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Safety and efficacy of obinutuzumab alone or with chemotherapy in previously untreated or relapsed/refractory chronic lymphocytic leukaemia patients: Final analysis of the Phase IIIb GREEN study

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Summary

The manageable toxicity profile of obinutuzumab (GA101; G) alone or with chemotherapy in first-line (1L; fit and non-fit) and relapsed/refractory (R/R) patients with chronic lymphocytic leukaemia (CLL) was established in the primary analysis of the Phase IIIb GREEN trial (Clinicaltrials.gov: NCT01905943). The final analysis (cut-off, 31 January 2019) is reported here. Patients received G (1000 mg) alone (G-mono; fit and non-fit patients) or with chemotherapy [fludarabine and cyclophosphamide (FC; fit patients); chlorambucil (non-fit patients); bendamustine (any patient)]. Study endpoints were safety (primary) and efficacy (secondary). Subgroup analyses were performed on prognostic biomarkers in 1L CLL. Overall, 630 patients received 1L and 341 received R/R CLL treatment. At the final analysis, no new safety signals were observed [Grade ≥ 3 adverse events (AEs): 1L 82·7%, R/R 84·5%; serious AEs: 1L 58·1%, R/R 62·5%]. Neutropenia (1L 50·5%, R/R 53·4%) and thrombocytopenia (1L 14·6%, R/R 19·1%) were the most common Grade 3–5 AEs. G-mono-, G-bendamustine and G-FC-treated patients with unmutated immunoglobulin heavy chain trended towards shorter progression-free survival. Achievement of minimal residual disease negativity was greatest in 1L patients treated with G-FC. In this final analysis of the GREEN trial, the safety profile of G was consistent with current risk management strategies. Biomarker analyses supported efficacy in the specific subgroups.

Keywords: Obinutuzumab, chronic lymphocytic leukaemia, safety, *IGHV*, minimal residual disease.

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Introduction

Over the past decade, chemoimmunotherapy has played a key role in the management of chronic lymphocytic leukaemia (CLL), with rituximab established as the backbone of chemoimmunotherapy for managing patients with previously untreated first-line (1L) CLL.[1–4] Frontline rituximab with fludarabine and cyclophosphamide (FCR) has been the standard of care for physically fit (≤65 years) CLL patients.[5,6] Rituximab plus bendamustine (Benda-R) is often given to fit patients aged ≥65 years who are at higher risk of infections.[6] The potential toxicities of FCR have also led to the use of chlorambucil (Clb) plus obinutuzumab (GA101; G) as frontline chemoimmunotherapy for elderly patients (≥65 years) with reduced fitness and/or relevant comorbidities, as Clb is not associated with a higher infection rate.[7–9] G-Clb is preferred over rituximab-Clb because of its superior efficacy and higher rate of minimal residual disease (MRD)-negativity.[10–13]

Chemotherapy-free options are important for frail, elderly patients who cannot tolerate chemotherapy,[14] and for patients with genetic characteristics such as del17p, *TP53*mut and unmutated immunoglobulin heavy chain (*IGHV*), who show poor outcomes with chemoimmunotherapy.[15] Recently, the US Food and Drug Administration approved G plus ibrutinib,[16,17] venetoclax,[18,19] and acalabrutinib.[20,21] Despite these advances, chemoimmunotherapy is still considered to have an important role in CLL treatment, especially in patients with mutated *IGHV*, who reportedly receive sustained benefit from chemoimmunotherapy.[16,22–24] It, therefore, remains important to further investigate the safety of chemoimmunotherapy and to define the subgroups that derive particular benefit.

The GREEN trial (NCT01905943) is a safety study of G, alone or in combination with chemotherapy, in a broad population of CLL patients.[25,26] It was mandated by regulatory authorities following the approval of G in CLL; the primary safety analysis has been published previously.[27] Here, we report the final safety and efficacy analysis from the overall GREEN population, with 18 months additional follow-up. The potential value of prognostic biomarkers (*IGHV*, cytogenetic abnormalities and CD38 expression) in 1L and R/R patients was also evaluated.

Methods

Study design

The GREEN study is a non-randomised, four-cohort, open-label, international, multicentre Phase IIIb safety study. The study design and inclusion/exclusion criteria have been described previously.[27] The study was conducted according to the Declaration of Helsinki, Good Clinical Practice guidelines and local regulations. The study protocol (and amendments) were approved by participating centre review boards/ethics committees. Patients provided written informed consent to participation.

Patients and treatment

Patients with 1L or R/R (≤3 prior therapies) CLL received intravenous G (1000 mg split over 2 days) alone [G-mono; fit (Cumulative Illness Rating Scale; CIRS) ≤6 and creatinine clearance (CrCl) ≥70 ml/min] or non-fit patients (CIRS > 6 and/or CrCl < 70 ml/min) or in combination with chemotherapy, as selected by the investigator [intravenous or oral FC (fit patients), oral Clb (non-fit patients); or intravenous Benda (fit and non-fit patients)]. Dosing details are provided in Appendix S1.

Study endpoints and assessments

The current analysis aimed to detail safety post-final response assessment visit (FRA; 3 months after last dose of study treatment) and frequently reported Grade ≥ 3 adverse events (AEs) until 24 months after the end of treatment, serious AEs (SAEs), AEs of special/particular interest (AESI/AEPI), AEs leading to death and efficacy data.

Efficacy outcomes included best overall response (BOR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), time-to-next-anti-leukaemia-treatment (TTNT), duration of MRD negativity, MRD-negative status at the FRA and patient-reported outcomes (PROs). Assessment details are provided in Appendix S1.

Exploratory endpoints included central prognostic marker analysis (*IGHV* mutation status, genetic aberrations (del (11q), trisomy 12q, del(13q), del(17p) and CD38 expression)) in relation to efficacy (1L patients: PFS, OS and TTNT; 1L and R/R patients: objective response rate and MRD]).

Statistics

The GREEN study was non-comparative with no formal statistical testing and no power calculation. The final analysis was performed at the end of the study, which was 30 months after enrolment of the last patient, or sooner, if one of the following was documented for all treated patients: withdrawal from the study, loss to follow-up, death or study termination (data cut-off 31 January 2019).

Safety analyses were based on the safety population (patients who received ≥1 dose of study treatment). Efficacy analyses were performed in the intent-to-treat (ITT) population (all enrolled patients, regardless of whether they received treatment). Time-to-event variables (PFS, OS and TTNT) were presented graphically using Kaplan−Meier plots, and by prognostic markers. Patient-reported outcome endpoints were summarised at baseline and over time. MRD analyses were performed on the intent-to-ship (ITS) population, which comprised all patients from the ITT population with MRD samples (bone marrow [BM] and/or peripheral blood [PB]) at the FRA that could be shipped to the central laboratory within 48 h of sampling. Because of the exploratory nature of the prognostic marker analyses, no adjustment for multiplicity was made.

Results

Patients

Overall, 972 patients were enrolled in the GREEN study between October 2013 and March 2016 at 195 centres in 31 countries (ITT population; 1L 631 patients, R/R 341 patients); 789 (81·2%) patients completed all study treatments per the protocol. With the exception of one non-fit patient in the 1L group, all enrolled patients received ≥ 1 dose of the study drug and were included in the safety population (n = 971) (Figure S1).

Baseline demographics and disease characteristics are shown for the ITT population in Table I, and for 1L patients according to treatment and fitness status in Table SI. Treatment exposure is summarised in Table SII.

Safety

Median observation time was 43·7 months (range 0·3–59·2 months) and the median follow-up time across the four treatment arms in each patient group was 40–50 months.

In the safety population, 98·6% of 1L and 98·5% of R/R patients reported ≥ 1 any-grade AE, and 82·7% and 84·5% respectively, experienced Grade ≥ 3 AEs. The incidence of any-grade AEs and Grade ≥ 3 AEs was similar across treatments (Table II).

The most common Grade ≥ 3 AEs (≥ 10% of patients in the 1L or R/R group) were neutropenia (1L 50·5%, R/R 53·4%), thrombocytopenia (1L 14·6%, R/R 19·1%), anaemia (1L 8·9%, R/R 12·0%) and pneumonia (1L 8·4%, R/R 15·2%). SAEs occurred in 58·1% of 1L and 62·5% of R/R patients (Table II).

The most frequent SAEs (≥ 10% of patients in the 1L or R/R group) included pneumonia (1L 8·7%, R/R 15·8%) and neutropenia (1L 10·0%, R/R 12·3%).

Any-grade AESI/AEPI are summarised by treatment regimen in Table II. Grade ≥ 3 infusion-related reactions occurred in 19·4% of 1L patients and 19·6% of R/R patients. The most common infections were pneumonia (1L 12·5%; R/R 18·5%), bronchitis (1L 7·3%, R/R 9·7%) and upper respiratory tract infection (1L 7·0%, R/R 9·1%); 2·7% of 1L and 7·0% of R/R patients had a Grade 5 infection. Overall, 14·6% of 1L and 15·8% of R/R patients prematurely discontinued G treatment because of AEs.

Tumour lysis syndrome (TLS) occurred in 7·5% of 1L and 4·7% of R/R patients; TLS incidence was slightly higher

Table I. Baseline demographics and disease characteristics by treatment regimen (ITT population).

Characteristic	G-mono 1L (*N* = 63)	G-mono R/R (*N* = 65)	G-Clb 1L (*N* = 68)	G-Clb R/R (*N* = 46)	G-Benda 1L (*N* = 347)	G-Benda R/R (*N* = 190)	G-FC 1L (*N* = 153)	G-FC R/R (*N* = 40)	Total 1L (*N* = 631)	Total R/R (*N* = 341)
Median age, years (range)	66 (41–85)	72 (35–88)	77 (48–87)	77 (59–90)	67 (33–83)	67 (38–85)	57 (34–74)	58 (33–72)	65 (33–87)	68 (33–90)
Male	29 (46·0)	37 (56·9)	40 (58·8)	30 (65·2)	229 (66·0)	124 (65·3)	101 (66·0)	27 (67·5)	399 (63·2)	218 (63·9)
Aged ≥ 65 years	35 (55·6)	45 (69·2)	63 (92·6)	41 (89·1)	201 (57·9)	118 (62·1)	26 (17·0)	9 (22·5)	325 (51·5)	213 (62·5)
Aged ≥ 75 years	20 (31·7)	25 (38·5)	42 (61·8)	29 (63·0)	67 (19·3)	44 (23·2)	0	0	129 (20·4)	98 (28·7)
Race										
White	50 (79·4)	53 (81·5)	56 (82·4)	40 (87·0)	279 (80·4)	157 (82·6)	106 (69·3)	34 (85·0)	491 (77·8)	284 (83·3)
Black	0	0	1 (1·5)	0	2 (0·6)	0	0	2 (5·0)	3 (0·5)	2 (0·6)
Asian	4 (6·3)	3 (4·6)	1 (1·5)	0	15 (4·3)	5 (2·6)	0	1 (2·5)	20 (3·2)	9 (2·6)
NA, as per local regulations	5 (7·9)	7 (10·8)	5 (7·4)	4 (8·7)	50 (14·4)	26 (13·7)	43 (28·1)	3 (7·5)	103 (16·3)	40 (11·7)
Other	4 (6·3)	2 (3·1)	5 (7·4)	2 (4·3)	1 (0·3)	2 (1·1)	4 (2·6)	0	14 (2·2)	6 (1·8)
ECOG PS										
0	37 (58·7)	39 (60·0)	28 (41·2)	18 (39·1)	208 (59·9)	103 (54·2)	118 (77·1)	28 (70·0)	391 (62·0)	188 (55·1)
1	23 (36·5)	22 (33·8)	34 (50·0)	26 (56·5)	134 (38·6)	75 (39·5)	34 (22·2)	11 (27·5)	225 (35·7)	134 (39·3)
2	3 (4·8)	4 (6·2)	6 (8·8)	2 (4·3)	5 (1·4)	12 (6·3)	1 (0·7)	1 (2·5)	15 (2·4)	19 (5·6)
Circulating lymphocyte count										
≥25 × 10^9/l*	48 (76·2)	40 (61·5)	57 (83·8)	26 (56·5)	266 (76·7)	123 (64·7)	119 (77·8)	25 (62·5)	490 (77·7)	214 (62·8)
≥100 × 10^9/l*	17 (27·0)	14 (21·5)	34 (50·0)	10 (21·7)	113 (32·6)	39 (20·5)	59 (38·6)	14 (35·0)	223 (35·3)	77 (22·6)
Creatinine clearance										
<50 ml/min	10 (15·9)	13 (20·0)	23 (33·8)	19 (41·3)	29 (8·4)	20 (10·5)	0	0	62 (9·8)	52 (15·2)
<70 ml/min	28 (44·4)	36 (55·4)	52 (76·5)	34 (73·9)	139 (40·1)	78 (41·1)	11 (7·2)	1 (2·5)	230 (36·5)	149 (43·7)
CIRS total score										
>6	14 (22·2)	13 (20·0)	37 (54·4)	31 (67·4)	68 (19·6)	35 (18·4)	2 (1·3)	4 (10·0)	121 (19·2)	83 (24·3)
≤6	49 (77·8)	52 (80·0)	31 (45·6)	15 (32·6)	279 (80·4)	155 (81·6)	151 (98·7)	36 (90·0)	510 (80·8)	258 (75·7)
Bulky disease										
(≥5 cm)†	32 (50·8)	37 (56·9)	38 (55·9)	27 (58·7)	210 (60·5)	116 (61·1)	109 (71·2)	29 (72·5)	389 (61·6)	209 (61·3)
Binet stage at screening										
A	17 (27·0)	12 (18·5)	22 (32·4)	8 (17·4)	96 (27·7)	51 (26·8)	37 (24·2)	7 (17·5)	172 (27·3)	78 (22·9)
B	26 (41·3)	23 (35·4)	24 (35·3)	16 (34·8)	140 (40·3)	71 (37·4)	84 (54·9)	18 (45·0)	274 (43·4)	128 (37·5)
C	20 (31·7)	29 (44·6)	22 (32·4)	21 (45·7)	111 (32·0)	65 (34·2)	32 (20·9)	14 (35·0)	185 (29·3)	129 (37·8)
Missing	0	1 (1·5)	0	1 (2·2)	0	3 (1·6)	0	1 (2·5)	0	6 (1·8)
Biomarkers										
IGHV mutated	23 (36·5)	7 (10·8)	20 (29·4)	5 (10·9)	107 (30·8)	44 (23·2)	42 (27·5)	8 (20·0)	192 (30·4)	64 (18·8)
IGHV unmutated	28 (44·4)	37 (56·9)	33 (48·5)	26 (56·5)	180 (51·9)	103 (54·2)	86 (56·2)	22 (55·0)	327 (51·8)	188 (55·1)
IGHV missing	12 (19·0)	21 (32·3)	15 (22·1)	15 (32·6)	60 (17·3)	43 (22·6)	25 (16·3)	10 (25·0)	112 (17·7)	89 (26·1)
del(17p)	2 (3·2)	7 (10·8)	7 (10·3)	7 (15·2)	20 (5·8)	26 (13·7)	5 (3·3)	6 (15·0)	34 (5·4)	46 (13·5)
del(11q)	6 (9·5)	9 (13·8)	8 (11·8)	5 (10·9)	46 (13·3)	48 (25·3)	30 (19·6)	5 (12·5)	90 (14·3)	67 (19·6)
tris 12q	9 (14·3)	8 (12·3)	12 (17·6)	6 (13·0)	47 (13·5)	19 (10·0)	25 (16·3)	0	93 (14·7)	33 (9·7)

Table I. (*Continued*)

Characteristic	G-mono 1L (*N* = 63)	G-mono R/R (*N* = 65)	G-Clb 1L (*N* = 68)	G-Clb R/R (*N* = 46)	G-Benda 1L (*N* = 347)	G-Benda R/R (*N* = 190)	G-FC 1L (*N* = 153)	G-FC R/R (*N* = 40)	Total 1L (*N* = 631)	Total R/R (*N* = 341)
del(13q)	25 (39·7)	14 (21·5)	15 (22·1)	9 (19·6)	114 (32·9)	45 (23·7)	48 (31·4)	11 (27·5)	202 (32·0)	79 (23·2)
Other abnormality	1 (1·6)	4 (6·2)	2 (2·9)	0	13 (3·7)	7 (3·7)	9 (5·9)	5 (12·5)	25 (4·0)	16 (4·7)
Cytogenetics missing/not evaluable	10 (15·9)	19 (29·2)	14 (20·6)	13 (28·3)	44 (12·7)	26 (13·7)	16 (10·5)	9 (22·5)	84 (13·3)	67 (19·6)

1L, first-line; Benda, bendamustine; CIRS, Cumulative Illness Rating Scale; Clb, chlorambucil; ECOG PS, Eastern Cooperative Oncology Group performance status; FC, fludarabine/cyclophosphamide; G, obinutuzumab; *IGHV*, immunoglobulin heavy chain; ITT, intent-to-treat; mono, monotherapy; NA, not applicable; R/R, relapsed/refractory. Values are *n* (%) unless otherwise specified.

*A total of nine (0·9%) patients had missing information for lymphocyte count at baseline.

†A total of 110 patients [G-Benda; 65 (12·1%); G-mono; 13 (10·2%); G-FC; 17 (8·8%); G-Clb; 15 (13·2%)] had incomplete information for determination of bulky disease.

among non-fit (10·7%) vs. fit patients (4·7%). All patients with TLS experienced the AE only once during the study. Of the safety population (n = 971), 3·3% of patients had laboratory TLS and 3·2% had clinical TLS. All TLS AEs (except one Grade 1 AE) were Grade ≥ 3; overall, 38 patients had serious TLS events (1L 4·3%; R/R 3·2%). Two patients in the 1L G-Benda subgroup died as a result of TLS, one fit patient with lymphadenopathy and one non-fit patient with chronic renal failure and bulky disease; both died from cardiac events. Subsequent TLS risk minimisation measures were implemented (Table SIII).

In total, 80 1L (12·7%) and 107 R/R (31·4%) patients in the safety population died (Table III); 70 (7·2%) patients died from progressive disease (1L 3·8%, R/R 13·5%) and 117 (12·0%) died from AEs (1L 8·9%, R/R 17·9%). Fatal AEs reported in > 1% of patients were for system organ classes of infections and infestations [1L 2·7%, (n = 17); R/R 7·0% (n = 24)], neoplasms [1L 2·5% (n = 16); R/R 4·4% (n = 15)] and general disorders and administration site conditions [1L 2·5% (n = 16); R/R 4·4% (n = 15)]. The most commonly reported fatal AE by preferred term was pneumonia [1L 1·0% (n = 6); R/R 2·9% (n = 10)].

Efficacy

Response rates at the FRA and median DoR for 1L and R/R patients are summarised in Table IV. For 1L patients, median PFS was not reached in the G-FC group, and was 58·0 months in the G-Benda group, 30·2 months in the G-mono group and 31·8 months in the G-Clb group (Table IV and Fig 1). At the time of final analysis, median OS was not reached with any regimen. The 4-year OS rate was highest in the G-FC arm (Table IV and Fig 2). Median TTNT was not reached in 1L patients treated with G-FC, G-Benda or G-mono and was 53·7 months for 1L patients treated with G-Clb (Table IV and Fig 3).

Patient reported outcomes remained unchanged or improved over the course of the study and are reported in Appendix S1 and Table SIV).

MRD

From the ITS MRD assessment population (n = 811), 544 and 354 patients had MRD samples at the FRA from PB and BM respectively, available for analysis (Table SV). Of these, 536 and 275 patients were in the 1L and R/R groups respectively. MRD negativity rates were highest for 1L patients treated with G-FC (PB, 70·8%; BM, 40·1%) and G-Benda (PB, 64·2%; BM, 29·4%) (Table IV).

Median duration of MRD negativity in PB (based on patients in the ITT population with an MRD-negative result) was similar for 1L patients treated with G-Benda, G-FC and G-Clb (16·3–18·2 months) and was shorter in 1L G-mono-treated patients (10·1 months) and in R/R patients for all four treatment regimens (10·2–13·6 months). However, it

Table II. Safety summary (safety population).

	G-mono		G-Clb		G-Benda		G-FC		Total	
	1L (N = 62)	R/R (N = 65)	1L (N = 68)	R/R (N = 46)	1L (N = 347)	R/R (N = 190)	1L (N = 153)	R/R (N = 40)	1L (N = 630)	R/R (N = 341)
Median observation time (range), months	35·65 (0·6–55·7)	36·17 (0·4–56·1)	39·57 (2·0–57·7)	38·49 (0·3–57·2)	47·8 (0·5–59·2)	45·82 (1·5–57·9)	43·93 (1·1–58·0)	42·53 (2·5–58·4)	43·93 (0·5–59·2)	42·55 (0·3–58·4)
Number (%) of patients with										
Any grade AE	61 (98·4)	64 (98·5)	67 (98·5)	46 (100·0)	341 (98·3)	186 (97·9)	152 (99·3)	40 (100·0)	621 (98·6)	336 (98·5)
Grade ≥ 3 AE by PT*	46 (74·2)	52 (80·0)	55 (80·9)	37 (80·4)	287 (82·7)	161 (84·7)	133 (86·9)	38 (95·0)	521 (82·7)	288 (84·5)
G related	30 (48·4)	40 (61·5)	38 (55·9)	21 (45·7)	185 (53·3)	104 (54·7)	107 (69·9)	32 (80·0)	360 (57·1)	197 (57·8)
IRR	16 (25·8)	16 (24·6)	15 (22·1)	7 (15·2)	65 (18·7)	37 (19·5)	26 (17·0)	7 (17·5)	122 (19·4)	67 (19·6)
AEs leading to G discontinuation	15 (24·2)	15 (23·1)	7 (10·3)	6 (13·0)	54 (15·6)	26 (13·7)	16 (10·5)	7 (17·5)	92 (14·6)	54 (15·8)
SAE by PT*	36 (58·1)	35 (53·8)	38 (55·9)	28 (60·9)	209 (60·2)	126 (66·3)	83 (54·2)	24 (60·0)	366 (58·1)	213 (62·5)
Any grade AESI†	57 (91·9)	60 (92·3)	62 (91·2)	43 (93·5)	321 (92·5)	180 (94·7)	146 (95·4)	39 (97·5)	586 (93·0)	322 (94·4)
IRR	35 (56·5)	43 (66·2)	42 (61·8)	31 (67·4)	217 (62·5)	135 (71·1)	105 (68·6)	27 (67·5)	399 (63·3)	236 (69·2)
IRRs leading to G discontinuation	12 (34·3)	12 (27·9)	1 (2·4)	0	8 (3·7)	1 (0·7)	1 (1·0)	0	22 (5·5)	13 (5·5)
TLS	3 (4·8)	0	3 (4·4)	2 (4·3)	37 (10·7)	13 (6·6)	4 (2·6)	1 (2·5)	47 (7·5)	16 (4·7)
Infections	29 (46·8)	27 (41·5)	35 (51·5)	30 (65·2)	206 (59·4)	125 (65·8)	93 (60·8)	27 (67·5)	363 (57·6)	209 (61·3)
Neutropaenia	24 (38·7)	33 (50·8)	40 (58·8)	23 (50·0)	216 (62·2)	124 (65·3)	120 (78·4)	30 (75·0)	400 (63·5)	210 (61·6)
Any grade AEPI†	26 (41·9)	28 (43·1)	41 (60·3)	24 (52·2)	175 (50·4)	102 (53·7)	82 (53·6)	26 (65·0)	324 (51·4)	180 (52·8)
Thrombocytopaenia	12 (19·4)	17 (26·2)	23 (33·8)	15 (32·6)	105 (30·3)	69 (36·3)	58 (37·9)	16 (40·0)	198 (31·4)	117 (34·3)
Second malignancies by MedDRA SOC	5 (8·1)	7 (10·8)	14 (20·6)	5 (10·9)	55 (15·9)	26 (13·7)	14 (9·2)	7 (17·5)	88 (14·0)	45 (13·2)
Haemorrhagic events	4 (6·5)	4 (6·2)	5 (7·4)	5 (10·9)	34 (9·8)	18 (9·5)	13 (8·5)	3 (7·5)	56 (8·9)	30 (8·8)
Cardiac events	12 (19·4)	9 (13·8)	12 (17·6)	8 (17·4)	38 (11·0)	19 (10·0)	15 (9·8)	6 (15·0)	77 (12·2)	42 (12·3)
PML	0	1 (1·5)	0	0	0	0	0	0	0	1 (0·3)
Hepatitis B reactivation	0	0	0	0	2 (0·6)	2 (1·1)	0	0	2 (0·3)	2 (0·6)

1L, first-line; AE, adverse event; AEPI, adverse event of particular interest; AESI, adverse event of special interest; Benda, bendamustine; Clb, chlorambucil; FC, fludarabine/cyclophosphamide; G, obinutuzumab; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; mono, monotherapy; PML, progressive multifocal leukoencephalopathy; PT, preferred term; R/R, relapsed/refractory; SAE, serious adverse event; SOC, system organ class; TLS, tumour lysis syndrome.

*Data represent numbers of patients with AEs based on individual terms coding single medical concepts within the MedDRA database.

†Basket term – AESI/AEPI based on pre-defined list of coded terms used across all studies, rather than based on investigator judgement; AESI included TLS, IRRs, Infections (AEs from the SOC class "Infections and Infestations"), and neutropenia; AEPI were defined as PML, HBV reactivation, second malignancies, cardiac events, and haemorrhagic events.

Table III. Summary of deaths by treatment regimen (safety population).

AE (preferred term)	G-mono (*N* = 127)	G-Clb (*N* = 114)	G-Benda (*N* = 537)	G-FC (*N* = 193)	Total (*N* = 971)
Any death	28 (22·0)	36 (31·6)	103 (19·2)	20 (10·4)	187 (19·3)
<28 days after last study treatment	2 (1·6)	3 (2·6)	7 (1·3)	0	12 (1·2)
In follow-up phase	26 (20·5)	33 (28·9)	96 (17·9)	20 (10·4)	175 (18·0)
Death related to G	0	4 (3·5)	10 (1·9)	2 (1·0)	16 (1·6)
Primary cause of death:					
PD	11 (8·7)	16 (14·0)	34 (6·3)	9 (4·7)	70 (7·2)
AE	17 (13·4)	20 (17·5)	69 (12·8)	11 (5·7)	117 (12·0)
Underlying CLL a contributing factor	8 (47·1)	6 (30·0)	28 (40·6)	5 (45·5)	47 (40·2)

AE, adverse event; Benda, bendamustine; Clb, chlorambucil; FC, fludarabine/cyclophosphamide; G, obinutuzumab; mono, monotherapy; PD, progression of disease. Values are *n* (%).

Table IV. Overview of key efficacy results at the FRA (investigator assessment).

	G-mono		G-Clb		G-Benda		G-FC	
	1L (*N* = 63)	R/R (*N* = 65)	1L (*N* = 68)	R/R (*N* = 46)	1L (*N* = 347)	R/R (*N* = 190)	1L (*N* = 153)	R/R (*N* = 40)
BOR, n (%)	49 (77·8)	39 (60·0)	64 (94·1)	38 (84·8)	322 (92·8)	165 (86·8)	147 (96·1)	39 (97·5)
[95% CI]*	[65·5;87·3]	[47·1;72·0]	[85·6;98·4]	[71·1;93·7]	[89·5;95·3]	[81·2;91·3]	[91·7;98·5]	[86·8;99·9]
CR, n (%)	32 (50·8)	18 (27·7)	42 (61·8)	15 (32·6)	217 (62·5)	86 (45·3)	105 (68·6)	24 (60·0)
[95% CI]	[37·9;63·6]	[17·3;40·2]	[49·2;73·3]	[19·5;48·0]	[57·2;67·6]	[38·0;52·6]	[60·6;75·9]	[43·3;75·1]
Median (range) PFS, months	30·2 (0·0–55·4)	17·6 (0·0–52·9)	31·8 (2·0–52·5)	14·1 (0·0–53·7)	58·0 (0·0–59·2)	28·6 (0·0–57·7)	NR (N/A)	24·8 (2·5–52·5)
OS								
Number of pts at risk at 3 years	31	34	41	25	224	117	106	24
3-year rate	0·86	0·69	0·79	0·66	0·90	0·74	0·95	0·70
(95% CI)	(0·73;0·93)	(0·55;0·80)	(0·66;0·87)	(0·50;0·79)	(0·86;0·92)	(0·67;0·80)	(0·90;0·98)	(0·53;0·82)
Number of pts at risk at 4 years	14	16	13	11	150	76	61	11
4-year rate	0·83	0·59	0·67	0·54	0·85	0·68	0·94	0·70
(95% CI)	(0·67;0·91)	(0·43;0·71)	(0·53;0·79)	(0·37;0·69)	(0·81;0·89)	(0·60;0·75)	(0·89;0·97)	(0·53;0·82)
TTNT, months median (range)	NR (N/A)	22·5 (0·3–56·1)	53·7 (2·0–55·7)	20·4 (0·3–53·7)	NR (N/A)	38·3 (1·4–57·7)	NR (N/A)	32·6 (2·0–52·5)
DoR*	*n* = 49	*n* = 39	*n* = 64	*n* = 39	*n* = 322	*n* = 165	*n* = 147	*n* = 39
Median (range), months	32·0 (0·0–51·8)	15·0 (0·6–49·2)	28·1 (0·0–48·6)	12·3 (1·6–49·9)	55·0 (0·0–56·0)	25·5 (0·0–52·5)	NR (N/A)	21·2 (0·0–48·6)
MRD status at FRA in PB†	*n* = 50	*n* = 49	*n* = 53	*n* = 32	*n* = 296	*n* = 161	*n* = 137	*n* = 33
MRD-negative, n (%)‡	8 (16·0)	2 (4·1)	5 (9·4)	2 (6·3)	190 (64·2)	64 (39·8)	97 (70·8)	17 (51·5)
MRD status at FRA in BM†	*n* = 50	*n* = 49	*n* = 53	*n* = 32	*n* = 296	*n* = 161	*n* = 137	*n* = 33
MRD-negative, n (%)‡	2 (4·0)	1 (2·0)	3 (5·7)	1 (3·1)	87 (29·4)	24 (14·9)	55 (40·1)	8 (24·2)
Duration of MRD negativity§	*n* = 13	*n* = 2	*n* = 7	*n* = 3	*n* = 220	*n* = 74	*n* = 117	*n* = 17
Months, median (range)	10·1 (0·0–20·0)	10·2 (10·1–10·4)	18·2 (0·0–18·2)	13·6 (0·0–15·9)	16·3 (0·0–22·1)	10·6 (0·0–17·1)	16·3 (0·0–22·1)	10·3 (0·0–16·1)

1L, first-line; Benda, bendamustine; BM, bone marrow; BOR, best overall response; CI, confidence interval; Clb, chlorambucil; CR, complete response; CRi, complete response with incomplete bone marrow recovery; DoR, duration of response; FC, fludarabine/cyclophosphamide; FRA, final response assessment; G, obinutuzumab; ITS, intention-to-ship; mono, monotherapy; MRD, minimal residual disease; N/A, not available; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; TTNT, time to new (anti-leukaemia) therapy.

*Patients with BOR of CR, CRi, or PR.

†Intent-to-Ship population.

‡BM samples were only collected from patients with a CR or CRi at the FRA; PB samples for MRD analysis were collected from all patients with PR or CR, where possible. The proportion of patients with an MRD-negative result was calculated for the ITS population.

§Duration of MRD negativity is bsased on patients in the ITT population with an MRD-negative result in PB.

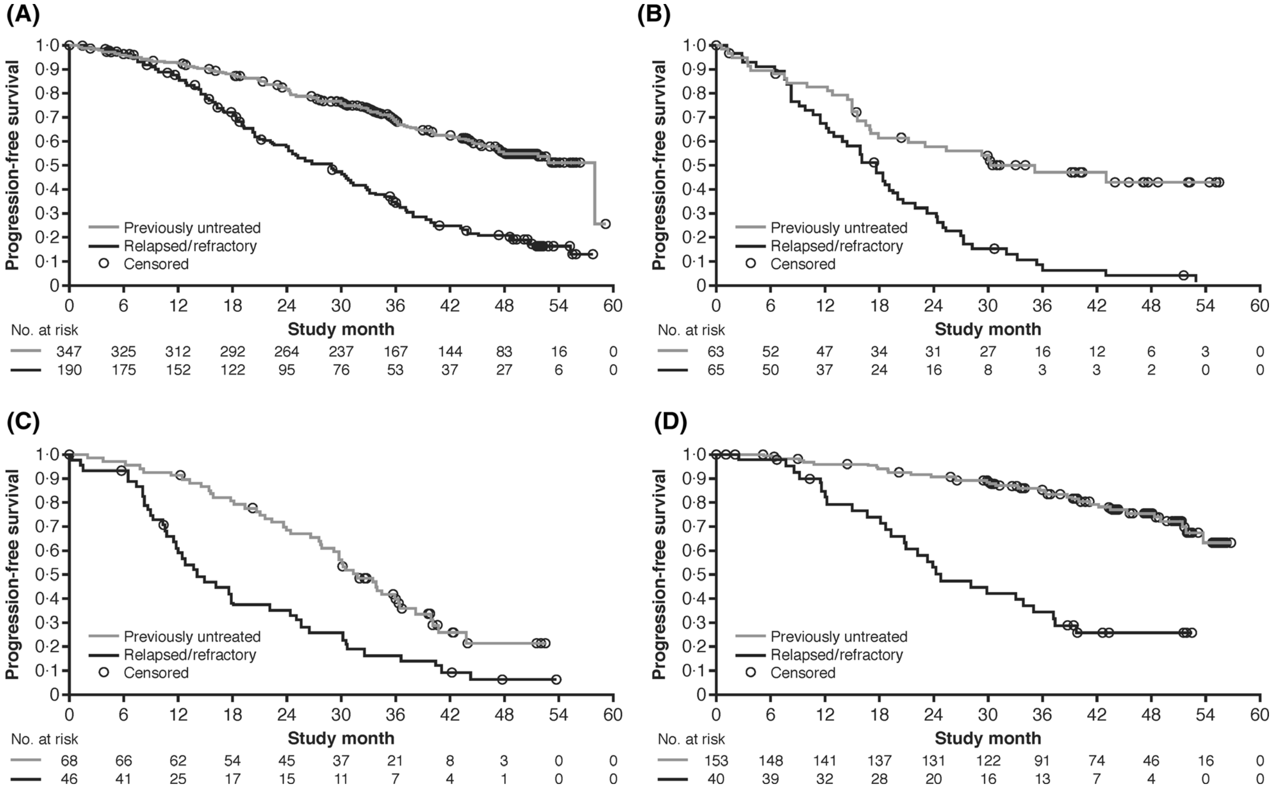

Fig 1. Kaplan–Meier plot of progression-free survival (intent-to-treat population) in previously untreated and relapsed/refractory/patients treated with (A) obinutuzumab (G) bendamustine (B) G-mono, (C) G- chlorambucil; and (D) G- fludarabine/cyclophosphamide

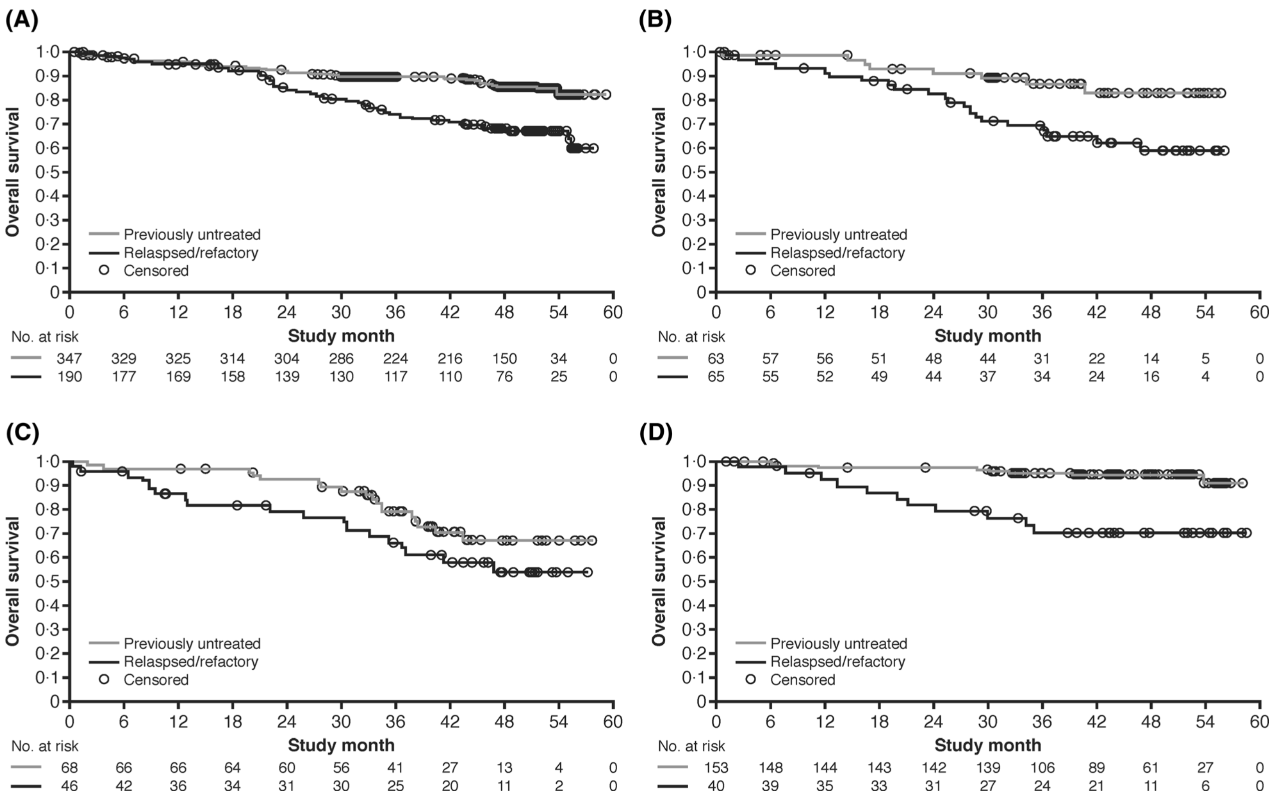

Fig 2. Kaplan–Meier plot of overall survival (intent-to-treat population) in previously untreated and relapsed/refractory patients treated with (A) obinutuzumab (G) bendamustine (B) G-mono, (C) G- chlorambucil and (D) G- fludarabine/cyclophosphamide

should be noted that the sample size for some of the subgroups was very small (Table IV).

Biomarker analysis

PFS, OS and TTNT according to *IGHV* mutation status are shown in Fig 4. Unmutated *IGHV* status was associated with a trend towards shorter PFS (Fig 4A). Unmutated *IGHV* was also associated with a trend towards less favourable OS and TTNT (Fig 4B–C).

PFS for patients with genetic aberrations is shown according to 1L treatment regimen in Fig S2A. Patients with the del (13q) and trisomy 12q aberrations, according to the hierarchical model, had the most favourable outcome, while patients with the del(17p) and del(11q) aberrations had the least favourable outcome. For OS and TTNT, del(17p) was also associated with the least favourable outcome of all genetic aberrations assessed (Figs S3A and S4A).

CD38 + expression was associated with a trend towards a shorter PFS (Fig S2B). Absence of CD38 expression was associated with a trend towards more favourable OS and TTNT (Figs S3B and S4B).

The objective response rate at the FRA by prognostic markers in 1L and R/R patients according to treatment received is detailed in Table SVI. MRD negativity at FRA in PB and BM by prognostic markers is presented in Tables SVII and SVIII.

Discussion

The GREEN study final analysis provides further evidence to support G-Clb as a treatment option for non-fit, 1L patients with CLL. It also supports G-Benda and G-FC as potential treatment options for fit and non-fit 1L CLL and for R/R CLL patients who are eligible to receive chemoimmunotherapy. Our subgroup analyses confirm that chemoimmunotherapy is an efficacious treatment in certain groups, for example, mutated *IGHV* and non-del(17p)/del(11q). No new safety signals were reported during the additional follow-up.

The safety data support the findings of previous studies with G.[11,13,28–32] Fatal AEs were reported in 18% of R/R patients (fatal infections in 7%), indicating that caution is needed when choosing therapy for R/R patients. Phase III studies of anti-CD20 therapy plus novel agents in R/R CLL show lower rates of fatal AEs than those seen with chemoimmunotherapy in the GREEN study (2–10%).[20,33,34]

Grade ≥ 3 TLS occurred in 7·3% of 1L and 4·7% of R/R patients in the GREEN study. This was higher than the rates of TLS reported in the CLL14 trial (1L CLL: 1·4% in G-venetoclax-treated patients and 2·3% in G-Clb-treated patients).[18] In view of the potential risk of TLS, risk mitigation strategies should be used to minimise the occurrence of TLS with G in clinical practice.[26] The two deaths from TLS (in 1L patients) in the current study highlight the importance of awareness of TLS symptoms and implementation of these strategies.

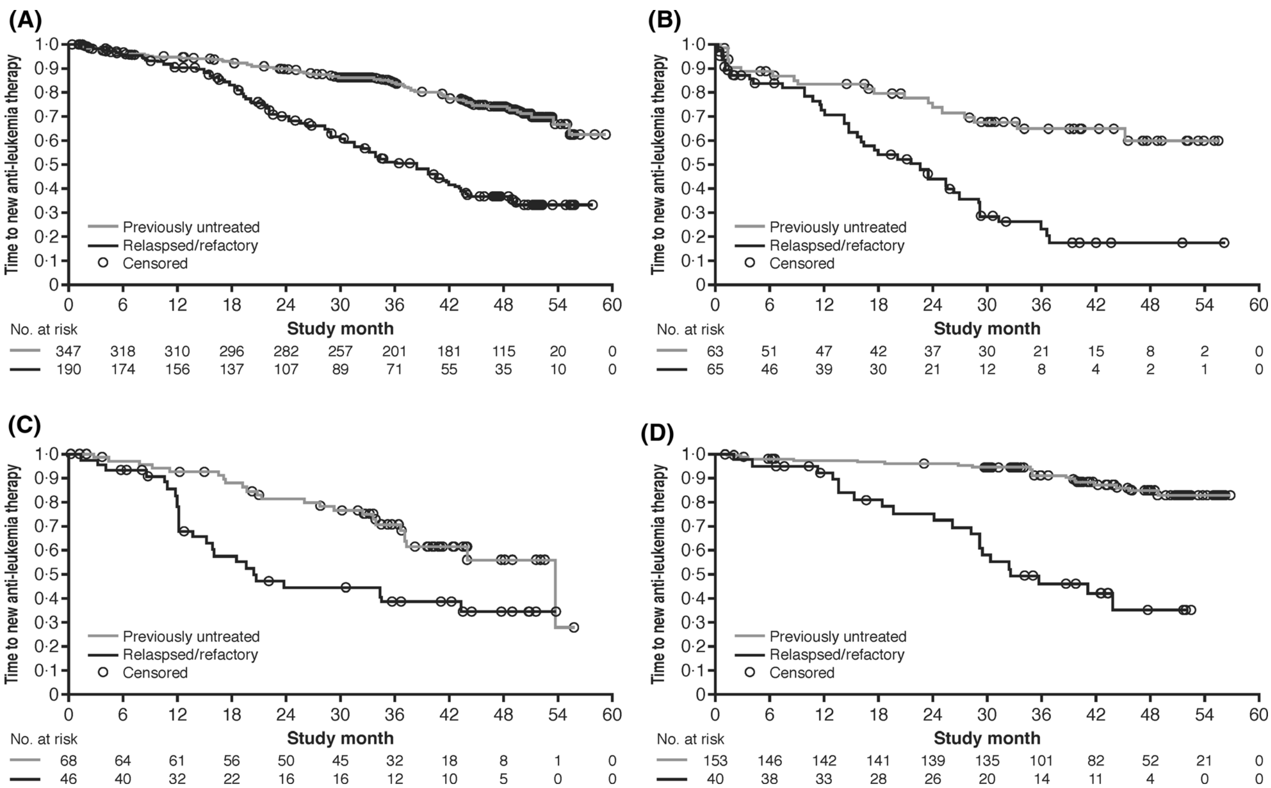

Fig 3. Kaplan−Meier plot of time to next (anti-leukaemia) treatment (intent-to-treat population) in previously untreated and relapsed/refractory patients treated with (A) obinutuzumab (G) bendamustine, (B) G-mono, (C) G-chlorambucil and (D) G- fludarabine/cyclophosphamide.

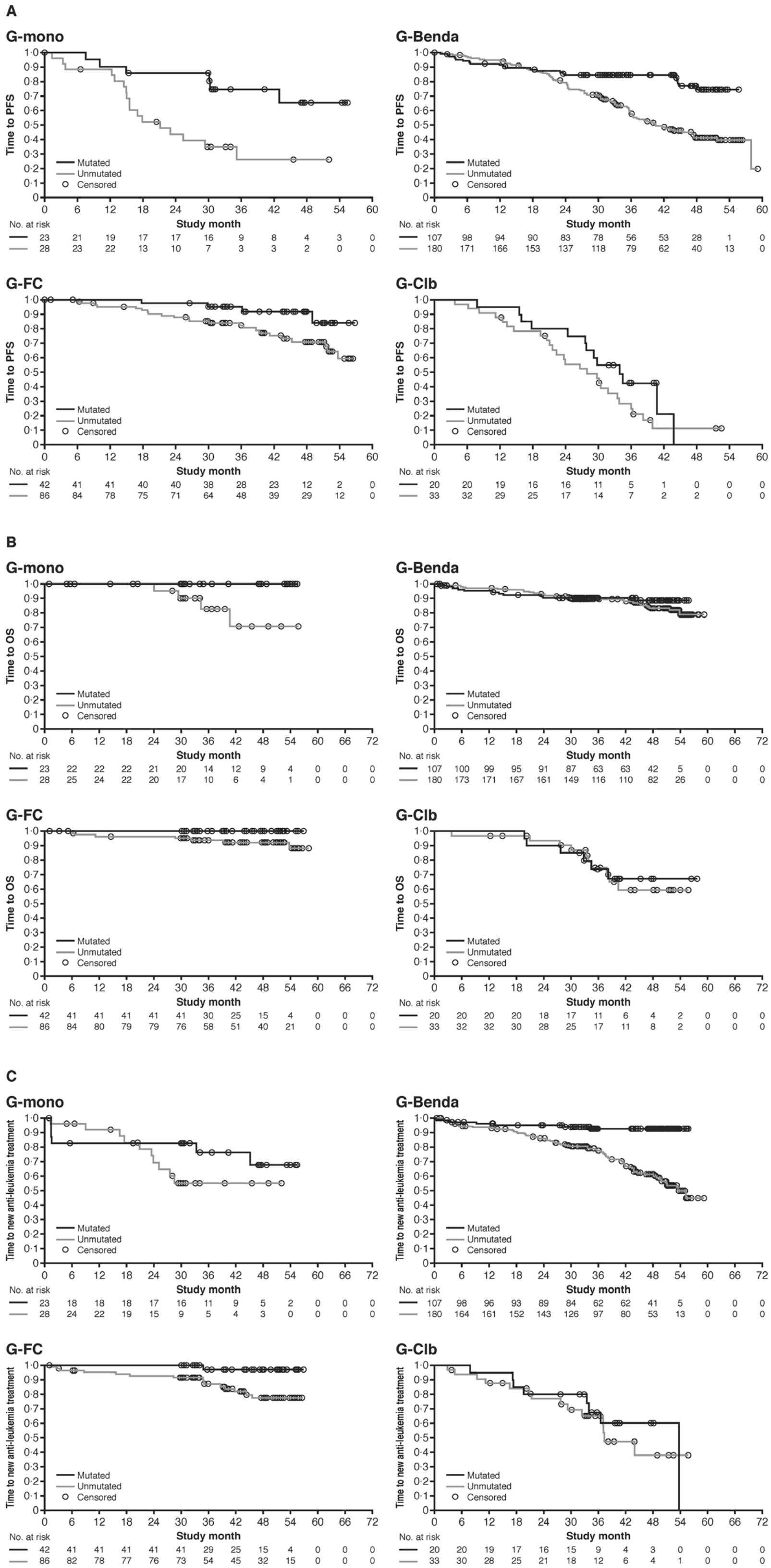

Fig 4. Kaplan–Meier plots of progression-free survival (A), overall survival (B) and time to next anti-leukaemia treatment (C) by immunoglobulin heavy chain mutation status in patients with chronic lymphocytic leukaemia who received first-line obinutuzumab (G)-mono, G bendamustine (Benda), G- fludarabine/cyclophosphamide (FC) or G-chlorambucil (Clb). PFS, progression-free survival; OS, overall survival.

The high response rates reported across all settings and regimens in the current study are consistent with previous findings demonstrating the promising benefit–risk profile of chemoimmunotherapy as well as G-mono, in patients with 1L and R/R CLL.[5,6,10-13,22,26,28-32,35–38] The BOR rate was within the expected range for CLL patients across the four regimens. Biomarker analysis was not prognostic for response rate; this may be due in part to the generally small patient subgroups.

Median PFS, OS and TTNT were not reached for 1L treatment with G-FC and were 58 months, not reached, and not reached respectively, for 1L G-Benda. Of note, G-FC was only administered to fit patients, whereas both fit and non-fit patients received G-Benda; therefore, the non-fit patients may have compromised the outcome of the G-Benda regimen. Time-to-event outcomes in G-mono-treated patients were comparable with outcomes in patients treated with G-Clb. Although not approved for CLL, it raises the question as to whether G-mono is a potentially useful treatment option for patients who want chemotherapy-free options, or for debulking prior to novel agents.

Mutated *IGHV* trended towards more favourable PFS compared with *IGHV*-unmutated status in all treatment groups, similar to findings from the ALLIANCE trial of rituximab-ibrutinib vs. Benda-R in older 1L CLL patients;[23] similarly, there was a trend towards worse OS and TTNT in patients with unmutated *IGHV*. A retrospective review of 404 CLL patients who received FCR as frontline chemoimmunotherapy found unmutated *IGHV*, del(11q) and del(17p) to be independently associated with PFS.[22] The authors found that patients with mutated *IGHV* and without del (11q) or del(17p) had a progressive reduction in risk of relapse from 4 years after FCR treatment, and had a similar life expectancy to the matched normal population.[22] Similarly, a follow-up of 300 patients from a Phase II study of FCR, at a median of 12·8 years posttreatment, found that mutated *IGHV* status was significantly associated with MRD negativity, and that unmutated *IGHV* was associated with inferior PFS and OS.[39] The authors noted that patients with mutated *IGHV* who achieved MRD negativity had excellent outcomes, with extended remissions.

In the current study, 1L patients with del(13q) and trisomy 12q experienced PFS comparable to patients with no abnormality, consistent with results from the CLL14 trial, which showed reduced PFS in all cytogenetic, high-risk subgroups, except trisomy 12q.[18] Del(11q) and, in particular, del (17p) trended towards worse PFS among all treatment groups, except for G-mono, where patients with trisomy 12q had worse PFS than patients with a normal karyotype. Lack of CD38 expression trended towards better PFS in all treatment groups, except in patients treated with G-FC. Del(17p) trended towards worse OS, whereas patients with del(13q), trisomy 12q, or del(11q) had comparable OS to patients with no abnormality. There was a trend toward worse OS for patients with CD38 expression, particularly in the G-mono group. Del(17p) showed a trend for the worst TTNT among the four molecular aberrations in all treatment groups. There was a trend towards worse TTNT for patients with CD38 expression, for all treatment groups. Therefore, our findings show that del(17p) and CD38 expression may be prognostic for poor PFS, OS and TTNT among all treatment groups, consistent with the published literature, and may identify candidate populations for treatment with novel agents.[40–42]

Baseline levels of quality of life (QoL), physical functioning and fatigue remained stable or improved over the course of treatment. CLL and its treatments can profoundly affect QoL, particularly in R/R patients; it is encouraging that the combinations explored here indicated no deterioration in QoL with the G-based combinations.

There is currently a lack of available treatment options for patients with R/R CLL who have experienced multiple relapses. Recently, anti-CD20 antibody-based, fixed-duration chemotherapy-free approaches have demonstrated efficacy in this setting in the MURANO trial.[43] Given that G has demonstrated greater efficacy than rituximab in other CLL studies,[10–13] it could be assumed that G may be the preferred backbone/partner in future novel combination therapies for patients with R/R CLL. Of note, G is already approved in combination with ibrutinib,[16,17] venetoclax,[18,19] and acalabrutinib[20,44] for patients with 1L CLL. However, it should be noted that rituximab-Clb and G-Clb are approved, and rituximab-based and G-based chemoimmunotherapy is widely available in North America and Europe. This contrasts with the newer chemotherapy-free options (e.g., ibrutinib and venetoclax), which may not be readily available in some countries, especially when treatment duration is unlimited. Furthermore, a substantial proportion of patients discontinue frontline ibrutinib because of toxicity.[45] Moreover, there is a proportion of CLL patients with a favourable genetic profile who can, potentially, achieve a functional cure with 1L chemoimmunotherapy.

As described previously,[27] the GREEN study had several limitations, including the non-comparative/non-randomised study design and potential investigator bias on patient allocation to cohorts/treatment, preventing the direct comparison of specific regimens, and resulting in difficulty interpreting biomarker data because of small patient subgroups. However, as most investigators followed current guidelines when selecting treatment,[1,3] this under-representation was as expected. All patients were analysed as treated, meaning that the G-mono group included patients who discontinued treatment because of AEs after their first dose of G before receiving their planned chemotherapy regimen, as well as patients who were only ever scheduled to receive single-agent G, resulting in higher than expected rates of AEs and discontinuations due to AEs in this group.[28,30]

This final analysis of the GREEN study supports G plus chemotherapy, beyond the approved G-Clb regimen, as a promising treatment option in both 1L and R/R CLL, irrespective of the partner chemotherapy. It also highlights the benefit of a 1L chemoimmunotherapy regimen for patient subgroups defined by genetic markers and mutated *IGHV* status.

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Author contributions

SS, FB, VL, RF and SR designed the study; SS, FB, VL, RF and SB conducted the study; SS, FB, OI, JK, BM, EM, DO, GR, SR, ET, MT, MW, SB, VL and SB recruited and followed up the patients; SS, VL, FB, RF, MVH, PT, SB and TP did the data analysis; JK, SR, VL, SS, FB, VL, RF, MVH and PT interpreted the data. All authors wrote and reviewed the manuscript. All authors read and approved the final manuscript

Disclosures

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Data Availability Statement

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 here (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 here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Baseline demographics and disease characteristics of 1L patients by treatment regimen and fit/non-fit status (ITT population).

Table SII. Summary of treatment exposure.

Table SIII. TLS mitigation strategies.

Table SIV. Mean change from baseline scores on the GHS/QOL, Physical function and Fatigue scales of the QLQ-C30, and the fatigue, treatment side effects and disease symptoms scales of the CLL-16 in 1L or R/R patients with CLL who received G-mono, G-Benda, G-FC or G-Clb.

Table SV. MRD analysis in peripheral blood and bone marrow.

Table SVI. Overall response rate at FRA by prognostic markers (cytogenetic abnormalities, CD38 and *IGHV*) in 1L or R/R patients with CLL who received G-mono, G-Benda, G-FC or G-Clb

Table SVII. Minimal residual disease in blood at FRA by prognostic markers (cytogenetic abnormalities, CD38, and *IGHV*) in 1L or R/R patients with CLL who received G-mono, G-Benda, G-FC or G-Clb.

Table SVIII. Minimal residual disease in bone marrow at FRA by prognostic markers (cytogenetic abnormalities, CD38 and *IGHV*) in 1L or R/R patients with CLL who received G-mono, G-Benda, G-FC or G-Clb.

Fig S1. Patient flow diagram.

Fig S2. Kaplan−Meier plots of PFS by prognostic markers in patients with CLL who received 1L G-mono, G-Benda, G-FC or G-Clb: (A) cytogenetic abnormalities (B) CD38. 1L, first-line; Benda, bendamustine; CI, confidence interval; Clb, chlorambucil; FC, fludarabine/cyclophosphamide; G, obinutuzumab; HR, hazard ratio; mono, monotherapy; PFS, progression-free survival; R/R, relapsed/refractory.

Fig S3. Kaplan−Meier plots of OS by prognostic markers in patients with CLL who received 1L G-mono, G-Benda, G-FC or G-Clb: (A) cytogenetic abnormalities (B) CD38. 1L: first-line; Benda, bendamustine; CI: confidence interval; Clb:

chlorambucil; FC: fludarabine/cyclophosphamide; G: obinutuzumab; HR: hazard ratio; mono: monotherapy; OS: overall survival; R/R: relapsed/refractory.

Fig S4. Kaplan−Meier plots of TTNT by prognostic markers in patients with CLL who received 1L G-mono, G-Benda, G-FC or G-Clb: (A) cytogenetic abnormalities (B) CD38.

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