Il concetto della terapia a durata fissa nel paziente pre-trattato

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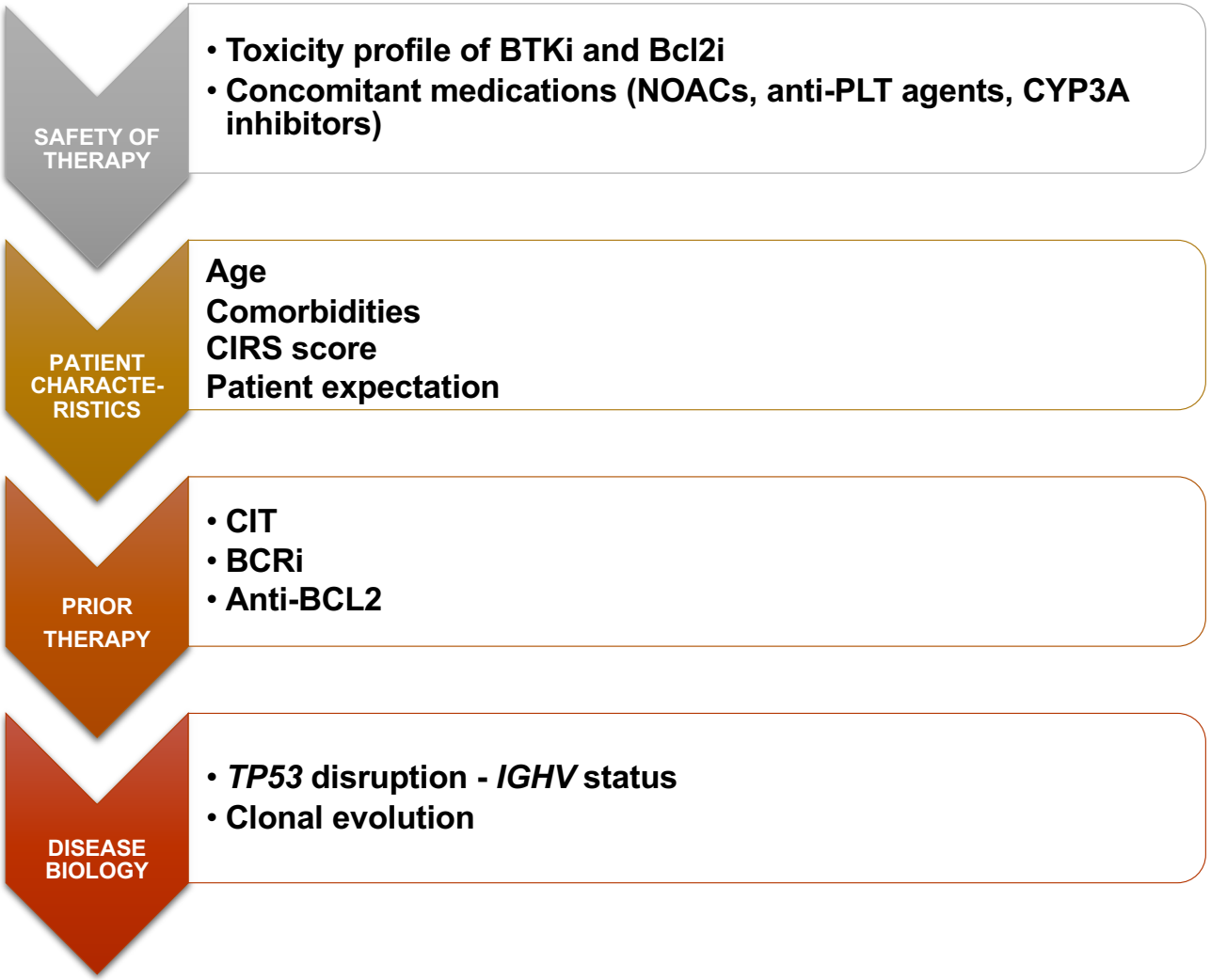
Disclosures of Isacco Ferrarini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	x					x	
Beigene	x					x	
Loxo Oncology	x						

Outline

- Choice of therapy and pros/cons of continuous treatment versus fixed duration
- Focus on fixed duration Ven-R for R/R CLL
- Re-treatment after fixed duration therapy

What influences the choice of therapy



Current treatment options in R/R CLL

	BTKi-based	BCL2i-based
	Ibrutinib **Acalabrutinib** **Zanubrutinib**	**Venetoclax+R**
Treatment duration →	Continuous	Fixed, time-limited

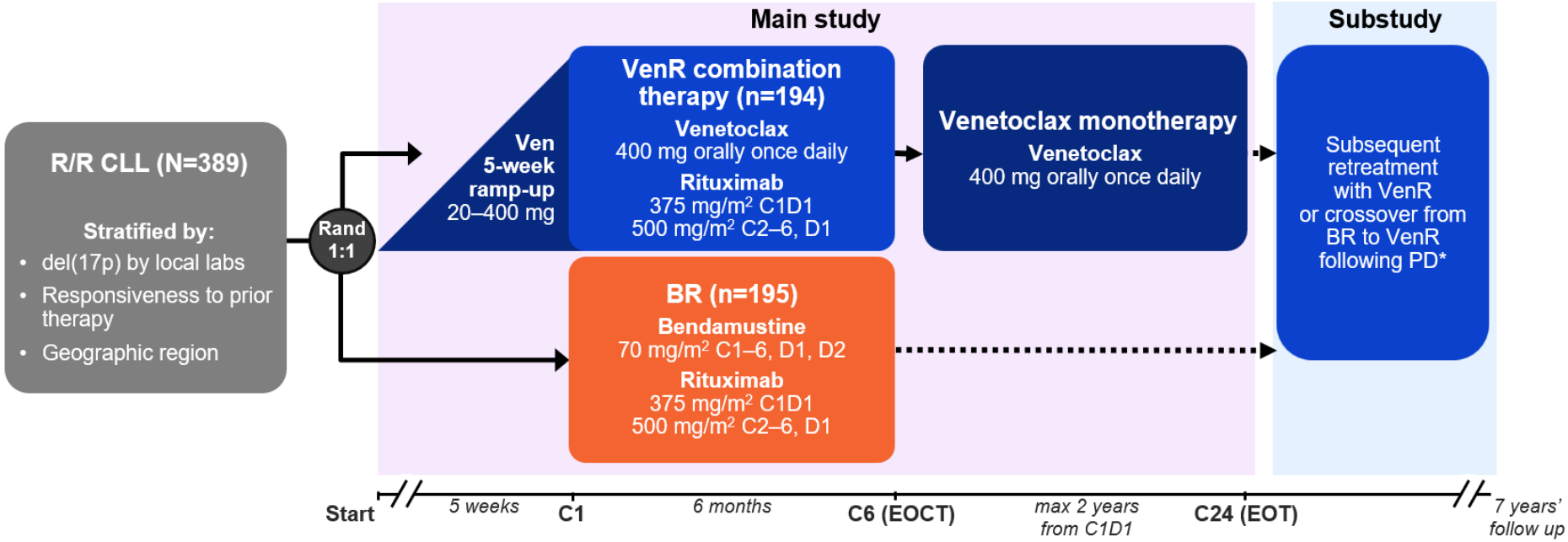
Continuous therapy	Vs	Time-limited therapy
Pros:		**Pros:**
▪ **Disease control** with continuous treatment but residual disease may remain ▪ **Easy treatment**: no need of hydration and initial hospitalization		▪ Time-limited exposure to **treatment-toxicities** ▪ **Treatment-free time** with improvement in the physical and emotional health in treatment-free patients ▪ **Deep response,** fixed treatment duration with potential for uMRD ▪ Potential for **cost saving** ▪ More **adherence** to therapy
Cons:		**Cons:**
▪ **Early toxicities**: bleeding events, atrial fibrillation, myalgias/arthralgias, headache, infections ▪ **Long term toxicity**: hypertension and cardiac risk, infections ▪ Psychological stress of an endless therapy ▪ Impact of **resistances**		▪ The risk of early **adverse events requires supportive measures** (hydration ± hospitalization) in the initial phase of treatment ▪ Suboptimal response in high risk disease

Outline

- Choice of therapy and pros/cons of continuous treatment versus fixed duration
- Focus on fixed duration Ven-R for R/R CLL
- Re-treatment with BTKi or venetoclax after fixed duration therapy

MURANO (NCT02005471): study design and prior findings

- Global, Phase III, open-label, randomized study[1]



  - Superior PFS and OS was observed with fixed-duration VenR vs BR in patients with R/R CLL[1]
  - At 48 months of follow up, deep responses with uMRD† were associated with favorable PFS[2]

*Investigator-assessed PD according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria. †uMRD is defined as <1 CLL cell/10,000 leukocytes.
BR, bendamustine-rituximab; C, cycle; D, day; del(17p), deletion 17p; EOCT, end of combination treatment; EOT, end of treatment; max, maximum; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Rand, randomization; (u)MRD, (undetectable) minimal residual disease.

1. Seymour JF, et al. N Engl J Med 2018;378(12):1107–20.
2. Kater AP, et al. J Clin Oncol 2020;38(34)4042–54.

Baseline characteristics in patients with R/R CLL

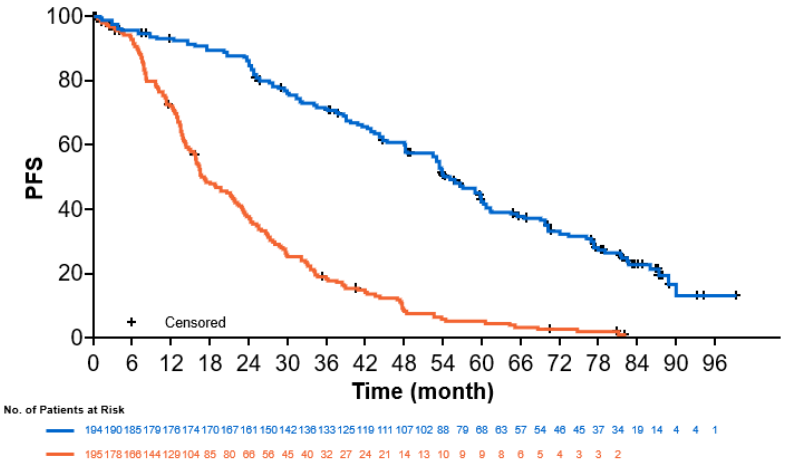
Characteristics		VenR (n=194)	BR (n=195)
Age[1]	Median, years (range)	64.5 (28–83)	66 (22–85)
Lymphocyte count, n (%)[1]	≥25×10^9/L	129 (66.5)	134 (68.7)
del(17p)–(FISH),* n/N (%)[1]	Deleted	46/173 (26.6)	46/169 (27.2)
TP53 mutational status, n/N (%)[1]	Mutated *TP53*	48/192 (25.0)	51/184 (27.7)
IGHV 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.

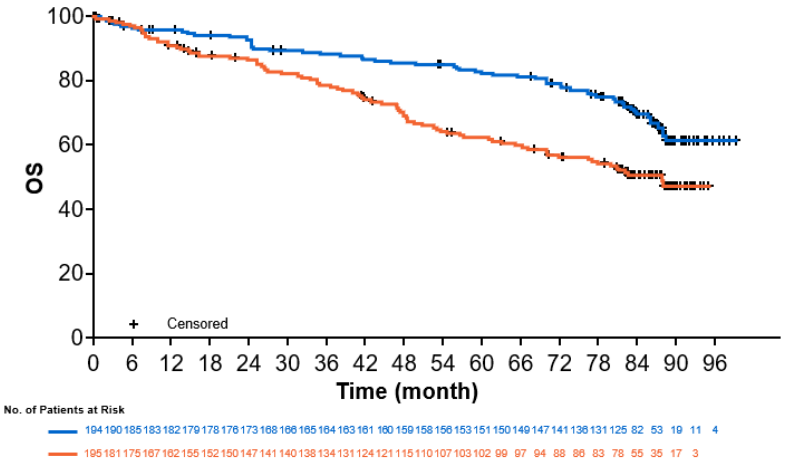
1. Seymour JF, *et al. N Engl J Med* 2018; **378:**1107–1120 (incl. suppl.);
2. Seymour JF, *et al.* ASH 2019. Abstract 355 (Oral);
4. VENCLYXTO® (venetoclax). EMA Summary of Product Characteristics (April 2020 update).

PFS and OS benefits with VenR over BR were sustained at 7 years

	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



	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



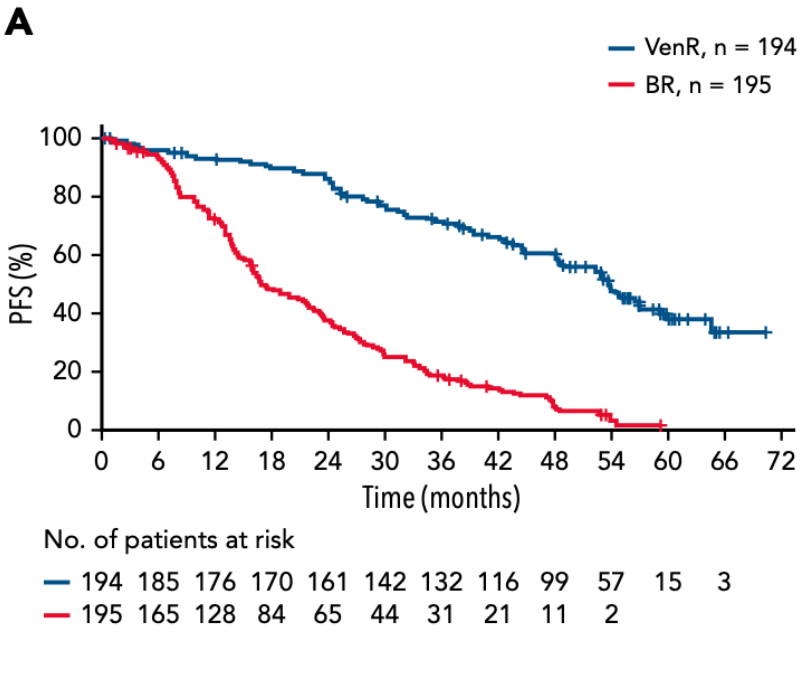
- Median follow up for efficacy (range) was 86.8 months (0.3–99.2) for VenR and 84.4 months (0.0−95.0) for BR
- No new safety signals were identified since the 5-year data cut,[1] with all patients outside of the AE reporting window§

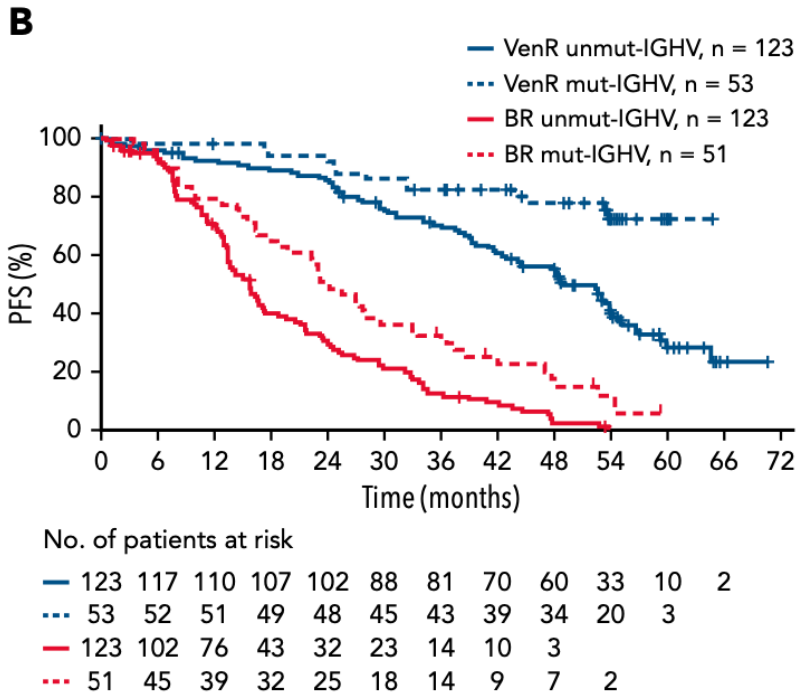
*Stratified HR is presented, unstratified HR=0.25. †P-values are descriptive only. ‡Stratified HR is presented, unstratified HR=0.54. §All AEs were reported until 28 days after the last dose of Ven or 90 days after last dose of R, whichever was longer. After this, only deaths, serious AEs, or AEs of concern that were believed to be Ven-related were reported. AE, adverse event; CI, confidence interval; HR, hazard ratio; NE, not estimable.

Seymour JF, et al. Blood 2022;140(8):839–50.

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

Venetoclax-Rituximab in R/R CLL: 5-year clinical update





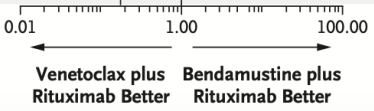
Treatment arm	Median PFS, months (95% CI)	HR (95% CI); *P* value*	5-year PFS, % (95% CI)
VenR	53.6 (48.4, 57.0)	0.19 (0.15, 0.26);	37.8 (28.8, 46.8)
BR	17.0 (15.5, 21.7)	< .0001	NE

Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	unmut-IGHV	52.2 (44.1, 53.8)	2.96 (1.64, 5.34);	28.7 (18.5, 38.9)
	mut-IGHV	NE	.0002	72.7 (59.7, 85.6)
BR	unmut-IGHV	15.7 (13.4, 17.3)	1.79 (1.24, 2.58);	NE
	mut-IGHV	24.2 (18.6, 32.8)	.0015	NE

Seymour JF et al, *Blood*, 2022

Venetoclax-Rituximab in R/R CLL

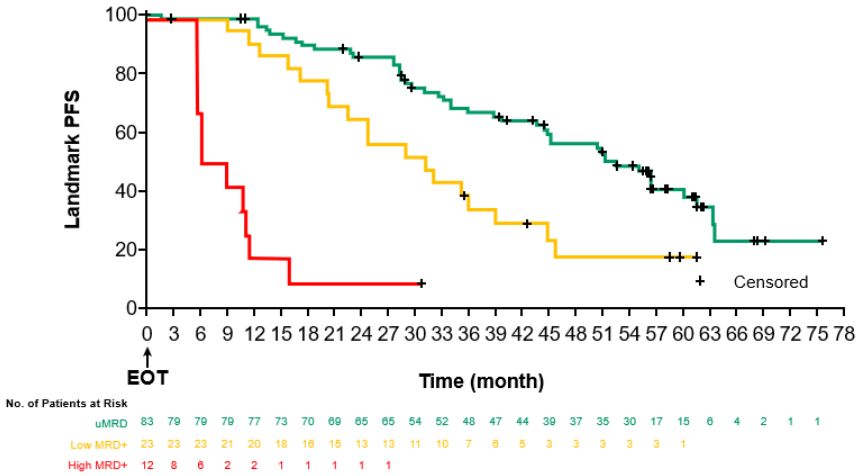
Subgroup	Total No.	Venetoclax–Rituximab Group		Bendamustine–Rituximab Group		Hazard Ratio (95% Wald CI)
		no.	*median (mo)*	*no.*	*median (mo)*	
All patients	389	194	NR	195	17.0	0.17 (0.12–0.26)
Age						
<65 yr	186	97	NR	89	15.4	0.11 (0.06–0.21)
≥65 yr	203	97	NR	106	21.7	0.24 (0.14–0.41)
CLL risk status						
Low	178	90	NR	88	21.6	0.14 (0.07–0.28)
High	211	104	NR	107	15.4	0.19 (0.11–0.30)
Geographic region						
United States and Canada	34	16	NR	18	15.8	0.29 (0.10–0.83)
Australia and New Zealand	86	44	NR	42	24.5	0.34 (0.16–0.72)
Western Europe	131	66	NR	65	17.1	0.11 (0.05–0.23)
Central and Eastern Europe	130	64	NR	66	15.5	0.13 (0.06–0.27)
Asia	8	4	NR	4	13.6	0.28 (0.03–2.69)
No. of previous therapies						
1	228	111	NR	117	16.6	0.14 (0.08–0.24)
2	100	57	NR	43	21.2	0.24 (0.11–0.50)
≥3	61	26	NR	35	10.5	0.24 (0.10–0.57)
Effect of most recent therapy						
CLL refractory to therapy	59	30	NR	29	13.6	0.32 (0.15–0.70)
Relapse of CLL	330	164	NR	166	18.6	0.14 (0.09–0.23)
Chromosome 17p deletion status						
Absent	250	127	NR	123	21.4	0.19 (0.12–0.32)
Present	92	46	NR	46	15.4	0.13 (0.05–0.29)
TP53 mutation status						
Unmutated	277	144	NR	133	21.2	0.15 (0.09–0.25)
Mutated	99	48	NR	51	12.9	0.19 (0.10–0.36)
Baseline *IGHV* mutation status						
Unmutated	246	123	NR	123	15.7	0.16 (0.10–0.26)
Mutated	104	53	NR	51	22.9	0.11 (0.04–0.31)



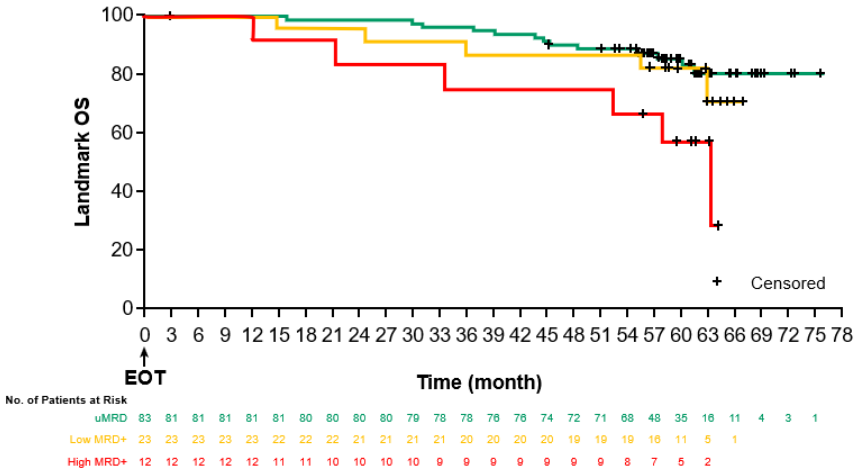
Seymour JF et al, *NEJM*, 2018

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



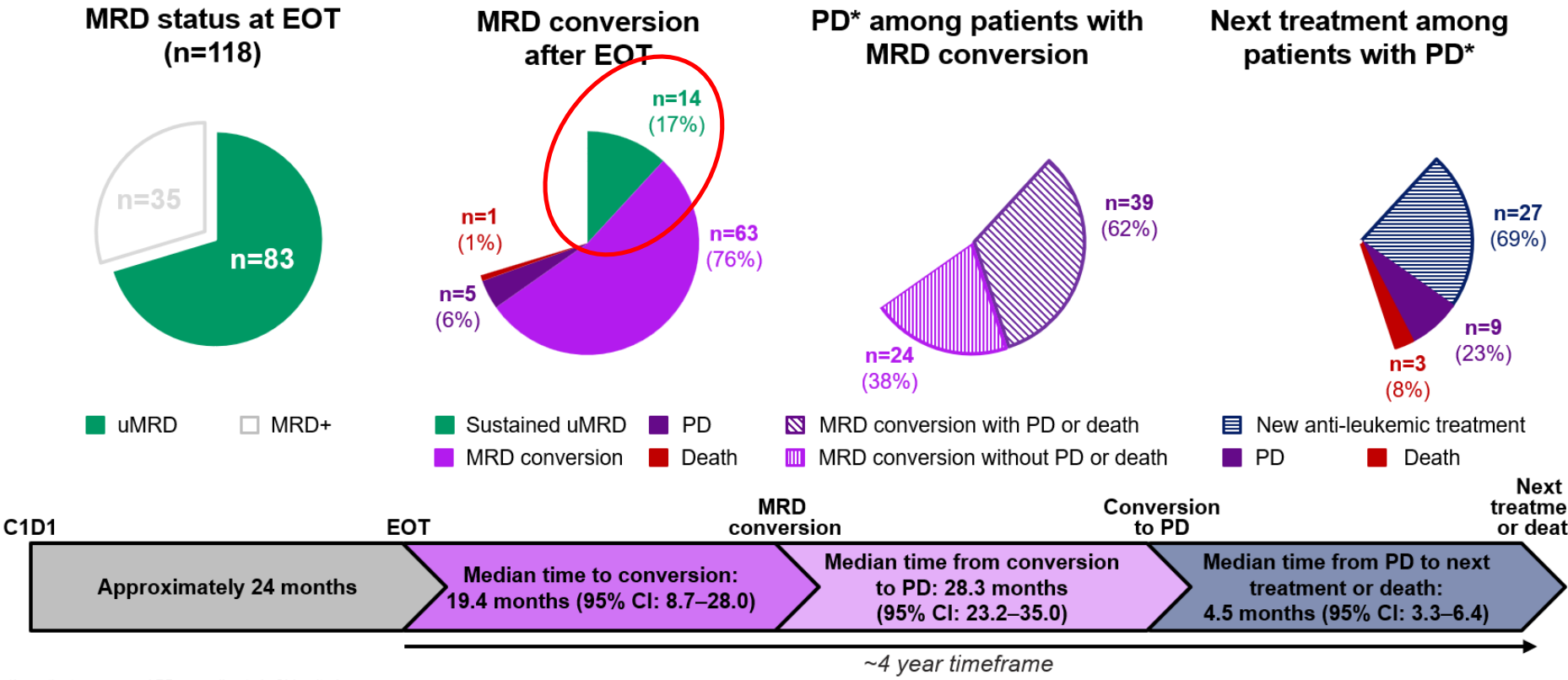
Achievement of uMRD was associated with prolonged PFS in VenR-treated patients

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

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

Venetoclax-Rituximab in R/R CLL
MRD kinetics

MRD status	ITT N = 194	IGHV		GC (≥3 CNA)		del(17p)	
		Unmut n = 123*	Mut n = 53*	GC n = 48*	No GC n = 94*	Present n = 17*	Absent n = 125*
uMRD at EOT	83 (42.8%)	56 (45.5%)	23 (43.4%)	18 (37.5%)	40 (42.5%)	4 (23.5%)	54 (43.2%)
Sustained uMRD	32 (16.5%)	20 (35.7%)	10 (43.5%)	5 (27.8%)	16 (40.0%)	0 (0%)	21 (38.9%)
Conversion to MRD (no PD)	28 (14.4%)	15 (26.8%)	12 (52.2%)	5 (27.8%)	16 (40.0%)	0 (0%)	21 (38.9%)
Conversion with subsequent PD	19 (9.8%)	21 (37.5%)	1 (4.3%)	8 (44.4%)	8 (20.0%)	4 (100%)	12 (22.2%)

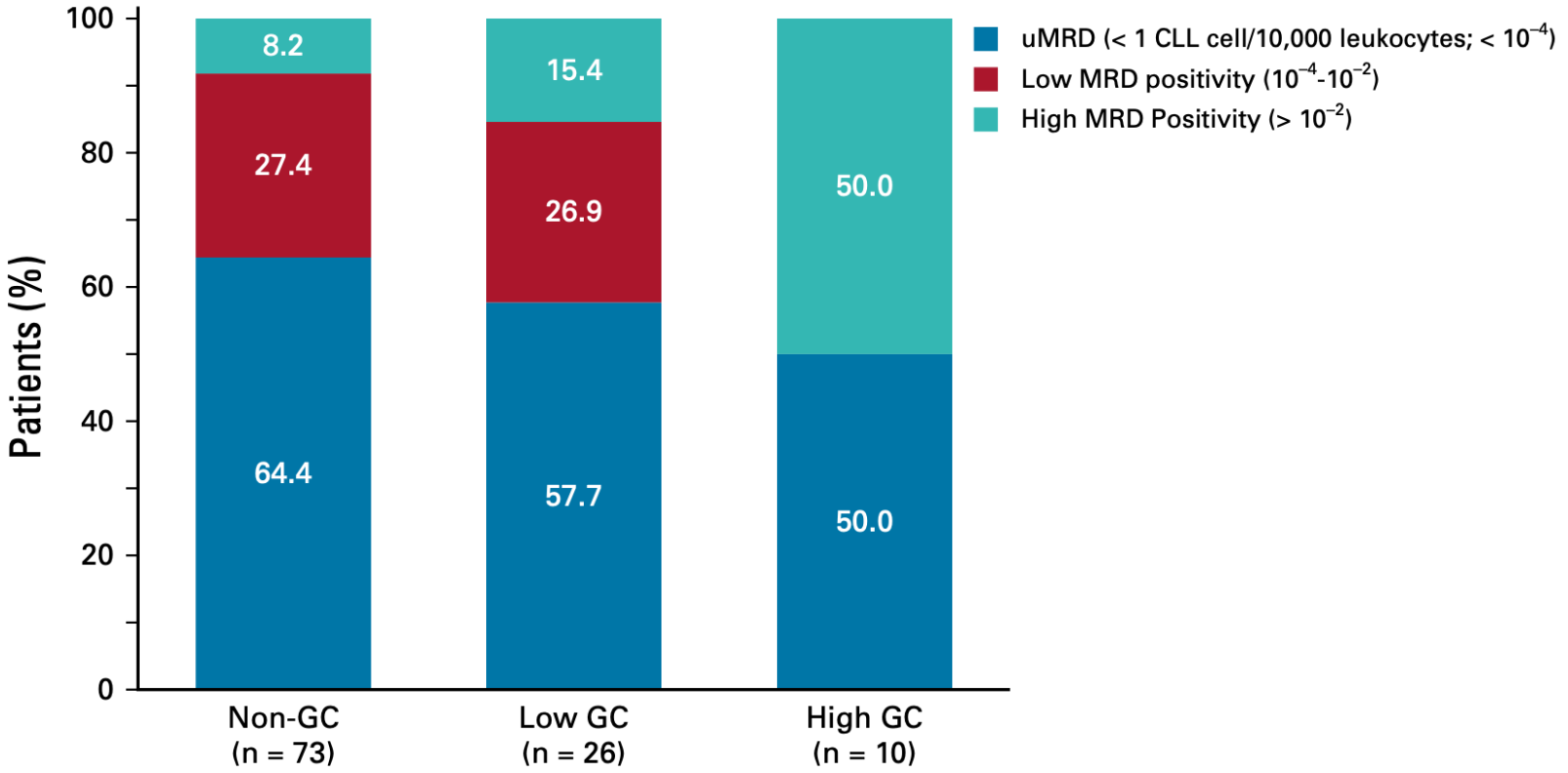
Seymour JF et al, *Blood*, 2022

Venetoclax-Rituximab in R/R CLL
MRD kinetics

Parameter	VenR (n = 91)		BR (n = 120)	
Median MRD at EOT	mut-IGHV (n = 22)	unmut-IGHV (n = 69)	mut-IGHV (n = 33)	unmut-IGHV (n = 87)
	3.40×10^{-5}	1.88×10^{-5}	1.11×10^{-3}	4.46×10^{-4}
	$P = .79$		$P = .6$	
	TP53-WT* (n = 73)	*TP53*-mut* (n = 18)	*TP53*-WT* (n = 98)	*TP53*-mut* (n = 22)
	1.87×10^{-5}	3.56×10^{-5}	1.94×10^{-2}	3.07×10^{-2}
	$P = .48$		$P = .002$	
Median MRD doubling time, d	mut-IGHV (n = 22)	unmut-IGHV (n = 69)	mut-IGHV (n = 33)	unmut-IGHV (n = 87)
	192	80	57	52
	$P = .0031$		$P = .093$	
	TP53-WT* (n = 73)	*TP53*-mut* (n = 18)	*TP53*-WT* (n = 98)	*TP53*-mut* (n = 22)
	101	66	54	45
	$P = .0012$		$P = .072$	
	Age ≥65 y (n = 44)	Age <65 y (n = 47)	Age ≥65 y (n = 75)	Age <65 y (n = 45)
	109	80	57	43
	$P = .012$		$P = .0036$	
	Low/medium TLS risk (n = 65)	High TLS risk (n = 26)	Low/medium TLS risk (n = 86)	High TLS risk (n = 34)
	105	63	56	51
	$P = .0001$		$P = .02$	

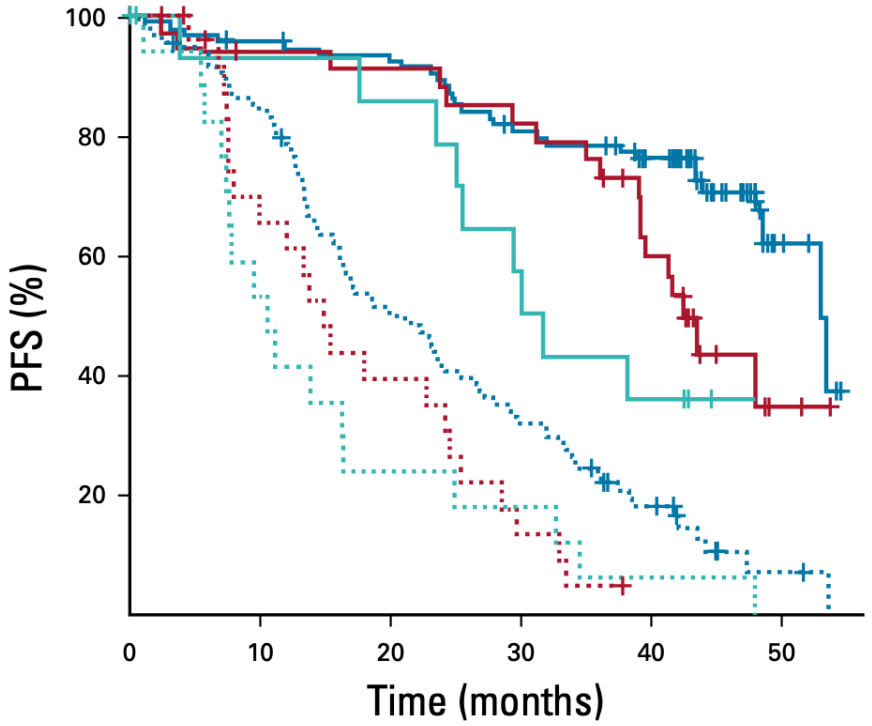
Seymour JF et al, *Blood*, 2022

Venetoclax-Rituximab in R/R CLL: impact of genomic complexity



Kater AP et al, *JCO*, 2020

Venetoclax-Rituximab in R/R CLL: impact of genomic complexity



No. at risk:

VenR non-GC	94	89	85	73	63	7
VenR low GC	34	31	30	27	18	2
VenR high GC	14	13	12	8	5	0
BR non-GC	100	78	46	29	14	2
BR low GC	29	15	9	3	0	0
BR high GC	17	9	4	3	1	0

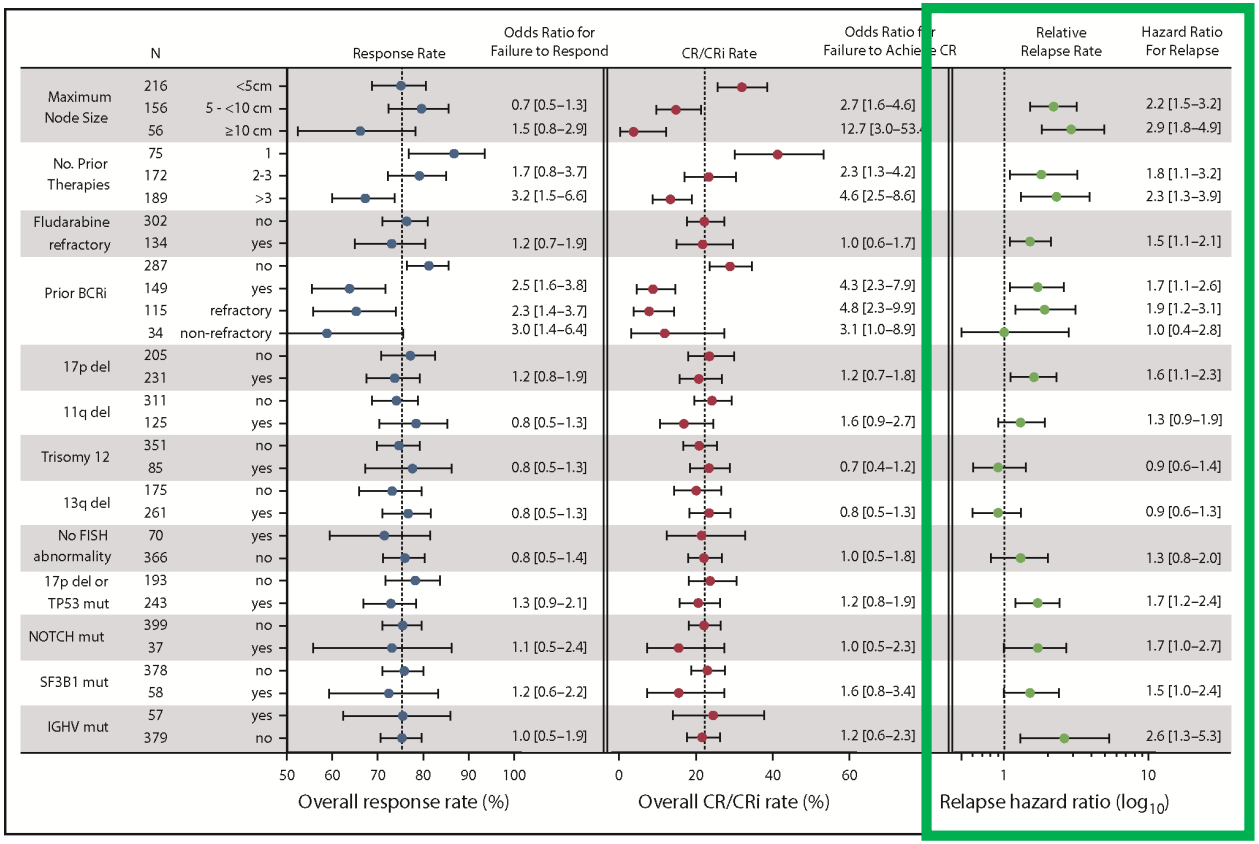
	Category	HR (95% CI)	*P*
VenR	Non-GC *v* low GC	2.0 (1.1 to 3.6)	.025
	Non-GC *v* high GC	2.9 (1.4 to 6.3)	.0057
	Low GC *v* high GC	1.5 (0.69 to 3.4)	.29
BR	Non-GC *v* low GC	1.7 (1.0 to 2.7)	.039
	Non-GC *v* high GC	1.9 (1.1 to 3.2)	.02
	Low GC *v* high GC	1.2 (0.61 to 2.2)	.65

Kater AP et al, *JCO*, 2020

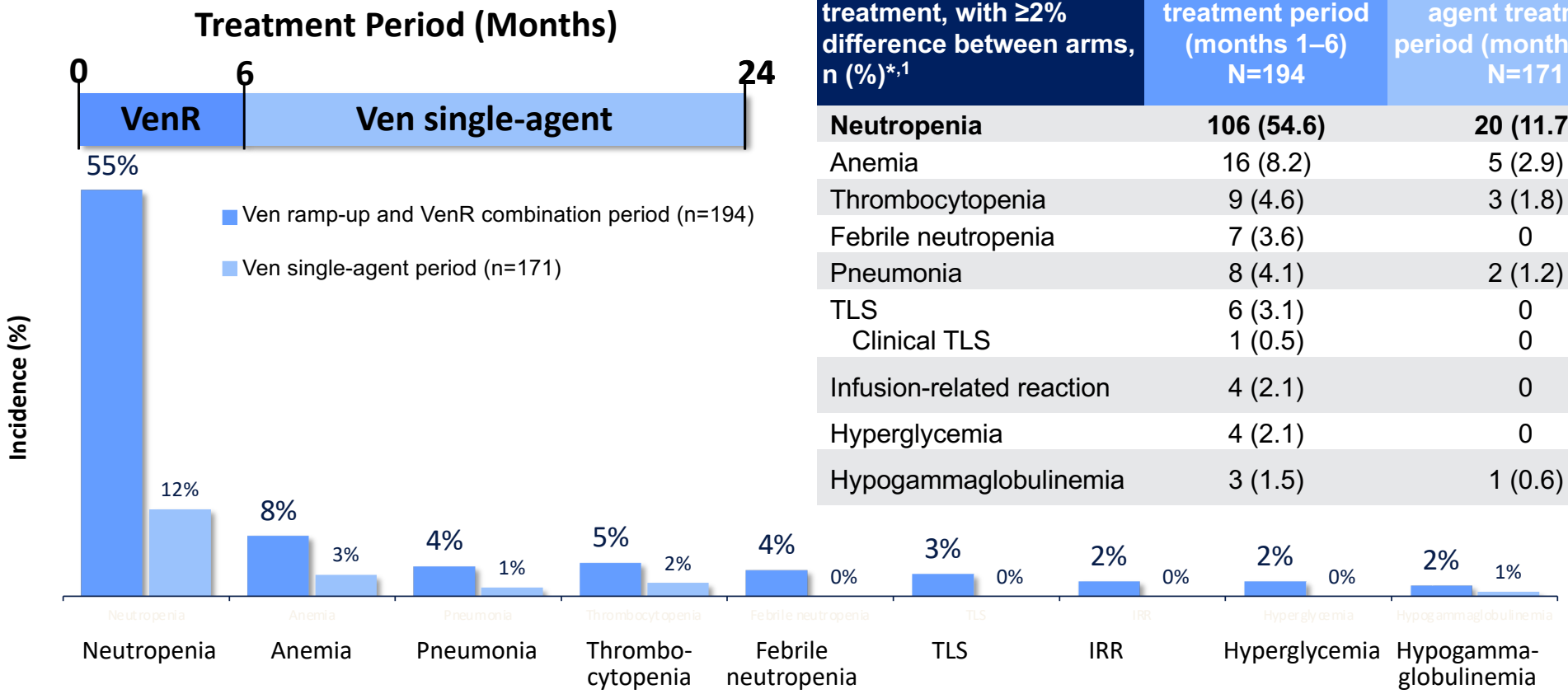
Efficacy of venetoclax in relapsed chronic lymphocytic leukemia is influenced by disease and response variables

Clinical Trials & Observations

Andrew W. Roberts, Shuo Ma, Thomas J. Kipps, Steven E. Coutre, Matthew S. Davids, Barbara Eichhorst, Michael Hallek, John C. Byrd, Kathryn Humphrey, Lang Zhou, Brenda Chyla, Jacqueline Nielsen, Jalaja Potluri, Su Young Kim, Maria Verdugo, Stephan Stilgenbauer, William G. Wierda, John F. Seymour



MURANO trial: Grade ≥3 AEs with incidence of ≥2% over time



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	6 (3.1)	0
Clinical TLS	1 (0.5)	0
Infusion-related reaction	4 (2.1)	0
Hyperglycemia	4 (2.1)	0
Hypogammaglobulinemia	3 (1.5)	1 (0.6)

- AE=Adverse Events. CLL=Chronic Lymphocytic Leukemia. IRR=Infusion-Related Reaction.
- R=Rituximab. R/R=Relapsed/Refractory. TLS=Tumor Lysis Syndrome. Ven=Venetoclax.

Seymour JF, et al. Oral #355. 61st ASH Annual Meeting. 2019

Infection rates in trials with venetoclax

- Common hematological toxicities, including grade 3 to 4 neutropenia, in ~40% of patients receiving single-agent venetoclax
- Grade 3 to 4 neutropenia more frequent in combination with anti-CD20 antibodies

R/R

MURANO	VR	BR
Infections (gr 3 or more)	17,5%	21,5%
Neutropenia	57,7%	38,8%
Febrile neutropenia	3,6%	8,5%

More neutropenia but less infections and febrile neutropenia

TN

CLL14	Venetoclax + Obi	CLB+ Obi
Infections (gr ≥3)	17,5	15
Febrile neutropenia	5,2	3,7
Pneumonia	4,2	3,7

Reporting time longer for Venetoclax +Obi

Stligenbauer, *Lancet Oncol* 2016; Seymour *NEJM* 2018; Fischer K, *NEJM* 2019

Venetoclax-Rituximab in R/R CLL: Impact of early discontinuation

- Median PFS for early discontinuation due to any reason except PD was 24.3 months, compared with 52.3 for all patients in the VenR arm and not reached in patients who completed venetoclax treatment.

- **Discontinuing treatment early (for any reason except PD) was significantly associated with shorter PFS (n=181; HR 5.98, 95% CI: 3.31–10.82; P<0.0001).**

Mato AR et al, *Haematologica*, 2022

Venetoclax-Rituximab in R/R CLL: Impact of early discontinuation

- Treatment interruption for AE occurred in 134 of 194 (69%) patients, most commonly due to neutropenia (84 of 194; 43%), per protocol requirements.
- Treatment interruption had no impact on PFS or OS, regardless of duration.

Table 6. **MURANO: impact of interruption of venetoclax treatment *versus* no interruption on outcomes for all patients.**

	Duration of treatment interruption (n=194 patients)			
	≥1 days	≥8 days	≥14 days	≥21 days
Patients, n	137 (70.6%)	76 (39.2%)	50 (25.8%)	34 (17.5%)
Progression-free survival				
Events, n (%)	49 (35.8)	29 (38.2)	20 (40.0)	13 (38.2)
HR (95% CI)	0.67 (0.38-1.19)	1.01 (0.59-1.71)	0.92 (0.51-1.65)	0.82 (0.41-1.65)
P-value	0.1709	0.9741	0.7671	0.5753
Overall survival				
Events, n (%)	17 (12.4)	11 (14.5)	8 (16.0)	5 (14.7)
HR (95% CI)	0.97 (0.43-2.21)	1.35 (0.60-3.02)	1.47 (0.63-3.45)	1.31 (0.46-3.73)
P-value	0.9474	0.4646	0.3730	0.6193

CI: confidence interval; HR: hazard ratio.

Mato AR et al, *Haematologica*, 2022

Venetoclax-Rituximab in R/R CLL: Impact of early discontinuation

- Dose reductions were required by 45 of 194 (23%) patients, but had no significant impact on outcomes.

Table 7. **MURANO: landmark analysis of progression-free surviva by venetoclax relative dose intensity quartiles.**

	Min (26.4%) – <Q1 (93.6%) n=33	Q1 (93.6%) – <Median (98.1%) n=35	Median (98.1) – <Q3 (99.5%) n=34	Q3 (99.5%) – Max (100.0%) n=35
Events, n (%)	8 (24.2)	7 (20.0)	9 (26.5)	11 (31.4)
Kaplan–Meier median, months (95% CI)	NE (22.9–NE)	NE (28.1–NE)	27.3 (18.8–NE)	27.7 (22.3–NE)
HR (95% CI)	1.0	0.57 (0.13–2.49)	1.01 (0.20–5.01)	0.95 (0.28–3.26)
P-value	1.0	0.4575	0.9952	0.9331

The landmark analysis was performed to study the effect of relative dose intensity on progression-free survival (PFS). The patients who completed venetoclax treatment and had not progressed or were censored at the last dose of venetoclax, were included. The PFS was calculated from the last dose of venetoclax to the first occurrence of progression or death from any cause. CI: confidence interval; HR: hazard ratio; Max: maximum; Min: minimum; NE: not estimable; PFS: progression-free survival; Q: quartile.

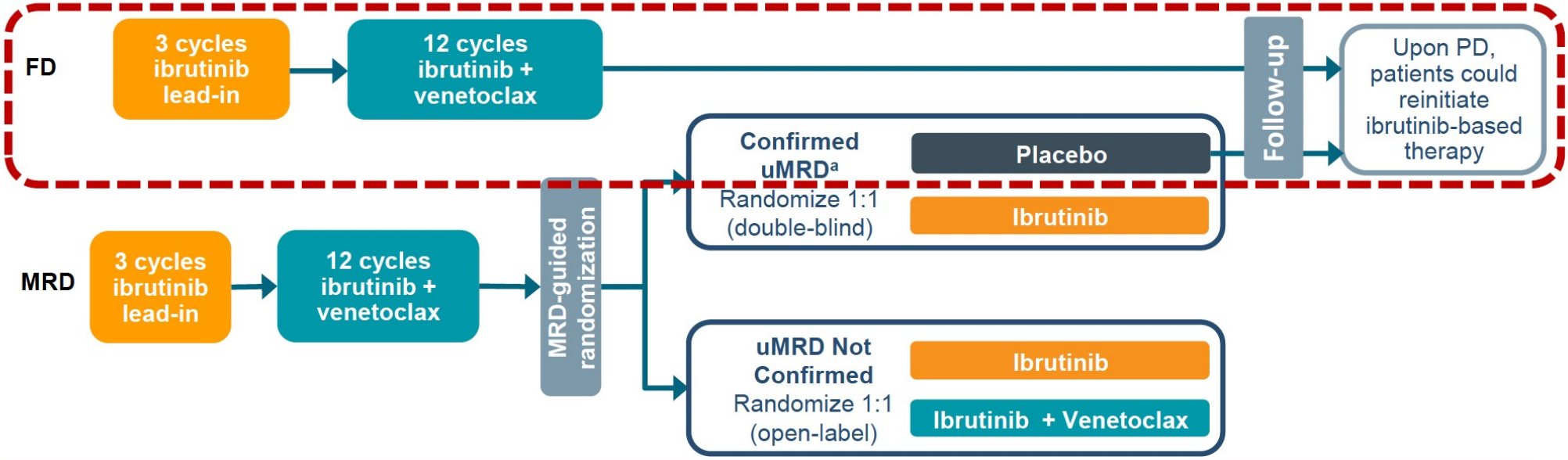
Mato AR et al, *Haematologica*, 2022

Outline

- Choice of therapy and pros/cons of continuous treatment versus fixed duration
- Focus on fixed duration Ven-R for CLL
- Re-treatment with BTKi or venetoclax after fixed duration therapy

CAPTIVATE Study Design

- CAPTIVATE (PCYC-1142; NCT02910583) is an international, multicenter phase 2 study evaluating first-line treatment with ibrutinib + venetoclax that comprises 2 cohorts: MRD[1] and FD[2]
  - Per protocol, patients with PD after completion of fixed-duration ibrutinib + venetoclax in the FD cohort or MRD cohort placebo arm could reinitiate treatment with single-agent ibrutinib
  - Patients with PD >2 years after treatment completion in the FD cohort could be retreated with the fixed-duration regimen (3 cycles of ibrutinib then 12 cycles of ibrutinib + venetoclax)



FD, fixed duration; MRD, minimal residual disease; PD, progressive disease.
[a]Confirmed uMRD was defined as uMRD ($<10^{-4}$ by 8-color flow cytometry) serially over at least 3 cycles in both peripheral blood and bone marrow.
[1]Wierda, WG. *J Clin Oncol.* 2021;39:3853-3865. [2]Tam CS et al. *Blood.* 2022;139:3278-3289.

Baseline Characteristics of Patients With and Without PD

- Of 202 patients treated with fixed-duration ibrutinib + venetoclax in the FD cohort (n=159) or the MRD cohort placebo arm (n=43), 53 have had PD to date
  - 49 patients with progressive CLL and 4 patients with Richter transformation

Characteristic	Patients With CLL PD[a] n=49	Patients Without PD n=149
Median age (range), years	61 (38–71)	60 (33–70)
Male, n (%)	34 (69)	94 (63)
Rai stage III/IV, n (%)	9 (18)	49 (33)
High-risk genomic features, n (%)		
Complex karyotype[b]	9 (18)	23 (15)
del(17p)/mutated *TP53*	11 (22)	17 (11)
del(11q)[c]	13 (27)	22 (15)
Unmutated IGHV	37 (76)	78 (52)
Any cytopenia, n (%)	13 (27)	59 (40)
ANC ≤1.5 × 10^9/L	2 (4)	16 (11)
Hemoglobin ≤11 g/dL	11 (22)	40 (27)
Platelet count ≤100 × 10^9/L	3 (6)	21 (14)
Bulky disease, n (%)		
≥5 cm	17 (35)	47 (32)
≥10 cm	1 (2)	4 (3)
Median ALC × 10^9/L (range)	76 (1–368)	56 (1–503)
ALC ≥25 × 10^9/L, n (%)	39 (80)	111 (74)

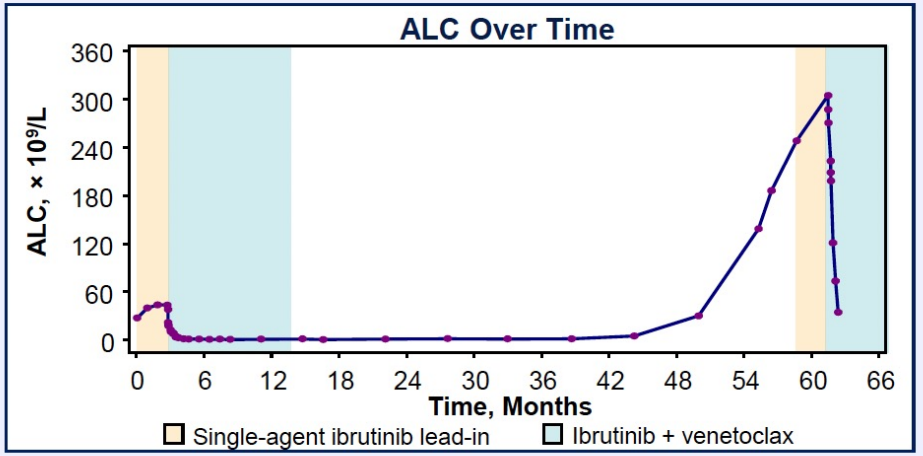
ALC, absolute lymphocyte count; ANC, absolute neutrophil count.
[a]Excluding 4 patients with Richter transformation. [b]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics; complex karyotype status was missing for 10/49 (20%) patients with PD and 20/149 (13%) patients without PD. [c]Without del(17p) per Döhner hierarchy.

Evaluation of *BTK*, *PLCG2*, and *BCL-2* Mutations in Patients with PD

- Samples collected at PD after fixed-duration treatment from 40 patients were evaluated for mutations in *BTK/PLCG2* or *BCL-2* associated with resistance to ibrutinib or venetoclax[a]
  - Median time from start of treatment to PD for these patients was 3.2 years (range, 1.4–4.2)
- No *BTK* or *PLCG2* mutations were identified in the 40 patients evaluated
- In 1 of 40 patients, an acquired subclonal mutation in *BCL-2* (A113G, VAF 8.3%) was identified
  - *BCL-2* A113G identified previously in patients with PD on venetoclax, usually in combination with *BCL-2* G101V (66-100% of cases), the most common venetoclax resistance mutation[1-3]
  - Emergence of subclonal *BCL-2* A113G in the absence of co-occurring *BCL-2* mutations has unclear clinical significance

Patient With *BCL-2* (A113G) at PD

- With initial fixed-duration ibrutinib + venetoclax:
  - uMRD (<0.01%) achieved in both PB and BM by C13 and maintained in PB until C31
  - CR achieved at C10 and maintained through C49
- PD occurred 3 years after EOT
- After PD, reinitiated fixed-duration ibrutinib + venetoclax
  - To date, the patient has PR-L after 4 months of retreatment (3 months of ibrutinib and 1 month of ibrutinib + venetoclax)



BM, bone marrow; C, cycle; PB, peripheral blood; PLCG2, phospholipase C gamma 2; PR-L, partial response with lymphocytosis; VAF, variant allele frequency.

[a]Resistance-associated variants in *BTK*, *PLCG2*, or *BCL-2* were assessed by next-generation sequencing using a custom panel with a limit of detection of 1% VAF.

[1]Popovic R et al, *Am J Hematol.* 2022;97(2):e47-e51. [2]Kotmayer L et al, *Int J Mol Sci.* 2023;24:5802. [3]Lucas F et al, *Blood.* 2020;135:2192-2195.

Time to Next Treatment and Retreatment After Fixed-Duration Ibrutinib + Venetoclax

- 202 patients treated with fixed-duration ibrutinib + venetoclax
  - Median TTNT not reached
  - Estimated 4.5-year rate of freedom from next-line treatment was 82% (95% CI, 76–87)

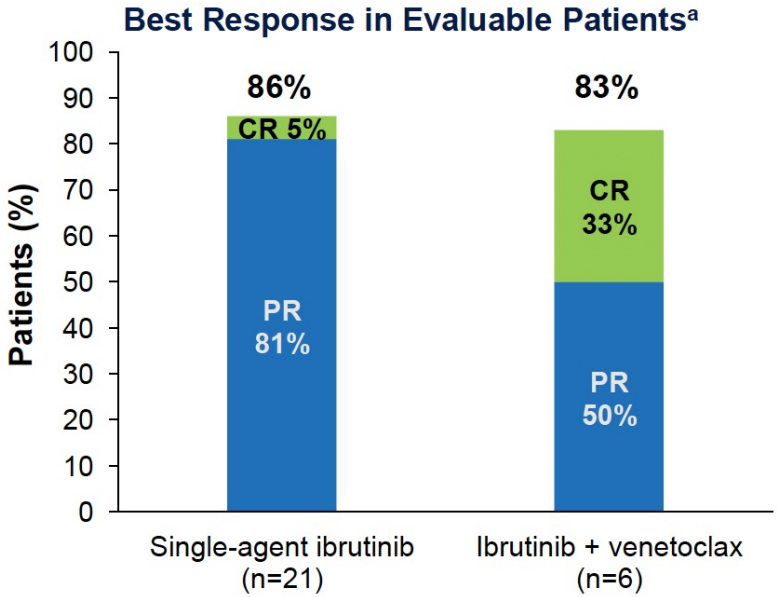
- Of the 53 patients with PD
  - 18 have not yet initiated subsequent treatment
  - 28 have reinitiated ibrutinib-based therapy
    - Median time from EOT to PD for these patients was 2.1 years (range, 0.2–4.3)[a]
    - 22 reinitiated with single-agent ibrutinib
    - 6 reinitiated with ibrutinib + venetoclax
  - 7 have initiated other subsequent therapies[b]

Characteristic	Patients With PD Retreated with Ibrutinib-Based Therapy (n=28)
Median age (range), years	62 (39–71)
Male, n (%)	19 (68)
Rai stage III/IV, n (%)	5 (18)
High-risk genomic features, n (%)	
Complex karyotype[c]	10 (36)
del(17p)/mutated *TP53*	9 (32)
del(11q)[d]	7 (25)
Unmutated IGHV	22 (79)
Any cytopenia, n (%)	9 (32)
ANC ≤1.5 × 10^9/L	0
Hemoglobin ≤11 g/dL	7 (25)
Platelet count ≤100 × 10^9/L	2 (7)
Bulky disease, n (%)	
≥5 cm	9 (32)
≥10 cm	1 (4)
Median ALC × 10^9/L (range)	74 (1–297)
ALC ≥25 × 10^9/L, n (%)	22 (79)

TTNT, time to next treatment.
[a]Per protocol, only patients with PD >2 years after completion of treatment were eligible to reinitiate ibrutinib + venetoclax. [b]Subsequent therapies included acalabrutinib, pirtobrutinib, umbralisib + ublituximab + venetoclax, venetoclax + rituximab, and stem cell transplant. [c]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics; complex karyotype status was missing for 5/28 (18%) patients. [d]Without del(17p) per Döhner hierarchy.

Responses and Safety With Reintroduction of Ibrutinib-Based Therapy

- Median time on retreatment:
  - 17 months (range, 0–45) for single-agent ibrutinib (n=22)
  - 14 months (range, 5–15) for ibrutinib + venetoclax (n=6)



AEs, n (%)	Single-agent ibrutinib (n=22)	Ibrutinib + venetoclax (n=6)
Any AE	18 (82)	6 (100)
Most frequent AEs[b]		
COVID-19[c]	6 (27)	2 (33)
Diarrhea	5 (23)	2 (33)
Hypertension	4 (18)	3 (50)
Pyrexia	3 (14)	0
Grade 3/4 AEs	5 (23)	2 (33)
Serious AEs	4 (18)	0
AEs leading to discontinuation	0	0
AEs leading to dose reduction	0	0

AE, adverse event; CR, complete response; PR, partial response.
[a]One patient who initiated single-agent ibrutinib retreatment had not yet undergone response assessment. [b]Occurring in ≥10% of patients with single-agent ibrutinib or ≥2 patients with ibrutinib + venetoclax. [c]All events were grade 1/2.

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Venetoclax retreatment of patients with chronic lymphocytic leukemia after a previous venetoclax-based regimen

Clinical Trials & Observations

Meghan C. Thompson, Rosemary A. Harrup, Catherine C. Coombs, Lindsey E. Roeker, Jeffrey J. Pu, Michael Y. Choi, Paul M. Barr, John N. Allan, Martin Šimkovič, Lori Leslie, Joanna Rhodes, Elise A. Chong, Manali Kamdar, Alan Skarbnik, Frederick Lansigan, Brittany McCall, Khalid Saja, Martin J. S. Dyer, Harriet S. Walter, Marcus Lefebure, Maria Thadani-Mulero, Michelle Boyer, Juliana Biondo, Kavita Sail, Beenish S. Manzoor, Richard Furman, Kurt S. Bantilan, Andre Goy, Tatyana Feldman, Dominic Labella, Stephen J. Schuster, Jae Park, Lia Palomba, Andrew Zelenetz, Toby A. Eyre, Arnon P. Kater, John F. Seymour, Anthony R. Mato

- 46 patients with CLL previously exposed to venetoclax were re-treated with venetoclax
- In most cases (91.3%), Ven1 was administered in the relapsed and/or refractory setting.
- The median number of prior therapies was 2 (0-10), and 40.0% of patients had received a Bruton's tyrosine kinase inhibitor (BTKi) prior to Ven1.
- Ven1 was commonly administered in combination with anti-CD20 antibody therapy (rituximab 47.8%; obinutuzumab 4.3%) or as monotherapy (37.0%).

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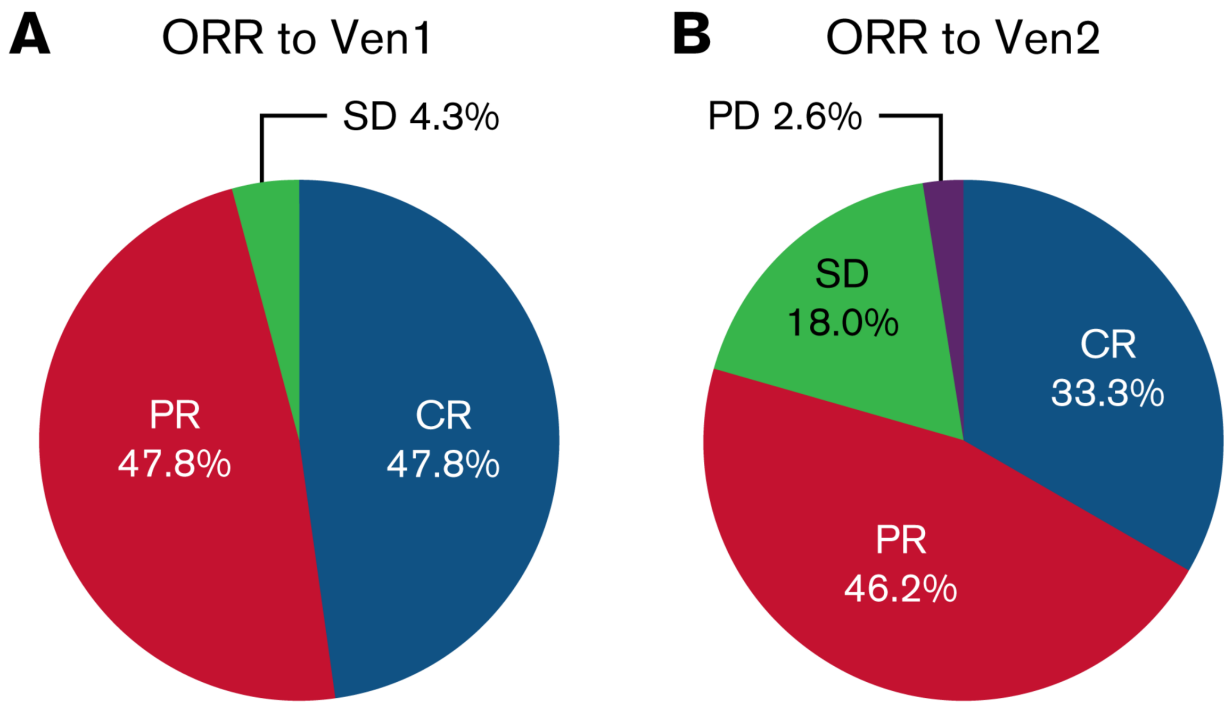

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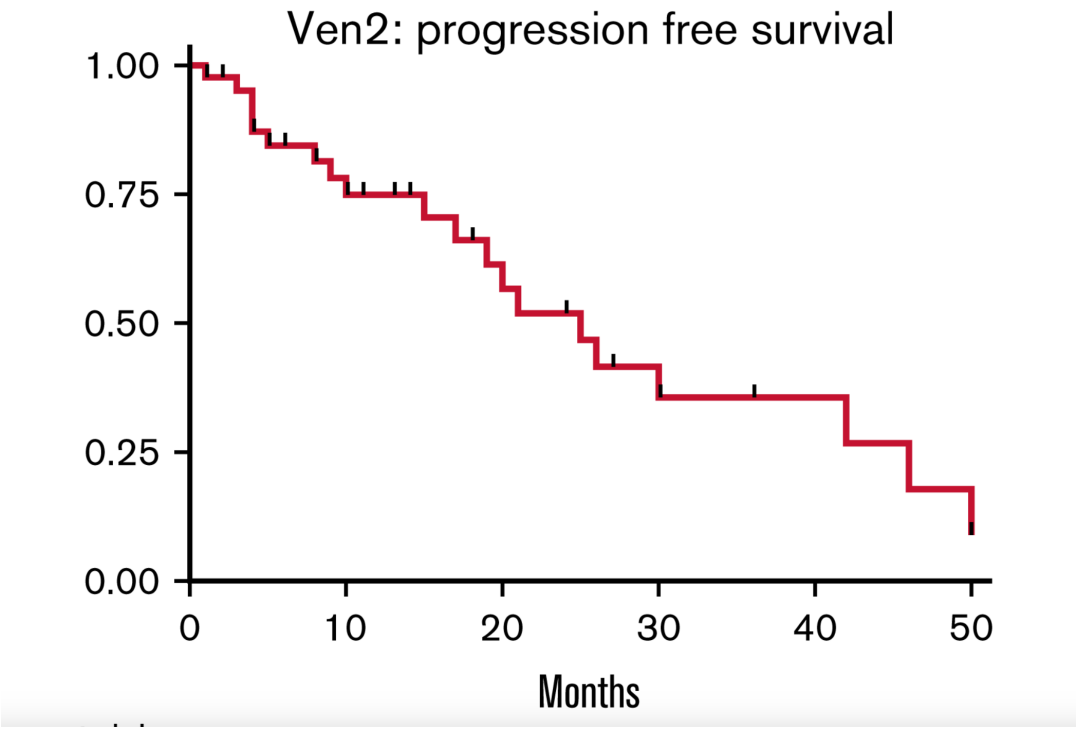


At a median follow-up of 10 months (range 1-50 months), the median Ven2 PFS for the overall cohort was 25 months

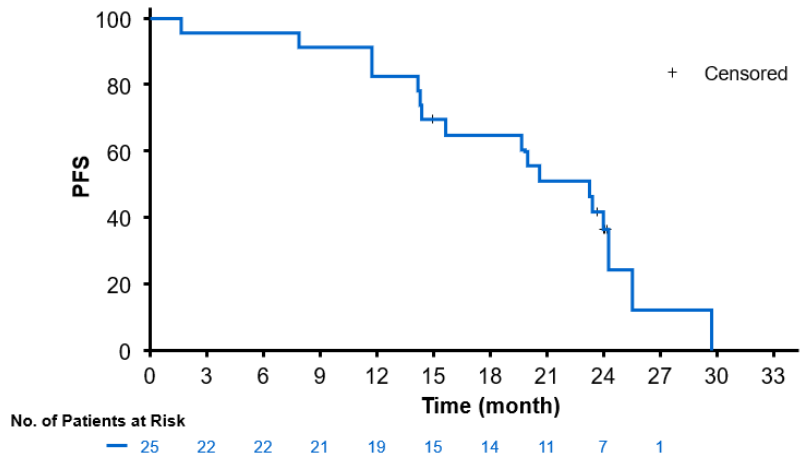
For the subgroup of patients with BTKi exposure prior to Ven1 (n = 18), the ORR to Ven2 was 56.3% (n = 16 patients with available response assessments) and the median PFS was 15 months (median follow-up 8 months, n = 18 patients)

VenR retreatment resulted in high response rates, which translated to meaningful PFS amongst retreated patients

- Amongst VenR-retreated patients, median follow up (range) was 33.4 months (2.7–44.0)
  - Median PFS (95% CI) was 23.3 months (15.6–24.3)
  - Best ORR was high at 72.0%; CR rates were 24%
  - Median OS was not reached

Response rates indicate that VenR retreatment is a viable option for pretreated patients

PFS for VenR-retreated patients in the substudy



CR, complete response.

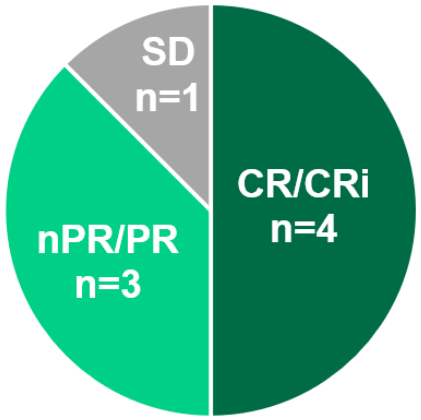
Kater A, *et al.* EHA 2023. Abstract S201 (Oral).

uMRD status was attainable upon retreatment with VenR but was not sustained for the duration of treatment

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

No patients retained their uMRD status at the retreatment EOT

Best ORR for VenR retreated patients who achieved uMRD



CR/CRi, complete remission/complete remission with incomplete count recovery; nPR/PR, nodular partial remission/partial remission; PR, partial remission' SD, stable disease.

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

Thank you for your attention