LESSONS LEARNED FROM PHASE 2+3 TRIALS

QUESTIONS STILL TO BE ANSWERED

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DISCLOSURE INFORMATION

SUSAN O'BRIEN, MD

I have the following financial relationships to disclose:

Sponsor/Company	Affiliation(s)
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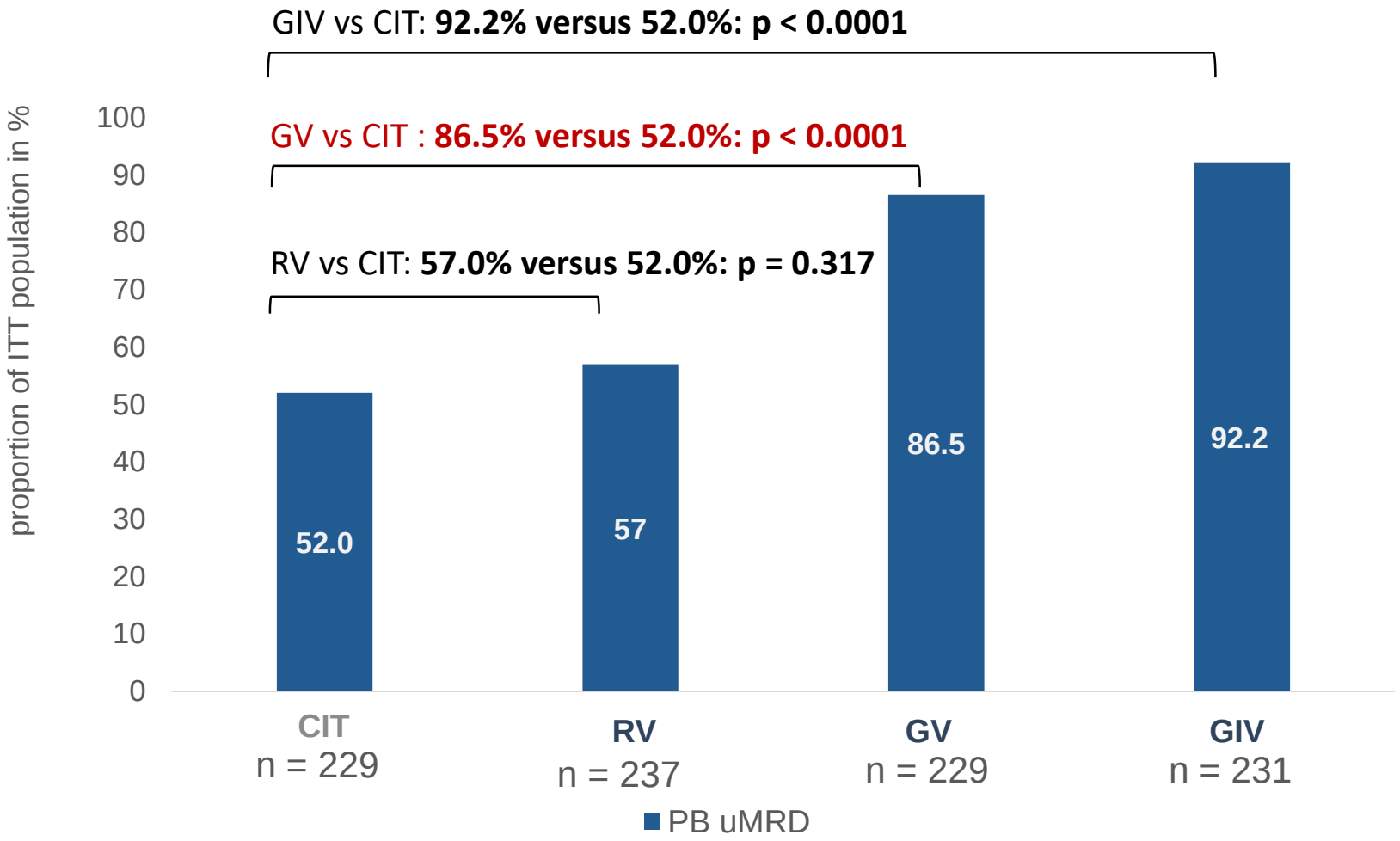
Updated August 2021

QUESTION 1:
WILL COMBINATION SMALL MOLECULES BE BETTER THAN VENG?

GAIA/CLL 4 ARM RANDOMIZED TRIAL: RESULTS OF COPRIMARY ENDPOINT RATE OF UNDETECTABLE MINIMAL RESIDUAL DISEASE (uMRD)

Coprimary endpoint: uMRD (< 10^{-4}) at Mo15 in PB by 4-colour-flow

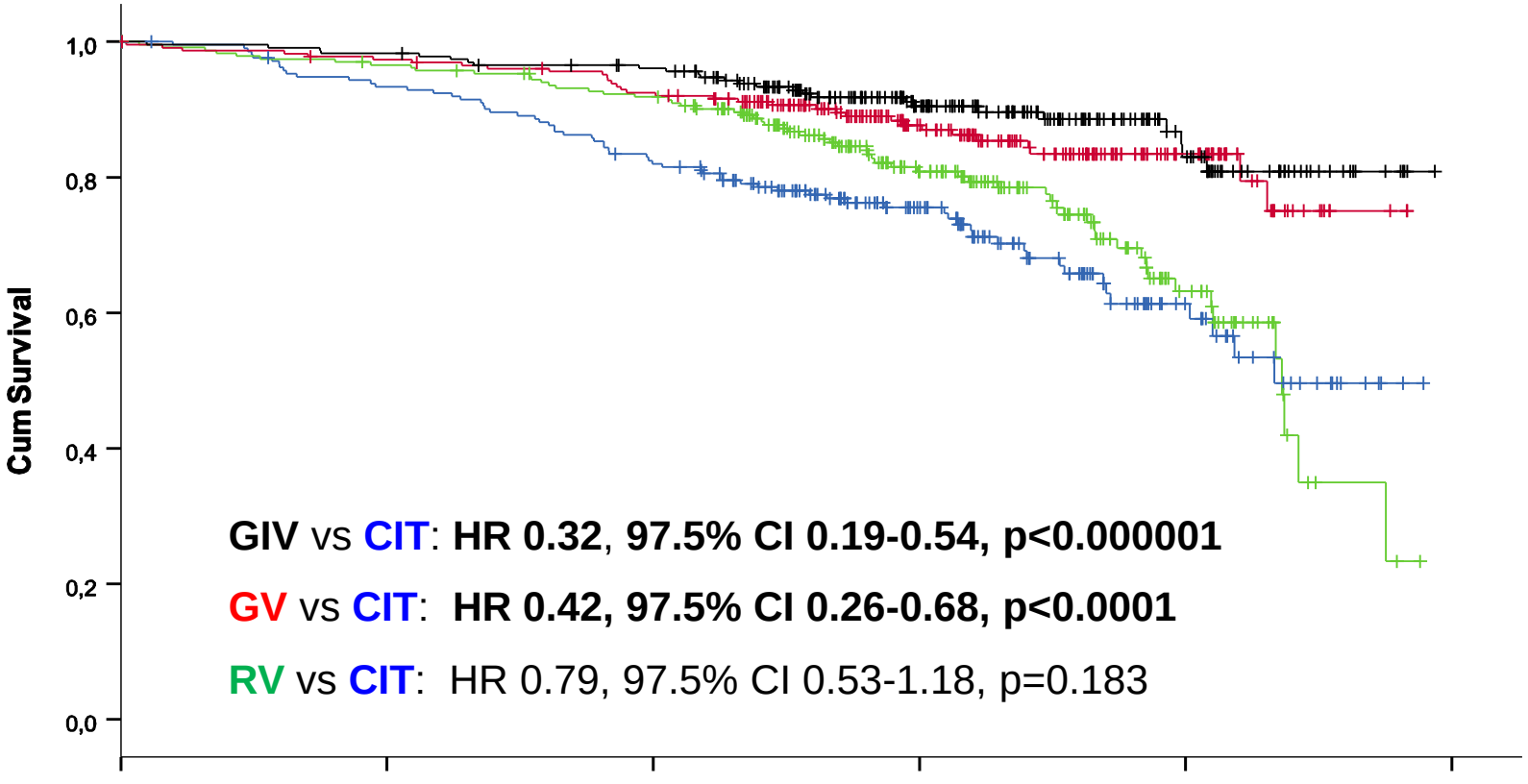


	uMRD%	97.5% CI
GIV	92.2	87.3 – 95.7
GV	86.5	80.6 – 91.1
RV	57.0	49.5 – 64.2
CIT	52.0	44.4 – 59.5

Eichhorst B. et al., ASH 2021: Abstract 72

RESULTS OF THE COPRIMARY ENDPOINT PROGRESSION-FREE SURVIVAL (PFS)

Median FU 38.8 months (range: 0.0 – 59.2)



CIT	229	197	172	98	28
RV	237	226	212	119	32
GV	229	221	208	125	42
GIV	231	227	217	132	44

PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	Not reached	87.7
GIV	Not reached	90.5

EVEN IF I+V IS NOT BETTER THEN VenG THE LACK OF A CD20 MONOCLONAL ANTIBODY MIGHT BE ATTRACTIVE

QUESTION 2:
WILL ANTIBODY ADD ANYTHING TO SMALL MOLECULE COMBINATIONS?

IBRUTINIB + VENETOCLAX: TREATMENT SCHEMA

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**

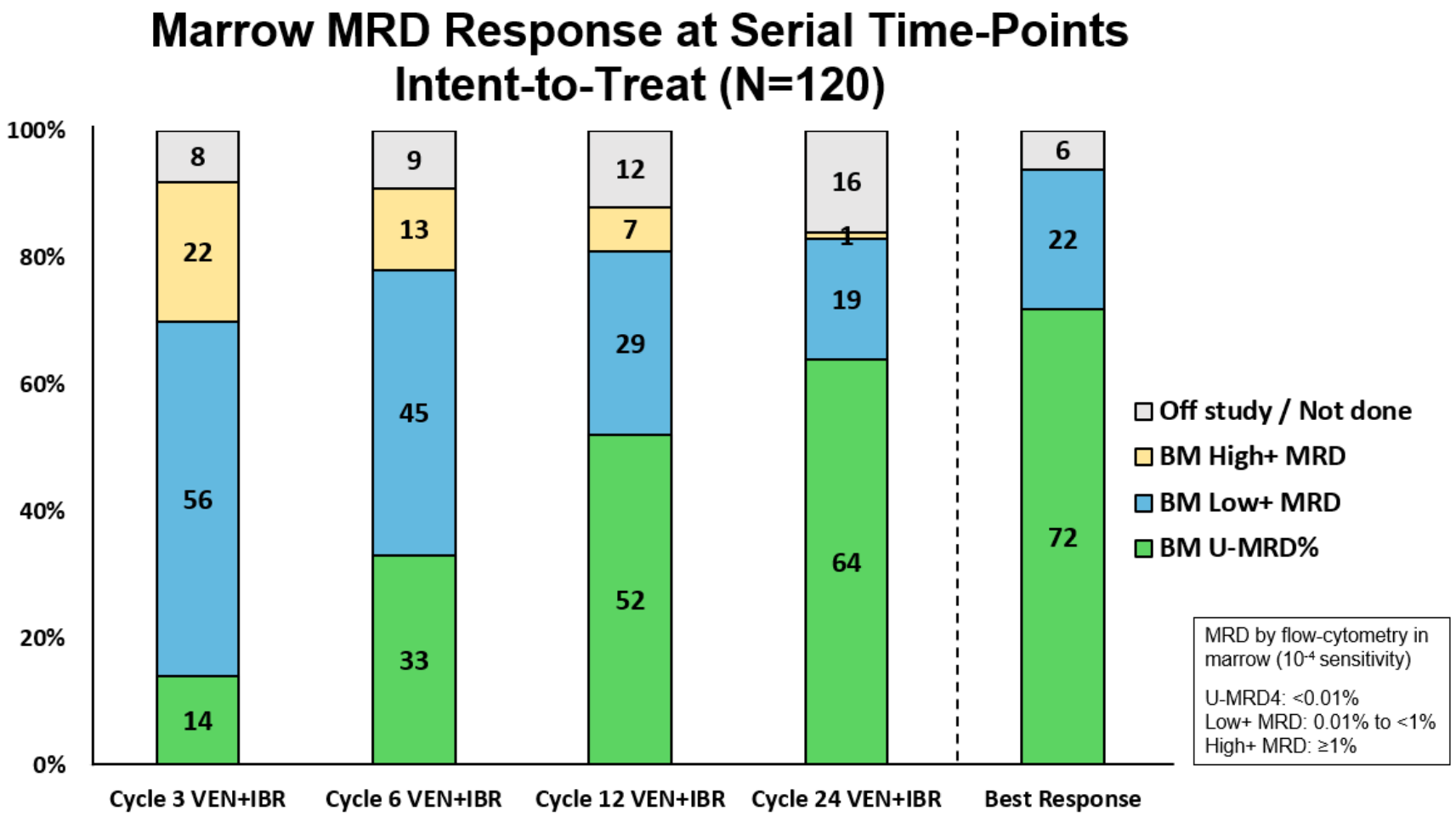
Duration of therapy: 24 cycles of combination treatment

- If BM MRD+ at 24 cycles, ibrutinib alone until PD

Protocol Amendment: up to 36 combination cycles allowed; as before, if still MRD + continue ibrutinib

Jain et al ASH 2019, Abs 34

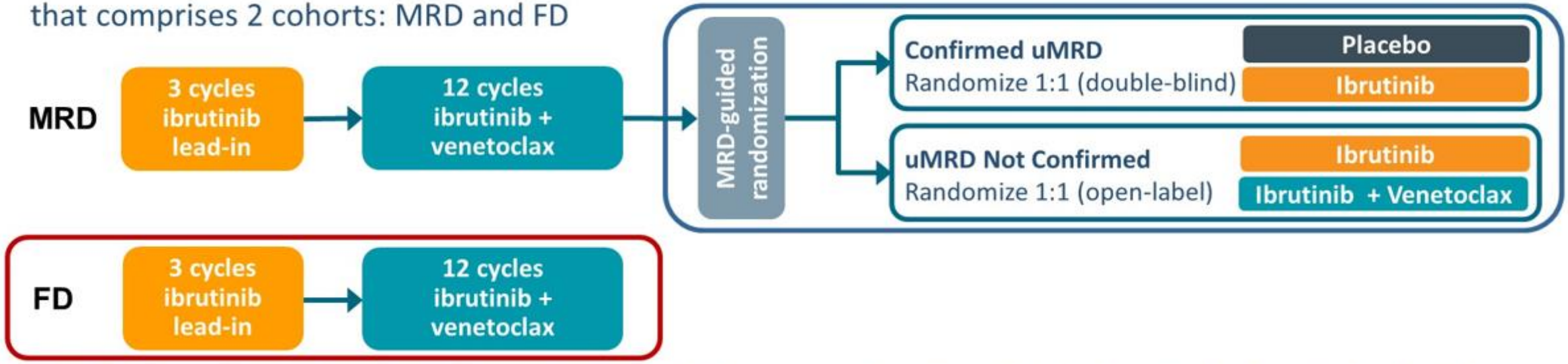
MARROW MRD RESPONSE



Jain et al ASH 2021

PHASE 2 CAPTIVATE STUDY

- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD



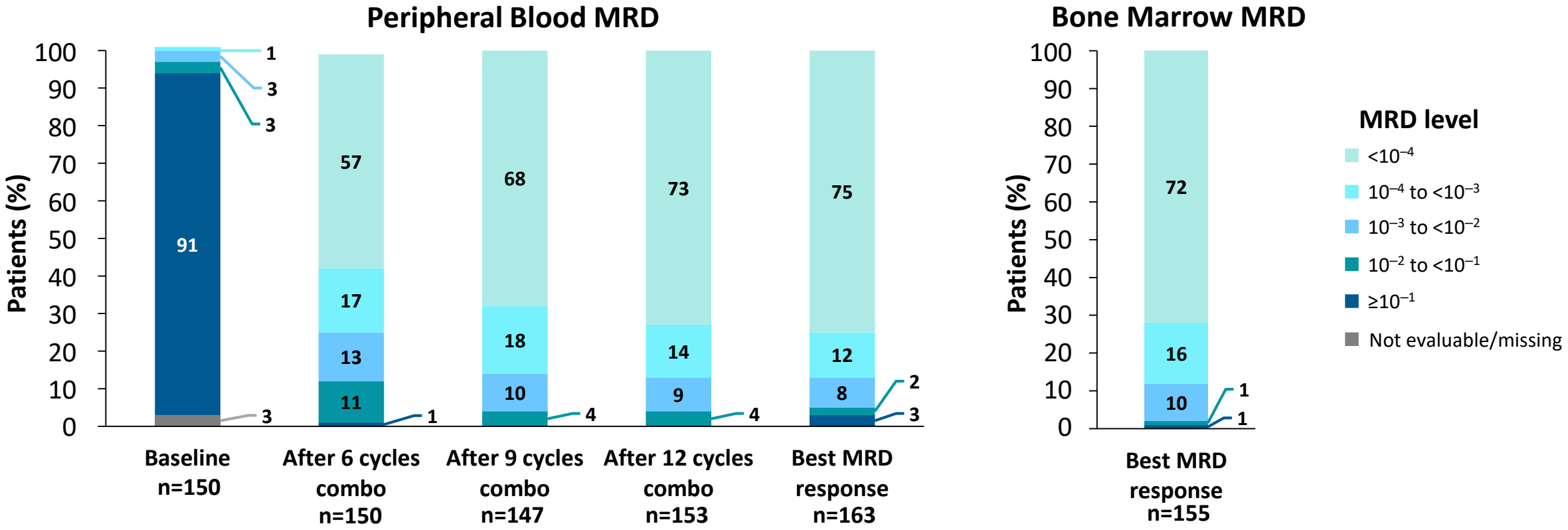
- Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients treated with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment[1]
- Primary analysis results from the FD cohort of CAPTIVATE are presented

BM, bone marrow; MRD, minimal residual disease; FD, fixed-duration; PB, peripheral blood; PFS, progression-free survival.

1. Wierda WG et al. ASH 2020, Abstract #123.

ASCO 2021, CAPTIVATE-FD; Ghia et al.

CAPTIVATE: A PHASE 2 STUDY OF IBRUTINIB + VENETOCLAX IN 1L CLL

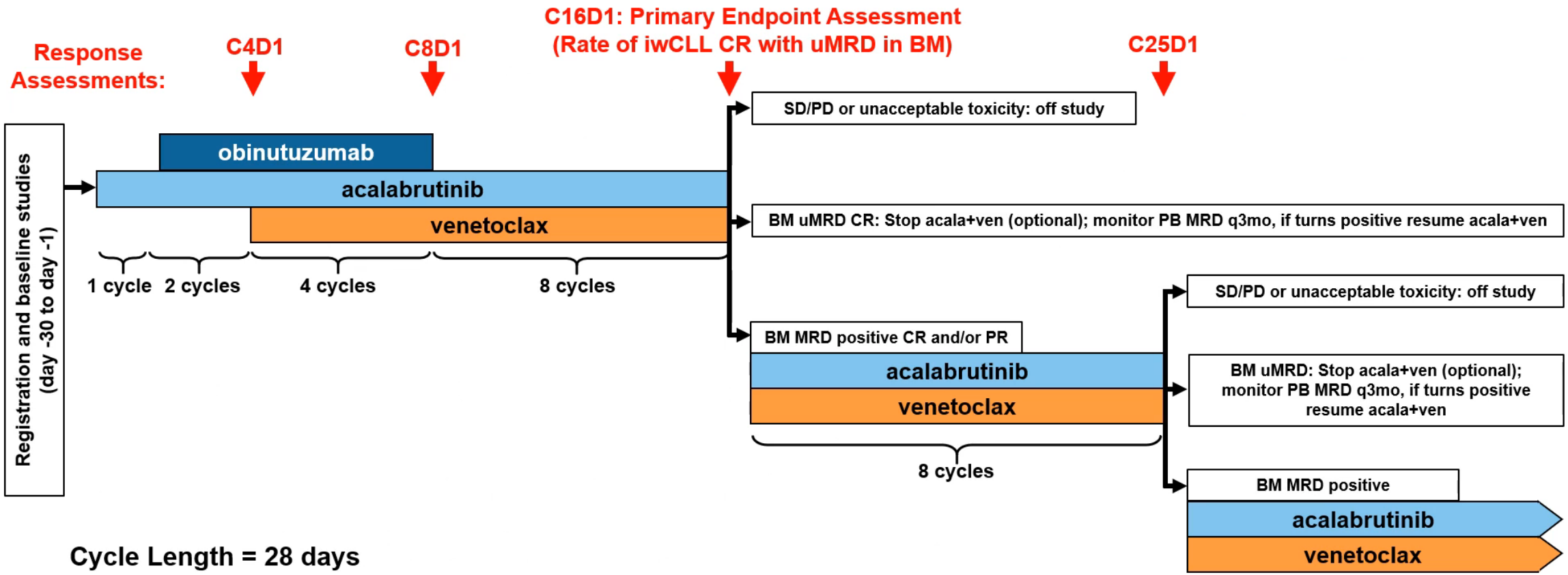


Proportion of patients with undetectable MRD in peripheral blood increased over the 12 cycles of combination therapy

[a]BM MRD assessment was scheduled after completion of 12 cycles of combination treatment.

ASH 2019, CAPTIVATE-MRD; Tam et al.

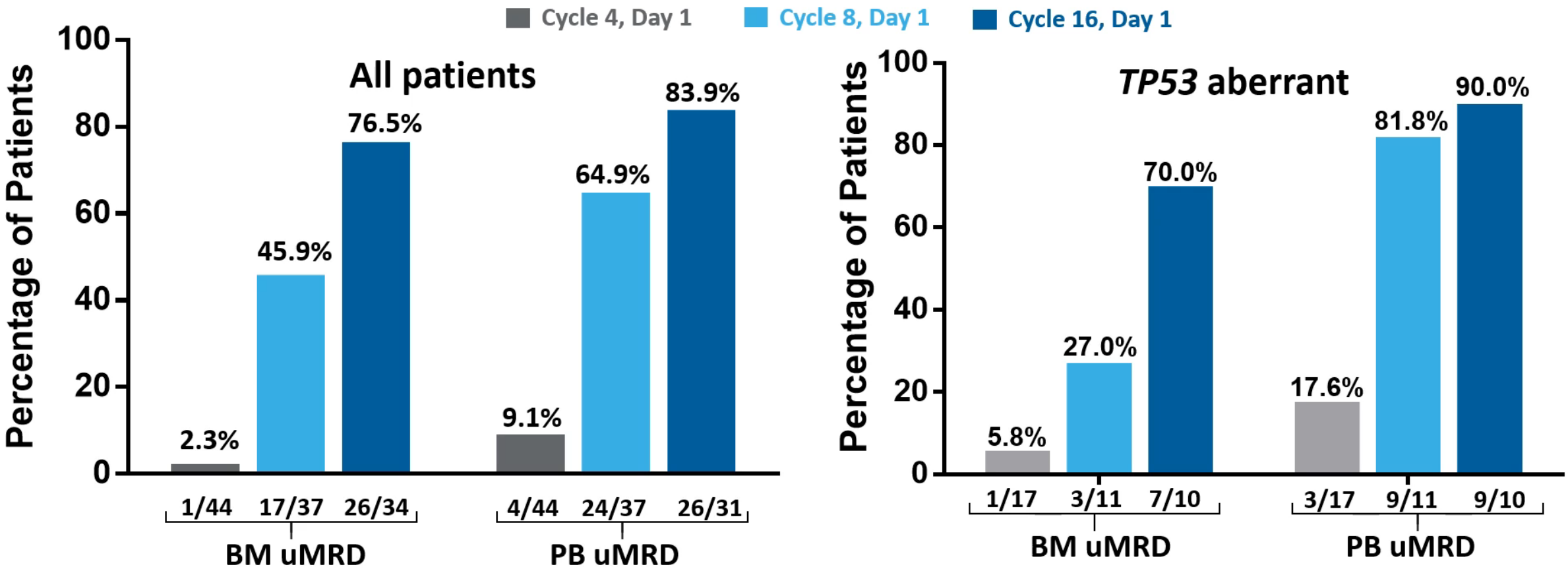
AVO TRIAL: METHODS: STUDY SCHEMA



Cycle Length = 28 days
Acalabrutinib and obinutuzumab at standard doses
Venetoclax 20 mg C4D1, 50mg C4D2, then standard ramp-up to 400mg dose
PJP and HSV/VZV PPX mandatory

Davids et al ASH 2020

EFFICACY ANALYSIS: MRD BY ITT



Note: All patients with unknown MRD status were counted as detectable in this ITT analysis: 15 pts had no BM MRD data at C4, 2 pts had no PB MRD data at C4, 1 pt had no BM/PB MRD data at C8, 2 pts had no BM MRD data at C16

- **11 pts in BM-uMRD CR discontinued therapy after C15, median time off therapy for these pts is 4 mos (range: 1-10)**
- **Median Follow-up: 19 cycles (range, 6-26), no pts have progressed or had recurrent MRD to date**

WHERE ARE WE HEADING IN 1L CLL?

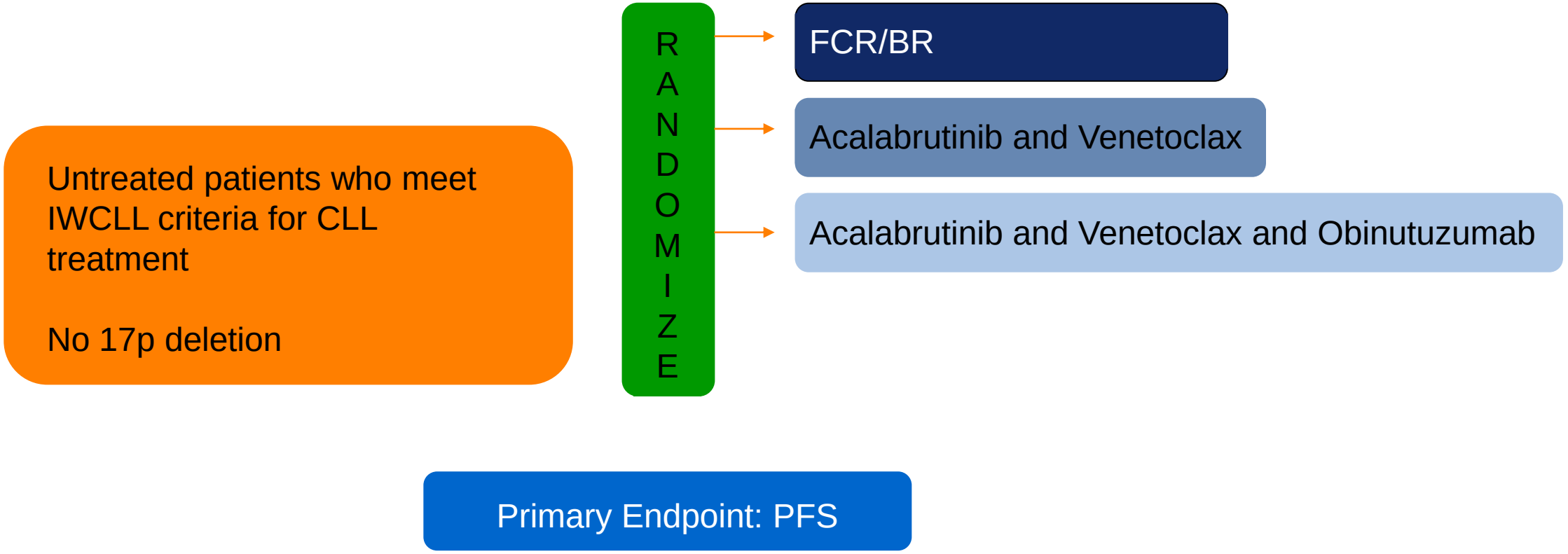
Ongoing phase 3 trials:

- CLL13/GAIA: FCR/BR vs. VR vs. VO vs. IVO (n=920)
- UK NCRI FLAIR: FCR vs. I vs. IV (vs. IR) (n=1,522)
- Alliance A041702: IO vs. IVO (older pts, n=454)
- ECOG EA9161: IO vs. IVO (younger pts, n=720)
- ACE-CL-311: FCR/BR vs AV vs AVO (n=780)
- CLL GLOW: IV vs. Chl/O (n=200)

Near future:

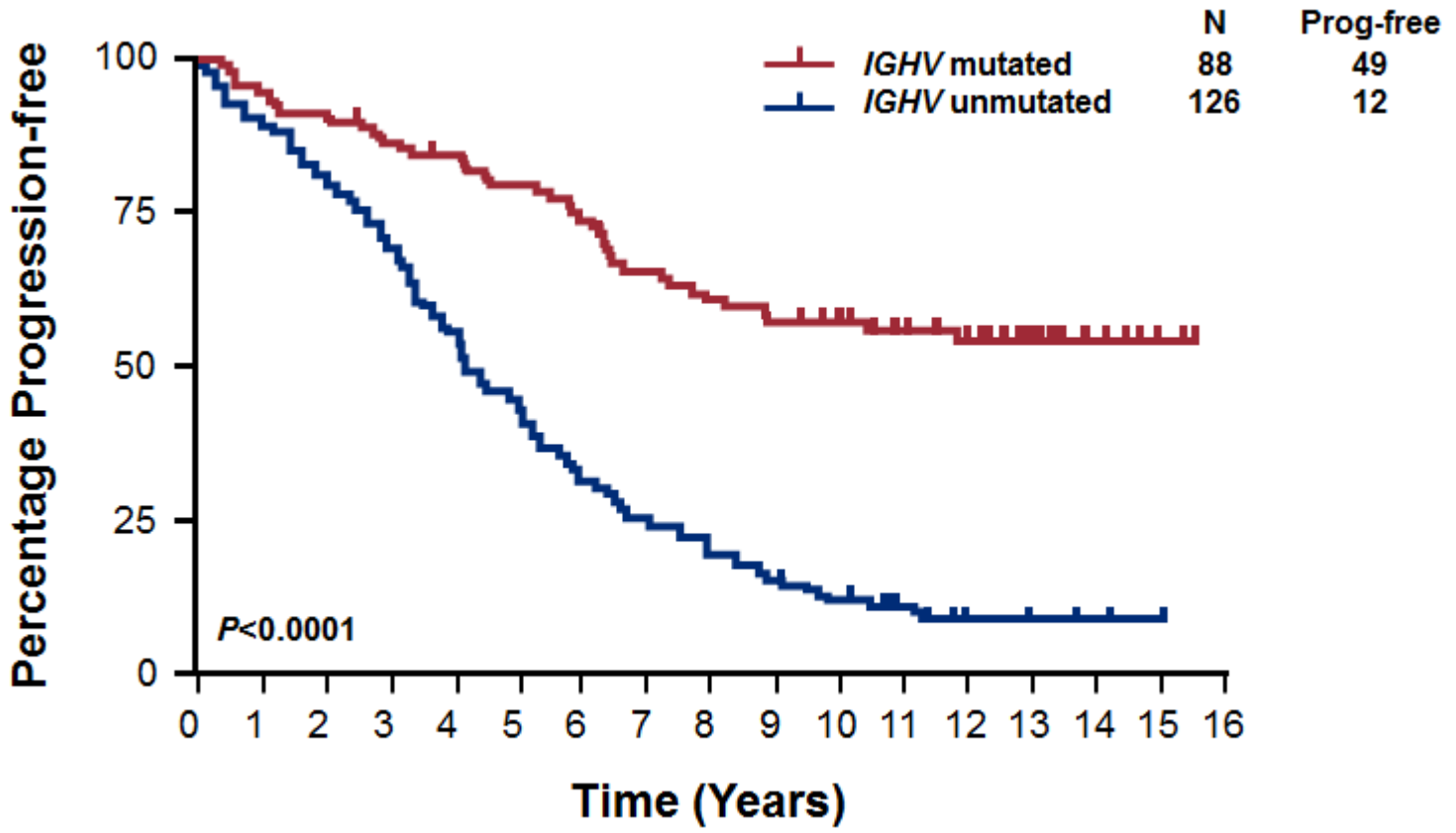
- CLL 17: I vs IV vs IVO (n=882)

ACALABRUTINIB (ACP-196) IN COMBINATION WITH VENETOCLAX (ABT-199), WITH AND WITHOUT OBINUTUZUMAB (GA101) VERSUS CHEMOIMMUNOTHERAPY FOR PREVIOUSLY UNTREATED CLL



QUESTION 3:
CAN SMALL MOLECULE THERAPY CURE ANYONE?

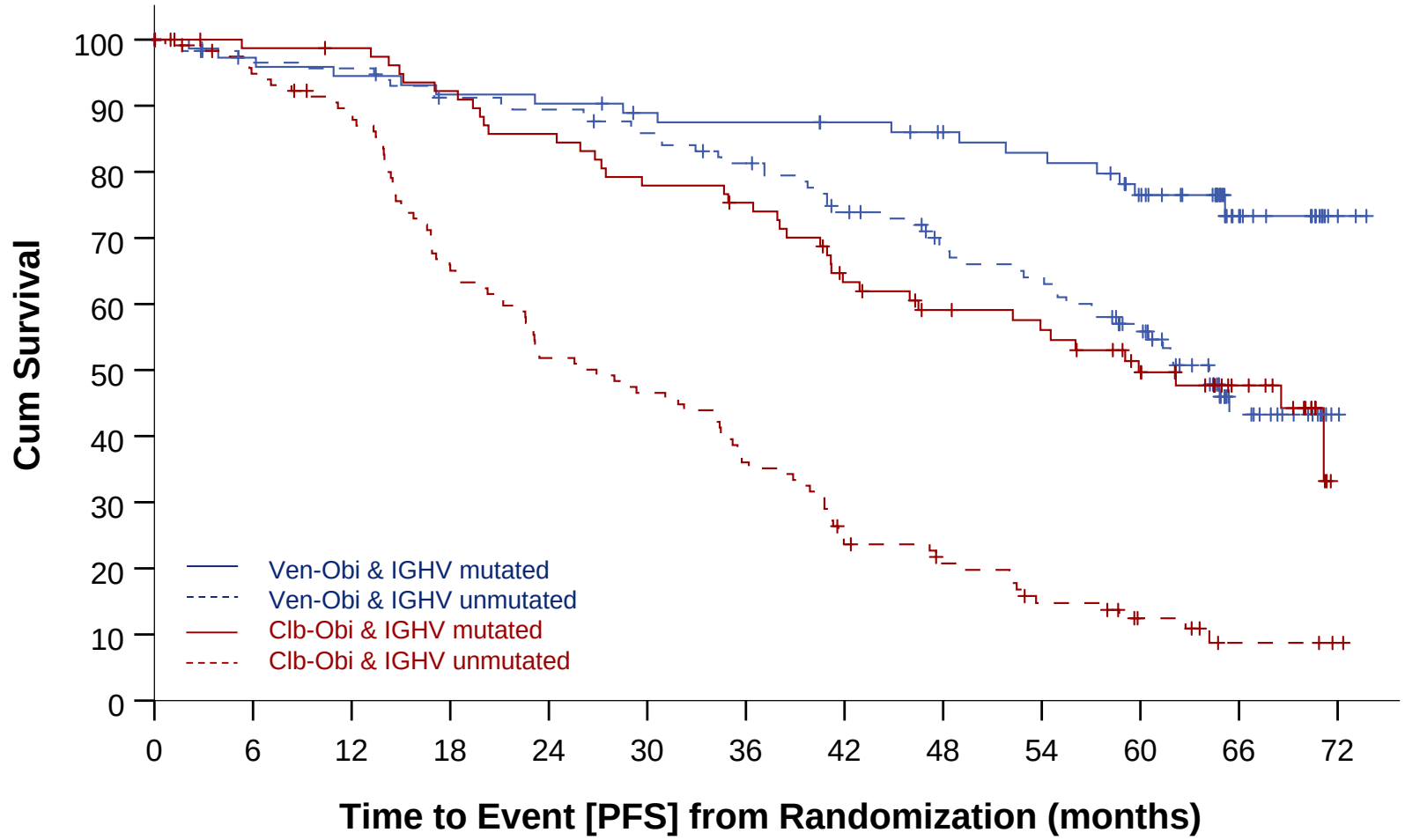
FAVORABLE LONG-TERM PFS WITH FIRSTLINE FCR IN *IGHV*-M SUBGROUP



Thompson et al Blood 2016

CLL 14 PROGRESSION-FREE SURVIVAL – IGHV STATUS

Median observation time 65.4 months



Ven-Obi & IGHV mutated	76	70	68	66	65	62	61	59	56	53	45	18	3
Ven-Obi & IGHV unmutated	121	110	109	102	100	95	89	79	69	64	49	16	1
Clb-Obi & IGHV mutated	83	77	76	71	66	60	57	46	40	37	29	17	0
Clb-Obi & IGHV unmutated	123	110	101	75	59	53	41	26	21	14	8	3	1

Median PFS

Ven-Obi & IGHVmut: NR

Ven-Obi & IGHVunmut: 64.2m

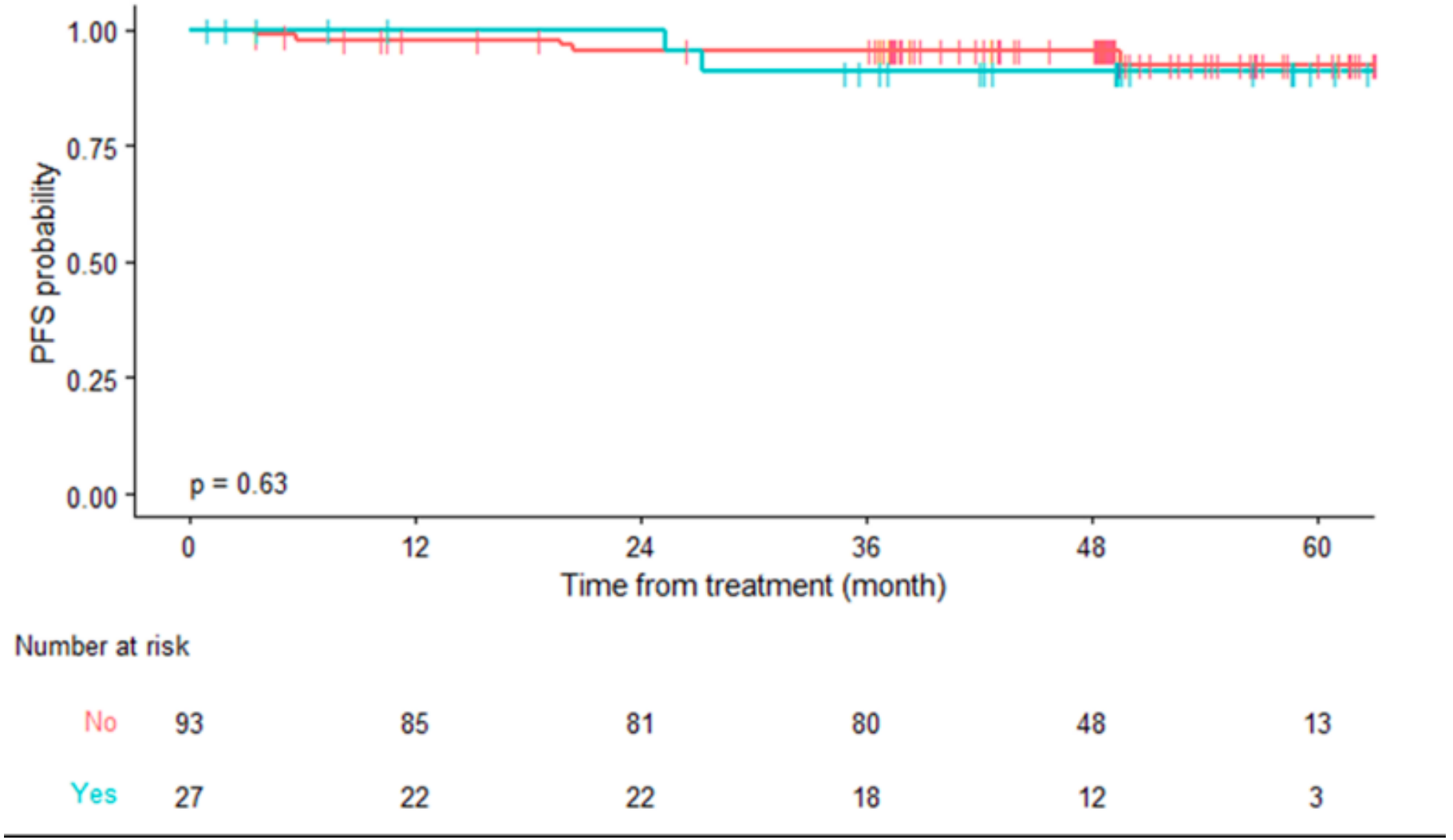
Clb-Obi & IGHVmut: 59.9m

Clb-Obi & IGHVunmut: 26.9m

IBR + VEN: PFS by TP53 Status (N = 120)

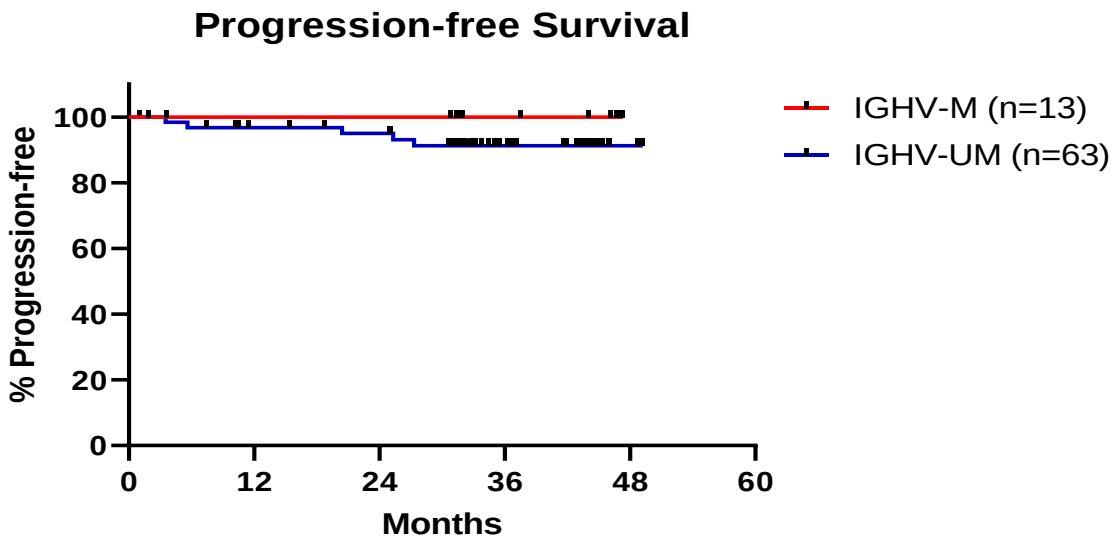
4 year PFS 94.5%;

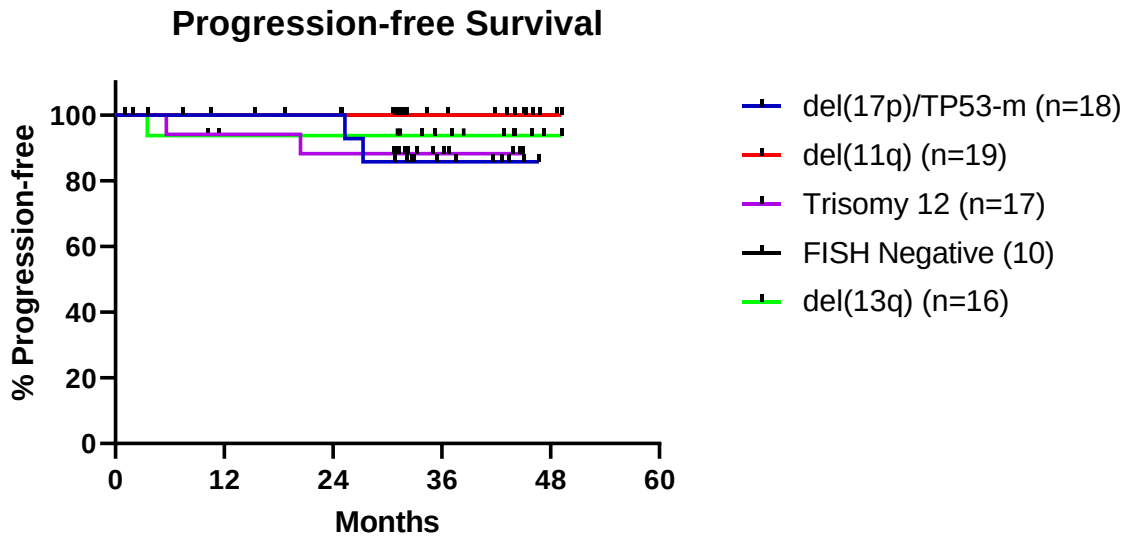
90.9% TP53 aberrant vs 95.5%

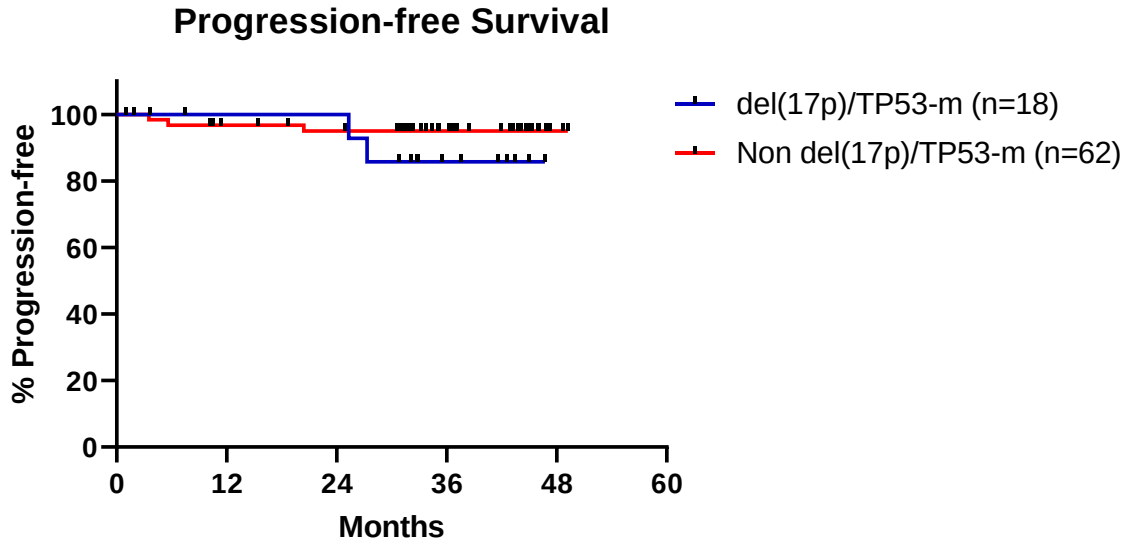


Jain et al ASH 2002 Abstract # 95

PFS BY *IGHV*, FISH AND *TP53* STATUS



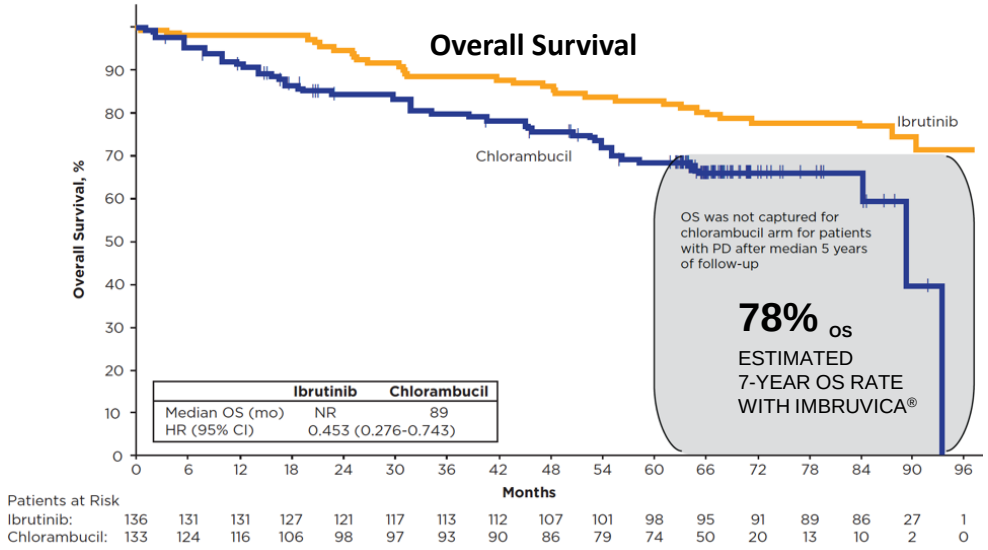


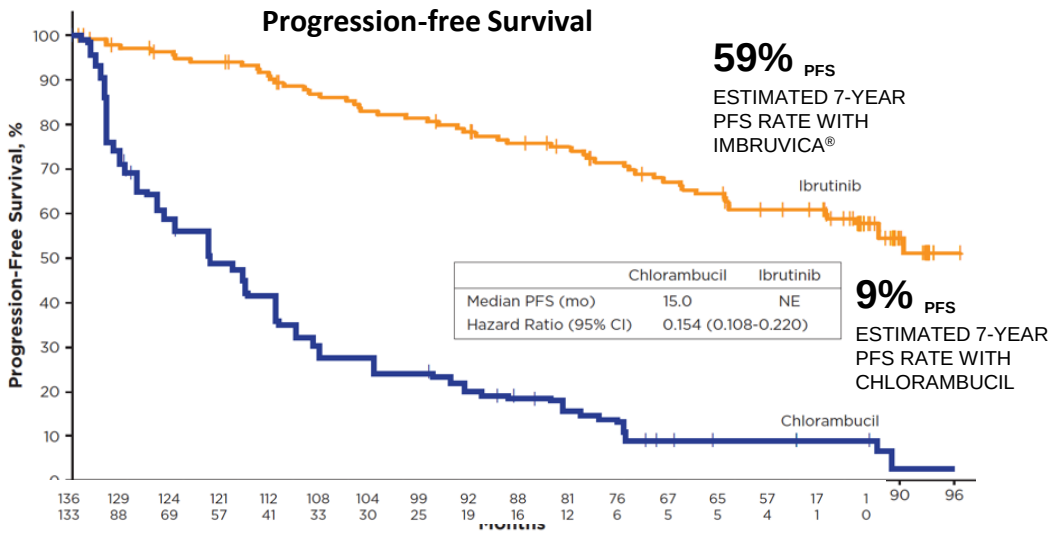


Jain et al ASH 2021

QUESTION 4:
WILL SMALL MOLECULE COMBINATIONS PRODUCE BETTER RESULTS THAN SEQUENCING SMALL MOLECULES?

UP TO 8 YEARS OF FOLLOW-UP IN RESONATE-2: OS AND PFS

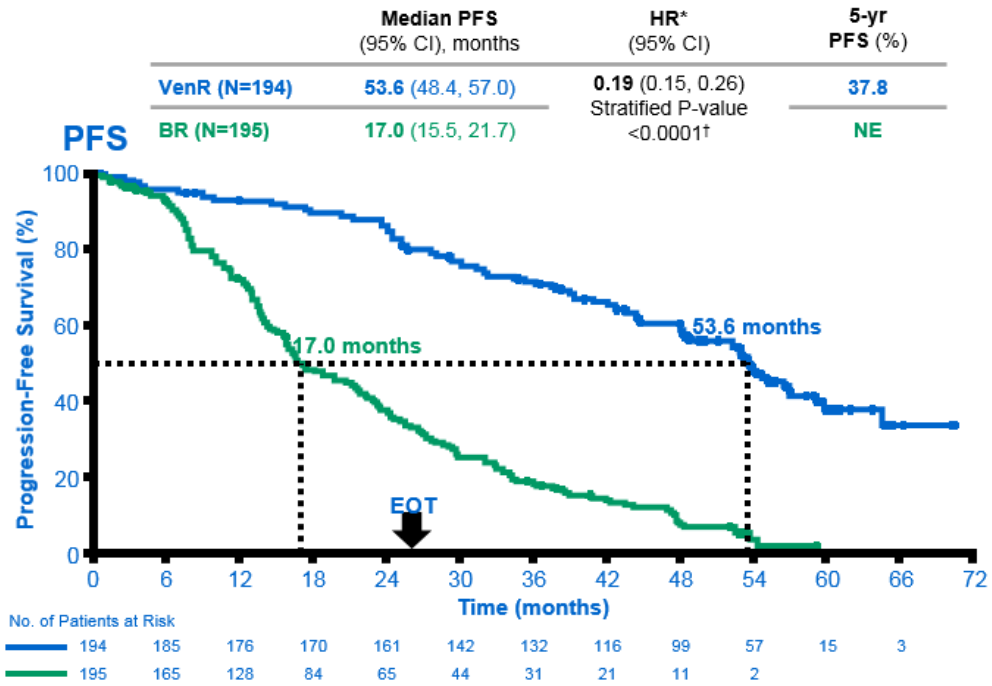


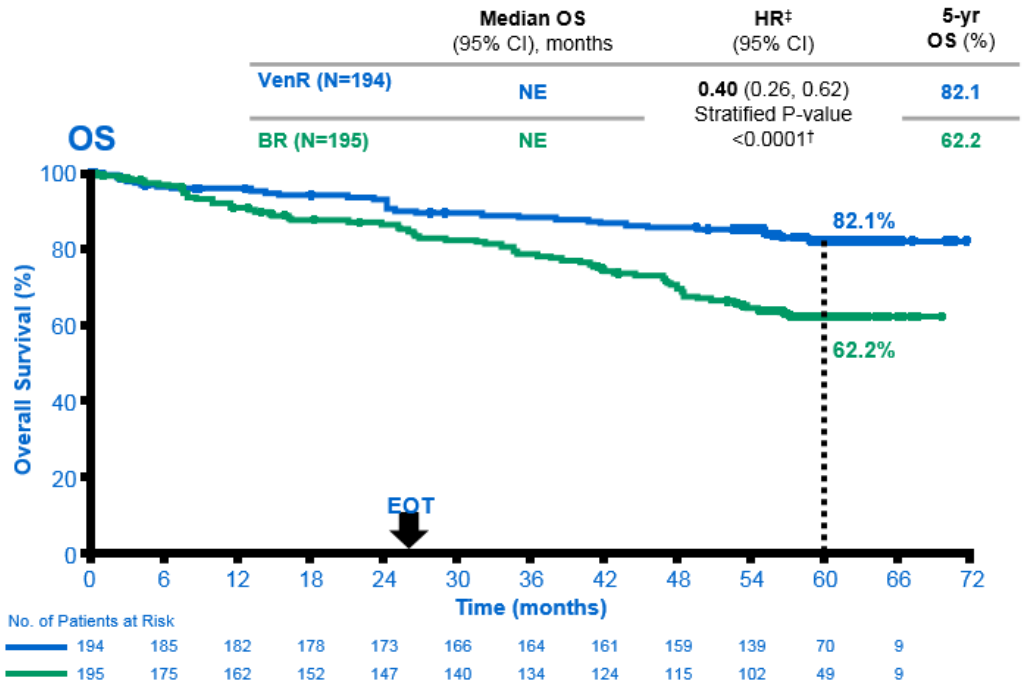


- **78%** taking Ibrutinib were estimated to be alive at 7 years
- **59%** taking Ibrutinib were estimated to be progression-free and alive at 7 years vs 9% of patients taking chlorambucil

1. Barr PM, Owen C, Robak T, et al. Up to 8 years follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Blood Adv. 2022 Apr 4:bloodadvances.2021006434.doi:10.1182/bloodadvances.2021006434

MURANO | PFS AND OS BENEFITS WITH VENR OVER BR WERE SUSTAINED 3 YEARS AFTER EOT



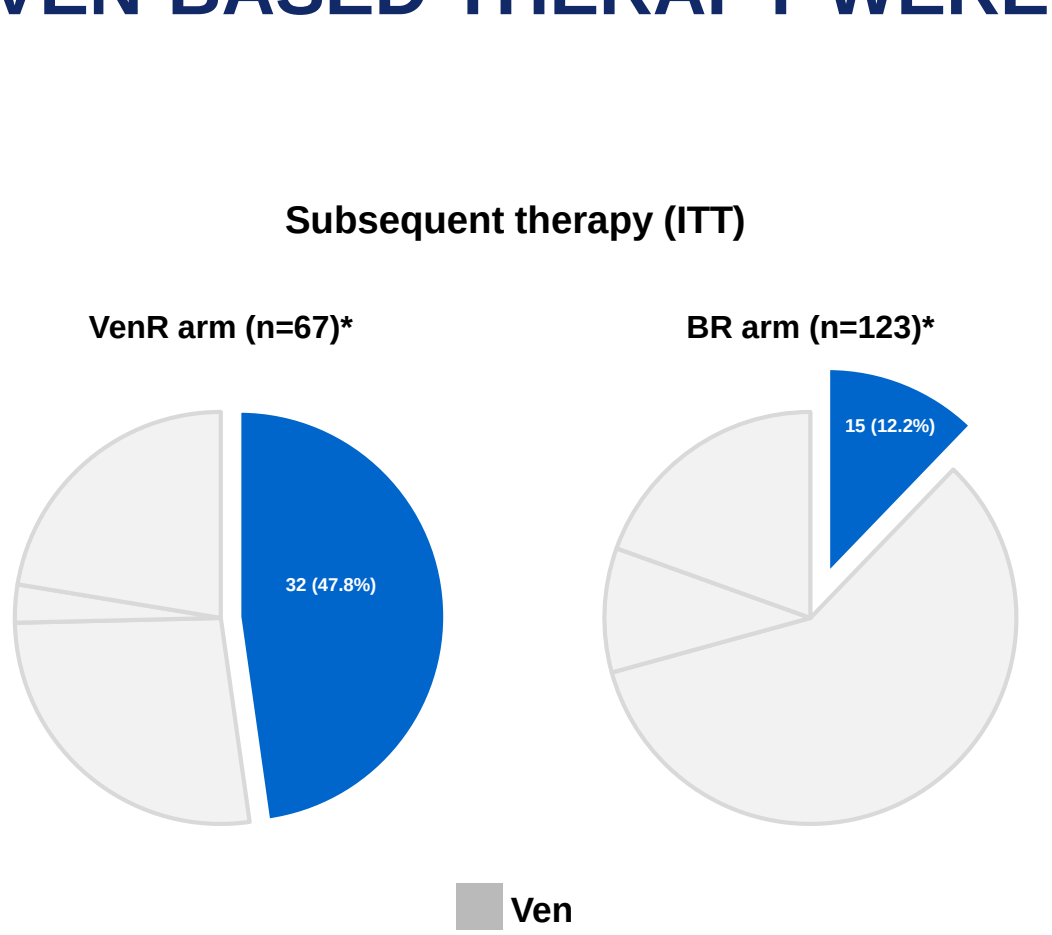


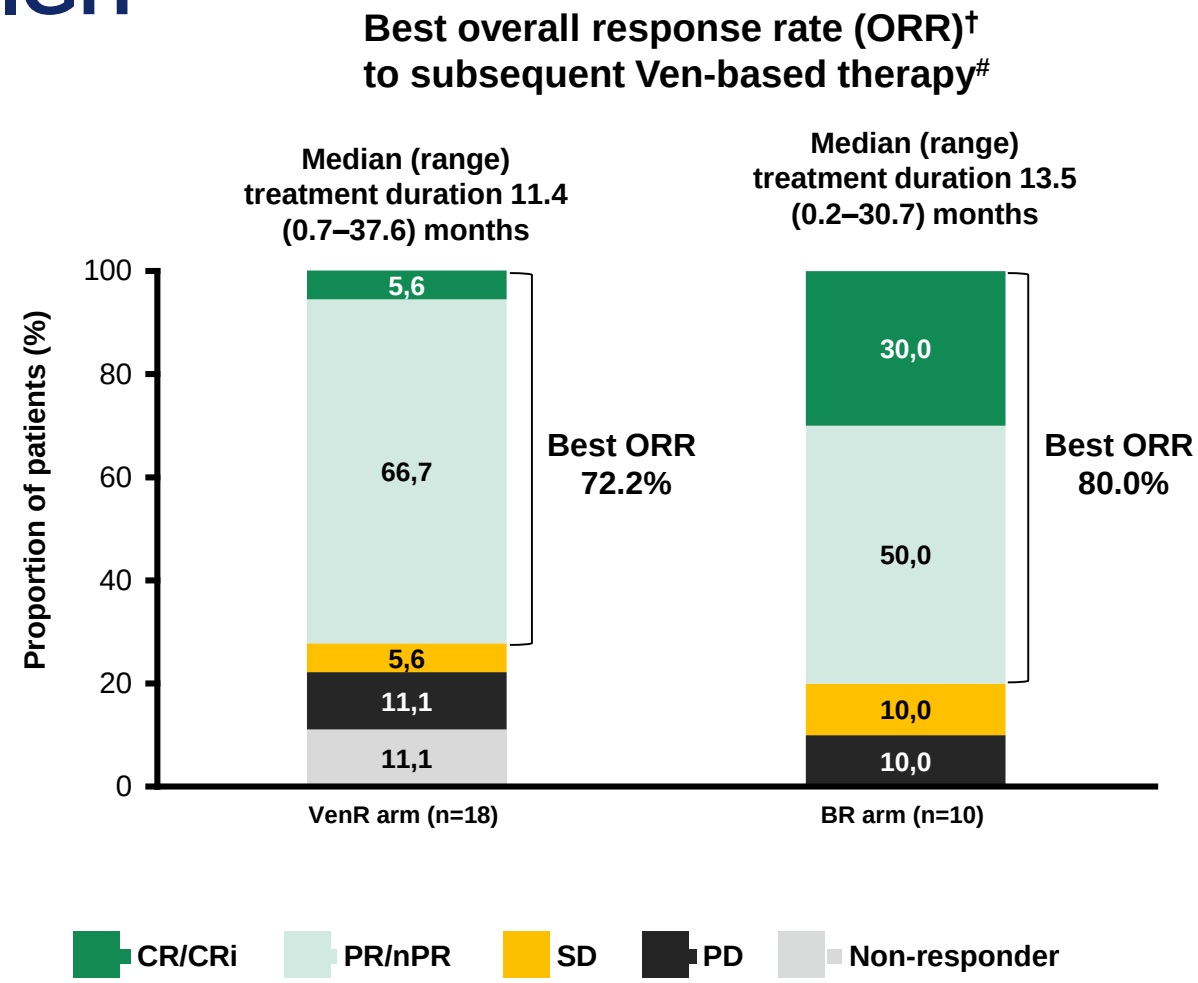
ASH 2020

- With this 5-year update we can now accurately define the median PFS of VenR-treated patients
- No new safety signals were identified 3 years after EOT with longer follow up and patients are outside of the adverse event reporting window

*Unstratified HR=0.21;‡Unstratified HR=0.42; †P-values are descriptive only; +, censored
BR, bendamustine-rituximab; CI, confidence interval; EOT, end of treatment; HR, hazard ratio; NE, not evaluable; OS, overall survival; PFS, progression-free survival; VenR, venetoclax-rituximab; yr, year

MURANO TRIAL: RESPONSE RATES TO SUBSEQUENT VEN-BASED THERAPY WERE HIGH



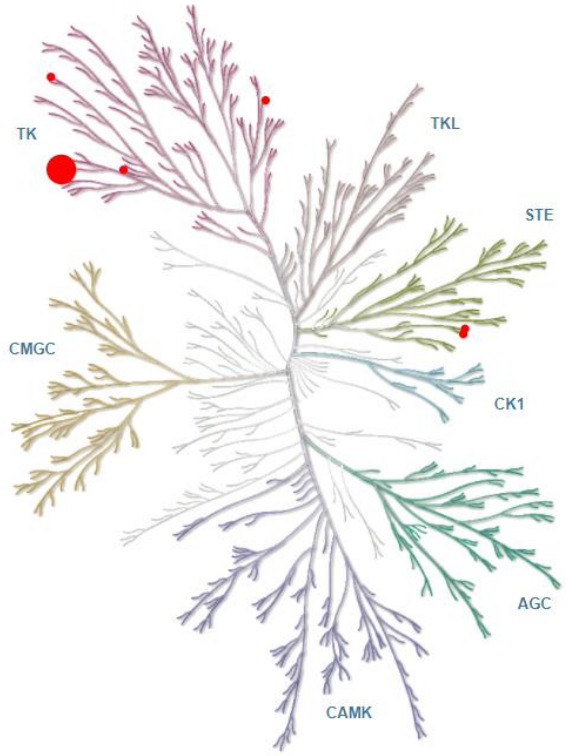


*Patients treated. †Best ORR, median treatment duration and number of patients remaining on therapy were calculated among patients with evaluable responses.
#Evaluable responses in treated patients. Responses were classed as evaluable if they were reported by the investigators prior to discontinuation or initiation of subsequent line of therapy. Responses in patients who were treated with their next line of therapy for insufficient time to have their response assessed, or those patients who had no response assessments reported, were considered unevaluable.BR, bendamustine-rituximab; CR(i), complete response with incomplete bone marrow recovery; ITT, intent-to-treat; ORR, overall response rate; (n)PR, nodular partial response; PD, progressive disease; SD, stable disease; Ven, venetoclax; VenR, venetoclax-rituximab

PIRTOBRUTINIB IS A HIGHLY POTENT AND SELECTIVE NON-COVALENT (REVERSIBLE) BTK INHIBITOR

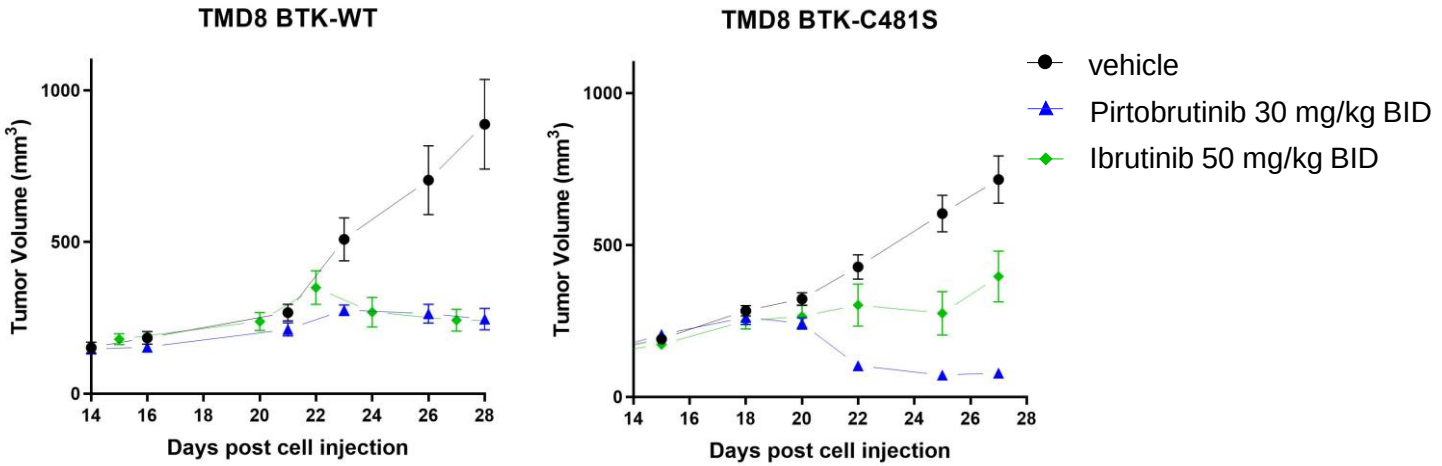
Kinome selectivity[1]

Highly selective for BTK



Xenograft models

In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S

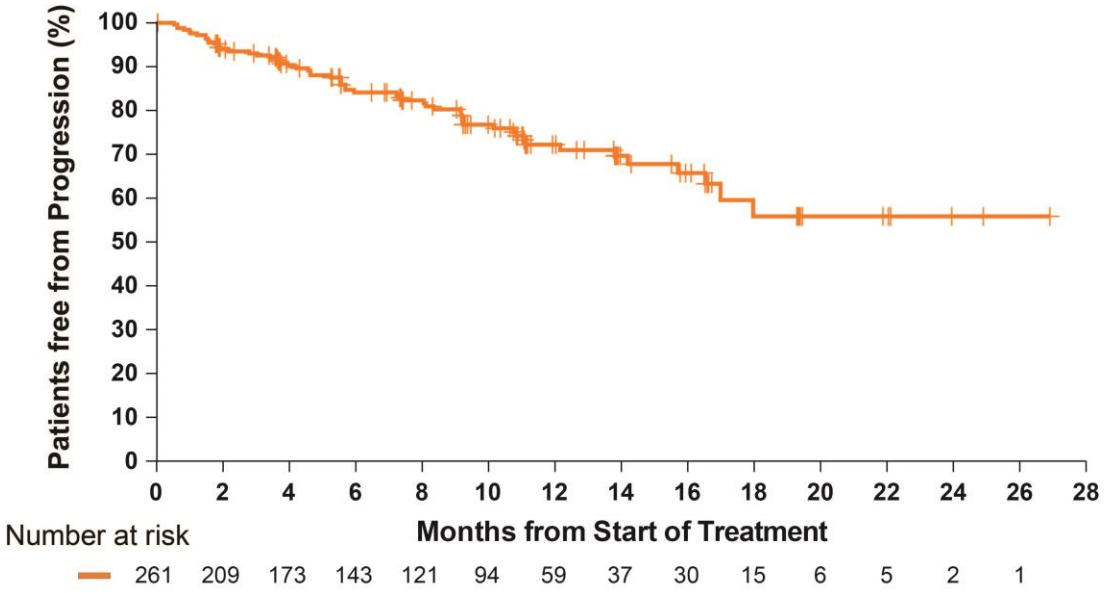


- >300-fold selectivity for BTK vs 370 other kinases[2]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[2]
- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[2]
- Due to reversible binding mode, BTK inhibition not impacted by a high intrinsic rate of BTK turnover[2]

BID, twice-daily; BTK, Bruton tyrosine kinase. [1]Mato et al, *Lancet*, 2021:397:892-901. [2]Brandhuber BJ, et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

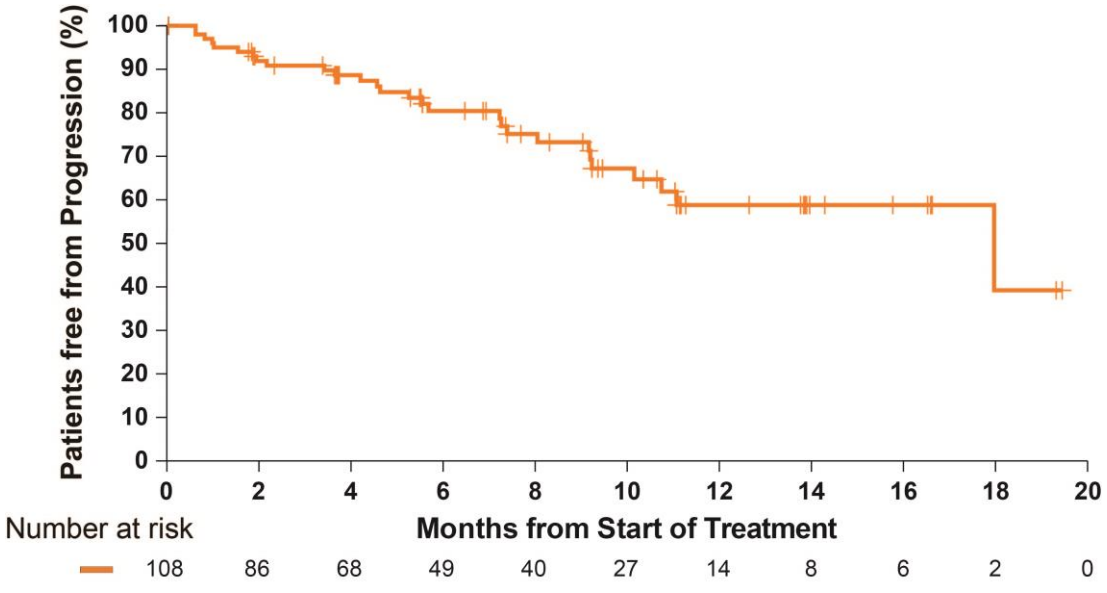
PROGRESSION-FREE SURVIVAL IN BTK PRE-TREATED CLL/SLL PATIENTS

PFS in at least BTK pre-treated patients
Median prior lines = 3



Median PFS: Not Estimable (95% CI: 17.0 months – Not Estimable)

PFS in at least BTK and BCL2 pre-treated patients
Median prior lines = 5



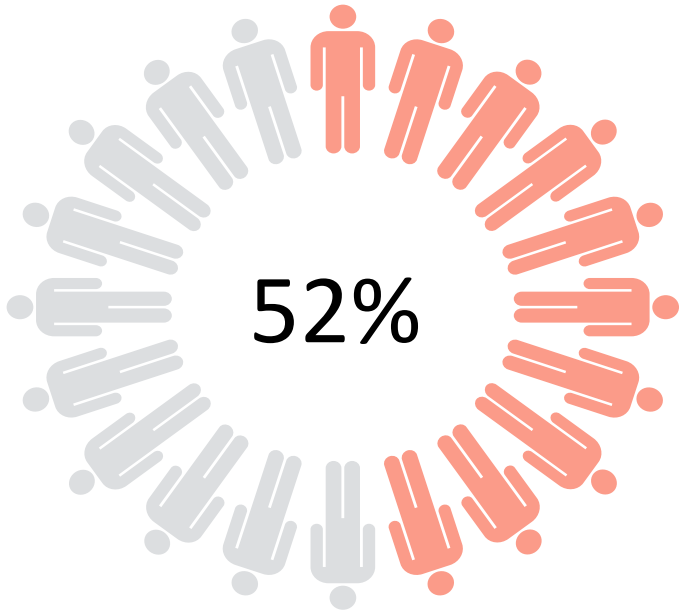
Median PFS: 18 months (95% CI: 10.7 months – Not Estimable)

- 74% (194/261) of BTK pre-treated patients remain on pirtobrutinib
- Median follow-up of 9.4 months (range, 0.3 – 27.4) for all BTK pre-treated patients

Data cutoff date of 16 July 2021. Response status per iwCLL 2018 according to investigator assessment.

QUESTION 5:
HOW DO WE RESTORE THE IMMUNE SYSTEM IN PATIENTS WITH CLL?

POST-DOSE 2 RESPONSE RATE



Response rate post-dose 2
(265/506)

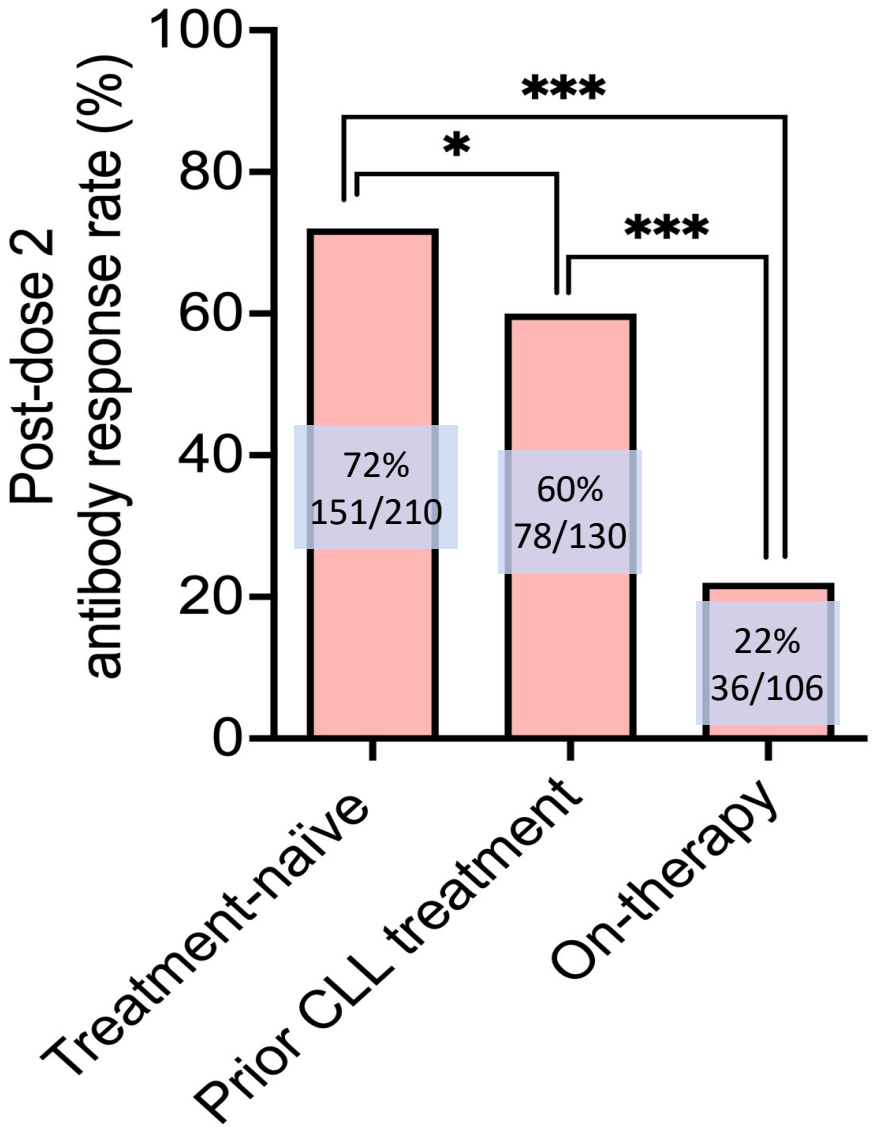
Factors associated with seroconversion
Univariate analysis

Variable		*p*-value	Odds ratio	95% CI
Vaccine type	mRNA-1273 - Moderna (%)			
	BNT162b2 – Pfizer BioNTech (%)	0.001	0.49	0.28-0.84
Age	Age ≤ 65 years			
	Age >65 years	< 0.001	0.49	0.33-0.73
CLL treatment	Treatment-naïve			
	Prior CLL treatment	0.02	0.59	0.37-0.93
	On therapy	< 0.001	0.11	0.07-0.17
Gamma-globulines	Gamma-globulins > 6g/L			
	Gamma-globulins ≤ 6g/L	<0.001	0.33	0.16-0.69

The variables associated with a lower seroconversion rate were age >65 years, BNT162b2 vaccine type, prior CLL treatment, ongoing CLL treatment and hypogammaglobulinemia.

Bagacean et al ASH 2021

POST-DOSE 2 RESPONSE RATE AND TREATMENT



Treatment-naïve patients had the highest response rate as compared with previously treated patients (*P*=0.02) and with patients on therapy (*P*<0.001)

* $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$; **** $P \leq 0.0001$

Bagacean et al ASH 2021

GAIA TRIAL: SECOND PRIMARY MALIGNANCY & RT

	CIT	RV	GV	GIV
Second primary malignancies*	**49**	**24**	**27**	**29**
Solid tumors	**18**	**9**	**13**	**15**
Hematological malignancies	**4**	**1**	**0**	**4**
Non-melanoma skin cancer	**27**	**14**	**14**	**10**
Basal cell carcinoma	16	13	7	6
Squamous cell carcinoma	11	1	7	4
Richter transformation	**6**	**4**	**6**	**2**

* Second primary malignancies counted as events not as patients affected

SUMMARY OF QUESTIONS

Question 1: Will combination small molecules be better than VenG?

Yes

Question 2: Do we really need an antibody with small molecule combinations?

Yes

Question 3: Can small molecule therapy cure anyone?

Yes

Question 4: Will small molecule combinations produce better results than sequencing small molecules?

Yes

Question 5: How do we restore the immune system in CLL?

I don’t have a clue