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Safety of obinutuzumab alone or combined with chemotherapy for previously untreated or relapsed/refractory chronic lymphocytic leukemia in the phase IIIb GREEN study

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ABSTRACT

The safety of obinutuzumab, alone or with chemotherapy, was studied in a non-randomized, open-label, non-comparative, phase IIIb study (GREEN) in previously untreated or relapsed/refractory chronic lymphocytic leukemia. Patients received obinutuzumab 1000 mg alone or with chemotherapy (investigator's choice of fludarabine-cyclophosphamide for fit patients, chlorambucil for unfit patients, or bendamustine for any patient) on days 1, 8 and 15 of cycle 1, and day 1 of cycles 2-6 (28-day cycles), with the cycle 1/day 1 dose administered over two days. The primary end point was safety/tolerability. Between October 2013 and March 2016, 972 patients were enrolled and 971 treated (126 with obinutuzumab monotherapy, 193 with obinutuzumab-fludarabine-cyclophosphamide, 114 with obinutuzumab-chlorambucil, and 538 with obinutuzumab-bendamustine). Grade ≥3 adverse events occurred in 80.3% of patients, and included neutropenia (49.9%), thrombocytopenia (16.4%), anemia (9.6%), and pneumonia (9.0%); rates were similar in first-line and relapsed/refractory patients, and in first-line fit and unfit patients. Using expanded definitions, infusion-related reactions were observed in 65.4% of patients (grade ≥3, 19.9%; mainly seen during the first obinutuzumab infusion), tumor lysis syndrome in 6.4% [clinical and laboratory; highest incidence with obinutuzumab-bendamustine (9.3%)], and infections in 53.7% (grade ≥3, 20.1%). Serious and fatal adverse events were seen in 53.1% and 7.3% of patients, respectively. In first-line patients, overall response rates at three months post treatment exceeded 80% for all obinutuzumab-chemotherapy combinations. In the largest trial of obinutuzumab to date, toxicities were generally manageable in this broad patient population. Safety data were consistent with previous reports, and response rates were high. (*clinicaltrials.gov identifier: 01905943*).

Introduction

Obinutuzumab (GA101) is a glycoengineered, type II anti-CD20 antibody, which has demonstrated significant activity and adequate tolerability in chronic lymphocytic leukemia (CLL), including studies where the drug was administered as monotherapy or combined with chemotherapy.[1-7] Based on the results of the pivotal phase III CLL11 trial,[2,3] in which the combination of obinutuzumab and chlorambucil (G-Clb) was shown to be clinically superior (in terms of progression-free survival and treatment response) to rituximab plus chlorambucil in adult patients with previously untreated CLL and comorbidities, obinutuzumab was approved

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(as G-Clb; in November 2013 in the US and May 2014 in Europe) for this indication.[8,9]

Following its approval in CLL, a large study (GREEN) was undertaken to further inform the risk-benefit profile of obinutuzumab in a broad population of patients that is representative of that encountered in everyday practice. GREEN (*clinicaltrials.gov identifier: 01905943*) is an ongoing phase IIIb safety study of obinutuzumab, as a single agent or in combination with chemotherapy, in fit [defined as a Cumulative Illness Rating Scale (CIRS) score of ≤6 and creatinine clearance (CrCl) ≥70 mL/minute (min)] and unfit (defined as a CIRS score of >6 and/or CrCl <70 mL/min) patients with previously untreated (first-line) or relapsed/refractory (R/R) CLL. This study is collecting safety data for the largest cohort of CLL patients treated with obinutuzumab to date.

This paper reports data for the primary objective of the GREEN study (a primary analysis snapshot), which was to assess the overall safety and tolerability of obinutuzumab-based treatment. An exploratory objective was to investigate the effectiveness of different approaches (including a modified initial obinutuzumab dosage, slower infusion rate and additional steroid pre-medication) to reduce infusion-related reactions (IRRs), which were observed during obinutuzumab infusion in the CLL11 trial, particularly during the first administration.[2]

Methods

Design

GREEN is a non-randomized, non-comparative, open-label study. Patients received intravenous obinutuzumab 1000 mg, alone or with chemotherapy [investigator's choice of fludarabine-cyclophosphamide (FC), Clb or bendamustine (benda), based primarily on fitness; see *Online Supplementary Appendix*], on days 1 (split over 2 consecutive days), 8 and 15 of cycle 1, and on day 1 of cycles 2-6 (six 28-day cycles). Alternative administration approaches for the first obinutuzumab infusion were studied in three first-line cohorts to assess their effect on IRR mitigation (*Online Supplementary Appendix*). Patients received intravenous prednisolone (or equivalent) 1 hour (h) pre-dose on day 1/day 2 of cycle 1.

Risk minimization measures, including prophylaxis and investigator training (*Online Supplementary Appendix*), were instigated for patients considered at risk of tumor lysis syndrome (TLS; defined initially as nodes ≥10 cm, or ≥5-<10 cm with lymphocytes ≥25×10^9/L; definition later expanded for G-benda-treated patients following 2 fatal TLS cases) (*Online Supplementary Appendix*). Neutropenia prophylaxis was also recommended (*Online Supplementary Appendix*).

GREEN was conducted according to the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws/regulations. Study documentation was approved by institutional review boards/ethics committees at each site. Patients gave written informed consent.

Patients

Patients were aged 18 years or over with CLL requiring treatment [National Cancer Institute/International Workshop on Chronic Lymphocytic Leukemia (NCI/iwCLL) criteria[10]], an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and adequate hematologic function (see *Online Supplementary Appendix* for eligibility criteria).

Study procedures

Adverse events (AEs) were graded by NCI Common Terminology Criteria for AEs version 4.0. Response was assessed by investigators according to NCI/iwCLL criteria[10] at the final response assessment, scheduled 84 days after the last dose of study medication.

Statistical analysis

The primary end point was safety/tolerability. Safety outcomes included AEs, grade ≥3 AEs (primary outcome of interest), serious AEs (SAEs), and AEs of special/particular interest (AESIs/AEPIs). Overall response rate (ORR) and complete response [(CR; including CR with incomplete marrow recovery (CRi)] at the final response assessment were among the secondary efficacy end points (*Online Supplementary Appendix*). Time-to-event end points are not presented due to insufficient follow up (median, 20.8-28.8 months, depending on treatment); post-treatment follow up is still ongoing for patients who have not discontinued the study.

IRRs were defined as any AE occurring during/within 24 h of obinutuzumab infusion and considered related to obinutuzumab. IRR incidence in first-line patients was an exploratory end point.

Safety was evaluated in patients treated with at least one dose of study medication. Response was assessed in the intent-to-treat (ITT) population comprising all enrolled patients. A sample size of 950 patients [630 first-line (approximately equal proportions of fit and unfit) and 320 R/R patients] was planned [based on adequate precision, by 95% Clopper-Pearson confidence intervals (CIs), to estimate incidence rate of grade ≥3 AEs if the observed rate was 1-25%], with no formal statistical hypothesis testing. As a non-randomized study, treatment comparability was not applicable.

Data are presented using descriptive statistics. Incidence rates and two-sided 95% Clopper-Pearson CI were calculated for grade ≥3 AEs and ORRs.

Additional AEs and response amendments were reported late by some sites. While not captured here, updates are reported in the *Online Supplementary Appendix*.

Results

Patients

Patients were enrolled between October 2013 and March 2016 at 169 centers in 31 countries in Africa, North and South America, Asia and Europe. This primary analysis took place after all treated patients had finished study treatment and undergone a final response assessment (data cut-off for primary snapshot analysis, December 29, 2016).

The ITT population comprised 972 patients and the safety population included 971 patients [630 (64.8%) first-line, including 339 (34.9%) fit (CIRS ≤6 and CrCl ≥70 mL/min) and 291 (29.9%) unfit (CIRS >6 and/or CrCl <70 mL/min) patients; and 341 (35.1%) R/R patients]; one first-line patient was enrolled but not treated and therefore not included in the safety population. Seven patients from one site in Romania were excluded from the analyses due to non-compliance with Good Clinical Practice guidelines.

At the data cut-off, 195 (20.1%; 80 first-line and 115 R/R) ITT patients had discontinued the study and 777 (79.9%; 551 first-line and 226 R/R) were still on study (all in follow up). Primary reasons for study discontinuation included death [n=105 (10.8%); 40 first-line and 65 R/R], withdrawal of consent (n=63, 6.5%), AE (n=10, 1.0%),

loss to follow up (n=9, 0.9%), investigator decision (n=4, 0.4%) and other (n=4, 0.4%).

In the ITT population, median age was 66.0 (range 33-90) years, 63.5% of patients were male, 59.6%/36.9%/3.5% had an ECOG performance status of 0/1/2, 79.2% had a CIRS score of ≤6 and 61.0% had CrCl ≥70 mL/min (Table 1). Binet stage distribution at screening was 25.3% stage A, 41.2% stage B, 32.9% stage C and 0.6% missing. Five hundred and thirty-three (54.8%) patients had a high tumor burden (with nodes ≥10 cm, or

Table 1. Demographics and baseline disease characteristics according to line of therapy and fitness of patients (intent-to-treat population).

Characteristic	First-line fit (n=339)	First-line unfit (n=292)	First-line all (n=631)	R/R (n=341)	Total (n=972)
Median age, (range) years	59.0 (33-82)	72.0 (45-87)	65.0 (33-87)	68.0 (33-90)	66.0 (33-90)
Age ≥65 years, n (%)	102 (30.1)	223 (76.4)	325 (51.5)	213 (62.5)	538 (55.3)
Age ≥75 years, n (%)	15 (4.4)	114 (39.0)	129 (20.4)	98 (28.7)	277 (28.5)
Male, n (%)	233 (68.7)	166 (56.8)	399 (63.2)	218 (63.9)	617 (63.5)
ECOG performance status, n(%)					
0	237 (69.9)	154 (52.7)	391 (62.0)	188 (55.1)	579 (59.6)
1	98 (28.9)	127 (43.5)	225 (35.7)	134 (39.3)	359 (36.9)
2	4 (1.2)	11 (3.8)	15 (2.4)	19 (5.6)	34 (3.5)
Binet stage, n(%)					
A	97 (28.6)	72 (24.7)	169 (26.8)	77 (22.6)	246 (25.3)
B	161 (47.5)	112 (38.4)	273 (43.3)	127 (37.2)	400 (41.2)
C	81 (23.9)	108 (37.0)	189 (30.0)	131 (38.4)	320 (32.9)
Missing	0	0	0	6 (1.8)	6 (0.6)
B symptoms, n (%)*	120 (35.4)	87 (29.8)	207 (32.8)	114 (33.4)	321 (33.0)
Bulky disease (≥5 cm), n(%)					
	240 (70.8)	149 (51.0)	389 (61.6)	210 (61.6)	599 (61.6)
Lymphocytes ≥25x10^9/L, n(%)	259 (76.4)	230 (78.8)	489 (77.5)	214 (62.8)	703 (72.3)
Total CIRS score, n(%)					
≤6	339 (100)	172 (58.9)	511 (81.0)	259 (76.0)	770 (79.2)
>6	0	120 (41.1)	120 (19.0)	82 (24.0)	202 (20.8)
CrCl at screening, n(%)					
<70 mL/min	0	230 (78.8)	230 (36.5)	149 (43.7)	379 (39.0)
≥70 mL/min	339 (100)	62 (21.2)	401 (63.5)	192 (56.3)	593 (61.0)
ZAP-70 expression, n(%)					
Negative	87 (25.7)	72 (24.7)	159 (25.2)	84 (24.6)	243 (25.0)
Positive	189 (55.8)	146 (50.0)	335 (53.1)	160 (46.9)	495 (50.9)
Missing	63 (18.6)	74 (25.3)	137 (21.7)	97 (28.4)	234 (24.1)
CD38 expression, n(%)					
Negative	140 (41.3)	104 (35.6)	244 (38.7)	93 (27.3)	337 (34.7)
Positive	134 (39.5)	115 (39.4)	249 (39.5)	153 (44.9)	402 (41.4)
Missing	65 (19.2)	73 (25.0)	138 (21.9)	95 (27.9)	233 (24.0)
Cytogenetics, n(%)					
17p deletion	14 (4.1)	20 (6.8)	34 (5.4)	46 (13.5)	80 (8.2)
11q deletion	55 (16.2)	33 (11.3)	88 (13.9)	67 (19.6)	155 (15.9)
12q trisomy	45 (13.3)	48 (16.4)	93 (14.7)	33 (9.7)	126 (13.0)
13q deletion	106 (31.3)	97 (33.2)	203 (32.2)	79 (23.2)	282 (29.0)
Other	18 (5.3)	7 (2.4)	25 (4.0)	16 (4.7)	41 (4.2)
No abnormality	58 (17.1)	43 (14.7)	101 (16.0)	33 (9.7)	134 (13.8)
Missing	43 (12.7)	44 (15.1)	87 (13.8)	67 (19.6)	154 (15.8)
IgVH mutation status, n (%)					
Mutated	101 (29.8)	90 (30.8)	191 (30.3)	64 (18.8)	255 (26.2)
Unmutated	181 (53.4)	146 (50.0)	327 (51.8)	188 (55.1)	515 (53.0)
Missing	57 (16.8)	56 (19.2)	113 (17.9)	89 (26.1)	202 (20.8)

R/R: relapsed/refractory; ECOG: Eastern Cooperative Oncology Group; CIRS: Cumulative Illness Rating Scale; CrCl: creatinine clearance; n: number; min: minute. *Patients with at least one B symptom (unexplained fever >38°C, drenching night sweats >1 month or weight loss >10% of body mass in preceding 6 months).

Table 2. Summary of adverse events according to line of therapy and fitness of patients (safety population).

N (%)	First-line fit (n=339)	First-line unfit (n=291)	First-line all (n=630)	R/R (n=341)	Total (n=971)
AEs of any grade (in ≥10% of patients in the safety population by preferred term)					
Any	328 (96.8)	288 (99.0)	616 (97.8)	334 (97.9)	950 (97.8)
Neutropenia	216 (63.7)	153 (52.6)	369 (58.6)	198 (58.1)	567 (58.4)
Pyrexia	112 (33.0)	98 (33.7)	210 (33.3)	101 (29.6)	311 (32.0)
Thrombocytopenia	99 (29.2)	89 (30.6)	188 (29.8)	115 (33.7)	303 (31.2)
Nausea	99 (29.2)	77 (26.5)	176 (27.9)	94 (27.6)	270 (27.8)
Anemia	68 (20.1)	79 (27.1)	147 (23.3)	83 (24.3)	230 (23.7)
Chills	47 (13.9)	53 (18.2)	100 (15.9)	57 (16.7)	157 (16.2)
Diarrhea	47 (13.9)	44 (15.1)	91 (14.4)	44 (12.9)	135 (13.9)
Vomiting	57 (16.8)	36 (12.4)	93 (14.8)	42 (12.3)	135 (13.9)
Fatigue	31 (9.1)	41 (14.1)	72 (11.4)	46 (13.5)	118 (12.2)
Pneumonia	28 (8.3)	33 (11.3)	61 (9.7)	55 (16.1)	116 (11.9)
Constipation	35 (10.3)	38 (13.1)	73 (11.6)	42 (12.3)	115 (11.8)
Cough	27 (8.0)	32 (11.0)	59 (9.4)	55 (16.1)	114 (11.7)
Leukopenia	43 (12.7)	20 (6.9)	63 (10.0)	46 (13.5)	109 (11.2)
Hypotension	26 (7.7)	36 (12.4)	62 (9.8)	42 (12.3)	104 (10.7)
Dyspnea	28 (8.3)	25 (8.6)	53 (8.4)	46 (13.5)	99 (10.2)
Grade ≥3 AEs (in ≥5% of patients in the safety population by preferred term)					
Any	266 (78.5)	233 (80.1)	499 (79.2)	281 (82.4)	780 (80.3)
Neutropenia	177 (52.2)	129 (44.3)	306 (48.6)	179 (52.5)	485 (49.9)
Thrombocytopenia	46 (13.6)	46 (15.8)	92 (14.6)	67 (19.6)	159 (16.4)
Anemia	23 (6.8)	30 (10.3)	53 (8.4)	40 (11.7)	93 (9.6)
Pneumonia	17 (5.0)	24 (8.2)	41 (6.5)	46 (13.5)	87 (9.0)
Febrile neutropenia	29 (8.6)	18 (6.2)	47 (7.5)	27 (7.9)	74 (7.6)
Leukopenia	26 (7.7)	11 (3.8)	37 (5.9)	29 (8.5)	66 (6.8)
TLS	14 (4.1)	32 (11.0)	46 (7.3)	16 (4.7)	62 (6.4)
Lymphopenia	20 (5.9)	9 (3.1)	29 (4.6)	20 (5.9)	49 (5.0)
Grade 5 (fatal) AEs (in ≥2 patients in the safety population by preferred term)					
Any	13 (3.8)	18 (6.2)	31 (4.9)	40 (11.7)	71 (7.3)
Pneumonia	1 (0.3)	4 (1.4)	5 (0.8)	7 (2.1)	12 (1.2)
Sepsis	1 (0.3)	2 (0.7)	3 (0.5)	2 (0.6)	5 (0.5)
Death	1 (0.3)	1 (0.3)	2 (0.3)	2 (0.6)	4 (0.4)
Richter syndrome	0	0	0	3 (0.9)	3 (0.3)
AML	1 (0.3)	0	1 (0.2)	0	2 (0.2)
Febrile neutropenia	0	2 (0.7)	2 (0.3)	0	2 (0.2)
Septic shock	0	0	0	2 (0.6)	2 (0.2)
TLS	1 (0.3)	1 (0.3)	2 (0.3)	0	2 (0.2)
SAEs (in ≥2% of patients in the safety population by preferred term)					
Any	148 (43.7)	171 (58.8)	319 (50.6)	197 (57.8)	516 (53.1)
Neutropenia	39 (11.5)	23 (7.9)	62 (9.8)	43 (12.6)	105 (10.8)
Pneumonia	20 (5.9)	24 (8.2)	44 (7.0)	48 (14.1)	92 (9.5)
Febrile neutropenia	25 (7.4)	18 (6.2)	43 (6.8)	25 (7.3)	68 (7.0)
Pyrexia	15 (4.4)	13 (4.5)	28 (4.4)	8 (2.3)	36 (3.7)
TLS	4 (1.2)	21 (7.2)	25 (4.0)	11 (3.2)	36 (3.7)
Thrombocytopenia	8 (2.4)	11 (3.8)	19 (3.0)	12 (3.5)	31 (3.2)
Grade ≥3 AESIs/AEPIs (basket terms)*					
Neutropenia	194 (57.2)	138 (47.4)	332 (52.7)	189 (55.4)	521 (53.7)
Infections	48 (14.2)	57 (19.6)	105 (16.7)	90 (26.4)	195 (20.1)
IRRs	60 (17.7)	65 (22.3)	125 (19.8)	68 (19.9)	193 (19.9)

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Thrombocytopenia	47 (13.9)	48 (16.5)	95 (15.1)	68 (19.9)	163 (16.8)
TLS	14 (4.1)	32 (11.0)	46 (7.3)	16 (4.7)	62 (6.4)
Second malignancies	12 (3.5)	23 (7.9)	35 (5.6)	26 (7.6)	61 (6.3)
Second malignancies†	12 (3.5)	20 (6.9)	32 (5.1)	24 (7.0)	56 (5.8)
Hemorrhagic events	2 (0.6)	2 (0.7)	4 (0.6)	5 (1.5)	9 (0.9)
HBV reactivation	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Cardiac events	9 (2.7)	14 (4.8)	23 (3.7)	9 (2.6)	32 (3.3)
PML	0	0	0	1 (0.3)	1 (0.1)

R/R: relapsed/refractory; AE: adverse event; TLS: tumor lysis syndrome; AML: acute myeloid leukemia; SAE: serious adverse event; AESI: adverse event of special interest; AEPI: adverse event of particular interest; IRR: infusion-related reaction; HBV: hepatitis B virus; PML: progressive multifocal leukoencephalopathy; MedDRA: Medical Dictionary for Regulatory Activities; n: number; h: hour. *Neutropenia and thrombocytopenia selection was *via* their MedDRA basket dataset subgroups; infection selection was *via* the MedDRA system order class 'Infections and Infestations'; IRRs were defined as any AE occurring during or within 24 h of obinutuzumab infusion and considered related to obinutuzumab; TLS and PML were defined by their preferred terms; second malignancy selection was *via* the MedDRA system organ class 'Neoplasms Benign, Malignant, and Unspecified' starting six months after the first study drug intake; hemorrhagic event selection was *via* the MedDRA basket dataset subgroup; HBV reactivation was defined as any AE with the preferred term containing 'hepatitis B' or 'hepatitis acute' that was additionally assessed as HBV reactivation *via* medical review; and cardiac event selection was *via* the MedDRA system order class 'Cardiac Disorders'. †Second malignancy selection [standardized MedDRA query (SMQ)], including malignant and unspecified tumors (wide) starting six months after the first study drug intake.

≥5 cm but <10 cm with lymphocytes ≥25x10^9/L) and were classified as being at increased risk of TLS. Other criteria also used to determine TLS risk are specified in the *Online Supplementary Appendix*. Median number of prior lines of therapy received by R/R patients was 1.0 (range 1.0-3.0) (*Online Supplementary Table S1*).

Treatment exposure

Treatment received was [G-mono; n=126 (12.9%); first-line n=62, R/R n=64), G-FC (n=193 (19.9%); first-line n=153, R/R n=40), G-Clb (n=114 (11.7%); first-line n=68, R/R n=46) and G-benda (n=538 (55.3%); first-line n=347, R/R n=191]. Seven hundred and eighty-nine (81.2%) patients completed all six cycles of protocol-specified treatment and 182 (18.7%) discontinued treatment prematurely. For all chemotherapy regimens, most patients received all six treatment cycles, i.e. 79.0% for benda, 84.5% for fludarabine, 85.0% for cyclophosphamide, and 76.3% for Clb. The main reasons for not completing study treatment were tolerability [including AEs; n=146 (15.0%)] and withdrawal of consent [n=15 (1.5%)].

Patients received a median of 9 (range 1-13) administrations of obinutuzumab, with 94.5% of patients receiving ≥90% of the planned dose. Median exposure time to obinutuzumab was 20.4 (range 0.1-30.1) weeks.

Safety

Median observation time was 24.5 (range 0.3-37.8) months. In the safety analysis, the most frequent treatment-emergent AEs (any grade, by preferred term), occurring in ≥20% patients, were neutropenia (58.4%), pyrexia (32.0%), thrombocytopenia (31.2%), nausea (27.8%), and anemia (23.7%), with no notable differences between the first-line and R/R, or fit and unfit subgroups (Table 2). Overall, 23.4% of patients (n=227) had at least one prolonged cytopenia (any grade, occurring during the treatment period and still present >24 days after end of treatment) and 2.4% (n=23) had at least one late-onset cytopenia (any grade, occurring during the post-treatment follow-up period, ≥24 days after end of treatment). AEs were considered related to obinutuzumab in 85.8% of patients, most commonly neutropenia (40.2%), thrombocytopenia (22.6%), nausea (16.8%), pyrexia (23.2%) and anemia (11.1%). AEs leading to discontinuation of obinutuzumab occurred in 14.6% of patients (first-line, 14.4%; R/R, 15.0%), with 5.4% discontinuing obinutuzumab due to IRRs, 3.9% due to neutropenia and 1.8% due to thrombocytopenia. Treatment-emergent AEs by treatment are shown in Table 3.

Severe and serious AEs

Grade ≥3 AEs (the primary safety outcome of interest) occurred in 79.2% (95% CI: 75.8-82.3%) of first-line patients 78.5% (95% CI: 73.7-82.7%) in fit and 80.1% (95% CI:75.0-84.5%) in unfit patients and 82.4% (95% CI:77.9-86.3%) of R/R patients (Table 2). Among the 80.3% of patients overall who experienced grade ≥3 AEs (Table 2), the most frequent events were neutropenia (49.9%), thrombocytopenia (16.4%), anemia (9.6%) and pneumonia (9.0%). The most common SAEs were neutropenia (10.8%), pneumonia (9.5%) and febrile neutropenia (7.0%); the overall rate of SAEs in the safety population was 53.1% (Table 2). Grade ≥3 AEs and SAEs generally occurred at a similar frequency in first-line and R/R patients, and in first-line fit and unfit patients (Table 2), although the overall rate of SAEs was higher in first-line unfit (58.8%) than first-line fit (43.7%) patients.

Deaths

A total of 112 (11.5%) patients died during the study (12 within 28 days of their last dose of study treatment and 100 during the post-treatment follow-up period), primarily due to AEs [n=71 (7.3%)]. AEs leading to death were numerically more common in R/R patients [n=40 (11.7%)] than in first-line patients [n=31 (4.9%)]; fit n=13, unfit n=18). Pneumonia [n=12 (1.2%)]) and sepsis [n=5 (0.5%)]) were the most common AEs leading to death (Table 2). By treatment received, the lowest rate of death due to AEs was observed in the G-FC group [4.7% (9/193)] *vs.* 7.9% (9/114) in the G-Clb group, 7.8% (42/538) in the G-benda group and 8.7% (11/126) in the G-mono group)] (Table 3). Two patients died due to TLS (both in the first-line G-benda subgroup). Disease progression was listed as the primary cause of death in 43 (4.4%) patients.

Adverse events of special or particular interest

AESIs/AEPIs (any grade, as defined in the footnote to Table 2 and Table 3) reported in the overall safety popula-

Table 3. Summary of adverse events according to treatment (safety population).

N (%)	G-mono (n=126)	G-FC (n=193)	G-Clb (n=114)	G-benda (n=538)
AEs of any grade (in ≥10% of patients in the safety population by preferred term)				
Any	123 (97.6)	191 (99.0)	113 (99.1)	523 (97.2)
Neutropenia	50 (39.7)	143 (74.1)	60 (52.6)	314 (58.4)
Pyrexia	29 (23.0)	69 (35.8)	28 (24.6)	185 (34.4)
Thrombocytopenia	28 (22.2)	69 (35.8)	36 (31.6)	170 (31.6)
Nausea	22 (17.5)	76 (39.4)	26 (22.8)	146 (27.1)
Anemia	20 (15.9)	52 (26.9)	26 (22.8)	132 (24.5)
Chills	17 (13.5)	30 (15.5)	17 (14.9)	93 (17.3)
Diarrhea	6 (4.8)	39 (20.2)	10 (8.8)	80 (14.9)
Vomiting	8 (6.3)	44 (22.8)	14 (12.3)	69 (12.8)
Fatigue	7 (5.6)	19 (9.8)	22 (19.3)	70 (13.0)
Pneumonia	14 (11.1)	17 (8.8)	19 (16.7)	66 (12.3)
Constipation	6 (4.8)	24 (12.4)	14 (12.3)	71 (13.2)
Cough	15 (11.9)	28 (14.5)	15 (13.2)	56 (10.4)
Leukopenia	5 (4.0)	25 (13.0)	8 (7.0)	71 (13.2)
Hypotension	14 (11.1)	17 (8.8)	17 (14.9)	56 (10.4)
Dyspnea	10 (7.9)	24 (12.4)	11 (9.6)	54 (10.0)
Grade ≥3 AEs (in ≥5% of patients in the safety population by preferred term)				
Any	95 (75.4)	169 (87.6)	87 (76.3)	429 (79.7)
Neutropenia	42 (33.3)	129 (66.8)	51 (44.7)	263 (48.9)
Thrombocytopenia	15 (11.9)	38 (19.7)	22 (19.3)	84 (15.6)
Pneumonia	11 (8.7)	12 (6.2)	15 (13.2)	49 (9.1)
Febrile neutropenia	8 (6.3)	21 (10.9)	2 (1.8)	43 (8.0)
Anemia	7 (5.6)	21 (10.9)	10 (8.8)	55 (10.2)
Hypotension	6 (4.8)	3 (1.6)	7 (6.1)	7 (1.3)
Leukopenia	3 (2.4)	20 (10.4)	3 (2.6)	40 (7.4)
TLS	2 (1.6)	5 (2.6)	5 (4.4)	50 (9.3)
Lymphopenia	0	10 (5.2)	0	39 (7.2)
Grade 5 (fatal) AEs (in ≥2 patients in the safety population by preferred term)				
Any	11 (8.7)	9 (4.7)	9 (7.9)	42 (7.8)
Pneumonia	1 (0.8)	2 (1.0)	3 (2.6)	6 (1.1)
Sepsis	1 (0.8)	2 (1.0)	0	2 (0.4)
Death	1 (0.8)	1 (0.5)	1 (0.9)	1 (0.2)
Richter syndrome	1 (0.8)	1 (0.5)	0	1 (0.2)
AML	0	1 (0.5)	1 (0.9)	0
Febrile neutropenia	1 (0.8)	0	0	1 (0.2)
Septic shock	1 (0.8)	0	0	1 (0.2)
TLS	0	0	0	2 (0.4)
SAEs (in ≥5% of patients in the safety population by preferred term)				
Any	67 (53.2)	87 (45.1)	57 (50.0)	305 (56.7)
Pneumonia	11 (8.7)	13 (6.7)	16 (14.0)	52 (9.7)
Neutropenia	9 (7.1)	28 (14.5)	6 (5.3)	62 (11.5)
Febrile neutropenia	6 (4.8)	20 (10.4)	2 (1.8)	40 (7.4)
Pyrexia	3 (2.4)	11 (5.7)	1 (0.9)	21 (3.9)
TLS	1 (0.8)	3 (1.6)	3 (2.6)	29 (5.4)
Grade ≥3 AESIs/AEPIs (basket terms)*				
Neutropenia	49 (38.9)	136 (70.5)	53 (46.5)	283 (52.6)
IRRs	31 (24.6)	35 (18.1)	24 (21.1)	103 (19.1)
Infections	27 (21.4)	30 (15.5)	23 (20.2)	115 (21.4)
Thrombocytopenia	16 (12.7)	39 (20.2)	24 (21.1)	84 (15.6)

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Second malignancies	6 (4.8)	9 (4.7)	7 (6.1)	39 (7.2)
Second malignancies[†]	5 (4.0)	8 (4.1)	6 (5.3)	37 (6.9)
TLS	2 (1.6)	5 (2.6)	5 (4.4)	50 (9.3)
Hemorrhagic events	1 (0.8)	0	0	8 (1.5)
HBV reactivation	0	0	0	1 (0.2)[‡]
Cardiac events	3 (2.4)	6 (3.1)	3 (2.6)	20 (3.7)
PML	1 (0.8)	0	0	0

G: obinutuzumab; mono: monotherapy; FC: fludarabine-cyclophosphamide; Clb: chlorambucil; benda: bendamustine; AE: adverse event; TLS: tumor lysis syndrome; AML: acute myeloid leukemia; SAE: serious adverse event; AESI: adverse event of special interest; AEPI: adverse event of particular interest; IRR: infusion-related reaction; HBV: hepatitis B virus; PML: progressive multifocal leukoencephalopathy; MedDRA: Medical Dictionary for Regulatory Activities; n: number; h: hour. *Neutropenia and thrombocytopenia selection was *via* their MedDRA basket dataset subgroups; infection selection was *via* the MedDRA system order class 'Infections and Infestations'; IRRs were defined as any AE occurring during or within 24 h of obinutuzumab infusion and considered related to obinutuzumab; TLS and PML were defined by their preferred terms; second malignancy selection was *via* the MedDRA system organ class 'Neoplasms Benign, Malignant, and Unspecified' starting six months after the first study drug intake; hemorrhagic event selection was *via* the MedDRA basket dataset subgroup; HBV reactivation was defined as any AE with the preferred term containing 'hepatitis B' or 'hepatitis acute' that was additionally assessed as HBV reactivation *via* medical review; and cardiac event selection was *via* the MedDRA system order class 'Cardiac Disorders'. [†]Second malignancy selection: standardized MedDRA query (SMQ), including malignant and unspecified tumors (wide) starting 6 months after the first study drug intake, [‡]Three patients had HBV reactivation in total, 2 of which were grade <3.

tion were IRRs (65.4%; grade ≥3, 19.9%), neutropenia (61.7%; grade ≥3, 53.7%), infections (53.7%; grade ≥3, 20.1%), thrombocytopenia (32.3%; grade ≥3, 16.8%), cardiac events (11.2%; grade ≥3, 3.3%), second malignancies [(8.4% by MedDRA system organ class, including grade ≥3, 6.3% (listed in full in *Online Supplementary Table S2)*; 7.7% by standardized MedDRA query, including grade ≥3, 5.8%)], hemorrhagic events (7.1%; grade ≥3, 0.9%), TLS (6.4%; all grade ≥3 by definition), hepatitis B virus reactivation (0.3%; grade ≥3, 0.1%) and progressive multifocal leukoencephalopathy (0.1%; grade ≥3, 0.1%). The most commonly reported infections by preferred term were pneumonia (11.9%), bronchitis (6.9%), upper respiratory tract infection (6.9%), nasopharyngitis (5.4%) and urinary tract infection (5.4%). Grade ≥3 AESIs/AEPIs were reported at a similar frequency in first-line and R/R patients, and in first-line fit and unfit patients (Table 2); however, grade ≥3 TLS as an AESI was more common in first-line (7.3%) than in R/R patients (4.7%), and in first-line unfit (11.0%) than in first-line fit (4.1%) patients, and grade ≥3 infections as AESIs were more common in R/R patients (26.4%) than in first-line patients (16.7%).

TLS and IRRs

In the 62 patients with TLS events, 32 cases had laboratory TLS and 30 had clinical TLS. Except for the 2 fatal cases described below, all TLS events resolved, none with sequelae, and there was no recurrence in any patient. In 41 of the 62 patients with TLS, no change in drug dosing was needed; treatment was interrupted or delayed in 17 patients and discontinued in 4 patients. A higher rate of TLS was observed in patients who received G-benda (9.3% overall; 6.6% in first-line fit, 14.4% in first-line unfit, and 6.8% in R/R patients) compared with the other regimens. Of the 2 patients with fatal TLS, one had bulky disease (age 79 years) and the other lymphadenopathy (age 45 years); the older patient also had chronic renal failure at baseline. Both patients died in hospital after cardiovascular events (sudden cardiac arrest and acute cardiac failure, respectively).

The frequency of IRRs was similar among the three dosing cohorts regardless of the IRR mitigation strategy used, although grade ≥3 IRRs, serious IRRs and IRRs leading to obinutuzumab discontinuation were more common in Cohort 3, along with TLS (as a preferred term) (Table 4).

Treatment response

Among first-line patients, the ORR in the ITT population at the final response assessment was 89.5% with G-FC, 82.4% with G-Clb, 81.8% with G-benda, and 63.5% with G-mono (Table 5); respective CR/CRi rates were 46.4%, 16.2%, 35.7% and 20.6%. In R/R patients, the ORR was 82.5% with G-FC, 54.3% with G-Clb, 72.8% with G-benda and 42.2% with G-mono; CR/CRi rates were 22.5%, 6.5%, 19.9% and 4.7%, respectively. Response rates for the 80 patients with 17p deletion are also shown in Table 5.

Discussion

GREEN evaluated the safety and tolerability of obinutuzumab, alone or combined with chemotherapy, in a broad CLL patient population, including first-line (fit and unfit) and R/R patients. The chemotherapy partner options that were available to GREEN investigators mirror those used in standard practice with anti-CD20 antibodies in CLL.[11,12] Notably, GREEN represents the first large-scale report of safety data for obinutuzumab in CLL patients following its approval.

While GREEN was subject to certain limitations, the study provides valuable information on the overall safety profile of obinutuzumab, alone or combined with chemotherapy, in a broad CLL population. Importantly, obinutuzumab-based treatment demonstrated a generally manageable toxicity profile. Because of the non-comparative/non-randomized study design and potential investigator bias on patient allocation to cohorts/treatment, specific treatment regimens could not be compared directly. Furthermore, as treatment allocation was based on investigator's choice, some subgroups were under-represented [e.g. first-line unfit and fit patients treated with G-mono (n=32 and n=31, respectively), and R/R patients treated with G-FC (n=40) or G-Clb (n=46)], making it difficult to draw conclusions from these small patient cohorts. However, this under-representation was not surprising given that most investigators followed current guideline recommendations for treatment.[11,12] All patients were also analyzed as treated; for example, the G-mono group included patients who discontinued treatment after their first obinutuzumab administration due to AEs before receiving their planned chemotherapy regimen (n=23), as

Table 4. Summary of infusion-related reactions according to the approach used to prevent or mitigate these events in first-line patients.

N (%)*	Cohort 1 (n=237)†	Cohort 2 (n=228)‡	Cohort 3 (n=151)§
Any IRR	141 (59.5)	153 (67.1)	96 (63.6)
Grade ≥3 IRRs	45 (19.0)	41 (18.0)	37 (24.5)
Serious IRRs	26 (11)	24 (10.5)	23 (15.2)
IRRs leading to any obinutuzumab discontinuation	4 (1.7)	5 (2.2)	12 (7.9)
IRRs (reported by ≥2% patients in any cohort, any grade by preferred term)			
Chills	49 (20.7)	26 (11.4)	13 (8.6)
Pyrexia	45 (19.0)	42 (18.4)	28 (18.5)
Nausea	24 (10.1)	34 (14.9)	7 (4.6)
Vomiting	16 (6.8)	14 (6.1)	4 (2.6)
TLS	14 (5.9)	6 (2.6)	15 (9.9)
Hypertension	12 (5.1)	10 (4.4)	5 (3.3)
Hypotension	12 (5.1)	31 (13.6)	4 (2.6)
Thrombocytopenia	8 (3.4)	16 (7.0)	9 (6.0)
Dyspnea	7 (3.0)	17 (7.5)	9 (6.0)
Hypersensitivity	7 (3.0)	1 (0.4)	1 (0.7)
Chest discomfort	6 (2.5)	10 (4.4)	3 (2.0)
Flushing	5 (2.1)	8 (3.5)	2 (1.3)
Hot flush	5 (2.1)	1 (0.4)	1 (0.7)
Anemia	5 (2.1)	3 (1.3)	5 (3.3)
Oxygen saturation decreased	5 (2.1)	3 (1.3)	N/R
Hyperhidrosis	5 (2.1)	7 (3.1)	1 (0.7)
Headache	3 (1.3)	12 (5.3)	5 (3.3)
Tremor	3 (1.3)	5 (2.2)	N/R
Rash	2 (0.8)	6 (2.6)	4 (2.6)
AST increased	2 (0.8)	8 (3.5)	6 (4.0)
ALT increased	2 (0.8)	6 (2.6)	6 (4.0)
Feeling hot	2 (0.8)	5 (2.2)	1 (0.7)
Dizziness	1 (0.4)	5 (2.2)	N/R

IRR: infusion-related reaction; TLS: tumor lysis syndrome; N/R: not reported; AST: aspartate aminotransferase; ALT: alanine aminotransferase; G: obinutuzumab; mono: monotherapy; FC: fludarabine-cyclophosphamide; Clb: chlorambucil; benda: bendamustine; n: number; h: hour. Patients within each cohort could have received any of the permitted immunochemotherapy regimens: G-mono (Cohort 1, n=15; Cohort 2, n=25; Cohort 3, n=20), G-FC (Cohort 1, n=61; Cohort 2, n=57; Cohort 3, n=33), G-Clb (Cohort 1, n=12; Cohort 2, n=40; Cohort 3, n=16) or G-benda (Cohort 1, n=149; Cohort 2, n=106; Cohort 3, n=82). *Sixteen previously untreated patients from the safety population were excluded from the cohort analysis as they did not receive treatment as planned (n=15) or were not assigned to any cohort (n=1). †Cycle 1 day 1 dose of obinutuzumab over two days: 25 mg (12.5 mg/h) + 975 mg (50-400 mg/h). ‡Cycle 1 day 1 dose of obinutuzumab over two 2 days: 100 mg (25 mg/h) + 900 mg (50-400 mg/h) with oral dexamethasone 20 mg (or equivalent) 12 h pre-dose. §Cycle 1 day 1 dose of obinutuzumab over two days: doses and infusion rates as in Cohort 1 with pre-medication scheme as in Cohort 2.

well as patients who were only ever planned to receive single-agent obinutuzumab. As such, patients in this subgroup had a higher rate of AEs and discontinuations due to AEs than would be expected for patients treated with G-mono, based on previous single-agent studies.[4,5]

The safety data from GREEN were generally in line with the safety profile for obinutuzumab-based immunochemotherapy previously observed in patients treated for CLL[1-7] and non-Hodgkin lymphoma.[13-18] Common AEs included IRRs (typically mild or moderate events observed almost exclusively during the first obinutuzumab infusion), infections and hematologic toxicities. The higher frequency of grade ≥3 AEs (including infections) and SAEs compared with the pivotal CLL11 study (which enrolled first-line patients with co-existing conditions[2,3]) likely reflects the broader patient population, and inclusion of more heavily pre-treated R/R patients. As expected, R/R patients in GREEN experienced more AEs and more deaths due to AEs or disease progression compared with first-line patients. While the rate of deaths due to AEs, particularly infections/sepsis, in first-line patients was higher than expected, it is reflective of that seen in clinical practice (rather than in classical clinical trials), where a broad range of patients and difficult-to-treat infections are also encountered. Predictably, there was a higher rate of SAEs and fatal AEs in first-line unfit *versus* fit patients; an observation that may have been due to the general health of the patients rather than the treatment regimen(s) received.

The high reported rates of AESIs/AEPIs, including neutropenia, thrombocytopenia, IRRs, infections and TLS, may have resulted from the inclusion of R/R and unfit patients who may be more vulnerable to the adverse effects of treatment, although this did not appear to markedly affect grade ≥3 AESI/AEPI rates. Furthermore, despite the additional risk minimization measures, the rate of IRRs, including TLS, remained relatively high, particularly in Cohort 3. During the initial stages of recruit-

Table 5. Summary of response at the final response assessment according to treatment (intent-to-treat population).

	G-mono (n=127)	G-FC (n=193)	G-Clb (n=114)	G-benda (n=538)
All patients (N=972)				
First-line, % (95% CI)				
ORR	63.5 (50.4-75.3)	89.5 (83.6-93.9)	82.4 (71.2-90.5)	81.8 (77.4-85.8)
CR (including CRi)	20.6	46.4	16.2	35.7
R/R, % (95% CI)				
ORR	42.2 (29.9-55.2)	82.5 (67.2-92.7)	54.3 (39.0-69.1)	72.8 (65.9-79.0)
CR (including CRi)	4.7	22.5	6.5	19.9
Patients with 17p deletion* (n=80)				
First-line, n/N (%)				
ORR	1/2 (50.0)	1/5 (20.0)	5/7 (71.4)	12/20 (60.0)
CR (including CRi)	0/2	1/5 (20.0)	1/7 (14.3)	5/20 (25.0)
R/R, n/N (%)				
ORR	2/6 (33.3)	5/6 (83.3)	5/7 (71.4)	12/27 (44.4)
CR (including CRi)	0/6	0/6	0/7	3/27 (11.1)

n/N: number; G: obinutuzumab; mono: monotherapy; FC: fludarabine-cyclophosphamide; Clb: chlorambucil; benda: bendamustine; CI: confidence interval; ORR: overall response rate; CR: complete response; CRi: complete response with incomplete marrow recovery; R/R: relapsed refractory. *17p deletion status was determined by fluorescence *in situ* hybridization.

ment into Cohort 3, up-dated and expanded definitions of patients at risk of TLS and additional TLS risk mitigation measures (for patients treated with G-benda) were implemented. Nonetheless, the TLS rate in GREEN, including 2 fatal cases, highlights the need for careful risk assessment, prophylaxis and monitoring, particularly in unfit patients [with a CIRS score of >6 and/or reduced renal function (CrCl <70 mL/min)] treated with the G-benda regimen, in whom a high incidence of TLS (14.4%) was observed. It should be noted that, because of the non-randomized study design, it is impossible to conclude whether the increase in TLS seen in G-benda-treated patients in this trial was due to the chemotherapy partner or to differences in patients' characteristics compared with the other treatment cohorts. The current labeling states that any patients with a high tumor burden, high circulating lymphocyte count (>25x10^9/L) or renal impairment, who are considered at greater risk for TLS, should receive appropriate TLS prophylaxis with anti-hyperuricemics (e.g. allopurinol or rasburicase) and hydration prior to obinutuzumab infusion.[8,9] Pre-treatment should then be followed by intensive monitoring of clinical signs/symptoms and laboratory parameters during the first few days of treatment. For IRRs, it is recommended that patients are pre-medicated with an intravenous corticosteroid, acetaminophen and antihistamine, and then monitored closely during obinutuzumab infusion.[8,9] Antimicrobial prophylaxis is advised for patients with prolonged severe neutropenia to prevent infection; granulocyte colony-stimulating factors should be considered in case of grade ≥3 neutropenia.

All four obinutuzumab-based immunochemotherapy regimens appeared manageable in both first-line (fit or unfit) and R/R patients with CLL. G-FC, which was the most intensive regimen, was associated with a high rate of grade ≥3 neutropenia, but this did not translate into an elevated incidence of infection; an observation that may be explained by the underlying fitness of patients who received G-FC. Fitness may also explain the low rate of deaths due to AEs in G-FC-treated patients.

Investigation of strategies to prevent or mitigate IRRs during the first infusion of obinutuzumab was inconclusive, with rates comparable to those reported for G-Clb in CLL11 (grade ≥3, 21%).[2] Despite efforts to minimize IRRs using approaches whereby the dosage of obinutuzumab was modified, the infusion rate slowed and/or additional corticosteroid was given as pre-medication, no one strategy appeared better than another. A recent nursing review of all IRR data from GREEN and CLL11 concluded that IRRs observed with obinutuzumab during the first infusion are generally manageable in CLL patients through treatment interruptions, but management could be improved considerably with extra vigilance during the first infusion.[19]

Analysis of anti-leukemic activity revealed high response rates across all settings and regimens, thus supporting findings from previous studies, including CLL11 and phase I/II trials, which have evaluated the G-Clb, G-FC, G-benda and G-mono regimens.[1-7] Response rates tended to be higher in first-line *versus* R/R patients, and in patients who received combination *versus* single-agent obinutuzumab therapy. The response rates also compared favorably with those reported for rituximab-containing immunochemotherapy (rituximab plus Clb, benda or FC) in CLL.[2,3,20-24] While longer-term data are required to confirm the efficacy of obinutuzumab-based therapy in GREEN, they do suggest that these regimens are clinically active and associated with a generally manageable toxicity profile.

In conclusion, in the largest obinutuzumab patient cohort analyzed to date, the GREEN primary safety data were in line with the safety and tolerability profile previously observed in patients receiving obinutuzumab-based treatment for CLL. Toxicities were generally manageable and response rates were encouraging in this broad population of CLL patients, including previously untreated, fit and unfit patients and those with R/R disease. Based on these data, future trials are warranted.

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