Poster 34

Association of a novel circulating tumor fraction DNA biomarker of treatment response monitoring and clinical outcomes in a real-world, diverse pan-cancer cohort treated with immunotherapy

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INTRODUCTION

- Clinical evidence suggests that longitudinal changes in circulating tumor DNA (ctDNA) could serve as an early indicator of patient response to immune checkpoint inhibitors (ICI)
- Current approaches to quantifying changes in ctDNA rely on shifts in variant allele frequencies (VAFs) and do not incorporate non-mutational genomic events
- The utility of ctDNA-based algorithms in pan cancer clinical practice is not well known
- **We present xF Monitor, a novel approach for determining circulating tumor fraction estimates (ctFE) which measures quantitative molecular changes by utilizing diverse genomic events, and the association of these changes to outcomes in a real-world pan-cancer cohort treated with standard of care ICI based therapy**

METHODS

- ctDNA profiling was performed using the 105-gene Tempus xF liquid biopsy assay
- xF ctFE was calculated using an ensemble model which builds upon single input models like somatic variant allele frequency (VAF) or copy number variation (CNV, Finkle et al, 2021), and dynamically incorporates CNV data, somatic and germline VAFs to account for observed failure modes from single input methodologies (Fig 1)

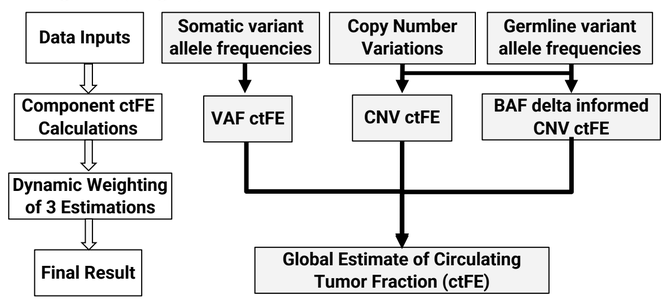


Figure 1: Circulating tumor fractions are estimated using an ensemble approach that leverages somatic and germline VAFs, along with CNV data as input

- Deidentified patient records from the Tempus multimodal database were analyzed if patients had an xF test ≤ 60 days prior to the start of ICI, alone or in combination with chemotherapy (CT), and an xF test 15-180 days post-ICI
- Molecular responders (MR) were defined as patients with a ≥50% decrease in ctFE; initially, a ≥25% decrease in ctFE was implemented and yielded similar results
- Clinical endpoints were defined from 15 days post ICI start to the first progression event or death (rwPFS) or death (rwOS), both censored on the last follow-up in event-free patients

Variable		Value
Cohort size	N	86
Indication	Breast	12 (14%)
	NSCLC	26 (30%)
	SCLC	16 (19%)
	Other	32 (37%)
Age at IO start	Median (Range)	64 (32-87)
Sex	Female	35 (41%)
Race	Asian	3 (3%)
	Black or African American	16 (19%)
	White	38 (44%)
	Other Race	4 (5%)
	Unknown	25 (29%)
Smoking history	Smoked	38 (44%)
	Never smoked	11 (13%)
	Unknown	37 (43%)
Stage	Stage 3	6 (7%)
	Stage 4	76 (88%)
	Unknown	4 (5%)
Treatment	ICI monotherapy	28 (33%)
	ICI + chemotherapy	58 (67%)
Line of Therapy	1L	43 (50%)
	2L+	43 (50%)

Table 1: Baseline patient characteristics of pan cancer xF Monitor cohort *Other cancers include colorectal cancer, gastric cancer, head and neck squamous cell carcinoma, biliary cancer, bladder cancer, endocrine tumor, kidney cancer

RESULTS

- xF ctFE has improved slope and correlation with the Tumor Informed Estimate vs. the Mean VAF in a historical, pan-cancer tumor sample population (n = 1659 patients) (Fig 2). The Tumor Informed Estimate is calculated from xF VAF data informed by FFPE tumor/normal somatic variant data
- The evaluable pan-cancer cohort (n= 86 patients) had > 10 solid tumor types including patients receiving ICI therapy alone (33%) and ICI + chemotherapy (67%) (Table 1)

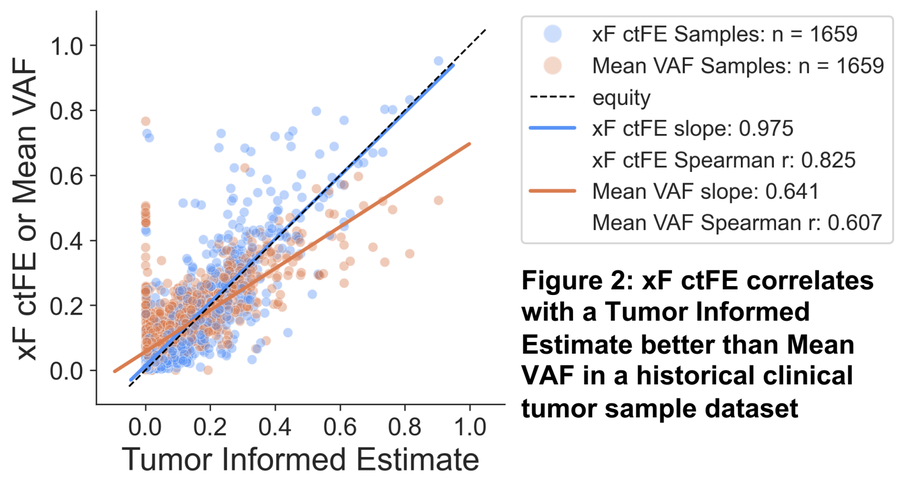
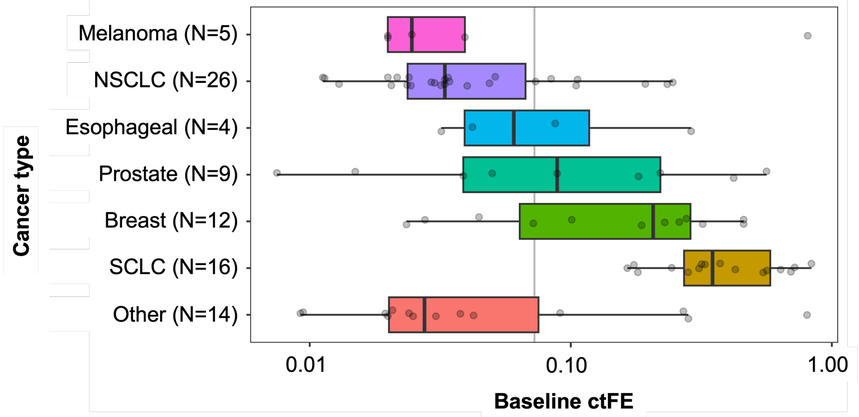


Figure 2: xF ctFE correlates with a Tumor Informed Estimate better than Mean VAF in a historical clinical tumor sample dataset



- Baseline xF monitor detection rate was 74% across all cancers with a median ctFE of 0.073; the highest indication specific median was observed in SCLC (0.35 ctFE), and lowest (0.025 ctFE) in melanoma (Fig 3)

Figure 3: Distributions of baseline ctFE values vary by cancer subtype. Grey vertical line depicts median ctFE across all subtypes.

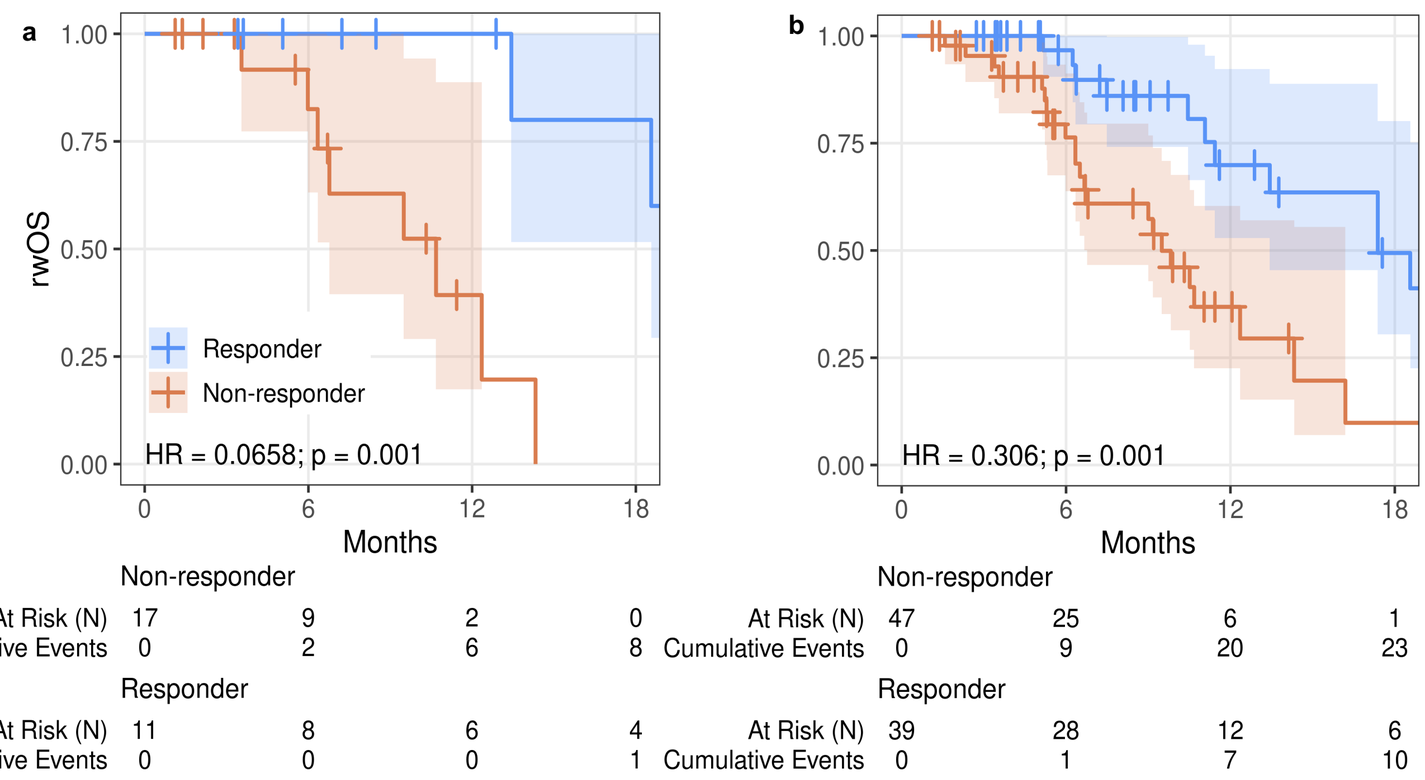


Figure 4: A ≥50% reduction in xF Monitor ctFE correlates strongly with real world overall survival in both (a) the ICI monotherapy cohort (N = 28), and (b) the full ICI cohort (IO mono + IO in combination with chemotherapy) (N = 86)

- MR patients within the IO monotherapy cohort had significantly longer rwPFS (HR = 0.11, log-rank p < 0.001) and rwOS (HR = 0.066, log-rank p = 0.001, Fig 4a) than non-MR patients
- MR patients in the full cohort (IO mono + IO in combination with chemotherapy) also had significantly longer rwPFS (HR = 0.32, wald p < 0.001) and rwOS (HR = 0.31, wald p < 0.001, Fig 4b) than non-MR patients

SIGNIFICANCE

- xF Monitor is a novel, sensitive, serial quantitative ctFE algorithm which runs off the Tempus xF assay that has the potential to be used clinically as a dynamic predictive biomarker to ICI therapy
- xF Monitor molecular changes correlate to patient outcomes on ICI therapy and will help optimize treatment decision on ICI therapy
- xF Monitor is currently being prospectively validated in a larger pan-cancer cohort

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