A molecular biomarker for longitudinal monitoring of therapeutic efficacy in a real-world cohort of advanced solid tumors treated with immune checkpoint inhibitors

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INTRODUCTION

Clinical validation studies have shown that early dynamic changes in circulating tumor DNA (ctDNA) tumor fraction (TF) can predict clinical outcomes. Yet few studies have explored the clinical value of longitudinal monitoring throughout the course of treatment. Here we evaluate associations between longitudinal changes in ctDNA TF and clinical outcomes in an advanced real-world pan-cancer cohort of patients treated with immune checkpoint inhibitors (ICIs).

METHODS

Cohort definitions:
- The **full cohort** comprises patients with advanced stage cancer from the Tempus de-identified clinicogenomic database with a pre-ICI baseline liquid biopsy up to 40 days prior to therapy start and on-treatment liquid biopsy 15-180 days after therapy start
- The **early on-treatment subcohort** includes patients with an on-treatment liquid biopsy within 6 weeks of ICI therapy start; four patients with ctDNA not detected were excluded
- The **longitudinal subcohort** included patients with ≥2 on-treatment timepoints

Tumor fraction quantification:
- ctDNA TF was quantified for each sample via an ensemble algorithm, xM for Treatment Response Monitoring, that uses pathogenic variant allele frequencies, copy number information, and germline information
- Limit of blank (LOB) is 0.09% and limit of quantification (LOQ) is 0.5%

Molecular response was determined at each on-treatment timepoint:
- **Molecular Responder (MR) if any:**
  - ≥50% decrease in ctDNA TF if baseline and on-treatment ≥ LOQ
  - Baseline > LOB and on-treatment ≤ LOB
  - Baseline ≥ LOQ and (LOB < on-treatment < LOQ)
- **Molecular Non-Responder (nMR) if any:**
  - <50% decrease in ctDNA TF if baseline and on-treatment ≥ LOQ
  - Baseline ≤ LOB and on-treatment > LOB
  - (LOB < baseline < LOQ) and on-treatment ≥ LOQ
- **Not evaluable if:**
  - (LOB < baseline < LOQ) and (LOB < on-treatment < LOQ)
- **ctDNA TF not detected if:**
  - Baseline and on-treatment ≤ LOB

Longitudinal molecular response was determined for each patient:
- **Longitudinal Molecular Responder** if there were no on-treatment samples classified as nMR
- **Longitudinal Molecular Non-responder** if one or more on-treatment sample was classified as nMR

Outcomes analyses:
- Real-world progression-free survival (rwPFS) was defined as the time from the first on-treatment timepoint to progression or death, with event-free patients censored at ICI therapy end or last known clinical record. Patients with progression events between ICI therapy start and the first on-treatment timepoint were excluded
- Real-world overall survival (rwOS) was defined as the time from the first on-treatment timepoint to death or last known clinical record
- Cox proportional hazards models were used to estimate the hazard ratio (HR) for MR status (MR vs. nMR) and median survival times
- P-values were obtained using the Wald test with a one-sided significance level of 5%

SUMMARY

- Quantitative longitudinal changes in ctDNA tumor fraction (TF) stratified patient outcomes in a real-world advanced pan-cancer cohort treated with ICIs as early as 6 weeks after starting treatment
- A longitudinal ctDNA TF molecular biomarker may be a useful clinical decision-making tool for monitoring treatment response to ICIs

RESULTS

Table 1. Demographics

Variable		Full cohort	Early on-treatment	Longitudinal
Cohort size	N	95	22	35
Age at ICI start	Median (Range)	65 (40-87)	61 (40-87)	64 (44-81)
Race	Asian	2 (2%)	2 (9%)	1 (3%)
	Black or African American	14 (15%)	5 (23%)	3 (9%)
	White	50 (53%)	9 (41%)	19 (54%)
	Other Race	5 (5%)	1 (5%)	3 (9%)
	Unknown	24 (25%)	5 (23%)	9 (26%)
Sex	Female	48 (51%)	7 (32%)	15 (43%)
Indication	NSCLC	30 (31.6%)	11 (50%)	11 (31.4%)
	SCLC	16 (16.8%)	0 (0%)	5 (14.3%)
	Breast	12 (12.6%)	1 (4.5%)	1 (2.9%)
	Prostate	8 (8.4%)	6 (27.3%)	7 (20%)
	Other	29 (30.5%)	4 (18.2%)	11 (31.4%)
Treatment	ICI monotherapy	40 (42.1%)	12 (54.5%)	19 (54.3%)
	ICI + chemotherapy	55 (57.9%)	10 (45.5%)	16 (45.7%)
Line of Therapy	1L	48 (50.5%)	6 (27.3%)	15 (42.9%)
	2L+	46 (48.4%)	15 (68.2%)	19 (54.3%)
	Unknown	1 (1.1%)	1 (4.5%)	1 (2.9%)

Figure 1. In the full cohort, MRs have longer rwPFS and rwOS than nMRs

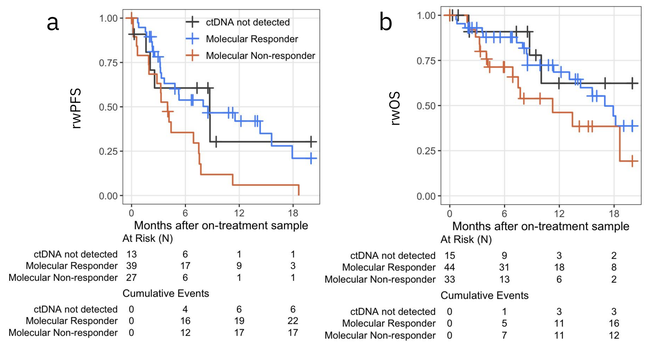

Figure 1. Kaplan Meier curves showing **(a)** rwPFS (N=79) and **(b)** rwOS (N=92) of Molecular Responders, Molecular Non-responders, and ctDNA TF not detected. Three "Not Evaluable" patients were removed from analyses: one with a death event 14 months after on-treatment liquid biopsy, and two censored at 9 and 20 months.
a) MR vs. nMR rwPFS HR = 0.43 (95% CI 0.23 - 0.80), P=0.004; median MR = 4.0 mo. (95% CI 2.8 - 7.6 mo.), median nMR = 8.5 mo. (95% CI 3.6 mo. - NA).
b) MR vs. nMR rwOS HR = 0.53 (95% CI 0.25 - 1.10), P=0.04; median MR = 11.3 mo. (95% CI 6.9 mo. - NA), nMR = 17.0 mo. (95% CI 13.1 mo. - NA).

Figure 2. In the early on-treatment subcohort (≤6 weeks), MRs have longer rwPFS and rwOS than nMRs

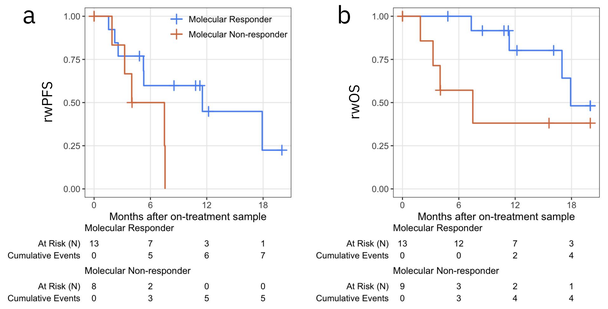

Figure 2. Kaplan Meier curves showing **(a)** rwPFS (N = 21) and **(b)** rwOS (N = 22) for the subset of patients with on-treatment samples ≤ 6 weeks of ICI start.
a) MR vs. nMR HR = 0.34 (95% CI 0.10 - 1.20), P = 0.047; median MR = 11.5 mo. (95% CI 5.2 mo. - NA), nMR = 5.7 mo. (95% CI 3.3 mo. - NA).
b) MR vs. nMR HR = 0.31 (95% CI 0.08 - 1.25), P = 0.050; median MR = 17.9 (95% CI 17.0 mo. - NA), nMR = 7.5 mo. (95% CI 3.3 mo. - NA).

Figure 3. Longitudinal MRs have longer rwOS than longitudinal nMRs

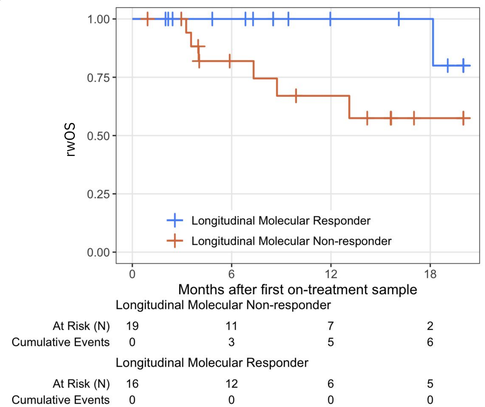

Figure 3. Kaplan Meier curves showing the rwOS of longitudinal MRs and longitudinal nMRs. HR = 0.16 (95% CI 0.02 - 1.37), P = 0.047.

Figure 4. Changes in ctDNA TF over time in the longitudinal subcohort

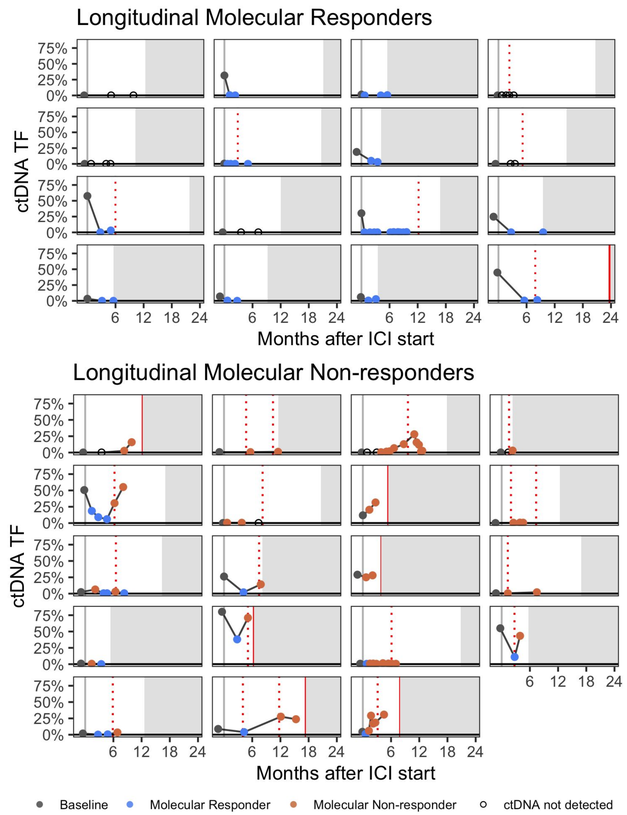

Figure 4. ctDNA TF values (circles) for patients in the longitudinal subcohort, colored by Molecular Response status at baseline and each on-treatment time point. Grey vertical lines are ICI start date; red dotted vertical lines are progression events; red solid lines are death events; black horizontal lines denote the LOB at y = 0.09% ctDNA TF; grey shaded boxes are where patient data is censored or truncated at 20 mo. after ICI start.

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