Detection of circulating tumor DNA predicts survival in advanced HCC patients treated with personalized therapeutic DNA cancer vaccine in combination with immune-checkpoint blockade

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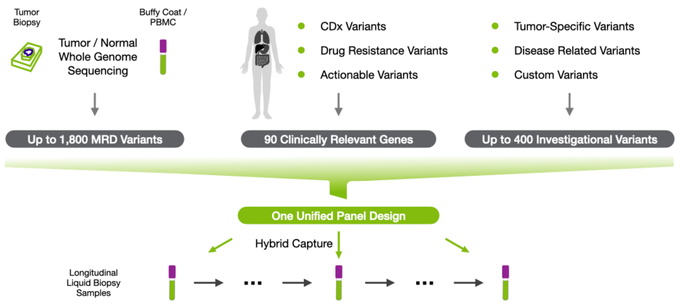
Background: Circulating tumor DNA (ctDNA) has enabled the non-invasive monitoring of molecular residual disease (MRD) which reflects therapeutic response/resistance prior to conventional imaging approaches. However, little is known about the applications of ctDNA in the neoantigen-targeted personalized cancer vaccine setting, potentially due to the limited sensitivity of current ctDNA assays. NeXT Personal®, an ultra-sensitive tumor-informed ctDNA assay was used to longitudinally track ctDNA in advanced hepatocellular carcinoma (HCC) patients treated with GNOS-PV02 (a personalized therapeutic DNA cancer vaccine) in combination with pembrolizumab.

Methods: Advanced unresectable or metastatic HCC patients that progressed on, or were intolerant to, first-line TKI therapy were enrolled into the Phase 1b/2a GT-30 study [NCT04251117]. Whole exome/transcriptome tumor sequencing was used for the design of GNOS-PV02. Patients were treated with GNOS-PV02 (1mg; Q3W x 4, Q9W) and plasmid-encoded IL-12 (0.3mg; Q3W x 4, Q9W) in combination with pembrolizumab (200mg; Q3W). Clinical Response was evaluated by RECIST 1.1 at baseline and Q9W. The ctDNA analysis and tracking for progression was performed as an exploratory objective. Over 200 prospective baseline and on-treatment plasma samples from 30 patients were collected and analyzed using NeXT Personal. WGS was performed to identify up to ~1,800 selected tumor variants to create a personalized panel for MRD detection. NeXT Personal has been analytically validated to detection thresholds down to 1-3 parts per million (PPM) of ctDNA with >99.95% specificity.

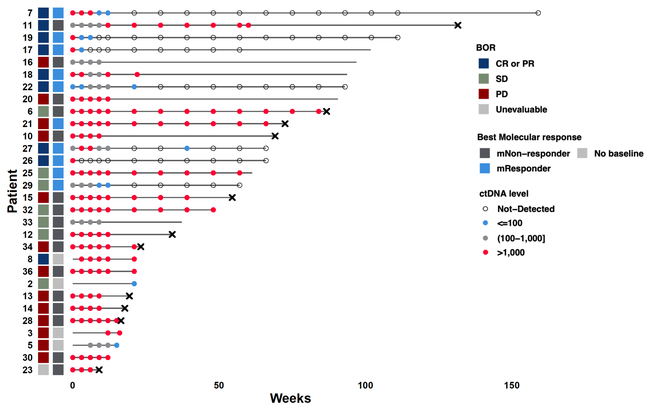
Results: ctDNA was detected in 165 of 226 plasma samples with a dynamic range of 1.66 – 167,319 PPM. The limit of ctDNA detection ranged down to 0.83 PPM. 100% (26/26) of patients were baseline ctDNA+. The percentage change of ctDNA relative to baseline at week 9 (C4D1) significantly correlated with best overall response (CR/PR vs. SD/PD: P = 0.031). The ctDNA change from baseline to week 9 was predictive of OS (P = 0.0038), with 30.8% 2-yr OS (95% CI: 13.2 – 71.8%) for molecular non-responders vs 100% 2-yr OS (95%CI: 100 - 100%) for molecular responders. In addition, the ctDNA levels at week 9 were predictive of best overall response (P = 0.0050). ctDNA burden at week 9 was significantly correlated with overall survival (HR = 6.01, 95%CI: 1.99 – 18.16; P = 0.001; C-index = 0.891). ctDNA clearance was observed in all 3 CR patients with a lead time of 483, 147 and 105 days compared with MRI.

Conclusions: This ultra-sensitive ctDNA assay shows significant association between ctDNA change and clinical response and survival, and can be used to accurately predict clinical outcome. The convenience of non-invasive liquid biopsy and rapid availability of data could enable the use of ctDNA to allow real-time monitoring of personalized cancer immunotherapy.

NeXT PERSONAL® WORKFLOW

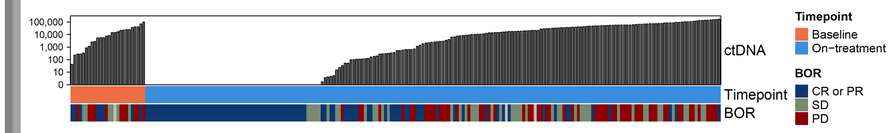


LONGITUDINAL CTDNA DETECTION

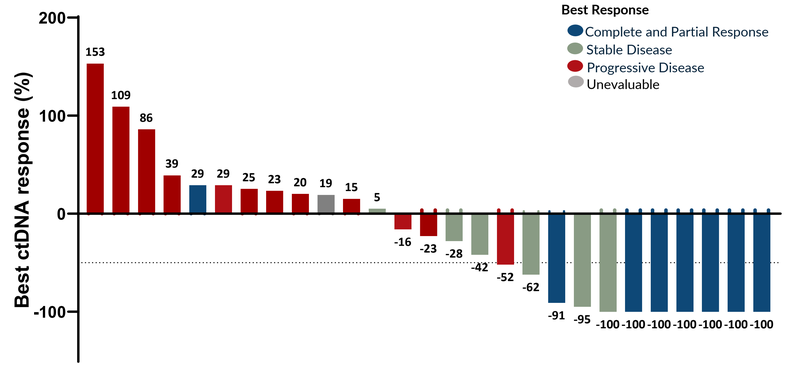


CTDNA DETECTION OVERVIEW

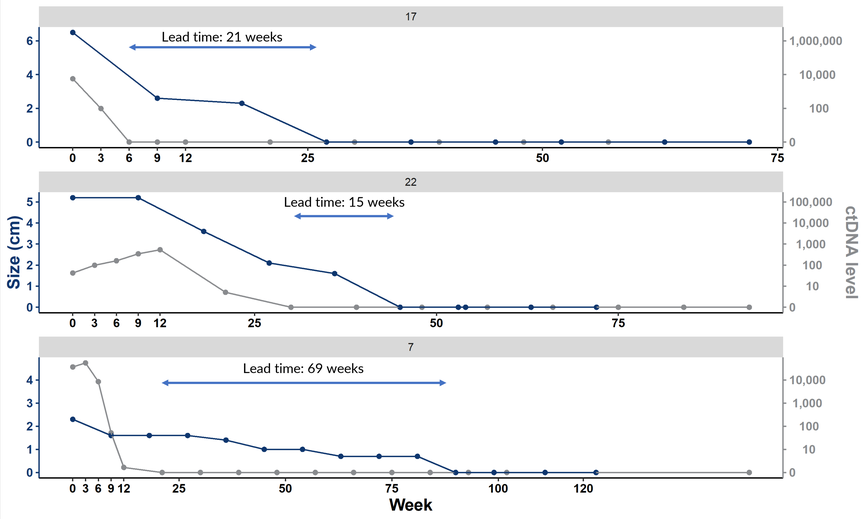
- ctDNA was detected in 165 out of 226 plasma timepoints with a dynamic range of 1.66 to 167,319 PPM
- The limit of ctDNA detection ranged down to 0.83 PPM
- Baseline detection rate was 100% (26/26)



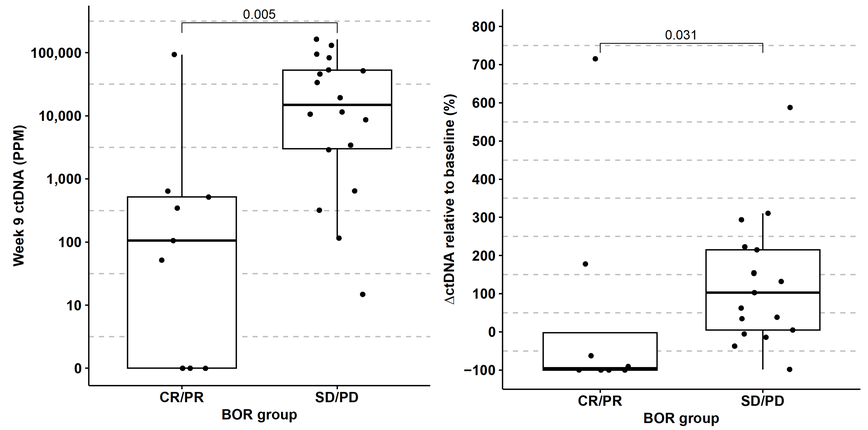
RESPONSE BY CTDNA CROSS-REFERENCED TO RESPONSE BY RECIST 1.1



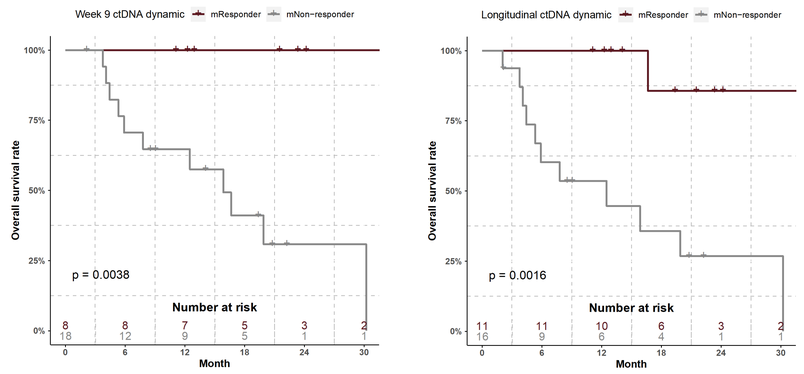
OBJECTIVE COMPLETE CLINICAL RESPONSE TO TREATMENT IS ASSOCIATED WITH CTDNA CLEARANCE AND CTDNA RESPONSE PRECEDES MRI RESPONSE



ABSOLUTE CTDNA LEVEL AND CHANGE IN CTDNA RELATIVE TO BASELINE AT WEEK 9 SIGNIFICANTLY CORRELATED WITH CLINICAL OUTCOME



MOLECULAR RESPONSE (> 50% ctDNA REDUCTION) IS SIGNIFICANTLY ASSOCIATED WITH IMPROVED SURVIVAL



CONCLUSIONS

- The NeXT Personal® platform (Personalis, Inc.), an ultra-sensitive tumor-informed ctDNA assay that leverages whole genome sequencing of tumor/normal samples to generate personalized liquid biopsy panels, was used to longitudinally monitor molecular residual disease (MRD).
- Each panel includes up to 1,800 selected variants of the highest value specific to each patient, enabling detection of ultra-low traces of residual cancer, as low as 1 – 3 parts per million (PPM).
- Among all CR and PR patients for whom ctDNA data is available, the reductions in ctDNA level (molecular response) have preceded improvement by MRI.
- Four additional patients have achieved a complete molecular response (CMR) by the NeXT Personal® analysis. The ctDNA dropped below the limit of detection in all four patients. By RECIST1.1, three of these four patients are durable partial responses (PR) and one a durable stable disease (SD). Applying mRECIST criteria as additional evaluation, each of the three PR patients is a CR and the SD patient is a PR.
- Retrospective analysis indicated that changes in ctDNA levels relative to baseline following treatment correlated well with disease status and were detected prior to confirmation of clinical response by RECIST 1.1. ctDNA change on treatment could be a predictive tool for clinical outcome.