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ORIGINAL ARTICLE

Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities

Arnon P. Kater, M.D., Ph.D.,[1] Carolyn Owen, M.D.,[2] Carol Moreno, M.D.,[3] George Follows, B.M.Bch., Ph.D.,[4] Talha Munir, M.B.B.S.,[5] Mark-David Levin, M.D.,[6] Ohad Benjamini, M.D.,[7] Ann Janssens, M.D., Ph.D.,[8] Anders Osterborg, M.D., Ph.D.,[9] Tadeusz Robak, M.D., Ph.D.,[10] Martin Simkovic, M.D., Ph.D.,[11] Don Stevens, M.D.,[12] Sergey Voloshin, M.D., Ph.D.,[13] Vladimir Vorobyev, Ph.D.,[14] Loic Ysebaert, M.D., Ph.D.,[15] Rui Qin, Ph.D.,[16] Andrew J. Steele, Ph.D.,[17] Natasha Schuier, M.D.,[18] Kurt Baeten, Ph.D.,[19] Donne Bennett Caces, M.D., Ph.D.,[16] and Carsten U. Niemann, M.D., Ph.D.,[20] for the GLOW Investigators*

Abstract

BACKGROUND GLOW is a phase 3 trial evaluating the efficacy and safety of ibrutinib-venetoclax in older patients and/or those with comorbidities with previously untreated chronic lymphocytic leukemia (CLL).

METHODS We randomly assigned (1:1) patients 65 years of age or older or those 18 to 64 years of age who also had a Cumulative Illness Rating Scale (CIRS) score greater than 6 (CIRS scores range from 0 to 56, with higher scores indicating more impaired function of organ systems) or creatinine clearance of less than 70 ml/min, to ibrutinib-venetoclax (3 cycles ibrutinib lead-in, then 12 cycles ibrutinib-venetoclax) or chlorambucil-obinutuzumab (6 cycles). The primary end point was progression-free survival (PFS) assessed by an independent review committee. Secondary end points included undetectable minimal residual disease (uMRD), response rates, and safety.

RESULTS This study enrolled 211 patients, with 106 randomly assigned to ibrutinib-venetoclax and 105 to chlorambucil-obinutuzumab. With a median follow-up of 27.7 months, there were 22 PFS events for ibrutinib-venetoclax and 67 events for chlorambucil-obinutuzumab. PFS was significantly longer for ibrutinib-venetoclax than for chlorambucil-obinutuzumab (hazard ratio, 0.216; 95% confidence interval [CI], 0.131 to 0.357; P<0.001). The improvement in PFS with ibrutinib-venetoclax was consistent across predefined subgroups, including patients 65 years of age or older or with a CIRS score greater than 6. The best uMRD rate in bone marrow by next-generation sequencing was significantly higher for ibrutinib-venetoclax (55.7%) than for chlorambucil-obinutuzumab (21.0%; P<0.001). The proportion of patients with sustained uMRD in peripheral blood from 3 to 12 months after end of treatment was 84.5% for ibrutinib-venetoclax and 29.3% for

A complete list of GLOW trial investigators is provided in the Supplementary Appendix, available at evidence.nejm.org.

The author affiliations are listed at the end of the article.

Dr. Kater can be contacted at a.p.kater@amsterdamumc.nl or at Amsterdam University Medical Centers, Meibergdreef 9, Amsterdam 1105AZ, Netherlands.

chlorambucil-obinutuzumab. Four patients treated with ibrutinib-venetoclax required subsequent therapy compared with 27 patients receiving chlorambucil-obinutuzumab (hazard ratio, 0.143; 95% CI, 0.050 to 0.410). Adverse events grade 3 or greater occurred for 80 (75.5%) and 73 (69.5%) patients receiving ibrutinib-venetoclax and chlorambucil-obinutuzumab, respectively, with neutropenia being most common in both arms (37 [34.9%] and 52 [49.5%]). There were 11 (10.4%) and 12 (11.4%) all-cause deaths in the ibrutinib-venetoclax and chlorambucil-obinutuzumab arms, respectively.

CONCLUSIONS Ibrutinib-venetoclax, an all-oral, once-daily, fixed-duration combination, demonstrated superior PFS and deeper and better sustained responses versus chlorambucil-obinutuzumab as first-line CLL treatment in older patients and/or those with comorbidities. (Funded by Janssen Research & Development, LLC, and Pharmacyclics; ClinicalTrials.gov number, NCT03462719.)

Introduction

Chronic lymphocytic leukemia (CLL) is a disease that primarily affects elderly individuals, with chemoimmunotherapy historically serving as standard first-line therapy.[1-5] While chlorambucil-obinutuzumab has been a first-line treatment for elderly and comorbid patients without *TP53* alterations, it requires cumbersome infusions, and remission durations are suboptimal in many patients.[5-9] More effective treatments with increased convenience are of interest for older patients and/or those with comorbidities, including options that avoid the use of chemotherapy and risk of infusion-related reactions.

Ibrutinib, a first-in-class Bruton tyrosine kinase inhibitor given once a day, has proven survival benefits in randomized phase 3 trials in first-line CLL, including in elderly patients with comorbidities, and is recommended as first-line treatment for CLL in treatment guidelines.[5,10-15] Despite the demonstrated advantages of continuous monotherapy, deep remissions are rare and resistance mutations can emerge with time. Venetoclax, a once-daily, oral inhibitor of B-cell lymphoma-2 (BCL-2), has demonstrated progression-free survival (PFS) benefit in previously untreated older patients and those with comorbidities with CLL when combined in a fixed-duration regimen with obinutuzumab.[16-18] Given their distinct and complementary mechanisms of action, ibrutinib and venetoclax work synergistically to eradicate CLL by eliminating both dividing and resting leukemic subpopulations.[19-25] Ibrutinib effectively inhibits tumor cell proliferation, while mobilizing leukemic cells from protective lymphoid niches.[21,23] Further, ibrutinib increases the sensitivity of CLL cells to BCL-2 inhibition, thereby accelerating apoptotic cell killing by venetoclax.[19,20] This mechanistic synergy has been demonstrated in vivo in a mouse model.[24] Combining ibrutinib and venetoclax has the potential to induce deep responses with time-limited therapy, enabling treatment-free remissions for patients (Fig. S1 in the Supplementary Appendix, available at evidence.nejm.org).

Various phase 2 studies have evaluated time-limited treatment with ibrutinib-venetoclax.[26-29] In the phase 2 CAPTIVATE trial of 159 previously untreated young/fit patients, including 17% with aberrated *TP53*, the 2-year PFS with 12 cycles of fixed-duration ibrutinib-venetoclax was 95%, with 60% of patients achieving undetectable minimal residual disease (uMRD) in bone marrow.[30] In a phase 2 single-center trial of 80 previously untreated patients, 23% of whom had aberrated *TP53*, ibrutinib-venetoclax administered for 24 cycles provided an estimated 3-year PFS rate of 93%, with 75% of patients achieving uMRD in bone marrow.[26] Studies of ibrutinib-venetoclax in relapsed/refractory CLL have demonstrated uMRD rates of 36% to 39% in bone marrow at 14 to 15 months after initiation of treatment, with durable remissions noted.[28,29]

GLOW is a randomized phase 3 trial evaluating fixed-duration ibrutinib-venetoclax versus the standard chemoimmunotherapy combination chlorambucil-obinutuzumab in older patients and/or those with comorbidities with previously untreated CLL.

Methods

PATIENTS

The GLOW trial enrolled patients 65 years of age or older or individuals 18 to 64 years of age with a Cumulative Illness Rating Scale (CIRS) score greater than 6 (CIRS scores range from 0 to 56, with higher scores indicating more impaired function of organ systems) and/or creatinine clearance less than 70 ml/min (using the Cockcroft-Gault equation). Patients had active CLL/small lymphocytic lymphoma requiring treatment per International

Workshop on Chronic Lymphocytic Leukemia criteria.[31] Exclusion criteria included the presence of del(17p) (tested locally using fluorescence in situ hybridization [FISH]) or *TP53* mutation (if known), bleeding disorders, central nervous involvement, Richter's syndrome, or uncontrolled autoimmune hemolytic anemia or thrombocytopenia (details in the Protocol, available with the full text of the article at evidence.nejm.org).

STUDY OVERSIGHT AND CONDUCT

The GLOW trial was registered on ClinicalTrials.gov (NCT03462719), approved by the institutional review board or independent ethics committee at participating institutions, and conducted in accordance with ethical principles defined by the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent. The study was sponsored and designed by Janssen Research & Development, LLC, with input from investigators. Data were collected by investigators under the oversight of an independent data monitoring committee and were confirmed and analyzed by the sponsor. All authors confirmed adherence to the protocol, had access to data under confidentiality, and vouched for data accuracy. The manuscript was written based on author guidance with the assistance of a medical writer supported by the sponsor, and all authors critically reviewed drafts and approved the manuscript for publication.

RANDOMIZATION AND TREATMENT

This open-label, phase 3 trial was conducted in 67 sites across 14 countries (details in Supplementary Appendix). Patients were randomly assigned 1:1 to receive ibrutinib-venetoclax or chlorambucil-obinutuzumab and stratified according to centrally tested immunoglobulin heavy-chain variable region (IGHV) gene mutational status by Sanger sequencing (mutated vs. unmutated vs. unavailable) and locally tested del(11q) status by FISH (yes/no). The primary analysis was planned after 71 PFS events occurred following randomization.

Patients randomly assigned to ibrutinib-venetoclax received three cycles of ibrutinib lead-in at 420 mg once daily, followed by 12 cycles of ibrutinib-venetoclax. Venetoclax was initiated in cycle 4 with dose ramp-up per label over 5 weeks (20, 50, 100, 200, and 400 mg/day) and continued at 400 mg/day dose from cycle 5 onward. Ibrutinib and venetoclax were administered on 28-day cycles. Patients in the chlorambucil-obinutuzumab arm received six 28-day cycles of 1000 mg/day of intravenous obinutuzumab (on days 1 [or 100 mg/day on day 1 and 900 mg/day on day 2], 8, and 15 of cycle 1 and day 1 of cycles 2 to 6) plus chlorambucil per label (0.5 mg/kg body weight on days 1 and 15 of each cycle).[32] After the initial fixed-duration treatment, patients from both arms with independent review committee (IRC)–confirmed disease progression and with active disease requiring treatment per International Workshop on Chronic Lymphocytic Leukemia criteria were eligible to receive subsequent therapy with single-agent ibrutinib.

ASSESSMENTS AND END POINTS

The primary end point was IRC-assessed PFS, defined as time from randomization to disease progression or death from any cause, whichever occurred first. A supplementary analysis using investigator-assessed PFS was performed. Secondary end points included best uMRD rate in bone marrow as assessed by next-generation sequencing, complete and overall response rates, overall survival, time-to-next-treatment, and safety (details in Supplementary Appendix).

Patients with documented *TP53* mutation at screening were excluded from study participation. Central evaluation of *TP53* status was performed for all randomly assigned patients using next-generation sequencing (variable allele frequency cutoff >5%; Personalis, Menlo Park, CA), and patients with mutated *TP53* were included in efficacy and safety analyses. Timing of disease evaluations and computerized tomography scans are described in Figure S2. Disease response was assessed according to modified 2008 International Workshop on Chronic Lymphocytic Leukemia criteria.[31] For patients with partial response or better, peripheral blood samples were collected every 12 weeks and bone marrow samples at 36 and 72 weeks (months 9 and 18) postrandomization for minimal residual disease (MRD) evaluation. The case definition for uMRD was less than 1 CLL cell per 10,000 leukocytes (<0.01%). MRD was assessed via the clonoSEQ assay (Adaptive Biotechnologies, Seattle, WA)[33] and separately by eight-color flow cytometry (Navigate Biopharma, Carlsbad, CA) in accordance with the European Research Initiative on CLL guidelines 2016.[34] Concordance on uMRD between bone marrow and peripheral blood was calculated for patients with uMRD in peripheral blood at 3 months after end of treatment who had a paired bone marrow sample.

STATISTICAL ANALYSIS

The GLOW trial aimed to enroll approximately 200 patients (100 in each study arm) and was powered to

assess superiority of the primary end point. Sample size was estimated based on detecting a hazard ratio of 0.5 for the ibrutinib-venetoclax arm relative to the chlorambucil-obinutuzumab arm (corresponding to a 100% improvement in median PFS) with 80% power at a two-sided significance level of 0.05.

Efficacy end points were analyzed in the intent-to-treat population. Safety analyses included randomly assigned patients who received at least one dose of study treatment. Multiplicity incurred from testing primary and secondary end points was controlled using the serial gatekeeping procedure. The hypothesis for a secondary end point was tested if and only if the null hypotheses for the primary end point and for the preceding secondary end point(s) were rejected. The statistical testing hierarchy for secondary end points, in order, was uMRD rate in bone marrow, complete response rate, overall response rate, and overall survival.

Kaplan–Meier estimates were provided for time-to-event variables. Comparisons between arms were performed using the Cochran-Mantel-Haenszel chi-square test for discrete variables and log-rank test for time-to-event variables. All tests were conducted at a two-sided alpha level of 0.05 with 95% confidence intervals (CIs), unless stated otherwise.

Results

PATIENTS

Between May 2018 and April 2019, 211 patients were enrolled, with 106 randomly assigned to ibrutinib-venetoclax and 105 to chlorambucil-obinutuzumab (Fig. 1). The median age was 71 years (range, 47 to 93; 34.1% were 75 years of age or older), 57.8% were men, and the median creatinine clearance was 64.8 ml/min (Table 1). The median CIRS scores were 9 (range, 1 to 20) in the ibrutinib-venetoclax arm and 8 (range, 0 to 22) in the chlorambucil-obinutuzumab arm. There were more patients in the ibrutinib-venetoclax arm than the chlorambucil-obinutuzumab arm with a CIRS score greater than 6 (69.8% vs. 58.1%) or of 10 or greater (43.4% vs. 33.3%). Most patients had preexisting hypertension (66.8%) and/or metabolism disorders (57.8%) (Table S1). Of 163 patients with known IGHV status, 66.9% had unmutated IGHV and 33.1% had mutated IGHV. Overall, 18.0% had del(11q) and 4.3% had *TP53* mutations. Reasons for discontinuation of all study treatment in the ibrutinib-venetoclax and chlorambucil-obinutuzumab arms were adverse events (AEs) (10.4% vs. 1.9%), treatment refusal (3.8% vs. 1.0%),

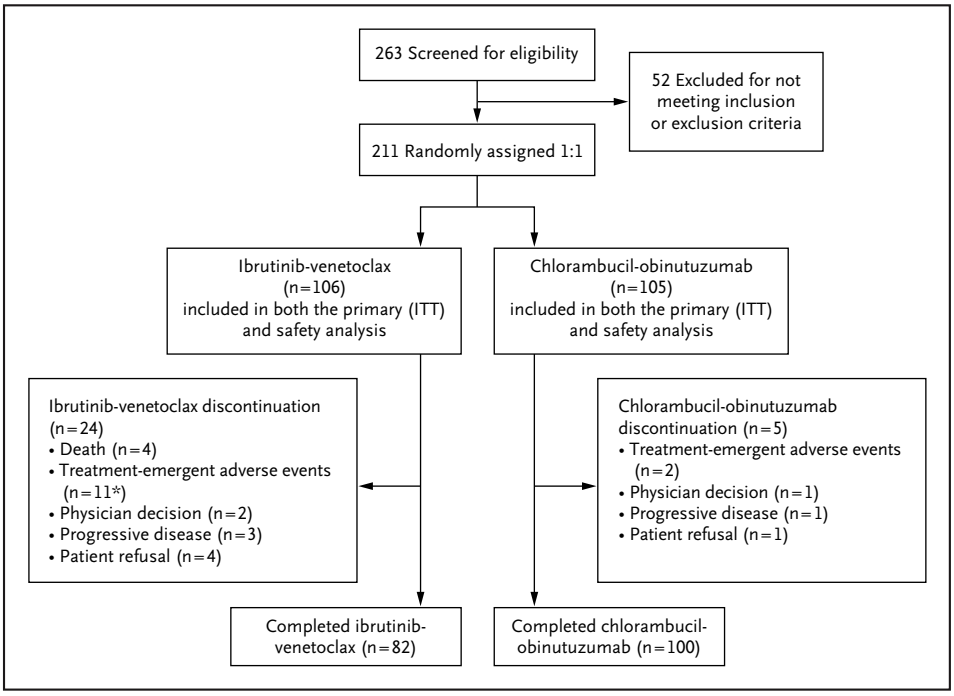

Figure 1. Consort Diagram for Screening, Treatment, and Follow-up.

* This category includes three patients who discontinued study treatment due to treatment-emergent adverse events that later resulted in death. ITT denotes intent to treat.

Table 1. Baseline Patient Demographics and Disease Characteristics (Intent-to-Treat Population).*

Characteristic	Ibrutinib-Venetoclax (n=106)	Chlorambucil-Obinutuzumab (n=105)
Age, yr	71.0 (47–93)	71.0 (57–88)
≥75	35 (33.0)	37 (35.2)
Men	59 (55.7)	63 (60.0)
ECOG PS 1 to 2	71 (67.0)	66 (62.9)
CIRS score	9 (1–20)	8 (0–22)
>6†	74 (69.8)	61 (58.1)
CrCl, ml/min‡	66.5 (34.0–168.1)	63.2 (32.3–180.9)
Rai stage III to IV§	55 (57.3)	53 (52.5)
Binet stage (CLL only)	96	101
A	7 (7.3)	8 (7.9)
B	46 (47.9)	53 (52.5)
C	43 (44.8)	40 (39.6)
Ann Arbor stage (SLL only)	10	4
IV	10 (100)	4 (100)
Bulky disease ≥5 cm	41 (39.0)	38 (36.2)
Elevated LDH¶	35 (33.0)	51 (48.6)
IGHV status		
Mutated	27 (25.5)	27 (25.7)
Unmutated	55 (51.9)	54 (51.4)
Unknown	24 (22.6)	24 (22.9)
Del(11q)	20 (18.9)	18 (17.1)
TP53 mutation	7 (6.6)	2 (1.9)

* Data are presented as the mean (range), n (%), or n. CIRS denotes Cumulative Illness Rating Scale, CLL chronic lymphocytic leukemia, CrCl creatinine clearance, Del(11q) 11q deletion, ECOG PS Eastern Cooperative Oncology Group performance status, IGHV immunoglobulin heavy-chain variable region, LDH lactate dehydrogenase, and SLL small lymphocytic leukemia.

† CIRS scores range from 0 to 56, with higher scores indicating more impaired function of organ systems. There was a >10% numerical difference between arms for individuals with a CIRS greater than 6.

‡ Using the Cockcroft-Gault equation.

§ Rai stage ranges from 0 to IV, with higher numbers indicating more severe disease.

¶ Denotes a >10% numerical difference between arms.

death (3.8% vs. 0), and disease progression (2.8% vs. 1.0%); 77.4% and 95.2% of patients completed treatment, respectively (Table S2). Six patients were still receiving randomized treatment with ibrutinib-venetoclax at the start of the Covid-19 pandemic in March 2020.

EFFICACY

With a median follow-up of 27.7 months (range, 1.7 to 33.8) at primary analysis, 22 IRC-assessed PFS events occurred in ibrutinib-venetoclax–treated patients versus 67 in chlorambucil-obinutuzumab–treated patients, resulting in a significantly longer PFS with ibrutinib-venetoclax versus chlorambucil-obinutuzumab (hazard ratio, 0.216; 95% CI, 0.131 to 0.357; P<0.001) (Fig. 2A). Investigator-assessed PFS was consistent with IRC findings (Fig. 2B). Median IRC-assessed PFS was not reached (95% CI, 31.2 to not reached) for ibrutinib-venetoclax and 21.0 months (95% CI, 16.6 to 24.7) for chlorambucil-obinutuzumab; estimated 24-month PFS rates were 84.4% and 44.1%, respectively. A benefit in IRC-assessed PFS was shown in patients treated with ibrutinib-venetoclax across stratification factors (del(11q) status and IGHV mutational status), and in prespecified subgroups, including patients 65 years of age or older or with a CIRS score greater than 6 (Figs. 3 and S3). There was one Covid-19–related death before disease progression in the ibrutinib-venetoclax arm (day 899). With an additional 6 months of study follow-up (median 34.1 months), the estimated 30-month PFS rates were 80.5% for ibrutinib-venetoclax and 35.8% for chlorambucil-obinutuzumab, and the hazard ratio for PFS was consistent with the primary analysis (Fig. S4).

The best uMRD rate in bone marrow by next-generation sequencing at time of primary analysis was significantly higher for patients treated with ibrutinib-venetoclax than those treated with chlorambucil-obinutuzumab (55.7% vs. 21.0%; P<0.001). At 3 months after end of treatment, the proportion of patients in the ibrutinib-venetoclax arm who achieved uMRD in bone marrow was 51.9% compared with 17.1% of patients in the chlorambucil-obinutuzumab arm. In peripheral blood, these values were 54.7% versus 39.0%, respectively (Fig. 2C). Concordance of uMRD between bone marrow and peripheral blood was 92.9% (52 of 56) for the ibrutinib-venetoclax arm compared with 43.6% (17 of 39) for the chlorambucil-obinutuzumab arm. Table S3 reports rates of uMRD by flow cytometry. The proportion of patients with sustained uMRD in peripheral blood from 3 to 12 months after end of treatment was 84.5% (49 of 58) for the ibrutinib-venetoclax arm and 29.3% (12 of 41) for the chlorambucil-obinutuzumab arm (Fig. 2D). Detectable MRD of 10^{-4} cells/ml or greater was less likely to worsen or lead to disease progression within the first year post-treatment in patients treated with ibrutinib-venetoclax than in those treated with chlorambucil-obinutuzumab (Fig. 2D).

Patients treated with ibrutinib-venetoclax achieved a significantly higher rate of complete response, including complete response with incomplete bone marrow recovery, than those treated with chlorambucil-obinutuzumab as assessed by IRC (41 [38.7%] vs. 12 [11.4%], respectively;

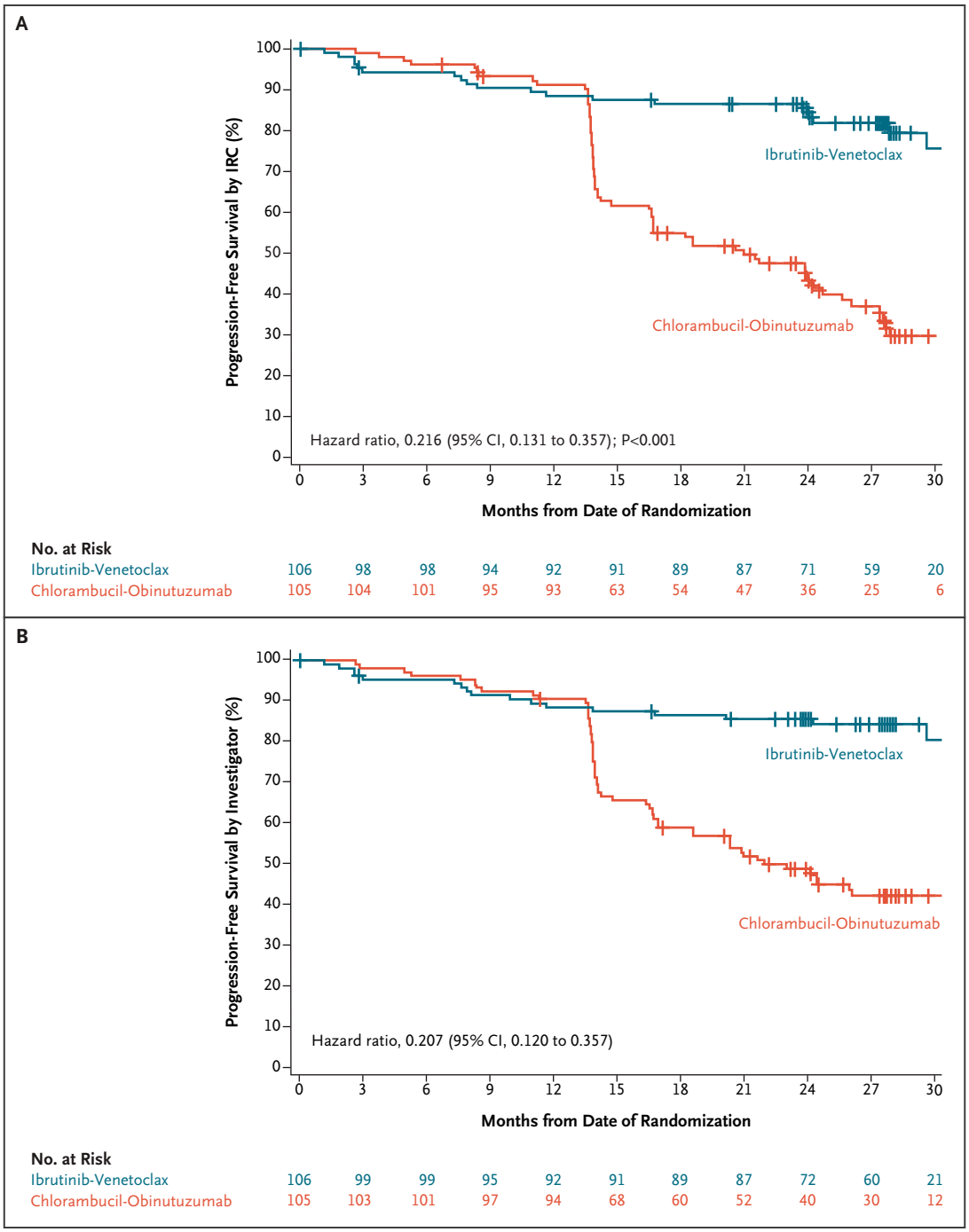

Figure 2. Efficacy Outcomes.

Panel A shows independent review committee–assessed progression-free survival. Panel B shows investigator-assessed progression-free survival. Panel C shows undetectable minimal residual disease (uMRD) rates in bone marrow and peripheral blood at 3 months after the end of treatment by next-generation sequencing (NGS; intent-to-treat population). Panel D shows dynamics of minimal residual disease (MRD) status in peripheral blood from 3 to 12 months after the end of treatment by next-generation sequencing (intent-to-treat population). Panel E shows independent review committee–assessed tumor response (intent-to-treat population). CR denotes complete response, CRi complete response with incomplete bone marrow recovery, EOT+# number of months after end of treatment, IRC independent review committee, nPR nodular partial response, NR nonresponder, ORR overall response rate, PD progressive disease, PR partial response, and SD stable disease.

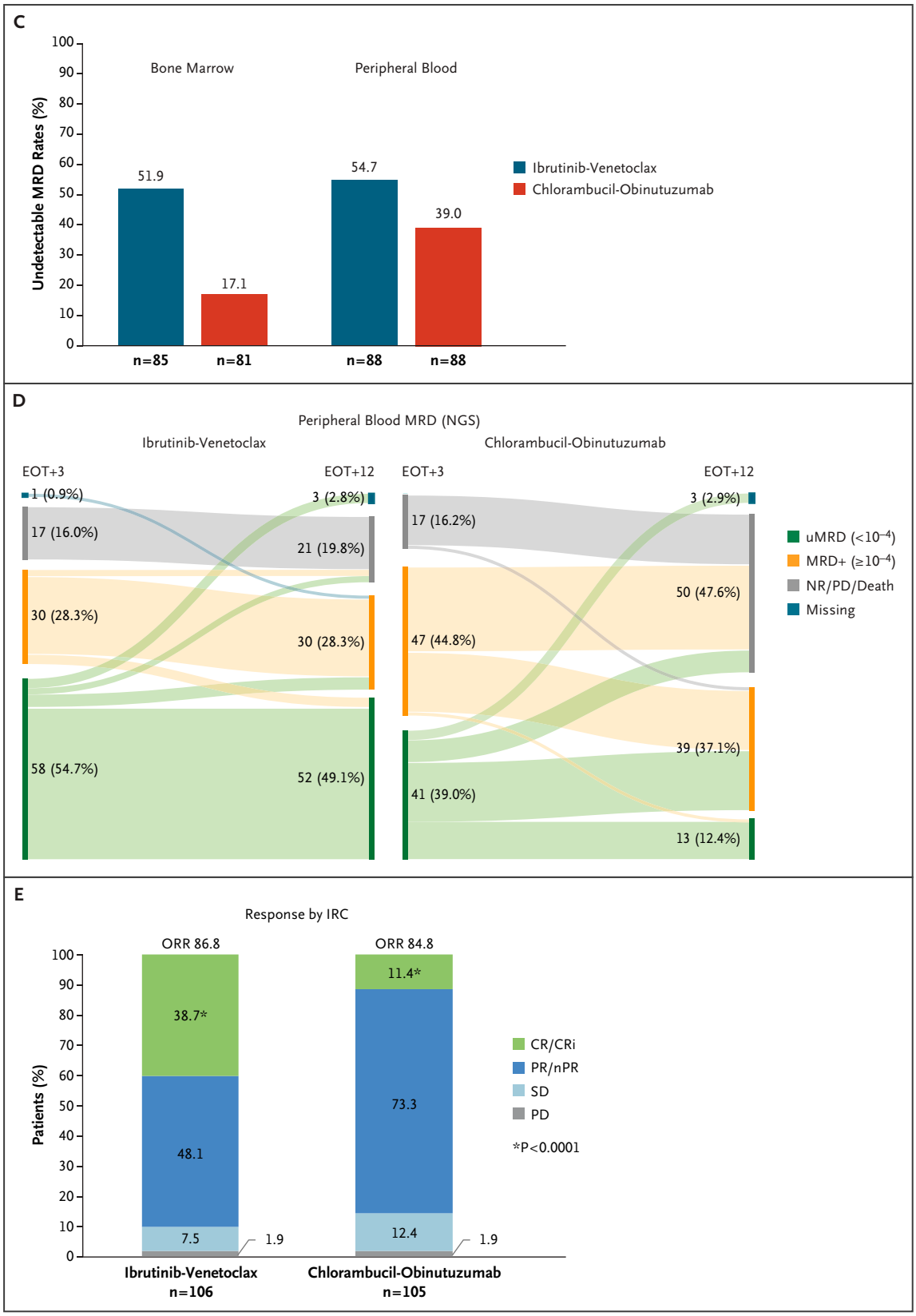

Figure 2. Continued.

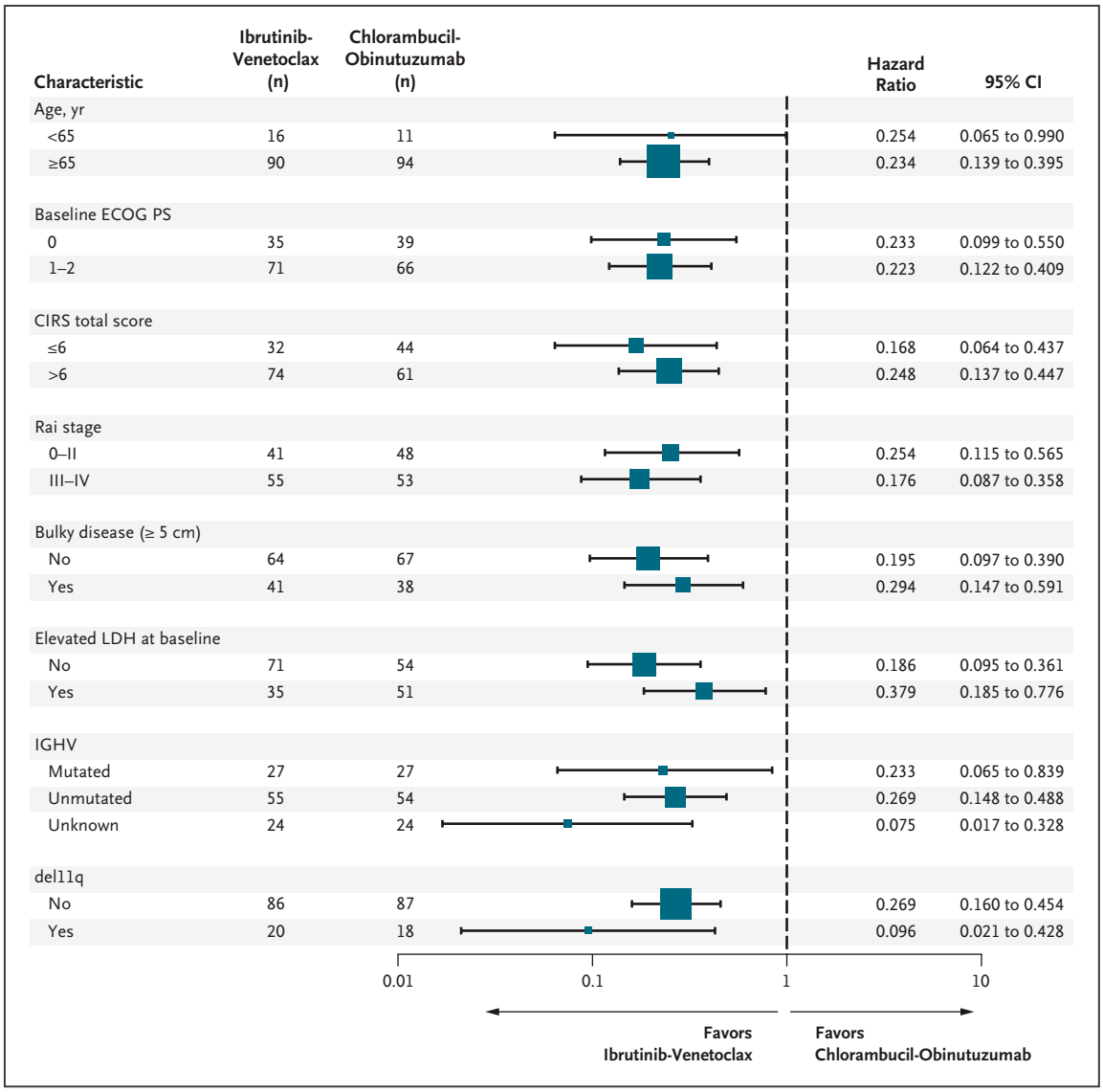

Figure 3. Subgroup Analysis of Independent Review Committee–Assessed Progression-Free Survival (Intent-to-Treat Population).

Larger boxes denote larger sample sizes in the subgroup comparison. CI denotes confidence interval, CIRS Cumulative Illness Rating Scale (scores range from 0 to 56, with higher scores indicating more impaired function of organ systems), ECOG PS Eastern Cooperative Oncology Group performance status (scores range from 0 to 5, with higher scores indicating more impairment of daily living abilities), IGHV immunoglobulin heavy-chain variable region, and LDH, lactate dehydrogenase.

P<0.001). Investigator-assessed rates were 45.3% versus 13.3%, respectively. The overall response rate as assessed by IRC was similar between treatment arms (86.8% vs. 84.8%) (Fig. 2E); therefore, testing of subsequent secondary end points according to the prespecified testing hierarchy was exploratory. The 24-month duration of response rates were 90% and 41% in the ibrutinib-venetoclax and chlorambucil-obinutuzumab arms, respectively. Figure S5 shows lymph node responses as measured by change from baseline in sum of the products of perpendicular dimensions of predefined target lesions. Lymph node responses were largely maintained over time in the ibrutinib-venetoclax arm.

At the time of primary analysis, there were 11 deaths in the ibrutinib-venetoclax arm and 12 in the chlorambucil-obinutuzumab arm, with no difference in overall survival between arms (hazard ratio, 1.048; 95% CI, 0.454 to 2.419])

(Fig. S6A). Infections (n=10; 5 due to Covid-19) or cardiac events (n=4) were the most common causes of death overall (Table S4). With an additional 6 months of study follow-up (median 34.1 months), there were four additional deaths, all in the chlorambucil-obinutuzumab arm. In total, there were 11 deaths in the ibrutinib-venetoclax arm and 16 deaths in the chlorambucil-obinutuzumab arm (hazard ratio, 0.760; 95% CI, 0.352 to 1.642; Fig. S6B).

At the time of primary analysis, Richter's transformation occurred in 3 patients (2.8%) treated with ibrutinib-venetoclax and 2 patients (1.9%) treated with chlorambucil-obinutuzumab. The number of patients requiring subsequent anticancer therapy was 4 (2 for CLL progression and 2 for Richter's transformation) in the ibrutinib-venetoclax arm compared with 27 (25 for CLL progressive disease and 2 for Richter's transformation) in the chlorambucil-obinutuzumab arm (Fig. S7). In the ibrutinib-venetoclax arm, neither patient receiving subsequent anticancer treatment for CLL had mutated *TP53*; one patient completed all 15 cycles of therapy with a treatment-free interval of 13 months, and the other discontinued ibrutinib-venetoclax treatment during cycle 7 due to suspected progressive disease. In the chlorambucil-obinutuzumab arm, 22 patients received subsequent anticancer treatment with a Bruton tyrosine kinase inhibitor (21 received ibrutinib and 1 acalabrutinib).

SAFETY

After three cycles of ibrutinib lead-in, 2 patients (1.9%) remained at high tumor burden per tumor lysis risk category, reduced from 26 (24.5%) at baseline (Fig. S8). There were no cases of tumor lysis syndrome reported in the ibrutinib-venetoclax arm compared with six cases (5.7%) reported in the chlorambucil-obinutuzumab arm.

Treatment exposure was greater than twofold longer for ibrutinib-venetoclax versus chlorambucil-obinutuzumab (Table S2). Diarrhea (54 [50.9%]) and neutropenia (44 [41.5%]) were the most common any-grade AEs in the ibrutinib-venetoclax arm, and neutropenia (61 [58.1%]) and infusion-related reactions (31 [29.5%]) were the most common AEs in the chlorambucil-obinutuzumab arm (Table S5). Of patients experiencing diarrhea in the ibrutinib-venetoclax arm, more than three-quarters (43 [79.6%]) had low-grade single events; overall, the median time to resolution was 13 days. AEs grade 3 or greater occurred in 80 (75.5%) and 73 (69.5%) patients in the ibrutinib-venetoclax and chlorambucil-obinutuzumab arms, respectively (Table 2); neutropenia was most common in both arms, with 2 (1.9%) and 3 (2.9%) patients with febrile neutropenia, respectively. The most common serious AEs were infections (13 [12.3%] vs. 9 [8.6%], with 6 [5.7%] cases of pneumonia in each arm) and atrial fibrillation (7 [6.6%] vs. 0; Table S6). Any-grade atrial fibrillation occurred in 15 patients (14.2%) receiving ibrutinib-venetoclax and 2 (1.9%) receiving chlorambucil-obinutuzumab; 2 patients (1.9%) discontinued ibrutinib due to atrial fibrillation while continuing venetoclax. Diarrhea and pneumonia were the most common AEs leading to discontinuation of ibrutinib-venetoclax (3 [2.8%] each).

Secondary primary malignancies during the entire study follow-up occurred in 8 patients (7.5%) receiving ibrutinib-venetoclax and 10 (9.5%) receiving chlorambucil-obinutuzumab (Table S7); after excluding those with non-melanoma skin cancers, the number of patients was 5 (4.7%) and 8 (7.6%), respectively.

There were seven (6.6%) treatment-emergent deaths in the ibrutinib-venetoclax arm, including four during ibrutinib lead-in, and two (1.9%) in the chlorambucil-obinutuzumab arm. Four cardiac or sudden deaths occurred during treatment in the ibrutinib-venetoclax arm, all in patients with a CIRS score of 10 or greater or an Eastern Cooperative Oncology Group performance-status score (ECOG PS) of 2 (scores range from 0 to 5, with higher scores indicating more impairment of daily living abilities[35]), and with a history of hypertension, cardiovascular disease, and/or diabetes (Table S8). The remaining three on-treatment deaths in the ibrutinib-venetoclax arm were due to lung infection (cycle 2), metastatic carcinoma (cycle 2), and ischemic stroke (confirmed nonembolic event upon autopsy) secondary to obliterating atherosclerosis (cycle 8). Of the two treatment-emergent deaths in the chlorambucil-obinutuzumab arm, one attributable to pneumonia and one to cholestasis.

Discussion

Building on several phase 2 studies in previously untreated and relapsed/refractory CLL,[26-28] the phase 3 GLOW study demonstrated that an all-oral, once-daily, fixed-duration combination of ibrutinib-venetoclax was superior to chlorambucil-obinutuzumab with respect to PFS in elderly patients and those with comorbidities with previously untreated, non-del(17p) CLL.[36,37] The demographics of the patients we studied were generally representative of

Table 2. Grade 3 or 4 Adverse Events Occurring in 5% or More of Either Arm and Grade 5 Adverse Events Occurring in Any Patient (Safety Population).*

	Ibrutinib-Venetoclax (n=106)		Chlorambucil-Obinutuzumab (n=105)	
Treatment exposure — mo, median (range)	13.8 (0.7–19.5)		5.1 (1.8–7.9)	
Adverse events — n (%)	**Grade 3/4**	**Grade 5**	**Grade 3/4**	**Grade 5**
Patients with ≥1 adverse events	73 (68.9)	7 (6.6)	71 (67.6)	2 (1.9)
Neutropenia†	37 (34.9)	0	52 (49.5)	0
Infections and infestations‡	16 (15.1)	2 (1.9)§	11 (10.5)	1 (1.0)
Diarrhea¶	11 (10.4)	0	1 (1.0)	0
Hypertension	8 (7.5)	0	2 (1.9)	0
Atrial fibrillation	7 (6.6)	0	0	0
Thrombocytopenia	6 (5.7)	0	21 (20.0)	0
Hyponatremia	6 (5.7)	0	0	0
Cardiac failure	3 (2.8)	1 (0.9)§	0	0
Sinus node dysfunction	1 (0.9)	1 (0.9)§	0	0
Cholestasis	1 (0.9)	0	0	1 (1.0)
Sudden death	0	2 (1.9)	0	0
Ischemic stroke	0	1 (0.9)	0	0
Malignant neoplasm	0	1 (0.9)	0	0
Cardiac arrest	0	1 (0.9)	0	0
Tumor lysis syndrome	0	0	6 (5.7)	0

* Fifteen 28-day cycles are equivalent to 13.8 months for ibrutinib-venetoclax, and six 28-day cycles are equivalent to 5.5 months for chlorambucil-obinutuzumab. Patients may have treatment exposure times exceeding these limits due to cycle holds.

† Includes "neutrophil count decreased." Rates of febrile neutropenia (grade ≥3): 1.9% for ibrutinib-venetoclax versus 2.9% for chlorambucil-obinutuzumab.

‡ Includes multiple preferred terms. Only pneumonia (grade ≥3) occurred in 5% or more of patients in the ibrutinib-venetoclax (7 [6.6%]) and chlorambucil-obinutuzumab (6 [5.7%]) arms.

§ Both grade 5 adverse events were pneumonia (one patient experienced three grade 5 adverse events: pneumonia, cardiac failure, and sinus node dysfunction).

¶ In the ibrutinib-venetoclax arm, 3 diarrhea (grade ≥3) resolved or improved after a median of 9.0 days.

what would be expected for this patient population (Table S9). The median PFS for chlorambucil-obinutuzumab in the GLOW trial was consistent with that from the CLL11 trial (median PFS, 26.7 months).[32] Ibrutinib-venetoclax significantly enhanced PFS versus chlorambucil-obinutuzumab, and this benefit was consistent across prespecified subgroup, such as older patients and those with comorbidities, and stratification factors such as IGHV mutational status. Of note, in the fixed-duration cohort of the CAPTIVATE trial in young/fit patients with previously untreated CLL, 24-month PFS rates were similar for patients with mutated (97%) and unmutated (93%) IGHV CLL.[30] Additional study follow-up is warranted in the GLOW trial to evaluate the predictive value of IGHV mutational status on PFS with ibrutinib-venetoclax.

Ibrutinib-venetoclax improved the depth and sustainability of responses versus chlorambucil-obinutuzumab, as demonstrated by the greater than threefold higher rates of complete response, an almost threefold higher uMRD in bone marrow, a greater than twofold proportion of responders maintaining tumor response over 24 months, and a nearly threefold higher rate of sustained uMRD during the first year posttreatment. The best uMRD rates by flow cytometry for ibrutinib-venetoclax in the GLOW trial were consistent with rates reported in the phase 2 CAPTIVATE study in younger, fitter patients.[30] Additional study follow-up from the GLOW trial will be important to further characterize the depth and durability of uMRD responses with ibrutinib-venetoclax and the impact of MRD status on PFS. The finding that most patients maintained their MRD status (undetectable or detectable) without clinical progression during the first year posttreatment differentiates ibrutinib-venetoclax from chemoimmunotherapy and provides reassurance that few patients with non-del(17p) CLL who receive ibrutinib-venetoclax will progress quickly to second-line treatment. Only two patients treated with ibrutinib-venetoclax

required second-line treatment for CLL with a median 27.7 months of study follow-up.

The combination of ibrutinib and venetoclax acts in a synergistic fashion to eradicate CLL from multiple tissue compartments, not limited to the usual sites for MRD assessments (peripheral blood and bone marrow).[22,38] The absence of early clinical progressions in patients with detectable MRD at end of treatment suggests that treatment with the doublet has reduced the quantity of proliferating CLL cells in lymphoid compartments that typically refuel disease regrowth after cessation of treatment.[19-21,23,24] Data from the GLOW trial further confirm that lymph node responses with ibrutinib-venetoclax were well maintained with current study follow-up. The high uMRD concordance between compartments further suggests that CLL is cleared from bone marrow and peripheral blood to a similar degree in a similar timeframe, and we speculate that peripheral blood uMRD status could be used as a reasonable surrogate for bone marrow clearance with ibrutinib-venetoclax.

The side-effect profile of the combination was consistent with the known side-effect profiles of ibrutinib and venetoclax and what would be expected with CLL treatment of elderly patients with comorbidities. There were more patients with multiple comorbid conditions at study entry in the ibrutinib-venetoclax arm than the chlorambucil-obinutuzumab arm, which may have impacted the side-effect profiles observed. Incidence of certain nonhematologic AEs grade 3 or greater (diarrhea, hypertension, and atrial fibrillation) was higher with ibrutinib-venetoclax. Incidence of hematologic AEs grade 3 or greater (neutropenia [34.9% vs. 49.5%] and thrombocytopenia [5.7% vs. 20.0%]) was lower for ibrutinib-venetoclax versus chlorambucil-obinutuzumab. Few AEs were treatment limiting with ibrutinib-venetoclax, as nearly 80% of patients completed treatment.

Although the overall number of deaths during the study was similar between arms at the time of primary analysis and increased in the chlorambucil-obinutuzumab arm with additional follow-up, there were more deaths during randomized treatment in the ibrutinib-venetoclax arm. Three deaths were due to causes likely unrelated to ibrutinib-venetoclax treatment, including lung infection with pulmonary edema and pleural effusion present before treatment initiation, metastatic carcinoma (likely but not known for certain to be present at baseline), and ischemic (confirmed nonembolic) stroke secondary to chronic obliterating atherosclerosis. Among the four on-treatment cardiac/sudden deaths, the common feature was a CIRS score of 10 or greater and/or an ECOG PS of 2, suggesting that patients in the GLOW trial with a significant comorbidity burden were potentially at an increased risk of these events. Risk of cardiac arrhythmias, including serious or fatal events, is described in the ibrutinib product label, with cardiovascular risk factors (including hypertension) noted as potential underlying risks for arrhythmias with Bruton tyrosine kinase inhibitors.[10,39,40] Data from the GLOW trial, in which two thirds of patients had preexisting hypertension, emphasize the importance of careful assessment of underlying cardiac risk factors when initiating treatment.[5] The results further highlight the need for improved predictive markers for cardiac events among elderly patients and/or those with comorbidities undergoing CLL treatment.[41]

While follow-up in the GLOW trial is limited and study populations differ, particularly with respect to inclusion of patients with del(17p), there are now multiple phase 3 trials evaluating non-chemoimmunotherapy treatments (single-agent ibrutinib [NCT01722487], ibrutinib-rituximab [NCT01886872], venetoclax-obinutuzumab [NCT02242942], and ibrutinib-venetoclax [NCT03462719]) in older patients and/or those with comorbidities with previously untreated CLL that demonstrate high 24-month PFS rates ranging from 84% to 89%.[13,16,42] The ongoing phase 3 CLL17 trial (NCT04608318) is comparing standard-of-care single-agent ibrutinib versus fixed-duration ibrutinib-venetoclax and venetoclax-obinutuzumab in first-line treatment of CLL.[43]

All-oral, once-daily, fixed-duration ibrutinib-venetoclax provided deeper and better sustained responses in the GLOW trial versus chlorambucil-obinutuzumab and significantly extended PFS in older, comorbid patients with previously untreated CLL.

Disclosures

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The data sharing policy of the Janssen Pharmaceutical Companies of Johnson & Johnson is available at www.janssen.com/clinical-trials/transparency. Requests for access to data from select studies can be submitted through the Yale Open Data Access (YODA) Project site at yoda.yale.edu.

Author Affiliations

[1] Amsterdam University Medical Centers, Cancer Center Amsterdam, University of Amsterdam, on behalf of the HOVON CLL Working Group, Amsterdam

[2] Tom Baker Cancer Centre, Calgary, Alberta, Canada

[3] Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Barcelona

[4] Addenbrooke's Hospital, Cambridge, UK

[5] St James's Hospital, Leeds, UK

[6] Albert Schweitzer Hospital, Dordrecht, Netherlands

[7] Sheba Medical Center, Ramat Gan, Israel

[8] Universitaire Ziekenhuizen Leuven, Leuven, Belgium

[9] Karolinska University Hospital, Stockholm

[10] Medical University of Łódź, Copernicus Memorial Hospital, Łódź, Poland

[11] University Hospital Hradec Králové, Hradec Králové, Czech Republic

[12] Norton Cancer Institute, Louisville, KY

[13] Russian Scientific Research Institute of Hematology and Transfusiology, St. Petersburg, Russia

[14] S.P. Botkin Moscow City Clinical Hospital, Moscow

[15] Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France

[16] Janssen Research & Development, Raritan, NJ

[17] Janssen Research & Development, San Diego, CA

[18] Janssen Research & Development, Düsseldorf, Germany

[19] Janssen Research & Development, Beerse, Belgium

[20] Rigshospitalet Copenhagen University Hospital, Copenhagen

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