Molecular progression defined by longitudinal ctDNA dynamics for prediction of outcomes in immune checkpoint inhibitor–treated solid tumors

Allegheny Health Network

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Background

- Immune checkpoint inhibitors (ICIs) have transformed treatment for advanced solid tumors, but only ~20% to 30% of patients achieve durable benefit, making early identification of non-responders essential to avoid prolonged ineffective therapy and overlapping toxicities.
- Standard-of-care imaging is often performed at ~3-month intervals and is constrained by scan accessibility, cost, and atypical immunotherapy patterns (pseudo-progression, mixed response, delayed response).
- ctDNA offers a non-invasive, longitudinally feasible biomarker that simultaneously reflects tumor burden and biology. However, tumor-informed assays require an upfront biopsy and tracking a small number of somatic variants.
- Existing single-timepoint thresholds (e.g., ≥50% or ≥90% drop) capture only a fraction of on-treatment kinetics and frequently misclassify non-responders.

Study Aim

To determine whether serial monitoring with Northstar Response® — a tumor-naive, methylation-based ctDNA assay — can be used to define molecular progression using ctDNA dynamics for earlier identification of progression under ICI treatment.

Methods

Study Schema

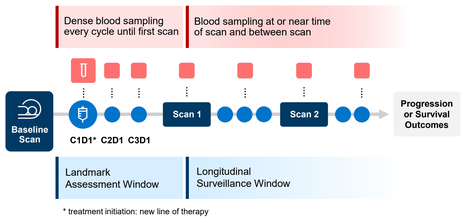

Figure 1. Schematic of the serial ctDNA blood sampling protocol using the Northstar Response assay. Blood was collected at baseline and at every treatment cycle (cycle 1 day 1 [C1D1], C2D1, C3D1) during the landmark assessment window. Following the first restaging scan, sampling continued at or near the time of each scan, as well as between scans throughout the longitudinal surveillance window. Progression-free and overall survival were captured as outcome endpoints.

Patient Population

Characteristic	
Median age	**67**
Stage IV	**92%**
First-line	**86%**
IO monotherapy	**48%**
Tumor Type	
Lung	**42%**
Melanoma	**18%**
Kidney	**17%**
Other	**23%**

Patient Cohorts (N = 137 total)

- **Primary AHN Cohort** (n = 65): Advanced cancer patients on ICI mono- or combination therapy at AHN with serial plasma at baseline and on treatment
- **Validation Cohort** (n = 72): Pan-cancer ICI-treated patients across a hospital network and 11 community oncology sites

Molecular progression (mPD): a clinically reportable increase in TMS between timepoints (status carried forward)

Statistics: Cox PH for PFS/OS; Wilcoxon rank-sum for lead-time; RECISTv1.1 reviewed by 3 board-certified radiologists with blinded independent central review (BICR).

Results

Tumor Methylation Score dynamics at each cycle of therapy better predict immune checkpoint inhibitor benefit than a single on-treatment timepoint by the C3D1 landmark assessment

In the Primary AHN Cohort (n=65), commonly used static cutoffs (any drop, ≥50%, ≥90%) produced comparable PFS for responders but converged at ~1-year PFS among non-responders. mPD informed by serial sampling delivered the strongest, most durable stratification (red lines).

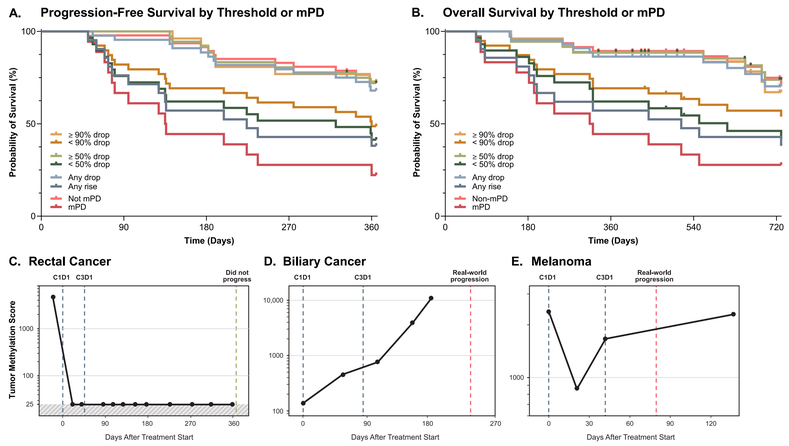

Figure 2A-B. Kaplan-Meier curves of PFS **(A)** and OS **(B)** stratified by single-timepoint thresholds versus serial-sampling mPD (red); mPD separates non-responders earliest and most durably.

mPD PFS: HR 5.3 (95% CI 2.5–11)
mPD OS: HR 4.9 (95% CI 2.2–11)

Figure 2C-E Individual patient TMS trajectories illustrating: **(C)** durable molecular responder with rectal cancer. TMS decreased dramatically by C2D1 and was maintained below or near the limit of quantification (hatched region) across multiple timepoints over 360 days, with no radiographic progression event. **(D)** molecular progressor with biliary cancer. TMS increased from baseline through C3D1 to radiographic confirmed progression, **(E)** a complex rebound pattern in a patient with melanoma. This kinetic signature would be misclassified as a favorable response by a single baseline-to-C3D1 landmark comparison. C1D1 and C3D1 timepoints are indicated by dashed vertical lines. Real-world progression is indicated by a red dashed vertical line.

Validation in an independent pan-cancer cohort

Applying the identical landmark mPD classifier (C3D1) to an independent multi-site pan-cancer cohort (n = 72) — including immune monotherapy and chemo-IO — reproduced strong survival stratification, confirming generalizability across regimens and tumor types.

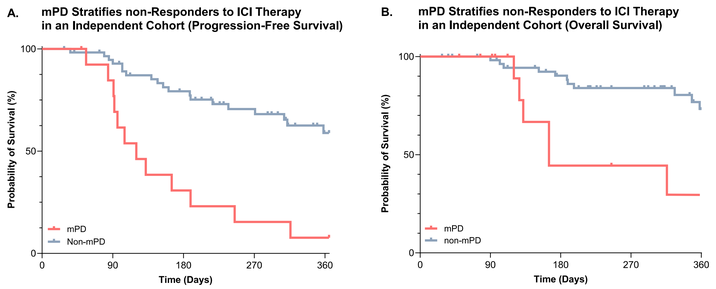

Figure 3. Independent pan-cancer validation cohort: mPD vs non-mPD stratifies both PFS **(A)** and OS **(B)**; hazard ratios closely mirror the discovery cohort.

PFS: HR 4.6 (95% CI 2.2–9.7)
OS: HR 4.3 (95% CI 1.6–12)

Longitudinal monitoring detects progression earlier than imaging

Beyond C3D1, longitudinal monitoring captured emerging progression at any on-treatment timepoint. These TMS increases preceded clinical and radiographic events by ~9 to 11 weeks, which may be a potentially actionable window to escalate, change, or hold therapy.

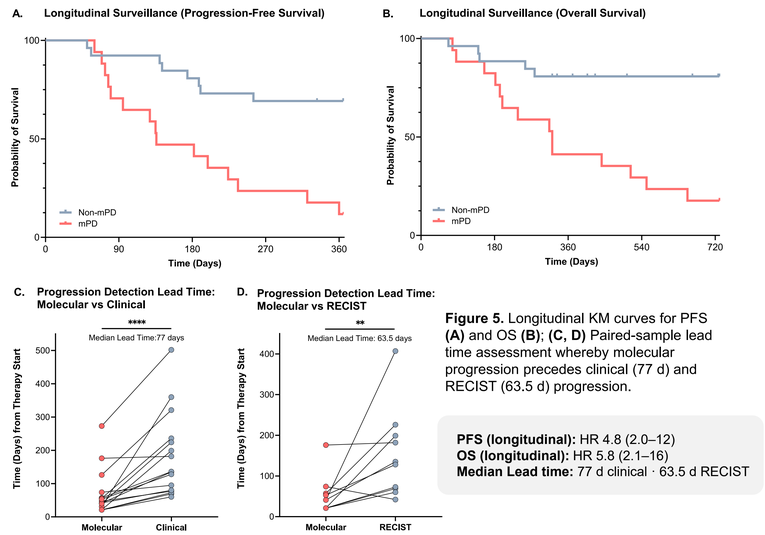

Figure 5. Longitudinal KM curves for PFS **(A)** and OS **(B)**; **(C, D)** Paired-sample lead time assessment whereby molecular progression precedes clinical (77 d) and RECIST (63.5 d) progression.

PFS (longitudinal): HR 4.8 (2.0–12)
OS (longitudinal): HR 5.8 (2.1–16)
Median Lead time: 77 d clinical · 63.5 d RECIST

Molecular progression provides independent and incremental predictive information beyond radiographic assessment

Versus centrally-reviewed RECISTv1.1 (~9 weeks), mPD was equivalent for PFS and showed stronger OS stratification than RECIST. Among RECIST 6-mo non-progressors, mPD identified 7/36 patients (~20%) with occult progression and markedly worse survival.

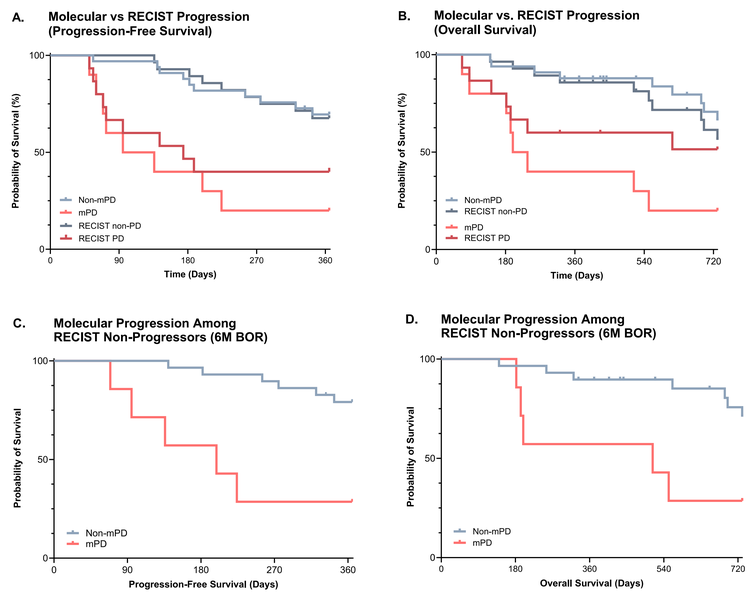

Figure 4. Kaplan-Meier curves for overall survival (OS) among 43 patients from the AHN cohort with both ctDNA and BICR RECISTv1.1 scoring available, stratified simultaneously by TMS-based molecular progressive disease (mPD vs. non-mPD) and RECIST at the C3D1 timepoint (PD vs. non-PD).

OS (mPD vs RECIST): HR 5.3 vs 1.6
Occult-PFS: HR 6.7 (2.0–22)
Occult-OS: HR 4.5 (1.4–14)

Conclusion

Across two cohorts (N = 137), serial tumor naive methylation-based ctDNA monitoring with Northstar Response identifies immunotherapy non-responders earlier than imaging, outperforms RECIST for survival prediction, and detects progression weeks sooner, enabling timelier treatment decisions.

Key Findings

- Early on-treatment ctDNA dynamics outperform single-timepoint fold-change measurements.
- Molecular progression provides independent predictive value beyond RECIST, even among RECIST non-progressors.
- TMS increases precede imaging by ~9 to 11 weeks, supporting earlier therapeutic adaptation.
- Tumor-naive assay design makes monitoring feasible regardless of tissue availability or shedding rate.