Health-related quality of life with fixed-duration venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: Results from the randomized, phase 3 CLL14 trial

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Abstract
Chronic lymphocytic leukemia (CLL)-related symptoms impair the well-being of patients, making improvement of health-related quality of life (QoL) a goal of treatment. The CLL14 trial demonstrated higher efficacy of fixed-duration venetoclax-obinutuzumab (Ven-Obi) compared to chlorambucil-obinutuzumab (Clb-Obi) in patients with previously untreated CLL. To assess patients’ QoL, the following patient-reported outcomes (PRO) measures were assessed: the M.D. Anderson Symptom Inventory (MDASI) core instrument and CLL module and the EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). At treatment start, physical functioning (mean 75.9 [standard deviation (SD) ± 20.1] in the Clb-Obi arm and 76.9 [±19.4] in the Ven-Obi arm), role functioning (73.6 [±27.86] and 72.6 [±26.9]) and GHS/QoL (63.6 [±21.0] and 60.3 [±20.5]) were comparable between treatment arms per EORTC QLQ-C30 scale scores. Baseline levels of physical and role functioning were maintained throughout treatment and follow-up, with no relevant improvement or deterioration. On average, patients treated with Ven-Obi showed a meaningful improvement of GHS/QoL during treatment and follow-up by at least eight points at cycle three, whereas improvement was delayed until cycle eight with Clb-Obi. According to MDASI scores, CLL symptoms (1.5 [±1.2] and 1.6 [±1.3]), core cancer symptoms (1.5 [±1.4] and 1.8 [±1.7]) and symptom interference (2.1 [±2.3] and 2.3 [±2.3]) were generally low and comparable between treatment arms at baseline and were maintained throughout treatment and follow-up. This analysis demonstrates that the higher efficacy of Ven-Obi is not associated with QoL impairment and that Ven-Obi achieves early relief of CLL-related symptoms in elderly unfit patients.

1 | INTRODUCTION

One of the main aims of treatment optimization for patients with chronic lymphocytic leukemia (CLL) is the improvement of remission...
rates as well as depth of remissions by novel targeted compounds. This has led to numerous targeted agents being used for CLL therapy, particularly among elderly patients with coexisting conditions unable to tolerate intensive chemoimmunotherapy such as fludarabine, cyclophosphamide and rituximab (FCR).

Less toxic approaches, however, initially developed to be more tolerable, did not yield similar efficacy. Recently, the CLL14 trial showed that a combination treatment with the targeted agents venetoclax plus obinutuzumab over a fixed period of time can achieve considerable rates of undetectable minimal residual disease (uMRD) in elderly patients with coexisting conditions. In this trial, patients with previously untreated CLL and coexisting conditions were randomized to receive six cycles of obinutuzumab together with either 12 cycles of venetoclax or 12 cycles of chlorambucil (hereafter Ven-Obi vs Clb-Obi). A significantly longer progression-free survival was shown with Ven-Obi compared to Clb-Obi and uMRD levels of 76% were observed at the end of treatment. The rate and types of adverse events were comparable between both arms, with no excess toxicities observed among this vulnerable group of patients.

To ensure that higher treatment efficacy was not achieved at the expense of patients’ health-related quality of life (HRQoL), and to further evaluate the effects of treatment on symptoms as well as functional/HRQoL burden associated with both disease and treatment within this patient population, patient-reported outcomes (PROs) assessments were conducted during and after treatment in both arms. Here, we report the analyses of PRO data from the CLL14 study.

2 | METHODS

2.1 | Patients and study design

The CLL14 study is an ongoing global, phase III, open-label, randomized study of Ven-Obi compared with Clb-Obi in patients with previously untreated CLL and coexisting conditions. Details on the study design and eligibility criteria were outlined previously. Patients with previously untreated CLL and coexisting conditions, defined by a cumulative illness rating scale score >6 and/or impaired renal with a creatinine clearance <70 ml/min were randomized to receive six cycles of 28 days of obinutuzumab (starting with 100 mg on Day 1 and 900 mg on Day 2 [or 1000 mg on Day 1], 1000 mg on Day 8 and Day 15 of cycle one, and subsequently 1000 mg on Day 1 of cycles two through six) together with either 12 cycles of daily chlorambucil (oral chlorambucil at 0.5 mg/kg bodyweight on Days 1 and 15 of each cycle for 12 cycles) or daily venetoclax (initiated on Day 22 of cycle 1 [28-day cycles], with a 5-week dose ramp-up [20 mg, 50 mg, 100 mg, and 200 mg, then 400 mg daily for 1 week], thereafter continuing at 400 mg daily until completion of cycle 12). The primary endpoint was investigator-assessed progression-free survival (PFS). The protocol was registered at US and EU clinical trial registries (NCT02242942, EudraCT 2014-001810-24) and approved by ethical review boards responsible for each participating center. The study was performed according to the principles of the Declaration of Helsinki. All patients provided written informed consent to participate.

2.2 | Patient-reported outcomes measures

Patient-reported outcomes measures administered in this study included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) version 3, a 30-item cancer questionnaire with sive functional and eight symptom scales (and a scale measuring financial difficulties not reported here), asking respondents to rate the severity or impact of symptoms/functional/global health-related quality of life burden over the last 7 days, and the MD Anderson Symptom Inventory (MDASI) with the CLL module (MDASI-CLL), comprised of 25 items allocated across three scales corresponding to core cancer symptom severity, CLL-specific symptom severity, and interference due to symptoms over the previous 24 h.

Changes in physical functioning, role functioning, and global health status/quality of life (GHS/QoL) as well as cognitive functioning, emotional functioning, social functioning, dyspnea, fatigue, insomnia, pain, nausea/vomiting, constipation, diarrhea, and appetite loss were assessed using the EORTC QLQ-C30. Higher scores (range 0–100) for the functioning and GHS/QoL denote a better level of functioning (i.e., a better state of the patient), while higher scores on the symptom and single-item scales indicate a higher level of symptoms (i.e., a worse state of the patient).

Note, CLL symptoms, core cancer symptoms, and symptom interference were assessed using the MDASI-CLL. Lower MDASI-CLL scores (range 0–10) indicate lower symptom severity or interference.

Patients were asked to complete the questionnaires at enrolment and subsequently on Day 1 of each treatment cycle (cycle two to cycle 12), at Day 28 after treatment completion and then at follow-up month 3, 6, 12, 15, 18, 24 and 30.

Key PRO endpoints evaluating disease and treatment-related symptoms following treatment with Ven-Obi or Clb-Obi as measured by the MDASI-CLL scale, and changes in physical functioning, role functioning, and global health status as measured by the EORTC QLQ-C30 scales, were used to compare study arms.

2.3 | Statistical analysis

For this analysis, mean score and mean change from baseline values in all scales of the EORTC QLQ-C30 and MDASI-CLL symptom scale are provided at each assessment. Trends in mean scores over time were further explored graphically in longitudinal plots for key domains of EORTC QLQ-C30 physical functioning, role functioning, GHS/QoL and MDASI-CLL symptoms, core cancer symptoms, and symptom interference. In addition, Mixed-Effect Model Repeated Measure (MMRM) analyses were conducted to compare scores between treatment arms over the course of the trial for physical functioning, role functioning, and GHS/QoL. The models were adjusted for baseline scores and included
covariates for Binet stage, geographic region, treatment group, visit, and the interaction between treatment and visit.

For scales that showed clinically meaningful improvement, additional Kaplan-Meier plots were produced along with responder analyses illustrating proportions of patients experiencing respective improvement, worsening, and stability in scores between arms at each time point per published thresholds (i.e., improvement corresponding to an eight or more point increase for GHS/QoL scale score and a nine or more point decrease for dyspnea, fatigue, and insomnia; worsening corresponding to a decrease of 10 points or more for GHS/QoL, and increase of 11, 10, and nine points or more in the other respective scale scores). Linear mixed effects models were also used to explore associations between those measures and MRD status (positive vs negative), as assessed via blood and bone marrow sampling methods and clinical response status (complete [CR], complete response with incomplete bone marrow recovery [CRi], and partial response [PR]). Further exploratory analyses examined these measures across disease burden and B-symptom subgroups. Associations between MRD recrudescence, that is, MRD negativity at end of treatment not sustained during follow up, and a wider range of PRO measures were examined as well.

3 | RESULTS

3.1 | Patient characteristics

We have previously described the patient characteristics along with efficacy and safety results. In summary, 216 patients were randomized to receive Ven-Obi and 216 patients were randomized to receive Clb-Obi. Median age was 72 years, median CIRS was eight points and 57% of patients had an impaired renal function with a creatinine clearance below 70 ml/min (Table S1). Median treatment duration was 11.1 months in the Ven-Obi arm and 10.8 months in the Clb-Obi arm.

3.2 | EORTC QLQ-C30 results

For both questionnaires, the proportion of patients completing PRO assessments at baseline was 100% and at least 90% in both arms during treatment. During follow-up, completion rate remained above 85% past the 18-month mark as reported here.

At baseline, patient-reported physical functioning (mean score 76.9 with Ven-Obi vs. 75.9 with Clb-Obi), role functioning (72.6 vs. 73.6) and GHS/QoL (60.3 vs. 63.6) were comparable between both arms (Table 1), reflecting moderate-to-high functioning and moderate global health status. Baseline scores on the additional functioning and symptom scales were similarly comparable between arms (Table 1), showing moderate-to-high functioning and low symptom severity.

During treatment and follow-up, patients in both arms reported similarly stable mean physical functioning and role functioning scores at all time points (Figure 1(A), (B)). In addition, improvement in the mean GHS/QoL was observed in both study arms (Figure 1(C)) with clinically meaningful improvements of ≥8 points in cycle three in the Ven-Obi arm and cycle eight in the Clb-Obi arm. These improvements were maintained for the remainder of treatment and follow-up. The MMRM analyses showed no difference between treatment arms and no interaction between treatment and time. Kaplan-Meier plots show improvement trends in both arms, with separation favoring Ven-Obi at each time point based on the higher proportion of GHS/QoL responders (i.e., patients showing improvement). Further responder analyses similarly showed higher percentages of patients meeting meaningful improvement thresholds, and lower percentages meeting worsening thresholds, in the Ven-Obi arm at each timepoint (Tables S2 and S3, Figures S1 and S2).

Individual symptoms of insomnia and fatigue were elevated at baseline and each demonstrated improvement of ≥9 points change in mean score starting at cycle three in the Ven-Obi arm and cycle four for insomnia and cycle six for fatigue in the Clb-Obi arm. Improvements of mean dyspnea scores by ≥9 points were observed starting at cycle three in the Ven-Obi arm, although this was not maintained in the follow-up (Figure 1(D), (F)). The K-M plots for these symptom scale scores show increasing proportions of patients experiencing meaningful improvement in both arms, but with minimal difference between arms and no consistent superiority for Ven-Obi (Figure 2(B)–(D)). Percentages of patients experiencing improvement were similar between arms, but

| Table 1 | EORTC QLQ-C30 functioning domains and symptom severity, and MDASI-CLL scale at baseline |
|---------|--------------------------------------------------------------------------------------------|
|                     | Venetoclax-obinutuzumab (N = 197) | Chlorambucil-obinutuzumab (N = 198) |
| **EORTC QLQ-C30**   |                                   |                                   |
| Physical functioning | 76.9                               | 75.9                               |
| Role functioning     | 72.6                               | 73.6                               |
| Global health status/QoL | 60.3                               | 63.6                               |
| Cognitive functioning| 82.9                               | 84.4                               |
| Emotional functioning| 75.7                               | 79.0                               |
| Social functioning   | 80.0                               | 85.0                               |
| Dyspnea             | 24.8                               | 21.3                               |
| Fatigue             | 39.2                               | 35.8                               |
| Insomnia            | 30.8                               | 26.9                               |
| Pain                | 18.4                               | 16.8                               |
| Nausea/vomiting     | 5.9                                | 4.3                                |
| Constipation        | 12.8                               | 10.9                               |
| Diarrhea            | 7.3                                | 9.1                                |
| Appetite loss       | 15.6                               | 14.7                               |
| **MDASI-CLL**       |                                   |                                   |
| MDASI CLL symptoms  | 1.6                                | 1.5                                |
| MDASI core cancer symptoms | 1.8 | 1.5 |
| MDASI symptom interference | 2.3 | 2.1 |

Note: Lower score (0–100) for functioning domains indicate better functioning, lower scores (0–100) for symptoms indicate lower symptom severity. For MDASI-CLL scale, mean CLL Symptoms, Core Symptoms and Symptom Interference are outlined. Lower scores (range 0–10) indicate lower severity or interference.

*N = 199 for MDASI questionnaire.*
 numerically higher for the Ven-Obi group at each timepoint. Improvement in PRO scores continued beyond timepoints of maximal clinical responses (cycle nine to follow-up month 3) and beyond end of treatment. Percentages of patients experiencing worsening were also comparable between arms, with fewer patients receiving Ven-Obi experiencing an increase in symptoms at most timepoints (Tables S4–S8 and Figures S3–S7).

The remaining functioning scales (social, cognitive, and emotional) demonstrated moderate-to-high scores at baseline that were stable during treatment and follow-up (Figures S9–S11). Further symptom scales (nausea/vomiting, pain, constipation, diarrhea, appetite loss, financial difficulties) were low at baseline and remained stable during treatment (Figures S12–S17). In line with the previous report of diarrhea as an initial frequent adverse event with Ven-Obi, the PRO questionnaires indicated a transient increase on the diarrhea scale that returned to baseline by the end of treatment (Figure S15).

3.3 | MDASI-CLL results

At baseline, mean scores of CLL symptoms (1.6 in the Ven-Obi arm vs. 1.5 in the Clb-Obi arm), core cancer symptoms (1.8 vs. 1.5) and symptom interference (2.3 vs. 2.1) indicated low severity and interference in both study arms (Table 1). Scores for both arms remained stable, but showed a tendency toward improvement (i.e., decreased symptom severity and interference) during treatment and follow-up (Figure 3). The MMRM analyses showed no difference between treatment arms and no interaction between treatment and time.

3.4 | Exploratory MRD analyses

In order to explore whether depth of remission, as measured by MRD status at the end of treatment, correlates with specific PROs, a linear mixed effects model was established: MRD levels, measured by ASO-PCR in both peripheral blood and bone marrow, was examined in relation to scores for EORTC QLQ-C30 GHS/QOL, dyspnea, insomnia, and fatigue scales. In a mixed effect model, no clear association between detectable and undetectable MRD status in peripheral blood or bone marrow and GHS/QOL, dyspnea, insomnia or fatigue was observed, also when controlling for covariates age and Cumulative Illness Rating Scale (CIRS) score (Table S10). To further evaluate whether changes in MRD levels are perceptible to patients, PRO scores were compared across groups experiencing MRD recrudescence (peripheral blood level >10⁻⁴ by PCR) at follow-up time points versus those who did not (i.e., uMRD
status maintained following treatment). No clear associations between MRD status and PRO scores were observed (Tables S12).

3.5 | Exploratory clinical response analyses

Similar linear mixed effects models were used to evaluate clinical response in relation to these PROs. Both age and CIRS were initially included as covariates, but did not improve models and were ultimately excluded. Results showed no differences in PRO scores, with the exception of GHS/QOL in the Clb-Obi arm (Table S11). Plots of mean PRO score changes showed overlapping 95% confidence intervals and no consistent trends in most cases (Figure S18).

3.6 | Exploratory subgroup analyses

Further subgroup analyses examined the same set of PROs across groups defined by disease burden (as captured by high/medium/low TLS risk status) and B symptoms (positive or negative). For the former, overall findings suggest that greater PRO improvement observed with Ven-Obi was driven by patients with higher disease burden; for the Clb-Obi arm, this trend was less pronounced (dyspnea, fatigue) or reversed (GHS/QOL, insomnia) (Figures S19–S22). The latter B symptoms showed a similar trend toward PRO improvement for the B symptom positive group which was again more pronounced in the Ven-Obi arm, particularly for fatigue (Figures S23–S26).

4 | DISCUSSION

The importance of patient quality of life has been emphasized by many cancer societies and organizations as well as funding and reimbursement agencies. PRO data from randomized trials are of high value as they allow for a direct comparison of multiple treatment regimens and provide insight into patients’ experience of treatment. Moreover, they can be a sensitive tool to detect common toxicities of a treatment in addition to adverse event reporting by physicians, even within clinical trials. It has been shown that chemoimmunotherapy as well as targeted treatment with BTK inhibitors and PI3K inhibitors can improve HRQoL, although agent-specific toxicities need to be considered. Previous reports on venetoclax in patients with relapsed/refractory CLL indicated improvement based on some PRO measures. However, these reports were based on single-agent, continuous treatment with venetoclax in relapsed/refractory CLL and did not include a comparative treatment arm.

The aim of this report was to analyze the impact of a novel fixed-duration frontline treatment for CLL on the overall quality of life, as
FIGURE 3  Patient reported outcomes according to MDASI-CLL scale. (A) CLL symptom severity according to MDASI-CLL scale. (B) Core cancer symptoms according to MDASI-CLL scale. (C) Symptom interference according to MDASI-CLL scale.
well as key symptoms and aspects of functioning. Considering the elderly and unfit patient cohort of CLL14, it was important not to impair the quality of life of patients by using the more effective treatment regimen of Ven-Obi.

This analysis showed that patients receiving Ven-Obi did not experience impairment to baseline functioning and global health status during treatment or during follow-up. Likewise, symptom burden and interference did not increase during or after treatment, while patients on average saw fatigue and insomnia scale scores improve by ≥9 points, which is considered clinically meaningful.7

While the pattern of improvements was quite similar between Ven-Obi and Clb-Obi, earlier improvement in GHS/QoL, insomnia and fatigue was observed with Ven-Obi. Responder analyses further show greater proportions of patients receiving Ven-Obi experiencing meaningful improvements across these measures, and fewer experiencing decline or worsening. Such earlier, and more likely, symptom relief and quality of life improvement can be of particular value for elderly and unfit patients, suffering from co-existing conditions or comorbidities.15 Post-hoc, exploratory analyses reported here indeed suggest that such improvements can be of particular benefit for these groups.

As with other types of indolent lymphoma, relapses or disease progressions after CLL treatment do not necessarily mandate initiation of a next line of therapy.20 In most cases, patients are not aware of disease progression, as slight increases of lymph nodes or lymphocyte count often occur silently. Likewise, achieving deep uMRD levels does not necessarily correlate with the subjective perception of benefit cancer patients may experience based on the therapy they are receiving.9 Therefore, endpoints such as PFS, ORR or uMRD rate do not always reflect the patients’ perspective sufficiently.21 This is also reflected by the fact that in this analysis, depth of remission, that is, rates of uMRD, at the end of treatment did not correlate well with changes in PRO. Likewise, increase of MRD levels after end of therapy were not associated with meaningful changes in PRO scores. However, while quantification of MRD allows for an immediate assessment of treatment response, relief of disease-related symptoms after anti-neoplastic treatment generally requires more time to manifest.14,22 This is indicated by the steady improvement reflected in PRO scores over time in this analysis. Given that only patients with pre-existing conditions were enrolled into this study, HRQoL was likely to be also affected by other comorbidities that were not targeted by the study treatment. This potentially limits the possibility to distinguish the impact of the study treatment and comorbidities on HRQoL.

The CLL14 trial has shown that it is possible to achieve very deep responses and long-term disease control in elderly and unfit patients. Given the risk that such efficacy might be achieved at the cost of the patient’s well-being, these results importantly show treatment goals being achieved without compromising patients’ functioning and overall quality of life. Overall, Ven-Obi maintained or partly improved the HRQoL of elderly and unfit patients with previously untreated CLL.

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CONFLICT OF INTEREST
Othman Al-Sawaf reports personal fees and non-financial support from AbbVie, Roche, Gilead, and Janssen, during the conduct of study; Brittan Gentile: employed by Genentech; Jacob Devine: employed by Genentech; Kavita Sail: employment and ownership interests (AbbVie); Maneesh Tandon: employment and ownership interests (F. Hoffmann-La Roche); Anna-Maria Fink reports personal fees from Celgene, Janssen, and Hoffmann-LaRoche, outside the submitted work. Nadine Kutsch: research funding (Gilead), travel, accommodation, expenses (Mundipharma, AbbVie, Janssen); Clemens-Martin Wendtner reports personal fees from Hoffmann-LaRoche, AbbVie, Janssen-Cilag, Gilead, and MorphoSys, outside the submitted work; Barbara Eichhors reports grants from Hoffmann-La Roche, Abbie, and Janssen; personal fees from Hoffmann-La Roche, Abbvie, Celgene, Novartis, ArQule, BeiGene,Gilead, AstraZeneca, Oxford Biomedica (UK), and Adaptive Biotechnologies, outside the submitted work; Michael Hallek reports grants, non-financial support, and personal fees from Roche, Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, and AbbVie, outside the submitted work; Kirsten Fischer reports personal fees from AbbVie and Hoffmann-La Roche, outside the submitted work. Can Zhang declares no conflict of interest.

AUTHOR CONTRIBUTIONS
Othman Al-Sawaf, Jacob Devine, Can Zhang, Kirsten Fischer drafted the manuscript. Othman Al-Sawaf, Anna-Maria Fink, Clemens-Martin Wendtner, Barbara Eichhorst, Michael Hallek, Kirsten Fischer conducted the study. Othman Al-Sawaf, Brittan Gentile, Jacob Devine, Can Zhang, Kirsten Fischer performed the data analysis. All authors reviewed the data and the manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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