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First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia

B. Eichhorst, C.U. Niemann, A.P. Kater, M. Fürstenau, J. von Tresckow, C. Zhang, S. Robrecht, M. Gregor, G. Juliusson, P. Thornton, P.B. Staber, T. Tadmor, V. Lindström, C. da Cunha-Bang, C. Schneider, C.B. Poulsen, T. Illmer, B. Schöttker, T. Nösslinger, A. Janssens, I. Christiansen, M. Baumann, H. Frederiksen, M. van der Klift, U. Jäger, M.B.L. Leys, M. Hoogendoorn, K. Lotfi, H. Hebart, T. Gaska, H. Koene, L. Enggaard, J. Goede, J.C. Regelink, A. Widmer, F. Simon, N. De Silva, A.-M. Fink, J. Bahlo, K. Fischer, C.-M. Wendtner, K.A. Kreuzer, M. Ritgen, M. Brüggemann, E. Tausch, M.-D. Levin, M. van Oers, C. Geisler, S. Stilgenbauer, and M. Hallek, for the GCLLSG, the HOVON and Nordic CLL Study Groups, the SAKK, the Israeli CLL Association, and Cancer Trials Ireland*

ABSTRACT

BACKGROUND

Randomized trials of venetoclax plus anti-CD20 antibodies as first-line treatment in fit patients (i.e., those with a low burden of coexisting conditions) with advanced chronic lymphocytic leukemia (CLL) have been lacking.

METHODS

In a phase 3, open-label trial, we randomly assigned, in a 1:1:1:1 ratio, fit patients with CLL who did not have *TP53* aberrations to receive six cycles of chemoimmunotherapy (fludarabine–cyclophosphamide–rituximab or bendamustine–rituximab) or 12 cycles of venetoclax–rituximab, venetoclax–obinutuzumab, or venetoclax–obinutuzumab–ibrutinib. Ibrutinib was discontinued after two consecutive measurements of undetectable minimal residual disease or could be extended. The primary end points were undetectable minimal residual disease (sensitivity, $<10^{-4}$ [i.e., <1 CLL cell in 10,000 leukocytes]) as assessed by flow cytometry in peripheral blood at month 15 and progression-free survival.

RESULTS

A total of 926 patients were assigned to one of the four treatment regimens (229 to chemoimmunotherapy, 237 to venetoclax–rituximab, 229 to venetoclax–obinutuzumab, and 231 to venetoclax–obinutuzumab–ibrutinib). At month 15, the percentage of patients with undetectable minimal residual disease was significantly higher in the venetoclax–obinutuzumab group (86.5%; 97.5% confidence interval [CI], 80.6 to 91.1) and the venetoclax–obinutuzumab–ibrutinib group (92.2%; 97.5% CI, 87.3 to 95.7) than in the chemoimmunotherapy group (52.0%; 97.5% CI, 44.4 to 59.5; P<0.001 for both comparisons), but it was not significantly higher in the venetoclax–rituximab group (57.0%; 97.5% CI, 49.5 to 64.2; P=0.32). Three-year progression-free survival was 90.5% in the venetoclax–obinutuzumab–ibrutinib group and 75.5% in the chemoimmunotherapy group (hazard ratio for disease progression or death, 0.32; 97.5% CI, 0.19 to 0.54; P<0.001). Progression-free survival at 3 years was also higher with venetoclax–obinutuzumab (87.7%; hazard ratio for disease progression or death, 0.42; 97.5% CI, 0.26 to 0.68; P<0.001), but not with venetoclax–rituximab (80.8%; hazard ratio, 0.79; 97.5% CI, 0.53 to 1.18; P=0.18). Grade 3 and grade 4 infections were more common with chemoimmunotherapy (18.5%) and venetoclax–obinutuzumab–ibrutinib (21.2%) than with venetoclax–rituximab (10.5%) or venetoclax–obinutuzumab (13.2%).

CONCLUSIONS

Venetoclax–obinutuzumab with or without ibrutinib was superior to chemoimmunotherapy as first-line treatment in fit patients with CLL. (Funded by AbbVie and others; GAIA–CLL13 ClinicalTrials.gov number, NCT02950051; EudraCT number, 2015-004936-36.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Eichhorst can be reached at barbara.eichhorst@uk-koeln.de or at the Department I of Internal Medicine and Center of Integrated Oncology Aachen–Bonn–Cologne–Düsseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Kerpenerstrasse 62, 50937 Cologne, Germany.

*Members of the German CLL Study Group (GCLLSG), the Hemato-Oncology Foundation for Adults in the Netherlands (HOVON) CLL Study Group, the Nordic CLL Study Group, the Swiss Group for Clinical Cancer Research (SAKK), the Israeli CLL Association, and Cancer Trials Ireland are listed in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Approved first-line treatments for fit patients (i.e., those with a low burden of coexisting conditions) with chronic lymphocytic leukemia (CLL) are fixed-duration chemoimmunotherapy,[1] a continuous Bruton's tyrosine kinase (BTK) inhibitor,[2] the time-limited B-cell lymphoma 2 (BCL2) inhibitor venetoclax plus the anti-CD20 antibody obinutuzumab,[3] and a BTK inhibitor plus venetoclax.[4-6] However, data from prospective, randomized clinical trials evaluating the safety and efficacy of venetoclax–obinutuzumab in fit patients with CLL and normal renal function are lacking.

The combination of venetoclax plus obinutuzumab or rituximab as first-line therapy has led to a high incidence of undetectable minimal residual disease and long progression-free survival among patients who are not fit and patients with relapsed disease.[3,7-11] Furthermore, combinations of BTK inhibitors and BCL2 inhibitors have induced undetectable minimal residual disease and led to promising durations of disease control.[6,12-17] In the GAIA–CLL13 trial, we evaluated the efficacy and safety of two fixed-duration regimens and one time-limited combination of venetoclax plus anti-CD20 antibodies (venetoclax–rituximab, venetoclax–obinutuzumab, and venetoclax–obinutuzumab–ibrutinib) as compared with chemoimmunotherapy as first-line treatment in fit patients with CLL.

Methods

Trial Design and Participants

This prospective, open-label, phase 3, randomized trial was conducted by the German CLL Study Group, the HOVON (the Hemato-Oncology Foundation for Adults in the Netherlands) CLL Study Group, and the Nordic CLL Study Group. The trial was performed at 159 sites by six trial groups in nine European countries and Israel (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Adult patients with previously untreated, advanced CLL that warranted treatment according to the International Workshop on CLL criteria[18] and who did not have del(17p) or *TP53* mutations were eligible. All the patients underwent central screening for review of fitness criteria, to determine whether therapy was warranted, for laboratory confirmation of the CLL diagnosis by central flow cytometry, and for genetic testing. Eligible patients had to have a low burden of coexisting conditions (a score of ≤6 on the Cumulative Illness Rating Scale; scores range from 0 to 56, with higher scores indicating more impaired function of organ systems) (Table S1 in the Supplementary Appendix),[19] a normal creatinine clearance (≥70 ml per minute), and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 to 2 (on a 5-point scale on which higher numbers reflect greater disability). All the patients provided written informed consent.

The trial was performed in accordance with the principles of the Declaration of Helsinki. The institutional review board or ethics committee at each institution approved the trial protocol (available at NEJM.org). An independent data and safety monitoring board reviewed safety data throughout the trial period until the interim analysis. The trial sponsor, the University of Cologne, was represented by the German CLL Study Group, which was responsible for data collection, data cleaning, and medical review. The trial was designed by the authors at the University of Cologne in cooperation with scientists from the above-mentioned trial groups; all the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All the authors contributed to drafting the manuscript, and no one who is not an author contributed to writing the manuscript. The monitoring of the trial was performed with the help of the German Competence Network Malignant Lymphomas.

Randomization and Procedures

We used a computer-generated randomization list to assign patients in a 1:1:1:1 ratio to one of four treatment groups. Randomization was stratified according to trial group, age (≤65 years or >65 years), and Binet stage at staging before the initiation of therapy (A, B, or C).[20]

Standard care consisted of six 28-day cycles of chemoimmunotherapy. Patients who were 65 years of age or younger received intravenous fludarabine (25 mg per square meter of body-surface area per day) and cyclophosphamide (250 mg per square meter per day) on day 1 to 3 of each cycle, and patients older than 65 years of age received intravenous bendamustine (90 mg per square meter per day) on day 1 and 2 of each cycle. Rituximab at a dose of 375 mg per square

meter was added to chemotherapy intravenously on day 1 of cycle 1 and at a dose of 500 mg per square meter on day 1 of each of the next five cycles.

The three experimental regimens contained venetoclax at a dose of 400 mg orally daily for 10 28-day cycles after a 5-week ramp-up phase from day 22 in cycle 1 until the end of cycle 2 (details are provided in Table S2). In the venetoclax–rituximab group, rituximab at a dose of 375 mg per square meter was administered intravenously on day 1 of cycle 1 and at a dose of 500 mg per square meter on day 1 of each of the next five cycles. In the obinutuzumab-containing regimens, obinutuzumab was administered at a dose of 100 mg intravenously on day 1, 900 mg on day 2, and then 1000 mg on day 8 and 15 of cycle 1. On day 1 of the subsequent five cycles, obinutuzumab at a dose of 1000 mg was administered. In the triple-combination regimen (venetoclax–obinutuzumab–ibrutinib), ibrutinib at a dose of 420 mg orally daily was initiated together with the first obinutuzumab infusion on day 1 of cycle 1 and was continued throughout the 12 treatment cycles, to which venetoclax was added as described for the venetoclax–obinutuzumab regimen above. If minimal residual disease was undetectable in peripheral blood in two consecutive local measurements (cycle 9 of 12 or cycle 12 of 15) or in peripheral blood and consecutive bone marrow aspirations, ibrutinib treatment was discontinued. Otherwise, ibrutinib was continued until cycle 36 or until unacceptable toxic effects occurred.

ASSESSMENTS AND END POINTS

Baseline assessments included physical examination, determination of ECOG performance status, and computed tomographic or magnetic resonance imaging (or ultrasonographic examination of the abdomen if these imaging methods were not available). Radiographic imaging as well as a complete blood count were performed at the final restaging 3 months after the last treatment cycle, on month 15 at the latest. Response and disease progression were assessed by the investigators and were classified according to the response criteria of the International Workshop on CLL.[18] Minimal residual disease status was analyzed centrally at the University of Kiel with the use of four-color flow cytometry to detect minimal residual disease with a sensitivity of at least 10^{-4} (i.e., <1 cell in 10,000 leukocytes).[21] In all patients who had a clinical complete remission confirmed by physical examination and blood count at the end of treatment, a bone marrow biopsy including central assessment of minimal residual disease was performed at final restaging.

Adverse events (clinical and laboratory-confirmed) were reported until day 28 after the last dose of trial medication. Adverse events of interest (infections of any grade, cardiac events, and late-onset neutropenia) were reported until the start of the next treatment, and all autoimmune complications and secondary neoplasia were reported until the end of the trial. Severe adverse events were reported during the whole trial period. The severity of adverse events was graded with the use of the National Cancer Institute Common Toxicity Criteria, version 4.

The trial had two primary end points that were analyzed and interpreted independently. The first primary end point was undetectable minimal residual disease in peripheral blood at month 15 (with a cutoff of 10^{-4}). The second primary end point was progression-free survival, which was defined as the time from randomization to disease progression or death from any cause. The secondary end points were the following: undetectable minimal residual disease in peripheral blood at months 2, 9, and 12; undetectable minimal residual disease in bone marrow at final restaging; overall and complete response; safety; overall and event-free survival; time to the next treatment for CLL; and health-related quality of life.

STATISTICAL ANALYSIS

We calculated the sample size on the basis of both primary end points using a split two-sided alpha level of 0.025 for each hypothesis being tested. To assess the potential superiority of venetoclax–obinutuzumab over chemoimmunotherapy with regard to undetectable minimal residual disease at month 15, at least 80% power was assumed to show a between-group difference of 20 percentage points in the percentage of patients with a response (from 30% in the chemoimmunotherapy group to 50% in the venetoclax–obinutuzumab group) with the use of a Cochran–Mantel–Haenszel test stratified according to age (≤65 years or >65 years) and Binet stage.

To assess the potential superiority of the triple-combination regimen over chemoimmunotherapy on the basis of a two-sided log-rank test stratified according to age (≤65 years or >65 years) and Binet stage, we calculated that 213 events (disease progression or death) would provide the trial with approximately 80% power to detect a hazard ratio of 0.65. An interim analysis was planned to be performed after 138 of 213 events (65%) had occurred or 61 months after the first patient had undergone randomization, whichever occurred first. Altogether, we aimed to recruit 920 patients (i.e., 230 per treatment group) to allow for balanced comparisons.

The primary end point analysis of undetectable minimal residual disease (including analysis of response) was performed with a data-cutoff date of February 28, 2021. The interim analysis of progression-free survival (a primary end point), including analysis of further time-to-event end points and safety, was conducted at a fixed time point of month 61 with a data-cutoff date of January 20, 2022. The corresponding significance level was determined with the use of the Lan–DeMets alpha-spending function with an O'Brien–Fleming boundary (based on the observed number of events with venetoclax–obinutuzumab–ibrutinib and chemoimmunotherapy) so that the overall two-sided type I error rate would be maintained at the 0.025 level. At month 61, a total of 93 events were observed in the triple-combination and chemoimmunotherapy groups, resulting in a significance level of 0.000393 and 0.024864 for the interim and final analysis of progression-free survival, respectively. The results of the interim analysis were assessed as being significant because the P value was lower than the prespecified boundary for early stopping (P≤0.000393). Therefore, the independent data and safety monitoring board recommended conducting the full analysis of the primary and secondary end points.

All efficacy analyses were performed in the intention-to-treat population, which was defined as all patients who had undergone randomization. All safety analyses were performed in the safety population, which was defined as all patients who had received at least one course of trial treatment. Comparisons of undetectable minimal residual disease at month 15 and progression-free survival in the treatment groups were performed with the use of prespecified hierarchical testing procedures. All statistical tests were two-sided, and a P value of less than 0.025 was considered to indicate statistical significance.

RESULTS

PATIENTS

Between December 13, 2016, and October 13, 2019, a total of 1080 patients underwent screening. Of these patients, 154 patients did not meet the inclusion criteria, so the intention-to-treat population consisted of 926 patients (229 in the chemoimmunotherapy group, 237 in the venetoclax–rituximab group, 229 in the venetoclax–obinutuzumab group, and 231 in the venetoclax–obinutuzumab–ibrutinib group) (Fig. 1).

All the treatment groups were well balanced with respect to patient characteristics (Table 1). The treatment adherence to the planned number of cycles in each group was high, ranging from 81.5% in the chemoimmunotherapy group to 93.9% in the venetoclax–obinutuzumab group. In the venetoclax–obinutuzumab–ibrutinib group, 209 of 231 patients (90.5%) received at least 12 cycles of therapy, 42 discontinued therapy after 12 cycles, 145 discontinued therapy between cycle 13 and 15, and 22 discontinued therapy after cycle 16 (Table S4). A total of 177 of 198 patients discontinued ibrutinib in accordance with the protocol because of confirmed undetectable minimal residual disease, 6 completed 36 cycles, and 15 had missing information.

Early discontinuation of treatment across all groups was mostly due to adverse events or intercurrent illness. Dose reductions greater than 20% with any of the agents were performed at least once during treatment in 14.8% of the patients in the chemoimmunotherapy group to 37.4% of the patients in the venetoclax–obinutuzumab–ibrutinib group.

EFFICACY

At month 15, a significantly higher percentage of patients in the venetoclax–obinutuzumab group than in the chemoimmunotherapy group had undetectable minimal residual disease in peripheral blood (the first primary end point) (86.5% [97.5% confidence interval {CI}, 80.6 to 91.1] vs. 52.0% [97.5% CI, 44.4 to 59.5]; P<0.001) (Fig. 2A). According to the a priori defined sequence of comparisons, the percentage of patients

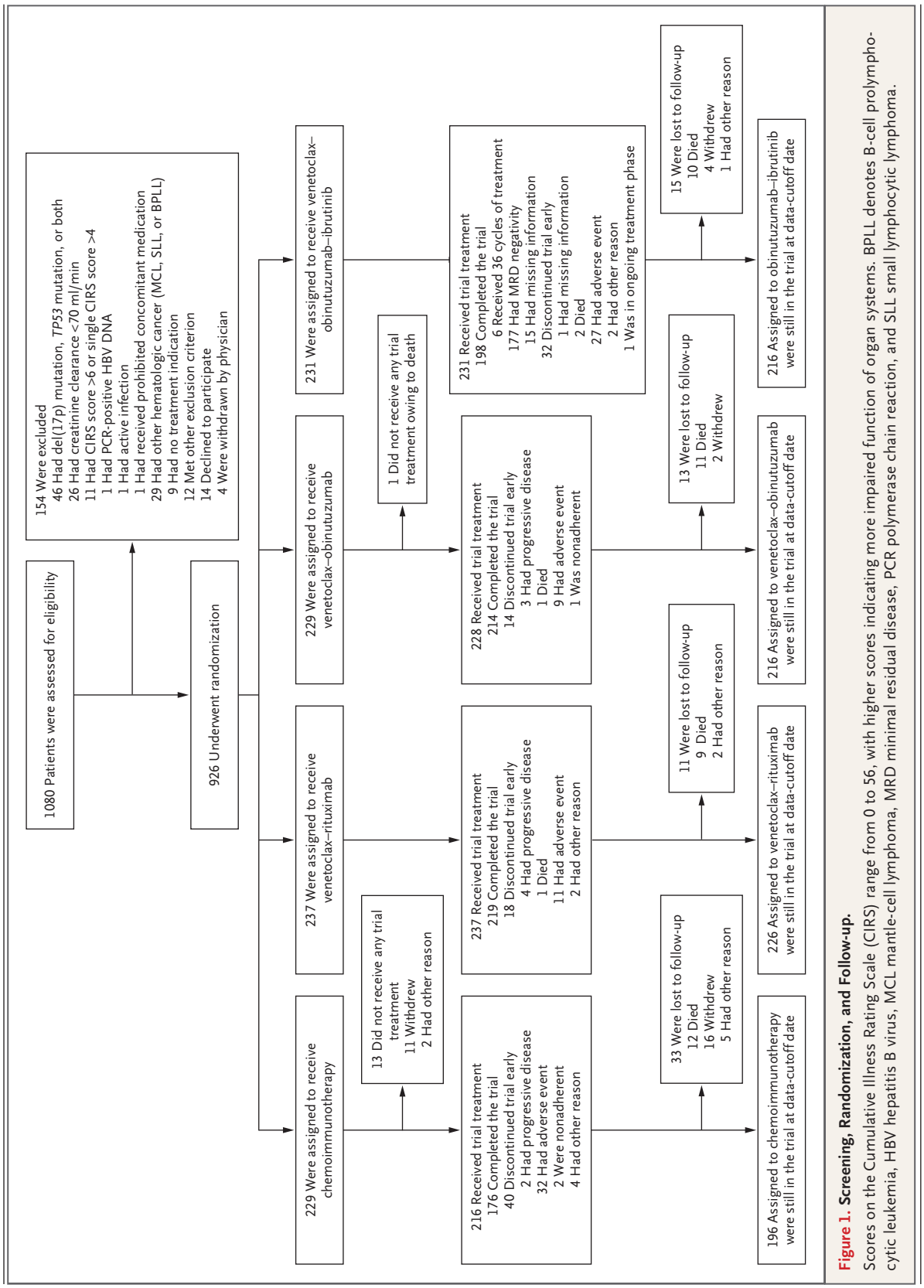


Figure 1. Screening, Randomization, and Follow-up.

Scores on the Cumulative Illness Rating Scale (CIRS) range from 0 to 56, with higher scores indicating more impaired function of organ systems. BPLL denotes B-cell prolymphocytic leukemia, HBV hepatitis B virus, MCL mantle-cell lymphoma, MRD minimal residual disease, PCR polymerase chain reaction, and SLL small lymphocytic lymphoma.

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Chemoimmunotherapy (N=229)	Venetoclax–Rituximab (N=237)	Venetoclax–Obinutuzumab (N=229)	Venetoclax–Obinutuzumab–Ibrutinib (N=231)
Median age (range) — yr	61 (29–84)	62 (27–84)	62 (31–83)	60 (30–84)
Age >65 yr — no. (%)	79 (34.5)	85 (35.9)	82 (35.8)	83 (35.9)
Male sex — no. (%)	163 (71.2)	175 (73.8)	171 (74.7)	158 (68.4)
ECOG performance-status score of 0 — no. (%)†	164 (71.6)	172 (72.6)	165 (72.1)	163 (70.6)
CIRS score‡				
Median (range)	2 (0–6)	2 (0–7)	2 (0–6)	2 (0–7)
Score ≤1 — no. (%)	93 (40.6)	94 (39.7)	90 (39.3)	84 (36.4)
Median creatinine clearance (range) — ml/min§	86.3 (39.5–223.6)	84.5 (42.6–268.3)	86.3 (41.5–180.2)	86.2 (43.5–178.5)
Tumor lysis syndrome risk category — no./total no. (%)¶				
Low	31/214 (14.5)	23/220 (10.5)	31/211 (14.7)	28/226 (12.4)
Intermediate	132/214 (61.7)	146/220 (66.4)	127/211 (60.2)	154/226 (68.1)
High	51/214 (23.8)	51/220 (23.2)	53/211 (25.1)	44/226 (19.5)
Binet stage — no. (%)‖				
A	61 (26.6)	62 (26.2)	60 (26.2)	63 (27.3)
B	85 (37.1)	90 (38.0)	90 (39.3)	84 (36.4)
C	83 (36.2)	85 (35.9)	79 (34.5)	84 (36.4)
Rai stage — no./total no. (%)**				
0	7/227 (3.1)	8/237 (3.4)	13/228 (5.7)	7/230 (3.0)
I or II	113/227 (49.8)	124/237 (52.3)	122/228 (53.5)	121/230 (52.6)
III or IV	107/227 (47.1)	105/237 (44.3)	93/228 (40.8)	102/230 (44.3)
Cytogenetic subgroup — no. (%)				
Deletion in 11q	41 (17.9)	45 (19.0)	44 (19.2)	32 (13.9)
Trisomy 12	34 (14.8)	34 (14.3)	47 (20.5)	35 (15.2)
No abnormalities	53 (23.1)	45 (19.0)	44 (19.2)	59 (25.5)
Deletion in 13q	101 (44.1)	113 (47.7)	94 (41.0)	105 (45.5)
IGHV mutation status — no./total no. (%)				
Mutated	95/229 (41.5)	95/237 (40.1)	89/228 (39.0)	101/231 (43.7)
Unmutated	131/229 (57.2)	134/237 (56.5)	130/228 (57.0)	123/231 (53.2)
Could not be evaluated	3/229 (1.3)	8/237 (3.4)	9/228 (3.9)	7/231 (3.0)
$Beta_2$-microglobulin				
Median (range)	4.2 (1.4–15.5)	3.9 (1.7–11.4)	4.0 (2.0–16.2)	4.1 (1.3–11.9)
>3.5 mg/liter — no./total no. (%)	155/228 (68.0)	150/236 (63.6)	136/227 (59.9)	146/229 (63.8)
CLL-IPI risk group — no./total no. (%)††				
Low	36/225 (16.0)	39/228 (17.1)	32/217 (14.7)	36/222 (16.2)
Intermediate	67/225 (29.8)	66/228 (28.9)	76/217 (35.0)	85/222 (38.3)
High	122/225 (54.2)	123/228 (53.9)	109/217 (50.2)	101/222 (45.5)

Table 1. (Continued.)

Characteristic	Chemoimmunotherapy (N=229)	Venetoclax–Rituximab (N=237)	Venetoclax–Obinutuzumab (N=229)	Venetoclax–Obinutuzumab–Ibrutinib (N=231)
Very high	0	0	0	0
Complex karyotype — no./total no. (%)				
<3 aberrations	177/223 (79.4)	187/231 (81.0)	182/218 (83.5)	196/223 (87.9)
≥3 and <5 aberrations	30/223 (13.5)	34/231 (14.7)	25/218 (11.5)	21/223 (9.4)
≥5 aberrations	16/223 (7.2)	10/231 (4.3)	11/218 (5.0)	6/223 (2.7)
Median time from diagnosis to trial entry (IQR) — mo	26.7 (9.2–59.1)	32.9 (9.7–62.1)	27.7 (8.3–62.0)	28.7 (9.4–58.6)

* The intention-to-treat population was defined as all patients who had undergone randomization. Percentages may not total 100 because of rounding. Baseline characteristics in patients who received fludarabine–cyclophosphamide–rituximab or bendamustine–rituximab are shown in Table S3. Patients with a creatinine clearance below 70 ml per minute were eligible if central review confirmed impaired renal function due to abdominal lymphadenopathy; there were 41 such patients in the chemoimmunotherapy group (17.9%), 50 in the venetoclax–rituximab group (21.1%), 47 of 228 in the venetoclax–obinutuzumab group (20.5%), and 43 in the venetoclax–obinutuzumab–ibrutinib group (18.6%). CLL denotes chronic lymphocytic leukemia, *IGHV* immunoglobulin heavy-chain variable region, and IQR interquartile range.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating greater disability. A score of 0 indicates that the patient is fully active and able to carry on all predisease performance without restriction, a score of 1 that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, and a score of 2 that the patient is ambulatory and capable of all self-care but is unable to carry out any work activities.

‡ Scores on the Cumulative Illness Rating Scale (CIRS) range from 0 to 56, with higher scores indicating more impaired function of organ systems. One patient in the venetoclax–rituximab group and two patients in the venetoclax–obinutuzumab–ibrutinib group were classified as having a CIRS score of 7 on the basis of a monitoring visit after randomization.

§ Creatinine clearance was measured according to the Cockcroft–Gault equation. Data were missing for one patient in the venetoclax–obinutuzumab group.

¶ Tumor lysis syndrome risk categories were low (absolute lymphocyte count $<25\times10^3$ per cubic millimeter and largest diameter of all measurable lymph nodes <5 cm), intermediate (absolute lymphocyte count $\geq25\times10^3$ per cubic millimeter or largest diameter of any measurable lymph node ≥5 cm and <10 cm), and high (absolute lymphocyte count $\geq25\times10^3$ per cubic millimeter and largest diameter of any measurable lymph node ≥5 cm and <10 cm, or largest diameter of any measurable lymph node ≥10 cm, regardless of absolute lymphocyte count).

‖ Binet stages indicate the degree of advancement of CLL and are based on organ and lymph-node involvement, hemoglobin levels, and platelet counts.

** In the Rai staging system, stage 0 denotes low-risk disease, stage I or II intermediate risk, and stage III or IV high risk.

†† The International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI) categorizes risk (low, intermediate, high, or very high) on the basis of weighted individual risk factors (i.e., status with respect to 17p deletion and *TP53* mutation, *IGHV* mutation status, serum beta$_2$-microglobulin level [<3.5 mg per liter or ≥3.5 mg per liter], age, and clinical stage).

in the venetoclax–obinutuzumab–ibrutinib group with undetectable minimal residual disease (92.2%; 97.5% CI, 87.3 to 95.7) was also higher than that in the chemoimmunotherapy group (P<0.001). The percentage of patients in the venetoclax–rituximab group with undetectable minimal residual disease (57.0%; 97.5% CI, 49.5 to 64.2) was not significantly different from that in the chemoimmunotherapy group (P=0.32). Therefore, on the basis of the statistical testing hierarchy, no further tests between the groups were performed. Minimal residual disease in all four groups at all time points, including month 2, 9, and 12, is shown in Figure S1A through S1D, and minimal residual disease at month 15 for each chemoimmunotherapy group is shown in Table S6.

Bone marrow biopsy and measurement of minimal residual disease was requested only for patients with a clinical complete response; 69.0%, 81.0%, 86.9%, and 84.8% of the patients in the chemoimmunotherapy, venetoclax–rituximab, venetoclax–obinutuzumab, and venetoclax–obinutuzumab–ibrutinib groups, respectively, had bone marrow samples for evaluation. The percentage of patients with undetectable minimal residual disease in bone marrow was higher in the venetoclax–obinutuzumab groups (in 180 of 231 patients who received venetoclax–obinutuzumab with ibrutinib [77.9%] and 166 of 229 patients who received venetoclax–obinutuzumab without ibrutinib [72.5%]) and lower in the venetoclax–rituximab group (in 102 of 237 patients [43.0%]) and the chemoimmunotherapy

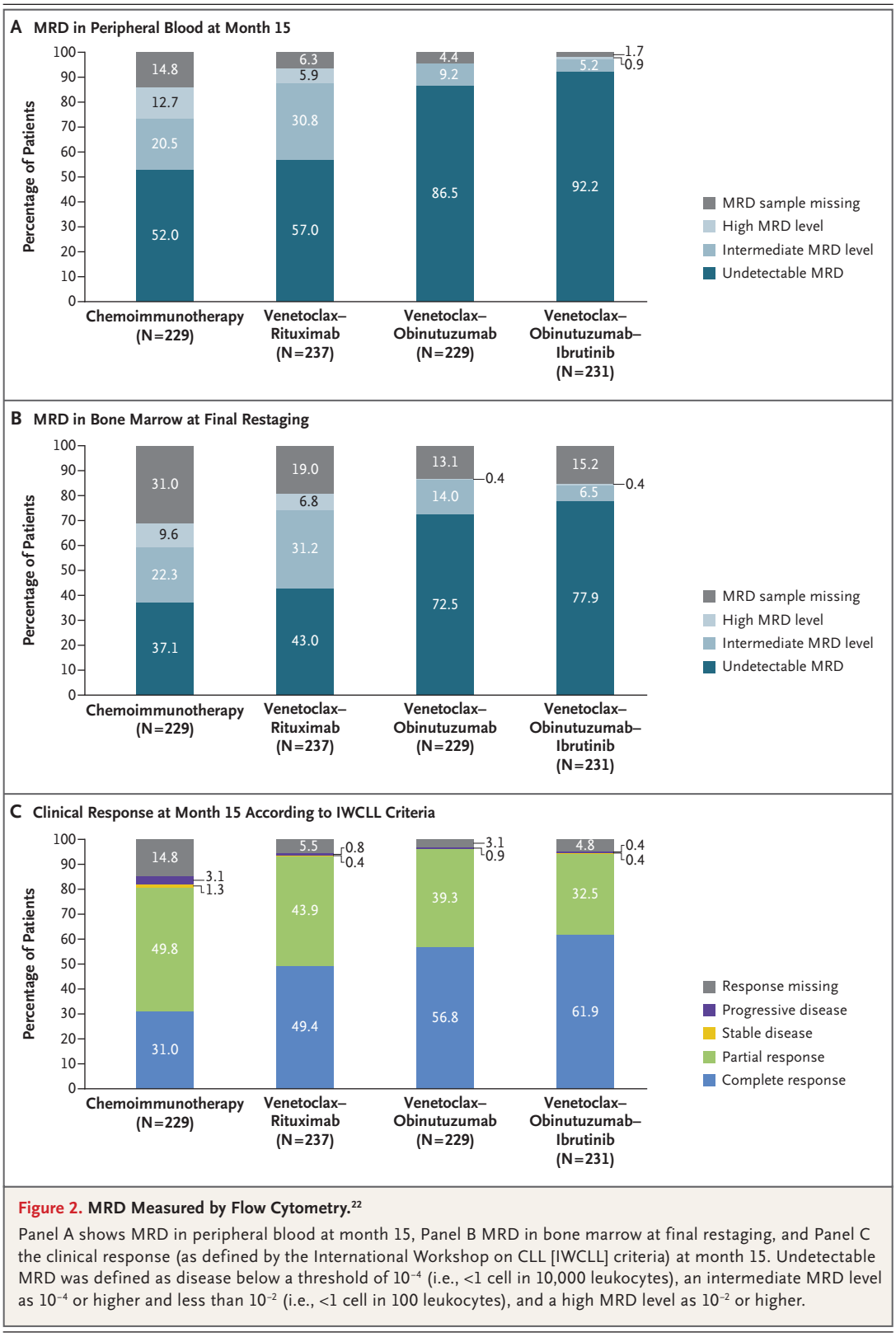


Figure 2. MRD Measured by Flow Cytometry.[22]

Panel A shows MRD in peripheral blood at month 15, Panel B MRD in bone marrow at final restaging, and Panel C the clinical response (as defined by the International Workshop on CLL [IWCLL] criteria) at month 15. Undetectable MRD was defined as disease below a threshold of 10^{-4} (i.e., <1 cell in 10,000 leukocytes), an intermediate MRD level as 10^{-4} or higher and less than 10^{-2} (i.e., <1 cell in 100 leukocytes), and a high MRD level as 10^{-2} or higher.

group (in 85 of 229 patients [37.1%]) (Fig. 2B). At month 15, complete responses as defined in the International Workshop on CLL guidelines were induced in 71 of 229 patients in the chemoimmunotherapy group (31.0%), 117 of 237 patients in the venetoclax–rituximab group (49.4%), 130 of 229 patients in the venetoclax–obinutuzumab group (56.8%), and 143 of 231 patients in the triple-combination group (61.9%) (Fig. 2C). The percentage of patients with a clinical best response (defined in accordance with International Workshop on CLL guidelines) until month 15 was particularly high in the chemoimmunotherapy group (Fig. S2).

After a median follow-up time of 38.8 months (interquartile range, 32.7 to 46.1), the interim analysis of progression-free survival (the second primary end point) showed superiority of venetoclax–obinutuzumab–ibrutinib combination therapy over chemoimmunotherapy, with a hazard ratio for disease progression or death of 0.32 (97.5% CI, 0.19 to 0.54; P<0.001). Although venetoclax–obinutuzumab was superior to chemoimmunotherapy with respect to progression-free survival (hazard ratio for disease progression or death, 0.42; 97.5% CI, 0.26 to 0.68; P<0.001), no significant difference was noted between the venetoclax–rituximab and chemoimmunotherapy groups (hazard ratio, 0.79; 97.5% CI, 0.53 to 1.18; P=0.18) (Fig. 3A). On the basis of the statistical testing hierarchy, no further tests between groups were performed. Among patients with unmutated immunoglobulin heavy-chain variable region (*IGHV*), the percentage of those with progression-free survival at 3 years was 86.6% in the venetoclax–obinutuzumab–ibrutinib group, 82.9% in the venetoclax–obinutuzumab group, 76.4% in the venetoclax–rituximab group, and 65.5% in the chemoimmunotherapy group, as compared with 96.0%, 93.6%, 87.0%, and 89.9%, respectively, among those with mutated *IGHV* (Fig. 3B and 3C). This benefit of venetoclax–obinutuzumab therapy with or without ibrutinib was also observed within prespecified subgroups, with the exception of the abovementioned *IGHV* mutation status, trisomy 12, normal karyotype, and intermediate International Prognostic Index for Chronic Lymphocytic Leukemia risk score (Fig. S3). Undetectable minimal residual disease at month 15 was associated with longer progression-free survival among patients who had a complete response or even a partial response (Fig. S4).

At 3 years, 98.4%, 94.2%, 93.0%, and 87.4% of the patients in the venetoclax–obinutuzumab–ibrutinib, venetoclax–obinutuzumab, venetoclax–rituximab, and chemoimmunotherapy groups, respectively, were not receiving additional treatment (Fig. S5). Across all the treatment groups, similar overall survival at 3 years was observed — 95.3%, 96.3%, 96.5%, and 95.0% in the venetoclax–obinutuzumab–ibrutinib, venetoclax–obinutuzumab, venetoclax–rituximab, and chemoimmunotherapy groups, respectively.

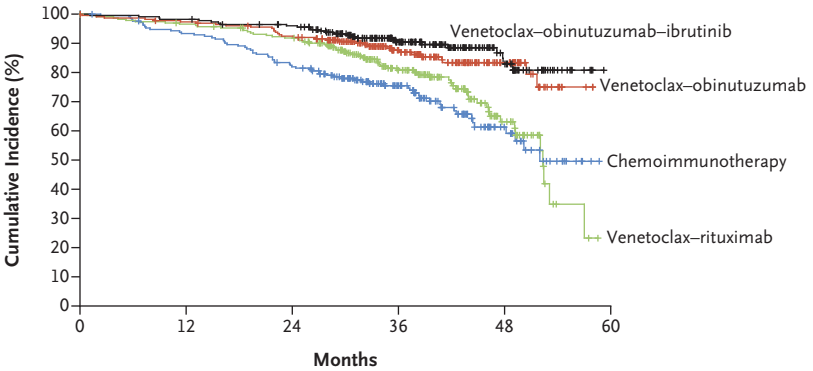
SAFETY

Adverse events were at least one of the reasons for early treatment discontinuation in 89 of 912 patients (9.8%). Early discontinuation of treatment owing to adverse events occurred in 33 of 216 patients in the chemoimmunotherapy group (15.3%), 14 of 237 patients in the venetoclax–rituximab group (5.9%), 13 of 228 patients in the venetoclax–obinutuzumab group (5.7%), and 29 of 231 patients in the triple-combination group (12.6%).

As shown in Table 2, the most common grade 3 and 4 adverse events across all four treatment groups were cytopenia and infections. Serious adverse events were reported in 103 of 216 patients who received chemoimmunotherapy (47.7%), 95 of 237 patients who received venetoclax–rituximab (40.1%), 102 of 228 patients who received venetoclax–obinutuzumab (44.7%), and 116 of 231 patients who received venetoclax–obinutuzumab–ibrutinib (50.2%); severe acute respiratory syndrome coronavirus 2 infections, including six fatal infections, were observed in 10 patients (2 who died), 22 patients (none of whom died), 11 patients (3 who died), and 12 patients (1 who died), respectively; 53 infections occurred during follow-up. Most clinical or laboratory-confirmed cases of tumor lysis syndrome, defined according to Cairo–Bishop criteria (see the Methods section in the Supplementary Appendix),[23] were grade 3, with no grade 5 events; these cases occurred more frequently in the venetoclax–rituximab and venetoclax–obinutuzumab groups than in the other two groups (Table 2).

A total of 36 of 912 patients (3.9%) had fatal adverse events; these deaths occurred in 10 of

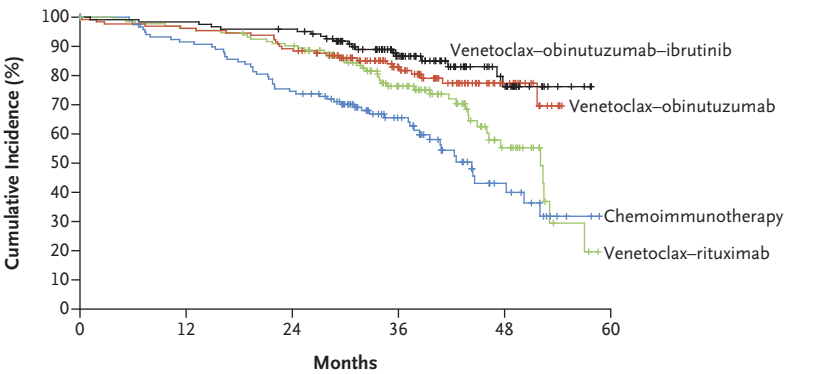
A Progression-free Survival, All Patients



No. at Risk

Chemoimmunotherapy	229	197	172	98	28	0
Venetoclax–rituximab	237	226	212	119	32	0
Venetoclax–obinutuzumab	229	221	208	125	42	0
Venetoclax–obinutuzumab–ibrutinib	231	227	217	132	44	0

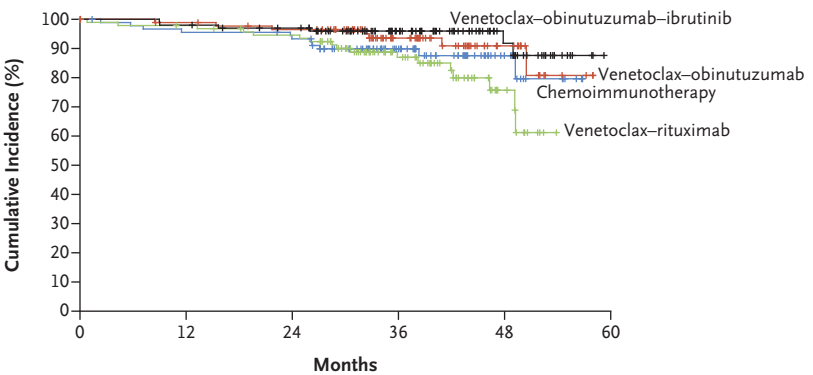
B Progression-free Survival, Patients with Unmutated *IGHV*



No. at Risk

Chemoimmunotherapy	131	108	88	48	14	0
Venetoclax–rituximab	134	128	119	67	20	0
Venetoclax–obinutuzumab	130	125	116	71	21	0
Venetoclax–obinutuzumab–ibrutinib	123	121	117	70	22	0

C Progression-free Survival, Patients with Mutated *IGHV*



No. at Risk

Chemoimmunotherapy	95	86	83	50	14	0
Venetoclax–rituximab	95	91	86	49	12	0
Venetoclax–obinutuzumab	89	86	82	48	17	0
Venetoclax–obinutuzumab–ibrutinib	101	99	94	59	22	0

Figure 3 (facing page). Progression-free Survival at 3 Years.

The percentages of all patients with progression-free survival at 3 years were 75.5% in the chemoimmunotherapy group, 80.8% in the venetoclax–rituximab group, 87.7% in the venetoclax–obinutuzumab group, and 90.5% in the venetoclax–obinutuzumab–ibrutinib group (Panel A). The percentages of patients with unmutated *IGHV* who had progression-free survival at 3 years were 65.5% (chemoimmunotherapy), 76.4% (venetoclax–rituximab), 82.9% (venetoclax–obinutuzumab), and 86.6% (venetoclax–obinutuzumab–ibrutinib) (Panel B), and the percentages of patients with mutated *IGHV* who had progression-free survival at 3 years were 89.9%, 87.0%, 93.6%, and 96.0%, respectively (Panel C). Tick marks indicate censored data.

216 patients in the chemoimmunotherapy group (4.6%), 8 of 237 in the venetoclax–rituximab group (3.4%), 9 of 228 in the venetoclax–obinutuzumab group (3.9%), and 9 of 231 in the venetoclax–obinutuzumab–ibrutinib group (3.9%). Twelve of these deaths occurred during therapy or up to week 12 after the end of treatment, and 24 occurred later during follow-up (Table S7).

Richter's transformation (disease progression to diffuse large-B-cell lymphoma or Hodgkin's lymphoma) occurred in 6, 4, 6, and 2 patients who received chemoimmunotherapy, venetoclax–rituximab, venetoclax–obinutuzumab, and venetoclax–obinutuzumab–ibrutinib, respectively, and secondary neoplasia was reported in 36 of 216 patients (16.7%), 21 of 237 patients (8.9%), 23 of 228 patients (10.1%), and 24 of 231 patients (10.4%), respectively. Table S8 lists all cases of secondary neoplasia. It is notable that nonmelanoma skin cancer was more frequently observed in the chemoimmunotherapy group than in the other groups.

DISCUSSION

The phase 3 GAIA–CLL13 trial showed that in patients with a low burden of coexisting conditions, time-limited venetoclax–obinutuzumab with or without ibrutinib was superior to chemoimmunotherapy with respect to inducing undetectable minimal residual disease and longer progression-free survival (the primary end points). The percentages of patients in the venetoclax–obinutuzumab and venetoclax–obinutuzumab–ibrutinib groups with undetectable minimal residual disease in peripheral blood were very high, at 86.5% and 92.2%, respectively; these percentages are among the highest reported in first-line therapy for CLL. Because the improved incidence of undetectable minimal residual disease translated into superior progression-free survival, the trial corroborates the high prognostic value of undetectable minimal residual disease at the end of time-limited treatment.[21] Data from this trial confirm the superiority of venetoclax–obinutuzumab over even more potent chemoimmunotherapy regimens than chlorambucil–obinutuzumab and are leading to the approval of venetoclax–obinutuzumab for CLL.[3]

The 3-year progression-free survival among patients in the venetoclax–obinutuzumab group (87.7%) and the venetoclax–obinutuzumab–ibrutinib group (90.5%) is similar to that among patients who received continuous administration of ibrutinib plus rituximab in two phase 3 trials involving physically fit patients who did not have a *TP53* aberration: the E1912 trial[2,24] and the Front-Line Therapy in CLL: Assessment of Ibrutinib-containing Regimes (FLAIR) trial.[25] Other studies evaluating a BTK inhibitor plus obinutuzumab as first-line therapy were performed in older patients or those who were not fit.[26,27] Acalabrutinib–obinutuzumab was associated with an 87% progression-free survival at 4 years in spite of the advanced median age of the participants in that trial.[26] Although continuous acalabrutinib–obinutuzumab therapy may lead to even longer progression-free survival than venetoclax–obinutuzumab, a fixed-duration regimen such as venetoclax–obinutuzumab can result in remarkable treatment-free intervals.[10] The superiority of targeted agents over each type of chemoimmunotherapy administered either as continuous therapy or as time-limited therapy should be the basis for comparison for future clinical trials.

Although the data in the venetoclax–obinutuzumab–ibrutinib group in the current trial confirm phase 2 trial results with respect to the efficacy of triple-combination regimens,[12-14] whether the triple combination is even more beneficial than other regimens such as continuous BTK inhibitor therapy or double combinations that include BCL2 inhibitors cannot be answered by our trial. Some of the benefits of the triplet therapy are neutralized by the need for dose reductions and early treatment discontinuation owing to adverse events.

Table 2. Adverse Events in the Safety Population, According to Maximum Grade.*

Event	Chemoimmunotherapy (N=216)			Venetoclax–Rituximab (N=237)			Venetoclax–Obinutuzumab (N=228)			Venetoclax–Obinutuzumab–Ibrutinib (N=231)		
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
	number of patients (percent)											
All	38 (17.6)	78 (36.1)	88 (40.7)	58 (24.5)	114 (48.1)	51 (21.5)	31 (13.6)	109 (47.8)	74 (32.5)	37 (16.0)	110 (47.6)	74 (32.0)
Blood and lymphatic system disorders	12 (5.6)	50 (23.1)	72 (33.3)	19 (8.0)	64 (27.0)	39 (16.5)	11 (4.8)	68 (29.8)	60 (26.3)	28 (12.1)	53 (22.9)	64 (27.7)
Neutropenia	7 (3.2)	34 (15.7)	64 (29.6)	14 (5.9)	56 (23.6)	38 (16.0)	8 (3.5)	51 (22.4)	52 (22.8)	14 (6.1)	39 (16.9)	56 (24.2)
Anemia	15 (6.9)	14 (6.5)	2 (0.9)	11 (4.6)	9 (3.8)	0	8 (3.5)	10 (4.4)	1 (0.4)	12 (5.2)	7 (3.0)	2 (0.9)
Leukopenia	7 (3.2)	19 (8.8)	7 (3.2)	11 (4.6)	1 (0.4)	0	7 (3.1)	12 (5.3)	1 (0.4)	13 (5.6)	3 (1.3)	1 (0.4)
Thrombocytopenia	14 (6.5)	14 (6.5)	4 (1.9)	9 (3.8)	4 (1.7)	4 (1.7)	6 (2.6)	25 (11.0)	9 (3.9)	24 (10.4)	15 (6.5)	11 (4.8)
Febrile neutropenia	0	23 (10.6)	1 (0.5)	0	10 (4.2)	0	1 (0.4)	7 (3.1)	0	0	15 (6.5)	3 (1.3)
Infections	89 (41.2)	38 (17.6)	2 (0.9)	113 (47.7)	24 (10.1)	1 (0.4)	121 (53.1)	30 (13.2)	0	123 (53.2)	48 (20.8)	1 (0.4)
Upper respiratory tract	42 (19.4)	2 (0.9)	0	73 (30.8)	5 (2.1)	0	82 (36.0)	5 (2.2)	0	78 (33.8)	2 (0.9)	0
Urinary tract	9 (4.2)	2 (0.9)	0	13 (5.5)	5 (2.1)	0	14 (6.1)	3 (1.3)	0	24 (10.4)	9 (3.9)	0
Pneumonia	6 (2.8)	12 (5.6)	0	4 (1.7)	4 (1.7)	0	9 (3.9)	12 (5.3)	0	14 (6.1)	14 (6.1)	1 (0.4)
Infection, NOS	11 (5.1)	5 (2.3)	0	5 (2.1)	1 (0.4)	0	7 (3.1)	4 (1.8)	0	5 (2.2)	4 (1.7)	0
Influenza	2 (0.9)	5 (2.3)	0	8 (3.4)	3 (1.3)	0	9 (3.9)	0	0	5 (2.2)	3 (1.3)	0
Gastrointestinal disorders	143 (66.2)	6 (2.8)	1 (0.5)	133 (56.1)	9 (3.8)	0	139 (61.0)	8 (3.5)	0	156 (67.5)	21 (9.1)	0
Diarrhea	26 (12.0)	0	1 (0.5)	68 (28.7)	4 (1.7)	0	71 (31.1)	4 (1.8)	0	106 (45.9)	13 (5.6)	0
General disorders and administration-site condition	125 (57.9)	13 (6.0)	0	114 (48.1)	5 (2.1)	0	133 (58.3)	8 (3.5)	0	122 (52.8)	9 (3.9)	0
Pyrexia	45 (20.8)	7 (3.2)	0	32 (13.5)	4 (1.7)	0	50 (21.9)	4 (1.8)	0	25 (10.8)	3 (1.3)	0
Skin and subcutaneous tissue disorders	77 (35.6)	8 (3.7)	0	87 (36.7)	3 (1.3)	0	85 (37.3)	3 (1.3)	0	110 (47.6)	8 (3.5)	0
Injury, poisoning, and procedural complications	65 (30.1)	14 (6.5)	0	73 (30.8)	21 (8.9)	1 (0.4)	100 (43.9)	27 (11.8)	0	64 (27.7)	13 (5.6)	0
Infusion-related reaction	59 (27.3)	12 (5.6)	0	65 (27.4)	19 (8.0)	0	91 (39.9)	26 (11.4)	0	44 (19.0)	10 (4.3)	0
Vascular disorders	24 (11.1)	4 (1.9)	0	33 (13.9)	7 (3.0)	0	37 (16.2)	7 (3.1)	0	49 (21.2)	20 (8.7)	0
Hypertension	3 (1.4)	3 (1.4)	0	11 (4.6)	5 (2.1)	0	17 (7.5)	4 (1.8)	0	16 (6.9)	13 (5.6)	0

Metabolism and nutrition disorders	27 (12.5)	14 (6.5)	2 (0.9)	44 (18.6)	32 (13.5)	3 (1.3)	36 (15.8)	27 (11.8)	4 (1.8)	67 (29.0)	22 (9.5)	7 (3.0)
Tumor lysis syndrome	1 (0.5)	9 (4.2)	0	5 (2.1)	23 (9.7)	1 (0.4)	6 (2.6)	17 (7.5)	2 (0.9)	4 (1.7)	12 (5.2)	3 (1.3)
Clinical	1 (0.5)	0	0	0	3 (1.3)	1 (0.4)	0	3 (1.3)	1 (0.4)	0	0	2 (0.9)
Laboratory-confirmed	0	3 (1.4)	0	5 (2.1)	19 (8.0)	0	5 (2.2)	10 (4.4)	1 (0.4)	4 (1.7)	10 (4.3)	1 (0.4)
Not specified	0	6 (2.8)	0	0	1 (0.4)	0	1 (0.4)	4 (1.8)	0	0	2 (0.9)	0
Hypophosphatemia	0	0	0	1 (0.4)	0	0	1 (0.4)	5 (2.2)	0	5 (2.2)	2 (0.9)	1 (0.4)
Musculoskeletal and connective-tissue disorders	38 (17.6)	6 (2.8)	0	87 (36.7)	6 (2.5)	0	91 (39.9)	2 (0.9)	0	106 (45.9)	10 (4.3)	0
Nervous system disorders	51 (23.6)	6 (2.8)	1 (0.5)	54 (22.8)	3 (1.3)	0	73 (32.0)	6 (2.6)	0	79 (34.2)	10 (4.3)	0
Syncope	2 (0.9)	2 (0.9)	0	2 (0.8)	0	0	1 (0.4)	4 (1.8)	0	0	6 (2.6)	0
Respiratory, thoracic, and mediastinal disorders	51 (23.6)	2 (0.9)	0	56 (23.6)	4 (1.7)	0	67 (29.4)	3 (1.3)	0	84 (36.4)	6 (2.6)	0
Investigations	29 (13.4)	10 (4.6)	15 (6.9)	40 (16.9)	22 (9.3)	13 (5.5)	37 (16.2)	33 (14.5)	22 (9.6)	56 (24.2)	28 (12.1)	6 (2.6)
Neutrophil count ↓	1 (0.5)	7 (3.2)	12 (5.6)	6 (2.5)	13 (5.5)	12 (5.1)	1 (0.4)	17 (7.5)	15 (6.6)	7 (3.0)	18 (7.8)	6 (2.6)
Platelet count ↓	5 (2.3)	3 (1.4)	1 (0.5)	5 (2.1)	2 (0.8)	1 (0.4)	6 (2.6)	5 (2.2)	3 (1.3)	10 (4.3)	11 (4.8)	0
White-cell count ↓	2 (0.9)	4 (1.9)	3 (1.4)	2 (0.8)	3 (1.3)	0	2 (0.9)	5 (2.2)	1 (0.4)	6 (2.6)	3 (1.3)	0
Alanine aminotransferase ↑	1 (0.5)	0	0	3 (1.3)	0	0	9 (3.9)	5 (2.2)	1 (0.4)	6 (2.6)	3 (1.3)	0
Neoplasms: benign, malignant, and unspecified	12 (5.6)	24 (11.1)	6 (2.8)	12 (5.1)	16 (6.8)	3 (1.3)	10 (4.4)	16 (7.0)	1 (0.4)	11 (4.8)	17 (7.4)	1 (0.4)
Nonmelanoma skin cancer	10 (4.6)	9 (4.2)	1 (0.5)	6 (2.5)	5 (2.1)	0	6 (2.6)	7 (3.1)	0	3 (1.3)	5 (2.2)	0
Solid tumors	2 (0.9)	11 (5.1)	3 (1.4)	0	6 (2.5)	1 (0.4)	1 (0.4)	7 (3.1)	0	4 (1.7)	6 (2.6)	1 (0.4)
Cardiac disorders	12 (5.6)	1 (0.5)	0	14 (5.9)	3 (1.3)	1 (0.4)	14 (6.1)	3 (1.3)	0	28 (12.1)	13 (5.6)	0
Atrial fibrillation	3 (1.4)	1 (0.5)	0	1 (0.4)	1 (0.4)	0	2 (0.9)	0	0	12 (5.2)	6 (2.6)	0
Reproductive system and breast disorders	10 (4.6)	0	0	6 (2.5)	1 (0.4)	0	5 (2.2)	1 (0.4)	0	14 (6.1)	6 (2.6)	0

* The safety population included all patients who had received at least one course of trial treatment. Adverse events of grade 3 or 4 that occurred in at least 2% of the patients either as a single term or as a high-level term (boldface) are shown. *Medical Dictionary for Regulatory Activities* superclass and preferred terms and the National Cancer Institute Common Terminology Criteria for Adverse Events grade are reported. NOS denotes not otherwise specified.

The combinations of venetoclax and ibrutinib showed promising progression-free survival in two cohorts (minimal residual disease–guided and fixed-duration treatment) in two phase 2 trials with a median observation time beyond 3 years.[4,5,28,29] The percentages of patients with undetectable minimal residual disease among those who received a 15-to-24-month course of venetoclax plus ibrutinib as fixed-duration treatment (77% with minimal residual disease in peripheral blood and 52% to 60% with minimal residual disease in bone marrow)[4,29] or a minimal residual disease–guided regimen (77% in peripheral blood and 69% in bone marrow)[5] were slightly lower than the percentages among those who received venetoclax–obinutuzumab or venetoclax–obinutuzumab–ibrutinib. Updated data from the phase 3 GLOW trial[6] evaluating fixed-duration treatment with venetoclax–ibrutinib showed that the incidence of undetectable minimal residual disease was higher among patients with unmutated *IGHV* than among those with mutated *IGHV* (59.7% vs. 40.6%), but this incidence did not translate into a greater progression-free survival benefit than that observed in patients with mutated *IGHV*.[30] In our trial, venetoclax–obinutuzumab or venetoclax–obinutuzumab–ibrutinib therapy produced a significant progression-free survival benefit among patients with unmutated *IGHV* but not among those with mutated *IGHV*. The high efficacy of the fludarabine, cyclophosphamide, and rituximab regimen in young, fit patients with mutated *IGHV* may be difficult to improve on (data not shown).

Whether one of the venetoclax regimens (venetoclax–obinutuzumab or venetoclax–ibrutinib) is noninferior to a continuous BTK inhibitor is currently being addressed in the phase 3 CLL17 trial (ClinicalTrials.gov number, NCT04608318). Although a venetoclax–rituximab regimen involving 24 cycles of venetoclax has led to promising results in patients with relapsed CLL,[7,9] minimal residual disease negativity and improvements in progression-free survival have not been shown to be significantly different from those with chemoimmunotherapy.

In our trial, the toxic-effect profiles in all three experimental groups were similar, as previously described.[3,7,15] Severe infections were more frequent in the chemoimmunotherapy group and the triple-combination group than in the other two groups. The incidence of tumor lysis syndrome was higher in our trial than in the CLL14 trial,[3] findings that reflect the different definition according to the Cairo–Bishop criteria in our trial as compared with the Howard criteria used in the CLL14 trial. However, no deaths attributed by the investigators to tumor lysis syndrome occurred in our trial. Venetoclax–obinutuzumab–ibrutinib was also associated with a higher incidence of tumor lysis syndrome than that reported with venetoclax plus ibrutinib; this was probably related to simultaneous administration of obinutuzumab with ibrutinib, which led to rapid CLL cell depletion. Atrial fibrillation occurred in 7.8% of the patients who received venetoclax–obinutuzumab–ibrutinib therapy. The higher incidence of atrial fibrillation in our trial than that in the E1912 trial (4.5% with the continuous use of ibrutinib only) is unexplained; however, the median age in the E1912 trial was younger (58 years) than in this trial (61 years).

With improved survival even among patients with advanced-stage CLL, secondary neoplasia has an increasing effect on overall life expectancy. Therefore, reducing the risk of secondary neoplasia might influence the choice of treatment, particularly in patients with CLL that expresses mutated *IGHV*. Chemoimmunotherapy in *IGHV*-mutated CLL yields a high level of progression-free survival that will be difficult to improve on. In the GAIA–CLL13 trial, among all types of cancer, only nonmelanoma skin cancers were less frequent in all three experimental groups than in the chemoimmunotherapy group, but further follow-up might show additional benefits with respect to the incidence of secondary neoplasia.

In this trial involving patients with CLL and a low burden of coexisting conditions, time-limited combinations of targeted agents such as venetoclax–obinutuzumab and venetoclax–obinutuzumab–ibrutinib led to longer and deeper responses than the current first-line chemoimmunotherapy standard (fludarabine–cyclophosphamide–rituximab or bendamustine–rituximab).

Presented in part at the 63rd annual meeting of the American Society of Hematology, Atlanta, December 11, 2021, and at the hybrid congress of the European Hematology Association, Vienna, June 12, 2022. Results regarding seven patients with coronavirus disease 2019 during therapy in the GAIA–CLL13 trial were reported by Fürstenau et al.,[31] but no details regarding therapy were reported.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' full names and academic degrees are as follows: Barbara Eichhorst, M.D., Carsten U. Niemann, M.D., Arnon P. Kater, M.D., Moritz Fürstenau, M.D., Julia von Tresckow, M.D., Can Zhang, Ph.D., Sandra Robrecht, Ph.D., Michael Gregor, M.D., Gunnar Juliusson, M.D., Patrick Thornton, M.D., Philipp B. Staber, M.D., Tamar Tadmor, M.D., Vesa Lindström, M.D., Caspar da Cunha-Bang, M.D., Christof Schneider, M.D., Christian B. Poulsen, M.D., Thomas Illmer, M.D., Björn Schöttker, M.D., Thomas Nösslinger, M.D., Ann Janssens, M.D., Ilse Christiansen, M.D., Michael Baumann, M.D., Henrik Frederiksen, M.D., Marjolein van der Klift, M.D., Ulrich Jäger, M.D., Maria B.L. Leys, M.D., Mels Hoogendoorn, M.D., Kourosh Lotfi, M.D., Holger Hebart, M.D., Tobias Gaska, M.D., Harry Koene, M.D., Lisbeth Enggaard, M.D., Jereon Goede, M.D., Josien C. Regelink, M.D., Anouk Widmer, M.D., Florian Simon, M.D., Nisha De Silva, M.D., Anna-Maria Fink, M.D., Jasmin Bahlo, Ph.D., Kirsten Fischer, M.D., Clemens-Martin Wendtner, M.D., Karl A. Kreuzer, M.D., Matthias Ritgen, M.D., Monika Brüggemann, M.D., Eugen Tausch, M.D., Mark-David Levin, M.D., Marinus van Oers, M.D., Christian Geisler, M.D., Stephan Stilgenbauer, M.D., and Michael Hallek, M.D.

The authors' affiliations are as follows: the Department I of Internal Medicine, Center for Integrated Oncology Aachen–Bonn–Cologne–Düsseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne (B.E., M.F., C.Z., S.R., F.S., A.-M.F., J.B., K.F., K.A.K., M. Hallek), the Clinic for Hematology and Stem Cell Transplantation, West German Cancer Center, University Hospital Essen, University of Duisburg–Essen, Essen (J.T.), the Division of Chronic Lymphocytic Leukemia, Department of Internal Medicine III, University of Ulm, Ulm (C.S., E.T., S.S.), Group Practice for Hematology and Oncology, Dresden (T.I.); the Hematology–Oncology Center, Würzburg (B.S.), Specialist Medical Practice of Hematology and Oncology, Mutlangen (H.H.), the Department of Hematology, Clinic for Hematology and Oncology, Centrum of Oncology, Brüderhospital St. Josef, Paderborn (T.G.), the Munich Clinic Schwabing, Academic Teaching Hospital, Ludwig Maximilian University, Munich (C.-M.W.); and the Department of Hematology, University Hospital Schleswig–Holstein, Campus Kiel (M.R., M. Brüggemann), Kiel — all in Germany; the Department of Hematology, Odense Rigshospitalet, Copenhagen University Hospital (C.U.N., C.C.-B., C.G.), and the Department of Hematology, Center for Cancer and Organ Diseases, Rigshospitalet (L.E.),Copenhagen, the Department of Hematology, Faculty of Medicine, Aalborg University Hospital, Aalborg (I.C.), the Department of Hematology, Zealand University Hospital, Roskilde (C.B.P.), and the Department of Hematology, Odense University Hospital, Odense (H.F.) — all in Denmark; the Department of Hematology, Cancer Center Amsterdam, Amsterdam University Medical Center, University of Amsterdam, Amsterdam (A.P.K., M.O.), the Department of Internal Medicine, Amphia Hospital, Breda (M.K.), the Department of Hematology, Maasstad Ziekenhuis, Rotterdam (M.B.L.L.), the Department of Hematology and Oncology, Medical Center Leeuwarden, Leeuwarden (M. Hoogendoorn), the Department of Hematology, St. Antonius Hospital Utrecht, Utrecht (H.K.), the Department of Hematology, Meander Medical Center, Amersfoort (J.C.R.), and the Department of Hematology, Albert Schweitzer Hospital, Dordrecht (M.-D.L.) — all in the Netherlands; the Department of Hematology, Luzerner Kantonsspital, Lucerne (M.G.), the Department of Hematology, Kantonsspital St. Gallen, St. Gallen (M. Baumann), the Department of Hematology, Clinic for Medical Oncology and Hematology, Kantonsspital Hospital Winterthur, Winterthur (J.G.), and the Department of Medical Oncology and Hematology Clinic, University Hospital Zürich, Zürich (A.W.) — all in Switzerland; the Department of Hematology, Lund University Cancer Center, Lund (G.J.), and the Department of Hematology, Linköping University Hospital, Linköping (K.L.) — both in Sweden; the Department of Hematology, Blackrock Health Member Hospitals, Hermitage Clinic, Dublin (P.T.); the Department of Medicine I, Division of Hematology and Hemostaseology (P.B.S.), the Department of Internal Medicine, University Hospital for Internal Medicine, Clinical Department of Hematology and Hemostaseology (U.J.), and the Comprehensive Cancer Center Vienna, Vienna General Hospital (P.B.S.), Medical University of Vienna, and the Department of Hematology and Oncology, Hanusch Hospital (T.N.) — both in Vienna; the Department of Hematology and Blood Bank, Bnai Zion Medical Center, Haifa, Israel (T.T.); the Department of Hematology, Comprehensive Cancer Center, Helsinki University Hospital, Helsinki (V.L.); the Department of Oncology, Universitair Ziekenhuis Leuven, Leuven, Belgium (A.J.); and the Department of Hematology, University College London, London (N.D.S.).

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