Frontline Therapy of CLL in 2026

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Disclosure Information

Susan O'Brien, MD

I have the following financial relationships to disclose:

Sponsor/Company	Affiliation(s)
AbbVie	Consultant
Alliance	Research Support
AstraZeneca	Consultant
Autolus	Consultant
Beigene, Ltd.	Consultant
Bristol Myers Squibb	Consultant
Caribou Biosciences, Inc.	Research Support
Eli Lilly and Company	Consultant
Epizyme	Consultant
Janssen Oncology	Consultant
Johnson and Johnson	Consultant
Nurix Therapeutics	Research Support
Phamacyclics	Consultant
Kegeneron	Research Support

12 years of oral targeted Rx approval in CLL

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

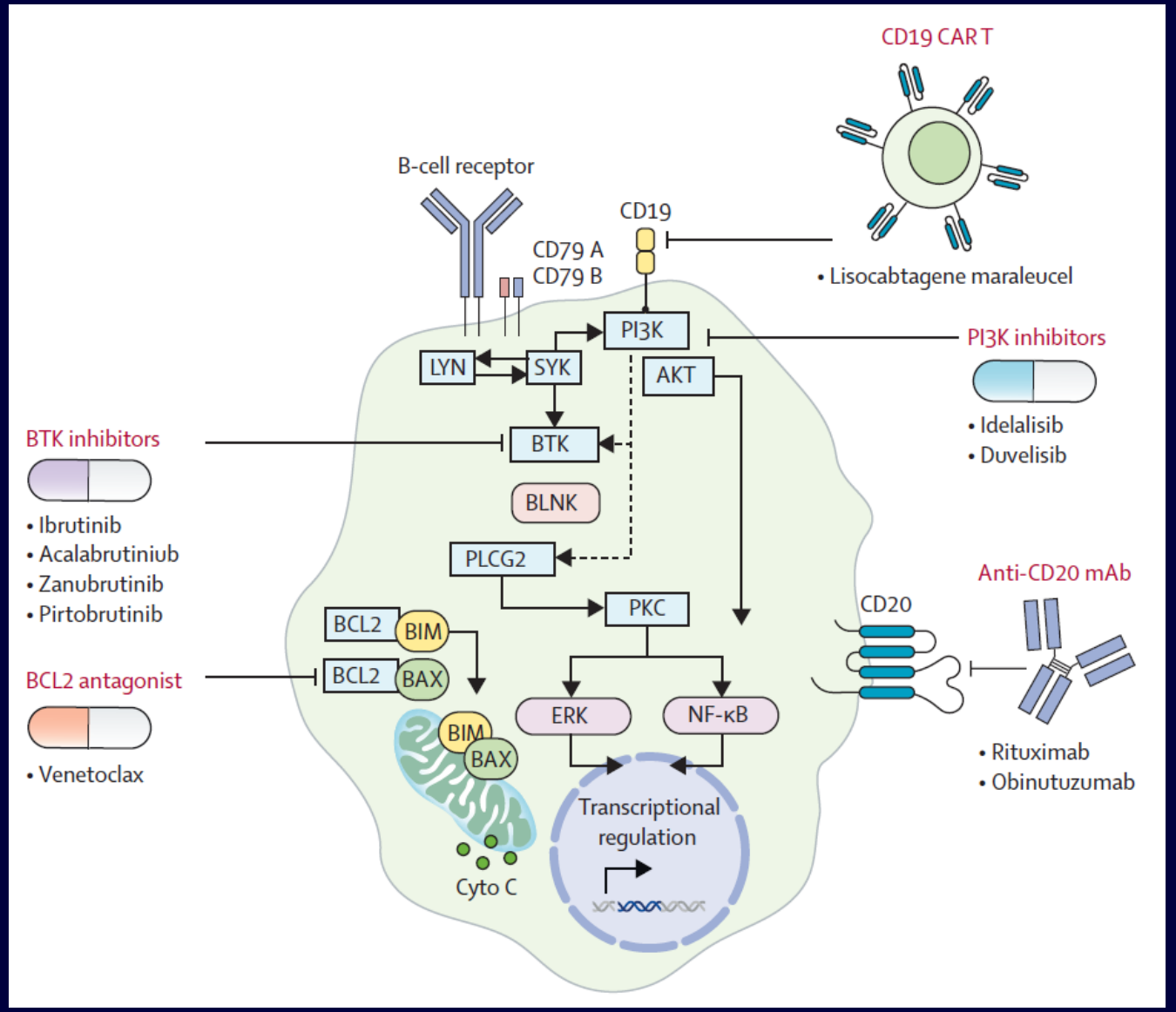
205552Orig2s000

Generic Name: Ibrutinib capsules, 140 mg

Approval Date: February 12, 2014

Indications: For the treatment of patients with Chronic Lymphocytic Leukemia (CLL) who have received at least one prior therapy.

CLL Therapy Armamentarium



Jain, Wierda, O'Brien. Lancet. 2024 Aug 17; 694-706.

Targeted Therapies in Frontline CLL

Indefinite

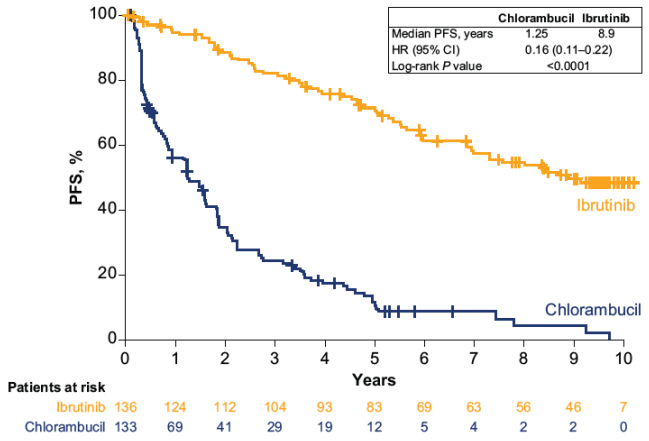
- Ibrutinib
- Acalabrutinib +/- obinutuzumab
- Zanubrutinib
- Pirtobrutinib likely coming

Time-limited

- 1 yr Ven + obinutuzumab
- 1 yr Ven + acalabrutinib
- 1 yr Ven + ibrutinib (approved ex-US)
- 1 yr Ven + acalabrutinib + obinutuzumab (NCCN guidelines)

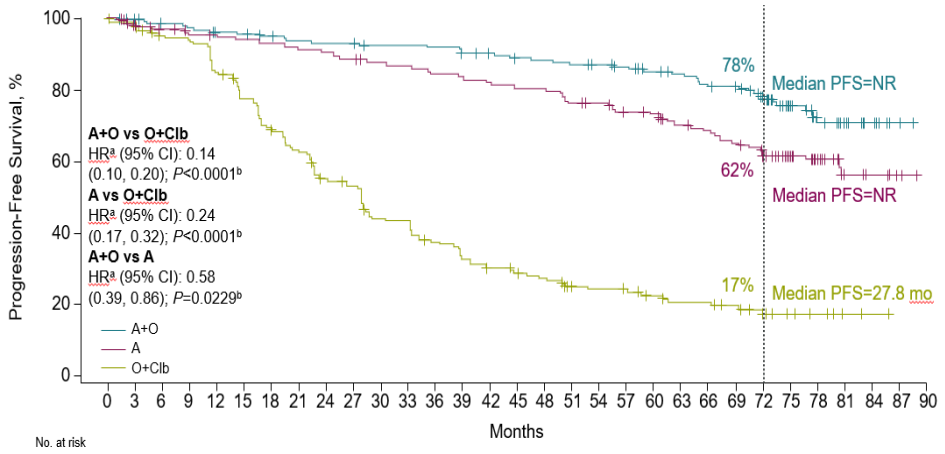
Firstline BTKi Phase 3 Trials

RESONATE-2



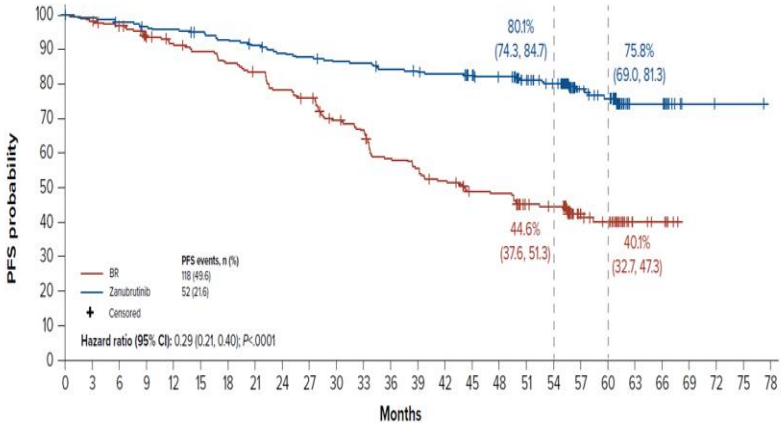
Burger et al. Blood. 2025 Jul 30

ELEVATE-TN



Sharman, ASH 2023

SEQUOIA

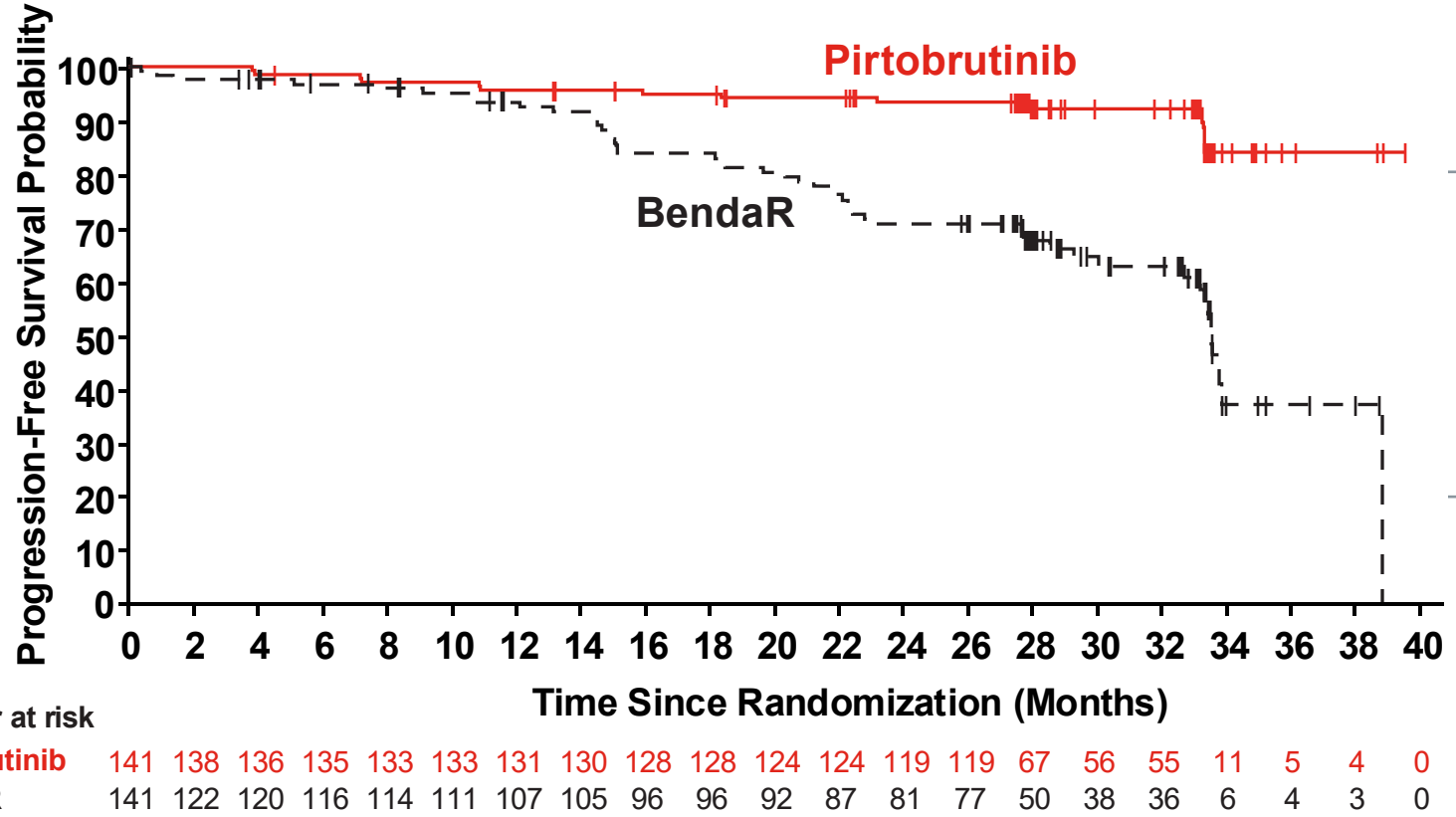


Shadman et al. J Clin Oncol. 2025

PFS for Continuous BTKi in Firstline CLL

		PFS	Time point
RESONATE 2	Ibrutinib	70%	5 years
ELEVATE TN	Acalabrutinib	72%	5 years
	Acalabrutinib + Obin	84%	5 years
SEQUOIA	Zanubrutinib	76%	5 years

Pirtobrutinib vs BR in Frontline CLL: Primary Endpoint: Progression-Free Survival



Number at risk

Pirtobrutinib	141	138	136	135	133	133	131	130	128	128	124	124	119	119	67	56	55	11	5	4	0
BendaR	141	122	120	116	114	111	107	105	96	96	92	87	81	77	50	38	36	6	4	3	0

	Pirtobrutinib (n=141)	BendaR (n=141)
Number of events, n (%)	13 (9.2)	48 (34.0)
24-month PFS rate, (95% CI)	**93.4** (87.6, 96.5)	**70.7** (61.5, 78.1)
Median follow-up, months	28.1	28.3
Hazard ratio (95% CI)	**0.20 (0.11, 0.37)**	
p-value[a]	<0.0001[a]	

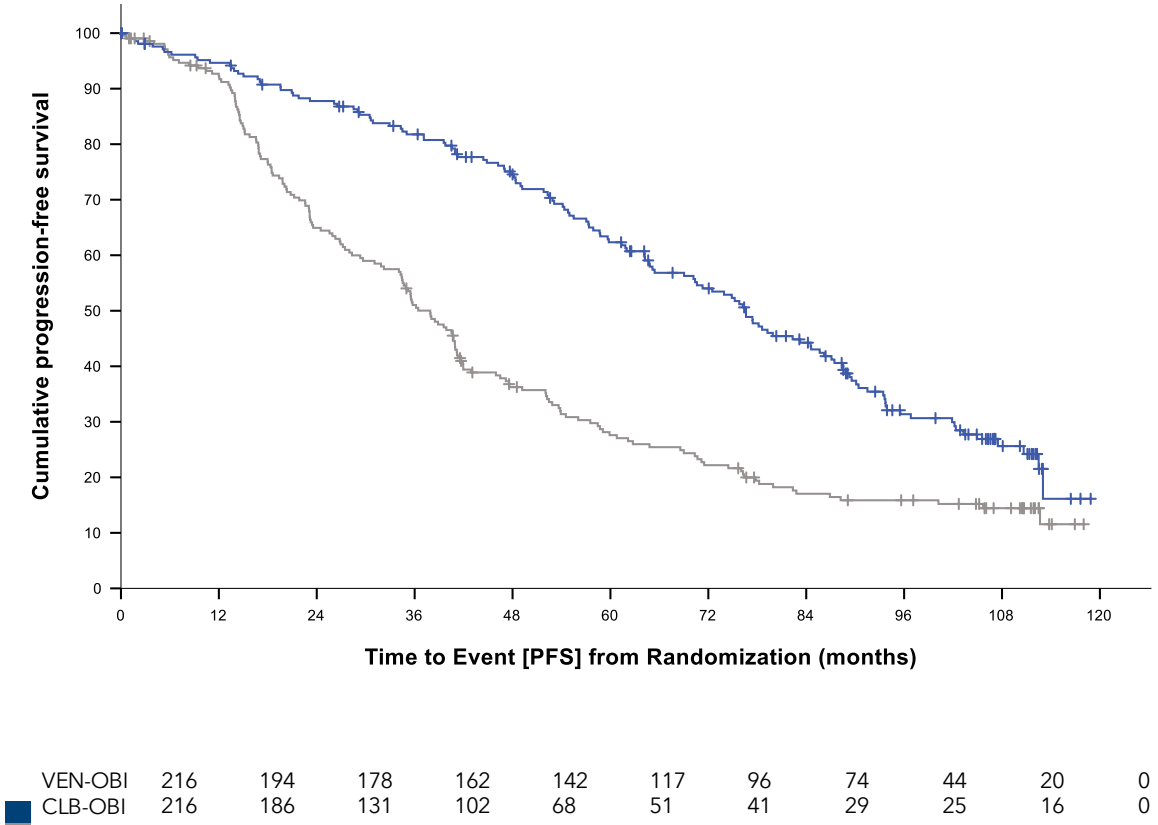
The PFS results presented are IRC assessed

Pirtobrutinib demonstrated a statistically significant and clinically meaningful PFS improvement, with an 80% reduction in risk of PD or death compared with BendaR

Wojciech et al ASH 2025

VENETOCLAX-OBINUTUZUMAB: FINAL ANALYSIS OF THE RANDOMIZED PHASE 3 CLL14 STUDY EHA 2026

Progression-Free Survival

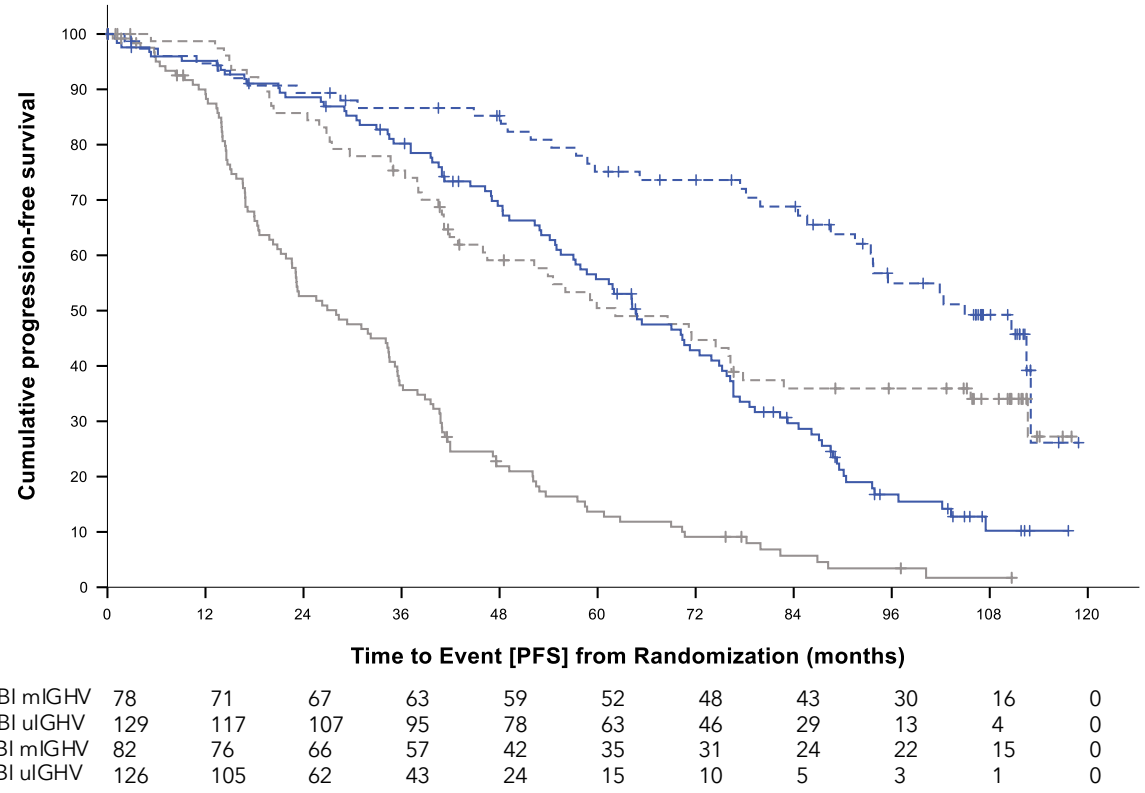


Fischer et al EHA 2026

MEDIAN OBSERVATION TIME	110.1 months
MEDIAN PFS VEN-OBI	76.6 months
9-YEAR PFS VEN-OBI	25.6%
MEDIAN PFS CLB-OBI	37.9 months
9-YEAR PFS CLB-OBI	14.4%
HAZARD RATIO	0.50, 95% CI 0.39-0.63
P VALUE	<0.001

MEDIAN PFS FOR VEN-OBI
6.4 YEARS

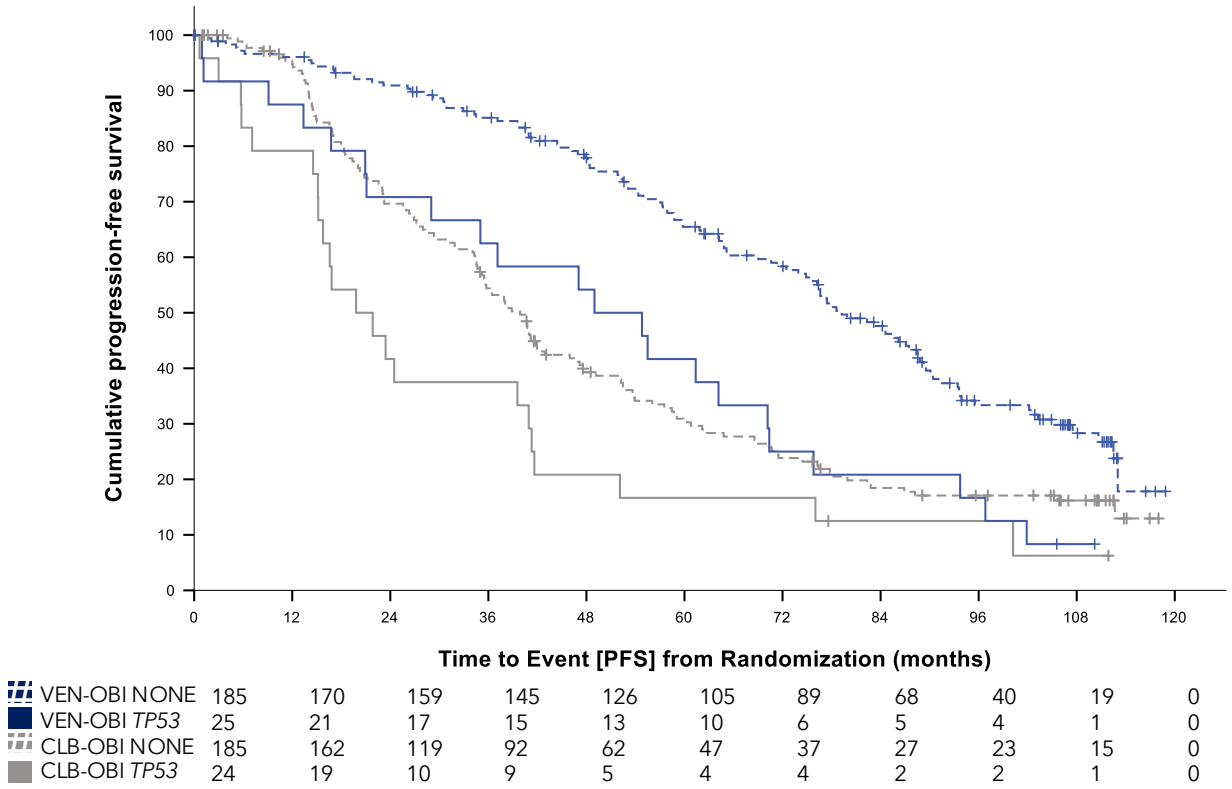
Progression-Free Survival By IGHV Mutational Status



MEDIAN OBSERVATION TIME	110.1 months
MEDIAN PFS VEN-OBI & mIGHV	104.9 months
MEDIAN PFS VEN-OBI & uIGHV	64.7 months
HAZARD RATIO	2.74, 95% CI 1.85-4.06
P VALUE	<0.001
MEDIAN PFS CLB-OBI & mIGHV	62.2 months
MEDIAN PFS CLB-OBI & uIGHV	28.0 months
HAZARD RATIO	3.13, 95% CI 2.21-4.45
P VALUE	<0.001

MEDIAN PFS VEN-OBI mIGHV 8.7 YEARS
MEDIAN PFS VEN-OBI uIGHV 5.4 YEARS

Progression-Free Survival By *TP53* Del/Mut



MEDIAN OBSERVATION TIME	110.1 months
MEDIAN PFS VEN-OBI & NONE	79.2 months
MEDIAN PFS VEN-OBI & *TP53*	49.0 months
HAZARD RATIO	2.15, 95% CI 1.36-3.40
P VALUE	=0.001
MEDIAN PFS CLB-OBI & NONE	39.9 months
MEDIAN PFS CLB-OBI & *TP53*	19.8 months
HAZARD RATIO	1.68, 95% CI 1.07-2.64
P VALUE	=0.024

MEDIAN PFS FOR VEN-OBI *TP53* 4.1 YEARS

Combined Ibrutinib and Venetoclax Treatment Schema

	C1	C2	C3	C4 --> 27 (24 cycles of Combined Rx)
Ibrutinib	**420mg daily**	**420mg daily**	**420mg daily**	**420mg daily**
Venetoclax	**-**	**-**	**-**	**20mg daily 1 week; 50mg daily 1 week; 100mg daily 1 week; 200mg daily 1 week; 400mg daily continuous**

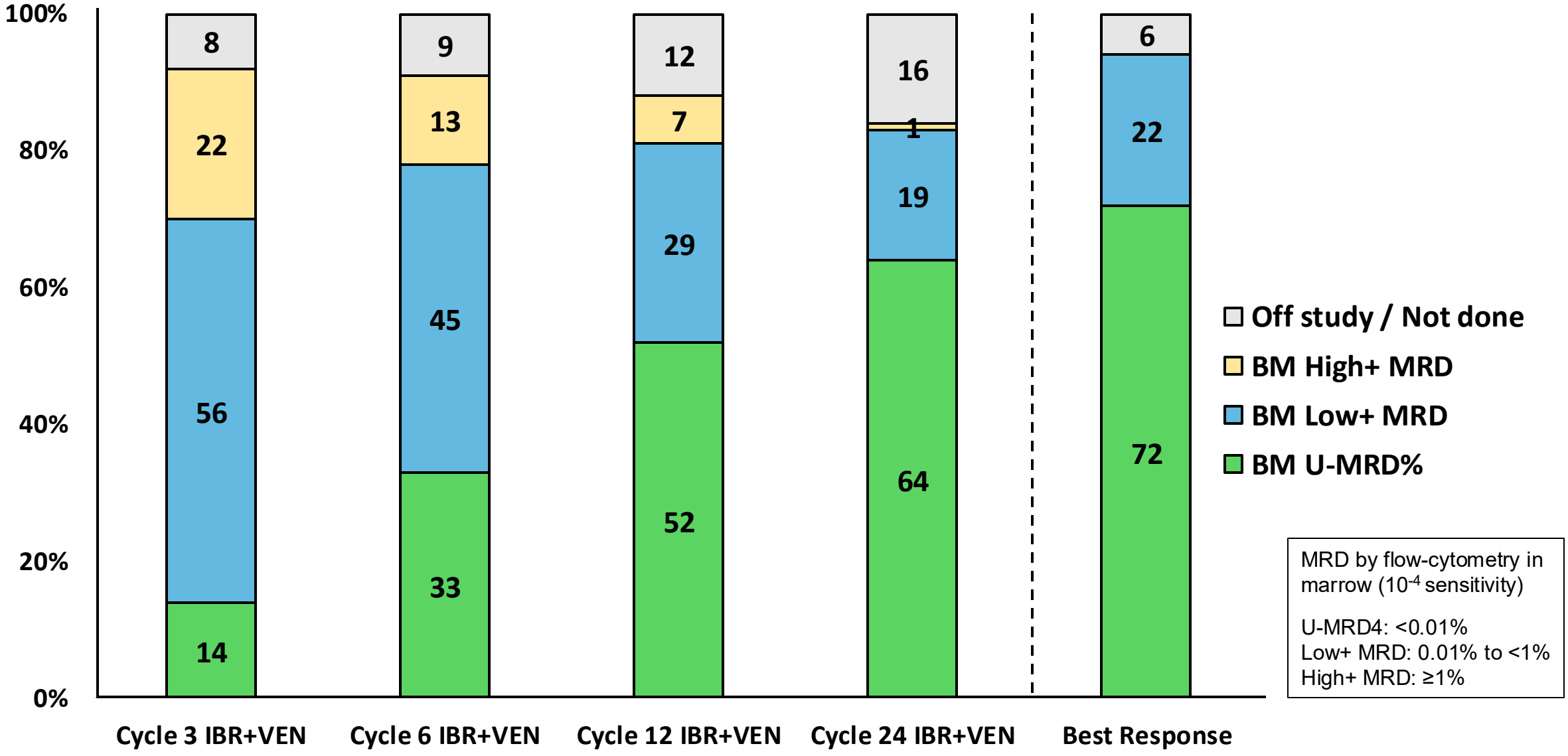
Duration of therapy: 24 cycles of combined IBR and VEN

Marrow MRD (flow cytometry) at end of cycle 24 of combined Rx

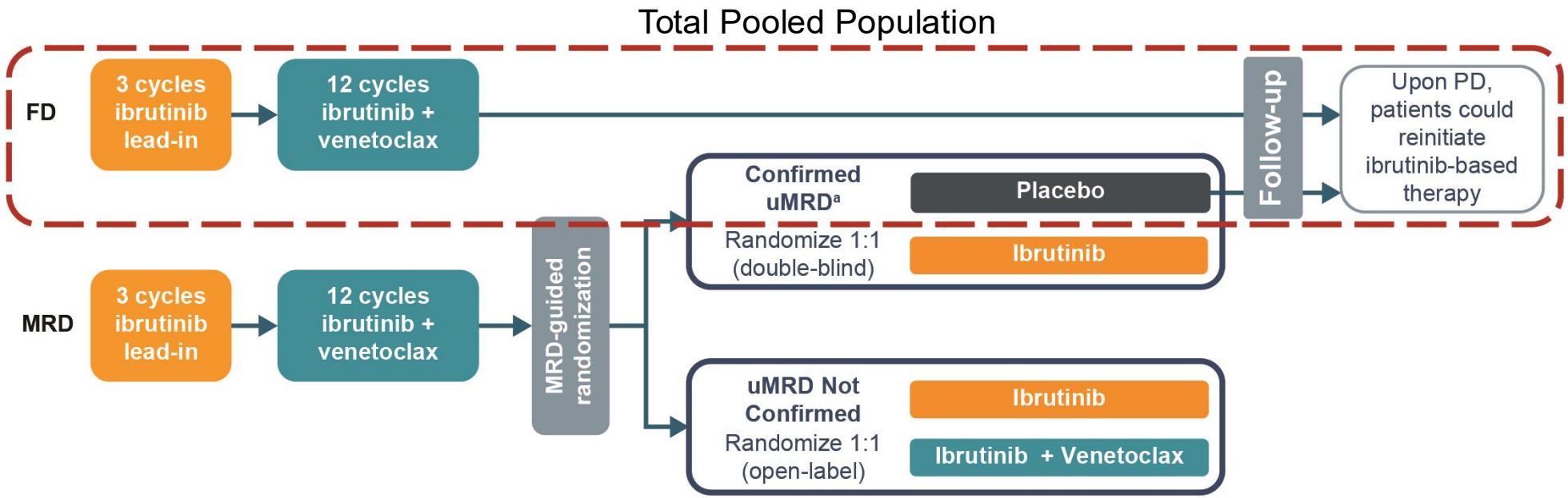
- Negative (<0.01%): Stop both IBR and VEN
- Positive (≥0.01%): Continue 12 additional cycles of IBR + VEN

Jain N et al. N Engl J Med. 2019 May 30;380(22):2095-2103.
Jain N et al. JAMA Oncol. 2021 Aug 1;7(8):1213-1219.

Marrow MRD Response at Serial Time-Points
Intent-to-Treat (N=120)



CAPTIVATE FINAL ANALYSIS EHA 2025: FD Cohort and MRD Cohort Placebo Arm



- Patients aged ≤70 years with previously untreated CLL/SLL received 3 cycles of ibrutinib, then 12 cycles of ibrutinib + venetoclax (ibrutinib, 420 mg/day orally; venetoclax, 5-week ramp up to 400 mg/day orally)
  - Patients in the FD cohort received no further treatment (n=159)
  - Patients in the MRD cohort placebo arm with confirmed uMRD4 (n=43) received 1 additional cycle of ibrutinib + venetoclax during the MRD-guided randomization, then placebo treatment
- In patients with confirmed PD, on-study retreatment included single-agent ibrutinib
  - FD cohort patients with PD occurring >2 years after EOT could be retreated with FD ibrutinib + venetoclax

[a]Patients with confirmed uMRD4 (defined as uMRD $<10^{-4}$ by 8-color flow cytometry serially over ≥3 cycles in both peripheral blood and bone marrow) after 12 cycles of ibrutinib + venetoclax were randomly assigned 1:1 to receive placebo or ibrutinib; the placebo arm was included in the current analysis.
EOT, end of treatment; PD, progressive disease; uMRD, undetectable minimal residual disease.

High Rate of uMRD With 12 Cycles of Combined Ibrutinib + Venetoclax

uMRD Rates With 12 Cycles of Combined Ibrutinib + Venetoclax

	Peripheral Blood n=163	Bone Marrow[a] n=155
Best response of undetectable MRD[1] in evaluable patients[b] (95% CI)	**75%** (69–82)	**72%** (65–79)

- In patients with uMRD in peripheral blood with matched bone marrow samples at Cycle 16, 93% had uMRD in both blood and bone marrow
- In all-treated patients (N=164), uMRD rate was 75% in peripheral blood and 68% in bone marrow

CI, confidence interval.
[a]BM MRD assessment was scheduled after completion of 12 cycles of combination treatment.
[b]Patients with undetectable MRD at any postbaseline assessment; evaluable patients are those who had at least 1 MRD sample taken postbaseline.

1. Siddiqi T et al. EHA 2020, Abstract #S158.

ASH 2020, CAPTIVATE-MRD; Wierda et al.

Flair FCR vs I vs I+V: Trial design

Patients with CLL requiring therapy by IWCLL Criteria (n=786)

R

F Oral Fludarabine (24mg/m²/day x 5 days; C1-6)
C Oral Cyclophosphamide (150mg/m²/days x 5 days; C1-6)
R Intravenous Rituximab (375mg/m² C1; 500mg/m²; C2-6)

6 monthly pb MRD until positive x3

n= 263

Max. 6 years

Ibrutinib (420mg/day)

n= 263

I+V given for 2 to 6 years

Venetoclax (400mg/day)

Ibrutinib (420mg/day)

n= 260

Primary objectives

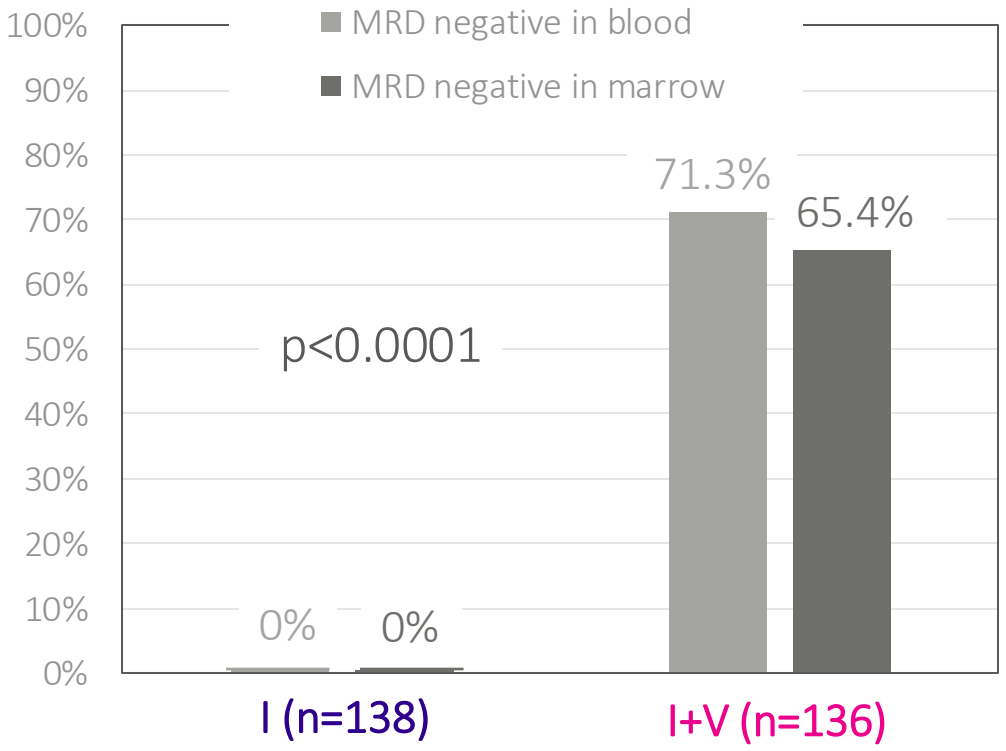
- *PFS: To assess whether I+V is superior to FCR*
- *MRD negativity: To assess whether I+V is superior to I*

Key Secondary objectives

- **PFS of I+V in comparison with I**
- **PFS of I in comparison with FCR**
- **Overall survival**
- Proportion of participants obtaining undetectable MRD
- IWCLL Response to therapy
- Safety and toxicity
- Health-related quality of life
- Cost-effectiveness

In ibrutinib and ibrutinib+venetoclax arms: PB MRD every 6 months. If PB MRD negative repeat after 3 months and then PB and BM at 6 months – if all MRD negative then first PB MRD negative result is time to MRD negativity.
Duration of therapy – double time to MRD negativity (minimum 2 years; maximum 6 years)

FLAIR PRIMARY END-POINT I VS I+V: MRD NEGATIVITY WITHIN 2 YEARS POST-RANDOMISATION



	Proportion (Percentage)|Exact 95% CI			
	I (n=138)		I+V (n=136)	
MRD Negative in the marrow	0 (0.0%)	[0.00%, 2.64%]	89 **(65.4%)**	[56.81%, 73.38%]
MRD Negative in the blood	0 (0.0%)	[0.00%, 2.64%]	97 **(71.3%)**	[62.95%, 78.75%]

- MRD assessed by 8-colour flow cytometry
- MRD negative defined by IWCLL criteria of <1 CLL cell in 10,000 leucocytes

National Cancer Research Institute

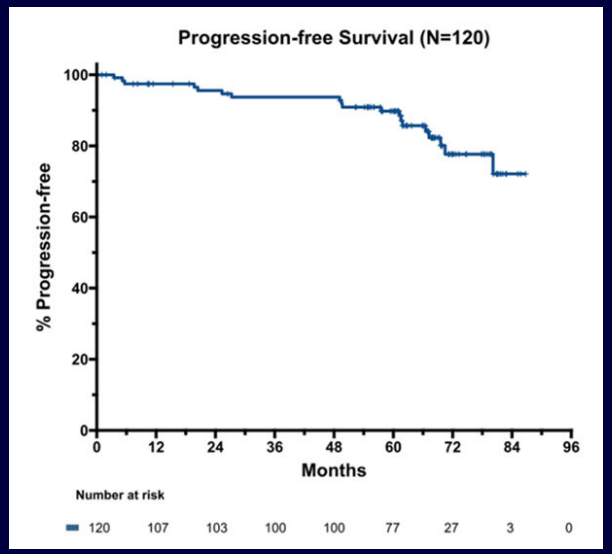
Data-lock: 2nd August 2021

Munir *et al.,* Abstract 94, ASH 2022

CANCER RESEARCH UK | ctru University of Leeds | LEEDS CLINICAL TRIALS UNIT

I + V Regimen Comparisons

MDACC, I+V 24 cycles

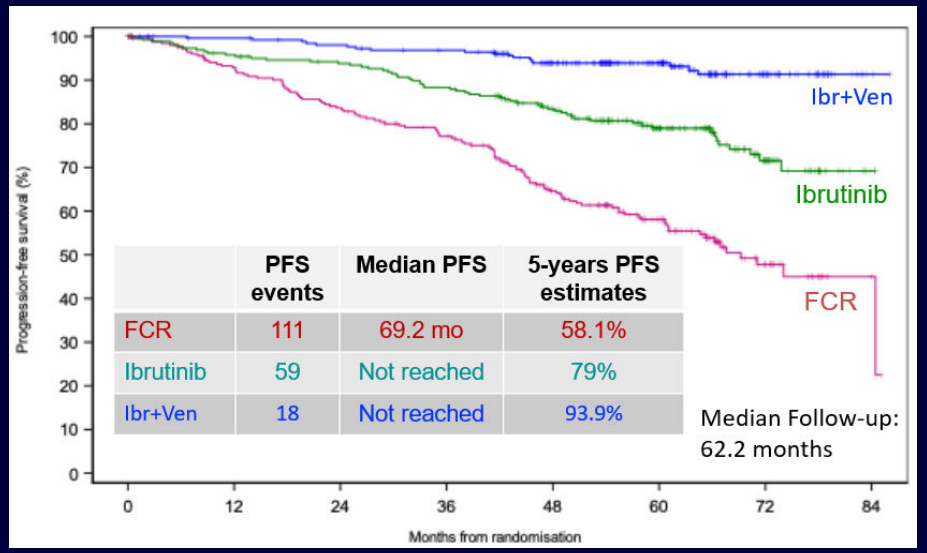


N=120
Median age = 64.5 yrs
IGHV-UM = 86%
Del(17p) / *TP53*-m = 23%

5 yr PFS = 89.8%

Jain, ASH 2023

FLAIR, UK, I+V 2-6 years



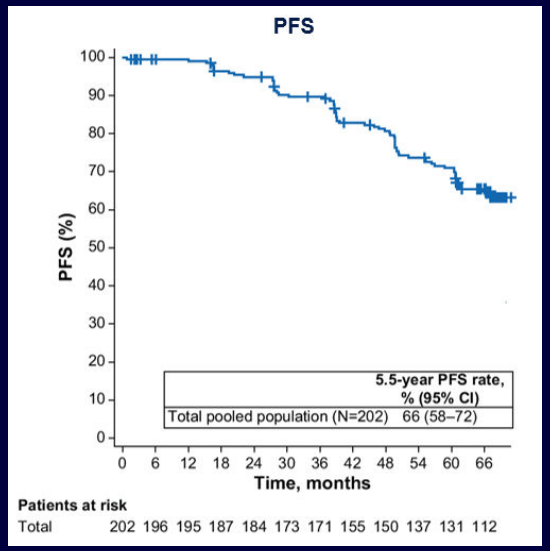
	PFS events	Median PFS	5-years PFS estimates
FCR	111	69.2 mo	58.1%
Ibrutinib	59	Not reached	79%
Ibr+Ven	18	Not reached	93.9%

N=260
Median age = 62 yrs
IGHV-UM = 48%
Del(17p) = excluded

5 yr PFS = 93.9%

Munir, EHA 2025

CAPTIVATE, I+V 12 cycles



N=202
Median age = 60 yrs
IGHV-UM = 59%
Del(17p) / *TP53*-m = 14%

5 yr PFS ≈ 70%

Wierda, EHA 2025

AMPLIFY Study Design

TN CLL (N=867)

Key inclusion criteria
- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria[1]
- 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

AMPLIFY: randomized, multicenter, open-label, Ph 3 trial

RANDOMIZE 1:1:1

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

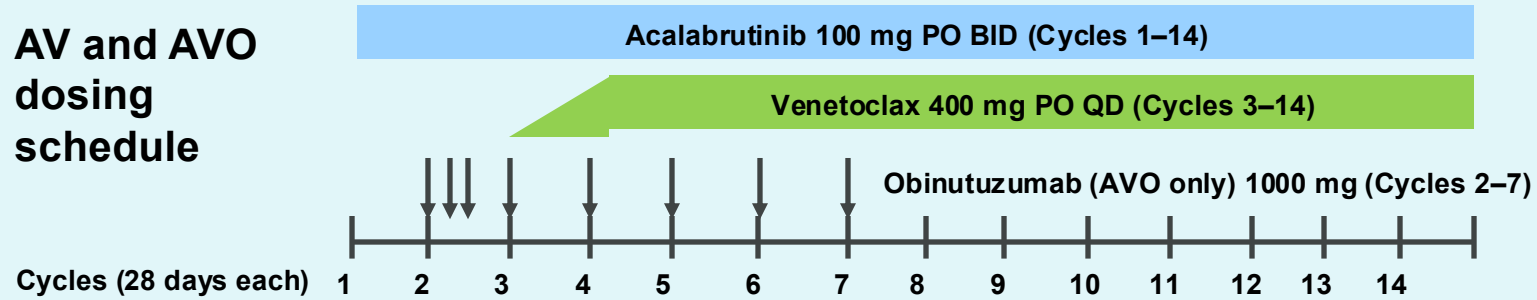
Crossover not built into protocol

Primary endpoint: IRC-assessed PFS (AV vs FCR/BR)

If primary endpoint met, secondary endpoints tested in fixed sequential hierarchy:

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

AV and AVO dosing schedule



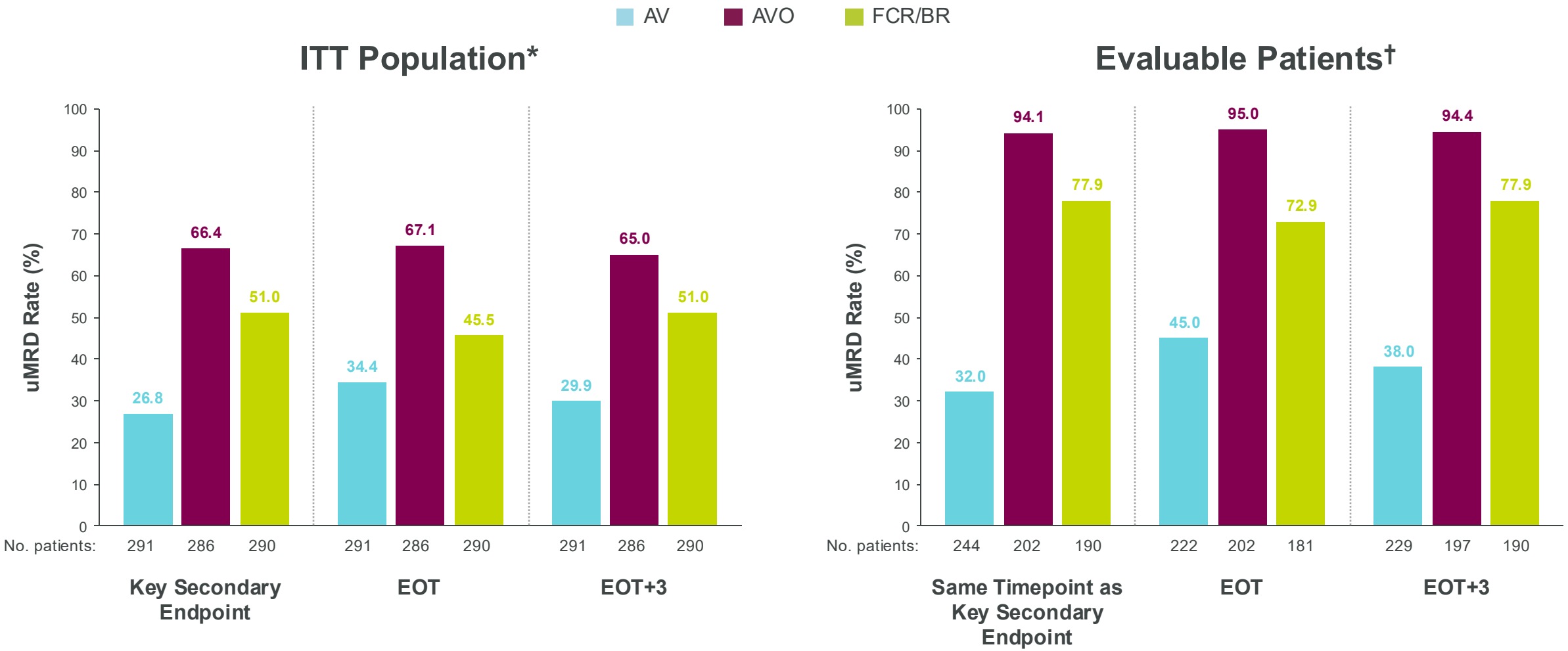
NCT03836261. Data cutoff: April 30, 2024.

[a]Assayed by central lab.

AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CIRS-Geriatric, Cumulative Illness Rating Scale-Geriatric; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine-cyclophosphamide-rituximab; IGHV, immunoglobulin heavy-chain variable region gene; iwCLL, International Working Group on CLL; OS, overall survival; PFS, progression-free survival; TN, treatment-naive; uMRD, undetectable measurable residual disease.

1. Hallek M, et al. *Blood.* 2018;131:2745-60.

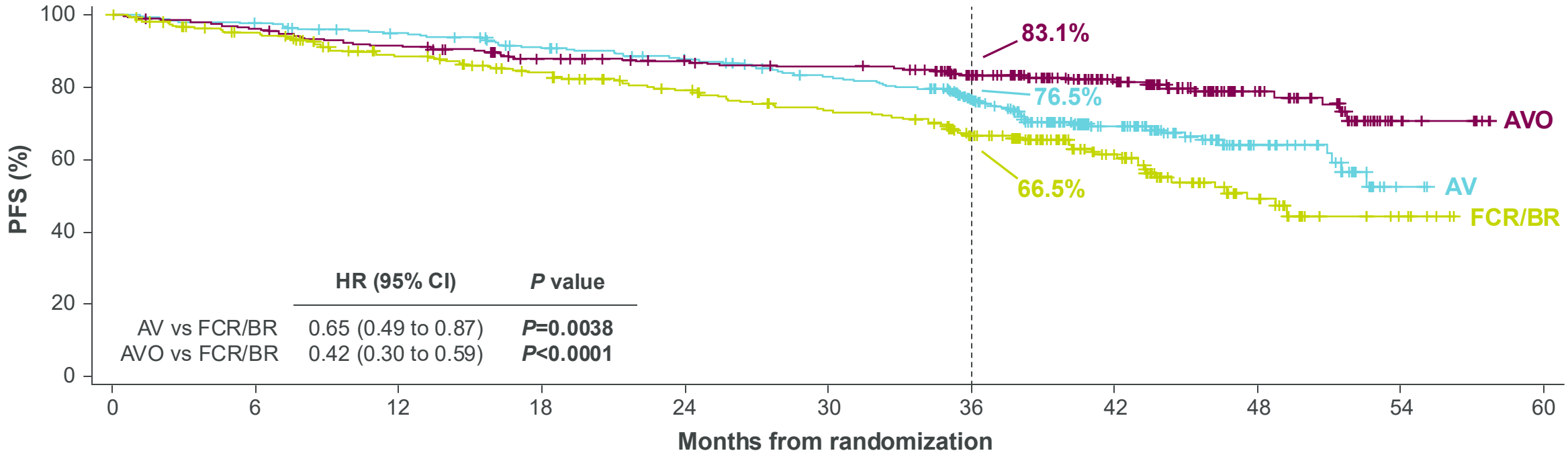
uMRD Rates (Flow Cytometry [<10^{-4}] in PB)



Key secondary endpoint timing: cycle 9, day 1 (AV arm), cycle 10, day 1 (AVO arm), and cycle 6, day 1 plus 12 weeks (FCR/BR)

Key secondary endpoint (ITT population): AV vs FCR/BR: *P*<0.0001 (favoring FCR/BR); AVO vs FCR/BR: *P*=0.0003 (favoring AVO).
*ITT population: all randomized patients regardless of whether MRD assessment was performed at the specified time point (missing assessments considered MRD+).
†Evaluable patients: those with MRD assessment at the specified timepoint.
EOT: cycle 14 day 28 for AV (± obinutuzumab); cycle 6 day 1 (±28-day window) (FCR/BR).
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; EOT, end of therapy; EOT+3, end of therapy plus 12 weeks; FCR, fludarabine-cyclophosphamide-rituximab; ITT, intent-to-treat; MRD+, detectable measurable residual disease; PB, peripheral blood; uMRD, undetectable measurable residual disease.

IRC-assessed PFS



Patients at risk

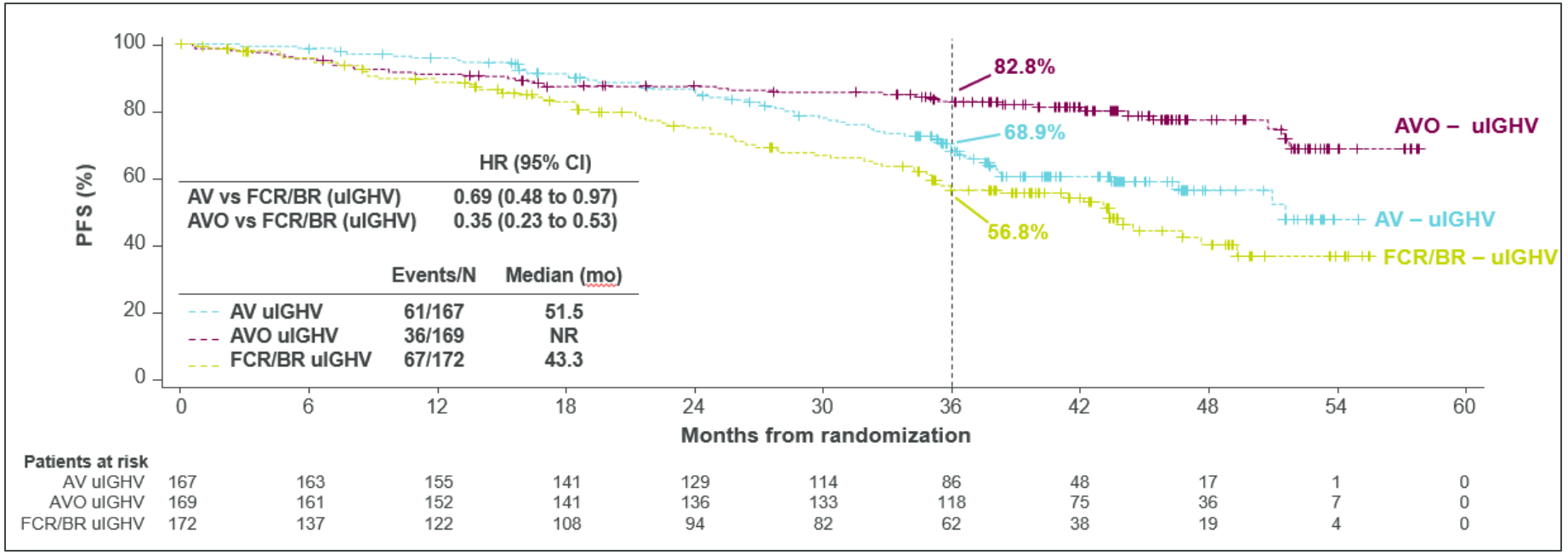
AV	291	282	269	251	237	219	177	102	35	3	0
AVO	286	272	258	237	225	219	191	116	51	7	0
FCR/BR	290	236	208	189	170	154	127	66	28	6	0

Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR

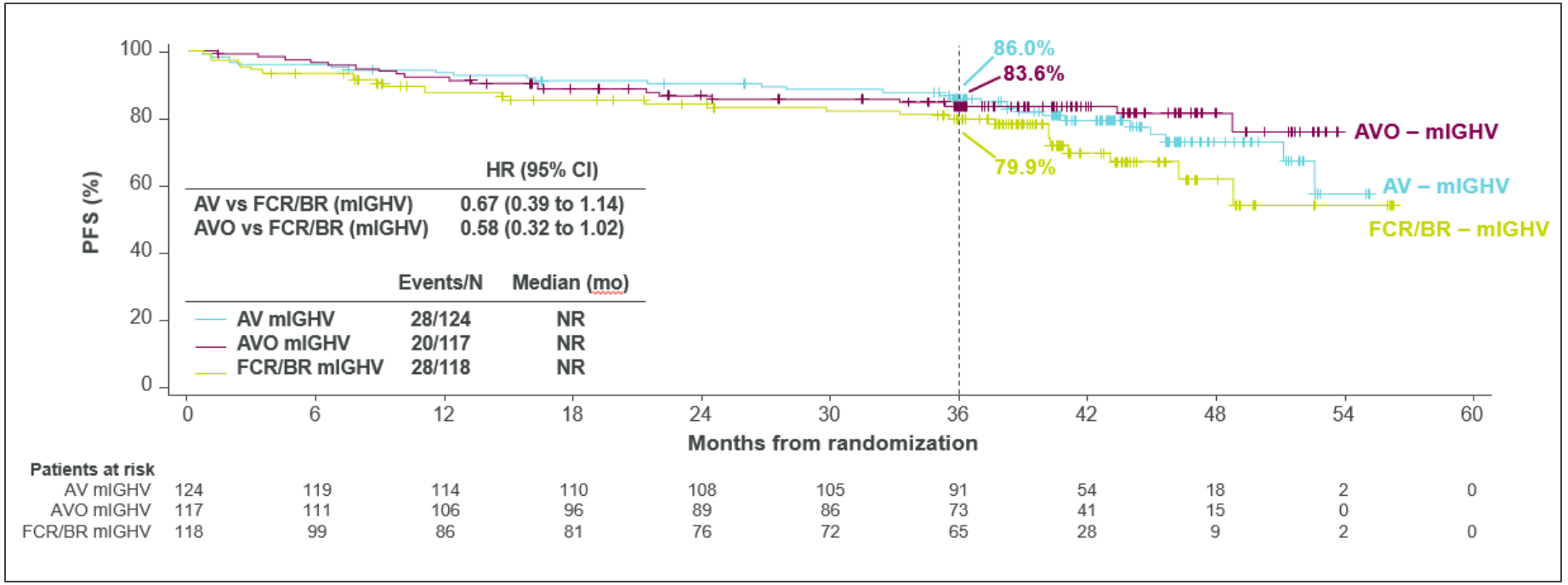
ITT population. Median follow-up from randomization: 40.8 months (range, 0–59 months).
Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; NR, not reached; PFS, progression-free survival.

PFS: AMPLIFY Trial

PFS in the uIGHV

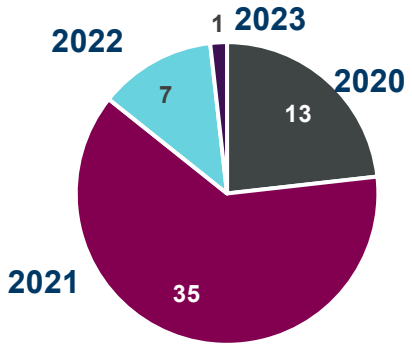


PFS in the mIGHV

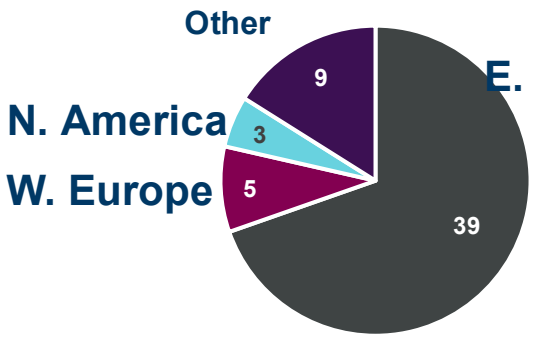


COVID-19 AEs, Treatment Discontinuations, and Deaths

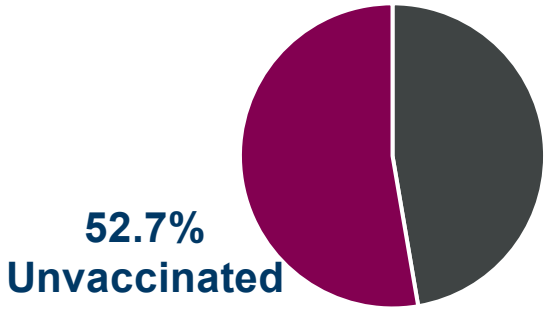
	AV (n=291)	AVO (n=284)	FCR/BR (n=259)
Any confirmed/suspected COVID-19 AE	64 (22.0)	69 (24.3)	10 (3.9)
Any confirmed/suspected COVID-19 AE leading to discontinuation of any treatment	7 (2.4)	23 (8.1)	3 (1.2)
Deaths due to COVID-19*	10 (3.4)	25 (8.7)	21 (7.2)



COVID-19 Deaths by Year



COVID-19 Deaths by Region



% COVID-19 Vaccinated

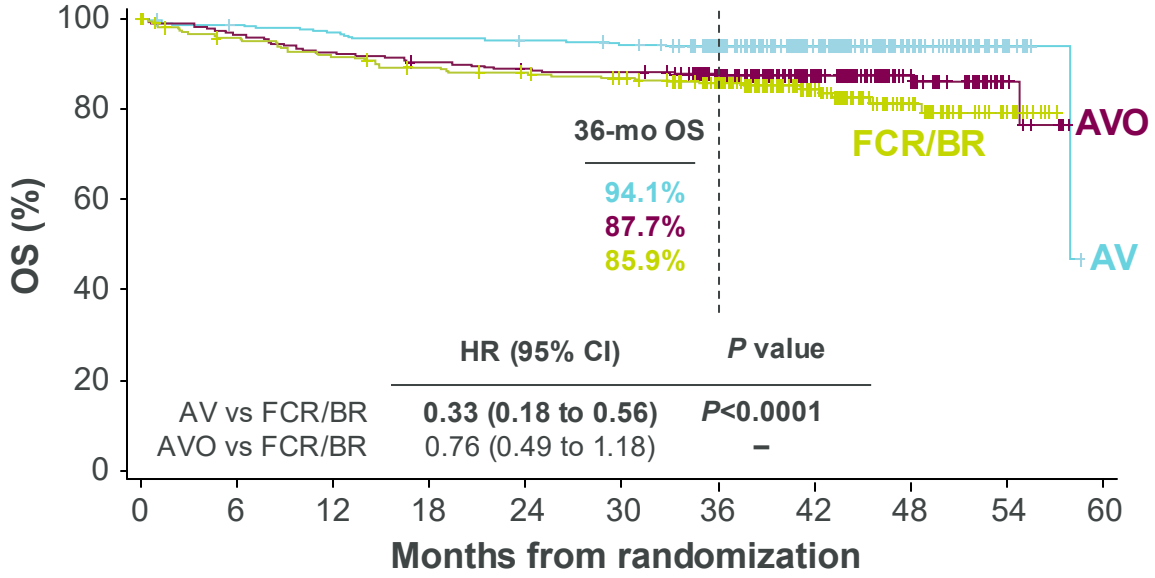
82% in 2020 or 1H2021

- Vaccination timing did not seem to differ by region

Data are n (%).
*Deaths due to COVID-19 are based on the ITT population (AV, n=291; AVO, n=286; FCR/BR, n=290).
AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; FCR, fludarabine-cyclophosphamide-rituximab.
AEs with an onset date or that worsened on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent anti-CLL therapy, whichever came first. Deaths included all deaths reported throughout the study.

Overall Survival

OS Prolonged With AV vs FCR/BR



Patients at risk

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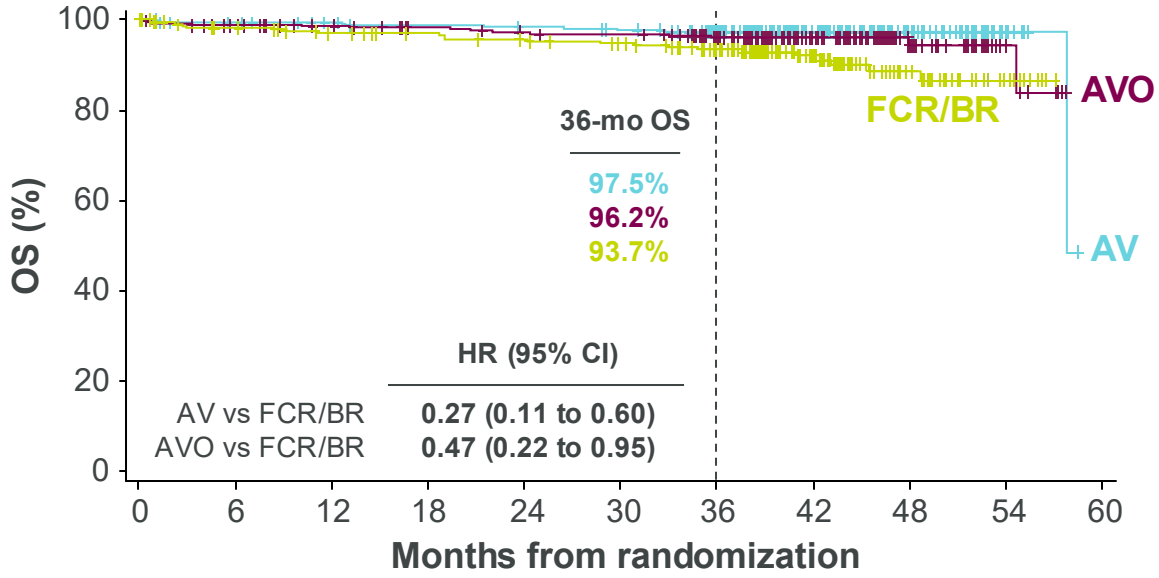
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

OS Prolonged With AV and AVO vs FCR/BR (COVID-19 Deaths Censored)



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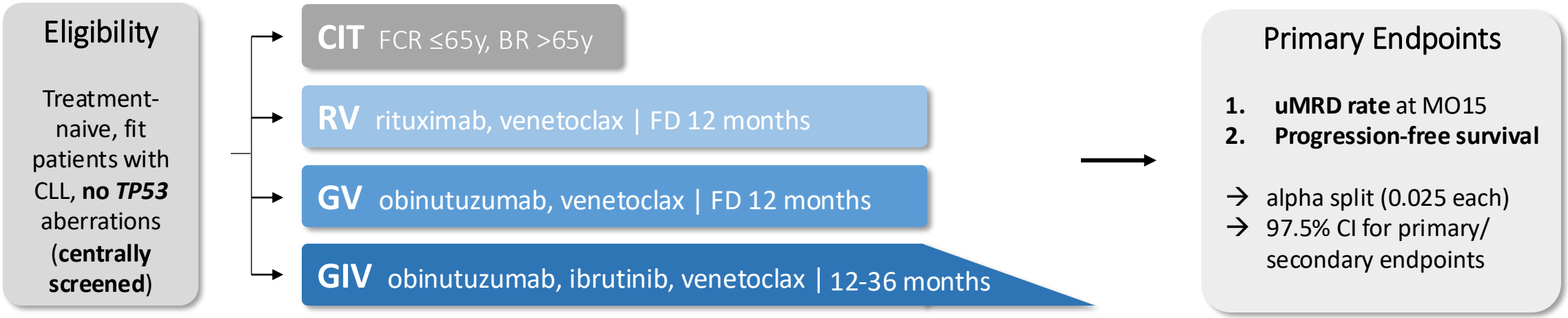
AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

COVID-19 deaths: 10 (AV), 25 (AVO), 21 (FCR/BR)

ITT population.
Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

Study Design - GAIA/CLL13



Key patient characteristics

Randomized patients (=ITT population): **n= 926**

Median age:	**61 years** (range: 27-84)
Median CIRS score:	**2** (range: 0-7)
Unmutated IGHV:	**56%** of all patients
Complex karyotype:	**17%** of all patients

Follow-up analysis (data cut-off: 01/2023)

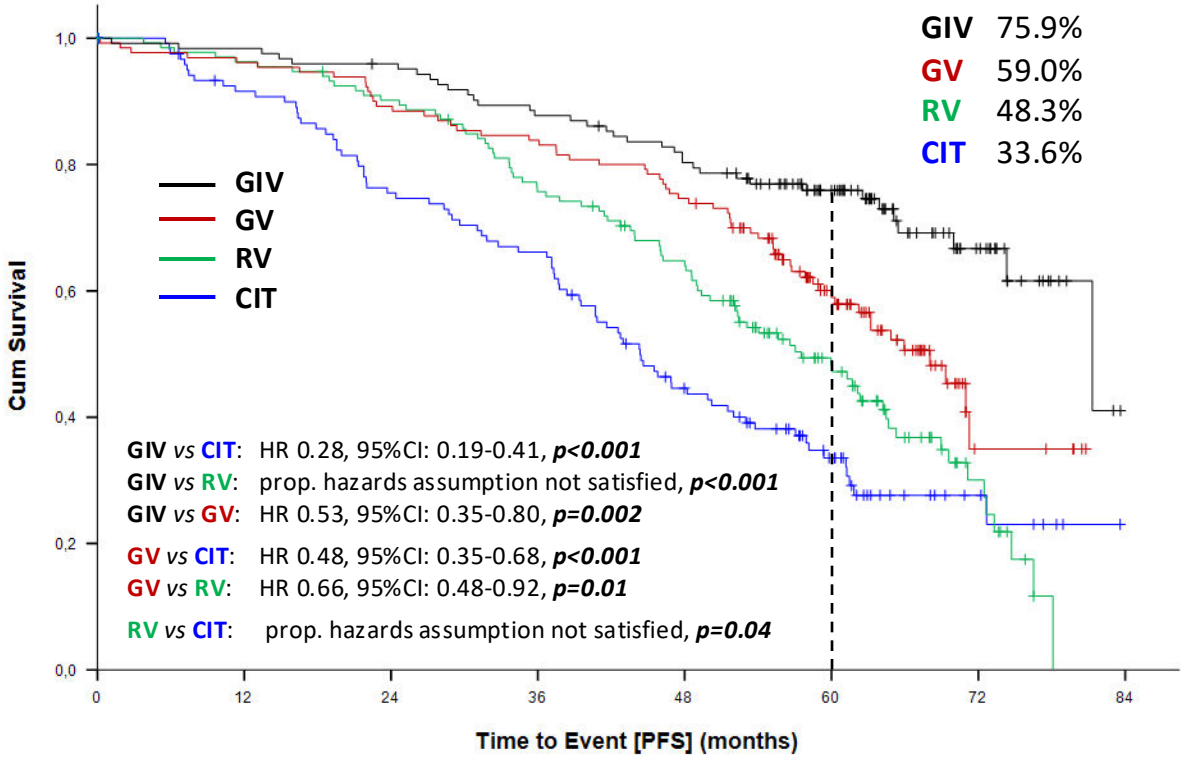
Median observation time
50.7 months (IQR: 44.6-57.9)

Median observation time after end of treatment
40.7 months (IQR: 34.5-47.9)

Furstenau et al EHA 2025

GAIA/CLL13: Efficacy – PFS

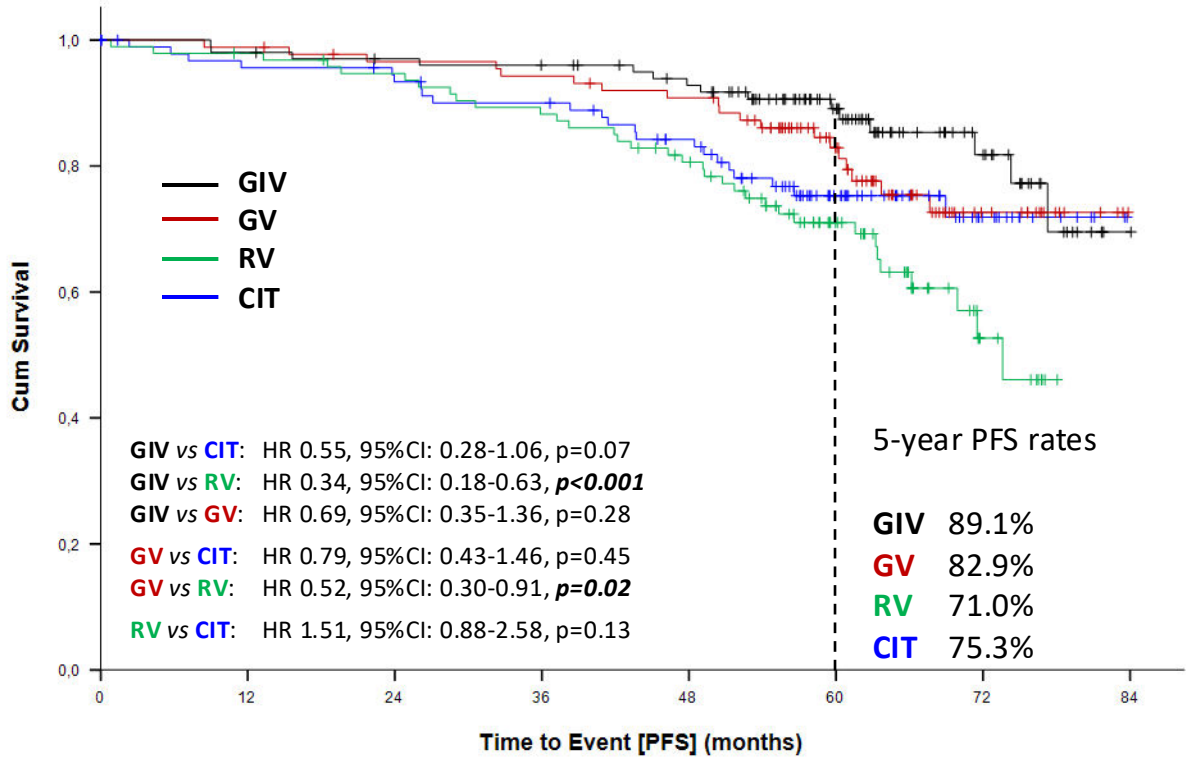
PFS – unmutated IGHV



Patients at risk

CIT	131	108	89	78	49	27	7
RV	134	128	119	99	82	44	11
GV	130	125	116	109	97	54	5
GIV	123	121	117	107	97	67	21

PFS – mutated IGHV



Patients at risk

CIT	95	87	84	80	70	40	14
RV	95	92	88	82	72	42	9
GV	89	88	84	82	78	49	15
GIV	101	99	96	94	87	57	23

Addition of obinutuzumab after one year of combined acalabrutinib and venetoclax is safer and effective than early obinutuzumab in a randomized phase II trial for treatment naïve CLL

Mahesh Swaminathan, *Philip A. Thompson, Jan A. Burger, Musa Yilmaz, Nitin Jain, Tapan M. Kadia, Lucia Masarova, Yesid Alvarado Valero, Prithviraj Bose, Alessandra Ferrajoli, Ghayas C. Issa, Steven M. Kornblau, Farhad Ravandi, Koji Sasaki, Gautam Borthakur, Kelly S. Chien, Courtney D. DiNardo, Danielle Hammond, Elias Jabbour, Guillermo Montalban-Bravo, Naveen Pemmaraju, Nicholas J. Short, Koichi Takahashi, Wei Qiao, Xu Xun, Naveen Garg, Michael J. Keating, William G Wierda.*

University of Texas MD Anderson Cancer Center

ASH 2025

Responses in ITT Population

Responses	ACA+VEN (n=42)	ACA+VEN+OBIN (n=42)	Odds ratio [95% CI]	p-value
	n (%)			
BM uMRD4				
End of C9	6 (14)	26 (62)	9.75 [3.48-28.99]	<0.0001
End of C14	11 (26)	30 (71)	7.04 [2.62-17.47]	<0.0001
End of C20	37 (88)	32 (76)	0.43 [0.15-1.39]	0.254
End of C26	35 (83)	30 (71)	0.60 [0.22-1.72]	0.420
CR/CRi				
End of C9	15 (36)	14 (33)	0.90 [0.38-2.10]	1.000
End of C14	21 (50)	19 (45)	0.82 [0.34-1.95]	0.827
End of C20	24 (57)	23 (55)	0.91 [0.37-2.17]	1.000
End of C26	31 (74)	27 (64)	0.64 [0.24-1.56]	0.479
Late Obin	**33 (78)**	9 (21)	-	-

AEs in ITT Population: C1-14

Adverse Events	ACA+VEN (n=42)		ACA+VEN+OBIN (n=42)		p-value	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
	Cycles 1-14					
	No. of patients (%)					
Non-hematological AEs						
Diarrhea	34 (81)	1 (2)	25 (60)	1 (2)	0.055	1.000
Headache	26 (62)	0	18 (43)	0	0.126	-
Nausea	22 (52)	0	16 (38)	0	0.273	-
Infections	16 (38)	2 (5)	27 (64)	11 (26)	0.029	0.013
Arthralgias	15 (36)	0	16 (38)	0	1.000	-
Dizziness	9 (21)	0	16 (38)	0	0.152	-
ALT elevation	7 (17)	2 (5)	11 (26)	1 (2)	0.426	1.000
Cough	4 (10)	0	13 (31)	0	0.028	-
Fever	3 (7)	0	14 (33)	0	0.006	-
Non-melanoma cancers	2 (5)	2 (5)	7 (17)	5 (12)	0.156	0.433
Hematological AEs						
Thrombocytopenia	26 (62)	3 (7)	37 (88)	11 (26)	0.011	0.038
Neutropenia	21 (50)	10 (24)	30 (71)	22 (52)	0.073	0.013
Anemia	18 (43)	0	25 (60)	0	0.190	-

AEs + Efficacy: C1-26

Adverse Events and BM uMRD4	ACA+VEN+LATE OBIN (n=33)		ACA+VEN+EARLY OBIN (n=33)		p-value	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
	No. of patients (%)					
BM uMRD4 at C26	29 (88)		24 (73)		0.215	
Non-hematological AEs						
Headache	17 (51)	0	12 (36)	0	0.321	-
Diarrhea	20 (61)	1 (3)	16 (48)	1 (3)	0.489	1.000
Nausea	14 (42)	0	11 (33)	0	0.612	-
Arthralgias	13 (39)	0	8 (24)	0	0.290	-
Infections	16 (48)	1 (3)	17 (51)	11 (33)	1.000	0.003
Dizziness	7 (21)	0	11 (33)	0	0.407	-
Cough	6 (18)	0	11 (33)	0	0.260	-
Fever	3 (9)	1 (3)	11 (33)	0	0.033	1.000
IRR	3 (9)	0	8 (24)	2 (6)	0.185	0.492
Hematological AEs						
Thrombocytopenia	27 (82)	7 (21)	30 (91)	10 (30)	0.475	0.574
Anemia	13 (39)	1 (3)	20 (61)	0	0.139	1.000
Bruising	18 (54)	0	15 (45)	1 (3)	0.623	1.000
Neutropenia	18 (54)	9 (27)	26 (79)	18 (54)	0.066	0.044

Conclusions. Frontline CLL

- Continuous cBTKi therapy results in long remissions, 5 year PFS 70-76%, PFS better with addition of Obinutuzumab, 84% . Better OS?
- Pirtobrutinib, the ncBTKi, may get a frontline indication, where to use?
- VenG is first fixed duration therapy given for 1 year with excellent outcomes. 3 yr PFS 82%. Median PFS 6.4 years, almost 9 years in mutated, but shorter PFS in unmutated and P53 aberrant
- Acalabrutinib and Venetoclax is first oral combination one year therapy with lower uMRD rates (then VenG or IV); 3 year PFS 69%
- Triplets: IVO, AVO appear more efficacious but more toxic, where to use? Delay the O and use especially in fit unmutated?