ctDNA-Based MRD as a Dynamic Biomarker for Monitoring Treatment Response and Relapse in Lymphoma

Poster# ABCL-573

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Background

- Lymphomas are a diverse group of immune system cancers, with nearly 80,000 new diagnoses projected in 2026[1].
- PET/CT imaging at end of treatment (EOT) has limited performance in predicting relapse, and improved prognostic tools are needed to better identify high-risk patients and personalize treatment strategies[2].
- Detection of molecular residual disease (MRD) via circulating tumor DNA (ctDNA) can inform treatment response, improve risk stratification, and enable early detection of recurrence for patients with lymphoma[3].
- NCCN recommends EOT ctDNA-MRD assessment with a sensitive MRD test to adjudicate positive PET/CT imaging if biopsy unfeasible.

Methods

- Retrospective analysis of 85 patients with lymphoma who underwent commercial ctDNA testing in the real-world clinical setting. Whole genome sequencing (WGS) was performed on residual tumor and paired normal samples to identify tumor-specific phased variants, structural variants, and single-nucleotide variants for ctDNA-MRD detection using a personalized, tumor-informed mPCR-NGS assay (Signatera™ Genome with Phased and Structural variants, Natera, Inc.).
- Subtype representation: Aggressive (N=72): DLBCL (n=49), Mantle cell (n=7), PTCL (n=3), tFL (n=3), Burkitt (n=2), Enteropathy-associated T-cell (n=2), Hodgkin (n=2), ALCL (n=1), Hepatosplenic (n=1), PCNSL (n=1), T-cell lymphoblastic (n=1). Indolent (N=13): Follicular (n=10), Marginal zone (n=3).
- Plasma samples (n=579) were collected prior to treatment (baseline), during first-line therapy (1L), at end-of-treatment (EOT), and during surveillance.
- ctDNA dynamics during 1L and ctDNA-MRD status at EOT and during surveillance was correlated with event-free survival (EFS: interval from the end of 1L therapy until progression, relapse, death, or salvage treatment).
- Prognostic performance of EOT ctDNA-MRD status vs. PET/CT is reported.
- Baseline ctDNA-MRD detection was 100% (42/42 evaluable samples).
- Signatera Genome with Phased and Structural variants demonstrated an analytical limit of detection (LOD95) below 1 ppm tumor fraction, with ctDNA detected at levels below 0.1 ppm, in a cell line dilution study.

Table 1. Predictive performance of surveillance ctDNA testing

Sensitivity	**100% (11/11)**
Specificity	**91.3% (21/23)**

Table 2. Patient and clinical characteristics

Characteristic		Overall (N=85)	Aggressive (N=72)	Indolent (N=13)
Age, median (Min, Max), years		62 (19, 84)	61 (19, 84)	64 (41, 83)
Sex, n (%)	Female	39 (45.9%)	37 (51.4%)	2 (15.4%)
	Male	46 (54.1%)	35 (48.6%)	11 (84.6%)
Stage, n (%)	I	9 (10.6%)	7 (9.7%)	2 (15.4%)
	II	17 (20.0%)	15 (20.8%)	2 (15.4%)
	III	7 (8.2%)	5 (6.9%)	2 (15.4%)
	IV	44 (51.7%)	40 (55.5%)	4 (30.8%)
	Unknown	8	5	3
Follow-up EFS, Median (range), months		23 (1, 74)	24 (1, 74)	19 (1, 41)
Deaths		15	14	1
ctDNA timepoints, Median (range)		6 (1, 27)	7 (1, 27)	4 (1, 12)
ctDNA detection* (levels)	**MTM/mL, Median (range)**	2.059 (0.003–12,292)	2.21 (0.003–12,292)	1,462 (0.015–4,980)
	ppm, Median (range)	1,155 (1.2–544,759)	1,188 (1.2–544,759)	1,122 (7.2–332,859)

**across all ctDNA timepoints. 53% (39/73) of ctDNA-positive patients were detected in the ultrasensitive range (<100 ppm), with lowest detection of 1.2 ppm.*

***Abbreviations**: mean tumor molecules/mL plasma, MTM/mL; ppm, parts per million.*

Signatera™ Genome with Phased and Structural variants identified 100% of relapse cases with lead time up to 10 months, and in analytical studies detected ctDNA below 0.1 ppm

Figure 1. On-treatment ctDNA dynamics and outcomes

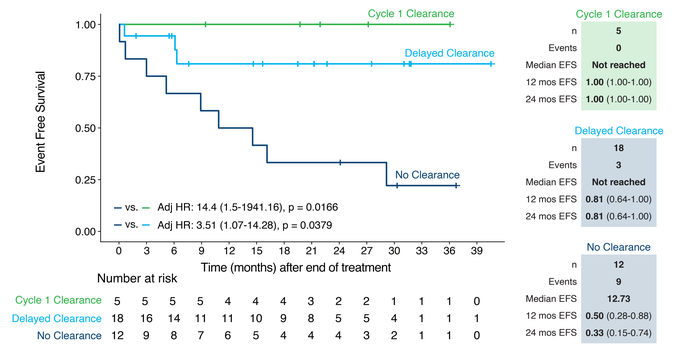

Figure 1. Compared to patients who remained ctDNA positive during 1L and through EOT, those who cleared ctDNA by cycle 1 (C1) of therapy had significantly improved EFS (**Adj HR: 14.4, p=0.0166**). Similarly, those with delayed clearance (≥C2) had improved outcomes vs. patients that were persistently ctDNA positive (**Adj HR: 3.51, p=0.0379**). All 5 patients that cleared ctDNA at C1 remained MRD-negative and relapse free.

Figure 2. ctDNA-MRD status is prognostic in post-1L surveillance

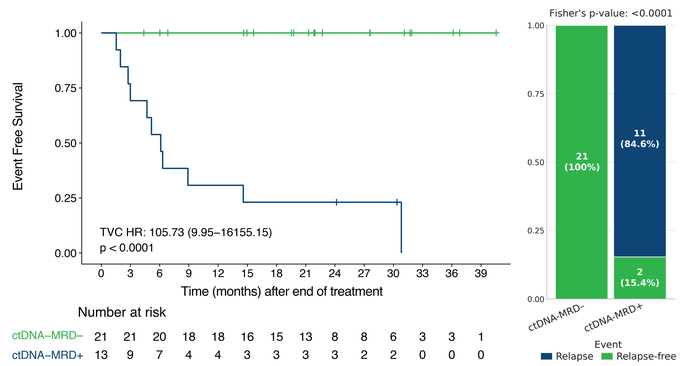

Figure 2. Among 34 patients with evaluable ctDNA testing time points during post-1L therapy surveillance, patients who remained ctDNA-MRD-negative had superior EFS compared to those who became ctDNA-MRD-positive (**Time-varying covariate HR: 105.73, p<0.0001**). Analysis adjusted for age, sex, and aggressive/indolent subtype. TVC: time varying covariate. Evaluable timepoints included ctDNA timepoints >4 weeks after 1L therapy completion. Exclusion: a negative ctDNA-MRD result prior to recurrence with an interval between the last negative test and recurrence of >6 months, or a positive ctDNA-MRD result without documented relapse with <18 months of clinical follow-up.

Citations

1. American Cancer Society. Cancer Facts & Figures 2026. Atlanta: American Cancer Society; 2026.
2. Adams HJ, et al. Prognostic value of complete remission status at end-of-treatment FDG-PET in R-CHOP-treated diffuse large B-cell lymphoma: systematic review and meta-analysis. *Br J Haematol*. 2015;170(2):185-191.
3. Galanina N, et al: ctDNA for MRD Assessment is Prognostic and Predictive in Newly Diagnosed and Relapsed/Refractory Lymphoma. *Blood Neoplasia*. 2026:100250.

Figure 3. Comparison of EOT ctDNA-MRD status vs. radiographic response

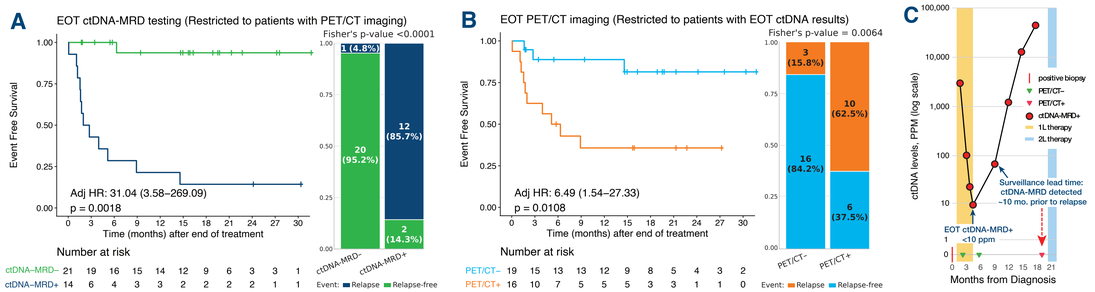

Figure 3A-B. At end of 1L therapy ctDNA-MRD status is a superior prognostic indicator of EFS compared to radiographic response. Among 35 patients with both a ctDNA sample and PET/CT at EOT, **(A)** ctDNA-MRD-positive patients had significantly inferior EFS compared to negative patients after multivariable analysis adjusting for aggressive vs indolent disease, stage, sex, and age **(Adj HR: 31.04 , p=0.0018)**. **(B)** Prognostication by PET/CT was inferior to ctDNA **(Adj HR: 6.49, p=0.0108)**. (**C**) Representative case of a patient with DLBCL who was considered a radiographic responder but did not clear ctDNA during 1L and remained ctDNA-MRD-positive in post-1L surveillance. Signatera Genome with Phased and Structural variants detected ctDNA-MRD (<10 PPM) ~10 months prior to clinical relapse.

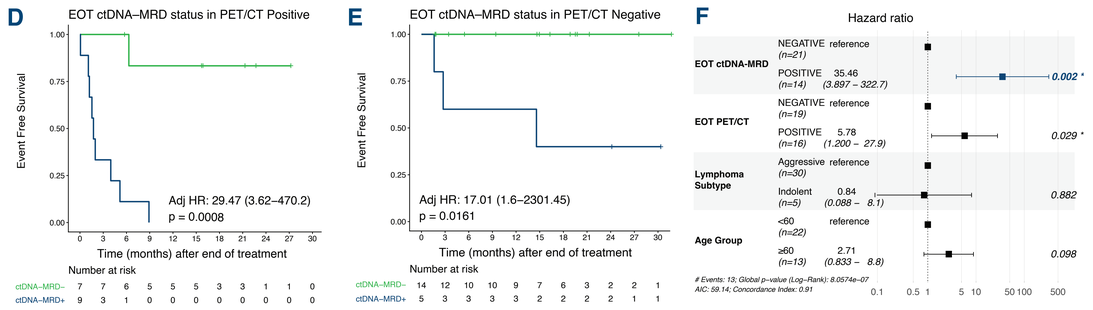

Figure 3D-F. ctDNA-MRD status provides additional risk stratification value among both radiographic responders and non-responders. Among patients with a ctDNA sample and known PET/CT status at EOT, patients who were EOT ctDNA-MRD-positive had significantly inferior EFS compared to EOT ctDNA-MRD-negative patients among those who were **(D)** EOT PET/CT-positive (**Adj HR: 29.47, p=0.0008**), and **(E)** EOT PET/CT-negative **(Adj HR: 17.01, p=0.0161)**. **(F)** Forest plot showing multivariate analysis of prognostic factors and their association with EFS analyzed across all evaluable patients who had both PET/CT and ctDNA-MRD assessments performed at EOT; EOT ctDNA-MRD status was the most significant prognostic factor **(p=0.002)**. Multivariable HR reported, accounting for EOT ctDNA-MRD status, EOT PET/CT status, age, sex, and aggressive/indolent subtype. Firth correction applied to hazard ratio analysis.

Conclusions

- Ultrasensitive tumor-informed ctDNA-MRD monitoring using Signatera Genome with Phased and Structural variants is prognostic of EFS across treatment, EOT, and surveillance.
- ctDNA clearance during 1L therapy (within cycle 1 or in later cycles) was strongly associated with superior EFS.
- While both EOT ctDNA-MRD and PET/CT are prognostic, ctDNA-MRD demonstrates superior prognostic value and refines risk stratification across both radiographic responders and non-responders.

Disclosures

DN, AT, MK, DK, HY, PM, MM, HW, RR, MC are employed by Natera, Inc., receive a salary and may hold stock or stock options. Poster development supported by Naira Abou-Ghali, PhD (Natera, Inc.).

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