International Journal of Hematology (2018) 108:499–509
https://doi.org/10.1007/s12185-018-2497-0

ORIGINAL ARTICLE

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

Ken Ohmachi[1] · Kensei Tobinai[2] · Tomohiro Kinoshita[3] · Takayuki Ishikawa[4] · Kiyohiko Hatake[5] · Satoshi Ichikawa[6] · Ken Ohmine[7] · Yuri Kamitsuji[8] · Ilseung Choi[9] · Takaaki Chou[10] · Kunihiro Tsukasaki[11] · Kyoya Kumagai[12] · Masafumi Taniwaki[13] · Toshiki Uchida[14] · Yoshitaka Kikukawa[15] · Kohmei Kubo[16] · Keichiro Mihara[17] · Norifumi Tsukamoto[18] · Koji Izutsu[19] · Isao Yoshida[20] · Fumihiro Ishida[21] · Noriko Usui[22] · Shinsuke Iida[23] · Tohru Murayama[24] · Eisuke Ueda[25] · Hiroshi Kuriki[25] · Kiyoshi Ando[1]

Received: 11 January 2018 / Revised: 3 July 2018 / Accepted: 11 July 2018 / Published online: 19 July 2018

Abstract

GALLIUM is a global phase III study that demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) with obinutuzumab plus chemotherapy (G-chemo) versus rituximab plus chemotherapy (R-chemo) in previously untreated patients with follicular lymphoma (FL). In this single-country subgroup analysis, we explored patterns of efficacy and safety in patients enrolled in the GALLIUM study in Japan (Japanese subgroup). Patients were randomized to open-label induction treatment with G-chemo or R-chemo. Responders received maintenance monotherapy with their randomized antibody for up to 2 years. The primary endpoint was investigator-assessed PFS. Overall, 123 patients with FL were randomized in the Japanese subgroup (G-chemo, $n=65$; R-chemo, $n=58$). The majority of patients received cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy (82.9 vs 33.1% in the global GALLIUM FL population). PFS at 3 years was 89.9% (G-chemo) vs. 74.7% (R-chemo); hazard ratio 0.42; 95% confidence interval 0.15, 1.15; $P=0.08$. Higher rates of grade 3–5 adverse events (96.9 vs. 89.7%) and serious adverse events (35.4 vs. 22.4%) were observed with G-chemo vs R-chemo, respectively. Neutropenia was frequent in the Japanese subgroup (92.3% G-chemo; 79.3% R-chemo). Overall, the results in the Japanese subgroup were consistent with those in the global GALLIUM population.

Keywords Obinutuzumab · Rituximab · Follicular lymphoma · Japan

Introduction

When added to chemotherapy, rituximab significantly improves outcomes in patients with follicular lymphoma (FL) [1–4]. In common with worldwide licensing, rituximab is approved in combination with chemotherapy for the treatment of B-cell non-Hodgkin lymphoma (NHL) in Japan [5]. The most commonly used first-line options are rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) or cyclophosphamide, vincristine and prednisone (R-CVP) [6]. Rituximab plus bendamustine (BR) is also approved for first-line FL treatment [7]. Rituximab maintenance is also used in patients who respond to rituximab-containing chemotherapy in Japan [8].

Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody that differs from rituximab by having lower complement-dependent cytotoxicity, but greater antibody-dependent cytotoxicity and phagocytosis and enhanced direct B-cell death [9–11]. The efficacy of obinutuzumab in combination with chemotherapy has been demonstrated in a variety of B-cell malignancies [12–15].

GALLIUM is a global phase III study comparing the efficacy and safety of obinutuzumab plus chemotherapy (G-chemo) versus rituximab plus chemotherapy (R-chemo),

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12185-018-2497-0) contains supplementary material, which is available to authorized users.

✉ Ken Ohmachi
8jmmd004@is.icc.u-tokai.ac.jp

Extended author information available on the last page of the article

followed by maintenance with anti-CD20 therapy alone, in previously untreated patients with indolent NHL [16]. GALLIUM met its primary endpoint of improved progression-free survival (PFS) with G-chemo vs R-chemo [hazard ratio (HR) 0.66; $P = 0.001$] in the intent-to-treat population of 1202 patients with FL in a preplanned interim analysis (median follow-up 34.5 months) [16].

Patients with FL account for 7–15% of cases of adult B-cell NHL in Japan and other Asian countries [17], compared with an estimated 29% globally [18, 19]; however, data from the early 2000s suggest that the frequency of FL is increasing in Japan [20, 21]. In view of the implications of the increasing incidence of FL, a single-country subgroup analysis was carried out in the patients with FL enrolled in the GALLIUM study within Japan (Japanese subgroup) to explore patterns of efficacy and safety specific to that population, the results of which are reported here.

Patients and methods

Study design and treatments

A brief summary of the patient population and study methods is provided here. For full details, please refer to the primary GALLIUM publication [16].

This was a single-country subgroup analysis from the global, open-label, randomized (1:1) phase III GALLIUM study (ClinicalTrials.gov, NCT01332968). Patients were enrolled between 6 July 2011 and 4 February 2014 and were randomized to receive obinutuzumab or rituximab plus bendamustine, CHOP or CVP as induction (Fig. 1). Intravenous (IV) infusions of obinutuzumab 1000 mg (Days 1, 8 and 15 of Cycle 1 and on Day 1 of subsequent cycles) or rituximab 375 mg/m^2 (Day 1 of each cycle) were given for six or eight cycles depending on the chemotherapy regimen used. The choice of chemotherapy was stipulated by the site. CHOP was given as cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 and vincristine 1.4 mg/m^2 (maximum dose 2 mg) by IV infusion on Day 1 plus prednisone 100 mg orally per day on Days 1–5 of six 21-day cycles. CVP was given at the same cyclophosphamide, vincristine, and prednisone doses as for CHOP for eight 21-day cycles. Bendamustine 90 mg/m^2 was given by IV infusion on Days 1 and 2 of six 28-day cycles. Patients who received CHOP received antibody monotherapy for an additional two cycles (i.e., for eight cycles of obinutuzumab or rituximab in total). Patients with a complete response (CR) or partial response (PR) 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 or withdrawal. Patients with stable disease (SD) did not receive maintenance therapy.

Patients were randomized via an interactive voice or online response system using a hierarchical dynamic randomization scheme, and were stratified by chemotherapy regimen and Follicular Lymphoma International Prognostic Index (FLIPI) risk group [22]—low (≤ 1 risk factor), intermediate (2 risk factors) or high (> 2 risk factors). The global GALLIUM population was also stratified by geographic region. The study was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice, and the study protocol was approved by all relevant local ethics committees. Written informed consent was obtained from all patients.

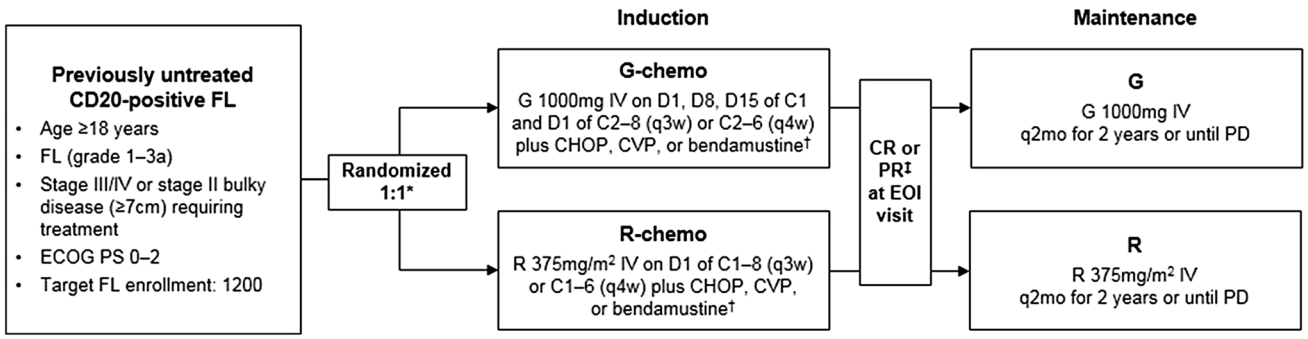

Fig. 1 GALLIUM study design. Asterisk: stratification factors: chemotherapy, FLIPI (FL patients) risk group, geographic region. Dagger: CHOP given q3w×6 cycles, CVP given q3w×8 cycles, bendamustine given q4w×6 cycles. Patients receiving CHOP received two additional cycles of obinutuzumab or rituximab monotherapy, for eight cycles total. Double dagger: patients with SD at EOI were followed for PD for ≤2 years. *C* cycle, *CHOP* cyclophosphamide, doxorubicin, vincristine and prednisone, *CR* complete response, *CVP* cyclophosphamide, vincristine and prednisone, *D* day(s), *ECOG PS* Eastern Cooperative Oncology Group performance status, *EOI* end of induction, *FL* follicular lymphoma, *FLIPI* Follicular Lymphoma International Prognostic Index, *G* obinutuzumab, *G-chemo* obinutuzumab-chemotherapy, *iNHL* indolent non-Hodgkin lymphoma, *IPI* International Prognostic Index, *IV* intravenous, *MZL* marginal zone lymphoma, *PD* progressive disease, *PR* partial response, *q2mo* every 2 months, *q3w* every 3 weeks, *q4w* every 4 weeks, *R* rituximab, *R-chemo* rituximab-chemotherapy, *SD* stable disease

Patient population

Included patients were aged ≥ 18 years, with histologically documented, previously untreated, CD20-positive FL of grades 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 (ECOG) performance status 0–2; adequate hematologic function; and requiring treatment according to Groupe d'étude des lymphomes folliculaires (GELF) criteria [23]. Full details of all inclusion and exclusion criteria are reported in the primary GALLIUM publication [16].

Study endpoints

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

Tumor responses were assessed using the Revised Response Criteria for malignant lymphoma [24] via contrast-enhanced computed tomography (CE-CT), or magnetic resonance imaging (MRI) if CE-CT was contraindicated. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) response assessment was introduced after a protocol amendment at sites where it was available. In cases with bone marrow (BM) involvement, any CR based solely on imaging without BM confirmation was classified as a PR. Responses were assessed after three bendamustine or four CHOP or CVP treatment cycles and at EOI, then every 2 months for 2 years (maintenance phase). Further assessments took place every 3–6 months thereafter, with CT every 6–12 months, until progression or withdrawal.

Adverse events (AEs) and serious adverse events (SAEs) were assessed and graded throughout the study (see primary manuscript for full details). Infusion-related reactions (IRRs) were AEs of special interest, defined as any AE occurring either during or within 24 h of infusion of any study treatment (antibody or chemotherapy) that was judged by the investigator to be related to drug administration (either antibody or chemotherapy). Safety data were periodically reviewed by an independent data monitoring committee.

The sponsor and medical staff employed by the German and UK trial groups reviewed the data, and histological diagnoses were confirmed retrospectively by central laboratories in Germany and the UK.

Statistical analysis

The sample size determination for the global GALLIUM population was designed to ensure 80% power to detect a difference in PFS between treatment arms corresponding to a 26% lower risk of progression, relapse, or death with G-chemo vs R-chemo in the global population only [16]. The study was not designed with sufficient power to detect differences in an exploratory single-country subgroup analysis such as this.

All randomized patients with FL were included in the efficacy analysis. The safety analysis was applied to all patients with FL who received any study treatment. Time-to-event endpoints (including PFS) were described using Kaplan–Meier estimates, and treatment arms were compared using log-rank tests, stratified by chemotherapy and FLIPI. Treatment effect estimates were expressed as HRs based on stratified Cox proportional-hazards models, to include 95% confidence intervals (CIs). Response rates were compared using Cochran–Mantel–Haenszel tests. Two-sided *P* values were reported.

Results

Patient population

Patient disposition for the Japanese subgroup is shown in Supplementary Fig. 1. In total, 123 patients with FL were randomized in Japan, 65 to G-chemo and 58 to R-chemo. Of these, 61 (93.8%) and 51 (87.9%), respectively, completed induction. AE was the most common reason for withdrawal from induction (three G-chemo, 4.6%; four R-chemo, 6.9%).

Baseline demographics and disease characteristics for the Japanese subgroup are summarized in Table 1. Baseline characteristics were well balanced between treatment groups, although there was a higher rate of bulky disease in the G-chemo arm (56.9 vs 48.3%). There were also more patients with B symptoms in the G-chemo group (27.7 vs 15.5%). There was a marked difference from the global GALLIUM FL population in assignment of chemotherapy; in Japan, 82.9% of patients received CHOP-based regimens, compared with 33.1% of the global GALLIUM FL population.

Median (range) duration of exposure to monoclonal antibody during induction was 26.3 (7.6–35.3) weeks for obinutuzumab and 25.3 (3.0–30.1) weeks for rituximab, and during maintenance was 91.8 (12.1–97.4) and 92.0 (11.3–94.1) weeks, respectively. Median antibody dose intensity was ≥ 90% in both treatment groups.

Table 1 Baseline patient demographics and disease characteristics (FL ITT population)

Characteristic	G-chemo ($n=65$)	R-chemo ($n=58$)
Median age, years (range)	61.0 (42–77)	61.5 (39–85)
Median weight, kg (range)	59.2 (35.3–91.4)	59.5 (32.4–81.5)
Median body surface area, m^2 (range)	1.59 (1.2–2.1)	1.62 (1.1–2.0)
Male, no. of patients (%)	22 (33.8)	24 (41.4)
Ann Arbor stage at diagnosis, no. of patients (%)		
I	0	0
II	4 (6.2)	4 (6.9)
III	23 (35.4)	19 (32.8)
IV	38 (58.5)	35 (60.3)
Missing	0	0
FLIPI, no. of patients (%)		
Low (0–1)	15 (23.1)	10 (17.2)
Intermediate (2)	17 (26.2)	23 (39.7)
High (≥ 3)	33 (50.8)	25 (43.1)
B symptoms present, no. of patients (%)	18 (27.7)	9 (15.5)
Bone marrow involvement, no. of patients (%)	34 (52.3)	27 (47.4)
Extranodal involvement, no. of patients (%)	40 (61.5)	37 (63.8)
Bulky disease (≥ 7 cm), no. of patients (%)	37 (56.9)	28 (48.3)
Median time from initial diagnosis to randomization, months (range)	1.3 (0.3–37.9)	1.2 (0.2–80.4)
Chemotherapy regimen, no. of patients (%)		
Bendamustine	6 (9.2)	6 (10.3)
CHOP	54 (83.1)	48 (82.8)
CVP	5 (7.7)	4 (6.9)

Data missing for bone marrow involvement at baseline for one patient in the R-chemo group

CHOP cyclophosphamide, doxorubicin, vincristine and prednisone, *CVP* cyclophosphamide, vincristine and prednisone, *FL* follicular lymphoma, *FLIPI* Follicular Lymphoma International Prognostic Index, *G-chemo* obinutuzumab-chemotherapy, *ITT* intent-to-treat, *R-chemo* rituximab-chemotherapy

Efficacy

The primary endpoint of investigator-assessed PFS in the ITT population of the Japanese subgroup is depicted in Fig. 2a. The estimated proportion of patients who were progression-free at 3 years was 89.9% (95% CI 78.7, 95.3) in the G-chemo group and 74.7% (95% CI 57.6, 85.8) in the R-chemo group. After a median follow-up of 28.5 months, the number of PFS events was 6 (9.2%) in the G-chemo group and 12 in the R-chemo group (20.7%); HR = 0.42; 95% CI 0.15, 1.15; $P=0.08$.

Independent review committee-assessed PFS was consistent with the investigator assessment [number of PFS events 4 (6.2%) for G-chemo, 7 (12.1%) for R-chemo; HR = 0.46; 95% CI 0.13, 1.58; $P=0.20$]. There was no relevant difference between treatment groups in OS for the FL population in Japan (Fig. 2b). The HR for the randomized treatment effect (G-chemo vs R-chemo) was 1.41 (95% CI 0.13, 15.51). There were three OS events (deaths), two in the G-chemo group (24-month assessment) and one in the R-chemo group (18-month assessment). Three-year OS was 96.9 versus 98.2% for G-chemo vs R-chemo.

Subgroup analyses of HRs for investigator-assessed PFS between treatment arms according to baseline characteristics and randomization stratification factors were consistent with the primary endpoint (Fig. 3), although patient numbers were small.

There were no relevant differences in CT-based response rates according to investigator assessment between treatment groups at EOI (Table 2). ORRs in the Japanese subgroup were 92.3 and 91.4% with G-chemo and R-chemo, respectively, compared with 88.5 and 86.9% in the global population [16]. CR rates for G-chemo and R-chemo were 35.4 and 34.5%, respectively, in the Japanese subgroup (Table 2), whereas the global population showed CR rates of 19.5 and 23.8% for G-chemo and R-chemo, respectively [16]. Improvements in event-free survival and time to start of new anti-lymphoma treatment were observed for G-chemo vs R-chemo (Supplementary Table 1).

Safety and tolerability

All patients in both treatment groups in the Japanese subgroup experienced at least one AE (Table 3; Supplementary

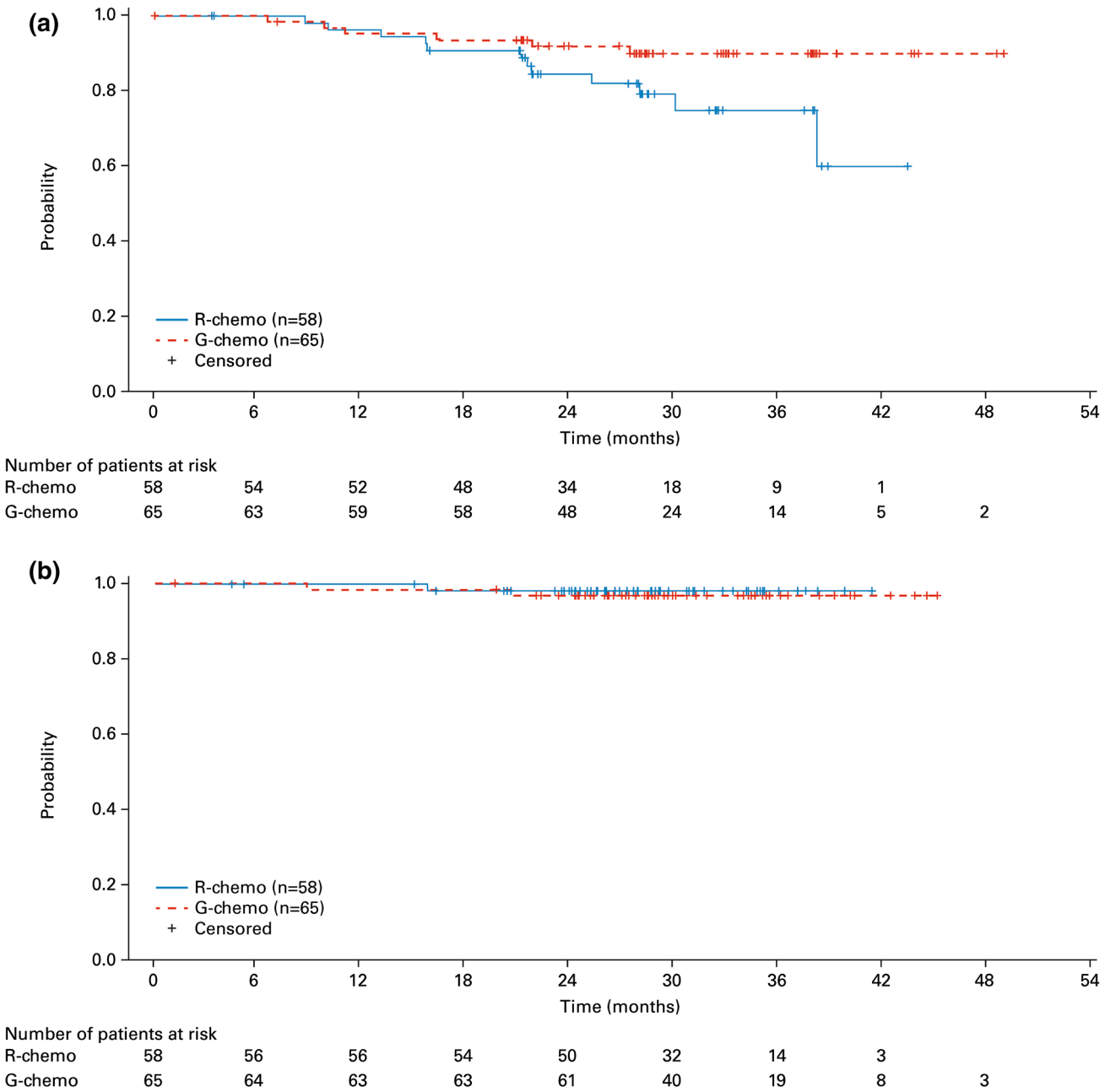

Fig. 2 **a** Investigator-assessed PFS; **b** investigator-assessed OS (FL ITT population). *FL* follicular lymphoma, *G-chemo* obinutuzumab-chemotherapy, *ITT* intent-to-treat, *OS* overall survival, *PFS* progression-free survival, *R-chemo* rituximab-chemotherapy

Table 2). There were higher rates of grade 3–5 AEs (96.9 vs 89.7%) and SAEs (35.4 vs 22.4%) for G-chemo than for R-chemo in the Japanese subgroup, similar to the global GALLIUM FL population (Table 3). Rates of grade 3–5 AEs and AEs leading to dose reduction (38.5 and 39.7% for G-chemo and R-chemo, respectively) were higher in the Japanese subgroup than in the global GALLIUM FL population (grade 3–5 AEs: 74.6% G-chemo, 67.8% R-chemo; AEs leading to dose reduction: 17.3% G-chemo, 14.9% R-chemo [16]).

Analysis of AEs of special interest showed higher rates of neutropenia (92.3 vs 79.3%) and infection (78.5 vs 69.0%) with G-chemo vs R-chemo in Japan (Table 3). This pattern of results was similar to that in the global GALLIUM FL population, but the rate of neutropenia in the Japanese subgroup was substantially higher than that of the global GALLIUM FL population, which reported 50.6 and 45.1% for G-chemo and R-chemo, respectively [16]. There were also higher rates of grade 3–5 neutropenia (90.8% G-chemo and 79.3% R-chemo, Table 3) for the Japanese subgroup

Baseline factors	Total N	R-chemo (n=58) N	R-chemo Events	R-chemo 1 year KM rate	G-chemo (n=65) N	G-chemo Events	G-chemo 1 year KM rate	HR	95% CI
All patients	123	58	12	96.296	65	6	95.186	0.39	0.15, 1.05
Sex									
Male	46	24	4	95.652	22	3	90.909	0.79	0.18, 3.54
Female	77	34	8	96.774	43	3	97.500	0.20	0.05, 0.80
Race									
Asian	123	58	12	96.296	65	6	95.186	0.39	0.15, 1.05
Bulky disease at baseline (7cm threshold)									
Yes	65	28	4	96.154	37	3	94.444	0.51	0.11, 2.27
No	58	30	8	96.429	28	3	96.296	0.33	0.09. 1.25
B symptoms ≥1 at baseline									
Yes	27	9	2	100.000	18	3	88.235	0.66	0.11, 3.98
No	96	49	10	95.652	47	3	97.778	0.27	0.07, 0.98
Ann Arbor stage									
II	8	4	0	100.000	4	1	100.000	>999.99	0.00, NE
III	42	19	3	100.000	23	2	95.238	0.46	0.08, 2.83
IV	73	35	9	93.750	38	3	94.737	0.26	0.07, 0.96
ECOG PS at baseline									
0–1	120	57	12	96.226	63	6	95.026	0.40	0.15, 1.06
2	3	1	0	100.000	2	0	100.000	NE	NE, NE
ADL at baseline									
5–6	117	55	12	96.078	62	6	94.943	0.39	0.15, 1.05
Outside valid range	6	3	0	100.000	3	0	100.000	NE	NE, NE
IADL at baseline									
1–4	1	0	0	0	1	0	100.000	NE	NE, NE
5–8	122	58	12	96.296	64	6	95.108	0.40	0.15, 1.07
FLIPI									
Low	25	10	3	100.000	15	1	100.000	0.19	0.02, 1.84
Intermediate	40	23	4	100.000	17	0	100.000	<0.01	0.00, NE
High	58	25	5	91.304	33	5	90.909	0.66	0.19, 2.27
Chemotherapy regimen									
CHOP	102	48	10	97.826	54	6	94.340	0.50	0.18, 1.37
CVP	9	4	2	50.000	5	0	100.000	<0.01	0.00, NE
Bendamustine	12	6	0	100.000	6	0	100.000	NE	NE, NE

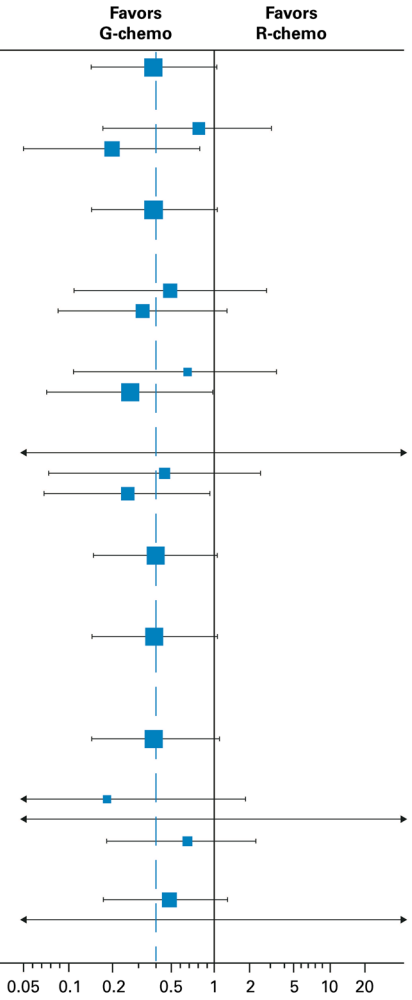

Fig. 3 Unstratified HRs for investigator-assessed PFS by patient subgroups **a** randomization stratification factors **b** baseline characteristics (FL ITT population). *ADL* activities of daily living, *CHOP* cyclophosphamide, doxorubicin, vincristine and prednisone, *CI* confidence interval, *CVP* cyclophosphamide, vincristine and prednisone, *ECOG PS* Eastern Cooperative Oncology Group performance status, *FL* follicular lymphoma, *FLIPI* Follicular Lymphoma International Prognostic Index, *G-chemo* obinutuzumab-chemotherapy, *HR* hazard ratio, *IADL* instrumental activities of daily life, *ITT* intent-to-treat, *KM* Kaplan–Meier, *NE* not estimable, *PFS* progression-free survival, *R-chemo* rituximab-chemotherapy

when compared with the global GALLIUM FL population (45.9 and 39.5%, respectively [16]). Overall, 62 (95.4%) G-chemo-treated and 51 (87.9%) R-chemo-treated patients in the Japanese subgroup took granulocyte colony-stimulating factors (G-CSFs), compared with 287/601 (47.8%) and 275/601 (45.8%), respectively, in the global GALLIUM FL population (data on file). Thirty-four (52.3%) G-chemo-treated and 26 (44.8%) R-chemo-treated patients received G-CSFs for prophylaxis, compared with 168/595 (28.2%) and 163/597 (27.3%), respectively, in the global GALLIUM FL population (data on file). Infections occurred in 51 (78.5%) G-chemo-treated and 40 (69.0%) R-chemo-treated patients, which was consistent with the findings in the global GALLIUM FL population [460 (77.3%) and 418 (70.0%) patients, respectively]. The most common infections, occurring in ≥ 10% of patients the Japanese subgroup in either treatment arm (G-chemo vs R-chemo) included nasopharyngitis [27 (41.5%) vs 24 (41.4%)], upper respiratory tract infection [5 (7.7%) vs 8 (13.8%)], herpes zoster [9 (13.8%) vs 2 (3.4%)], and influenza [4 (6.2%) vs 6 (10.3%)]. Secondary neoplasms occurred in three patients (4.6%) treated with G-chemo; adenocarcinoma of the colon (grade 2), meningioma (grade 3), and prostate cancer (grade 1).

During induction, the most common adverse events were neutropenia (90.8% G-chemo; 75.9% R-chemo), constipation (69.2% G-chemo, 60.3% R-chemo), infusion-related reactions (66.2% G-chemo; 60.3% R-chemo), nausea (44.6% G-chemo, 60.3% R-chemo) and alopecia (58.5% G-chemo;

Table 2 Overall response at end of induction (FL ITT population)

	G-chemo($n=65$)		R-chemo ($n=58$)
Overall response (OR)	60 (92.3%)		53 (91.4%)
Difference (95% CI); *P* value*		0.93 (−9.7, 11.6); 0.75	
Complete response (CR)	23 (35.4%)		20 (34.5%)
Difference (95% CI); *P* value*		0.90 (−17.0, 18.8); 0.94	
Partial response (PR)	37 (56.9%)		33 (56.9%)
Difference (95% CI); *P* value*		0.03 (−18.5, 18.6); 0.91	
Stable disease (SD)	0		0
Progressive disease (PD)	1 (1.5%)		0
Unable to evaluate (NE)	3 (4.6%)		2 (3.4%)
Missing	1 (1.5%)		3 (5.2%)

CI confidence interval, *FL* follicular lymphoma, *FLIPI* Follicular Lymphoma International Prognostic Index, *G-chemo* obinutuzumab-chemotherapy, *ITT* intent-to-treat, *R-chemo* rituximab-chemotherapy

*Cochran–Mantel–Haenszel test, stratified by FLIPI, chemotherapy regimen

55.2% R-chemo). During maintenance, adverse events were less common, with nasopharyngitis (31.7% G-chemo; 37.3% R-chemo) and neutropenia (28.3% G-chemo; 17.6% R-chemo) being the most frequently reported (Supplementary Table 2). During induction, neutropenia was the most common grade 3–5 AE (89.2% G-chemo; 75.9% R-chemo) (Supplementary Table 3), while febrile neutropenia was the most common serious AE reported (6.2% G-chemo; 1.7% R-chemo) (Supplementary Table 4).

Three patients in the Japanese subgroup died during the study; two were due to PD (1 G-chemo, 1-R-chemo). The third case (in the G-chemo group) was a patient diagnosed with bronchiolitis (non-serious AE, treatment-related) who later died at home (cause of death unknown; suspected airway obstruction by mucinous sputum during sleep), the death was deemed by the investigator to be related to obinutuzumab treatment.

Discussion

The current analysis investigated the efficacy and safety of G-chemo vs R-chemo in the Japanese subgroup of 123 patients with FL who took part in the global GALLIUM study. The findings in the Japanese subgroup were generally consistent with the global GALLIUM population, which demonstrated significantly improved PFS and manageable toxicity with G-chemo.

There were no clinically relevant imbalances between treatment groups in terms of patient or disease characteristics at baseline. There was a tendency towards higher rates of patients with bulky disease and B symptoms in the G-chemo arm. These trends were not seen in the global population [16], although the prevalence of B symptoms overall was considerably higher worldwide (approximately a third of all patients in both treatment arms) than in the Japanese subgroup.

Investigator-assessed PFS in the Japanese subgroup was consistent with that seen in the global GALLIUM FL population. As with the global GALLIUM FL population, no relevant difference between groups in OS was apparent, and these results remain immature.

EOI response rates by CT were similar between groups, but were higher than those reported in the global GALLIUM FL population [16]. This was driven by a relatively high CR rate in the Japanese subgroup. The similarities in CT-based response rates despite the trend for increased PFS in G-chemo- versus R-chemo-treated patients may be due to the limitations of CT-based response assessment, including limited accuracy to detect lymphoma in small lymph nodes, bone marrow or extranodal sites [25]. Response assessment using FDG-PET [26], had this been available at all centers, might have been more informative both here and in the global population. An exploratory analysis of independent review committee-assessed FDG-PET response in the global population has shown higher CR rates with G-chemo vs R-chemo (71.4 vs 59.7%) when assessed by the International Harmonisation Project (IHP) 2007 criteria; EOI FDG-PET CR was prognostic for longer PFS [27]. In the patients from the Japanese subgroup for whom investigator-assessed FDG-PET response was available (G-chemo $n=17$; R-chemo $n=15$), the CR rate was also higher than that on CT-based assessment (G-chemo 82.4 vs 35.4%; R-chemo 60.0 vs 34.5%); the difference between treatment groups was not significant, $P=0.17$; however, the number of patients was low. Minimal residual disease measurement, which reflects treatment efficacy and which may be a prognostic marker at EOI in FL patients treated with immunochemotherapy, has also been shown to be associated with outcomes in an exploratory analysis in the global GALLIUM FL population

Table 3 Summary of treatment-emergent adverse events (FL safety evaluable population)

	G-chemo ($N=65$)	R-chemo ($N=58$)
Total number of patients with ≥ 1 event	65 (100)	58 (100)
Deaths	2 (3.1)	1 (1.7)
At least one of		
AE with fatal outcome	1 (1.5)	0
Grade 3–5 AE	63 (96.9)	52 (89.7)
Serious AE[a]	23 (35.4)	13 (22.4)
Serious AE[a] leading to withdrawal from any treatment	4 (6.2)	3 (5.2)
Serious AE[a] leading to dose reduction	3 (4.6)	0
Serious AE[a] leading to dose interruption	10 (15.4)	4 (6.9)
Treatment-related[b] serious AE[a]	19 (29.2)	12 (20.7)
AE leading to withdrawal from any treatment	11 (16.9)	11 (19.0)
AE leading to dose reduction	25 (38.5)	23 (39.7)
AE leading to dose interruption	55 (84.6)	39 (67.2)
Treatment-related[b] AE	65 (100)	58 (100)
Treatment-related[b] AE leading to withdrawal from any treatment	8 (12.3)	10 (17.2)
Treatment-related[b] AE leading to dose reduction	25 (38.5)	23 (39.7)
Treatment-related[b] AE leading to dose interruption	55 (84.6)	39 (67.2)
Grade 3–5 AEs with incidence ≥ 10%		
Neutropenia	59 (90.8)	46 (79.3)
Leukopenia	14 (21.5)	7 (12.1)
Febrile neutropenia	13 (20.0)	6 (10.3)
AEs of special interest (any grade)		
Infections	51 (78.5)	40 (69.0)
Neutropenia	60 (92.3)	46 (79.3)
Thrombocytopenia	3 (4.6)	1 (1.7)
Infusion related reactions	45 (69.2)	36 (62.1)
Cardiac events	4 (6.2)	2 (3.4)
Gastrointestinal perforation	0	1 (1.7)
Tumor lysis syndrome	0	0
Secondary neoplasm[c]	3 (4.6)	0

Data are no. patients (%)

AE adverse event, *FL* follicular lymphoma, *G-chemo* obinutuzumab-chemotherapy, *R-chemo* rituximab-chemotherapy

[a]AEs that were fatal or life-threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant disability/incapacity, were congenital anomalies/birth defects in a neonate/infant born to a mother exposed to the investigational product(s), or were considered a significant medical event by the investigator

[b]AEs considered by the investigator to be related to study treatment(s)

[c]Includes tumors that were diagnosed at least 6 months after the start of treatment

[28]. This method might also have given additional insights into response patterns in the current subgroup.

Safety in the Japanese subgroup was found to be manageable. AEs were consistent with the known safety profiles of G- and R-chemo, and in broad agreement with the global study results [16]. As in the global population, there were higher rates of grade 3–5 AEs and SAEs with G-chemo than with R-chemo; however, a substantially higher rate of neutropenia was observed in the Japanese subgroup than in the global GALLIUM FL population, despite more patients in the Japanese subgroup receiving G-CSFs as prophylaxis. It is not possible to comment definitively on the reasons for this, although there are a number of possible contributing factors. The choice of chemotherapy regimen in Japan differed from the global GALLIUM FL population, with the large majority of patients in the Japanese subgroup receiving treatment based on CHOP, which may reflect Japanese clinical practice during the study period and is likely to have influenced AE profiles. In addition, it may be that blood cell counts were more frequently monitored in the Japanese subgroup compared with the global population, particularly during the first induction cycle. In contrast to the global

GALLIUM population, a very small number of patients in Japan received bendamustine, as this drug was approved for first-line use only in B-cell NHL in Japan in December 2016 [29]. Of interest, the incidence of febrile neutropenia seen in the present study with R-CHOP was of the order that might be anticipated on the basis of previous experience, including a recently published study from Japan in 466 patients with B-cell NHL who were treated with this regimen [30]. Consistent with the global GALLIUM FL population, secondary neoplasms occurred more often in the G-chemo treatment arm (three, compared with none in the R-chemo arm), although there was no meaningful difference between the treatment arms. No secondary hematologic malignancies occurred in the Japanese subgroup, compared with six occurring in the global GALLIUM FL population.

Limitations to the study include the insufficient power to detect between-group differences in this single-country subgroup analysis.

In conclusion, the findings of this exploratory analysis of the GALLIUM results in the Japanese subgroup with previously untreated FL were consistent with the results for the global population, which showed clinically meaningful improvements in PFS in first-line FL patients treated with G-chemo vs R-chemo. The high rates of neutropenia seen in the Japanese subgroup may reflect the extensive use of CHOP chemotherapy in Japan, with only very few patients receiving bendamustine.

Acknowledgements The authors would like to thank the UK and German study groups (UK National Cancer Research Institute, German Low Grade Lymphoma Study Group and the East German Study Group Hematology and Oncology) for their scientific support of the GALLIUM study, all of the GALLIUM study investigators, their teams, and the patients for their participation. The GALLIUM trial was sponsored by F. Hoffmann-La Roche Ltd. Medical writing support for this article was provided by Lynda McEvoy, PhD (Gardiner-Caldwell Communications, Macclesfield, UK), funded by Chugai Pharmaceutical Co Ltd.

Compliance with ethical standards

Conflict of interest KO reports personal fees from Chugai Pharmaceutical Co Ltd, Kyowa Hakko Kirin Co Ltd, Eisai Co Ltd, Pfizer Inc and Takeda Pharmaceutical Co Ltd. KT reports Grants and personal fees from Chugai Pharmaceutical Co Ltd/Roche, Celgene, Eisai, Janssen Pharmaceuticals, Kyowa Hakko Kirin, Mundipharma, Ono Pharmaceutical and Takeda; Grants from Abbvie, GlaxoSmithKine and Servier; and personal fees from HUYA Bioscience and Zenyaku Kogyo. TK reports Grants and personal fees from Chugai Pharmaceutical Co Ltd, Ono, Gilead, MSD and Zenyaku; Grants from Takeda and Solaisia; and personal fees from Bristol, Kyowa Kirin, Eisai and Janssen. TI, KKumagai, SI, YK, IC, TC, YK, KKubo, KM and NT report no conflicts of interest. KH reports Grants from Chugai Pharmaceutical Co. KO reports Grants and personal fees from Chugai Pharmaceutical Co Ltd and Takara-Bio Inc; and personal fees from Kyowa Hakko Kirin Co Ltd, Ono Pharmaceutical Co Ltd, Bristol-Meyers Squibb, Chugai Pharmaceutical Co Ltd and Alexion Pharmaceuticals Inc. KT reports Grants from Chugai Pharmaceutical Co Ltd, Celgene, Takeda and Mundipharma; consultancy from Huya and Ono Pharma, and lecture fees from Zenyaku Kogyo, Celgene, Huya, Kyowa Hakko Kirin and Chugai Pharmaceutical Co Ltd. MT reports Grants and personal fees from Chugai/Roche, Celgene, BMS, and Janssen Pharmaceuticals; Grants from Kyowa Hakko Kirin; and personal fees from Mundipharma. TU reports personal fees from Janssen Pharmaceuticals, Mundipharma, Celgene, Teijin, Novartis, Nippon Shinyaku, Pfizer, Briston-Myers Squibb, and Meiji Seika Pharama. KI reports Grants from Kenyaku Kogyo, Mundhi, Abbvie, Solasia, Celltrion, Symbio, Astellas, Astellas Amgen, Novartis and Sanofi; Grants and personal fees from Takeda, Eisai, Chugai Pharmaceutical Co Ltd, Gilead, Janssen, Ono, Celgene, MSD, Bayer and Daiichi-Sankyo, personal fees from Kyowa Hakko Kirin; and discloses a relationship with HUYA Bioscience International. IY reports research funding and honoraria from Kyowa Hakko Kirin; research funding from Chugai; and honoraria from Celgene. FI reports Grants and personal fees from Chugai Pharmaceutical Co Ltd, Kyowa Hakko Kirin, and Takeda; Grants from Bristol-Myers-Squibb; and personal fees from Celgene. NU reports research Grants from AMED, Pfizer Co, Sysmex Co, Kyowa Hakko Kirin Co, Bristol-Myers-Squibb, Novartis, Nippon Shinyaku, Fujimoto and Celgene; payment for data monitoring committee membership from CIMIC Co, Takeda Bio Development Center, Lilly Japan, Pfizer Co, Nippon Boehringer-Ingelheim Co, Janssen Pharmaceutical Co, Zenyaku Kogyo Co, Kyowa Hakko Kirin Co, Otsuka Pharm Co, Celgene Co, SymBio Pharmaceutical Co, Huya Bioscience International, and Astellas Pharmaceutical Co; and payment for speaker's bureau for Chugai Pharmaceutical Co Ltd and Bristol-Myers-Squibb. SI reports Grants from Chugai Pharmaceutical Co Ltd, Kyowa Hakko Kirin, Astellas, Toyama Chemicals, Teijin Pharma, Sanofi, Bayer, J-Pharma, Eli Lilly, and Daiichi Sankyo; and Grants and personal fees from Ono, Janssen, Celgene, Bristol-Myers-Squibb, Novartis, and Takeda. TM reports personal fees from Bristol-Myers-Squibb, Celgene, Esai, Janssen Pharmaceutical, Kyowa Hakko Kirin, Nippon Shinyaku, Novartis, Ono Pharmaceuticals, Otsuka Pharmaceuticals, Pfizer, Sanofi, Siemens Healthcare Diagnostics, Sumitomo Dainippon Pharma, and Taiho Pharmaceutical. EU and HK are employees of Chugai Pharmaceutical Co Ltd. HK reports stock ownership for Chugai Pharmaceutical Co Ltd. KA reports subsidies or donations from Meiji Seika Pharma Co Ltd, Takeda Pharmaceutical Co Ltd, Eizai Co Ltd, Kyowa Kirin and the Japan Blood Products Organization.

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Affiliations

Ken Ohmachi[1] · Kensei Tobinai[2] · Tomohiro Kinoshita[3] · Takayuki Ishikawa[4] · Kiyohiko Hatake[5] · Satoshi Ichikawa[6] · Ken Ohmine[7] · Yuri Kamitsuji[8] · Ilseung Choi[9] · Takaaki Chou[10] · Kunihiro Tsukasaki[11] · Kyoya Kumagai[12] · Masafumi Taniwaki[13] · Toshiki Uchida[14] · Yoshitaka Kikukawa[15] · Kohmei Kubo[16] · Keichiro Mihara[17] · Norifumi Tsukamoto[18] · Koji Izutsu[19] · Isao Yoshida[20] · Fumihiro Ishida[21] · Noriko Usui[22] · Shinsuke Iida[23] · Tohru Murayama[24] · Eisuke Ueda[25] · Hiroshi Kuriki[25] · Kiyoshi Ando[1]

[1] School of Medicine, Tokai University, 143 Shimokasuya, Isehara, Kanagawa, Japan

[2] National Cancer Center Hospital, Tokyo, Japan

[3] Aichi Cancer Center, Nagoya, Aichi, Japan

[4] Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan

[5] The Cancer Institute Hospital, Tokyo, Japan

[6] Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

[7] Jichi Medical University, Shimotsuke, Tochigi, Japan

[8] Matsushita Memorial Hospital, Moriguchi, Osaka, Japan

[9] National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

[10] Niigata Cancer Center Hospital, Niigata, Japan

[11] National Cancer Center Hospital East, Chiba, Japan

[12] Chiba Cancer Center, Chiba, Japan

[13] Kyoto Prefectural University of Medicine, Kyoto, Japan

[14] Japanese Red Cross Nagoya Daini Hospital, Nagoya, Aichi, Japan

[15] Kumamoto University Graduate School of Medicine, Kumamoto, Japan

[16] Aomori Prefectural Central Hospital, Aomori, Japan

[17] Hiroshima University Hospital, Hiroshima, Japan

[18] Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

[19] Toranomon Hospital, Tokyo, Japan

[20] National Hospital Organization Shikoku Cancer Center, Matsuyama, Ehime, Japan

[21] Shinshu University School of Medicine, Nagano, Japan

[22] The Jikei University School of Medicine, Tokyo, Japan

[23] Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan

[24] Hyogo Cancer Center, Akashi, Hyogo, Japan

[25] Chugai Pharmaceutical Co., Ltd., Tokyo, Japan