The association of changes in circulating tumor fraction and in actionable variant allele frequencies with clinical outcomes in a real-world diverse cohort of advanced patients treated with tyrosine kinase inhibitors

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INTRODUCTION

- Limited data exists on the clinical validity of circulating tumor DNA (ctDNA) for treatment response monitoring (TRM) in patients with advanced solid tumors treated with Tyrosine Kinase Inhibitors (TKIs)
- Currently ctDNA is used for TRM of TKIs by tracking target alterations with few studies demonstrating the association between tumor fraction and clinical outcomes
- We have previously demonstrated that a ctDNA TF biomarker (xM for TRM) is associated with real-world overall survival in a pan-cancer cohort treated with TKIs
- Here, we evaluate if xM TRM provides additional predictive information over target alterations in this pan-cancer real-world cohort of patients treated with TKIs

METHODS

- Tempus xM for TRM is a ctDNA assay encompassing 105 genes that quantifies changes in ctDNA TF (Fig 1) and classifies patients as MRs (≥50% reduction in ctDNA TF between baseline and on-treatment time points or if the on-treatment sample is below the limit of blank detection (LoB) for the algorithm) or nMRs
- De-identified patient records from the Tempus multimodal database were included if a patient had a baseline test ≤ 15 weeks prior to TKI start and an on-treatment test result 3-25 weeks post-TKI initiation
- Actionable SNV/indels and matched TKIs were defined per ESMO guidelines
- Patients were evaluable for subset variant allele frequency (VAF) concordance analysis if an actionable alteration was detected at either the baseline and/or on-treatment time point
- Patients with targetable alterations detected were further sub-classified into increasing or decreasing VAF based on an increase or decrease in VAF from the baseline to the on-treatment time point
- Patients with a target alteration not detected at baseline but at the on-treatment time point were classified as having increasing VAF and patients with target alteration detected at baseline but not at the on-treatment time point were classified as decreasing VAF
- Differences in rw-overall survival (rwOS) were assessed using a log-rank test with follow-up times censored at 18 months

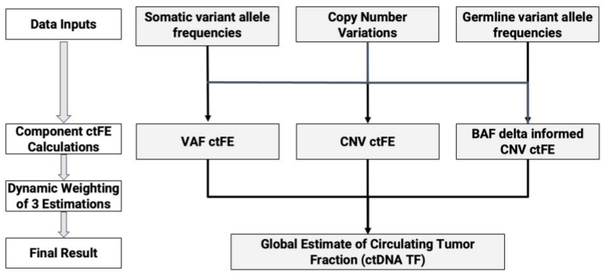

Figure 1: Circulating tumor fractions are estimated using an ensemble approach of somatic and germline VAFs, along with CNV data being utilized as input.

SUMMARY

- xM for TRM, a dynamic circulating tumor fraction biomarker for treatment response monitoring, was significantly associated with real-world overall survival in a pan-cancer cohort of patients treated with TKIs
- When limited to only patients with decreasing actionable variant VAF, there was a significant difference in rwOS between molecular responders and molecular non-responders as defined by xM, suggesting that xM for TRM adds additional value in predicting clinical outcomes compared to tracking actionable variants alone

RESULTS

Variable		Value
Cohort size	N	31
Indication	NSCLC	15 (48%)
	Breast	13 (42%)
	CRC	2 (6%)
	Other	1 (3%)
Age at TKI start	Median (Range)	63 (25-78)
Sex	Female	25 (81%)
Race	Asian	2 (6%)
	Black or African American	2 (6%)
	White	15 (48%)
	Other Race	2 (6%)
	Unknown	10 (32%)
Stage	Stage 3	1 (3%)
	Stage 4	30 (97%)
Days from TKI start to on-treatment test	Median (Range)	88 (21-167)

Table 1: clinical characteristics of cohort

Concordance of Molecular Response and VAF directionality

N=31	VAF increasing (N=10)	VAF decreasing (N=21)
MR (N=13)	1 (8%)	12 (92%)
nMR (N=18)	9 (50%)	9 (50%)

Table 2 - Concordance of Molecular Response (MR) and VAF directional changes. The table highlights concordance (in black) vs discordance (red) between molecular response and VAF results. Note: Actionable variants here include ALK (for Alectinib), ROS1 (for Crizotinib), BRAF (for Dabrafenib and Encorafenib, EGFR (for Osimertinib), ERBB2 (for Neratinib), MET (for Capmatinib) and PIK3CA (for Alpelisib)

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Majority of MR show concordance with VAF, while half of nMR have decreasing VAF in target alterations

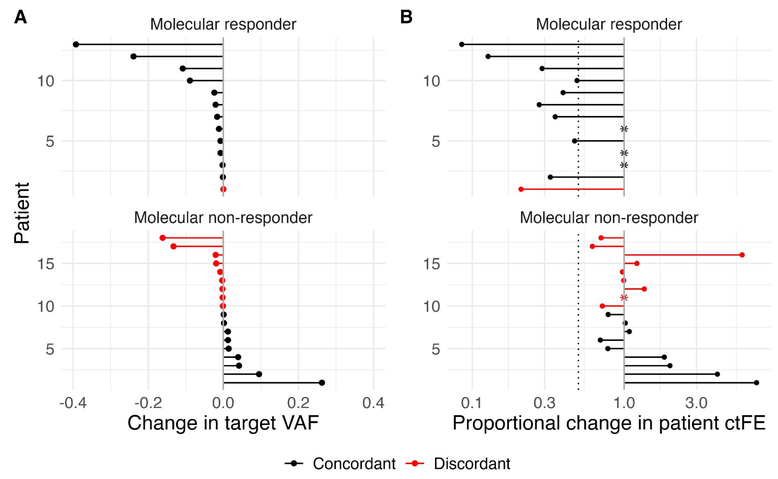

Figure 2 - In patients with actionable alterations, (A) change in VAF of target alteration and (B) proportional change from baseline to on-treatment circulating tumor fraction estimates (ctFE) were plotted for both molecular responders and non-molecular responders. Dotted line represents a 50% decrease in ctFE from baseline to the on-treatment time point. Stars represent three patients that were classified as MR and one patient classified as nMR because their baseline/on-treatment samples fell above/below the limit of blank rather than due to shift in proportional change in ctFE. Other patients shown as filled circles

xM Monitor provides additional predictive value beyond tracking actionable matched TKI-targeted VAFs

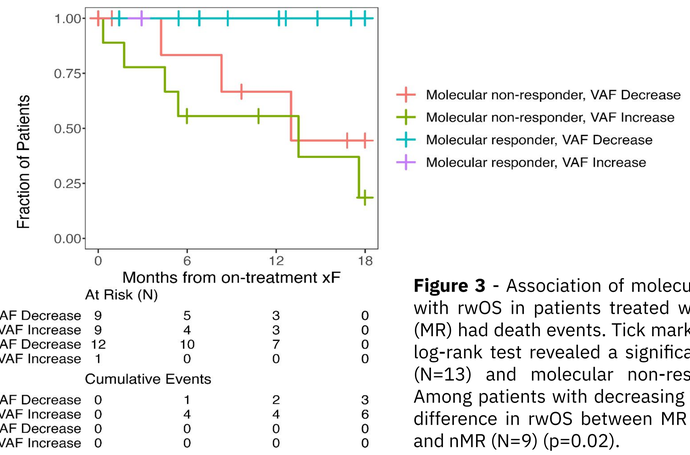

Figure 3 - Association of molecular response and VAF directionality with rwOS in patients treated with TKIs. No molecular responders (MR) had death events. Tick marks represent censored data points. A log-rank test revealed a significant difference in rwOS between MR (N=13) and molecular non-responders (nMR, N=18) (p=0.004). Among patients with decreasing VAF (N=21), there was a significant difference in rwOS between MR (N=12, no death events observed) and nMR (N=9) (p=0.02).