SESSIONE 1
Il concetto della "durata fissa" dal farmacologo all'ematologo

Nel paziente pretrattato

Paolo Sportoletti

Università degli Studi di Perugia

REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Roma, 11 aprile 2024
UNAHOTELS Decò

Il sottoscritto **SPORTOLETTI PAOLO**
in qualità di moderatore e relatore

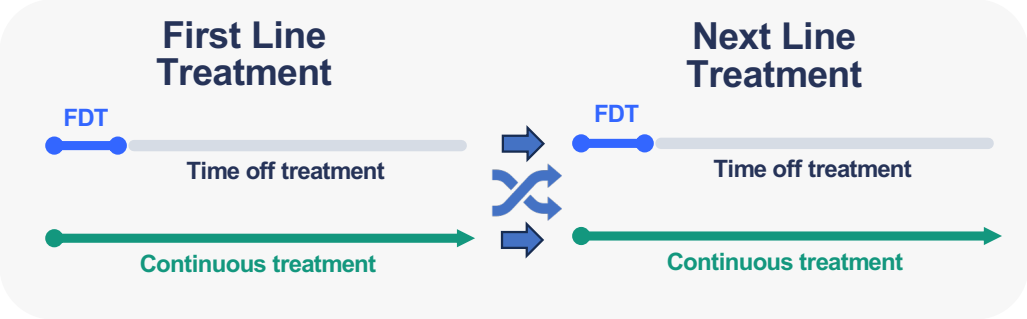
ai sensi dell'art. 76 sul Conflitto di Interessi, pag. 34 dell'Accordo Stato-Regione del 2 Febbraio 2017

dichiara
che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:
Abbvie, J&J, Astrazeneca, Beigene, Gilead

Fixed vs continuous treatment: general considerations in the sequencing of therapies for R/R CLL

Both cBTKi and BCL2i-anti-CD20 mAb are highly effective therapies for R/R CLL

These therapies may be used sequentially in either order (independent mechanisms of action and resistance)

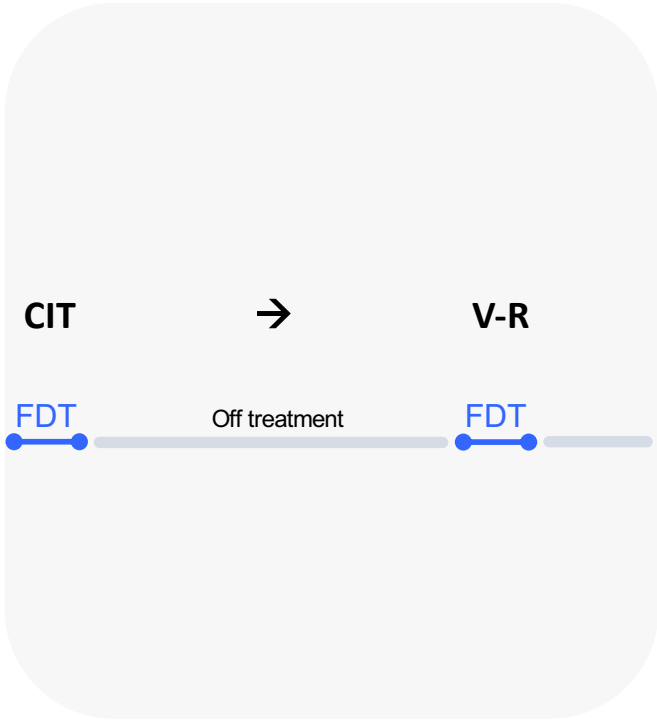


There are limitations to this understanding:

- a lack of randomized data informing the efficacy of both possible sequences

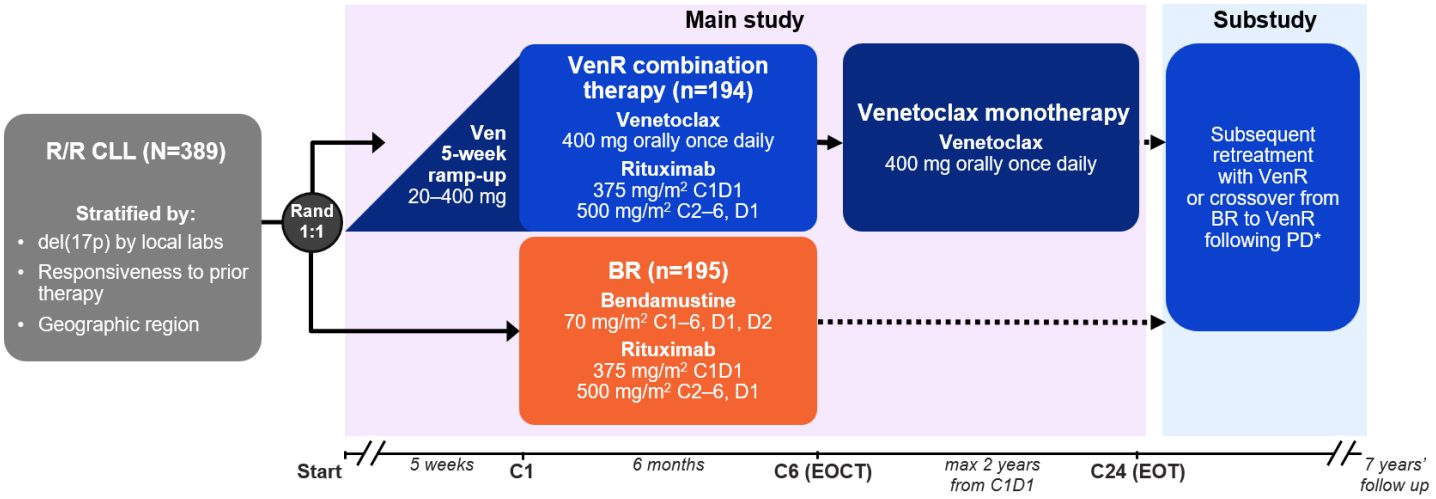
- a lack of comprehensive distinction between novel therapy-exposed and -refractory patients

- most patients with RR CLL in pivotal studies have previously received CIT.


CIT
V-R
FDT
Off treatment
FDT

MURANO 7 years follow up: final analyses aims

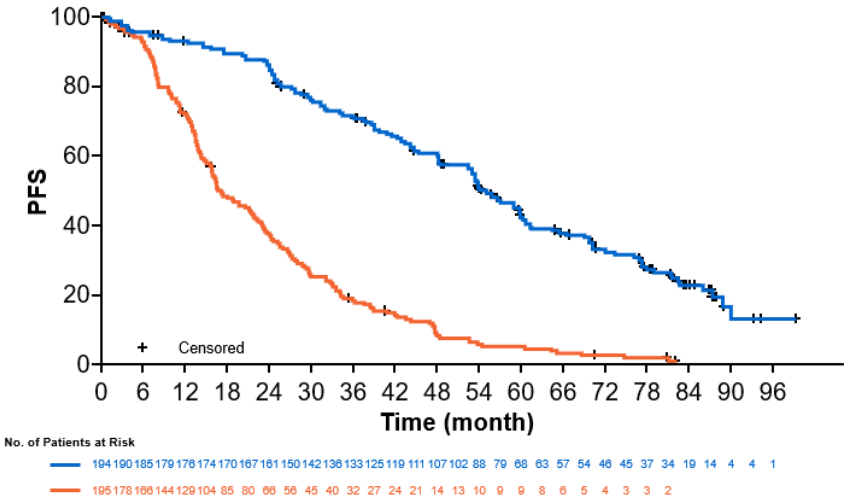
- Update PFS and OS
- Information on time to next anti-leukemic treatment (TTNT)
- Impact of MRD status on long term outcomes



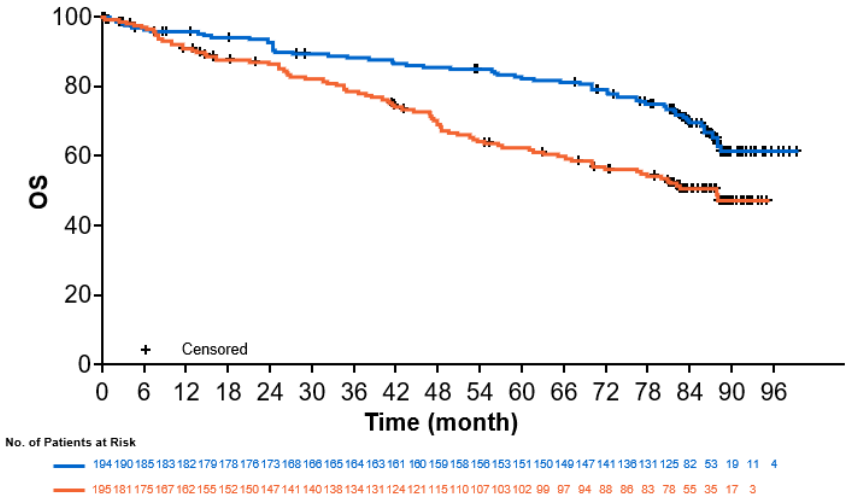
Kater AP, *et al.* EHA 2023. Abstract S201 (Oral).

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.

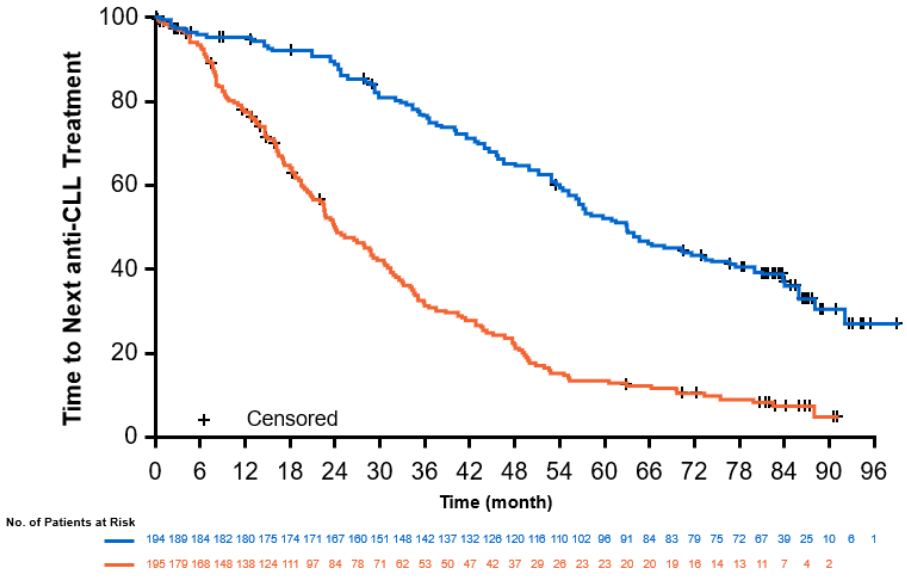
1. Seymour JF, et al. Blood 2022;140(8):839–50.
Kater AP, *et al.* EHA 2023. Abstract S201 (Oral).

A longer TTNT with VenR was observed vs BR

Overall, 95 (49.0%) VenR-treated patients and 131 (67.2%) BR-treated patients received subsequent anti-leukemic treatment

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

TTNT

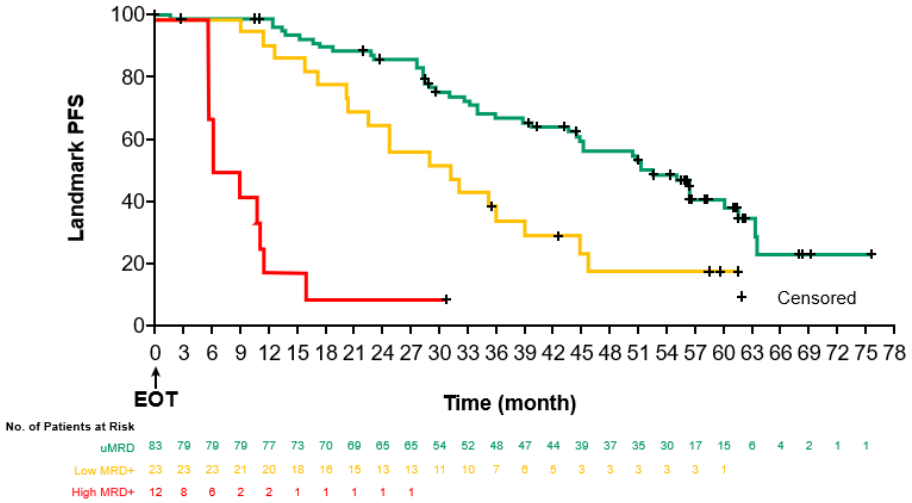


*Stratified HR is presented, unstratified HR=0.32. †P-values are descriptive only.

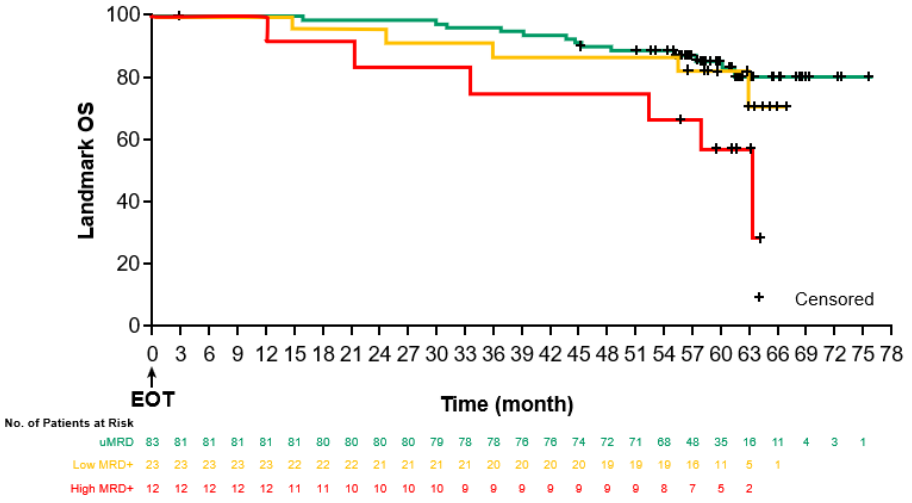
Kater AP, *et al.* EHA 2023. Abstract S201 (Oral).

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



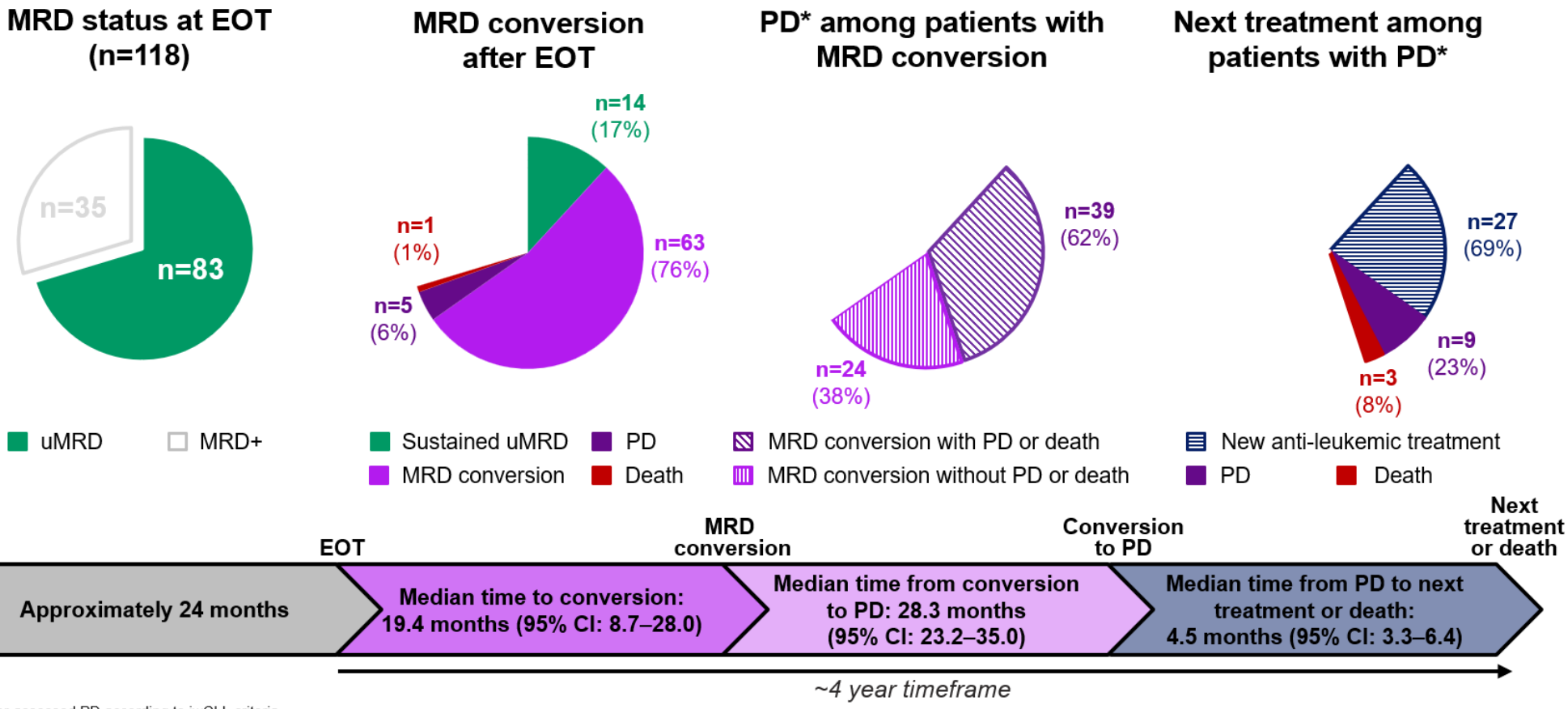
Achievement of uMRD was associated with prolonged PFS in VenR-treated patients

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.

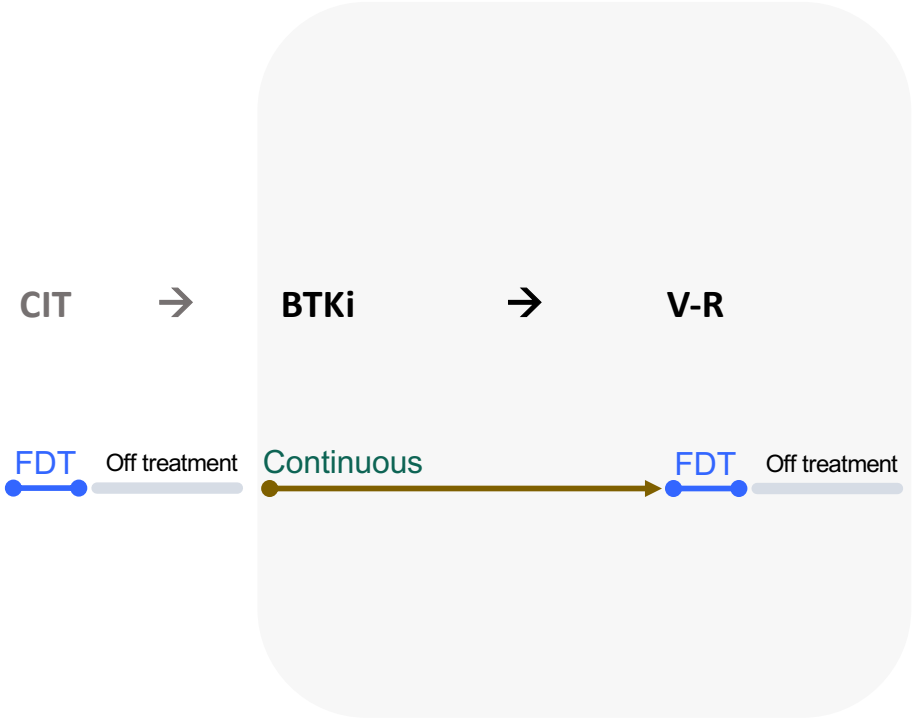
1. Kater A, *et al.* EHA 2023. Abstract S201 (Oral); 2. Seymour JF, *et al. Blood* 2022; **140:**839–850.

Prior therapies at baseline were mainly CIT in the Murano trial

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	123/180 (68.3)	123/180 (68.3)
	Mutated IGHV	53/180 (29.4)	51/180 (28.3)
	Unknown	4/180 (2.2)	6/180 (3.3)
Number of prior therapies, n (%)[2]	1	111 (57.2)	117 (60)
	2	58 (29.9)	43 (22.1)
	≥3	25 (12.9)	35 (17.9)
Prior therapies, n (%)[2]	Alkylating agent	185 (95.4)	182 (93.3)
	Purine analog†	158 (81.4)	157 (80.5)
	Anti-CD20 antibody	148 (76.3)	153 (78.5)
	BCRi	3 (1.5)	5 (2.6)
	Bendamustine	4 (2.1)	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).


CIT
BTKi
V-R
FDT
Off treatment
Continuous
FDT
Off treatment

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

The largest series of patients receiving VEN-R intended as time-limited therapy for cBTKi-exposed CLL

Retrospectively reviewed records of 47 consecutive patients

Treated at the Royal Melbourne Hospital and Peter MacCallum Cancer Centre (Melbourne), the Princess Alexandra Hospital (Brisbane), and Royal North Shore Hospital (Sydney)

November 2016 and February 2023

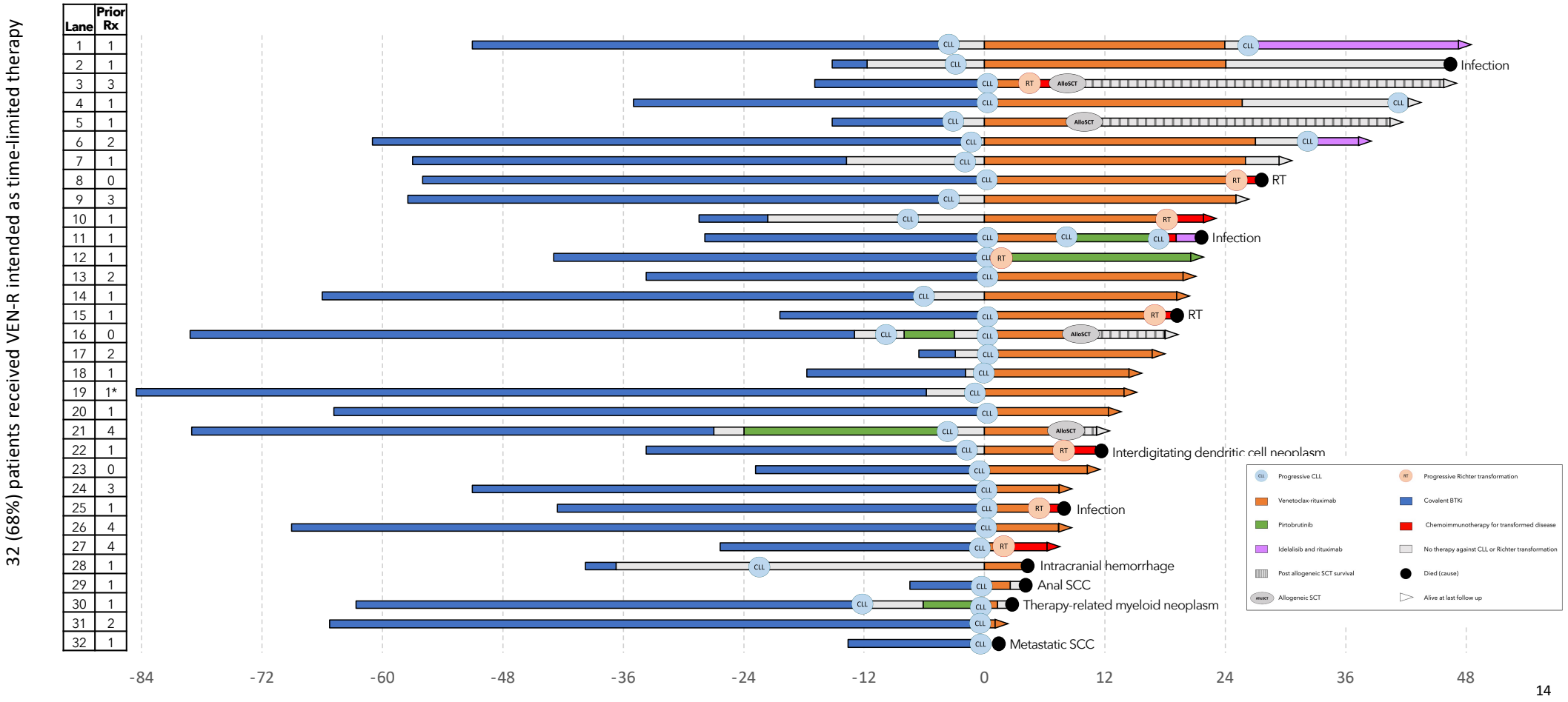
Received VEN-containing therapy for cBTKi-exposed CLL

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)
Intervening therapy between cBTKi-containing regimen and VEN			
None	29 (91%)	13 (87%)	42 (89%)
Bendamustine-R	0 (0%)	1 (7%)	1 (2%)
Methylprednisolone-R	0 (0%)	1 (7%)	1 (2%)
Pirtobrutinib	3 (9%)	0 (0%)	3 (6%)
Genetics before VEN-containing regimen			
IGHV unmutated	13 of 15 (87%)	5 of 6 (83%)	18 of 21 (86%)
Genomic complexity (≥5 lesions)	8 of 16 (50%)	3 of 8 (38%)	11 of 24 (46%)
del17p and/or *TP53* mutated	17 of 24 (71%)	9 of 14 (64%)	26 of 38 (68%)
BTKi resistance mutation(s) detected	13 of 16 (81%)	2 of 5 (40%)	15 of 21 (71%)
Outcomes after VEN-based therapy			
Best iwCLL response to VEN-based regimen			
CR¶	6 (19%)	3 (20%)	9 (19%)
PR	20 (63%)	4 (27%)	24 (51%)
SD	3 (9%)	4 (27%)	7 (15%)
PD	2 (6%)	0 (0%)	2 (4%)
Not evaluated†	1 (3%)	4 (27%)	5 (11%)
uMRD attained in PB or BM‡	7 of 10 (70%)	1 of 5 (20%)	8 of 15 (53%)
Reason for VEN cessation			
PD	9 (28%)	6 (40%)	15 (32%)
Remains on VEN at last follow-up	10 (31%)	3 (20%)	13 (28%)
Completed time-limited therapy	6 (19%)	0 (0%)	6 (13%)
Proceeded to allo-SCT	3 (9%)	1 (7%)	4 (9%)
Toxicity§	1 (3%)	3 (20%)	4 (9%)
Other‖	3 (9%)	2 (13%)	5 (11%)

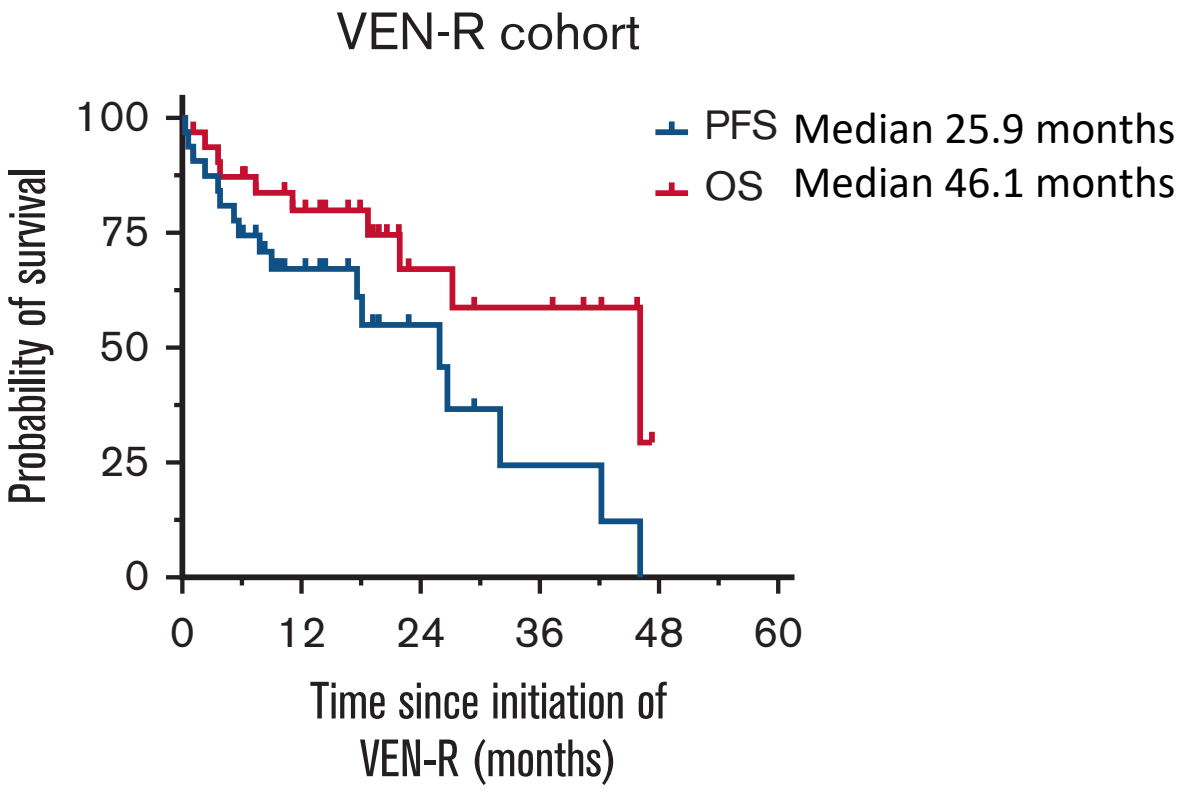
Thomas E. Lew et al, Blood Adv 2024

Sequence of therapies for patients receiving VEN-R for cBTKi-exposed CLL



Lew et al, Blood Adv 2024

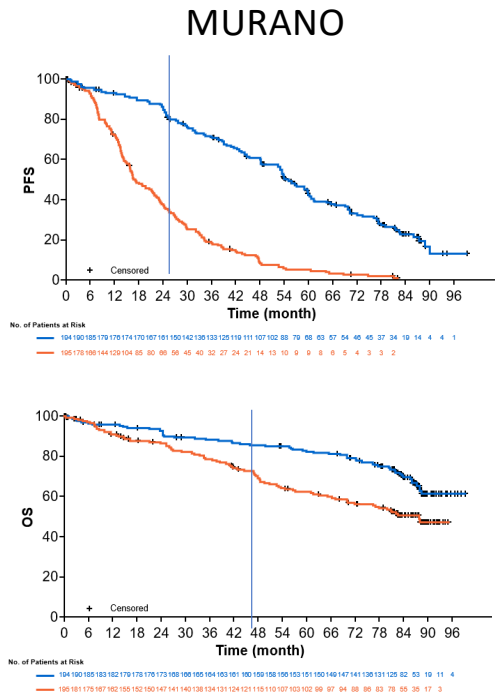
Outcomes after VEN-R for patients with cBTKi-exposed CLL



PFS	32	15	6	2
OS	32	24	8	6

Lew et al, Blood Adv 2024

VS



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

Venetoclax monotherapy is an effective strategy for treating BCRi-naive and BCRi-pretreated patients *(VENICE-1 trial)*

Open-label, single-arm, phase 3b trial (VENICE-1) assessing activity and safety of venetoclax monotherapy in R/R CLL stratified by previous exposure to a BCRi

Median duration of treatment exposure: 108 weeks

	all	BCR naive	BCR treated
Previous lines of chronic lymphocytic leukaemia-directed treatments			
1	106 (41%)	101 (53%)	5 (7%)
2	64 (25%)	47 (25%)	17 (25%)
≥3	88 (34%)	43 (23%)	45 (67%)

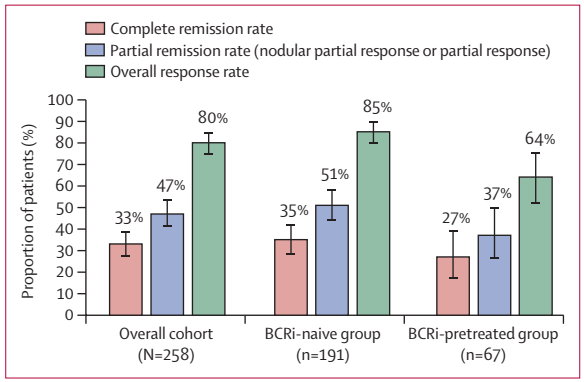
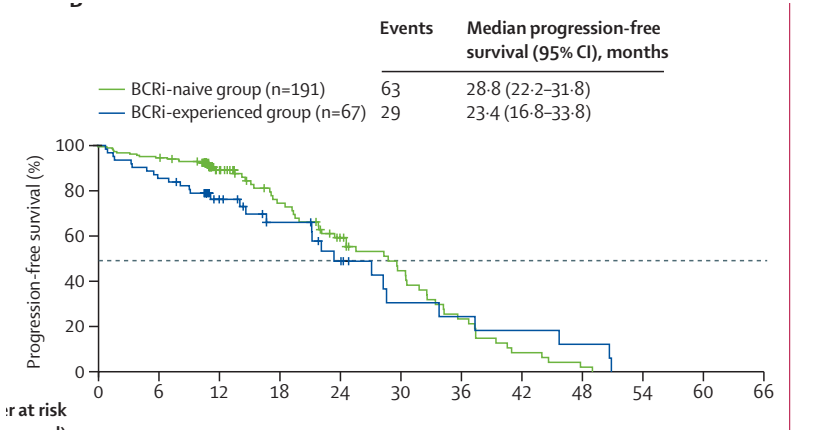
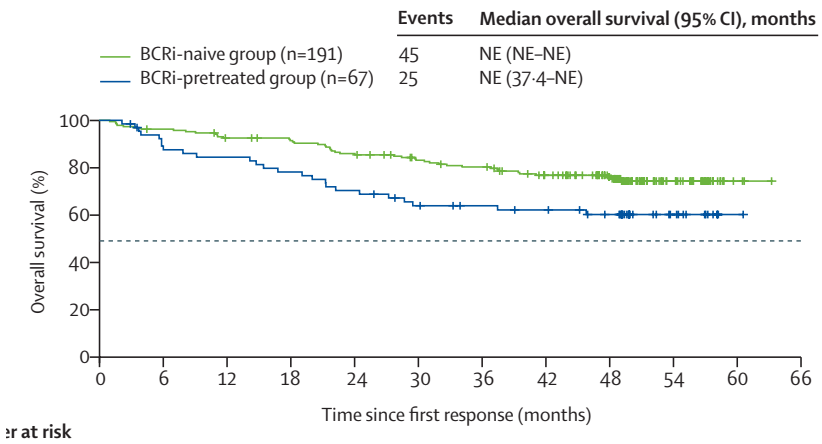
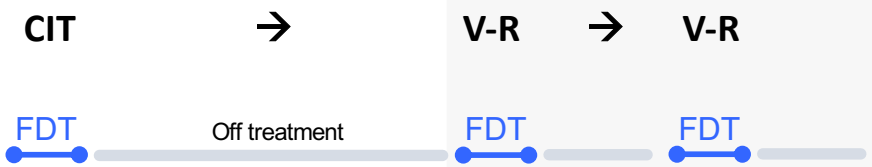


Figure 2: **Response rates for patients with relapsed or refractory chronic lymphocytic leukaemia treated with venetoclax monotherapy at week 48**
BCRi=B-cell receptor pathway inhibitor. Partial response needed to be confirmed later than 7 weeks or more for overall response.





Kater et al Lancet Oncology 2024


CIT
V-R
V-R
FDT
Off treatment
FDT
FDT

Retreatment in the MURANO trial

Figure 2. Subsequent anti-CLL therapies.

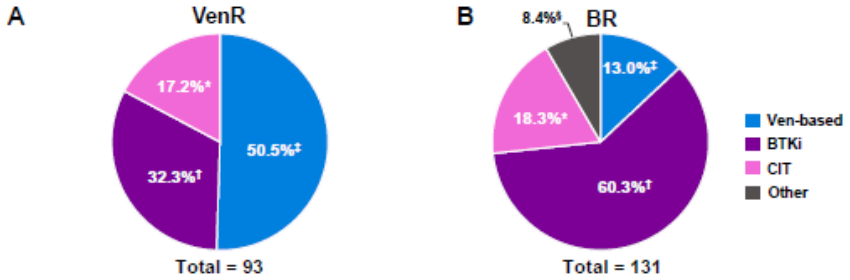
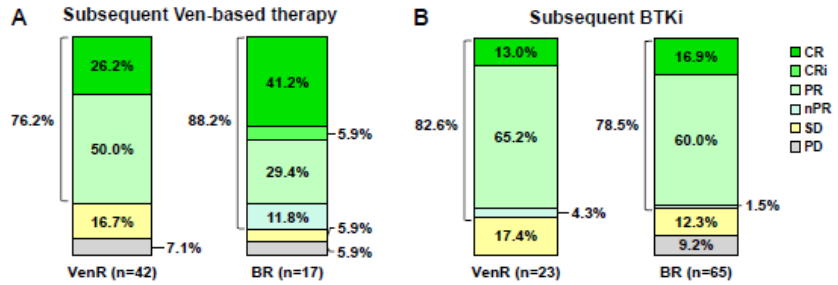
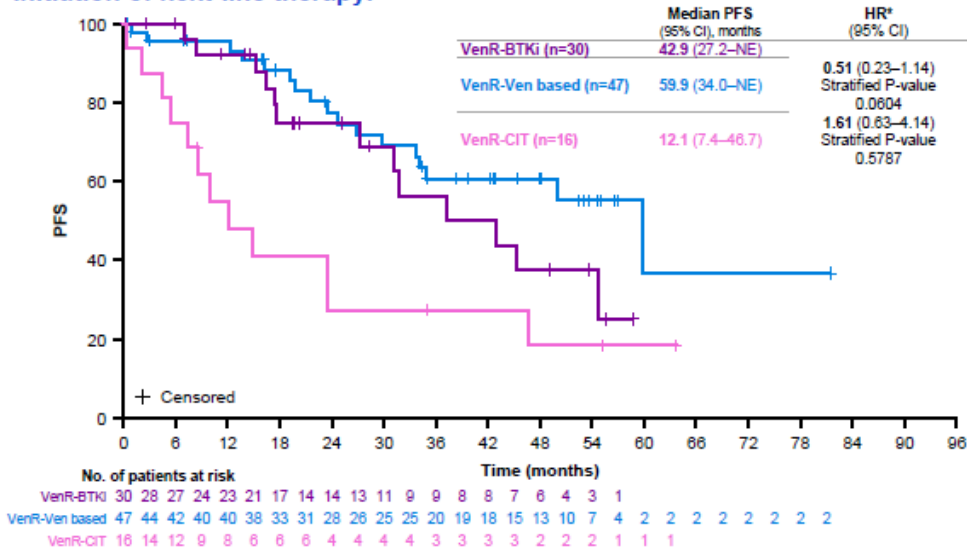


Figure 3. Response rates to subsequent VenR and BTKi therapies among evaluable patients.



SD, stable disease.

Figure 5. Kaplan Meier plot of PFS for patients in the VenR arm who received a subsequent therapy by treatment type; landmark (time zero) taken at initiation of next-line therapy.

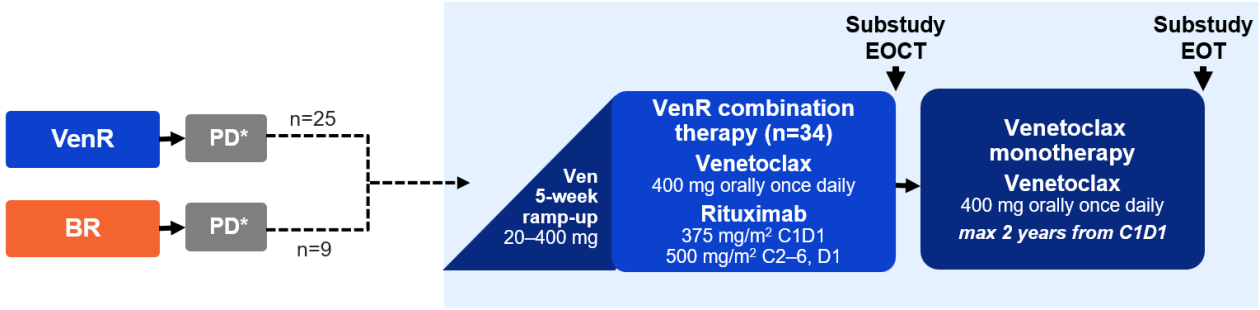


*Stratified HR is presented.

Harrup R et al., ASH 2023

MURANO retreatment/crossover substudy: additional final analyses aims

- ORR and PFS in retreatment substudy analysis
- MRD evaluation in retreatment study analysis



- Out of the 34 patients with PD who entered the substudy, 25 were retreated with VenR
  - Median time (range) from the final study drug dose in the main study and Ven retreatment in the substudy was 2.3 years (1.2–3.1)

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

Most patients who received VenR retreatment were classified as high risk

Patient characteristic at substudy baseline	Patients retreated with VenR (n=25)
Median age, years (range)	66 (49–82)
No. of prior therapies*, n (%)	
2	20 (80.0)
3	4 (16.0)
≥4	1 (4.0)
del(17p)† and/or *TP53* mutation‡, n (%)	
yes	8 (32.0)
no	5 (20.0)
unknown/not assessed	12 (48.0)
del(17p)†, n (%)	
deleted	7 (28.0)
not deleted	8 (32.0)
unknown/not assessed	10 (40.0)

Patient characteristic at substudy baseline	Patients retreated with VenR (n=25)
TP53‡, n (%)	
mutated	5 (20.0)
unmutated	17 (68.0)
unknown/not assessed	3 (12.0)
IGHV§, n (%)	
mutated	1 (4.0)
unmutated	22 (88.0)
unknown/not assessed	2 (8.0)
GC†, n (%)	
0–2	9 (36.0)
3–4	3 (12.0)
≥5	8 (32.0)
unknown/not assessed	5 (20.0)

*Including the VenR treatment they received in the main study. †Assessed by array comparative genomic hybridization. ‡Assessed by NGS. §Assessed by PCR. GC of ≥3 copy number alterations, or del(17p) and/or *TP53* mutations.
GC, genomic complexity.

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

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

Median follow up 33.4 months

Median prior LOT before first VenR: 2
92% high risk features

VenR — Off treatment — VenR2

Median Time Off Treatment: **2.3 years**

Best ORR 72.0%

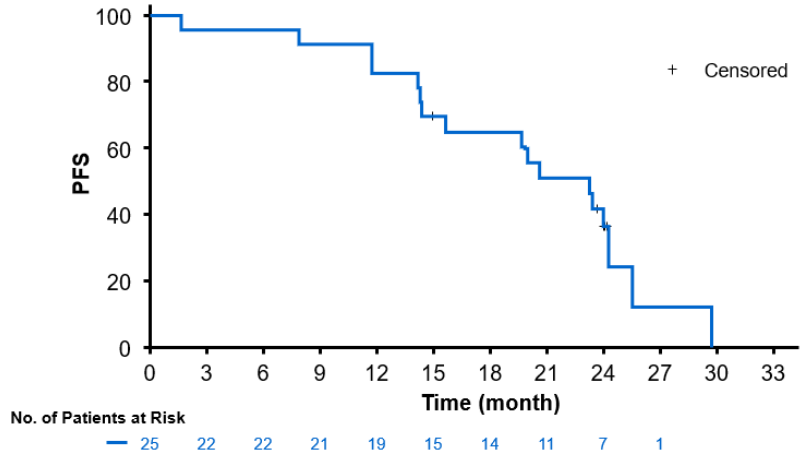
Median PFS: **23.3** months

Retreatment 3-year OS rate: 53.1%

Median OS 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.

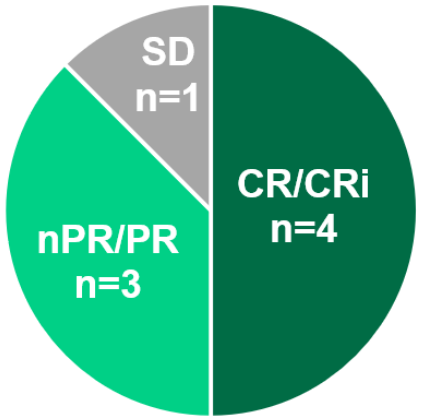
Kater A, *et al.* EHA 2023. Abstract S201 (Oral).

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

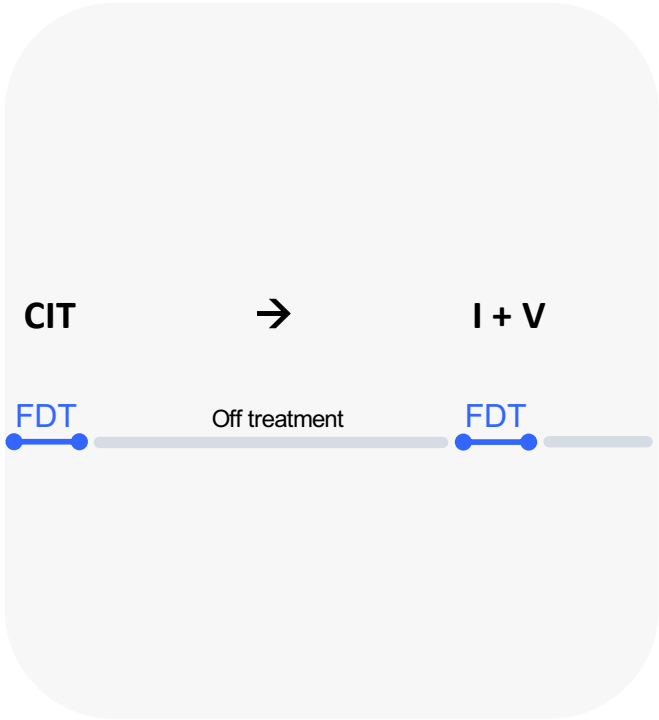
No patients retained their uMRD status at the retreatment EOT

Best ORR for VenR retreated patients who achieved uMRD



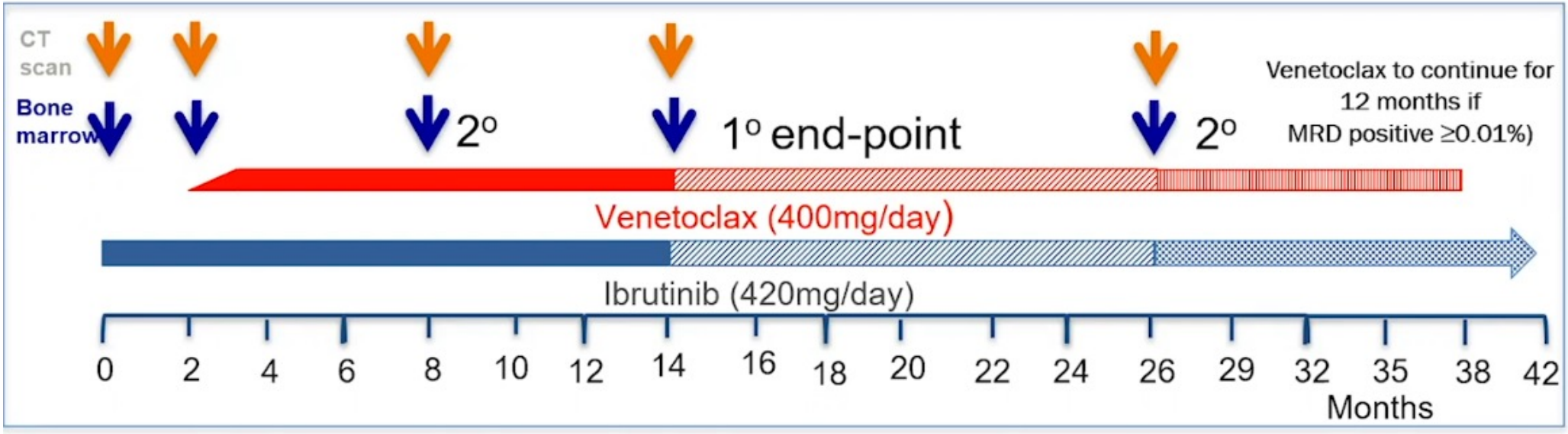
CR/CRi, complete remission/complete remission with incomplete count recovery; nPR/PR, nodular partial remission/partial remission; PR, partial remission' SD, stable disease.

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


CIT
I + V
FDT
Off treatment
FDT

Bloodwise TAP Clarity Study: Ibrutinib + Venetoclax in R/R CLL (no prior I or V)

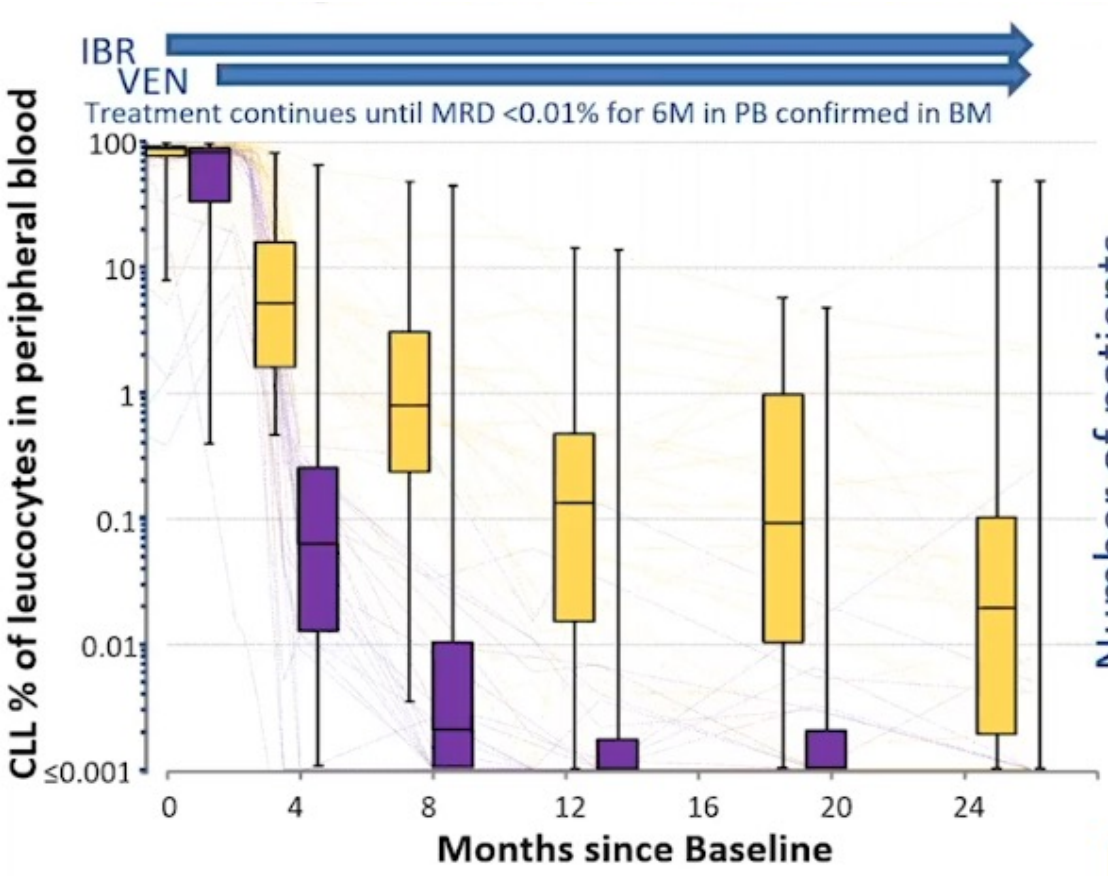
Treatment Schedule and Stopping Rules

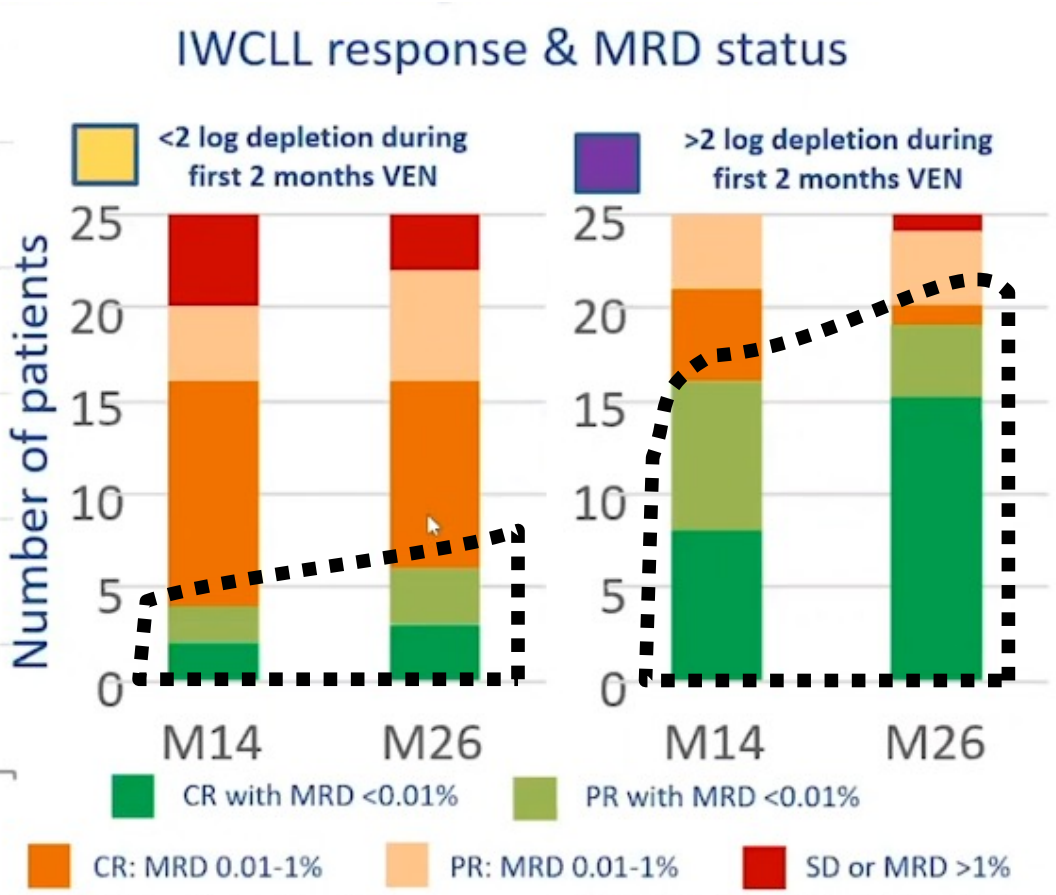


Duration of VEN therapy: 3 consecutive MRD4 (<0.01% CLL) in PB confirmed in BM:
MRD <0.01% at M8 → stop I+V at M14; MRD <0.01% at M14/26 → stop I+V at M26
MRD negative (<0.01%) at M38 → stop I+V at M38, if MRD positive (≥0.01%) continue IBR

Rawstron et al, EHA 12-Jun-2020; 294984; S164: Peripheral blood kinetics predicts long term responses to IBR +VEN for R/R CLL in the Bloodwise TAP CLARITY trial.

MRD response correlates with initial leucocytes depletion rate

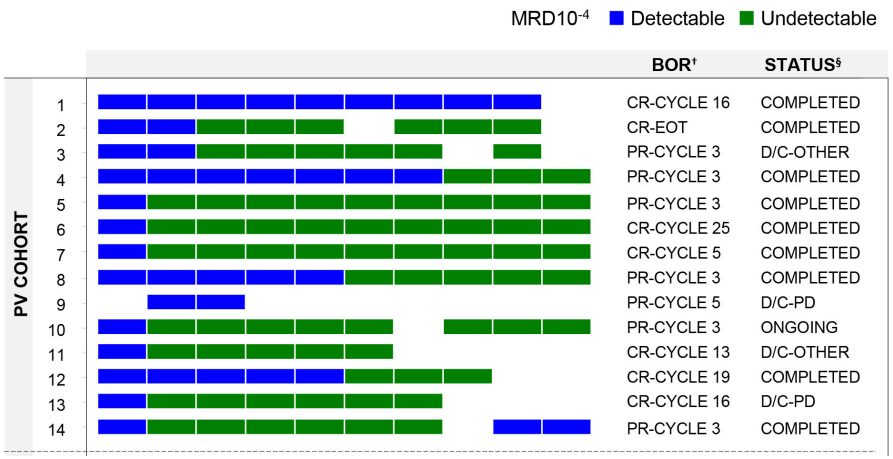


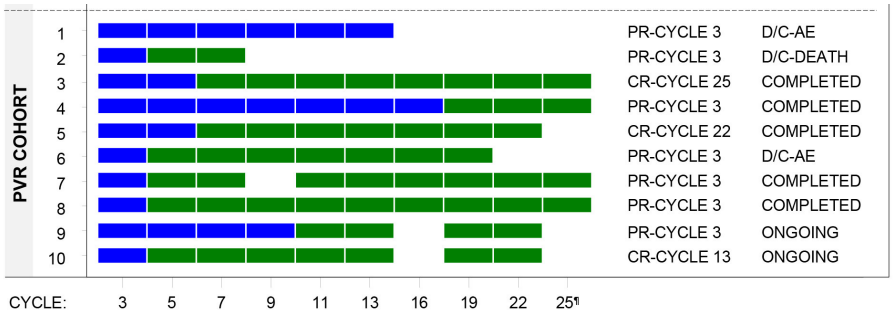


Rawstron et al, EHA 12-Jun-2020; 294984; S164: Peripheral blood kinetics predicts long term responses to IBR +VEN for R/R CLL in the Bloodwise TAP CLARITY trial.

Fixed-Duration Pirtobrutinib Combined with Venetoclax ± Rituximab in R/R CLL: Updated Results, Including MRD Data, from the BRUIN Phase 1b Study

Figure: Swimmer's Plot of MRD and Best Overall Response to Fixed-duration Pirtobrutinib in Combination with Venetoclax ± Rituximab in R/R CLL





† Best overall response was based on investigator assessment.

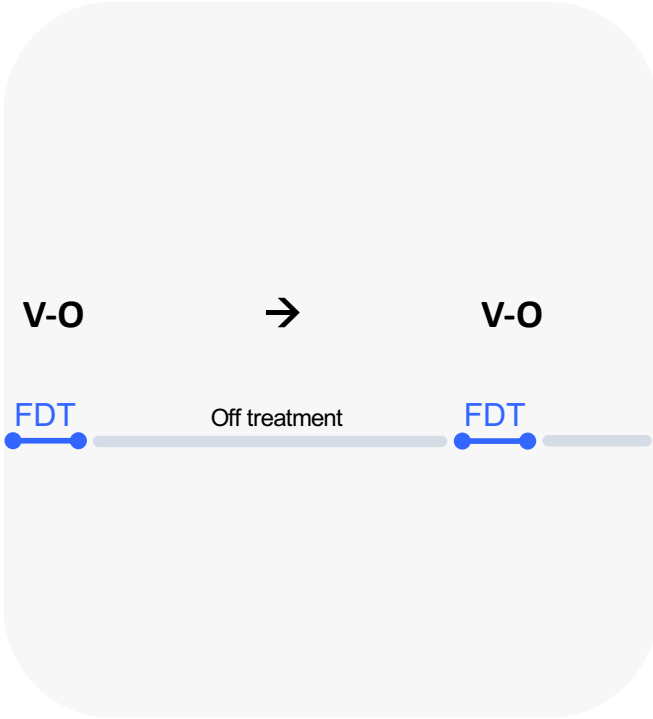
§ One patient in the PV cohort discontinued treatment because of protocol noncompliance. The calibration sample (i.e., pre-treatment) for this patient failed to identify a clonal sequence and subsequent MRD tracking by clonoSEQ was not possible. MRD data are therefore missing for this patient and not presented in the figure.

¶ Study protocol required a lead-in cycle of pirtobrutinib monotherapy followed by up to 24 cycles of combination therapy with venetoclax, for a total of 25 cycles.

Abbreviations: AE, adverse event; BOR, best overall response; CR, complete response; D/C, discontinued; MRD, minimal residual disease; PD, progressive disease; PR, partial response

The majority of pts had IGHV unmutated CLL (PV=73%; PVR=89%). ORR was 93.3% (95% CI, 68.1-99.8) for the 15 pts receiving PV and 100% (95% CI, 69.2-100.0) for the 10 pts receiving PVR, with 10 complete responses (PV=7; PVR=3).

Roeker LE et al , Blood, 2023


V-O
V-O
FDT
Off treatment
FDT

A pooled analysis of 13 pts with two consecutive time-limited V-containing therapies

GCLLSG 5 multi-center Phase 2 and 3 trials (N=13)[3]

Retreatment with venetoclax-based regimens

Median prior LOT: 2.5 (1-4)

No progression at a median observation time of 19 months

Ven1 — Off treatment — Ven2

ORR 100%
uMRD 92%

Median Time Off Treatment: **28** months

ORR 100%
uMRD 69%

Ven1:
VenO n=10
Ibr+VenO n=3

Ven2:
VenO n=4
Acala+VenO n=9

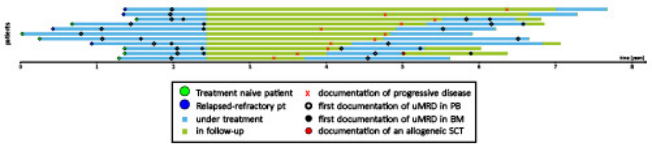


Figure 1: Swimmers plot of 11 pts with 2 Ven-containing therapies (2 pts from CLL13 trial excluded due to unavailable data regarding progression-free survival):

Plot shows duration of first and second venetoclax-containing therapy (blue parts of the bar) and of observation time in between and after V1 and V2, respectively (green part of the bar); time point of first documentation of undetectable MRD (uMRD) in peripheral blood (PB, circle) and bone marrow (BM, black dot), as well as of the disease progression (red X).

Mainly pts with adverse risk factors and a short remission duration

V-based re-treatment appeared to be safe and efficacious:

- all pts responded with at least 2/3 achieving uMRD again

- no increased rate of AEs was seen

VenR2=Retreatment with VenR after VenR.
Ven1, First Venetoclax Treatment; Ven2, Second Venetoclax Treatment.

3. Cramer P, et al. EHA 2022. Abstract P641 (Poster).

CLL14: Response to second-line treatment (4 years post randomization)

Phase 3, randomized, open-label, multicenter study evaluating VenO vs OClb in patients with 1L CLL (N=432)

- **Median observation time: 52 months**
- **All patients off treatment for ≥3 years**

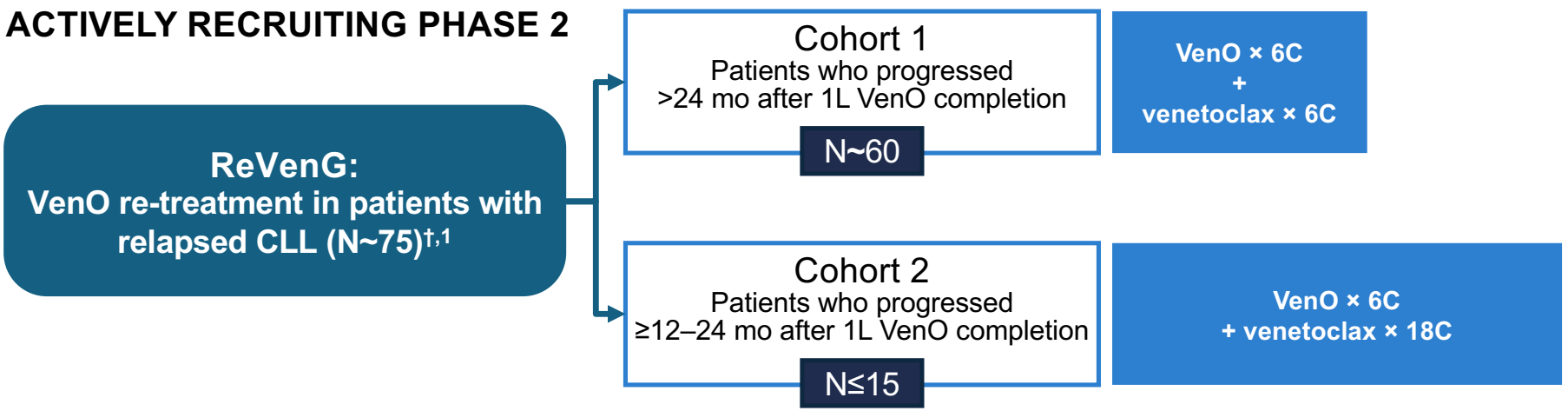
2nd-line therapy, n	VenO					OClb				
	All	OR	SD	PD	Unknown	All	OR	SD	PD	Unknown
Total	**14**	7		1	6	**63**	27	12	2	22
BTKi	**8**	3		1	4	**35**	15	4	2	14
Venetoclax	**2**	1			1	**8**	4			4
CIT	**3**	3				**15**	5	7		3
PI3Ki						**1**		1		
Rituximab monotherapy						**1**				1
Others	**1**				1	**3**	3			

BTKi was the most common second-line therapy used. Early data show that with VenO, a response was observed in many patients treated with a second-line BTKi, suggesting BTKi post venetoclax therapy is an effective sequence

BTKi, Bruton's tyrosine kinase inhibitor; CIT, chemoimmunotherapy; OClb, obinutuzumab and chlorambucil; OR, overall response; PI3Ki, phosphoinositide 3-kinase inhibitor; VenO, venetoclax and obinutuzumab.

Al-Sawaf O, *et al.* EHA 2021. Abstract S146 (Oral).

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:

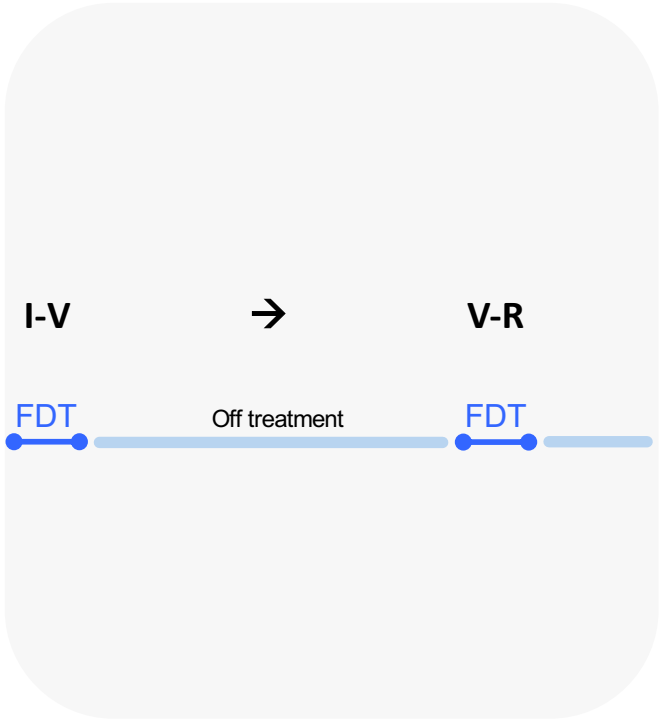
- CR/CRi at EoCT and EoT
- ORR at EoT
- uMRD at EoCT and EoT
- PFS
- OS
- TTNT
- Safety

† 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).

This slide contains information on uses of venetoclax that have not been approved.


I-V
V-R
FDT
Off treatment
FDT

AGENZIA ITALIANA DEL FARMACO

DETERMINA 26 febbraio 2024

Modifica delle condizioni e modalita' di monitoraggio nell'ambito dei registri AIFA del medicinale per uso umano «Venclyxto». (Determina n. 2/2024). (24A01189)

(GU n.55 del 6-3-2024)

E	*Campo obbligatorio ai fini dell'eleggibilità*	VENCLYXTO (venetoclax)
O	*Campo obbligatorio*	Leucemia Linfatica Cronica (LLC)

1. VENCLYXTO in monoterapia è indicato per il trattamento della Leucemia Linfatica Cronica (LLC) in presenza della delezione 17p o della mutazione TP53 in pazienti adulti non idonei o che hanno fallito la terapia con un inibitore della via del recettore delle cellule B.

2. VENCLYXTO in monoterapia è indicato per il trattamento di pazienti adulti con LLC in assenza della delezione 17p o mutazione TP53 che hanno fallito la chemioimmunoterapia e la terapia con un inibitore della via del recettore delle cellule B.

3. Venclyxto in combinazione con rituximab è indicato per il trattamento di pazienti adulti con leucemia linfatica cronica (LLC) che hanno ricevuto almeno una terapia precedente.

4. Venclyxto in combinazione con obinutuzumab è indicato per il trattamento di pazienti adulti con leucemia linfatica cronica (LLC) non trattati in precedenza.
Indicazione ammessa alla rimborsabilità:
Venclyxto in combinazione con obinutuzumab è indicato per il trattamento di pazienti adulti con leucemia linfatica cronica (LLC) non trattati in precedenza e non candidabili ad immunochemioterapia di prima linea tipo FCR

Precedenti trattamenti	Chlorambucil +/- Rituximab	
	Obinutuzumab + Chlorambucil	
	Ofatumumab + Chlorambucil (o Bendamustina)	
	Rituximab in monoterapia	
	R-CVP	
	R-CHOP	
	Corticosteroidi in monoterapia	
	Ibrutinib o altro BTKi	*Solo per le indicazioni 1 e 2 se non selezionata una di queste opzioni, si apre una domanda (vd sotto)*
	Idelalisib +/- Rituximab	
	Altro inibitore della via del recettore delle cellule B	
	Ofatumumab in monoterapia	
	Regimi contenenti Alemtuzumab	
	Altro	

Se selezionato "Ibrutinib o altro BTKi" tra i precedenti trattamenti, si apre la domanda sottostante			
O	Il paziente è stato sottoposto a trattamento con Ibrutinib in associazione a venetoclax?	Si	
		No	
Se risposto "Si" alla domanda precedente, si apre la domanda sottostante			
E	Il paziente ha manifestato tossicità inaccettabile oppure è risultato refrattario al trattamento (recidiva o progressione di malattia nell'arco dei 6 mesi successivi al termine della terapia)?	Si	*blocca*
		No	

Considerations to optimize treatment sequencing

- Prior drug exposure and response to prior treatment
- Reason for end of prior therapy (progress or intolerance)
- Patient preferences

- Patient clinical status
- Financial considerations
- Upcoming new MOAs

- Regulatory authority