MEET THE
EXPERT *in CLL*

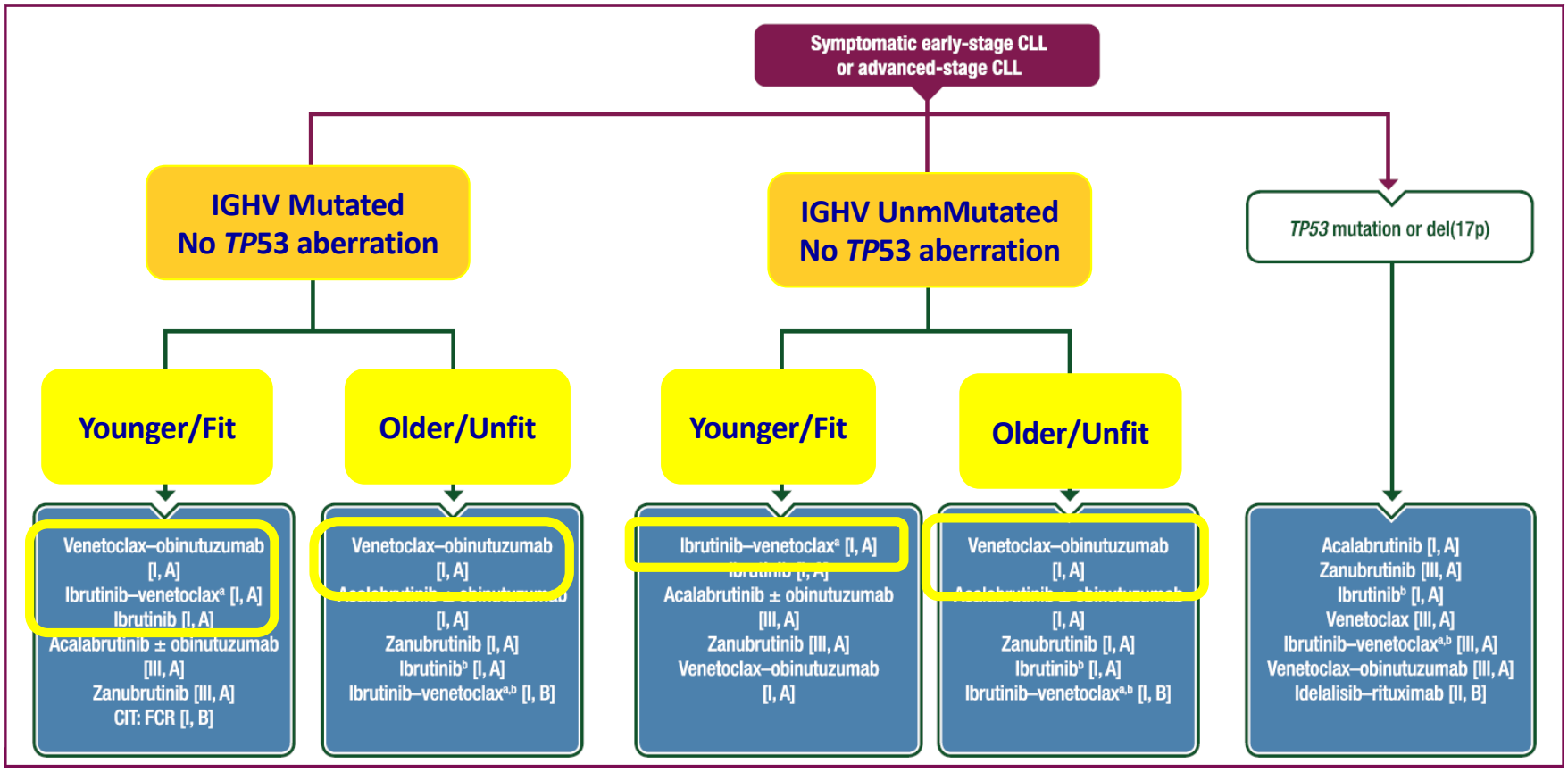
POTENZA, 2 LUGLIO 2025
Ospedale San Carlo – Aula B

Terapia a durata fissa nel paziente di prima linea e nel paziente ricaduto/refrattario

FRANCESCA R MAURO
DISCLOSURES

	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen					**x**	**x**	
AstraZeneca					**x**	**x**	
Abbvie	**x**				**x**	**x**	
BeOne					**x**	**x**	
Lilly					**x**		

2024 ESMO Treatment guidelines: 1L treatment for CLL

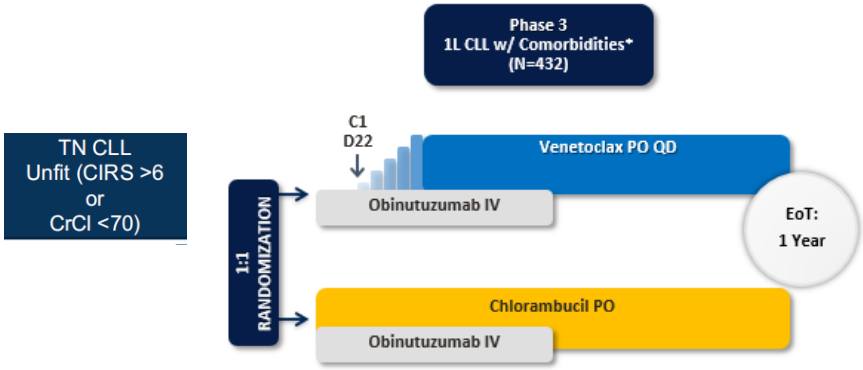


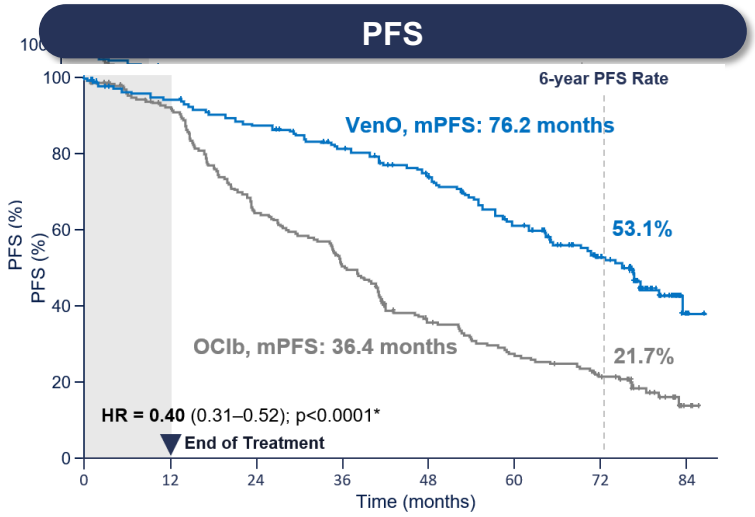
Eichhorst B & Ghia P Annals of Oncology, 2024

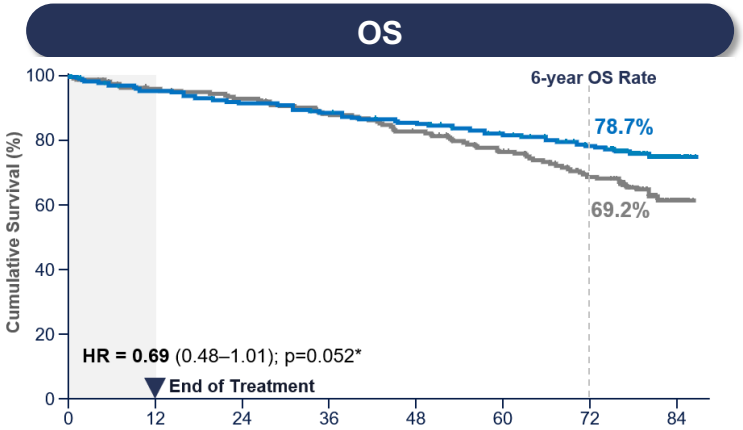
Priority to Time-Limited Therapy for CLL patients without *TP53* disruption

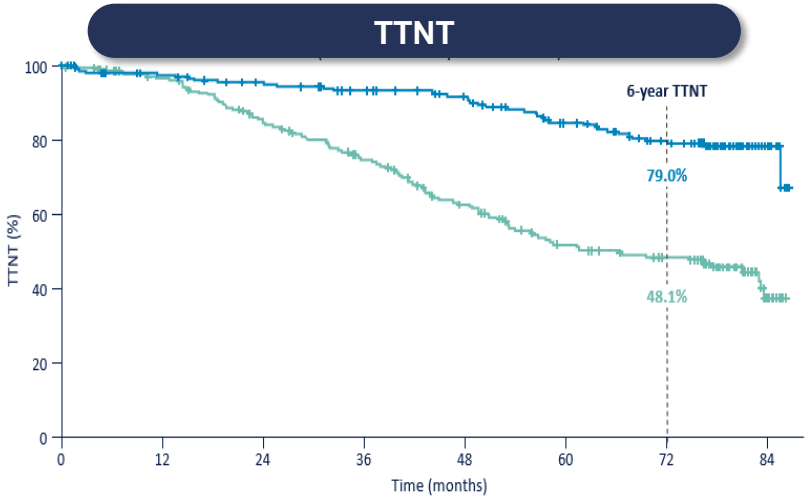
1. **Efficacy**
   - uMRD
   - PFS
   - Treatment-free interval
2. **Potential retreatment**
3. **Safety profile**
4. **Costs**
5. **Patient preference**

CLL14 - V+O vs. ClbO: 6-yr FOLLOW-UP



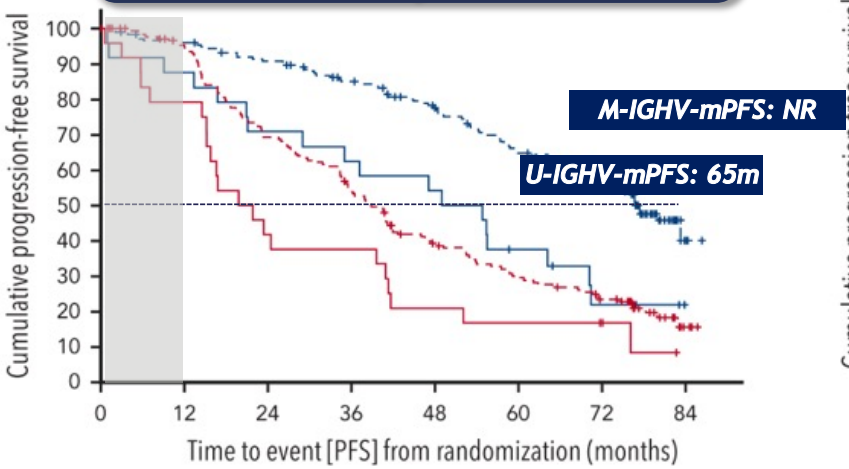




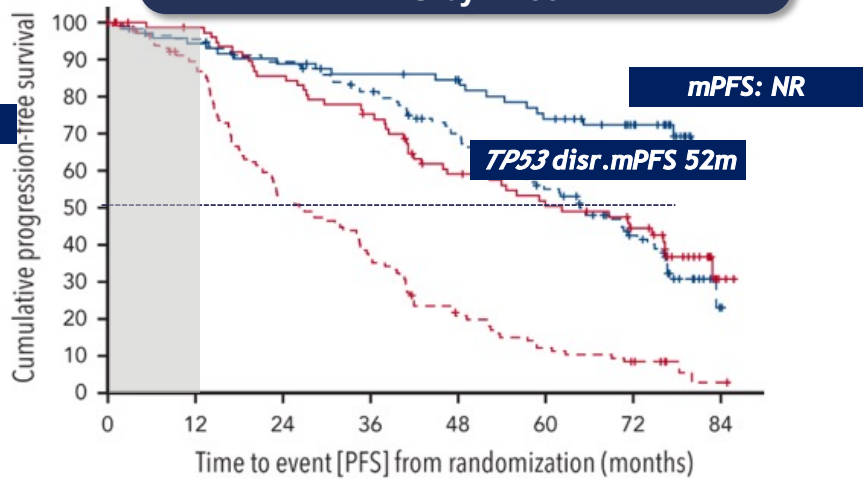


CLL14 - V+O vs. ClbO: 6-yr FOLLOW-UP

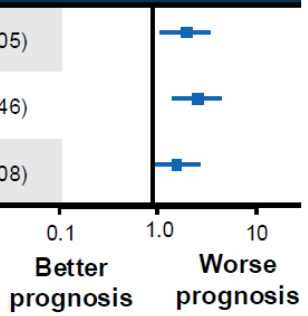
PFS by IGHV



PFS by TP53

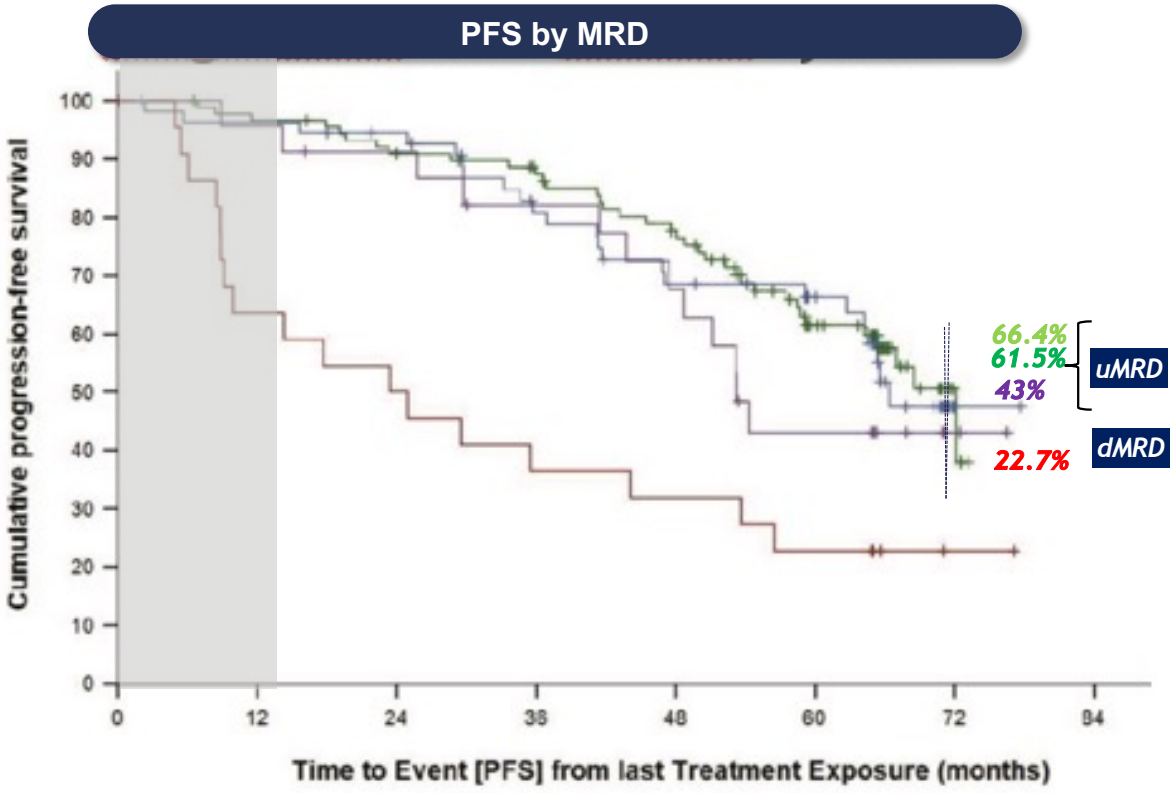


Cox Regression PFS	HR (95% Wald CI)
IGHV mutational status Unmutated vs mutated	2.310 (1.300-4.105)
Del(17p)/*TP53*mut vs no del(17p)/*TP53*mut	2.941 (1.532-5.646)
Lymph node size, cm ≥5 vs <5	1.768 (1.114-2.808)



Al Sawaf et al, Blood 2024

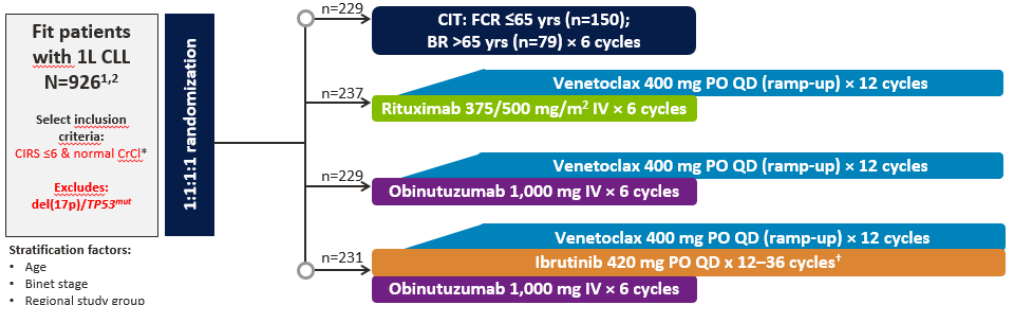
CLL14 - V+O vs. ClbO: 6-yr FOLLOW-UP



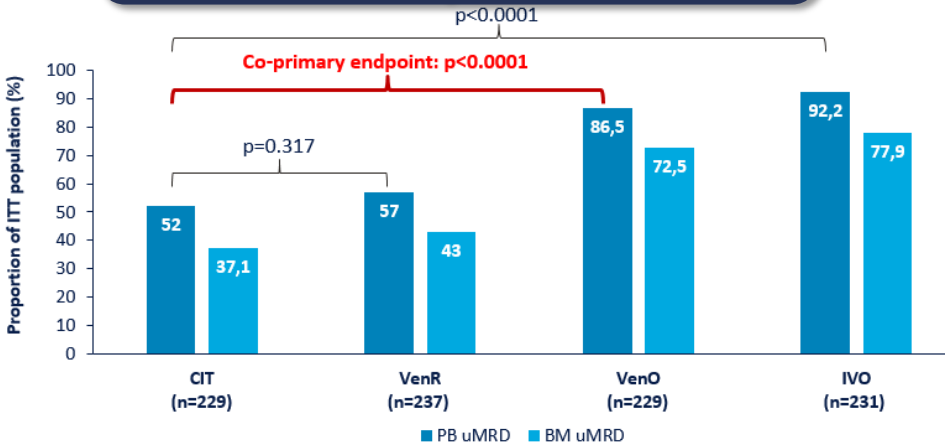
Al Sawaf et al, Blood 2024

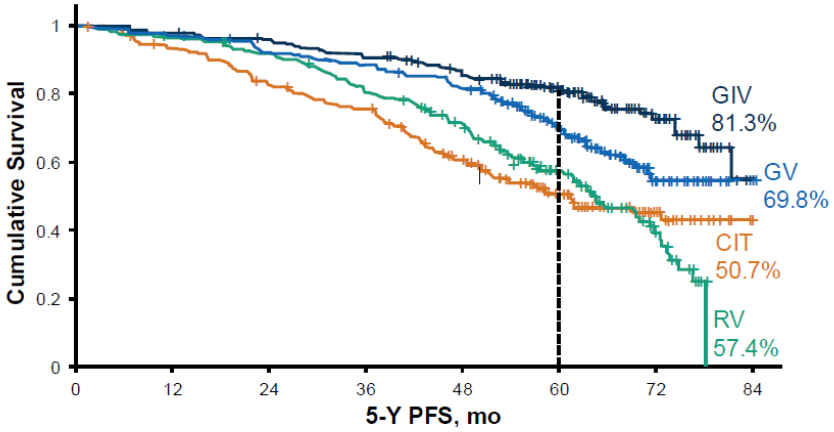
CLL13 trial: >5y follow-up

Study design



uMRD rates by treatment arm



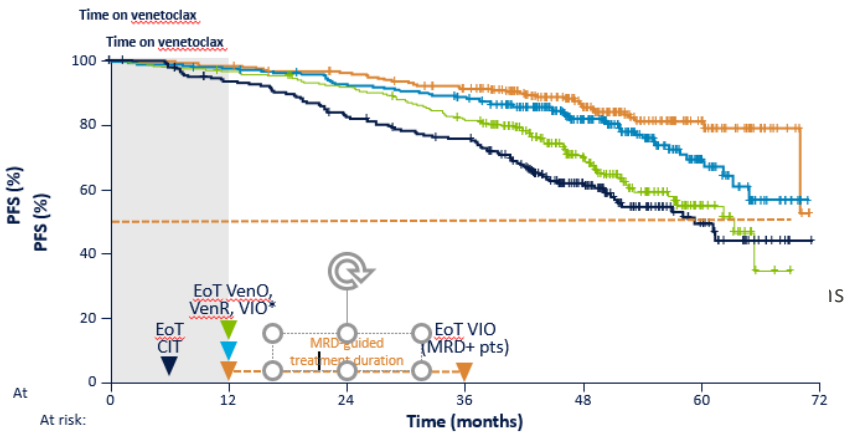


	HR (97.5% CI)	P
GIV vs CIT	0.34 (0.24-0.50)	<.001
GIV vs RV	0.35 (0.24-0.51)	<.001
GIV vs GV	0.61 (0.41-0.91)	.0046
GV vs RV	0.59 (0.42-0.81)	<.001
GV vs CIT	Not satisfied	<.001
RV vs CIT	Not satisfied	.53

- Fürstenau M, *et al. Lancet Oncol* 2024

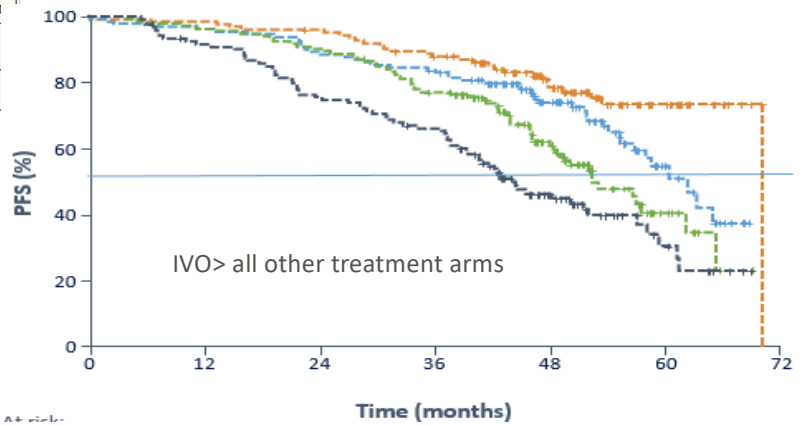
CLL13 trial: >5y follow-up

PFS by treatment arm



	CIT	VenR	VenO	VIO
HR vs CIT (97.5% CI) p-value[1]	–	– p=0.10†	0.47 (0.32–0.69) p<0.0001	0.30‡ (0.19–0.47) p<0.0001
4-year PFS, %[1]	62.0	70.1	81.8	85.5
Median PFS, months[2]	59.4	63.2	NR	NR

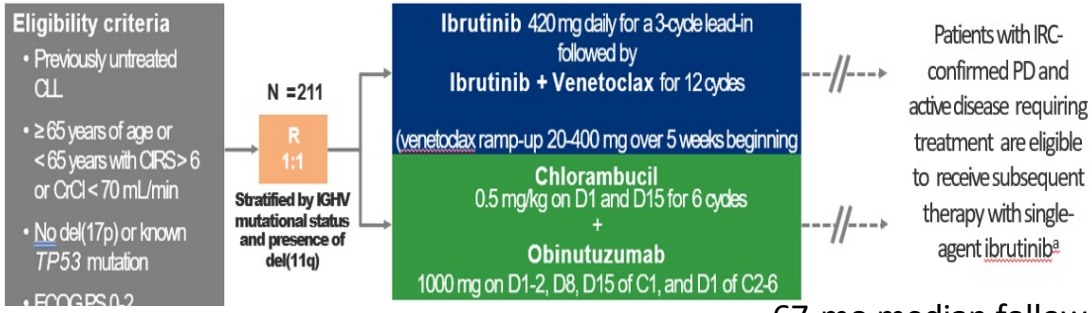
PFS by treatment arm in IGHV unmutated patients



- Fürstenau M, *et al. Lancet Oncol* 2024

GLOW trial: 5.5y Follow-up

Study Design

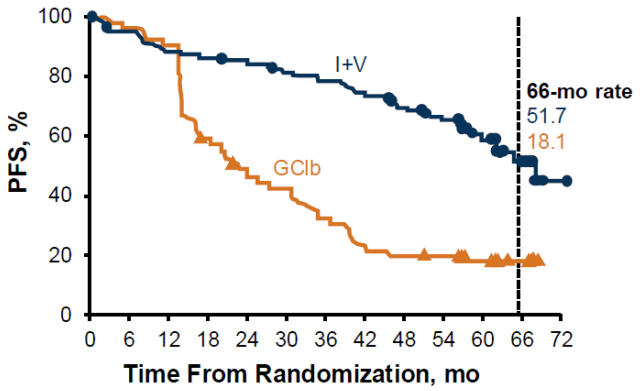


67-mo median follow-up

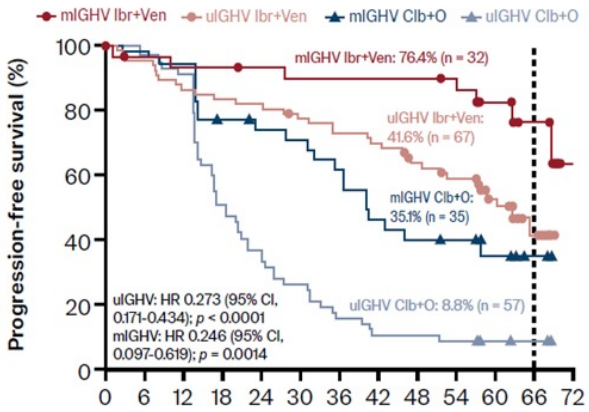
Patients characteristics

	IV	OClb
No patients	106	105
Median age, yrs	71	71
U-IGHV	63%	54%
TP53 mut.	6.6%	1.9%

PFS



PFS by IGHV



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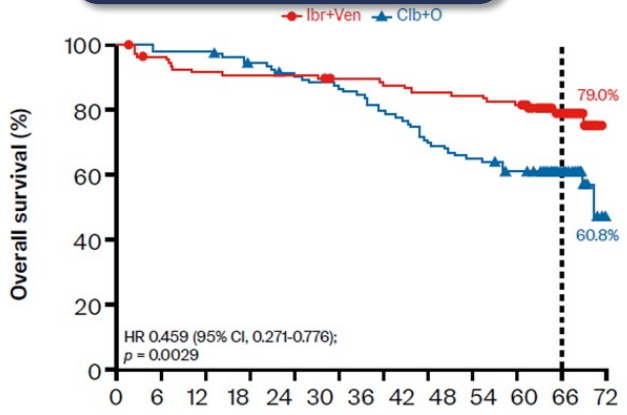
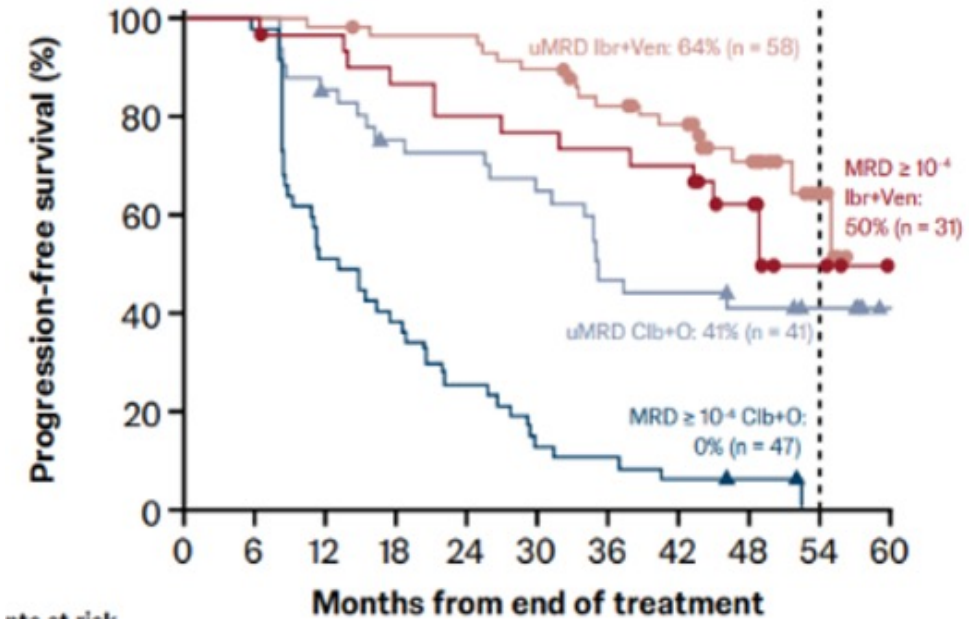


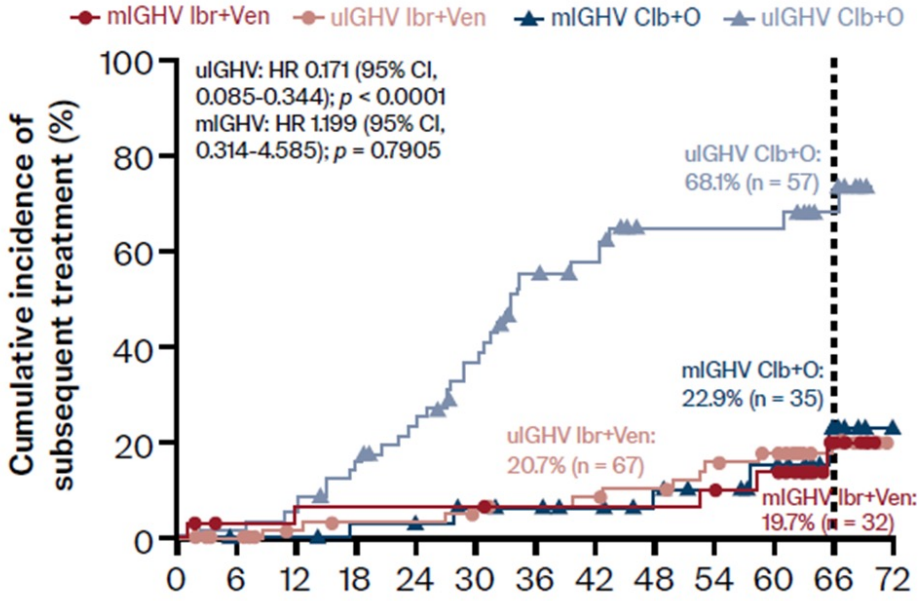
Niemann, et al. ASH 2024

GLOW trial: 5.5y Follow-up

PFS by MRD



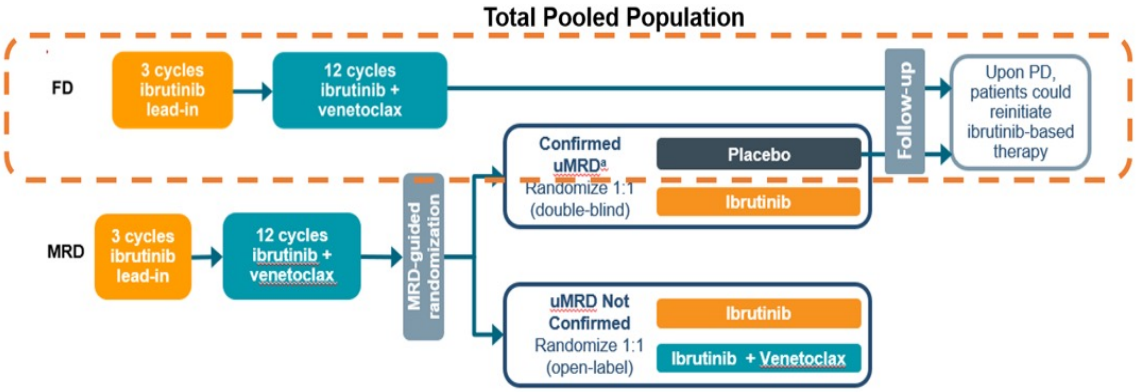
TTNT



Niemann, et al. ASH 2024

CAPTIVATE study: Final analysis of FD ibrutinib + Venetoclax for CLL/SLL

Study Design



Patients characteristics

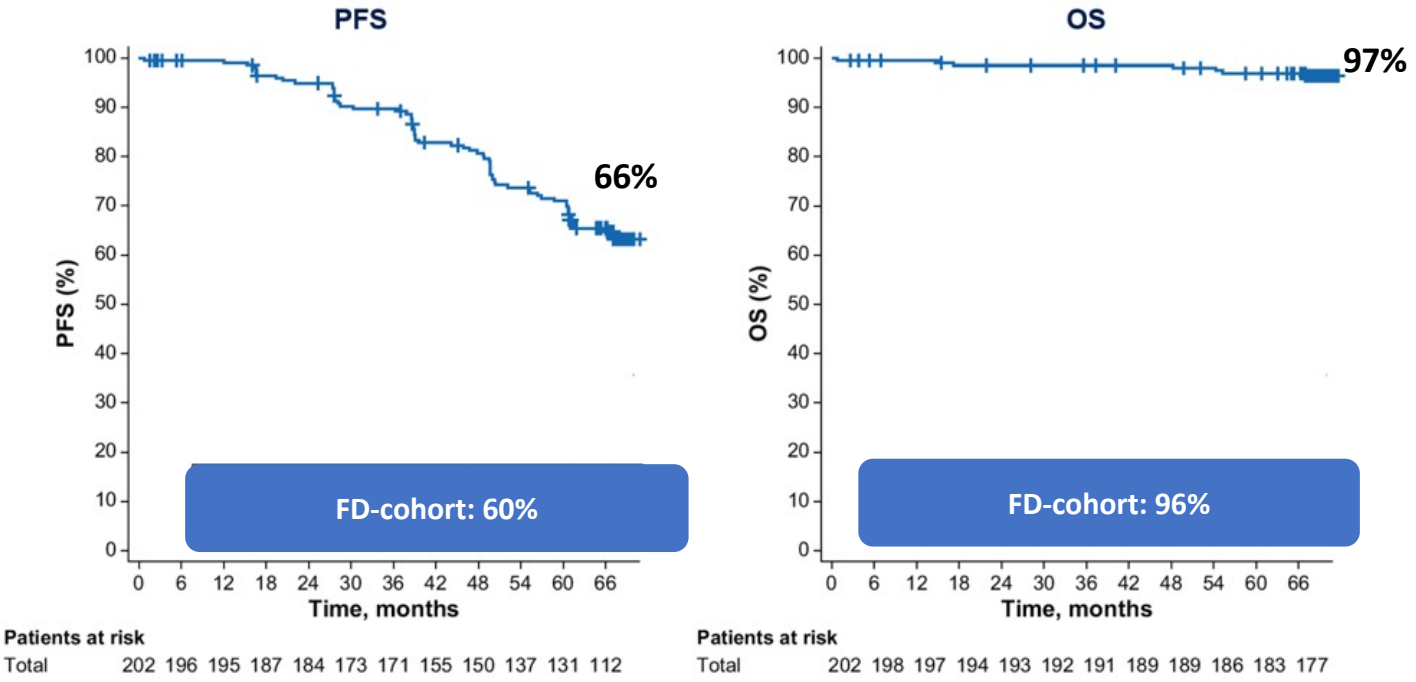
Characteristic	Total Pooled Population (N=202)	FD Cohort Only (N=159)
Median age (range), years	60.0 (33–71)	60.0 (33–71)
Male, n (%)	131 (65)	106 (67)
Rai stage III/IV, n (%)	59 (29)	44 (28)
High-risk genomic features, n (%)		
uIGHV	119 (59)	89 (56)
del(17p)/TP53	29 (14)	27 (17)
del(11q)[a]	36 (18)	28 (18)
CK (≥3 abnormalities)[b]	35 (17)	31 (20)
CK (≥5 abnormalities)[b]	19 (9)	16 (10)
Bulky LN disease, n (%)		
≥5 cm	66 (33)	48 (30)
≥10 cm	6 (3)	5 (3)

Wierda et al. EHA 2025

CAPTIVATE study: Final analysis of FD ibrutinib + Venetoclax for CLL/SLL

Median FU: 69 months

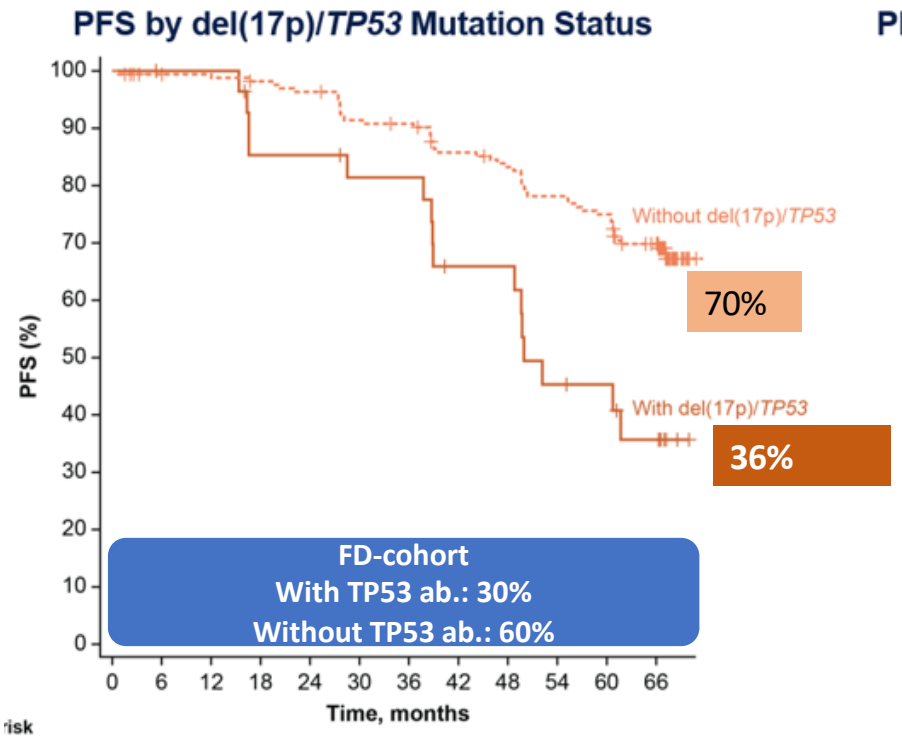
5.5 yr PFS and OS: Total population (N=202)

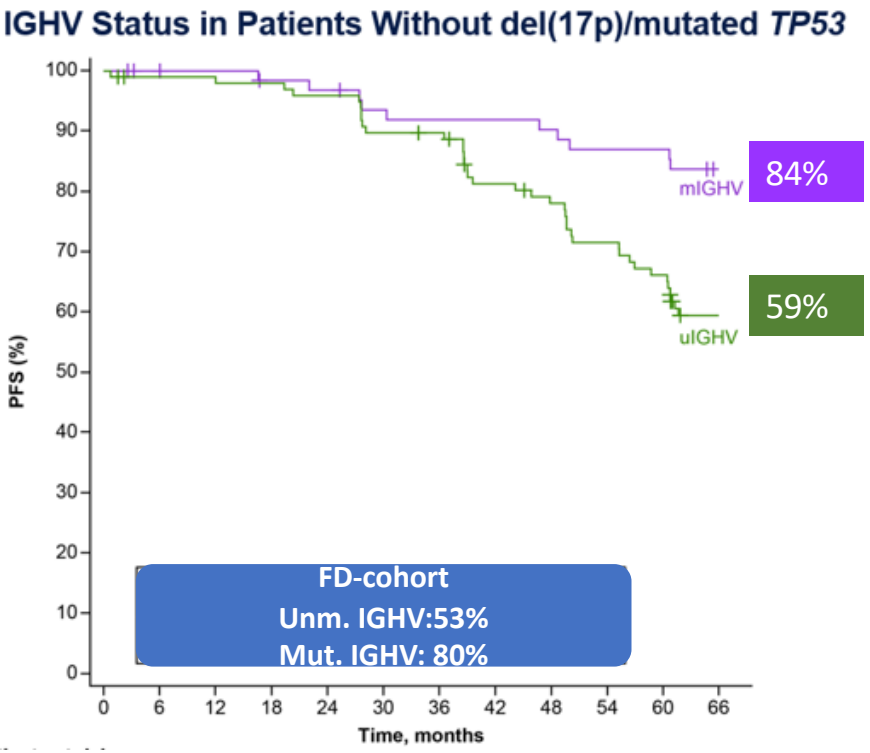


Wierda et al. EHA 2025

CAPTIVATE study: Final analysis of FD ibrutinib + Venetoclax for CLL/SLL

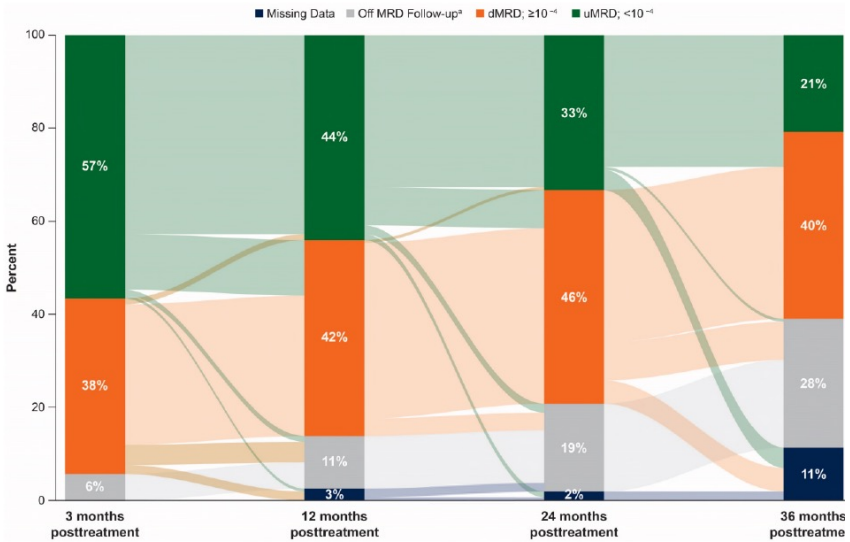
PFS : Total population (N=202)

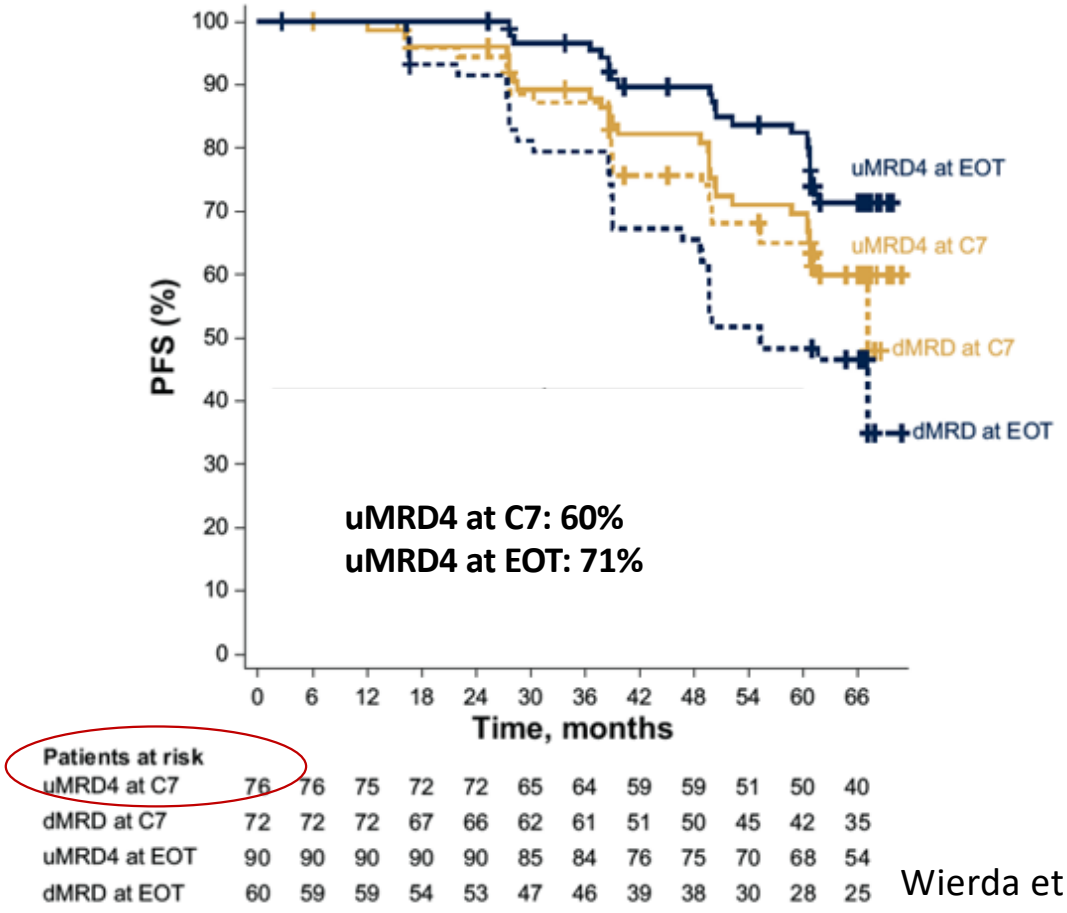




Wierda et al. EHA 2025

FD-CAPTIVATE: Impact of uMRD4 measured at C7 and EOT on PFS



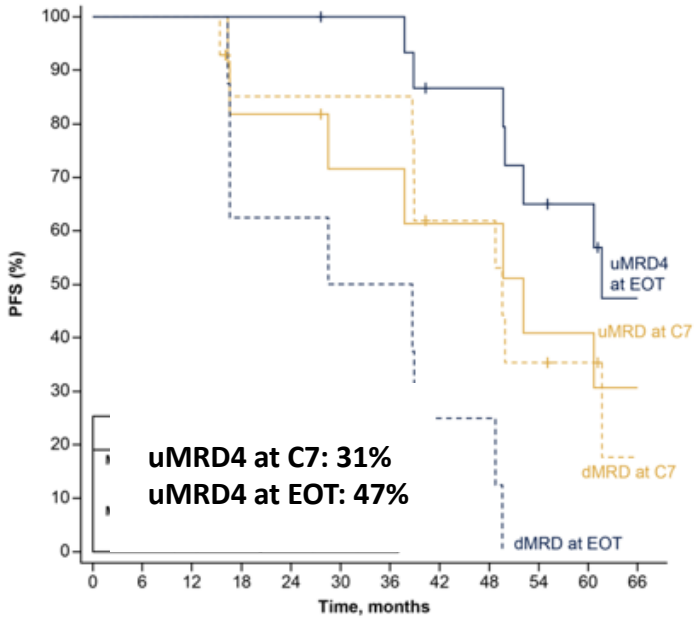


Patients at risk												
uMRD4 at C7	76	76	75	72	72	65	64	59	59	51	50	40
dMRD at C7	72	72	72	67	66	62	61	51	50	45	42	35
uMRD4 at EOT	90	90	90	90	90	85	84	76	75	70	68	54
dMRD at EOT	60	59	59	54	53	47	46	39	38	30	28	25

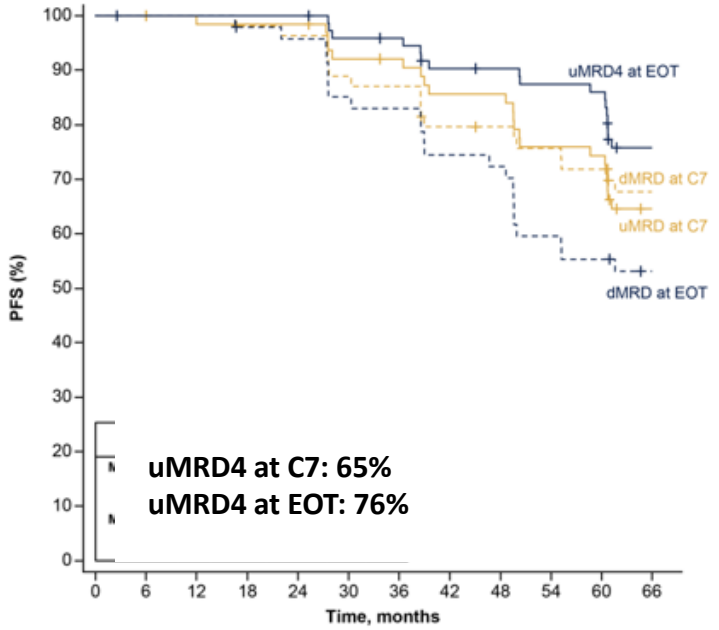
Wierda et al. EHA 2025

FD-CAPTIVATE: Impact of uMRD4 measured at C7 and EOT on PFS

PFS by MRD Status in Patients With del(17p)/mutated *TP53* (FD Cohort only)



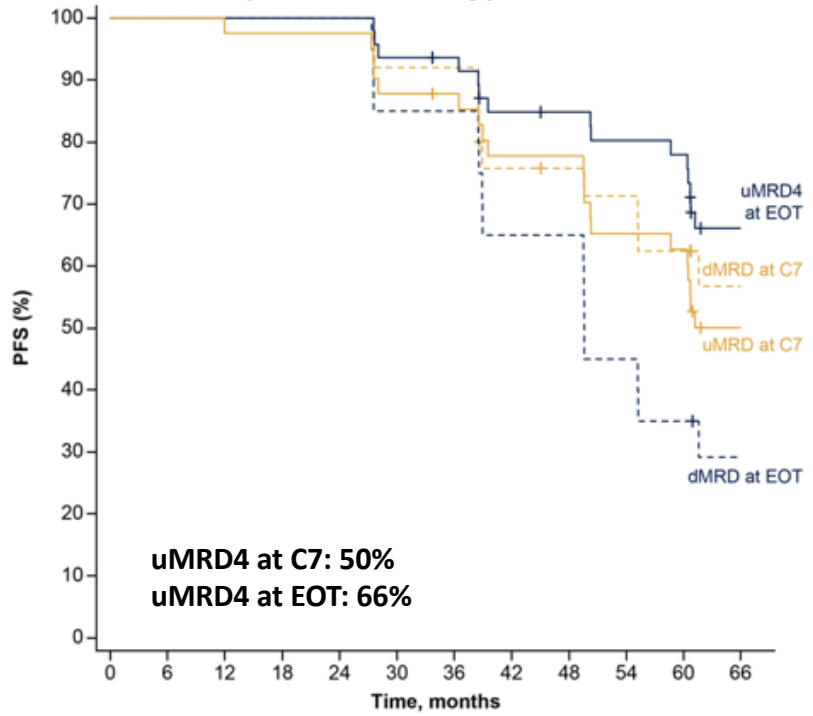
PFS by MRD Status in Patients Without del(17p)/mutated *TP53* (FD Cohort only)



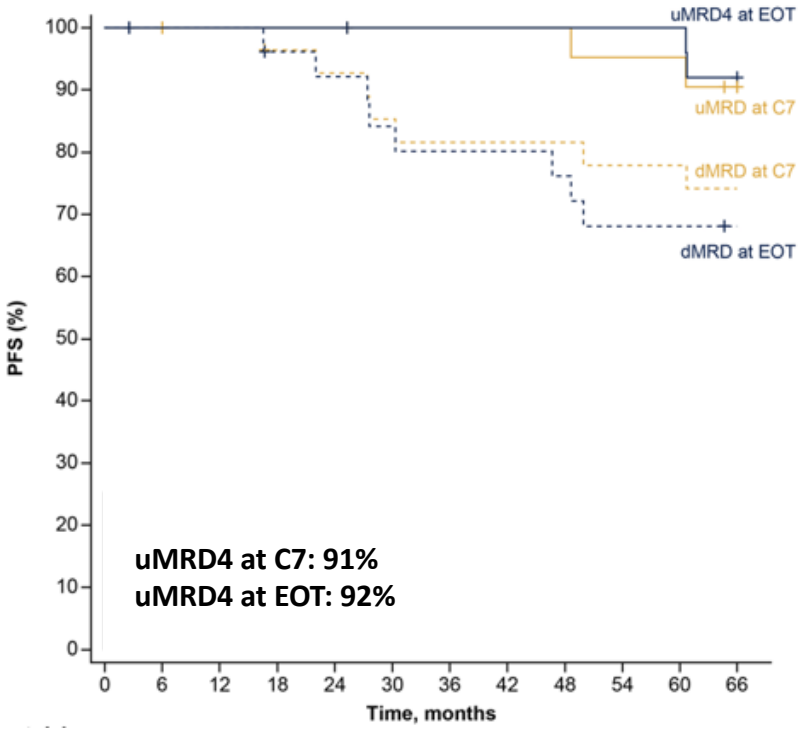
Wierda et al. EHA 2025

FD-CAPTIVATE: Impact of uMRD4 measured at C7 and EOT on PFS

PFS by MRD Status in Patients Without del(17p)/*TP53* and With uIGHV (FD Cohort only)



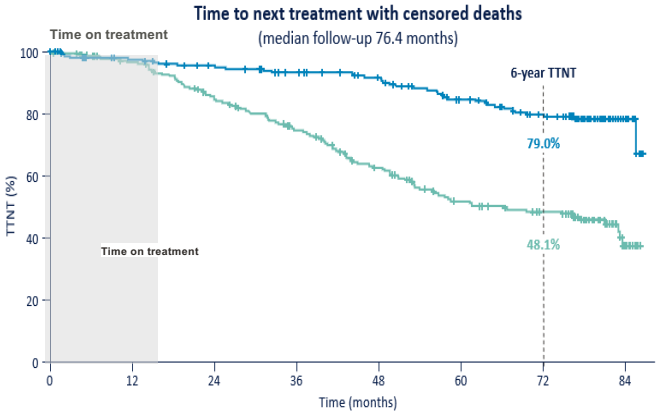
PFS by MRD Status in Patients Without del(17p)/*TP53* and With mIGHV (FD Cohort only)



Wierda et al. EHA 2025

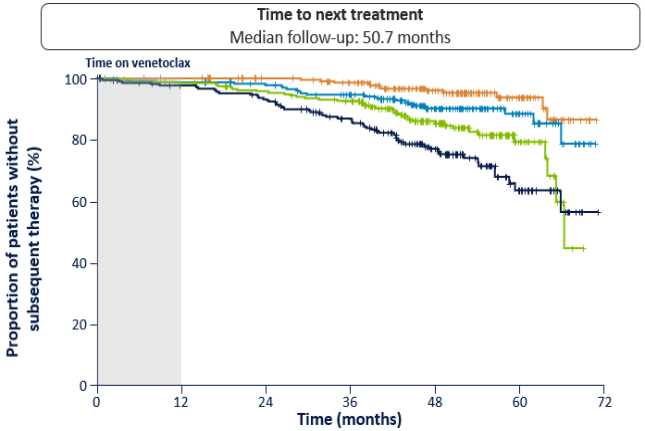
1L Fixed-Duration treatment for CLL: TTNT

V+O - CLL14



6yTTNT
79,0%

V+O - CLL13



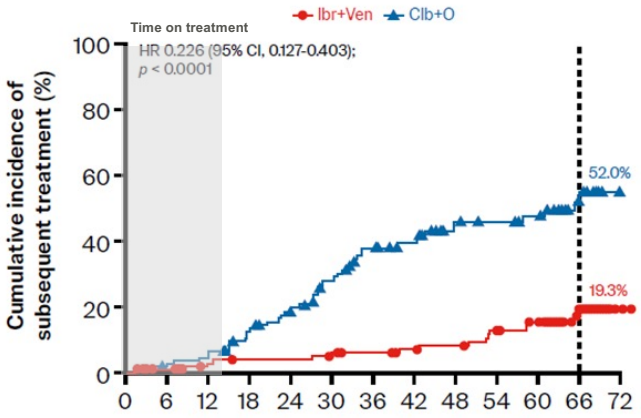
4y TTNT
90,4%

Al-Sawaf O, *et al.* Blood 2024; Fürstenau M, *et al. Lancet Oncol* 2024

La combinazione Venetoclax + Ibrutinib è riportata nella RCP del medicinale a base di ibrutinib.

1L Fixed-Duration treatment for CLL: TTNT

V+I - GLOW



5.5y TTNT
80,7%*

*calculated as 100 - 19.3

At 5.5 years, 73% of patients required no additional treatment

5.5y TTNT
73.3%

Niemann et al. ASH 2024

AMPLIFY: 1L Fixed-Duration Acalabrutinib + Venetoclax ± Obinutuzumab vs CIT in

TN CLL (N=867)

Key inclusion criteria
- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria[3]
- Without del(17p) or *TP53*[a]
- ECOG PS ≤2

Key exclusion criteria
- CIRS-Geriatric >6
- Significant cardiovascular disease

Stratification
- Age (>65 vs ≤65 years)
- *IGHV* mutational status
- Rai stage (≥3 vs <3)
- Geographic region

NCT03836261. Data cutoff: April 30, 2024.

AMPLIFY: randomized, multicenter, open-label, Phase III trial

RANDOMIZE 1:1:1

- AV (14 cycles)
- AVO (14 cycles)
- FCR/BR (6 cycles)

Crossover not built into protocol

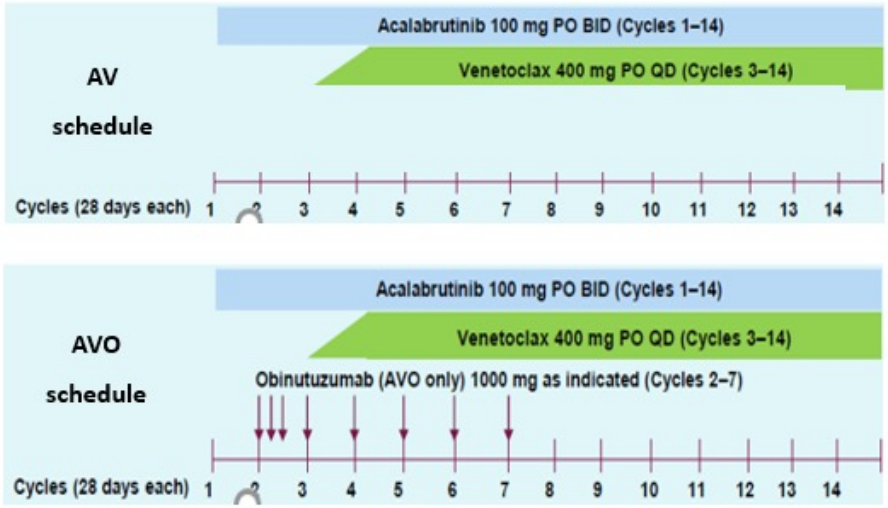
Primary endpoint

IRC-assessed PFS (AV vs FCR/BR)

If primary endpoint met, the following were

Secondary endpoints (tested in fixed sequential hierarchy)

1) IRC-PFS (AVO vs FCR/BR)
2) uMRD (AV vs FCR/BR) in PB by FC
3) uMRD (AVO vs FCR/BR) in PB by FC
4) OS (AV vs FCR/BR)
5) OS (AVO vs FCR/BR)

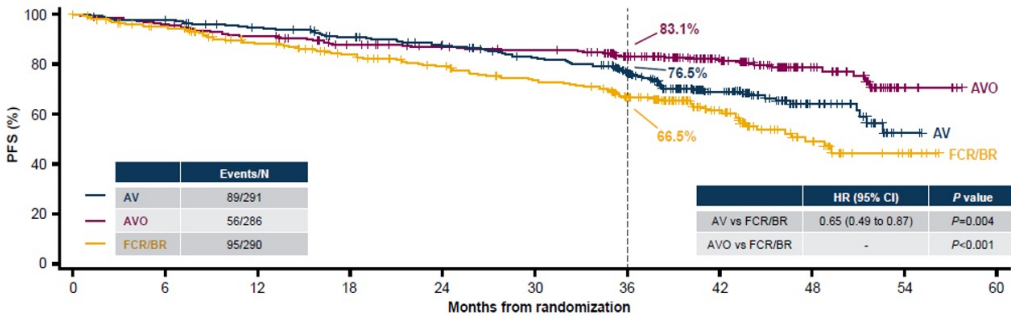


Characteristic	AV (n = 291)	AVO (n = 286)	FCR/BR (n = 290)
Median age, yr (range)	61 (31-84)	61 (29-81)	61 (26-86)
ECOG PS 2, n (%)	28 (9.6)	14 (4.9)	26 (9.0)
Rai stage			
▪ 0-II	154 (52.9)	170 (59.4)	163 (56.2)
▪ III-IV	137 (47.1)	116 (40.6)	127 (43.8)
del(11q) present	51 (17.5)	56 (19.6)	46 (15.9)
Unmutated *IGHV*	167 (57.4)	169 (59.1)	172 (59.3)

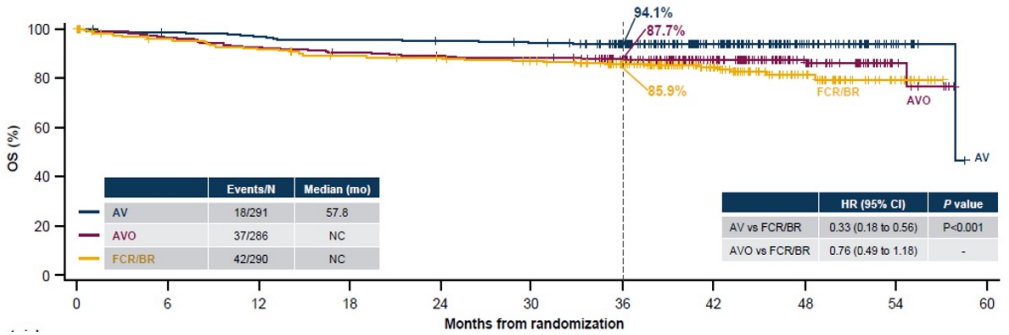
Amplify trial: AV vs. AVO vs CIT

Median follow-up from randomization: 40.8 months (range, 0-59),

PFS



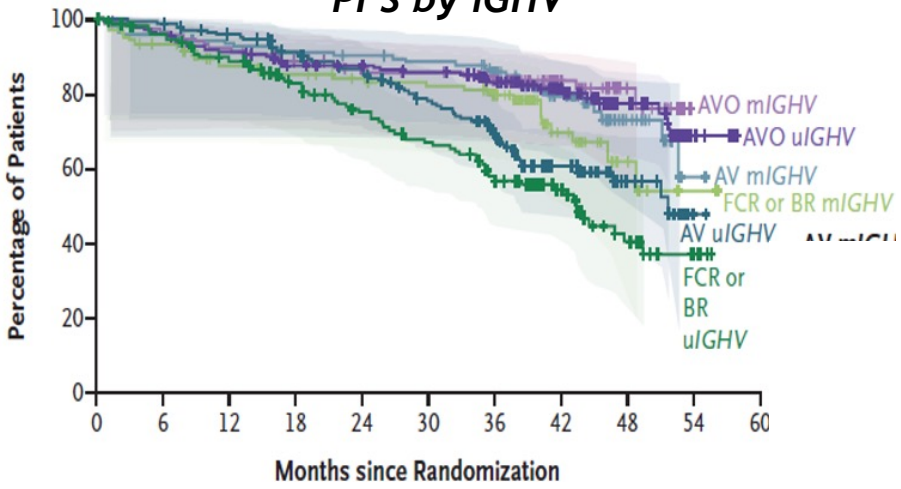
OS



Brown et al., NEJM 2025

AMPLIFY: 1L Fixed-Duration Acalabrutinib + Venetoclax ± Obinutuzumab vs CIT in

PFS by IGHV



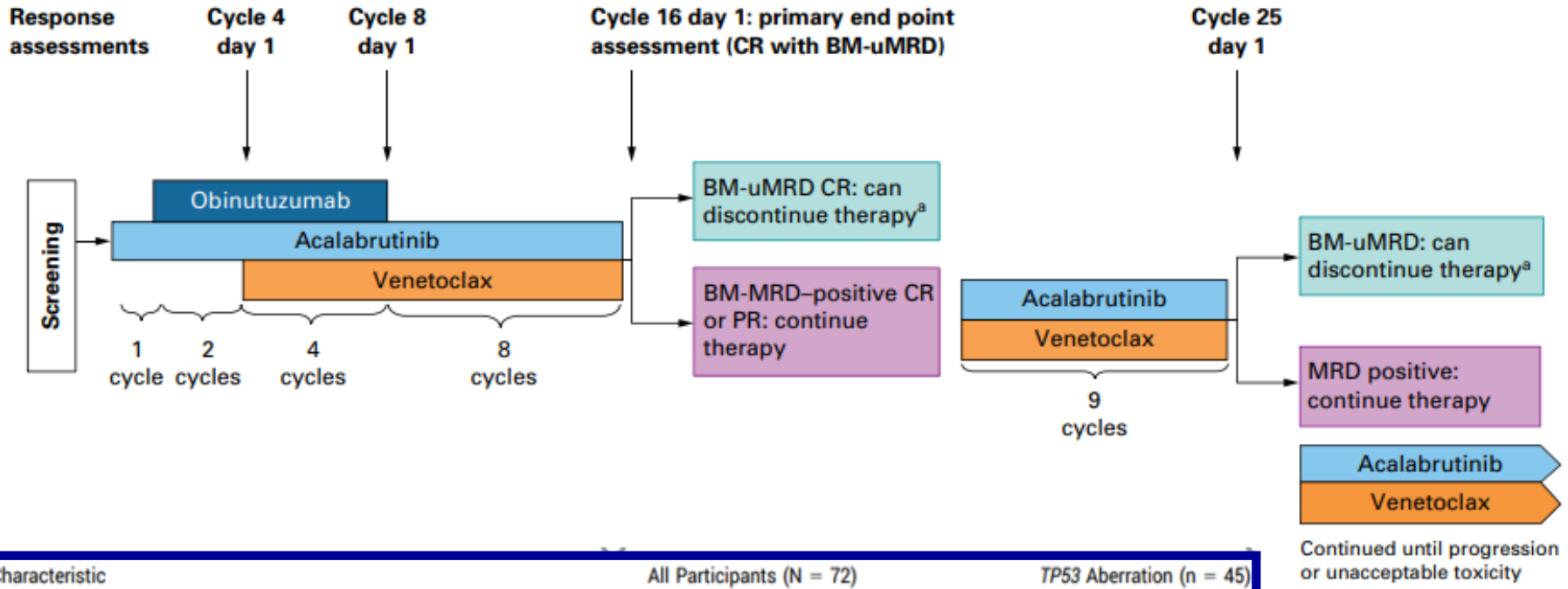
	No. of Events/ Total No. of Patients	Median Progression-free Suvival	Progression-free Survival at 36 Months
		mo	%
AV m*IGHV*	28/124	NC	86.0
AV u*IGHV*	61/167	51.5	68.9
AVO m*IGHV*	20/117	NC	83.6
AVO u*IGHV*	36/169	NC	82.8
FCR or BR m*IGHV*	28/118	NC	79.9
FCR or BR u*IGHV*	67/172	43.1	

AEs of Clinical Interest

AEs of Clinical Interest, n (%)	AV (n = 291)		AVO (n = 284)		FCR/BR (n = 259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac events	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
▪ Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
▪ Ventricular tachyarrhythmias	2 (0.7)	0	3 (1.1)	0	0	0
Hypertension	12 (4.1)	8 (2.7)	11 (3.9)	6 (2.1)	7 (2.7)	2 (0.8)
Hemorrhage	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
▪ Major hemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Neutropenia	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infections	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Secondary primary malignancy	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0
▪ Excluding nonmelanoma skin cancer	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
TLS	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

Brown et al., NEJM 2025

Phase II Study of Acalabrutinib, Venetoclax, and Obinutuzumab in a TNCLL Population Enriched for HR

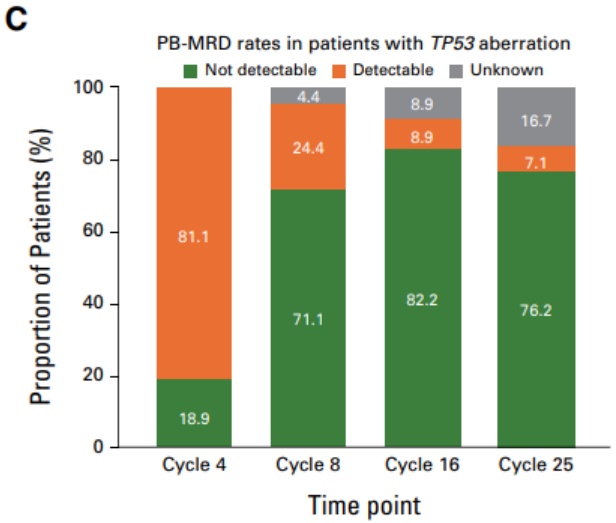


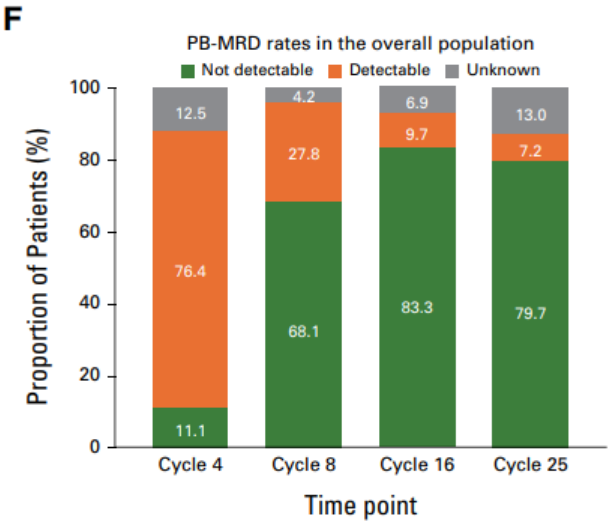
Characteristic	All Participants (N = 72)	*TP53* Aberration (n = 45)
Age, years, median (range)	63 (36-80)	65 (36-80)
TP53 aberration	45 (62.5)	45 (100.0)
Del(17p) with *TP53* mutation	31 (43.1)	31 (68.9)
Del(17p) without *TP53* mutation or *TP53* unknown	3 (4.2)	3 (6.7)
TP53 mutation without del(17p) or del(17p) unknown	11 (15.3)	11 (24.4)
IGHV status, unmutated	54 (75.0)	37 (82.2)

Davids et al. JCO 2025

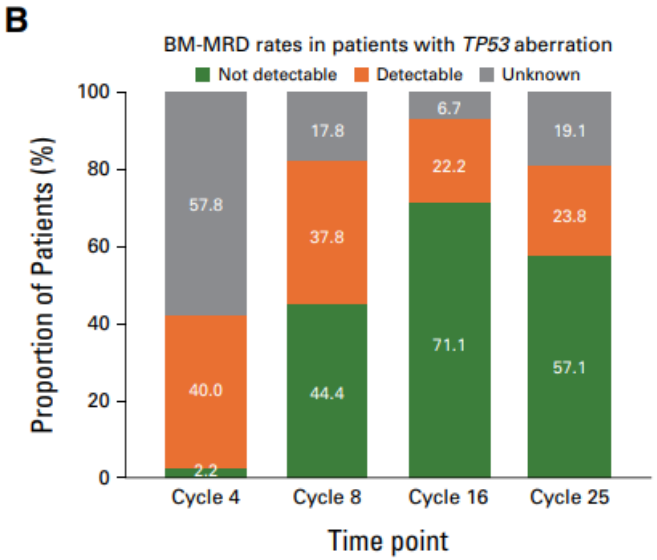
A+V e A+V+O sono approvati da EMA ma non ancora rimborsati da AIFA.

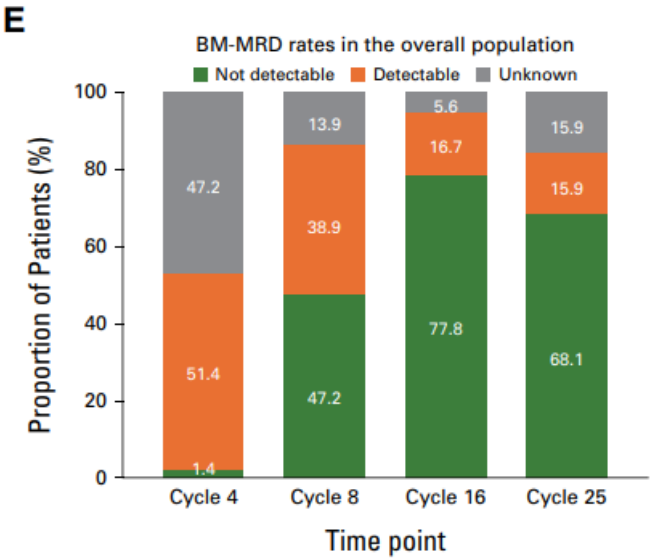
uMRD in PB





uMRD in BM





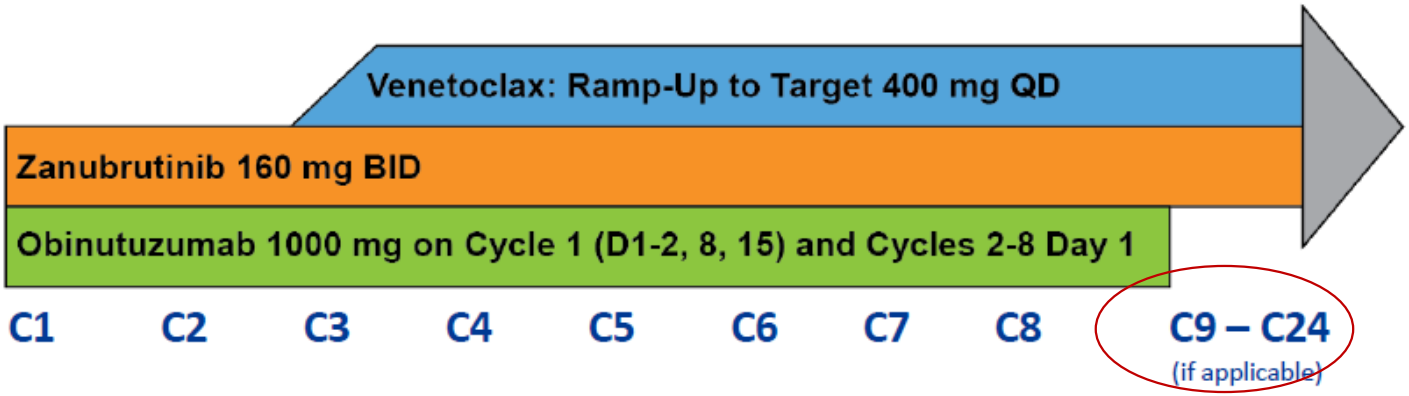
Davids et al. JCO 2025

A+V e A+V+O sono approvati da EMA ma non ancora rimborsati da AIFA.

BOVEN REGIMEN: 1L zanubrutinib+venetoclax+obinutuzumab

Key eligibility criteria

Previously untreated CLL/SLL
Requires treatment (iwCLL guidelines)
ECOG 0-2
ANC ≥1,000, PLT count ≥75 (unless due to CLL)
Coumadin and dual antiplatelet excluded

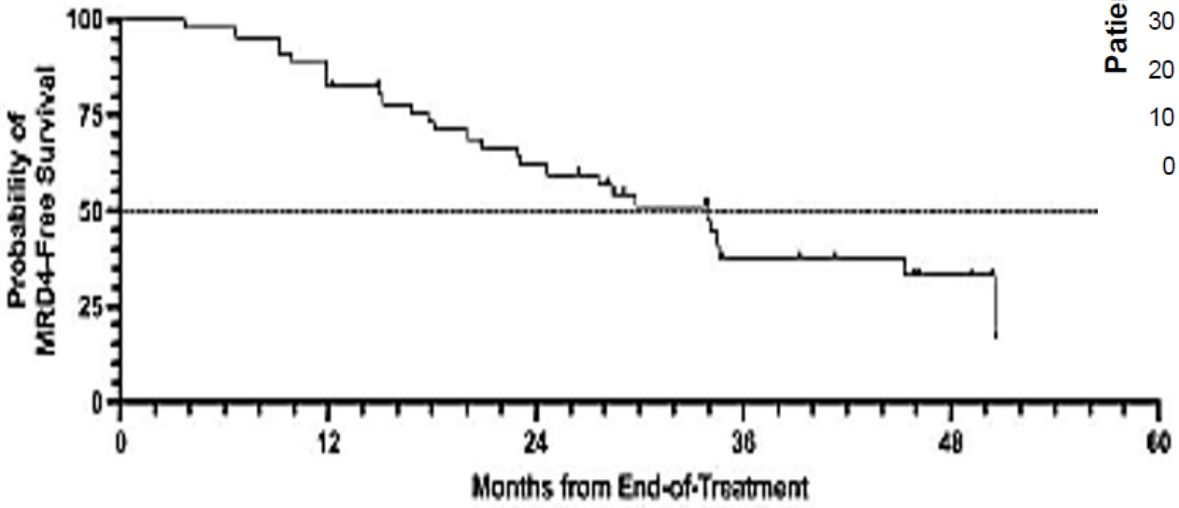


Treatment duration / MRD-directed treatment discontinuation criteria

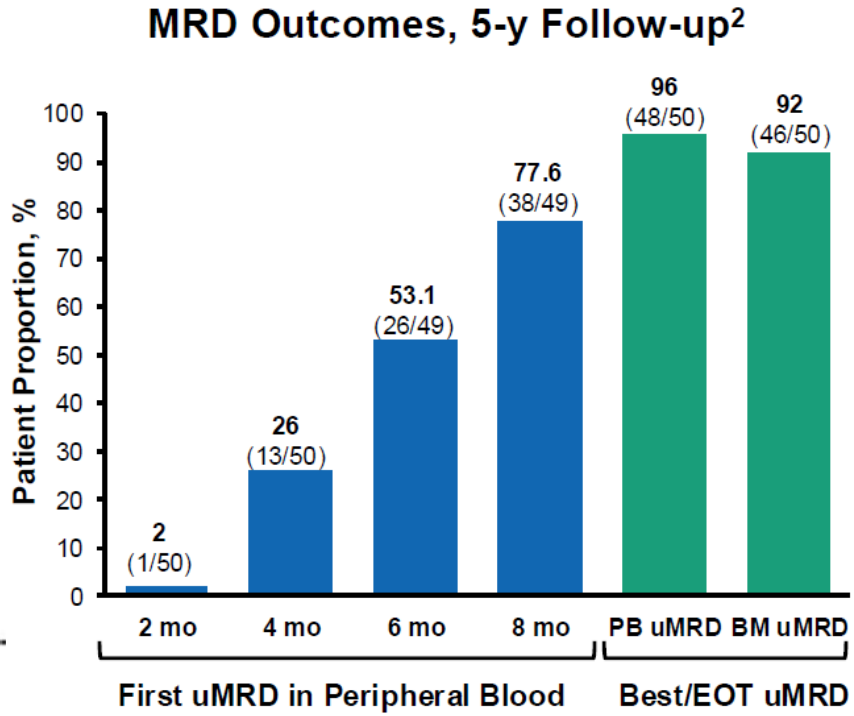
- Treatment duration: Min 8 months to Max 24 months (including 2-month doublet lead-in prior to venetoclax)
- Peripheral blood MRD (flow cytometry) assessed every 2 cycles
  - If PB uMRD $<10^{-4}$ (flow), then BM MRD assessment within 14 days
  - If PB and BM uMRD $<10^{-4}$ (flow), then repeat PB MRD assessment after 2 additional cycles
  - If PB x 2 (consecutively) and BM uMRD $<10^{-4}$ (primary endpoint), treatment is discontinued

Soumerai et al., ASH 2024

	52 patients
Median FU	57 mo
Med. age	62 yrs
Unmutated IGHV	71%
TP53 del/mut	17%
Response evaluable	50/52

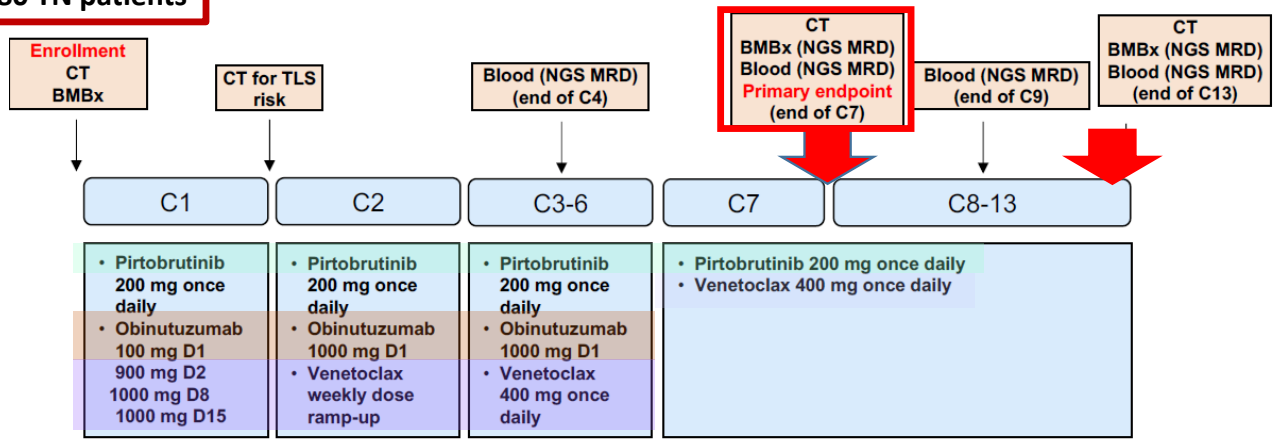


- Median MRD4-free survival of 92% (46/50) achieving BM uMRD4: 34 mo (95% CI 23 – NR)



Combined Pirtobrutinib, Venetoclax, and Obinutuzumab As First-Line Treatment of Patients with CLL

80 TN patients



		n (%) or median [range], N=80
Age, years		63 [38-78]
	≥70	21 (26)
Gender, M		60 (75)
ALC, K/µL		65.1 [1.1-331.1]
PLT, K/µL		142 [61-284]
HGB, g/dL		11.3 [7.5-14.8]
B2M, mg/L		4.0 [1.6-12.8]
FISH (Dohner classification)	Del(17p)	7 (9)
	Del(11q)	23 (29)
	Trisomy 12	16 (20)
	Normal	13 (16)
	Del(13q)	21 (26)
IGHV status	Unmutated	63 (79)
Mutations	*NOTCH1*	25 (31)
	SF3B1	17 (21)
	KRAS/NRAS	11 (14)
	BIRC3	8 (10)
	TP53	8 (10)
Del(17p) / *TP53*-mutated		10 (13)

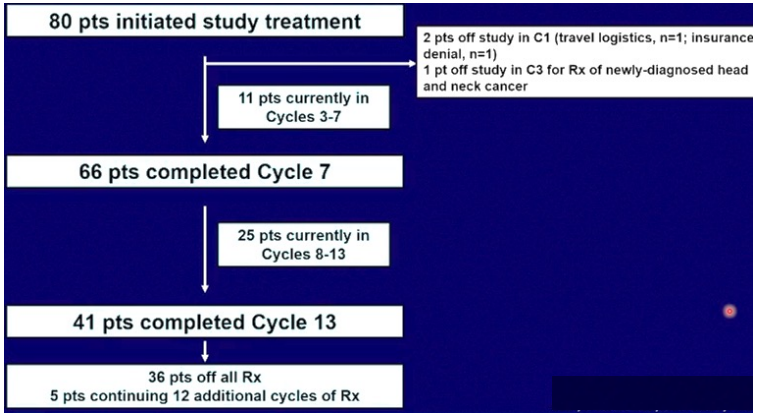
- Patients with treatment-naïve CLL/SLL
- ≥18 years
- ECOG PS 0-2
- Adequate organ function
  - GFR ≥50 ml/min

Primary Objective

- Estimate the therapeutic activity (U-MRD rate) of combined pirtobrutinib, venetoclax, and obinutuzumab in patients with previously untreated CLL/SLL

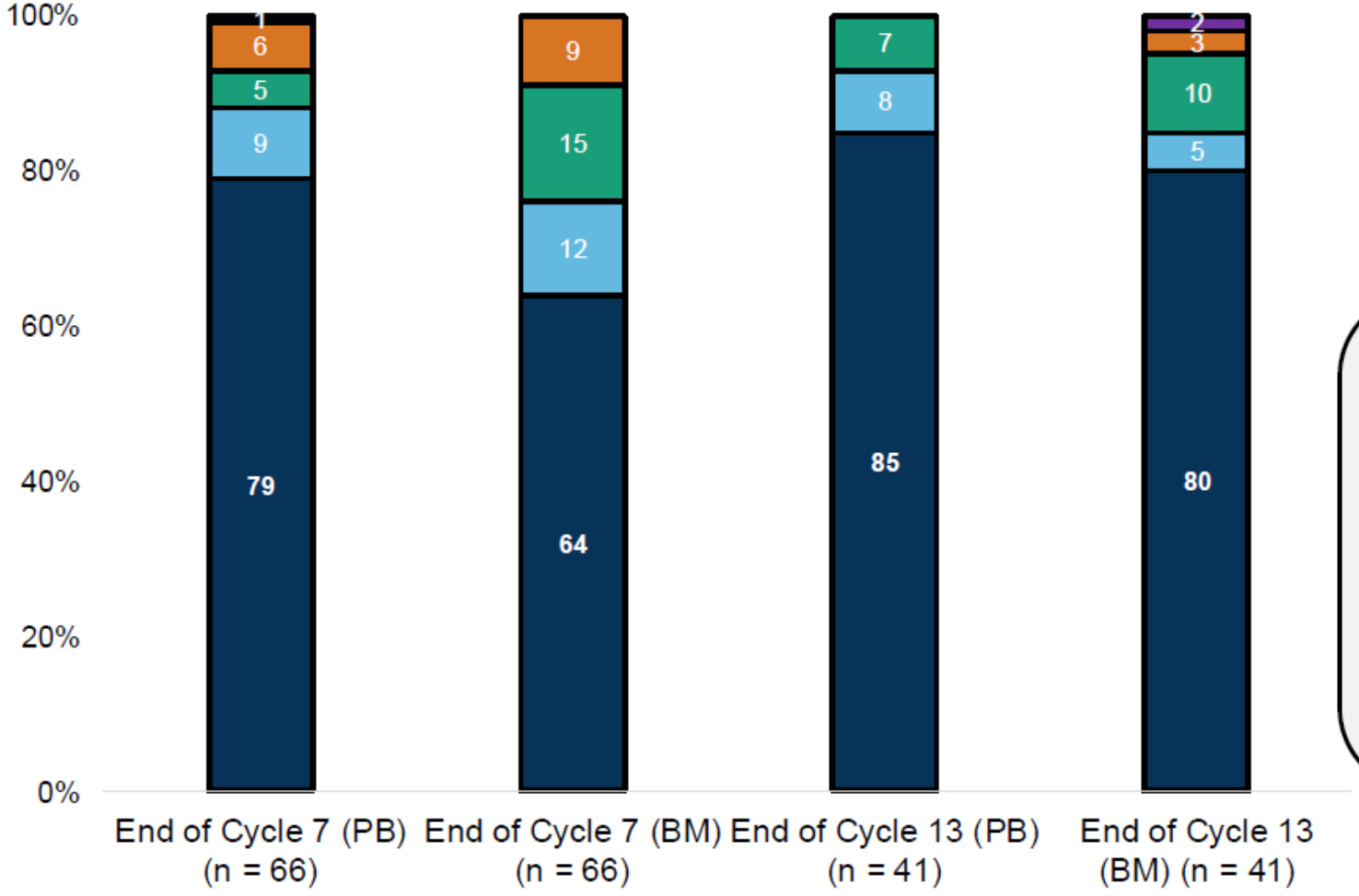
Secondary Objectives

- Estimate overall response rate (CR/CRi/PR), PFS, and OS
- Estimate the safety and tolerability



Jain et al., 2024 ASH, abstract #1867

Time-Limited Pirtobrutinib, Venetoclax, Obinutuzumab (PVO) Induced Deep, MRD-Negative Remissions in TN CLL[1]



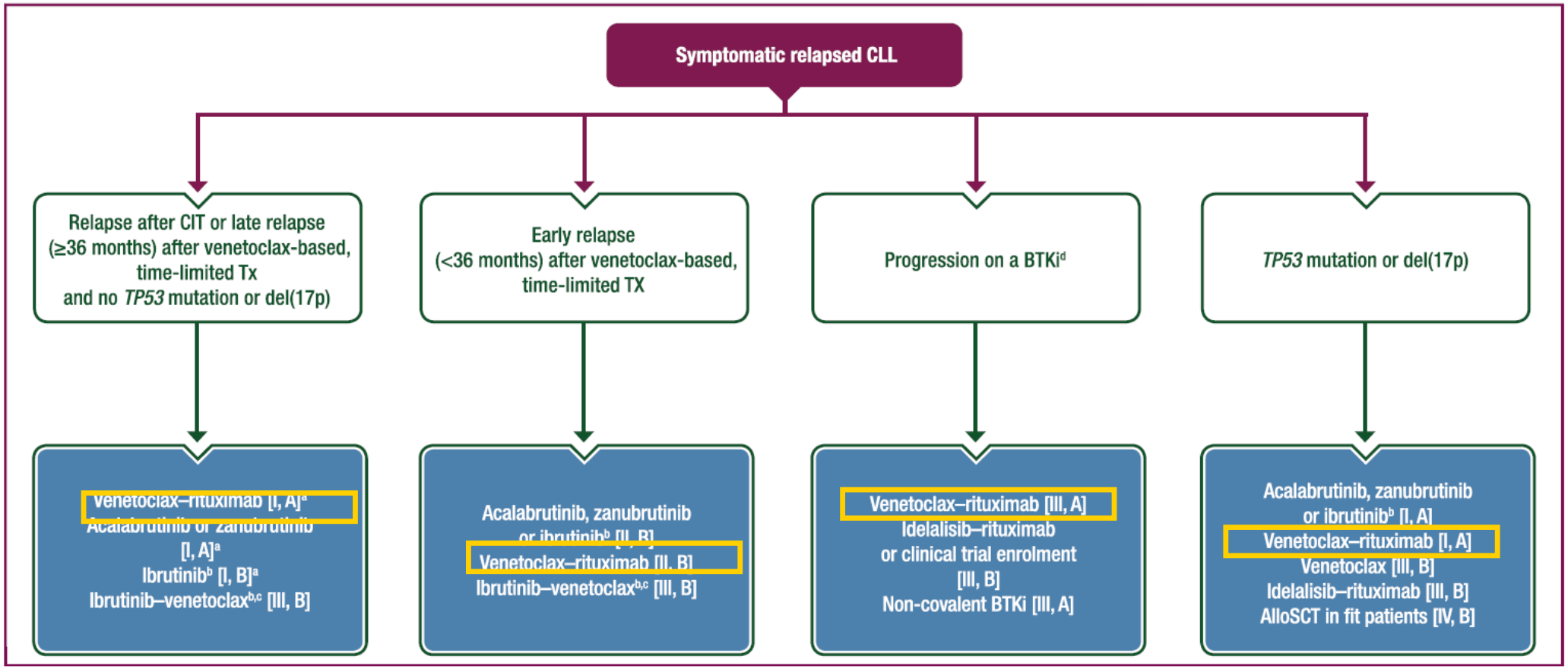
High rates of U-MRD6 remission with PVO

- 6 mo: U-MRD6 BM 64%; PB 79%
- 12 mo: U-MRD6 BM 80%; PB 85%

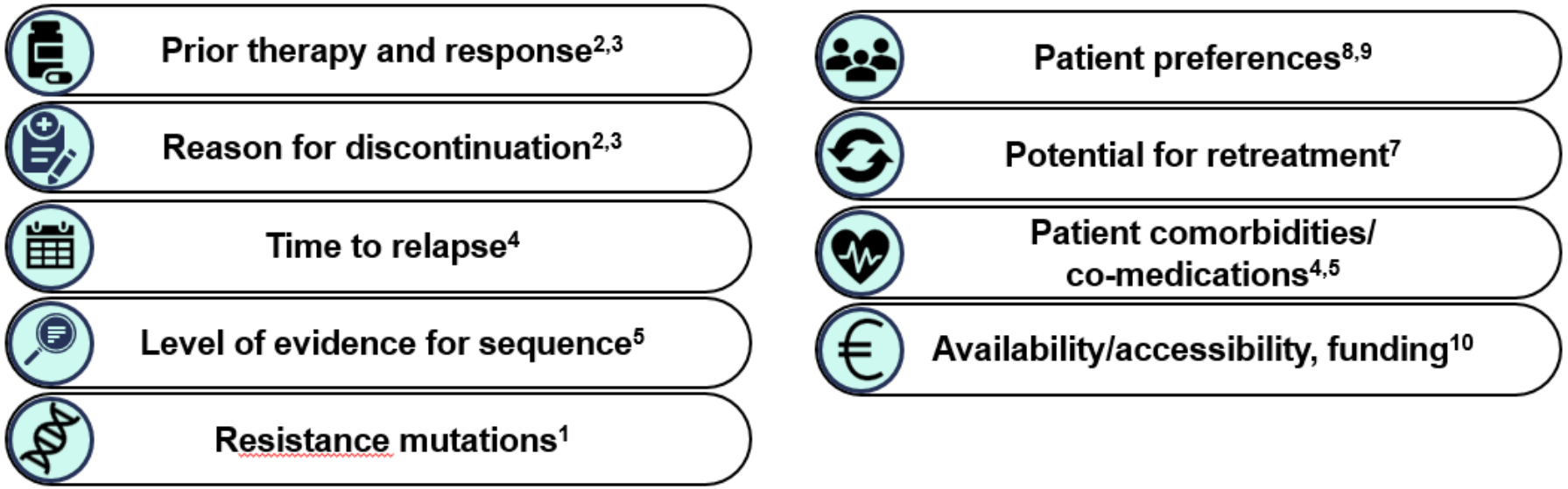
With a median follow-up of 11.9 mo, no patient has progressed/died

1. Jain N et al. ASH 2024. Abstract 1011.

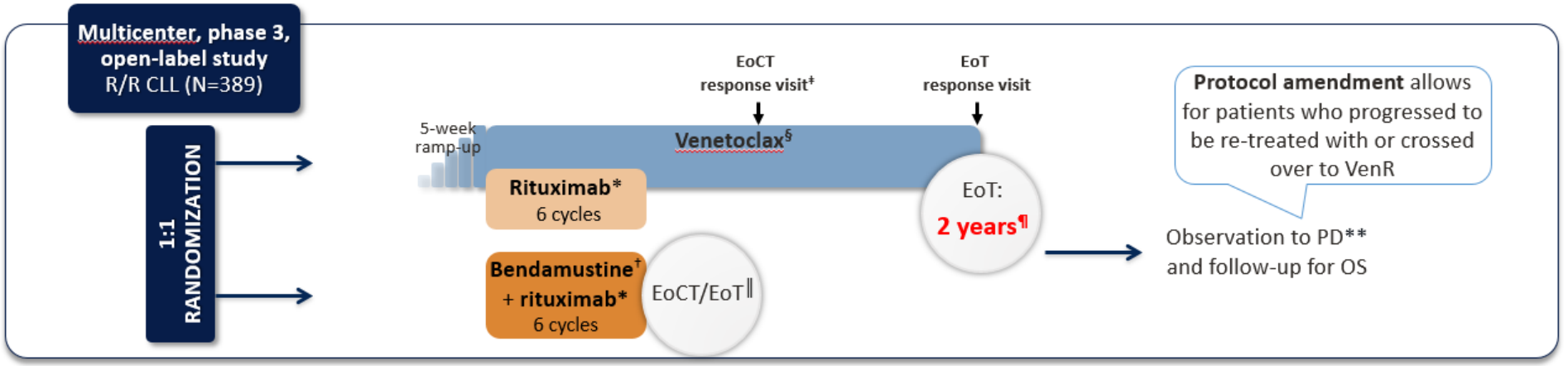
PeerView


Symptomatic relapsed CLL
Relapse after CIT or late relapse (≥36 months) after venetoclax-based, time-limited Tx and no *TP53* mutation or del(17p)
Early relapse (<36 months) after venetoclax-based, time-limited TX
Progression on a BTKi[d]
TP53 mutation or del(17p)
Venetoclax–rituximab [I, A][a]
Acalabrutinib or zanubrutinib [I, A][a]
Ibrutinib[b] [I, B][a]
Ibrutinib–venetoclax[b,c] [III, B]
Acalabrutinib, zanubrutinib
Venetoclax–rituximab [II, B]
Ibrutinib–venetoclax[b,c] [III, B]
Venetoclax–rituximab [III, A]
Idelalisib–rituximab or clinical trial enrolment [III, B]
Non-covalent BTKi [III, A]
Acalabrutinib, zanubrutinib or ibrutinib[b] [I, A]
Venetoclax–rituximab [I, A]
Venetoclax [III, B]
Idelalisib–rituximab [III, B]
AlloSCT in fit patients [IV, B]

Considerations to optimize treatment sequencing



MURANO TRIAL: VR vs. BR in R/R patients with CLL: 7 years follow-up



Primary endpoint:
- INV-assessed PFS

Key secondary endpoints:
- IRC-assessed PFS
- PFS in patients with del(17p)
- ORR (IRC- and INV-assessed) at EoCT
- OS, uMRD at EoCT, DoR, EFS, TTNT

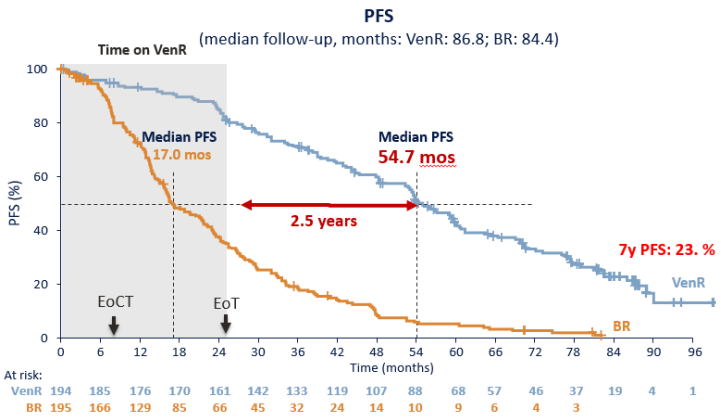
Key inclusion criteria
- 1–3 lines of prior therapy††
- Prior bendamustine if DoR was ≥2 years
- ECOG PS ≤1

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)

Kater et al Blood 2025

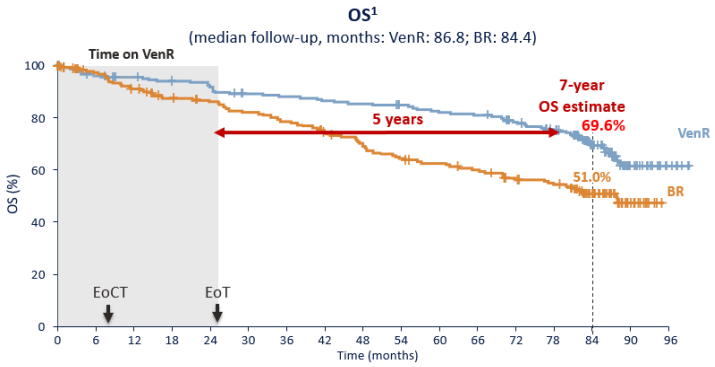
MURANO TRIAL: VR vs. BR in R/R patients with CLL: 7 years follow-up

INV-assessed PFS



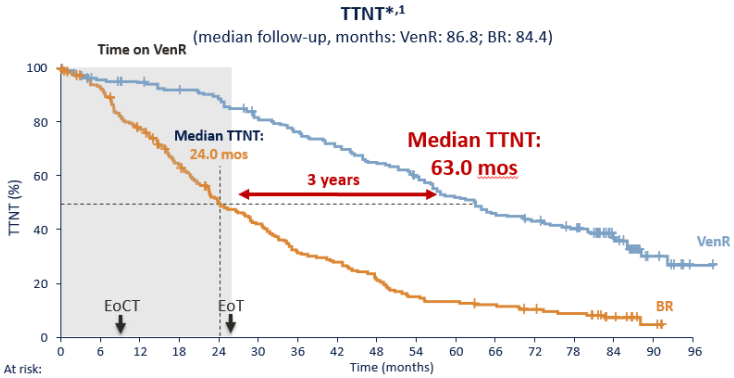
	VenR	BR
HR (95% CI) p value	0.23 (0.18–0.29)* Stratified p<0.0001†	
Estimated 7-year PFS, %	23.0	NE

OS



	VenR	BR
HR (95% CI)[1]	0.53 (0.37–0.74)* Stratified p<0.0002†	
Median OS[1]	NE	87.8

TTNT



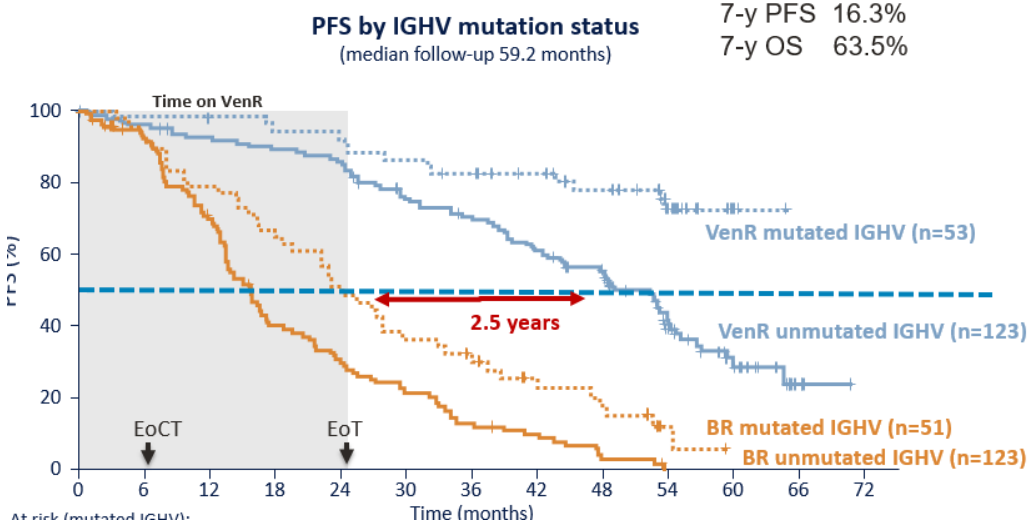
	VenR	BR
HR (95% CI) p value	HR=0.30 (0.23–0.39)† Stratified p<0.0001‡	

Kater et al Blood 2025

MURANO TRIAL: VR vs. BR in R/R patients with CLL: 7 years follow-up

PFS by IGHV mutation status

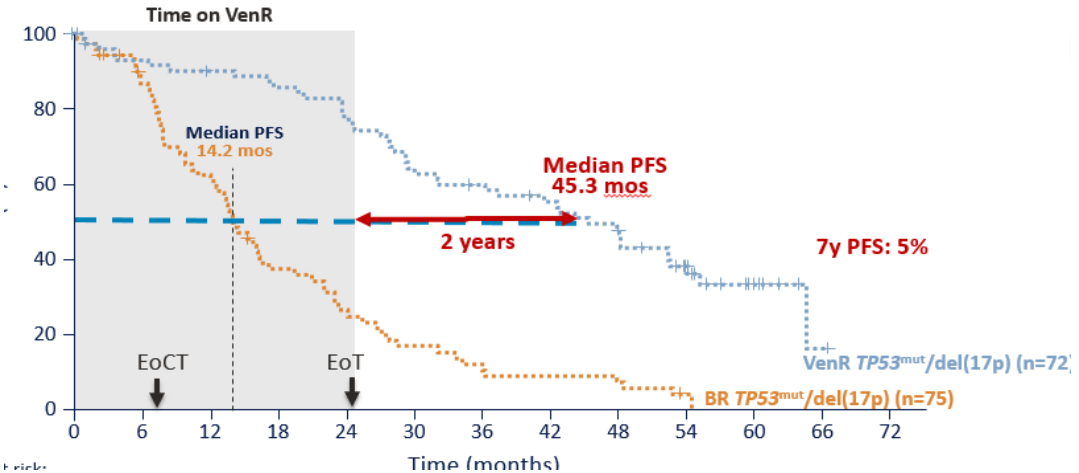
unmutated IGHV patients
Med PFS: 52.5 months
7-y PFS 16.3%
7-y OS 63.5%



	VenR		BR	
	Unmutated IGHV	Mutated IGHV	Unmutated IGHV	Mutated IGHV
HR (95% CI) p value	Unmutated IGHV vs mutated IGHV 2.96 (1.64–5.34) 0.0002		Unmutated IGHV vs mutated IGHV 1.79 (1.24–2.58) 0.0015	
Median PFS, months	52.2	NE	15.7	24.2

PFS by *TP53* deletion/mutation

Med PFS: 45.3 monnths
7-y PFS 5%
7-y OS 50.6%

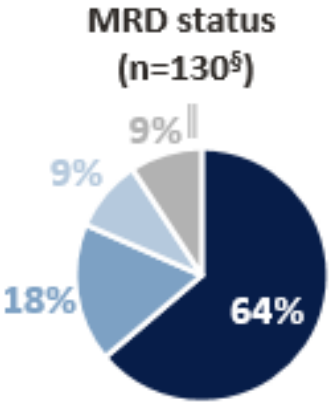


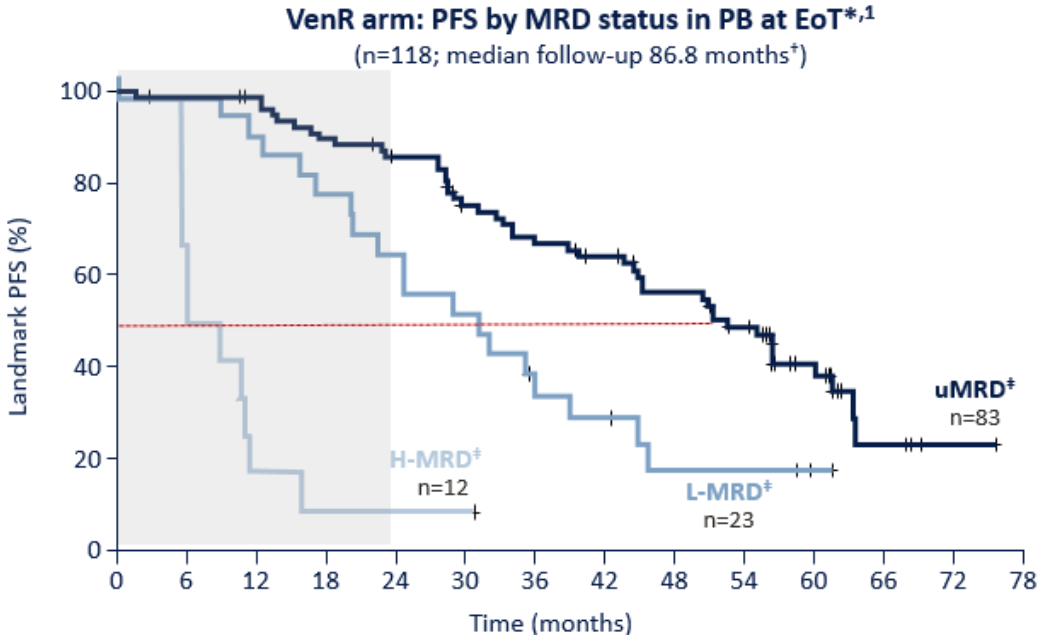
	TP53mut and/or del(17p) by FISH	
	VenR	BR
HR (95% CI)	0.26 (0.17–0.38)	

Kater et al Blood 2025

MURANO TRIAL: VR vs. BR in R/R patients with CLL: 7 years follow-up

PFS by MRD status in PB at EoT





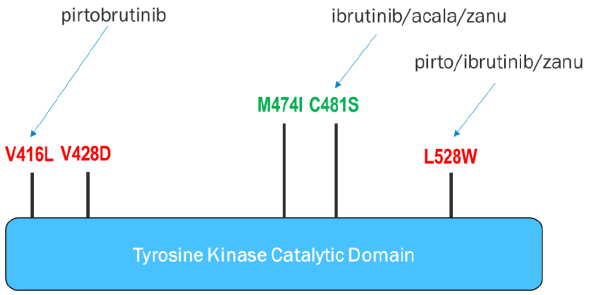
	uMRD	L-MRD+	H-MRD+
Median PFS since EoT, months (95% CI)	52.5 (44.5–61.5)	29.3 (20.2–37.5)	4.6 (2.8–8.3)

Kater et al Blood 2025

Mutations preventing effective target inhibition rare with FD therapy

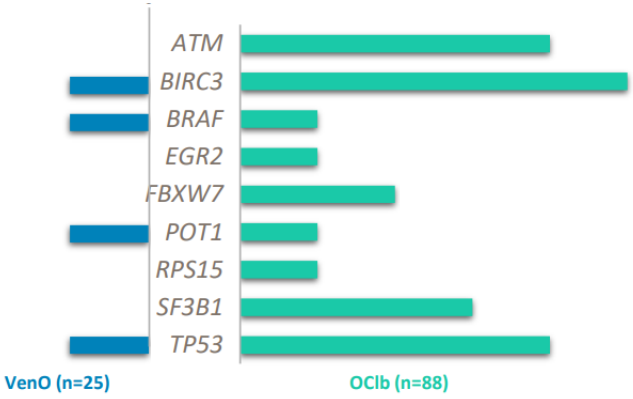
Regimens with continuous BTKi

BTK mutations the dominant reason for PD CLL after cBTKi



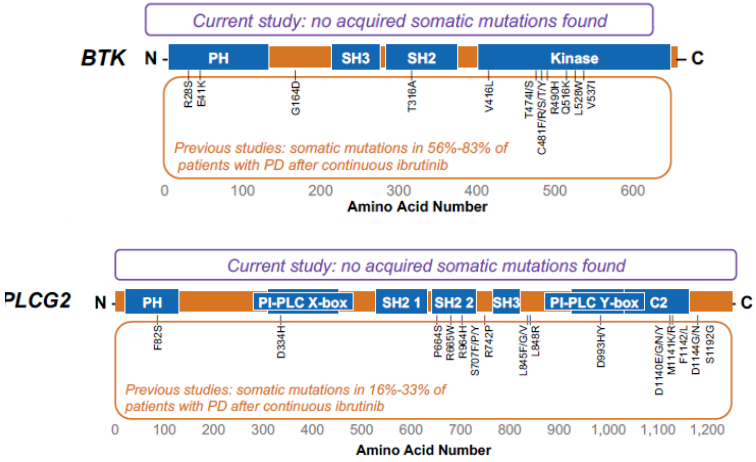
CLL14 trial

No acquired mutations in BCL2 family genes
after 12 cycles of VenO or OClb



CAPTIVATE trial

no *BTK, PLCG2,* mutations in 25/29 patients with PD after 15 cycles of IV



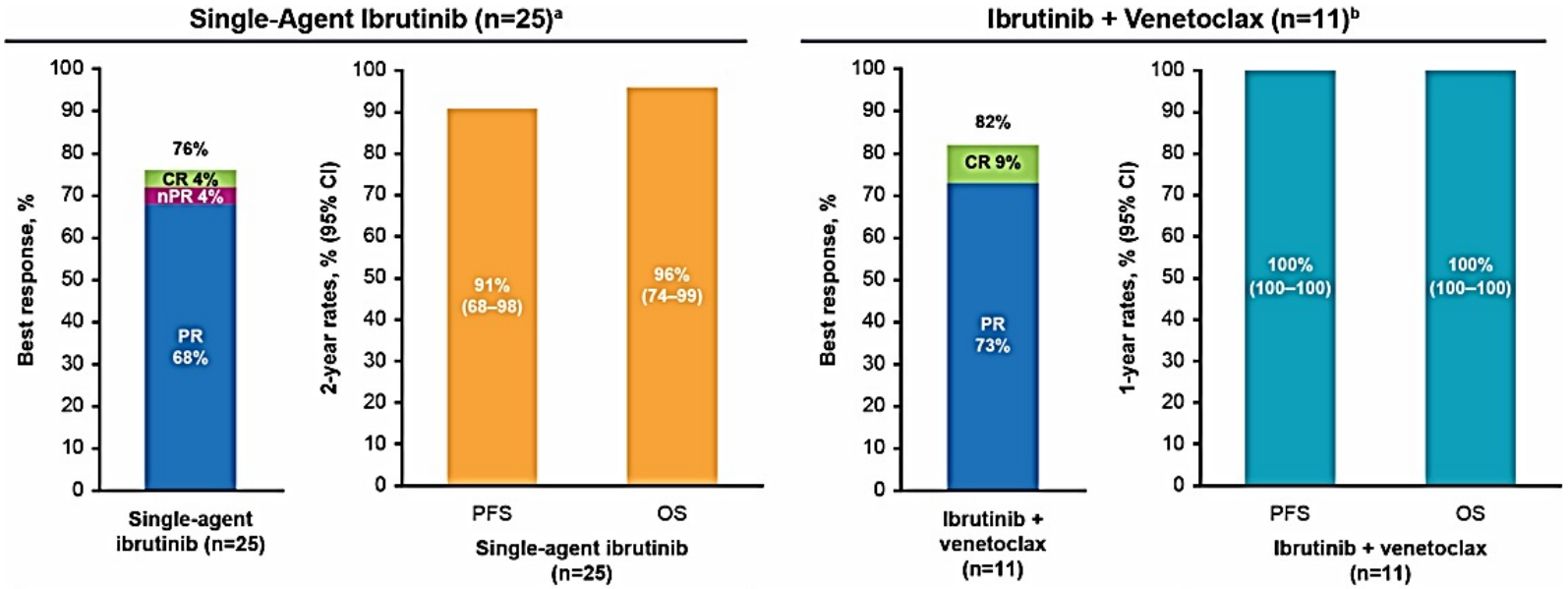
Less prolonged drug exposure = lower risk of mutations

Montoya S, Thompson MC. *Cancers.* 2023;15:3648. Blombery P et al. *Blood Adv*. 2022;6:5589-5592; Woyach J et al. *Blood.* 2024;144:1061-1068. Brown J et al. *Blood.* 2023;142 (suppl 1):1890. Jain et al. . Tausch E, et al. EHA 2021. Abstract S144 (Oral); 2. Tam CS, et al. Blood 2022; 139:3278–3289

CAPTIVATE-FD: RETREATMENT

No patients had resistance-associated mutations in *BTK* or *PLCG2* at PD among 53 patients with available samples

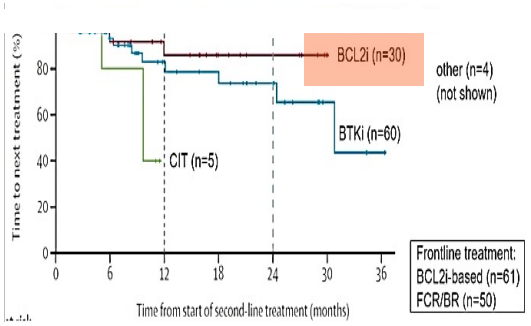
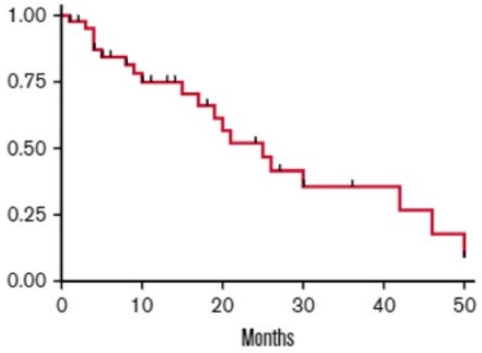
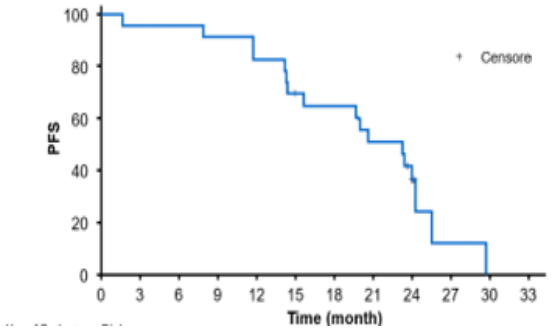
Two patients were found with a subclonal *BCL2 A113G* mutation of unclear significance at PD: variant allele frequencies were only 8% and 9.3%, respectively



	Single-agent ibrutinib	FD ibrutinib + venetoclax
Median duration of follow-up, months (range)	28.4 (3.7–59.1)	15.2 (7.4–29.3)
Median duration of retreatment, months (range)	27.0 (1.1–59.1)	13.8 (6.7–18.3)

Wierda et al., EHA 2025

≥2L venetoclax-based re-treatment

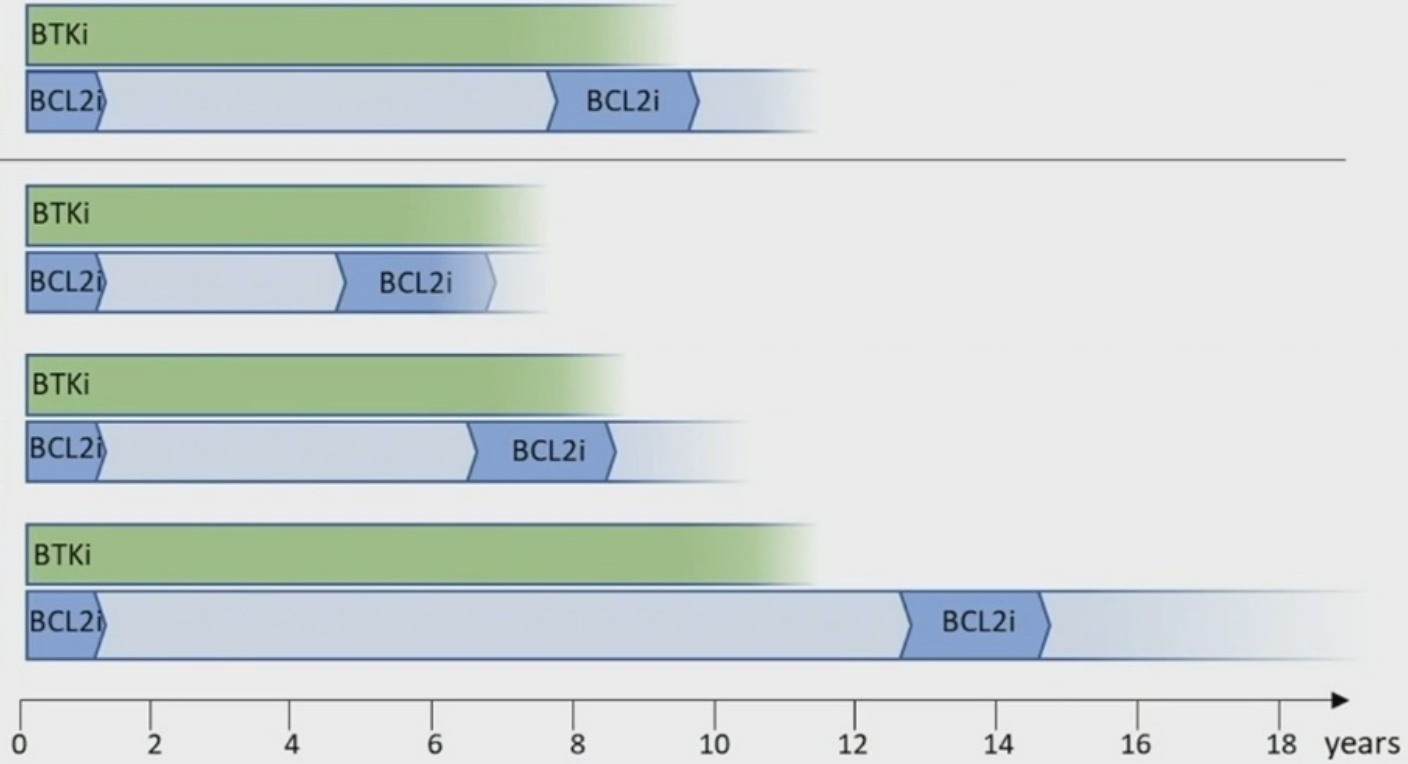
Venetoclax-based CLL13	Venetoclax-based RW retrospective	Venetoclax-Rituximab MURANO
Med. Prior treatments: 1	Med. Prior treatments: 2	Med. Prior treatments: ≥2 (CIT)
Ven-based: N=30	N=46	N=25
		
Ven-based Median-PFS: NR	Median PFSs: 25 mo. ORR2: 79.5% (ORR2 in BTKi-exp: 56%)	Median PFS: 23.3.mo. ORR2: 72% (uMRD: 32%)
Fursteneau et al. Lancet Oncol. 2024	Thompson et al. Blood Adv 2022	Kater et al. Blood 2025

Model: Overall Time to Treatment Class Failure of the two Paradigms

- Continuous BTKi (acalabrutinib, zanubrutinib, ibrutinib)

- Finite BCL2i-based (obinutuzumab + venetoclax, ibrutinib + venetoclax)

	Treatment Type	Approx. Median PFS1 [y]	Approx. Median TFS [y]	Approx. Median PFS2 [y]
All	BTKi	8 - 9	9 - 10	
	BCL2i	6 - 7	7 - 8	3 - 4
17p- *TP53*mut	BTKi	7 - 8	7 - 8	
	BCL2i	4 - 5	4 - 5	2 - 3
uIGHV	BTKi	7 - 8	8 - 9	
	BCL2i	5 - 6	6 - 7	3 - 4
mIGHV	BTKi	9 - 10	11 - 12	
	BCL2i	11 - 12	13 - 14	5 - 6



Tausch E. Schneider C. Stilgenbauer S. Risk-stratification in frontline CLL: standard of care; ASH Education Program 2024