Fixed-duration ibrutinib–venetoclax versus chlorambucil–obinutuzumab in previously untreated chronic lymphocytic leukaemia (GLOW): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial

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Summary

Background In the GLOW study, fixed-duration ibrutinib–venetoclax showed superior progression-free survival versus chlorambucil–obinutuzumab in patients with previously untreated chronic lymphocytic leukaemia who were older or had comorbidities, or both, at a median follow up of 27·7 months. In this Article, we report updated outcomes from GLOW after a 46-month median follow-up.

Methods GLOW was a randomised, multicentre, phase 3 study done at 67 hospital centres across 14 countries. Patients aged 65 years and older or 18–64 years with previously untreated chronic lymphocytic leukaemia and a cumulative illness rating scale score of more than 6 or creatinine clearance less than 70 mL/min, or both, and an Eastern Cooperative Oncology Group performance status of 2 or less were randomly assigned (1:1) via an interactive web system with permuted blocks (block size of four) and stratified by *IGHV* mutational status and the presence of del11q aberration to the ibrutinib–venetoclax group (three cycles of ibrutinib lead-in [420 mg/day, orally], followed by 12 cycles of ibrutinib plus venetoclax [400 mg/day, orally, including a 5-week dose ramp-up]) or the chlorambucil–obinutuzumab group (six cycles of chlorambucil [0·5 mg/kg, orally, on days 1 and 15 of each cycle], and obinutuzumab [1000 mg, intravenously, on days 1 (or 100 mg on day 1 and 900 mg on day 2), 8, and 15 of cycle 1 and day 1 of cycles 2–6]). The primary endpoint was progression-free survival in the intention-to-treat population, assessed by an independent review committee. The safety population included all randomised patients who received at least one dose of the study treatment. This study is registered with ClinicalTrials.gov (NCT03462719) and the EU Clinical Trials Register (EudraCT 2017-004699-77).

Findings Between May 4, 2018, and April 5, 2019, 211 patients (122 [58%] were male and 89 [42%] were female) were randomly assigned to receive ibrutinib–venetoclax (n=106) or chlorambucil–obinutuzumab (n=105). At a median of 46 months (IQR 43–47) of follow-up, progression-free survival remained superior for the ibrutinib–venetoclax group (hazard ratio 0·214 [95% CI 0·138–0·334]; p<0·0001); 42-month progression-free survival rates were 74·6% (95% CI 65·0–82·0) for ibrutinib–venetoclax and 24·8% (16·5–34·1) for chlorambucil–obinutuzumab. Following the primary analysis, one patient in the chlorambucil–obinutuzumab group had a serious adverse event of myelodysplastic syndrome. Treatment-related deaths were reported in one patient receiving ibrutinib–venetoclax (cardiac failure, pneumonia, and sinus node dysfunction) and in one patient receiving chlorambucil–obinutuzumab (pneumonia). There were 15 deaths in the ibrutinib–venetoclax group (of which three were due to post-treatment infections) and 30 deaths in the chlorambucil–obinutuzumab group (of which 10 were due to post-treatment infections).

Interpretation After 4 years of follow-up, ibrutinib–venetoclax continues to significantly prolong progression-free survival (*vs* chemoimmunotherapy) in patients with previously untreated chronic lymphocytic leukaemia, supporting its use as a first-line option.

Funding Janssen Research & Development and Pharmacyclics.

Lancet Oncol 2023; 24: 1423–33

Published **Online** November 6, 2023 https://doi.org/10.1016/S1470-2045(23)00452-7

See **Comment** page 1294

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Introduction

BTK inhibitors have changed the treatment landscape of chronic lymphocytic leukaemia, particularly in patients with high-risk disease.[1] Ibrutinib is the most extensively studied BTK inhibitor, with up to 8 years of follow-up data in people with chronic lymphocytic leukaemia.[2] Phase 3 clinical studies of continuous treatment with ibrutinib either as a single agent or in combination with an anti-CD20 antibody have shown superior progression-free survival and overall survival rates compared with other regimens, such as chemotherapy or chemo-immunotherapy.[2–7] The BCL-2 inhibitor venetoclax in

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Research in context

Evidence before this study

We searched PubMed from inception through to April 30, 2023, using the search terms "chronic lymphocytic leukemia" and "ibrutinib" and "venetoclax" and "minimal residual disease", with no restrictions on language of publication. We found that ibrutinib and venetoclax have complementary mechanisms of action that work synergistically, and that the ibrutinib–venetoclax combination has been evaluated in the first-line setting as a fixed-duration treatment for patients with chronic lymphocytic leukaemia in phase 2 trials but not in phase 3 trials. Ibrutinib and venetoclax work together to eradicate both resting and dividing chronic lymphocytic leukaemia cells, thereby potentially enhancing the clearance of minimal residual disease (MRD). The literature showed that MRD status at the end of treatment can be predictive of survival outcomes with fixed-duration treatments, such as chemoimmunotherapy or venetoclax plus anti-CD20 combinations. However, the long-term relationship between MRD status and survival outcomes for fixed-duration ibrutinib–venetoclax had not been evaluated. GLOW was the first phase 3, randomised, open-label study to establish the efficacy and safety of fixed-duration ibrutinib–venetoclax compared with chlorambucil–obinutuzumab in patients with previously untreated chronic lymphocytic leukaemia who are older or have comorbidities, or both. It showed high progression-free survival rates with ibrutinib–venetoclax regardless of *IGHV* mutation status and sustained, undetectable MRD rates 1 year after treatment. However, longer-term follow-up for fixed-duration ibrutinib–venetoclax was needed to provide greater insight into the predictive impact of end-of-treatment MRD on the durability of progression-free survival over time, and to ascertain whether this combination could lead to a survival advantage.

Added value of this study

With 4 years of follow-up reported in this Article, we show that progression-free survival outcomes are maintained and, moreover, we now observe an overall survival advantage in patients treated with fixed-duration ibrutinib–venetoclax compared with chlorambucil–obinutuzumab. Additionally, we demonstrate the variability of MRD kinetics while pointing to the potential difference in the predictive impact of achieving undetectable MRD status between *IGHV* subgroups.

Implications of all the available evidence

The 4-year follow-up in the GLOW trial is, to our knowledge, the first fixed-duration combination to demonstrate (1) an overall survival advantage relative to chemoimmunotherapy, (2) undetectable MRD kinetics with less than 10% decline per year during follow-up, and (3) sustainable nodal responses independent of MRD status for this patient population. The fatalities observed in the chlorambucil–obinutuzumab group were driven by infections, mainly on progression before indication for next line of treatment, supporting the concern that relapse correlates with worsened immune dysfunction and emphasising the need for further supportive measures to reduce infectious risk for relpased or refractory disease. This study also further improves our understanding of the potential relevance of MRD kinetics on outcomes for different molecular subgroups: achieving undetectable MRD in the unmutated *IGHV* subgroup was important for achieving high progression-free survival rates 2 years after treatment, whereas MRD status was less important for achieving high rates in the mutated *IGHV* subgroup. Further research into the predictive value of achieving undetectable MRD at the end of treatment is needed to fully inform the use of this marker in clinical decision making across patient groups. Finally, these data inform clinical practice as the outcomes observed at this 4-year timepoint warrant the consideration of the ibrutinib–venetoclax combination as an all-oral, chemotherapy-free, fixed-duration treatment option for patients with previously untreated chronic lymphocytic leukaemia who are older or have comorbidities, or both.

combination with obinutuzumab was the first non-chemotherapy-based, fixed-duration treatment for previously untreated patients with chronic lymphocytic leukaemia and improved long-term progression-free survival and minimal residual disease (MRD) clearance.[8] Disadvantages of anti-CD20 antibodies include short-term side-effects, such as infusion-related reactions, and long-term side-effects, such as B-cell depletion.[9]

Ibrutinib and venetoclax have complementary mechanisms of action that work synergistically.[10,11] Ibrutinib mobilises chronic lymphocytic leukaemia cells out of lymphoid compartments, and the combination eradicates both resting and dividing subpopulations, leading to deep remissions.[10,12,13] Ibrutinib–venetoclax combination has been widely studied in the phase 2 setting and shows deep, durable responses and improvements in progression-free survival, including in patients with high-risk disease features.[13–16] As the first all-oral, chemotherapy-free, fixed-duration treatment option, ibrutinib–venetoclax has the potential to provide a highly potent and infusion-free fixed-duration alternative for patients with chronic lymphocytic leukaemia.[13–15]

GLOW is a phase 3, randomised, open-label study conducted to establish the efficacy and safety of fixed-duration ibrutinib–venetoclax compared with chlorambucil–obinutuzumab, as a standard first-line treatment at the time of study initiation,[17] in patients with previously untreated chronic lymphocytic leukaemia who are older or have comorbidities, or both.[18] Previous analyses from GLOW demonstrated high progression-free survival rates with ibrutinib–venetoclax regardless of *IGHV* mutation status and sustained undetectable MRD 1 year after treatment, but so far, no clear correlation was observed between MRD status 3 months after the end of

the treatment and progression-free survival.[19] Longer-term follow-up for fixed-duration ibrutinib–venetoclax is needed to provide greater insight into the predictive impact of MRD at the end of treatment on progression-free survival outcomes for different molecular subgroups to inform clinical decision making. In this Article, we report clinical outcomes and MRD kinetics from GLOW after a median follow-up of 46 months, with a focus on outcomes in *IGHV* subgroups. Additionally, we report details on overall survival events that occurred during the longer-term follow-up.

Methods

Study design and participants

GLOW is a randomised, multicentre, phase 3 study in patients with previously untreated chronic lymphocytic leukaemia requiring treatment per criteria from the International Workshop on Chronic Lymphocytic Leukemia. The study was conducted at 67 hospital centres across 14 countries (appendix pp 2–4). To be eligible, participants had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less and be either aged 65 years and older or 18–64 years with comorbidities on the basis of a cumulative illness rating scale (CIRS) score of more than 6 or a creatinine clearance of less than 70 mL/min (using the Cockcroft–Gault equation), or both.[18] Patients with del17p mutation or known *TP53* mutations at baseline were excluded from the study; however, *TP53* mutational status was subsequently assessed centrally for all randomly assigned patients using next-generation sequencing (variable allele frequency cutoff was 5%), and these patients with mutated *TP53* were included in efficacy and safety analyses. To adopt insights from the relevant phase 2 CAPTIVATE study,[12] the original protocol was amended on Jan 22, 2019 to remove the last three cycles of ibrutinib monotherapy. The study was approved by the ethical review boards of all participating sites. All patients provided written informed consent.

Randomisation and masking

Patient were randomly assigned (1:1) to either the ibrutinib–venetoclax group or the chlorambucil–obinutuzumab group; treatment randomisation was generated via an interactive web system by using permuted blocks with a block size of four and was stratified by *IGHV*-mutation status (mutated *vs* unmutated *vs* not available) and the presence of del11q aberration (yes *vs* no). Neither investigators nor patients were masked to treatment allocation. The independent review committee was masked to treatment assignment. No aggregated analyses were done by the study sponsor until the time of primary analysis.

Procedures

Patients in the ibrutinib–venetoclax group received ibrutinib (420 mg daily given orally as lead-in for three cycles) plus venetoclax orally (ramp-up starting at cycle 4 over the first 5 weeks from 20–400 mg daily) for 12 cycles of combination therapy. Patients in the chlorambucil–obinutuzumab group received chlorambucil (0·5 mg/kg bodyweight on days 1 and 15 of each cycle) orally plus obinutuzumab (1000 mg on days 1 [or 100 mg on day 1 and 900 mg on day 2], 8, and 15 of cycle 1 and day 1 of cycles 2–6) intravenously for six cycles. Each cycle was 28 days. Dose modifications of ibrutinib, venetoclax, and chlorambucil were allowed for the management of adverse events. Patients were withdrawn from the study in the case of consent withdrawal or loss to follow-up. CT or MRI scans were performed at baseline, at weeks 12, 36, 60, and 72, then every 16 weeks through to week 152, then every 24 weeks thereafter until disease progression or death, whichever occurred first. CT scans were reviewed by an independent review committee to assess response and disease progression on the basis of the International Workshop on Chronic Lymphocytic Leukemia 2008 criteria. *IGHV*-mutation status was determined by Sanger Sequencing (Navigate, Biopharma, Carlsbad, CA, USA). A retrospective reclassification was conducted using the clonoSEQ assay (Adaptive Biotechnologies, Seattle, WA, USA) and all *IGHV* results in this Article are based on the clonoSEQ classification. Del11q aberration was assessed using the Kreatech chronic lymphocytic leukaemia FISH probes (LabCorp Center for Molecular Biology and Pathology, Durham, NC, USA). Peripheral blood samples were collected at each disease evaluation (every 12 weeks until week 72, every 16 weeks until week 152, and every 24 weeks thereafter as detailed in the protocol) and bone marrow samples at 36 and 72 weeks after randomisation for all patients with partial response or better for evaluation of MRD status. MRD was assessed by next-generation sequencing via the clonoSEQ assay and by an eight-colour flow cytometric assay (Navigate, Biopharma, Carlsbad, CA, USA). Undetectable MRD was defined as less than one chronic lymphocytic leukaemia cell per 10 000 leukocytes ($<10^{-4}$); patients with one or more chronic lymphocytic leukaemia cells per 10 000 leukocytes ($\geq 10^{-4}$) were considered to have detectable MRD.[20] Safety evaluations, including adverse event monitoring by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and laboratory tests, were performed from screening throughout treatment until 30 days after the last dose of study treatment or start of subsequent antileukaemic therapy as described in the protocol, whichever occurred first.

See Online for appendix

Outcomes

The primary endpoint was independent review committee-assessed progression-free survival, defined as the time from randomisation to disease progression or death from any cause, whichever occurred first. Secondary endpoints included MRD negativity rate (ie, the proportion of patients who had undetectable MRD in bone marrow), complete response rate (ie, the proportion

of patients who achieved complete response or complete response with incomplete bone marrow recovery), overall response rate (ie, the proportion of patients who achieved complete response, complete response with incomplete bone marrow recovery, or partial response), overall survival (ie, the time from randomisation to death from any cause), duration of complete response (ie, the time from initial complete response or complete response with incomplete bone marrow recovery to disease progression or death from any cause, whichever occurred first), time to next treatment (ie, the time from randomisation to the start of any subsequent anticancer therapy), and safety. For this follow-up analysis, key primary and secondary efficacy outcomes are reported.

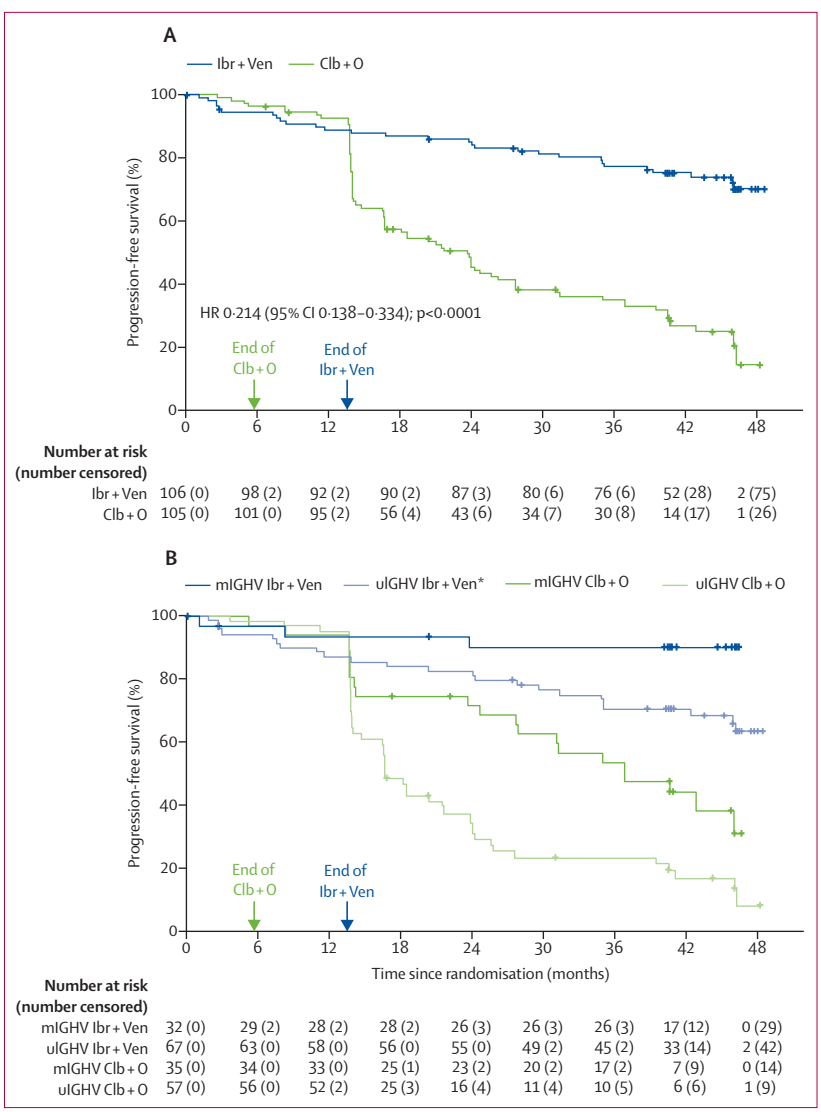


Figure 1: **Independent review committee-assessed progression-free survival**
(A) Progression-free survival for all patients. (B) Progression-free survival by *IGHV* mutational status. Clb + O=chlorambucil–obinutuzumab. HR=hazard ratio. Ibr + Ven=ibrutinib–venetoclax. mIGHV=mutated *IGHV*. uIGHV=unmutated *IGHV*. *The progression-free survival curve for patients with uIGHV in the ibrutinib–venetoclax group reflects six of seven on-treatment deaths before disease progression.

Patient-reported health status and fatigue, haematological improvement, and trough levels of ibrutinib–venetoclax are not being reported here.

Statistical analysis

Efficacy assessments were analysed in the intention-to-treat population. The safety population included all randomised patients who received at least one dose of the study treatment. To show superiority at an alternate hazard ratio (HR) of 0·5 (ibrutinib–venetoclax *vs* chlorambucil–obinutuzumab) with approximately 80% power at a two-sided significance level of 0·05, 71 events (progression or death) were needed (reported previously as the primary analysis).[18] The sample size was set to 200 to observe the number of events in a reasonable timeframe on the basis of a median progression-free survival of 27 months for the chlorambucil–obinutuzumab group.

For progression-free survival, overall survival, and time to next treatment, the Kaplan–Meier method was used to estimate the distribution of the endpoint for each treatment group. The treatment comparison was based on a log-rank test stratified by *IGHV* and del11q status. The HR and its 95% CI was estimated using a stratified Cox proportional-hazards model. The assumption of proportional hazards was not verified as it was not prespecified in the analysis plan. A sensitivity analysis of overall survival censoring death due to COVID-19 was preplanned and used the same methods as described above. For the post-hoc subgroup analyses of progression-free survival by *IGHV*-mutation status within each treatment group and time to next treatment by *IGHV*-mutation status, an unstratified log-rank test and Cox regression model were used. A post-hoc sensitivity analysis that censored for treatment-emergent pre-progression deaths in progression-free survival by *IGHV*-mutation status within the ibrutinib–venetoclax group was also conducted. Correlation between post-treatment progression-free survival (defined as the time from end of treatment to disease progression or death, whichever occurred first) and MRD status at 3 months after the end of treatment, overall and by *IGHV*-mutation status, was assessed post hoc. Kaplan-Meier method was used to estimate the progression-free survival rates 2 years after the end of treatment. Univariable and multivariable analyses to assess potential risk factors for progression-free survival and overall survival (post-hoc) were conducted using the Cox proportional-hazards model.

Overall response rate, complete response rate, and undetectable MRD rate were summarised using the number and percentage of patients with corresponding 95% CIs based on the Clopper–Pearson method. The treatment comparison was done using the Cochran–Mantel–Haenszel test stratified by *IGHV* and del11q status. Duration of complete response was summarised with the Kaplan–Meier method. Analyses of MRD rates

at different timepoints overall and by *IGHV*-mutation status to show MRD kinetics were done post hoc, and descriptive statistics were provided. Lymph node clearance by *IGHV* and MRD status were also analysed post hoc.

The analyses at the 46-month follow-up were not preplanned; hence all p values reported are nominal. We did not adjust for multiplicity and all tests were conducted at a two-sided alpha level of 0·05. All statistical analyses were done using SAS, version 9.4, and R, version 4.2.1. The trial is registered with ClinicalTrials.gov, NCT03462719, and the EU Clinical Trials Register, EudraCT 2017-004699-77.

Role of the funding source

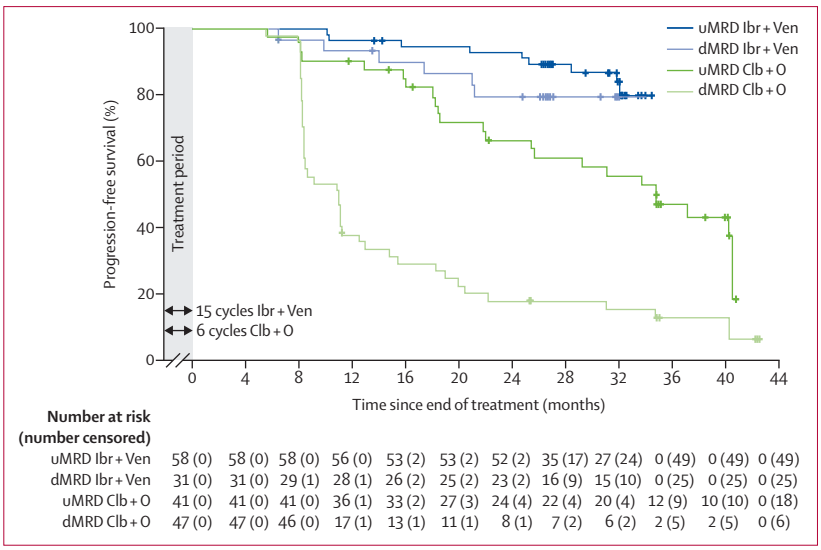
The study was sponsored and designed by Janssen Research & Development, with input from investigators. Data were collected by investigators under the oversight of an independent data monitoring committee and were confirmed and analysed by the sponsor. The Article was written on the basis of author guidance with the assistance of a medical writer supported by the sponsor. Data analysis and interpretation was conducted by sponsor and non-sponsor co-authors.

Results

Between May 4, 2018 and April 5, 2019, 211 patients were randomised and included in the intention-to-treat and safety analyses; 106 patients received ibrutinib–venetoclax and 105 received chlorambucil–obinutuzumab. 122 participants (58%) were male and 89 (42%) were female. Baseline disease characteristics, as previously reported,[18] and reclassified *IGHV* mutational status are shown in the appendix (p 5).

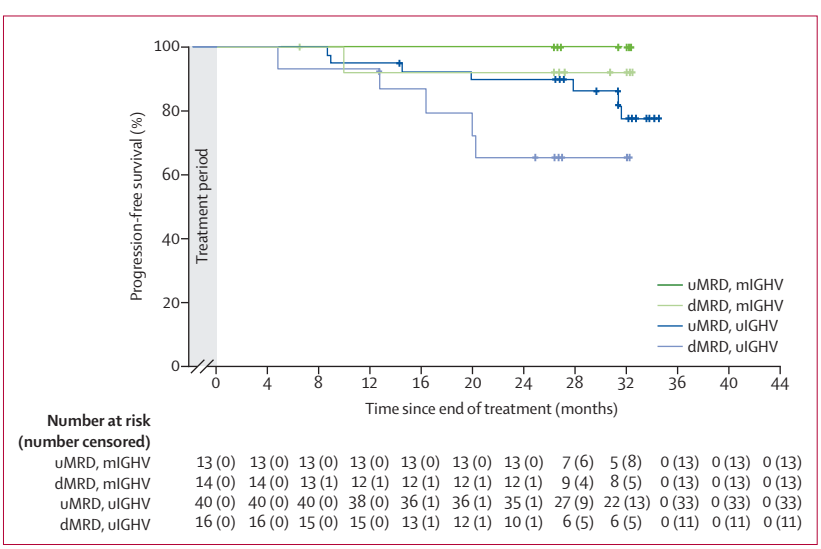
With a median follow-up of 46 months (IQR 43–47), independent review committee-assessed progression-free survival remained superior for the ibrutinib–venetoclax group (29 events) compared with the chlorambucil–obinutuzumab group (78 events; HR 0·214 [95% CI 0·138–0·334]; p<0·0001; figure 1A). Median progression free survival was not reached for ibrutinib–venetoclax and was 21·7 months (95% CI 16·7–26·1) for chlorambucil–obinutuzumab. The estimated 42-month progression-free survival rate was 74·6% (95% CI 65·0–82·0) for ibrutinib–venetoclax and 24·8% (95% CI 16·5–34·1) for chlorambucil–obinutuzumab.

When assessing progression-free survival per *IGHV* mutation status, 42-month rates in the ibrutinib–venetoclax group were 69·8% (95% CI 57·2–79·4; 23 events) in patients with unmutated *IGHV* compared with 90·0% (72·0–96·7; three events) in patients with mutated *IGHV* (HR 3·775 [95% CI 1·133–12·576]; p=0·031; figure 1B; appendix p 6). In univariable and multivariable analyses, *IGHV* status (unmutated and mutated) conferred a significant difference with respect to progression-free survival in the ibrutinib–venetoclax group (appendix p 6). Of note, six of seven treatment-emergent pre-progression deaths in the ibrutinib–venetoclax group occurred in patients with unmutated *IGHV*. In a sensitivity analysis censoring for treatment-emergent pre-progression deaths, there was no significant association with progression-free survival for patients with unmutated *IGHV* (HR 2·806 [95% CI



Number at risk (number censored)												
uMRD Ibr + Ven	58 (0)	58 (0)	58 (0)	56 (0)	53 (2)	53 (2)	52 (2)	35 (17)	27 (24)	0 (49)	0 (49)	0 (49)
dMRD Ibr + Ven	31 (0)	31 (0)	29 (1)	28 (1)	26 (2)	25 (2)	23 (2)	16 (9)	15 (10)	0 (25)	0 (25)	0 (25)
uMRD Clb + O	41 (0)	41 (0)	41 (0)	36 (1)	33 (2)	27 (3)	24 (4)	22 (4)	20 (4)	12 (9)	10 (10)	0 (18)
dMRD Clb + O	47 (0)	47 (0)	46 (0)	17 (1)	13 (1)	11 (1)	8 (1)	7 (2)	6 (2)	2 (5)	2 (5)	0 (6)

Figure 2: **Progression-free survival by minimal residual disease status**
Progression-free survival is shown from the end of treatment. MRD status was evaluated in peripheral blood 3 months after the end of treatment. uMRD was defined as <1 CLL cell per 10 000 leukocytes (<10^{-4}); patients with ≥1 CLL cell per 10 000 leukocytes (≥10^{-4}) were considered to have dMRD. Clb + O=chlorambucil–obinutuzumab. CLL=chronic lymphocytic leukaemia. dMRD=detectable MRD. Ibr + Ven=ibrutinib–venetoclax. MRD=minimal residual disease. uMRD=undetectable MRD.



Number at risk (number censored)												
uMRD, mIGHV	13 (0)	13 (0)	13 (0)	13 (0)	13 (0)	13 (0)	13 (0)	7 (6)	5 (8)	0 (13)	0 (13)	0 (13)
dMRD, mIGHV	14 (0)	14 (0)	13 (1)	12 (1)	12 (1)	12 (1)	12 (1)	9 (4)	8 (5)	0 (13)	0 (13)	0 (13)
uMRD, uIGHV	40 (0)	40 (0)	40 (0)	38 (0)	36 (1)	36 (1)	35 (1)	27 (9)	22 (13)	0 (33)	0 (33)	0 (33)
dMRD, uIGHV	16 (0)	16 (0)	15 (0)	15 (0)	13 (1)	12 (1)	10 (1)	6 (5)	6 (5)	0 (11)	0 (11)	0 (11)

Figure 3: **Progression-free survival by minimal residual disease and *IGHV*-mutation status for patients in the ibrutinib–venetoclax group**
Progression-free survival is shown from the end of treatment. MRD status was evaluated in peripheral blood 3 months after the end of treatment. uMRD was defined as <1 CLL cell per 10 000 leukocytes (<10^{-4}); patients with ≥1 CLL cell per 10 000 leukocytes (≥10^{-4}) were considered to have dMRD. CLL=chronic lymphocytic leukaemia. dMRD=detectable MRD. mIGHV=mutated *IGHV*. MRD=minimal residual disease. uIGHV=unmutated *IGHV*. uMRD=undetectable MRD.

0·822–9·578]; p=0·085). This analysis was done in the ibrutinib–venetoclax group only. In the chlorambucil–obinutuzumab group, 42-month progression-free survival rates were 15·0% (95% CI 6·7–26·4; 47 events) in unmutated *IGHV* versus 43·1% (26·1–59·0; 21 events) in mutated *IGHV* subgroups (HR 2·172 [95% CI 1·289–3·660; p=0·0036; figure 1B, appendix p 7) *IGHV* status (unmutated and mutated) conferred a significant difference in progression-free survival in the chlorambucil–obinutuzumab group in both univariable and multivariable analyses (appendix p 7).

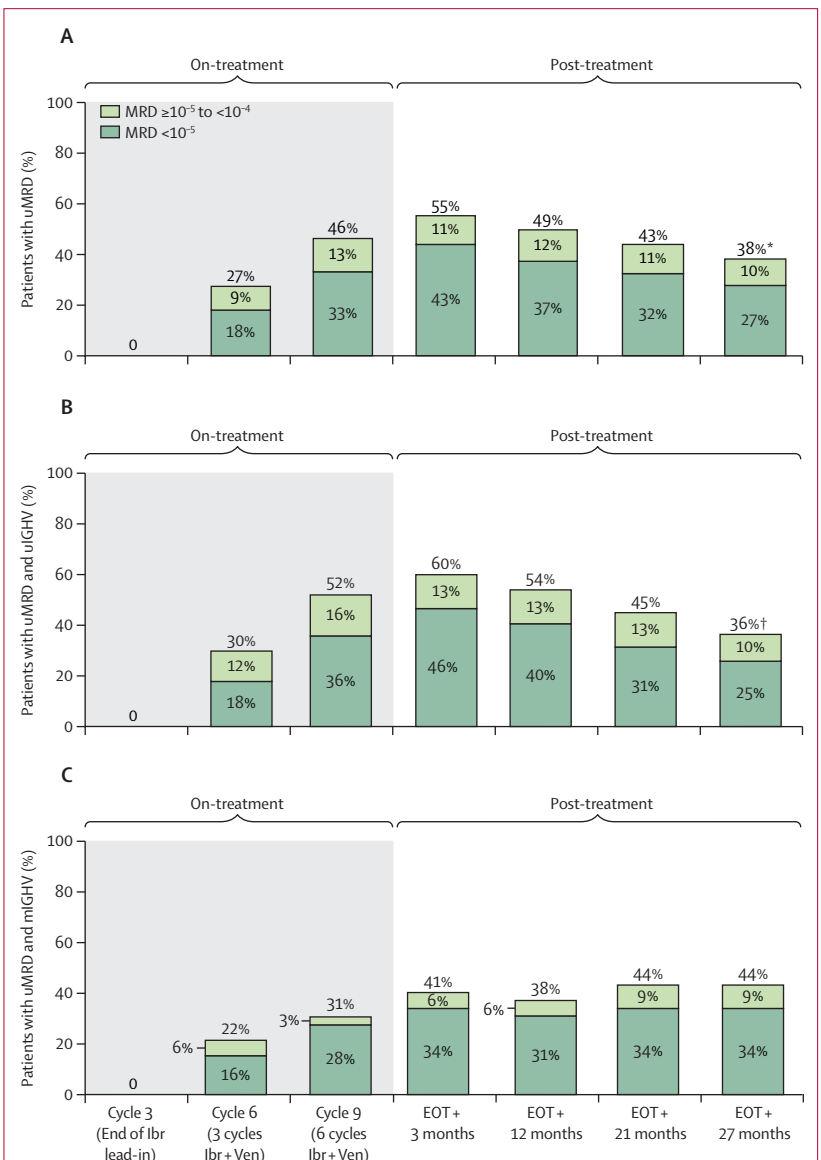


Figure 4: **Undetectable minimal residual disease dynamics for the ibrutinib–venetoclax group**
(A) uMRD rates in all patients (n=106). (B) uMRD rates in patients with uIGHV (n=67). (C) uMRD rates in patients with mIGHV (n=32). Numbers might not add up to exact total due to rounding. EOT=end of treatment. Ibr=ibrutinib. Ibr+Ven=ibrutinib–venetoclax. mIGHV=mutated *IGHV*. MRD=minimal residual disease. uIGHV=unmutated *IGHV*. uMRD=undetectable MRD. *Eight (8%) of 106 patients with uMRD (including six with uMRD <10^{-5}) at EOT + 21 months had missing samples and were considered not uMRD at EOT + 27 months. †Seven (10%) of 67 patients with uMRD (including five with uMRD <10^{-5}) at EOT + 21 months had missing samples and were considered not uMRD at EOT + 27 months.

Progression-free survival rates 2 years after ibrutinib–venetoclax treatment were 93·0% (95% CI 82·4–97·3; nine events) in 58 patients with undetectable MRD and 79·6% (60·1–90·3; six events) in 31 patients with detectable MRD 3 months after the end of treatment, for patients who had a post-treatment disease evaluation visit (n=89; figure 2). In the chlorambucil–obinutuzumab group, progression-free survival rates 2 years after treatment were 66·6% (49·4–79·1; 23 events) in 41 patients with undetectable MRD and 18·0% (8·5–30·3; 41 events) in 47 patients with detectable MRD 3 months after the end of treatment.

In patients with a post-treatment disease evaluation visit who received ibrutinib–venetoclax, and had mutated *IGHV*, progression-free survival rates 2 years after treatment were 92·3% (56·6–98·9; one event) for 14 patients with detectable MRD and 100% (100–100; no events) for 13 patients with undetectable MRD 3 months after the end of treatment. Among patients with unmutated *IGHV*, progression-free survival rates 2 years after treatment were 67·0% (37·9–84·7; five events) for 16 patients with detectable MRD and 89·9% (75·2–96·1; seven events) for 40 patients with undetectable MRD 3 months after the end of treatment (figure 3).

47 (81%) of 58 patients who achieved undetectable MRD (<10^{-4}) in peripheral blood 3 months after the end of treatment in the ibrutinib–venetoclax group had done so by cycle 9 (six cycles of ibrutinib–venetoclax combination; figure 4A). Post-treatment, undetectable MRD rates in the ibrutinib–venetoclax group were maintained in the majority of these patients, from 58 (55%) of 106 participants 3 months after the end of treatment to 40 (38%) of 106 participants 27 months after the end of treatment (a decrease in overall undetectable MRD rate of 18 [17%] of 106 participants during the 2-year post-treatment period). Among the 40 patients with undetectable MRD (<10^{-4}) in the ibrutinib–venetoclax group 27 months after the end of treatment, 29 (73%) achieved deeper responses of undetectable MRD (<10^{-5}) at this timepoint (figure 4A).

In a post-hoc analysis investigating MRD levels in the ibrutinib–venetoclax group by *IGHV*-mutation status, by cycle 9, undetectable MRD rates were found in 35 (52%) of 67 participants in the unmutated *IGHV* subgroup (figure 4B) and ten (31%) of 32 in the mutated *IGHV* subgroup (figure 4C). During the period from 3 months to 27 months after the end of treatment, undetectable MRD rates in the unmutated *IGHV* subgroup declined from 40 (60%) of 67 participants to 24 (36%), whereas undetectable MRD rates in the mutated *IGHV* subgroup remained relatively stable, from 13 (41%) of 32 participants to 14 (44%). Five of seven patients with mutated *TP53* had undetectable MRD 3 months after the end of treatment, and three of five sustained undetectable MRD status through to 27 months after the end of treatment. The

independent review committee-assessed complete response or complete response with incomplete bone marrow recovery rate was 45 (43% [95% CI 33–52]) of 106 in the ibrutinib–venetoclax group and 13 (12% [6–19]) of 105 in the chlorambucil–obinutuzumab group with a 36-month duration of complete response or complete response with incomplete bone marrow recovery estimate at 93% (95% CI 79–98) versus 60% (23–84), respectively.

For patients treated with ibrutinib–venetoclax, lymph node clearance was well maintained throughout the 46-month median follow-up (IQR 43–47), regardless of *IGHV* mutational status or MRD status in peripheral blood 3 months after the end of treatment (appendix p 17). By contrast, for patients treated with chlorambucil–obinutuzumab, lymph node clearance was not maintained as well, especially for patients with unmutated *IGHV* compared with mutated *IGHV* or detectable MRD versus undetectable MRD at 3 months after the end of treatment (appendix p 18).

At the 46-month median follow-up, median time to next treatment was not reached in both treatment groups. Among patients receiving first-line ibrutinib–venetoclax, eight (8%) of 106 required second-line treatment, compared with 41 (39%) of 105 among the chlorambucil–obinutuzumab-treated patients (HR 0·155 [95% CI 0·072–0·333]; p<0·0001; figure 5A; appendix p 8). Among patients who received subsequent therapy in the chlorambucil–obinutuzumab group, 39 (37%) of 105 received either a BTK inhibitor or venetoclax. Per protocol, three (3%) of 106 patients in the ibrutinib–venetoclax group and 23 (22%) of 105 patients in the chlorambucil–obinutuzumab group initiated subsequent single-agent ibrutinib. For the three patients in the ibrutinib–venetoclax group, one patient had a complete response, one patient had a partial response, and one patient had a partial response with lymphocytosis as the best response (appendix p 8). Most patients in the ibrutinib–venetoclax group had not initiated subsequent therapy at 3·5 years, regardless of *IGHV*-mutation status (61 [91%] of 67 patients with unmutated *IGHV* and 30 [94%] of 32 patients with mutated *IGHV* who did not require the next line of therapy), whereas 25 (44%) of 57 patients with unmutated *IGHV* and 33 (94%) of 35 patients with mutated *IGHV* in the chlorambucil–obinutuzumab group had not initiated subsequent therapy at 3·5 years (figure 5B; appendix p 9).

At the 46-month median follow-up, the ibrutinib–venetoclax group demonstrated an overall survival advantage compared with the chlorambucil–obinutuzumab group with an HR of 0·487 (95% CI 0·262–0·907; p=0·021; figure 6). The estimated 42-month overall survival rate was 87·5% (95% CI 79·4–92·5) for patients in the ibrutinib–venetoclax group and 77·6% (68·2–84·5) for patients in the chlorambucil–obinutuzumab group. There were twice as many deaths in the chlorambucil–obinutuzumab group (30 [29%] of 105) than in the ibrutinib–venetoclax group (15 [14%] of 106; appendix pp 10, 19). In the ibrutinib–venetoclax group, one death was due to progression and seven were from treatment-emergent adverse events, including one that was assessed as treatment-related by the investigator (adverse events: cardiac failure, pneumonia, and sinus node dysfunction). Of the other seven deaths, six occurred in patients in remission and one occurred during subsequent therapy. In the chlorambucil–obinutuzumab group, one death was due to progressive disease and two were from treatment-emergent adverse events, including one that was assessed as treatment-related by the investigator (adverse event: pneumonia). Of the other 27 deaths, six occurred in patients in remission, 13 occurred after disease progression but before start of subsequent therapy, and eight occurred during subsequent therapy (appendix p 19). Infection-related

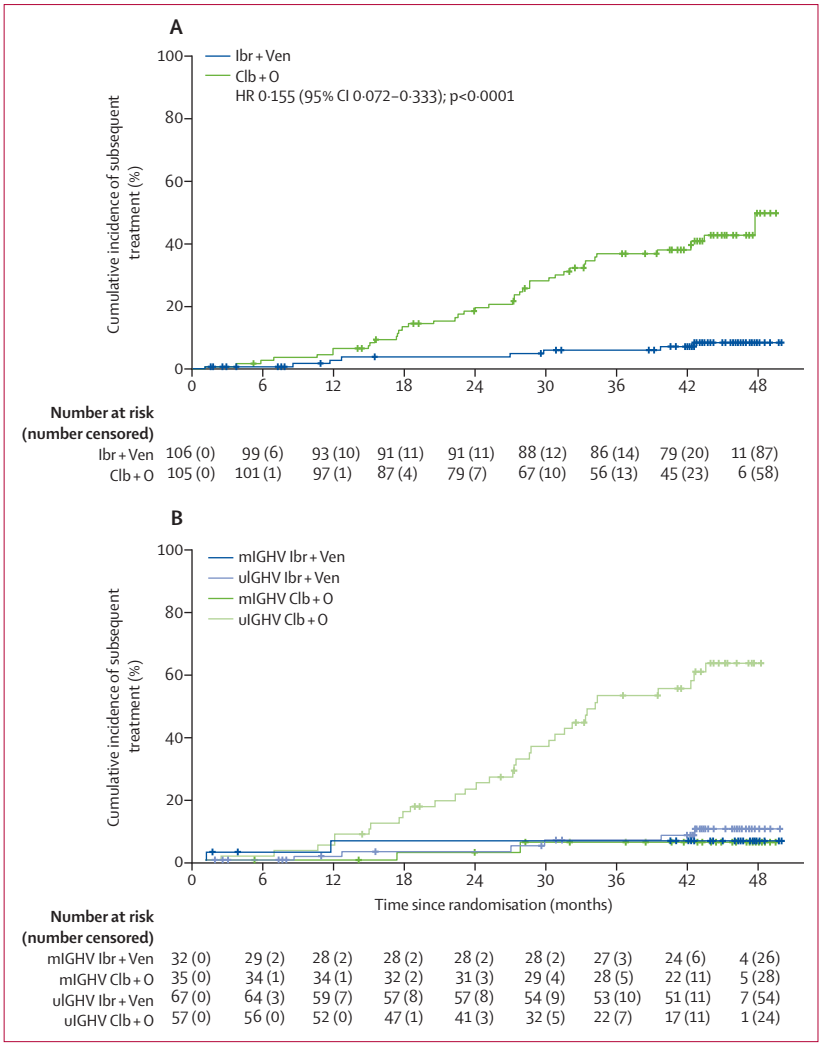


***Figure 5*: Time to next treatment**
(A) Time to next treatment for all patients. (B) Time to next treatment by *IGHV* status. Patients were censored at death. Clb + O=chlorambucil–obinutuzumab. HR=hazard ratio. Ibr + Ven=ibrutinib–venetoclax. mIGHV=mutated *IGHV*. uIGHV=unmutated *IGHV*.

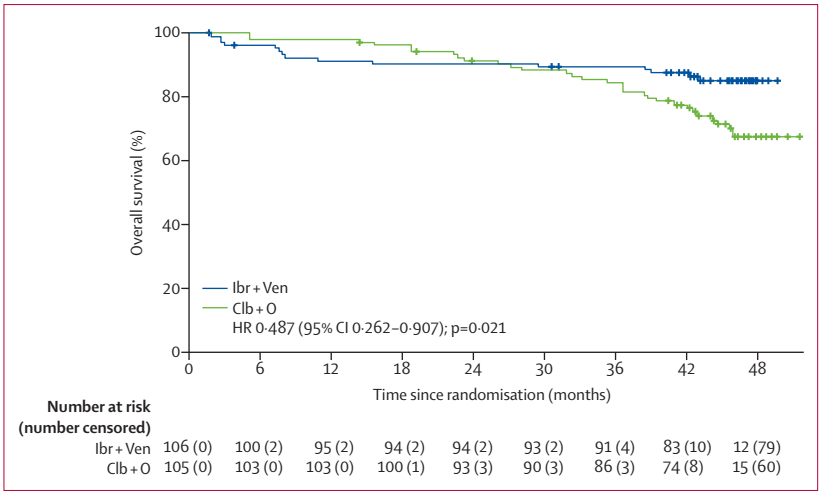


Figure 6: **Overall survival**
Clb + O=chlorambucil–obinutuzumab. HR=hazard ratio. Ibr + Ven=ibrutinib–venetoclax.

deaths were more common in the chlorambucil–obinutuzumab group (n=11, six COVID-19-related) than in the ibrutinib–venetoclax group (n=4, two COVID-19-related), with all post-treatment infection-related deaths for the chlorambucil–obinutuzumab group occurring at least 12 months after the last dose of study treatment (appendix p 10–11). In the ibrutinib–venetoclax group, three post-treatment infection-related deaths were noted, two of which occurred at least 12 months after the last dose (appendix p 11). In a sensitivity analysis censoring patients who died due to COVID-19 (post-censoring 13 events in the ibrutinib–venetoclax group and 24 events in the chlorambucil–obinutuzumab group), the HR for overall survival was 0·527 (95% CI 0·268–1·035; p=0·058). Notably, 11 (73%) of 15 patients in the ibrutinib–venetoclax group and ten (33%) of 30 patients in the chlorambucil–obinutuzumab group who died either during or after the randomised treatment had a CIRS score of 10 or higher or an ECOG performance status of 2, or both (appendix p 12). In univariable and multivariable analyses, no risk factors related to baseline disease characteristics were identified for overall survival for ibrutinib–venetoclax or chlorambucil–obinutuzumab (appendix pp 13–14).

All patients were off treatment and past the treatment-emergent adverse event period at the time of primary analysis and the only notable safety observation since then (appendix p 15) is the report of one patient from the chlorambucil–obinutuzumab group who developed a serious adverse event of myelodysplastic syndrome/myeloproliferative neoplasm. Seven additional patients were reported to have developed a non-treatment-emergent secondary malignancy. Overall, 11 (10%) of 106 patients in the ibrutinib–venetoclax group and 14 (13%) of 105 patients in the chlorambucil–obinutuzumab group developed a secondary malignancy with longer-term follow-up (appendix p 16).

Discussion

This 4-year follow-up of the GLOW trial showed that fixed-duration ibrutinib–venetoclax treatment significantly extends progression-free survival compared with chlorambucil–obinutuzumab, while also demonstrating overall survival advantage. The significant improvements in progression-free survival in the ibrutinib–venetoclax group compared with the chlorambucil–obinutuzumab group in previous analyses[18,19] were maintained through a median of 46 months of follow-up; at 3·5 years, progression-free survival was 74·6% (95% CI 65·0–82·0) for ibrutinib–venetoclax and 24·8% (16·5–34·1) for chlorambucil–obinutuzumab. For patients treated with ibrutinib-venetoclax with mutated *IGHV*, whether with undetectable or detectable MRD at end of treatment, and for patients with unmutated *IGHV* and undetectable MRD at end of treatment, the progression-free survival rate 2 years after the end of treatment was more than 90%, compared with 67% at this timepoint for patients with detectable MRD and unmutated *IGHV*. The predictive value of MRD on long-term progression-free survival outcomes is less definitive with ibrutinib–venetoclax treatment than with regimens containing anti-CD20 antibodies and differs between patients with unmutated and mutated *IGHV* chronic lymphocytic leukaemia. This study suggests that attainment of undetectable MRD status with ibrutinib–venetoclax is less predictive for progression-free survival maintenance post-treatment in patients of chronic lymphocytic leukaemia with mutated *IGHV*. Similar to outcomes reported for fixed-duration venetoclax–obinutuzumab, and in contrast to outcomes reported with continuous ibrutinib, our study shows that progression-free survival with fixed-duration ibrutinib–venetoclax was less robust in patients with unmutated *IGHV* than in patients with mutated *IGHV*. However, patients with unmutated *IGHV* who achieved undetectable MRD 3 months after the end of treatment with ibrutinib–venetoclax in GLOW, which was the majority of unmutated *IGHV* patients, also achieved a progression-free survival rate similar to that in patients with mutated *IGHV*. This finding suggests that attainment of deep responses might be more critical for patients with more aggressive disease, such as those with unmutated *IGHV*, in the context of fixed-duration treatments. Several studies, including GLOW, have shown that ibrutinib–venetoclax preferentially drives deeper MRD responses in patients with unmutated *IGHV* than in patients with mutated *IGHV*, suggesting that most patients treated with this regimen can benefit from an extended treatment-free remission. For patients with unmutated *IGHV* who did not achieve undetectable MRD 3 months after the end of treatment, progression-free survival was shorter than for patients who achieved a deeper response. For these patients, additional studies are needed to define treatment strategies that can further improve outcomes. One such study is the phase 3 FLAIR study, evaluating an MRD-guided treatment strategy with ibrutinib–venetoclax.[21]

Another is the HOVON 158 study, evaluating an additional 6 months of obinutuzumab–ibrutinib for patients with detectable MRD upon ibrutinib–venetoclax treatment.[22]

Ibrutinib–venetoclax maintained MRD clearance in the majority of patients through 2 years post-treatment with a 17 percentage-point decline from 3 months to 27 months after the end of treatment. Treatment with venetoclax–obinutuzumab in the CLL14 study resulted in undetectable MRD ($<10^{-4}$) rates of 26·9% through to 29 months after the end of treatment, with a decline of 47·6 percentage points from 74·5% at 3 months after the end of treatment.[8] Although MRD clearance was better maintained after treatment for patients with mutated *IGHV*, on-treatment MRD clearance was more frequent and faster in patients with unmutated *IGHV*. As such, MRD kinetics varied for different molecular subgroups. The results pertaining to MRD clearance are consistent with previous reports of ibrutinib–venetoclax eradicating both resting and dividing chronic lymphocytic leukaemia cells, thereby enhancing the clearance of MRD and depth of response.[10,12,13,16,18] Analyses for predictive factors for achieving undetectable MRD with ibrutinib–venetoclax are currently being performed. We acknowledge the value of these analyses and plan to present the results in a future publication.

Longer-term follow-up of GLOW demonstrated that ibrutinib–venetoclax treatment reduced the need for subsequent antileukaemic therapy compared with chemoimmunotherapy. Eight patients in the ibrutinib–venetoclax group received subsequent therapy. Of these, three patients received single-agent ibrutinib as a second-line therapy as part of the study; these patients had a best response of partial response, partial response with lymphocytosis, and complete response. In the CAPTIVATE study, which evaluated fixed-duration ibrutinib–venetoclax in patients with chronic lymphocytic leukaemia aged 70 years or younger in the first-line setting, 12 patients were retreated with single-agent ibrutinib and nine achieved at least a partial response.[23] Furthermore, the CAPTIVATE study showed that patients who progressed after ibrutinib–venetoclax (n=13) did not have evidence of known treatment-emergent BTK or BCL-2 mutations associated with resistance.[15] Although the numbers were small, these results indicate that the use of fixed-duration ibrutinib–venetoclax to treat patients with chronic lymphocytic leukaemia in the first line preserves the ability to use single-agent ibrutinib or venetoclax-based regimens after relapse in patients who might require retreatment.

With about 4 years of follow-up in GLOW, ibrutinib–venetoclax is, to our knowledge, the first fixed-duration treatment to achieve an overall survival advantage versus chemoimmunotherapy. During treatment, two deaths were observed in the chlorambucil–obinutuzumab group and seven deaths in the ibrutinib–venetoclax group. As described previously,[18] three of the seven deaths in the ibrutinib–venetoclax group were due to lung infection, metastatic carcinoma, and non-embolic ischaemic stroke. Of the remaining four cardiac or sudden deaths on treatment, which were probably related to the known cardiac toxicity of BTK inhibitors, all patients had a CIRS score of 10 or higher or an ECOG performance status of 2, or both, suggesting the risk of these events might have been increased due to substantial comorbidities. Similarly, for the non-treatment-emergent deaths during follow-up in the ibrutinib–venetoclax group, most patients were severely comorbid at baseline (five of eight patients had a CIRS score >10 or an ECOG performance status of 2), and most patients (six of eight) remained in response (ie, with no progressive disease) to ibrutinib–venetoclax at the time of death. By contrast, in the chlorambucil–obinutuzumab group, most events occurred in patients who had progressed after chlorambucil–obinutuzumab treatment (22 of 28 patients). Although there was no clear pattern for off-treatment deaths in the ibrutinib–venetoclax group, the most common cause of death for patients treated with chlorambucil–obinutuzumab were infection-related events (ten of 28 events), occurring at least 12 months after the end of treatment and after disease progression, with five of ten patients with fatal infections having initiated subsequent therapy. Six infection-related deaths in the chlorambucil–obinutuzumab group were due to COVID-19, compared with two fatal COVID-19 infections in the ibrutinib–venetoclax group, all occurring before COVID-19 vaccines became globally available. Although the total number of fatal COVID-19 infections in the chlorambucil–obinutuzumab group might have contributed to a lower overall survival than that observed for chlorambucil–obinutuzumab in previous trials,[8,24,25] the overall survival benefit for ibrutinib–venetoclax was sustained in the sensitivity analyses that censored patients who died due to COVID-19. Furthermore, an increased risk of fatal COVID-19 infection in the chlorambucil–obinutuzumab group during follow-up could be due to the treatment and the leukaemia itself, which might be reflective of the general risk of fatal infections for patients with immune dysfunction.[26] With only three post-treatment infection-related deaths in the ibrutinib–venetoclax group, these data might suggest that the robust disease control obtained with ibrutinib–venetoclax and the positive impact of ibrutinib on circulating immune cells in patients with chronic lymphocytic leukaemia[27] led to diminished susceptibility to severe and fatal infections, including COVID-19, whereas patients with reduced chronic lymphocytic leukaemia control might be more susceptible. This hypothesis is in line with recently reported observations that, in patients with haematological malignancies, including chronic lymphocytic leukaemia, COVID-19 is likely to have a more severe course and is more frequently fatal in patients with active or uncontrolled disease not responding to treatment than in patients with controlled disease.[28,29] This observation might point to limitations of the current study—the trial was running during the COVID-19 pandemic, which might have led to more infectious deaths overall.

Additionally, this trial did not enrol patients with either del17p or *TP53* mutations, so is unable to draw conclusions for this patient subgroup. However, other trials, such as CAPTIVATE, provide information about the utility of this regimen in patients with these disease characteristics.[15] Finally, since the design of GLOW, the standard of care for untreated chronic lymphocytic leukaemia has evolved to include BTK inhibitors with or without obinutuzumab regimens, or venetoclax with obinutuzumab.[2,6,8,28] The ongoing CLL17 trial will compare ibrutinib monotherapy with fixed-duration venetoclax–obinutuzumab and ibrutinib–venetoclax in this patient population.

Overall, the efficacy of fixed-duration ibrutinib–venetoclax at nearly 4 years of follow-up in GLOW is similar to that observed for continuous BTK inhibitor regimens. The estimated 42-month progression-free survival rate for ibrutinib–venetoclax (74·6%) was similar to rates achieved with continuous ibrutinib–obinutuzumab in iLLUMINATE (74% at 42 months), continuous ibrutinib in RESONATE-2 (70% at 60 months), and continuous acalabrutinib in ELEVATE-TN (78% at 48 months).[2,6,25] Similarly, the overall survival estimate in GLOW was similar to that observed for single-agent ibrutinib in RESONATE-2 (83% at 60 months).[2] Notwithstanding the caveats associated with naive cross-study comparisons (eg, unmatched populations), these are clinically meaningful observations considering that the GLOW study outcomes were achieved with fixed-duration therapy. In the context of fixed-duration regimens, 4-year progression-free survival rates for venetoclax–obinutuzumab in the CLL14 study (74%) were also similar to what we observed for ibrutinib–venetoclax in GLOW.[8] In addition to undetectable MRD kinetics showing a decline of less than 10% per year, and sustainable nodal responses independent of MRD status for ibrutinib–venetoclax, the GLOW study is the first fixed-duration targeted combination, to our knowledge, to show overall survival benefit at a timepoint of 46 months of follow-up. Of note, in recent frontline trials in older and comorbid patients with chronic lymphocytic leukaemia (eg, iLLUMINATE and CLL14), patients were reported to have fared better with chlorambucil–obinutuzumab as control treatment than they did in GLOW; 4-year overall survival estimates in the experimental group and chlorambucil–obinutuzumab control group were 81% for both groups in iLLUMINATE, 85% and 83% in CLL14, and 86% and 69% in GLOW, respectively.[6,8] The poorer overall survival outcome for control group patients in GLOW versus iLLUMINATE, in part, could be due to a higher proportion of patients who were older than 65 years (94% *vs* 79%), had an ECOG performance status of 1–2 (63% *vs* 54%), or had a CIRS score of higher than 6 at study entry (58% *vs* 31%).[6] Similarly, the proportion of patients with an ECOG performance status of 1–2 was lower in CLL14 (52%) than in GLOW (63%).[8] Furthermore, chlorambucil–obinutuzumab was given for 12 cycles in CLL14 instead of six in GLOW, which might account for better disease control and reduced susceptibility to chronic lymphocytic leukaemia-related fatal events in this study.[8] When considering clinically relevant long-term toxic effects, it is of note that ibrutinib–venetoclax in GLOW demonstrated a lower rate of secondary primary malignancies than that reported in phase 3 studies of venetoclax–obinutuzumab in CLL14 and acalabrutinib in ELEVATE-TN.[8,25]

In conclusion, these data should inform clinical practice as the outcomes observed at this 4-year timepoint support the use of ibrutinib–venetoclax combination as an all-oral, chemotherapy-free, fixed-duration treatment option for patients with previously untreated chronic lymphocytic leukaemia.

Contributors

CUN, TM, M-DL, LY, NS, KB, AH, DBC, and APK were involved in the conception and design of the study. All authors verified and accessed the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CUN received consultancy fees and research funding from AbbVie, Janssen, Octapharma, and AstraZeneca; received research funding from the Novo Nordisk Foundation, Danish Cancer Society, and Alfred Benzon foundation; and provided consultancy to CSL Behring, Genmab, Takeda, and BeiGene. TM served on the board of directors or advisory committee for Janssen, AstraZeneca, Alexion, AbbVie, Novartis, and Roche; and received honoraria from Janssen, AstraZeneca, Alexion, Sobi, Novartis, Roche, AbbVie, and Gilead. CM provided consultancy and served on the board of directors or advisory committee and speaker's bureau for AbbVie, Janssen, AstraZeneca, and BeiGene; and received research funding from Janssen and AbbVie. CO provided consultancy and received honoraria from AbbVie and AstraZeneca; and received honoraria from Janssen, Roche, Merck, Gilead, and Servier. GAF provided consultancy and served on the speaker's bureau for Roche, AbbVie, Janssen, and Takeda; and provided consultancy for Janpix. OB provided consultancy to AbbVie, Janssen, and AstraZeneca. AJ is an employee of Genmab. M-DL received reimbursements for travel expenses from AbbVie, Roche, and Janssen. TR received honoraria from AbbVie; provided consultancy, received honoraria, and research funding from Janssen, AstraZeneca, and BeiGene; and received honoraria and research funding from Octapharma, Regeneron, and GSK. MS provided consultancy, received honoraria, served on the board of directors or advisory committee, and received travel grants from Janssen-Cilag, AstraZeneca, and AbbVie. SV received honoraria from Janssen, AbbVie, and Sanofi; and provided non-financial support to clinical trials for Janssen, AbbVie, Sanofi, Novartis, and Pfizer. LY served on the board of directors or advisory committee and received research funding from AbbVie, AstraZeneca, Janssen, Roche, BeiGene, and BMS/Celgene. APK received research funding from AbbVie, AstraZeneca, BMS, Janssen, and Roche/Genentech; received patent royalties from Janssen and LAVA; and served on the board of directors or advisory committees for AstraZeneca, BMS, Roche/Genentech, Janssen, AbbVie, and LAVA; and received speaker's fees from AbbVie, AstraZeneca, and Janssen. KQ, QQ, LP, SS, NS, KB, and DBC are employees of Janssen or have stock ownership, or both. PS was an employee of Janssen at the time of the study. AH is an employee and equity holder of Janssen Research and Development. VV and MY declare no competing interests.

Data sharing

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. The data sharing request will be considered on case-by-case basis. The study protocol is provided in the appendix of this publication. The statistical analysis plan and informed consent form will be made available upon request to the corresponding author.

Acknowledgments

The study was sponsored by Janssen Research & Development. We would like to acknowledge Keerthi Pothuri, Xiaozhen Han, and Vidyasagar Palli for data generation and Emma Smith for contributions to the manuscript revisions. Writing assistance was provided by Saba Choudhary of Parexel and funded by Janssen Global Services.

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