NICOLE LAMANNA, MD
Columbia University Herbert Irving
Comprehensive Cancer Center
New York, New York

19TH ULTMANN
CHICAGO LYMPHOMA SYMPOSIUM

THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

19TH INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

#IUCLS2022

WHAT'S NOW AND NEXT FOR CLL?

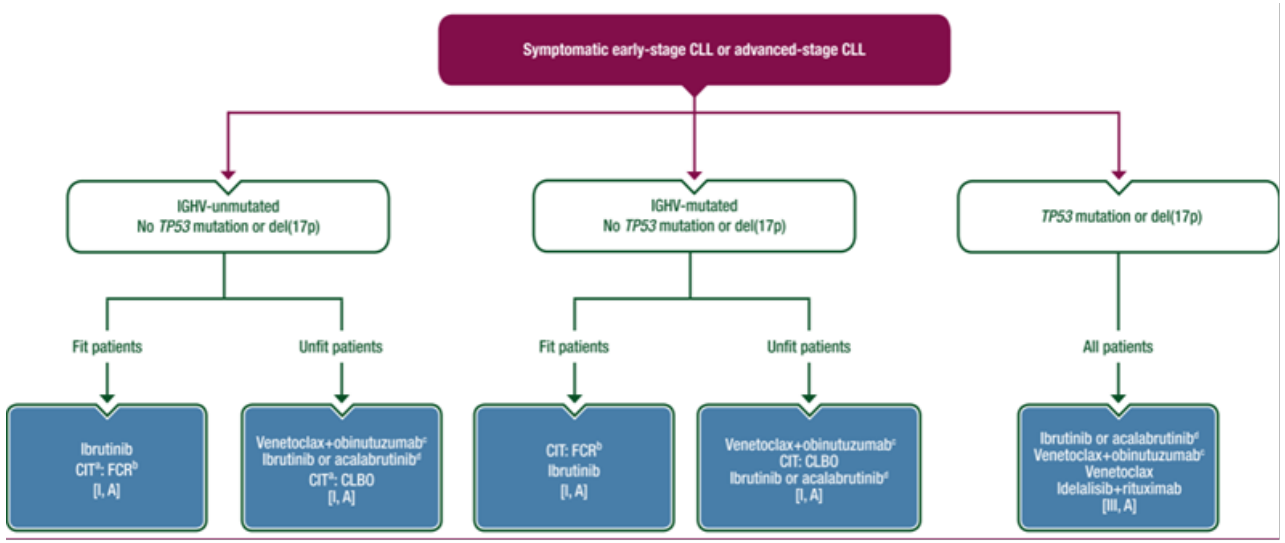
Disclosures
Nicole Lamanna, MD

I have the following financial relationships to disclose:

SAB/Consultant/Honoraria: AbbVie, Adaptive Biosciences, Astra-Zeneca, Bei-Gene, Celgene, Genentech, Janssen, LOXO/Eli Lilly, Pharmacyclics

Institutional Research funding: AbbVie, Astra-Zeneca, BeiGene, Genentech, LOXO/Eli Lilly, MingSight, Octapharma, Oncternal, TG Therapeutics, Verastem

Currently in CLL/SLL, Therapeutic Progress Has Been Recognized by Leading US and EU Groups Across Disease Subtypes



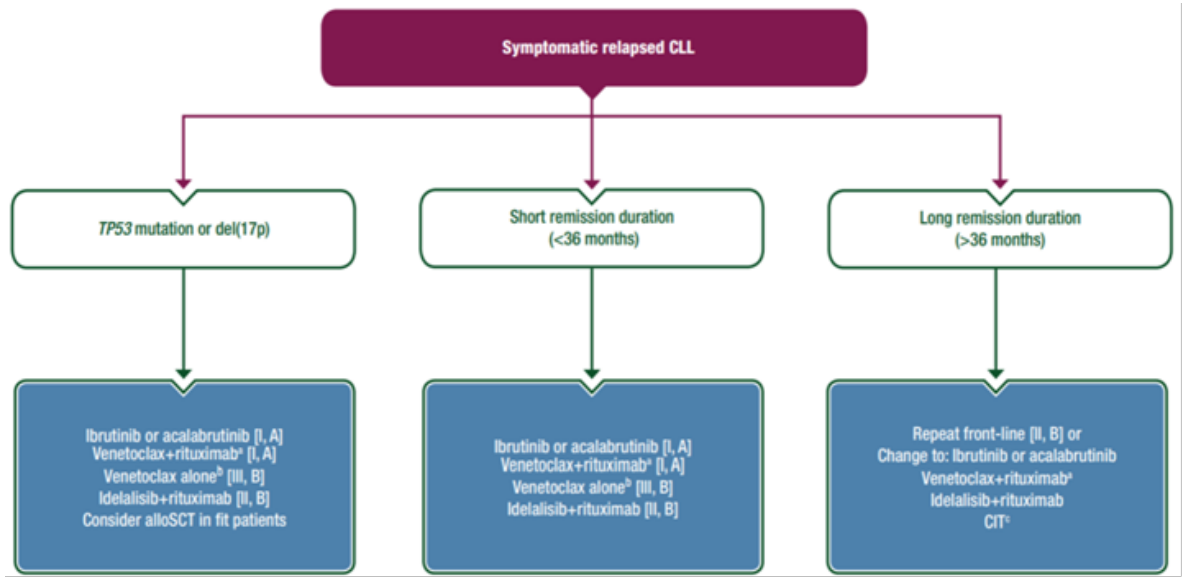
First- and second-generation BTK inhibitors and venetoclax incorporated into ESMO Guidelines …

… as well as NCCN Guidelines

In patients with TN CLL meeting indications for treatment, the NCCN recommends …

✓ Frail, with significant comorbidities ✓ Aged ≥65 y ✓ Younger patients, significant comorbidities (CrCl <70 mL/min)	✓ Patients aged <65 y without significant comorbidities	✓ Patients with mutated *TP53*/del(17p)
• Acalabrutinib ± obinutuzumab (category 1) • Ibrutinib (category 1) • Venetoclax + obinutuzumab (category 1)	• Acalabrutinib ± obinutuzumab (category 1) • Ibrutinib (category 1) • Venetoclax + obinutuzumab	• Acalabrutinib ± obinutuzumab • Ibrutinib • Venetoclax + obinutuzumab

Progress in CLL Care is Also Reflected in Recommendations for R/R Disease



First- and second-generation BTK inhibitors and venetoclax incorporated into ESMO and NCCN Guidelines for patients with relapsed CLL

✓ Frail, with significant comorbidities ✓ Aged ≥65 y ✓ Younger patients, significant comorbidities (CrCl <70 mL/min)	✓ Patients aged <65 y without significant comorbidities	✓ Patients with mutated *TP53*/del(17p)
	• Acalabrutinib (category 1) • Ibrutinib (category 1) • Venetoclax + rituximab (category 1) • Duvelisib • Idelalisib + rituximab	

Targeted Therapy FDA Approvals and Current Status in CLL[1-7]

Agent	Target	Status in CLL/SLL
Ibrutinib	BTK	Approved
Acalabrutinib		Approved
Zanubrutinib		Phase 3 (SEQUOIA)
Pirtobrutinib		Phase 3 (NCT04666038)
Venetoclax	BCL-2	Approved
Idelalisib	PI3K	Approved
Duvelisib		Approved
Umbralisib		Phase 3

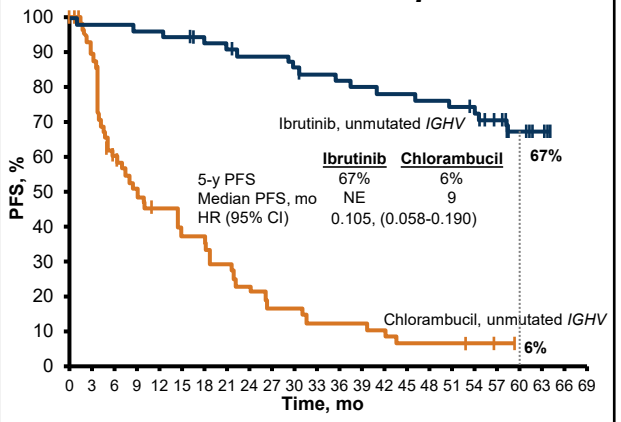
1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf. 2. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. 3. Brukinsa (zanubrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf. 4. Venclexta (venetoclax) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf. 5. Zydelig (idelalisib) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf. 6. Copiktra (duvelisib) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211155s000lbl.pdf. 7. Ukoniq (umbralisib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213176s000lbl.pdf.

Consistent Benefit With BTKi Therapy Over CIT in Unmutated IGHV Subgroups

Treatment-Naïve Elderly Patients or Those With Coexisting Medical Conditions

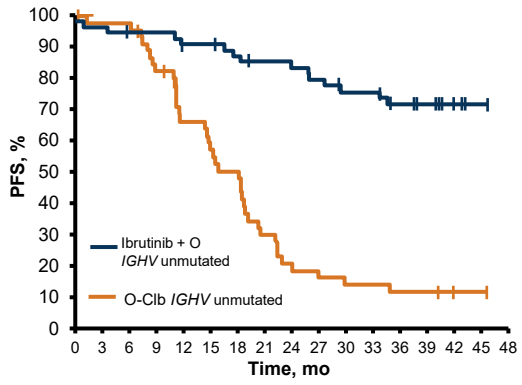
PFS in IGHV Unmutated Patients Treated With Ibrutinib

RESONATE-2:
Ibrutinib vs Chlorambucil[1]
5-Year Follow-Up

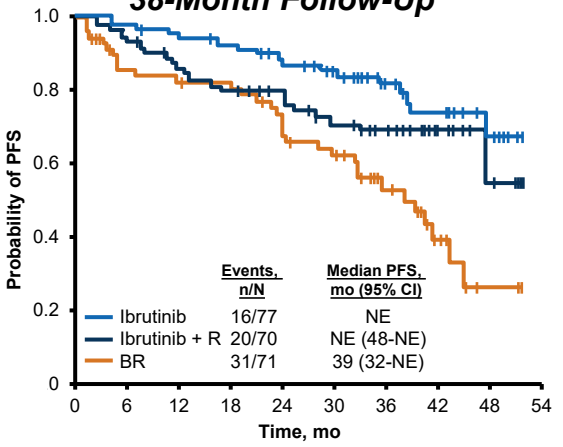


6.5-year PFS of 62% with ibrutinib (unmutated IGHV)[2]

iLLUMINATE:
O-Clb vs Ibrutinib + Obinutuzumab[3]
4-Year Follow-Up

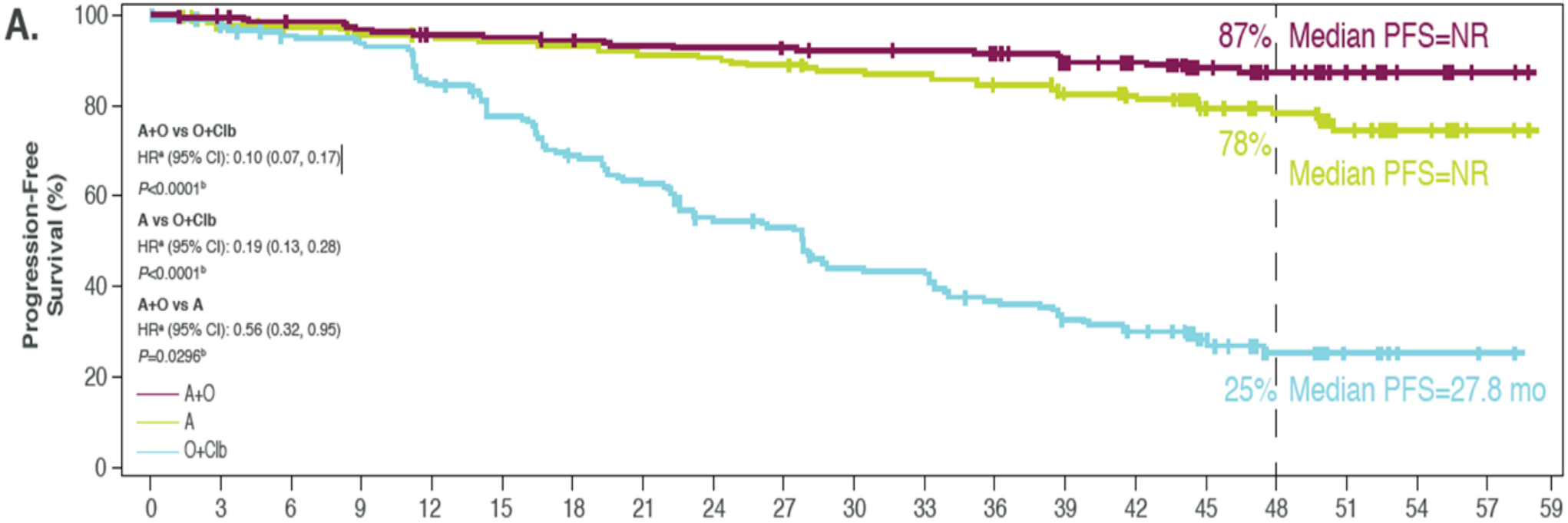


ALLIANCE: Ibrutinib vs Ibrutinib + Rituximab vs BR[4]
38-Month Follow-Up



1. Burger JA et al. *Leukemia*. 2020;34:787-798. 2. Barr P et al. ASCO 2021. Abstract 7523. 3. Moreno C et al. IWCLL 2019. Abstract 2069.
4. Woyach J et al. *N Engl J Med*. 2018;379:2517-2528.

ELEVATE-TN (Acalabrutinib ± Obinutuzumab): PFS (Primary Endpoint)[1]



A+O vs O+Clb

HR[a] (95% CI): 0.10 (0.07, 0.17)

P<0.0001[b]

A vs O+Clb

HR[a] (95% CI): 0.19 (0.13, 0.28)

P<0.0001[b]

A+O vs A

HR[a] (95% CI): 0.56 (0.32, 0.95)

P=0.0296[b]

Post-hoc analysis (original publication):[2] HR for PFS between acalabrutinib-obinutuzumab and acalabrutinib monotherapy was 0.49 (95% CI 0.26–0.95)

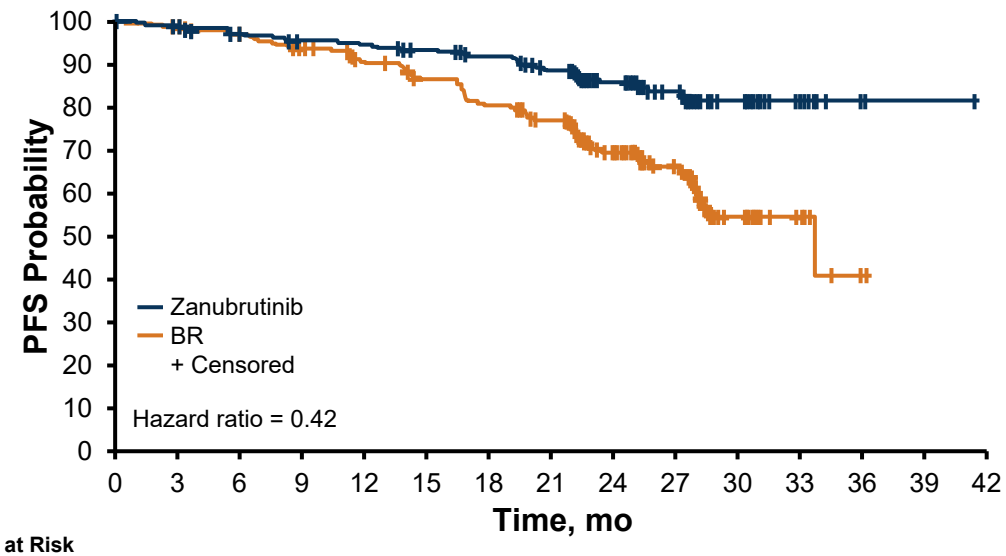
1. Sharman JP, et al. ASCO 2021. Abstract 7509. 2. Sharman JP et al. *Lancet*. 2020;395:1278-1291.

SEQUOIA: Zanubrutinib Prolongs PFS vs BR in TN CLL

ASH 2021: phase 3 trial of 479 patients with CLL without del(17p); subjects randomized to zanu (n = 241) and BR (n = 238)[1]

After median follow-up of 26.2 mo

- PFS significantly prolonged with zanu vs BR (HR = 0.42; *P* < .0001)
- Benefit with zanu was observed across subgroups for age, Binet stage, bulky disease, and del(11q)
- **Treatment benefit was also observed for patients with unmutated IGHV (HR = 0.24, 1-sided and 2-sided *P* < .0001),** but not for mutated IGHV



1. Tam C et al. ASH 2021. Abstract 396.

Pivotal 1L Studies Comparing CIT With BTKi Show Benefit of Targeted Therapy in *TP53* CLL Subgroups

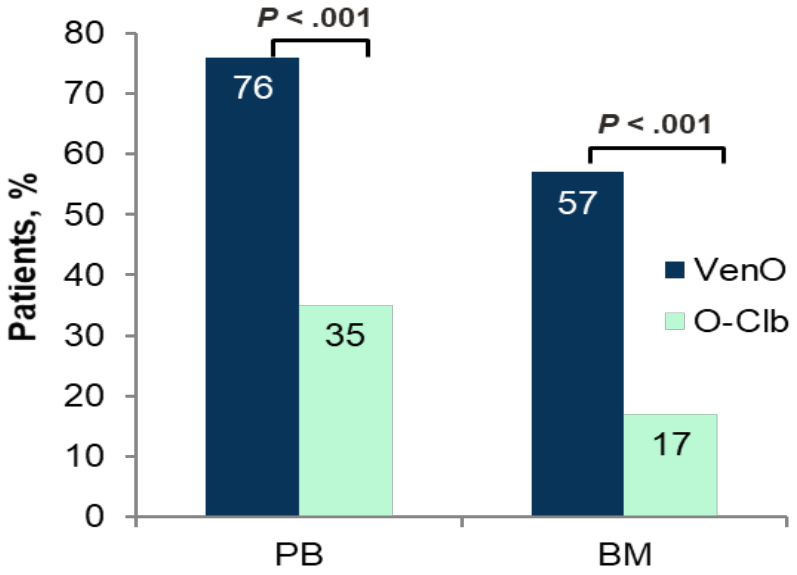
Study	Population	Design	Patients With *TP53*, n	PFS in *TP53* Subgroups
ALLIANCE[1]	Fit, older, del(17p) allowed	3 arm: BR vs IR vs I	51	Median not established for I or IR vs 7 mo for BR
iLLUMINATE[2]	Unfit (CIRS >6 or CrCl <70) or *TP53* del/mut	G + Cbl vs G + ibrutinib	29	Median not reached for I + G vs 11.3 mo for G + Cbl
ELEVATE-TN[3]	Unfit (CIRS >6 or CrCl <70)	G + Cbl vs acalabrutinib vs G + acalabrutinib	61	24-month PFS: 95% for acalabrutinib + G vs 19% for G + Cbl

1. Woyach JA et al. *N Engl J Med.* 2018;379:2517-2528. 2. Moreno C et al. *Lancet Oncol.* 2019;20:43-56. 3. Sharman JP et al. *Lancet.* 2020;395:1278-1291.

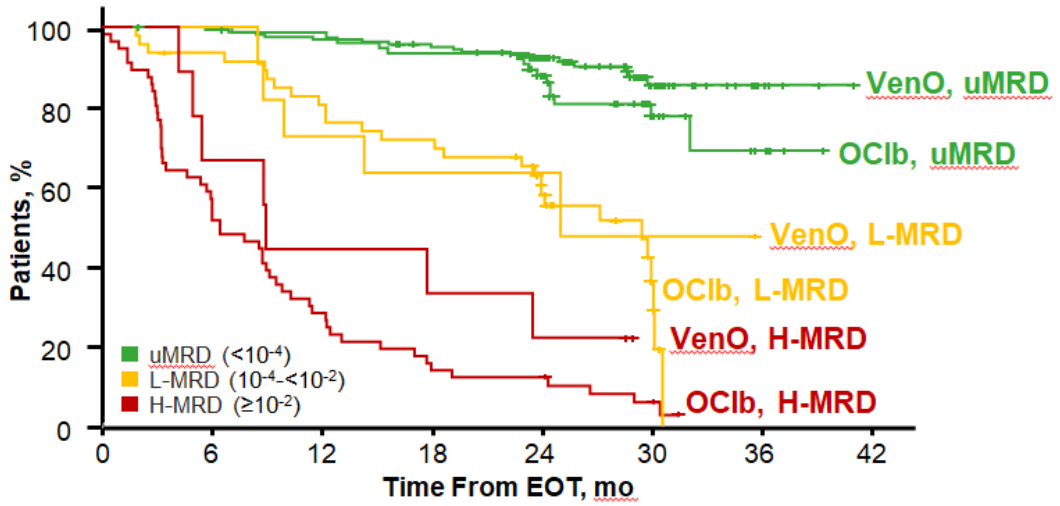
CLL14: VenO vs O-Clb as Initial Rx in Patients With CLL and Comorbidities (N = 432)[a]

VenO Achieves High uMRD Rates and Improved PFS

uMRD ($<10^{-4}$) by ASO-PCR 3 mo After EOT[1]



PFS by PB MRD Status at EOT (Median Follow-Up: 39.6 mo; 2 y after EOT)[2]

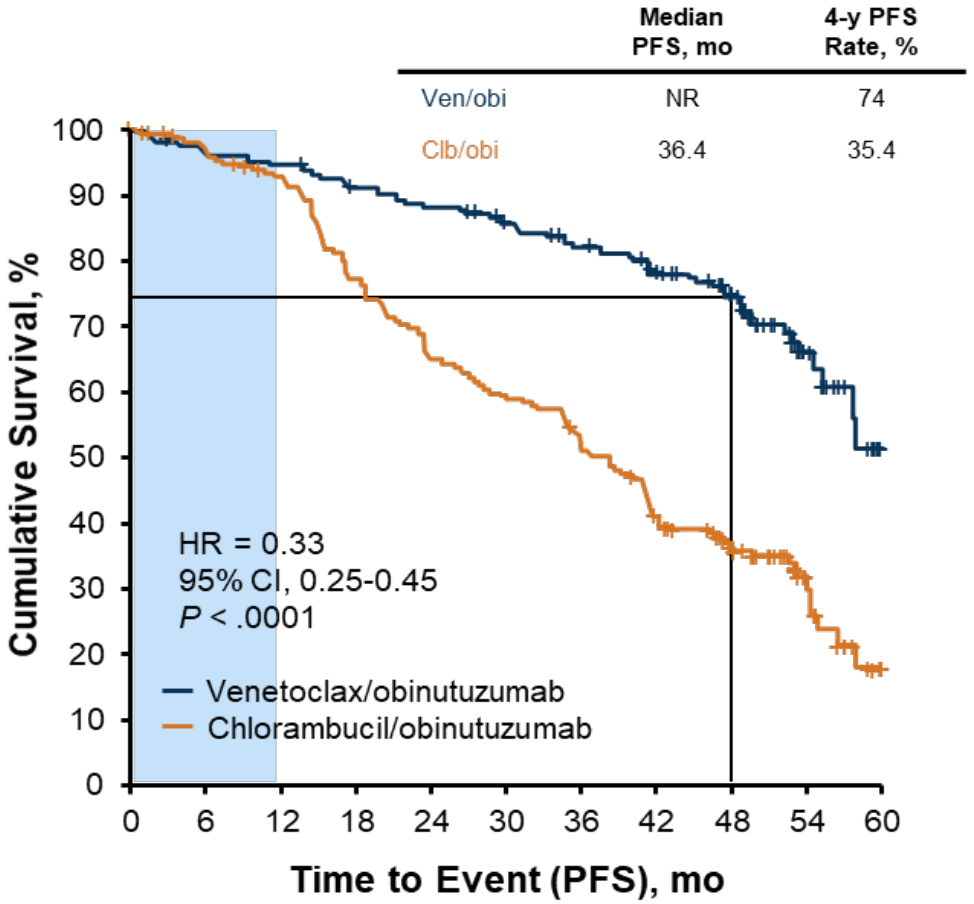


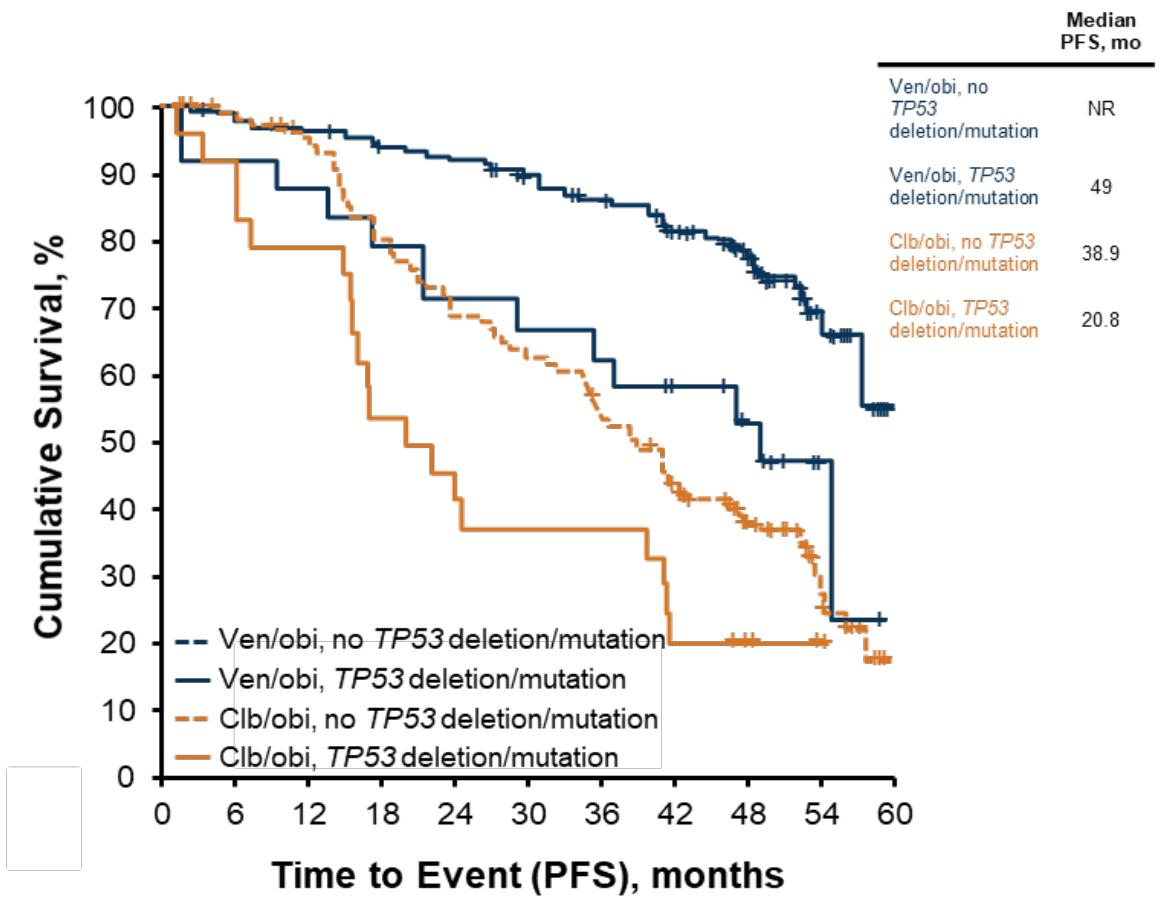
In a landmark analysis from EOT, uMRD patients had longer PFS versus L- or H-MRD (HR = 0.10; 95% CI, 0.06-0.15)

[a] Comparison done by Cochran-Mantel-Haenszel tests stratified by Binet stage and geographic region.

1. Fischer K et al. *N Engl J Med*. 2019;380:2225-2236. 2. Al-Sawaf O et al. *Lancet Oncol.* 2020;21:1188-1200.

CLL14: 4-y Follow-Up of VenO vs Clb + O in Patients Aged ≥65 Years[1,2]





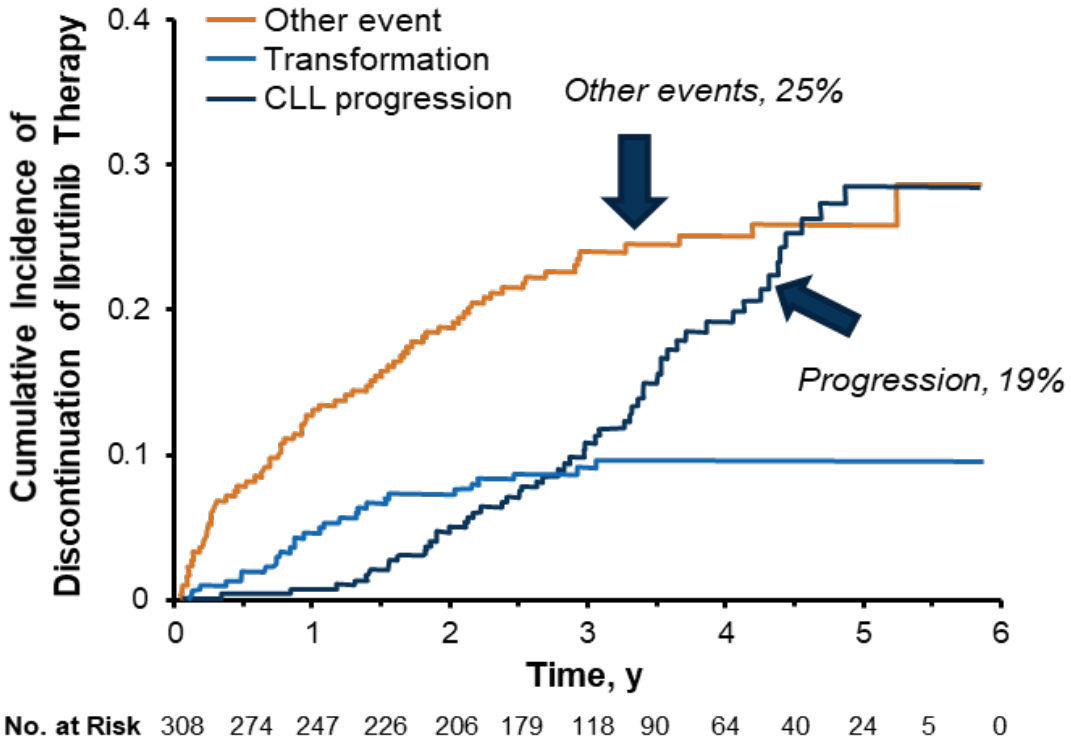
1. Al-Sawaf O et al. *Hematol Oncol.* 2021;39(suppl):201-203. 2. Al-Sawaf O et al. EHA 2021. Abstract S146.

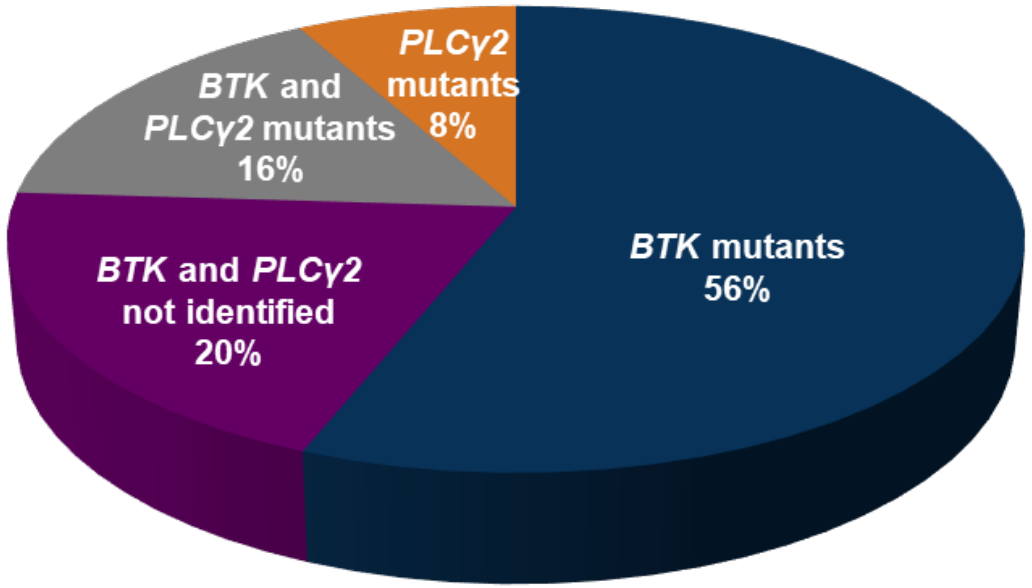
Choosing between a BTK vs BCL2 inhibitor

BTK Inhibitor[1-4]	BCL2 Inhibitor[4,5]
• Logistically very easy • Indefinite therapy • TLS not of concern • More cardiac risk/hypertension • Some favor in del(17p)/*TP53* mutation	• Cumbersome initiation/ramp-up • Fixed duration • Risk for TLS requires monitoring • GFR sensitivity • Question if best for high risk

1. Acalabrutinib PI. 2. Ibrutinib PI. 3. Zanubrutinib PI. 4. Awan. Am Soc Clin Oncol Educ Book. 2020;40:1. 5. Venetoclax PI.

Why Planning for Sequential Therapy Is Important: Resistance to Covalent BTK Inhibitors





- ***BTK* C481 mutations are the dominant reasons for progressive CLL after covalent BTK inhibitors[1-8]**
- ***BTK* C481 mutations prevent covalent BTK inhibitors from effective target inhibition[1-6]**

1. Woyach JA et al. *J Clin Oncol*. 2017;35;1437-1443. 2. Lampson BL, Brown JR. *Expert Rev Hematol*. 2018;11:185-194. 3. Burger JA et al. *Leukemia*. 2020;34:787-798. 4. Byrd JC et al. *N Engl J Med*. 2016;374:323-332. 5. Hershkovitz-Rokah O et al. *Br J Haematol*. 2018;181:306-319. 6. Woyach JA et al. *N Engl J Med*. 2014;370:2286-2294. 7. Woyach JA et al. *Blood*. 2019;134(suppl 1):504. 8. Xu L et al. *Blood*. 2017;129:2519-2525.

Mapping Sequential Therapy for CLL patients

If a patient		… then consider
Progresses on a BTKi ± resistance mutation	▶	Venetoclax[1] (PI3Ki may work but are less tested) Clinical trial: options include noncovalent BTKi (eg, pirtobrutinib, nemtabrutinib),[1,2,a] CAR-T therapy, bispecific monoclonal ABs, BTK degraders, other
Is unable to tolerate ibrutinib but has responded to therapy	▶	Sequencing to acalabrutinib (and zanubrutinib – NDA at FDA)[3,4,b]
Progresses or intolerant to Venetoclax/CD20 antibody	▶	Rechallenge with venetoclax; Sequencing to ibrutinib, acalabrutinib (and zanubrutinib – NDA at FDA)[5]

[a] Pirtobrutinib/Nemtabrutinib is experimental and only available as part of a clinical trial. [b] Zanubrutinib is off label for CLL but is included in the NCCN guidelines exactly for these circumstances.

1. Jones JA et al. *Lancet Oncol*. 2018;19:65-75. 2. Mato A et al. ASH 2020. Abstract 542. 3. Rogers K et al. *Haematologica*. 2021 Mar 18 [Online ahead of print]. 4. Shadman M et al. ASH 2020. Abstract 2947. 5. Mato A et al. *Clin Cancer Res*. 2020;26:3589-3596.

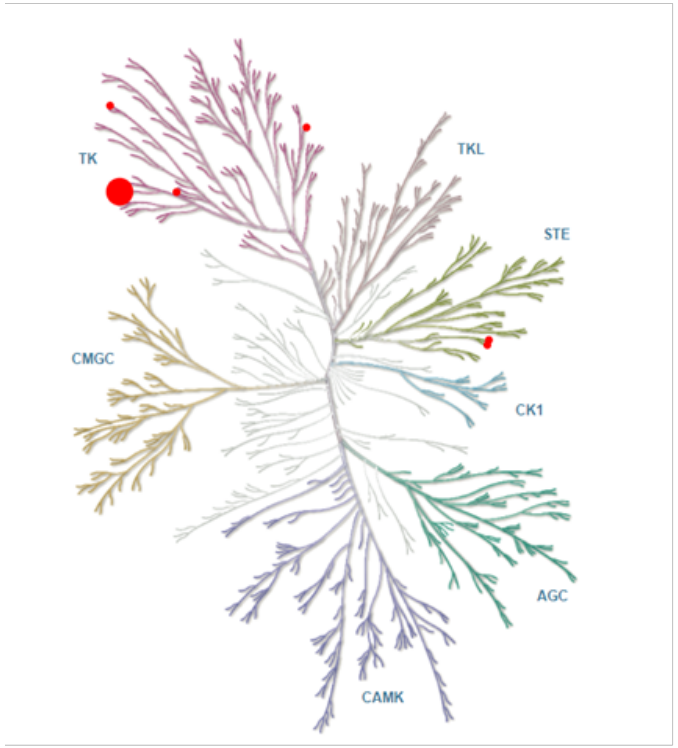
What's Next for CLL?

- Noncovalent BTKis, CAR-T, Bispecific antibodies, other novel agents
- Oral-Oral combinations – doublets, triplets

Pirtobrutinib is a Highly Potent and Selective Non-Covalent (Reversible) BTK Inhibitor

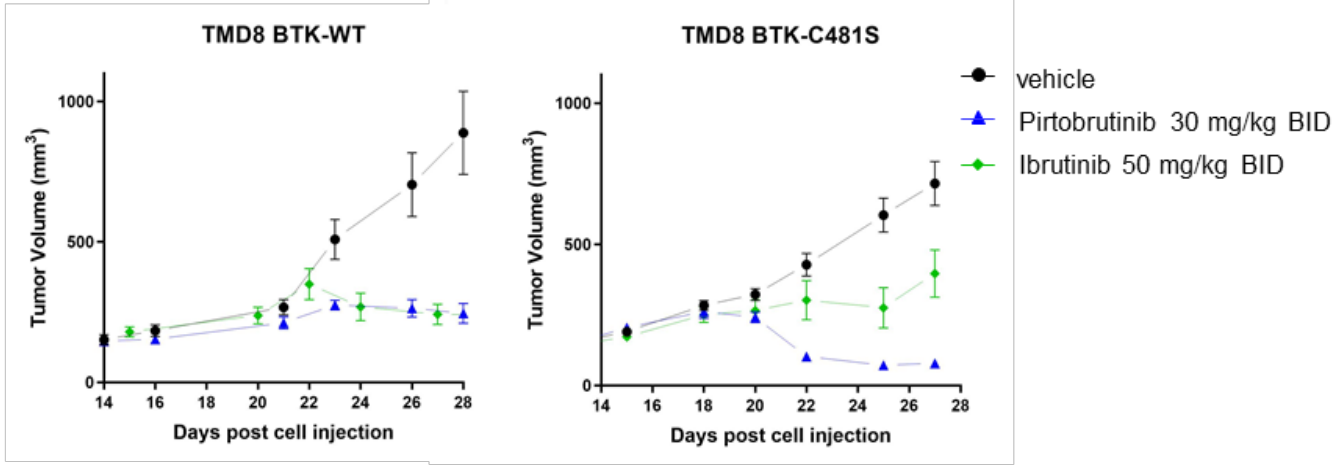
Kinome selectivity[1]

Highly selective for BTK



Xenograft models

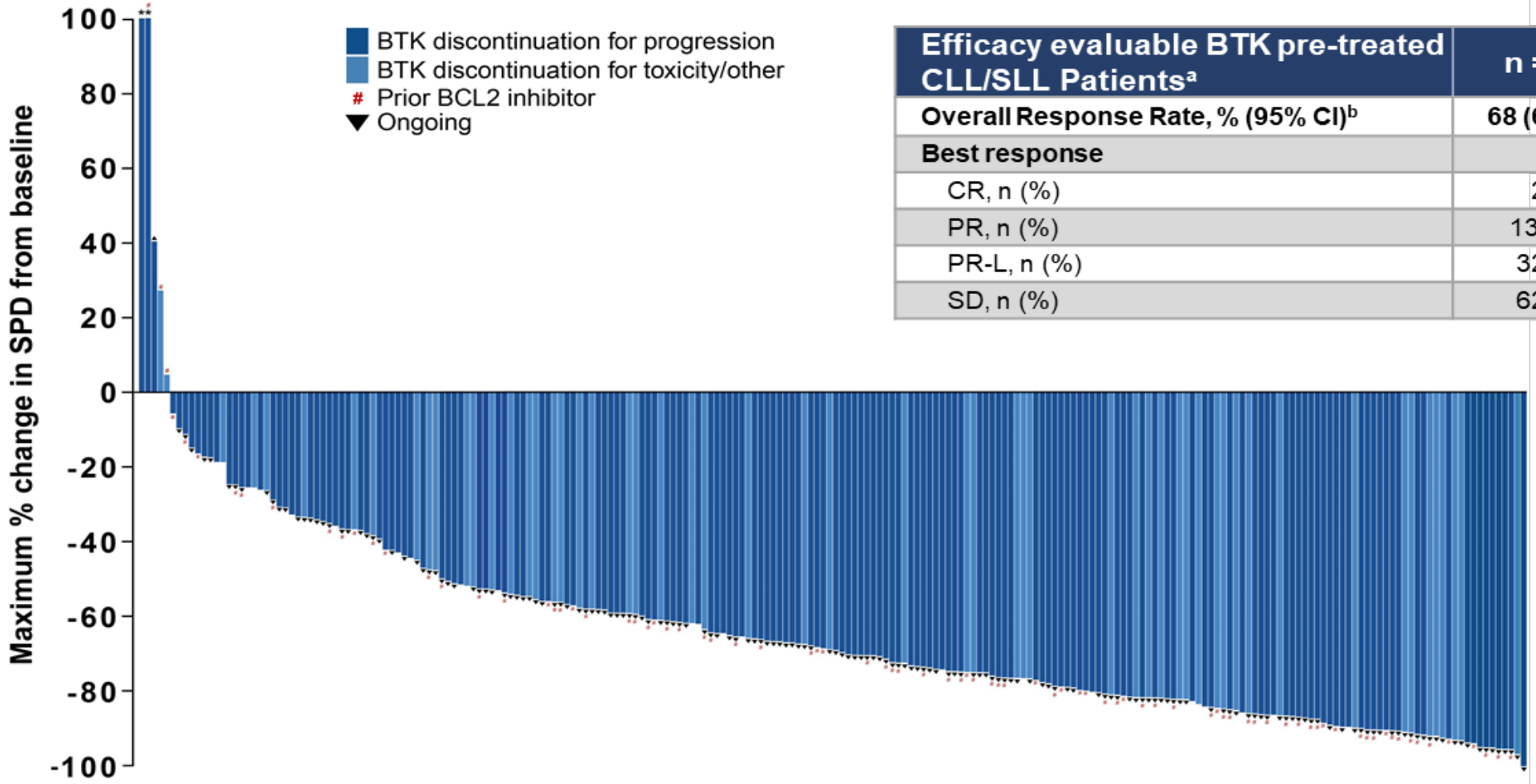
In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



- >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).

Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients

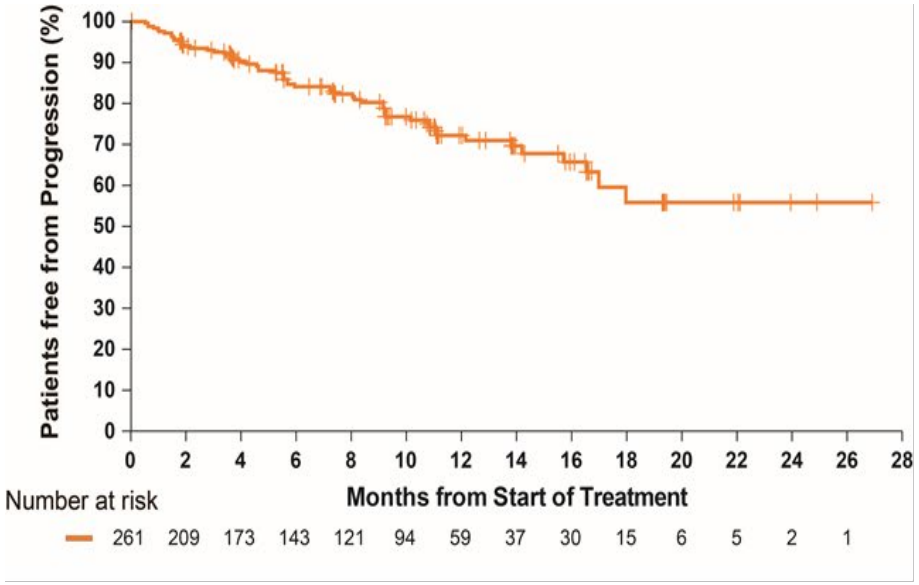


Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	**68 (62 – 74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Data cutoff date of 16 July 2021. *Patients with >100% increase in SPD. Data for 30 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to investigator assessment. Total % may be different than the sum of the individual components due to rounding.

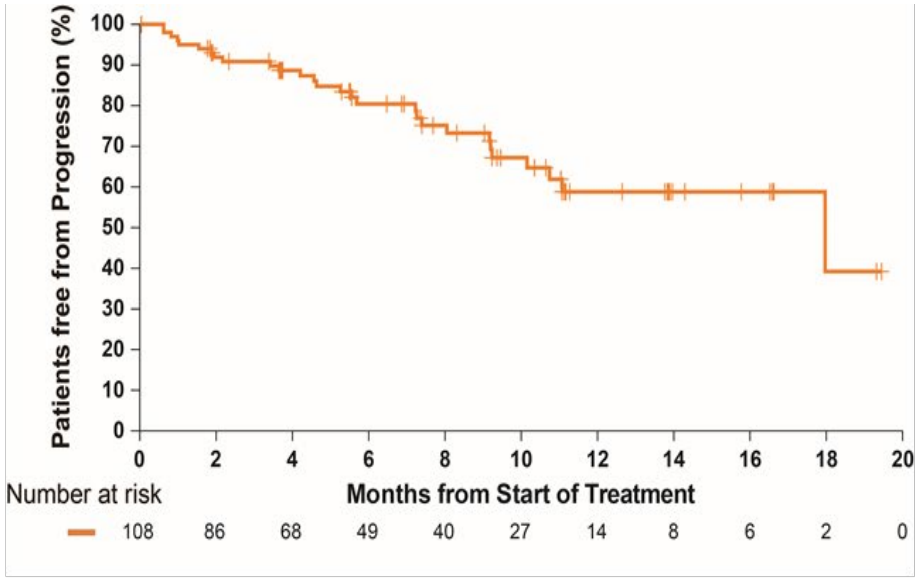
Progression-free Survival in BTK Pre-treated CLL/SLL Patients

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



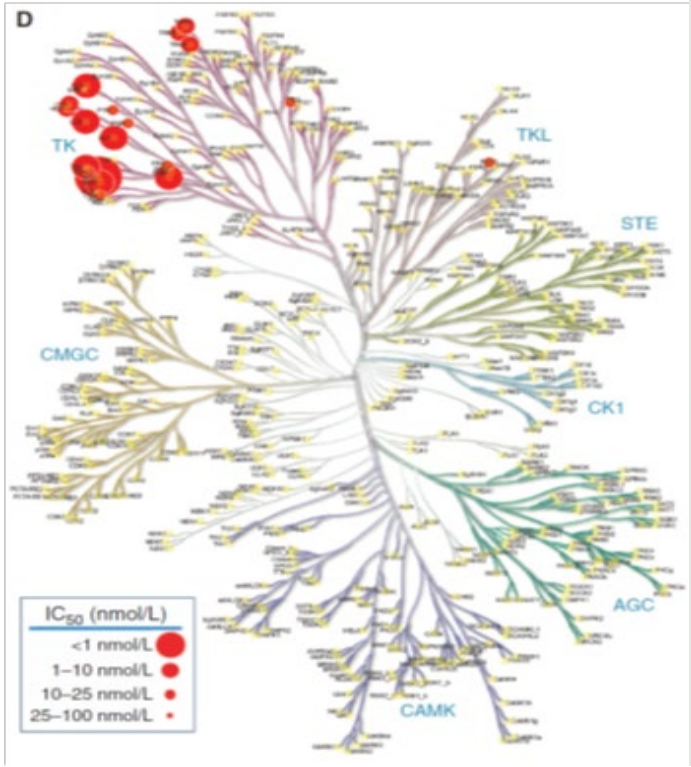
Median PFS: 18 months (95% CI: 10.7 months – Not Estimable)

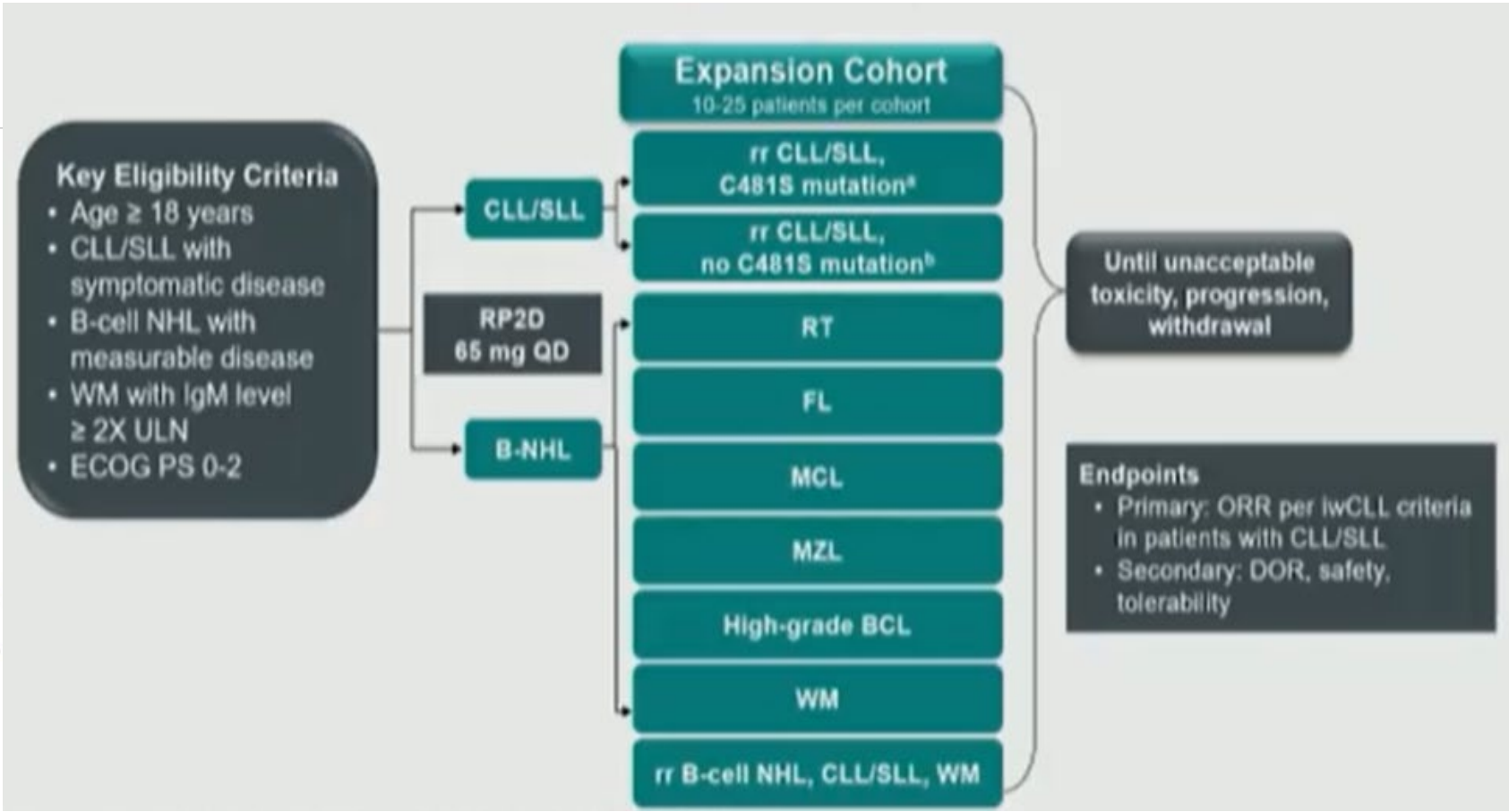
- 74% (194/261) of BTK pre-treated patients remain on pirtobrutinib
- Median follow-up of 9.4 months (range, 0.3 – 27.4) for all BTK pre-treated patients

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

Nemtabrutinib (MK-1026/ARG-531): Selectivity and Study Design

MK-1026[2] Kinome Selectivity





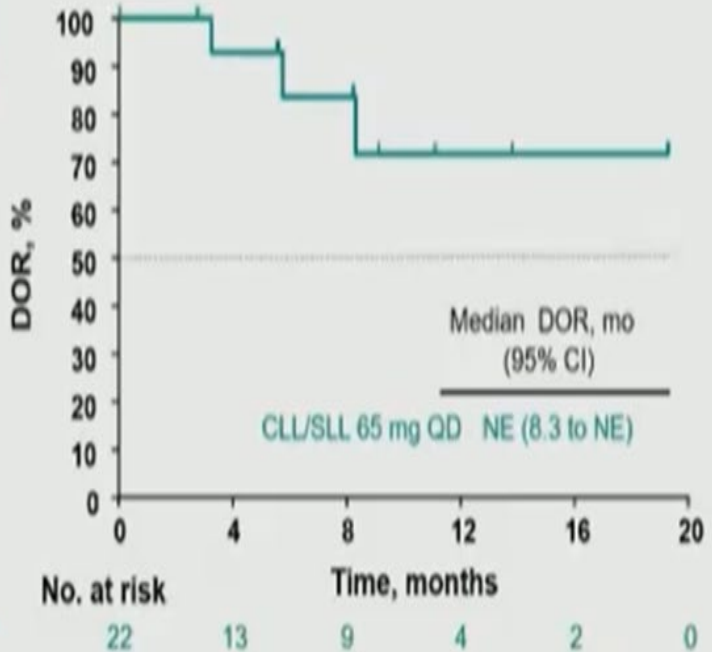
Reiff et al Cancer Discovery 2018; Woyach et al. ASH 2021.

Nemtabrutinib: Efficacy

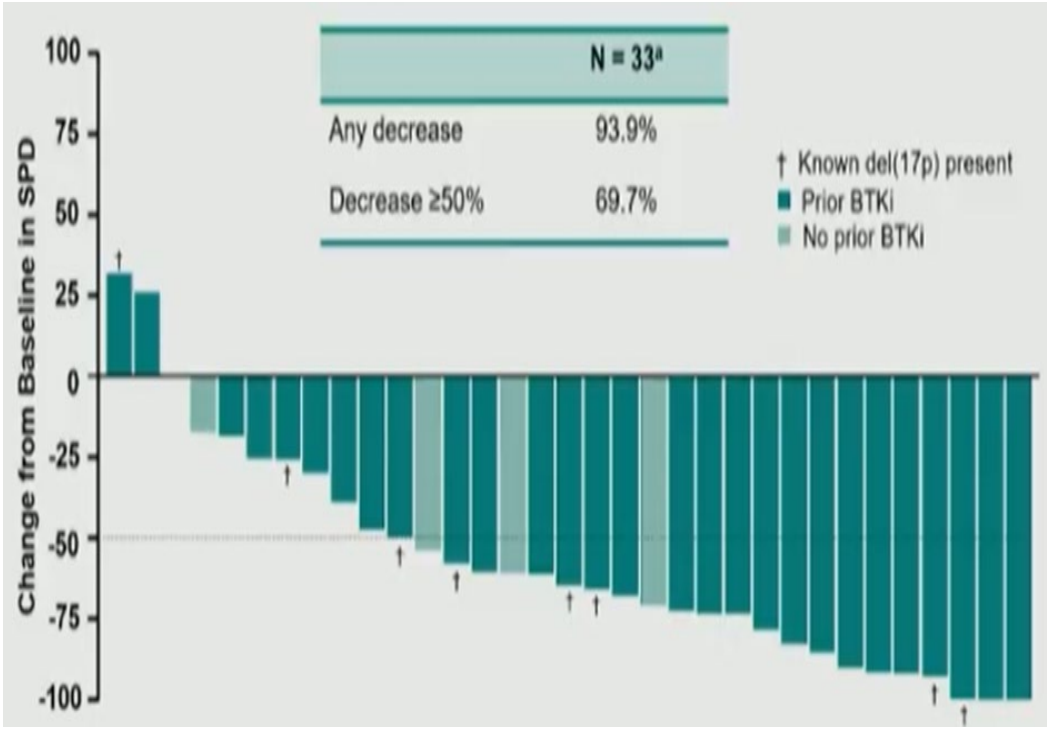
Response Rate

n (%) [95% CI]	CLL/SLL 65 mg QD N = 38[a]
ORR	22 (57.9%) [40.8-73.6]
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-5.6]

Duration of Response



Change in Baseline SPD



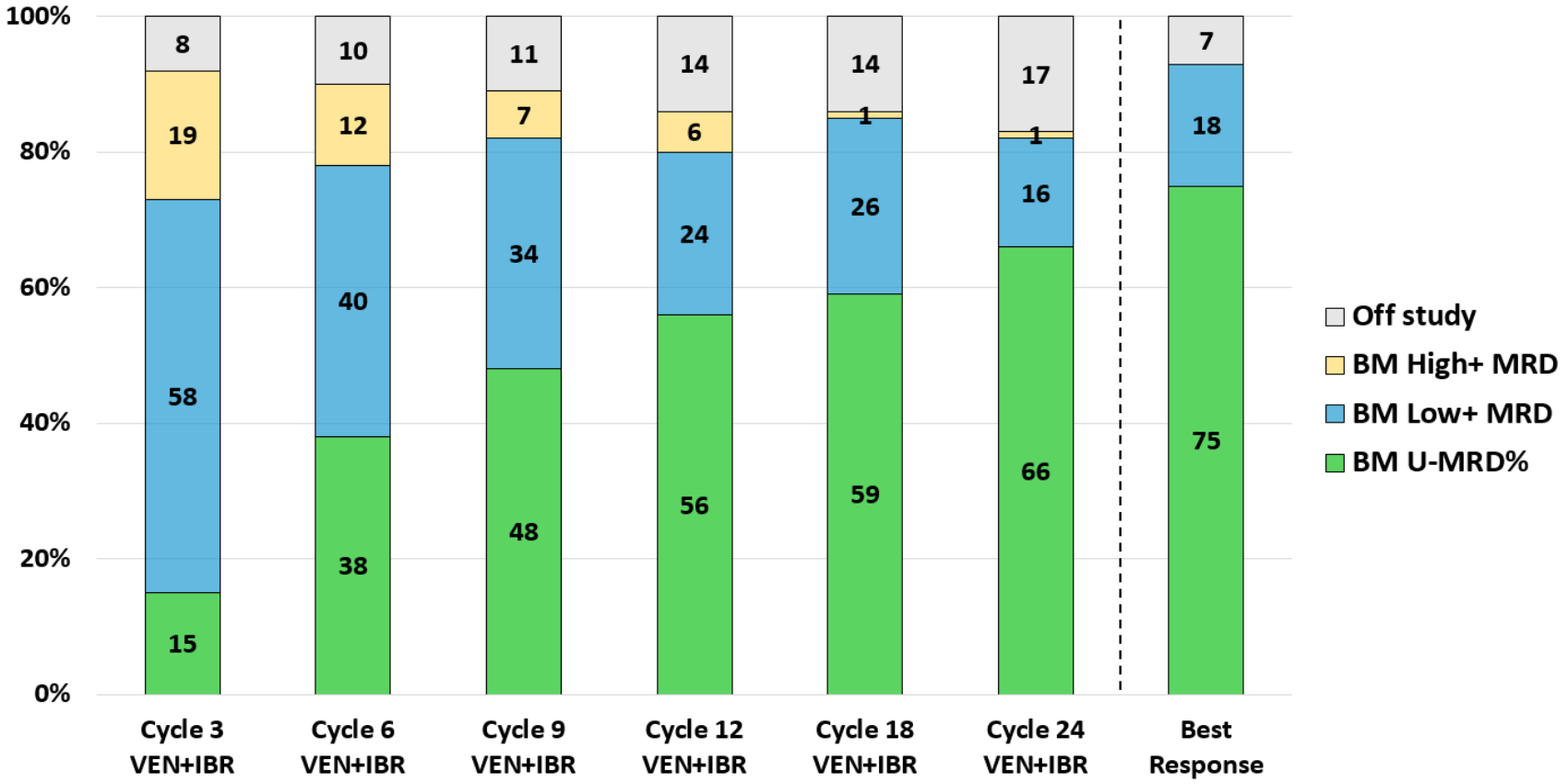
Woyach et al. ASH 2021.

Rationale for Combining BTKis + Venetoclax

- Non-overlapping mechanism of action
- Non-overlapping toxicity profile
- Act on CLL cells in different compartments
- Synergy in preclinical studies

Cervantes-Gomez, Clin Cancer Res. 2015; Deng, Leukemia 2017; Slinger, ASH 2017.

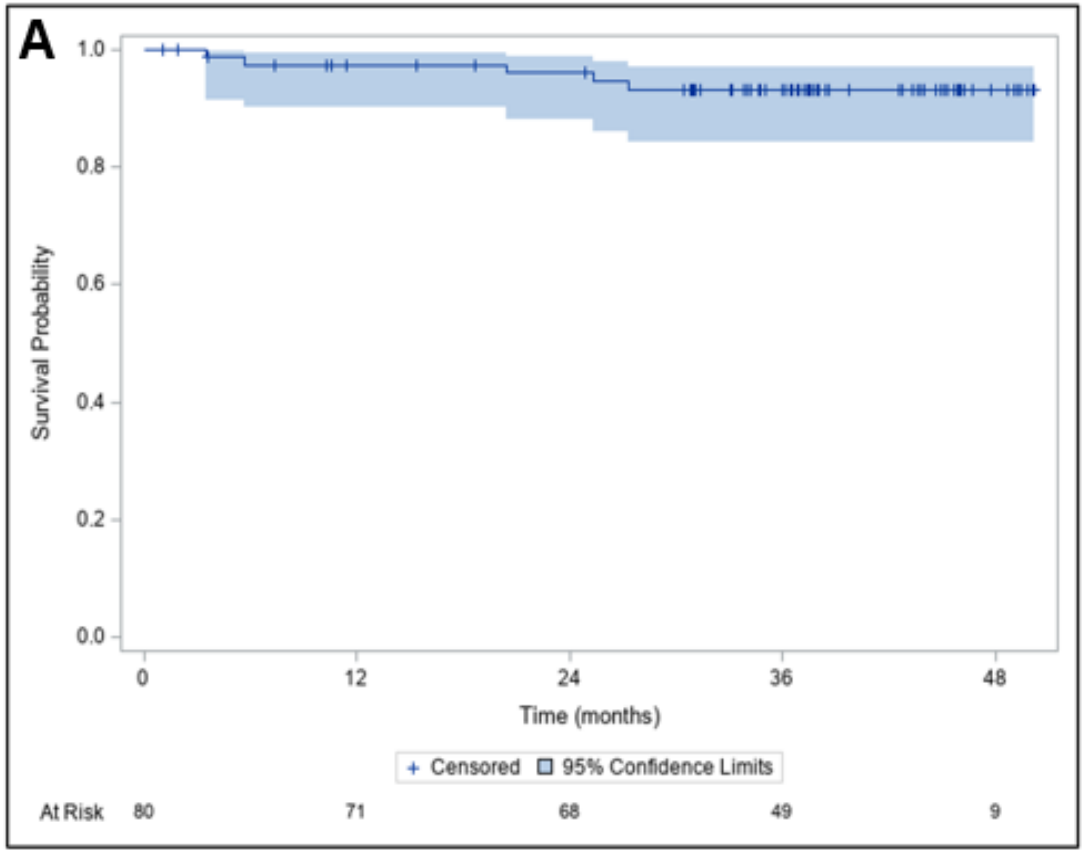
MDACC First-line IBR+VEN: BM MRD Responses Over Time[1]



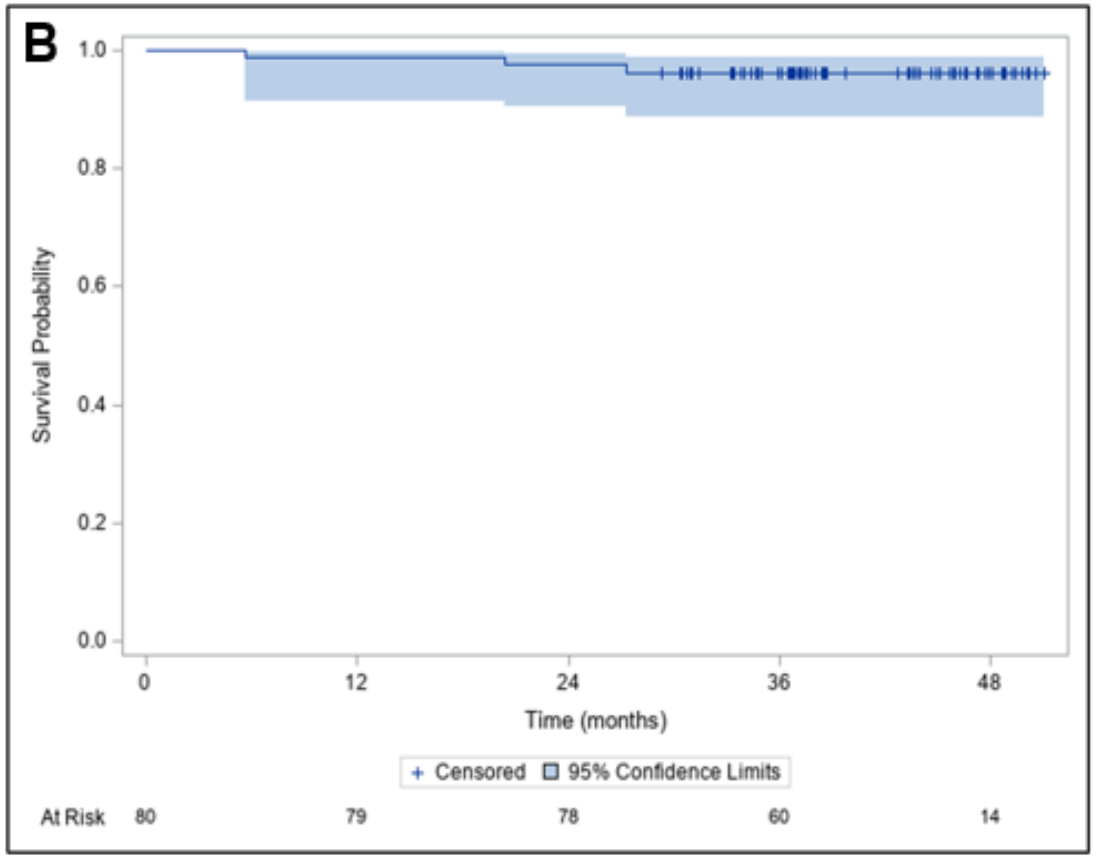
1. Jain N, et al., JAMA Oncology, 2021.

MDACC First-line IBR+VEN: Survival Outcomes[1]

Progression-free Survival

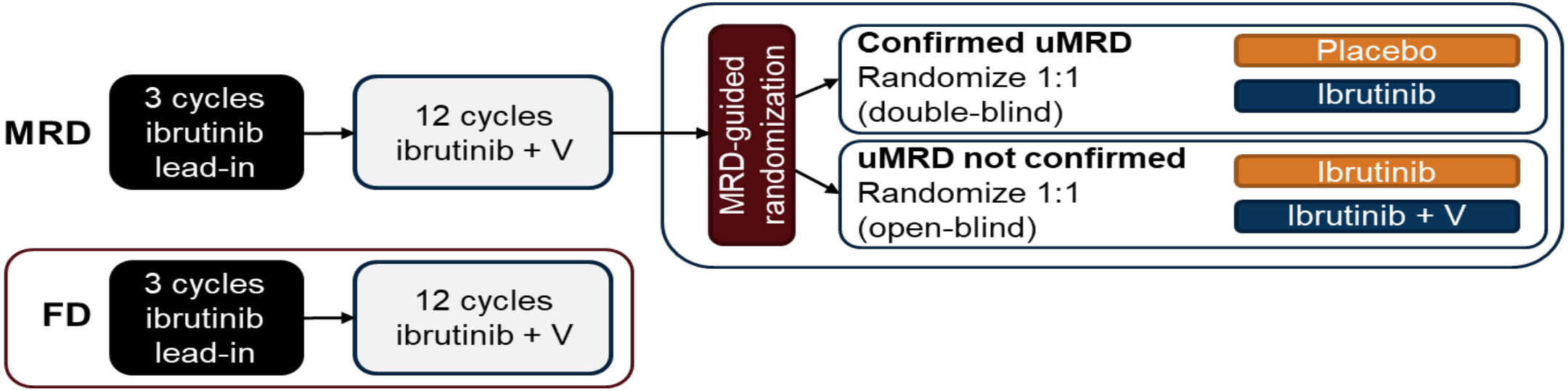


Overall Survival



1. Jain N, et al., JAMA Oncology, 2021.

Phase 2 CAPTIVATE Study Assessed Ibrutinib + Venetoclax in Two Cohorts[1,2,a]



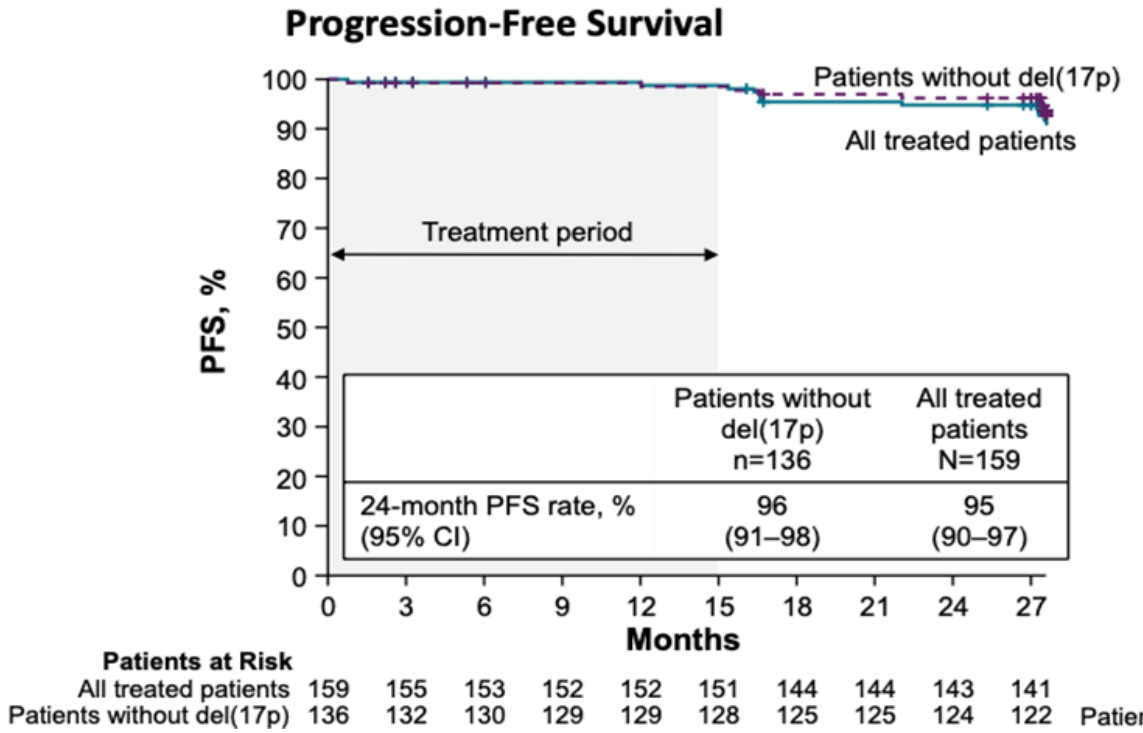
- Results presented for prerandomization phase of the CAPTIVATE-MRD cohort (N = 164) with 12 cycles of ibrutinib + venetoclax prior to MRD-guided randomization
- Time-limited therapy with 12 cycles of ibrutinib + venetoclax to be evaluated in separate fixed-duration cohort (N = 159)

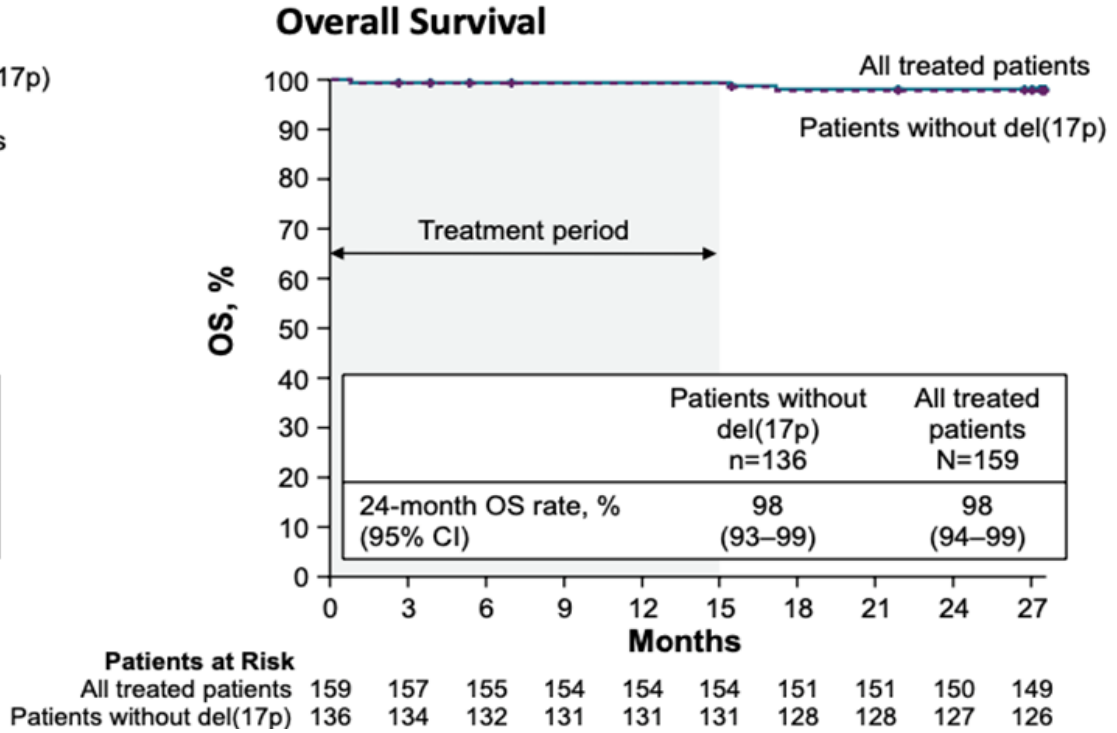
[a] One cycle = 28 days.

1. Wierda W et al. ASH 2020. Abstract 123. 2. Ghia P et al. ASCO 2021. Abstract 7501.

CAPTIVATE: FD Cohort Ibrutinib + Venetoclax Provides High Rates of PFS and OS[1]

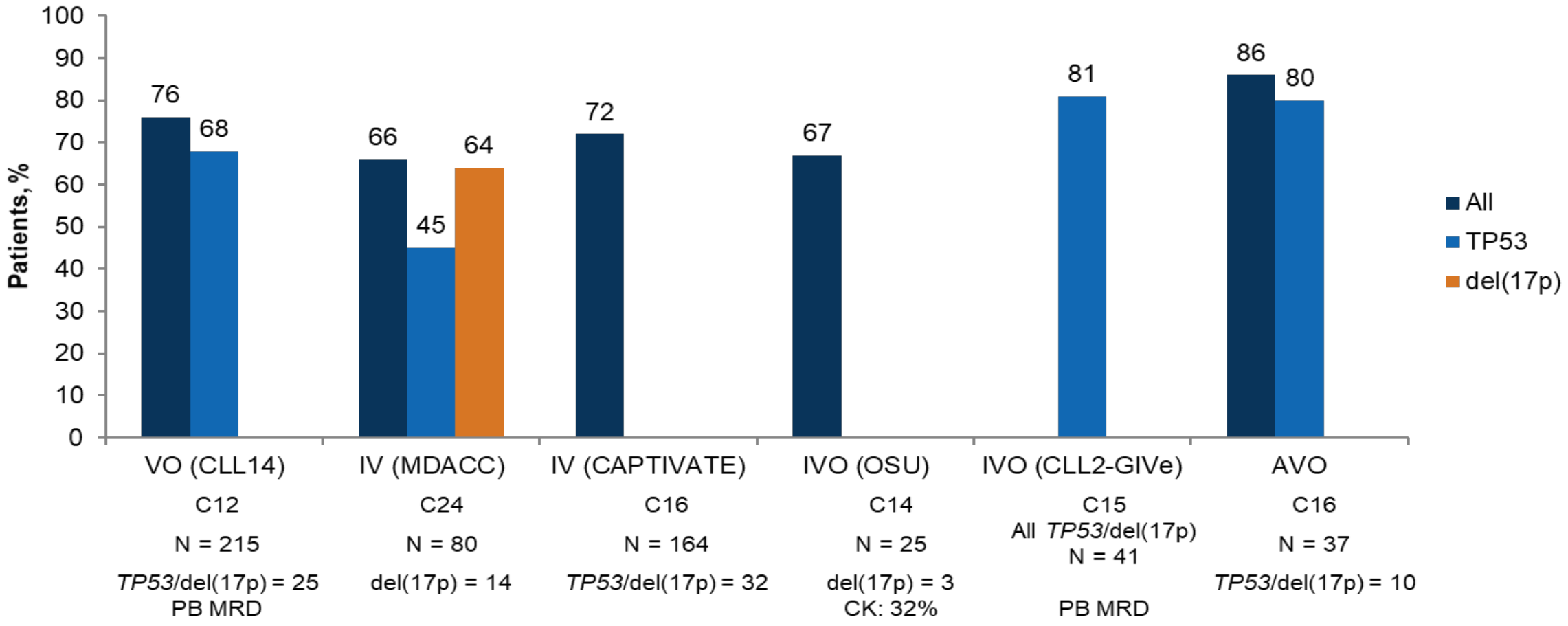
- Median follow-up: 27.9 mo (range, 0.8-33.2)
- Estimated 24-mo PFS rates were 93% (95% CI, 85-97) for patients with unmutated IGHV and 97% (95% CI, 88-99) for patients with mutated IGHV





1. Wierda W et al. iwCLL 2021.

uMRD Rates in TN CLL at the End of Ven-Based Therapy[1-6]



1. Al-Sawaf O et al. *Lancet Oncol.* 2020;21:1188-1200. 2. Jain N et al. *JAMA Oncol.* 2021;7:1213-1219. 3. Wierda WG et al. ASH 2020. Abstract 123. 4. Rogers KA et al. *J Clin Oncol*. 2020;38:3626-3637. 5. Huber H et al. EHA 2020. Abstract S157. 6. Davids MS et al. *Lancet Oncol.* 2021;22:1391-1402.

Select Ongoing Phase 3 Clinical Trials in First-line CLL

Trial	Subgroup	N	Status	MRD	Treatment Arms			
GAIA/CLL13 (NCT02950051)	Fit pts	920	Enrolled	Primary	**IbrVenOb**	VenOb	VenR	FCR/BR
GLOW (NCT03462719)	≥ 65 yo or unfit patients	211	Enrolled	Secondary	**IbrVen**			ChlOb
EA9161 (NCT03701282)	Fit, 18-69 yo	720	Enrolled	Secondary	**IbrVenOb**	IbrOb		
ACE-CL-311 (NCT03836261)	All pts	780	Enrolled	Secondary	**AcaVenOb**	**AcaVen**		FCR/BR
CRISTALLO (NCT04285567)	Fit pts	165	Enrolling*	Primary	VenOb			FCR/BR
A041702 (NCT03737981)	≥ 70 yo	454	Enrolling*	Secondary	**IbrVenOb**	IbrOb		
CLL17 (NCT04608318)	All pts	897	Enrolling*	Secondary	Ibr	VenOb	**IbrVen**	

*Enrolling patients as of June 2021.

Conclusions:

- BTK inhibitors (ibrutinib, acalabrutinib, soon zanubrutinib; noncovalent BTKis such as pirtobrutinib and nemtabrutinib) are highly effective therapies as single agents and in combination with CD20 antibodies. Patients can have a long PFS independent of IGHV mutation status, provided they stay on therapy.
- Ventoclax-based treatments can clear MRD in most patients after 1 year of therapy.
- Optimal sequencing of BTK inhibitors and BCL-2 inhibitors is not yet clear, but either option is effective when used sequentially.
- As data continue to emerge on the use of combinations such as BTKi + Ven (+/-CD20 antibodies), opportunities to treat CLL patients with a fixed duration of treatment rather than indefinite therapy may reduce the potential for longer-term toxicities.
- Time will tell whether patients will benefit from maintenance ibrutinib/BTKi (± venetoclax) therapy after 1 year of venetoclax and ibrutinib/BTKi therapy
- Given the impressive efficacy of BTKis and Venetoclax, appropriate management of toxicities are of critical importance, as these agents will remain a mainstay of therapy


THANK YOU!