Status talk: Where are we with the use of MRD to guide CLL treatment decisions?

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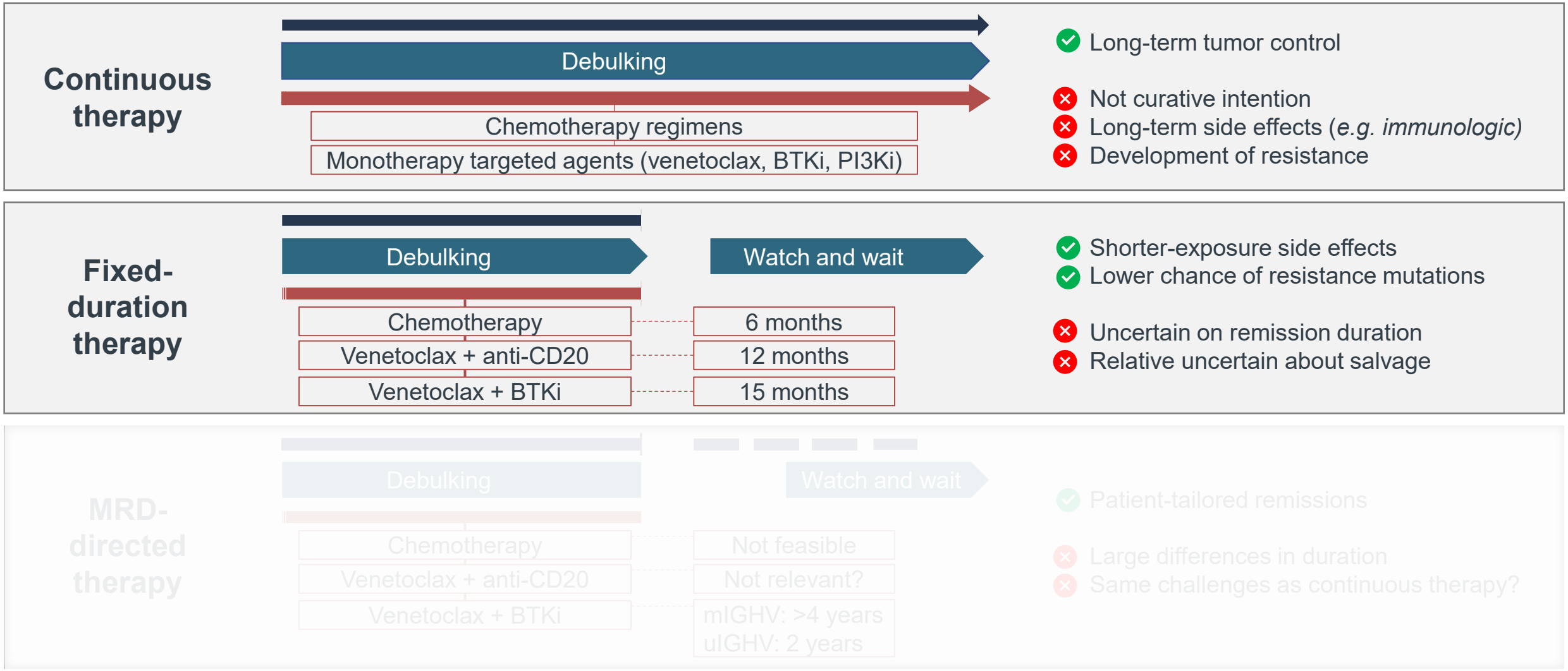
Disclosures

- Advisory board: AbbVie, AstraZeneca, Beigene, BMS, Genmab, Janssen, Lava, Roche/Genentech

- Research funding: AbbVie, AstraZeneca, BMS, Janssen, Roche/Genentech

- Steering committee: AbbVie, AstraZeneca, Genmab, Janssen, Lava

There are two approved treatment models for CLL



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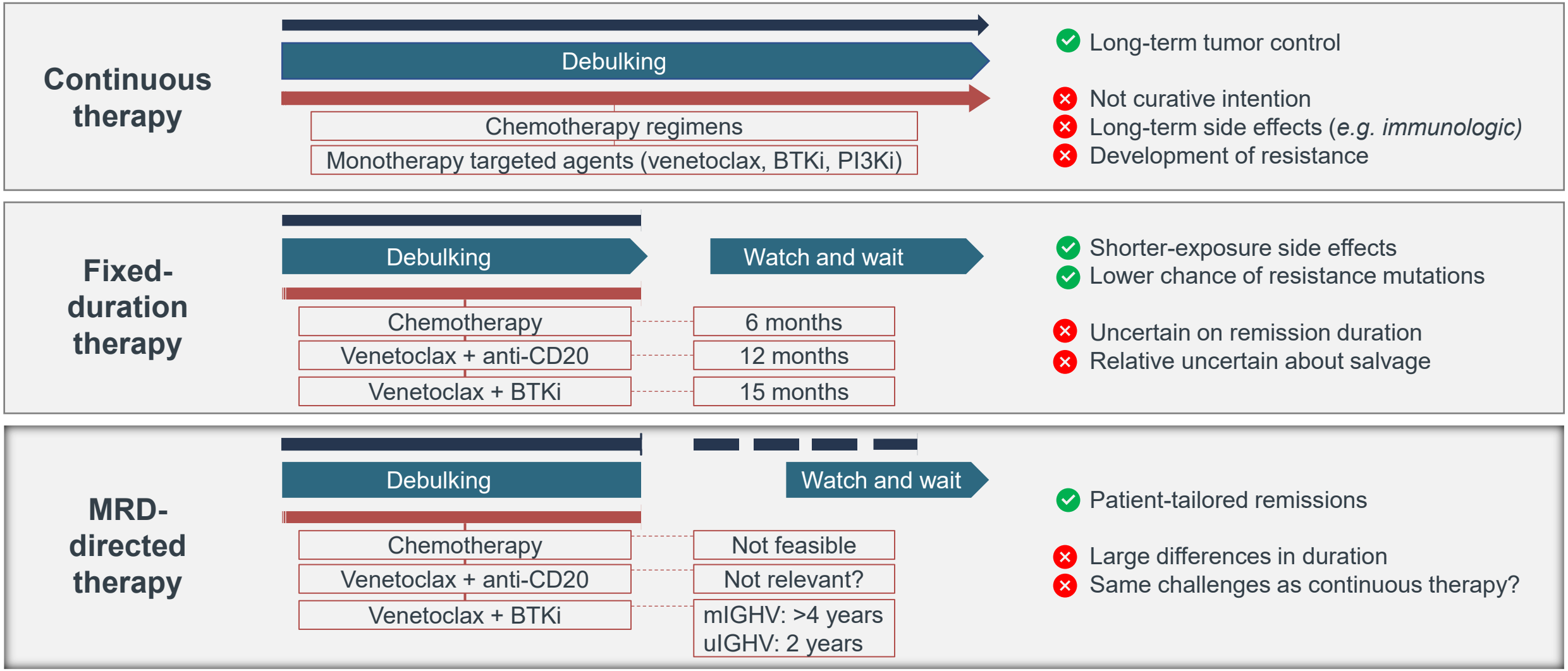
BTKi, Bruton's tyrosine kinase inhibitor; CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia; PI3Ki, phosphoinositide 3-kinase inhibitor. Slide courtesy of Arnon Kater.

Three treatment models are being explored in clinical trials



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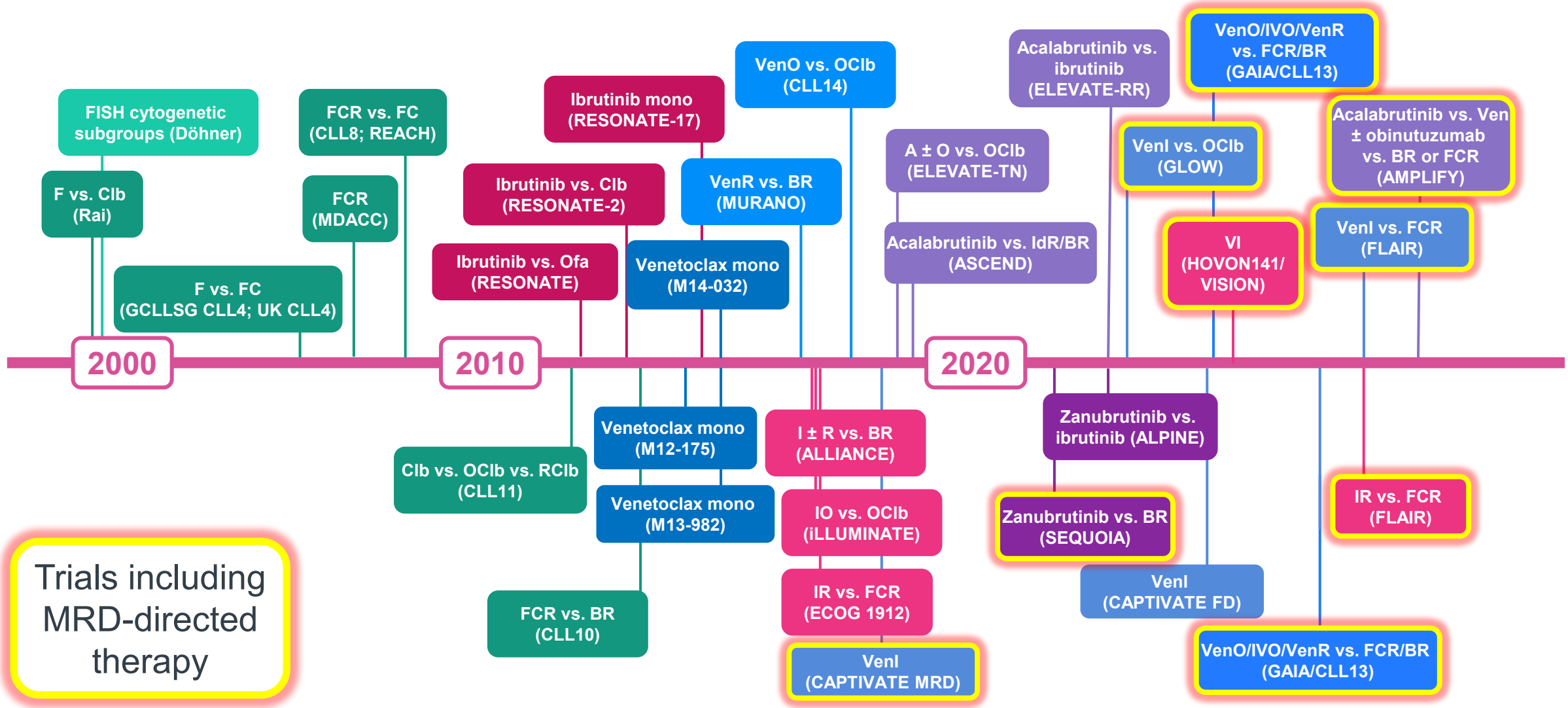
BTKi, Bruton's tyrosine kinase inhibitor; CD20, cluster of differentiation 20; (m/u)IGHV, (mutated/unmutated) immunoglobulin heavy chain variable; MRD, minimal residual disease; PI3Ki, phosphoinositide 3-kinase inhibitor. Slide courtesy of Arnon Kater.

MRD-directed therapy is a common feature of recent trials in CLL



A, acalabrutinib; B, bendamustine; C, cyclophosphamide; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; F, fludarabine; FISH, fluorescence *in* situ hybridization; I, ibrutinib; Id, idelalisib; mono, monotherapy; MRD, minimal residual disease; O, obinutuzumab; Ofa, ofatumumab; R, rituximab; V/Ven, venetoclax.
Slide courtesy of Arnon Kater.

Audience question 1

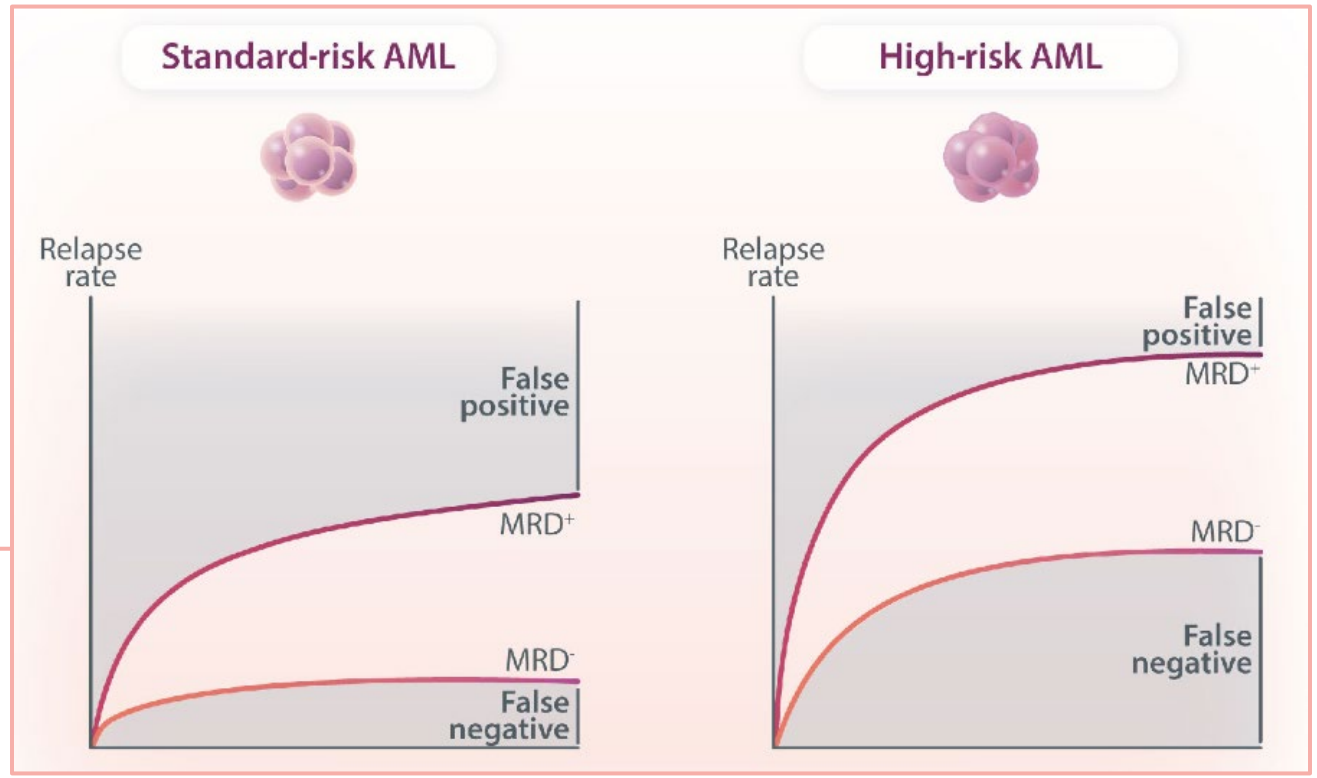
What is your experience with MRD in CLL?

- I have monitored MRD in the context of a clinical trial
- I have monitored MRD outside of a clinical trial
- Both of the above
- I have no experience with MRD

CLL, chronic lymphocytic leukemia; MRD, minimal residual disease.

MRD-based treatment is well established in CML and AML but still reserved for clinical trials in CLL

- **CML**: One driver mutation, one compartment[1]
- **AML**: Multiple driver mutations, one compartment[2,3]



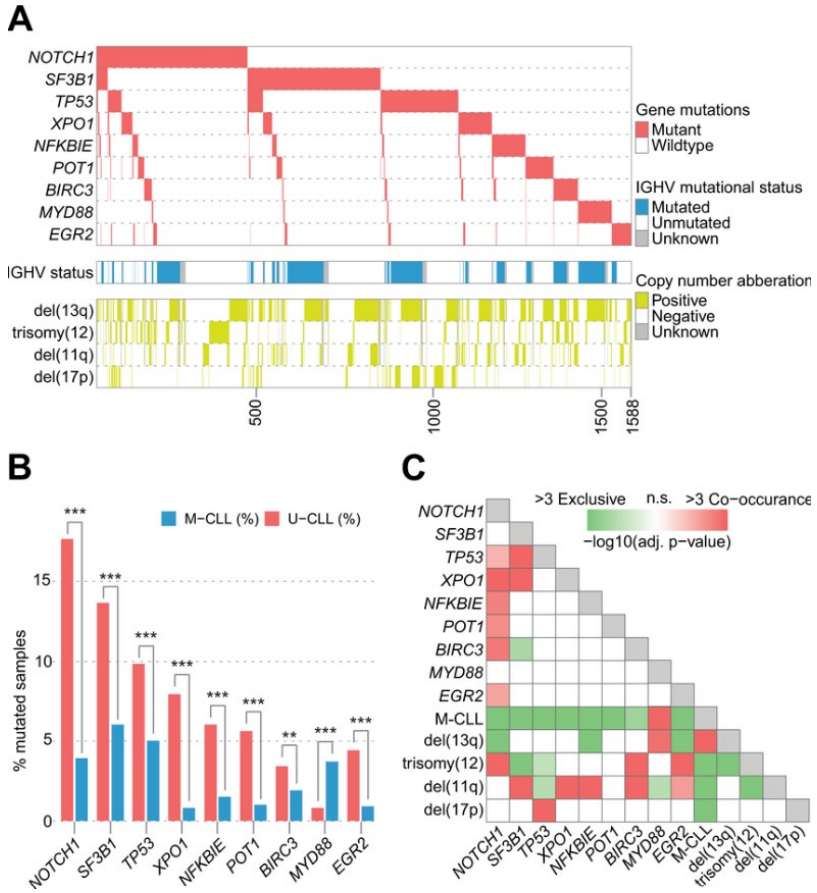
What is different about CLL?...

AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MRD, minimal residual disease.

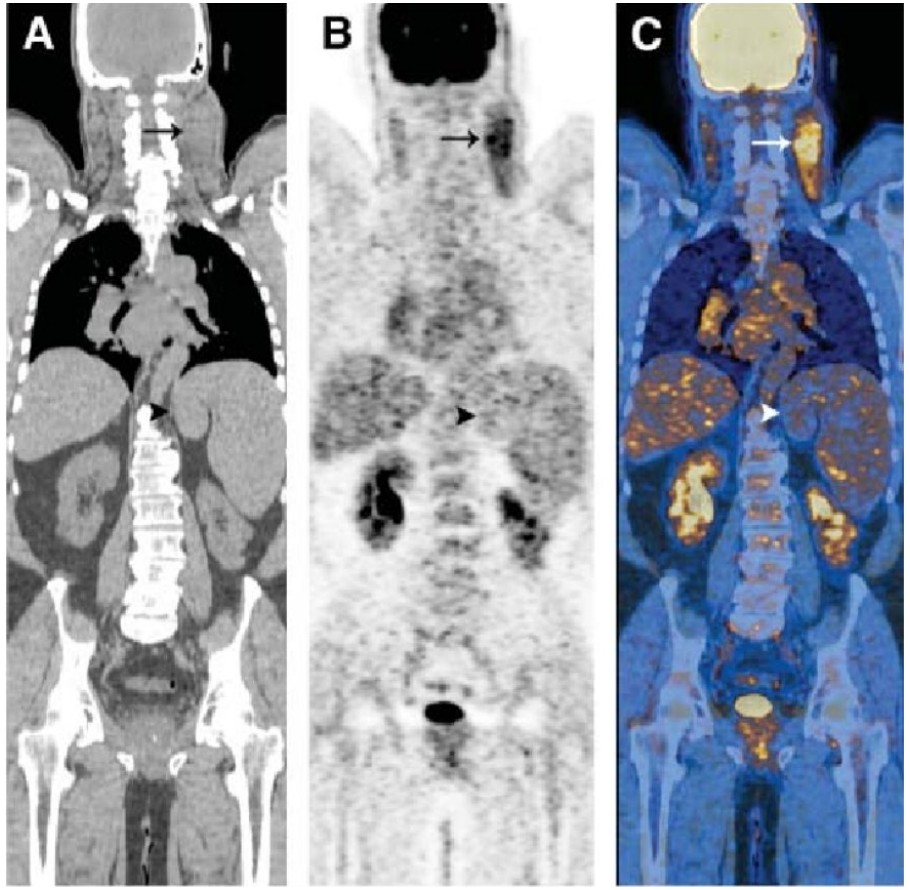
1. Deininger MW *et al*. *Blood* 2000; 96 (10): 3343–3356. 2. Gruszka AM *et al*. *Int J Hematol Oncol* 2017; 6 (2): 43–53. 3. Ofran Y *et al*. *Haematologica* 2023; 109 (1): 6–7.

CLL has multiple driver mutations and multiple compartments

Overview of 1,588 CLL cases carrying mutations in recurrently mutated genes[1]



CT (A), PET (B), and fused PET/CT (C) of a 60-year-old man with a 3-year history of CLL with bulky multicompartmental lymphadenopathy[2]

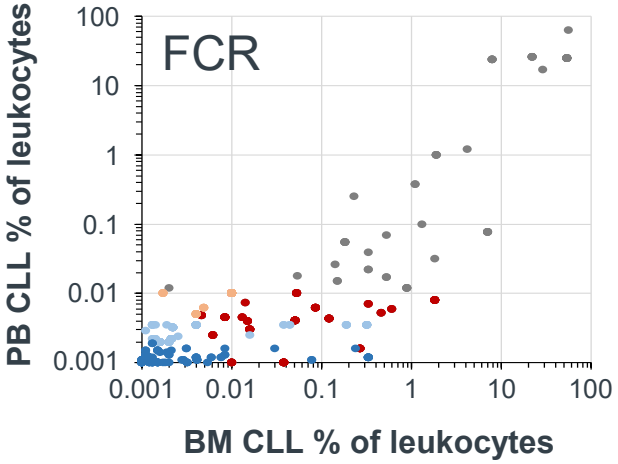


CLL, chronic lymphocytic leukemia; CT, computed tomography; IGHV, immunoglobulin heavy chain variable; M, mutated; ns, not significant; PET, positron emission tomography; U, unmutated.

1. Mansouri L *et al*. *Leukemia* 2023; 37 (2): 339–347. 2. Bruzzi JF *et al*. *J Nucl Med* 2006; 47 (8): 1267–1273.

Does uMRD in peripheral blood equate to uMRD in bone marrow?

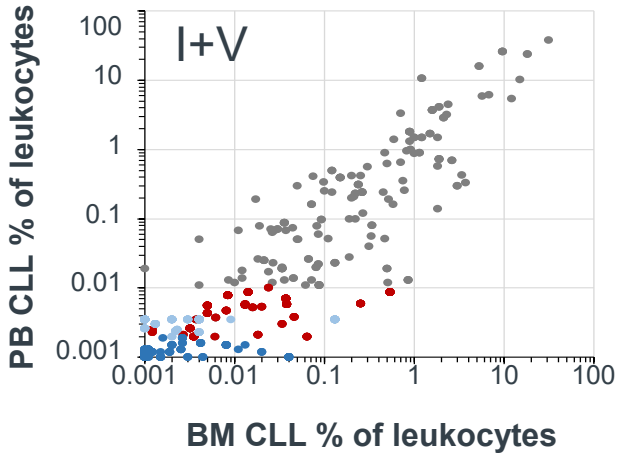
Concordance of uMRD in the PB and BM in different arms of the FLAIR trial



Log difference in BM vs. PB MRD: 0.54 (−0.78, 2.1)

Proportion with BM uMRD4 (<0.01%):

- >90% with PB uMRD5 (<0.001%)
- <25% with PB dMRD5 (0.001%–0.01%)



Log difference in BM vs. PB MRD: 0.01 (−1.05, 1.82)

Proportion with BM uMRD4 (<0.01%):

- >90% with PB uMRD5 (<0.001%)
- <50% with PB dMRD5 (0.001%–0.01%)

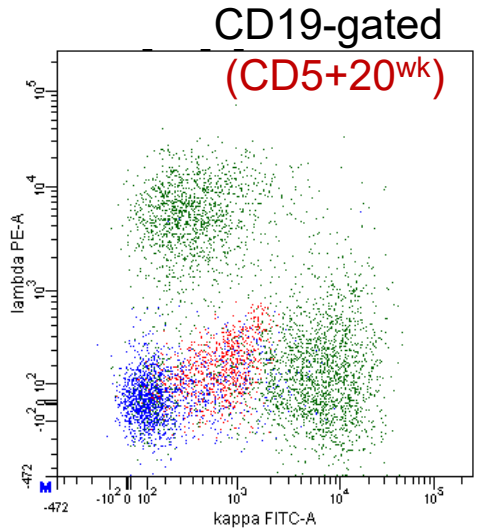
BM assessment may be substituted with PB MRD monitoring if a 0.001%/MRD5 threshold is used

BM, bone marrow; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; I, ibrutinib; (d/u)MRD, (detectable/undetectable) minimal residual disease; PB, peripheral blood; V, venetoclax.

Rawstron A *et al*. Oral presentation 632 at ASH 2023; San Diego, CA, USA, December 9–12, 2023.

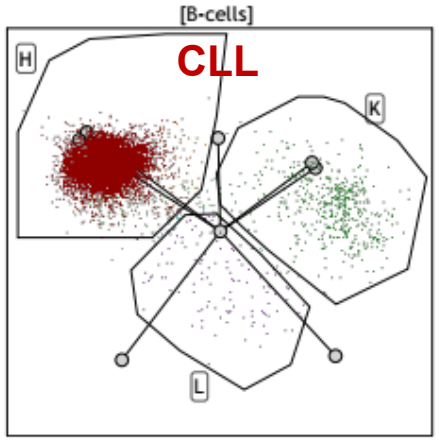
Broad access to MRD5 technology (MRD-flow or q/ddPCR or HTS)

Basic flow cytometry[1]

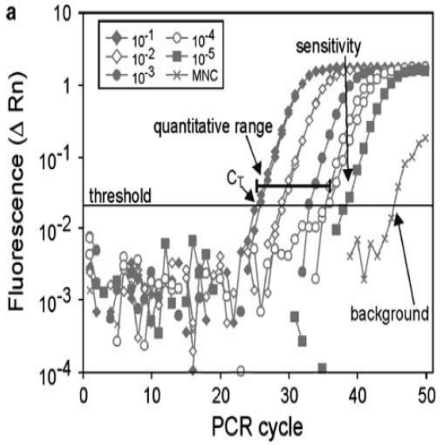


- Variable detection
- All hospitals
- Rapid and cheap
- May not be quantitative

MRD-flow[2]

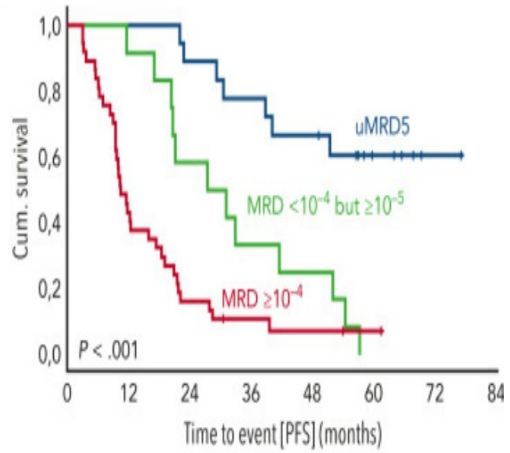


ddPCR or qPCR[3]



- Can detect MRD at 10^{-5}/0.001%
- Reference centers – several per country
- Flow: Rapid turnround, fresh samples only
- qPCR: Can use stored DNA
- Quantitative

High-throughput sequencing[4]



- Can detect 10^{-6}
- Can be expensive at MRD6
- Some assays not quantitative
- FDA cleared

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

CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; dd, droplet digital; DNA, deoxyribonucleic acid; FDA, US Food and Drug Administration; HTS, high-throughput screening; MRD, minimal residual disease; PCR, polymerase chain reaction; q, quantitative. 1. Rawstron A *et al*. *Leukemia* 2013; 27 (1): 142–149. 2. Rawstron A *et al*. *Leukemia* 2016; 30 (4): 929–936. 3. Van der Velden *et al*. *Leukemia* 2007; 21 (4): 604–611. 4. Hengeveld PJ *et al*. *Blood* 2023; 141 (5): 519–528.

Audience question 2

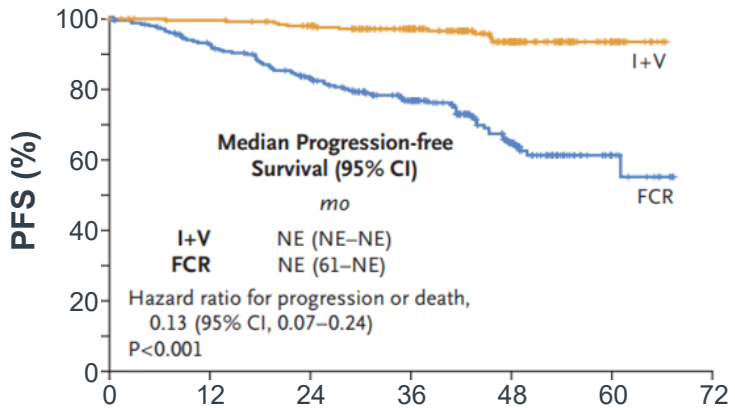
Is MRD ready to guide clinical decision-making outside the context of clinical trials in CLL?

- Yes, it is ready now
- It will be ready in the next 2 years
- It will be ready in 2–5 years
- I don’t know

CLL, chronic lymphocytic leukemia; MRD, minimal residual disease.

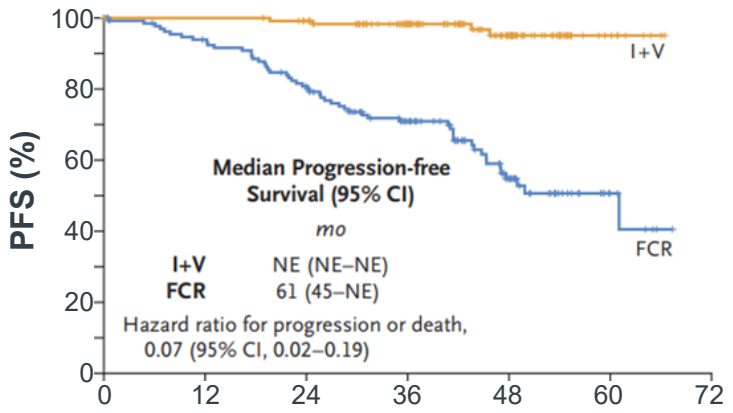
In the first-line FLAIR trial, venetoclax-ibrutinib duration was determined by interim MRD status in treatment-naive CLL

PFS: Full population



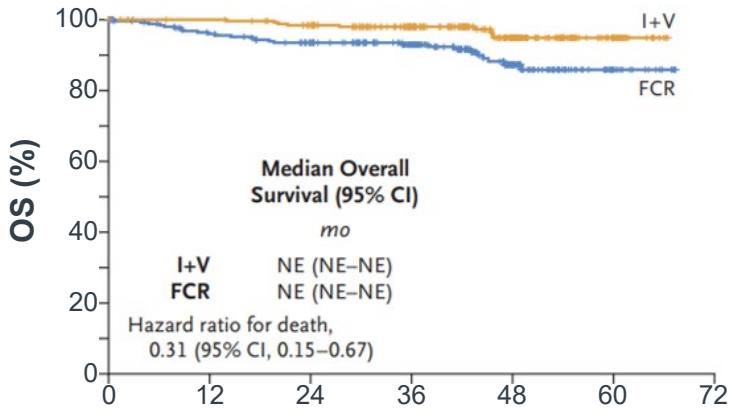
No. at Risk (no. with data censored)							
I+V	260 (1)	253 (6)	239 (16)	183 (70)	99 (151)	21 (227)	0 (248)
FCR	263 (2)	227 (18)	194 (28)	145 (63)	68 (126)	12 (177)	0 (188)

PFS: uIGHV CLL



No. at Risk (no. with data censored)							
I+V	123 (1)	122 (1)	117 (5)	89 (32)	47 (72)	8 (111)	0 (119)
FCR	138 (1)	122 (8)	103 (10)	76 (25)	35 (54)	6 (80)	0 (85)

OS: Full population



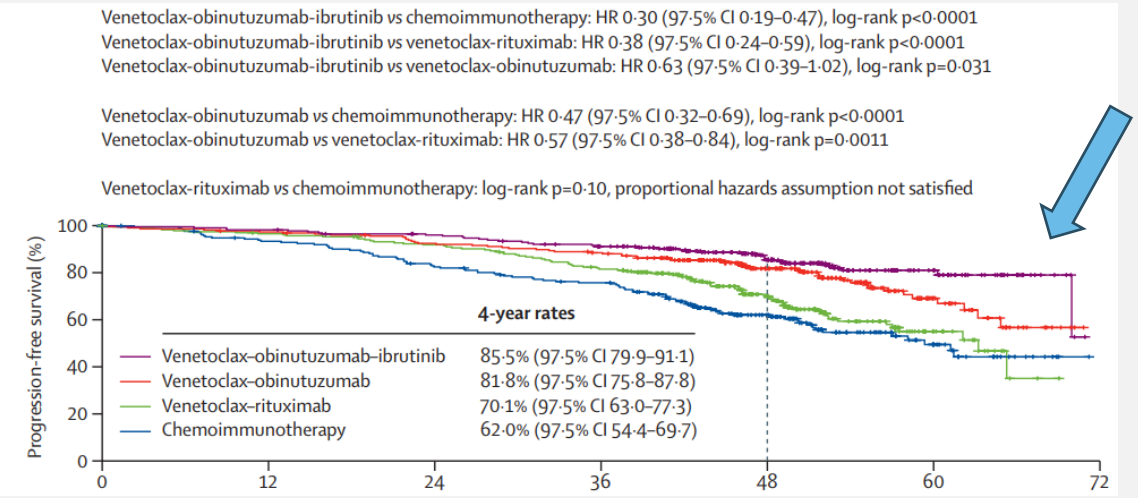
No. at Risk (no. with data censored)							
I+V	260 (1)	254 (6)	240 (16)	185 (70)	100 (153)	22 (229)	0 (251)
FCR	263 (2)	234 (19)	213 (34)	166 (80)	79 (162)	15 (223)	0 (238)

CI, confidence interval; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; I, ibrutinib; MRD, minimal residual disease; NE, not estimable; OS, overall survival; PFS, progression-free survival; uIGHV, unmutated immunoglobulin heavy chain variable; V, venetoclax.

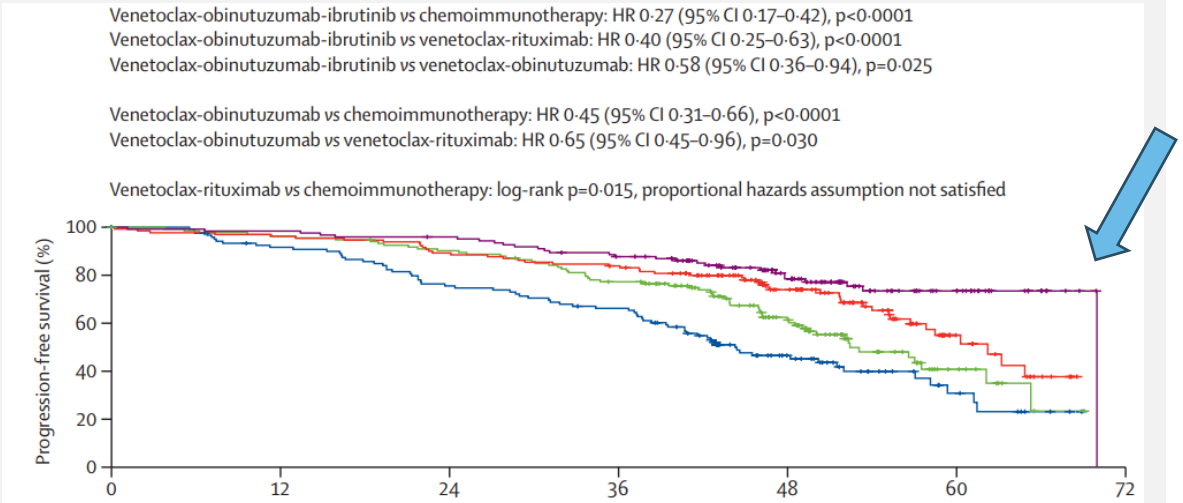
Munir T *et al. N Engl J Med* 2024; 390 (4): 326-337.

MRD-guided triplet therapy in GAIA in treatment-naive CLL

Full trial population



uIGHV CLL



Duration of therapy in the venetoclax-ibrutinib-obinutuzumab arm was determined by interim MRD status

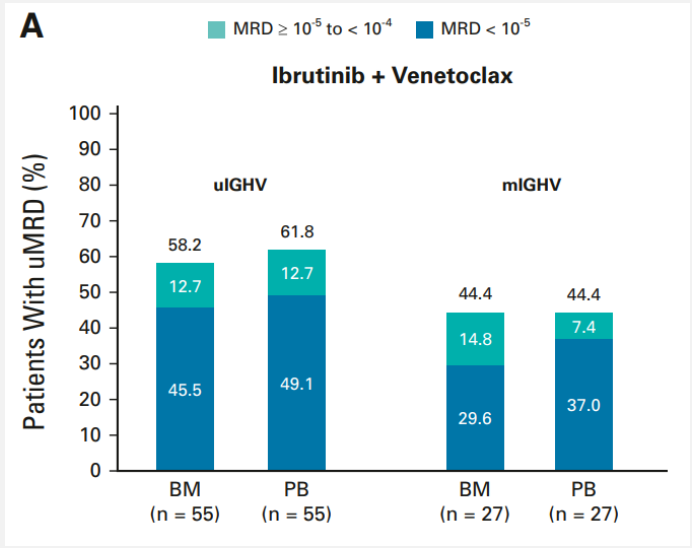
PFS was superior vs. all other arms in uIGHV CLL patients

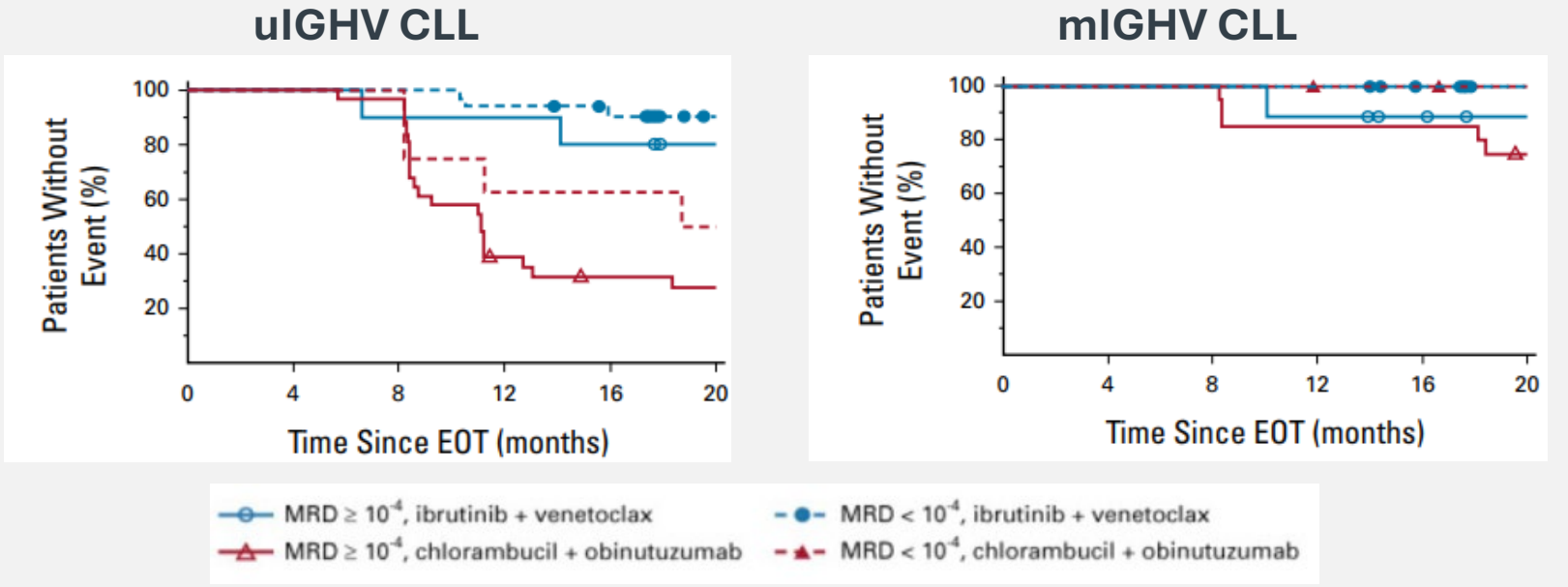
CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio; MRD, minimal residual disease; PFS, progression-free survival; uIGHV, unmutated immunoglobulin heavy chain variable.

Fürstenau M *et al*. *Lancet Oncol* 2024; 25 (6): 744–759.

Slide courtesy of Arnon Kater.

To date, MRD responses in uIGHV patients did not translate into improved PFS with fixed-duration ibrutinib + venetoclax in the GLOW trial



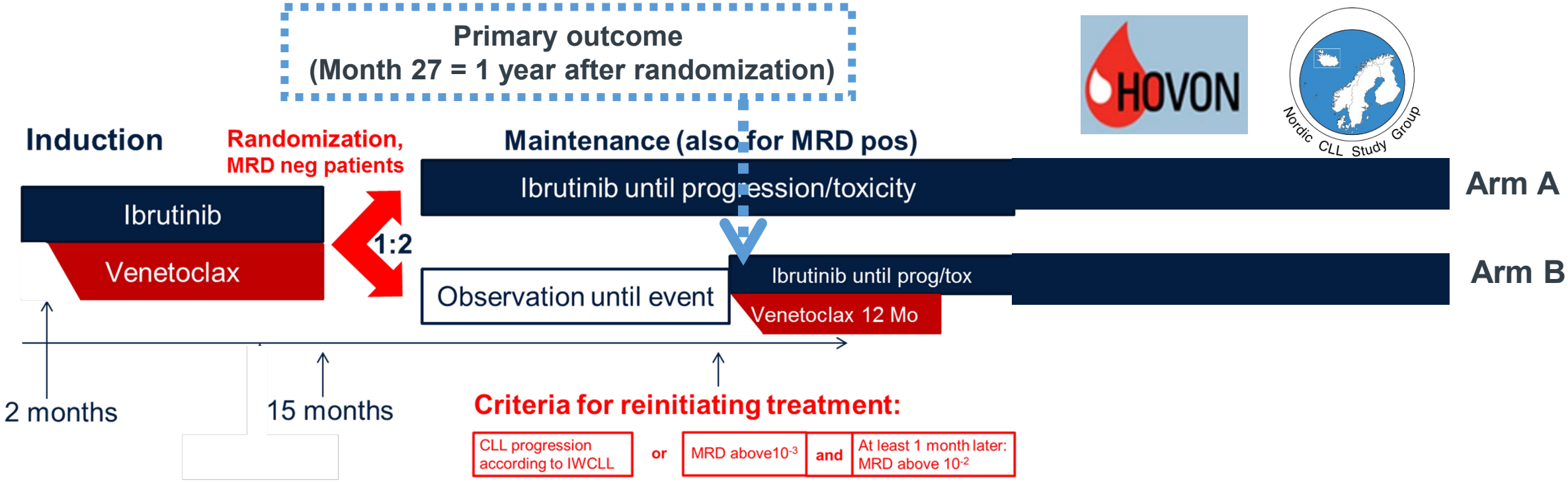


BM, bone marrow; CLL, chronic lymphocytic leukemia; EOT, end of treatment; (m/u)IGHV, (mutated/unmutated) immunoglobulin heavy chain variable; (u)MRD, (undetected) minimal residual disease; PB, peripheral blood; PFS, progression-free survival.

Munir T *et al*. *J Clin Oncol* 2023; 41 (21): 3689–3699.

Slide courtesy of Arnon Kater.

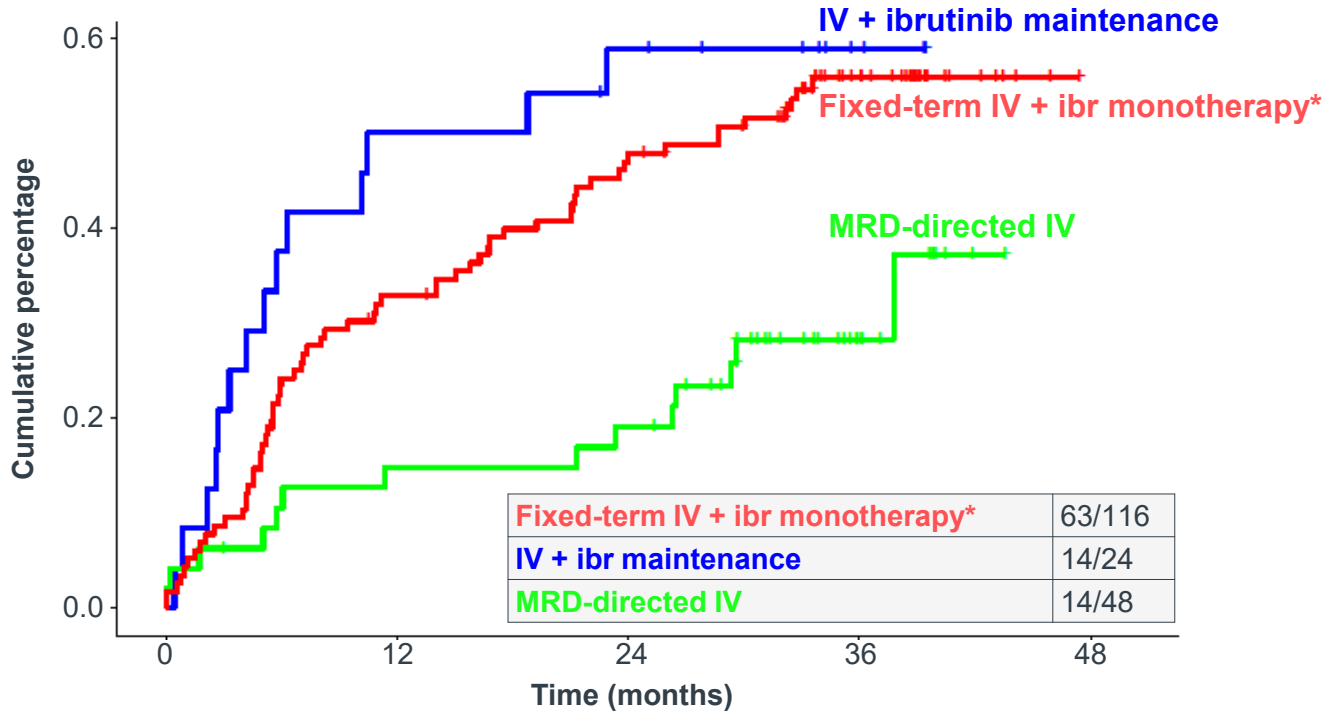
In HOVON141/VISION, venetoclax + ibrutinib duration was determined by interim MRD status in R/R CLL



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.

Audience question 3

Are molecular NGS-based assays better than flow cytometry for measuring MRD?

One answer only

A. Yes, this is what we use
B. Yes, but we cannot access NGS yet
C. No, it depends on the application – both have utility
D. No, flow cytometry is preferable
E. I am not sure

MRD, minimal residual disease; NGS, next-generation sequencing.
Slide courtesy of Arnon Kater.

Molecular vs. cellular assays for MRD

Feature	Multicolor flow cytometry	ASO-qPCR	NGS-based
Target	Surface marker patterns	IG gene rearrangement	IG gene rearrangement
Sensitivity	Routinely 10^{-4}, up to 10^{-5}	Routinely 10^{-4}, up to 10^{-5}	Routinely 10^{-5}, up to 10^{-6}
Starting material	Freshly isolated cells	DNA	DNA
Target stable over time?	Not necessarily	Yes	Yes
Advantages	• Widely available • Highly standardized • Rapid turnover time • Universal assay	• Samples may be frozen • High specificity	• Low LoD (3.4×) • High sensitivity • High specificity • Universal assay • Standardization possible • Evaluates IGHV repertoire
Disadvantages	• High LoD (>20–50 events) • Markers may be targeted by new drugs • Samples must be fresh	• Assay design not always possible • Patient-specific assay • Hard to standardize • Limited sensitivity	• Requires batching • Longer turnover time

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

ASO, allele-specific oligonucleotide; DNA, deoxyribonucleic acid; IG, immunoglobulin; IGHV, immunoglobulin heavy chain variable; LoD, limit of detection; MRD, minimal residual disease; NGS, next-generation sequencing; qPCR, quantitative polymerase chain reaction. Slide courtesy of Arnon Kater.

Audience question 4

Is MRD kinetics using multiple (early) timepoints more informative than a single, end-of-treatment measurement?

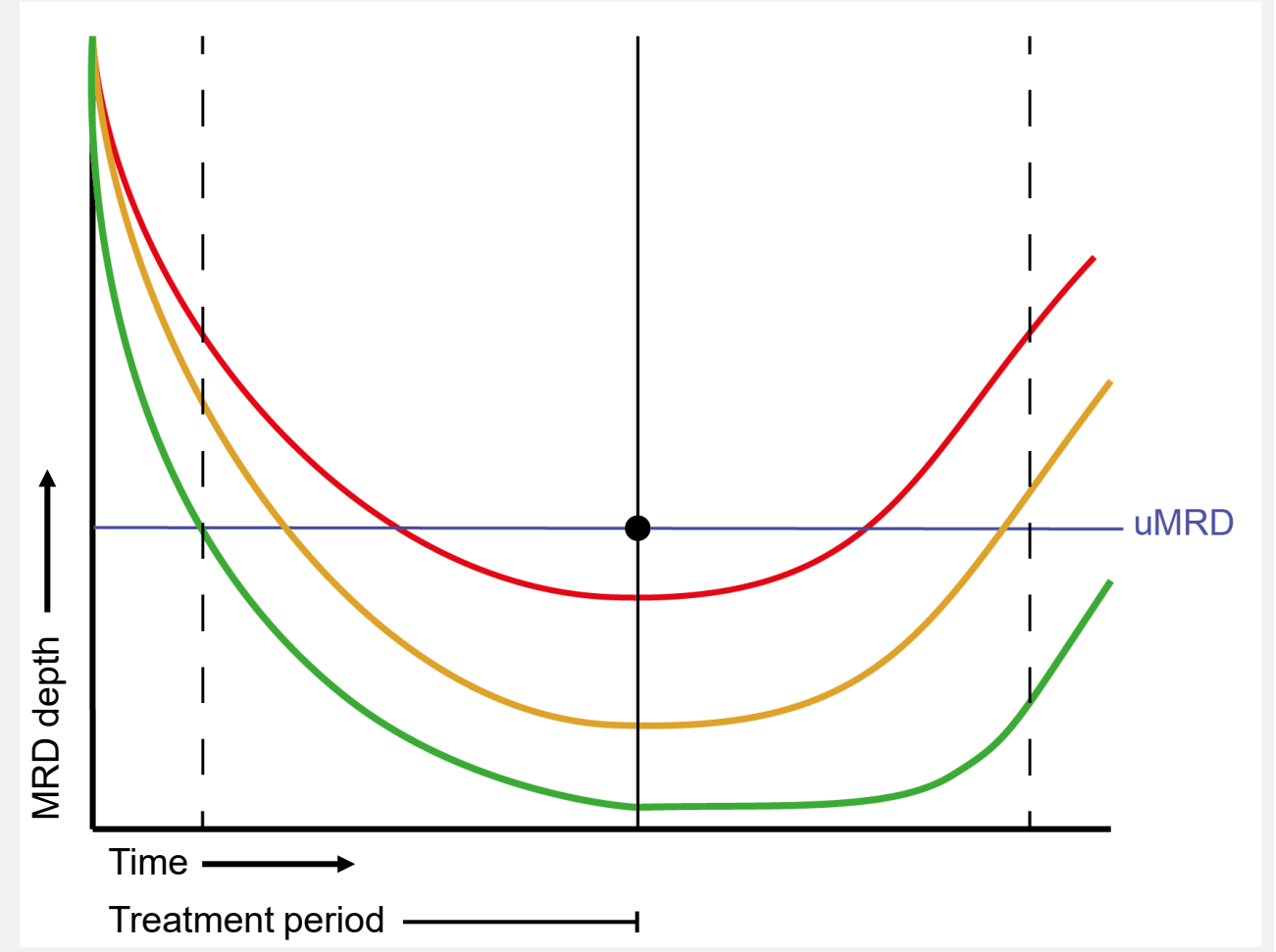
One answer only

A. Yes, a single timepoint is not informative
B. Yes, but we still need a definitive single response timepoint
C. No, kinetics assessments are too difficult to apply outside of clinical trials
D. No, it depends on the situation
E. I am not sure

MRD, minimal residual disease.
Slide courtesy of Arnon Kater.

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

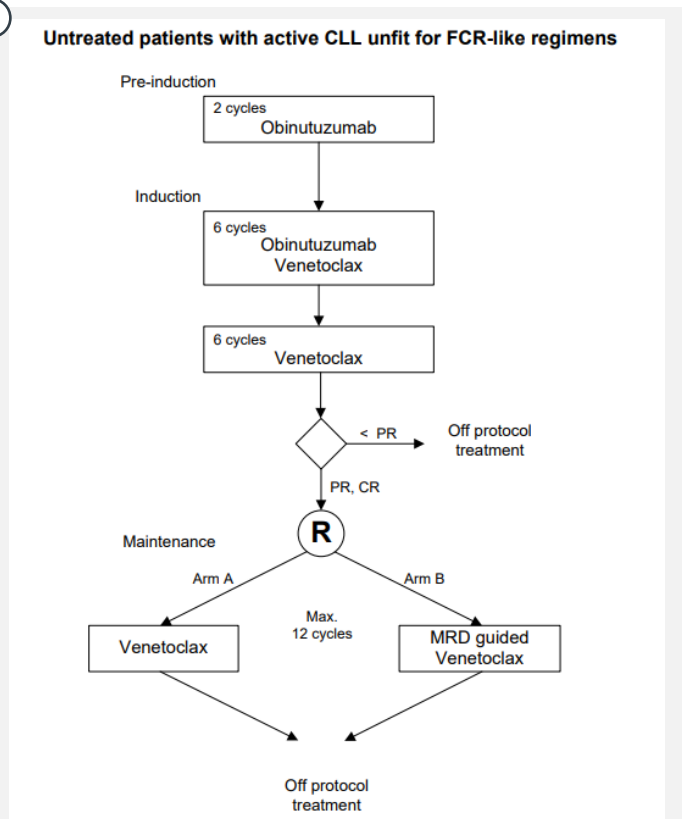
- (Ideally) fixed-duration treatment induces high uMRD rates
- MRD follows an L-shaped trajectory
- Serial measurements may yield additional information



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

1



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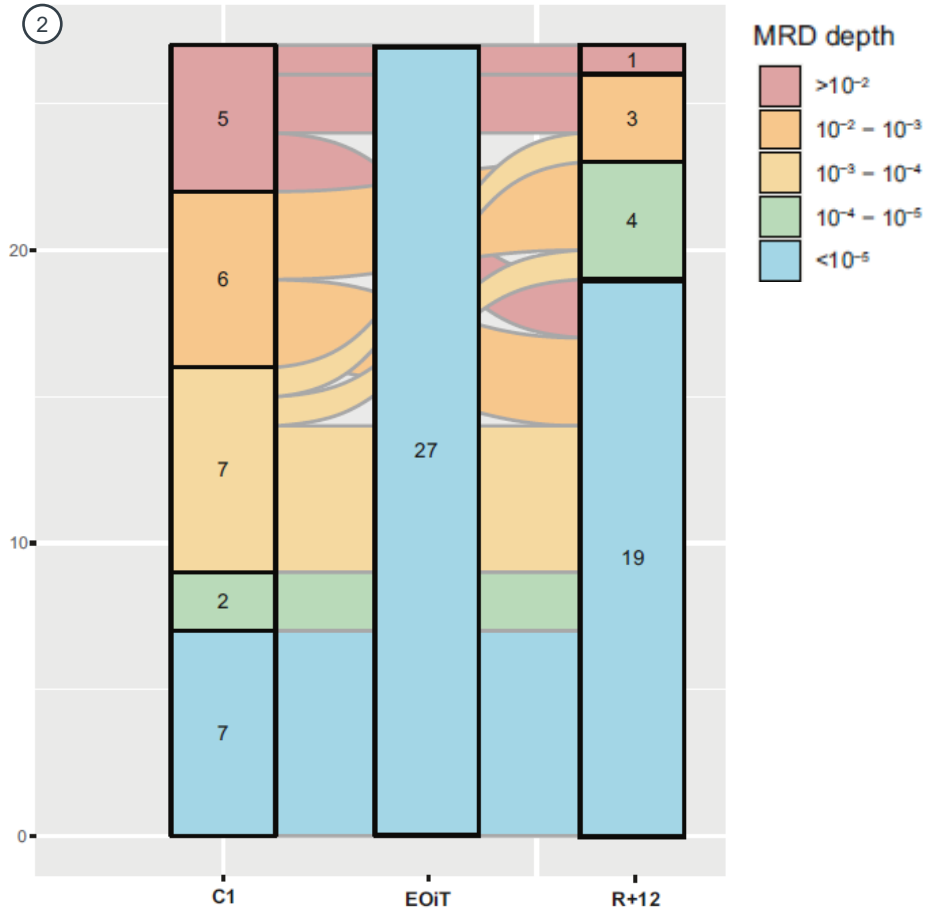

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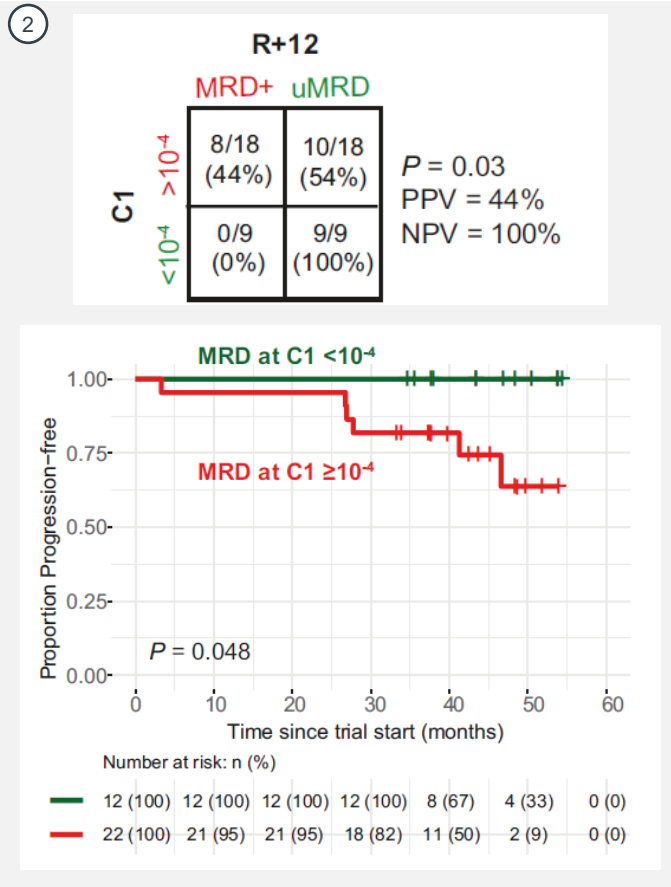

CLL, chronic lymphocytic leukemia; CR, complete response; FCR, fludarabine, cyclophosphamide, and rituximab; (u)MRD, (undetectable) minimal residual disease; NPV, negative predictive value; Obi, Obinutuzumab; PPV, positive predictive value; PR, partial response; R, randomization; V, venetoclax.

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.

Changes in MRD may have prognostic value

HOVON-139[1]

10,000× reduction in MRD after 11 weeks of 1L Ven-Obi predicts reaching uMRD5 after 14 months (AUC 0.93)

CLARITY[2]

100× reduction in MRD after 2 months of I+V for R/R CLL correlated with sustained MRD after 3 years

BOVEN[3]

400× reduction in MRD after five cycles of 1L Zanu + Ven + Obi predicted the likelihood of uMRD by the end of Cycle 8

1L, first-line; AUC, area under the curve; CLL, chronic lymphocytic leukemia; I, ibrutinib; (u)MRD, (undetectable) minimal residual disease; Obi, obinutuzumab; R/R, relapsed/refractory; V/Ven, venetoclax; Zanu, zanubrutinib.

1. Hengeveld PJ *et al*. *Blood Cancer J* 2023; 13 (1): 102. 2. Munir T *et al*. Abstract 642 presented at ASH 2022. *Blood* 2022; 140 (Suppl.1): 222–223. 3. Soumerai JD *et al*. *Lancet Haematol* 2021; 8 (12): e879–e890.

Audience question 5

What would be the main use of measuring MRD in clinical practice?

One answer only

A. To determine a patient's prognosis
B. To guide treatment duration
C. To recognize early relapse and/or reinitiate treatment
D. All of the above
E. MRD measurement has no place in clinical practice
F. I am not sure / I do not know

MRD, minimal residual disease.
Slide courtesy of Arnon Kater.

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

CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain variable; MRD, minimal residual disease.
Slide courtesy of Arnon Kater.

For discussion

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?

When and how should you alter treatment?

What questions do you have regarding MRD in CLL?

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

Thank you for your attention