemo, 12.1%) was higher in the Chinese subpopulation than in the global FL population in both treatment arms (thrombocytopenia: G-chemo, 11.4%; R-chemo, 7.5%; neutropenia: G-chemo, 51.3%; R-chemo, 45.1%; grade 3 to 5 IRRs: G-chemo, 12.4%; R-chemo, 6.7%). Of note, the higher incidence of neutropenia did not lead to an increased incidence of infection, which may have been mitigated by the use of granulocyte colony-stimulating factor prophylaxis in the G-chemo arm

(number of patients receiving granulocyte colony stimulating factor: G-chemo, 14 [56.0%]; R-chemo, 18 [54.5%]). In contrast to the global FL population, grade 3 to 5 AEs were more frequent in patients receiving R-chemo (97.0%) than in those receiving G-chemo (88.0%).

Although the patient and disease characteristics at baseline were generally similar between the treatment groups, Chinese patients in the G-chemo arm tended to have higher rates of advanced-stage disease (FLIPI $\geq$ 3) than those in the R-chemo arm. The choice of chemotherapy regimens in China differed from the global GALLIUM FL population, which may have been influenced by the higher proportion of patients with a high FLIPI in the Chinese population and differences in the age of patients at baseline (ie, the Chinese subpopulation was younger than the global FL population [median age: G-chemo, 52 *vs*. 60 years; R-chemo, 48 *vs*. 58 years]). The number of patients allocated to receive CHOP was higher in the Chinese subpopulation (R-chemo, 93.9%; G-chemo, 88.0%) than in the global FL population (R-chemo, 33.8%; G-chemo, 32.4%). AE profiles may have been influenced by the selection of chemotherapy. An exploratory analysis of the GALLIUM results in Japanese patients also demonstrated high rates of neutropenia, and this finding was possibly related to the extensive use of CHOP chemotherapy because bendamustine was only approved in Japan in December 2016.[22]

The limitations of this Chinese subpopulation analysis included the small number of patients in each treatment arm, which limited the interpretation of the results because of the insufficient power to detect between-group differences. Furthermore, because this trial was not designed to compare CHOP and CVP chemotherapy regimens and because the selection of chemotherapy regimens was not randomized, there may be confounding differences between the CHOP and CVP subgroups regarding the baseline characteristics of patients.

In conclusion, the results of this exploratory analysis of Chinese patients with previously untreated FL in the GALLIUM study were consistent with the results of the global GALLIUM FL population, which revealed clinically meaningful improvements in PFS in the G-chemo arm in the first-line setting. Furthermore, the results of this subgroup analysis support G-chemo as a well-tolerated and effective treatment option for previously untreated Chinese patients with FL.

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Conflicts of interest

Anastasiia Kinkolykh is a consultant at F. Hoffmann-La Roche Ltd. (Basel, Switzerland) via GCE Solutions – an IQVIA business. Andrea Knapp is an employee of F. Hoffmann-La Roche Ltd. All other authors declare that they have no competing interests.

Availability of Data and Materials

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available online (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

References

1. Li XQ, Li GD, Gao ZF, Zhou XG, Zhu XZ. Distribution pattern of lymphoma subtypes in China: a nationwide multicenter study of 10002 cases. J Diagn Concepts Pract 2012;11:111–115.
2. Yang QP, Zhang WY, Yu JB, Zhao S, Xu H, Wang WY, *et al*. Subtype distribution of lymphomas in Southwest China: analysis of 6382 cases using WHO classification in a single institution. Diagn Pathol 2011;6:77. doi: 10.1186/1746-1596-6-77.
3. National Health Commission of the People's Republic of China. Chinese guidelines for diagnosis and treatment of malignant lymphoma 2018 (English version). Chin J Cancer Res 2019;31:557–577. doi: 10.21147/j.issn.1000-9604.2019.04.01.
4. Liu W, Liu J, Song Y, Wang X, Zhou M, Wang L, *et al*. Mortality of lymphoma and myeloma in China, 2004-2017: an observational study. J Hematol Oncol 2019;12:22. doi: 10.1186/s13045-019-0706-9.
5. Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, *et al*. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725–3732. doi: 10.1182/blood-2005-01-0016.
6. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, *et al*. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105:1417–1423. doi: 10.1182/blood-2004-08-3175.
7. Herold M, Haas A, Srock S, Neser S, Al-Ali KH, Neubauer A, *et al*. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. J Clin Oncol 2007;25:1986–1992. doi: 10.1200/JCO.2006.06.4618.
8. Salles G, Mounier N, de Guibert S, Morschhauser F, Doyen C, Rossi JF, *et al*. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. Blood 2008;112:4824–4831. doi: 10.1182/blood-2008-04-153189.
9. Hematology Committee of Chinese Medical Association; Hematological Oncology Committee of China Anti-Cancer Association; Chinese Working Group for Chronic Lymphocytic Leukemia. The guidelines for diagnosis and treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma in China (2018 edition) (in Chinese). Natl Med J China 2018;39:353–358. doi: 10.3760/cma.j.issn.0253-2727.2018.05.001.
10. Hematology Branch of Chinese Medical Association, China. Guidelines for the diagnosis and treatment of follicular lymphoma in, China. Cancer Biol Med 2013;10:36–42. doi: 10.7497/j.issn.2095-3941.2013.01.006.
11. Mössner E, Brünker P, Moser S, Püntener U, Schmidt C, Herter S, *et al*. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 2010;115:4393–4402. doi: 10.1182/blood-2009-06-225979.
12. Klein C, Jamois C, Nielsen T. Anti-CD20 treatment for B-cell malignancies: current status and future directions. Expert Opin Biol Ther 2021;21:161–181. doi: 10.1080/14712598.2020.1822318.

13. NCCN Guidelines for Treatment of Cancer by Site. B-cell Lymphomas; 2020. Available from: http://www.nccn.org/. [Last accessed on May 12, 2020]
14. GAZYVARO Summary of Product Characteristics; 2019. Available from: https://www.ema.europa.eu/en/documents/product-information/gazyvaro-epar-product-information_en.pdf. [Last accessed on February 6, 2020]
15. GAZYVA Highlights of Prescribing Information. Genentech Inc.; 2017. Available from: https://www.gene.com/download/pdf/gazyva_prescribing.pdf. [Last accessed on January 8, 2020]
16. Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C, *et al*. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 2017;377:1331–1344. doi: 10.1056/NEJMoa1614598.
17. Townsend W, Buske C, Cartron G, Cunningham D, Dyer MJS, Gribben JG, *et al*. Comparison of efficacy and safety with obinutuzumab plus chemotherapy versus rituximab plus chemotherapy in patients with previously untreated follicular lymphoma: updated results from the phase III Gallium Study. J Clin Oncol 2020;38 Suppl:8023–8023. doi: 10.1200/JCO.2020.38.15_suppl.8023.
18. Qin Y, Song Y, Shen Z, Du X, Ji W, Hsu W, *et al*. Safety and efficacy of obinutuzumab in Chinese patients with B-cell lymphomas: a secondary analysis of the GERSHWIN trial. Cancer Commun (Lond) 2018;38:31. doi: 10.1186/s40880-018-0300-5.
19. Brice P, Bastion Y, Lepage E, Brousse N, Haïoun C, Moreau P, *et al*. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1997;15:1110–1117. doi: 10.1200/jco.1997.15.3.1110.
20. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, *et al*. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–586. doi: 10.1200/jco.2006.09.2403.
21. Trotman J, Luminari S, Boussetta S, Versari A, Dupuis J, Tychyj C, *et al*. Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. Lancet Haematol 2014;1:e17–e27. doi: 10.1016/s2352-3026(14)70008-0.
22. Ohmachi K, Tobinai K, Kinoshita T, Ishikawa T, Hatake K, Ichikawa S, *et al*. Efficacy and safety of obinutuzumab in patients with previously untreated follicular lymphoma: a subgroup analysis of patients enrolled in Japan in the randomized phase III GALLIUM trial. Int J Hematol 2018;108:499–509. doi: 10.1007/s12185-018-2497-0.

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