Advances in Management of Chronic Lymphocytic Leukemia (CLL)

Speaker/Moderator: Adam Kittai, MD, MBA

Date: 4/8/2026

OMNI Oncology

Agenda

- Discuss updates to NCCN guidelines for TN CLL
- Review my thought-process for 1st line CLL
- Dive into the data for TN time-limited options

Patient Case

- 82 y/o woman ECOG-1 with a history of controlled HTN and DM2.
- Presented with fatigue and incidentally detected leukocytosis.
- Diagnosed with del17p positive, IGHV mutated CLL.
  - WBC 300, Hb 10, plt 100
  - LDH is 1000
  - Uric acid is 8.0
- She has no treatment preference but wants to avoid hospitalization for side effects where possible.

NCCN Guidelines

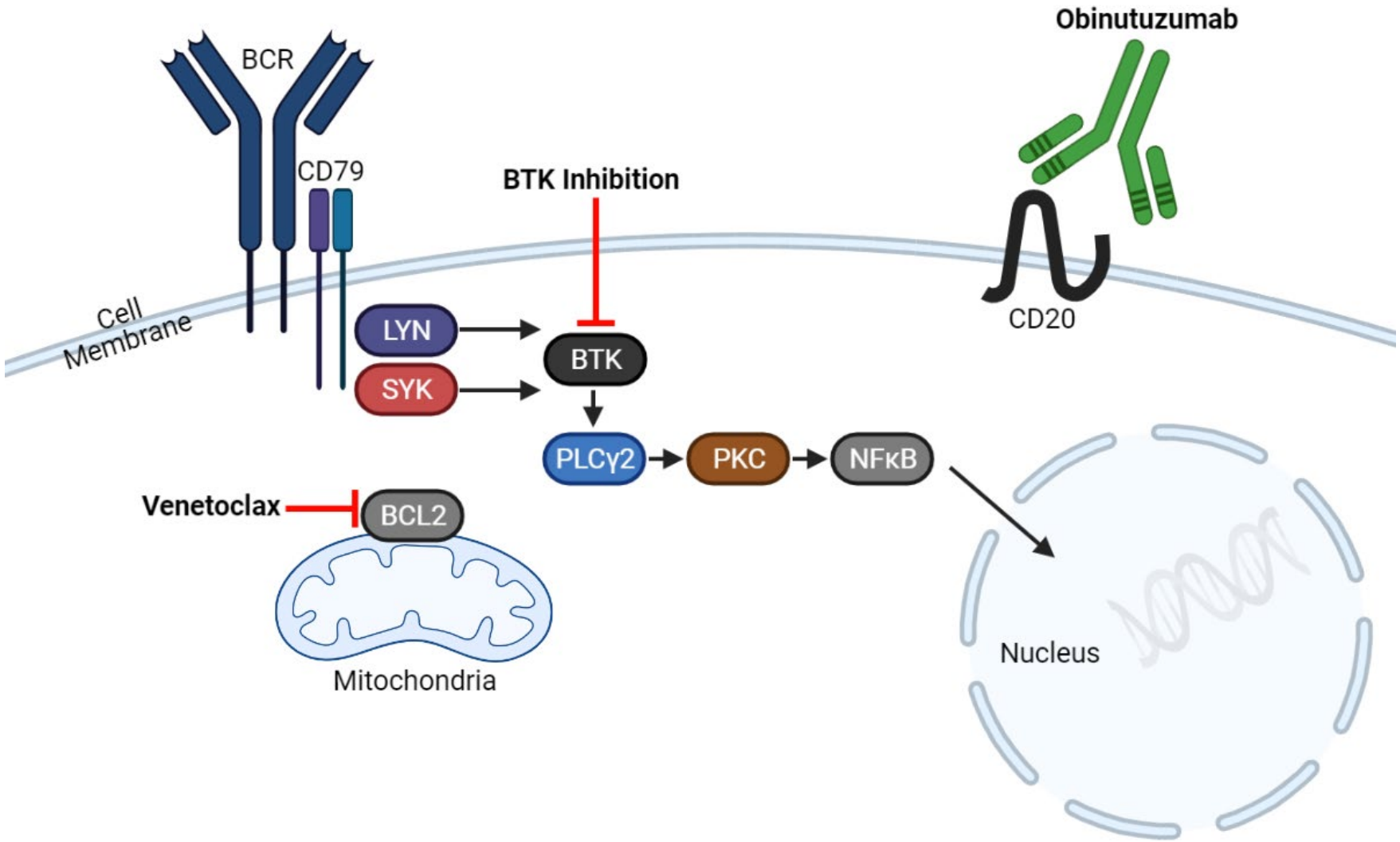
CLL/SLL without del(17p)/*TP53* Mutation (alphabetical by category)

FIRST-LINE THERAPY[e,f,g]		
Preferred	**Other Recommended**	**Useful in Certain Circumstances**
• BCL2i-containing regimens ▸ Venetoclax/Acalabrutinib[j] ± Obinutuzumab (fixed duration)[h] (category 1) ▸ Venetoclax + Obinutuzumab (fixed duration) (category 1) • cBTKi-based regimens[i,j] ▸ Acalabrutinib (continuous) ± Obinutuzumab (category 1) ▸ Zanubrutinib (continuous) (category 1)	• BCL2i-containing regimen ▸ Venetoclax/Ibrutinib[j] (category 1; fixed duration)[k] ▸ Venetoclax/Ibrutinib[j] (category 1; MRD-guided)[l]	• BCL2i-containing regimen ▸ Venetoclax/Zanubrutinib[j] (MRD-guided)[m] • cBTKi-based regimens[i,j] ▸ Ibrutinib[n] (continuous) (category 1) ▸ Ibrutinib (continuous) + anti-CD20 mAb (category 2B)[o] • High-dose methylprednisolone (HDMP) + anti-CD20 mAb[o] (category 2B; category 3 for patients <65 y without significant comorbidities) • Consider only when cBTKi and BCL2i are not available or not feasible ▸ Bendamustine[p] + anti-CD20 mAb[o,q] ▸ FC (Fludarabine/Cyclophosphamide)[r,s,t] + Rituximab ▸ Chlorambucil[u] + Obinutuzumab ▸ Obinutuzumab

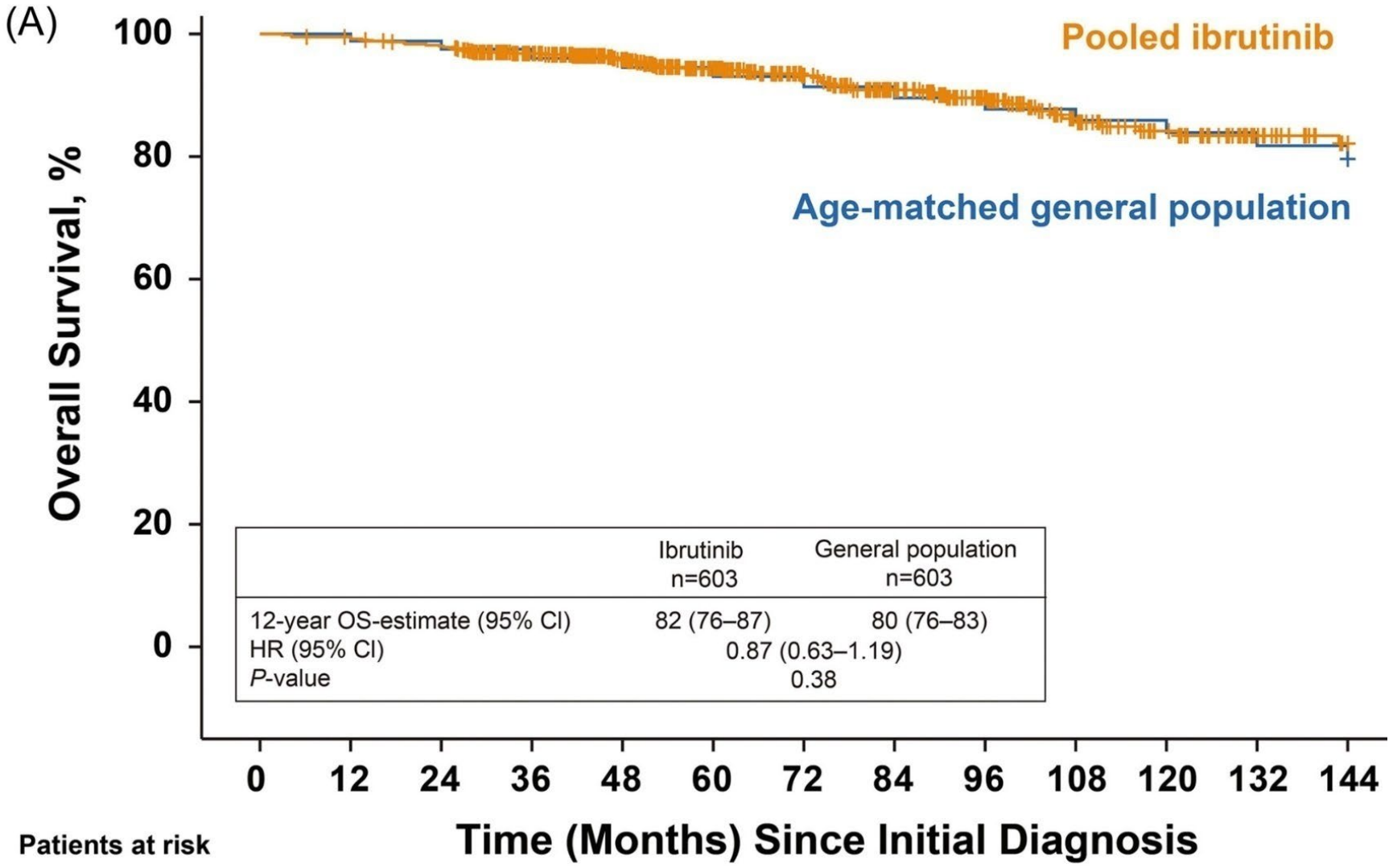
CLL/SLL with del(17p)/*TP53* Mutation (alphabetical by category)

FIRST-LINE THERAPY[e,f,g]		
Preferred	**Other Recommended**	**Useful in Certain Circumstances**
• BCL2i-containing regimens ▸ Venetoclax + Obinutuzumab (fixed duration) ▸ Venetoclax/Acalabrutinib + Obinutuzumab (MRD-guided)[v] ▸ Venetoclax/Zanubrutinib[j] (MRD-guided)[m] • cBTKi-based regimens[i,j] ▸ Acalabrutinib (continuous) ± Obinutuzumab ▸ Zanubrutinib (continuous)	• BCL2i-containing regimen ▸ Venetoclax/Ibrutinib[j,w] (fixed duration)	• cBTKi-based regimen[i,j] ▸ Ibrutinib[n] (continuous) • HDMP + anti-CD20 mAb[o] • Consider only when cBTKi and BCL2i are not available or not feasible ▸ Obinutuzumab

Mechanism of Action of Targeted Agents



Patients Living as Long as Age-Matched Controls



Ghia et al. *HemaSphere.* 2024.

How Do I Decide Which Treatment to Pick for Our Treatment-Naive Patients?

Patient Preference

Why Is Patient Preference the #1 Consideration?

- #1) Patients generally will do well no matter what we pick
- **CLL17 data**

- #2) The patient is the one who will get treated

When Do I Favor Continuous Therapy for Treatment-Naive CLL?

- Older patients
  - Cumulative data with BTKi is in the older age group
  - Comorbidity precluding BCL2i based therapy

- Less intensive upfront regimen
  - No infusions, less monitoring → Less "time off life" ?

High-risk disease ?

When Do I Favor Time-Limited Therapy for Treatment-Naive 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

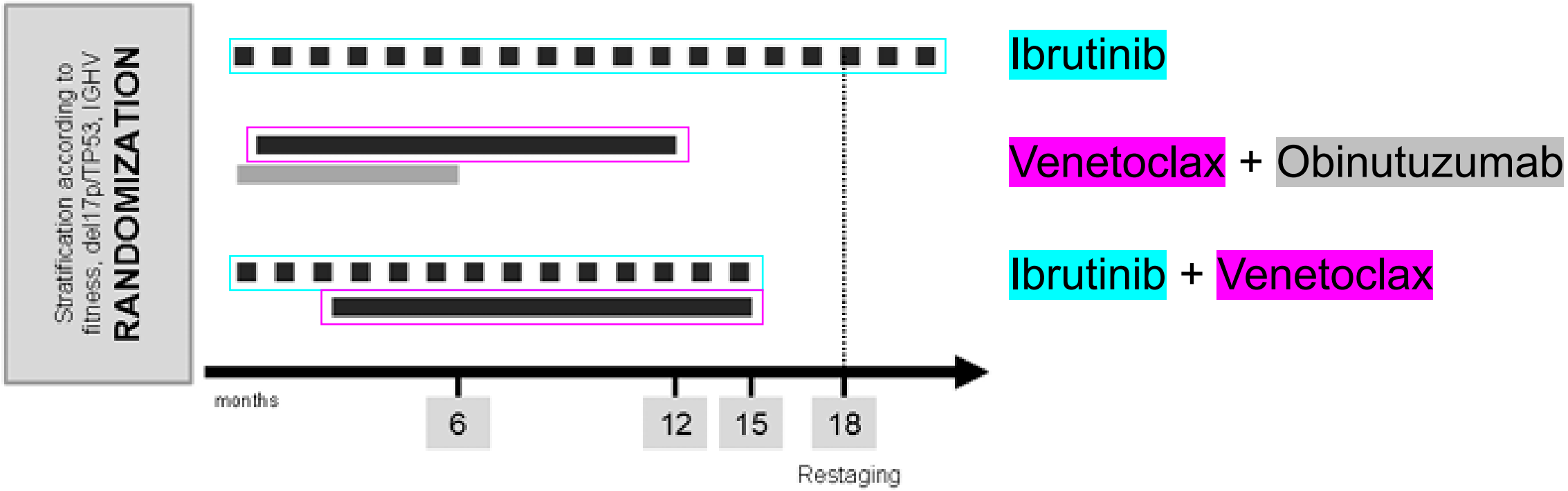
Comorbidity precluding BTKi based therapy ?

General concepts to consider:

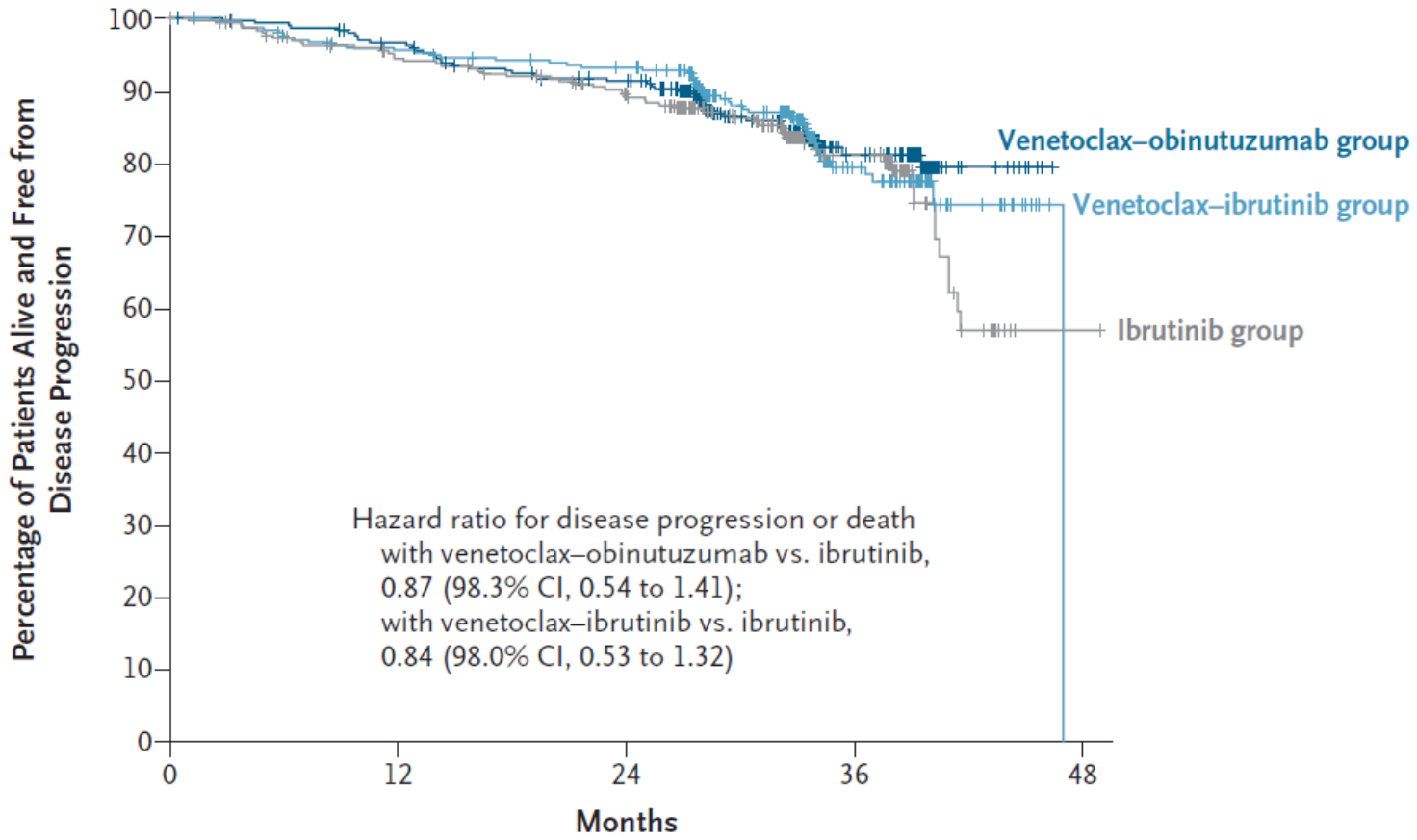
- Efficacy
  - Consideration of high-risk features – IGHV and TP53
- Safety/Ease of administration
  - Tumor lysis syndrome
  - Infection
  - Atrial Fibrillation
  - Ease of use
    - Avoiding obinutuzumab

Efficacy

CLL17: Trial Design



CLL17—Fixed-Duration or Continuous Therapy for Frontline Treatment of CLL

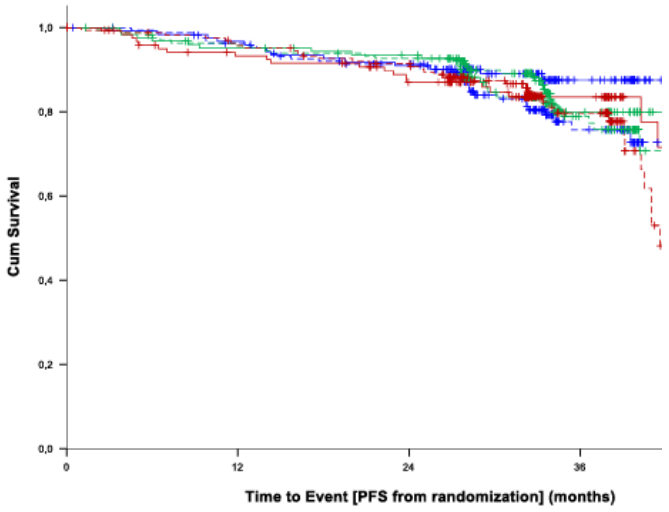


No. at Risk					
Venetoclax–obinutuzumab	303	278	256	77	0
Venetoclax–ibrutinib	305	278	267	82	0
Ibrutinib	301	267	243	94	1

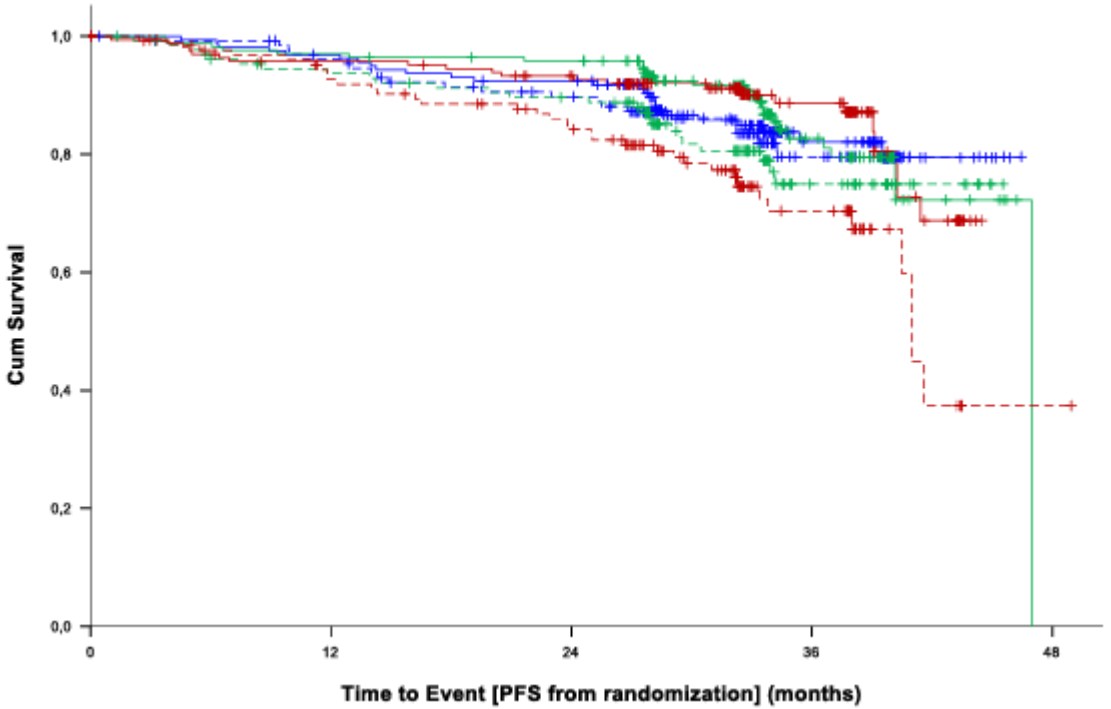
Al-Sawaf O, et al. *N Engl J Med.* 2025 Dec 6.

CLL17 – PFS curves by risk features

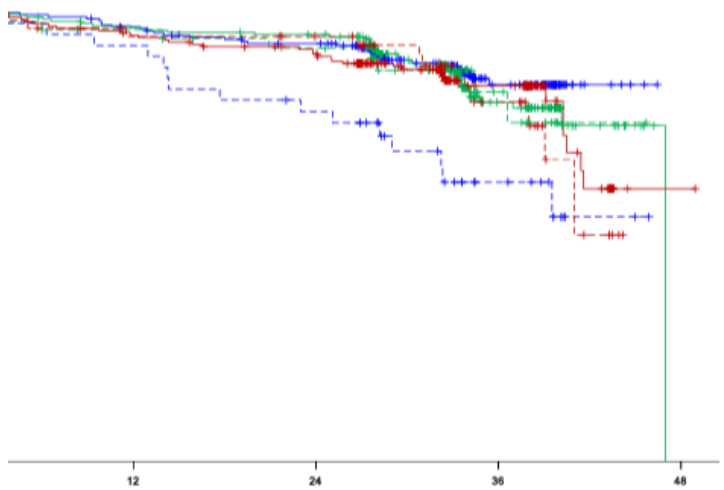
IGHV



Fitness



Complex Karyotype

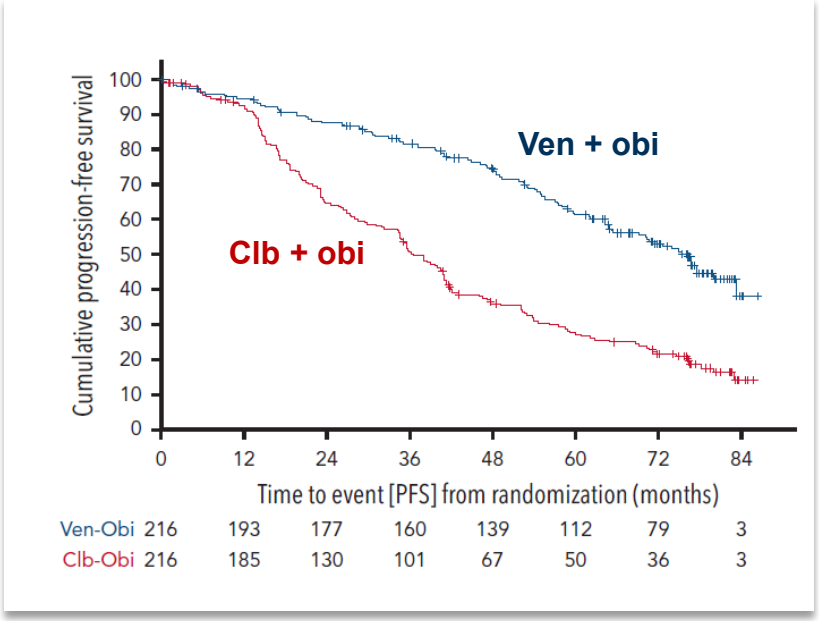


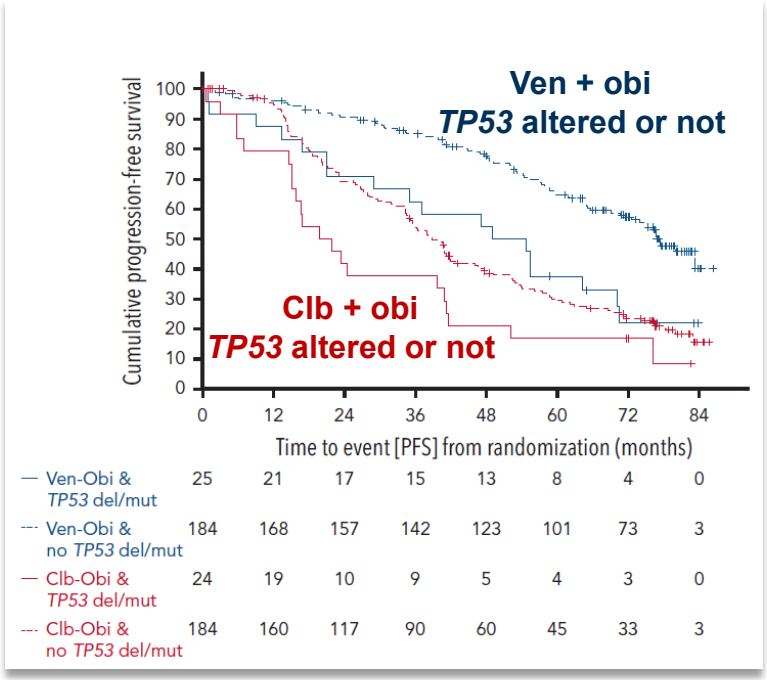
Blue – VO
Green – IV
Red - Ibr

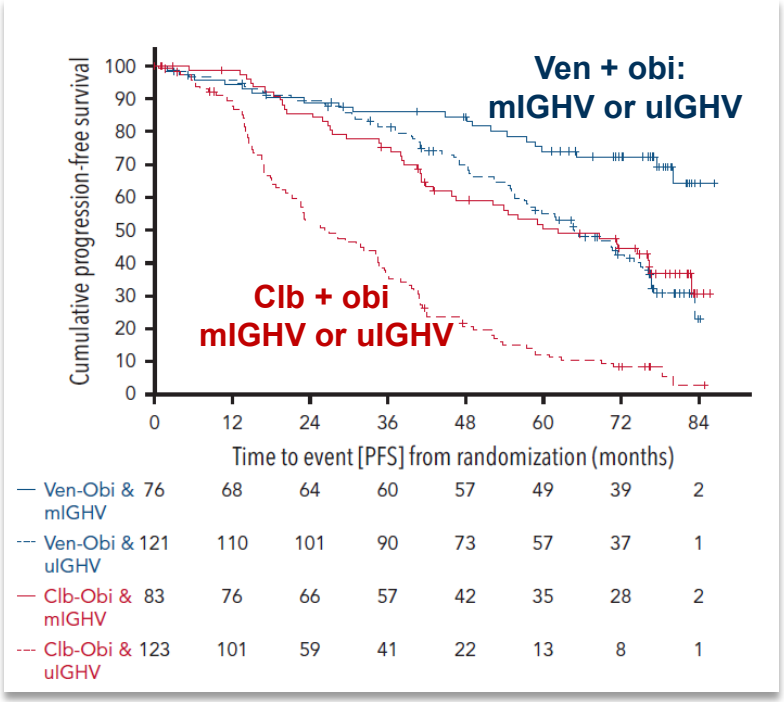
Al-Sawaf O, et al. *N Engl J Med.* 2025 Dec 6.

CLL14—Time-Limited Frontline Treatment With Venetoclax + Obinutuzumab

PFS Is Shorter for *TP53* Altered and uIGHV CLL



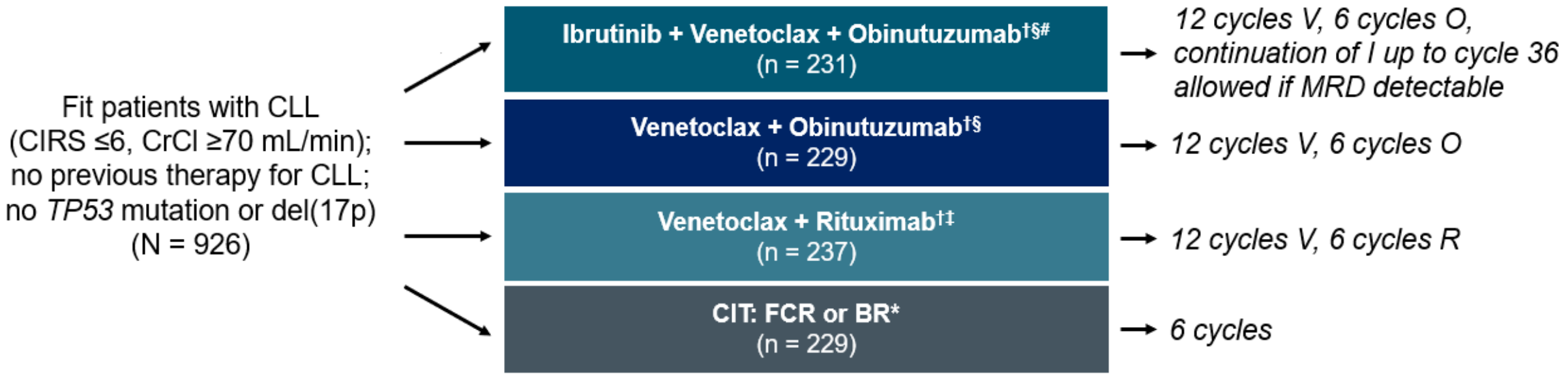




- **Median observation time:** 76.4 months
- **Median PFS for ven-obi-treated patients:** 76.2 months (all); 51.9 months (*TP53* mutated); 64.8 months for uIGHV

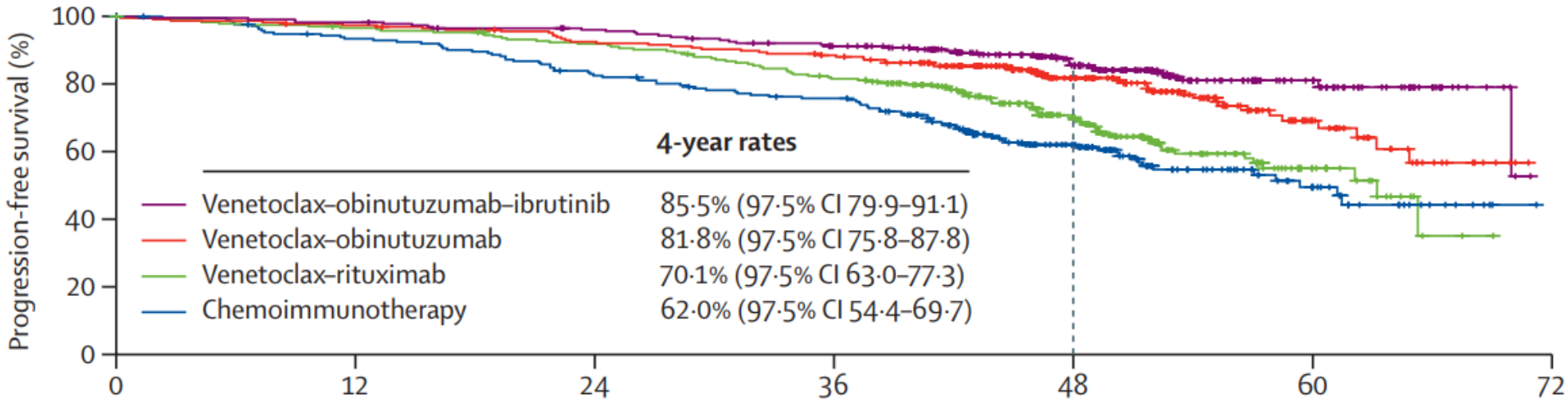
Al-Sawaf O, et al. *Blood.* 2024;144:1924-1935.

CLL13: Venetoclax Regimens vs CIT



Eichhorst B, et al. *N Engl J Med*. 2023;388:1739-1754.

CLL13: PFS at 4 Years



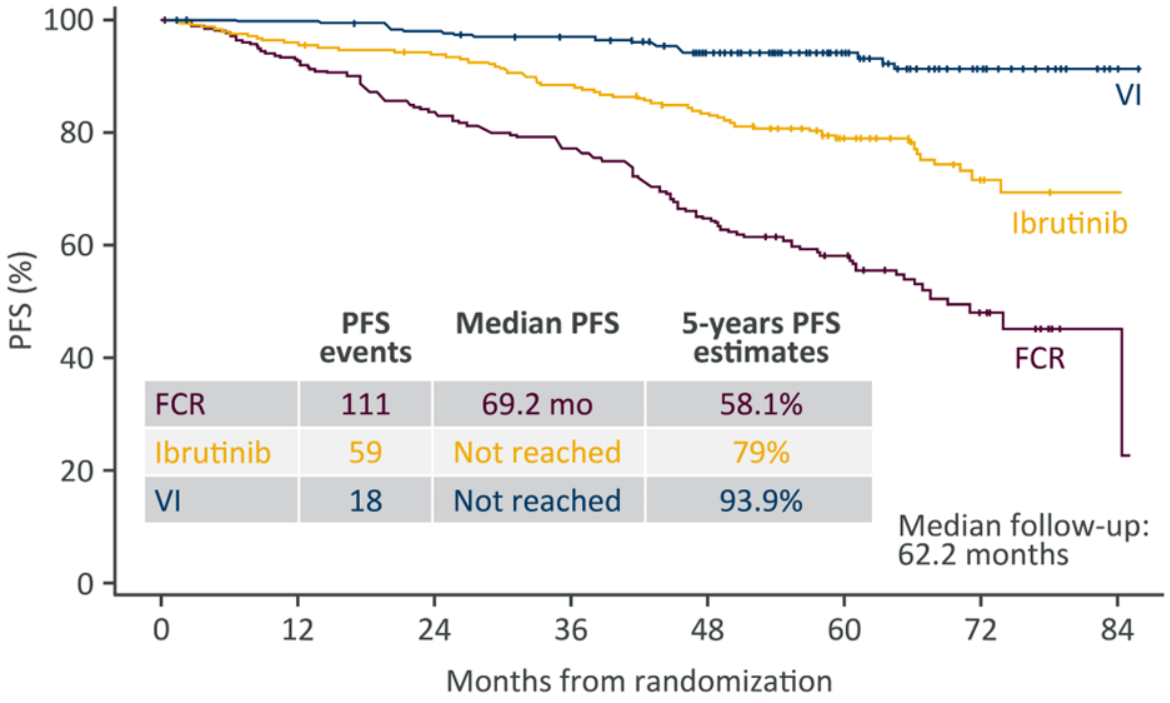
Number at risk (number censored)							
Chemoimmunotherapy	229 (0)	197 (18)	173 (19)	156 (22)	84 (68)	24 (117)	.. (..)
Venetoclax–rituximab	237 (0)	227 (2)	214 (4)	188 (6)	106 (67)	21 (135)	.. (..)
Venetoclax–obinutuzumab	229 (0)	222 (1)	209 (3)	198 (5)	121 (69)	32 (146)	.. (..)
Venetoclax–obinutuzumab–ibrutinib	231 (0)	227 (0)	218 (4)	201 (10)	130 (71)	44 (152)	.. (..)

Fürstenau M, et al. *Lancet Oncol.* 2024;25:744-759.

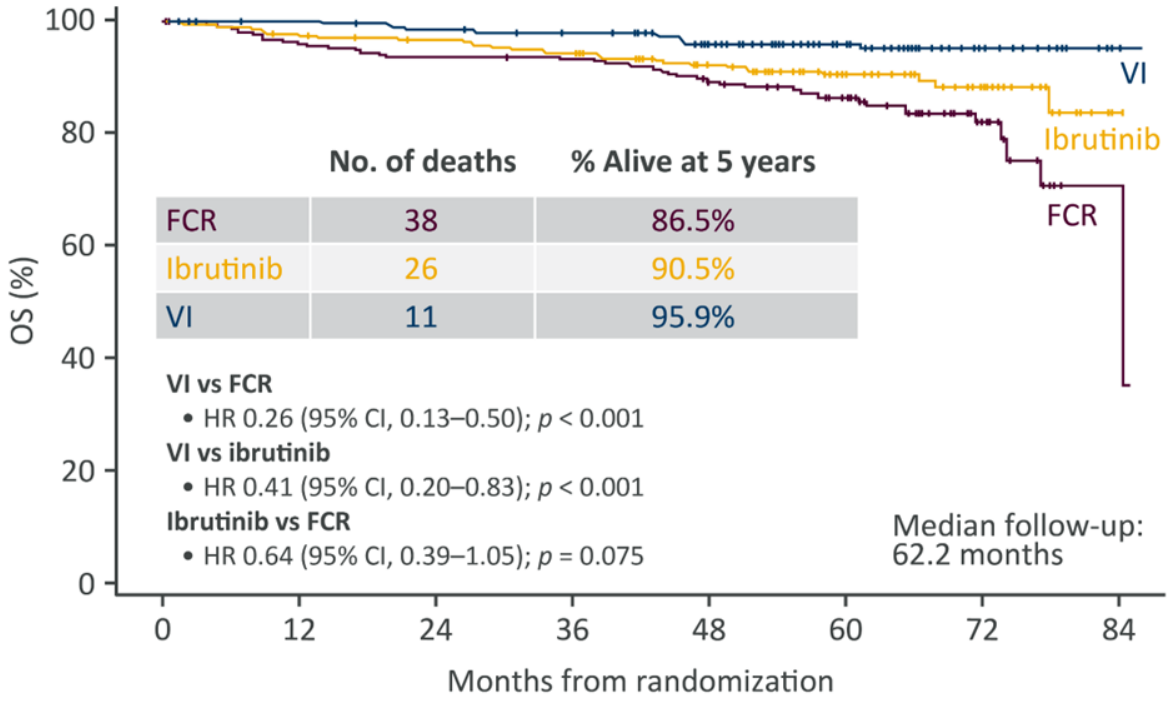
FLAIR: MRD-guided IV demonstrated survival benefit

PFS and OS rates were high with MRD-guided IV

Final analysis (62.2-month follow-up)



	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); $p < 0.001$

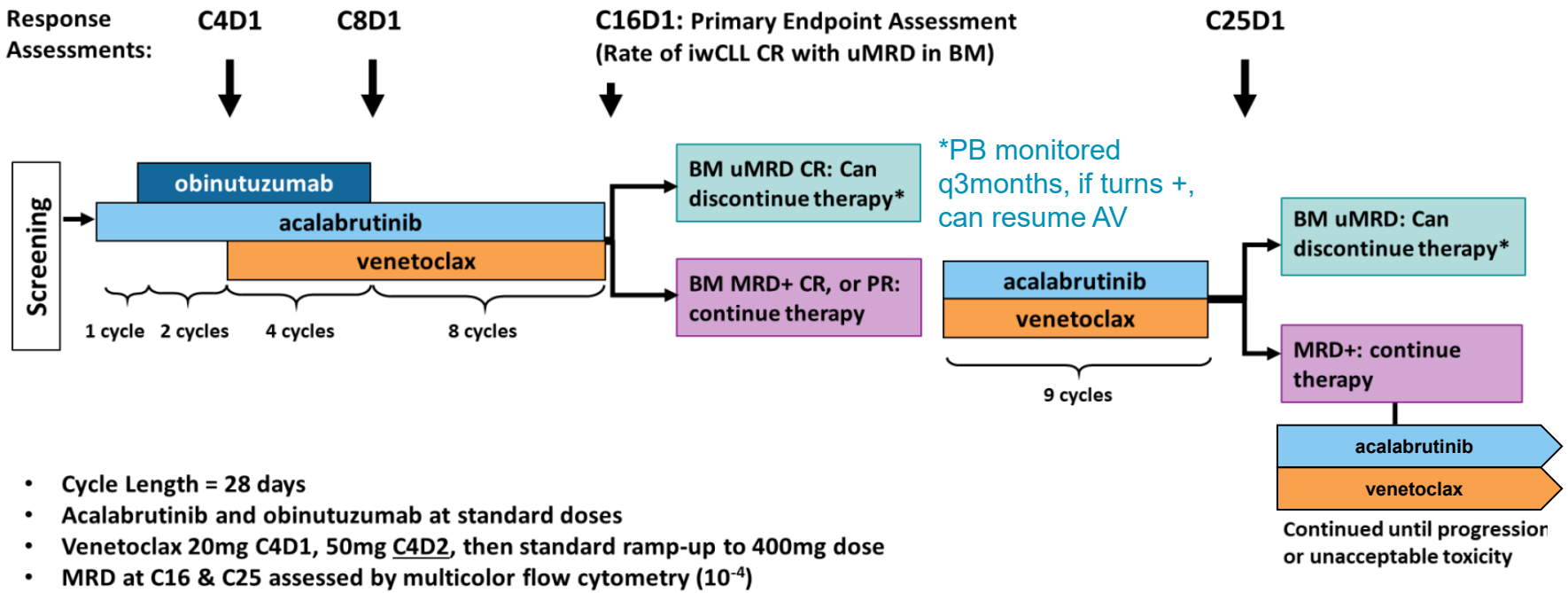
Ibrutinib vs FCR
- HR 0.64 (95% CI, 0.39–1.05); $p = 0.075$

Munir T *et al.* [presentation]. Presented at EHA 2025

AVO in High-Risk Patients

Key Eligibility Criteria

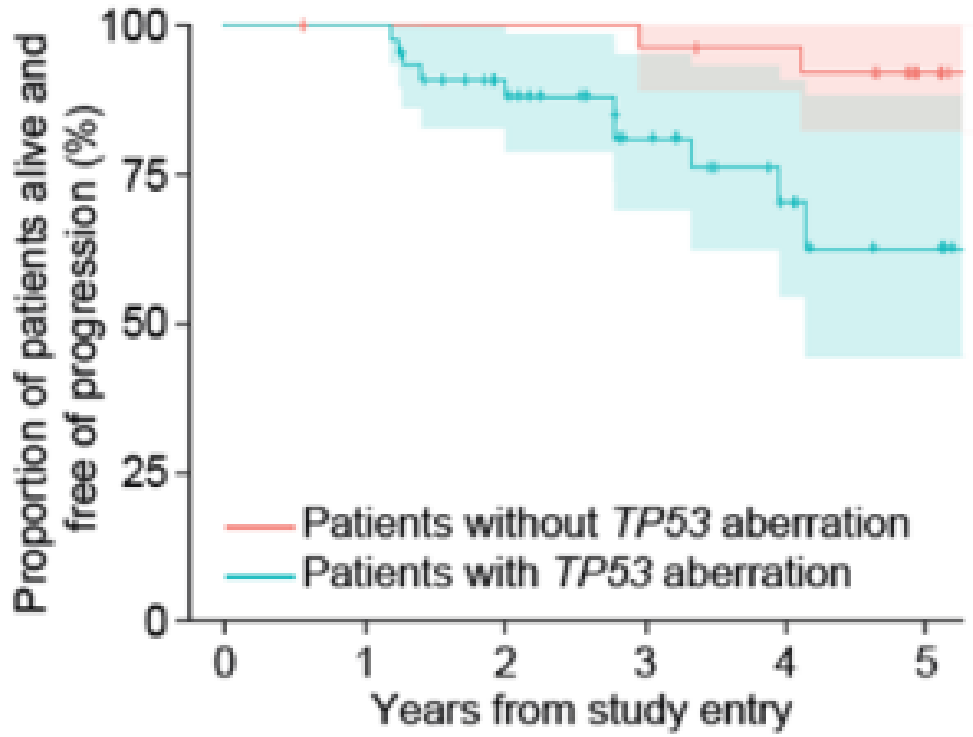
- Aged ≥18 years and ECOG PS ≤2
- Expansion cohort: *TP53*-aberrant disease (del[17p] or *TP53*mut [any VAF eligible])
- No Richter transformation or CNS involvement



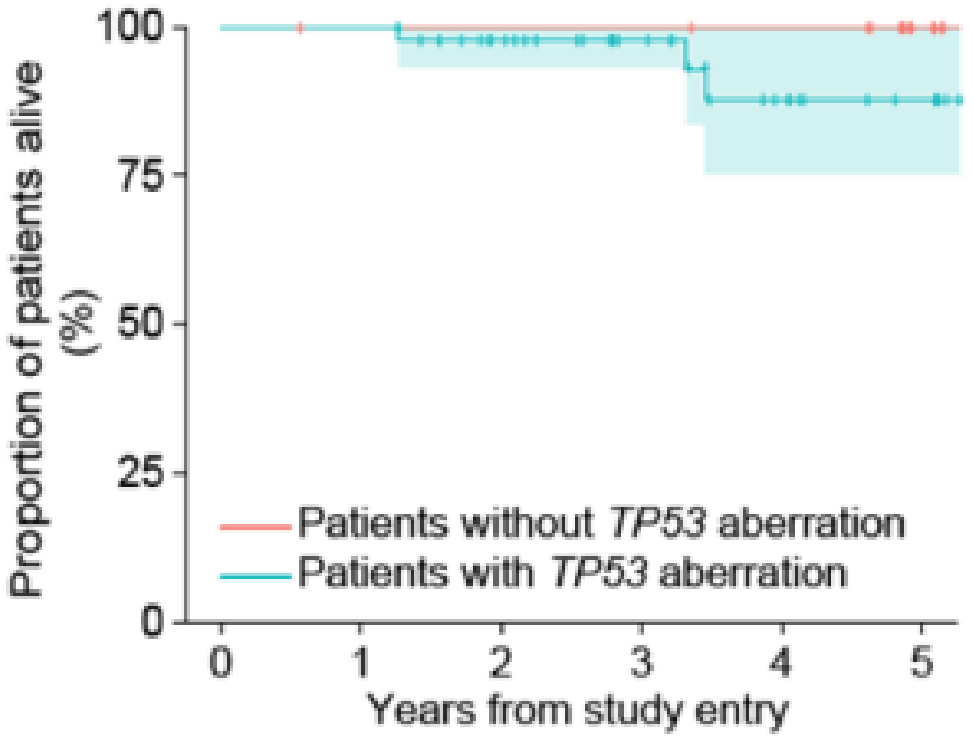
- Cycle Length = 28 days
- Acalabrutinib and obinutuzumab at standard doses
- Venetoclax 20mg C4D1, 50mg C4D2, then standard ramp-up to 400mg dose
- MRD at C16 & C25 assessed by multicolor flow cytometry (10^{-4})

Davids MS, et al. *J Clin Oncol.* 2024;43:788-799.

Outcomes by *TP53* Status



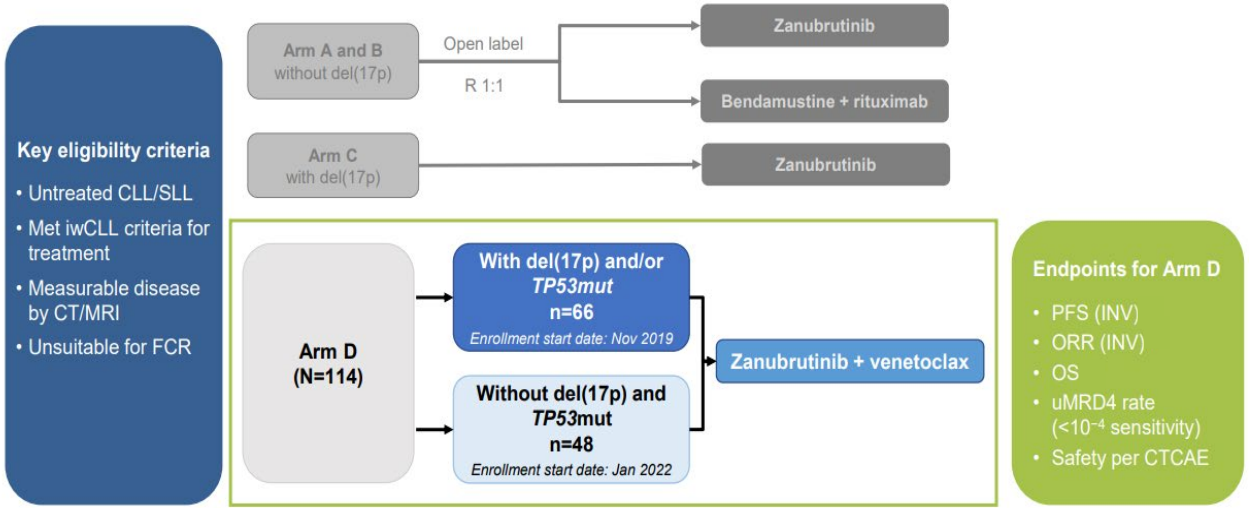
Number at risk						
Patients without *TP53* aberration	27	26	26	25	24	15
Patients with *TP53* aberration	45	45	32	20	11	6

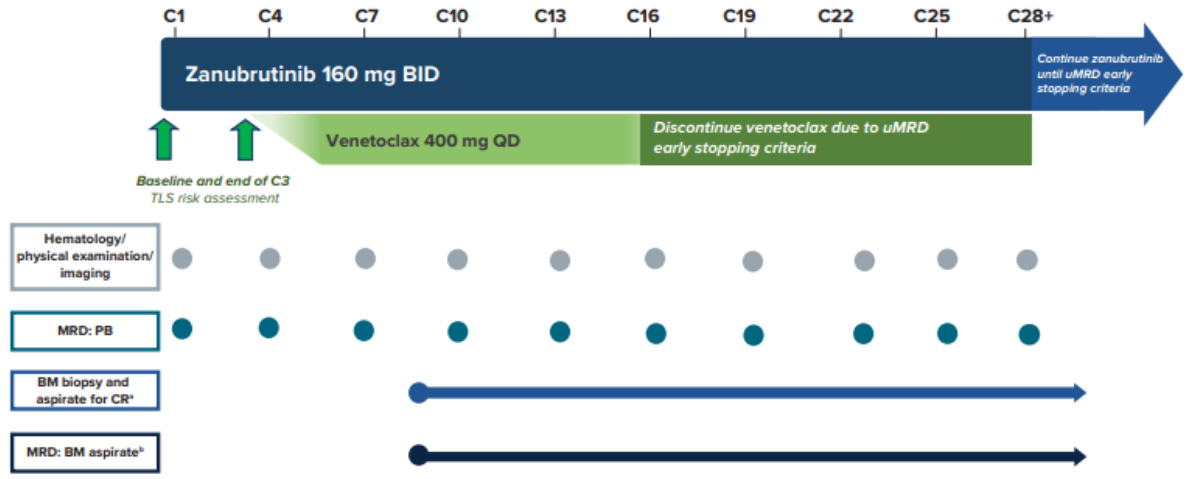


Number at risk						
Patients without *TP53* aberration	27	26	26	26	25	17
Patients with *TP53* aberration	45	45	35	24	14	8

Davids MS, et al. *J Clin Oncol.* 2024;43:788-799.

SEQUOIA ARMD – MRD Directed therapy in TP53 pos and neg CLL





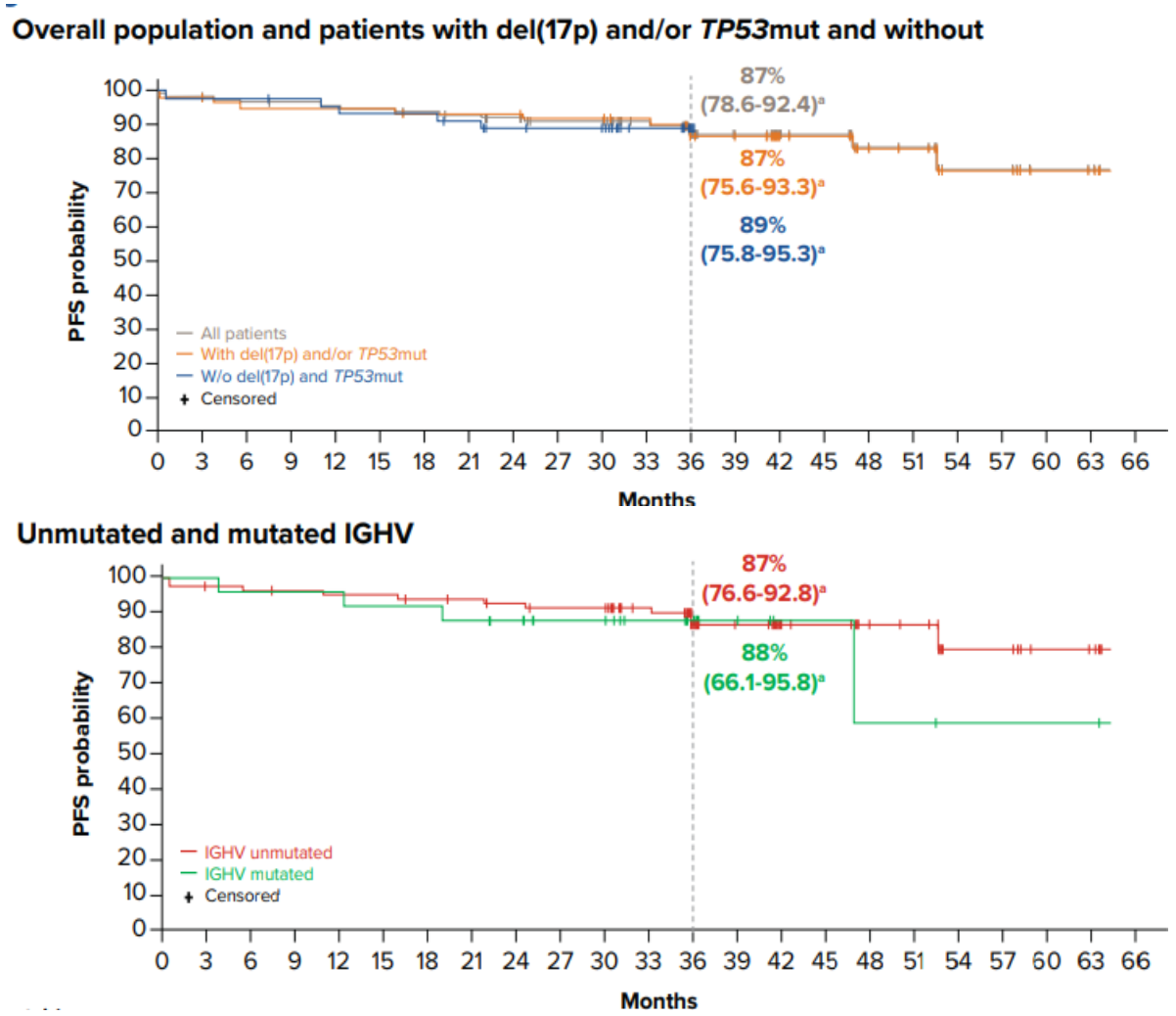
Stringent uMRD-guided stopping criteria

All conditions must be met

1. Response assessed as CR or CRi confirmed by a BM biopsy
2. uMRD <1 × 10^{-4} (uMRD4) achieved in two consecutive peripheral blood MRD tests conducted ≥12 weeks apart
3. uMRD4 achieved in two consecutive BM aspirate MRD tests conducted ≥12 weeks apart
4. Received
   - i) Minimum of 12 cycles of venetoclax (to stop venetoclax early)
   - ii) Minimum of 27 cycles of zanubrutinib (to stop zanubrutinib early)

Shadman M, et al. ASH 2025. Abstract 5669.

SEQUOIA ARMD – MRD Directed therapy in TP53 pos and neg CLL



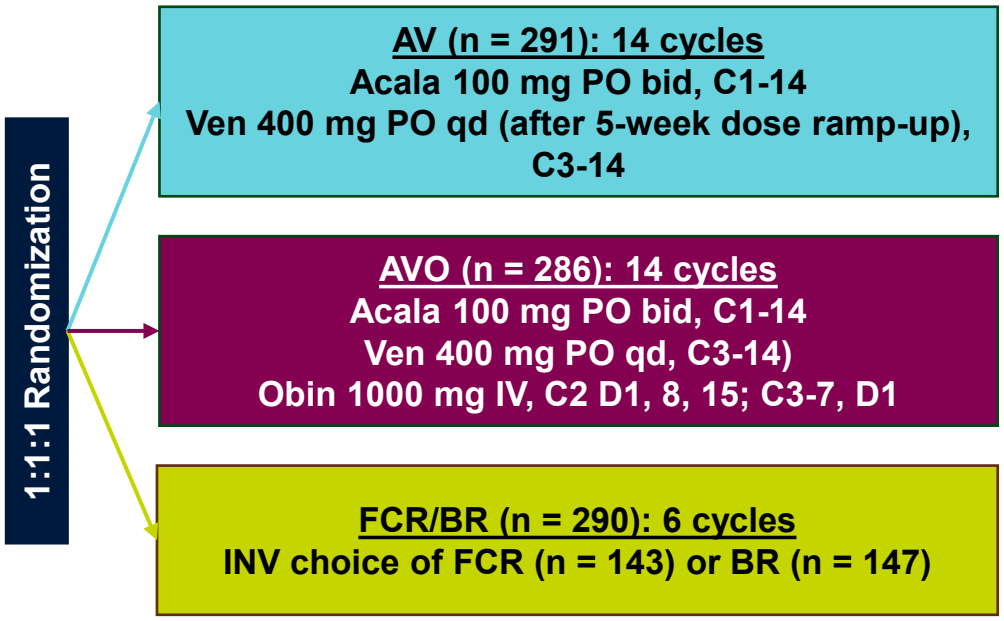
84/113 patients continued on zanubrutinib after completion of ZV

Shadman M, et al. ASH 2025. Abstract 5669.

Safety/ Ease of Use

AMPLIFY Study: Acal + Ven ± Obin vs Chemoimmunotherapy

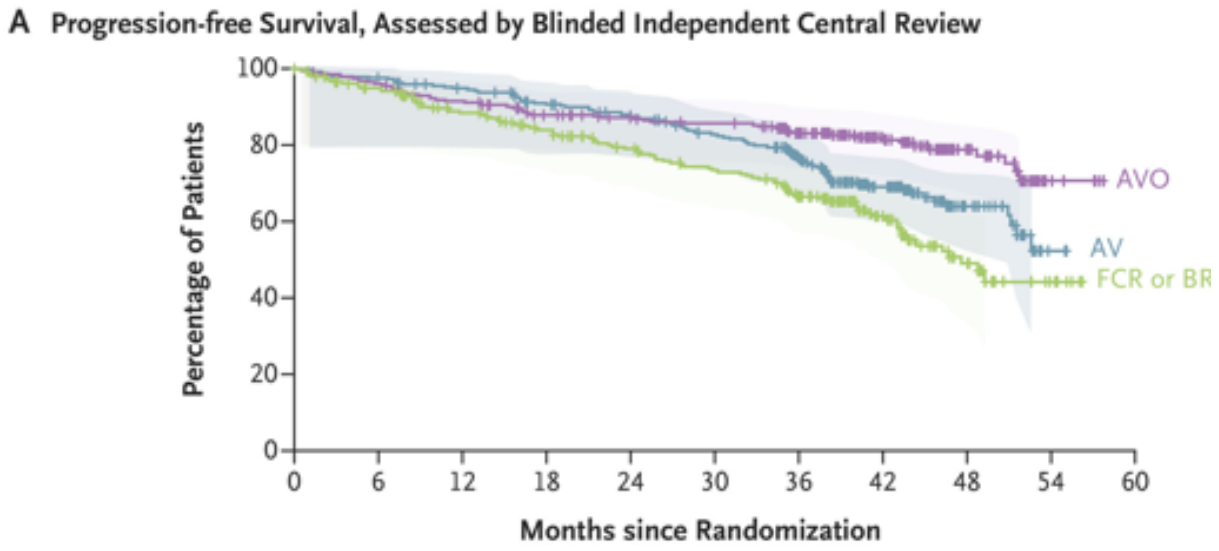
Key Eligibility Criteria
- Aged ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria
- Without del(17p) or *TP53*
- ECOG PS ≤2

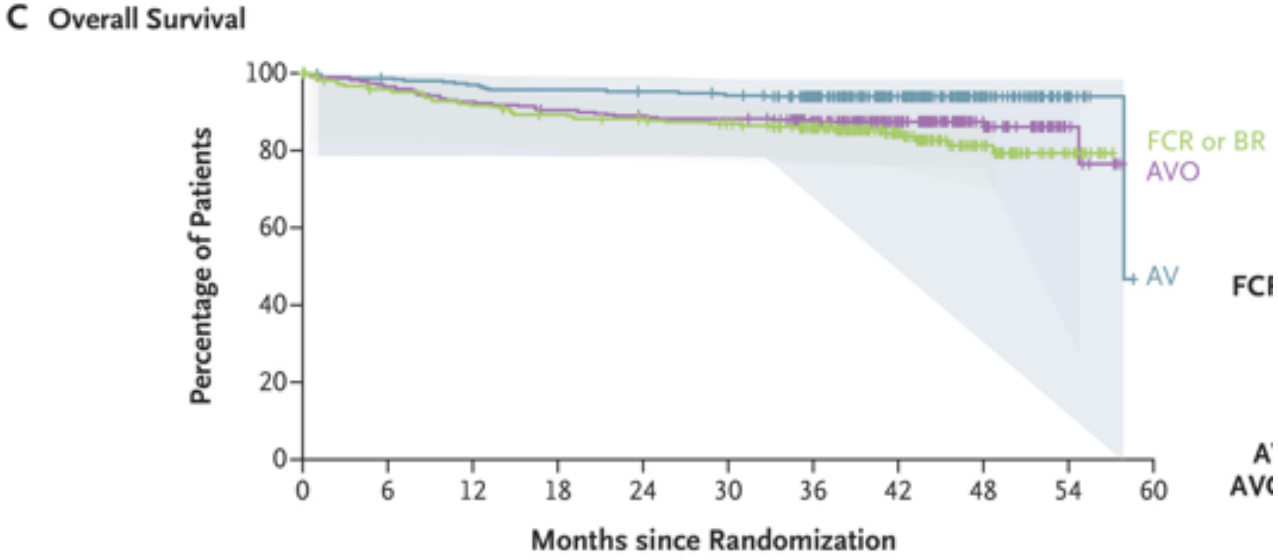


Patient Characteristics (ITT)	AV (n = 291)	AVO (n = 286)	FCR/BR (n = 290)
Median age (range), years	61 (31-84)	61 (29-81)	61 (26-86)
Rai stage III-IV, n (%)	137 (47.1)	116 (40.6)	127 (43.8)
Del[11q], n (%)	51 (17.5)	56 (19.6)	46 (15.9)
Unmutated *IGHV*, n (%)	167 (57.4)	169 (59.1)	172 (59.3)
Complex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

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

AMPLIFY: PFS and OS





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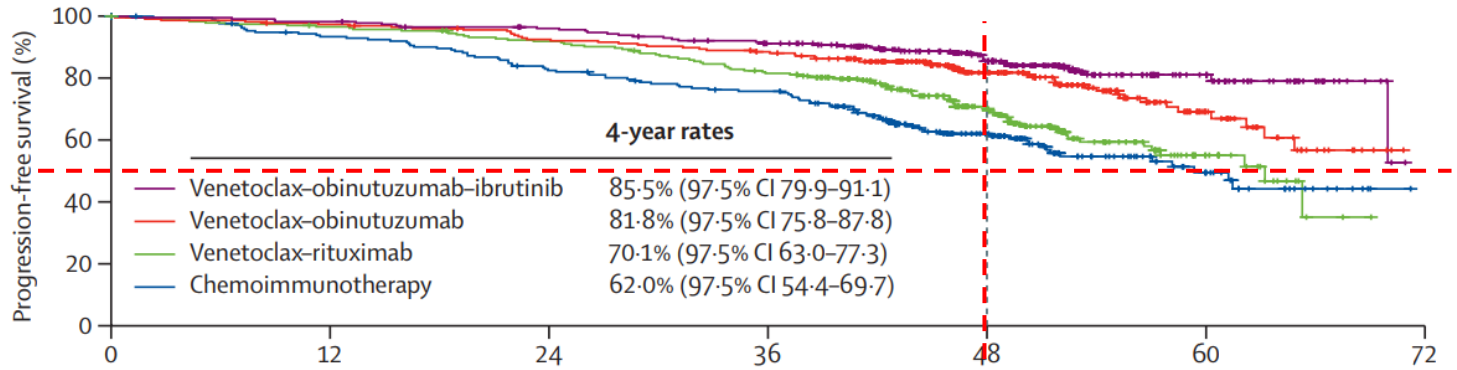

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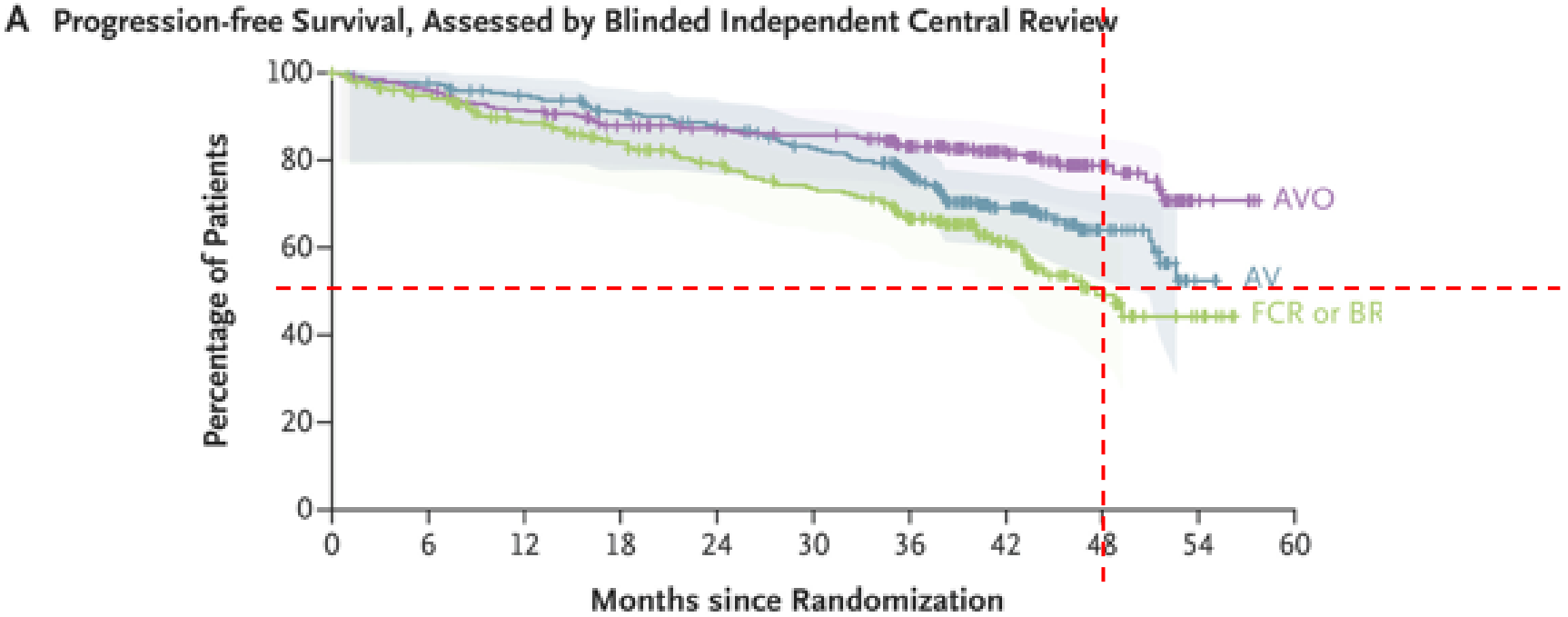


4-month PFS

IVO 85%

VO 81.8%

AVO ~80%

AV ~65%

48-month PFS – chemo

CLL13 62%

AMPLIFY 50%

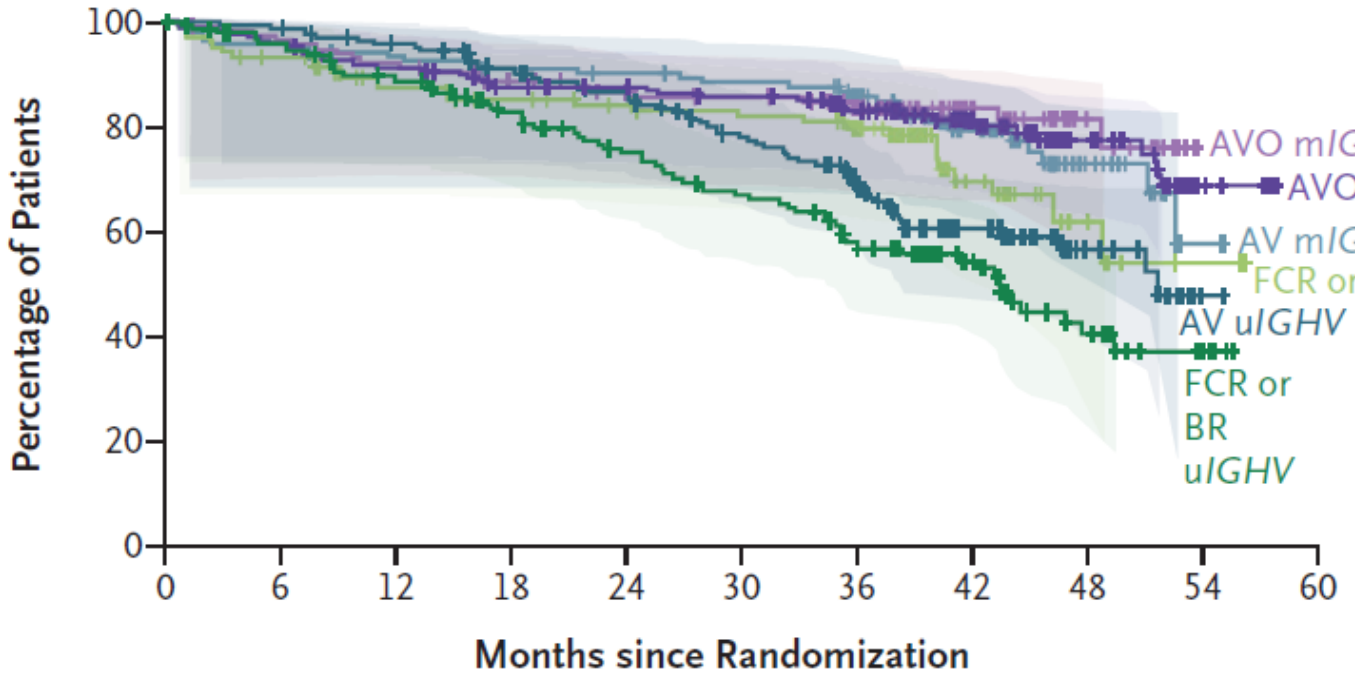
Brown JR, et al. *N Engl J Med*. 2025;392:748-762, Fürstenau M, et al. *Lancet Oncol.* 2024;25:744-759.

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)

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

AMPLIFY— PFS by IGHV status



No. at Risk											
AV m*IGHV*	124	119	114	110	108	105	91	54	18	2	0
AV u*IGHV*	167	163	155	141	129	114	86	48	17	1	0
AVO m*IGHV*	117	111	106	96	89	86	73	41	15	0	
AVO u*IGHV*	169	161	152	141	136	133	118	75	36	7	0
FCR or BR m*IGHV*	118	99	86	81	76	72	65	28	9	2	0
FCR or BR u*IGHV*	172	137	122	108	94	82	62	38	19	4	0

	No. of Events/ Total No. of Patients	Median Progression-free Suvival	Progression-free Survival at 36 Months
		mo	%
AV m*IGHV*	28/124	NC	86.0
AV u*IGHV*	61/167	51.5	68.9
AVO m*IGHV*	20/117	NC	83.6
AVO u*IGHV*	36/169	NC	82.8
FCR or BR m*IGHV*	28/118	NC	79.9
FCR or BR u*IGHV*	67/172	43.3	56.8

	Hazard Ratio for Disease Progression or Death (95% CI)
AV vs. FCR or BR (m*IGHV*)	0.67 (0.39–1.14)
AV vs. FCR or BR (u*IGHV*)	0.69 (0.48–0.97)
AVO vs. FCR or BR (m*IGHV*)	0.58 (0.32–1.02)
AVO vs. FCR or BR (u*IGHV*)	–

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

Risk of TLS is alleviated with BTKi + Venetoclax Combo

CAPTIVATE – 3 cycles lead in of ibrutinib

- -21% of patients were in the high tumor burden category for tumor lysis syndrome (TLS) risk; after ibrutinib lead-in, only 1% remained
- -0 clinical TLS observed
    - Rasburicase used for 8 patients for prophylaxis

AMPLIFY – 2 cycles lead in of acalabrutinib

-2 out of 577 patients had TLS in the acalabrutinib then venetoclax treated patients treated patients

New data challenges some of our assumptions

- **CLL17** – Time-limited therapy = Continuous therapy
- **FLARE** – MRD-Guided therapy increases survival
  - But how much therapy is actually needed?
- **SEQUOIA ARMD/ AVO MRD Directed** – MRD-Guided therapy may ameliorate high-risk features that give pause to use 1-year of therapy
- **AMPLIFY** – All oral therapy is associated with low TLS, and improved safety
  - Can we avoid obinutuzumab in the future?

Discussion

Patient Case

- 82 y/o woman ECOG-1 with a history of controlled HTN and DM2.
- Presented with fatigue and incidentally detected leukocytosis.
- Diagnosed with **del17p positive, IGHV mutated CLL**.
  - WBC 300, Hb 10, plt 100
  - LDH is 1000
  - Uric acid is 8.0
- She has no treatment preference but wants to avoid hospitalization for side effects where possible.

Questions

- What's your preferred front-line treatment for CLL?
  - Based on CLL17, does the data push you to favor time-limited therapy?
  - How do you decide between time-limited and continuous therapy?

- What are the biggest barriers to using time-limited therapy, either finite or MRD-directed, in your clinic?
  - TLS monitoring, venetoclax ramp-up, obinutuzumab infusions and reactions, specific patient concerns? Anything else?

- Now having an all-oral time-limited regimen available, is this something you can see treating patients with?
  - What are the factors that might sway you to use it and not use it?

- How about 2nd line, what's the primary driver of your decisions here?

- Any other questions or cases you want to discuss?

Thanks!