SUPPLEMENTARY APPENDIX

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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Supplementary material

Methods

Inclusion criteria

Disease-related inclusion criteria:

1. Previously untreated patients with documented chronic lymphocytic leukemia (CLL) and requiring treatment according to National Cancer Institute (NCI)/International Workshop on CLL (iwCLL) criteria[1] OR relapsed and/or refractory patients with documented CLL requiring treatment according to NCI/IWCLL criteria[1] (patients with up to three relapses were eligible)

2. Refractory patients if their last treatment was with single-agent therapy, single-agent chemotherapy or single-agent antibody

3. Patients with 17p deletion and/or *TP53* mutation could be included at the investigator's discretion.

General inclusion criteria:

4. Signed informed consent

5. Age ≥18 years

6. Eastern Cooperative Oncology Group performance status 0–2

7. Life expectancy of >6 months according to the investigator's opinion

8. Adequate hematologic function, defined as follows (unless cytopenia is caused by the underlying disease, i.e. no evidence exists of additional bone marrow dysfunction such as myelodysplastic syndrome or hypoplastic bone marrow):

- Hemoglobin ≥9.0 g/dL

- Absolute neutrophil count ≥1.5×10^9/L
- Platelets ≥75×10^9/L
- For patients who will receive bendamustine: leukocyte count >3000/μL

9. Able to comply with study protocol procedures.

Exclusion criteria

Disease-related exclusion criteria:

1. Patients who had received more than three previous CLL treatment lines

2. Documented transformation of CLL to aggressive lymphoma (Richter's transformation)

3. Patients who were refractory to immunochemotherapy.

Biochemical and organ function exclusion criteria:

4. Any of the following abnormal laboratory values (unless any of these abnormalities were due to underlying lymphoma):

- Calculated creatinine clearance (CrCl) <30 mL/min (using the Cockcroft–Gault formula)
- Aspartate transaminase or alanine transaminase >2.5×upper limit of normal (ULN)
- Total bilirubin ≥3×ULN

5. At least one individual organ or system with an impairment score of 4 as assessed by the Cumulative Illness Rating Scale (CIRS) definition, excluding the eyes, ears, nose, throat and larynx organ system

General exclusion criteria:

6. Patients with a history of confirmed progressive multifocal leukoencephalopathy

7. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy

8. Known hypersensitivity to the study drugs

9. History of prior malignancy, unless the malignancy had been treated with a curative intent and in remission without treatment for ≥5 years prior to enrollment, and with the exception of curatively treated basal cell carcinoma, squamous cell carcinoma of the skin, low-grade *in situ* carcinoma of the cervix and low-grade, early-stage localized prostate cancer treated surgically with curative intent

10. Regular treatment (i.e. >5 consecutive days) with corticosteroids during the 28 days prior to the start of cycle 1, day 1, unless administered for indications other than CLL at a dose of prednisone ≤30 mg/day or equivalent

11. Regular treatment with immunosuppressive medications following previous organ transplantation

12. Evidence of significant, uncontrolled co-existing diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, severe arrhythmia, myocardial infarction within the previous 6 months, unstable arrhythmias and unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)

13. Known active bacterial, viral, fungal, mycobacterial, parasitic or other infection (excluding fungal infections of nail beds), or any major episode of infection requiring treatment with intravenous antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 28 days prior to the start of cycle 1, day 1

14. Vaccination with live vaccines within 28 days prior to start of cycle 1, day 1

15. Major surgery (within 28 days prior to the start of cycle 1, day 1), other than for diagnosis

16. Positive test results for chronic hepatitis B infection (defined as positive hepatitis B virus surface antigen [HBsAg] serology) and/or hepatitis B core antibody (HBcAb); patients who had protective titers of hepatitis B surface antibody (HBsAb) after vaccination were eligible

17. Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing). Patients positive for HCV antibody were eligible only if polymerase chain reaction was negative for HCV ribonucleic acid (RNA)

18. Known history of human immunodeficiency virus (HIV) infection with seropositive status

19. Positive test results for human T-lymphotropic virus 1 (HTLV-1). HTLV testing was required in patients from disease-endemic countries (Japan, countries in the Caribbean basin, South America, Central America, sub-Saharan Africa and Melanesia)

20. Women who were pregnant or lactating

21. Fertile men or women of childbearing potential unless: (1) surgically sterile or ≥2 years after the onset of menopause; (2) willing to use a highly effective contraceptive method (Pearl Index <1) – such as oral contraceptives, an intrauterine device, sexual abstinence or a barrier method of contraception in conjunction with spermicidal jelly – during study treatment and in female patients for 12 months after the end of antibody treatment and in male patients for 6 months after the end of chemotherapy treatment

22. Participation in another clinical trial with drug intervention within 28 days prior to the start of cycle 1, day 1 and during the study.

Chemotherapy

The choice of chemotherapy was at the investigator's discretion based on the fitness of the patient, commercial availability of permitted agents, possible previous treatment with obinutuzumab (G) and accepted local practice. Chemotherapy options were fludarabine/cyclophosphamide (25/250 mg/m^2 intravenously or 40/250 mg/m^2 orally on days 1-3; G-FC) for fit patients only (defined as a CIRS score of ≤6 and CrCl ≥70 mL/minute [min]), chlorambucil (0.5 mg/kg orally on days 1 and 15; G-Clb) for unfit patients (defined as a CIRS score of >6 and/or CrCl <70 mL/min) only or bendamustine (benda) for any patient (70 mg/m^2 [relapsed/refractory {R/R} patients] or 90 mg/m^2 [first-line] on days 1 and 2; 50 or 70 mg/m^2 was permitted as a starting dose for R/R patients and unfit first-line patients, respectively; G-benda). Patients who had relapsed after, or who were refractory to, previous obinutuzumab monotherapy (G-mono) had to receive obinutuzumab with chemotherapy. Switching chemotherapy was not allowed during the study.

Granulocyte colony-stimulating factor (G-CSF) was used for prophylaxis of neutropenia, to be administered according to institutional guidelines, e.g. those of the American Society of Clinical Oncology. Platelet transfusions could be used in cases of thrombocytopenia according to institutional practice, at the discretion of the treating physician. Antimicrobial prophylaxis was not mandated by the study protocol in GREEN but could be given at the investigator's discretion in accordance with local guidelines.

Infusion-related reaction mitigation cohorts

While the primary objective of the study was to evaluate safety/tolerability, a pre-specified exploratory objective was to investigate approaches to mitigate or prevent infusion-related reactions (IRRs) in first-line patients, in whom the first dose of obinutuzumab was administered over 2 days. Three cohorts were enrolled sequentially and were treated, as follows:

- Cohort 1, 25 mg at 12.5 mg/hour (h) on day 1 and 975 mg at 50-400 mg/h on day 2;

- Cohort 2, 100 mg at 25 mg/h on day 1 and 900 mg at 50-400 mg/h on day 2, with oral dexamethasone 20 mg or equivalent given 12 h pre-dose;
- Cohort 3, in which doses/infusion rates were as Cohort 1 and pre-medication was as Cohort 2.

In R/R patients, obinutuzumab was administered according to the label (100 mg at 25 mg/h on day 1 and 900 mg at 50-400 mg/h on day 2 of cycle 1).[2,3]

In addition to these measures, all patients received intravenous prednisolone (or equivalent) 1 h pre-dose on cycle 1, day 1/day 2. Pre-medication with acetaminophen and an antihistamine was also stipulated approximately 30 min prior to the start of the obinutuzumab infusion on cycle 1 day 1/day 2.

Safety data relating to IRRs were reviewed in each cohort when approximately 150 patients had completed at least one cycle of obinutuzumab.

Tumor lysis syndrome risk minimization measures

Risk minimization measures, including prophylaxis (allopurinol [or a suitable alternative] and appropriate hydration) and investigator training, were instigated for patients considered at risk of tumor lysis syndrome (TLS), defined initially as those with a tumor burden ≥10 cm, or ≥5 but <10 cm with lymphocytes ≥25×10^9/L. G-CSF use was allowed; primary prophylaxis was advised for patients aged ≥60 years and/or with comorbidities. Allopurinol or a suitable alternative (e.g. rasburicase) was started at least 72 h prior to the first infusion of obinutuzumab on cycle 1, day 1. Hydration consisted of an oral fluid intake of approximately 3 L/day, starting 1-2 days before the first dose of obinutuzumab. Patients still considered at risk of TLS because of a persistently high tumor burden (i.e. lymphocytes ≥25×10^9/L) before the second and subsequent infusions of obinutuzumab could continue to receive TLS prophylaxis and adequate hydration until the risk had abated, as determined by the investigator. Patients considered at risk of TLS were monitored carefully during the initial stages of study treatment particularly with respect to their renal function, potassium and uric acid values.

Chemotherapy was not resumed until all symptoms of TLS (clinical or laboratory) had disappeared.

Following the occurrence of two fatal TLS cases in patients treated with G-benda, the definition of TLS risk was expanded (by protocol amendment) for patients receiving the G-benda combination, as follows:

1. Any measurable lymph node ≥10 cm
2. Any measurable lymph node ≥5 cm and <10 cm AND
    - Lymphocytes $\geq 25 \times 10^9$/L OR
    - Renal impairment, defined as CrCl <70 mL/min
3. Lymphocytes $\geq 25 \times 10^9$/L AND CrCl <70 mL/min.

Additional TLS risk minimization measures were also implemented for patients treated with G-benda, including: further investigator training; patient education on recognizing the signs/symptoms of TLS; an extended period of TLS prophylaxis and hydration (from day -3 to day 8 of cycle 1), including intravenous hydration (3 L/day) on day 1/day 2; pre-infusion laboratory (uric acid, calcium, phosphorus, potassium and creatinine) monitoring with results known prior to administering study treatment; supplementary guidance for managing laboratory/clinical TLS; and nephrology consult/laboratory monitoring for patients with impaired renal function who were not considered at risk of TLS.

Secondary outcome measures

Secondary efficacy outcome measures in the GREEN study included:

- Overall response rate (defined as the proportion of patients with a complete response [CR]/CR with incomplete marrow recovery [CRi] or partial response [PR]) and CR (including CRi) at the time of the final response assessment visit (approximately 3 months after the last dose of study medication), as determined by the investigator[1]

- Progression-free survival, defined as the time from the date of treatment initiation until the first documented progression of disease or death from any cause, whichever occurred first
- Time to response, defined as the interval from the date of treatment initiation to the first documentation of CR or PR
- Event-free survival, defined as the time from treatment initiation to first occurrence of progression or relapse, as assessed by the investigator, or initiation of a non-protocol-specified anti-leukemia therapy or death, whichever occurred first
- Best overall response, defined as the proportion of patients with the best response obtained throughout the trial with CR, CRi or PR, as determined by the investigator[1]
- Overall survival, defined as the time from the date of treatment initiation until the date of death, regardless of the cause of death
- Time to new anti-leukemia therapy, defined as the time between the date of treatment initiation and first intake of new anti-leukemic therapy
- Duration of response, defined as the period from the date of initial confirmed PR or CR until the date of disease progression or death from any cause.

Results

Late reporting

After the data snapshot was taken for analysis, a further 52 adverse events in 42 patients (AEs; 0.5% of total AEs) were reported late by the sites for the initial cut-off day on the database, which remained open to continue collecting information until the final analysis. Similarly, responses at the final analysis were reclassified in 11/971 (1.1%) patients. These updates are not part of the statistical analysis summary tables and listings, as they were reported after the analysis was done. A review was completed and suggested no impact on the safety and overall efficacy conclusions. These updates were not included in the statistical analysis summary tables; listings for the primary analysis will be done at the time of final analysis of the study.

The 52 additional AEs included 26 grade ≥3 AEs (19 grade 3 and seven grade 4 AEs, including eight grade ≥3 neutropenia events) and 11 serious AEs (dyspnea, febrile neutropenia, headache, hemorrhagic stroke, hepatitis E, influenza, invasive pulmonary aspergillosis, lung infection, polytrauma, sepsis and squamous cell cancer; each n=1). Response status was amended in 11 patients, as follows (by study treatment): G-FC (one CR to CRi and two CR to PR), G-Clb (one CR to PR and one stable disease [SD] to PR), G-benda (three CR to PR, one SD to PR, one PR to CR and one progressive disease [PD] to PR) and G-mono (no changes). The overall conclusions from GREEN were not considered to have been impacted by this late reporting.

References

1. Hallek M, Cheson BD, Catovsky D, et al; International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-5456.
2. Gazyva® (obinutuzumab) injection, for intravenous infusion. Full prescribing information. Revised 2/2016.
3. Gazyvaro® (obinutuzumab) 1,000 mg concentrate for solution for infusion. Summary of product characteristics. Last updated 28/07/2016.

Supplementary tables

Supplementary Table 1. Summary of most common (≥10% of patients) previous lines of therapy for R/R patients (ITT population).

n (%)	R/R* (n=110)
Rituximab	50 (45.5)
Chlorambucil	49 (44.5)
Fludarabine	42 (38.2)
Cyclophosphamide	40 (36.4)
Steroids	19 (17.3)
Bendamustine	18 (16.4)
R-chemo	13 (11.8)
Chemo combination	11 (10.0)

*Patients receiving monotherapy and chlorambucil with medication history reported.
Chemo: chemotherapy; R: rituximab; R/R: relapsed/refractory.

Supplementary Table 2. Summary of second malignancies 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)
Any second malignancy	16 (4.7)	34 (11.7)	50 (7.9)	32 (9.4)	82 (8.4)
Basal cell carcinoma	4 (1.2)	9 (3.1)	13 (2.1)	7 (2.1)	20 (2.1)
Squamous cell carcinoma	1 (0.3)	4 (1.4)	5 (0.8)	5 (1.5)	10 (1.0)
Squamous cell carcinoma of the skin	1 (0.3)	6 (2.1)	7 (1.1)	2 (0.6)	9 (0.9)
Malignant melanoma	0	3 (1.0)	3 (0.5)	2 (0.6)	5 (0.5)
Richter's syndrome	0	1 (0.3)	1 (0.2)	4 (1.2)	5 (0.5)
Adenocarcinoma gastric	1 (0.3)	2 (0.7)	3 (0.5)	1 (0.3)	4 (0.4)
Adenocarcinoma of the colon	2 (0.6)	0	2 (0.3)	2 (0.6)	4 (0.4)
Prostate cancer	1 (0.3)	1 (0.3)	2 (0.3)	2 (0.6)	4 (0.4)
Acute myeloid leukemia	2 (0.6)	0	2 (0.3)	1 (0.3)	3 (0.3)
Bowen's disease	0	2 (0.7)	2 (0.3)	0	2 (0.2)
Lung adenocarcinoma	0	1 (0.3)	1 (0.2)	1 (0.3)	2 (0.2)
Lung cancer metastatic	0	1 (0.3)	1 (0.2)	1 (0.3)	2 (0.2)
Myelodysplastic syndrome	0	0	0	2 (0.6)	2 (0.2)
Adenocarcinoma	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Breast cancer	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Bronchial carcinoma	0	0	0	1 (0.3)	1 (0.1)
Cholangiocarcinoma	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Chronic myeloid leukemia	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Clear cell renal cell carcinoma	0	0	0	1 (0.3)	1 (0.1)

Endometrial cancer	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Hepatocellular carcinoma	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Intraductal proliferative breast lesion	0	0	0	1 (0.3)	1 (0.1)
Laryngeal cancer	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Lung neoplasm malignant	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Melanocytic nevus	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Metastatic bronchial carcinoma	0	0	0	1 (0.3)	1 (0.1)
Metastatic carcinoma of the bladder	0	0	0	1 (0.3)	1 (0.1)
Metastatic renal cell carcinoma	1 (0.3)	0	1 (0.2)	0	1 (0.1)
Metastatic squamous cell carcinoma	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Myelofibrosis	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Neoplasm malignant	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Pancreatic carcinoma metastatic	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Primary myelofibrosis	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Rectal adenocarcinoma	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Refractory cytopenia with multilineage dysplasia	0	0	0	1 (0.3)	1 (0.1)
Seborrheic keratosis	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Skin cancer	0	0	0	1 (0.3)	1 (0.1)
Spinal meningioma benign	0	1 (0.3)	1 (0.2)	0	1 (0.1)

R/R: relapsed/refractory.