CHRONIC LYMPHOCYTIC LEUKEMIA

MRD AS A CLINICAL ENDPOINT IN FRONTLINE THERAPY - PRO

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DDHO 2024

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DISCLOSURES

Consultancy: AstraZeneca

WHAT IS MRD AND WHY DO WE NEED IT?

Measures depth of remission (sensitivity to treatment)

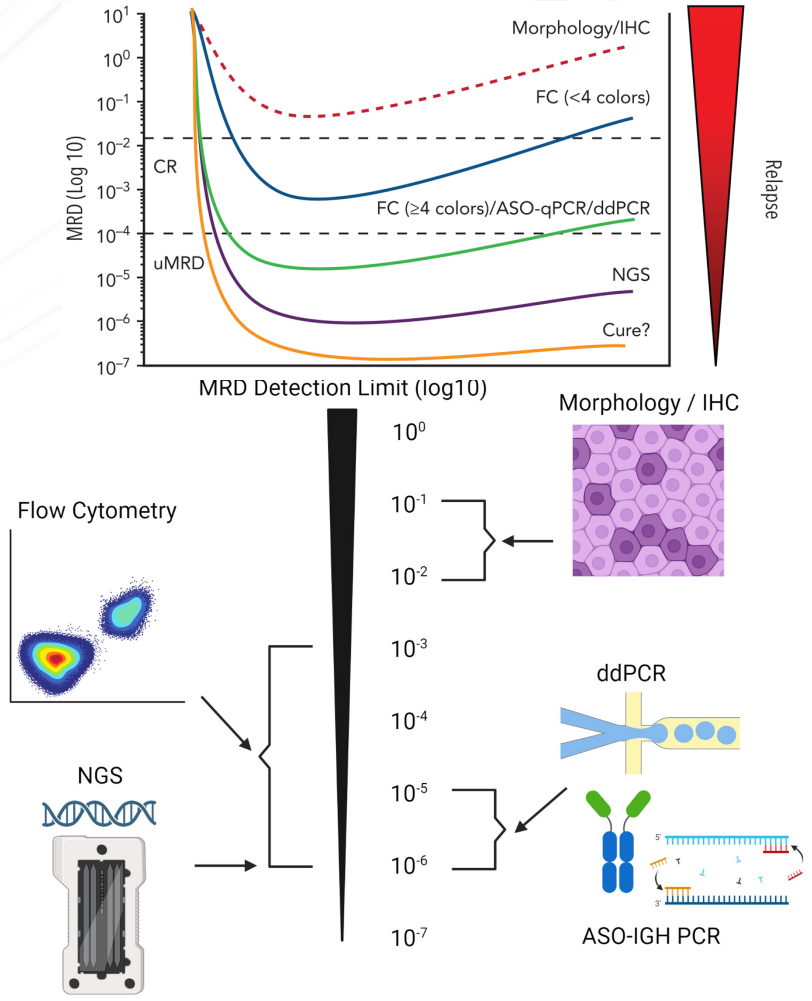
One size does not fit all in CLL treatment

- Define treatment **prognosis** (IGHV, FISH, TP53 mutation – none are perfect)
- Need strategies that **guide treatment** – tailored, personalized approach

Outcomes are better with novel treatments (long PFS and OS)… but not cure yet

- Need earlier readout for clinical trials

To get to cure we need to get to uMRD first

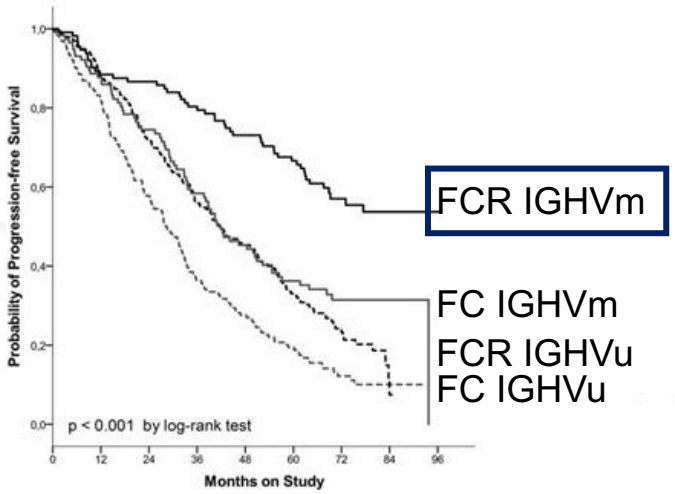


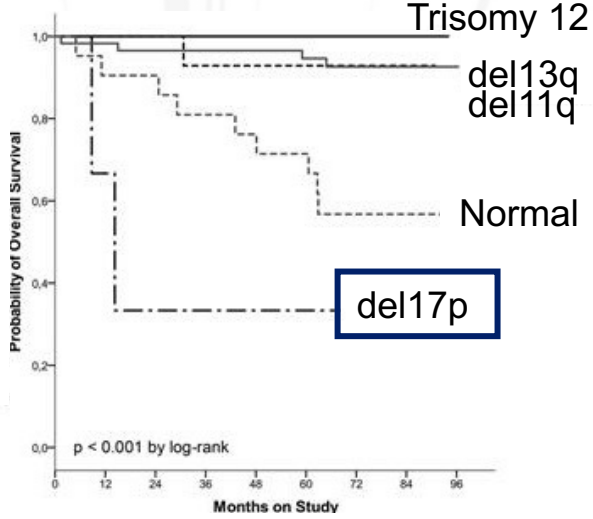
This image was created with Biorender

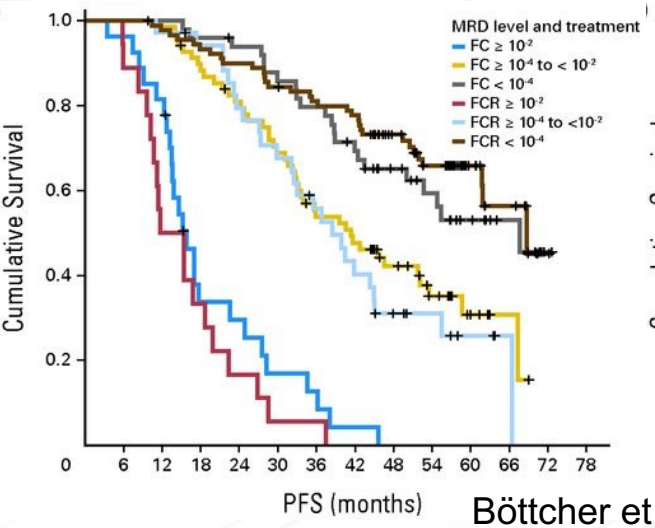
Adapted from Moreno and Mora, Blood 2021
Rhodes, et al. Hematology ASH Educ Prog, 2023

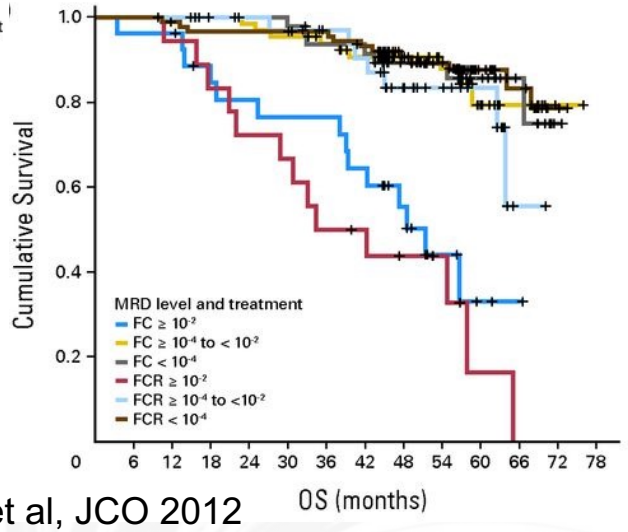
MRD CAN BE PROGNOSTIC

CLL 8, phase 3 FC vs FCR x 6



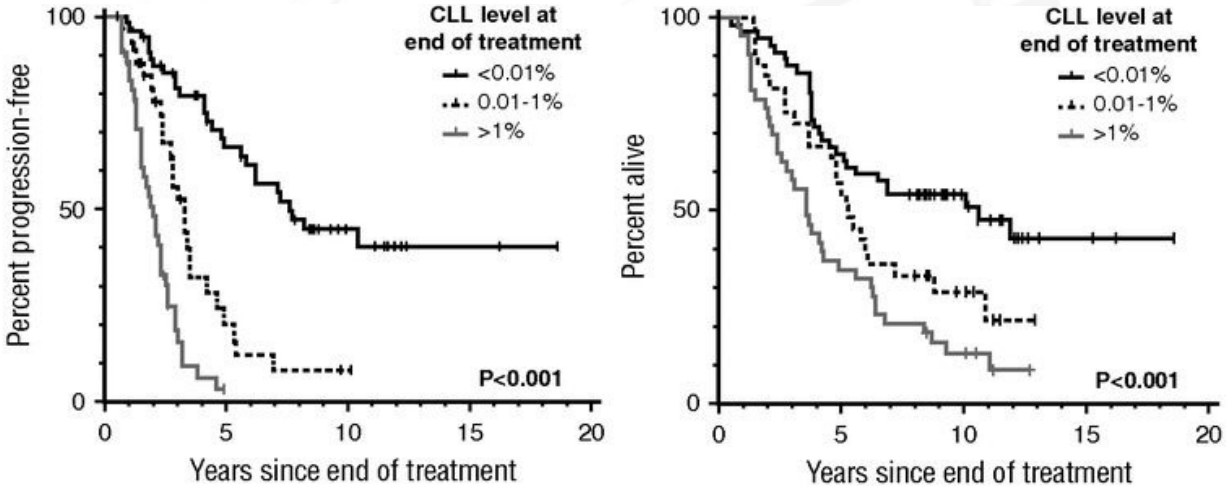


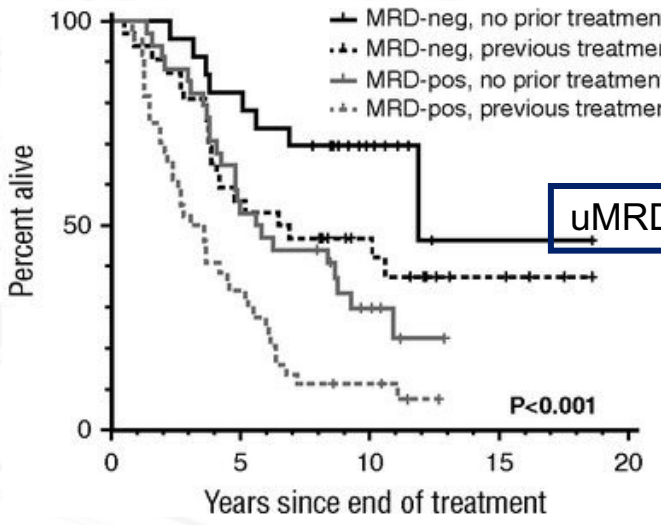




Böttcher et al, JCO 2012

MRD predictive of 10-year PFS and OS in chemoimmunotherapy era





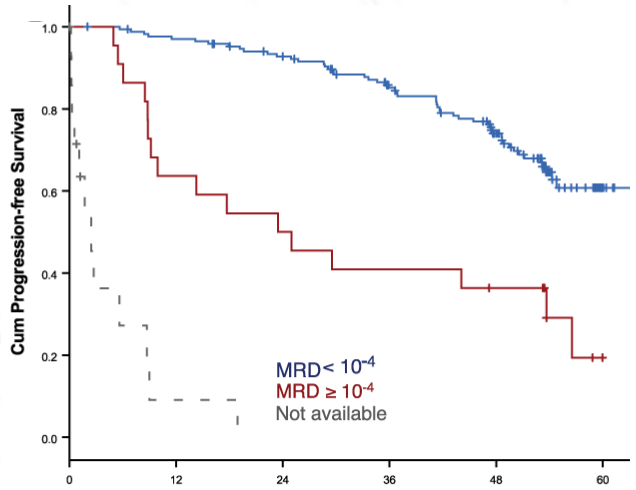
uMRD, no prior tx

Kwok et al, Blood 2016

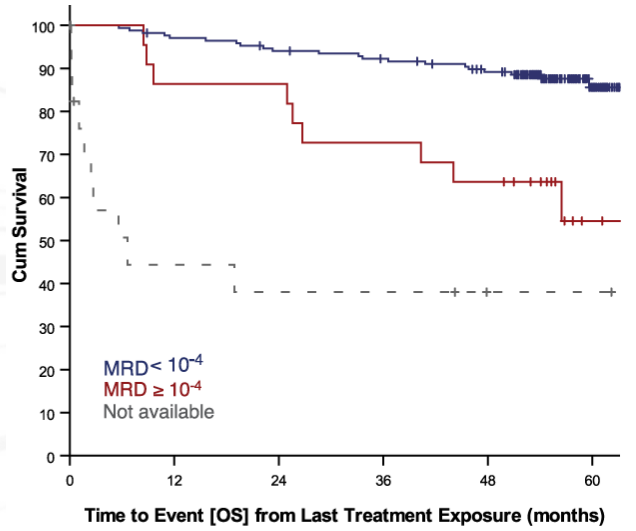
MRD CAN BE PROGNOSTIC

CLL 14, phase 3 Obi-Chb vs Ven-Obi

PFS

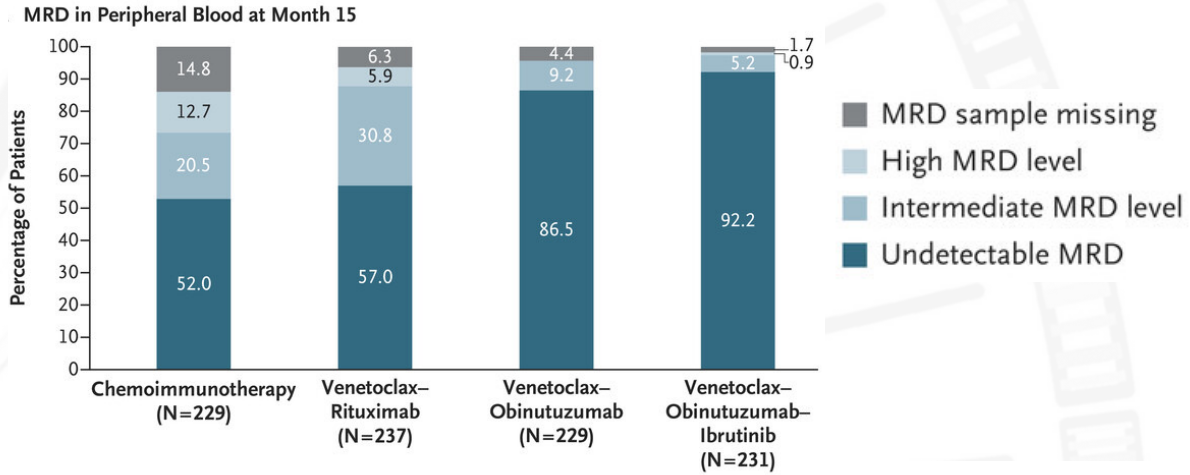


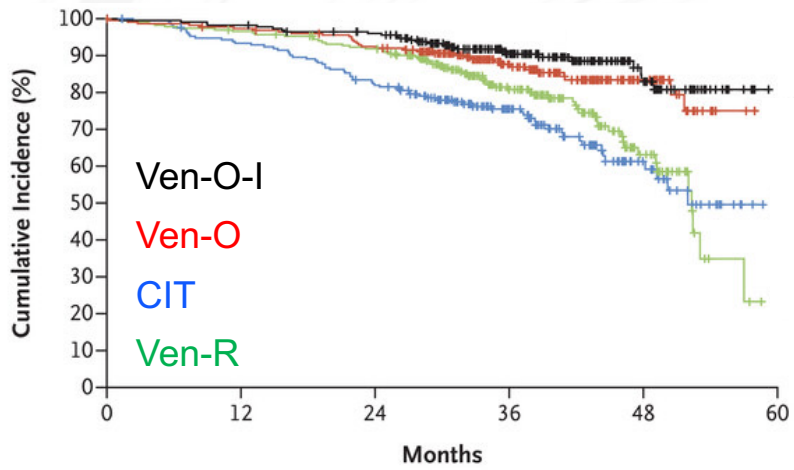
OS

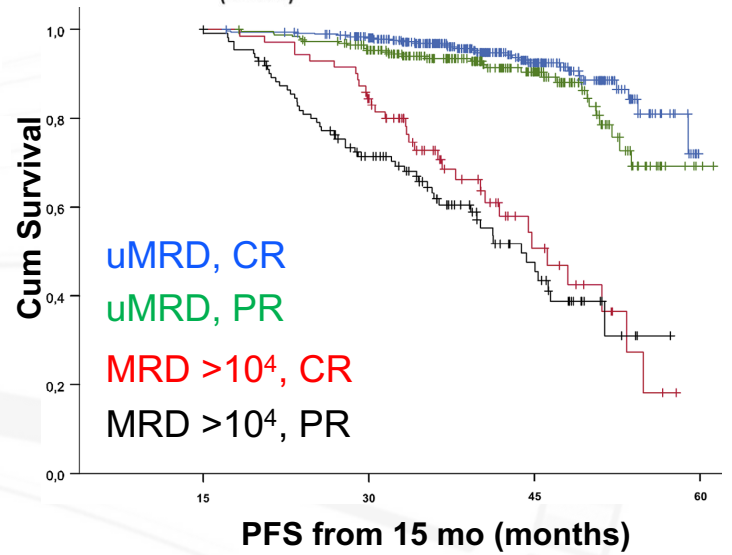


Al-Sawaf et al, Nat Comm 2023

GAIA - CLL 13, phase 3 CIT and Venetoclax therapies







Eichhorst et al, NEJM 2023

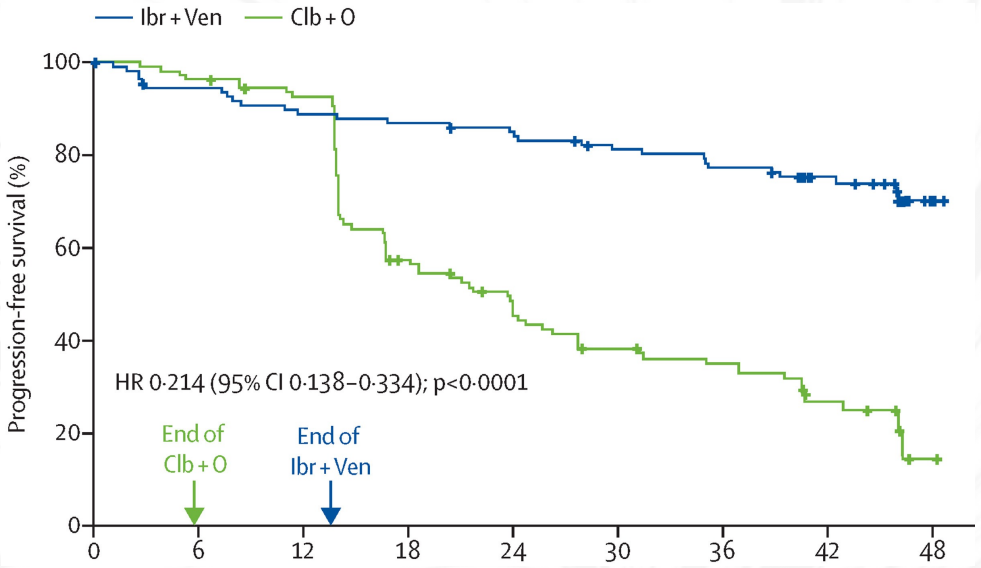
MRD CAN GUIDE THERAPY

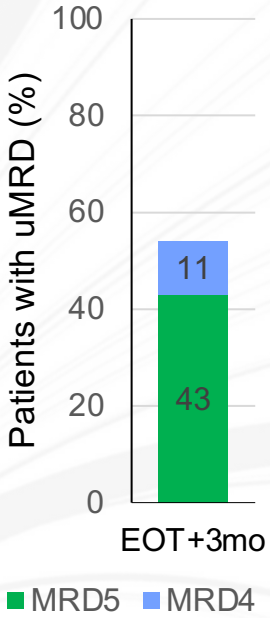
Measures disease sensitivity to a treatment

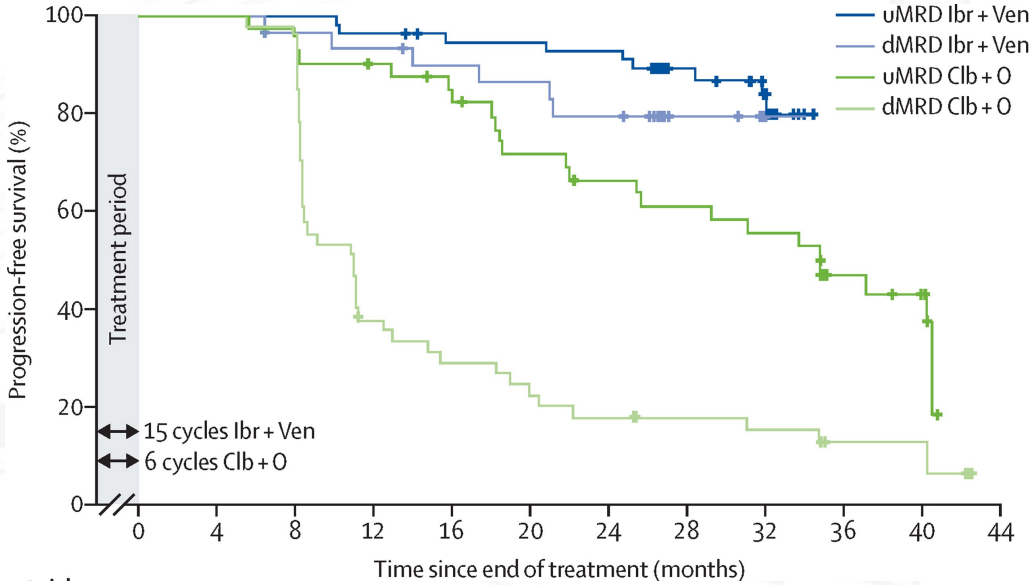
Allows for better strategies for discontinuation of therapy

Lower side effects, risk of resistant mutations, and cost. Improve adherence

GLOW Study: phase 3, fixed duration I+V vs Chb+Obin



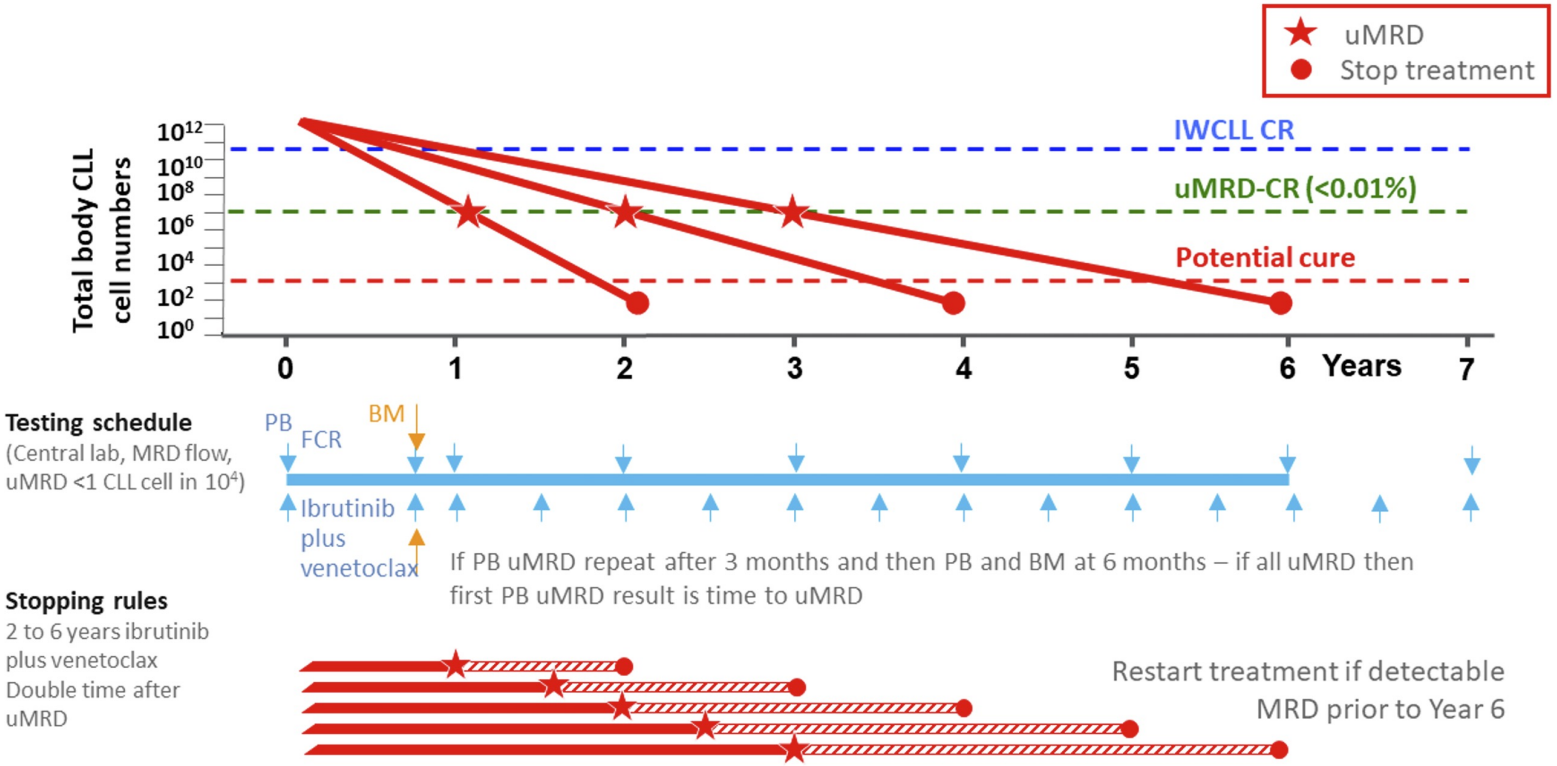




Niemann et al, Lancet Onc, 2023

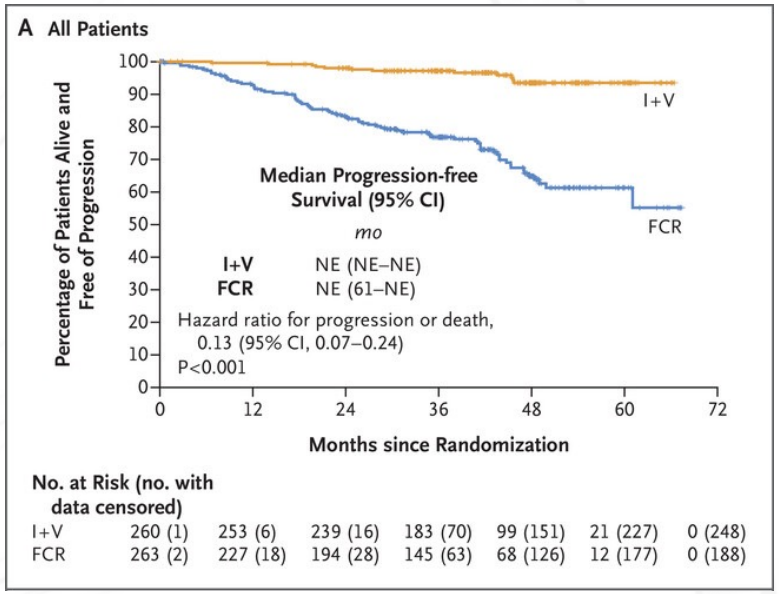
MRD CAN GUIDE THERAPY

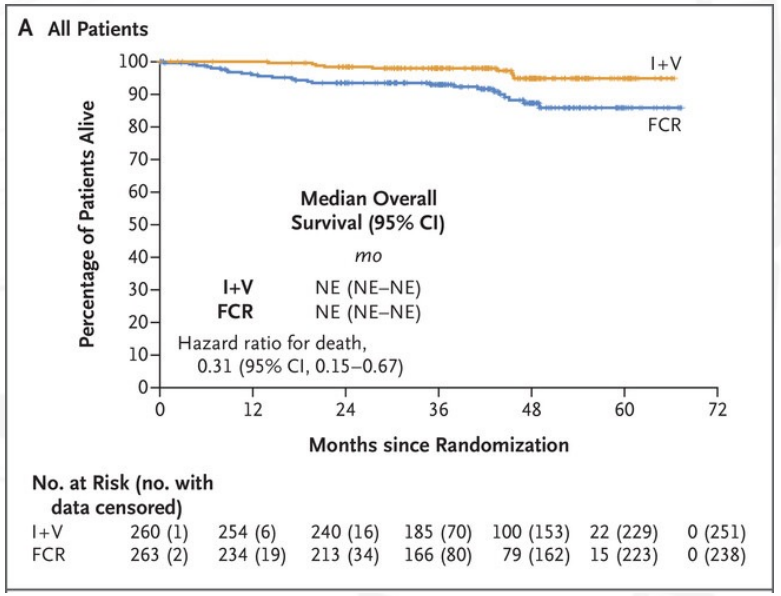
FLAIR Study: phase 3, fixed duration I+V vs FCR



%uMRD	12mo	24mo	36mo	48mo	60mo
PB	47.5	70.5	83.2	89.2	92.7
BM	35.6	52.4	64.0	65.9	65.9

78.4% of patients discontinued treatment per stopping rules at 60mo

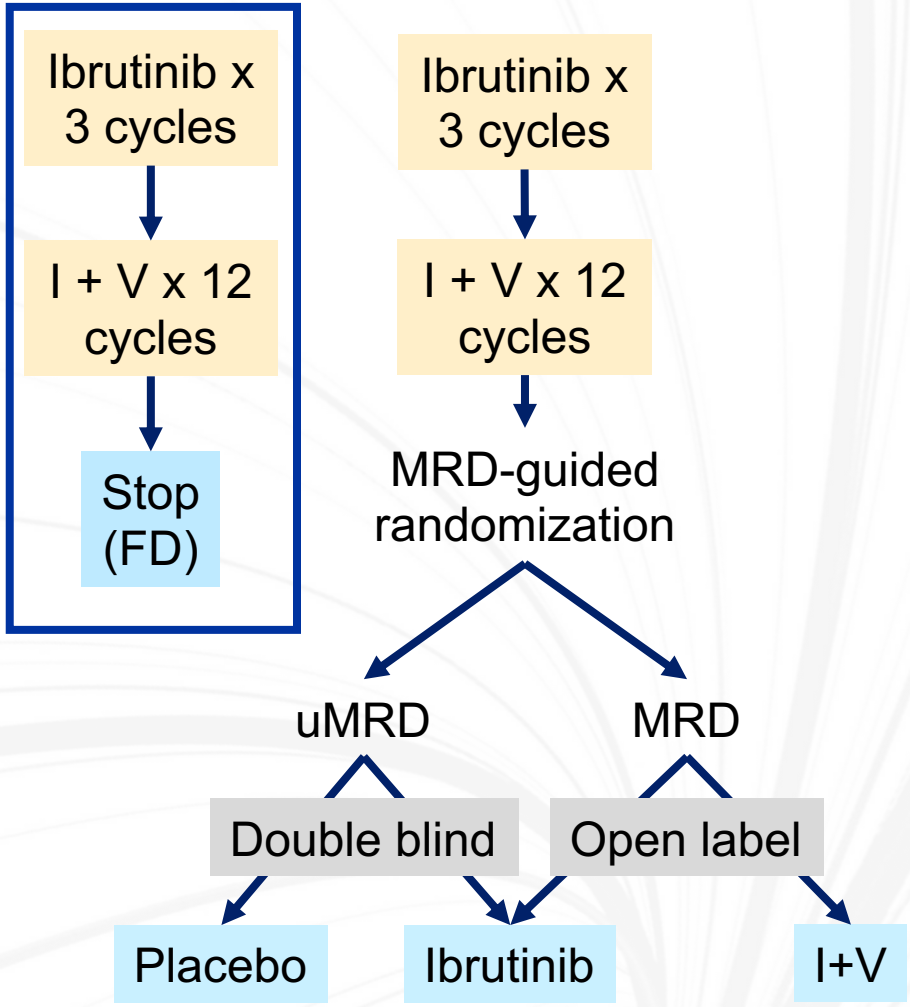


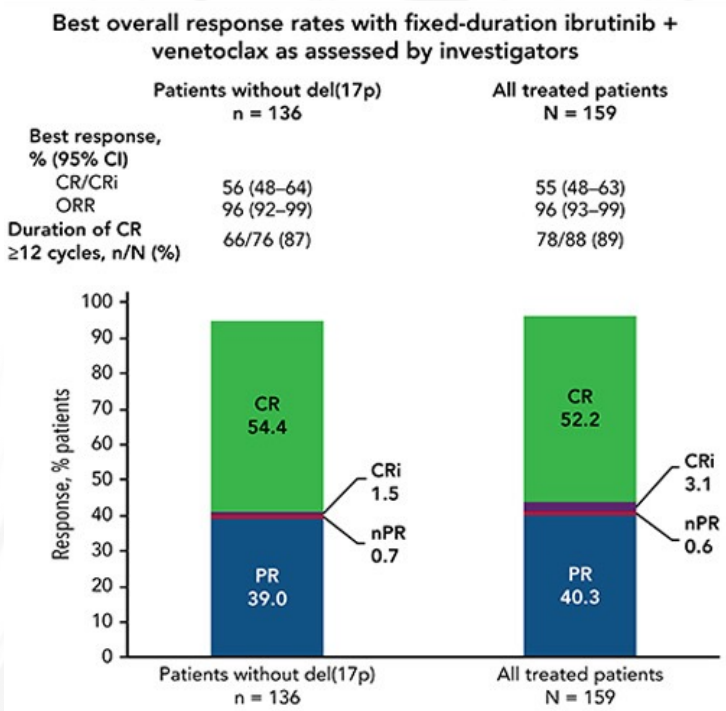


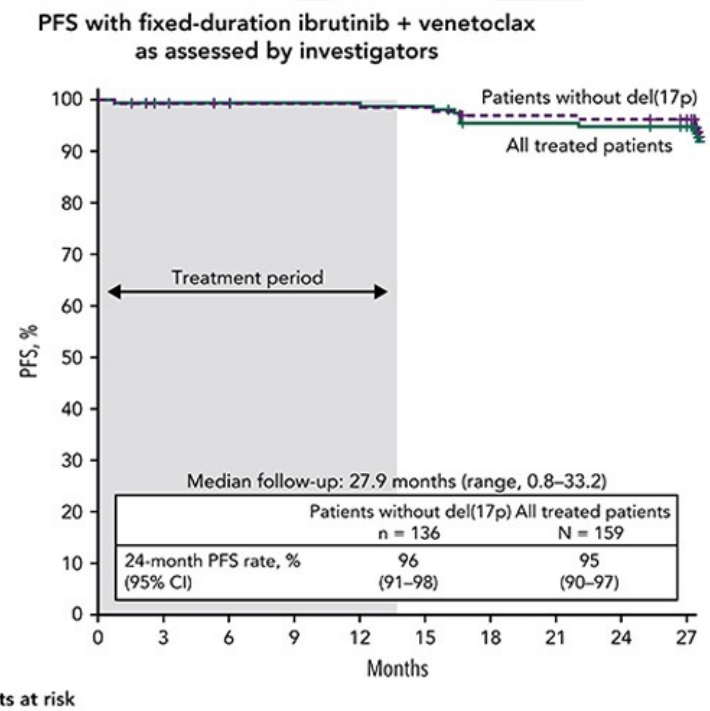
Munir et al, NEJM 2024

MRD CAN GUIDE THERAPY

CAPTIVATE: phase 2, I+V fixed vs MRD-guided





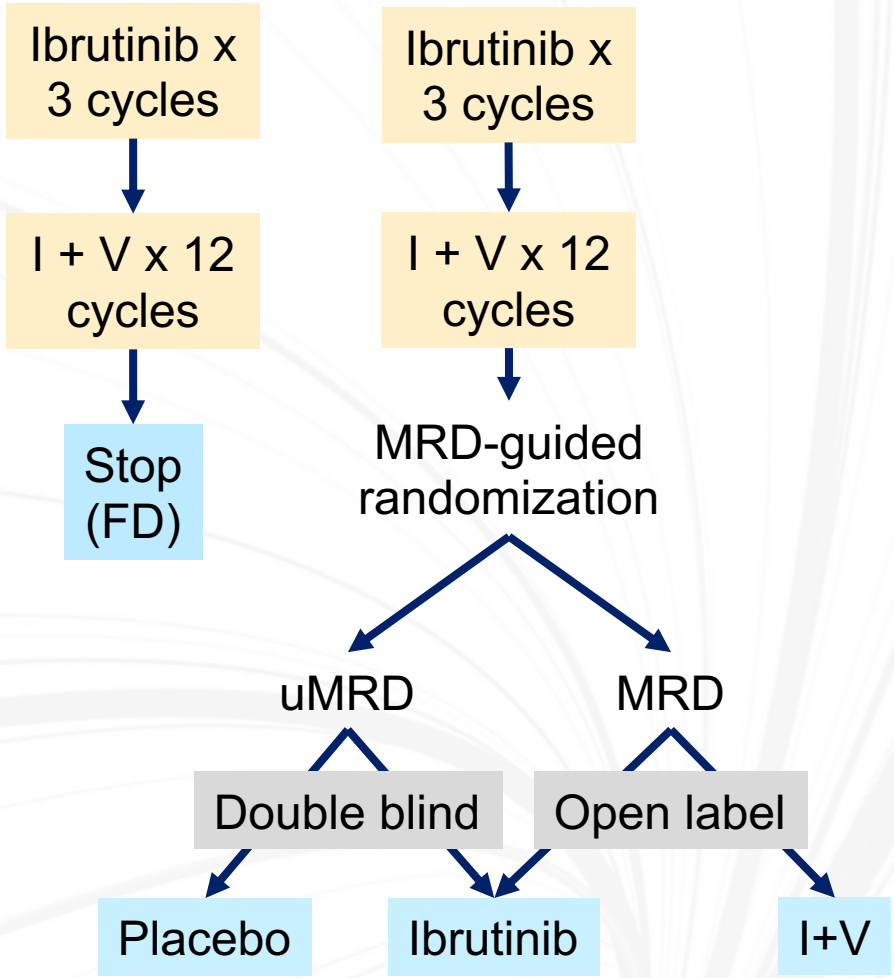


	uMRD 3mo EOT	MRD+	Overall
5y PFS	83% / 84%	48% / 50%	67%
5y OS			96%

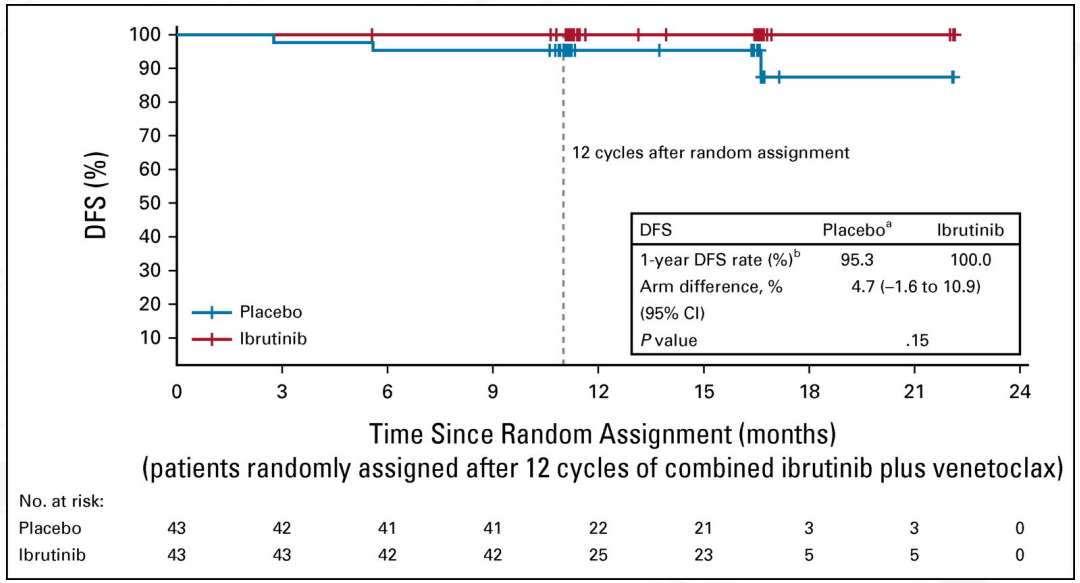
Tam et al, Blood 2022; Wierda et al, ASCO 2024

MRD CAN GUIDE THERAPY

CAPTIVATE: phase 2, I+V fixed vs MRD-guided



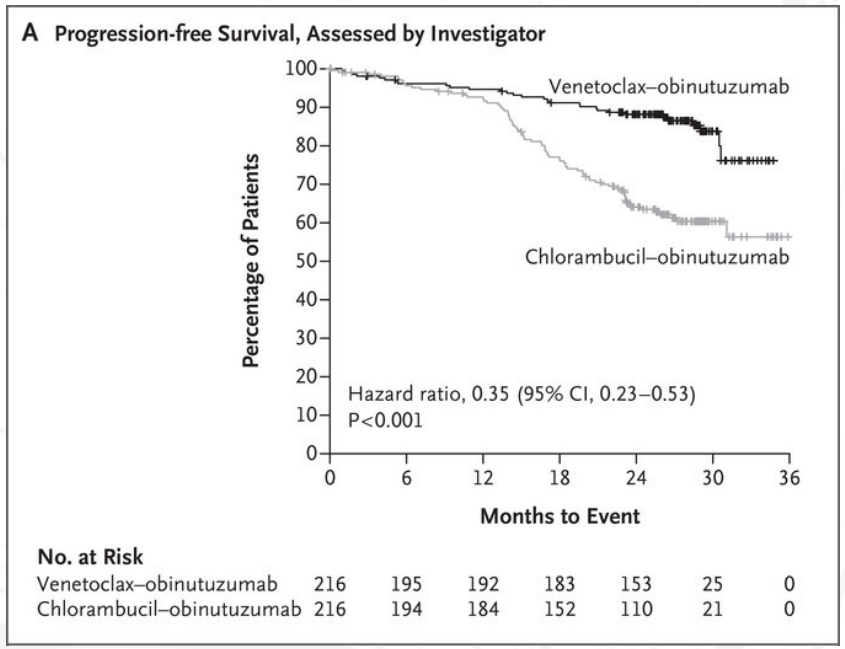
	Confirmed uMRD		uMRD Not Confirmed	
	Placebo n=43	Ibrutinib n=43	Ibrutinib n=31	Ibrutinib plus venetoclax n=32
Median	NE	NE	NE	NE
30-month PFS rate, %	95.3	100	95.2	96.7
95% CI	82.7-98.8	100-100	70.7-99.3	78.6-99.5

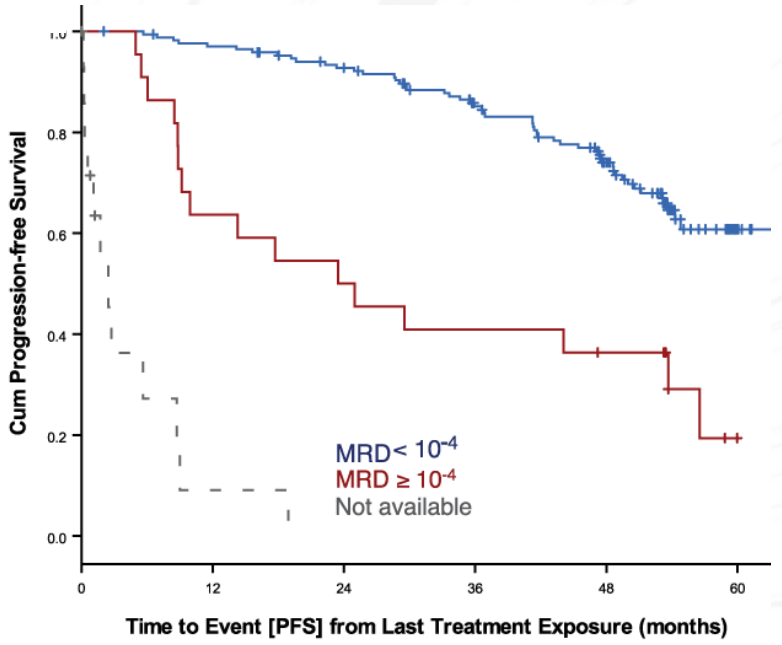


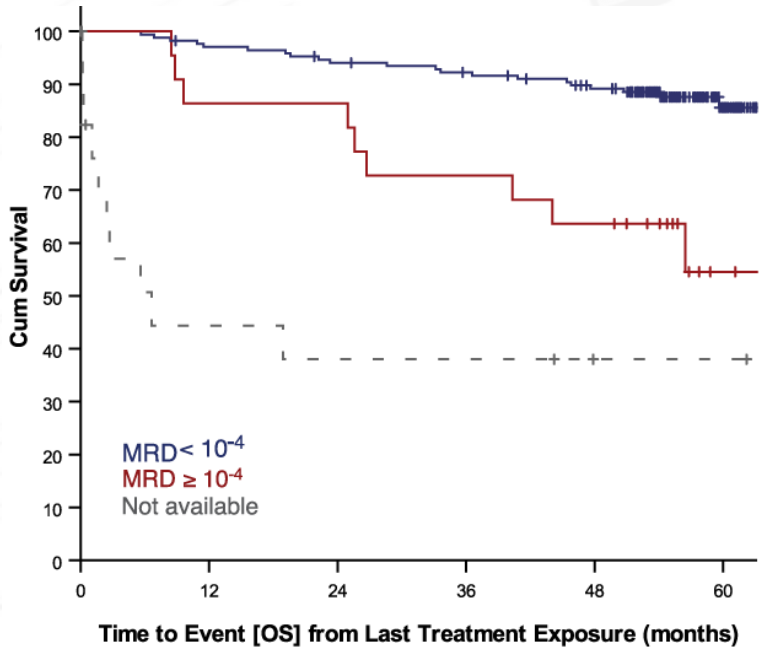
Tam et al, Blood 2022; Wierda et al, ASCO 2024

MRD PROVIDES EARLIER TRIAL READOUT

CLL 14, phase 3 Obi-Chb vs Ven-Obi







Median follow up: 28.1 mo
24mo PFS: 88.2% vs 64.1%

PFS and OS based on end of treatment MRD levels

Fisher et al, NEJM 2019

Al-Sawaf et al, Nat Comm 2023

CONCLUSION

One size does not fit all in CLL treatment

- MRD has prognostic value in the era of novel therapies
- MRD can be used to guide time-limited therapy approaches
  - Lower: side effects, risk of resistant mutations, cost
  - Improved: adherence

Allows for earlier readout for clinical trials

Undetectable MRD is the first step towards cure