Baseline prognostic factors do not predict end of treatment ctDNA MRD status and have limited impact on MRD prognostic performance in DLBCL

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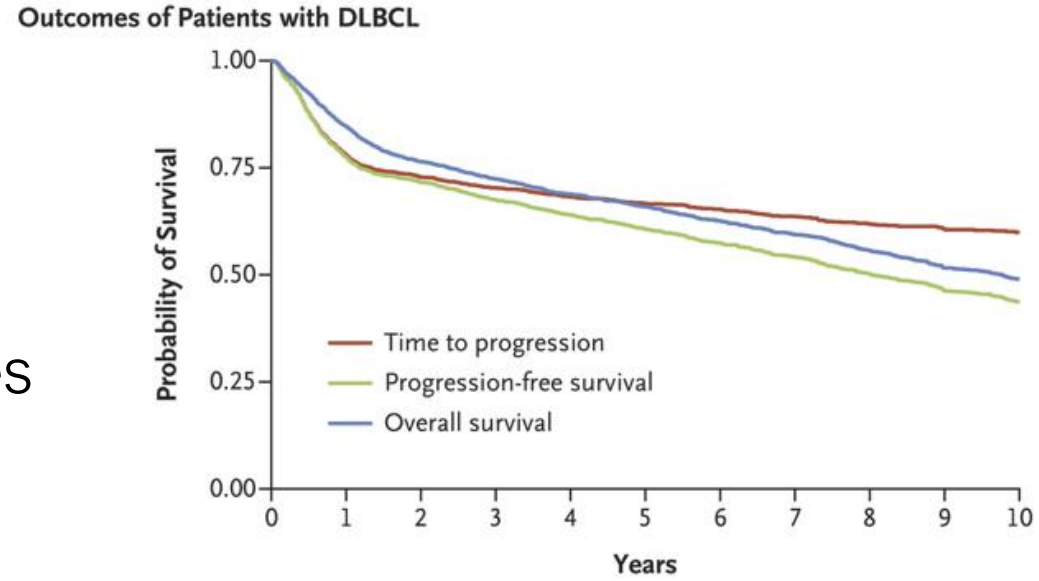
Diffuse Large B-cell Lymphoma (DLBCL)

- DLBCL is a biologically and clinically heterogeneous disease
- First-line treatment with anthracycline-based chemoimmunotherapy leads to varied outcomes



- Improving first-line outcomes by individualizing therapy has been limited in part by insufficient prognostic and disease monitoring tools
  - Novel prognostic tools are being developed
  - Understanding their relationship may be key to optimizing outcomes

Sehn & Salles, NEJM 2022

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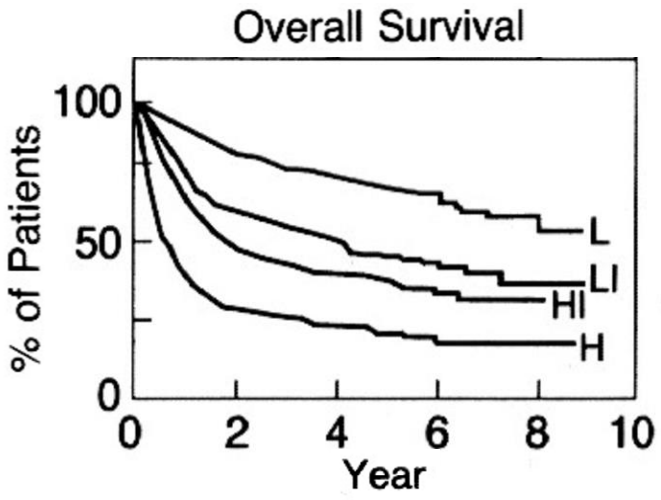
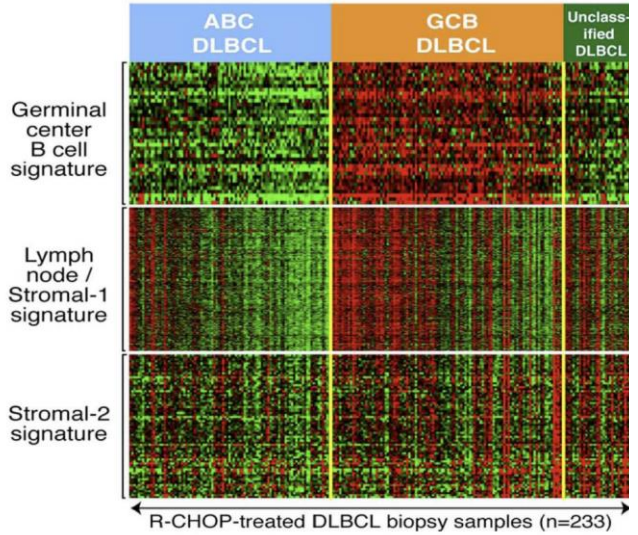
Baseline prognostic tools in DLBCL

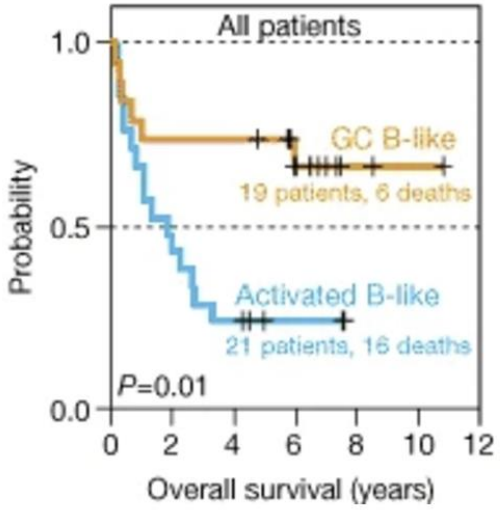
Clinical Factors

IPI
Age > 60
ECOG PS > 1
Stage > 2
Extranodal sites
LDH > ULN



Biological Factors





Shipp et al., NEJM 1993; Alizadeh et al., Nature 2000

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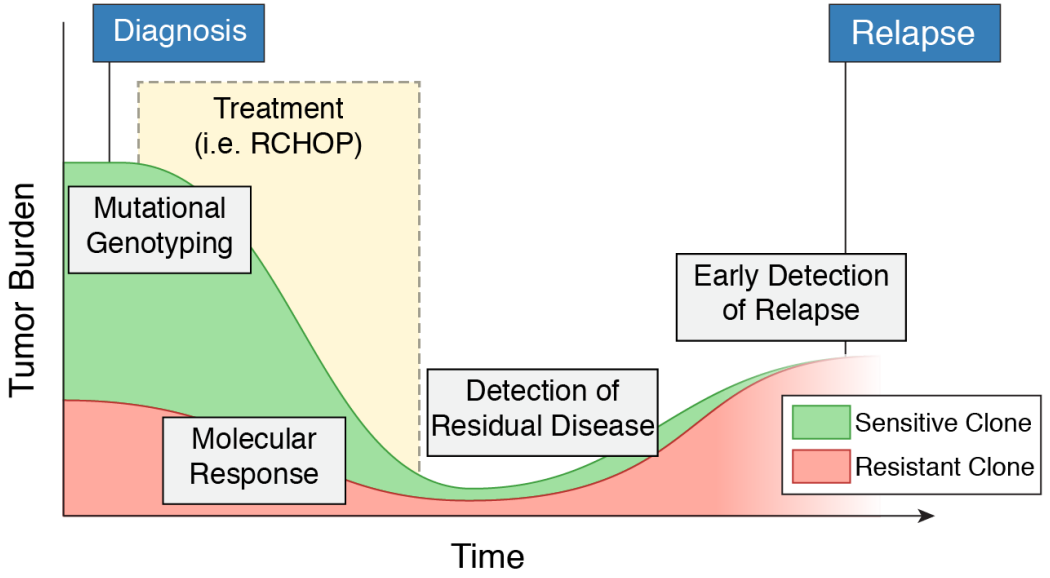
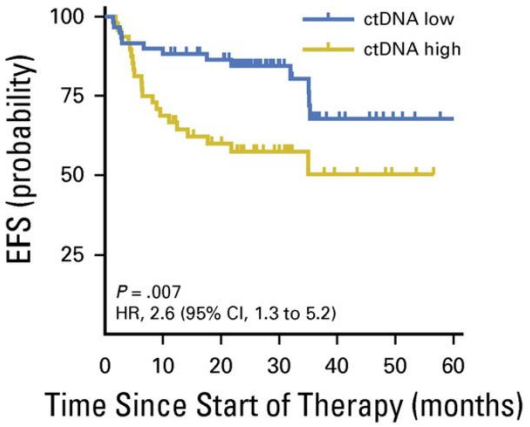
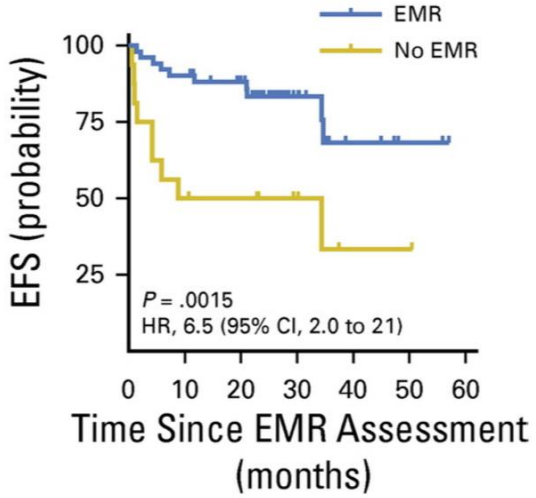
ctDNA is an emerging biomarker in DLBCL



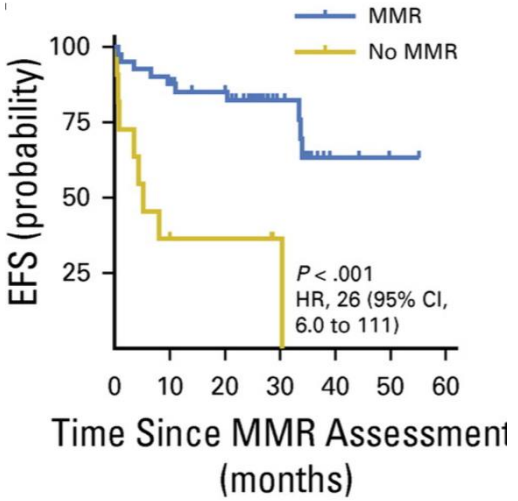
Pre-treatment ctDNA level



Early Molecular Response (EMR)
2-log fold ctDNA decrease from C1 to C2



Major Molecular Response (MMR)
2.5-log fold decrease from C1 to C3



Kurtz et al., JCO 2018

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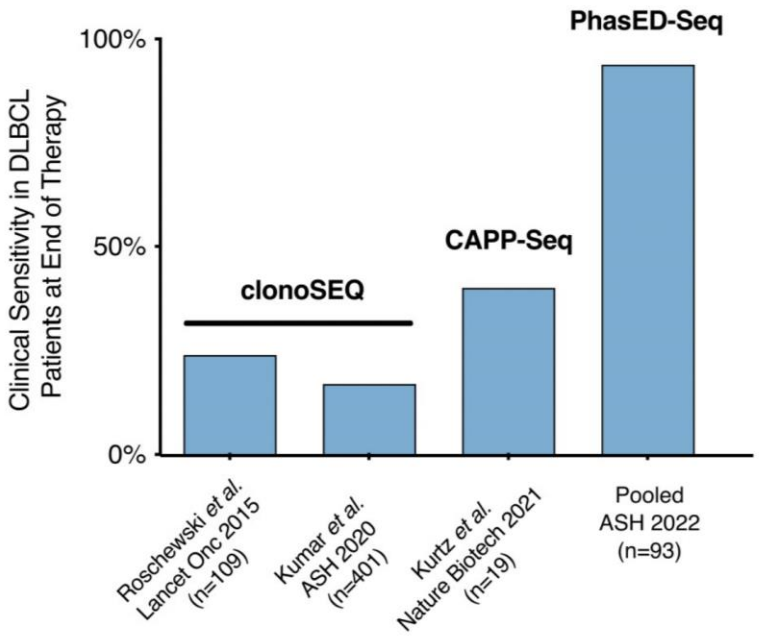
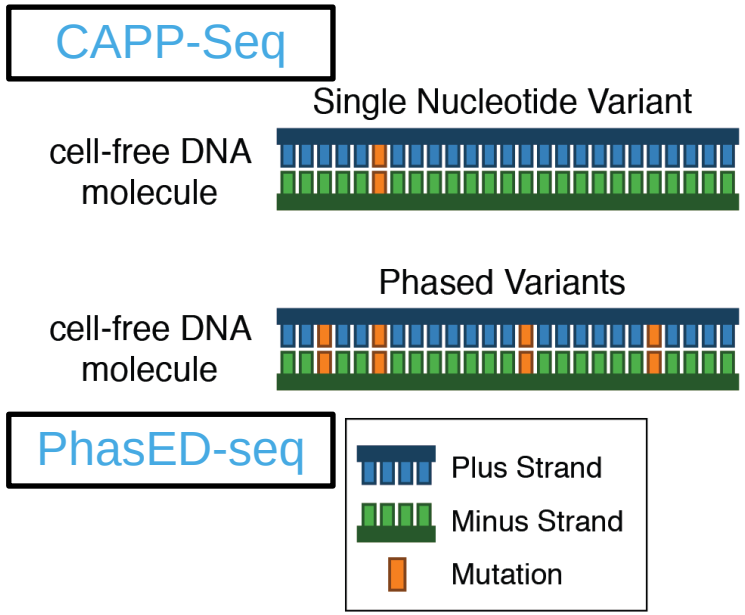
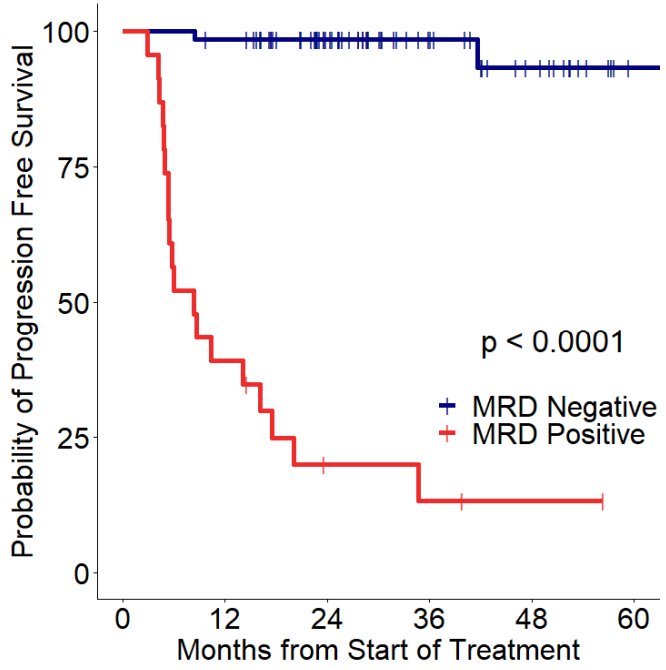
ctDNA for EOT MRD detection in DLBCL

Clinical Sensitivity of ctDNA MRD Assays at EOT





PFS by PhasED-seq Status at EOT



Roschewski et al., ASH 2022 & ICML 2023

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Motivation & Hypothesis

- ctDNA MRD assays have potential utility for DLBCL management
  - Starting to be adapted clinically
- Relationship of known prognostic factors with EOT MRD is unexplored
- Understanding the relationship between prognostic factors and MRD assay performance can optimize clinical trial design and practice
- We hypothesized that baseline factors are associated with EOT MRD status and impact ctDNA MRD assay performance

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Methods

Used a **pooled cohort of DLBCL patients** undergoing 1L therapy with prospectively collected samples

ctDNA analyzed using PhasED-seq

Treated with anthracycline-based chemotherapy

Cases were selected based on having:

- High quality pre-treatment genotyping
- Available EOT plasma samples

Assessed **association of baseline and interim clinical and biologic factors with EOT MRD** status by PhasED-seq

Variables assessed:

- IPI
- Stage
- Age
- Sex
- COO Subtype
- Pre-treatment VAF
- Interim PET
- EMR & MMR

Assessed **predictive ability for PFS of EOT ctDNA MRD** stratified by baseline prognostic variables

- Stratified KM curves
- Time-dependent ROC curves

Cohort

- Pooled meta-cohort of 145 patients with prospectively collected samples from 5 different cohorts

Cohort	Trial	Anthracycline-based Regimen	Trial Therapy	Patients
NCI (Roschewski et al., ASH 2023)	NCT04002947	R-CHOP or DA-EPOCH-R	Acalabrutinib	27
UW (Lynch et al., Blood Adv 2023)	NCT04231877	DA-EPCH-R	Polatuzumab	17
MDACC (Cherng et al., Blood Adv 2023)	NCT02529852	CHOP	Lenalidomide Obinutuzumab	18
Samsung (Sworder et al., ASH 2023)	Observational	R-CHOP-like	N/A	64
Stanford (Kurtz et al, Nat Biotech 2021)	NCT00398177 Observational	R-CHOP or DA-EPOCH-R	N/A	19

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Baseline Characteristics

Characteristics	Total Patients (n = 145)
IPI	
Low (0-1)	28 (21%)
Intermediate (2-3)	82 (61%)
High (4-5)	25 (19%)
Stage	
Early (I & II)	42 (29%)
Advanced (III & IV)	102 (71%)
Age	
≤ 60	79 (54%)
> 60	66 (46%)
COO (IHC)	
Non-GCB	54 (44%)
GCB	68 (56%)

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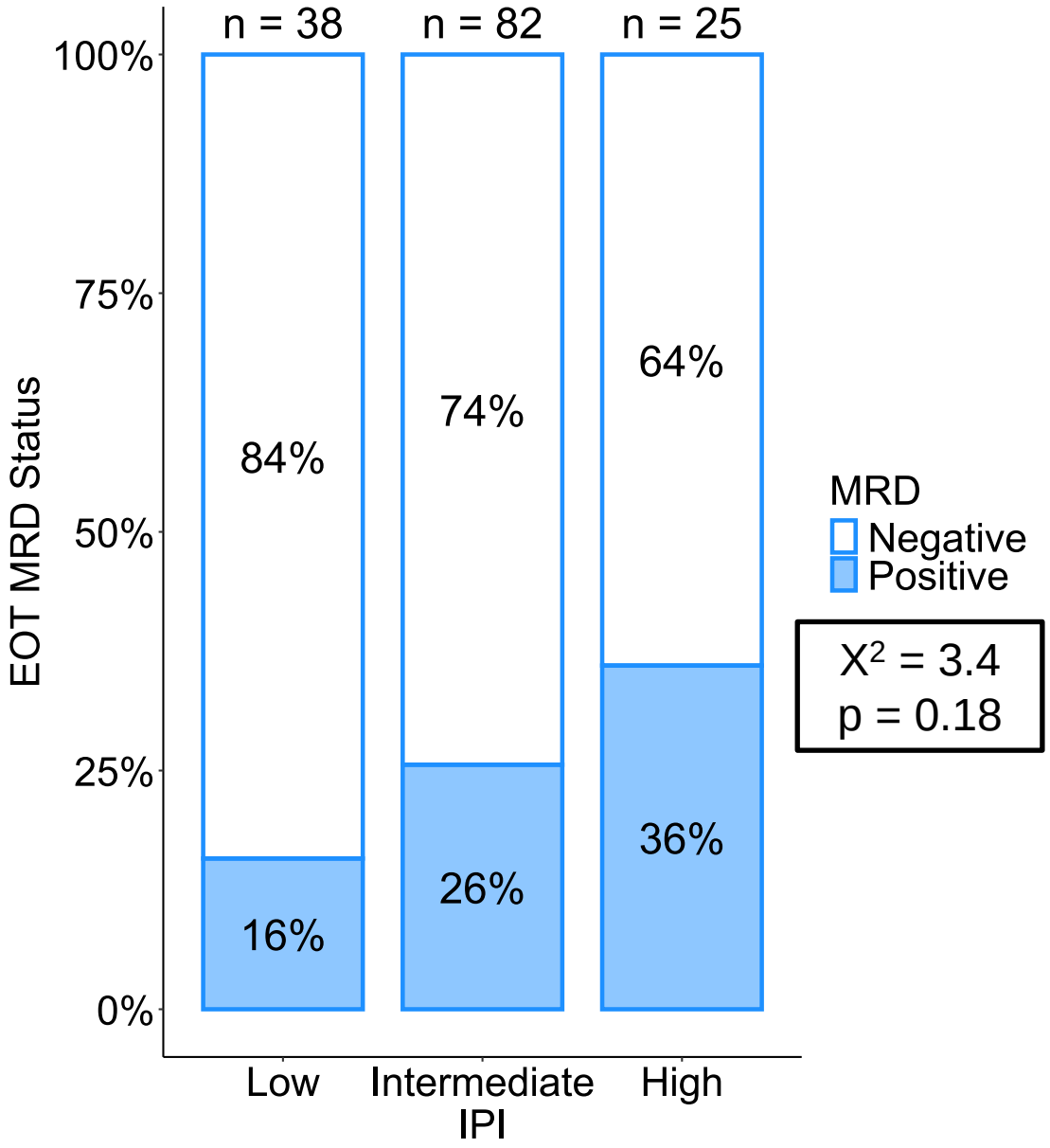
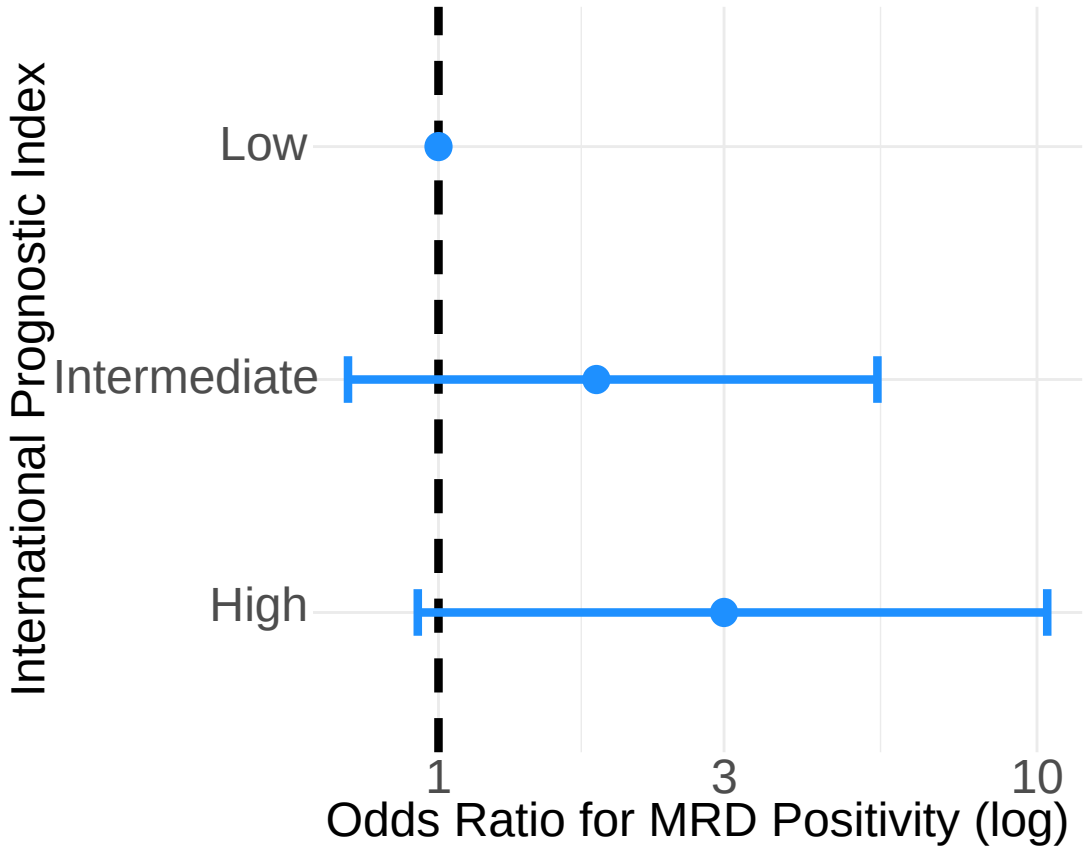
IPI does not strongly predict EOT MRD status





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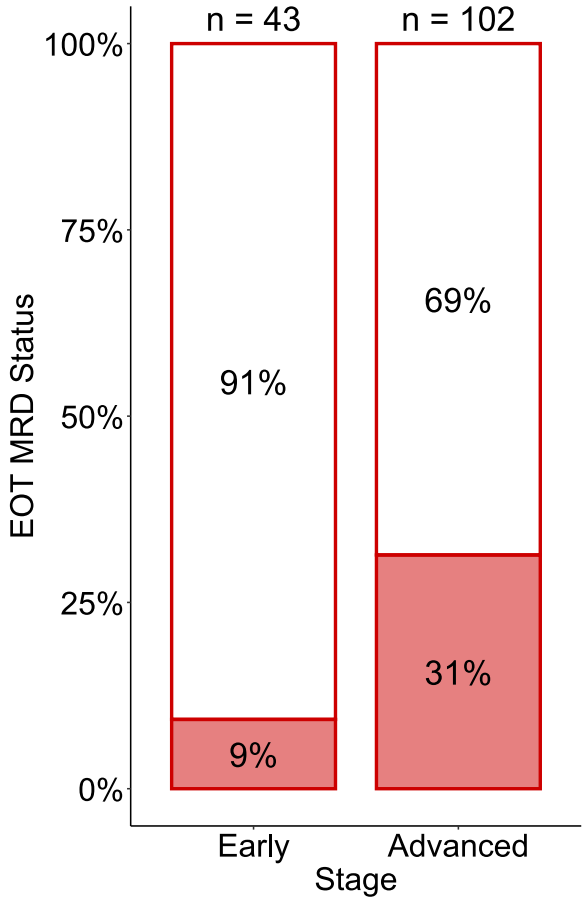
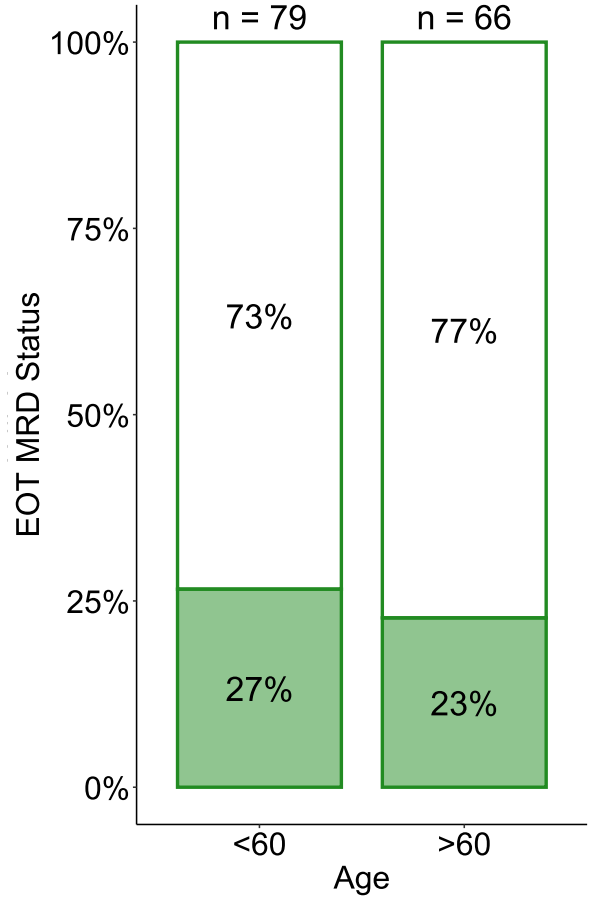
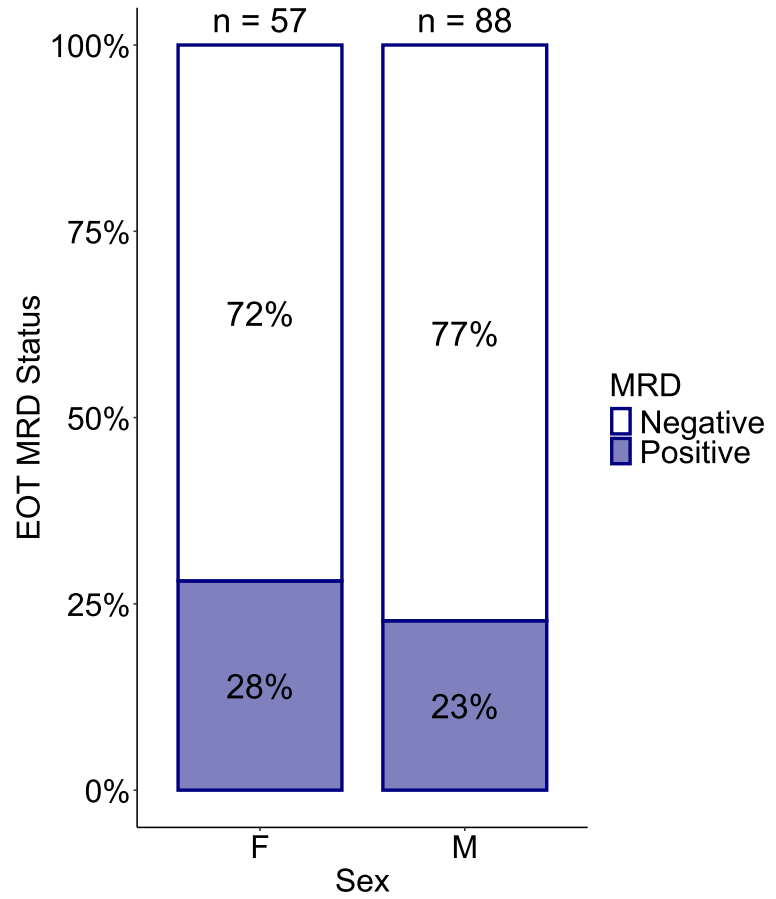
Stage, but not sex or age, is associated with EOT MRD status

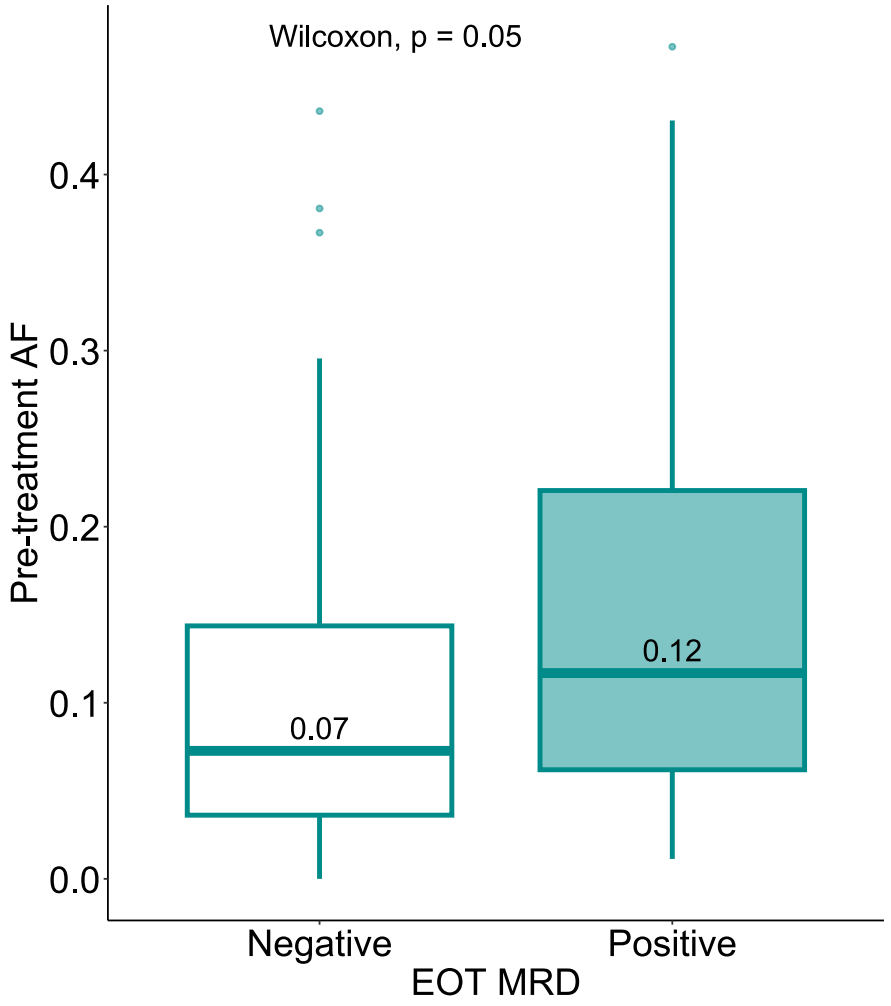


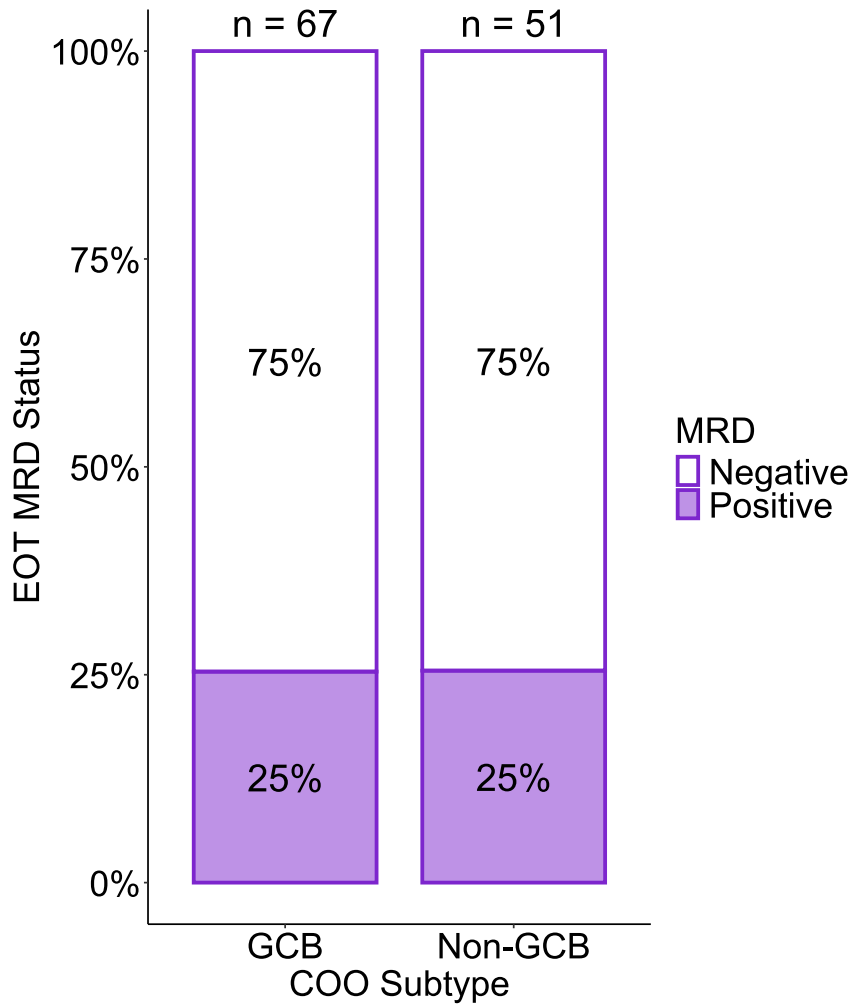




Statistic	Stage	Age	Sex
OR (95% CI)	4.5 (1.6, 16)	0.8 (0.4, 1.7)	0.75 (0.4, 1.6)
P-value (X^2)	0.01 (6.8)	0.7 (0.1)	0.6 (0.3)

ctDNA burden predicts EOT MRD status, while COO subtype does not





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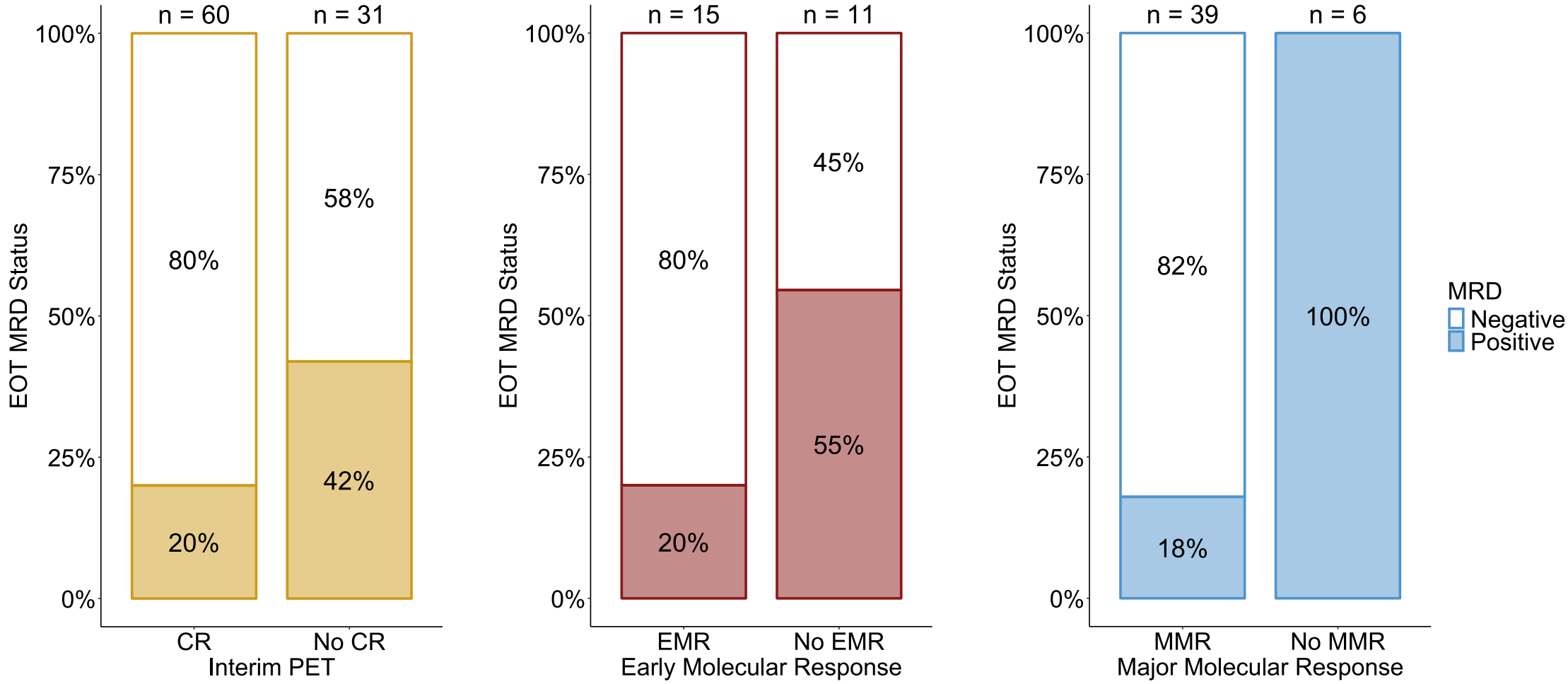
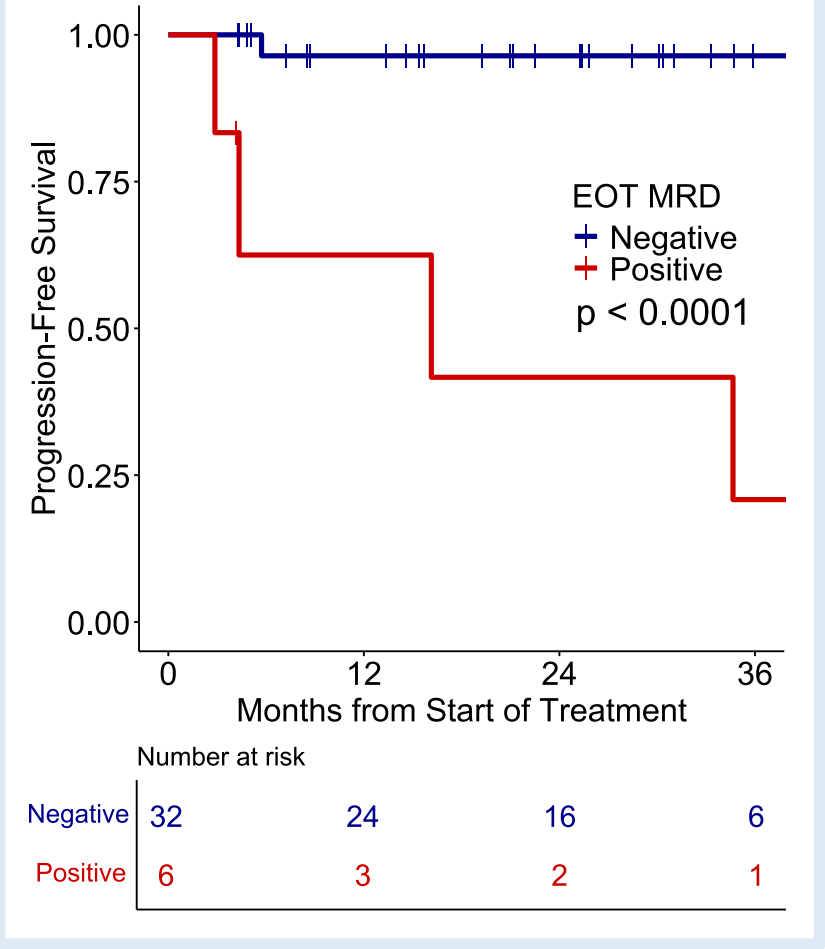
Interim assessments are associated with EOT MRD



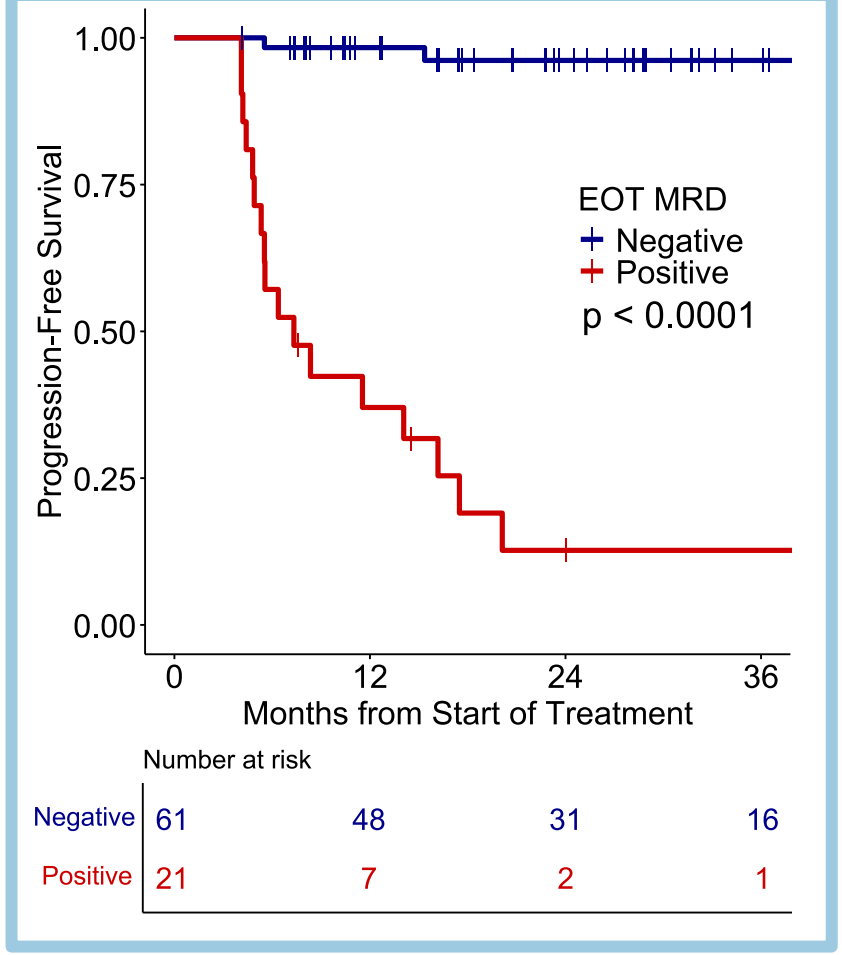
Statistic	Interim PET	Early Molecular Response	Major Molecular Response
OR (95% CI)	2.9 (1.1, 7.6)	4.8 (0.9, 31)	Inf
P-value (X^2)	0.05 (3.9)	0.15 (2)	0.0002 (13)

EOT MRD is highly prognostic regardless of IPI

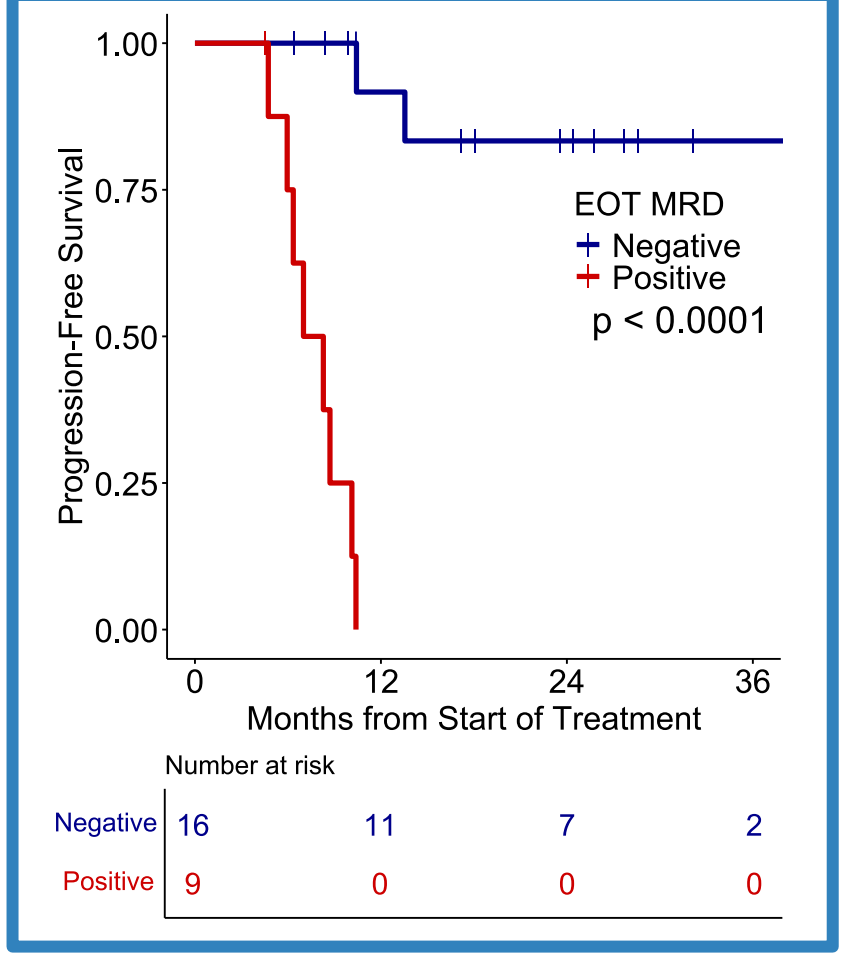
Low



Intermediate



High



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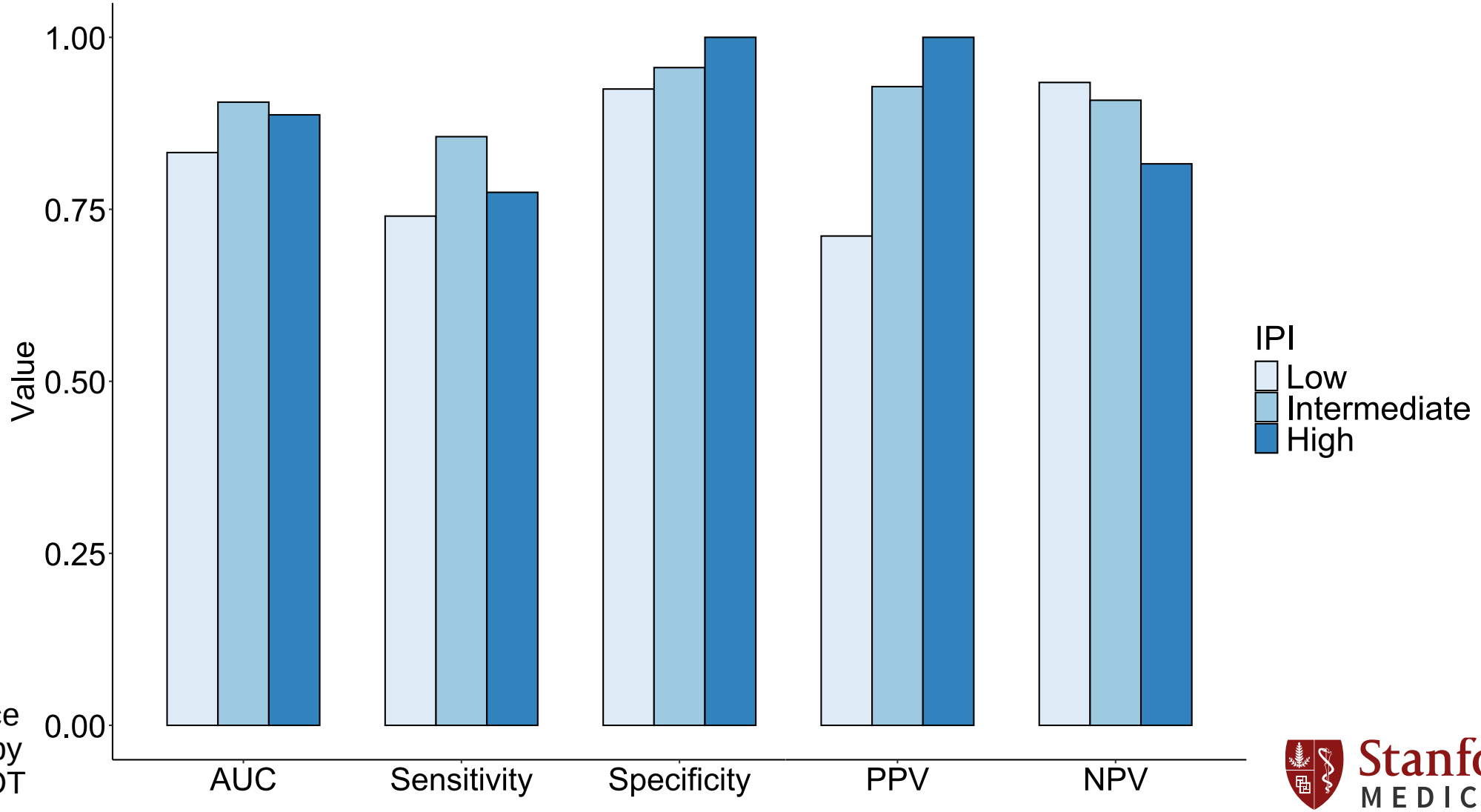
EOT MRD by PhasED-seq predicts PFS regardless of IPI



AUC = performance in predicting PFS by PhasED-seq at EOT

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Conclusions

- IPI is not strongly associated with EOT MRD status
- Stage and pre-treatment ctDNA are associated with EOT MRD status
  - Interim assessments are associated with MRD status
- PhasED-seq maintains high performance for predicting PFS regardless of IPI
  - Risk-adapted therapies and disease monitoring may be independent of other clinical factors
- Important implications for trial design and eventual clinical practice

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Acknowledgements

Mentors

- Ash Alizadeh
- David Kurtz

Collaborators

- Mark Roschewski
- Won Seog Kim
- Sang Eun Yoon
- Seok Jin Kim
- Jason Westin
- Ryan Lynch
- Stefan Alig
- Sandra Close
- Jake Chabon
- Davide Rossi
- Wyndham Wilson
- Max Diehn

FORESIGHT DIAGNOSTICS

Research Support

AMERICAN SOCIETY OF HEMATOLOGY

Lymphoma Research Foundation

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