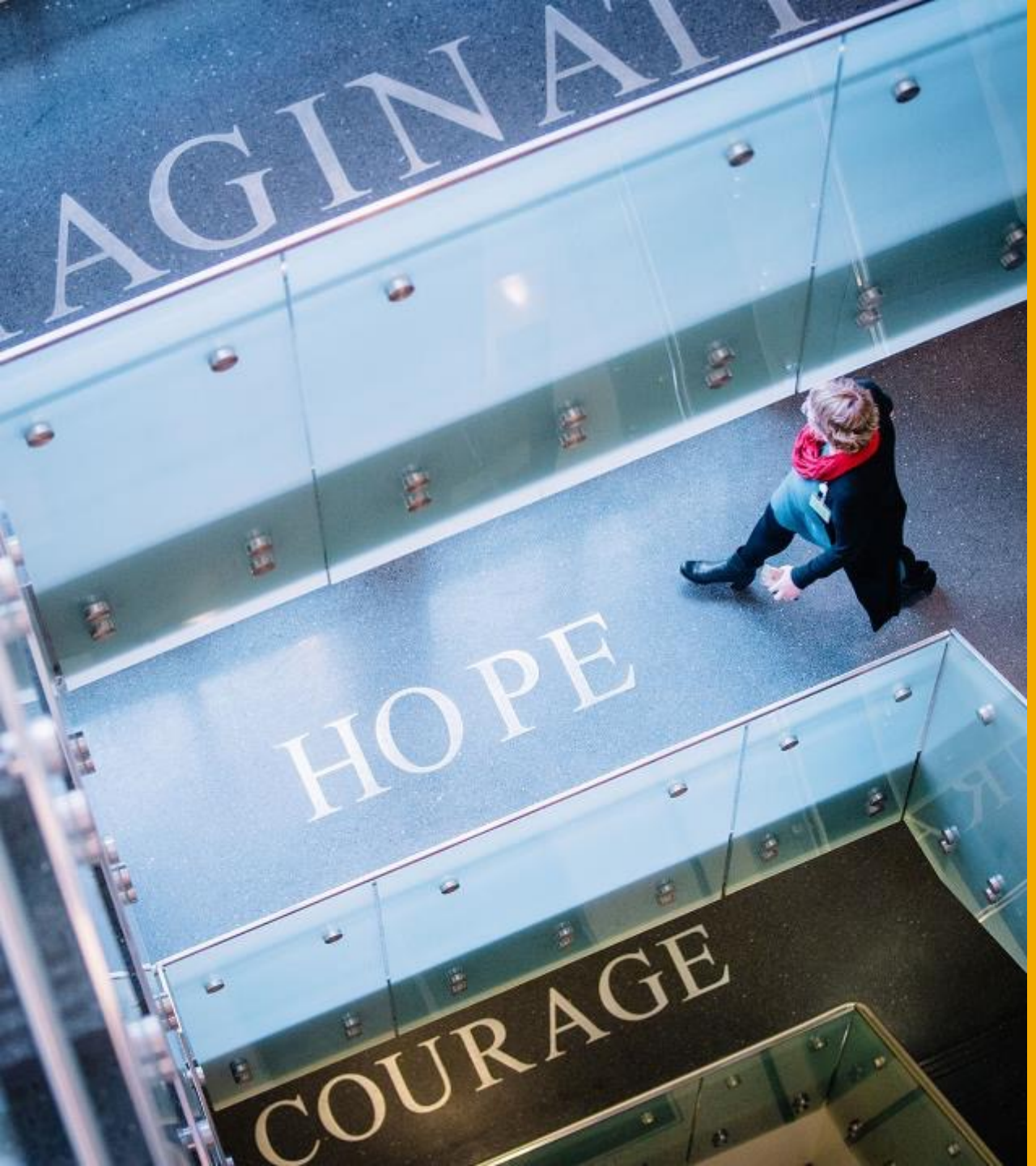

CHRONIC LYMPHOCYTIC LEUKEMIA

MRD IS A USEFUL TOOL IN THE MANAGEMENT OF PATIENTS WITH CLL – NOT YET

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DDHO 2025

EMORY WINSHIP CANCER INSTITUTE

NCI Designated Comprehensive Cancer Center

Disclosures

Consultancy: AstraZeneca, Abbvie

Current Standard of Care in CLL

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

First line (preferred)

- Venetoclax + obinutuzumab
- **Venetoclax + acalabrutinib +/- obin**
- Acalabrutinib +/- obin
- Zanubrutinib

Other recommended first line regimens

- Ibrutinib
- Venetoclax + ibrutinib

Subsequent lines (preferred)

- Venetoclax +/- obinutuzumab
- Acalabrutinib
- Zanubrutinib
- Pirtobrutinib

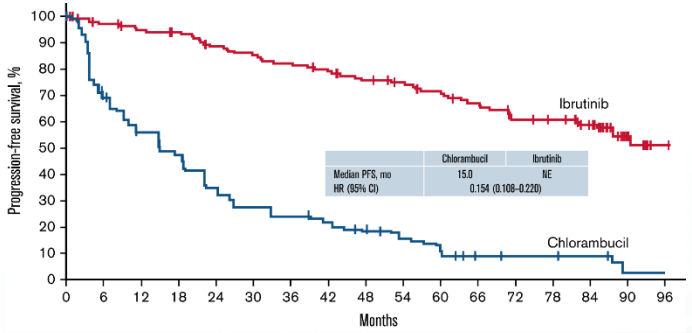
After prior BTKi and Bcl2i-containing regimens

- Lisocabtagene maraleucel

Summary: most treatment regimens are based on BTK inhibitors and venetoclax

BTKi Produce Long PFS Without Attaining uMRD

Ibrutinib

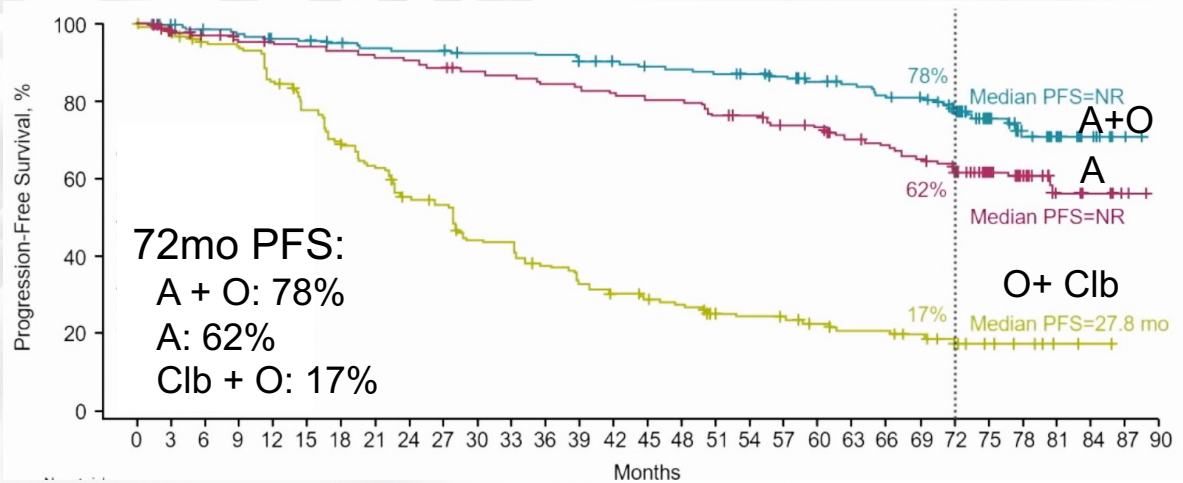


RESONATE-2
Median DOT: 6.2 yrs
9-yr PFS: 49.7%

Barr et al, Blood Adv 2022
and Burger et al, CLML 2024

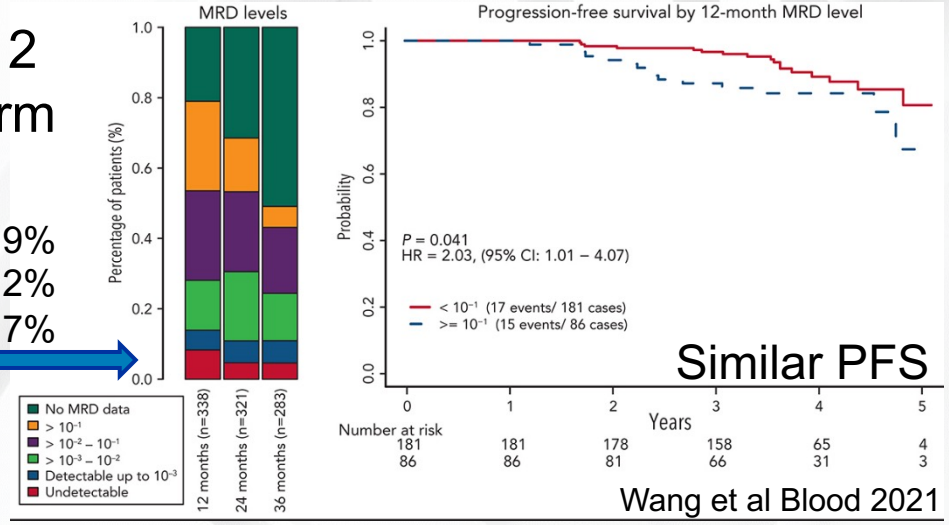
NCI study: uMRD4 at 4 yrs = 10.2%. No difference in PFS between MRD+ and uMRD (Ahn, et. al, Blood 2018)

Acalabrutinib
ELEVATE-TN



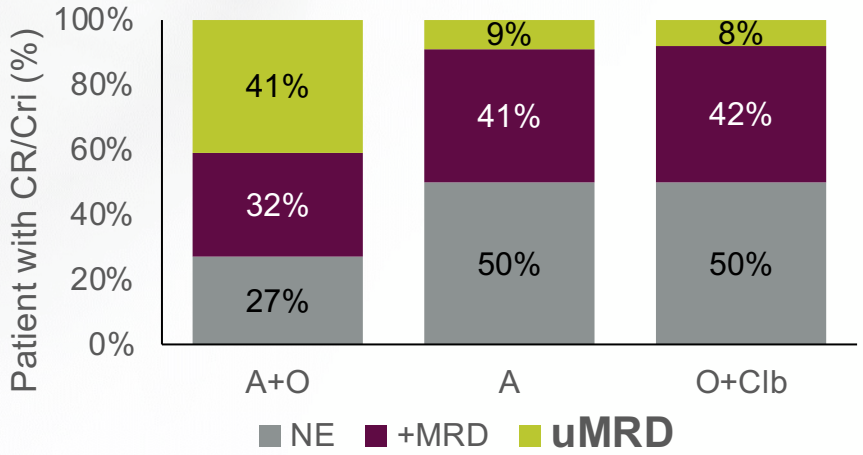
E1912
I+R arm

12 mo: 7.9%
24 mo: 4.2%
36 mo: 3.7%



Similar PFS

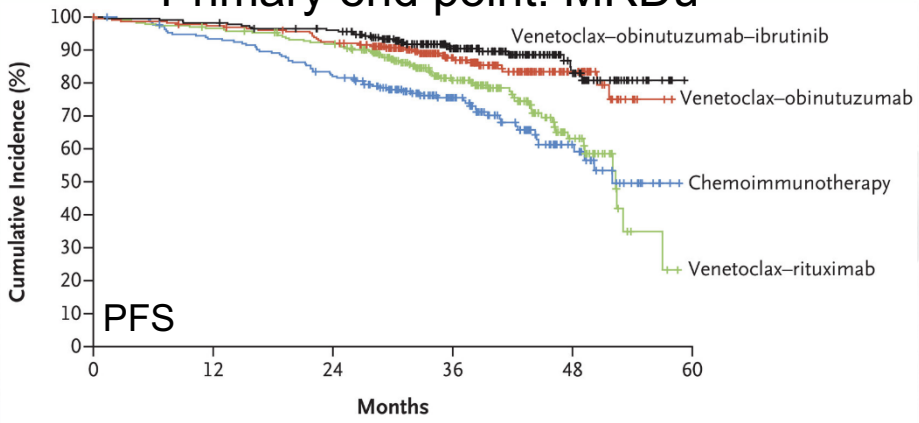
Wang et al Blood 2021

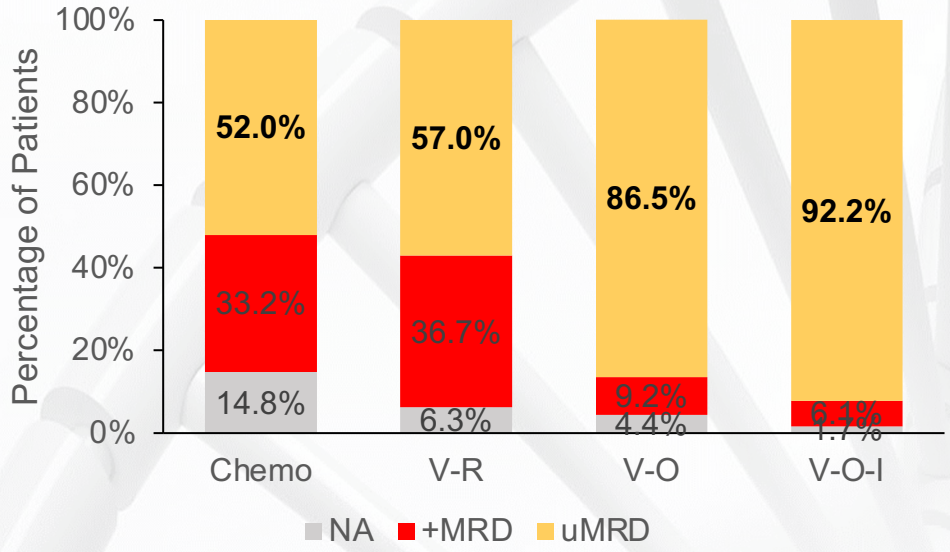


Sharman, et al, Leukemia 2022

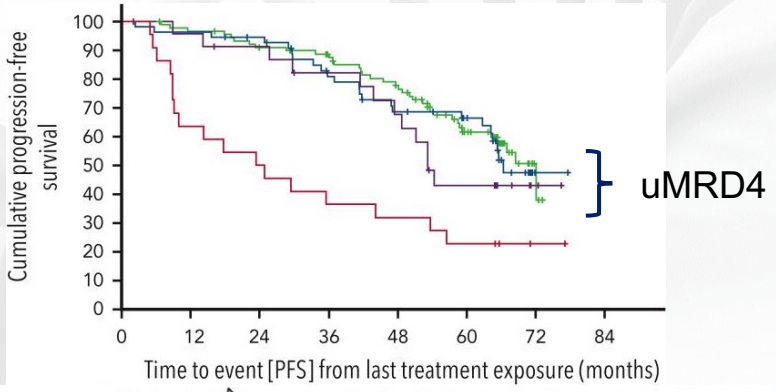
No Decisions are Made in Venetoclax-based Regimens based on MRD

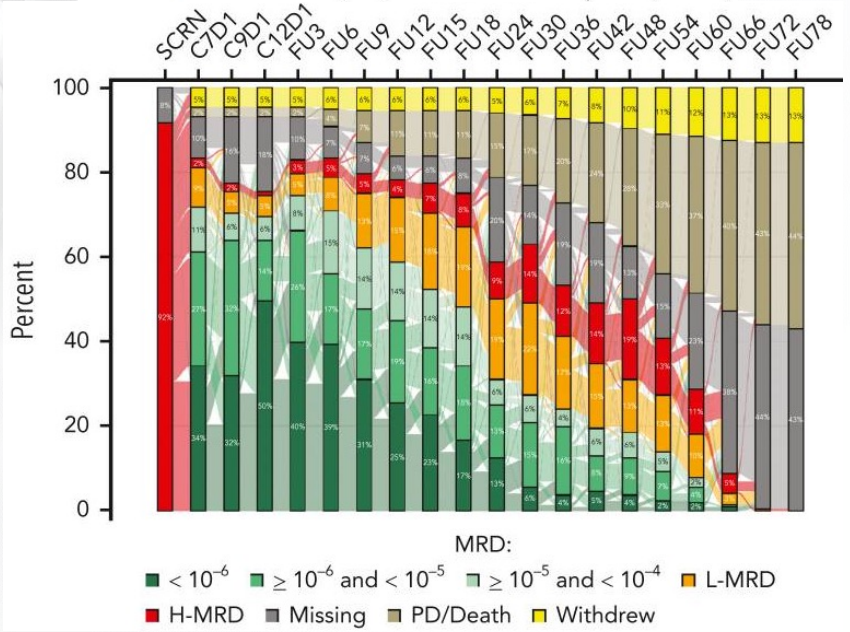
CLL-13. Del17p excluded
Primary end point: MRDu





CLL-14
Median PFS **76 mo**!





For both trials, what happens if:

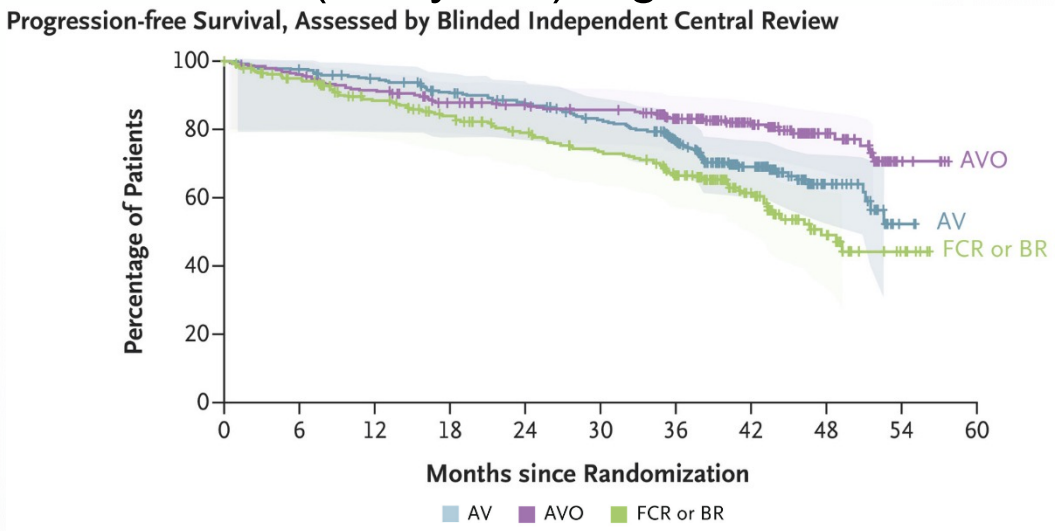
uMRD at EOT?
Stop therapy

+MRD at EOT?
Stop therapy

Eichhorst et al, NEJM 2023
Al-Sawaf et al, Blood 2024

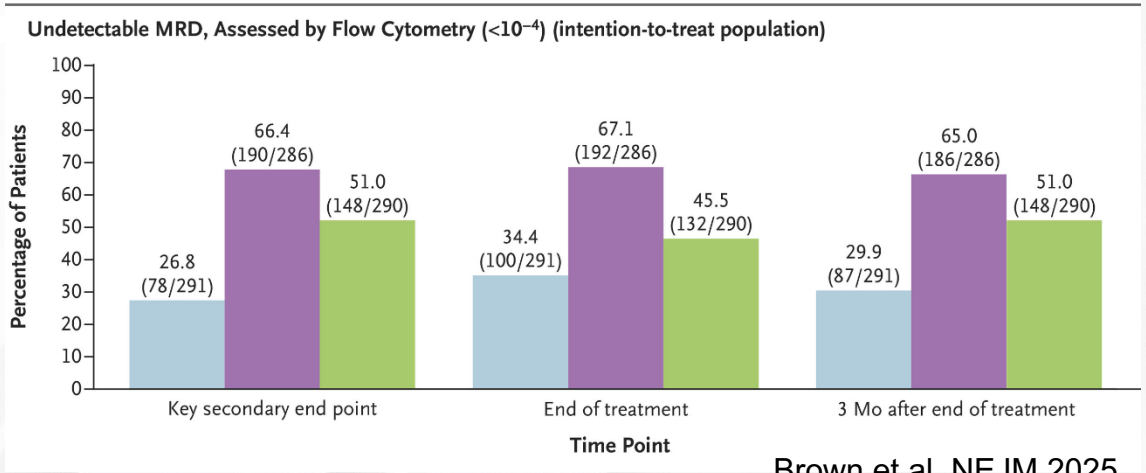
Is MRD-Guided Therapy Really Better?

AMPLIFY: already in NCCN Guidelines
Time limited (14 cycles) regardless of MRD



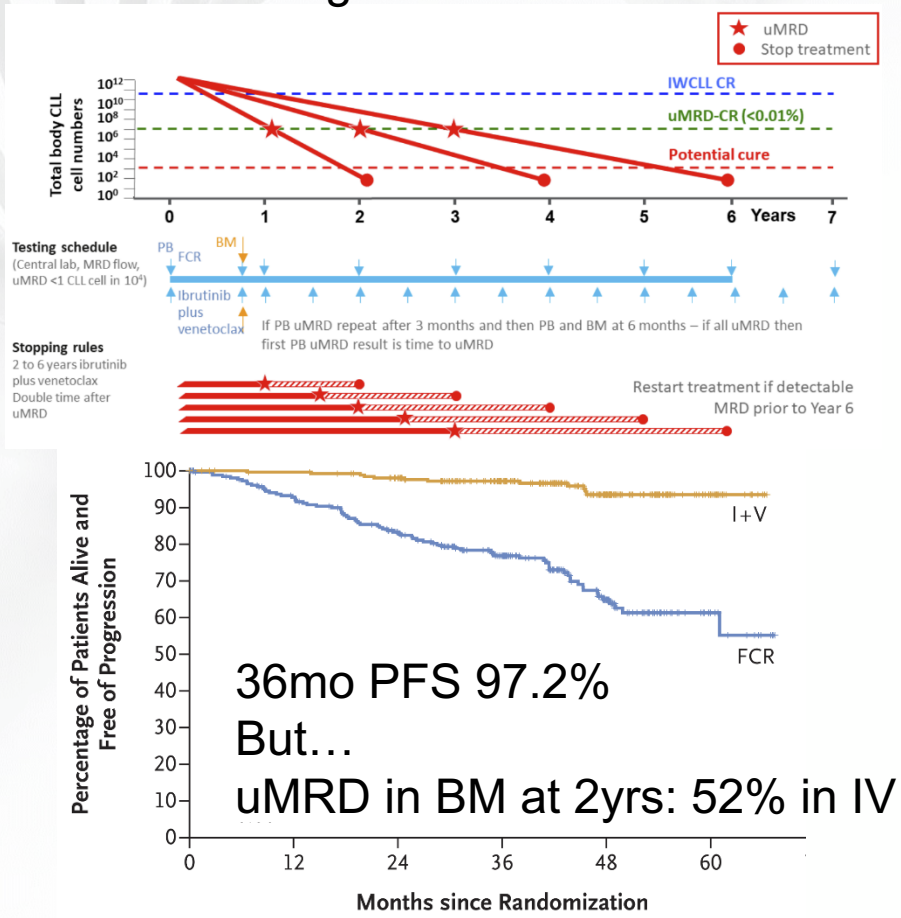
36mo PFS:

AV: 76.5%
AVO 83.1%
FCR: 66.5%



Brown et al, NEJM 2025

FLAIR: not in NCCN Guidelines
MRD-guided treatment

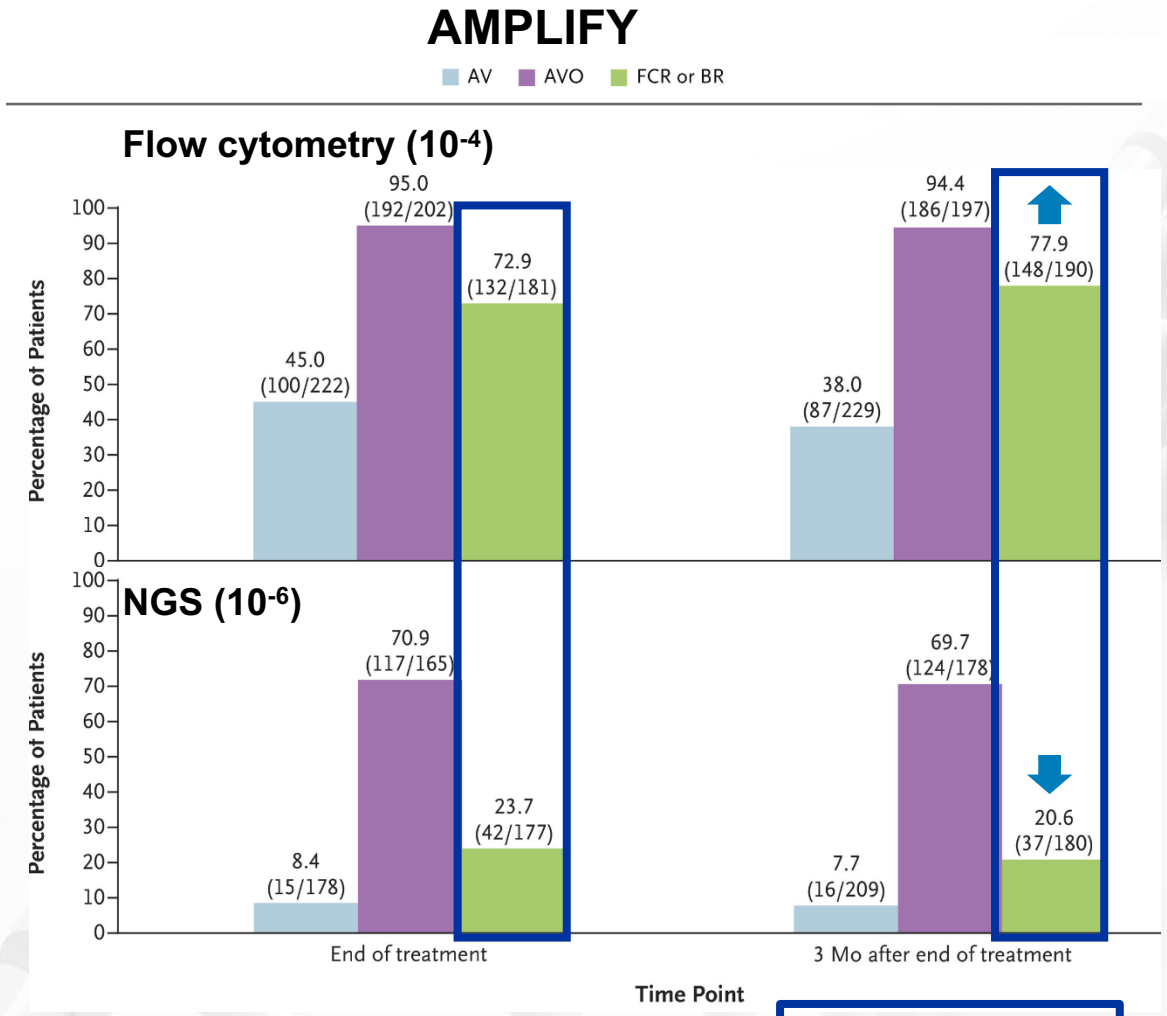


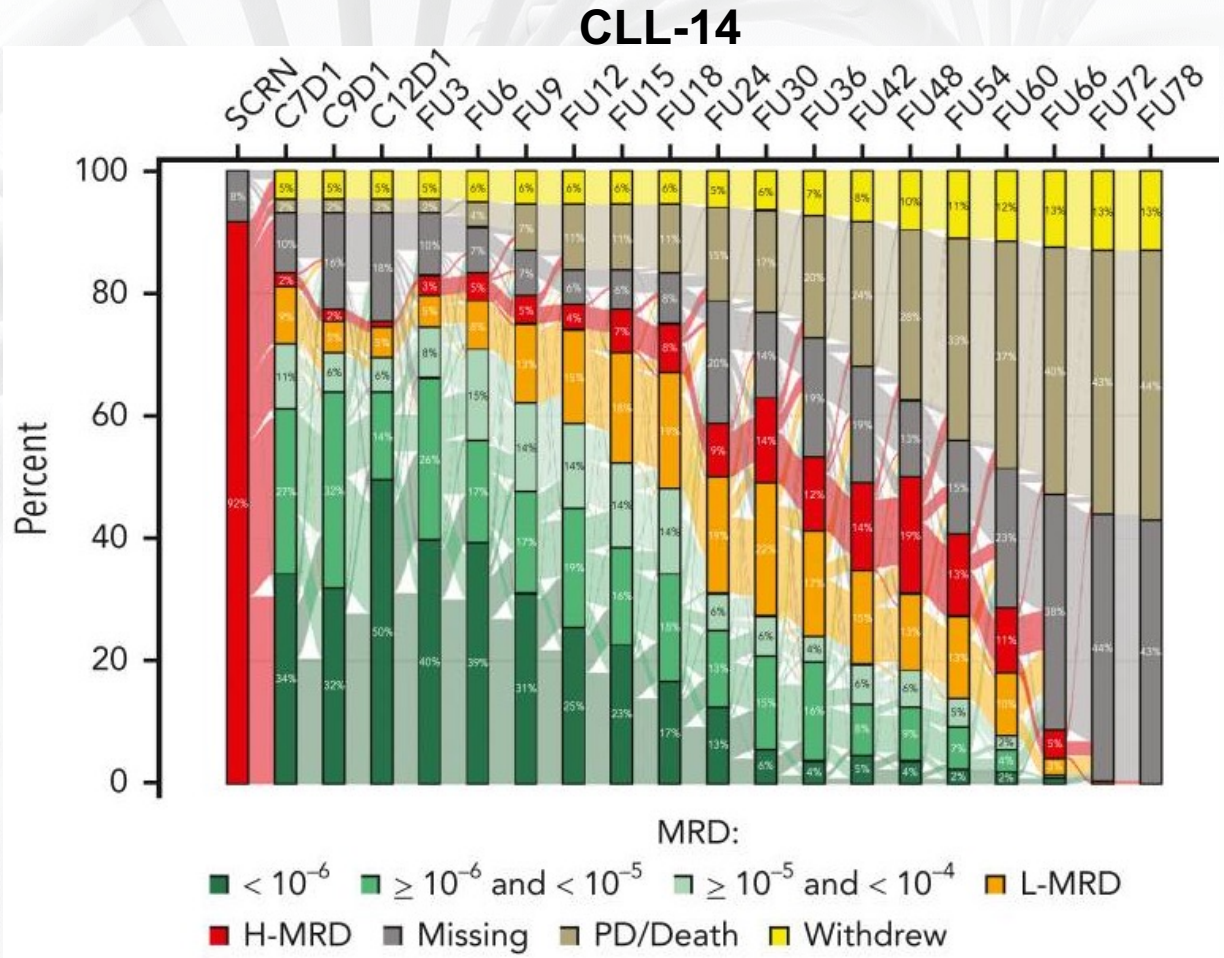
36mo PFS 97.2%
But…
uMRD in BM at 2yrs: 52% in IV

Median number of cycles 27

Munir et al, NEJM 2024

Problem: How/When/What to Test for MRD?





Al-Sawaf et al, Blood 2024

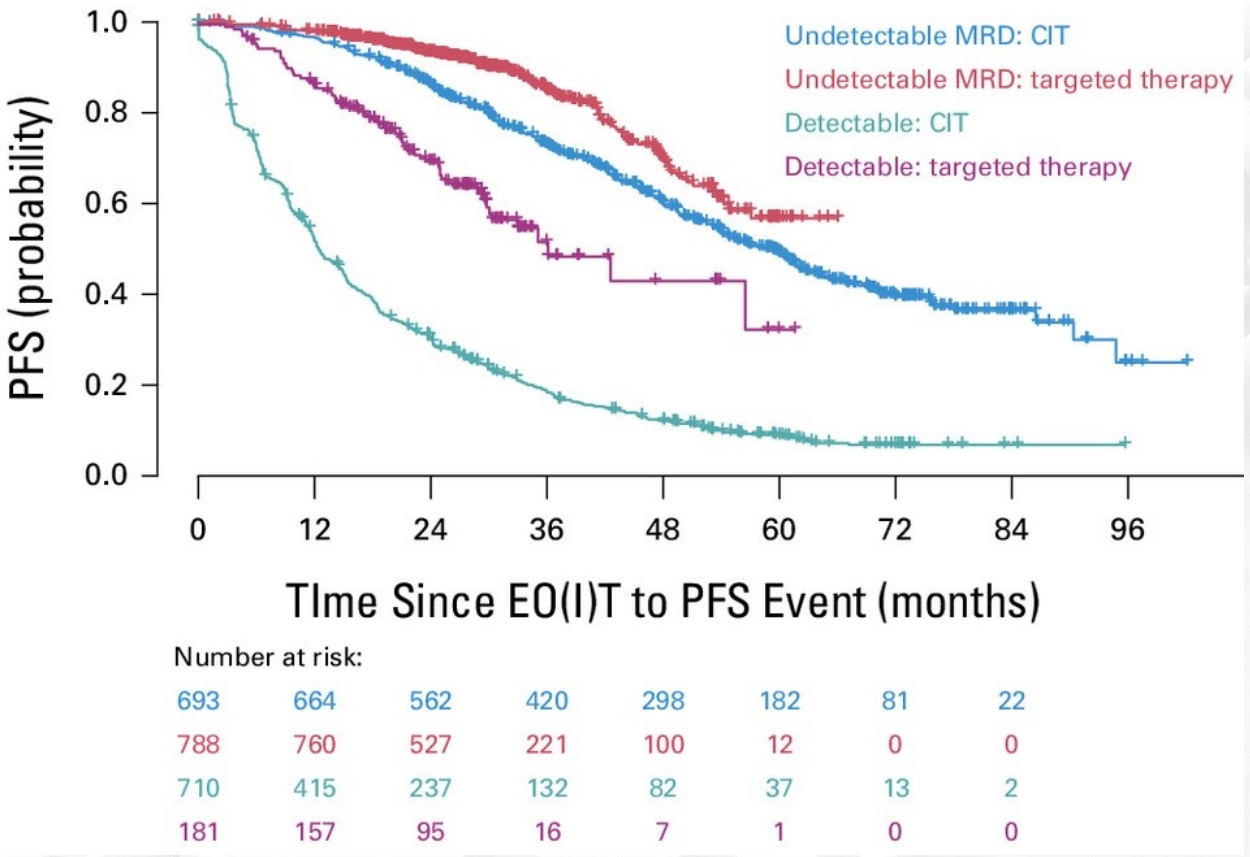
Does MRD Correlate with Clinical Outcomes?

	Setting	Tx	% uMRD PB	% uMRD BM	PFS	OS	
ELEVATE TN	Tx naïve	A AO CO	**9%** **41%** **8%**		78% 87% 25%	NR NR NR	**4 year**
CLL-14	Tx naïve	VO CO	**76%** **35%**	57% 17%	53% 22%	79% 69%	**6 year**
CLL-13	Tx naïve	FCR/BR VR VO VIO	**52%** **57%** **86%** **92%**	37% 43% 72% 78% *Among CR/CRi	76% 81% 88% 90%	95% 96% 96% 95%	**MRD: 15mo** **PFS: 3 year**
MURANO	Relapsed refractory	BR VR	**13%** **62%**	2% 27%	17 mo 54 mo	62% 82%	**mPFS/60mo**
TRANSCEND 004	Relapsed refractory	Liso-cel	**63%**	59%	18 mo	43 mo	

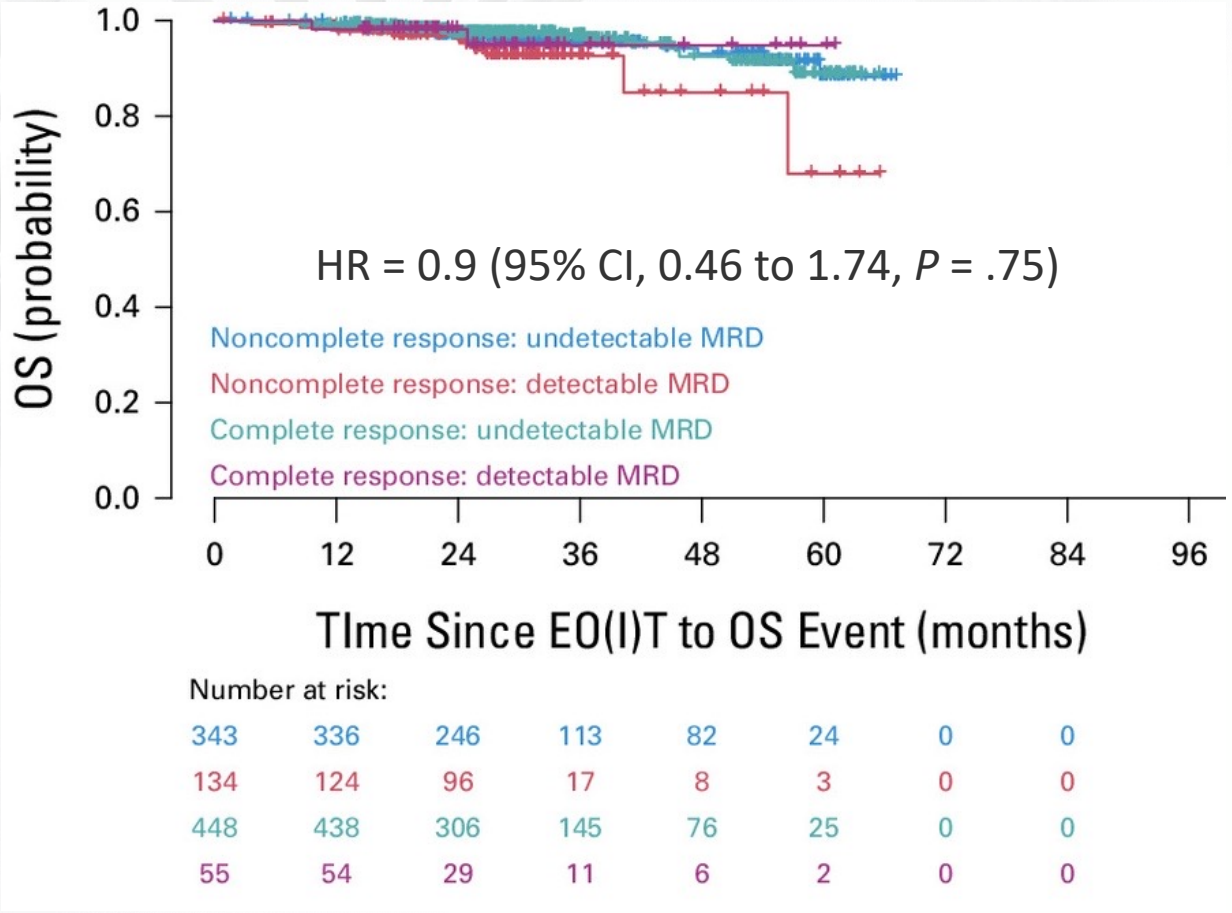
Rates of uMRD in BM are lower than in PB
Unclear role when comparing among novel therapies

Sharman et al, Blood 2025. Al-Sawaf et al, Blood 2024. Eichhorst et al, NEJM 2023. Seymour et al, NEJM 2018. Siddiqi et al, Lancet 2023.

MRD Correlates with PFS but not OS in Patients Treated with Time-limited Regimens



For targeted treatments



Simon et al, JCO 2024

Conclusion – in 2025

MRD is a NOT a useful tool in the management of patients with CLL (yet)

Clinical significance of uMRD is not clear

What do we do IN CLINIC with MRD information? - Nothing in 2025

Unclear what to test, when to test, and how to test

- Bone marrow vs Peripheral blood
- Flow cytometry vs next-generation sequencing
- Test at EOT? After 3 months? 6 months? 1 year?
- What is the MRD cutoff?

More studies are needed to clarify these answers