Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax-rituximab

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Supplementary materials

Supplementary methods

MRD analysis of peripheral blood

For minimal residual disease (MRD) in peripheral blood, results from allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and flow cytometry were combined to enable a robust dataset and a conservative approach to MRD-negativity calculation (described below) while minimizing missing data caused by the technical failure of individual methodologies noticed during the conduct of the study. The feasibility of combining the MRD results from the two methods is supported by the concordance rate of 85.4% from 1,291 pairs of post-baseline peripheral blood samples measured by both ASO-PCR and flow cytometry.

Given the overall high concordance rate between ASO-PCR and flow cytometry,[29] a conservative hierarchical algorithm for combining MRD results from the two assays was established to determine MRD status for each patient at each timepoint:

- Step 1. MRD positive by either ASO-PCR or flow = MRD positive
- Step 2. A sample not MRD positive by Step 1, and MRD negative by ASO-PCR and/or flow = MRD negative
- Step 3. MRD undetermined by both ASO-PCR and flow = MRD positive

In addition, patients for whom no post-baseline MRD assessment was available at a specific time point were considered “MRD positive" for that particular time point. These measures ensure a conservative approach for reporting MRD results in this study.

MRD doubling time analysis

The logistic model was based on a population-based clonal growth model using longitudinal MRD assessment data post-end of treatment (EOT). The EOT MRD level below the limit of detection was simulated for each individual, based on the MRD model and the identified covariates. This model is longitudinal in nature and was developed considering both measurable and unmeasurable data, in a way that the entire MRD dynamic at, and post-EOT could be simulated numerically, including samples that were below the limit of detection. Prognostic markers and patient demographics were screened as covariates for impact on key model parameters, based on statistical and graphical assessments. Variables with >20% missing data or with low representation (<10% in any category) were excluded.

Individual MRD regrowth trajectories post-EOT were simulated based on the parameter estimates and the identified covariates from the MRD model. Doubling time was derived from the MRD regrowth trajectory for each patient, defined as the time needed to double the estimated MRD value at the first post-EOT MRD sample.

Supplementary results

Progression-free survival (PFS) disease growth amongst patients with undetectable (u)MRD at EOT by immunoglobulin heavy chain gene (IGHV) mutation status

Among patients with mutated IGHV disease in the venetoclax plus rituximab (VenR) arm who achieved uMRD status at EOT, only one PFS event (4.3%) was recorded, compared with 21 PFS events (37.5%) in patients with unmutated IGHV disease achieving the same landmark depth of response. The median PFS for those with unmutated IGHV disease was 39.7 months (95% confidence interval [CI]: 29.0, not evaluable [NE]). Median PFS in patients with mutated IGHV disease was not reached (NR; supplemental Figure 4A). Time to MRD relapse was similar for both mutated and unmutated IGHV groups, with a median time from EOT to MRD conversion of 22.6 months (95% CI: 8.1, NE) and 18.2 months (95% CI: 8.4, 28.0), respectively (supplemental Figure 4B). Those with mutated IGHV disease, however, demonstrated a slower rate of disease progression manifestation (by International Workshop Group on CLL [iwCLL] criteria) following MRD conversion compared with those with unmutated IGHV disease: median time to progressive disease from MRD conversion was NR among the mutated IGHV group vs 20.7 months (95% CI: 14.7, 25.6) for the unmutated IGHV group (supplemental Figure 4C).

Patients treated with VenR who are able to achieve uMRD at EOT have already demonstrated durable, long-term responses. These data indicate that this long-term PFS benefit is stratified by unmutated IGHV status, with those with mutated IGHV disease having the most durable benefit.

Supplemental Table 1. Baseline disease characteristics by MRD response status* at the EOT visit in VenR-treated patients with completed 2 years of PFS

Characteristic, n (%)	uMRD n = 83	Low-MRD+ n = 23	High-MRD+ n = 12
Time from first diagnosis (years), n	83	23	12
Mean (SD)	7.37 (5.34)	8.50 (5.00)	7.11 (3.85)
Median (range)	5.80 (0.5–28.4)	7.12 (0.8–19.7)	6.07 (1.4–13.9)
ECOG performance status	83	23	12
0	46 (55.4)	18 (78.3)	8 (66.7)
≥1	37 (44.6)	5 (21.7)	4 (33.3)
Fludarabine-refractory†	82	22	11
Yes	9 (11.0)	2 (9.1)	2 (18.2)
No	73 (89.0)	20 (90.9)	9 (81.8)
Creatinine clearance‡	83	23	12
<50 mL/min	1 (1.2)	1 (4.3)	1 (8.3)
≥50 mL/min	82 (98.8)	22 (95.7)	11 (91.7)
Baseline TLS risk	83	23	12
High	23 (27.7)	3 (13.0)	5 (41.7)
Medium	46 (55.4)	14 (60.9)	6 (50.0)
Low	14 (16.9)	6 (26.1)	1 (8.3)
Bulky disease (lymph nodes with the largest diameter)	76	21	12
<5 cm	37 (48.7)	17 (81.0)	7 (58.3)
≥5 cm	39 (51.3)	4 (19.0)	5 (41.7)
<10 cm	64 (84.2)	20 (95.2)	10 (83.3)
≥10 cm	12 (15.8)	1 (4.8)	2 (16.7)
Absolute lymphocyte count	83	23	12
<25 x 10^9/L	26 (31.3)	6 (26.1)	3 (25.0)

≥25 x 10^9/L	57 (68.7)	17 (73.9)	9 (75.0)
<100 x 10^9/L	60 (72.3)	17 (73.9)	9 (75.0)
≥100 x 10^9/L	23 (27.7)	6 (26.1)	3 (25.0)
Presence of B-symptoms	83	23	12
Fever	1 (1.2)	0	0
Night sweats	26 (31.3)	11 (47.8)	1 (8.3)
Weight loss	4 (4.8)	1 (4.3)	0
del(17p) status	58	19	9
Not deleted	54 (93.1)	18 (94.7)	6 (66.7)
Deleted	4 (6.9)	1 (5.3)	3 (33.3)
Stratification factor: risk status (derived)[§]	83	23	12
High	49 (59.0)	7 (30.4)	7 (58.3)
Low	34 (41.0)	16 (69.6)	5 (41.7)
IGHV mutation status	82	21	11
Mutated	23 (28.0)	7 (33.3)	3 (27.3)
Unmutated	56 (68.3)	13 (61.9)	8 (72.7)
Unknown	3 (3.7)	1 (4.8)	0
TP53 mutation status	82	23	12
Mutated	13 (15.9)	4 (17.4)	4 (33.3)
Unmutated	69 (84.1)	19 (82.6)	8 (66.7)
Beta-2 microglobulin	81	23	11
≤3.5 mg/L	26 (32.1)	11 (47.8)	6 (54.5)
>3.5 mg/L	55 (67.9)	12 (52.2)	5 (45.5)
Number of prior cancer therapies	83	23	12
1	51 (61.4)	18 (78.3)	5 (41.7)
2	26 (31.3)	4 (17.4)	3 (25.0)
≥3	6 (7.2)	1 (4.3)	4 (33.3)

Note: Patients with missing results are not included in the summary.

ASO-PCR, allele-specific oligonucleotide polymerase chain reaction; del(17p), chromosome 17p deletion; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; IGHV, immunoglobulin heavy chain gene; MRD, minimal residual disease; PFS, progression-free survival; SD, standard deviation; TLS, tumor lysis syndrome; uMRD, undetectable minimal residual disease; Ven, venetoclax; VenR, venetoclax-rituximab.

*MRD blood response status was derived from combining ASO-PCR and flow cytometry results; [†]per investigator assessment. Indicating not fludarabine-refractory did not mean patients were exposed to fludarabine; [‡]based on Cockcroft–Gault formula; [§]high-risk status was defined as having ANY of the following features: del(17p), or no response to front-line chemotherapy-containing regimen, or relapsed disease within 12 months after chemotherapy alone or within 24 months after chemoimmunotherapy. All others were considered to be of low-risk status. One patient in the VenR arm and two patients in the BR arm had an unknown or missing risk status.

Supplemental Table 2. MRD growth model covariates: baseline variables available for covariate testing from the 211 included patients

Baseline Variables	Definition	% of missing	Lowest patient number in certain category	Corresponding status of the category	Exclusion Flag 1	Exclusion Flag 2
SCREENING	MRD level at screening	0	NA	NA	0	0
ARM	Treatment arm	0	91	VenR	0	0
IGHV	IGHV mutation status	8.1	55	Mutated	0	0
P17/*TP53*	del(17p)/*TP53* mutation status	1.4	51	Mutated	0	0
AGE	Age	0	NA	NA	0	0
SEX	Gender	0	55	Female	0	0
BWT	Body weight	0.5	NA	NA	0	0
ATM	*ATM* mutation status	32.2	36	Mutated	0	1
BIRC3	*BIRC3* mutation status	32.3	7	Mutated	1	1
NFKBIE	*NFKBIE* mutation status	32.2	12	Mutated	1	1
NOTCH1	*NOTCH1* mutation status	32.2	31	Mutated	0	1
TP53	*TP53* mutation status	3.3	40	Mutated	0	0
SF3B1	*SF3B1* gene mutation	32.2	23	Mutated	0	1
XPO1	*XPO1* mutation	32.2	22	Mutated	0	1
COMP3	Complex karyotype with ≥3 abnormalities	24.6	45	Abnormal	0	1
COMP5	Complex karyotype with ≥5 abnormalities	24.6	12	Abnormal	1	1
aCGH17p13	deletion of 17p13 by aCGH	24.6	15	Mutated	1	1
FISH17p	deletion of 17p by FISH	0	34	Mutated	0	0
CH11QDLC	Chromosome 11q deletion	9.5	67	Abnormal	0	0
CH12TRIC	Trisomy 12	9.5	35	Abnormal	0	0
MS13QDLC	Monosomy 13q deletion	9.5	52	Abnormal	0	0

NS13QDLC	Nullisomy 13q deletion	9.5	65	Abnormal	0	0
CH13QDLC	Chromosome 13q deletion	9.5	40	Abnormal	0	0
RSP	Responder (PR/CR) or non-responder (PD/SD) to treatment	0.5	28	Responder	0	0
TLS	Tumor lysis syndrome risk category	0	60	High risk	0	0
CLLPRLN	Prior line of CLL therapy category	0	75	≥2 prior lines of therapy	0	0

Exclusion Flag 1 was set to 1 if the lowest number of patients in a certain category for a binary outcome was lower than or equal to 10% of the study population, which was 21 patients; Exclusion Flag 2 was set to 1 if the missing data exceeded 20%; The covariate screening used the variables with Exclusion Flag 1 & 2 = 0. “Lowest patient number in certain Category” and “Corresponding Status of the Category” were set to NA for the continuous covariates; TLS risk category and CLLPRLN were dichotomized into binary variables before the analysis.

aCGH, array comparative genomic hybridization; ATM, ataxia telangiectasia mutated; CLL, chronic lymphocytic leukemia; CR, complete response; del(17p), chromosome 17p deletion; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy chain gene; MRD, minimal residual disease; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; VenR, venetoclax-rituximab.

Supplemental Table 3. Multivariate Cox analysis for PFS among the patients who 2 years of Ven therapy without PD and who had a valid MRD assessment at EOT (n = 118)

Effect/covariate included in the model	Degrees of freedom	Parameter estimate (standard error)	HR (95% CI)	*P* value*
MRD status at EOT (reference: positive, n = 35)				
Negative, n = 83	1	−1.59197 (0.310)	0.20 (0.11, 0.37)	< .0001
Age at screening (reference: <65 years, n = 60)				
≥65 years, n = 58	1	−0.40333 (0.327)	0.67 (0.35, 1.27)	.2181
Baseline IGHV (reference: unmut, n = 77)	2			.0214
Mut, n = 33	1	−1.49031 (0.546)	0.23 (0.08, 0.66)	.0063
Other*, n = 8	1	−0.45325 (0.544)	0.64 (0.22, 1.84)	.4045
TLS risk at screening (reference: high, n =31)				
Low/medium, n = 87	1	−0.46762 (0.326)	0.63 (0.33, 1.19)	.1518
TP53 (reference: mut, n = 21)	1			.1819
Unmut, n = 96	1	−0.46358 (0.347)	0.63 (0.32, 1.24)	.1819
Other*, n = 1	0	0.00000 (NE)	NE (NE, NE)	NE

Grade 3–4 AEs with ≥2% difference in incidence rate between treatment arms within the safety evaluable population are shown. Treatment-emergent AEs and AEs reported in the post-treatment period are included. Multiple occurrences of the same AE in an individual are counted only once on individual rows.

AE, adverse event; CI, confidence interval; EOT, end of treatment; HR, hazard ratio; IGHV, immunoglobulin heavy chain gene; TLS, tumor lysis syndrome; MRD, minimal residual disease; mut, mutated; NE, not estimable; PD, progressive disease; PFS, progression-free survival; unmut, Unmutated; ven, venetoclax.

*Missing/unknown/undetermined.

Supplemental Table 4. ORR* to subsequent BTKi-based therapy or Ven-based therapy in evaluable patients with PD following initial treatment in MURANO.

	VenR arm (n = 67)	BR arm (n = 123)
Response to Ven-based subsequent therapy†		
Evaluable patients overall	**n = 18**	**n = 10**
Best ORR	13 (72.2)	8 (80.0)
CR/CRi	1 (5.6)	3 (30.0)
PR/nPR	12 (66.7)	5 (50.0)
SD	1 (5.6)	1 (10.0)
PD	2 (11.1)	1 (10.0)
Non-responder	2 (11.1)	0
Patients with unmut-IGHV‡	**n = 17**	**n = 4**
ORR	12 (70.6)	4 (100)
CR	1 (5.9)	1 (25.0)
PR/nPR	11 (64.7)	3 (75.0)
Patients with mut-IGHV‡	**n = 0**	**n = 3**
ORR	NA	1 (33.3)
CR	NA	0
PR/nPR	NA	1 (33.3)
Response to BTKi-based subsequent therapy§		
	n = 14	**n = 56**
Best ORR	14 (100)	47 (83.9)
CR/CRi	1 (7.1)	9 (16.1)
PR/nPR	13 (92.9)	38 (67.9)
SD	0	5 (10.7)
PD	0	3 (5.4)
Patients with unmut-IGHV¶	**n = 8**	**n = 41**
ORR	8 (100)	33 (80.5)
CR	0	7 (17.1)
PR/nPR	8 (100)	26 (63.4)
Patients with mut-IGHV¶	**n = 4**	**n = 10**
ORR	4 (100)	90 (90.0)
CR	1 (25.0)	2 (20.0)
PR/nPR	3 (75.0)	7 (70.0)

Values are n (%)

*Best ORR, median treatment duration and number of patients remaining on therapy were calculated among patients with evaluable responses; responses were classed as evaluable if they were reported by the investigators prior to discontinuation or initiation of subsequent line of therapy. Responses in patients who were treated with their next line of therapy for insufficient time to have their response assessed, or those patients who had no response assessments reported, were considered unevaluable; †Median (range) treatment duration 11.4 (0.7–37.6) months in the VenR arm and 13.5

(0.2–30.7) months in the BR arm; ‡IGHV status not available for 1 patient (nPR) in the VenR arm and 3 patients in the BR arm (2 CR and 1 PR); §Median (range) treatment duration 21.9 (5.6–59.2) months in the VenR arm and 26.6 (0–50.4) months in the BR arm; ¶IGHV status not available for 2 patients in the VenR arm (2 PR) and 5 patients in the BR arm (5 PR).

CR, complete response; CRi, complete response with incomplete bone marrow recovery; PR, partial response; nPR, nodular partial response; SD, stable disease.

Supplemental Table 5. Overview of safety data from the MURANO trial for both study arms (clinical cutoff date: May 8, 2020)

AE, n (%)	VenR n = 194	BR n = 188
Grade 3–4 AEs		
Neutropenia	115 (59.3)	76 (40.4)
Anemia	21 (10.8)	26 (13.8)
Thrombocytopenia	12 (6.2)	19 (10.1)
Febrile neutropenia	7 (3.6)	18 (9.6)
Pneumonia	10 (5.2)	15 (8.0)
Infusion-related reaction	4 (2.1)	10 (5.3)
Tumor lysis syndrome*	6 (3.1)	2 (1.1)
Hyperglycemia	4 (2.1)	0
Hypotension	0	5 (2.7)
Hypogammaglobulinemia	4 (2.1)	0
Richter's transformation	7 (3.6)	6 (3.2)
Second primary malignancies†	30 (15.5)	24 (12.8)
Basal cell carcinoma	9 (4.6)	5 (2.7)
Squamous cell carcinoma of skin	8 (4.1)	2 (1.1)
Squamous cell carcinoma	2 (1.0)	4 (2.1)
Myelodysplastic syndrome	3 (1.5)	1 (0.5)
Metastatic malignant melanoma	2 (1.0)	1 (0.5)
Malignant melanoma	1 (0.5)	1 (0.5)
Acute myeloid leukemia	1 (0.5)	1 (0.5)
Colorectal cancer	2 (1.0)	0
Adenocarcinoma of colon	0	1 (0.5)

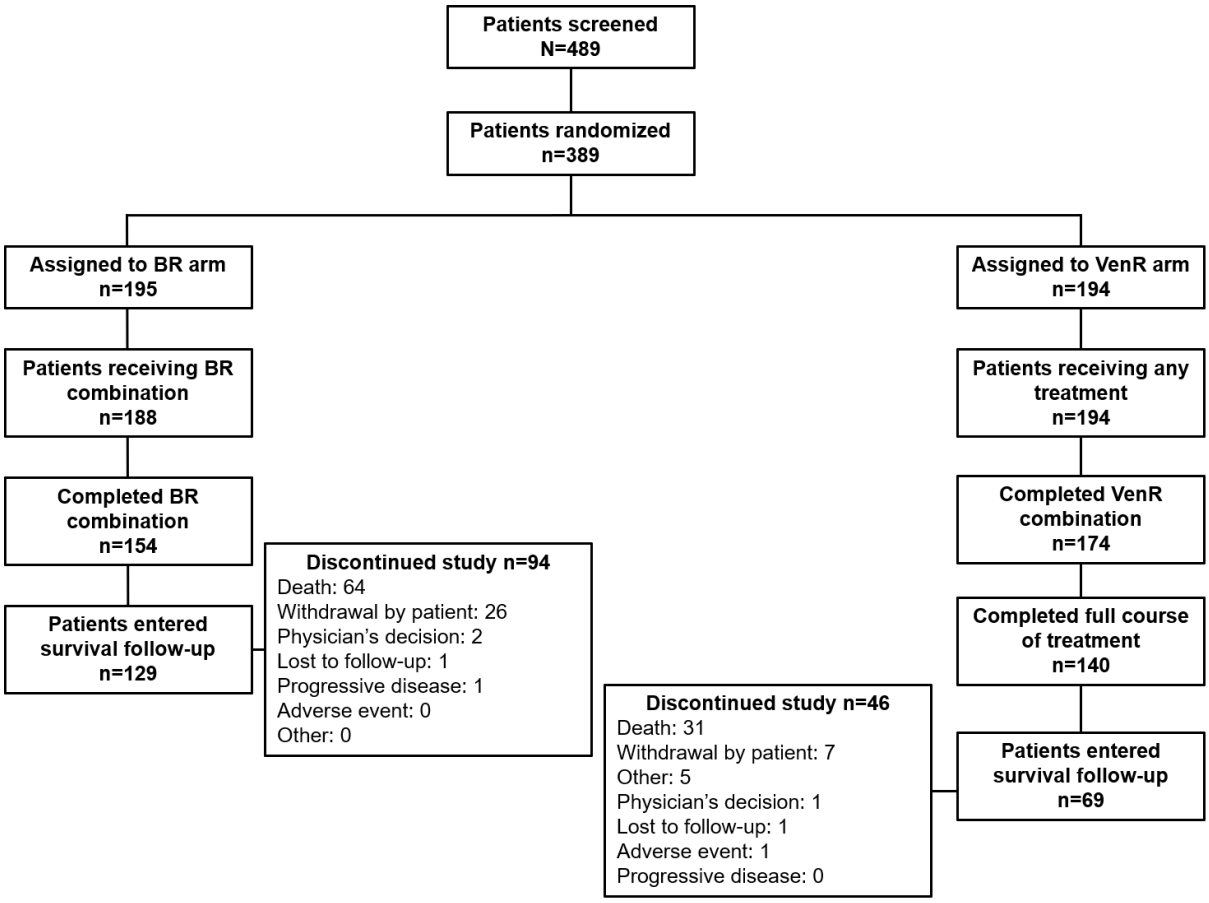
Colorectal adenocarcinoma	0	1 (0.5)
Colon cancer	1 (0.5)	0
Lung neoplasm malignant	0	2 (1.1)
Prostate cancer	1 (0.5)	1 (0.5)
Adenocarcinoma gastric	1 (0.5)	0
Breast cancer	1 (0.5)	0
Keratoacanthoma	1 (0.5)	0
Lung adenocarcinoma stage III	1 (0.5)	0
Lymphoma	0	1 (0.5)
Medullary thyroid cancer	0	1 (0.5)
Metastases to lung	0	1 (0.5)
Metastasis	1 (0.5)	0
Pancreatic carcinoma	1 (0.5)	0
Plasma cell myeloma	1 (0.5)	0
Skin squamous cell carcinoma recurrent	0	1 (0.5)
Transitional cell carcinoma	0	1 (0.5)

Grade 3–4 AEs with ≥2% difference in incidence rate between treatment arms within the safety evaluable population are shown. Treatment-emergent AEs and AEs reported in the post-treatment period are included. Multiple occurrences of the same AE in an individual are counted only once on individual rows.

AE, adverse event; BR, bendamustine-rituximab; TLS, tumor lysis syndrome; VenR, venetoclax-rituximab.

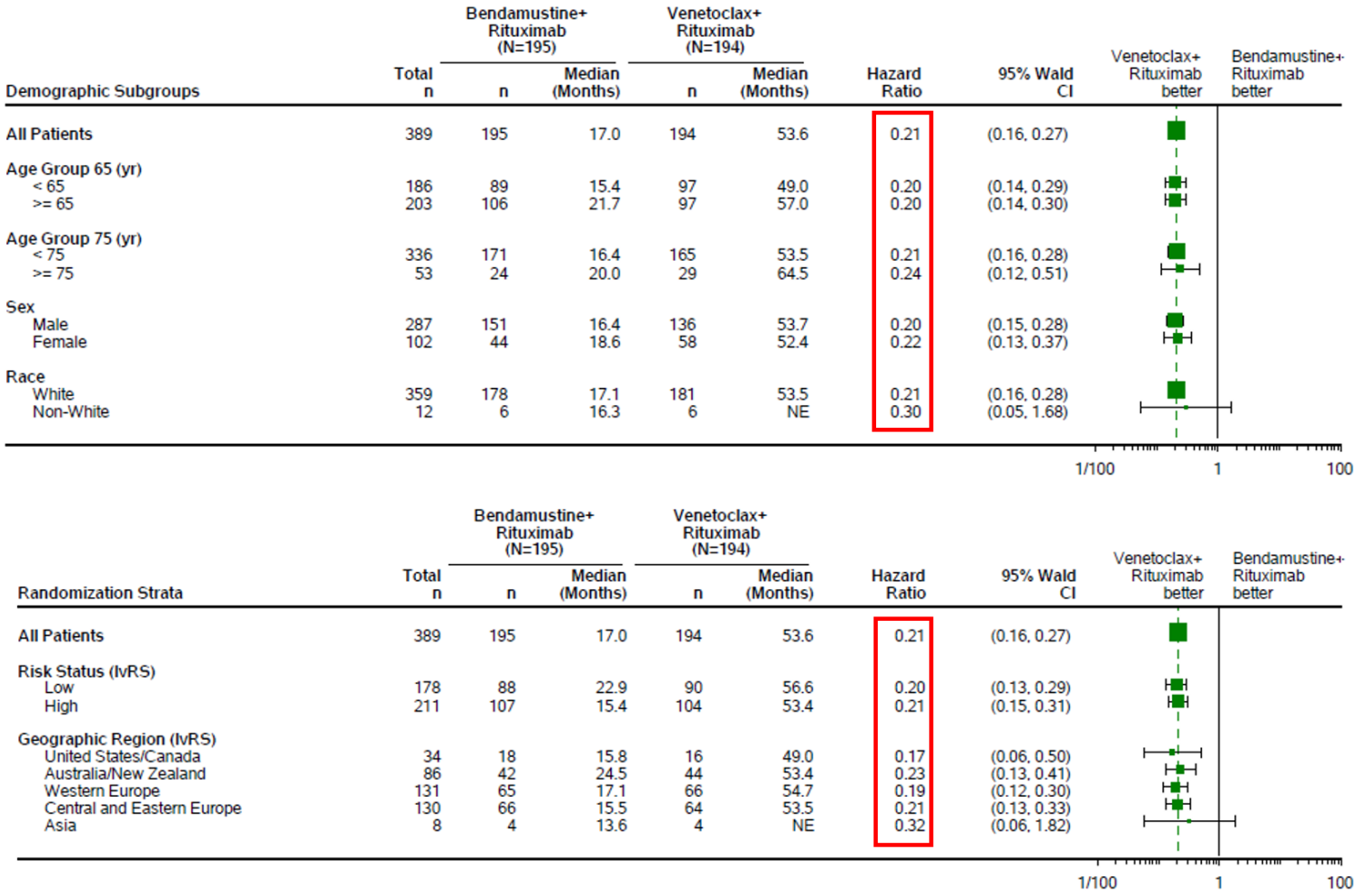
*Laboratory-confirmed TLS; †any grade reported.

Supplemental Figure 1. Patient disposition through the study and 5-year follow-up.

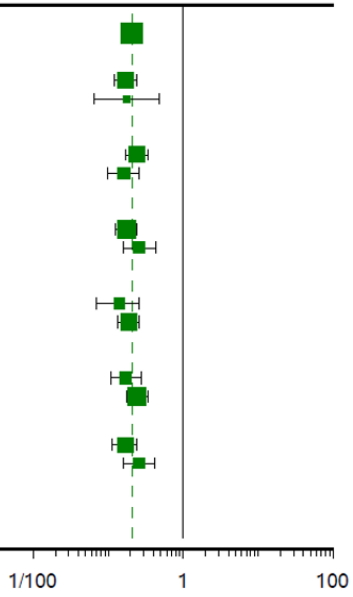


BR, bendamustine-rituximab; VenR, venetoclax-rituximab.

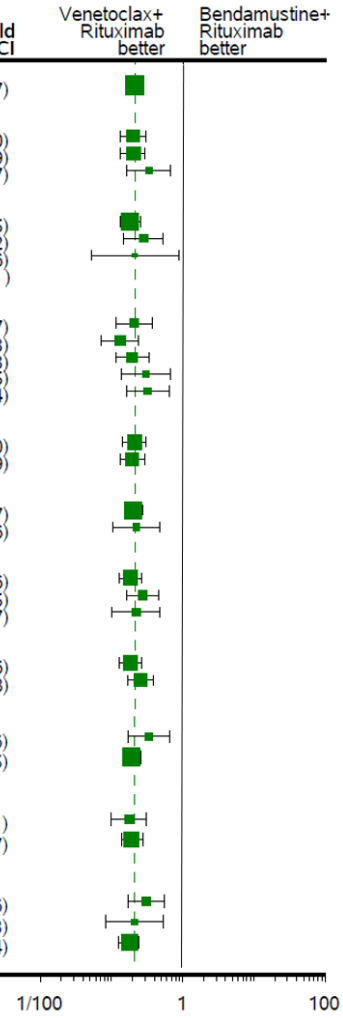
Supplemental Figure 2. Forest plots for investigator-assessed PFS subgroup analyses: demographics; stratification factors; biomarkers; and baseline characteristics.



Biomarker	Total n	Bendamustine+ Rituximab (N=195) n	Median (Months)	Venetoclax+ Rituximab (N=194) n	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	389	195	17.0	194	53.6	0.21	(0.16, 0.27)
Chromosome 17p Deletion (by aCGH)							
Normal	249	124	19.6	125	56.6	0.17	(0.12, 0.24)
Abnormal	39	22	7.8	17	29.5	0.18	(0.07, 0.48)
Chromosome 11q Deletion							
Normal	217	105	22.1	112	53.7	0.24	(0.17, 0.34)
Abnormal	125	64	15.7	61	53.8	0.16	(0.10, 0.26)
p53 Mutation							
Unmutated	276	132	20.5	144	54.7	0.18	(0.13, 0.24)
Mutated	99	51	12.9	48	37.4	0.26	(0.16, 0.43)
Baseline IgVH Mutation Status							
Mutated	104	51	24.2	53	NE	0.14	(0.07, 0.26)
Unmutated	246	123	15.7	123	52.2	0.19	(0.13, 0.26)
Baseline Beta-2 Microglobulin							
<= 3.5 mg/L	123	59	16.3	64	NE	0.17	(0.11, 0.28)
> 3.5 mg/L	252	127	18.7	125	53.4	0.24	(0.18, 0.34)
p53 Mutation and/or 17p Deletion (by aCGH)							
Unmutated	202	98	19.6	104	56.6	0.17	(0.11, 0.25)
Mutated	108	55	13.4	53	37.4	0.26	(0.16, 0.42)

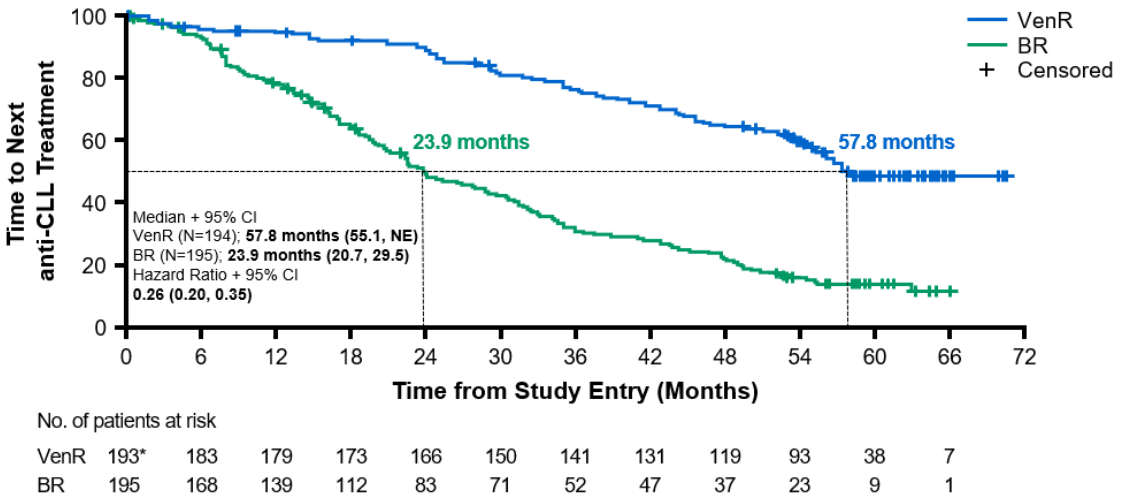


Baseline Characteristics	Total n	Bendamustine+ Rituximab (N=195) n	Bendamustine+ Rituximab (N=195) Median (Months)	Venetoclax+ Rituximab (N=194) n	Venetoclax+ Rituximab (N=194) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	389	195	17.0	194	53.6	0.21	(0.16, 0.27)
Renal Impairment Status							
Normal	157	78	14.2	79	53.0	0.20	(0.13, 0.30)
Mild	184	90	21.0	94	54.7	0.20	(0.13, 0.29)
Moderate	48	27	20.5	21	44.3	0.33	(0.16, 0.67)
Hepatic Impairment Status							
Normal	296	150	16.6	146	53.4	0.18	(0.13, 0.25)
Mild	74	37	17.1	37	53.8	0.28	(0.15, 0.52)
Moderate	18	7	15.4	11	NE	0.21	(0.05, 0.86)
Severe	1	1	33.9			NE	(NE , NE)
Rai Stage							
Stage 0	82	39	19.5	43	NE	0.20	(0.11, 0.37)
Stage 1	107	59	15.5	48	56.6	0.13	(0.07, 0.23)
Stage 2	104	56	21.2	48	53.5	0.19	(0.11, 0.33)
Stage 3	45	22	24.2	23	53.7	0.30	(0.14, 0.65)
Stage 4	51	19	14.1	32	44.6	0.32	(0.16, 0.64)
Bulky Disease (Lymph Nodes with the Largest Diameter)							
< 5 cm	197	97	16.6	100	53.8	0.21	(0.14, 0.30)
>= 5 cm	172	88	15.8	84	48.4	0.19	(0.13, 0.29)
Bulky Disease (Lymph Nodes with the Largest Diameter)							
< 10 cm	319	158	17.0	161	53.6	0.20	(0.15, 0.27)
>= 10 cm	50	27	13.5	23	41.7	0.22	(0.10, 0.46)
Number of Prior Regimens							
1	228	117	16.4	111	54.0	0.18	(0.13, 0.26)
2	101	43	21.2	58	53.5	0.27	(0.16, 0.45)
>=3	60	35	12.9	25	48.5	0.22	(0.10, 0.47)
Number of Prior Regimens							
1	228	117	16.4	111	54.0	0.18	(0.13, 0.26)
> 1	161	78	18.6	83	53.1	0.25	(0.17, 0.38)
Refractory vs. Relapse to Most Recent Prior Therapy							
Refractory	59	29	13.6	30	31.9	0.34	(0.17, 0.66)
Relapse	330	166	18.6	164	53.8	0.19	(0.14, 0.25)
Response Duration to Most Recent Prior Therapy							
< 12 Months	92	43	15.8	49	53.5	0.18	(0.10, 0.31)
>= 12 Months	238	123	19.6	115	54.0	0.19	(0.14, 0.27)
p53 Mutation High Low Clone							
High Clone (> 20%)	66	36	11.1	30	36.0	0.31	(0.17, 0.56)
Low Clone (5% to =< 20%)	33	15	15.2	18	47.9	0.21	(0.08, 0.53)
Unmutated	276	132	20.5	144	54.7	0.18	(0.13, 0.24)



aCGH, array comparative genomic hybridization; CI, confidence interval; IgHV, immunoglobulin heavy chain gene; IvRS, interactive voice response system; NE, not estimable; PFS, progression-free survival; yr, year.

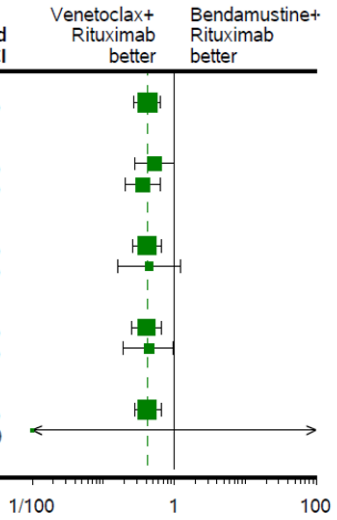
Supplemental Figure 3. Kaplan–Meier estimates of TTNT in the overall intent-to-treat population.



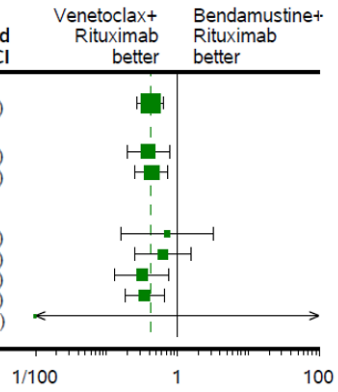
TTNT is defined as time from initiation of BR or VenR to next anti-CLL treatment, or death (whichever occurs first).†1 patient omitted due to invalid date for commencement of follow-up therapy. BR, bendamustine-rituximab; CI, confidence interval; CLL, chronic lymphocytic leukemia; NE, not estimable; TTNT, time to next treatment; VenR, venetoclax-rituximab.

Supplemental Figure 4. Forest plots for OS subgroup analyses: demographic; stratification factors; biomarkers; and baseline characteristics.

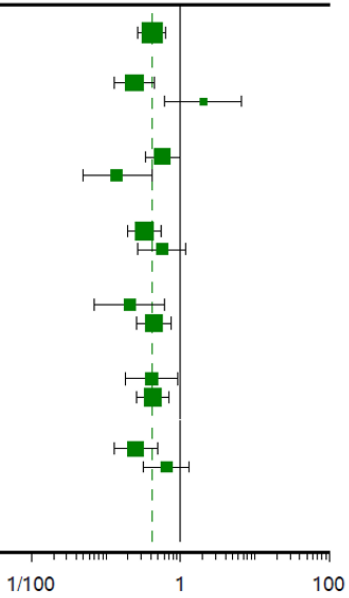
Demographic Subgroups	Total n	Bendamustine+ Rituximab (N=195) n	Bendamustine+ Rituximab (N=195) Median (Months)	Venetoclax+ Rituximab (N=194) n	Venetoclax+ Rituximab (N=194) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	389	195	NE	194	NE	0.42	(0.27, 0.64)
Age Group 65 (yr)							
< 65	186	89	NE	97	NE	0.53	(0.28, 1.01)
>= 65	203	106	NE	97	NE	0.36	(0.20, 0.64)
Age Group 75 (yr)							
< 75	336	171	NE	165	NE	0.41	(0.26, 0.65)
>= 75	53	24	NE	29	NE	0.44	(0.16, 1.22)
Sex							
Male	287	151	NE	136	NE	0.41	(0.25, 0.68)
Female	102	44	NE	58	NE	0.44	(0.19, 0.99)
Race							
White	359	178	NE	181	NE	0.42	(0.27, 0.66)
Non-White	12	6	NE	6	NE	<0.01	(0.00, NE)

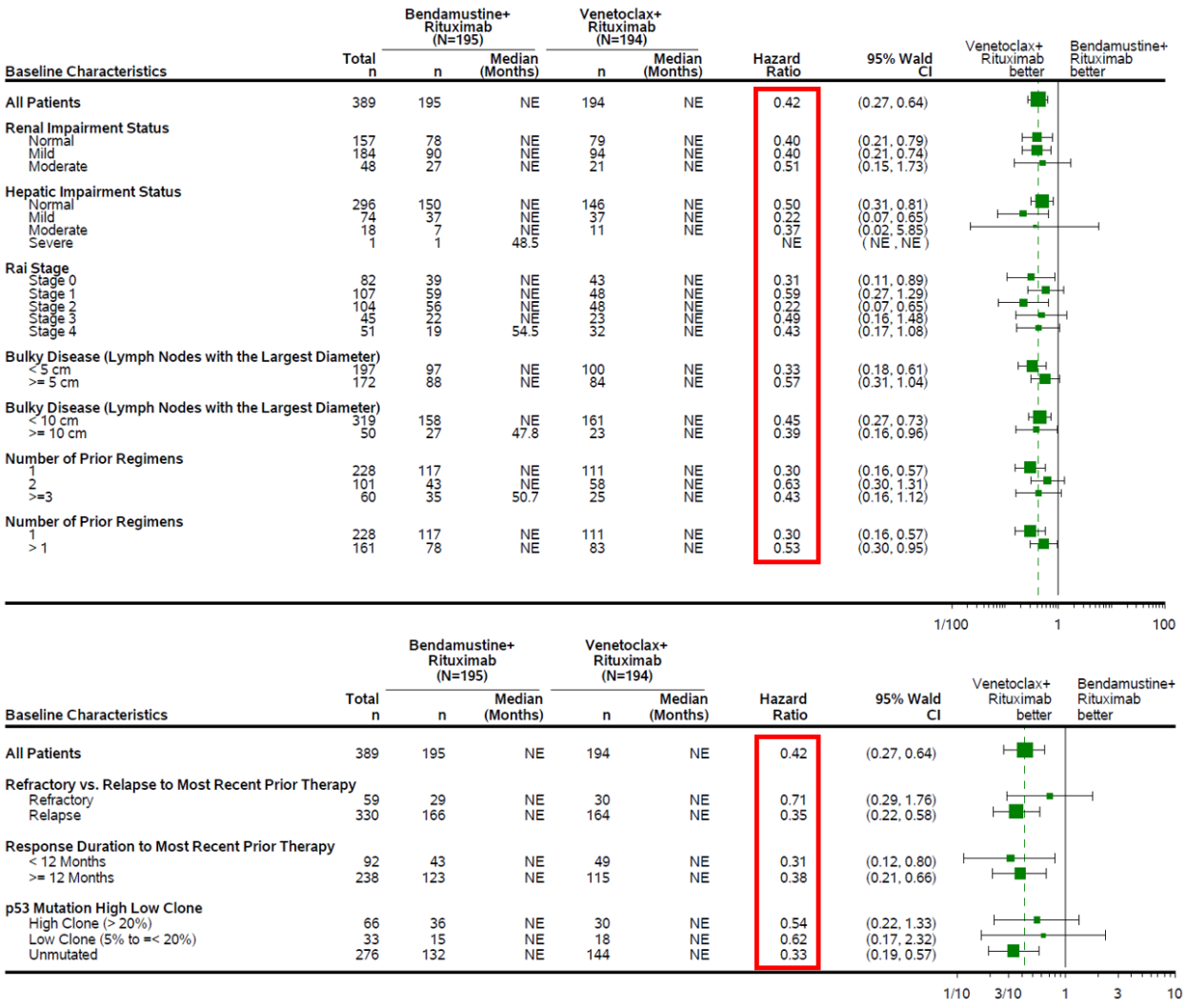


Randomization Strata	Total n	Bendamustine+ Rituximab (N=195) n	Bendamustine+ Rituximab (N=195) Median (Months)	Venetoclax+ Rituximab (N=194) n	Venetoclax+ Rituximab (N=194) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	389	195	NE	194	NE	0.42	(0.27, 0.64)
Risk Status (IvRS)							
Low	178	88	NE	90	NE	0.39	(0.20, 0.78)
High	211	107	NE	104	NE	0.43	(0.25, 0.74)
Geographic Region (IvRS)							
United States/Canada	34	18	NE	16	NE	0.72	(0.16, 3.24)
Australia/New Zealand	86	42	NE	44	NE	0.62	(0.25, 1.55)
Western Europe	131	65	NE	66	NE	0.32	(0.13, 0.75)
Central and Eastern Europe	130	66	53.0	64	NE	0.35	(0.19, 0.67)
Asia	8	4	NE	4	NE	<0.01	(0.00, NE)



Biomarker	Total n	Bendamustine+ Rituximab (N=195) n	Bendamustine+ Rituximab (N=195) Median (Months)	Venetoclax+ Rituximab (N=194) n	Venetoclax+ Rituximab (N=194) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	389	195	NE	194	NE	0.42	(0.27, 0.64)
Chromosome 17p Deletion (by aCGH)							
Normal	249	124	NE	125	NE	0.24	(0.13, 0.45)
Abnormal	39	22	NE	17	58.5	2.02	(0.61, 6.74)
Chromosome 11q Deletion							
Normal	217	105	NE	112	NE	0.57	(0.34, 0.98)
Abnormal	125	64	NE	61	NE	0.14	(0.05, 0.41)
p53 Mutation							
Unmutated	276	132	NE	144	NE	0.33	(0.19, 0.57)
Mutated	99	51	NE	48	NE	0.57	(0.27, 1.20)
Baseline IgVH Mutation Status							
Mutated	104	51	NE	53	NE	0.21	(0.07, 0.62)
Unmutated	246	123	NE	123	NE	0.45	(0.27, 0.76)
Baseline Beta-2 Microglobulin							
<= 3.5 mg/L	123	59	NE	64	NE	0.41	(0.18, 0.94)
> 3.5 mg/L	252	127	NE	125	NE	0.43	(0.26, 0.71)
p53 Mutation and/or 17p Deletion (by aCGH)							
Unmutated	202	98	NE	104	NE	0.25	(0.13, 0.50)
Mutated	108	55	NE	53	NE	0.66	(0.32, 1.34)

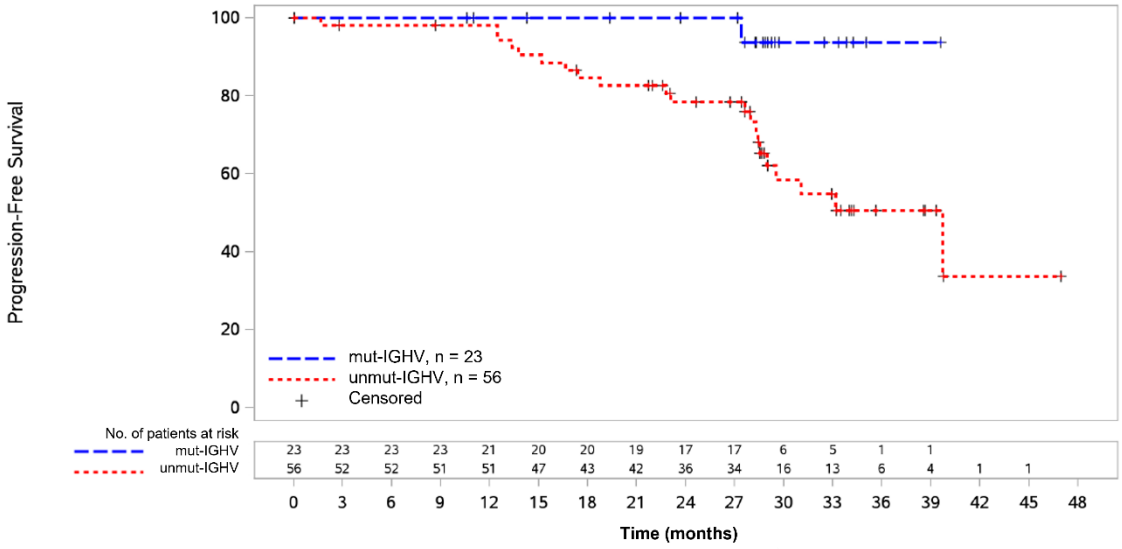




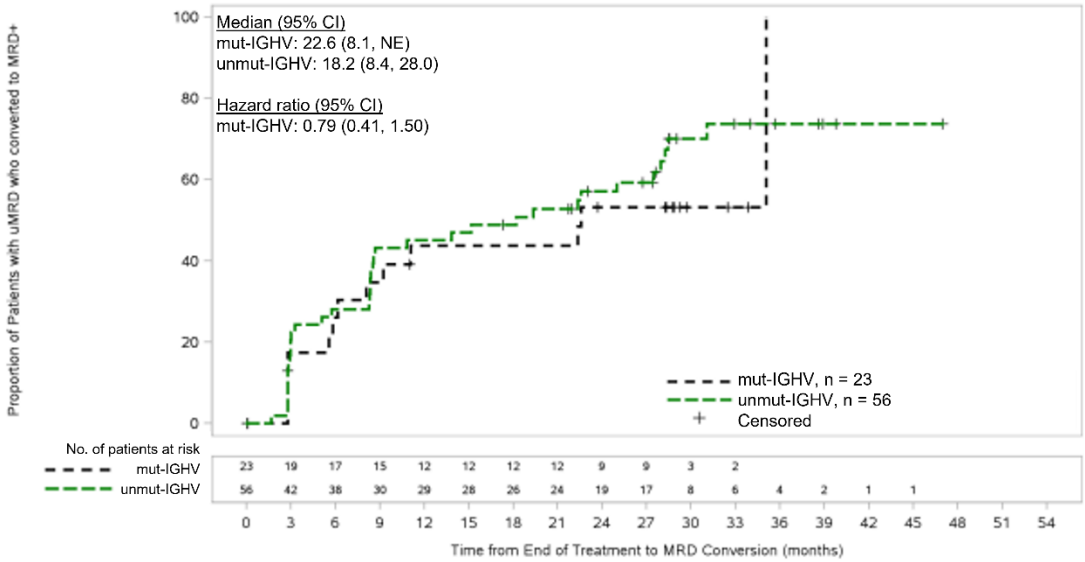
aCGH, array comparative genomic hybridization; CI, confidence interval; IgHV, immunoglobulin heavy chain gene; IvRS, interactive voice response system; NE, not estimable; OS, overall survival; yr, year.

Supplemental Figure 5. Kaplan–Meier estimates by IGHV status amongst patients in the VenR arm.

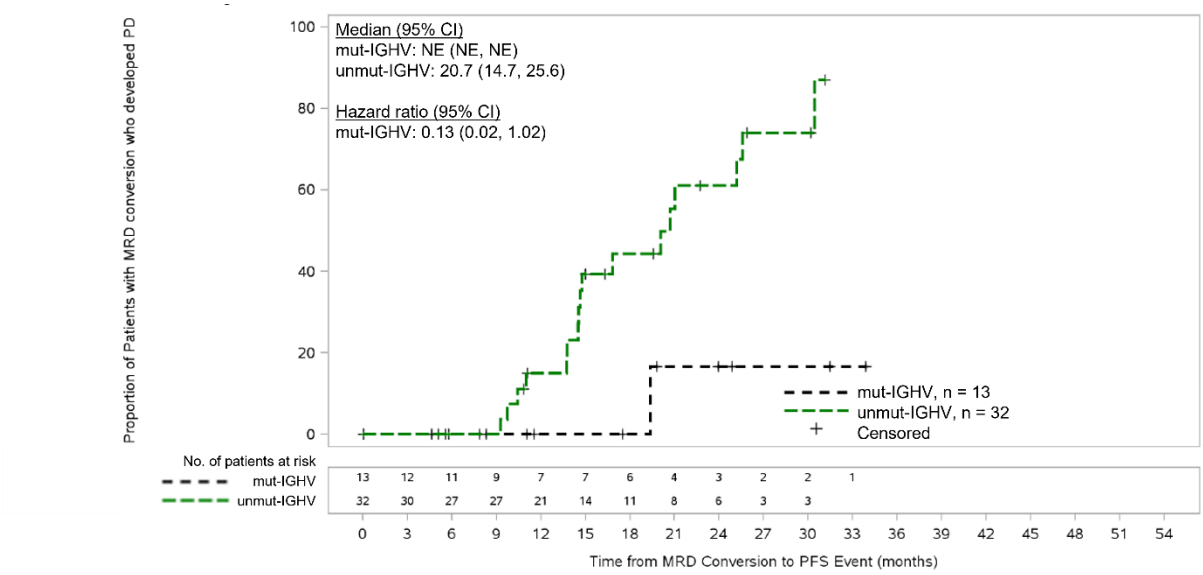
(A) Investigator-assessed PFS from EOT in patients with uMRD status at EOT



(B) Time from EOT to MRD conversion in patients with uMRD status at EOT

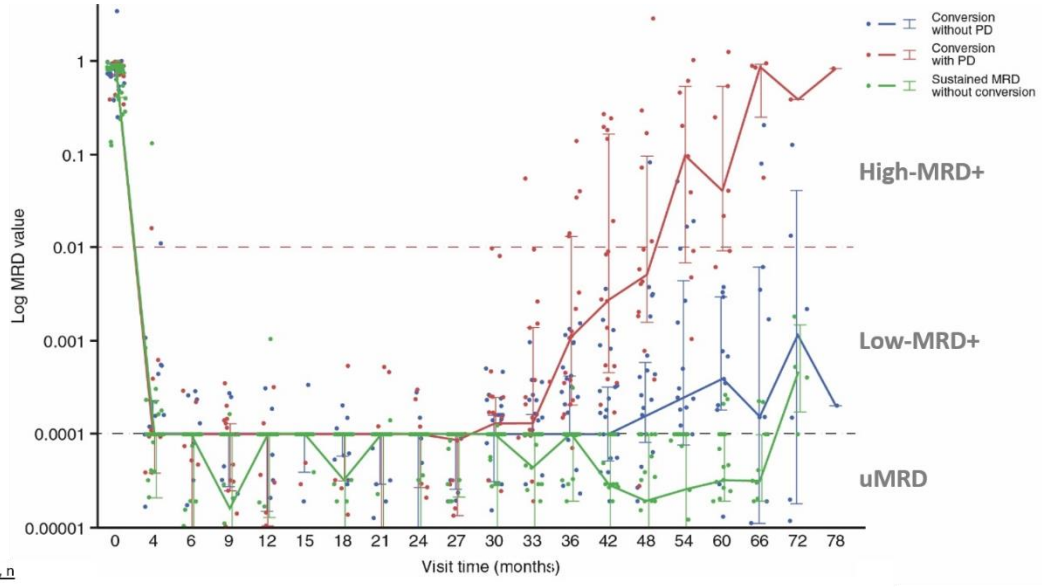


(C) Time from MRD conversion to PFS event



CI, confidence interval; EOT, end of treatment; IGHV, immunoglobulin heavy chain gene; MRD, minimal residual disease; mut, mutated; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; uMRD, undetectable minimal residual disease; unmut, unmutated; VenR, venetoclax-rituximab.

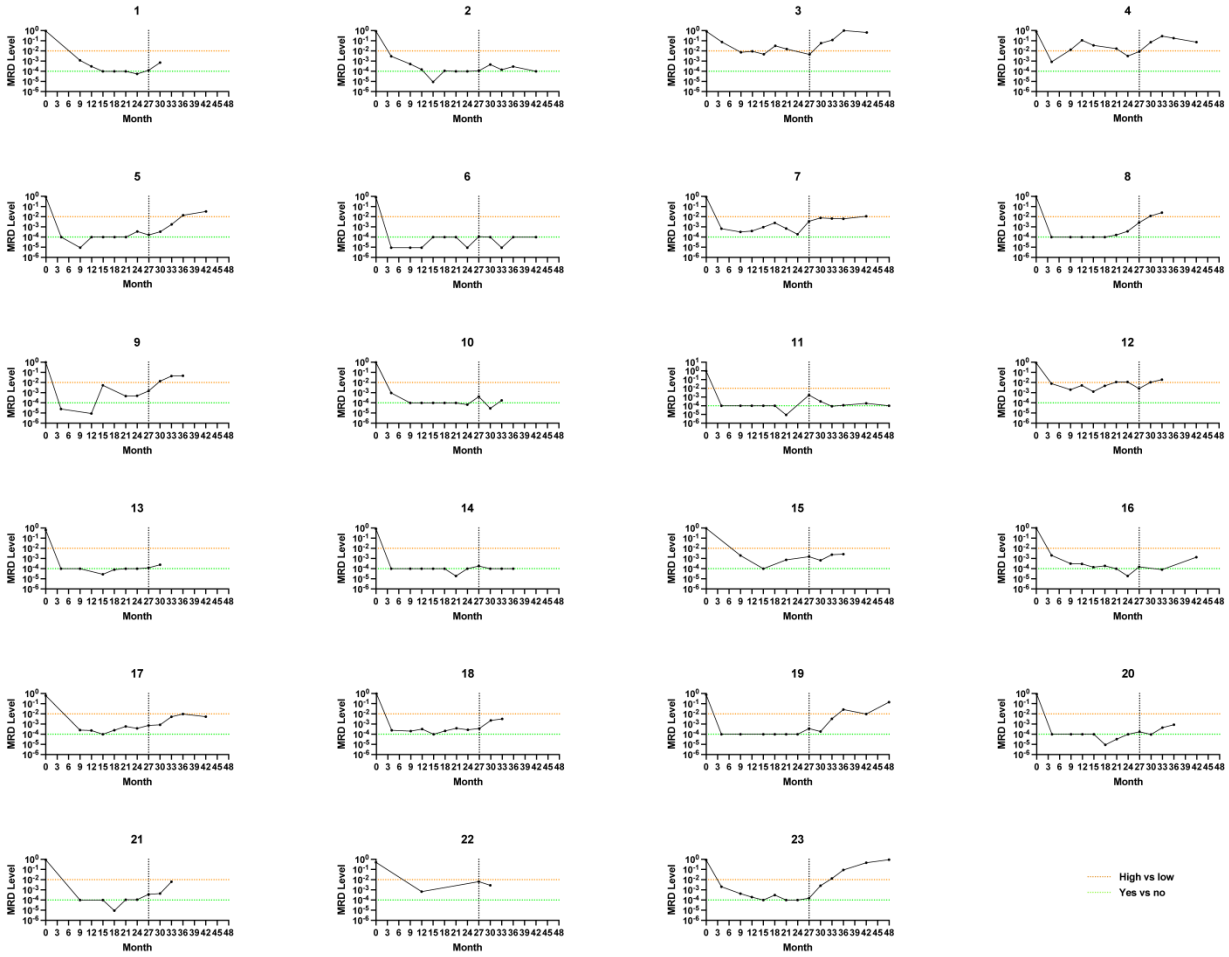
Supplemental Figure 6. MRD conversion plot by conversion/PD status (patients completing 2 years of VenR, with uMRD at EOT [n = 83]).



MRD conversion status, n																			
Conversion without PD	28	22	27	25	25	24	28	25	28	28	26	27	27	26	25	18	12	12	6	1
Conversion with PD	19	18	18	19	19	19	19	18	19	19	19	18	19	17	14	9	7	4	1	1
Sustained MRD without conversion	32	29	31	32	30	27	31	31	30	32	31	29	27	23	22	16	19	11	4	
Total	79	69	76	76	74	70	78	74	77	79	76	74	73	66	61	43	38	27	11	2

MRD shown as median and interquartile range. uMRD <1 CLL cell/10,000 leukocytes. EOT, end of treatment; MRD, minimal residual disease; PD, progressive disease; uMRD, undetectable minimal residual disease; VenR, venetoclax-rituximab.

Supplemental Figure 7. Pre-EOT MRD levels for the 23 patients with low-MRD+ at EOT.



Green line represents threshold for uMRD status ($<10^{-4}$); orange line represents threshold for low-MRD+ ($\leq 10^{-4}$ to $<10^{-2}$) to high-MRD+ ($\geq 10^{-2}$). EOT, end of treatment; MRD, minimal residual disease.