A novel approach to define ctDNA molecular response to immunotherapy

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INTRODUCTION

Molecular biomarkers that quantify changes in circulating tumor DNA (ctDNA) can help to predict clinical outcomes. However, there is no consensus yet on how to best classify molecular responders (MRs) and molecular non-responders (nMRs) who would benefit from early treatment intervention. Here, we compare two approaches to classifying MRs vs. nMRs in a real-world pan-cancer cohort of patients treated with immune checkpoint inhibitor (ICI) therapy. First, as previously described, we use a ≥ 50% decrease in ctDNA tumor fraction (TF) between baseline and on-treatment time points (MR50) to classify MRs. Second, hypothesizing that patients with consistently low TF may represent an additional subgroup with prolonged outcomes, we explore and apply a "low TF" threshold whereby patients are classified as MRs when TF remains below the threshold at both timepoints (MRlow), while still classifying patients that qualify as MR50 as MRs.

METHODS

- The full cohort consisted of advanced cancer patients from the Tempus de-identified clinicogenomic database who received a liquid biopsy at pre-treatment baseline and within 21-180 days after starting ICI therapy and prior to completion of ICI therapy.
- TF was quantified for each sample via an ensemble algorithm, xM for Treatment Response Monitoring, that incorporates pathogenic variant allele frequencies, copy number information, and germline information.
- Evaluable patients had at least one blood sample with a TF ≥ the limit of blank of 0.09%.
- The final evaluable cohort consisted of 71 advanced pan-cancer patients with >10 cancer types, most commonly NSCLC (38%, n=27) and small cell lung cancer (20%, n=14).
- Real-world overall survival (rwOS) was defined as the time from on-treatment testing to death or, in event-free patients, last known clinical record.
- Cox proportional hazards models were used to estimate the hazard ratio (HR) for MR status (MR vs. nMR)
- The effect of an MRlow threshold was explored by applying a range of potential thresholds from 0% to 2% TF, reclassifying MRs accordingly, and then assessing the change in HR of MR vs. nMR
- Tests for significance were conducted using 1-sided Wald tests at a 5% significance level.
- Twenty-five patients (35%) were treated with ICI monotherapy and 46 (65%) were treated with ICI-chemotherapy combination.

SUMMARY

- Patients treated with approved ICIs that have consistently low TF (<1%) at baseline and on-treatment timepoints, denoted MRlow, have similar survival rates to molecular responders that show ≥50% decrease in TF
- MRlow patients with consistent low TF at baseline, and on therapy represent a good prognostic group
- These preliminary results should validated in larger studies

RESULTS

Differential survival of MRs vs. nMRs is greater with the incorporation of MRlow

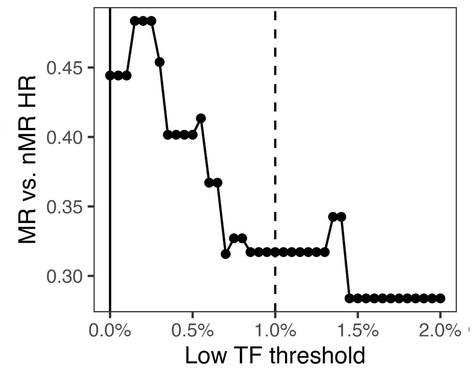

Figure 1 (left). Change in MR vs. nMR hazard ratios across a range of low TF thresholds. Each filled circle shows the hazard ratio (HR) from a Cox proportional hazards model wherein patients were classified as MRs if they either had a 50% decrease in TF or if they qualified as MRlow when applying the corresponding low TF threshold on the x-axis. Note the total number of MRs increases (and the total number of nMRs concomitantly decreases) from 44/71 to 55/71 as additional patients qualify as MRlow with an increasing low TF threshold. A 1.0% low TF threshold, denoted with the vertical dashed line, is used in this study for the modeling of MRlow patients as it meaningfully improves the ability to predict rwOS outcomes while ensuring detection of nMR at lower TF thresholds. Importantly, results are not sensitive to changes in threshold from 0.7% to 2% TF, as evidenced by the consistent HRs in this range.

Incorporation of MRlow leads to the reclassification of 9 of 27 (33%) nMRs to MRs

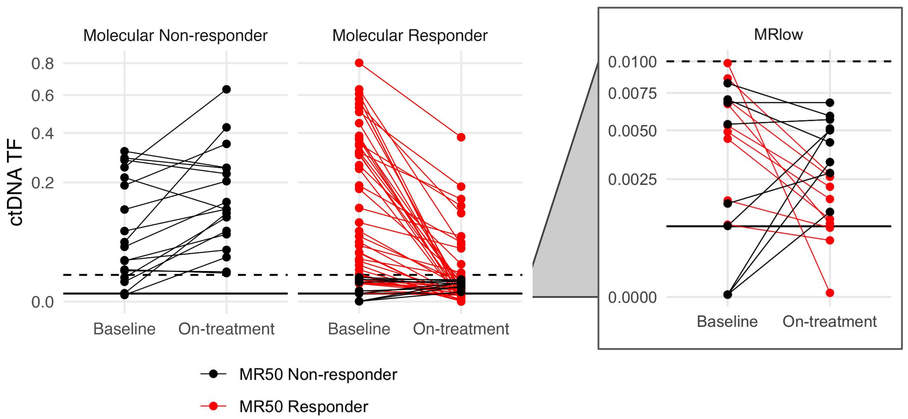

Figure 2 (above). Baseline and on-treatment ctDNA TF values and their corresponding MR classifications, with and without the incorporation of MRlow. Each pair of filled circles, connected with a line, shows the baseline and on-treatment ctDNA TF values for a given patient, organized into two stacks of patients (left and center) based on thier MR status. The panel at right shows the subset of patients (N = 18) who qualify as MRlow because their TFs remain consistently below 1%, most notably the nine patients (filled black circles) that are consequently reclassified as MRs from nMRs.

MRlow and MR50 patients have similar survival rates, supporting their merging into a single MR classification

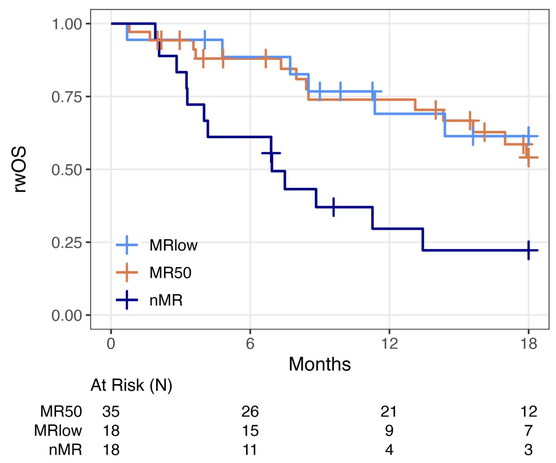

Figure 3 (left). KM curves comparing rwOS rates for nMRs (N = 18), MRlow (N = 18) and MR50 (N = 35). Censored patients are shown as vertical bars; curves are truncated at 18 months due to diminished sample size.

Comparison of Cox PH model results of MR vs. nMR rwOS with/without MRlow

	MR50	MR50 + MRlow
Low TF threshold	-	0.01
N Total	71	71
N MRs	44	53
N MRs MR50	44	35
N MRs MRlow	0	18
N NMRs	27	18
One-sided Wald p-value	0.012	0.001
MR vs. nMR HR (95CI)	0.44 (0.22-0.9)	0.32 (0.15-0.65)
MR Median rwOS	-	-
nMR Median rwOS	8.84	6.93

Table 1 (left). Comparison of CoxPH results with and without MRlow incorporated into the MR definition. Under the "MR50" column, patients are classified as MRs only if they qualify as MR50; under the "MR50 + MRlow" patients are classified as MRs if they qualify for either MR50 or MRlow. Note the reclassification of nine nMRs to MR due to MRlow (i.e., a drop from 27 to 18), and the associated improvement in HR and significance.

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