UNIVERSITÀ DEL PIEMONTE ORIENTALE

Dalla biopsia liquida al paziente: il valore prognostico

Che cosa abbiamo imparato nei disordini linfoproliferativi?

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Agenda

- Prognostic impact of liquid biopsy in DLBCL
- Prognostic impact of liquid biopsy in Hodgkin lymphoma
- Prognostic impact of liquid biopsy in indolent lymphomas

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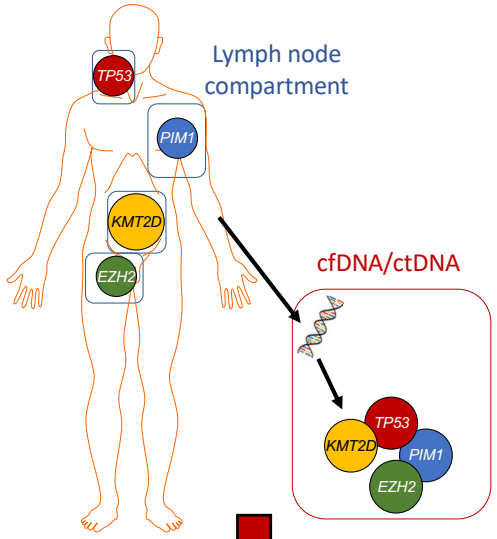
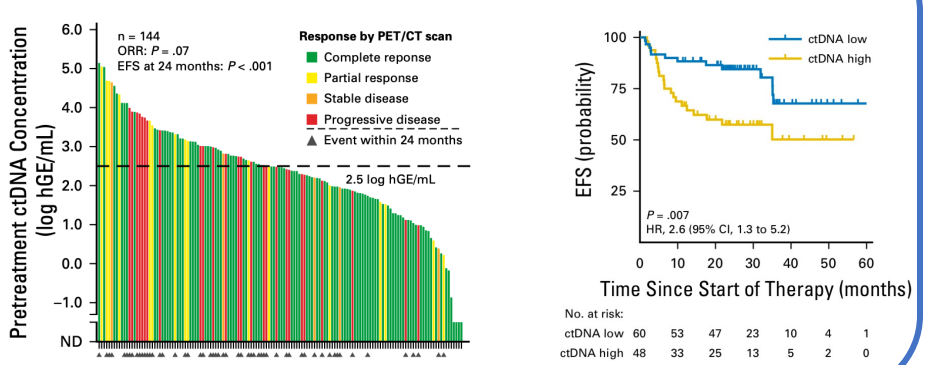
Clues potentially exploited from cfDNA/ctDNA



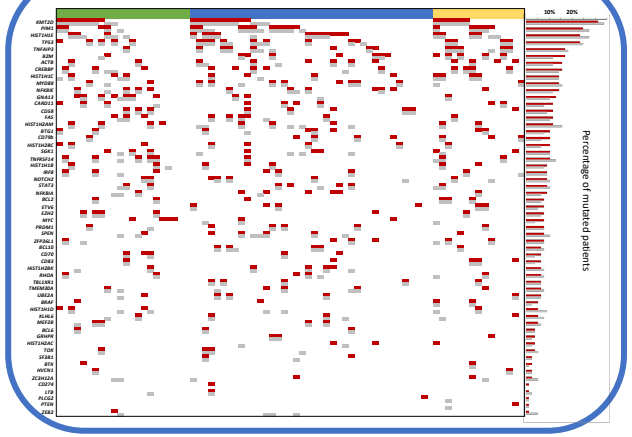
Relies on the detection of somatic mutations

Does not rely on the detection of somatic mutations

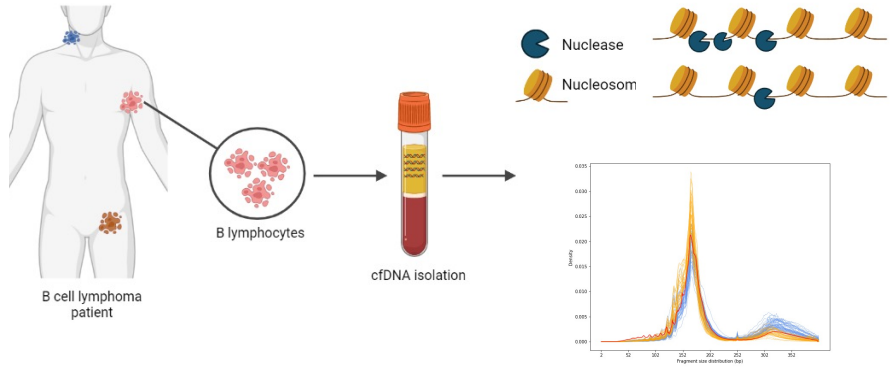
ctDNA levels



Molecular characterization

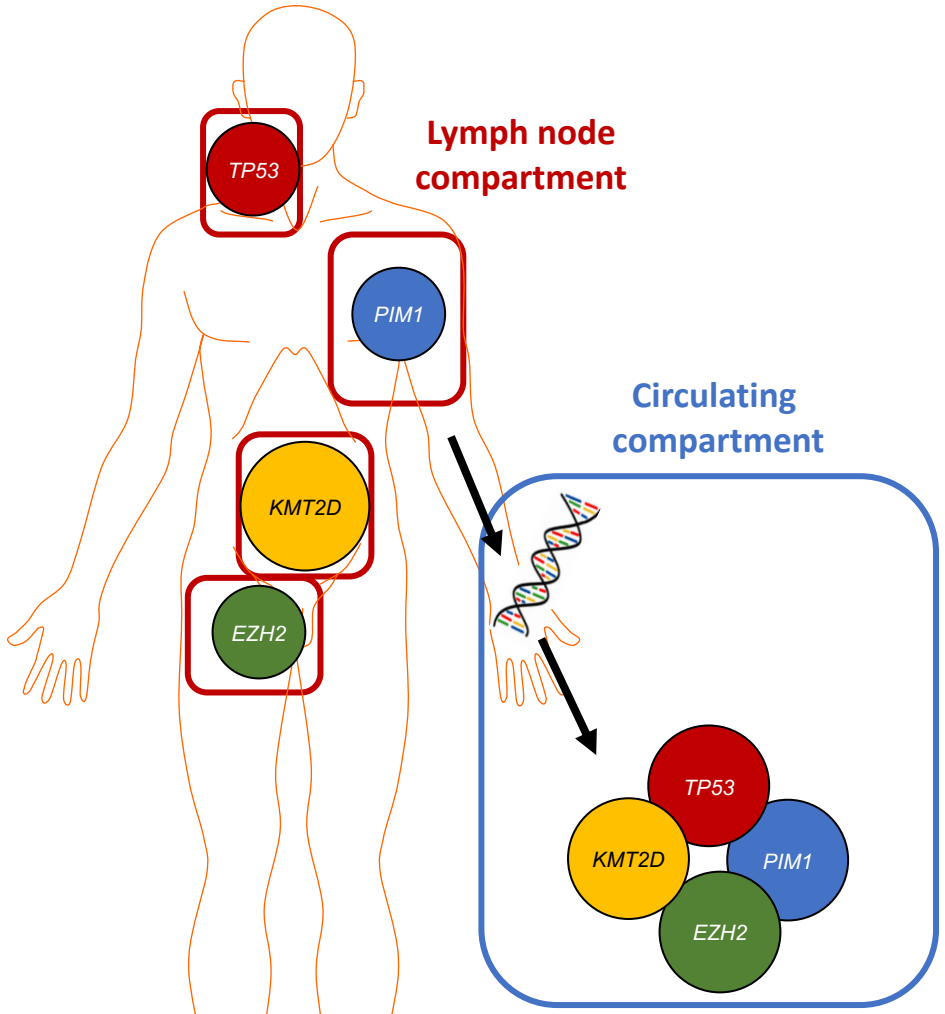


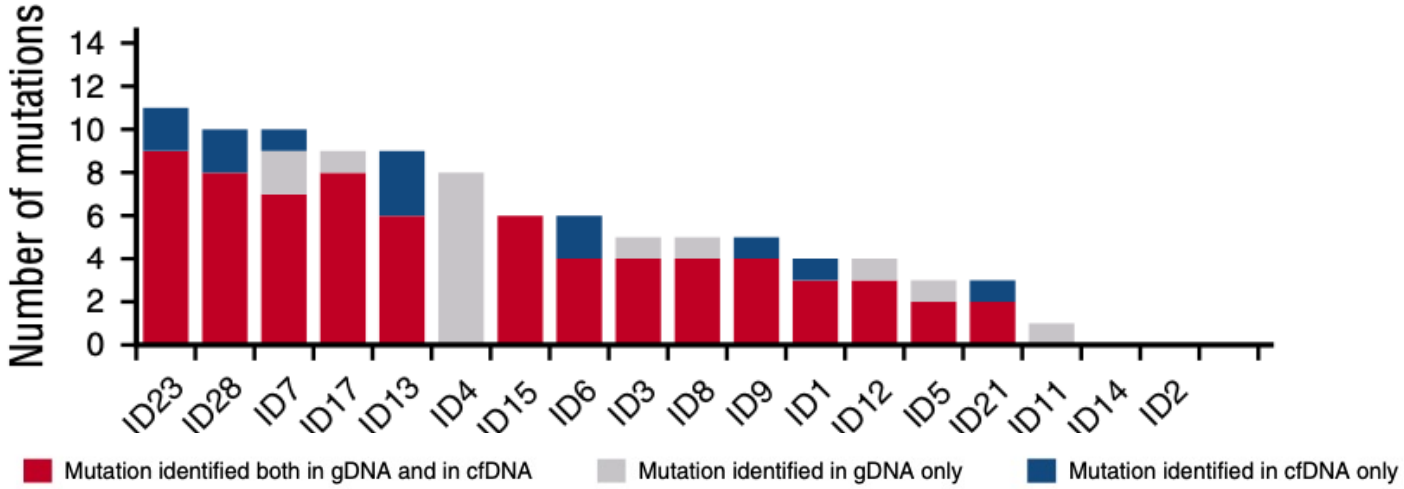
cfDNA fragmentation profile

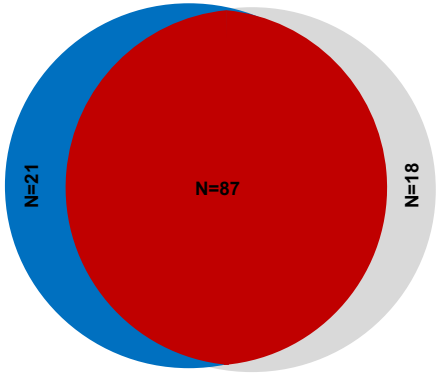


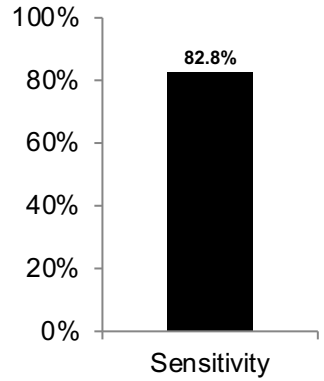
Kurtz *et al., JCO.* 2018; Chapuy *et al., Nat Med*. 2018; Schmitz *et al., NEJM*. 2018; Lacy *et al., Blood*. 2020; Wright *et al., Cancer Cell*. 2020; Esfahani *et al., Nat. Biotechnol*. 2022; Mouliere *et al., Sci Transl Med*. 2018; Cristiano *et al., Nature*. 2019.

ctDNA is a tool for DLBCL genotyping



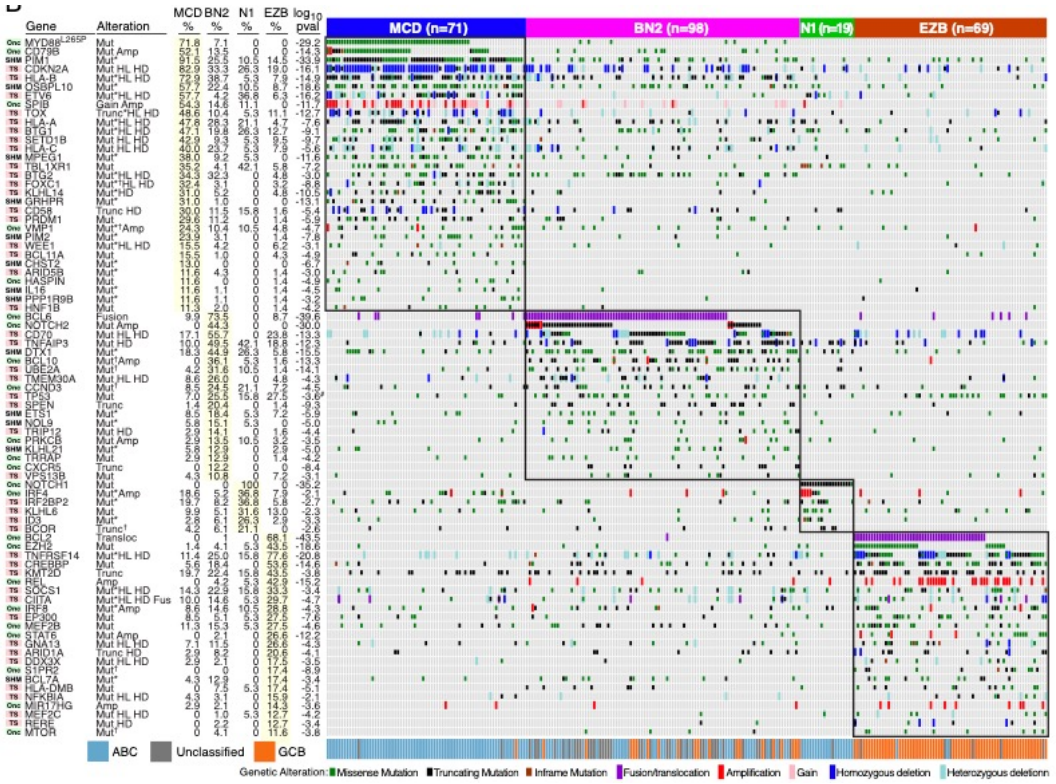


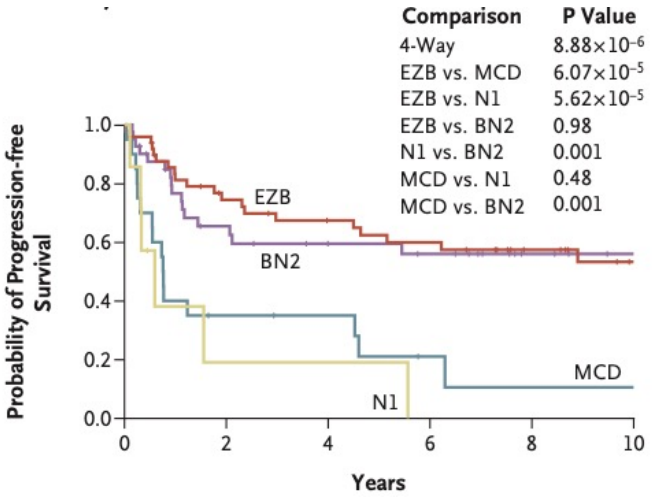




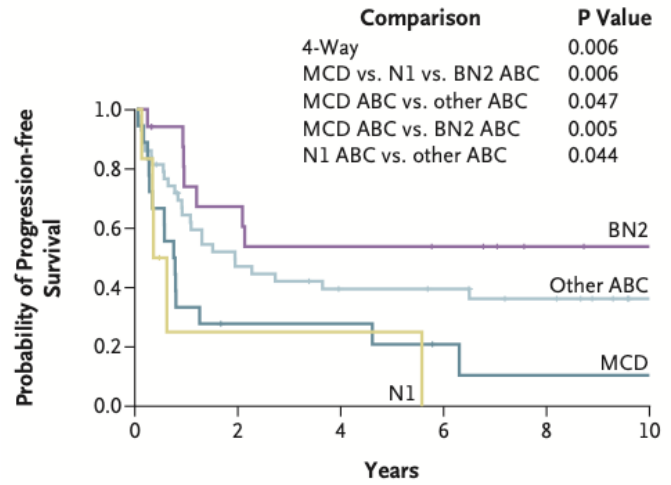
Rossi *et al., Blood*. 2017

Molecular cluster on lymph node biopsy

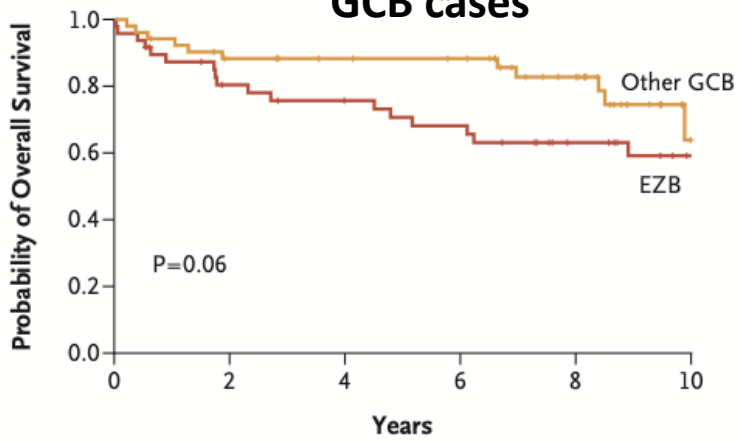




ABC cases



GCB cases



Schmitz *et al., NEJM*. 2018

Experimental workflow

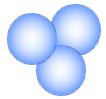
Università Piemonte Orientale

Sapienza University

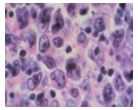
Aviano

166 newly diagnosed DLBCL patients treated with R-CHOP

cfDNA from plasma



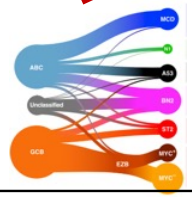
Peripheral blood cells



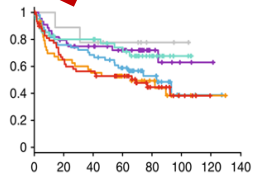
Tumor gDNA from LN (Fresh and FFPE) N=77 patients

CAPP-Seq panel of genes recurrently mutated in mature B-cell malignancies

CNV analysis on ctDNA



Cluster generation using the LymphGen tool[1] in LN vs ctDNA



Stratify patients outcome

Moia *et al., Blood Advances*. 2025

Liquid biopsy reflects the molecular characteristics and clinical impact of molecular clusters identified on tissue biopsy

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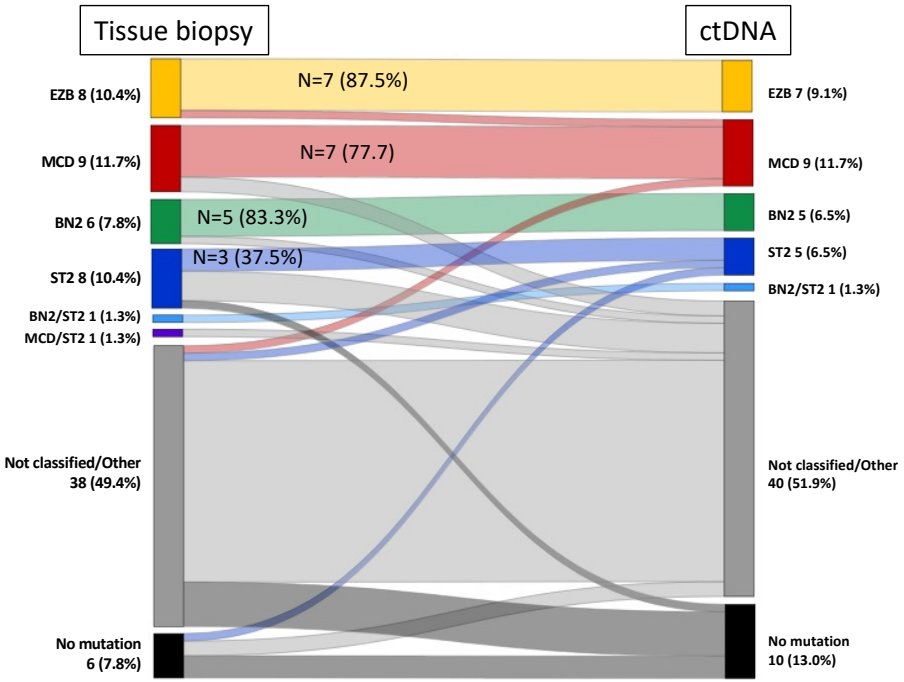
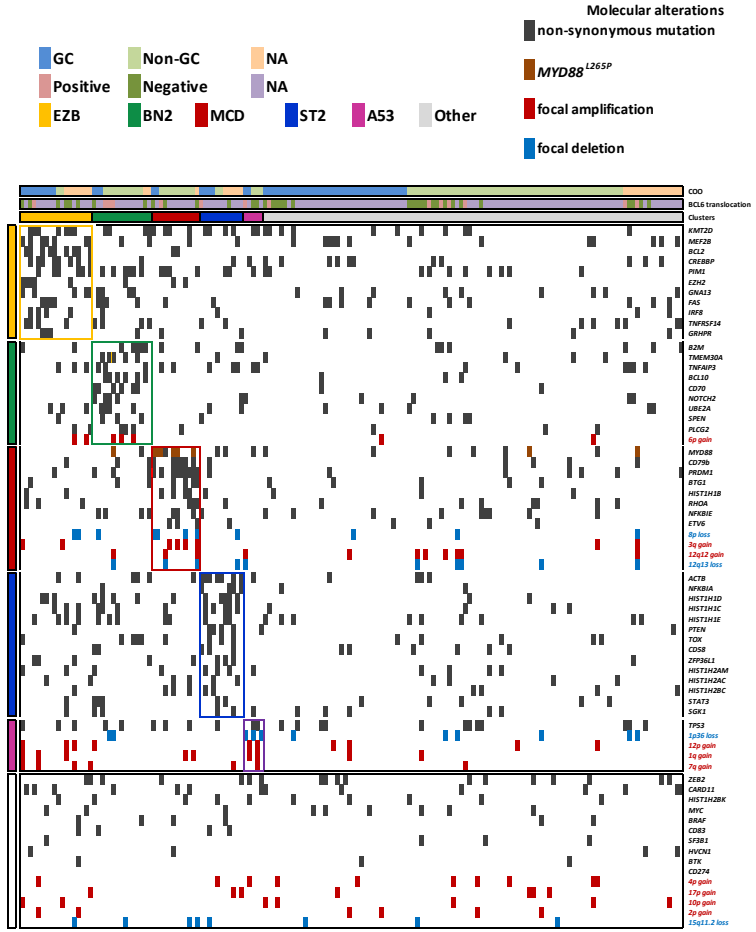
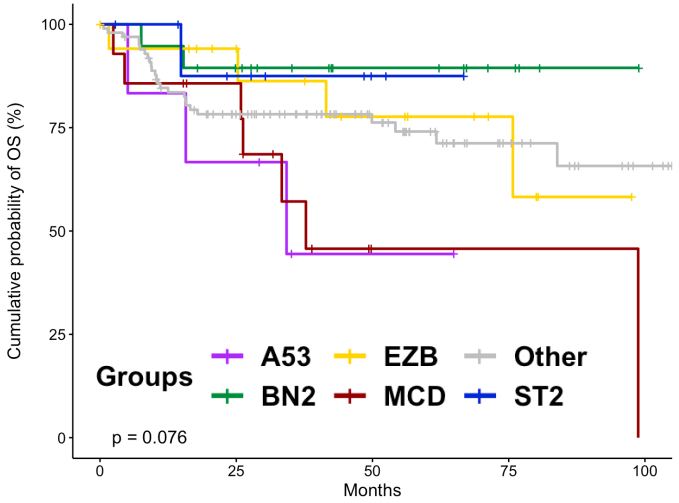
N=77 DLBCL



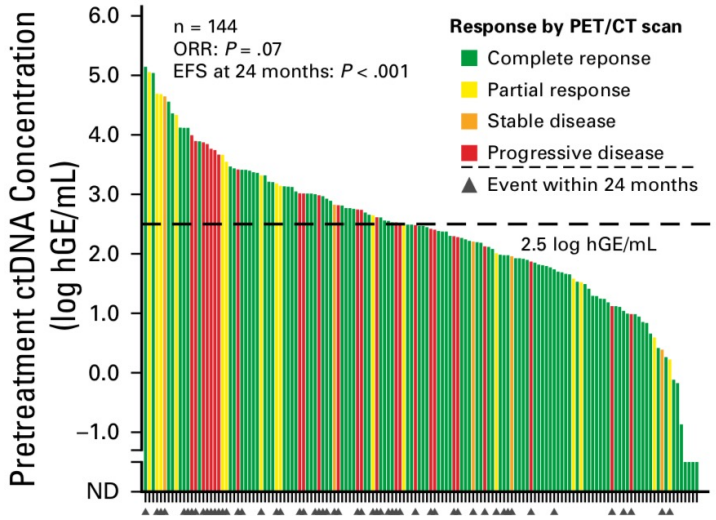
N=166 DLBCL

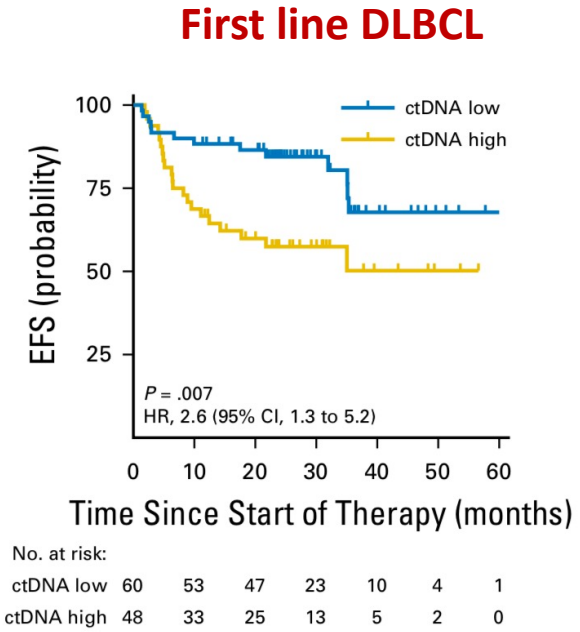


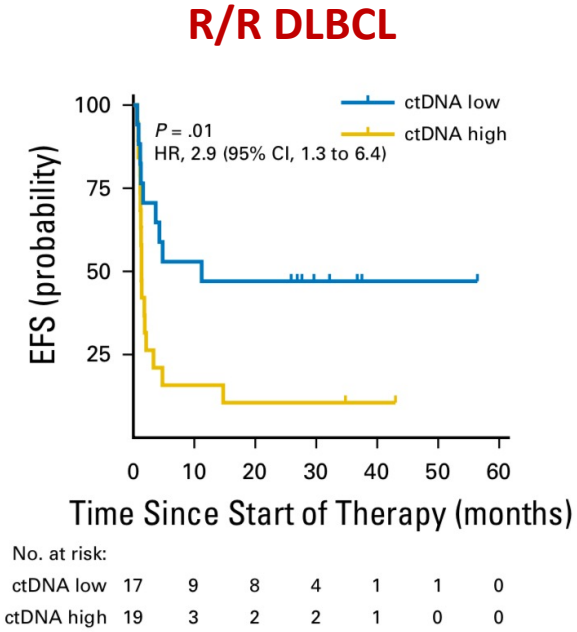


Moia *et al., Blood Advances*. 2025

Pretreatment ctDNA is a robust biomarker in DLBCL



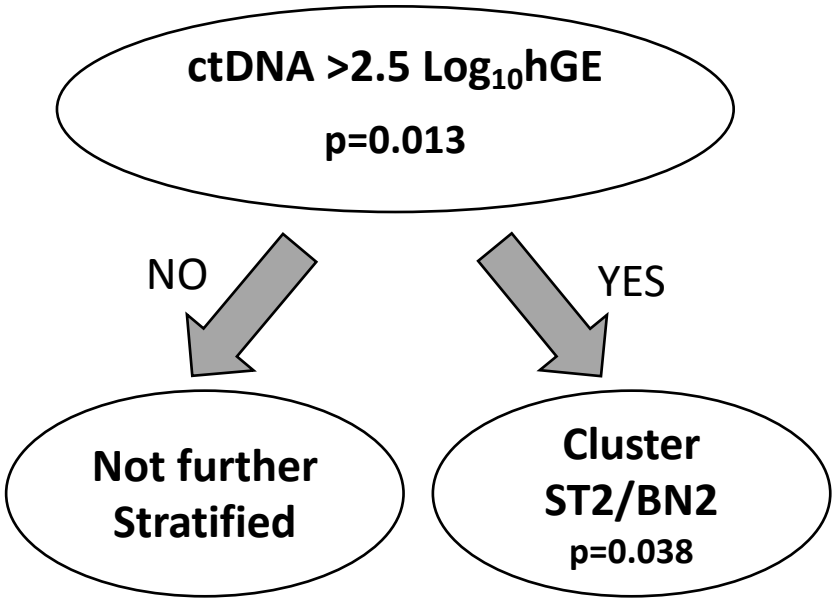


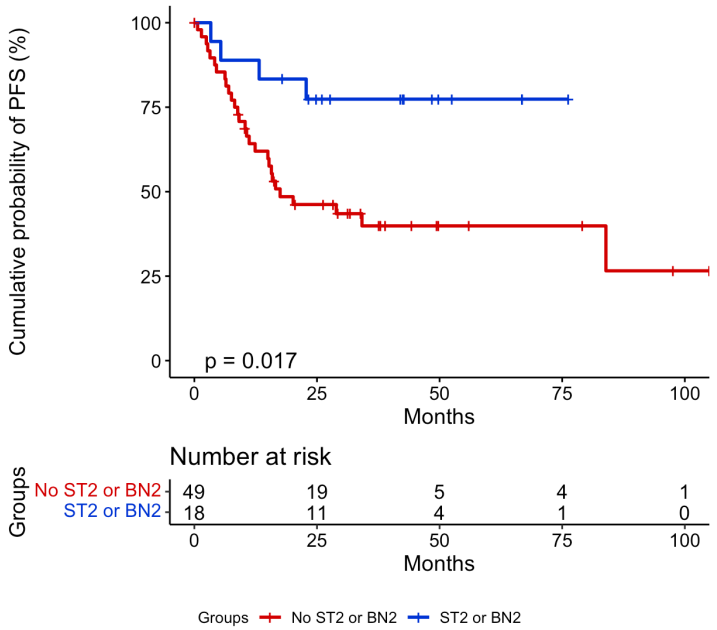


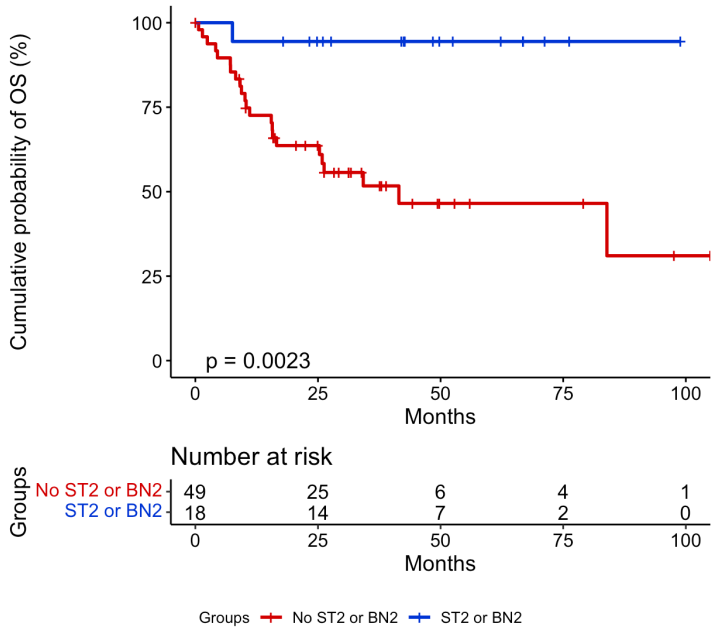
- Pre-treatment levels of ctDNA correlate with Event Free Survival (EFS) in both first line and in relapsed/refractory DLBCL

Kurtz DM, et al., *JCO*, 2018

BN2/ST2 clusters predict outcome in patients with ctDNA levels >2.5 Log_{10} hGE

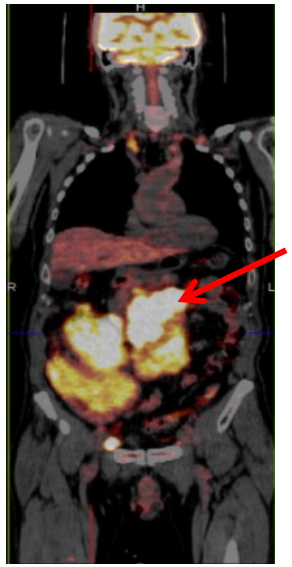






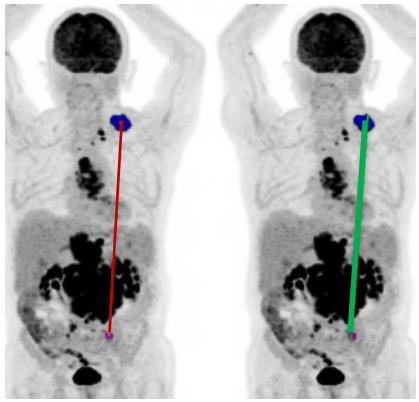
Moia *et al., Blood Advances*. 2025

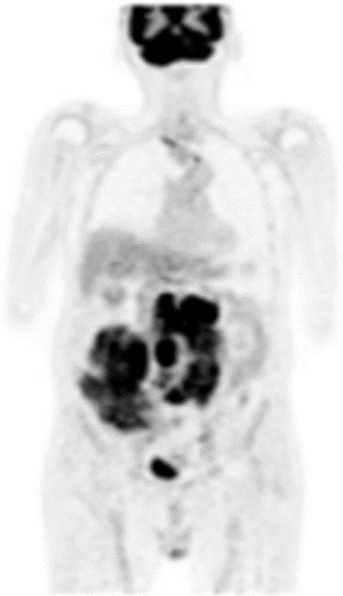
[18F]FDG-PET/CT radiomics features



SUVmax
The peak of standardized uptake volume

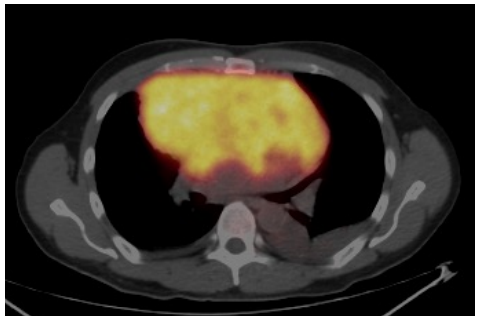
Dmax
The maximum distance between tumor lesions



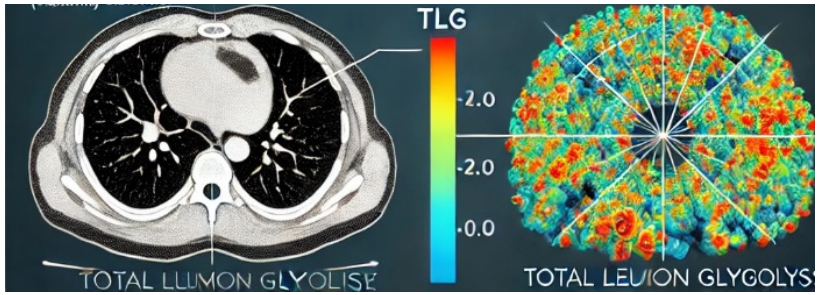


[18 F]FDG-PET image

MTV
Metabolic tumor volume



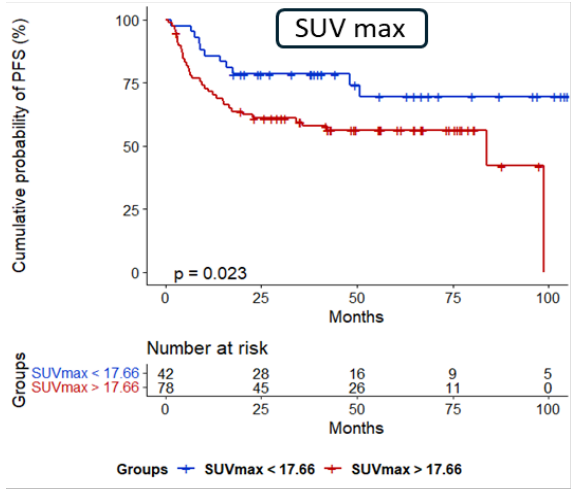
TLG
Total lesion glycolysis
(MTV x SUV mean)

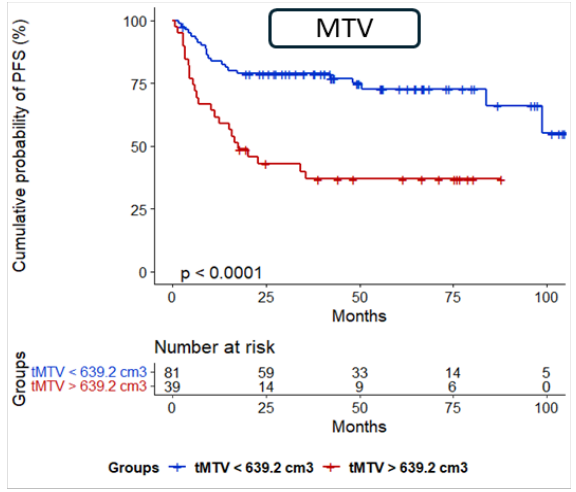


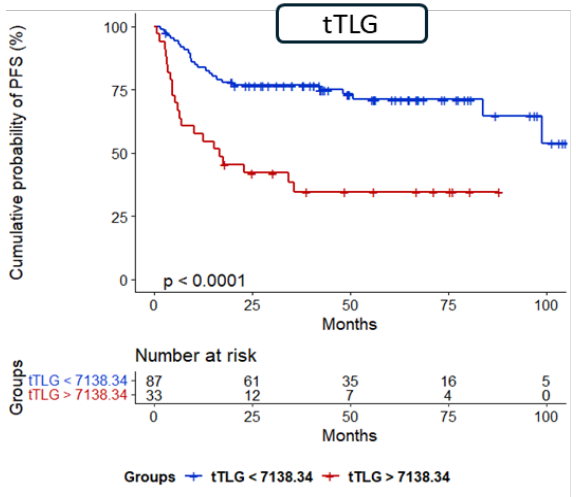
The best PET/CT parameter cutoffs for predicting PFS

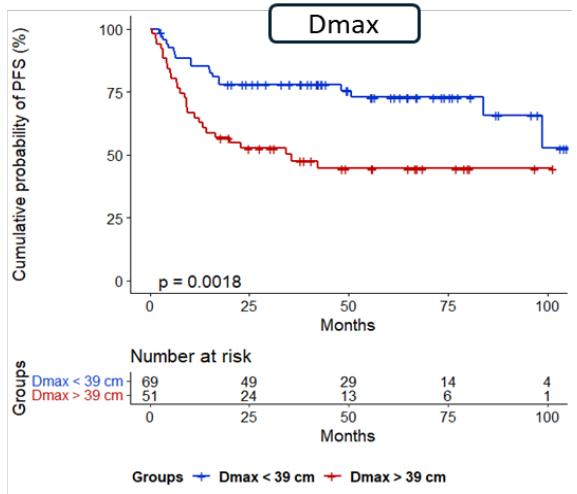
Maxstat test

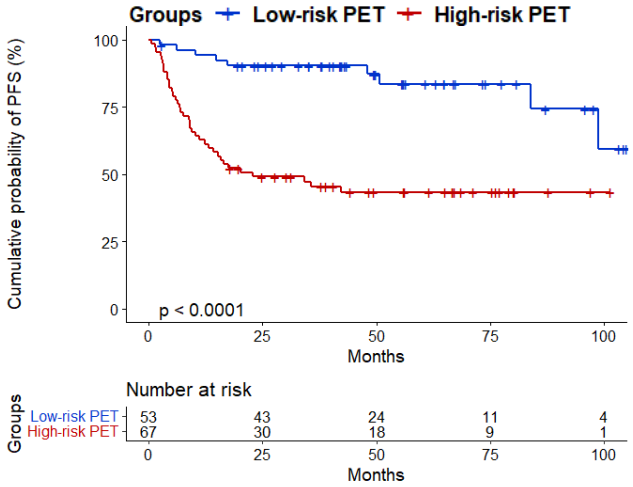
PET parameter	cutoff
SUVmax	17.66
MTV	639.2 cm^3
TLG	7138.34
Dmax	39 cm











Dondolin *et al., ASH*. 2024. #2980

PET parameters, ctDNA levels and BN2/ST2 clusters independently predict PFS: A three-variable prognostic model

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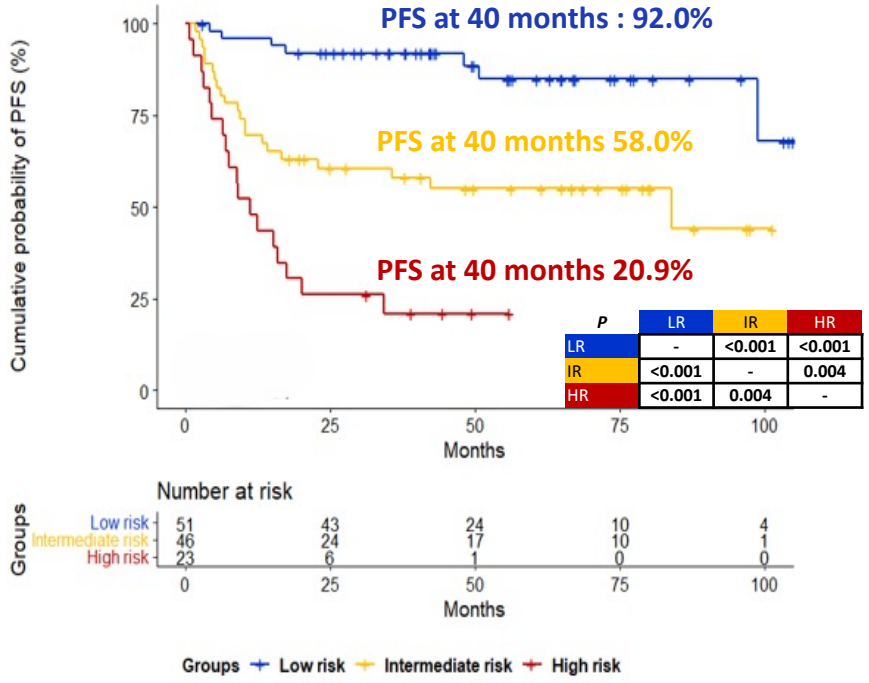
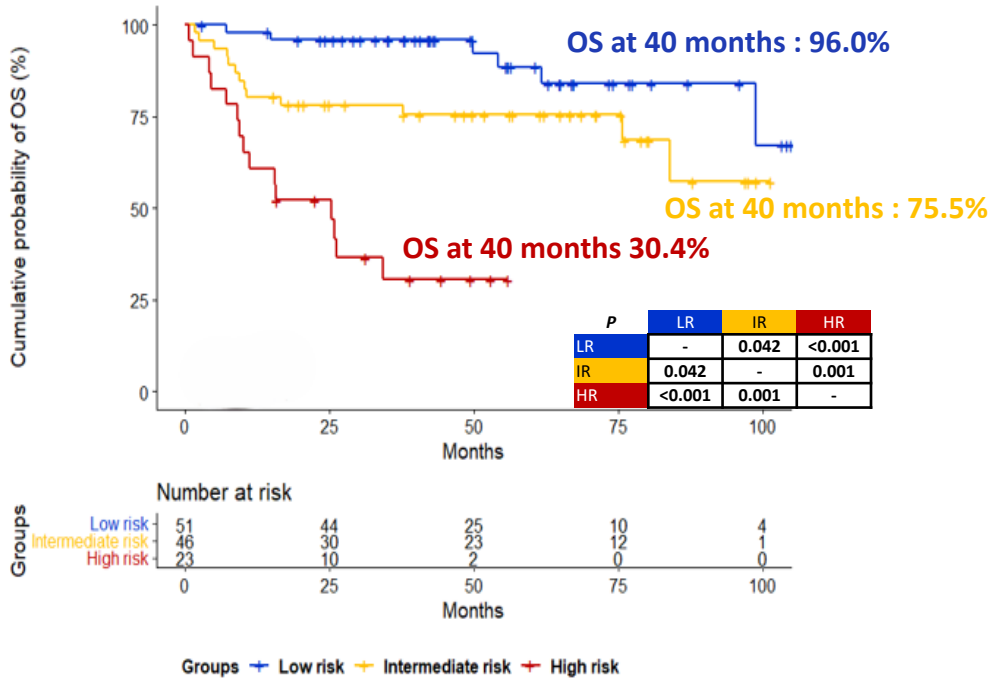
Multivariate analysis for PFS

Variable	Points	N	Hazard ratio	95% CI	β	p
PET-positive	+1.5	120		3.98 (1.84, 8.59)	1.381	<0.001
ctDNA-high	+1	120		2.53 (1.34, 4.78)	0.929	0.004
ST2/BN2	-1	120		0.37 (0.15, 0.90)	-0.988	0.029

Low risk	-1 to 0.5 points
Intermediate risk	1 to 1.5 points
High risk	2.5 points





Dondolin *et al., ASH*. 2024. #2980

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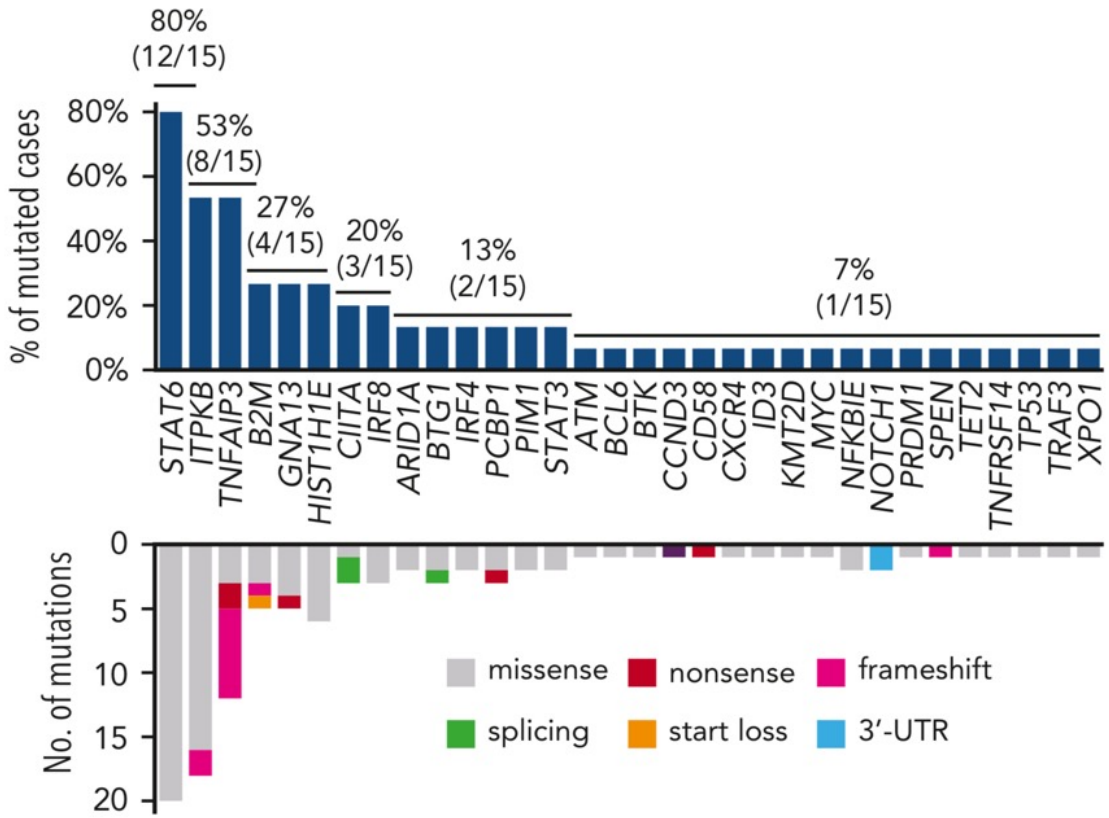
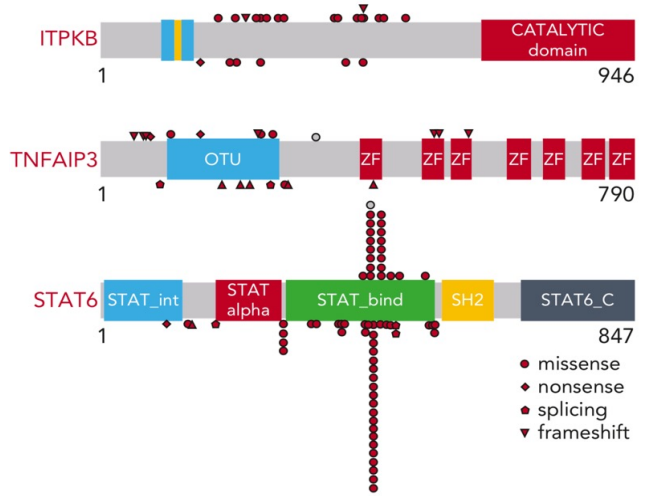
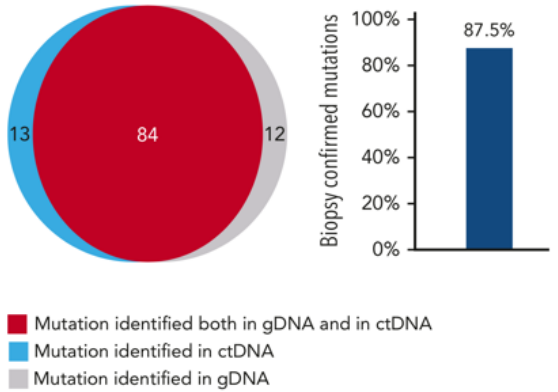
The liquid biopsy mirrors the genetics of cHL

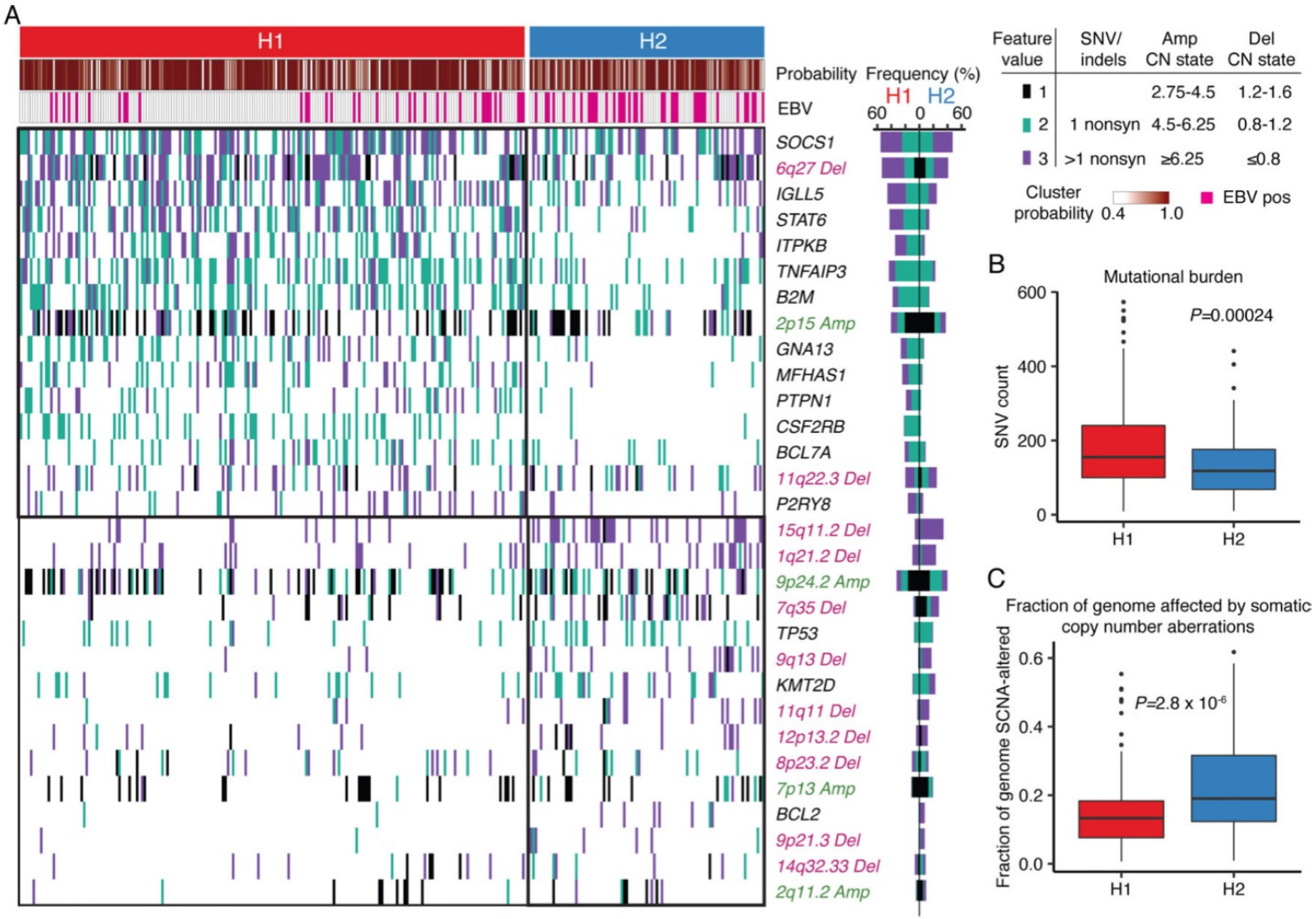


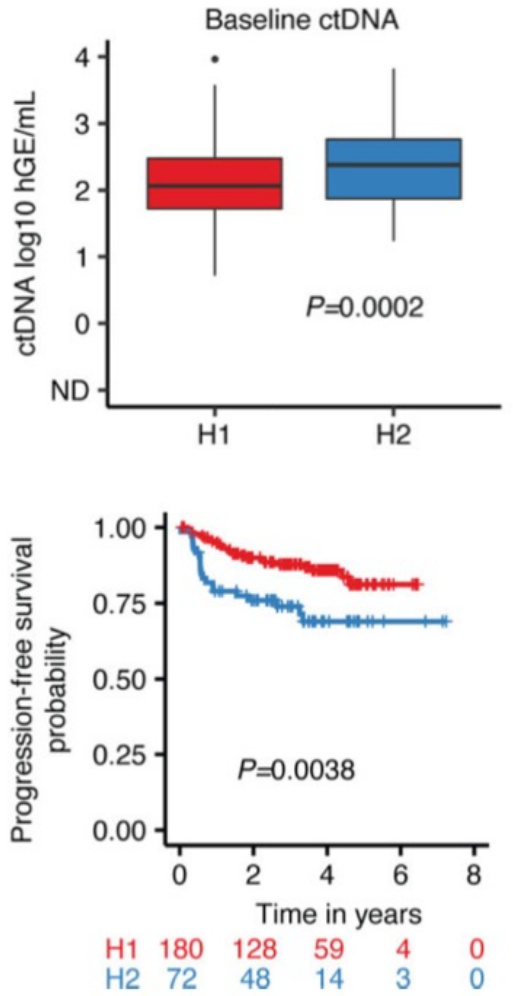




Spina *et al., Blood.* 2018

Distinct Hodgkin lymphoma subtypes identified on liquid biopsy *(i)*

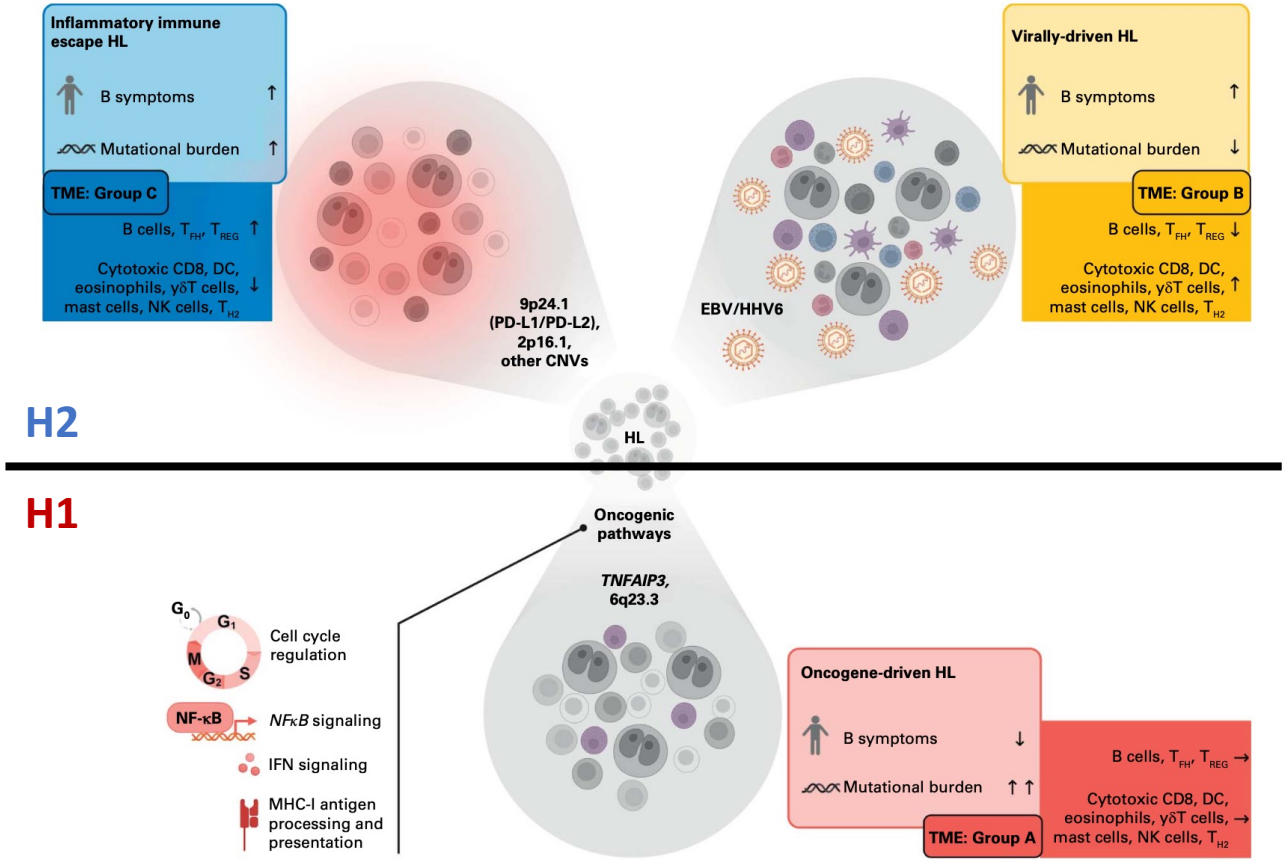


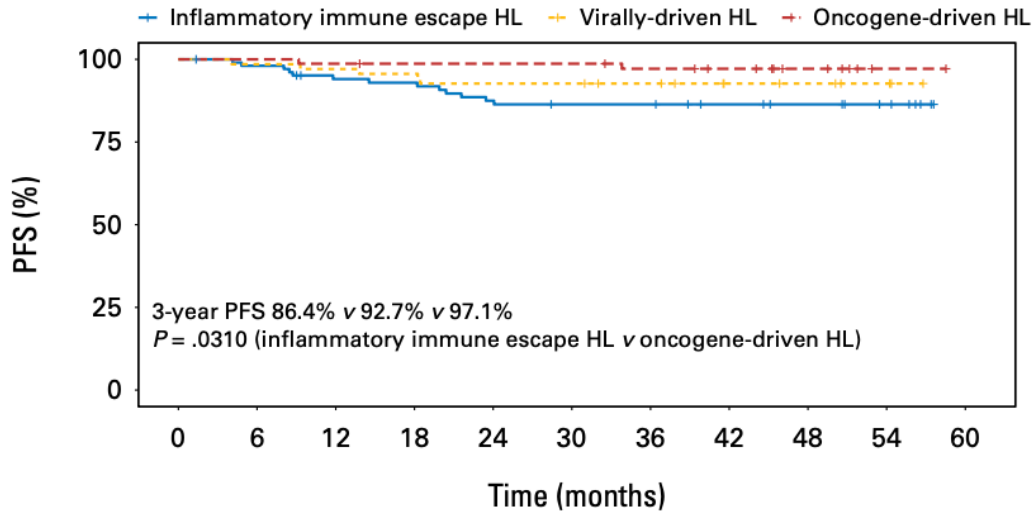


Alig *et al., Nature.* 2024

Distinct Hodgkin lymphoma subtypes identified on liquid biopsy *(ii)*

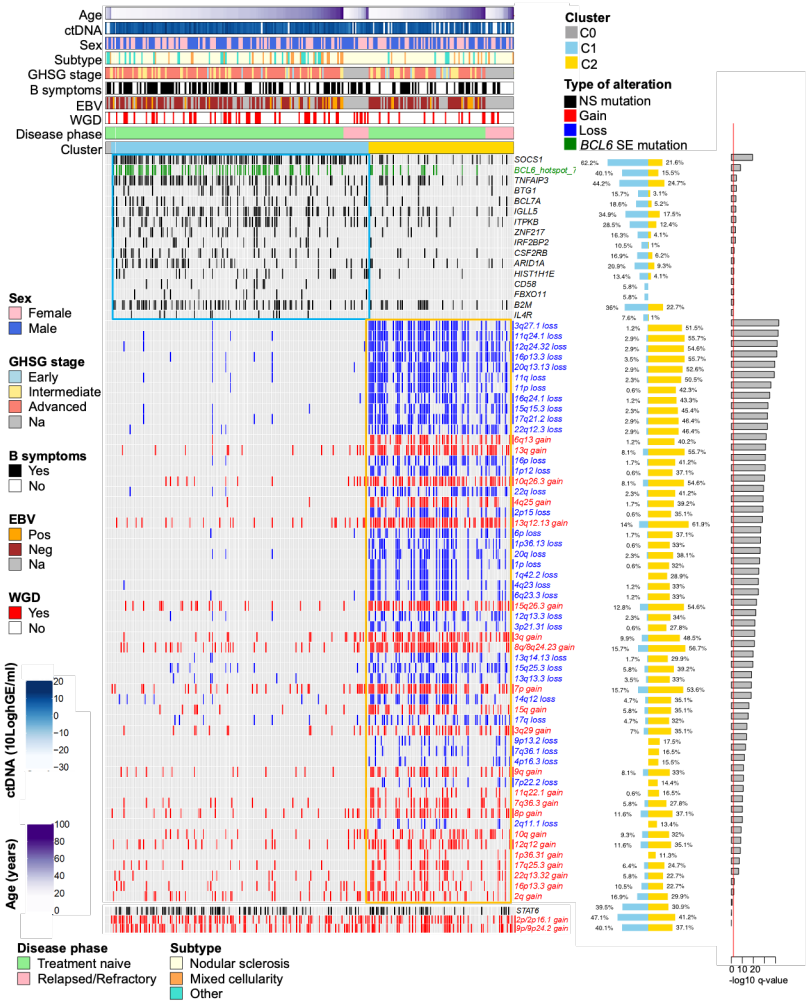
243 patients from German Hodgkin Study Group trials



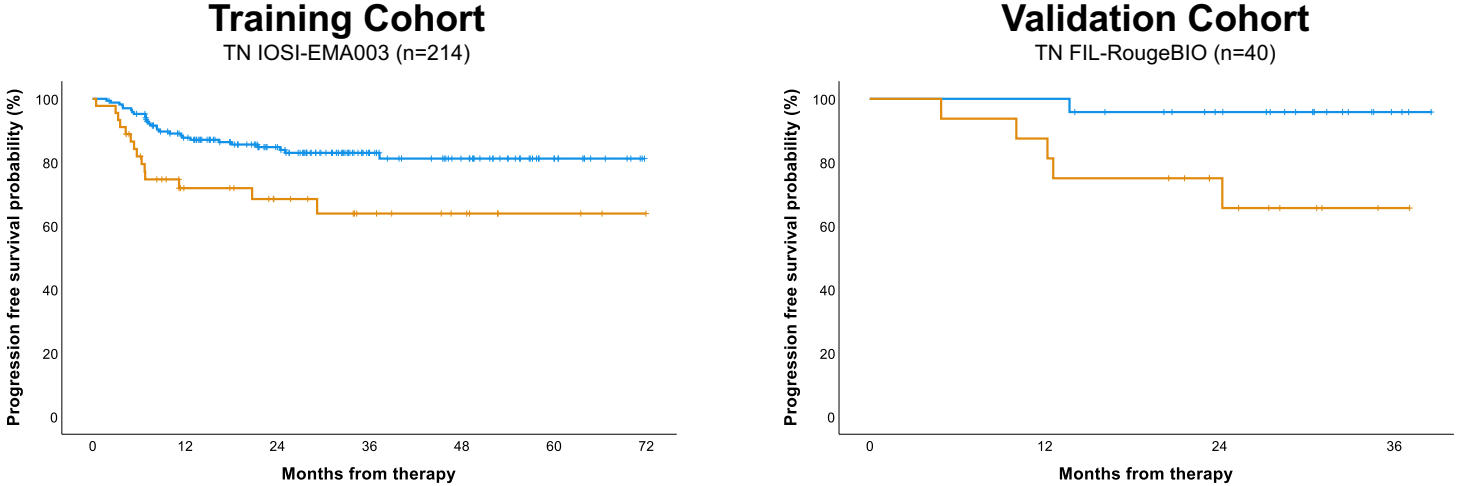


Heger *et al., JCO.* 2024

Distinct Hodgkin lymphoma subtypes identified on liquid biopsy *(iii)*



Genetic subtypes of cHL are driven by genetic instability rather than mutation clustering



Multivariate Cox regression

	HR	95% CI	p
MTV (continuous)	1.001	1.000-1.002	0.061887
GHSG stage	1.505	0.696-3.256	0.298710
IPS >2	2.787	1.340-5.769	0.006092
WGD+	2.411	1.125-5.165	0.023602

Whole-genome duplication is the sole genetic factor significantly linked to prognosis

Salehi *et al.*, ASH 2024, #854

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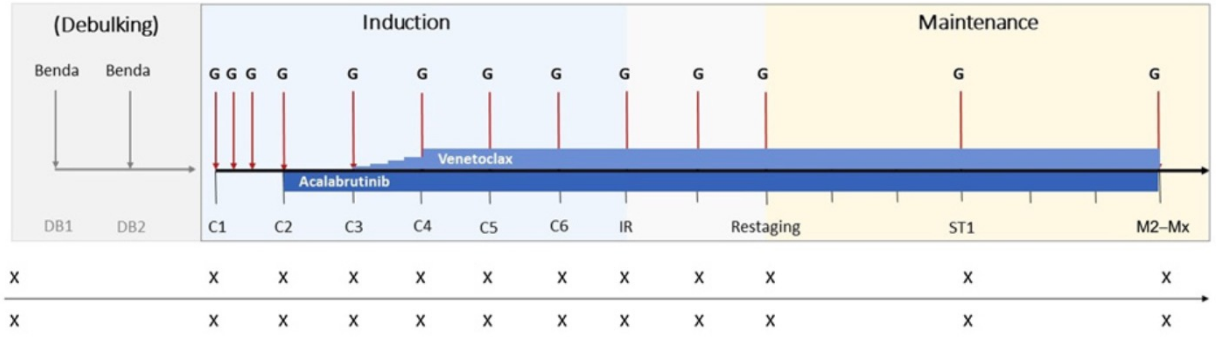
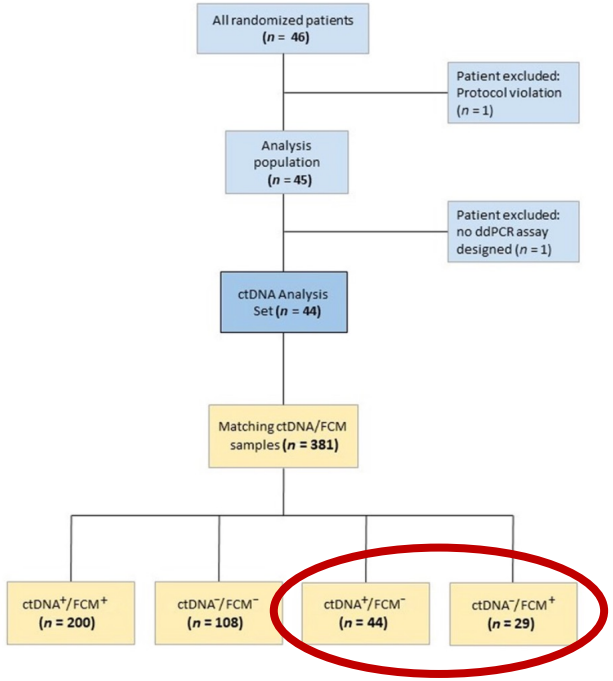
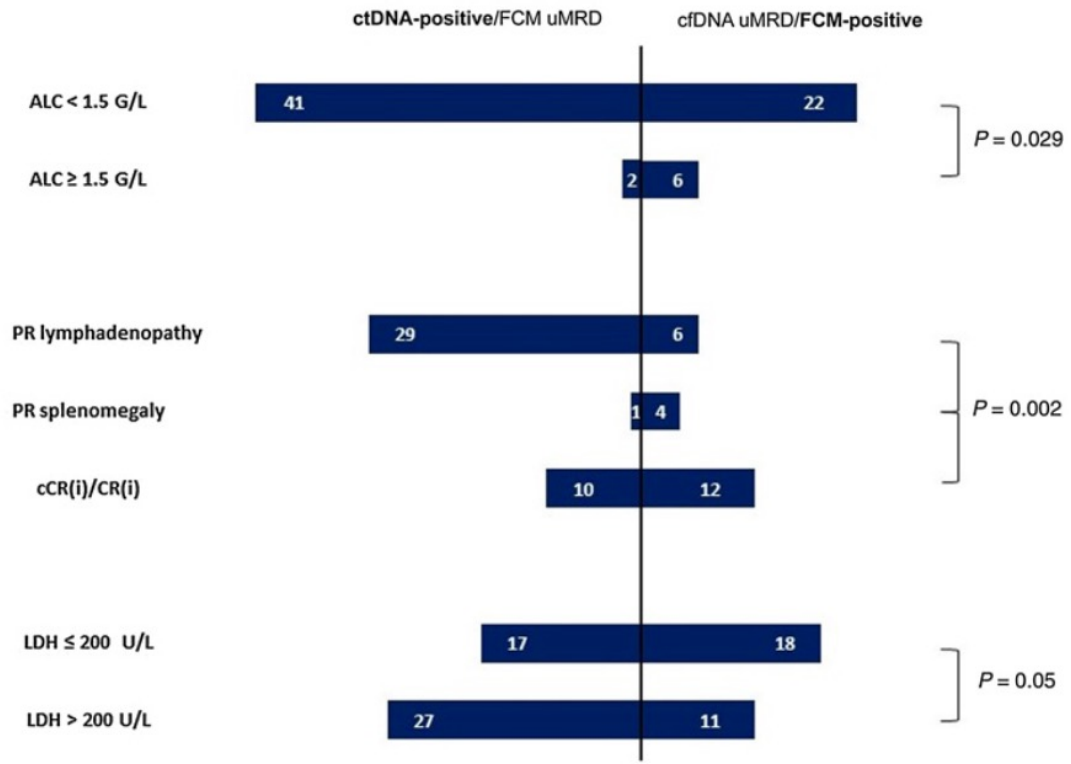
Minimal residual disease analysis by ctDNA in CLL

CLL2-BAAG trial



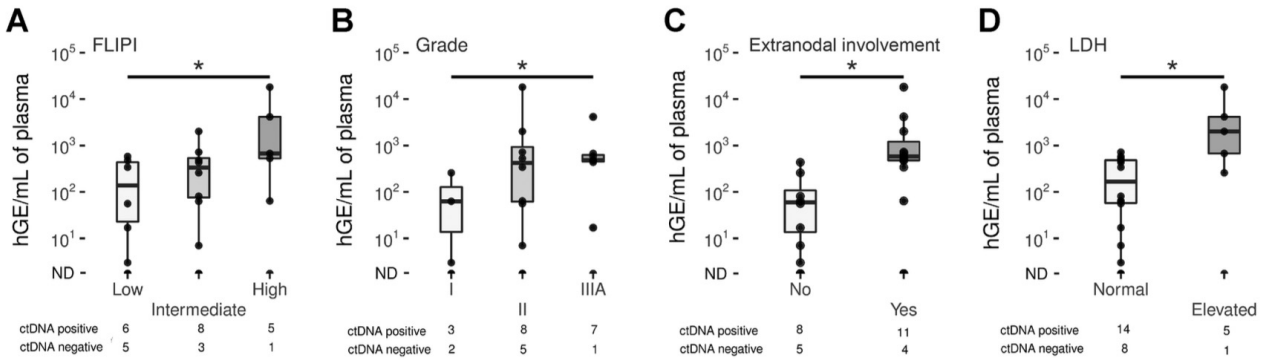




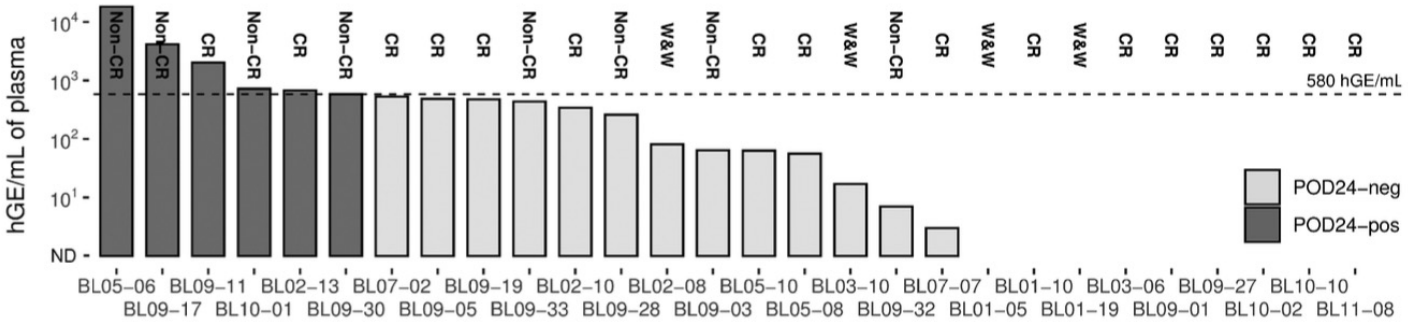
ctDNA appears to reflect the residual CLL burden outside the PB as it had advantages in patients with predominantly nodal disease

Fürstenau *et al., Clin Cancer Res*. 2022

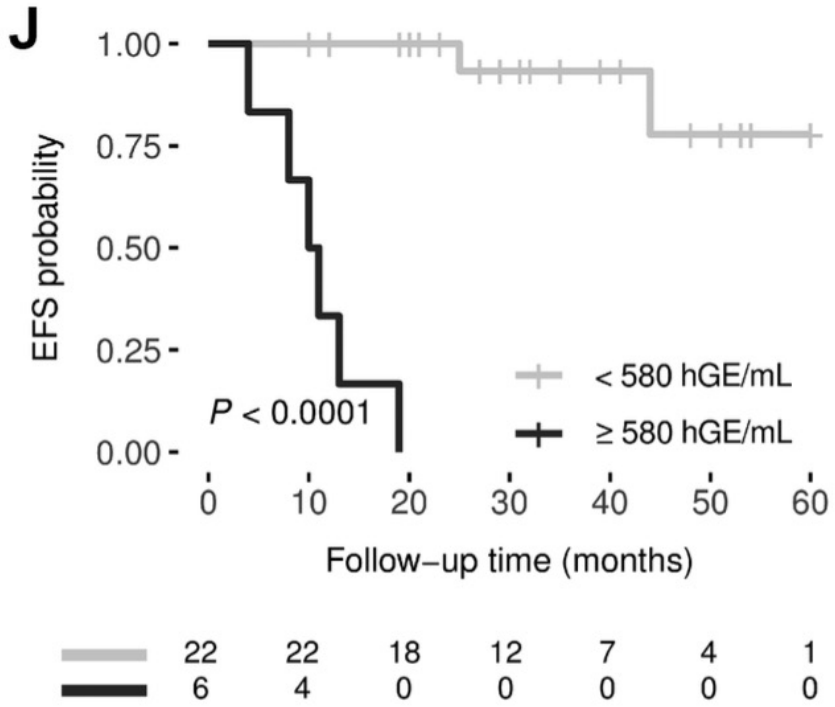
Correlation of baseline ctDNA levels with patient outcomes



Higher levels of ctDNA correlates with FLIPI, Grade, extranodal involmente and LDH



580 hGE/mL was established as the optimal cut-off for POD24 prediction



Fernandez-Miranda *et al., Clin Canc Res*. 2023

Conclusions

- Liquid biopsy recapitulates with a non-invasive approach the molecular landscape and the prognostic impact of DLBCL molecular clusters
- Liquid biopsy allows a non-invasive molecular characterization of Hodgkin lymphoma, improves patients' prognostic stratification and identifies potential therapeutic targets
- Liquid biopsy is less studied in indolent lymphoproliferative neoplasm, but initial evidences also suggest its potential prognostic impact in this context
- The integration of liquid biopsy, PET parameters and other clinical and histopathological features should be used to design clinical trials with novel agents for high-risk patients

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