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Minimal residual disease-guided stop and start of venetoclax plus ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia (HOVON141/VISION): primary analysis of an open-label, randomised, phase 2 trial

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Summary

Background Targeted time-limited treatment options are needed for patients with relapsed or refractory chronic lymphocytic leukaemia. The aim of this study was to investigate the efficacy of minimal residual disease (MRD)-guided, time-limited ibrutinib plus venetoclax treatment in this patient group.

Methods HOVON141/VISION was an open-label, randomised, phase 2 trial conducted in 47 hospitals in Belgium, Denmark, Finland, the Netherlands, Norway, and Sweden. Eligible participants were aged 18 years or older with previously treated chronic lymphocytic leukaemia with or without *TP53* aberrations; had not been exposed to Bruton tyrosine-kinase inhibitors or BCL2 inhibitors; had a creatinine clearance rate of 30 mL/min or more; and required treatment according to International Workshop on Chronic Lymphocytic Leukemia 2018 criteria. Participants with undetectable MRD ($<10^{-4}$; less than one chronic lymphocytic leukaemia cell per 10 000 leukocytes) in peripheral blood and bone marrow after 15 28-day cycles of oral ibrutinib (420 mg once daily) plus oral venetoclax (weekly ramp-up 20 mg, 50 mg, 100 mg, 200 mg, up to 400 mg once daily) were randomly assigned (1:2) to ibrutinib maintenance or treatment cessation. Patients who were MRD positive continued to receive ibrutinib monotherapy. Patients who became MRD ($>10^{-2}$) during observation reinitiated treatment with ibrutinib plus venetoclax. The primary endpoint was progression-free survival at 12 months after random assignment in the treatment cessation group. Progression-free survival was analysed in the intention-to-treat population. All patients who received at least one dose of study drug were included in the safety assessment. The study is registered at ClinicalTrials.gov, NCT03226301, and is active but not recruiting.

Findings Between July 12, 2017, and Jan 21, 2019, 230 patients were enrolled, 225 of whom were eligible. 188 (84%) of 225 completed treatment with ibrutinib plus venetoclax and were tested for MRD at cycle 15. After cycle 15, 78 (35%) patients had undetectable MRD and 72 (32%) were randomly assigned to a treatment group (24 to ibrutinib maintenance and 48 to treatment cessation). The remaining 153 patients were not randomly assigned and continued with ibrutinib monotherapy. Median follow-up of 208 patients still alive and not lost to follow-up at data cutoff on June 22, 2021, was 34·4 months (IQR 30·6–37·9). Progression-free survival after 12 months in the treatment cessation group was 98% (95% CI 89–100). Infections (in 130 [58%] of 225 patients), neutropenia (in 91 [40%] patients), and gastrointestinal adverse events (in 53 [24%] patients) were the most frequently reported; no new safety signals were detected. Serious adverse events were reported in 46 (40%) of 116 patients who were not randomly assigned and who continued ibrutinib maintenance after cycle 15, eight (33%) of 24 patients in the ibrutinib maintenance group, and four (8%) of 48 patients in the treatment cessation group. One patient who was not randomly assigned had a fatal adverse event (bleeding) deemed possibly related to ibrutinib.

Interpretation These data point to a favourable benefit–risk profile of MRD-guided, time-limited treatment with ibrutinib plus venetoclax for patients with relapsed or refractory chronic lymphocytic leukaemia, suggesting that MRD-guided cessation and reinitiation is feasible in this patient population.

Funding AbbVie and Janssen.

Introduction

Chemoimmunotherapy regimens have been widely used as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukaemia until approximately 5 years ago, resulting in progression-free survival of 1·5–2 years.[1] Duration of progression-free survival in patients with relapsed or refractory chronic lymphocytic leukaemia increased substantially with the continuous

Research in context

Evidence before this study

We searched PubMed until March 1, 2022, using the search terms "chronic lymphocytic leukemia" AND "venetoclax" AND "ibrutinib", with no restrictions on language or publication date. Preclinical studies showed synergy for the combination of Bruton tyrosine-kinase inhibitors and BCL2 inhibitors. We found that the combination of the BCL2 inhibitor venetoclax and the Bruton tyrosine-kinase inhibitor ibrutinib has been assessed in phase 1 and 2 studies, which showed a high response rate with undetectable minimal residual disease (MRD) and manageable toxicity. We found no trials that specifically studied response-guided, time-limited ibrutinib plus venetoclax cessation and reinitiation treatment in the setting of relapsed or refractory chronic lymphocytic leukaemia.

Added value of this study

Based on our literature search, HOVON141/VISION is, to the best of our knowledge, the first trial to study side-by-side treatment continuation or MRD-guided treatment cessation and reinitiation following a fixed duration of venetoclax plus ibrutinib treatment in patients with relapsed or refractory chronic lymphocytic leukaemia. The primary analysis showed that therapy can be stopped for the approximately 40% of patients with undetectable MRD at the 10^{-4} level in bone marrow and peripheral blood. Within the first year after stopping therapy, only one patient met the 10^{-2} MRD level for reinitiating therapy. With longer follow-up, seven patients reinitiated therapy, six of whom were evaluated for response and had no clinical progression. Furthermore, no new safety signals were detected for the combination of ibrutinib plus venetoclax for relapsed or refractory chronic lymphocytic leukaemia. These data add to recently published data on a fixed-duration treatment with venetoclax plus ibrutinib (regardless of MRD status) in the first-line setting (the GLOW study, NCT03462719).

Implications of all the available evidence

MRD-guided, time-limited ibrutinib plus venetoclax therapy in the setting of relapsed or refractory chronic lymphocytic leukaemia is feasible and shows a favourable benefit–risk profile. *TP53* aberrations, complex karyotype, and *IGHV* gene mutational status did not affect the rate of undetectable MRD. No patients with undetectable MRD progressed after treatment cessation, and patients who became MRD positive successfully reinitiated therapy. The well known risk of cardiovascular events with ibrutinib in this population was confirmed. Thus, in the context of other recent clinical trials assessing MRD after the combination of ibrutinib plus venetoclax, MRD-guided treatment cessation and MRD-based reinitiation of targeted therapy is feasible for patients with relapsed or refractory chronic lymphocytic leukaemia, and could also potentially be extrapolated to the first-line treatment setting.

use of the Bruton tyrosine-kinase inhibitor ibrutinib.[2] Treatment with the highly selective BCL2 inhibitor venetoclax, either given as continuous monotherapy or as a fixed-duration treatment in combination with rituximab, was also shown to induce high rates of long-lasting responses in patients with relapsed or refractory chronic lymphocytic leukaemia.[3,4] However, neither of these regimens are curative, resulting in a patient population requiring repeated or continuous treatment and at risk of developing resistance to treatment, which can induce disease progression.[5] Consequently, the number of patients with double class-resistant disease and for whom there are no effective salvage regimens is increasing.[6]

Concomitant administration of ibrutinib and venetoclax, which have distinct and complementary modes of action, has recently been shown to be synergistic in an in-vivo chronic lymphocytic leukaemia mouse model.[7] Ibrutinib inhibits adhesion and migration to the lymph node tumour microenvironment, thereby blocking pro-survival and proliferative stimuli.[7–10] Venetoclax activates the apoptosis pathway,[11] unless BH3-only peptides released from BCL2 bind to other anti-apoptotic proteins.[10] Expression of these anti-apoptotic proteins is specifically increased within the tumour microenvironment.[12] Preliminary phase 2 results of ibrutinib plus venetoclax combination trials have shown high response rates as first-line treatment and in the relapsed or refractory chronic lymphocytic leukaemia setting.[13–16]

Ample evidence suggests that targeted treatment with BCR-ABL tyrosine-kinase inhibitors can be safely discontinued in patients with chronic myeloid leukaemia who have a sustained complete molecular remission. Approximately half of such patients remain in complete molecular remission, and patients with increasing disease burden typically respond to the reintroduction of imatinib.[17] Undetectable minimal residual disease (MRD) can be used as a surrogate marker for deep remission in patients with chronic lymphocytic leukaemia.[18] We aimed to investigate whether response-based treatment cessation with the option to reinitiate treatment on the basis of regular MRD assessments was a feasible approach in patients with chronic lymphocytic leukaemia. The interim analysis for the first 51 patients during the treatment phase has been previously reported.[15]

Methods

Study design and participants

The protocol of this study was designed by the Dutch–Belgian Cooperative Trial Group for Hemato-oncology (HOVON). HOVON141/VISION was an open-label, randomised, phase 2 trial, conducted in 47 hospitals in Belgium, Denmark, Finland, the Netherlands, Norway, and Sweden (appendix pp 4–5). Eligible participants were aged 18 years or older with previously treated chronic

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See **Online** for appendix

lymphocytic leukaemia with or without *TP53* aberrations; had not been exposed to Bruton tyrosine-kinase inhibitors or BCL2 inhibitors; had a creatinine clearance rate of 30 mL/min or more; and required treatment according to International Workshop on Chronic Lymphocytic Leukemia 2018 criteria.[19] Key exclusion criteria included severe bleeding disorders, CNS involvement, Richter's syndrome, or uncontrolled infections. Full inclusion and exclusion criteria are in the appendix (pp 6–7).

The review boards of participating institutions approved the study protocol, which was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written, informed consent. Data were collected by investigators under the oversight of an independent data monitoring committee (appendix p 3). The trial protocol has been published previously.[20]

Randomisation and masking

Participants with undetectable MRD after 15 cycles of treatment with ibrutinib plus venetoclax were randomly assigned (1:2) to continuing ibrutinib treatment or treatment cessation. Randomisation was done by computer program (ALEA; version 18.1) and was stratified by centre, degree of comorbidity (Cumulative Illness Rating Scale ≤6 *vs* >6), and *TP53* aberration (presence *vs* absence of *TP53* mutation, del[17p13], or both), with a minimisation procedure, ensuring balance within each stratum and overall balance. The randomisation sequence and the assignment to trial groups was generated by the ALEA software and the enrolment was done by the local principle investigator. Because this trial was open-label, neither patients nor investigators were masked to treatment group assignment.

Procedures

All patients received 15 cycles (28 days each) of oral ibrutinib 420 mg once daily. Ibrutinib was given as monotherapy during the first two cycles and oral venetoclax was added from day 1 of cycle 3. The starting dose for venetoclax was 20 mg once daily, increased weekly to 50 mg, 100 mg, 200 mg, up to the target of 400 mg once daily (ie, during cycles 3 and 4), which was the dose administered until completion of the 15 cycles.

Patients were followed up by MRD assessment from peripheral blood samples at the end of cycle 9, end of cycle 12, and on day 15 of cycle 15 (this timepoint also included MRD assessment from bone marrow aspirates). Thereafter, patients were followed up for MRD assessment from peripheral blood every 3 months for 2 years, and every 4 months in the third year; a second MRD assessment from bone marrow aspirates was at month 27 after start of treatment. Patients with undetectable MRD (sensitivity, 10^{-4} on flow cytometry as detailed in the appendix [p 8]; ie, less than one chronic lymphocytic leukaemia cell per 10 000 leukocytes)[18] on day 15 of cycle 15 in peripheral blood and bone marrow samples were randomly assigned, after completion of cycle 15, to either continuous ibrutinib treatment until toxicity or progression or to treatment cessation. An early protocol amendment on Dec 20, 2018, defined that undetectable MRD at the end of cycle 12 in peripheral blood was not required for eligibility for random assignment. Patients with undetectable MRD who were assigned to treatment cessation were closely monitored for clinical signs of relapse or progression along with MRD assessments every 3 months for 2 years, then every 4 months for the third year. Patients who became MRD positive (defined as MRD $\geq 10^{-3}$ upon assessment and as MRD $\geq 10^{-2}$ at least 1 month later) or with symptomatic chronic lymphocytic leukaemia[19] reinitiated treatment with ibrutinib plus venetoclax for 12 cycles and continued ibrutinib treatment until toxicity or progression (appendix p 10). Patients not reaching MRD negativity in peripheral blood or bone marrow at cycle 15 continued ibrutinib until toxicity or progression (patients not randomly assigned). Central laboratory assessments were done at baseline for *TP53* mutational analysis, and *IGHV* and genomic array analysis at the indicated timepoints for MRD analyses (appendix p 8).

Prophylaxis for *Pneumocystis jirovecii* pneumonia was recommended for all patients and the use of granulocyte colony-stimulating factor (G-CSF) was recommended in case of neutropenia of grade 4 according to the Common Terminology Criteria for Adverse Events (CTCAE). The administration of prophylaxis was not recorded. All adverse events grade 2 or worse were recorded and were continually monitored by the HOVON data centre.

Outcomes

The primary endpoint was the proportion of patients remaining free from progression or death 12 months after stopping therapy (27 months after starting treatment) in the treatment cessation group. The primary endpoint was locally assessed. Treatment reinitiation due to either MRD positivity or symptomatic chronic lymphocytic leukaemia[19] within 12 months after random assignment followed by a response (at least stable disease) on re-treatment before or at 12 months after random assignment was not considered a progression event.

The secondary endpoints were MRD level at cycles 9, 12, 15 in the overall patient population, and after cessation of treatment (month 27) in all three groups of patients (ibrutinib group, treatment cessation group, and not randomly assigned), progression-free survival (defined as the time from registration to disease progression or death, whichever occurred first), time to reinitiation of treatment (defined as the time from random assignment to reinitiation of therapy; only for treatment cessation group), time to treatment failure (defined as the time from reinitiating therapy to progression or death from any cause; only for treatment

cessation group), time to next treatment (defined as the time from registration to next new line treatment), overall survival (defined as the time from registration to death from any cause), overall response rate (defined as a response equal to or better than partial response [ie, complete remission, complete remission with incomplete blood count recovery, or partial response]), duration of response (defined as the time from first response to progression or death from any cause; for patients with at least one partial response), association between MRD in bone marrow and peripheral blood, association between MRD in bone marrow aspirates and peripheral blood and progression-free survival and overall survival, adverse events, and quality of life. The prespecified outcome of time to treatment failure was not analysed because none of the reinitiated patients had treatment failure after treatment reinitiation. Quality-of-life data that were collected in this study will be analysed at a later stage and reported separately.

Evaluation of the relationship between various baseline markers (*TP53* mutation, *IGHV* mutational status, and cytogenetic aberrations including genomic complexity defined as ≥3 aberrations, as detailed in appendix p 8), and clinical outcome parameters including MRD were defined as exploratory outcomes.

Statistical analysis

The primary assumption of the trial was that progression-free survival would improve to 75% at 12 months after cessation of therapy (27 months after starting treatment) for patients in the treatment cessation group compared with historical trials in which progression-free survival was 60% for patients with relapsed or refractory chronic lymphocytic leukaemia.[21,22] The sample size was estimated on this basis and was calculated using an A'Hern design, based on H_0 P=60% and H_1 P=75%, a one-sided α of 0·05, and a power of (1−β) 80%, resulting in a sample size of 62 patients in the treatment cessation group with at least 44 patients remaining progression free to warrant further investigation. Taking into account that two parallel maintenance treatment groups are included in the analysis (randomly assigned [1:2] ibrutinib *vs* treatment cessation and observation), 93 participants were needed in total. Considering that a putative 55% of patients were expected not to have undetectable MRD after induction and a 10% ineligibility rate, 230 patients were planned to be enrolled. The maintenance treatment groups were analysed separately without formal comparisons between groups. We originally expected 55% of patients not to have undetectable MRD after induction at 12 and 15 cycles. However, because of lower than expected number of patients with undetectable MRD in peripheral blood at cycle 12, a protocol amendment was made on Dec 20, 2018, to allow undetectable MRD only at cycle 15. This change led to a greater proportion of enrolled patients being eligible for random assignment (36%), but still meant that the study as performed (compared with as planned) was underpowered because of the lower than expected undetectable MRD rate, which would affect negative outcomes but not positive findings. Consequently, the main study question as to whether treatment discontinuation in patients with undetectable MRD was associated with a difference in survival outcomes should be regarded as a preliminary investigation.

For the primary endpoint analysis and secondary endpoints with a binary outcome, a binomial exact test was used and point estimates with 95% CIs were calculated. The time-to-event endpoints (progression-free survival, event-free survival, and overall survival) were estimated using the Kaplan-Meier method.

Primary and secondary endpoints were assessed in the intention-to-treat population. Secondary endpoints were

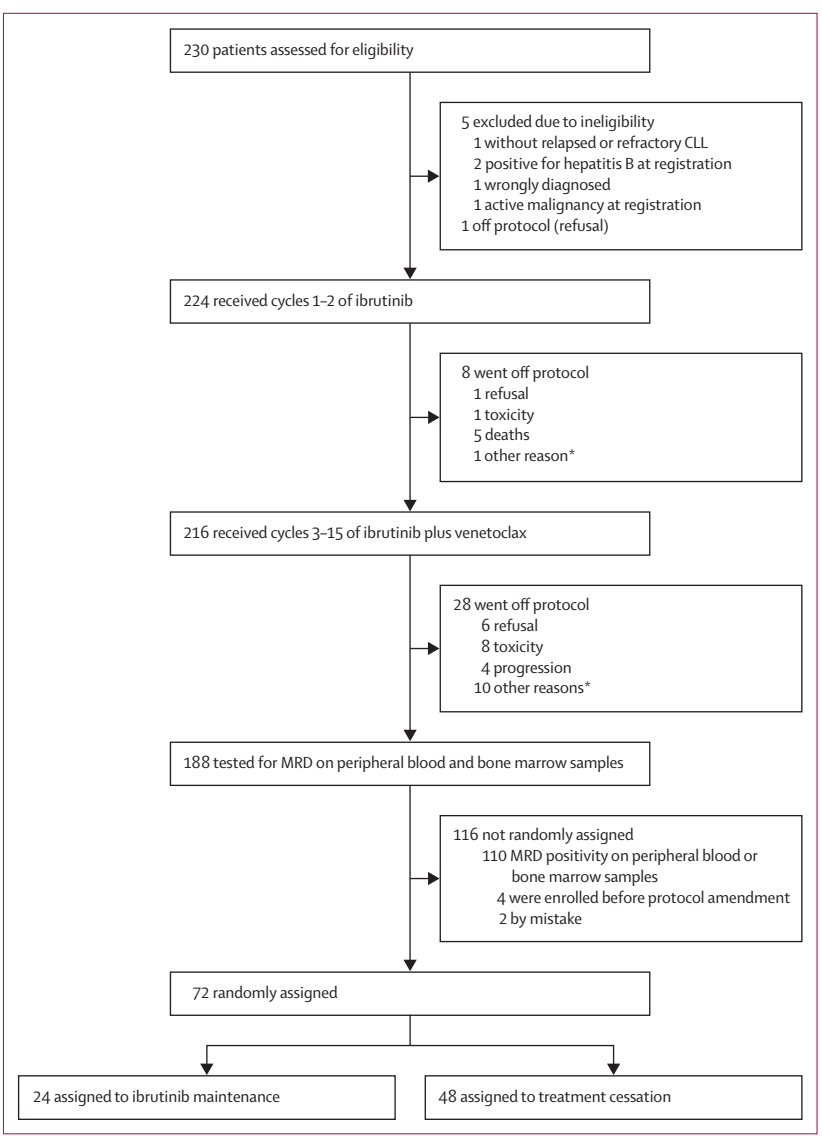

Figure 1: **Trial profile**
CLL=chronic lymphocytic leukaemia. MRD=minimal residual disease. *Other reasons specified in the appendix (p 17).

	Ibrutinib continuation group (n=24)	Treatment cessation group (n=48)	Patients not randomly assigned (n=153)	All patients (n=225)
Sex				
Male	19 (79%)	33 (69%)	105 (69%)	157 (70%)
Female	5 (21%)	15 (31%)	48 (31%)	68 (30%)
Age, years	66 (58–72)	71 (64–73)	68 (61–72)	68 (61–72)
WHO performance status				
0	18 (75%)	28 (58%)	95 (62%)	141 (63%)
1	5 (21%)	20 (42%)	51 (33%)	76 (34%)
2	1 (4%)	0	6 (4%)	7 (3%)
3	0	0	1 (1%)	1 (<1%)
Binet classification				
A	3 (13%)	4 (8%)	25 (16%)	32 (14%)
B	11 (46%)	21 (44%)	60 (39%)	92 (41%)
C	9 (38%)	22 (46%)	67 (44%)	98 (44%)
Data not available	1 (4%)	1 (2%)	1 (1%)	3 (1%)
Creatinine clearance, mL/min	73 (62–85)	71 (59–86)	70 (61–87)	71 (60–87)
Baseline tumour lysis syndrome risk				
Low	5 (21%)	9 (19%)	24 (16%)	38 (17%)
Medium	9 (38%)	22 (46%)	76 (50%)	107 (48%)
High	10 (42%)	16 (33%)	51 (33%)	77 (34%)
Data not available	0	1 (2%)	2 (1%)	3 (1%)
Cumulative Illness Rating Scale score	2 (1–5)	2 (1–4)	2 (1–4)	2 (1–4)
White blood cell count, $\times 10^9$/L	35 (13–137)	49 (19–129)	65 (25–142)	58 (22–135)
Platelets, $\times 10^9$/L	136 (94–199)	116 (92–157)	115 (86–160)	116 (90–164)
Haemoglobin concentration, g/dL	12·6 (11·2–13·6)	12·2 (11·3–13·4)	11·8 (10·3–13·4)	11·9 (10·5–13·4)
TP53 mutation				
Not present	17 (71%)	38 (79%)	109 (71%)	164 (73%)
Present	6 (25%)	8 (17%)	38 (25%)	52 (23%)
Not tested or technical failure	1 (4%)	2 (4%)	6 (4%)	9 (4%)
11q deletion				
Not present	16 (67%)	29 (60%)	104 (68%)	149 (66%)
Present	7 (29%)	18 (38%)	42 (27%)	67 (30%)
Not tested or technical failure	1 (4%)	1 (2%)	7 (5%)	9 (4%)
17p13 deletion				
Not present	20 (83%)	43 (90%)	126 (82%)	189 (84%)
Present	3 (13%)	5 (10%)	25 (16%)	33 (15%)
Not tested or technical failure	1 (4%)	0	2 (1%)	3 (1%)
Trisomy 12				
Not present	19 (79%)	42 (88%)	133 (87%)	194 (86%)
Present	4 (17%)	5 (10%)	13 (8%)	22 (10%)
Not tested or technical failure	1 (4%)	1 (2%)	7 (5%)	9 (4%)
TP53 pathway aberration (17p13 deletion, *TP53* mutation, or both)				
Not present	17 (71%)	37 (77%)	107 (70%)	161 (72%)
Present	6 (25%)	9 (19%)	40 (26%)	55 (24%)
Not tested or technical failure	1 (4%)	2 (4%)	6 (4%)	9 (4%)
Genomic complexity				
Absence of genomic complexity (<3)	15 (63%)	32 (67%)	116 (76%)	163 (73%)
Low genomic complexity (3–4)	5 (21%)	12 (25%)	22 (14%)	39 (17%)
High genomic complexity (≥5)	3 (13%)	4 (8%)	13 (9%)	20 (9%)
Not tested or technical failure	1 (4%)	0	2 (1%)	3 (1%)
IGHV mutational status				
Unmutated	14 (58%)	32 (67%)	98 (64%)	144 (64%)
Mutated	7 (29%)	12 (25%)	45 (29%)	64 (28%)
Not available or no clonality found	3 (12%)	4 (8%)	10 (7%)	17 (8%)
Previous lines of treatment for chronic lymphocytic leukaemia	1 (range 1–3; IQR 1–2)	1 (range 1–8; IQR 1–2)	1 (range 1–15; IQR 1–2)	1 (range 1–15; IQR 1–2)

Data are n (%) or median (IQR) unless otherwise specified.

Table 1: **Baseline characteristics**

assessed in all three patient groups except where otherwise specified. Safety was assessed in all patients who received at least one dose of study drug, and are reported descriptively.

Five safety and efficacy interim analyses were done (appendix p 9). An independent data monitoring committee (appendix p 3) reviewed the results of all interim analyses.

All analyses were performed using Stata (version 16.1) and a p value of 0·05 was considered statistically significant.

This trial was registered with the EU Clinical Trials Register, EudraCT 2016-002599-29; trialregister.nl, NL6110; and ClinicalTrials.gov, NCT03226301.

Role of the funding source

The funders of the study had the opportunity to review the manuscript, but had no role in data collection, data analysis, data interpretation, or writing of the report. The funders had the option to review and comment on the study protocol.

Results

Between July 12, 2017, and Jan 21, 2019, 230 patients with relapsed or refractory chronic lymphocytic leukaemia were enrolled, including five ineligible patients (one did not have relapsed or refractory chronic lymphocytic leukaemia, two were positive for hepatitis B at registration, one was wrongly diagnosed, and one had an additional active malignancy at time of registration; figure 1). Median age was 68 years (IQR 61–72). 157 (70%) of the 225 eligible participants were men and 68 (30%) were women, 160 (71%) had received previous standard chemoimmunotherapy, and 59 (27%) of 222 had genomic complexity (defined as ≥3 aberrations; table 1). Data on race and ethnicity were not collected. Planned treatment with ibrutinib plus venetoclax until random assignment at cycle 15 was completed by 188 (84%) of 225 patients (figure 1). Reasons for treatment discontinuation due to other reasons are specified in the appendix (p 17).

At cycle 15, 81 (36%) of 225 patients in the intention-to-treat population had undetectable MRD in both peripheral blood (112 [50%] of 225) and bone marrow (84 [37%] of 225; figure 2). The depth of response as assessed on peripheral blood improved during treatment from cycle 9 (74 [33%] patients had undetectable MRD) to cycle 12 (99 [44%] patients had undetectable MRD; figure 2). The agreement between peripheral blood and bone marrow MRD status at cycle 15 was 77% for the 188 patients who received 15 cycles of treatment: 78 (73%) of 107 patients with undetectable MRD in peripheral blood also had undetectable MRD in bone marrow and 27 (26%) of 107 had intermediate MRD (between 10^{-2} to 10^{-4}) in bone marrow. One patient had MRD greater than 10^{-2} in bone marrow, and one patient was not assessable (appendix p 18).

No significant differences in baseline characteristics were seen between patients who were not randomly assigned (patients with MRD or patients going off protocol; 153 [68%]) and randomly assigned patients (those with undetectable MRD; 72 [32%]; table 1). 24 (11%) patients with undetectable MRD were randomly assigned to receive continued ibrutinib treatment and 48 (21%) patients were assigned to treatment cessation (table 1; figure 1).

Median follow-up of the 208 patients still alive at data cutoff on June 22, 2021, and not lost to follow-up, was 34·4 months (IQR 30·6–37·9). 197 (88%) of the 225 enrolled patients were free from progression and alive at 27 months (figure 3A), with estimated progression-free survival of 88% (95% CI 83–92).

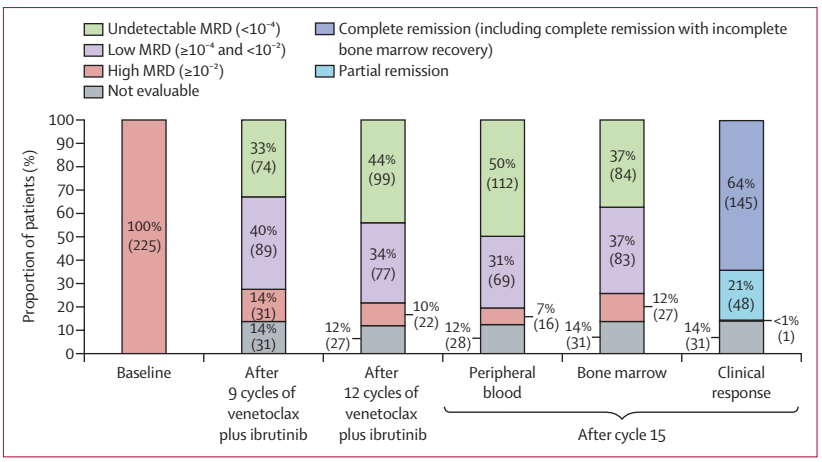

Figure 2: **MRD and responses**
MRD rates in the intention-to-treat population (n=225) from baseline until the end of cycle 15, and clinical responses at cycle 15. MRD analysed by flow cytometry (appendix p 8). MRD=minimal residual disease.

The primary endpoint was met, with a progression-free survival at month 27 (after 12 months of observation) of 98% (95% CI 89–100) in the treatment cessation group (figure 3B), which is greater than the prespecified 75% assumption. Only one progression-free survival event occurred in the treatment cessation group during observation: one patient died after developing myelodysplastic syndrome. For patients in the ibrutinib maintenance group, the estimated progression-free survival at month 27 was 96% (95% CI 79–100; figure 3C). Among the 116 patients continuing ibrutinib after cycle 15 because they did not have undetectable MRD in both peripheral blood and bone marrow (including two patients who erroneously were not randomly assigned despite having undetectable MRD), the estimated progression-free survival at month 27 was 97% (95% CI 93–99; figure 3D).

In the overall patient population, after 15 cycles of treatment, 193 (86%) of 225 patients had an overall response and 145 (64%) patients had a complete remission, including incomplete bone marrow recovery (figure 2). No difference in undetectable MRD in peripheral blood at cycle 15 was seen between patients with or without the prespecified high-risk features: *TP53* aberrations (81 [50%] of 161 patients with *TP53* wild-type *vs* 25 [45%] of 55 patients with *TP53* aberrations had undetectable MRD); *IGHV* mutational status (32 [50%] of 64 patients with mutations *vs* 72 [50%] of 144 patients with no mutations had undetectable MRD); and genomic complexity (79 [48%] of 163 patients with no genomic complexity *vs* 22 [56%] of 39 patients with low genomic complexity *vs* ten [50%] of 20 patients with high genomic complexity had undetectable MRD; appendix p 11).

For patients who were not randomly assigned and who continued single-agent ibrutinib (n=116), the proportion

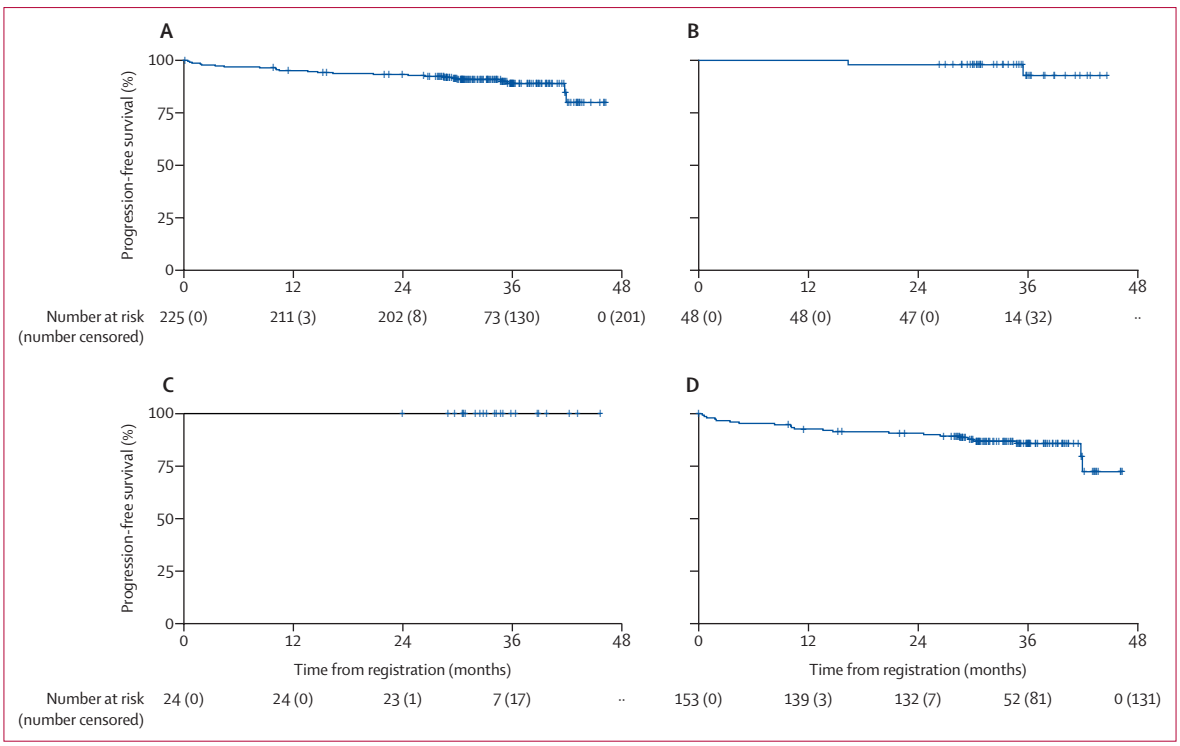

Figure 3: **Progression-free survival**
Progression-free survival was defined as time from registration to progression or death from any cause, whichever came first. Crosses denote censored patients. (A) Progression-free survival in all eligible patients. (B) Progression-free survival in the treatment cessation group. (C) Progression-free survival in the ibrutinib maintenance group. (D) Progression-free survival in patients not randomly assigned to a treatment group.

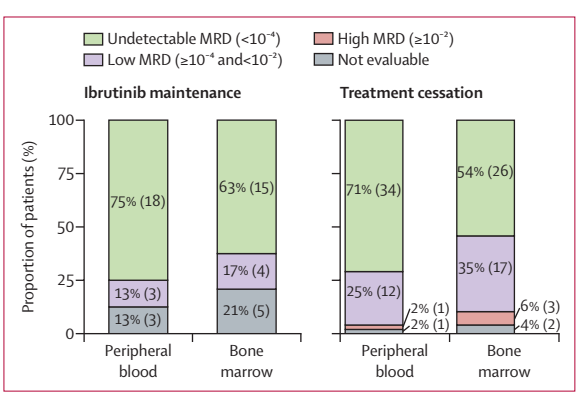

Figure 4: **MRD rates in peripheral blood and bone marrow aspirates at month 27 after treatment start for patients in the ibrutinib maintenance group or treatment cessation group**
MRD analysed by flow cytometry (appendix p 8). MRD=minimal residual disease.

of patients with undetectable MRD in either peripheral blood or bone marrow was stable until month 27: 35 (30%) patients had undetectable MRD in peripheral blood at cycle 15 compared with 34 (29%) at month 27, and eight (9%) had undetectable MRD in bone marrow at cycle 15 compared with 15 (13%) at month 27 (appendix p 12). A similar proportion of patients with undetectable MRD at cycle 15 assigned to ibrutinib maintenance or treatment cessation did not have MRD after 12 months (month 27 after treatment start; figure 4, appendix p 13). One patient in the treatment cessation group without signs of progression reinitiated ibrutinib plus venetoclax per protocol due to MRD positivity before month 27. Seven (15%) patients (one with del[17p13] and none with *TP53* mutations) in the treatment cessation group reinitiated therapy according to protocol (three were re-treated due to MRD positivity and four due to clinical relapse); the six patients who were evaluated for response showed clinical remission (appendix pp 14–15).

The estimated overall survival was 94% (95% CI 90–97) at month 27 for all eligible patients (figure 5A, appendix p 16). Five patients died during cycle 1–2 of ibrutinib monotherapy and six patients died during combination therapy with ibrutinib plus venetoclax up to cycle 15. In addition, one patient died during observation in the treatment cessation group (figure 5B). No patients died during observation in the ibrutinib maintenance group (figure 5C), and two patients died during ibrutinib maintenance among the patients not randomly assigned (figure 5D). Estimated overall survival at month 27 was 100% (95% CI 86–100) in the ibrutinib maintenance group, 98% (89–100) in the treatment cessation group, and 92% (86–95) in the not randomly assigned group. Causes of death are listed in the appendix (p 19).

Results for the secondary outcomes of duration of response, time to next treatment, time to reinitiation of

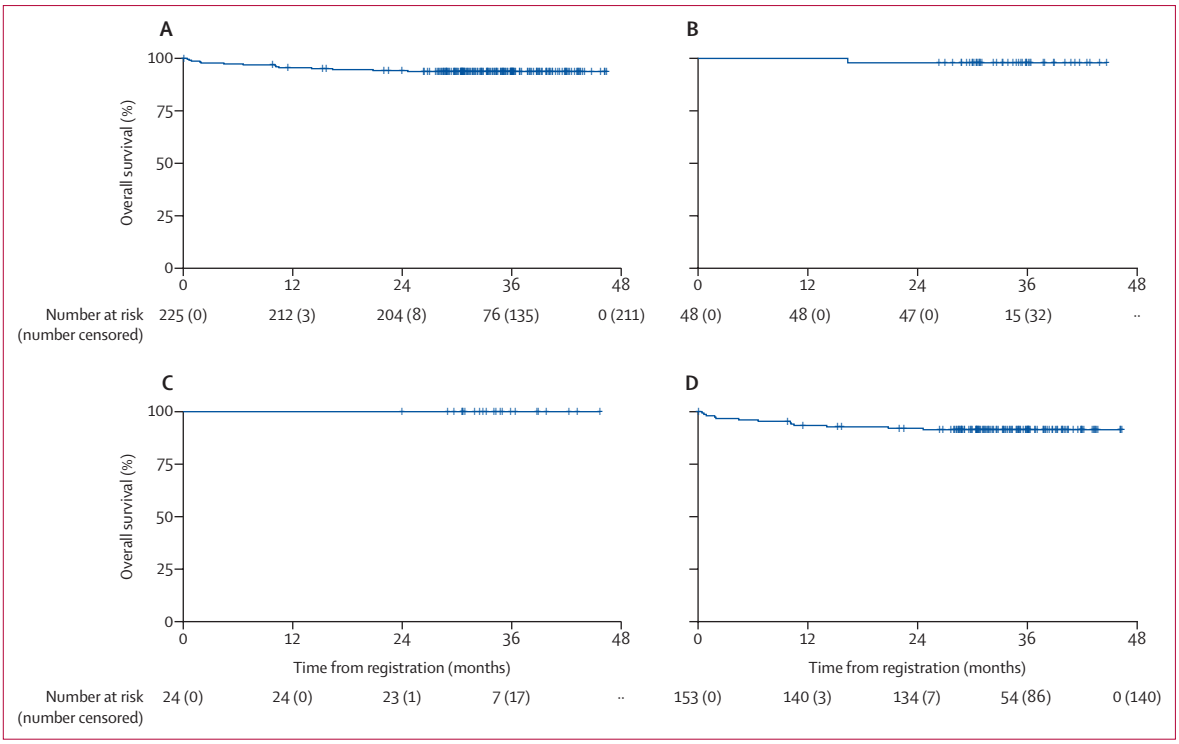

Figure 5: **Overall survival**
Overall survival from registration is shown for each group. Crosses denote censored patients. (A) Overall survival in all eligible patients. (B) Overall survival in patients in the treatment cessation group. (C) Overall survival in patients in the ibrutinib maintenance group. (D) Overall survival in patients not randomly assigned to a treatment group.

therapy due to MRD positivity or progression, and the association between MRD in bone marrow aspirates and peripheral blood and progression-free survival and overall survival are shown in the appendix (pp 24–26),

During the 15 cycles of therapy before randomisation, 206 (92%) of 225 patients reported at least one adverse event. 56 (25%) reported grade 2 adverse events, 90 (40%) reported grade 3 adverse events, and 60 (27%) reported grade 4 adverse events (appendix p 20). During the first 15 cycles, 37 patients went off protocol: nine patients due to ibrutinib toxicity, four patients due to disease progression, 19 patients due to refusal to continue or other reasons; and five patients due to death. During the first 15 cycles of therapy, 107 (48%) of 225 patients had serious adverse events (there were 176 serious adverse events in total). 46 (40%) of 116 patients who were not randomly assigned developed a serious adverse event on ibrutinib maintenance, and eight (33%) of 24 patients developed a serious adverse event while taking ibrutinib maintenance in the ibrutinib maintenance group; four (8%) of 48 patients developed a serious adverse event in the treatment cessation group. All serious adverse events are shown in the appendix (pp 21–23).

Infections were the most frequently reported adverse event during the first 15 cycles, seen in 130 (58%) of 225 patients overall; 68 (30%) patients had grade 2 events and 62 (28%) patients had events of grade 3 or worse during the first 15 cycles (appendix p 20). 14 (58%) of 24 patients reported infections after random assignment in the ibrutinib maintenance group and seven (15%) reported infections after random assignment in the treatment cessation group; 48 (41%) of 116 patients who were not randomly assigned reported infections. During the first 15 cycles, neutropenia adverse events were the second most frequently reported (11 [5%] of 225 patients reported grade 2 neutropenia, 39 [17%] reported grade 3, and 41 [18%] reported grade 4) and gastrointestinal events were the third most frequently reported adverse event (40 [18%] patients reported grade 2 and 13 [6%] reported grade 3; appendix p 20). G-CSF use in cases of neutropenia CTCAE grade 4 is shown in the appendix (p 20). 23 (10%) of 225 patients had hypertension during the first 15 cycles; in the ibrutinib maintenance group, an additional three [7%] of 24 patients reported hypertension after random assignment. No new hypertension was reported after random assignment in the treatment cessation group. 29 (13%) of 225 patients had atrial fibrillation during the first 15 cycles; an additional one (4%) of 24 patients had atrial fibrillation in the ibrutinib maintenance group after random assignment and no atrial fibrillation events were reported in the treatment cessation group after random assignment. 32 (14%) of all 225 eligible patients had grade 2–3

	Ibrutinib continuation group (n=24)			Treatment cessation group (n=48)			Patients not randomly assigned (n=116)			
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 5
Patients with any adverse event, highest grade only	9 (38%)	7 (29%)	2 (8%)	7 (15%)	7 (15%)	0	37 (32%)	40 (34%)	7 (6%)	1 (1%)
Infections	9 (38%)	5 (21%)	0	5 (10%)	2 (4%)	0	31 (27%)	14 (12%)	2 (2%)	1 (1%)
Neutropenia	0	0	0	0	2 (4%)	0	2 (2%)	2 (2%)	2 (2%)	0
Diarrhoea, abdominal discomfort	2 (8%)	0	0	1 (2%)	0	0	7 (6%)	0	0	0
Bleeding	1 (4%)	1 (4%)	0	0	0	0	10 (9%)	0	0	0
Arthralgia, muscle pain	1 (4%)	0	0	1 (2%)	0	0	3 (3%)	0	0	0
Atrial fibrillation	1 (4%)	0	0	0	0	0	3 (3%)	0	0	0
Malignancies, neoplasm	0	1 (4%)	1 (4%)	3 (6%)	1 (2%)	0	4 (3%)	7 (6%)	0	0
Hypertension	2 (8%)	1 (4%)	0	0	0	0	5 (4%)	2 (2%)	0	0
Headache	0	0	0	2 (4%)	0	0	0	0	0	0
Nail changes	0	0	0	0	0	0	1 (1%)	0	0	0
Other	6 (25%)	2 (8%)	1 (4%)	5 (10%)	3 (6%)	0	30 (26%)	19 (16%)	3 (3%)	0

Grade 1 adverse events were not collected.

Table 2: **Summary of treatment-related adverse events after cycle 15**

bleeding events during the first 15 cycles (two [8%] of 24 patients during ibrutinib maintenance in the ibrutinib maintenance group, and ten [9%] of 116 patients who were not randomly assigned). One additional fatal bleeding event was reported before random assignment (appendix p 20). Tumour lysis syndrome grades 2–3 (all laboratory, none clinical according to CTCAE) was reported for 11 (5%) of 225 patients during venetoclax ramp up (appendix p 20). Treatment-related adverse events reported after cycle 15 are shown in table 2.

Discussion

To our knowledge, HOVON141/VISION is the first trial investigating whether response-based treatment cessation with the option to reinitiate treatment in case of subclinical (MRD conversion) progression is feasible for patients with relapsed or refractory chronic lymphocytic leukaemia, using the all-oral, once-daily, fixed-duration combination of ibrutinib plus venetoclax.[13,14,16] The primary endpoint (regarded as a preliminary investigation due to a lack of power) of the trial was met, with 47 (98%) patients assigned to treatment cessation remaining free from progression at 27 months, including one patient reinitiating therapy according to protocol without clinical progression. The study was designed as a randomised phase 2 study and no comparisons between groups were made. The trial population was representative of previously published trials in populations with relapsed or refractory chronic lymphocytic leukaemia.[4,21] The original trial assumption (progression-free survival at 12 months of 75% in the treatment cessation group following random assignment) was based on comparisons with chemoimmunotherapy trials in the relapsed and refractory setting. With a progression-free survival of 84·9% (95% CI 79·1–90·6) at 24 months in the venetoclax plus rituximab treatment group in the MURANO trial, our assumption appears to still be valid in the era of chemotherapy-free regimens in this setting. However, the study population in both the MURANO trial and our study received chemoimmunotherapy as first-line treatment, whereas an increasing number of patients are beginning to receive targeted agents as their first-line treatment in clinical practice. Novel agents targeting the B-cell receptor pathway or BCL-2 are increasingly being used in the first-line setting. Further studies are required to establish whether the observed effect persists in a relapsed or refractory chronic lymphocytic leukaemia study population previously treated with either fixed-duration or MRD-guided targeted drugs.

Our results show that MRD kinetics were different from the other chemotherapy-free fixed-duration regimen in relapsed or refractory chronic lymphocytic leukaemia: venetoclax plus rituximab. In the MURANO study that assessed this treatment combination, the rate of undetectable MRD in peripheral blood reached a plateau of around 60% after 9 months of treatment.[4] With ibrutinib plus venetoclax, the rate of undetectable MRD continued to improve over the first 15 months, as also shown in other recent first-line trials.[14,16,23] Another remarkable difference between the two regimens is the ability to target the lymph nodes, the bone marrow, and the peripheral blood compartments. Normalisation of lymph node sizes was seen for less than 10% of patients on venetoclax plus rituximab[4] compared with more than 50% of patients on ibrutinib plus venetoclax in this trial and the CLARITY study[13]. Thus, ibrutinib plus venetoclax seems to have improved clearance of the three

different disease-containing compartments (peripheral blood, bone marrow, and lymph nodes), but might take longer to produce maximal responses.

These differences in treatment efficacy within the different tumour containing compartments of chronic lymphocytic leukaemia might also correlate with differences in MRD kinetics after treatment cessation or change to monotherapy. Patients taking venetoclax plus rituximab for relapsed or refractory chronic lymphocytic leukaemia gradually lose undetectable MRD status in peripheral blood, whereas in this study, the distribution of MRD levels appeared stable for the first 15 months after the switch to ibrutinib maintenance or cessation of therapy. Even for patients with detectable MRD who were not randomly assigned (and therefore continued ibrutinib), no clear progression in MRD levels were found. This observation might reflect the synergy between ibrutinib and venetoclax, both targeting the tumour microenvironment niche in lymph nodes and the more indolent chronic lymphocytic leukaemia cells in the peripheral blood and the bone marrow.[7–10,16,24]

Despite the promising results reported here, only 50% of patients had undetectable MRD in the peripheral blood. Importantly, *TP53* aberrations, complex karyotype, and unmutated immunoglobulin heavy variable genes did not affect the rate of undetectable MRD status, contrasting with what has been shown with chemoimmunotherapy, fixed-duration venetoclax plus rituximab, and ibrutinib monotherapy.[25] Thus, identification of novel biomarkers for patients with a high likelihood of reaching or not reaching undetectable MRD on ibrutinib plus venetoclax is warranted.

An important goal of this study was to test the concept of reinitiation of ibrutinib plus venetoclax treatment at early signs of MRD relapse for those patients who had previously had an undetectable MRD response and stopped treatment. All seven patients who became positive for MRD during observation successfully reinitiated therapy with the same regimen according to protocol without clinical progression. This finding argues against development of resistance during the relatively short induction period. Indeed, acquisition of novel gene mutations associated with resistance to venetoclax or ibrutinib such as in the *BCL2*, *BTK*, or *PLCG2* genes has been reported to occur after periods of treatment longer than the 15 cycles used in this study.[26] MRD-guided, time-limited therapy for patients with relapsed or refractory chronic lymphocytic leukaemia might therefore reduce the risk of developing resistance to treatment and the risk of adverse events associated with ibrutinib maintenance, with regular (every 3 months) MRD monitoring allowing for safe management of preclinical progression with reinitiation of therapy.[27]

In this relapsed or refractory chronic lymphocytic leukaemia population, including patients with clinically significant comorbidity but with a median low Cumulative Illness Rating Scale score (meaning that comorbidity was low in most patients), the safety profile of ibrutinib plus venetoclax was consistent with previously published data on ibrutinib or venetoclax monotherapy. Infections were reported as the most frequent adverse event, reflecting the inherent immune dysfunction of patients with relapsed or refractory chronic lymphocytic leukaemia and the increased risk of infections that might, to some degree, be attributed to treatment with ibrutinib and venetoclax.[28] In line with the well known risk of cardiovascular events, including atrial fibrillation and hypertension, these adverse events were reported during the full periods of treatment with ibrutinib,[29] but, along with bleeding events, were not reported by patients in the treatment cessation group.

In conclusion, our data suggest a favourable benefit–risk profile with MRD-guided ibrutinib plus venetoclax treatment cessation and reinitiation, but in view of the underpowering of the trial these results should be considered descriptive and definitive data regarding long-term survival are awaited. No patients progressed after treatment cessation and patients showing MRD successfully reinitiated therapy. This study suggests that MRD-guided treatment cessation and MRD-based reinitiation of targeted therapy for patients with relapsed or refractory chronic lymphocytic leukaemia is feasible and could potentially be extrapolated to the first-line treatment setting, as tested in the HOVON139/GIVE trial[30] and is being investigated in the ongoing HOVON158 NEXT STEP trial (NCT04639362).

Contributors

APK, M-DL, and CUN designed the trial, wrote the manuscript, and conducted the study. KN made the statistical assumptions and analysed results. JD coordinated the central laboratory and analysed the data. APK, KN, CUN, and JD accessed and verified the data. CHMM, A-MFvdK-K, and JAD did central laboratory assays. All authors were responsible for locally conducting the study and revised the manuscript. APK, JD, KN, M-DL, and CUN interpreted the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

APK reports research grants from Celgene, Janssen, AbbVie, Roche/Genentech, and AstraZeneca; speakers fees from AbbvVie and AstraZeneca; and participation in advisory boards of AbbVie, Janssen, AstraZeneca, and Roche. M-DL reports advisory board compensation from Janssen, AbbVie, and Roche; and travel reimbursement from Janssen, AbbVie, and Roche. JD reports research funding from Roche/Genentech. MM reports lecture remuneration from Janssen and advisory board compensation from AbbVie. SK reports fees from Janssen, AbbVie, and Celgene; and research funding from AbbVie, Janssen, AstraZeneca, and Roche/Genentech. JR reports consultancy fees from AbbVie, Janssen, and AstraZeneca. CB reports honoraria from AstraZeneca and Octapharma outside this study. HF reports consultancy fees from AstraZeneca, Janssen, Novartis, and Sanofi; participation in advisory boards for AstraZeneca, Janssen, Sobi, Novartis, Sandoz, Merck Sharp & Dohme, Incyte, and Beigene; and speaker fees from AstraZeneca, Janssen, Sobi, Incyte, Novartis, AbbVie, Amgen, Takeda, and Beigene. HF reports research grants from Sanofi and Novartis and honoraria for lectures from Sanofi. HTTT reports consultancy fees from Janssen-Cilag, AbbVie, Bayer, Novartis, and AstraZeneca. CUN reports research grants from AbbVie and Janssen; advisory board compensation from AbbVie, Janssen, Gilead, Roche, AstraZeneca, Acerta, and Sunesis; travel reimbursement from Gilead, Roche, and Novartis; and consultancy compensation from CSL Behring. All other authors declare no competing interests.

Data sharing

The HOVON CLL study group will consider data sharing requests on a case-by-case basis. Requests by academic study groups for de-identified 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. The study protocol has been previously published.[20] The statistical analysis plan and informed consent form will be made available upon request to the corresponding author.

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References

1 Awan FT, Hillmen P, Hellmann A, et al. A randomized, open-label, multicentre, phase 2/3 study to evaluate the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide and rituximab versus fludarabine, cyclophosphamide and rituximab alone in subjects with relapsed chronic lymphocytic leukaemia. *Br J Haematol* 2014; **167:** 466–77.

2 Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med* 2014; **371:** 213–23.

3 Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2016; **374:** 311–22.

4 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.

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 Lew TE, Lin VS, Cliff ERS, et al. Outcomes of patients with CLL sequentially resistant to both BCL2 and BTK inhibition. *Blood Adv* 2021; **5:** 4054–58.

7 Kater AP, Slinger E, Cretenet G, et al. Combined ibrutinib and venetoclax treatment *vs* single agents in the TCL1 mouse model of chronic lymphocytic leukemia. *Blood Adv* 2021; **5:** 5410–14.

8 Herman SE, Mustafa RZ, Gyamfi JA, et al. Ibrutinib inhibits BCR and NF-κB signaling and reduces tumor proliferation in tissue-resident cells of patients with CLL. *Blood* 2014; **123:** 3286–95.

9 Slinger E, Thijssen R, Kater AP, Eldering E. Targeting antigen-independent proliferation in chronic lymphocytic leukemia through differential kinase inhibition. *Leukemia* 2017; **31:** 2601–07.

10 Haselager MV, Kielbassa K, Ter Burg J, et al. Changes in Bcl-2 members after ibrutinib or venetoclax uncover functional hierarchy in determining resistance to venetoclax in CLL. *Blood* 2020; **136:** 2918–26.

11 Anderson MA, Deng J, Seymour JF, et al. The BCL2 selective inhibitor venetoclax induces rapid onset apoptosis of CLL cells in patients via a TP53-independent mechanism. *Blood* 2016; **127:** 3215–24.

12 Bojarczuk K, Sasi BK, Gobessi S, et al. BCR signaling inhibitors differ in their ability to overcome Mcl-1-mediated resistance of CLL B cells to ABT-199. *Blood* 2016; **127:** 3192–201.

13 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.

14 Jain N, Keating M, Thompson P, et al. Ibrutinib and venetoclax for first-line treatment of CLL. *N Engl J Med* 2019; **380:** 2095–103.

15 Niemann CU, Levin MD, Dubois J, et al. Venetoclax and ibrutinib for patients with relapsed/refractory chronic lymphocytic leukemia. *Blood* 2021; **137:** 1117–20.

16 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.

17 Mahon FX, Réa D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol* 2010; **11:** 1029–35.

18 Rawstron AC, Böttcher 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 disease monitoring in CLL. *Leukemia* 2013; **27:** 142–49.

19 Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood* 2018; **131:** 2745–60.

20 Levin MD, Kater AP, Mattsson M, et al. Protocol description of the HOVON 141/VISION trial: a prospective, multicentre, randomised phase II trial of ibrutinib plus venetoclax in patients with creatinine clearance ≥30 mL/min who have relapsed or refractory chronic lymphocytic leukaemia (RR-CLL) with or without *TP53* aberrations. *BMJ Open* 2020; **10:** e039168.

21 Robak T, Dmoszynska A, Solal-Céligny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J Clin Oncol* 2010; **28:** 1756–65.

22 Fornecker LM, Aurran-Schleinitz T, Michallet AS, et al. Salvage outcomes in patients with first relapse after fludarabine, cyclophosphamide, and rituximab for chronic lymphocytic leukemia: the French intergroup experience. *Am J Hematol* 2015; **90:** 511–14.

23 Munir T, Moreno C, Owen C, et al. First prospective data on minimal residual disease (MRD) outcomes after fixed-duration ibrutinib plus venetoclax (Ibr+Ven) versus chlorambucil plus obinutuzumab (Clb+O) for first-line treatment of CLL in elderly or unfit patients: the Glow study. *Blood* 2021; **138** (suppl 1)**:** 70.

24 Mathews Griner LA, Guha R, Shinn P, et al. High-throughput combinatorial screening identifies drugs that cooperate with ibrutinib to kill activated B-cell-like diffuse large B-cell lymphoma cells. *Proc Natl Acad Sci USA* 2014; **111:** 2349–54.

25 Ahn IE, Tian X, Ipe D, et al. Prediction of outcome in patients with chronic lymphocytic leukemia treated with ibrutinib: development and validation of a four-factor prognostic model. *J Clin Oncol* 2021; **39:** 576–85.

26 Blombery P, Anderson MA, Gong JN, et al. Acquisition of the recurrent gly101val mutation in *BCL2* confers resistance to venetoclax in patients with progressive chronic lymphocytic leukemia. *Cancer Discov* 2019; **9:** 342–53.

27 Aarup K, Rotbain EC, Enggaard L, et al. Real-world outcomes for 205 patients with chronic lymphocytic leukemia treated with ibrutinib. *Eur J Haematol* 2020; **105:** 646–54.

28 Moreno C, Muñoz C, Terol MJ, Hernández-Rivas JA, Villanueva M. Restoration of the immune function as a complementary strategy to treat chronic lymphocytic leukemia effectively. *J Exp Clin Cancer Res* 2021; **40:** 321.

29 Abdel-Qadir H, Sabrie N, Leong D, et al. Cardiovascular risk associated with ibrutinib use in chronic lymphocytic leukemia: a population-based cohort study. *J Clin Oncol* 2021; **39:** 3453–62.

30 Kersting S, Dubois J, Nasserinejod K, et al. Venetoclax consolidation after fixed-duration venetoclax plus obinutuzumab for previously untreated chronc lymphocytic leukaemia (HOVON139/GiVe): primary endpoint analysis of a multicentre, open-label, randomised, parallel-group, phase 2 trial. *Lancet Haematol* 2022; **9:** e190–99.