IL CONCETTO DELLA "DURATA FISSA" DAL FARMACOLOGO ALL'EMATOLOGO

Nel paziente pretrattato

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REVOLUTIONARY ROAD IN CLL

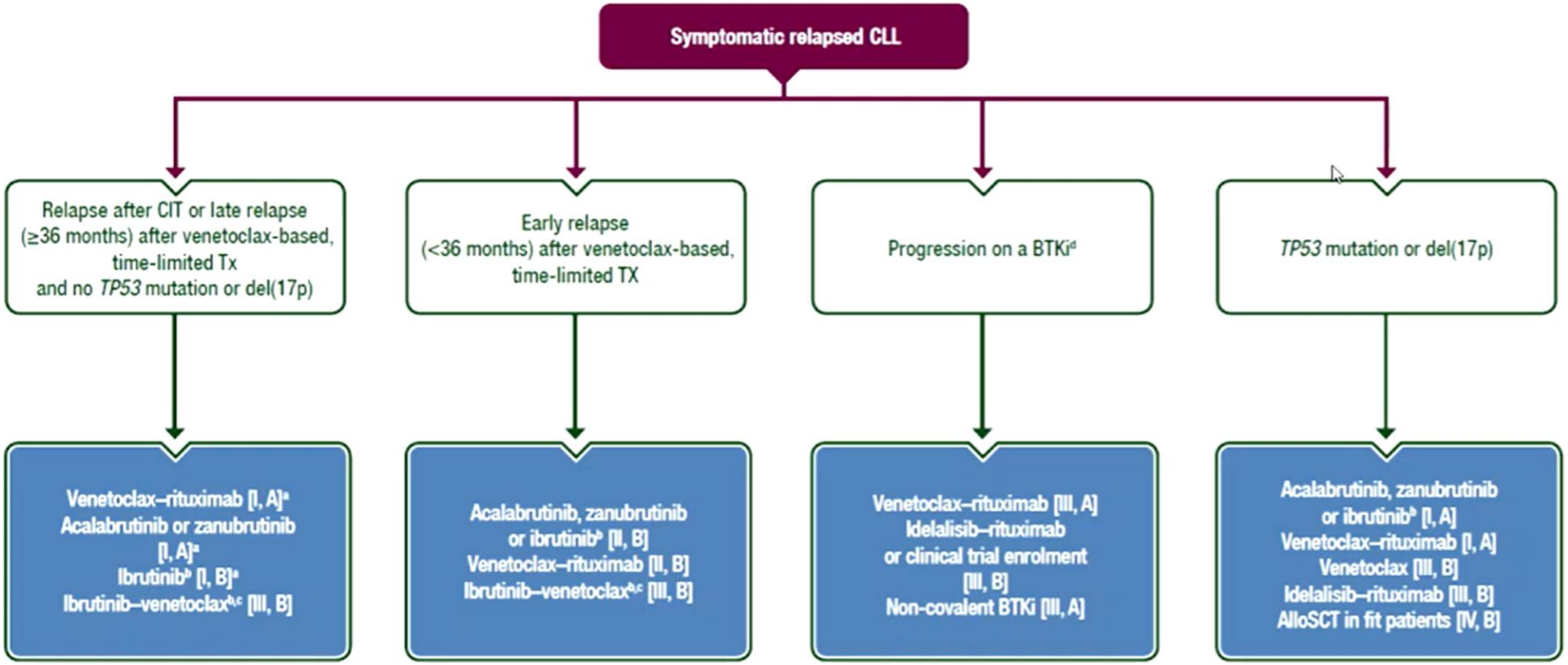
Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Milano, 10 luglio 2024
Starhotels E.c.ho.

Disclosures: Lydia Scarfò

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AstraZeneca						x	
AbbVie						x	
MSD			x				
BeiGene			x			x	
Janssen			x			x	
Lilly/Loxo						x	

2024 ESMO Guidelines



[a]For relapse after CIT, BTKis or venetoclax–rituximab should be considered equally, depending on comorbidities, comedication, access and preference.
[b]Ibrutinib should be considered carefully particularly in older patients with cardiac comorbidities. [c]Not EMA approved, not FDA approved in relapse.
[d]If a patient relapses after prior treatment with a BTKi, which was stopped due to side-effects, changing to a different BTKi or rechallenge could be considered [III, B].

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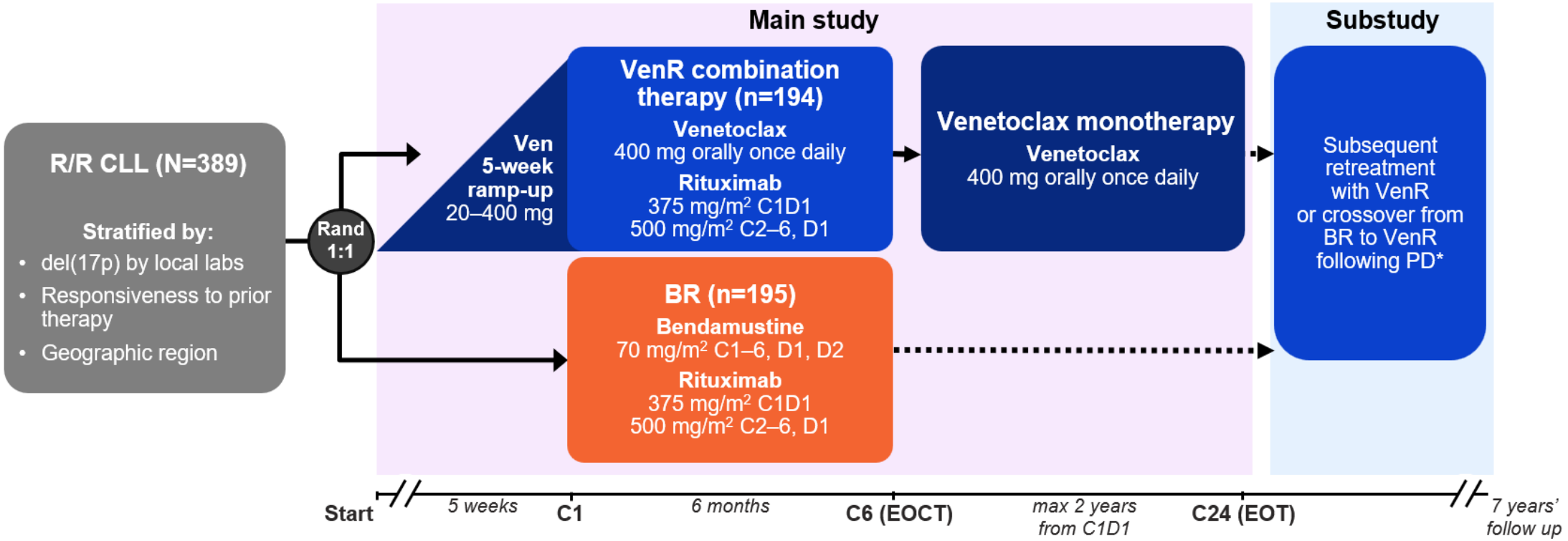
Eichhorst B. & Ghia P. et al., submitted 2024

VenR vs BR in RR CLL: the MURANO Study

- 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.

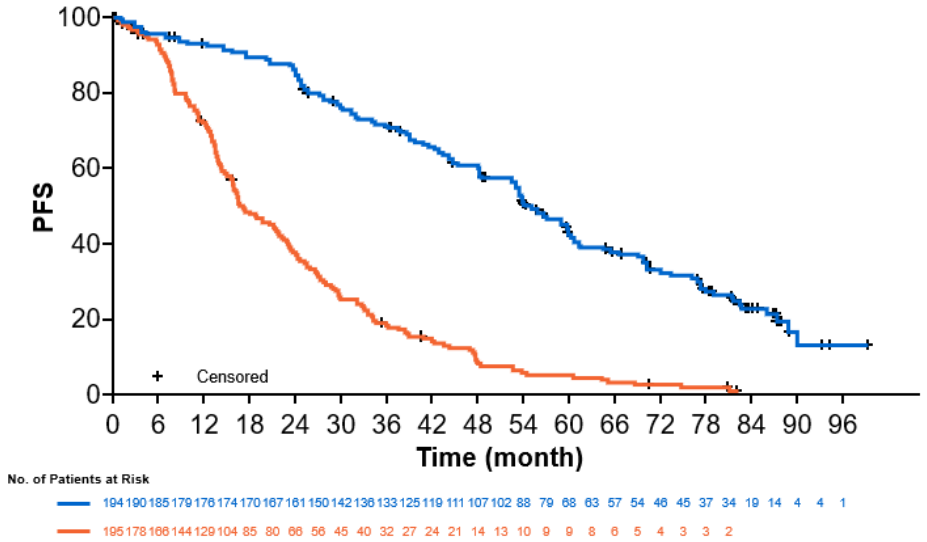
VenR vs BR in RR CLL: Baseline Pt Characteristics

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)

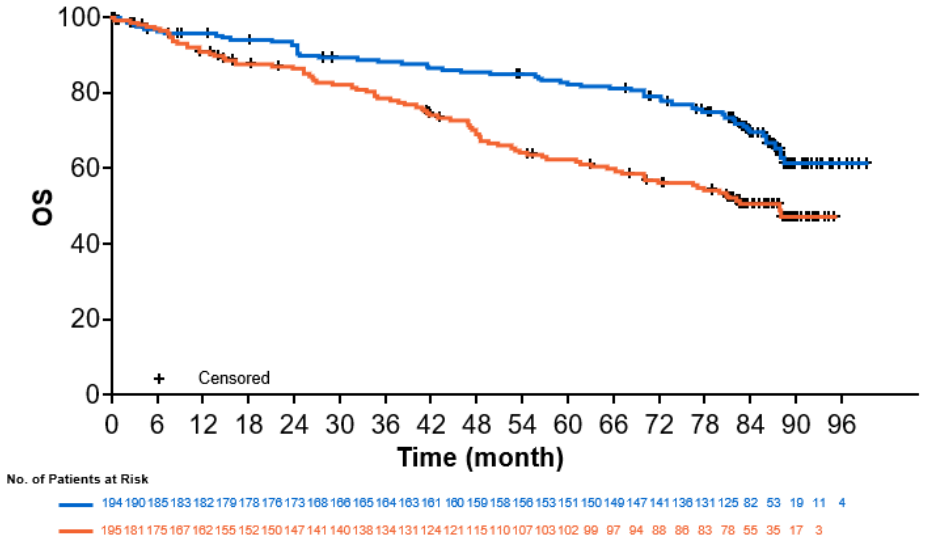
1. Seymour JF, *et al. N Engl J Med* 2018; **378:**1107–1120 (incl. suppl.); 2. Seymour JF, *et al.* ASH 2019. Abstract 355 (Oral); 4. VENCLYXTO® (venetoclax). EMA Summary of Product Characteristics (April 2020 update).

7y PFS and OS favor VenR over BR

	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



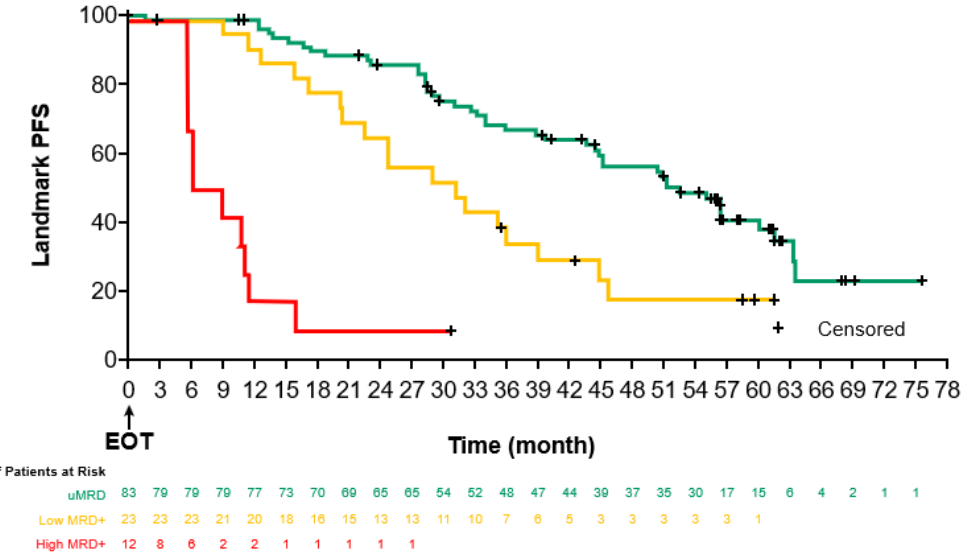
- Median follow up for efficacy (range) was 86.8 months (0.3–99.2) for VenR and 84.4 months (0.0−95.0) for BR
- No new safety signals were identified since the 5-year data cut,[1] with all patients outside of the AE reporting window§

*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.

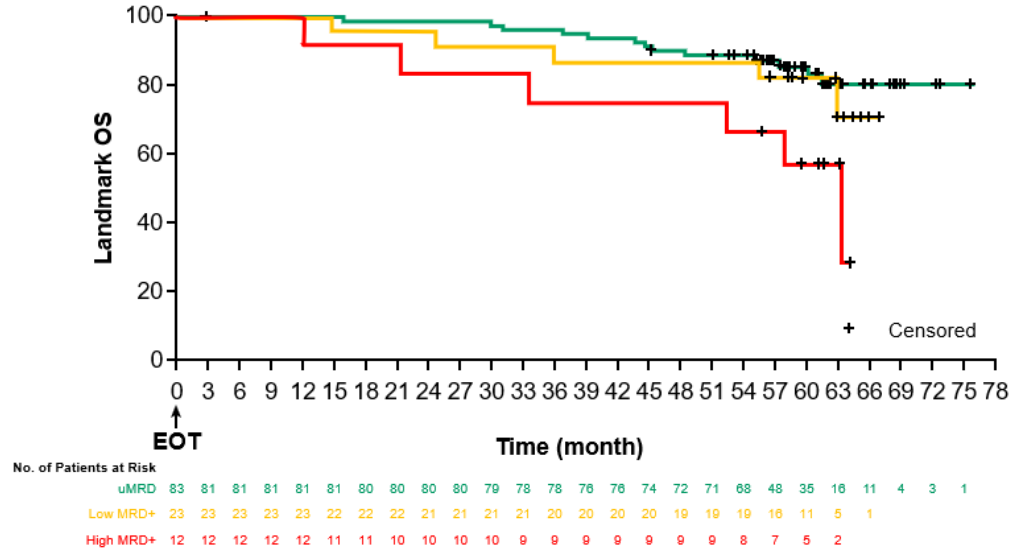
1. Seymour JF, et al. Blood 2022;140(8):839–50.

EOT uMRD predicts better outcome in pts treated with VenR

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



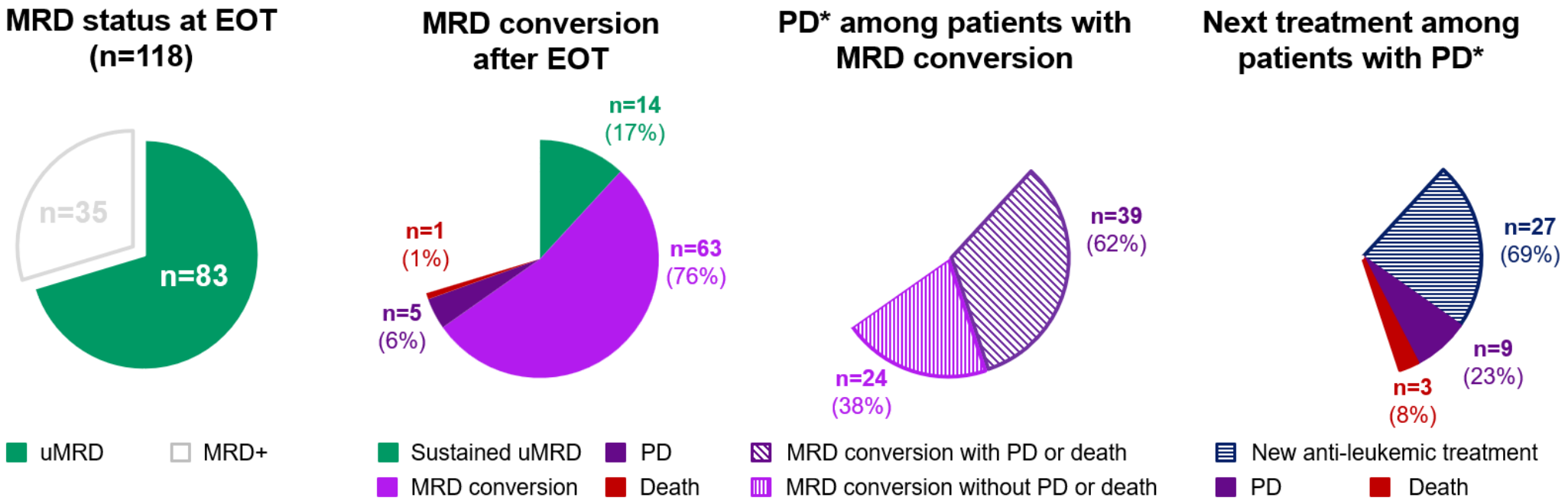
Achievement of uMRD was associated with prolonged PFS in VenR-treated patients

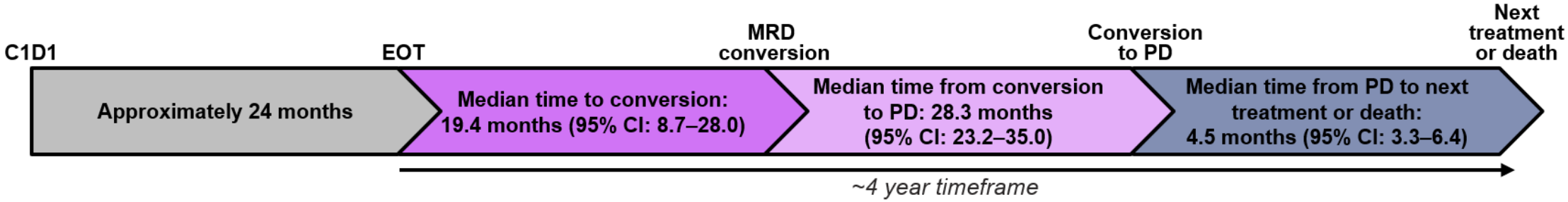
Low MRD+ is defined as ≥1 CLL cell/10,000 leukocytes to <1 CLL cell/100 leukocytes, high MRD+ is defined as ≥1 CLL cell/100 leukocytes. Stratified HR (95% CI) for Low MRD+ vs High MRD+ = PFS, 3.22 (1.04–9.97), P=0.0350; OS, 2.27 (0.44–11.69), P=NS.

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

Kater A, *et al.* EHA 2023

Median 4 years interval from MRD conversion to PD



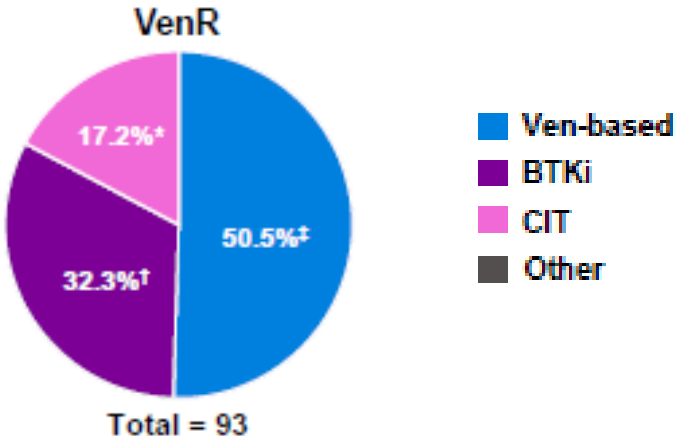


*Investigator-assessed PD according to iwCLL criteria.

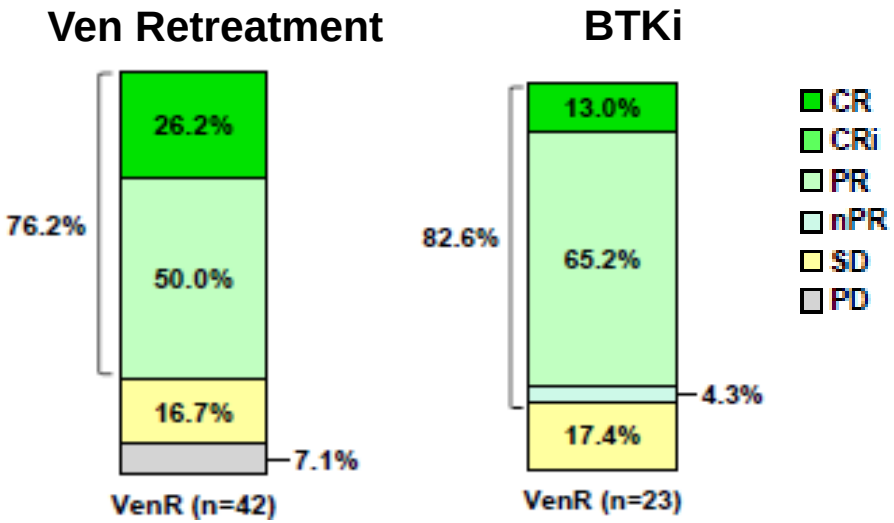
Kater A, *et al.* EHA 2023

PFS after VenR in pts treated with BTKi vs Ven-based vs CIT

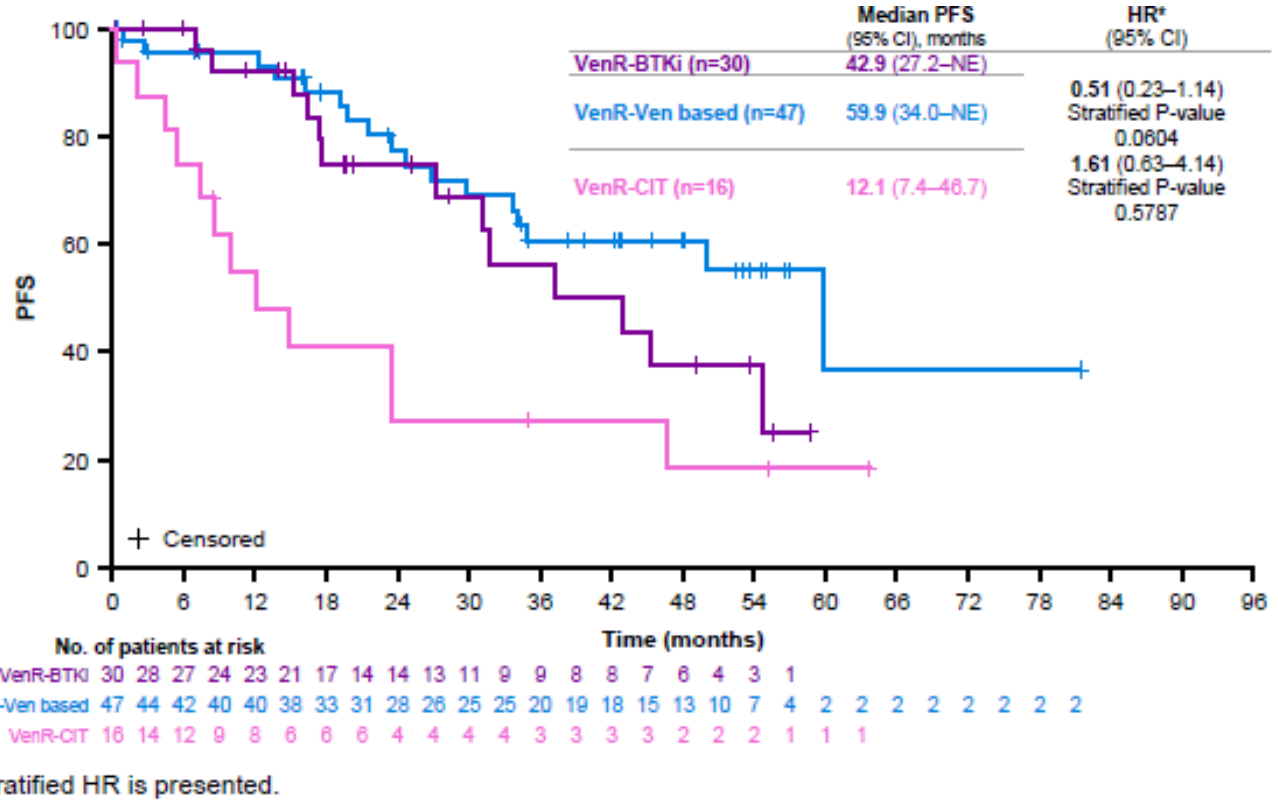
Patient disposition



Best ORR



Progression-free survival



*Stratified HR is presented.

Harrup R, *et al.* ASH 2023

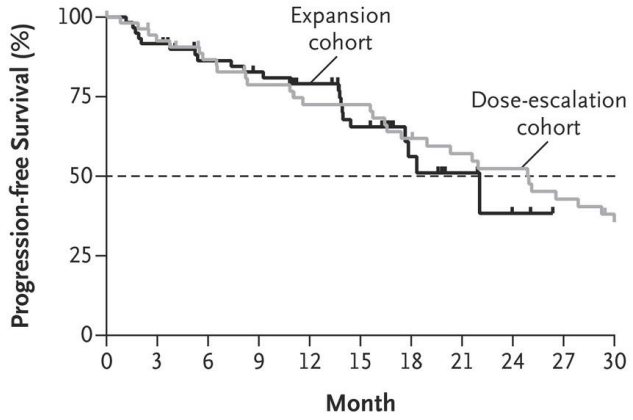
GIMEMA CLL1920 Study Design

AIMS: To investigate the use of **venetoclax-based combinations** in **a real-world population** and define the **outcome** of patients **with R/R CLL treated with venetoclax-based regimens outside clinical trials in Italy**

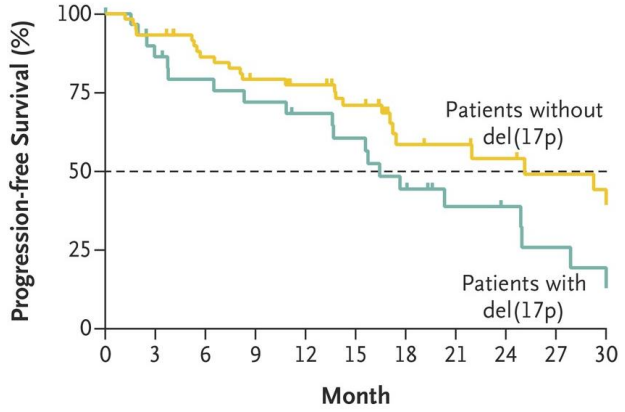
PRIMARY OBJECTIVE: to estimate the **PFS** in patients with relapsed/refractory **(R/R) CLL treated with venetoclax-based regimens** according to the local label **outside clinical trials in Italy**

PRIMARY ENDPOINT: To estimate the **PFS at 15 months from the start of venetoclax treatment**

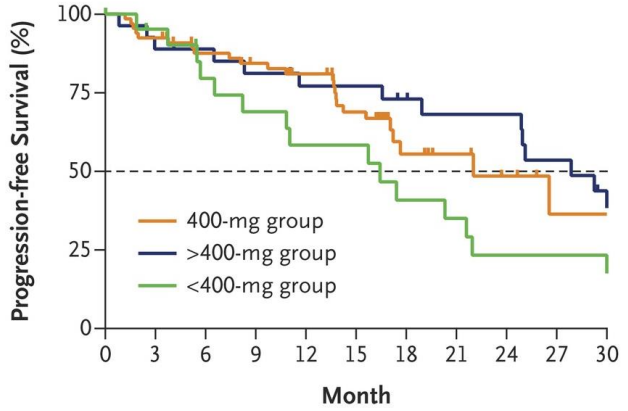
TIME INTERVAL: start of Venetoclax Named Patient Program **(March 2016)** until **October 31st, 2021**



No. at Risk											
Expansion cohort	60	55	48	45	40	29	10	5	2		
Dose-escalation cohort	56	49	44	39	34	34	27	24	22	18	15



out	60	56	49	44	39	33	16	14	12	10	9
	31	31	25	22	18	15	11	7	6	4	3

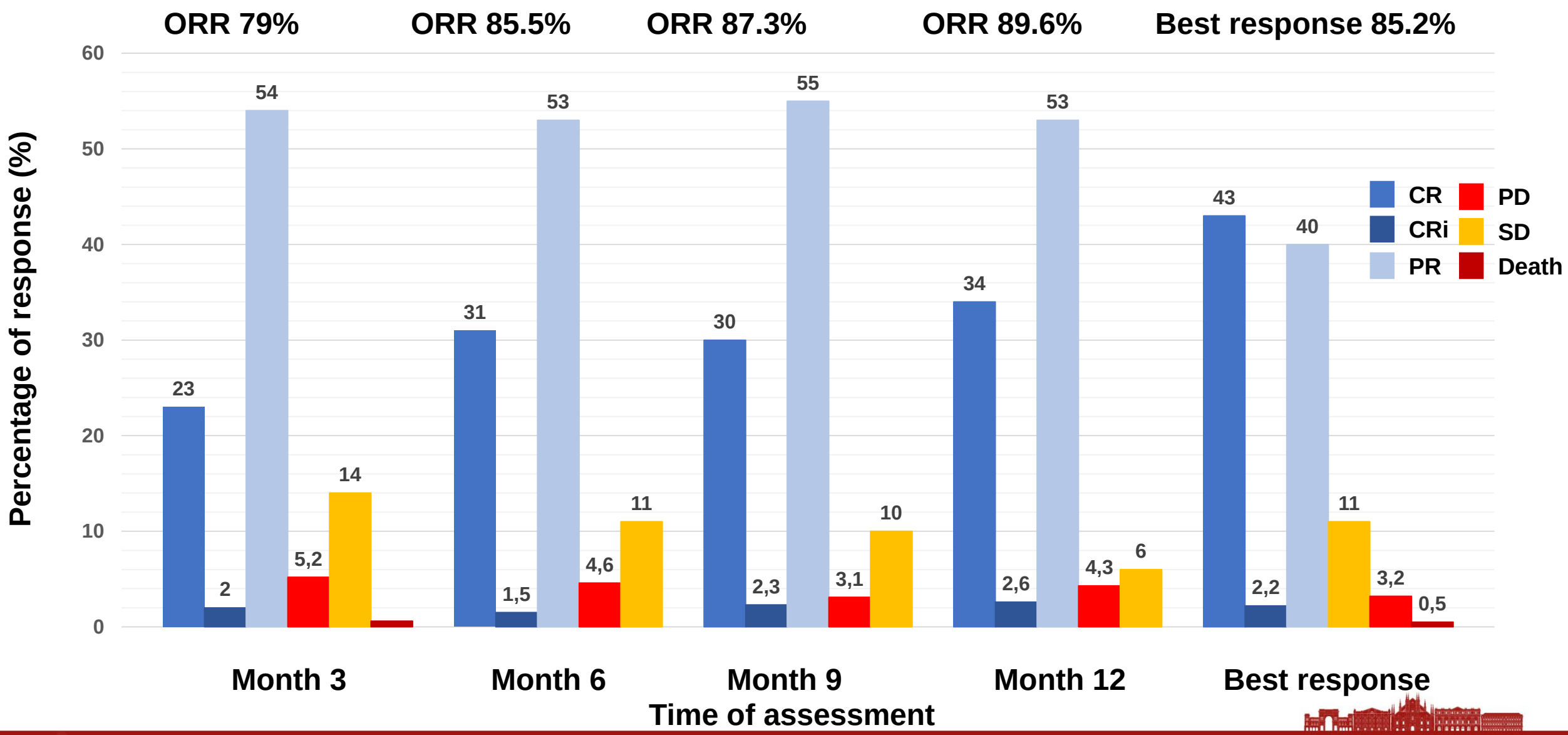


p	67	61	54	50	45	34	14	9	6	3	3
up	27	24	23	21	19	19	16	14	14	11	8
up	22	19	15	13	10	10	7	5	4	4	4

GIMEMA CLL1920 Baseline Pt Characteristics

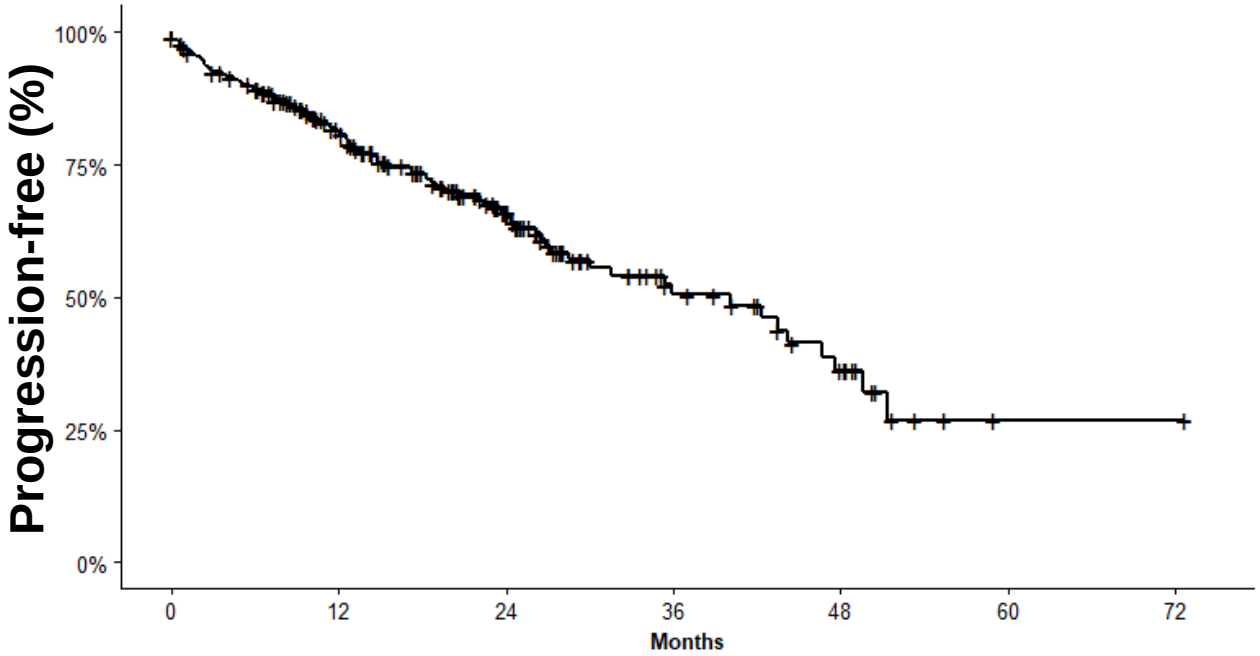
	Whole cohort (n=223)	Venetoclax mono (n=117)	Venetoclax + rituximab (n=88)
Median age at VEN initiation, years (range)	70 (40-86)	**71 (44-84)**	**68 (40-86)**
M:F (ratio)	153:70 (2.2:1)	79:38 (2.1:1)	62:26 (2.4:1)
Rai stage III/IV	84/189 (44%)	42/99 (42%)	37/79 (45%)
***TP53* aberrant**	67/179 (37%)	41/92 (45%)	22/75 (29%)
Unmutated IGHV	125/155 (81%)	66/82 (80%)	51/63 (81%)
Median number of prior therapies (range)	3 (2-10)	**4 (2-10)***	**2 (2-6)***
Previous ibrutinib treatment	120/217 (55%)	**85/117 (73%)***	**25/83 (34%)***

Early and deep responses were obtained in the whole cohort

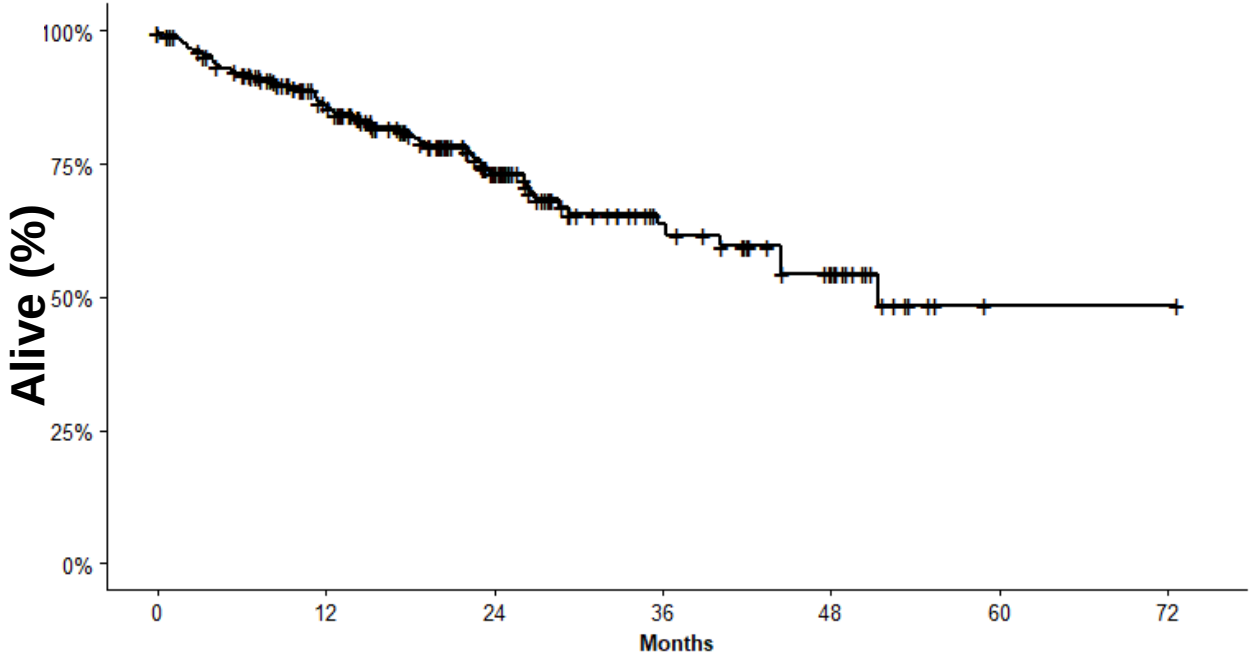


PFS and OS for the whole cohort

Progression-free Survival
12m PFS 81.3% (76.1-86.9)
15m PFS 75.5% (69.6-81.8)



Overall Survival
12m OS 86.0% (81.3-91.0)
15m OS 83.1% (78.0-88.6)



Median Follow-Up: 23.3 (0-72.8) **months**

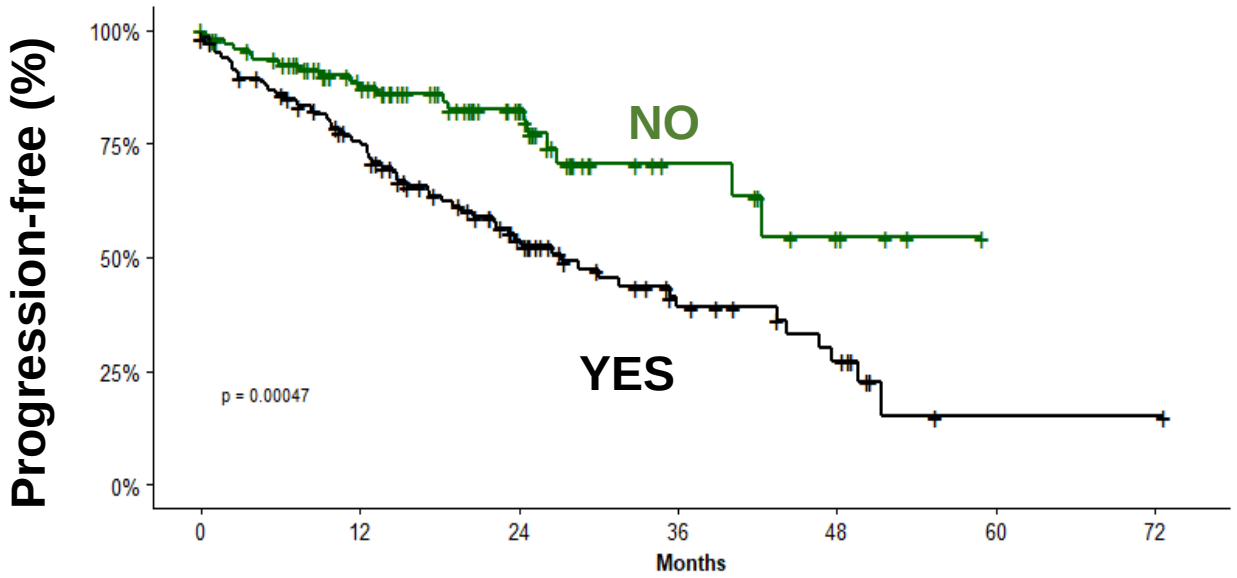
Median Follow-up Ven mono: 31.1 (20.3-48.3) **months**

Median Follow-up VenR: 19.9 (11.5-24.8) **months**

PFS and OS for BTKi-exposed Pts

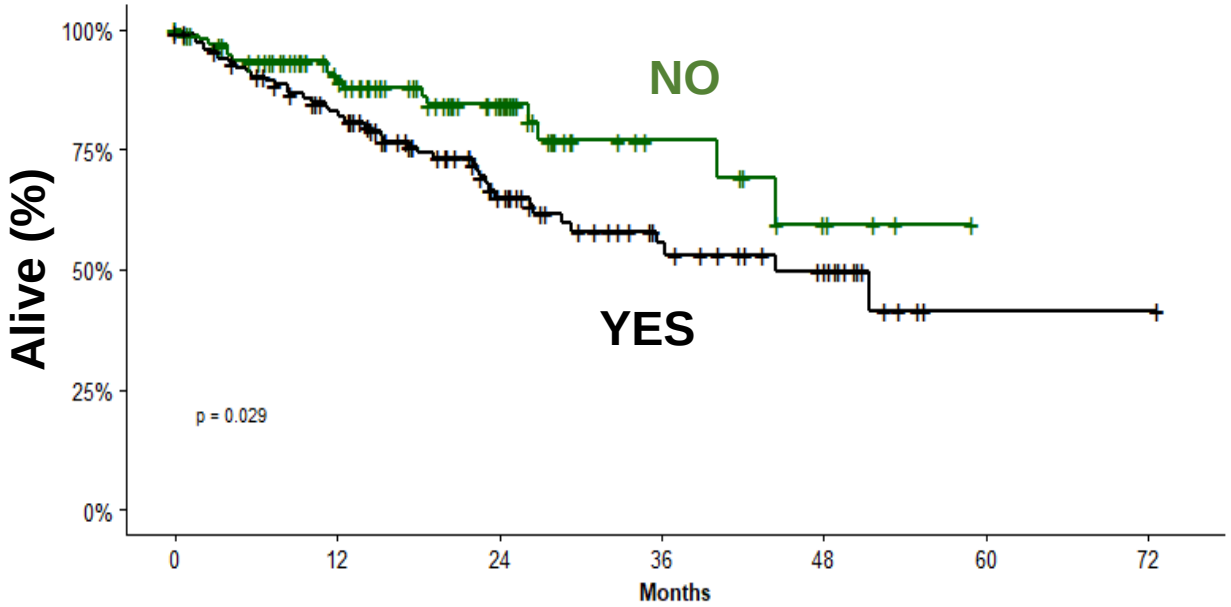
Ibrutinib-exposure

Progression-free Survival



Previous Ibrutinib	12 Month	15 Month
NO	**87.4%** (80.7-94.7)	**86.0%** (78.9-93.8)
YES	**75.7%** (68.1-84.1)	**66.8%** (58.4-76.3)

Overall Survival



Previous Ibrutinib	12 Month	15 Month
NO	**89.4%** (83.0-96.2)	**88.0%** (81.2-95.3)
YES	**82.9%** (76.1-90.2)	**78.9%** (71.6-87.0)

Multivariate Analysis for PFS and OS

Multivariate Analysis for PFS

Characteristic	HR[1]	95% CI[1]	p-value
LDH	**3.18**	**1.84, 5.48**	**<0.001**
Lines of treatment			
2	—	—	
3	2.16	0.97, 4.80	0.058
4+	**2.43**	**1.10, 5.40**	**0.029**
Ibrutinib			
No	—	—	
Yes	**2.04**	**1.12, 3.70**	**0.019**

Multivariate Analysis for OS

Characteristic	HR[1]	95% CI[1]	p-value
LDH	**4.53**	**2.01, 10.2**	**<0.001**
ibrutinib			
No	—	—	
Yes	1.56	0.75, 3.25	0.2
Lines of treatment			
2	—	—	
3	2.84	0.98, 8.24	0.054
4+	**3.10**	**1.07, 8.98**	**0.037**
Venetoclax-based regimen			
Venetoclax alone	—	—	
Venetoclax-Rituximab	1.00	0.47, 2.10	>0.9

[1]HR = Hazard Ratio, CI = Confidence Interval

Venetoclax-related AE of any grade in ≥2 pts (Data cut Sep 2022)

System Organ Class	Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Total
Blood and lymphatic system disorders	Anaemia	1	9	4		14
	Febrile neutropenia			2		2
	Neutropenia	4	33	76	32	145
	Thrombocytopenia	2	5	1		8
Gastrointestinal disorders	Diarrhoea	7	5			12
	Nausea	4	1	1		6
	Vomiting	1		1		2
General disorders and administration site conditions	Asthenia			2		2
	Fatigue	1		2		3
	Pyrexia		3			3
	Bronchitis bacterial		2			2
	Cystitis		2			2
	Gastroenteritis	3	2			5
	Infection	1	4			5
	Infections		2			2
	Pharyngitis		3			3
	Pneumonia		2	2		4
Investigations	Neutrophil count decreased		1		2	3
	Transaminases increased		2			2
Metabolism and nutrition disorders	Tumour lysis syndrome	2				2
Respiratory, thoracic and mediastinal disorders	Upper-airway cough syndrome		3			3
Total		**26**	**79**	**91**	**34**	**230**

In total 247 venetoclax-related AEs (127 G3-4) were reported; **2 grade 3 TLS** met SAE criteria

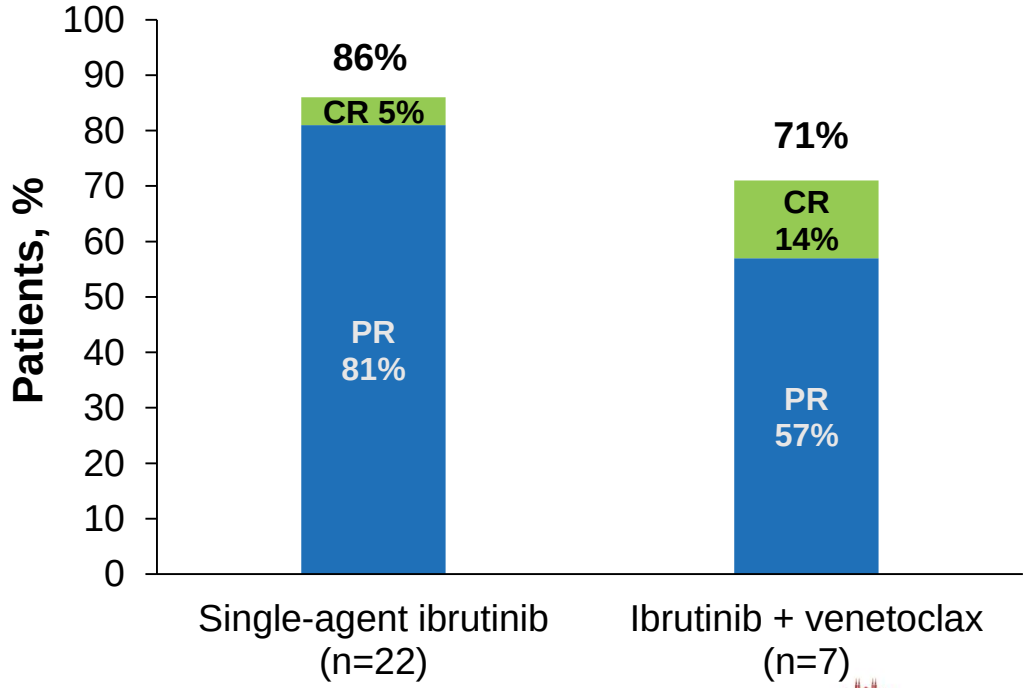
Only scanty data with I+V retreatment after I+V

- Of 61 patients with CLL PD after completion of fixed-duration ibrutinib + venetoclax, 32 (52%) initiated retreatment with single-agent ibrutinib (n=25) or ibrutinib + venetoclax (n=7)[a]
- Median time on retreatment on study:
  - 21.9 months (range, 0.0–50.4) for single-agent continuous ibrutinib
  - 13.8 months (range, 3.7–15.1) for 15-month fixed-duration ibrutinib + venetoclax[a,b]

Study Entry Baseline Characteristics: Retreated Patients

Characteristic	Single-agent ibrutinib (n=25)	Ibrutinib + venetoclax (n=7)	All Retreated Patients (n=32)
Median age (range), years	56 (39–71)	63 (49–69)	59 (39–71)
Male, n (%)	15 (60)	6 (86)	21 (66)
Rai stage III/IV, n (%)	4 (16)	2 (29)	6 (19)
High-risk genomic features, n (%)			
Unmutated IGHV	20 (80)	5 (71)	25 (78)
del(17p)/mutated *TP53*	5 (20)	5 (71)	10 (31)
del(11q)[d]	6 (24)	1 (14)	7 (22)
Complex karyotype[e]	9 (36)	2 (29)	11 (34)
Bulky LN disease ≥5 cm, n (%)	10 (40)	1 (14)	11 (34)

Best Response in Evaluable Patients to Date[c]

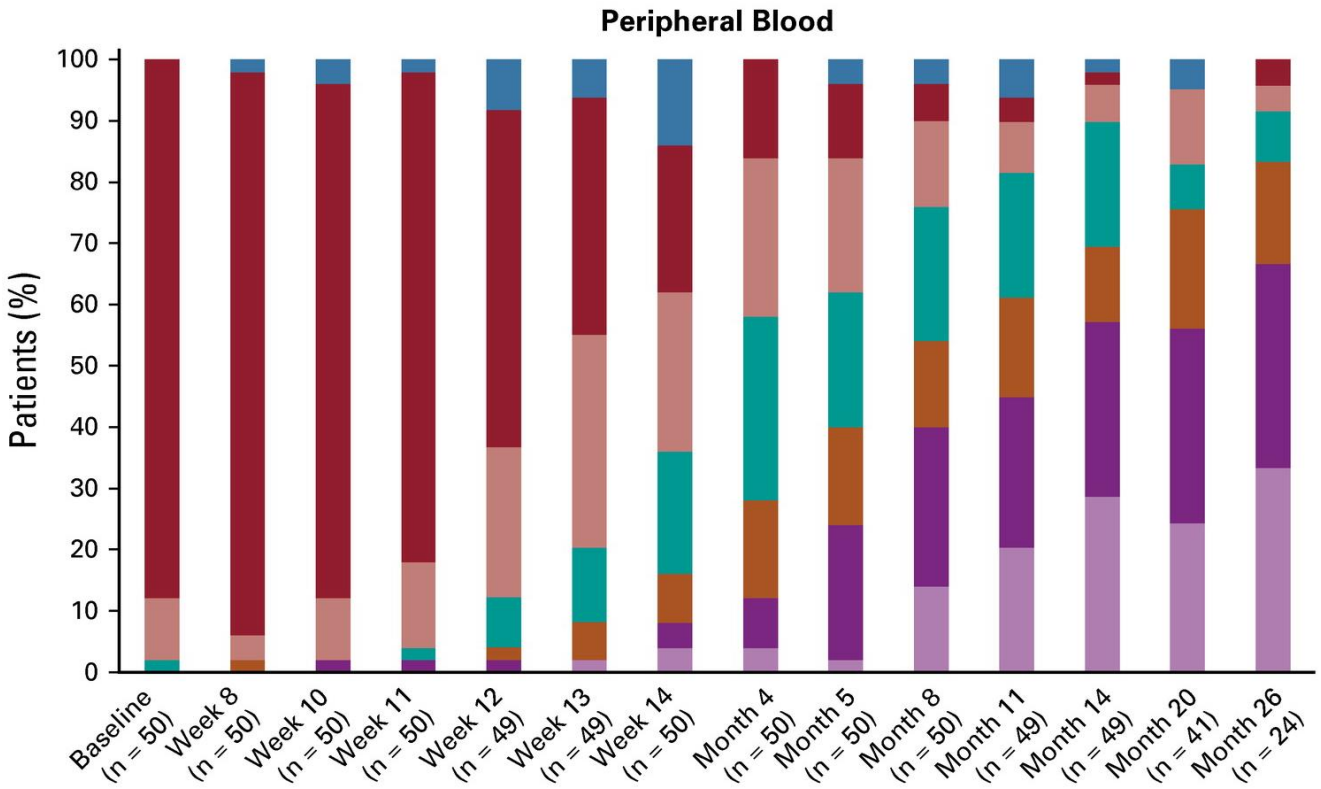


Wierda W et al, ASCO 2024

I+V in RR CLL: the CLARITY Study

Characteristic	Patients, No. (%)
No. of patients	54
Sex	
Male	37 (69)
Female	17 (31)
Median age, years (range)	64 (31-83)
Current Binet stage	
A	12 (22)
B	18 (33)
C	22 (41)
NK	2 (4)
Lymph nodes, bulky ≥ 5 cm	4 (7)
ECOG performance status	
0	32 (59)
1	18 (33)
2	3 (6)
NK	1 (2)
IGVH gene use	
Mutated	10 (19)
Unmutated	40 (74)
VH3-21	3 (6)
Failed	1 (2)
Del(17p)	11 of 50 (22)
Del(11q), not del(17p)	9 of 45 (20)
Median prior therapies (range)	1 (1-6)
Previous FCR or BR	45 of 54 (83)
Del(17p) in those who had previous FCR or BR	7 of 41 (17)
Previous FCR or BR in those with del(17p)	7 of 11 (64)
Relapse within 3 years of BR or FCR	21 of 54 (39)
Previous idelalisib	11 of 54 (20)

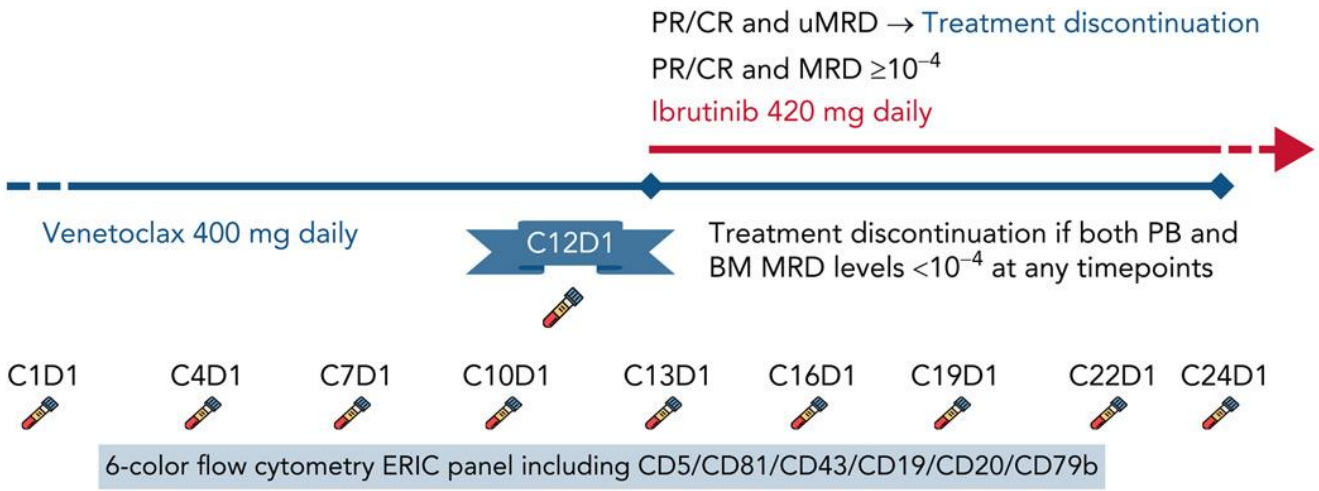
uMRD rate over time

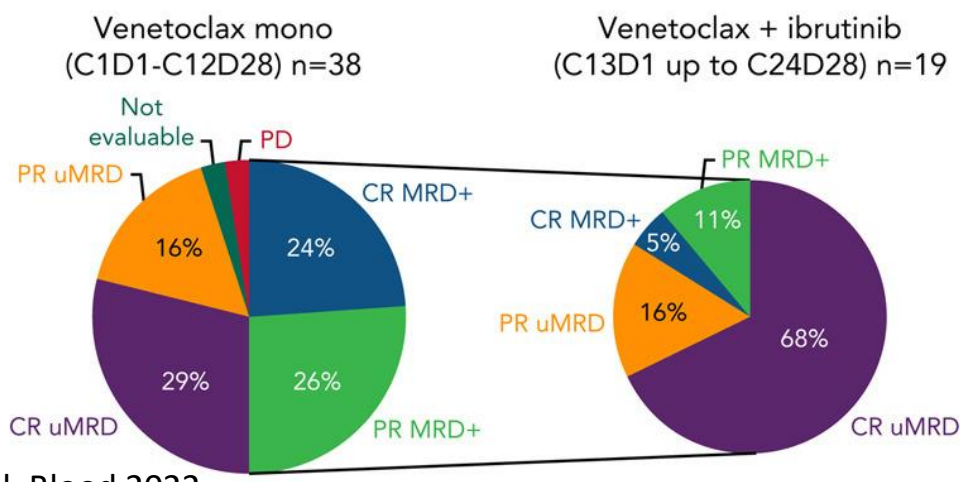


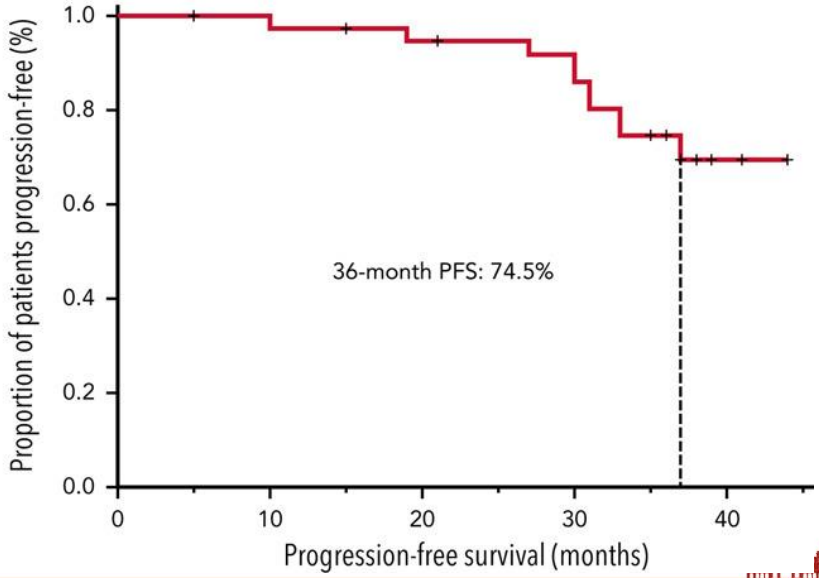
uMRD in PB at Month 14: 53% (28/53)
uMRD in BM at Month 14: 36% (19/53)

Hillmen P, *et al.* JCO 2020

I+V in RR CLL: the IMPROVE Study







Scarfò L, Heltai S et al, Blood 2022

Venetoclax consolidation in High-risk CLL on ibrutinib

Eligibility:
- CLL/SLL, treated with ibrutinib for ≥ 12 months with measurable MRD AND no clinical disease progression
- ≥1 high risk feature*:
  - Del(17p) or *TP53*mut
  - Del(11q)
  - Complex karyotype
  - Elevated B2M

Response assessment pre-venetoclax and q6m CT and bone marrow with MRD4 analysis

Continue ibrutinib at current dose.

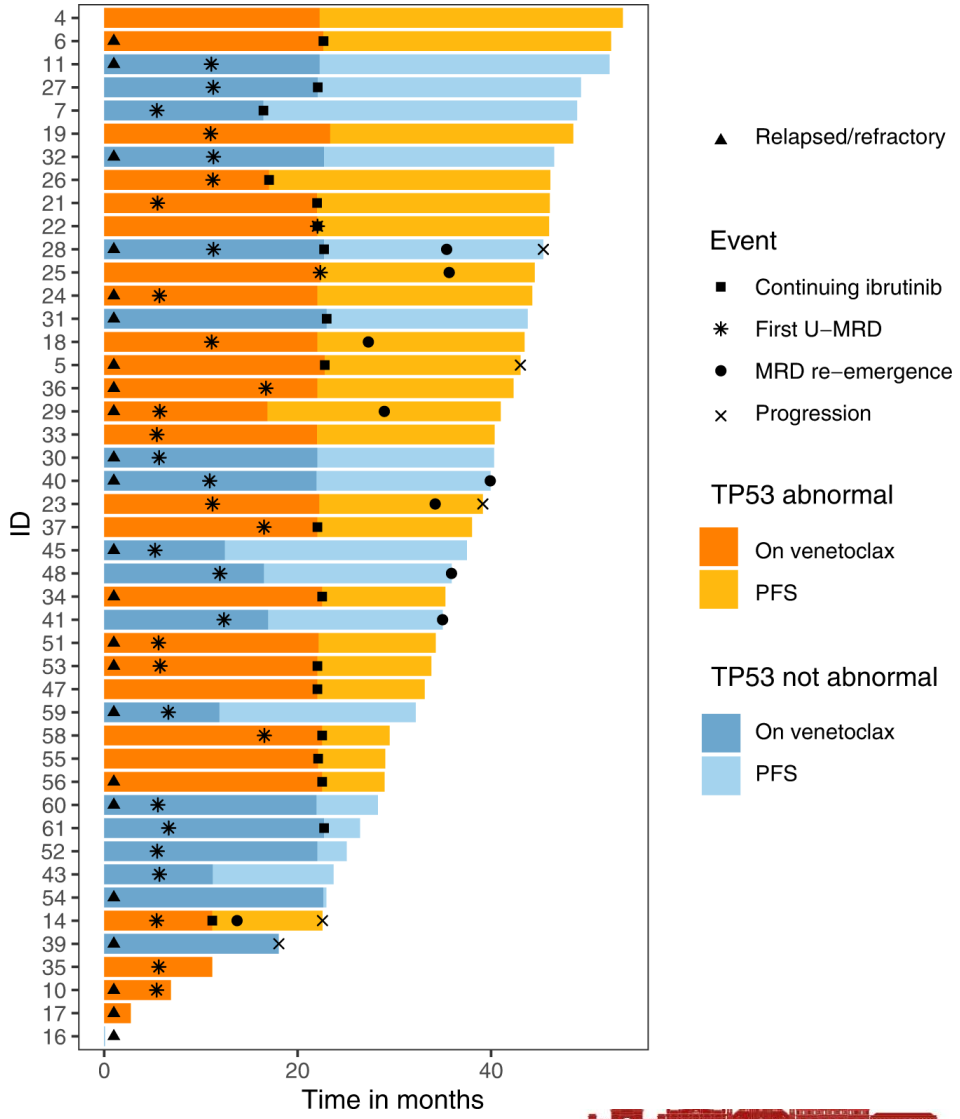
Venetoclax standard weekly dose escalation x 28 days, followed by 400mg/d, for max. 24 cycles (28d each) total*

MRD q6m in PB during maintenance/observation

MRD+ → Ibrutinib maintenance

MRD- → Stop therapy or Ibrutinib maintenance (Physician's choice)

*MRD-directed therapy: patients who achieve CR with U-MRD4 on two consecutive occasions, 6 months apart, will stop venetoclax.



Thompson P et al, Leukemia 2023

Conclusions

- ✓ **Venetoclax alone** or combined **with rituximab** proved to be **effective** and **well-tolerated** in a **both clinical trials and real-world experiences in RR CLL**
- ✓ Depth of response and in particular **uMRD status** correlates with **prolonged PFS** in patients treated with **venetoclax + anti-CD20 monoclonal antibody**
- ✓ **Neutropenia** is the **most frequent G3-4** adverse event while **TLS** events occur **rarely**
- ✓ **Limited data are available for the combination of venetoclax + BTKi in RR CLL**
- ✓ **How to optimize sequencing and time limited and/or MRD driven approaches** in the current chemo-free era remains worth investigating

Thank you!

Prof Paolo Ghia

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