Supplemental data

Supplemental Table 1. Poststudy treatment.

Patient	Reason for study discontinuation	Poststudy treatment	Best response	Treatment notes and survival status
A	Withdrew consent	Ibrutinib	PR	Alive
B	Progressive disease; started new therapy	Idelalisib + rituximab + obinutuzumab (4 cycles for intensification)	PR	Alive
		Allogeneic SCT		
C	AE related to progression	Ibrutinib	PR	Discontinued treatment due to atrial fibrillation and start of anticoagulation
		Idelalisib	PR	Deceased; death due to CNS fungal infection
D	Progressive disease	Ibrutinib + rituximab (switched to ofatumumab)	PR	Switched from rituximab to ofatumumab due to serum sickness with rituximab. Deceased; progressed with Richter's transformation after ibrutinib failure
		Idelalisib + rituximab	No response	
E	Progressive disease	Ibrutinib	PR	Alive

F	Progressive disease (post-retreatment)	Ibrutinib	PR	Alive
G	Progressive disease	Zanubrutinib	PR	Alive[a]
		Venetoclax + ibrutinib	PR	
H	Progressive disease	Ibrutinib	PR	Alive
I	Progressive disease	Ibrutinib + cirmtuzumab	Unknown	Alive
J	AE (neuropathy)	Cirmtuzumab	Unknown	Alive
K	Progressive disease	Ibrutinib	Unknown	Alive

[a]Patient passed away due to disease progression after the 04 Jun 19 data cut.
Abbreviations: AE, adverse event; CNS, central nervous system; PR, partial remission; SCT, stem cell transplant.

Supplemental Table 2. Demographics in response subgroups.				
	Deep responders (achieved CR or uMRD)			**No CR or uMRD**
	Continuous Ven (n = 14)	**Limited-duration Ven (n = 19)**	**Total (N = 33)**	**Total (N = 16)**
Characteristic				
Age, median (range), years	65 (50–76)	68 (55–84)	66 (50–84)	71 (58–88)
ECOG performance status, n (%)				
0	6 (43)	12 (63)	18 (55)	7 (44)
1	8 (57)	7 (37)	15 (46)	9 (56)
Rai stage at diagnosis, n (%)				
0	5 (36)	5 (28)	10 (31)	1 (8)
1	3 (21)	10 (56)	13 (41)	2 (15)
2	2 (14)	1 (6)	3 (9)	2 (15)
3	1 (7)	0	1 (3)	3 (23)
4	3 (21)	2 (11)	5 (16)	5 (38)
Missing	0	1	1	3
ALC [× 10^9/L], n (%)				
<25	9 (64)	8 (42)	17 (52)	10 (62)
≥25 to <100	3 (21)	6 (32)	9 (27)	3 (19)
≥100	2 (14)	5 (26)	7 (21)	3 (19)
Bulky nodes, n (%)[a]				
≥5 cm	7 (50)	6 (32)	13 (39)	9 (56)
Genomic characteristics, n/N (%)[b]				
IGHV unmutated	2/7 (29)	10/14 (71)	12/21 (57)	7/7 (100)
TP53 mutation and/or del(17p)[d]	2/14 (14)	5/19 (26)	7/33 (21)	6/16 (37)
NOTCH1 mutated[c]	1/7 (14)	1/14 (7)	2/21 (10)	2/11 (18)
Cytogenetic abnormalities[d]				
17p deletion	2/13 (15)	4/19 (21)	6/32 (19)	3/15 (20)
11q deletion	7/13 (54)	5/19 (26)	12/32 (38)	8/14 (57)
Trisomy 12	3/13 (23)	4/18 (22)	7/31 (23)	6/14 (43)
13q deletion	8/13 (62)	9/19 (47)	17/32 (53)	6/14 (43)

[a]One patient with bulky disease; nodes = 10 cm.
[b]Percentages were calculated on nonmissing values.
[c]Analysis of *NOTCH1* mutations was completed only for the 34/49 patients who signed the additional informed consent for pharmacogenetic testing.
[d]Cytogenetic abnormalities by FISH are investigator reported.
Abbreviations: ALC, absolute lymphocyte count; BM, bone marrow; CR, complete response; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy-chain variable; MRD, minimal residual disease; uMRD, undetectable MRD; Ven, venetoclax.

Supplemental Table 3. Current status of patients re-treated with venetoclax.

	Patient 1	Patient 2	Patient 3	Patient 4
Time on initial therapy,[a] months	6.7	4.6	9.2	32.7
Time to first response, months	0.7	2.8	3.2	3.0
Best response on initial therapy	CR	CR	CRi	CR
Best MRD status (%)	MRD positive (1.2%)	uMRD	MRD positive (0.4%)	uMRD
Time off therapy, months (years)[b]	25.7 (2.1)	43.6 (3.6)	29.5 (2.5)	37.6 (3.1)
Time on retreatment, months (years)	18.9 (1.6)	18.7 (1.6)	40.3 (3.4)	0.5
Best response with retreatment	PR[c]	PR[d]	PR[d]	Pending[e]
Time to response post-retreatment, months[f]	1.0	10.6	1.0	NA
Bone marrow response with retreatment	10%	ND	ND	ND
Current status	Relapsed at 51.2 months; off study for another therapy	On therapy	On therapy	On therapy
Duration of venetoclax benefit, months (years)[g]	51.2 (4.3)	66.8 (5.6), ongoing	79.0 (6.6), ongoing	70.7 (5.9), ongoing

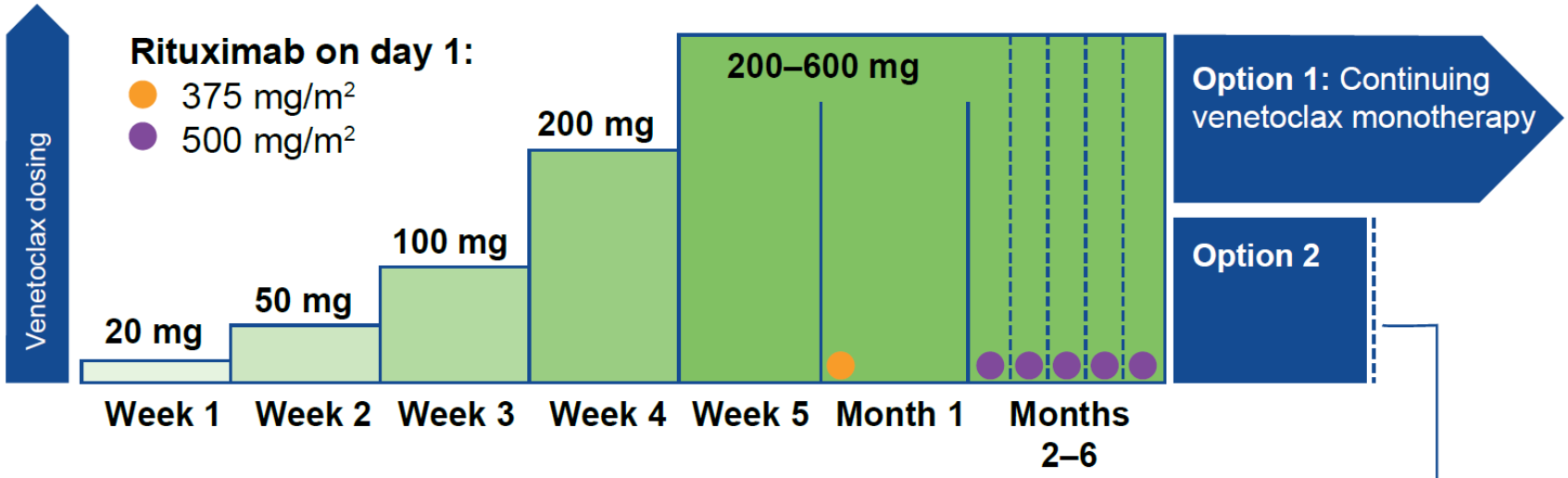
[a]Patients 1 and 3 discontinued venetoclax while under protocol amendment 1. Patient 2 discontinued venetoclax while under protocol amendment 3.
[b]Time from last dose of initial venetoclax monotherapy to first dose of venetoclax retreatment. Rituximab was added to retreatment at subsequent timepoints post-venetoclax retreatment as follows: 8.3 months, Patient 1; 2.8 months, Patient 2; 3.9 months, Patient 3. Patient 4 did not receive subsequent rituximab retreatment.

[c]PR met all CR criteria, except for 10% residual CLL in marrow.
[d]PR met all CR criteria, except no bone marrow testing was performed.
[e]Achieved PR after 6 months of retreatment; not included in formal data analysis, as outside data cutoff.
[f]Time from first dose of venetoclax retreatment to first response post-retreatment.
[g]Duration of venetoclax benefit is defined as time from study entry to venetoclax failure or death, or data cutoff (for patients in ongoing response), with venetoclax failure defined as either PD during ongoing venetoclax therapy (retreatment), or failure to respond to retreatment.
Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete marrow recovery; MRD, minimal residual disease; ND, not determined; PD, progressive disease; PR, partial response; uMRD, undetectable MRD.

Supplemental Table 4. Secondary malignancies.	
	After 2 years of treatment All patients n = 21[a]
Prostate	2 (10)
Squamous cell carcinoma	2 (10)
Basal cell carcinoma[b]	1 (5)
Melanoma[b]	1 (5)

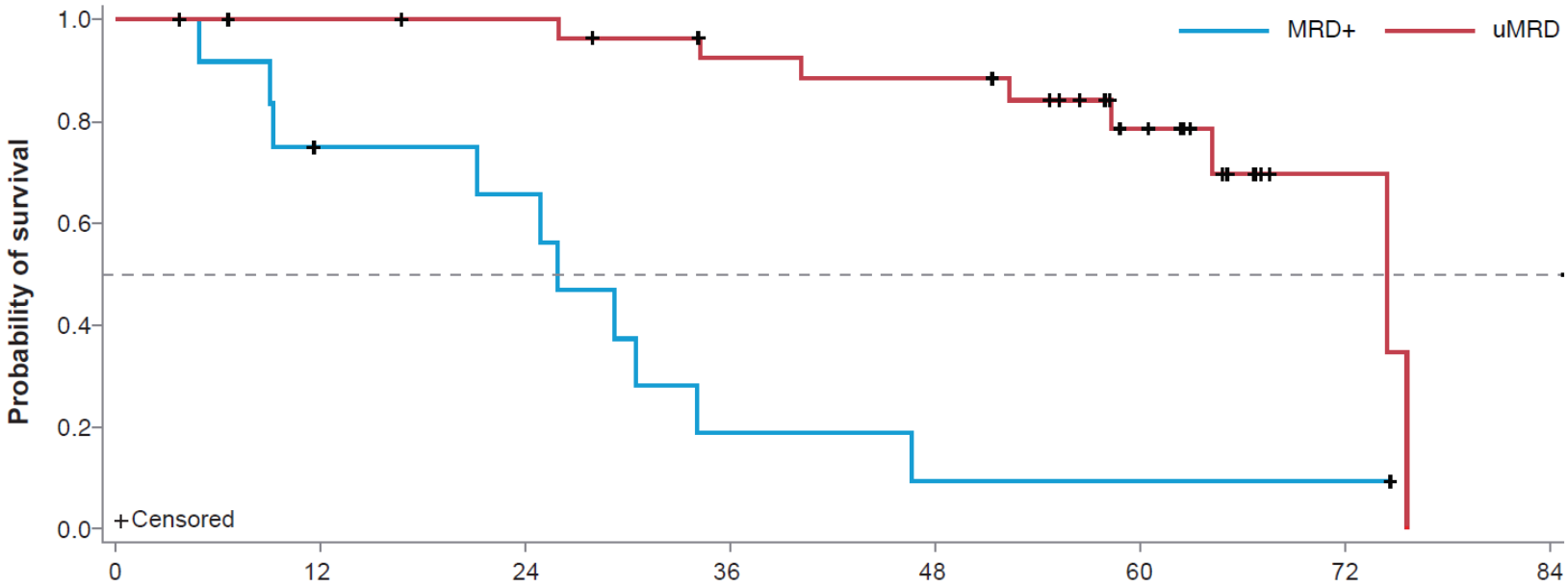
[a]Patients with >2 years of venetoclax treatment, including patients who discontinued venetoclax.
[b]Reported in same patient.

Supplemental Figure 1. Study design. CR, complete response; uMRD, undetectable minimal residual disease.



- **Option 2:** Treating physicians had the option to discontinue active venetoclax treatment if patient had a CR or CRi (irrespective of MRD status), or PR with uMRD

Supplemental Figure 2. Duration of response for patients who achieved uMRD at any time on study (red line) and those who remained MRD positive (blue line). MRD, minimal residual disease; MRD+, detectable MRD; uMRD; undetectable MRD.

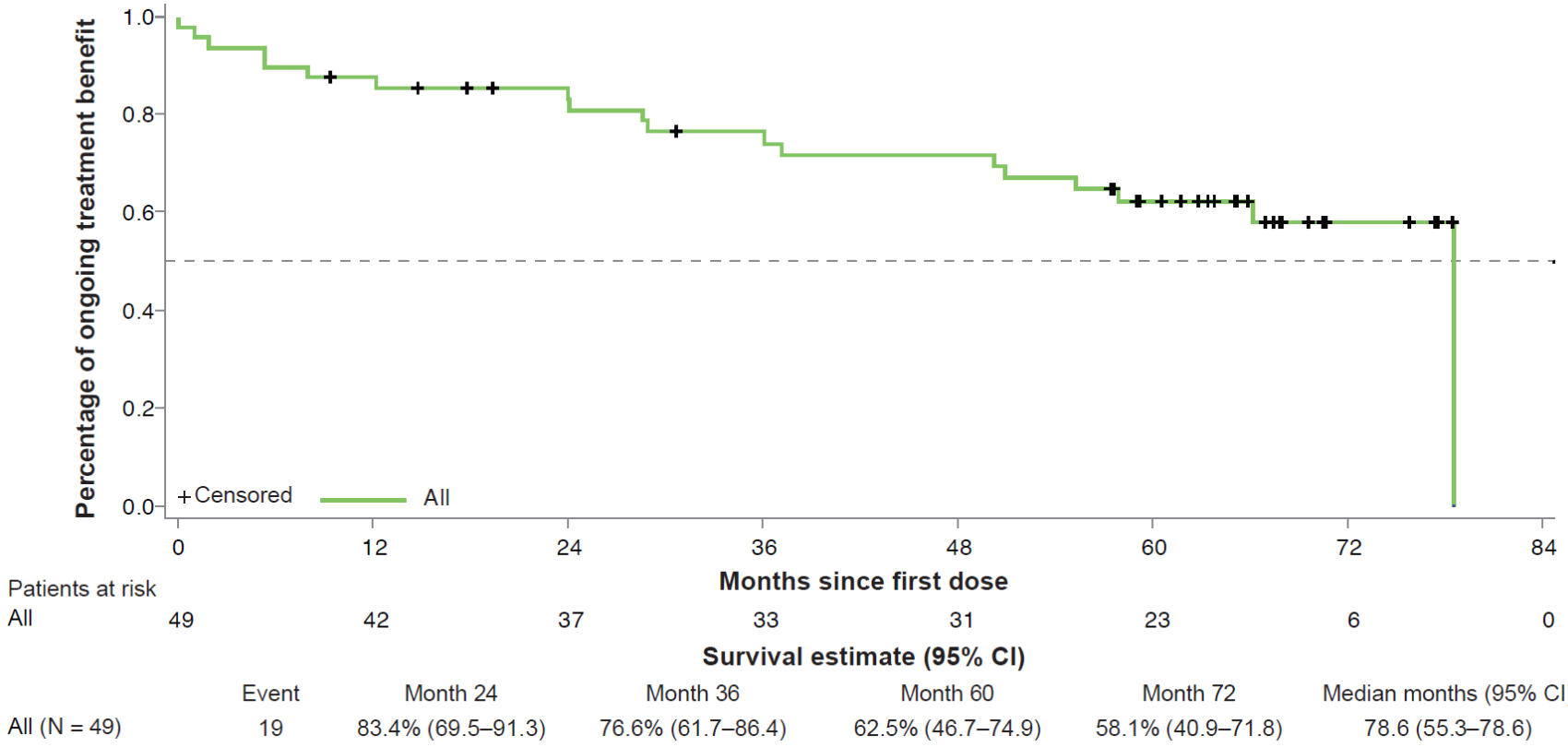


Patients at risk								
MRD+	12	8	7	2	1	1	1	0
uMRD	30	28	27	23	22	13	2	0

Survival estimate (95% CI)

	Event	Month 24	Month 36	Month 60	Month 72	Median months (95% CI)
MRD+ (N = 12)	10	65.6% (32.0–85.6)	18.8% (3.0–45.1)	9.4% (0.6–34.0)	9.4% (0.6–34.0)	25.9 (9.0–34.0)
uMRD (N = 30)	8	100% (100–100)	92.3% (72.5–98.0)	78.5% (55.1–90.6)	69.7% (41.9–86.1)	74.4 (64.3–75.7)

Supplemental Figure 3. Duration of benefit as measured by TTVF for all patients on study. TTVF, time to venetoclax failure.



Supplemental Figure 4. Long term analysis of immunoglobulins. Within each box, the horizontal black line denotes the median and the circle denotes the mean. Boxes extend from the 25th to the 75th percentile of the distribution of values observed within each time period. The whiskers represent the minimum and maximum observations within the lower and upper fences, and open circles denote outliers. IVIG, intravenous immunoglobulin.