City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Chronic Lymphocytic Leukemia: Time-Limited Therapy for Treatment Naïve Disease

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City of Hope

Disclosures

- Consultant for Guardant Health & Sobi; Grant Research Support from AstraZeneca, BeOne Medicines, Century Therapeutics & Incyte. But relationship has ended with all of them.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Cultural diversity in the epidemiology and treatment of patients with CLL.*
- *Patient population at need who may experience disparities in care and how we may be able to offer more novel time limited treatment approaches in managing their CLL.*

Presentation Objectives

- Review current treatment strategies for TN CLL
- Discuss emerging therapies and clinical trial data
- Address cultural diversity and disparities in care
- Evaluate MRD and survival outcomes
- Consider adverse events and treatment tolerability

TN CLL 2025

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

Prior to 2025 TN CLL

FIRST-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• 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)	• BCL2i-containing regimen ▸ Venetoclax[f,h] + ibrutinib[f,g] • cBTKi-based regimen ▸ Ibrutinib[f,g,i] (category 1)	• 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 if single 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)

VenO

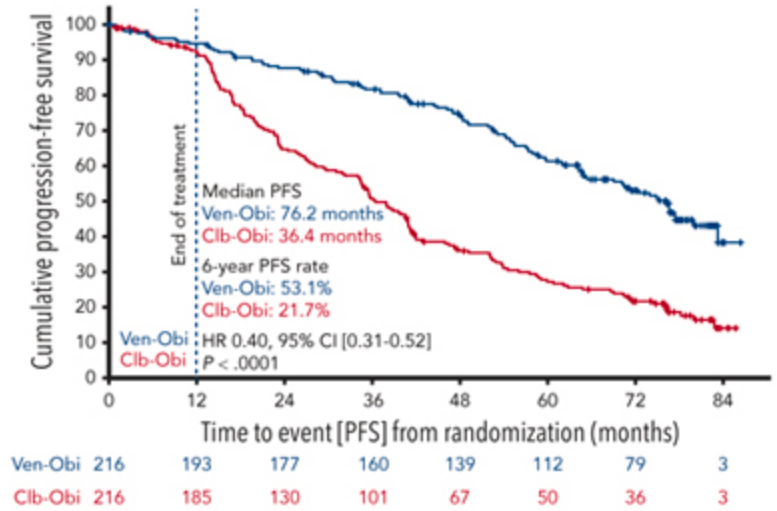
Continuous single agent BTKi

BCL2i + BTKi

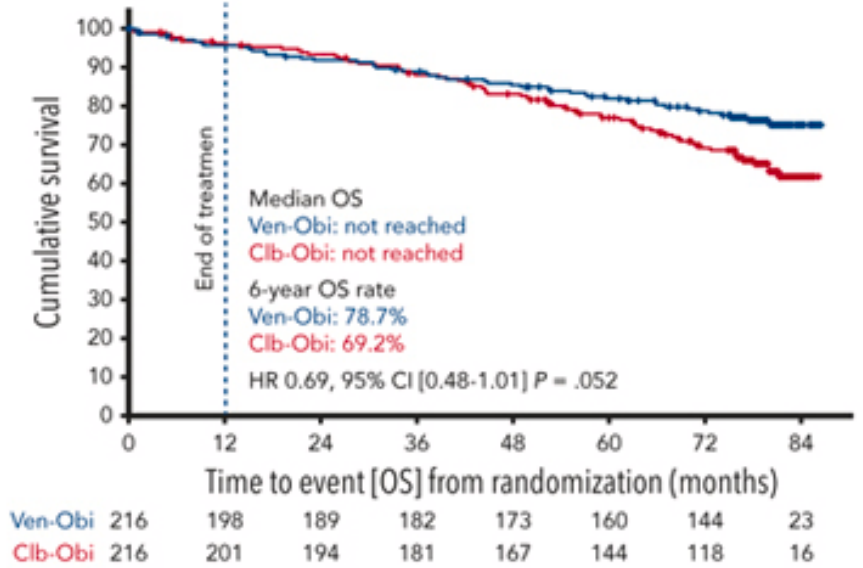
Fixed Duration VenO - CLL14 Trial

Main Findings

- **Progression-free survival**

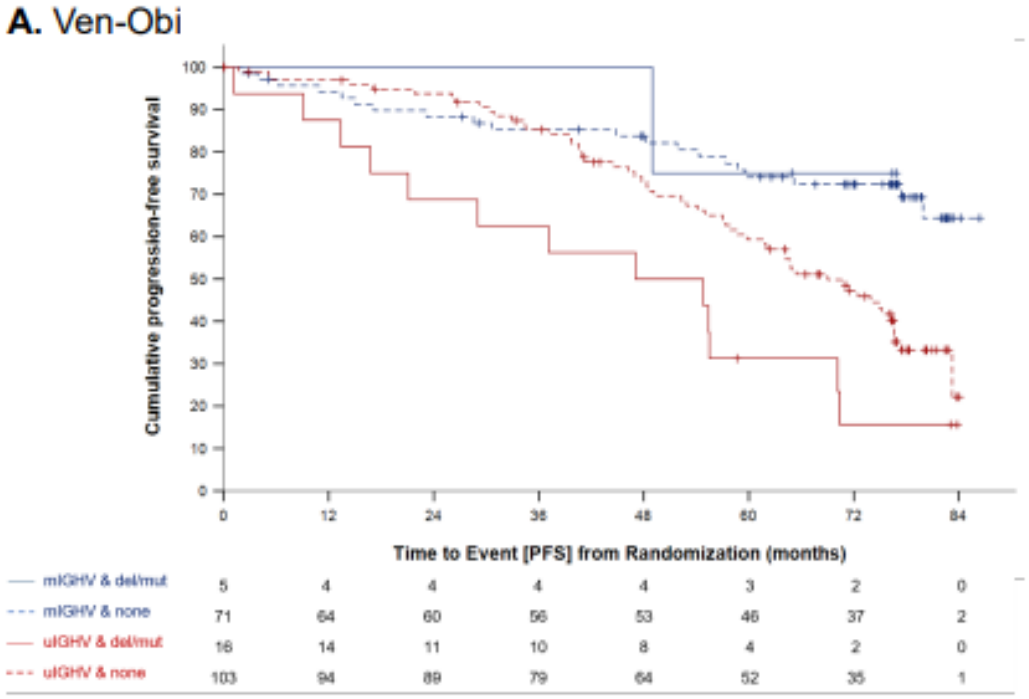


- **Overall survival**



Blood (2024) 144 (18): 1924–1935.

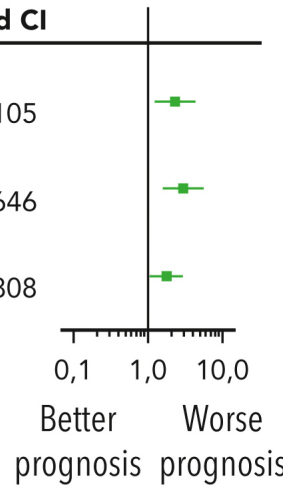
Subgroup analysis of VenO



D

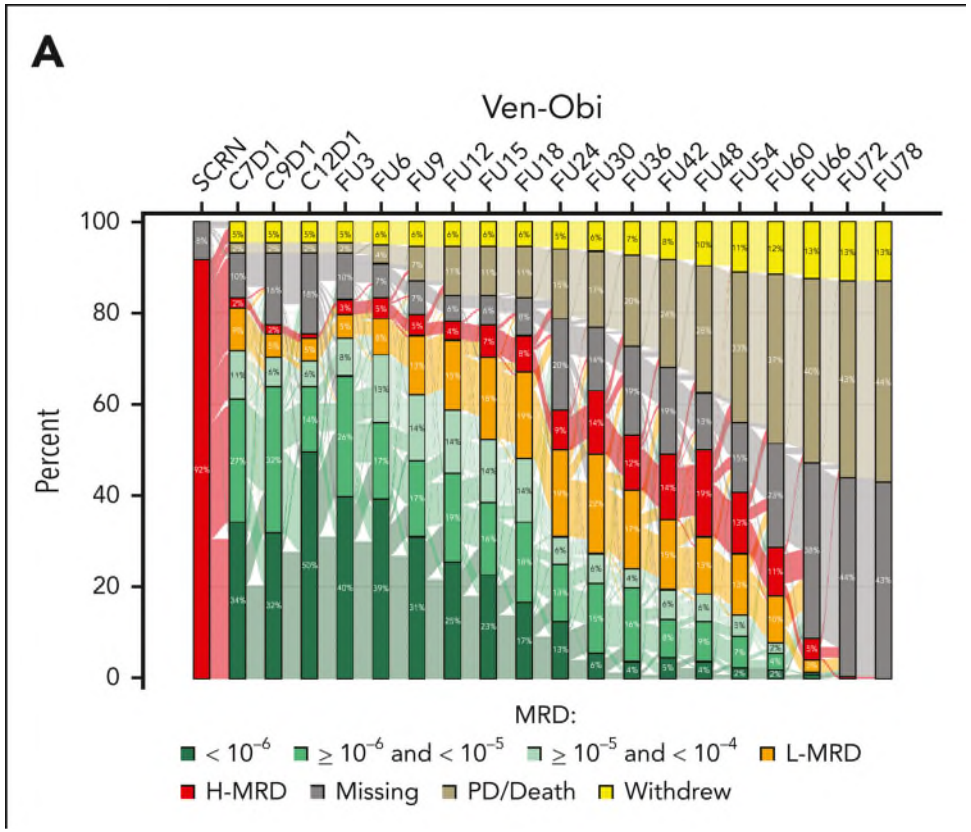
Ven-Obi

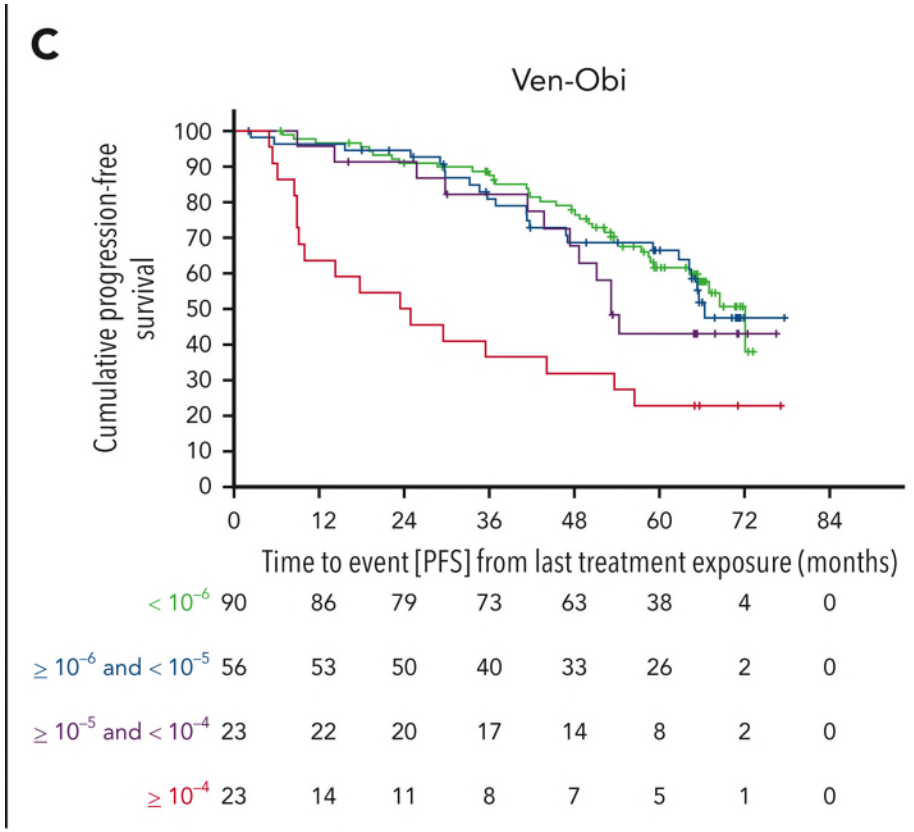
Cox regression PFS		Hazard ratio	95% Wald CI
IGHV mutational status			
unmutated	vs. mutated	2.310	1.300-4.105
Deletion 17p			
del(17p)	vs. no del(17p)	2.941	1.532-5.646
Lymph node size			
≥ 5 cm	vs. < 5 cm	1.768	1.114-2.808



Blood (2024) 144 (18): 1924–1935.

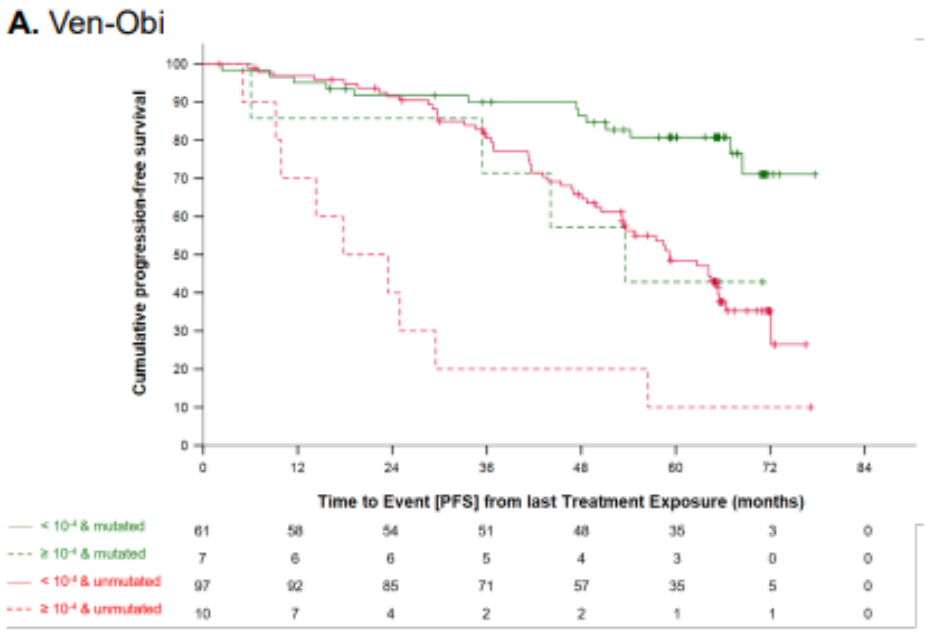
MRD after Treatment with VenO

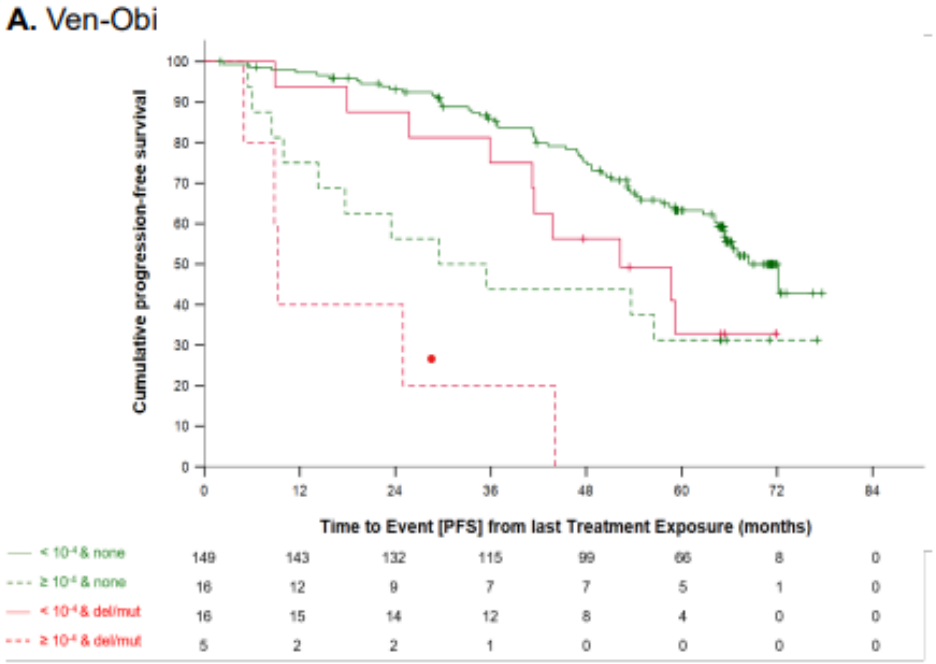




Nat Commun 14, 2147 (2023)

Survival by MRD and Risk Profile





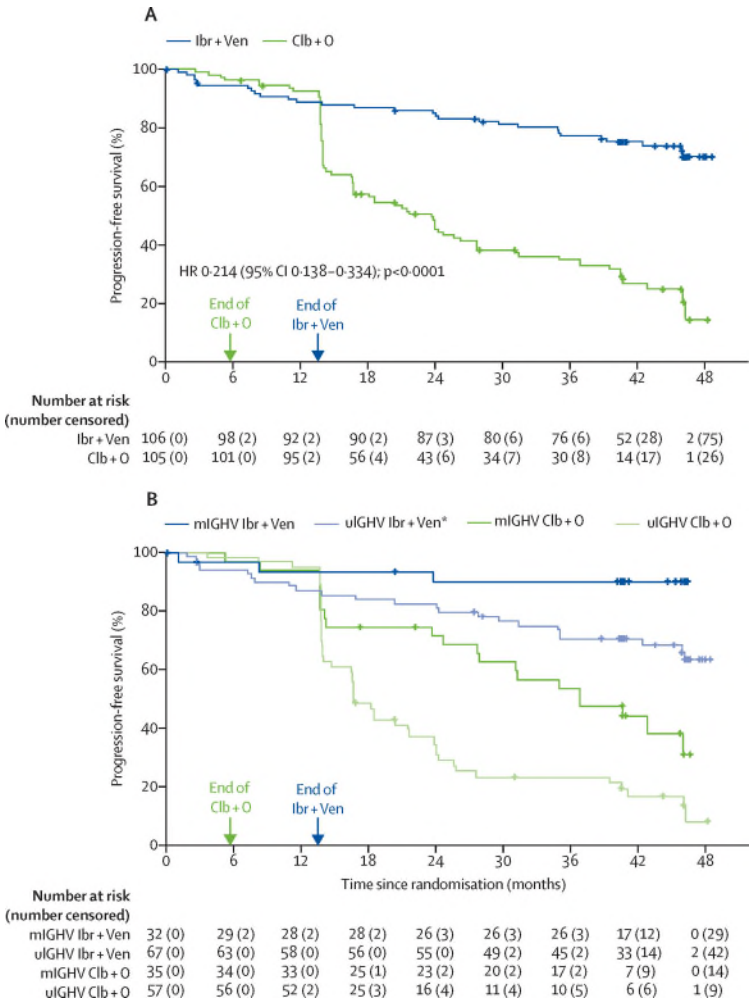
Blood (2024) 144 (18): 1924–1935.

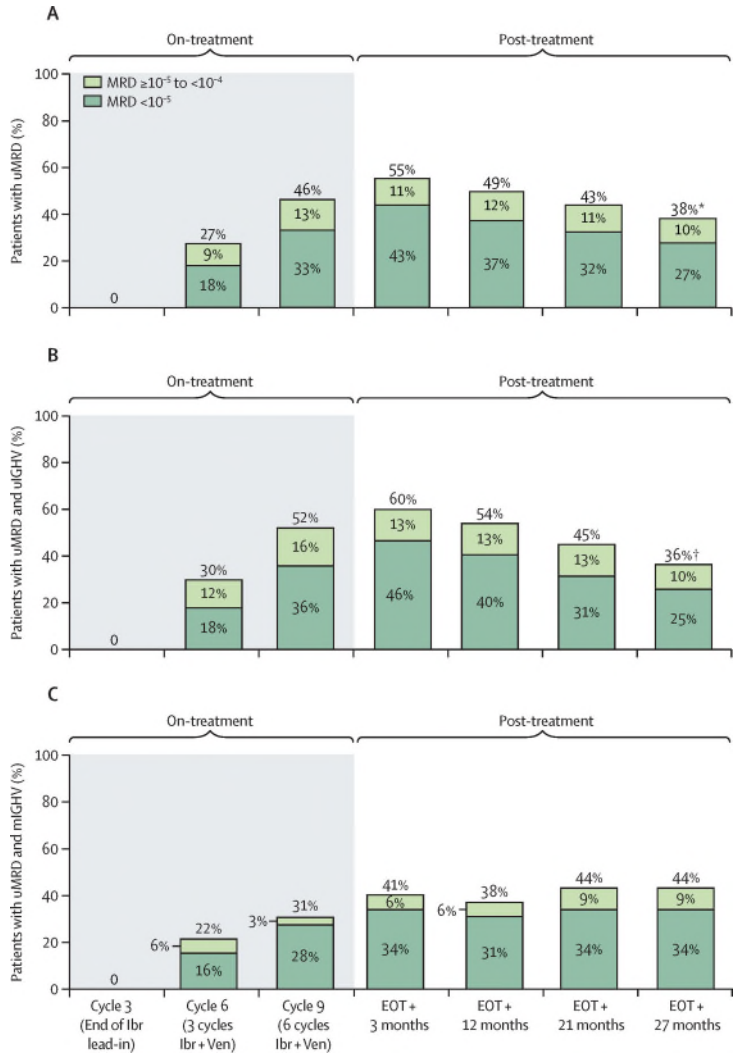
Common G3/4 AEs with VenO

	Clb-Obi (n=214)	Ven-Obi (n=212)
Total number of patients with at least one Grade 3,4 adverse event	163 (76.2%)	176 (83.0%)
NEUTROPENIA	102 (47.7%)	112 (52.8%)
THROMBOCYTOPENIA	32 (15.0%)	30 (14.2%)
INFUSION RELATED REACTION	22 (10.3%)	19 (9.0%)
ANAEMIA	14 (6.5%)	18 (8.5%)
PNEUMONIA	9 (4.2%)	14 (6.6%)
FEBRILE NEUTROPENIA	8 (3.7%)	11 (5.2%)

Blood (2024) 144 (18): 1924–1935.

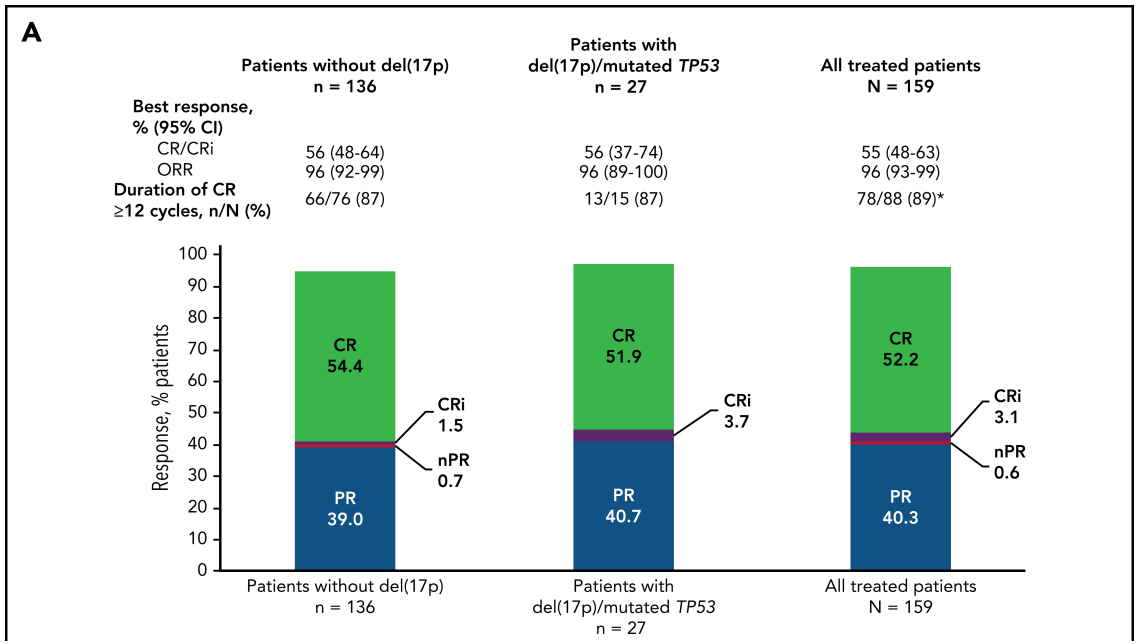
BTKi + BCL2i Combinations: I + V (GLOW)

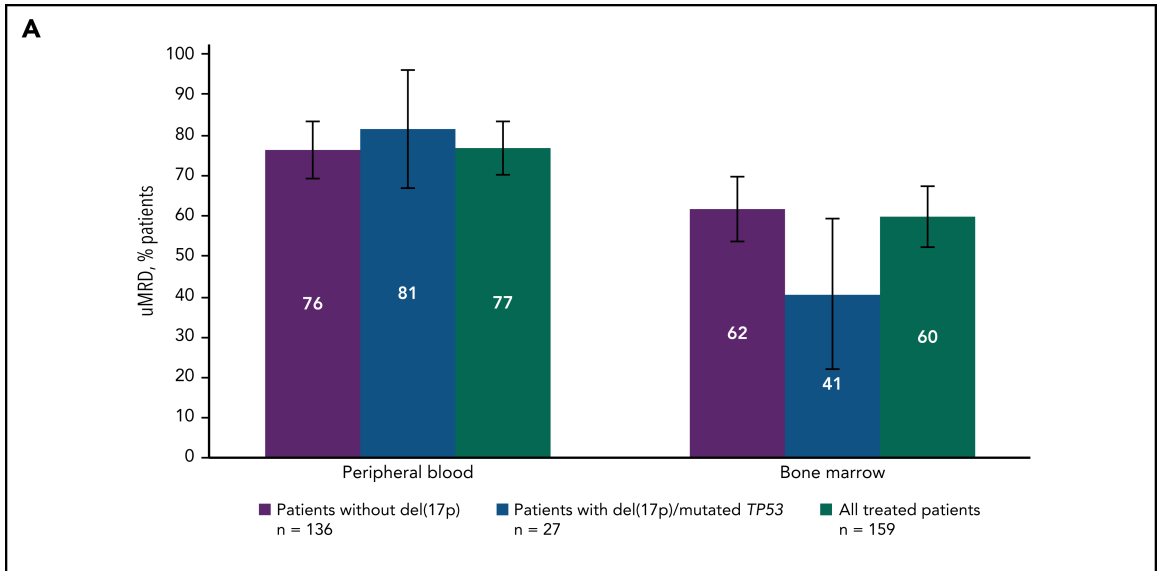




Lancet Oncology. 2023;24(12)

Captivate





Blood. 2022; 139 (22): 3278–3289.

Captivate – Fixed Duration Cohort I + V

FD cohort	With high-risk genomic feature[a]		Without high-risk genomic feature[a]	
	n	5-y PFS rate, % (95% CI)	n	5-y PFS rate, % (95% CI)
del(17p)/mutated *TP53*	27	41 (21–59)	129	73 (64–80)
CK[b]	31	57 (37–72)	102	72 (61–80)
Unmutated IGHV[c]	40	68 (50–80)	44	85 (69–93)
del(11q)[c]	11	64 (30–85)	74	79 (67–87)

JCO. 2024; 42, 7009-7009.

AE with I+V

AEs	All treated patients (n = 159), n (%)	
	Any grade	Grade 3/4
Most common AEs[*]		
Diarrhea	99 (62)	5 (3)
Nausea	68 (43)	2 (1)
Neutropenia	66 (42)	52 (33)
Arthralgia	53 (33)	2 (1)
Hypertension	25 (16)	9 (6)
Neutrophil count decreased	16 (10)	8 (5)
Other AEs of clinical interest		
Atrial fibrillation	7 (4)	2 (1)
Major hemorrhage[†]	3 (2)	2 (1)
Laboratory safety parameters		
Hematology		
Neutrophils decreased	115 (72)	60 (38)
Platelets decreased	94 (59)	20 (13)

Blood. 2022; 139 (22): 3278–3289.

Amplify

TN CLL (N=867)

Key inclusion criteria

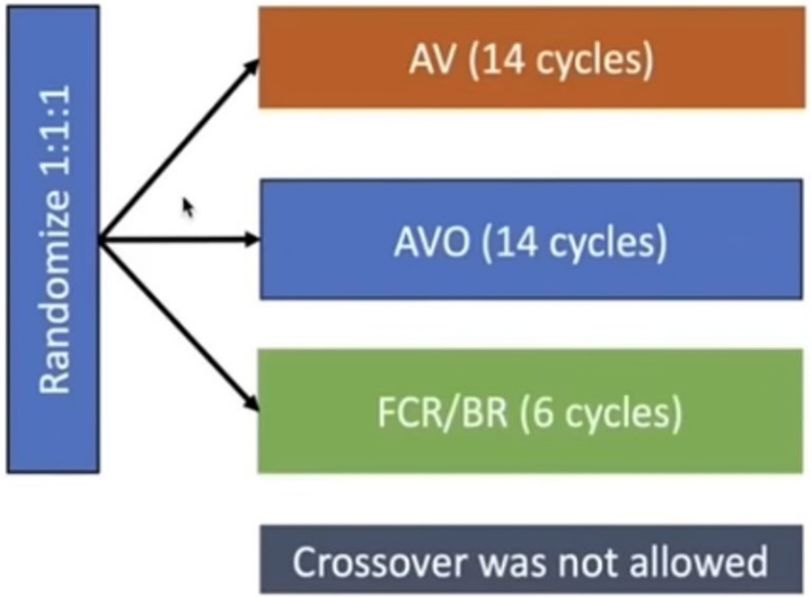
- Age 218 years
- TN CLL requiring treatrment per iwCLL 2018
- Without del(17p) or TP53
- ECOG PS≤2

Key exclusion criteria

- CIRS-Geriatric > 6
- Significant cardiovascular disease

Stratification

- Age (>65 vs ≤65 years)
- IGHV mutational status
- Rai stage (≥3 vs <3)
- Geographic region



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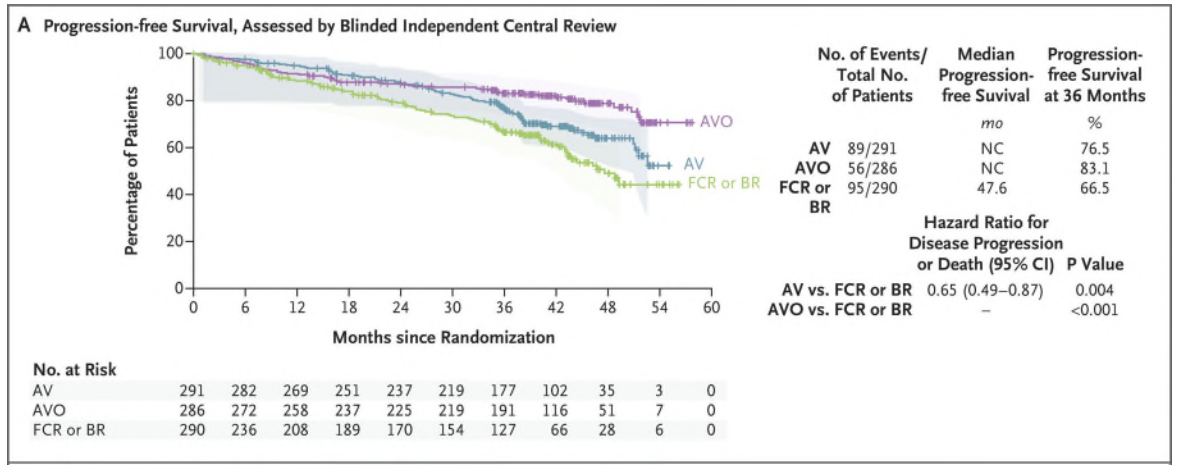
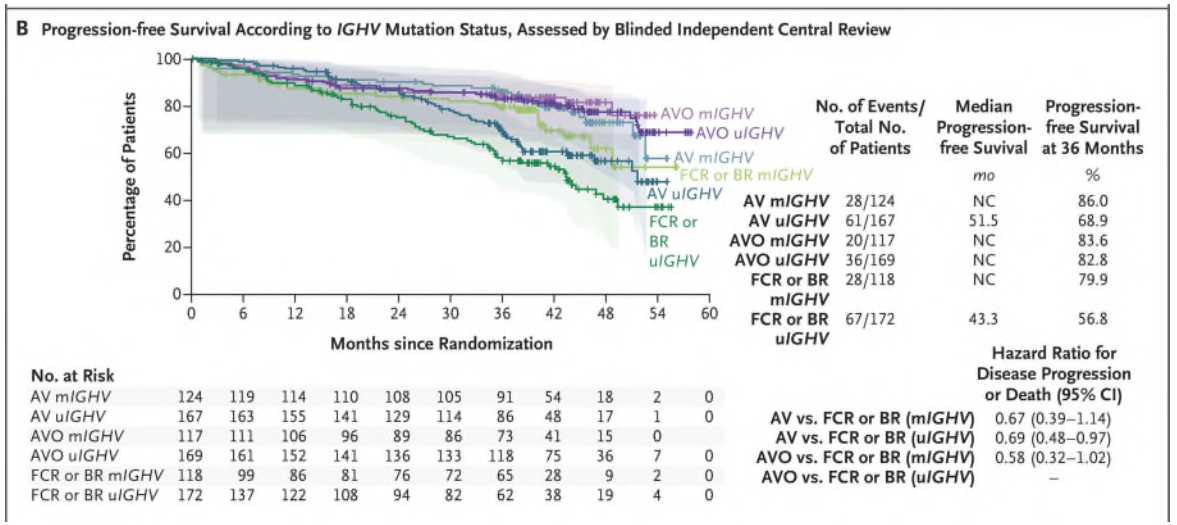
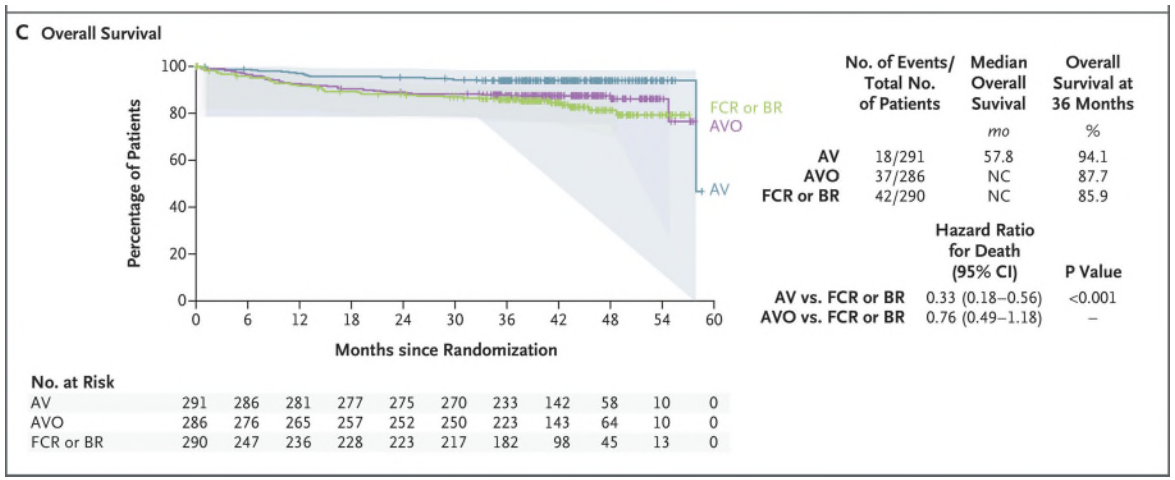
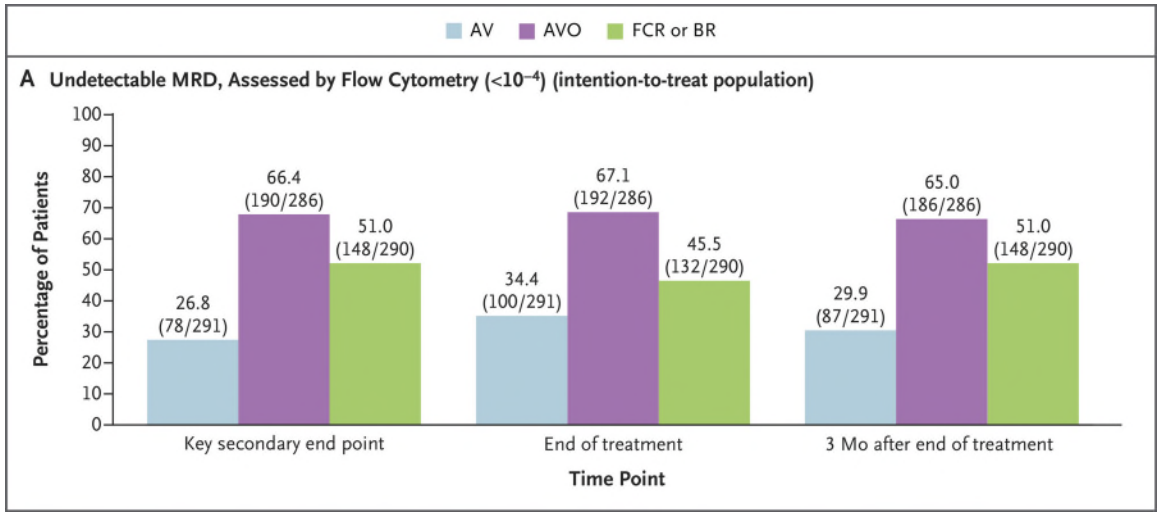




N Engl J Med 2025;392:748-762

OS and MRD





N Engl J Med 2025;392:748-762

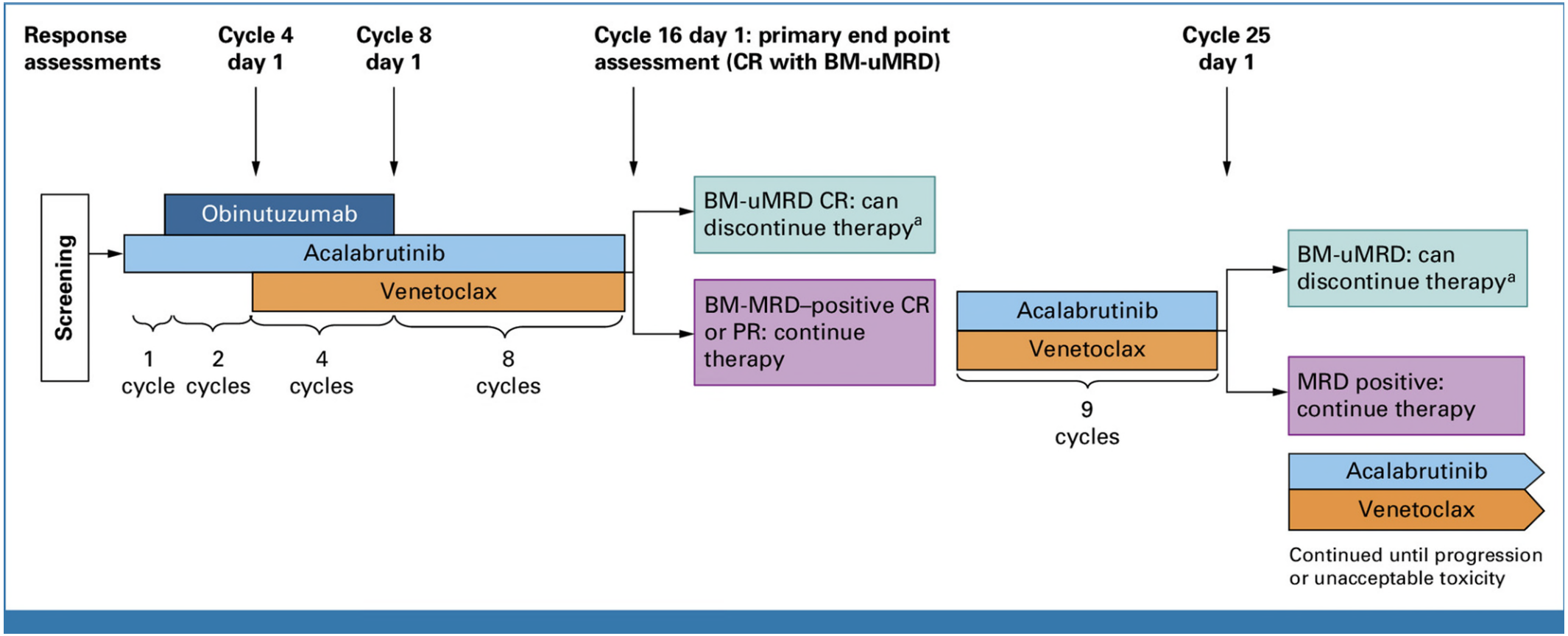
Adverse Events

Table 2. Adverse Events and Selected Events of Clinical Interest (Safety Population).*

Adverse Events	Acalabrutinib–Venetoclax (N=291)		Acalabrutinib–Venetoclax–Obinutuzumab (N=284)		Chemoimmunotherapy (N=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)					
Events						
Any adverse event	270 (92.8)	156 (53.6)	269 (94.7)	197 (69.4)	236 (91.1)	157 (60.6)
Any serious adverse event	72 (24.7)		109 (38.4)		71 (27.4)	
Serious adverse event leading to death						
Any	10 (3.4)		17 (6.0)		9 (3.5)	
Due to Covid-19	8 (2.7)		15 (5.3)		7 (2.7)	
Adverse event leading to treatment discontinuation	23 (7.9)		57 (20.1)		28 (10.8)	

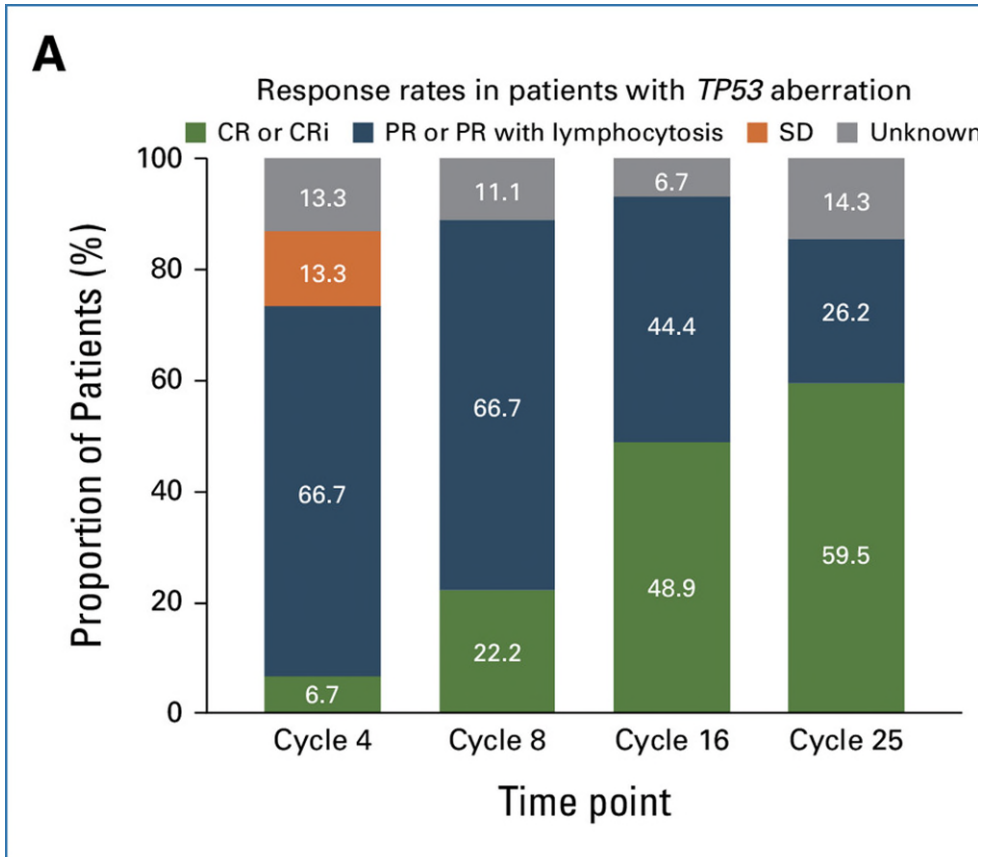
N Engl J Med 2025;392:748-762

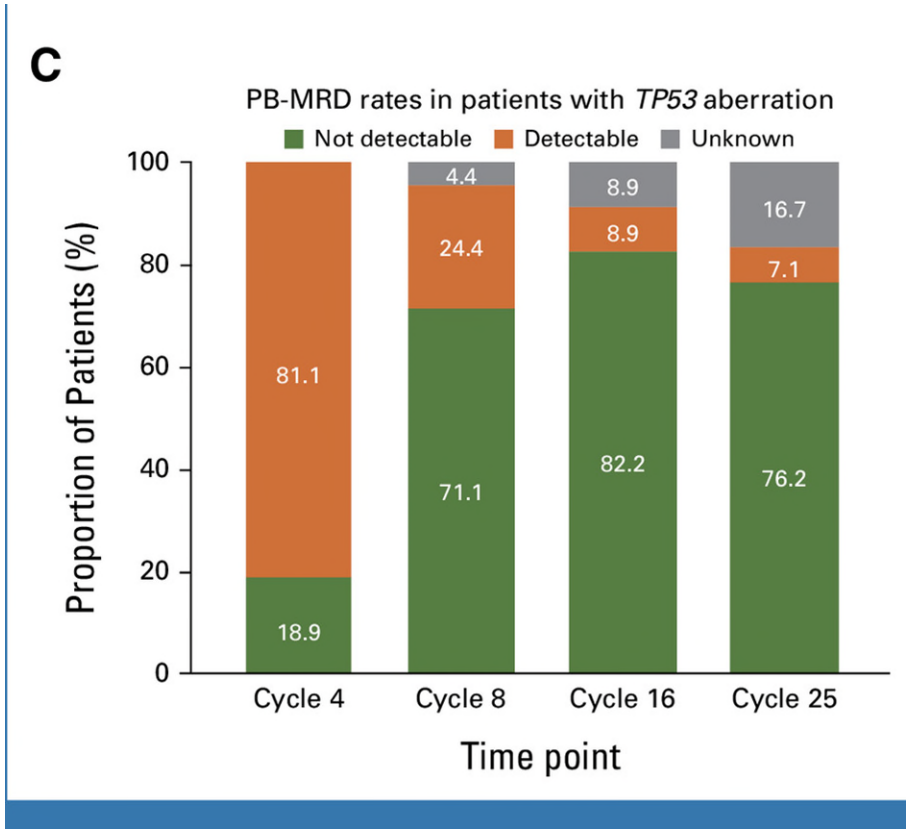
AVO in High-Risk CLL



JCO. 2025; 43:788-799.

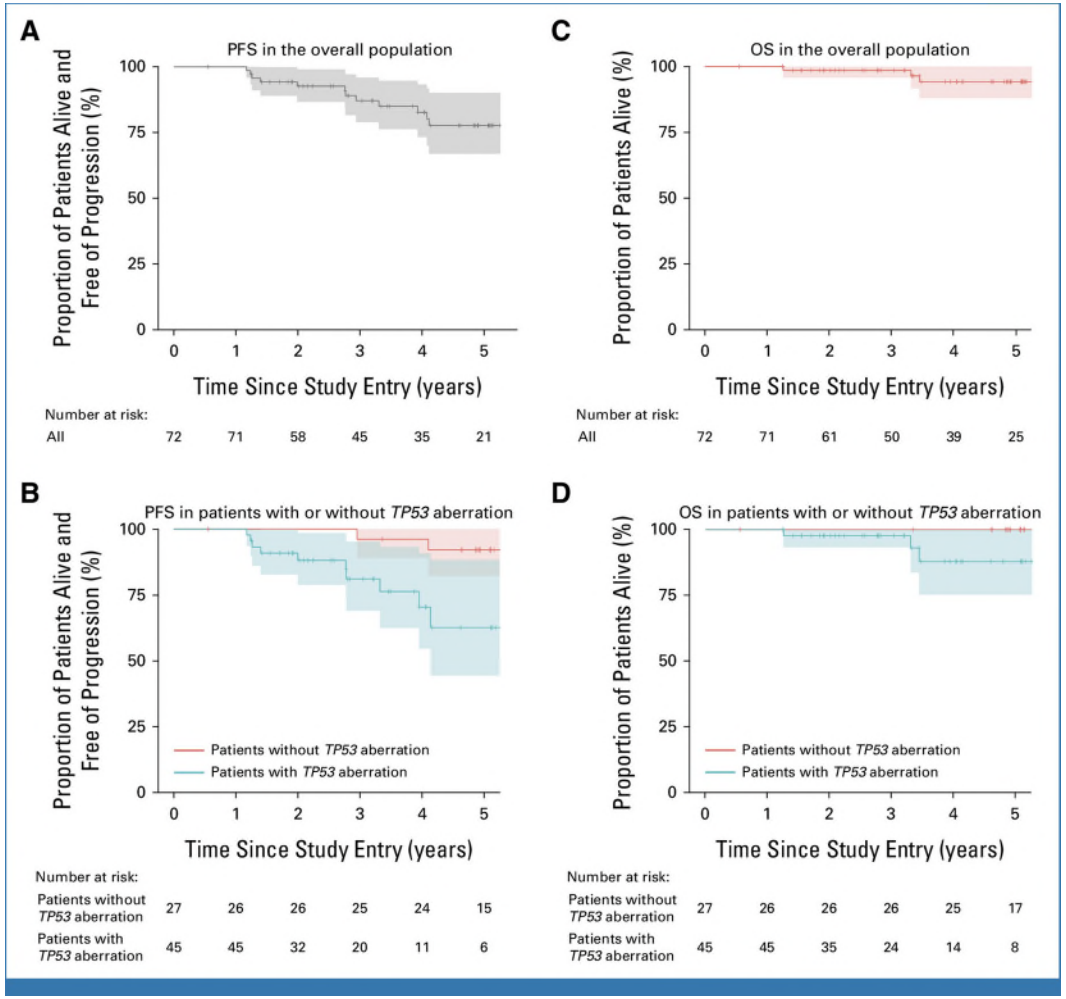
Outcomes of AVO in High-Risk CLL





J Clin Oncol 43:788-799

Survival after AVO in High-Risk CLL



J Clin Oncol 43:788-799

Treatment Patterns in the US – Impact on Cultural Diversity and Disparities of Care

Table. Treatment Patterns by Line of Therapy of Patients with CLL/SLL

Lines of therapy	First line *(Based on 1L only)*
All patients	
Number of patients, n	5,226
Observation period, years, mean ± SD [median]	2.8 ± 1.9 [2]
Treatment with antineoplastic therapies during LOT, n (%)	
CLL therapy	4,132 (79.1)
CIT	1,199 (22.9)
Chemotherapy	410 (7.8)
Targeted therapy	2,516 (48.1)
Ibrutinib single agent	970 (18.6)
Rituximab single agent	902 (17.3)
Acalabrutinib single agent	176 (3.4)
Venetoclax single agent or combination	177 (3.4)
Non-CLL therapy	1,094 (20.9)
Stratified analyses - Patients with a first CLL diagnosis 2014–2017	
Number of patients, n	2,585
Observation period, years, mean ± SD [median]	3.9 ± 2.1 [4]
Treatment with antineoplastic therapies during LOT, n (%)	
CLL therapy	2,026 (78.4)
CIT	778 (30.1)
Chemotherapy	162 (6.3)
Targeted therapy	1,082 (41.9)
Rituximab single agent	476 (18.4)
Ibrutinib single agent	439 (17.0)
Acalabrutinib single agent	25 (1.0)
Venetoclax single agent or combination	23 (0.9)
Non-CLL therapy	559 (21.6)
Stratified analyses - Patients with a first CLL diagnosis 2018–2021	
Number of patients, n	2,641
Observation period, years, mean ± SD [median]	1.8 ± 1.1 [2]
Treatment with antineoplastic therapies during LOT, n (%)	
CLL therapy	2,106 (79.7)
CIT	421 (15.9)
Chemotherapy	248 (9.4)
Targeted therapy	1,434 (54.3)
Ibrutinib single agent	531 (20.1)
Rituximab single agent	426 (16.1)
Acalabrutinib single agent	151 (5.7)
Venetoclax single agent or combination	150 (5.7)
Non-CLL therapy	535 (20.3)

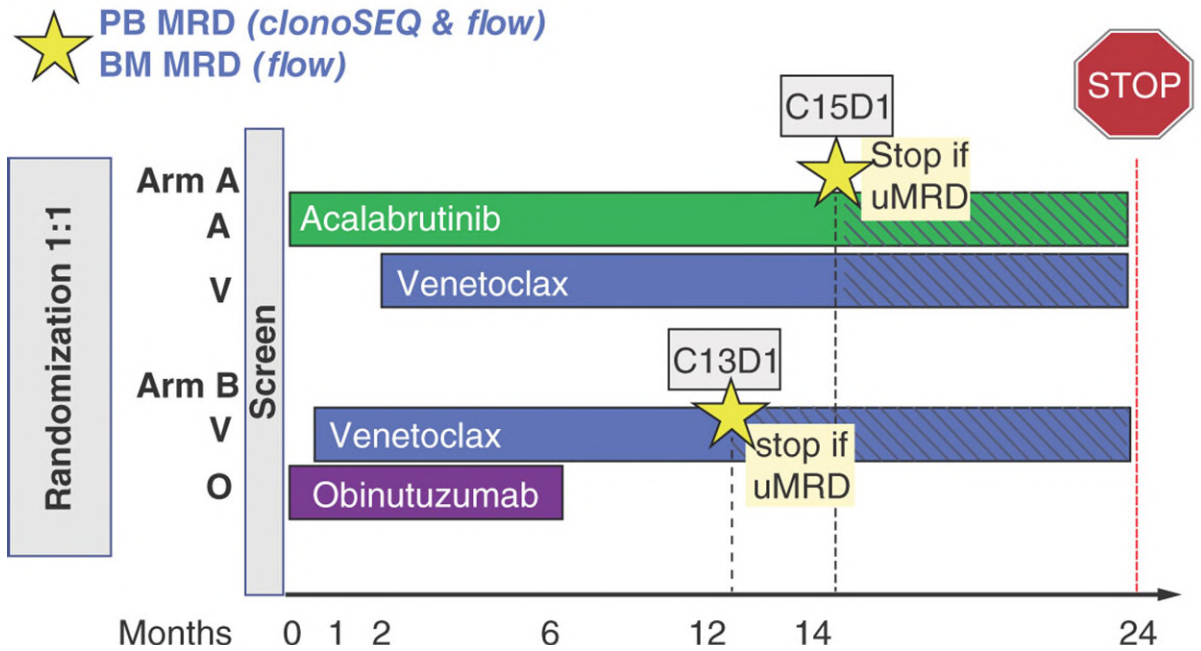
Hemasphere. 2023 Aug 8;7(Suppl):e6855326.

MAJIC Trial

MAJIC schema

Arm A **Acalabrutinib (A)** 100 mg po BID,
Venetoclax (V) 400 mg po daily (C3D1–C14), including 5 week ramp up
STOP if uMRD and at least PR. If MRD+ continue AV to 24 months

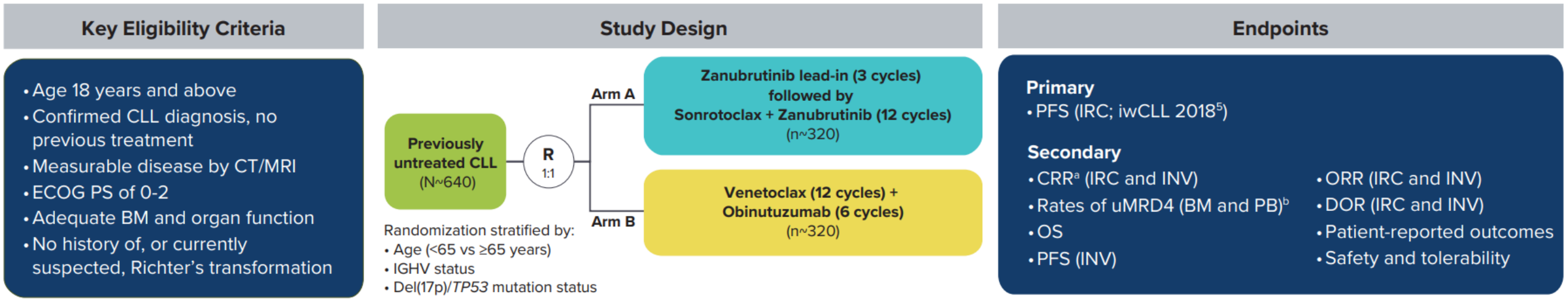
Arm B **Venetoclax (V)** 400 mg po daily (C1D22–C12), including 5 week ramp up
Obinutuzumab (O) 1000 mg iv. (C1D1-2/8/15, C2-6 D1)
STOP if uMRD and at least PR. If MRD+ continue V to 24 months



Future Oncology, 18(33), 3689–3699

Celestial Trial

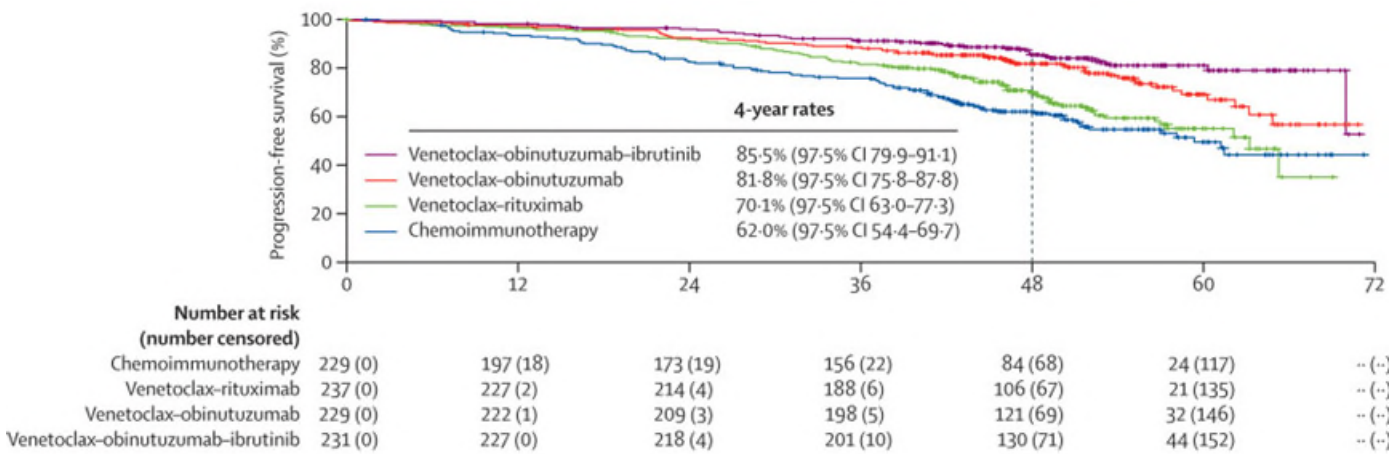
Figure 1. CELESTIAL-TNCLL Study Design

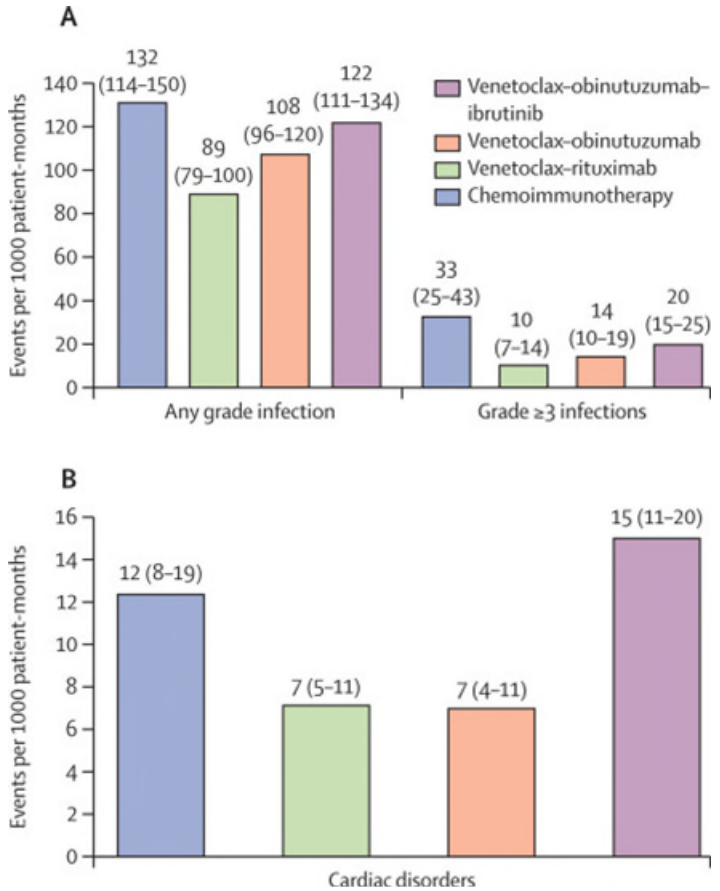


JCO. 2024; 42 TPS7087-TPS7087.

Questions

Is there 3 drugs better then 2? – CLL-13 Trial





Lancet Oncol 2024; 25: 744–59