# Il concetto della "durata fissa" dal farmacologo all'ematologo nel paziente pretrattato

Dott.ssa A. Giordano

REVOLUTIONARY ROAD IN CLL

**Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica**

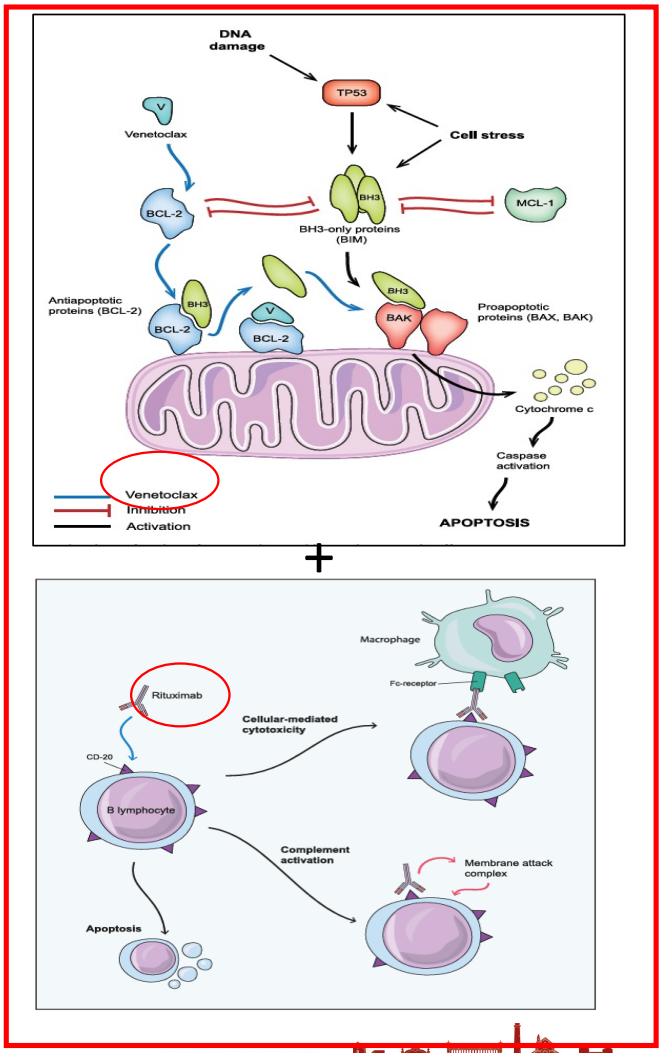
**Bari, 29 maggio 2024**
Mercure Villa Romanazzi Carducci

# DISCLOSURE
## Annamaria Giordano

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| Janssen | | | X | | X | X | |
| | | | | | | | |
| Abbvie | | | | | X | X | |
| | | | | | | | |
| Asta Zeneca | | | X | | X | | |

# CLL second line treatment

| Response to 1L therapy | Fitness | Therapy |
|---|---|---|
| Refractory or progress within 3 years | Go go | Change to: venetoclax + rituximab, ibrutinib, or acalabrutinib. Other options include: idelalisib + R, FA, FCR (after BR), venetoclax, A-Dex, lenalidomide (+ R), BR (after FCR). Discuss consolidation with allogeneic SCT |
| | Slow go | Change to: venetoclax + rituximab, ibrutinib, or acalabrutinib. Other options include idelalisib + R, A, FCR-lite, BR, lenalidomide (+R), ofatumumab, HD-R |
| Progress after 3 years | All | Repetition of 1L therapy could be considered, but change to targeted therapy if chemotherapy previously given |

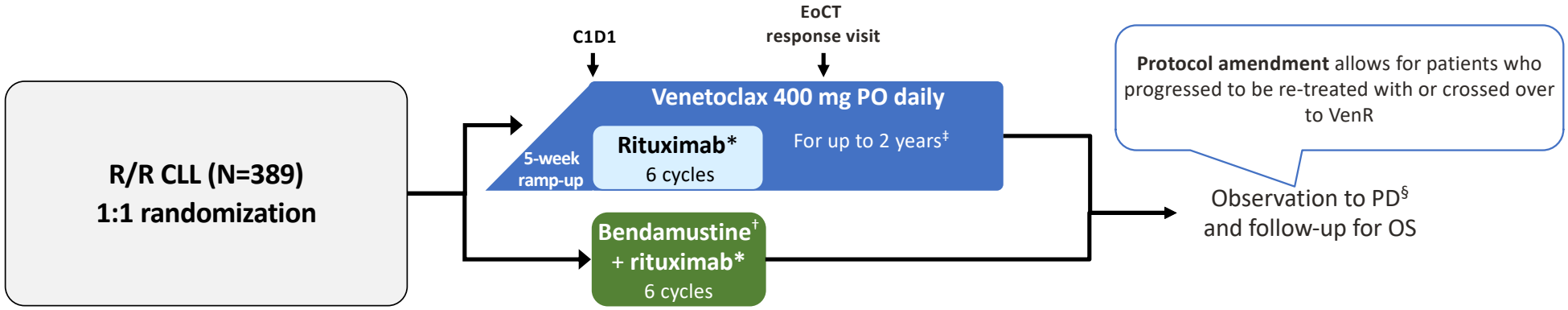



**24 cycles of fixed-duration VenR is currently a standard treatment for patients with CLL R/R**

Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures

WILEY AJH HALLEK AND AL-SAWAF

# MURANO: Study design




**Primary endpoint:**
- INV-assessed PFS

**Key secondary endpoints:**
- IRC-assessed PFS
- PFS in patients with del(17p) (IRC- and INV-assessed)
- ORR (CR, CRi, nPR, PR) (IRC- and INV-assessed) at EoCT
- OS, rates of MRD clearance, DoR, EFS, TTNT

**Key inclusion criteria**
- 1–3 lines of prior therapy, including ≥1 chemotherapy-containing regimen
- Prior bendamustine only if DoR was ≥2 years (i.e. not refractory or resistant to prior BR)
- ECOG PS ≤1

* Rituximab: 375 mg/m$^2$ C1D1 and 500 mg/m$^2$ D1C2–6;
† Bendamustine: 70 mg/m$^2$ days 1 and 2 of each cycle;
‡ Or until PD or unacceptable toxicity; § Or end of study.

Kater AP, *et al. J Clin Oncol* 2020; **38**:4042–4054.

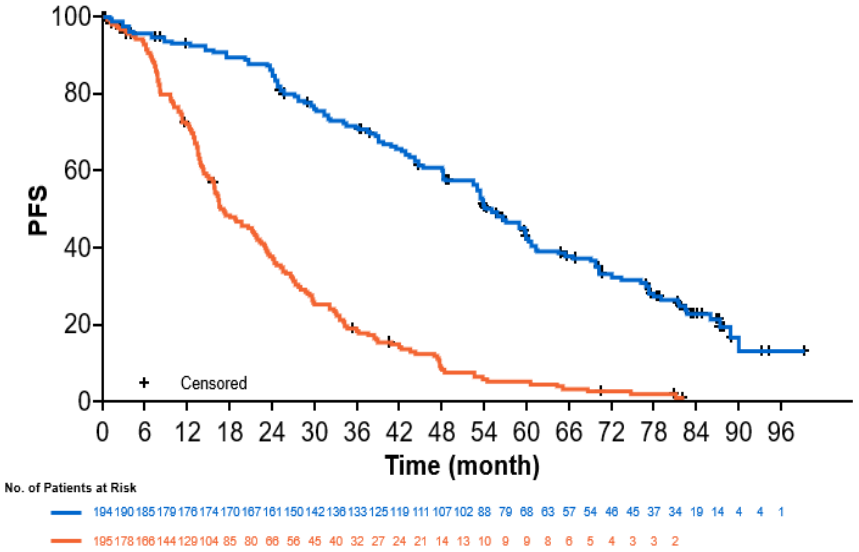
| Characteristics | | VenR (n=194) | BR (n=195) |
|---|---|---|---|
| Age[1] | Median, years (range) | 64.5 (28–83) | 66 (22–85) |
| Lymphocyte count, n (%)[1] | ≥25×10$^9$/L | 129 (66.5) | 134 (68.7) |
| del(17p)–(FISH),* n/N (%)[1] | Deleted | 46/173 (26.6) | 46/169 (27.2) |
| *TP53* mutational status,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

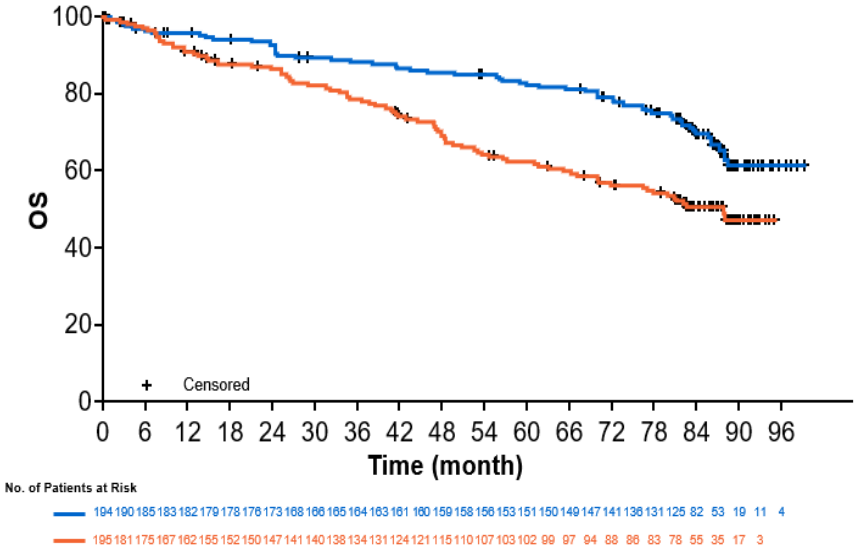
1. Seymour JF, *et al. N Engl J Med* 2018; **378:**1107–1120 (incl. suppl.);
2. Seymour JF, *et al.* ASH 2019. Abstract 355 (Oral);
4. VENCLYXTO® (venetoclax). EMA Summary of Product Characteristics (April 2020 update).

# EFFICACY: PFS AND OS

| | 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 |



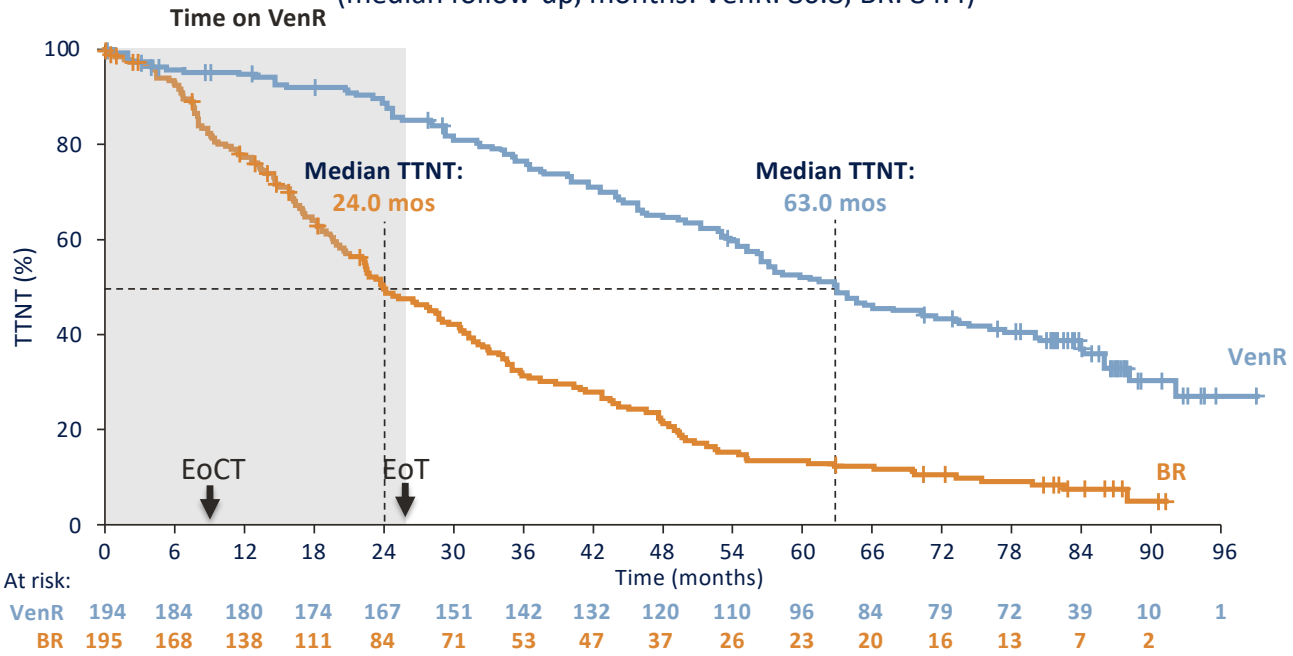

- Median follow up for efficacy (range) was 86.8 months (0.3–99.2) for VenR and 84.4 months (0.0−95.0) for BR

Seymour JF, *et al. Blood* 2022; 140:839–850

# EFFICACY: TTNT at the 7-y final analysis

**Time to next treatment***

(median follow-up, months: VenR: 86.8; BR: 84.4)




| | VenR | BR |
|---|---|---|
| HR (95% CI) | HR=0.30 (0.23–0.39)† | |
| p value | Stratified p<0.0001‡ | |

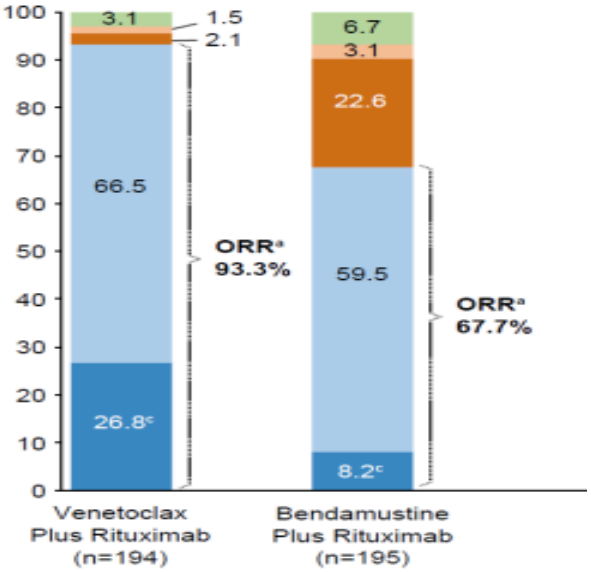
**Risk of starting another anti-CLL treatment or death was reduced by 70% with VenR vs BR;**
**50% of VenR patients were without new treatment approximately 3 years after completion of treatment**

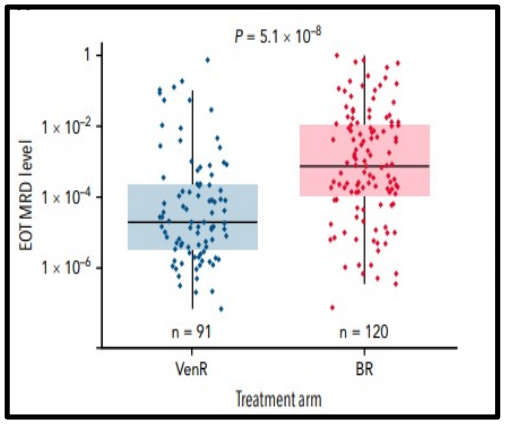
* Time to next treatment was defined as time from initiation of BR/VenR to next anti-CLL treatment or death (whichever occurs first);
† Stratified HR value presented, unstratified HR=0.32; ‡ p values are descriptive only.
EoCT, end of combination treatment; EoT, end of treatment; FTD, fixed-treatment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



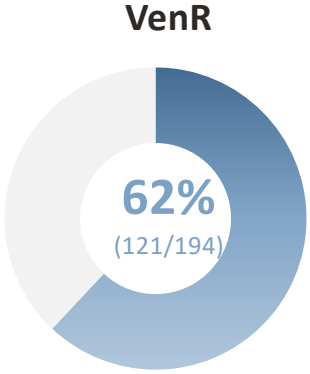
Kater AP, et al. EHA 2023. Abstract S201 (Oral).

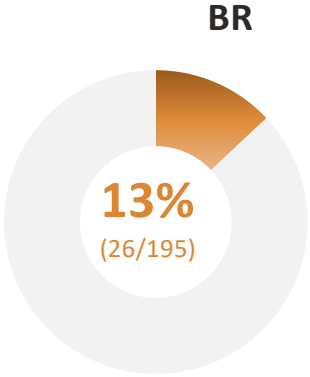
# DEEP RESPONSES :MRD



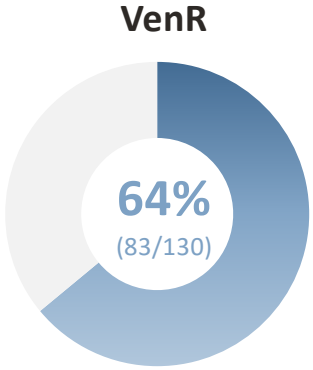




## uMRD* in PB at EoCT†,1

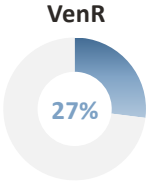


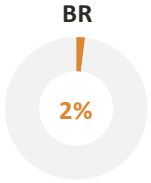




## uMRD* in PB at EoT2




**Best uMRD in BM on study‡**




* uMRD (<$10^{-4}$) assessed centrally in PB with ASO-PCR or flow cytometry; † 3 mo after combination treatment completion;
‡ BM was only assessed in responders (CR or PR). BM, bone marrow; EoCT, end of combination treatment; EoT, end of treatment; PB, peripheral blood.

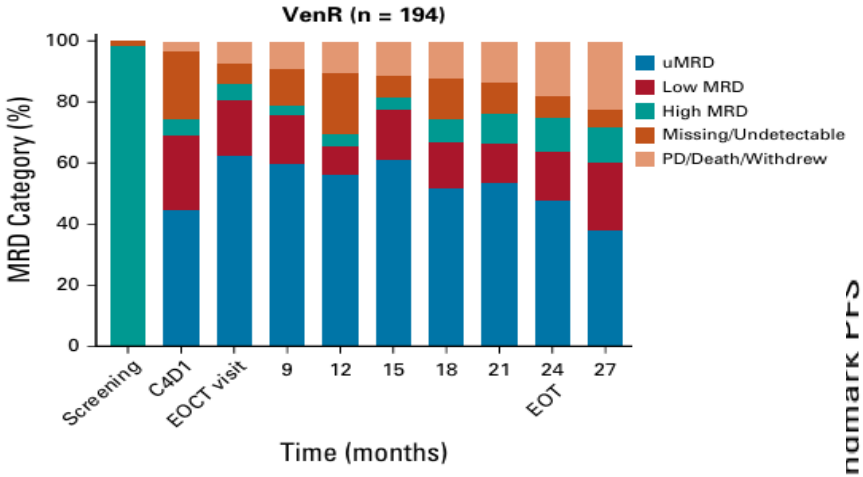
The model predicted that **median MRD level at EOT was significantly lower post-VenR** (1.88 3 1025 ) **vs post-BR** (7.06 3 1024 ; P 5 5.1 3 1028 )

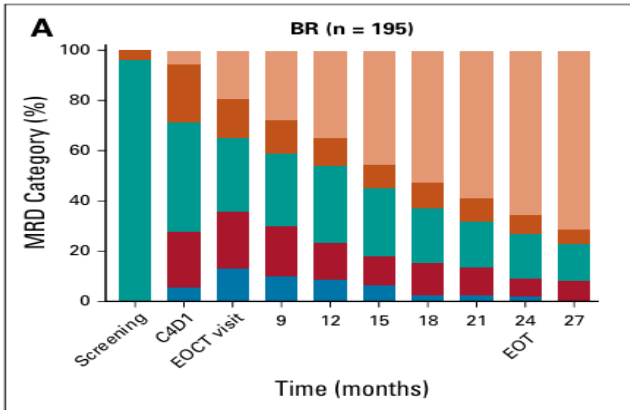
**Seymour JF, et al. Blood 2022; 140:839–850**


1. Seymour JF, *et al. N Engl J Med* 2018; **378**(12):1107–1120;
2. Kater AP, *et al. J Clin Oncol* 2019; **37**(4):269–277.

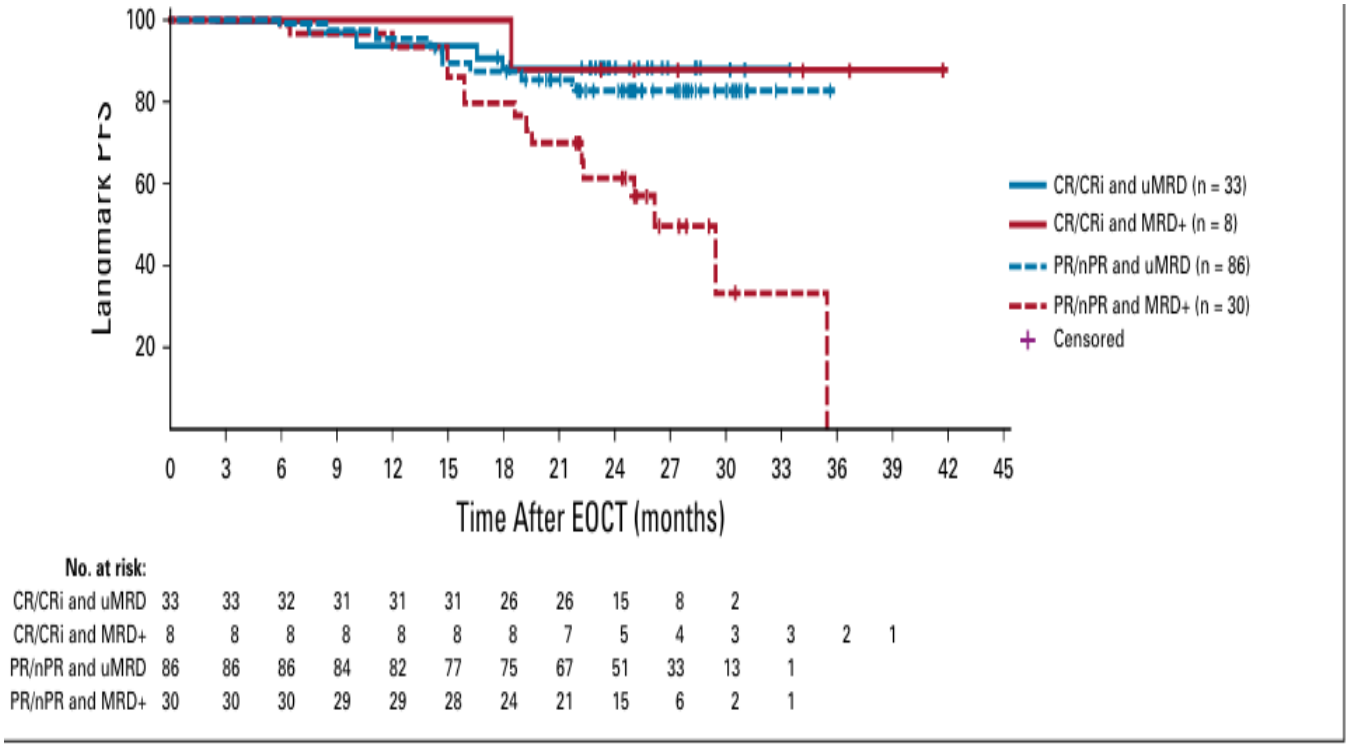
## MRD

## Patients in PR have a similar outcome as patients with CR when uMRD levels are achieved




**PFS by response status and by MRD status in PB at EoCT†**
(median follow-up of 36 months)

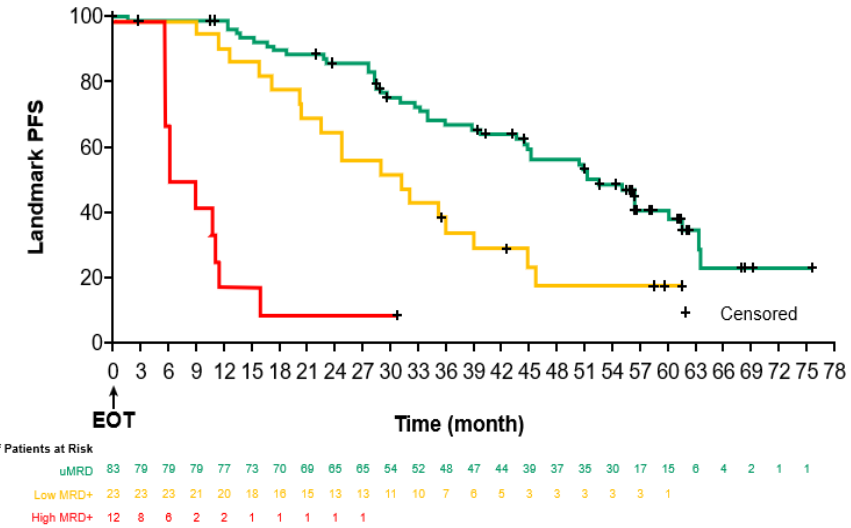



Seymour JF, *et al. Blood* 2022; 140:839–850

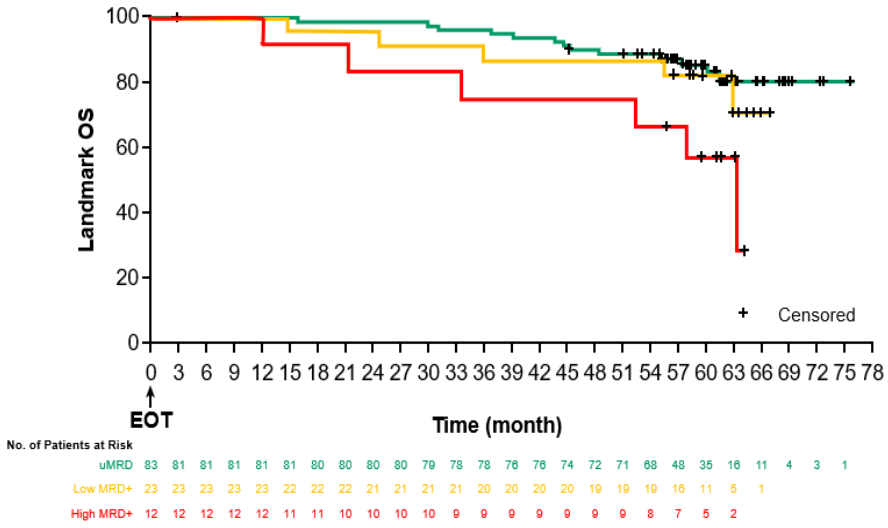
Kater et all ournal of Clinical Oncology, 2018

# 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 |

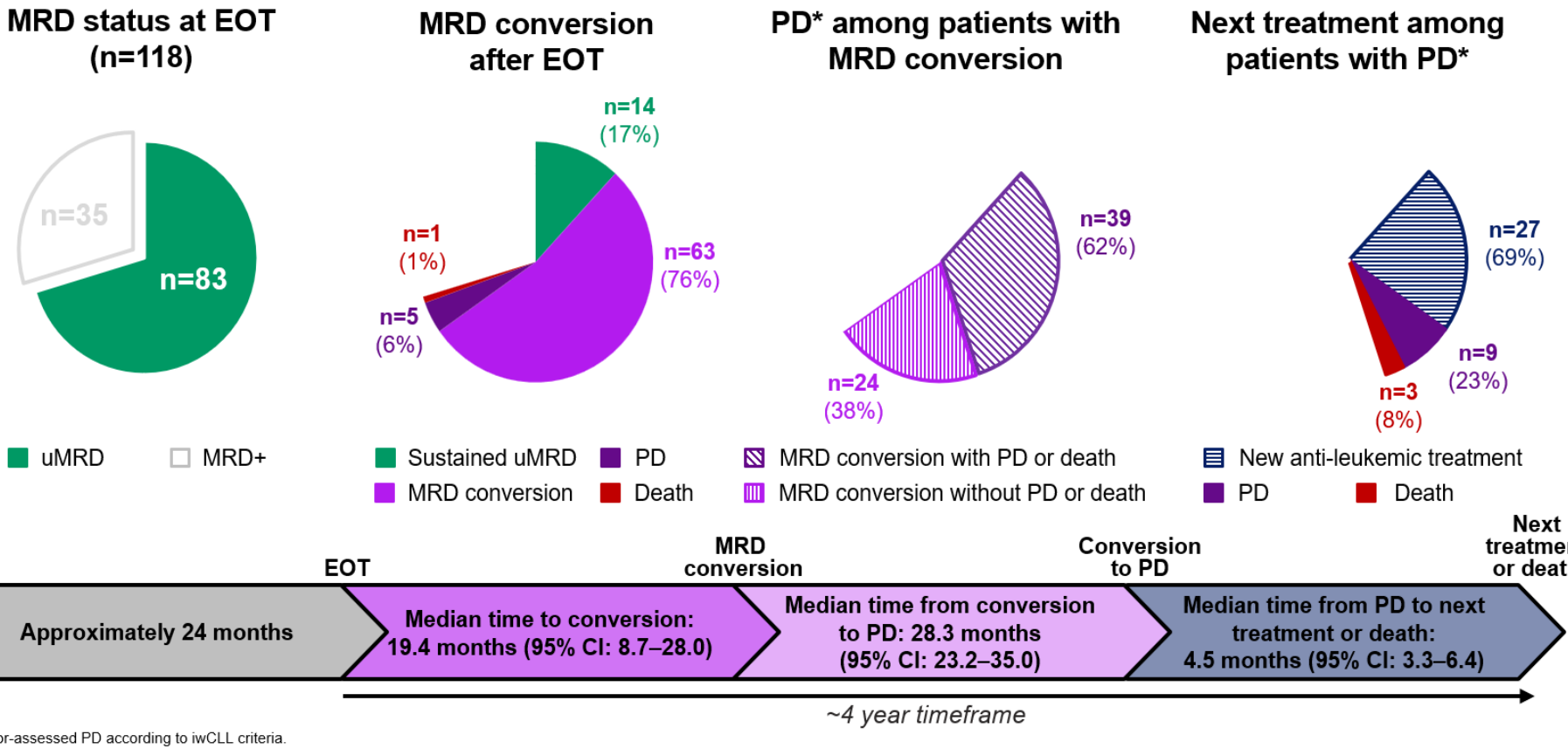



Achievement of uMRD was associated with prolonged PFS in VenR-treated patients

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.

# 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

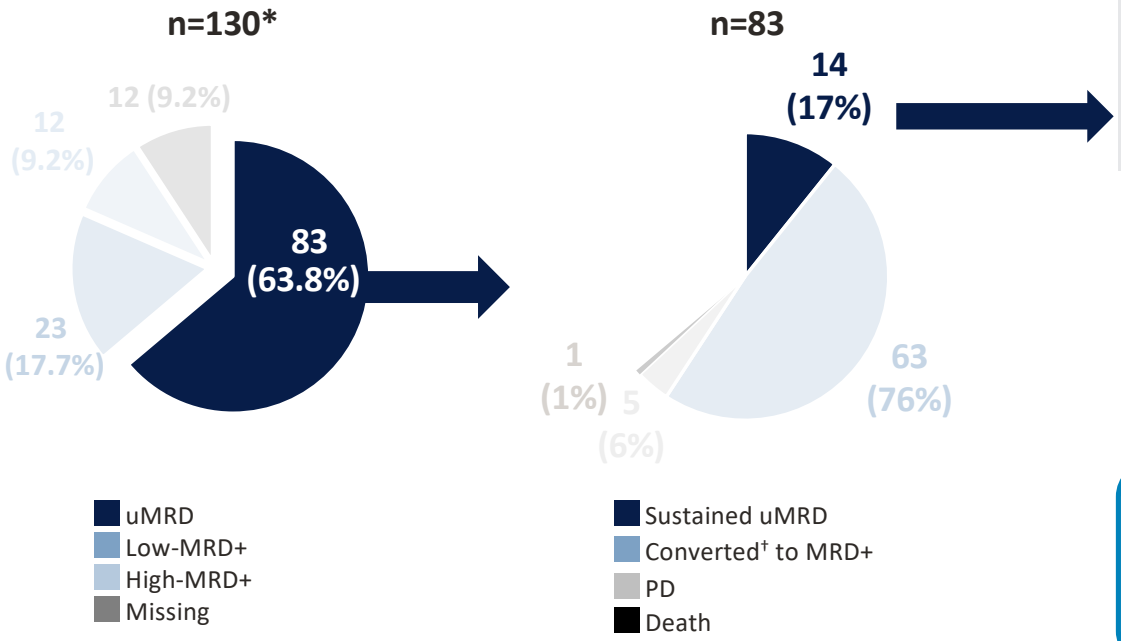



*Investigator-assessed PD according to iwCLL criteria.

# Baseline characteristics among patients with enduring uMRD

MRD status **at EoT** in VenR patients without PD[1,2]

MRD conversion after EoT[1]




| VenR-treated patients, n (%)[1] | Patients with sustained uMRD (n=14) | Patients without sustained uMRD (n=180) |
|---|---|---|
| ***TP53*‡ (N=192)§** | | |
| Unmutated (N=144) | 13/14 (92.9) | 131/180 (72.8) |
| Mutated (N=48) | 1/14 (7.1) | 47/180 (26.1) |
| **IGHV‖ (N=176)§** | | |
| Mutated (N=53) | 7/14 (50.0) | 46/180 (25.6) |
| Unmutated (N=123) | 6/14 (42.9) | 117/180 (65.0) |

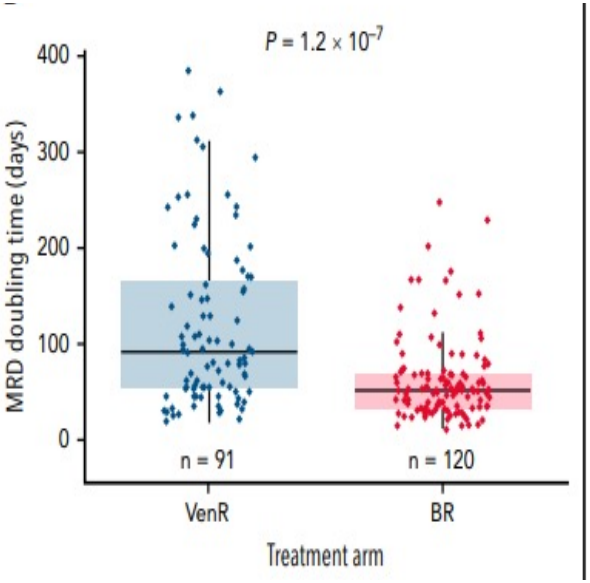
**Among patients with sustained uMRD at EoT**

Median number of prior therapies: 1 (range=1–3)

* 118 were evaluable for MRD status; † MRD conversion = 2 consecutive MRD+ assays;[2]
‡ Assessed by NGS; § Biomarker evaluable population; ‖ Assessed by PCR.
EoT, end of treatment; NGS, next-generation sequencing; PCR, polymerase chain reaction.

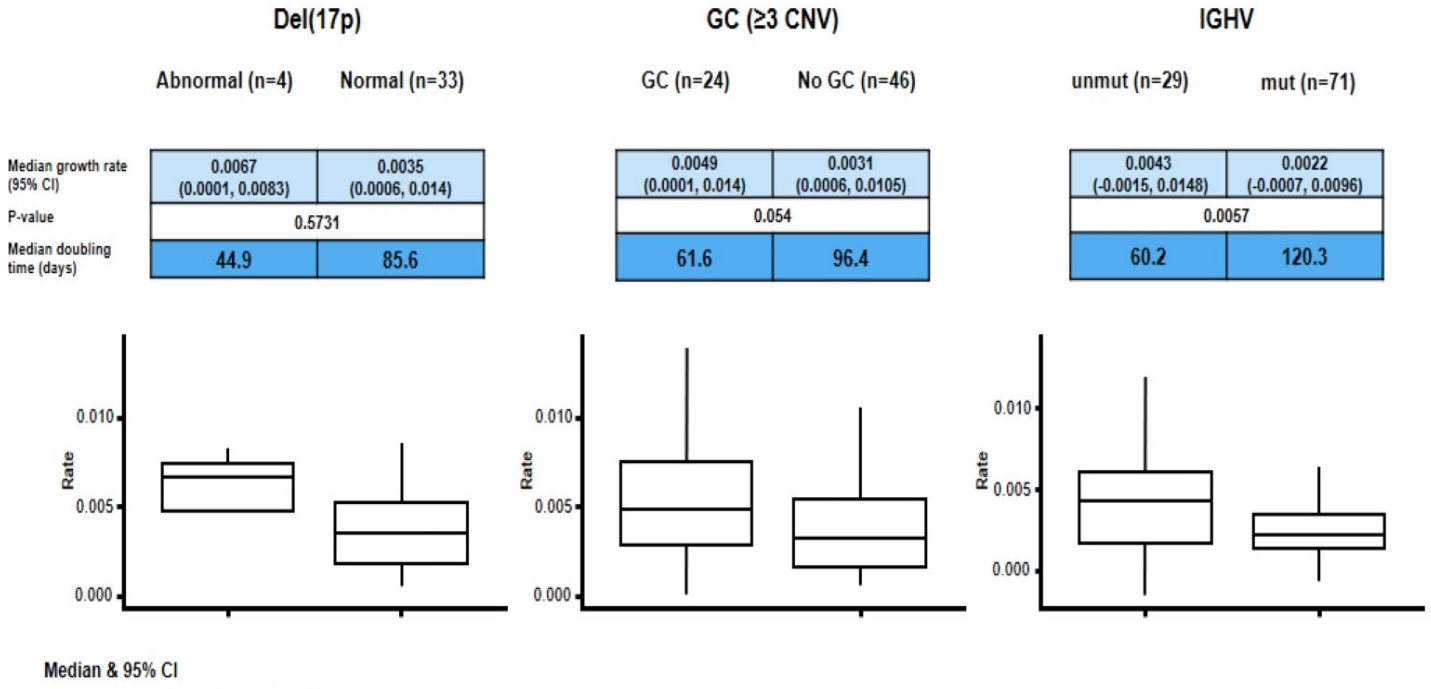
1. Kater A, *et al.* EHA 2023. Abstract S201 (Oral); 2. Seymour JF, *et al. Blood* 2022; **140**:839–850.

# MRD doubling time post-EOT




median **MRD doubling time** post-EOT was **significantly longer for patients treated with VenR** (93 days; n 5 91) **vs BR** (53 days; n 5 120; P 5 1.2 3 1027 )

**Median MRD doubling time post-EOT according to biological factors**




.Seymour JF, *et al. Blood* 2022; 140:839–850

# Safety overview

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

## Updated safety profile*,[1–3]

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

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

* Grade 3–4 AEs were not actively monitored after EoT; only deaths, SAEs, or other AEs of concern believed to be related to prior treatment with study drug were reported; † Throughout the study to 5-year analysis (data cut-off May 8, 2020), Richter transformation was reported in 7 (3.6%) patients in the VenR arm and 6 (3.5%) patients in the BR arm; ‡ Median follow-up 86.8 months for VenR. EoT, end of treatment; TLS, tumor lysis syndrome.

1. Seymour JF, *et al.* ASH 2019. Abstract 355 (Oral);
2. Kater AP, *et al.* ASH 2020. Abstract 125;
3. Seymour JF, *et al. Blood* 2022; **140**:839–850;
4. Kater A, *et al.* EHA 2023. Abstract S207 (Oral).

# The impact of early discontinuation/dose modification of venetoclax on outcomes in patients with relapsed/refractory chronic lymphocytic leukemia: post-hoc analyses from the phase III MURANO study

Table 3. **MURANO: discontinuation of venetoclax treatment for all patients, due to adverse events and due to progressive disease.**

| | Patients who discontinued venetoclax | | |
|---|---|---|---|
| | For any reason (n=54) | Due to AE (n=29) | Due to PD (n=12) |
| Duration of Ven treatment, months | | | |
| Mean (SD) | 11.7 (8.0) | 10.6 (7.1) | 15.4 (7.8) |
| Median (range) | 11.3 (0.1-24.9) | 11.3 (0.5-23.3) | 16.4 (4.4-24.9) |
| Ven discontinuation at | | | |
| 0 to <6 months*, n (%) | 16 (29.6) | 10 (34.5) | 1 (8.3) |
| 6 to <12 months, n (%) | 13 (24.1) | 7 (24.1) | 4 (33.3) |
| 12 to <18 months, n (%) | 9 (16.7) | 6 (20.7) | 1 (8.3) |
| 18 to <24 months, n (%) | 10 (18.5) | 5 (17.2) | 3 (25.0) |
| ≥24 months | 6 (11.1) | 1 (3.4) | 3 (25.0) |

Early discontinuation of venetoclax was reported **in 28%** of patients participating in the MURANO study,

**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.

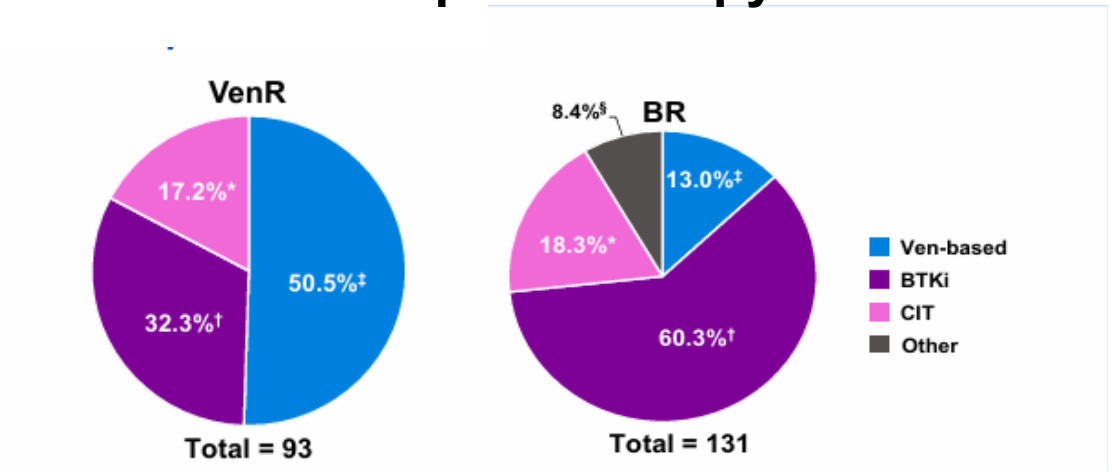
Of the 194 pts receveing VR **137(70,6%**) required interrumptions to venetoclax treatment Dose reduction occurred **in 45 of 194 (23.2**%) of patients in the MURANO study and had no statistically significant effect on PFS or OS

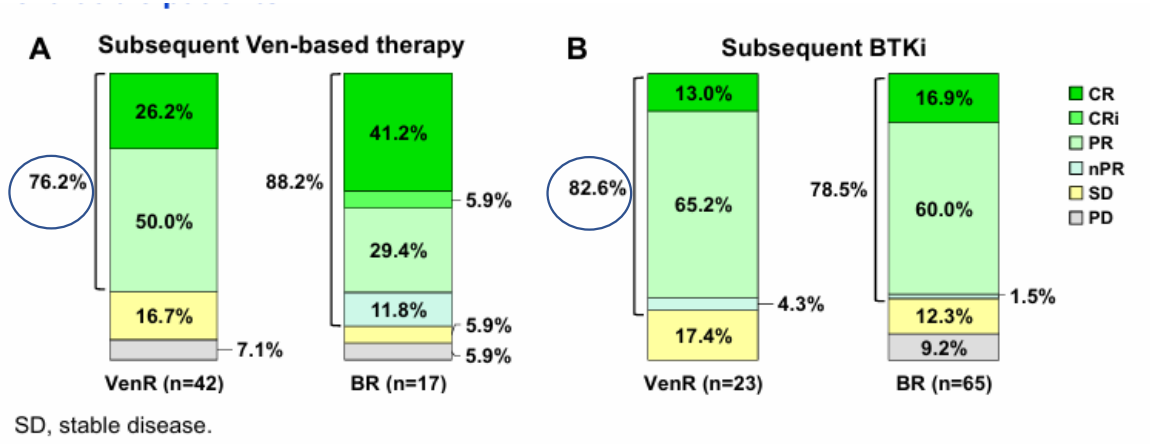
Discontinuing treatment early (for any reason except PD) was significantly associated with shorter PFS (n=181; HR 5.98, 95% CI: 3.31–10.82 P<0.0001).

**Treatment interruption, regardless of duration (≥1, ≥8, ≥14 and ≥21 consecutive days of missed venetoclax treatment) had no statistically significant effect on clinical outcomes(PFS and OS)** compared with no treatment interruption.

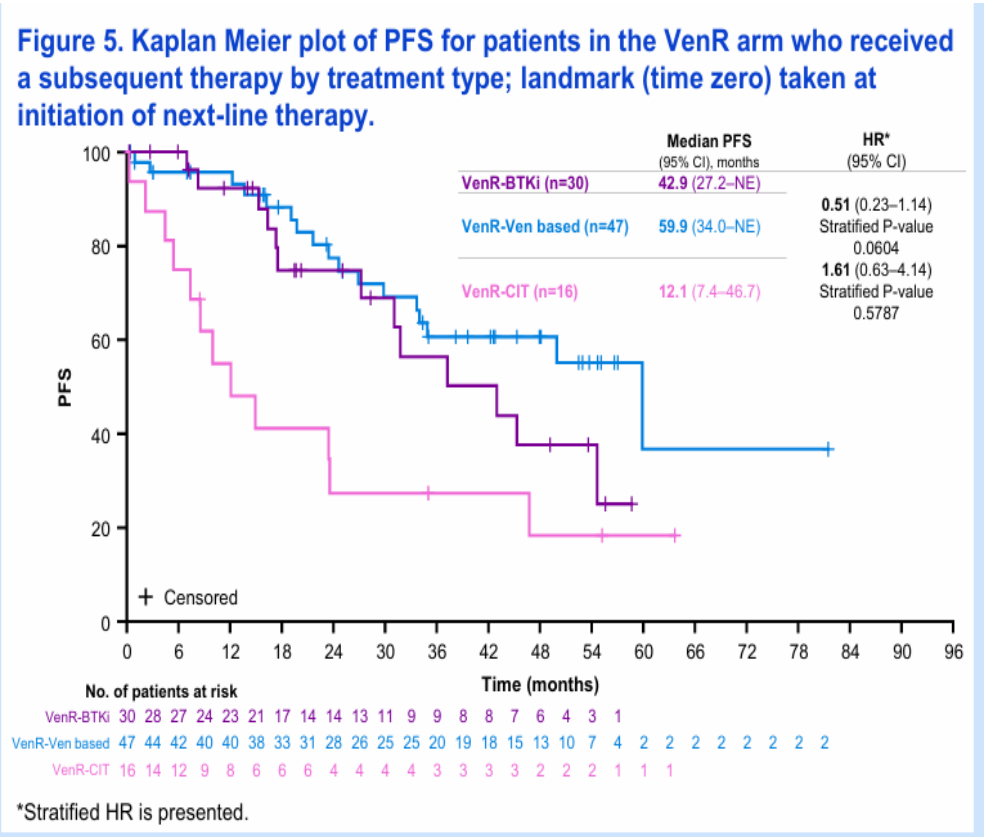
Mato et al, Haematologica 2022

# Subsequent therapy in the MURANO trial and response rates




SD, stable disease.

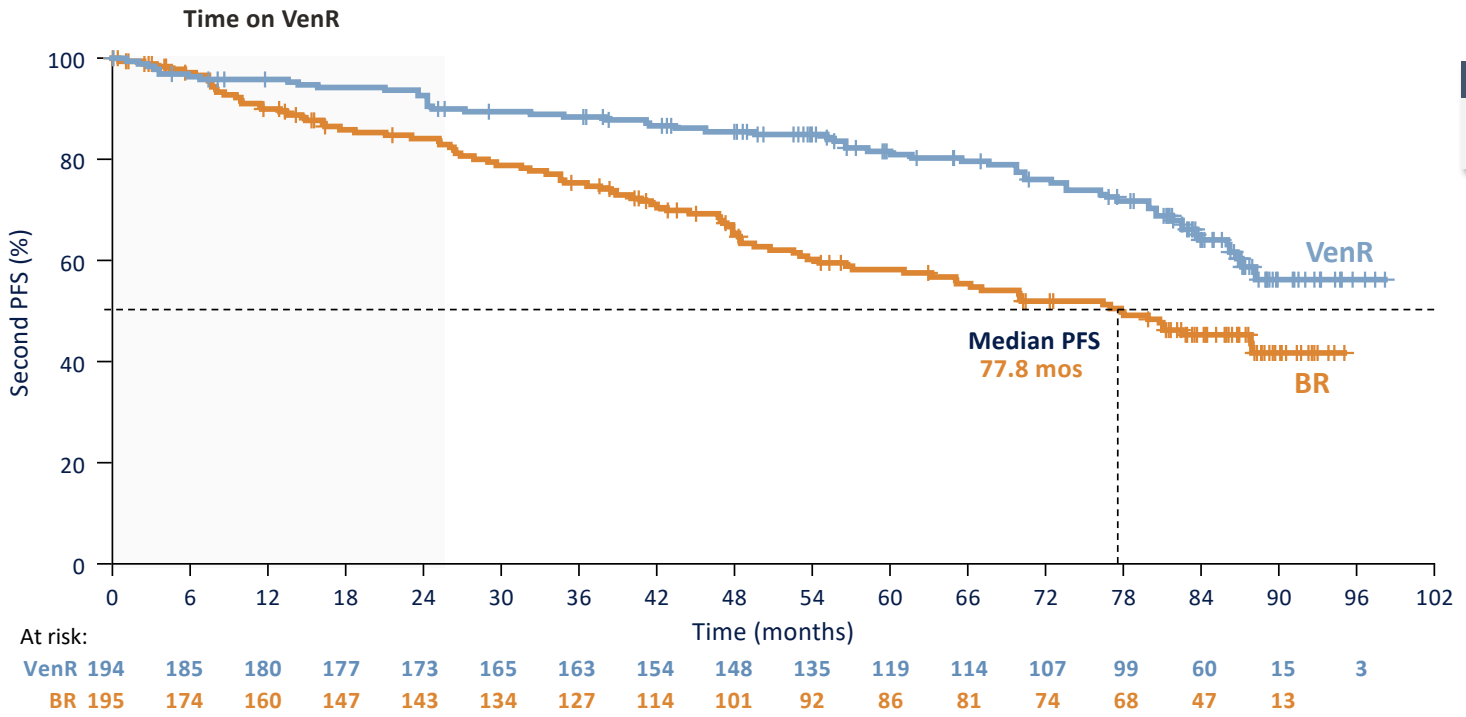



Following PD, 95/194 (49.0%) pts randomized to VenR and 131/195 (67.2%) pts randomized to BR had received subsequent anti-CLL therapy

Overall, 73/194 (37.6%) pts in the VenR arm had not receivedanext-line therapy at the nal cutoff, and 26 ptshaddiedwithout subsequent therapy. M

Harrup R, *et al.* ASH 2023. Abstract P1898 (Poster).

## Second PFS*
(median follow-up: 85.7 months)




| | VenR | BR |
|---|---|---|
| HR (95% CI) | 0.49 (0.35–0.69)† | |
| p value | Stratified p<0.0001 | |

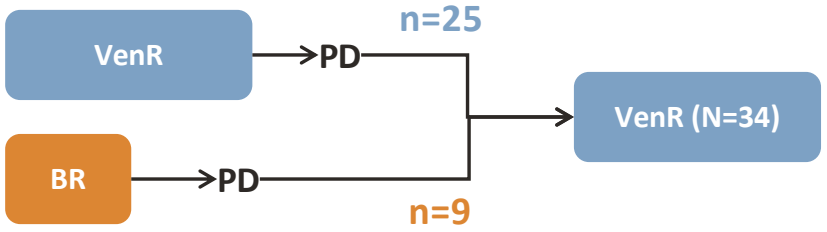
**Patients initially randomized to VenR had a longer time to second PFS event than those initially randomized to BR**

* Updated censoring was applied as a correction for patients who received a next-line therapy and had not progressed a second time, who were censored too early (at the time of PD in the main study, before administration of the next-line therapy); † Stratified HR presented.

Harrup R, *et al.* ASH 2023. Abstract P1898 (Poster).

# MURANO substudy: MURANO protocol amendment for re-treatment/crossover

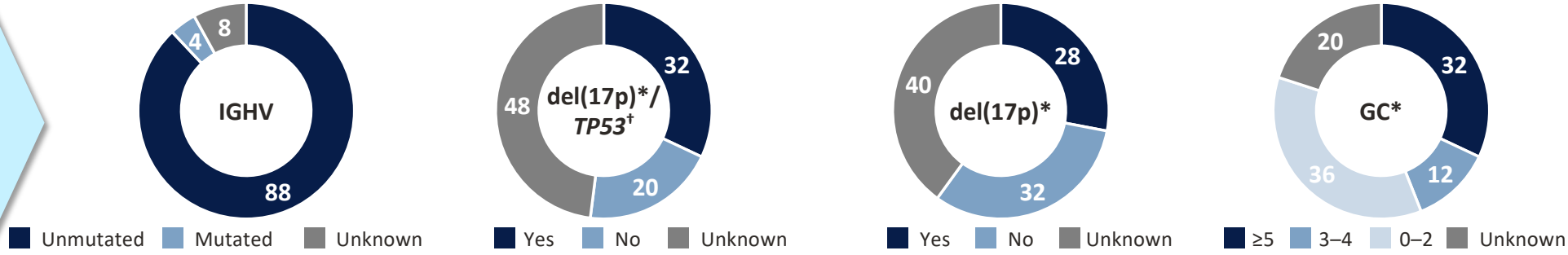
**N=34 enrolled in the MURANO re-treatment / crossover substudy[1,2]**




**n=25 VenR sub-study re-treated patients**

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

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




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

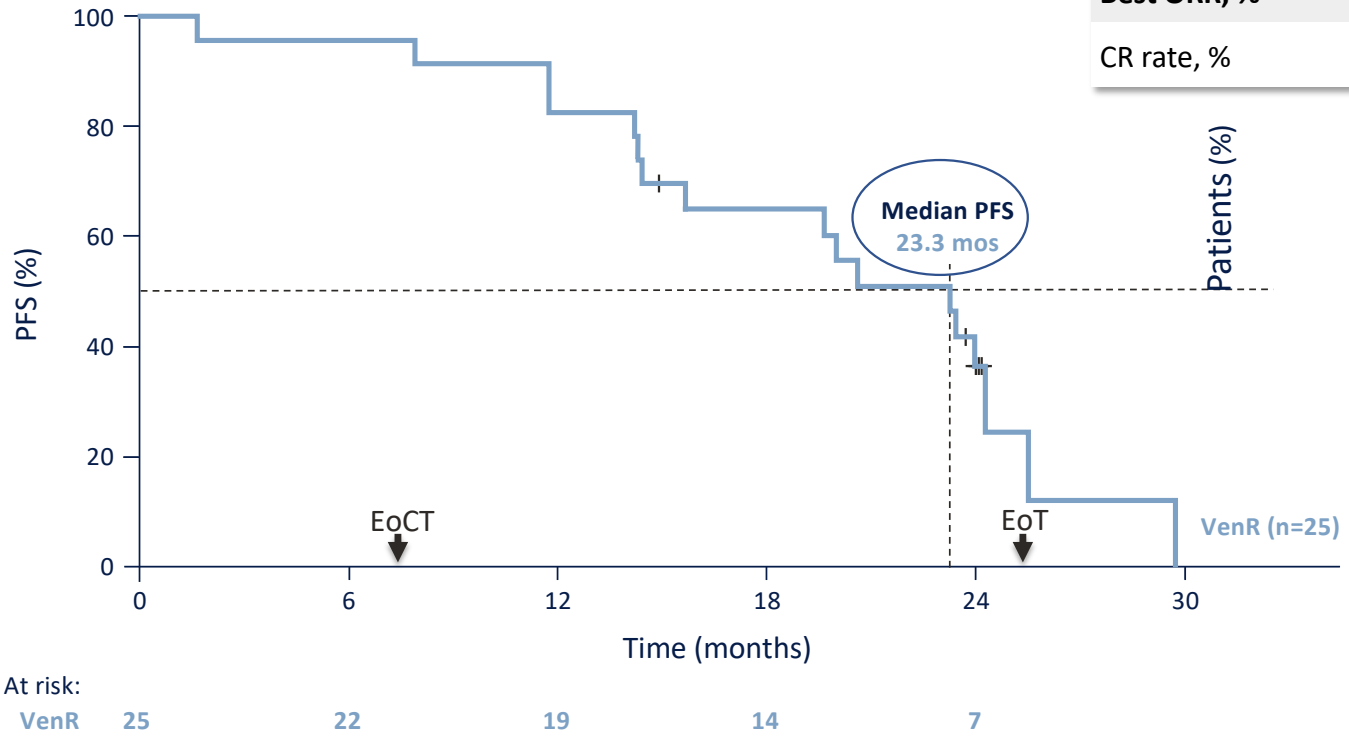
* Assessed by array comparative genomic hybridization; † Assessed by NGS.
GC, genomic complexity; IGHV, immunoglobulin heavy chain variable region; NGS, next-generation sequencing.

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

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

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

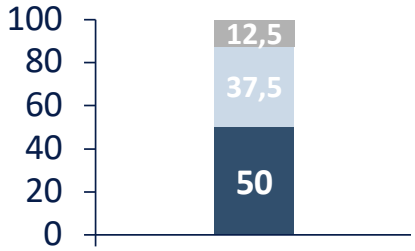
**PFS for VenR-re-treated patients**
(median follow-up 33.4 months)




At risk:

| | | | | | |
|---|---|---|---|---|---|
| VenR | 25 | 22 | 19 | 14 | 7 |

**Best ORR in the substudy for patients who achieved uMRD at EoT in main study**




Patients who were retreated with VenR (n=8)

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

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

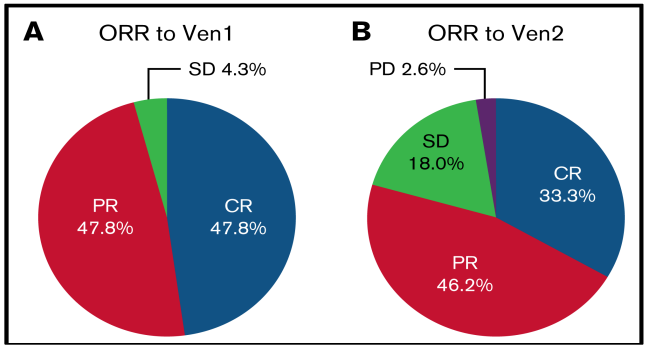
NR, not reported.

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

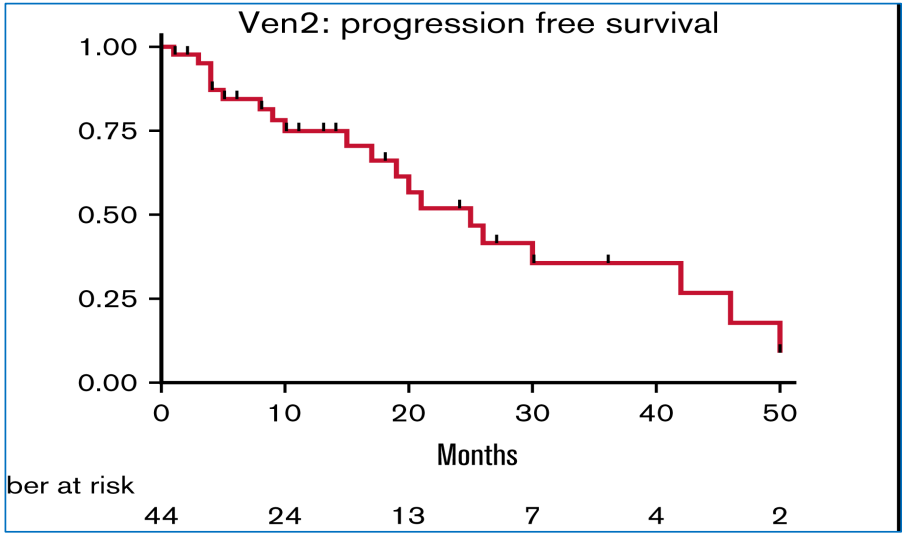
multicenter, international retrospective study (11 patients from the MURANO trial)

**Table 1. Patient baseline characteristics and clinical data for initial venetoclax (Ven1) and re-treatment (Ven2) regimens**

| Baseline characteristics* | Results | (n = patients with available data) |
|---|---|---|
| Median age at CLL diagnosis, y (range) | 55.5 (24-75) | n = 46 |
| Median age at Ven1 start, y (range) | 64 (31-75) | n = 46 |
| Male sex | 73.9% | n = 46 |
| Race | 83.3% White | n = 42 |
| | 9.5% Black | |
| | 7.1% Other | |
| Ven1 administered as part of a clinical trial | 56.5% | n = 46 |
| Ven1 as monotherapy | 37.0% | n = 46 |
| Ven1 as first-line treatment | 8.7% | n = 46 |
| Median prior lines of therapy (range) | 2 (0-10) | n = 46 |
| Prior BTKi | 40.0% | n = 45 |
| Del(17p) | 25.0% | n = 44 |
| *TP53* mutation | 15.6% | n = 32 |
| Complex karyotype | 20.5% | n = 39 |
| *IGHV* unmutated | 82.1% | n = 39 |




**ORR of 79.5% to re-exposure**

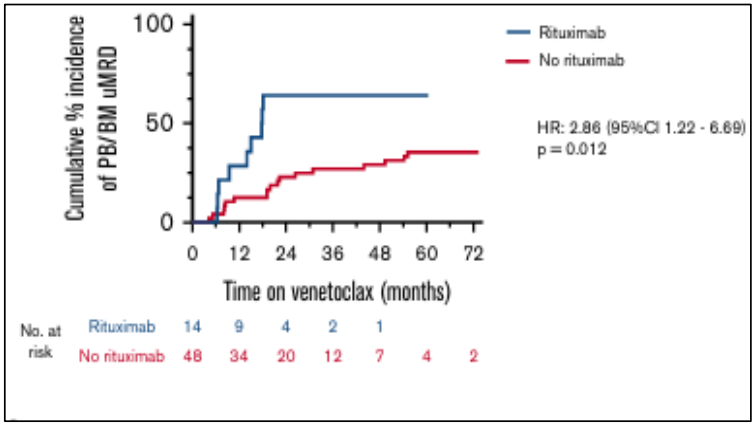


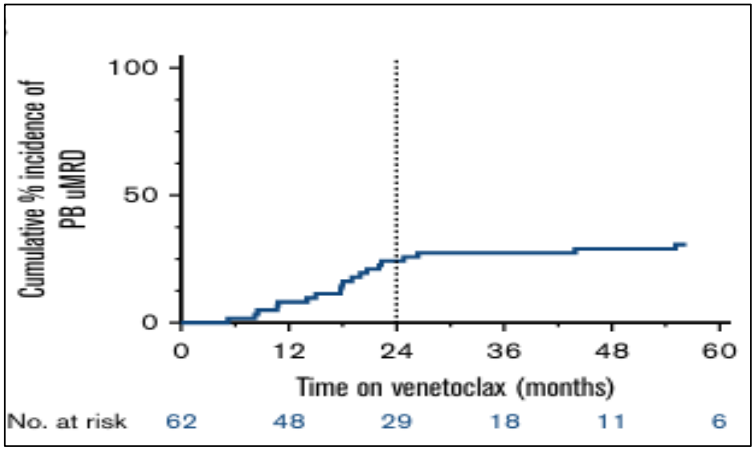

At a median follow-up of 10 months (range 1-50 months), the median **Ven2 PFS for the overall cohort was 25 months** (95% CI, 17-42 months

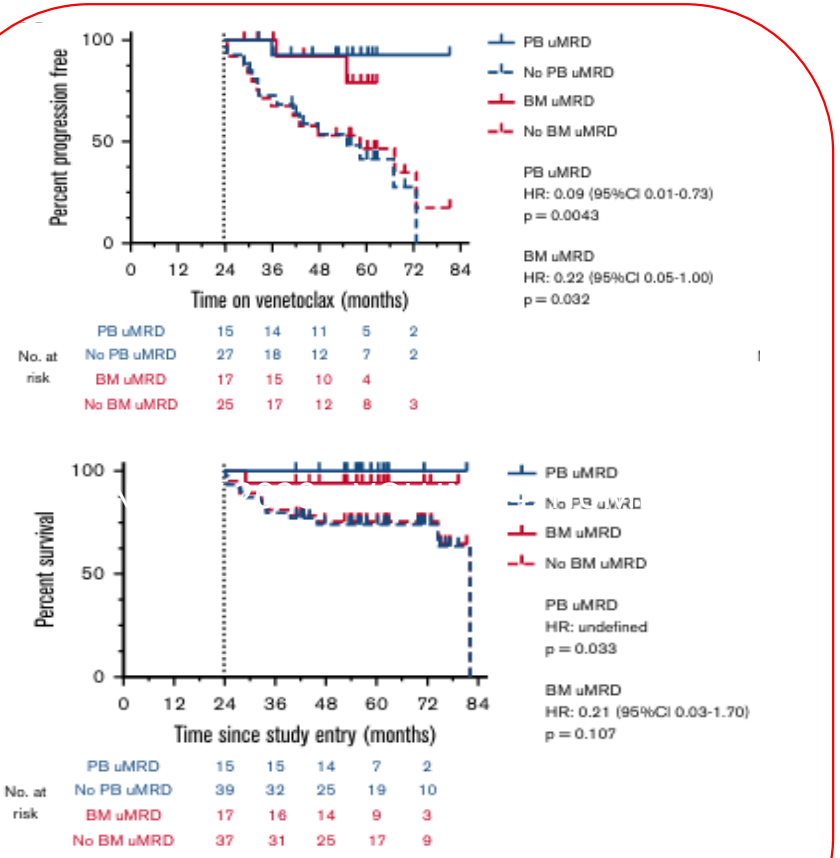
**Thompson et al , Blood Adv, 2022.**

# Undetectable peripheral blood MRD should be the goal of venetoclax in CLL, but attainment plateaus after 24 months

**Retrospective analysis was performed on data from 62 patients treated with venetoclax**



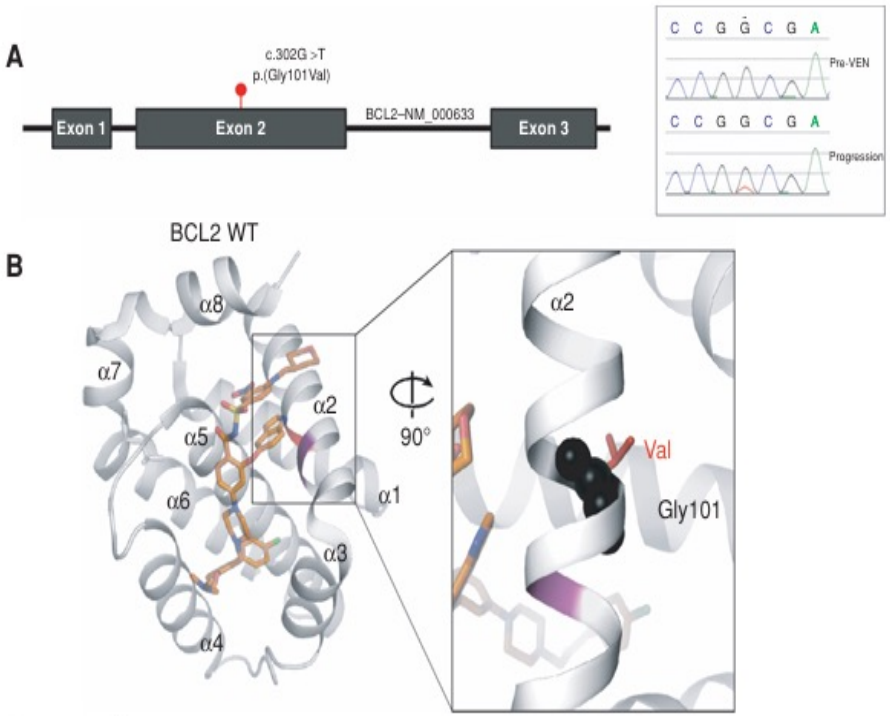



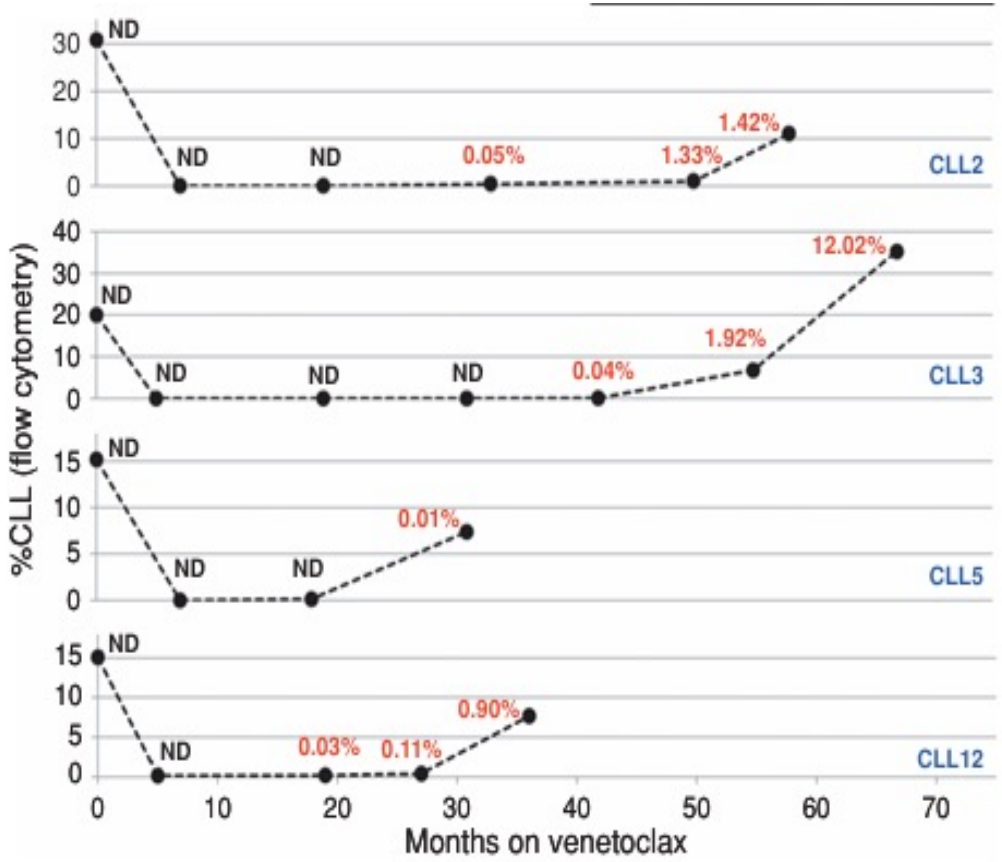

the majority of patients who ultimately achieve uMRD with venetoclax therapy do so within 24 months, and ongoing unaltered therapy beyond this time rarely eradicates persistent MRD.

the favorable outcomes associated with uMRD attainment are comparably predicted by PB or BM assessment.

# Acquisition of the Recurrent Gly101Val Mutation in BCL2 Confers Resistance to Venetoclax



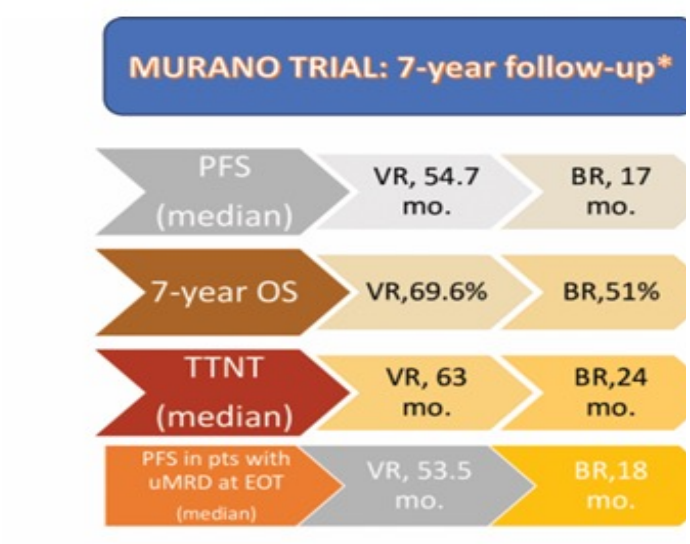

Acquired point mutation in BCL2 arising recurrently and exclusively in venetoclax-treated patients., after sustained venetoclax exposure (median 36 months)

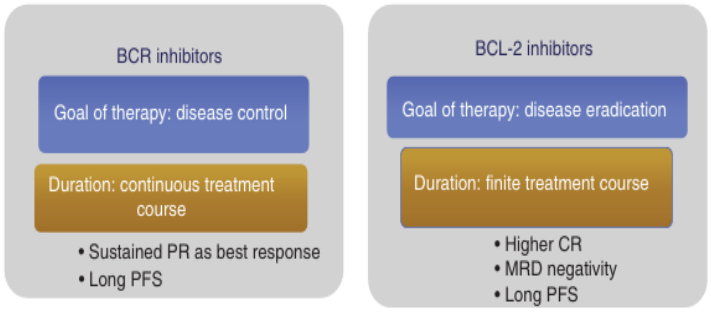


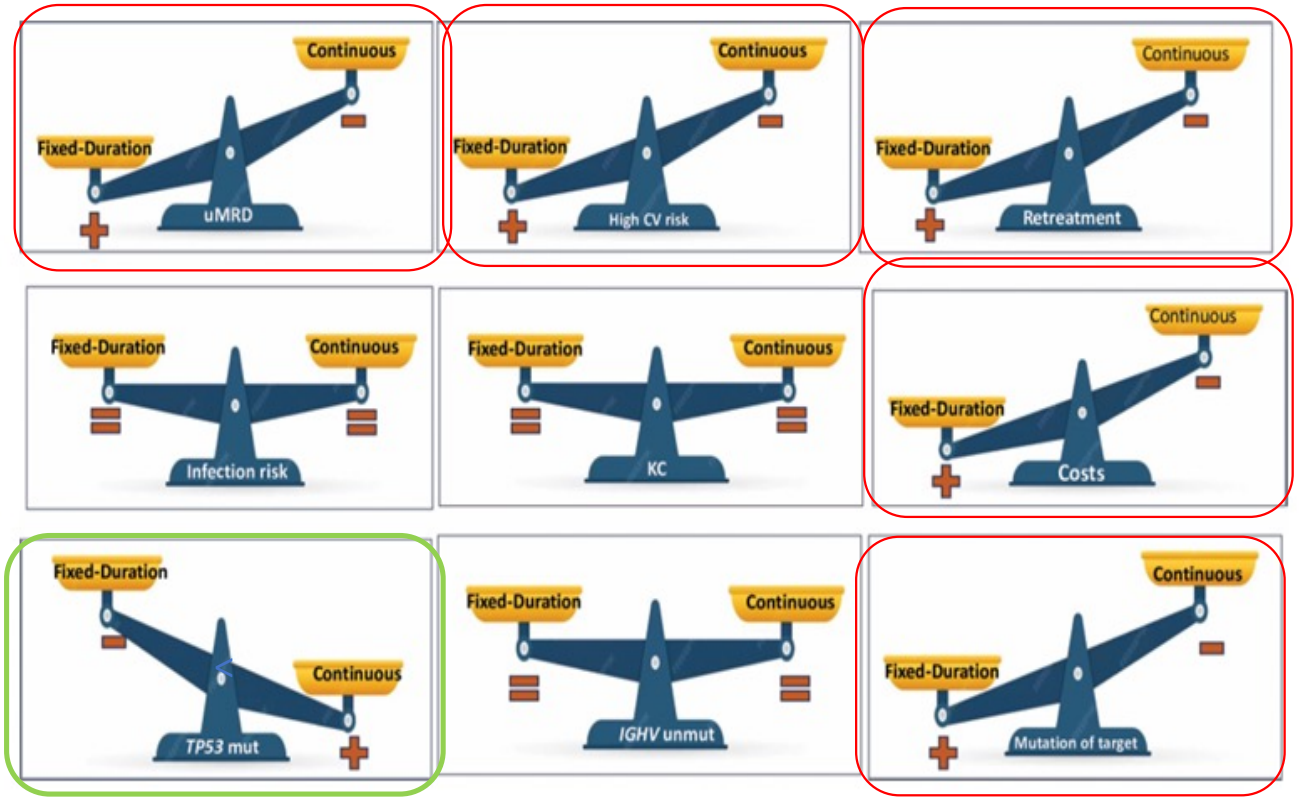

*BCL2 G101V* mutations: preceded PD by **≤25 months,** median 32 months on venetoclax)

1. Ahn IE, *et al. Blood* 2017; **129:**1469–1479; 2. Blombery P, *et al. Cancer Disov* 2019; **9:**342–353.

# Fixed-duration therapy comes of age in CLL: long-term results of MURANO and CLL14 trials



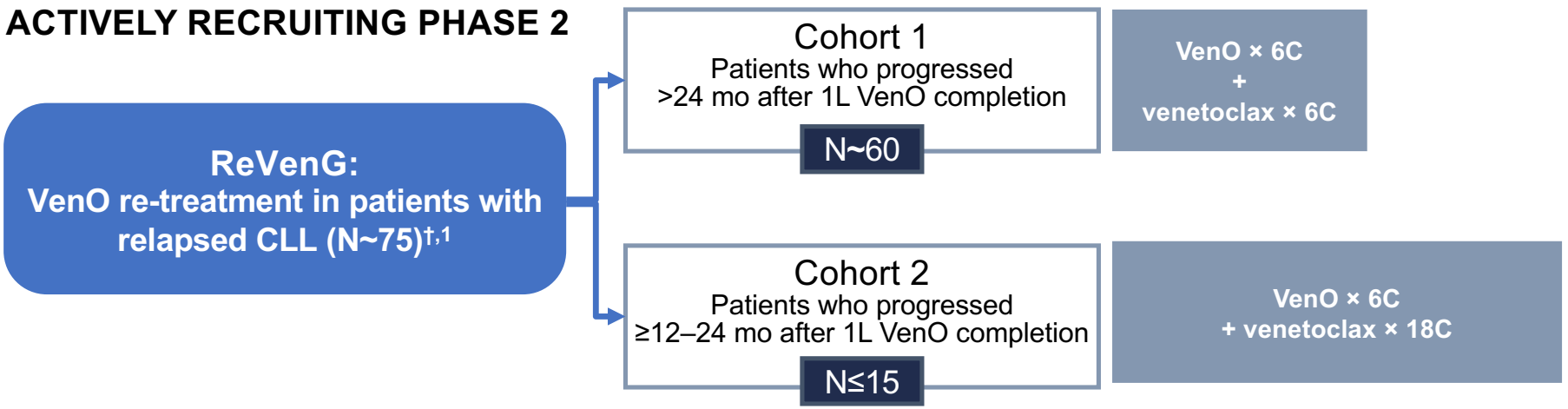




Stefano Molica and David Allsup EXPERT REVIEW OF ANTICANCER THERAPY 2024,

# Algorithm for relapsed/refractory CLL


Florian Simon· Jan-Paul Bohn Current Oncology Reports (2023)

# 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;

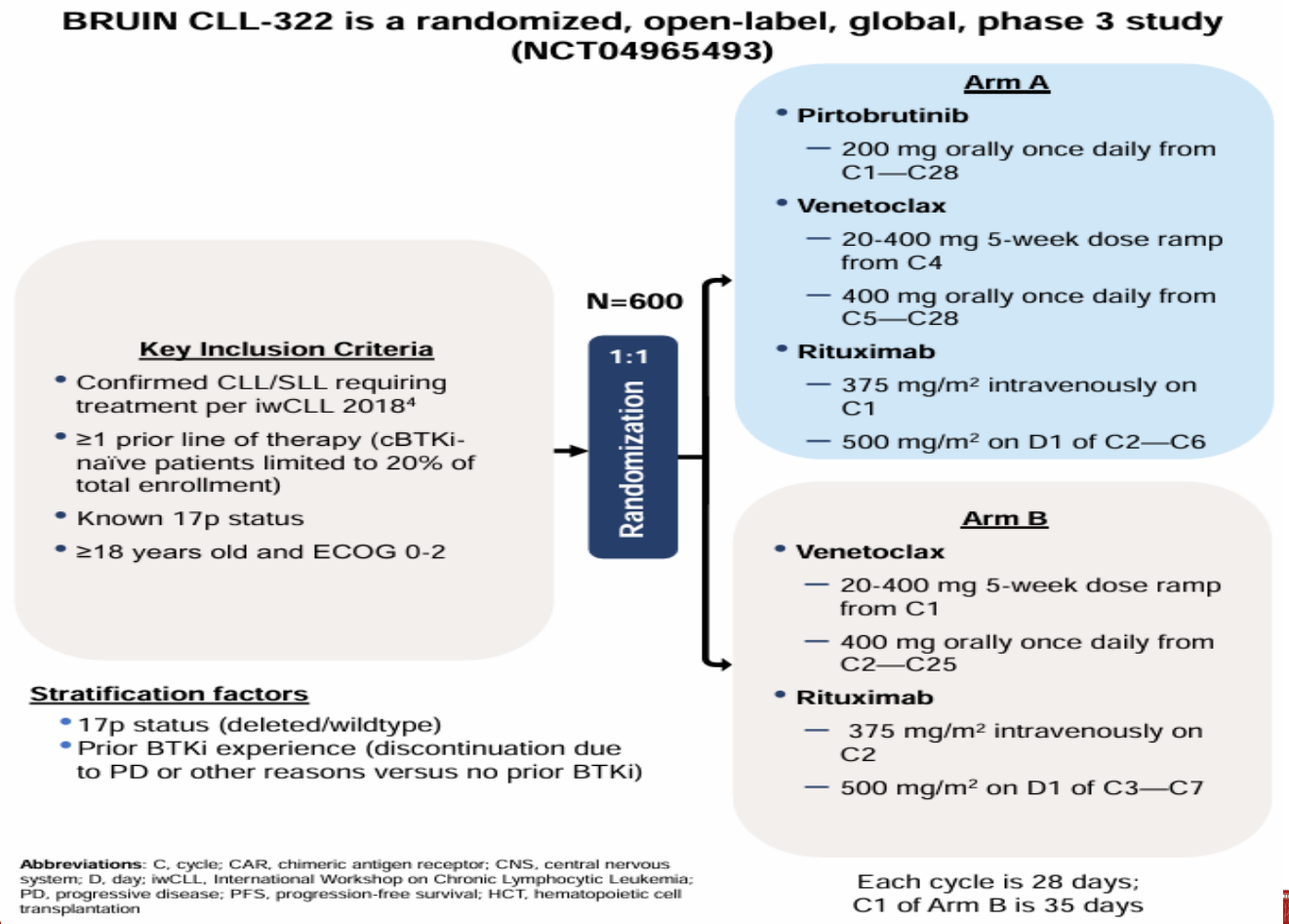
1. Davids M, et al. ASH 2021. Abstract 2634 (Poster).



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

# BRUIN CLL-322: A Phase 3 Open-Label, Randomized Study of Fixed Duration Pirtobrutinib Plus Venetoclax and Rituximab Versus Venetoclax and Rituximab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Trial in Progress)

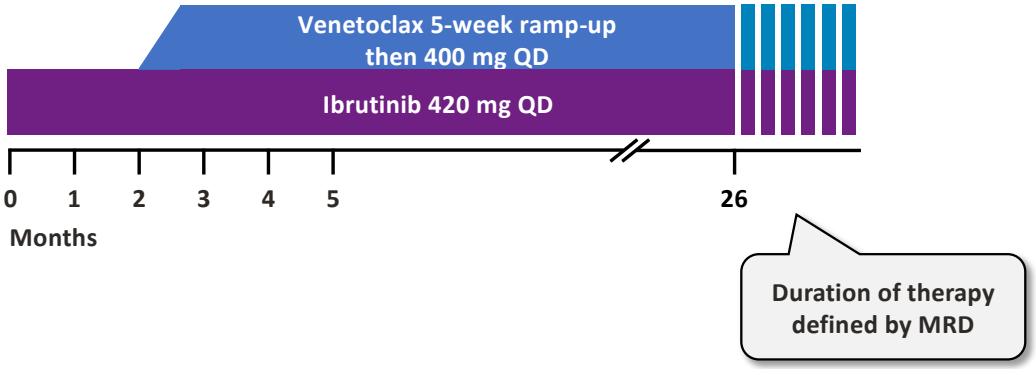
The study's objective is to assess the superiority of adding time limited pirtobrutinib to the MURANO regimen, hypothesized to **delay disease progression in a largely BTKi-pretreated population**




Woyach, et al. ASCO 2023, Poster # 131b

# Ibrutinib Plus Venetoclax in Relapsed/Refractory Chronic Lymphocytic Leukemia: The CLARITY Study

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



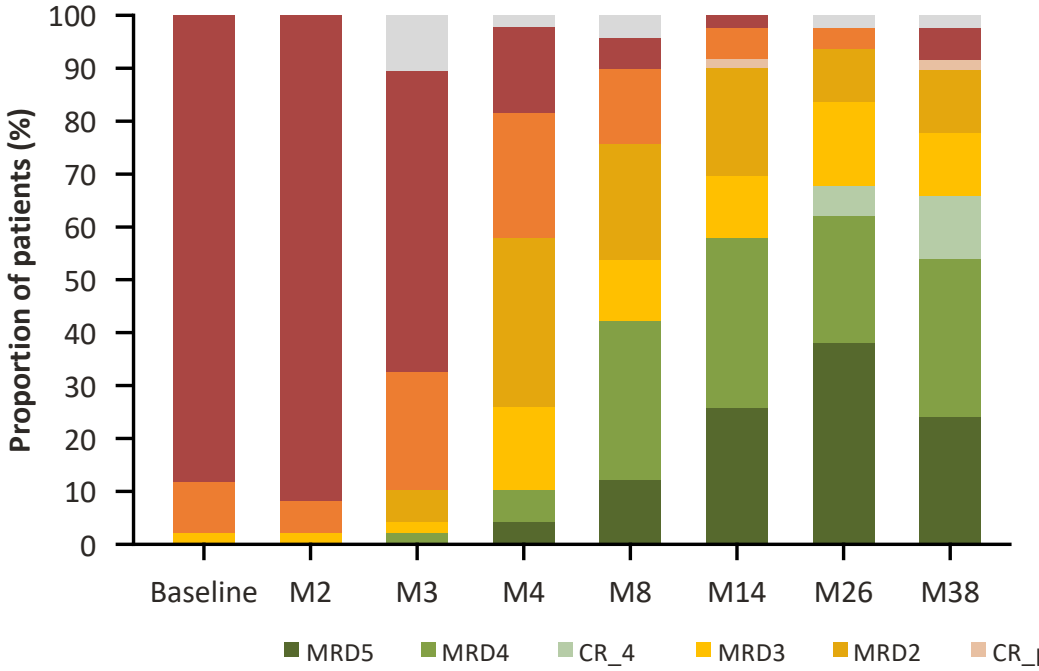

| Baseline Characteristics[2] | IVen (N=54)* |
|---|---|
| **Median age, years (range)** | 64 (31–83) |
| **Male sex, n (%)** | 37 (69) |
| **Current Binet Stage, n (%)** | |
| A | 12 (22) |
| B | 18 (33) |
| C | 22 (41) |
| Not known | 2 (4) |
| **Lymph nodes, bulky ≥5 cm, n (%)** | 4 (8) |
| **del(17p),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

Response assessment, including assessment of MRD, was performed at screening (before ibrutinib), week 8 (before venetoclax), month 8 (6 months of combination treatment), month 14 (12 months of combination treatment), and month 26 (24 months of combination treatment). uMRD defined as $<10^{-4}$ in PB and BM by flow cytometry.
* Four patients stopped ibrutinib before adding venetoclax because of AEs; 50 patients successfully initiated venetoclax.
BR, bendamustine + rituximab; CIT, chemoimmunotherapy; FCR, fludarabine + cyclophosphamide + rituximab; IVen, ibrutinib + venetoclax.

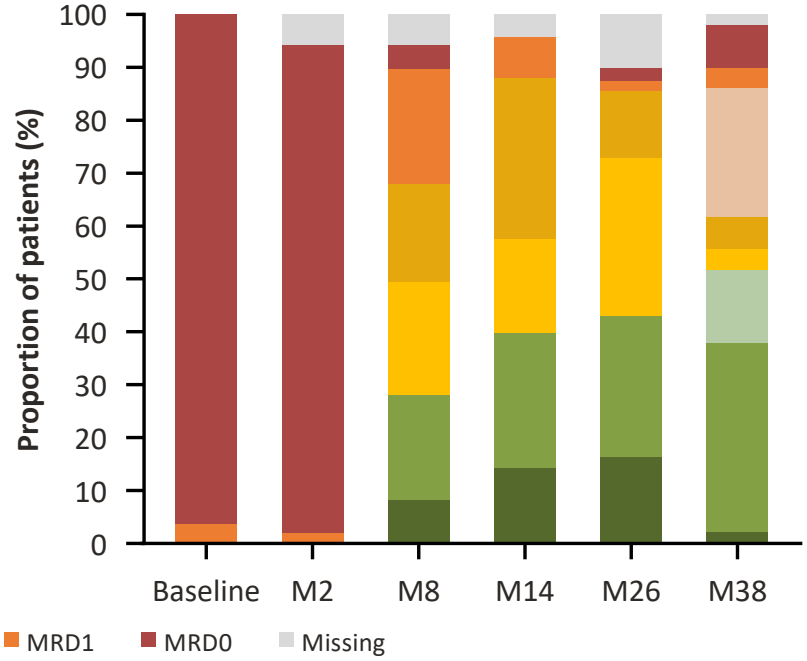

1. Hillmen P, *et al. J Clin Oncol* 2019; **37**:2722–2729;
2. Munir T, *et al.* ASH 2022. Abstract 91 (Oral).

MRD negativity was achieved in the blood of 28 (**53%**) and the marrow of 19 (**36%**).

**PB MRD* Responses over Time**




**BM MRD* Responses over Time**



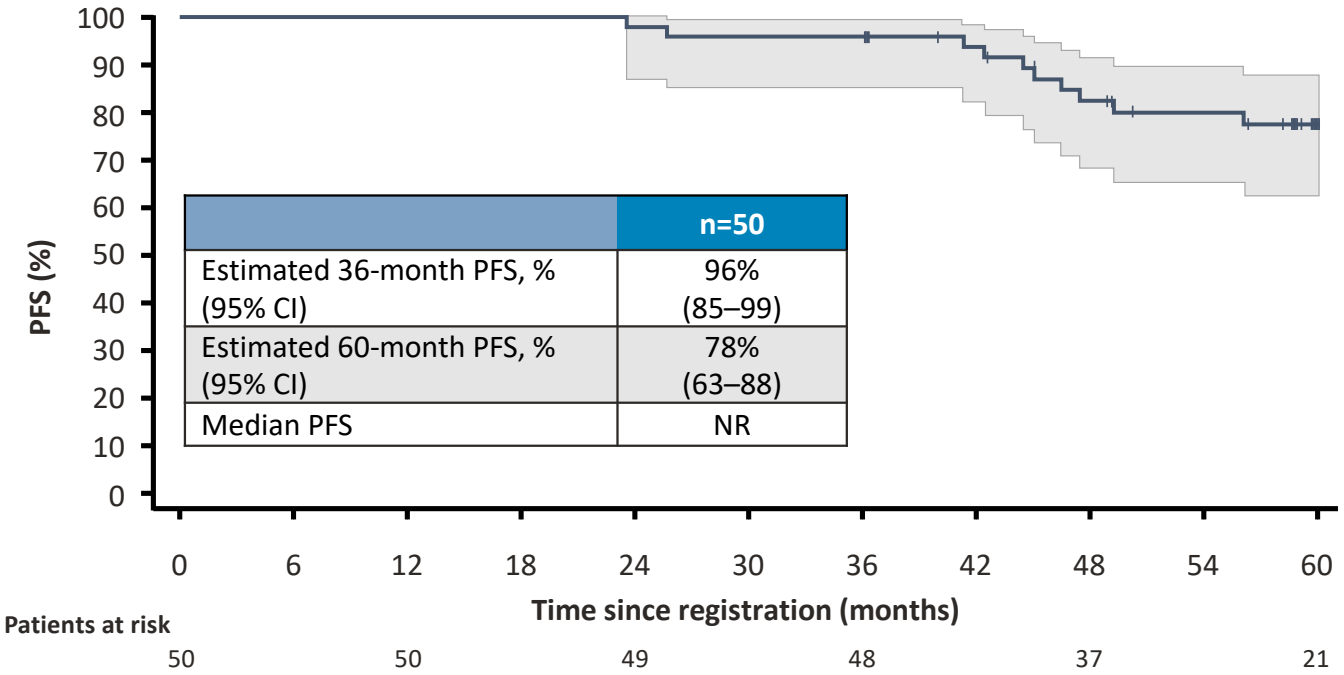

MRD5 MRD4 CR_4 MRD3 MRD2 CR_pos MRD1 MRD0 Missing

**IVen led to improvement in the depth of PB and BM MRD reduction over time, which persisted to month 38**

Data lock: November 1, 2022. * uMRD defined as $<10^{-4}$ in PB and BM by flow cytometry.
BM, bone marrow; PB, peripheral blood; IVen, ibrutinib + venetoclax.

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

## PFS (n=50)




| | n=50 |
|---|---|
| Estimated 36-month PFS, % (95% CI) | 96% (85–99) |
| Estimated 60-month PFS, % (95% CI) | 78% (63–88) |
| Median PFS | NR |

## OS (n=50)

| | n=50 |
|---|---|
| Estimated 36-month OS, % (95% CI) | 98% (86–100) |
| Estimated 60-month OS, % (95% CI) | 91% (78–97) |
| Median OS | NR |

**IVen combination therapy resulted in 60-month PFS and OS rates of 78% and 91%, respectively**

Data lock: November 1, 2022.
NR, not reached; IVen, ibrutinib + venetoclax.

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

| AEs of Interest ≥5% Any Grade, Events (Patients) | IVen (N=54) | | | |
|---|---|---|---|---|
| **Grade** | **Any** | **1/2** | **3** | **4** |
| Neutrophil count decreased | 37 (13) | 3 (3) | 24 (11) | 10 (5) |
| Bruising | 38 (20) | 38 (20) | 0 | 0 |
| Blood blister(s)/bleeding | 14 (10) | 12 (8) | 2 (2) | 0 |
| Atrial fibrillation/flutter | 6 (5) | 3 (3) | 3 (2) | 0 |
| Eye hemorrhage | 6 (5) | 5 (4) | 1 (1) | 0 |

- **1 case of Grade 3 TLS**

**Safety profiles showed no new safety signals or increases in known AEs**

Data lock: November 1, 2022.
TLS, tumor lysis syndrome; IVen, ibrutinib + venetoclax.

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

# CASISTICA DEI PAZIENTI SOTTOPOSTI A TERAPIA CON VENETOCLAX E RITUXIMAB (POLICLINICO DI BARI)

| | |
|---|---|
| Numero pazienti | 36 |
| Età mediana | 69 |
| Numero di terapie precedenti: | |
| 1 | 22(61%) |
| 2 | 11(30%) |
| 3 | 3( 8,3%) |
| Precedenti BTKi | 9 (25%) |
| del(17p) /Tp53 mt | 6 (16%) |
| IGHV non mutato | 21 (58%) |
| High tumor burden | 8 (22%) |

| **tossicita** | **qualsiasi grado** |
|---|---|
| Neutropenia | 31 (86%) |
| Infezioni | 15(41%) |
| TLS | 0 |
| Tossicita gastroeneterologica | 9(25%) |
| Covid sintomatico (con ricovero) | 2(5%) |

| **Risposte** | **Numero pazienti36** |
|---|---|
| RC | 21(58%) |
| RP | 9 (25%) |
| PD | 5(13%) |
| SD | 0 |
| Richter | 1 (2,7 %) |
| EXITUS | 2 (5 %) |

| **Pazienti in corso di trattamento** | **9 (25%)** |
|---|---|
| PZ che hanno completato il trattamento | 21 (58%) |
| Pazienti che hanno interrotto il trattamento per PD/SR | 4 (11%) |
| Pazienti che hanno interrotto il trattamento EA (HCC in cht) | 1 (2,7%) |
| Pazienti che hanno interrotto per trapianto allogenico | 1 (2,7%) |

| Terapie successive: 6 | |
|---|---|
| BTKi | 4 (66%) |
| R-CHT | 1 (16%) |
| Trapianto allogenico | 1 (16%) |

# Conclusioni

- La terapia a durata fissa di associazione Venetoclax e Rituximab rappresenta una terapia standard nella CLL R/R con ottimi risultati di  MRD, ORR, PFS, OS, TTNT e ritrattamento
- Importanza della MRD e necessita di standardizzazione nella pratica clinica
- Nuovi studi con schemi di terapia MRD guidati per una terapia individualizzata e  limitata nel tempo