Measuring MRD is the Standard of Care in CLL

Joanna M. Rhodes, MD, MSCE

Director, Lymphoma Program

Rutgers Cancer Institute of New Jersey

Disclosures

- **Consulting/Speaking:** AbbVie, ADC Therapeutics, Beigene, Epizyme, Genentech, Janssen, MorphoSys, Pharmacyclics, Seagen, TG Therapeutics, Verastem, Loxo Oncology

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Measuring MRD at end of treatment for patients with CLL treated with fixed duration venetoclax-based regimens is standard

What I’m not Debating

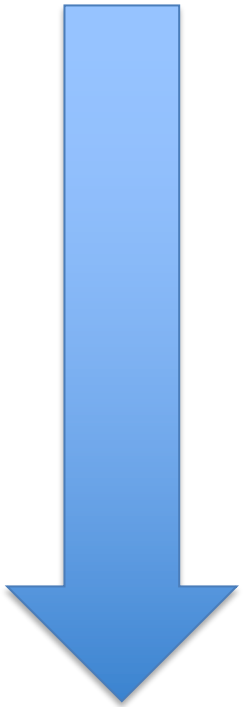
- uMRD should be the treatment goal in all patients
- All patients should have routine MRD testing
- MRD testing can be used to tailor treatment duration

Measurable Residual Disease: Nomenclature

Minimal Residual Disease

Measurable Residual Disease

iwCLL defintion



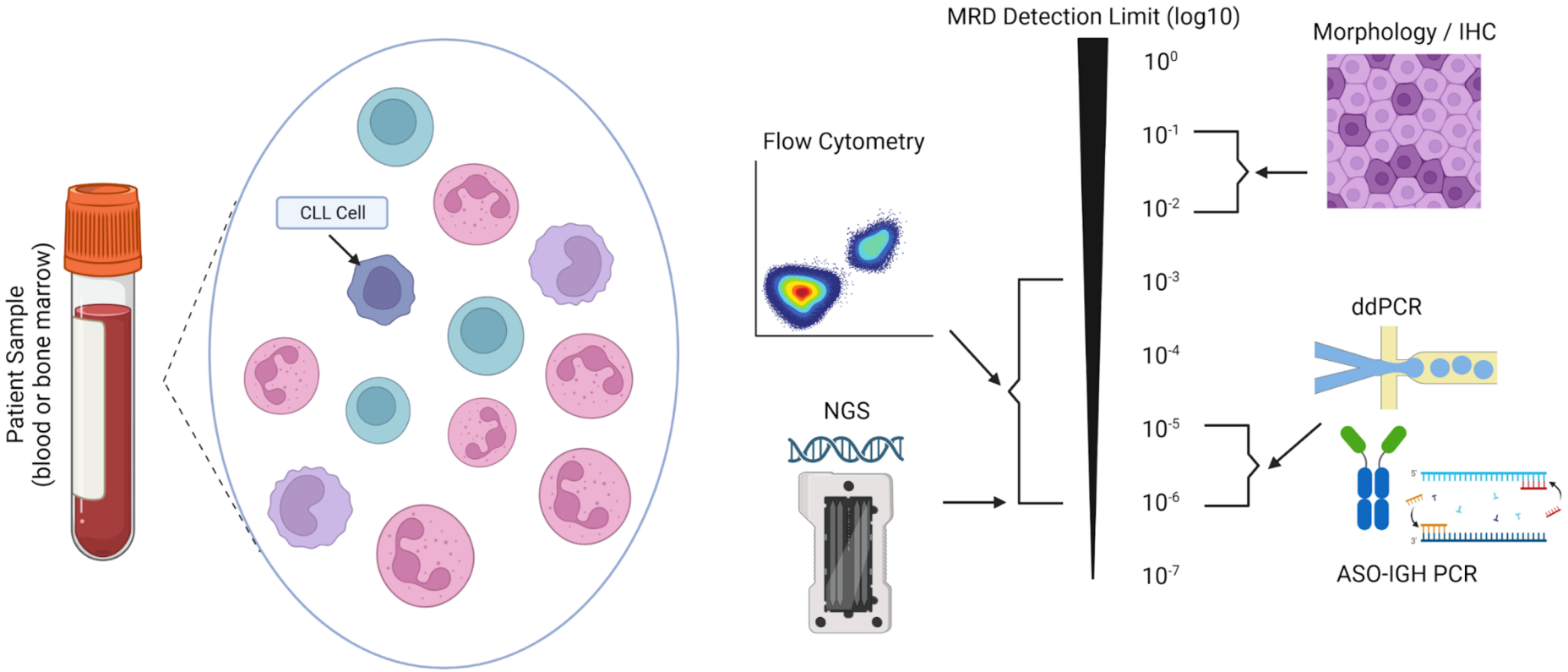
10^{-4} MRD4

10^{-5} MRD5

10^{-6} MRD6

Wierda et al, *Leuk* 2021

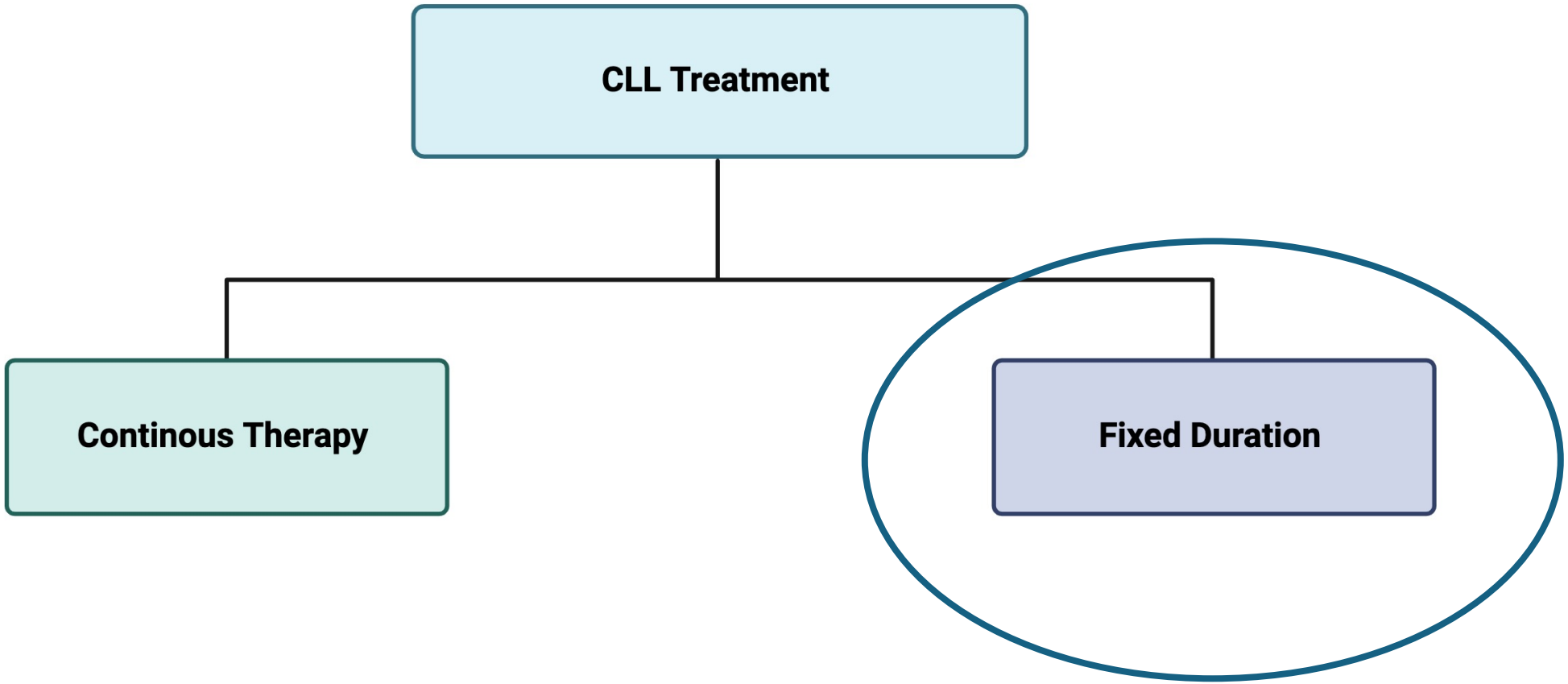
Measurable Residual Disease Testing Modalities



IHC: Immunohistochemistry; ddPCR: droplet digital polymerase chain reaction [PCR]; NGS Next-generation sequencing; ASO-IGH PCR: allele-specific oligonucleotide immunoglobulin heavy locus PCR

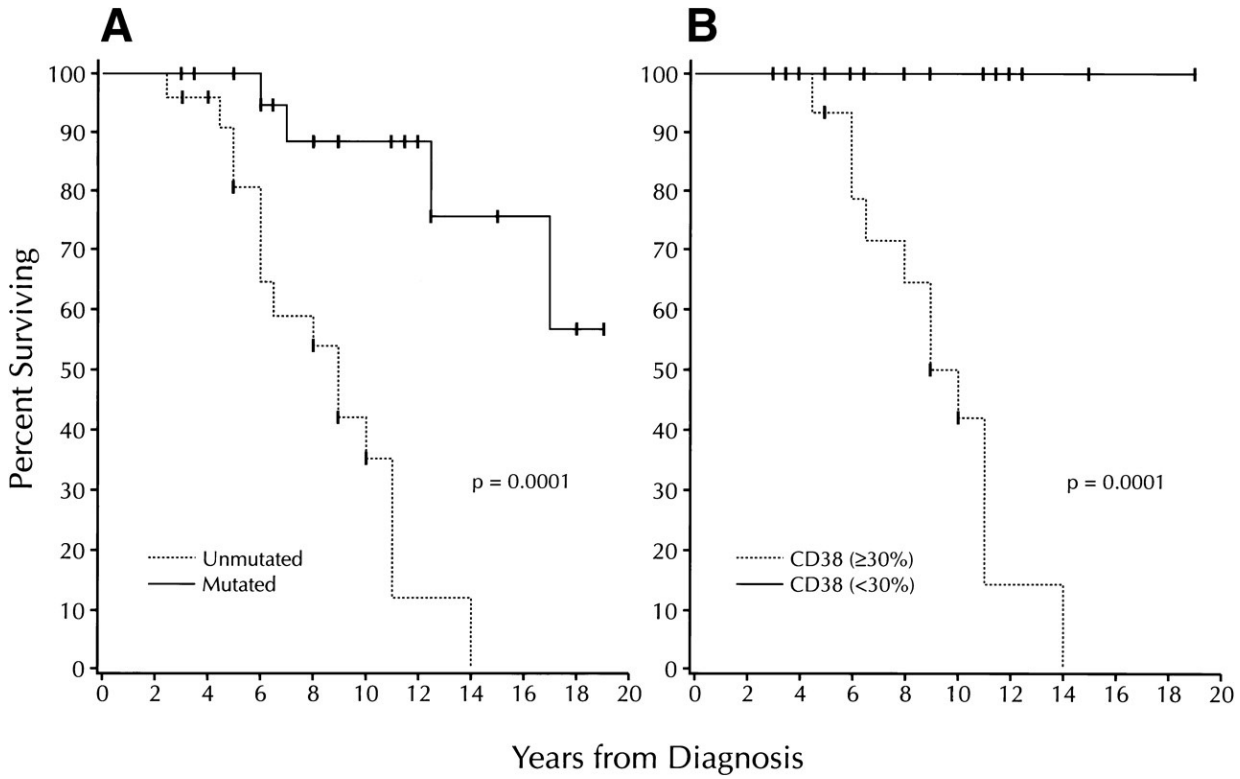
Created with Biorender

Current Treatment Paradigms for CLL

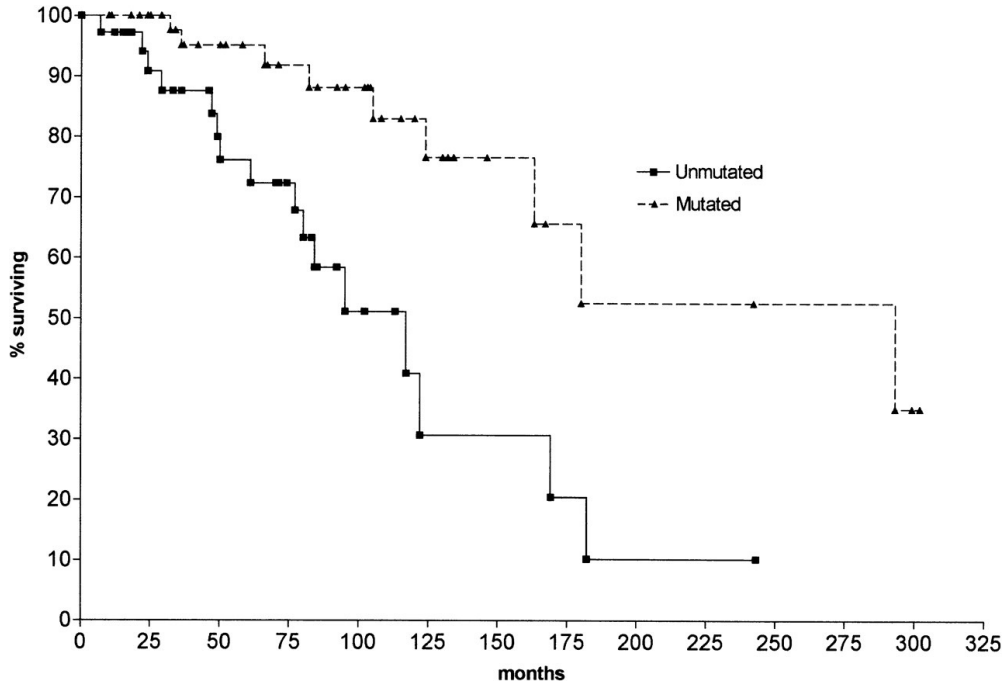


Where has MRD testing been used?

Prognostic markers in CLL: IGHV mutation



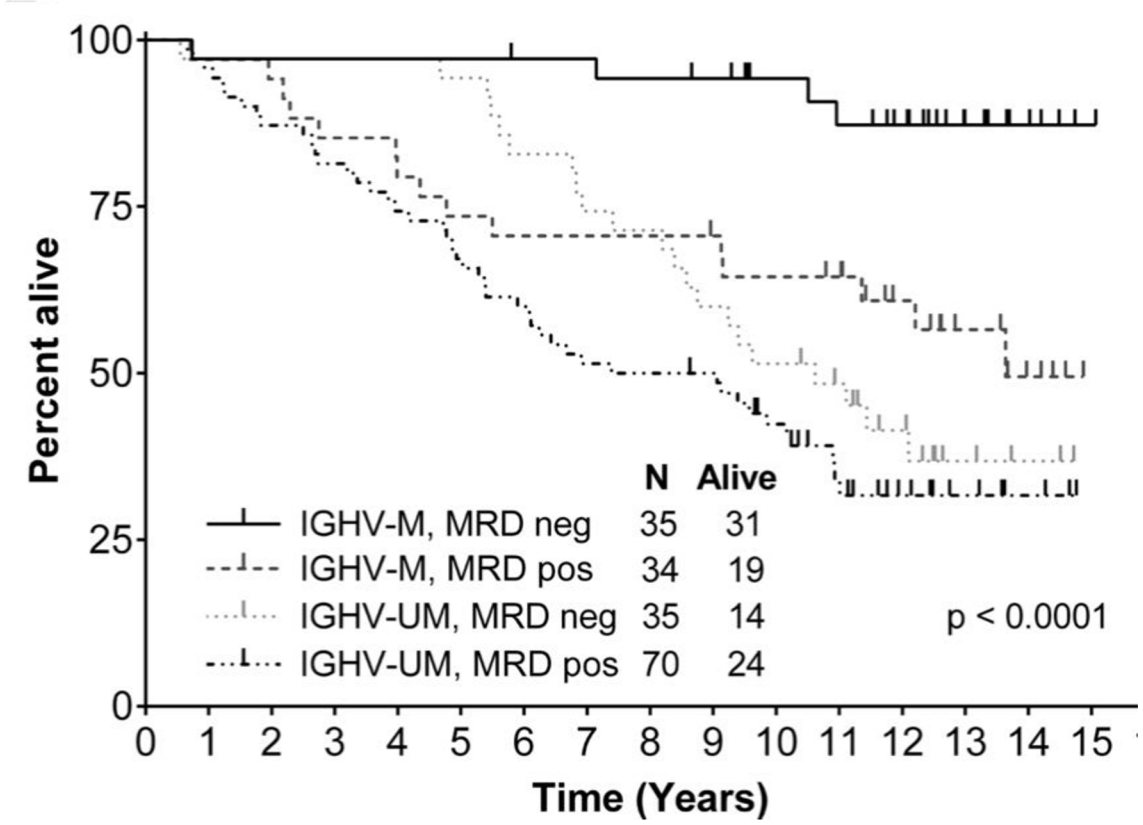
Damle et al Blood 1999



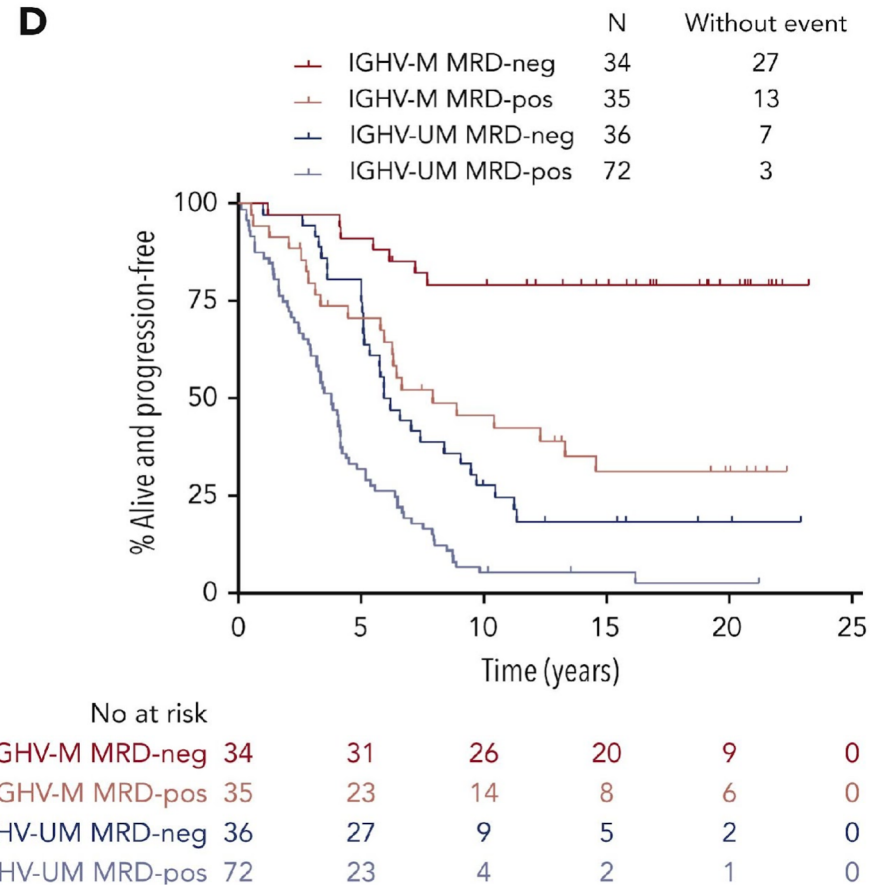
Hamblin et al Blood 1999

Long-term Follow Up: uMRD Patients with FCR

Median follow up: 12.7 years



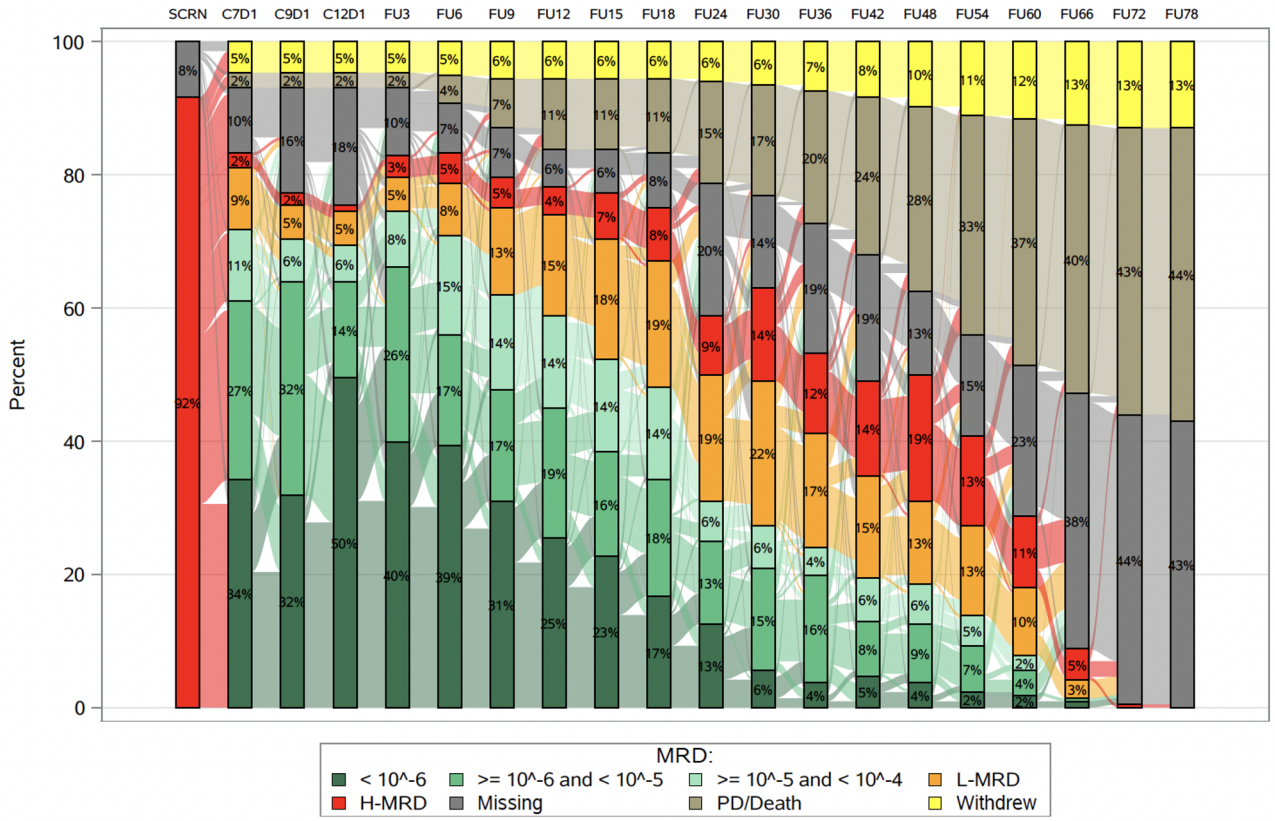
Median follow up: 19 years

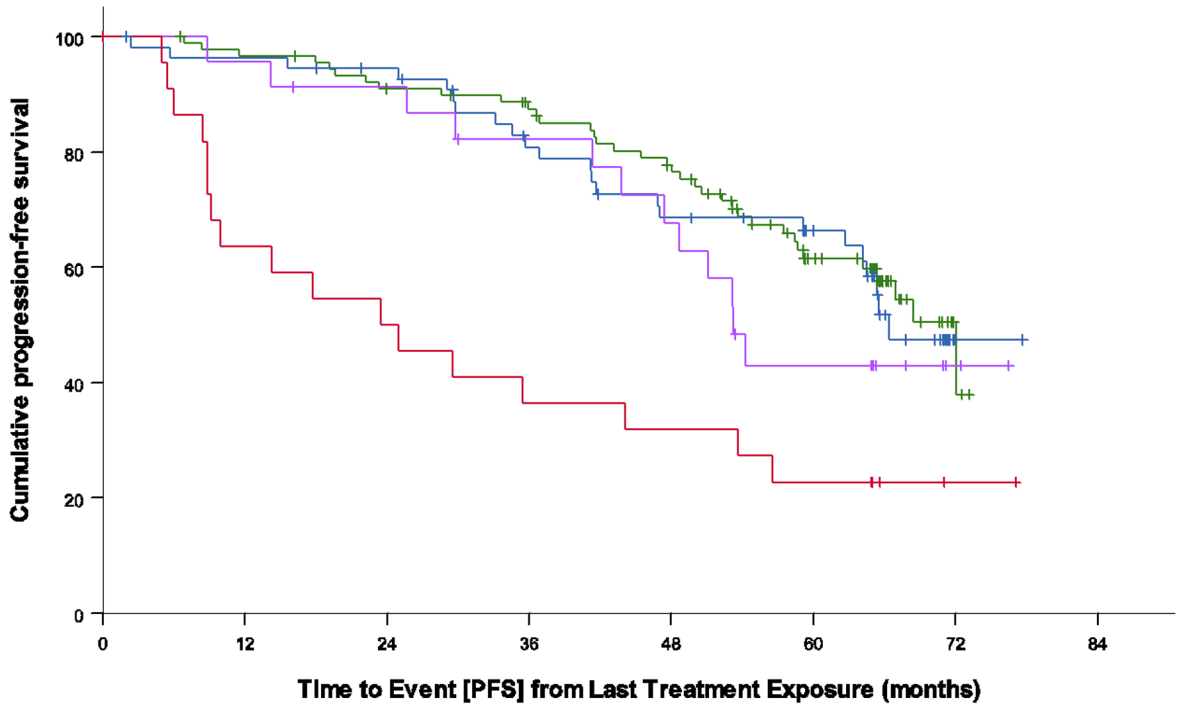


Thompson et al. *Blood*, 2016
Thompson et al. *Blood*, 2023

What Role Does MRD Play in the Era of Targeted Agents?

CLL14: uMRD with Fixed Duration Regimens: Venetoclax-Obinutuzumab



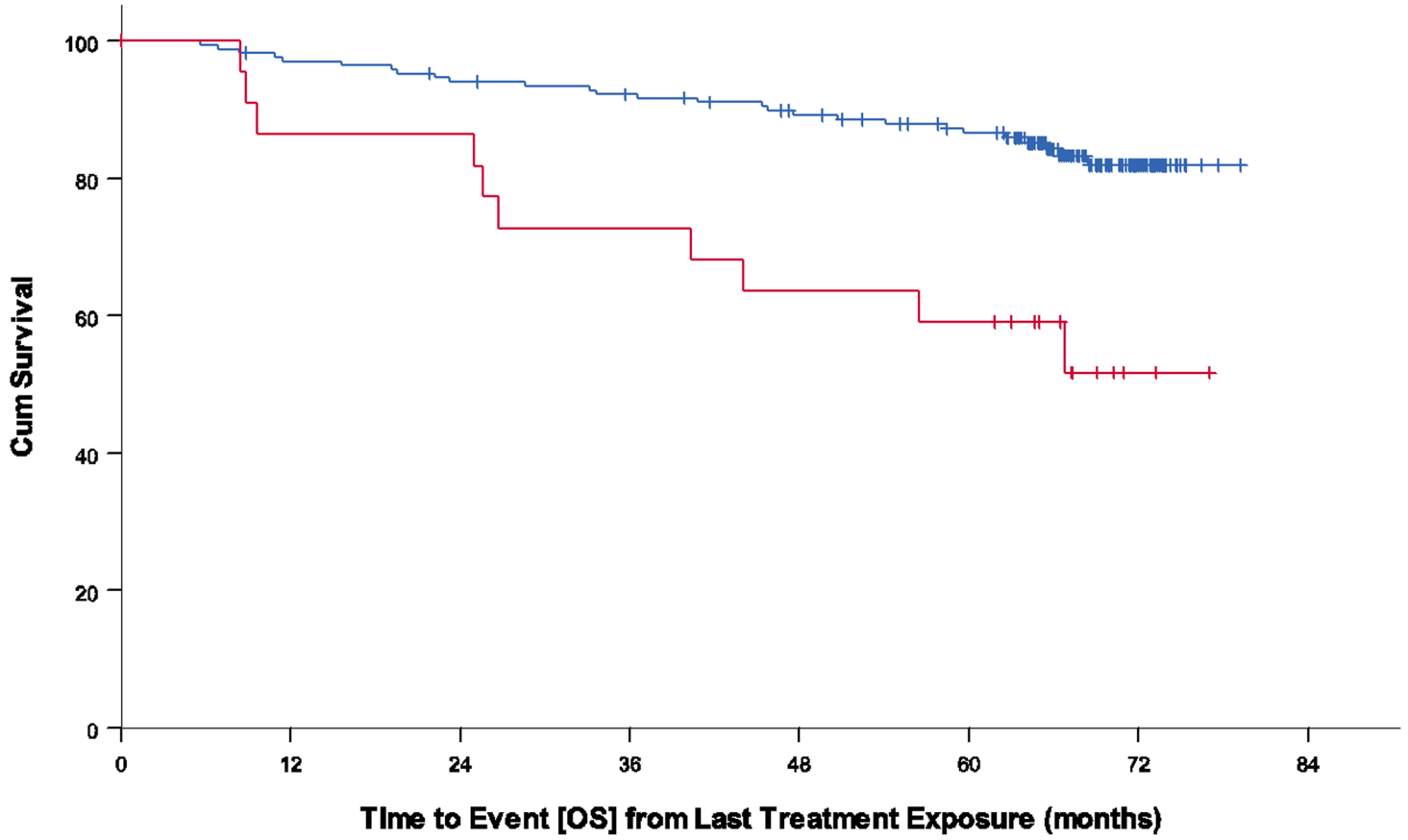


5-year uMRD rate: 7.9%

MRD < 10^{-6}	90	86	79	73	63	38	4	0
MRD ≥ 10^{-6} and < 10^{-5}	56	53	50	40	33	26	2	0
MRD ≥ 10^{-5} and < 10^{-4}	23	22	20	17	14	8	2	0
MRD ≥ 10^{-4}	23	14	11	8	7	5	1	0

Al-Sawaf et al. Nat Comm, 2023
Al-Sawaf et al, *Hemasphere* (abst), 2023

CLL14: uMRD Prognostic of Overall Survival

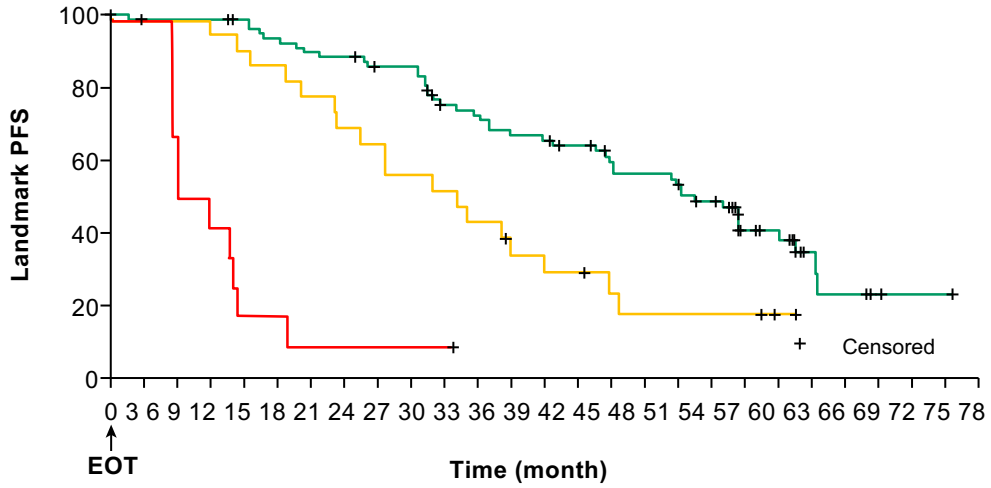


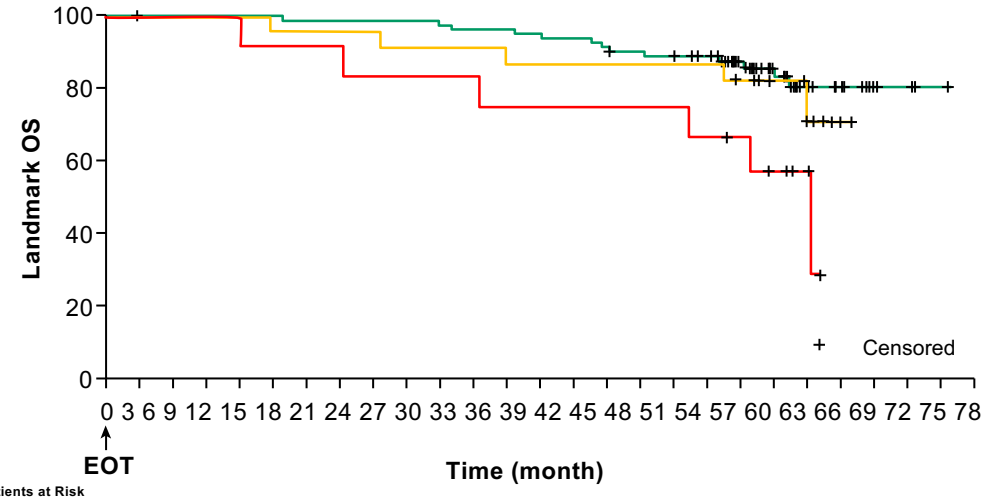
Patients with uMRD have longer overall survival with venetoclax-obinutuzumab treatment

MRD < 10^{-4}	169	163	157	152	143	131	32	0
MRD ≥ 10^{-4}	23	19	19	16	14	13	2	0

Al-Sawaf et al. Nat Comm, 2023
Al-Sawaf et al, *Hemasphere* (abst), 2023

MURANO: uMRD Associated with Improved PFS





No. of Patients at Risk

uMRD	83	79	79	79	77	73	70	69	65 65 54 52 48 47 44 39
Low MRD+	23	23	23	21	20	18	16	15	13 13 11 10 7 6 5 3
High MRD+	12	8	6	2	2	1	1	1	1 1

uMRD	83	81	81	81 81 81	80	80	80	80	79
Low MRD+	23	23	23	23 23 22	22	22	21	21	21
High MRD+	12	12	12	12 12 11	11	10	10	10	10

uMRD	78	78	76	76	74	72	71 68	48 35	16 11 4 3 1
Low MRD+	21	20	20	20	20	19	19 19	16 11	5 1
High MRD+	9	9	9	9	9	9	9 8	7 5	2

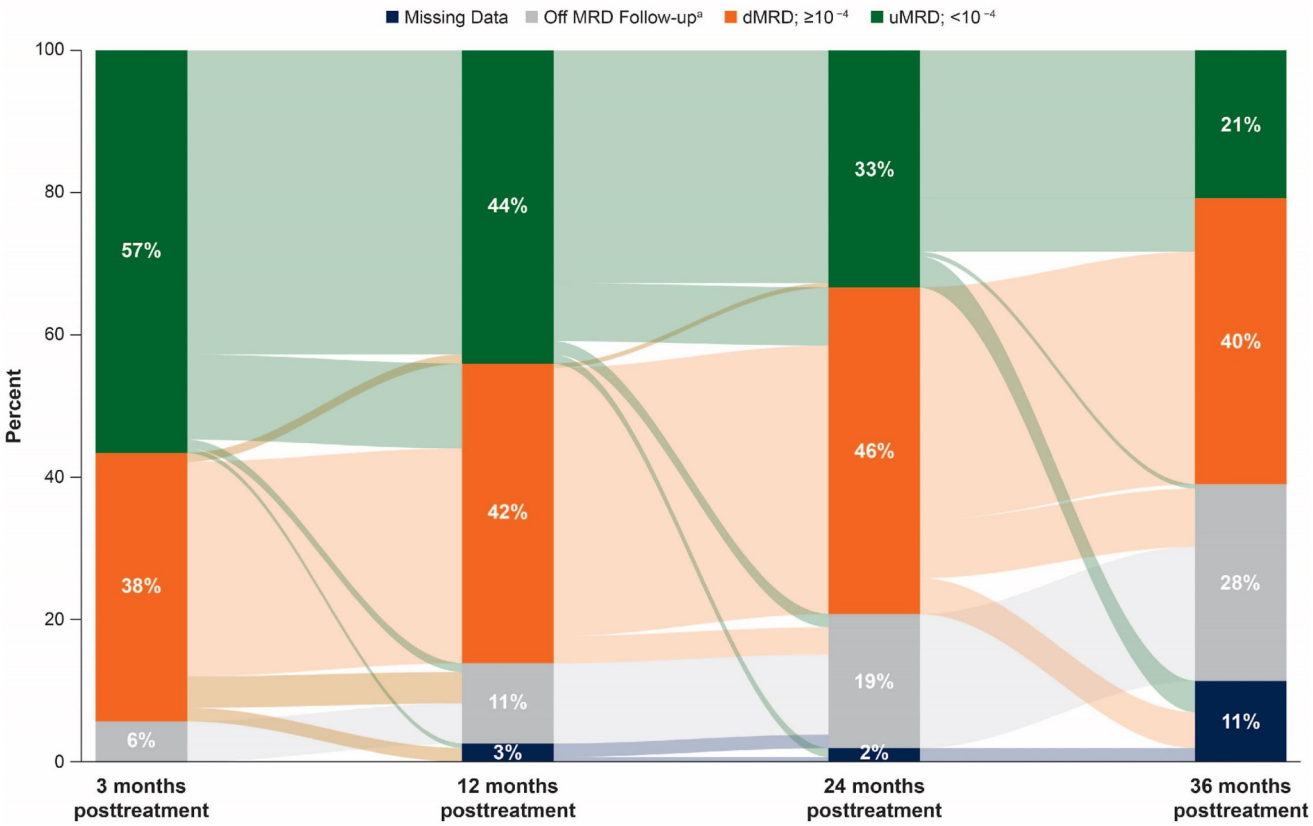
Patients who completed 2 years of Ven without PD*	Median PFS since EOT (95% CI), months	HR (95% CI); P-value†
uMRD (n=83)	**52.5** (44.5–61.5)	
Low MRD+ (n=23)	**29.3** (20.2–37.5)	vs uMRD: **3.46** (1.75–6.86); <0.0001
High MRD+ (n=12)	**4.6** (2.8–8.3)	vs uMRD: **17.22** (5.70–52.00); <0.0001

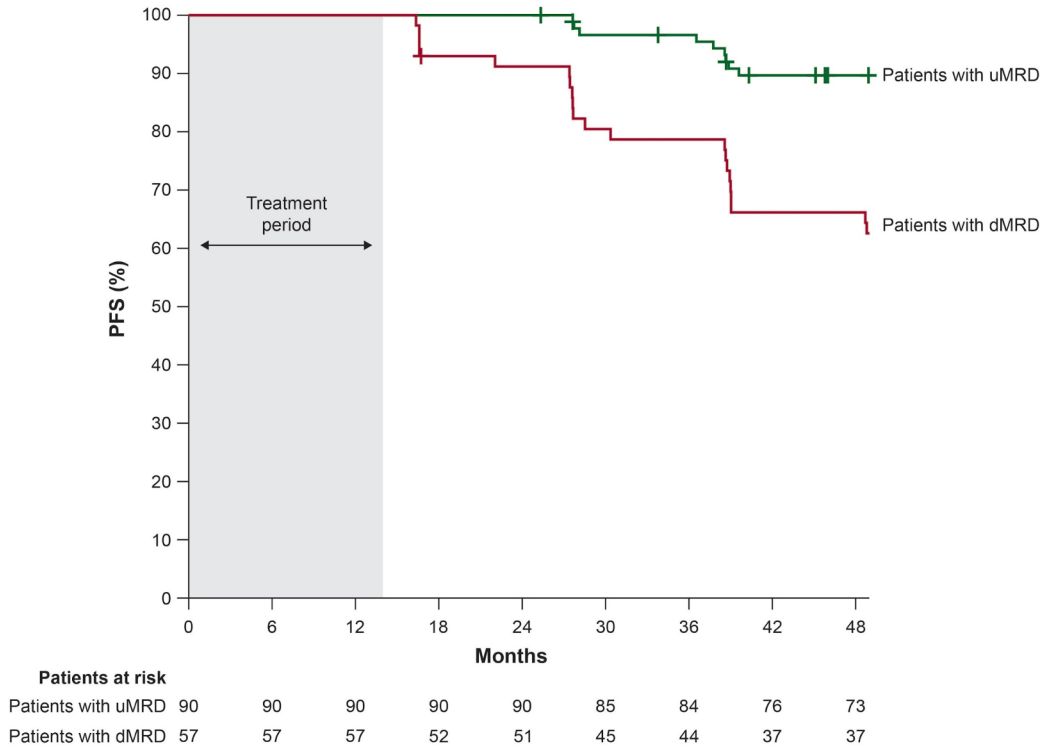
Patients who completed 2 years of Ven without PD*	Median OS since EOT (95% CI), months	HR (95% CI); P-value†
uMRD (n=83)	**NE** (NE–NE)	
Low MRD+ (n=23)	**NE** (62.7–NE)	vs uMRD: **1.07** (0.34–3.35); NS
High MRD+ (n=12)	**63.1** (51.5–NE)	vs uMRD: **2.39** (0.73–7.80); NS

Kater et al Hemasphere 2023

CAPTIVATE: Improved PFS with uMRD at 3 Months Post Treatment

Landmark PFS 48 months: 90% uMRD vs 66% detectable MRD

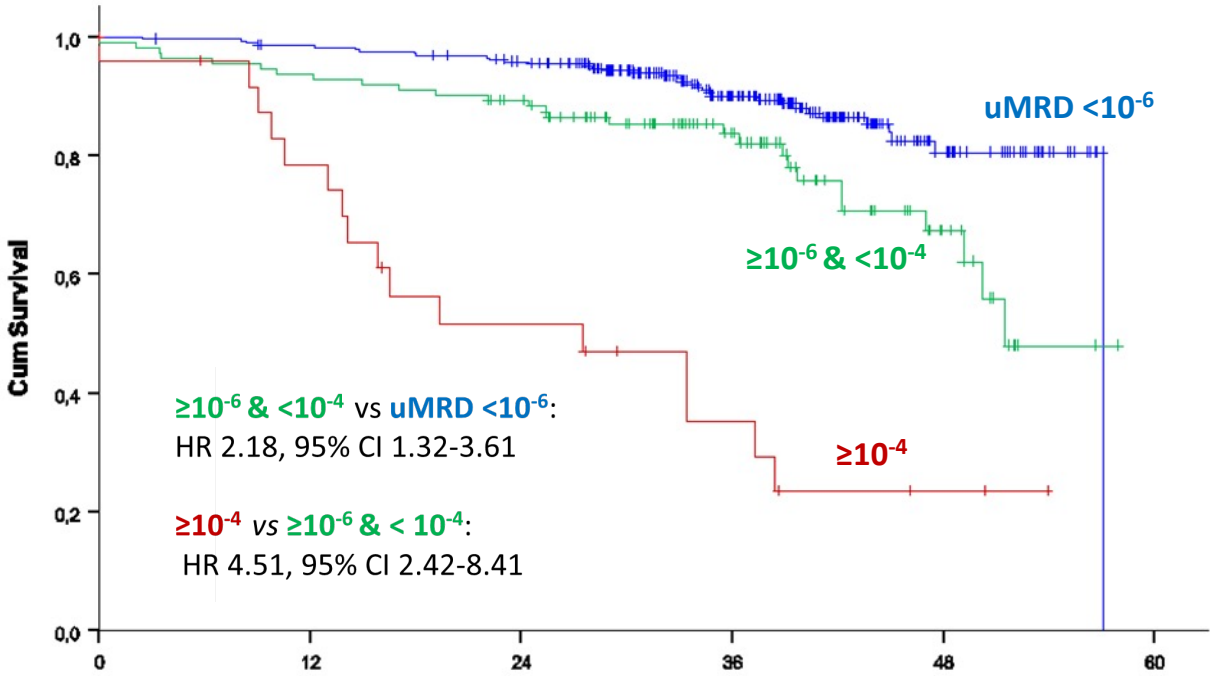




Ghia et al, Hema, 2023

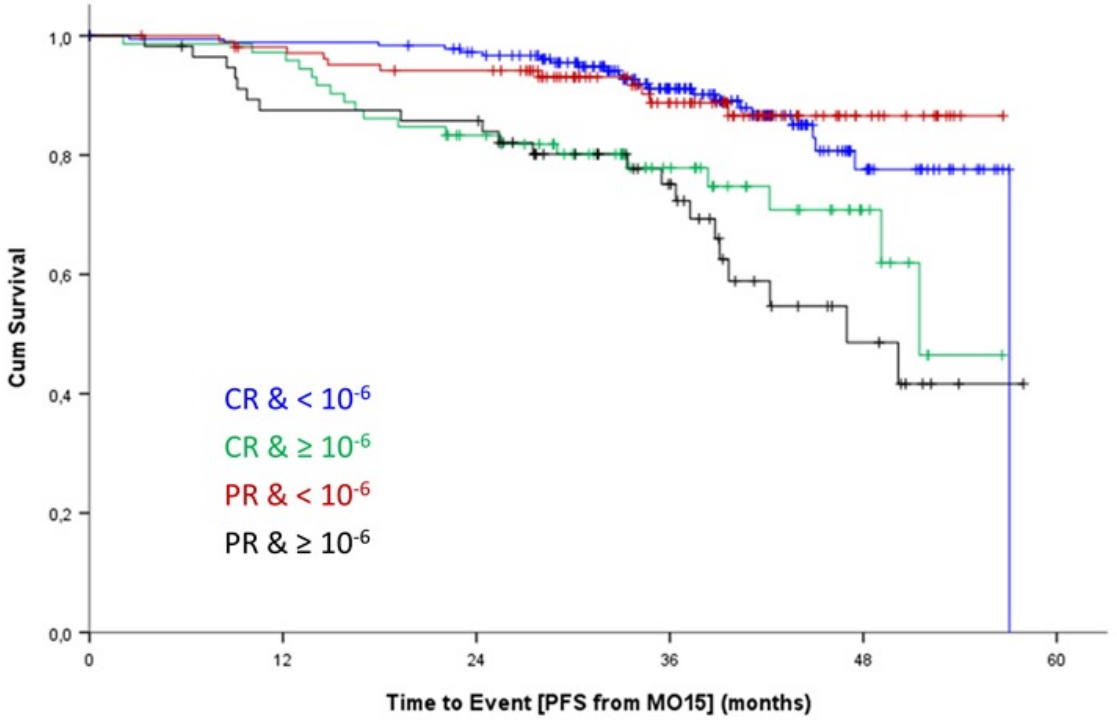
CLL13: uMRD leads to improved PFS

PFS by MRD level at MO15, GV/GIV



Pts at risk					
uMRD <10-6	291	283	269	162	39
≥10-6 & <10-4	112	105	95	53	15
≥10-4	25	18	11	6	2

PFS by MRD level & response at MO15, GV/GIV



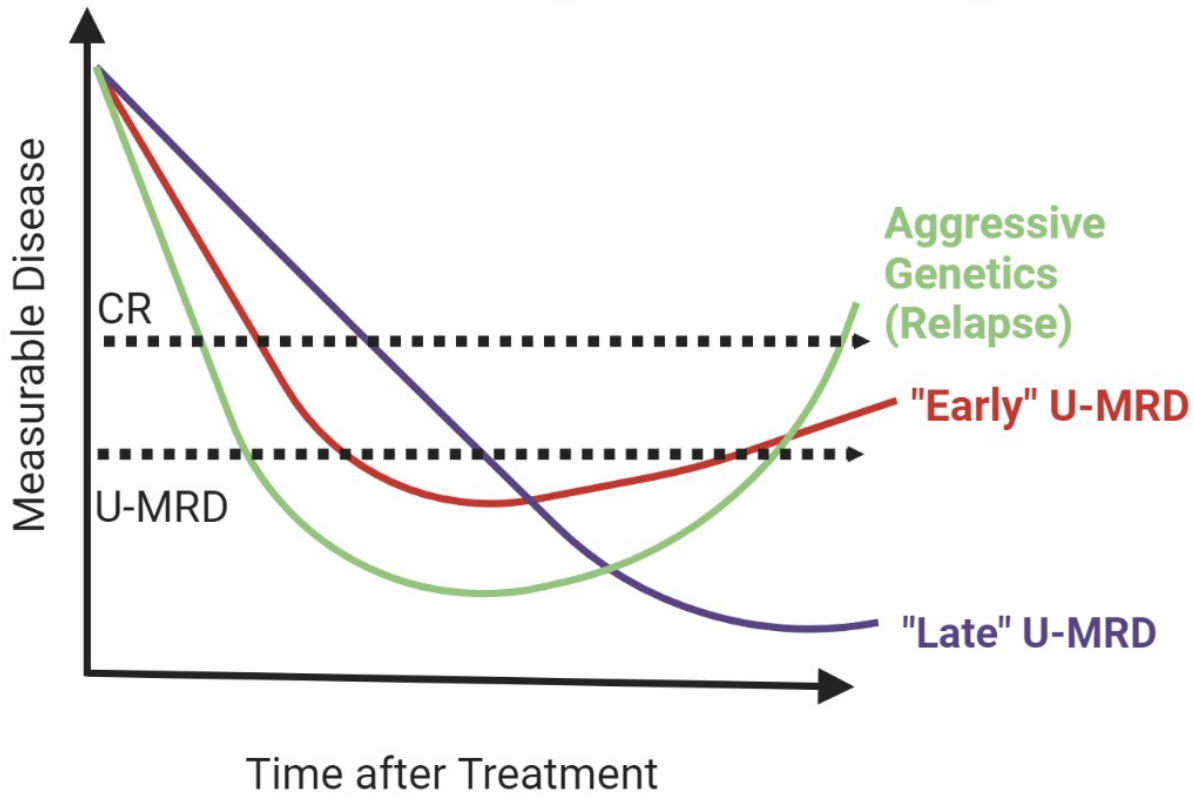
Pts at risk					
CR & <10-6	183	180	172	105	25
CR & ≥10-6	72	70	56	29	9
PR & <10-6	105	100	95	56	13
PR & ≥10-6	58	49	48	28	8

Abstract #635

uMRD at End of Treatment is Associated with PFS and (OS) with Fixed Duration Venetoclax-Based Therapy

- CLL14
  - PFS/OS benefit if uMRD 3 months from end of treatment (MRD4 by ASO-PCR)
- MURANO
  - PFS benefit if uMRD at end of treatment (MRD4, ASO-PCR and flow cytometry)
- CAPTIVATE FD
  - PFS benefit if uMRD 3 months from end of treatment (MRD4, 8 color flow cytometry)
- CLL13
  - Improved PFS if uMRD at month 15 in obinutuzumab-venetoclax arms (MRD4, 4 color flow cytometry and ASO-PCR)

Factors Confounding "Ideal" U-MRD Target

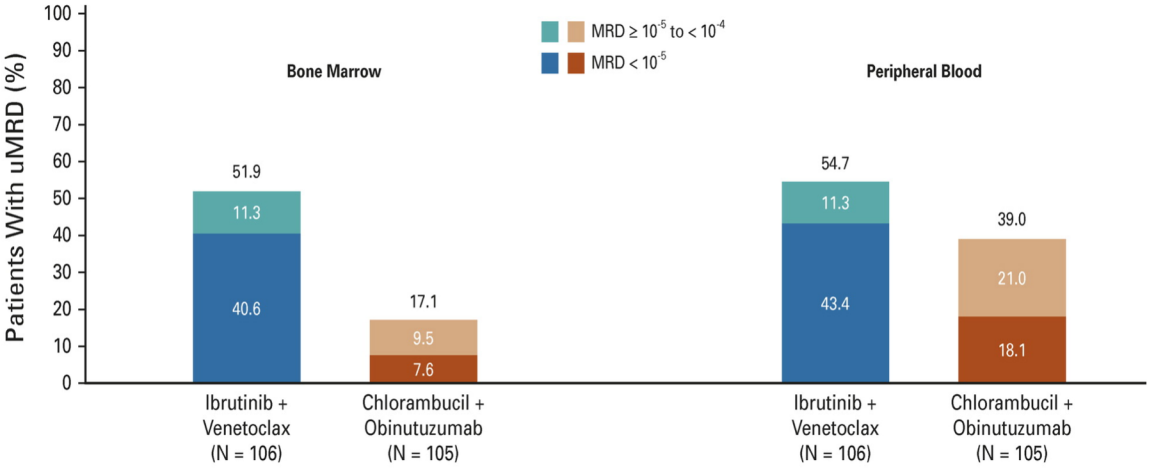


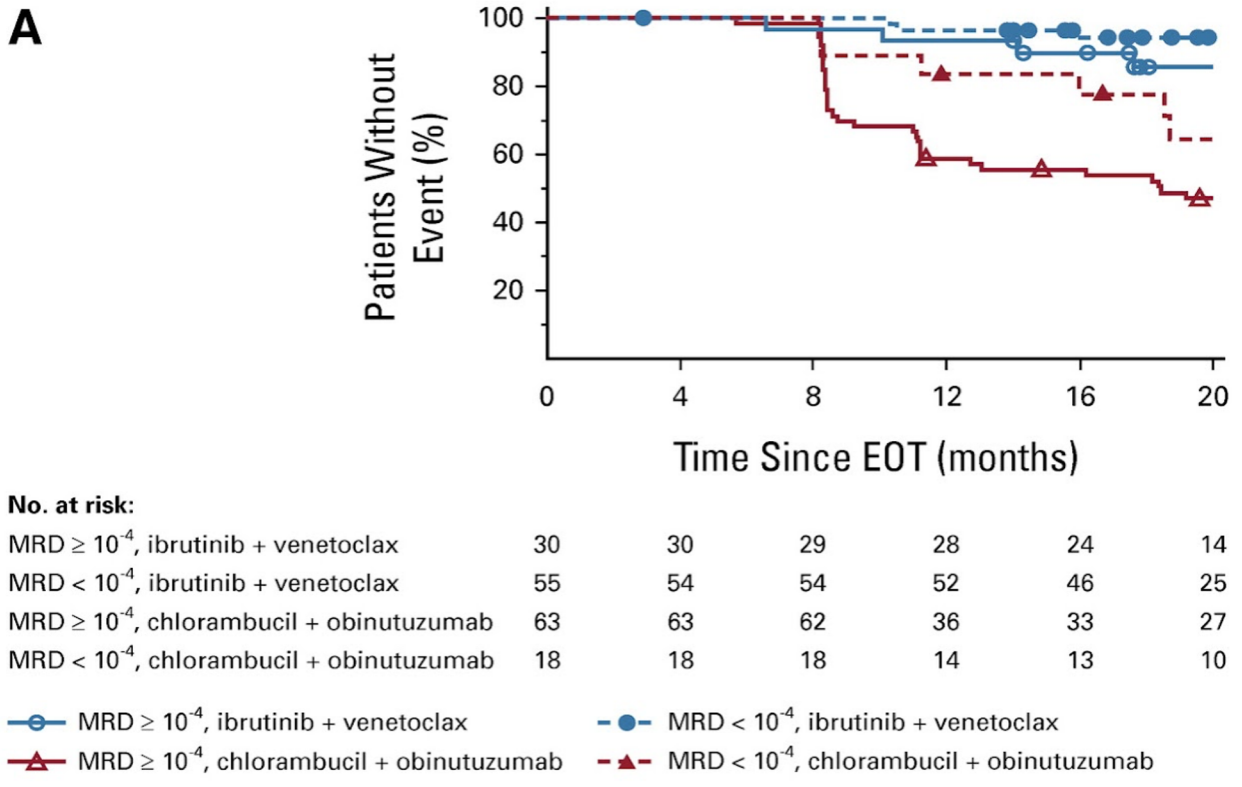
Disease with high-risk genomics (del17p, IGHVu) may achieve initial U-MRD but still relapse, affecting prognostication

Testing too early or with too insensitive a method might underestimate utility of U-MRD to predict PFS

Some continuous regimens (e.g. FLAIR) can take longer to achieve UMRD

GLOW: uMRD Status Not Associated with 12- month PFS

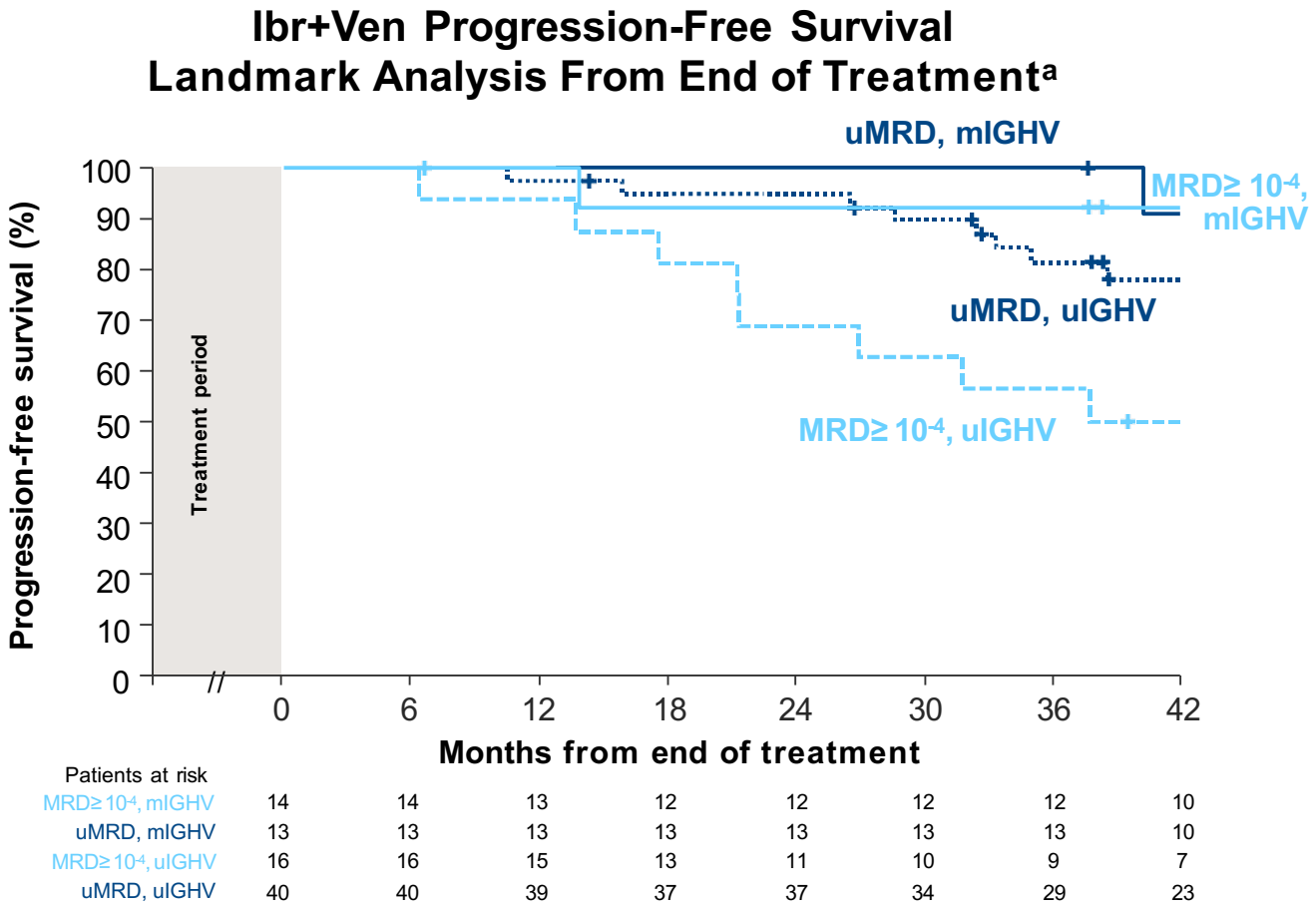




No significant difference in PFS based on uMRD status for patients treated with ibrutinib-venetoclax

Munir et al JCO, 2023

GLOW: PFS by MRD and IGHV status for Ibr+Ven



- With Ibr+Ven, achieving uMRD at EOT+3 is more critical for long-term PFS benefit in uIGHV versus mIGHV
- Estimated PFS rates at 42 months post treatment:
  - **mIGHV** CLL:
    - 91% for patients with uMRD at EOT+3
    - 92% for patients with MRD ≥ 10^{-4} at EOT+3
  - **uIGHV** CLL:
    - 78% for patients with uMRD at EOT+3
    - 50% for patients with MRD ≥ 10^{-4} at EOT+3

[a]Curves generated from EOT (C15 for Ibr+Ven, C6 for Clb+O)
All patients who had MRD outcome at EOT+3 were included in this analysis; uMRD was defined as < 1 CLL cell per 10,000 leukocytes (< 10^{-4}). Results based on updated IGHV reclassifications.

Presented by George Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

What are the Key Questions for MRD Testing?

- Standardization of testing recommendations
  - Modality
    - Flow cytometry, NGS based testing?
  - Optimal depth of response
    - MRD4? MRD5? MRD6?
  - Optimal compartment
    - PB, BM, both
- Frequency of MRD monitoring
- MRD-adapted therapy

- No utility in continuous regimens

Despite these Caveats: uMRD at End of Treatment is Associated with PFS and (OS) Benefits with Fixed Duration Venetoclax Based Therapy

- CLL14
  - PFS/OS benefit if uMRD 3 months from end of treatment (MRD4 by ASO-PCR)
- MURANO
  - PFS benefit if uMRD 3 months from end of treatment (MRD4, ASO-PCR and flow cytometry)
- CAPTIVATE FD
  - PFS benefit (MRD4, 8 color flow cytometry)
- CLL13
  - Improved PFS if uMRD in obinutuzumab-venetoclax arms (MRD4, 4 color flow cytometry and ASO-PCR)

So if uMRD at EOT is Prognostic with Fixed duration Venetoclax Treatment

And prognostic tests like IGHV mutation and FISH are Standard of Care in CLL treatment

MRD testing at end of treatment is the standard for patients on fixed duration venetoclax-based regimens

Who is Really Winning?

Yes	Vote: 12		
Christopher Hourigan	Christopher Lieu	David Mitchell (CR)	Grzegorz Nowakowski ...
Jorge Nieva	Mark Conaway	Matthew Maurer	Michael Riotto
Neil Vasan	Ranjana Advani	Ravi Madan	Thomas Martin
No	Vote: 0		
Abstain	Vote: 0		
No-Voting	Total: 0		

WEEK IN REVIEW:
Dr. Brian G.M. Durie

A Historic Turning Point: ODAC Unanimously Votes in Favor of MRD Testing as an Early Endpoint in Myeloma Clinical Trials to Support Accelerated Approvals of New Treatments

Post date: *April 18, 2024*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