Use of circulating tumor DNA to genotype aggressive lymphoma

Davide Rossi, M.D., Ph.D.

Hematology
IOSI - Oncology Institute of Southern Switzerland
IOR - Institute of Oncology Research
USI – Universita' della Svizzera Italiana
Bellinzona - Switzerland

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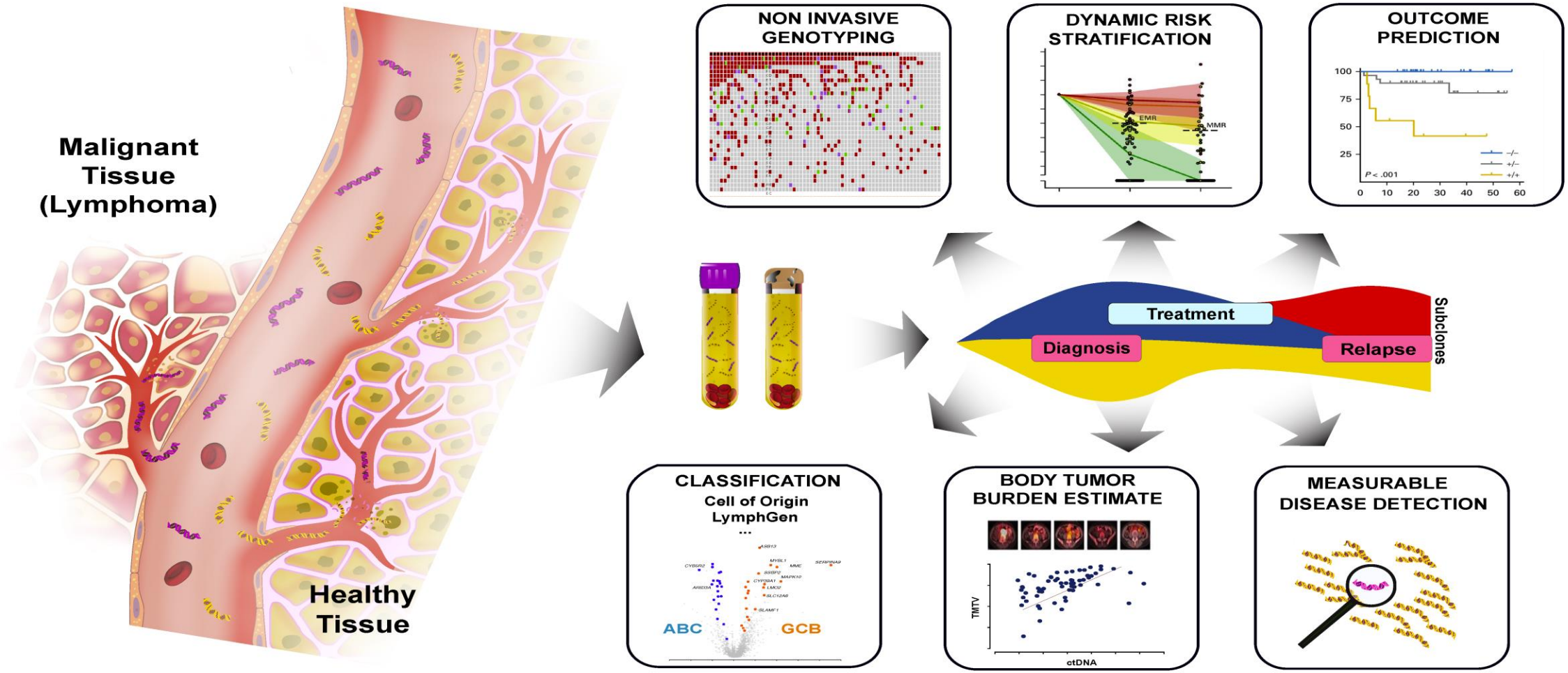
AstraZeneca	X					X	
BeiGene	X					X	
BMS						X	
Janssen	X					X	
MSD	X						

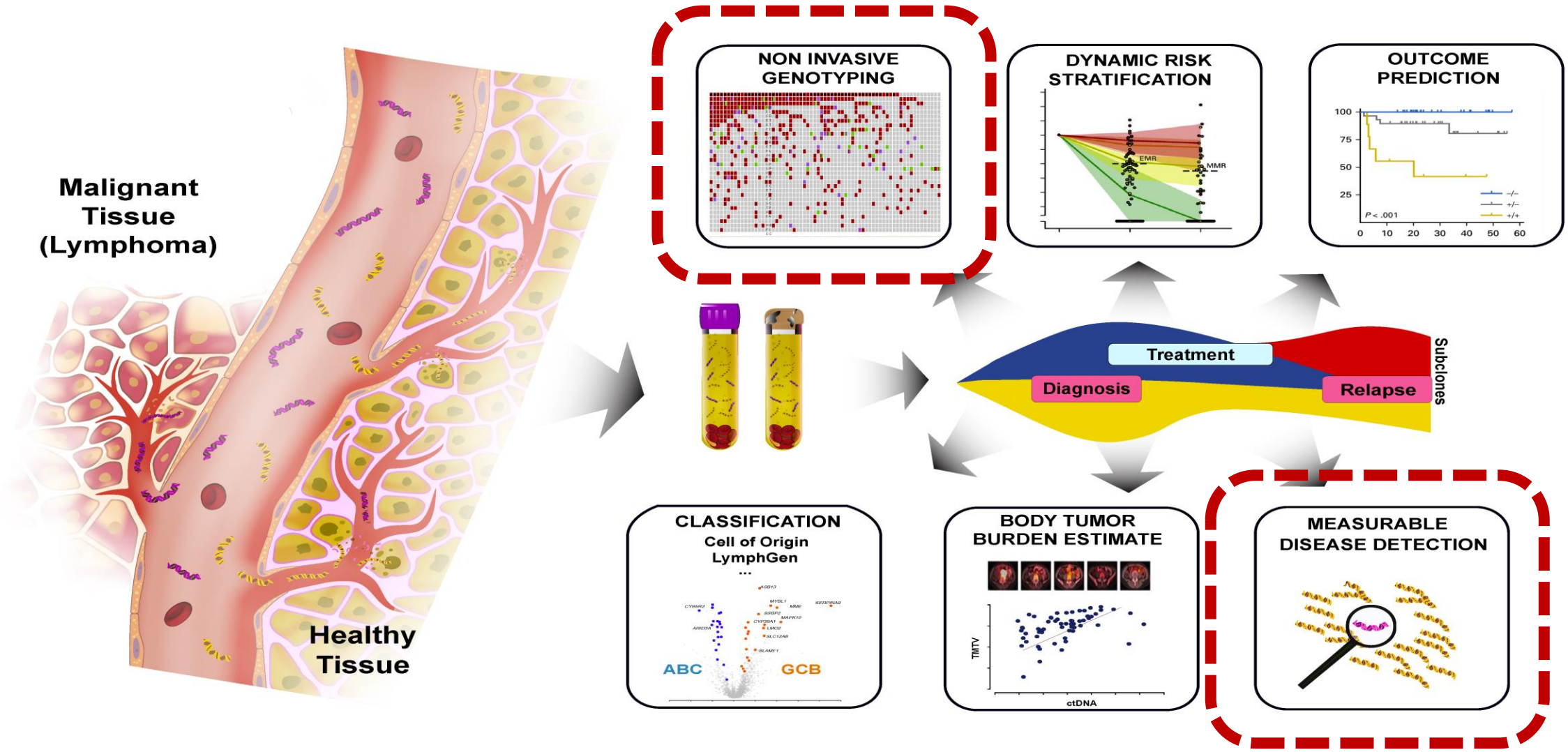
Background

Cell free DNA (cfDNA) - Circulating tumor DNA (ctDNA)



De Level L, Blood 2022

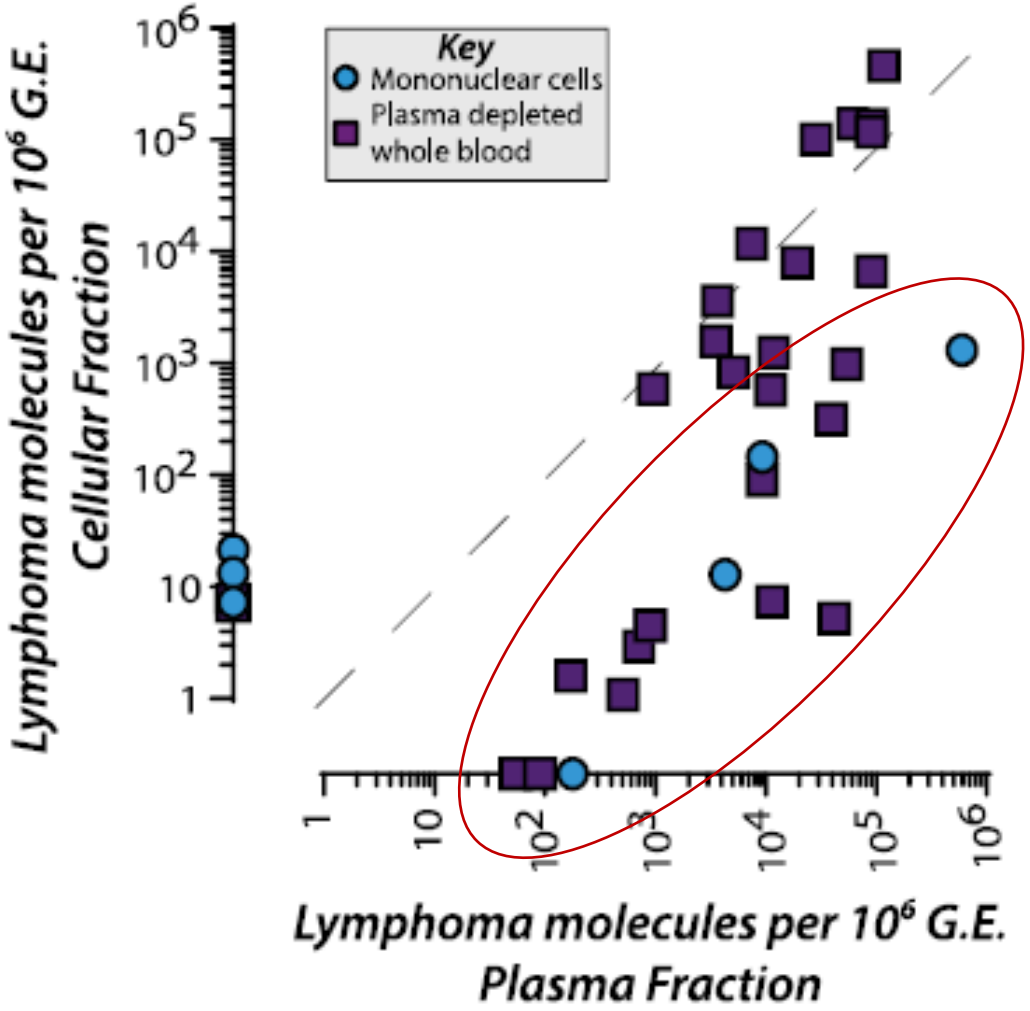
Cell free DNA (cfDNA) - Circulating tumor DNA (ctDNA)



De Level L, Blood 2022

Why and how assessing ctDNA in DLBCL?

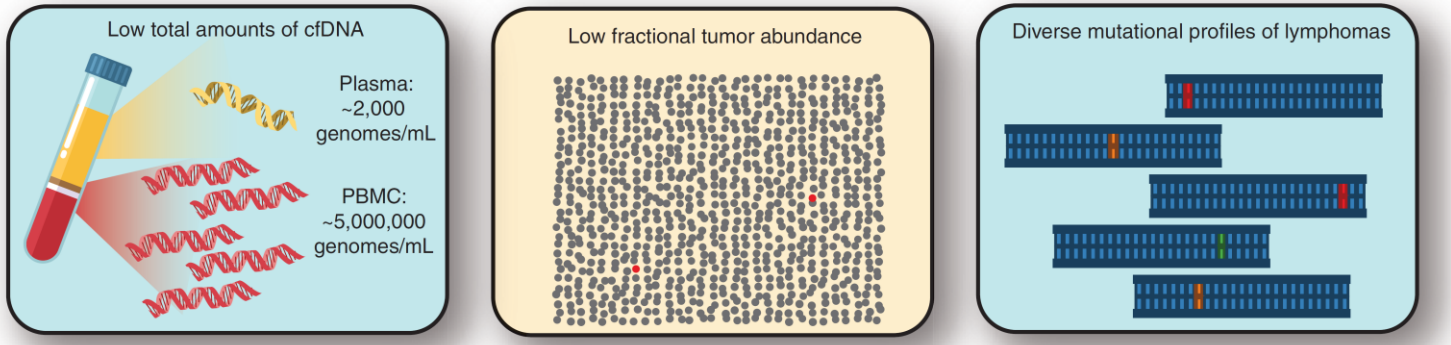
Lymphoma DNA is 150-fold more abundant in plasma than PBMC



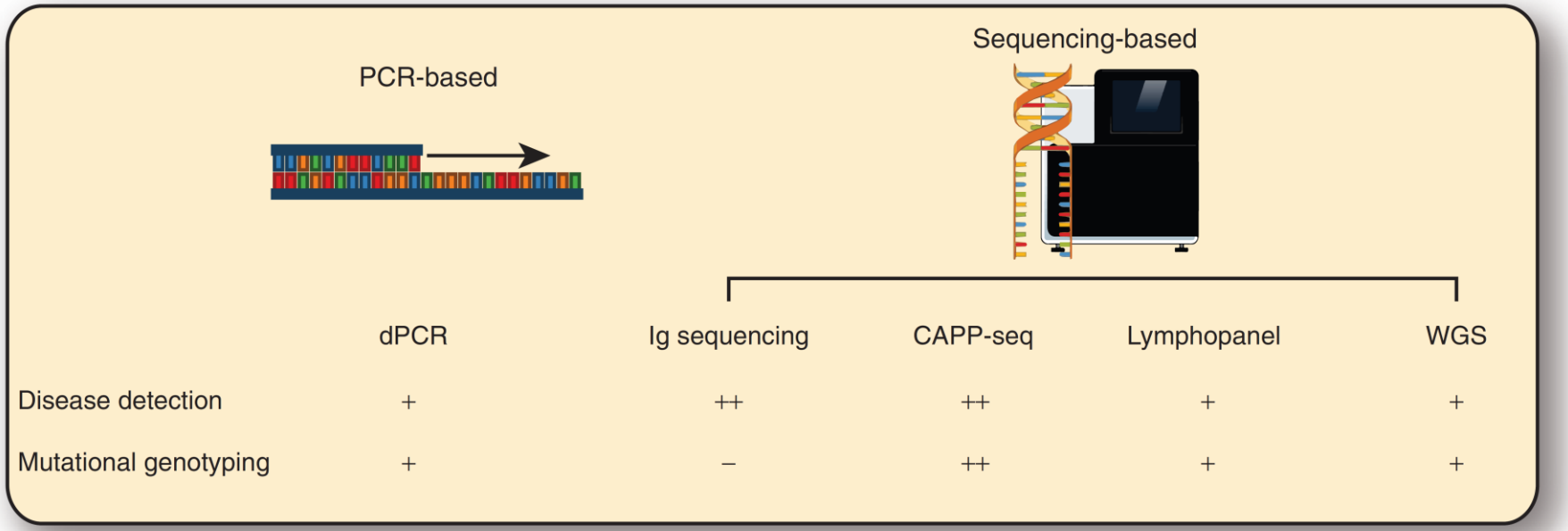
Kurtz DM et al. Blood, 2015
Herrera AF et al. Br J Haematol 2016

ctDNA detection in lymphomas across common methodologies

Challenges for ctDNA in lymphomas



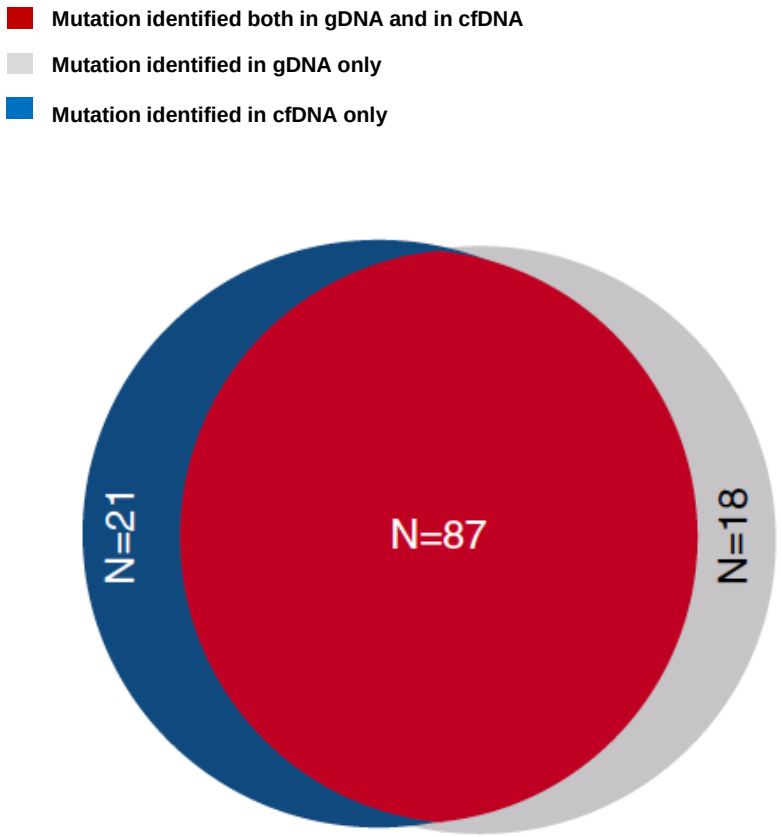
ctDNA methodologies applied to lymphomas

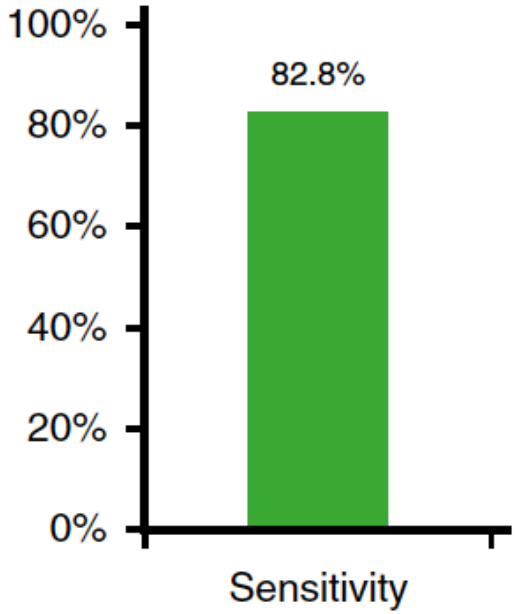


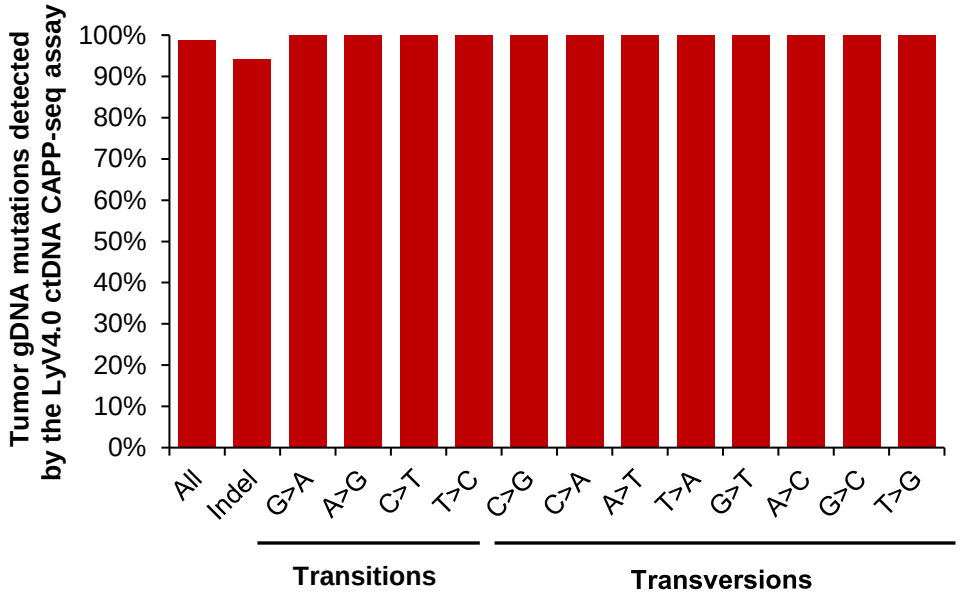
Roschewski M, et al. Blood Cancer Discov. 2022

Identification of genetic lesions

Diagnostic performance of DLBCL mutation profiling on ctDNA

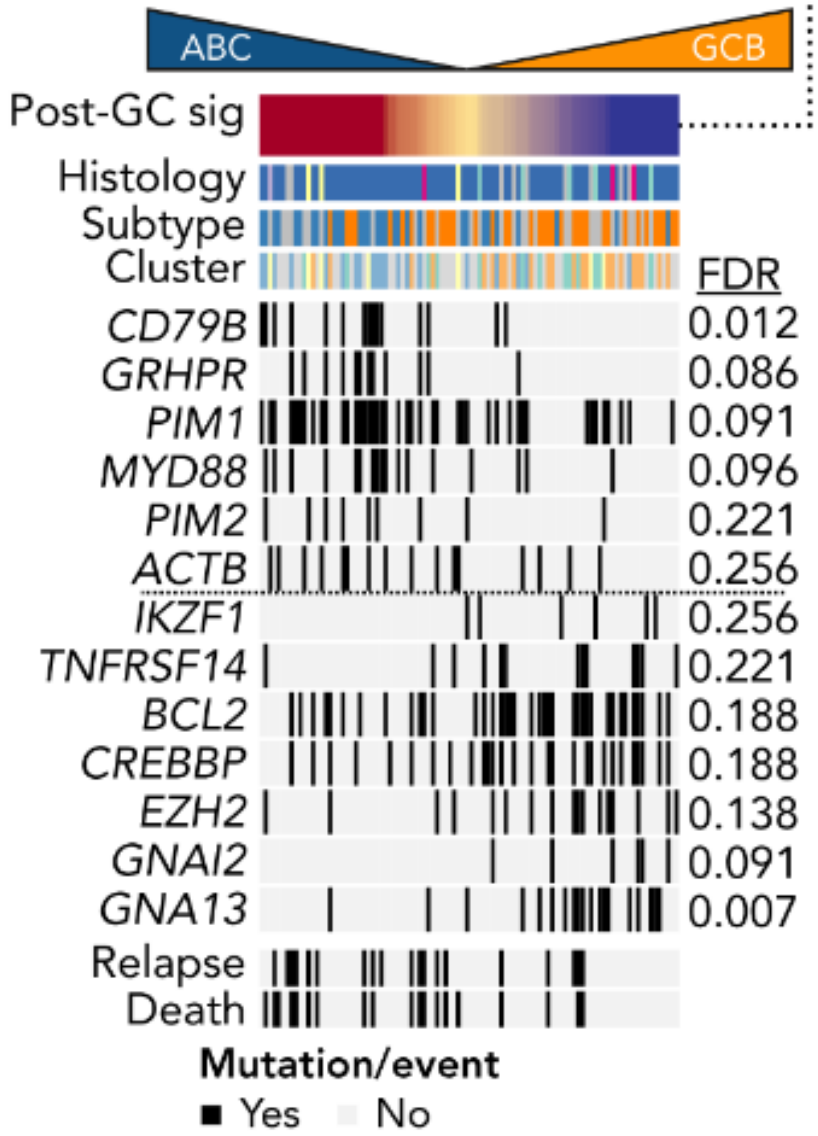






Scherer F, Sci Transl Med. 2016
Rossi D, *Blood.* 2017
Bruscaggin A, at al. Blood Adv. 2021
Meriranta L, Blood. 2022

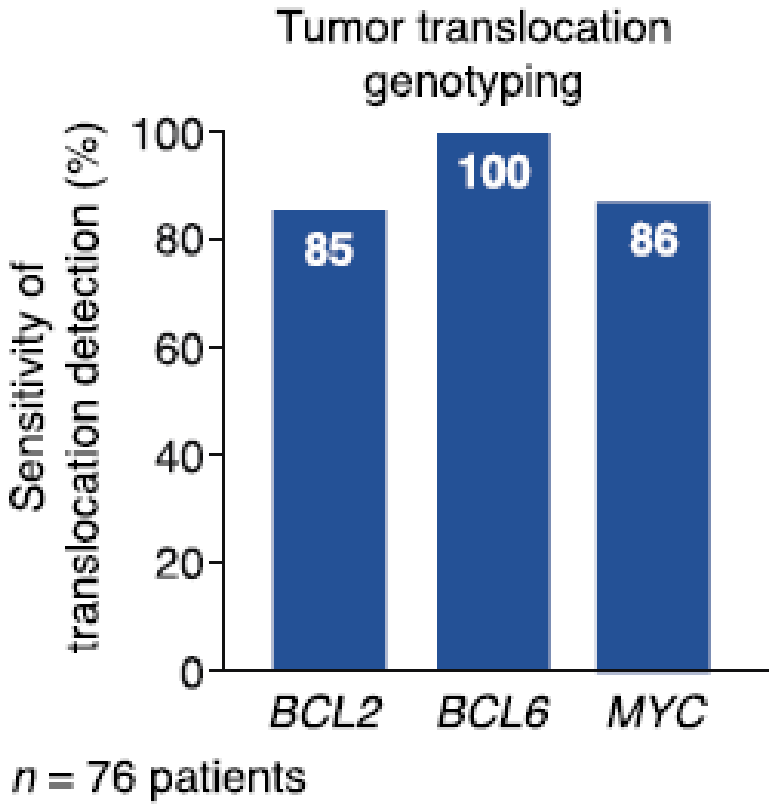
DLBCL subtype identification by mutation analysis of ctDNA



Meriranta L, et al, Blood 2022

Identification of SV by using CAPP-seq

BN2/C1 subtype includes BCL6 translocation among biomarkers
EZB/C3 subtype includes BCL2 translocation among biomarkers
EZB-MYC subtype includes BCL2 and MYC translocations among biomarkers

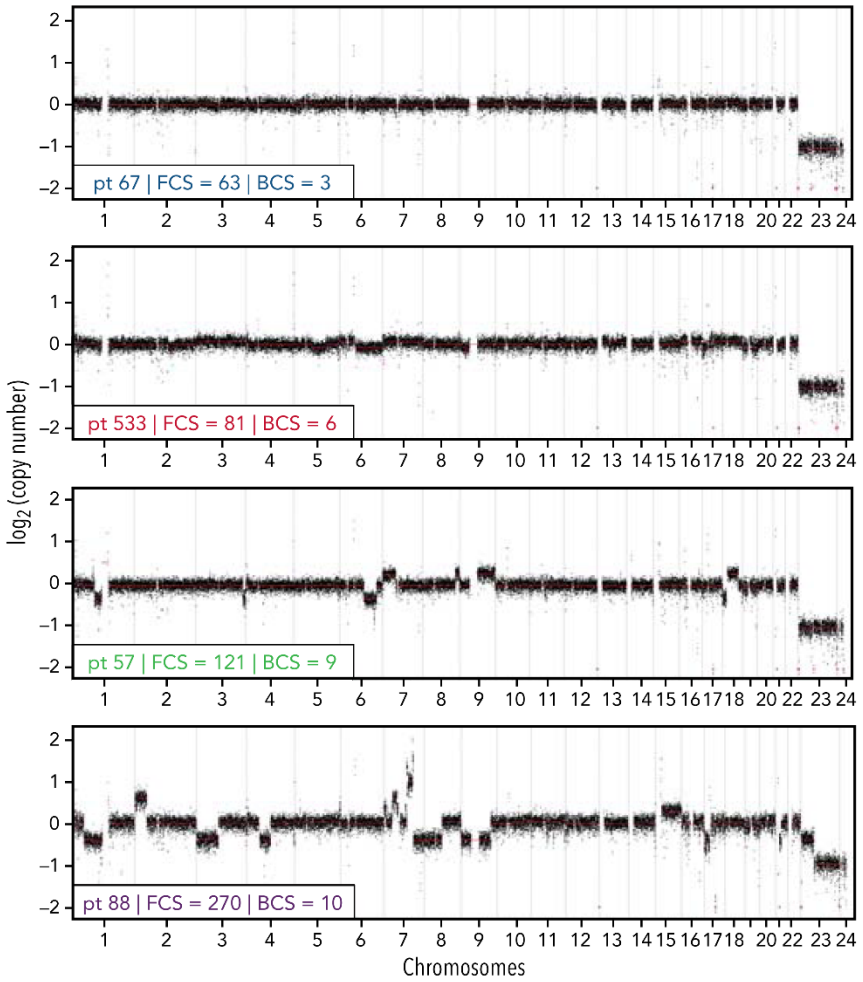


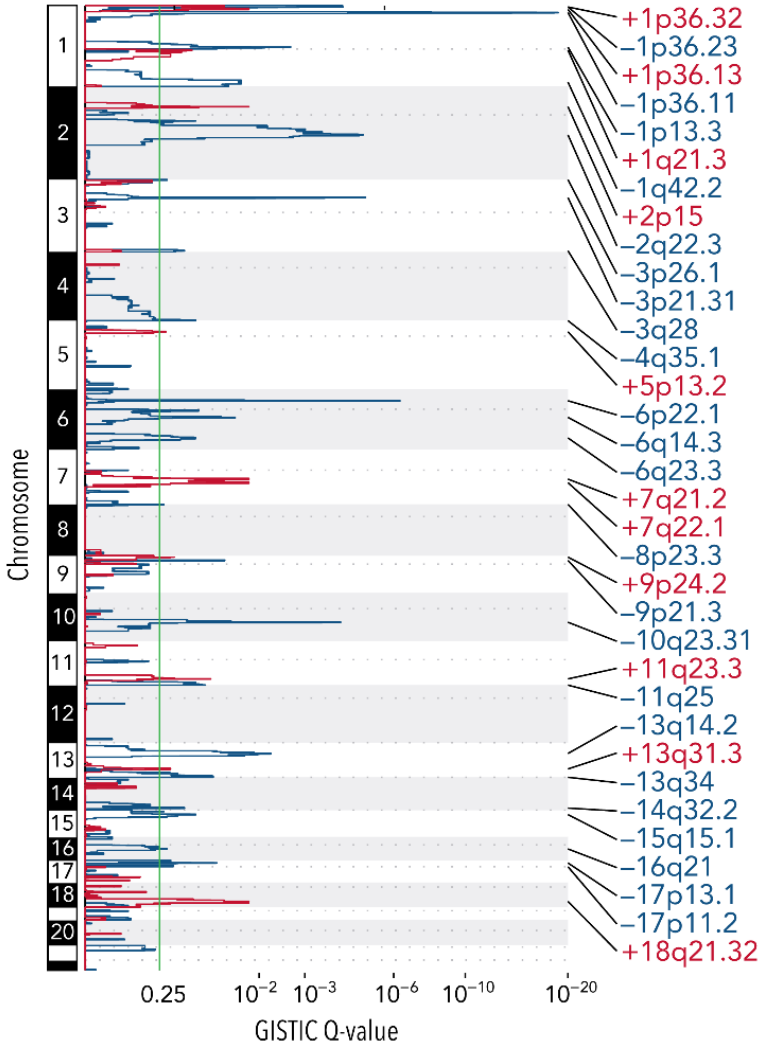
BCL2/IGH breakpoint coverage: 70%
BCL6 breakpoint translocation coverage: 85%
MYC breakpoint coverages: 90%

Scherer F, Sci Transl Med. 2016

Identification of tumor copy number abnormalities by using low pass WGS

A53/C2 subtype includes multiple CNA among biomarkers

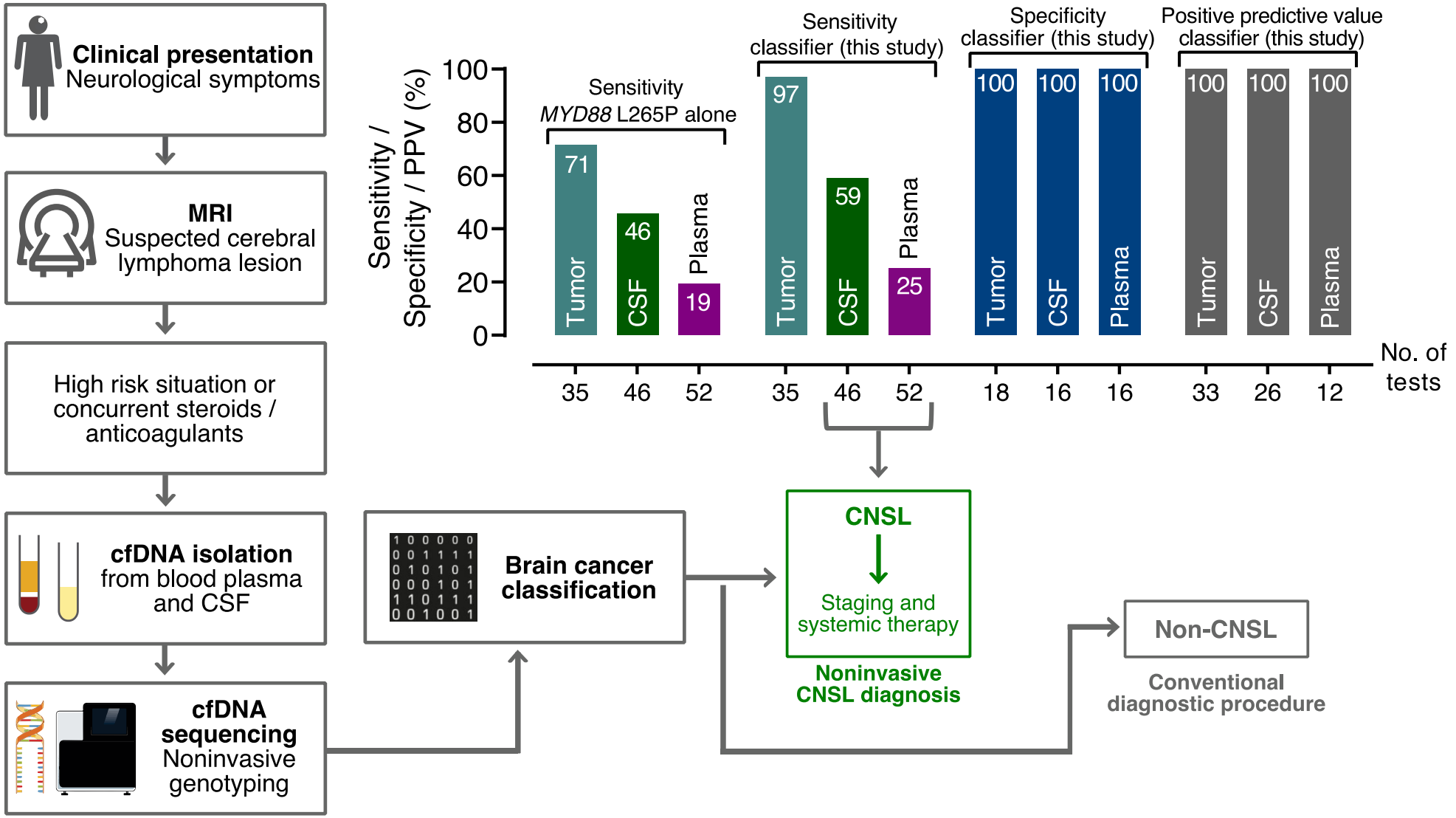




Cherng HJ, et al. Blood 2022

Clinical applications in LBCL: diagnosis

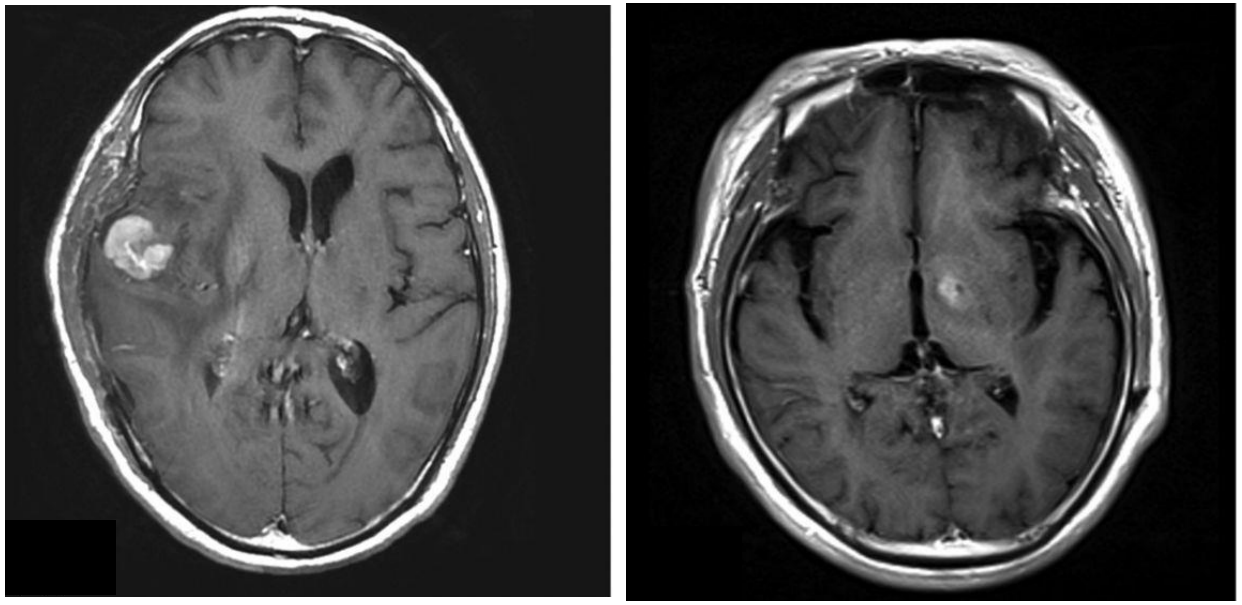
Biopsy-free CNSL classification



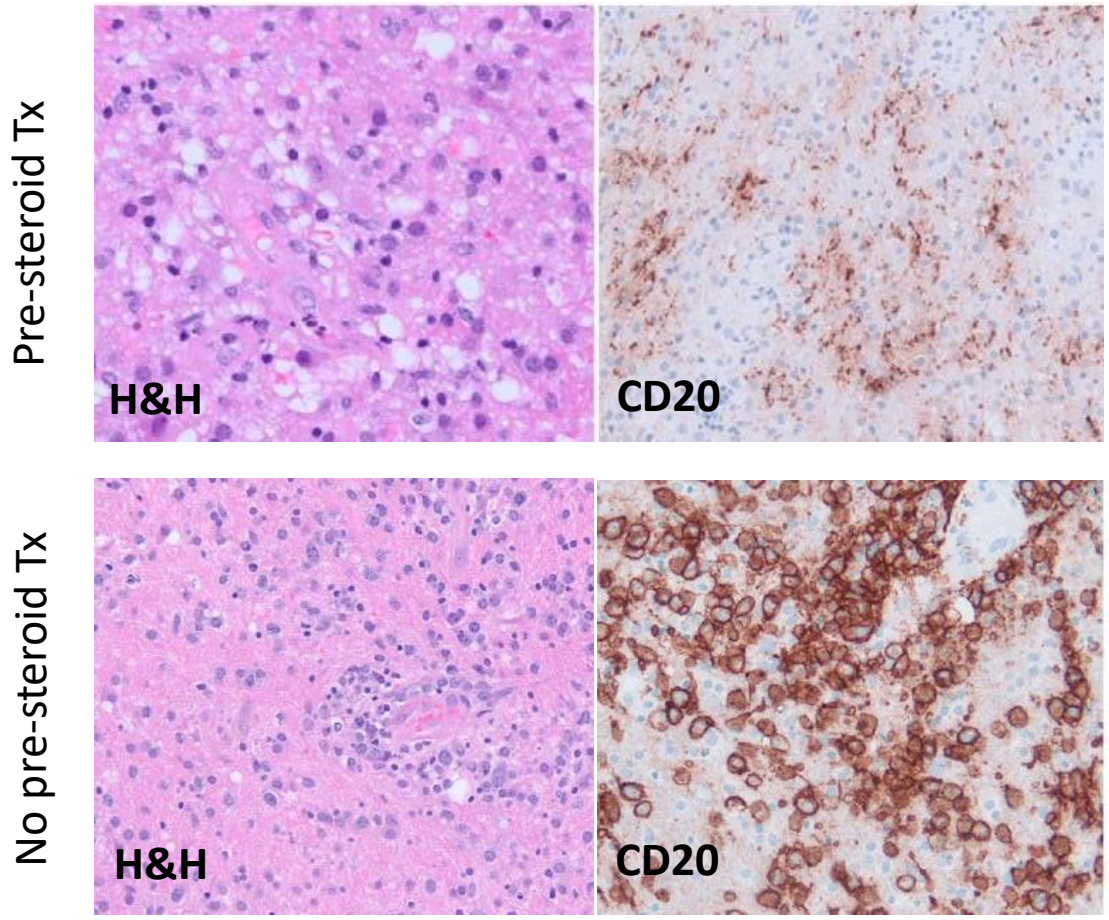
Mutter JA*, Alig S* et al., ASH Plenary Session, 2021

Diagnostic challenges of PCNSL

Accessibility of the lesion



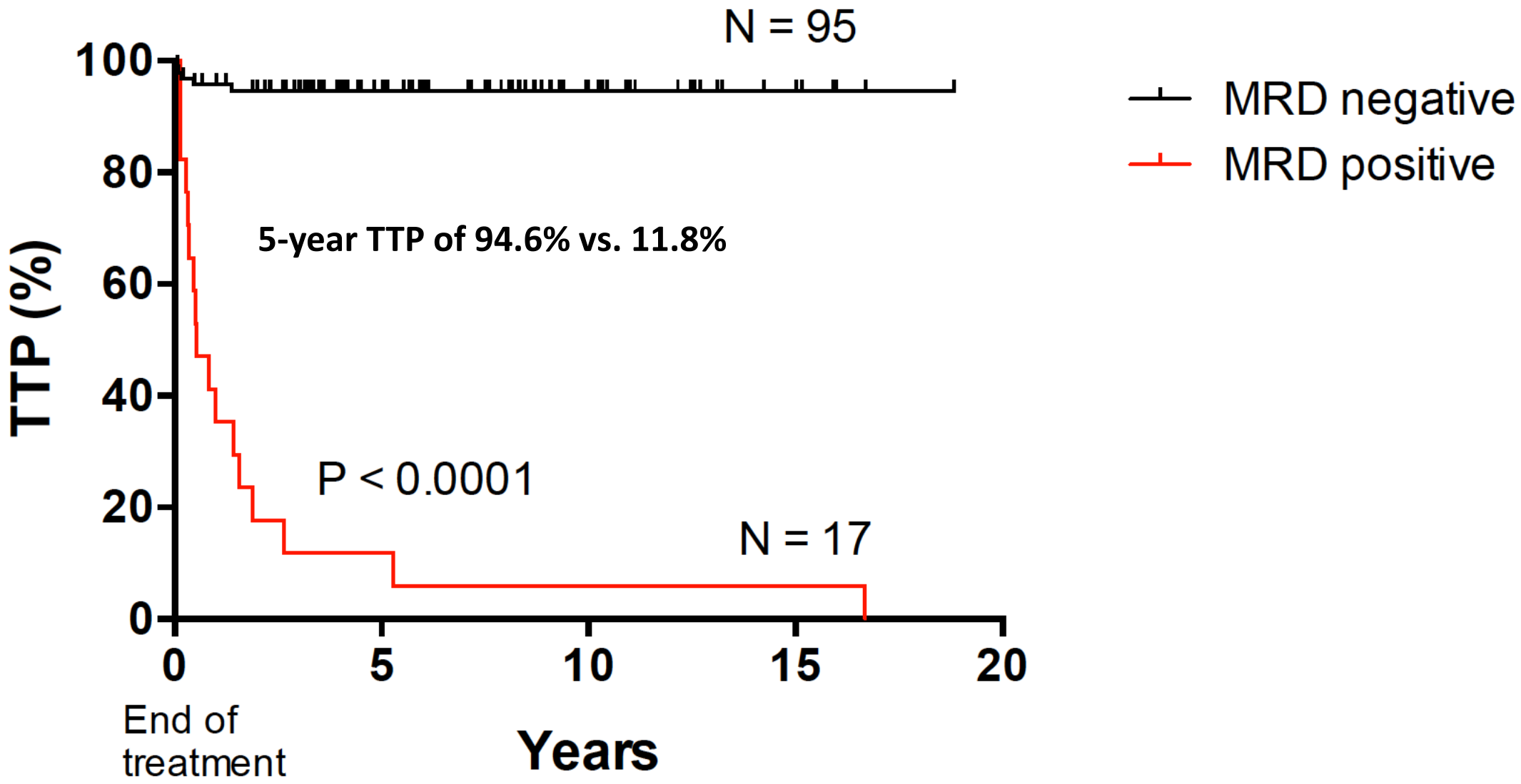
PCNSL vanishing after steroid pre-treatment



Abrey LE, J Clin Oncol. 2005.

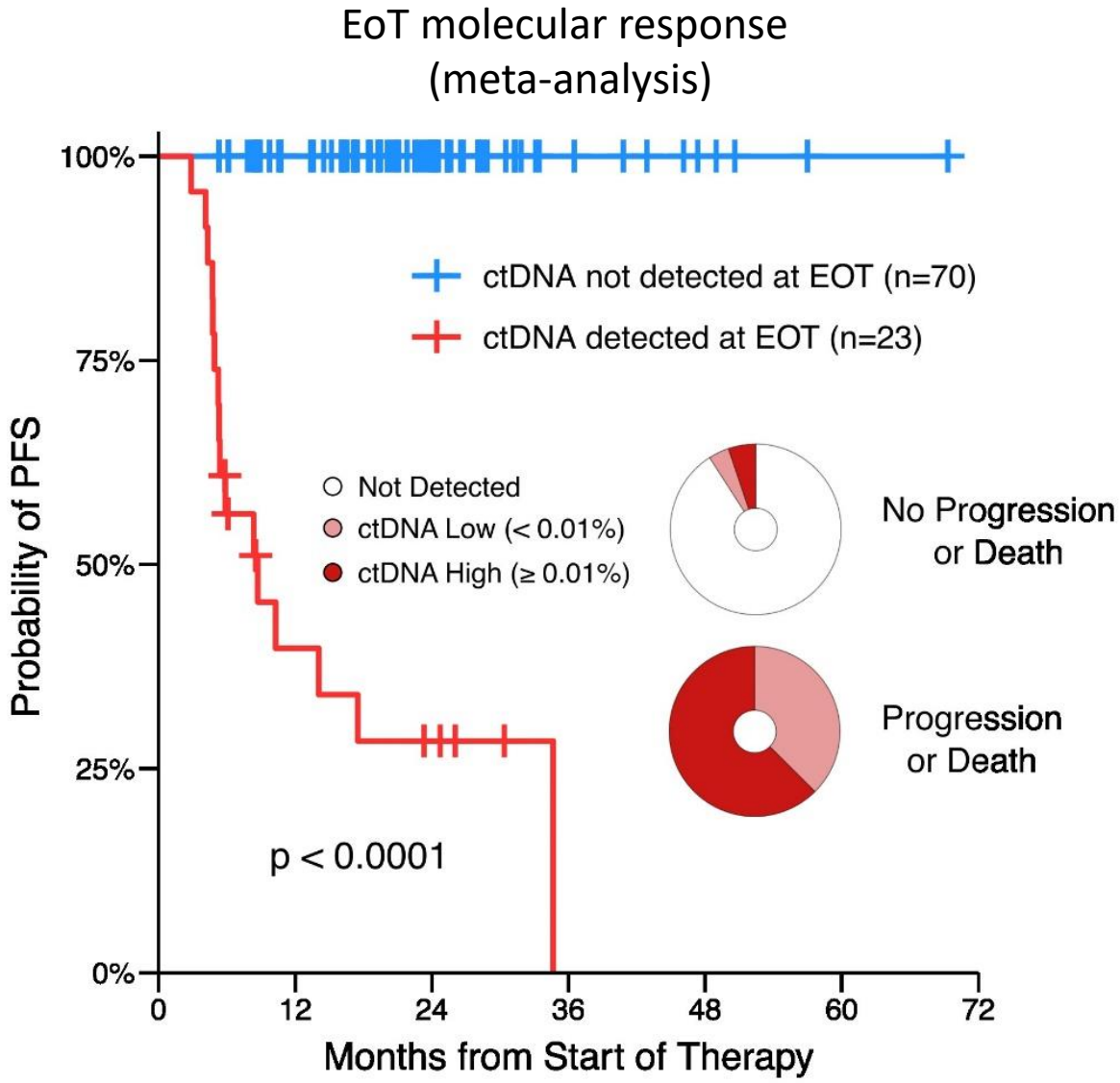
Clinical applications in LBCL: monitoring

Surveillance MRD at EoT predicts progression



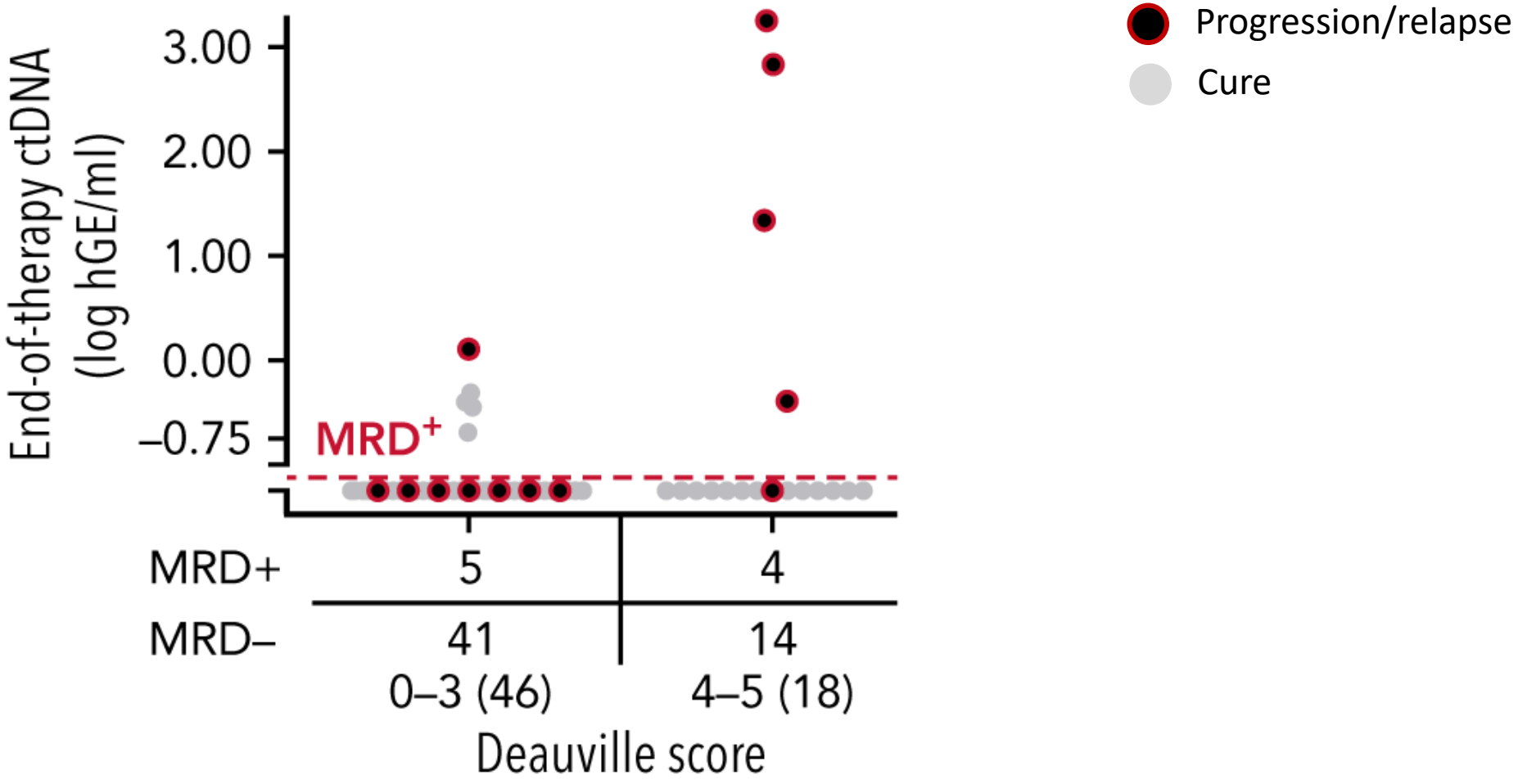
Roschewski MR et al. *Lancet Oncology*. 2015.

Validation of EoT molecular response as DLBCL biomarker



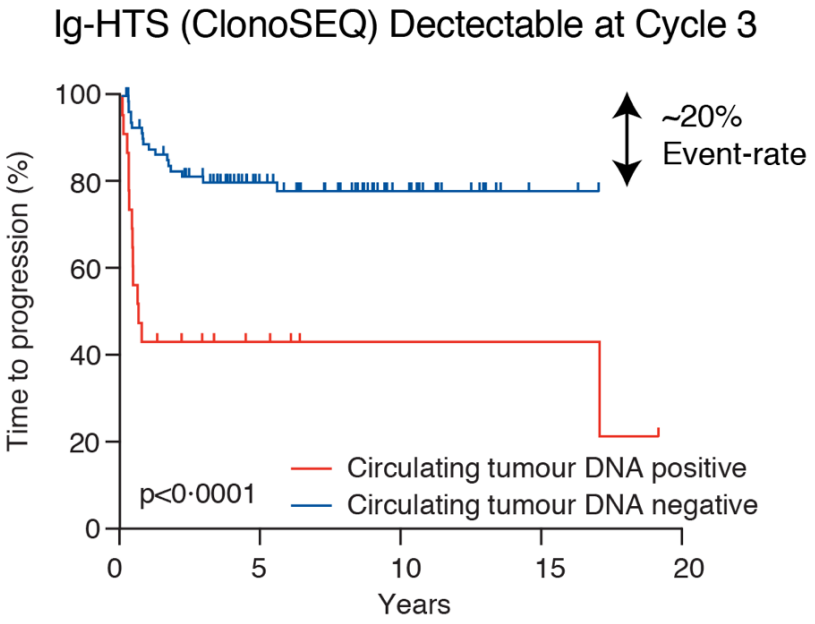
Roschewski M, ASH 2022: 322

MRD after therapy identify false positive PET/CT

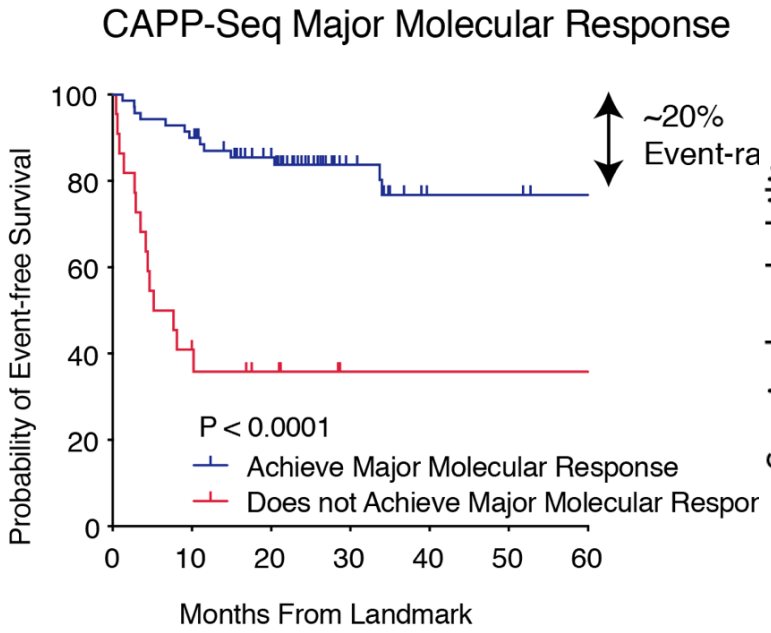


Meriranta L, Blood. 2022 Mar 24;139(12):1863-1877

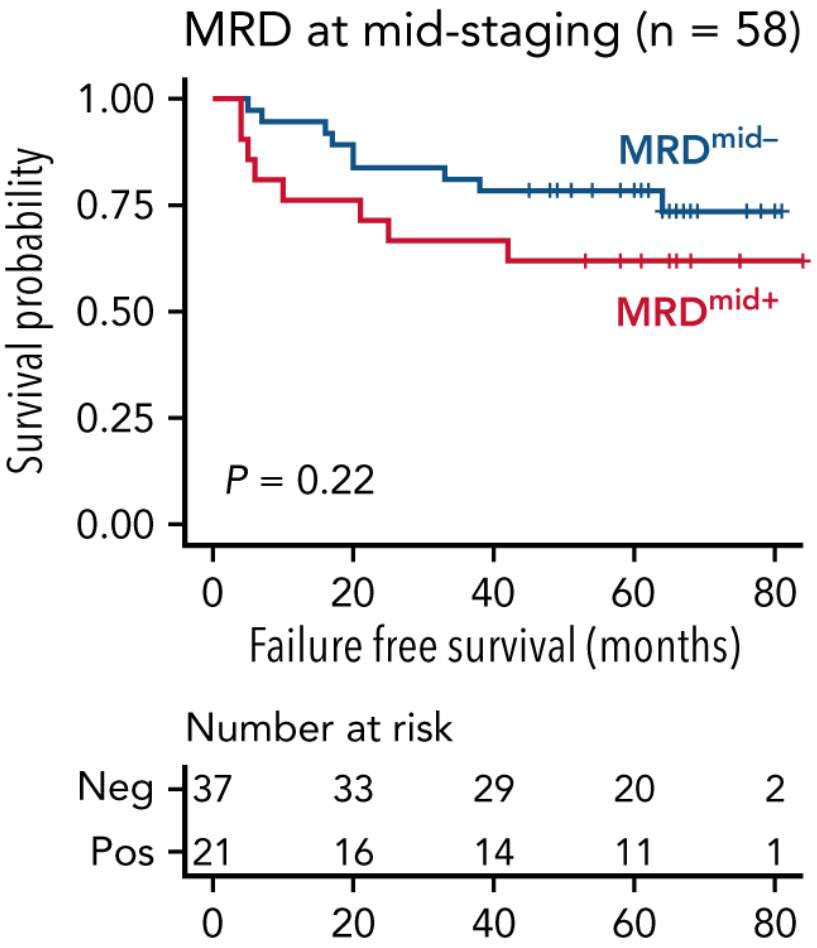
Surveillance MRD at the interim timepoint predicts progression



Roschewski MR et al. *Lancet Oncology*. 2015.



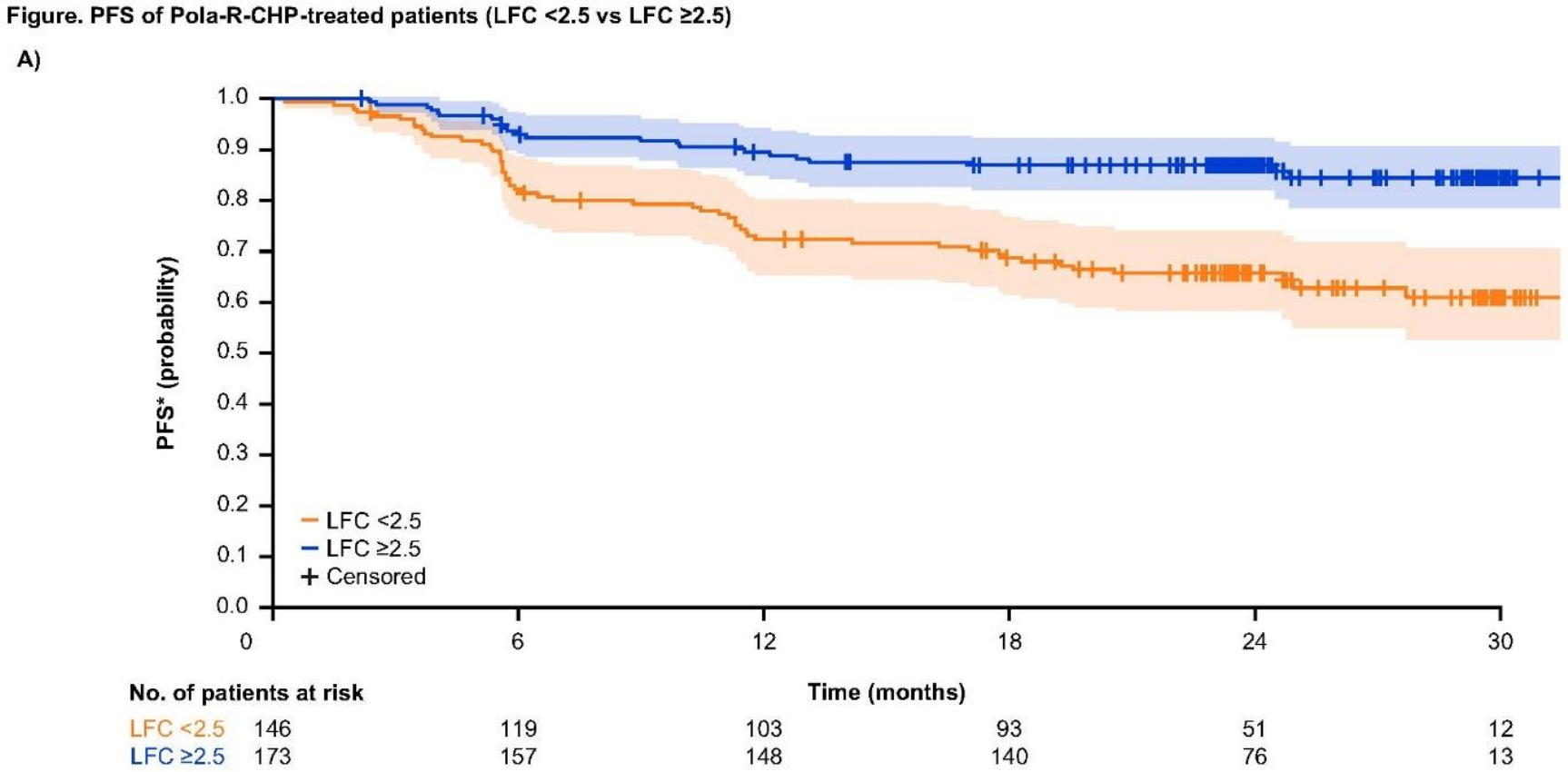
Kurtz et al, *JCO.* 2018



Meriranta L, *Blood*. 2022

Validation of interim molecular response as DLBCL biomarker

Interim molecular response
(POLARIX trial)

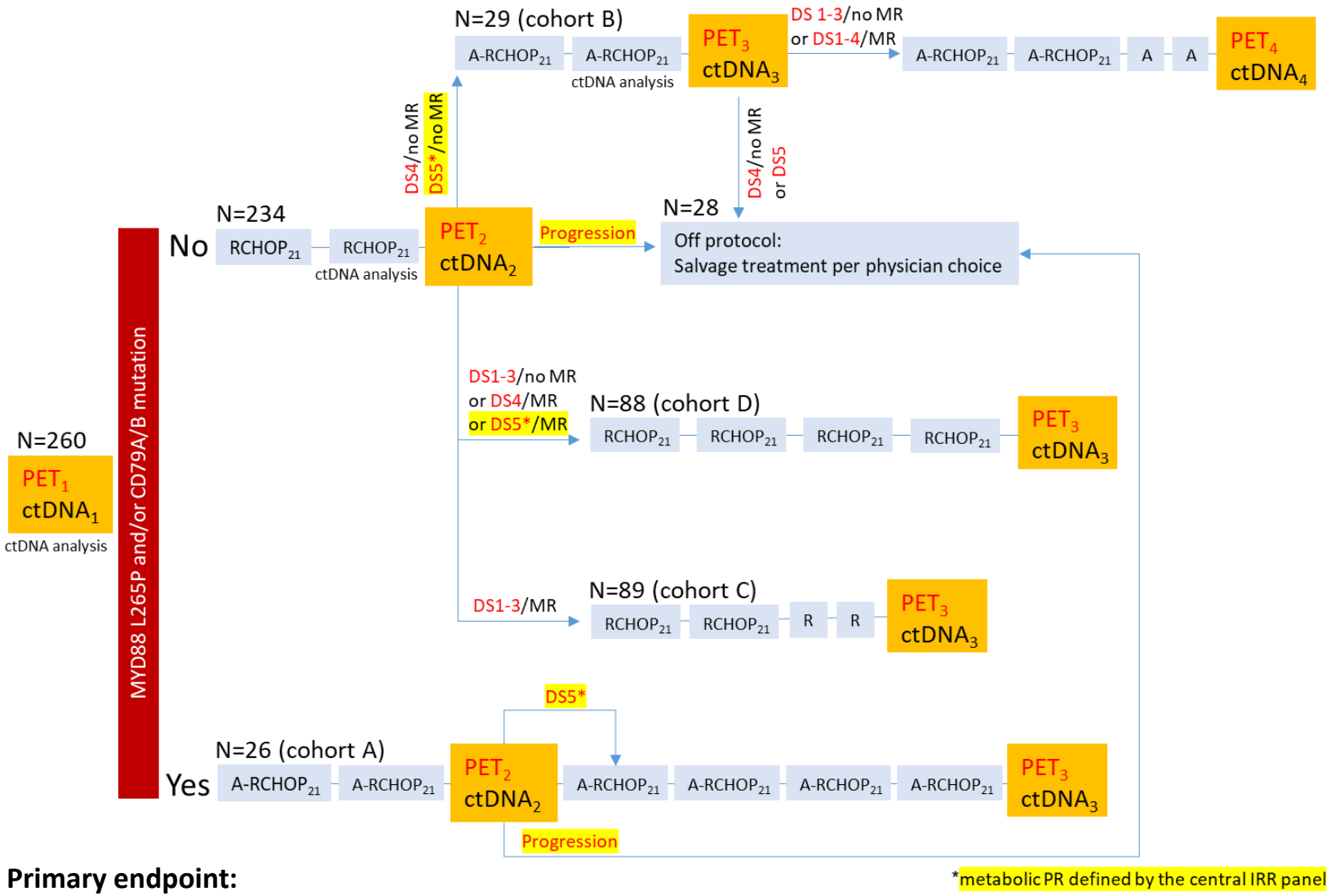


Herrera AF, ASH 2022: 542

Summary

- Baseline ctDNA in CSF aids in the diagnosis of PCNSL
- Baseline ctDNA profile can capture genetic subtypes of DLBCL, but accuracy should be improved
- EOT MRD measured by ctDNA corrects false positive EOT PET/CT
- Interim MRD measured by ctDNA needs further studies (best time-point, assay sensitivity, threshold)

SAKK 38/19 PEDRO: Trial Design



*metabolic PR defined by the central IRR panel

Timely delivery of **ctDNA** samples (analysis 10-14 days) at:

1. Baseline
2. C2D8 for non-mutated patients
3. C4D8 for cohort B

Upload **PET/CT** scans to WIDEN (42-1 day prior to registration)

Primary endpoint:

- Progression free survival according to the Lugano criteria (Cohorts A, C and D)
- Complete remission rate according to the Lugano criteria (Cohort B)

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SAKK 38/19 PEDRO

Main inclusion criteria

- Histologically confirmed, treatment-naïve DLBCL NOS
- Ann Arbor stage I-IV
- Eligible for 6 cycles of R-CHOP;
- Metabolically active measurable disease by 18FDG PET-CT
- At least 1 measurable site of disease
- Quantifiable and qualifiable circulating tumor DNA

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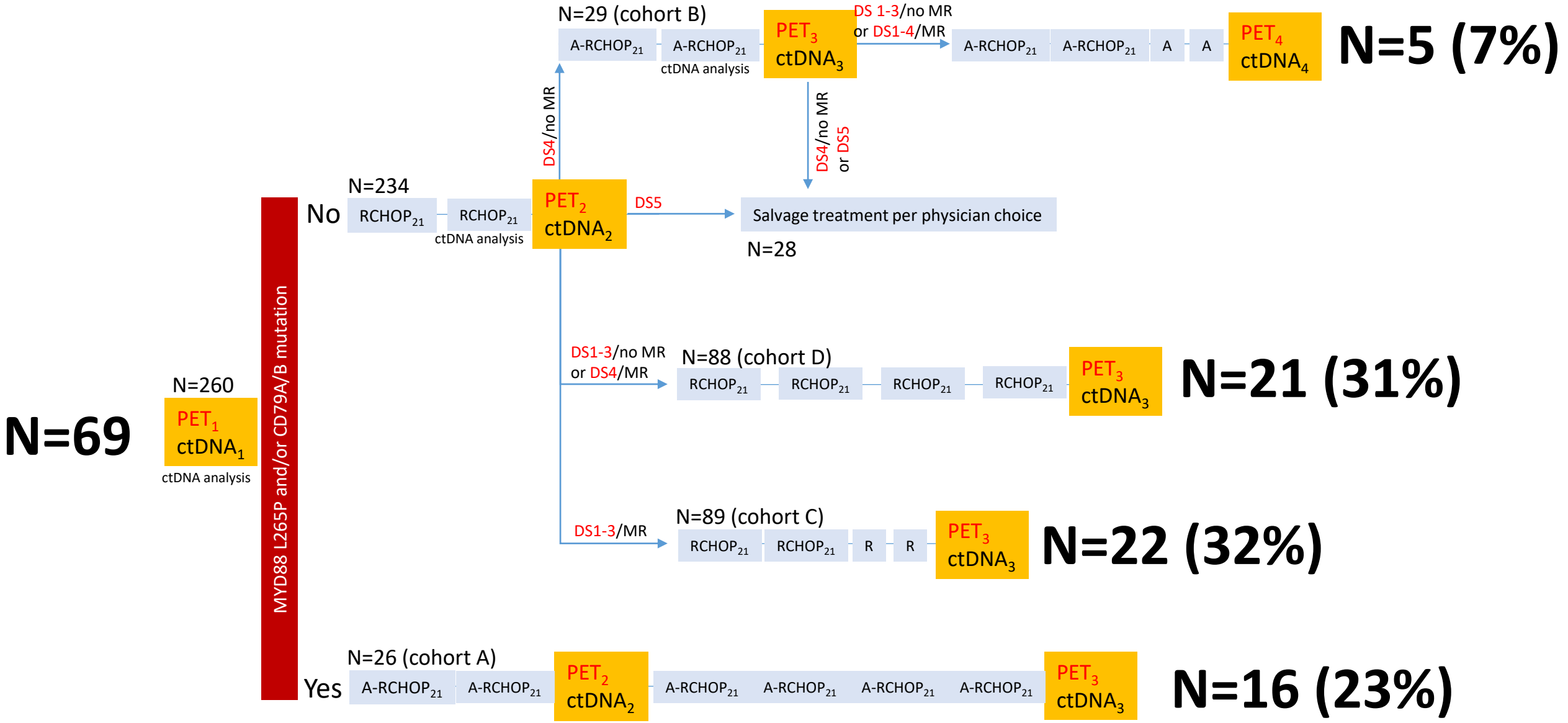
ctDNA-driven therapy of DLBCL: SAKK 38/19



SAKK 38/19 PEDRO: Screening Failures

Incl./Excl. criteria	n	Details (n)

6.1.2	29	• Not DLBCL, NOS (**16**)
		  • Transformed lymphoma (4)
		  • Hodgkin lymphoma (3)
		  • High-grade B-cell lymphoma (1)
		  • Follicular Lymphoma (1)
		  • Other (6)
		• No detectable ctDNA (**10**)
		• No measurable disease (3)

6.1.6	1	• Platelet count too low
6.1.7	1	• Bilirubin and ALAT too high
6.1.8	1	• Creatinine clearance
6.2.10	1	• Testis involvement
Physician's decision / Other	18	• PI decision: no further reason (6) • Patient's withdrawal of consent (4) • Not in need of / not fit for 6 cycles of R-CHOP (3) • Missing info (3) • Worsening of condition / in need of therapy (2)
Total	51	

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Acknowledgment

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