ORIGINAL ARTICLE

Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions

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ABSTRACT

BACKGROUND

The BCL2 inhibitor venetoclax has shown activity in patients with chronic lymphocytic leukemia (CLL), but its efficacy in combination with other agents in patients with CLL and coexisting conditions is not known.

METHODS

In this open-label, phase 3 trial, we investigated fixed-duration treatment with venetoclax and obinutuzumab in patients with previously untreated CLL and coexisting conditions. Patients with a score of greater than 6 on the Cumulative Illness Rating Scale (scores range from 0 to 56, with higher scores indicating more impaired function of organ systems) or a calculated creatinine clearance of less than 70 ml per minute were randomly assigned to receive venetoclax–obinutuzumab or chlorambucil–obinutuzumab. The primary end point was investigator-assessed progression-free survival. The safety of each regimen was also evaluated.

RESULTS

In total, 432 patients (median age, 72 years; median Cumulative Illness Rating Scale score, 8; median creatinine clearance, 66.4 ml per minute) underwent randomization, with 216 assigned to each group. After a median follow-up of 28.1 months, 30 primary end-point events (disease progression or death) had occurred in the venetoclax–obinutuzumab group and 77 had occurred in the chlorambucil–obinutuzumab group (hazard ratio, 0.35; 95% confidence interval [CI], 0.23 to 0.53; P<0.001). The Kaplan–Meier estimate of the percentage of patients with progression-free survival at 24 months was significantly higher in the venetoclax–obinutuzumab group than in the chlorambucil–obinutuzumab group: 88.2% (95% CI, 83.7 to 92.6) as compared with 64.1% (95% CI, 57.4 to 70.8). This benefit was also observed in patients with *TP53* deletion, mutation, or both and in patients with unmutated immunoglobulin heavy-chain genes. Grade 3 or 4 neutropenia occurred in 52.8% of patients in the venetoclax–obinutuzumab group and in 48.1% of patients in the chlorambucil–obinutuzumab group, and grade 3 or 4 infections occurred in 17.5% and 15.0%, respectively. All-cause mortality was 9.3% in the venetoclax–obinutuzumab group and 7.9% in the chlorambucil–obinutuzumab group. These differences were not significant.

CONCLUSIONS

Among patients with untreated CLL and coexisting conditions, venetoclax–obinutuzumab was associated with longer progression-free survival than chlorambucil–obinutuzumab. (Funded by F. Hoffmann–La Roche and AbbVie; ClinicalTrials.gov number, NCT02242942.)

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Most patients with chronic lymphocytic leukemia (CLL) are older than 70 years of age and have clinically relevant coexisting conditions.[1] Such patients require more effective but less toxic regimens.[2] The CLL11 trial established chlorambucil–obinutuzumab as a standard of care in these patients.[3-6] BCL2 is an antiapoptotic protein that is overexpressed in various B-cell cancers, including CLL.[7] Venetoclax is an orally administered, BCL2 homology domain 3 (BH3)–mimetic compound that disrupts antiapoptotic signaling through BCL2, thereby inducing programmed cell death of CLL cells.[8] In patients with CLL, venetoclax has shown remarkable efficacy.[9-11] To evaluate whether venetoclax–obinutuzumab is superior to chlorambucil–obinutuzumab, we designed the CLL14 trial as a multinational, open-label, phase 3 trial involving previously untreated patients with CLL and coexisting conditions.

Methods

Patients

In this open-label, randomized trial, we enrolled patients who had previously untreated CD20+ CLL that had been diagnosed in accordance with the criteria of the International Workshop on CLL and had been determined by the treating clinician and confirmed during the central screening process to require therapy (Binet stage C [low hemoglobin or platelet count from bone marrow infiltration of CLL cells] or symptomatic disease) (see the Supplementary Appendix, available with the full text of this article at NEJM.org).[12] Because new treatment options were approved during the recruitment period, patients with *TP53* deletion or mutation were enrolled at the investigator's discretion. A notification letter to all the investigators about the enrollment of such patients is shown in the Supplementary Appendix. Patients underwent central review to confirm their eligibility, including the presence of coexisting conditions with a total score of greater than 6 on the Cumulative Illness Rating Scale (scores range from 0 to 56, with higher scores indicating more impaired function of organ systems[13]) (see the Supplementary Appendix) or a creatinine clearance (calculated with the Cockcroft–Gault formula) of less than 70 ml per minute.[14] Additional eligibility criteria are summarized in the Supplementary Appendix. All patients provided written informed consent.

Trial Oversight and Conduct

The trial was approved by the institutional review board or independent health authorities at each participating institution and was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. The trial design was developed by the German CLL Study Group and approved by the sponsors (F. Hoffmann–La Roche and AbbVie). The authors collected the data during the trial, with oversight by an independent data and safety monitoring committee. The sponsors and the German CLL Study Group analyzed the data. All the authors had access to the data and vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol, available at NEJM.org. The manuscript was written by four of the academic authors and was reviewed critically and revised by all the authors. All the authors contributed to the writing and critical revision of the manuscript for intellectual content. Third-party editing and administrative support was funded by F. Hoffmann–La Roche. Agreements between F. Hoffmann–La Roche and the investigators and German CLL Study Group included data confidentiality.

Randomization and Treatment

The trial was conducted in 21 countries at 196 sites. The initial safety and side-effect profile of venetoclax–obinutuzumab had been established during a safety run-in phase.[11] Patients were randomly assigned in a 1:1 ratio to receive either venetoclax–obinutuzumab or chlorambucil–obinutuzumab with the use of a Web and voice mail system based on a computer-generated randomization schedule. A block size of six was used to balance the randomization. Patients were stratified according to Binet stage and geographic region.

The treatment duration in both groups consisted of 12 cycles lasting 28 days each; no crossover was allowed. Obinutuzumab was administered intravenously for 6 cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8 and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6. Chlorambucil was administered orally at 0.5 mg per kilogram of body weight on days 1 and 15 of each cycle until completion of 12 cycles. The daily oral venetoclax regimen was initiated on day 22 of cycle 1, starting

with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week), thereafter continuing at 400 mg daily until completion of cycle 12. The risk of tumor lysis syndrome was assessed on the basis of the absolute lymphocyte count and lymph-node size to guide prophylactic measures (see the Supplementary Appendix).

ASSESSMENTS AND END POINTS

The primary end point was investigator-assessed progression-free survival, defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause. Key secondary end points were progression-free survival as assessed by an independent review committee, minimal residual disease negativity (with a cutoff of 10^{-4} [i.e., <1 cell in 10,000 leukocytes]) in peripheral blood and bone marrow, overall and complete response, minimal residual disease negativity in patients with complete response in peripheral blood and bone marrow (all assessed 3 months after treatment completion), and overall survival. Other secondary end points included the duration of response, event-free survival, and time to new antileukemic treatment.

Baseline assessments conducted at screening included immunophenotyping of circulating lymphocytes, central analysis of genomic aberrations with fluorescence in situ hybridization, mutational analysis of the immunoglobulin heavy-chain variable-region gene (*IGHV*) and *TP53* by DNA sequencing, and evaluation of lymph-node size by physical assessment and computed tomographic scanning or magnetic resonance imaging. Disease was assessed in all patients at baseline and at similar time points in both treatment groups during the trial, including an assessment of the response to therapy 3 months after the completion of treatment, with complete and partial response defined in accordance with International Workshop on CLL guidelines as of 2008 (see the Supplementary Appendix).[12] After the completion of treatment, patients were followed for progression and safety every 3 months for 2 years, and then every 6 months. Minimal residual disease was analyzed centrally in accordance with international guidelines[15,16] with the use of an allele-specific oligonucleotide polymerase-chain-reaction (ASO-PCR) assay. Peripheral-blood monitoring was performed at baseline and at cycles 7, 9, and 12, and then serially every 3 months. In patients with a treatment response, minimal residual disease in bone marrow was assessed at cycle 9 and 3 months after completion of treatment. An independent data and safety monitoring committee reviewed safety regularly (see the Supplementary Appendix).

STATISTICAL ANALYSIS

Sample size was estimated on the basis of an assumed hazard ratio for progression or death of 0.65, with 170 events providing power of approximately 80% on the basis of a two-sided log-rank test stratified according to Binet stage and geographic region, with an alpha level of 0.05. An interim analysis was planned to be performed after 110 of 170 events (65%) had occurred. After data review, the results of the interim analysis were assessed as significantly favoring venetoclax–obinutuzumab and were judged to be robust and reliable, because the P value for the primary end point was lower than the prespecified statistical boundary for early stopping (107 investigator-assessed events observed at the time of interim analysis required $P \leq 0.0009146$). Therefore, the independent data and safety monitoring committee recommended conducting the primary analysis of the primary and secondary end points.

All efficacy end points were analyzed in the intention-to-treat population. For patients who were alive and had not had disease progression or relapse, the data for progression-free survival were censored on the date of the last disease assessment. In the analysis of minimal residual disease negativity and response to treatment, patients without a sample or response assessment that could be evaluated were counted as not being negative for residual disease or as not having a response, respectively. To control for multiplicity, the above-listed key secondary efficacy end points were analyzed with a prespecified hierarchical testing procedure after a fallback procedure.[17] All reported P values for secondary efficacy end points refer to the alpha-controlled key secondary end points. Additional details are provided in the Supplementary Appendix.

RESULTS

PATIENTS

Of the 432 enrolled patients, 216 were randomly assigned to receive venetoclax–obinutuzumab and 216 were assigned to receive chlorambucil–obinutuzumab; these patients made up the intention-

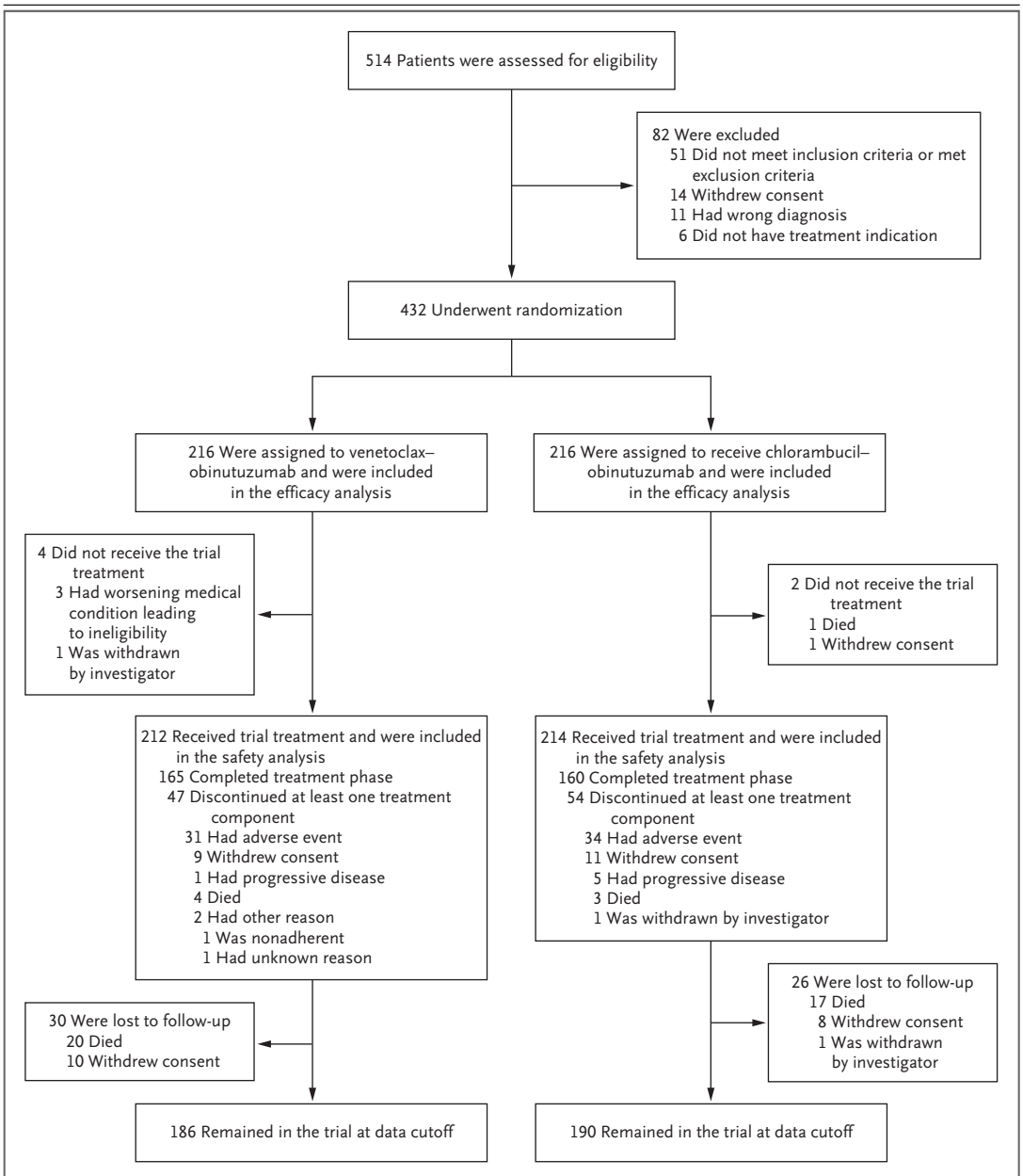


Figure 1. Screening, Randomization, and Follow-up.

to-treat population (Fig. 1). The demographic and disease characteristics were well balanced between the two treatment groups (Table 1, and Table S1 in the Supplementary Appendix). The median age of the patients was 72 years (range, 41 to 89), the median Cumulative Illness Rating Scale score was 8 (range, 0 to 28) (Table S2 in the Supplementary Appendix), and the median creatinine clearance was 66.4 ml per minute (range, 0.1 to 3670.0). Altogether, 13.8% of the patients had *TP53* deletion, mutation, or both and 59.8% had unmutated *IGHV*. With regard to the risk of tumor lysis syndrome, 13.4%, 64.4%, and 22.2% of the patients in the venetoclax–obinutuzumab group were at low, medium, and high risk, respectively. The safety population included 426 patients (Fig. 1). A total of 77.8% of the patients in the venetoclax–obinutuzumab group

Table 1. Selected Patient Demographic and Disease Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	Venetoclax–Obinutuzumab (N=216)	Chlorambucil–Obinutuzumab (N=216)
Age ≥75 yr — no. (%)	72 (33.3)	78 (36.1)
Male sex — no. (%)	146 (67.6)	143 (66.2)
Binet stage — no. (%)†		
A	46 (21.3)	44 (20.4)
B	77 (35.6)	80 (37.0)
C	93 (43.1)	92 (42.6)
Tumor lysis syndrome risk category — no. (%)		
Low	29 (13.4)	26 (12.0)
Intermediate	139 (64.4)	147 (68.1)
High	48 (22.2)	43 (19.9)
Total CIRS score >6 — no. (%)‡	186 (86.1)	177 (81.9)
Calculated creatinine clearance <70 ml/min — no./total no. (%)	128/215 (59.5)	118/213 (55.4)
Cytogenetic subgroup — no./total no. (%)§		
Deletion in 17p	17/200 (8.5)	14/193 (7.3)
Deletion in 11q	36/200 (18.0)	38/193 (19.7)
Trisomy 12	36/200 (18.0)	40/193 (20.7)
No abnormalities	50/200 (25.0)	42/193 (21.8)
Deletion in 13q alone	61/200 (30.5)	59/193 (30.6)
IGHV mutational status — no./total no. (%)		
Mutated	76/200 (38.0)	83/208 (39.9)
Unmutated	121/200 (60.5)	123/208 (59.1)
Could not be evaluated	3/200 (1.5)	2/208 (1.0)
TP53 mutational status — no./total no. (%)		
Mutated	19/171 (11.1)	13/157 (8.3)
Unmutated	152/171 (88.9)	144/157 (91.7)

* There were no significant differences between the groups at baseline. Percentages may not total 100 because of rounding.
† Binet stages indicate the degree of advancement of chronic lymphocytic leukemia and are based on organ and lymph-node involvement, hemoglobin levels, and platelet counts.
‡ Scores on the Cumulative Illness Rating Scale (CIRS) range from 0 to 56, with higher scores indicating more impaired function of organ systems.
§ Cytogenetic subgroups were determined according to the hierarchical model of Döhner at al.[18]

and 74.8% of the patients in the chlorambucil–obinutuzumab group received the planned number of 12 treatment cycles, with a median treatment duration of 11.1 months (range, 0.0 to 14.1) and 10.8 months (range, 0.0 to 13.6), respectively. The median relative dose intensity was 95.1% (range, 21 to 100) for venetoclax, 95.4% (range, 4 to 111) for chlorambucil, and 100% (range, 0 to 111) for obinutuzumab, with dose modifications in 43.3%, 26.9%, and 38.3% of patients, respectively.

EFFICACY

At the data cutoff, all patients had stopped treatment for a median of 17.1 months (range, 0.0 to 30.4) in the venetoclax–obinutuzumab group and 17.9 months (range, 0.0 to 30.2) in the chlorambucil–obinutuzumab group. After a median follow-up of 28.1 months (range, 0.0 to 35.9), 30 primary end-point events had occurred in the venetoclax–obinutuzumab group (14 events of disease progression and 16 deaths among 216 patients) and 77 primary end-point events had oc-

curred in the chlorambucil–obinutuzumab group (69 events of disease progression and 8 deaths among 216 patients) (hazard ratio for progression or death, 0.35; 95% confidence interval [CI], 0.23 to 0.53; P<0.001). The Kaplan–Meier estimate of the percentage of patients with investigator-assessed progression-free survival at month 24 was significantly higher in the venetoclax–obinutuzumab group than in the chlorambucil–obinutuzumab group (88.2% [95% CI, 83.7% to 92.6%] vs. 64.1% [95% CI, 57.4% to 70.8%]) (Fig. 2A). This benefit was also observed in patients with *TP53* deletion, mutation, or both, in patients with unmutated *IGHV*, and in other prespecified subgroups (Figs. S1, S2, and S3 in the Supplementary Appendix). An analysis of progression-free survival as assessed by the independent review committee confirmed the results (Fig. 2B).

Three months after treatment completion, in the intention-to-treat population, higher percentages of patients in the venetoclax–obinutuzumab group than in the chlorambucil–obinutuzumab group were negative for minimal residual disease in peripheral blood (75.5% vs. 35.2%, P<0.001) and in bone marrow (56.9% vs. 17.1%, P<0.001) (Table S3 in the Supplementary Appendix). Minimal residual disease negativity was consistently more common across all subgroups and was more sustainable with venetoclax–obinutuzumab than with chlorambucil–obinutuzumab (Figs. S4 and S5 in the Supplementary Appendix). These results, as assessed by ASO-PCR, were confirmed by flow cytometry (Fig. S6 and Table S4 in the Supplementary Appendix). The percentages of patients with any response to treatment or with a complete response to treatment were significantly higher in the venetoclax–obinutuzumab group than in the chlorambucil–obinutuzumab group (percentage of patients with response, 84.7% vs. 71.3% [P<0.001]; percentage of patients with complete response, 49.5% vs. 23.1% [P<0.001]) (Fig. 2C). The percentages of patients with both a complete response and minimal residual disease negativity in peripheral blood or bone marrow were significantly higher with venetoclax–obinutuzumab than with chlorambucil–obinutuzumab (peripheral blood, 42.1% vs. 14.4% [P<0.001]; bone marrow, 33.8% vs. 10.6% [P<0.001]). The results for other secondary time-to-event end points showed consistent superiority of venetoclax–obinutuzumab (Figs. S7, S8, and S9 in the Supplementary Appendix).

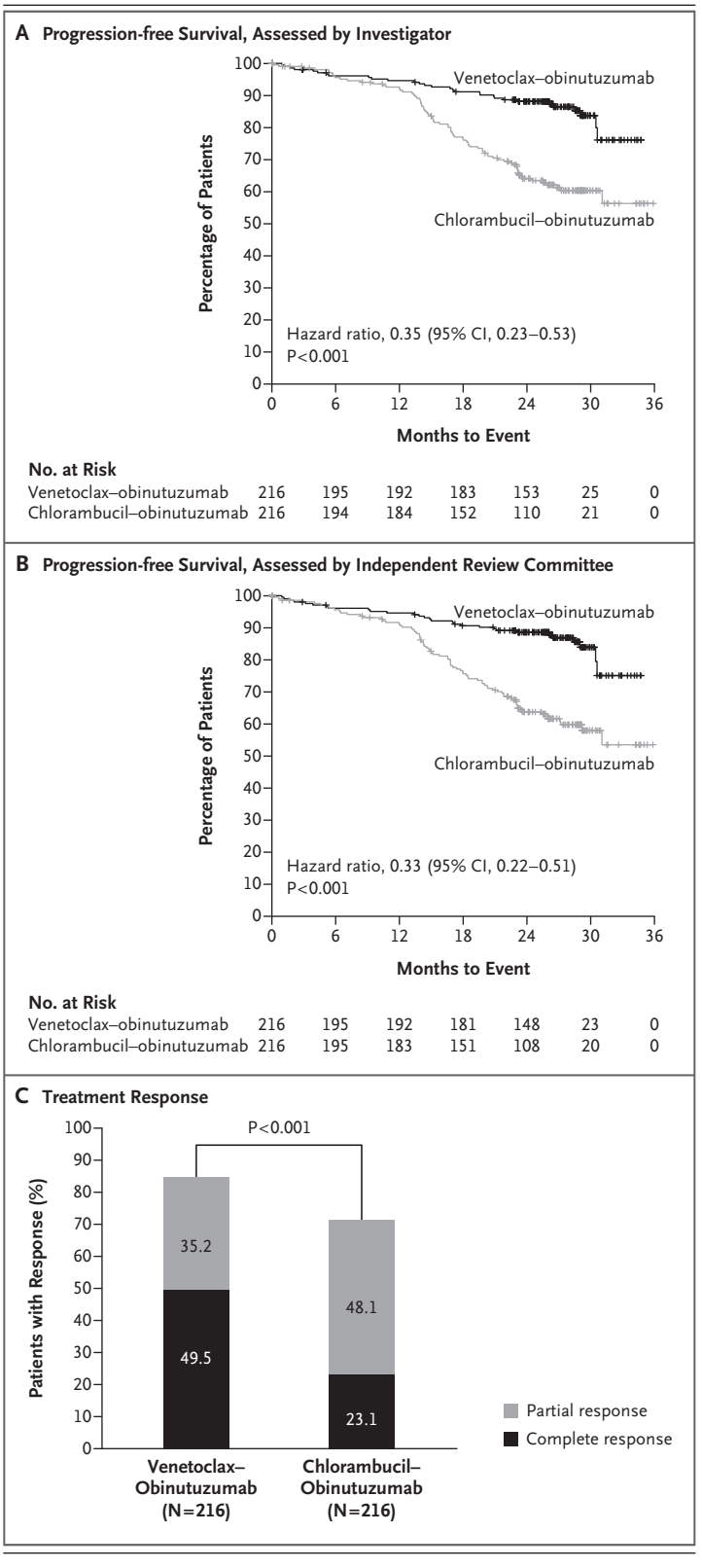
The median overall survival was not reached in either group. Over the complete observation period, overall survival did not differ significantly between the venetoclax–obinutuzumab group (20 deaths from any cause among 216 patients; all-cause mortality, 9.3%) and the chlorambucil–obinutuzumab group (17 deaths from any cause among 216 patients; all-cause mortality, 7.9%) (Kaplan–Meier estimate of the percentage of patients alive at 24 months, 91.8% [95% CI, 88.1 to 95.5] and 93.3% [95% CI, 90.0 to 96.7], respectively; hazard ratio for death, 1.24; 95% CI, 0.64 to 2.40; P=0.52) (Fig. S10 in the Supplementary Appendix). The results for all key secondary end points in accordance with the hierarchical testing procedure are summarized in Table S5 in the Supplementary Appendix.

SAFETY

At least one adverse event of any grade occurred in 94.3% of patients in the venetoclax–obinutuzumab group and in 99.5% of patients in the chlorambucil–obinutuzumab group (Table S6 in the Supplementary Appendix), with adverse events leading to treatment discontinuation occurring in 16.0% and 15.4% of patients, respectively. The most common grade 3 or 4 adverse event was neutropenia (Table 2). Grade 3 or 4 febrile neutropenia and grade 3 or 4 infections were reported in 5.2% and 17.5% of patients in the venetoclax–obinutuzumab group, respectively, and in 3.7% and 15.0% of patients in the chlorambucil–obinutuzumab group; 43.5% of patients in the venetoclax–obinutuzumab group and 45.8% of patients in the chlorambucil–obinutuzumab group were treated with granulocyte colony-stimulating factor. Tumor lysis syndrome was reported in three patients in the venetoclax–obinutuzumab group (all cases occurred during treatment with obinutuzumab and before treatment with venetoclax) and in five patients in the chlorambucil–obinutuzumab group. None of these events met the Howard criteria for clinical tumor lysis syndrome (i.e., the presence of specific electrolyte changes and clinical manifestations; see the Supplementary Appendix).[19] Grade 3 or 4 infusion-related reactions occurred in similar percentages of patients in the two treatment groups (9.0% and 10.3%). A

Figure 2. Progression-free Survival and Treatment Response.

Shown are the percentages of patients with investigator-assessed progression-free survival (Panel A), independent review committee–assessed progression-free survival (Panel B), and treatment response 3 months after completion of treatment (Panel C). Tick marks indicate censored data.



summary of the serious adverse events is provided in Table S7 in the Supplementary Appendix.

During treatment, 5 fatal adverse events occurred in the venetoclax–obinutuzumab group (of these, 2 occurred in patients who received obinutuzumab only and no venetoclax) and 4 occurred in the chlorambucil–obinutuzumab group. After completion of treatment, 11 fatal adverse events occurred in the venetoclax–obinutuzumab group and 4 occurred in the chlorambucil–obinutuzumab group (Table 3, and Table S8 in the Supplementary Appendix). Second primary cancers were reported in 13.7% of patients in the venetoclax–obinutuzumab group and in 10.3% of patients in the chlorambucil–obinutuzumab group (Table S9 in the Supplementary Appendix). Richter's transformation (progression to diffuse large B-cell lymphoma) occurred in two patients in the venetoclax–obinutuzumab group and in one patient in the chlorambucil–obinutuzumab group.

DISCUSSION

In this phase 3 trial, we investigated fixed-duration targeted treatment with venetoclax–obinutuzumab as compared with fixed-duration chemoimmunotherapy
with chlorambucil–obinutuzumab in previously untreated patients with CLL and coexisting conditions. Significantly longer progression-free survival was noted with venetoclax–obinutuzumab. In all patients and across all the major prognostic subgroups analyzed, venetoclax–obinutuzumab was consistently superior to chlorambucil–obinutuzumab with regard to key efficacy outcome measures, including minimal residual disease negativity in peripheral blood and bone marrow and overall or complete response. With a median age of 72 years and a median Cumulative Illness Rating Scale score of 8, the trial population was representative of most patients with CLL.[20]

Table 2. Grade 3 or 4 Adverse Events (Safety Population).*

Adverse Event	Venetoclax–Obinutuzumab (N=212)†			Chlorambucil–Obinutuzumab (N=214)		
	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4
	number of patients (percent)					
Adverse event of grade 3 or 4	81 (38.2)	86 (40.6)	167 (78.8)	93 (43.5)	71 (33.2)	164 (76.6)
Adverse events of grade 3 or 4 that occurred in ≥3% of the patients in either treatment group‡						
Blood and lymphatic system disorders	59 (27.8)	69 (32.5)	128 (60.4)	61 (28.5)	57 (26.6)	118 (55.1)
Neutropenia	52 (24.5)	60 (28.3)	112 (52.8)	56 (26.2)	47 (22.0)	103 (48.1)
Thrombocytopenia	20 (9.4)	9 (4.2)	29 (13.7)	19 (8.9)	13 (6.1)	32 (15.0)
Anemia	16 (7.5)	1 (0.5)	17 (8.0)	13 (6.1)	1 (0.5)	14 (6.5)
Febrile neutropenia	7 (3.3)	4 (1.9)	11 (5.2)	4 (1.9)	4 (1.9)	8 (3.7)
Leukopenia	5 (2.4)	0	5 (2.4)	9 (4.2)	1 (0.5)	10 (4.7)
Infections and infestations	31 (14.6)	6 (2.8)	37 (17.5)	31 (14.5)	1 (0.5)	32 (15.0)
Pneumonia	8 (3.8)	1 (0.5)	9 (4.2)	8 (3.7)	0	8 (3.7)
Injury, poisoning, and procedural complications	21 (9.9)	5 (2.4)	26 (12.3)	29 (13.6)	1 (0.5)	30 (14.0)
Infusion-related reaction	16 (7.5)	3 (1.4)	19 (9.0)	21 (9.8)	1 (0.5)	22 (10.3)
Investigations	26 (12.3)	6 (2.8)	32 (15.1)	16 (7.5)	7 (3.3)	23 (10.7)
Neutrophil count decreased	7 (3.3)	2 (0.9)	9 (4.2)	4 (1.9)	6 (2.8)	10 (4.7)
Aspartate aminotransferase increased	5 (2.4)	0	5 (2.4)	7 (3.3)	0	7 (3.3)
Alanine aminotransferase increased	4 (1.9)	0	4 (1.9)	7 (3.3)	0	7 (3.3)
Metabolism and nutrition disorders§	19 (9.0)	6 (2.8)	25 (11.8)	11 (5.1)	1 (0.5)	12 (5.6)
Hyperglycemia	6 (2.8)	2 (0.9)	8 (3.8)	2 (0.9)	1 (0.5)	3 (1.4)
Gastrointestinal disorders ¶	16 (7.5)	1 (0.5)	17 (8.0)	6 (2.8)	1 (0.5)	7 (3.3)
Diarrhea‖	9 (4.2)	0	9 (4.2)	1 (0.5)	0	1 (0.5)
Cardiac disorders	9 (4.2)	1 (0.5)	10 (4.7)	10 (4.7)	2 (0.9)	12 (5.6)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	10 (4.7)	3 (1.4)	13 (6.1)	7 (3.3)	1 (0.5)	8 (3.7)
Vascular disorders**	12 (5.7)	2 (0.9)	14 (6.6)	7 (3.3)	0	7 (3.3)
General disorders and administration-site conditions ††	14 (6.6)	0	14 (6.6)	6 (2.8)	0	6 (2.8)

Nervous system disorders	9 (4.2)	1 (0.5)	10 (4.7)	7 (3.3)	0	7 (3.3)
Respiratory, thoracic, and mediastinal disorders	10 (4.7)	0	10 (4.7)	5 (2.3)	1 (0.5)	6 (2.8)
Musculoskeletal and connective-tissue disorders	6 (2.8)	0	6 (2.8)	7 (3.3)	0	7 (3.3)
Skin and subcutaneous tissue disorder ‡‡	2 (0.9)	0	2 (0.9)	8 (3.7)	0	8 (3.7)

* Summaries of all adverse events of any grade and all serious adverse events are provided in Tables S6 and S7, respectively, in the Supplementary Appendix. Toxic effects in the two treatment groups were similar in severity, with significant differences detected only in the percentage of patients with metabolism and nutrition disorders and gastrointestinal disorders, including diarrhea.

† Nine patients received obinutuzumab only.

‡ Adverse events are reported according to *Medical Dictionary for Regulatory Activities* superclass and preferred terms and National Cancer Institute Common Terminology Criteria for Adverse Events grade.

§ Category includes tumor lysis syndrome and changes in electrolyte levels, each occurring in less than 3% of patients in each group. The two-sided P value was 0.02 for the between-group difference.

¶ The two-sided P value was 0.03 for the between-group difference.

‖ The two-sided P value was 0.01 for the between-group difference.

** Category includes hypertension and hypotension, each occurring in less than 3% of patients in each group.

†† Category includes asthenia, pyrexia, fatigue, and chest pain, each occurring in less than 3% of patients in each group.

‡‡ Category includes different types of rash, each occurring in less than 3% of patients in each group.

The CLL11 trial previously showed a median progression-free survival of 31.5 months, with approximately 49% of patients who received chlorambucil–obinutuzumab surviving without progression at 30 months.[3,4] In the current trial, the median progression-free survival in the chlorambucil–obinutuzumab group was not reached, and 60% of the patients receiving chlorambucil–obinutuzumab were surviving without progression at 30 months, most likely because of the 6-months-longer treatment duration with chlorambucil in this trial than in the CLL11 trial. Despite the favorable results in the comparator group, venetoclax–obinutuzumab was associated with significantly longer progression-free survival than chlorambucil–obinutuzumab. Moreover, approximately half the patients in the venetoclax–obinutuzumab group had a complete response (49.5%), which compares favorably to other therapies that are frequently used in this older population of patients with CLL.[2]

In the intention-to-treat population, the percentages of patients who were negative for minimal residual disease were high in the venetoclax–obinutuzumab group: 75.5% were negative in peripheral blood, and 56.9% were negative in bone marrow. Initial data from phase 1 and phase 2 trials of venetoclax–obinutuzumab reported slightly higher percentages of patients who were negative for minimal residual disease, with up to 92% of patients negative in peripheral blood.[11,21,22] However, these percentages were observed in smaller numbers of patients and in patients with fewer coexisting conditions. The percentages of patients with minimal residual disease negativity in the chlorambucil–obinutuzumab group in the current trial (35.2% in peripheral blood and 17.1% in bone marrow) were similar to those in previous results in peripheral blood in the CLL11 trial.[3] Longitudinal assessment showed that minimal residual disease negativity occurred early and was sustained after the completion of therapy in most patients treated with venetoclax–obinutuzumab, whereas a rapid increase in minimal residual disease was seen in the chlorambucil–obinutuzumab group.

After all the patients had completed treatment for at least 1 year, progressive disease was more frequent with chlorambucil–obinutuzumab than with venetoclax–obinutuzumab (69 vs. 14 patients; 6 of the 14 in the venetoclax–obinutuzumab group had *TP53* mutation, deletion, or

Table 3. Fatal (Grade 5) Adverse Events (Safety Population).*

Adverse Event	Venetoclax–Obinutuzumab (N=212)†	Chlorambucil–Obinutuzumab (N=214)
	number of patients (percent)	
Grade 5 adverse event during treatment	5 (2.4)‡	4 (1.9)
Infections and infestations	4 (1.9)	3 (1.4)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	1 (0.5)	1 (0.5)
Grade 5 adverse event after completion of treatment	11 (5.2)	4 (1.9)
Cardiac disorders	3 (1.4)	1 (0.5)
Infections and infestations	4 (1.9)	0
Neoplasms benign, malignant, and unspecified, including cysts and polyps	2 (0.9)	2 (0.9)
Other event	2 (0.9)	1 (0.5)

* A complete overview of all fatal adverse events is provided in Table S8 in the Supplementary Appendix.
† Nine patients received obinutuzumab only.
‡ Two patients received obinutuzumab only.

both). No significant difference in overall survival was observed between patients treated with chlorambucil–obinutuzumab and those treated with venetoclax–obinutuzumab. Thus, given the relatively short follow-up period of 28 months and the limited number of events that occurred in both treatment groups, it may be too early to detect any difference in overall survival.

The safety profile of both treatments in this trial showed no new safety signals or higher incidences of known toxic effects. The toxic effects in the two treatment groups were similar in severity, and significant differences were detected only in the incidence of metabolism disorders and gastrointestinal disorders. The number of fatal adverse events was higher in the venetoclax–obinutuzumab group than in the chlorambucil–obinutuzumab group (16 [7.5%] vs. 8 [3.7%]). Although the difference did not reach significance, it bears monitoring going forward; the overall percentage of patients with fatal adverse events was similar to those in the CLL11 trial (4 to 9%).[3]

In contrast to the findings in a previous trial, we did not find that venetoclax–obinutuzumab was associated with a higher frequency of tumor lysis syndrome.[22] This finding suggests that the safety measures implemented in this trial, such as prophylactic treatment after risk stratification, weekly dose ramp-up of venetoclax, and starting the treatment with obinutuzumab, allowed for effective prevention of tumor lysis syndrome. Recently, three trials reported that continuous ibrutinib therapy was superior to fixed-duration chemoimmunotherapy with regard to progression-free survival among young[23] and elderly[24,25] patients with previously untreated CLL. In contrast, the current trial evaluated a fixed-duration, noncytotoxic regimen, venetoclax–obinutuzumab. The fixed duration venetoclax–obinutuzumab combination regimen warrants a comparison with continuous ibrutinib monotherapy.[26,27] Venetoclax–obinutuzumab proved to be effective and to have a low incidence of high-grade toxic effects in patients with relevant coexisting conditions, as shown by the completion of treatment by almost 80% of patients. In contrast, recent data indicate that up to 41% of patients discontinue treatment with ibrutinib after a median of 7 months; of these patients, approximately 60% discontinue because of toxic effects.[28-33]

In conclusion, fixed-duration, targeted treatment with venetoclax–obinutuzumab was effective in previously untreated patients with CLL and coexisting conditions and resulted in a significantly higher percentage of patients with progression-free survival than standard treatment with chlorambucil–obinutuzumab. Longer follow-up is necessary to assess the durability of the responses.

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APPENDIX

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