REGULAR ARTICLE

blood advances

Long-term follow-up of MRD-guided ibrutinib plus venetoclax in relapsed CLL: phase 2 VISION/HO141 trial

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Key Points

- MRD-guided cessation and reinitiation of I+V for R/R CLL is feasible.
- MRD-guided I+V for R/R CLL reduces toxicity, with OS and PFS comparable with other available regimens.

Patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) are treated with fixed-duration B-cell lymphoma 2 inhibitors + CD20 monoclonal antibodies or continuous Bruton tyrosine kinase (BTK) inhibitors. Although continuous treatment may lead to cumulative toxicity or resistance, fixed-duration treatment may lead to undertreatment and early relapse. Efficacy and safety of minimal residual disease (MRD)-guided treatment cessation of ibrutinib + venetoclax (I+V) with reinitiated I+V upon MRD conversion was evaluated in the randomized VISION/HO41 phase 2 study. Four-year follow-up including long-term toxicity and MRD kinetics are reported. Patients received ibrutinib for 2 (28-day) cycles followed by 13 cycles of I+V. Patients reaching undetectable MRD at 4 years ($<10^{-4}$, flow cytometry) in the blood and bone marrow at cycle 15 (C15) were randomized 2:1 between treatment cessation with reinitiated I+V upon detectable MRD2 (dMRD2; sensitivity of $\geq 10^{-2}$ by flow cytometry) and ibrutinib maintenance. MRD4-positive patients at C15 remained on ibrutinib (dMRD4 arm, defined by MRD sensitivity of $\geq 10^{-4}$ by flow cytometry). With a median of 51.7 months, the estimated 4-year overall survival (OS) was 88%, progression free survival (PFS) was 81%; 14% of patients required next-line treatment (NT). For patients randomized to treatment cessation, 40% had reinitiated therapy per protocol because of dMRD2. No difference between treatment cessation, ibrutinib maintenance, or the dMRD4 arm continuing ibrutinib was seen for OS, PFS, or NT in landmark analysis from C15 time of randomization. Lower toxicity was demonstrated for

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The study was previously published in Lancet Oncology (Lancet Oncol. 2022; 23(6):818-828) and the protocol description was published in the British Medical Journal Open (BMJ Open. 2020;10(10):e039168).

The Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON) CLL study group will consider data sharing requests on a case-by-case basis. 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, Carsten U. Niemann (carsten.utoft.niemann@regionh.dk), and it will be evaluated by the HOVON CLL study group. The statistical analysis plan and informed consent form will be made available on request from the corresponding author.

The full-text version of this article contains a data supplement.

the treatment-cessation arm. MRD-guided cessation and reinitiation of I+V for R/R CLL is feasible, reduces toxicity compared with indefinite BTK inhibitor, while providing comparable PFS rates. This trial was registered at www.clinicaltrials.gov as #NCT03226301.

Introduction

In recent years, treatment options used for patients with chronic lymphocytic leukemia (CLL) have greatly expanded through the introduction of targeted agents such as the Bruton tyrosine kinase inhibitor ibrutinib and the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax, alone or in combination with CD20-targeting monoclonal antibodies. Although these new inhibitors induce durable responses and are generally well tolerated, they are not curative. Continuous, but also sequential treatment, can lead to development of resistance, already reported for both classes of inhibitors.[1,2] This is particularly seen in patients with relapsed or refractory (R/R) CLL. All currently approved regimens are based on either continuous or fixed duration treatment.[3] However, tailoring cessation and reinitiation based on minimal residual disease (MRD) response has not yet been implemented into clinical practice.

Assessment of MRD by flow cytometry or DNA-based methods with patient-specific assays or next-generation sequencing-based assays have been established and are implemented in clinical trials as proxy for clinical outcomes.[4] Achievement of undetectable MRD (uMRD) at the end of treatment is associated with improved progression-free survival (PFS) and, in trials with long follow-up, even overall survival (OS), with chemoimmunotherapy treatment as well as fixed duration treatment with venetoclax and CD20-targeting monoclonal antibodies.[5-8] For first-line combination treatment of CLL with BTK inhibitors plus BCL-2 inhibitors, the correlation between achieving uMRD at end of treatment and longer PFS is only clear for patients with unmutated immunoglobulin heavy-chain variable gene region (IGHV).[9,10]

Based on preclinical and clinical evidence of synergistic effects of combining ibrutinib and venetoclax, we initiated the VISION/HOVON 141 study evaluating feasibility of MRD-guided treatment cessation and reinitiation in patients with R/R CLL after induction treatment with 15 cycles of venetoclax + ibrutinib.[11] The primary analysis showed that therapy can safely be stopped for the ~40% of patients achieving uMRD4 in the bone marrow and peripheral blood at cycle 15.[12]

We here present the 51-month follow up on PFS, response to treatment-reinitiation and safety with focus on the randomized comparison of continuous maintenance versus MRD-guided treatment cessation and reinitiation in patients achieving uMRD at cycle 15.

Methods

Study design and patients

The HOVON141/VISION trial is a multicenter, international, open-label, randomized, phase 2 trial, conducted at 47 sites in Belgium, Denmark, Finland, The Netherlands, Norway, and Sweden, and included 225 patients with R/R CLL. Eligible patients were aged ≥18 years with previously treated CLL with or without *TP53* aberrations; had not previously been exposed to BTK inhibitors or BCL-2 inhibitors; had a creatinine clearance rate of ≥30 mL/min; and required treatment according to International Workshop on CLL 2018 criteria. Major exclusion criteria included severe bleeding disorders, central nervous system involvement, Richter transformation, or uncontrolled infections.[13]

The study was conducted in accordance with International Conference on Harmonization guidelines for good clinical practice, and principles of the Declaration of Helsinki. The protocol was approved by institutional review boards or independent ethics committees of all participating institutions. All patients provided written, informed consent. Data were collected by investigators under the oversight of an independent data monitoring committee. The primary analysis of the trial was previously published, with a median 34.4 months follow-up, in the current report we report the outcome with a median 50.7 months follow-up. This study is registered with the EU Clinical Trials Register, EudraCT 2016-002599-29; trialregister.nl, NL6110; and www.clinicaltrials.gov as #NCT03226301.[12]

Treatment, assessments, and random assignment

All patients received 15 cycles (28 days each) of oral ibrutinib 420 mg once daily. Ibrutinib was given as monotherapy during the first 2 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 at week 5, administered until completion of the 15 cycles.

MRD status was assessed centrally from peripheral blood samples at baseline; at the end of cycle 2, 9, and 12; and on day 15 of cycle 15 (this time point also included MRD assessment from bone marrow aspirates); then every 3 months for 2 years and every 4 months from the third year until month 51.[12] A second MRD assessment from bone marrow aspirates was performed at month 27 after start of treatment.

Patients with uMRD (sensitivity 10^{-4} by flow cytometry, defined as uMRD4) on day 15 of cycle 15 in the peripheral blood and bone marrow were randomly assigned (1:2) to either continue ibrutinib until toxicity or progression, or to treatment cessation after completion of cycle 15. Randomization was done by computer program (ALEA; version 18.1) and was stratified by site, degree of comorbidity, and *TP53* aberration, with a minimization procedure, ensuring balance within each stratum and overall balance. For clarification of MRD nomenclature: uMRD2 defines MRD sensitivity of $<10^{-2}$, uMRD3 defines MRD $<10^{-3}$, detectable MRD4 (dMRD4) defines detectable MRD of $>10^{-4}$, dMRD3 of $>10^{-3}$, and dMRD2 of $>10^{-2}$.

Patients with uMRD4 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, with a data cutoff on 24 October 2023 for the MRD assessments. Patients who became MRD positive (defined as MRD of $\geq 10^{-3}$ upon assessment and as MRD $\geq 10^{-2}$ at least 1 month later) or with symptomatic CLL, reinitiated

treatment with ibrutinib plus venetoclax for 12 cycles and continued ibrutinib treatment until toxicity or progression thereafter. Patients not reaching MRD negativity in the peripheral blood or bone marrow at cycle 15 continued ibrutinib until toxicity or progression (no randomization; supplemental Figure 1). All adverse events (AEs) grade ≥2 were recorded during treatment including the patients randomized to cessation of treatment and were continually monitored by the HOVON data center.

Outcomes

The primary end point was PFS, defined as the time from registration to disease progression or death, whichever occurred first, in the treatment cessation group, 12 months after random assignment. MRD progression with reinitiation of treatment did not count as progression.

The secondary end points were MRD level at cycles 9, 12, and 15, and after cessation of treatment in all patients; PFS; time to reinitiation of treatment, defined as the time from random assignment to treatment cessation until reinitiation of therapy; time to treatment failure, defined as the time from (re)initiating therapy to progression or death from any cause; time to next-line treatment (NT), defined as the time from registration to NT (reinitiation according to protocol not counting as new line of treatment); OS, 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; duration of response, defined as the time from first response to progression or death from any cause; association between MRD in the bone marrow and peripheral blood; association between MRD in bone marrow aspirates and the peripheral blood and PFS and OS; AEs; and quality of life. The latter will be reported separately in a later publication.

Statistical analysis

The sample size was estimated based on the assumption that PFS would be at least 75% at 12 months after cessation of therapy resulting in a sample size of 62 patients in the treatment cessation group. Given that 2 parallel maintenance treatment groups are included in the analysis and estimating an MRD undetectable rate of 45% and 10% ineligibility, 230 patients were planned to be included. Because of lower numbers of patients achieving uMRD4 in the peripheral blood at cycle 12, a protocol amendment was made on 20 December 2018, to allow also uMRD4 only at cycle 15. It is important to note that the study was not designed to be statistically powered for comparative efficacy assessments between the randomized arms.

Analyses of binary end points were performed using a binomial exact test with calculation of 95% confidence intervals. All time-to-event end points were estimated using the Kaplan-Meier method. For incorporating the time-varying covariates (MRD values) in the survival model, a joint modeling of longitudinal and time-to-event data was used. All analyses were performed using Stata (version 16.1) R program (version 4.2.2), and a *P* value of 0.05 was considered statistically significant.

Results

Patient population

Between 12 July 2017 and 21 January 2019, 225 patients with R/R CLL were enrolled from 47 sites across 6 European countries. The median age was 68 years (interquartile range [IQR], 61-72) and 68 patients (30%) were female. The median cumulative illness rating scale-geriatric score was 2 (IQR, 1-4), 84% were Binet stage B/C, 64% had unmutated IGHV status, and 24% had TP53 aberrations. MRD rates at cycle 9, 12, and 15 were previously published.[12] Overall, 72 patients (32%) achieved uMRD4 in both the blood and bone marrow at cycle 15, which was lower than expected in the power calculation in the design of this study, and were randomized 1:2 between ibrutinib maintenance (arm A; n = 24), and treatment cessation (arm B; n = 48). Patients who did not achieve uMRD4 (n = 116) continued ibrutinib maintenance, whereas 37 patients went off protocol before randomization (Figure 1). No clear differences in terms of baseline characteristics or prognostic factors, including lines of treatments, IGVH-mutation status, TP53 status, and cytogenetic abnormalities, could be found between patients not achieving uMRD4 (nonrandomized, 116 patients) and patients achieving uMRD4 (arm A, ibrutinib maintenance, 24 patients; and arm B, treatment cessation, 48 patients); nor were significant imbalances found between the 2 randomized arms (Table 1).

Efficacy

After 51.7 months of median follow-up (IQR, 47.9-53.8), PFS, NT received, and OS at 4-years was 81%, 14%, and 88%, respectively, for the full intention-to-treat population (Figure 2A-C). For patients randomized to ibrutinib maintenance (arm A), PFS, NT, and OS were 90%, 14%, and 95%, respectively. For patients randomized to treatment cessation (arm B), PFS, NT, and OS were 85%, 12%, and 91%, respectively. For patients who continued ibrutinib (nonrandomized), PFS, NT, and OS were 76%, 19%, and 86%, respectively (Figure 2D-F).

Treatment reinitiation and MRD kinetics

At cycle 15, 107 (57%) of 188 patients still on protocol had achieved uMRD4 in the peripheral blood and 81 (43%) had achieved uMRD4 in the bone marrow. At cycle 39, 16 (67%) patients randomized to arm A (ibrutinib maintenance) and 18 (38%) patients randomized to arm B (treatment cessation), remained uMRD4 (supplemental Figure 2). In arm B, treatment was reinitiated per-protocol because of MRD conversion (dMRD2) in 19 (40%) patients, of whom 4 went off-protocol because of progression (n = 2, includes 1 death) or other reasons (n = 2; Figure 3A; Figure 1). After 12 cycles of retreatment with venetoclax and ibrutinib, complete remission was obtained in 10 (53%) patients; whereas 2 (11%) progressed at month 11 of reinitiation, of whom 1 died; and the remaining 7 patients had not finished the 12 cycles of retreatment. At last available MRD data cutoff (24 October 2023), 29 (60%) patients in arm B (treatment cessation) had not received retreatment. Among those, 4 patients had experienced dMRD2 but did not reinitiate treatment because of either going off protocol (n = 2), dying (n = 1), or unknown reason (n = 1), whereas 14 (48%) patients were still uMRD4, 7 patients had dMRD3, and 3 patients had dMRD4 (Figure 3B). One patient was not assessable because of missing data at this time of follow-up. For the 19 (40%) patients that reinitiated treatment, the MRD kinetics until reinitiation is visualized in Figure 3C and under retreatment in Figure 3D . Of those, 11 (58%) re-achieved uMRD4 after 12 cycles of retreatment, whereas 5 (26%) and 2 (11%) achieved uMRD2 and dMRD2, respectively (Figure 3D). For comparison, among patients in arm A (ibrutinib maintenance), 1 patient

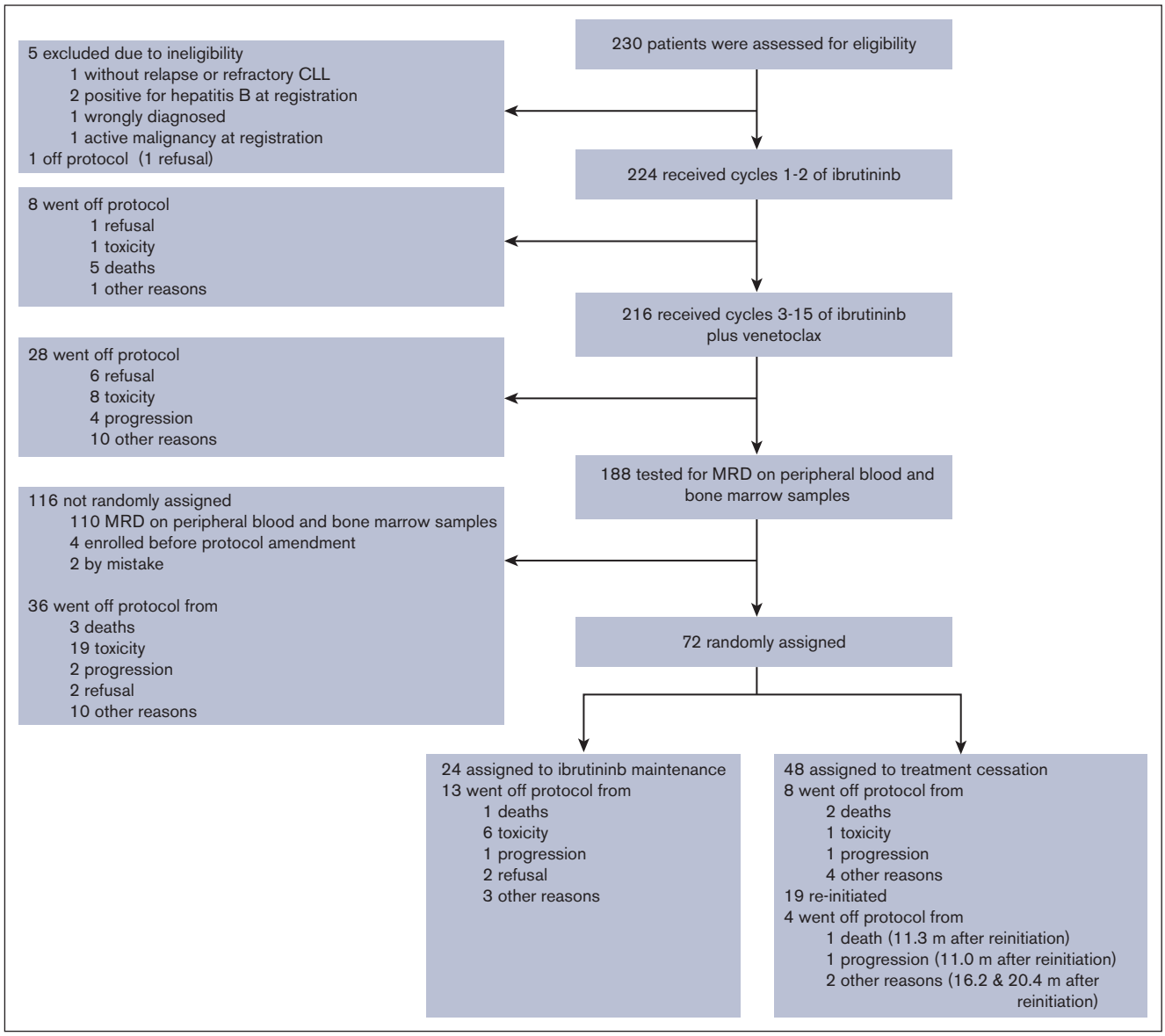

Figure 1. CONSORT diagram. m, months.

developed dMRD2 (the cut-off for reinitiation in arm B) followed by a clinical progression at month 51 (supplemental Figure 3). MRD levels among patients who were not randomized because of dMRD at cycle 15 and continued ibrutinib and for whom follow-up MRD data were available were as follows: 28 (39%) had achieved uMRD4 in the peripheral blood at month 51, whereas 24 (34%) achieved uMRD2 (dMRD4) in the peripheral blood, and 19 (27%) still had dMRD2 in the peripheral blood (supplemental Figure 4). Due to budget restrictions, MRD testing was not performed for all patients at all time points in the nonrandomized arm.

In arm B (treatment cessation), enrichment of patients with genomic complexity (≥3 aberrations) and/or presence of TP53 aberrations was observed for patients who had MRD conversion to dMRD2 (19 reinitiated patients plus 4 patients not reinitiated but experiencing dMRD2) as compared with the 25 patients who did not: genomic complexity of 48% vs 20%; and TP53 aberrations of 22% vs 16%. No pattern of difference was detected for IGHV status (supplemental Table 1).

Safety

Eleven fatalities (5%) were reported until cycle 15.[12] During the 3 years after the cycle 15 follow-up period, 14 fatalities (7%) were reported. Of these, 1 (4%) occurred in arm A (ibrutinib maintenance; infection and COVID-10), 4 (8%) in arm B (treatment cessation; caused by infection [COVID-19]), Richter transformation, myelodysplastic syndrome, other malignancies; 1 each), and 9 (8%) in the nonrandomized arm (cause by CLL [n = 3], other malignancies [n = 3)], infections [n = 2, 1 COVID-19], and unknown [n = 1]; Table 2). In total, 61 patients (27%) went off protocol. Reasons for going off protocol differed per postcycle-15 treatment cohort. Of the nonrandomized patients continuing

Table 1. Baseline characteristics at inclusion

Characteristic	Arm A n = 24	Arm B n = 48	Nonrandomized n = 116	Total N = 188
Sex, n (%)				
Female	5 (21)	15 (31)	34 (29)	54 (29)
Age, y				
Median (range)	66 (48-81)	71 (45-87)	68 (36-84)	68 (36-87)
WHO performance, n (%)				
0	18 (75)	28 (58)	76 (62)	122 (65)
1	5 (21)	20 (42)	34 (33)	59 (31)
2	1 (4)	0 (0)	6 (4)	7 (4)
3	0 (0)	0 (0)	0 (0)	0 (0)
Binet classification, n (%)				
A	3 (13)	4 (8)	18 (16)	25 (13)
B	11 (46)	21 (44)	47 (41)	79 (42)
C	9 (38)	22 (46)	51 (44)	82 (44)
Creatinine clearance, mL/min				
Median (range)	73 (41-125)	71 (38-127)	72 (41-123)	72 (38-127)
Baseline tumor lysis syndrome risk, n (%)				
Low	5 (21)	9 (19)	22 (19)	36 (19)
Medium	9 (38)	22 (46)	52 (45)	83 (44)
High	10 (42)	16 (33)	41 (35)	67 (36)
CIRS score				
Median (range)	2 (0-7)	2 (0-12)	2 (0-10)	2 (0-12)
>6	2 (8)	1 (2)	8 (7)	11 (6)
White blood cells, $\times 10^9$/L				
Median (range)	35 (4-425)	49 (4-391)	60 (4-408)	58 (4-425)
Platelets, $\times 10^9$/L				
Median (range)	136 (43-277)	116 (44-374)	113 (17-363)	115 (17-374)
Hemoglobin, g/dL				
Median (range)	12.6 (8.1-16)	12.2 (8.5-16)	11.9 (7.1-16.3)	12.1 (7.1-16.3)
β2-microglobulin, mg/L				
Median (range)	3.8 (1.7-8.5)	5.3 (2.0-18.2)	4.7 (0.8-63.0)	4.7 (0.8-63)
***TP53* mutation, n (%)**				
Present	6 (25)	8 (17)	29 (25)	43 (23)
11q deletion, n (%)				
Present	6 (25)	18 (38)	34 (29)	58 (31)
17p13 deletion, n (%)				
Present	3 (13)	5 (10)	18 (16)	26 (14)
13q14 deletion, n (%)				
Present	13 (54)	24 (50)	76 (66)	113 (60)
Trisomy 12, n (%)				
Present	4 (17)	5 (10)	10 (9)	19 (10)
***TP53* pathway aberration (17p deletion and/or *TP53* mutation), n (%)**				
Present	6 (25)	9 (19)	30 (26)	45 (24)
GC, n (%)				
Absence (<3)	15 (62)	32 (67)	89 (77)	136 (72)
Low (3-4)	5 (21)	12 (25)	18 (16)	35 (19)
High (≥5)	3 (12)	4 (8)	9 (8)	16 (9)

Baseline characteristics for all included patients (total) and by treatment arm. Data are presented as n (%) unless otherwise indicated.

CIRS, cumulative illness rating scale; del, deletion; FISH, fluorescence in situ hybridization; GC, genome complexity; IPI, International Prognostic Index; TLS, tumor lysis syndrome; WHO, World Health Organization.

Table 1 (continued)

Characteristic	Arm A n = 24	Arm B n = 48	Nonrandomized n = 116	Total N = 188
IGHV mutational status, n (%)				
Unmutated	14 (58)	32 (67)	71 (61)	117 (62)
Previous CLL treatment, n (%)				
1	16 (67)	30 (63)	78 (68)	124 (66)
2	6 (25)	9 (19)	17 (15)	32 (17)
3	2 (8)	7 (15)	15 (13)	24 (13)
≥4	0 (0)	2 (4)	5 (5)	7 (6)
Time since last treatment, mo				
Median (range)	41 (2-113)	32 (2-85)	32 (0-205)	34 (0-205)
FISH results				
Normal	7 (29)	12 (25)	21 (18)	40 (21)
CLL IPI score, n (%)				
Low risk	1 (4)	0 (0)	5 (4)	6 (3)
Intermediate risk	6 (25)	5 (10)	16 (14)	27 (14)
High risk	8 (33)	29 (60)	53 (46)	90 (48)
Very high risk	5 (21)	8 (17)	27 (23)	40 (21)

Baseline characteristics for all included patients (total) and by treatment arm. Data are presented as n (%) unless otherwise indicated.
CIRS, cumulative illness rating scale; del, deletion; FISH, fluorescence in situ hybridization; GC, genome complexity; IPI, International Prognostic Index; TLS, tumor lysis syndrome; WHO, World Health Organization.

ibrutinib, 36 (31%) went off protocol because of toxicity (n = 19, 16%), progression (n = 2, 2%), death (n = 3, 3%), or other reasons (n = 12, 10%). For the 24 patients randomized to ibrutinib maintenance in arm A, 13 (54%) went off protocol because of toxicity (n = 6, 25%), progression (n = 1, 4%), death (n = 1, 4%), or other reason (n = 5, 21%). For the 48 patients in treatment cessation arm B, 29 (60%) continued treatment cessation according to protocol; 8 of these (28%) went off protocol because of toxicity (n = 1), progression (n = 1), death (n = 2), and other reasons (n = 4). Of 19 (40%) patients in arm B that reinitiated treatment according to protocol, 4 (21%) went of protocol because of death, toxicity, progression, or other reason (n = 1 each; Figure 1).

The most commonly reported AEs after cycle 15 included infections (higher in ibrutinib maintenance arms, with 35% [nonrandomized] and 25% [randomized ibrutinib maintenance] grade 3-5 infections vs 8% in arm B, treatment cessation) and bleeding (ibrutinib arms only), whereas atrial fibrillation (ibrutinib arms only) was also reported (Table 2). Next, we assessed whether the patients with uMRD4 randomized to treatment cessation (arm B) had a different AE profile as compared with patients randomized to ibrutinib maintenance (arm A) and to nonrandomized patients. The landmark analysis from end of cycle 15 demonstrated both a longer time to, and a lower rate of, infections for patients in the treatment cessation arm B, with 31% having had an infection (grade ≥2) at 3 years after cycle 15, as compared with 63% in arm A ibrutinib maintenance and 55% among patients with dMRD4 continuing ibrutinib (Figure 4). The median time to infection was 10 months in arm A, 29 months in the nonrandomized arm, and not reached in arm B. The infection-free probability at 36 months after randomization was 72%, 41%, and 44% in treatment cessation arm B, ibrutinib maintenance arm A, and the nonrandomized arm, respectively. Across the 3 arms of the study after cycle 15, patients in treatment cessation arm B had fewer and lower grade AEs for all groups of AEs except neutropenia (Table 2).

Discussion

In this multicenter, international, open label, randomized, phase 2 trial we demonstrate that treatment with a regimen of 2 single-agent ibrutinib cycles followed by 13 cycles of ibrutinib plus venetoclax for R/R CLL provides high rates of uMRD4 with the possibility to safely guide cessation and reinitiation of treatment, if required, based on MRD. The regimen demonstrated rates of OS, PFS, and NT exceeding those of other time-limited regimens for R/R CLL such as venetoclax + rituximab,[14] whereas lowering long-term toxicity if compared with continuous-treatment regimens with the 3 marketed covalent BTK inhibitors.[15-17]

OS rates at 4 years were 88% for the full trial population of patients with R/R CLL, which is at least comparable with data from the MURANO trial of venetoclax + rituximab for R/R CLL (4-year OS, 85.3%) that currently defines the standard for later-line time-limited treatment.[3,18] These rates were also comparable with what has been achieved with continuous single-agent ibrutinib (median OS, 67.7 months) or acalabrutinib (42-month OS, 78%) for patients with R/R CLL.[19-21] In this study, the 4-year PFS rate was 81%, which is higher than observed for venetoclax + rituximab in the MURANO trial (57%), but again comparable with what has been observed with continuous BTK inhibitors (median PFS, 44.1 months for ibrutinib; 46.5 month, 60% PFS rate for acalabrutinib). Importantly, PFS rates were equally high in patients randomized to MRD-guided treatment cessation and reinitiation, emphasizing the potential to reduce treatment exposure and toxicity by MRD-guided treatment in the R/R CLL setting. Assessing NT, 49% of patients in the venetoclax + rituximab arm of

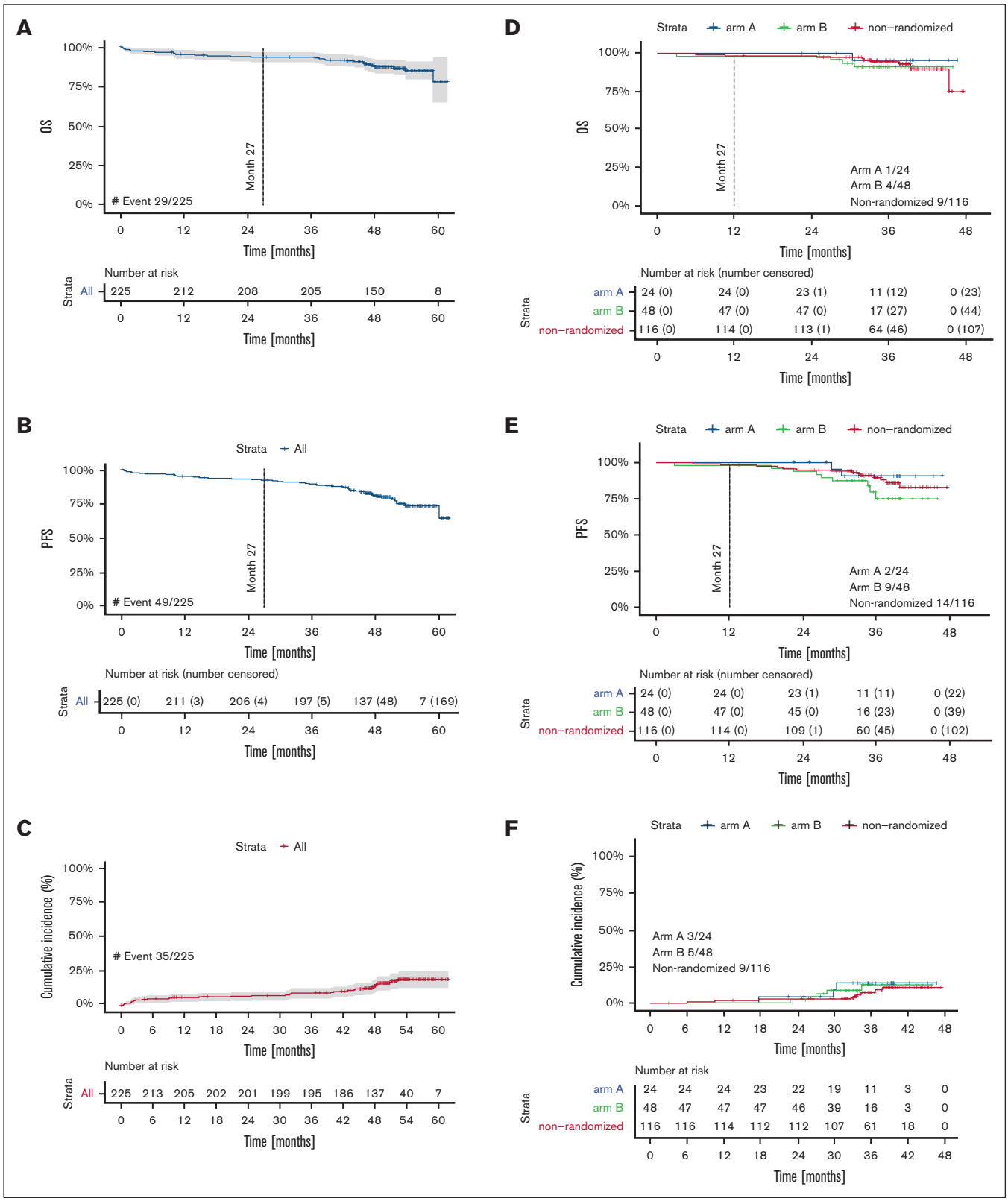

Figure 2. OS, PFS, and time to NT. Outcome visualized as Kaplan-Meier curves on the intention to treat population (n = 225) for (A): OS, (B) PFS, and (C) time to NT from start of treatment. Landmark analyses for (D) OS, (E) PFS, and (F) NT are presented from time point of randomization at end of cycle 15 for arm A, ibrutinib maintenance; arm B, treatment cessation; and the nonrandomized arm.

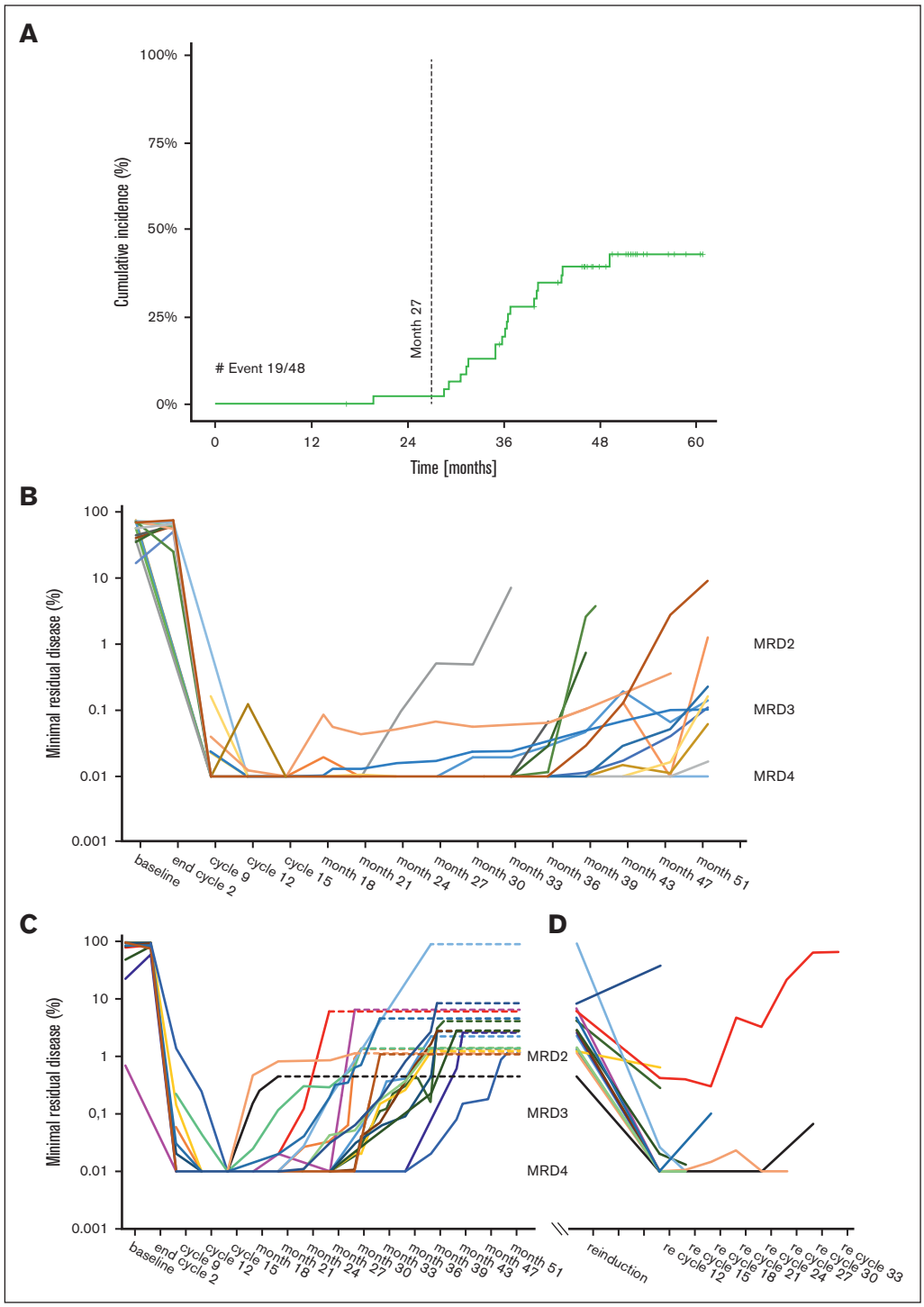

Figure 3. Reinitiation and dynamics of response per patient. For patients in arm B (treatment cessation), (A) time to reinitiation of treatment per protocol is provided. For those who did not reinitiate treatment, (B) MRD kinetics are provided. Please note that 4 patients met the dMRD2 criteria without reinitiating therapy (see text for details). (C) Dynamics of MRD until reinitiation for the patients reinitiating treatment per protocol, dashed lines indicate the level of dMRD for individual patients at time of reinitiating therapy, whereas (D) provides the MRD kinetics for those patients after reinitiation. Data cutoff for panels B-D is 24 October 2023, MRD results tested every 3 to 4 months. MRD levels are indicated, MRD2 = 1% = 10^{-2}, MRD3 = 0.1% = 10^{-3}, and MRD4 = 0.01% = 10^{-4}.

the MURANO trial received NT with a median follow-up of 48 months, as compared with 14% receiving NT after ibrutinib + venetoclax with a median follow-up of 51.7 months. Time to NT is not reported for the ibrutinib R/R CLL treatment in the RESONATE trial, whereas for acalabrutinib in R/R CLL in the ASCEND trial, 64% were reported NT free at 42 months.[21] With the improved

Table 2. AEs in the 3 groups of patients from randomization + 3 years (month 51)

	Grade 2			Grade 3			Grade 4		Fatalities*		
CTCAE grade	Non-rdm Ibr (n = 116)	Arm A Ibr (n = 24)	Arm B Obs (n = 48)	Non-rdm Ibr (n = 116)	Arm A Ibr (n = 24)	Arm B Obs (n = 48)	Non-rdm Ibr (n = 116)	Arm A Ibr (n = 24)	Non-rdm Ibr (n = 116)	Arm A Ibr (n = 24)	Arm B Obs (n = 48)
Any	27 (23%)	9 (38%)	10 (21%)	58 (50%)	8 (33%)	18 (38%)	10 (9%)	3 (13%)	9 (8%)	1 (4%)	4 (8%)
Infections	24 (21%)	9 (38%)	11 (23%)	32 (28%)	4 (17%)	3 (6%)	6 (5%)	1 (4%)	2 (2%)	1 (4%)	1 (2%)
TLS	0	0	0	0	0	0	0	0	0	0	0
Atrial fibrillation	4 (3%)	1 (4%)	0	2 (2%)	1 (4%)	0	0	0	0	0	0
Neutropenia	2 (2%)	0	3 (6%)	2 (2%)	0	2 (4%)	2 (2%)	0	0	0	0
Arthralgia	8 (7%)	1 (4%)	1 (2%)	1 (1%)	0	0	0	0	0	0	0
Diarrhea	8 (7%)	2 (8%)	2 (4%)	2 (2%)	0	2 (4%)	0	0	0	0	0
Bleeding	13 (11%)	1 (4%)	0	1 (1%)	1 (4%)	0	0	0	0	0	0
Malignancies	6 (5%)	0	3 (6%)	8 (7%)	2 (8%)	3 (6%)	0	1 (4%)	6 (5%)	0	2 (4%)
Hypertension	5 (4%)	3 (13%)	0	4 (3%)	1 (4%)	0	0	0	0	0	0
Nail changes	1 (1%)	0	0	0	0	0	0	0	0	0	0
Headache	1 (1%)	0	2 (4%)	0	0	0	0	0	0	0	0
AE other	38 (33%)	8 (33%)	8 (17%)	24 (21%)	3 (13%)	12 (25%)	3 (3%)	1 (4%)	1 (1%)	0	1 (2%)

Summary of AEs after cycle 15. Data are presented as n (%) unless otherwise indicated.

Fatalities in non-rdm arm: CLL (n = 3, included under malignancies in table), other malignancies (n = 3), infections (n = 2, 1 COVID-19), unknown (n = 1); fatalities in obs arm B: infection (COVID-19), Richter's transformation, myelodysplastic syndrome, and other malignancies (n = 1 each); fatality in ibr arm A: infection (n = 1, COVID-19).

CTCAE, common terminology criteria for AEs; ibr, arm A, ibrutinib maintenance; non-rdm, nonrandomized; obs, arm B, treatment cessation; TLS, tumor lysis syndrome.

*Fatalities are included whether considered an AE or not.

outcome for patients with CLL, sequencing of treatment becomes more important. Based on data from the MURANO trial and the GAIA/CLL13 trial, it has been demonstrated that retreatment with rituximab-venetoclax as well as ibrutinib-venetoclax is feasible after venetoclax plus rituximab or obinutuzumab,[14] whereas the data presented here indicate that early retreatment upon molecular but

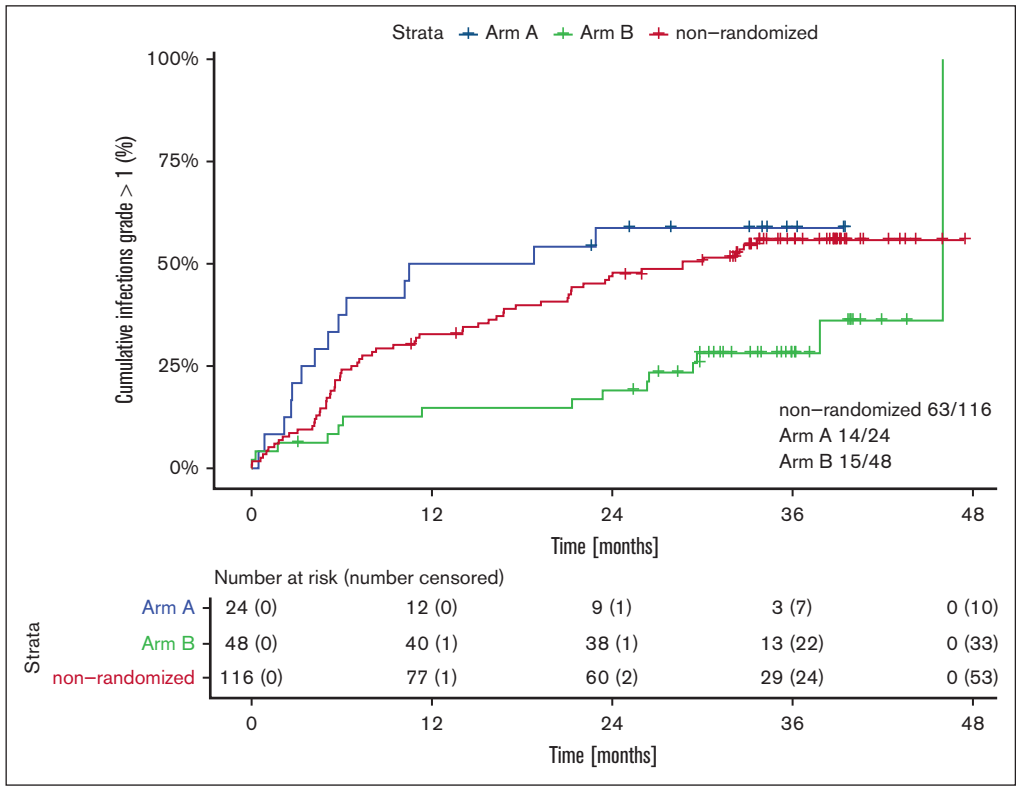

Figure 4. Risk of infection. Risk of infection (CTCAE grade ≥2) from end of cycle 15 for arm A (ibrutinib maintenance), arm B (treatment cessation), and nonrandomized patients continuing ibrutinib. CTCAE, common terminology criteria for AEs.

not clinical progression with ibrutinib-venetoclax results in long second PFS.

Two major concerns for continuous BTK inhibitor treatment are: (1) the high discontinuation rate mainly because of patient-assessed toxicity, resulting in a median time to discontinuation outside clinical trials of <3 years and (2) the increased risk of longer exposure to develop resistance mutations leading to treatment failure.[15,22] We here demonstrate that AEs are less frequent among patients randomized to MRD-guided treatment cessation and reinitiation. Thus, although keeping high PFS rates as for rates on continuous BTK inhibitors for R/R CLL, toxicity can be reduced by this MRD-guided approach. At the same time, the risk of subclonal development and resistance reported on continuous targeted treatment may be at least, in part, avoided by this MRD-guided approach.[23-25] Finally, the reinitiation upon MRD conversion demonstrated that clinical progressions could be avoided, which have previously been linked to increased risk of immune dysfunction and fatal infections.[9-11] The lower rate and/or grade of infections among patients randomized to MRD-guided treatment, emphasizes the option for improved balance between CLL-derived and treatment-derived immune dysfunction with this treatment regimen.

Because of the strict criteria for entry into the randomized part of this trial: achieving uMRD4 in both the peripheral blood and bone marrow; only 40% of patients were eligible for randomization between MRD-guided treatment cessation and ibrutinib maintenance. This was lower than the 55% expected at the time of study design and resulted in the study being underpowered to adequately assess the primary end point in the MRD-guided treatment cessation arm, potentially affecting the interpretation of negative results. Additionally, the study was not designed to be statistically powered for comparative efficacy assessments between the randomized arms, because it was exploratory in nature, aimed at investigating feasibility, and generating hypotheses rather than confirming them. However, recent publications of ibrutinib plus venetoclax for treatment-naïve CLL indicate that stringent MRD cutoffs might be unnecessary, because patients only achieving intermediate MRD in the peripheral blood have long and stable PFS, in particular for patients with IGHV-mutated disease.[9-11] In the frontline setting, the FLAIR trial tested MRD-guided ibrutinib with venetoclax for younger fit patients. They used a longer duration of treatment requiring doubling the treatment duration from the time point of achieving uMRD4.[26,27] Thus, extrapolating from these data and the here presented results, MRD-guided treatment with a combination of BTK inhibitor plus BCL-2 inhibitor allowing treatment cessation for patients upon uMRD3 with reinitiation at dMRD2 could be a valid option for both treatment-naïve and previously treated CLL.

MRD-guided cessation and reinitiation of ibrutinib plus venetoclax for R/R CLL is feasible and reduce toxicity as compared with indefinite BTK inhibitor treatment while providing PFS rates above what has been reported for other time-limited treatment options for R/R CLL. The MRD-guided approach may also allow for improved patient compliance, thus offering an alternative to the high discontinuation rates reported outside clinical trials for continuous BTK inhibitors.

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Authorship

Contribution: A.P.K., C.U.N., and M.-D.L. designed the trial; W.R. and R.H. managed the trial, including data management and sponsor management; K.N. was the responsible statistician; J.D., C.B., J.A.D., and I.S. were responsible for biobank, genetic analyses, and minimal residual disease analyses; all co-authors except W.R., R.H., K.N., J.D., J.A.D., and I.S. were investigators on the trial; C.U.N., A.P.K., J.D., M.-D.L., C.d.C.-B., and K.N. wrote the first version of the manuscript; and all authors reviewed and contributed and approved the final version of the manuscript.

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