# Venetoclax consolidation after fixed-duration venetoclax plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (HOVON 139/GiVe): primary endpoint analysis of a multicentre, open-label, randomised, parallel-group, phase 2 trial

*Sabina Kersting, Julie Dubois, Kazem Nasserinejad, Johan A Dobber, Clemens Mellink, Anne-Marie F van der Kevie-Kersemaekers, Ludo M Evers, Fransien de Boer, Harry R Koene, John Schreurs, Marjolein van der Klift, Gerjo A Velders, Ellen van der Spek, Hanneke M van der Straaten, Mels Hoogendoorn, Michel van Gelder, Eduardus F M Posthuma, Hein P J Visser, Ilse Houtenbos, Cecile A M Idink, Djamila E Issa, Ellen C Dompeling, Henk C T van Zaanen, Hendrik Veelken, Henriette Levenga, Lidwine W Tick, Wim E Terpstra, Sanne H Tonino, Michelle Boyer, Mehrdad Mobasher, Mark-David Levin*, Arnon P Kater*, on behalf of the HOVON CLL study group†*

*Lancet Haematol* 2022; 9: e190–99

See **Comment** page e169

*Contributed equally

†Members are listed in the appendix (p 115)

**Department of Hematology, HAGA Teaching Hospital, The Hague, Netherlands** (S Kersting MD); **Department of Hematology, Cancer Center Amsterdam, Lymphoma and Myeloma Center Amsterdam, Amsterdam, Netherlands** (J Dubois MD, S H Tonino MD, Prof A P Kater MD); **Department of Hematology, HOVON Data Center, Erasmus MC Cancer Institute, Rotterdam, Netherlands** (K Nasserinejad PhD); **Department of Laboratory Special Hematology** (J A Dobber PhD, L M Evers) **and Department of Human Genetics, Section Cytogenetics** (C Mellink PhD, A-M F van der Kevie-Kersemaekers PhD), **Amsterdam University Medical Center, Amsterdam, Netherlands; Department of Internal Medicine, Ikazia Hospital, Rotterdam, Netherlands** (F de Boer MD); **Department of Hematology, Antonius Hospital, Nieuwegein, Netherlands** (H R Koene MD); **Department of Internal Medicine, Martini Hospital, Groningen, Netherlands** (J Schreurs MD); **Department of Internal Medicine, Amphia Hospital, Breda, Netherlands** (M van der Klift MD); **Department of Internal Medicine, Gelderland Valley Hospital, Ede, Netherlands** (G A Velders MD); **Department**

## Summary

**Background** Fixed-duration 12 cycles of venetoclax plus obinutuzumab is established as first-line treatment for patients with chronic lymphocytic leukaemia. We aimed to determine the activity and safety of 12 cycles of venetoclax consolidation after fixed-duration venetoclax plus obinutuzumab for previously untreated patients with chronic lymphocytic leukaemia who were unfit for fludarabine-based treatment, and whether this could be guided by minimal residual disease status.

**Methods** We conducted an open-label, randomised, parallel-group, phase 2 trial (HOVON 139/GiVe) at 25 hospitals in the Netherlands. Eligible patients were aged 18 years or older with previously untreated chronic lymphocytic leukaemia, had an ECOG performance status of 0–2, and were unfit for fludarabine-based treatment. All patients received two debulking cycles of intravenous obinutuzumab (100 mg on day 1, 900 mg on day 2, and 1000 mg on days 8, 15, and day 1 of cycle two), followed by fixed-duration venetoclax plus obinutuzumab for 12 cycles (six cycles of intravenous obinutuzumab 1000 mg on day 1 and 12 during 28-day cycles of oral venetoclax, starting with a 5-week ramp-up and then 400 mg once daily until completion of cycle 12). Patients were then randomly assigned (1:1) by minimal residual disease status in peripheral blood, to receive either 12 cycles of venetoclax consolidation irrespective of minimal residual disease or venetoclax consolidation only if minimal residual disease was detected at randomisation. The primary endpoint was undetectable minimal residual disease in bone marrow and no progressive disease 3 months after end of consolidation treatment (or corresponding timepoint) by intention-to-treat. Safety was assessed in all patients who received at least one dose of any study drug. This is the primary endpoint analysis of this trial, which is ongoing and is registered with EudraCT (2015-004985-27).

**Findings** Between Oct 28, 2016, and May 31, 2018, 70 patients were enrolled, of whom 67 (47 [70%] men and 20 [30%] women) received fixed-duration treatment and 62 were randomly assigned to receive 12 cycles of venetoclax consolidation (n=32) or minimal residual disease-guided venetoclax consolidation (n=30; one of whom was minimal residual disease positive at randomisation). Median follow-up was 35·2 months (IQR 31·5–41·3). 16 (50% [95% CI 32–68]) of 32 patients in the consolidation group and 16 (53% [34–72]) of 30 in the minimal residual disease-guided consolidation group met the primary endpoint of undetectable minimal residual disease in bone marrow and no progressive disease. 22 (69%) of 32 patients in the venetoclax consolidation group and 11 (37%) of 30 in the minimal residual disease-guided consolidation group had any adverse event (grade 2–4; mainly infections). The most common grade 3 or worse adverse events were infection (two [6%] of 32 patients in the consolidation group and one [3%] of 30 in the minimal residual disease-guided consolidation group) and neutropenia (two [6%] and two [7%]). There were no treatment-related deaths.

**Interpretation** Consolidation with venetoclax 12-cycle treatment increases the duration of known side-effects and does not prevent the loss of minimal residual disease response and subsequent risk of disease relapse.

**Funding** F Hoffmann-La Roche.



## Introduction

Chemoimmunotherapy was the gold standard for first-line treatment of progressive chronic lymphocytic leukaemia until 2020.[1,2] In the past 5 years, new effective treatment options targeting specific proteins have emerged. The most prominent targets are Bruton

## Research in context

### Evidence before this study

We searched PubMed from database inception to Nov 4, 2021, using the terms "chronic lymphocytic leukemia" AND "venetoclax" AND "obinutuzumab", with no language restrictions. We found that the combination of venetoclax and obinutuzumab has been assessed in phase 1, 2, and 3 studies and has shown high response rates with undetectable minimal residual disease (MRD) and manageable toxicity. We found no trials that specifically studied the additional value of venetoclax consolidation in relation to MRD status following fixed-duration venetoclax plus obinutuzumab in the first-line setting for patients with chronic lymphocytic leukaemia.

### Added value of this study

To our knowledge, HOVON 139/GiVe is the first study to evaluate a predetermined 12-cycle venetoclax consolidation versus MRD-guided venetoclax consolidation following fixed-duration venetoclax plus obinutuzumab. Venetoclax consolidation did not show added activity; loss of MRD response occurred irrespective of consolidation. Prolonged venetoclax use was accompanied by treatment-related adverse events, such as infections, neutropenia, and gastrointestinal toxicity.

### Implications of all the available evidence

12 cycles of fixed-duration venetoclax plus obinutuzumab leads to deep responses and high rates of undetectable MRD, which are not improved further by consolidation treatment. Loss of MRD response occurs regardless of prolonged venetoclax exposure. A more dynamic approach than an MRD measurement at one timepoint, accounting for depth and regrowth kinetics of MRD, is likely to be needed to select patients who could benefit from consolidation.

tyrosine kinase (BTK), a key kinase involved in B-cell receptor signalling, and the B-cell lymphoma 2 (Bcl-2) protein, a crucial regulator of apoptosis.[2,3] Both the covalent inhibitors of BTK, such as ibrutinib, acalabrutinib, and zanabrutinib, and the selective Bcl-2 inhibitor venetoclax, have been shown to be highly efficacious as single-agent treatments in chronic lymphocytic leukaemia.[4] However, responses are mostly partial and a single-agent treatment requires continuous dosing until the occurrence of either unbearable toxicity or resistant disease, whichever occurs first.[5] Fixed-duration combination treatment strategies have the advantages of lower costs, fewer side-effects, and lower chances of development of resistance.[6]

One such strategy is a combination of venetoclax with an anti-CD20 antibody. In the MURANO study,[7] venetoclax was combined with rituximab for six 28-day cycles followed by 18 cycles of venetoclax monotherapy in patients with relapsed or refractory chronic lymphocytic leukaemia, which resulted in a 2-year progression-free survival of 84·9%.[7] The combination of venetoclax with obinutuzumab was studied in the first-line setting in the CLL14 study.[8] Patients received six cycles of venetoclax in combination with obinutuzumab but, by contrast with the MURANO study, this was followed by only six additional cycles of venetoclax monotherapy, resulting in a 2-year progression-free survival of 88·2%. On the basis of these studies, both fixed-duration combination regimens have been approved by the US Food and Drug Administration and European Medicines Agency; venetoclax plus rituximab for relapsed or refractory chronic lymphocytic leukaemia and venetoclax plus obinutuzumab for first-line treatment. However, the durations of venetoclax exposure (24 cycles in relapsed or refractory disease and 12 cycles in the first-line setting) were arbitrarily chosen and therefore an optimal duration of treatment is unknown.

It became evident from analyses of trials with time-limited chemoimmunotherapy that patients who had undetectable minimal residual disease (MRD; $<10^{-4}$; ie, less than one chronic lymphocytic leukaemia cell per 10 000 leukocytes) had superior outcomes, irrespective of whether they attained partial response or complete response.[9] The predictive value of MRD, irrespective of levels of response, was also observed in the aforementioned fixed-duration venetoclax plus anti-CD20 antibody studies.[8,10–12] As well as being a surrogate marker for progression-free survival, MRD status might also reflect the individual sensitivity for a given treatment. As such, timing of undetectable MRD attainment might be used to tailor duration of therapy. We hypothesised that consolidation treatment with venetoclax could be beneficial for obtaining, as well as continuation of, undetectable MRD, either for all patients or for patients with MRD following fixed-duration venetoclax plus obinutuzumab.

We aimed to determine the efficacy and safety of 12 cycles of venetoclax consolidation after fixed-duration venetoclax plus obinutuzumab for previously untreated patients with chronic lymphocytic leukaemia who were unfit for fludarabine-based treatment, and whether this could be guided by MRD status.

## Methods

### Study design and participants

We conducted an open-label, randomised, parallel-group, phase 2 trial (HOVON 139/GiVe) at 25 hospitals in the Netherlands (appendix p 1; study protocol shown in the appendix pp 2–112). Eligible patients were aged 18 years or older with previously untreated symptomatic chronic lymphocytic leukaemia requiring treatment according to the International Workshop on Chronic Lymphocytic

**of Internal Medicine, Rijnstate Hospital, Arnhem, Netherlands** (E van der Spek MD); **Department of Internal Medicine, St Jansdal Hospital, Harderwijk, Netherlands** (H M van der Straaten MD); **Department of Internal Medicine, Medical Center Leeuwarden, Leeuwarden, Netherlands** (M Hoogendoorn MD); **Department of Hematology, MUMC, Maastricht, Netherlands** (M van Gelder MD); **Department of Internal Medicine, RDGG, Delft, Netherlands** (E F M Posthuma MD); **Department of Internal Medicine, Northwest Clinics, Alkmaar, Netherlands** (H P J Visser MD); **Department of Internal Medicine, Spaarne Gasthuis, Hoofddorp, Netherlands** (I Houtenbos MD); **Department of Internal Medicine, ZorgSaam hospital, Terneuzen, Netherlands** (C A M Idink MD); **Department of Internal Medicine, Jeroen Bosch hospital, 's-Hertogenbosch, Netherlands** (D E Issa MD); **Department of Hematology, Isala Hospital, Zwolle, Netherlands** (E C Dompeling MD); **Department of Internal Medicine, St Franciscus Hospital, Rotterdam, Netherlands** (H C T van Zaanen MD); **Department of Hematology, LUMC, Leiden, Netherlands** (Prof H Veelken MD); **Department of Internal Medicine, Groene Harthospital, Gouda, Netherlands** (H Levenga MD); **Department of Internal Medicine, Maxima MC, Eindhoven, Netherlands** (L W Tick MD); **Department of Internal Medicine, OLVG, Amsterdam, Netherlands** (W E Terpstra MD); **Roche Products Limited, Welwyn Garden City, UK** (M Boyer PhD); **Genentech, South San Francisco, CA, USA** (M Mobasher PhD); **Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, Netherlands** (M-D Levin MD)

Correspondence to:
Dr Sabina Kersting, Department of Hematology, HAGA Teaching Hospital, The Hague 2545 AA, Netherlands
**s.kersting@hagaziekenhuis.nl**

See **Online** for appendix

Leukemia (IwCLL) criteria,[13] had an ECOG performance status of 0, 1, or 2, and were considered unfit for first-line fludarabine-based treatment by their treating physician. Other eligibility criteria were platelet count of at least $50\times10^9$ cells per L and absolute neutrophil count of at least $1{\cdot}0\times10^9$ cells per L (unless due to bone marrow infiltration), and creatinine clearance of at least 45 mL/min. Further eligibility criteria are provided in the appendix (pp 18–19). Patients were recruited by their treating physician and provided written informed consent to participate. The study was approved by the Medical Ethical Committee of the Academic Medical Centre of Amsterdam and was conducted according to the principles of the Declaration of Helsinki.

### Randomisation and masking

Eligible patients received two debulking cycles of obinutuzumab, followed by six cycles of obinutuzumab and 12 cycles of venetoclax. Next, patients were randomly assigned (1:1) to receive either 12 cycles of venetoclax consolidation irrespective of MRD status (consolidation group), or venetoclax consolidation for only as long as MRD positivity was shown in peripheral blood (for a maximum of 12 cycles; MRD-guided consolidation group). Randomisation for consolidation treatment was performed after cycle 12 of fixed-duration venetoclax plus obinutuzumab if the patient had at least a partial response according to IwCLL guidelines.[13] Patients were randomly assigned, stratified by MRD status in peripheral blood (undetectable MRD *vs* MRD-positive), with a minimisation procedure, ensuring balance within each stratum and overall balance by a computer-generated randomisation schedule at the HOVON data centre (Rotterdam, Netherlands). Randomisation group assignment results were given to the investigators immediately by phone or using a web-based system and confirmed by fax or email. Neither the investigators nor patients were masked to treatment assignment.

### Procedures

Treatments were administered in 28-day cycles. There were three treatment phases: pre-induction for debulking with two cycles of intravenous obinutuzumab monotherapy (starting with 100 mg on day 1 and 900 mg on day 2, 1000 mg on days 8 and 15, and subsequently 1000 mg on day 1 of cycle two); fixed-duration 12 cycles of venetoclax plus obinutuzumab (six cycles of intravenous obinutuzumab 1000 mg on day 1 and 12 cycles of oral venetoclax, starting with a 5-week dose ramp-up [each week, with 20 mg, 50 mg, 100 mg, and 200 mg, then 400 mg once daily until completion of cycle 12); and consolidation with either 12 cycles of oral venetoclax 400 mg, irrespective of MRD status in the consolidation group, or venetoclax only if MRD positivity was shown in peripheral blood (until undetectable MRD was reached or for a maximum of 12 cycles) in the MRD-guided consolidation group. Dose modifications and interruptions were allowed for management of adverse events. At first occurence of neutropenia grade 3–4 and thrombocytopenia grade 4, venetoclax and obintuzumab were withheld until recovery to grade 2 or better and restarted at the same dose level. At reappearance of the adverse event, subsequent dose level reduction of venetoclax (200 mg, 100 mg, 50 mg, 20 mg) was advised after withholding until recovery, with restart of obinutuzumab. For non-haematological toxicity grade 2–4, delay of venetoclax and obintuzumab was recommended until recovery to grade 1 or better, with dose level reductions of venetoclax for reappearance of grade 3–4 toxicity. In case of one infusion-related reaction of grade 4 or three of grade 3, obintuzumab was discontinued permanently.

Response assessment according to IwCLL guidelines[14] based on clinical parameters, full blood count, and CT scan was done by the site investigator after two cycles of pre-induction, at fixed-duration cycle 12 (including bone marrow biopsy), 3 months after consolidation cycle 12 or at a corresponding timepoint (including bone marrow biopsy), and at progression. MRD responses in peripheral blood and bone marrow were assessed at the central laboratory of the University Medical Centre of Amsterdam (Amsterdam, Netherlands) by six-colour flow cytometry with a sensitivity of at least $10^{-4}$, as previously validated against immunoglobulin heavy-chain allele-specific quantitative real-time PCR,[14] using an international standardised approach.[15] MRD in bone marrow was assessed at fixed-duration cycle 12 and 3 months after consolidation cycle 12 (or corresponding timepoint). MRD in peripheral blood was assessed at fixed-duration cycle six and 12 and at consolidation cycles three, six, nine, and 12, and 3 months after consolidation cycle 12 (or corresponding timepoint). MRD values were categorised as undetectable ($<10^{-4}$; ie, less than one chronic lymphocytic leukaemia cell per 10 000 leukocytes), low positive ($\geq10^{-4}$ and $<10^{-2}$), and high positive ($\geq10^{-2}$). Baseline genetic markers and biomarkers were also analysed at the central laboratory of the University Medical Centre of Amsterdam (appendix p 113).Tumour lysis syndrome risk was assessed on the basis of absolute lymphocyte count and lymph node size and graded into three categories with corresponding prophylactic measures, and tumour lysis syndrome scored according to Cairo–Bishop guidelines (appendix p 90).[16,17] Adverse events were reported after each fixed-duration cycle and every 3 months after randomisation until 30 days after the last dose of any drug from the protocol. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4. Until 1 year after the last patient had completed protocol treatment, an annual safety report was submitted to the Ethics Committees and competent authorities of the respective member states.

### Outcomes

The primary endpoint was centrally assessed undetectable MRD in bone marrow and no progressive

disease according to IwCLL criteria at the completion of trial assessment (3 months after end of consolidation cycle 12 or corresponding timepoint, by the local investigator). Secondary endpoints were overall response rate (patients with partial or complete response), progression-free survival (defined as the time from the date of enrolment to disease progression or death), event-free survival (defined as the time from enrolment to fixed-duration treatment failure [no partial or complete response], death, or disease progression), overall survival (defined as the time between enrolment and death due to any cause), MRD response rate (determined as the proportion of patients with undetectable, low-positive, and high-positive MRD) measured in peripheral blood or bone marrow, and toxicity of venetoclax ramp-up. Quality of life, geriatric assessments, and resistance mechanisms were also secondary endpoints but will be analysed and reported separately. Analysis of the prognostic value for response of the baseline characteristics immunoglobulin heavy-chain variable region (IGHV) mutation status, genomic complexity, and *TP53* status was an exploratory post-hoc endpoint.

### Statistical analysis

The sample size needed for the primary endpoint was estimated on the basis of the undetectable MRD results of the CLL11 trial in patients with previously untreated chronic lymphocytic leukaemia and coexisting conditions.[18] Sample size was calculated using an A'hern design, based on a 25% probability boundary for the null hypothesis and a 50% probability boundary for the alternative hypothesis, an $\alpha$ of 0·05, and a power of (1−$\beta$) 80%, which resulted in a sample size of 26 patients in each consolidation treatment group, with at least 11 successes needed to warrant further investigation. Considering a putative 20% fixed-duration treatment failure and 5% ineligibility rate, 70 patients were planned to be enrolled in the trial. Patients were withdrawn from the study in case of death, non-eligibility in hindsight, disease progression during treatment, failure at the end of fixed-duration treatment (defined as no partial or complete response), excessive toxicity according to the treating physician, or patient decision to discontinue protocol treatment. The consolidation treatment groups were analysed separately, and no formal comparison between the treatment groups was made. Because a single primary endpoint for each treatment group was defined, no adjustment for multiple testing in the sample size calculation was needed. The primary endpoint was analysed in all patients who were randomly assigned to a treatment group.

For the primary endpoint analysis and secondary proportion endpoints, a binomial exact test was used and point estimates with 95% CIs were calculated according to the Clopper–Pearson method.[19] For the primary endpoint, the null hypothesis was rejected in favour of the alternative hypothesis if the lower bound of the 95% CI was larger than 0·25. The time-to-event endpoints (progression-free survival, event-free survival, and overall survival) were estimated for the intention-to-treat population (defined as all eligible enrolled patients) using the Kaplan-Meier method.

Safety was assessed in all patients who received at least one dose of any study drug. Toxicities were tabulated as adverse events. All analyses were performed using Stata (version 16.1) and a p value of less than 0·05 was considered significant.

One safety interim analysis was performed on Feb 1, 2018, when the first 30 patients had completed the first three cycles of therapy.[16] An independent data monitoring committee reviewed the results of interim analyses with respect to safety and efficacy.

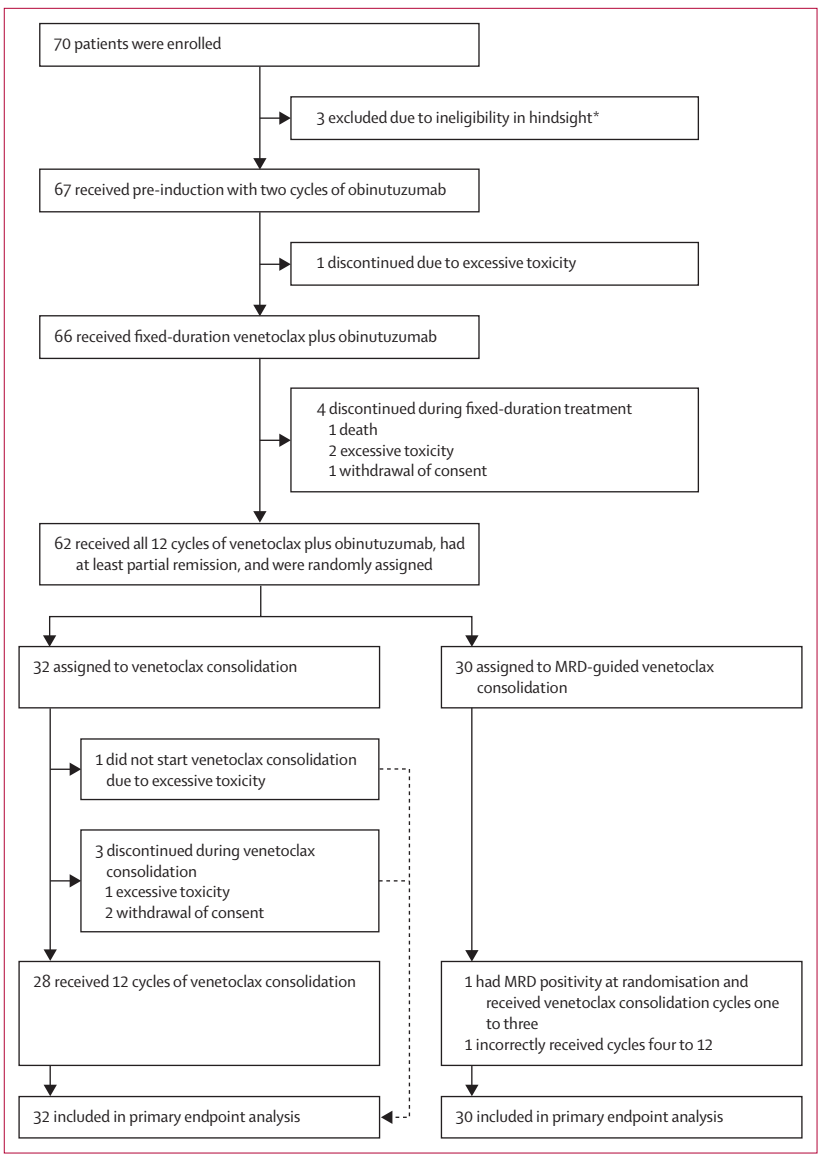


***Figure 1:*** **Trial profile**
MRD=minimal residual disease. *One patient had small lymphocytic lymphoma, one had splenic lymphoma, and one had synchronous breast cancer.

| | Consolidation group (n=32) | Minimal residual disease-guided consolidation group (n=30) | Patients not randomly assigned (n=5) |
|---|---|---|---|
| Age, years | 72 (69–75) | 71 (68–74) | 76 (71–77) |
| Sex | | | |
| Male | 24 (75%) | 20 (67%) | 3 (60%) |
| Female | 8 (25%) | 10 (33%) | 2 (40%) |
| ECOG performance status | | | |
| 0 | 17 (53%) | 14 (47%) | 4 (80%) |
| 1 | 14 (44%) | 14 (47%) | 1 (20%) |
| 2 | 1 (3%) | 2 (7%) | 0 |
| Binet stage | | | |
| A | 6 (19%) | 3 (10%) | 0 |
| B | 14 (44%) | 11 (37%) | 1 (20%) |
| C | 12 (38%) | 16 (53%) | 4 (80%) |
| Cumulative Illness Rating Scale score | 3 (1–5) | 3 (1–5) | 2 (1–6) |
| IGHV mutational status | | | |
| Mutated | 13 (41%) | 11 (37%) | 2 (40%) |
| Unmutated | 17 (53%) | 14 (47%) | 2 (40%) |
| Not available | 2 (6%) | 5 (17%) | 1 (20%) |
| TP53 aberration* | 5 (16%) | 4 (13%) | 0 |
| Genomic complexity | | | |
| None (0–2 copy number aberrations) | 25 (78%) | 23 (77%) | 4 (80%) |
| Low (3–4 copy number aberrations) | 5 (16%) | 5 (17%) | 0 |
| High (≥5 copy number aberrations) | 2 (6%) | 2 (7%) | 1 (20%) |
| Haemoglobin concentration, g/dL | 12 (10–13) | 11 (10–12) | 12 (10–12) |
| Platelet count, $\times 10^9$ cells per L | 143 (109–210) | 111 (79–220) | 127 (91–172) |
| White blood cell count, $\times 10^9$ cells per L | 110 (65–217) | 82 (55–175) | 79 (9–159) |
| Lymphocyte count, $\times 10^9$ cells per L | 95 (62–160) | 82 (55–175) | 72 (6–155) |
| $\beta_2$ microglobin concentration, mg/L | 4 (4–5) | 4 (3–6) | 5 (4–5) |
| Creatinine clearance, mL/min | 71 (57–79) | 73 (65–87) | 77 (63–83) |
| CLL-IPI risk group | | | |
| Low risk (score 0–1) | 0 | 2 (7%) | 0 |
| Intermediate risk (score 2–3) | 8 (25%) | 2 (7%) | 0 |
| High risk (score 4–6) | 18 (56%) | 18 (60%) | 3 (60%) |
| Very high risk (score 7–10) | 5 (16%) | 4 (13%) | 0 |
| Missing | 1 (3%) | 4 (13%) | 2 (40%) |

Data are n (%) or median (IQR) . IGHV=immunoglobulin heavy-chain variable region. CLL-IPI=Chronic Lymphocytic Leukaemia International Prognostic Index. *del(17p) or *TP53* mutation.

***Table 1:*** **Baseline characteristics**

This is the primary endpoint analysis of this trial, which is ongoing and is registered with EudraCT (2015-004985-27) and the Netherlands Trial Register (NTR6043).

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

Between Oct 28, 2016, and May 31, 2018, 70 patients were enrolled, of whom three were later excluded because of ineligibility in hindsight (one patient with small lymphocytic lymphoma, one with splenic lymphoma, and one with synchronous breast cancer; figure 1). 67 (47 [70%] men and 20 [30%] women) patients received fixed-duration treatment, five of whom discontinued during fixed-duration treatment due to death (n=1), withdrawal of consent (n=1), or excessive toxicity (n=3) and did not proceed to randomisation. 62 patients were randomly assigned to a treatment group (table 1). 32 patients were assigned to the consolidation group, 28 of whom received 12 cycles of venetoclax consolidation (four patients in this group discontinued earlier due to excessive toxicity or withdrawal of consent). 30 patients were assigned to the MRD-guided consolidation group, one of whom received venetoclax consolidation cycles one to three because of MRD positivity at randomisation and subsequently showed undetectable MRD in peripheral blood; 29 (97%) of 30 had undetectable MRD at randomisation and therefore did not receive consolidation, although one patient with undetectable MRD at randomisation incorrectly received venetoclax consolidation cycles four to 12 after showing MRD positivity (figure 1).

At the data cutoff date of Feb 11, 2021, all patients had been off treatment for at least 8 months, with a median follow-up of 35·2 months (IQR 31·5–41·3). 16 (50% [95% CI 32–68]) of 32 patients in the consolidation group, at 3 months after the last consolidation cycle, and 16 (53% [34–72]) of 30 in the MRD-guided consolidation group, at the corresponding timepoint, met the primary endpoint of undetectable MRD in bone marrow and no progressive disease. In the intention-to-treat population, 63 (94%) of 67 patients on fixed-duration treatment had an overall response (21 [31%] had a complete response). Best response on treatment (including consolidation) was complete response in 37 (55%) of 67 patients, partial response in 26 (39%), and stable disease in two (3%). At completion of trial assessment, 13 (41%) of 32 patients in the consolidation group and 18 (60%) of 30 in the MRD-guided consolidation group had a complete response, 25 (78%) and 29 (97%) had overall response; progressive disease occurred in three (9%) and one (3%), respectively. 3-year progression-free survival was 85% (95% CI 72–92; seven [10%] of 67 patients had disease progression and two [3%] died), 3-year overall survival was 94% (95% CI 83–98; three [4%] died), and 3-year event-free survival was 83% (95% CI 72–90; three [4%] had no partial response after fixed-duration treatment, seven [10%] had disease progression, and one [1%] died; figure 2).

In the intention-to-treat population, undetectable MRD in peripheral blood was reached after cycle six of venetoclax plus obinutuzumab in 56 (84%) of 67 patients and after cycle 12 in 59 (88%). Undetectable MRD in bone marrow was reached after cycle 12 of venetoclax plus obinutuzumab in 53 (79%) of 67 patients. In patients assigned to the

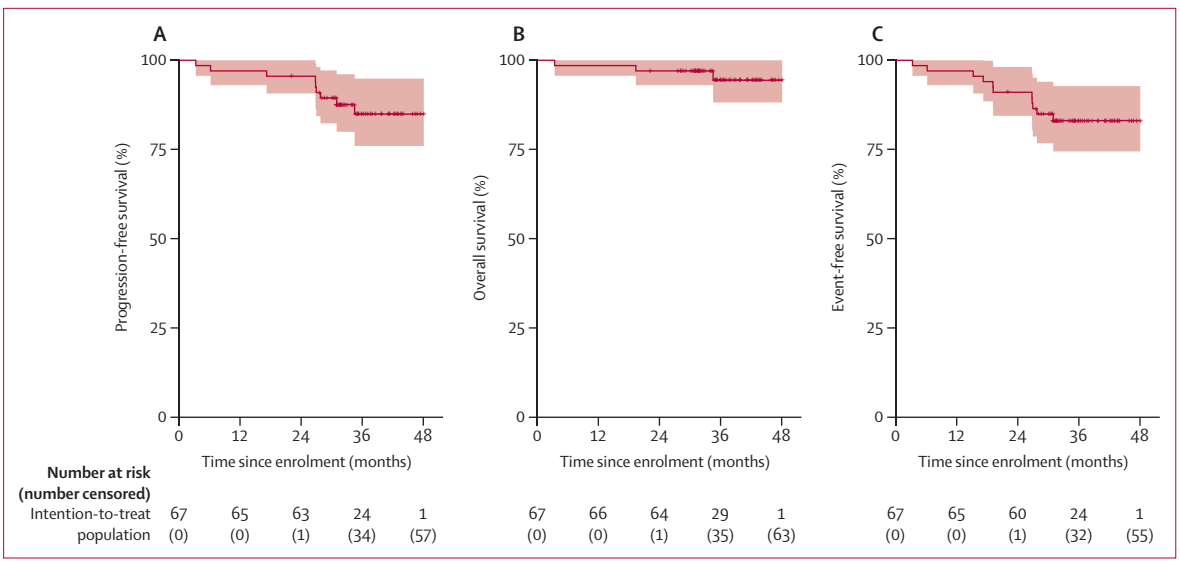


***Figure 2:*** **Kaplan-Meier survival curves**
(A) Progression-free survival. (B) Overall survival. (C) Event-free survival. Ticks indicate censored patients. Shading indicates 95% CIs.

consolidation group, 27 (84%) of 32 had undetectable MRD in bone marrow at the time of randomisation; 3 months after consolidation cycle 12, the proportion had decreased to 19 (59%). Data on bone marrow MRD were missing in seven (22%) patients in the consolidation group. 30 (94%) of 32 patients had undetectable MRD in peripheral blood at the time of randomisation; 3 months after consolidation cycle 12, the proportion had decreased to 23 (72%; figure 3). In patients assigned to the MRD-guided consolidation group, 26 (87%) of 30 had undetectable MRD in bone marrow at the time of randomisation; at the end of trial evaluation, the proportion had decreased to 17 (57%). Data on bone marrow MRD were missing in three (10%) patients in the MRD-guided consolidation group. 29 (97%) of 30 patients had undetectable MRD in peripheral blood at the time of randomisation; at the end of trial assessment, the proportion had decreased to 17 (57%). Three patients died, of whom one was on protocol treatment and the death was deemed unrelated to treatment.

Adverse events leading to discontinuation of study treatment occurred in three (4%) of 67 patients (one severe pneumonia, one possible meningitis, and one unknown) during fixed-duration treatment and two (6%) of 32 patients in the consolidation group discontinued consolidation treatment because of toxicity (one heart failure and one neutropenic fever). During fixed-duration treatment, 51 (76%) of 67 patients had venetoclax dose reductions, mainly for haematological toxicity (neutropenia). In the consolidation group, eight (25%) of 32 patients had venetoclax dose reductions and in the MRD-guided consolidation group, two (100%) of two who received venetoclax had dose reductions. 28 (42%) of 67 patients received granulocyte colony-stimulating factor (G-CSF) to treat or prevent neutropenia.

During pre-induction and fixed-duration cycles, all patients had at least one adverse event. Any adverse event of grade 2 occurred in 14 (21%) of 67 patients, grade 3 in 35 (52%), and grade 4 in 17 (25%). One patient died of aspiration pneumonia unrelated to treatment. Any adverse events of grade 2–4 (mainly infections) occurred in 22 (69%) of 32 patients in the consolidation group and 11 (37%) of 30 in the MRD-guided consolidation group (table 2). The most common grade 3 or worse adverse events were infection (two [6%] of 32 patients in the consolidation group and one [3%] of 30 in the MRD-guided consolidation group) and neutropenia (two [6%] and two [7%]). Five malignancies occurred, of which four were localised skin tumours and one was prostate cancer.

Two pre-induction cycles of obinutuzumab reduced tumour lysis syndrome risk; at baseline 19 (28%) patients were categorised as high risk, 40 (60%) as intermediate risk, and eight (12%) as low risk. After two cycles of obinutuzumab, one (1%) patient was categorised as high risk, ten (15%) as intermediate risk, and 54 (81%) as low risk for tumour lysis syndrome. Four (6%) patients developed laboratory tumour lysis syndrome (two grade 1 and two grade 3). Only two patients developed laboratory tumour lysis syndrome during venetoclax ramp-up (grade 1 and grade 3). All cases of laboratory tumour lysis syndrome resolved with hydration and rasburicase. No patients developed clinical tumour lysis syndrome.

Exploratory analyses for baseline genetic markers of possible prognostic value showed no clear effect for mutational status, *TP53* status, or genomic complexity on reaching undetectable MRD (appendix p 114).

## Discussion

This primary endpoint analysis of the open-label, randomised, parallel-group, phase 2 HOVON 139/GiVe

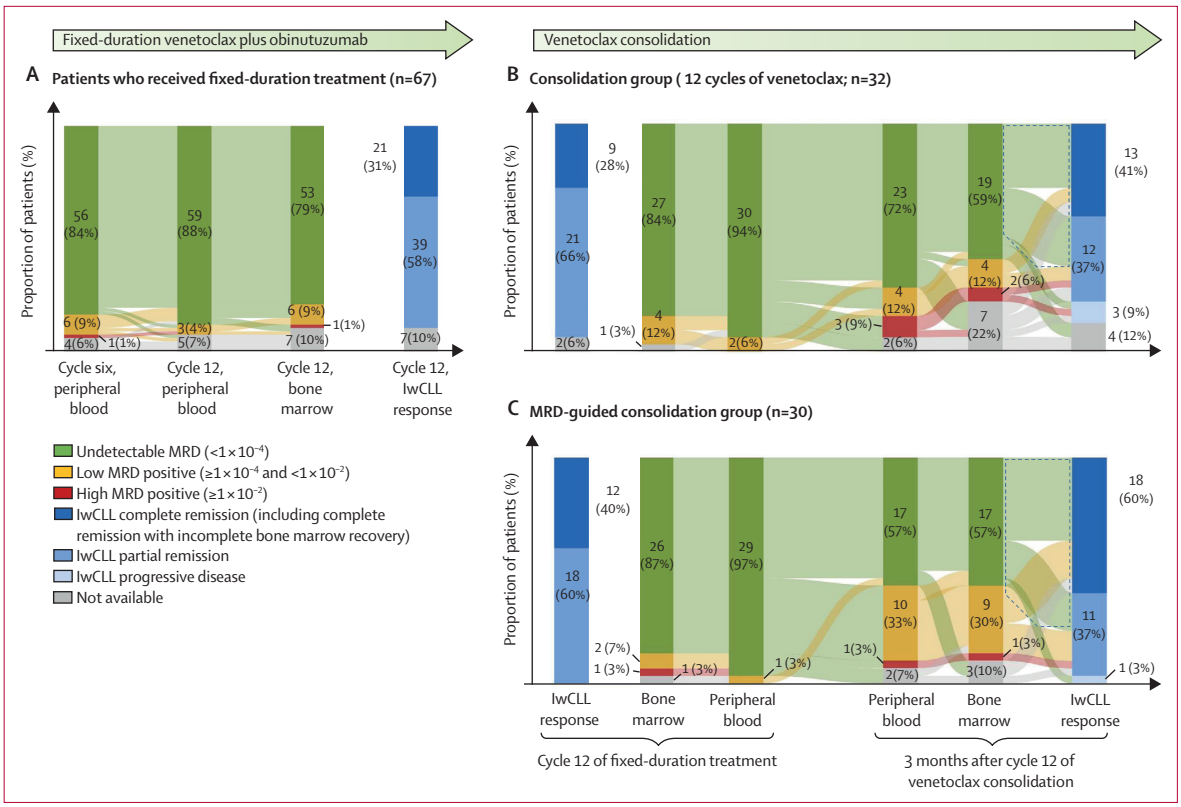


***Figure 3:*** **Sankey plot showing MRD kinetics**
MRD kinetics are shown for the intention-to-treat population from baseline until end of fixed-duration treatment cycle 12 (A) and for the randomly assigned population in the consolidation group (B) and the MRD-guided consolidation group (C) from end of fixed-duration treatment until 3 months after end of consolidation or corresponding timepoint, respectively. The three MRD categories (undetectable, low positive, and high positive) are depicted in peripheral blood and in bone marrow. IwCLL clinical responses are shown at cycle 12 of fixed-duration treatment and at 3 months after end of consolidation (consolidation group) or corresponding timepoint (MRD-guided consolidation group). Patients who had both undetectable MRD in bone marrow and absence of progressive disease at 3 months after end of consolidation or corresponding timepoint are highlighted by dashed line boxes and represent the primary endpoint success rate. MRD=minimal residual disease. IwCLL=International Workshop on Chronic Lymphocytic Leukemia.

| | During pre-induction and fixed-duration treatment (n=67) | | | | During venetoclax consolidation in the consolidation group (n=32) | | | | During observation or venetoclax consolidation in the minimal residual disease-guided consolidation group (n=30) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
| Any | 14 (21%) | 35 (52%) | 17 (25%) | 1 (1%) | 14 (44%) | 6 (19%) | 2 (6%) | 0 | 7 (23%) | 4 (13%) | 0 | 0 |
| Infection | 30 (45%) | 7 (10%) | 0 | 0 | 14 (44%) | 2 (6%) | 0 | 0 | 5 (17%) | 1 (3%) | 0 | 0 |
| Neutropenia | 3 (4%) | 24 (36%) | 12 (18%) | 0 | 0 | 0 | 2 (6%) | 0 | 0 | 2 (7%) | 0 | 0 |
| Diarrhoea, abdominal discomfort, or stomach complaints | 8 (12%) | 2 (3%) | 0 | 0 | 0 | 1 (3%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Malignancy or neoplasm | 2 (3%) | 1 (1%) | 0 | 0 | 1 (3%) | 1 (3%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypertension | 5 (7%) | 1 (1%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Data are n (%). Grade 2 events with frequency 10% or higher and grade 3–5 events with frequency 1% or higher are shown. Data on grade 1 adverse events were not collected and are therefore not present.

***Table 2:*** **Adverse events**

trial showed that 12 cycles of fixed-duration venetoclax plus obinutuzumab resulted in a high rate of undetectable MRD in previously untreated patients with chronic lymphocytic leukaemia who were unfit for fludarabine-based treatment. MRD measurement in peripheral blood following fixed-duration treatment was not suitable to

guide venetoclax consolidation, because nearly all patients (97%) already had undetectable MRD.

The proportion of patients who met the primary endpoint of MRD-negative bone marrow and no progressive disease at the end of trial assessment was similar in both study groups (50% in the consolidation group and 53% in the MRD-guided consolidation group). After six cycles of venetoclax plus obinutuzumab, 84% of patients already had undetectable MRD in peripheral blood, which was similar to the proportion after cycle 12 (88%). An early plateau in undetectable MRD was also seen in the CLL14 trial,[12] although with slightly lower percentages (70% in peripheral blood at cycle seven and 72% at cycle 12). This difference between the trials might be explained by the additional two pre-induction cycles of obinutuzumab in the HOVON 139/GiVe trial. This finding suggests that the two pre-induction cycles of obinutuzumab not only result in effective debulking for tumour lysis syndrome risk mitigation,[16] but might also improve the undetectable MRD rate.

In both study groups, undetectable MRD rate in bone marrow and peripheral blood was higher after end of fixed-duration venetoclax plus obinutuzumab than after consolidation or the observation period, indicating loss of MRD response despite continuous treatment. A similar observation was found in the CLL14 trial, where half of the MRD-positive patients showed increasing MRD levels while on treatment.[20] In the MURANO study[7] of venetoclax plus rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia with 2 years of venetoclax treatment, loss of undetectable MRD occurred before treatment cessation. This finding indicates that, in some patients, chronic lymphocytic leukaemia subclones emerge that are venetoclax resistant. Consequently, such patients will not benefit from consolidation treatment.[10] This occurrence has not yet been observed with the combination of venetoclax plus ibrutinib, where responses have been shown to deepen over time, although head-to-head comparisons have not been done.[21,22]

It is well known that undetectable MRD is a predictor for progression-free survival after chemoimmunotherapy.[9,23] Undetectable MRD following both first-line and second-line treatment with venetoclax and anti-CD20 is highly predictive for prolonged progression-free survival.[24] It has also been shown that the MRD growth dynamics differ between chemoimmunotherapy and venetoclax plus obinutuzumab, with slower MRD increase after venetoclax-based treatment.[25,26] In CLL14, progression-free survival was lower for patients with *TP53* mutations than for those without, even if treated with venetoclax, but no difference was found by IGHV mutation status.[27] Additionally, patients with complex karyotype had similar responses on venetoclax.[28] Dynamics of MRD are influenced by depth of MRD as well as acceleration of regrowth in high-risk disease. We were unable to identify an association between baseline genetic markers and post-treatment MRD status, which might have been due to the low number of patients in these subgroups.

As well as the small number of patients, another limitation to the MRD-guided approach was the unexpectedly high rate of undetectable MRD in peripheral blood after fixed-duration treatment, resulting in only one patient receiving venetoclax consolidation in the MRD-guided consolidation group. Because MRD was not measured between cycles six and 12, our data cannot be used to consider MRD-guided treatment cessation before 12 cycles of treatment. It might be, however, that a more dynamic approach than an MRD measurement at one timepoint provides better selection of patients who benefit from consolidation.

Another limitation of this study is the missing data on MRD in bone marrow at the completion of trial assessment, which could potentially obscure deep responses, with 22% missing in the consolidation group and 10% missing in the MRD-guided consolidation group. To address this limitation, a follow-up study using a next-generation sequencing approach to analyse MRD of less than one chronic lymphocytic leukaemia cell per 100 000 leukocytes in peripheral blood will be performed.

Complete response rates increased from end of fixed-duration treatment to completion of trial assessment in both study groups, which suggests that there is ongoing activity of venetoclax, specifically in the lymph node compartment, even after treatment cessation. Whether the same occurred in CLL14 is not known, as no mandatory CT scan during follow-up was performed in that study.[8] It is known from the MURANO study that undetectable MRD is more strongly associated with superior progression-free survival than IwCLL response.[10] Due to the short follow-up of nearly 3 years in our study, no conclusions on survival can be made, but a longer follow-up study is currently being conducted.

By contrast with CLL14, where all patients had a total score of greater than 6 on the Cumulative Illness Rating Scale or a creatinine clearance of less than 70 mL/min, the median score in our trial was only 3, indicating a fitter population. All these patients were deemed unfit for fludarabine-based treatment by their treating physician because of age older than 65 years or coexisting conditions, according to the national guidelines.[29] Because new agents were not yet reimbursed for treatment-naive patients in the Netherlands by the start of this trial, patient or physician preferences for chemotherapy-free regimens might have had a role in the selection of this fitter population.

We confirm that toxicity of fixed-duration venetoclax plus obinutuzumab is manageable for patients with chronic lymphocytic leukaemia who are unfit for fludarabine-based treatment. No new safety signals and no treatment-related fatal adverse events were observed. Similar to what is known from chemoimmunotherapy, neutropenia and infections were the most prevalent

adverse events, despite treatment with G-CSF. Toxicity or patient decision to stop were the main reasons to discontinue fixed-duration treatment (four patients). Moreover, four additional patients discontinued during venetoclax consolidation, indicating the effect of side-effects during prolonged venetoclax exposure. This finding was emphasised by the small number of adverse events in patients who did not receive consolidation venetoclax. Reduced drug exposure has economic benefits and might result in better quality of life, which will be analysed in further studies.

The main goal in tailoring venetoclax duration is to improve quality of life by increasing the duration of treatment-free response without compromising long-term treatment outcome, as learned from chronic myeloid leukaemia.[30] In this study, we showed that an optimal response is found after 12 cycles of fixed-duration venetoclax plus obinutuzumab in the majority of patients with chronic lymphocytic leukaemia. Consolidation with venetoclax 12-cycle treatment increases the duration of known side-effects and does not prevent the loss of MRD response and subsequent risk of disease relapse.

#### Contributors

SK, APK, and M-DL designed the research; collected, analysed, and interpreted the data; and wrote the first draft of the manuscript. JD performed the MRD analysis and wrote the first draft of the manuscript. KN performed the statistical analysis and wrote the first draft of the manuscript. JAD, CM, and A-MFvdK-K did the central laboratory assessments. SK, JD, KN, M-DL, and APK accessed and verified the masked data, and confirmed its accuracy and completeness. LME, FdB, HRK, JS, MvdK, GAV, EvdS, HMvdS, MH, MvG, EFMP, HPJV, IH, CAMI, DEI, ECD, HCTvZ, HV, HL, LWT, WET, SHT, MB, and MM had full access to all data and interpreted and reviewed the data. All authors critically reviewed and approved the manuscript. All authors had final responsibility for the decision to submit for publication.

#### Declaration of interests

APK reports personal fees from AbbVie, LAVA, Genmab, Janssen, AstraZeneca, Roche/Genentech, and Bristol Myers Squibb; and research funding from AbbVie, Janssen, AstraZeneca, Roche/Genentech, and Bristol Myers Squibb. EvdS reports honoraria from Janssen and Amgen; and support for attending meetings from Janssen. JD reports research funding from Roche/Genentech. SK reports personal fees from Janssen, AbbVie, Novartis, Gilead, and Celgene; and research funding from AbbVie, Janssen, AstraZeneca, and Roche/Genentech. M-DL reports personal fees from AbbVie, Janssen, and Roche; and research funding from AbbVie, Janssen, AstraZeneca, and Roche/Genentech. SHT reports personal fees from Roche, Takeda, Incyte, Kite/Gilead, and Celgene. All other authors declare no competing interests.

#### Data sharing

The HOVON CLL study group and Roche will consider data sharing requests on a case-by-case basis. Upon 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 HOVON CLL study group and Roche. The study protocol is provided in the appendix (pp 2–112). The statistical analysis plan and informed consent form will be made available upon request to the corresponding author.

#### Acknowledgments

This study was funded by F Hoffmann-La Roche (ML29995). We thank all the patients, their families, and the nurses and physicians for their participation in the trial. The study was conducted by the HOVON study group on behalf of the HOVON CLL working group (appendix p 115). Data were analysed at the Erasmus University Medical Centre in Rotterdam, Netherlands, and we thank all team members involved.

#### References

1 von Tresckow J, Eichhorst B, Bahlo J, Hallek M. The treatment of chronic lymphatic leukemia. *Dtsch Arzebl Int* 2019; **116:** 41–46.
2 Awan FT, Al-Sawaf O, Fischer K, Woyach JA. Current perspectives on therapy for chronic lymphocytic leukemia. *Am Soc Clin Oncol Educ Book* 2020; **40:** 1–10.
3 Sengar M, Jain H, Rajendra A, Rengaraj K, Thorat J. Frontline therapy of chronic lymphocytic leukemia: changing treatment paradigm. *Curr Hematol Malig Rep* 2020; **15:** 168–76.
4 Scheffold A, Stilgenbauer S. Revolution of chronic lymphocytic leukemia therapy: the chemo-free treatment paradigm. *Curr Oncol Rep* 2020; **22:** 16.
5 Burger JA, O'Brien S. Evolution of CLL treatment—from chemoimmunotherapy to targeted and individualized therapy. *Nat Rev Clin Oncol* 2018; **15:** 510–27.
6 Schiattone L, Ghia P, Scarfò L. The evolving treatment landscape of chronic lymphocytic leukemia. *Curr Opin Oncol* 2019; **31:** 568–73.
7 Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med* 2018; **378:** 1107–20.
8 Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med* 2019; **380:** 2225–36.
9 Kovacs G, Robrecht S, Fink AM, et al. Minimal residual disease assessment improves prediction of outcome in patients with chronic lymphocytic leukemia (CLL) who achieve partial response: comprehensive analysis of two phase III studies of the German CLL study group. *J Clin Oncol* 2016; **34:** 3758–65.
10 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* 2019; **37:** 269–77.
11 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* 2020; **38:** 4042–54.
12 Al-Sawaf O, Fink A-M, Robrecht S, et al. Prevention and management of tumor lysis syndrome in patients with CLL and coexisting conditions treated with venetoclax–obinutuzumab or chlorambucil–obinutuzumab: results from the randomized CLL14 trial. *Blood* 2019; **134** (suppl 1): 4315 (abstr).
13 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* 2008; **111:** 5446–56.
14 Böttcher S, Stilgenbauer S, Busch R, et al. Standardized MRD flow and ASO IGH RQ-PCR for MRD quantification in CLL patients after rituximab-containing immunochemotherapy: a comparative analysis. *Leukemia* 2009; **23:** 2007–17.
15 Rawstron AC, Fazi C, Agathangelidis 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* 2016; **30:** 929–36.
16 Kater AP, Kersting S, van Norden Y, et al. Obinutuzumab pretreatment abrogates tumor lysis risk while maintaining undetectable MRD for venetoclax + obinutuzumab in CLL. *Blood Adv* 2018; **2:** 3566–71.
17 Gribben JG. Practical management of tumour lysis syndrome in venetoclax-treated patients with chronic lymphocytic leukaemia. *Br J Haematol* 2020; **188:** 844–51.
18 Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* 2014; **370:** 1101–10.
19 Westfall P. Simultaneous small-sample multivariate Bernoulli confidence intervals. *Biometrics* 1985; **41:** 1001–13.
20 Fischer K, Ritgen M, Al-Sawaf O, et al. Quantitative analysis of minimal residual disease (MRD) shows high rates of undetectable MRD after fixed-duration chemotherapy-free treatment and serves as surrogate marker for progression-free survival: a prospective analysis of the randomized CLL14 trial. *Blood* 2019; **134** (suppl 1): 36 (abstr).

21 Hillmen P, Rawstron AC, Brock K, et al. Ibrutinib plus venetoclax in relapsed/refractory chronic lymphocytic leukemia: the CLARITY study. *J Clin Oncol* 2019; **37:** 2722–29.

22 Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: primary analysis results from the minimal residual disease cohort of the randomized phase II CAPTIVATE study. *J Clin Oncol* 2021; **39:** 3853–65.

23 Böttcher 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* 2012; **30:** 980–88.

24 Al-Sawaf O, Seymour JF, Kater AP, Fischer K. Should undetectable minimal residual disease be the goal of chronic lymphocytic leukemia therapy? *Hematol Oncol Clin North Am* 2021; **35:** 775–91.

25 Al-Sawaf O, Zhang C, Robrecht S, et al. Clonal dynamics after venetoclax–obinutuzumab therapy: novel insights from the randomized, phase 3 CLL14 trial. *Blood* 2020; **136** (suppl 1)**:** 22–23 (abstr).

26 Kater AP, Kipps TJ, Eichhorst B, et al. Five-year analysis of MURANO study demonstrates enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients (Pts) following fixed-duration venetoclax–rituximab (VenR) therapy (Tx). *Blood* 2020; **136** (suppl 1)**:** 19–21 (abstr).

27 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* 2020; **135:** 2402–12.

28 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* 2020; **135:** 866–70.

29 Kersting S, Neppelenbroek SIM, Visser HPJ, et al. Clinical practice guidelines for diagnosis and treatment of chronic lymphocytic leukemia (CLL) in the Netherlands. *Clin Lymphoma Myeloma Leuk* 2018; **18:** 52–57.

30 Mahon FX. Treatment-free remission in CML: who, how, and why? *Hematology (Am Soc Hematol Educ Program)* 2017; **2017:** 102–09.