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Current
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HEmatology in
Salerno

Updates in **Chronic Lymphocytic Leukemia** and **Lymphomas**

Salerno | 14 aprile 2025 | Grand Hotel Salerno

MRD in the targeted therapy era: a necessary question?

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Disclosures Alessandra Tedsechi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
J&J					x	x	
Beigene					x	x	
Abbvie					x	x	
Lilly					x	x	
Astrazeneca						x	

The role of MRD in CLL

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
EMA/629967/2014
Committee for Medicinal Products for Human Use (CHMP)

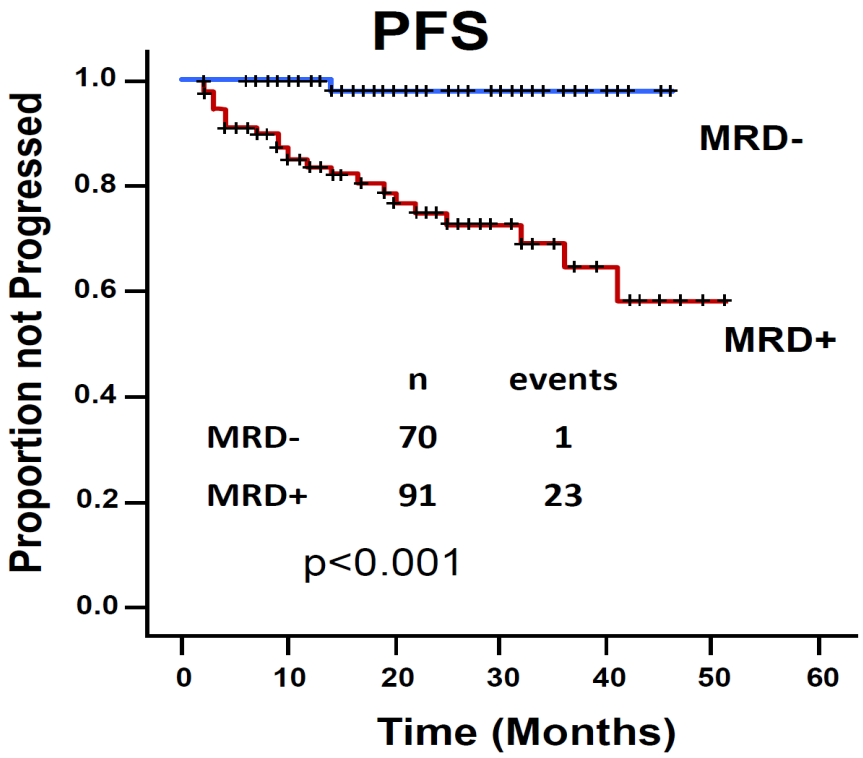
Guideline on the use of minimal residue disease as an endpoint in chronic lymphocytic leukaemia studies

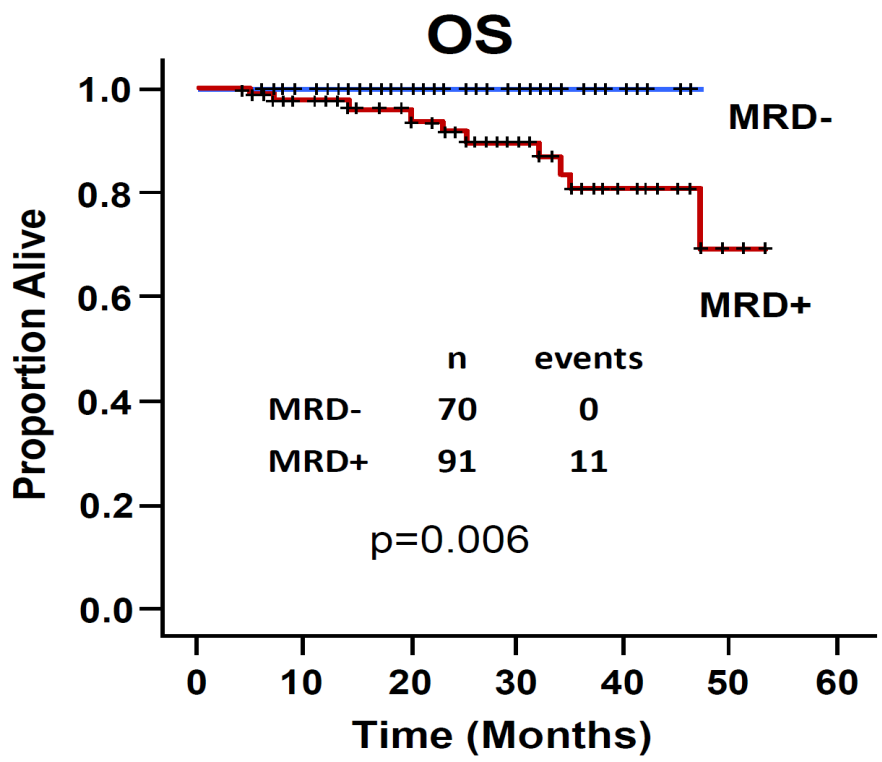
*iwCLL guidelines recommend that «**in clinical trials** aimed at maximizing the depth of remission, the presence of MRD after therapy **should be assessed».***

MRD as endpoint for licensure

A difference in MRD response rates can be used as primary evidence of clinical benefit to obtain early licensure in randomised CLL trials designed to show superiority in terms of PFS provided all the following conditions are met:

First-line FCR: PFS and OS by MRD Status





Strati P, *et al. Blood* 2014; **123**:3727–3732.

Table 3. Recommendations regarding the response assessment in CLL patients

Diagnostic test	General practice	Clinical trial
History, physical examination	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	At cytopenia of uncertain cause	At CR or cytopenia of uncertain cause
Assessment for minimal residual disease	NGI	Desirable
Ultrasound of the abdomen*	Possible, if previously abnormal	NGI
CT scans of chest, abdomen, and pelvis	NGI	Recommended if previously abnormal and otherwise with a CR and PR

For a detailed description of these parameters, see section 5. General practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial.

*Used in some countries to monitor lymphadenopathy and organomegaly.

Hallek M, Blood 2018

Key questions with MRD in CLL

What technique should you use to measure MRD?

How should you define MRD?

What compartment should you monitor?

Should you use static or dynamic MRD evaluation?

When should you stop treatment?

When should you extend treatment?

When should you retreat?

CLL, chronic lymphocytic leukemia; MRD, minimal residual disease.
Slide courtesy of Arnon Kater.

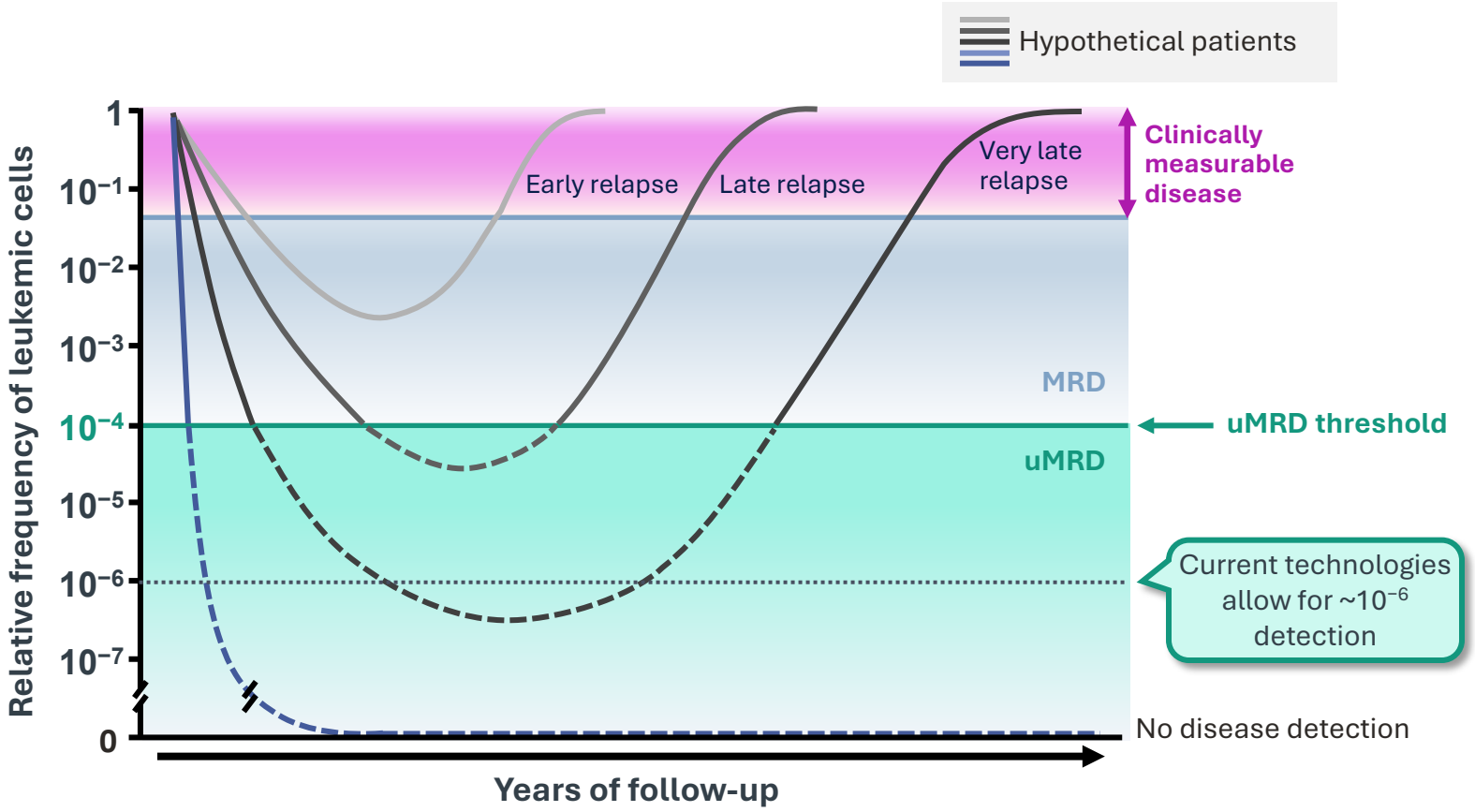
Different methods to detect MRD in CLL

Method	Features	Advantages	Disadvantages
Flow cytometry (FC)	• Detection of surface markers by established antibody panels, eg, CD5/CD19, CD20/CD38, CD81/CD22, CD79b/CD43 • Sensitivity: 10^{-4} (4-colour flow) 10^{-5} (6- or 8-colour flow)	• ERIC consensus guidelines available • Widely accessible • Relatively affordable • Quantified results • Relatively quick	• Fresh (<48-hour) PB or BM samples necessary • Sufficient number of cells required to achieve sensitivity (→ post-treatment cytopenia can be challenging) • Sensitivity lower than PCR or NGS
ASO PCR	• Quantification based on allele- and patient-specific primers for hypervariable CDR3 of Ig • Sensitivity 10^{-5}	• High sensitivity • Uses DNA (instead of fresh material) • Quantified results	• Patient-specific primers required • Baseline reference sample necessary • Relatively time and labour intensive
NGS	• Measurement of CLL-specific Ig sequences based on consensus primers • Sensitivity 10^{-6}	• High sensitivity • Uses DNA • Quantified results • Tracking of clones possible	• Relatively expensive • Not widely used yet

NGS, specifically clonoSEQ, identify and quantify rearranged B-cell receptor gene sequences, including IgH (VDJ), IgH (DJ), IgK, and IgL and translocated BCL1/IgH (J) and BCL2/IgH (J) sequences in DNA extracted from blood and bone marrow.
ASO PCR: polymerase chain reaction using allele-specific oligonucleotides; BM: bone marrow; CD: cluster of differentiation; CDR3: complementarity-determining region 3; ERIC: European Research Initiative on CLL; FLC, free light chain; Ig: immunoglobulin; NGS: next-generation sequencing; PB: peripheral blood; PCR: polymerase chain reaction.

A potential solution
MRD-guided therapy

Hypothetical disease outcomes based on depth of response[1–3]



Pros

- Allows tailored treatment

Concerns

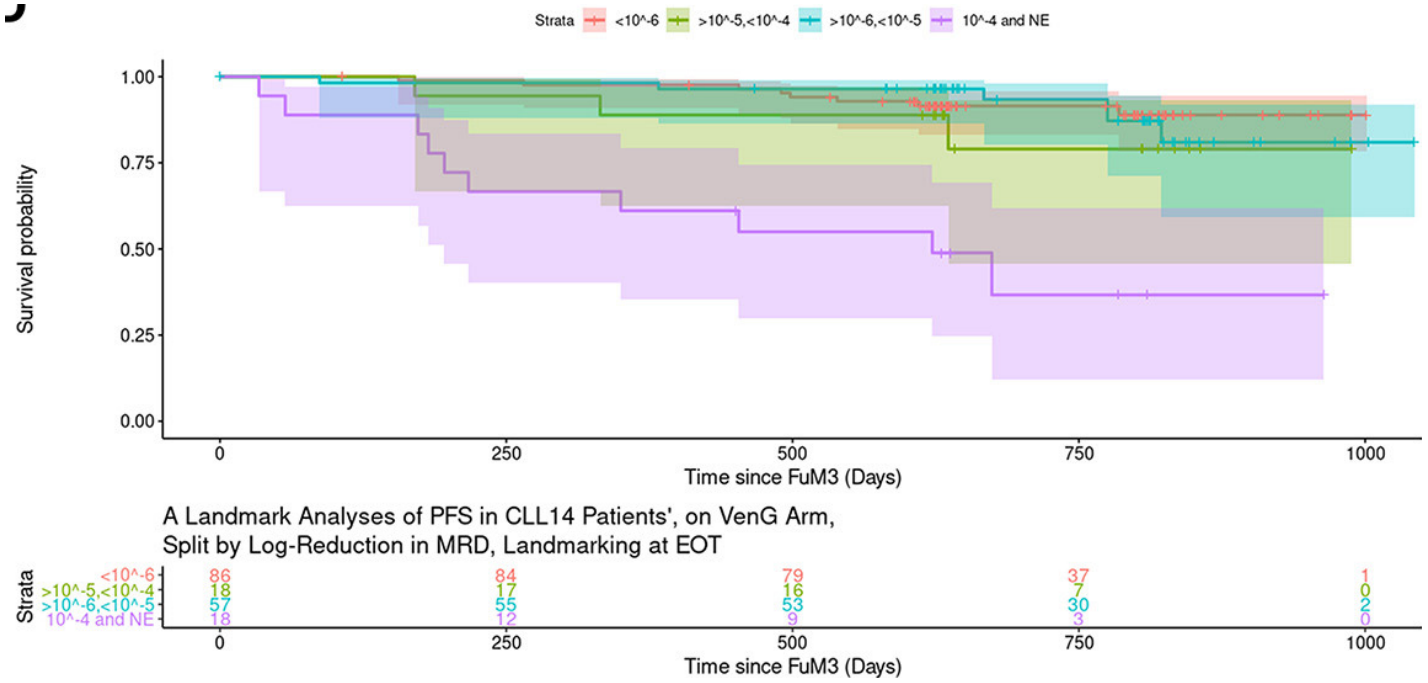
- Method standardization
- Availability
- Role of disease compartment
- Different dynamics for mutated/unmutated IGHV

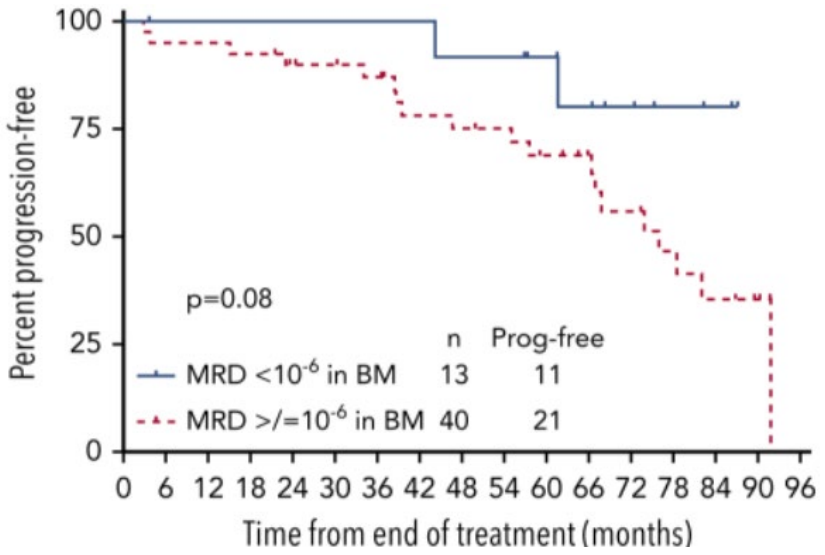
IGHV, immunoglobulin heavy chain variable; (u)MRD, (undetectable) minimal residual disease.

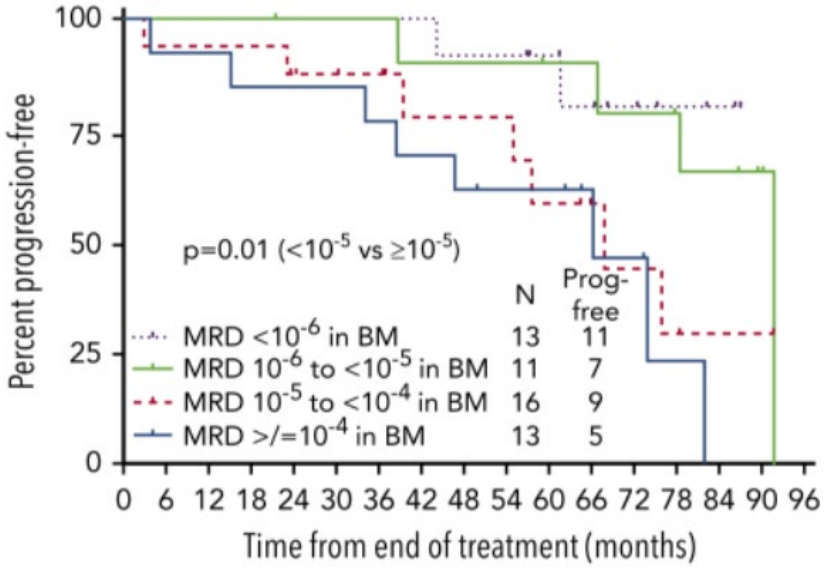
1. Szczepański T *et al*. *Lancet Oncol* 2001; 2: 409–417. 2. Böttcher S *et al*. *J Clin Oncol* 2012; 30: 980–988. 3. Böttcher S *et al*. *Hematol Oncol Clin North Am* 2013; 27: 267–288.

What should be the optimal threshold?

- Linear improvement in PFS per log MRD reduction
- <10^{-6} potentially curative
- But little difference between 10^{-5} and 10^{-6} over 5 yrs FU



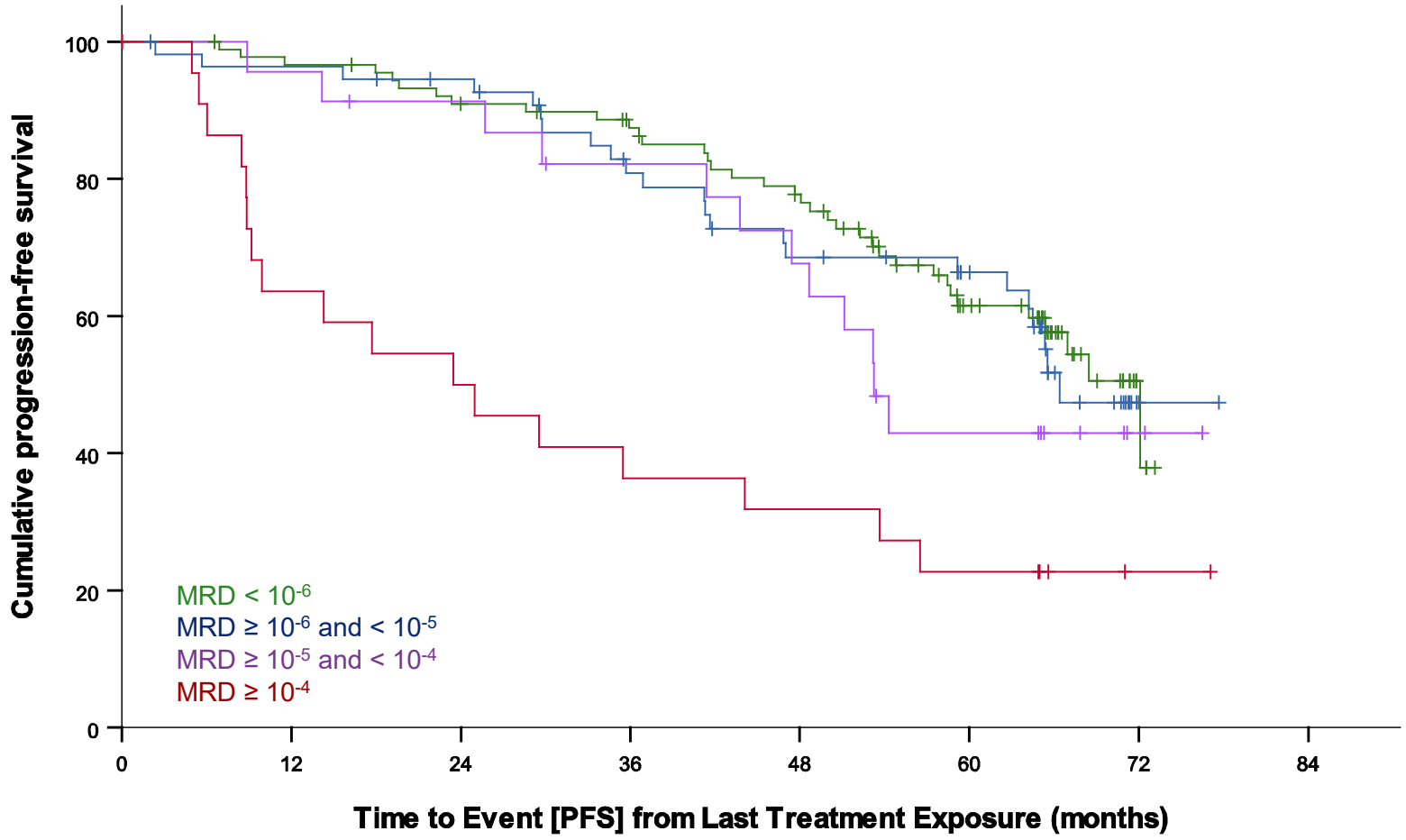




Thompson Blood 2019; Al Sawaf ASH 2020

PFS AFTER VEN-OBI ACCORDING TO *MRD STATUS*

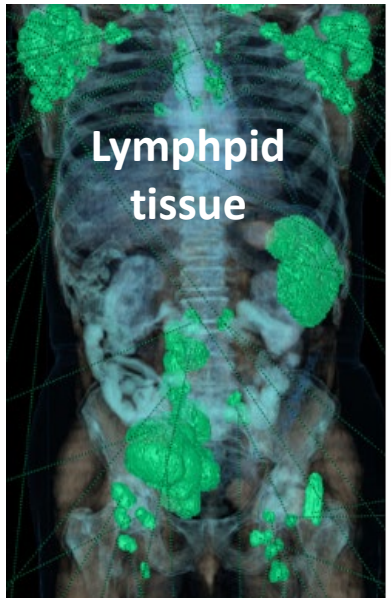
End-of-treatment MRD status in peripheral blood, by NGS

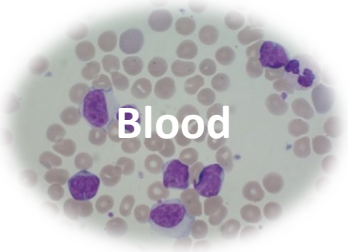


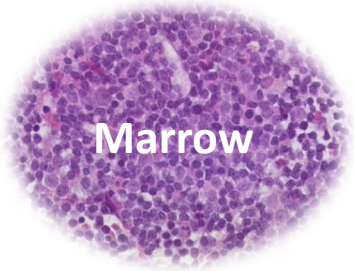
MRD < 10^{-6}	90	86	79	73	63	38	4	0
MRD ≥ 10^{-6} and < 10^{-5}	56	53	50	40	33	26	2	0
MRD ≥ 10^{-5} and < 10^{-4}	23	22	20	17	14	8	2	0
MRD ≥ 10^{-4}	23	14	11	8	7	5	1	0

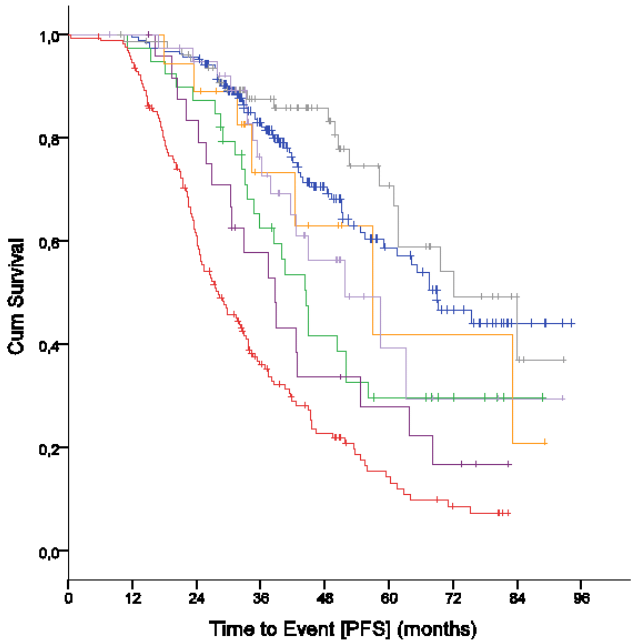
Depth of remission correlates with **long-term PFS**, indicating the prognostic value of the end-of-treatment MRD status.

Is MRD negativity in PB an appropriate surrogate of cure?









	Median PFS
MRD- CRs	68.9 mo
MRD- PRs:	
- with splenom.	72.0 mo
- with ly. node	38.7 mo
- with BM	56.8 mo
- > 1 above	51.8 mo
MRD+ CRs	44.4 mo
MRD+ PRs	28.1 mo

Kovacs G, et al. J Clin Oncol 2016

→ multicompartmental disease

- Standard MRD technologies probe solely PB and BM

- CT scan is the most sensitive tool to probe MRD LN
- Residual LN by CT scans impacts as having residual disease in PB

ERIC guidelines 2021

3A) PB vs. BM MRD assessment

- Bone marrow may be the most informative compartment for MRD analysis but is not appropriate for many applications.
- Treatment-related differences between PB and BM MRD are largely known:
  - Steady state: PB MRD ~0.2log lower than BM
  - Therapeutic antibody: PB MRD **0.5-2 log** lower than BM up to 1 year after last dose
  - BCRi: PB MRD levels **equivalent** to BM
  - BCL2i: PB MRD **~0.5log** lower than BM
- **? Should the updated guidance seek consensus on which applications can be achieved using PB analysis only and which applications require bone marrow MRD assessment**

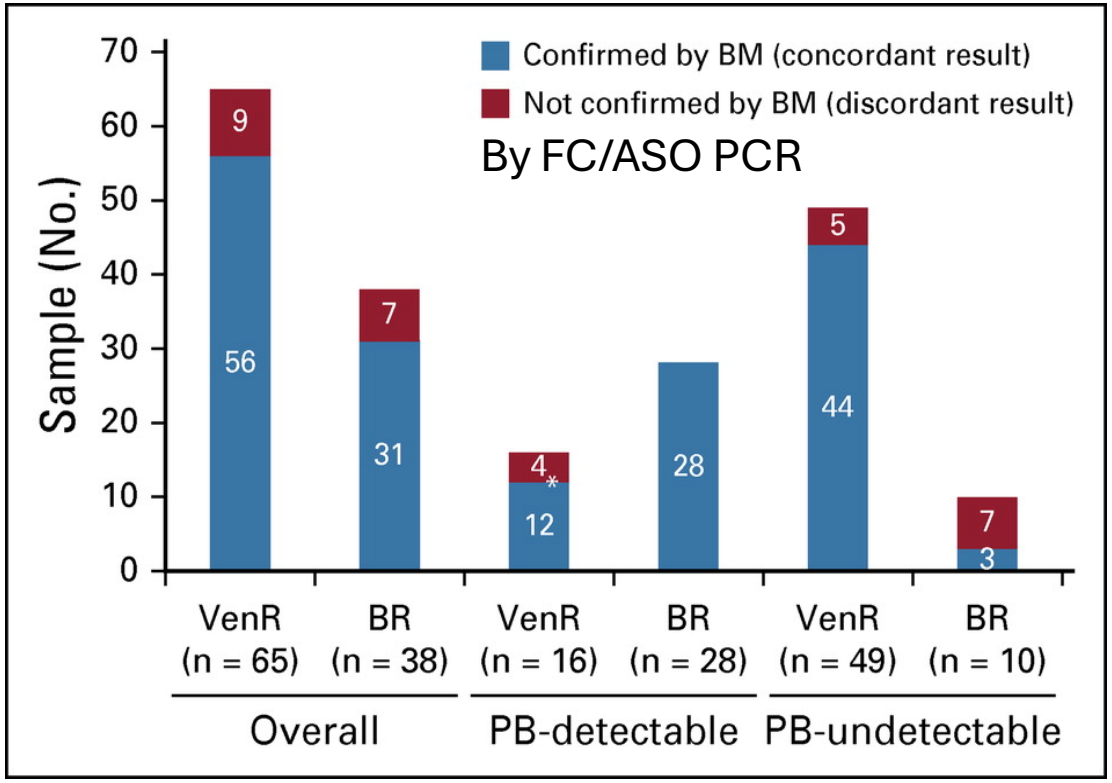
- Rituximab: 0.7-log higher MRD levels in BM than in PB
- Alemtuzumab: 2-log higher MRD levels in BM than in PB

PB or BM?

- In both PB and BM MRD status is strongly prognostic for PFS and OS
- BM evaluation is needed when MRD is undetectable in PB

Wierda GW, Leukemia 2021

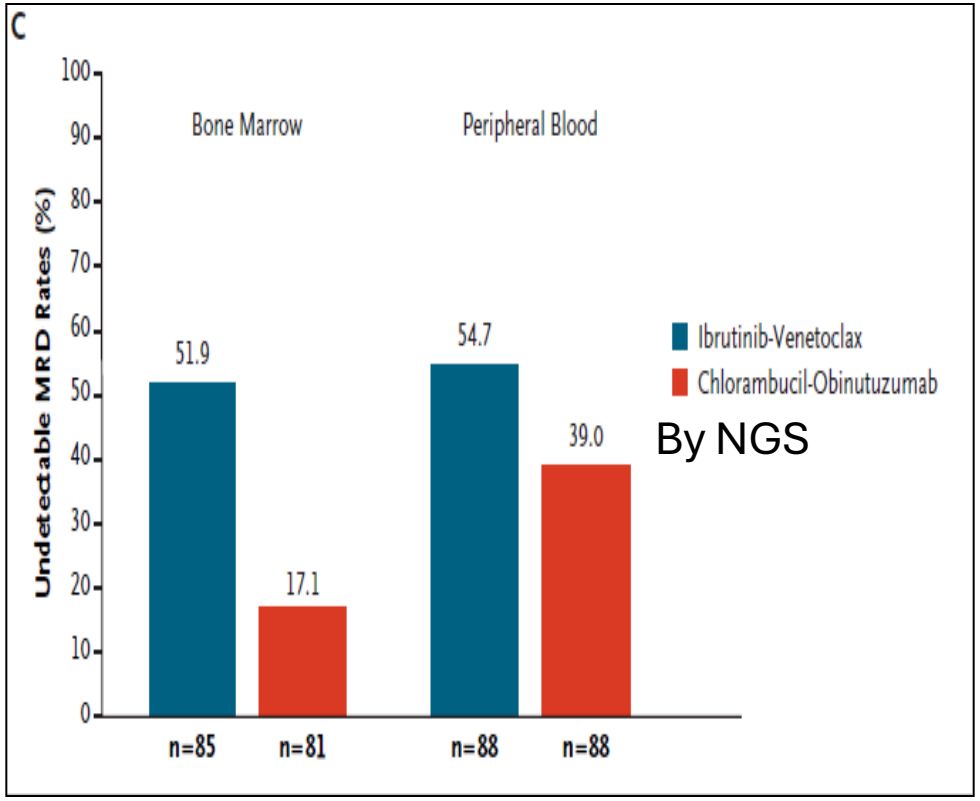
Concordance PB/BM in Murano study



EoT U-MRD in PB 62,4% and BM 27,3%
IN PAIRED SAMPLES CONCORDANCE OF 90%

Kater AP, JCO 2019

Concordance PB/BM in GLOW study at 3m EoT



3-m EoT U-MRD in PB 54.7% and BM 51.9%

Kater AP, NEJM 2022

ERIC guidelines 2021

3A) PB vs. BM MRD assessment

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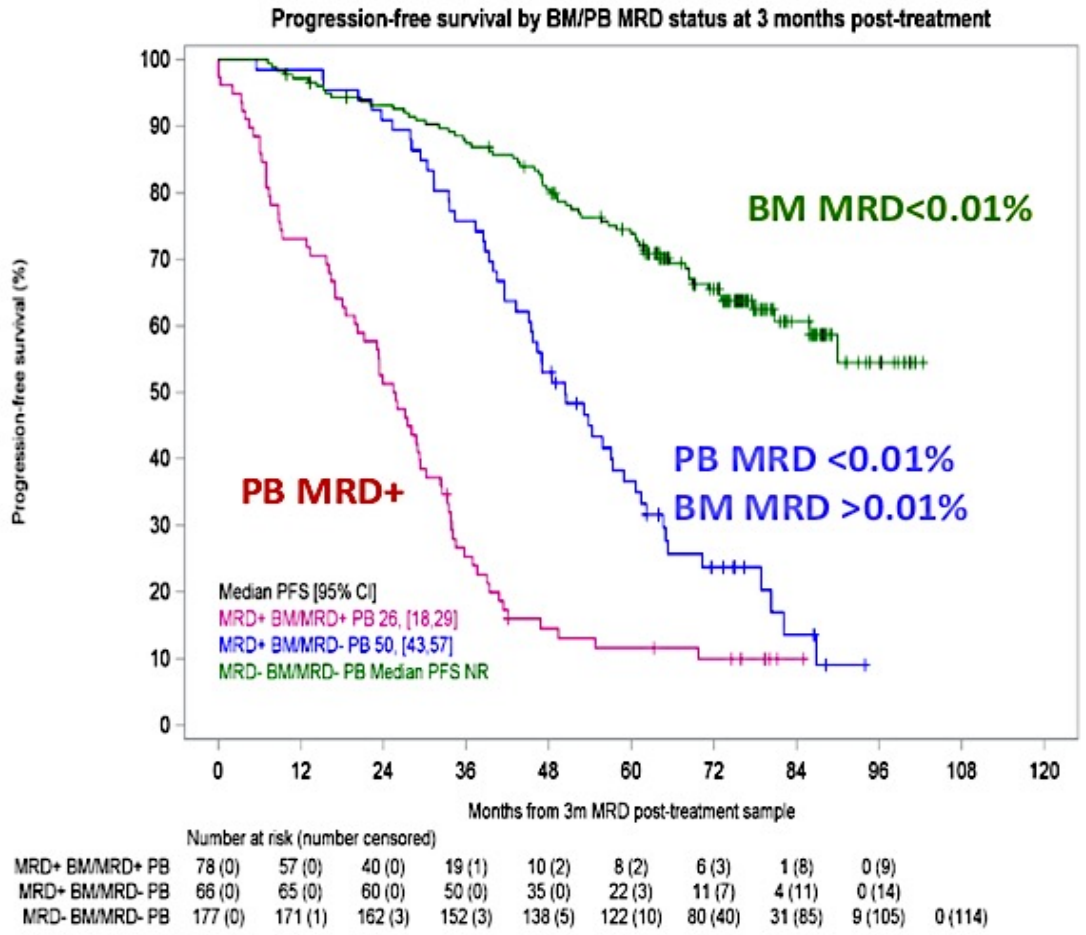
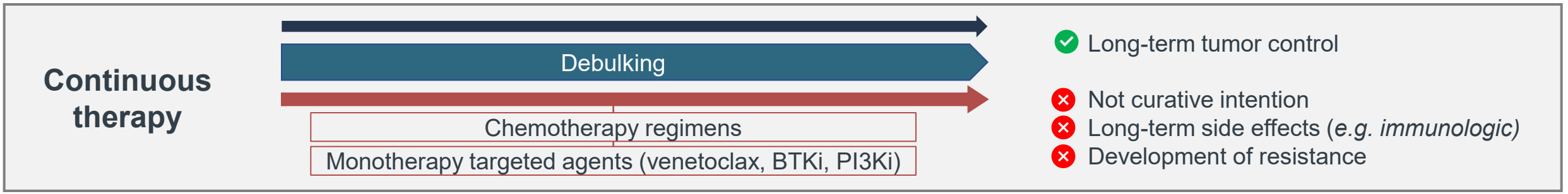
- **? Should the updated guidance seek consensus on which applications can be achieved using PB analysis only and which applications require bone marrow MRD**



It is recommended that patients are screened for CLL eradication in the PB first.

If MRD is not detectable in PB, it may be important to confirm MRD status in the BM.

There are two approved treatment models for CLL

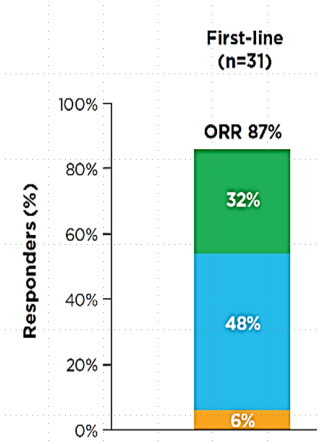


The content on the slide reflects the speaker's personal opinion, drawn from their own experience and expertise.

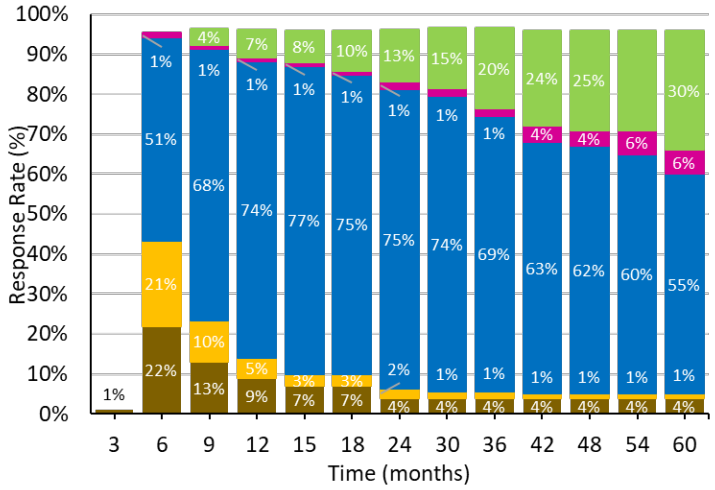
BTKi, Bruton's tyrosine kinase inhibitor; CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia; PI3Ki, phosphoinositide 3-kinase inhibitor. Slide courtesy of Arnon Kater.

Long term responses with ibrutinib
Ibrutinib does not require MRD eradication

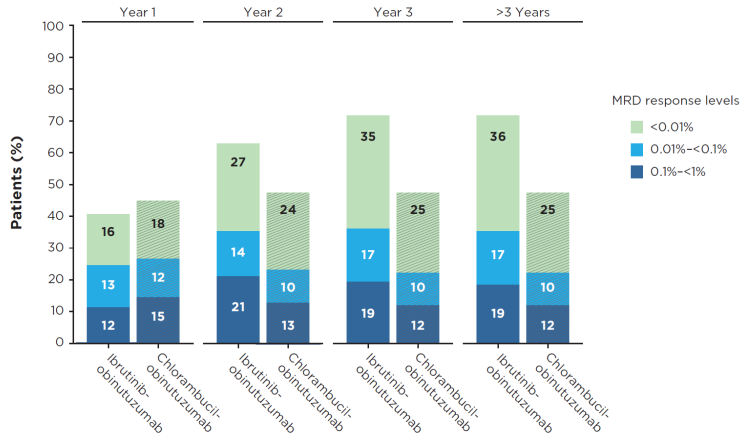
PCYC 1102[a]
Median treatmen duration 72m



Resonate-2[b]
Cumulative Best Response Over Time on Study

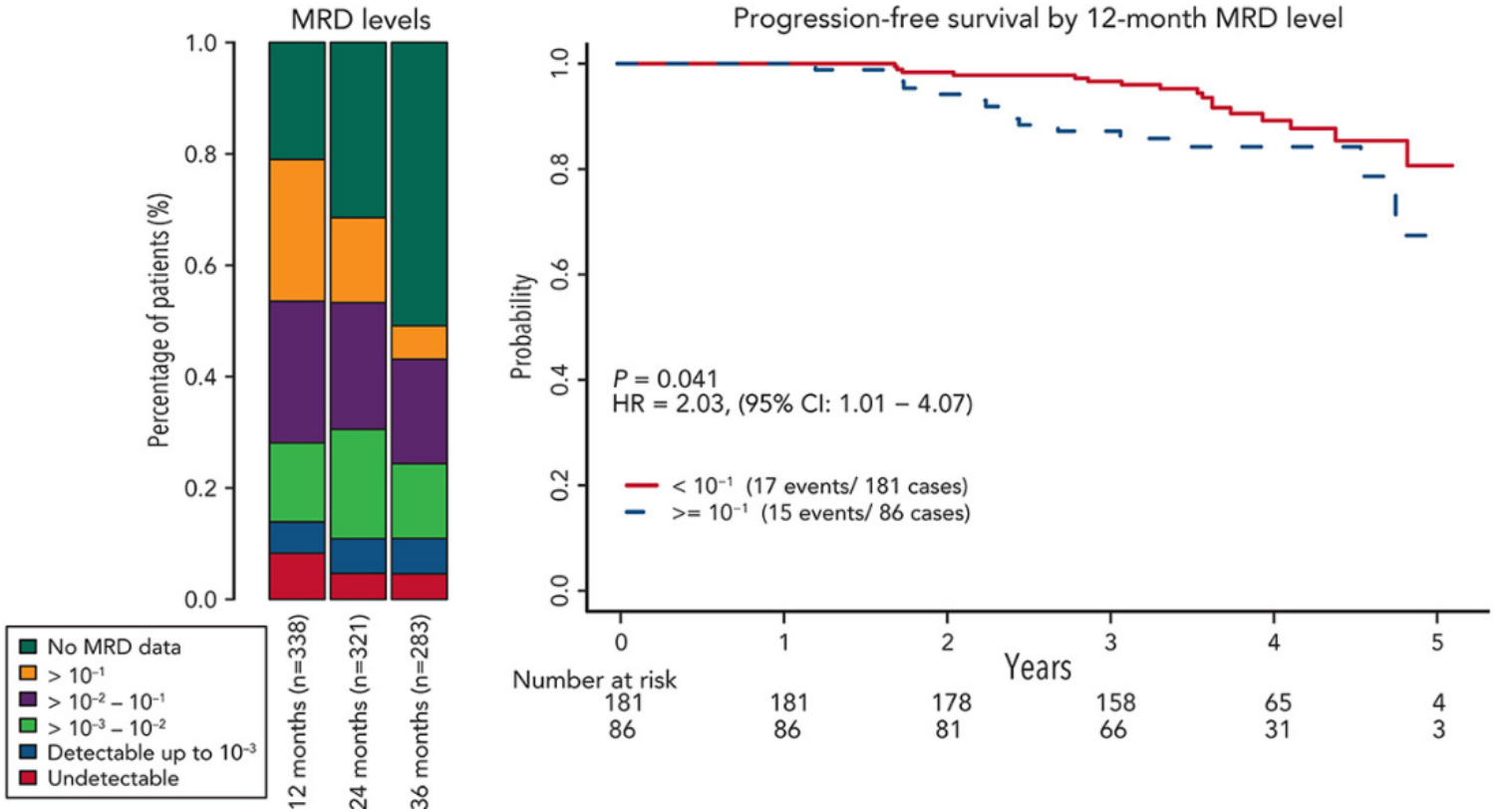


Illuminate[c]
Cumulative rates of MRD responses



[a]Byrd et al., 2018; [b]Burger et al., 2019; [c]Moreno et al., 2019

uMRD may be not so important with BTKi



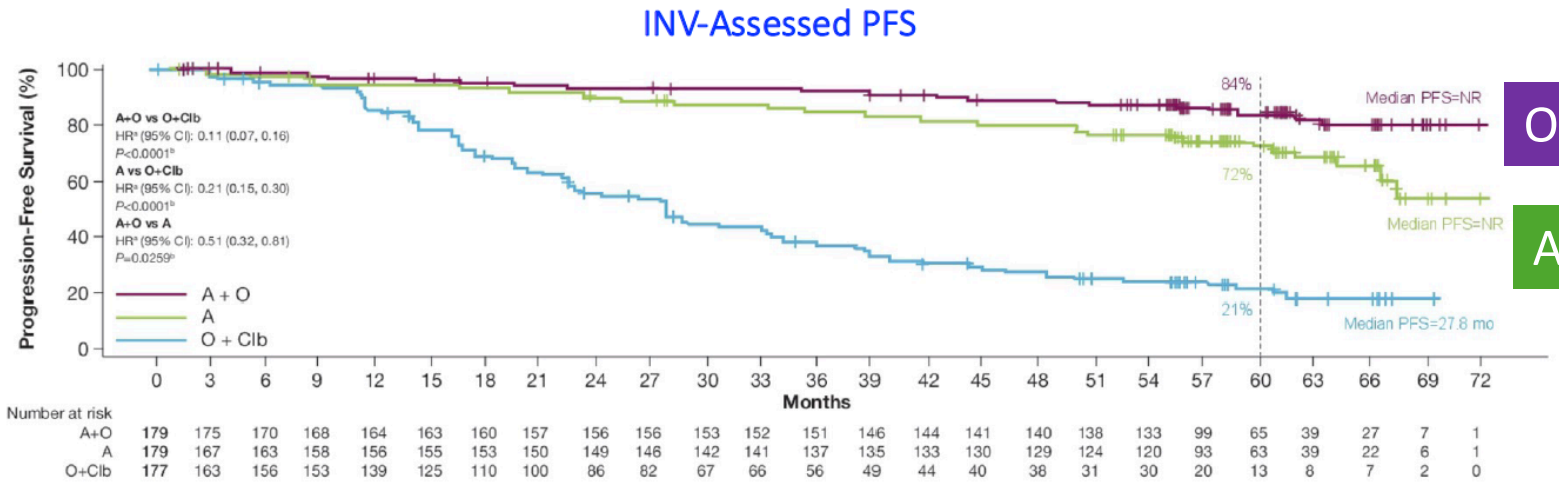
ECOG1912 study

no difference in PFS by uMRD status in the IR arm

Wang Blood 2021

MDR & acalabrutinib

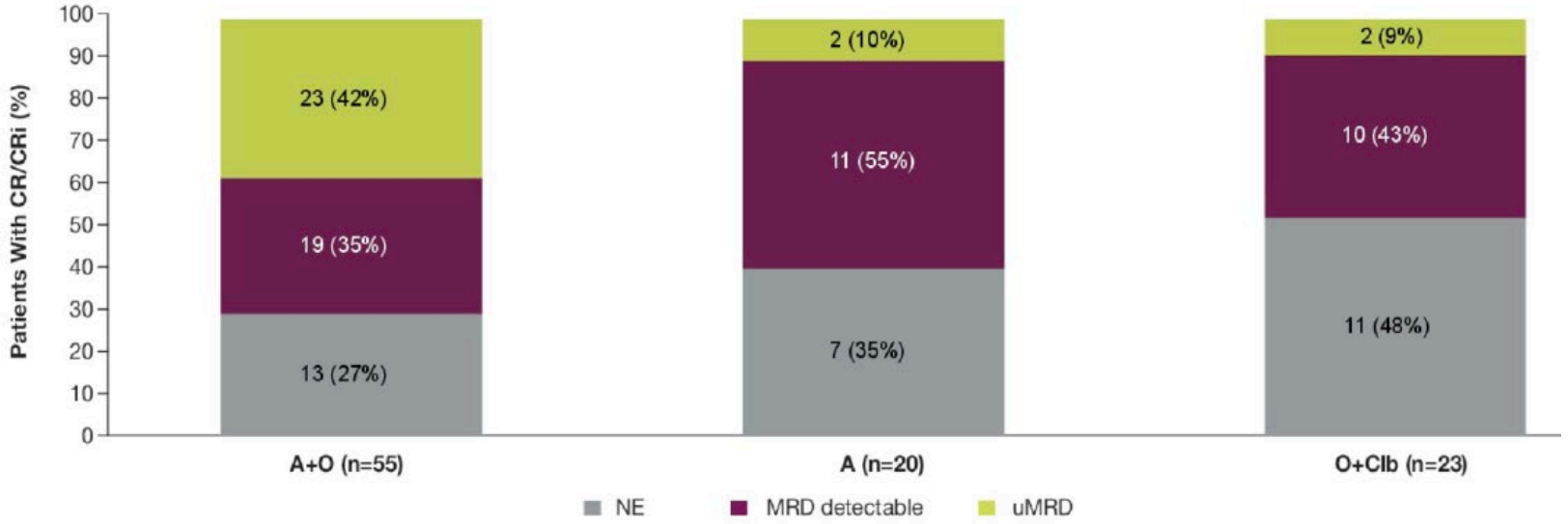
5-Year Follow-Up of the ELEVATE-TN Phase 3 Study: PFS



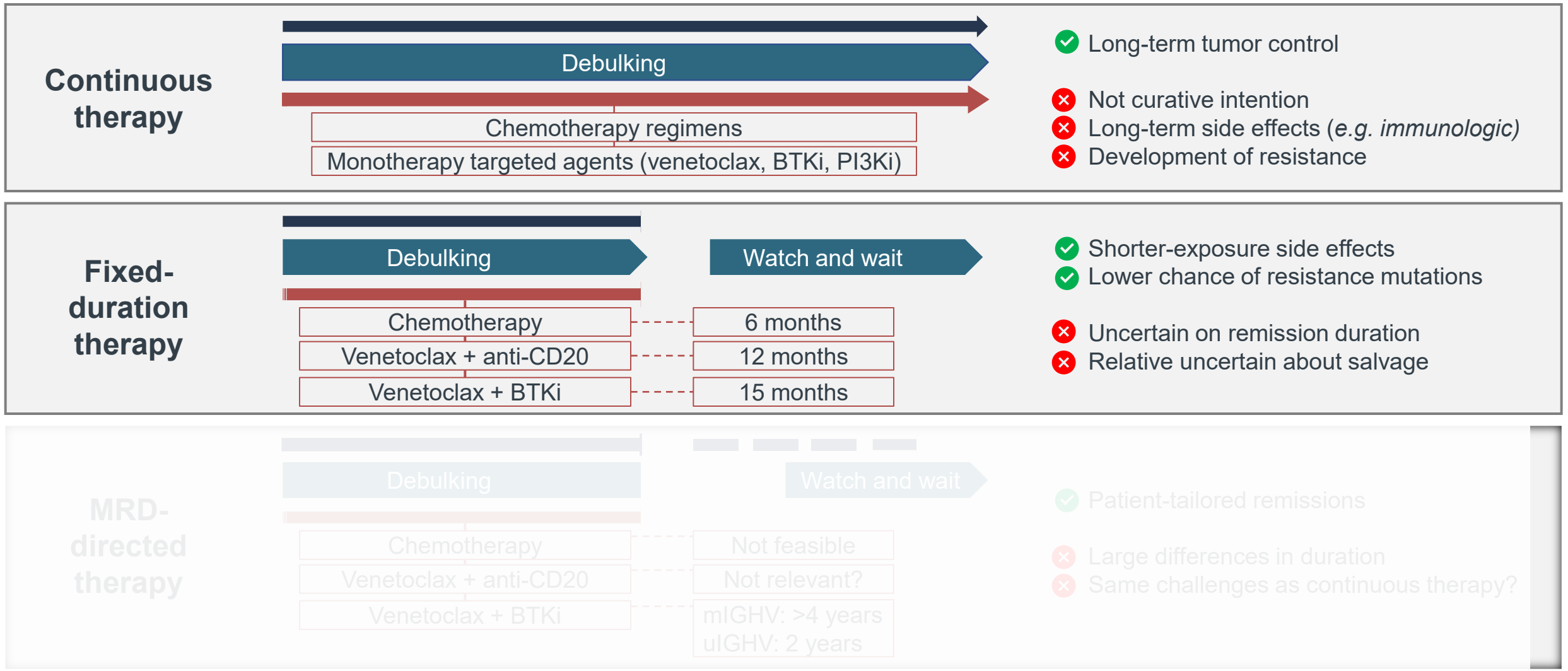
O-Acala 84%

Acala 72%

Median follow-up:
58.2 months
(range, 0.0-72.0)



There are two approved treatment models for CLL



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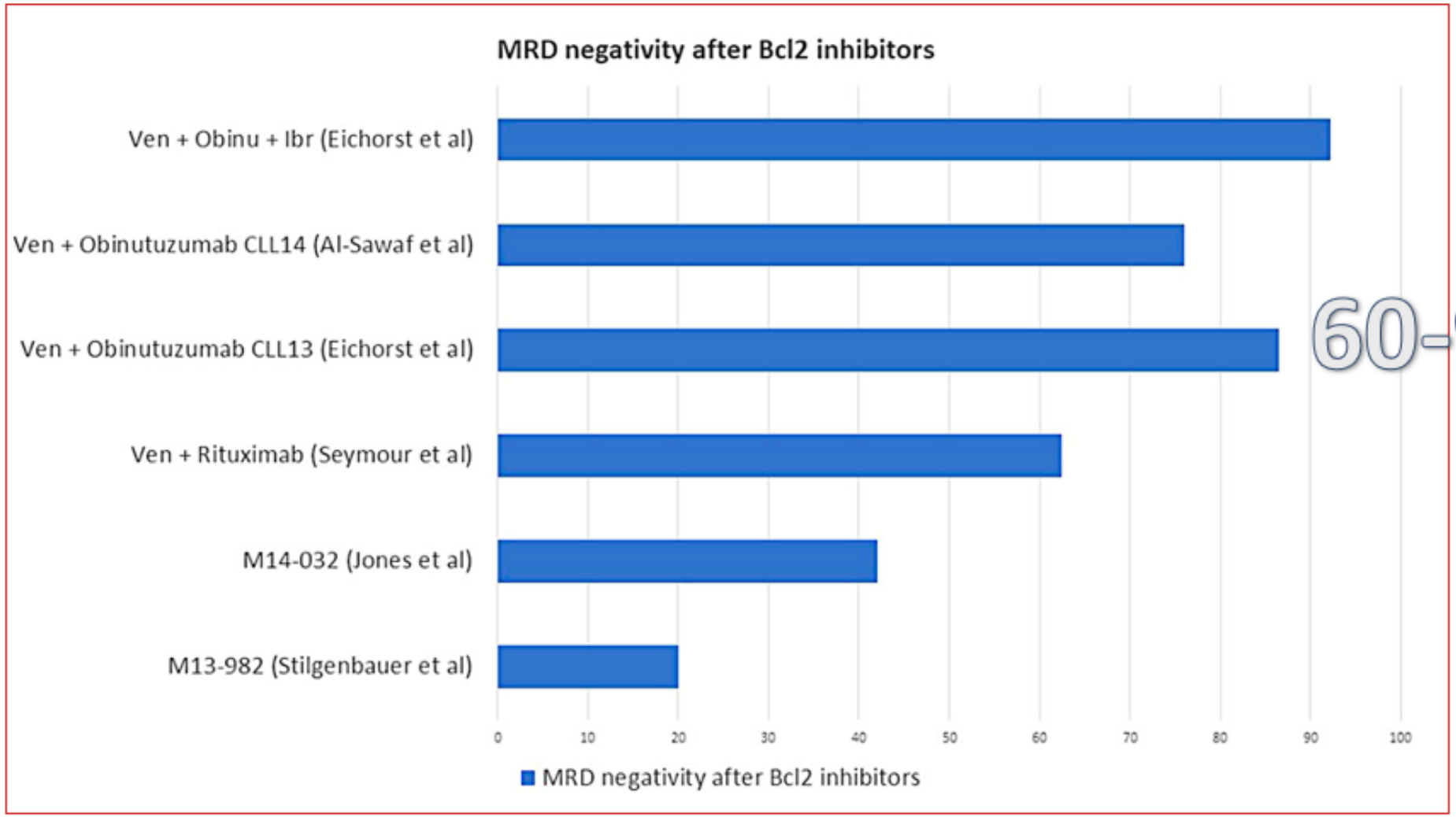
BTKi, Bruton's tyrosine kinase inhibitor; CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia; PI3Ki, phosphoinositide 3-kinase inhibitor. Slide courtesy of Arnon Kater.

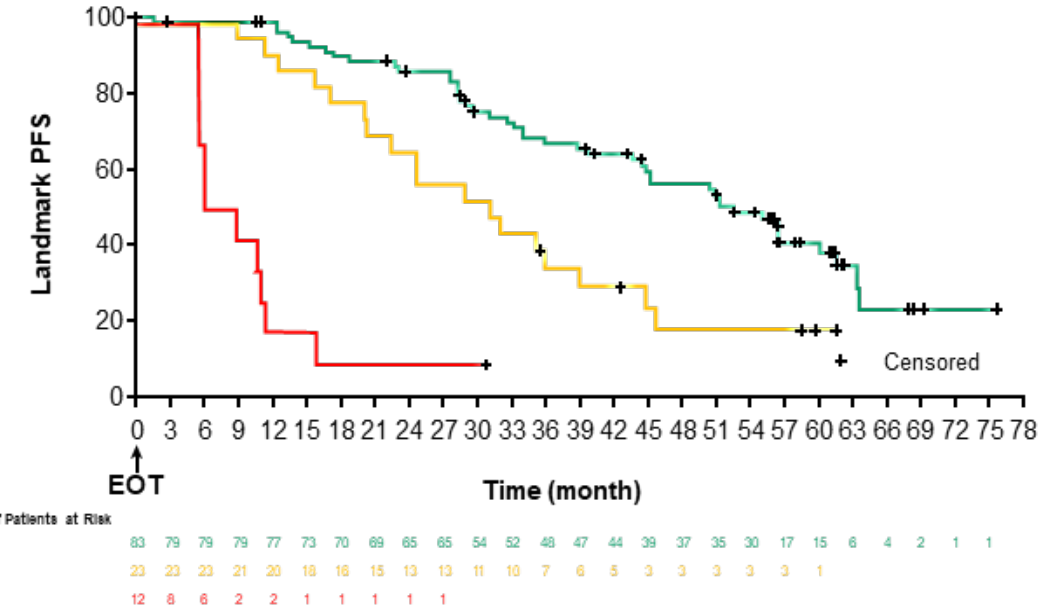
MRD & venetoclax



Achievement of uMRD was associated with prolong PFS in VenR-treated patients

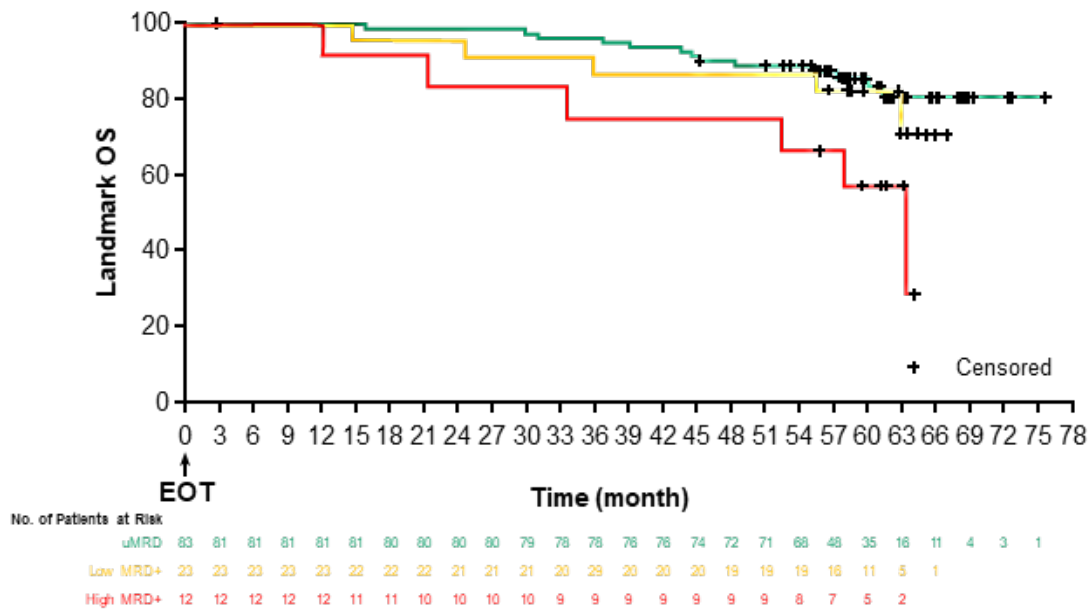
Progression-free survival[1]

VenR-treated patients who completed 2 years of Ven without PD	Median PFS since EOT (95% CI), months	HR* (95% CI)
uMRD (n=83)	**52.5** (44.5–61.5)	**4.47** (2.39–8.36) Stratified P-value <0.0001†
MRD+ (n=35)	**18.0** (8.5–29.3)	



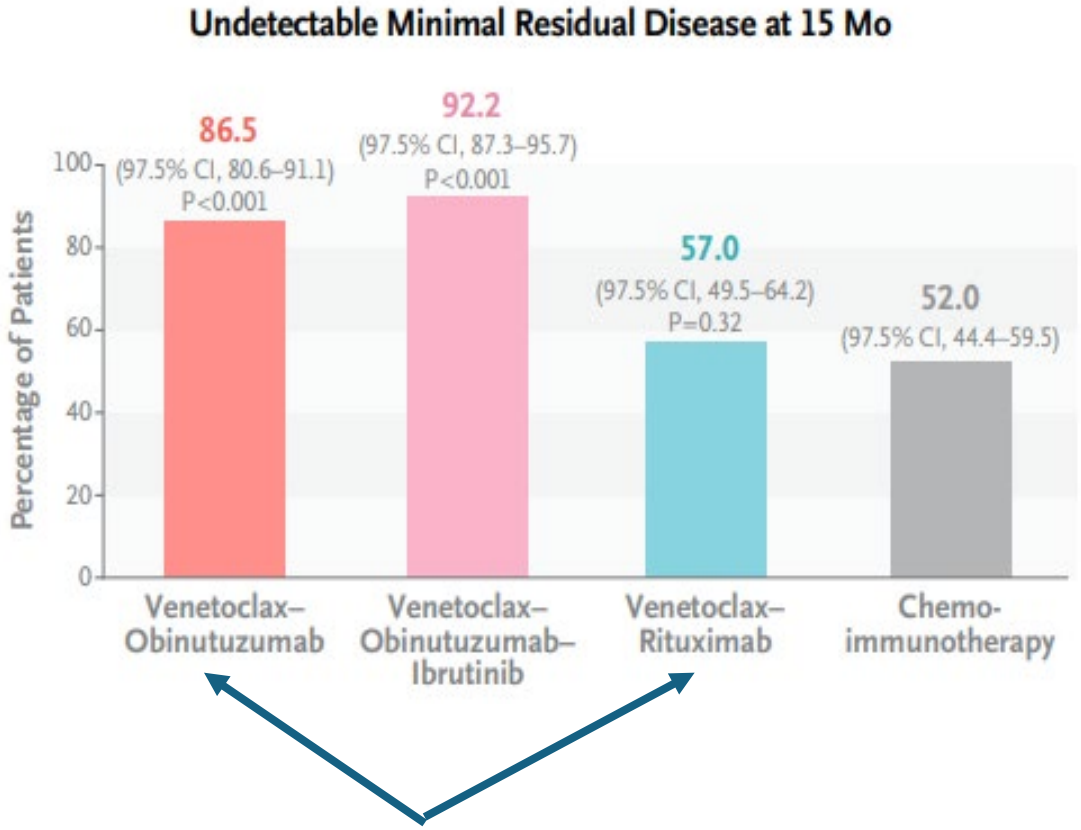
Overall survival

VenR-treated patients who completed 2 years of Ven without PD	Median OS since EOT (95% CI), months	HR‡ (95% CI)
uMRD (n=83)	**NE** (NE–NE)	**1.50** (0.60–3.77) Stratified P-value <0.3805†
MRD+ (n=35)	**NE** (62.7–NE)	

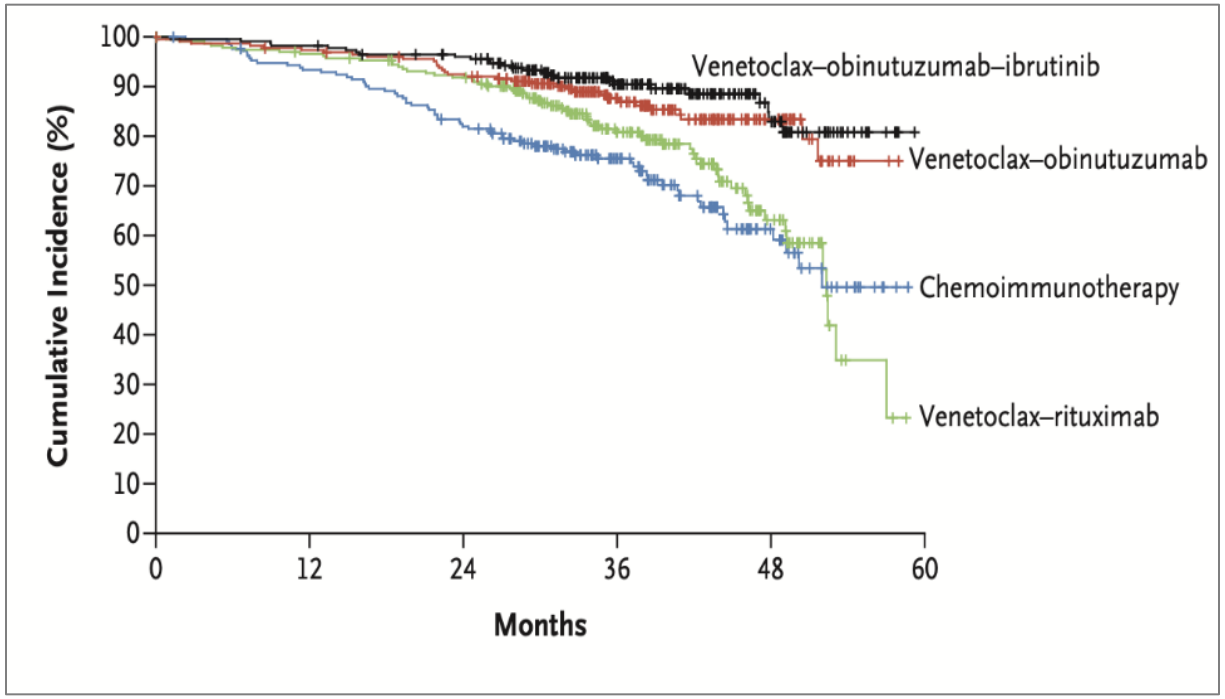


Low MRD+ is defined as ≥1 CLL cell/10,000 leukocytes to <1 CLL cell/100 leukocytes, high MRD+ is defined as ≥1 CLL cell/100 leukocytes.
*Stratified HR is presented, unstratified HR=3.45. †P-values are descriptive only. ‡Stratified HR is presented, unstratified HR=0.0796. .
EOT, end of treatment; HR, hazard ratio; OS, overall survival; PD; progressive disease; (u)MRD, undetectable minimal residual disease.
1. Kater AP, et al. EHA 2023: Abstract S201; 2. Kater AP, et al. EHA 2023: Abstract S201; oral presentation.

Ven+Obi is superior to Ven + R



Venetoclax + Obi results in significantly deeper MRD than Venetoclax + R



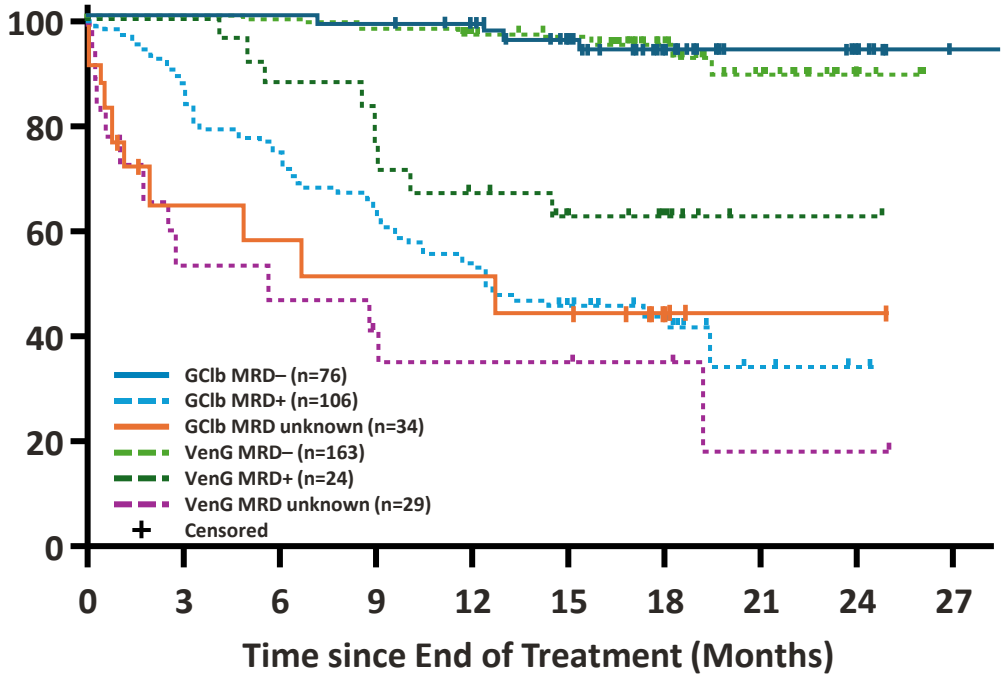
PFS significantly longer with Ven +Obi vs Ven+R

Eichhorst B NEJM 2023

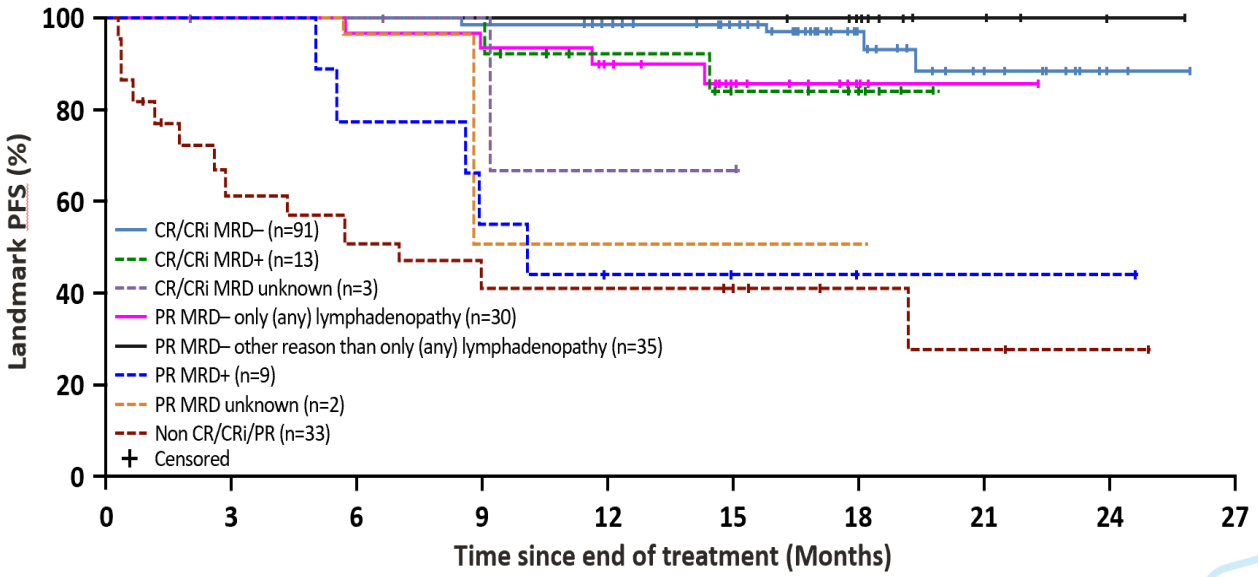
VENETOCLAX OBINUTUZUMAB FD:
MRD Negativity Is a Predictor of Improved Long-Term Outcomes Irrespective of Clinical Response

CLL14: VenG vs GClb in 1L CLL with Comorbidities[1]

Landmark 24 Months' PFS by MRD Status at EOT



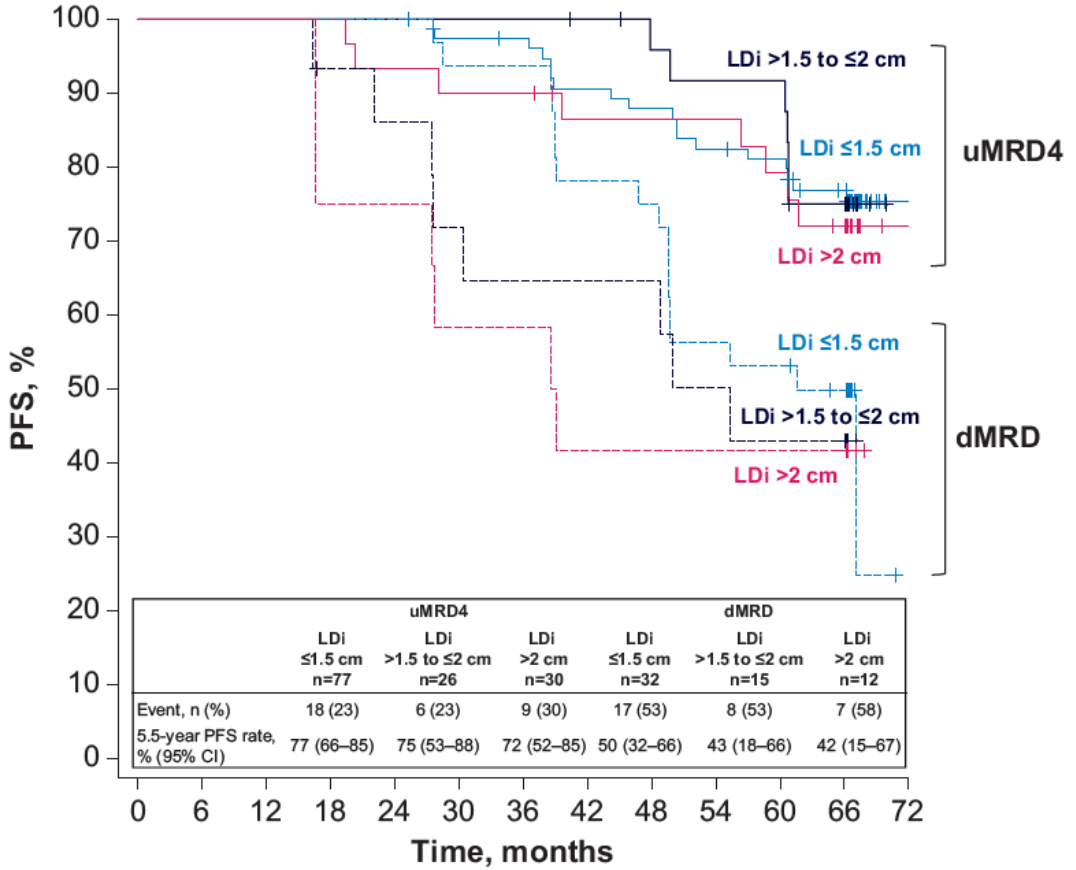
Landmark 24 Months' PFS by Clinical Response and MRD Status



MRD negativity resulted in improved PFS regardless of the clinical response status at EOT with VenG treatment

Fischer K, *et al.* 2019

Long-Term PFS Impact of Combined EOT Peripheral Blood MRD Status and Residual Lymph Node Longest Diameter (≤1.5 cm, >1.5 to ≤2 cm, >2 cm)



	uMRD4			dMRD		
	LDi ≤1.5 cm n=77	LDi >1.5 to ≤2 cm n=26	LDi >2 cm n=30	LDi ≤1.5 cm n=32	LDi >1.5 to ≤2 cm n=15	LDi >2 cm n=12
Event, n (%)	18 (23)	6 (23)	9 (30)	17 (53)	8 (53)	7 (58)
5.5-year PFS rate, % (95% CI)	77 (66–85)	75 (53–88)	72 (52–85)	50 (32–66)	43 (18–66)	42 (15–67)

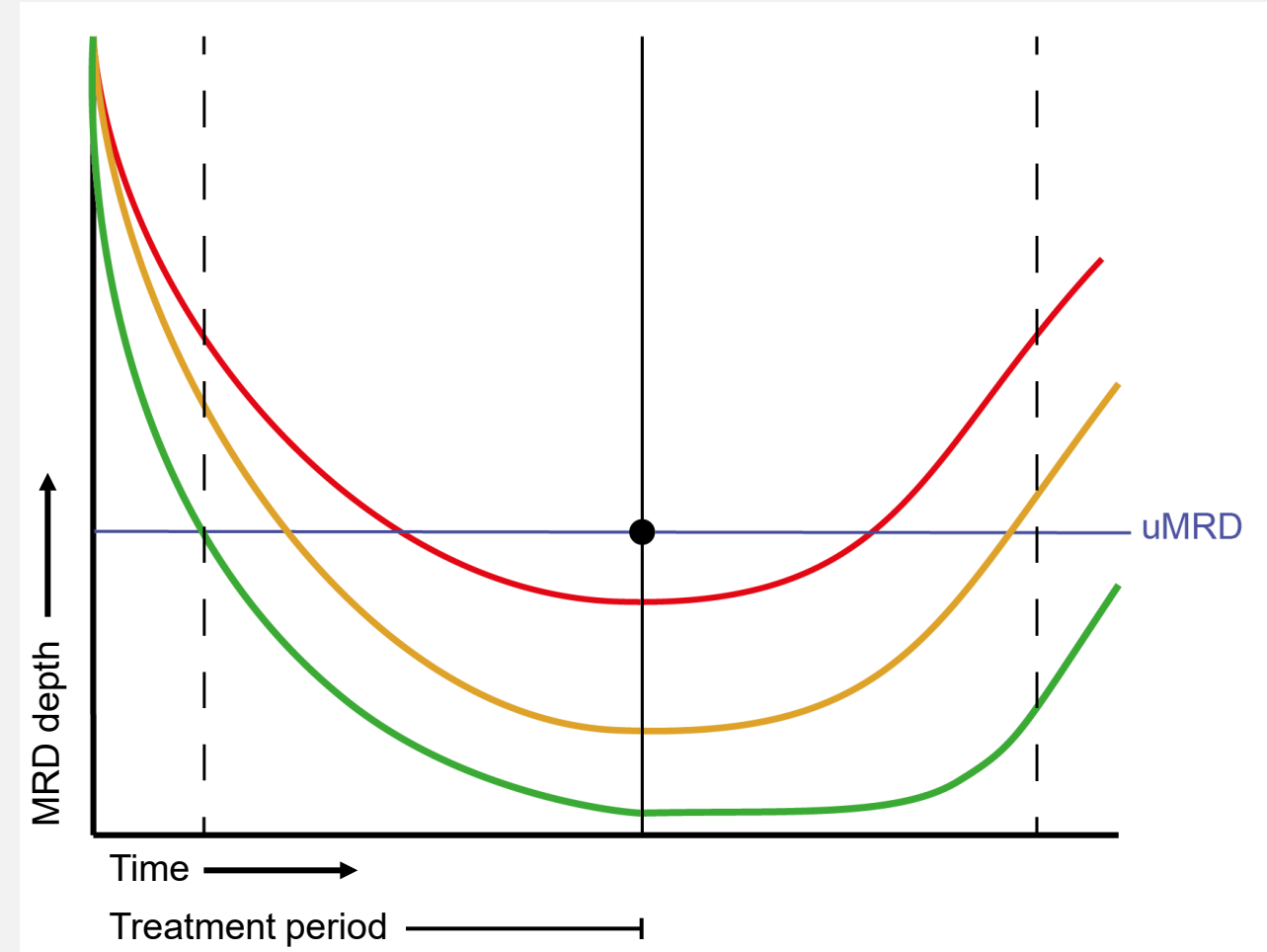
Patients at risk

uMRD4	LDi ≤1.5 cm	77	77	77	77	77	73	72	67	65	61	59	51	2
	LDi >1.5 to ≤2 cm	26	26	26	26	26	26	26	25	23	22	22	17	0
	LDi >2 cm	30	30	30	30	28	27	27	24	24	24	22	19	1
dMRD	LDi ≤1.5 cm	32	32	32	32	32	30	30	25	24	18	17	14	0
	LDi >1.5 to ≤2 cm	15	15	15	13	12	10	9	9	9	7	6	6	0
	LDi >2 cm	12	12	12	9	9	7	7	5	5	5	5	5	0

- Corresponding PFS rates according to bone marrow MRD status were very consistent with those according to peripheral blood MRD status across subgroups by EOT longest diameter (**Supplement**)

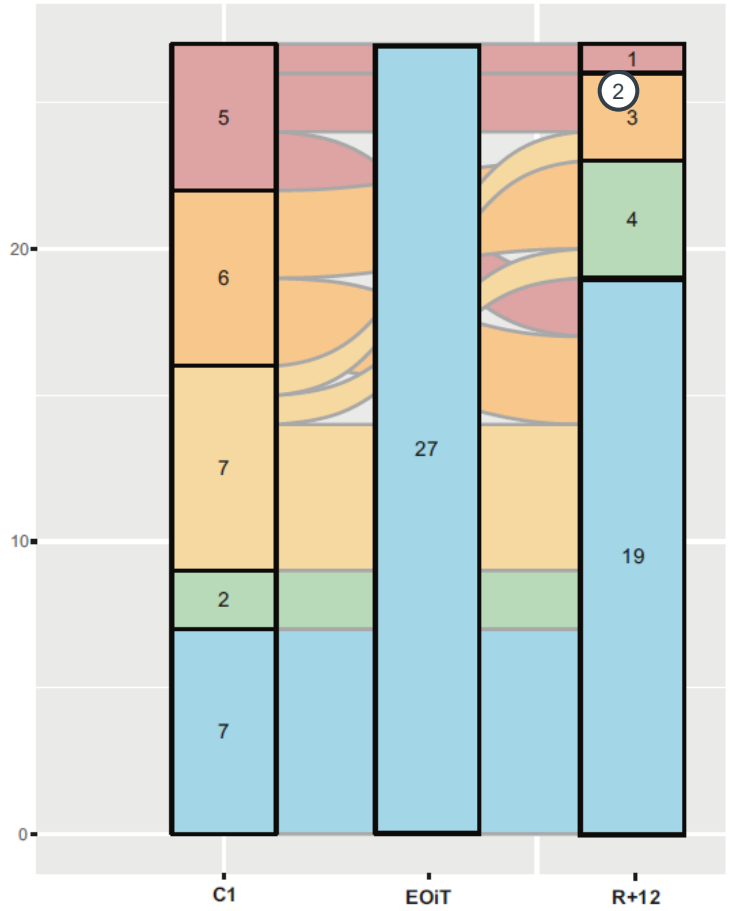
Characterization of MRD kinetics may be more informative than a single, end-of-treatment measurement

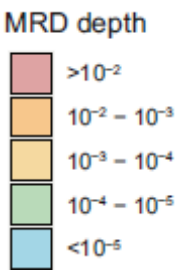
- (Ideally) fixed-duration treatment induces high uMRD rates
- MRD follows an L-shaped trajectory
- Serial measurements may yield additional information

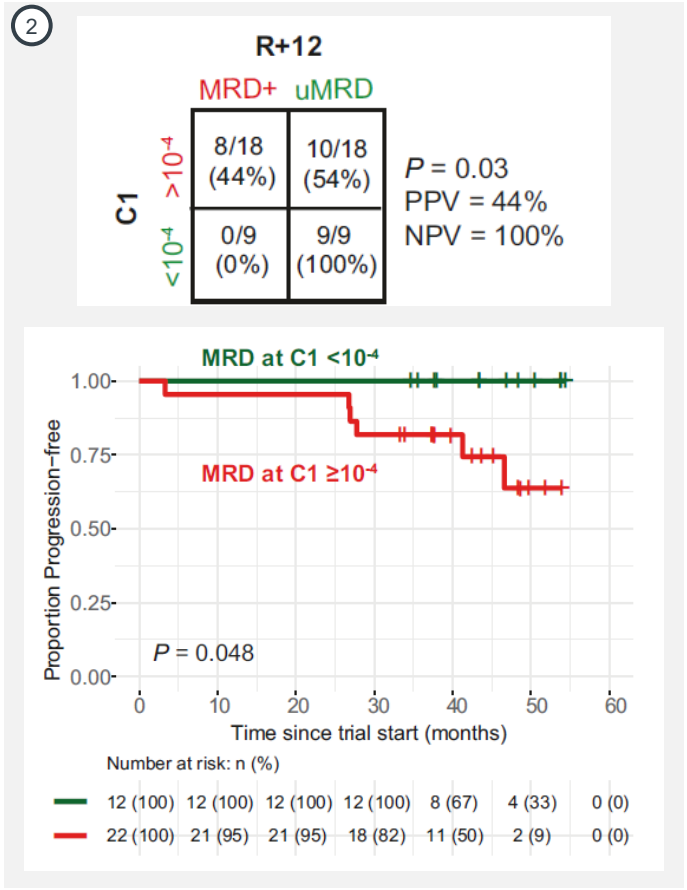


The content on the slide reflects the speaker's personal opinion, drawn from their own experience and expertise.
(u)MRD, (undetectable) minimal residual disease.
Slide courtesy of Arnon Kater.

Early MRD kinetics predicts outcomes with first-line Ven-Obi





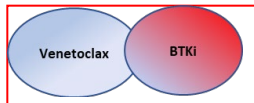


CLL, chronic lymphocytic leukemia; CR, complete response; FCR, fludarabine, cyclophosphamide, and rituximab; (u)MRD, (undetectable) minimal residual disease; NPV, negative predictive value; Obi, Obinutuzumab; PPV, positive predictive value; PR, partial response; R, randomization; V, venetoclax.

1. HOVON HO139 CLL. Available at: https://hovon.nl/nl/trials/ho139. Accessed February 2025. 2. Hengeveld PJ *et al*. *Blood Cancer J* 2023; 13 (1): 102.

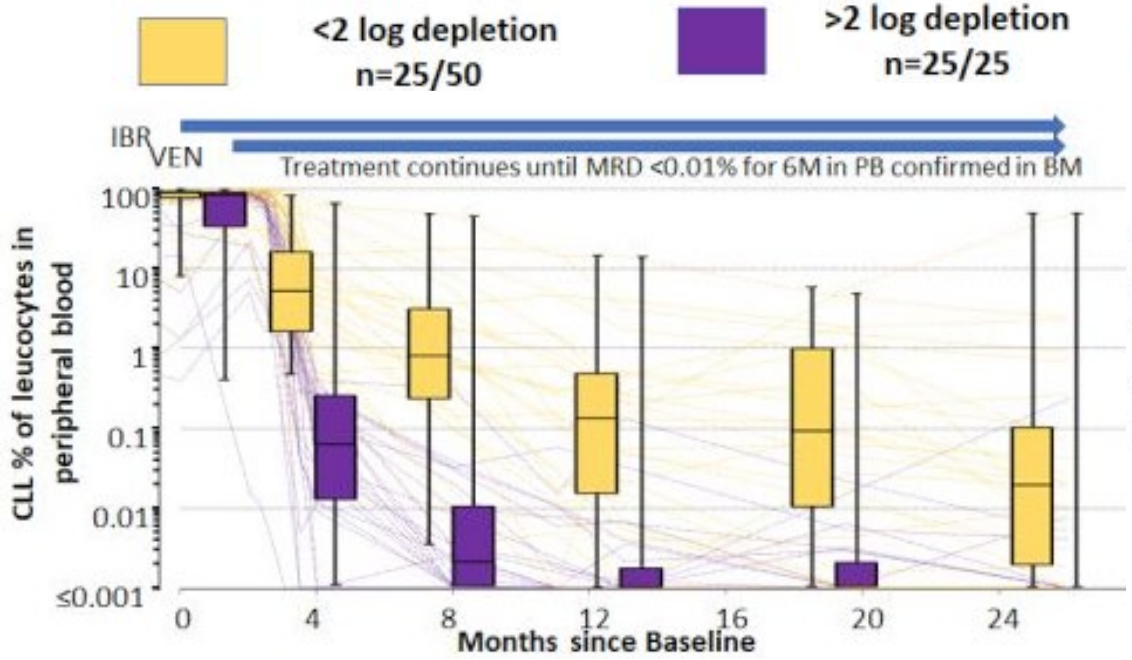
Slide courtesy of Arnon Kater.

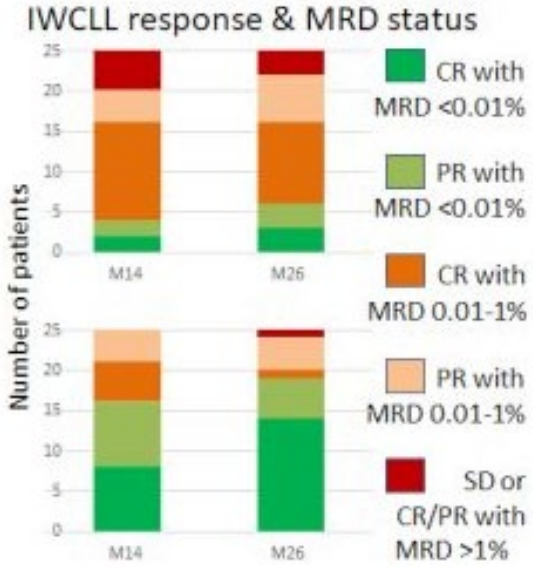
Early uMRD as a predictor of MRD kinetics



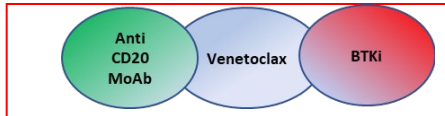
CLARITY

MRD kinetics at C4 is predictive for MRD response at C26



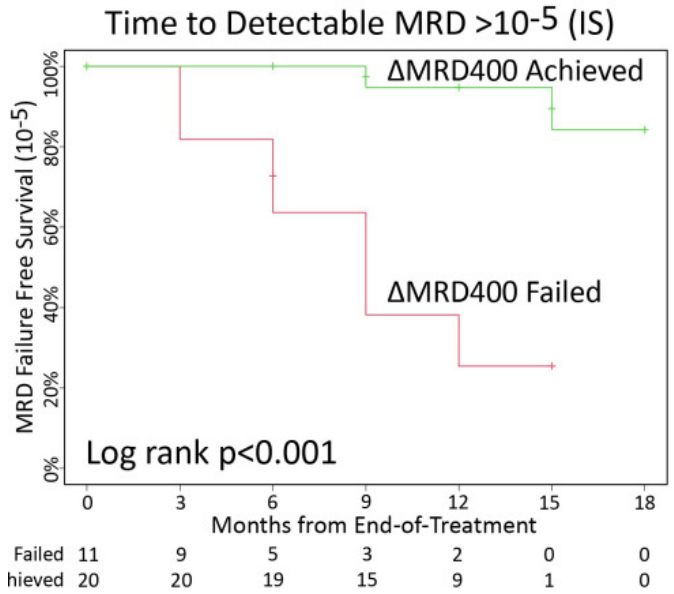


Rawstron EHA 2020



BoVen

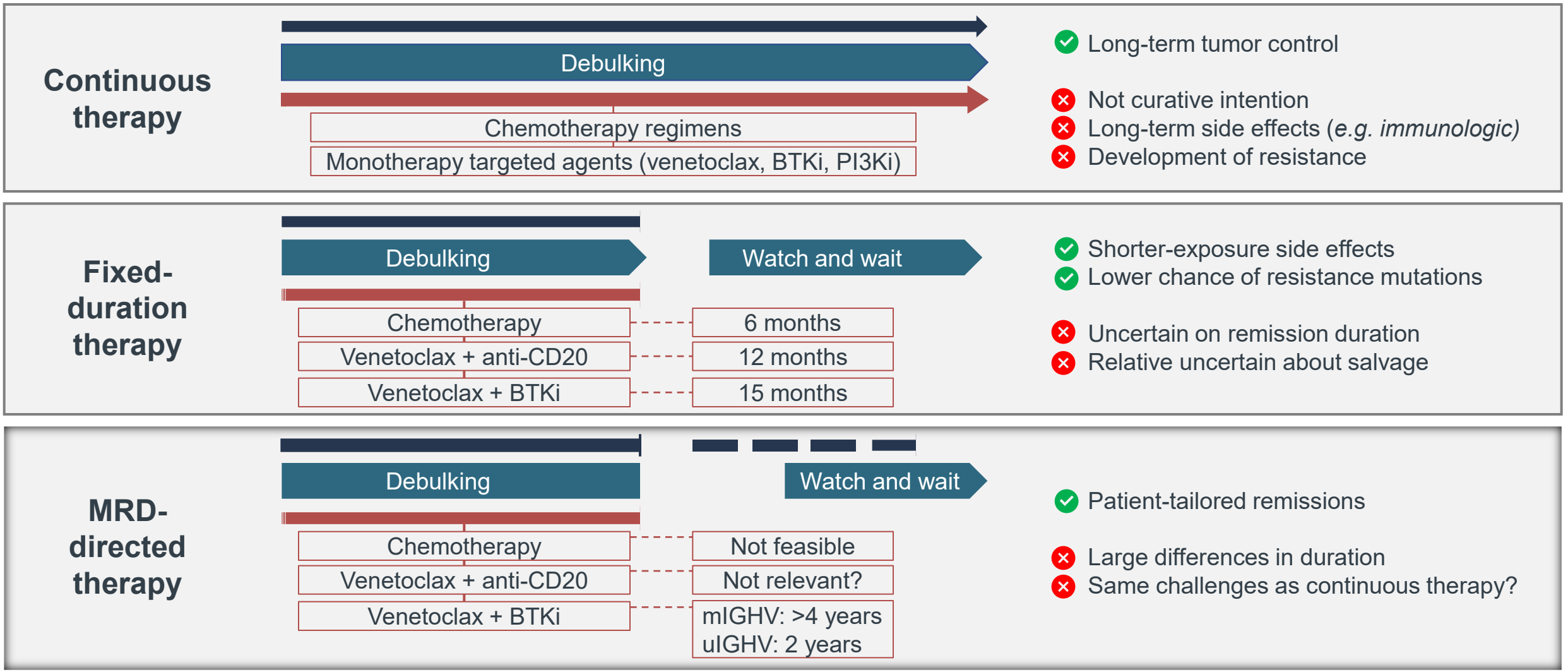
A ≥400-fold reduction in PB MRD-IS after 4 cycles is predictive of attaining BM uMRD in ≤8mo



Soumerai ASH 2021

MRD TO DEFINE DURATION OF FD THERAPY

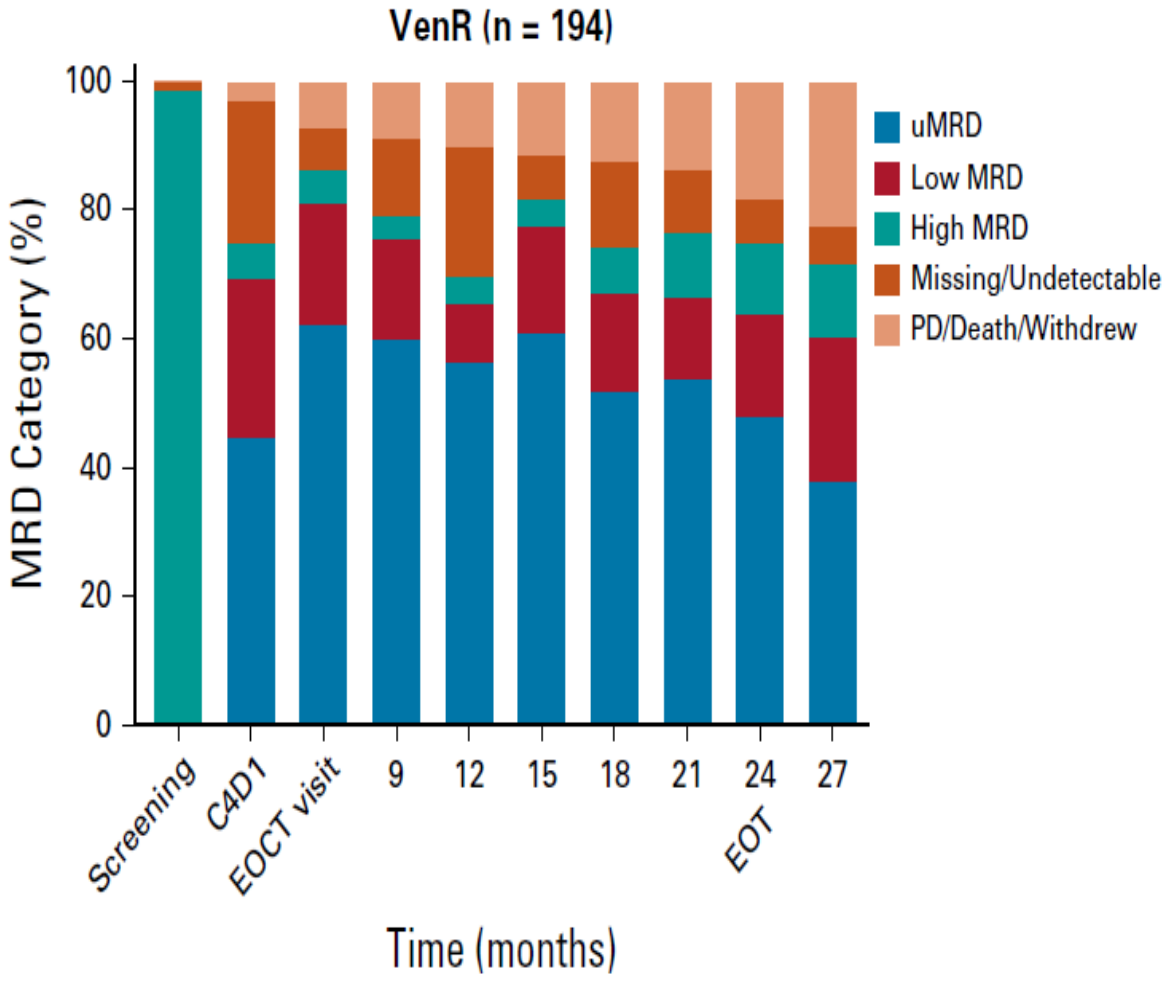
Three treatment models are being explored in clinical trials

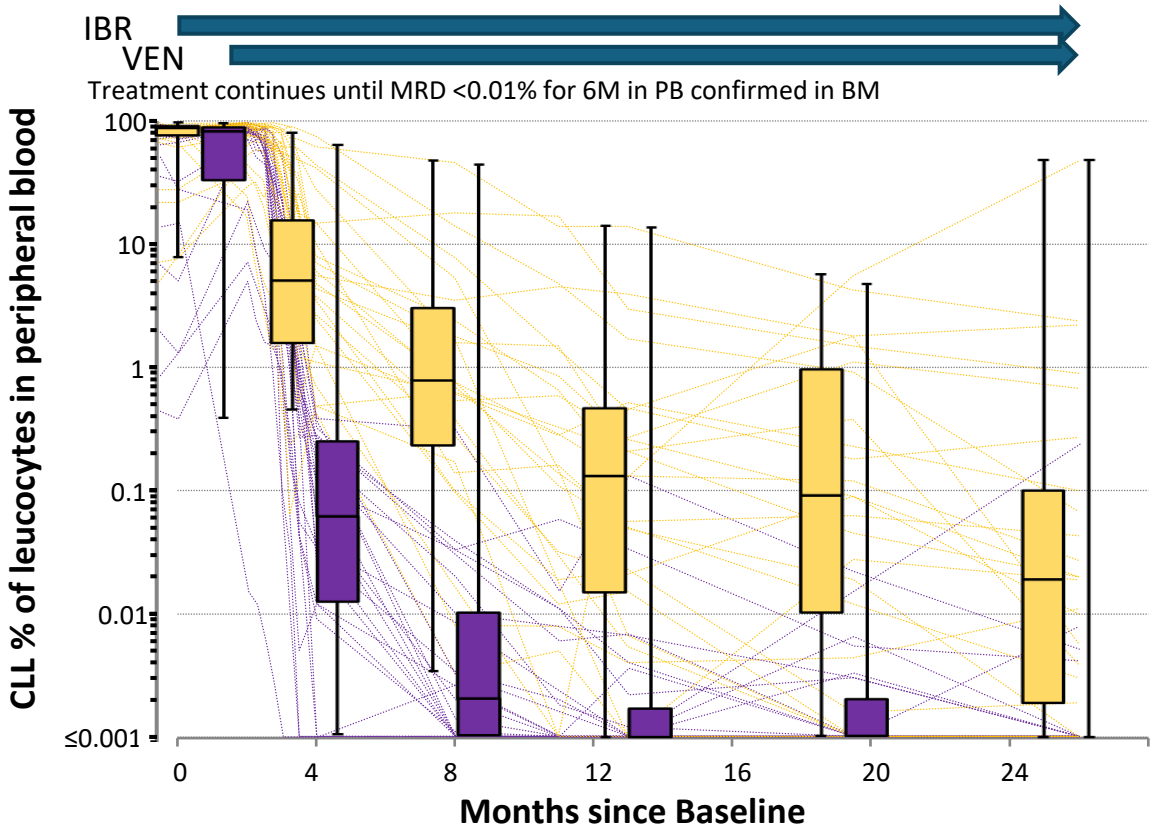


The content on the slide reflects the speaker's personal opinion, drawn from their own experience and expertise.

BTKi, Bruton's tyrosine kinase inhibitor; CD20, cluster of differentiation 20; (m/u)IGHV, (mutated/unmutated) immunoglobulin heavy chain variable; MRD, minimal residual disease; PI3Ki, phosphoinositide 3-kinase inhibitor. Slide courtesy of Arnon Kater.

BCL2-pathway inhibition: overall peak response to occurs during first year of treatment with very rapid depletion in some patients



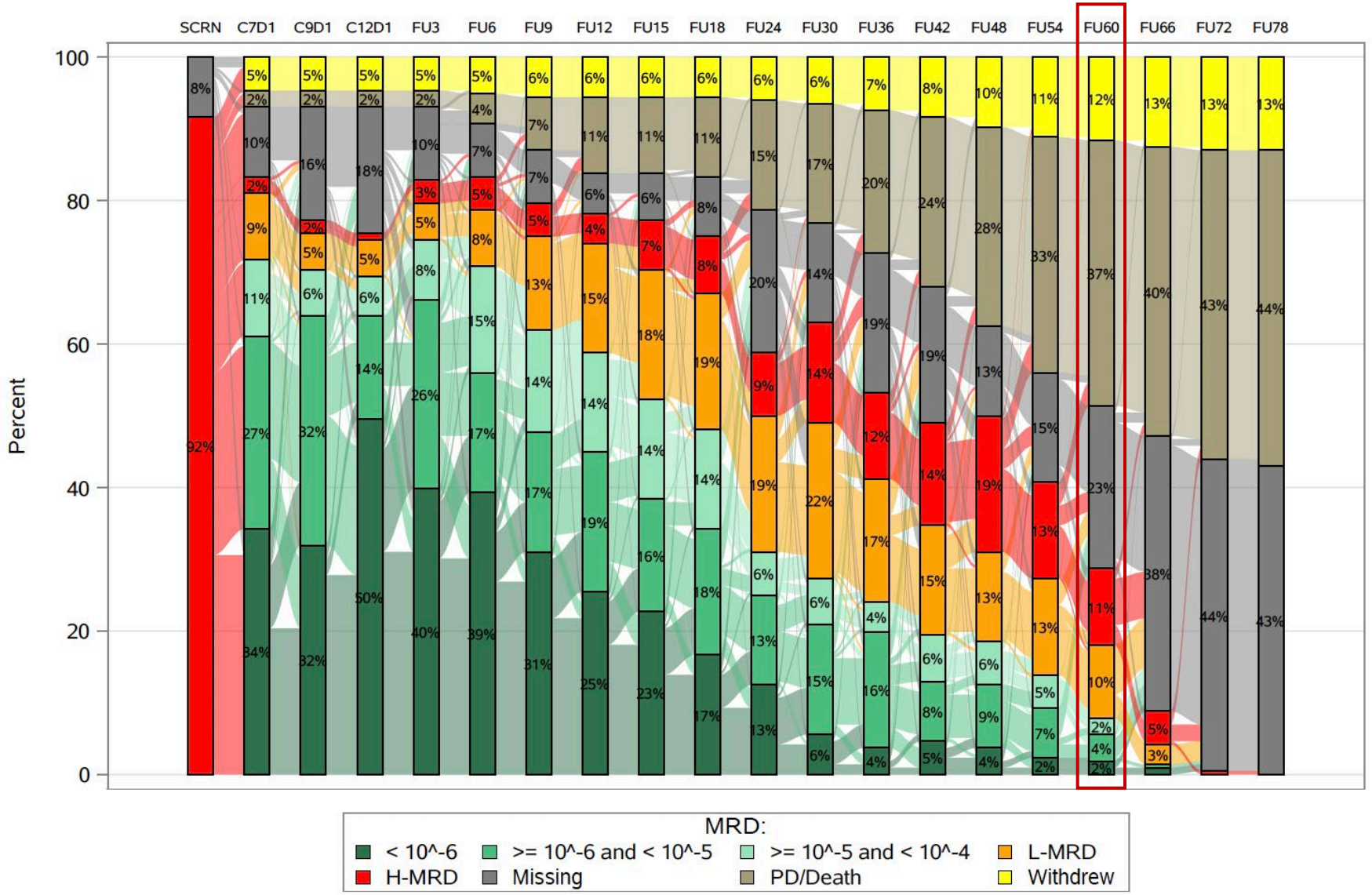


- 1. Seymour JF, *et al. N Engl J Med* 2018; **378:**1107–1120 (incl. suppl.);
2. Kater AP and Seymour JF, *et al. J Clin Oncol* 2018; DOI: 10.1200/JCO.18.01580.

Date of data lock:06-Nov-2020

Munir *et al.* ASH 2020; Abst 182

- By NGS in peripheral blood: **Ven-Obi**



5 years after Ven-Obi, **7.9%** of patients had sustained MRD $<10^{-4}$.

FIXED DURATION
Venetoclax Ibrutinib

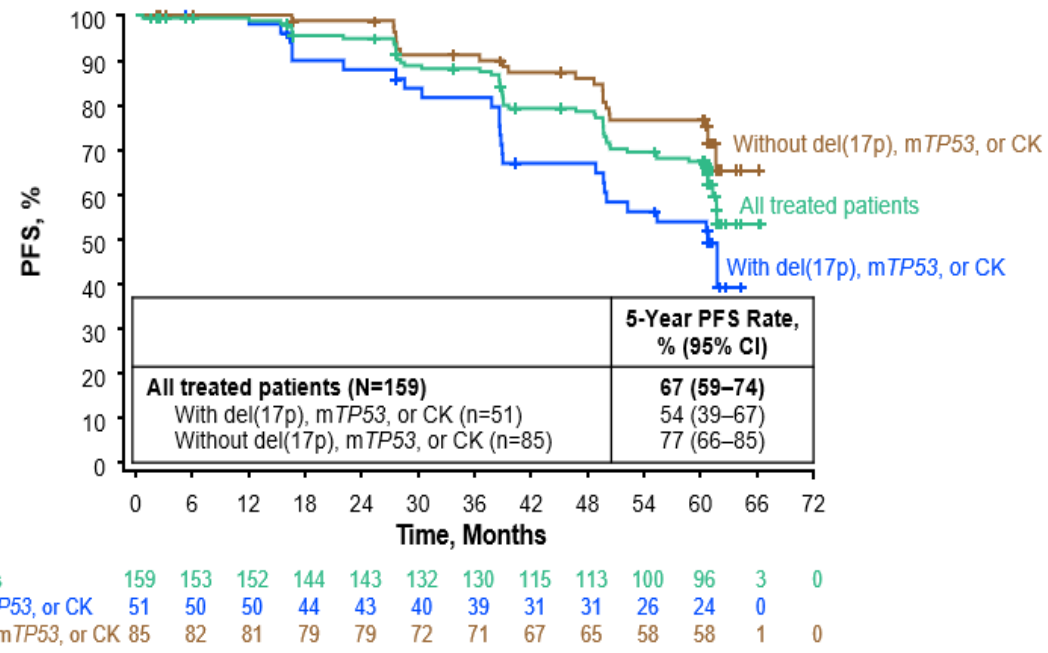
Young FIT → Elderly Unfit

CAPTIVATE (PCYC-1142)

Median age: 60y

5.5 y follow-up

PFS in All Treated Patients and by del(17p), m*TP53*, or CK Status



High-risk feature	With feature n	With feature 5-Year PFS rate, % (95% CI)	Without feature n	Without feature 5-Year PFS rate, % (95% CI)
del(17p)/m*TP53*	27	41 (21–59)	129	73 (64–80)
CK[a]	31	57 (37–72)	102	72 (61–80)
del(11q)[b]	11	64 (30–85)	74	79 (67–87)

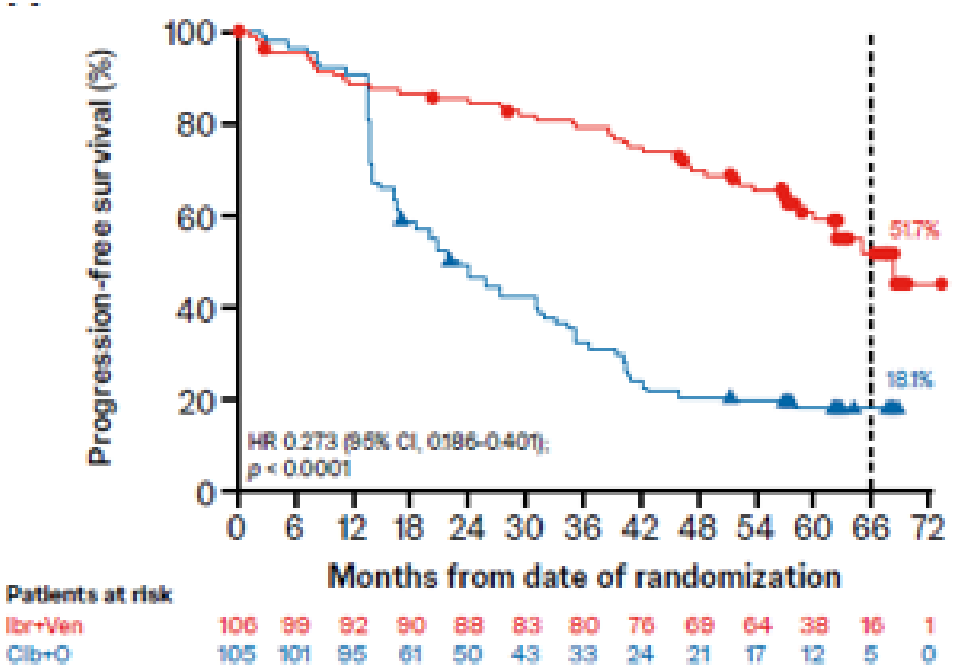
Wierda et al., ASCO 2024

GLOW: Ibrutinib Venetoclax vs Chl OB

Median age: 71y

67 m follow-up

PFS



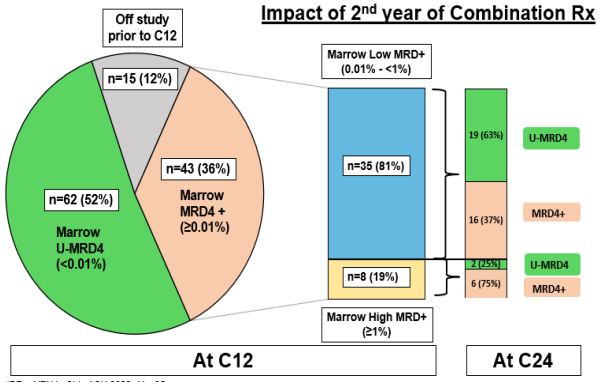
Niemman , et al. ASH 2024

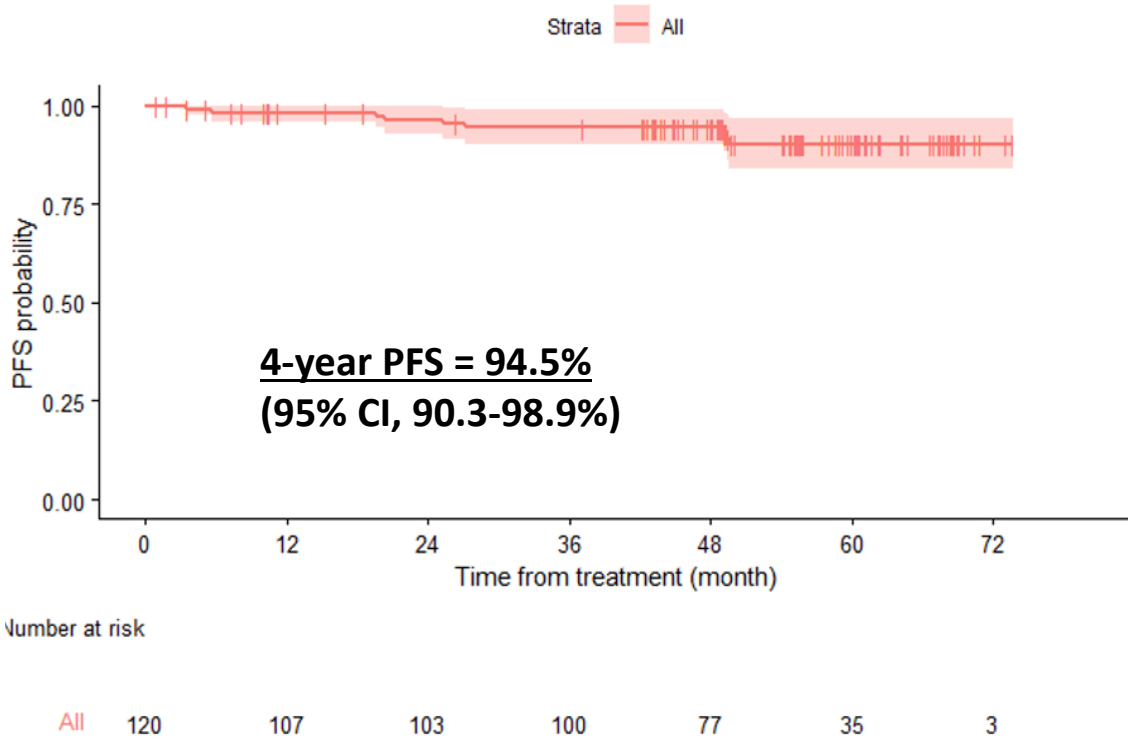
I plus V: 24 or 36 cycles according to MRD

Duration of therapy: 24 cycles of combined IBR and VEN

Marrow MRD (flow cytometry) at end of cycle 24 of combined Rx

- **Negative (<0.01%): Stop both IBR and VEN**
- **Positive (≥0.01%): Continue 12 additional cycles of IBR + VEN**





4-year PFS = 94.5%
(95% CI, 90.3-98.9%)

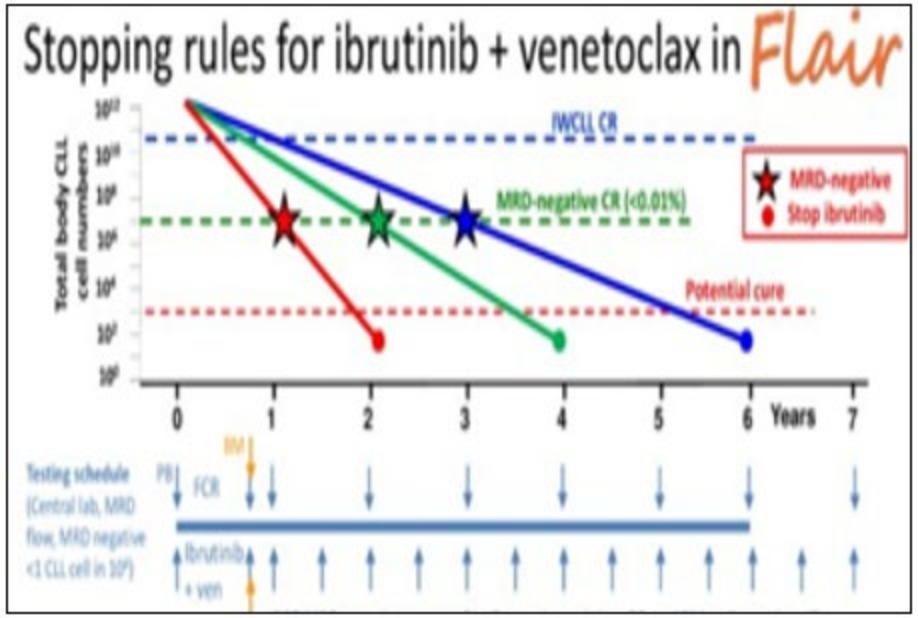
Group	4-year PFS	Lower CI	Upper CI
ighv2=Mutated	100%	100%	100%
ighv2=Unmutated	93.44%	88.49%	98.66%

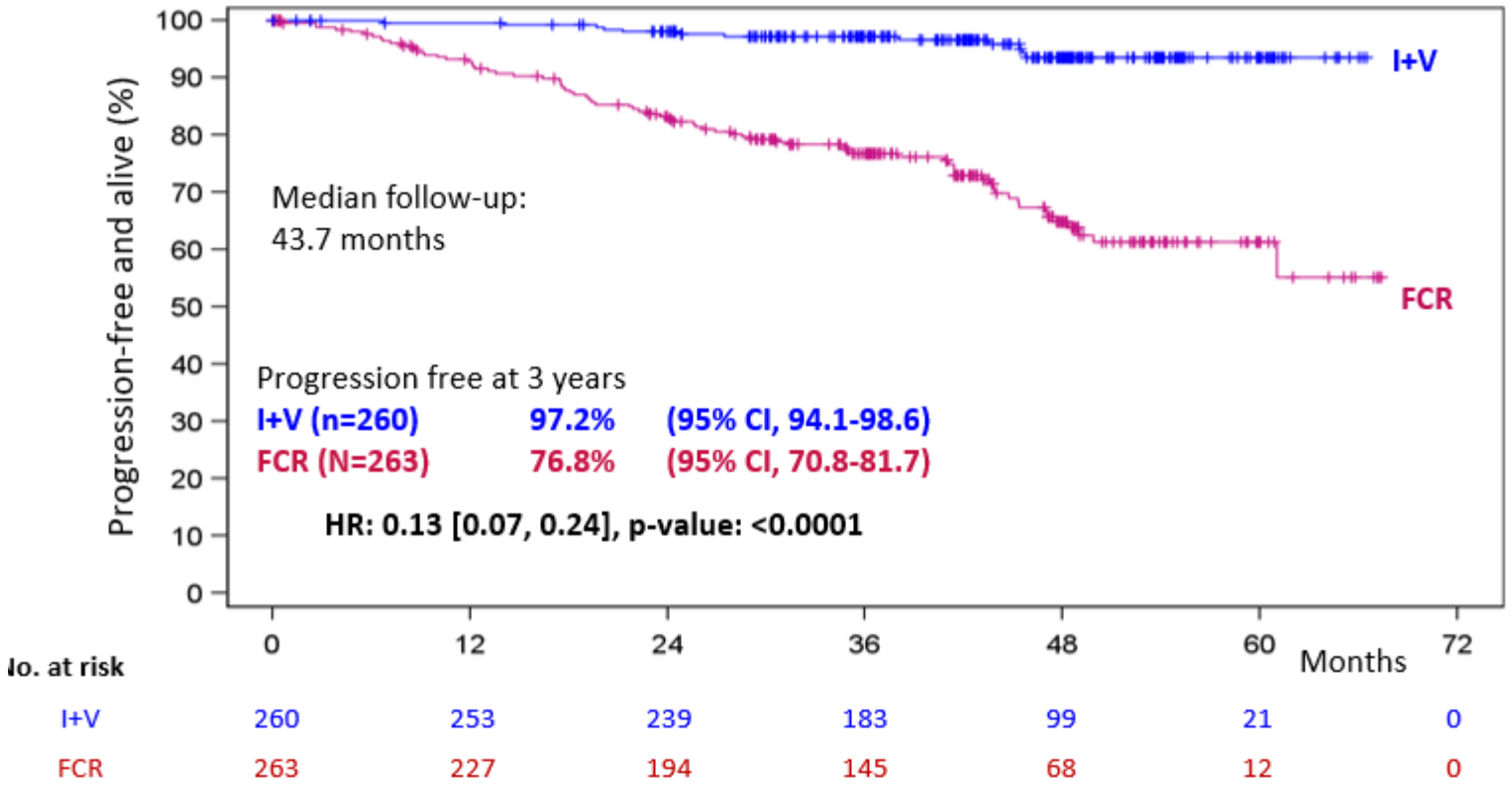
Group	4-year PFS	Lower CI	Upper CI
tp53.aber=No	95.47%	91.22%	99.91%
tp53.aber=Yes	90.91%	79.66%	100%

Jain N et al 2022

HOW CAN WE IMPROVE EFFICACY OF FIXED DURATION THERAPY?

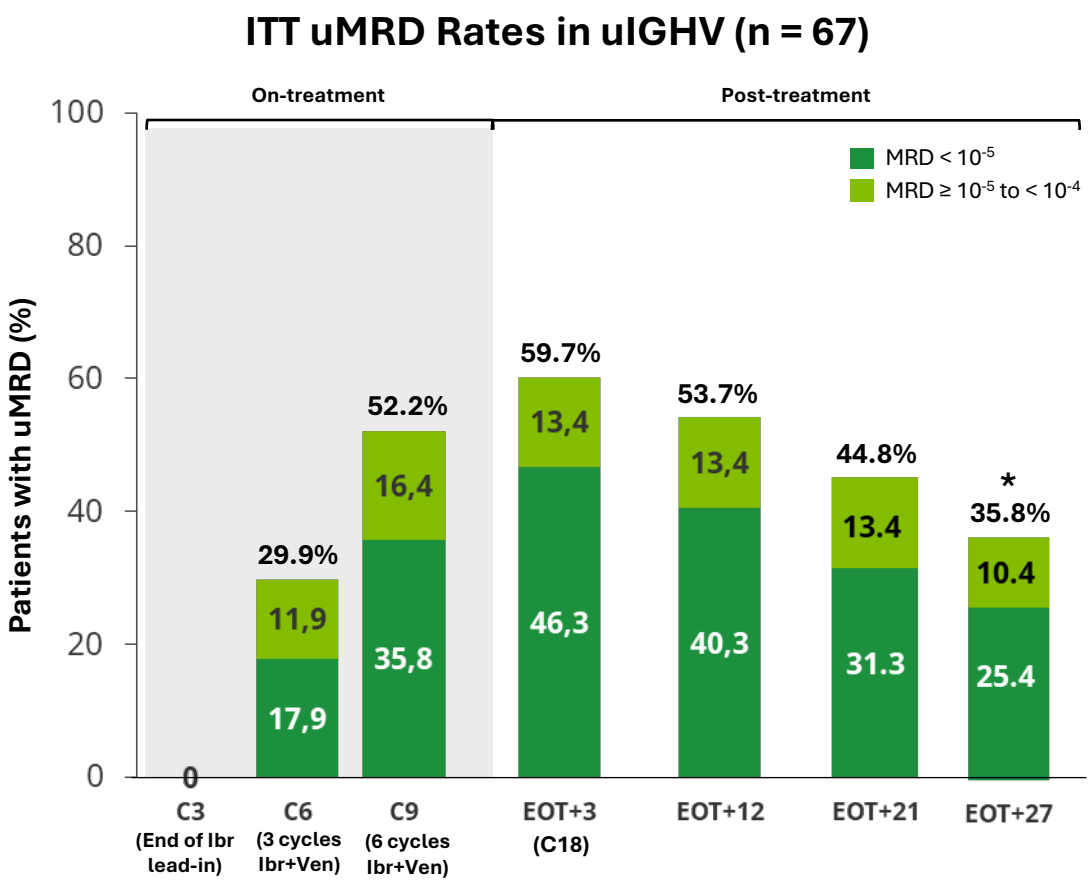
I+V duration MRD guided

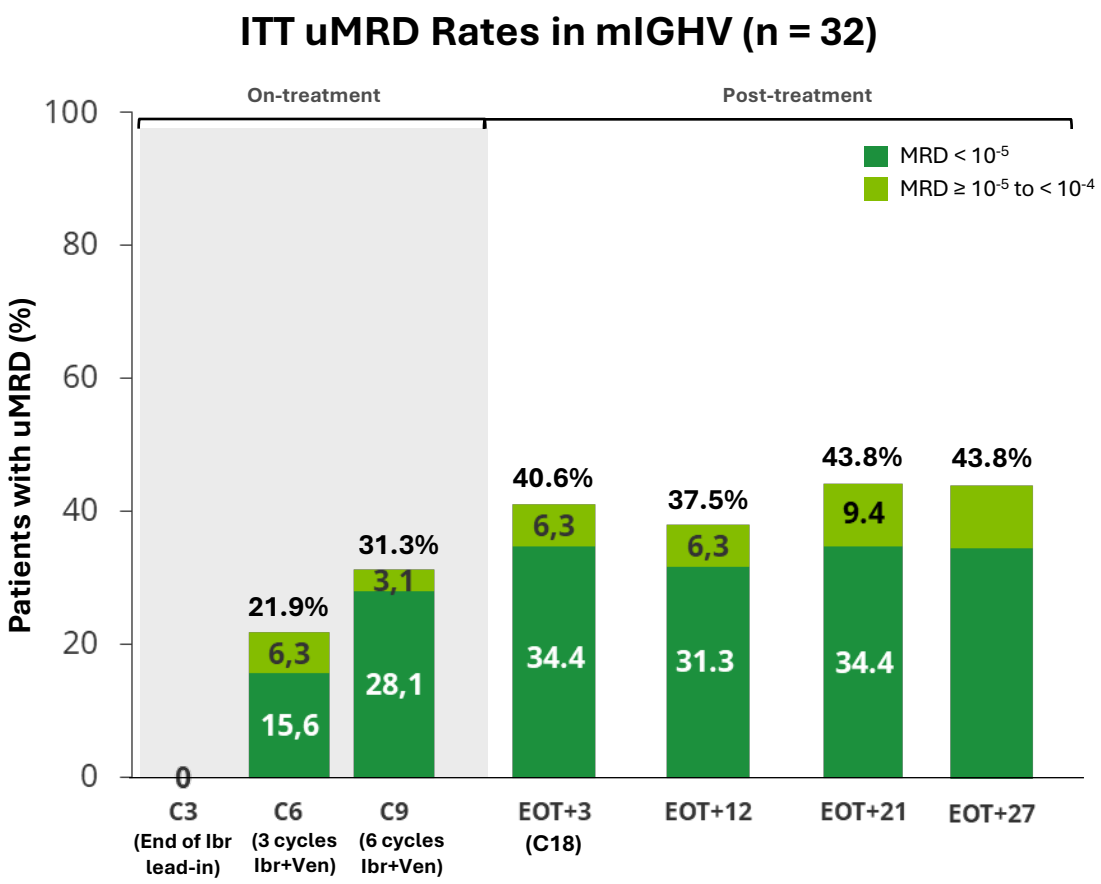




Hillmen P et al ASH 2023

GLOW: Ibr+Ven On-treatment and Post-treatment uMRD Dynamics According to IGHV Status



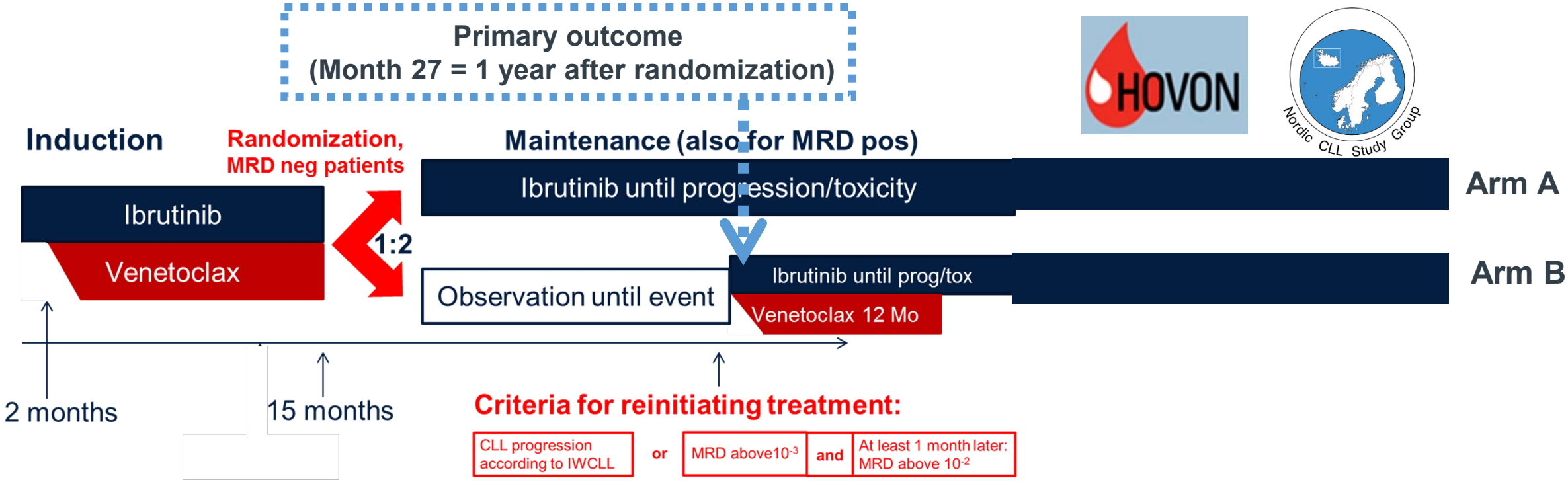


- uMRD rates (including < 10^{-5}) were higher and uMRD was achieved faster in patients with uIGHV versus mIGHV CLL
- uMRD was better sustained post-treatment in patients with mIGHV CLL

*7 (10.4%) patients with uMRD (including 5 with uMRD < 10^{-5}) at EOT+21 had missing samples at EOT+27 and were considered not uMRD.
Numbers may not add up to exact total due to rounding. ITT, intent to treat; uMRD, undetectable minimal residual disease; mIGHV, mutated IGHV; uIGHV, unmutated IGHV; C, cycle.

MRD TO CONSIDER
STOP OF THERAPY
OR REINITIATION OF THERAPY

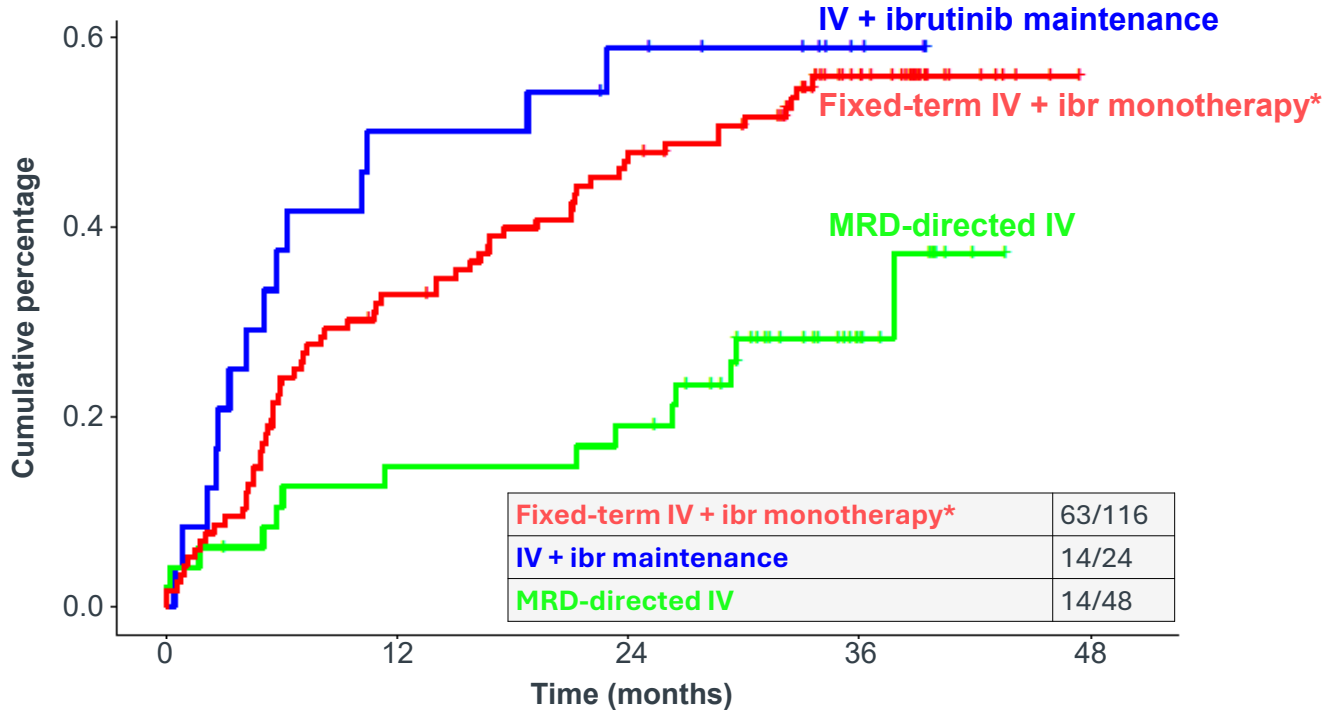
In HOVON141/VISION, venetoclax + ibrutinib duration was determined by interim MRD status in R/R CLL



CLL, chronic lymphocytic leukemia; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; Mo, months; MRD, minimal residual disease; neg, negative; pos, positive; prog, progression; R/R, relapsed/refractory; tox, toxicity.

Kater AP *et al*. *Lancet Oncol* 2022; 23 (6): 818–828.

Early treatment cessation led to reduced infections without impacting efficacy



At risk (censored)					
Fixed-term IV + ibr monotherapy*	24 (0)	12 (0)	9 (1)	3 (7)	0 (10)
IV + ibr maintenance	48 (0)	40 (1)	38 (1)	12 (23)	0 (34)
MRD-directed IV	116 (0)	77 (1)	60 (2)	29 (24)	0 (53)

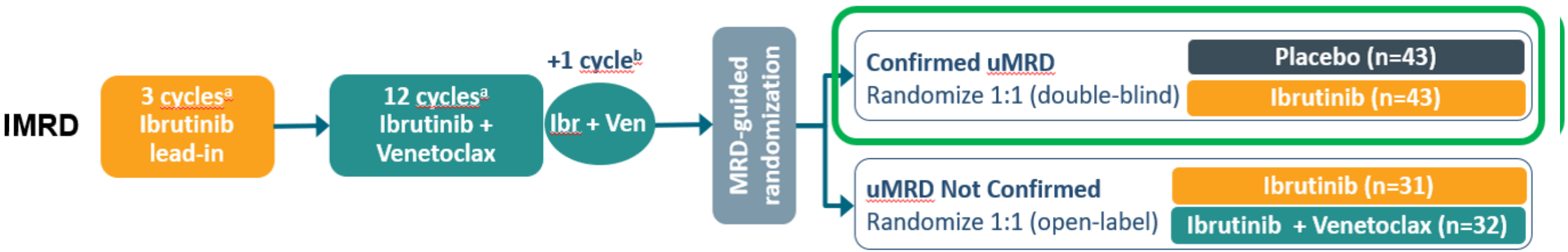
Time and rate of Grade ≥2 infections after randomization:

- Nonrandomized: 55%
- Arm A: 63%
- Arm B: 31%

*In this nonrandomized arm, patients who were MRD-positive continued to receive ibrutinib monotherapy. Patients who became MRD (>10^{-2}) during observation reinitiated treatment with ibrutinib plus venetoclax.
I/ibr, ibrutinib; MRD, minimal residual disease; V, venetoclax.
Unpublished data. Slide courtesy of Arnon Kater.

Treatment Outcomes After Undetectable MRD With First-Line Ibrutinib (Ibr) Plus Venetoclax (Ven): Fixed-Duration Treatment (Placebo) Versus Continued Ibr With Up to 5 Years Median Follow-up in the CAPTIVATE Study

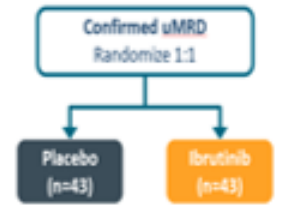
- CAPTIVATE (NCT02910583) is an international, multicenter phase 2 study evaluating first-line treatment with the Ibr + Ven combination
- The CAPTIVATE study comprises 2 cohorts: FD[1] and MRD[2]
- In this MRD cohort, after completion of Ibr + Ven, patients with Confirmed uMRD* were randomly assigned to double-blind treatment with placebo (ie, a fixed-duration regimen), or continued ibrutinib



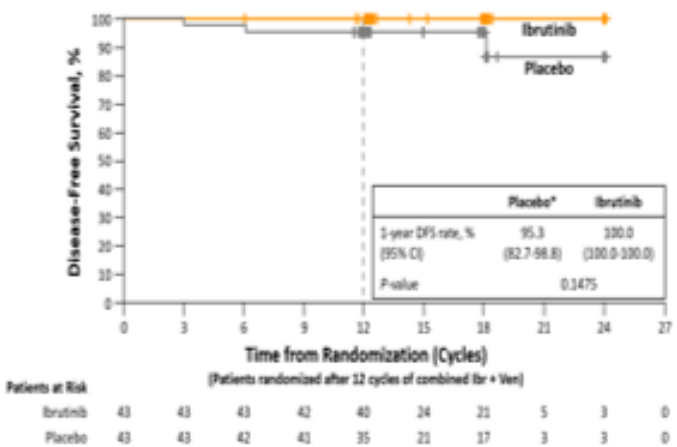
CAPTIVATE

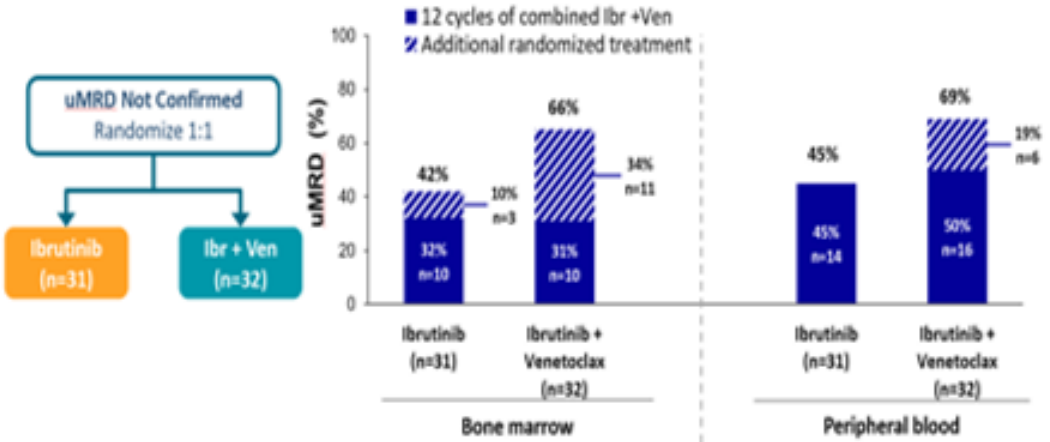
uMRD Rates With 12 Cycles of Combined Ibrutinib + Venetoclax

	Peripheral Blood n=163	Bone Marrow[a] n=155
Best response of undetectable MRD[1] in evaluable patients[b] (95% CI)	**75%** (69–82)	**72%** (65–79)



- DFS: freedom from MRD relapse (≥10^{-2} confirmed on 2 separate occasions), and without disease progression or death
- Median follow-up time 16.6 months post-randomization

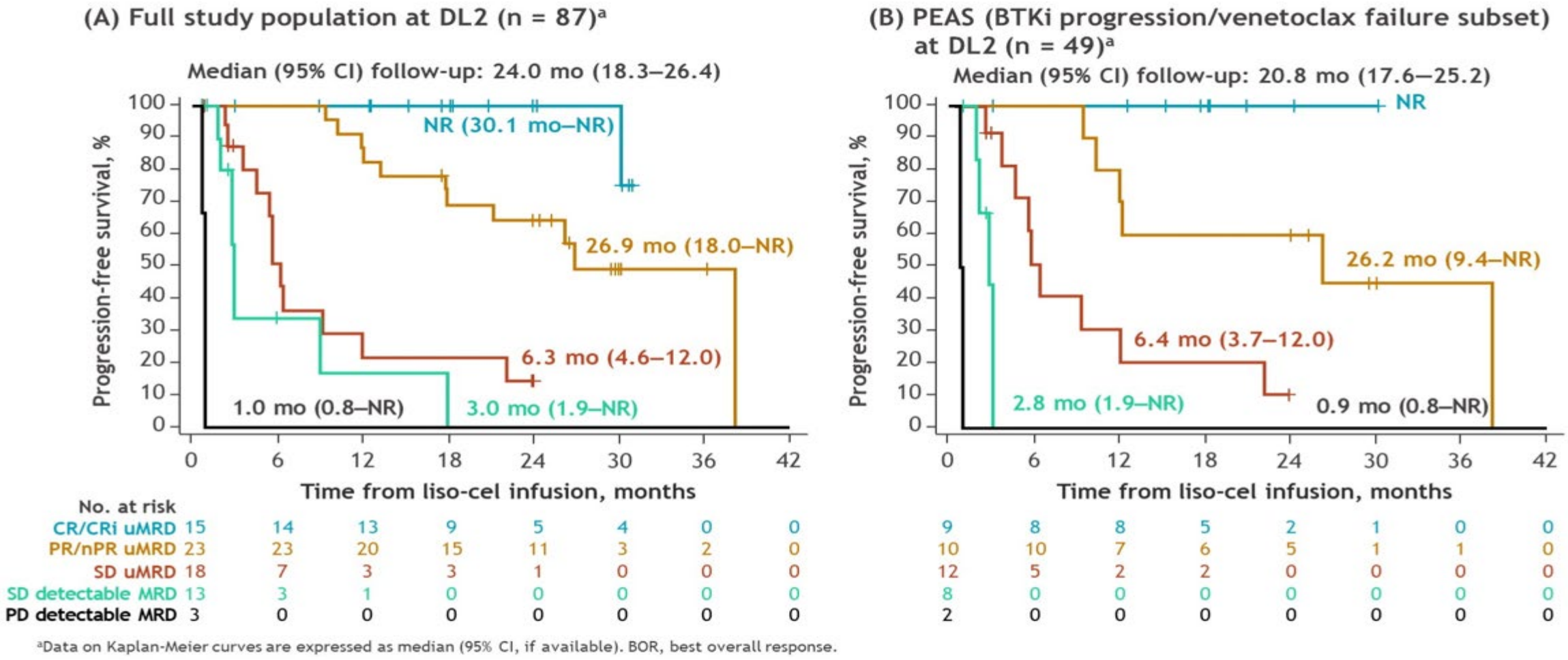




- In patients without confirmed uMRD[a] after 12 cycles of combined ibrutinib + venetoclax, increases in uMRD were greater with continued ibrutinib + venetoclax versus ibrutinib alone

Wierda ASH 2020

PFS by response and uMRD in PB by NGS at 10^4 sensitivity



[a]Data on Kaplan-Meier curves are expressed as median (95% CI, if available). BOR, best overall response.

Siddiqui et al, ASCO 2023

- Summary

MRD-directed treatment arms are included in many ongoing clinical trials in CLL but measuring MRD in CLL currently has **limited utility in clinical practice**

The prognostic relevance of undetectable MRD differs between treatment types and according to patient characteristics, such as IGHV mutational status

For adoption within clinical practice, consensus is needed on the technological and methodological approaches to measuring MRD in CLL and how this should inform management of patients