

# Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study

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**PURPOSE** The MURANO study demonstrated significant progression-free survival (PFS) benefit for fixed-duration venetoclax-rituximab compared with bendamustine-rituximab in relapsed/refractory chronic lymphocytic leukemia. With all patients off treatment, we report minimal residual disease (MRD) kinetics and updated outcomes.

**METHODS** Patients were randomly assigned to 2 years of venetoclax plus rituximab during the first six cycles, or six cycles of bendamustine-rituximab. Primary end point was PFS. Safety and peripheral blood (PB) MRD status—at cycle 4, 2 to 3 months after end of combination therapy (EOCT), and every 3 to 6 months thereafter—were secondary end points.

**RESULTS** Of 194 patients, 174 (90%) completed the venetoclax-rituximab phase and 130 (67%) completed 2 years of venetoclax. With a median follow-up of 36 months, PFS and overall survival remain superior to bendamustine-rituximab (hazard ratio, 0.16 [95% CI, 0.12 to 0.23]; and hazard ratio, 0.50 [95% CI, 0.30 to 0.85], respectively). Patients who received venetoclax-rituximab achieved a higher rate of PB undetectable MRD (uMRD; less than  $10^{-4}$ ) at EOCT (62% v 13%) with superiority sustained through month 24 (end of therapy). Overall, uMRD status at EOCT predicted longer PFS. Among those with detectable MRD, low-level MRD ( $10^{-4}$  to less than  $10^{-2}$ ) predicted improved PFS compared with high-level MRD ( $10^{-2}$  or greater). At a median of 9.9 months (range, 1.4 to 22.5 months) after completing fixed-duration venetoclax-rituximab, overall only 12% (16 of 130) of patients developed disease progression (11 high-level MRD, three low-level MRD). At the end of therapy, 70% and 98% of patients with uMRD remained in uMRD and without disease progression, respectively.

**CONCLUSION** With all patients having finished treatment, continued benefit was observed for venetoclax-rituximab compared with bendamustine-rituximab. uMRD rates were durable and predicted longer PFS, which establishes the impact of PB MRD on the benefit of fixed-duration, venetoclax-containing treatment. Low conversion to detectable MRD and sustained PFS after completion of 2 years of venetoclax-rituximab demonstrate the feasibility of this regimen.

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## INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a malignancy of mature CD5<sup>+</sup> B cells.<sup>1</sup> Treatment options for relapsed/refractory (R/R) disease have evolved from rituximab monotherapy or chemoimmunotherapy (CIT), including bendamustine-rituximab,<sup>2</sup> to such novel agents as the kinase inhibitors ibrutinib<sup>3</sup> or idelalisib,<sup>4</sup> resulting in improved progression-free survival (PFS) and overall survival (OS). However, these novel therapies require continuous treatment to disease progression, which can be problematic as a result of patient intolerance,<sup>5</sup> the

high cost of therapy,<sup>6</sup> and potential for selecting resistant subclones.<sup>7</sup> There is therefore a need for efficacious fixed-duration targeted treatments.

Venetoclax is a highly selective inhibitor of B-cell lymphoma 2, an antiapoptotic protein that is constitutively overexpressed in CLL.<sup>8,9</sup> Venetoclax acts independently of functional TP53<sup>10</sup> and has proven efficacy in patients with heavily pretreated CLL.<sup>11,12</sup>

Deep remissions, including eradication of minimal residual disease (MRD) in blood or marrow, are desirable therapeutic goals in patients with CLL, as

## ASSOCIATED CONTENT

### Appendix

### Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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attainment of undetectable MRD (uMRD) after CIT is associated with prolonged PFS and OS.<sup>13-18</sup> Venetoclax combined with rituximab, followed by continuous venetoclax monotherapy, can result in such deep remissions<sup>19</sup> and is therefore the first novel agent that might allow for a fixed-duration regimen. Whether MRD levels predict clinical outcome with such a regimen is currently unknown.

We compared the efficacy and safety of fixed-duration venetoclax-rituximab in R/R CLL with standard bendamustine-rituximab in the phase III MURANO study. At the time of the preplanned analysis of the primary end point, the majority of patients in the venetoclax-rituximab arm were still receiving venetoclax monotherapy. Analysis revealed that venetoclax-rituximab-treated patients had significantly superior PFS and increased rates of uMRD compared with bendamustine-rituximab-treated patients.<sup>20</sup> With this follow-up and all patients now having completed therapy, we present analyses of clinical outcomes and the impact of MRD levels on these outcomes with fixed-duration, venetoclax-based therapy.

## METHODS

### Study Design and Conduct

MURANO (ClinicalTrials.gov identifier: NCT02005471) is an ongoing global, phase III, open-label, randomized study investigating the efficacy and safety of venetoclax-rituximab therapy compared with bendamustine-rituximab in patients with R/R CLL. Eligibility criteria and study design have been described previously.<sup>20</sup> The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practice guidelines.<sup>21,22</sup> The trial protocol was approved by the ethics committee at each participating institution. All patients provided written informed consent to participate.

### Treatment

Patients were randomly assigned 1:1 to receive six 28-day cycles of venetoclax-rituximab followed by venetoclax 400 mg once per day for a total of 2 years—calculated from day 1 of cycle 1 after the venetoclax dose ramp-up— or six cycles of standard bendamustine-rituximab,<sup>2</sup> unless disease progression or unacceptable toxicity occurred sooner. Dosing, prophylactic measures, and monitoring were as described previously.<sup>20</sup>

### Assessments

Primary efficacy end point was investigator-assessed PFS, which was defined as the time from random assignment to the first occurrence of progression, relapse, or death, whichever occurred first. Peripheral blood (PB) MRD status 2 to 3 months after the end of combination therapy (EOCT) was a secondary end point and was also assessed at cycle 4 and every 3 to 6 months after EOCT. Other end points included clinical response—OS, complete response (CR), and partial response (PR)—and safety assessments. All

patients were observed for safety and efficacy every 3 to 6 months through year 3 from initiation of combination therapy. Disease status was assessed by computed tomography (CT) scan at screening, cycle 4, and the EOCT visit. During the venetoclax single-agent treatment period and at follow-up visits, response was assessed clinically. As the duration of venetoclax treatment from cycle 1, day 1 was 2 years, the time of treatment cessation is closest to the protocol-defined visit that occurred at approximately month 24 and was therefore considered to be the end of treatment (EOT) visit.

Central analysis of serial PB MRD samples was performed using allele-specific oligonucleotide-polymerase chain reaction (ASO-PCR) and/or flow cytometry on the basis of the European Research Initiative on CLL four-color assay (details in the Data Supplement). A hierarchical algorithm was used to determine MRD status using both methodologies (Appendix Table A1, online only). MRD was considered undetectable (uMRD) if the result was less than one CLL cell in 10,000 leukocytes (MRD value less than 0.0001,  $10^{-4}$ ). Low-level (L-)MRD was defined as  $10^{-4}$  to less than  $10^{-2}$ , and high-level (H-)MRD  $10^{-2}$  or greater. Safety evaluation included the monitoring of adverse events (AEs), premature study withdrawals, deaths, and venetoclax dose delays.

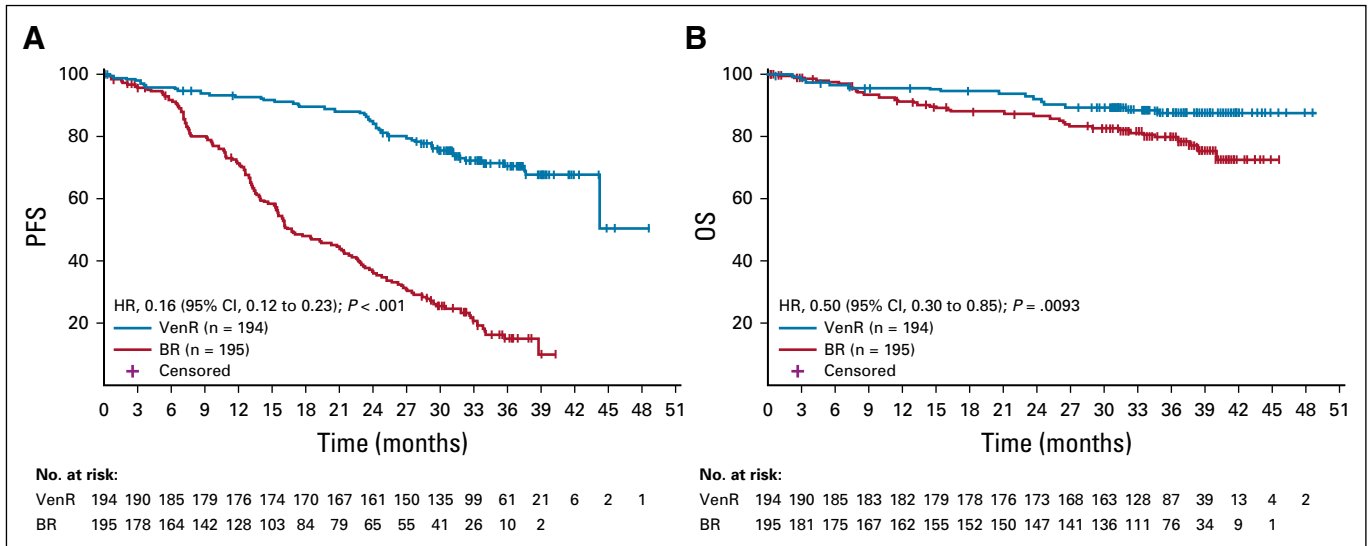
### Statistical Analyses

At a preplanned interim analysis, the independent data monitoring committee recommended that the study undergo full analysis because the prespecified statistical boundaries for PFS were crossed—this became the primary analysis, which was published earlier.<sup>20</sup> There is no alpha spending allocated to the current analysis of end points, performed with one more year of follow-up after the primary analysis. All *P* values are therefore descriptive. Kaplan-Meier estimates were used to analyze the time-to-event data. Log-rank test and Cox proportional hazards regression model—stratified by del(17p) status, risk status, and geographic region—were used to compare PFS and OS across arms. Fisher's exact test was performed to compare MRD status and clinical and cytogenetic risk factors in venetoclax-rituximab patients with and without progressive disease (PD) after EOT.

## RESULTS

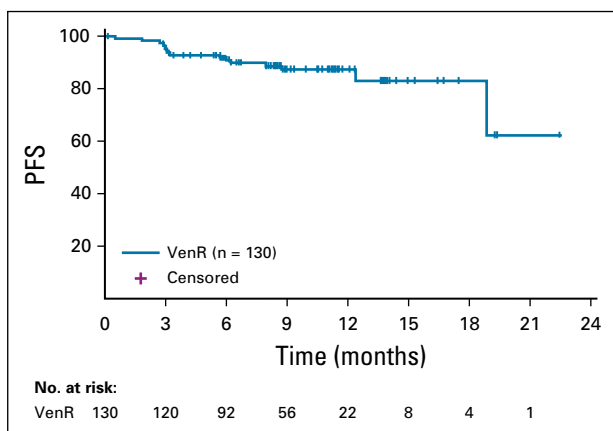
### Patients

The MURANO study enrolled 389 patients globally—194 patients in the venetoclax-rituximab arm and 195 in the bendamustine-rituximab arm (Appendix Fig A1, online only)—with well-balanced demographic and baseline disease characteristics.<sup>20</sup> Current data were analyzed using a cutoff date of May 8, 2018, when all patients were off treatment. In the venetoclax-rituximab arm, 174 patients (90%) completed the venetoclax-rituximab combination phase and 130 (65%) completed 2 years of planned



**FIG 1.** (A and B) Kaplan-Meier plot of (A) investigator-assessed progression-free survival (PFS) and (B) overall survival (OS) in the intention-to-treat population with 36-month median follow up. BR, bendamustine-rituximab; HR, hazard ratio; VenR, venetoclax-rituximab.

venetoclax without PD. The remainder of the patients receiving venetoclax-rituximab had PD (11%), died without PD (1%), or withdrew as a result of AEs (15%; Appendix Table A2, online only) or for another reason (6%). Characteristics of those with PD on therapy are shown in Appendix Table A3 (online only). Of those who withdrew from venetoclax treatment because of an AE ( $n = 32$ ), 10 remain free from PD; 10 had PD, five of whom received subsequent treatment; eight died because of the AE; and four died as a result of a different AE. Median venetoclax treatment duration from the start of ramp-up was 24.4 months (range, 0.1 to 27.9 months) and the relative dose intensity was 97.4% (range, 26% to 100%; Appendix Table A4, online only).



**FIG 2.** Kaplan-Meier plot of progression-free survival (PFS) for patients who completed 2 years of venetoclax without prior disease progression ( $n = 130$ ; median follow-up of 9.9 months off venetoclax). VenR, venetoclax-rituximab.

## Efficacy

At a median follow-up of 36.0 months, PFS with venetoclax-rituximab was superior to bendamustine-rituximab (hazard ratio [HR], 0.16 [95% CI, 0.12 to 0.23];  $P < .001$ ; median not reached  $v$  17.0 months; Fig 1A). Three-year PFS estimates were 71.4% (95% CI, 64.8% to 78.1%) and 15.2% (95% CI, 9.1% to 21.4%), respectively. A consistent magnitude of treatment effect on PFS with venetoclax-rituximab was observed in all clinical and biologic subgroups (Appendix Fig A2, online only).

In the 130 patients who completed 2 years of venetoclax without PD, the 6- and 12-month PFS estimates from venetoclax cessation were 92% (95% CI, 87.3% to 96.8%) and 87% (95% CI, 81.1% to 93.8%), respectively (Fig 2), with a median of 9.9 months (range, 1.4 to 22.5 months) of follow-up off venetoclax. In univariate analysis, the presence of del(17p) and/or *TP53* mutation and the absence of del(11q) were associated with risk of PD after venetoclax cessation (both  $P < .03$ ; Table 1). However, the number of events in del(11q) patients was small ( $n = 1$ ) and the effect diminished when Döhner hierarchical testing was applied to evaluate del(11) cases without del(17p) ( $P = .25$ ).

In this analysis, improvement in OS was observed with venetoclax-rituximab compared with bendamustine-rituximab (HR, 0.50 [95% CI, 0.30 to 0.85];  $P = .0093$ ; 3-year estimate: 87.9%  $v$  79.5%; Fig 1B). Median time to next anti-CLL treatment or death was 23.9 months (range, 0.0 to 43.7 months) in the bendamustine-rituximab arm—there were too few patients at risk for this to be reliably assessed in the venetoclax-rituximab arm. Subsequent CLL-directed treatment administered after PD in 91 patients in the bendamustine-rituximab arm (Appendix Table A5, online only). Of these, 71 patients (78.0%)

**TABLE 1.** MRD Status and Clinical and Cytogenetic Risk Factors for PD in Venetoclax-Rituximab Arm Patients Alive Without Disease Progression at Month 24 (n = 130; univariate analysis)

Feature (No.)*	No. (%) With PD	P†
PB MRD at EOT (month 24)‡		< .001
uMRD (n = 83)	2 (2.4)	
L-MRD (n = 23)	3 (13.0)	
H-MRD (n = 14)	11 (78.6)	
Del(17p) and/or TP53 mutated		.01
At least one present (n = 43)	10 (23.3)	
Neither present (n = 78)	5 (6.4)	
Del(11q)		.03
Present (n = 38)	1 (2.6)	
Absent (n = 80)	13 (16.3)	
Del(11q) without del(17)p§		.25
Present (n = 32)	1 (3.1)	
Absent (n = 58)	7 (12.1)	
IGVH status		.14
Mutated (n = 38)	2 (5.3)	
Unmutated (n = 84)	13 (15.5)	
No. of previous therapies		.79
1 (n = 78)	9 (11.5)	
≥ 2 (n = 52)	7 (13.5)	
Bulky disease (largest lymph node diameter), cm		1.0
< 5 (n = 67)	9 (13.4)	
≥ 5 (n = 53)	7 (13.2)	
Residual disease at EOCT		.08
Low nodal burden (< 1.5 cm; n = 64)	5 (7.8)	
Intermediate nodal burden (≥ 1.5 to < 2 cm; n = 23)	2 (8.7)	
High nodal burden (≥ 2 cm; n = 39)	9 (23.1)	

Abbreviations: EOCT, end of combination therapy; EOT, end of therapy; (H-), high level; IGVH, immunoglobulin variable region heavy chain; (L-), low level; (u)MRD, (undetectable) measurable residual disease; PB, peripheral blood; PD, disease progression.

\*Categories do not sum to 130 as data elements are missing for some patients.

†P value is based on Fisher's exact test.

‡MRD status was not available for 10 patients at EOT.

§In Döhner hierarchical model.

received novel targeted agents, including 46 who received ibrutinib and seven who received venetoclax as next-line treatment. In the venetoclax-rituximab arm, 27 (13.9%) of 194 patients received subsequent therapy—13 (48.1%) of 27 patients received novel targeted agents as next treatment after PD, including eight who received ibrutinib and three who were retreated with venetoclax. Of those patients who received ibrutinib after venetoclax, two achieved PR, and efficacy data were unavailable for the remaining six

patients. Among the three patients who were retreated with venetoclax, one achieved PR, one had stable disease, and one lacked follow-up efficacy data.

### MRD at EOCT

MRD status assessed using ASO-PCR, and flow cytometry demonstrated high correlation ( $r = .89$ ) and concordance (Data Supplement and Appendix Fig A3, online only). There was also high concordance for MRD status between PB and bone marrow. Of 49 uMRD in PB, 44 (90%) were confirmed in bone marrow in available paired samples among patients who received venetoclax-rituximab (from 47 patients; Appendix Fig A4, online only). Higher rates of PB uMRD were observed in the venetoclax-rituximab arm than in the bendamustine-rituximab arm at EOCT (Table 2) and all assessments during and after venetoclax single-agent treatment (Fig 3A). H-MRD at EOCT was less frequent with venetoclax-rituximab (4.6%) than with bendamustine-rituximab (29.2%; Table 2). Overall, the rate of uMRD as best MRD response at any time during the study was higher with venetoclax-rituximab (82.5%) than with bendamustine-rituximab (23.1%).

At EOCT, patients with uMRD had a longer duration of PFS in each treatment arm (Fig 3B) than patients with detectable MRD. Among patients with detectable MRD, those with L-MRD had a longer duration of PFS compared with patients with H-MRD for either treatment arm (venetoclax-rituximab: HR, 0.24 [95% CI 0.08 to 0.72]; bendamustine-rituximab: HR, 0.22 [95% CI 0.13 to 0.38]). However, there were only six patients with H-MRD at EOCT in the venetoclax-rituximab arm.

Landmark analysis from EOCT demonstrated that patients in the venetoclax-rituximab arm who achieved an investigator-assessed PR with uMRD had PFS outcomes that were similar to those of patients who achieved CR with uMRD (Fig 3C; HR, 0.71 [95% CI, 0.24 to 2.14]). Conversely, patients who achieved PR/nodular PR with detectable MRD had inferior PFS compared with those with PR and uMRD from 18 months onwards after EOCT. Patients who achieved CR with detectable MRD—all of whom had L-MRD—had a PFS that was comparable to that of patients who achieved uMRD at this follow-up, although the number of such patients is small (HR, 1.07 [95% CI 0.12 to 9.55]; Fig 3C).

### MRD Kinetics

High rates of uMRD and L-MRD in the venetoclax-rituximab arm at EOCT were sustained with serial assessments (Appendix Fig A5A, online only) and also found at EOT among 130 patients who completed 2 years of venetoclax (uMRD: 83 [64%] of 130 patients; and L-MRD: 23 [18%] of 130 patients).

At this follow-up—median of 9.9 months off venetoclax—only two of 83 patients who were uMRD at EOT (2.4%) developed PD. Of the patients who had detectable

**TABLE 2.** MRD Status in All Patients and By Baseline Clinical and Cytogenetic Factors at EOCT

Factor	Venetoclax-Rituximab				Bendamustine-Rituximab				P*
	No.	uMRD (%)	L-MRD (%)	H-MRD (%)	No.	uMRD (%)	L-MRD (%)	H-MRD (%)	
All patients†	194	62.4	19.1	4.6	195	13.3	23.1	29.2	< .001
Age group, years									
< 65	97	61.9	15.5	6.2	89	12.4	15.7	31.5	< .001
≥ 65	97	62.9	22.7	3.1	106	14.2	29.2	27.4	< .001
Sex									
Male	136	61.0	20.6	3.7	151	10.6	23.8	31.8	< .001
Female	58	65.5	15.5	6.9	44	22.7	20.5	20.5	.001
No. of prior regimens									
1	111	64.0	21.6	4.5	117	12.0	26.5	31.6	< .001
> 1	83	60.2	15.7	4.8	78	15.4	17.9	25.6	< .001
Bulky disease (largest lymph node diameter), cm									
< 10	161	61.5	19.9	5.6	158	11.4	24.7	29.7	< .001
≥ 10	23	65.2	8.7	0	27	14.8	11.1	29.6	.0003
β2-microglobulin, mg/L									
≤ 3.5	64	64.1	18.8	3.1	59	10.2	22.0	30.5	< .001
> 3.5	125	62.4	17.6	5.6	127	15.7	24.4	29.1	< .001
IGVH									
Unmutated	123	61.0	18.7	6.5	123	14.6	21.1	31.7	< .001
Mutated	53	64.2	22.6	1.9	51	15.7	27.5	21.6	< .001
11q									
Deleted	61	65.6	11.5	4.9	64	10.9	26.6	29.7	< .001
Not deleted	112	62.5	24.1	5.4	105	16.2	21.0	28.6	< .001
Del(17p) and/or TP53 mutated									
Yes	72	56.9	19.4	2.8	75	5.3	18.7	34.7	< .001
No	106	66.0	18.9	6.6	95	20.0	26.3	25.3	< .001

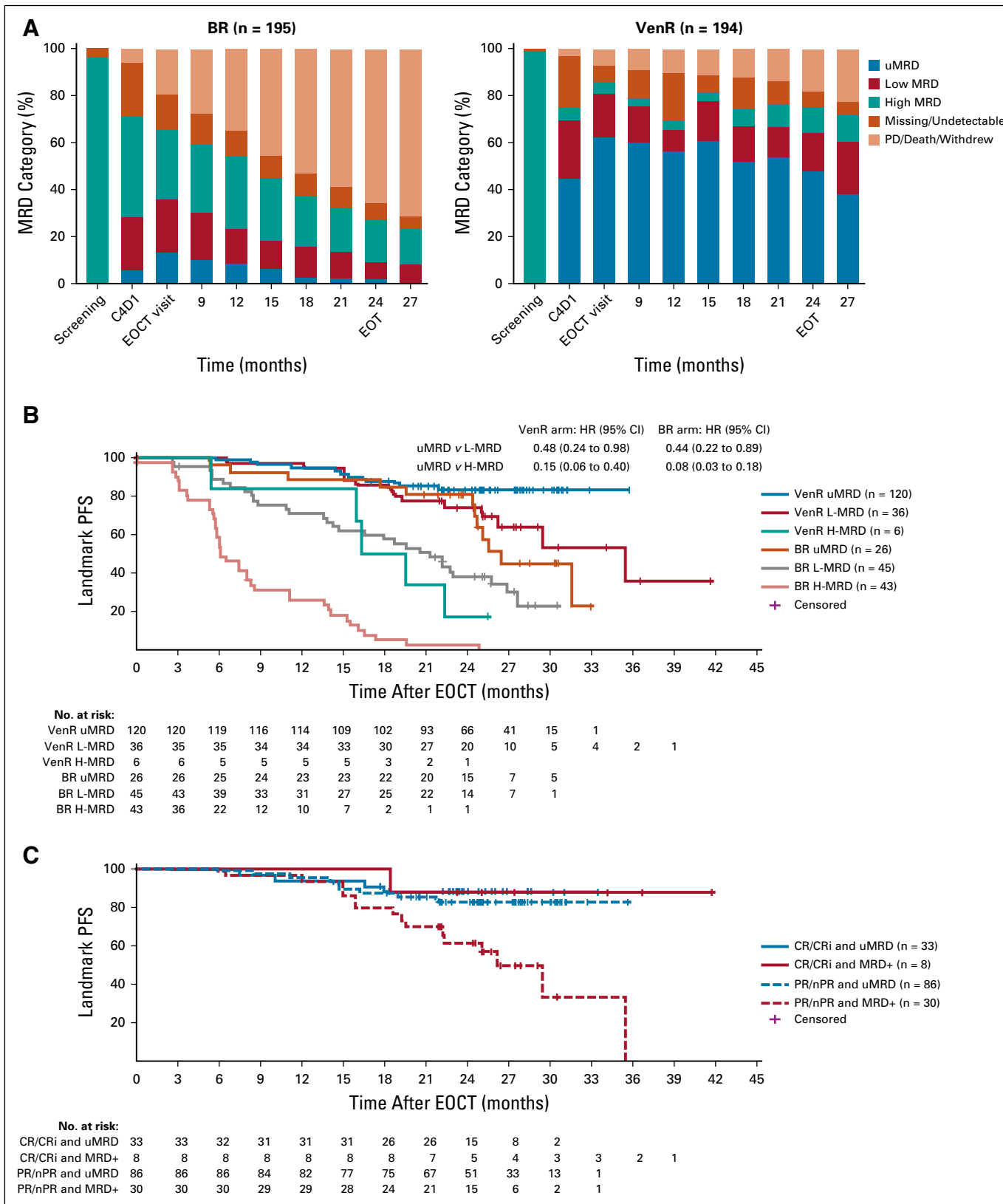
Abbreviations: EOCT, end of combination therapy; (H-), high level; IGVH, immunoglobulin variable region heavy chain; (L-), low level; (u)MRD, (undetectable) measurable residual disease; PD, progressive disease.

\*P value is based on Fisher's exact test.

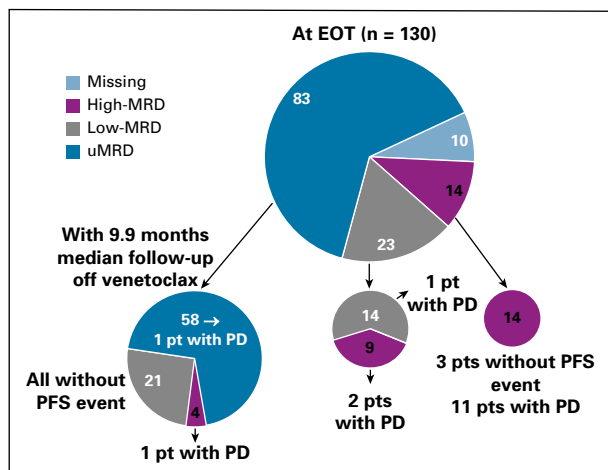
†Data from 43 patients were missing: 14 in the venetoclax-rituximab arm and 29 in the bendamustine-rituximab arm. There were 13 PD/death/withdrawals in the venetoclax-rituximab arm and 38 PD/death/withdrawals in the bendamustine-rituximab arm before the EOCT visit.

MRD at EOT, PD occurred in three (13%) of 23 and 11 (79%) of 14 patients with L-MRD and H-MRD, respectively (Fig 4). Details of the two patients in the uMRD group with PD can be found in the Data Supplement. Univariate analysis of 130 patients who completed treatment demonstrated a strong association between MRD level and progression, with uMRD being associated with better outcomes (Table 1). More patients without del(17p) and/or mutated TP53 had uMRD at EOT and remained PD free compared with those with del(17p) and/or mutated TP53 (Appendix Fig A5B, online only). The presence of minor residual adenopathy on CT scan at the EOCT visit was not predictive of achieving uMRD at EOT, nor of subsequent relapse (Table 1 and Appendix Fig A5C, online only).

Of patients with uMRD at EOT, most sustained uMRD (58 [70%] of 83 patients; Appendix Fig A5D, online only), whereas 25 (30%) of 83 patients developed detectable MRD. With current follow-up, this was typically L-MRD (21 [25%] of 83 patients), all of whom remained PFS event free. Four patients who had uMRD at EOT developed H-MRD (four [5%] of 83 patients) within a range of 6.0 to 13.4 months, one of whom subsequently developed PD, per International Workshop on CLL (iwCLL) criteria. Median time off venetoclax to the last MRD test in these 25 patients was 11.1 months (range, 5.3 to 19.3 months). Residual adenopathy on CT scan at the EOCT visit was not predictive of conversion from uMRD after drug cessation (Appendix Fig A5C). Of 25 patients who were uMRD at EOT and converted to detectable



**FIG 3.** (A) Measurable residual disease (MRD) response over time with venetoclax-rituximab versus bendamustine-rituximab. (B) Landmark progression-free survival (PFS) analysis according to peripheral blood (PB) MRD status at end of combined therapy (EOCT) response visit (intent-to-treat [ITT] population). The analysis subset includes patients who have not experienced progression, died, or withdrawn from study before EOCT response (continued on following page)



**FIG 4.** Measurable residual disease (MRD) changes in venetoclax-rituximab arm patients who were without a progression-free survival (PFS) event at end of treatment (EOT; n = 130). (u)MRD, (undetectable) measurable residual disease; pt, disease progression; pt, patient.

MRD, 10 had residual disease at the EOCT visit with at least one lymph node having a longest perpendicular diameter of 2 cm or greater, three had residual disease with at least one lymph node 1.5 cm or greater to less than 2 cm at EOCT, 11 had no residual disease at EOCT, and one patient had no CT scan.

### Safety

An overview of safety data for the MURANO trial during the combination and single-agent periods is provided in the Data Supplement (Appendix Table A2).

### Data Access

Qualified researchers may request access to individual patient-level data through the clinical study data request platform ([www.clinicalstudydatarequest.com](http://www.clinicalstudydatarequest.com)). Additional details on Roche's criteria for eligible studies are available here: <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>. For additional details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see the following: [https://www.roche.com/research\\_and\\_development/who\\_we\\_are\\_how\\_we\\_work/clinical\\_trials/our\\_commitment\\_to\\_data\\_sharing.htm](https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

## DISCUSSION

Analysis of the phase III global randomized MURANO study, after a median follow-up of 3 years, demonstrates substantial clinical benefit with a fixed-duration venetoclax-rituximab treatment regimen. With all patients having completed planned treatments, and with a median follow-up of 9.9 months off therapy, PFS with venetoclax-rituximab was superior to bendamustine-rituximab; improvements were consistent across all subgroups. These results substantiate the previously reported findings from the MURANO trial.<sup>20</sup> Incidence of PD after the completion of venetoclax was modest at 12%. Improved OS with venetoclax-rituximab was observed, despite a high rate of use of novel targeted agents in patients with PD in the bendamustine-rituximab arm. With longer follow-up, no new safety signals were identified, single-agent venetoclax after combination was tolerable, and the majority of patients completed planned treatment.

Higher rates of uMRD with venetoclax-rituximab were achieved at the EOCT response visit and as best MRD response compared with bendamustine-rituximab therapy.<sup>20</sup> The high uMRD response rate was found in all molecular and clinical subsets, including patients with high-risk features, such as del(17p) and/or *TP53* mutation. Residual H-MRD was less frequent in the venetoclax-rituximab arm than in the bendamustine-rituximab arm. Patients in each treatment arm with uMRD in PB at the EOCT response visit demonstrated prolonged PFS relative to patients who had detectable MRD. Prolonged PFS was also observed within the group with persistent MRD for those with L-MRD versus those with H-MRD.

Similar to observations with CIT in the first-line setting, eradication of detectable MRD at EOCT using venetoclax-rituximab was predictive of favorable outcome, including in patients with CR and PR/nodular PR.<sup>13-18</sup> Longer follow-up is needed to determine the impact of PB MRD status among patients achieving CR or CR with incomplete hematologic recovery who were treated with venetoclax-rituximab. These data highlight that uMRD is an important goal of therapy irrespective of treatment approach. These findings also confirm attainment of PB uMRD as a surrogate for PFS among patients who are treated with venetoclax-rituximab. In the venetoclax-rituximab study arm, we observed that high rates of uMRD were sustained over time and also seen at EOT among patients who completed 2 years of venetoclax treatment (64%). Of

(Continued). visit. MRD PB status derived from combining allele-specific oligonucleotide–polymerase chain reaction (ASO–PCR) and flow cytometry results. (C) Landmark PFS analysis in the venetoclax-rituximab arm according to PB MRD status and clinical response status at EOCT response visit (ITT population). The analysis subset includes patients who have not progressed, died, or withdrawn from study and have a complete response (CR), CR with incomplete hematologic recovery (CRi), nodular partial response (PR), or PR per investigator assessment at EOCT response visit. MRD PB status derived from combining ASO–PCR and flow cytometry results. BR, bendamustine-rituximab; C, cycle; CR, complete response; D, day; EOT, end of treatment; H-MRD, high-level MRD ( $\geq 10^{-2}$ ); HR, hazard ratio; L-MRD, low-level MRD ( $10^{-4}$  to  $< 10^{-2}$ ); (u)MRD, (undetectable) measurable residual disease; PD, progressive disease; (n)PR, (nodular) partial response; VenR, venetoclax-rituximab.

patients in the venetoclax-rituximab arm who developed detectable MRD after EOT, most became L-MRD and remained progression free. CLL progression was only observed in two patients with confirmed uMRD status at EOT.

Overall, with a median follow-up after drug cessation of approximately 10 months, the majority of patients who were treated with venetoclax-rituximab remained free of PD by conventional iwCLL criteria—87% at 12 months. This favorable overall outcome affirms the feasibility of fixed-duration therapy with venetoclax-rituximab in patients with R/R CLL, particularly given that either reintroduction of venetoclax or Bruton's tyrosine kinase inhibitor therapy can lead to resumed disease response in patients with progression.<sup>19,23</sup> To evaluate a larger number of cases with venetoclax reintroduction and the likelihood of the resumption of durable disease control, as has been shown in the context of chronic myeloid leukemia after attempted TKI withdrawal,<sup>24</sup> the MURANO protocol has been amended to prospectively collect such data. In a univariate analysis, conventional adverse pretreatment risk factors of *IGVH* mutational status, number of prior therapies, and disease bulk were not predictive of disease progression post-drug cessation. Presence of del(17p) and/or *TP53* mutation was associated with an increased risk of clinical PD post-treatment cessation ( $P = .01$ ), but this was confounded by MRD status. At this follow-up and with just 16 PD events to date, MRD status at EOT is emerging as a strong indicator of the risk of disease recurrence and might imply that patients with H-MRD are better managed by continuing venetoclax. Residual minor adenopathy on CT assessment—here on the basis of EOCT visit, as not all patients had repeat imaging at EOT—was not associated with an increased risk of disease recurrence,

which suggests that these persisting imaging findings may not represent a reservoir of viable disease. As previously reported after front-line treatment,<sup>17</sup> serial MRD assessment may identify those patients with rising disease burden many months before clinical disease recurrence, and our data suggest that patients frequently transition through intermediate MRD levels, which does not uniformly predict imminent relapse by iwCLL criteria. Longer observation of this cohort will be needed to define the spectrum of CLL doubling times and potentially predict the timing of clinical recurrence, which will allow for therapy reintroduction before patients reach high tumor burden status. Even if a proportion of patients are ultimately destined to develop PD by iwCLL criteria and require such retreatment as venetoclax reintroduction, a number of years off drug would have quality-of-life, toxicity, and societal economic benefit. This would also minimize clonal selection pressure, relevant with other targeted therapies.<sup>5-7</sup>

This longer follow-up confirms that fixed-duration venetoclax-rituximab therapy delivers durable clinical response and a survival advantage over bendamustine-rituximab therapy. Higher rates of PB uMRD at the EOCT response visit predicted prolonged benefit independent of clinical response, and patients with L-MRD also achieved better outcomes than did those with H-MRD. In the venetoclax-rituximab arm, high rates of uMRD were also sustained over time, and most of these patients remained PD free after drug cessation. These data support the feasibility of a fixed duration of venetoclax-rituximab in R/R CLL. Furthermore, levels of MRD are highly predictive of duration of remission during and after venetoclax cessation.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study**

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## APPENDIX

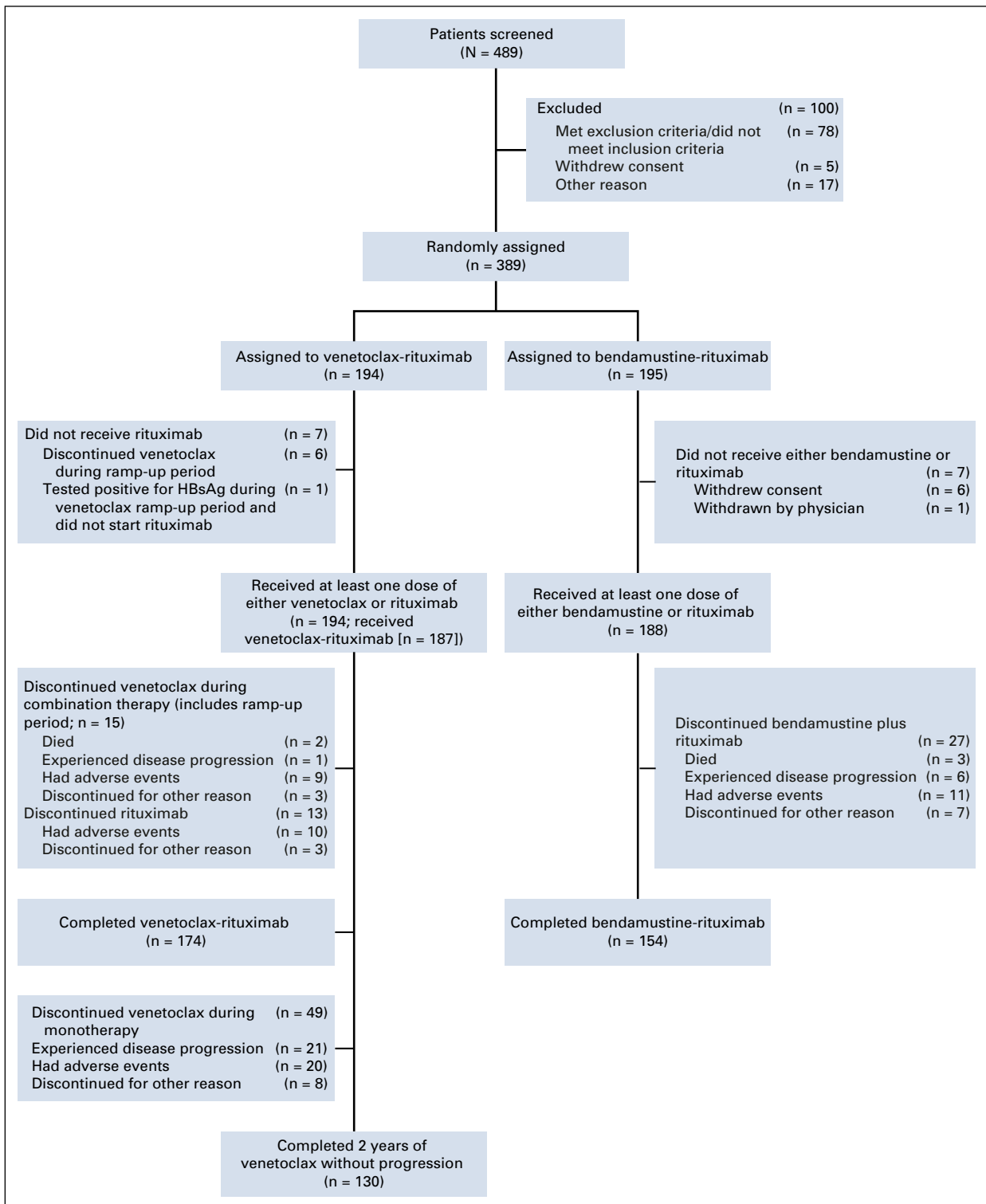
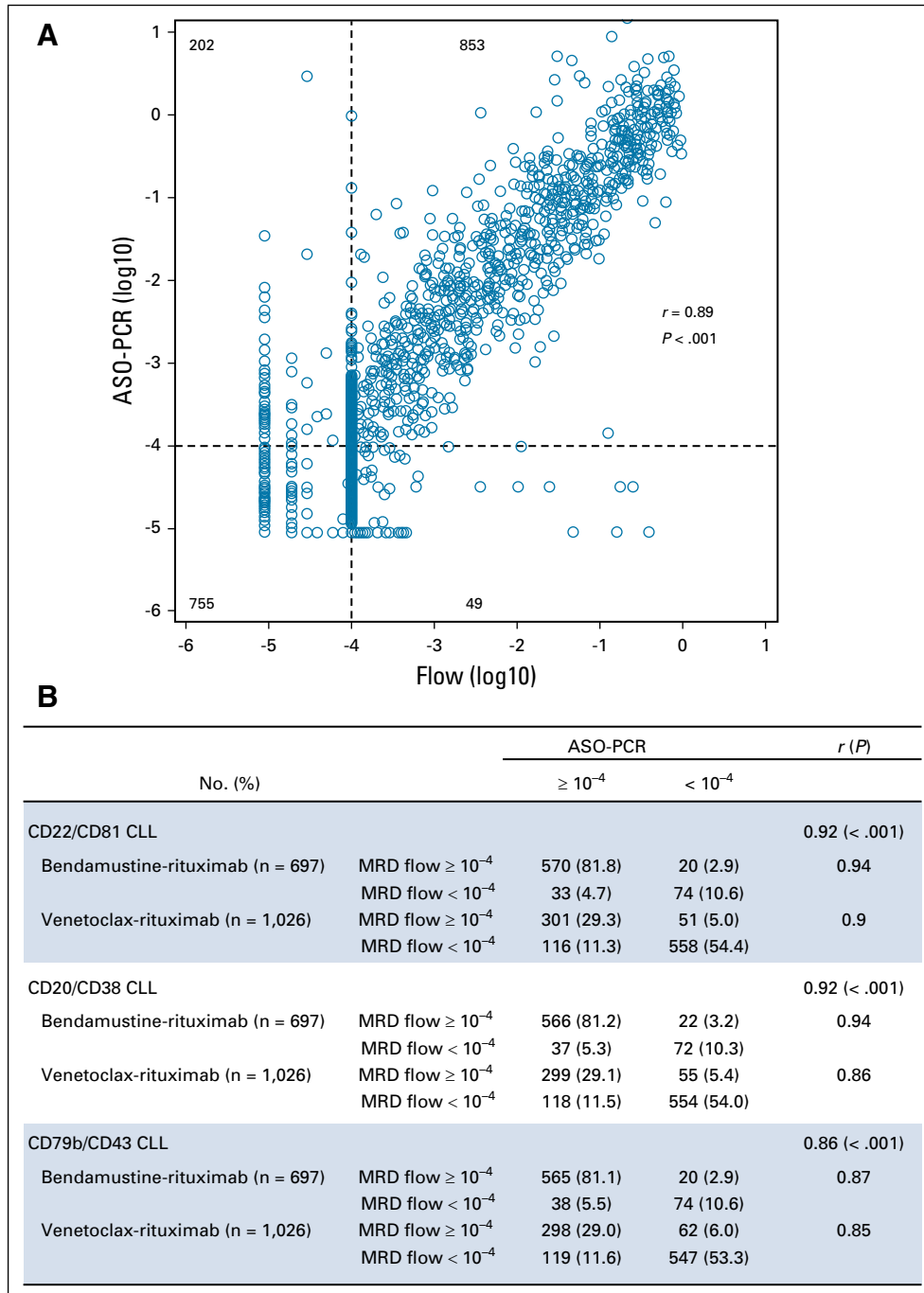


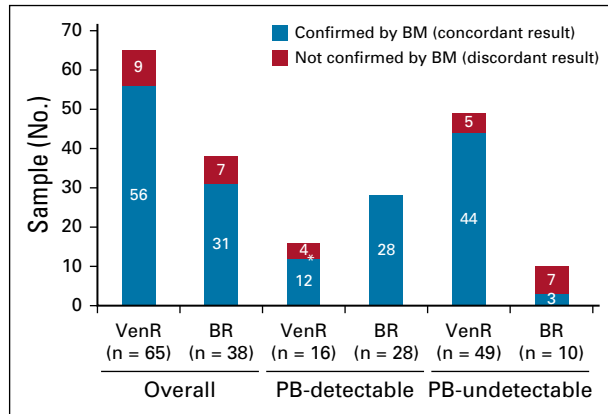
FIG A1. Patient disposition. HBsAg, hepatitis B surface antigen

Characteristic/Biomarker	Total No.	VenR (n = 194)		BR (n = 195)		Hazard Ratio	95% Wald CI	VenR Better	BR Better
		No.	Median† (months)	No.	Median (months)				
All patients	389	194	NE	195	17.0	0.19	(0.14 to 0.27)		
Age group, years									
< 65	186	97	NE	89	15.4	0.17	(0.11 to 0.27)		
≥ 65	203	97	NE	106	22.3	0.21	(0.14 to 0.33)		
Risk status*									
Low	178	90	44.3	88	23.3	0.17	(0.10 to 0.28)		
High	211	104	NE	107	15.4	0.21	(0.14 to 0.31)		
Geographic region									
United States/Canada	34	16	44.3	18	15.8	0.18	(0.06 to 0.52)		
Australia/New Zealand	86	44	NE	42	24.5	0.26	(0.13 to 0.52)		
Western Europe	131	66	NE	65	17.3	0.16	(0.09 to 0.29)		
Central and Eastern Europe	130	64	NE	66	15.5	0.17	(0.09 to 0.30)		
Asia	8	4	NE	4	13.6	0.46	(0.07 to 2.86)		
No. of prior regimens									
1	228	111	44.3	117	16.6	0.16	(0.10 to 0.25)		
2	101	58	NE	43	21.2	0.24	(0.13 to 0.43)		
≥ 3	60	25	NE	35	12.9	0.26	(0.12 to 0.55)		
Refractory v relapse to most recent prior therapy‡									
Refractory	53	30	31.9	29	13.6	0.40	(0.20 to 0.79)		
Relapse	330	164	NE	166	18.6	0.16	(0.11 to 0.23)		
Chromosome 17p deletion (central)									
No	250	127	NE	123	21.4	0.19	(0.13 to 0.29)		
Yes	92	46	NE	46	15.4	0.21	(0.11 to 0.39)		
TP53 mutated (central)									
No	276	144	NE	132	21.2	0.16	(0.10 to 0.24)		
Yes	99	48	36.0	51	12.9	0.25	(0.15 to 0.43)		
IGVH									
Mutated	104	53	NE	51	24.2	0.16	(0.07 to 0.33)		
Unmutated	246	123	44.3	123	15.7	0.16	(0.11 to 0.24)		

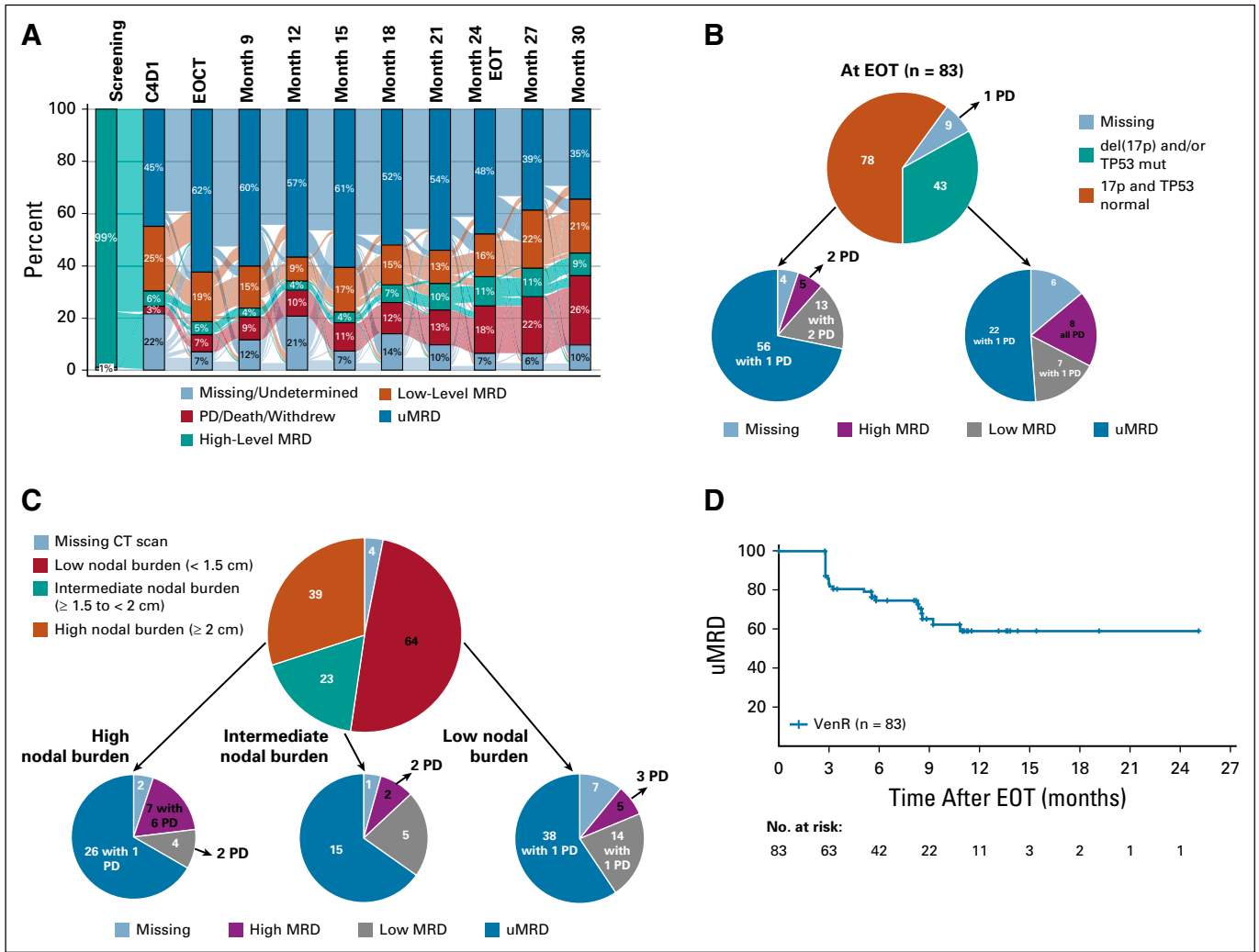
**FIG A2.** Prespecified subgroup analysis of investigator-assessed progression-free survival (PFS). (\*) Low risk: defined as relapse more than 12 months after chemotherapy or 24 months after chemoimmunotherapy. High risk: defined as harboring 17p deletion or no response to front-line chemotherapy-containing regimen or relapsed within 12 months after chemotherapy or within 24 months after chemoimmunotherapy. (†) Medians in the VenR arm could not be reliably estimated due to too few patients at risk. (‡) Defined as per iwCLL guidelines. Relapsed disease: a patient who previously achieved a complete or partial response, but after a period of 6 months or more demonstrates evidence of progression. Refractory disease: treatment failure or disease progression within 6 months of the last anti-leukemia. BR, bendamustine-rituximab; IGVH, immunoglobulin variable region heavy chain; iwCLL, International Workshop on CLL; NE, not estimable; VenR, venetoclax-rituximab



**FIG A3.** SO-PCR–flow concordance. (A) MRD concordance between MRD peripheral blood from flow and PCR (numerical): intent-to-treat population. (B) Correlation of quantitative MRD levels between ASO–PCR and all three antibody pairs by treatment arm. Based on data as of cut-off May 8, 2018. For MRD values below the limit of detection (LOD), LODs were represented in the graph. Correlation coefficient *r* and *P* value (t-test) are for positive sample only. ASO-PCR, allele-specific oligonucleotide–polymerase chain reaction; MRD, measurable residual disease.



**FIG A4.** PB MRD is a surrogate for bone marrow (BM) MRD. \* Reflects the error rate in samples with MRD levels close to the  $10^{-4}$  cutoff (iwCLL recommended cutoff). BR, bendamustine-rituximab; EOCT, end of combined therapy; EOT, end of treatment; MRD, measurable residual disease; PB, peripheral blood; BM, bone marrow; VenR, venetoclax-rituximab.



**FIG A5.** (A) Sankey plot is a flow diagram showing MRD kinetics in the intent-to-treat population in the venetoclax-rituximab study arm (N = 194) over the course of the study. The width of links between the categories within the vertical bars at each assessment time point represents the proportion of patients; the plot illustrates the dynamic change of their MRD status over time. The vertical bars are a summary of the population status at the time points labeled across the top of the chart. (B) MRD status at EOT in venetoclax-rituximab arm patients according to baseline del(17p) and/or TP53 status. (C) MRD status at EOT in venetoclax-rituximab arm patients according to residual disease status at the EOCV visit. (D) Kaplan-Meier plot of conversion to MRD+ in patients who had uMRD in peripheral blood at EOT (N=83). BM samples were not mandated in the protocol at EOT. EOT, end of treatment; PD, disease progression; (u)MRD, (undetectable) measurable residual disease; VenR, venetoclax-rituximab.

**TABLE A1.** Hierarchical Algorithm for Combining MRD Results from ASO-PCR and Flow Assays

Step No.	Step
1	Detectable MRD positive by either ASO-PCR or flow = detectable MRD
2	If a sample is not detectable MRD with Step 1 and undetectable MRD by ASO-PCR and/or flow = undetectable MRD
3	If MRD undetermined by both ASO-PCR and flow = MRD undetermined*

Abbreviations: ASO-PCR, allele-specific oligonucleotide-polymerase chain reaction; MRD, measurable residual disease.

\*MRD undetermined status and missing are treated as MRD positive in the intent-to-treat analysis.

**TABLE A2.** Overview of Safety Data for MURANO During Combination and Single-Agent Periods

Variable	Venetoclx-Rituximab Combination Therapy Period (n = 194)	Venetoclx Single-Agent Period* (n = 171)
Total No. of patients with $\geq 1$ AE	192 (99.0)	151 (88.3)
AE leading to withdrawal from venetoclax†	15 (7.7)	17 (9.9)
AE leading to dose reduction	24 (12.4)	7 (4.1)
AE leading to dose interruption	125 (64.4)	44 (25.7)
Grade 3-4 AEs	145 (74.7)	59 (34.5)
Fatal AEs	8 (4.1)	7 (4.1)

NOTE. Data are presented as No. (%).

Abbreviation: AE, adverse event.

\*For the purposes of the analysis, AEs that occurred with an onset date of more than 90 days after the last rituximab dose in patients who had received at least one venetoclax dose more than 90 days after the last rituximab dose were considered to have occurred during the venetoclax single-agent treatment period. AEs that occurred with an onset date before 90 days after the last rituximab dose were considered to have occurred during the venetoclax-rituximab combination treatment period.

†There was a total of 41 AEs that resulted in withdrawal from venetoclax therapy in 32 patients. AEs leading to withdrawal of venetoclax therapy during the combination period were neutropenia (n = 4; 2.1%), thrombocytopenia (n = 3; 1.5%), neoplasms (metastasis [unspecified], colorectal cancer [n = 2; 1.0%]), febrile neutropenia (n = 1; 0.5%), anemia (n = 1; 0.5%), autoimmune hemolytic anemia (n = 1; 0.5%), acute respiratory failure (n = 1; 0.5%), appendicitis (n = 1; 0.5%), peritoneal tuberculosis (n = 1; 0.5%), pneumonia (n = 1; 0.5%), pyrexia (n = 1; 0.5%), status epilepticus (n = 1; 0.5%), and sudden cardiac death (n = 1; 0.5%). AEs leading to withdrawal of venetoclax during the single-agent period were neoplasms (colorectal cancer, metastatic malignant melanoma, pancreatic cancer, lung and peritoneal neoplasms [n = 5; 2.6%]), neutropenia (n = 3; 1.5%), thrombocytopenia (n = 2; 1.0%), ALT increase (n = 1; 0.5%), ascites (n = 1; 0.5%), asthenia (n = 1; 0.5%), autoimmune hemolytic anemia (n = 1; 0.5%), Crohn's disease (n = 1; 0.5%), diarrhea (n = 1; 0.5%), immune thrombocytopenia purpura (n = 1; 0.5%), hydrothorax (n = 1; 0.5%), lung infection/pneumonia (n = 2; 1.0%), sudden death (n = 1; 0.5%), and vertigo (n = 1; 0.5%).



**TABLE A3.** Characteristics of Patients (n = 25) Who Experienced Progression Before End of Therapy

Characteristic	Value
No. of prior lines of therapy	
1	14 (56)
2	8 (32)
3	3 (12)
Del17p	
Deleted	6 (24)
Normal	16 (64)
Unknown	3 (12)
P53 mutation	
Mutated	12 (48)
Not mutated	12 (48)
Unknown	1(4)
P53 mutation and/or del17p	
No	9 (36)
Yes	13 (52)
Unknown	3 (12)
Median age, years (mean; range)	63 (59.7; 28-81)

NOTE. Data are presented as No. (%), unless otherwise noted.

**TABLE A4.** Study Treatment Exposure in Safety-Evaluable Patients

Variable	Venetoclax-Rituximab (n = 194)	Venetoclax-Rituximab Combination Period (n = 194)	Venetoclax-Rituximab Monotherapy Period* (n = 187)	Bendamustine- Rituximab (n = 188)
Venetoclax treatment duration (months)				
No.	194	194	173	NA
Mean (SD)	21.0 (7.2)	6.7 (2.1)†	16.0 (4.2)	NA
Median	24.4	6.7†	17.7	NA
Min-max	0.1-27.9	0.1-24.9†	0.5-21.9	NA
Dose intensity (%)				
No.	189	189	172	188
Mean (SD)	89.6 (17.1)	91.6 (14.5)	90.2 (18.3)	96.7 (8.2)
Median	97.4	97.2	99.3	100
Min-max	26-100	36-100	23-100	50-100

Abbreviations: NA, not applicable; SD, standard deviation.

\*From day 29 after the last dose of rituximab.

†One patient was not exposed to rituximab. In this patient, the duration of venetoclax exposure was treated as being in the combination period.

**TABLE A5.** Response to Subsequent Therapy After PD in the Venetoclax-Rituximab and Bendamustine-Rituximab Arms

<b>Patients Receiving Subsequent Therapy</b>						
<b>Treatment Arm</b>	<b>Total</b>	<b>CR</b>	<b>PR*</b>	<b>SD</b>	<b>PD</b>	<b>NE/NA</b>
<b>Venetoclax-rituximab arm</b>						
Ibrutinib monotherapy/combination	8	0	2	0	0	6
Venetoclax monotherapy	3	0	1	1	0	1
Idelalisib monotherapy/combination	1	0	0	1	0	0
Chemotherapy and/or immunotherapy	14	1	2	2	3	6
Investigational product (other)	1	0	0	0	1	0
<b>Bendamustine-rituximab arm</b>						
Ibrutinib monotherapy/combination	46	5	22	4	1	14
Venetoclax monotherapy	7	0	2	0	0	5
Idelalisib monotherapy/combination	7	1	4	0	1	1
Chemotherapy and/or immunotherapy	20	5	5	3	2	5
<b>Investigational product</b>						
BTKi†	7	0	4	2	1	0
Non-BTKi	3	0	2	0	1	0
Other	1	0	1	0	0	0

NOTE. Data are given as No.

Abbreviations: BTKi, Bruton's tyrosine kinase inhibitor; CR, complete response; NA, not assessed; NE, not evaluable; PD, disease progression; PR, partial response; SD, stable disease.

\*Includes one patient who achieved a nodular partial response.

†Excludes ibrutinib.