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ORIGINAL REPORT

# Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial

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## ABSTRACT

### Purpose

Venetoclax is an orally bioavailable B-cell lymphoma 2 inhibitor. US Food and Drug Administration and European Medicines Agency approval for patients with 17p deleted relapsed/refractory chronic lymphocytic leukemia [del(17p) CLL] was based on results from 107 patients. An additional 51 patients were enrolled in a safety expansion cohort. Extended analysis of all enrolled patients, including the effect of minimal residual disease (MRD) negativity on outcome, is now reported.

### Patients and Methods

Overall, 158 patients with relapsed/refractory or previously untreated (n = 5) del(17p) CLL received venetoclax 400 mg per day after an initial dose ramp up. Responses were based on 2008 International Workshop on Chronic Lymphocytic Leukemia criteria, with monthly physical exams and blood counts. Computed tomography scan was mandatory at week 36, after which assessment made was by clinical evaluation. Marrow biopsy was performed when complete remission was suspected. MRD was assessed by flow cytometry.

### Results

Patients had a median of two prior therapies (range, zero to 10 therapies), 71% had *TP53* mutation, and 48% had nodes that were ≥ 5 cm. Median time on venetoclax was 23.1 months (range, 0 to 44.2 months) and median time on study was 26.6 months (range, 0 to 44.2 months). For all patients, investigator-assessed objective response rate was 77% (122 of 158 patients; 20% complete remission) and estimated progression-free survival at 24 months was 54% (95% CI, 45% to 62%). For 16 patients who received prior kinase inhibitors, objective response rate was 63% (10 of 16 patients) and 24-month progression-free survival estimate was 50% (95% CI, 25% to 71%). By intent-to-treat analysis, 48 (30%) of 158 patients achieved MRD below the cutoff of $10^{-4}$ in blood. Common grade 3 and 4 adverse events were hematologic and managed with supportive care and/or dose adjustments.

### Conclusion

Venetoclax achieves durable responses and was well tolerated in patients with del(17p) CLL. A high rate of blood MRD $< 10^{-4}$ was achieved in this high-risk population.

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## INTRODUCTION

Chronic lymphocytic leukemia (CLL) that harbors either the deletion of chromosome 17p [del(17p)] or mutation in *TP53* has poor prognosis. Treatment of patients with this high-risk disease remains challenging.[1] Until recently, allogeneic hematopoietic stem cell transplantation was considered to be the most effective treatment approach for these patients; however, the emergence of targeted agents that are effective for patients with del(17p) CLL has changed the therapeutic landscape,[2,3] and most patients who are at high risk receive B-cell receptor pathway inhibitors (BCRis) when available as first-line therapy.

Venetoclax is a selective, orally bioavailable inhibitor of B-cell lymphoma 2 that targets the intrinsic apoptosis pathway.[4] A recent study

ASSOCIATED CONTENT

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demonstrated that in vitro sensitivity to venetoclax was not significantly different for CLL cells that harbored del(17p) and *TP53* mutation compared with cells with intact chromosome 17p and wild-type *TP53*.[5] Clinical studies of venetoclax monotherapy also demonstrated no difference in objective response rates (ORRs) for patients with or without del(17p).[6,7]

Venetoclax is approved for some patients who have been previously treated for CLL.[8,9] Initial US Food and Drug Administration and European Medicines Agency approval of venetoclax was based on an ORR of 79% and a complete remission (CR) rate of 8%—using independent review committee assessment—reported after a median follow-up of 1 year for the first 107 patients with relapsed/refractory del(17p) CLL who were enrolled in this trial.[7] Here, we provide efficacy, safety, and minimal residual disease (MRD) assessment for the full trial population of 158 patients, which includes the 107 patients in the main cohort and 51 additional patients who were enrolled in a safety expansion cohort who now have a median time on study of more than 2 years, including five first-line patients and 16 who had experienced disease progression on, or who were intolerant to, BCRi therapy.

## PATIENTS AND METHODS

### Study Design and Oversight

This phase II, open-label, M13-982 study started in June 2013 and completed enrollment of patients with relapsed/refractory or previously untreated del(17p) CLL, with follow-up ongoing. At each participating site, an institutional review board approved the study protocol and amendments. The trial was conducted under the relevant International Conference on Harmonization Good Clinical Practice guidelines and in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before participation.

### Patients

Adults with relapsed/refractory or previously untreated—from December 2014 onwards—del(17p) CLL were eligible if they required therapy according to criteria of the 2008 International Workshop on Chronic Lymphocytic Leukemia.[10] Complete enrollment criteria are described in the Data Supplement.

### Treatment

Venetoclax monotherapy was administered orally, once daily, until disease progression or study discontinuation. Because venetoclax can induce rapid tumor debulking and poses a potential risk for tumor lysis syndrome (TLS),[6] therapy was initiated by stepwise dose ramp-up with prophylaxis and monitoring to mitigate TLS risk. As previously described, patients in the main cohort received a single dose of venetoclax 20 mg on day 1 and, on the basis of laboratory assessments, gradually ramped up to the target dose of 400 mg once daily over 4 to 5 weeks.[7] In the main cohort, all patients were hospitalized for the first 20-mg and 50-mg doses during ramp-up. On the basis of additional evaluation of venetoclax dosing as well as prophylaxis and monitoring for TLS across the venetoclax CLL study program, the protocol was amended and all patients in the expansion cohort received venetoclax 20 mg once daily for 1 week, followed by weekly ramp-up to the target dose of 400 mg once daily over 5 weeks, per the prescribing information (Data Supplement).[9,11] TLS prophylaxis and management for patients in the expansion cohort were based on tumor burden categories assessed at baseline (Data Supplement).[6,7,11]

**Table 1.** Patients Demographics and Clinical Characteristics

| Demographic and/or Characteristic | All Patients (N = 158) |
|---|---|
| Median age (range), years | 67 (29-85) |
| Sex | |
| Female | 59 (37) |
| Male | 99 (63) |
| ECOG performance status | |
| 0 | 69 (44) |
| 1 | 78 (49) |
| 2 | 11 (7) |
| CLL-IPI category* | |
| Low | 3 (2) |
| Intermediate | 6 (4) |
| High | 116 (73) |
| Very high | 33 (21) |
| Rai stage at screening | |
| 0 | 1 (.6) |
| 1 | 32 (20) |
| 2 | 52 (33) |
| 3 | 26 (16) |
| 4 | 47 (30) |
| No. of prior therapies, median (range) | 2 (0-10)† |
| Fludarabine-containing regimen | 103 (65) |
| Fludarabine refractory | 45 (28) |
| Cyclophosphamide-containing regimen (without fludarabine) | 38 (24) |
| Anti-CD20 monoclonal antibody-containing regimen | 123 (78) |
| Bendamustine-containing regimen | 69 (44) |
| Chlorambucil-containing regimen | 27 (17) |
| Alemtuzumab-containing regimen | 24 (15) |
| Cladribine- or pentostatin-containing regimen | 4 (3) |
| Steroid only | 7 (4) |
| Other agents | 7 (4) |
| Other chemotherapy | 5 (3) |
| Prior B-cell pathway receptor inhibitor | 16 (10) |
| Treatment naïve | 5 (3) |
| TLS risk category‡ | |
| Low | 36 (23) |
| Medium | 60 (38) |
| High | 62 (39) |
| Median ALC (range), $\times 10^9$/L | 25 (0.3-399) |
| $\geq 25 \times 10^9$/L | 79 (50) |
| Bulky nodes | |
| $\geq 5$ cm | 76 (48) |
| $\geq 10$ cm | 21 (13) |
| Unmutated IGHV | 45 of 58 (78) |
| *TP53* mutation¶ | 55 of 77 (71) |
| Chromosome 11q deletion | 38 of 157 (24) |
| Median serum β2-microglobulin (range), μg/mL | 3.6 (1.3-31) |

NOTE. Data presented as No. (%) unless otherwise noted.
Abbreviations: ALC, absolute lymphocyte count; CLL-IPI, Chronic Lymphocytic Leukemia International Prognostic Index; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy chain variable; TLS, tumor lysis syndrome.
*CLL-IPI categories are based on data for 17p deletion, *TP53* mutation, unmutated IGHV, β2-microglobulin, Rai or Binet stage, and age > 65 years. Missing values were imputed using Multiple Imputation.
†Includes five previously untreated patients enrolled in the safety expansion cohort.
‡TLS risk categories are defined as follows: low: all lymph nodes < 5 cm and ALC $< 25 \times 10^9$/L; medium: any lymph node ≥ 5 cm to < 10 cm or ALC $> 25 \times 10^9$/L; high: any lymph node > 10 cm or any lymph node ≥ 5 cm and ALC $> 25 \times 10^9$/L.
¶Assessed by targeted next-generation sequencing (methods described in the Data Supplement).

### Study Assessments

Disease assessments were performed at screening and at each study visit starting on week 4 or 5. Responses and disease progression (PD) were evaluated according to 2008 International Workshop on Chronic Lymphocytic Leukemia criteria[10] with clinical laboratory tests, physical

  

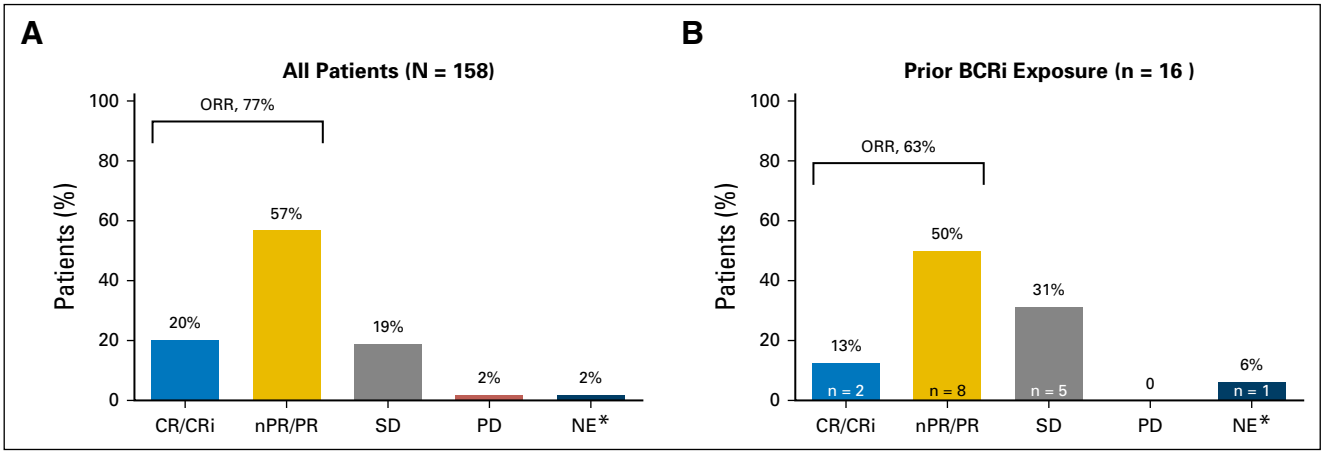


**Fig 1.** Best objective response rates (ORRs) with venetoclax for patients with 17p deleted relapsed/refractory chronic lymphocytic leukemia [del(17p) CLL]. Objective responses shown for all enrolled patients (N = 158) and patients who had received prior B-cell receptor pathway inhibitor (BCRi) therapy (n=16). (*) One patient discontinued after the first dose of venetoclax, one patient died after 3 weeks of treatment as a result of liver dysfunction and rapid clinical deterioration with highly $^{18}$F-labeled fluorodeoxyglucose positron emission tomography avid disease interpreted as Richter transformation (event not related to venetoclax), and one patient had pseudo-obstruction of the small bowel mesentery and retroperitoneum during dose ramp-up and discontinued the study. CR, complete remission; CRi, complete remission with incomplete marrow recovery; NE, not evaluated for response; nPR, nodular partial remission; PD, disease progression; PR, partial remission, SD, stable disease.

examination, computed tomography (CT) scan, bone marrow aspirate, and biopsy. CT scans were performed to determine response—CR or partial remission (PR) —and if CT demonstrated the resolution of disease, then a bone marrow biopsy was required to establish CR. CT scans were also performed at 36 weeks for all patients. Peripheral blood and bone marrow assessments for MRD were conducted in patients with CR or CR with incomplete bone marrow recovery (CRi), or for patients with nodular PR (nPR) or PR and nodal masses that were $<$ 2 cm in maximal dimension. MRD was assessed by multicolor flow cytometry per established protocols (Data Supplement).

Safety assessments were conducted from screening and up to 30 days post-treatment. Adverse events (AEs) and laboratory abnormalities were graded on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[12] Methods for pharmacokinetic assessments are described in the Data Supplement.

### *Statistical Analyses*

Data cutoff for this analysis was April 4, 2017, and includes all patients who were enrolled in the main and safety expansion cohorts. Efficacy and safety analyses included all patients who received at least one dose of venetoclax. Descriptive statistics were calculated, and Kaplan-Meier methods were used for time-to-event analyses. SAS (SAS/STAT User's Guide; SAS Institute, Cary, NC) was used to generate all statistical summaries. Statistical significance was determined using two-sided $P < .05$. Details regarding sample size determination are in the Data Supplement.

## RESULTS

### *Patients*

A total of 158 patients with del(17p) CLL were enrolled in the study. Key demographic and clinical characteristics are summarized in Table 1. Eighteen patients with medium or low risk of TLS received initial venetoclax dosing in the outpatient setting. Patients had received a median of two prior lines of therapy (range, zero to 10 therapies; five patients were previously untreated), including 16 patients (11%) who had received prior BCRi (14 patients discontinued prior BCRi as a result of PD and two as a result of AEs). In addition to del(17p), patients had other high-risk prognostic features, including unmutated immunoglobulin heavy chain variable region gene (78%; 45 of 58 patients tested), deletion of chromosome 11q (24%; 38 of 157 patients tested), or *TP53* mutation (71%; 55 of 77 patients tested). Approximately one half of patients had bulky lymphadenopathy ($\geq$ 5 cm, 48%; $\geq$ 10 cm, 13%) at study entry. Ten patients did not have local laboratory results for del(17p) confirmed by central laboratory analysis using the Vysis fluorescent in situ hybridization probe (Abbott Laboratories, Chicago, IL; cutoff of $>$ 7%), although nine patients had local laboratory evidence of del(17p). These patients are nonetheless included in all analyses.

### *Disposition on Treatment*

As of April 4, 2017, median time on venetoclax was 23.1 months (range, 0 to 44.2 months), and median time on study was 26.6 months (range, 0 to 44.2 months). Seventy-nine patients (50%) remain on study (median time on study, 27.8 months; range, 16.3 to 36.2 months), with 72 (46%) still on venetoclax, six in post-treatment follow-up (no longer taking venetoclax), and one who temporarily interrupted therapy at the time of analysis. Primary reasons for permanent discontinuation of venetoclax were CLL progression (n = 37; 23%), Richter's transformation (n = 21; 13%), AEs (n = 18; 11%), elective discontinuation to proceed to stem cell transplantation (n = 4; 3%), consent withdrawal (n = 3; 2%), noncompliance (n = 1; 0.6%), and patient decision to stop therapy (n = 2; 1%). Fifty-three patients died while on the study, with 44 deaths (83%) a result of PD (Data Supplement). Of the nine other reasons for death, one death as a result of pneumonia was deemed possibly related to the study drug and all others were deemed unrelated.

### *Efficacy*

Investigator-assessed ORR for all patients was 77% (122 of 158 patients), with a best response of CR/CRi in 20% (32 of 158 patients) and nPR/PR in 57% (90 of 158 patients; Fig 1). Median

time to first response was 1 month (range, 0.5 to 4.4 months), and time to first documentation of CR/CRi was 9.8 months (range, 2.7 to 31.1 months), which clustered with the timing of the mandatory CT scan at 36 weeks. Thirty patients had stable disease as the best response, three had PD, and three were not evaluable. Details on patients with relapsed/refractory versus previously untreated del (17p) CLL and responses by subgroups are in the Data Supplement.

For the 122 patients who achieved a response, the Kaplan-Meier duration of response (DOR) estimate at 24 months was 66% (95% CI, 55% to 74%), with an estimated median DOR of 33.2 months (95% CI, 26.7 months to not reached; Fig 2A). For all patients, 24-month estimates of progression-free survival (PFS) and overall survival (OS) were 54% (95% CI, 45% to 62%) and 73% (95% CI, 65% to 79%), respectively (Figs 2B and 2C). Estimated median PFS was 27.2 months (95% CI, 21.9 months to not reached; Fig 2B) and was not reached for patients with CR/CRi (Fig 2D). Median OS cannot be estimated currently.

For 16 patients who received prior BCRi therapy, median time on venetoclax was 16 months (range, 0.9 to 35 months) and ORR was 63% (10 of 16 patients), with two patients attaining CR. Median DOR, PFS, and OS had not yet been reached for these patients. Twenty-four–month estimates are 82% (95% CI, 45% to 95%) for DOR, 50% (95% CI, 25% to 71%) for PFS, and 55% (95% CI, 28% to 76%) for OS (Data Supplement).

### *MRD*

MRD was evaluated by flow cytometry, with blood specimens and bone marrow specimens evaluable for 101 and 68 patients, respectively. By intent-to-treat analysis, 30% (48 of 158) of

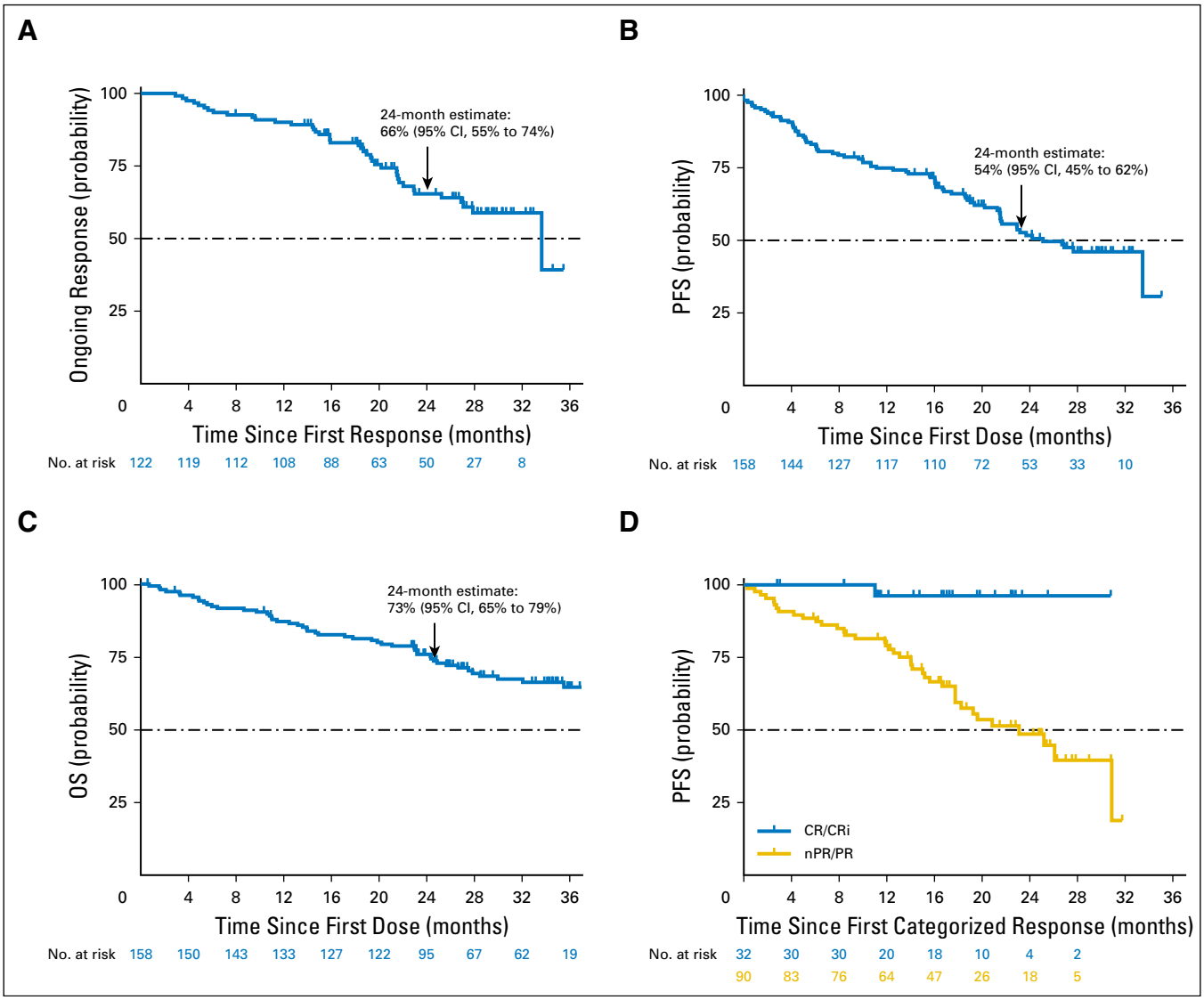


**Fig 2.** Outcomes on venetoclax monotherapy. Shown are the Kaplan-Meier curves for investigator-assessed (A) duration of response for 122 patients who achieved a response as well as (B) progression-free survival (PFS) and (C) overall survival (OS) for all 158 enrolled patients. (D) Progression-free survival since the time of first categorized response for patients who achieving complete remission/complete remission with incomplete marrow recovery (CR/CRi) or nodular partial remission/partial remission (nPR/PR). For 32 patients with CR/CRi, PFS is shown since the time that CR/CRi was achieved, and for 90 patients with nPR/PR, PFS is shown since the time that PR was confirmed by second assessment. Below each curve is the number of patients at risk for the event at each time point. Tick marks represent patients who were censored for each outcome measure.

  

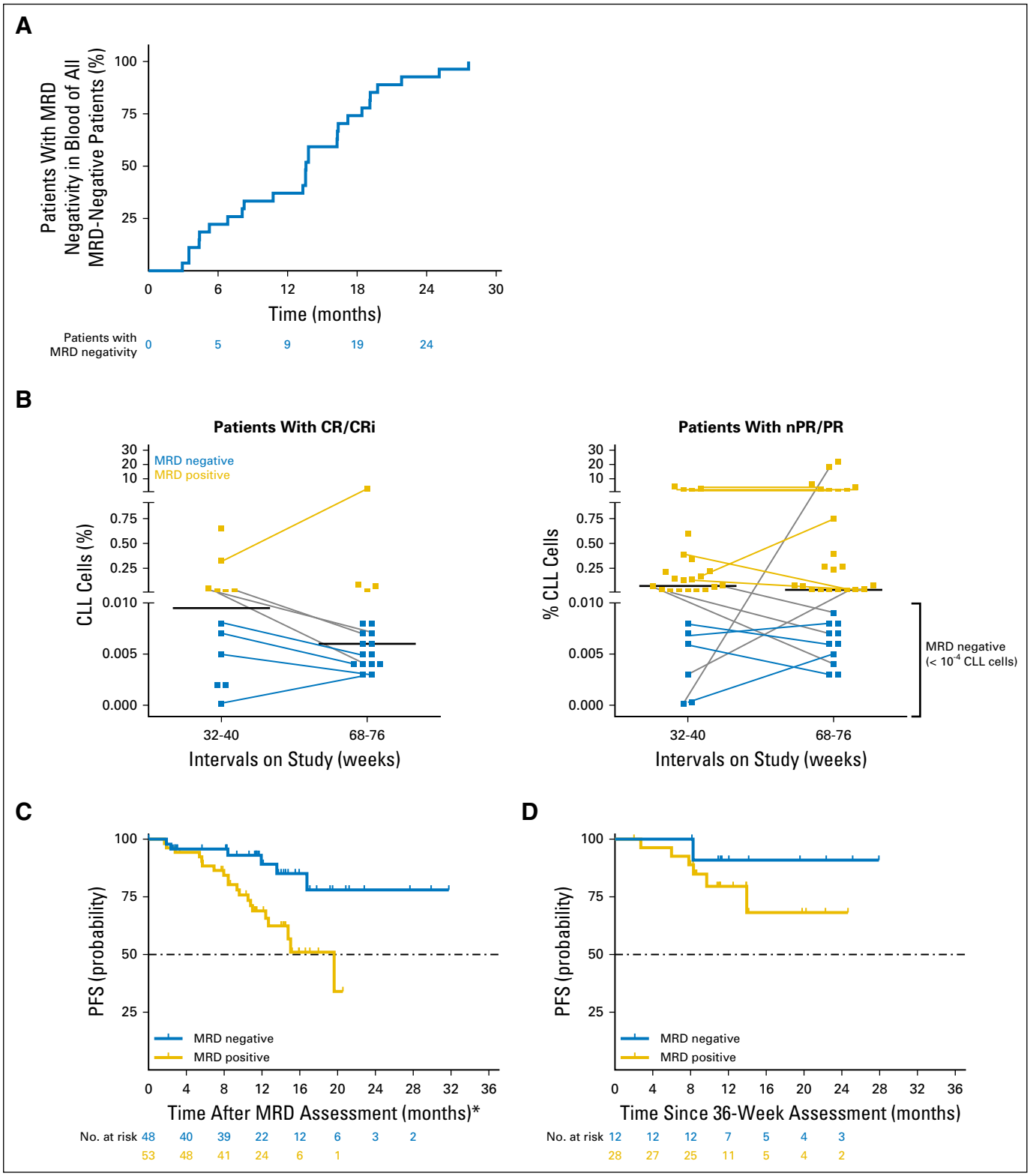


**Fig 3.** Minimal residual disease (MRD) negativity in blood as an indication of long-term outcomes with venetoclax monotherapy. (A) Of 59 patients with samples evaluated for MRD at a single regional center on the basis of MRD assessment criteria (patients with complete remission/complete remission with incomplete marrow recovery [CR/CRi], or for patients with nodular partial remission/partial remission [nPR/PR] and nodal masses < 2 cm in maximal dimension), shown is the time to first MRD-negative assessment in the peripheral blood by flow cytometry for 27 patients who had MRD below the cutoff of $10^{-4}$. (B) MRD assessments for patients who were assessed at the 36-week (± 4 weeks) landmark (32 to 40 weeks on study) when computed tomography scanning was mandated, and then at 72 ± 4 weeks (68 to 76 weeks on study). Connecting lines between the intervals are for patients with assessments at both time points, with blue lines indicating those patients who remained MRD negative, gold lines indicating patients who remained MRD positive, and gray lines showing a change in MRD status from the 36- to 72-week (continued on next page)

patients, including one patient who experienced failure with prior BCRi therapy, had MRD below the cutoff of $10^{-4}$ CLL cells (MRD negative) in the blood for at least one assessment, which corresponded to 48% (48 of 101) of patients who had MRD evaluated. Contemporaneous bone marrow assessment was available for 28 of 48 patients with blood MRD $< 10^{-4}$, 20 of whom were MRD negative in the bone marrow and eight of whom had low, but detectable residual disease (range, 0.012% to 0.083%).

To determine the most reliable estimates of the temporal pattern of achieving MRD negativity in the blood, assessment of serial MRD data from 59 patients at a single regional center was performed. For 27 of 59 patients who achieved MRD negativity in the blood, median time to MRD negativity was 13.6 months (range, 2.9 to 27.6 months; Fig 3A).

Stability of MRD status over time was then evaluated across the study. At the 36-week (± 4 weeks) landmark when CT scanning was mandated, 40 patients had MRD assessed in the blood (at one of three regional centers), of whom 12 (30%) were MRD negative. At this time point, six patients had MRD-negative CR/CRi and six had MRD-negative nPR/PR, whereas six CR/CRi patients had MRD $> 10^{-4}$ (MRD positive), and 22 had MRD-positive nPR/PR (Fig 3B). MRD levels in this small cohort largely remained relatively stable between the 36-week (± 4 weeks) landmark and evaluation at 72 ± 4 weeks, although some patients had reductions in MRD level at this later time point (Fig 3B). Patients who achieved MRD negativity at any point were less likely to experienced PD or to die than those patients who achieved a response who did not achieve MRD negativity, with an estimated PFS at 18 months after MRD attainment of 78% (95% CI, 54% to 91%) for patients who achieved MRD negativity versus 51% (95% CI, 32% to 68%) for patients who were MRD positive (Fig 3C). To avoid any guaranteed time bias, a landmark analysis of those patients who were assessed at the 36-week (± 4 weeks) time point was also performed. Whereas median PFS had not yet been reached for MRD-negative or -positive patients (Fig 3D), only one of 12 MRD-negative patients experienced PD compared with six of 28 MRD-positive patients.

**Table 2.** Summary of Adverse Events

| Adverse Event | All Patients (N = 158) |
|---|---|
| Any grade adverse event* | 155 (98) |
| Neutropenia | 67 (42) |
| Diarrhea | 62 (39) |
| Nausea | 59 (37) |
| Anemia | 39 (25) |
| Fatigue | 37 (23) |
| Thrombocytopenia | 32 (20) |
| Grade 3 or 4 adverse event† | 119 (75) |
| Neutropenia | 63 (40) |
| Thrombocytopenia | 23 (15) |
| Anemia | 23 (15) |
| Serious adverse event‡ | 91 (58) |
| Pneumonia | 16 (10) |
| Autoimmune hemolytic anemia | 8 (5) |
| Pyrexia | 8 (5) |
| Febrile neutropenia | 7 (4) |
| Tumor lysis syndrome | 5 (3) |
| Anemia | 5 (3) |
| Neutropenia | 4 (3) |
| Thrombocytopenia | 4 (3) |
| General physical health deterioration | 4 (3) |
| Adverse events leading to dose reduction‡ | 27 (17) |
| Neutropenia | 12 (8) |
| Adverse events leading to dose interruption‡ | 63 (40) |
| Neutropenia | 9 (6) |
| Pyrexia | 6 (4) |
| Pneumonia | 6 (4) |
| Febrile neutropenia | 5 (3) |
| Nausea | 5 (3) |
| Tumor lysis syndrome | 5 (3) |
| Hyperphosphatemia | 5 (3) |
| Vomiting | 4 (3) |

NOTE. All data are presented as No. (%). The severity of each adverse event was rated by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[12] Per these criteria, grade 3 events were defined as severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. Grade 4 events were defined as life-threatening consequences; urgent intervention indicated. Serious adverse events were defined as any event meeting the following criteria: death of the patient, life-threatening, hospitalization or prolongation of hospitalization, congenital anomaly, persistent or significant disability or incapacity, or any important medical event requiring medical or surgical intervention to prevent serious outcome (Data Supplement).

*Common any grade adverse events reported for ≥ 20% of patients.

†Common grade 3 and 4 adverse events reported for ≥ 10% of patients.

‡Common serious adverse events and adverse events leading to dose reductions or interruptions reported for ≥ 2% of patients.

### *Safety*

The most common all-grade AEs were neutropenia (42%), diarrhea (39%), nausea (37%), anemia (25%), fatigue (23%), and thrombocytopenia (20%; Table 2). Grade 3 or 4 AEs were primarily hematologic, including neutropenia (40%), thrombocytopenia (15%), and anemia (15%). The most common serious AE was pneumonia (10%; Table 2). Twenty-seven patients (17%) reduced venetoclax dosing and 63 (40%) interrupted dosing as a result of AEs, with neutropenia being the most common reason for dose adjustments (8% of neutropenia AEs of any grade led to dose reduction and 6% led to dose interruption). Infection rate was 81% for AEs of any grade, with the most common infections being upper respiratory tract infection (20%), nasopharyngitis (16%), and pneumonia (15%). Forty patients (25%) had grade ≥ 3 infection (four cases were fatal: RSV, *Klebsiella* sepsis, septic shock, and pneumonia), and 12 patients experienced events within the first 6 months on treatment at an exposure-adjusted rate of 0.44 per 100 patient months. Seven patients had opportunistic infections, with three grade 3 or 4 events (*Pneumocystis jirovecii* pneumonia [n = 2; both with prior fludarabine exposure] and dermatomal herpes zoster [n = 1]).

(Continued) assessment. Black line indicates median the percent chronic lymphocytic leukemia (CLL) cells at each time point. MRD was assessed at one of three regional centers. (C) Kaplan-Meier curves for progression-free survival (PFS) from the date of MRD attainment for all patients with an MRD assessment at any point. (D) Kaplan-Meier curves for PFS for patients who had $< 10^{-4}$ CLL cells on MRD assessment (MRD negative) or who had MRD $> 10^{-4}$ threshold (MRD positive) at the 36-week (± 4 weeks) landmark. Below each curve is the number of patients at risk for the event at each time point. Tick marks represent patients who were censored for each outcome measure. Local laboratory assessments in the peripheral blood at the 36-week (± 4 weeks) landmark were included for three patients, of whom only one had MRD levels $< 10^{-4}$ (assessments conformed to the ERIC principles and were deemed to be of adequate sensitivity and reliability). ERIC, European Research Initiative in CLL. *MRD assessment defined as the first measurement at which MRD (below $10^{-4}$ cutoff) was attained for each patient.

  

No episodes of clinical TLS were reported. Laboratory TLS on the basis of criteria developed by Howard et al[13] was reported in eight patients (5%), and all of these cases occurred—days 1 to 39—during the dose ramp-up period. Four patients with laboratory TLS were considered to be at high risk for TLS at screening and four were medium risk. Five of these patients were treated as inpatients and three were treated in an outpatient setting. Five patients had interruptions of venetoclax dosing. Management of TLS included intravenous hydration and standard management of laboratory abnormalities. All cases resolved and all patients reached the target dose of 400 mg once daily.

### *Pharmacokinetics*

Median 8-hour postdose concentration increased gradually during the dose ramp-up to reach 1.74 μg/mL on week 5, day 1 at the 400-mg dose. Median predose concentration ranged between 0.33 and 0.74 μg/mL across visits. Steady state was achieved by the week 8 visit. Comparability of venetoclax exposure in this study, in which meal content was not specified to that observed under low-fat conditions the first-in-human study,[14] indicates that venetoclax can be administered with food and without specific recommendations for fat content.[15]

## DISCUSSION

Prior publication of preliminary results from this trial reported an ORR of 79% for the main cohort of 107 patients—a CR rate of 8% by independent review and 16% per investigator assessment—with 17% of patients having MRD $< 10^{-4}$ in the blood. Many of the deeper clinical responses reported here occurred after the week 36 assessment point.[7] With up to an additional 11 months on therapy across all 158 enrolled patients, we now report an ORR of 77%, with a 20% investigator-assessed CR/CRi rate. MRD data also demonstrate that 30% of patients by intent-to-treat analysis had MRD below the cutoff of $10^{-4}$ in the blood by flow cytometry. Compared with our previous results, the increased number of patients with MRD negativity in the blood reported here confirms that the depth of response increases with longer time on therapy, as initially observed in the phase I study.[6] Of importance, for patients who achieved MRD negativity in the peripheral blood at any time during the study (Fig 3C), estimated PFS was 78% at 18 months after attainment of MRD negativity compared with estimated PFS of 51% for MRD-positive patients. These data support the concept of the attainment of MRD negativity as a marker for long-term outcomes in CLL, which may add value to clinical response assessments.

Median time on study for patients who had received prior therapy with BCRi and who were enrolled in the expansion cohort was shorter than that for all patients, although ORR was 63% and median PFS was not reached at the time of this analysis. With the increase in the depth of response observed here for patients in the main cohort compared with our prior publication,[7] it is possible that patients with prior BCRi exposure may have improved response to venetoclax with a longer time on therapy.

Venetoclax was well tolerated, and the safety profile was consistent with that of previous reports of monotherapy in relapsed/refractory CLL, including the safety results reported previously for the 107 patients in the main cohort of this study.[6,7] All patients initiated venetoclax via stepwise dose ramp-up, and the current label-recommended five-step dose ramp-up was followed by patients in the expansion cohort.[9,11] Episodes of laboratory TLS in eight (5%) of 158 patients were managed with intravenous hydration, standard management of laboratory abnormalities, and/or dose interruptions. No patients permanently discontinued venetoclax as a result of TLS. As such, clinicians who start venetoclax in patients with del(17p) CLL outside of a clinical trial setting should closely follow label recommendations to minimize the risk of TLS and to manage any cases that occur so that treatment can continue at the target dose of 400 mg once daily. As would be expected in this patient population, cytopenias were common but manageable with supportive care and/or dose adjustments, and only one patient discontinued venetoclax as a result of autoimmune hemolytic anemia. Rate of infection and the spectrum of identified infections were consistent with the underlying disease.

With several targeted agents now available to treat del(17p) CLL, long-term trial data are critical to inform practice. Here, we demonstrate that venetoclax monotherapy achieves durable responses for patients with high-risk relapsed/refractory del(17p) CLL, including a subset of patients who had received prior BCRi therapy. Continued observation of patients in this trial is needed to provide additional data on the potential for venetoclax to achieve long-term PFS for patients with CLL.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial**

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