Il concetto della durata fissa nel paziente

Nel paziente pretrattato

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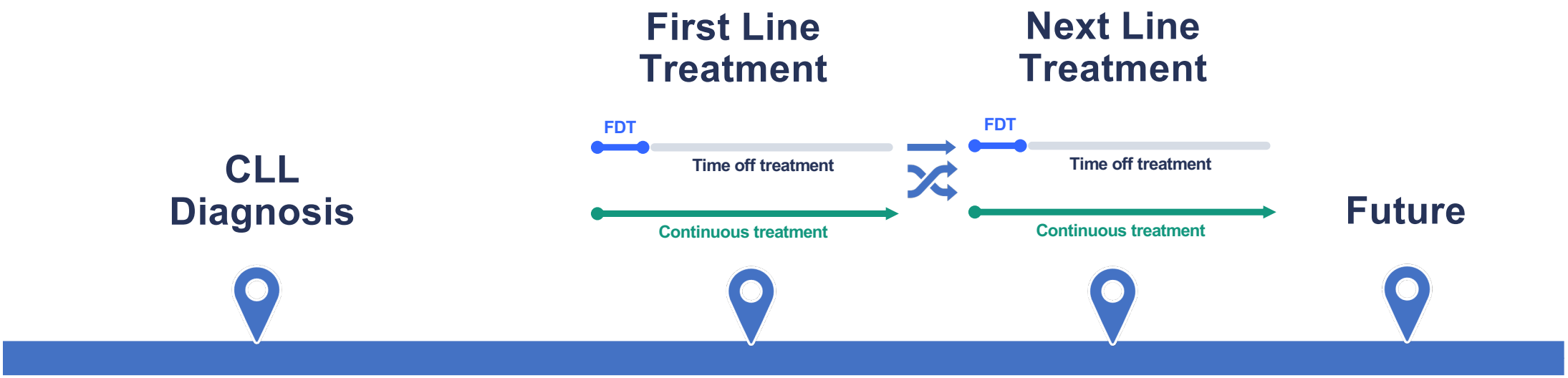
REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Catania, 28 maggio 2024
Palace Catania UNA Esperienze

CLL Journey

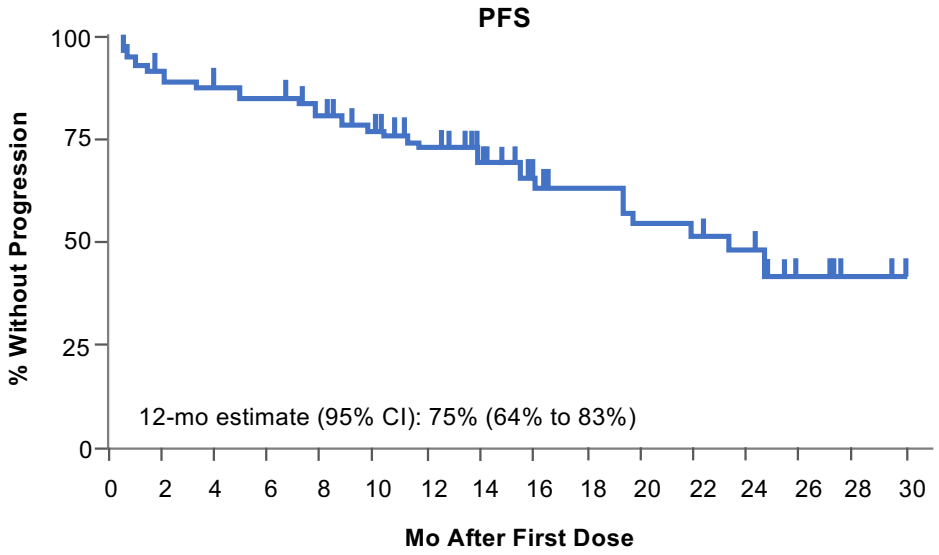

First Line Treatment
Next Line Treatment
CLL Diagnosis
FDT
Time off treatment
Continuous treatment
FDT
Time off treatment
Continuous treatment
Future

AVAILABLE TREATMENTS IN R/R CLL: 2024 scenario

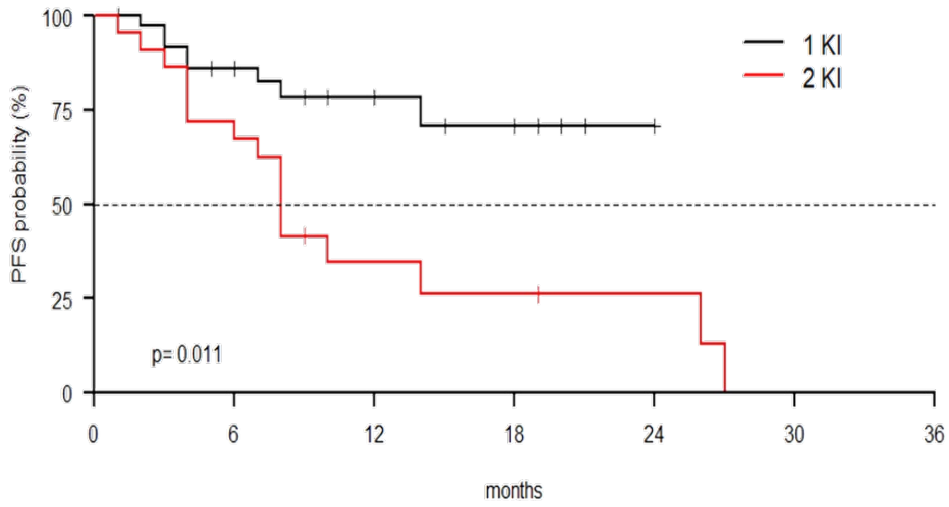
	Ibrutinib	Acalabrutinib	Zanubrutinib	R+Venetoclax	Cont. Venetoclax monotherapy
Standard arm: CIT/Ofa	RESONATE	ASCEND	-	MURANO	
TP53 aberrations	RESONATE 17				NCT01889186
vs ibrutinib		RESONATE RR	ALPINE		
BTK exposed					VENICE

Venetoclax for patients progressed after/during Ibrutinib

Phase II study of venetoclax for patients with CLL relapsed after or refractory to ibrutinib*



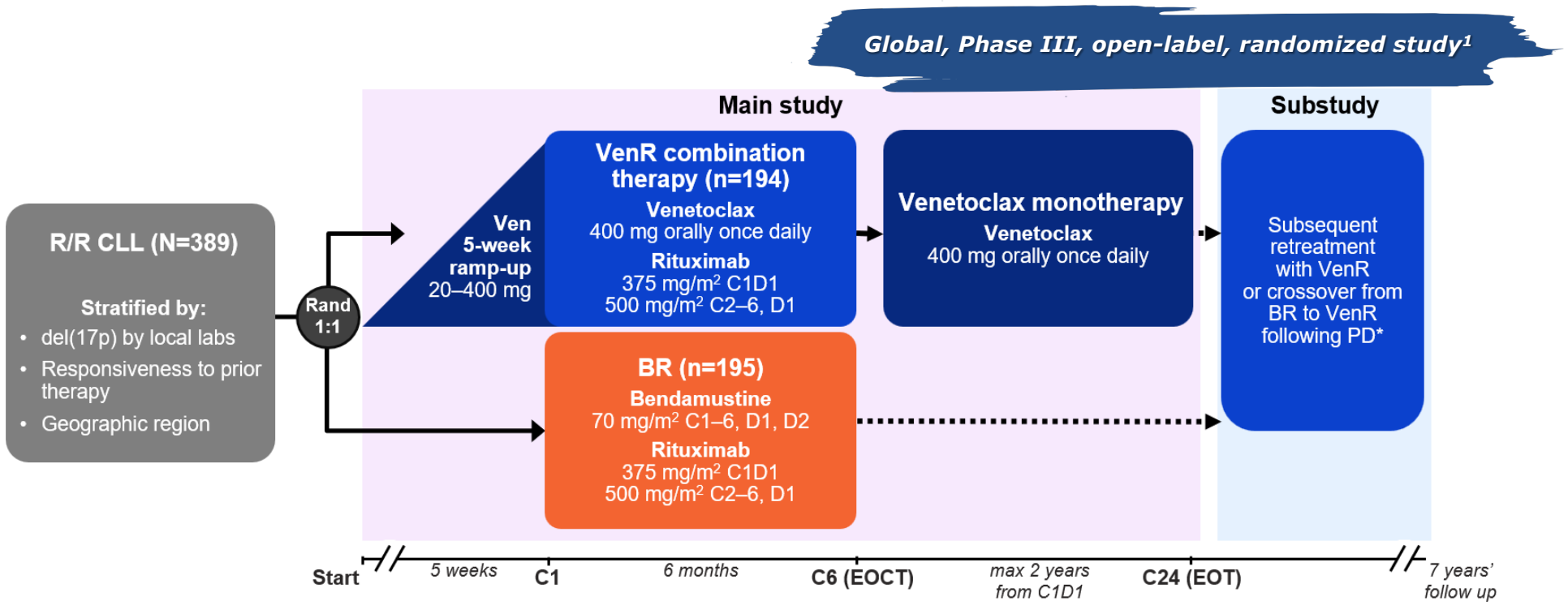
Real world study on CLL relapsed after or refractory to 1 or 2 KI*



*Included patients who discontinued ibrutinib for AEs and progressed when off therapy.

Jones. Lancet. 2018

MURANO (NCT02005471): study design and prior findings



- 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]

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

Baseline Patient Characteristics

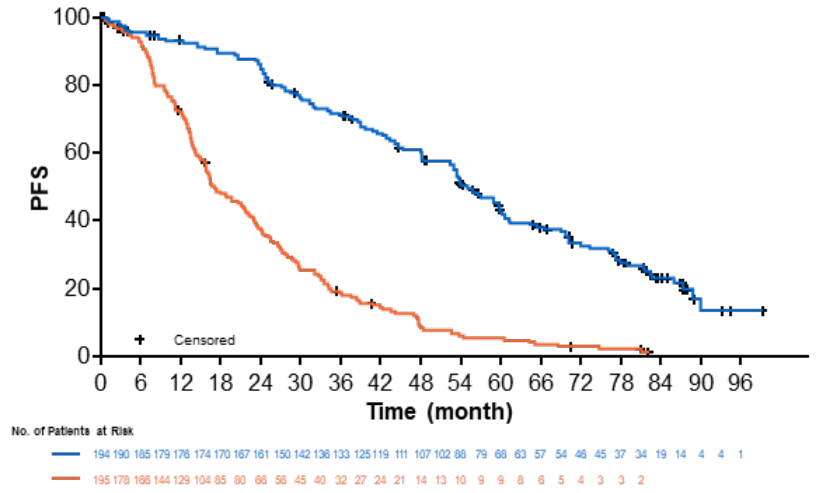
Characteristics		VenR (n=194)	BR (n=195)
Age	Median, years (range)	64.5 (28–83)	66 (22–85)
Lymphocyte count (ALC), n (%)	≥25 × 10^9/L	129 (66.5)	134 (68.7)
del(17p) – central lab,* n/N (%)	Deleted	46/173 (26.6)	46/169 (27.2)
***TP53* mutational status, n/N (%)**	Mutated *TP53*	48/192 (25.0)	51/184 (27.7)
***IGHV* mutational status, n/N (%)**	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 (%)	1 2 3 >3	111 (57.2) 57 (29.4) 22 (11.3) 4 (2.1)	117 (60) 43 (22.1) 34 (17.4) 1 (0.5)
Prior therapies, n (%)	Alkylating agent Purine analog Anti-CD20 antibody BCRi	185 (95.4) 158 (81.4) 148 (76.3) 3 (1.5)	182 (93.3) 157 (80.5) 153 (78.5) 5 (2.6)
Prior bendamustine, n (%)	Yes	4 (2.1)	5 (2.6)
Fludarabine refractory, n/N (%)	Yes	27/191 (14.1)	30/194 (15.5)

* Cut-off for 17p positive is 7%.

MURANO: 7-year PFS and OS benefits of VenR compared to BR

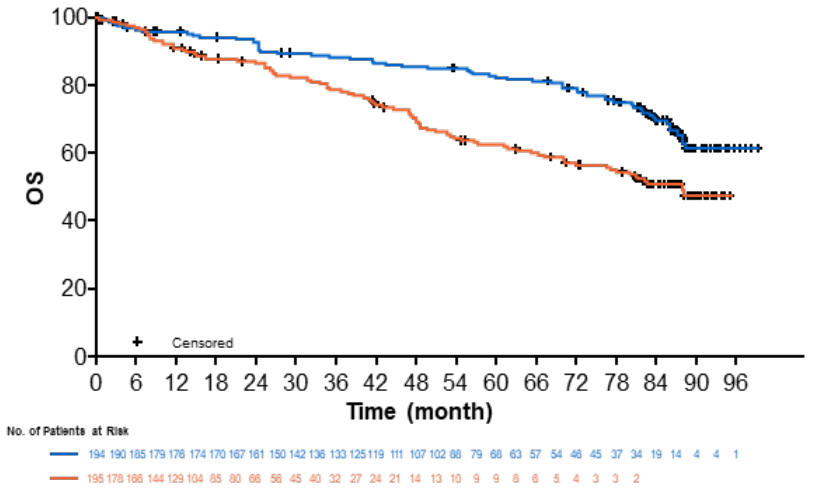
Progression-free survival

	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



Overall survival

	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



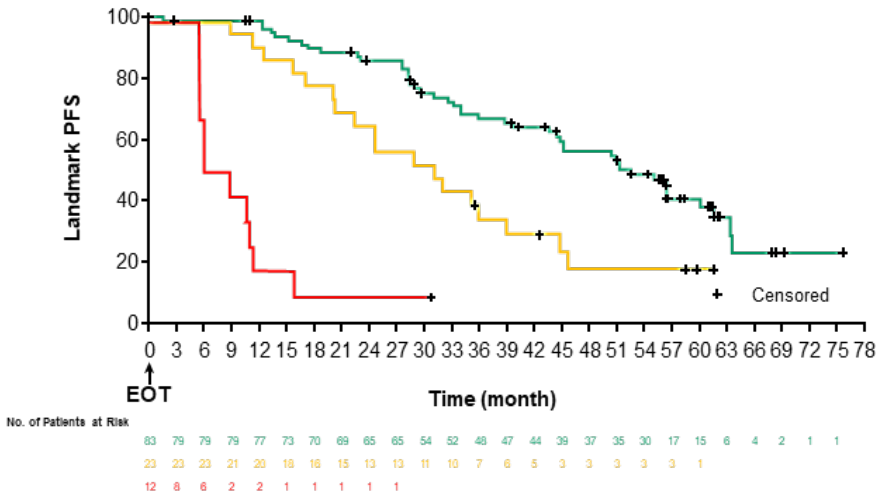
Median follow up for efficacy (range) was 86.8 months (0.3–99.2) for VenR and 84.4 months (0.0–95.0) for BR

Kater, EHA 2023

Achievement of uMRD was associated with prolong PFS with VenR

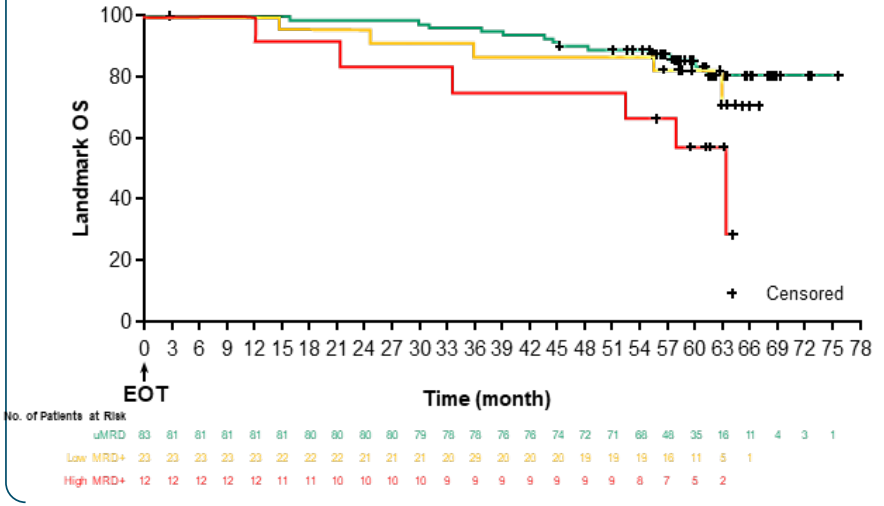
Progression-free survival[1]

VenR-treated patients who completed 2 years of Ven without PD	Median PFS since EOT (95% CI), months	HR* (95% CI)
83 pts=43% uMRD (n=83)	**52.5** (44.5–61.5)	**4.47** (2.39–8.36) Stratified P-value <0.0001†
MRD+ (n=35)	**18.0** (8.5–29.3)	



Overall survival

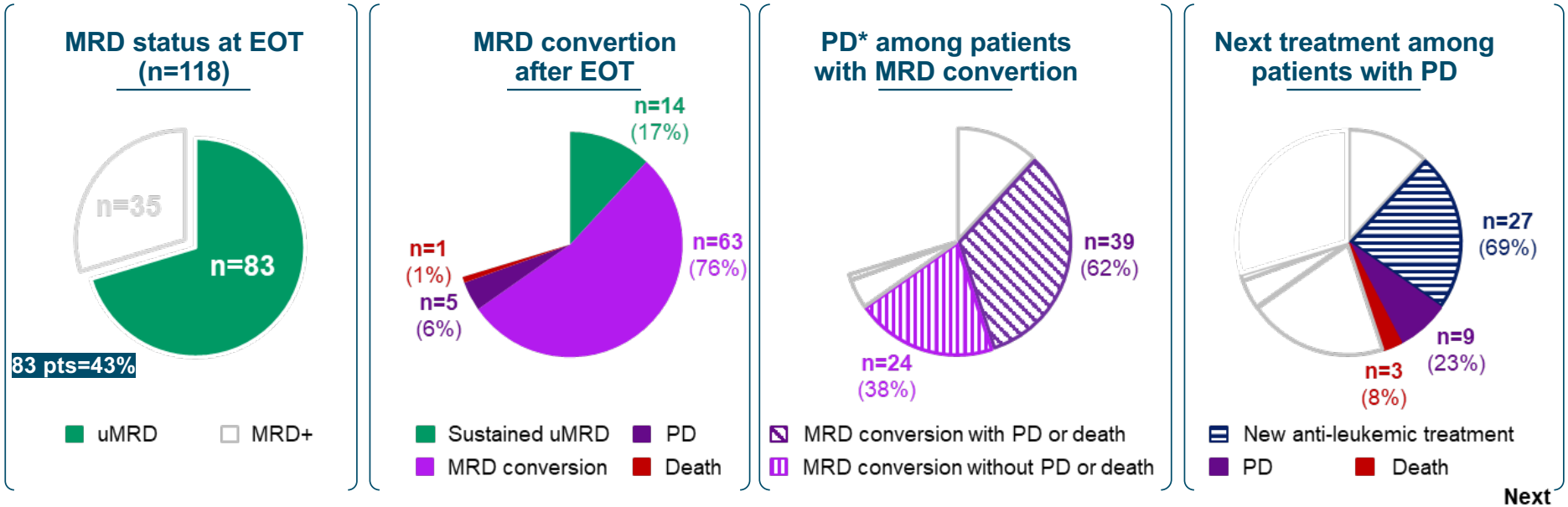
VenR-treated patients who completed 2 years of Ven without PD	Median OS since EOT (95% CI), months	HR‡ (95% CI)
uMRD (n=83)	**NE** (NE–NE)	**1.50** (0.60–3.77) Stratified P-value <0.3805†
MRD+ (n=35)	**NE** (62.7–NE)	



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 is presented, unstratified HR=3.45. †P-values are descriptive only. ‡Stratified HR is presented, unstratified HR=0.0796. .

Kater AP, et al. EHA 2023

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.Kater, EHA 2023

1. Kater AP, et al. EHA 2023

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

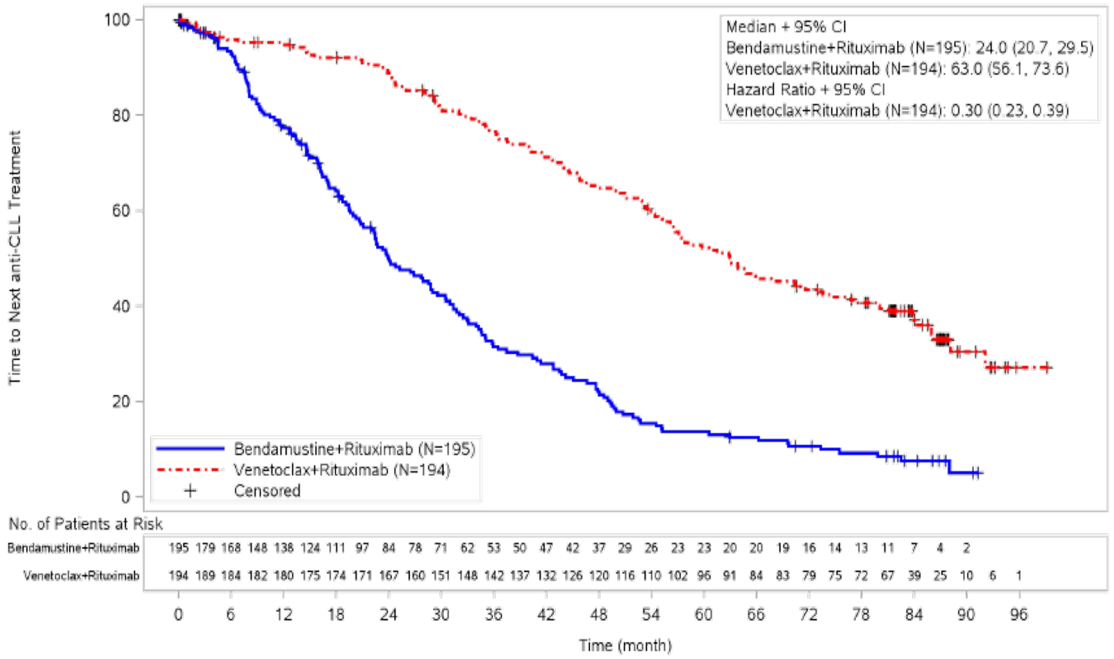
- Among the 14 patients with sustained uMRD after EOT, median number of **prior therapies** was 1 (range 1–3)
- ***TP53* status** among VenR-treated patients:
  - 13/144 (9.0%) patients without TP53 mutation (wild-type) had sustained uMRD vs 1/48 (2.1%) patients with TP53 mutation
- **IGHV status** among VenR-treated patients:
  - 7/53 (13.5%) patients who had mutated IGHV had sustained uMRD vs 6/123 (4.9%) patients with unmutated IGHV

VenR-treated patients, n (%)	*TP53** (n=192)†		IGHV‡ (n=176)†	
	unmutated (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)

*.

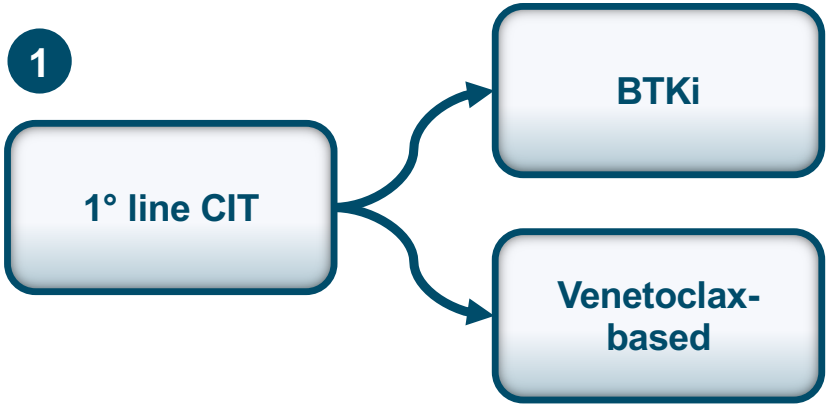
1. Kater AP, et al. EHA 2023

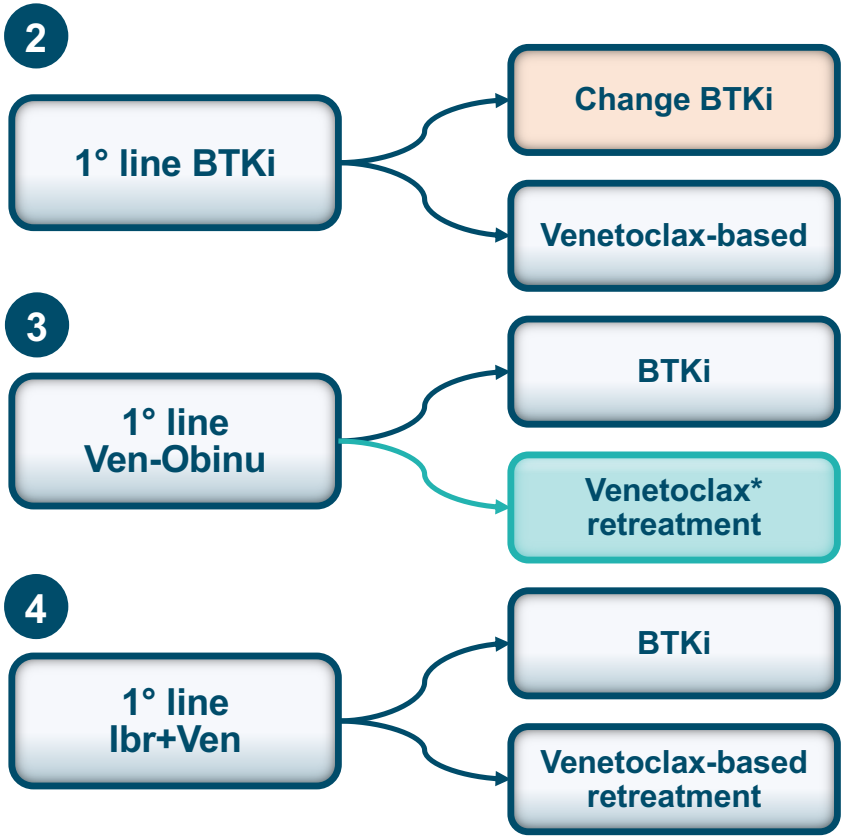
Time To Next anti-leukaemic Treatment (TTNT)



	Median TTNT (95% CI), months	HR* (95% CI)
VenR	**63.0** (56.1–73.6)[1]	**0.30** (0.23–0.39) Stratified P-value <0.0001[1†]
BR	**24.0** (20.7–29.5)[1]	

CLL treatment sequencing options



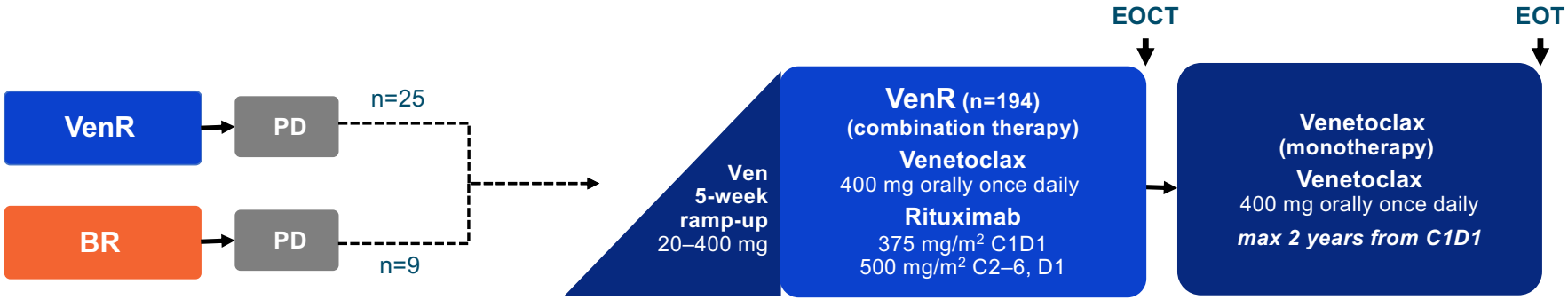


Il regime terapeutico venetoclax + ibrutinib è stato approvato da EMA ed è inserito all'interno dell'RCP di Ibrutinib.

***Venetoclax re-treatment is not approved after VO**

In Italia, il ritrattamento con venetoclax è rimborsato dal SSN solo dopo regime di prima linea V+I

MURANO re-treatment/crossover sub-study



- In total, **34 patients** with PD entered the substudy, **25 were retreated with VenR** and **9 crossed over from BR to VenR**
  - Median (range) **time from the final study drug dose** in the main study **and Ven retreatment or crossover** in the substudy was **2.3 years** (1.2–3.1) or **3.7 years** (3.3–4.9), respectively

In Italia, il ritrattamento con venetoclax è rimborsato dal SSN solo dopo regime di prima linea V+I

Patient characteristics from the MURANO retreatment/sub-study

92% of patients who received VenR re-treatment were classified as high risk[1]

	Patients retreated with VenR (n=25)	Patients who crossed over from BR to VenR (n=9)
Median age, years (range)	66 (49–82)	67 (26–84)
No. of prior therapies*, n (%)		
2	**20 (80.0)**	7 (77.8)
3	4 (16.0)	0 (0.0)
≥4	1 (4.0)	2 (22.2)
del(17p)† and/or *TP53* mutation‡, n (%)		
yes	**8 (32.0)**	1 (11.1)
no	5 (20.0)	5 (55.6)
unknown/not assessed	12 (48.0)	3 (33.3)

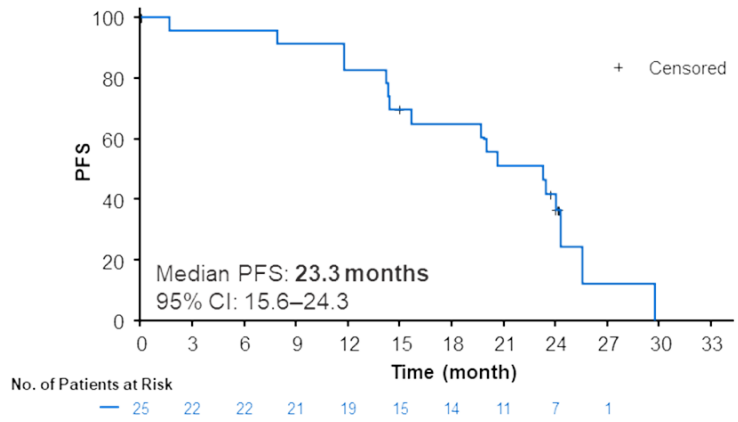
	Patients retreated with VenR (n=25)	Patients who crossed over from BR to VenR (n=9)
IGHV§, n (%)		
mutated	1 (4.0)	3 (33.3)
unmutated	**22 (88.0)**	5 (55.6)
unknown/not assessed	2 (8.0)	1 (11.1)
GC†, n (%)		
0–2	9 (36.0)	4 (44.4)
3–4	3 (12.0)	3 (33.3)
≥5	**8 (32.0)**	1 (11.1)
unknown/not assessed	5 (20.0)	1 (11.1)

*Including the VenR or BR treatment they received in the main study. †Assessed by array comparative genomic hybridization. ‡Assessed by NGS. §Assessed by PCR. ¶Had at least one of the following high-risk features: IGHV-unmutated disease, GC of ≥3 copy number alterations, or del(17p) and/or *TP53* mutations. GC, genomic complexity.

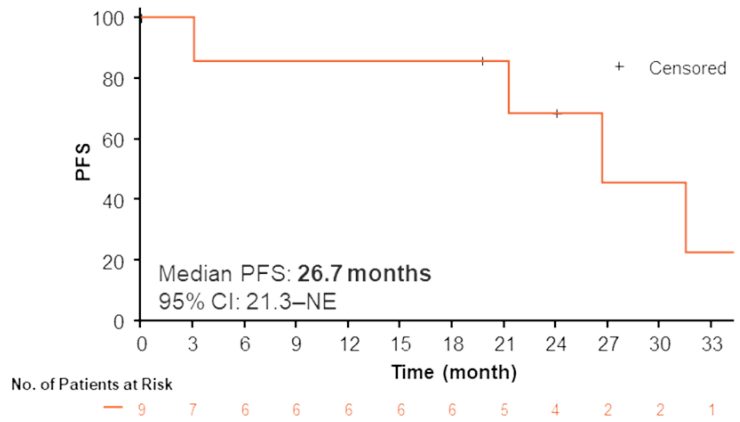
Kater EHA 2023

Clinical outcomes indicate that VenR is a feasible option for pre-treated patients

PFS for VenR-retreated patients in the substudy



PFS for patients who crossed over from BR to VenR in substudy



- Median follow up (range) was 33.4 months (2.7–44.0)
- Best ORR was high for both retreated patients (72.0%) and patients who crossed over (88.9%)
- Median duration of response (95% CI) was 15.5 months (11.5–NE) for retreated patients and 22.5 months (12.7–NE) for patients who crossed over
- Median OS was not reached for either the retreated patients or patients who crossed over

C.
1. Kater AP, et al. EHA 2023: Abstract S201; 2. Kater AP, et al. EHA 2023: Abstract S201; oral presentation.

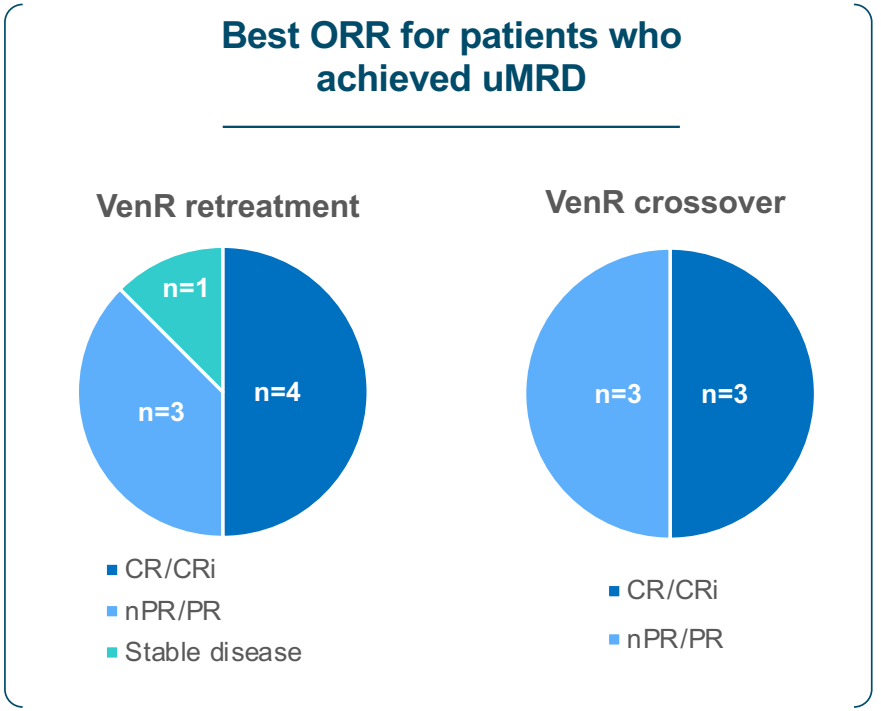
In Italia, il ritrattamento con venetoclax è rimborsato dal SSN solo dopo regime di prima linea V+I

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

- Over half (56%) of patients in the substudy achieved uMRD at EOT in the main study

VenR retreatment arm

- Amongst retreated patients, 8 (32%) achieved uMRD at the re-treatment EOCT;[1] all responded, with 7/8 achieving CR/PR



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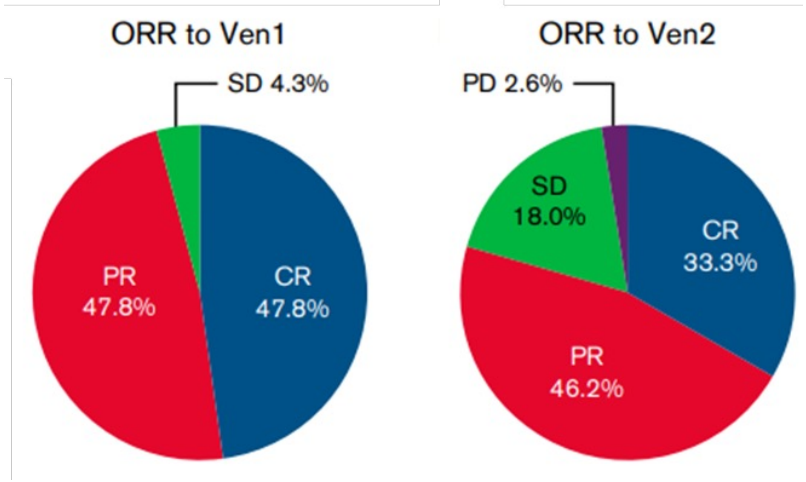
Responses and survival of venetoclax re-treatment

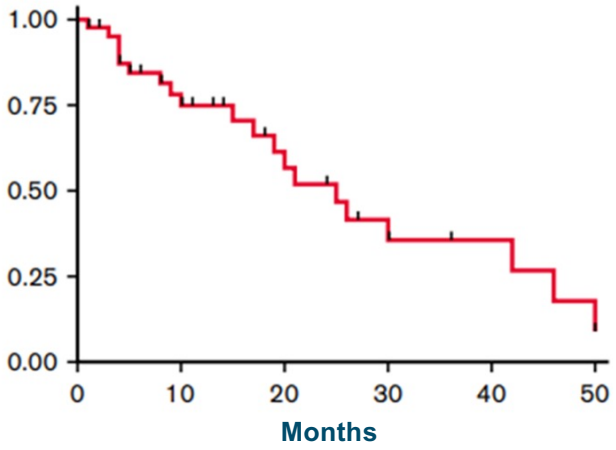
Median prior therapies: 2 (range: 0-10)

Venetoclax-based regimen in any line of therapy → retreatment with second venetoclax-based regimen

N = 46 pts
(real world + MURANO dataset)



Ven2: progression free survival



m prior lines: 2 (0-1)
40% previously treated with BTKi

Thompson Blood Adv 2022

In Italia, il ritrattamento con venetoclax è rimborsato dal SSN solo dopo regime di prima linea V+I

BCL2i retreatment: ReVenG study

A Phase 2 Open-Label Study of Venetoclax Plus Obinutuzumab Retreatment in Patients with Relapsed CLL

Cohort 1
Patients who progressed >24 months after completion of 1L CLL therapy with venetoclax + anti-CD20 Ab ± X (n = 60)

→ 6 Cycles VenO + 6 Cycles Ven Monotherapy

Cohort 2
Patients who progressed ≥12-24 months after completion of 1L CLL therapy with venetoclax + anti-CD20 Ab ± X (n ≤15)

→ 6 Cycles VenO + 18 Cycles Ven Monotherapy[a]

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

[a]Patients in Cohort 2 with detectable MRD (MRD ≥10^{-4}) may continue Ven monotherapy beyond 24 cycles until progressive disease per the investigator's discretion.

Objectives[b]

Primary
- Overall Response at EoCT (3 months after completion of 1L Venetoclax + anti-CD20 Ab ± X)

Secondary
- CR/CRi at EoCT and EoT (3 months after completing Ven monotherapy)
- Overall Response at EoT
- TTR
- DOR
- uMRD (<10^{-4}) measured in PB at EoCT and EoT
- PFS
- OS
- TTNT
- Safety

[b]Primary and secondary objectives are for Cohort 1. Assessments for Cohort 2 are exploratory.

ClinicalTrials.gov (NCT04895436)

CONCLUSIONS

- **Most of patients we are treating now at relapse, never received CIT**
- **Even in the setting R/R, FD duration and re-treatment are feasible options**
  - *most of pts completing 2 yrs VR had uMRD and did not progress until 4 yrs after EOT*
  - *~5 years to next line after VR in MURANO*
- **Need of data on sequencing after I+V**

Grazie per l’attenzione