REGULAR ARTICLE

blood advances

Six-year follow-up and subgroup analyses of a phase 2 trial of venetoclax for del(17p) chronic lymphocytic leukemia

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Key Points

- Continuous venetoclax monotherapy for untreated or R/R del(17p) CLL led to a median PFS of 28.2 months and median OS of 62.5 months.
- Subgroup analysis suggests that venetoclax efficacy for del(17p) CLL is not notably affected by the presence of adverse biological features.

Chromosome 17p deletion (del[17p]) is associated with poor prognosis in patients with chronic lymphocytic leukemia (CLL). Venetoclax is approved for treatment of previously untreated and relapsed/refractory (R/R) CLL, including patients with del(17p), based on the open-label, multicenter, phase 2 M13-982 trial (NCT01889186). Here, we detail the 6-year follow-up analysis for M13-982. A total of 158 patients with previously untreated (n = 5) or R/R (n = 153) del(17p) CLL received 400 mg venetoclax daily after initial ramp-up until progressive disease. After a median follow-up of 70 months, the best objective response rate (ORR) was 77% (21% complete remission [CR] and 49% partial remission [PR]), with a median duration of response (DOR) of 39.3 months (95% confidence interval [CI], 31.1-50.5). The median progression-free survival (PFS) was 28.2 months (95% CI, 23.4-37.6), and median overall survival (OS) was 62.5 months (95% CI, 51.7-not reached), with 16% of patients remaining on treatment after 6 years. Multivariable analysis did not identify statistically significant correlation between patient subgroups defined by clinical or laboratory variables and ORR or PFS. The most common grade ≥3 adverse events were neutropenia (42%), infections (33%), anemia (16%), and thrombocytopenia (16%). Post hoc comparative analyses of PFS and OS from treatment initiation, from a 24-month landmark, and by minimal residual disease status were performed between patients with del(17p) in the M13-982 and MURANO studies in the interest of understanding these data in another context. These long-term data show the continued benefits of venetoclax in patients with del(17p) CLL. The trial was registered at www.clinicaltrials.gov as #NCT01889186.

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Introduction

In chronic lymphocytic leukemia (CLL), deletion of chromosome 17p (del[17p]) and mutated *TP53* are both associated with poor prognosis, and management of patients with these aberrations remains challenging.[1-4] Allogeneic stem cell transplantation has curative potential, but few patients are eligible; for those who are eligible, its use is limited by significant toxicities and a substantial risk of nonrelapse mortality.[5-7] More recently, noncytotoxic targeted therapies, such as inhibitors of BTK and BCL-2, have emerged as a preferred therapeutic approach for these patients at high risk.[1,2]

Venetoclax is an oral selective BCL-2 inhibitor, which targets the intrinsic apoptotic pathway via a mechanism independent of p53 function.[8-10] The phase 3 MURANO study (NCT02005471) evaluated the efficacy and safety of fixed-duration venetoclax plus rituximab (VenR) for 6 months followed by venetoclax monotherapy for up to a total duration of 2 years vs bendamustine plus rituximab (BR) for 6 months in patients with relapsed/refractory (R/R) CLL.[11] A significant 2-year progression-free survival (PFS) benefit with VenR vs BR was observed in the primary analysis, and in a subsequent analysis with most patients off therapy for 3 years, benefits in PFS were maintained (median PFS, 53.6 months [95% confidence interval [CI], 48.4-57.0] for VenR and 17.0 months [95% CI, 15.5-21.7] for BR; $P < .0001$).[12] In addition, the PFS benefit of VenR vs BR was observed across all analyzed subgroups, including patients with del(17p) and/or mutated *TP53* (VenR, n = 53; BR, n = 55; median PFS, 37.4 vs 13.4 months).

In the pivotal phase 2 M13-982 study (NCT01889186) of patients with R/R or previously untreated CLL carrying del(17p), venetoclax monotherapy administered until progressive disease (PD) demonstrated an objective response rate (ORR) of 77% and was well tolerated.[13,14] These results led to the approval of venetoclax for the treatment of CLL or small lymphocytic lymphoma (SLL) in both the newly diagnosed and R/R settings, including specific indications for patients with del(17p) or mutated *TP53*.[15,16] Here, we report the final analyses from the M13-982 study 5 years after the last patient enrolled (median follow-up, 70 months), including post hoc subgroup analyses of prognostic markers and minimal residual disease (MRD), as well as a comparative analysis with the *TP53*-aberrant subset of patients from MURANO.

Methods

Study design and patients

M13-982 is a phase 2, open-label, multicenter, global trial. Detailed methods were previously described.[13,14] Briefly, patients aged ≥18 years with previously untreated or R/R del(17p) CLL per 2008 modified International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines[17] were enrolled. Patients had Eastern Cooperative Oncology Group performance status 0 to 2 and creatinine clearance ≥50 mL per minute. The presence of del(17p) was determined centrally via Vysis CLL fluorescence in situ hybridization probe kit with a diagnostic threshold of 7% via central laboratory for the first 107 patients enrolled; del(17p) could be confirmed by either local or central laboratory for the later 51 patients enrolled. All patients provided written informed consent. The study was approved by each local ethics committee or institutional review board, and the study was carried out in accordance with the Declaration of Helsinki and the International Council for Harmonisation and Good Clinical Practice guidelines.

Treatment

To mitigate the risk of tumor lysis syndrome, venetoclax was initiated via stepwise dose ramp-up with prophylaxis and monitoring.[15,16] After dose ramp-up (4-5 weeks), patients received venetoclax monotherapy 400 mg orally once daily continuously until PD or unacceptable toxicity. After a protocol amendment, patients with PD could continue to receive venetoclax (either as monotherapy or combined with another agent) for up to 5 years after the enrollment of the last patient at the discretion of the investigator if they continued to derive clinical benefit, and it was in the patient's best interest to remain on therapy.

Outcomes and assessments

The primary end point was ORR in the main cohort and safety in the safety expansion cohort. Secondary end points included complete remission (CR) rate, partial remission (PR) rate, duration of response (DOR), PFS, overall survival (OS), and safety. Disease assessments were conducted per 2008 iwCLL criteria,[17] using laboratory values, physical examinations, computed tomography scans, and bone marrow examinations at screening and at each study visit after week 5. Time to next treatment (TTNT) was defined as the number of days from the date of first dose to the date of first dose of new, nonprotocol antileukemia therapy. An exploratory end point, MRD was assessed in peripheral blood via flow cytometry, allele-specific oligonucleotide polymerase chain reaction, and/or clonoSEQ next-generation sequencing. If multiple MRD assessments were available for a given time point, the highest result was used. Per protocol, MRD in peripheral blood was requested for patients achieving CR or CR with incomplete bone marrow recovery (CRi) or for patients with nodular PR (nPR) or PR and residual lymph nodes measuring 1.5 to 2 cm in greatest diameter. Per iwCLL criteria, undetectable MRD (uMRD) is reported at $<10^{-4}$.[17,18] Adverse events (AEs) were graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and assessed from the date of the first dose of study drug until 30 days after the last dose.

Post hoc subgroup analyses of efficacy outcomes were conducted in biological subgroups by immunoglobulin heavy-chain variable region (IGHV) status (unmutated vs mutated); del(17p) clone size (<20% vs ≥20%); del(17p) and mutated *TP53* status (either vs both); number of distinct *TP53* mutations (1 vs ≥2); *SF3B1*, *NOTCH1*, and *BIRC3* status (mutated vs unmutated); and genomic complexity (GC; high, ≥5 copy number aberrations [CAs] vs low/noncomplex, 3-4 CAs/0-2 CAs, respectively). To assess *TP53* mutations, targeted next-generation sequencing was performed using the TruSeq Custom Amplicon assay (Illumina, San Diego, CA). Variants were called using custom pipeline (including BWA-Mem, VarScan2 Annovar) and/or Illumina's Somatic Variant Caller and European Research Initiative on CLL recommendations applied for reporting (mutation listed in the International Agency for Research on Cancer *TP53* database and variant allele frequency >10%).[19] Mutations in other genes had a minimum 3% variant allele frequency, were predicted to be deleterious, and were previously reported in the Catalogue of Somatic Mutations in Cancer v71. Gene mutation and IGHV analyses were done as previously

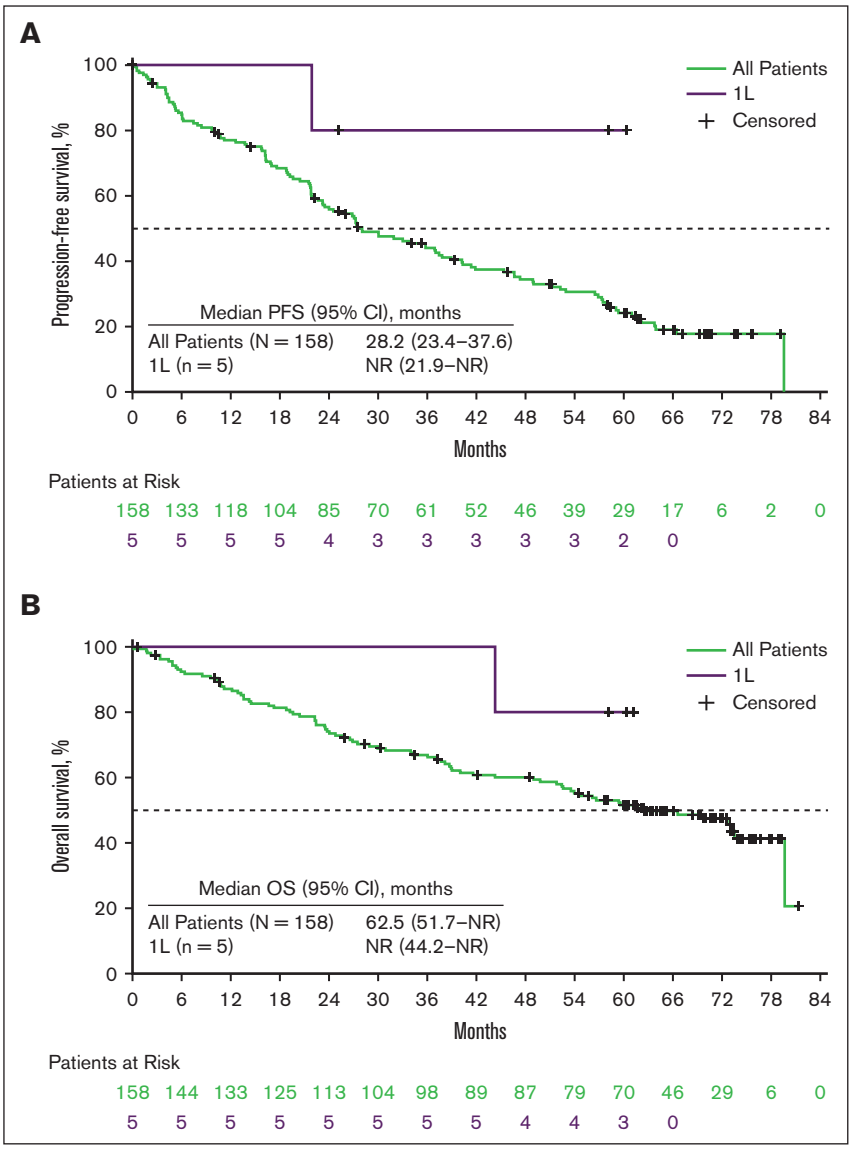

Figure 1. PFS and OS. Median PFS (A) and median OS (B) in the all treated population, with a median follow-up of 70 months. 1L, first line.

reported.[3,20] GC was determined by high-density single nucleotide polymorphism (SNP) array (CytoScan HD array, Affymetrix, Santa Clara, CA).

Statistical analyses

Efficacy and safety analyses included all patients who received ≥1 venetoclax dose. Time-to-event analyses used Kaplan-Meier methodology. A stratified, 2-sided log-rank test with a type 1 error rate of 0.05 was used to determine statistical significance. Estimated rates and corresponding 95% CIs were determined using the Wilson score method. R and SAS were used for all statistical summaries. The data cutoff was 15 December 2020.

Post hoc comparison with MURANO

Full details of the phase 3 MURANO study were previously reported.[11] Analyses included patients from MURANO who had a *TP53* mutation (via central next-generation sequencing) and/or del(17p) (via array-based comparative genomic hybridization). The clinical cutoff for this study was 8 May 2020.[12] Time-to-event analyses were conducted via Kaplan-Meier methods. For M13-982, the MRD assessments that were collected at ~24 months were used for analysis. MRD assessments for month 24 in MURANO was defined as ~2 to 3 months after finishing 2 years of VenR treatment.

Results

Patients and disposition

A total of 158 patients (153 previously treated and 5 treatment-naïve) were enrolled and treated. Patients had a median 2 prior lines of therapy (range, 0-10; supplemental Table 1), including 16 patients (11%) who had previously undergone treatment with a B-cell pathway receptor inhibitor.[14]

Overall, 113 of 138 patients (82%) who were tested had at least 1 *TP53* mutation, and 118 of 158 patients (75%) had ≥20% del(17p) clone size by fluorescence in situ hybridization

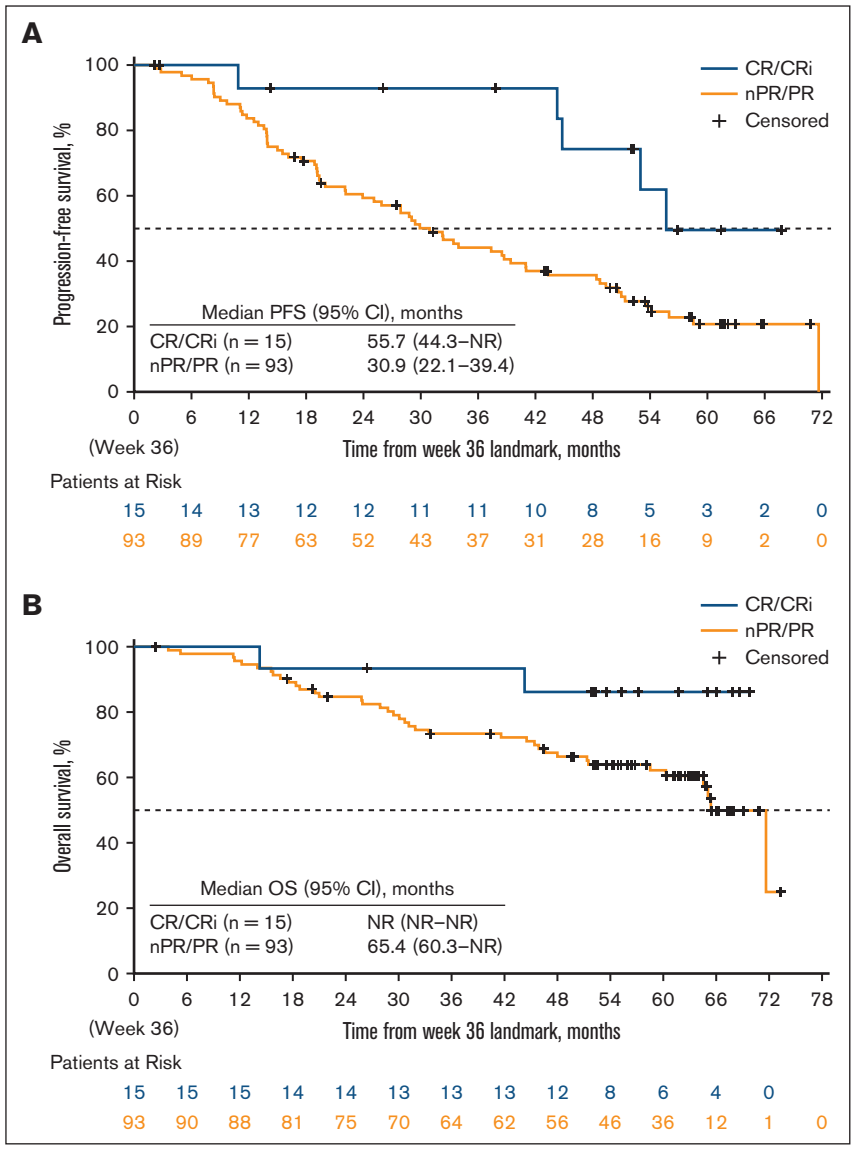

Figure 2. Landmark analysis of PFS and OS. (A) PFS and (B) OS by response at week 36 (± 4 weeks).

(supplemental Table 2). Among the patients who were tested, unmutated IGHV was found in 81% and mutated *SF3B1*, *NOTCH1*, *ATM,* and *BIRC3* in 20%, 16%, 9%, and 5%, respectively. As of this updated analysis, median duration of treatment for all patients was 27.4 months (range, 0-79.3 months); median treatment duration in the main cohort was 21.7 months (range, 0-79.3) and in the safety expansion cohort, 36.2 months (range, 0.9-68.4). Reasons for study discontinuation are shown (supplemental Table 3). At study close, 77 patients (49%) remained alive; 26 patients (16%) remained on venetoclax treatment. Four of these 26 patients had progressed before study close but continued venetoclax at investigator discretion; 1 patient added obinutuzumab to treatment, 1 patient added ibrutinib to treatment, and 2 patients remained on venetoclax monotherapy.

Efficacy

ORR (best response) in all 158 treated patients was 77%, with 21% CR, 3% CRi, 49% PR, and 4% nPR (supplemental Table 4). Of 122 patients who achieved any response, median DOR was 39.3 months (95% CI, 31.1-50.5). Median DOR was 58.3 months for patients achieving CR and 60.4 months for patients achieving CR/CRi. Nineteen percent of patients had stable disease as best response, 2% had PD, and 2% were not evaluable. In the 5 previously untreated patients, 4 achieved a response (80%): 3 (60%) CR/CRi and 1 (20%) PR; median DOR was not reached (NR; 95% CI, 19.9 to NR). Among patients with previous B-cell pathway receptor inhibitor (BCRi) treatment (n = 16), ORR was 62.5%.

With a median follow-up of 70 months, median PFS in all treated patients was 28.2 months (95% CI, 23.4-37.6), and median OS was 62.5 months (95% CI, 51.7 to NR; Figure 1). In patients with prior BCRi treatment, median PFS was 15.43 months (95% CI, 4.21 - 41.95). In the full population, the actuarial 5-year PFS and OS rates were 24% and 52%, respectively. A landmark analysis of PFS and OS by response from week 36 (ie, week 36 ± 4 weeks), a mandatory assessment time point for all patients, was also conducted. Among the 15 patients who achieved CR/CRi by that time,

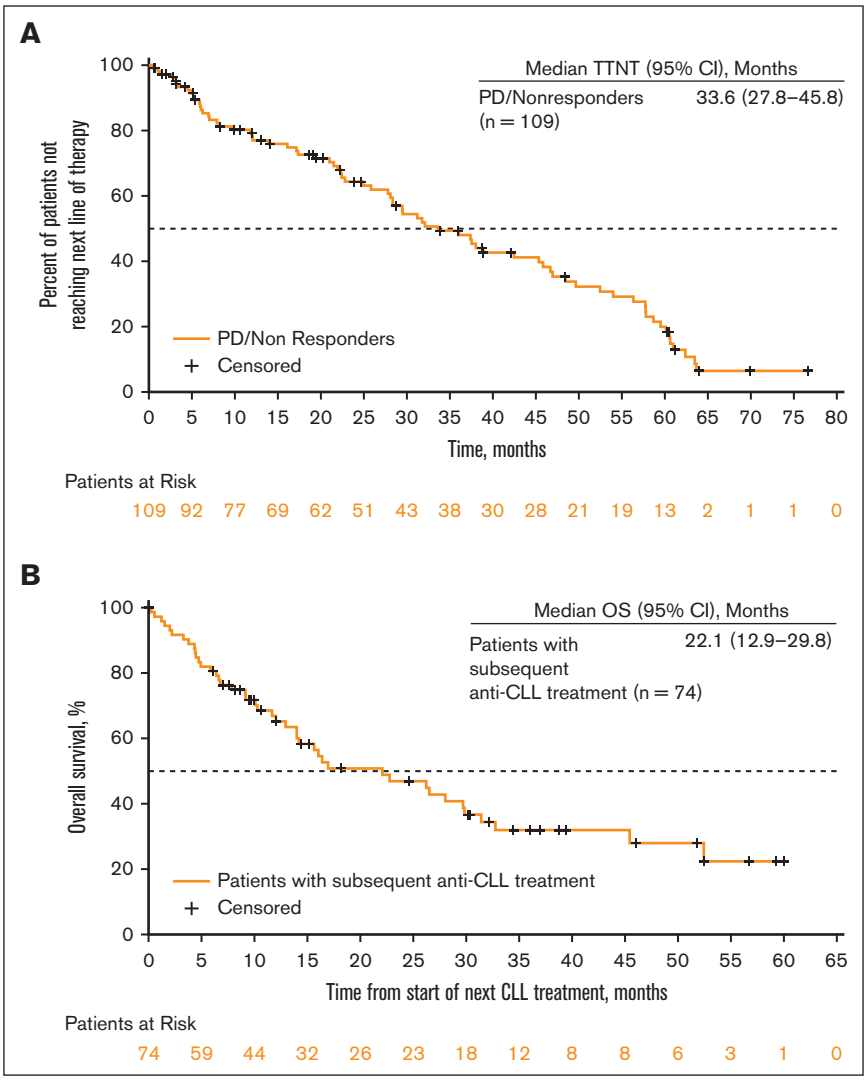

Figure 3. Time to next line of therapy and OS after next therapy. (A) Time to next line of therapy in patients who had PD or did not attain a response. (B) OS from start of next anti-CLL treatment.

median PFS and OS were 55.7 months (95% CI, 44.3 to NR) and NR (95% CI, NR to NR; 4-year OS estimate, 60.1%), respectively (Figure 2). In the 93 patients who achieved nPR/PR, median PFS and median OS were 30.9 months (95% CI, 22.1-39.4) and 65.4 months (95% CI, 60.3 to NR), respectively. In the 5 previously untreated patients, median PFS and OS were NR (95% CI, 21.9 to NR) and NR (95% CI, 44.2 to NR), respectively.

Among 122 patients who achieved a response, 98 subsequently discontinued venetoclax due to PD (80.3%); 74 patients had CLL progression, and 24 had Richter transformation as first manifestation of PD. By month 24, a total of 47% of all CLL progressions and 83% of Richter progressions had occurred (supplemental Figure 1). Of 109 patients who either had PD (n = 98) or did not attain a response (n = 11), cumulative incidence rates of CLL progression and Richter transformation were 67.9% (95% CI, 58.3-76.5) and 22.0% (95% CI, 14.6-31.0), respectively. Lymphadenopathy was the most reported feature of PD among the 98 responders (50%) who discontinued venetoclax due to PD (supplemental Table 5). Median TTNT was 33.6 months (Figure 3A). For all patients who developed PD, median OS from time of PD was 16.2 months (95% CI, 10.9-27.3); for those with CLL progression, median OS was 27.2 months (95% CI, 16.2-42.4), whereas median OS from time of Richter transformation was 5.7 months (95% CI, 1.1-10.5). Median TTNT from CLL progression was 57 days (95% CI, 32-92) and from Richter transformation was 24 days (95% CI, 10-48). A total of 74 patients (46%) received a subsequent line of therapy, with median OS 22.1 months (95% CI, 14.0-29.8; Figure 3B) from the start of the next line of any therapy. Ibrutinib was the next line of therapy in 41 patients (supplemental Table 6), and median OS from initiation was 28.0 months (95% CI, 17.0-45.4).

The acquisition of *BCL2* mutations among 25 of 158 patients enrolled in this study was previously reported.[21] Of these 25 patients, 9 (36%) had ≥1 acquired mutations in *BCL2*, 4 (16%) in *PMAIP1* (*NOXA*), and 1 (4%) in *BAX*. Median time on therapy for these patients was 313 days (range, 35-1828 days).

Safety

No new safety signals were observed compared with prior analyses (Table 1).[13,14] Overall, after a median follow-up of 70 months, 98%

Table 1. Summary of TEAEs

	All patients (N = 158)	
TEAE*, n (%)	Any grade	Grade ≥3
Any TEAE	155 (98)	140 (89)
Neutropenia	73 (46)	67 (42)
Diarrhea	70 (44)	5 (3)
Nausea	60 (38)	2 (1)
Anemia	43 (27)	26 (16)
Fatigue	43 (27)	0
Upper respiratory tract infection	40 (25)	2 (1)
Thrombocytopenia	37 (23)	25 (16)
Pneumonia	35 (22)	20 (13)
Cough	30 (19)	0
Pyrexia	30 (19)	1 (1)
Headache	28 (18)	0
Nasopharyngitis	28 (18)	0
Malignant neoplasm progression	25 (16)	23 (15)
Urinary tract infection	23 (15)	3 (2)
Back pain	21 (13)	3 (2)
Vomiting	21 (13)	2 (1)
Arthralgia	20 (13)	2 (1)
Constipation	20 (13)	0
Abdominal pain	19 (12)	5 (3)
Hypertension	19 (12)	9 (6)
Hypokalemia	19 (12)	4 (3)
Peripheral edema	17 (11)	4 (3)
Rash	17 (11)	1 (1)
Dyspnea	16 (10)	0
Autoimmune hemolytic anemia	12 (8)	10 (6)
Leukopenia	11 (7)	8 (5)
Febrile neutropenia	10 (6)	10 (6)

*Any-grade TEAEs reported in ≥10% of patients or grade ≥3 TEAEs reported in ≥5% of patients.

of patients experienced an any-grade treatment-emergent AE (TEAE), and 89% experienced a grade ≥3 TEAE. Neutropenia (46%), diarrhea (44%), and nausea (38%) were the most common any-grade TEAEs. The most common grade ≥3 TEAEs were neutropenia (42%), infections (33%), anemia (16%), and thrombocytopenia (16%), with median times to first occurrence of 28, 279, 10, and 50 days, respectively. Grade ≥3 febrile neutropenia was reported in 6% of patients. The most common grade ≥3 infection was pneumonia (13%). No additional patient in this final report had a tumor lysis syndrome event beyond those reported in the last interim report.[14] Second primary malignancies (SPMs) were reported in 31 patients (20%), most commonly cutaneous basal cell carcinoma (5 patients [3%]), myelodysplastic syndrome (MDS; 5 patients [3%]), and squamous cell carcinoma of the skin (4 patients [3%]; supplemental Table 7). Overall, 8 patients had MDS/acute myeloid leukemia (AML) SPMs, including 5 cases of MDS and 4 cases of AML (1 patient diagnosed with acute erythroid leukemia as well as AML and MDS). These 8 patients had received a median of 2.5 prior therapies; 7 (87.5%) had received prior fludarabine.

AEs led to venetoclax dose reduction for 29 patients (18%). AEs leading to a venetoclax dose reduction in >1 patient were neutropenia (8%), febrile neutropenia (2%), autoimmune hemolytic anemia (1%), thrombocytopenia (1%), and herpes zoster (1%). Seventy-seven patients (49%) experienced a venetoclax interruption due to AEs, most commonly due to neutropenia (8%), pneumonia (6%), febrile neutropenia (4%), hyperphosphatemia (4%), thrombocytopenia (3%), and nausea (3%). AEs led to venetoclax discontinuation in 55 patients (35%); causes of discontinuations in >1 patient included malignant neoplasm progression (13%), MDS (3%), AML (1%), pneumonia (1%), thrombocytopenia (1%), autoimmune hemolytic anemia (1%), and general physical health deterioration (1%).

Most patients (144/158 [91%]) received 75% to 100% of the target relative dose intensity over the first 24 months of therapy, including patients who stopped therapy before 24 months due to PD (58 patients) or AEs unrelated to PD (21 patients). Eighty-nine patients (56%) received granulocyte colony-stimulating factor at any time during the study. Of 77 patients who remained on therapy and were progression free at month 24, only 2 received a lower-dose intensity of venetoclax (50%-75% of the target dose over that time); median PFS and OS in the 75 patients with >75% to 100% dose intensity were 58.5 months (95% CI, 49.1-63.9) and 79.7 months (95% CI, 79.7 to NR), respectively. Overall, 36 of these 77 patients (47%) received growth factor support. Thirteen patients (16.9%) discontinued venetoclax before the end of the study for reasons other than progression; 9 discontinued due to AEs not related to progression, 2 due to stem cell transplantation, 1 due to COVID-19 logistical restrictions, 1 due to investigator request, and 1 due to patient choice.

Eighty-one patients died on study, of whom 62 died >30 days from the last dose of venetoclax. Fifty-one deaths (63%) were disease related. Four patients died from infection, 1 of which (pneumonia) was considered possibly related to venetoclax.

Post hoc genetic subgroup efficacy analyses

Univariable analysis was used to evaluate ORR and PFS in patient subgroups. No significant differences were observed for ORR across subgroups (Figure 4A). Median PFS ranged from 16.4 months in patients with mutated *SF3B1* to 40.4 months in patients with mutated IGHV (Figure 4B), with the only statistically significant difference observed between unmutated vs mutated *SF3B1* ($P = .0071$; Figure 5). Multivariable analysis (variables included ≥2 prior therapies, unmutated IGHV, nodal size ≥5 cm, *SF3B1* mutation, and ≥2 *TP53* mutations) did not identify statistical significance for any comparisons for ORR or PFS. However, in multivariable analyses that added GC ≥5 CAs to the above variables, both *SF3B1* and GC were associated with PFS in favor of unmutated *SF3B1* (hazard ratio [HR], 0.52; 95% CI, 0.28-0.97) and in favor of noncomplex/low GC (HR, 0.59; 95% CI, 0.36-0.96), respectively.

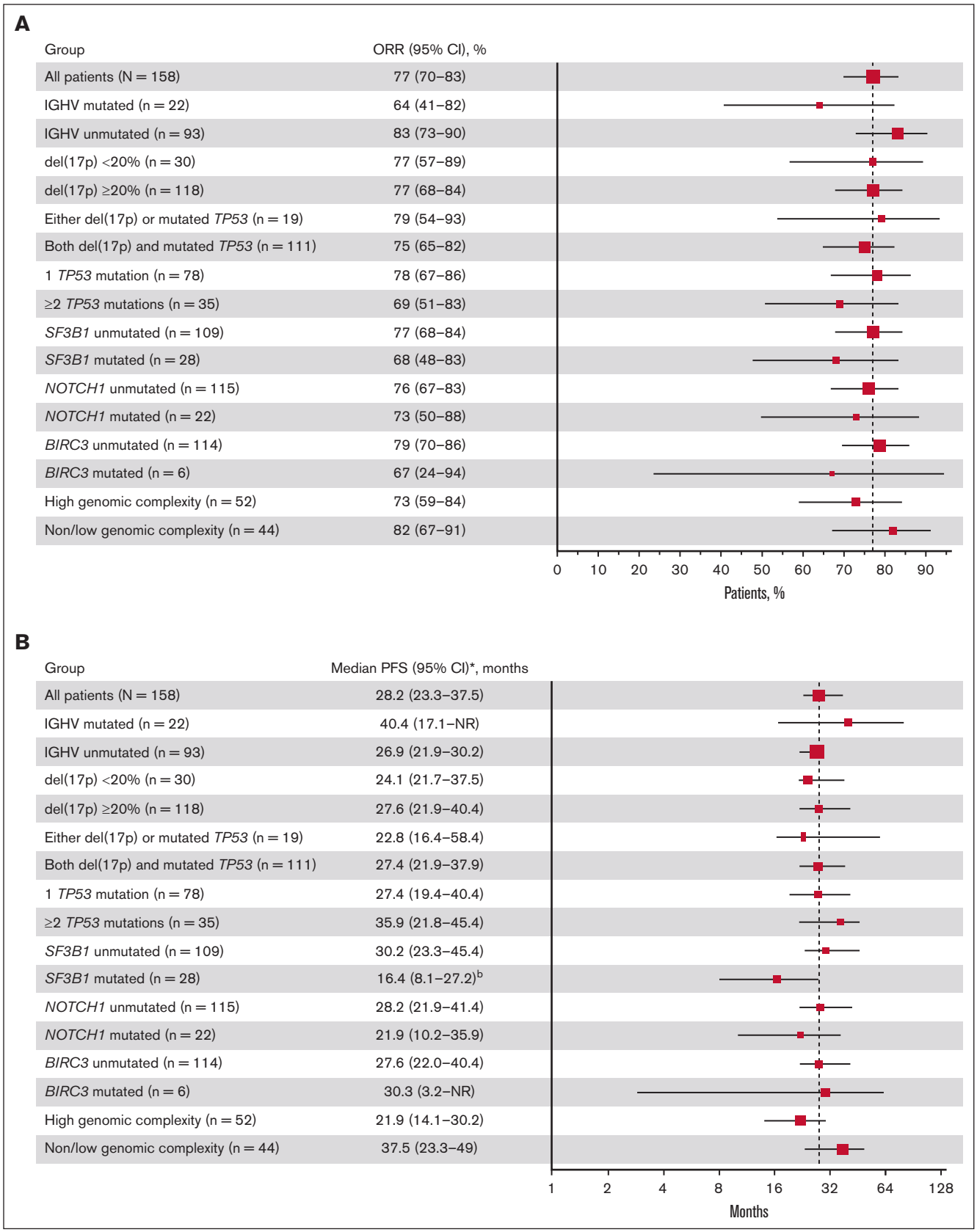

Figure 4. Univariable analyses of efficacy outcomes. (A) Univariable subgroup analyses of overall response rate and (B) PFS in biological subgroups. *For the IGHV mutated and *BIRC3* mutated groups, the upper bounds of the 95% CIs were not reached. Therefore, the lines in the forest plot have been extended to the last observed time.

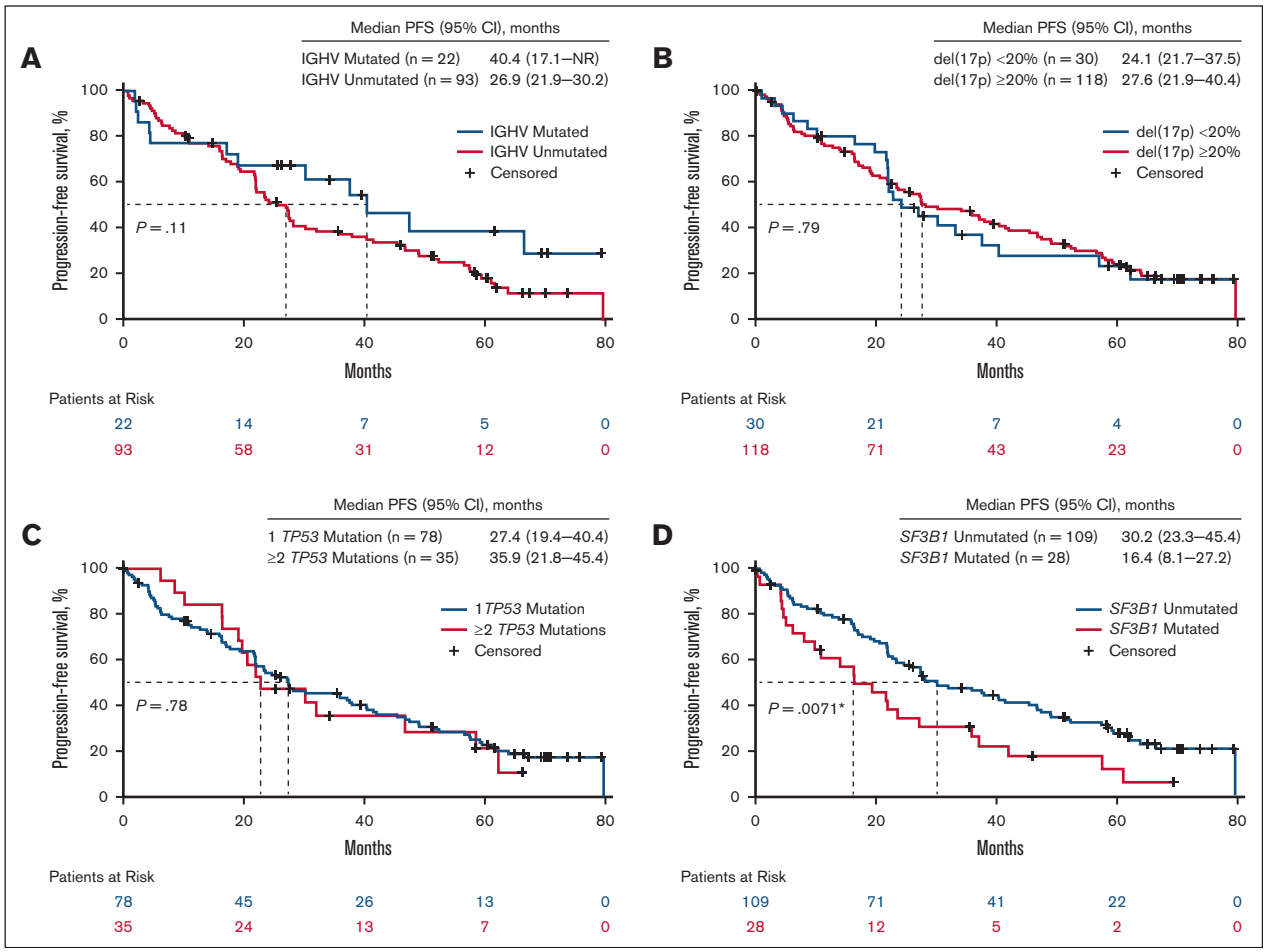

Figure 5. PFS based on presence or absence genetic alterations. (A) PFS by unmutated vs mutated IGHV, (B) del(17p) clone size (<20% vs ≥20%), (C) 1 vs ≥2 *TP53* mutations, and (D) unmutated vs mutated *SF3B1*. *In the multivariable analysis, no significance was observed. The multivariable analysis included the following variables: ≥2 prior therapies, unmutated IGHV, nodal size ≥5 cm, and >1 *TP53* mutation.

Fixed-duration venetoclax vs continuous venetoclax for ≥2 years in *TP53*-aberrant CLL: a post hoc comparative analysis of M13-982 and MURANO

To explore potential efficacy differences between continuous single-agent venetoclax for ≥2 years vs time-limited VenR in patients with R/R CLL with del(17p)/*TP*53 mutation, we performed a post hoc analysis of PFS from treatment initiation (M13-982) or randomization (MURANO). Baseline characteristics of the 153 patients from M13-982 with R/R disease and 53 patients with del(17p)/*TP*53 mutation from MURANO were generally similar; however, the proportion of patients with ≥3 prior therapies was higher in the M13-982 set (44% and 15%; supplemental Table 8), and the methodology for determining the presence of del(17p) was inconsistent between the 2 studies, leading to the inclusion of patients in MURANO who were positive for mutated *TP53* but not del(17p). Median PFS was 27.6 months (95% CI, 22.8-37.1) from treatment initiation in the M13-982 set and 37.4 months (95% CI, 29.4-52.3) from randomization in the MURANO set (Figures 6A and 6B). The estimated 60-month OS rates were 50.6% and 70.2%, respectively (Figures 6C and 6D). Among patients from each study who had completed at least 2 years of venetoclax therapy (n = 74 in M13-982; n = 31 in MURANO; supplemental Table 9), median PFS from treatment initiation among the 74 responders in the M13-982 set was 57.5 months (95% CI, 47.4-62.2; Figure 7A). Median PFS from randomization in the MURANO set was 52.3 months (95% CI, 37.4-64.5; Figure 7B). The estimated 60-month OS rates were 83% in the M13-982 set and 79% in the MURANO set (Figures 7C and 7D).

A post hoc landmark analysis was conducted to assess PFS and OS by MRD status at month 24 in responding patients who received at least 2 years of venetoclax therapy in each study. Of 74 responding patients in M13-982 who completed ≥2 years of venetoclax monotherapy, peripheral blood MRD status at month 24 was undetectable in 15 patients (20%), low-MRD$^+$ status (defined as MRD 10^{-4} to 10^{-2}) was detected in 18 (24%), and high-MRD$^+$ status (defined as MRD $>10^{-2}$) was detected in 20 (27%). Of 31 patients from MURANO in the VenR del(17p)/*TP53* mutation cohort, 18 (58%), 7 (23%), and 4 (13%) had uMRD, low-MRD$^+$ status, and high-MRD$^+$ status, respectively, in peripheral blood at month 24.

In the M13-982 set, median PFS from month 24 was NR (95% CI, 43.8 to NR) in patients with uMRD, 29.2 months (95% CI, 36.3 to

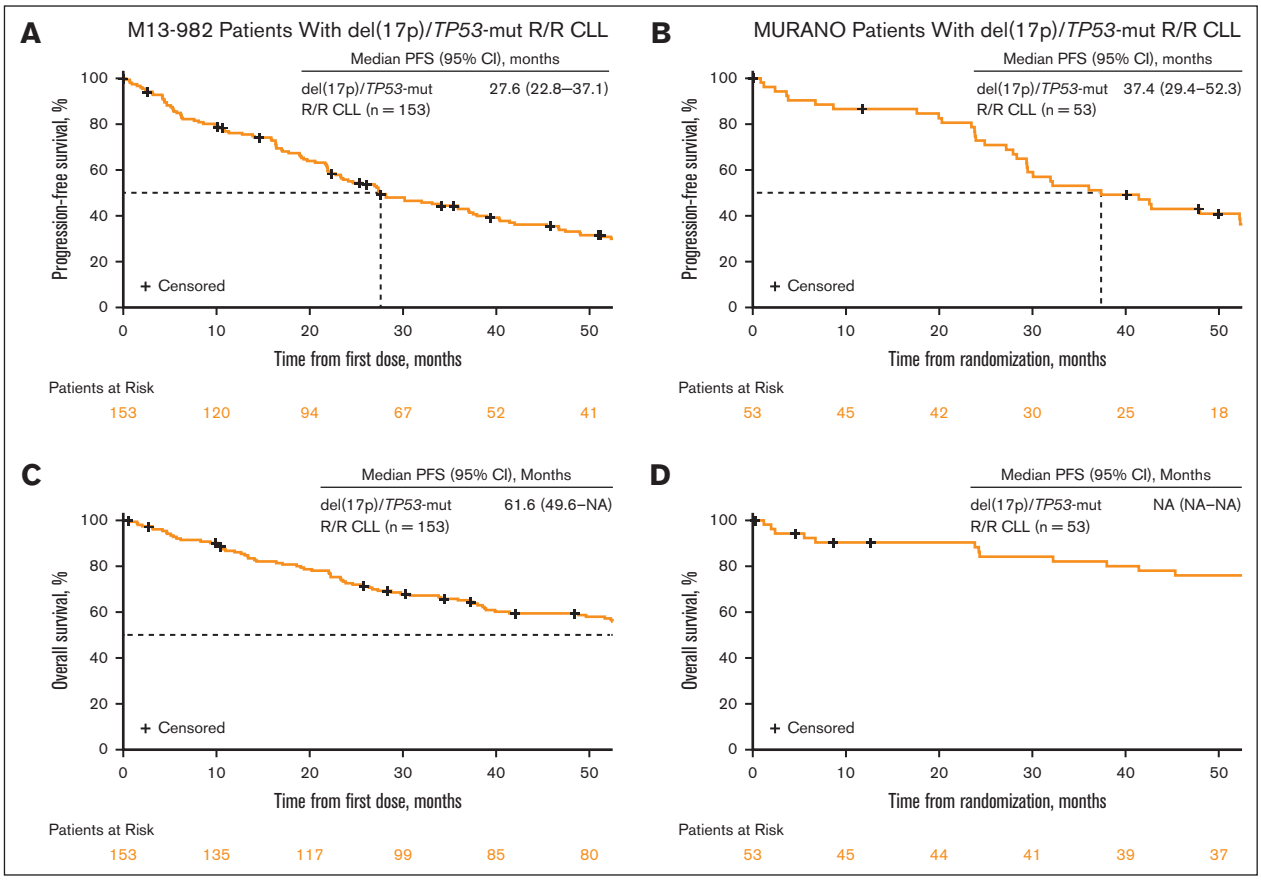

Figure 6. PFS and OS in M13-982 patients with R/R CLL and in MURANO patients with R/R CLL and del(17p)/*TP53* mutation. (A) PFS from treatment initiation in 153 patients from M13-982. (B) PFS from randomization in 53 patients from MURANO. (C) OS in 153 patients from M13-982. (D) OS in 53 patients from MURANO. mut, mutated; NA, not applicable.

NR) in patients with low-MRD$^+$ status, and 10.1 months (95% CI, 49.4-NR) in patients with high-MRD$^+$ status (supplemental Figure 2A). Among those in the del(17p)/*TP53* mutation MURANO set, median PFS from month 24 was 29.5 months (95% CI, 24.6 to NR), 20.2 months (95% CI, 9.9 to NR), and 2.8 months (95% CI, 0.2-3.1) in patients with uMRD, low-MRD$^+$ status, and high-MRD$^+$ status, respectively (supplemental Figure 2B). OS in these cohorts is shown (supplemental Figures 2C and 2D).

Discussion

This final analysis of the pivotal phase 2 M13-982 study, conducted 5 years after the last patient enrolled, confirms the long-term efficacy of continuous venetoclax dosing in patients with del(17p) R/R CLL. The ORR was 77%, with almost one-fourth of patients achieving CR/CRi. With a median follow-up of 70 months, median PFS exceeded 2 years, and median OS exceeded 5 years. Encouraging PFS and OS outcomes were observed even in patients who did not achieve CR/CRi but had nPR/PR as best response. Similarly, landmark analyses of PFS and OS by MRD status at month 24 demonstrated superior survival outcomes in long-term responders, with uMRD and low-MRD$^+$ status over those of responders with high-MRD$^+$ status. After a median follow-up of 70 months, 49% of patients were alive, and 16% remained on venetoclax treatment. The venetoclax toxicity profile was similar to that of prior analyses, with no new safety signals observed. The number of patients who experienced SPMs of MDS/AML were low, and nearly all had received prior fludarabine.

The study population comprised patients with high-risk disease; 75% of patients had ≥20% del(17p) clone size, and 82% had a *TP53* mutation. Other high-risk prognostic indicators included mutated *SF3B1* (20%) and *NOTCH1* (16%). We conducted post hoc subgroup analyses of ORR and PFS to evaluate the impact of these additional prognostic indicators on outcomes with venetoclax in del(17p) CLL. Overall, outcomes were generally not affected by the presence of any additionally evaluated features. The only statistically significant correlation was observed in the univariable PFS analysis, which showed PFS with mutated *SF3B1* as inferior to unmutated *SF3B1* (16.4 vs 30.2 months; $P = .0071$); however, in multivariable analysis, its significance depended upon the variable included. Although these genomic features are considered indicative of adverse prognosis individually, they do not appear to further affect outcomes in the context of del(17p) CLL and venetoclax continuous monotherapy.

In addition to continuous venetoclax monotherapy, VenR is approved for a treatment duration of 2 years as an option for R/R

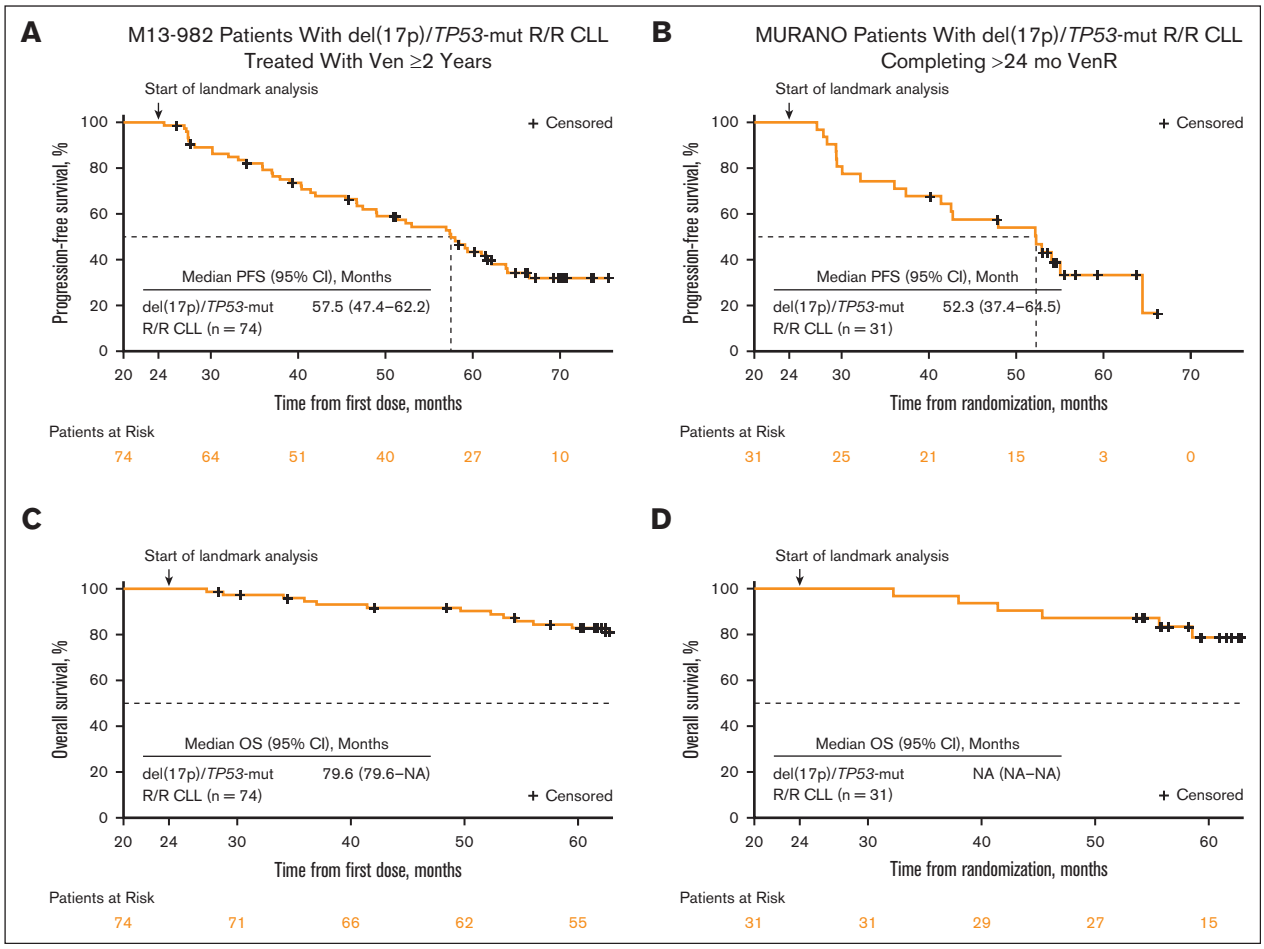

Figure 7. PFS and OS in patients from M13-982 and MURANO with R/R CLL with del(17p) or *TP53* mutation who completed ≥2 years of venetoclax therapy. (A) PFS from treatment initiation in 74 responders from M13-982 who remained on venetoclax for ≥2 years. (B) PFS from randomization in 31 patients from MURANO with del(17p)/*TP53* mutation who completed VenR therapy without PD. (C) OS in 74 responders from M13-982 who remained on venetoclax for ≥2 years. (D) OS in 31 patients from MURANO with del(17p)/*TP53* mutation who completed VenR therapy without PD. mut, mutated; NA, not applicable.

CLL, irrespective of del(17p) status.[15,22] To better understand the data from each treatment approach, we carried out a post hoc analysis of PFS and OS in this study and those reported in the phase 3 MURANO study with del(17p)/*TP53* mutation.[11] Direct comparison of these studies based on the reported data should be avoided, given the caveats of the post hoc cross-trial comparison, including the disparity of patients receiving ≥3 prior lines of therapy across the 2 trials and the differences in methodology for evaluating del(17p). However, based on these findings, both continuously dosed venetoclax monotherapy and fixed-duration VenR appear to be effective and reasonable treatment choices. Importantly, early data suggest that some patients can derive benefit from venetoclax retreatment after PD after fixed-duration treatment.[23-26] However, this benefit may be reduced in patients with adverse genetic risk factors; notably, patients in MURANO with elevated GC and mutations in *TP53*, *NOTCH1*, *XPO1*, and *BRAF* exhibited a decreased incidence of uMRD upon treatment completion.[27] In addition, an analysis investigating VenR in R/R CLL showed that although some patients did benefit from this combination, the benefit was lower among patients carrying del(17p) or *TP53* mutations who did not achieve uMRD after initial venetoclax monotherapy; however, this study had a limited sample size.[28]

Bruton tyrosine kinase inhibitors have also been evaluated in the R/R del(17p) CLL setting. In the randomized phase 3 ALPINE R/R CLL study, PFS was higher with zanubrutinib than with ibrutinib in patients with del(17p)/*TP53* mutation (HR for progression or death, 0.53).[29] The open-label phase 2 RESONATE-17 del(17p) R/R CLL/SLL study evaluating ibrutinib demonstrated an ORR of 83% and 24-month PFS and OS rates of 63% and 75%, respectively.[30] Overall, efficacy outcomes with venetoclax monotherapy in our study of R/R del(17p) CLL appear comparable with those reported with ibrutinib in RESONATE-17. Similarly, ORR appears comparable with that reported with zanubrutinib in patients with R/R del(17p)/*TP53* mutation CLL in ALPINE. However, caveats regarding cross-trial comparisons must be kept in mind. These observations were also supported in a retrospective analysis of outcomes with first-line ibrutinib in CLL with and without del(17p), demonstrating significantly inferior median OS (57.7 months vs NR) and TTNT (49.4 months vs NR) in patients with vs without del(17p) CLL.[4] Further studies to define the optimal

treatment option for del(17p) CLL are warranted. The CLL17 trial includes, among others, patients with del(17p) CLL and has completed accrual to compare ibrutinib with venetoclax plus obinutuzumab or venetoclax plus ibrutinib.[31]

Limitations of this analyses include a lack of racial heterogeneity in the patient population (97% white) and those inherent in cross-trial comparisons in which patient characteristics differ between studies. Specifically, differences between this study and MURANO were noted above. A propensity score analysis comparison of results would have been more appropriate but was not possible owing to the limited sample size. Although potentially informative, any such comparison of single-agent venetoclax with venetoclax-rituximab in patients with R/R CLL must be viewed in the context of current treatment practices under which such patients typically receive venetoclax in combination therapy.[32]

Bearing these limitations in mind, this final analysis of the phase 2 M13-982 study confirms the long-term efficacy and feasibility of continuously dosed venetoclax in patients with del(17p) CLL. The analyses conducted in subgroups by additional biological features suggest that the efficacy of venetoclax in the del(17p) patient population is not materially affected by the presence of other individually adverse biological features. The comparison with the phase 3 MURANO study indicates benefit for patients continuously dosed for ≥2 years, as well as for those on fixed-duration VenR.

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Authorship

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