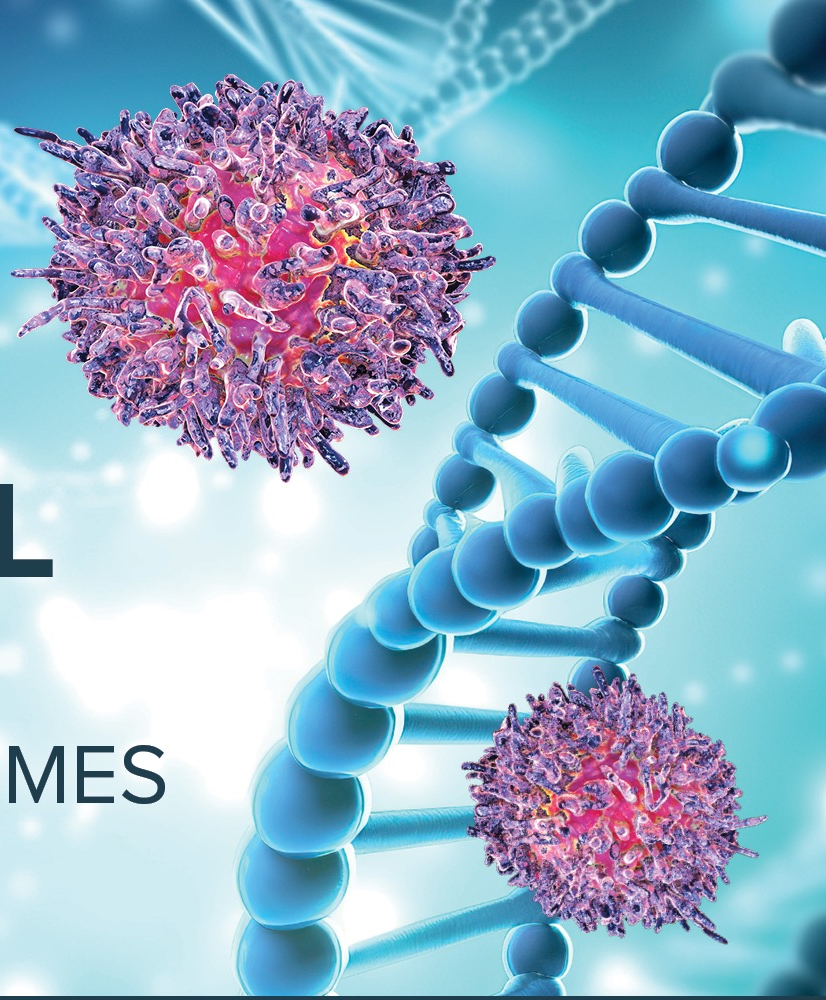
A Global Spotlight on CLL

SHIFTING STRATEGIES AND OPTIMIZING OUTCOMES



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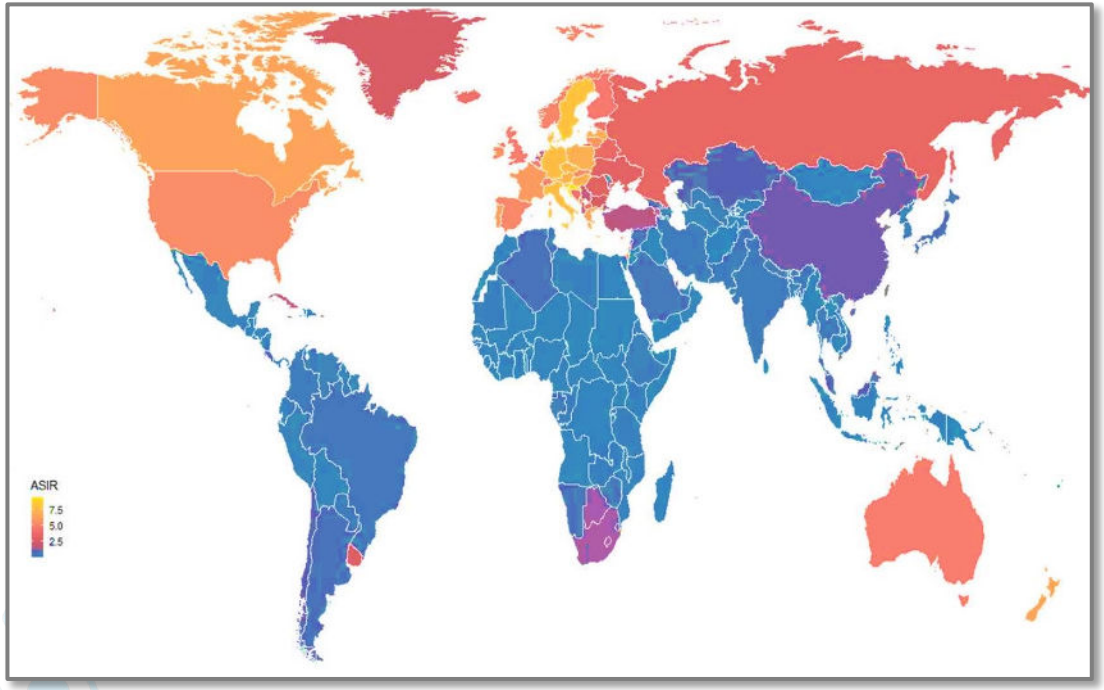
Learning Objectives

- Assess testing strategies that may inform clinical decision making in the management of chronic lymphocytic leukemia (CLL).
- Utilize updated guidelines and evidence supporting the integration of targeted agent classes in CLL as single agents or as part of combination regimens, including continuous therapy, fixed-duration options, and novel combinatorial regimens.
- Evaluate recent clinical evidence on current and emerging therapeutic approaches that have been evaluated for the treatment of patients with relapsed/refractory (R/R) CLL and/or therapeutic intolerance.

Global CLL Incidence Rate

Age-standardized Incidence Rate (ASIR)



1990–2019 Estimated Annual Percentage Changes in Age-standardized Rates	Incidence	Death
Overall	1.86 (1.79–1.92)	1.17 (1.07–1.27)
Male	1.78 (1.71–1.85)	1.13 (1.03–1.23)
Female	1.93 (1.86–1.99)	1.21 (1.12–1.31)
High SDI	1.11 (1.08–1.15)	0.53 (0.48–0.59)
High-middle SDI	3.13 (3.07–3.18)	1.70 (1.62–1.78)
Middle SDI	5.19 (5.07–5.32)	3.09 (2.95–3.24)
Low-middle SDI	2.84 (2.71–2.97)	2.20 (2.07–2.34)
Low SDI	1.27 (1.13–1.41)	0.92 (0.77–1.06)

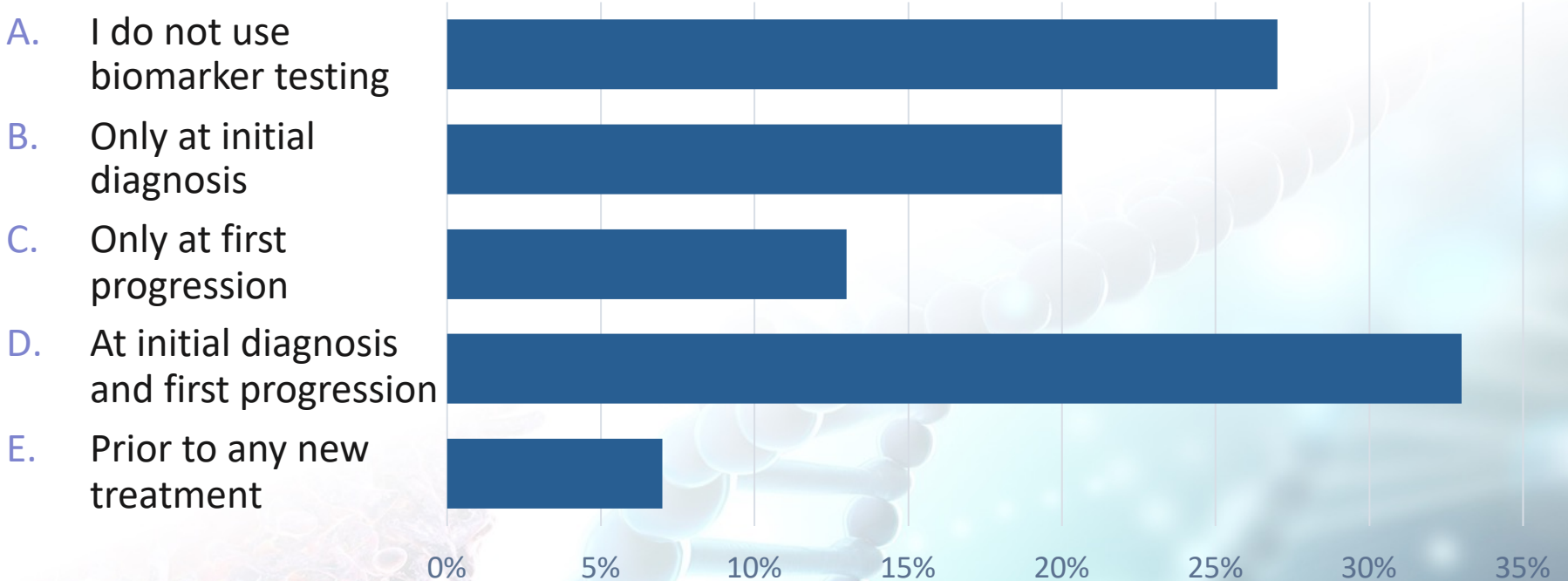
SDI, social-demographic index.

Yao Y, et al. *Biomed Eng Online*. 2022;21(1):4.

When do you use biomarker testing for patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)?

A. I do not use biomarker testing
B. Only at initial diagnosis
C. Only at first progression
D. At initial diagnosis and first progression
E. Prior to any new treatment

When do you use biomarker testing for patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)?



Biomarker Testing

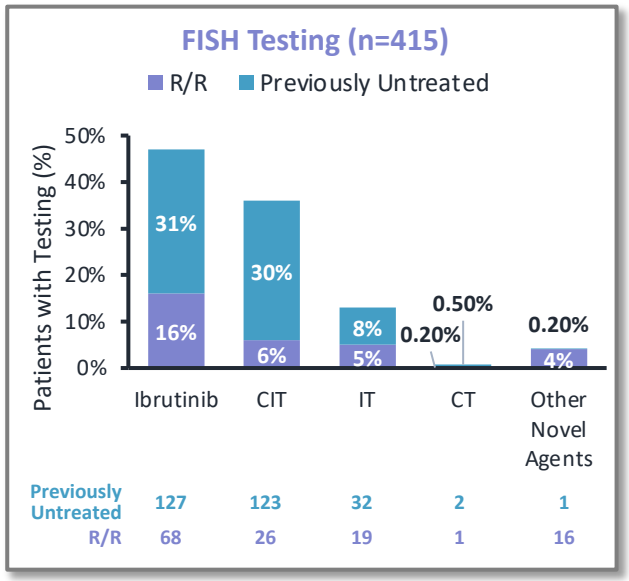
- Minimum testing should include fluorescence in situ hybridization (FISH), *TP53*, and immunoglobulin heavy chain variable region (IGHV) mutation
- Adverse prognostic factors
  - Deletions of chromosomes 17p or 11q—del(17p) or del(13q)
  - *TP53* gene mutation
  - Unmutated IGHV gene
  - High karyotype complexity
- Favorable prognostic factors
  - del(13q) with no other chromosome abnormalities found by FISH
  - Mutated IGHV gene
- Retest before each line of treatment
- Access to testing varies by location
  - Resource-limited settings pose greater challenges

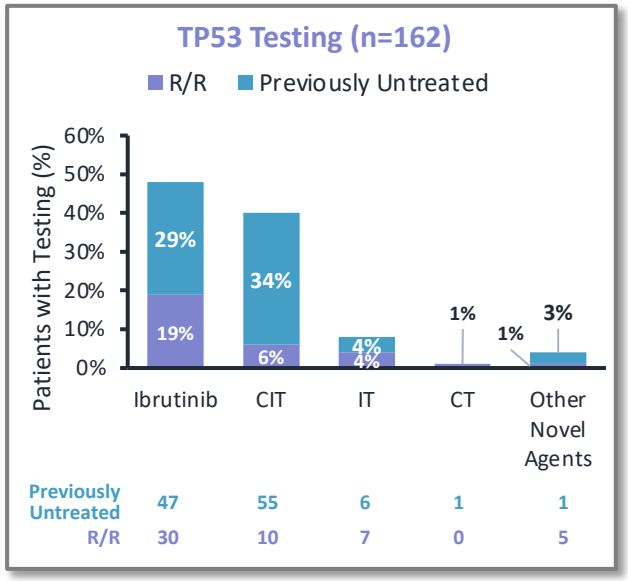
NCCN Guidelines. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. v3.2023.

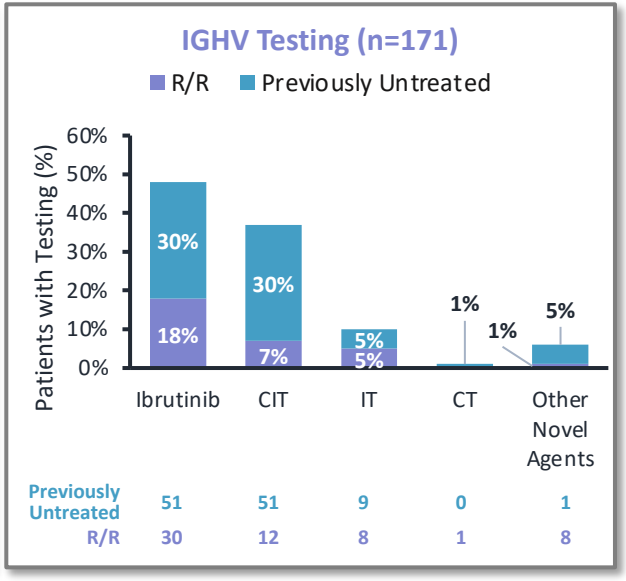
Inadequate Biomarker Testing

Biomarker Testing by Treatment (2015–2019, United States)

- More than **half** did **not** receive biomarker testing at all
- Of those who did receive biomarker testing, 99% had it performed prior to treatment
- Of treatment-naïve patients with del(17p), over a quarter received chemotherapy that was almost certainly of no value (but was still toxic) instead of newer and better treatment options, such as ibrutinib (Ibr), acalabrutinib (Acal), or venetoclax (Ven)







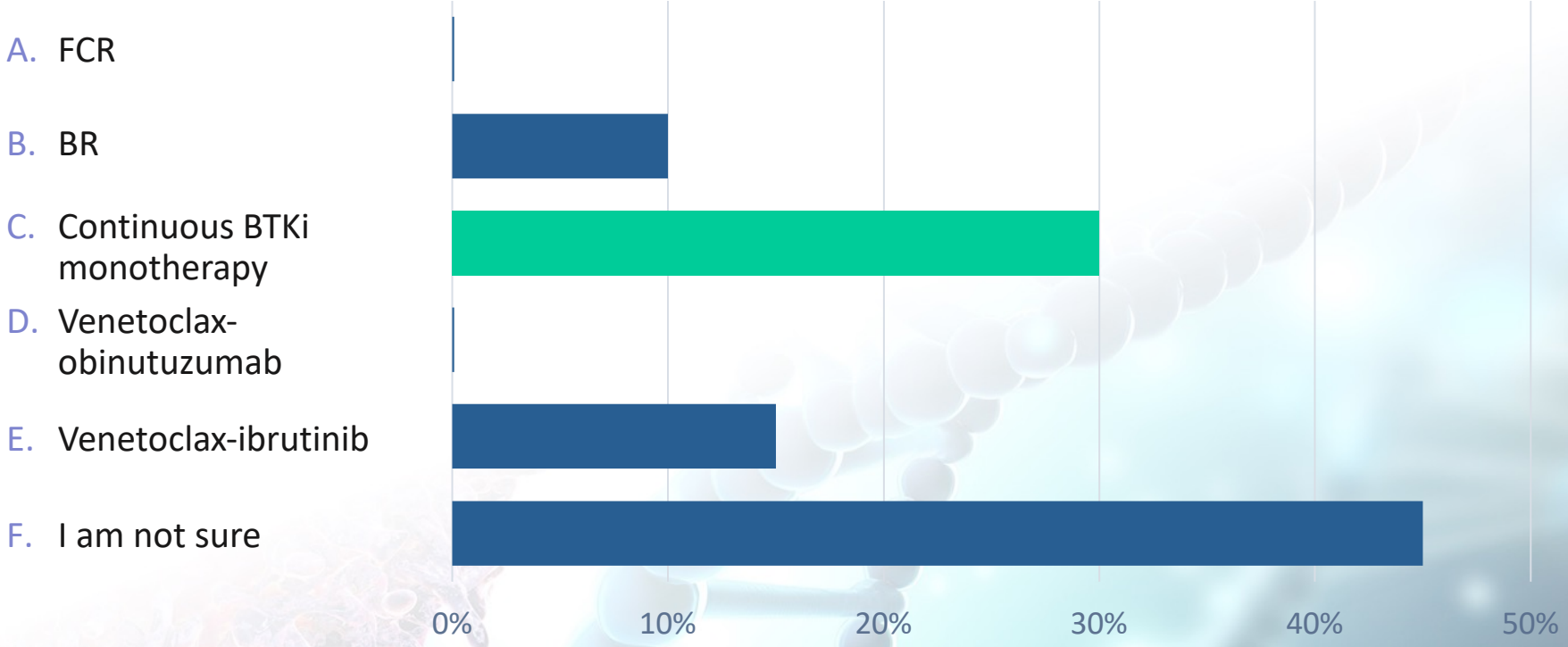
CIT, chemoimmunotherapy; CT, chemotherapy; IT, immunotherapy.

Mato AR, et al. *Blood*. 2020;136(Suppl 1):42–43.

Your 62-year-old patient presents to you with leukocyte count of approximately 120,000/µl (80% lymphocytes), hemoglobin level of 8.5 g/dl, and platelet count 85,000/µl. Immunophenotyping confirms that he has CLL, which carries del(17p). Which of the following is the best choice of therapy for your patient with newly-diagnosed CLL?

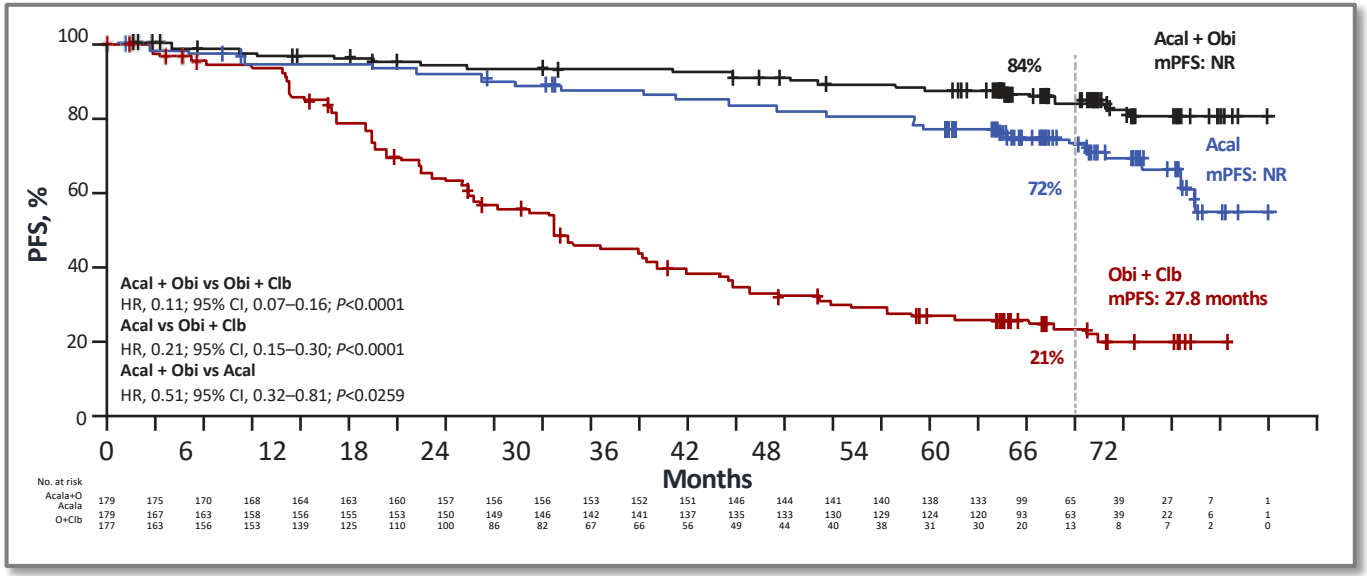
A. Fludarabine-cyclophosphamide-rituximab (FCR)
B. Bendamustine-rituximab (BR)
C. Continuous BTKi monotherapy
D. Venetoclax-obinutuzumab
E. Venetoclax-ibrutinib
F. I am not sure

Your 62-year-old patient presents to you with leukocyte count of approximately 120,000/µl (80% lymphocytes), hemoglobin level of 8.5 g/dl, and platelet count 85,000/µl. Immunophenotyping confirms that he has CLL, which carries del(17p). Which of the following is the best choice of therapy for your patient with newly-diagnosed CLL?



ELEVATE-TN

5-year Follow-up of Acal ± Obi vs Clb-Obi for Previously Untreated CLL



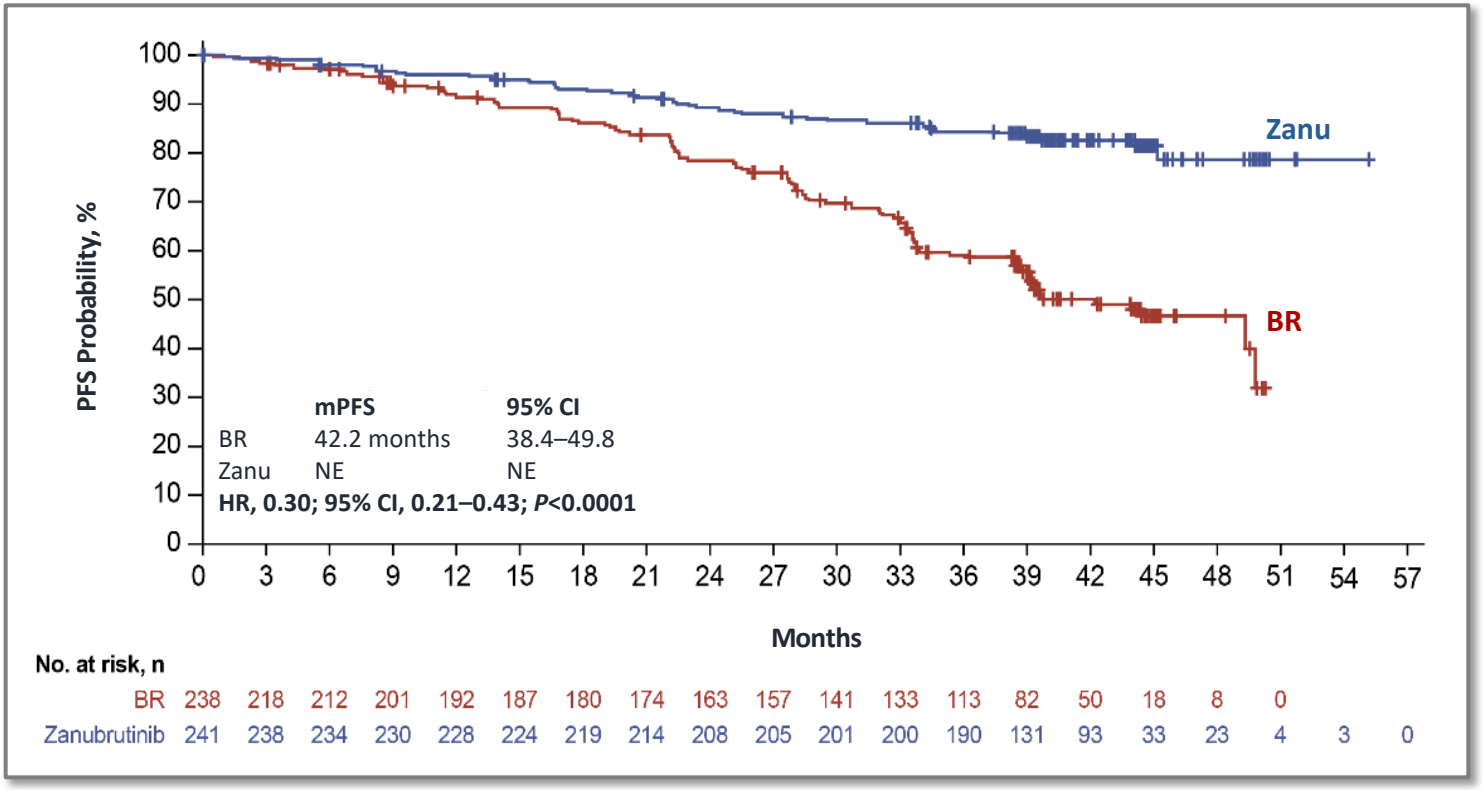
- PFS benefit is greater with Acal-Obi vs Acal monotherapy
- Low incidence of cardiovascular AEs (Afib/flutter and hypertension)
- Low rates of treatment discontinuation despite longer treatment exposure

Acal, acalabrutinib; AE, adverse event; Afib, atrial fibrillation; Clb, chloambucil; mPFS, median PFS; Obi, obinutuzumab; PFS, progression-free survival.

Sharman JP, et al. *Leukemia.* 2022;36:1171–1175. Sharman JP, et al. *Blood.* 2019;134(Suppl 1):31. Sharman JP, et al. *J Clin Oncol*. 2022;40(16_suppl):7539.

SEQUOIA

Zanu vs BR for Previously Untreated CLL



mPFS, median PFS; Zanu, zanubrutinib.

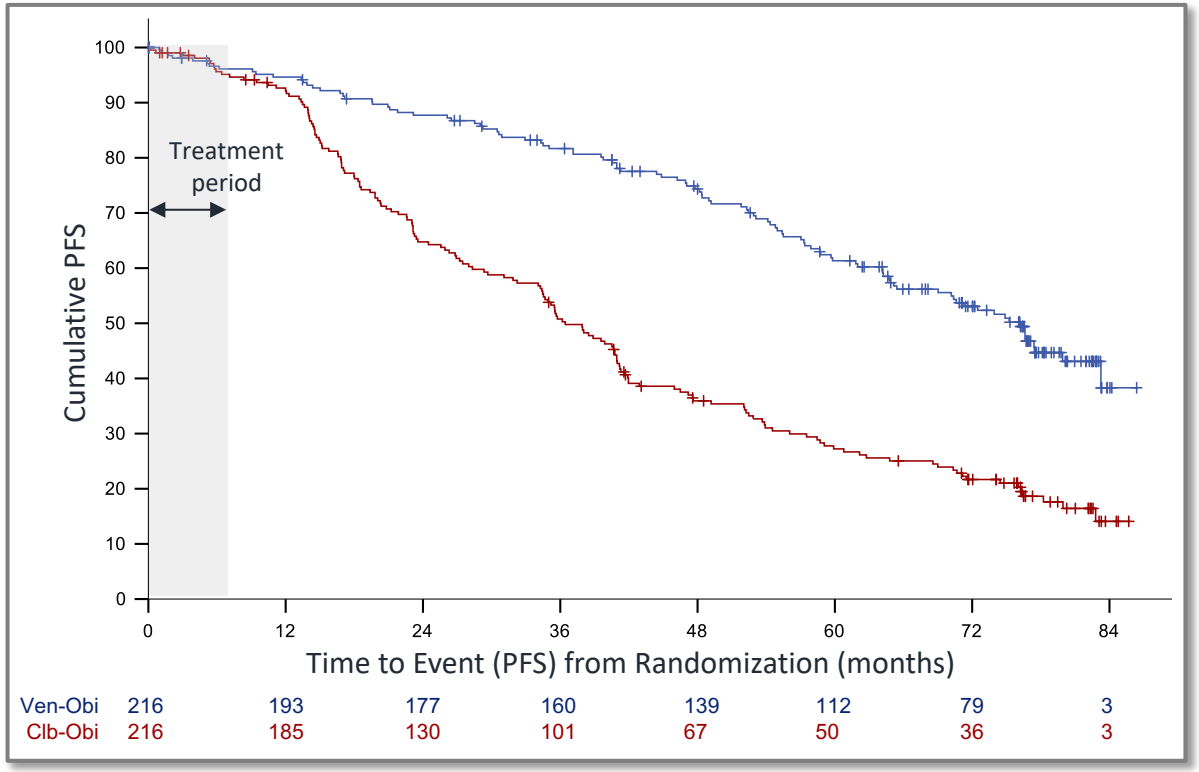
Shadman M, et al. *Hematol Oncol.* 2023;41(S2):235–238.

CLL14

6-year PFS Follow-up of Ven-Obi for Previously Untreated CLL

- Long-term efficacy and safety of fixed-duration Ven-Obi vs Clb-Obi
- Median follow-up: 76.4 months
  - 12% del(17p)/*TP53* mut
  - ~60% unmutated IGHV

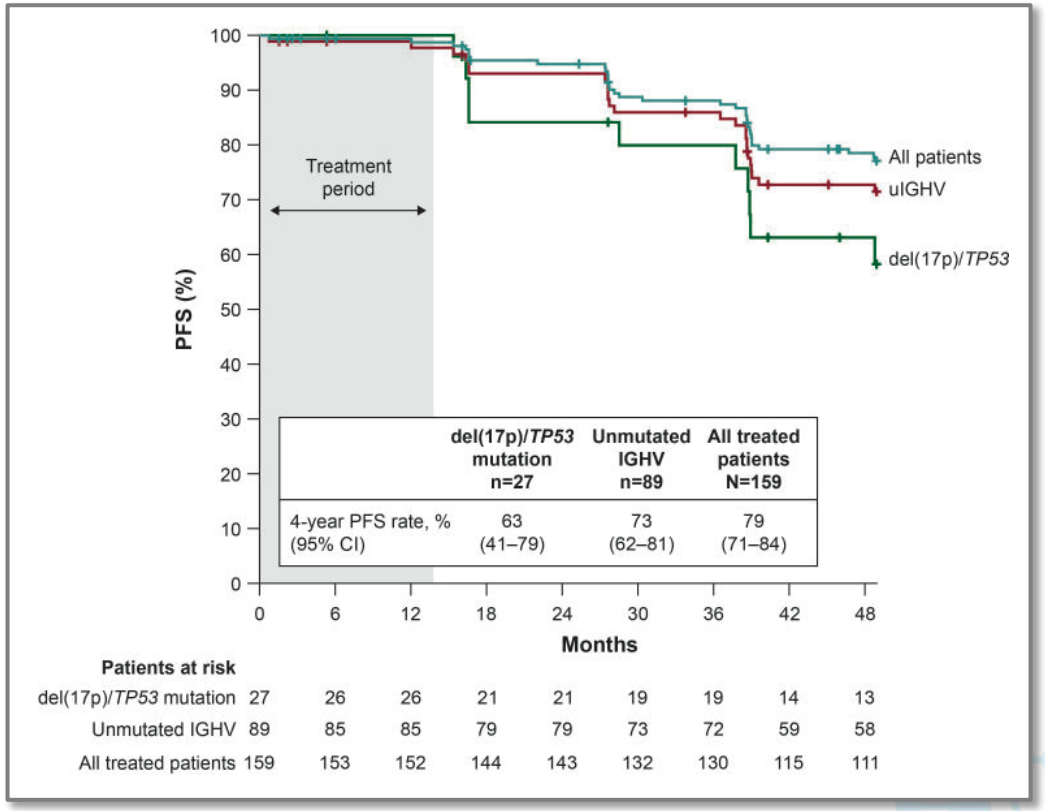
	Median PFS	6-year PFS
Ven-Obi	76.2 months	53.1%
Clb-Obi	36.4 months	21.7%
HR (95% CI)	0.40 (0.31–0.52); *P*<0.0001	



CAPTIVATE

4-year PFS Follow-up of Ven-Ibr for Previously Untreated CLL/SLL

- Long-term efficacy and safety of fixed-duration Ven-Ibr
- Median follow-up: 49.8 months
- High-risk features
  - 56% IGHV mut
  - 30% del(17p)/*TP53* mut



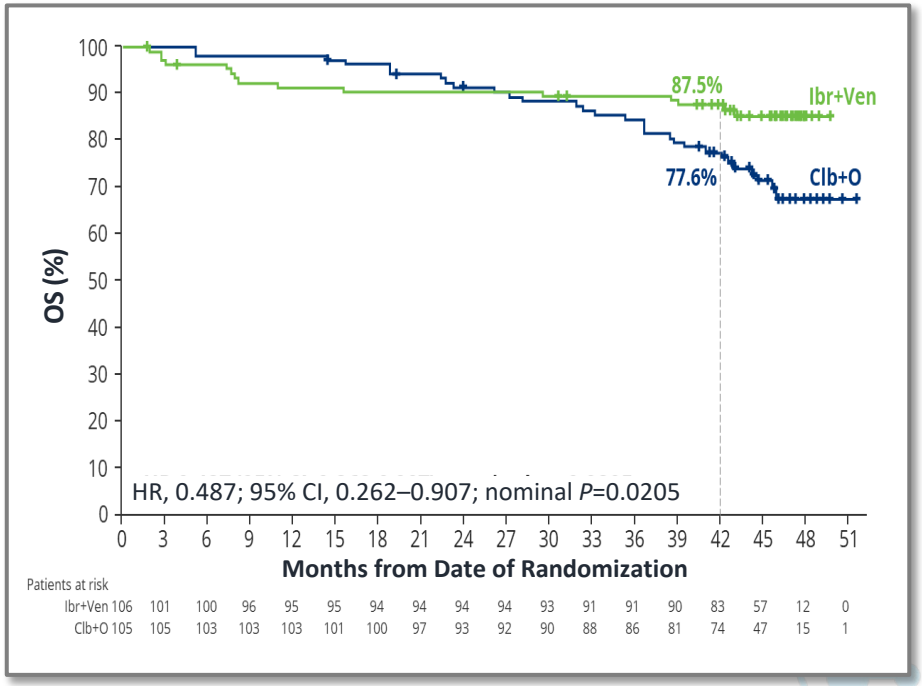
SLL, small lymphocytic lymphoma; uIGHV, unmutated IGHV.

Ghia P, et al. 2023 International Conference on Malignant Lymphoma. Abstract 155.

GLOW

4-year OS Follow-up of Ven-Ibr vs Clb-Obi for Previously Untreated CLL

- At 28-month follow-up, the median PFS was not reached for Ven-Ibr and 21 months for Clb-Obi (HR, 0.22; 95% CI, 0.13–0.36; *P*<0.001)[1]
  - At 46 months, the PFS HR was essentially unchanged (HR, 0.21; 95% CI, 0.14–0.33; *P*<0.0001)[2]
- With a median follow-up of 46 months in GLOW, fixed-duration Ven-Ibr achieved significantly improved OS vs Clb-Obi across most genomic subgroups of patients with previously untreated CLL[2]



[1]Kater Arnon P, et al. *NEJM Evidence*. 2022;1(7):EVIDoa2200006. [2]Kater A, et al. 2023 European Hematology Association Congress. Abstract 620.

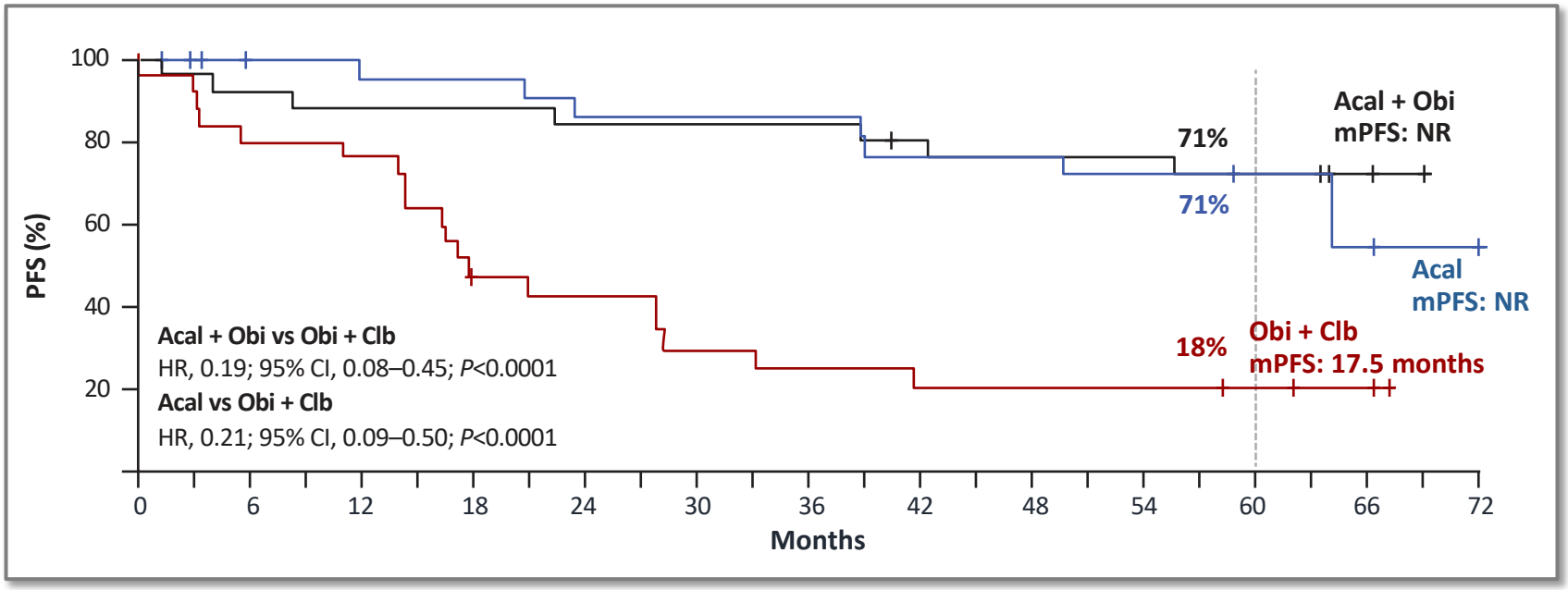
Summary of Studies in Previously Untreated CLL

Trial	Treatment Regimen	PFS	OS
ELEVATE-TN[1] (5-year data)	Acalabrutinib + obinutuzumab Acalabrutinib Chlorambucil + obinutuzumab	84% 72% 21%	90% 84% 82%
SEQUOIA[6] (42-month data)	Zanubrutinib, with/without del(17p) Bendamustine + rituximab, without del(17p)	79%/82% 50%	90%/89% 88%
CLL14[2] (6-year data)	Venetoclax + obinutuzumab Chlorambucil + obinutuzumab	53% 22%	79% 69%
CAPTIVATE[3] (4-year data)	Venetoclax + ibrutinib	79%	98%
GLOW[4,5] (4-year data)	Venetoclax + ibrutinib Chlorambucil + obinutuzumab	HR, 0.21 95% CI, 0.14–0.33	HR, 0.49 95% CI, 0.26–0.91

[1]Sharman JP, et al. *J Clin Oncol*. 2022;40(16 Suppl):7539. [2]Al-Sawaf O, et al. *Hematol Oncol.* 2023;41(S2):58–60.
[3]Ghia P, et al. 2023 International Conference on Malignant Lymphoma. Abstract 155. [4]Kater Arnon P, et al. *NEJM Evidence*. 2022;1(7):EVIDoa2200006.
[5]Kater A, et al. 2023 European Hematology Association Congress. Abstract P620. [6]Shadman M, et al. *Hematol Oncol*. 2023;41(S2):235–238.
ClinicalTrials.gov. Identifiers: NCT02475681, NCT02242942, NCT02910583, NCT03462719, NCT03336333.

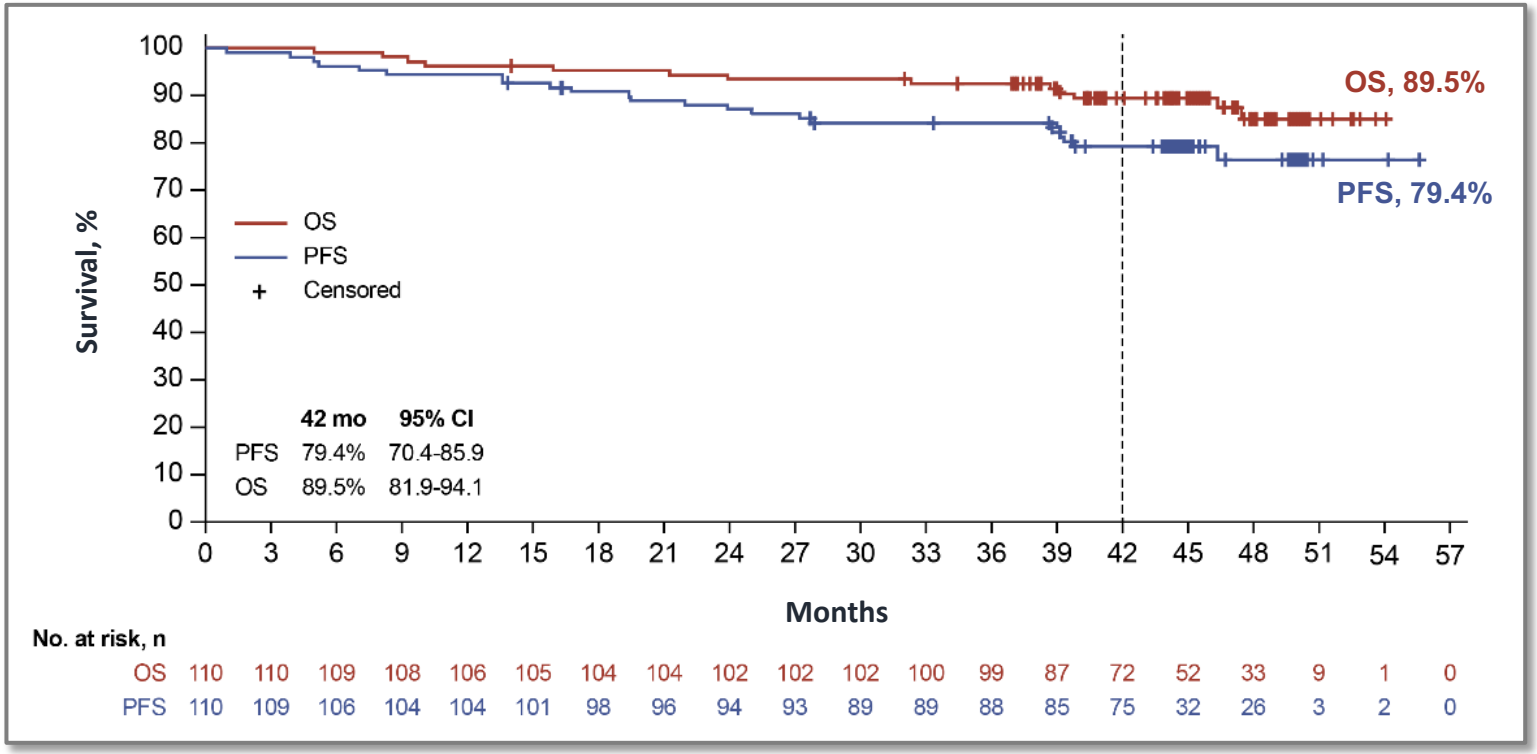
ELEVATE-TN

PFS in Patients with Del(17p) or mutated TP53



SEQUOIA

PFS and OS in Patients with Del(17p) with Zanu

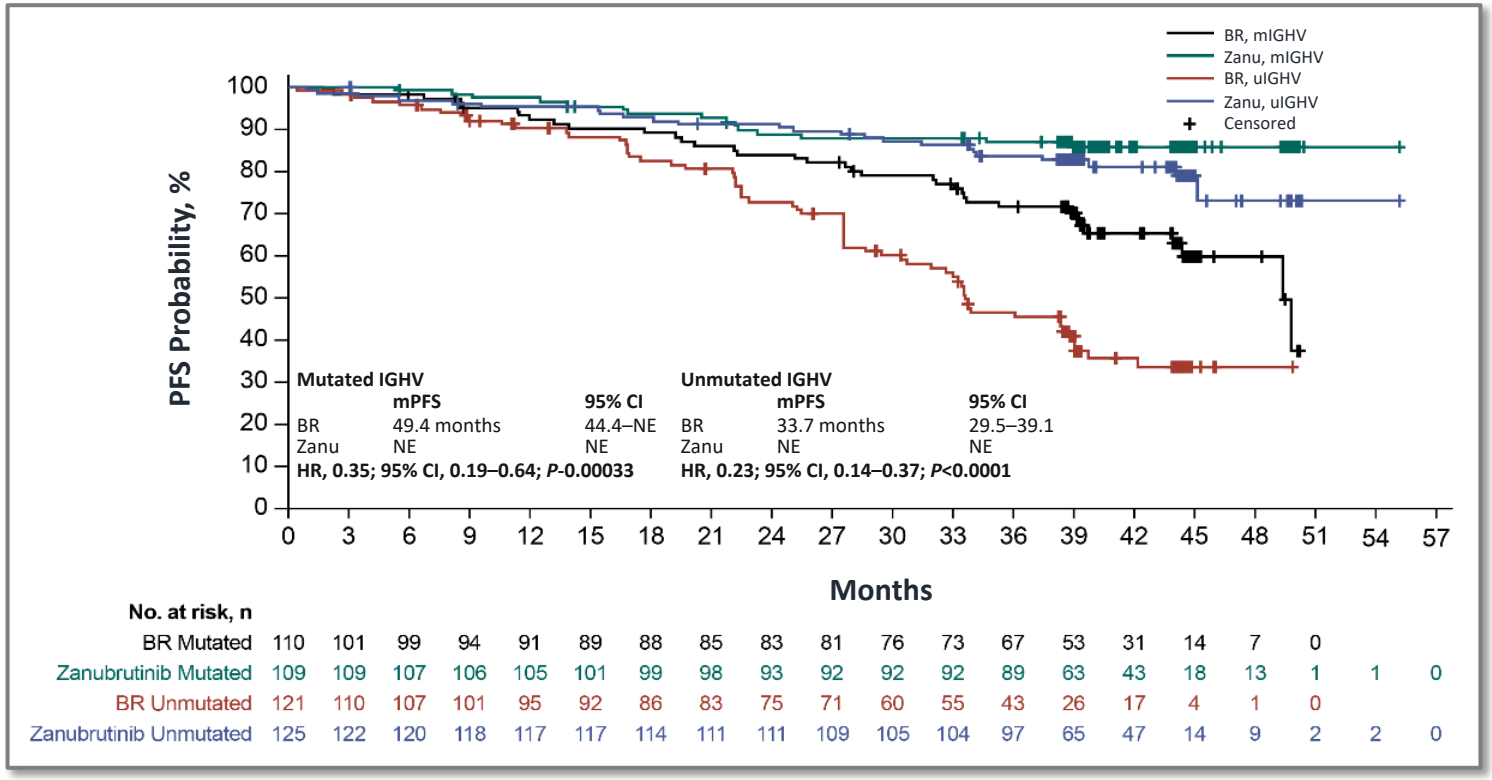


OS, overall survival.

Shadman M, et al. *Hematol Oncol*. 2023;41(S2):235–238.

SEQUOIA

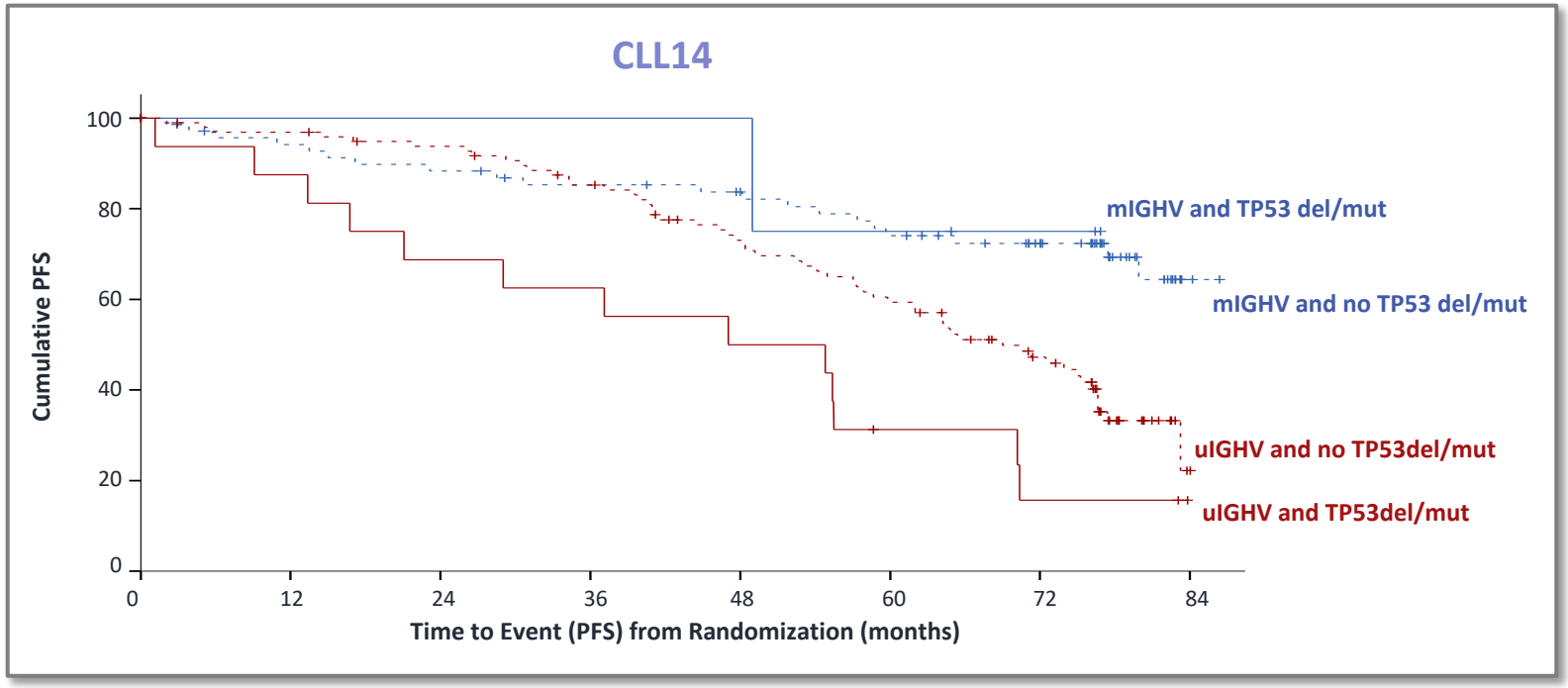
PFS in Patients without Del(17p) by IGHV Status



Shadman M, et al. *Hematol Oncol*. 2023;41(S2):235–238.

CLL14

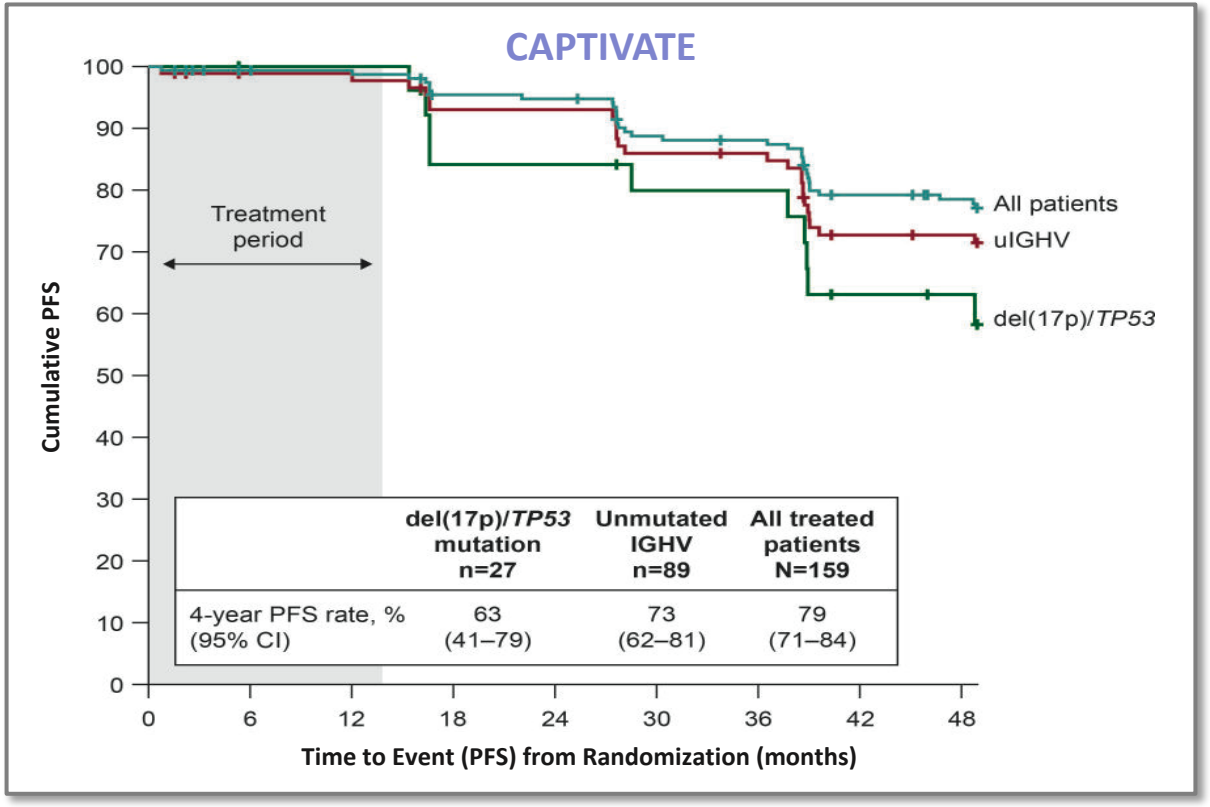
PFS by IGHV and TP53 *Status*



Al-Sawaf O, et al. *Hematol Oncol*. 2023;41(S2):58–60.

CAPTIVATE

PFS by IGHV and TP53 *Status*



	del(17p)/*TP53* mutation n=27	Unmutated IGHV n=89	All treated patients N=159
4-year PFS rate, % (95% CI)	63 (41–79)	73 (62–81)	79 (71–84)

GAIA/CLL13
Design

Eligibility
Treatment-naive, fit patients with CLL, **no *TP53*** aberrations (**centrally screened**)

- **CIT** FCR ≤65 yrs, BR >65 yrs
- **VenR** | 12 mos
- **Obi-Ven** | 12 mos
- **GIVe** | 12–36 mos

Baseline → X → Disease progression

Chromosome Analysis (CBA)

Mitogen: CpG/IL-2

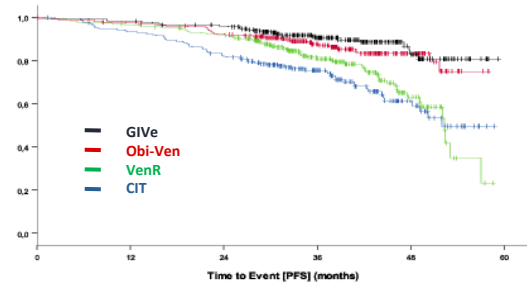
Presence of **CKT/hCKT/iCKT**
Presence of (specific) **translocations**

CBA at Progression

Presence of **karyotype evolution**
Changes in number of abnormalities

Primary Endpoint Analysis, PFS

Data cut 01/22, median OT: 38.8 months, n=926



GIVe vs **CIT**
HR, 0.32; 97.5% CI, 0.19–0.54; ***P*<0.000001**

Obi-Ven vs **CIT**
HR, 0.42; 97.5% CI, 0.26–0.68; ***P*<0.0001**

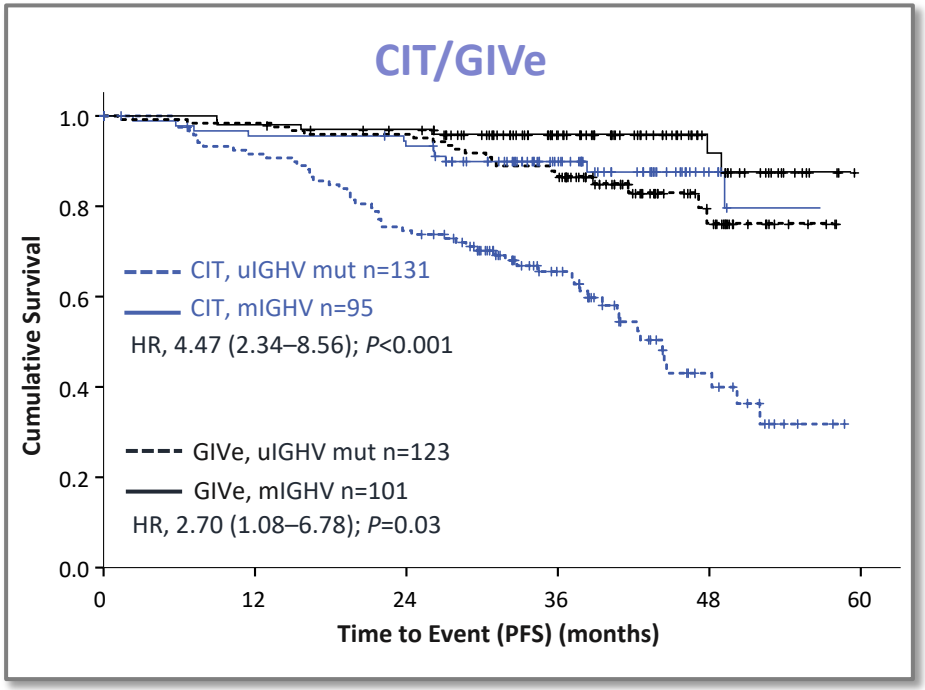
VenR vs **CIT**
HR, 0.79; 97.5% CI, 0.53–1.18; *P*=0.183

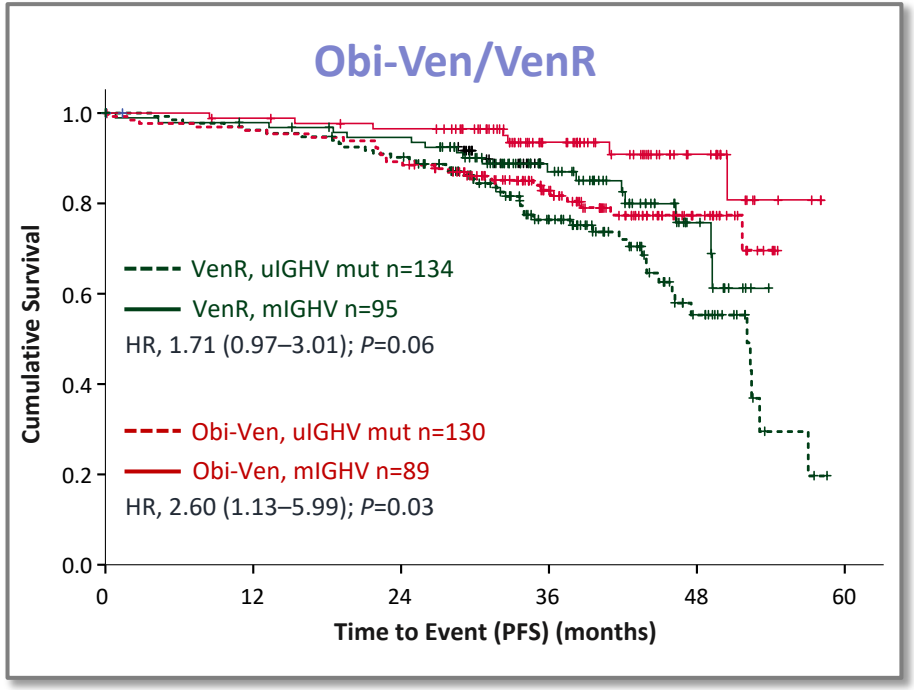
BR, bendamustine + rituximab; CKT, complex karyotype; FCR, fludarabine + cyclophosphamide + rituximab; hCKT highly CKT; iCKT, intermediate CKT; nCKT, no CKT; OT, on therapy.

Fürstenau M, et al. *Blood.* 2022;140(Suppl 1):842–845.

GAIA/CLL13

PFS with CIT, Obi-Ven, GIVe, and VenR and Unmutated-IGHV

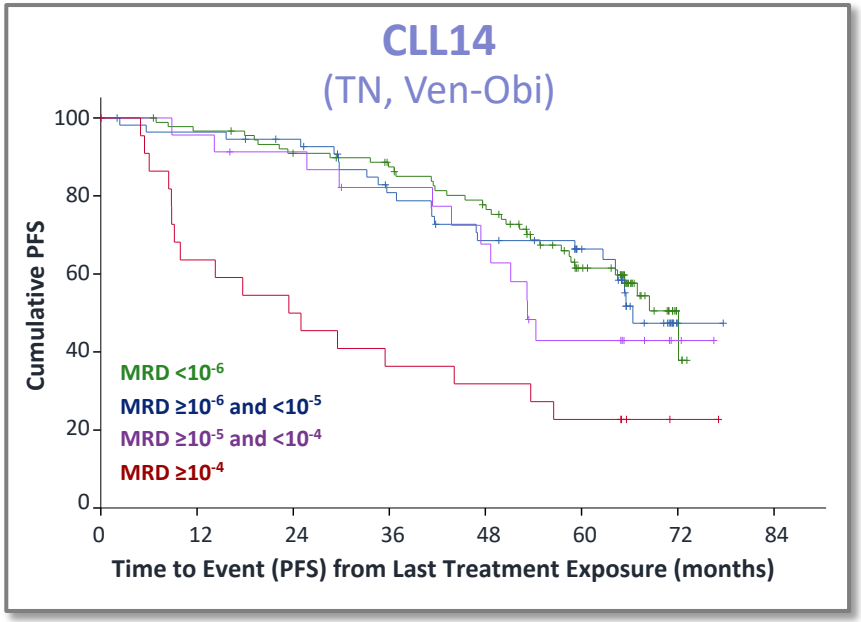


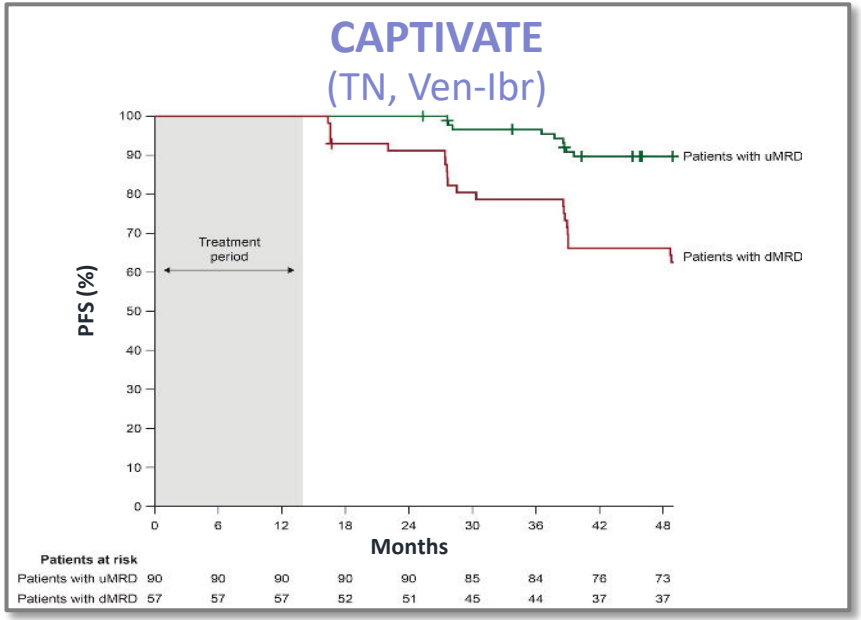


mIGHV, mutated IGHV; uIGHV, unmutated IGHV.

Tausch E, et al. *Blood.* 2022;140(Suppl 1):839–841.

Minimal Residual Disease



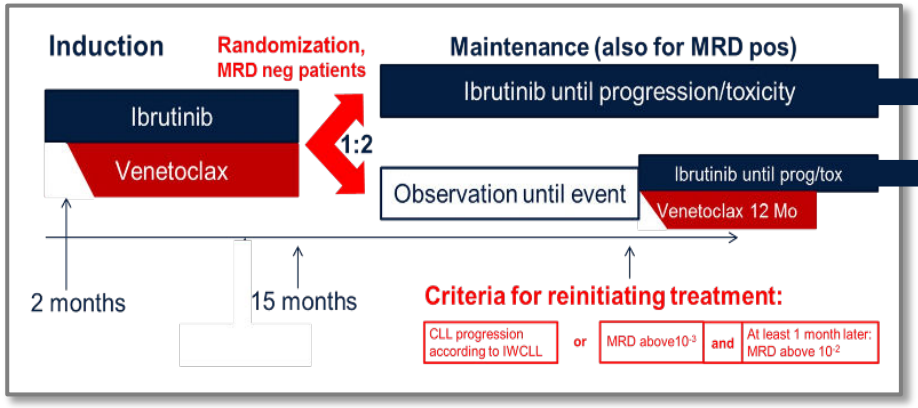


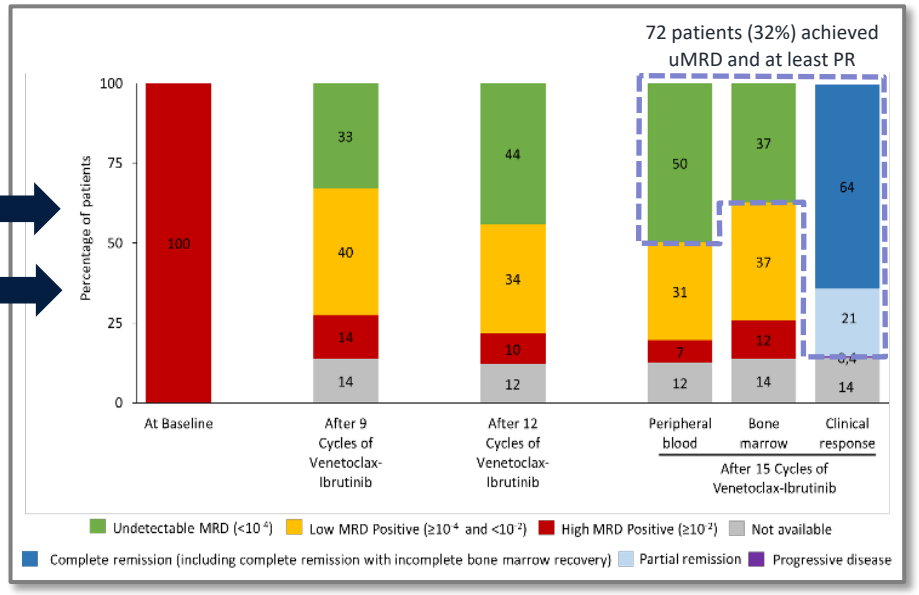
Depth of remission correlates with long-term PFS and OS in treatment-naïve (TN) CLL, indicating the prognostic value of the EoT MRD status.

Al-Sawaf O, et al. *Hematol Oncol*. 2023;41(S2):58–60. Ghia P, et al. 2023 International Conference on Malignant Melanoma. Abstract 155.

Vision/HO141

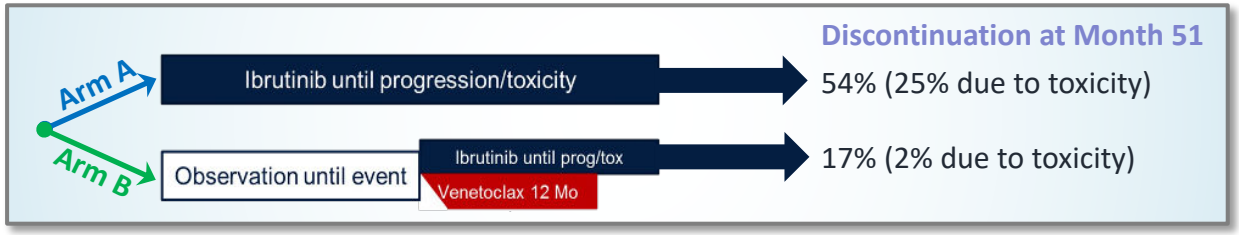
MRD-guided Stop/Start in R/R CLL

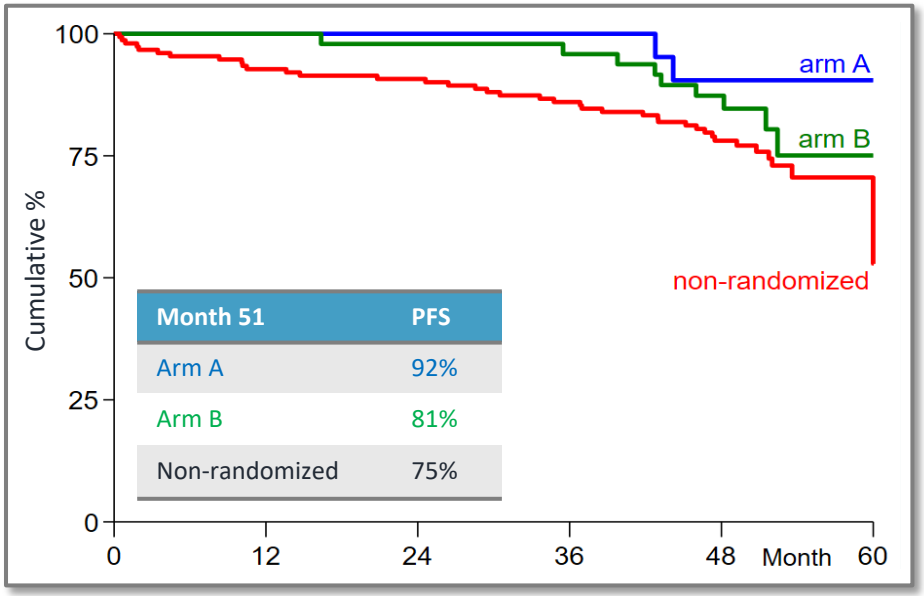




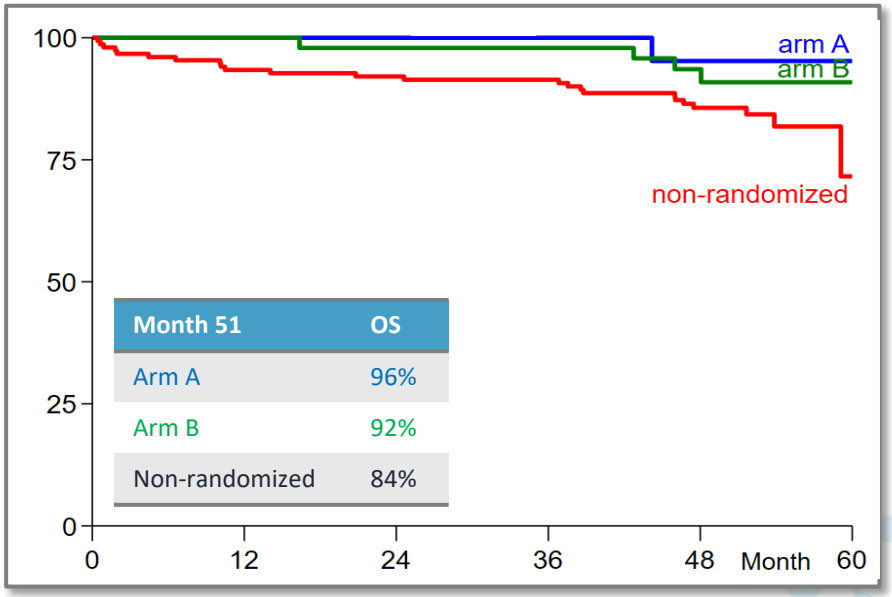
Vision/HO141

MRD-guided Stop/Start in R/R CLL





Month 51	PFS
Arm A	92%
Arm B	81%
Non-randomized	75%



Month 51	OS
Arm A	96%
Arm B	92%
Non-randomized	84%

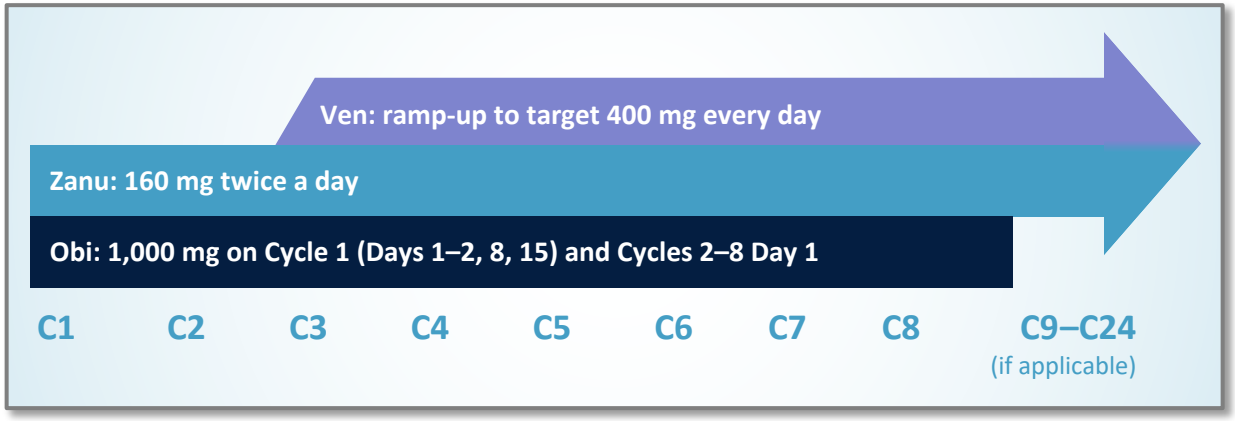
Kater AP, et al. 2023 European Hematology Association Congress. Abstract S148.

BOVen

Zanu-Obi-Ven for Previously Untreated CLL/SLL

Key Eligibility Criteria

- Previously untreated CLL/SLL
- Requires treatment (iwCLL guidelines)
- ECOG 0–2
- ANC ≥1,000, PLT count ≥75 (unless due to CLL)
- Coumadin and dual antiplatelet excluded



Treatment Duration/MRD-directed Treatment Discontinuation Criteria

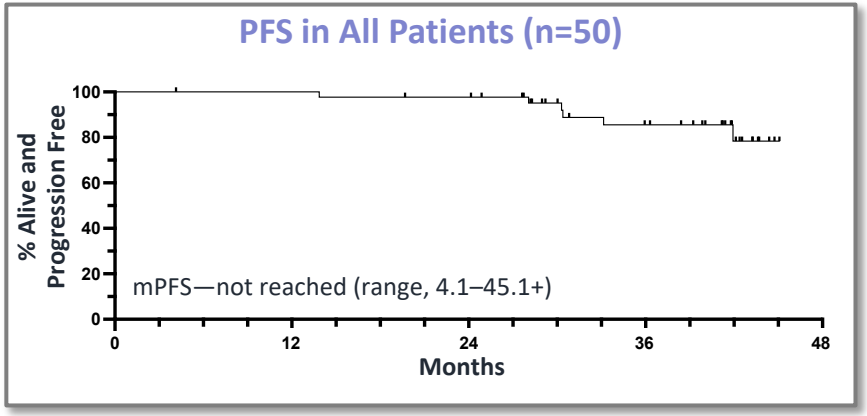
- Treatment duration: minimum 8 months to maximum 24 months (including 2-month doublet lead-in prior to Ven)
- PB MRD (flow cytometry) assessed every 2 cycles
  - If PB uMRD $<10^{-4}$ (flow), then BM MRD assessment within 14 days
  - If PB and BM uMRD $<10^{-4}$ (flow), then repeat PB MRD assessment after 2 additional cycles
  - If PB × 2 (consecutively) and BM uMRD $<10^{-4}$ (primary endpoint), treatment is discontinued

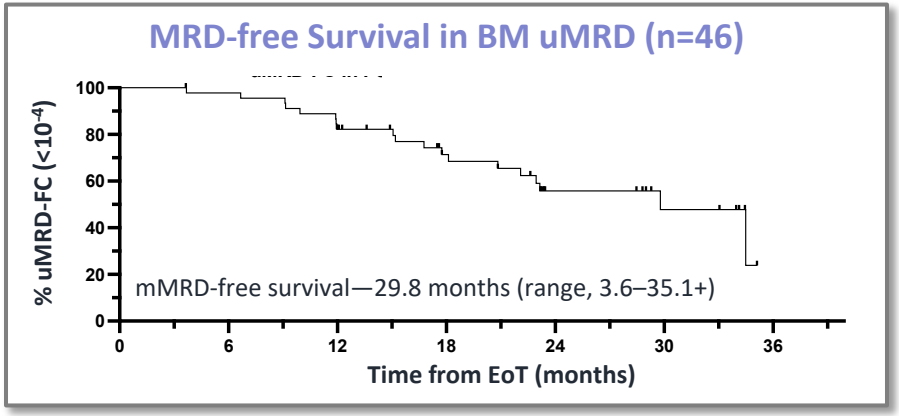
ANC, absolute neutrophil count; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; PB, peripheral blood; PLT, platelet; uMRD, undetectable MRD.

Soumerai J, et al. *Hematol Oncol*. 2023;41:233–235.

BOVen

Zanu-Obi-Ven for Previously Untreated CLL/SLL





- BOVen was well tolerated with no additional safety signals with long-term follow-up
- BOVen achieved frequent uMRD ($<10^{-4}$) in PB (96%) and BM (92%)
- Median duration of therapy was 10 months (IQR 8–12) including 2-month lead-in

ΔMRD400	n	Median Time on Therapy	Median MRD-free Survival
Achieved	21	8 months	Not reached
Failed	13	13 months	18.1 months
		HR, 4.02 (95% CI, 1.37–11.81); *P*=0.003	

ΔMRD400 is decrease in PB MRD at C5D1 (1 month of Ven at target dose) and 400-fold reduction optimal cutoff for predicting uMRD at $<10^{-4}$ within 8 months

EoT, end of treatment; IQR, interquartile range; mMRD, median MRD; uMRD-FC, undetectable MRD at $<10^{-4}$ by flow cytometry.

Soumerai J, et al. *Hematol Oncol*. 2023;41:233–235.

Your 71-year-old patient received first-line venetoclax-obi and second-line ibrutinib therapies for her CLL (unmutated IGHV, intact TP53), and now comes to you after 3 years of continuous ibrutinib therapy with increasing circulating lymphocyte counts and decreasing hemoglobin levels. Which is the best choice of therapy for your patient?

A. Bendamustine-rituximab (BR)
B. Zanubrutinib monotherapy
C. Idelalisib monotherapy
D. Clinical trial with a non-covalent BTK inhibitor
E. I am not sure

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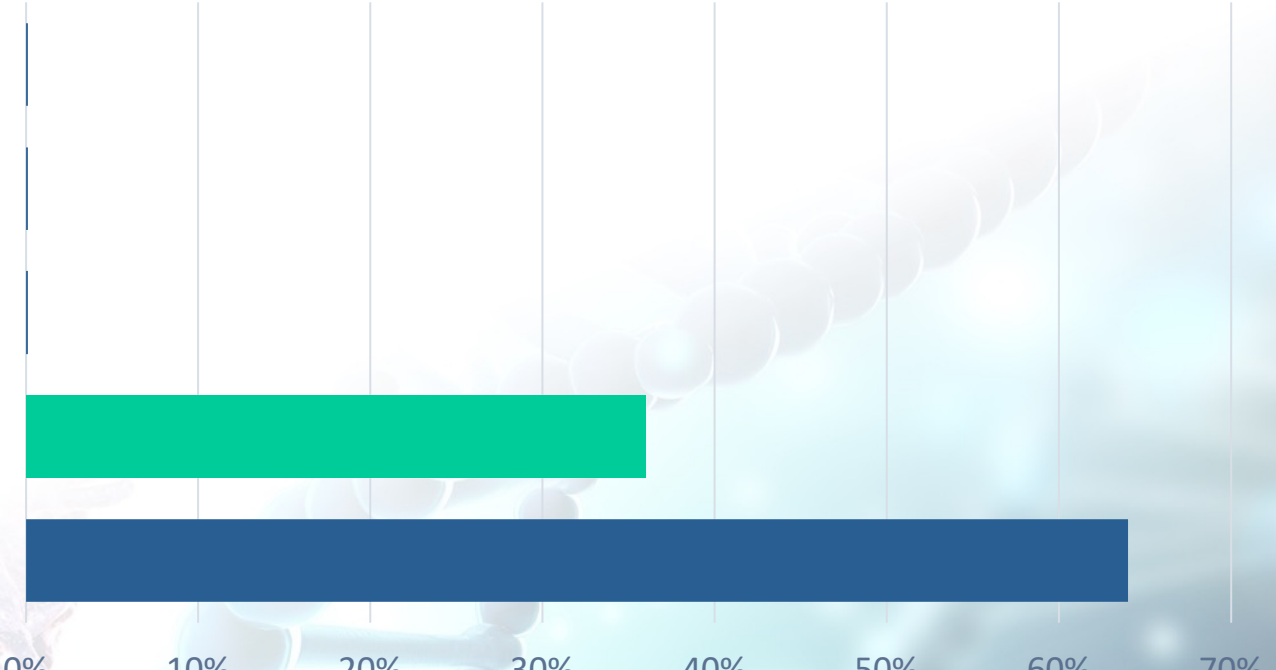


BTKi Resistance

- 16%–23% of patients on continuous BTKi therapy develop BTKi resistance
  - Most information comes from studies with ibrutinib
    - However, similar mechanisms were reported for acalabrutinib
  - The two most common alterations are C481S or C481R in the ATP binding site
    - The mutations prevent attachment of first- and second-generation covalent BTKis
- Resistance typically arises with indefinite treatment
  - More common in pretreated patients and patients with TP53 abnormalities

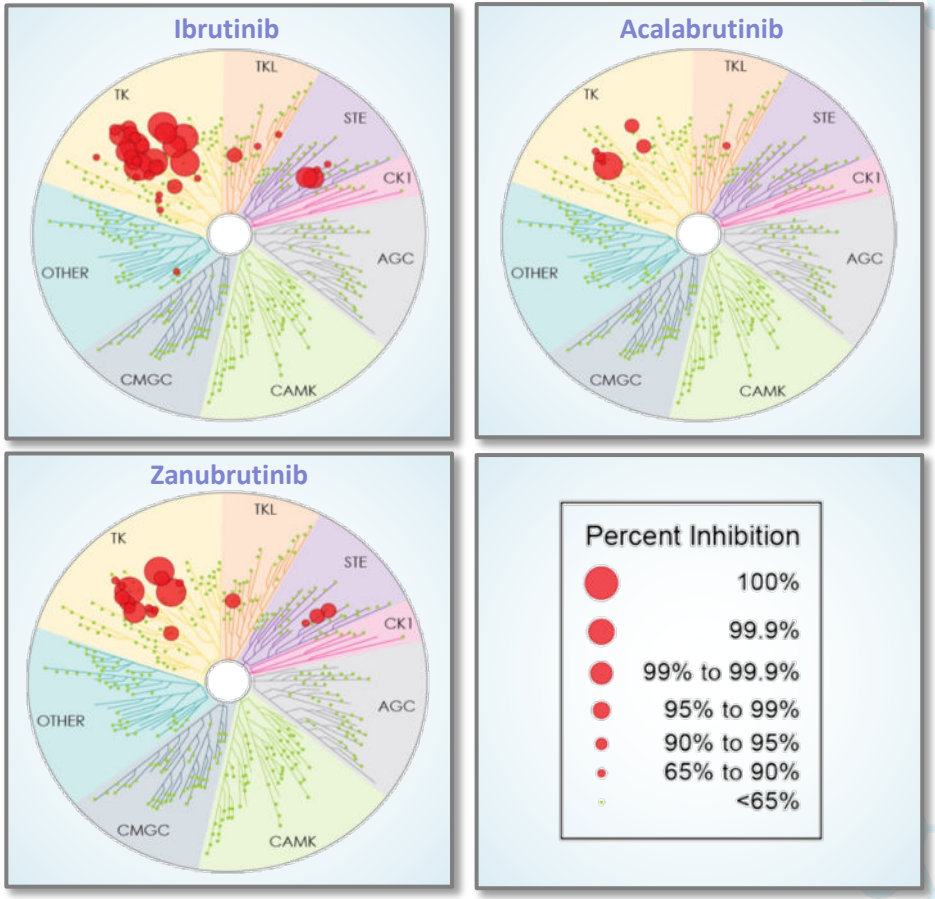
MOA, mechanism of action.

Munir T, et al. *Am J Hematol.* 2019;94(12):1353–1363. Hampel PJ, et al. *Blood Cancer J.* 2022;12(9):124. Barr PM, et al. *Blood Adv.* 2022;6(11):3440–3450. Frustaci AM, et al. *Cancers (Basel).* 2023;15(5).

BTKi Resistance

- Non-covalent BTKis do not require attachment to residue 481
  - Highly selective, reversible binding
  - Can act on both wild-type and Cys481-mutated BTK
  - MOA may reduce off-target effects and associated toxicity

Inhibitor name	Binding mechanism
Ibrutinib	Covalent, irreversible
Acalabrutinib	Covalent, irreversible
Zanubrutinib	Covalent, irreversible
Fenebrutinib	Noncovalent, reversible
Nemtabrutinib	Noncovalent, reversible
Pirtobrutinib	Noncovalent, reversible

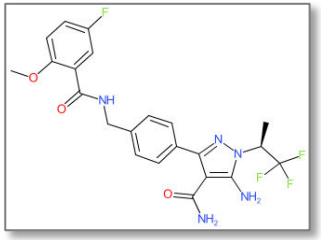


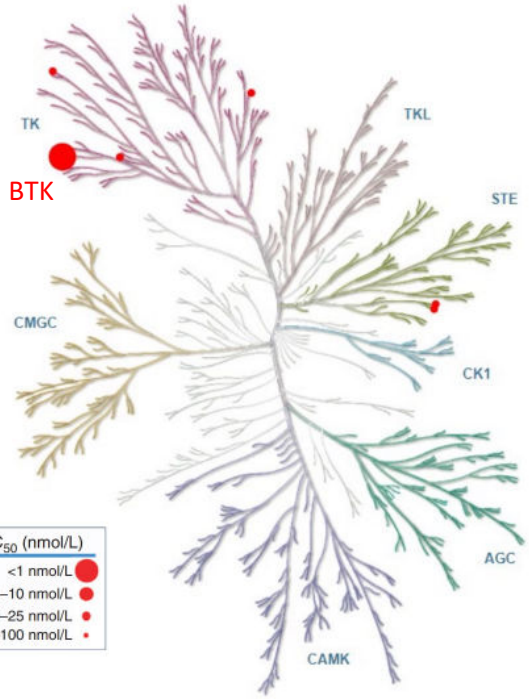
MOA, mechanism of action.

Kaptein A, et al. *Blood*. 2018;132(Suppl 1):1871.

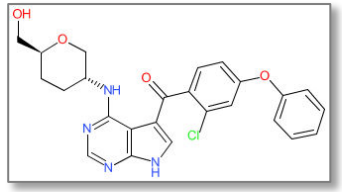
Characteristics of Reversible BTK Inhibitors

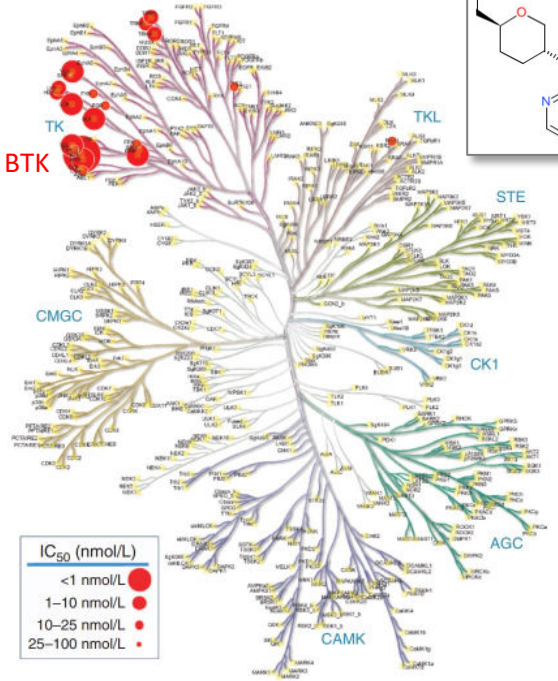
Pirtobrutinib





Nemtabrutinib

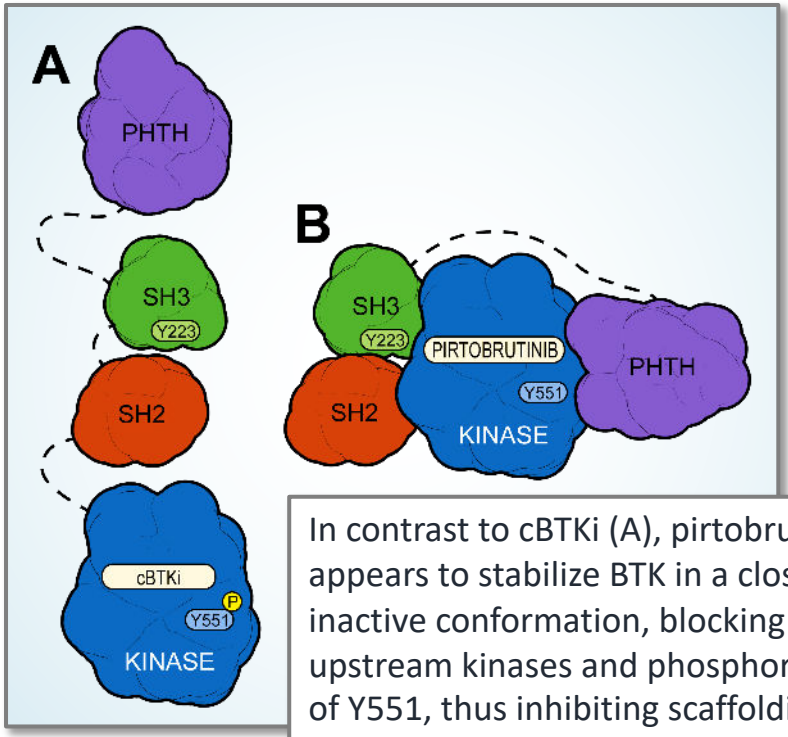




Reiff SD, et al. *Cancer Discov*. 2018;8(10):1300–1315. Mato AR, et al. *Lancet*. 2021;397(10277):892–901.

Pirtobrutinib

- Pirtobrutinib is approved in the United States to treat relapsed or refractory MCL after at least two lines of systemic therapy, including prior BTK inhibitor[1]
- Inhibits both WT and C481-mutant BTK with equal low nM potency in *in vitro* models[2] and CLL cells[3]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a pirtobrutinib-BTK binding complex half-life of about 2 hours

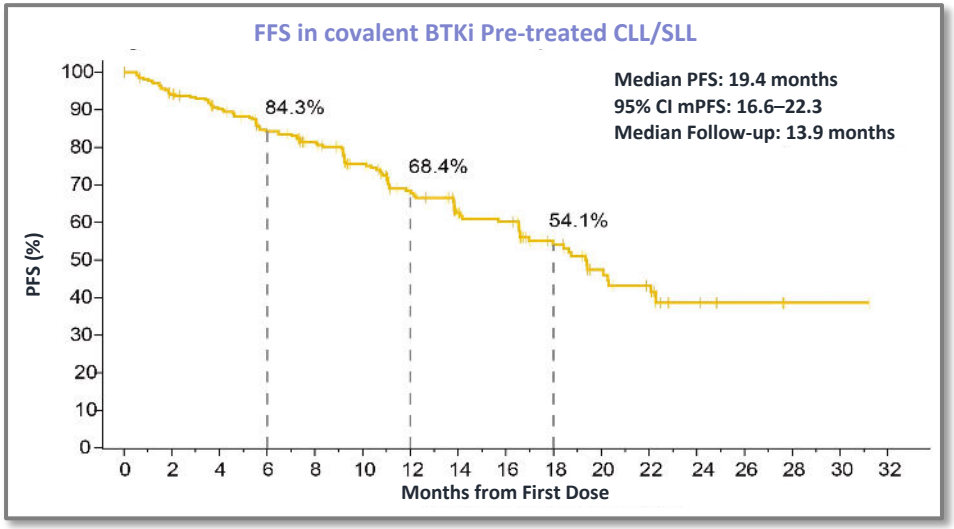


In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[3]

[1]FDA Prescribing Information: Pirtobrutinib. Revised January 2023. [2]Gomez EB, et al. *Blood.* 2023;142(1):62–72. [3]Aslan B, et al. *Blood Cancer J*. 2022;12(5):80.

Pirtobrutinib

- BRUIN-CLL
  - Phase 1/2, open-label, pirtobrutinib monotherapy, N=170
  - Median 3 prior therapies
  - 25% del(17p), 30% *TP53*-mut, 88% unmutated IGHV



		BTKi Pretreated CLL/SLL	Response Evaluable Cohort, n	ORR, % (95% CI)	mPFS, months (95% CI)	Estimated 12-month PFS rate, % (95% CI)	Estimated 18-month PFS rate, % (95% CI)
Overall		276	273	74 (68–79)	19.4 (16.6–22.3)	68 (62–74)	54 (46–61)
Age	≥75	57	56	71 (58–83)	20.1 (15.7–NE)	78 (63–87)	62 (44–75)
	<75	219	217	74 (68–80)	18.7 (16.6–NE)	66 (58–73)	52 (43–60)
At least prior BTKi and BCL2i	Yes	122	119	73 (64–81)	14.1 (11.1–18.7)	58 (47–68)	42 (29–55)
	No	154	154	74 (66–81)	22.1 (18.4–NE)	75 (67–82)	62 (52–70)
Del(17p) and/or TP53 mutation	Yes	99	98	80 (70–87)	16.6 (13.8–22.1)	69 (58–78)	47 (33–59)
	No	107	107	67 (58–76)	19.4 (14.1–NE)	66 (55–75)	58 (46–68)
BTK C481 status*	Mutated	85	85	81 (71–89)	17.0 (13.8–20.3)	69 (57–79)	49 (35–61)
	Unmutated	91	91	65 (54–75)	20.3 (13.8–NE)	63 (52–73)	54 (40–65)
Reason for prior BTKi discontinuation	Disease progression	206	205	73 (66–79)	18.6 (13.9–20.3)	66 (58–73)	50 (41–59)
	Intolerance and other	68	66	76 (64–85)	NE (18.4–NE)	77 (64–86)	67 (51–79)

*Patients with available mutation data who progressed on any prior covalent BTKi, excluding those who were covalent BTKi intolerant.

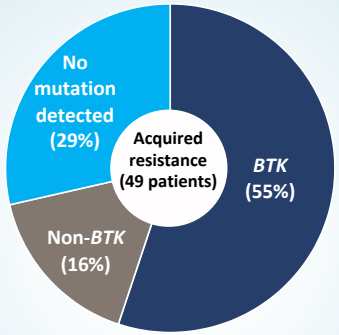
N, number of patients; n, number of response evaluable patients in sample; NE, not evaluable.

- ORR 74% (n=232); 1% CR; 64% PR; 8% PR with lymphocytosis
- 20% grade 3/4 neutropenia, hypertension (3%) and hemorrhage (2%), 1% Afib

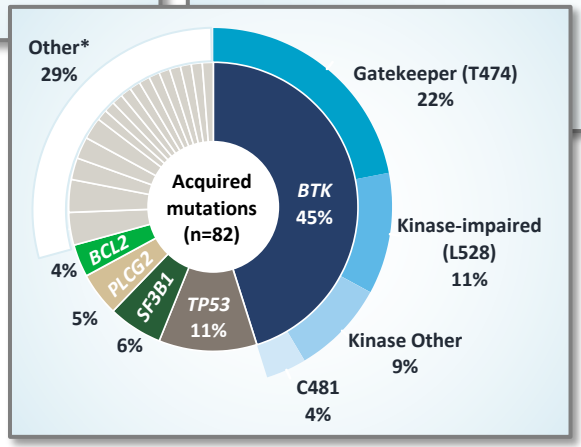
CR, complete response; PR, partial response.

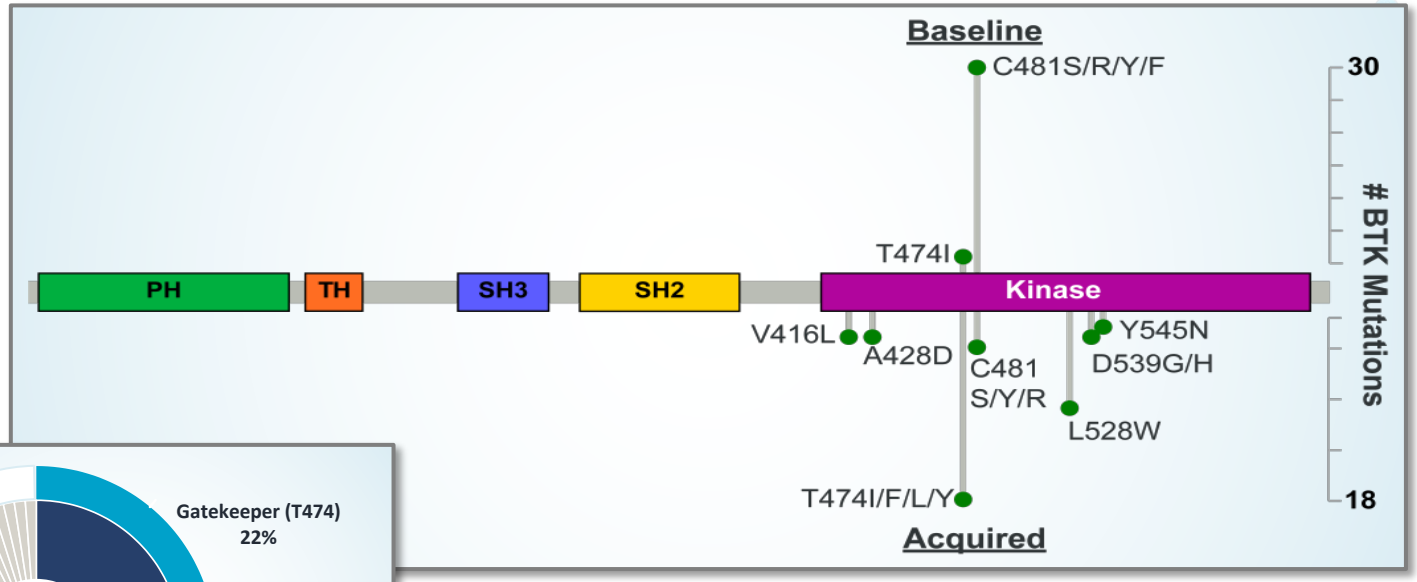
Mato AR, et al. *Blood*. 2022;140(Suppl 1):2316–2320.

Pirtobrutinib Resistance



- 71% of patients had at least one acquired mutation at progression
- Total of 82 acquired mutations in 35 patients

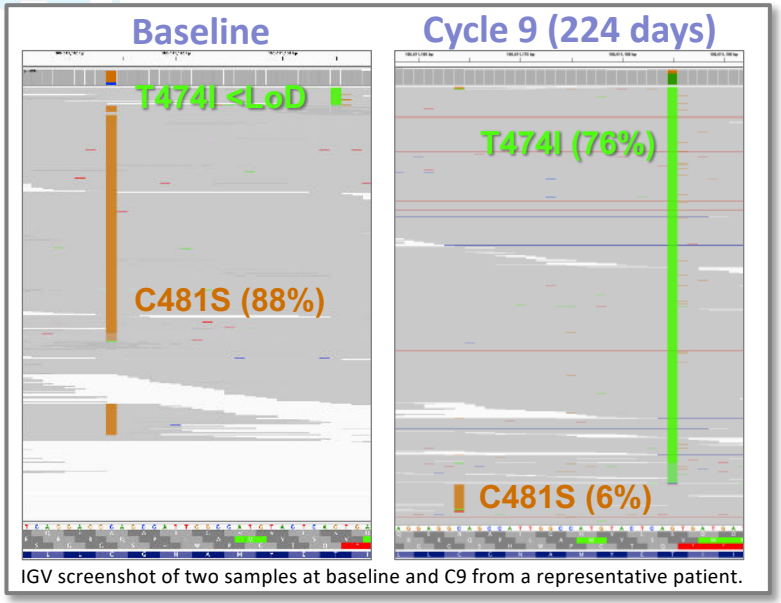




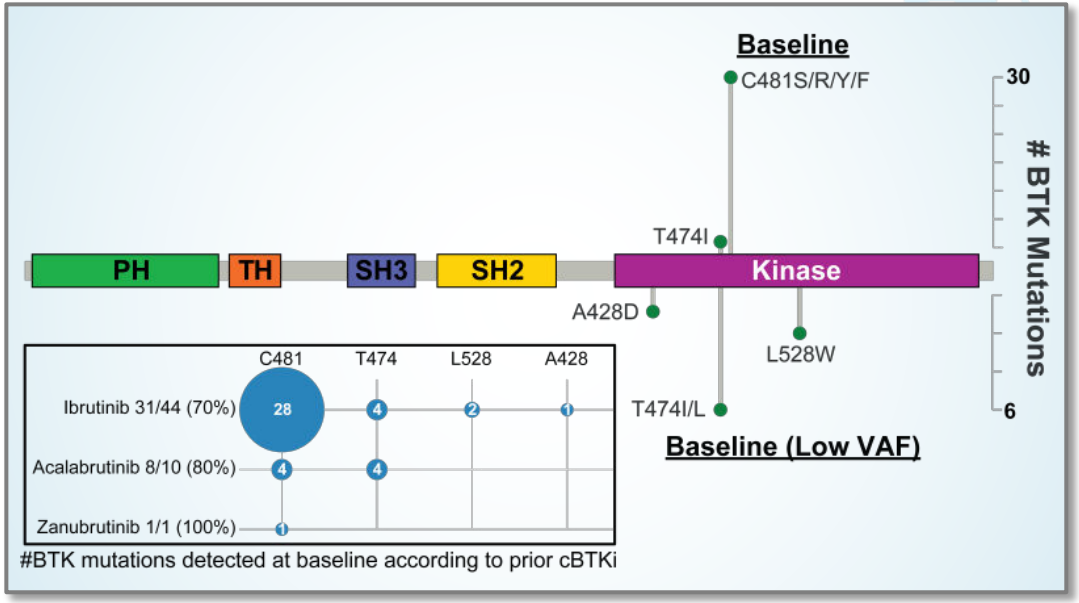
Approximately half of patients acquired a BTK mutation, and a resistance mechanism could not be identified in 29%

Mato AR, et al. *Blood*. 2022;140(Suppl 1):2316–2320. Patel K, et al. *Hematol Oncol*. 2023;41:185–187.

BTK Mutations Found at Low VAF at Baseline



IGV screenshot of two samples at baseline and C9 from a representative patient.



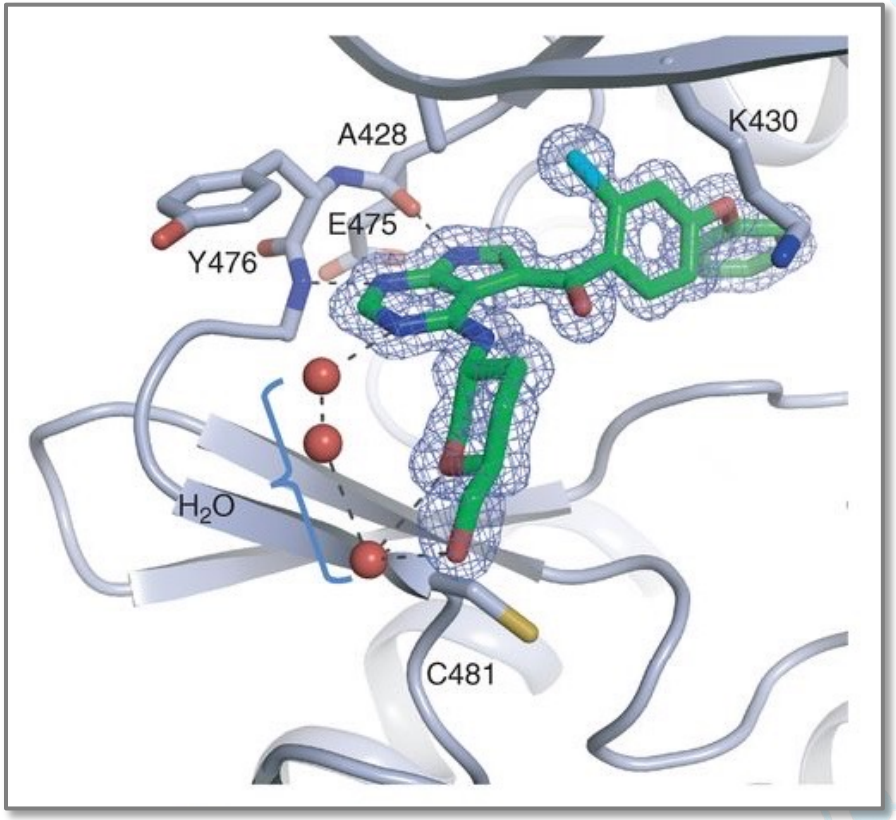
#BTK mutations detected at baseline according to prior cBTKi

- 9/37 (24%) acquired non-C481 BTK mutations at PD (median VAF at PD: 40% [range, 9–84]) pre-existed at baseline at low VAFs (1%–3%)[a]
- These patients had similar responses to pirtobrutinib (6/8, 75% ORR [95% CI, 35–97], median time on pirtobrutinib of 11.2 months, range [3.9–14.5 months]) and included patients who received prior ibrutinib (n=4), acalabrutinib (n=3), and ibrutinib + acalabrutinib (n=1)

[a]In 8 unique patients.
VAF, variant allele frequency.

Nemtabrutinib

- Nemtabrutinib noncovalently binds to the kinase domain's ATP binding region and competes with ATP[1,2]
- Nemtabrutinib forms hydrogen bonds with the backbone residues G475 and Y476[2]
- The solvent-exposed polar tetrahydropyran methanol side chain facilitates an extensive hydrogen bonding network through exposure to water molecules[2]
- Binding of nemtabrutinib is not dependent on C481, suggesting mutations at this residue should not impact binding[2]



[1]Bond DA, Woyach JA. *Curr Hematol Malig Rep*. 2019;14(3):197–205. [2]Reiff SD, et al. *Cancer Discov*. 2018;8(10):1300–1315.

Nemtabrutinib

BELLWAVE-001

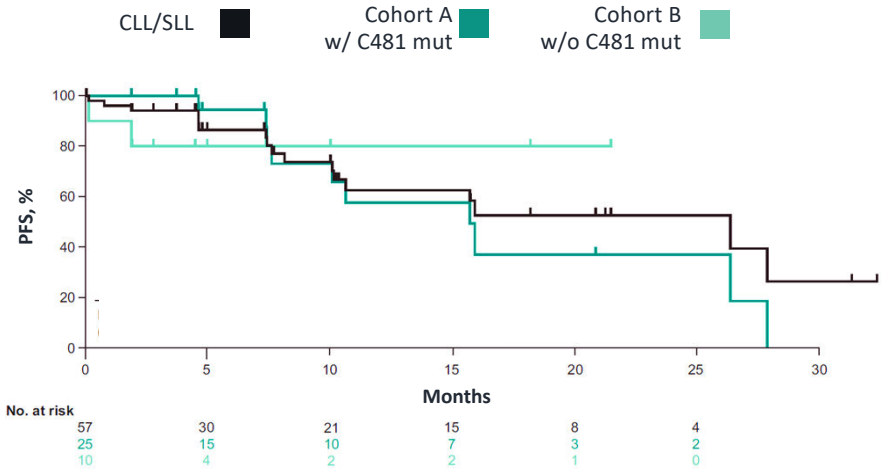
- Phase 1/2, open-label
- Cohort A
  - ≥2 prior therapies, including a covalent BTKi
  - With a C481 mutation
- Cohort B
  - ≥2 prior therapies, intolerant to a BTKi
  - Without a C481 mutation
- Among all patients with B-cell malignancies treated with twice daily 65 mg nemtabrutinib
- 73% had any-grade treatment-related AEs
  - Grade 3 or 4 AEs occurred in 45 patients (40%); 17% neutrophil count decreased
  - The most common AEs of special interest: hypertension (30%) and arthralgia (20%)

Characteristic, n (%)	CLL/SLL N=57
Age, median (range), years	66 (45–86)
Sex	
Male	41 (72)
Race	
White	49 (86)
Black	4 (7)
Other	4 (7)
ECOG PS	
0 or 1	50 (88)
2	6 (11)
Prior therapy, median (range)	4 (1–18)
Prior BTK inhibitor therapy	54 (95)
Prior BTK inhibitor therapy and BCL2 therapy	24 (42)
Mutations	
BTK^{C481S}	36 (63)
TP53	18 (32)
del(11q)	22 (39)
del(17p)	19 (33)
IGHV	3 (5)

Woyach JA, et al. *Blood*. 2022;140(Suppl 1):7004–7006. Woyach J, et al. 2023 European Hematology Association Congress. Abstract P628.

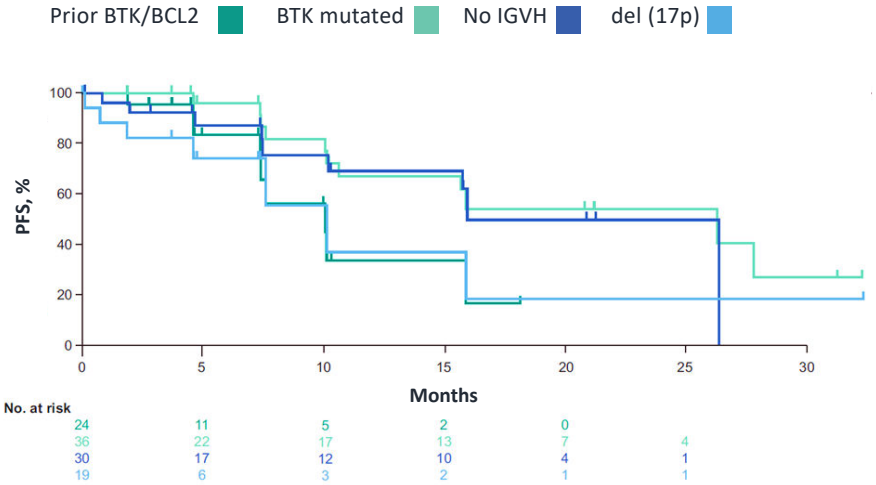
Nemtabrutinib
Progression-free Survival

Progression-free Survival (PFS)[a]



Responders	CLL/SLL N=32	Cohort A N=15	Cohort B N=4
Median PFS months (95% CI)	26.3 (10.1–NR)	15.7 (7.6–NR)	NR (0.1–NR)

PFS in Subgroups of Patients with CLL/SLL

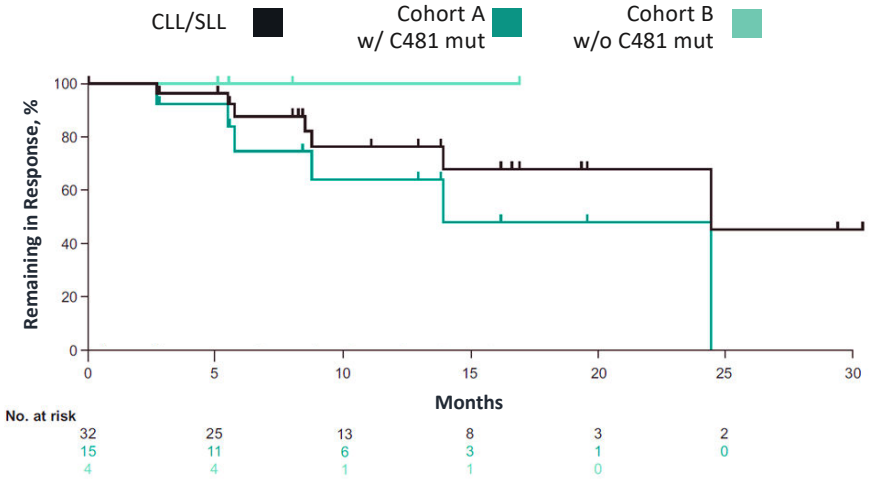


Responders	Prior BTK and BCL2 Inhibitor N=24	BTK-C481S Mutated N=36	No IGVH Mutation N=30	Del(17p) N=19
Median PFS months (95%CI)	10.1 (7.4–15.9)	26.3 (10.1–NR)	15.9 (7.4–NR)	10.1 (4.6–NR)

Woyach JA, et al. *Blood.* 2022;140(Suppl 1):7004–7006. Woyach J, et al. 2023 European Hematology Association Congress. Abstract P628.

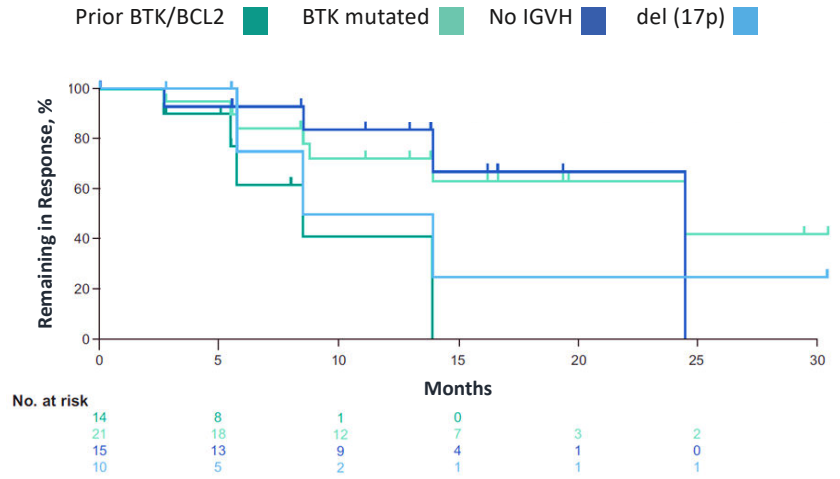
Nemtabrutinib
Duration of Response

Duration of Response (DOR)[a]



Responders	CLL/SLL N=32	Cohort A N=15	Cohort B N=4
Median DOR month (95%CI)	24.4 (13.9–NR)	13.9 (5.5–NR)	NR (NR–NR)

DOR in Subgroups of Patients with CLL/SLL



Responders	Prior BTK and BCL2 Inhibitor N=14	BTK-C481S Mutated N=21	No IGVH Mutation N=15	Del(17p) N=10
Median DOR months (95% CI)	26.3 (10.1–NR)	15.7 (7.6–NR)	NR (0.1–NR)	11.2 (5.7–NE)

Woyach JA, et al. *Blood.* 2022;140(Suppl 1):7004–7006. Woyach J, et al. 2023 European Hematology Association Congress. Abstract P628.

BTKi Therapy Sequencing

Covalent BTKi Resistance

Ibrutinib → Nemtabrutinib/pirtobrutinib

Acalabrutinib → Nemtabrutinib/pirtobrutinib

Zanubrutinib → Nemtabrutinib/pirtobrutinib (Non-L528W mutation ??)

Covalent BTKi Intolerance

Ibrutinib → Acalabrutinib or zanubrutinib or nemtabrutinib/pirtobrutinib

Acalabrutinib → Zanubrutinib or nemtabrutinib/pirtobrutinib

Zanubrutinib → Nemtabrutinib/pirtobrutinib

To Ask a Question

Please select the **Ask Question** tab.

If your question is for a specific faculty member, please include their name.

Summary

- Longer follow-up data confirm the utility of BTKi-based combination therapy for CLL
- Fixed-duration therapies are associated with lower toxicity and equivalent efficacy
- IGHV and TP53 mutation status and karyotype complexity have prognostic implications
- MRD-guided stop/start therapy in R/R CLL may reduce toxicity and discontinuation, while retaining OS
- Mutations arising after first-/second-generation BTKi may suggest most appropriate next-line therapy
- Noncovalent BTKis offer opportunity to circumvent resistance to first-/second-generation BTKis

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Clinicians should ensure that patients receive the minimal biomarker testing for *IGHV* and *TP53* mutations and del(17p) and discuss the prognostic implications of the results with their patients.
- Clinicians should recommend BTK inhibitor doublet therapy in all eligible patients.
- Clinicians should discuss with patients who achieve undetectable MRD after first-line treatment the benefits and risks of stopping therapy until such time that their disease progresses.
- Clinicians should encourage clinical trial participation, particularly for patients whose disease has progressed after BTK inhibitor therapy or are intolerant of BTK inhibitor therapy.

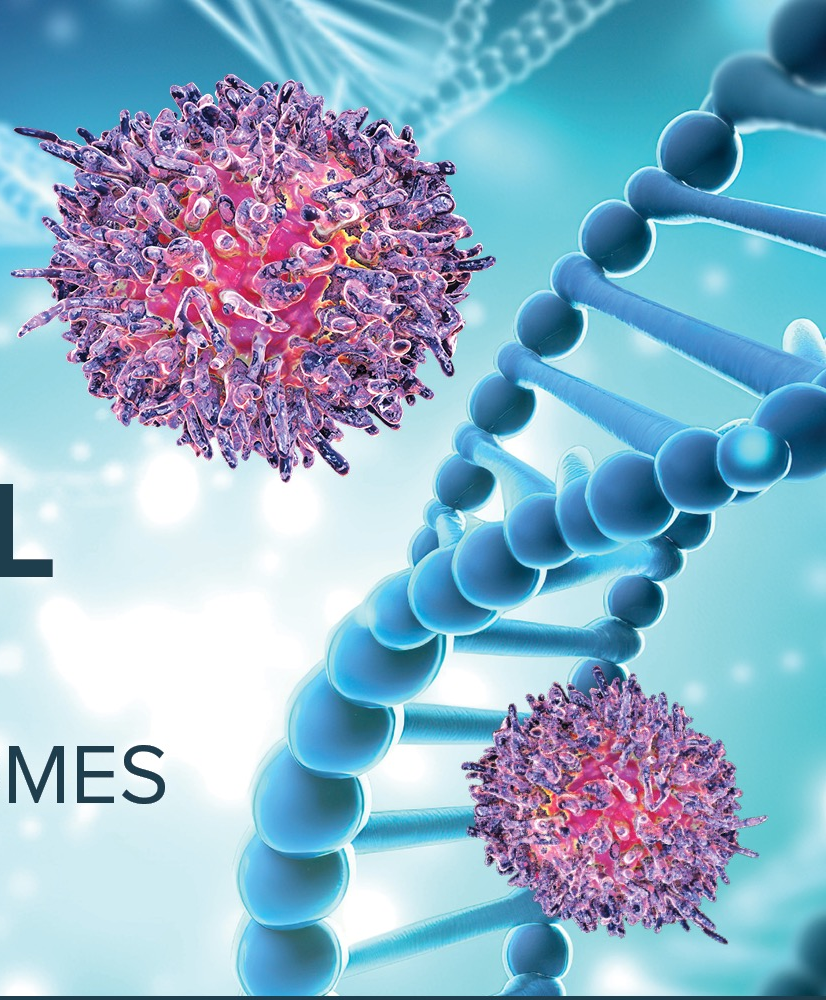
CME/CE Credit

To receive CME/CE credit for this activity, participants must **complete the post-test** and **evaluation** online.

Participants will be able to download and print their certificate immediately upon completion.

A Global Spotlight on CLL

SHIFTING STRATEGIES AND OPTIMIZING OUTCOMES



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