Minimal Residual Disease Dynamics after Venetoclax-Obinutuzumab Treatment: Extended Off-Treatment Follow-up From the Randomized CLL14 Study

Othman Al-Sawaf, MD1,2,3; Can Zhang, PhD1; Tong Lu, PhD4; Michael Z. Liao, PhD4; Anesh Panchal, MSc5; Sandra Robrecht, PhD1; Travers Ching, PhD6; Maneesh Tandon, MBChB5; Anna-Maria Fink, MD1; Eugen Tausch, MD7; Christof Schneider, MD7; Matthias Rüttgen, MD5; Sebastian Böttcher, MD9; Karl-Anton Kreuzer, MD1; Brenda Chyla, PhD10; Dale Miles, PhD4; Clemens-Martin Wendtner, MD11; Barbara Eichhorst, MD1; Stephan Stilgenbauer, MD7; Yanwen Jiang, PhD4; Michael Hallek, MD1; and Kirsten Fischer, MD1

INTRODUCTION

Measurement of minimal residual disease (MRD) of chronic lymphocytic leukemia (CLL) is particularly relevant for fixed-duration combination therapies, as the level of MRD at the end of treatment (EoT) has been shown to be prognostic for progression-free survival (PFS). However, EoT-MRD is only one snapshot in the highly dynamic process of this heterogeneous disease. Some patients might eventually show increasing MRD levels over time that can be difficult to identify clinically, as standard blood counts or flow cytometry requires more sensitivity to detect CLL cells below 10−4. Therefore, capturing MRD dynamics by regular and more sensitive MRD measurements during and after treatment might yield valuable information on disease-specific kinetics. Previously, the CLL14 study demonstrated that the combination of the BCL2 inhibitor venetoclax with the CD20 antibody obinutuzumab (venetoclax and obinutuzumab [Ven-Obi]) induces deep remissions after a fixed-treatment duration of 12 cycles in patients with previously untreated CLL with coexisting conditions. In addition to the high rates of undetectable MRD (uMRD), a significantly longer PFS was observed with Ven-Obi compared with chlorambucil-obinutuzumab (Clb-Obi). On the basis of these findings, one year fixed-duration treatment with Ven-Obi was approved by the US Food and Drug Administration and the
European Medicines Agency for treatment of patients with previously untreated CLL. With all patients now being off treatment for at least 3 years, we present here a detailed analysis of patients’ long-term outcomes after Ven-Obi and Clb-Obi treatment with a particular focus on serial MRD levels and MRD dynamics.

PATIENTS AND METHODS

Study Design and Participants
The CLL14 study is an ongoing 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.5,6 The Protocol (online only) was registered at US and EU clinical trial registries (NCT, 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. The data cutoff date was September 11, 2020.

Procedures
Previously untreated patients in need of therapy and with coexisting medical conditions (assessed by the Cumulative Illness Rating Scale with a threshold of ≥ 6 and/or creatinine clearance < 70 mL/min) were randomly assigned 1:1 to receive either Clb-Obi or Ven-Obi. Treatment in both groups was administered for 12 cycles, each lasting 28 days. Dosing, prophylactic measures, and monitoring were described previously.5,6

Assessments
The primary end point was investigator-assessed PFS, defined as the time from random assignment to the first occurrence of progression, relapse, or death from any cause. Key secondary end points included rate of uMRD (cutoff 10⁻⁴) in peripheral blood (PB) and bone marrow (BM), by an allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), overall and complete response rates by iwCLL criteria7 (assessed 2 months after treatment completion, ie, follow-up [FU] month 3), and overall survival (OS). Exploratory end points included uMRD rates with the cutoff of 10⁻⁴, 10⁻⁵, and 10⁻⁶, by next-generation sequencing (NGS). MRD in PB and BM was analyzed centrally according to international guidelines,8-10 by means of ASO-PCR; additionally, Adaptive’s clonoSEQ Assay for NGS was used for MRD measurements in PB samples.4 MRD in BM was assessed in patients with treatment response at cycle 9 and 2 months after completion of treatment (EoT). MRD in PB was assessed at baseline, cycles 7, 9, and 12, and every 3 months after treatment completion until FU month 18, and then every 6 months until 9 years from last patient enrollment. Reporting of adverse events was required until a next line of therapy or progression of disease (PD) occurred. Only study drug–related serious adverse events and second primary malignancies (SPMs) were reported throughout FU.

Statistical Analyses
Statistical analyses were performed on an intention-to-treat (ITT) basis including all patients with available information for the corresponding analyses. All randomly assigned patients were included in the ITT population. All randomly assigned patients who received at least one dose of study medication were included in the safety analyses (safety population).

Model of MRD dynamics. For the longitudinal analyses of MRD dynamics, patients in the ITT population with at least two measurable MRD samples by NGS on and after FU month 3 were included. Data below the lower limit of quantification were considered using a likelihood-based approach.11 A population-based logistic growth model with the nonlinear mixed effects approach was developed to

CONTEXT

Key Objective
This analysis of the phase III CLL14 study investigated long-term minimal residual disease (MRD) dynamics and clinical outcomes of patients with previously untreated chronic lymphocytic leukemia treated with fixed-duration venetoclax-obinutuzumab (Ven-Obi) versus chlorambucil-obinutuzumab (Clb-Obi).

Knowledge Generated
Appearance of detectable MRD after end of treatment is significantly slower after Ven-Obi than Clb-Obi therapy. At a median follow-up of 52 months, progression-free survival and undetectable MRD rates remained superior with Ven-Obi.

Relevance
These data demonstrate a sustained long-term benefit of 12 cycles of Ven-Obi in frontline chronic lymphocytic leukemia across all clinically relevant risk groups. The MRD analyses indicate a deep clearance of residual disease across compartments by Ven-Obi compared with Clb-Obi. Longer follow-up and further randomized studies are warranted to compare this regimen with other frontline treatment strategies.
estimate the growth parameters at population and patient levels, to assess the interindividual variability around the parameters, and to identify covariates with a significant impact on the appearance of detectable MRD.\textsuperscript{12} Prognostic and predictive markers at FU month 3 were screened as covariates for their impact on the key model parameters on the basis of statistical (with –2-log-likelihood as the objective function) and graphical assessment. Statistical inference on time from FU month 3 MRD assessment to MRD doubling and time to reach the MRD level of $10^{-2}$ was derived for the stratified subgroups. A detailed outline of the model setup is provided in the Data Supplement (online only).

**Clinical outcomes.** Kaplan-Meier estimates were used to analyze time-to-event data. The log-rank test and Cox proportional hazards regression model—stratified by Binet stage and geographic region—were used to compare PFS, time to next treatment, and OS from random assignment across arms. Landmark analyses from last treatment exposure were performed for PFS and OS as post hoc with regard to the MRD level at EoT by ASO-PCR in BM (for PFS) and by NGS in PB (for OS). For patients with the uMRD level $<10^{-4}$ by NGS at EoT, time to MRD conversion by NGS from MRD assessment date at EoT was analyzed using the Kaplan-Meier method and was compared using a nonstratified Cox proportional hazards regression model across arms. Apart from redetection of MRD level $\geq 10^{-4}$ in two consecutive visits, patients with PD or death of PD also counted toward total patients in the Ven-Obi arm, uMRD levels $<10^{-6}$ at cycle 7, that is, after completing combination therapy with Ven-Obi. In 55 (25.5%) of the patients in the Ven-Obi arm, MRD response deepened after continuing with six cycles of venetoclax monotherapy (Fig 2A). Of the 14 patients in the Ven-Obi arm with detectable MRD ($=10^{-4}$) at FU month 3 and available MRD assessment at cycle 7, 7 (50%) had decreasing MRD values from cycle 7 to FU month 3 and 7 (50%) had increasing MRD values until EoT (Fig 2B).

On the basis of the inclusion criteria for the population-based MRD analysis, 154 patients from the Clb-Obi arm and 153 patients from the Ven-Obi arm were included for the MRD model (Data Supplement). The model was overall well calibrated with high concordance between observed and predicted MRD values (Fig 3A). On the basis of a covariate screening of 32 biologic and clinical characteristics, a significant impact on the appearance of detectable MRD was observed by Ven-Obi treatment, MRD levels at the start of treatment, CLL-IPI, $11q$ deletion, disease burden (definition in the Data Supplement), response to treatment, immunoglobulin heavy-chain variable-region (IGHV) gene status, and complex karyotype ($P<.05$; Data Supplement). The median MRD doubling time was significantly longer after Ven-Obi than Clb-Obi therapy (median days 80 v 69 days, $P=.0039$; Fig 3B, Data Supplement). The median time from FU month 3 to the MRD level of $10^{-2}$ was also significantly longer after Ven-Obi therapy compared with Clb-Obi therapy (median 1,259 days v 233 days, $P<.0001$; Fig 3C).

**RESULTS**

**Patients**

Between August 2015 and August 2016, 432 patients were included defining the ITT population. Overall, 216 patients were randomly assigned to Ven-Obi and 216 to Clb-Obi (Data Supplement). Patient characteristics were previously reported.\textsuperscript{6} The median observation time from random assignment was 52.4 months. All patients have been off study treatment for at least 3 years.

**MRD Dynamics**

At FU month 3, 86 (39.8%) patients in the Ven-Obi arm had uMRD levels $<10^{-6}$, 57 (26.4%) $\geq 10^{-6}$ and $<10^{-5}$, 18 (8.3%) $\geq 10^{-5}$ and $<10^{-4}$, 11 (5.1%) $\geq 10^{-4}$ and $<10^{-2}$, and 7 (3.2%) $\geq 10^{-2}$. Thirty-seven (17.1%) had missing MRD results (22 because of missing MRD samples, five because of PD or death, and 10 because of withdrawal from the study, by NGS on the basis of ITT population, Fig 1). For patients in the Clb-Obi arm, uMRD levels $<10^{-6}$ were found in 14 (6.5%) patients, levels $\geq 10^{-6}$ and $<10^{-5}$ in 27 (12.5%), 30 (13.9%) had levels $\geq 10^{-5}$ and $<10^{-4}$, 46 (21.3%) had levels $\geq 10^{-4}$ and $<10^{-2}$, and 57 (26.4%) $\geq 10^{-2}$. Forty-two (19.4%) had missing MRD results (24 because of missing MRD samples, 14 because of PD or death, and four because of withdrawal from study).

In the Ven-Obi arm, most of the 86 patients (55.8%) who had uMRD levels $<10^{-6}$ at FU month 3 already had uMRD levels $<10^{-6}$ at cycle 7, that is, after completing combination therapy with Ven-Obi. Of the 14 patients in the Ven-Obi arm with detectable MRD ($=10^{-4}$) at FU month 3 and available MRD assessment at cycle 7, 7 (50%) had decreasing MRD values from cycle 7 to FU month 3 and 7 (50%) had increasing MRD values until EoT (Fig 2B).

On the basis of the inclusion criteria for the population-based MRD analysis, 154 patients from the Clb-Obi arm and 153 patients from the Ven-Obi arm were included for the MRD model (Data Supplement). The model was overall well calibrated with high concordance between observed and predicted MRD values (Fig 3A). On the basis of a covariate screening of 32 biologic and clinical characteristics, a significant impact on the appearance of detectable MRD was observed by Ven-Obi treatment, MRD levels at the start of treatment, CLL-IPI, $11q$ deletion, disease burden (definition in the Data Supplement), response to treatment, immunoglobulin heavy-chain variable-region (IGHV) gene status, and complex karyotype ($P<.05$; Data Supplement). The median MRD doubling time was significantly longer after Ven-Obi than Clb-Obi therapy (median days 80 v 69 days, $P=.0039$; Fig 3B, Data Supplement). The median time from FU month 3 to the MRD level of $10^{-2}$ was also significantly longer after Ven-Obi therapy compared with Clb-Obi therapy (median 1,259 days v 233 days, $P<.0001$; Fig 3C). Patients with detectable MRD in BM ($\geq 10^{-4}$) and uMRD in PB had a shorter MRD doubling time than patients with uMRD in both PB and BM (60 days v 80 days in the Ven-Obi arm and 42 v 52 days in the Clb-Obi arm; Data Supplement).

On the basis of Kaplan-Meier analysis, the median time to MRD conversion by NGS, defined as an increase in patients with MRD levels $<10^{-4}$ at EoT to MRD levels $\geq 10^{-4}$, was 21.0 months for patients in the Ven-Obi arm and 6.0 months for patients in the Clb-Obi arm (Fig 3D). In the Ven-Obi arm, 16 of 169 (9.5%) patients with uMRD at EoT showed an increase to low (L)-MRD ($\geq 10^{-4}$ and $<10^{-2}$).
and 75 of 169 (44.4%) patients had an increase to high (H)-MRD ($10^{-2}$; Data Supplement).

The difference in MRD conversion time between Ven-Obi and Clb-Obi was also observed in patients with BM uMRD in both arms: in the Ven-Obi arm, patients with BM uMRD had a median MRD conversion time of 21.7 months, compared with 9.2 months in the Clb-Obi arm (Fig 3E). However, patients with detectable BM MRD had a similarly short MRD conversion time in both arms (6.0 months and 5.5 months). This was also reflected in PFS, where patients

**FIG 1.** Follow-up month 3 (ie, 2 months after treatment completion) minimal residual disease status by next-generation sequencing on the basis of intention-to-treat population. Clb-Obi, chlorambucil-obinutuzumab; MRD, minimal residual disease; NE, not evaluable; PD, progressive disease; Ven-Obi, venetoclax-obinutuzumab.

**FIG 2.** (A) Sankey plot for MRD levels by NGS between cycle 7 and FUm3 (ie, 2 months after treatment completion) in the Ven-Obi arm (patients during Ven-Obi treatment). (B) Waterfall plot for the 14 patients with detectable MRD ($10^{-4}$) at FUm3 in the Ven-Obi arm and available MRD assessment at cycle 7 by NGS, with each bar representing absolute log changes from cycle 7 to FUm3 per patient. FUm3, follow-up month 3; H-MRD, high minimal residual disease; L-MRD, low minimal residual disease; MRD, minimal residual disease; NGS, next-generation sequencing; PD, progressive disease; Ven-Obi, venetoclax-obinutuzumab.
with detectable BM had a shorter PFS than patients with uMRD in BM (Fig 3F).

Twenty-nine months after treatment completion (ie, FU month 30), 58 (26.9%) patients in the Ven-Obi arm had uMRD levels below $10^{-4}$, 47 (21.8%) had L-MRD, and 29 (13.4%) had H-MRD (Fig 4). MRD results were missing for 82 (38.0%) patients (35 because of missing samples, 36 because of PD or death, and 11 because of study withdrawal). In the Clb-Obi arm, 7 (3.2%, $P < .0001$) patients had uMRD levels, 19 (8.8%, $P < .001$) L-MRD, and 61 (28.2%, $P < .001$) H-MRD, compared with the Ven-Obi arm. MRD results were missing for 129 (59.7%) patients.
Baseline characteristics for patients with sustained uMRD levels at FU month 30 are presented in the Data Supplement.

In multivariate analysis, independent prognostic factors for MRD conversion were treatment arm, disease burden (definition in the Data Supplement), CLL-IPI, and BM MRD status at EoT (Data Supplement).

Clinical Outcomes

At a median observation time of 52.4 months (interquartile range 49.5-56.2), patients in the Ven-Obi arm had a significantly longer PFS than patients in the Clb-Obi arm. The median PFS was not reached in the Ven-Obi arm and was 36.4 months in the Clb-Obi arm (hazard ratio [HR] 0.33; 95% CI, 0.25 to 0.45; *P* < .0001). Four years after random assignment, the PFS rate was 74.0% in the Ven-Obi arm and 35.4% in the Clb-Obi arm (Fig 5A). The PFS benefit with Ven-Obi was observed across all clinical and biologic risk groups (Data Supplement). Patients with *TP53* aberrations, that is, deletion and/or mutation, had a significantly longer PFS in the Ven-Obi arm than in the Clb-Obi arm (median 49.0 months vs 20.8 months; HR 0.44; 95% CI, 0.21 to 0.91; *P* = .03; Fig 5B). PFS was shorter for patients with *TP53* aberrations in both arms compared with patients without *TP53* aberrations (Fig 5B).
aberrations (Ven-Obi arm: HR 2.50; 95% CI, 1.35 to 4.63; \( P = .004 \) and Clb-Obi arm: HR 1.74; 95% CI, 1.07 to 2.83; \( P = .03 \)).

For patients with both unmutated and mutated \( IGHV \), PFS was significantly longer with Ven-Obi than with Clb-Obi. In the mutated \( IGHV \) group, the median PFS was not reached.
with Ven-Obi and was 54.5 months with Clb-Obi (HR 0.36; 95% CI, 0.19 to 0.68; P = .002; Fig 5C). In the unmutated IGHV group, the median PFS was 57.3 months versus 26.9 months (HR 0.25; 95% CI, 0.17 to 0.37; P < .0001). In both arms, PFS was longer for patients with mutated IGHV compared with unmutated IGHV (Ven-Obi arm: HR 0.47; 95% CI, 0.25 to 0.87; P = .02 and Clb-Obi arm: HR 0.33; 95% CI, 0.22 to 0.48; P < .0001).

Of the 61 PFS events in the Ven-Obi arm, 35 were PDs and 26 were deaths (Data Supplement). Seventeen patients received a next line of antileukemic treatment in the Ven-Obi arm and 70 in the Clb-Obi arm. Time to next treatment was significantly longer in the Ven-Obi arm compared with the Clb-Obi arm (HR 0.46; 95% CI, 0.32 to 0.65; P < .0001; Fig 6A). Most patients received Bruton tyrosine kinase (BTK) inhibitor monotherapy as second-line treatment after progressive disease in both arms (47.1% in the Ven-Obi arm and 50% in the Clb-Obi arm). For cases where investigator-assessed response was available, most patients responded to second-line BTK inhibitor therapy (Data Supplement).

No difference in OS was observed. Thirty-four (15.7%) patients died in the Ven-Obi arm, and 41 (19.0%) in the Clb-Obi arm (HR 0.85; 95% CI, 0.54 to 1.35; P = .49; Fig 6B). Four years after random assignment, the Kaplan-Meier estimate of OS was 85.4% in the Ven-Obi arm and 83.1% in the Clb-Obi arm. Three years after last treatment exposure, patients with uMRD by NGS at EoT had the highest OS rate in both arms (92.2% after Ven-Obi and 94.6% after Clb-Obi), compared with patients with detectable MRD (72.7% and 82.7%; Data Supplement).

In multivariate analysis, independent prognostic factors associated with PFS were treatment arm, disease burden (high vs intermediate or low), IGHV mutation, 17p deletion, and complex karyotype (Data Supplement). For OS, independent prognostic factors were age (cutoff: 75 years), serum β2-microglobulin (cutoff: 3.5 mg/L), and 17p deletion (Data Supplement). In the Ven-Obi arm, only 17p deletion and high disease burden were independent prognostic factors for PFS (Data Supplement).

**Safety**

For the safety population, the rates of adverse events during treatment were reported previously. The current analysis does not reveal new treatment-related adverse events. SPMs of any grade including nonmelanoma skin cancers were observed in 40 (18.9%) patients in the Ven-Obi arm and 30 (14.0%) in the Clb-Obi arm (Data Supplement). Overall, 47 SPM events were reported in the Ven-Obi arm and 42 in the Clb-Obi arm. Most frequent SPMs were basal cell carcinoma (8 [3.8%] and 3.7%) patients in both arms, respectively) and squamous cell carcinoma of skin (7 [3.3%] vs 8 [3.7%]). Three cases of Richter transformation have been reported in the Clb-Obi arm, and two in the Ven-Obi arm. Four SPMs had a fatal outcome in the Ven-Obi arm and seven in the Clb-Obi arm (Data Supplement).

**DISCUSSION**

The first aim of this report was to analyze longitudinal MRD assessments, to develop an MRD model, and to characterize and compare MRD kinetics in a prospective, randomized setting. The second aim of this report was to outline the long-term efficacy of first-line Ven-Obi therapy compared with Clb-Obi, once all patients were off treatment for at least 3 years. Previously, several studies have shown the close correlation of EoT MRD status with PFS and OS. The depth of remission should therefore be proportional to the time to disease relapse. On the basis of this understanding, different treatment strategies for fixed-duration therapy have been suggested for patients who do not reach uMRD at EoT, including continuation of treatment or treatment intensification. In this analysis, half of the 14 patients with detectable MRD at EoT showed decreasing MRD levels while on treatment, suggesting a continuous benefit from venetoclax continuation. The other half of the patients showed increasing MRD levels while on treatment and are therefore unlikely to benefit from continuation beyond 12 cycles. For this group, addition of other agents might facilitate MRD response. Ultimately, individualized strategies taking the potential benefit of increasing the remission depth beyond 10^{-4} into account need to be explored in further clinical studies.

The longitudinal MRD assessments by NGS were used to establish a population-based growth model. The higher efficacy of Ven-Obi compared with that of Clb-Obi was previously mainly attributed to the significantly higher rate of uMRD at FU month 3 (75% vs 33%, by NGS-MRD < 10^{-4}). To our knowledge, we show here for the first time that the appearance of detectable MRD after Ven-Obi is significantly slower than after Clb-Obi. This finding seems to be supported by the deeper remissions in the Ven-Obi arm not only in PB but also in BM, suggesting that sufficient compartment clearance is critical for long-term disease control after fixed-duration treatment. Furthermore, the assessment of serial MRD kinetics is particularly informative for patients with high-risk features: previous analyses showed high rates of uMRD at EoT even for patients with TP53 aberrations, unmutated IGHV status, or complex karyotype, suggesting a similar depth of remission in all subgroups after Ven-Obi treatment. Conversely, the calculation of MRD kinetics indicates that despite similar rates of uMRD after EoT, the growth dynamics of clones in patients with high-risk disease features are accelerated. Therefore, EoT uMRD status alone might yield limited information on the durability of deep remissions in these high-risk subgroups.

The differences in MRD dynamics between Ven-Obi-treated and Clb-Obi-treated patients fit with the significant differences in clinical events between both arms: With a 4-year PFS rate of 74.0%, the most Ven-Obi–treated patients remain without PD despite being off treatment for at least 3 years. Only 17 patients have so far required a next line of treatment after Ven-Obi. Similar to the Clb-Obi arm, most patients...
received BTK inhibitors as a second-line treatment and responded to therapy. In both arms, patients with TP53 aberrations or unmutated IGHV status had a shorter PFS than patients with unaltered TP53 or mutated IGHV status. This finding differs from previous analyses with shorter FU.

Overall, our findings show that the outcome of this high-risk population can be improved markedly with targeted agents; however, similar to other agents such as BTK inhibitors, the adverse impacts of TP53 aberrations and unmutated IGHV status have not been entirely overcome yet.

In contrast to the strong PFS differences, no differences in OS were observed between both study arms, although EoT uMRD status was associated with longer OS. The high median age and presence of coexisting conditions in all patients represent a competing risk for CLL-related OS. The number of CLL-related deaths was higher in the Clb-Obi arm (16 CLL-related deaths) than in the Ven-Obi arm (seven CLL-related deaths), indicating that the impact of the more effective CLL therapy with Ven-Obi might indeed be masked by comorbidities. No new safety signals were
reported with the current extended FU. Although previous analyses had reported an increase in the frequency of SPMs in the Ven-Obi arm, this finding has mostly balanced out in the current FU with 47 SPM events in the Ven-Obi arm and 42 in the Clb-Obi arm.

Our exploratory analyses of the MRD model have a few methodologic limitations. Since CLL14 is so far the only phase III study with mature frontline Ven-Obi data, there is no appropriate external validation cohort available. Nevertheless, multiple internal validation strategies indicate a reasonable model calibration. Another caveat might be uncertainties because of imputation of missing data, although this affected < 10% of the data and was conducted using established methods.11,26 Also, some open questions need to be considered. Although different growth dynamics have been observed between Ven-Obi and Clb-Obi, the composition of clones and gene sets driving disease growth is yet to be clarified. Differences in clonal composition of residual disease, in addition to the different compartment clearance, might be contributing to differences in the appearance of detectable MRD. First analyses indicated that the frequency of acquired mutations is higher at relapse and that certain clones such as TP53 mutations or BIRC3 mutations do expand more after Clb-Obi than after Ven-Obi.27 Further analyses are part of ongoing work.

In conclusion, this analysis shows that serial MRD assessments can be used within clinical studies to assess disease dynamics after a fixed-duration treatment. Patients who received Ven-Obi had slower appearance of detectable MRD than patients after Clb-Obi treatment. This finding translated into a sustained clinical benefit for patients who received Ven-Obi as frontline treatment, with only 7.9% of patients requiring a next line of therapy over 3 years after treatment cessation. Thus, these 4-year results of the CLL14 study confirm the sustained efficacy and safety of 12-month fixed-duration Ven-Obi for patients with previously untreated CLL and coexisting conditions.

**FIG 6.** Kaplan-Meier analysis for (A) TTNT per study arm and (B) OS per study arm. Clb-Obi, chlorambucil-obinutuzumab; OS, overall survival; TTNT, time to next anti-leukemic treatment; Ven-Obi, venetoclax-obinutuzumab.

**AFFILIATIONS**

1University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, German CLL Study Group, Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf, Germany
2The Francis Crick Institute, London, United Kingdom
3UCL Cancer Institute, University College London, London, United Kingdom
4Genentech, San Francisco, CA
5Roche Products Ltd, Welwyn Garden City, United Kingdom
6Adaptive Biotechnologies Corp, Seattle, WA
7Department of Internal Medicine III, Ulm University, Ulm, Germany
8Department II of Internal Medicine, University of Schleswig-Holstein, Kiel, Germany
9Clinic III, Special Hematology Laboratory, Rostock University Medical School, Rostock, Germany
10AbbVie Inc, Chicago, IL
11Department of Hematology, Oncology, Immunology, Palliative Care, Infectious Diseases and Tropical Medicine, Munich Clinic Schwabing, Munich, Germany
12Department of Internal Medicine I, Saarland University Medical Center, Homburg, Germany

**CORRESPONDING AUTHOR**

Kirsten Fischer, MD, University Hospital of Cologne, Kerpener Str 62, 50937 Cologne, Germany; e-mail: kirsten.fischer@uk-koeln.de.

**EQUAL CONTRIBUTION**

M.H. and K.F. contributed equally and are co-corresponding authors to this work.
**Prior Presentation**
Presented in part at the 63rd ASH Annual Meeting (virtual), December 5-8, 2020.

**Support**
Supported by F. Hoffmann-La Roche Ltd and AbbVie Inc. Also supported in part by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Projektnummer 467697427 (O.A.-S.).

**Clinical Trial Information**
NCT02242942

**Authors’ Disclosures of Potential Conflicts of Interest**
Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.01181.

**Data Sharing Statement**
The German CLL Study Group, Roche, and AbbVie will consider data sharing requests on a case-by-case basis. With publication, requests by academic study groups for deidentified patient data with the intent-to-achieve aims of the original proposal can be forwarded to the corresponding author and will be evaluated by the German CLL Study Group, Roche, and AbbVie.

**References**
1. Del Giudice I, Raponi S, Della Starza I, et al: Minimal residual disease in chronic lymphocytic leukemia: A new goal? Front Oncol 9:689, 2019
2. Thompson M, Brander D, Nabhan C, et al: Minimal residual disease in chronic lymphocytic leukemia in the era of novel agents: A review. JAMA Oncol 4:394-400, 2018
3. Rawstron AC, Fazi C, Agathangeliadis A, et al: A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: An European Research Initiative on CLL study. Leukemia 30:929-936, 2016
4. Ching T, Duncan ME, Newman-Eerkes T, et al: Analytical evaluation of the clonoSEQ Assay for establishing measurable (minimal) residual disease in acute lymphoblastic leukemia, chronic lymphocytic leukemia, and multiple myeloma. BMC Cancer 20:612, 2020
5. Al-Sawaf O, Zhang C, Tandon M, et al: Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): Follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 21:1188-1200, 2020
6. Fischer K, Al-Sawaf O, Bahlo J, et al: Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med 380:2225-2236, 2019
7. Hallek M, Cheson BD, Catovsky D, et al: Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: A report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 111:5446-5456, 2008
8. Rawstron AC, Bottcher S, Letestu R, et al: Improving efficiency and sensitivity: European Research Initiative in CLL (ERIC) update on the international harmonised approach for flow cytometric residual monitoring in CLL. Leukemia 27:142-149, 2013
9. Rawstron AC, Villanor N, Ritgen M, et al: International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. Leukemia 21:956-964, 2007
10. van der Velden VH, Cazzaniga G, Schrauder A, et al: Analysis of minimal residual disease by Ig/TCR gene rearrangements: Guidelines for interpretation of real-time quantitative PCR data. Leukemia 21:604-611, 2007
11. Bergstrand M, Karlsson MO: Handling data below the limit of quantification in mixed effect models. AAPS J 11:371-380, 2009
12. Mould DR, Upton RN: Basic concepts in population modeling, simulation, and model-based drug development. CPT Pharmacometrics Syst Pharmacol 1:e6, 2012
13. Bottcher S, Ritgen M, Fischer K, et al: Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: A multivariate analysis from the randomized GCLLSG CLL8 trial. J Clin Oncol 30:980-986, 2012
14. Kater AP, Seymour JF, Hillmen P, et al: Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: Post-treatment follow-up of the MURANO phase III study. J Clin Oncol 37:269-277, 2019
15. Kater AP, Wu JQ, Kipps T, et al: Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-Year results and evaluation of impact of genomic complexity and gene mutations from the MURANO phase III study. J Clin Oncol 38:4042-4054, 2020
16. Kovacs G, Robrecht S, Fink AM, et al: Minimal residual disease assessment improves prediction of outcome in patients with chronic lymphocytic leukaemia (CLL) who achieve partial response: Comprehensive analysis of two phase III studies of the German CLL Study Group. J Clin Oncol 34:3758-3765, 2016
17. Patel K, Pagel JM: Current and future treatment strategies in chronic lymphocytic leukemia. J Hematol Oncol 14:69, 2021
18. Bottcher S, Hallek M, Ritgen M, et al: The role of minimal residual disease measurements in the therapy for CLL: Is it ready for prime time? Hematol Oncol Clin North Am 27:267-288, 2013
19. Scarfo L, Heltai S, Abi E, et al: Minimal residual disease-driven treatment intensification by sequential addition of ibritinib to venetoclax in relapsed/refractory chronic lymphocytic leukemia: Results of the monotherapy and combination phases of the improve study. Presented at the ASH 2020, 2020
20. Al-Sawaf O, Lilienweiss E, Bahlo J, et al: High efficacy of venetoclax plus obinutuzumab in patients with complex karyotype and chronic lymphocytic leukemia. Blood 135:866-870, 2020

**Author Contributions**
Conception and design: Othman Al-Sawaf, Can Zhang, Tong Lu, Michael Z. Liao, Yanwen Jiang, Michael Hallek, Kirsten Fischer

Administrative support: Othman Al-Sawaf, Can Zhang, Kirsten Fischer

Provision of study materials or patients: Othman Al-Sawaf, Eugen Tausch, Matthias Ritgen, Karl-Anton Kreuzer, Clemens-Martin Wendtner, Barbara Eichhorst, Stephan Stilgenbauer, Michael Hallek, Kirsten Fischer

Collection and assembly of data: Othman Al-Sawaf, Tong Lu, Michael Z. Liao, Travers Ching, Anna-Maria Fink, Eugen Tausch, Christoph Schneider, Matthias Ritgen, Karl-Anton Kreuzer, Clemens-Martin Wendtner, Stephan Stilgenbauer, Yanwen Jiang, Michael Hallek, Kirsten Fischer

Data analysis and interpretation: Othman Al-Sawaf, Can Zhang, Tong Lu, Michael Z. Liao, Anesh Panchal, Maneesh Tandon, Anna-Maria Fink, Eugen Tausch, Matthias Ritgen, Sebastian Böttcher, Karl-Anton Kreuzer, Brenda Chylia, Dale Miles, Clemens-Martin Wendtner, Barbara Eichhorst, Stephan Stilgenbauer, Yanwen Jiang, Michael Hallek, Kirsten Fischer

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

**Acknowledgment**
We thank the patients, their families, and their nurses and physicians for their participation in the trial. The authors thank Michele Porro Lurà and Juliana Biondo (Roche/Genentech) for invaluable support in the conception and conduct of the study.
21. Tausch E, Schneider C, Robrecht S, et al: Prognostic and predictive impact of genetic markers in patients with CLL treated with obinutuzumab and venetoclax. Blood 135:2402-2412, 2020
22. Moreno C, Greil R, Demirkan F, et al: Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (ILLUMINATE): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 20:43-56, 2019
23. Shanafelt TD, Wang XV, Kay NE, et al: Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med 381:432-443, 2019
24. Sharman JP, Egryd M, Jurczak W, et al: Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): A randomised, controlled, phase 3 trial. Lancet 395:1278-1291, 2020
25. Woyach JA, Ruppert AS, Heerema NA, et al: Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. N Engl J Med 379:2517-2528, 2018
26. Beal SL: Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn 28:481-504, 2001
27. Tausch E, Schneider C, Yosifov D, et al: Genetic markers and outcome with front line obinutuzumab plus either chlorambucil or venetoclax—Updated analysis of the CLL14 trial. Hematologic Oncol 39:62-64, 2021
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Minimal Residual Disease Dynamics After Venetoclax-Obinutuzumab Treatment: Extended Off-Treatment Follow-up From the Randomized CLL14 Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/lwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Othman Al-Sawaf
Honoraria: Janssen-Cilag, Roche, Gilead Sciences, AbbVie, AstraZeneca, Adaptive Biotechnologies, BeiGene
Consulting or Advisory Role: Roche, Janssen-Cilag, Gilead Sciences, AbbVie
Research Funding: BeiGene, Janssen-Cilag, Roche, AbbVie, Gilead Sciences

Tong Lu
Employment: Genentech/Roche
Stock and Other Ownership Interests: Roche

Anesh Panchal
Employment: Genentech/Roche

Travers Ching
Employment: Adaptive Biotechnologies
Stock and Other Ownership Interests: Adaptive Biotechnologies

Maneesh Tandon
Employment: Roche (I)
Stock and Other Ownership Interests: Roche Pharma AG

Anna-Maria Fink
Research Funding: Celgene/Bristol Myers Squibb (Inst), AstraZeneca (Inst)

Eugen Tausch
Consulting or Advisory Role: Roche, AbbVie
Speakers’ Bureau: Roche, AbbVie, Janssen-Cilag
Travel, Accommodations, Expenses: AbbVie

Matthias Ritten
Honoraria: Roche, Janssen Oncology, AstraZeneca, AbbVie, MSD
Consulting or Advisory Role: Roche, Roche, AstraZeneca
Research Funding: Roche (Inst), AbbVie (Inst)

Sebastian Böttcher
Honoraria: Roche, AbbVie, AstraZeneca, Janssen, Sanofi
Consulting or Advisory Role: AstraZeneca, Janssen
Research Funding: Janssen (Inst)

Karl-Anton Kreuzer
Honoraria: Roche, AbbVie
Consulting or Advisory Role: Roche, AbbVie
Speakers’ Bureau: Roche, AbbVie
Research Funding: Roche (Inst), AbbVie (Inst)
Expert Testimony: Roche, AbbVie
Travel, Accommodations, Expenses: Roche, AbbVie

Brenda Chyla
Employment: AbbVie
Stock and Other Ownership Interests: AbbVie

Dale Miles
Employment: Genentech
Stock and Other Ownership Interests: Genentech
Travel, Accommodations, Expenses: Genentech

Clemens-Martin Wendtner
Honoraria: Roche, Janssen-Cilag, AbbVie/Genentech, AstraZeneca, Gilead Sciences
Consulting or Advisory Role: Roche, Janssen-Cilag, AbbVie/Genentech, AstraZeneca, Gilead Sciences
Research Funding: Roche, Janssen-Cilag, AbbVie/Genentech, AstraZeneca, Gilead Sciences

Barbara Eichhorst
Honoraria: Roche, AbbVie, Gilead Sciences, Janssen, Novartis, Hexal, AstraZeneca, Adaptive Biotechnologies, Oxford Biomedia, Miltenyi Biotec
Consulting or Advisory Role: Gilead Sciences, Janssen-Cilag, Roche, AbbVie, Novartis, Celgene, AstraZeneca, ArQule
Speakers’ Bureau: Roche/Genentech, Janssen-Cilag, Gilead Sciences, Celgene, AbbVie, Novartis
Research Funding: Roche, AbbVie, Gilead Sciences, Janssen, Beijing Genomics Institute
Travel, Accommodations, Expenses: Roche, AbbVie, Gilead Sciences, Janssen

Stephan Stilgenbauer
Honoraria: AbbVie, AstraZeneca, Celgene, Gilead Sciences, GlaxoSmithKline, Roche, Janssen
Consulting or Advisory Role: AbbVie, AstraZeneca, Celgene, Gilead Sciences, GlaxoSmithKline, Roche, Janssen
Speakers’ Bureau: AbbVie, AstraZeneca, Celgene, Gilead Sciences, GlaxoSmithKline, Roche, Janssen
Travel, Accommodations, Expenses: AbbVie, AstraZeneca, Celgene, Gilead Sciences, GlaxoSmithKline, Roche, Janssen

Yanwen Jiang
Employment: Genentech
Stock and Other Ownership Interests: Genentech

Michael Hallek
Honoraria: Roche, Janssen, AbbVie, Gilead Sciences, AstraZeneca
Consulting or Advisory Role: Janssen, AbbVie, Gilead Sciences, Genentech/Roche, AstraZeneca
Speakers’ Bureau: Janssen, AbbVie, Gilead Sciences, Roche/Genentech, AstraZeneca
Research Funding: Roche (Inst), AbbVie (Inst), Janssen (Inst), Gilead Sciences (Inst), AstraZeneca (Inst), Travel, Accommodations, Expenses: Roche, Janssen

Kirsten Fischer
Honoraria: AbbVie, Roche
Consulting or Advisory Role: AbbVie, Roche
Travel, Accommodations, Expenses: Roche

No other potential conflicts of interest were reported.