5573

Use of circulating tumor DNA (ctDNA) for early assessment of treatment response in patients with non-small cell lung cancer (NSCLC): A real-world (RW) analysis incorporating baseline ctDNA level and molecular response

Sean Gordon, Bojan Losic, Katie Quinn, Kyle Chang, Jing Wang, Jiemin Liao, and Han-Yu Chuang
Guardant Health, Inc. Palo Alto, CA

Background

Background: Data suggests that changes in ctDNA quantity correlate with response to therapy in patients with advanced solid malignancies. Furthermore, absolute baseline (pre-treatment) ctDNA level has been shown to be associated with patient prognosis. However, there is little information on how these variables can be combined to better interpret ctDNA results and enhance predictive power of treatment response. Here, we develop approaches to incorporate the effects of both baseline ctDNA level as well as relative ctDNA change in order to identify very high/low risk patient populations as measured by real world data.

Methods

- We queried the Guardant INFORM database, which comprises aggregated commercial payer health claims and de-identified records from >225,000 individuals with ctDNA testing via Guardant360 (G360).
- Patients with aNSCLC who received a ctDNA test within 15 weeks prior to treatment initiation (any line of therapy) and a second test 3-15 weeks after treatment initiation were retrospectively evaluated using the G360 Response algorithm.
  - Patients were grouped by treatment into immune checkpoint inhibitor-based combination therapy (ICI) and EGFR kinase inhibitor-based (osimertinib, erlotinib, afatinib, gefitinib) therapy (TKI)
  - Cox proportional hazards (CPH) were used for RW time to next treatment (TTNT) and overall survival (OS) analyses.
  - A ≥60% and ≥90% decrease in mean variant allele fraction ratio from pre-treatment to on-treatment was used to define TTNT molecular responder (R)/non-responder (N) molecular status in ICI and TKI cohorts, respectively.
  - Patients classified as ctDNA-low (i.e. having low tumor shed at both timepoints) were grouped with molecular responders when assessing response.
  - 1.6% and 0.6% maximum variant allele fraction (MVAF) was used as thresholds to assign TTNT high/low baseline cfDNA tumor fraction categories in ICI and TKI cohorts, respectively.
  - Gender, age, line of therapy (LOT), and comorbidities were included as covariates in CPH.
  - Median TTNT and OS were calculated by Kaplan Meier.

References

1. Zhang Q et al. *Cancer Discov* 2020. 2. Thompson J et al. *JCO PO* 2021.

Results

KEY FINDING: Molecular Response and baseline ctDNA identifies very high/low risk patient populations across therapies in aNSCLC

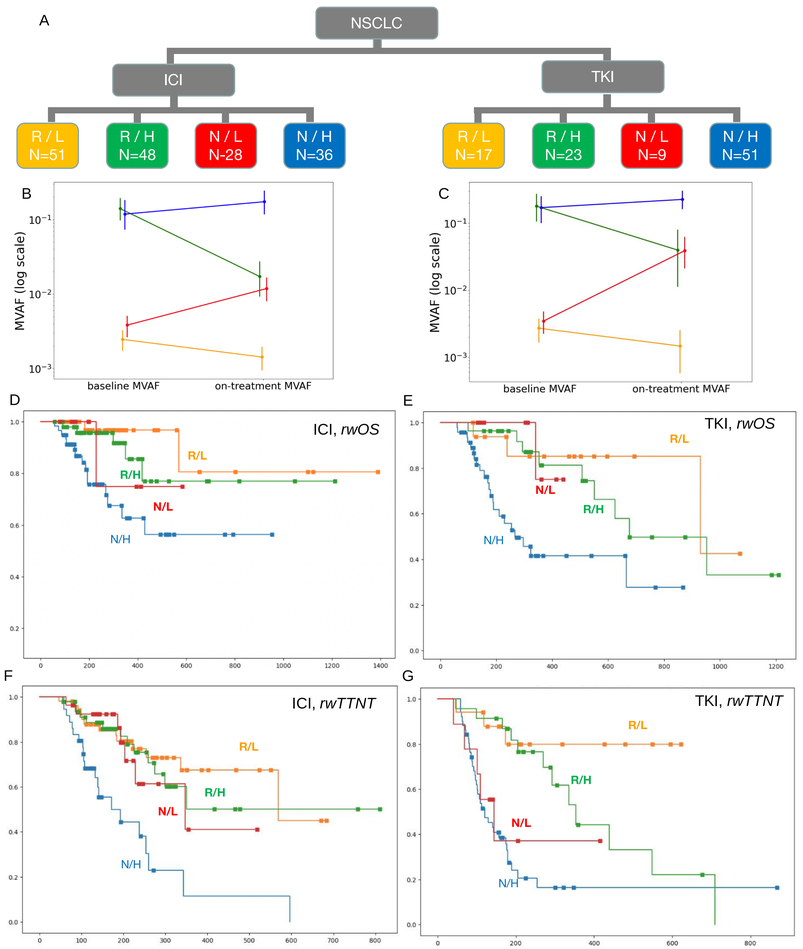

Figure 1. A) Patients within ICI and TKI treatment cohorts were categorized into 4 categories: responder/low baseline (R/L), responder/high baseline (R/H), non-responder/low baseline (N/L), non-responder/high baseline (N/H) based on molecular responder (R) / non-responder (N) and high (H) or low (L) baseline ctDNA level. Patient counts and plots reflect thresholds optimized for rwTTNT individually. B-C) Maximum variant allele fraction (MVAF) is plotted (mean and 95% CI) between baseline and on-treatment timepoint for respective MR/MVAF groups within ICI cohort (B) and TKI cohort (C). Kaplan Meier plots of rwOS (D) and rwTTNT (F) in the ICI cohort and rwOS (E) and rwTTNT (G) in the TKI cohort.

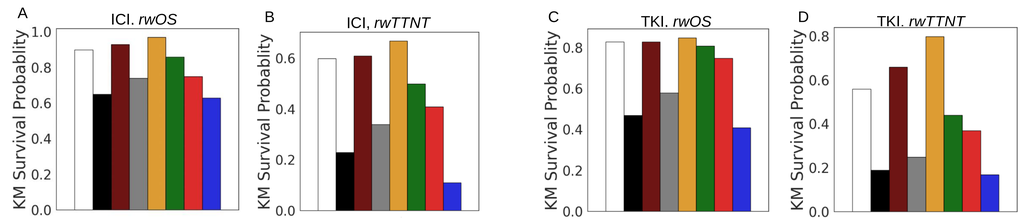

Figure 2. One year survival probability for *rwOS* and *rwTTNT* for groups in Fig1A. Molecular responders (R, white) and **nonresponders (N, black), low baseline ctDNA (L, maroon),** high baseline ctDNA (H, grey) , **responder/low baseline (R/L, orange), responder/high baseline (R/H, green), non-responder/low baseline (N/L, red), non-responder/high baseline (N/H, blue)** in ICI (A,B) and TKI cohorts (C,D).

Cohort	Group	Reference Group	CPH HR	CPH HR, p-value	Median TTNT in months [CI]
ICI	N	R	2.83 [1.58-5.09]	< 0.005	N: 7.9 [6.4-11.6]; R: 19.0 [11.2-NR]]
ICI	H	L	1.76 [0.99-3.15]	0.056	H: 9.1 [7.5-19.9]; L: 19.0 [11.2-NR]
ICI	N/H	R/L	4.31 [1.97-9.43]	< 0.005	N/H: 5.7 [4.4-8.7]; R/L: 19.0 [11.2-NR]
TKI	N	R	4.28 [2.18-8.40]	< 0.005	N: 4.0 [3.4-5.8]; R: 14.6 [9.8-23.6]
TKI	H	L	2.88 [1.19-6.98]	0.019	H: 6.0 [4.0-8.5]; L: NR [4.8-NR]
TKI	N/H	R/L	14.86 [3.19-69.15]	< 0.005	N/H: 4.0 [3.2-5.8]; R/L: NR [5.8-NR]

Table 1. Hazard of *rwTTNT*. High baseline ctDNA molecular nonresponders (N/H) have 14 times the hazard for TTNT event (proxy for progression) compared to low baseline ctDNA molecular responders (R/L) in the TKI cohort. Abbreviations: Molecular responders (R), nonresponders (N), low baseline ctDNA (L), high baseline ctDNA (H) , responder/low baseline (R/L), non-responder/high baseline (N/H); NR=Not reached.

Cohort	CPH Model	C-index	AIC	CPH HR
ICI	MR+MVAF+covariates	0.65	418	N=2.82; H=1.72
ICI	MR+covariates	0.64	418	R=2.83
ICI	MVAF+covariates	0.58	427	H=1.76
TKI	MR+MVAF+covariates	0.76	366	N=3.99; H=2.36
TKI	MR+covariates	0.76	369	N=4.28
TKI	MVAF+covariates	0.63	381	H=2.88

Table 2. CPH model with both MR and MVAF has trend towards higher concordance index and reduced AIC as compared to the same model but including only MR or TF as the sole ctDNA metric. MR p-value in combined model was <0.005 for both cohorts. MVAF p-value in combined model was borderline significant (0.068, 0.063)

Conclusions

Patients with aNSCLC classified as **molecular responders via the G360 Response algorithm had significantly prolonged time on treatment and overall survival** compared to non-responders.

Further stratification of molecular response by baseline ctDNA level identifies patients at particularly high/low risk. Preliminary data shows that methylation-based estimate of ctDNA tumor fraction (see poster 3123) is significantly associated with *rwTTNT* and may be an improvement over MVAF-based estimates (data not shown).

Compared to tumor biomarkers, **ctDNA has a short half-life, which can allow for early response assessment**, as shown in this study. These findings are relevant for clinical care, **with future potential to allow for adaptive clinical trial design.**