

4th edition

Unmet challenges in high risk hematological malignancies: from bedside to clinical practice

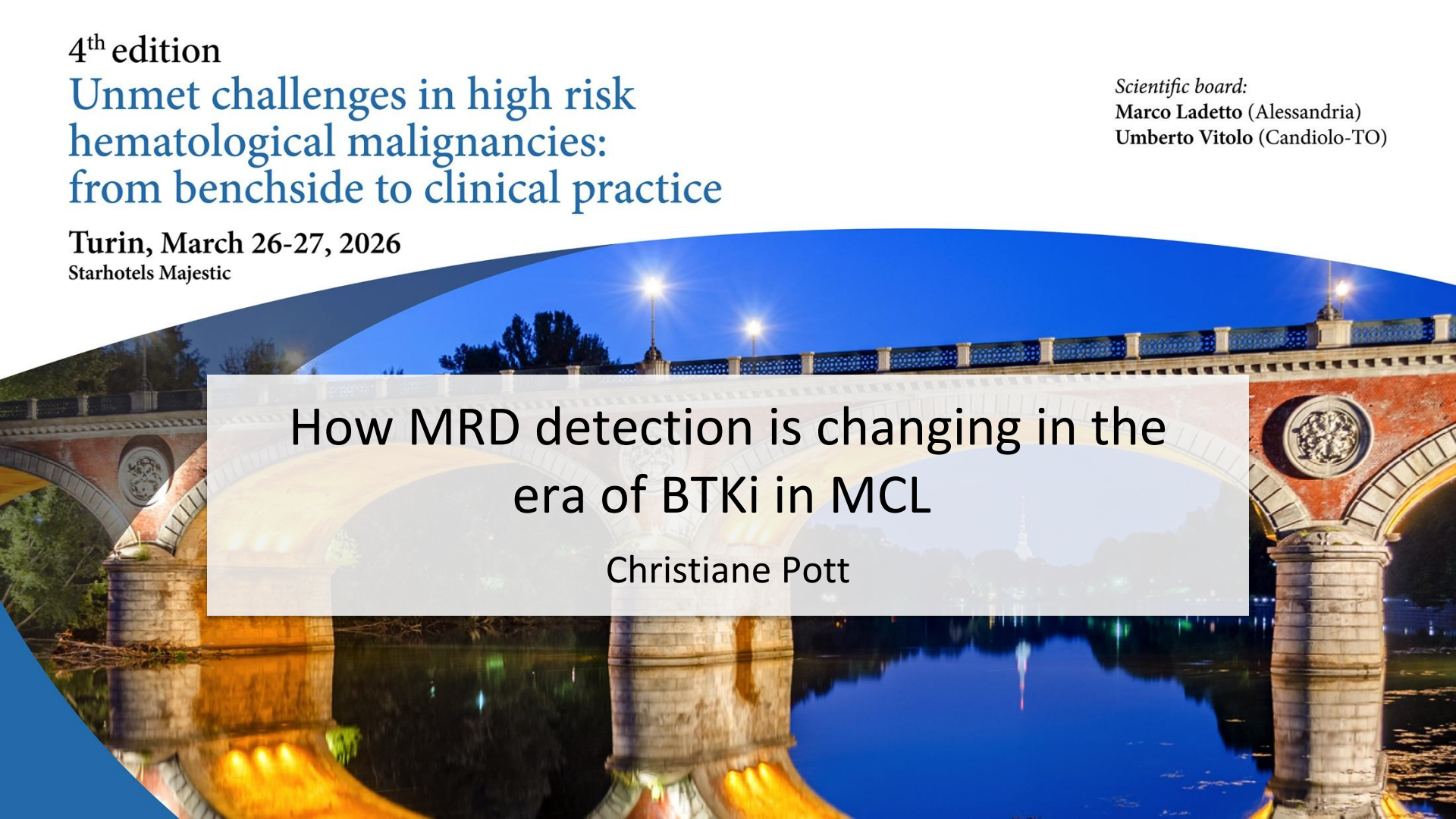
Turin, March 26-27, 2026

Starhotels Majestic

Scientific board:

Marco Ladetto (Alessandria)

Umberto Vitolo (Candiolo-TO)



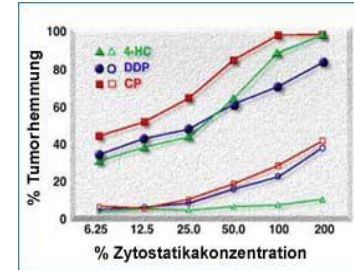
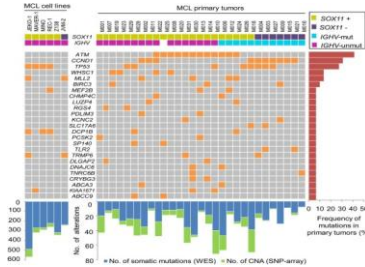
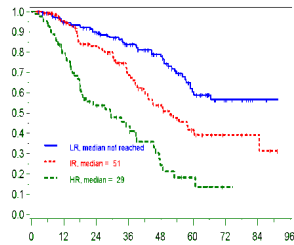
How MRD detection is changing in the
era of BTKi in MCL

Christiane Pott

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche	x		x			x	
Incyte	x		x				
BMS			x			x	
Lilly						x	
Abbvie						x	
Johnson and Johnson			x			x	
Sobi						x	
Kite/Gilead						x	

Minimal Residual Disease “MRD” - the concept -



Pretherapeutic
Risk factors
IPI
FLIPI
MIPI



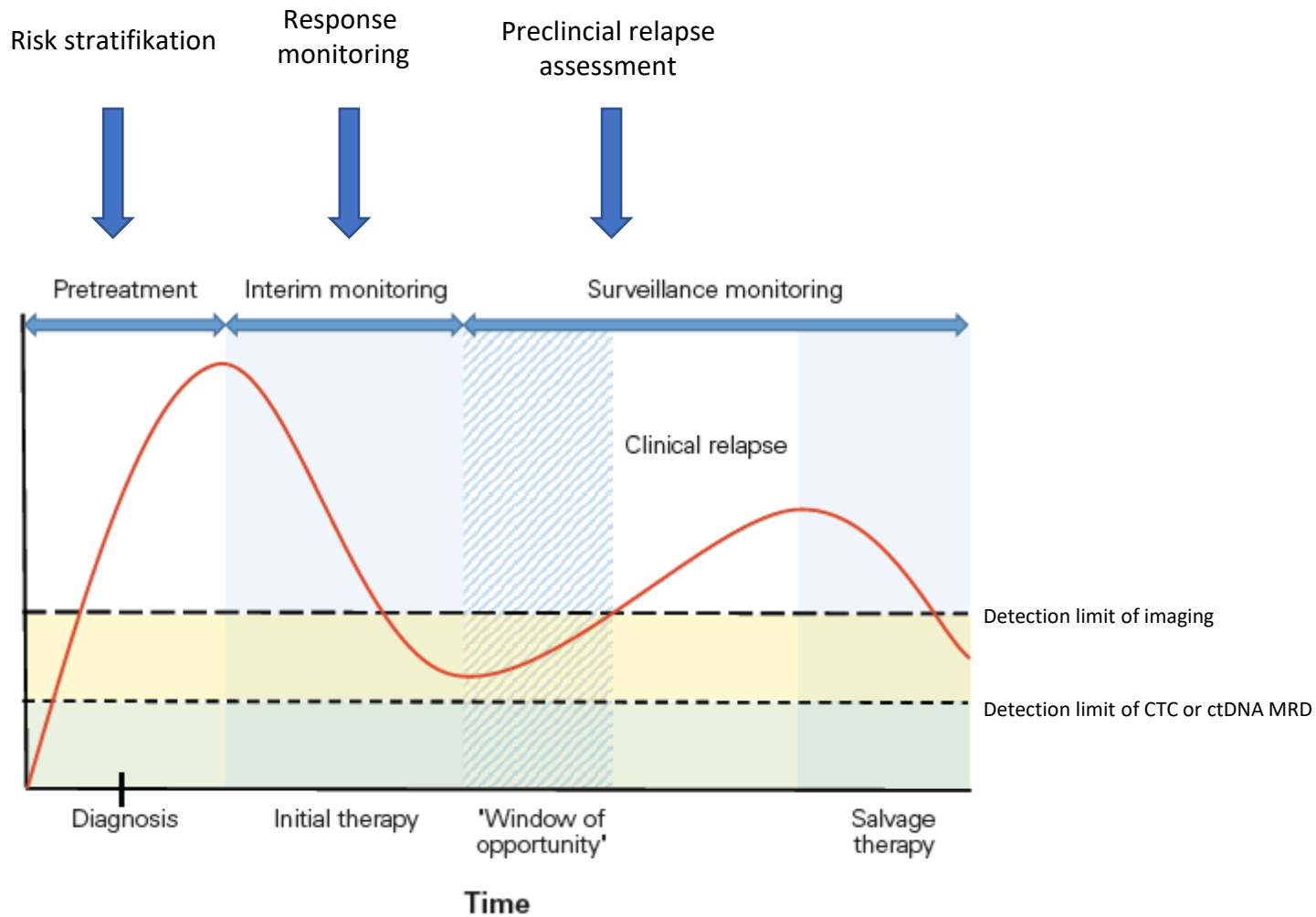
Genetic factors
Loss of tumorsuppressorgenes,
somatic hypermutation
Genetic instability



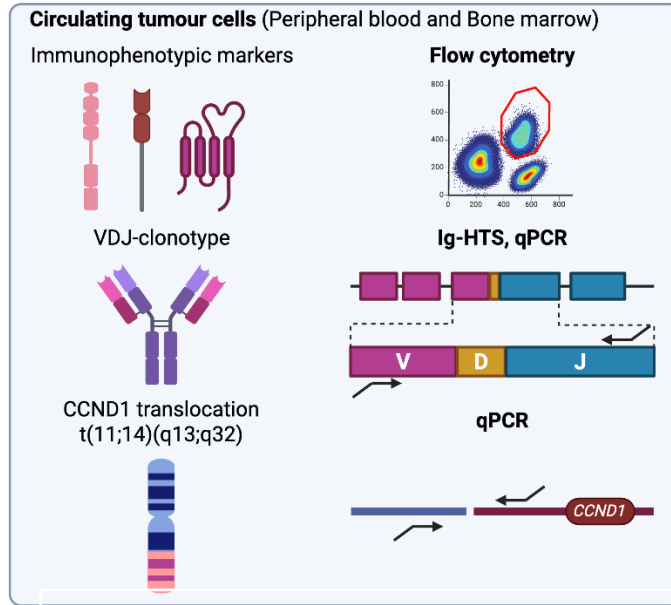
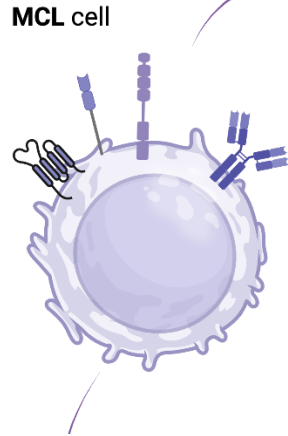
Mechanism of
resistance



MRD as a function of tumor and host biology



MRD assessment in MCL



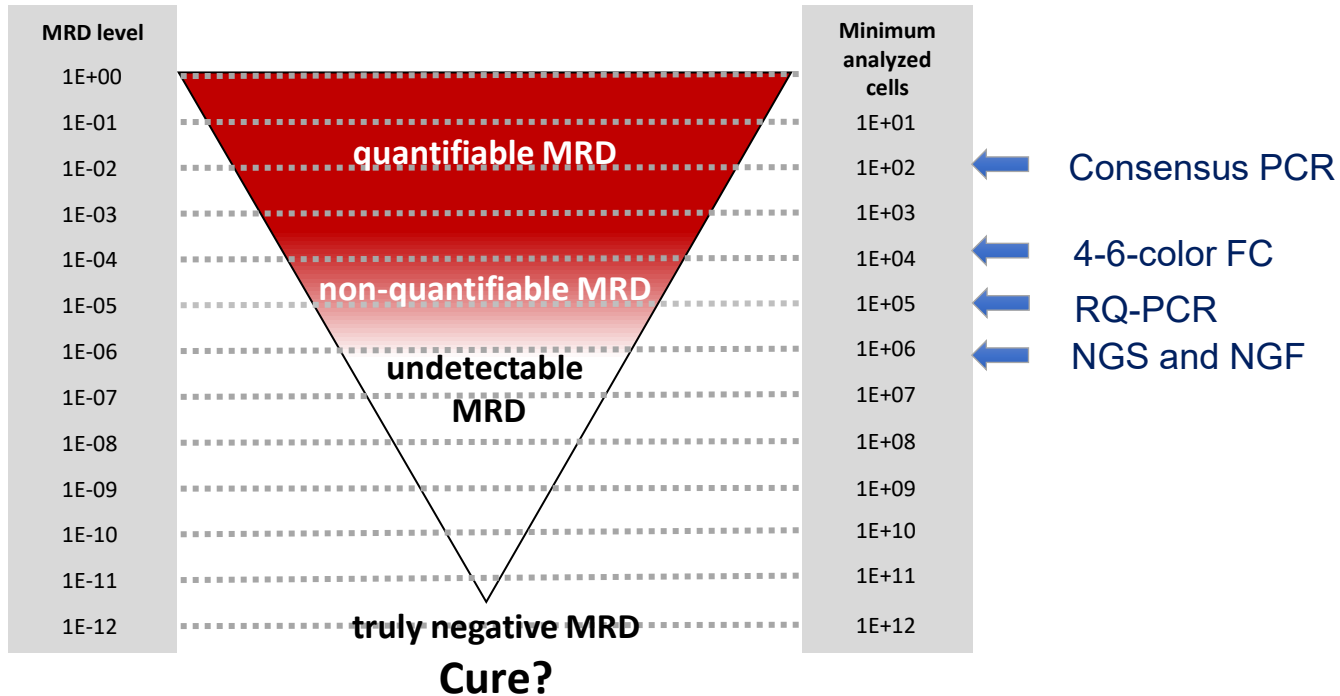
MRD target:

- circulating lymphoma cells
- BM infiltrating cells

Factors defining sensitivity:

- input DNA
- Limit of detection of respective method

Assessment of MRD in circulating tumour cells differences: to be MRD negative is not the same...

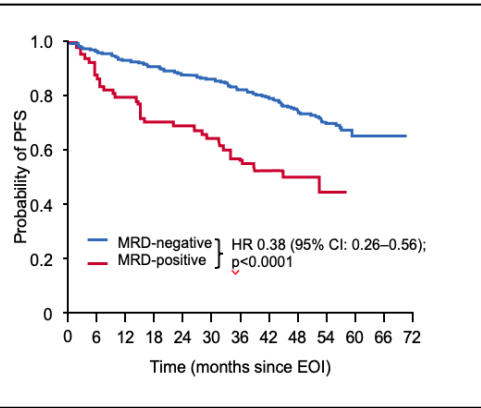


The technique and the biology of the disease impacts on the definition of „undetectable MRD“

MRD measured in CTC:

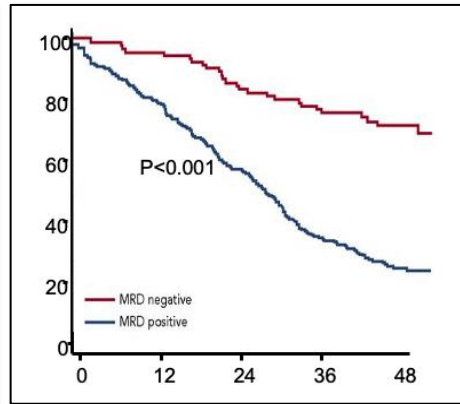
Prognostic evidence of MRD response in different lymphoma entities:
results from prospectively randomized Phase III trials

Follicular lymphomas
Gallium trial



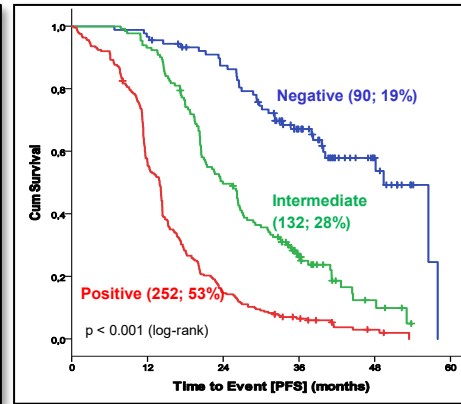
Pott et al. 2023

Multiple Myeloma
IFM/DFCI 2009
GEM2012 trial



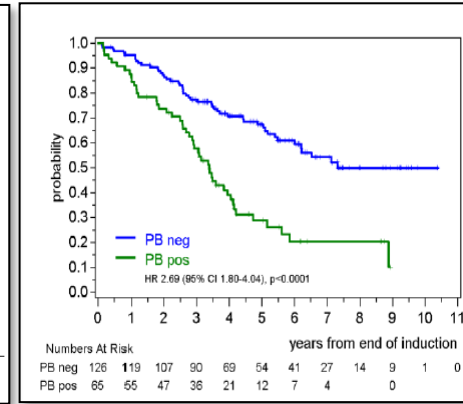
Perrot 2018, Paiva 2019

CLL
CLL8, CLL11



Böttcher 2012, Ritgen 2014

MCL
EU-MCL Younger and Elderly

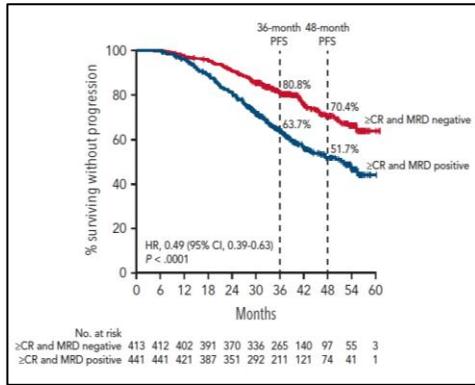


Pott et al. 2023, Hermine 2016

MRD measured in CTC:

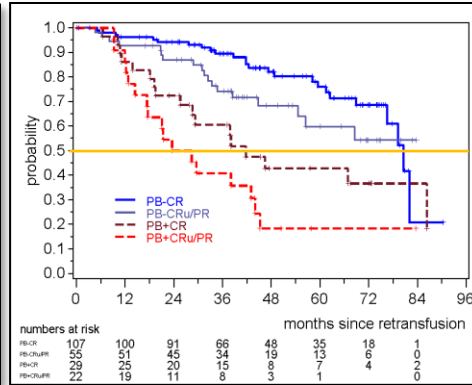
Patients with MRD negative CR have improved PFS/OS independent of disease, irrespective of therapy or disease setting.

Multiple Myeloma



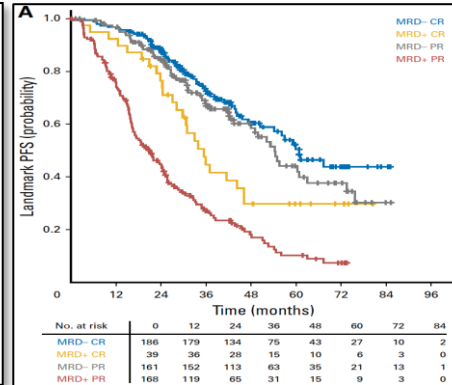
Cavo Blood 2022

MCL



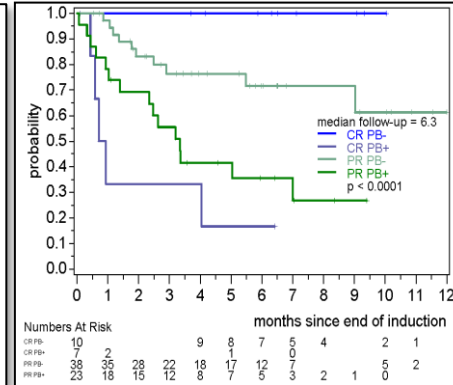
Pott Blood 2014

CLL



Kovacs JCO 2016

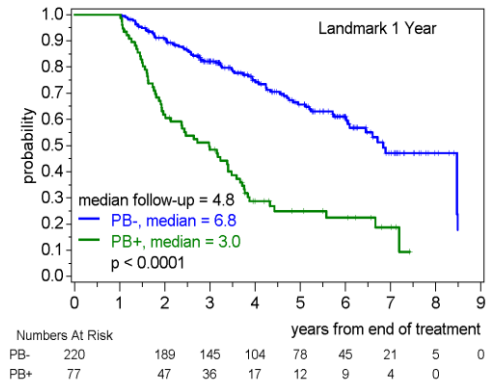
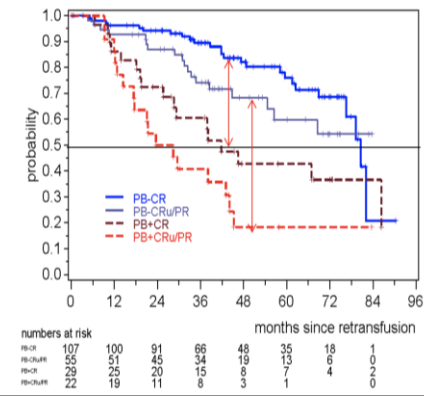
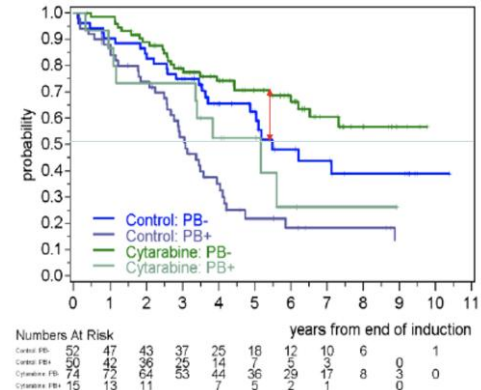
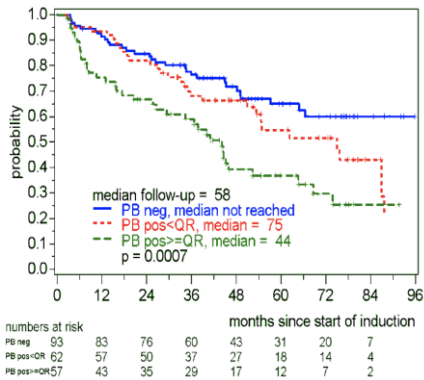
FL



Pott 2023

MRD measured in CTC:

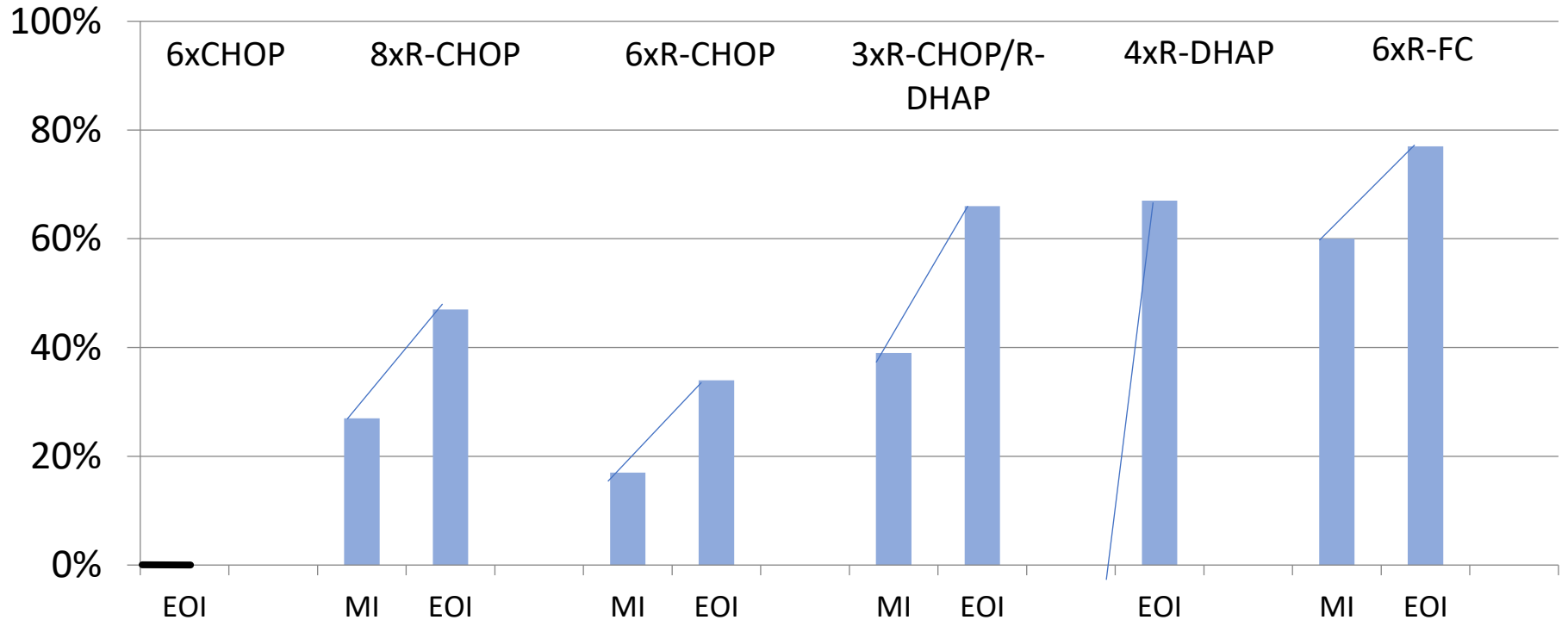
Established timepoints for outcome prediction



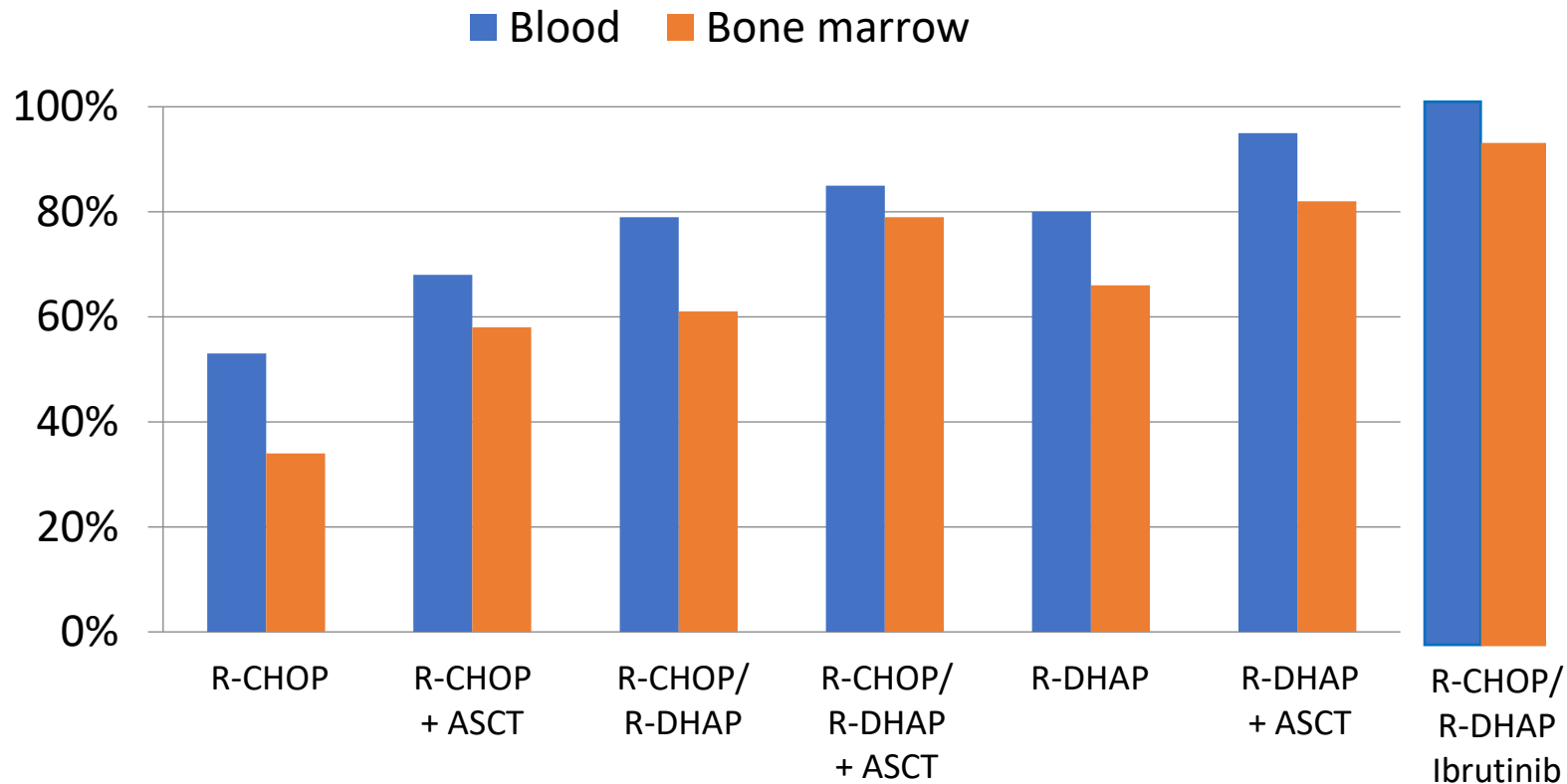
Why do we need other MRD techniques?

- Sensitivity is a challenge in highly efficient treatment
- > 90% MRD response: which risk groups can we still assess?

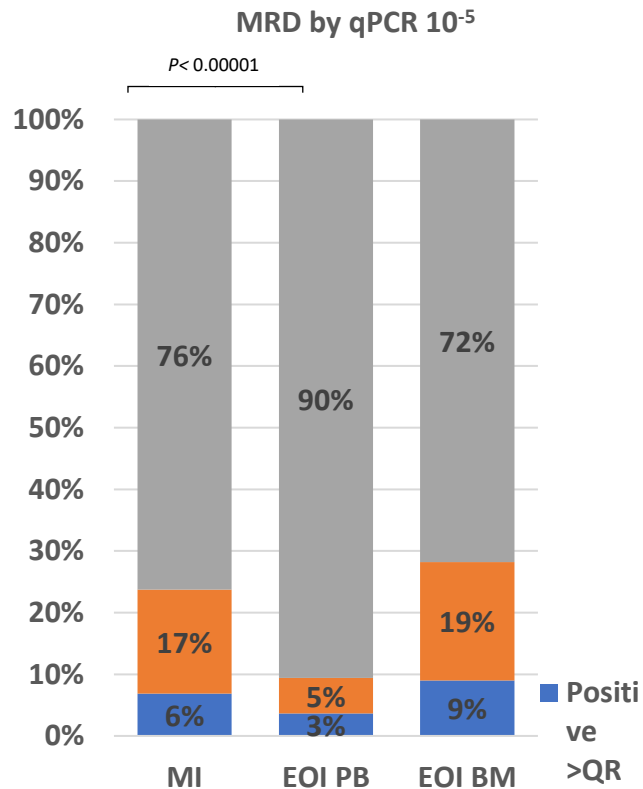
Kinetic of MRD-response during treatment: comparison of induction regimen



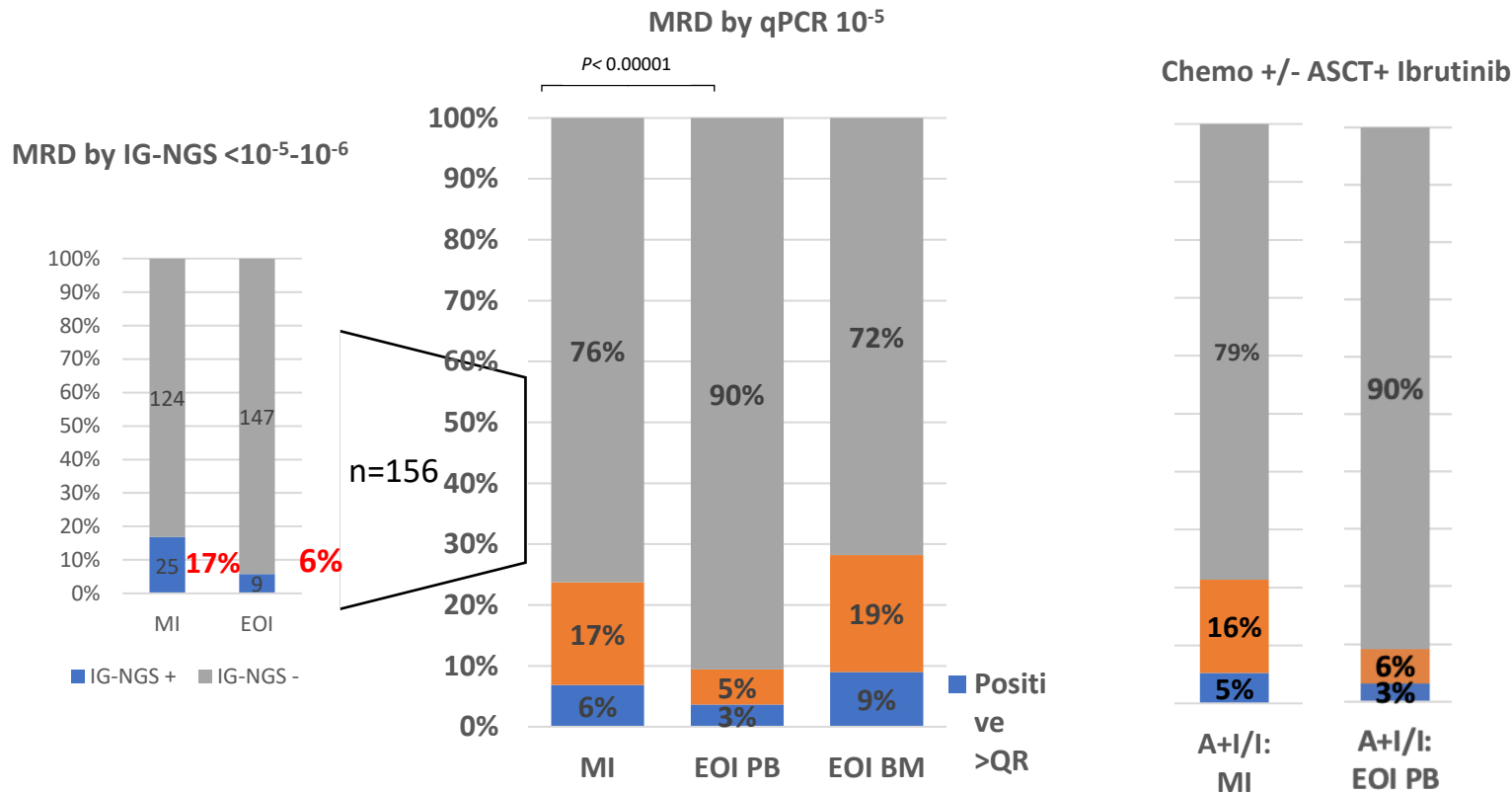
MRD-response in MCL: increasing MRD-neg rates due to more effective treatments



TRIANGLE: MRD response during and at end of induction



TRIANGLE: MRD response during and at end of induction



➤ Higher sensitivity by IG-NGS identifies 17% more MRD at MI and 6% at EOI

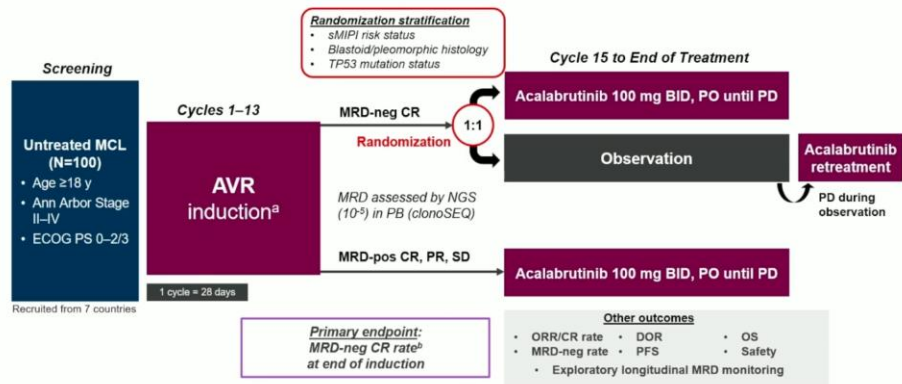
MRD guided trials with novel agents in 1L MCL

Trial	Regimen	Used biomarker (HR)	N	Line	Outcome
ALTAMIRA(77)	R-Acalabrutinib HR continuous, LR stop after 1y	<i>TP53</i> ^{mut} , blastoid, Ki67>30%	81	1L E	HR: 2-y PFS 32% LR: 2-y PFS 91%
BOVen(78)	Zanubrutinib, obinutuzumab, venetoclax. MRD guided duration.	<i>TP53</i> ^{mut} only	25	1L	HR: 2-y PFS 72%
MAVO(79)	Acalabrutinib, venetoclax, obinutuzumab. MRD guided duration.	<i>TP53</i> ^{mut} or p53>50%	24	1L	2-y PFS 79%
TrAVeRse (80)	Rituximab, venetoclax, acalabrutinib. MRD neg randomized to A maintenance.	<i>TP53</i> ^{mut} , blastoid, MIPI high (<i>TP53</i> ^{mut} n=17)	108	1L	Overall: 1-y PFS 95% <i>TP53</i> ^{mut} : 1-y PFS 88%

#884 Acalabrutinib Plus Venetoclax and Rituximab in Patients With Treatment-Naive Mantle Cell Lymphoma: Results From the Phase 2 TrAVeRseStudy

Hawkes et al. ASH 2025

TrAVeRse Study Design: Multicenter, Open-label, Phase 2 Trial



NCT05951959.

^aAVR induction: acalabrutinib 100 mg BID (C1-C13), also given in C14 post-induction; venetoclax (C2-C13) [5-week ramp-up in C2: 20 mg up to 400 mg daily]; rituximab (375 mg/m² day 1 of C1-12). MRD-neg (in PB by NGS 10⁻²-clonoSEQ) while in CR (per Lugano criteria).

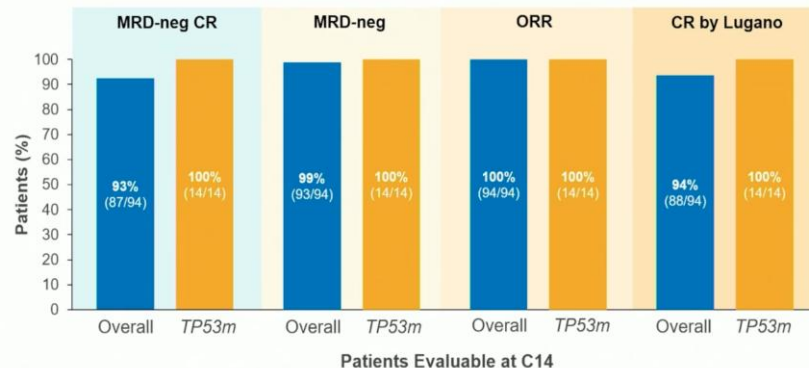
^bAVR: acalabrutinib + venetoclax + rituximab, BID, twice daily, C, cycle; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MRD, measurable residual disease; neg, negative; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PD, progressive disease; PFS, progression-free survival; PO, orally; pos, positive; PR, partial response; SD, stable disease; sMIP1, simplified Mantle Cell Lymphoma International Prognostic Index; TN, treatment-naive.

TrAVeRse



Outcomes at End of Induction in Patients With TP53 Mutation

Among evaluable patients who completed induction, those with TP53m have comparable benefit



9

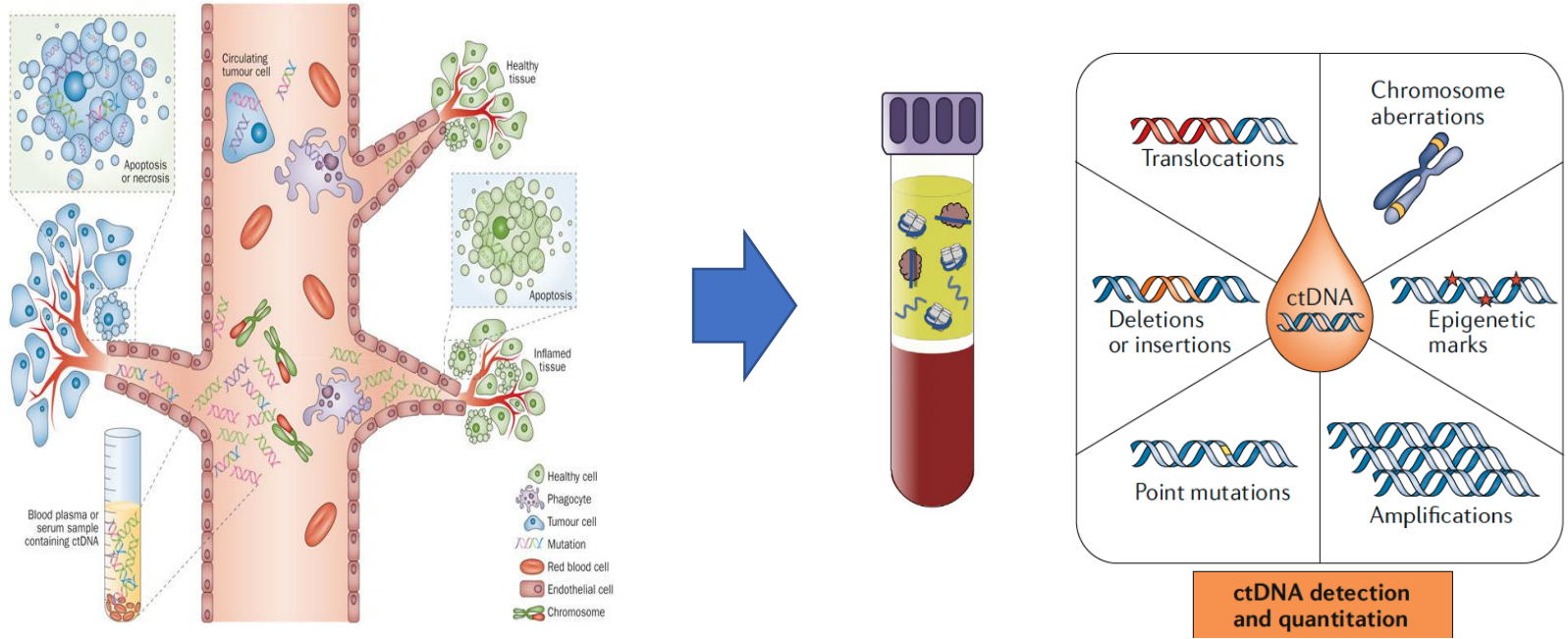
C, cycle; CR, complete response; MRD-neg, measurable residual disease-negative; ORR, overall response rate; TP53m, TP53 mutation.

TrAVeRse



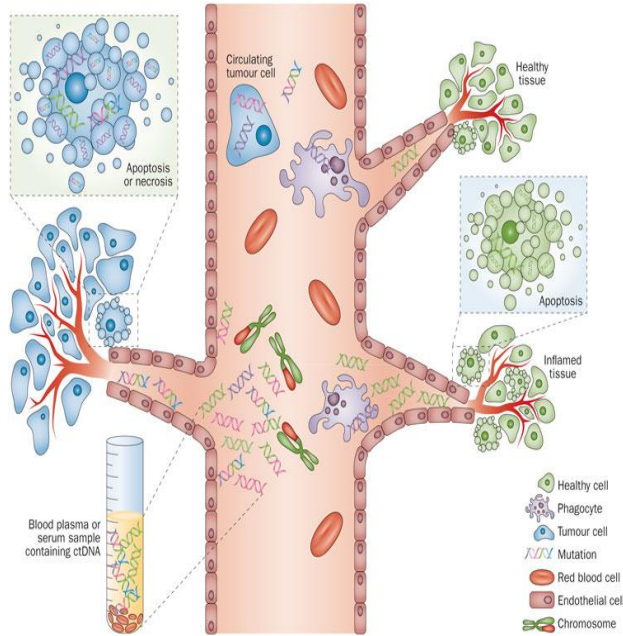
➤ MRD in other compartments?

Analysis of cfDNA: the „Liquid Biopsy“ concept



Crowley, Nat Rev Clin Oncol. 2013

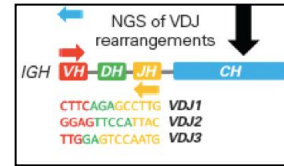
Analysis of cfDNA: the „Liquid Biopsy“ concept



Crowley, Nat Rev Clin Oncol. 2013

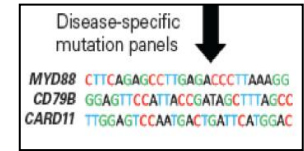
MRD Methoden

NGS



IG rearrangements

Sensitivity 10⁻⁰⁴



Capture Mutation panels

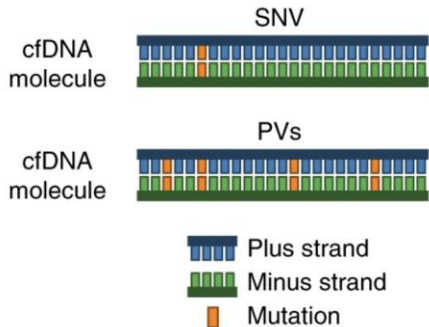
Sensitivity 10⁻⁰⁵
10⁻⁰⁶

Capture based sequencing of ctDNA

Phased variants

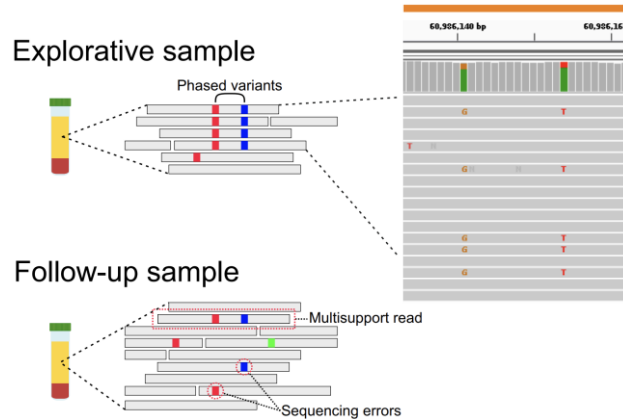


Enhanced detection of minimal residual disease by targeted sequencing of phased variants in circulating tumor DNA



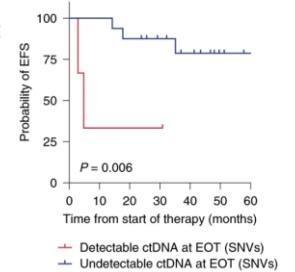
Kurtz et al. 2021

Phased variant patterns for error rate adjustment

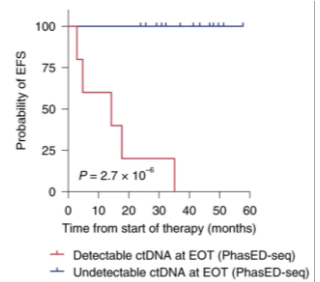


Meriranta et al. 2022

SNVs only:



Phased variants:

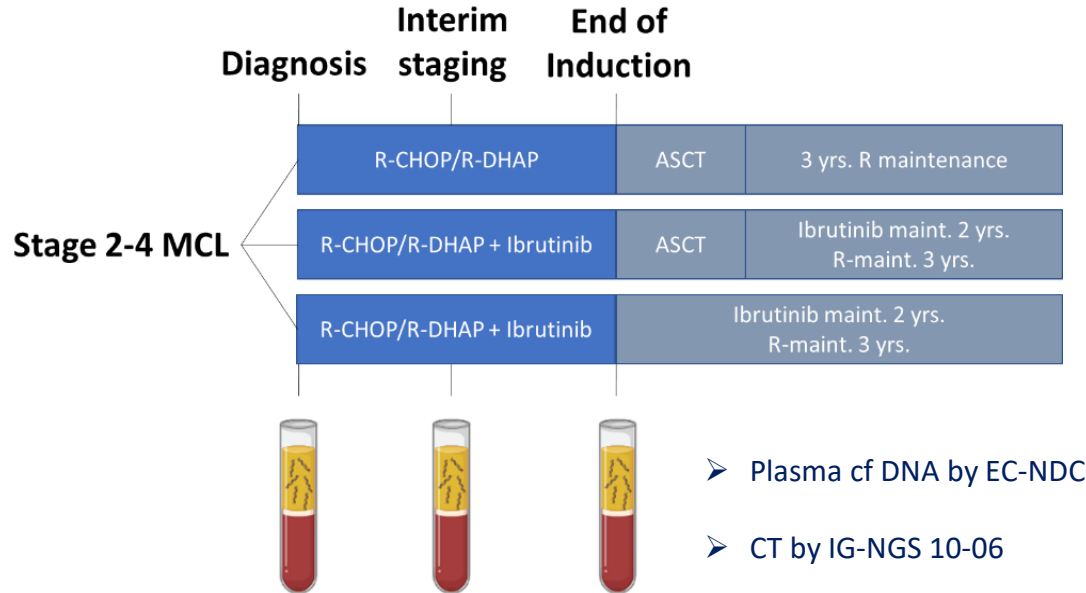


Limited to 2-5% of variants

Kurtz et al. 2021

Additional benefit for MRD using cfDNA in MCL?

Exploratory study from the TRIANGLE trial (Autologous SCT after Ibrutinib/R-CHOP in 1L MCL)



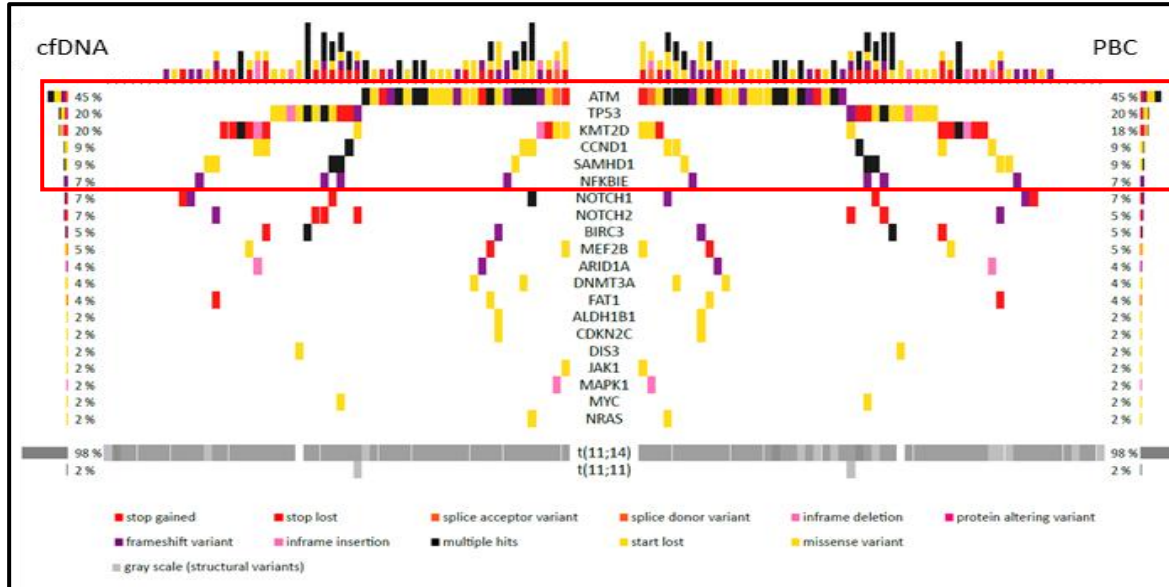
Objectives:

- Explore the suitability of cfDNA for genotyping
- Assess the prognostic impact of ctDNA for MRD

Tumor genotyping from cfDNA and CTC in patients with MCL

Concordance between CTC and cfDNA

High concordant genotyping in CTC and cfDNA by EC-NDC



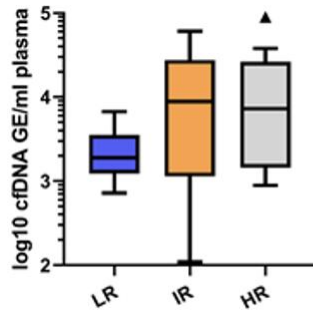
- 100% concordance of IG clonotypes identified in CTC and cfDNA
- Identification of a CCND1::IGH gene fusion in 56/57 cases
- Identification of ~6 MRD target/patient in each compartment (range 2-10)

Circulating tumor DNA in MCL

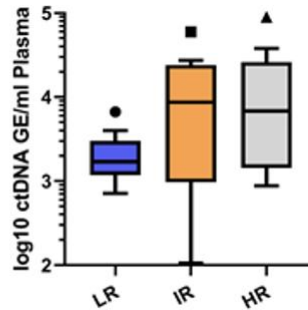
Prognostic value of cfDNA and ctDNA at diagnosis

MIPI:
Age
performance status
LDH
leukocyte count

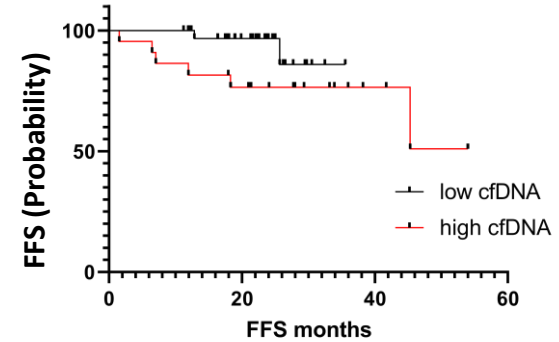
Correlation of cfDNA levels at diagnosis with MIPI scoring



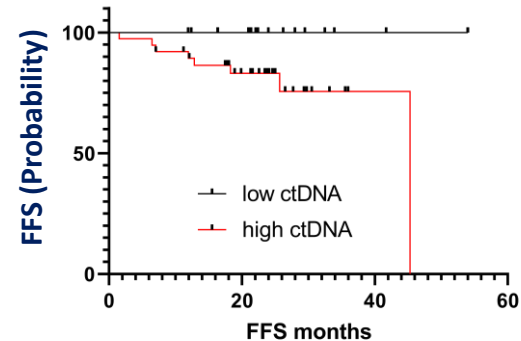
Correlation of ctDNA levels at diagnosis with MIPI scoring



- Baseline cfDNA and ctDNA levels correlate with clinical prognostic factors and predict patient outcome



High cfDNA: ≥ 50 ng/ml plasma

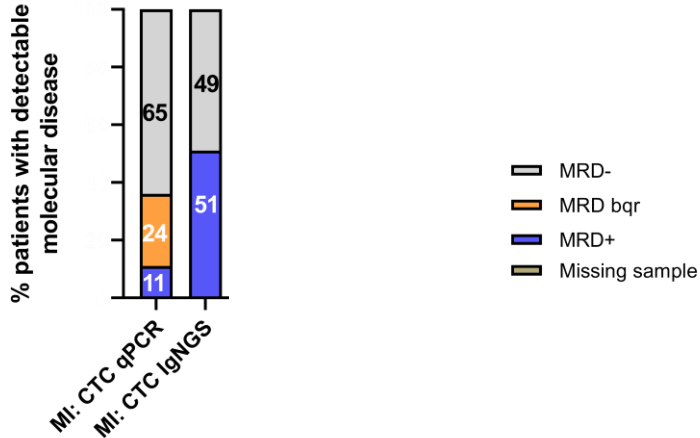


High ctDNA: $\geq 40\%$ infiltration

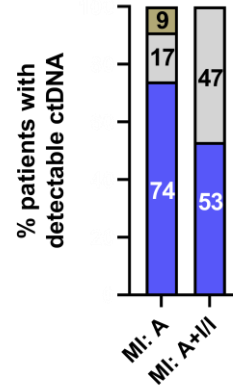
MRD assessment in CTC and cfDNA

More frequent disease clearance under Ibrutinib induction

MRD status in CTC vs cfDNA



MRD status in cfDNA by treatment arm



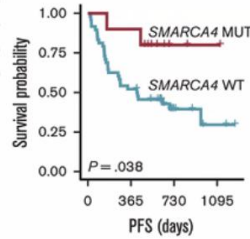
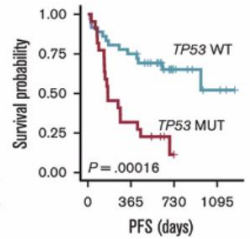
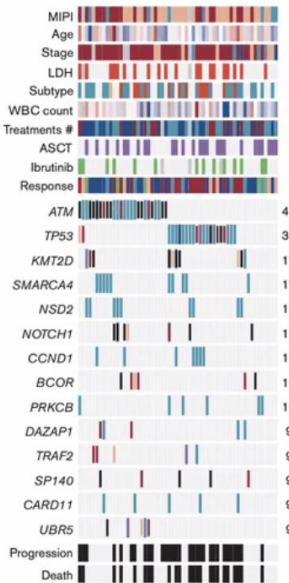
- Higher frequency of MRD positivity in ctDNA at MI and EoI

ctDNA for genotyping and MRD in the VALERIA trial in r/rMCL

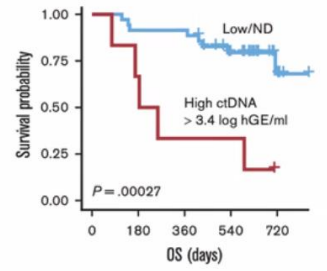
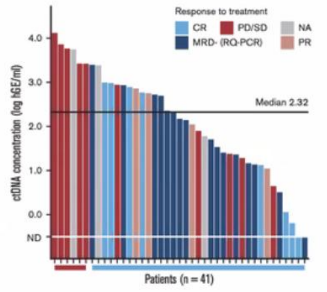
VEN-R2: Venetoclax + Lenalidomide + Rituximab therapy



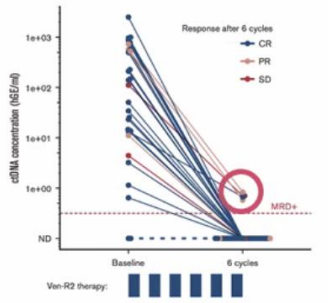
Genotyping



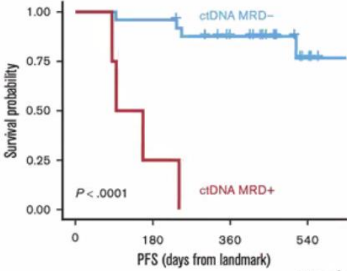
ctDNA quantification



ctDNA MRD



ALL RQ-PCR negative!



Meriranta et al. 2025



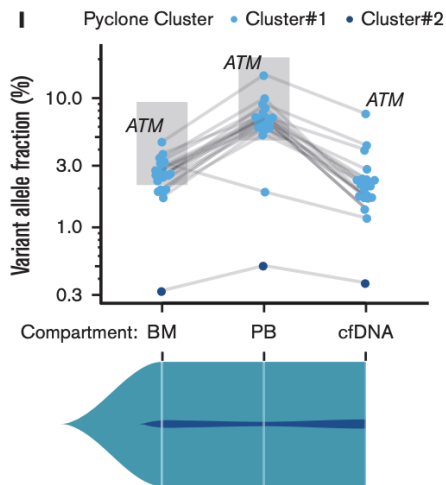
HUS & HELSINGIN YLIOPISTO YHTEISTYÖSSÄ
HUS & HELSINGFORS UNIVERSITET I SAMARBETE
A COLLABORATION BETWEEN HUS & UNIVERSITY OF HELSINKI

Esittäjä

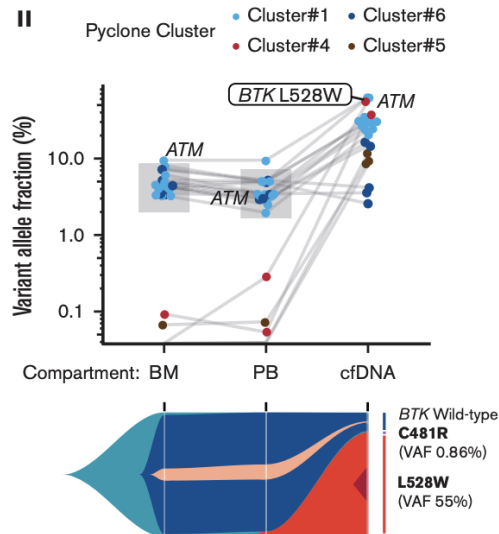
Spatial heterogeneity and clonal hematopoiesis

Suitability to measure clonal evolution

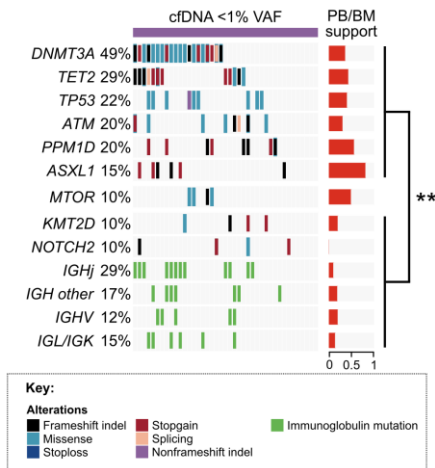
Variable concordance between ctDNA and PB/BM



Subclonal *BTK* resistance mutations in the cfDNA only

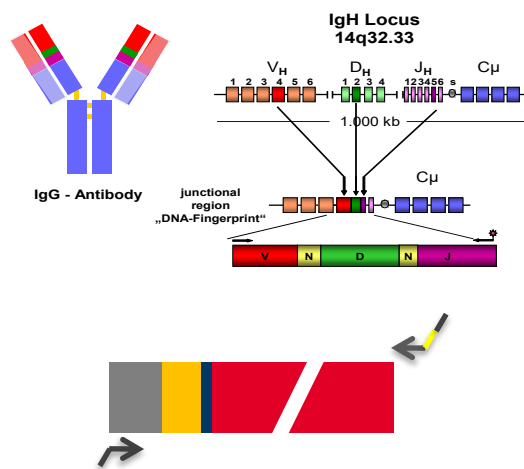


cfDNA compartment has rich clonal hematopoiesis



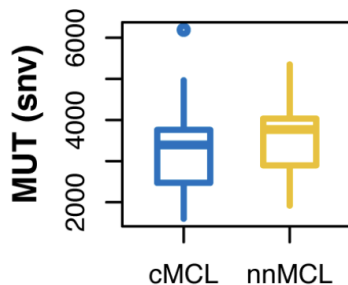
Limitations to MCL ctDNA analysis

Clonotype detection insensitive:
fragmented, low DNA input



Low mutation rate limits use of
off-the-shelf panels

1.2 mut / Mb

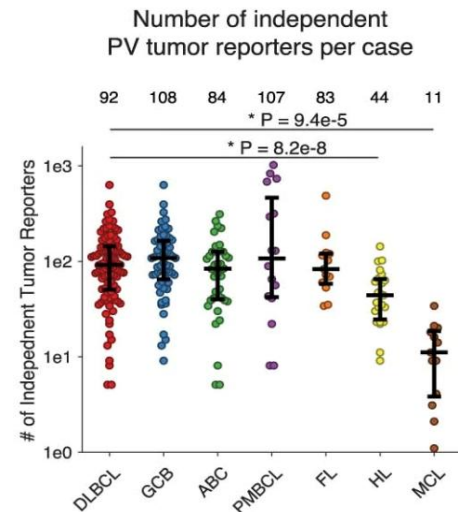


Median (Range)

Total = 3445 (1599–6192)
cMCL = 3394 (1599–6192)
nnMCL = 3768 (1920–5350)
 $p = 0.201$

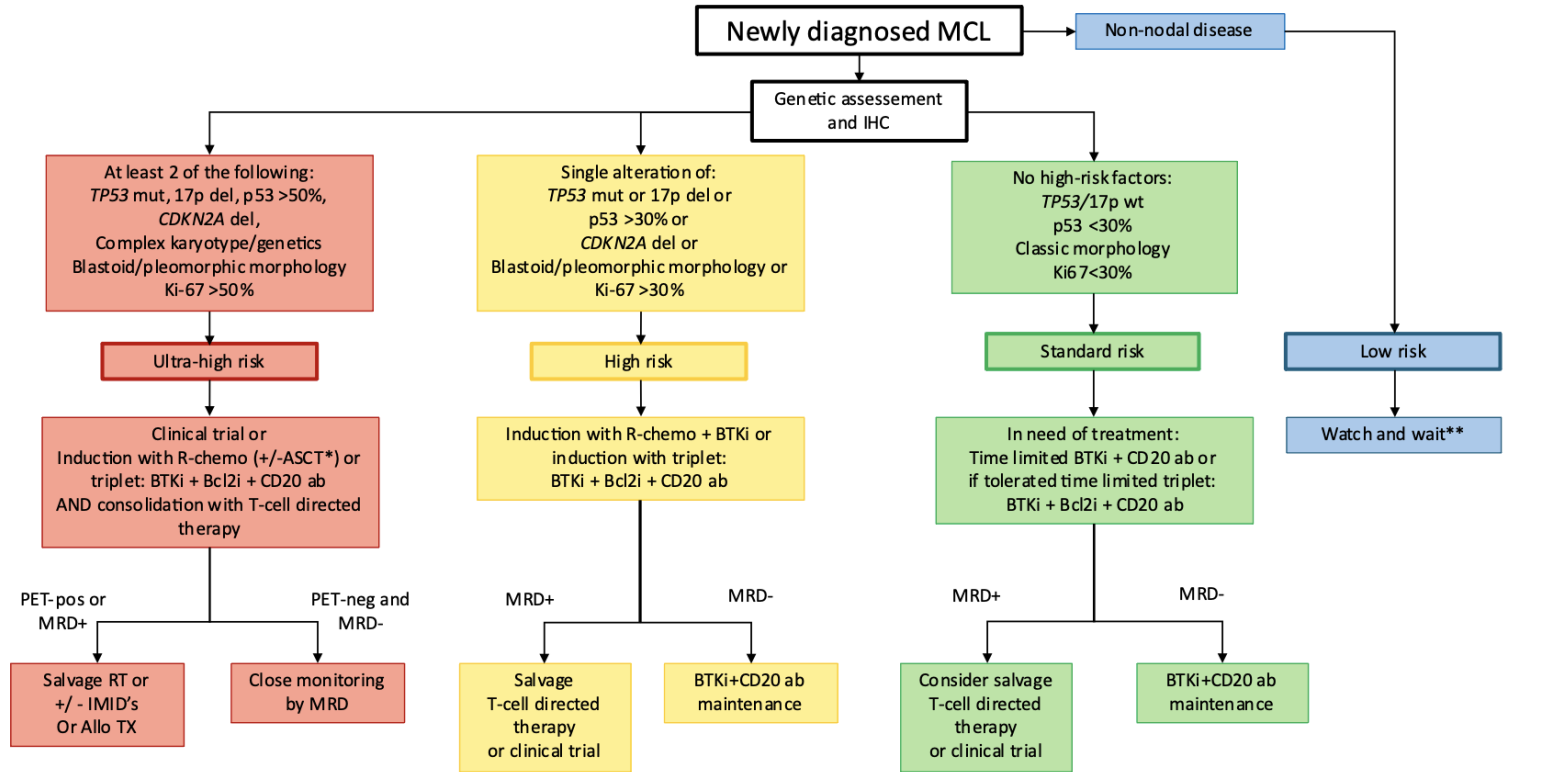
Nadeu et al. 2020

Lack of phased variants for
detection



Kurtz et al. 2021

Future approaches for treatment in MCL



* Highly proliferative Ki67>50% or blastoid might need ASCT
 ** Consider treatment for indolent disease with symptoms, high WBC, or MIPI high

Thank you very much



Kiel Team

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Peter James Stewart



Eva Hoster

Martin Dreyling



Hämatologie
Labor Kiel