Sessione 1

Il concetto della "durata fissa" dal farmacologo all'ematologo

Nel paziente pretrattato

Roberto Marasca

UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

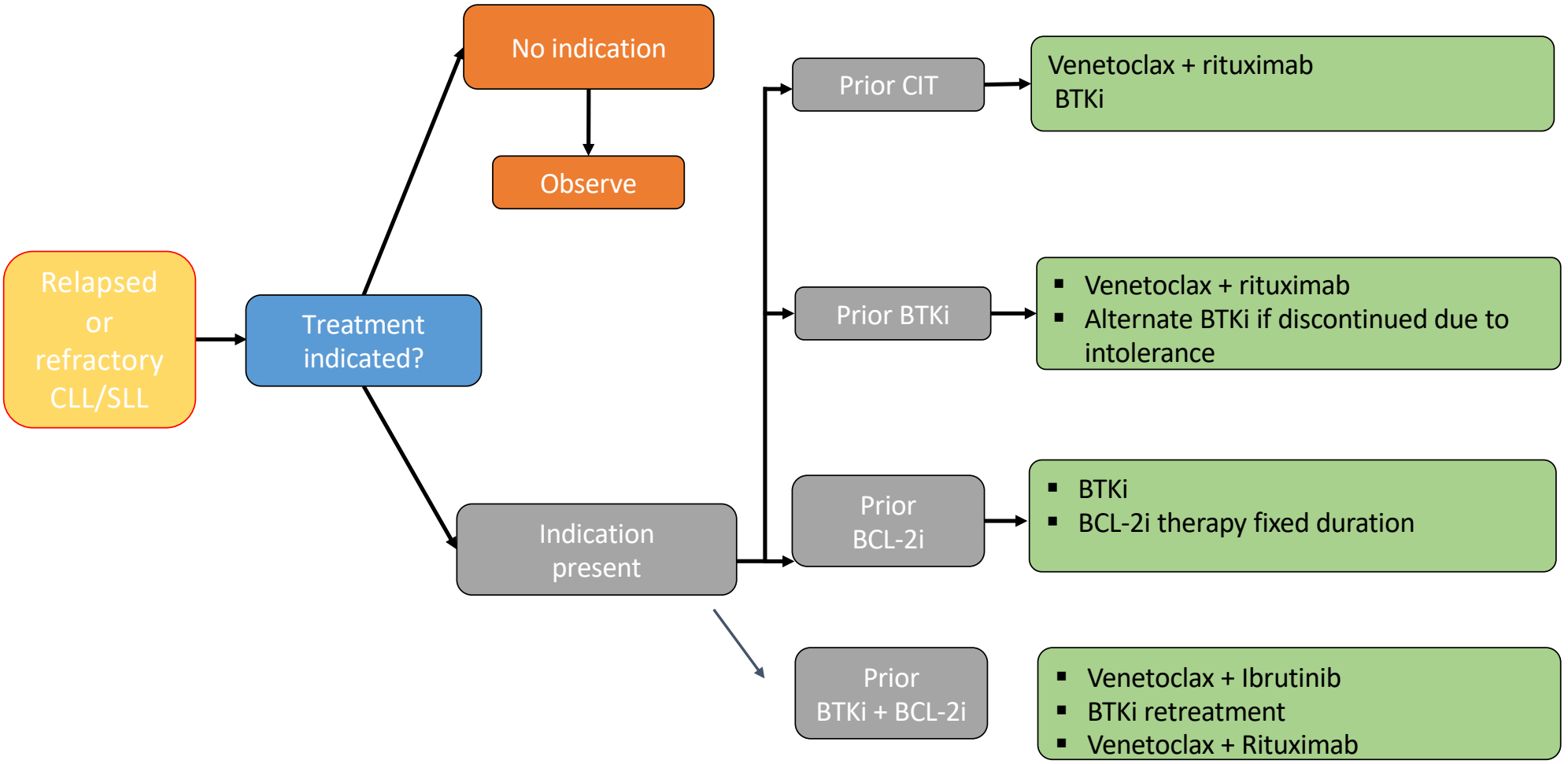
REVOLUTIONARY ROAD IN CLL

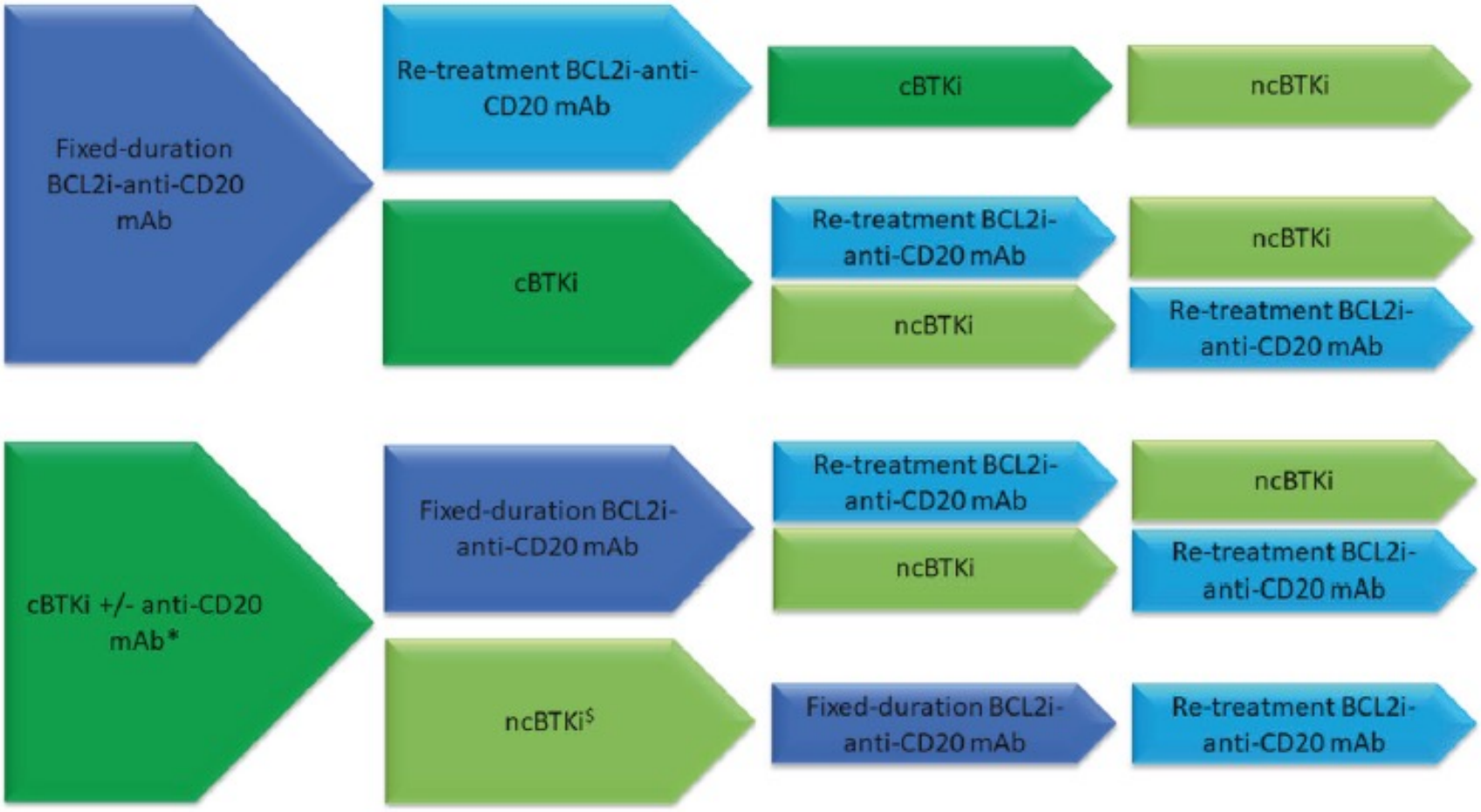
Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Bologna, 20 maggio 2024
Royal Hotel Carlton

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
J&J					x	x	
Astrazeneca					x	x	
Abbvie					x	x	x
Beigene					x	x	x
Lilly						x	

Therapy for Relapsed/Refractory CLL/SLL



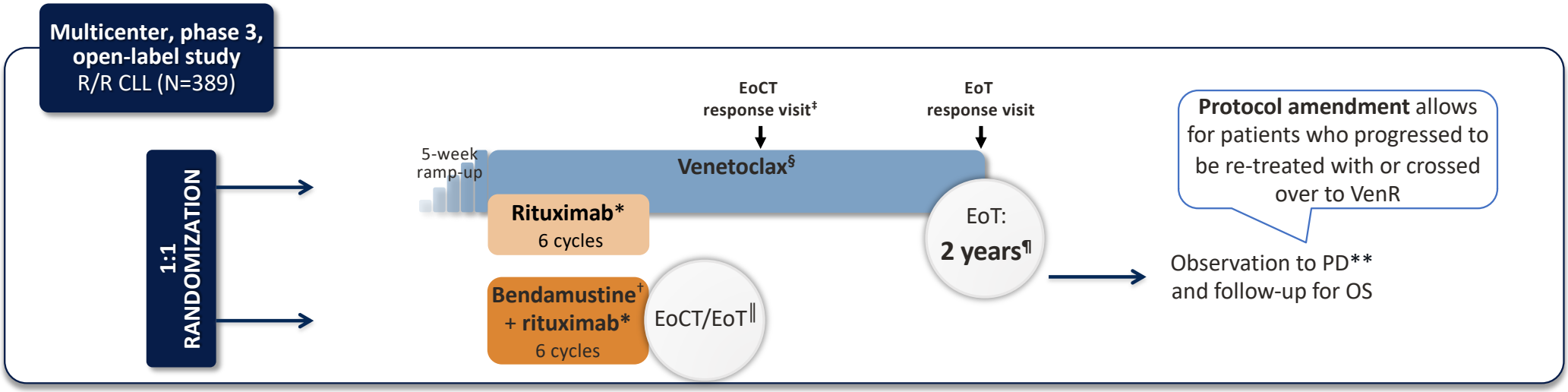


Bennet R, Blood Cancer Journal (2024) 14:33

Outline

- Treatment with a FD regimen in CIT RR
  - 7 yrs Fup Murano trial
  - BTKi-Ven
- Treatment with a FD regimen in BTKi exposed
- Retreatment with FD after FD Venetoclax-Based Regimen
  - Murano retreatment sub-study
  - real life
- Final discussion and remarks

Final 7-year follow-up and re-treatment substudy analysis of the MURANO trial:VenR vs. BR in R/R patients with CLL



Primary endpoint:
- INV-assessed PFS

Key secondary endpoints:
- IRC-assessed PFS
- PFS in patients with del(17p)
- ORR (IRC- and INV-assessed) at EoCT
- OS, uMRD at EoCT, DoR, EFS, TTNT

Key inclusion criteria
- 1–3 lines of prior therapy††
- Prior bendamustine if DoR was ≥2 years
  ECOG PS ≤1

MRD was a secondary efficacy endpoint, not a determinant of treatment duration

* Rituximab: 375 mg/m^2 C1D1 and 500 mg/m^2 D1C2–6; † Bendamustine: 70 mg/m^2 days 1 and 2 of each cycle; ‡ 8 to 12 weeks after C6D1; § Venetoclax 400 mg PO daily; ‖ EoCT corresponds to EoT in BR arm; patients received a total treatment of 6 cycles; ¶ From C1D1; ** Or unacceptable toxicity; †† Including ≥1 chemotherapy-containing regimen. EoCT, end of combination therapy; EoT, end of treatment; INV, investigator; IRC, independent review committee; TTNT, time to next treatment.

Kater AP, *et al. J Clin Oncol* 2020; **38:**4042–4054; ClinicalTrials.gov. NCT02005471 (accessed January 2022).

Baseline characteristics in patients with R/R CLL

Characteristics		VenR (n=194)	BR (n=195)
Age[1]	Median, years (range)	64.5 (28–83)	66 (22–85)
Lymphocyte count, n (%)[1]	≥25×10^9/L	129 (66.5)	134 (68.7)
del(17p)–(FISH),* n/N (%)[1]	Deleted	46/173 (26.6)	46/169 (27.2)
TP53 mutational status, n/N (%)[1]	Mutated *TP53*	48/192 (25.0)	51/184 (27.7)
IGHV mutational status, n/N (%)[1]	Unmutated IGHV Mutated IGHV Unknown	123/180 (68.3) 53/180 (29.4) 4/180 (2.2)	123/180 (68.3) 51/180 (28.3) 6/180 (3.3)
Number of prior therapies, n (%)[2]	1 2 ≥3	111 (57.2) 58 (29.9) 25 (12.9)	117 (60) 43 (22.1) 35 (17.9)
Prior therapies, n (%)[2]	Alkylating agent Purine analog† Anti-CD20 antibody BCRi Bendamustine	185 (95.4) 158 (81.4) 148 (76.3) 3 (1.5) 4 (2.1)	182 (93.3) 157 (80.5) 153 (78.5) 5 (2.6) 5 (2.6)
Fludarabine refractory, n/N (%)[1]	Yes	27/191 (14.1)	30/194 (15.5)

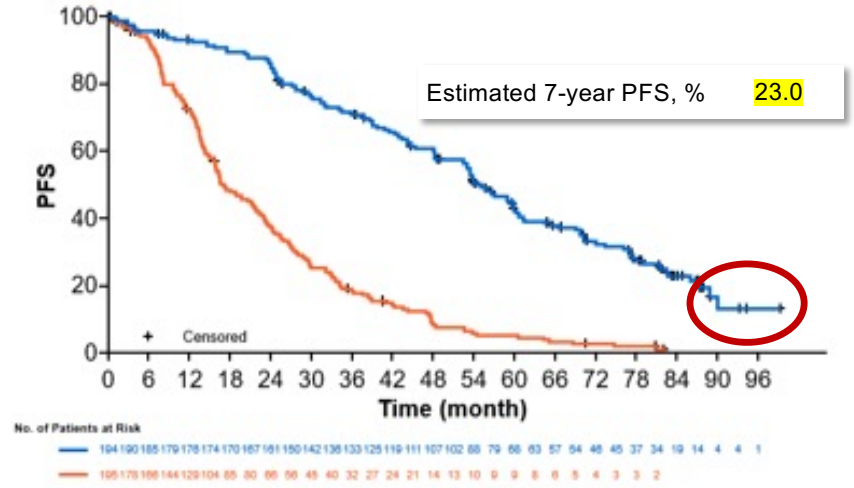
Note: 'Number of prior therapies' in above table are correct;[3] values in the N Engl J Med manuscript[1] were incorrect.
* 7% cutoff for 17p; assessed at central lab;[1] † Across both treatment groups, 55% of patients who had a prior purine analog received FCR[4]; BCRi, B-cell receptor pathway inhibitors; FCR, fludarabine, cyclophosphamide and rituximab; IGHV, immunoglobulin heavy chain variable region.

1. Seymour JF, *et al. N Engl J Med* 2018; **378:**1107–1120 (incl. suppl.);
2. Seymour JF, *et al.* ASH 2019. Abstract 355 (Oral);
4. VENCLYXTO® (venetoclax). EMA Summary of Product Characteristics (April 2020 update).

Final 7-year follow-up and re-treatment substudy analysis of the MURANO trial:VenR vs. BR in R/R patients with CLL

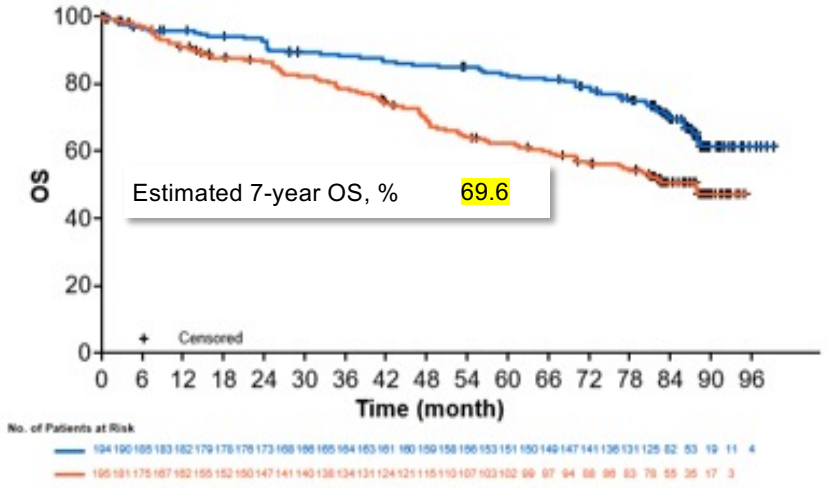
PFS

	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	54.7 (52.3–59.9)	0.23 (0.18–0.29) Stratified P-value <0.0001†	23.0
BR (n=195)	17.0 (15.5–21.7)		NE



OS

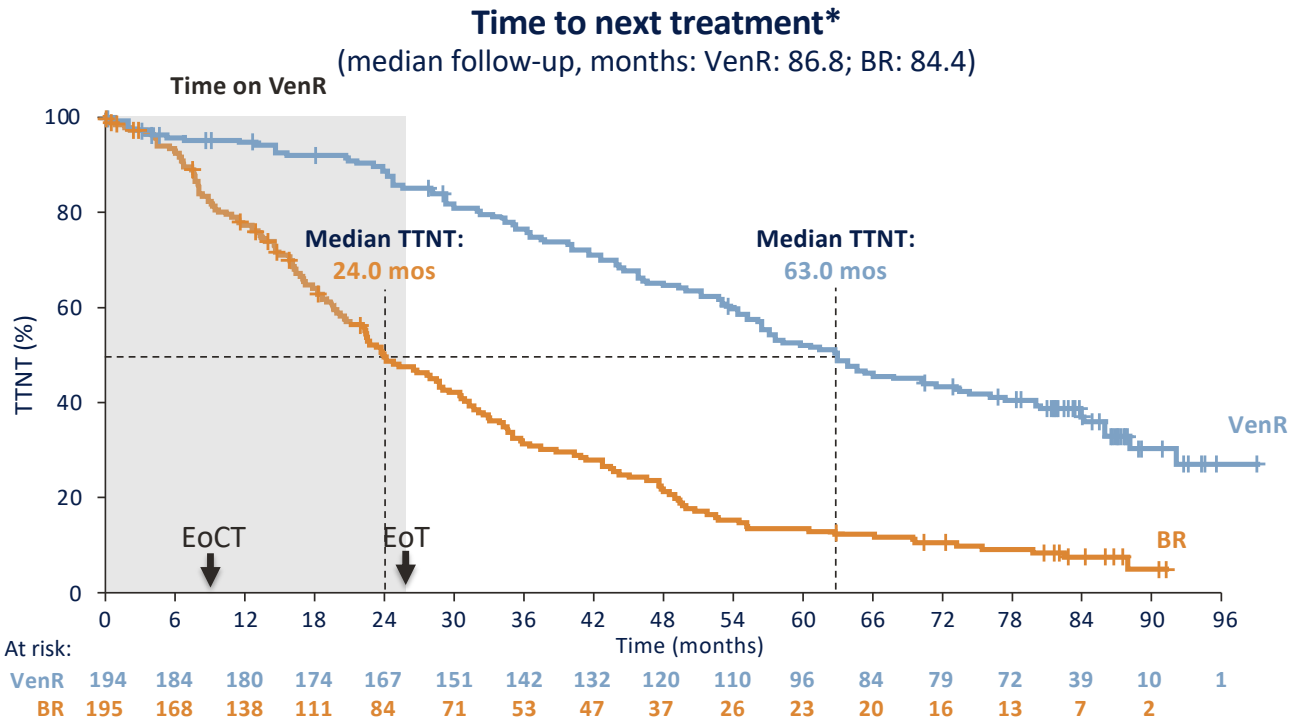
	Median OS (95% CI), months	HR‡ (95% CI)	7-year OS (%)
VenR (n=194)	NE	0.53 (0.37–0.74) Stratified P-value <0.0002†	69.6
BR (n=195)	87.8 (70.1–NE)		51.0



median follow-up
59.2 months

Kater et al., EHA 2023

TTNT at the 7-y final analysis

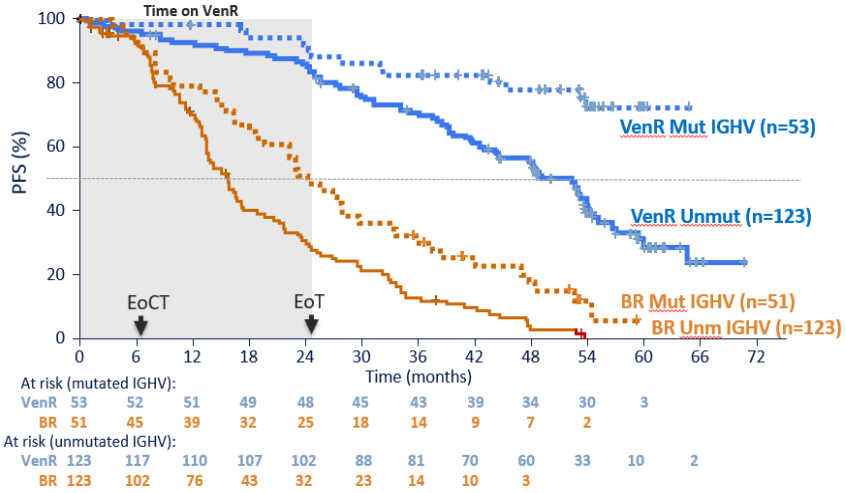


* Time to next treatment was defined as time from initiation of BR/VenR to next anti-CLL treatment or death (whichever occurs first);
† Stratified HR value presented, unstratified HR=0.32; ‡ p values are descriptive only.
EoCT, end of combination treatment; EoT, end of treatment; FTD, fixed-treatment duration; mos, months; TTNT, time to next treatment.

Kater AP, *et al.* EHA 2023. Abstract S201 (Oral).

Final 7-year follow-up and re-treatment substudy analysis of the MURANO trial:VenR vs. BR in R/R patients with CLL

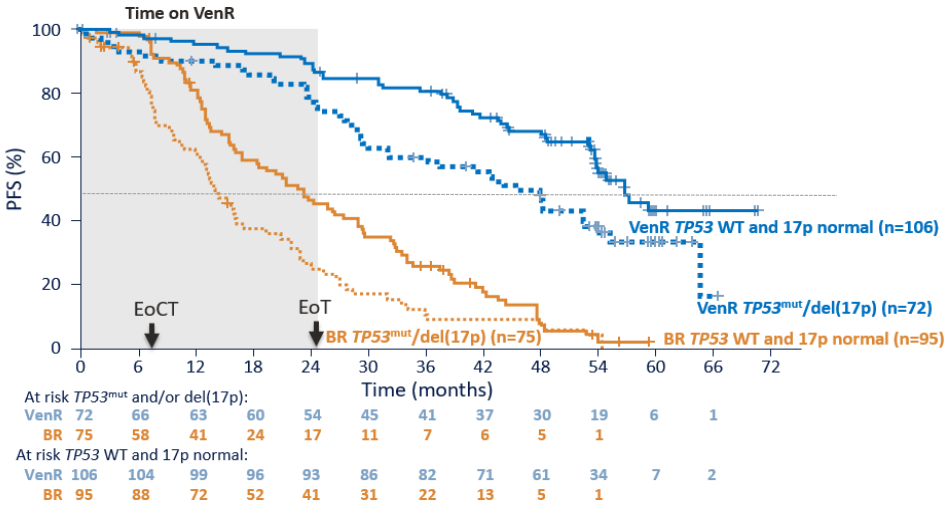
PFS by IGHV



median follow-up
59.2 months

	VenR		BR	
	Unmutated IGHV	Mutated IGHV	Unmutated IGHV	Mutated IGHV
HR (95% CI) p value	Unmutated IGHV vs mutated IGHV 2.96 (1.64–5.34) 0.0002		Unmutated IGHV vs mutated IGHV 1.79 (1.24–2.58) 0.0015	
Median PFS, months	**52.2**	**NE**	**15.7**	**24.2**

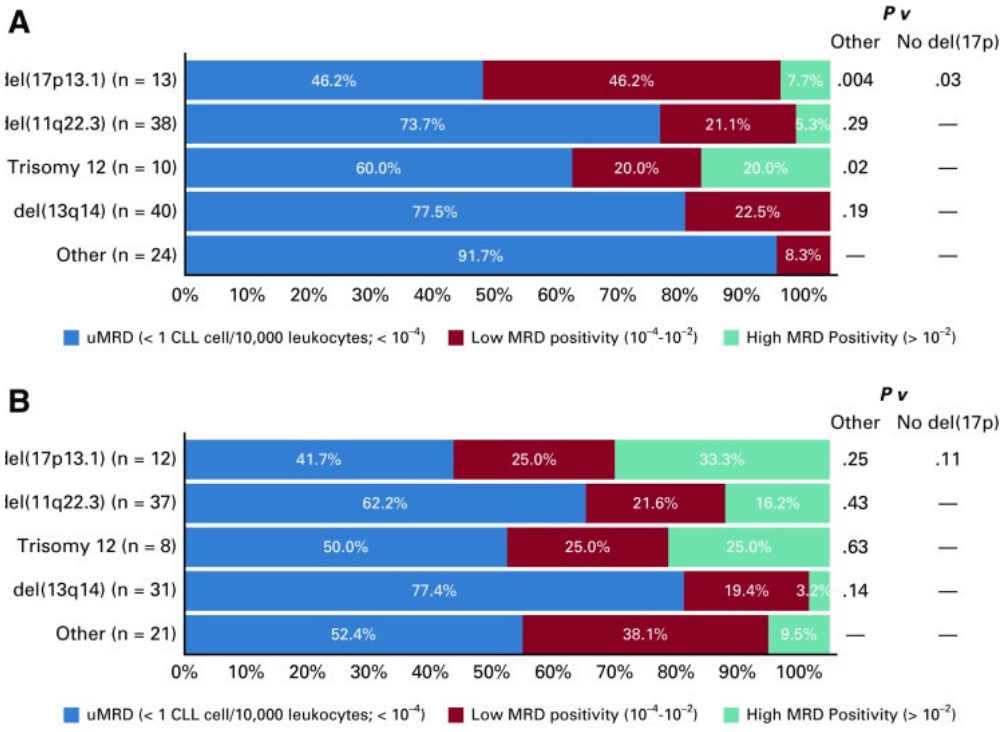
PFS by TP53mut and/or del(17p)

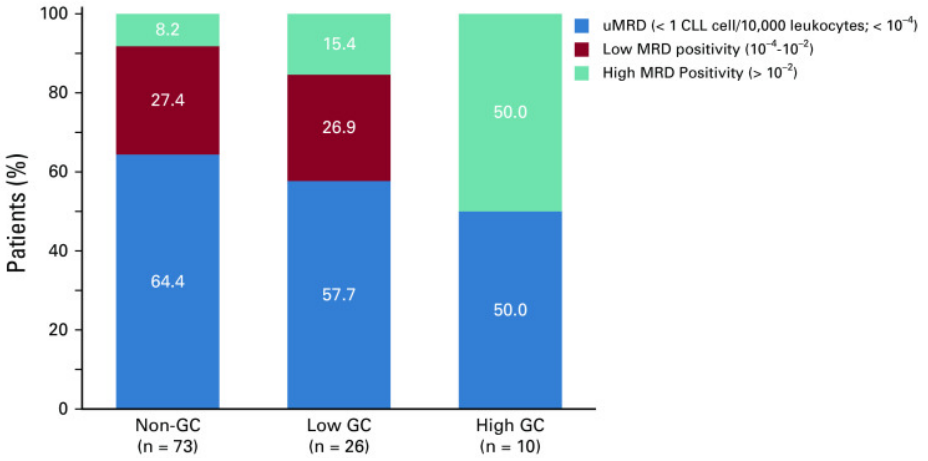


	VenR		BR	
	TP53mut and/or del(17p)	TP53 WT and 17p normal	TP53mut and/or del(17p)	TP53 WT and 17p normal
HR (95% CI)	With TP53mut and/or del(17p) vs without NR		With TP53mut and/or del(17p) vs without NR	
Median PFS, months	**45.3**	**56.6**	**14.2**	**22.9**

Seymour JF, et al. Blood 2022

Impact of genomic alterations on minimal residual disease (MRD) response in patients treated with venetoclax plus rituximab



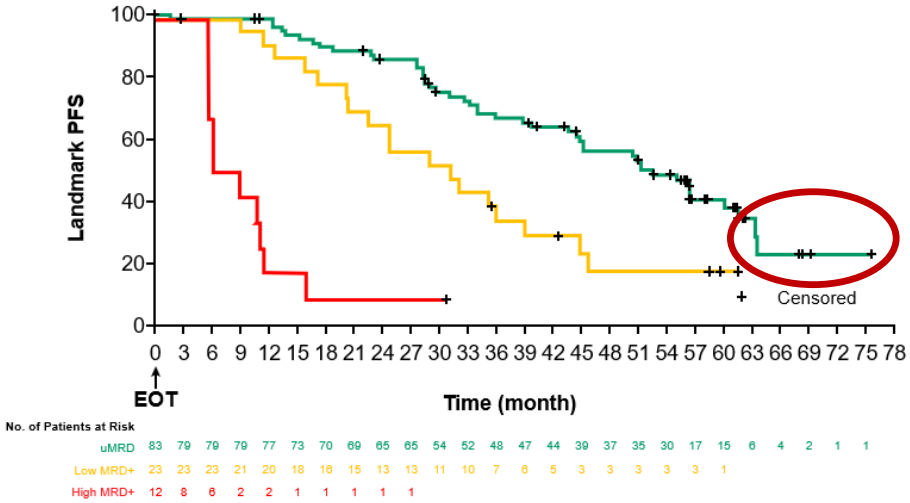


A: EOCT; B: EOT

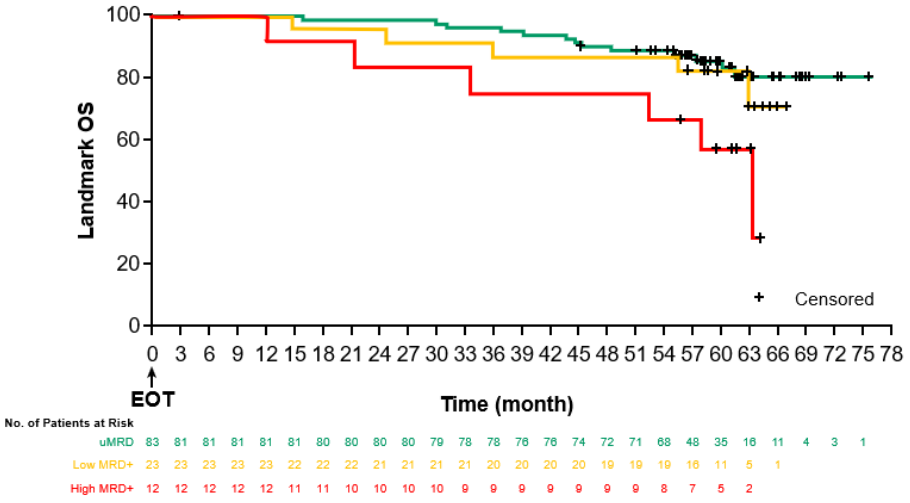
Kater AP, JCO 2020; 38(34): 4042–4054.

uMRD at EOT is associated with improved outcomes in the VenR arm

Patients who completed 2 years of Ven without PD*	Median PFS since EOT (95% CI), months	HR (95% CI); P-value†
uMRD (n=83)	52.5 (44.5–61.5)	
Low MRD+ (n=23)	29.3 (20.2–37.5)	vs uMRD: 3.46 (1.75–6.86); <0.0001
High MRD+ (n=12)	4.6 (2.8–8.3)	vs uMRD: 17.22 (5.70–52.00); <0.0001



Patients who completed 2 years of Ven without PD*	Median OS since EOT (95% CI), months	HR (95% CI); P-value†
uMRD (n=83)	NE (NE–NE)	
Low MRD+ (n=23)	NE (62.7–NE)	vs uMRD: 1.07 (0.34–3.35); NS
High MRD+ (n=12)	63.1 (51.5–NE)	vs uMRD: 2.39 (0.73–7.80); NS



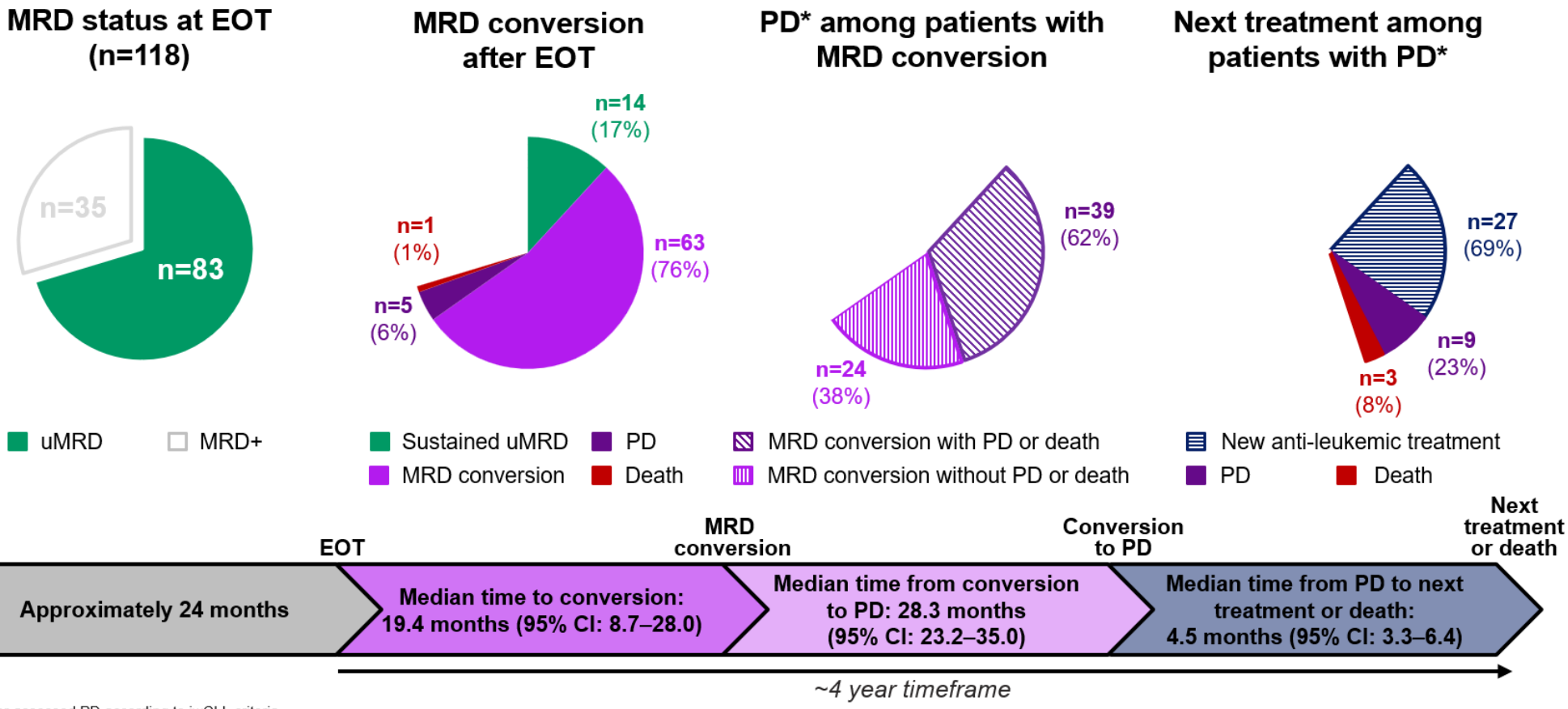
Achievement of uMRD was associated with prolonged PFS in VenR-treated patients

Low MRD+ is defined as ≥1 CLL cell/10,000 leukocytes to <1 CLL cell/100 leukocytes, high MRD+ is defined as ≥1 CLL cell/100 leukocytes. Stratified HR (95% CI) for Low MRD+ vs High MRD+ = PFS, 3.22 (1.04–9.97), P=0.0350; OS, 2.27 (0.44–11.69), P=NS.

*Investigator-assessed PD according to iwCLL criteria. †Stratified HRs and P-values are presented, P-values are descriptive only. NS, not significant.

Kater AP, *et al.* EHA 2023. Abstract S201 (Oral);
Kater AP, *et al.* ASH 2020. Abstract 125 (Oral);
Seymour JF, *et al. Blood* 2022; **140**:839–850.

Most patients who received the full 2 years of VenR treatment had uMRD at EOT; generally MRD conversion with subsequent PD did not occur until ~4 years post EOT



*Investigator-assessed PD according to iwCLL criteria.

1. Kater A, *et al.* EHA 2023. Abstract S201 (Oral); 2. Seymour JF, *et al. Blood* 2022; **140:**839–850.

Favorable baseline characteristics were over-represented among patients with enduring uMRD

- Among the 14 patients with sustained uMRD after EOT, median number of prior therapies was 1 (range 1–3)

VenR-treated patients, n (%)	*TP53** (n=192)†		IGHV§ (n=176)†	
	wild-type‡ (n=144)	mutated (n=48)	mutated‡ (n=53)	unmutated (n=123)
Patients with sustained uMRD (n=14)	13/144 (9.0)	1/48 (2.1)	7/53 (13.2)	6/123 (4.9)
Patients without sustained uMRD (n=180)	131/144 (91.0)	47/48 (97.9)	46/53 (86.8)	117/123 (95.1)

Among the small group of patients with favorable disease biology there is a portion (7/43 [16.3%]) who have very long term enduring uMRD following 2 years of VenR

*Assessed by NGS. †Biomarker evaluable population. ‡Favorable characteristic. §Assessed by PCR. IGHV, immunoglobin heavy chain variable region genes; NGS, next generation sequencing; PCR, polymerase chain reaction; *TP53*, tumour protein 53.

Safety overview

Grade 3–4 AEs during treatment, with ≥2% difference between arms, n (%)*,[1]	VenR combination treatment period (months 1–6) N=194	Venetoclax single-agent treatment period (months 7–24) N=171
Neutropenia	**106 (54.6)**	**20 (11.7)**
Anemia	16 (8.2)	5 (2.9)
Thrombocytopenia	9 (4.6)	3 (1.8)
Febrile neutropenia	7 (3.6)	0
Pneumonia	8 (4.1)	2 (1.2)
TLS Clinical TLS	6 (3.1) 1 (0.5)	0 0
Infusion-related reaction	4 (2.1)	0
Hyperglycemia	4 (2.1)	0
Hypogammaglobulinemia	3 (1.5)	1 (0.6)

Updated safety profile*,[1–3]

- Excluding non-melanoma skin cancer, 2 new secondary malignancies were reported since the previous update:[3]
  - VenR: n=2 (1 AML, 1 plasma cell myeloma)
  - BR: n=0
- There were no new reported events of Richter transformation[†,2,3]
- No new safety signals were observed with 11 patients enrolled in the re-treatment sub-study[1]
- In the final analysis,[‡] no new safety signals identified 5 years after EoT[4]

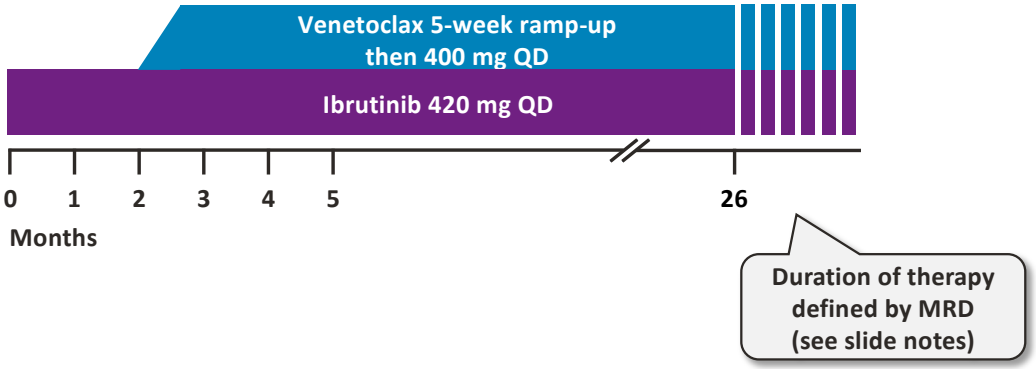
The safety profile of venetoclax regimens is manageable, with rates of Grade 3–4 AEs reducing over the course of treatment and no new safety signals identified 5 years after treatment

* Grade 3–4 AEs were not actively monitored after EoT; only deaths, SAEs, or other AEs of concern believed to be related to prior treatment with study drug were reported; † Throughout the study to 5-year analysis (data cut-off May 8, 2020), Richter transformation was reported in 7 (3.6%) patients in the VenR arm and 6 (3.2%) patients in the BR arm; ‡ Median follow-up 86.8 months for VenR. EoT, end of treatment; TLS, tumor lysis syndrome.

1. Seymour JF, *et al.* ASH 2019. Abstract 355 (Oral);
2. Kater AP, *et al.* ASH 2020. Abstract 125;
3. Seymour JF, *et al. Blood* 2022; **140:**839–850;
4. Kater A, *et al.* EHA 2023. Abstract S201 (Oral).

CLARITY: Venetoclax + Ibrutinib in R/R CLL

Phase 2 Trial in Patients with R/R CLL (Prior Therapy with CIT/Presence of del[17p] and Prior Therapy Failure)[1]



Baseline Characteristics[2]	IVen (N=54)*
Median age, years (range)	64 (31–83)
Male sex, n (%)	37 (69)
Current Binet Stage, n (%)	
A	12 (22)
B	18 (33)
C	22 (41)
Not known	2 (4)
Lymph nodes, bulky ≥5 cm, n (%)	4 (8)
del(17p), n/N (%)	10/50 (20)
del(11q), n/N (%)	13/51 (25)
IGHV unmutated, n (%)	40 (74)
Prior therapies, median (range)	1 (1–6)
Prior FCR/BR, n/N (%)	44/54 (82)
Relapse ≤3 years of FCR/BR, n/N (%)	22/44 (50)
Prior idelalisib, n/N (%)	11/54 (20)

Response assessment, including assessment of MRD, was performed at screening (before ibrutinib), week 8 (before venetoclax), month 8 (6 months of combination treatment), month 14 (12 months of combination treatment), and month 26 (24 months of combination treatment). uMRD defined as $<10^{-4}$ in PB and BM by flow cytometry.

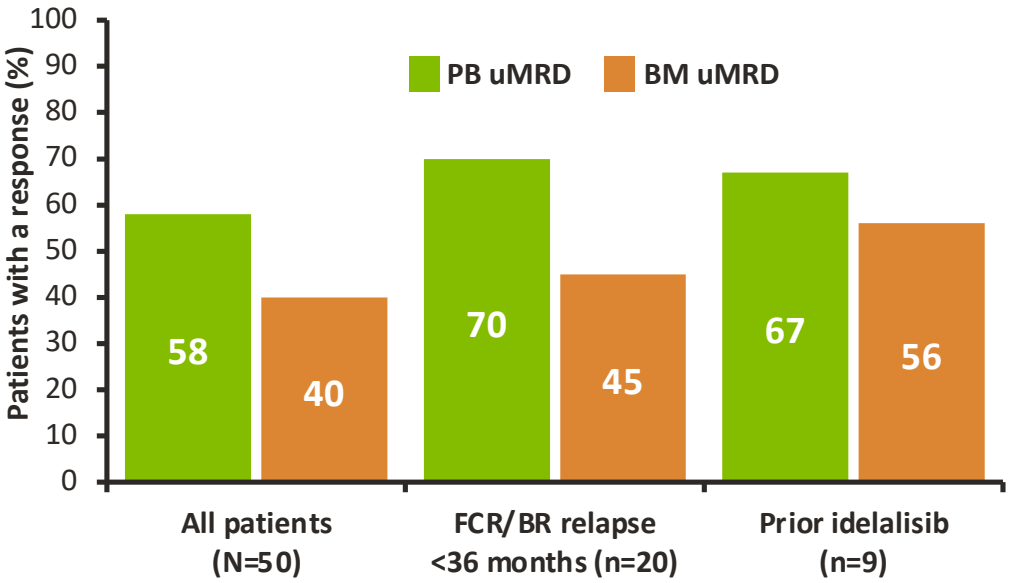
* Four patients stopped ibrutinib before adding venetoclax because of AEs; 50 patients successfully initiated venetoclax.

BR, bendamustine + rituximab; CIT, chemoimmunotherapy; FCR, fludarabine + cyclophosphamide + rituximab; IVen, ibrutinib + venetoclax.

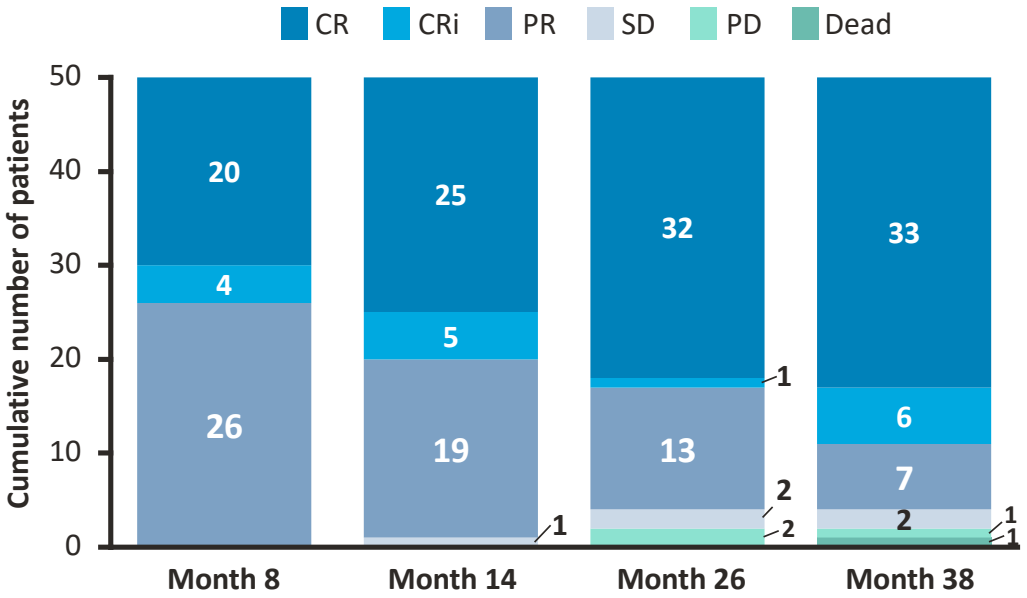
1. Hillmen P, *et al. J Clin Oncol* 2019; **37:**2722–2729;
2. Munir T, *et al.* ASH 2022. Abstract 91 (Oral).

CLARITY: uMRD and response rates

uMRD* ($<10^{-4}$) Rates at 12 Months' IVen



Response rates over time

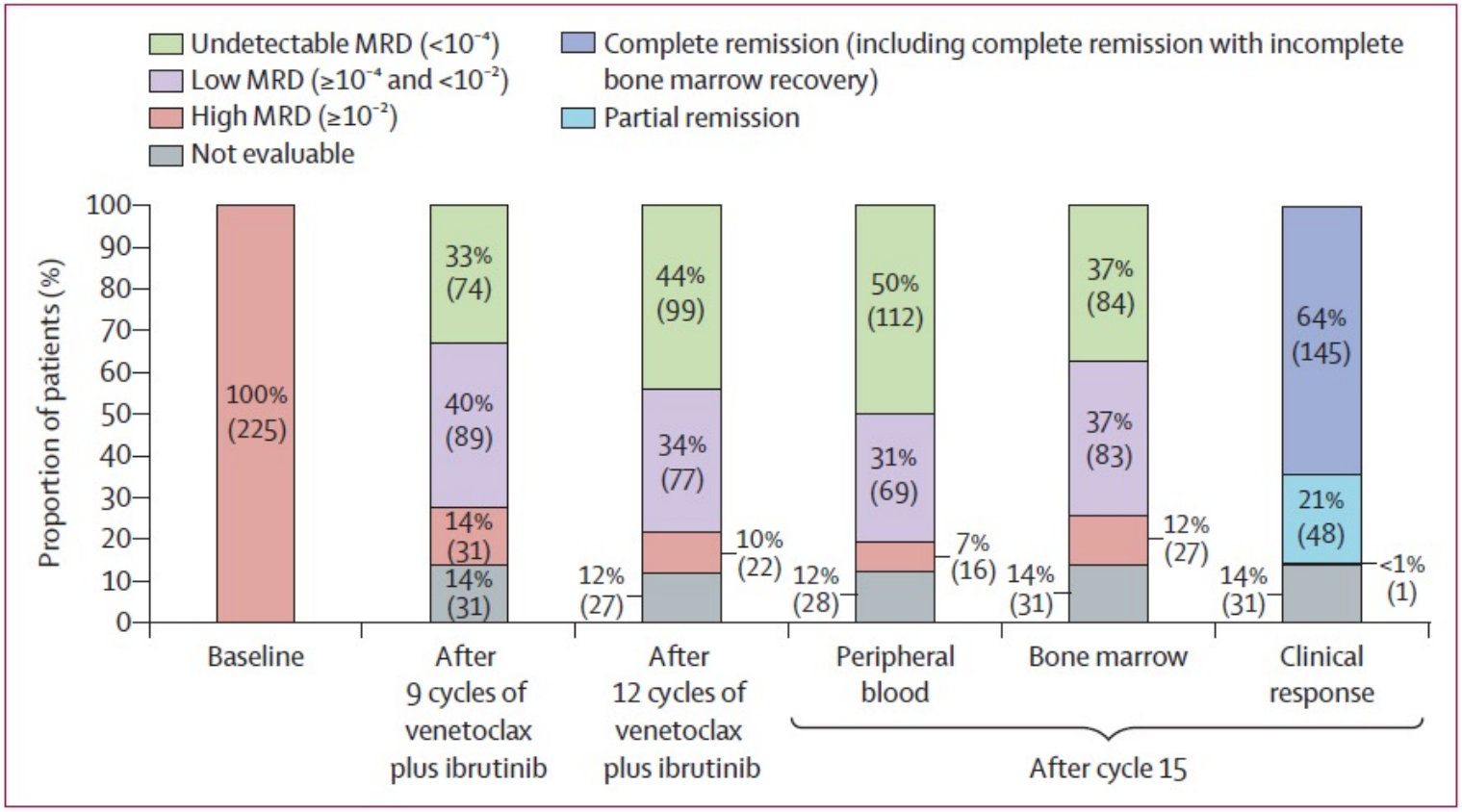


High rates of uMRD observed in all patients, regardless of prior therapy.
By month 38, 39/50 (78%) patients achieved CR/CRi

Data lock: November 1, 2022. Response assessment, including assessment of MRD, was performed at screening (before ibrutinib), week 8 (before venetoclax), month 8 (6 months of combination treatment), month 14 (12 months of combination treatment), and month 26 (24 months of combination treatment). Additional PB samples were taken at multiple time points. * Assessed by flow cytometry.
BM, bone marrow; BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab; PB, peripheral blood; IVen, ibrutinib + venetoclax.

Munir T, *et al.* ASH 2022. Abstract 91 (Oral).

MRD-guided stop and start of venetoclax plus ibrutinib for patients with RR CLL (HOVON141/VISION)



Kater AP, Lancet Oncol 2022; 23: 818–28

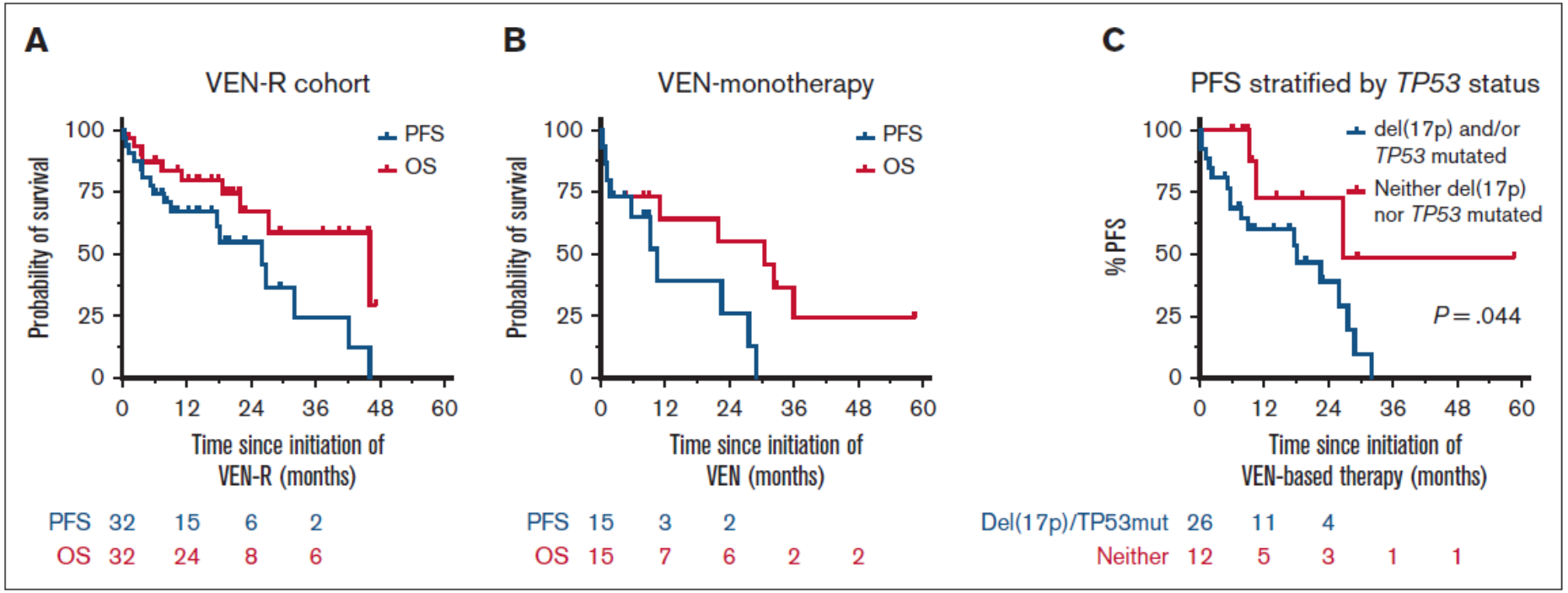
VEN-R for cBTKi- and chemoimmunotherapy-exposed R/R CLL

Table 1. Patient characteristics before VEN-containing regimen

	VEN-R	VEN monotherapy	Whole cohort
Clinico-pathologic characteristics before VEN			
n	32	15	47
Age, y (median, range)	70.5 (49-84)	68 (47-86)	70 (47-86)
Treatments (n) before VEN (including cBTKi)*	2 (1-5)	3 (1-7)	2 (1-7)
Chemoimmunotherapy exposed	28 (89%)	14 (93%)	42 (89%)
Fludarabine refractory (<PR or PD within 6 mos)	3 (9%)	1 (7%)	4 (9%)
First cBTKi-containing therapy			
Ibrutinib	23 (72%)	14 (93%)	37 (79%)
Acalabrutinib	1 (3%)	0 (0%)	1 (2%)
Zanubrutinib	8 (25%)	1 (7%)	9 (19%)
Reason for BTKi cessation			
PD	25 (78%)	13 (87%)	38 (81%)
Toxicity	7 (22%)	2 (13%)	9 (19%)
Time to progression after cBTKi initiation, mos (median, range)	32 (6.3-83.1)	24.0 (1.1-90.7)	31.5 (1.1-90.7)

Lew TE, Blood Adv, 2024; 8: 1439-1441

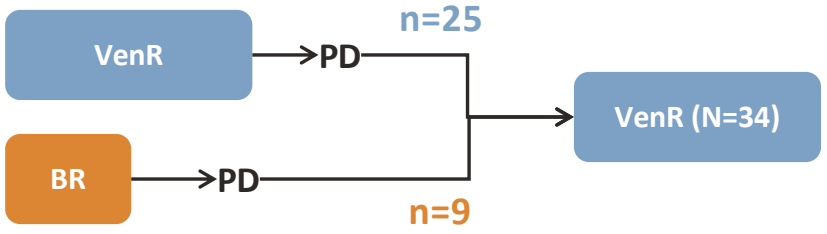
VEN-R for cBTKi- and chemoimmunotherapy-exposed R/R CLL



Lew TE, Blood Adv, 2024; 8: 1439-1441

MURANO substudy: protocol amendment for re-treatment/crossover

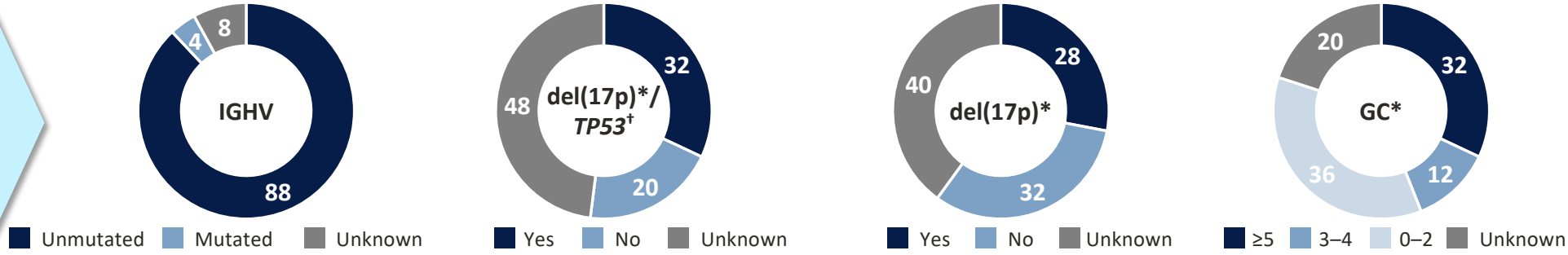
N=34 enrolled in the MURANO re-treatment / crossover substudy[1,2]



n=25 VenR sub-study re-treated patients

- Baseline characteristics: generally unfavorable genetics
- Median PFS1: 45.7 months (range 36–58)[2]
- Median treatment-free interval to PD: 23.6 months (range 10–32)[2]

VenR-re-treated patients, % (n=25)



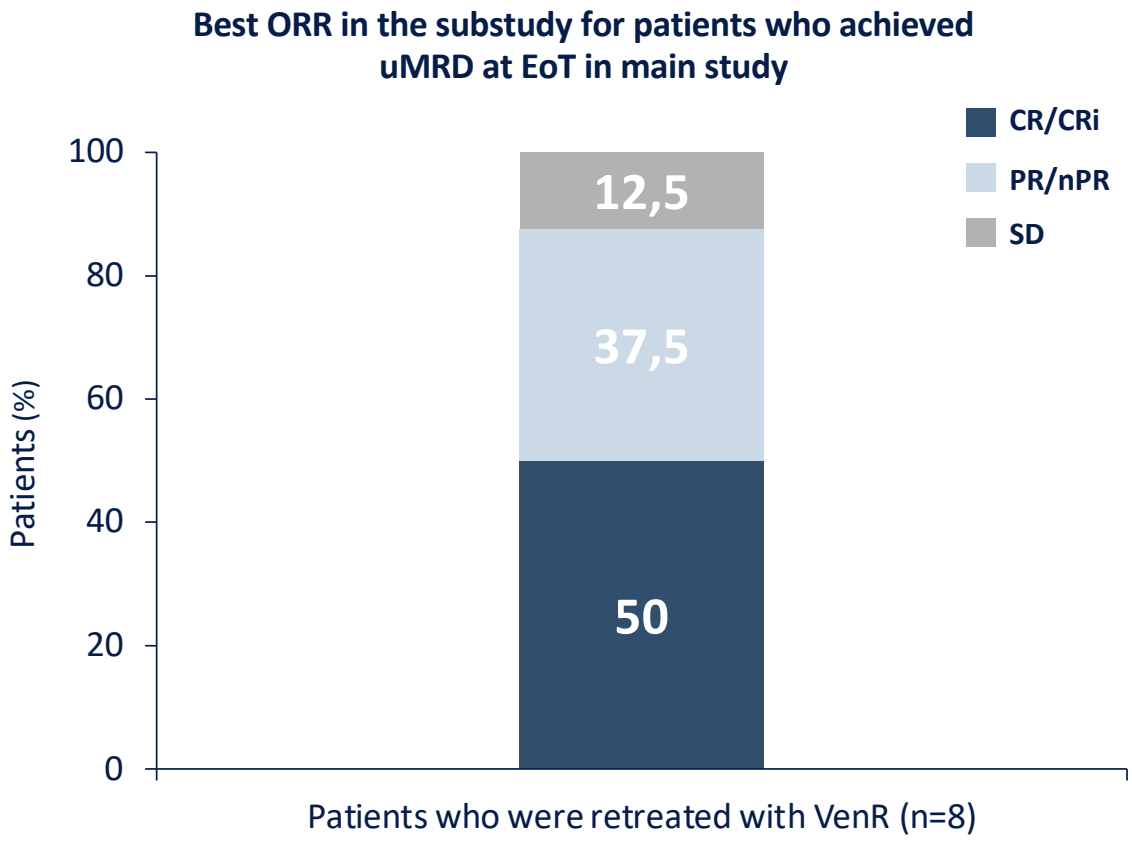
Unfavorable baseline characteristics were over-represented among VenR re-treated patients

* Assessed by array comparative genomic hybridization; † Assessed by NGS.
GC, genomic complexity; IGHV, immunoglobulin heavy chain variable region; NGS, next-generation sequencing.

1. Kater A, *et al.* EHA 2023. Abstract S201 (Oral); 2. Kater AP, *et al.* ASH 2020. Abstract 125 (Oral).

MURANO substudy: Best ORR in patients who achieved uMRD

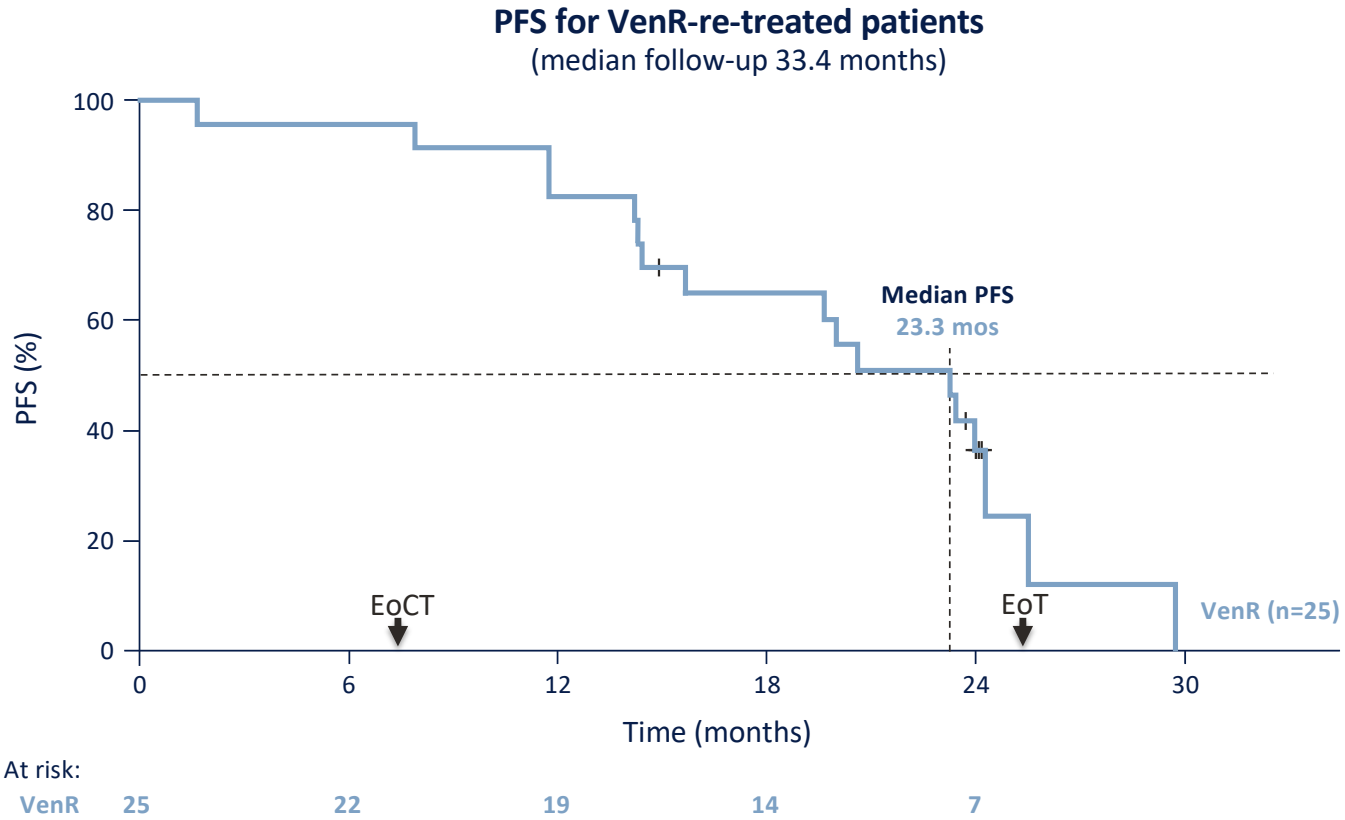
- 44% of patients in the substudy never achieved uMRD in the main study;
- Amongst Ven-R retreated patients, 8 (32%) achieved uMRD at the retreatment EOCT; all responded with 7/8 achieving CR/PR.



EoT, end of treatment.

Kater A, *et al.* EHA 2023. Abstract S201 (Oral).

MURANO substudy: Clinical outcomes for patients re-treated with VenR



	VenR
Median OS, months	NR
Best ORR, %	72.0
CR rate, %	24

Among VenR-retreated patients (25), median FU was 33.4 months

- Median PFS was 23.3 months (15.6-24.3)
- Best ORR was high at 72%; CR were 24%
- Median OS: not reached

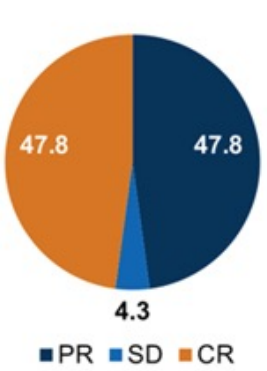
NR, not reported.

Kater A, *et al.* EHA 2023. Abstract S201 (Oral).

Venetoclax retreatment: a retrospective Study

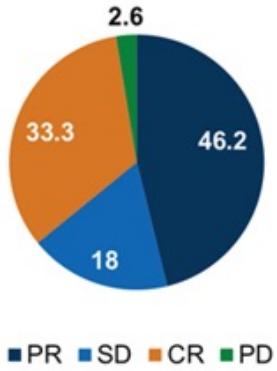
Retrospective study investigating outcomes of 46 patients treated with a venetoclax-based regimen (Ven1) in any line of therapy and retreated with venetoclax (Ven2)
(Medical centers: n=30; RWE DB: n=5; MURANO: n= 11)

Baseline Characteristics	Results
Median age at CLL diagnosis, y (range)	55.5 (24-75)
Median age at Ven1 start, y (range)	64 (31-75)
Men	73.9%
Race	83.3% White 9.5% Black 7.1% other
Ven1 administered as part of a clinical trial	56.5%
Ven1 as monotherapy	37%
Ven1 as first-line treatment	8.7%
Median prior lines of therapy (range)	2 (0-10)
Prior BTKi	40%
del(17p)	25%
TP53 mutation	15.6%
Complex karyotype	20.5%
IGHV unmutated	82.1%



Ven1:

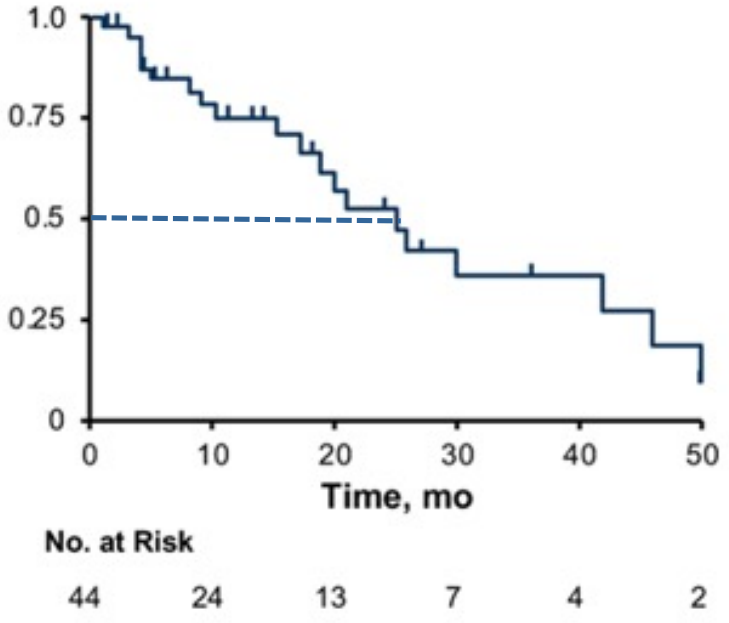
ORR 95.6%



Ven2:

ORR 79.5%
(BTK-exposed: 56.3%)

PFS for Ven2



Thompson, Blood Adv. 2022

Real-world evidence of obinutuzumab and venetoclax in previously treated patients with chronic lymphocytic leukemia or small lymphocytic lymphoma

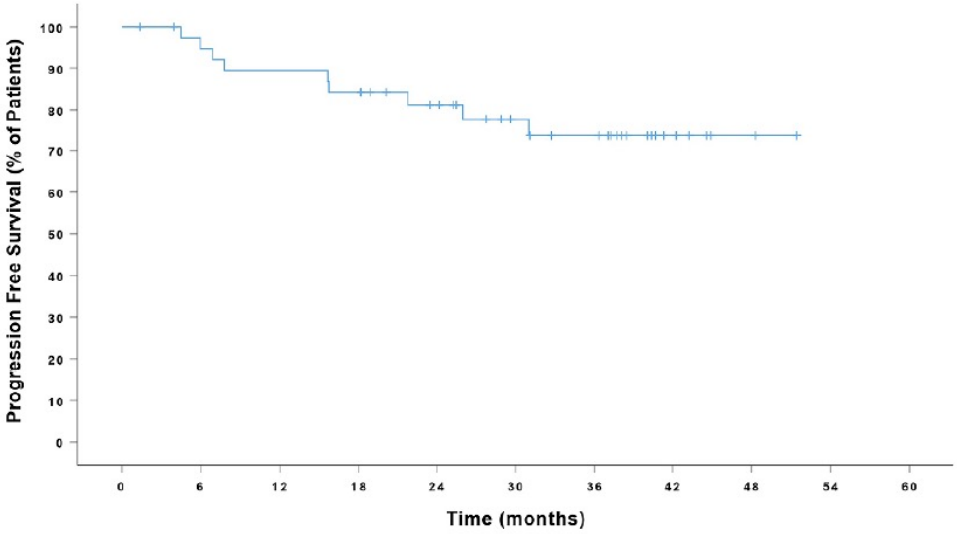


Figure 1. Progression-free survival for all patients median progression-free survival has not been reached after a median follow-up duration of 32+ months (range, 1.4-51.4). The 2-year progression-free survival was 81.2% (95% confidence interval, 69.5-94.8).

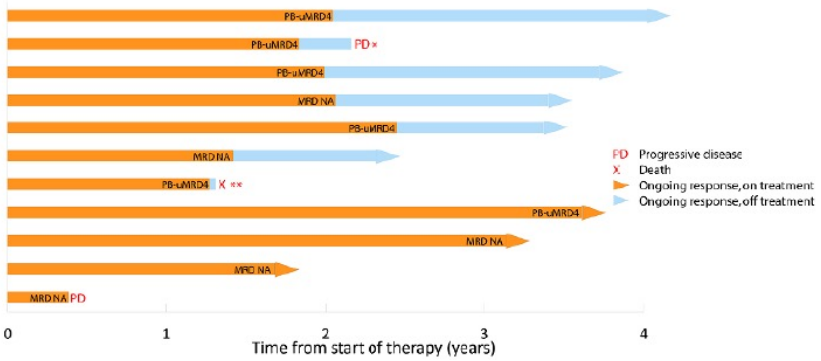
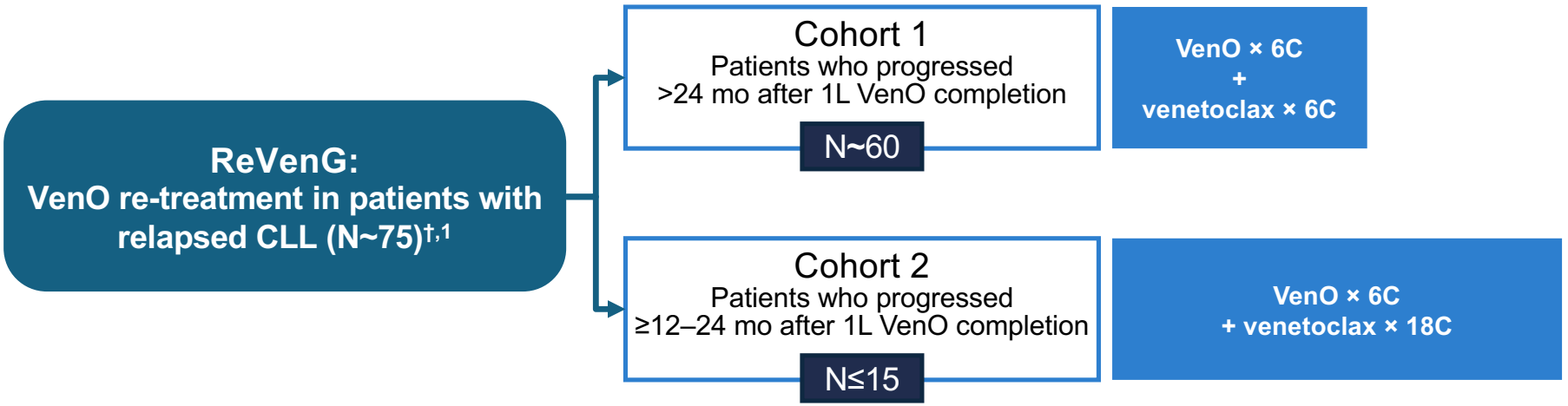


Table 1. Baseline characteristics.

	All patients $N=40$
Age, median (range)	72 (51-94)
Age ≥65 years, n (%)	31 (77.5)
Female sex, n (%)	9 (22.5)
White race, n (%)	37 (92.5)
ECOG PS ≥2, n (%)	4 (10)
Del(17p) or TP53 mutated, n (%)	11/39 (28.2)
TP53 mutated*	7/28 (25)
Del(17p)**	7/39 (17.9)
Unmutated IGHV, n (%)***	21/32 (65.6)
Complex karyotype, n (%)**	11/39 (28.2)
Number of prior lines, median (range)	1 (1-6)
≥2 prior therapies, n (%)	15 (37.5)
Previous cytotoxic chemotherapy, n (%)	28 (70)
Previous chemoimmunotherapy (no BTK/ BCL2 inhibitor)	18 (45)
Previous bendamustine	18 (45)
Previous fludarabine	13 (32.5)
Previous chlorambucil	4 (10)
Previous anti-CD20 monoclonal antibody, n (%)	31 (77.5)
Previous covalent BTK inhibitor therapy, n (%)	22 (55)
Previous cBTKi discontinued for progression	15 (37.5)
Previous cBTKi discontinued for intolerance	7 (17.5)
Previous venetoclax therapy, n (%)	1 (2.5)

Lei MM, Leuk & Lymph 2024

The prospective ReVenG study investigates the efficacy of fixed duration VenO retreatment in patients with CLL after prior Ven-based therapy



Primary endpoint:

ORR at EoCT
(3 months after completing 6 cycles of VenO)

Key secondary endpoints:

- CR/CRi at EoCT and EoT
- ORR at EoT
- uMRD at EoCT and EoT
- PFS
- OS
- TTNT
- Safety

† 28-day cycles, O: 100 mg (IV) D1, 900 mg D2, 1,000 mg D8 and D15 of C1, then 1,000 mg IV D1 C2–6; Ven: 5-week ramp-up (20–400 mg) PO QD D22 of C1, then 400 mg OD C3–12 (Cohort 1) or C3–C24 (Cohort 2).

EoCT, End of Combination Treatment;

1. Davids M, et al. ASH 2021. Abstract 2634 (Poster).

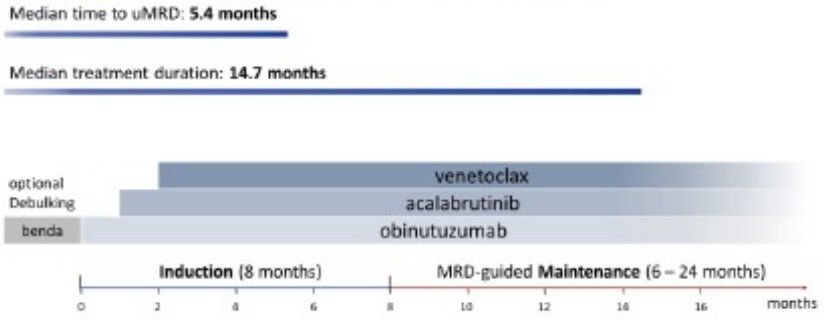
Acalabrutinib, Venetoclax, and Obinutuzumab in Relapsed CLL: Final Efficacy and Circulating Tumor DNA (ctDNA) Analysis of the CLL2-BAAG Trial

Study Design and Exposure (ClinicalTrials.gov Identifier: NCT03787264)

Phase 2 CLL2-BAAG study

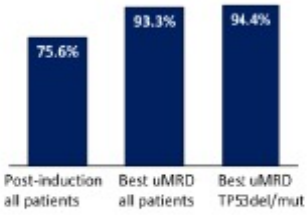
46 patients with r/r CLL

- Unmutated IGHV: 75.6%
- TP53 aberration(s): 31.8%
- Prior BTKi/venetoclax: 40.0%

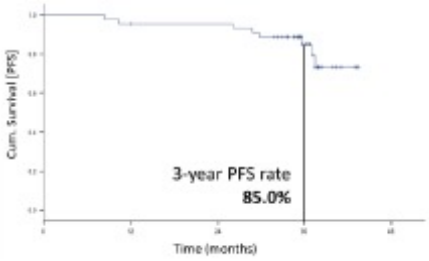


Main Findings (median follow-up 36.3 months)

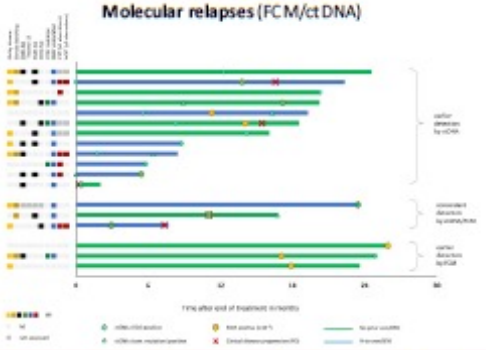
PB undetectable MRD rates



Progression-free survival



Molecular relapses (FCM/ctDNA)

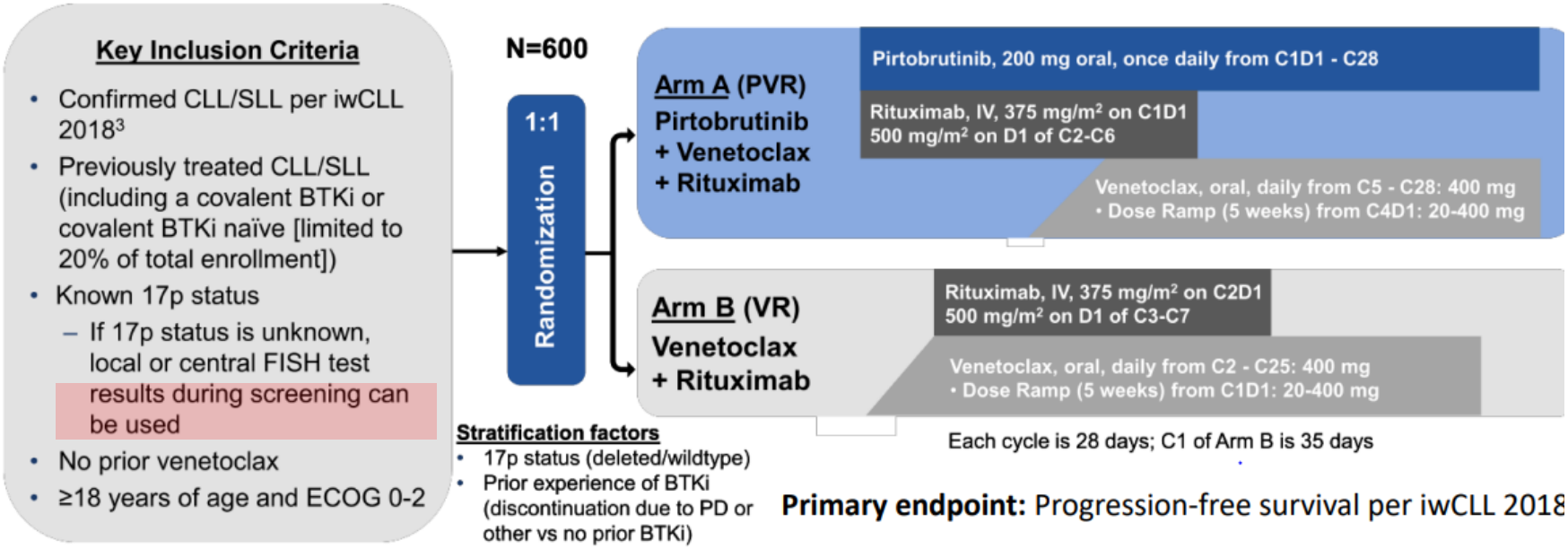


Conclusions: Time-limited acalabrutinib, venetoclax, and obinutuzumab induced deep and ongoing remissions in patients with relapsed/refractory CLL, including those with *TP53* aberrations and prior BTKi/venetoclax exposure.

Fürstenau et al. DOI: 10.xxxx/blood.2024xxxxxx

***Blood* Visual Abstract**

Fixed duration pirtobrutinib plus venetoclax and rituximab versus venetoclax and rituximab in R/R CLL/SLL. (BRUIN CLL-322)



NCT04965493

Discussion and Remarks

FD treatment strategy is an efficient and well tolerated treatment with long PFS, OS and TTNT in RR CLL

FD Ven-R regimen demonstrate high efficacy and tolerability in previously CIT exposed patients

Ven-R re-treatment is a reasonable choice, as well as BTKi options

However, limited data are available from clinical trials, exploring efficacy in CLL yet exposed to TA, in particular in patients CIT free

Multiple and new therapeutic options for patients with RR CLL are available or will be available in the next future


Thanks for your attention!
Sunset from Pesaro, Baia Flaminia, 13 June 2022