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Novel Targeted Therapeutics and Essential Strategies for Optimized Outcomes in Chronic Lymphocytic Leukemia

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Disclosures

- **Adam S. Kittai, MD, MBA:** Advisory Board Participation and Consulting—Abbvie, AstraZeneca, BMS, Eli Lilly, Galapagos; speaking engagements—AstraZeneca, BeOne, Eli Lilly, Janssen

Learning Objectives

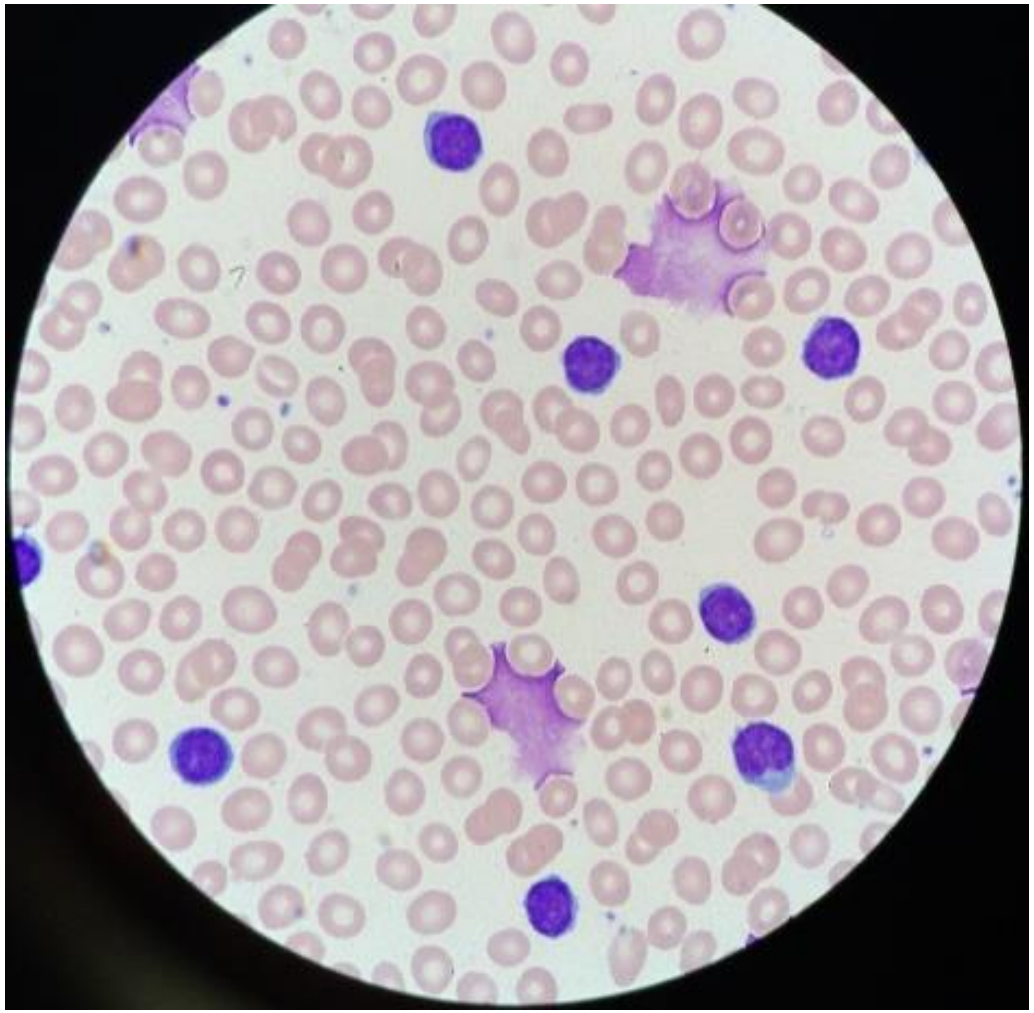
- Describe the most recent clinical data and real-world evidence associated with approved and emerging novel targeted therapies for CLL/SLL
- Evaluate tailored approaches to CLL management in the context of risk stratification, available treatment options, current recommended guidelines, and patient characteristics and preferences to optimize outcomes
- Summarize the importance of MRD evaluation and molecular profiling for treatment selection and sequencing in CLL/SLL

CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; MRD = measurable/minimal residual disease.

CLL/SLL Overview

CLL Diagnostic Criteria

- Dx requires
  - ≥5000 clonal lymphocytes
  - Persistent for >3 months
- Immunophenotype
  - CD19, CD20, CD23 with CD5
  - Low/dim CD20, CD79b
- Differential: MCL
  - Check for t(11;14)



Dx = diagnosis; MCL = mantle cell lymphoma.
Hallek M, et al. *Blood*. 2018;131(25):2745-2760.

Initial Prognostic Testing

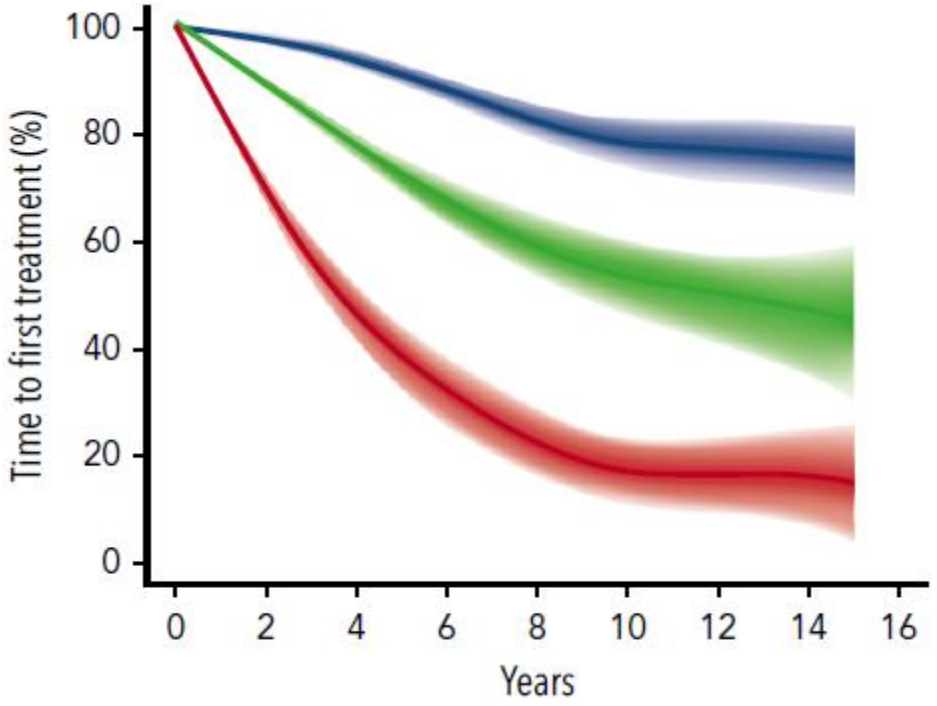
- IGHV status
  - Unmutated—intermediate
- FISH
  - Del13q—good!
  - Del11q—used to be bad, not so much anymore
  - Trisomy 12
  - Del17p—still bad
- Karyotype testing
  - Must be stimulated
  - >3 abnormalities (but really >/= 5)—bad
- NGS—*TP53* mutation

FISH = fluorescence in situ hybridization; NGS = next-generation sequencing.

Time to First Treatment

1 point for each

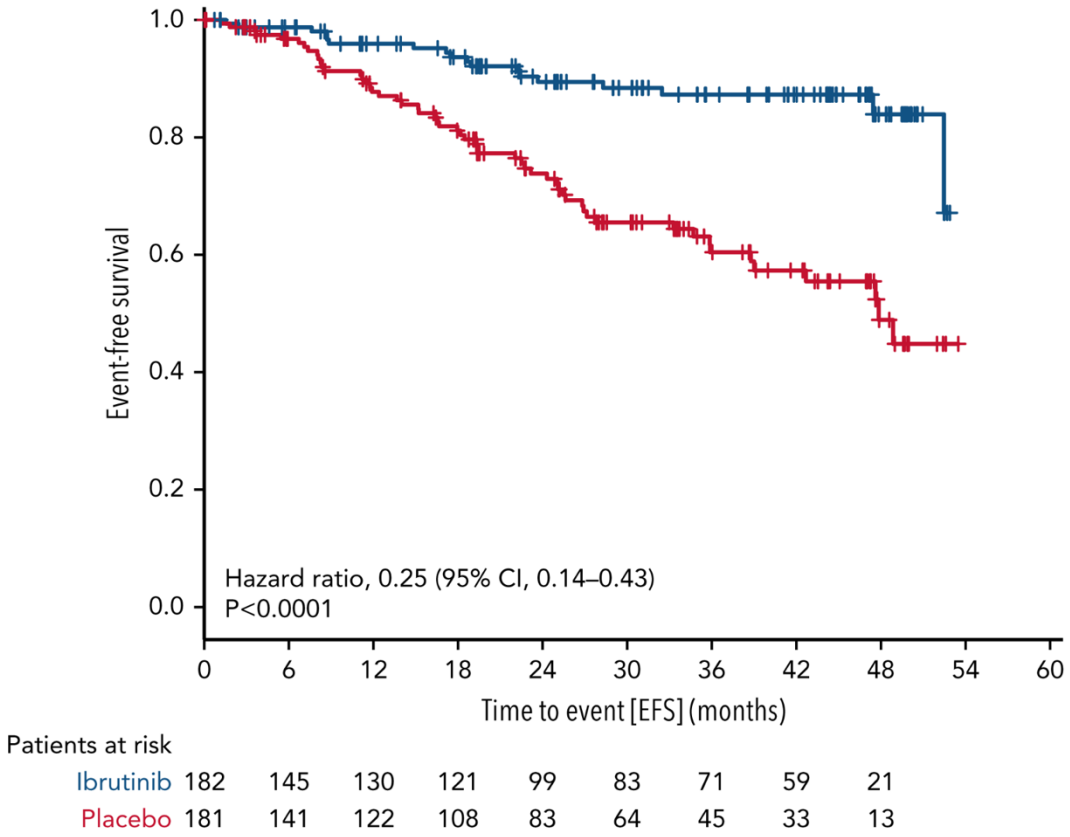
- Unmutated IGHV
- Absolute lymphocyte count >15,000
- Palpable lymph nodes

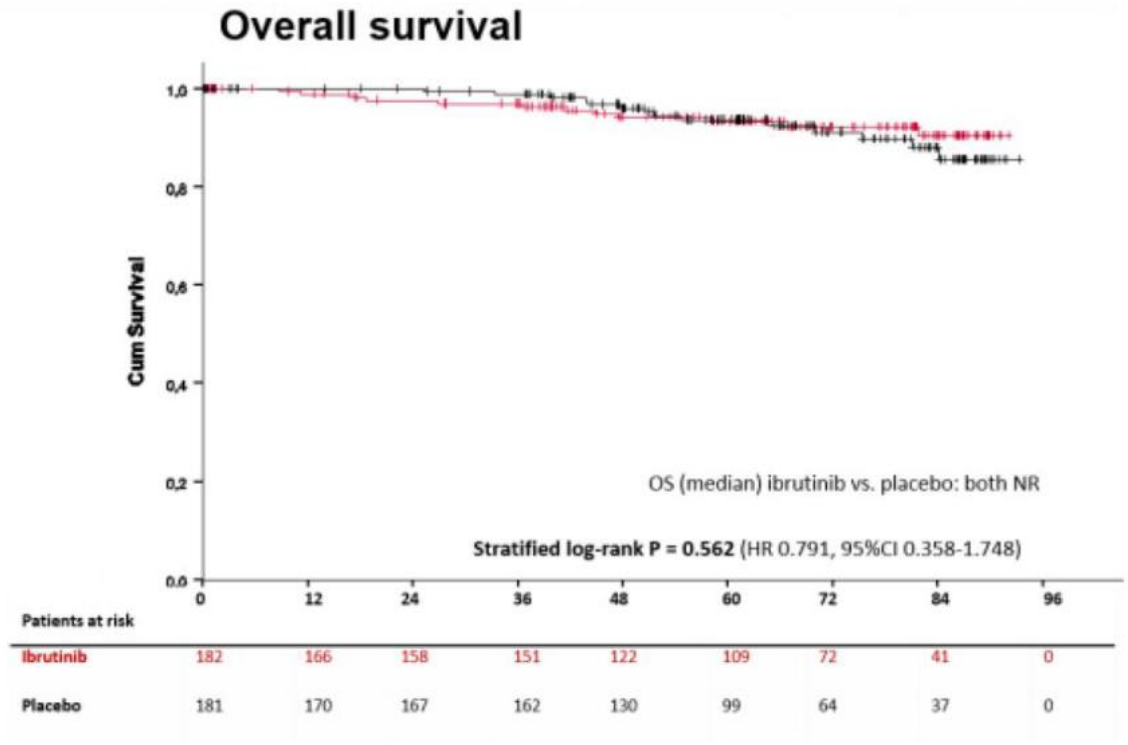


Risk group	Score
Low risk	0
Intermediate risk	1
High risk	2-3

Condoluci A, et al. *Blood*. 2020;135(21):1859-1869.

Watch and Wait: Ibrutinib vs Placebo



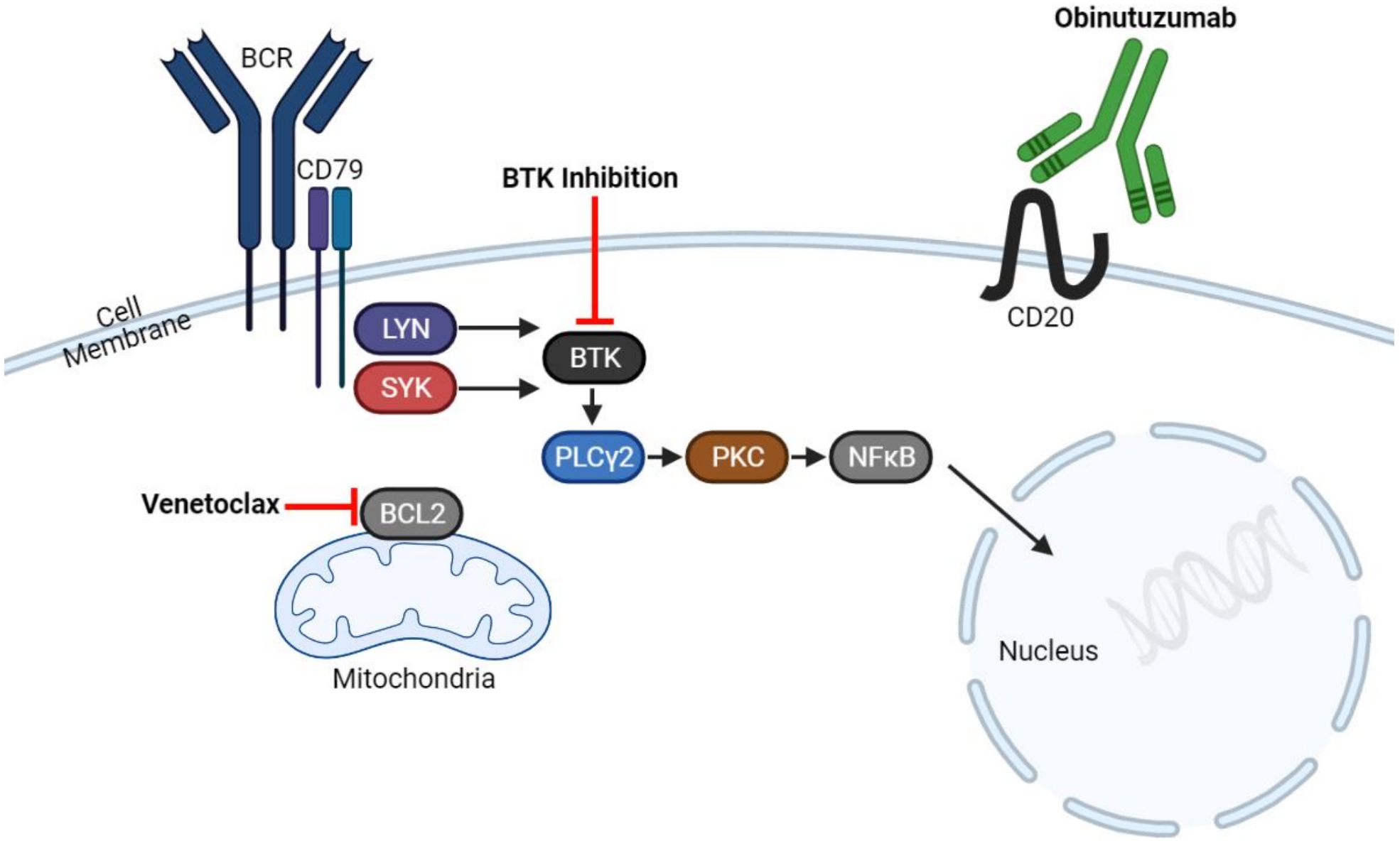


Langerbeins P, et al. *Blood*. 2022;139(2):177-187. Langerbeins P, et al. *Hematol Oncol*. 2023;41(52 Suppl):56-58.

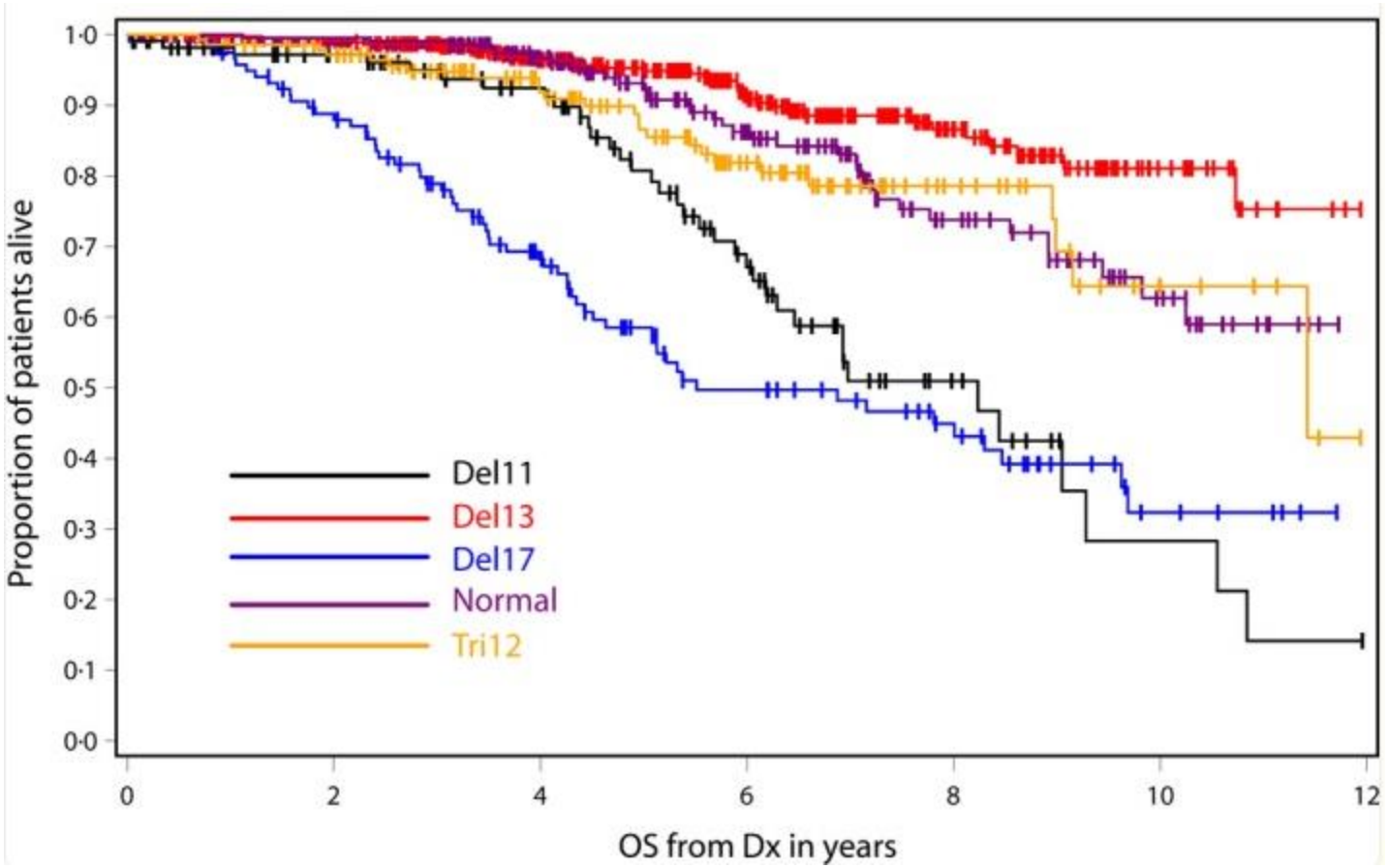
Key Learning Points

- Test prognostic factors at diagnosis and at first treatment
- Time to first treatment is measured in **many** years
- Watch and wait still the standard for CLL

Current National Comprehensive Cancer Network® (NCCN®) Preferred CLL/SLL Targeted Treatments


Obinutuzumab
BCR
CD79
BTK Inhibition
Cell Membrane
CD20
LYN
SYK
BTK
PLCγ2
PKC
NFκB
Venetoclax
BCL2
Mitochondria
Nucleus

Poor Outcomes with Del17p/*TP53* and Chemotherapy



OS = overall survival.
Van Dyke DL, et al. *Br J Haematol*. 2016;173(1):105-113.

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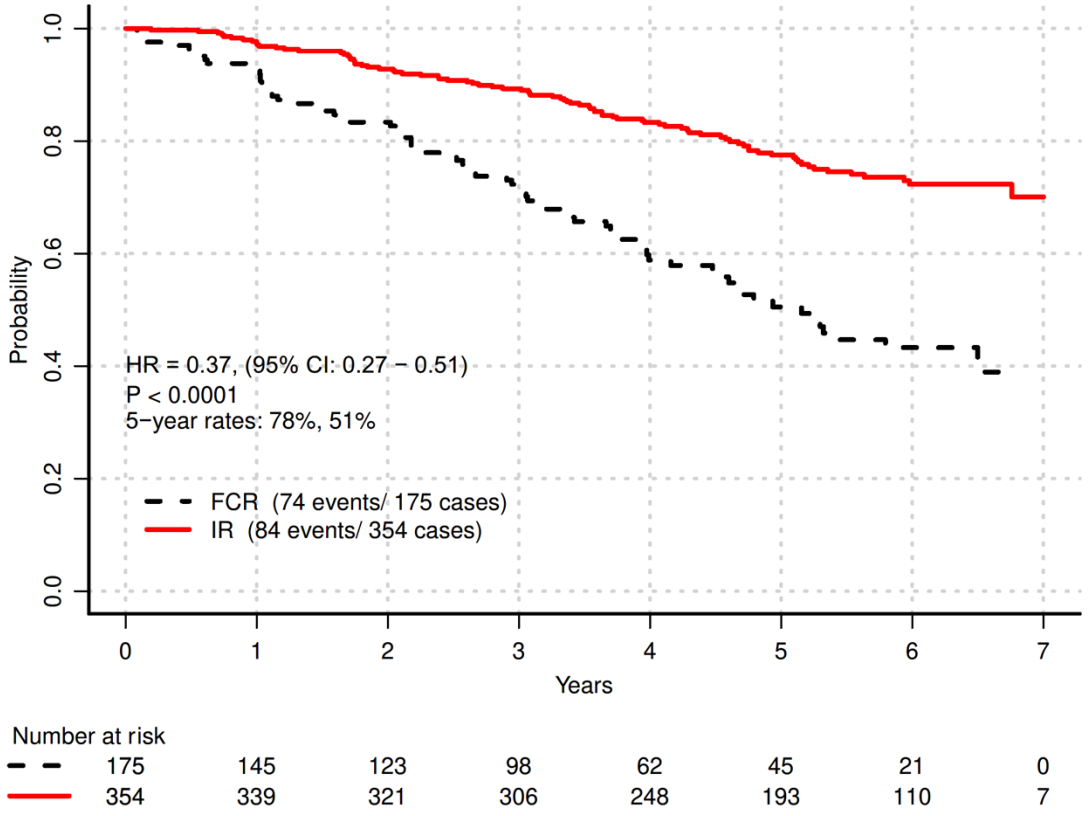
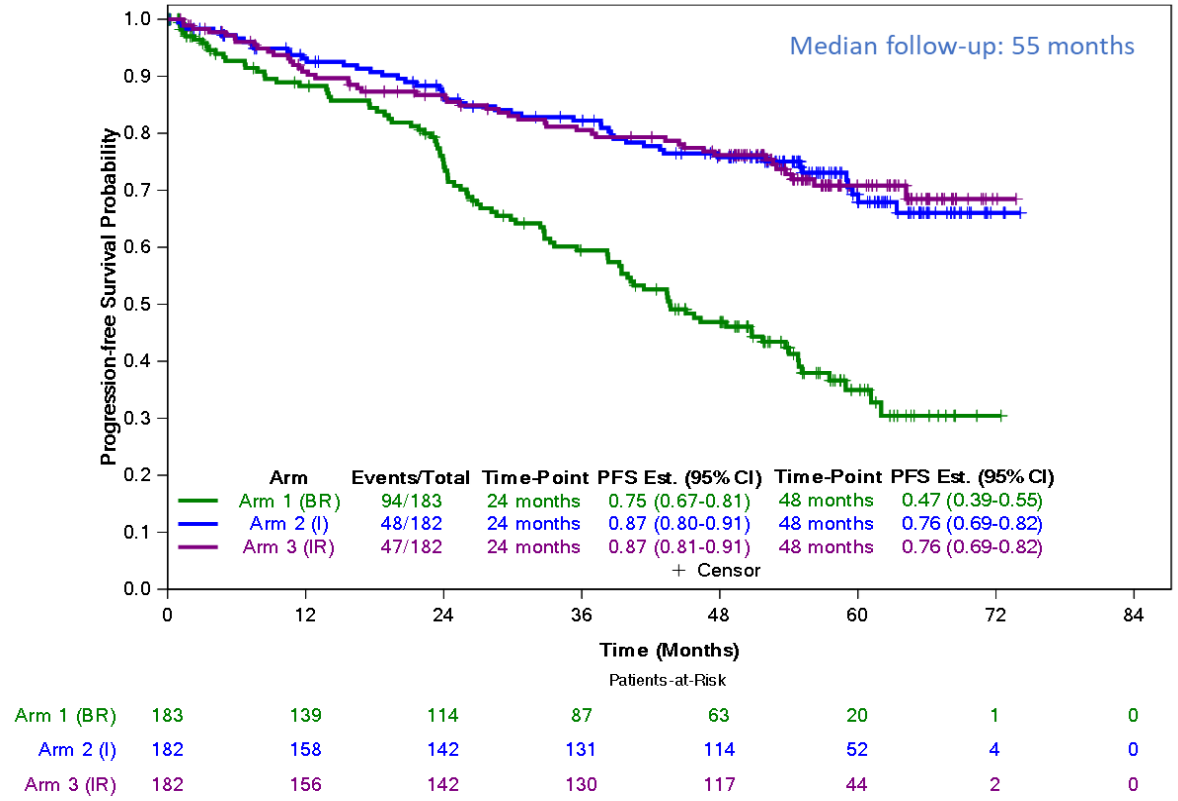
Avoiding Chemoimmunotherapy

EA9161 Progression-Free Survival

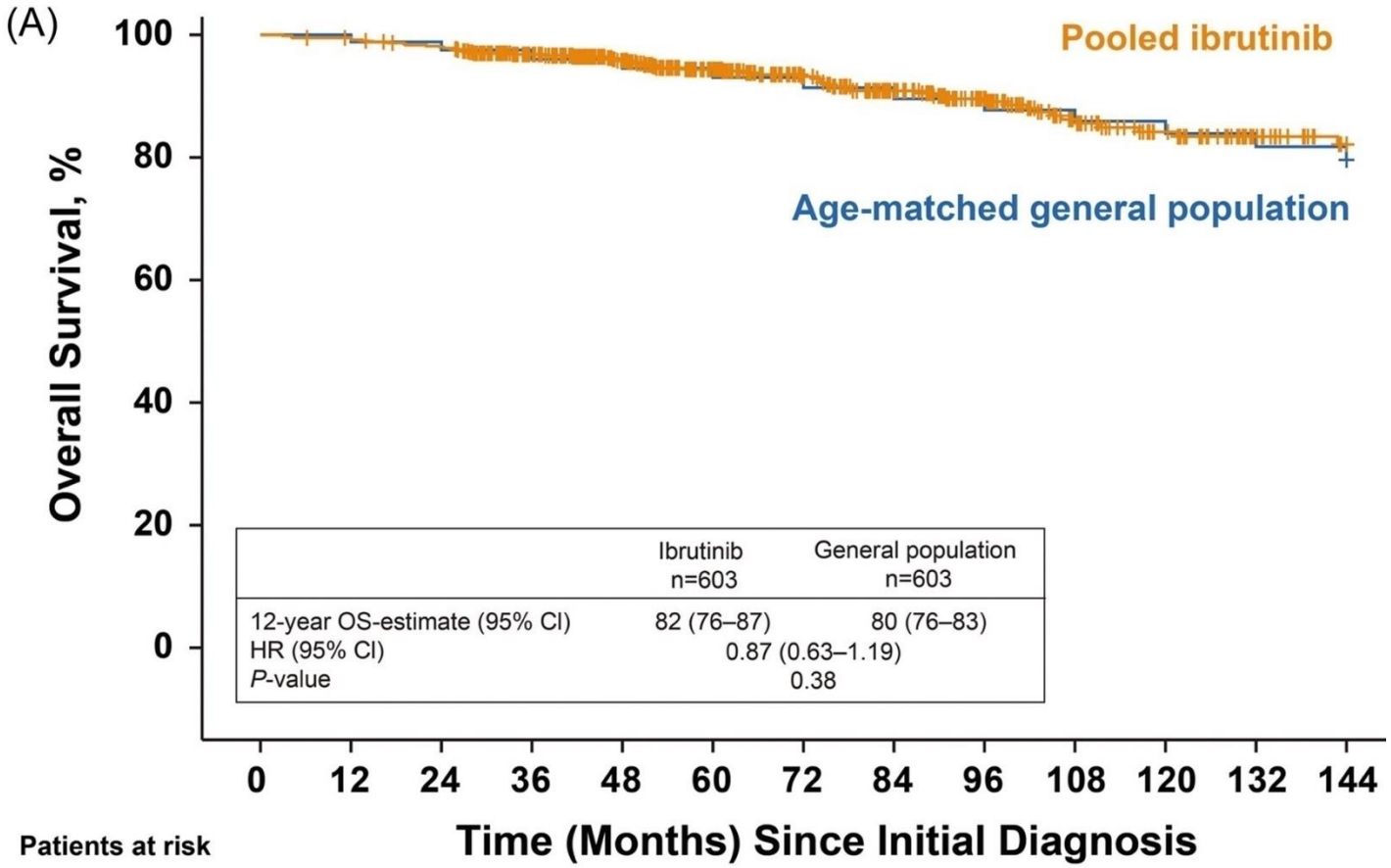


A041202 Progression-Free Survival



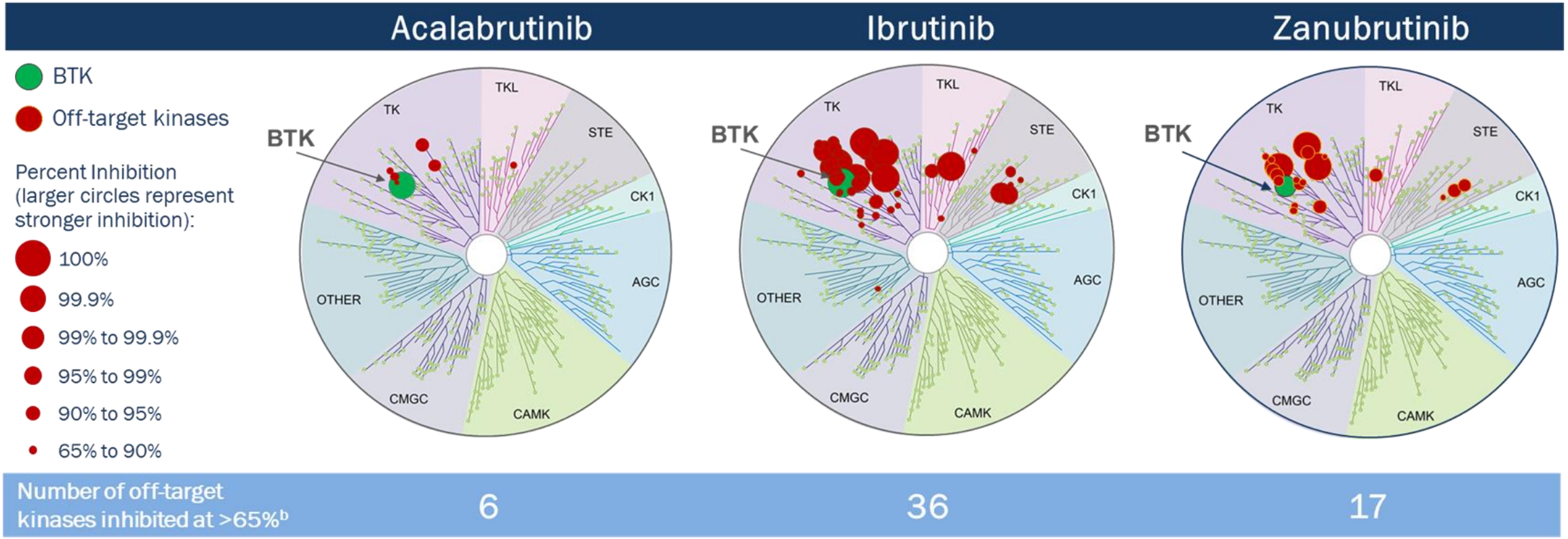
FCR = fludarabine, cyclophosphamide, rituximab; IR = ibrutinib, rituximab; PFS = progression-free survival.
Shanafelt TD, et al. *Blood*. 2022;140(2):112-120. Woyach J, et al. *Blood*. 2024;143(16):1616-1627.

Patients Living as Long as Age-Matched Controls



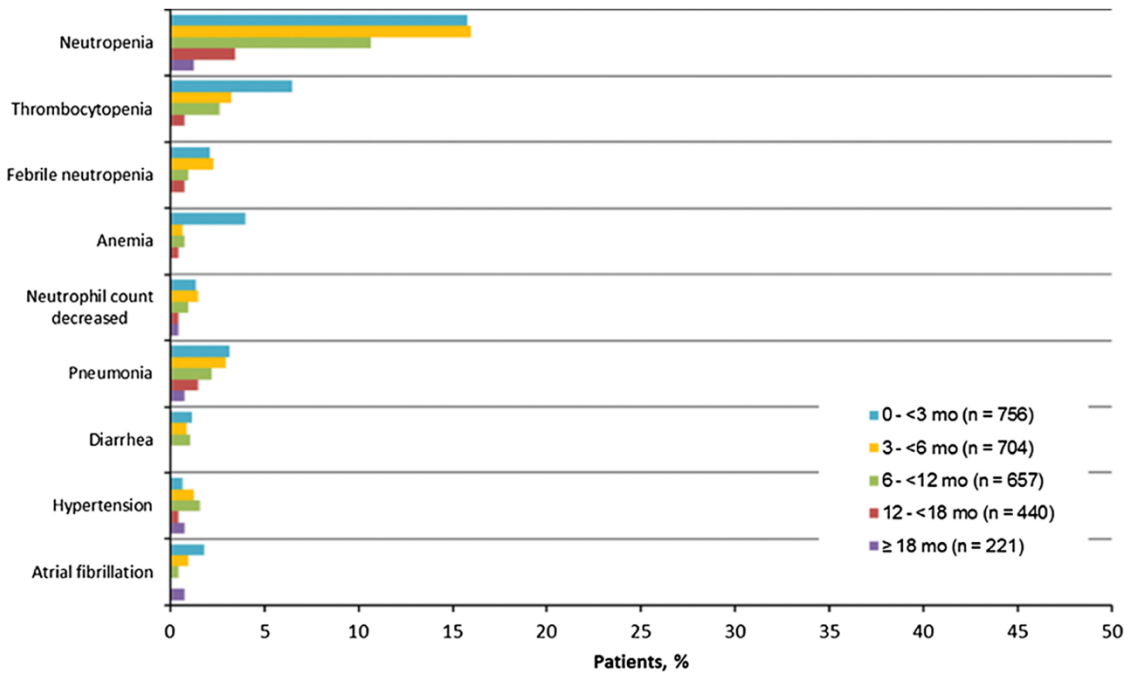
Ghia P, et al. *Hemasphere*. 2024;8(5):e74.

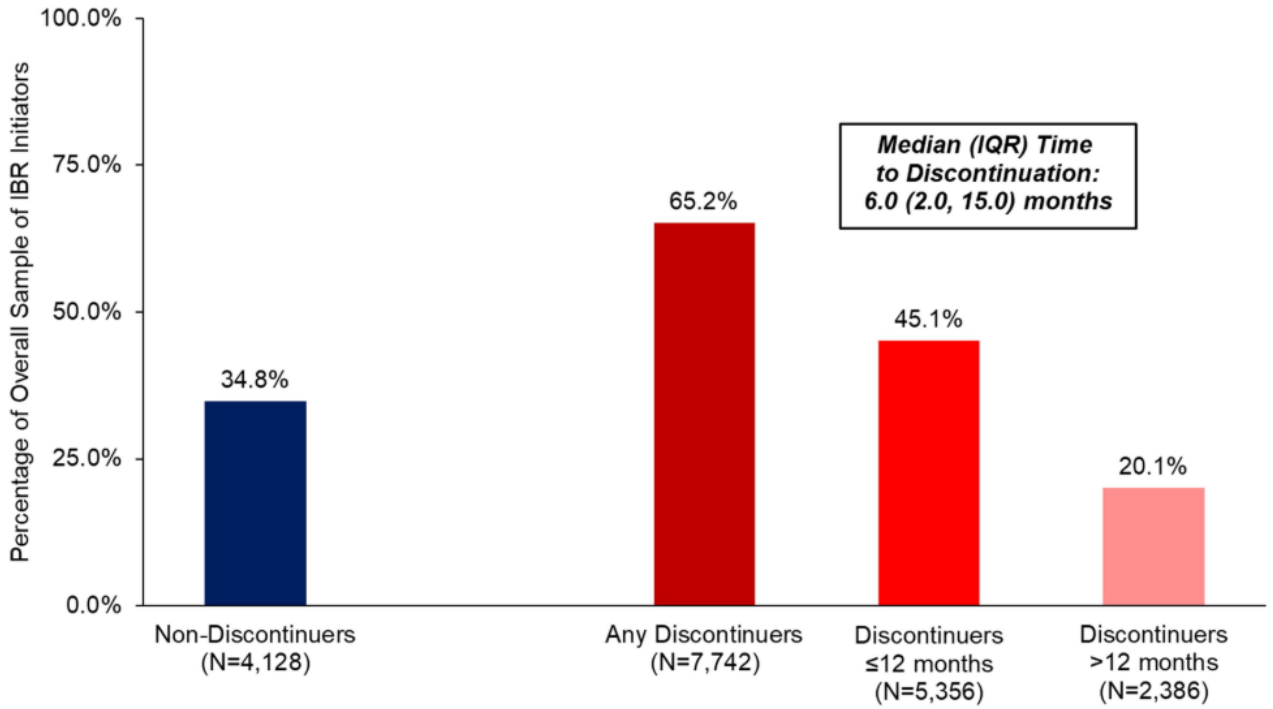
BTK Inhibitor Evolution



Estupiñán HY, et al. *Front Cell Dev Biol*. 2021;9:630942. Liu L, et al. Future Med Chem. 2018;10(3):343-356. Bond DA, Woyach JA. *Curr Hematol Malig Rep*. 2019;14(3):197-205. Byrd JC, et al. *N Engl J Med*. 2016;374(4):323-332. Tam CS, et al. *Future Oncol*. 2018;14(22):2229-2237.

Ibrutinib Adverse Events/Discontinuations over Time

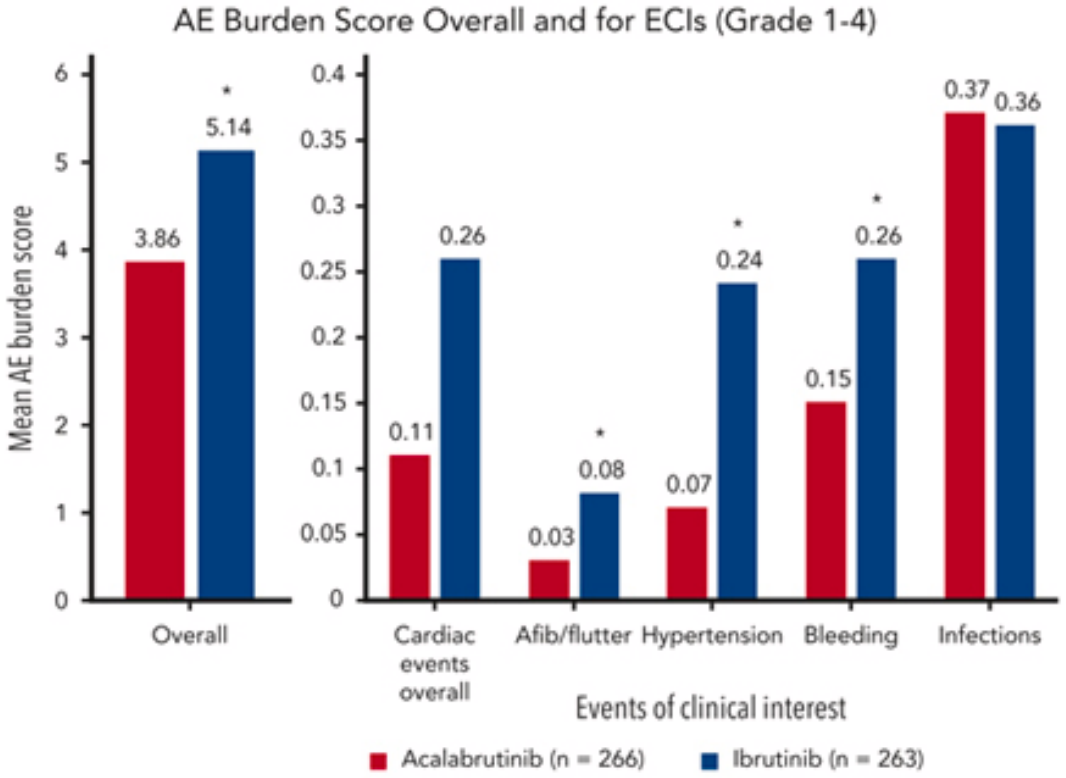




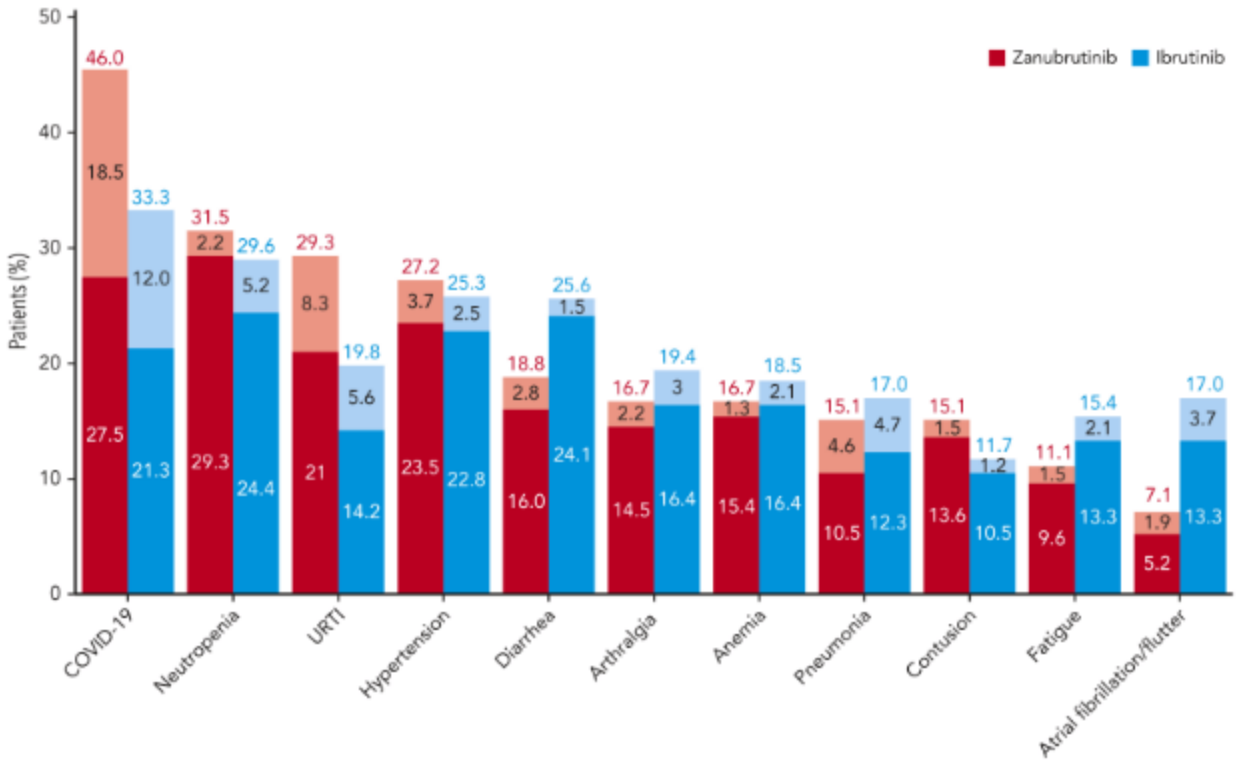
IQR = interquartile range.

O'Brien S, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(10):648-657. Huntington SF, et al. *Leuk Lymphoma*. 2023;64(14):2286-2295.

Ibrutinib vs Second-Generation BTKi

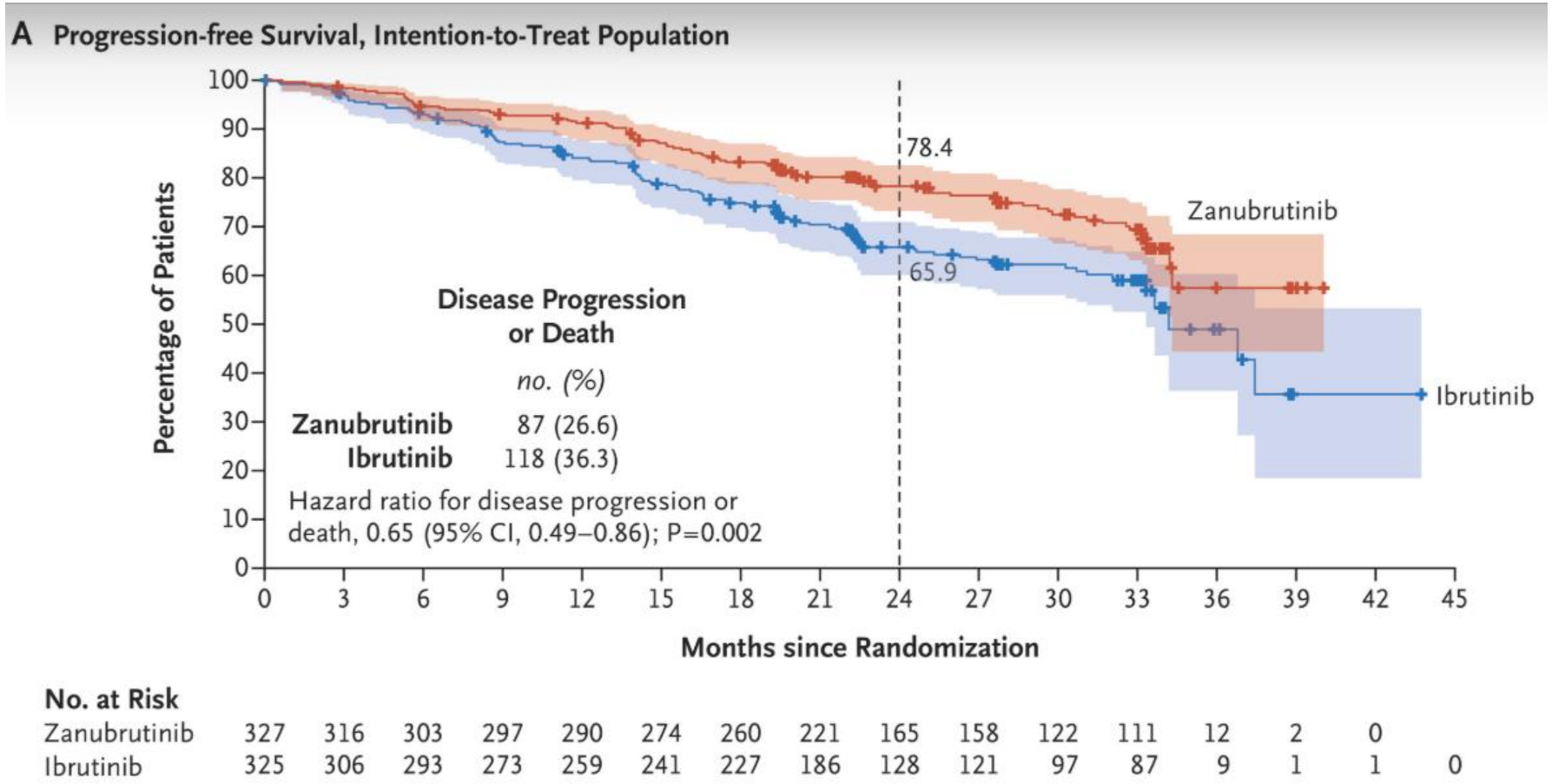


*Two-sided *P*-value < .05 without multiplicity adjustment based on Wilcoxon rank-sum test.
P-value compares difference in overall distribution rather than mean score.



BTKi = BTK inhibitor; AE = adverse event; ECI = event of clinical interest.
Seymour JF, et al. *Blood*. 2023;142(8):687-699. Brown JR, et al. *Blood*. 2024;144(26):2706-2717.

Zanubrutinib Improved PFS vs Ibrutinib in RR CLL



RR = relapsed/refractory.
Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

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

FIRST-LINE THERAPY[e]

Preferred Regimens

- BCL2i-containing regimens
  - Venetoclax[f,h] + obinutuzumab (category 1)
  - Venetoclax[f,h] + acalabrutinib ± obinutuzumab (category 1)
- cBTKi-based regimens
  - Acalabrutinib[f,g] ± obinutuzumab (category 1)
  - Zanubrutinib[f,g] (category 1)

Other Recommended Regimens

- BCL2i-containing regimen
  - Venetoclax[f,h] + ibrutinib[f,g]
- cBTKi-based regimen
  - Ibrutinib[f,g,i] (category 1)

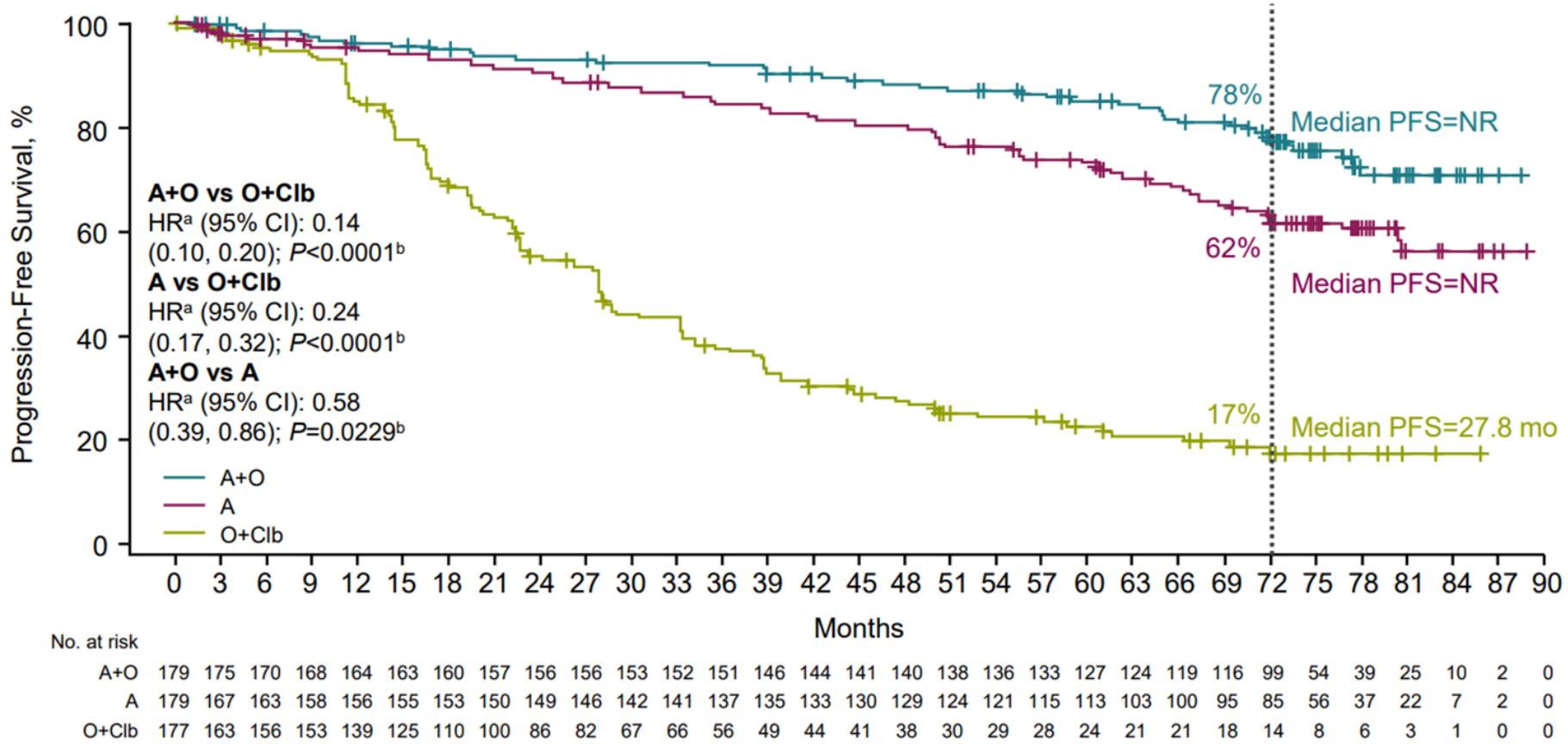
Useful in Certain Circumstances

- Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities
  - FCR (fludarabine, cyclophosphamide, rituximab)[j,k]
- cBTKi-based regimen
  - Ibrutinib[f,g] + anti-CD20 mAb (category 2B)[l]
- Consider when cBTKi and BCL2i are not available or contraindicated or rapid disease debulking needed
  - Bendamustine[m] + anti-CD20 mAb[l,n]
  - Obinutuzumab ± chlorambucil[o]
  - High-dose methylprednisolone (HDMP) + anti-CD20 mAb[l] (category 2B; category 3 for patients <65 y without significant comorbidities)

[a] See references for regimens on CSLL-D 5 of 6 and CSLL-D 6 of 6.
[b] Supportive Care for Patients with CLL/SLL (CSLL-C).
[c] Rituximab and hyaluronidase human injection for subcutaneous use may be used in patients who have received at least one full dose of a rituximab product by intravenous route.
[d] Re-challenge with the same mAb is not recommended in patients experiencing rare complications (eg, mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis). It is unclear whether re-challenge with alternative anti-CD20 mAbs poses the same risk of recurrence.

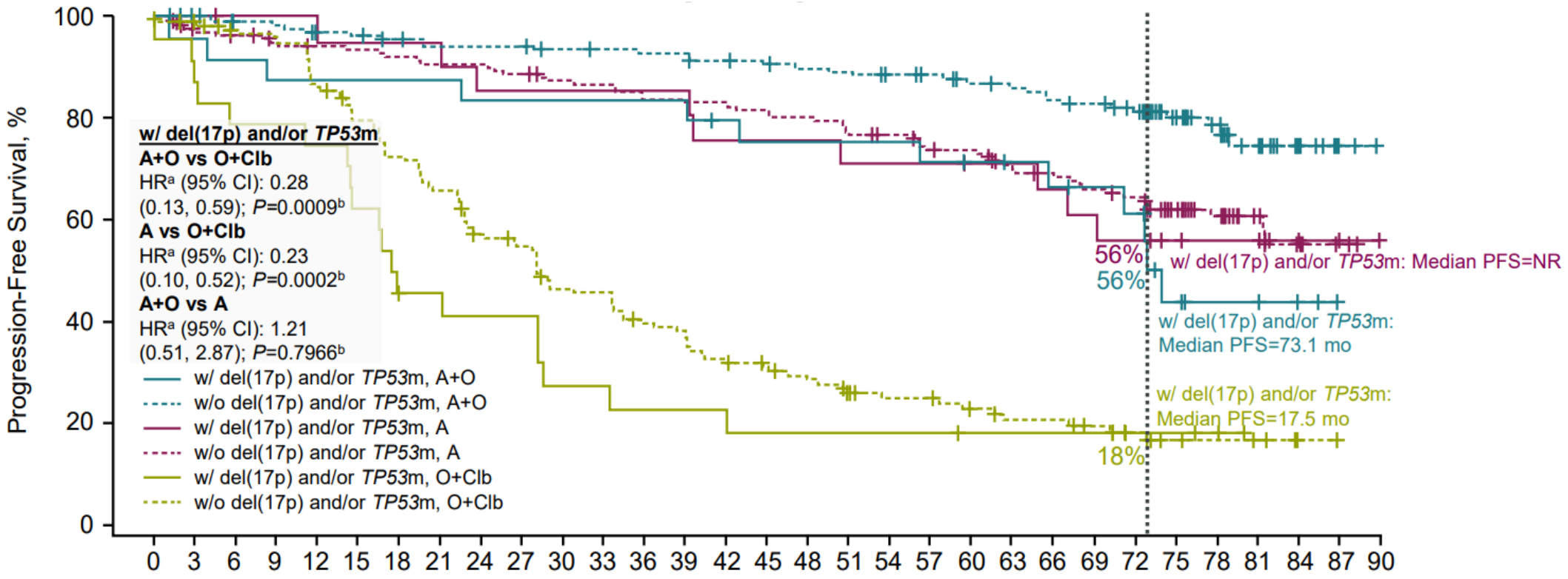
cBTKi = covalent BTKi.

Acalabrutinib—ELEVATE-TN



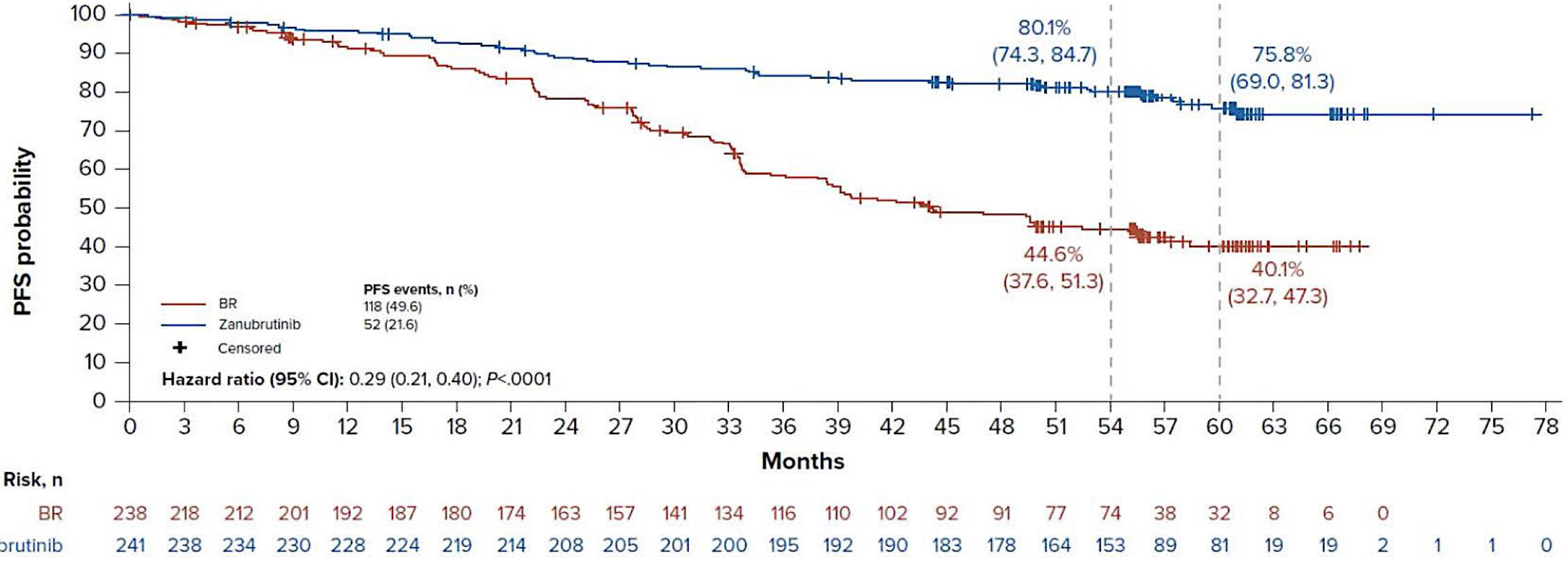
A = acalabrutinib; O = obinutuzumab; Clb = chlorambucil.
Sharman JP, et al. *Blood*. 2023;142(suppl 1):636.

Acalabrutinib—ELEVATE-TN—Stratified by TP53



Sharman JP, et al. *Blood*. 2023;142(suppl 1):636.

5-Year Follow-Up SEQUOIA—Zanu vs BR



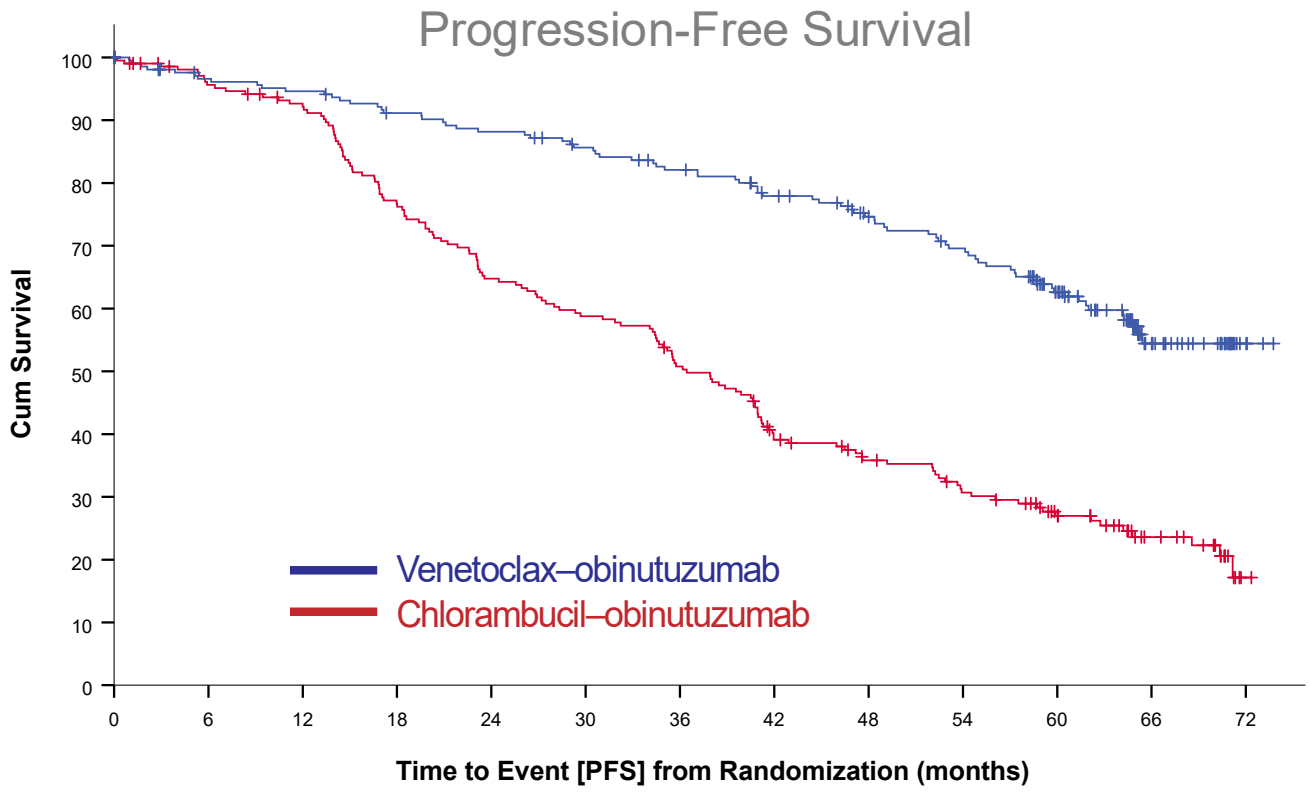
No. at Risk, n

BR	238	218	212	201	192	187	180	174	163	157	141	134	116	110	102	92	91	77	74	38	32	8	6	0			
Zanubrutinib	241	238	234	230	228	224	219	214	208	205	201	200	195	192	190	183	178	164	153	89	81	19	19	2	1	1	0

BR = bendamustine, rituximab.

Shadman M, et al. *Blood*. 2024;144(Suppl 1):3249. Shadman M, et al. *J Clin Oncol*. 2024;43(7):780-787.

Venetoclax + Obinutuzumab—CLL14



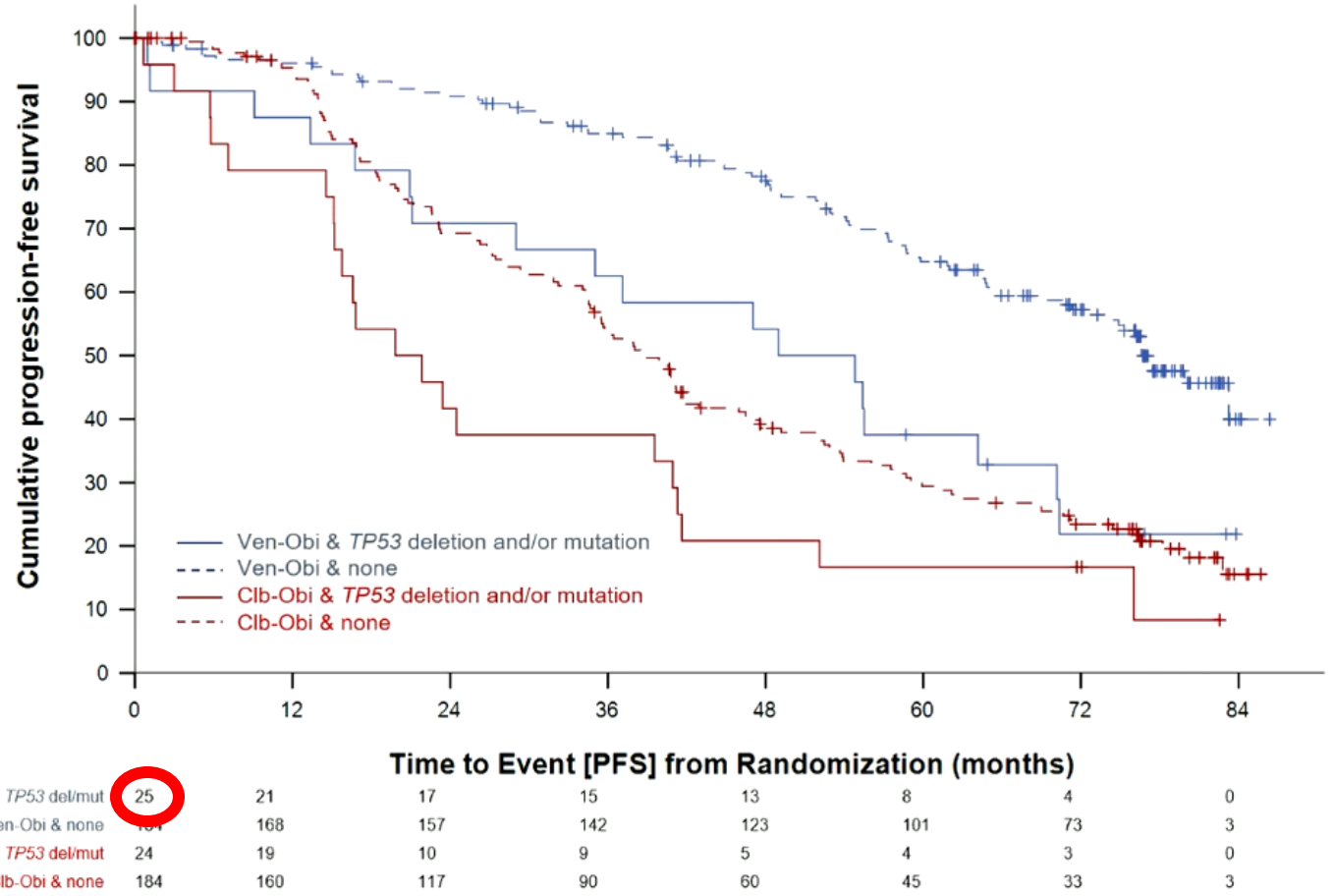
Median observation time 65.4 months

Recent Update

- 6-year follow-up—OS data
- Ven + obin—78.7%
- Chlor + obin—69.2%
- HR—0.69, *P*=0.052

Al-Sawaf O, et al. *HemaSphere*. 2022;6(Suppl 3):49-50.

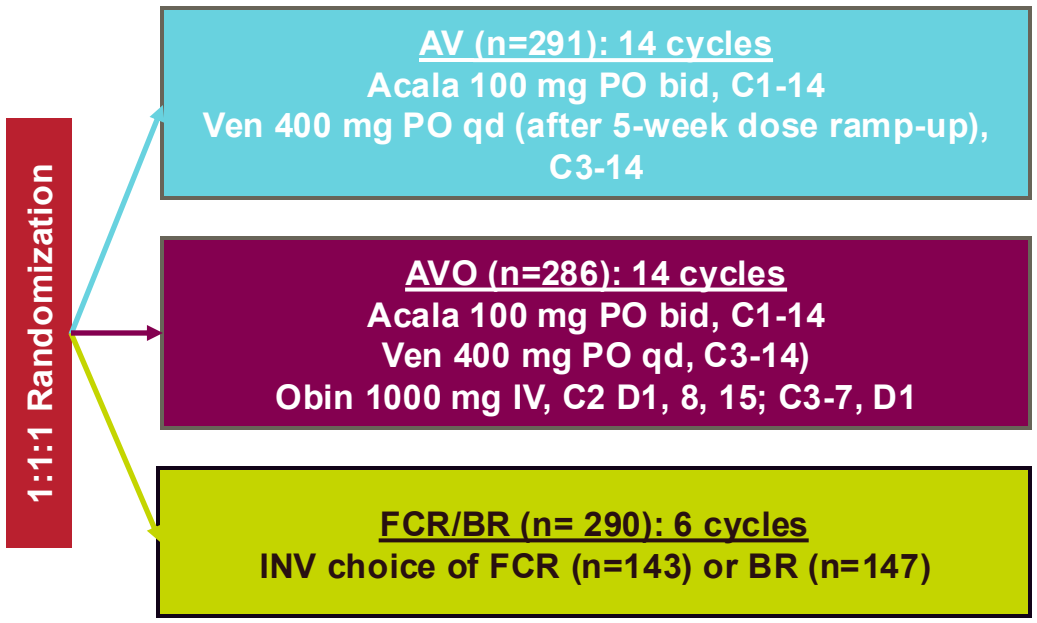
Venetoclax + Obinutuzumab—*TP53* Data



Ven-Obi & *TP53* del/mut	25	21	17	15	13	8	4	0
Ven-Obi & none	184	168	157	142	123	101	73	3
Clb-Obi & *TP53* del/mut	24	19	10	9	5	4	3	0
Clb-Obi & none	184	160	117	90	60	45	33	3

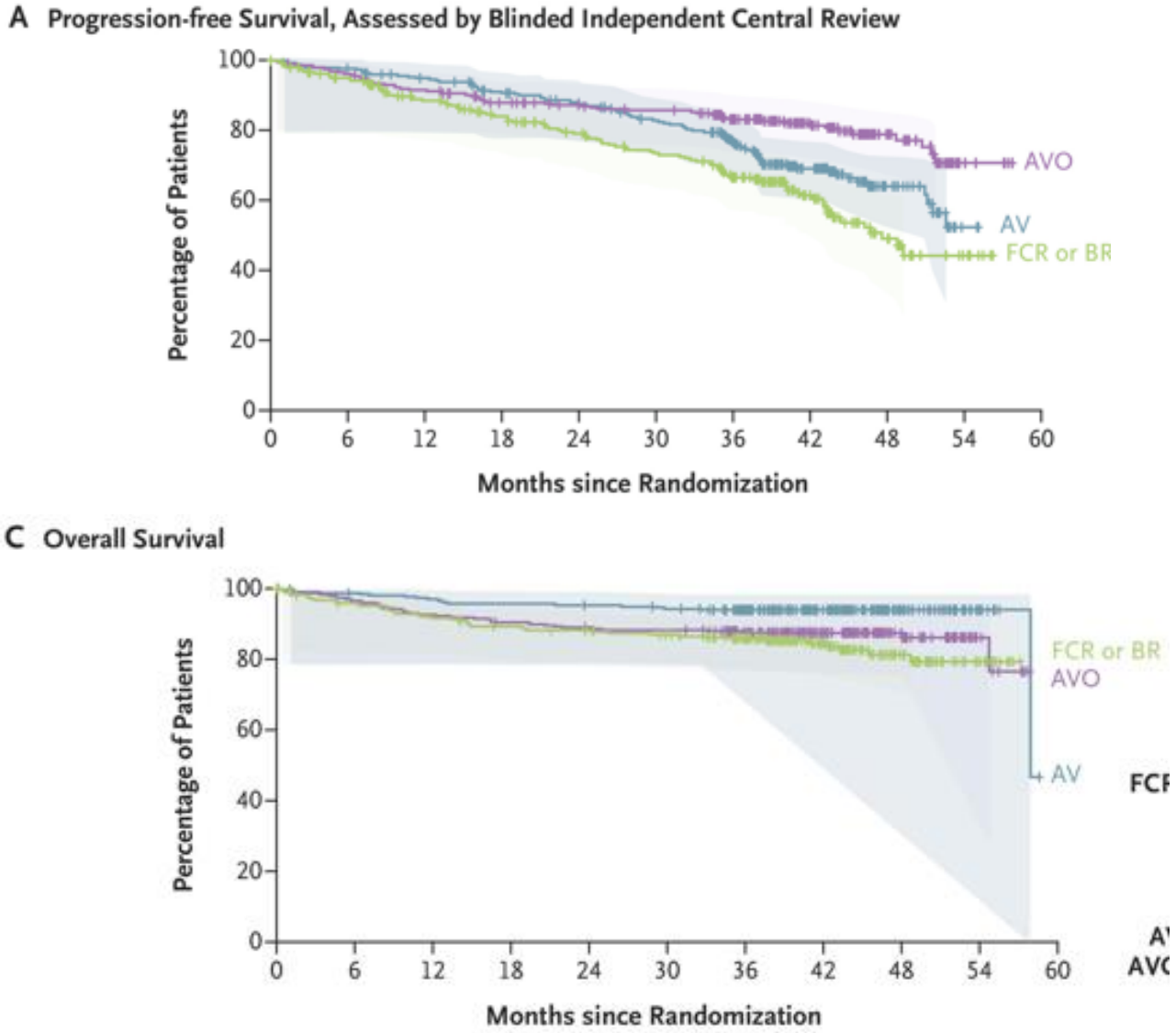
Al-Sawaf O, et al. *HemaSphere*. 2023;7(Suppl 3):2023.

AMPLIFY Study—Acal + Ven +/- Obin vs Chemoimmunotherapy



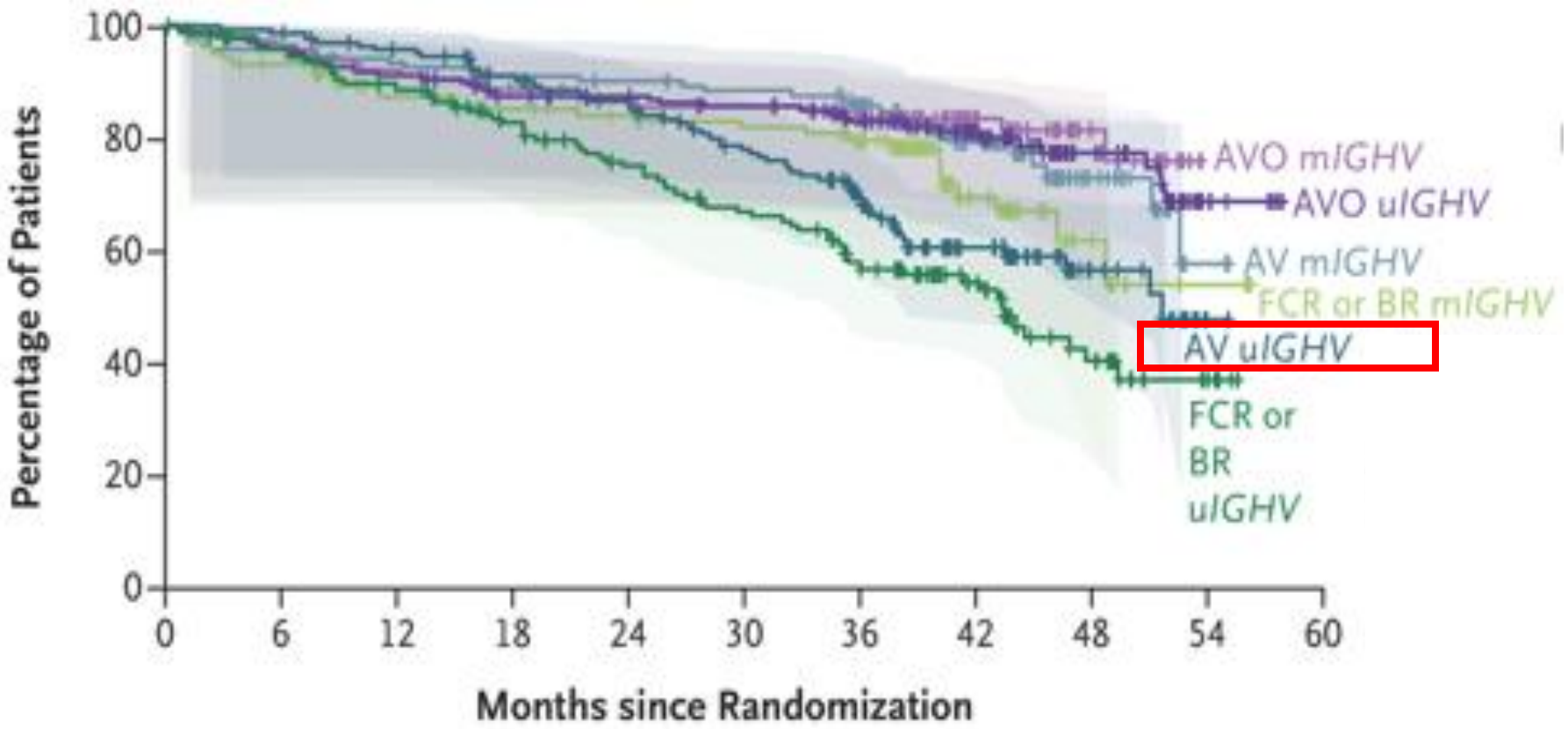
Patient Characteristics (ITT)	AV (n=291)	AVO (n=286)	FCR/BR (n=290)
Median age (range), years	61 (31-84)	61 (29-81)	61 (26-86)
Rai stage III-IV, n (%)	137 (47.1)	116 (40.6)	127 (43.8)
del(11q), n (%)	51 (17.5)	56 (19.6)	46 (15.9)
Unmutated *IGHV*, n (%)	167 (57.4)	169 (59.1)	172 (59.3)
Complex karyotype (≥3 aberrations), n (%)	45 (15.5)	46 (16.1)	42 (14.5)

C = cycle; D = day; INV = investigator; ITT = intent-to-treat.
Brown JR, et al. *N Engl J Med*. 2025;392(8):748-762.



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

AMPLIFY—By IGHV Status

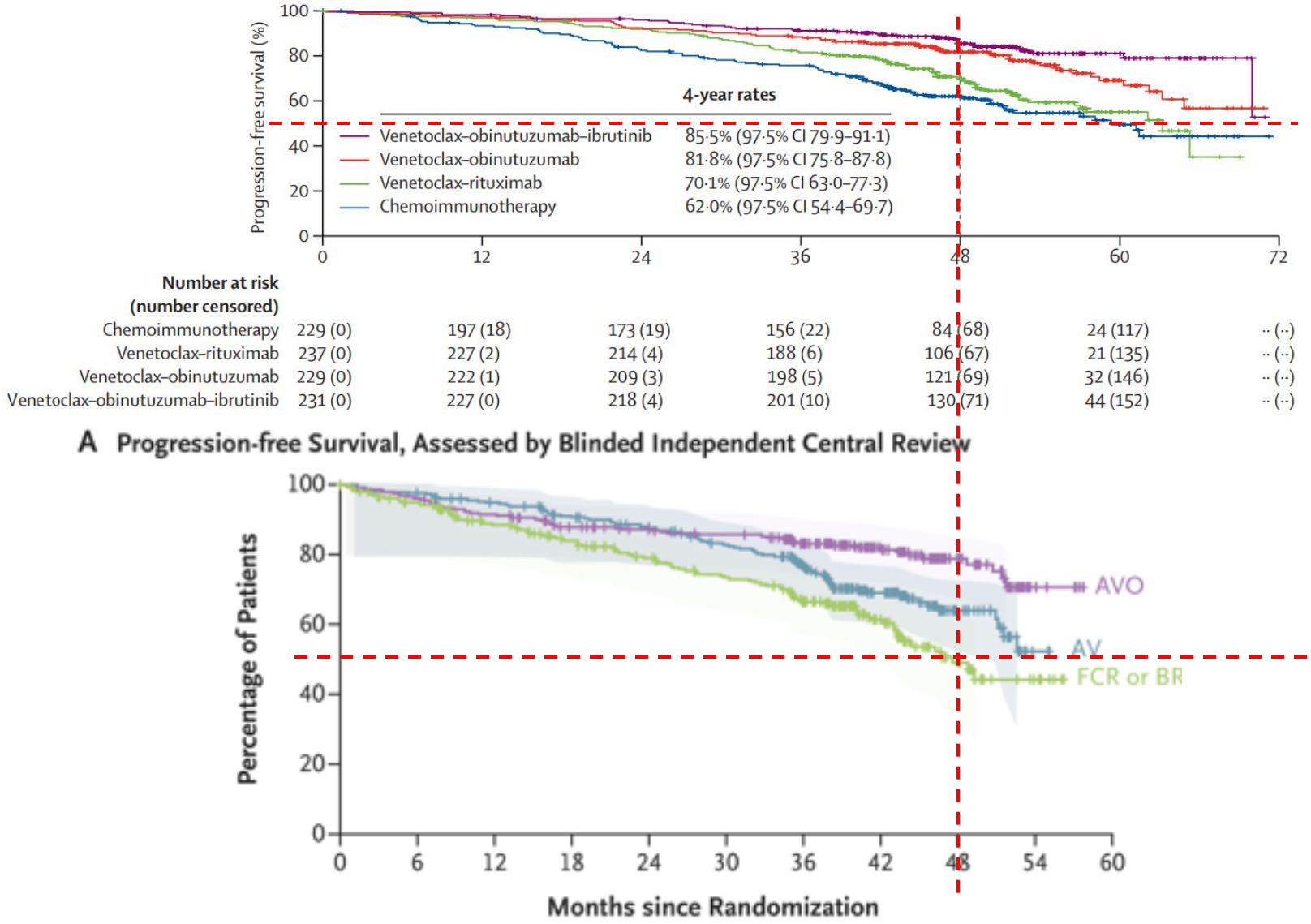


Brown JR, et al. *N Engl J Med*. 2025;392(8):748-762.

Selected AEs

Toxicities	AV (n=291)	AVO (n=286)	FCR/BR (n=290)
Grade >/= 3	156 (53.6)	197 (69.4)	157 (60.7)
AE leading to discontinuation	23 (7.9)	57 (20.1)	28 (10.8)
Afib or flutter (any grade)	2(0.7)	3 (1.1)	0
Hemorrhage (any)	94 (32.3)	86 (30.3)	11 (2.2)
Hemorrhage (major)	3 (1.0)	8 (2.8)	2 (0.8)
Neutropenia (any)	108 (37.1)	143 (50.4)	132 (51.0)
Infection (grade >/=3)	36 (12.4)	67 (23.6)	26 (10)
TLS (any)	1 (0.3)	1 (0.4)	8 (3.1)

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



48 months PFS

IVO—85%

VO—81.8%

AVO— ~80%

AV— ~65

48 months PFS—chemo

CLL13—62%

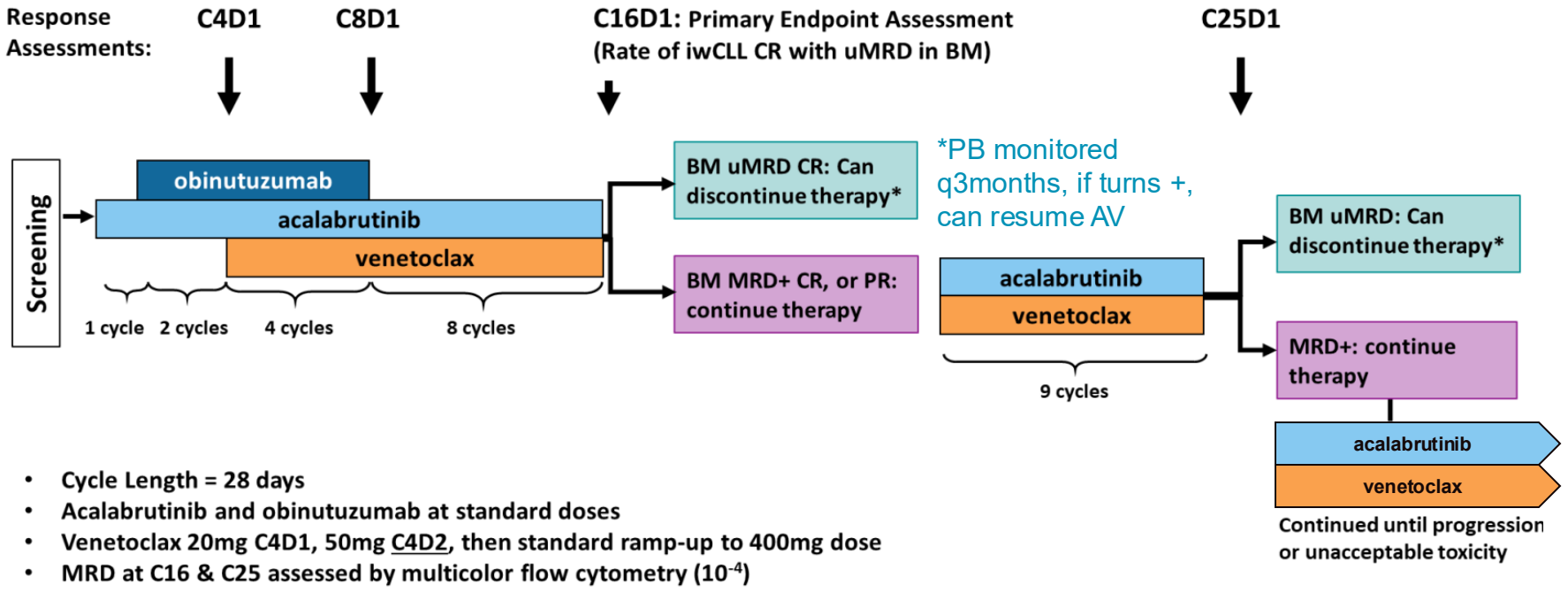
Amplify—50%

Brown JR, et al. *N Engl J Med*. 2025;392(8):748-762. Fürstenau M, et al. *Lancet Oncol*. 2024;25(6):744-759.

AVO in High-Risk Patients

Key Eligibility Criteria

- Aged ≥18 years and ECOG PS ≤2
- Expansion cohort: *TP53*-aberrant disease (del[17p] or *TP53*mut [any VAF eligible])
- No Richter transformation or CNS involvement

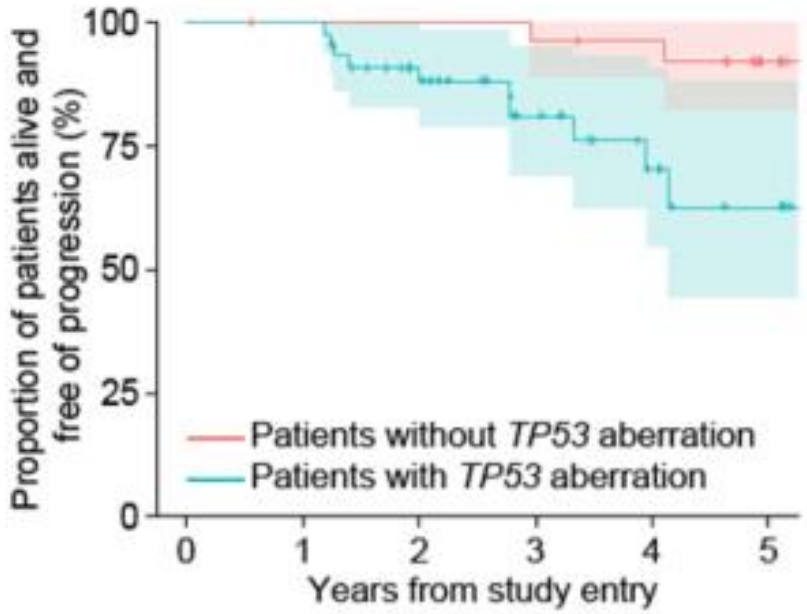


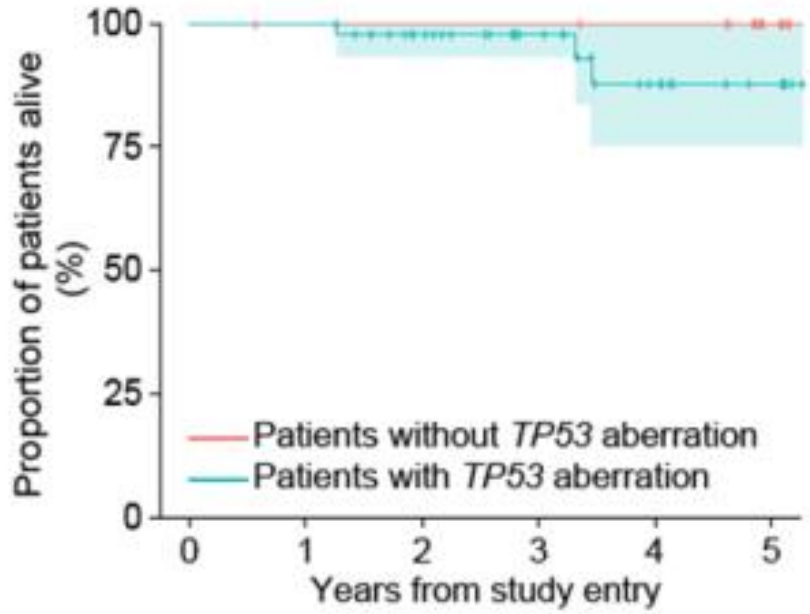
- Cycle Length = 28 days
- Acalabrutinib and obinutuzumab at standard doses
- Venetoclax 20mg C4D1, 50mg C4D2, then standard ramp-up to 400mg dose
- MRD at C16 & C25 assessed by multicolor flow cytometry (10^{-4})

ECOG PS = Eastern Cooperative Oncology Group performance status; VAF = variant allele fraction; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; CNS = central nervous system; CR = complete response; PR = partial response; BM = bone marrow; PB = peripheral blood; uMRD = undetectable MRD.

Davids MS, et al. *J Clin Oncol*. 2025;43(7):788-799.

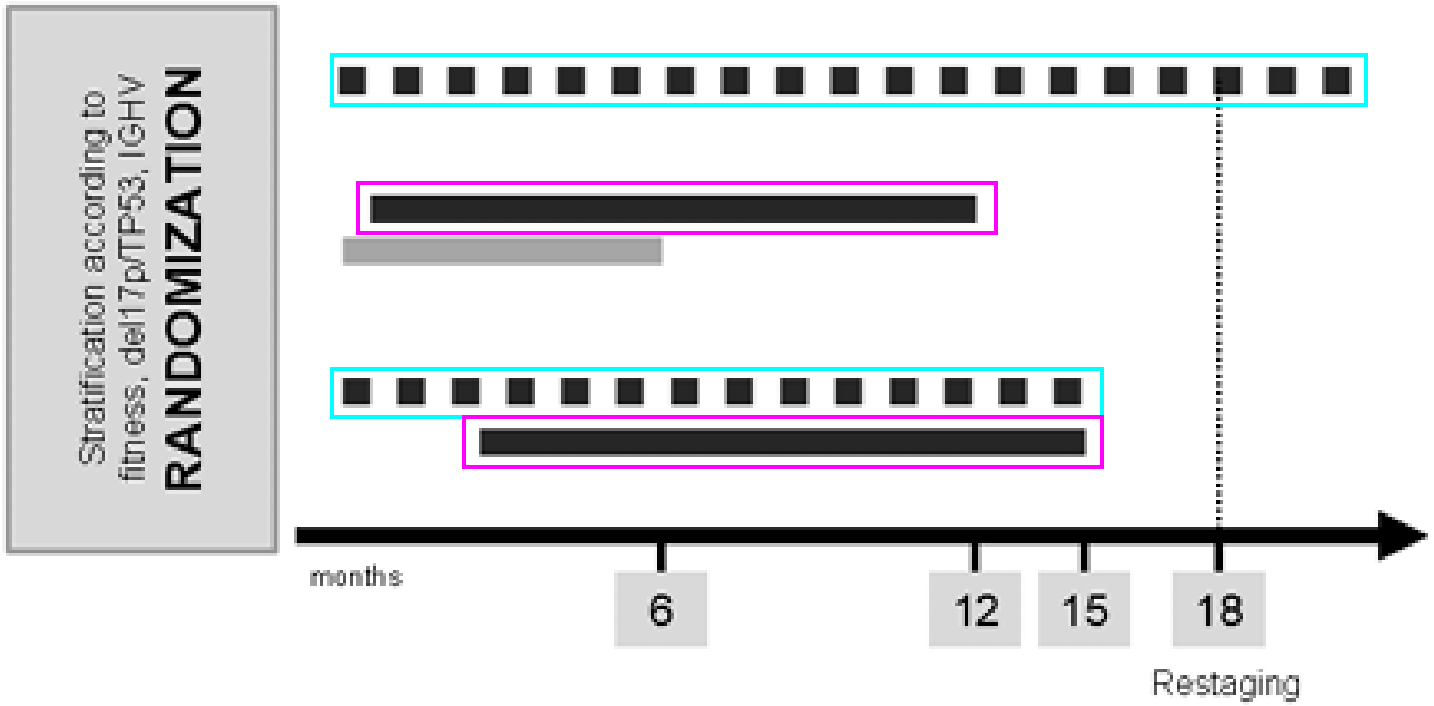
Outcomes by *TP53* Status





Davids MS, et al. *J Clin Oncol*. 2025;43(7):788-799.

CLL17: Trial Design



Ibrutinib

Venetoclax + Obinutuzumab

Ibrutinib + Venetoclax

Doublet and Triplet Regimens Being Evaluated

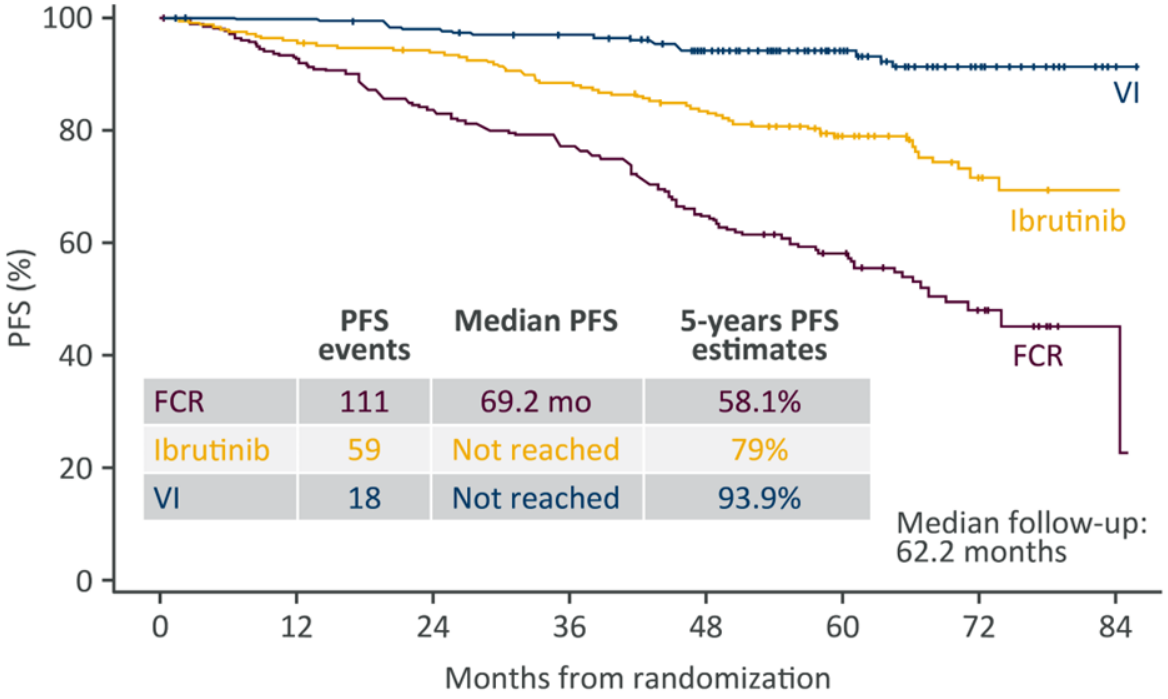
Doublet

- Ibrutinib + venetoclax
- Acalabrutinib + venetoclax
- Zanubrutinib + sonrotoclax

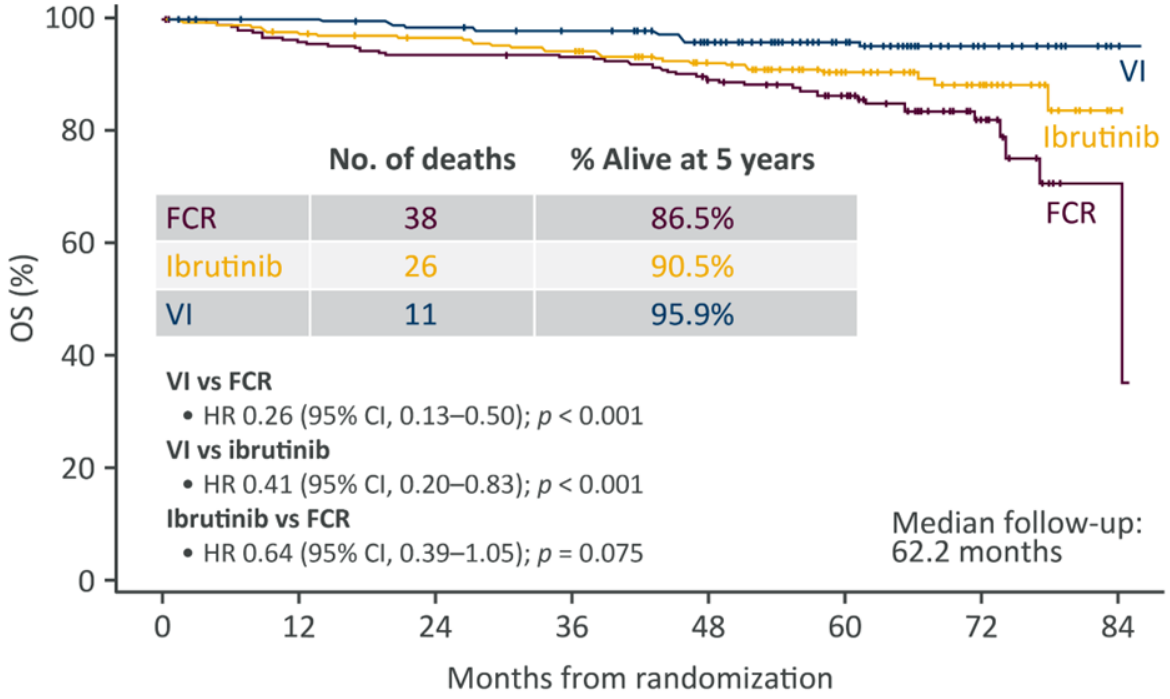
Triplet

- Ibrutinib + venetoclax + obinutuzumab
- Acalabrutinib + venetoclax + obinutuzumab
- Zanubrutinib + venetoclax + obinutuzumab
- Pirtobrutinib + venetoclax + rituximab
- Pirtobrutinib + venetoclax + obinutuzumab

FLAIR: MRD-Guided IV Demonstrated Survival Benefit



	PFS events	Median PFS	5-years PFS estimates
FCR	111	69.2 mo	58.1%
Ibrutinib	59	Not reached	79%
VI	18	Not reached	93.9%



	No. of deaths	% Alive at 5 years
FCR	38	86.5%
Ibrutinib	26	90.5%
VI	11	95.9%

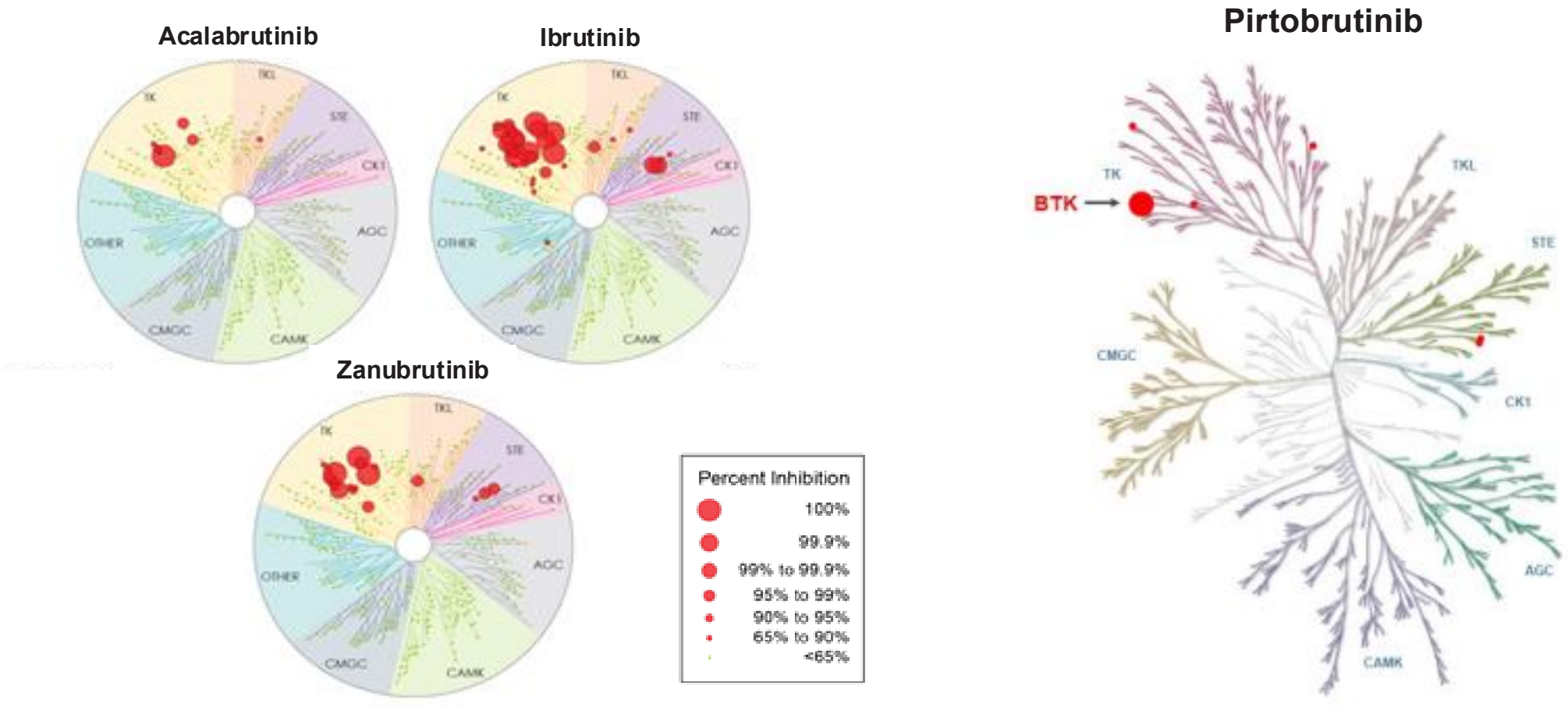
VI vs FCR
- HR 0.26 (95% CI, 0.13–0.50); $p < 0.001$

VI vs ibrutinib
- HR 0.41 (95% CI, 0.20–0.83); $p < 0.001$

Ibrutinib vs FCR
- HR 0.64 (95% CI, 0.39–1.05); $p = 0.075$

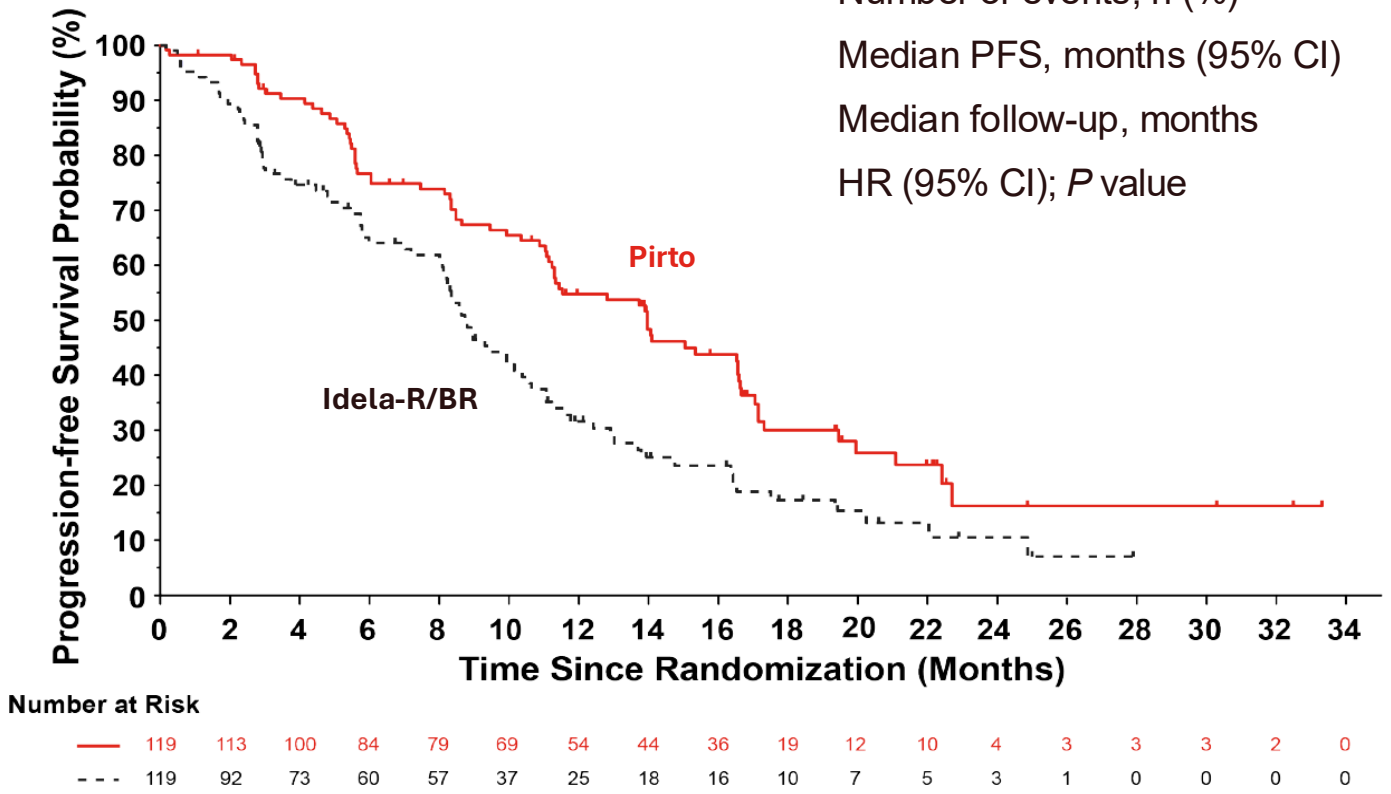
Munir T, et al. Presented at: European Hematology Association (EHA) Congress; 2025.

Pirtobrutinib—The Non-Covalent BTK Inhibitor



Kaptein A, et al. *Blood*. 2018;132(Suppl 1):1871. Barf T, et al. *J Pharmacol Exp Ther*. 2017;363(2):240-252. Mato AR, et al. *Lancet*. 2021;397(10277):892-901.

Pirtobrutinib—PFS Compared to Investigator's Choice



PFS by IRC	Pirto (n=119)	Idela-R/BR(n=119)
Number of events, n (%)	74 (62)	79 (66)
Median PFS, months (95% CI)	14.0 (11.2-16.6)	8.7 (8.1-10.4)
Median follow-up, months	19.4	17.7
HR (95% CI); *P* value	0.54 (0.39-0.75); 0.0002	

IRC = independent review committee.

Sharman JP, et al. *Blood*. 2024;144(Suppl 1):886.

Pirtobrutinib Safety—Adverse Events of Interest

AEs of Interest	Pirto (n=116)	
	Any Grade	Grade ≥3
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)
Without COVID-19	67 (57.8)	30 (25.9)
AFib and atrial flutter	3 (2.6)[a]	2 (1.7)
Hypertension	8 (6.9)	3 (2.6)

- Median time on treatment: pirto, 15.1 months; idela, 7.1 months; BR, 4.7 months
- Drug-related AEs led to discontinuation in 6 (5.2%) patients with pirto and 23 (21.1%) with idela-R/BR

Sharman JP, et al. *Blood*. 2024;144(Suppl 1):886.

Press Release—Pirtobrutinib Superior to Ibrutinib?

Pirtobrutinib showed superior ORR compared with ibrutinib in a phase 3 trial for patients with CLL/SLL, indicating potential efficacy.

The BRUIN CLL-314 trial included treatment-naive and previously treated patients, with promising PFS trends for pirtobrutinib.

More data to come…

ORR = overall response rate.

Gerlach A [www.pharmacytimes.com]. Last updated July 31, 2025. https://www.pharmacytimes.com/view/pirtobrutinib-outperforms-ibrutinib-in-head-to-head-phase-3-trial-for-cll-sll.

Key Learning Points

- Second-generation BTKi safer than ibrutinib
- Unclear if time-limited versus continuous therapy is preferred method of treatment
  - Both appear effective
- Counsel patients on potential lower efficacy of time-limited therapy in high-risk disease
- Pirtobrutinib safe and effective for relapsed/refractory CLL

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Clinical Considerations in First- and Subsequent-Line Therapy

How Do I Decide What Treatment to Pick for Our TN Patients?

Patient preference

TN = treatment-naïve.

Why Is Patient Preference #1 Consideration?

- No randomized phase 3 data in TN setting
- The patient is the one who will get treated
- Our treatments generally work well for most patients

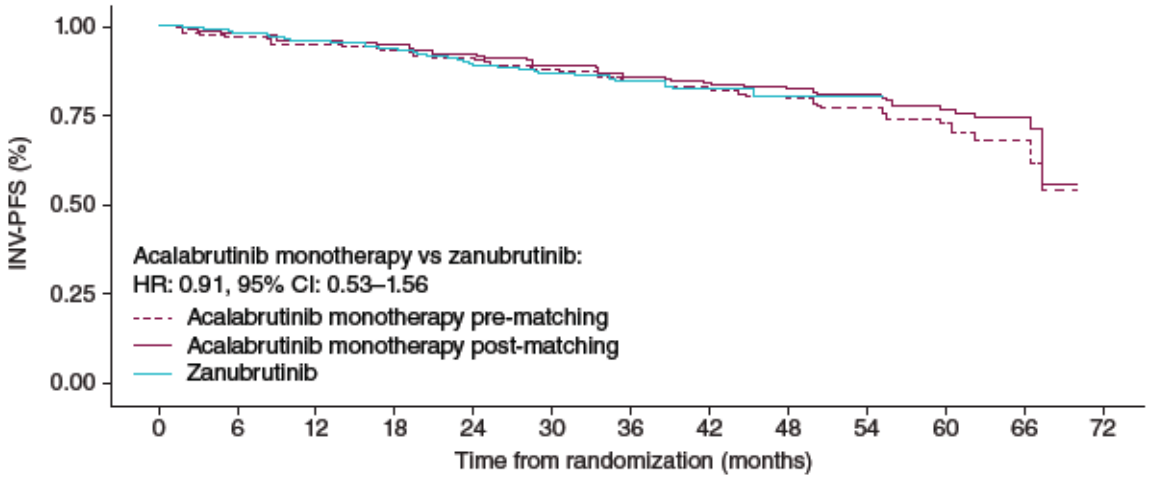
When Do I Favor Continuous Therapy for TN CLL?

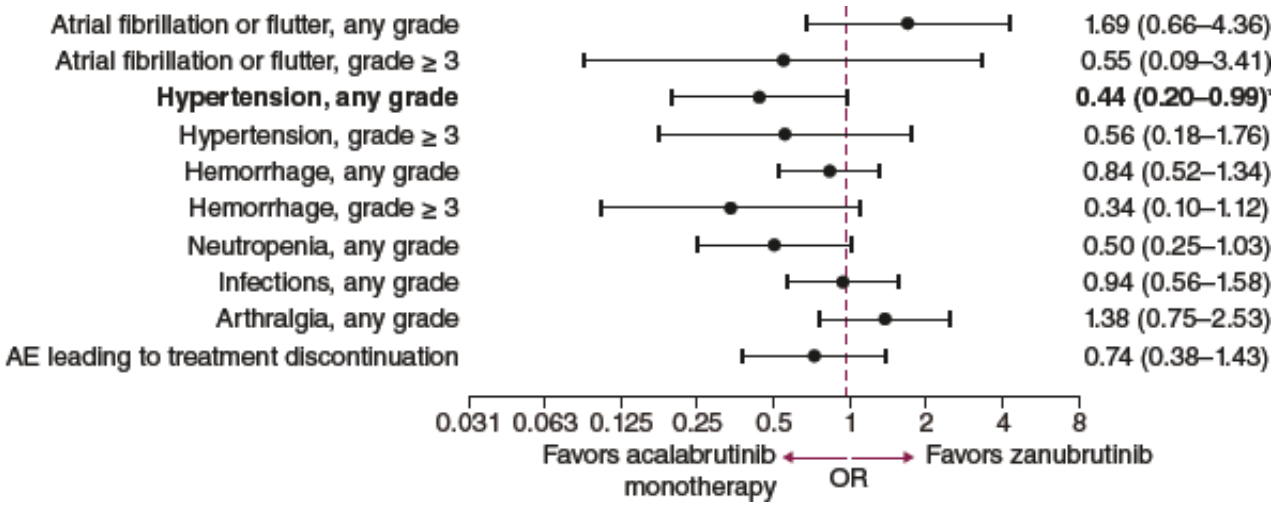
- Older patients
  - Cumulative data with BTKi is in the older age group
- Less intensive upfront regimen
  - No infusions, less monitoring → Less “time off life”
- Kidney dysfunction—higher risk for BCL2i
  - Increased tumor lysis and infusion reaction risk

When Do I Favor Time-Limited Therapy for TN CLL?

- Younger patients
  - Cumulative toxicity of BTKi over time
    - *CLL14 (VO vs ChlorO) was in “frail” patients
- Good risk disease
  - Data in patients with TP53 aberrations
- Cardiac risk—higher risk for BTKi
  - It’s complicated

Which 2nd-Generation BTKi Do I Prefer?





Key points

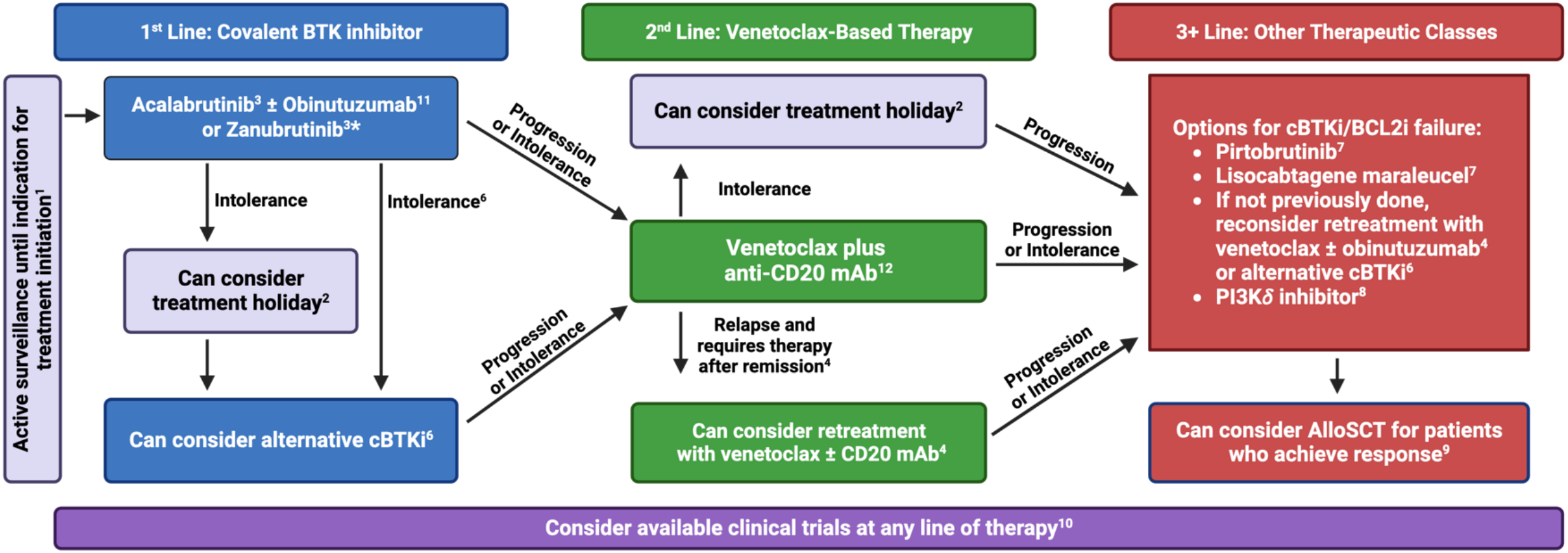
- ELEVATE-TN (acalabrutinib +/- obinutuzumab vs CO) and SEQUOIA (zanubrutinib vs. BR)
- Acalabrutinib had equal efficacy to zanubrutinib, with less hypertension

Kittai AS, et al. *Blood Adv*. 2024;8(11):2861-2869.

How Should We Sequence?

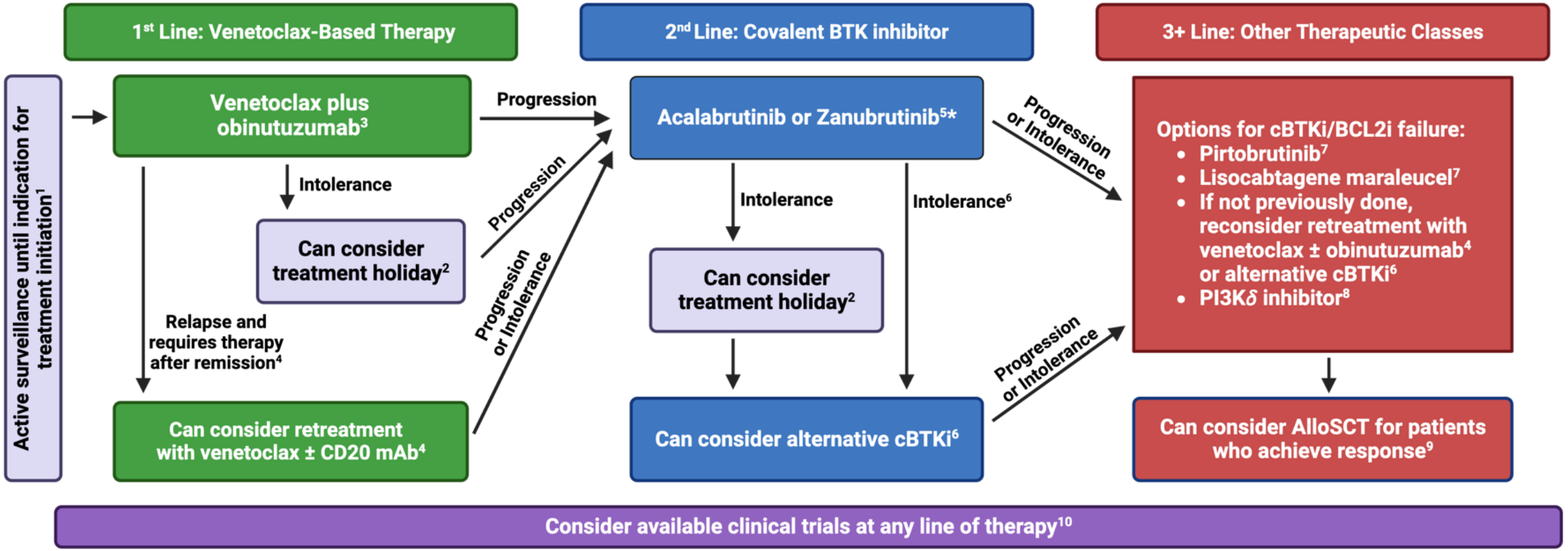
- No one really knows!
- Mostly depends on how the patient did in the front line
- More robust data available for ven after BTKi
  - More data overall for BTKi after chemoimmunotherapy
- Will resistance mutations come into play?

BTKi First



mAb = monclonal antibody; alloSCT = allogeneic stem cell transplantation.
Soumerai JD, et al. *Blood Adv*. 2025;9(5):1213-1229.

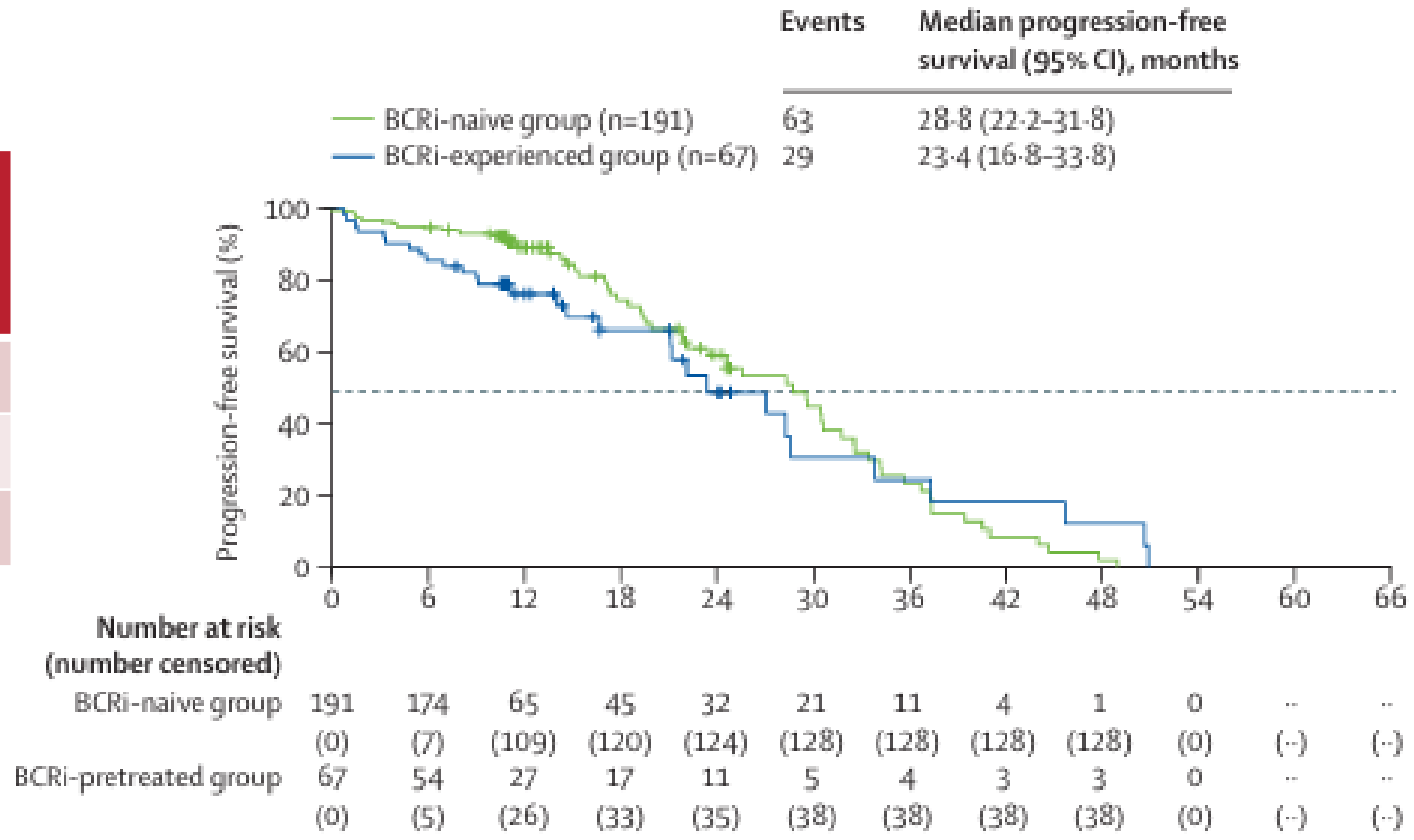
BCL2i Combo First



Soumerai JD, et al. *Blood Adv*. 2025;9(5):1213-1229.

Venice-1 Trial—Venetoclax after BTKi

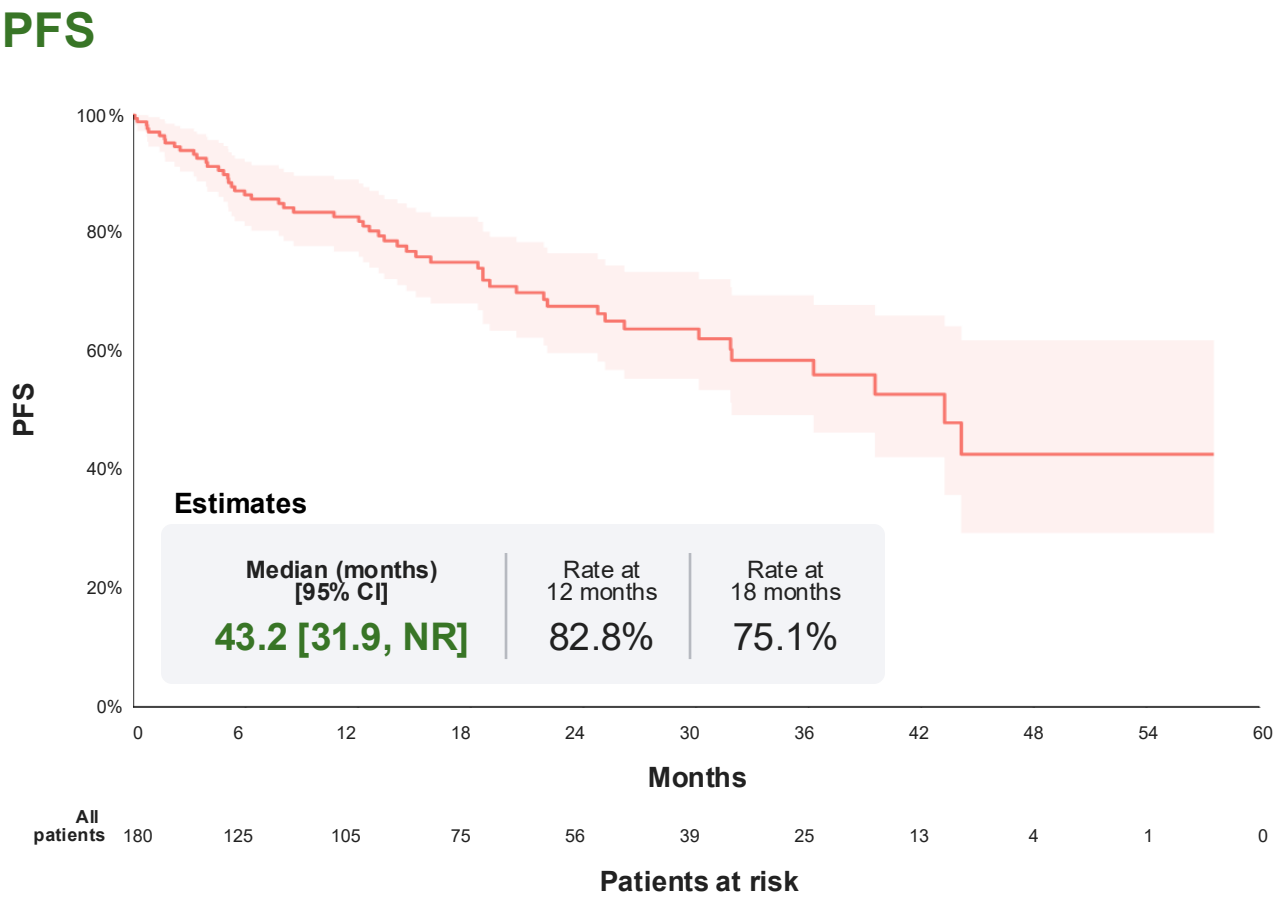
Prior Lines of Therapy	BTKi-naïve (n=191)	BTKi-pretreated (n=67)
1	101 (53%)	5 (7%)
2	47 (25%)	18 (25%)
>/= 3	43 (23%)	45 (67%)



Kater AP, et al. *Lancet Oncol*. 2024;25(4):463-473.

RWE—Venetoclax after cBTKi

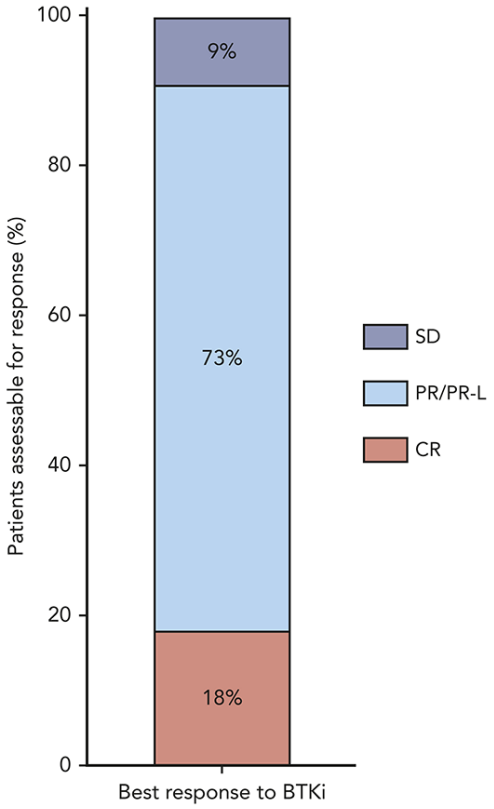
Prior Lines of Therapy	BTKi-pretreated (205)
1	71 (34.6%)
2	73 (43.7%)
>/= 3	61 (31.5%)



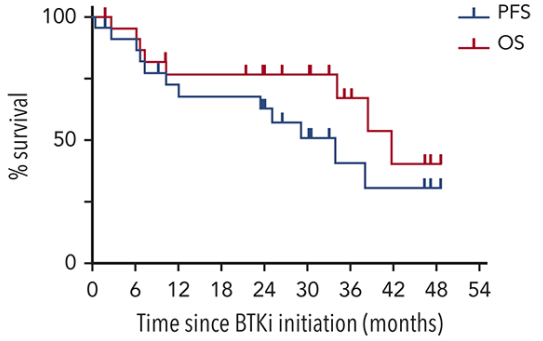
RWE = real-world evidence.
Ghosh N, et al. Presented at: American Society of Hematology (ASH) Annual Meeting & Exposition; 2023. Ghosh N, et al. *Am J Hematol*. 2025;100(3):511-515.

cBTKi after Venetoclax

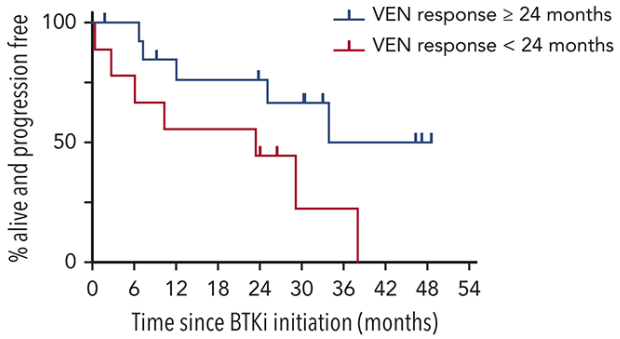
N=23
Median # prior lines of therapy: 4 (range 2-9)



BTK inhibitors are effective against venetoclax-resistant CLL



Durability of response to BTK inhibitor is associated with length of remission to prior venetoclax therapy

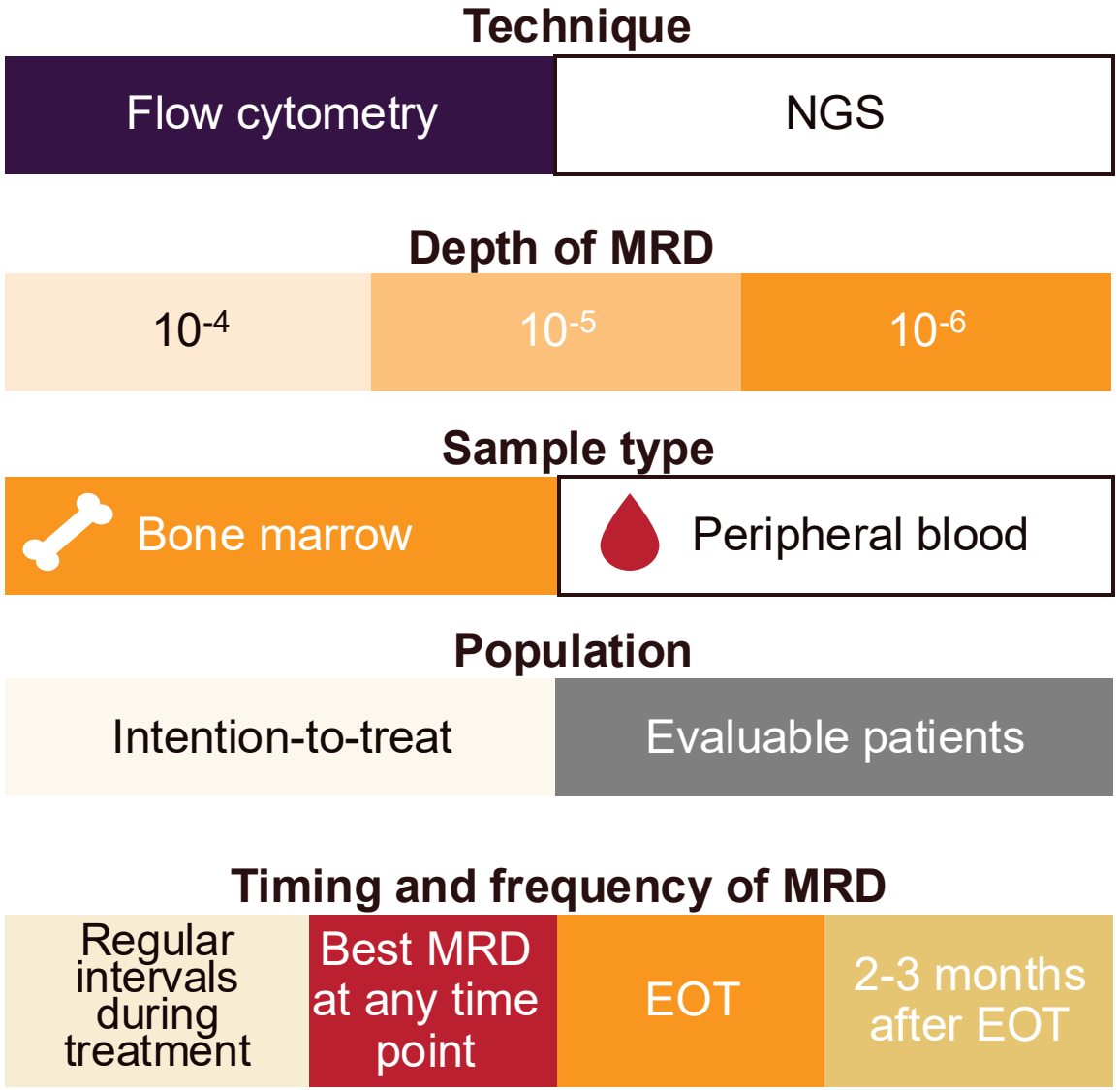


Lin VS, et al. *Blood*. 2020;135(25):2266-2270.

Sequencing Summary

- Not much data on the sequencing
- Ultimately, choice of 2nd-line therapy depends on choice of 1st-line therapy
  - Decision of why you chose BTKi or ven-based regimen likely is still at play
- Ultimately, it will fall on real-world analyses rather than clinical trials
  - ReVENGe trial
  - cBTKi to ncBTKi trial
- Pirtobrutinib appears to be effective after both cBTKi and BCL2i

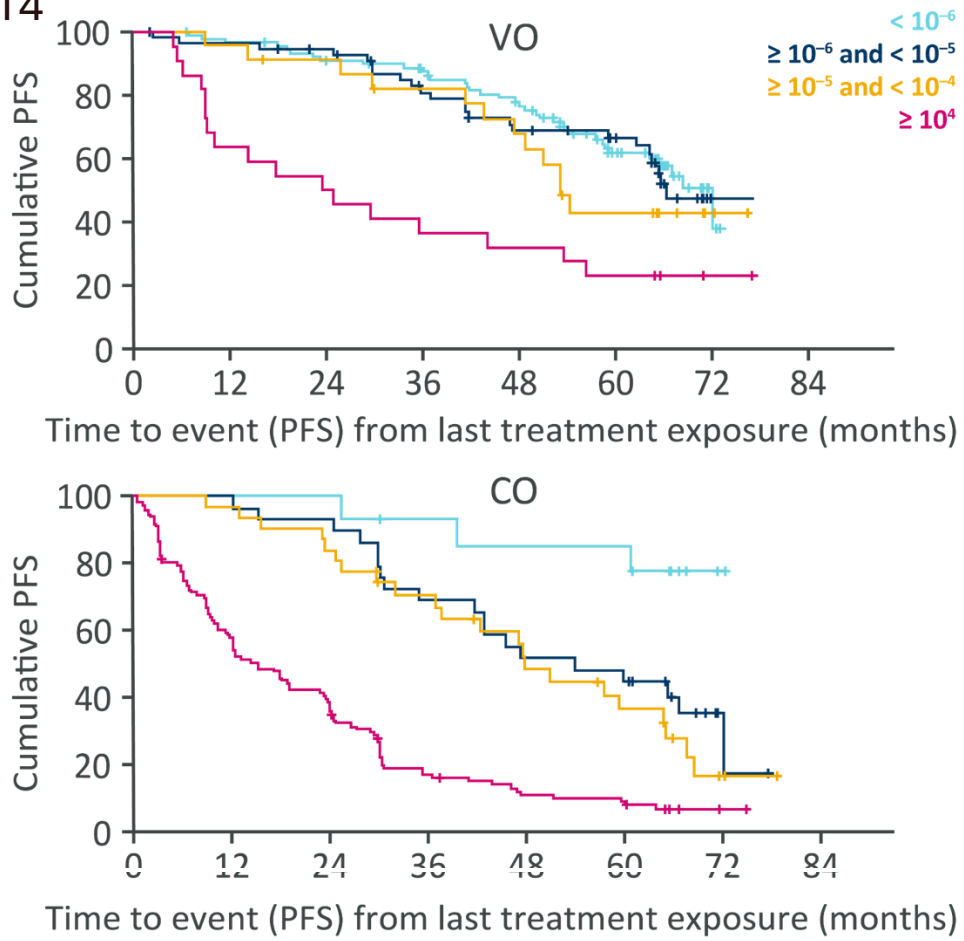
ncBTKi = non-covalent BTKi.



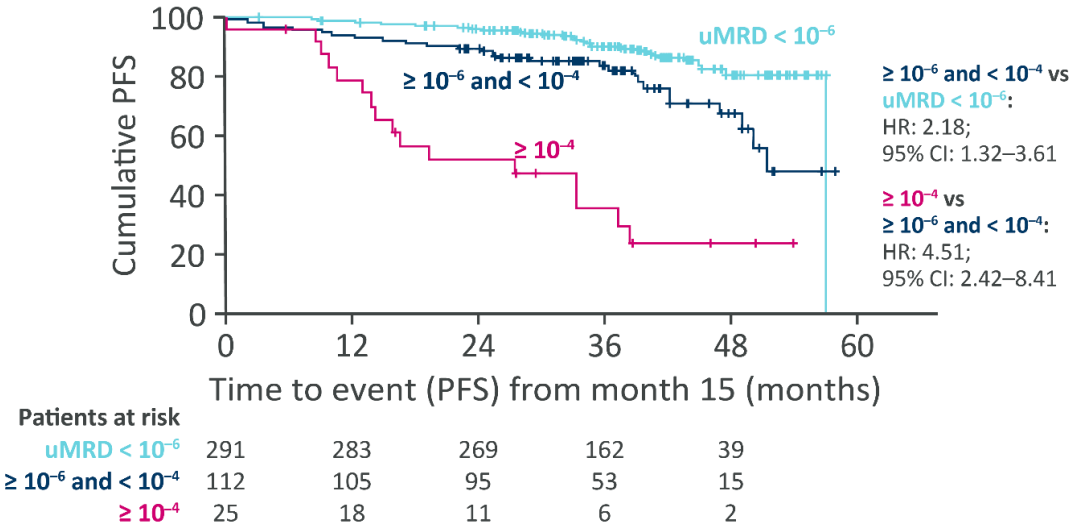
EOT = end of treatment.

Prognostic Value of MRD

CLL14



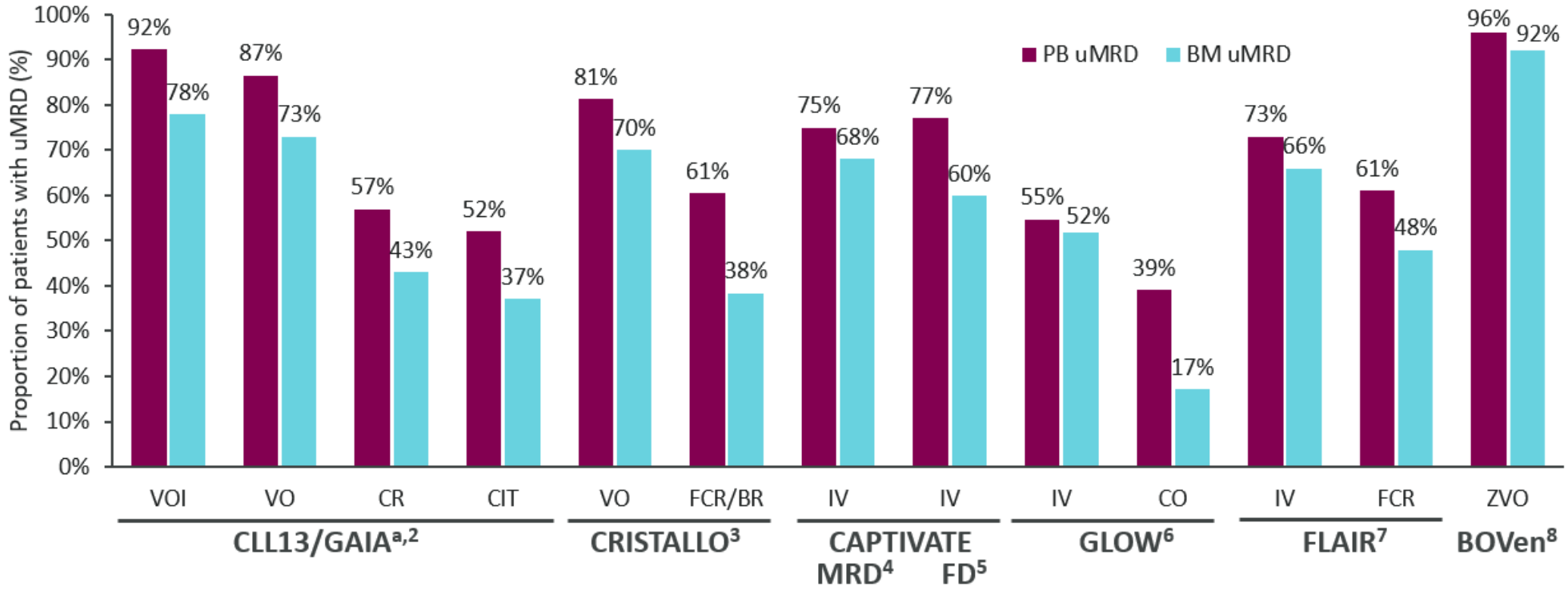
CLL13



Patients at risk					
uMRD < 10^{-6}	291	283	269	162	39
≥ 10^{-6} and < 10^{-4}	112	105	95	53	15
≥ 10^{-4}	25	18	11	6	2

Al Sawaf O, et al. *Blood.* 2024;144(18):1924-1935. Fürstenau M, et al. *Blood.* 2023;142(Suppl 1):635.

MRD Concordance in Marrow and Peripheral Blood



Wierda WG, et al. *Leukemia*. 2021;35(11)3059-3072. 2. Eichhorst B, et al. *N Engl J Med*. 2023;388(19):1739-1754. 3. Sharman JP, et al. *Blood*. 2024;144(Suppl 1):3237. 4. Wierda WG, et al. *J Clin Oncol*. 2021;39(34):3853-3865. 5. Tam CS, et al. *Blood*. 2022;139(22):3278-3289. 6. Munir T, et al. *J Clin Oncol*. 2023;41(21):3689-3699. 7. Munir T, et al. Presented at: EHA Congress; 2025. 8. Soumerai JD, et al. *Blood*. 2024;144(Suppl 1):1867.

Key Learning Points

- Choice of frontline therapy should be based on patient preference and comorbidities
- Choice of second-line therapy should be based on what the patient got in the front line
- Unclear which sequence is better: BTKi → BCL2i or BCL2i → BTKi
- uMRD appears to be prognostic of survival and should be obtained after time-limited therapies

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Q&A Session