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MRD-Negativity after Frontline DLBCL Therapy: A Pooled Analysis of 6 Clinical Trials

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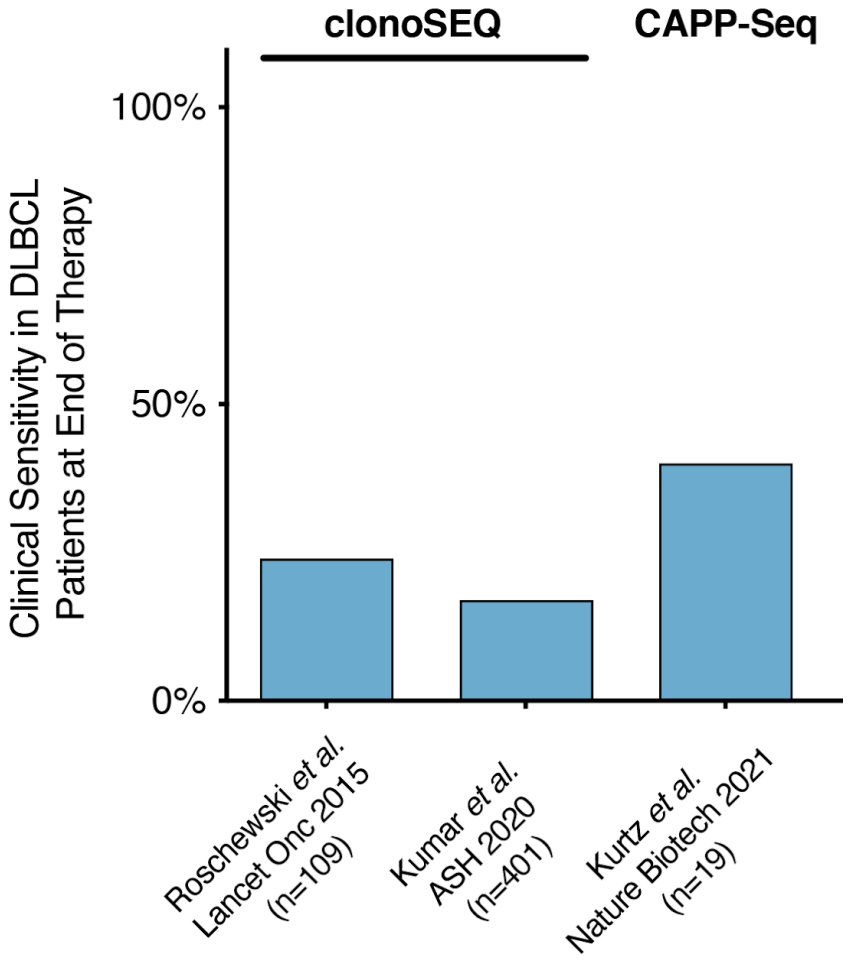
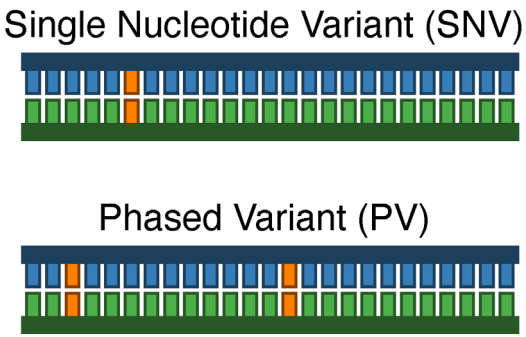
Background

- Current DLBCL response criteria rely on imaging cans that cannot measure disease at molecular level.
- Prognostic utility of circulating tumor DNA (ctDNA) is established in DLBCL before and early during therapy (Roschewski et al. 2015 *Lancet Oncol*; Kurtz et al. 2018 *J Clin Oncol*).
- Detection of ctDNA at the end of therapy (**EOT**) is challenging using approaches that have limits of detection (LOD) in plasma of ~1 part in 10,000 cfDNA molecules (Moding et al. 2021 *Cancer Discovery*).

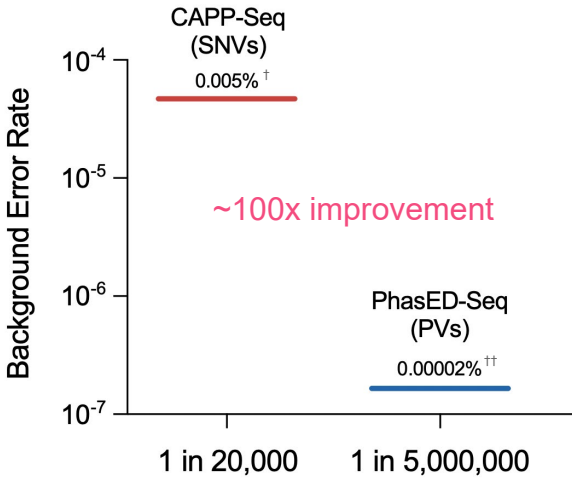


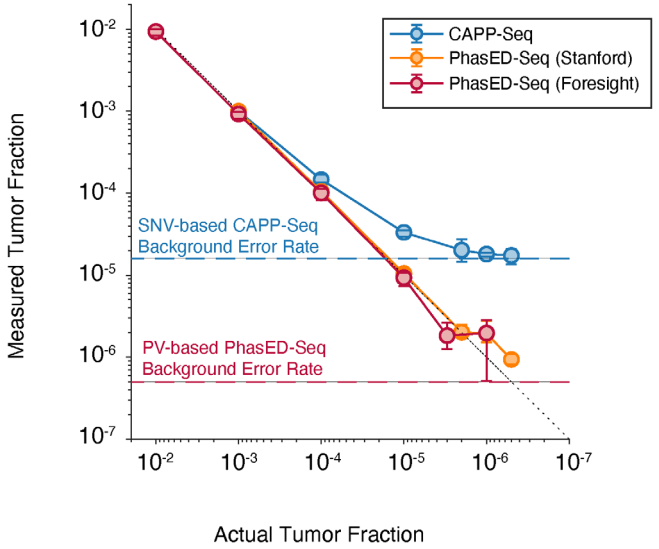
PhasED-Seq enables higher sensitivity (~1x10^{-6})

(Phased Variant Enrichment & Detection Sequencing)†



- Biologically relevant mutations in B-cell malignancies
- Reflects aberrant somatic hypermutation (aSHM) driven by activation-induced deaminase (AID)





† Kurtz DM et al, Nat Biotechnol 2021
†† Foresight data

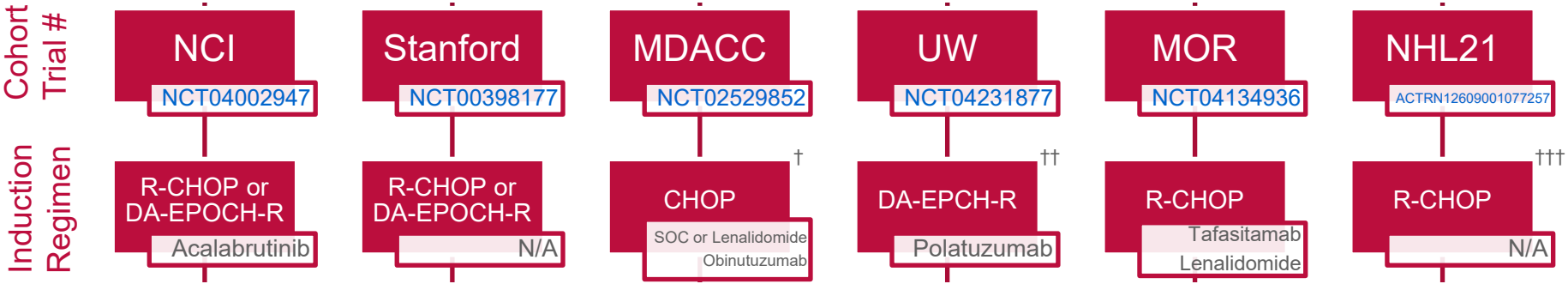
Hypothesis:

- We hypothesized that PhasED-seq, an ultrasensitive ctDNA MRD method, could achieve improved disease detection at EOT.

Methods: Subjects, Trials, & Outcomes

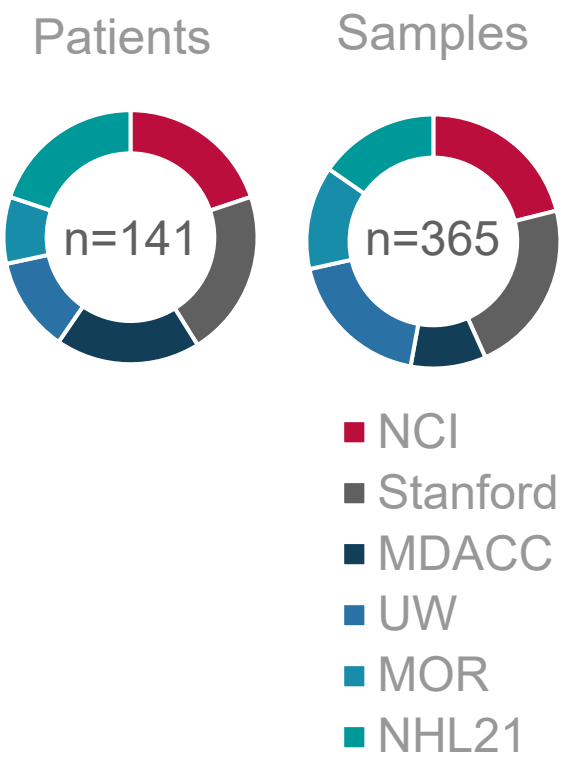
- We pooled integrated PhasED-seq MRD data from 6 prospective frontline studies in LBCL
- We assessed prognostic value of ctDNA MRD to predict PFS during and EOT
- We compared the predictive value of ctDNA MRD at EOT to conventional response criteria using PET/CT scans

Details of Cohorts Pooled, Induction Regimens, & Specimens



† Cherng et al, Blood Adv 2022
†† Lynch et al Blood Adv 2023
††† Hertzberg et al Haematologica 2017

Patient Characteristics



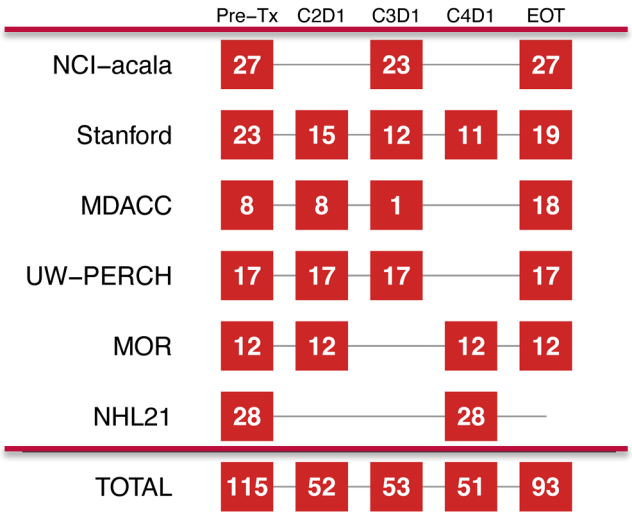
Characteristic	Value
Sex	
Female	36%
Not Available	3%
Age	60 (20-85)
IPI	
0-1	26%
2	25%
3	31%
4-5	18%
Stage	
1-2	25%
3-4	75%
Subtype	
GCB-DLBCL	49%
Non-GCB-DLBCL	20%
HGBL-DH	3%
PMBCL	3%
Not Available	25%

Methods: Specimens & Logistics

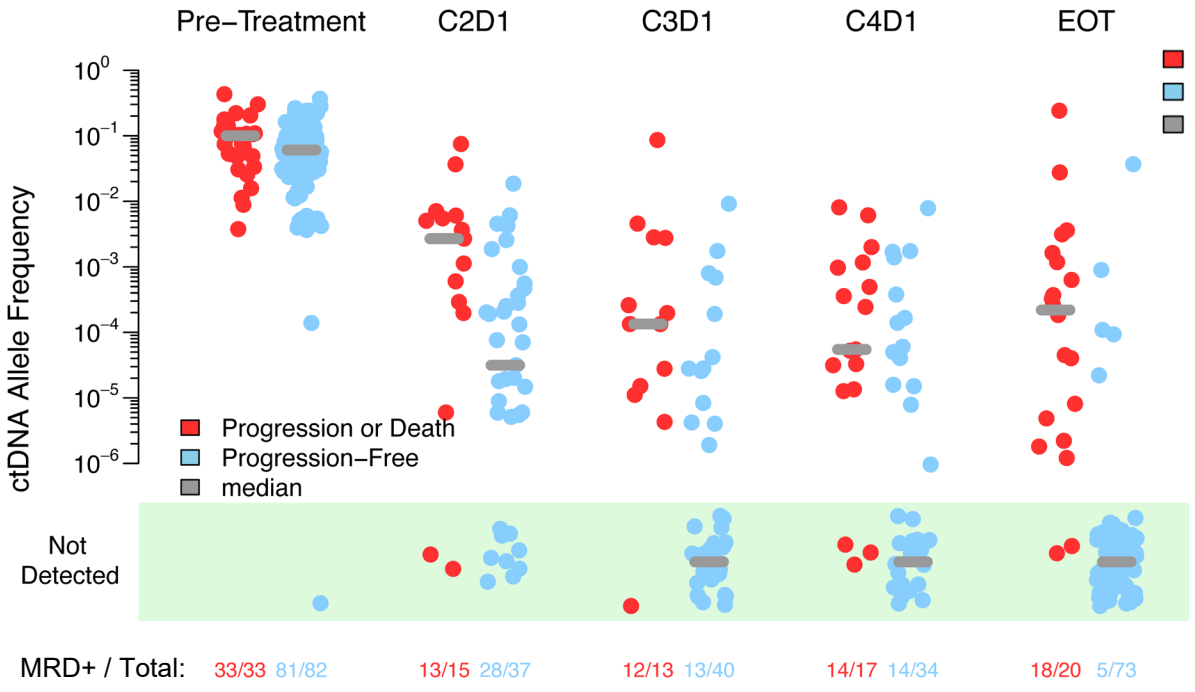
- Pre-treatment tumor or plasma & PBMC specimens were used to identify Phased Variants (PVs); these were tracked as MRD in subsequent plasma specimens collected at interim timepoints (C2D1, C3D1, C4D1), and EOT

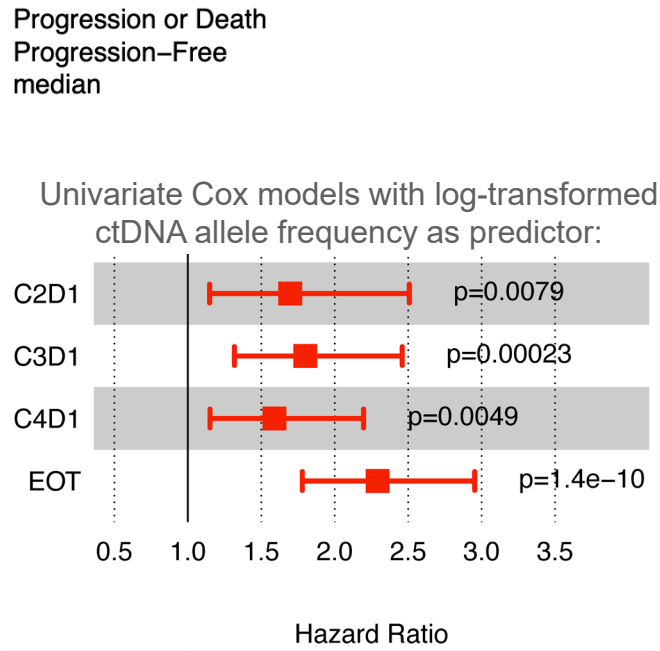
Results: Overview

- 141 patients were evaluated for PVs blinded to clinical outcomes
- 138 pts (98%) were successfully genotyped from plasma or tumor tissue
- ctDNA MRD was successfully profiled from 364 blood specimens for:
  - 115 patients at baseline (pretreatment)
  - 52 patients at C2D1
  - 53 patients at C3D1
  - 51 patients at C4D1
  - 93 patients at EOT

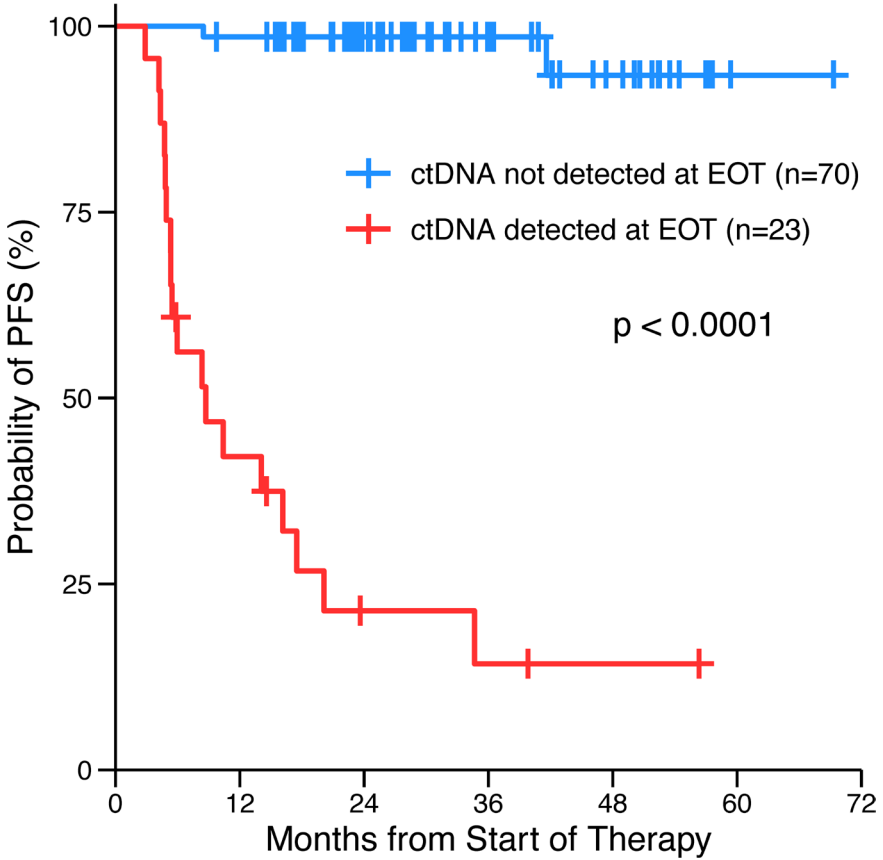


Results: ctDNA Dynamics During Therapy



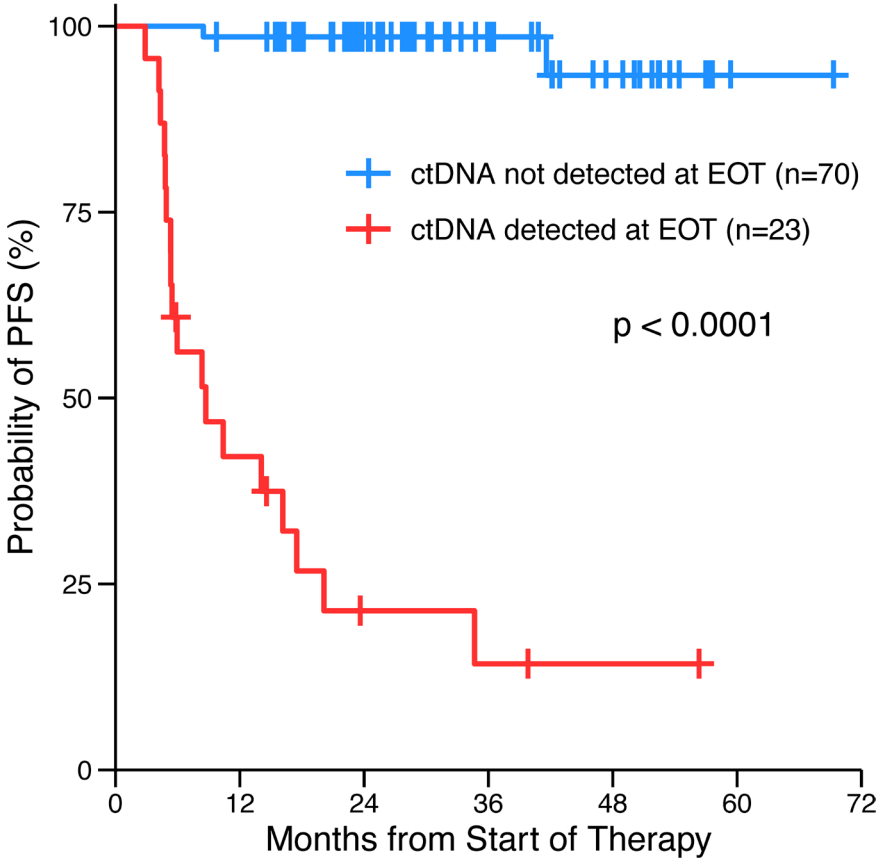


Results: MRD at EOT Best Stratifies Outcomes



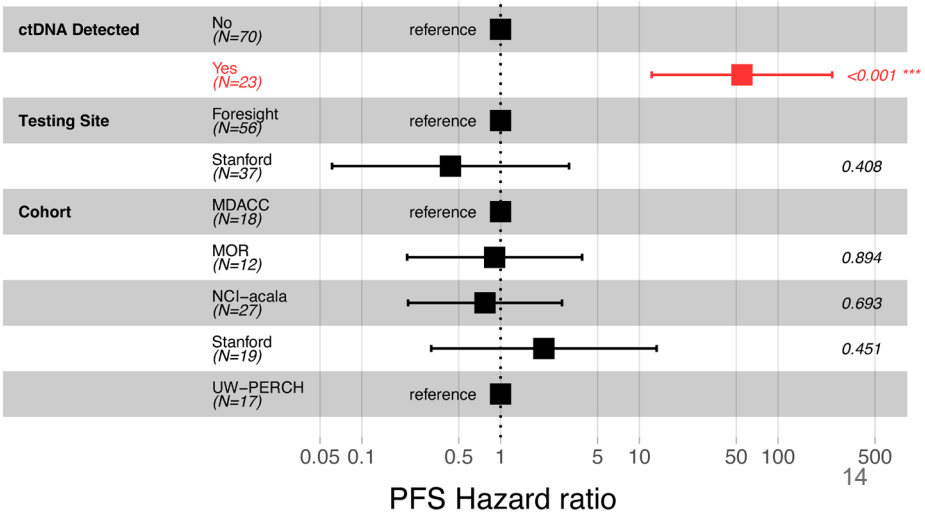
- Persistently detectable at the EOT identified the highest risk group (log-rank p<0.0001, Cox HR=84).
- EOT ctDNA MRD detection by PhasED-seq demonstrated 90% sensitivity (18/20) for identifying PFS events, with lead times up to ~30 months.
- 97% of patients with undetectable ctDNA at EOT (68/70) remained without progression with a median follow up of 17 months (range 0-64 months).

Results: EOT MRD Was Independent of Testing Site or Trial Cohort

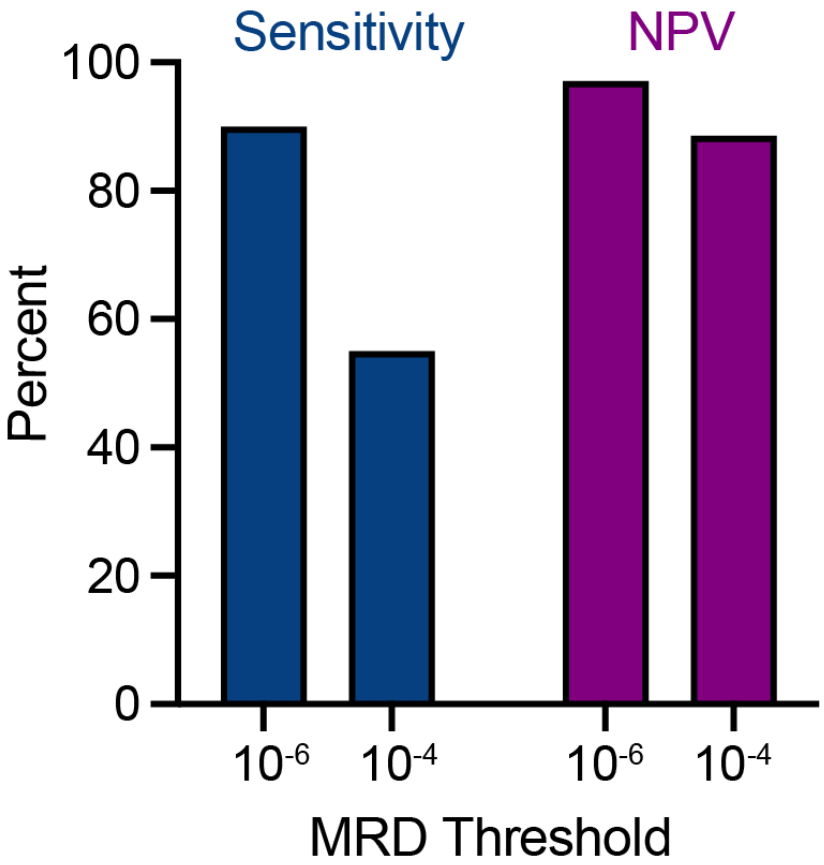


MRD status during therapy or at EOT remained strongly associated with outcomes in multivariable Cox models after controlling for:

- Clinical Study
  - Institution/Site & Induction Therapy Regimen
- Testing Site

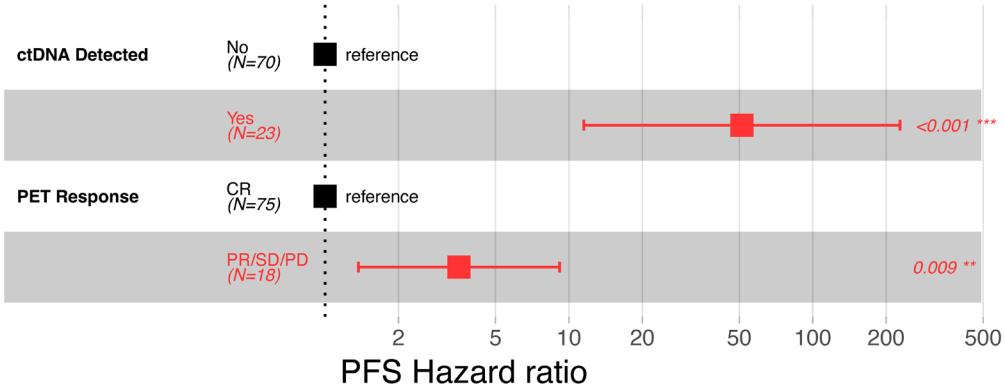


Analytical Sensitivity Improves Clinical Sensitivity at EOT

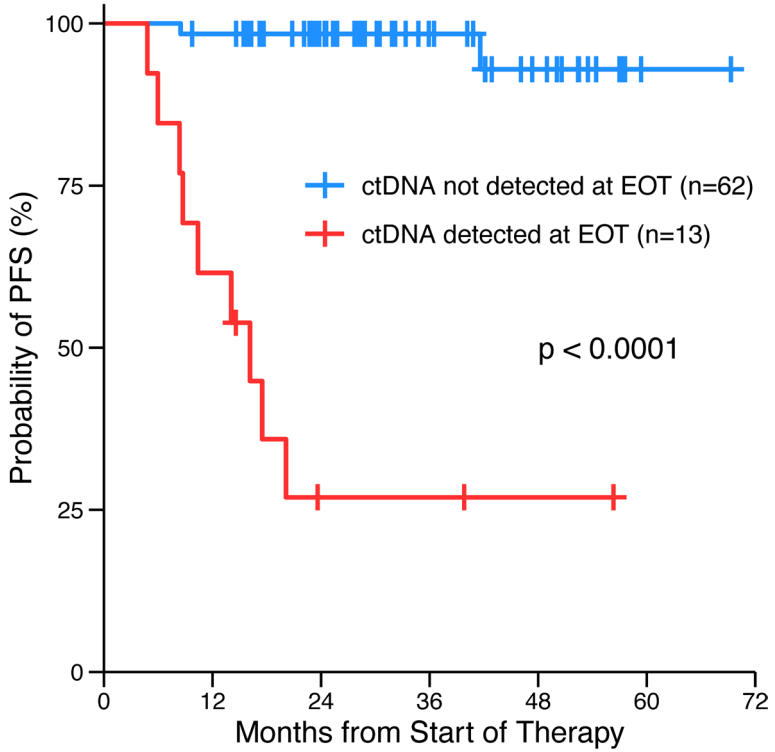


Results: ctDNA at EOT further stratifies PET/CT remissions

- PhasED-Seq performed better than PET/CT at EOT
- In MVA, both EOT PET and PhasED-Seq MRD at EOT were prognostic for PFS
  - MRD-status at EOT was more significantly associated with outcome



PFS of patients in CR at EOT Stratified by PhasED-Seq MRD



Conclusions

- PhasED-Seq ctDNA is a highly prognostic biomarker for DLBCL with MRD status at the EOT the most predictive
- Limits of detection of $1x10^{-6}$ are critical to reliably detect MRD at EOT
- EOT MRD-status may enhance current response criteria; promise as a surrogate clinical trial endpoint
- Clinical trials for DLBCL should prospectively collect plasma at baseline, during therapy and at EOT for the analysis of MRD

Acknowledgments

- Patients, their families, and caregivers
- Foresight Diagnostics
- MorphoSys