A longitudinal, circulating tumor molecular response biomarker as a predictor of clinical outcomes in a real-world cohort of patients with advanced solid tumors treated with tyrosine kinase inhibitors

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INTRODUCTION

Studies have shown that early changes in quantitative measures of circulating tumor DNA (ctDNA) tumor fraction (TF) can predict clinical outcomes in response to immunotherapy and help separate molecular responders (MRs) from molecular non-responders (nMRs) who may benefit from a change in therapy. However, it remains to be seen if a similar approach can be used for patients treated with targeted therapies like tyrosine kinase inhibitors (TKis). Here we evaluate the use of a longitudinal, molecular biomarker for treatment response monitoring, xM for TRM, in a real-world advanced, pan-cancer cohort treated with targeted therapies.

METHODS

- The full cohort consisted of 132* deidentified patients from the Tempus clinicogenomic database with stage IV solid tumors and ctDNA NGS.
- Each patient had a pre-treatment baseline liquid biopsy sample (T0) and on-treatment sample 21-180 days after initiating targeted therapy (T1), as defined by the Tempus Medical Ontology and validated with the NCI Metathesaurus (NCI Code C1967).
- ctDNA TF was estimated via an ensemble algorithm (Figure 1) that uses pathogenic variant allele frequencies, copy number information, and germline information.
- Evaluable patients had at least one sample with TF ≥ the limit of blank of 0.09%.
- Patients were classified as a Molecular Responder (MR) if their ctDNA tumor fraction (TF) decreased by at least 50% from T0 to T1, or if their TF was consistently low (< 1%) at both T0 and T1, in line with previous work demonstrating that consistently low TF correlates positively with prolonged clinical outcomes (see poster 5850); patients not meeting these criteria were classified as a Molecular Non-responder (nMR).
- Real-world overall survival (rwOS) was defined as T1 to death, or, in event-free patients, as T1 to the date of the last known clinical record.
- Hazard ratios (HR; MR vs. nMR) were estimated using Cox proportional hazards models, stratified by line of therapy (LOT, first line, 1L vs. ≥ second-line, 2L+).
- Significance was assessed at the 5% level using a 1-sided Wald test.
- Predicted rwOS was estimated from Cox models for LOT 1 and LOT 2+.
- Sensitivity analysis was conducted by cancer type (stratified by LOT) and LOT (unstratified)

*Six patients from the original cohort at the time of abstract submission were removed due to data quality issues.

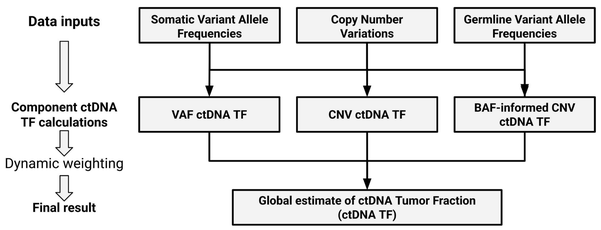

Figure 1. The ctDNA TF algorithm receives three types of molecular input data from a given sample and then dynamically weights three intermediate TF estimates for a final ctDNA TF result.

SUMMARY

- ctDNA tumor fraction (TF) quantitative changes for Tumor Response Monitoring, predicted rw OS in an advanced, pan-cancer cohort treated with targeted therapies.
- Rw outcomes were consistent across cancer subtype and line of therapy.
- These findings demonstrate that longitudinal TF quantitative measure may be a valuable clinical tool for molecular response monitoring of therapy that complement other standard of care modalities.

RESULTS

Table 1. Cohort Demographics

Variable		MR	nMR	Overall
Cohort size	N	59	45	104
Age at diagnosis	Median (Range)	61 (26-84)	56 (33-85)	58 (26-85)
Age at TKi start	Median (Range)	62 (35-84)	59 (38-85)	62 (35-85)
Race	American Indian or Alaska Native	1 (2%)	0 (0%)	1 (1%)
	Asian	4 (7%)	2 (4%)	6 (6%)
	Black or African American	7 (12%)	3 (7%)	10 (10%)
	White	21 (36%)	24 (53%)	45 (43%)
	Other Race	13 (22%)	5 (11%)	18 (17%)
	Unknown	13 (22%)	11 (24%)	24 (23%)
Sex	Female	42 (71%)	32 (71%)	74 (71%)

Table 2. Clinical and Molecular Characteristics

Variable		MR	nMR	Overall
Indication	NSCLC	34 (58%)	16 (36%)	50 (48%)
	Breast	15 (25%)	20 (44%)	35 (34%)
	Melanoma	1 (2%)	2 (4%)	3 (3%)
	CRC	1 (2%)	2 (4%)	3 (3%)
	Other	8 (14%)	5 (11%)	13 (12%)
Stage at initial diagnosis	Stage 1	4 (7%)	2 (4%)	6 (6%)
	Stage 2	4 (7%)	10 (22%)	14 (13%)
	Stage 3	6 (10%)	3 (7%)	9 (9%)
	Stage 4	40 (68%)	25 (56%)	65 (62%)
	Missing	5 (8%)	5 (11%)	10 (10%)
Brain mets observed	Yes	15 (25%)	13 (29%)	28 (27%)
	No	44 (75%)	32 (71%)	76 (73%)
Targeted TKi	Yes	52 (88%)	39 (87%)	91 (88%)
	No	7 (12%)	6 (13%)	13 (12%)
Line of therapy	1	43 (73%)	18 (40%)	61 (59%)
	2+	16 (27%)	27 (60%)	43 (41%)
Targeted medication	Osimertinib	23 (39%)	10 (22%)	33 (32%)
	CDK4/6 inhibitor	10 (17%)	13 (29%)	23 (22%)
	Alpelisib	5 (8%)	6 (13%)	11 (11%)
	Lorlatinib	2 (3%)	3 (7%)	5 (5%)
	Alectinib	4 (7%)	0 (0%)	4 (4%)
	Imatinib	2 (3%)	2 (4%)	4 (4%)
	Lenvatinib	2 (3%)	2 (4%)	4 (4%)
	Regorafenib	2 (3%)	2 (4%)	4 (4%)
	Other	9 (15%)	7 (16%)	16 (15%)
EGFR mutation present	Yes	23 (39%)	11 (24%)	34 (33%)
	No	36 (61%)	34 (76%)	70 (67%)
PIK3CA mutation present	Yes	5 (8%)	6 (13%)	11 (11%)
	No	54 (92%)	39 (87%)	93 (89%)

Predicted survival curves for molecular responders vs. molecular non-responders, grouped by line of therapy

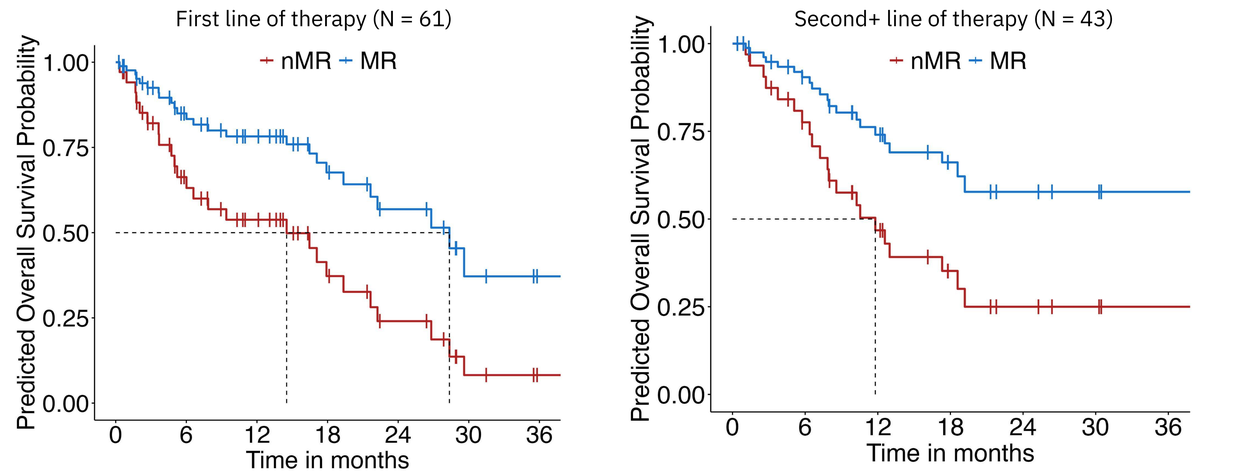

Figure 2. Left panel shows predicted survival curves for patients treated with targeted therapy in the first-line setting, grouped by responder status (N = 61; median MR survival = 28.4 months (95% CI 19.4 - NA); median nMR survival = 14.5 months (95% CI 5.0 - 22.2)). Right panel shows the same for patients treated with targeted therapies in the second-line setting or later (N = 43; median nMR survival = 11.8 months (95% CI 7.2 - 18.6); median MR survival = NA (95% CI 13.0 - NA).

Survival by molecular responder status

	MR (N=59)	nMR (N=45)
Median rwOS (95% CI)	28.4 months (19.2, NA)	12.6 months (7.9, 22.2)
12-month rwOS rate (95% CI)	0.754 (0.64, 0.89)	0.513 (0.38, 0.70)
MR vs nMR HR	0.40 (p = 0.003)	

Table 3. Median OS and 12-month survival rate were estimated from KM curves without stratification by LOT, due to limited number of patients in LOT 2+. HR was estimated from a stratified Cox model with stratification by LOT and one-sided p-value for testing HR<1 at the 5% significance level.

HRs are consistent across cancer subtypes and lines of therapy

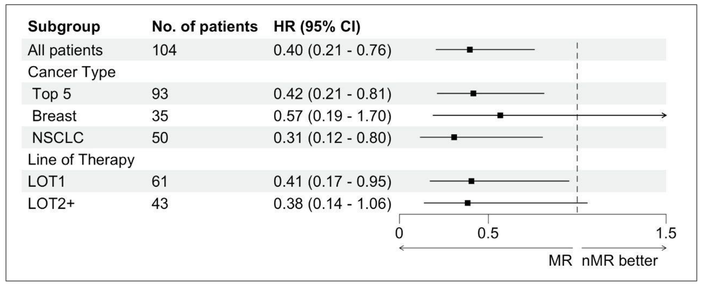

Figure 4. Forest plot showing MR vs. nMR hazard ratios and confidence intervals across clinically relevant subgroups.

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