Association of a ctDNA biomarker of treatment response with clinical outcomes in a real-world pan-cancer cohort treated with tyrosine kinase inhibitors

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INTRODUCTION

- Clinical evidence suggests that early changes in circulating tumor DNA tumor fraction (ctDNA TF) is predictive of patient response to immune checkpoint inhibitors and may be used for treatment response monitoring.
- Applicability of longitudinal ctDNA TF biomarkers for assessing treatment response to Tyrosine Kinase Inhibitors (TKIs) is not well known.
- Here, we evaluate our previously published algorithm, xM used for treatment response monitoring (TRM), a novel approach for determining quantitative changes in ctDNA TF utilizing diverse genomic events, and its association of to outcomes in a real-world pan-cancer cohort treated with TKI therapy.

METHODS

- ctDNA profiling was performed using the 105-gene Tempus liquid biopsy assay
- ctDNA TF was calculated using an ensemble model which builds upon single input models such as somatic VAF or copy number variant (CNV) information, instead dynamically incorporating CNV data, somatic and germline VAFs to account for observed failure modes from aforementioned single input methodologies (Figure 1)
- TKI therapies were classified by the Tempus Medical Ontology, which was validated using the NCI Metathesaurus TKI concept (NCI Code C1967)
- Deidentified patient records from the Tempus multimodal database were analyzed if patients had a baseline test 14 weeks prior to the start of TKI, alone or in combination with another mediation, and another test 15-180 days post-TKi therapy initiation
- Molecular responders (MR) were defined as patients with ≥50% reduction in ctDNA TF between baseline and on-treatment time points, consistent with our previously established threshold. This includes patients that were above Limit of Blank (LoB) at baseline sampling but fell below LoB at the on-treatment time point
- Clinical endpoints were defined from the second test to the first progression event or death (rwPFS) or death (rwOS), both censored on the last follow-up in event-free patients
- Kaplan Meier analysis and Cox proportional hazard models were fitted to compare MR status and survival outcomes on TKI

Algorithm Design

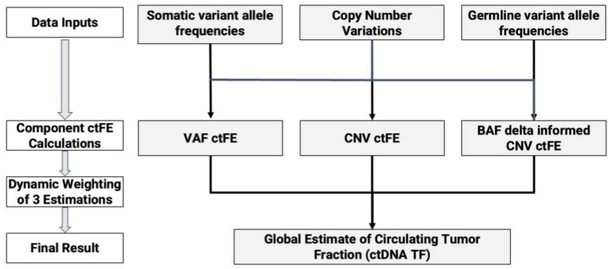

Figure 1. Overview of algorithm design and components that feed into ctDNA tumor fraction estimation

SUMMARY

- xM used for treatment response monitoring (TRM) is a robust, serial quantitative ctDNA TF algorithm that has the potential to be used clinically as a dynamic quantitative biomarker to evaluate response to TKI therapy.
- In a real-world heterogeneous cohort, xM used for TRM molecular changes were significantly associated with patient outcomes (rwPFS HR=0.45, p=0.02 and rwOS HR=0.16, p=0.005).
- This biomarker may help optimize treatment decision making and spare ineffective therapy for patients that do not respond to their TKI regimen.

RESULTS

Clinical Characteristics

Characteristic	N (%)
Total Cohort	64
Cancer Indication	
Breast	15 (23%)
NSCLC	23 (36%)
CRC	8 (12%)
Other	18 (28%)
Age at TKI Start Median (range)	62 (25 - 78)
Therapy Type	
Mono	37 (58%)
Combination	27 (42%)
Sex	
Female	41 (64%)
Race	
Asian	4 (6%)
Black or African American	9 (14%)
White	28 (44%)
Other Race	5 (8%)
Unknown	18 (28%)
Stage	
Stage III	2 (3%)
Stage IV	62 (97%)

Table 1: Clinical characteristics The evaluable pan-cancer cohort (N=64 patients) had > 10 solid tumor types including patients receiving TKI alone (58%) and TKIs in combination with other meds (42%).

Molecular Response prevalence by cancer type

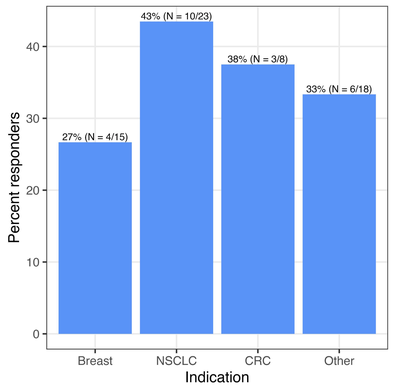

Figure 2. Distribution of molecular response (Molecular Responders (MR) = 23, Molecular Non-responders (nMR) = 41) based on cancer type. Numbers represent intra group composition of MR and nMR. Note, cancer represented in the "Others" category include biliary, bladder, melanoma, kidney, pancreatic, prostate, sarcoma, thyroid and gastrointestinal stromal tumors.

Change in tumor fraction estimates and response over sequential testing

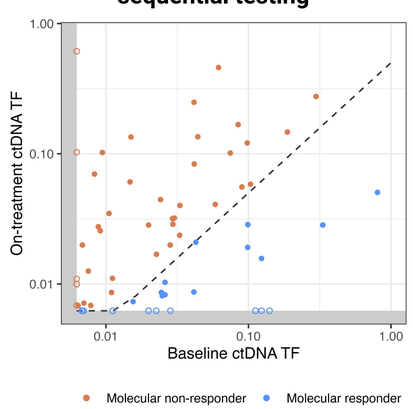

Figure 3. Distribution of baseline and on-treatment ctDNA tumor fractions in molecular responders and molecular non-responders. Dashed line represents the 50% cut-off for molecular response determination. Samples that are below LoB at any time point are represented as non-filled circles.

Association of Molecular Response and rwPFS

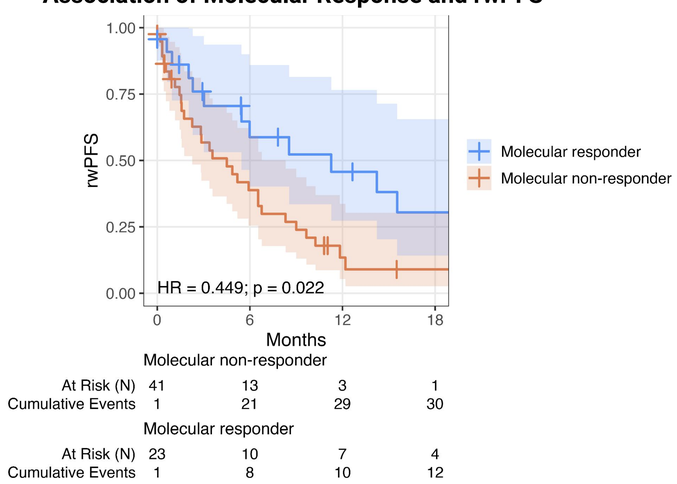

Figure 4. Association of ctDNA molecular response with rwPFS in patients treated with TKIs [HR = 0.449 (0.226-0.892), p=0.022].

Association of Molecular Response and rwOS

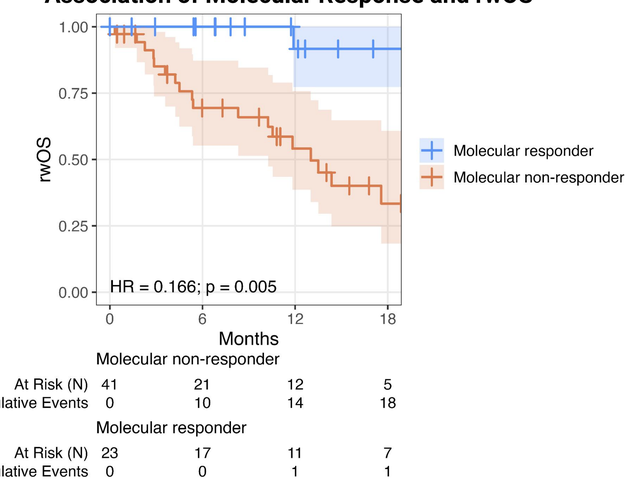

Figure 5. Association of ctDNA molecular response with rwOS in patients treated with TKIs [HR = 0.166 (0.048-0.574), p=0.005].

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