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Advances in Precision Therapy in CLL: Integrating BTK and BCL-2 Inhibition Across the Treatment Continuum

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Disclosures

- **Andrew Zelenetz, MD, PhD:** Consultant – Abbvie, AstraZeneca, Beigene, Brightly Network, Curio Science, DAVA Oncology, Eli Lilly, Genentech/Roche, Gilead, Ibsen, MEI Pharma, grant/research support – Arvinas, Beigene, Genentech/Roche, GSK; other financial/material support – BMS, Celgene, Juno; speaker's bureau – Pharmacyclics
- **John Allan:** Consultant – Abbvie, Adaptive Biotechnology, ADC Therapeutics, AstraZeneca, BeOne Medicines, Genentech, Johnson and Johnson, Lilly, Merck, NeoGenomics, Research Funding- Adaptive Biotechnology, BeOne Medicines, Genentech

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Learning Objectives

- Evaluate the latest clinical evidence supporting fixed-duration, chemotherapy-free regimens using BTK and BCL-2 inhibitors in frontline and relapsed CLL settings
- Describe rational sequencing strategies that incorporate next-generation BTK inhibitors and emerging BCL-2 partners to overcome resistance and extend treatment-free remission
- Interpret MRD results and genomic insights to personalize therapy duration and optimize outcomes within evolving CLL frameworks

CLL = chronic lymphocytic leukemia; BTK = Bruton's tyrosine kinase; BCL = B-cell lymphoma; MRD = minimal/measurable residual disease.

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One, Two, or Three Drugs for CLL: What Is the Optimal Approach, and for Whom? Can MRD Help Guide Therapy?

Andrew D. Zelenetz, MD, PhD

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What Is MRD and How Can It Be Used?

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MRD Testing in CLL

- **MRD = residual leukemic cells detectable by high-sensitivity assays** in patients who otherwise meet clinical complete remission criteria (2018 iwCLL)
- Provides a **deeper measure of treatment efficacy** than conventional clinical/radiographic response
- **Undetectable MRD (uMRD)** is an independent predictor of longer progression-free survival (PFS) and overall survival (OS) across treatment settings
- Now a **standard endpoint in CLL trials**
  - EMA accepts uMRD in patients in clinical CR as an intermediate endpoint for licensure in randomized, well-controlled superiority trials, provided certain conditions are met
  - US FDA does not accept MRD-testing results as a validated intermediate/surrogate endpoint for PFS in CLL; all BTKi and BCL-2i approvals to date rest on improved PFS, not MRD

iwCLL = International Workshop on Chronic Lymphocytic Leukemia; FDA = Food and Drug Administration; EMA = European Medicines Agency.

Hallek M, et al. *Blood.* 2018;131(25):2745-2760. Benintende G, et al. *Front Oncol.* 2023;13:1112616. Letestu R, et al. *Leukemia.* 2021;35(6):1597-1609. Rios-Olais FA, et al. *JAMA Oncol.* 2024;10(9):1221-1227. Wang Y, et al. *Leukemia.* 2026;40(7):1439-1447.

Terminology: Undetectable MRD (uMRD)

- The threshold of MRD is based on the test being used
  - For example, in CLL
    - Multiparameter flow has a sensitivity of 1 cell in 10,000
    - Immunosequencing can detected 1 cell in 1,000,000 (with adequate input DNA)
  - **EXAMPLE:** A sample with 50 cells per 1,000,000 would be “negative” on flow and positive by immunosequencing
- When discussing MRD it is essential to discuss in the context of the limit of detection (LOD) for a given assay
- **Best Practice**
  - Avoid “negative” MRD and report uMRD
  - Include the nominal sensitivity of the assay as the –log
    - An assay with sensitivity of 1 in 10,000 that is undetectable would be uMRD4
    - If the assay was positive, then the detectable MRD should be used, dMRD4

Methods for Detection of MRD Used in CLL

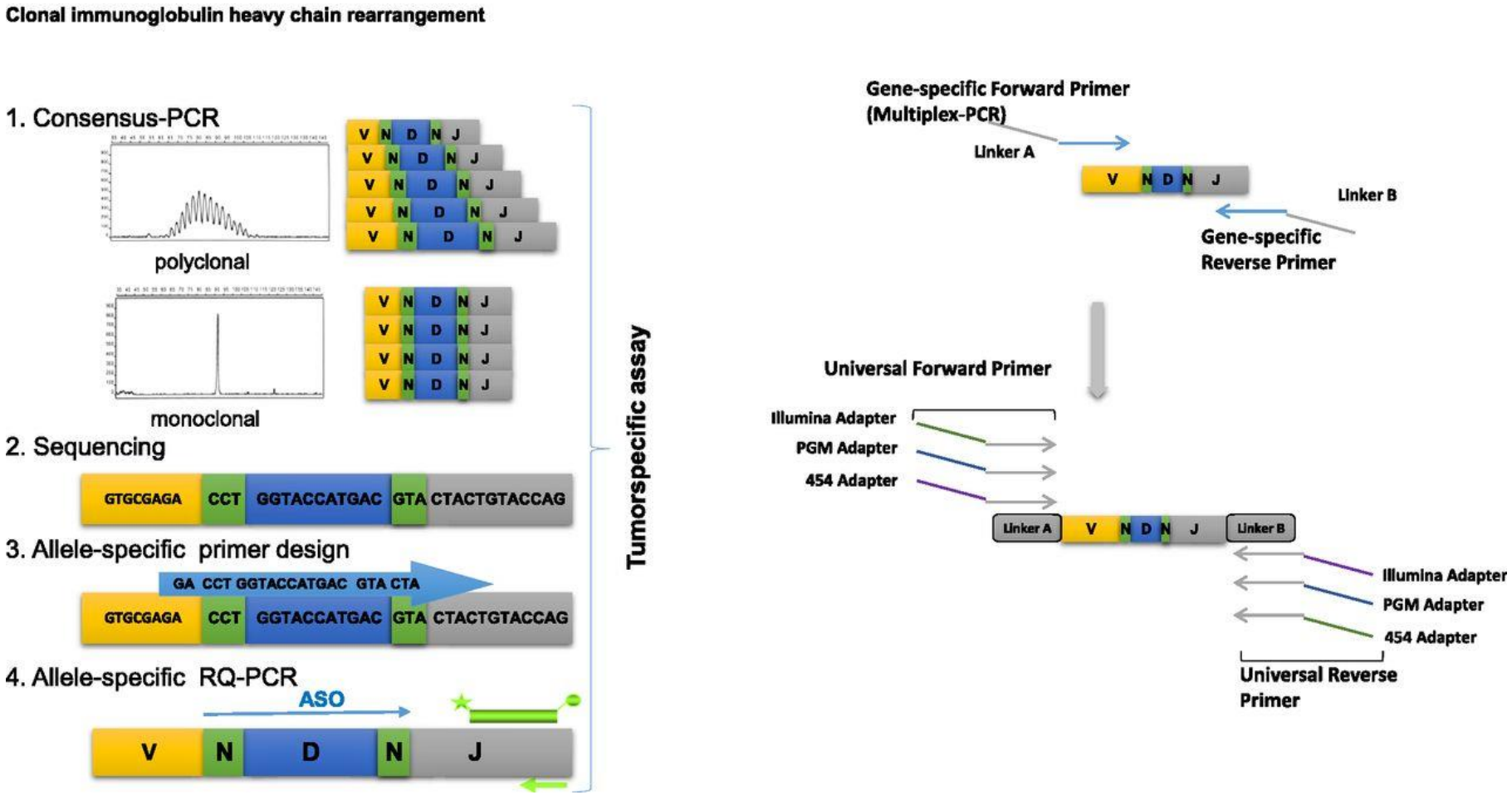
Method	Sensitivity	Key features
≥6–8 multicolor flow cytometry (MFC)	10^{-4} to 10^{-6}	Rapid, accessible, cost-effective; no baseline sample needed; ERIC-standardized; most widely used clinically
ASO-PCR (IGH RQ-PCR)	10^{-5}	Patient-specific primers; requires pretreatment sample; suited to batch testing
Next generation sequencing (NGS)	10^{-6}	Highest sensitivity; tracks clonal sequences; uses stored DNA; sensitivity dependent on amount of input DNA
Droplet digital PCR / ctDNA	10^{-5}	Emerging; ctDNA may better capture nodal disease
Phased variant sequencing	10^{-6}	Phase variants allow for suppression of polymerase induced error; however, low mutation burden of CLL may limit utility

- **ASO-PCR and 6-color MFC are the two validated methods at 10^{-4}–10^{-5}; NGS extends to 10^{-6}**
- **Either flow or NGS is acceptable** provided the limit of detection of at least 10^{-4} is met

ERIC = European Research Initiative on CLL.

Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for CLL/SLL V.2.2027. © National Comprehensive Cancer Network, Inc. 2027. All rights reserved. Accessed Oct 14, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. Wierda WG, et al. *Leukemia.* 2021;35(11):3059-3072.

Immunoglobulin Gene-Based Methods: Allele-Specific RQ-PCR and Platform Independent IG Gene Sequencing

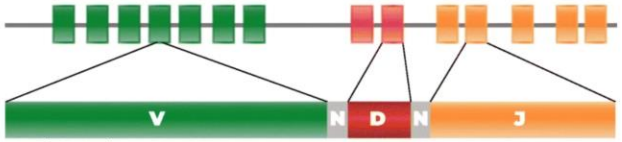


Hoster E, Pott C. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):437-445.

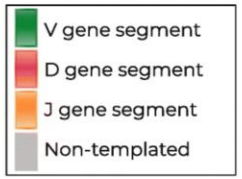
Immunosequencing of Dominant Clone

SEQUENCE

Polymerase chain reaction (PCR) of gDNA for BCR IgH (VJ, DJ), IgK/L (VJ), or TCRβ/γ

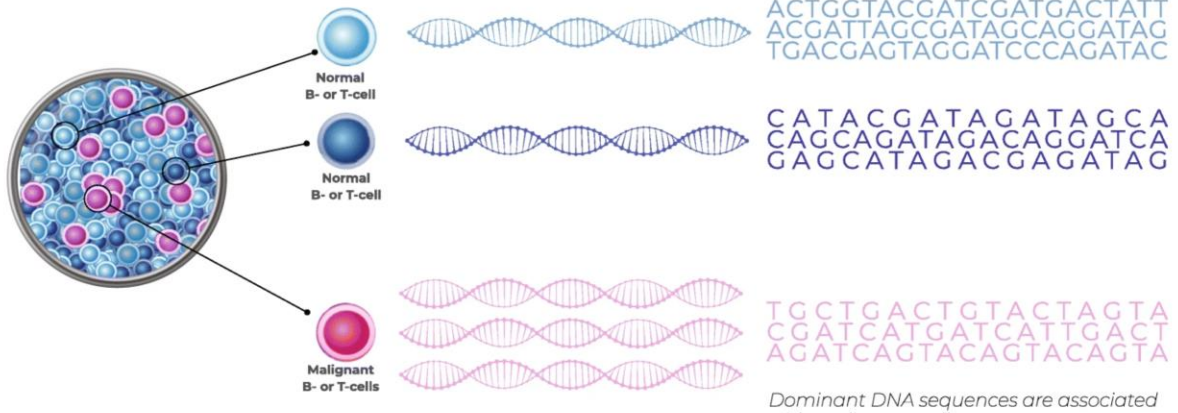


Multiple PCR primers for each V and J gene segment ensure quantitative amplification.



IDENTIFY

CDR3 regions of lymphoid cells are sequenced by NGS and dominant DNA sequence(s) are identified

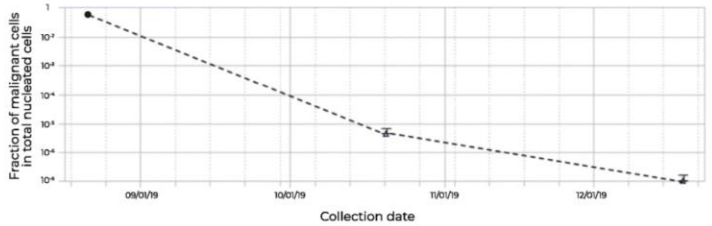


TRACK

Previously identified dominant sequence(s) are quantified and tracked over time

TGCTGACTGTACTAGTA
CGATCATGATCATTGACT
AGATCAGTACAGTACAGTA

Previously identified dominant sequence



Ching T, et al. *BMC Cancer*. 2020;20(1):612.

Tumor Reservoirs

Site	Diseases	Comment
Peripheral Blood	SLL/CLL; SMZL; MCL; HCL	Easily accessible, collection in CPT tubes
Bone Marrow	SLL/CLL; SMZL; MCL; HCL; FL	Invasive
Residual tumor site	All nodal NHL	Invasive, subject to sampling error

Site	Disease	Comment
Circulating tumor DNA (ctDNA)	Potentially all NHL	Possible differential sensitivity based on the disease; sample collection needs to be optimized*
*Literature supports use of Streck BCT, PAXgene cfDNA, RochecfDNA, CellSave, or Blood Exo DNAProTeck tube cell free DNA analysis highly dependent on pre-analytical and analytical workflows		

BCT = blood collection tube; SLL = small lymphocytic lymphoma; SMZL = splenic marginal zone lymphoma; MCL = mantle cell lymphoma; HCL = hairy cell leukemia; FL = follicular lymphoma; NHL = non-Hodgkin lymphoma.
Greytak SR, et al. *Clin Cancer Res*. 2020;26(13):3104-3109.

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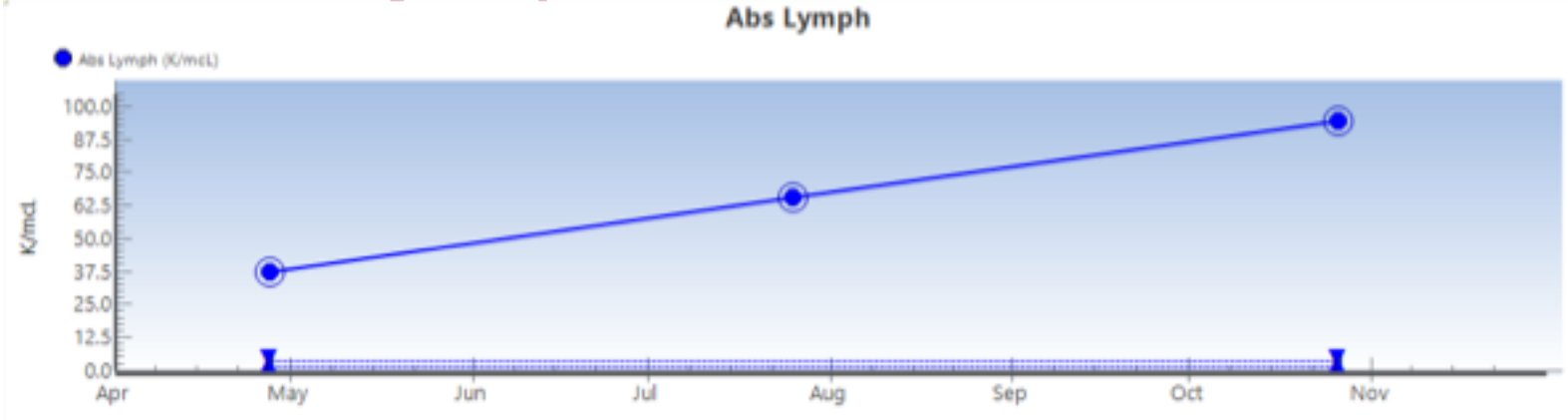
Clinical Case

Case of Too Many Options

- 66-year-old man was noted to have a lymphocytosis on routine blood work in 01/2023: WBC 31.1, ALC 23.1, HGB 14.6, PLT 180. Lymphocytosis was confirmed on repeat CBC 03/27/2023
- Peripheral blood flow cytometry demonstrated a monotypic lambda-restricted B-cell population which **EXPRESSED** CD5, CD19 (dim), CD20 (dim), ROR1, CD22, CD79b, CD200 and **DID NOT EXPRESS** CD10, CD 23, kappa, CD25
- IGHV VH13 mutated; FISH del(13q), del(17p) and NO t(11;14); NGS panel demonstrated mutations in TP53, ARIDIA, CCND3, TERT
- CT CAP 03/27/2023 demonstrated hepatosplenomegaly.
- Diagnosis consistent with variant CLL (CD23-negative), recommended active surveillance

WBC = white blood count; ALC = absolute lymphocyte count; HGB = hemoglobin; PLT = platelet; CBC = complete blood count.

Case of Too Many Options



- Patient meets iwCLL criteria for treatment: **Lymphocyte doubling time of < 6 mos**
- Has poor risk feature of TP35 mutation and deletion, should this impact treatment choice?
- There is a plethora of treatment options:

Monotherapy
BTKi monotherapy

Two drug therapy:
Obinutuzumab + Venetoclax
BTKi + Venetoclax

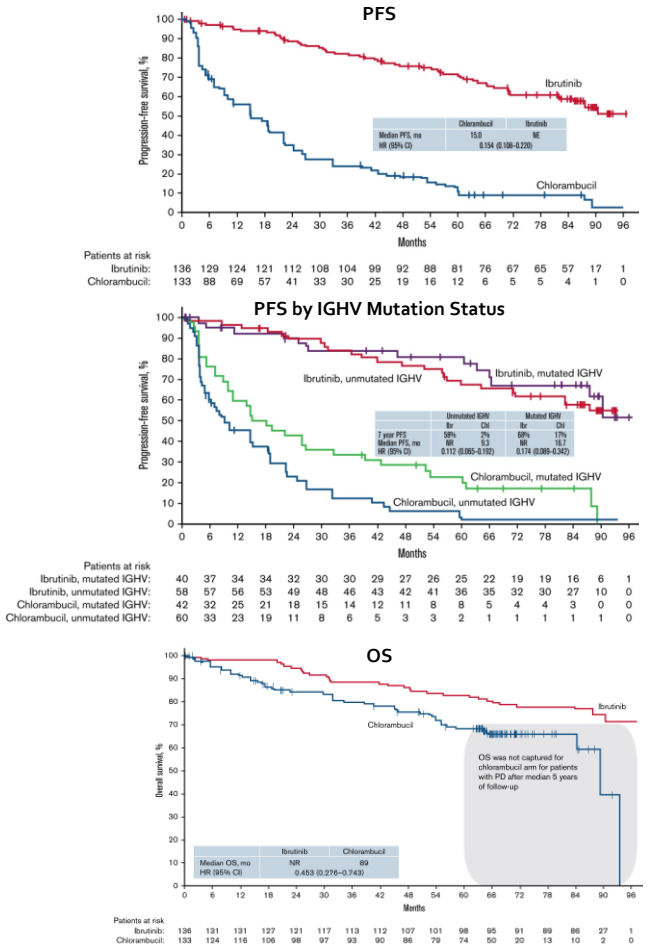
Three drug therapy:
Ibrutinib-Venetoclax-Obinutuzumab
Acalabrutinib-Venetoclax-Obinutuzumab
Zanubrutinib-Venetoclax-Obinutuzumab

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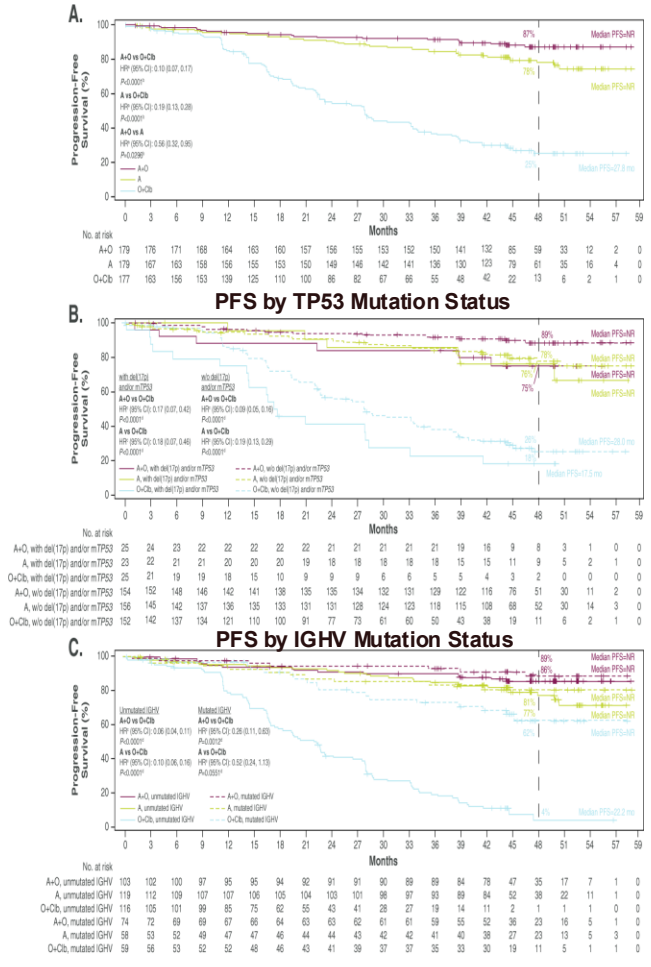
Should You Use 1 Drug?

BTKi Monotherapy Provides Durable PFS

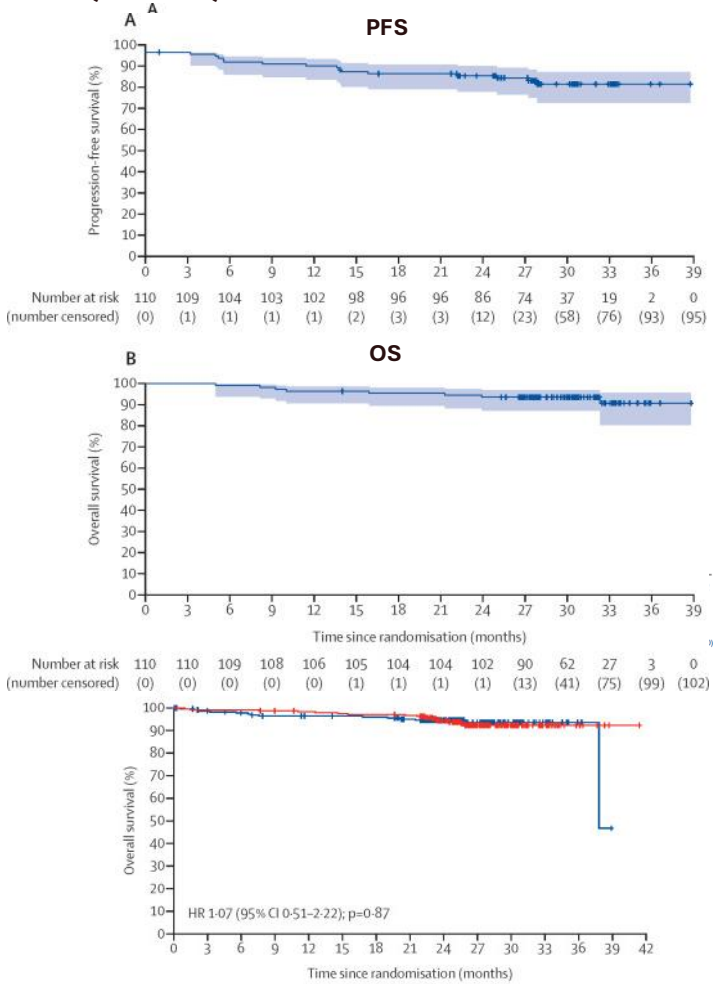
RESONATE 2: Ibrutinib v chlorambucil



ELEVATE TN: Acala v acala-ob v chlob



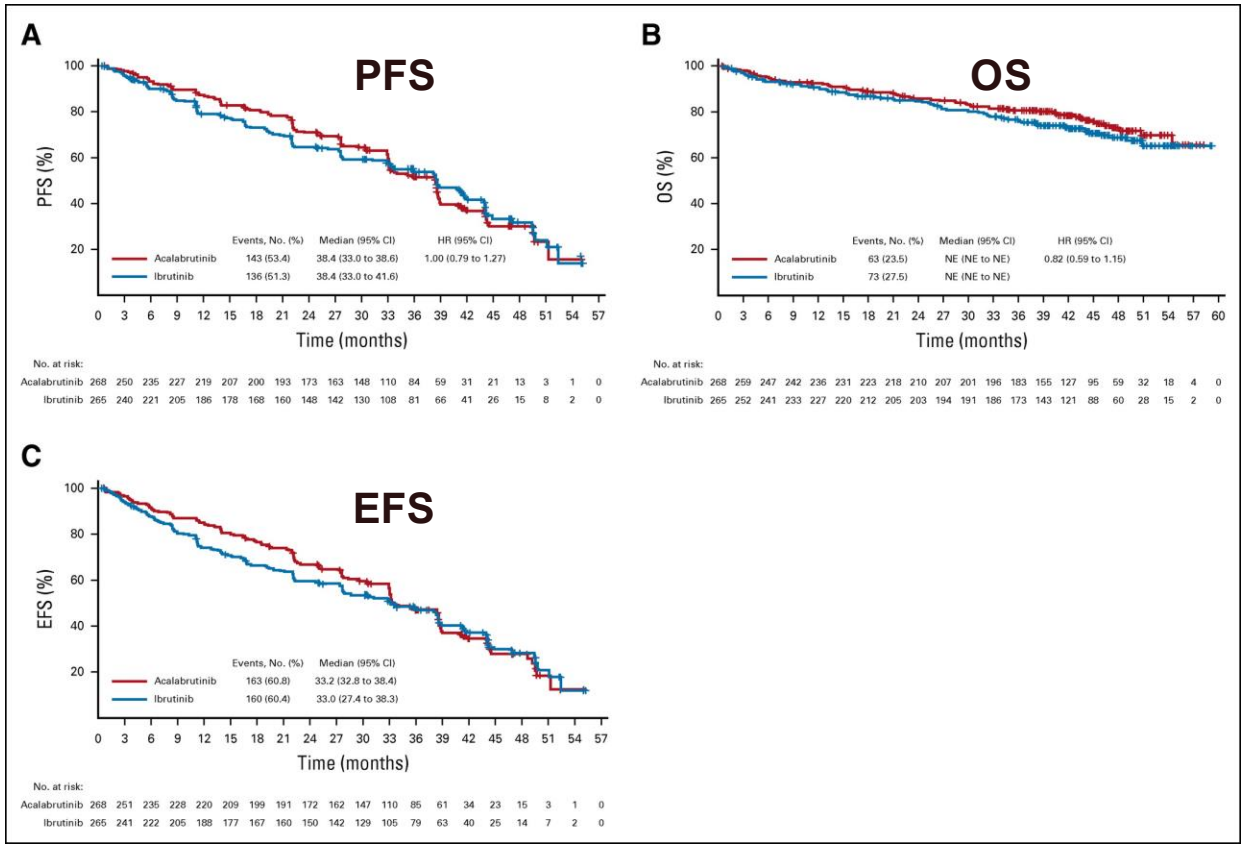
SEQUOIA: Zanubrutinib for TP53 aberrant



Barr PM, et al. *Blood Adv*. 2022;6(11):3440-3450. Sharman JP, et al. *Leukemia*. 2022;36(4):1171-1175. Tam CS, et al. *Lancet Oncol*. 2022;23(8):1031-1043.

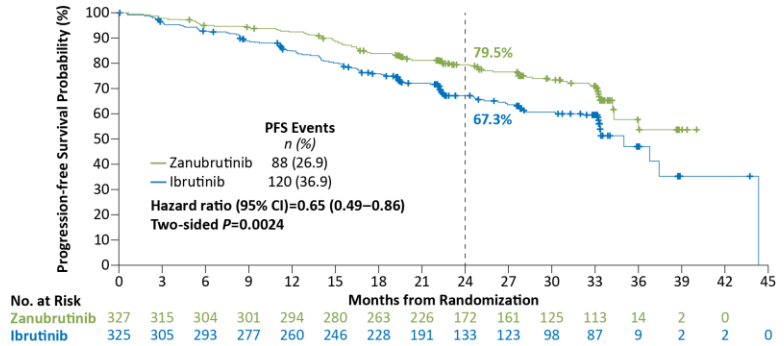
Second Generation BTKi Are at Least as Effective as Ibrutinib for R/R Disease

Acalabrutinib v Ibrutinib

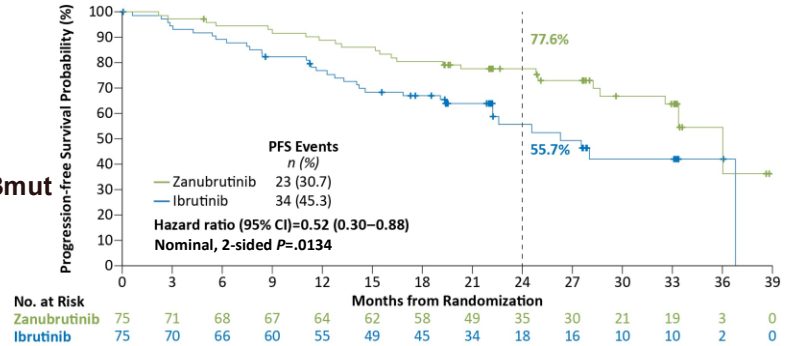


Zanubrutinib v Ibrutinib

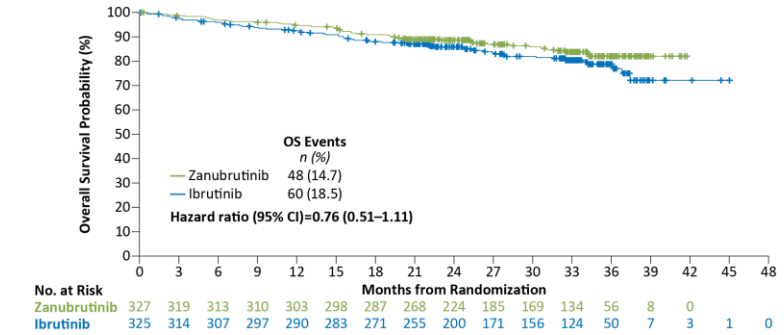
PFS



PFS
del(17p)/TP53mut



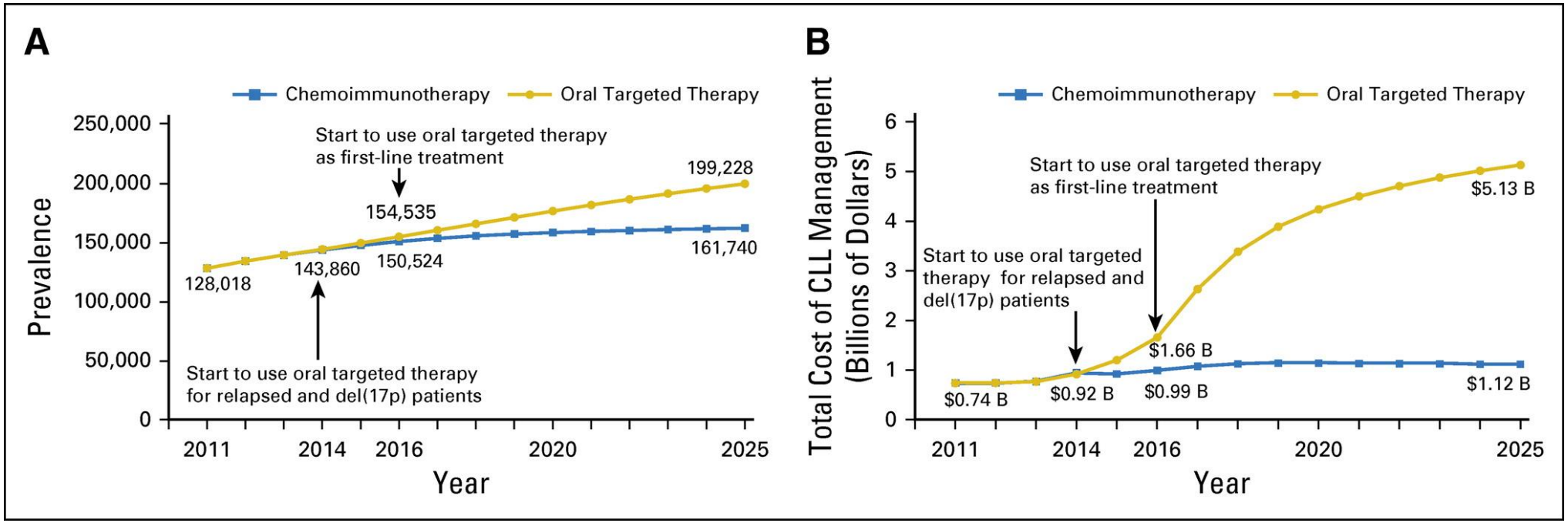
OS



EFS = event-free survival; R/R = relapsed/refractory.

Byrd JC, et al. *J Clin Oncol.* 2021;39(31):3441-3452. Brown JR, et al. *Blood.* 2022;140(suppl 2):LBA-6

Oral Therapy Is Associated with a Major Economic Burden



- Annual cost in CLL management is expected to increased from $0.74 billion in 2011 to $5.13 billion (593% increase) in 2025

Chen Q, et al. *J Clin Oncol*. 2017;35(2):166-174.

If You Are Going to Use 1 Drug…

- Second generation BTKis acalabrutinib and zanubrutinib appear to have an improved safety profile compared to the ibrutinib
  - Marked reduction in atrial fibrillation
  - Decreased in ventricular events and sudden death

- Efficacy compared to ibrutinib (in R/R patients) is equivalent with acalabrutinib, appears to be slightly higher with zanubrutinib

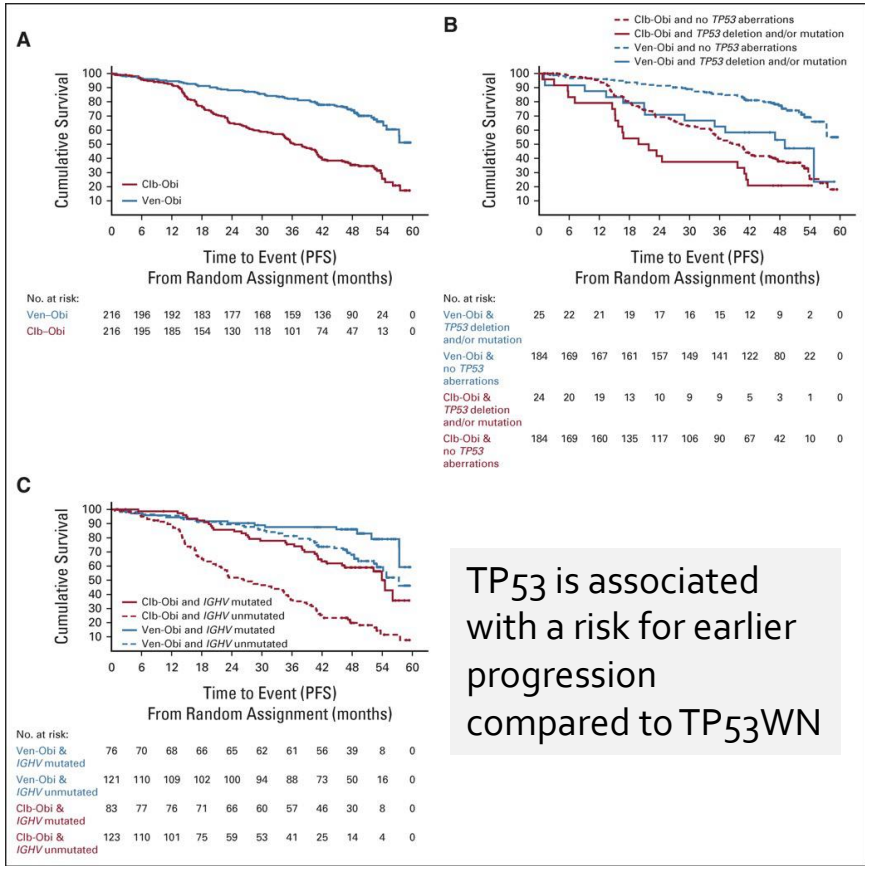
- Continuous therapy exposes patients to risk for adverse events
  - Persistent B-cell aplasia
  - Financial toxicity for patients and the health care system

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Should You Use 2 Drugs?

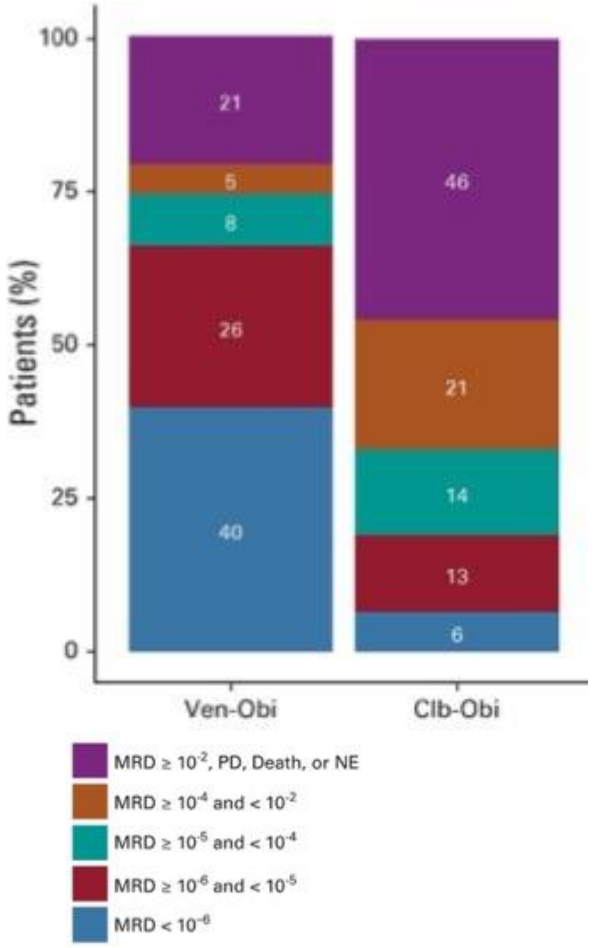
Obinutuzumab Venetoclax Is a Time Limited Therapy for CLL

Obinutuzumab with venetoclax or chlorambucil

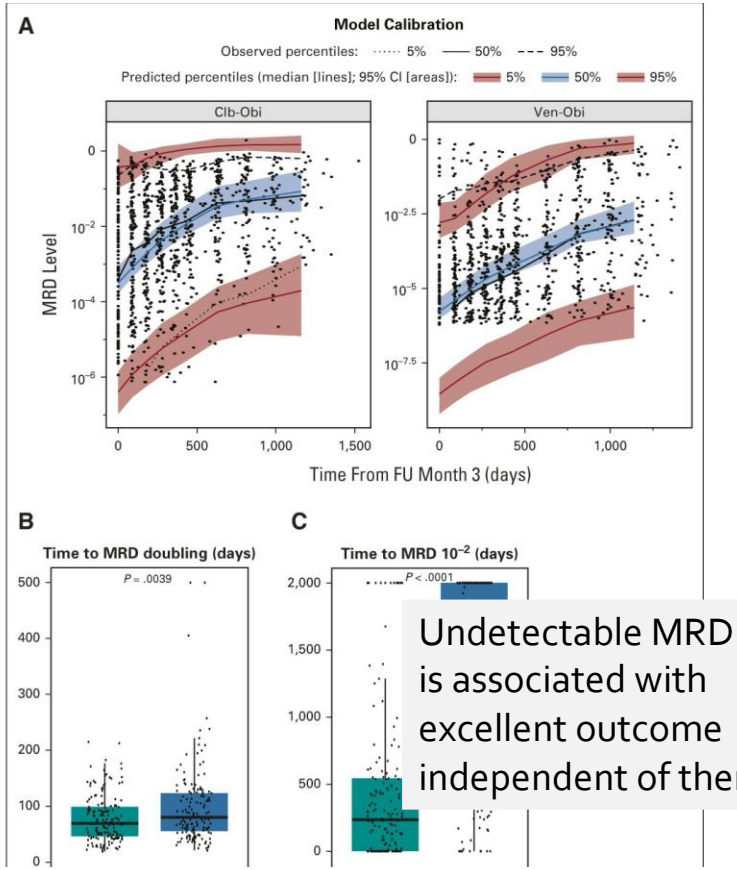


TP53 is associated with a risk for earlier progression compared to TP53WN

MRD 2 months after EOT



Time to MRD conversion (>10^{-4})

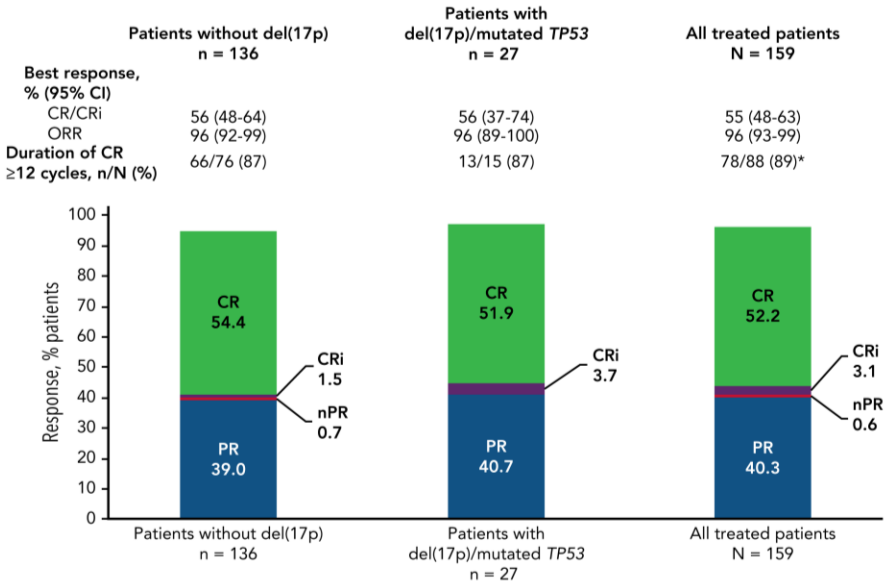


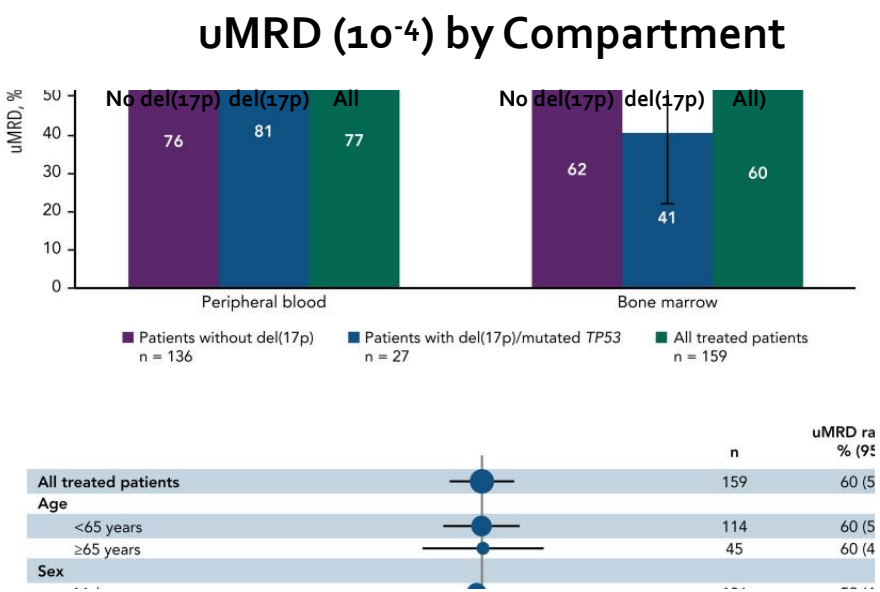
Undetectable MRD (10^{-6}) is associated with excellent outcome independent of therapy

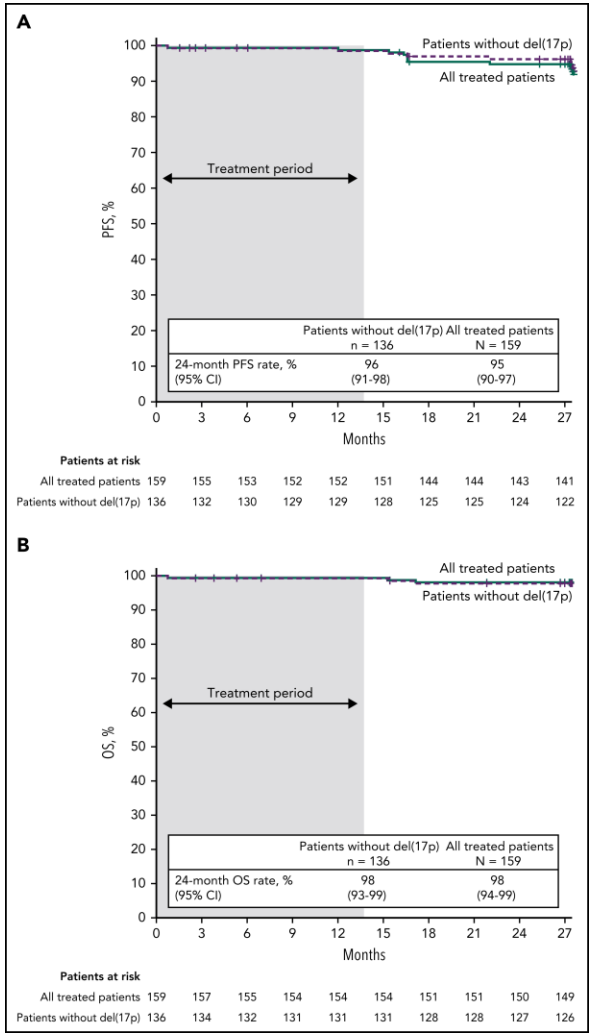
EOT = end of treatment.

Fischer K, et al. *N Engl J Med.* 2019;380:2225-2236. Al-Sawaf O, et al. *J Clin Oncol*. 2021;39(36):4049-4060.

CAPTIVATE: Ibrutinib 3-Month Lead-in followed by Ibrutinib-Venetoclax for 12 Months







Tam CS, et al. *Blood*. 2022;139(22):3278-3289.

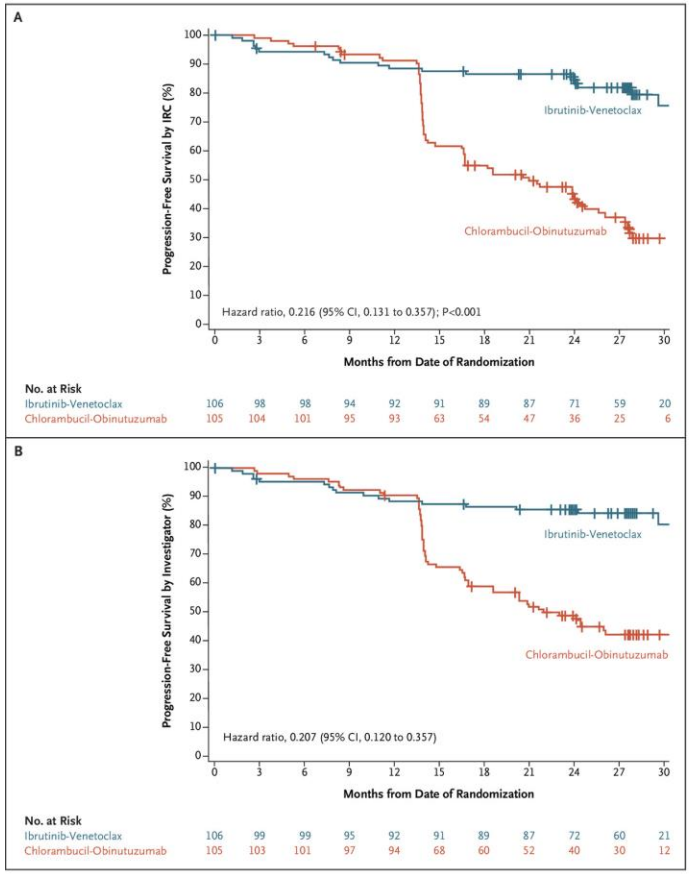
GLOW: Ibrutinib-Venetoclax vs Obinutuzumab-Chlorambucil for 1L CLL

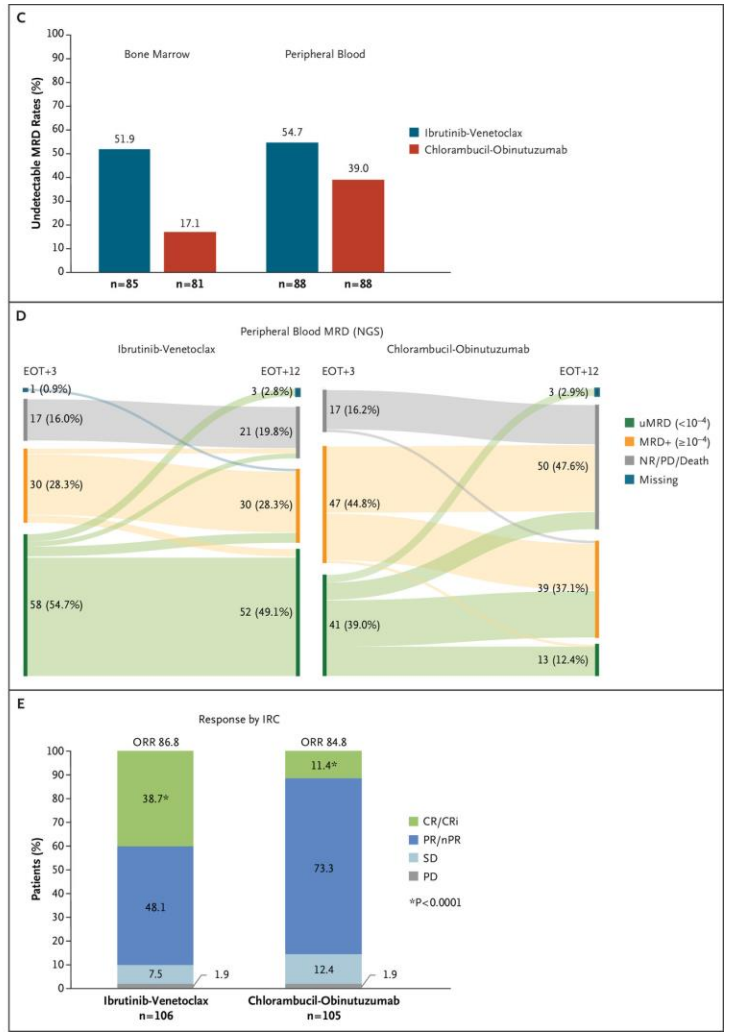
Randomized phase 2

Patient ≥65 or 18-64 with CIRS>6

No del(17p) or TP53 mutation

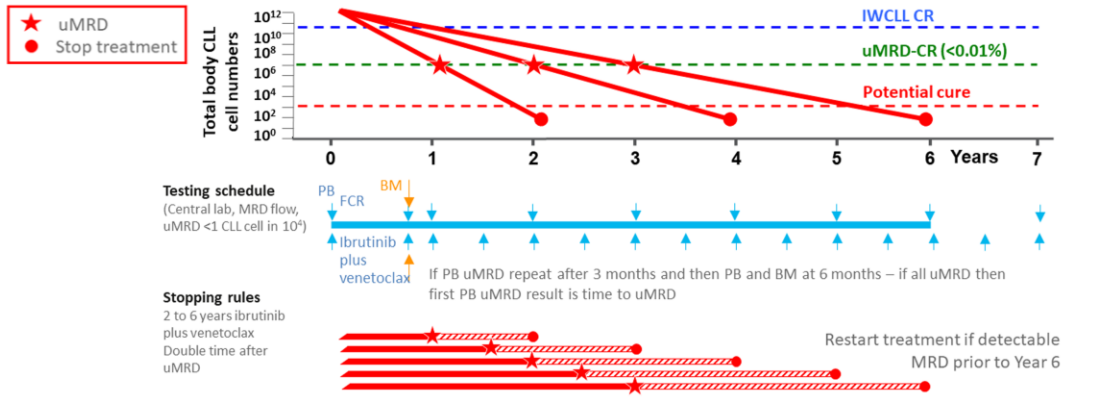
Fixed duration of 12 cycles of therapy



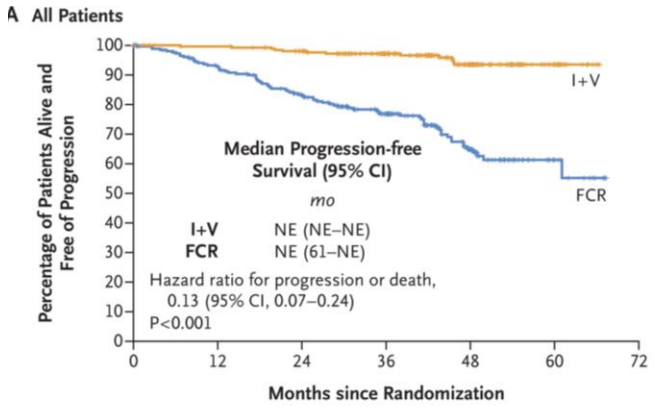


Kater AP, et al. *NEJM Evid*. 2022;1(7):EVIDoa2200006.

Can MRD Optimize Benefit of 2 Drugs? UK FLAIR Trial: MRD-Guided Therapy

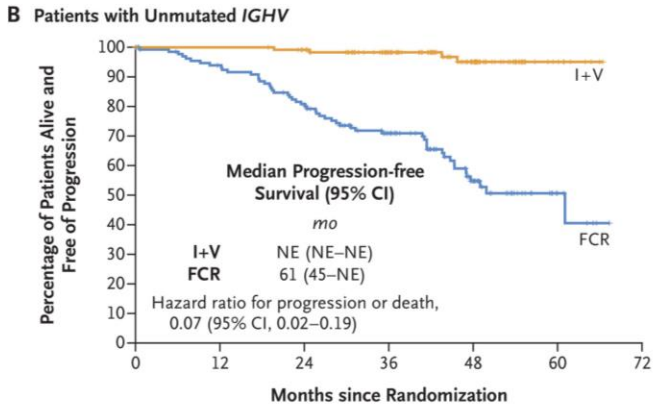


Technique and reagents: Flow cytometry performed following the ERIC–standardized/compliant approach.
Sensitivity: Detection limit of **1 CLL cell in 100,000 leukocytes (0.001%, 1 × 10^{-5})**.
uMRD threshold: uMRD (termed uMRD4) was defined as **<0.01% (<10^{-4})** CLL cells of total leukocytes; detectable MRD was ≥0.01%. [1-2]
Sampling schedule: In the ibrutinib-containing arms, the first assessment (PB and BM) was at 9 months post-randomization, followed by PB 12 months and every 6 months thereafter. The FCR arm was assessed every 12 months.



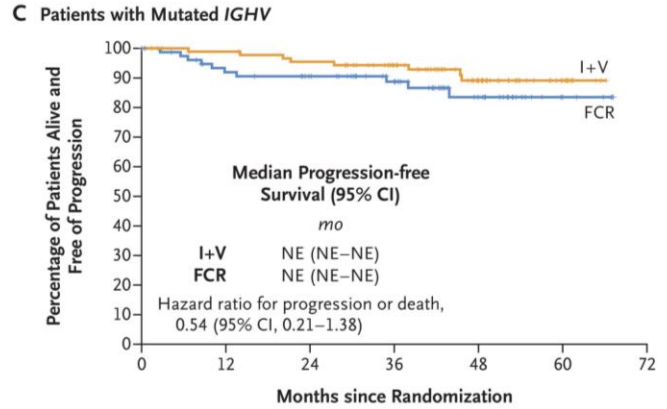
No. at Risk (no. with data censored)

I+V	260 (1)	253 (6)	239 (16)	183 (70)	99 (151)	21 (227)	0 (248)
FCR	263 (2)	227 (18)	194 (28)	145 (63)	68 (126)	12 (177)	0 (188)



No. at Risk (no. with data censored)

I+V	123 (1)	122 (1)	117 (5)	89 (32)	47 (72)	8 (111)	0 (119)
FCR	138 (1)	122 (8)	103 (10)	76 (25)	35 (54)	6 (80)	0 (85)



No. at Risk (no. with data censored)

I+V	93 (0)	88 (4)	84 (5)	70 (18)	42 (45)	11 (74)	0 (85)
FCR	80 (1)	67 (7)	61 (12)	49 (23)	25 (45)	5 (65)	0 (70)

Therapy Discontinuation with I +V

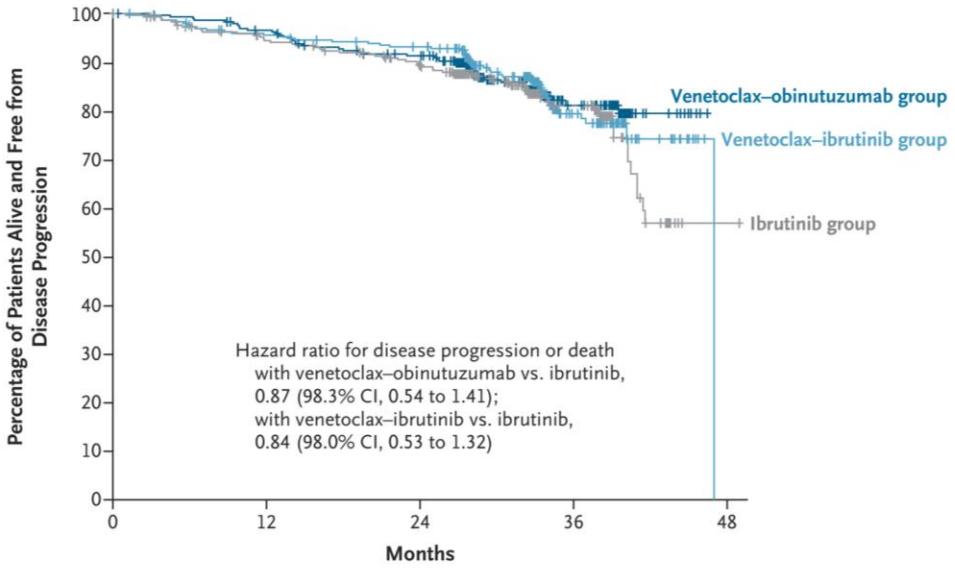
2-years	28.0%
3-years	58%

FCR = fludarabine-cyclophosphamide-rituximab; BM = bone marrow.
Munir T, et al. *N Engl J Med.* 2024;390(4):326-337.

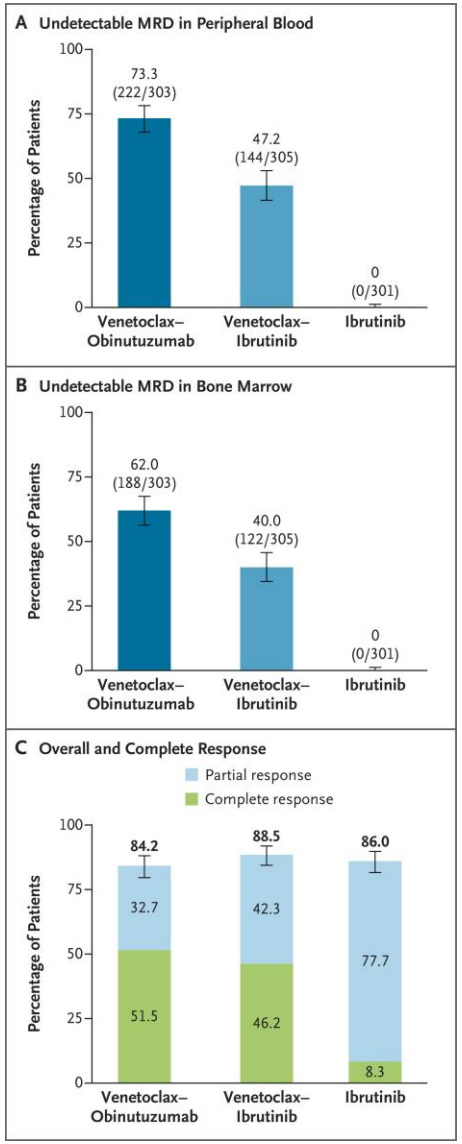
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CLL17: 1 Drug vs Two Options for 2 Drugs

Patients: Treatment naïve CLL
Randomization: 1:1:1
ibrutinib (continuous)
venetoclax–obinutuzumab (fixed-duration)
venetoclax–ibrutinib (fixed-duration)
Primary end point: Investigator-assessed PFS
Design: Noninferiority with margin for the hazard ratio, 1.608 (noninferiority margin of 8 percentage points at 3 years)
Secondary end points: MRD, ORR, OS, safety



No. at Risk					
Venetoclax–obinutuzumab	303	278	256	77	0
Venetoclax–ibrutinib	305	278	267	82	0
Ibrutinib	301	267	243	94	1

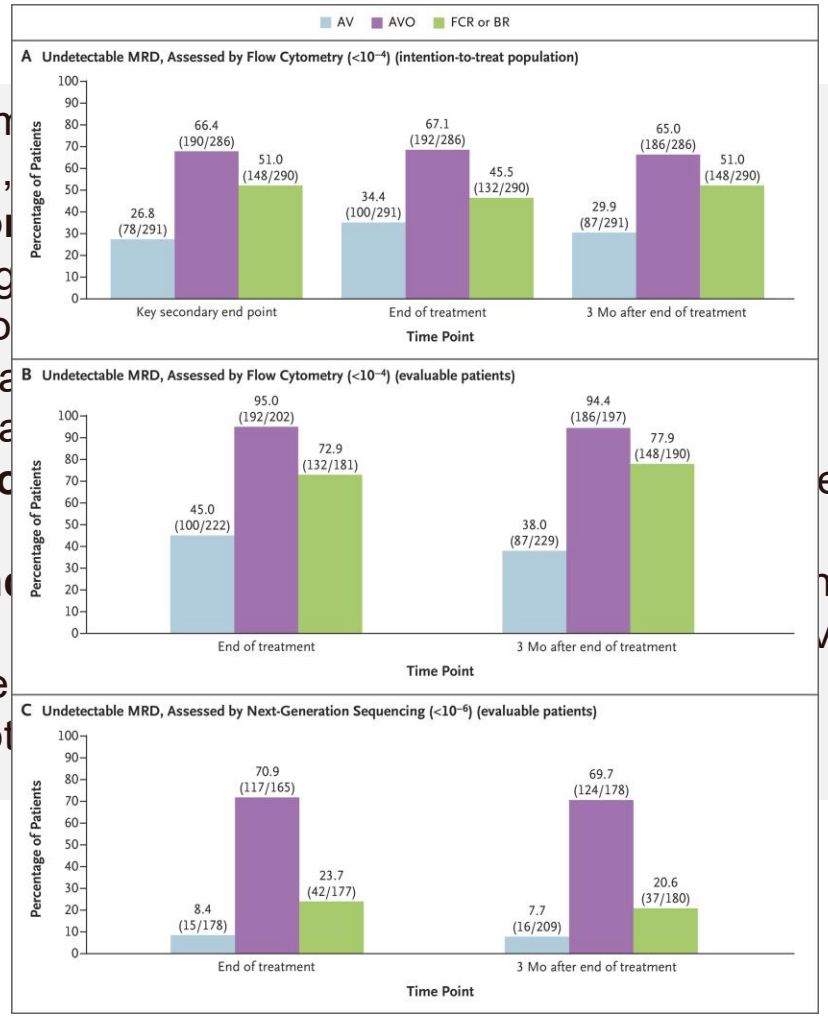


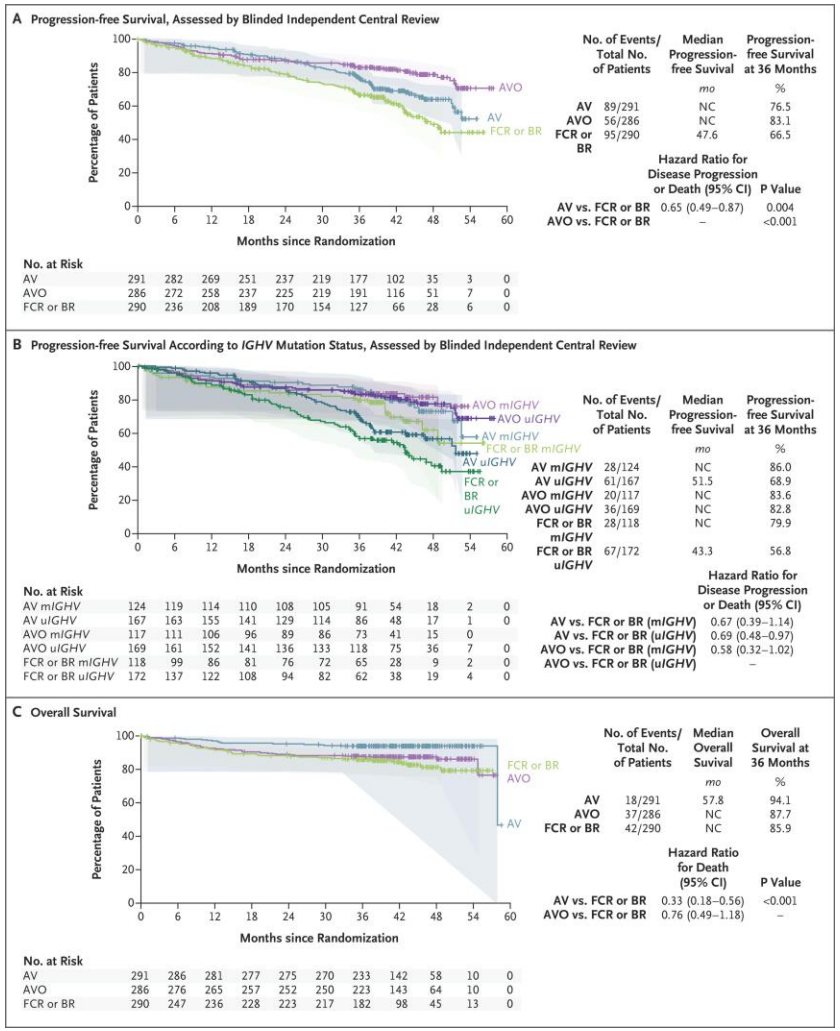
ORR = overall response rate.
Al-Sawaf O, et al. *N Engl J Med*. 2026;394(11):1084-1096.

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AMPLIFY: 2 Drugs vs 3 Drugs

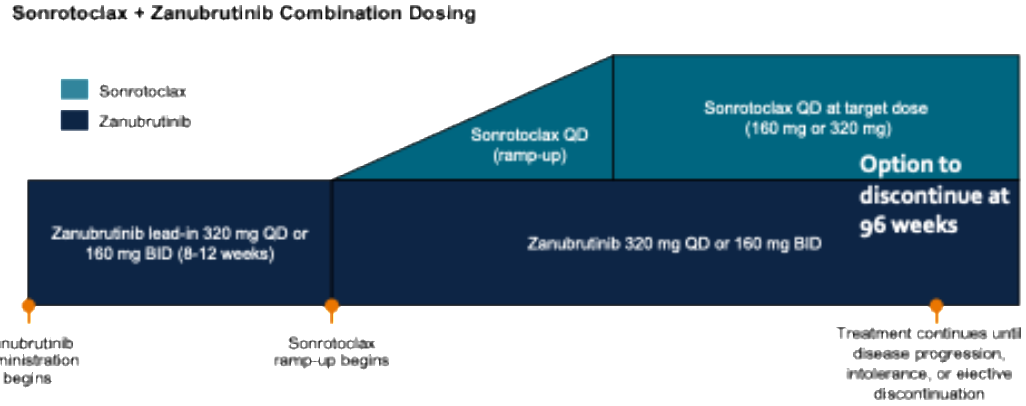
Patient: Treatm
TP53 mutation,
Randomizatio
status, Rai stag
BR o
Acala
Acala
Primary endpo ew)
AV vs chemo
Secondary en he
start of cycle 9
arm, or 12 wee VO
chemoimmunot

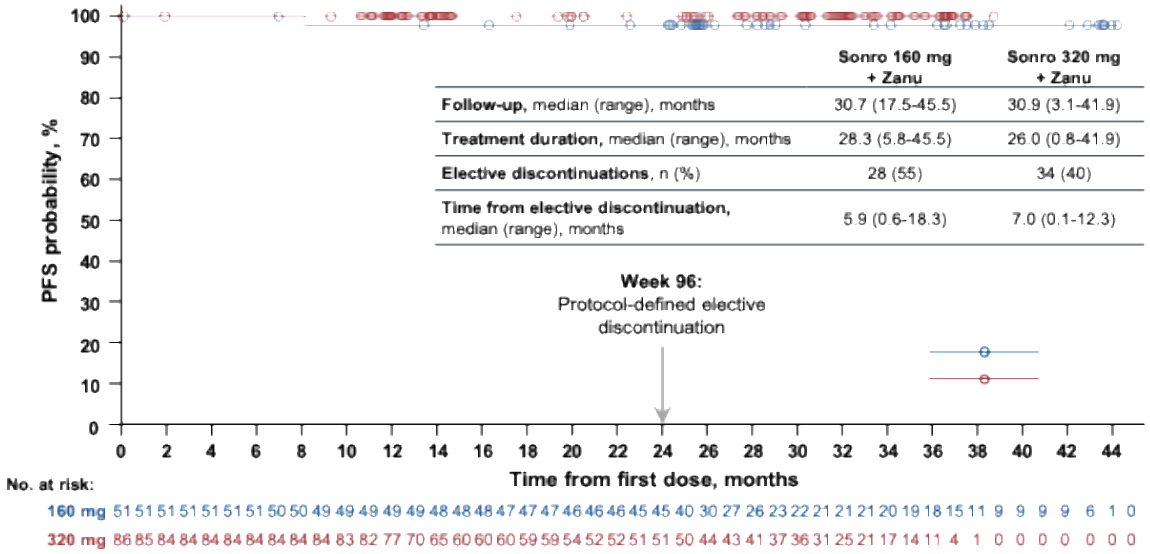


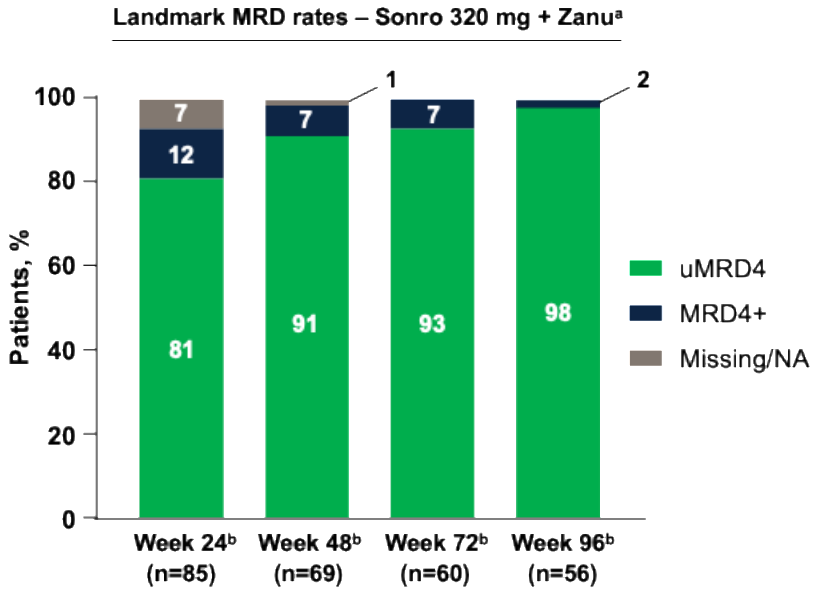


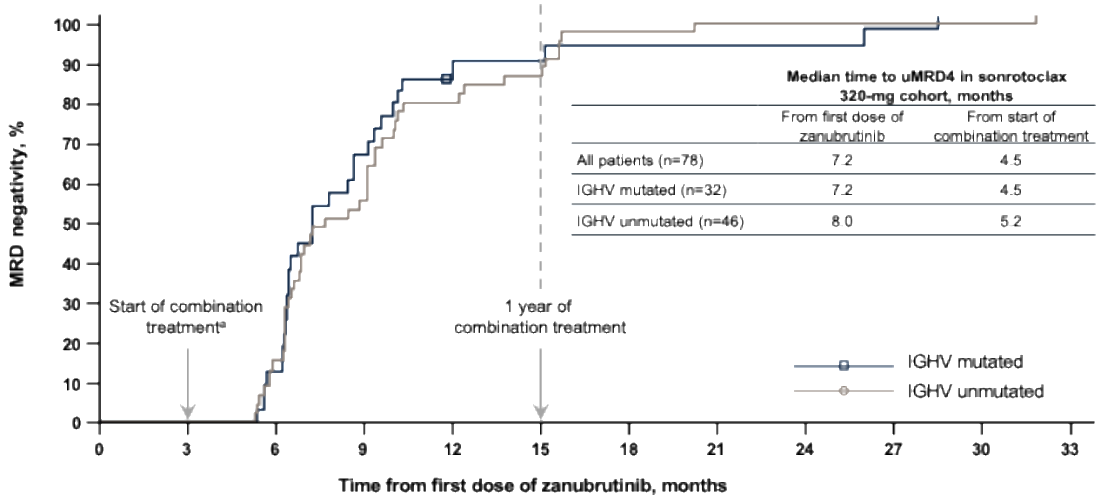
Brown JR, et al. *N Engl J Med.* 2025;392(8):748-762.

Sonrotoclax + Zanubrutinib









Tam C, et al. Presented at: American Society of Hematology (ASH) Annual Meeting; December 6-9, 2025; Orlando, FL. 3891.

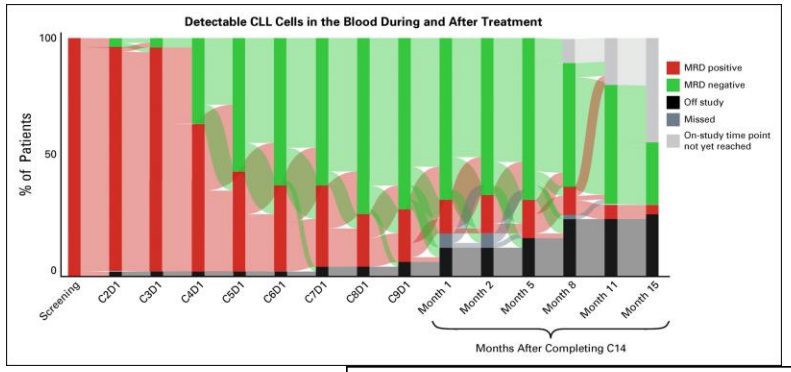
If You Are Going to Use 2 Drugs…

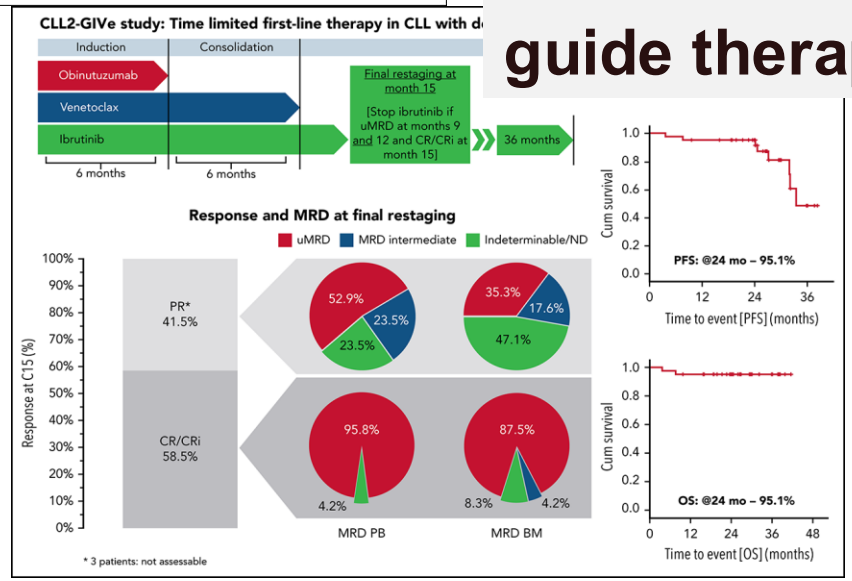
- Obin-ven is a time-limited regimen that achieves high rates of uMRD (10^{-6})
  - TP53 aberration associated with higher risk of progression
    - Some recommend continuous BTKi for these patients
    - Retreatment needs to be explored
- Ibrutinib and venetoclax can be administered as a time-limited treatment with high rates of uMRD (10^{-4}) as demonstrated in both CAPTIVATE and GLOW
  - del(17p) patients in the CAPTIVATE study appear to have similar PFS and the WT patients; however, the uMRD rate in the BM is lower
  - **NOT FDA approved**
- Second generation BTKi + BH3 mimetic (venetoclax or sonrotoclax)
  - Preliminary PFS with acalabrutinib and venetoclax looks favorable, but uMRD rates are concerning for durability
  - Zanubrutinib and sonorotoclax has very high uMRD4 rates; however, we await the results of CELESTIAL TNCLL (zanu-sonro v obin-ven)

Should You Use 3 Drugs?

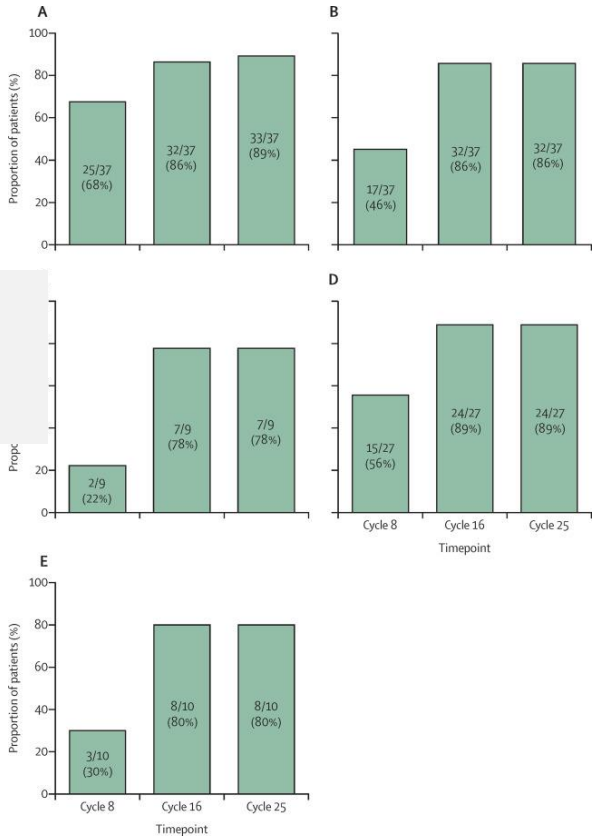
Three Drug Combinations Result in High Rates of uMRD (10^{-4})

Ibrutinib-Venetoclax-Obinutuzumab (IVO, GIVe)





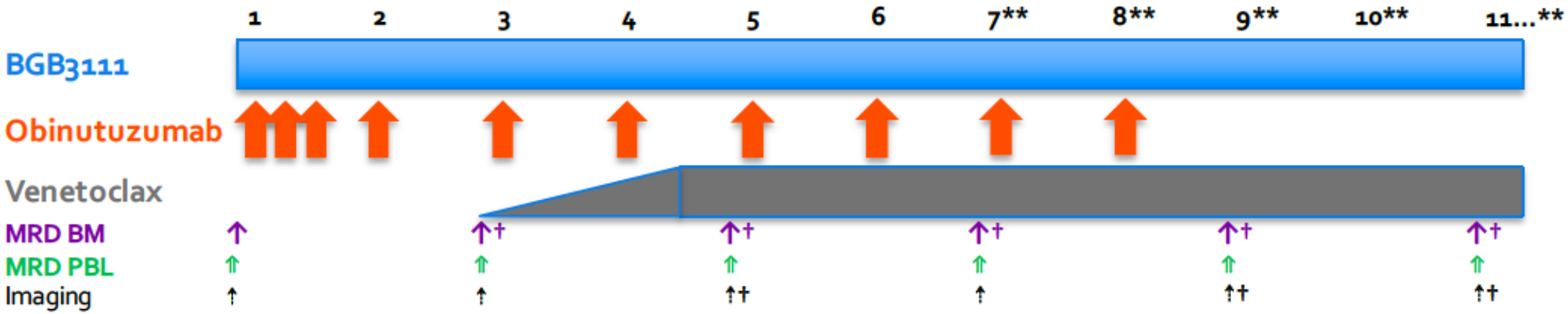
Acalabrutinib-Venetoclax-Obinutuzumab (AVO)



Can uMRD be used to guide therapy in CLL?

Rogers KA, et al. *J Clin Oncol.* 2020;38(31):3626-3637. Davids MS, et al. *Lancet Oncol.* 2021;22(10):1391-1402. Huber H, et al. *Blood.* 2022;139(9):1318-1329.

BOVen: Triple Combination with Response-Adapted Discontinuation



Dosing:

BGB3111 160 mg oral twice daily
Until EOT or intolerance**

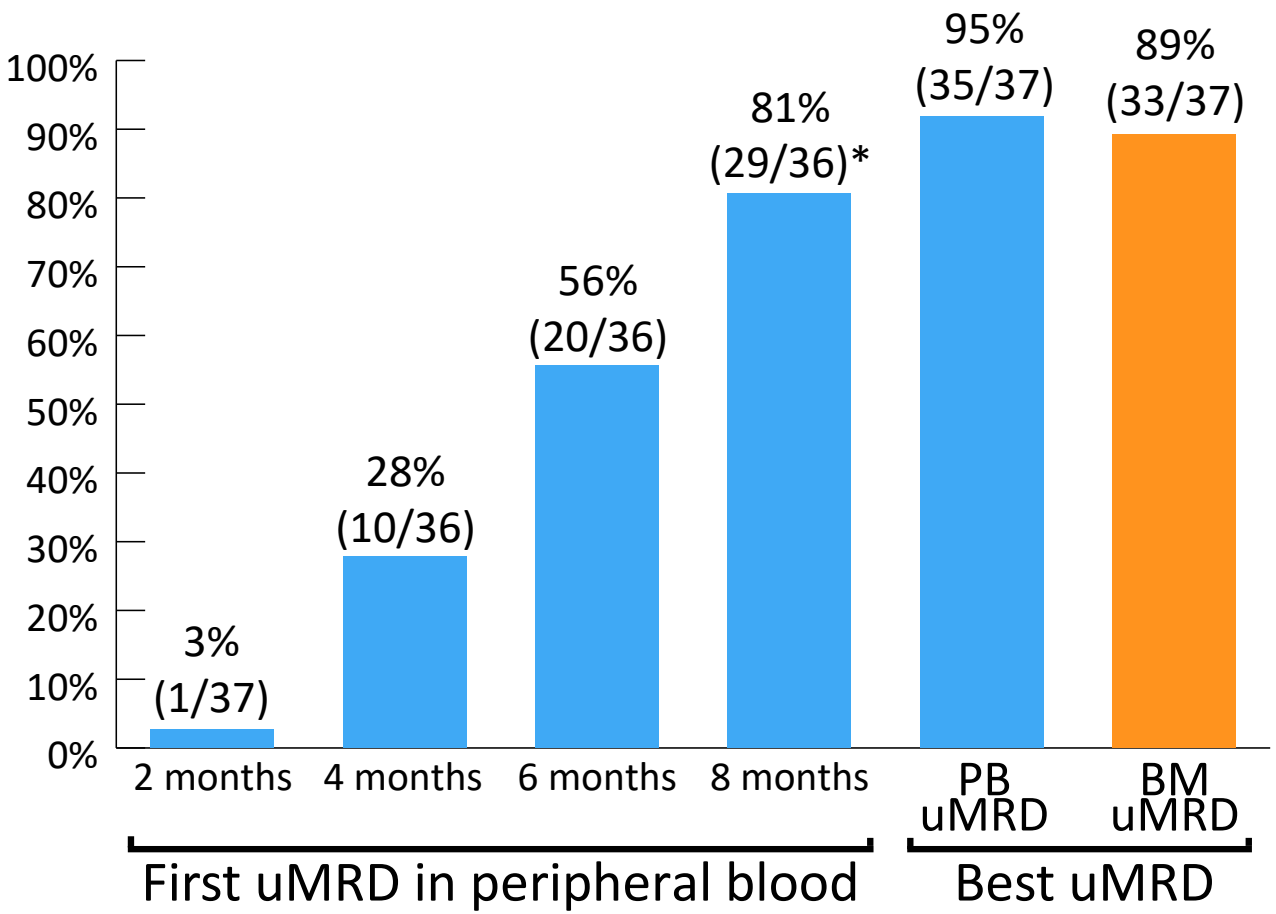
Obinutuzumab 1000 mg IVPB
Cycle 1: day 1, 8, 15
Cycle 2-8: day 1

Venetoclax 400mg oral daily
5-week ramp-up: 1 week each of 20mg; 50mg; 100mg; 200mg; 400 mg oral daily
Until EOT or intolerance**

†BM MRD and imaging at these time points only done if PBL MRD is negative
**End of therapy (EOT) occurs when MRD negative on 2 consecutive measurements, intolerance, progression or after 2 years of therapy

Soumerai JD, et al. Blood Adv. 2026 Jun 30:bloodadvances.2026020221 [Epub ahead of print].

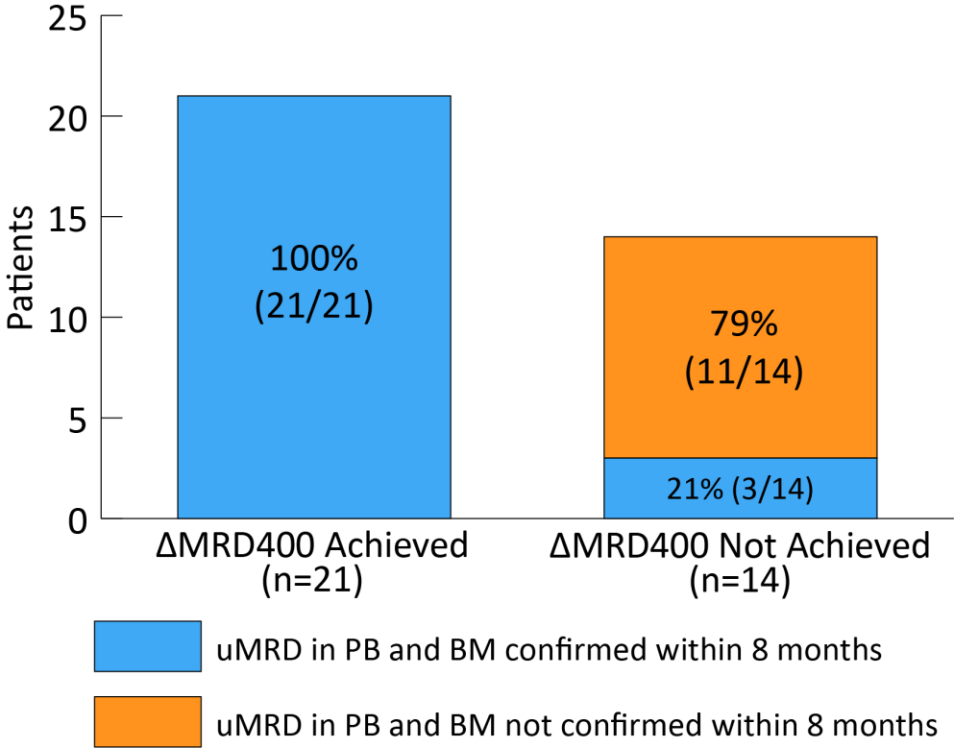
BOVen: uMRD4 Outcomes



- 95% (35/37) uMRD (10-4) in PB
- 89% (33/37) uMRD (10-4) in both PB and BM
  - All met prespecified MRD endpoint / treatment discontinuation criterion and stopped Tx after a median of 10 months (IQR 8-12 months)

Soumerai JD, et al. *Lancet Haematol.* 2021;8(12):e879-e890.

ΔMRD400 for Predicting Early BM uMRD4



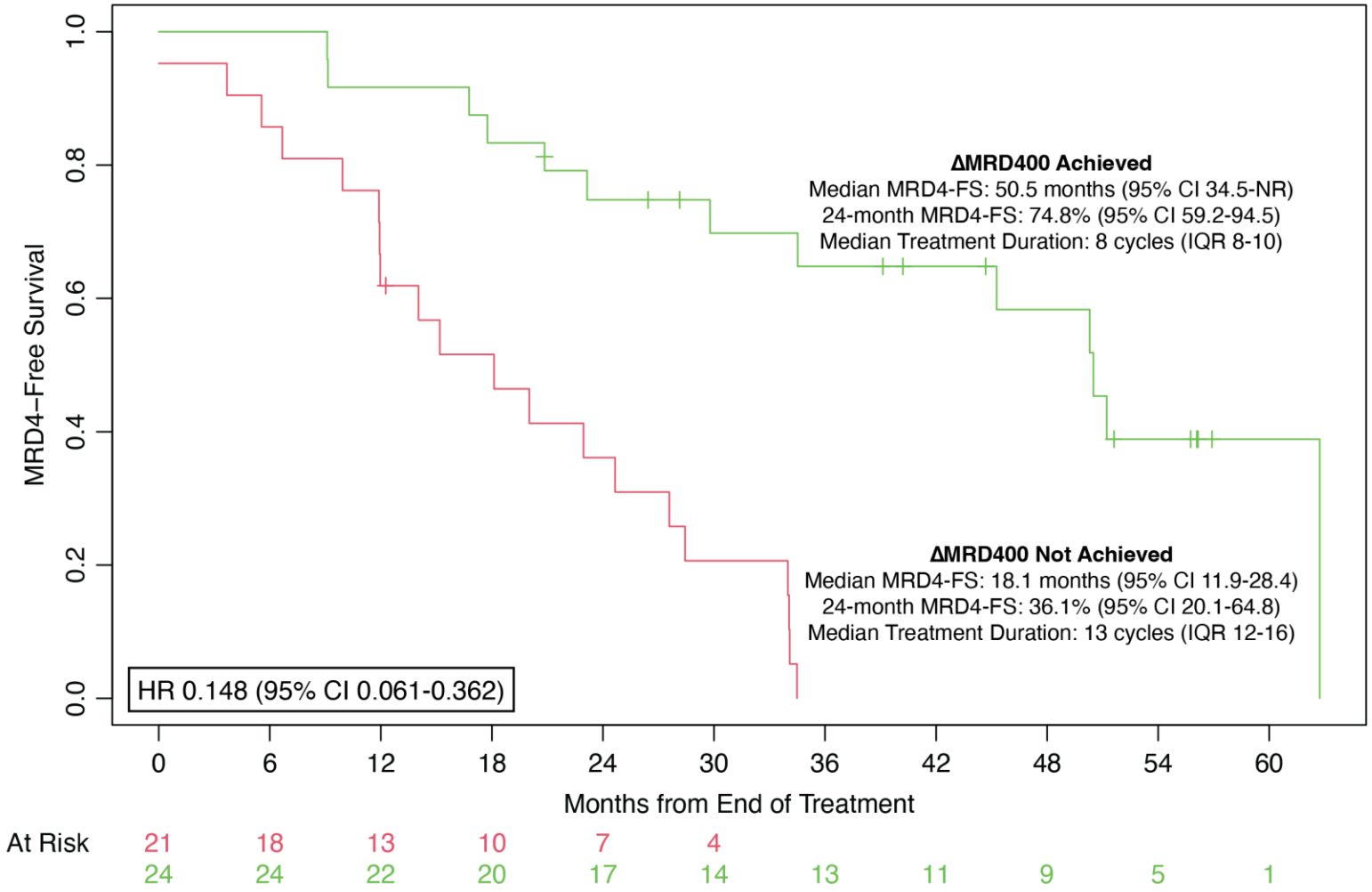
- ΔMRD is decrease in MRD from baseline to C5D1 (after 1 month of venetoclax at the target dose)
- 400-fold reduction (2·6 log) identified as the optimal cutoff for predicting uMRD ≤8 months (Youden Index)
- 19% of ΔMRD400 achievers had del(17p)/TP53M
- 7% of ΔMRD400 failures had del(17p)/TP53M

ΔMRD400	BM uMRD in ≤8 mo	Time to BM uMRD	Time on therapy
Achieved (n=21)	100% (21/21)	6 mo (IQR 6-6)	8 mo (IQR 8-10)
Failed (n=14)	21% (3/14)	11 mo (IQR 10-15.5)	13 mo (IQR 12-17.5)

Soumerai JD, et al. *Lancet Haematol.* 2021;8(12):e879-e890.

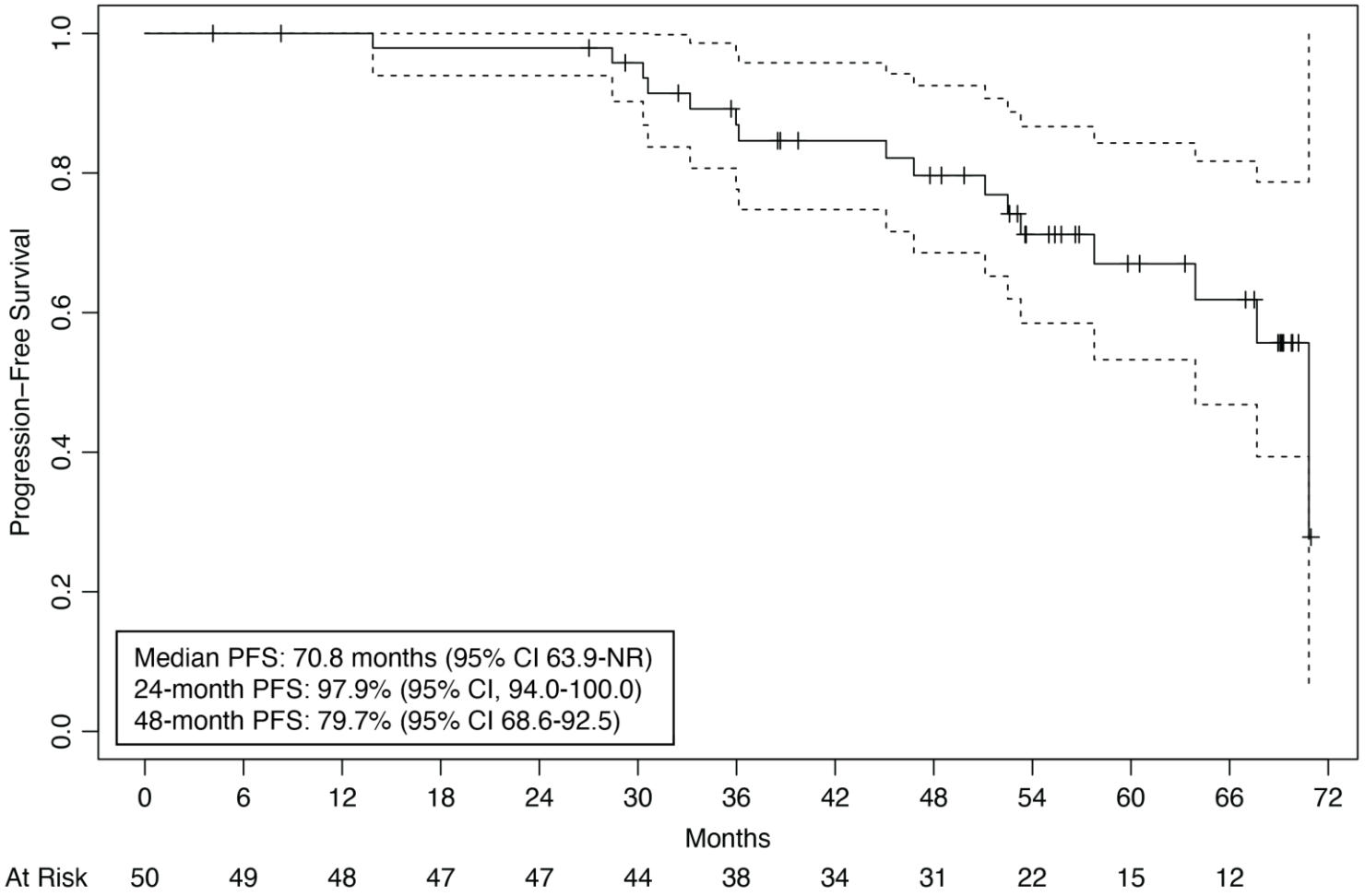
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ΔMRD400 Predicts Post-Treatment MRD Outcomes



Soumerai JD, et al. *Lancet Haematol.* 2021;8(12):e879-e890. Soumerai JD, et al. Blood Adv. 2026 Jun 30:bloodadvances.2026020221 [Epub ahead of print].

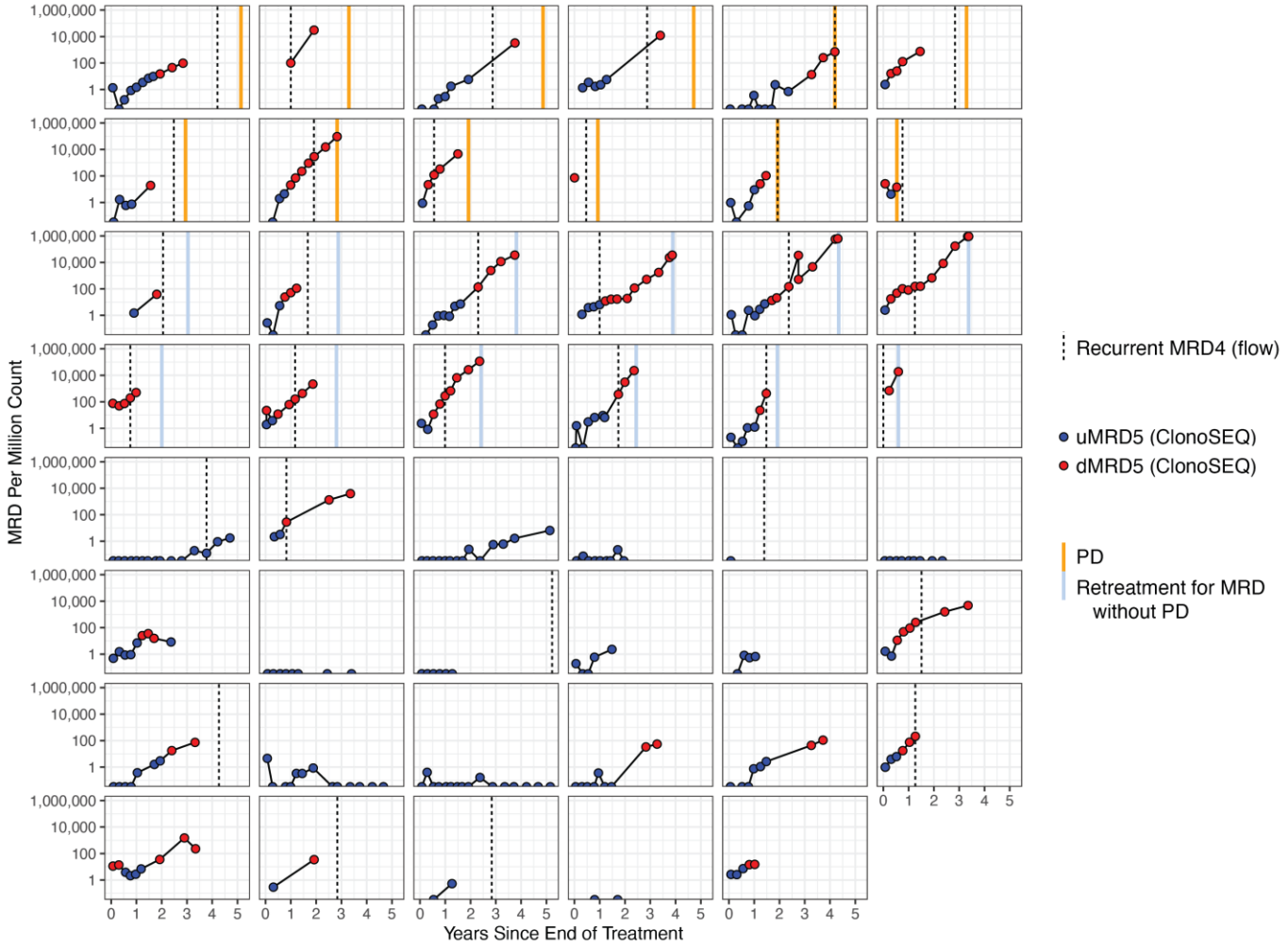
BOVen Cohort 1: PFS



Soumerai JD, et al. *Lancet Haematol.* 2021;8(12):e879-e890. Soumerai JD, et al. Blood Adv. 2026 Jun 30:bloodadvances.2026020221 [Epub ahead of print].

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BOVen Cohort 1 CLL: MRD Kinetics of Individual Cells



Soumerai JD, et al. Blood Adv. 2026 Jun 30:bloodadvances.2026020221 [Epub ahead of print].

BOVen Cohort 1 CLL: Retreatment

	Retreatment with Zanubrutinib + Venetoclax (N=23)
Age, median (range)	64 (29-80)
Sex, n (%)	Female, 6 (26%); Male, 17 (74%)
ΔMRD400 with initial therapy, n (%)	
Achieved	8 (34.8%)
Not achieved	15 (65.2%)
Deletion 17p and/or TP53 mutated, n (%)	6 (26.1%)
Preexisting at initial therapy	4 (17.4%)
Acquired at retreatment	2 (8.7%)
Unmutated IGHV, n (%)	21 (91%)
B2-microglobulin, mg/L (IQR)	2.43 (2.08-3.04)
Absolute lymphocyte count, cells/μl (IQR)	2.02 (1.72-6.08)
Treatment-free interval, months (range)	34.5 (7.1-63.1)
Disease status at retreatment, n (%)	
Progressive disease	10 (43.5)
Ongoing PR with MRD ≥1%	7 (30%)
Ongoing CR with MRD ≥1%	6 (26.1%)

Retreatment Criteria:

Detectable MRD ≥1% or iwCLL PD

Median retreatment follow-up:

16.6 months (range, 1-47.6)

Median treatment duration:

14.8 months (range, 1-22.6).

Patient with iwCLL PD (10, 9 evaluable):

ORR 100%, CR 33%, PR 66.7%

MRD Assessment (22 patients evaluable):

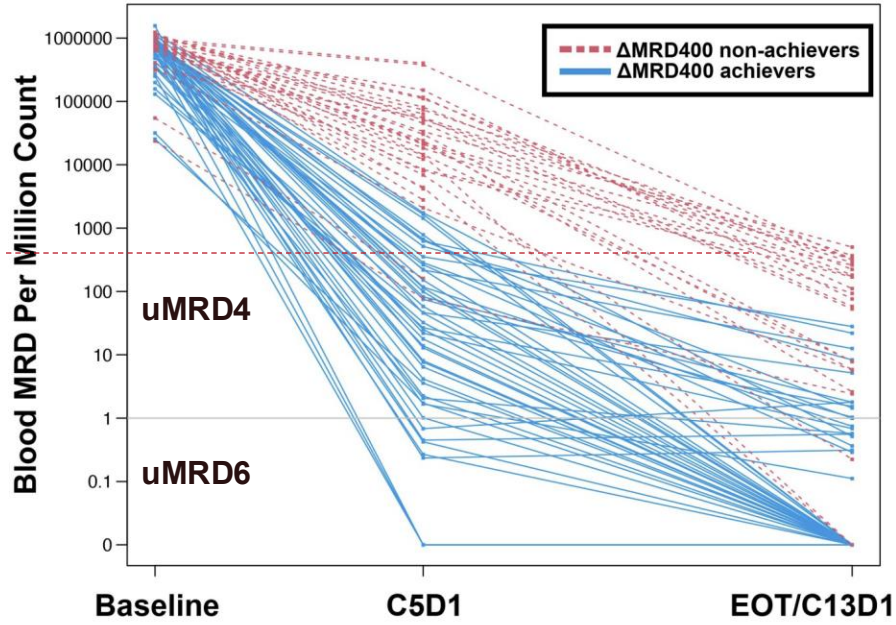
≥1-log Reduction 100%

uMRD4 (Peripheral Blood): 36.4% (8)

Soumerai JD, et al. Blood Adv. 2026 Jun 30:bloodadvances.2026020221 [Epub ahead of print].

BOVen CLL Cohort 4: Validation of Δ400

- Cohort 4: Prospective assessment of Δ400
- BOVen, assess clonal burden by immuno-sequencing at C5D1
  - If Δ400: Complete 10 cycles of BOVen
  - Not Δ400: Complete 24 cycles of BOVen



	ΔMRD400 Achievers (N=47)
TP53 mutation or deletion, % (N)	35% (N=16)
IGHV unmutated, % (N)	55% (N=26)
ΔMRD (Pre to C5), median (IQR)	12,008 (3,039-16,0349)
EOT (10-mo) Blood uMRD4, % (N)	100%: (47/47)
EOT (10-mo) Blood uMRD5, % (N)	94% (44/47)
	ΔMRD400 Non-Achievers (N=31)
TP53 mutation or deletion, % (N)	42% (N=13)
IGHV unmutated, % (N)	55% (N=17)
ΔMRD (Pre to C5), median (IQR)	34 (12-102)
C13D1 Blood uMRD4, % (N)	52% (13/25)
C13D1 Blood uMRD5, % (N)	36% (9/25)

ΔMRD = Baseline MRD level ÷ C5D1 MRD level measured by clonoSEQ testing.
ΔMRD400 achievers demonstrate a ΔMRD of ≥400, i.e., a ≥400-fold MRD reduction.

Soumerai J, et al. Presented at: European Hematology Association (EHA) 2026; June 11, 2026; Stockholm, SE. PS1689.

If You Are Going to Use 3 Drugs…

- The only approved 3-drug combination is AVO (based on AMPLIFY)
- Three drug combinations of BTKi-venetoclax-obinutuzumab achieve high rates of uMRD (10-4) in PB and BM
- Progression after GIVe in TP53 aberrant patients needs further evaluation
- Since treatment is not administered to resistance, retreatment is a viable option
  - Preliminarily, we have seen second uMRD responses to retreatment with zanubrutinib and venetoclax in the BOVen study
- Treatment duration base on MRD kinetics has been validated in BOVen cohort 4

Case of Too Many Options

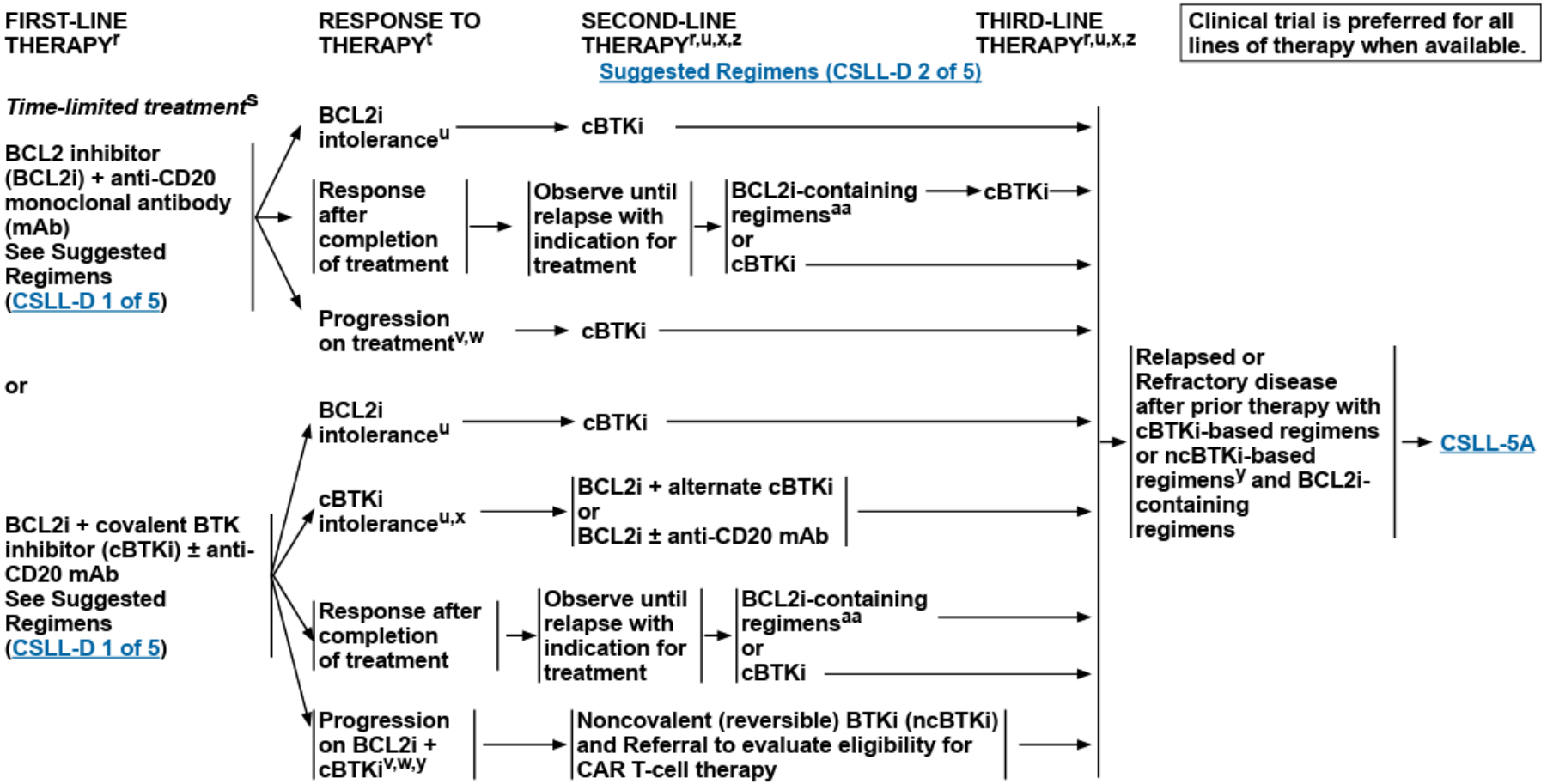
- Patient had a difficult time choosing
  - He wanted oral therapy
  - He wanted time-limited therapy
  - The acalabrutinib-venetoclax combination is now approved; however, the follow-up is limited and the uMRD rate was low
- Patient ultimately chose
  - Agree to participate in the BOVen study (cohort 4, response-adapted)

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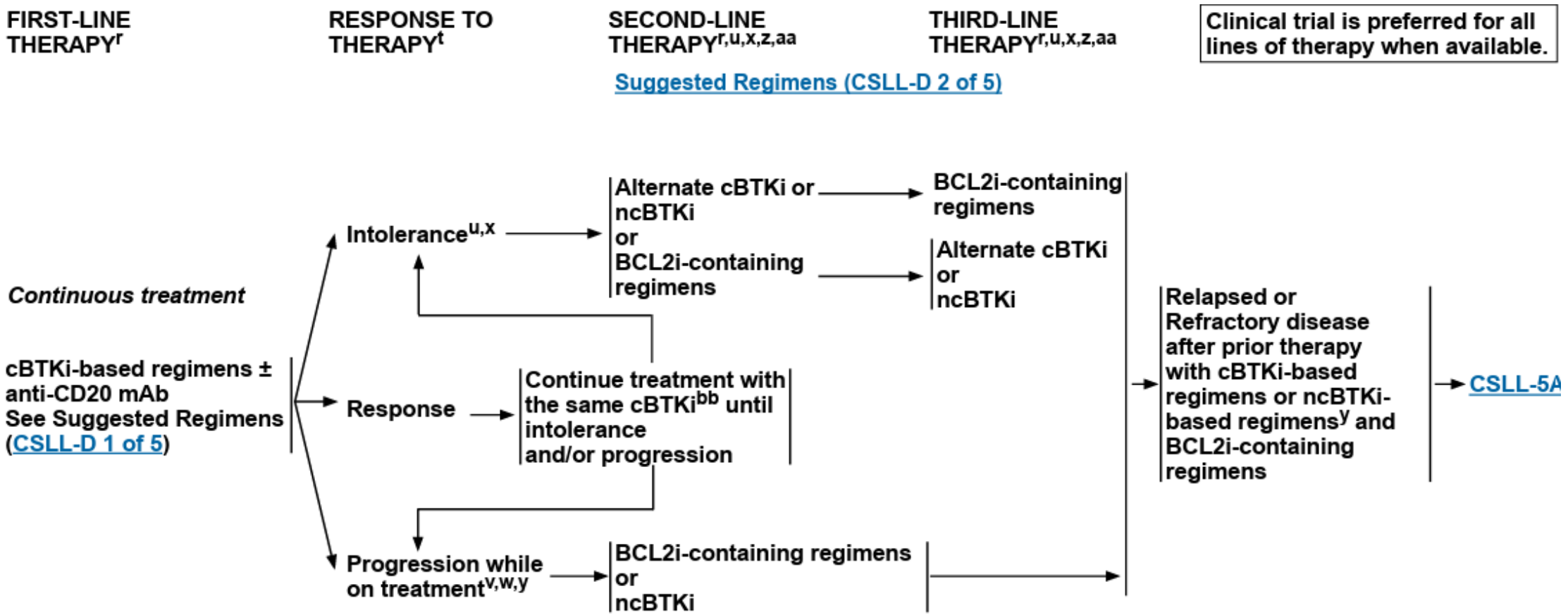
Optimizing Strategies in Relapsed CLL/SLL: Sequencing Strategies, Combo Approaches, and Novel Targets

John Allan

So How Should We Sequence? Well, It Depends…



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Quick Overview of NCCN Guidelines for Relapsed CLL/SLL

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL with or without del(17p)/*TP53* Mutation
(alphabetical by category)

SECOND-LINE OR SUBSEQUENT THERAPY[e,f]	
Preferred	**Other Recommended**
• BCL2i-containing regimen[*] ▸ Venetoclax + Obinutuzumab • cBTKi-based regimens[i,j,aa] ▸ Acalabrutinib (continuous) (category 1) ▸ Zanubrutinib (continuous) (category 1) • ncBTKi-based regimen ▸ Pirtobrutinib (continuous) (category 1) (resistance or intolerance to prior cBTKi-based regimens)	• BCL2i-containing regimens[*] ▸ Venetoclax + Rituximab (category 1) ▸ Venetoclax[*] ▸ Venetoclax/cBTKi (Acalabrutinib, Ibrutinib, Zanubrutinib)(time-limited [fixed duration or MRD-guided])[i,j,aa,bb] • cBTKi-based regimen[i,j] ▸ Ibrutinib[q] (continuous) (category 1)

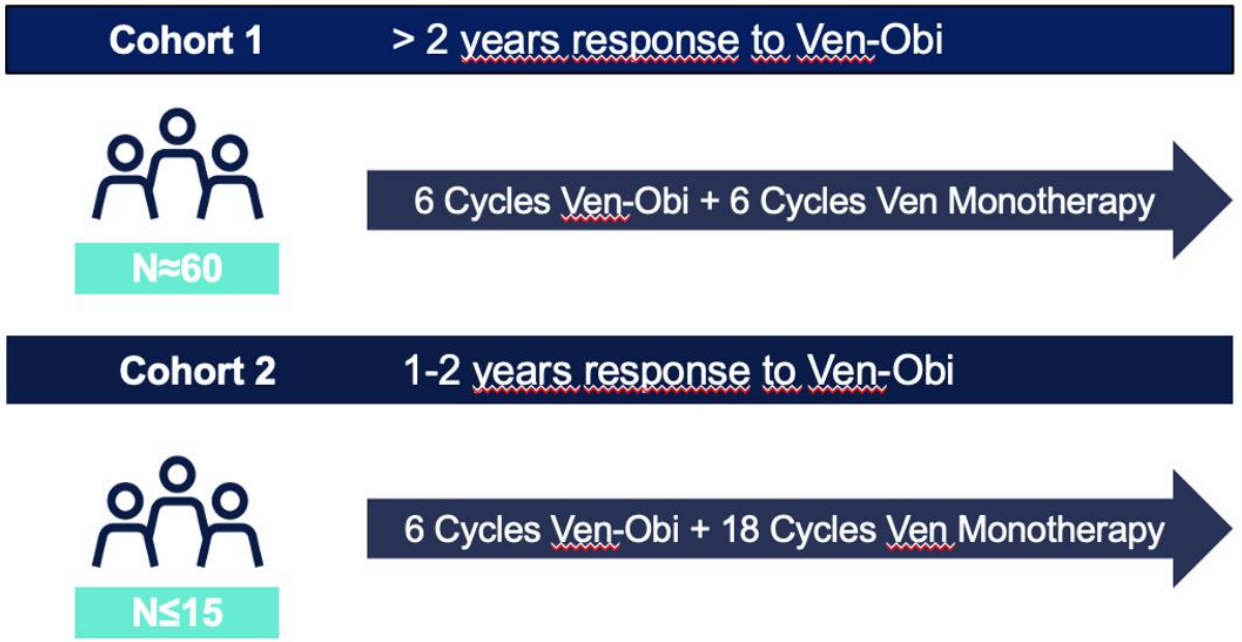
[*] Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) or venetoclax + cBTKi is a treatment option for relapse after a period of remission. Single-agent venetoclax (continuous) can also be considered a treatment option for relapse after a period of remission.

THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi-BASED AND BCL2i-CONTAINING REGIMENS[e,f]	
Preferred	**Other Recommended**
• CAR T-cell therapy ▸ Lisocabtagene maraleucel (CD19-directed)[cc] ± Ibrutinib[j] • ncBTKi-based regimen: ▸ Pirtobrutinib (continuous) (category 1) (if not previously given)	• PI3Ki-based regimens ▸ Duvelisib ▸ Idelalisib[dd] ± Rituximab • FC + Rituximab[w,x,**] • Lenalidomide[ee] ± Rituximab • Obinutuzumab • Alemtuzumab[ff] ± Rituximab (with del[17p]/*TP53* mutation) • Bendamustine[t] + Rituximab[u,**] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities) • HDMP + anti-CD20 mAb[s] (category 2A with del[17p]; category 2B without del[17p])

[**] Not recommended for CLL/SLL with del(17p)/*TP53* mutation.

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Thinking about Retreatment after Fixed Duration Therapy: VenG->ReVenG



25 subjects enrolled: 22 cohort 1, 3 cohort 2

Endpoints

Primary Endpoint

ORR after EOCT + 3 Mo

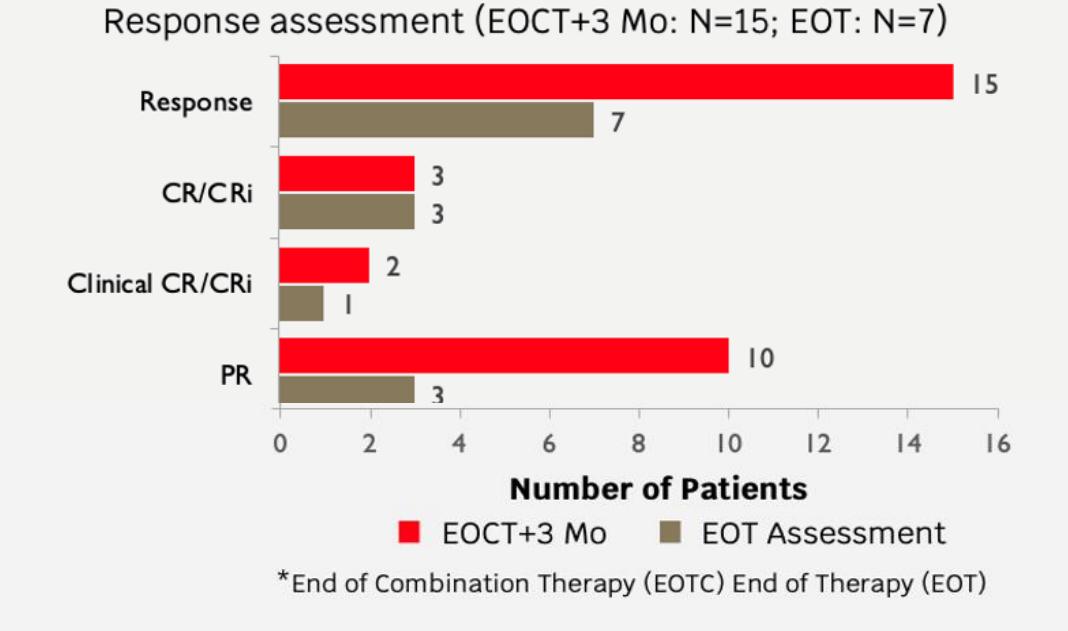
Secondary Endpoints

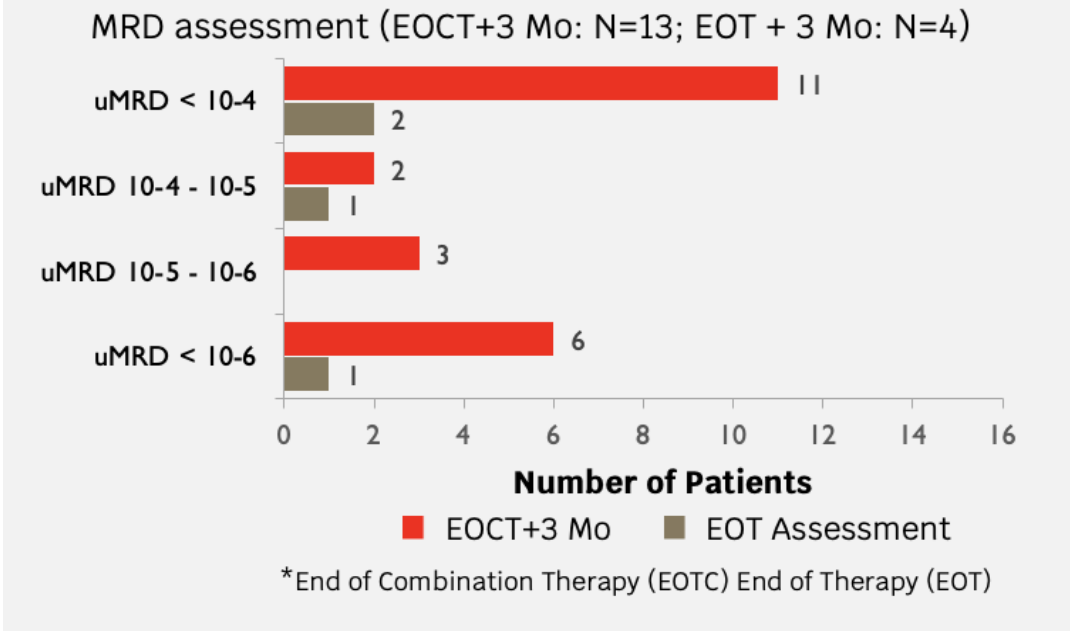
ORR after EOT
CR/CRi after EOCT + 3 Mo and EOT
TTR and DOR
uMRD rates (NGS)
PFS
OS
TTNT
Toxicity

TTNT = time to next treatment; DOR = duration of response.
Davids M, et al. Presented at: EHA 2026; June 11, 2026; Stockholm, SE. PF575.

ReVenG: Early Evidence of Efficacy

In all 25 patients, with a median follow-up of 10 mo. (range 2.4–25.1 mo.), 1 pt has progressed, and all 25 pts are alive



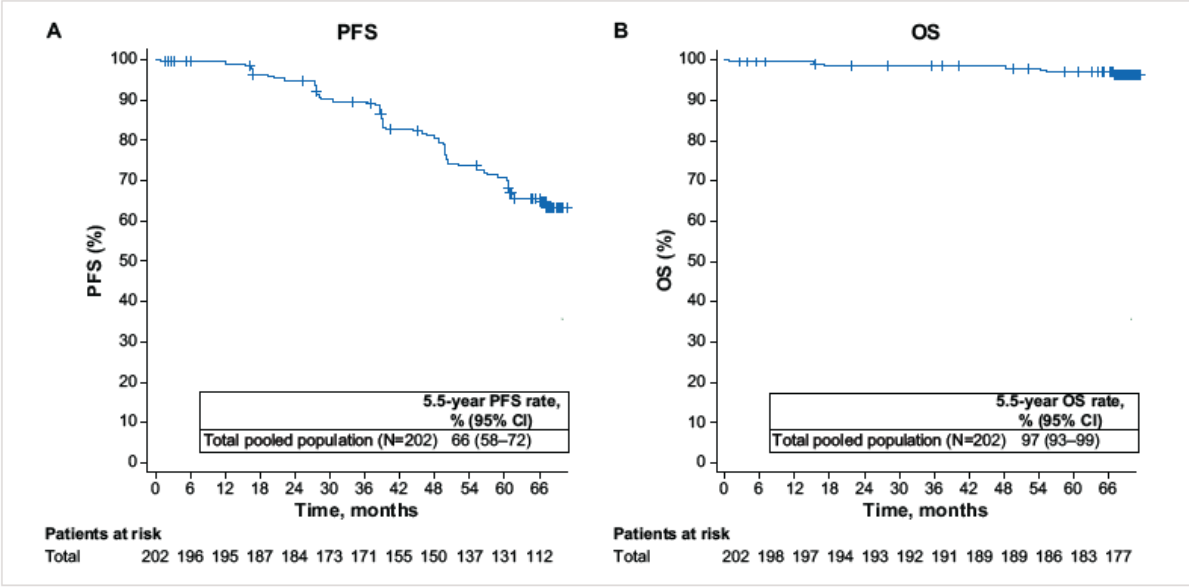


All patients at or beyond EOCT+3 have responded

Davids M, et al. Presented at: EHA 2026; June 11, 2026; Stockholm, SE. PF575.

Retreatment after BTKi/BCL2: CAPTIVATE

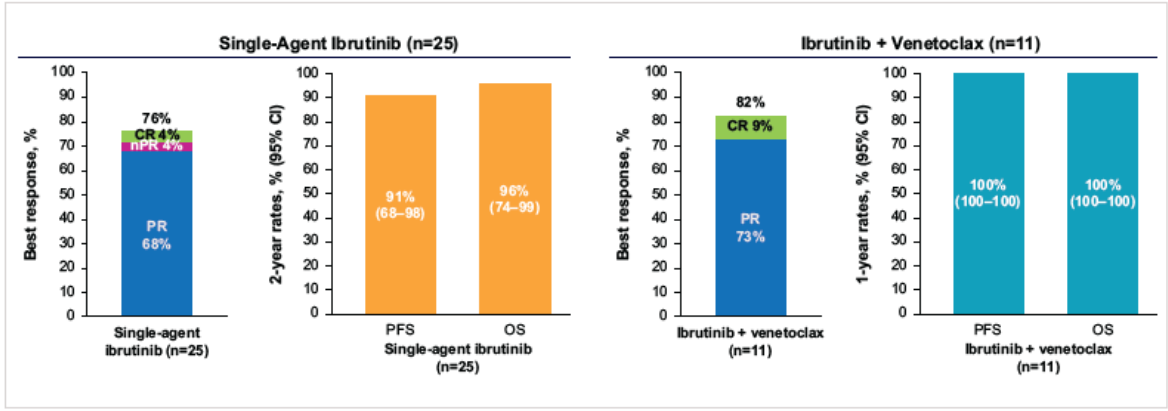
Overall Median PFS and OS Were Not Reached With Up to 7 Years of Follow-Up (Total Pooled Population)



OS, overall survival.

- Assessed in FD cohort patients only, 5.5-year PFS and OS rates were 60% (95% CI, 52–68) and 96% (95% CI, 91–98), respectively

Ibrutinib-Based Retreatment Confers Promising Overall Response Rates, PFS, and OS in Patients Needing Subsequent Treatment



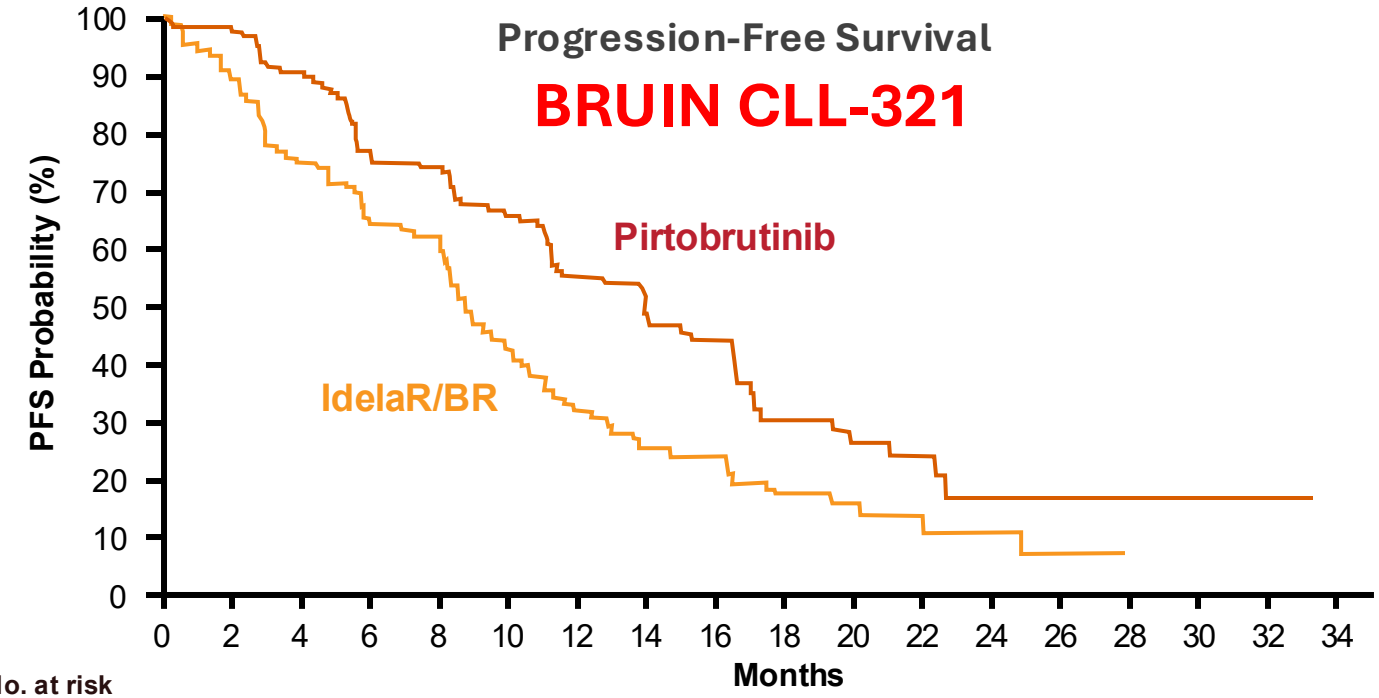
CR, complete response; nPR, nodular partial response; PR, partial response.

In the total pooled population with a median follow-up of more than 5.5 years, 64/202 pts (32%) had PD after FD ib + ven treatment
No pts had resistance-associated mutations in BTK or PLCG2 at PD among 53 pts with available samples

At final analysis, med duration of **follow-up was 28.4 mos** (range, 3.7-59.1) from the start of retreatment with **single-agent ibrutinib** and **15.2 mos** (range, 7.4–29.3) from the start of retreatment with **FD ib + ven**
Med duration of retreatment was 27.0 months (range, 1.1–59.1) with single-agent ibrutinib and 13.8 months (range, 6.7–18.3) with FD ib + ven

Ghia P, et al. *J Clin Oncol*. 2025;43(16_suppl):7036.

What about Progression after a BTKi and/or BCL2?



Pirto reduced the risk of progression or death by 46% according to IRC assessment

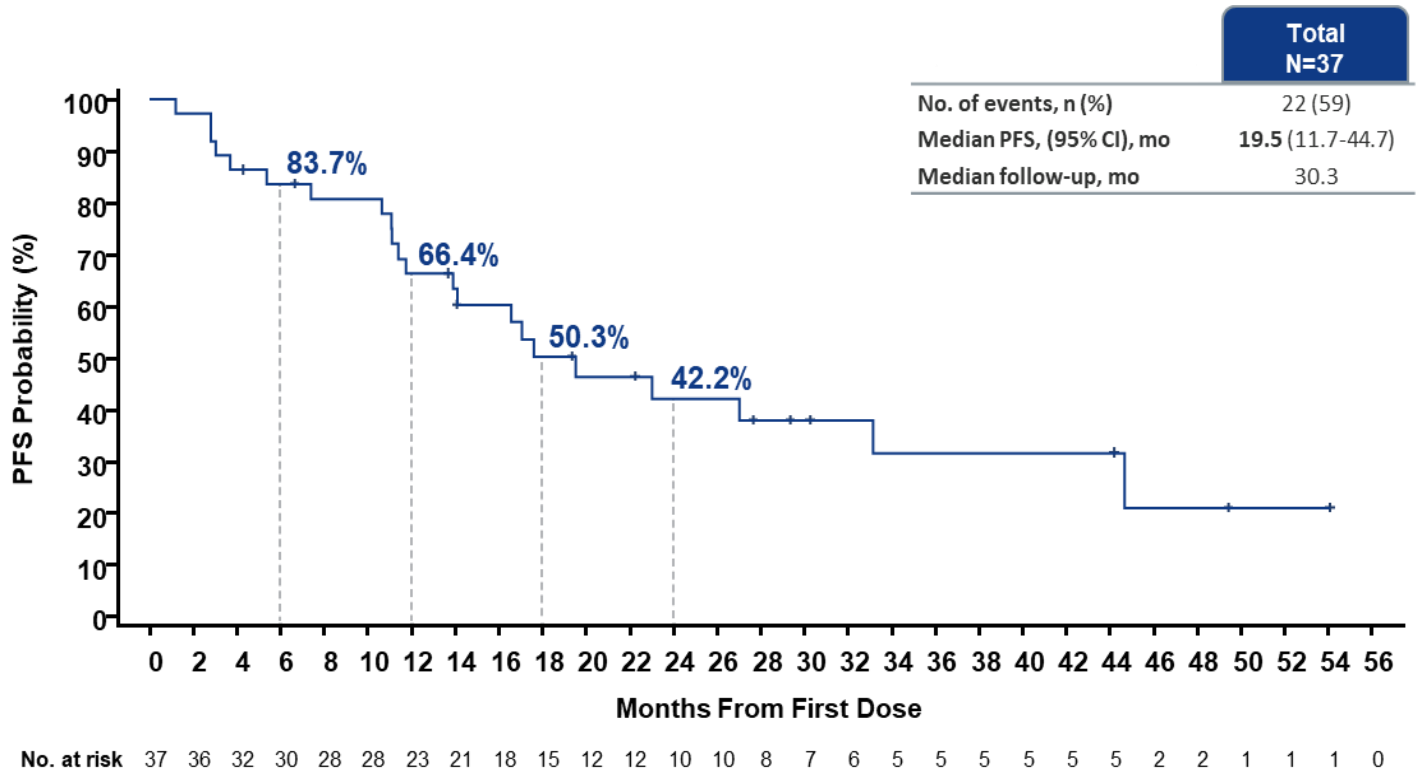
	Pirtobrutinib n = 119	IdelaR/BR n = 119
Number of Events, *n* (%)	**74** (62)	**79** (66)
Median PFS, mo (95% CI)	**14.0** (11.2–16.6)	**8.7** (8.1–10.4)
Median follow-up, mo	**19.4**	**17.7**
HR (95% CI)	**0.54** (0.39–0.75)	
Stratified log-rank 1-sided *P* value	0.0002**	

Study met the primary endpoint at earlier data cutoff (August 2023)
IRC HR = 0.58 (95% CI 0.38-0.89); *P* = 0.01

Adverse Events of Interest (AEI)	Pirtobrutinib (n=116) Any Grade n (%)	Grade 3+ n (%)
Bleeding	25 (21.6)	4 (3.4)
Bruising	9 (7.8)	1 (0.9)
Petechiae and purpura	6 (5.2)	1 (0.9)
Hemorrhage	18 (15.5)	3 (2.6)
Anemia	24 (20.7)	13 (11.2)
Neutropenia	31 (26.7)	24 (20.7)
Thrombocytopenia	11 (9.5)	9 (7.8)
Infection	74 (63.8)	34 (29.3)
Infection without COVID-19	67 (57.8)	30 (25.9)
Atrial fibrillation and atrial flutter	3 (2.6)	2 (1.7)
Hypertension	8 (6.9)	3 (2.6)

**nominal *P*-value.
BR = bendamustine + rituximab; IdelaR = idelalisib + rituximab; IRC = independent review committee.
Sharman JP, et al. *J Clin Oncol.* 2025;43(22):2538-2549.

Sequencing 1L cBTKi->2L Pirto: Pooled BRUIN 321 and Phase 1/2



[a]Response as assessed by investigator based on iwCLL 2018 criteria.
CI, confidence interval; mo, month; PFS, progression-free survival.

- For the 37 patients receiving who
  - 21 progressed on 1L cBTKi-> 2L pirto mPFS was 13 months
  - 13 had Intolerance on 1L cBTKi->2L pirto mPFS 44 months

Eyre T, et al. Presented at: ASH 2025; December 6-9, 2025; Orlando, FL. 5670.

BRUIN-CLL-322: Phase 3 Trial of Pirto + Ven + Rituximab (PVR) vs VR in RR CLL

Patient population

- Confirmed CLL/SLL requiring treatment (iwCLL 2018)
- Age ≥18 years
- R/R disease, ≥1 prior line (may include cBTKi)
- Known del(17p) status (FISH)
- ECOG PS ≤2
- No prior noncovalent BTKi or venetoclax/BCL2i

Participants stratified by

- Del(17p) status (negative vs positive)
- Prior cBTKi exposure
  - Discontinuation due to PD vs
  - Discontinuation due to other reasons vs
  - No prior cBTKI exposure[a]

N = 600 estimated

R 1:1

Pirtobrutinib + Venetoclax + Rituximab (PVR)

Pirtobrutinib, 200 mg QD (C1–C28)
Venetoclax, 400 mg QD (C5–C28, with C4/C5 weekly ramp up from 20 mg to 400 mg)
Rituximab, 375 mg/m^2 IV (C1D1), 500 mg/m^2 IV (C2–C6, D1)
Fixed duration, 28 cycles

No crossover permitted

Venetoclax + Rituximab (VR)

Venetoclax 400 mg QD (C2–C25, with C1 weekly ramp-up from 20 mg to 400 mg)
Rituximab 375 mg/m^2 IV (C2D1), 500 mg/m^2 IV (C2–C7, D1)
Fixed duration, 25 cycles

Primary Endpoint

- PFS assessed by IRC

Key Secondary Endpoints

- OS
  PFS assessed by INV
- TTNT
- ORR assessed by IRC
- Safety

Exploratory Endpoint

- MRD (peripheral blood, clonoSEQ®)

[a]cBTKi-naïve enrollment capped at ~20% of total enrollment. *This regimen is not yet FDA-approved. Data cutoff: February 2, 2026.
ECOG PS = Eastern Cooperative Oncology Group Performance Status; INV = investigator; PD = progressive disease.
Davids M, et al. Presented at: EHA 2026; June 14, 2026; Stockholm, SE. LB5001. NCT04965493.

BRUIN-CLL-322 Trial: Participant Characteristics

Characteristics	PVR n = 321	VR n = 318
Median age, years (range)	68 (32,85)	67 (37,87)
Male, n (%)	216 (67.3)	223 (70.1)
Region, n (%)		
Europe	149 (46.4)	141 (44.3)
North America	104 (32.4)	110 (34.6)
Asia	55 (17.1)	50 (15.7)
Australia/New Zealand	8 (2.5)	9 (2.8)
Middle East	5 (1.6)	8 (2.5)
ECOG PS, n (%)		
0–1	300 (93.5)	301 (94.7)
2	20 (6.2)	16 (5.0)
RAI stage, n (%)		
0–II	188 (64.2)	180 (61.4)
III–IV	105 (35.8)	113 (38.6)
Median duration of disease, yrs, (range)	8.6 (0.4, 33.7)	8.4 (0.2, 27.9)
Bulky disease, n (%)	116 (36.1)	107 (33.6)
High-risk features n (%)		
IGHV unmutated	203 (63.2)	225 (70.8)
Complex karyotype (≥3 abnormalities)	84 (26.2)	117 (36.8)
Del(17p)	66 (20.6)	71 (22.3)
TP53 mutation	106 (33.0)	112 (35.2)
TP53 mutation and/or *Del(17p)*, n (%)	126 (39.3)	132 (41.5)

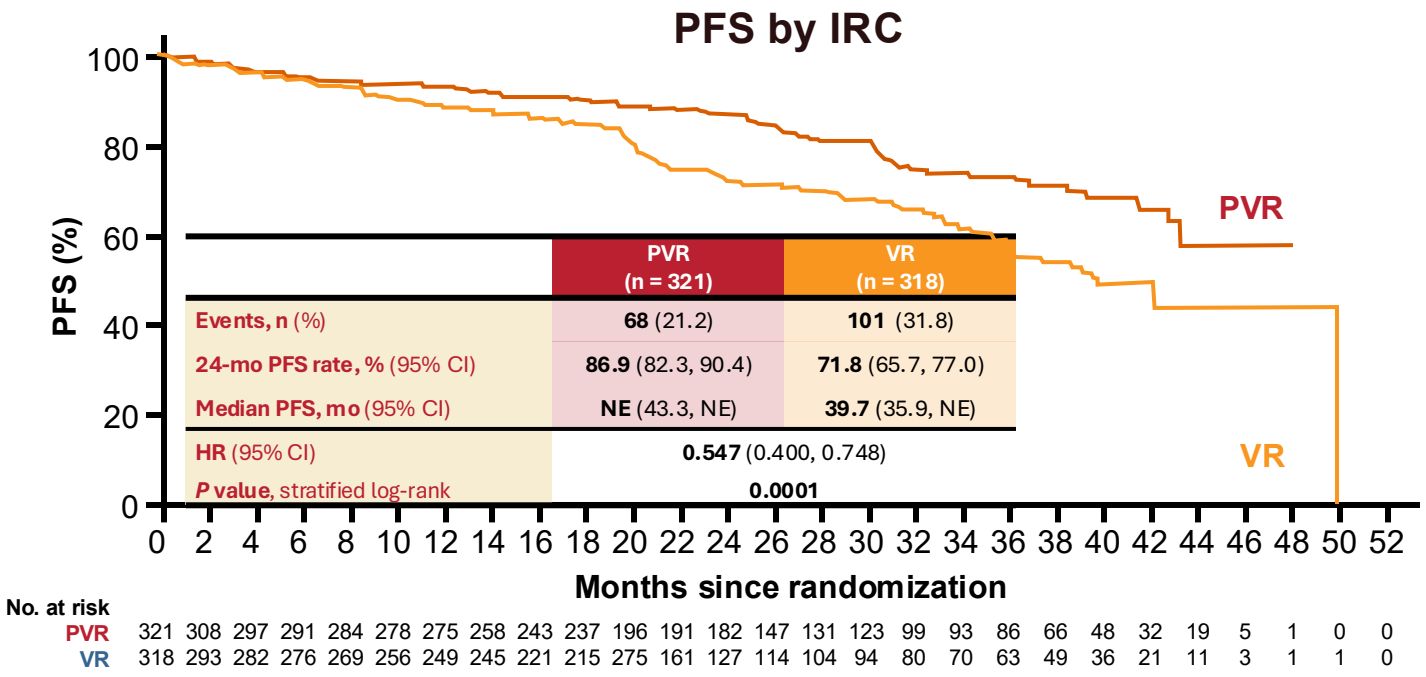
Characteristics	PVR n = 321	VR n = 318
Median lines of prior systemic therapy, n (range)	2 (1, 7)	3 (1, 9)
Prior lines of systemic therapy, n (%)		
1	135 (42.1)	143 (45.0)
2	90 (28.0)	88 (27.7)
≥3	96 (29.9)	87 (27.4)
Prior therapy, n (%)		
cBTKi	256 (79.8)	254 (79.9)
Ibrutinib	168 (65.6)	175 (68.9)
Acalabrutinib	64 (25.0)	57 (22.4)
Zanubrutinib	38 (14.8)	39 (15.4)
Other	23 (9.0)	20 (7.9)
Anti-CD20 antibody	219 (68.2)	210 (66.0)
Chemotherapy	213 (66.4)	208 (65.4)
Other	75 (23.4)	76 (23.9)
Prior cBTKi experience, n (%)		
Discontinued due to PD	181 (56.4)	181 (56.9)
Discontinued due to intolerance	44 (13.7)	35 (11.0)
Discontinued due to other reasons	31 (9.7)	38 (11.9)
No prior cBTKi	65 (20.2)	65 (20.1)

Baseline characteristics represented a contemporary R/R CLL population.
~80% of patients had received a prior cBTKi

CAR = chimeric antigen receptor; VR = venetoclax + rituximab.
Davids M, et al. Presented at: EHA 2026; June 14, 2026; Stockholm, SE. LB5001.

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BRUIN-CLL-322: PFS by IRC: ITT Population



16 events of Richter Transformation occurred in the VR arm vs 8 events in the PVR arm.

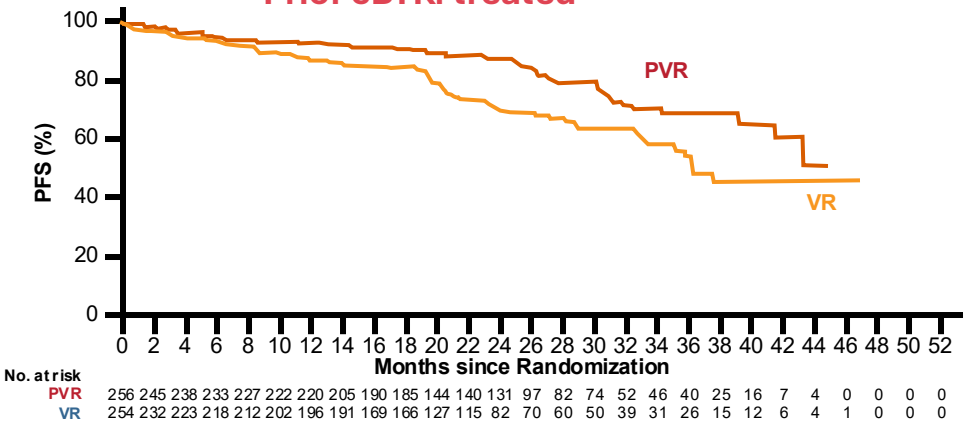
MRD4 rates in ~50% of enrolled and evaluable patients were higher in PVR 86.3% vs 60.7%

- PFS assessments were consistent between investigators and IRCs
- All prespecified subgroups experienced PFS benefits
  - *Including those with high-risk features*
- PFS benefit with PVR was mostly consistent across subgroups with prior cBTKi exposure
  - *Including in those with PD after prior cBTKi exposure*

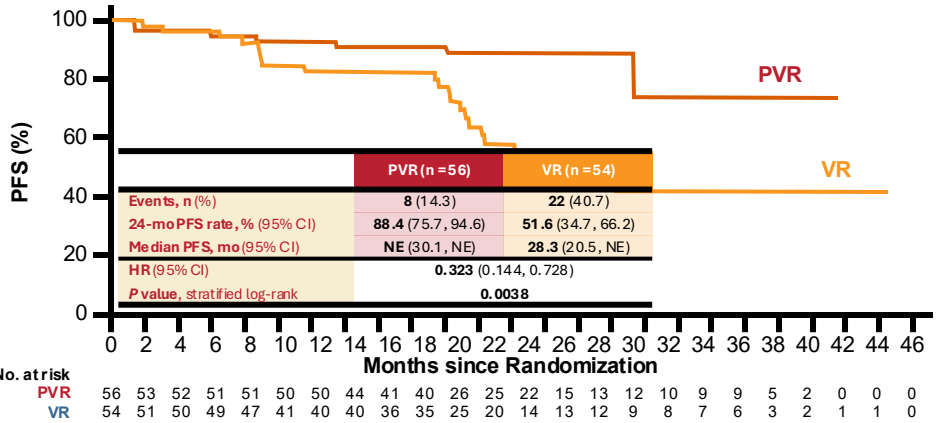
ITT = intent-to-treat.
Davids M, et al. Presented at: EHA 2026; June 14, 2026; Stockholm, SE. LB5001.

BRUIN-CLL-322: PFS by IRC (Prior cBTKi Subgroups)

Prior cBTKi treated

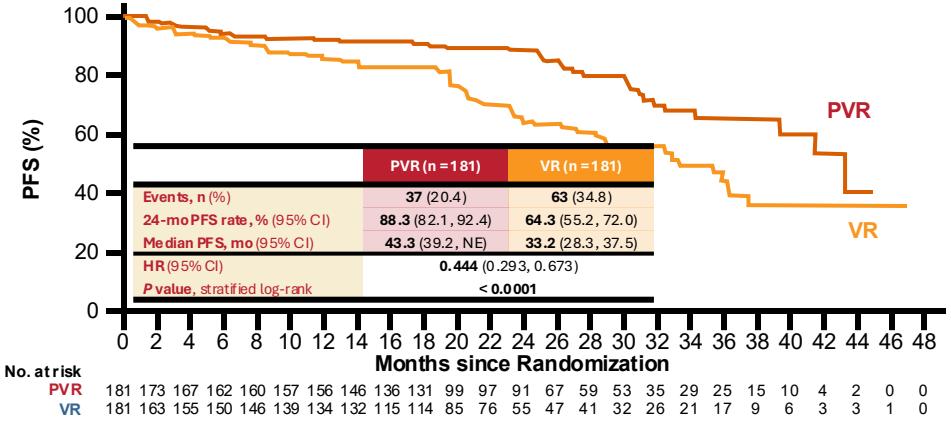


One prior line (cBTKi) and discontinued due to PD



	PVR (n = 256)	VR (n = 254)
Events, n (%)	**48** (18.8)	**74** (29.1)
24-mo PFS rate, % (95% CI)	**87.7** (82.4, 91.4)	**70.0** (62.7, 76.1)
Median PFS, mo (95% CI)	**NE** (41.5, NE)	**36.2** (33.2, NE)
HR (95% CI)	**0.509** (0.351, 0.738)	
P value, stratified log-rank	**0.0003**	

Prior cBTKi discontinued due to PD

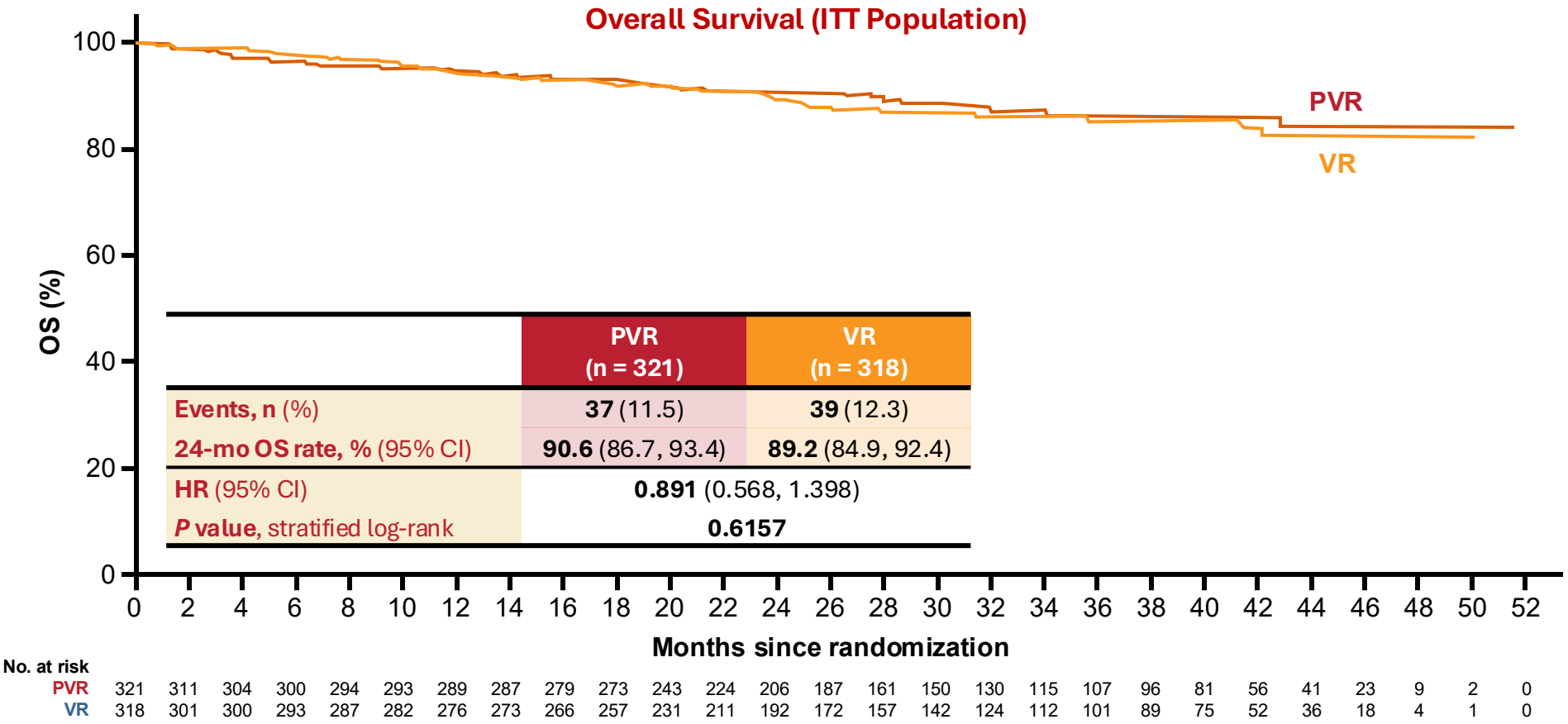


PVR improved PFS over VR in patients previously treated with a cBTKi, including those who progressed on prior cBTKi, and particularly those with cBTKi as their only prior therapy.

[a]Stratified by Del(17p) presence and is reported as a nominal value.

Davids M, et al. Presented at: EHA 2026; June 14, 2026; Stockholm, SE. LB5001.

BRUIN-CLL-322: Overall Survival



	PVR (n = 321)	VR (n = 318)
Events, n (%)	**37** (11.5)	**39** (12.3)
24-mo OS rate, % (95% CI)	**90.6** (86.7, 93.4)	**89.2** (84.9, 92.4)
HR (95% CI)	**0.891** (0.568, 1.398)	
***P* value**, stratified log-rank	**0.6157**	

At a median follow-up of 30.6 months, OS interim data were immature

Median OS was not estimable in both arms. [a]Stratified by prior experience of BTK inhibitor, Del17p presence.

Davids M, et al. Presented at: EHA 2026; June 14, 2026; Stockholm, SE. LB5001.

BRUIN CLL-322: AEs of Interest: Safety Population

Adverse Event, n (%)	PVR n = 316		VR n = 311	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infections	249 (78.8)	107 (33.9)	224 (72.0)	72 (23.2)
COVID-19	98 (31.0)	17 (5.4)	80 (25.7)	12 (3.9)
Upper respiratory infection	69 (21.8)	5 (1.6)	64 (20.6)	6 (1.9)
Pneumonia	56 (17.7)	35 (11.1)	46 (14.8)	23 (7.4)
Neutropenia	194 (61.4)	159 (50.3)	168 (54.0)	136 (43.7)
Febrile neutropenia	8 (2.5)	7 (2.2)	11 (3.5)	11 (3.5)
Thrombocytopenia	84 (26.6)	31 (9.8)	84 (27.0)	34 (10.9)
Bleeding	82 (25.9)	9 (2.8)	44 (14.1)	8 (2.6)
Hemorrhage	45 (14.2)	9 (2.8)	33 (10.6)	8 (2.6)
Bruising	40 (12.7)	0	16 (5.1)	0
Petechiae and purpura	12 (3.8)	0	1 (0.3)	0
Atrial fibrillation/flutter	11 (3.5)	6 (1.9)	8 (2.6)	3 (1.0)
Hypertension	38 (12.0)	16 (5.1)	23 (7.4)	9 (2.9)
Tumor lysis syndrome	4 (1.3)	3 (0.9)	13 (4.2)	12 (3.9)

PVR preserved pirtobrutinib's **favorable cardiovascular profile**, with low rates of AF/flutter, hemorrhage, and hypertension. This is consistent with prior pirtobrutinib monotherapy data, and with **reduction of tumor lysis syndrome risk** prior to venetoclax ramp-up.

Davids M, et al. Presented at: EHA 2026; June 14, 2026; Stockholm, SE. LB5001.

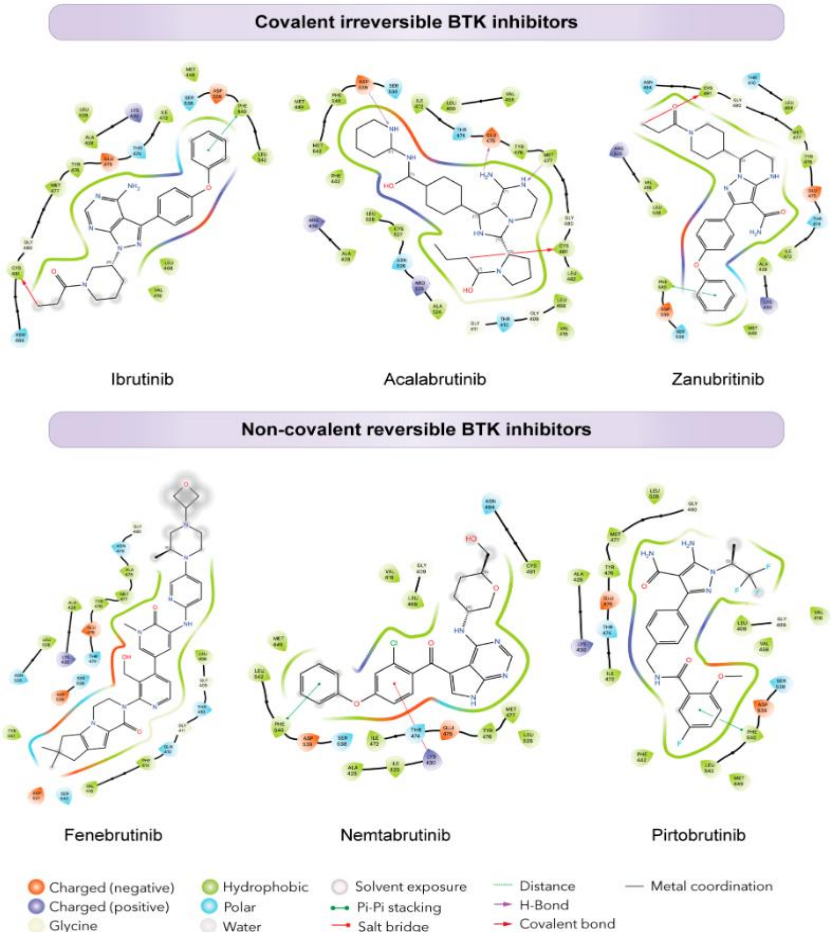
Key Learning Points

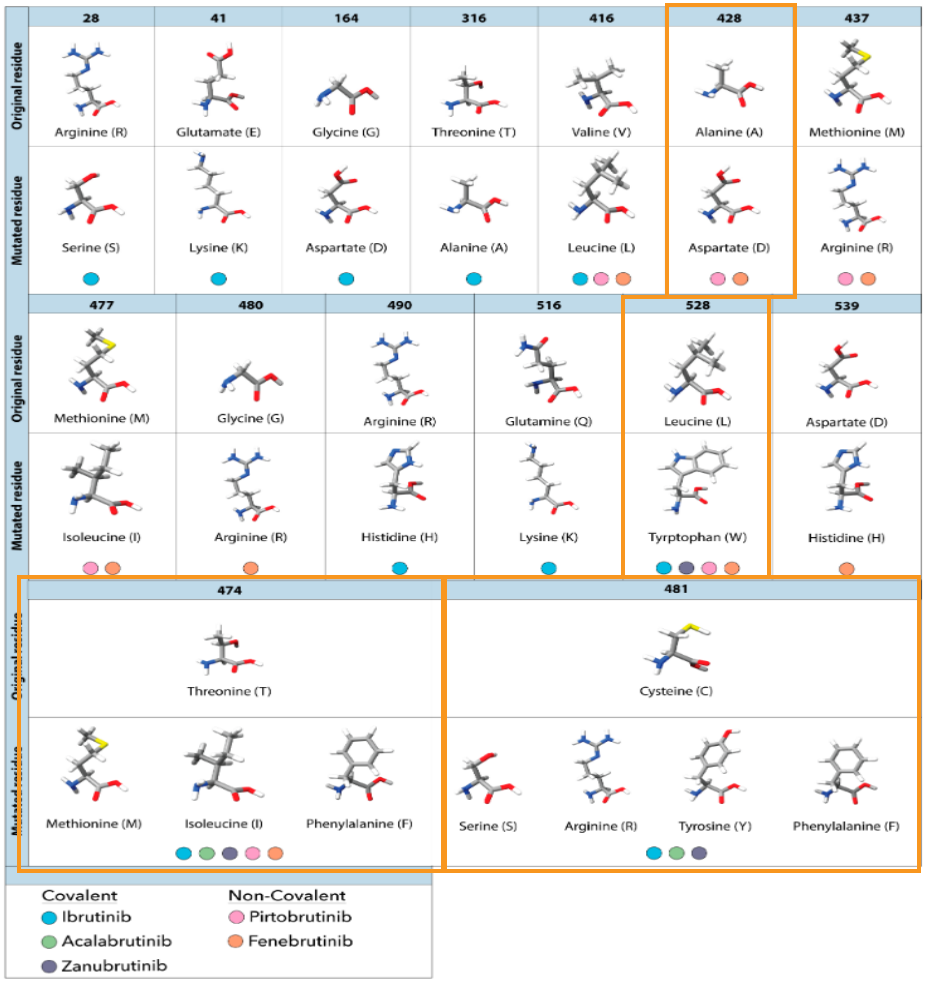
- After a FD approach, retreatment is feasible and early data suggests deep, durable disease control
  - Think about your patient's journey, if not progressing on therapy, no class of drug has yet failed and reevaluation regarding fitness, molecular characteristics and preference is important
- After PD/failure on cBTKi, two options remain available
  - ncBTKi vs venetoclax/antiCD20 (no h2h data but…)
  - Data (BRUIN-321) suggests PVR provides deeper and more durable remissions with acceptable safety over VR and thus may be a new standard in the near future
    - Most relevant PVR appears to improve outcomes even in those 1L cBTKi treated patients with PD over VR

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Addressing Resistance

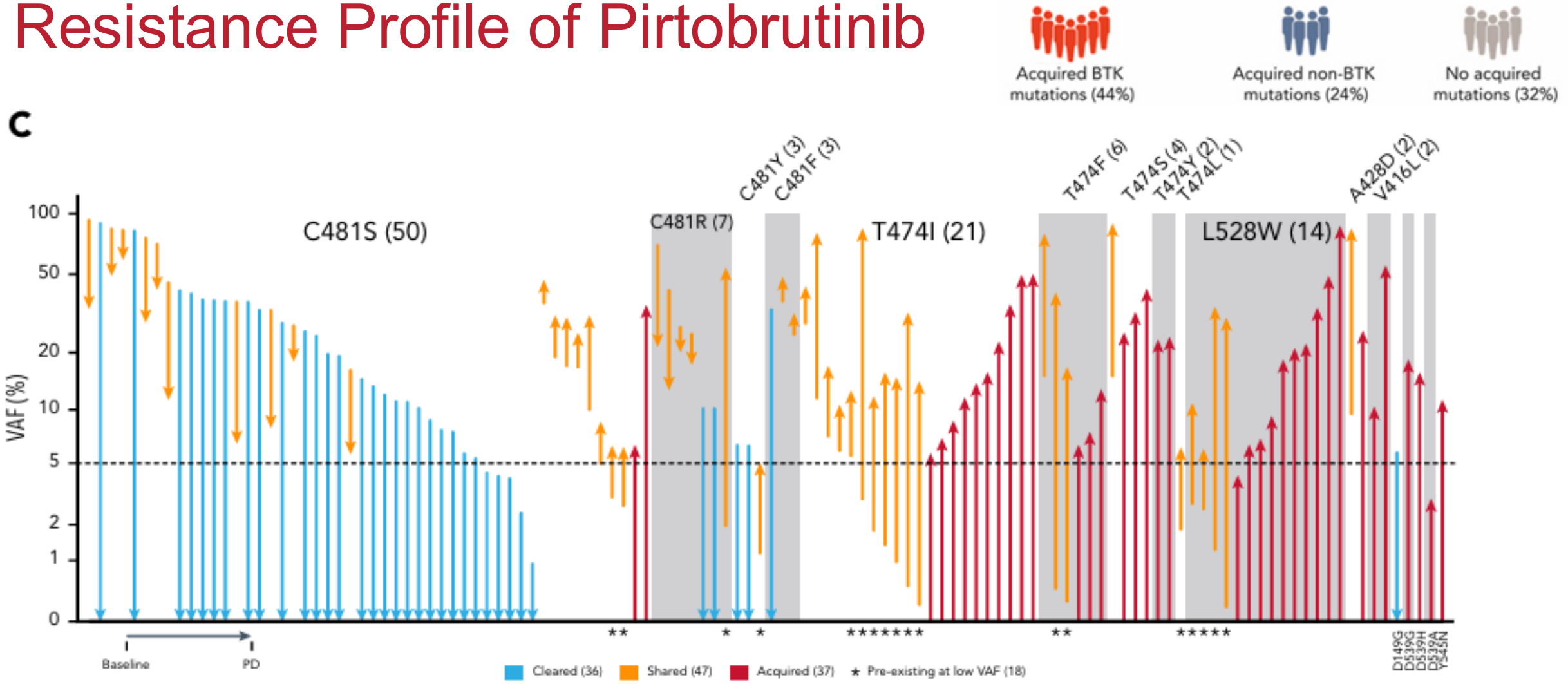
Structurally Unique BTKi Have Led to Observation of Many BTK Mutations Outside of C481





Chirino A, et al. *Genes (Basel).* 2023;14(12):2182.

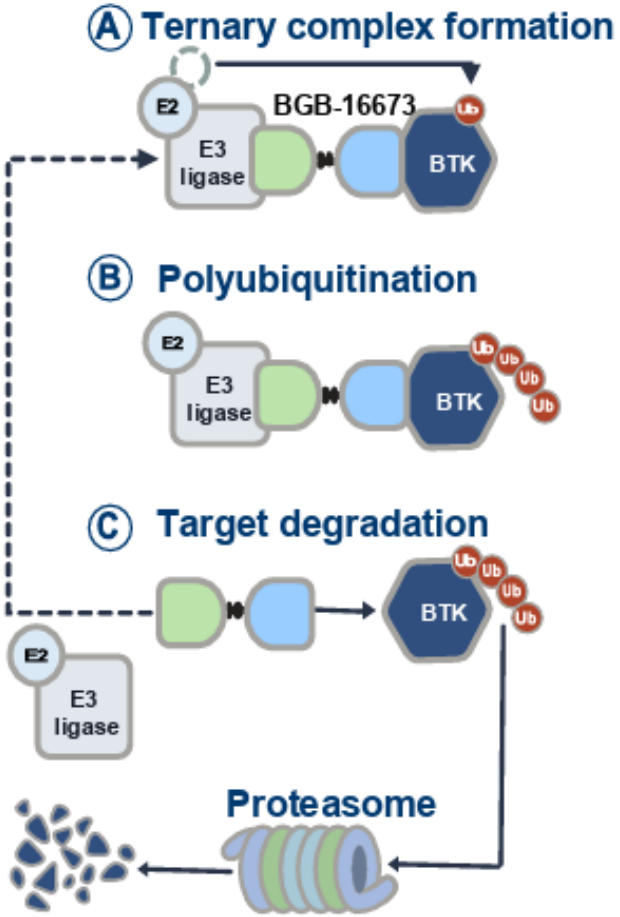
Resistance Profile of Pirtobrutinib



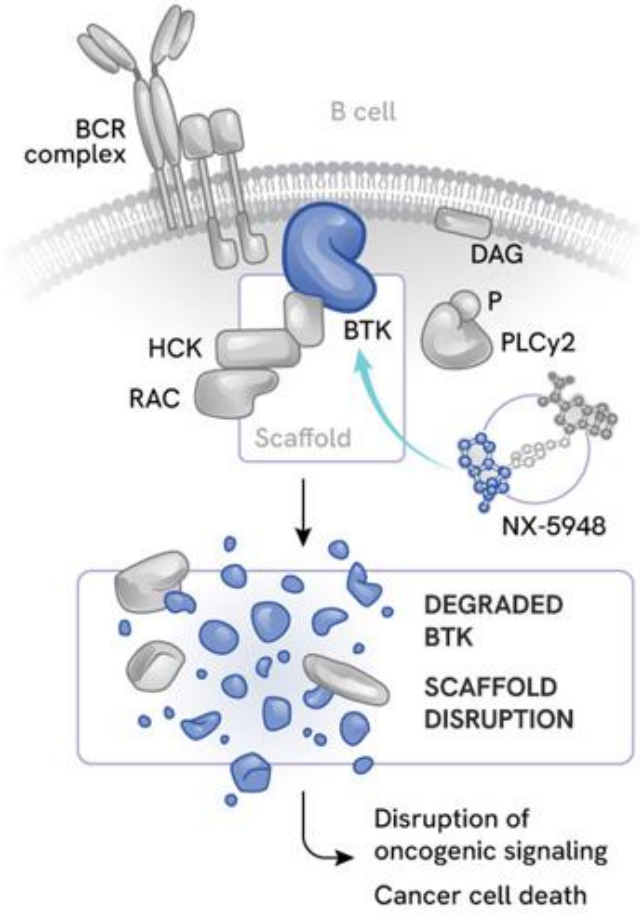
Brown J, et al. *Blood*. 2026;147(1):24-34.

BTK Degradation in Order to Overcome Resistance

Tacabrutideg (BGB16673)



Bexobrutideg (NX5948)



Stilgenbauer S, et al. Presented at: EHA 2026; June 12, 2026; Stockholm, SE. S152. Munir T, et al. Presented at: EHA 2026; June 12, 2026; Stockholm, SE. PS1718.

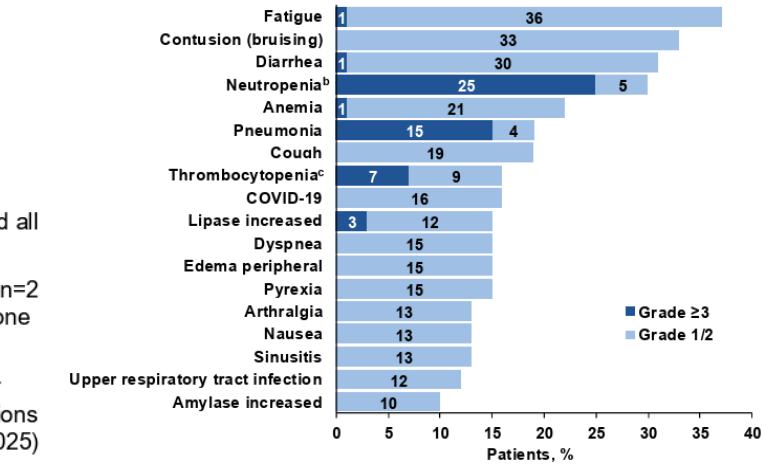
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BTK Degradation Demonstrates Safety in R/R CLL...

CADENCE-101 (Tacabrutideg)

No. of prior lines of therapy, median (range)	4 (2-10)

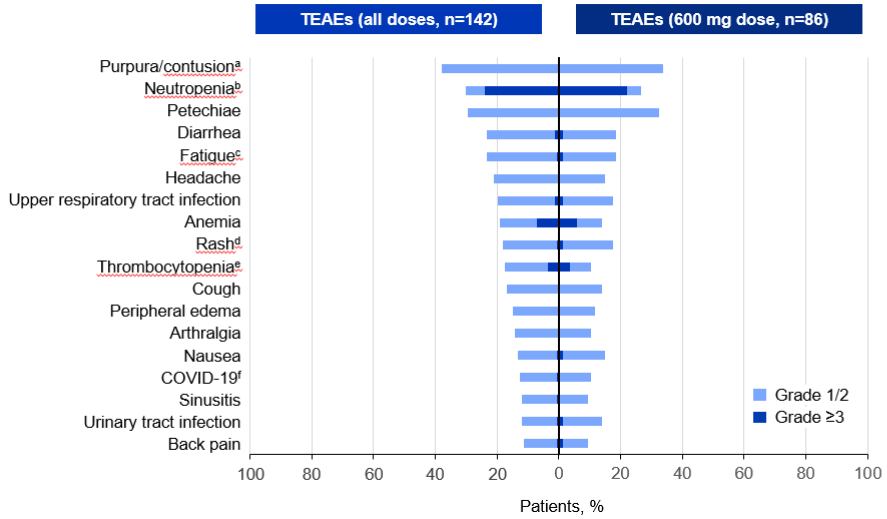
- Grade ≥3 neutropenia: n=17 (25.4%); 15 patients (22.4%) had grade ≥2 neutropenia at baseline
  - Febrile neutropenia: n=1
- Grade ≥3 infection: n=24 (35.8%)
- Atrial fibrillation: n=3 (grade 1 and 2); all transient (2 of them lasting 1 day and all in the context of infection and PD)
- Treatment-related major hemorrhage[a]: n=2 (one grade 3 subdural hematoma and one grade 3 post-procedural hematuria)
- No new cases of atrial fibrillation, major hemorrhage, and invasive fungal infections since the last data cutoff (August 22, 2025)



Leading to dose reduction	9 (13.4)
Treatment-related	5 (7.5)
Leading to treatment discontinuation	12 (17.9)
Treatment-related	4 (6.0)
Leading to death	5 (7.5)
Treatment-related	0

Ph1a/b (Bexobrutideg)

Median prior lines of therapy, n (range)	4.0 (2–12)



- Tolerable safety profile consistent with prior disclosures
- No dose-limiting toxicities
- Three Grade 5 AE, all deemed not related (pneumonia, pulmonary embolism, NOS)

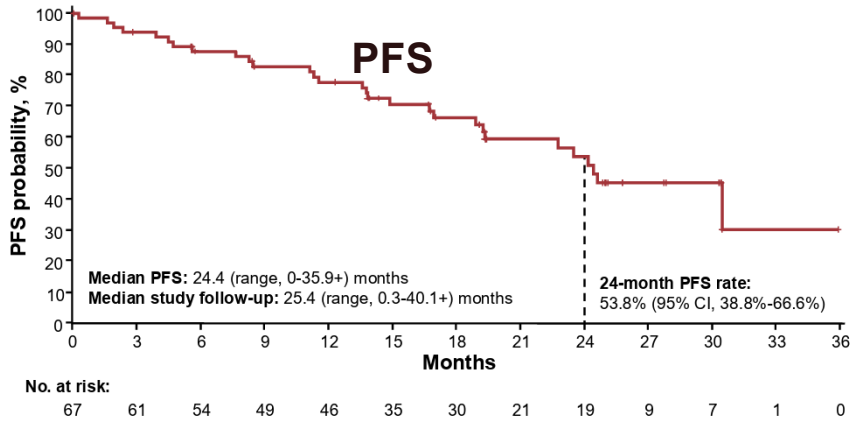
Leading to treatment discontinuation	8 (5.6)	5 (5.8)	3 (5.4)
Treatment related	6 (4.2)	3 (3.5)	3 (5.4)
DLT	0	0	0
Median exposure time, months (range)	7.3 (0.03–35.8)	5.1 (0.03–21.5)	12.5 (0.2–35.8)

Stilgenbauer S, et al. Presented at: EHA 2026; June 12, 2026; Stockholm, SE. S152. Munir T, et al. Presented at: EHA 2026; June 12, 2026; Stockholm, SE. PS1718.

...and Efficacy in RR/CLL

CADENCE-101 (Tacabrutideg)

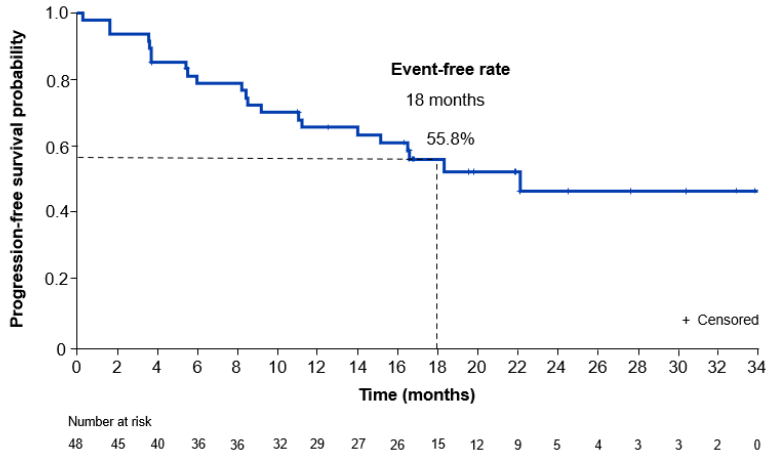
Characteristic, n/N with known status (%)	ORR[a]
Prior cBTKi + BCL2i (no ncBTKi)	40/43 (93.0)
Prior cBTKi + ncBTKi + BCL2i	9/12 (75.0)
Refractory to last cBTKi + last BCL2i	31/37 (83.8)
5 or more prior lines of therapy	25/29 (86.2)
del(17p) and/or *TP53* mutation	35/44 (79.5)
Unmutated IGHV	38/43 (88.4)
Complex karyotype (≥3 abnormalities)	17/23 (73.9)
BTK mutation	19/25 (76.0)
PLCG2 mutation	9/10 (90.0)



24 m OS ~75%

Ph1a/b (Bexobrutideg)

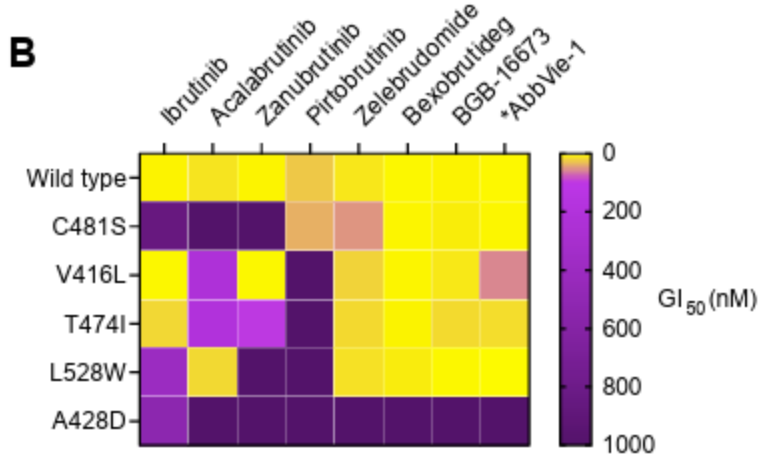
ORR summary	
	n=47[b]
ORR, % (95% CI)[c]	**83.0** (69.2–92.4)
CR	2 (4.3)
nPR	1 (2.1)
PR	36 (76.6)
SD	6 (12.8)
PD	2 (4.3)
Median follow-up,[d] months (range)	22.4 (16.9–35.7)



Stilgenbauer S, et al. Presented at: EHA 2026; June 12, 2026; Stockholm, SE. S152. Munir T, et al. Presented at: EHA 2026; June 12, 2026; Stockholm, SE. PS1718.

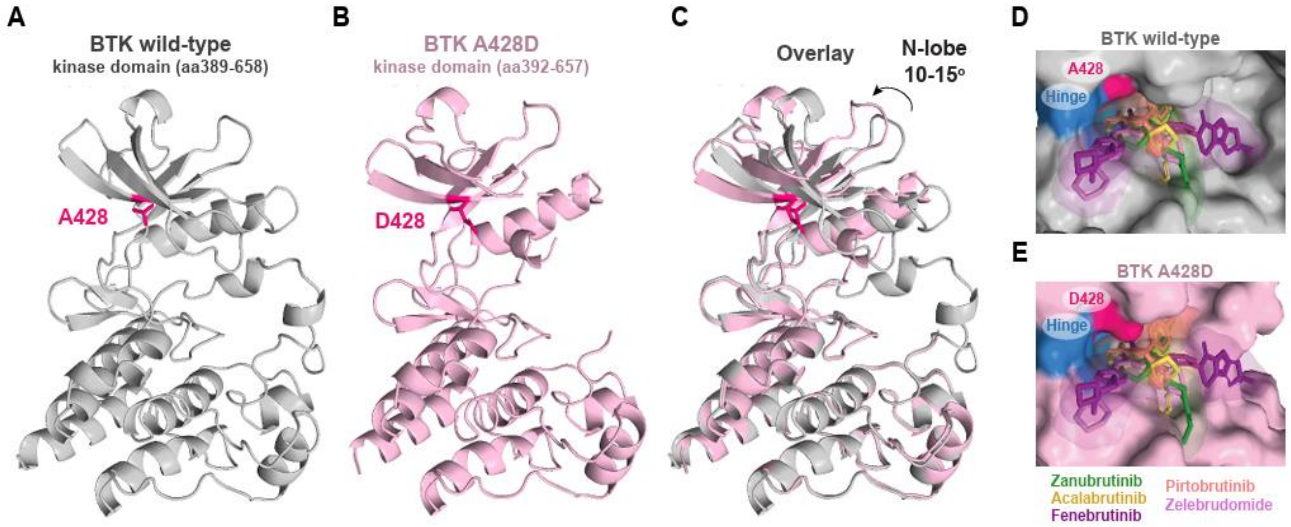
Resistance Is Now Being Defined for Degraders through BTK A428D Mutations

Growth Inhibition Concentrations



A428D confers growth disadvantage and thus why we see it rarely

Crystral Structure Demonstrating Steric Hinderance of BTKi Via the Hinge Moiety within Kinase Pocket

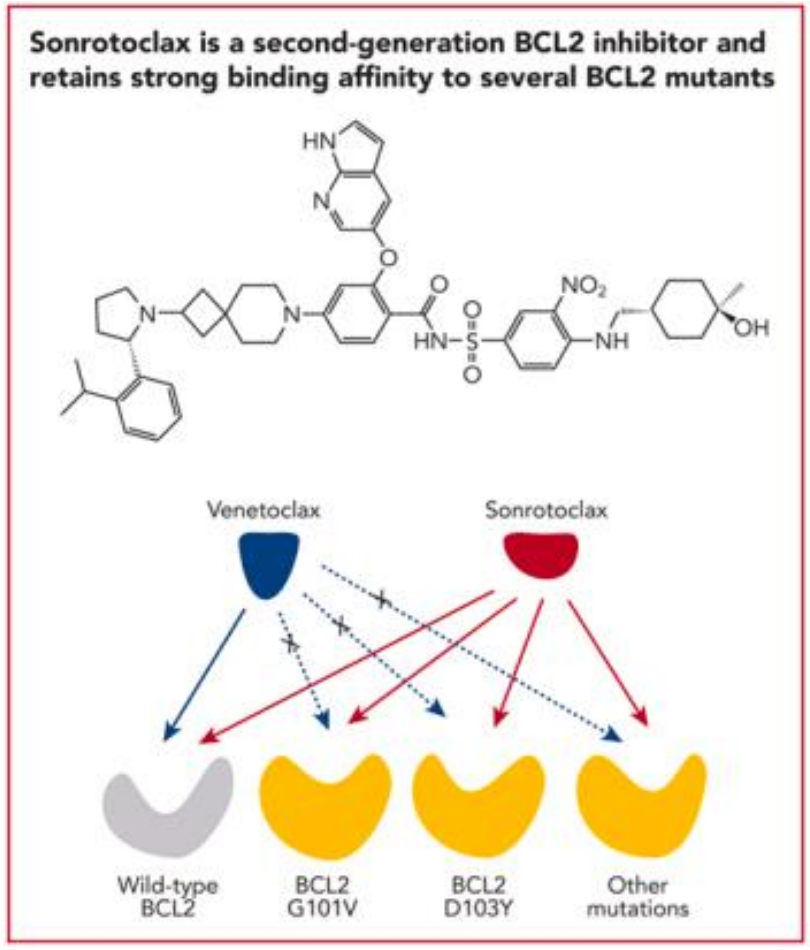


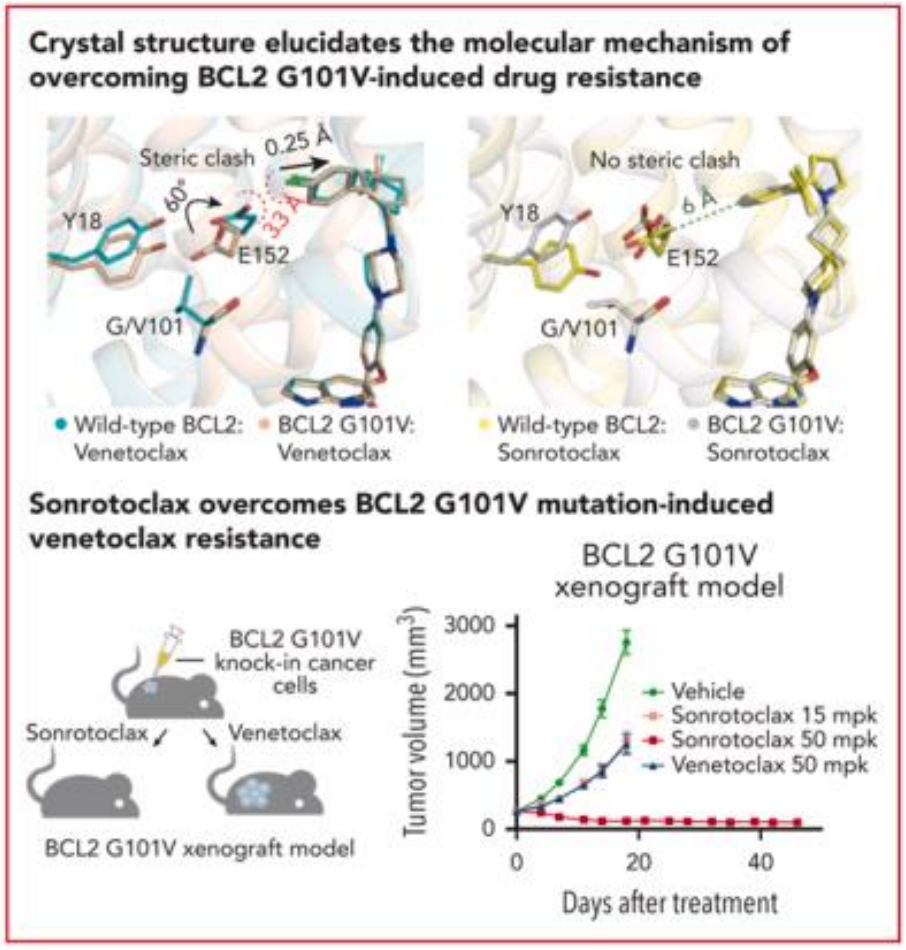
Drug class	Compound	Full length, K_D (nM)	
		BTK WT	BTK A428D
Covalent	Ibrutinib	Binding	No binding
	Acalabrutinib	Binding	No binding
	Zanubrutinib	Binding	No binding
Noncovalent	Pirtobrutinib	1.3 ± 0.2	No binding
	Nemtabrutinib	1.1 ± 0.7	No binding
Degrader	*AbbVie-1	1.1 ± 0.2	No binding
	BGB-16673	0.69 ± 0.21	No binding
	Zelebrudomide	20 ± 2	No binding
	Bexobrutideg	3.2 ± 0.4	No binding

No BTKi or BTKdeg can bind to A428D

Sievers Q, et al. *Cancer Discov.* 2026. [Epub ahead of print.] PMID: 42484277.

Sonrotoclax Has Potential to Overcome Resistance to BCL2 Mutations Seen on Venetoclax

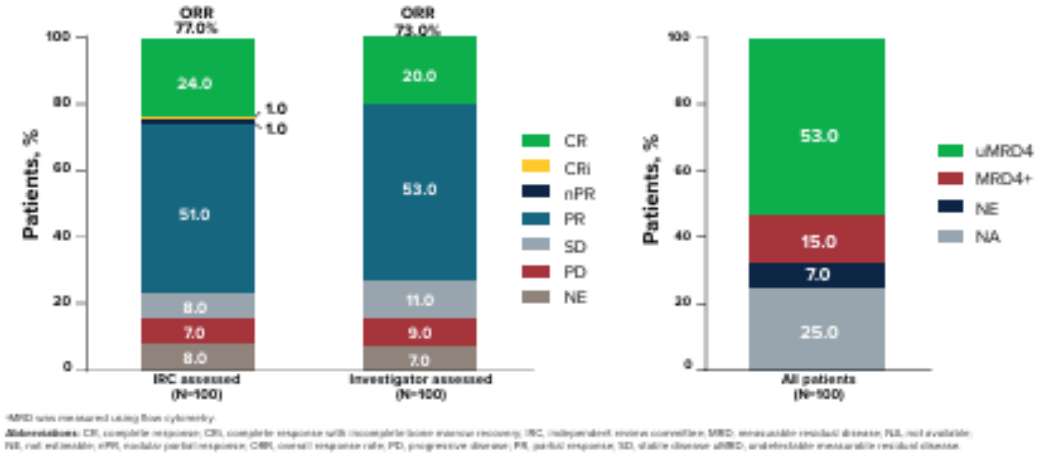


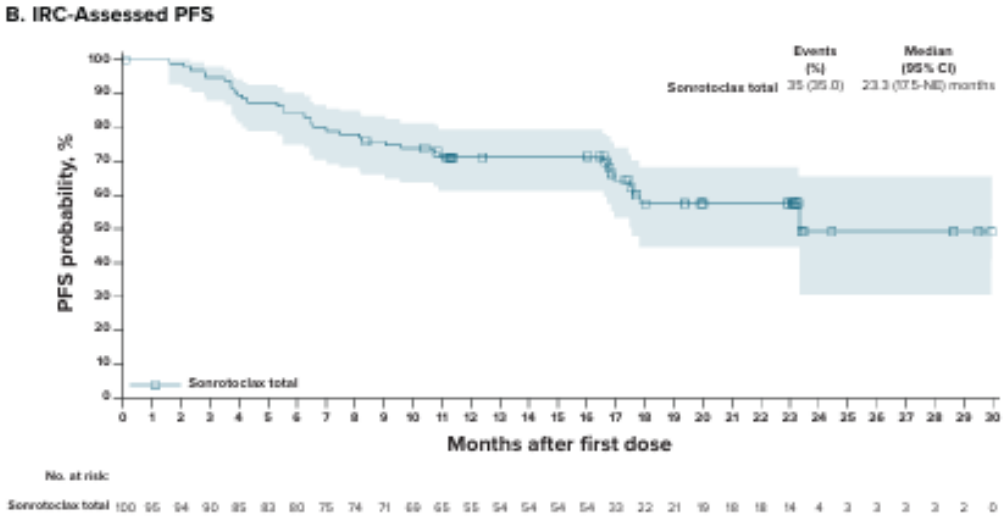


Liu J, et al. *Blood.* 2024;143(18):1825-1836.

Sonrotoclax Monotherapy in RR/CLL

Figure 2. IRC- and Investigator-Assessed Response Rates and Best Blood MRD[a] Rates in the Intent-To-Treat Population



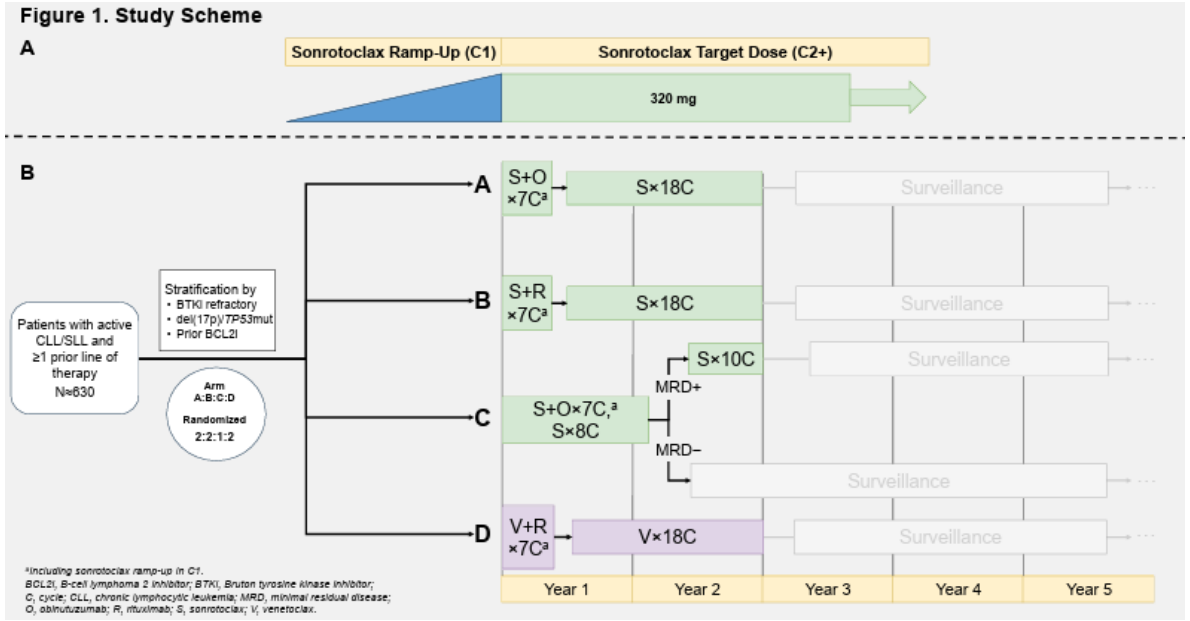


- 66.0% of patients experienced a grade ≥3 TEAE
- Neutrophil count decreased was the most common TEAE of any grade and grade ≥3, and was observed in 58.0% and 33.0% of patients, respectively
- No clinical tumor lysis syndrome (TLS) nor fatal TLS occurred
  - Laboratory TLS was reported in 4.0% of patients; all events of laboratory TLS were grade 3, manageable, and resolved without sequelae within a median of 3.5 days (range, 2-8 days)
- TEAEs led to death in 5 patients, none of which were related to treatment

Yi S, et al. *Blood*. 2025;146(suppl 1):5666.

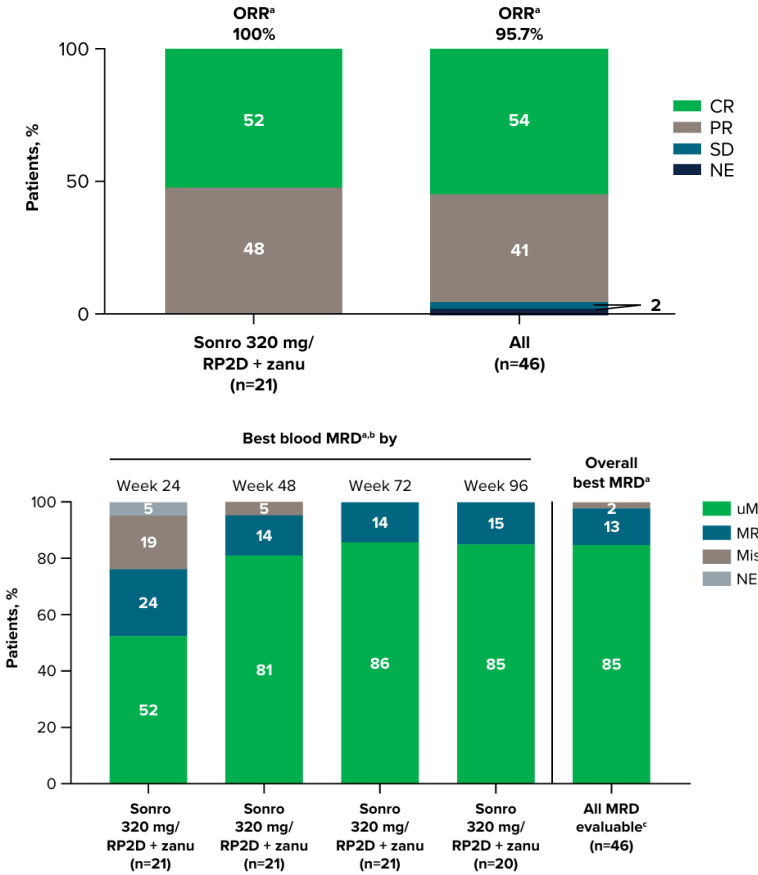
Ongoing Development in R/R CLL with Sonro Combinations

CELESTIAL-RRCLL (SO vs SR vs VR)



CaDAnCE 104 SS1 (Tacabrutideg + Sonro) in RRCLL and WM

Zanu and Sonro in Ph1 RRCLL



30-month PFS 94.7%

1. Al-Sawaf O, et al. Presented at: 67th ASH Annual Meeting & Exposition; 2025. 2. Opat S, et al. Presented at: EHA Congress; 2026.

Key Learning Points

- Sequencing is dependent on prior therapy, whether fixed duration or continuous treatment and whether there was progression or intolerance on drug vs progression early or late after treatment cessation
  - Retreatment with fixed duration strategies is emerging as a practical strategy with data supporting its use, thereby extending therapeutic opportunities over the patient's lifetime
- In general, seeking new mechanisms of action or novel combinations in true progressors or treatment failures are likely to improve long-term outcomes, achieve deeper remissions, and overcome resistance development
- Novel therapeutics and combinations are in development to address resistance with optimal sequencing remaining undetermined and are still dependent on a host of patient factors and molecular characteristics