ORIGINAL ARTICLE

Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia

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ABSTRACT

BACKGROUND

Venetoclax inhibits BCL2, an antiapoptotic protein that is pathologically overexpressed and that is central to the survival of chronic lymphocytic leukemia cells. We evaluated the efficacy of venetoclax in combination with rituximab in patients with relapsed or refractory chronic lymphocytic leukemia.

METHODS

In this randomized, open-label, phase 3 trial, we randomly assigned 389 patients to receive venetoclax for up to 2 years (from day 1 of cycle 1) plus rituximab for the first 6 months (venetoclax–rituximab group) or bendamustine plus rituximab for 6 months (bendamustine–rituximab group). The trial design did not include crossover to venetoclax plus rituximab for patients in the bendamustine–rituximab group in whom progression occurred. The primary end point was investigator-assessed progression-free survival.

RESULTS

After a median follow-up period of 23.8 months, the rate of investigator-assessed progression-free survival was significantly higher in the venetoclax–rituximab group (32 events of progression or death in 194 patients) than in the bendamustine–rituximab group (114 events in 195 patients); the 2-year rates of progression-free survival were 84.9% and 36.3%, respectively (hazard ratio for progression or death, 0.17; 95% confidence interval [CI], 0.11 to 0.25; P<0.001 by the stratified log-rank test). The benefit was maintained across all clinical and biologic subgroups, including the subgroup of patients with chromosome 17p deletion; the 2-year rate of progression-free survival among patients with chromosome 17p deletion was 81.5% in the venetoclax–rituximab group versus 27.8% in the bendamustine–rituximab group (hazard ratio, 0.13; 95% CI, 0.05 to 0.29), and the 2-year rate among those without chromosome 17p deletion was 85.9% versus 41.0% (hazard ratio, 0.19; 95% CI, 0.12 to 0.32). The benefit of venetoclax plus rituximab over bendamustine plus rituximab was confirmed by an independent review committee assessment of progression-free survival and other secondary efficacy end points. The rate of grade 3 or 4 neutropenia was higher in the venetoclax–rituximab group than in the bendamustine–rituximab group, but the rates of grade 3 or 4 febrile neutropenia and infections or infestations were lower with venetoclax than with bendamustine. The rate of grade 3 or 4 tumor lysis syndrome in the venetoclax–rituximab group was 3.1% (6 of 194 patients).

CONCLUSIONS

Among patients with relapsed or refractory chronic lymphocytic leukemia, venetoclax plus rituximab resulted in significantly higher rates of progression-free survival than bendamustine plus rituximab. (Funded by Genentech and AbbVie; ClinicalTrials.gov number, NCT02005471.)

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Relapsed or refractory chronic lymphocytic leukemia remains incurable, despite advances in treatment over the past 5 years.[1-7] When disease progression occurs, especially after treatment with DNA-damaging agents, chronic lymphocytic leukemia cells serially accumulate adverse biologic features and increasingly develop resistance to therapies.[8] Hence, additional treatments that have alternative mechanisms of action and that are effective and have an acceptable side-effect profile are needed.

The antiapoptotic protein BCL2, a key regulator of the intrinsic apoptotic pathway,[9] is constitutively overexpressed in chronic lymphocytic leukemia cells; therefore, BCL2 represents a rational therapeutic target.[10-12] Venetoclax, an orally administered, highly selective, potent BCL2 inhibitor,[13] acts independently of *TP53* to induce both high rates of response and good quality of response when administered as monotherapy to patients with heavily pretreated chronic lymphocytic leukemia, including patients who have adverse features such as chromosome 17p deletion.[14-16] The combination of venetoclax with the CD20 antibody rituximab, an established component of chronic lymphocytic leukemia therapy,[17-19] was found to be able to overcome microenvironment-induced resistance to venetoclax[20]; in addition, it has been shown to be not prohibitively toxic and to have promising efficacy over venetoclax monotherapy.[16,21] This combination can also clear all evidence of minimal residual disease (at a threshold of 1 tumor cell per 10^4 white cells), a robust surrogate for long-term outcome.[22-26]

In the phase 3 MURANO trial, we compared venetoclax in combination with rituximab with a standard chemoimmunotherapy — bendamustine in combination with rituximab — in patients with relapsed or refractory chronic lymphocytic leukemia.[1,27-29] We report results from the primary analysis, which was conducted when the protocol-specified criteria for the primary endpoint analysis were met.

Methods

Trial Conduct

This was an international, randomized, open-label, phase 3 trial. The review board at each participating institution approved the trial protocol (available with full text of this article at NEJM.org). The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.[30,31] All the patients provided written informed consent. An independent data monitoring committee (whose members are listed in the Supplementary Appendix, available at NEJM.org) reviewed safety data periodically and also reviewed the efficacy results of the planned interim analysis. An independent review committee, whose members were unaware of the treatment-group assignments, assessed all the patients for disease response and disease progression with the use of clinical data, imaging, and bone marrow biopsies.

Trial investigators (see the Supplementary Appendix for a list of the investigators) and employees of the sponsors (Genentech and AbbVie) designed the trial. The data were collected by the investigators, and the analyses were conducted by the trial statistician, who was employed by Genentech. All the authors vouch for the completeness and accuracy of the data and analysis and for the fidelity of the trial to the protocol. Each of the authors had access to the primary data, contributed to the preparation of the manuscript, for which they had full editorial control, and made the decision to submit the manuscript for publication. Medical and editorial writing assistance was provided by medical writers at Envision Pharma Group, funded by F. Hoffmann–La Roche.

Patients

Patients were eligible for the trial if they were 18 years of age or older, had a diagnosis of relapsed or refractory chronic lymphocytic leukemia that required therapy,[32] had received one to three previous treatments (including at least one chemotherapy-containing regimen), had an Eastern Cooperative Oncology Group performance status score of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability), and had adequate bone marrow, renal, and hepatic function (additional details of the eligibility criteria are provided in the Supplementary Appendix). Patients who had received previous treatment with bendamustine were eligible provided that the duration of response after the treatment was at least 24 months.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to receive venetoclax plus rituximab or bendamustine plus rituximab. Randomization was stratified according to the presence or absence of chromosome 17p deletion, responsiveness to previous therapy (details are provided in the Supplementary Appendix), and geographic region.

Venetoclax was administered according to a 5-week schedule of a gradual increase in the dose (ramp-up) from 20 mg per day to 400 mg per day; prophylactic and monitoring measures (Table S1 in the Supplementary Appendix) were instituted to mitigate the potential for development of the tumor lysis syndrome.[14] After completion of the dose ramp-up period for venetoclax, administration of rituximab (375 mg per square meter of body-surface area intravenously for the first dose [day 1 of cycle 1] and 500 mg per square meter intravenously thereafter [day 1 of cycles 2 through 6]) was initiated in 28-day treatment cycles, while daily administration of venetoclax was continued. Administration of venetoclax at a dose of 400 mg per day was continued for 2 years (which was calculated from day 1 of cycle 1) unless disease progression or unacceptable toxic effects occurred sooner. Bendamustine at a dose of 70 mg per square meter was administered intravenously on days 1 and 2 of each 28-day cycle for six cycles in combination with rituximab according to the aforementioned dosing schedule.[1] Crossover to treatment with venetoclax and rituximab after disease progression was not permitted, and therapy after the occurrence of disease progression was at the investigators' discretion.

ASSESSMENTS AND END POINTS

Efficacy analyses were based on the intention-to-treat population, which included all patients who underwent randomization. The primary end point was investigator-assessed progression-free survival, which was defined as the time from randomization to the first occurrence of disease progression or relapse or death from any cause, whichever occurred first. Secondary efficacy end points included independent review committee–assessed progression-free survival, investigator-assessed and independent review committee–assessed progression-free survival among patients with chromosome 17p deletion, the investigator-assessed and independent review committee–assessed overall response rate and complete response rate, overall survival, rates of clearance of minimal residual disease (to below the threshold of 1 tumor cell per 10^4 white cells), the duration of response, event-free survival (defined as the time from randomization to the date of disease progression or relapse, death from any cause, or the start of a new therapy for chronic lymphocytic leukemia), and the time to the next treatment for chronic lymphocytic leukemia (Table S2 in the Supplementary Appendix). Disease was assessed in all patients at baseline and at set times during the trial on the basis of the 2008 guidelines of the International Workshop on Chronic Lymphoid Leukemia (iwCLL) (Table S3 in the Supplementary Appendix)[32]; assessments included immunoglobulin heavy-chain variable (*IGHV*) gene mutation status, chromosome 17p deletion status, and *TP53* mutation status,[33,34] all of which were evaluated centrally. Complete responses were confirmed by computed tomography and by bone marrow histologic analysis. Minimal residual disease status was assessed centrally in peripheral blood with the use of both an allele-specific oligonucleotide polymerase-chain-reaction assay and flow cytometry[32] and also in bone marrow aspirate by flow cytometry (Table S2 in the Supplementary Appendix).

STATISTICAL ANALYSIS

We estimated that a sample of 370 patients with a total of 186 events of disease progression or relapse or death would provide the trial with 80% power to detect a risk of disease progression or relapse or death that was lower by 34% (hazard ratio, 0.66) with venetoclax plus rituximab than with bendamustine plus rituximab, at a two-sided alpha level of 0.05. These values would correspond to a median progression-free survival of 15.2 months in the bendamustine–rituximab group[1] as compared with 23 months in the venetoclax–rituximab group. One prespecified interim analysis was to be performed after an aggregated 140 investigator-assessed events of progression or relapse or death (i.e., 75% of the planned events for the final analysis) had occurred. At the time of data review on September 6, 2017, the independent data monitoring committee recommended that the primary analysis be conducted at that time because the prespecified

statistical boundaries for early stopping were crossed for progression-free survival on the basis of stratified log-rank tests. Therefore, formal statistical testing of key secondary efficacy end points was subsequently performed with the use of a prespecified hierarchical approach (further details are provided in the Supplementary Appendix).[35]

RESULTS

TRIAL POPULATION

From March 31, 2014, to September 23, 2015, a total of 389 patients were enrolled at 109 sites in 20 countries and were randomly assigned to receive venetoclax plus rituximab (venetoclax–rituximab group; 194 patients) or bendamustine plus rituximab (bendamustine–rituximab group; 195 patients) (Fig. 1). The demographic and disease characteristics of the two groups were well balanced at baseline (Table S4 in the Supplementary Appendix). Across the two treatment groups, the median age was 65 years (range, 22 to 85), and a majority of the patients (73.8%) were men. In total, 92 of 342 patients (26.9%) who were assessed for chromosome 17p deletion status had chromosome 17p deletion, 99 of 376 patients (26.3%) who were tested for *TP53* mutation status had *TP53* mutations, and 246 of 360 patients (68.3%) who were tested for *IGHV* mutational status had unmutated *IGHV*.

At the time of the data cutoff for the primary analysis (May 8, 2017), 78 of the patients in the venetoclax–rituximab group (40.2%) were still receiving venetoclax monotherapy. In the bendamustine–rituximab group, 154 patients (79.0%) had completed all six cycles of treatment. The median relative dose intensity (the proportion of administered doses relative to planned doses) was 97% with venetoclax and 100% with bendamustine. Exposure to rituximab was similar in the two treatment groups; both groups received the drug for a median of six cycles, and the median relative dose intensity in both groups was 100%. In total, 68 patients (35.1%) in the venetoclax–rituximab group completed the scheduled 2 years of treatment, of whom 56 had less than 3 months of follow-up after cessation of venetoclax treatment.

All the patients in the venetoclax–rituximab group had a dose ramp-up period of 5 weeks, with the exception of 14 patients. These patients had a dose ramp-up period of 4 weeks to less than 5 weeks because they were enrolled before implementation of a protocol amendment that required a dose ramp-up period of 5 weeks.

A total of 7 patients in the bendamustine–rituximab group did not receive any trial treatment but were included in the efficacy analyses since they met the criteria for inclusion in the intention-to-treat population. In the venetoclax–rituximab group, 7 patients never received rituximab. Overall, 48 patients discontinued venetoclax prematurely: 15 during either the dose ramp-up period or the period during which they received combination treatment and 33 during the monotherapy phase after the combination-treatment phase. Among the 36 patients (18.6%) who discontinued venetoclax prematurely for reasons other than disease progression or relapse or death, the median time to discontinuation was 10.0 months (range, 0.3 to 24.5). In the bendamustine–rituximab group, 34 patients, including the 7 patients who never received treatment, did not complete the six cycles of treatment (Fig. 1, and Table S5 in the Supplementary Appendix).

EFFICACY

After a median follow-up period of 23.8 months (range, 0.0 to 37.4), the median investigator-assessed progression-free survival was significantly longer in the venetoclax–rituximab group than in the bendamustine–rituximab group; the median progression-free survival was not reached in the venetoclax–rituximab group (32 events of progression or death in 194 patients) and was 17 months in the bendamustine–rituximab group (114 events in 195 patients) (Fig. 2A). The 2-year rate of investigator-assessed progression-free survival was 84.9% (95% confidence interval [CI], 79.1 to 90.6) in the venetoclax–rituximab group and 36.3% (95% CI, 28.5 to 44.0) in the bendamustine–rituximab group (hazard ratio for progression or death, 0.17; 95% CI, 0.11 to 0.25; P<0.001 by the stratified log-rank test). The results of the analysis of progression-free survival as assessed by the independent review committee showed a risk of disease progression or relapse or death that was of similar magnitude to that seen in the analysis of investigator-assessed progression-free survival (Fig. S1 in the Supple-

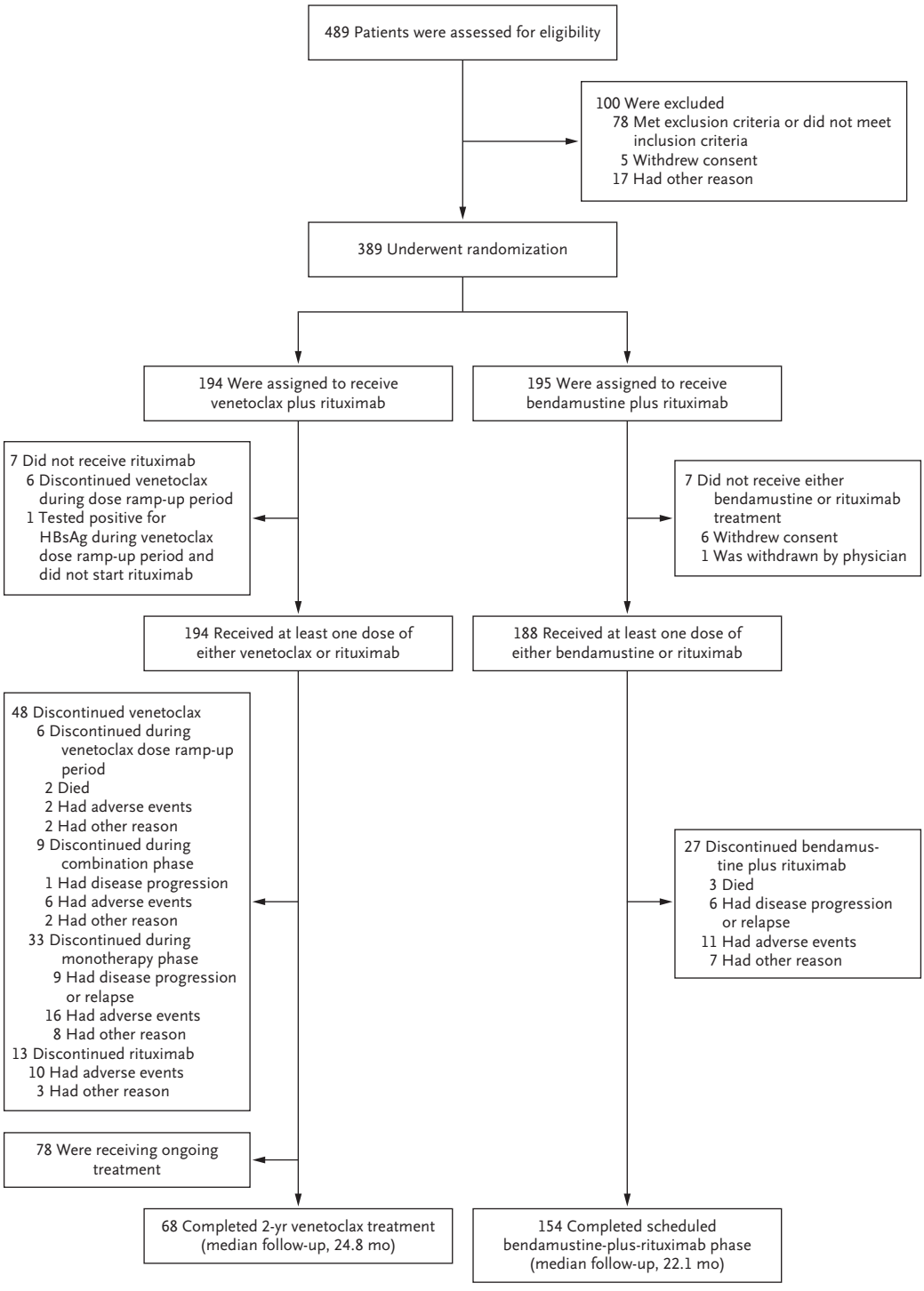

Figure 1. Randomization, Treatment, and Follow-up.

All 389 patients who underwent randomization (194 in the venetoclax–rituximab group and 195 in the bendamustine–rituximab group) were included in the primary analysis. HBsAg denotes hepatitis B surface antigen.

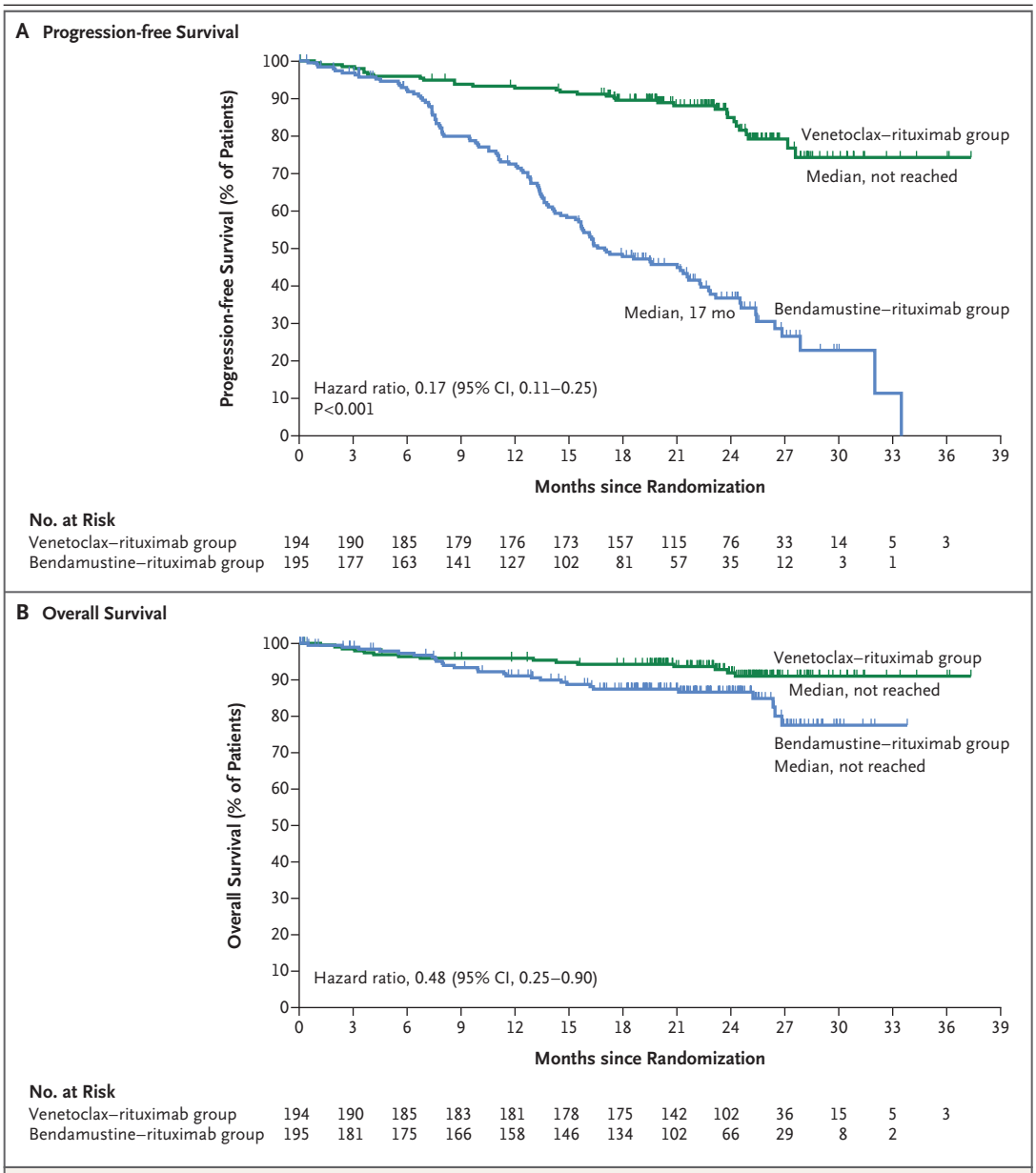

Figure 2. Progression-free Survival and Overall Survival.

Panel A shows Kaplan–Meier estimates of investigator-assessed progression-free survival, and Panel B shows Kaplan–Meier estimates of overall survival. Both analyses were performed in the intention-to-treat population. Tick marks in Panel A represent data censored at the last time the patient was known to be alive and without disease progression or relapse, and tick marks in Panel B represent data censored at the last time the patient was known to be alive.

mentary Appendix). Consistent benefit in favor of venetoclax plus rituximab was observed in prespecified subgroup analyses (Fig. 3), as well as across all sensitivity analyses of the primary end point, in which 2-year progression-free survival rates ranged from 82.8 to 85.8% in the venetoclax–rituximab group and from 36.6 to 39.4% in the bendamustine–rituximab group (range of hazard ratios, 0.16 to 0.20) (Table S6 in the Supplementary Appendix). The 2-year rate of investigator-assessed progression-free survival was higher in the venetoclax–rituximab group than

Subgroup	Total No.	Venetoclax–Rituximab Group		Bendamustine–Rituximab Group		Hazard Ratio (95% Wald CI)
		no.	*median (mo)*	*no.*	*median (mo)*	
All patients	389	194	NR	195	17.0	0.17 (0.12–0.26)
Age						
<65 yr	186	97	NR	89	15.4	0.11 (0.06–0.21)
≥65 yr	203	97	NR	106	21.7	0.24 (0.14–0.41)
CLL risk status						
Low	178	90	NR	88	21.6	0.14 (0.07–0.28)
High	211	104	NR	107	15.4	0.19 (0.11–0.30)
Geographic region						
United States and Canada	34	16	NR	18	15.8	0.29 (0.10–0.83)
Australia and New Zealand	86	44	NR	42	24.5	0.34 (0.16–0.72)
Western Europe	131	66	NR	65	17.1	0.11 (0.05–0.23)
Central and Eastern Europe	130	64	NR	66	15.5	0.13 (0.06–0.27)
Asia	8	4	NR	4	13.6	0.28 (0.03–2.69)
No. of previous therapies						
1	228	111	NR	117	16.6	0.14 (0.08–0.24)
2	100	57	NR	43	21.2	0.24 (0.11–0.50)
≥3	61	26	NR	35	10.5	0.24 (0.10–0.57)
Effect of most recent therapy						
CLL refractory to therapy	59	30	NR	29	13.6	0.32 (0.15–0.70)
Relapse of CLL	330	164	NR	166	18.6	0.14 (0.09–0.23)
Chromosome 17p deletion status						
Absent	250	127	NR	123	21.4	0.19 (0.12–0.32)
Present	92	46	NR	46	15.4	0.13 (0.05–0.29)
TP53 mutation status						
Unmutated	277	144	NR	133	21.2	0.15 (0.09–0.25)
Mutated	99	48	NR	51	12.9	0.19 (0.10–0.36)
Baseline *IGHV* mutation status						
Unmutated	246	123	NR	123	15.7	0.16 (0.10–0.26)
Mutated	104	53	NR	51	22.9	0.11 (0.04–0.31)

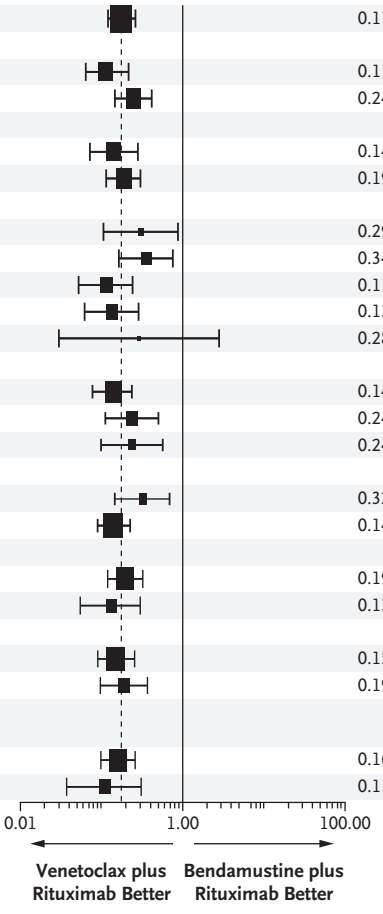

Figure 3. Prespecified Subgroup Analysis of Investigator-Assessed Progression-free Survival.

A hazard ratio of less than 1.00 indicates a lower risk of disease progression or relapse or death with venetoclax plus rituximab than with bendamustine plus rituximab. The size of each square is proportional to the amount of data available. CLL denotes chronic lymphocytic leukemia, IGHV immunoglobulin heavy-chain variable, and NR not reached.

in the bendamustine–rituximab group among patients with chromosome 17p deletion (81.5% vs. 27.8%; hazard ratio, 0.13; 95% CI, 0.05 to 0.29) as well as among patients without chromosome 17p deletion (85.9% vs. 41.0%; hazard ratio, 0.19; 95% CI, 0.12 to 0.32) (Fig. S2 in the Supplementary Appendix). Results of analyses of progression-free survival according to chromosome 17p deletion clone size (7 to 20% 17p deleted nuclei vs. >20% 17p deleted nuclei) are shown in Figure S3 in the Supplementary Appendix. Among the 36 patients who discontinued venetoclax prematurely for reasons other than disease progression or relapse or death, 55.6% remained progression-free at the last follow-up (median duration of follow-up after cessation of venetoclax, 5.24 months; range, 0.03 to 26.25).

The rate of independent review committee–assessed complete response or complete response with incomplete hematologic recovery in the venetoclax–rituximab group as compared with the bendamustine–rituximab group was the first of the secondary end points to be tested hierarchically. The difference between the two groups was found not to be significant (8.2% in the venetoclax–rituximab group and 3.6% in the benda-

Table 1. Minimal Residual Disease Status Determined on the Basis of Peripheral-Blood Samples.*

Minimal Residual Disease Status†	At 9-Mo Combination-Treatment Response Assessment Visit		At Any Time during Trial	
	Venetoclax–Rituximab Group (N=194)	Bendamustine–Rituximab Group (N=195)	Venetoclax–Rituximab Group (N=194)	Bendamustine–Rituximab Group (N=195)
	number of patients (percent)			
Negative‡	121 (62.4)	26 (13.3)	162 (83.5)	45 (23.1)
Non-negative	73 (37.6)	169 (86.7)	32 (16.5)	150 (76.9)
Assay positive	46 (23.7)	102 (52.3)	24 (12.4)	134 (68.7)
Assay failure	2 (1.0)	2 (1.0)	1 (0.5)	0
Disease progression or relapse or death, or withdrawal from trial	13 (6.7)	38 (19.5)	NA	NA
Missing sample	12 (6.2)	27 (13.8)	7 (3.6)	16 (8.2)

* The assessment of minimal residual disease status was performed in the intention-to-treat population. NA denotes not applicable.
† The threshold for minimal residual disease was 1 tumor cell per 10^4 white cells. Results below this threshold were considered negative. Minimal residual disease was assessed with the use of both an allele-specific oligonucleotide polymerase-chain-reaction assay and flow cytometry.
‡ The absolute difference between the treatment groups in the rate of clearance of minimal residual disease was 49.0 percentage points (95% CI, 40.4 to 57.6) at the time of the 9-month combination-treatment response assessment visit and 60.4 percentage points (95% CI, 52.3 to 68.6) at any time during the trial.

mustine–rituximab group; P=0.08) (Fig. S4 in the Supplementary Appendix).

The independent review committee–assessed overall response rate was 92.3% in the venetoclax–rituximab group and 72.3% in the bendamustine–rituximab group (difference between the groups, 20.0 percentage points; 95% CI, 12.4 to 27.6). The investigator-assessed overall response rate was 93.3% in the venetoclax–rituximab group and 67.7% in the bendamustine–rituximab group. Changes from baseline in lymph node size are shown in Figure S5 in the Supplementary Appendix. The rate of investigator-assessed complete response or complete response with incomplete hematologic recovery was 26.8% in the venetoclax–rituximab group as compared with 8.2% in the bendamustine–rituximab group (Fig. S4 in the Supplementary Appendix). Of the 68 patients across the two treatment groups who had a complete response or complete response with incomplete hematologic recovery according to investigator assessment, 50 patients were classified as having a partial response and 1 as having stable disease according to assessment by the independent review committee. The main reason for the discordance in the rates of investigator-assessed and independent review committee–assessed complete response or complete response with incomplete hematologic recovery was divergent interpretation of residual adenopathy on computed tomography, specifically with respect to lesions measuring 30 mm or smaller, despite bone marrow clearance (Table S7 in the Supplementary Appendix).

Assessments of minimal residual disease were available for 366 patients (94.1%) on the basis of peripheral-blood samples and from 115 patients (29.6%) on the basis of bone marrow aspirate. At the 9-month time point (the time of the combination-treatment response assessment visit), the rate of clearance of minimal residual disease on the basis of peripheral-blood samples was higher in the venetoclax–rituximab group than in the bendamustine–rituximab group (121 of 194 patients [62.4%] vs. 26 of 195 patients [13.3%]). The rate was also higher in the venetoclax–rituximab group than in the bendamustine–rituximab group at any time during the trial (162 of 194 patients [83.5%] vs. 45 of 195 patients [23.1%]) (Table 1). The higher rate of clearance of minimal residual disease in the venetoclax–rituximab group was also maintained over time (Fig. 4). At the time of the combination-treatment response assessment visit, minimal residual disease status

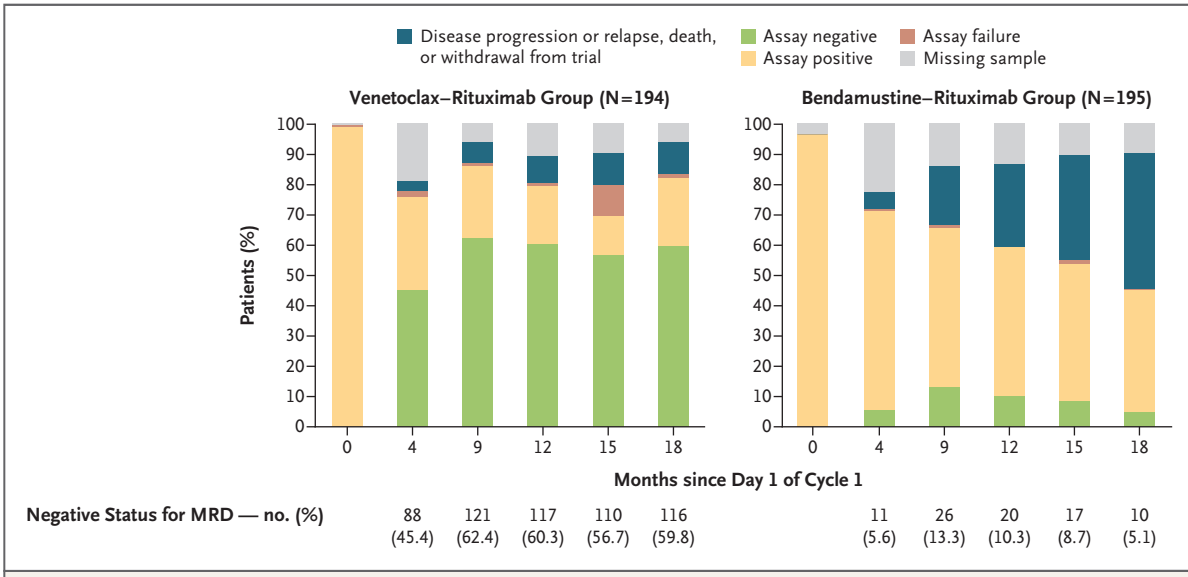

Figure 4. Rate of Clearance of Minimal Residual Disease over Time.

Shown is the percentage of patients in the venetoclax–rituximab group and the bendamustine–rituximab group who were negative for minimal residual disease (MRD), on the basis of peripheral-blood samples, over time. Samples were listed as missing when patients reached a specific time point but a sample was not obtained from them at that time or when patients did not yet reach a specific time point owing to reasons other than disease progression or relapse or death. The threshold for MRD was defined as 1 tumor cell per 10^4 white cells.

was predictive of subsequent progression-free survival (Fig. S6 in the Supplementary Appendix). Higher rates of clearance of minimal residual disease in the venetoclax–rituximab group were also seen in the assessment of bone marrow aspirate (53 of 194 patients [27.3%] in the venetoclax–rituximab group vs. 3 of 195 patients [1.5%] in the bendamustine–rituximab group) (Table S8 in the Supplementary Appendix).

The rate of overall survival was higher in the venetoclax–rituximab group than in the bendamustine–rituximab group, with 24-month rates of 91.9% and 86.6%, respectively (hazard ratio, 0.48; 95% CI, 0.25 to 0.90) (Fig. 2B). Event-free survival was longer in the venetoclax–rituximab group than in the bendamustine–rituximab group; at 2 years, 84.9% of the patients in the venetoclax–rituximab group and 34.8% in the bendamustine–rituximab group were event-free (hazard ratio for disease progression, death, or initiation of new treatment for chronic lymphocytic leukemia, 0.17; 95% CI, 0.11 to 0.25). The time to the next treatment for chronic lymphocytic leukemia was also longer in the venetoclax–rituximab group than in the bendamustine–rituximab group; at 2 years, 90.0% and 52.1%, respectively, had not received a next treatment for chronic lymphocytic leukemia (hazard ratio for receipt of next treatment or death, 0.19; 95% CI, 0.12 to 0.31) (Figs. S7 and S8 in the Supplementary Appendix). A total of 3 patients (1.5%) in the venetoclax–rituximab group and 40 (20.5%) in the bendamustine–rituximab group received targeted chronic lymphocytic leukemia therapies, such as B-cell receptor signaling and BCL2 inhibitors, after disease progression occurred (Table S9 in the Supplementary Appendix).

SAFETY

The reporting period for adverse events was longer in the venetoclax–rituximab group than in the bendamustine–rituximab group owing to the longer duration of treatment with venetoclax. At the time of the data cutoff, the median duration of exposure to venetoclax was 22.1 months (range, 0.1 to 27.9). Overall, 379 patients (99.2%) had at least one adverse event: all 194 patients (100.0%) in the venetoclax–rituximab group and 185 patients (98.4%) in the bendamustine–rituximab group. The most common adverse event of any

grade in both treatment groups was neutropenia (60.8% of the patients in the venetoclax–rituximab group and 44.1% of the patients in the bendamustine–rituximab group) (Table S10 in the Supplementary Appendix). Adverse events of grade 3 or 4 were reported in 82.0% of patients in the venetoclax–rituximab group and in 70.2% in the bendamustine–rituximab group. Neutropenia was the most common grade 3 or 4 adverse event, with a higher incidence in the venetoclax–rituximab group than in the bendamustine–rituximab group (57.7% vs. 38.8%); however, the incidence of grade 3 or 4 febrile neutropenia and of grade 3 or 4 infections or infestations was lower in the venetoclax–rituximab group (Table 2). Events of neutropenia (of any grade) also accounted for most of the adverse events that led to dose interruption in the venetoclax–rituximab group (Table S5 in the Supplementary Appendix); the median duration of neutropenia with a highest grade of 3 was 8 days (range, 1 to 712), and the median duration of neutropenia with a highest grade of 4 was 8 days (1 to 212). In total, 47.9% of the patients in the venetoclax–rituximab group and 43.1% of the patients in the bendamustine–rituximab group received growth factor. Grade 3 or 4 tumor lysis syndrome was reported in 6 patients (3.1%) in the venetoclax–rituximab group and in 2 patients (1.1%) in the bendamustine–rituximab group (Table 2, and Table S11 in the Supplementary Appendix). Clinical tumor lysis syndrome was reported by the investigator in 1 patient in each treatment group: a patient in the bendamustine–rituximab group had grade 4 acute renal failure and a patient in the venetoclax–rituximab group had a transient increase in creatinine (grade 2) that occurred during the 4-week dose ramp-up period (the patient was enrolled before implementation of the 5-week dose ramp-up schedule) (see the Supplementary Methods section and Table S12 in the Supplementary Appendix). All other cases of the tumor lysis syndrome were based on changes in laboratory values only. The rate of grade 3 or 4 infections and infestations was lower in the venetoclax–rituximab group than in the bendamustine–rituximab group (17.5% and 21.8%, respectively).

The incidence of serious adverse events was similar in the two groups (Table 2). Richter's transformation (i.e., conversion into an aggressive lymphoma, typically diffuse large B-cell lymphoma) was confirmed in 6 patients in the venetoclax–rituximab group and in 5 patients in the bendamustine–rituximab group. Adverse events that resulted in death were reported in 5.2% of the patients in the venetoclax–rituximab group and in 5.9% of the patients in the bendamustine–rituximab group (4 fatal infections or infestations in each group) (Table 2, and Table S13 in the Supplementary Appendix).

DISCUSSION

The primary analysis of the phase 3 MURANO trial of venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukemia showed a significantly higher rate of progression-free survival with venetoclax plus rituximab than with a standard chemoimmunotherapy, with benefit observed in all subgroups analyzed. Prespecified secondary efficacy measures, including the complete response rate, the overall response rate, and overall survival, also showed consistent patterns of clinically meaningful benefit with venetoclax plus rituximab, with substantial rates of clearance of minimal residual disease on the basis of both peripheral-blood samples and bone marrow aspirate. This enhanced disease control was observed in a multinational setting, with a safety profile that included common but manageable myelosuppression.

Complete response rates were lower when response was assessed by the independent review committee than when assessed by the investigator, owing to divergent interpretation of residual adenopathy on computed tomographic scans obtained at set, comparable time points in the two treatment groups. Guidelines regarding iwCLL response are being revised to include size criteria for pathologic lymph nodes and incorporation of an analysis of minimal residual disease status.[26] All 42 investigator-assessed complete responses in the venetoclax–rituximab group that were inconsistent with the independent review committee assessment were associated with clear bone marrow biopsy results (i.e., findings that met the complete response criteria), and 37 of the patients were negative for minimal residual disease on the basis of peripheral-blood samples at either that time point or the subsequent visit. Although the achievement of a complete response has been shown to lead to a longer duration of response and longer overall survival than achieve-

Table 2. Adverse Events.*

Event	Venetoclax–Rituximab Group (N=194)	Bendamustine–Rituximab Group (N=188)
Grade 3 or 4 adverse event — no. of patients (%)	159 (82.0)	132 (70.2)
Total no. of events	335	255
Grade 3 or 4 adverse events with at least 2% difference in incidence between groups — no. of patients (%)	130 (67.0)	104 (55.3)
Neutropenia†	112 (57.7)	73 (38.8)
Infections and infestations	34 (17.5)	41 (21.8)
Anemia	21 (10.8)	26 (13.8)
Thrombocytopenia	11 (5.7)	19 (10.1)
Febrile neutropenia	7 (3.6)	18 (9.6)
Pneumonia	10 (5.2)	15 (8.0)
Infusion-related reaction	3 (1.5)	10 (5.3)
Tumor lysis syndrome‡	6 (3.1)	2 (1.1)
Hypotension	0	5 (2.7)
Hyperglycemia	4 (2.1)	0
Hypogammaglobulinemia	4 (2.1)	0
Serious adverse events with at least 2% incidence in either group — no. of patients (%)	90 (46.4)	81 (43.1)
Pneumonia	16 (8.2)§	15 (8.0)
Febrile neutropenia	7 (3.6)	16 (8.5)
Pyrexia	5 (2.6)	13 (6.9)
Anemia	3 (1.5)	5 (2.7)
Infusion-related reaction	1 (0.5)	6 (3.2)
Sepsis	1 (0.5)	4 (2.1)
Tumor lysis syndrome	4 (2.1)	1 (0.5)
Hypotension	0	5 (2.7)
Fatal adverse events — no. of patients (%)	10 (5.2)§	11 (5.9)

* Before the initiation of a trial drug, only serious adverse events that were considered to have been caused by a protocol-mandated intervention were reported (e.g., serious adverse events related to invasive procedures, such as biopsies). After the initiation of a trial drug, all adverse events, regardless of the relationship to the trial drug, were reported through 28 days after the last dose of trial drug (a maximum of 2 years for the venetoclax–rituximab group) or through 90 days after the last dose of rituximab, whichever was longer. After this period, investigators were to report any deaths, serious adverse events, or other adverse events of concern that were believed to be related to previous treatment with the trial drug.

† A higher percentage of new-onset events of neutropenia occurred during the combination-treatment period than during the venetoclax monotherapy phase (54.1% vs. 11.1%). Protocol-mandated dose interruption for all grade 3 or 4 events of neutropenia occurred in 43.3% of the patients in the venetoclax–rituximab group. In total, 47.9% of the patients in the venetoclax–rituximab group and 43.1% of the patients in the bendamustine–rituximab group received growth factor.

‡ Additional information on the events of the tumor lysis syndrome can be found in Table S12 in the Supplementary Appendix.

§ Two serious adverse events of pneumonia that resulted in death occurred in patients who had both disease progression and confirmed Richter's transformation (i.e., conversion into an aggressive lymphoma, typically diffuse large B-cell lymphoma).

ment of a partial response,[36] more recent evidence suggests that patients who have a partial response and who are negative for minimal residual disease on the basis of peripheral-blood samples have better survival outcomes than patients who have a complete response and are positive for minimal residual disease.[23]

The high rates of clearance of minimal re-

sidual disease that were observed in the venetoclax–rituximab group exceed those previously attained with other agents and combinations of agents in trials of relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma,[7,37] findings that suggest that greater efficacy results can be attained by replacing chemotherapy with venetoclax than by adding other targeted agents to chemoimmunotherapy.[7] Clearance of minimal residual disease on the basis of peripheral-blood samples was reached by month 4 and was generally durable in the venetoclax–rituximab group. Longer follow-up is required to evaluate the duration of benefit after discontinuation of therapy, but previous findings indicate that disease control endures among patients who are negative for minimal residual disease on the basis of bone marrow aspirate after treatment with venetoclax plus rituximab.[21] Given the fixed duration of treatment with venetoclax, the potential for a treatment-free period exists for patients with relapsed or refractory chronic lymphocytic leukemia.

No new safety events were observed in either treatment regimen.[7,21] Neutropenia is a known on-target effect of venetoclax,[38] and the higher rates of grade 3 or 4 events that were observed in the venetoclax–rituximab group as compared with the bendamustine–rituximab group were not unexpected,[39] especially given the longer duration of treatment with venetoclax. Nonetheless, infections and infestations in the venetoclax–rituximab group were uncommon. It is possible that events of neutropenia that resulted in the dose modifications of venetoclax (which were mandated by the trial protocol if an event of grade 3 or 4 neutropenia occurred) may be mitigated with improved guidance on the management of neutropenia with granulocyte colony-stimulating factor. The relatively small number of patients in the venetoclax–rituximab group who had the tumor lysis syndrome shows the effectiveness of the risk-mitigation procedures that were implemented during the trial and the generally safe delivery of the treatment in a multinational trial.

In conclusion, among patients with relapsed or refractory chronic lymphocytic leukemia, venetoclax in combination with rituximab resulted in a markedly higher rate of progression-free survival than standard bendamustine in combination with rituximab. The substantial rate of clearance of minimal residual disease in the venetoclax–rituximab group may indicate improved disease control over a longer term even when therapy is discontinued. Additional follow-up will be needed to assess the durability of such responses.

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APPENDIX

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