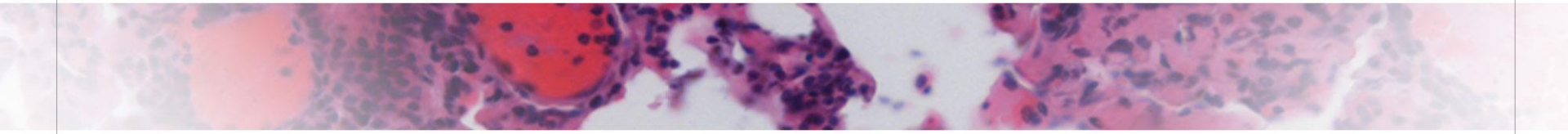
American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



Prognostic utility of Minimal Residual Disease (MRD) after curative intent induction therapy for DLBCL: A prospective real-world ctDNA study

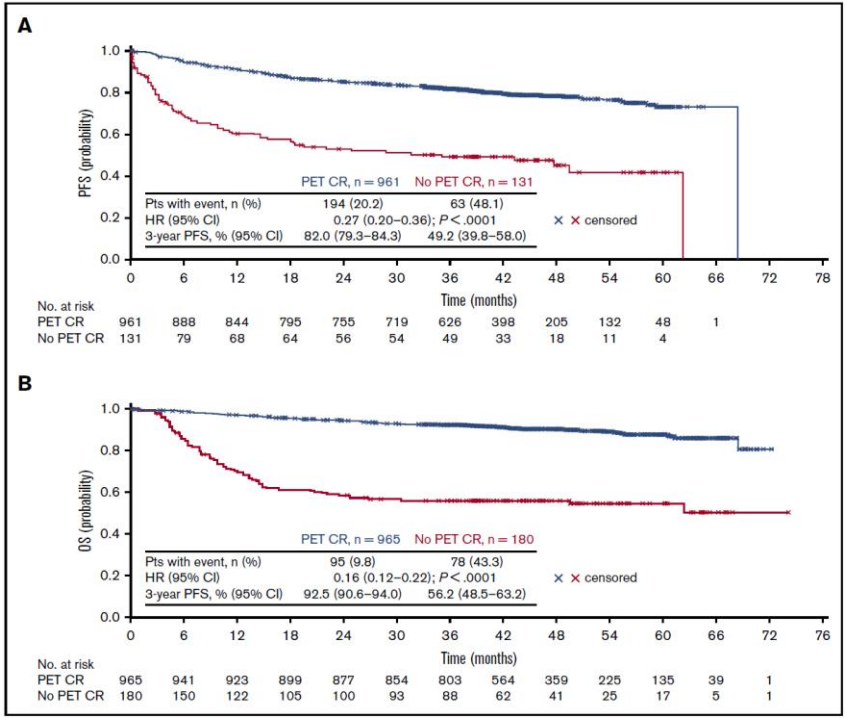
Brian J Sworder, Sang Eun Yoon, Seok Jin Kim, Andre Schultz, Greg Hogan, Sandra Close, Jacob J Chabon, Maximilian Diehn, David M Kurtz, Ash A Alizadeh, Won Seog Kim

SUNG KYUN KWAN UNIVERSITY (SKKU) School of Medicine

UCI Health

Standard of Care Response Assessment

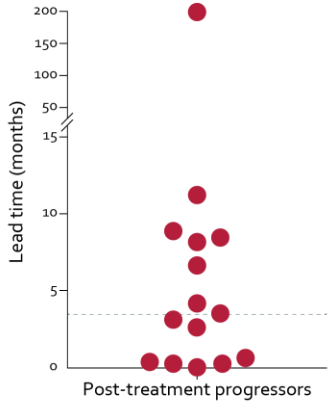
- PET/CT is the current standard of care to assess response during and after treatment to inform clinical decision making.
- However, the GOYA trial showed that 49% of patients who were PET positive did not have a progression event within 3 years.
- This suggests that improved prognostication at EOT could limit overtreatment and reduce the need for additional testing.



Kostakoglu L, Martelli M, Sehn LH, et al. End-of-treatment PET/CT predicts PFS and OS in DLBCL after first-line treatment: results from GOYA. *Blood Advances*. 2021;5(5):1283-1290.

MRD Detection in DLBCL

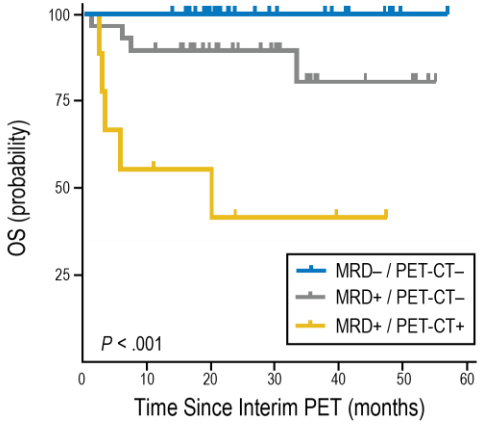
- Circulating tumor DNA (ctDNA) Minimal Residual Disease (MRD) detection has the potential to improve prognostication in diffuse large B-cell lymphoma.



Lead-time between detection of disease by ctDNA and detection by CT or flow cytometry in 15 DLBCL patients who relapsed after treatment.

Dashed line shows median lead time of 3.5 months.

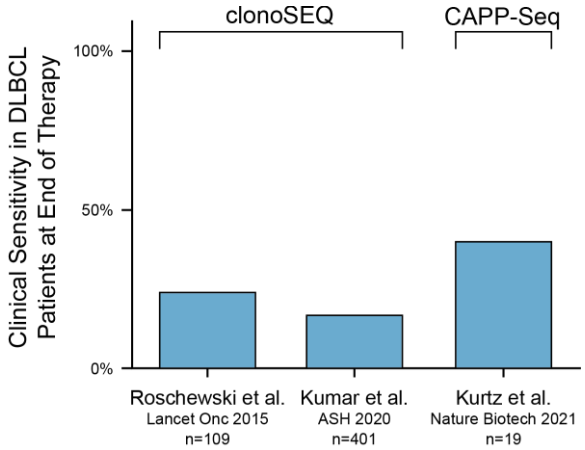
Roschewski et al. *Lancet Oncol*. 2015;16(5):541-9.



Overall survival in patients with LBCL stratified by interim PET-CT results and molecular response.

Kurtz et al. *J Clin Oncol*. 2018;36(28):2845-2853.

- First generation MRD detection tests have shown limited sensitivity.



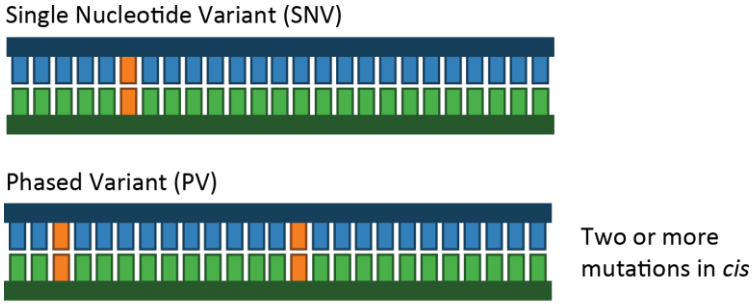
Roschewski et al. *Lancet Oncol*. 2015;16(5):541-9.

Kumar et al. *Blood*. 2020; 136 (Supplement 1): 46–47.

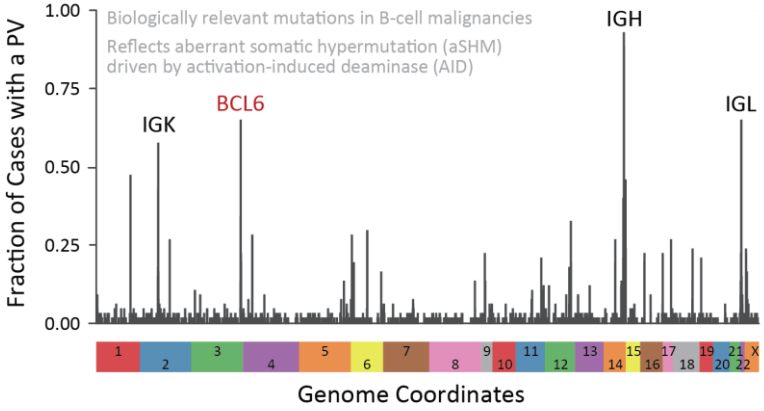
Kurtz et al. *Nat Biotechnol*. 2021;39:1537-1547.

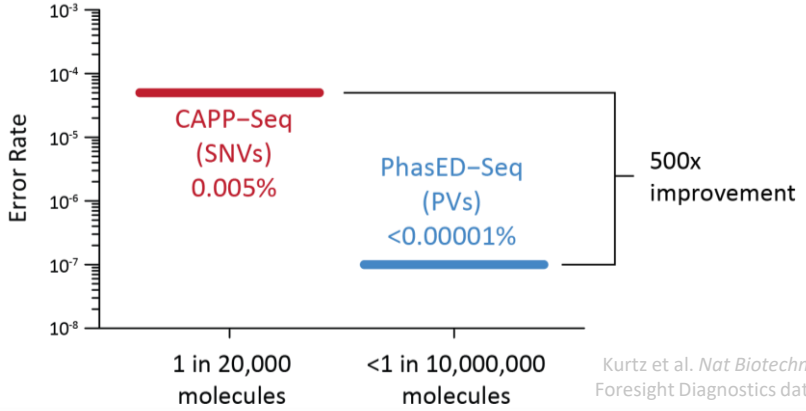
PhasED-Seq improves detection of MRD

Phased Variant Enrichment and Detection Sequencing



- Detection of phased variants greatly reduces background error rate in comparison to SNV detection
- Allows for reliable MRD detection when ctDNA is present at very low levels





Kurtz et al. *Nat Biotechnol*. 2021
Foresight Diagnostics data on file

Study Design

- We prospectively enrolled a real-world cohort from Samsung Medical Center who were diagnosed with Diffuse Large B-Cell Lymphoma through histopathological diagnostic procedures, with or without previous treatment.

- MRD levels were compared to standardized responses by:
  - PET/CT Imaging (Lugano 2014)
  - Progression-Free Survival
  - Overall Survival

Enrolled Patients with Stage I-IV DLBCL

- Newly diagnosed with DLBCL
- Undergoing first-line therapy with R-CHOP or EPOCH-R

Blood Collection for ctDNA Profiling

- Blood collection (Streck) at 3 pre-defined milestones
  - Baseline (pre-treatment)
  - Interim (typically following cycle 3)
  - End of treatment (EOT)

ctDNA-MRD Testing

- PhasED-Seq testing (Foresight Diagnostics, Inc.)

ctDNA-MRD Testing

- Patients were included in the analysis if:
  - Baseline plasma (median 4mL) was available, *and*
  - Was collected prior to treatment or had sufficient tumor burden for testing
- 364 samples from 99 patients were tested in a blinded manner by PhasED-Seq (Foresight Diagnostics, Inc.)
- Evaluable patients had a viable sample and PET/CT results at the relevant timepoint
  - 83 evaluable patients for interim timepoint
  - 77 evaluable patients for EOT timepoint

Tumor-Specific PVs Identified

- Targeted sequencing of pre-treatment plasma (ctDNA) and paired PBMCs (genomic DNA) using a fixed panel that includes regions of biological relevance for LBCL
- Tumor-specific PV list generated by selecting PVs that are present in ctDNA and are absent or present at low levels in gDNA

MRD Assessed at Interim and EOT Timepoints

- ctDNA-MRD assessed at interim and EOT timepoints using tumor-specific PV list
- MRD positive if ctDNA levels exceeded an analytical detection threshold (~1:10^6 cfDNA molecules) corresponding to 98% specificity

Cohort Description (N=99)

Demographics

Characteristic		N (%)
Age	Median	58
	IQR	48, 66
Sex	Female	38 (38%)
	Male	61 (62%)
Stage	I	8 (8%)
	II	25 (25%)
	III	12 (12%)
	IV	54 (55%)

Disease Characteristics

Characteristic		N (%)
IPI	0-1	27 (27%)
	2	20 (20%)
	3	31 (31%)
	4-5	21 (12%)
Cell of Origin*	ABC	54 (55%)
	GCB	30 (30%)
	Undetermined	15 (15%)
Double-Hit Status	Non-double hit	66 (67%)
	Double-hit	5 (5%)
	NA	28 (28%)

Therapy & Response

Characteristic		N (%)
Therapy	R-CHOP	93 (94%)
	DA-EPOCH-R or R-EPOCH	6 (6%)
Interim PET Response	CMR	70 (70%)
	Non-CMR	25 (25%)
	NA	4 (4%)
End of Therapy PET Response	CMR	71 (71%)
	Non-CMR	13 (13%)
	NA	15 (15%)

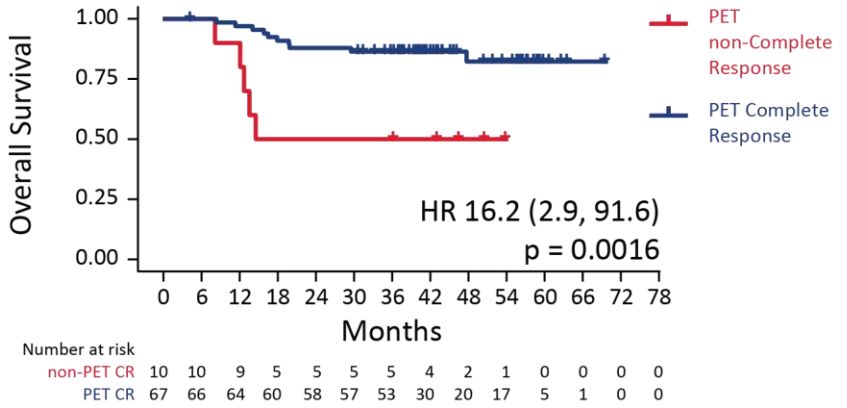
*Cell of origin was determined by NanoString or Hans

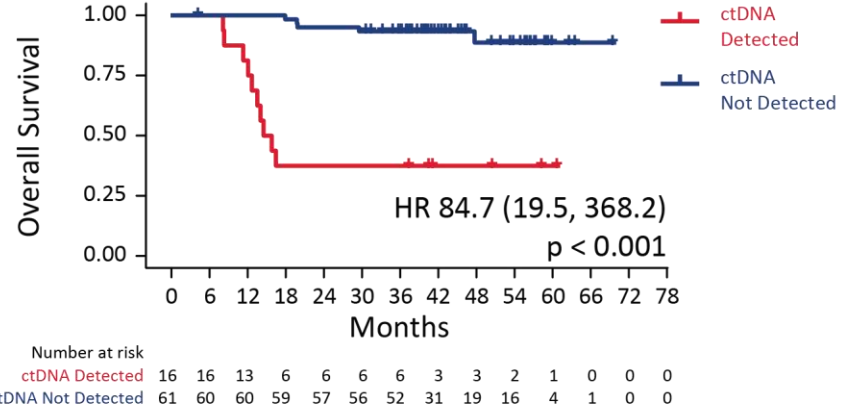
ctDNA outperforms PET for response assessment

- Stratification of patient outcomes by either PET/CT scan or ctDNA-MRD at the end of therapy

	PET-CT		ctDNA-MRD	
	Positive non-CR	**Negative** CR	**Positive** ctDNA detected	**Negative** ctDNA not detected
PFS at 24 mos	40%	74%	25%	82%
OS at 24 mos	50%	86%	38%	93%

Presented at ASH 2023

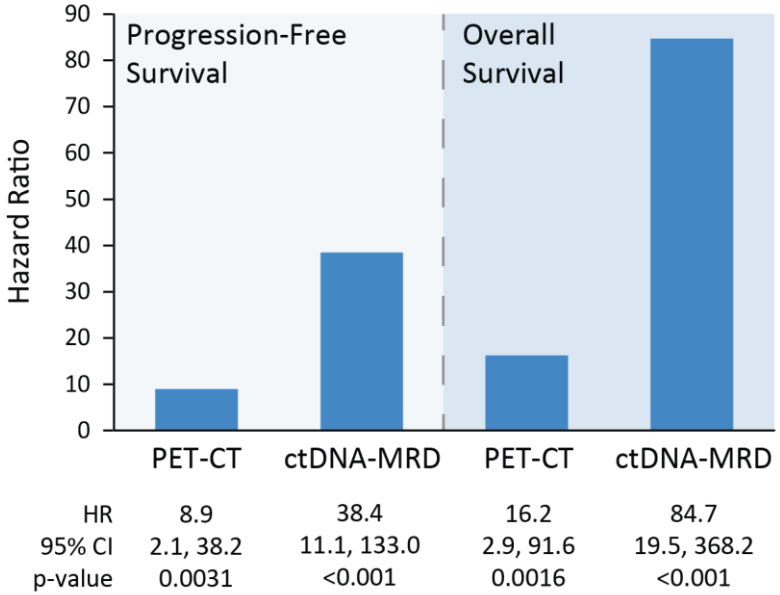




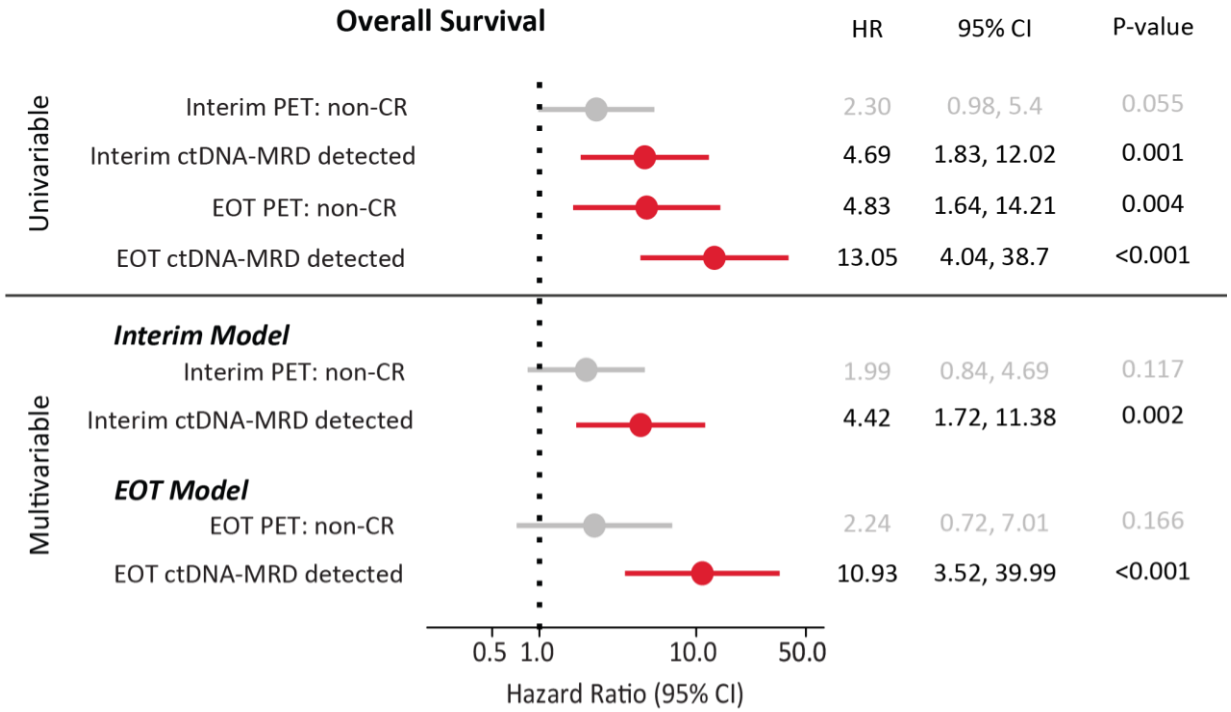
ctDNA outperforms PET for response assessment

- Standard response assessment in DLBCL depends on PET/CT scan at EOT
  - Interpreted using Lugano 2014 criteria
- ctDNA-MRD assessment better stratified patient outcomes (PFS and OS) than standard response assessment

	PET-CT		ctDNA-MRD	
	Positive non-CR	**Negative** CR	**Positive** ctDNA detected	**Negative** ctDNA not detected
PFS at 24 mos	40%	74%	25%	82%
OS at 24 mos	50%	86%	38%	93%



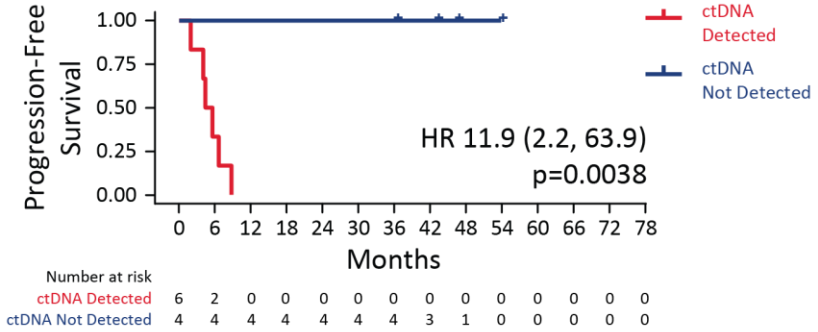
ctDNA-MRD outperforms PET/CT scan at interim and EOT time-points

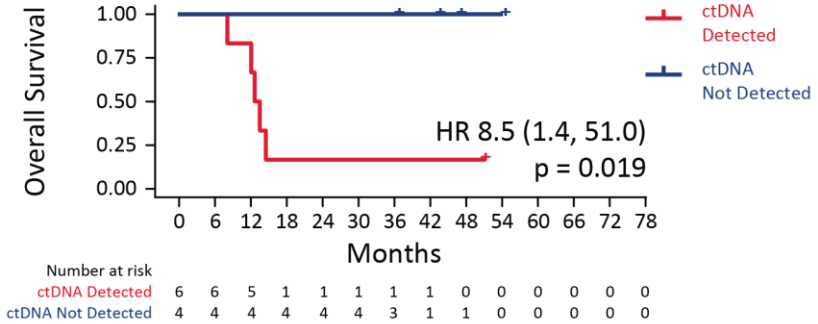


ctDNA-MRD predicts outcomes when PET/CT is positive at EOT

- Stratification of outcomes by ctDNA-MRD in the subset of **patients who were PET/CT positive** at the end of therapy
- ctDNA-MRD provides additional risk stratification that could inform treatment decisions

	MRD Positive ctDNA detected	MRD Negative ctDNA not detected
PFS at 24 mos	0%	100%
OS at 24 mos	17%	100%

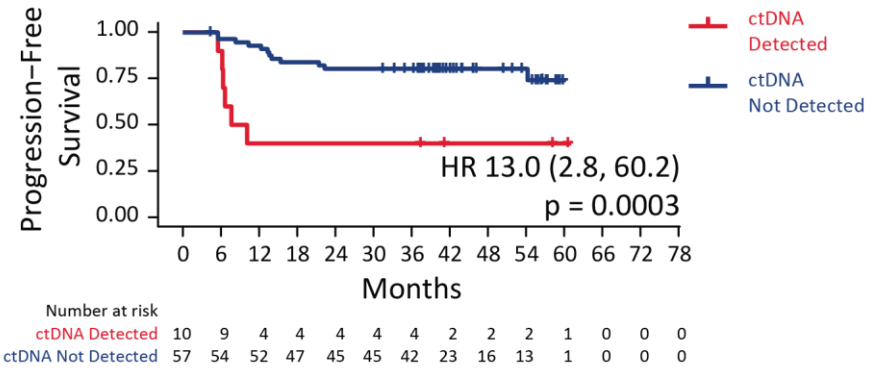


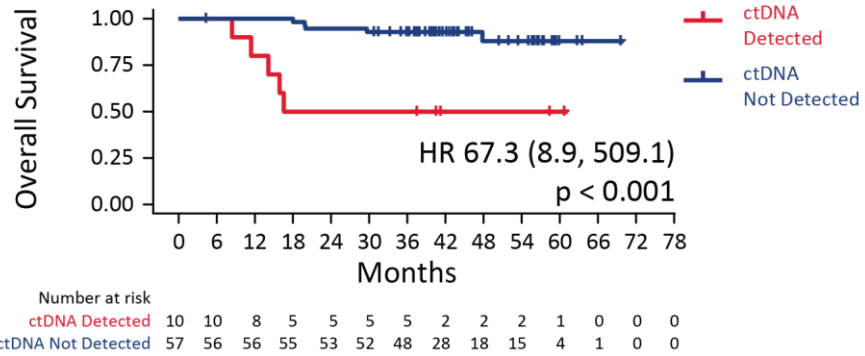


ctDNA-MRD predicts outcomes when PET/CT is negative at EOT

- Stratification of outcomes by ctDNA-MRD in the subset of **patients who were PET/CT negative** at the end of therapy
- ctDNA-MRD identified patients who were PET/CT negative at EOT who experienced disease progression or death

	MRD Positive ctDNA detected	MRD Negative ctDNA not detected
PFS at 24 mos	40%	80%
OS at 24 mos	50%	93%

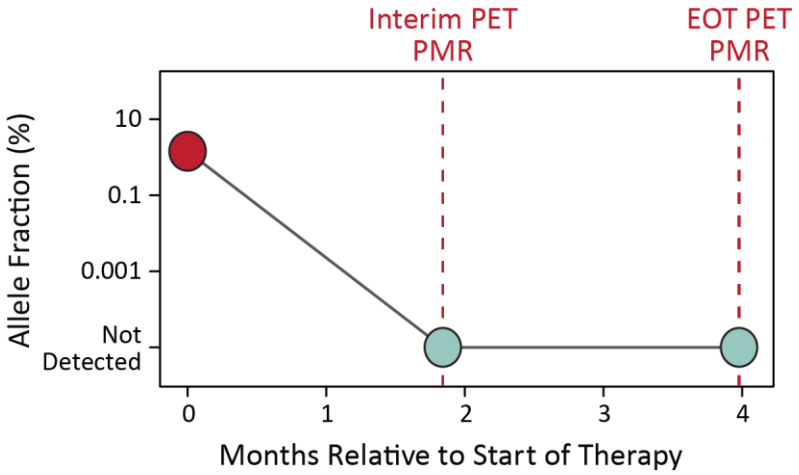




ctDNA-MRD predicts outcomes when discordant with PET/CT at EOT

Patient 1

EOT PET positive and **ctDNA-MRD negative**

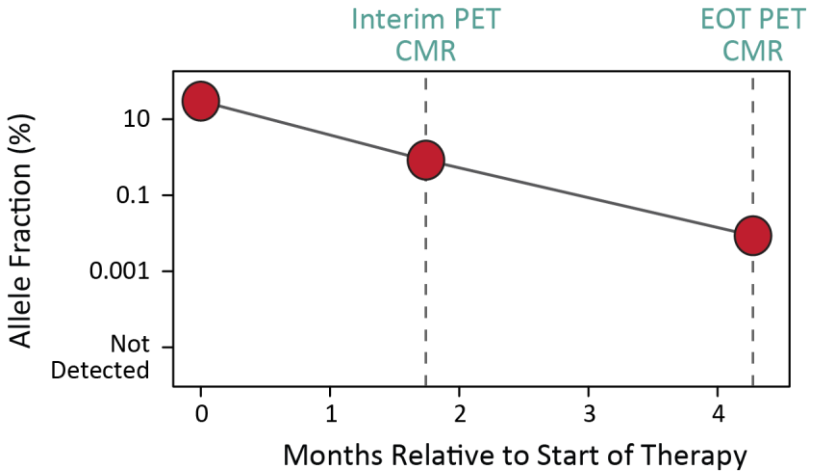


No Progression

PFS 45.6 months (3.8 years)

Patient 2

EOT PET negative and **ctDNA-MRD positive**

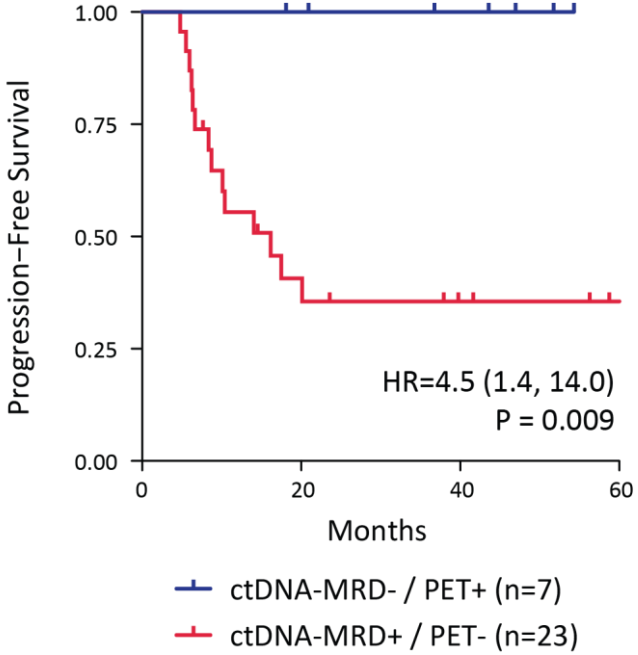


Progression

PFS 5.5 months

ctDNA-MRD predicts outcomes when discordant with PET/CT at EOT

- Comparison of PFS in cases where **PET/CT and ctDNA-MRD response assessments at the end of therapy are discordant**
  - Pooled analysis of current dataset and previously reported dataset (N=92, Roschewski M et al, ASH 2022*)
  - PET/CT scans read according to standard of care
- Cases with ctDNA-MRD+ / PET- have significantly inferior PFS to those with ctDNA-MRD- / PET+



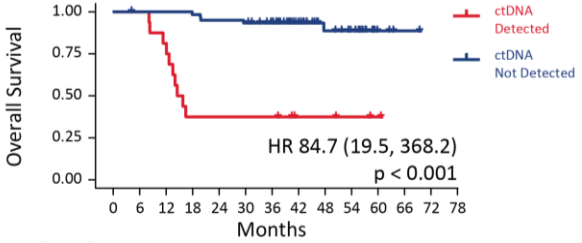
*Roschewski et al cohort included LBCL cases with EOT plasma and PET/CT available. Genotyping performed using plasma or tumor tissue.

Limitations

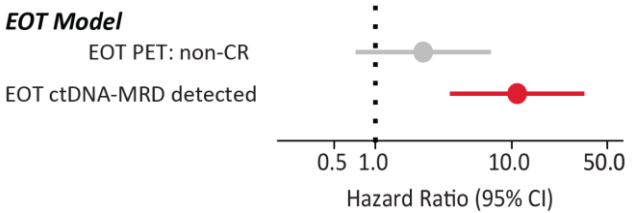
- Genotyping was completed using pre-treatment plasma samples with relatively low volumes (median 4 mL pre-treatment plasma).
    - Genotyping using tumor tissue may have identified more phased variants (PVs) to improve MRD detection at interim and EOT timepoints.

Conclusions

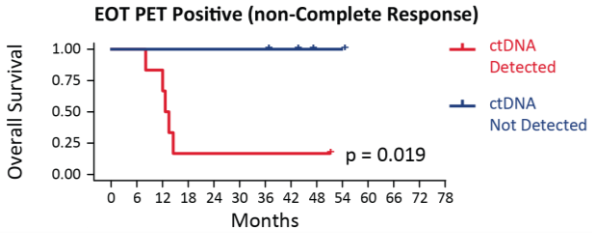
These data demonstrate the feasibility and the prognostic utility of ctDNA-MRD during and after SOC induction therapy for DLBCL in a real-world population using an ultrasensitive ctDNA-MRD assay.



The higher predictive value and accuracy of detectable ctDNA-MRD as compared with PET/CT suggest opportunities for integration of such assays in lymphoma response criteria, to potentially inform future clinical decision making.



Use of ctDNA-MRD for confirmatory testing in PET-CT positive patients at EOT could eliminate the need for confirmatory biopsy to inform treatment decisions following the completion of first-line therapy.



Acknowledgements

SKKU Samsung Medical Center Team

- Sang Eun Yoon
- Seok Jin Kim
- Won Seog Kim

Stanford University Team

- David Kurtz
- James Hamilton
- Mari Olsen
- Max Diehn
- Ash Alizadeh

Foresight Diagnostics Team

- Andre Schultz
- Greg Hogan
- Krystal Brown
- Sandra Close
- Jacob Chabon