Fred Hutch
Cancer Center

Monotherapy vs. Doublets vs. Triplets in CLL

Mazyar Shadman, MD MPH
Professor | Innovators Network Endowed Chair
Deputy Chief Medical Officer
Medical Director, Cellular Immunotherapy
Fred Hutch Cancer Center and University of Washington
Seattle, WA

UW Medicine

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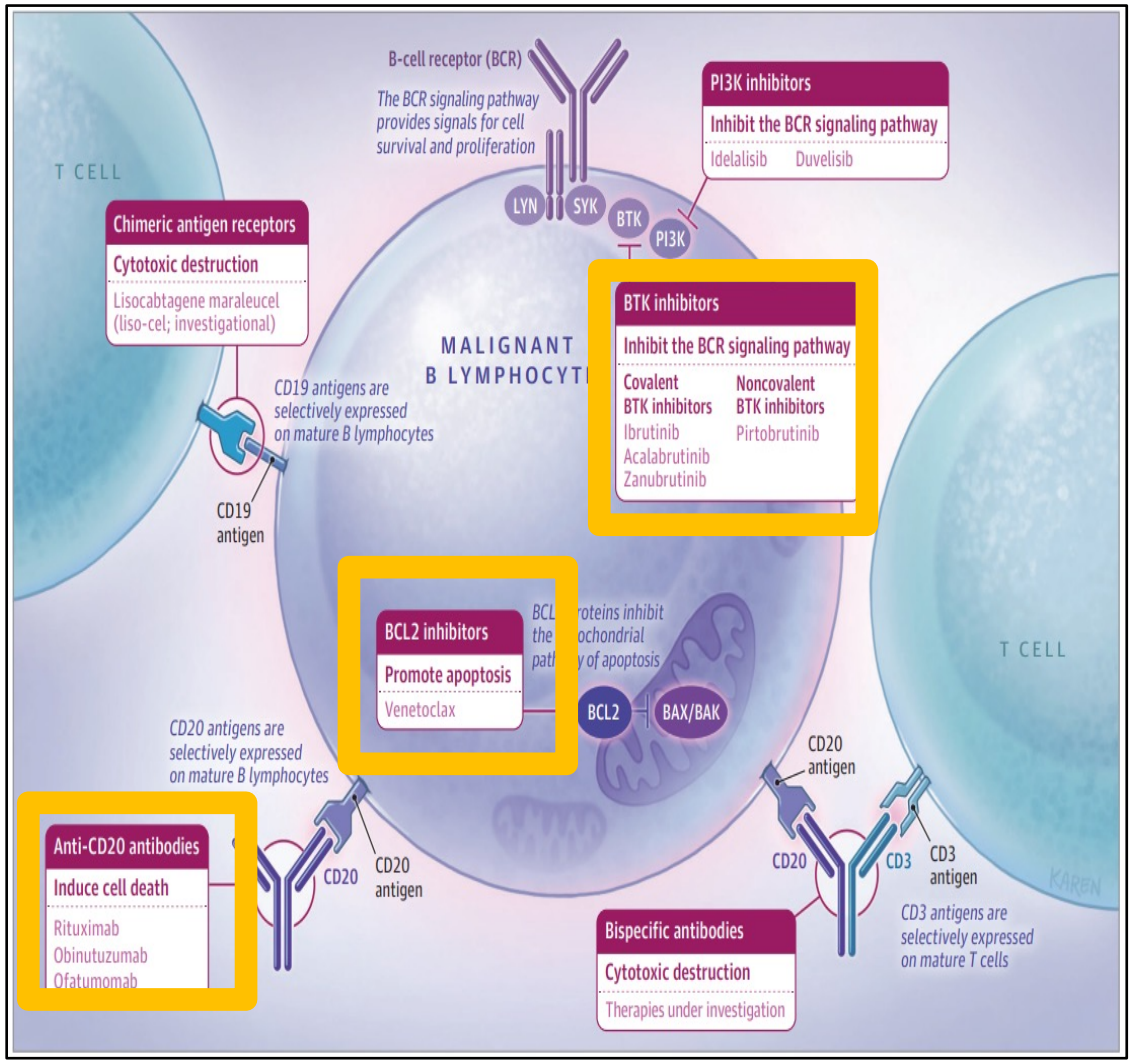
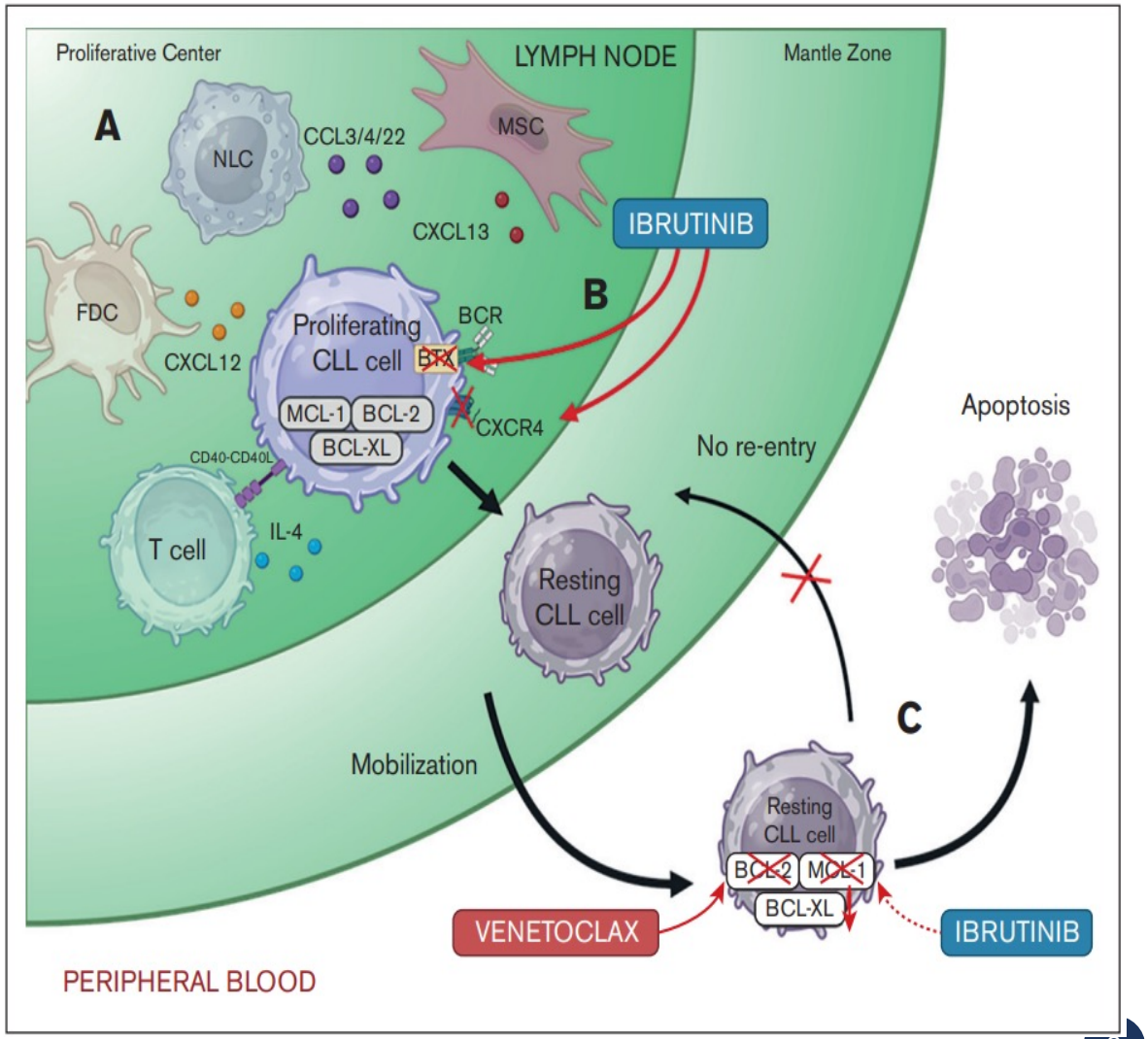
Novel CLL Drugs and Rationale for Combinations

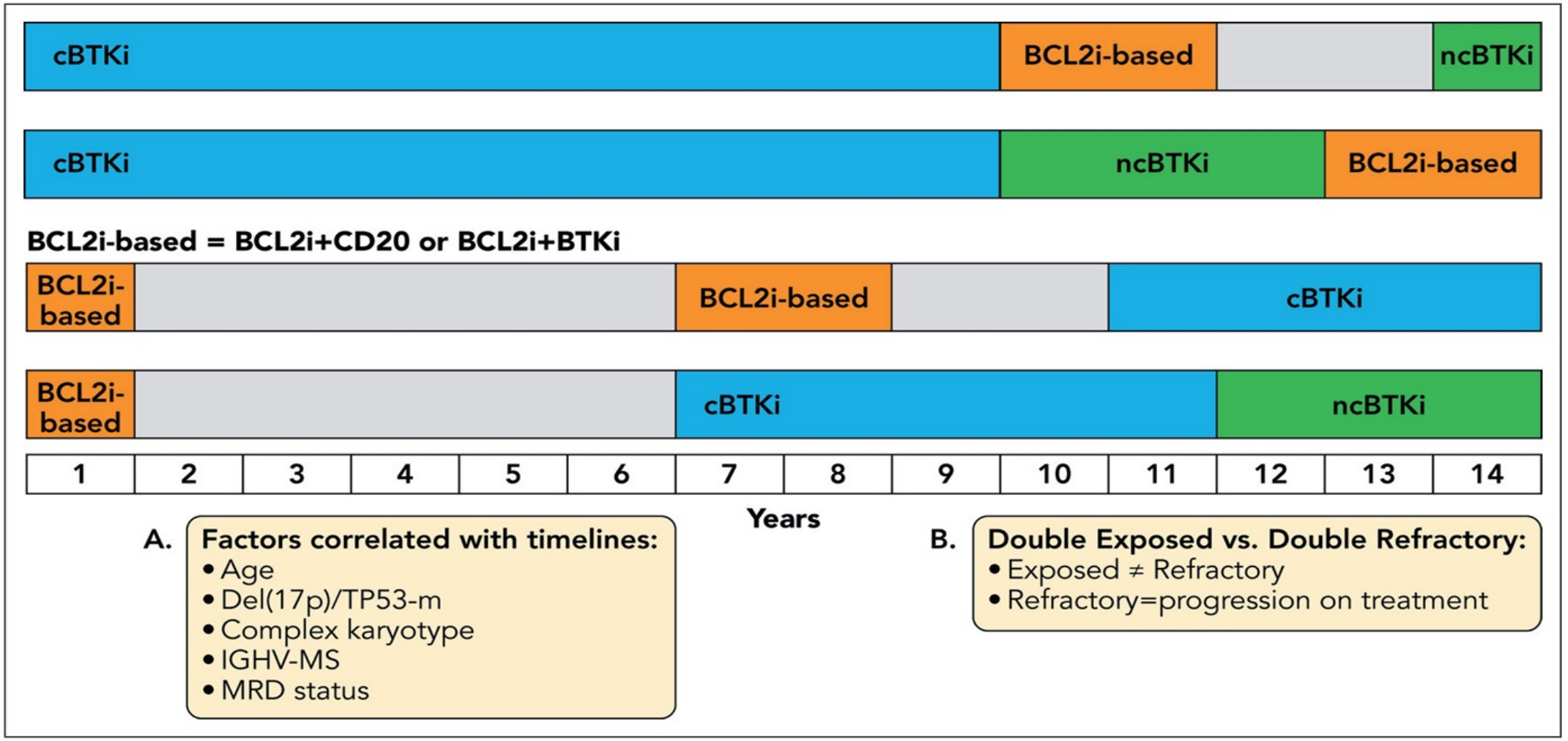




Shadman M, JAMA,2023

Timofeeva, Blood Neoplasia,2024

Treatment Strategies in CLL/SLL



Wierda W, et al, Blood, 2025

5-year PFS in Selected First-line CLL Trials

Trial	Regimen	Median Age	IGHV-M (%)	IGHV-UM (%)	Strategy
RESONATE-2	Ibrutinib	73	80	70	Continuous
ELEVATE-TN	Acalabrutinib	70	80	70	Continuous
ELEVATE-TN	Acala + Obinutuzumab	70	84	82	Continuous
SEQUOIA	Zanubrutinib	70	80	75	Continuous
BRUIN CLL-313	Pirtobrutinib	65	97 (2y)	91 (2y)	Continuous
CLL14	Ven + Obinutuzumab	72	74	55	Fixed
MDACC	Ibr + Ven (2y)	64	86	90	Fixed
CAPTIVATE	Ibr + Ven (1y)	60	80	56	Fixed
GLOW	Ibr + Ven (1y)	71	82	52	Fixed
FLAIR	Ibr + Ven (2–6y)	62	90	95	MRD-guided
CLL13	Ven + Obinutuzumab	62	83	59	Fixed
CLL13	Ibr + Ven + Obin	60	89	76	Triplet
AMPLIFY	Acala + Ven	61	86 (3y)	69 (3y)	Fixed
AMPLIFY	Acala + Ven + Obin	61	84 (3y)	83 (3y)	Triplet
CLL17	Ven + Obin	66	88 (3y)	76 (3y)	Fixed
CLL17	Ibr + Ven (1y)	66	80 (3y)	79 (3y)	Fixed

Slide courtesy: Dr. Nitin Jain

Randomized Trials Comparing Novel CLL Treatments

		MONOTHERAPY					DOUBLETS											TRIPLETS				
		I	A	Z	P	N	IR	IO	IV	VO	VR	SO	AO	AV	ZV	ZS	PV	NV	IVO	AVO	ZVO	PVO	PVR
MONOTHERAPY	I																						
	A	ELEVATE-RR																					
	Z	ALPINE	—																				
	P	BRUIN-CLL 314	—	—																			
	N	BELLWAVE-011	BELLWAVE-011	—	—																		
DOUBLETS	IR	A041202	—	—	—	—																	
	IO	—	—	—	—	—	—																
	IV	UK FLAIR	—	—	—	—	—	—															
	VO	CLL17	—	—	—	—	—	—	CLL17														
	VR	—	—	—	—	—	—	—	—	CLL13													
	SO	—	—	—	—	—	—	—	—	CELESTIAL-RR	CELESTIAL-RR												
	AO	—	ELEVATE-TN	—	—	—	—	—	—	—	—	—											
	AV	—	—	—	—	—	—	—	—	MAJIC	—	—	—										
	ZV	—	—	—	—	—	—	—	—	—	—	—	—	—									
	ZS	—	—	—	—	—	—	—	—	CELESTIAL-TN1	—	—	—	CELESTIAL-TN2	—								
	PV	—	—	—	—	—	—	—	—	CLL18	—	—	—	—	—	—							
	NV	—	—	—	—	—	—	—	—	—	BELLWAVE-010	—	—	—	—	—	—						
TRIPLETS	IVO	—	—	—	—	—	—	A041702 / EA9161	—	CLL13	CLL13	—	—	—	—	—	—	—					
	AVO	—	—	—	—	—	—	—	—	CLL16	—	—	—	AMPLIFY	—	—	—	—	—				
	ZVO	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
	PVO	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
	PVR	—	—	—	—	—	—	—	—	—	BRUIN CLL-322	—	—	—	—	—	—	—	—	—	—	—	

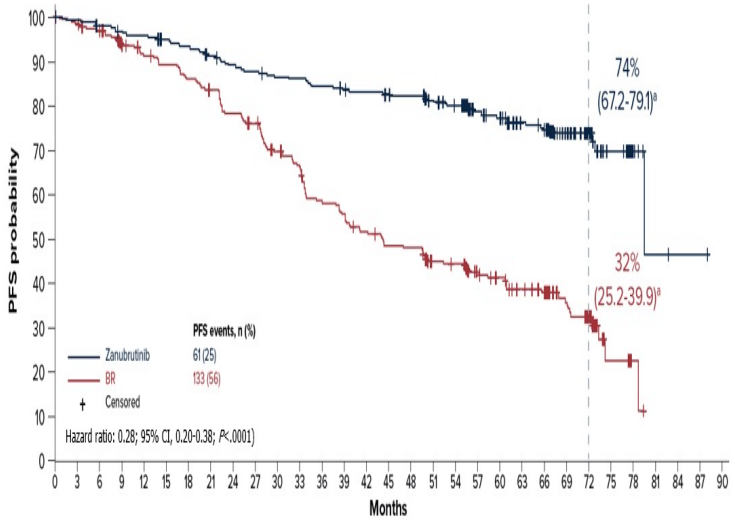
I= ibrutinib
A=Acalabrutinib
Z=Zanubrutinib
P=Pirtobrutinib
N=Nemtabrutinib
R=Rituximab
O=Obinutuzumab
V=Venetoclax
S=Sonrotoclax

Cell colors — Mono vs. Mono | Mono vs. Doublet | Doublet vs. Doublet | Doublet vs. Triplet | — = not directly compared | [gray] = not applicable (upper triangle)

Outstanding Efficacy with Treat until Progression with second generation covalent BTKis

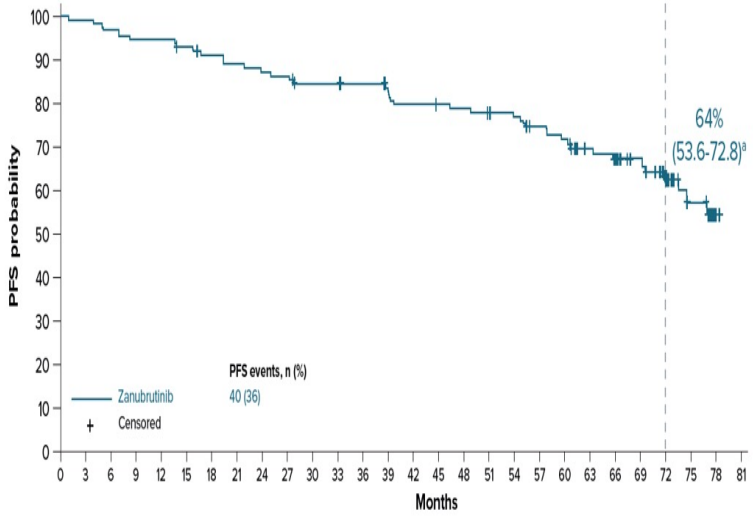
SEQUOIA Arm A and C: Zanubrutinib Monotherapy in First-Line

No del17p



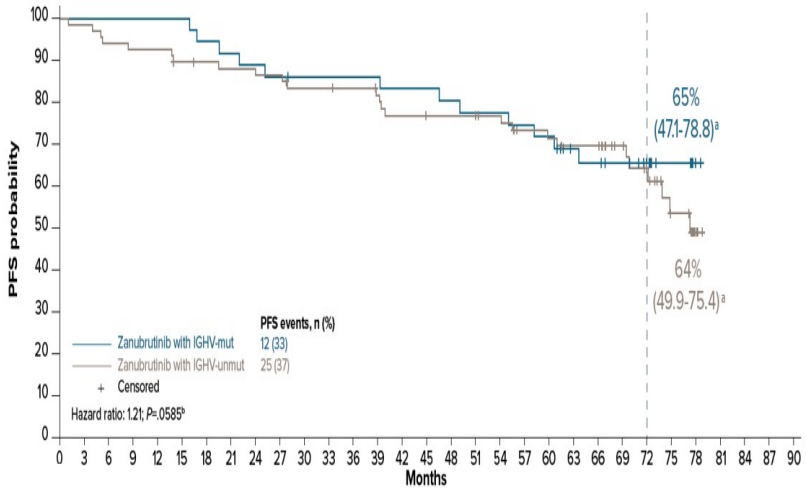
6-year PFS: 74%

del17p



6-year PFS: 64%

Del17p by IGHV status



6-year PFS:
65% (mIGHV) and 64% (uIGHV)

Lessons learned:

- cBTKi monotherapy provides high efficacy regardless of high-risk features

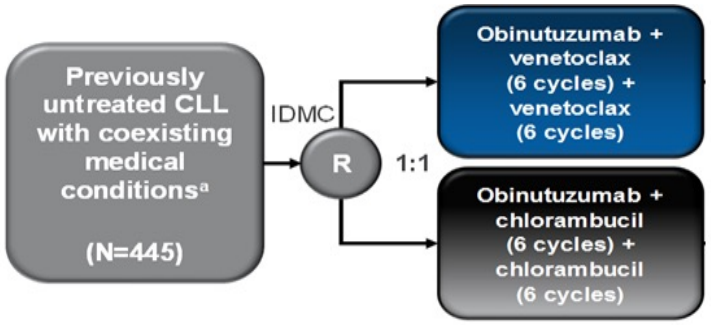
Shadman M, JCO, 2025; Tam C. et al, ASH, 2025

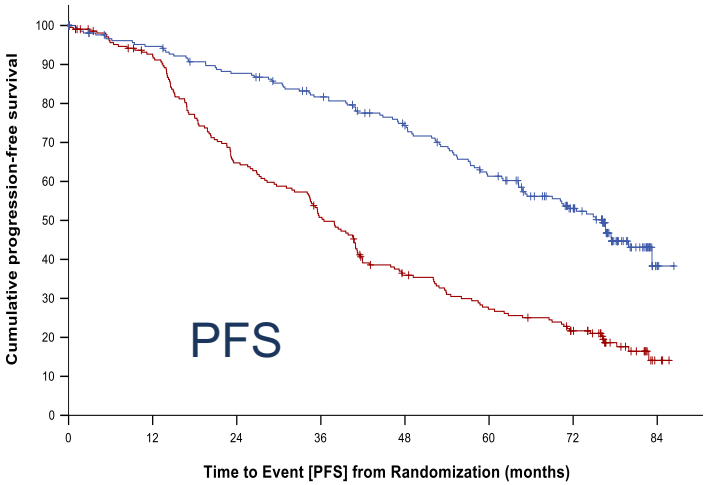
Why Time-limited Treatment?

- Freedom from treatment
- Reduced cumulative toxicity
- No (lower risk for) acquired resistance during treatment and preservation of future options
- Cost saving
- Potential for cure in TP53 WT and mIGHV with time-limited therapy
- Psychological impact of “not being on cancer treatment”

BCL2i plus anti-CD20 Doublets

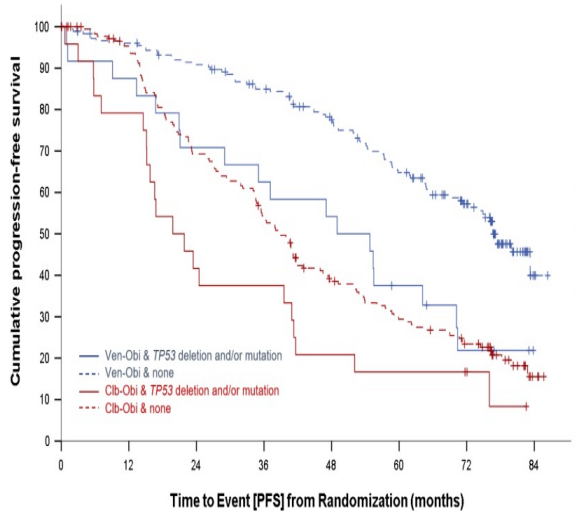
CLL14: Venetoclax plus Obinutuzumab vs. CIT





PROGRESSION-FREE SURVIVAL – *TP53* status

Median observation time 76.4 months



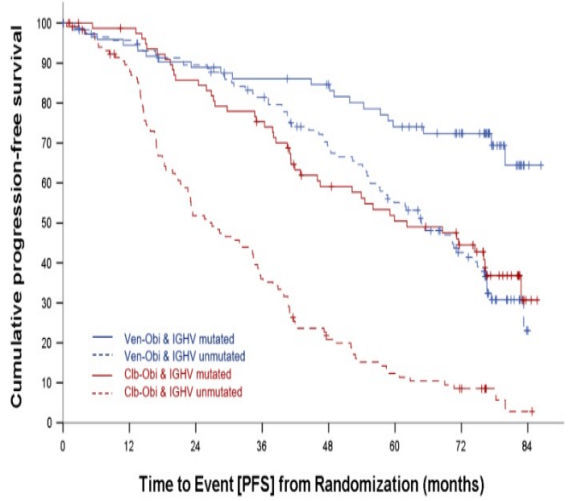
Median PFS

Ven-Obi & no *TP53*del/mut: 76.6 m
Ven-Obi & *TP53*del/mut: 51.9 m
HR 2.29, 95% CI [1.37-3.83], p=0.001

Clb-Obi & no *TP53*del/mut: 38.9 m
Clb-Obi & *TP53*del/mut: 20.8 m
HR 1.66, 95% CI [1.05-2.63], p=0.03

PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 76.4 months



Median PFS

Ven-Obi & IGHVmut: NR
Ven-Obi & IGHVunmut: 64.8 m
HR 0.38, 95%CI [0.23-0.61], p<0.001

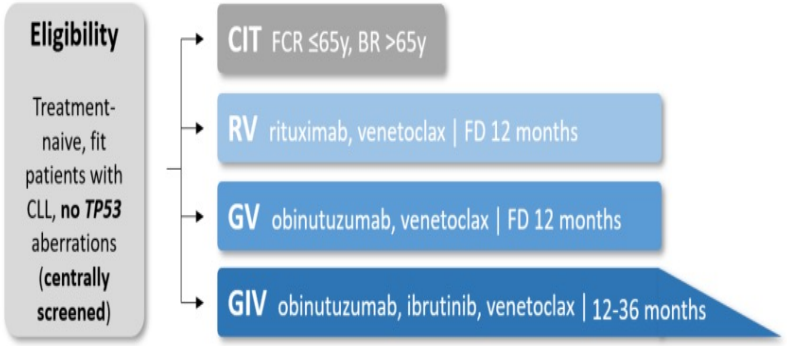
Clb-Obi & IGHVmut: 62.2 m
Clb-Obi & IGHVunmut: 26.9 m
HR 0.33, 95% CI [0.23-0.47], p<0.001

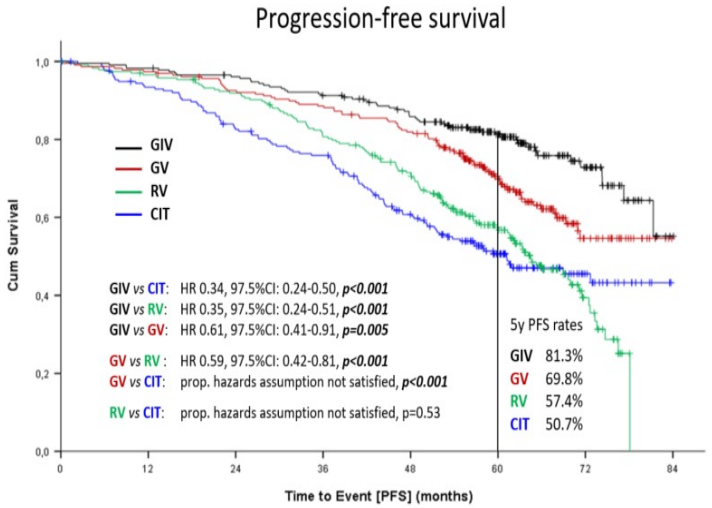
Lessons learned:

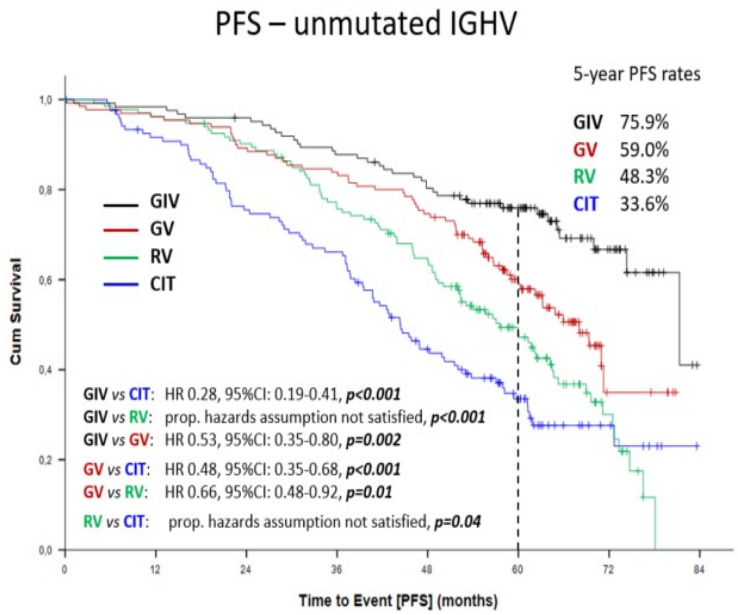
- High PFS and TTNT with time limited doublet (VO)
- TP53 and IGHV predict shorter PFS

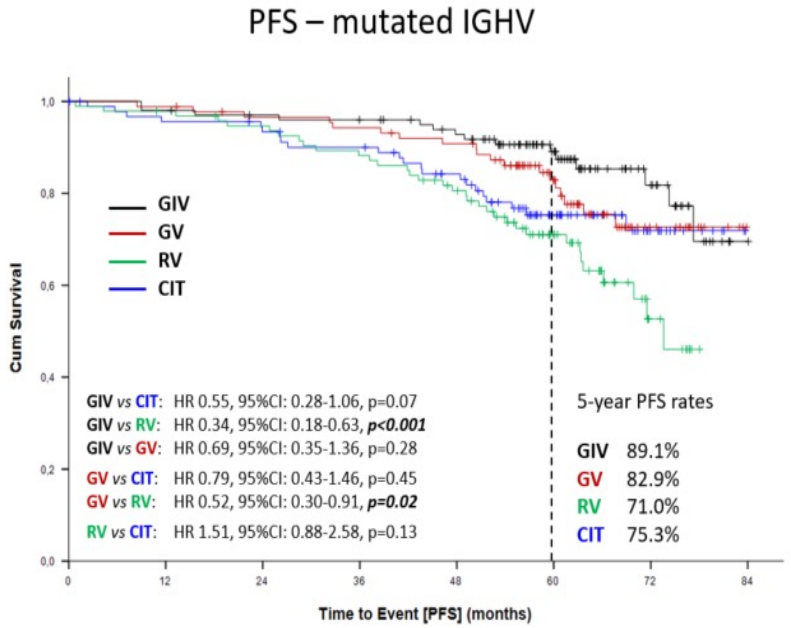
Al-Sawaf et. al, Blood, 2024

GAIA/CLL13: Ibrutinib plus Venetoclax plus Obinutuzumab vs. Venetoclax plus Obinutuzumab vs. Venetoclax plus Rituximab vs. CIT





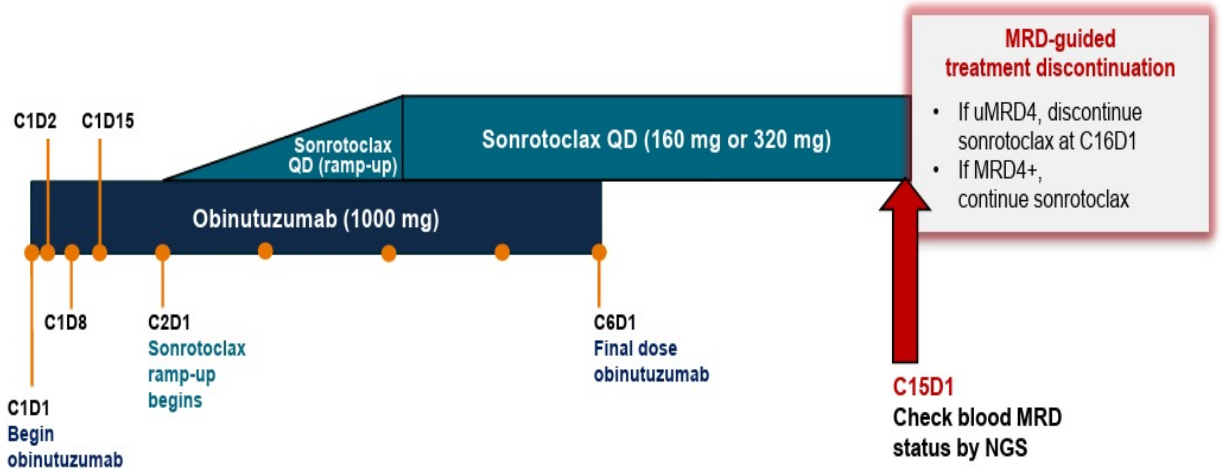


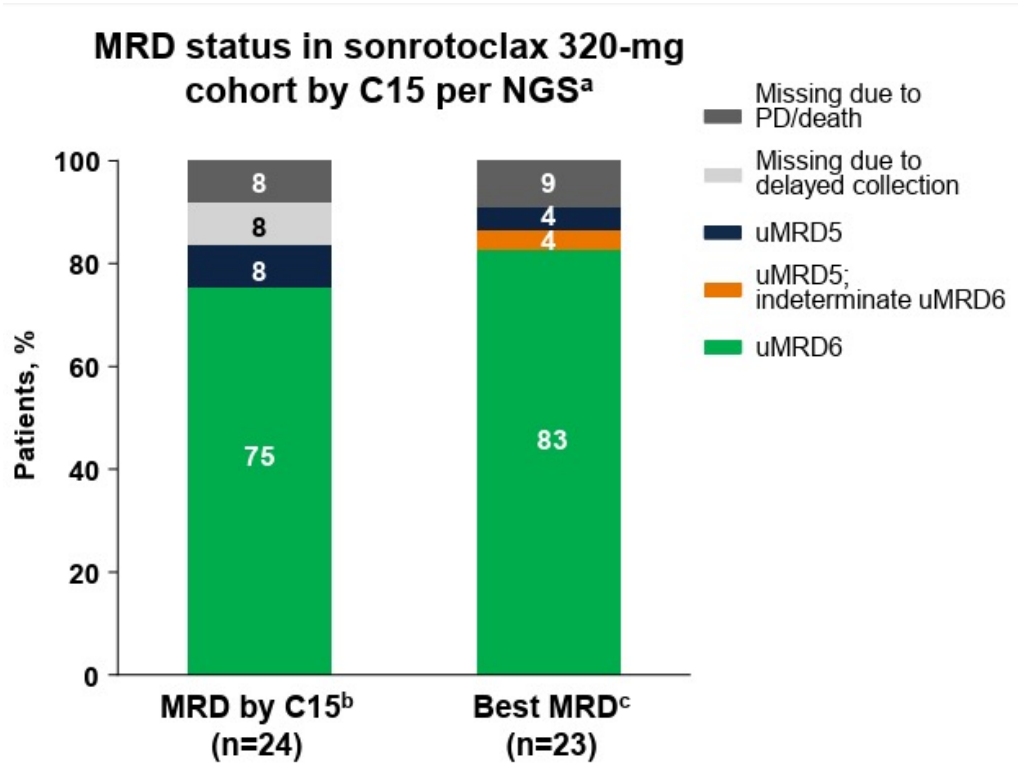


Lessons learned:
- VO and IVO superior to VR and CIT
- IVO had a better PFS compared to VO
- uIGHV status is independently associated with shorter PFS is all arms
- NO difference in the OS

Fürstenau M, et al, Blood, 2026

MRD-Guided Sonrotoclax plus Obinutuzumab





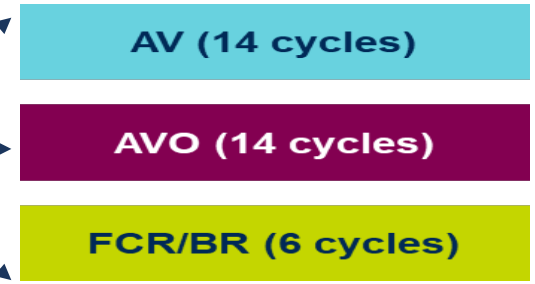
- All patients who reached C15 with a NGS sample analyzed (n=21) achieved at least uMRD5 and discontinued therapy as defined per protocol (ie, achieved at least uMRD4)
- 19/21 (91%) achieved uMRD6
- All patients remain in remission with a median time off treatment of 7.2 months

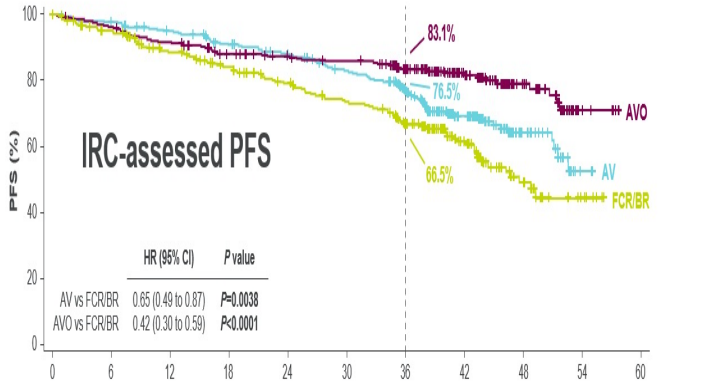
Fürstenau M, et al, Blood, 2026

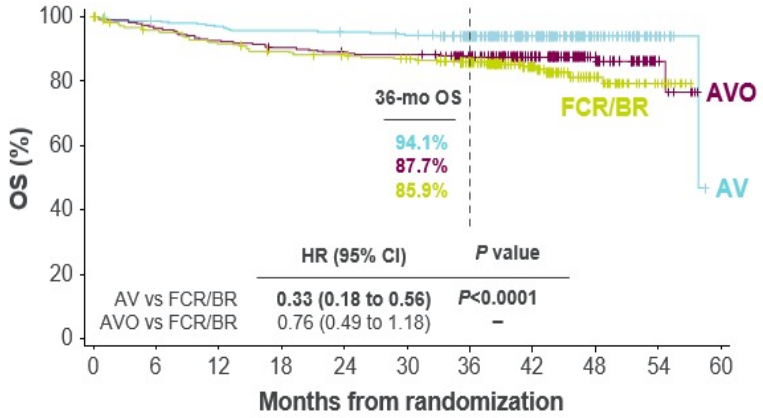
Fixed-duration cBTKi plus BCL2i: Added “value” anti-CD20 ab

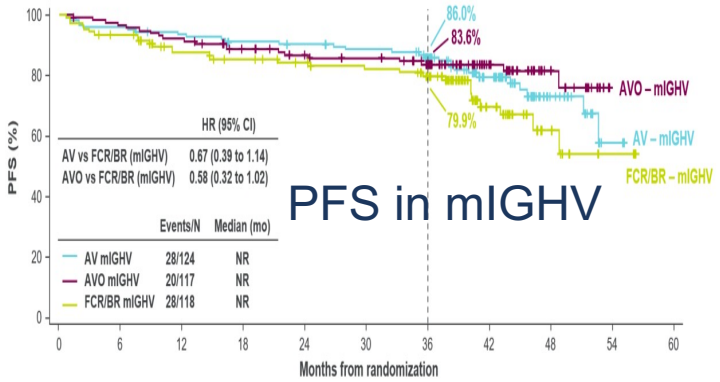
AMPLIFY Trial:
Acalabrutinib plus Venetoclax ± Obinutuzumab vs. FCR/BR

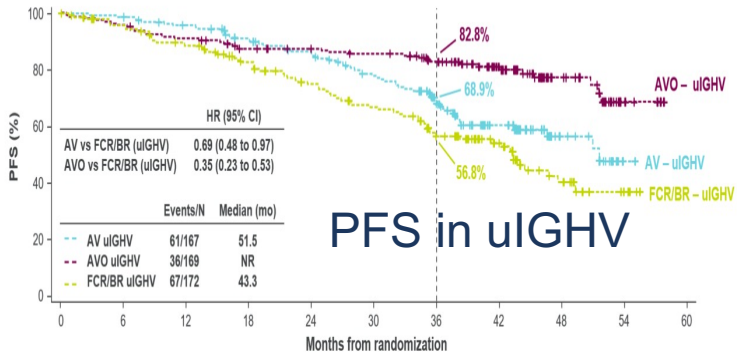
- TN CLL/SLL
- TP53 WT
- CIRS≤6











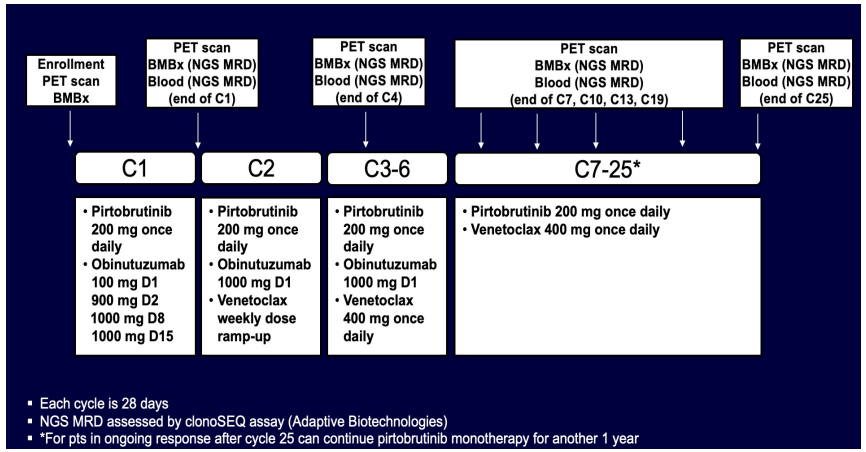
	AV (n=291)	AVO (n=284)	FCR/BR (n=259)
Any confirmed/suspected COVID-19 AE	64 (22.0)	69 (24.3)	10 (3.9)
Any confirmed/suspected COVID-19 AE leading to discontinuation of any treatment	7 (2.4)	23 (8.1)	3 (1.2)
Deaths due to COVID-19*	10 (3.4)	25 (8.7)	21 (7.2)

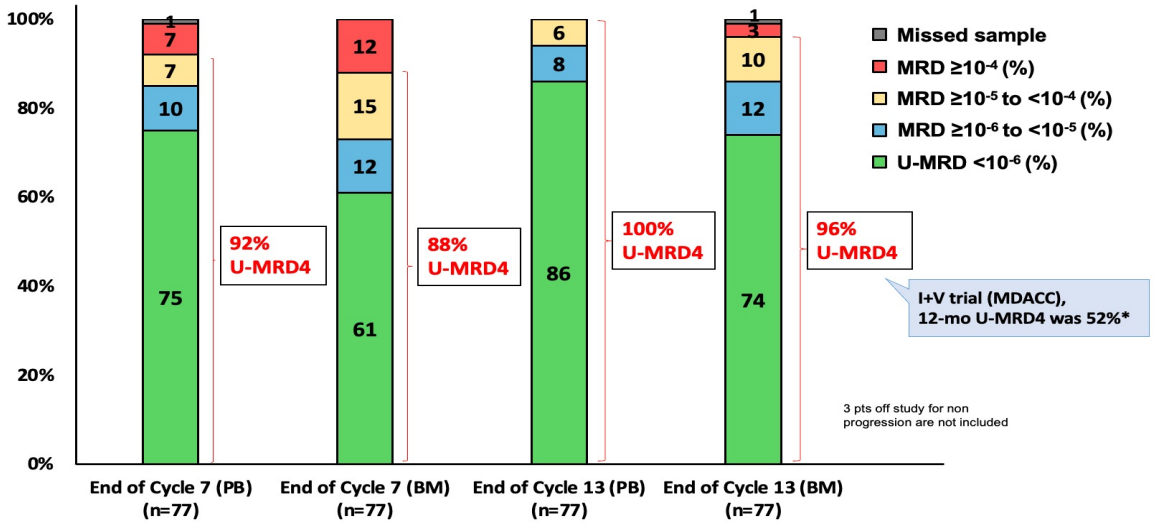
Lessons learned:

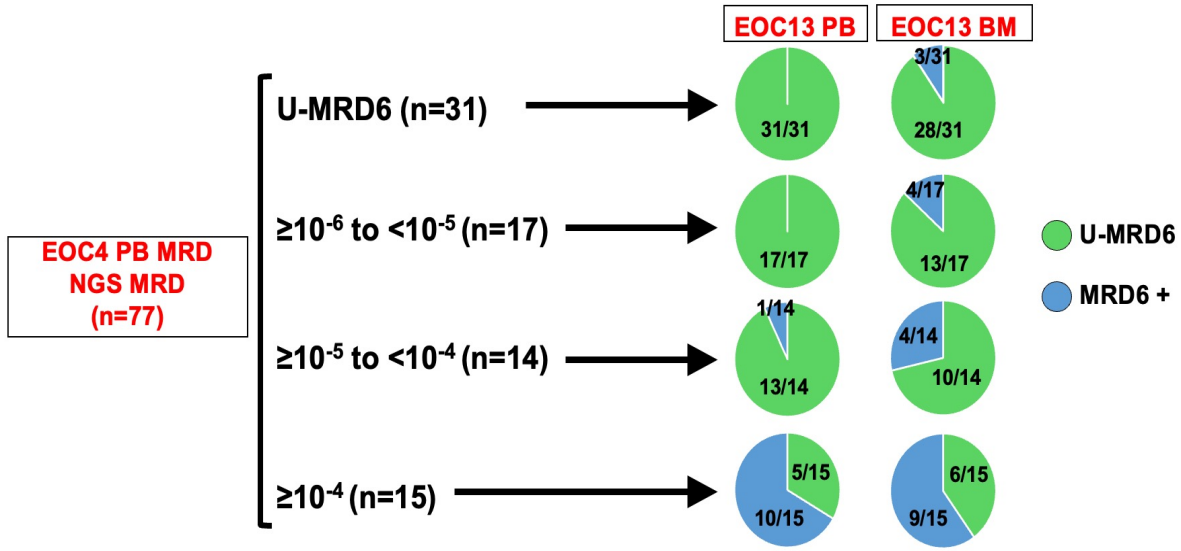
- AVO resulted in improved PFS over AV
- AVO advantage more pronounced in uIGHV population
- High infections and deaths in AVO
- PFS did NOT translate to an OS benefit

Brown J et al, NEJM, 2025

MDACC PVO Trial for CLL







- 6-mo: U-MRD6 PB 75%; BM 61%
- 12-mo: U-MRD6 PB 86%; BM 74%

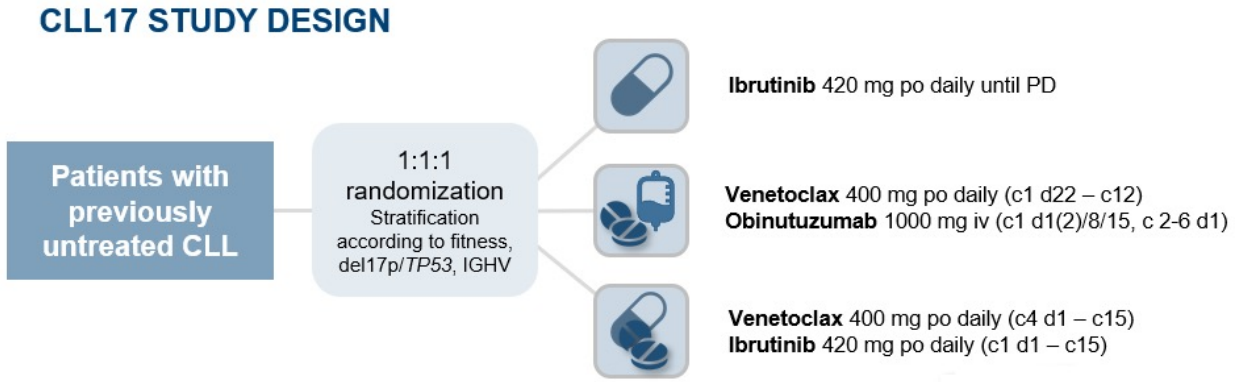
- Toxicity data is important to follow

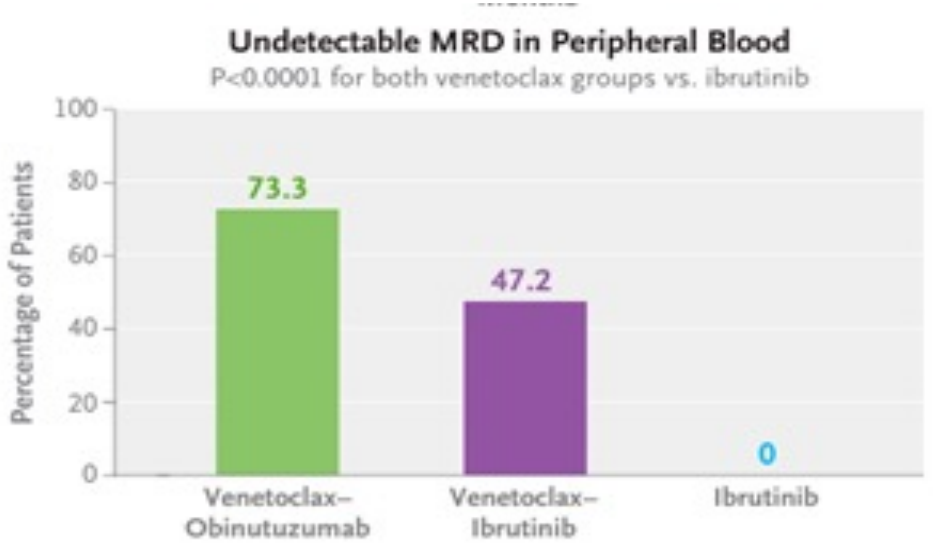
Jain N.et al, ASH, 2025

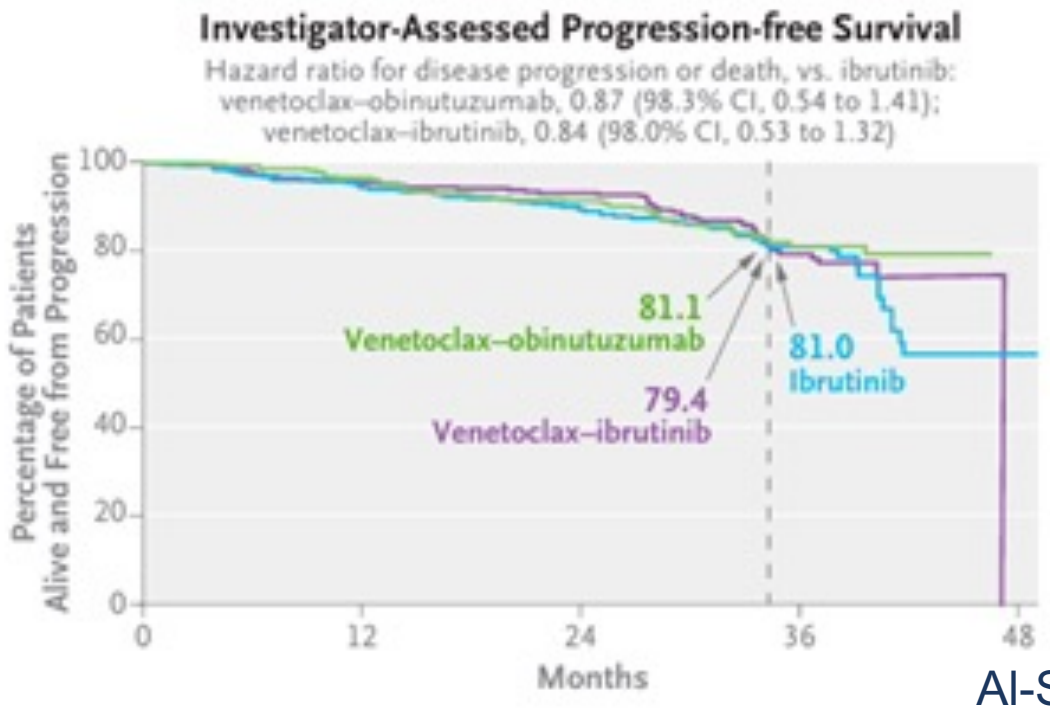
Are Ven-based fixed-duration doublets inferior to cBTKi treat to progression?

- RCT: IV vs. VO vs. I
- Indirect comparison: Z vs. AV

CLL17 Trial:
Venetoclax plus Obinutuzumab vs. Venetoclax plus Ibrutinib vs. Ibrutinib





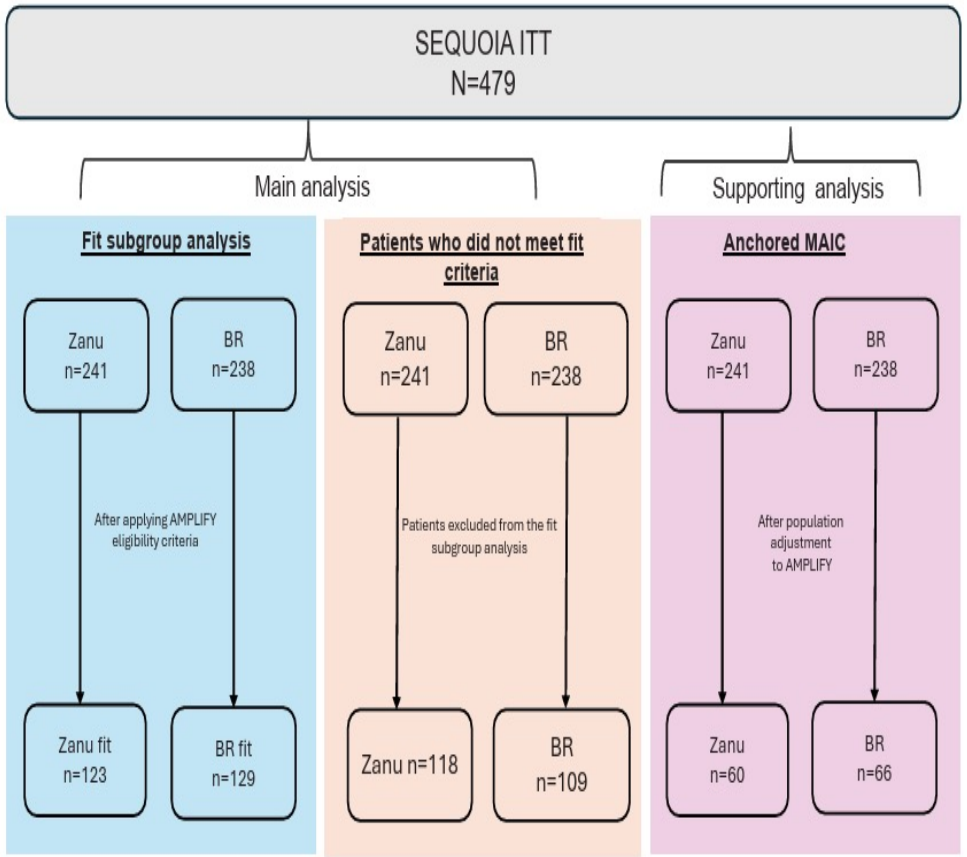


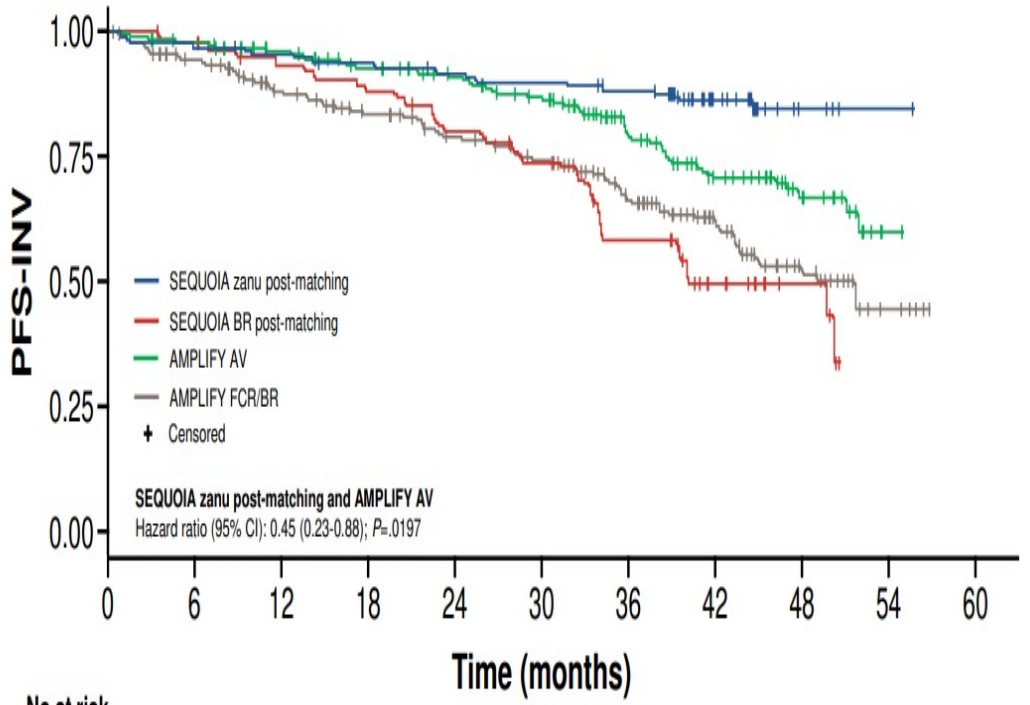
Lessons learned:

- With 3 years of follow-up, FD doublets were non-inferior to I monotherapy for PFS
- Higher uMRD rate with VO compared to VI
- Risk of infection is relevant with all therapies
- VO: more neutropenia, more grade 3-5 infections and COVID-19
- VO: May be preferred for unfit
- VI and I: numerical trend for better PFS in TP53 aberrant

Al-Sawaf O, NEJM, 2025

Indirect comparison Zanubrutinib vs. Acalabrutinib plus Venetoclax



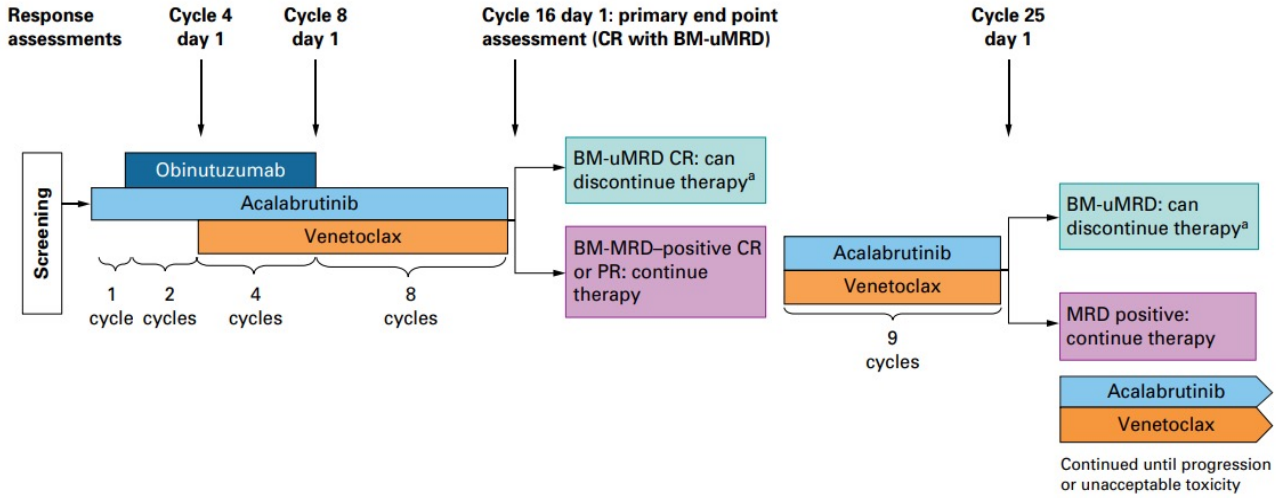


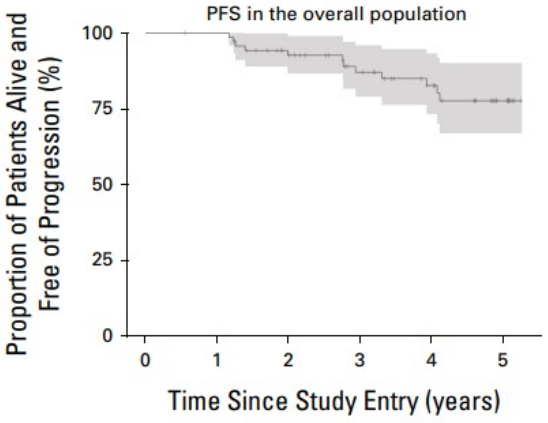
No at risk											
SEQUOIA zanu post-matching	102	97	95	93	90	89	84	42	9	1	0
SEQUOIA BR post-matching	103	87	82	77	69	64	48	21	4	0	0
AMPLIFY AV	291	282	272	258	246	231	182	105	34	2	0
AMPLIFY FCR/BR	290	236	210	192	176	161	130	68	31	8	0

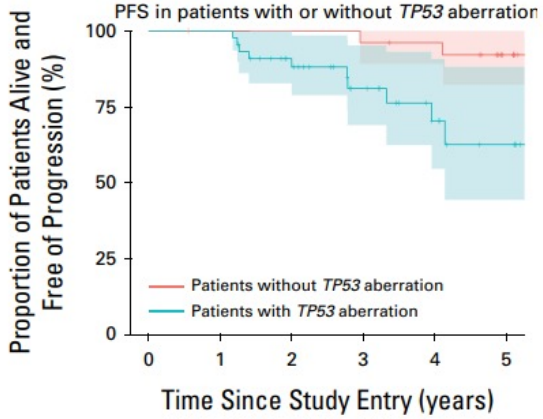
Shadman M et al., Blood Adv, 2025

MRD Guided Triplets and Doublets

DFCI AVO Trial:
MRD guided Acalabrutinib plus Venetoclax plus Obinutuzumab





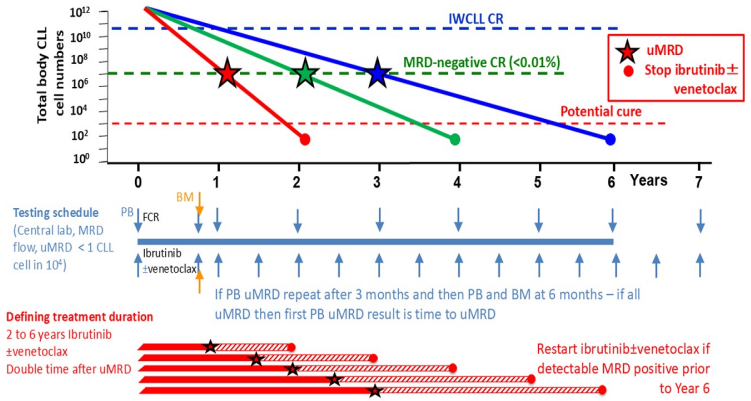


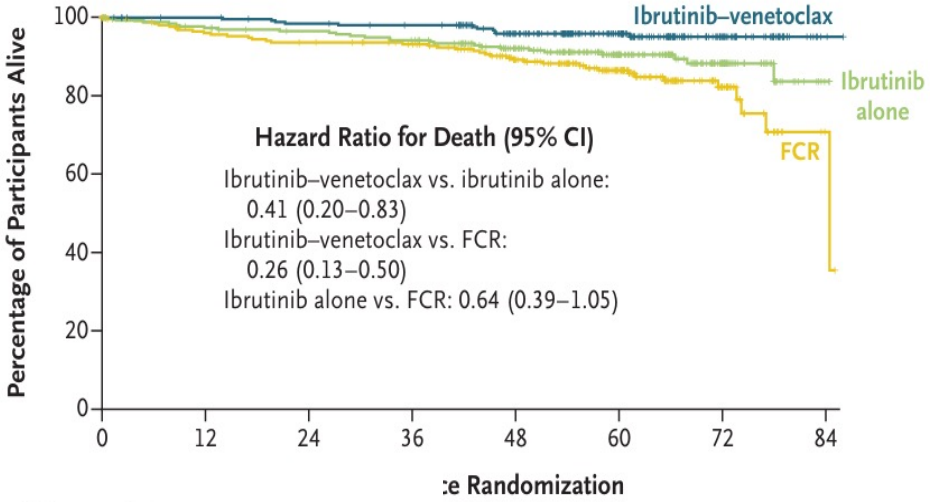
Lessons learned:

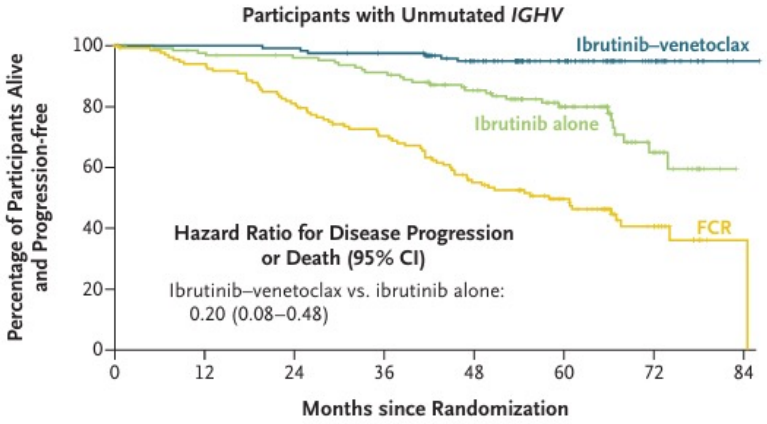
- CR and uMRD rate similar in patients with TP53 aberration and all comers
- 4-year PFS in TP53 aberrant 70% and TP53 WT 96%
- Important MRD guided FD option for high-risk patients
- Only 1 (of 72) patients died due to COVID-19
- Highlights the importance of supportive care with triplets are considered

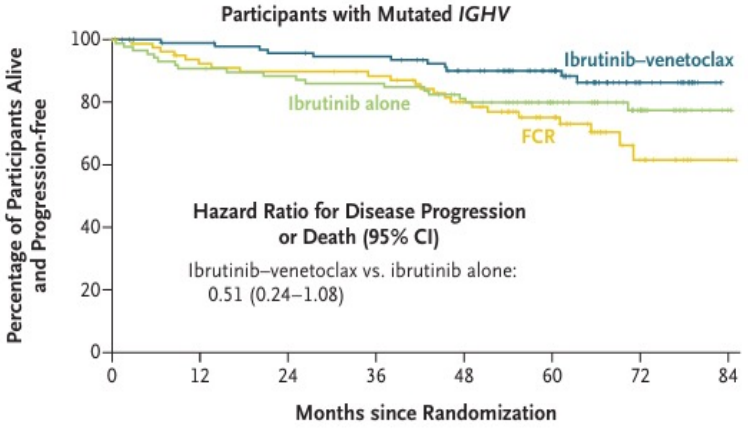
Davids M et al, JCO, 2025

UK FLAIR Trial:
MRD Guided Ibrutinib plus Venetoclax





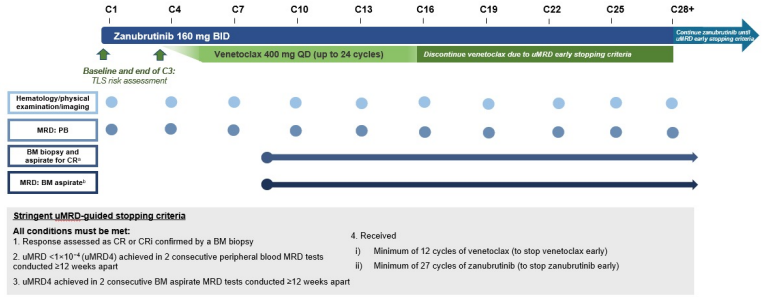


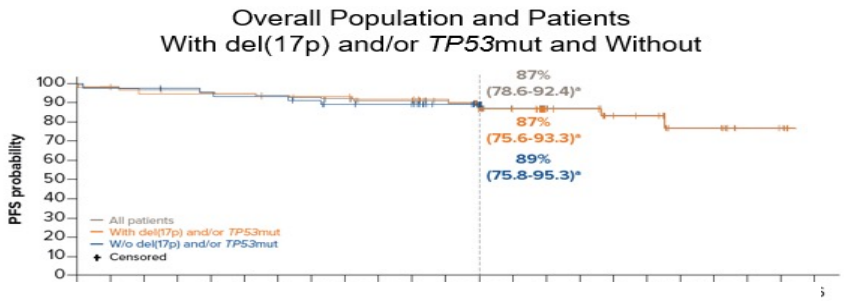


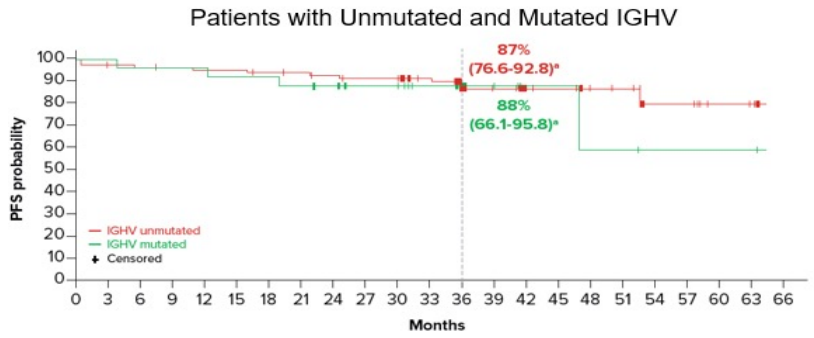
Lessons learned:
- High efficacy of MRD guided BTKi and BCL2i
- Importance of considering an MRD approach in high-risk patients

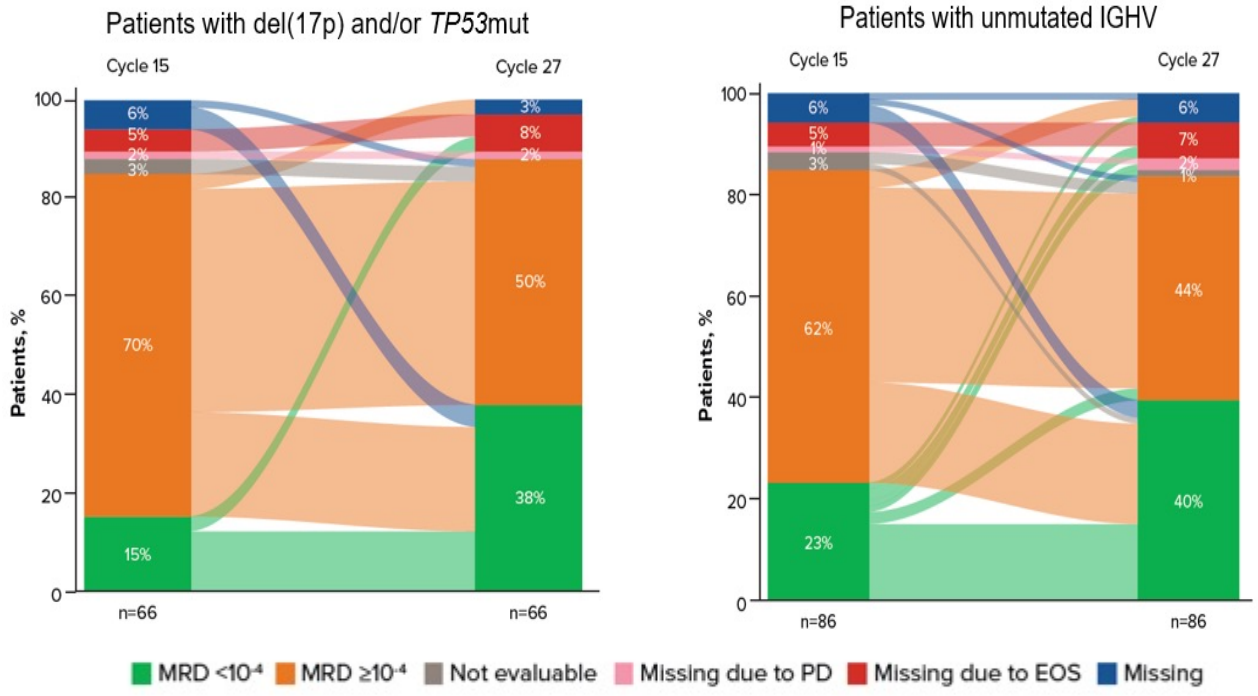
Munir T et al, NEJM, 2025

SEQUOIA Arm D:
MRD-guided Zanubrutinib plus Venetoclax in High-risk CLL





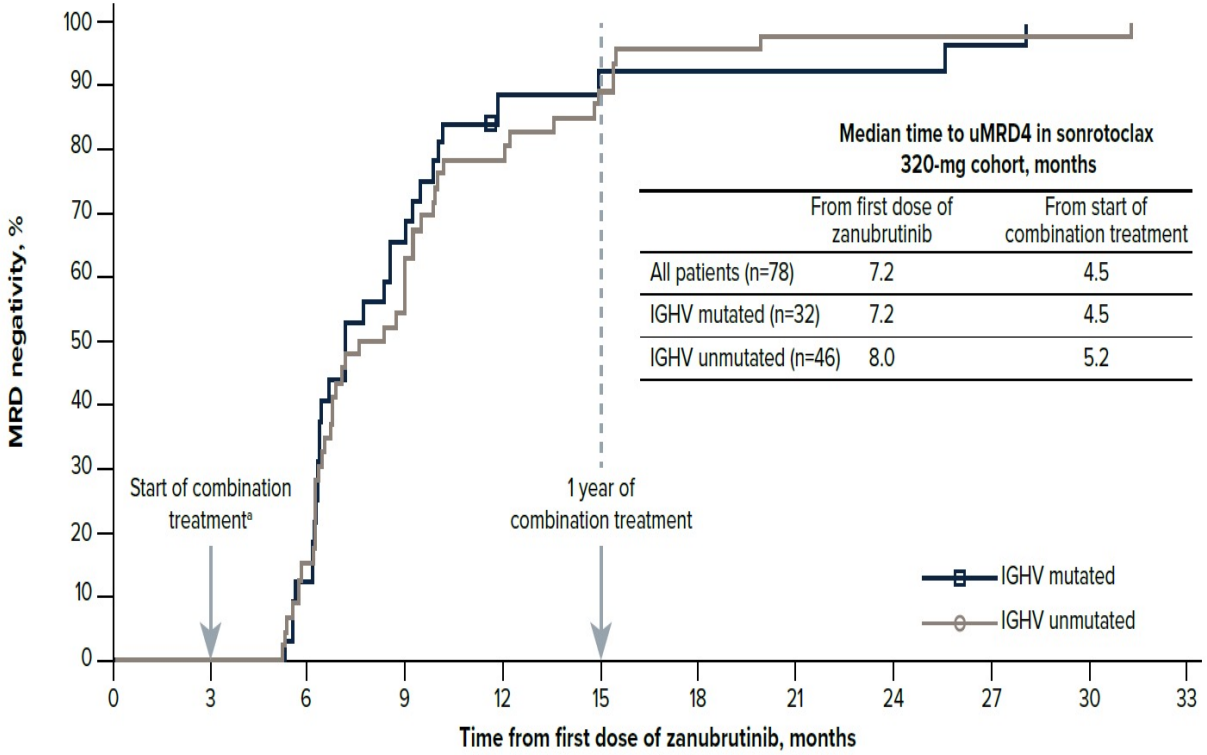




Lessons learned:
- High efficacy of MRD guided BTKi and BCL2i
- Improvement in quality of response with longer treatment in high-risk groups
- Importance of considering an MRD approach in high-risk patients

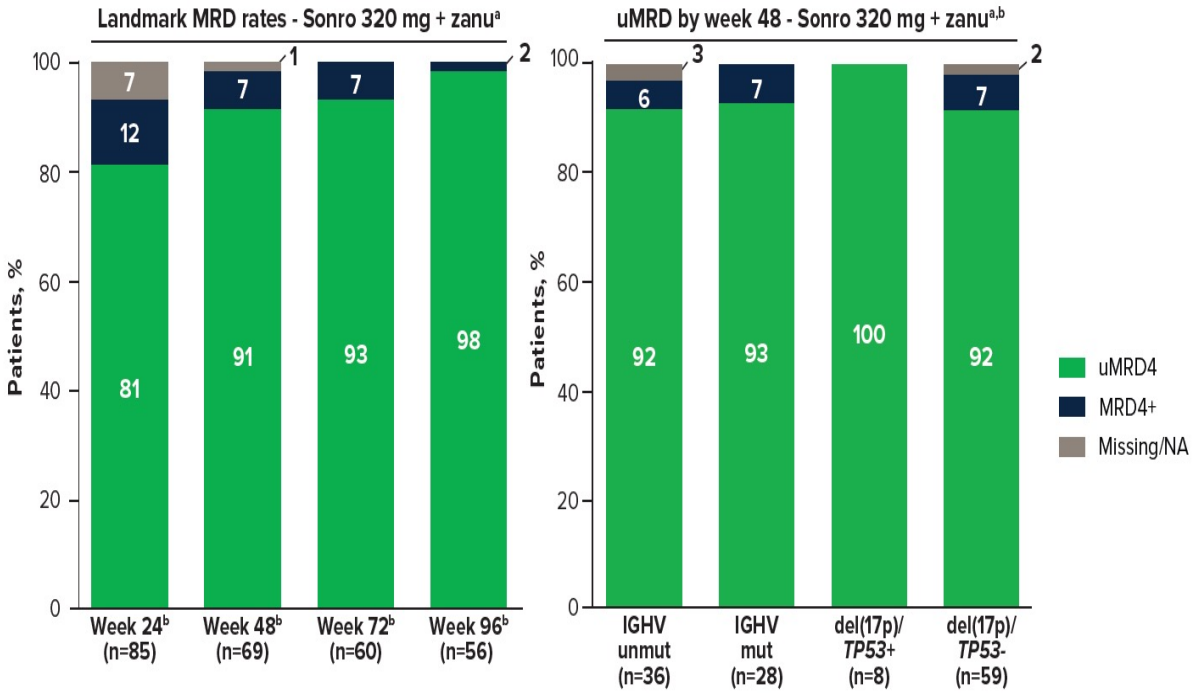
Shadman M, et al, JCO, 2025 ; Shadman M et al, ASH, 2025

Sonrotoclax plus Zanubrutinib for TN CLL



Median time to uMRD4 in sonrotoclax 320-mg cohort, months

	From first dose of zanubrutinib	From start of combination treatment
All patients (n=78)	7.2	4.5
IGHV mutated (n=32)	7.2	4.5
IGHV unmutated (n=46)	8.0	5.2



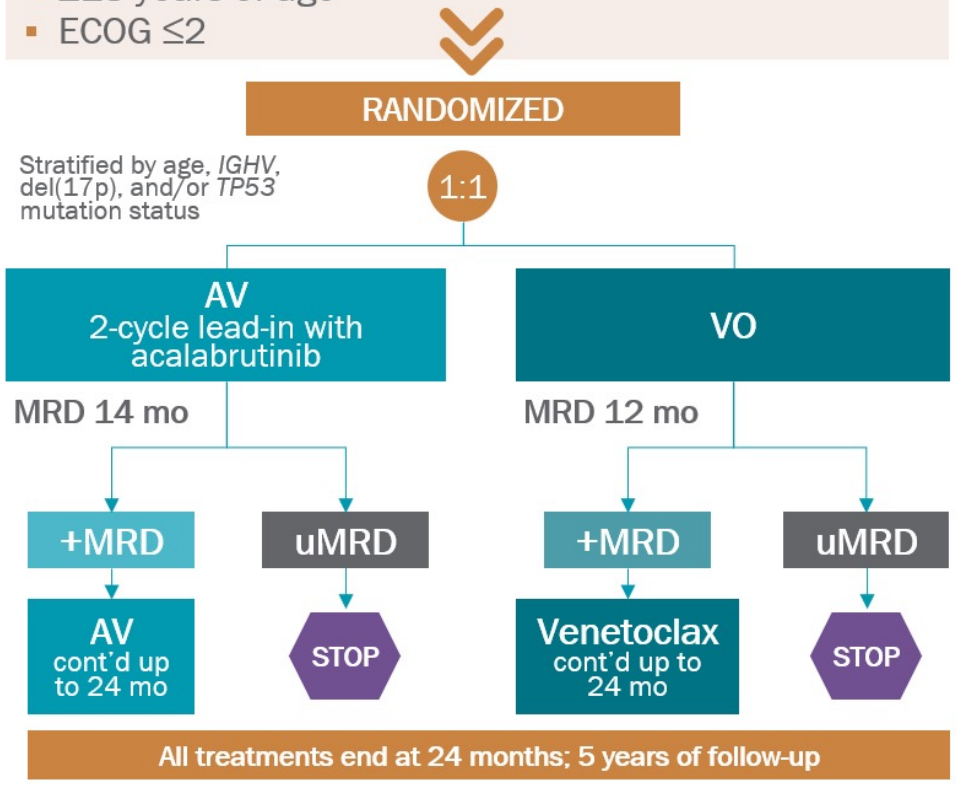
Tam C. et al, ASH, 2025

Key Ongoing and Anticipated Trials in CLL

MAJIC:
Acalabrutinib + Venetoclax vs Venetoclax + Obinutuzumab

Key Eligibility Criteria

- Previously untreated CLL
- ≥18 years of age
- ECOG ≤2



Primary endpoint

- INV-assessed PFS

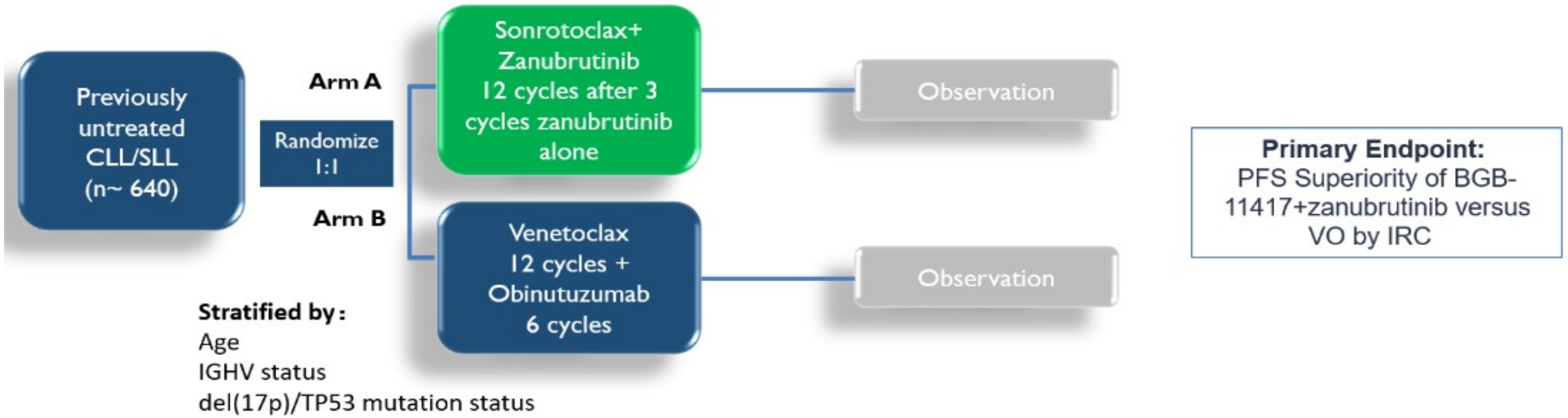
Key secondary endpoints

- uMRD rates at sequential timepoints (after 6 and 12 cycles of V and yearly thereafter [key timepoint: after 12 cycles of V])
- OS
- EFS
- ORR
- CR rate (per uMRD)
- Quality of life/patient-reported outcomes
- Safety and tolerability

CELESTIAL-CLLTN-1:
Sonrotoclax + Zanubrutinib vs. Venetoclax + Obinotuzumab

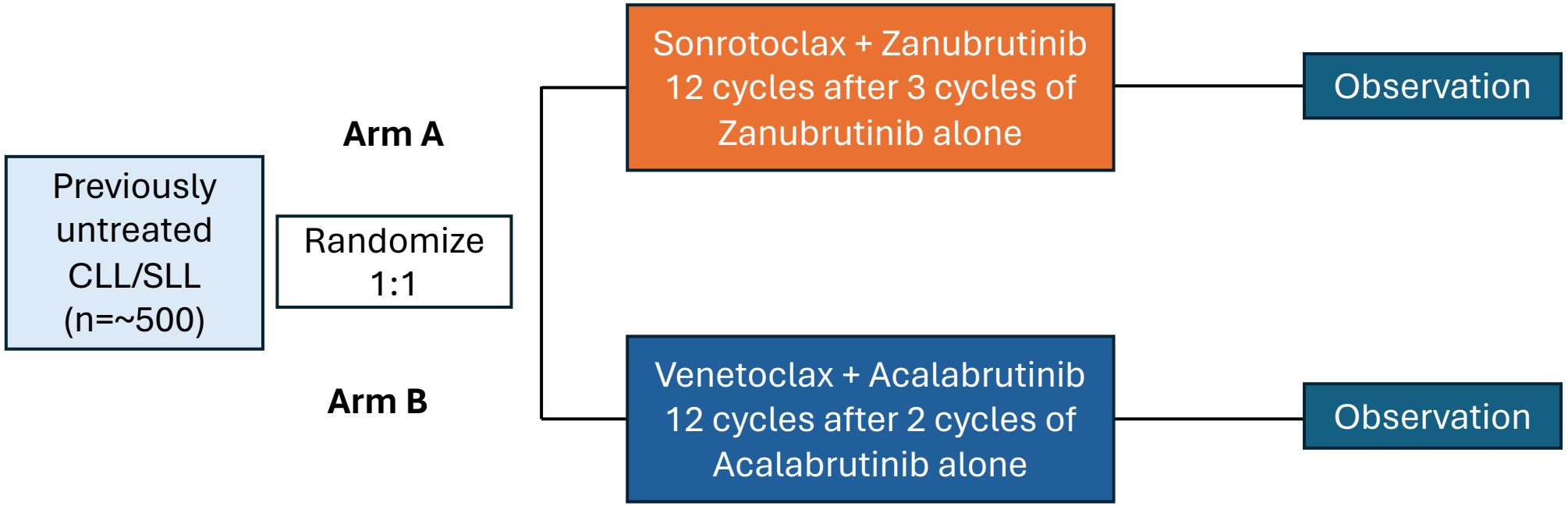
BGB-11417-301: 2-arm fixed duration study design

Phase 3 registrational trial



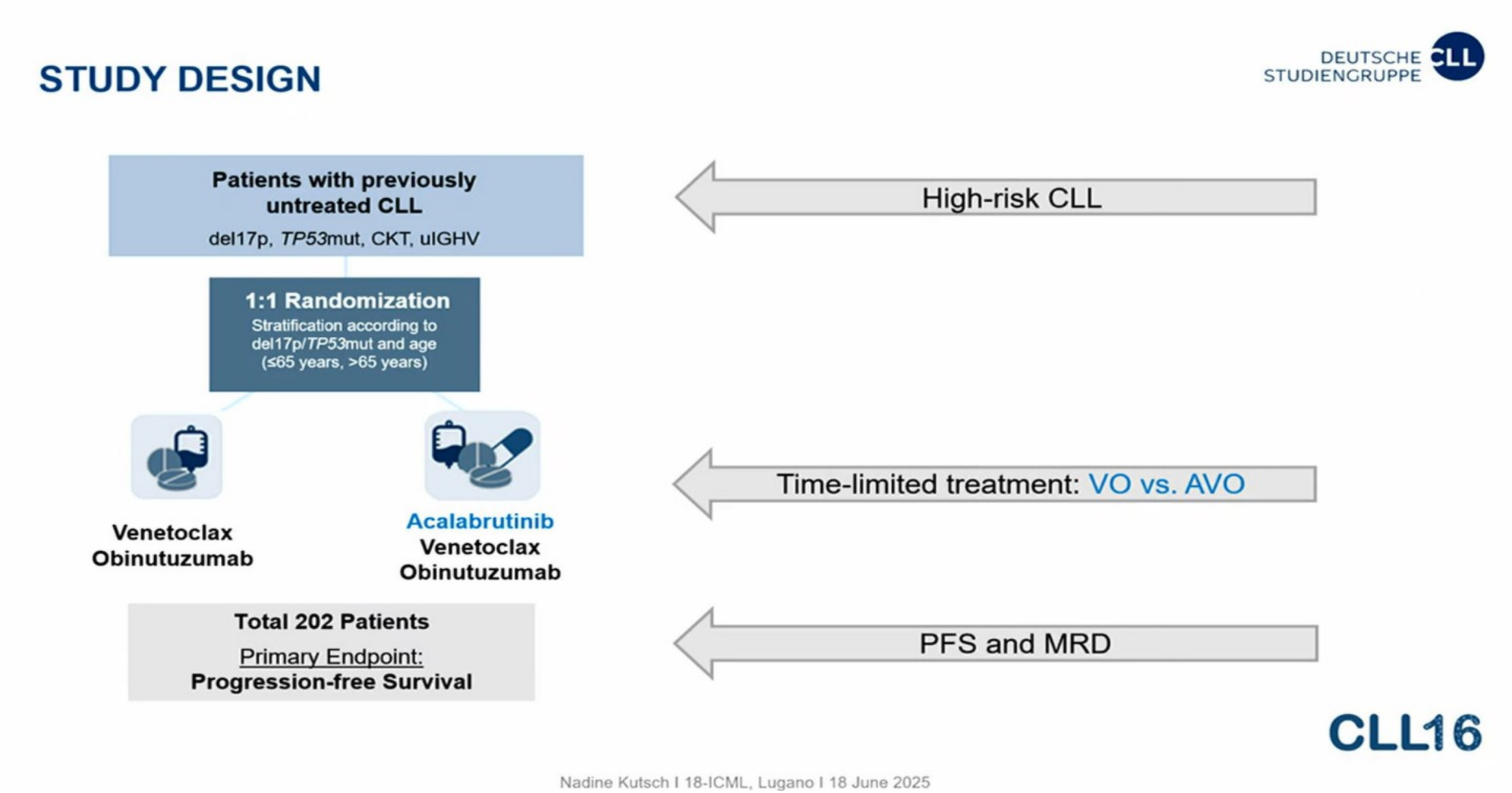
Shadman M, ASCO, 2024 (TiP)

CELESTIAL-CLLTN-2:
Sonrotoclax + Zanubrutinib vs. Venetoclax + Acalabrutinib

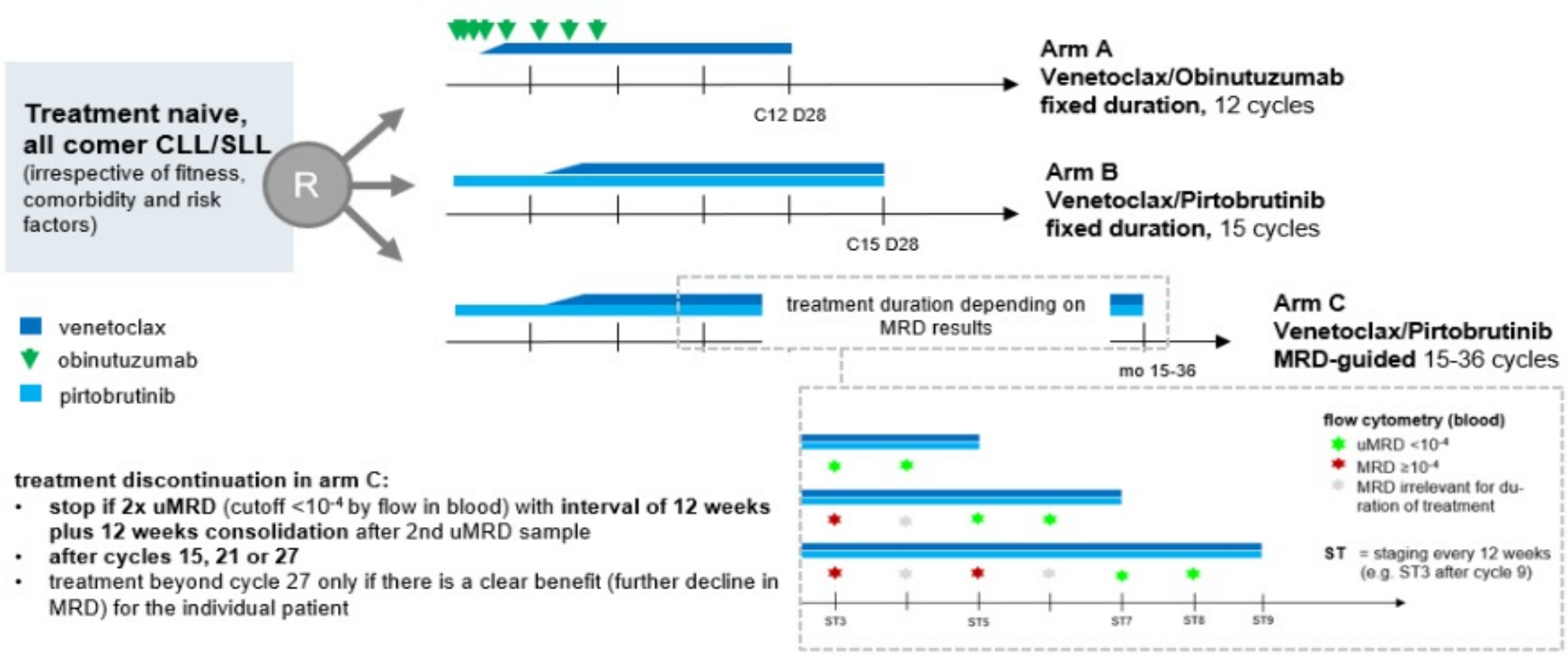


- The primary endpoint is PFS by IRC
- Intermediate endpoint of uMRD4 rate in PB and BM

CLL16:
Acalabrutinib plus Venetoclax plus Obinotuzumab vs. Venetoclax plus Obinotuzumab



CLL18/MOIRAI:
Pirtobrutinib plus Venetoclax vs. Venetoclax plus Obinotuzumab

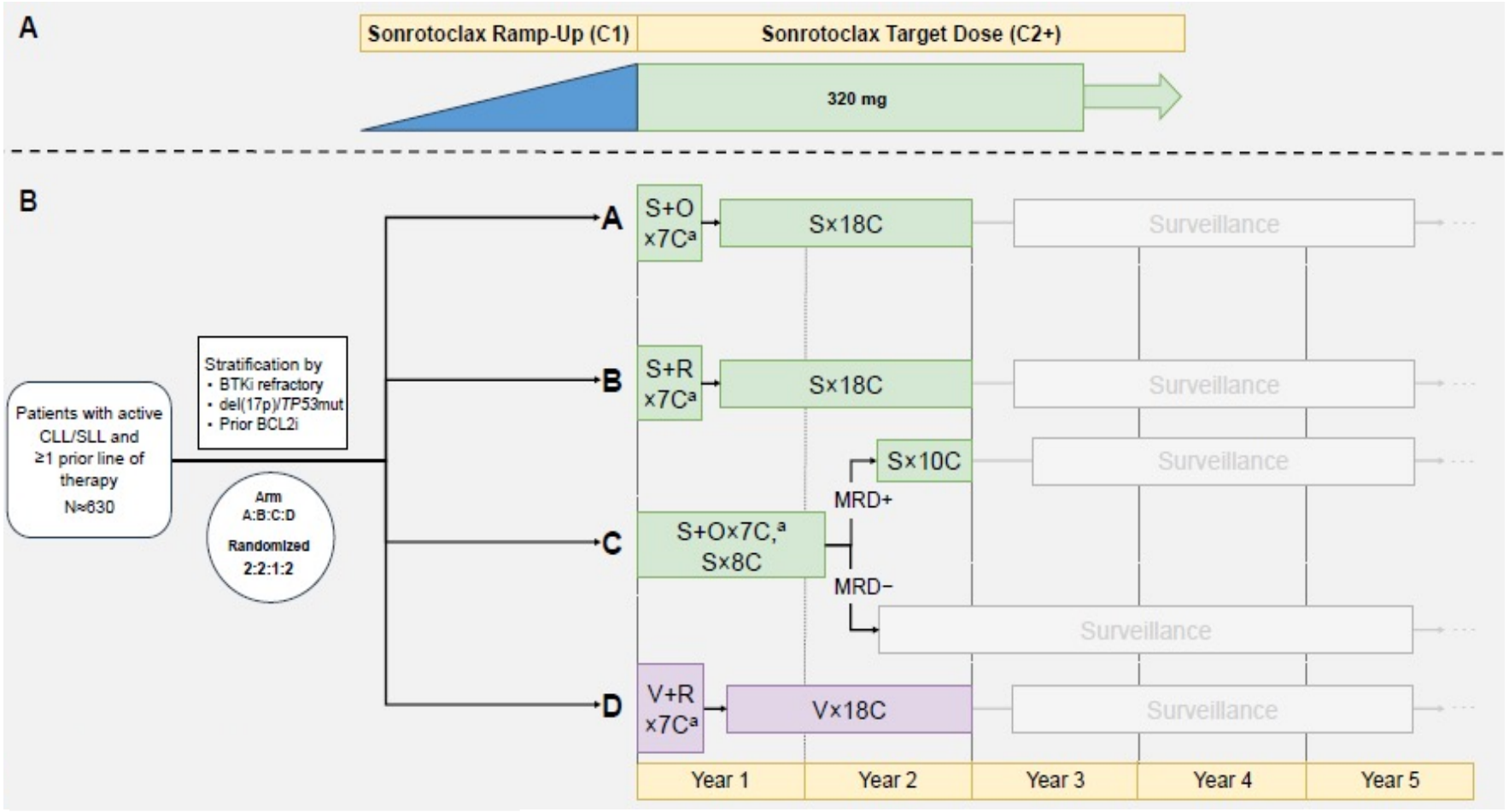


treatment discontinuation in arm C:

- **stop if 2x uMRD** (cutoff <10^{-4} by flow in blood) with **interval of 12 weeks plus 12 weeks consolidation** after 2nd uMRD sample
- **after cycles 15, 21 or 27**
- treatment beyond cycle 27 only if there is a clear benefit (further decline in MRD) for the individual patient

Cramer P et al., EHA, 2025

CELESTIAL-RRCLL



Al-Sawaf et al, ASH, 2025 (TiP)

Putting it All Together

Monotherapy with cBTKi

- Excellent efficacy irrespective of high-risk features
- Improved safety with second generation cBTKis but cumulative toxicity is still relevant
- Risk of resistance mutations at progression with treat to progression approach
- Limited use in patients with bleeding disorder or major cardiac issues

Doublet: BCL2 +anti CD20

- Longest follow-up for finite treatment
- Treatment of choice when BTKi is not an option
- Cross-trial comparison shows higher uMRD rate compared to the approved oral doublets
- Inconvenience of intravenous treatment
- Infection risk with anti CD20 ab
- Obinutuzumab is superior to rituximab
- Awaiting SO vs. Ven-anti CD20 study in R/R setting

Doublet: cBTKi + BCL2i

- All oral is an attractive option for patients
- uMRD rates after FD approved regimens with cBTKi (IV/AV/ZV) seem lower that VO with cross trial comparison
- MRD guided approaches result in high efficacy in high-risk pts
- New BCL2i (Sonrotoclax) combination (ZS) seem to provide high uMRD rate
- Important to await some ongoing trials
- Limited use in patients with bleeding disorder or major cardiac issues

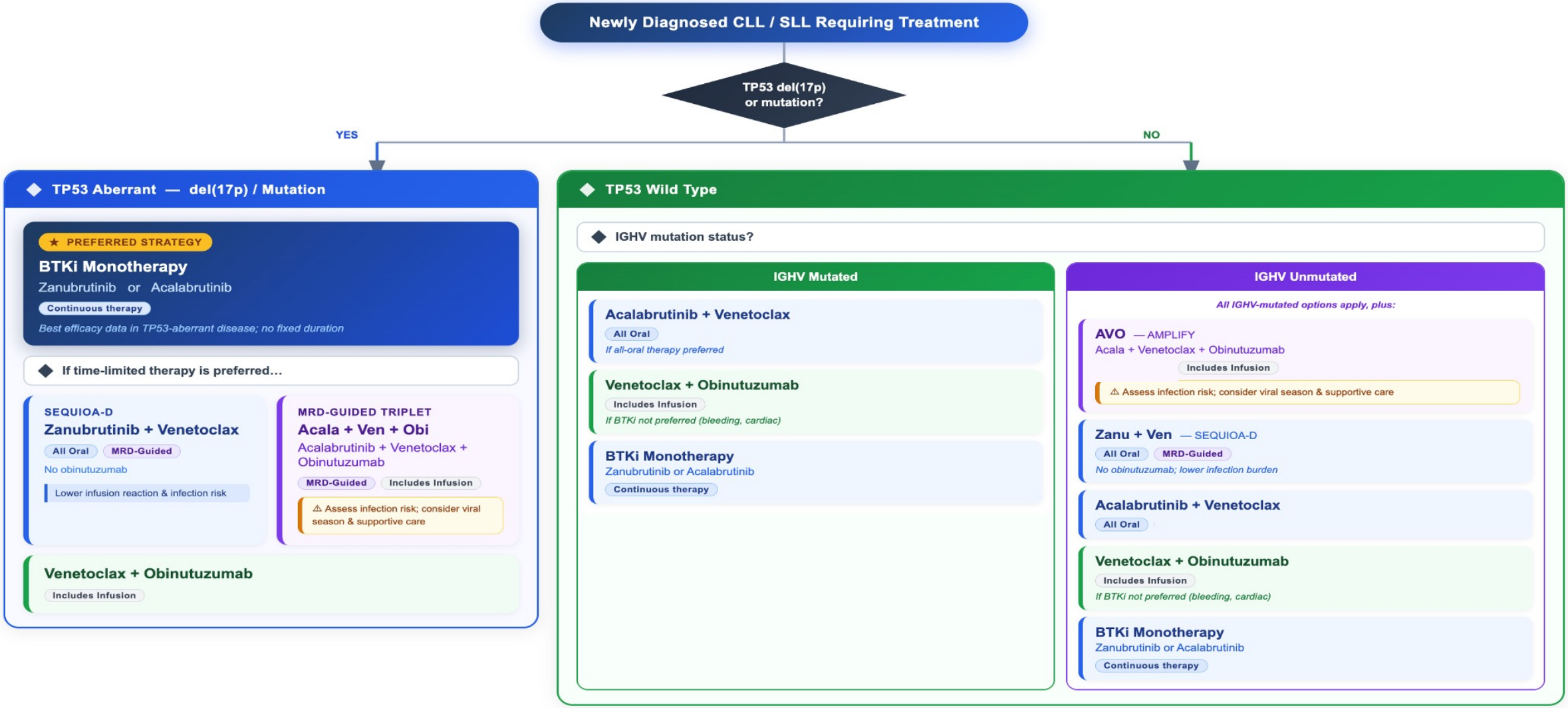
Triplets: cBTKi + BCL2i+anti CD20

- Very high efficacy
- Consider in pts with high-risk features
- MRD guided approaches (AVO) result in high efficacy
- Risk of infection should be waited against the benefit
- Importance of supportive care

(my) Proposed Approach

First-line Treatment Algorithm in CLL / SLL

V = venetoclax · O = obinutuzumab · A = acalabrutinib · Z = zanubrutinib · MRD = minimal residual disease · ★ = preferred strategy



Thank You!

Fred Hutch Cancer Center

@mshadman

W Medicine UNIVERSITY of WASHINGTON