Impact of Minimal Residual Disease on Progression-Free Survival Outcomes After Fixed-Duration Ibrutinib-Venetoclax Versus Chlorambucil-Obinutuzumab in the GLOW Study

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ABSTRACT

PURPOSE In GLOW, fixed-duration ibrutinib + venetoclax showed superior progression-free survival (PFS) versus chlorambucil + obinutuzumab in older/comorbid patients with previously untreated chronic lymphocytic leukemia (CLL). The current analysis describes minimal residual disease (MRD) kinetics and any potential predictive value for PFS, as it has not yet been evaluated for ibrutinib + venetoclax treatment.

METHODS Undetectable MRD (uMRD) was assessed by next-generation sequencing at <1 CLL cell per 10,000 ($<10^{-4}$) and <1 CLL cell per 100,000 ($<10^{-5}$) leukocytes. PFS was analyzed by MRD status at 3 months after treatment (EOT+3).

RESULTS Ibrutinib + venetoclax achieved deeper uMRD ($<10^{-5}$) rates in bone marrow (BM) and peripheral blood (PB), respectively, in 40.6% and 43.4% of patients at EOT+3 versus 7.6% and 18.1% of patients receiving chlorambucil + obinutuzumab. Of these patients, uMRD ($<10^{-5}$) in PB was sustained during the first year post-treatment (EOT+12) in 80.4% of patients receiving ibrutinib + venetoclax and 26.3% receiving chlorambucil + obinutuzumab. Patients with detectable MRD (dMRD; $\geq 10^{-4}$) in PB at EOT+3 were more likely to sustain MRD levels through EOT+12 with ibrutinib + venetoclax versus chlorambucil + obinutuzumab. PFS rates at EOT+12 were high among patients treated with ibrutinib + venetoclax regardless of MRD status at EOT+3: 96.3% and 93.3% in patients with uMRD ($<10^{-4}$) and dMRD ($\geq 10^{-4}$) in BM, respectively, versus 83.3% and 58.7% for patients receiving chlorambucil + obinutuzumab. PFS rates at EOT+12 also remained high in patients with unmutated immunoglobulin heavy-chain variable region (IGHV) receiving ibrutinib + venetoclax, independent of MRD status in BM.

CONCLUSION Molecular and clinical relapses were less frequent during the first year post-treatment with ibrutinib + venetoclax versus chlorambucil + obinutuzumab regardless of MRD status at EOT+3 and IGHV status. Even for patients not achieving uMRD ($<10^{-4}$), PFS rates remained high with ibrutinib + venetoclax; this is a novel finding and requires additional follow-up to confirm its persistence over time.

ACCOMPANYING CONTENT

Editorial, p. 3676

Appendix

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) primarily affects older adults, with a median age at diagnosis of 70 years.[1] Chemoimmunotherapy with chlorambucil + obinutuzumab is a first-line treatment option for CLL patients without *TP53* alterations who are older (age 65 years and older) and/or have comorbidities,[2,3] resulting in a median progression-free survival (PFS) of 26.7 months.[4] However, chlorambucil + obinutuzumab provides suboptimal disease control (with a complete response [CR] rate of 20.7%)[4] and requires frequent infusions that carry the risk of infusion-related reactions.[4,5] Besides venetoclax + obinutuzumab,[6] other time-limited treatment options with different modes of

CONTEXT

Key Objective

Minimal residual disease (MRD) status is associated with progression-free survival (PFS) after treatment with chemoimmunotherapy and fixed-duration venetoclax + anti-CD20, but this relationship has not been explored with ibrutinib + venetoclax. This analysis evaluates whether MRD status at the end of treatment is correlated with PFS outcomes during the first year off treatment in patients who received fixed-duration ibrutinib + venetoclax for frontline treatment of chronic lymphocytic leukemia (CLL).

Knowledge Generated

Regardless of MRD status at the end of treatment, PFS rates at 12 months after the end of treatment with ibrutinib + venetoclax were high: 96.3% and 93.3% in patients with undetectable MRD ($<10^{-4}$) and detectable MRD ($\geq 10^{-4}$), respectively. The lack of a clear impact of MRD status at the end of treatment and PFS outcomes at 12 months after treatment is a novel finding and requires additional follow-up to confirm its persistence over time.

Relevance *(S. Lentzsch)*

Older and frail CLL patients treated with ibrutinib + venetoclax have a better PFS regardless of the MRD status than patients receiving chlorambucil + obinutuzumab. Ibrutinib + venetoclax should be the preferred regimen for this patient population. Longer follow-up from the GLOW study will be essential to determine if the current trend with ibrutinib + venetoclax persists.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

action that affect both the CLL cells and the immune system could provide additional clinical value. Moreover, different administration profiles (ie, all-oral treatments) might provide advances in certain settings.

Ibrutinib and venetoclax, each approved for treating CLL alone or in combination with CD20 antibodies,[7,8] have complementary mechanisms of action that work synergistically.[9-14] In addition to inhibiting proliferation of CLL cells, ibrutinib mobilizes cells out of lymphoid niches into peripheral blood (PB) and increases the sensitivity of CLL cells to BCL-2 inhibition by venetoclax.[9-11,13] Together, the doublet eradicates both resting and dividing CLL cell subpopulations, thereby enhancing the clearance of minimal residual disease (MRD) and depth of response, providing an opportunity for fixed-duration treatment or MRD-guided treatment.[9,15-18]

To our knowledge, GLOW is the first phase III trial to evaluate the efficacy and safety of fixed-duration ibrutinib + venetoclax versus chlorambucil + obinutuzumab in patients with previously untreated CLL who were older and/or had comorbidities. The primary analysis (median follow-up of 27.7 months) showed PFS was superior for ibrutinib + venetoclax versus chlorambucil + obinutuzumab (hazard ratio, 0.216; 95% CI, 0.131 to 0.357; $P < .001$).[17] Best undetectable MRD (uMRD $< 10^{-4}$) rates in bone marrow (BM) were significantly higher for ibrutinib + venetoclax versus chlorambucil + obinutuzumab (55.7% *v* 21.0%; $P < .001$).[17]

MRD status has been shown to be predictive of survival outcomes with fixed-duration treatments such as chemoimmunotherapy[19,20] or venetoclax plus anti-CD20 combinations.[6,21,22] Whether a similar relationship exists for ibrutinib + venetoclax in frontline CLL has not yet been evaluated. The aim of the current analysis of GLOW was to further evaluate MRD kinetics and any potential association between MRD and PFS outcomes.

METHODS

Study Design

The phase III GLOW (ClinicalTrials.gov identifier: NCT03462719) study included patients with previously untreated CLL who were age 65 years and older or age 18-64 years with comorbidities and an Eastern Cooperative Oncology Group performance status ≤2, as described previously.[17] Patients were randomly assigned 1:1 to ibrutinib + venetoclax or chlorambucil + obinutuzumab (Fig 1). Patients were stratified by immunoglobulin heavy-chain variable region (IGHV) mutational status (as assessed by Sanger sequencing, per protocol) and presence of 11q deletion (del11q). Patients with del17p or known *TP53* mutations at screening were excluded; *TP53* mutational status was subsequently assessed centrally in enrolled patients.

The study was 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 International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent.

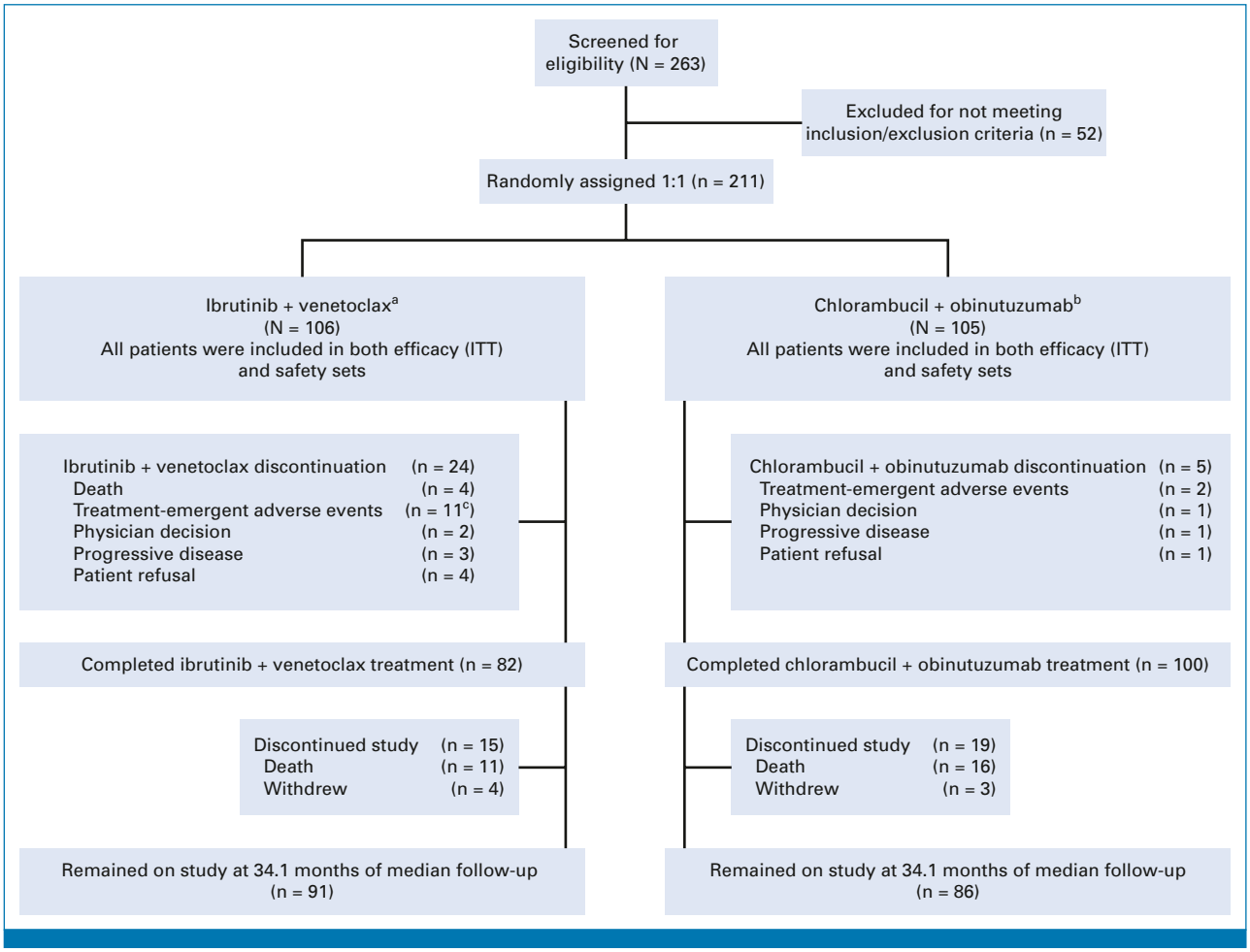

FIG 1. CONSORT diagram. [a]Ibrutinib (420 mg once-daily three-cycle lead-in) followed by ibrutinib + venetoclax for 12 cycles (venetoclax ramp-up starting at C4 over the first 5 weeks from 20 to 400 mg once daily). [b]Chlorambucil (0.5 mg/kg once on D1 and D15 for six cycles) plus obinutuzumab (1,000 mg once on D1-D2, D8, D15 of C1, and D1 of C2 to C6). [c]Includes three patients who discontinued because of treatment-emergent adverse events that later resulted in death. A cycle was defined as 28 days. C, cycle; D, day; ITT, intent-to-treat.

Assessments

MRD was assessed by next-generation sequencing via clonoSEQ (Adaptive Biotechnologies, Seattle, WA) using uMRD cutoffs of <1 CLL cell per 10,000 leukocytes ($<10^{-4}$) and <1 CLL cell per 100,000 leukocytes ($<10^{-5}$).[23] Detectable MRD (dMRD) was defined as having ≥1 CLL cell per 10,000 leukocytes ($\geq10^{-4}$) with low dMRD at $\geq10^{-4}$ to $<10^{-2}$ and high dMRD at $\geq10^{-2}$. Samples for MRD evaluation were collected every 3-4 months from PB and at 9 and 18 months from BM after random assignment for patients with a partial response (PR) or better (nodular PR [nPR], or CR/CR with incomplete BM recovery [CRi]). Each month was a 4-week period. Concordance in uMRD between BM and PB was calculated for patients with uMRD in PB at 3 months after end of treatment (EOT+3) who had a paired BM sample. Sustained uMRD was calculated for each treatment using longitudinal patient samples at EOT+3 and 12 months after end of treatment (EOT+12). Worsening in MRD from undetectable ($<10^{-4}$) to detectable ($\geq10^{-4}$) levels was considered a molecular relapse, whereas disease progression was considered a clinical relapse. For the analysis of PFS according to MRD status, all patients with a PR or better (nPR, or CR/CRi) who had a known MRD status at EOT+3 were included. Lymph node clearance was assessed by measuring the change from baseline in sum of the products of perpendicular dimensions of predefined target lesions.

Statistical Analysis

Descriptive statistics were provided for MRD assessments and tumor response rates (PR and CR/CRi) for each treatment arm with no formal statistical comparison conducted. Kaplan-Meier estimates were generated for PFS, overall survival (OS), and time to next treatment (TTNT). Hazard ratios for time-to-event end points in the ibrutinib + venetoclax arm relative to the chlorambucil + obinutuzumab arm (and associated 95% CIs) were calculated on the basis of the stratified Cox regression model, and *P* values from log-rank test were provided. All *P* values reported are nominal without

adjustments for multiple testing (two-sided alpha level of 0.05). The study was not powered to detect differences between or within treatment arms and subgroups at this data cutoff.

RESULTS

Patients

In total, 211 patients were randomly assigned and included in the intent-to-treat and safety analyses; 106 patients received ibrutinib + venetoclax and 105 received chlorambucil + obinutuzumab. Baseline characteristics were generally well balanced between the treatment groups (Appendix Table A1, online only).[17] For this analysis, the median follow-up time from random assignment was 34.1 months.

Efficacy

With 34.1 months of median follow-up, independent review committee–assessed PFS remained superior for ibrutinib + venetoclax versus chlorambucil + obinutuzumab (hazard ratio, 0.212; 95% CI, 0.129 to 0.349; $P < .001$); estimated 30-month PFS rates were 80.5% versus 35.8%, respectively. There were 11 deaths in the ibrutinib + venetoclax arm and 16 deaths in the chlorambucil + obinutuzumab arm; the hazard ratio for OS was 0.76 (95% CI, 0.352 to 1.642; $P = .484$).[17]

The estimated 30-month duration of response rate was 86.7% in the ibrutinib + venetoclax arm and 35.5% in the chlorambucil + obinutuzumab arm. At 34.1 months of median follow-up, six patients in the ibrutinib + venetoclax arm (three with Richter's transformation during treatment) and 35 patients in the chlorambucil + obinutuzumab arm (two with Richter's transformation during treatment) required subsequent anticancer therapy (Appendix Table A2, online only). TTNT was prolonged for patients receiving ibrutinib + venetoclax compared with those receiving chlorambucil + obinutuzumab (Appendix Fig A1, online only). The risk of needing second-line therapy was reduced by 85.3% with first-line ibrutinib + venetoclax versus chlorambucil + obinutuzumab (hazard ratio, 0.147; 95% CI, 0.062 to 0.350; $P < .0001$).

MRD Kinetics

MRD at EOT+3 in All Patients

A higher percentage of patients receiving ibrutinib + venetoclax compared with chlorambucil + obinutuzumab had uMRD ($<10^{-4}$) at EOT+3 in BM (51.9% and 17.1%, respectively) and PB (54.7% and 39.0%, respectively; Fig 2A).[17] The proportion of patients with deeper uMRD $< 10^{-5}$ at EOT+3 was higher in the ibrutinib + venetoclax arm than in the chlorambucil + obinutuzumab arm in BM (40.6% and 7.6%, respectively) and PB (43.4% and 18.1%, respectively; Fig 2A). Concordance between BM and PB at uMRD $< 10^{-5}$ was 90.9% for the ibrutinib + venetoclax arm and 36.8% for the chlorambucil + obinutuzumab arm, consistent with the concordance at the $<10^{-4}$ level (92.9% and 43.6%, respectively) as reported previously.[17] In the ibrutinib + venetoclax arm, concordance increased to 97.8% when using a stricter cutoff in PB ($<10^{-5}$) than in BM ($<10^{-4}$).

Among patients with known MRD status in BM at EOT+3 who achieved a best response of CR/CRi, uMRD $< 10^{-4}$ rates were 66.7% (28/42) in the ibrutinib + venetoclax arm and 30.8% (4/13) in the chlorambucil + obinutuzumab arm. For patients achieving a best response of PR, uMRD $< 10^{-4}$ rates in BM at EOT+3 were 64.1% (25/39) and 21.3% (13/61) in the ibrutinib + venetoclax and chlorambucil + obinutuzumab arms, respectively.

MRD at EOT+3 by Subgroups

Across subgroups, higher rates of uMRD in BM (Fig 2B) with deeper responses in both BM and PB (Fig 3) were consistently observed in the ibrutinib + venetoclax arm compared with the chlorambucil + obinutuzumab arm. Among patients with unmutated IGHV (uIGHV), the uMRD $< 10^{-5}$ rate in BM was 45.5% with ibrutinib + venetoclax and 5.6% with chlorambucil + obinutuzumab (Fig 3A). Likewise, among patients with mutated IGHV (mIGHV), uMRD $< 10^{-5}$ in BM was higher for ibrutinib + venetoclax (29.6%) than chlorambucil + obinutuzumab (14.8%). In PB, higher uMRD $< 10^{-5}$ rates were also observed in patients with uIGHV in the ibrutinib + venetoclax arm (49.1%) compared with the chlorambucil + obinutuzumab arm (13.0%). Although a higher proportion of patients with mIGHV in the chlorambucil + obinutuzumab arm (63.0%) achieved uMRD $< 10^{-4}$ in PB compared with the ibrutinib + venetoclax arm (44.4%), a greater proportion of patients achieved deeper uMRD $< 10^{-5}$ with ibrutinib + venetoclax (37.0%) than chlorambucil + obinutuzumab (29.6%).

Higher rates of uMRD $< 10^{-5}$ were also observed in the ibrutinib + venetoclax arm compared with the chlorambucil + obinutuzumab arm in both BM (40.0% and 5.6%, respectively) and PB (45.0% and 22.2%, respectively) for patients with del11q (Fig 3B). Five of seven patients in the ibrutinib + venetoclax arm with a *TP53* mutation achieved uMRD $< 10^{-5}$ responses in both BM and PB, while neither of the two patients in the chlorambucil + obinutuzumab arm achieved uMRD.

Sustained MRD at EOT+12 in All Patients

At EOT+12, uMRD $< 10^{-5}$ in PB was 36.8% for ibrutinib + venetoclax and 6.7% for chlorambucil + obinutuzumab (Fig 4). uMRD rates were better sustained longitudinally in the first year post-treatment for ibrutinib + venetoclax; 80.4% (37/46) of patients maintained uMRD $< 10^{-5}$ in the ibrutinib + venetoclax arm and 26.3% (5/19) of patients in the chlorambucil + obinutuzumab arm, consistent with rates of sustained uMRD $< 10^{-4}$ (84.5% *v* 29.3%, respectively).[17] Moreover, patients with dMRD $\geq 10^{-4}$ at EOT+3 in the ibrutinib + venetoclax arm were less likely to have increasing

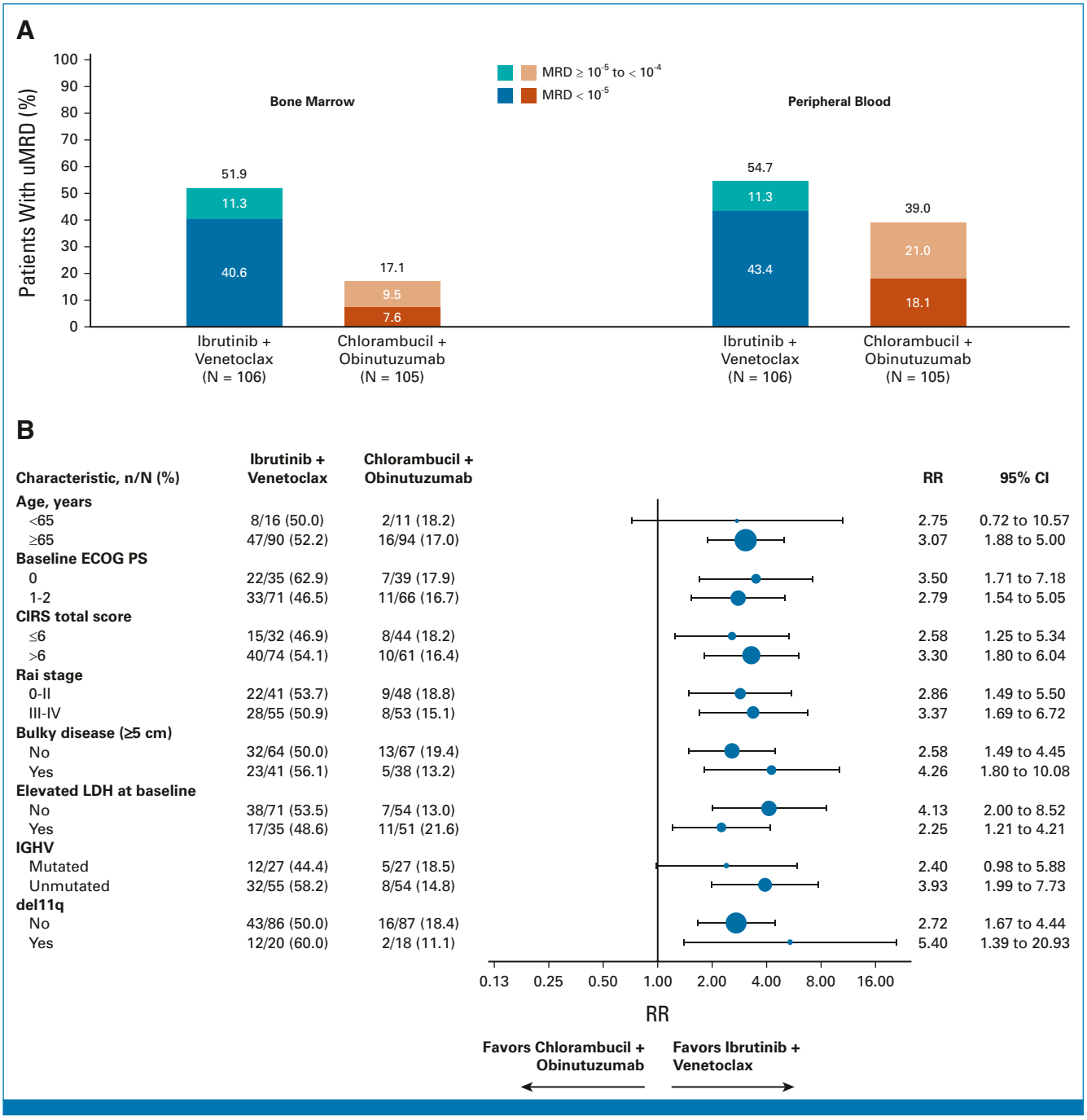

FIG 2. (A) Rates of uMRD in BM and PB for all patients and (B) rates of uMRD ($<10^{-4}$) in BM across prespecified subgroups. MRD results by next-generation sequencing at EOT+3. Numbers may not add up to exact total because of rounding. Size of the blue dot represents relative size of each subgroup including both treatment arms. BM, bone marrow; CIRS, Cumulative Illness Rating Scale score; del11q, 11q deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT+3, 3 months after end of treatment; IGHV, immunoglobulin heavy-chain variable region; LDH, lactate dehydrogenase; MRD, minimal residual disease; PB, peripheral blood; RR, relative risk; uMRD, undetectable MRD.

levels of MRD and/or progress clinically compared with patients in the chlorambucil + obinutuzumab arm (Fig 4). Of the patients with low dMRD ≥ 10^{-4} to $<10^{-2}$, 3/24 (12.5%) in the ibrutinib + venetoclax arm and 12/37 (32.4%) in the chlorambucil + obinutuzumab arm experienced increasing levels of dMRD ≥ 10^{-2} from EOT+3 to EOT+12. Furthermore, of the patients with low dMRD ≥ 10^{-4} to $<10^{-2}$ at EOT+3, no patients in the ibrutinib + venetoclax arm and 17 patients in the chlorambucil + obinutuzumab arm had progressed clinically at EOT+12.

Sustained MRD at EOT+12 by Subgroups

In patients with uIGHV who achieved uMRD < 10^{-4} at EOT+3, 29/34 (85%) in the ibrutinib + venetoclax arm sustained their uMRD status during the first year post-treatment

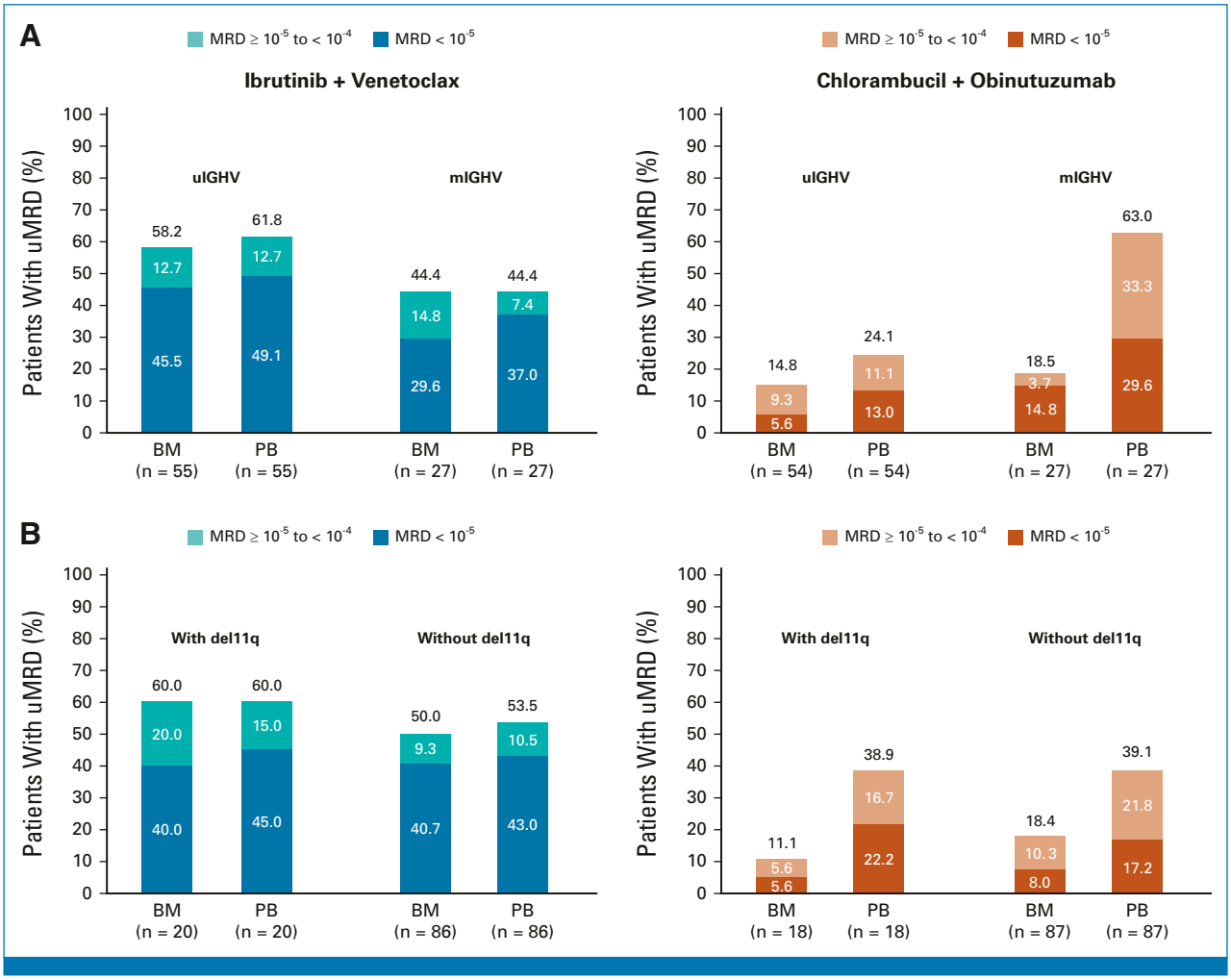

FIG 3. Rates of uMRD in BM and PB at EOT+3 for patients in the ibrutinib + venetoclax arm (left) and chlorambucil + obinutuzumab arm (right) by (A) IGHV mutational status and (B) presence of del11q. IGHV status was unknown in 24 patients in each treatment arm. MRD results by next-generation sequencing at EOT+3. Numbers may not add up to exact total because of rounding. BM, bone marrow; del11q, 11q deletion; EOT+3, 3 months after end of treatment; IGHV, immunoglobulin heavy-chain variable region; mIGHV, mutated IGHV; MRD, minimal residual disease; PB, peripheral blood; uIGHV, unmutated IGHV; uMRD, undetectable MRD.

compared with 4/13 (31%) in the chlorambucil + obinutuzumab arm. Of the patients with uIGHV and low dMRD ≥ 10^{-4} to <10^{-2}, 4/6 in the ibrutinib + venetoclax arm and 2/25 in the chlorambucil + obinutuzumab arm sustained their MRD status during the first year post-treatment.

In patients with mIGHV who achieved uMRD < 10^{-4} at EOT+3, 9/12 (75%) in the ibrutinib + venetoclax arm sustained their uMRD status in the first year post-treatment compared with 6/17 (35%) in the chlorambucil + obinutuzumab arm. Of the three remaining patients with mIGHV in the ibrutinib + venetoclax arm, one had molecular relapse without clinical progression between EOT+3 and EOT+12, and two were missing MRD assessments at EOT+12 such that it was not possible to assess for sustained uMRD. Of the patients with mIGHV and low dMRD ≥ 10^{-4} to <10^{-2}, 6/9 patients in the ibrutinib + venetoclax arm and none of the six patients in the chlorambucil + obinutuzumab arm sustained their MRD status during the first year post-treatment.

PFS by MRD Status, IGHV Status, and Tumor Response

The PFS rate in the first year post-treatment was maintained independent of MRD status at EOT+3 in the ibrutinib + venetoclax arm, but not in the chlorambucil + obinutuzumab arm (Fig 5A). The estimated PFS rate at EOT+12 in the ibrutinib + venetoclax arm was 96.3% (95% CI, 86.0 to 99.1) for patients with uMRD (<10^{-4}) in BM and 93.3% (95% CI, 75.9 to 98.3) for patients with dMRD (≥10^{-4}), compared with 83.3% (95% CI, 56.8 to 94.3) and 58.7% (95% CI, 45.6 to 69.7) in the chlorambucil + obinutuzumab arm, respectively. In the chlorambucil + obinutuzumab arm, early relapse was more common regardless of MRD status at EOT+3. Trends were

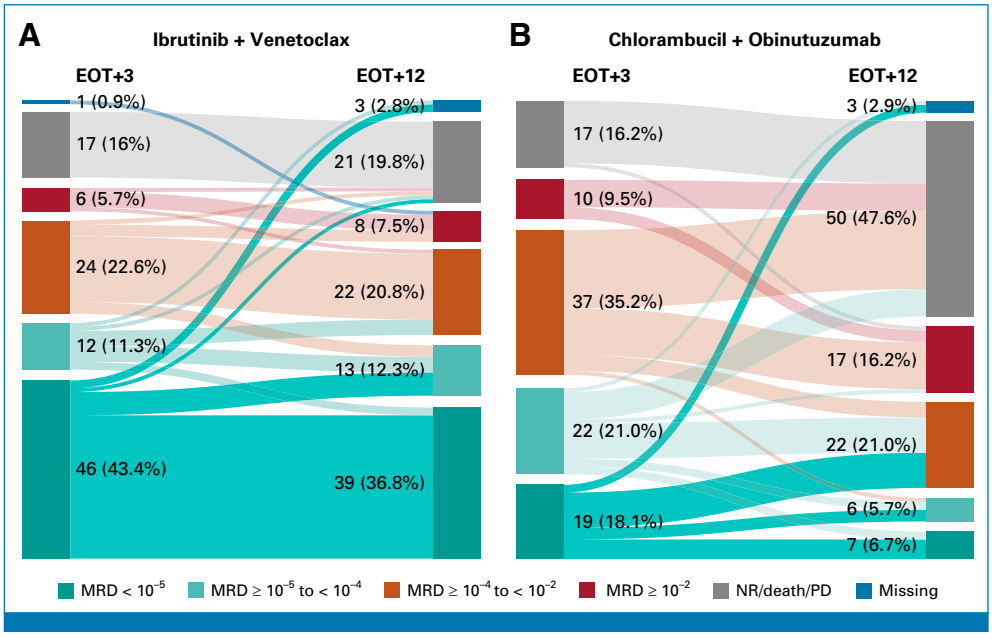

FIG 4. Sustained MRD in PB from EOT+3 to EOT+12 in the (A) ibrutinib + venetoclax arm and (B) chlorambucil + obinutuzumab arm for all patients. Percent calculations are based on ITT population; totals may not add to exactly 100% because of rounding. EOT+3, 3 months after end of treatment; EOT+12, 12 months after end of treatment; ITT, intent-to-treat; MRD, minimal residual disease; NR, nonresponder; PB, peripheral blood; PD, disease progression.

similar according to MRD status in PB (Appendix Fig A2, online only).

Among patients with uIGHV, the PFS rate was high in the first year post-treatment, independent of MRD status in BM, with ibrutinib + venetoclax; however, PFS was lower and dependent on MRD status in the chlorambucil + obinutuzumab arm (Fig 5B). PFS rates at EOT+12 were 93.8% (95% CI, 77.3 to 98.4) and 90.0% (95% CI, 47.3 to 98.5) in the ibrutinib + venetoclax arm for patients with uMRD ($<10^{-4}$) and dMRD ($\geq 10^{-4}$), respectively, compared with 62.5% (95% CI, 22.9 to 86.1) and 38.7% (95% CI, 22.0 to 55.1) in the chlorambucil + obinutuzumab arm. Among patients with mIGHV who achieved uMRD in BM, no clinical progressions or deaths occurred during the first year post-treatment in either treatment arm (Fig 5C).

In the ibrutinib + venetoclax arm, 30-month PFS rates were similar regardless of whether best tumor response was a CR or PR, whereas in the chlorambucil + obinutuzumab arm, the 30-month PFS rate was lower in patients with a best response of PR versus CR (Appendix Fig A3, online only).

Lymph Node Response

Lymph node clearance was largely maintained after stopping treatment in both arms among patients who achieved uMRD ($<10^{-4}$) at EOT+3 (Fig 6A). Among patients with dMRD ($\geq 10^{-4}$) at EOT+3, nodal response was maintained after treatment in patients in the ibrutinib + venetoclax arm, but not in the chlorambucil + obinutuzumab arm (Fig 6A). Compared with the chlorambucil + obinutuzumab, nodal response in the ibrutinib + venetoclax arm was better maintained after treatment in patients with uIGHV regardless of MRD status (Fig 6B).

Safety

As all patients were off treatment at the primary analyses (median follow-up of 27.7 months), no major changes in safety were noted at 34.1 months of median follow-up except one patient in the chlorambucil + obinutuzumab arm who was diagnosed with new serious treatment-emergent adverse events (myelodysplastic syndrome/myeloproliferative neoplasm). The number of patients with a second primary malignancy (SPM) during the study increased from 8 (7.5%)[17] to 10 (9.4%) in the ibrutinib + venetoclax arm and from 10 (9.5%)[17] to 12 (11.4%) in the chlorambucil + obinutuzumab arm. Of the patients with an SPM, four in the ibrutinib + venetoclax arm and three in the chlorambucil + obinutuzumab arm had nonmelanoma skin cancers (Appendix Table A3, online only).

DISCUSSION

At a median follow-up of 34.1 months in GLOW, patients with CLL who were older and/or had comorbidities receiving ibrutinib + venetoclax achieved higher rates of uMRD and deeper ($<10^{-5}$) responses, with higher concordance between BM and PB, compared with patients receiving chlorambucil + obinutuzumab. In the ibrutinib + venetoclax arm, >80% of

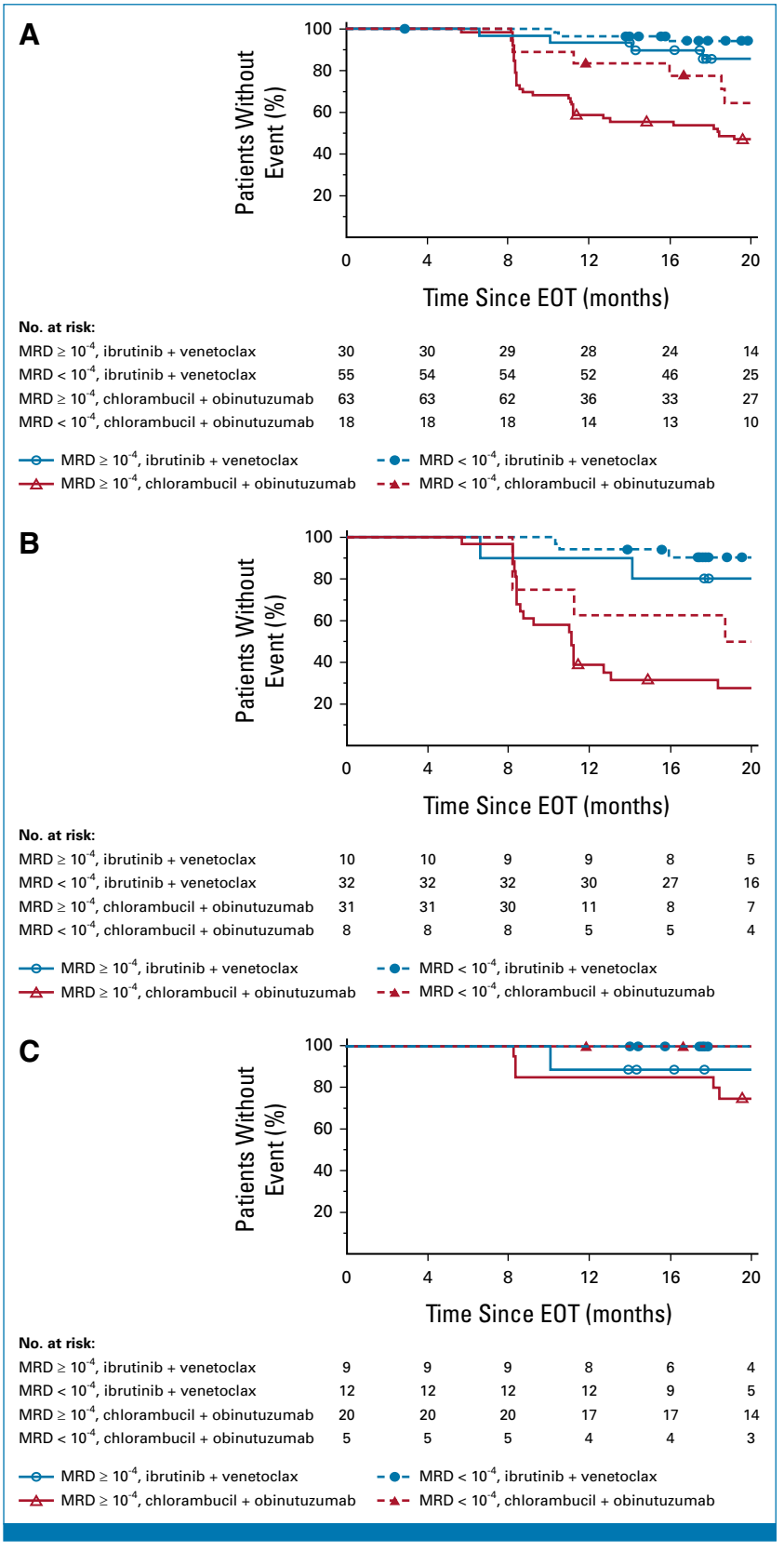

FIG 5. PFS by MRD status in BM at EOT+3 in (A) all patients, (B) patients with unmutated IGHV, and (C) patients with mutated IGHV. BM, bone marrow; EOT+3, 3 months after end of treatment; IGHV, immunoglobulin heavy-chain variable region; MRD, minimal residual disease; PFS, progression-free survival.

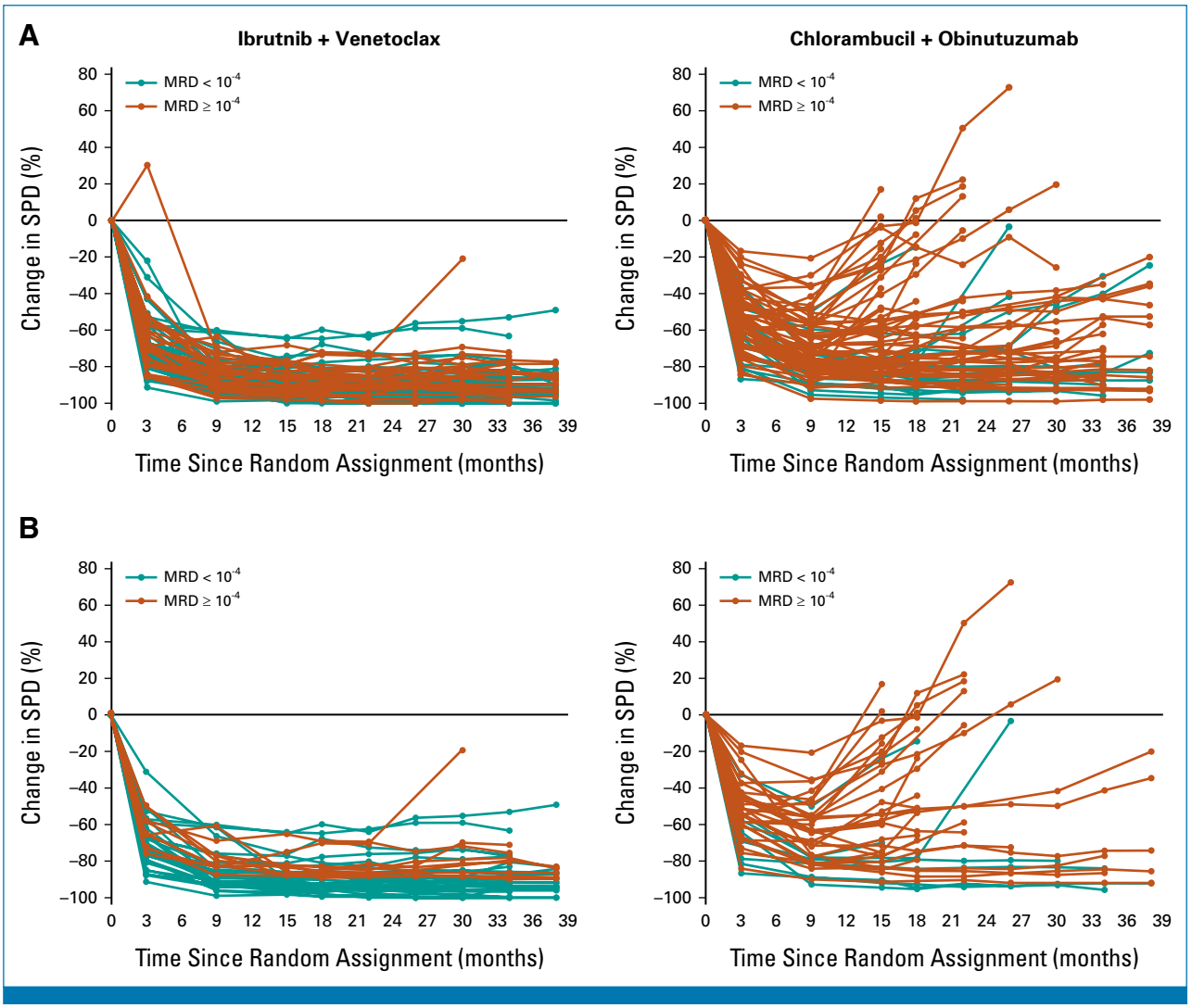

FIG 6. Lymph node response by MRD status in BM at EOT+3 in the ibrutinib + venetoclax arm (left) and chlorambucil + obinutuzumab arm (right) in (A) all patients and (B) patients with unmutated IGHV. BM, bone marrow; EOT+3, 3 months after end of treatment; IGHV, immunoglobulin heavy-chain variable region; MRD, minimal residual disease; SPD, sum of the product of perpendicular dimensions.

patients sustained their uMRD status in PB during the first year post-treatment. Irrespective of MRD status, estimated PFS in the ibrutinib + venetoclax arm was >90% at 1 year post-treatment. As MRD has been shown to correlate with PFS with other fixed-duration treatments such as venetoclax + anti-CD20 and chemoimmunotherapy,[6,19-22] longer follow-up from the GLOW study will be important to determine if the current trend with ibrutinib + venetoclax persists over time.

Molecular and clinical relapses were less frequent with ibrutinib + venetoclax than chlorambucil + obinutuzumab, likely owing to the synergistic mechanisms of ibrutinib and venetoclax,[9-14] which enables the combination to eliminate CLL cell reservoirs in multiple compartments to inhibit the return of disease. The high concordance in uMRD between BM and PB (90.9%-92.9% using $<10^{-4}$ or $<10^{-5}$ cutoff) achieved with ibrutinib + venetoclax has the potential to reduce the need for BM aspirates in clinical practice. Given that 97.8% of patients with uMRD $< 10^{-5}$ in PB had uMRD $< 10^{-4}$ in BM, use of more stringent PB uMRD cutoffs may further improve confidence in BM status; however, MRD testing at this level is not yet standard clinical practice.

MRD and PFS outcomes consistently favored ibrutinib + venetoclax across prespecified subgroups, including in patients with high-risk features (eg, uIGHV or del11q). The depth of response and lack of early progressions (irrespective of MRD status) seen in the uIGHV subgroup are particularly notable as outcomes for patients with uIGHV have historically been poor.[24,25] Enhanced B-cell receptor signaling and heightened Bruton's tyrosine kinase–dependent cell proliferation in uIGHV CLL lead to increased sensitivity to ibrutinib,[26] and

continuous single-agent ibrutinib therapy has demonstrated similar 7-year PFS outcomes for patients with uIGHV and mIGHV.[27] Moreover, in the GAIA study, the venetoclax + obinutuzumab + ibrutinib triplet demonstrated improved uMRD rates and a better PFS trend versus the venetoclax + obinutuzumab doublet in patients with previously untreated uIGHV CLL.[28,29] Taken together, these data suggest a role for ibrutinib in this subgroup of patients.

Previous studies with chemoimmunotherapy and fixed-duration combinations of venetoclax with an anti-CD20 antibody have demonstrated an association between MRD status at EOT with subsequent survival outcomes.[6,19-21,30] In previously untreated patients, fixed-duration venetoclax + obinutuzumab has shown inferior survival outcomes for patients who do not achieve uMRD at EOT.[6] In GLOW, we observed that during the first year off treatment, patients in the ibrutinib + venetoclax arm who had dMRD versus uMRD at EOT+3 had similar PFS rates at EOT+12 (93.3% *v* 96.3%, respectively). Additionally, in the ibrutinib + venetoclax arm, patients with dMRD sustained their MRD status and lymph node clearance during the first year off treatment, in contrast to patients in the chlorambucil + obinutuzumab arm. The sustained responses among patients with residual disease suggest a different dynamic for ibrutinib + venetoclax than reported previously with venetoclax + obinutuzumab.[6,31] The sustained lymph node responses seen with ibrutinib + venetoclax, irrespective of MRD, are likely driven by the unique mechanism of the ibrutinib + venetoclax combination. These findings raise important questions about the potential biological and therapeutic benefits of combining treatments with complementary, rather than overlapping, mechanisms of action. They also suggest that the relationship between MRD status and PFS may be regimen-dependent.

The current lack of a clear relationship between MRD status at EOT+3 and PFS with ibrutinib + venetoclax is a novel finding. Although there are rational mechanistic explanations, we observed that the dMRD subgroup was slightly enriched with patients with less proliferative disease (ie, patients with mIGHV), and the post-treatment outcomes may reflect that these patients had a lower propensity for early disease progression.

A few limitations should be noted. Further follow-up is needed to provide greater insight into these findings. Patient numbers for some subgroups were small. The reporting of outcomes according to uMRD or dMRD status at the end of treatment does not account for any potential imbalances in baseline characteristics between groups. As several samples did not have sufficient cell yields, samples could not be analyzed at uMRD < 10^{-6}.

In conclusion, patients with previously untreated CLL treated with fixed-duration ibrutinib + venetoclax are less likely to progress clinically during the first year post-treatment, irrespective of their MRD status at EOT+3 and IGHV status, compared with patients treated with chlorambucil + obinutuzumab.

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Impact of Minimal Residual Disease on Progression-Free Survival Outcomes After Fixed-Duration Ibrutinib-Venetoclax Versus Chlorambucil-Obinutuzumab in the GLOW Study

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APPENDIX

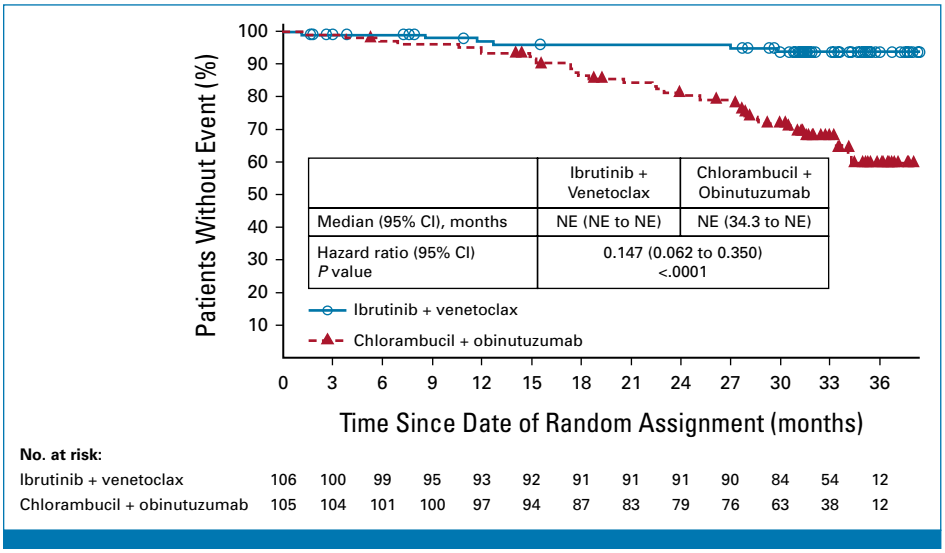

FIG A1. Time to next treatment. NE, not estimable.

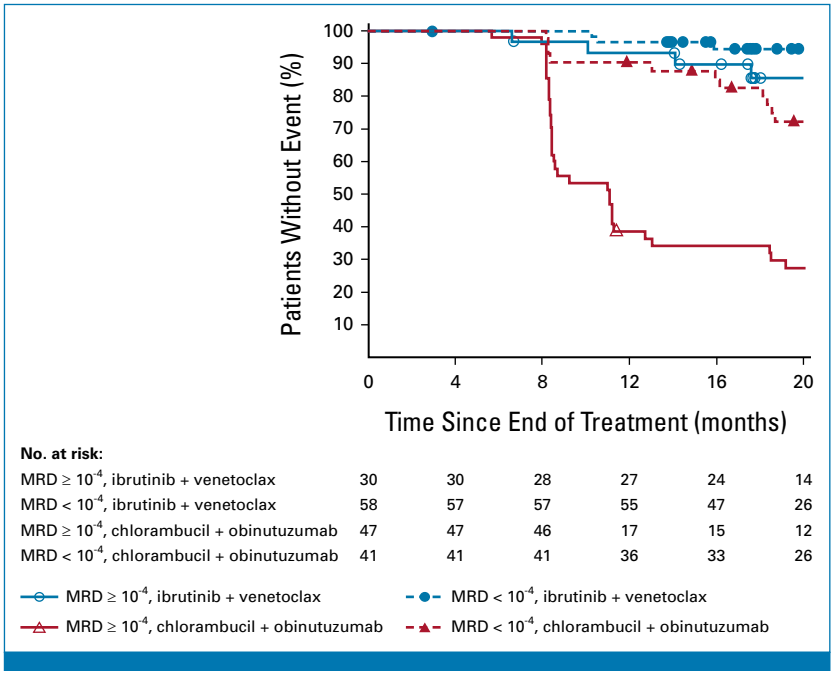

FIG A2. PFS by MRD status in PB at EOT+3 in all patients. EOT+3, 3 months after end of treatment; MRD, minimal residual disease; PB, peripheral blood; PFS, progression-free survival.

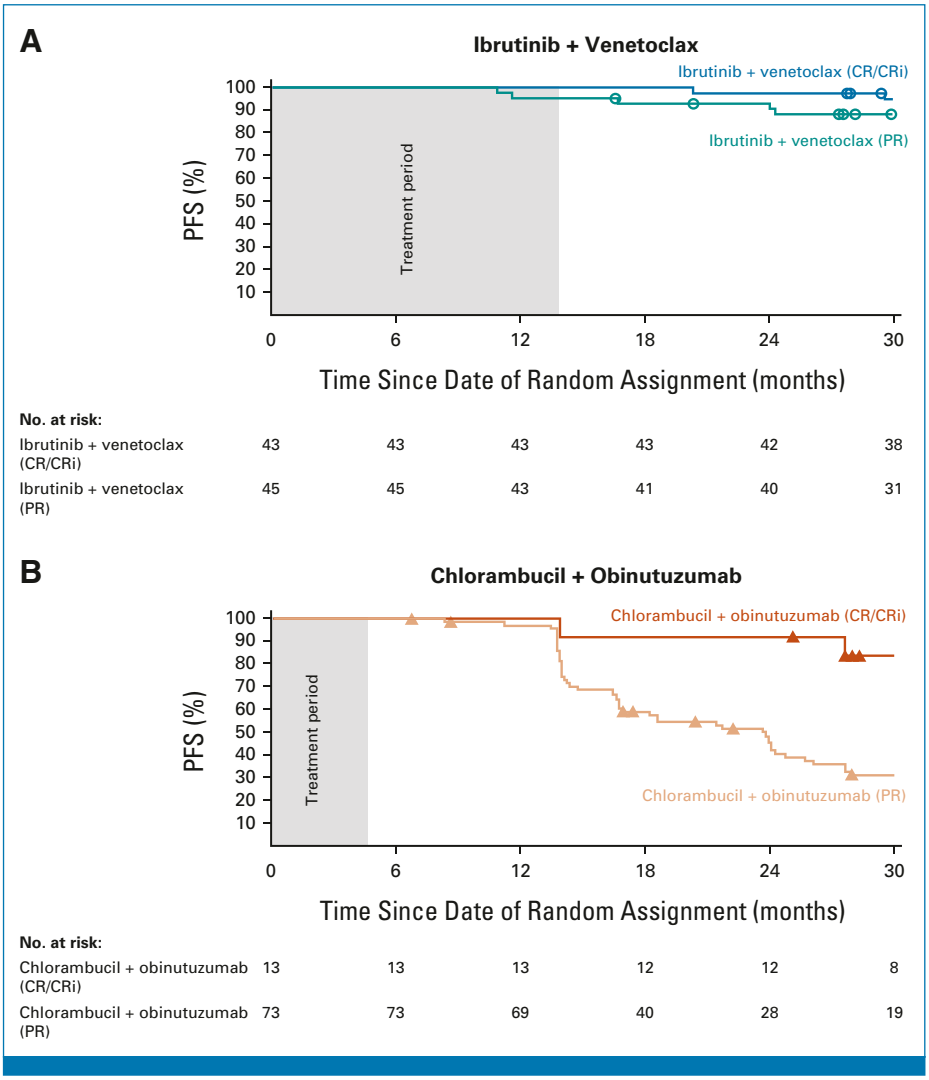

FIG A3. PFS by best tumor response in the (A) ibrutinib + venetoclax arm and (B) chlorambucil + obinutuzumab arm. CR, complete response; CRi, CR with incomplete bone marrow recovery; PFS, progression-free survival; PR, partial response.

TABLE A1. Patient Demographics and Disease Characteristics at Baseline (ITT Population)

Characteristic	Ibrutinib + Venetoclax (N = 106)	Chlorambucil + Obinutuzumab (N = 105)
Age, years, median (range)	71.0 (47-93)	71.0 (57-88)
≥75, No. (%)	35 (33.0)	37 (35.2)
<65, No. (%)	16 (15.1)	11 (10.5)
Sex, No. (%)		
Male	59 (55.7)	63 (60.0)
Female	47 (44.3)	42 (40.0)
ECOG PS 1-2, No. (%)	71 (67.0)	66 (62.9)
CIRS score, median (range)	9 (1-20)	8 (0-22)
>6,[a] No. (%)	74 (69.8)	61 (58.1)
CrCl,[b] mL/min, median (range)	66.5 (34.0-168.1)	63.2 (32.3-180.9)
Rai stage III-IV, No. (%)	55 (57.3)	53 (52.5)
Binet stage (CLL only), No.	96	101
A, No. (%)	7 (7.3)	8 (7.9)
B, No. (%)	46 (47.9)	53 (52.5)
C, No. (%)	43 (44.8)	40 (39.6)
Ann Arbor stage (SLL only), No.	10	4
IV, No. (%)	10 (100)	4 (100)
Bulky disease ≥5 cm, No. (%)	41 (39.0)	38 (36.2)
Elevated LDH,[a] No. (%)	35 (33.0)	51 (48.6)
IGHV status, No. (%)		
Mutated	27 (25.5)	27 (25.7)
Unmutated	55 (51.9)	54 (51.4)
Unknown	24 (22.6)	24 (22.9)
del11q, No. (%)	20 (18.9)	18 (17.1)
TP53 mutation,[c] No. (%)	7 (6.6)	2 (1.9)

Abbreviations: CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; del11q, 11q deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region; ITT, intent-to-treat; LDH, lactate dehydrogenase; SLL, small lymphocytic leukemia.
[a]Denotes a >10% numerical difference between arms.
[b]Using the Cockcroft-Gault equation.
[c]Central assessment.

TABLE A2. Subsequent Anticancer Systemic Therapies

Category	Ibrutinib + Venetoclax (N = 106)	Chlorambucil + Obinutuzumab (N = 105)
Patients receiving subsequent anticancer therapy, No. (%)	6 (5.7)	35 (33.3)
Venetoclax, No.	0	4[a]
Ibrutinib,[b] No.	2	25
Acalabrutinib, No.	0	3
Idelalisib, No.	0	1
Other, No.	4	2

[a]Includes three patients who received venetoclax + rituximab and one patient who received venetoclax monotherapy.
[b]Includes 20 patients who received subsequent single-agent ibrutinib per protocol (one patient in the ibrutinib + venetoclax arm and 19 patients in the chlorambucil + obinutuzumab arm).

TABLE A3. Second Primary Malignancies at 34.1 Months of Median Follow-Up

Category	Ibrutinib + Venetoclax (N = 106), No. (%)	Chlorambucil + Obinutuzumab (N = 105), No. (%)
Patients with at least one other malignancy	10 (9.4)	12 (11.4)
Nonmelanoma skin cancer	4 (3.8)	3 (2.9)
Basal cell carcinoma	3 (2.8)	2 (1.9)
Squamous cell carcinoma of skin	1 (0.9)	1 (1.0)
Squamous cell carcinoma	0	1 (1.0)
Melanoma skin cancer	0	2 (1.9)
Malignant melanoma	0	2 (1.9)
Non-skin cancer (malignant)	7 (6.6)	7 (6.7)
Plasma cell myeloma	2 (1.9)	0
Hepatocellular carcinoma	1 (0.9)	0
Invasive lobular breast carcinoma	1 (0.9)	0
Lung neoplasm malignant	1 (0.9)	0
Neoplasm malignant	1 (0.9)	0
T-cell lymphoma	1 (0.9)	0
Adenocarcinoma gastric	0	1 (1.0)
Lung adenocarcinoma	0	1 (1.0)
Metastases to peritoneum	0	1 (1.0)
Myelodysplastic syndrome	0	1 (1.0)
Myeloproliferative neoplasm	0	1 (1.0)
Papillary thyroid cancer	0	1 (1.0)
Prostate cancer	0	1 (1.0)
Prostate cancer metastatic	0	1 (1.0)

NOTE. Patients could experience more than one event type. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.